HETEROCYCLIC ANALOGUES OF STEROIDS CONTAINING A BRIDGEHEAD NITROGEN

by

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A Thesis presented for the Degree of Doctor of Philosophy

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Declaration

I declare this thesis is my own composition, that the work of which it is a record has been carried out by myself, and that it has not been submitted in any previous application for a Higher Degree.

This thesis describes results of research carried out in the Department of Chemistry, University of Edinburgh, under the supervision of Dr. Peter J. Sykes between April 1976 and March 1979.

The following courses were attended during the three years of research.

"Strategy of Organic Synthesis" (5 lectures) Dr. I. Gosney (University of Edinburgh); "Crawford to Kemball, 260-Years A-growing" (5 lectures) Dr. W. P. Doyle (University of Edinburgh); "Chemistry at its Most Colourfull" (5 lectures) I. C. I. Blackley; "Computer Course" (1 week) Dr. C. N. M. Pounder (University of Edinburgh); "High Performance Liquid Chromatography" (5 lectures) Professor J. H. Knox and Drs. Pryde and Done (University of Edinburgh); "Multiple Resonance" (5 lectures) Dr. W. MacFarlane (City of London Polytechnic).

[redacted]

A report on one aspect of this work has been published:

Steroidal Heterocycles: 2'-Thiocyanatoandrosteno-[3, 2-d]pyrimidines and -[17, 16-d]pyrimidines, Joginder S. Bajwa and Peter J. Sykes, J.C.S. Perkin I, 1978, 1618.

Table of Contents

Abbreviations

bs	broad singlet
^{13}C n. m. r.	carbon-13 nuclear magnetic resonance
d	doublet
dd	doublet of doublets
ε	extinction coefficient
h	hours
^{1}H n. m. r.	proton nuclear magnetic resonance
i. r.	infra-red
J	coupling constant
λ_{max}	wavelength of maximum absorption
lit.	literature
m	multiplet
m/e	mass to charge ratio
m. p.	melting point
M^{+}	molecular weight
p. p. m.	parts per million
δ	chemical shift
s	strong (i. r.), singlet (^{1}H n. m. r.)
t	triplet
u. v.	ultra-violet
Υ_{max}	frequency of maximum absorption

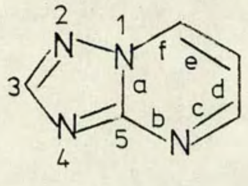
The configuration of the hydrogen atoms at the ring junctions of the steroids will be 5α, 8β, 9α, and 14α, unless otherwise specified.

In the diagrams the configurations are shown as follows:

A solid line indicates a β-configuration.

A broken line indicates an α-configuration.

A wavy line indicates an unknown configuration.



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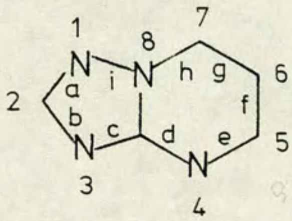

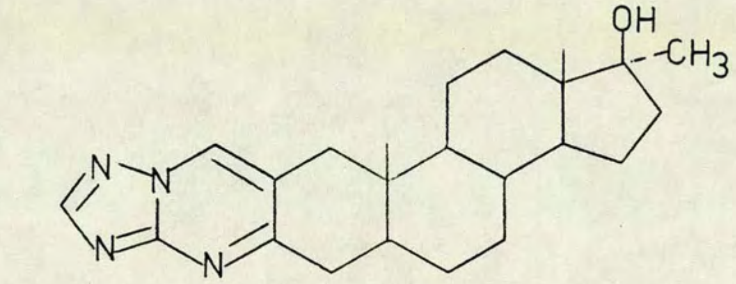

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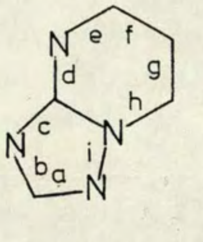

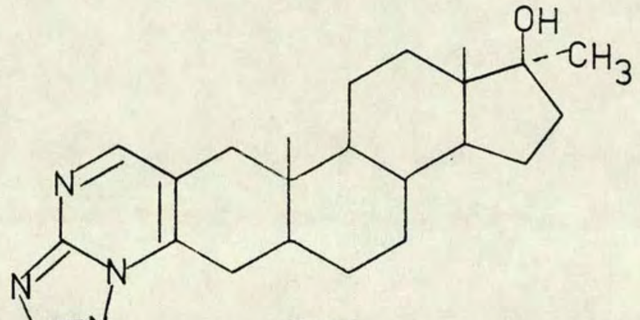

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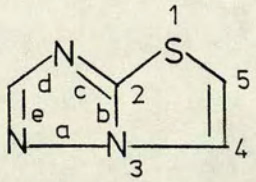

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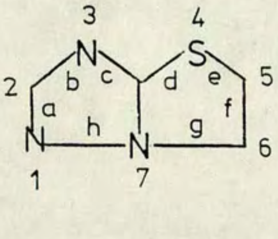

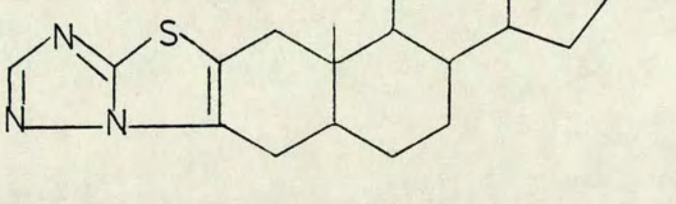

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Nomenclature

The naming of steroids with heterocyclic rings fused to the nucleus of the steroid, the syntheses of some of which are described in this present work, is somewhat complicated. The steroid fragments of these compounds have been named in accordance with IUPAC rules whilst the heterocyclic systems have been named after the analogous heterocyclic systems prepared by the condensation of simple aliphatic β-dicarbonyl compounds and various aminoazoles, and by the condensation of α-halo carbonyl compounds with 2-mercaptoimidazoles and 3-mercapto-1, 2, 4-triazoles. This procedure can be justified by the similarity in the properties of steroid heterocycles and the simple model compounds.

Thus, since structure (69) is known as s-triazolo[1, 5-a]pyrimidine, the steroid (210) has been assigned the name 17β-hydroxy-17α-methyl-5α-androstano[3, 2-f]-s-triazolo[1, 5-a]pyrimidine. [3, 2-f] describes the fusion of the steroid fragment to the pyrimidine ring of the s-triazolo-[1, 5-a]pyrimidinium fragment. Similarly the steroid (211) has been named as 17β-hydroxy-17α-methyl-5α-androst-2-eno[2, 3-g]-s-triazolo-[1, 5-a]pyrimidine.

Structure (74) is known as thiazolo[3, 2-b]-s-triazole and the analogous steroid (353) has been given the name, 17β-hydroxy-17α-methyl-5α-androst-2-eno[2, 3-f]thiazolo[3, 2-b]-s-triazole. [2, 3-f] describes the fusion of the steroid fragment to the thiazole ring of the thiazolo[3, 2-b]-s-triazole fragment.

ABSTRACT

The work contained in this thesis describes some of the many possible condensation reactions which take place between steroidal β-ketoaldehydes and aminoazoles; in all ten examples of β-dicarbonyl steroids were variously condensed with ten representative aminoazoles. Also reported are the reactions which are observed between steroidal α-bromo ketones and mercaptoazoles; nine examples of mercaptoazoles were used in conjunction with four steroids to illustrate these particular reactions. Throughout the above reactions, satisfactory mechanisms have been proposed to account for the observed products.

It is shown that when 2-amino-1,3,4-thiadiazole is condensed with 1,2-hydroxymethylene-3-oxo steroid, the product resulting from the cyclisation reaction, namely 2'-thiocyanato-5α-androst-2-eno[3,2-d]pyrimidine, contains a thiocyanato group formed by cleavage of the thiadiazole ring. A more typical reaction is observed during the condensation of 3-aminopyrazole with a 2-hydroxymethylene-3-oxo steroid. The reaction products are the linearly fused heterocycle, 5α-androstano[3,2-f]pyrazolo-[1,5-a]pyrimidine and the angularly fused isomer, 5α-androst-2-eno[2,3-g]-pyrazolo[1,5-a]pyrimidine.

The observance of two products from this type of condensation reaction appears to be quite general, however, the actual ratio of linearly fused to angularly fused isomer is found to be dependent upon the aminoazole as well as the steroid employed in the reaction. Condensation involving 2-hydroxymethylene-Δ^4-3-oxo steroids and 16-hydroxymethylene-17-oxo steroids always result in a single reaction product.

During the reaction between 3-amino-5-methylthio-1,2,4-triazole

and 16-hydroxymethylene-17-oxo steroids, the intermediate β-ketoanils were isolated. These intermediates could be cyclised to the angularly fused triazolopyrimidines. β-Ketoanils, independently prepared from 2-hydroxymethylene-3-oxo steroids and 2-aminopyridine, have been shown to react with various aminoazoles to afford linearly fused heterocyclic products and these observations lend support to the reaction mechanism proposed for the general condensation reaction. The linearly fused condensation products were distinguished from the angularly fused isomers with the help of i. r., u. v., ^{1}H n. m. r. and ^{13}C n. m. r. spectroscopy.

The reaction of various aminoazoles with 4,4-dimethoxybutan-2-one, 2-hydroxymethylenecyclohexanone, 2-hydroxymethylenecyclopentanone and their corresponding β-ketoanils obtained by the reaction of these β-ketoaldehydes with 2-aminopyridine, has also been investigated.

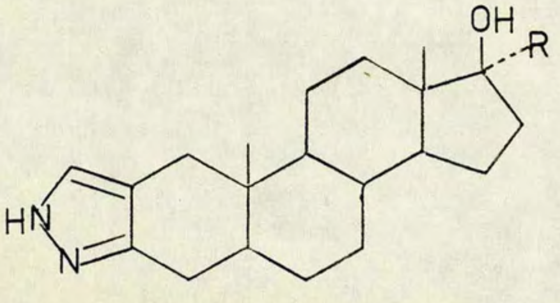
The reaction of 2-mercaptoimidazoles and 3-mercapto-1,2,4-triazoles with 2α-bromo-3-oxo steroids gave the expected cyclised products 5α-androst-2-eno[2,3-b]imidazo[2,1-b]thiazoles and 5α-androst-2-eno[2,3-f]-thiazolo[3,2-b]-s-triazoles respectively. However, the reaction of 2-mercaptoimidazole with 2α-bromo-5α-cholestan-3-one in ethanol gave 5α-cholestano[2,3-b]-3β-ethoxy-2',3'-dihydroimidazo[2,1-b]thiazole in addition to the expected cyclised product. The reaction of 3-mercapto-1,2,4-triazoles with 16α-bromo-3-methoxyoestra-1,3,5(10)-trien-17-one gave only 3-methyloestra-1,3,5(10)-trieno[16,17-f] 16β-ethoxy-5',6'-dihydrothiazolo[3,2-b]-s-triazoles.

1 Introduction

The study of structural modification of steroidal compounds, the scope of which is unequalled in any other branch of medicinal chemistry, has the aim of finding more active and more specific steroidal pharmaceutical preparations, free from harmful side action. Among the many known analogues of the steroids, a special place is occupied by heterocyclic derivatives, the synthesis of which is linked with the hope of obtaining compounds which exhibit instead of the ordinary hormonal action, completely different types of physiological activity-anabolic, anti-inflammatory, hypotensive, anti-tumor, etc.

The heterocyclic derivatives of steroids can be divided into two groups, the first of which includes compounds containing the heteroatom in the constitution of the cyclopentanoperhydrophenanthrene skeleton, and the second are the steroids with the normal carbon skeleton and heterocyclic substituents fused with it in some manner or other. The present work considers steroids with N and/or S atoms condensed with the steroid skeleton and having not less than two C atoms in common with it.

Kockakian,[1] in 1935, first observed that the androgens, the male sex hormones, possessed the ability to stimulate the synthesis of cellular protein, associated with the secondary male characteristic of muscle development. It was quickly appreciated that compounds with this property would provide valuable medications in the treatment of conditions involving abnormally low tissue protein content. However, the natural steroids which possess this anabolic effect were unacceptable for clinical use, particularly with women and children, because of the



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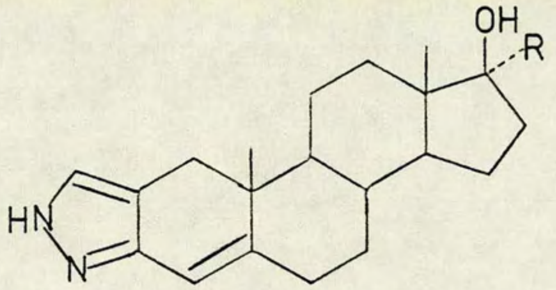

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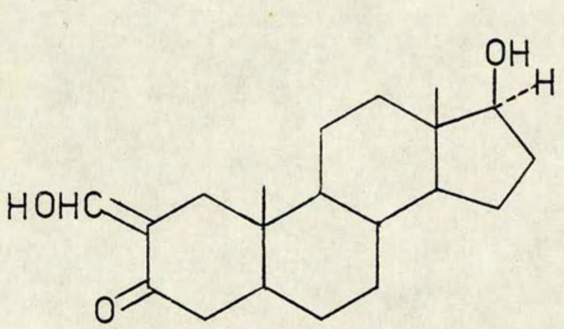

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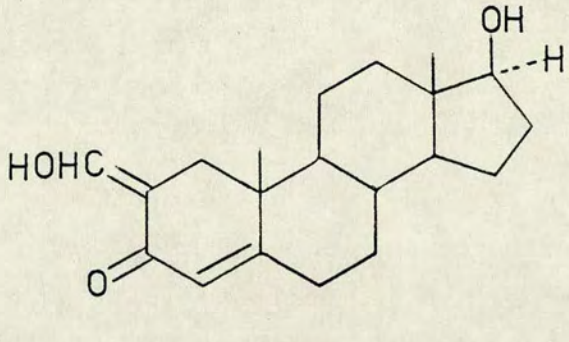

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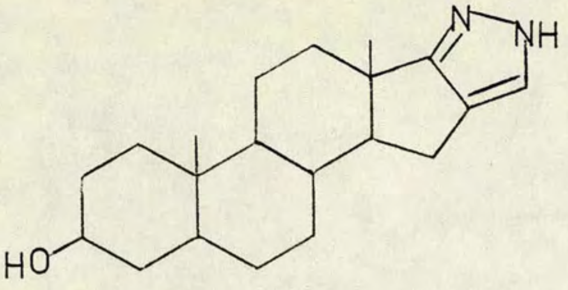
virilising androgen effect.[2]

An assay of the relative anabolic and adrogenic ratio was developed by Eisenberg and Gordan[3] and later modified by Herschberger et al.[4] Examination of the natural androgens showed that almost all had an anabolic/androgenic ratio of ca 1, 0, so that if strongly adrogenic they were also strongly anabolic but if only weak androgens, the anabolic effect was weak. The opinion of Kruskemper[5] that "the androgenic effect differs from the anabolic effect only in its location and not in its essence, thus anabolic steroids which possess no androgenic character cannot exist" is not universally shared and anabolic steroids with no adrogenic action are still sought.[6]

The need for an anabolic agent with few or no androgenic or progestational side effects led to attempts to vary endocrine activity patterns by means of alteration within, or substitutions on the steroid nucleus. It was assumed by most workers in this field that the target receptors (enzyme systems, for example) at the sites of anabolic and androgenic activities differed sufficiently to make at least theoretically feasible the synthesis of a compound which would "fit" only one of these cellular receptor systems. In 1961, Clinton et al.[7] in an attempt to alter the type or stability of receptor site bonding, by substituting an "aromatic" nitrogen for oxygen at 3-C position, prepared a series of 5α-androstano[3, 2-c]pyrazoles (1) and their Δ^4 analogues (2) by the reaction of hydrazine or a substituted hydrazine with 17β-hydroxy-2-hydroxymethylene-5α-androstan-3-one (3) and 17β-hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4) respectively. The fusion of a coplanar pyrazole ring to the steroid nucleus leads to substitution of the 3-oxygen atom by nitrogen which changes the nucleophilic environment in this region. In this, there is a change in the distance between the active centres of the steroid molecule at 3-C and 17-C, since the length of the C=N bond is 1.4Å, the length of the C=O bond in the original ketone is 1.2Å. This evidently shows some influence of the strength of the bond of the steroid molecule with the chelate receptors and can lead to selectivity in the reaction between the steroid and the receptor.[7] Indeed the introduction of a [3, 2-c]-pyrazole ring on to a steroid was found to produce quite pronounced changes in endocrinological activity especially in the altered anabolic/androgenic ratios and in the development of new types of activity. For example 17β-hydroxy-17α-methyl-5α-androstan-3-one has little clinical application as it is both anabolic and androgenic. The corresponding [3, 2-c]pyrazole (1, $R=CH_3$) is 120 times more anabolic than its precursor.[7] The high value of androstano[3, 2-c]pyrazoles as anabolic agents was also confirmed by the results of clinical tests.[8] The compounds (1, $R=CH_3$) and (2, $R=CH_3$) are now manufactured on an industrial scale for use as oral anabolitics.

Both anabolic and androgenic activities fall off abruptly in the 17α-alkyl-17β-hydroxy-5α-androstano[3, 2-c]pyrazoles when the 17-alkyl group is larger than ethyl indicating rather severe restrictions on "fit" to the cellular receptor site in the presence of the [3, 2-c]-pyrazole ring. N-Methylation also decreased both androgenic and anabolic activities in comparison with the parent steroidal[3, 2-c]-pyrazole, whilst acylation of the pyrazole ring imparted a low degree of estrogenicity to the androstano[3, 2-c]pyrazoles without affecting the anabolic/androgenic ratios, probably owing to the lability of the



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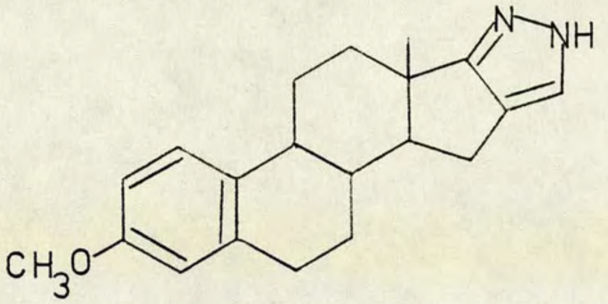

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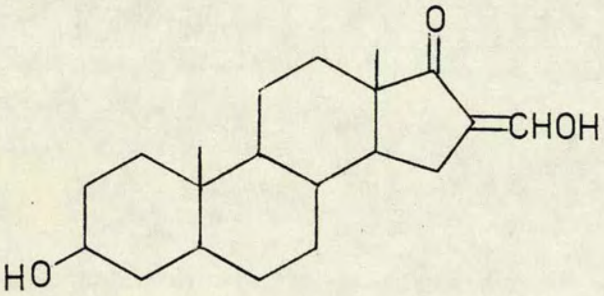

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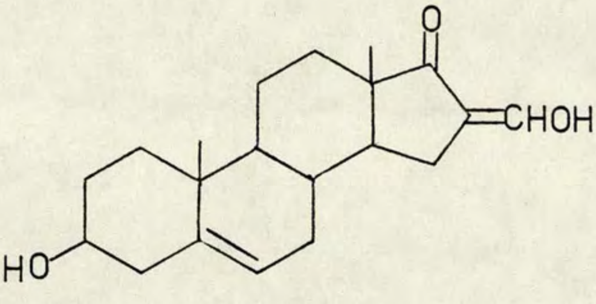

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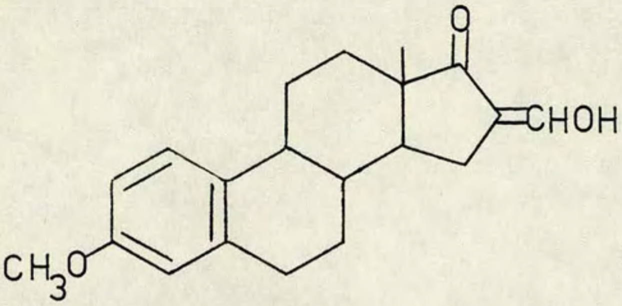

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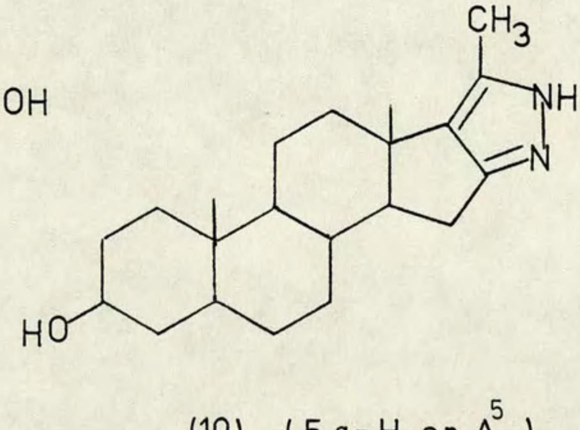

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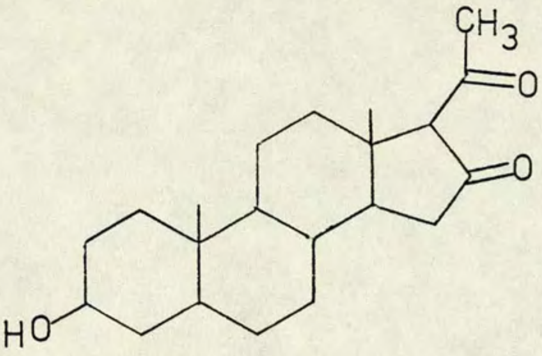
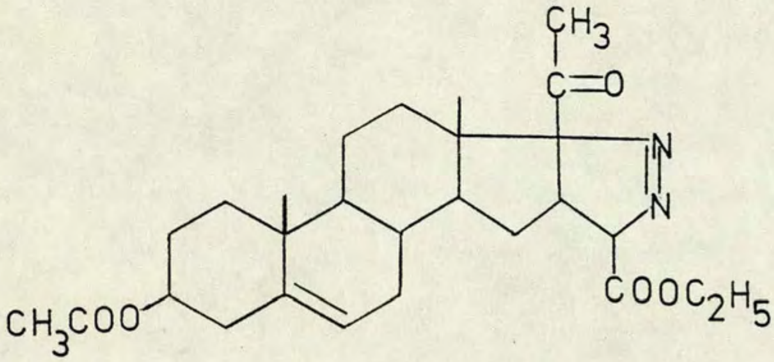


(11) (5 a-H or Δ^5)



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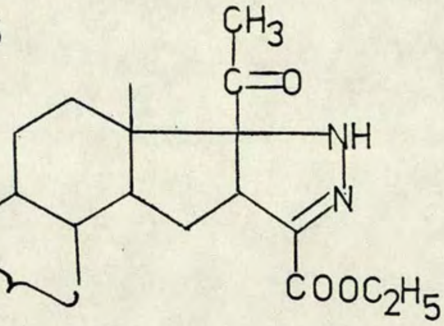

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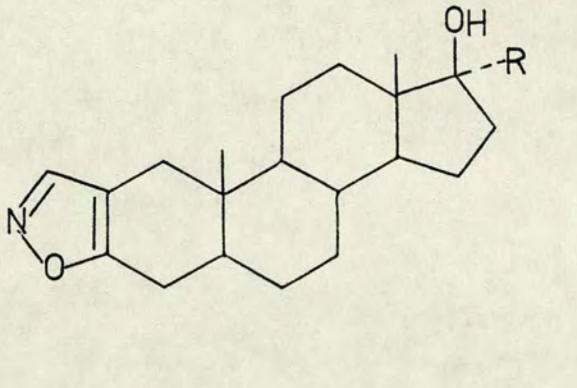

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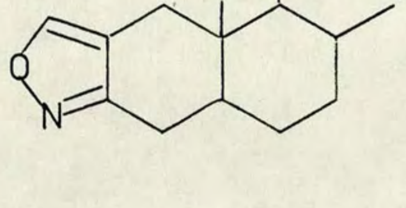

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N-acyl groups.[7]

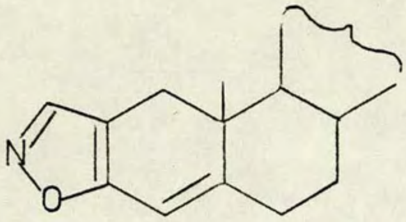
The series of 17β-hydroxyandrost-4-eno- and 17β-hydroxyandrost-4, 6-dieno[3, 2-c]pyrazoles had anabolic/androgenic ratios comparable to their saturated analogues in 5α-androstano[3, 2-c]pyrazole series.[7]

3β-Hydroxy-5α-androstano-, 3β-hydroxyandrost-5-eno- and 3-methoxy-oestra-1, 3, 5(10)-trieno[17, 16-c]pyrazoles (5) and (6) have been synthesised[9] by the action of hydrazine hydrate on the corresponding 16-hydroxymethylene-17-ketones (7), (8) and (9) respectively but have been found not to exhibit any androgenic or anabolic activity. However a number of 5α-androstano- and androst-5-eno[17, 16-c]-5'-methylpyrazoles (10) synthesised from pregnan- and pregn-ene-16, 20-diones (11) and hydrazine hydrate have been found to be useful as diuretic and anabolic steroids.[10]

Recently, cycloaddition of 3β-acetoxypregna-5,16-dien-20-one with diazoacetic acid ester at 20° and 14000 atm has been reported to give 75% of a 3:2 mixture of pregnenopyrazolines (12) and (13). The pyrazoline (12) isomerises to (13) in the presence of acids.[11]

It was shown by analogy with androstanopyrazoles that fusion of an isoxazole ring to the 2, 3-position of androstane also increases the anabolic activity and reduces the androgenic activity.[12] The most interesting preparation of this class was 17β-hydroxy-17α-methyl-5α-androst-2-eno[2, 3-d]isoxazole (14, $R=CH_3$) which in comparison with 17β-hydroxy-17α-methyl-5α-androstan-3-one exhibits 9. 7 times more anabolic, twice the miotropic, and 0. 24 times the androgenic activity.[13]

The androst-2-eno[2, 3-d]- and androstano[3, 2-c]isoxazoles (14) and (15) respectively have been prepared by the reaction of 2-hydroxy-



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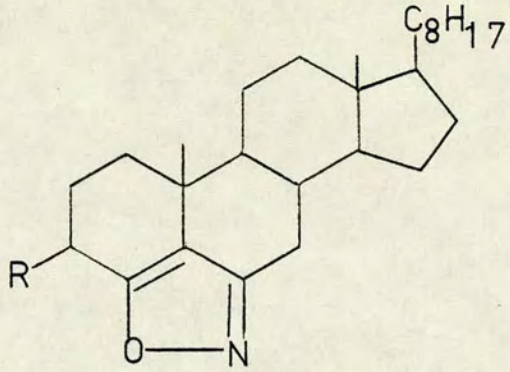

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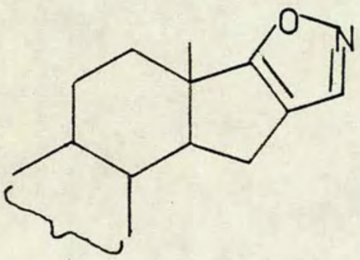

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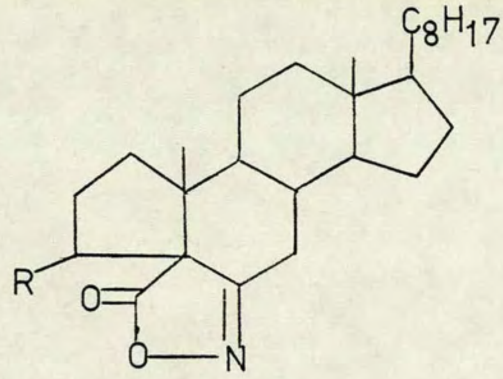

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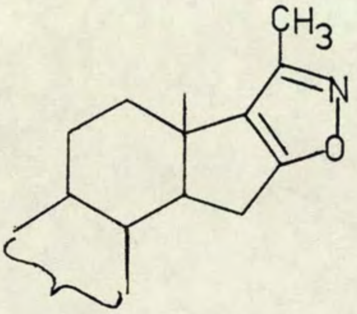

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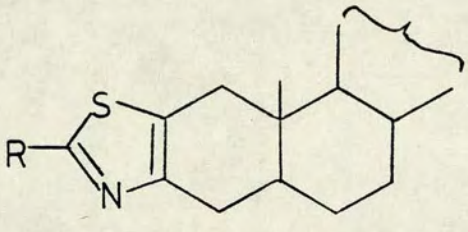

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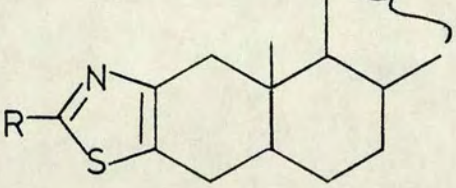

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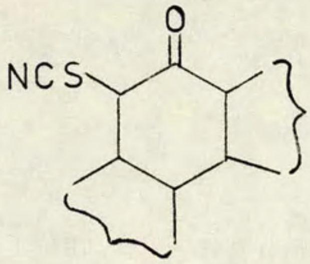
methylene-3-oxo steroids with hydroxylamine hydrochloride. The ratio of (15) to (14) depends upon the pH, the solvent and the temperature. Thus when the reaction was carried out in aqueous ethanol, 8% (15) and 82% (14) were obtained, but in pyridine solution the composition of the mixture is the reverse - 91% (15) and 6% (14).[13, 14] Androstano-[3, 2-c]isoxazoles (15) have also been synthesised by the reaction of 2-cyano-3-oxo steroids with hydroxylamine hydrochloride in pyridine.[15] The reaction of Δ^4-, $\Delta^{4,6}$-, and 4, 4-dimethylsteroids lead exclusively to [2, 3-d]isoxazoles, however these products exhibited lower activity of both types.[13] Results have been obtained,[16] on the presence of antitumour activity in the androst-4-eno[2, 3-d]isoxazoles (16).

Irradiation of 3β-acetoxy-6-nitrocholest-5-ene has been recently reported[17] to give cholestenoisoxazole (17, R=OAc) and A-norcholestanoisoxazolinone (18, R=OAc). Similarly 6-nitrocholest-5-ene upon irradiation gave (17, R=H) and (18, R=H).

Androst-16-eno[16, 17-d]isoxazoles (19) were obtained by the condensation of 16-hydroxymethylene-17-oxo steroids.[18] The preparation of the isomeric androst-16-eno[17, 16-d]-3'-methylisoxazole (20) has also been described.[19]

Steroidal[3, 2-d]thiazoles (21) have been prepared by boiling alcoholic solutions of 2α-bromo-3-oxo steroids of the androstane, pregnane and cholestane series with thiourea and its N-alkyl derivatives[20, 21] and also with thioamides.[21(b), 22-24] Reaction of 3β-bromo-2-oxo steroids with thioamides gave the isomeric [2, 3-d]thiazole derivatives (22).[25] High anabolic and low androgenic activity has been noted for both types of derivatives in the androstane series.[24, 25]



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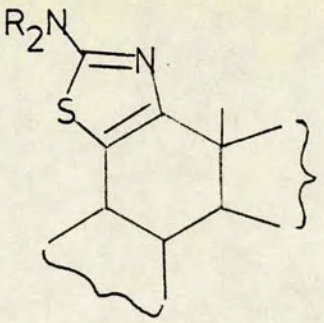

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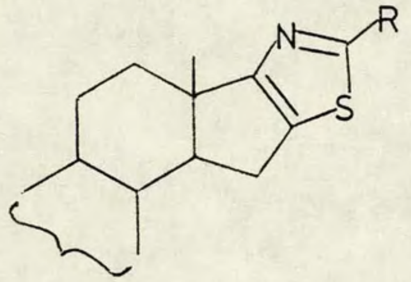
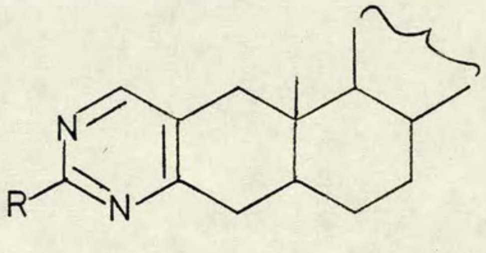
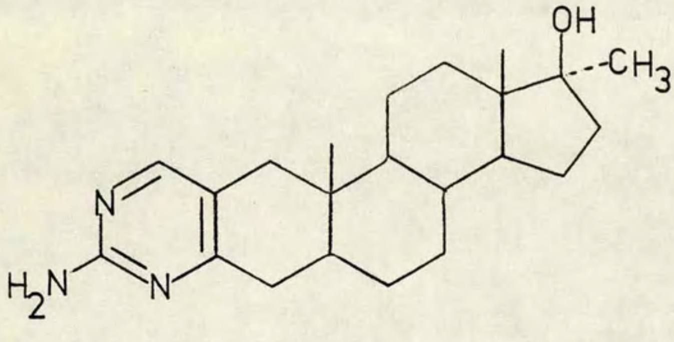


(25) R=CH_3, NH_2



(26) R=H, OH, SH, NH_2



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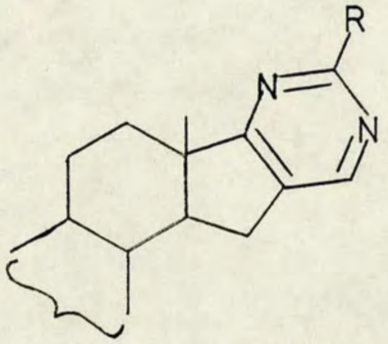
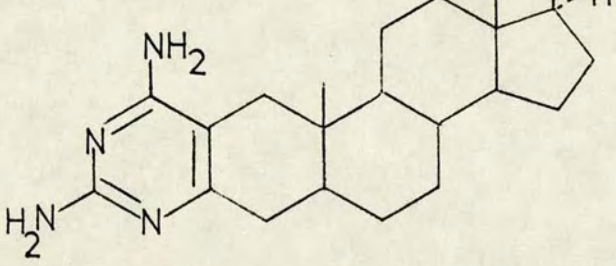


(29) R=H, CH_3, NH_2



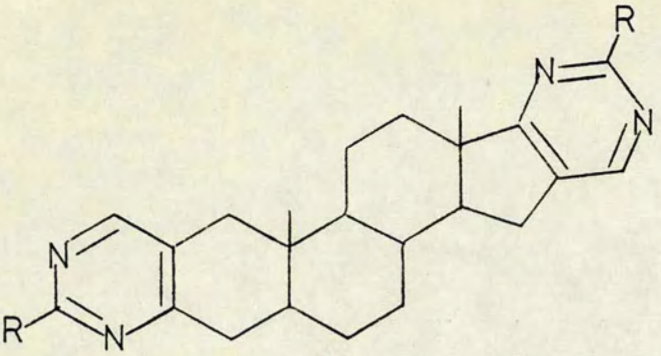
(28) (5 α-H or Δ^4)

The reaction of 12-oxo-11β-thiocyanatosteroids (23) of the cholane and spirostane series with secondary amines in dioxane led to 2'-piperidinosteroido[12, 11-d]thiazoles (24) or the corresponding 2'-morpholino-, 2'-piperazino- and 2'-diethylamino derivatives. The compounds obtained exhibit antihormonal activity.[26]

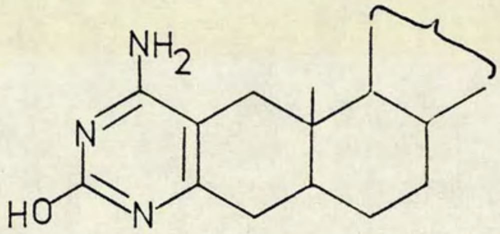
2'-Substituted [17, 16-d]thiazole derivatives (25) were obtained by heating 16 α-bromo-17-oxo steroids with thioacetamide or thiourea in ethanol.[27]

Various steroidal[3, 2-d]pyrimidines have been prepared by the well studied reaction of 2-hydroxymethylene-5 α-androstan-3-ones with guanidine, urea, and thiourea.[15] 2'-Amino-, 2'-hydroxy- and 2'-mercapto-derivatives (26) were obtained in this way. On treating the mercapto-derivative (26, R=SH) with Raney nickel, it was smoothly converted into the unsubstituted derivative (26, R=H).[15] 17β-Hydroxy-17 α-methyl-5 α-androstano[3, 2-d]-2'-aminopyrimidine (27) has been found to decrease nitrogen excretion in male and female humans but to increase 17-oxo steroid excretion in the female and decrease it in the male.[28] 17β-Hydroxy-5 α-androst-2-eno[3, 2-d]-2', 6'-diamino-pyrimidine and their Δ^4 analogue (28) have been prepared[29, 30] by the reactions of cyanoguanidine and 3-oxo steroids at 230-50°. These steroids have been reported to be androgenic and exhibit significant antibacterial activity against Gram-positive micro-organisms.[31]

The reaction of 16-hydroxymethylene-17-oxo steroids with tris-formylaminomethane, acetamidine or cyanoguanidine gave the corresponding [17, 16-d]pyrimidines (29). [3, 2-d: 17, 16-d]Dipyrimidines (30) were obtained from 2, 16-bishydroxymethylene-3, 17-bis oxo steroids by



(30) R = H, NH_2



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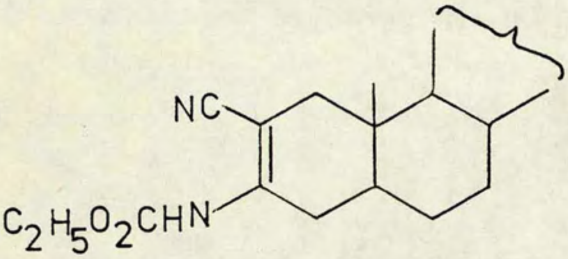

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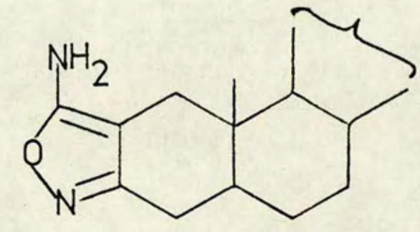

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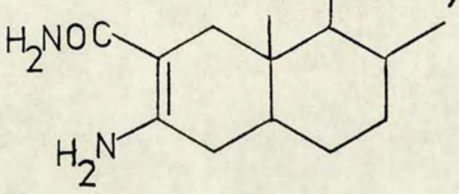

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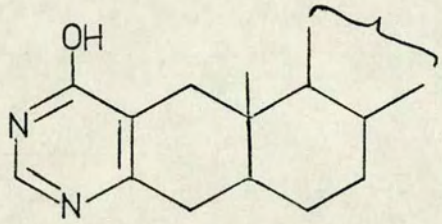

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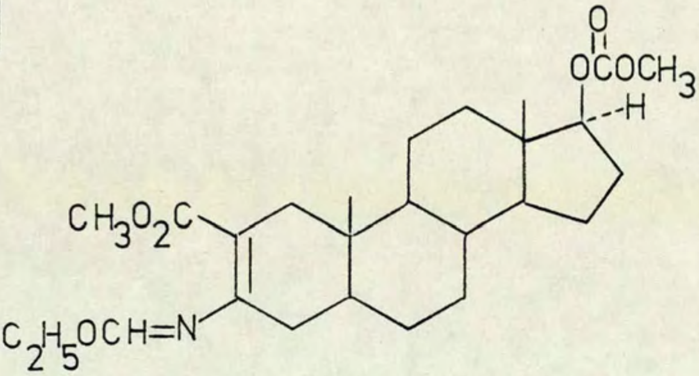

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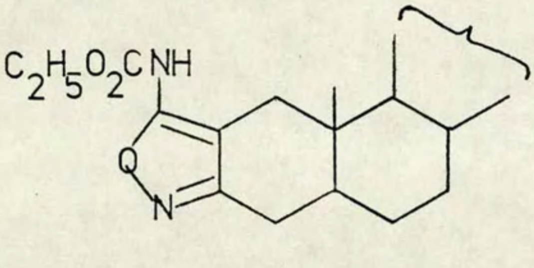

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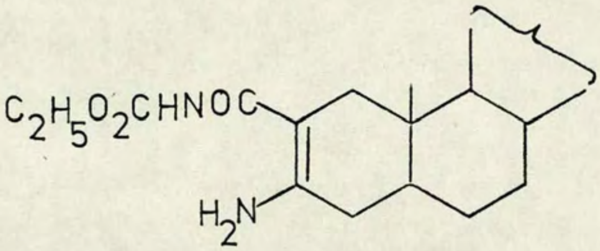

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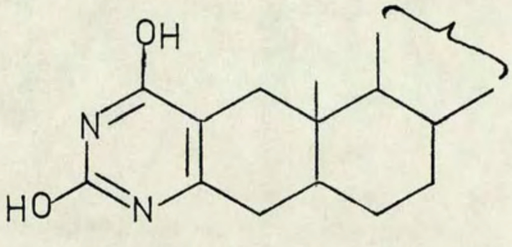
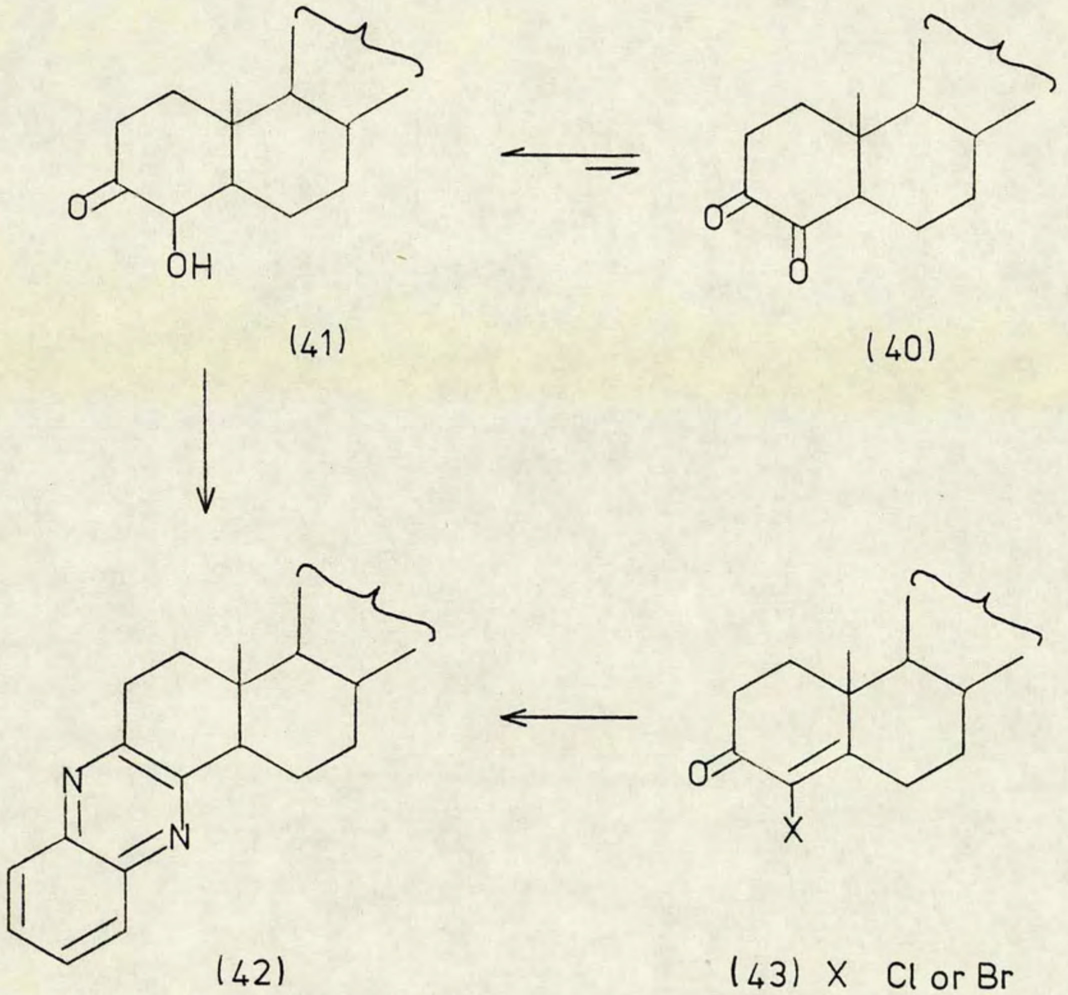


(39)

the same methods.[31-34]

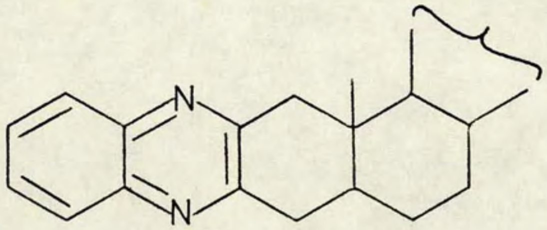
Greater variation in the substituents at the 2 and 6 positions in the pyrimidine ring has been obtained by the modification of 2-cyano-3-oxo steroids prior to either reaction with ammonia or hydroxylamine, or cyclisation at high temperature. De Ruggieri et al.[35(a)] prepared a series of androst-2-eno[3, 2-d]-6'-amino-2'-hydroxypyrimidines (31) from 2-cyano-3-oxo steroids by conversion of the latter to the 2-cyano-3-aminourethanoandrost-2-ene (32) in two stages followed by cyclisation at 130° in an autoclave. This mode of synthesis was further developed by the same workers[35(b)] who having prepared an androstano[3, 2-c]-5'-aminoisoxazole (33) by condensing hydroxylamine and 2-cyano-5α-androstan-3-one, opened the isoxazole ring by hydrogenation to give the enamine (34), which was then treated with ethyl orthoformate to give the androst-2-eno[3, 2-d]-6'-hydroxypyrimidine (35). The 17β-O-carbomethoxy derivative of this steroid has been prepared more recently[36] by treatment of 2α, 17β-O-dicarbomethoxy-3-ethoxyformimido-5α-androst-2-ene (36), derived from 2α, 17β-O-dicarbomethoxy-5α-androstan-3-one, with a saturated ethanolic ammonia solution. Formation of the 5'-N-ethylurethane derivative (37) of the steroidal[3, 2-c]-5'-aminoisoxazole (33) followed by reduction to give the enamine (38) and then treatment with base yielded the androst-2-eno[3, 2-c]-2', 6'-dihydroxypyrimidine (39).

N-Heterocyclic analogues of anabolic steroids with two ring systems are also known. The formation of quinoxaline derivatives of steroids on reaction with o-phenylenediamine served as a proof of the existence of α-dicarbonyl groupings in the molecule. Saturated α-diketones exist predominantly in the ketoenol form (41) and not in the



(41) (40)

(42) (43) X Cl or Br



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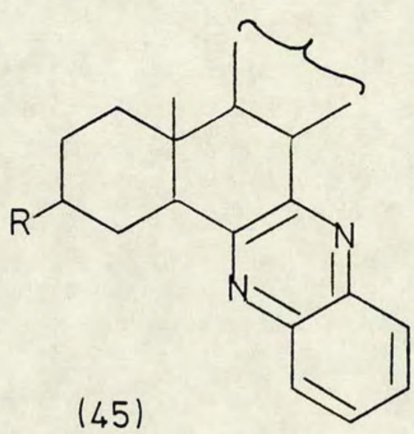

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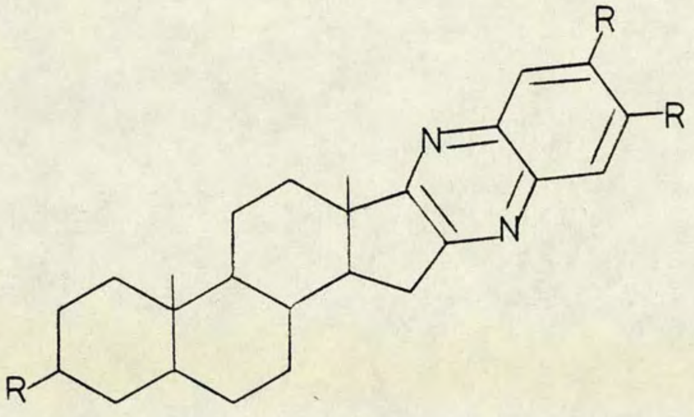
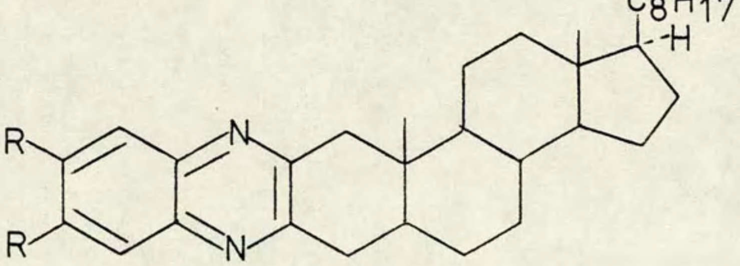
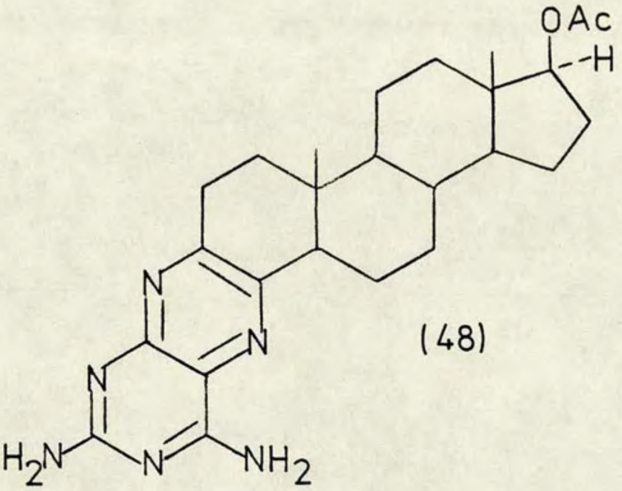


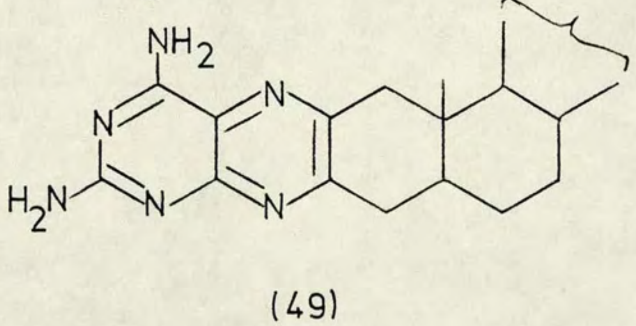
(46) (5α-H or Δ^5)



(47) R=H or CH_3



(48)



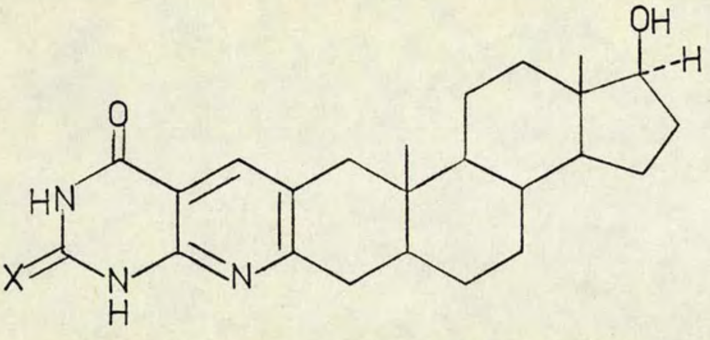
(49)

diketo form (40) and reacted with o-phenylenediamine only on fusion up to 120°.[37] The same product [3,4-b]quinoxaline (42) was also formed on boiling the 4-bromo- and 4-chloro-derivatives (43) with o-phenylenediamine in acetic acid.[38]

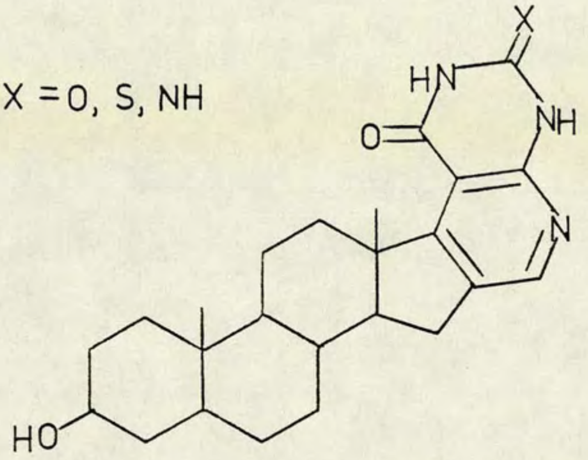
The preparation of quinoxaline derivatives (44) and (45) from 2,3-diketo,[39] 6,7-diketo-[40] steroids respectively has also been described.

More recently androst-16-eno[16,17-b]quinoxalines (46) have been prepared in good yield by refluxing 3β-hydroxy-16α-bromo-5α-androstan-17-one and 3β-acetoxy-16α-bromoandrost-5-en-17-one with o-phenylenediamine and 4,5-dimethyl-o-phenylenediamine in xylene. The reaction of 2α-bromo-5α-cholestan-3-one, 2α-acetoxycholestan-3-one, and 3β-acetoxy-2α,3α-oxido-5α-cholestane, with o-diphenylenediamine or 3,4-dimethyl-1,2-phenylenediamine have been reported to give the cholestano[2,3-b]quinoxalines (47).[41,42]

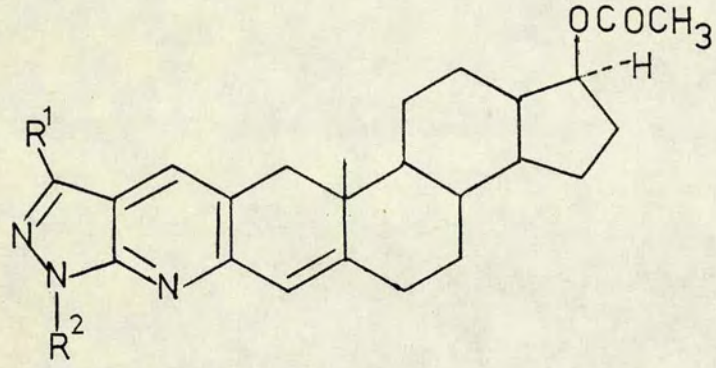
Bardos *et al.*[43] prepared 17β-acetoxy-5α-androst-3-eno[4,3-g]-2',4'-diaminopteridine (48) which was found to be folic acid antagonist with lipid solubility, by heating 4-chloro-17β-hydroxyandrost-4-en-3-one in a mixture of absolute alcohol and acetic acid with the bisulphite of 2,4,5,6-tetraaminopyrimidine. The analogous [2,3-g]-2',4'-diaminopteridine (49), synthesised from 2α-bromo-17β-hydroxy-5α-androstan-3-one, has oral anti-androgenic activity in rat and chick assays. Yoneda *et al.*[44] developed an alternative synthesis of 17β-hydroxy-5α-androst-2-eno[2,3-g]-2',4'-diaminopteridine by fusing 5-(1,2-diethoxycarbonylhydrazino)-2,4,6-triaminopyrimidine with 17β-hydroxy-3-morpholino-5α-androst-2-ene. The [2,3-g]-2'-amino-



(50) X = O, S, NH



(51) X = O, S, NH

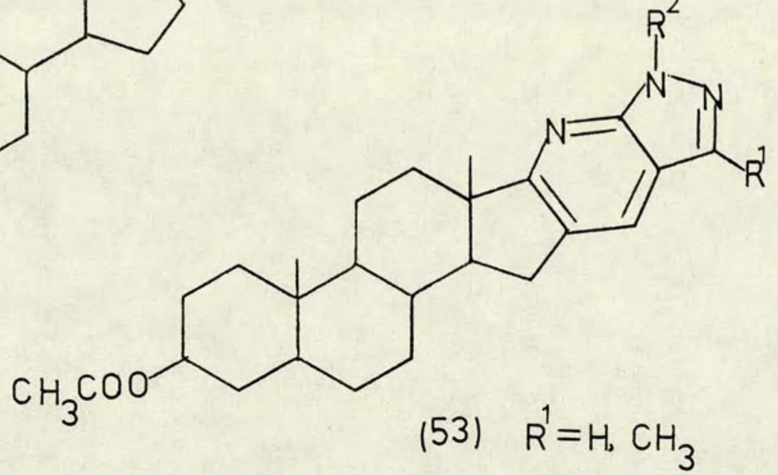


(52) $R^1 = H, CH_3$

$R^2 = CH_3$,

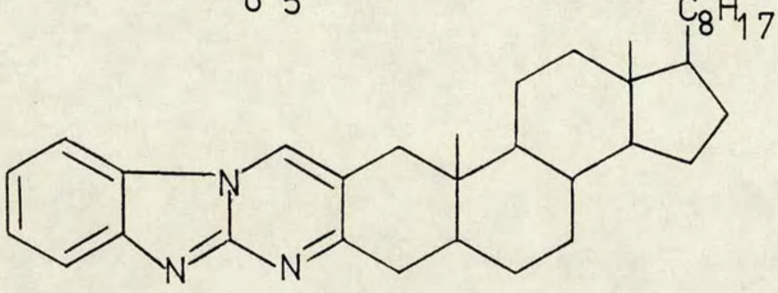
C_2H_5,

C_6H_5



(53) $R^1 = H, CH_3$

$R^2 = CH_3, C_2H_5, C_6H_5$



(54)

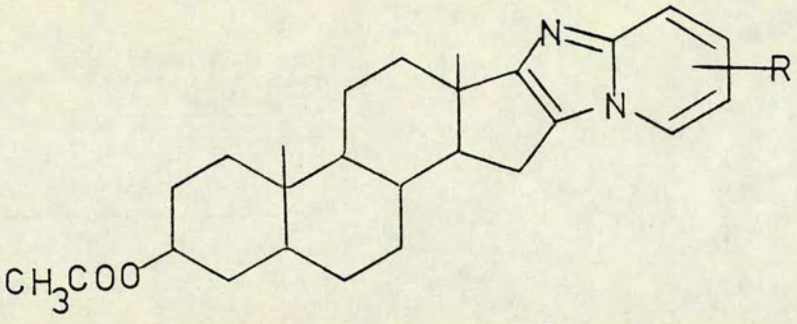
4'-hydroxypteridine derivative was similarly prepared. In a later paper,[45] the same authors describe improved methods of synthesis of pteridino steroids with a variety of substituents on the pteridine ring system.

The synthesis of steroidal pyrido[2,3-d]pyrimidines have been recently described.[46-48] 17β-Hydroxy-2-hydroxymethylene-5α-androstan-3-one (3) and 17β-hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4) on condensation with 4-aminouracils in aqueous acetic acid gave 17β-hydroxy-5α-androst-2-eno[2,3-g]-1',2',3',4'-tetrahydropyrido[2,3-d]-pyrimidine (50)[46] and the Δ^4 analogue[47] respectively. The analogous 3β-hydroxy-5α-androst-16-eno[17,16-f]-1',2',3',4'-tetrahydropyrido-[2,3-d]pyrimidine (51)[48] was synthesised from the 16-aminomethylene-17-oxo derivative of 3β-hydroxy-16-hydroxymethylene-5α-androstan-17-one (7).

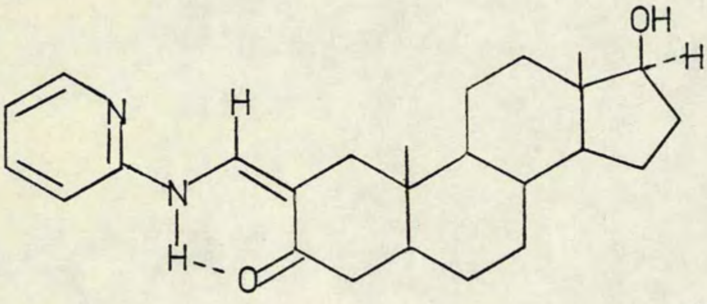
Steroidal pyrazolopyridines (52) and (53) have been prepared in 38-75% yield by condensing aminopyrazoles with 17β-hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4) and 3β-hydroxy-16-hydroxymethylene-5α-androstan-17-one (7) respectively.[49]

Steroids containing a bridgehead nitrogen atom

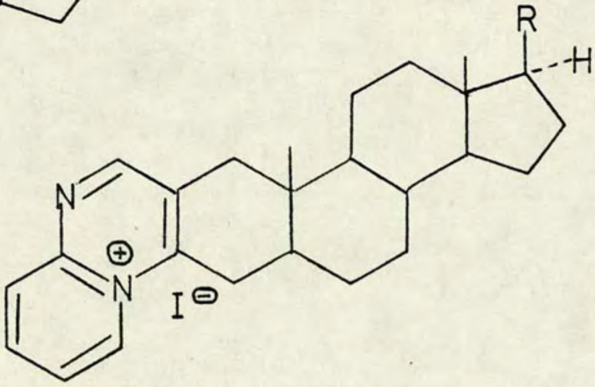
There have been only two reports so far on the synthesis of steroids containing a bridgehead nitrogen. In 1951, Antaki and Petrow[20] reported the synthesis of 5α-cholestano[3,2-b]benzimidazo[1,2-a]-pyrimidine (54) by the reaction of 2-hydroxymethylene-5α-cholestan-3-one with 2-aminobenzimidazole. However no evidence was given in support of structure (54).



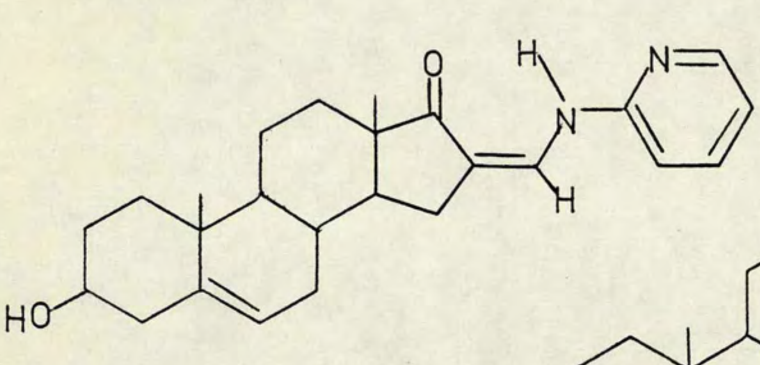
(55) (5α-H or Δ^5) R=H, CH_3



(56) (5α-H or Δ^4)



(57) (5α-H or Δ^4)



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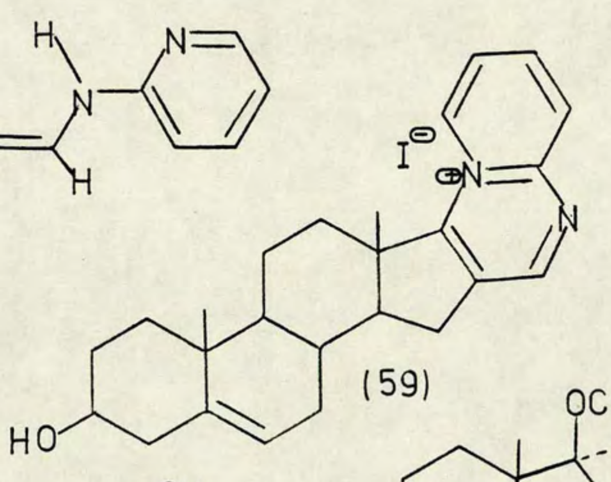

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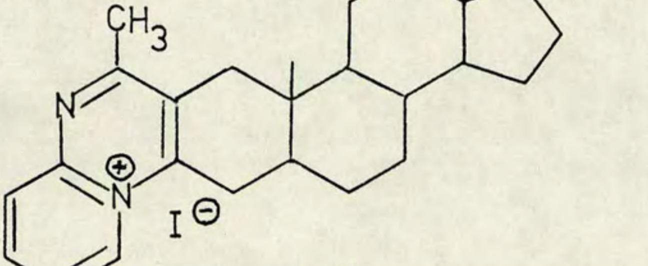
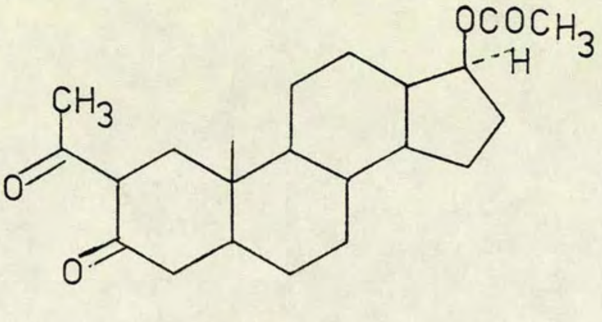


(60)

Catsoulacas and Souli[50] prepared steroidal imidazo[1,2-a]-pyridines (55) from 3β-acetoxy-16α-bromo-5α-androstan-17-one, its Δ^5 analogue and 2-aminomethylpyridines.

Recently, Burgess[51] has described the synthesis of androstane derivatives with a pyrido[1,2-a]pyrimidine ring system fused to the steroid nucleus. 17β-Hydroxy-2-hydroxymethylene-5α-androstan-3-one (3) and its Δ^4 analogue (4) condensed with 2-aminopyridine to give 17β-hydroxy-2(2'-pyridyl-aminomethylene)-5α-androstan-3-one and its Δ^4 analogue (56). The 17β-acetates of these enaminones (56) were cyclised in an acid catalysed reaction to give 17β-acetoxy-5α-androst-2-eno[2,3-e]pyrido[1,2-a]pyrimidin-5'-ium iodide and its Δ^4 analogue (57, R=OAc). 17β-Hydroxy-5α-androst-2-eno[2,3-e]pyrido[1,2-a]-pyrimidin-5'-ium iodide and its Δ^4 analogue (57, R=OH) were obtained in one step reaction when the corresponding 2-hydroxymethylene-3-oxo steroids were condensed with 2-aminopyridinium iodide.

3β-Hydroxy-16-hydroxymethyleneandrost-5-en-17-one reacted with 2-aminopyridine to give 3β-hydroxy-16(2'-pyridyl-aminomethylene)-androst-5-en-17-one (58). It was not possible to obtain 3β-hydroxy-androst-5,16-dieno[2,3-e]pyrido[1,2-a]pyrimidin-5'-ium iodide (59) by cyclisation of the enaminone (58) or by the condensation of β-ketoaldehyde (8) with 2-aminopyridinium iodide. 17β-Acetoxy-5α-androst-2-eno-[2,3-e]-2'-methylpyrido[1,2-a]pyrimidin-5'-ium iodide (60) was isolated in very low yield from the condensation of 17β-acetoxy-2α-acetyl-5α-androstan-3-one (61) and 2-aminopyridinium iodide. However the condensation of the β-diketone (61) with 2-aminopyridine failed to yield any product.



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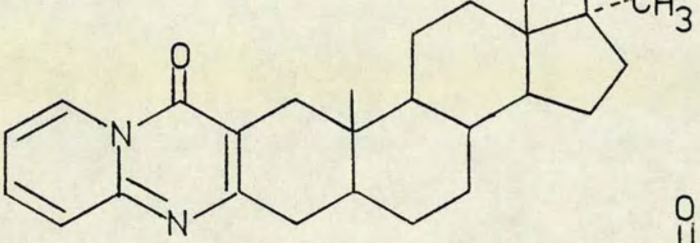

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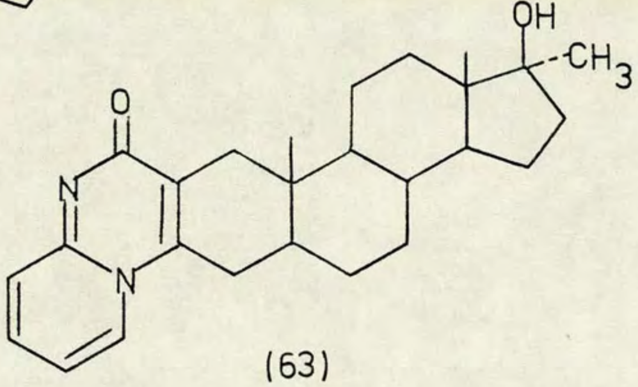

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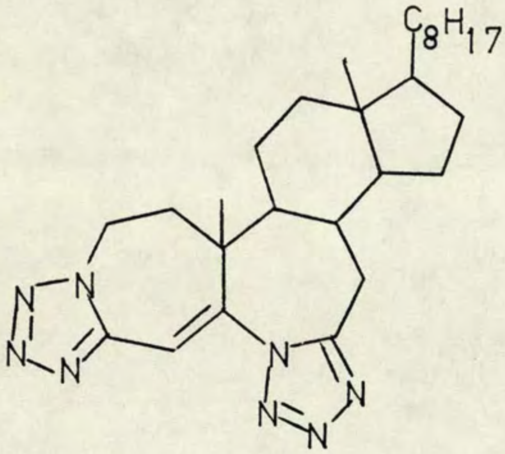

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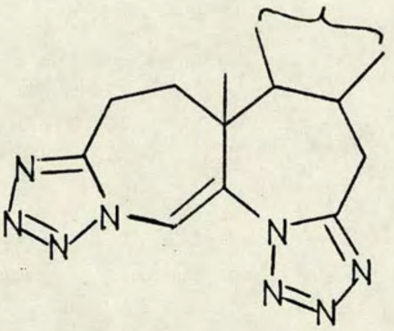

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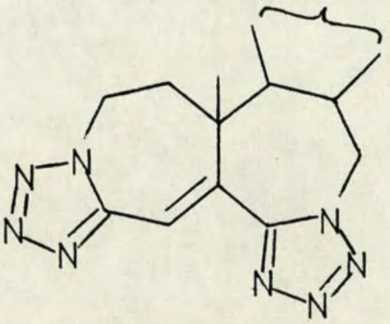

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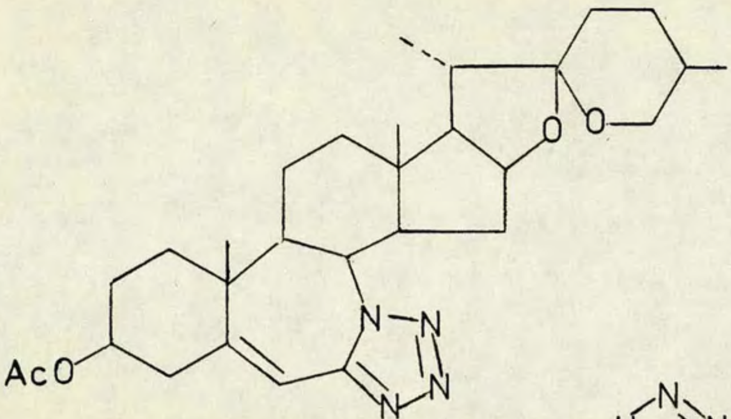

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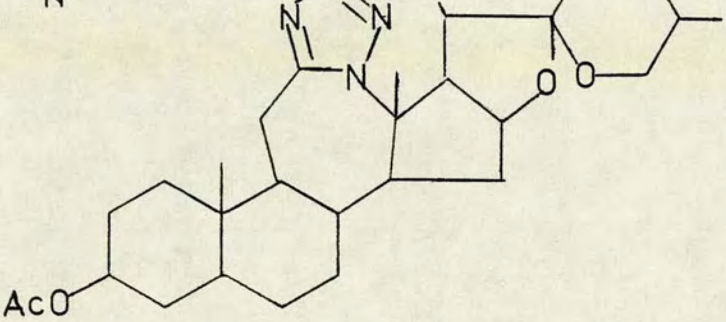

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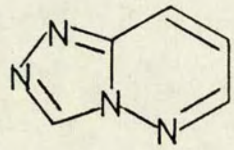

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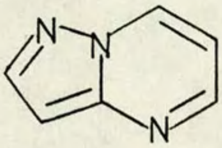

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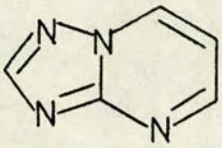

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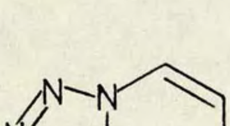
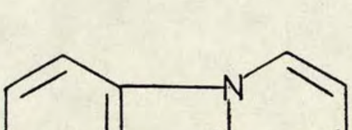
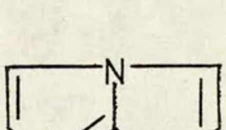


(70)



(71)



(72)

(73)

(74)

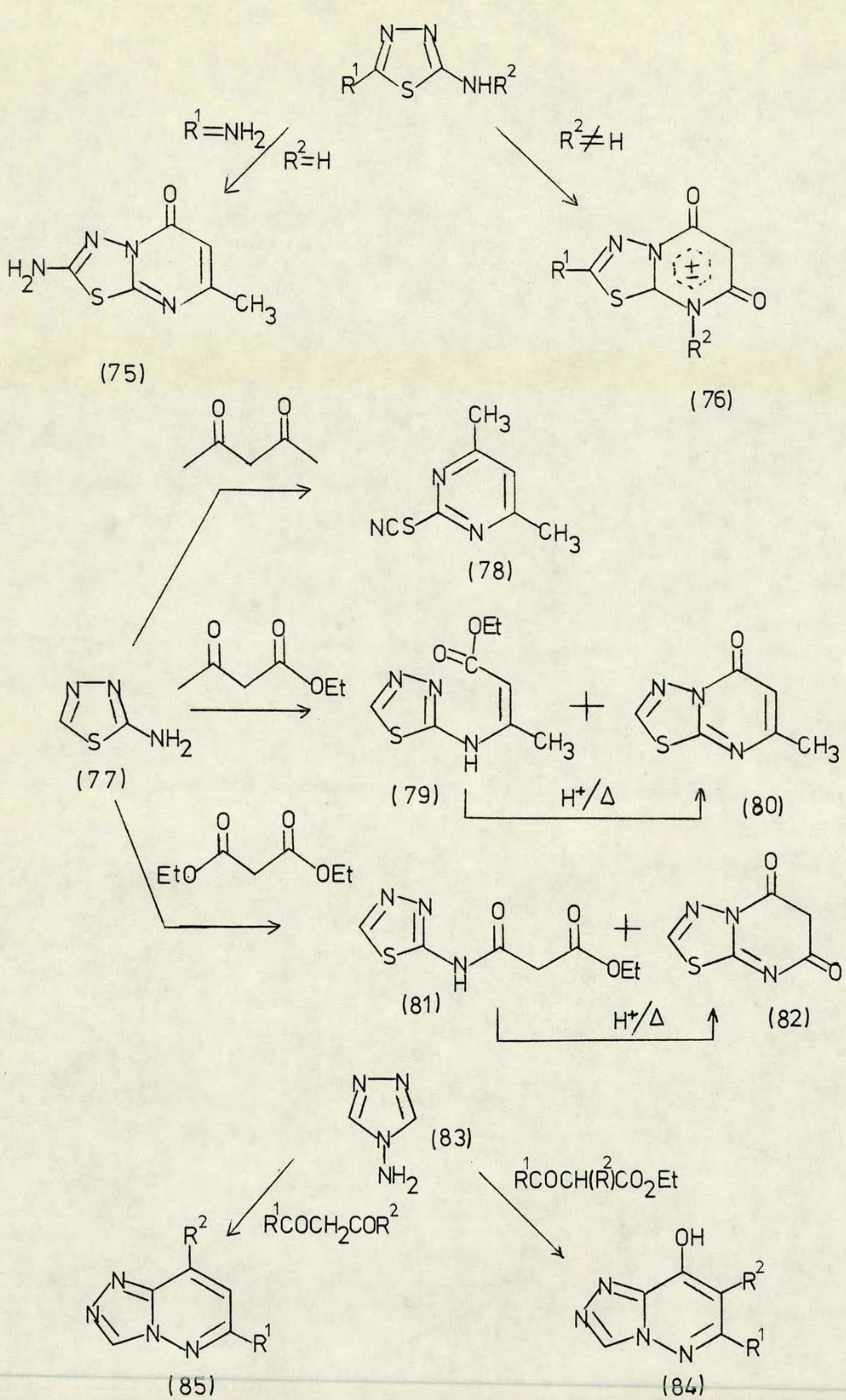
The synthesis of 17β-hydroxy-17α-methyl-5α-androst-2-eno-[3,2-d]-4'<u>H</u>-pyrido[1,2-a]pyrimidin-4'-one (62) and 17β-hydroxy-17α-methyl-5α-androst-2-eno[2,3-e]-2'<u>H</u>-pyrido[1,2-a]pyrimidin-2-one (63) has also been described.

Schmidt reaction (HN_3-BF_3) of cholest-4-en-3,6-dione has been recently reported[52] to give a mixture of three isomers (64a)-(64c). Similarly the Schmidt reaction of 7-oxaspirost-5-en-3β-yl acetate and hecogenin acetate gave azahomospirostenotetrazole (65) and azahomospirostanotetrazole (66) respectively.

The present work describes the synthesis of androstane derivatives in which the steroid nucleus is fused with one of the following ring systems which contain a bridgehead nitrogen: s-triazolo[4,3-b]-pyridazine (67), pyrazolo[1,5-a]pyrimidine (68), s-triazolo[1,5-a]-pyrimidine (69), tetrazolo[1,5-a]pyrimidine (70), pyrimido[1,2-a]-benzimidazole (71), imidazo[2,1-b]thiazole (72), thiazolo[3,2-a]benzimidazole (73) and thiazolo[3,2-b]-s-triazole (74). The preparation of some steroidal heterocycles containing 2'-thiocyanatopyrimidine ring fused to the steroid nucleus is also described.

The condensation of 1,3-dicarbonyl compounds with substituted 2-amino-1,3,4-thiadiazoles gave the expected fused bicyclic products (75) and (76). While examining reactions of this type Lauer and Zenchoff[53] discovered that in the case of the parent compound (77), two distinctively different products could be obtained depending upon the type of 1,3-dicarbonyl compound employed.

When 2,4-pentanedione and 2-amino-1,3,4-thiadiazole (77) were condensed in toluene at reflux in the presence of a catalytic amount of


R¹ = NH₂
R² = H
R² ≠ H
(75)
(76)
(78)
(77)
(79)
(80)
H⁺/Δ
EtO OEt
(81)
(82)
H⁺/Δ
(83)
R¹COCH(R²)CO₂Et
R¹COCH₂COR²
(85)
(84)

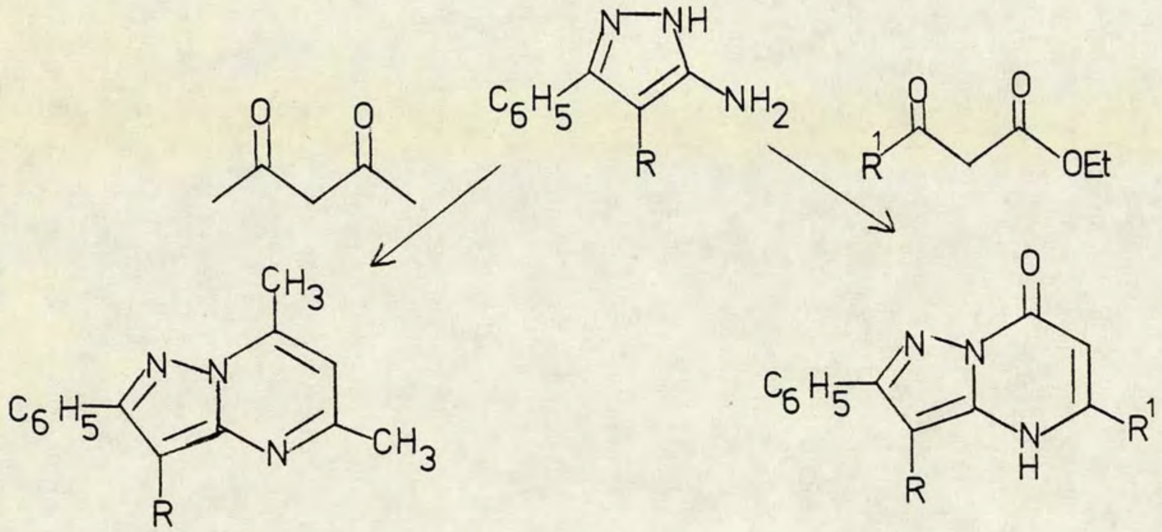
toluene-4-sulphonic acid, a single product was obtained in good yield. On the basis of spectroscopic and analytical data, the structure of this compound was ascertained to be that of 2-thiocyanato-4, 6-dimethylpyrimidine (78). With ethyl acetoacetate as the 1, 3-dicarbonyl component, the same reaction conditions produced the bicyclic product (80) plus some of its monocyclic precursor (79), which was converted into (80) by prolonged reflux in toluene. In the case of diethylmalonate as the 1, 3-dicarbonyl component, it was necessary to use 1, 2, 4-trichlorobenzene at reflux as the reaction medium and the product was found to be the monocyclic compound (81) which could be converted into the anticipated bicyclic product (82) by subsequent exposure to toluene-4-sulphonic acid in refluxing toluene. On the basis of this limited data, it appears that the pathway leading to the thiocyanatopyrimidine (78) is unique to the β-diketone type of 1, 3-dicarbonyl component, and the synthesis of steroidal pyrimidines is based upon this reaction.

β-Ketoesters and β-diketones react with 4-amino-1, 2, 4-triazole (83) leading to s-triozolo[4, 3-b]pyridazine derivatives.[54-59] In general, the structure (84) was not unambiguously ascertained and 8-hydroxy-s-triazolo-[4, 3-b]pyridazines (84) were assumed to result from the condensation of 4-amino-1, 2, 4-triazole (83) with β-ketoesters. This was proved to be correct for the condensation of aminotriazole (83) with ethyl acetoacetate, a reaction that afforded 6-methyl-8-hydroxy-s-triazolo[4, 3-b]pyridazine[55] (84, R^1=CH_3, R^2=H) contrary to an earlier report.[60]

The reaction of asymmetric β-diketones with 4-amino-1, 2, 4-triazole (83) which posed the problem of position isomerism has not been fully investigated. Bulow[61] treated 4-amino-1, 2, 4-triazole (83) with benzoylacetone

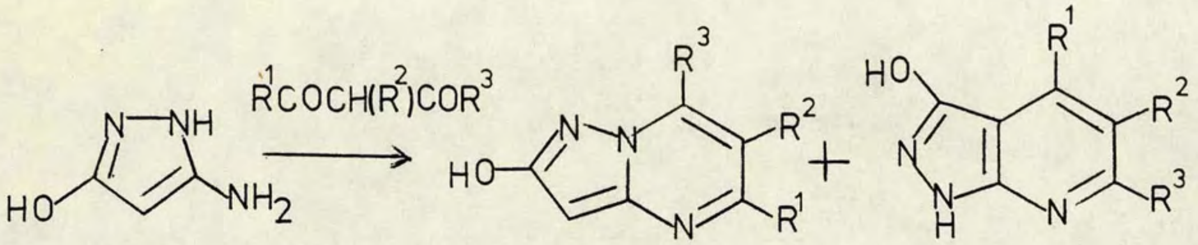
$CH_3COCH_2CH(OCH_3)_2$

(86)



(88)

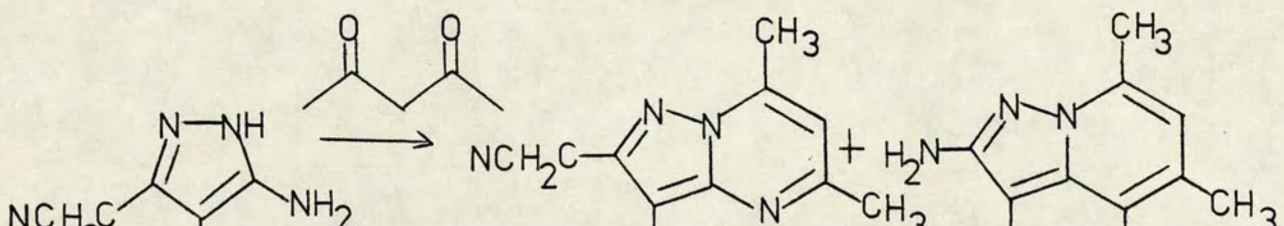
(87)



(89)

(90)

(91)



(92)

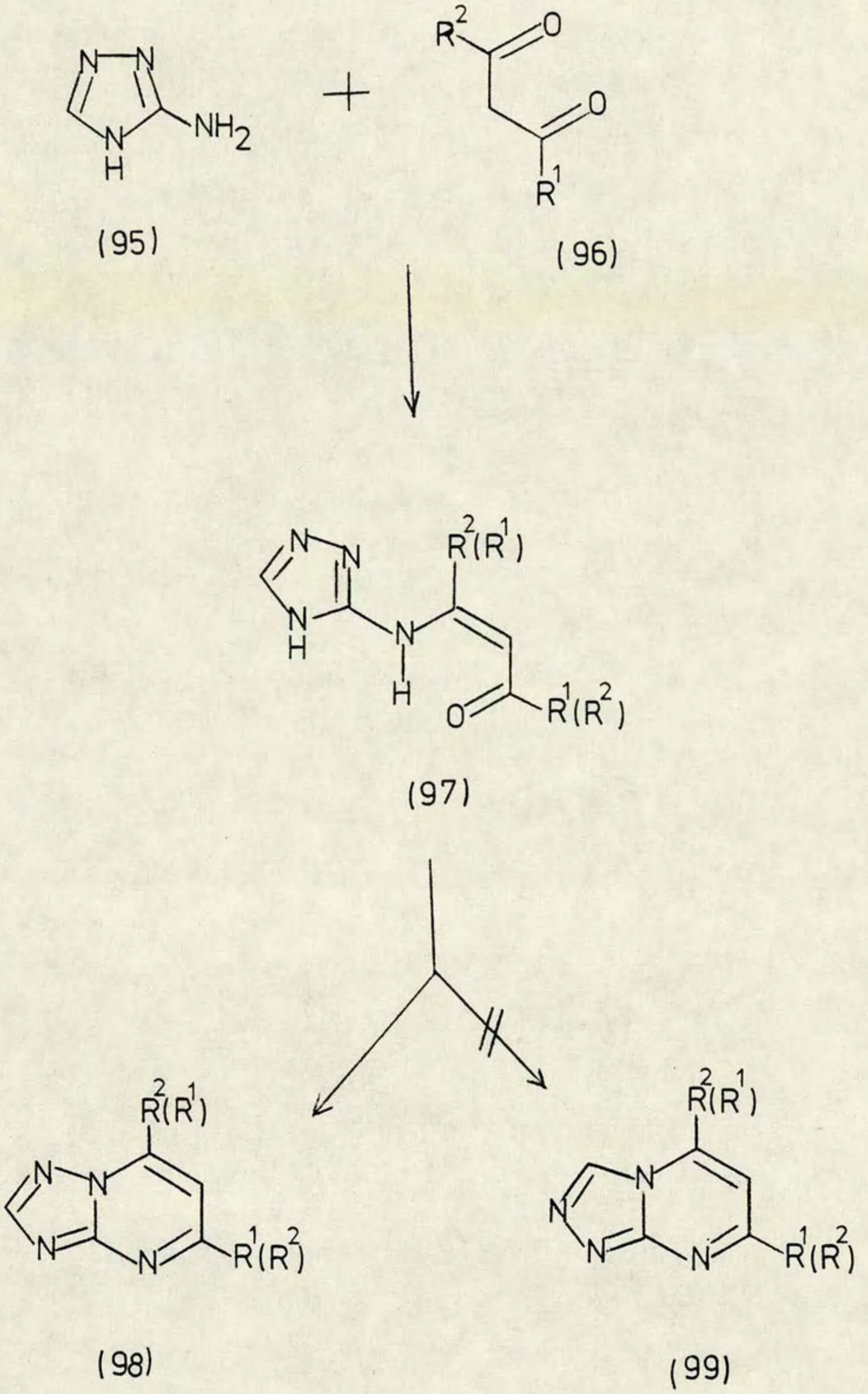
(93)

(94)

and obtained a single product which he formulated as 8-phenyl-6-methyl-s-triazolo[4, 3-b]pyridazine (85; R^1=CH_3, R^2=C_6H_5) without any proof of structure. Allen et al.[62d] as well as Libermann and Jacquier[54] obtained 6-methyl-s-triazolo[4, 3-b]pyridazine (85; R^1=CH_3, R^2=H) as the sole product from the reaction of 4-amino-1, 2, 4-triazole (83) and 4, 4-dimethoxybutan-2-one (86). However it will be seen in section 9 that the reaction of the aminotriazole (83) with 4, 4-dimethoxybutan-2-one (86) leads to a mixture of 6-methyl- and 8-methyl-s-triazolo-[4, 3-b]pyridazine (85; R^1=CH_3, R^2=H) and (85; R^1=H, R^2=CH_3) respectively.

The synthesis of s-triazolo[4, 3-b]pyridazine derivatives of steroids is based upon the reaction of 4-amino-1, 2, 4-triazole (83) with asymmetric β-diketones. The problem of position isomerism has been solved with the help of ^{1}H n. m. r. and ^{13}C n. m. r. spectroscopy.

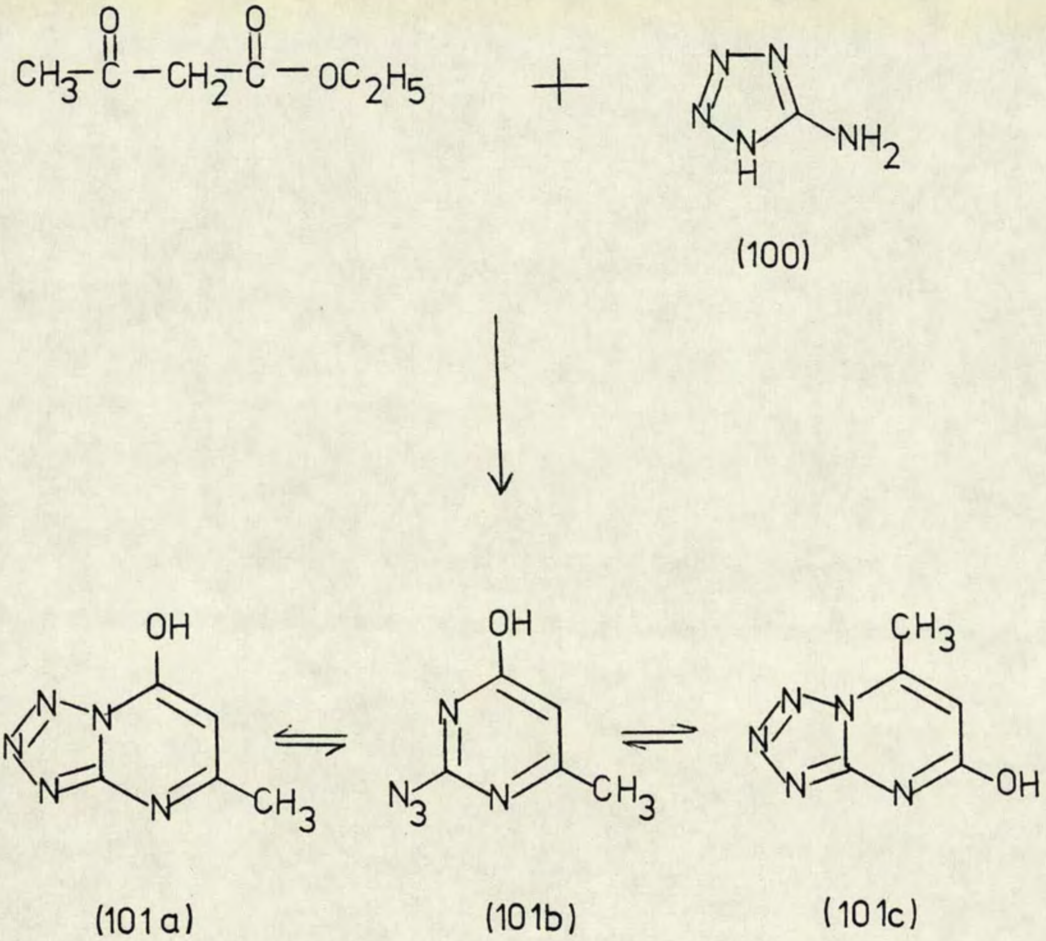
Checchi et al[63] treated 3-aminopyrazoles with acetoacetic and benzoylacetic esters and isolated products of type (87). Condensation of aminopyrazoles with acetylacetone yielded products (88). Later it was shown that the substituents on the pyrazole nucleus markedly influence the course of the condensation of 3-aminopyrazoles and β-dicarbonyl compounds. Thus the activation of position 4 of 3-amino-5-hydroxypyrazole (89) towards electrophilic attack induced the formation of the pyrazolo-[4, 3-b]pyridines (91) along with the expected pyrozolo[1, 5-a]pyrimidines (90). This observation caused a controversy over the actual structures of the products.[64] The influence of the substituents was also illustrated in this series by the condensation of 3-amino-4-cyano-5-cyanomethyl-pyrazole (92) and acetylacetone under basic conditions.[65]


(95)
(96)
(97)
(98)
(99)
NH$_2$
R^1
R^2
R^2(R^1)
R^1(R^2)

Precursors or derivatives of β-dicarbonyl compounds have also been condensed with 3-aminopyrazoles. Takamizawa and co-workers have studied the condensations of β-ketonitriles or their ketals and various 3-aminopyrazoles leading to 5-aminopyrazolo[1, 5-a]pyrimidines of pharmaceutical importance.[66, 67] Low yields of 5-hydroxy- and 7-hydroxypyrazolo[2, 3-a]pyrimidines have been reported from the reaction of 3-aminopyrazole and acetylenic esters.[68a] Diketene and cyanoacetylhydrazide yielded the same pyrazolo[4, 3-a]pyrimidine derivative as aminopyrazole (89) and ethyl acetoacetate.[69] The reaction of asymmetric β-diketones, β-ketoaldehydes or β-ketoacetals with aminopyrazoles has been almost untouched.[64]

Numerous investigations of the preparation of s-triazolo[1, 5-a]-pyrimidines from 3-amino-1, 2, 4-triazoles, often motivated by the practical importance of these compounds, have been carried out. Bulow and Hass[70] prepared the first examples of this ring system by condensing 3-amino-1, 2, 4-triazole (95) with various 1, 3-dicarbonyl compounds (96). With symmetrically constituted β-diketones such as acetylacetone (96; $R^1=R^2=CH_3$) products of either type (98; or 99; $R^1=R^2=CH_3$) might be expected. Bulow and Hass assigned structure (98) to their products but without any evidence.

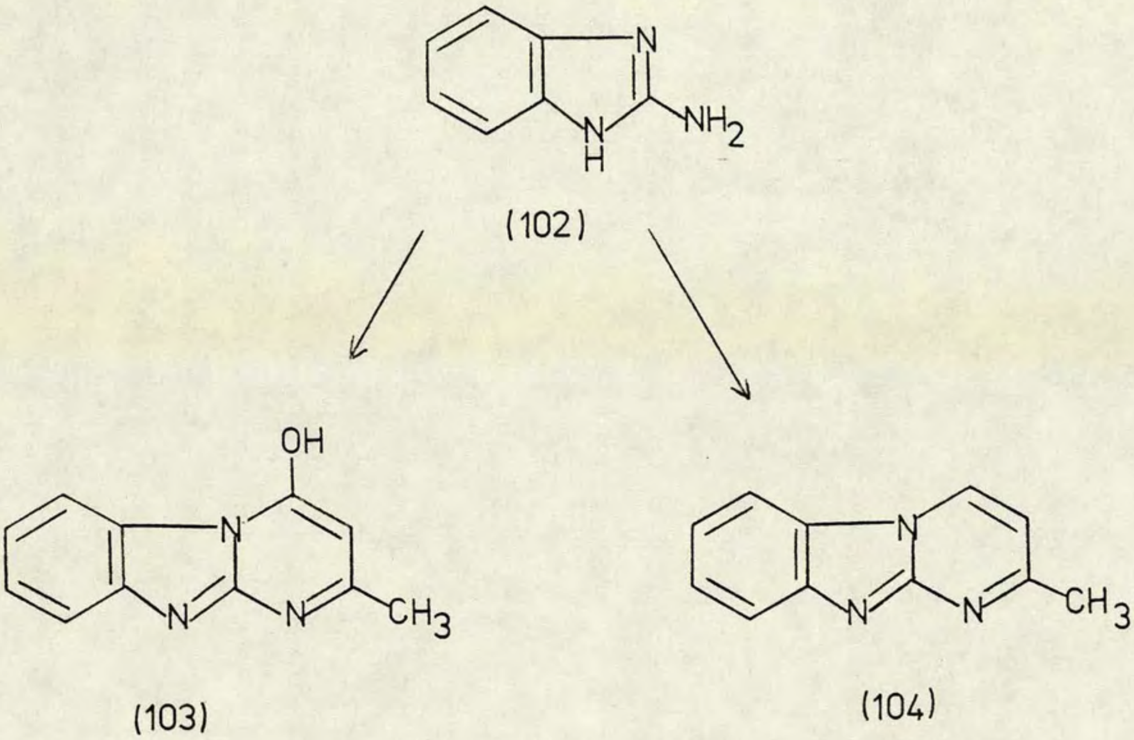
Mechanistic studies have been hampered by the many possible orientations of the condensation and the potential tautomerism of both, the β-dicarbonyl compound (96) and the aminotriazole (95). In discussing the condensation of 3-amino-1, 2, 4-triazole (95) with ethyl acetoacetate, Allen and co-workers, proposed a two step mechanism involvin first the interaction of the exocyclic amino group (assumed to be the

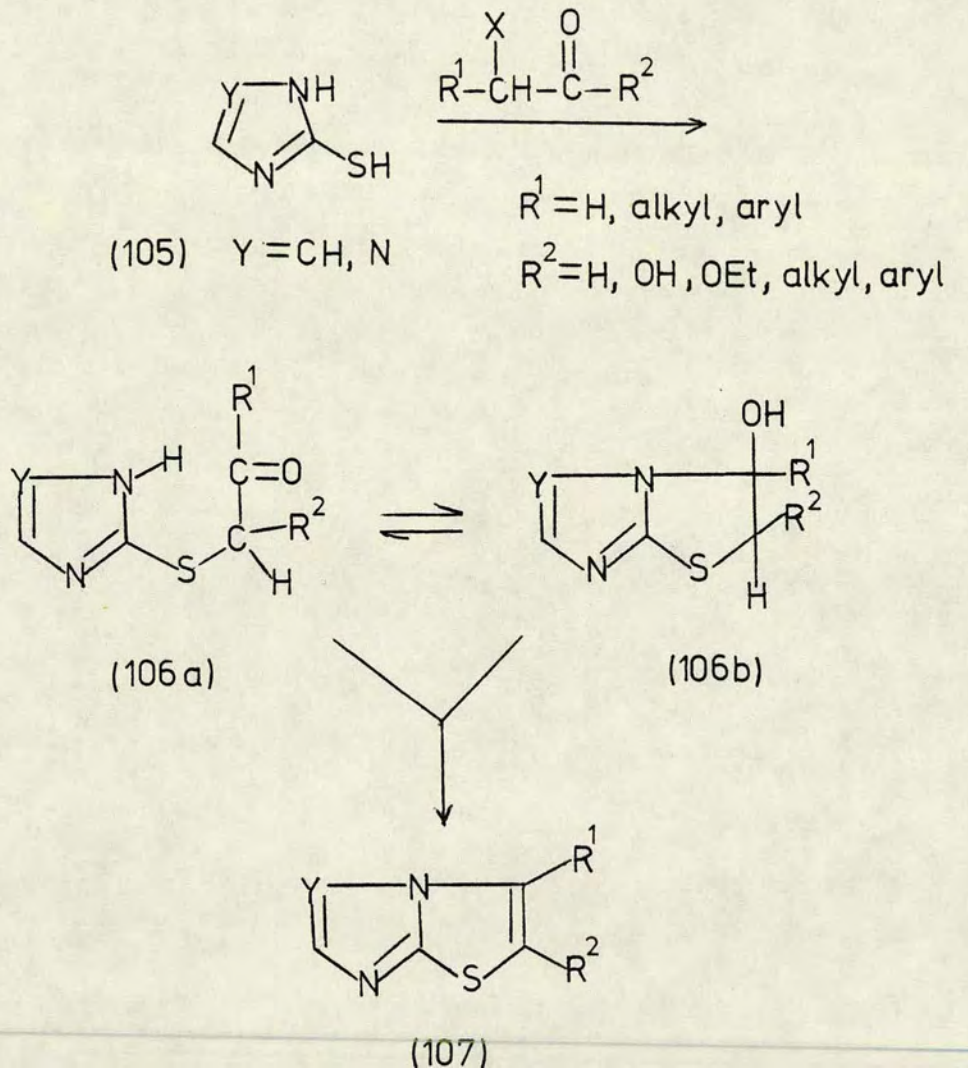

CH3–CO–CH2–CO–OC2H5
NH2
(100)
OH
CH3
N3
(101a)
(101b)
(101c)

most highly nucleophilic centre of the 3-amino-1, 2, 4-triazole nucleus) with the enol of the ketonic carbonyl. Cyclisation of the intermediate (97) then occurs with a nuclear nitrogen atom at position *a* or *a*' attacking the ester group.[62b] This proposition has been substantiated by the isolation of intermediates of type (97) in reactions involving 3-amino-pyrazoles[66, 71, 72] and 4-amino-imidazoles[73] and 3-amino-1, 2, 4-triazoles.[74, 75]

^{1}H N.m.r. spectroscopy[76-78] provided a means of determining the structures of the positional isomers and nuclear isomers and prompted new investigations into the direction of cyclisation of the reaction. Ring closure of the intermediate (97) always involves N-2 of the 3-amino-1, 2, 4-triazole nucleus. s-Triazolo[4, 3-a]pyrimidines (99) have never been obtained in this reaction,[79] however these have been prepared in good yields by the condensation of 2-hydrazinopyrimidines with one carbon-cyclising agents.[80a]

Tetrazolo[1, 5-a]pyrimidines have been prepared by the interaction of 5-aminotetrazole and β-dicarbonyl derivatives[62d, 81] or acetylenic esters,[68b] although this route has been much less utilized[62, 82, 83] than the synthesis from 2-hydrazinopyrimidines and nitrous acid. The tetrazolo-azido isomerism observed in this series caused a controversy over the actual structure of the products. For example, Allen and co-workers[62b] assigned structure (101a) to the product obtained by the condensation of 5-aminotetrazole (100) and ethyl acetoacetate in analogy with the structure of 7-hydroxy-5-methyl-s-triazolo[1, 5-a]pyrimidine (98; R^1=CH_3, R^2=OH). However Temple _et al._[84] have shown with the help of i.r. and ^{1}H n.m.r. spectroscopy that the compound (101) exists mainly


N
NH$_2$
N
H
(102)
OH
N
N
N
CH$_3$
(103)
N
N
N
CH$_3$
(104)


Y
NH
N
SH
(105)
Y = CH, N
X
O
R^1–CH–C–R^2
R^1 = H, alkyl, aryl
R^2 = H, OH, OEt, alkyl, aryl
R^1
Y
N–H
C=O
C–R^2
N
S
H
(106a)
OH
Y
N
R^1
R^2
N
S
H
(106b)
R^1
Y
N
N
S
R^2
(107)

as 7-methyltetrazolo [1, 5-a]pyrimidin-5-one (101c) in the solid state, and mainly as a mixture of (101a) and (101c) in most solvents.

The reaction of 2-aminobenzimidazole (102) with ethyl acetoacetate and 4, 4-dimethoxybutan-2-one has been reported to give 2-methylpyrimido-[1, 2-a]benzimidazol-4-ol (103) and 2-methylpyrimido[1, 2-a]benzimidazole (104) respectively. The structure of the products was elucidated by ^{1}H n. m. r. spectroscopy.[85]

The synthesis of pyrazolo[1, 5-a]pyrimidine, triazolo[1, 5-a]-pyrimidine, tetrazolo[1, 5-a]pyrimidine and benzimidazo[1, 2-a]pyrimidine derivatives of steroids is based upon the reaction of the above mentioned aminoazoles with asymmetric β-diketones and β-ketoacetals.

Imidazo[2, 1-b]thiazoles (107; Y=CH)and thiazolo[3, 2-b]-s-triazoles (107; Y=N) have been prepared by the reaction of compounds of type (105) with an α-halo carbonyl or α-halo carboxyl compound to give S-alkylated products, which have been shown to exist in the acyclic (106a) and cyclic alcohol (106b) forms,[86-88] which can then be dehydrated to give fused thiazoles (107).

Kochergin and Shchukina[89] have reported that acid or strong dehydrating agents are necessary to cyclise aldehydes and ketones of type (106; Y=N, R^1=H, alkyl, aryl) to fused triazoles (107; Y=N, R and R^1=H, alkyl, aryl). Phosphoryl chloride is the cyclising agent usually employed,[86] although sulphuric acid,[90] hydrochloric acid,[89] acetic acid[91a] and polyphosphoric[91b] acid have also been used. Acetic anhydride has also been used as a cyclodehydrating agent for ring closures of this type,[92] but it usually enters into the reaction. There are, however, some examples of the direct cyclisation of 3-mercapto-

1, 2, 4-triazoles (105, Y=N)[86, 93, 94] and 2-mercaptoimidazoles (105; Y=CH)[95, 96] upon treatment with α-halo ketones. The effect of substituents in the imidazole (or benzimidazole) rings on the direction of ring closure has also been studied.[92, 97]

The synthesis of imidazo[2, 1-b]thiazole and thiazolo[3, 2-b]triazole derivatives of steroids is based upon the direct cyclisation of thiols (105) upon treatment with α-halo ketones.

General Experimental Procedures

Melting points were determined on a Gallenkamp apparatus and are uncorrected.

Infra-red spectra were recorded in bromoform (unless otherwise stated) on a Perkin Elmer 157G spectrometer.

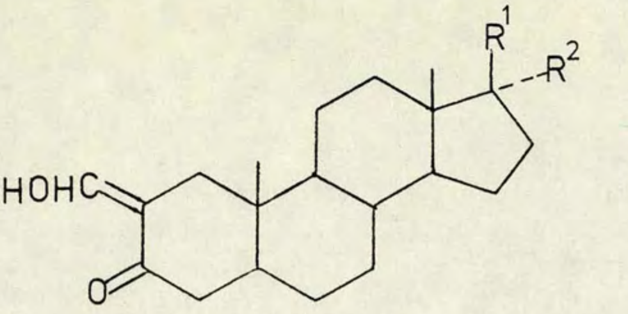
Ultra-violet spectra were recorded in methanol on a Unicam SP800 spectrometer.

^{1}H-Nuclear Magnetic Resonance Spectra were recorded in deuterated chloroform solution (unless otherwise stated) using tetramethylsilane as an internal standard on a Nuclear Magnetic Resonance Ltd EM-360 (60MHz) spectrometer or a Varian HA 100 (100MHz) spectrometer (operated by Mr. J. Millar).

^{13}C-Nuclear Magnetic Resonance Spectra were obtained in deuterated chloroform (unless otherwise stated) on a Varian CFT-20 spectrometer operating at 20-80MHz in the Fourier Transform mode at a probe temperature of 30°.

Mass spectrometry was carried out on an AEI MS 902 instrument (operated by Mr. D. Thomas).

Column chromatography was carried out using alumina, activity II.
Thin layer chromatography was performed on Merck silica gel GF 254. The eluting system was benzene-ethanol (9:1). The plates were developed with sulphuric acid in ethanol (1:19) spray and then heated. Where appropriate inspection of the plate was made with an ultraviolet lamp prior to developing.

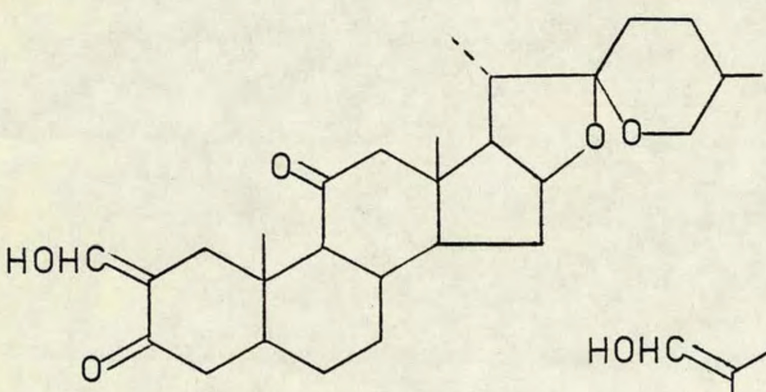


(3) $R^1 = OH, R^2 = H$

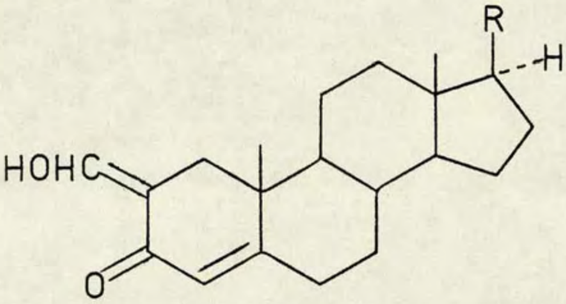
(108) $R^1 = OH, R^2 = CH_3$

(109) $R^1 = R^2 = H$

(110) $R^1 = C_8H_{17}, R^2 = H$

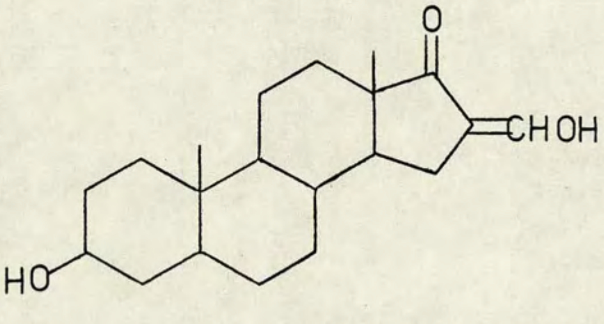


(111)



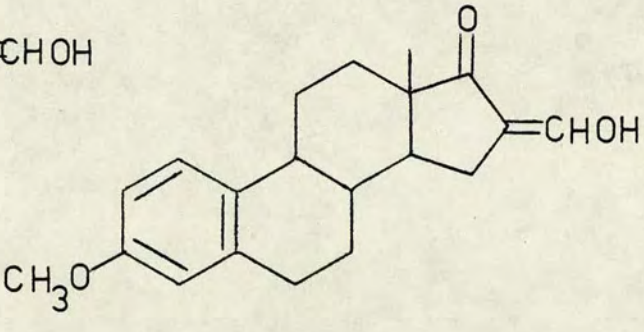
(4) R = OH

(112) $R = C_8H_{17}$



(7)

(8) Δ^5



(9)

2 Preparation of starting compounds

All the steroidal β-ketoaldehydes were prepared by the following procedure of Ringold et al.[98]

Sodium hydride (3 g) was added to a solution of 3- or 17-keto steroid (10 g) in dry benzene (300 ml) and ethyl formate (10 ml). The mixture was stirred overnight, then methanol (20 ml) was added to destroy excess sodium hydride. Water (400 ml) was added and the layers were separated. The aqueous solution was extracted with diethyl ether to remove any neutral material and then acidified with 30% hydrochloric acid (100 ml). The precipitate formed was filtered, washed with water, dried and recrystallised from a suitable solvent.

2.1 17β-Hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108) was prepared from 17β-hydroxy-17α-methyl-5α-androstan-3-one and recrystallised from ethyl acetate, m.p. 177-179° (70%) (lit.[98] m.p. 178-180).

2.2 17β-Hydroxy-2-hydroxymethylene-5α-androstan-3-one (3) was obtained from 17β-hydroxy-5α-androstan-3-one and recrystallised from ethanol, m.p. 140-142° (90%) (lit.[98] m.p. 140-146°).

2.3 2-Hydroxymethylene-5α-androstan-3-one (109) was obtained from 5α-androstan-3-one and recrystallised from acetone, m.p. 155-158° (68%) (lit.[99] m.p. 156-158°).

2.4 2-Hydroxymethylene-5α-cholestan-3-one (110) was prepared from 5α-cholestan-3-one and recrystallised from chloroform-ethanol, m.p. 178-180° (68%) (lit.[100] m.p. 180-181°).

2.5 2-Hydroxymethylene-5α-spirostan-3,11-dione (111) was obtained from 5α-spirostan-3,11-dione and recrystallised from ethanol, m.p. 165-166 (66%); i.r., γ_{max} 1700 (C=O), 1640 (CO·CH=CH·OH, $\gamma_{C=O}$), 1580 cm^{-1} (CO·CH=CH·OH, $\gamma_{C=C}$); ^1H n.m.r. (60 MHz), δ0.72, 0.95, 1.00 (methyl groups) and 8.60 (s, 1H, 2=CHO) (Found: C, 73.20; H, 8.91. $C_{28}H_{40}O_5$ requires C, 73.68; H, 8.77%).

2.6 17β-Hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4) was prepared from 17β-hydroxyandrost-4-en-3-one and recrystallised from ether, m.p. 163-165° (80%) (lit.[101] m.p. 165-165.5).

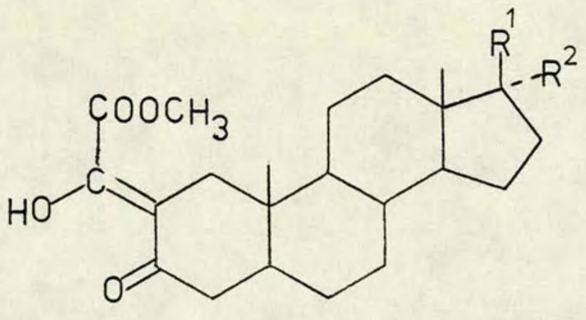
2.7 2-Hydroxymethylenecholest-4-en-3-one (112) was obtained from cholest-4-en-3-one and recrystallised from pentane, m.p. 108-110° (72%) (lit.[101] m.p. 109.5-111.5°)

2.8 3β-Hydroxy-16-hydroxymethylene-5α-androstan-17-one (7) was obtained from 3β-hydroxy-5α-androstan-17-one and recrystallised from acetone, m.p. 227-229° (77%) (lit.[102] m.p. 228-231°).

2.9 3β-Hydroxy-16-hydroxymethyleneandrost-5-en-17-one (8) was obtained from 3β-hydroxyandrost-5-en-17-one and recrystallised from ethanol, m.p. 237-239° (84%) (lit.[102] m.p. 238-239°).

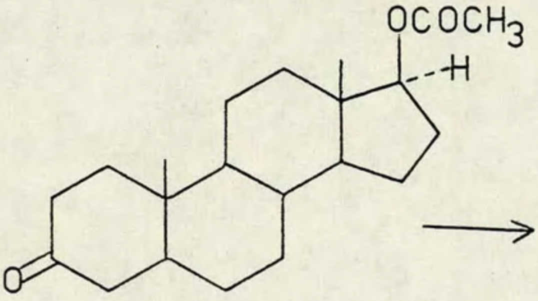
2.10 16-Hydroxymethylene-3-methoxyoestra-1,3,5(10)-trien-17-one (9) was obtained from 3-methoxyoestra-1,3,5(10)-trien-17-one and recrystallised from acetone, m.p. 226-229° (64%) (lit.[9] m.p. 228-230°).

17β-Hydroxy-2-methoxycarbonyl(hydroxy)methylene-17α-methyl-5α-androstan-3-one (113) and 2-methoxycarbonyl(hydroxy)-

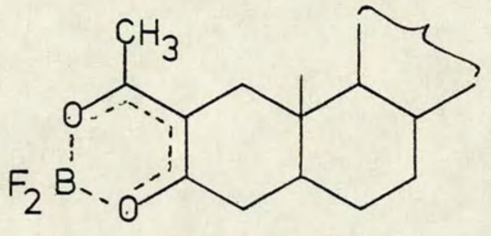


(113) $R^1 = OH$, $R^2 = CH_3$

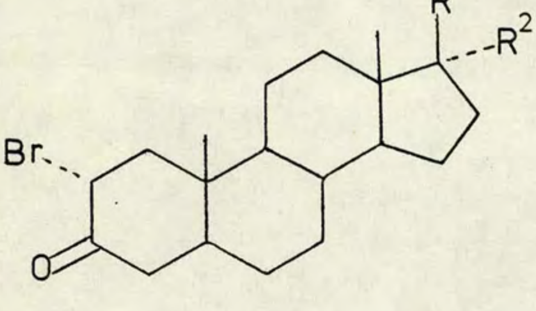
(114) $R^1 = C_8H_{17}$, $R^2 = H$



(115)

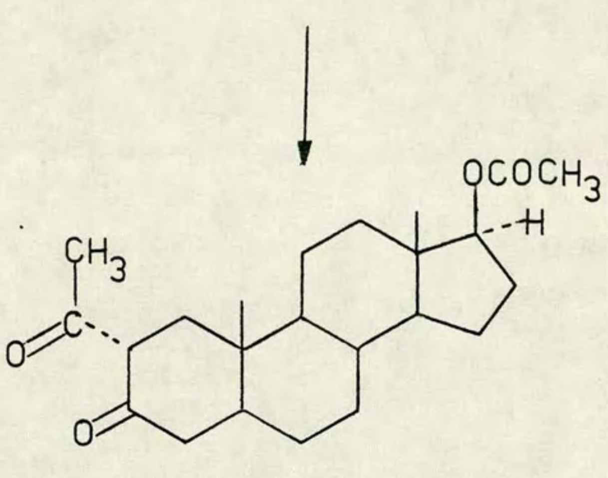


(116)

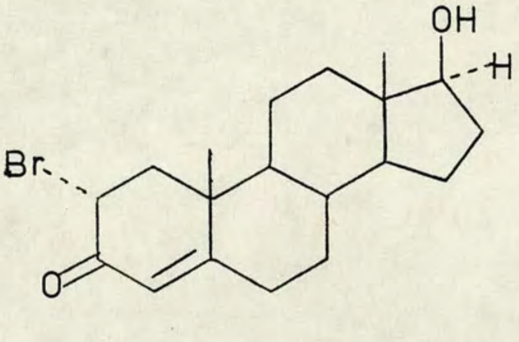


(117) $R^1 = OH$, $R^2 = CH_3$

(118) $R^1 = C_8H_{17}$, $R^2 = H$



(61)



(119)

methylene-5α-cholestan-3-one (114) were prepared from 17β-hydroxy-17α-methyl-5α-androstan-3-one and 5α-cholestan-3-one respectively by the procedure previously described except that ethyl formate was replaced by dimethyl oxalate.

2.11 17β-Hydroxy-2-methoxycarbonyl(hydroxy)methylene-17α-methyl-5α-androstan-3-one (113) could not be recrystallised. Yield of the crude product was 72%. I.r., γ_{max} 1740 (ester C=O), 1620 and 1575 (conj. C=O, chelate structure); ^{1}H n.m.r. (60 MHz), δ 0.80 (s, 3H, 18-CH_3), 0.85 (s, 3H, 19-CH_3), 1.22 (s, 3H, 17-CH_3), 3.85 (s, 3H, 2-C(OH)COOC$\underline{H}_3$) and 15.0 (s, 1H, 2-C(O$\underline{H}$)COOCH_3).

2.12 2-Methoxycarbonyl(hydroxy)methylene-5α-cholestan-3-one (114) was recrystallised from methanol, mp. 103-105° (80%) (lit.[103] m.p. 106-107).

2.13 17β-Acetoxy-5α-androstan-3-one (115)

A solution of 17β-hydroxy-5α-androstan-3-one (3.4 g, 1.2×10^{-2} mole) and acetic anhydride (1 ml) in pyridine (15 ml) was refluxed 1 h. On cooling, the mixture was poured into diethyl ether, washed successively with water, 5% hydrochloric acid, 5% sodium hydroxide and finally with water again. The ether solution was dried over anhydrous magnesium sulphate and evaporated to dryness to give 17β-acetoxy-5α-androstan-3-one (115) (3.8 g, 92%), m.p. 154-156 (lit.[104] m.p. 158-160).

2.14 17β-Acetoxy-2α-acetyl-5α-androstan-3-one (61) was prepared by a two step synthesis.

(a) Borofluoride complex (116). A solution of glacial acetic acid

(5.3 ml) in ethylene chloride (10 ml) was cooled on an ice bath. Boron trifluoride gas, washed through concentrated sulphuric acid, was poured into the stirred solution until saturation was reached. To the resulting white paste kept under nitrogen with continued cooling and stirring, a solution of 17β-acetoxy-5α-androstan-3-one (115) (3.8 g, 1.1×10^{-2} mole) and acetic anhydride (4 ml) in ethylene chloride (8 ml) was added. The addition required 15 min during which time the mixture became homogeneous. After a further 30 min in the ice bath, the solution was allowed to stand at room temperature for 3 h. The solution was then washed with water, saturated sodium bicarbonate solution and water again. The organic phase was dried over anhydrous magnesium sulphate and evaporated to dryness to give the borofluoride complex (116) (4.1 g, 91%), m.p. 254-264° (lit.[105] m.p. 265-277°).

(b) 17β-Acetoxy-2α-acetyl-5α-androstan-3-one (61). A mixture of borofluoride complex (4.1 g, 1.0×10^{-2} mole) in methanol (170 ml) containing sodium acetate (1.58 g), glacial acetic acid (1.09 ml) was refluxed for 2.5 h. On cooling and refrigeration crystals formed. These were filtered to give 17β-acetoxy-2α-acetyl-5α-androstan-3-one (61) (3.3 g, 88%), m.p. 181-182° (lit.[105] m.p. 180-181°).

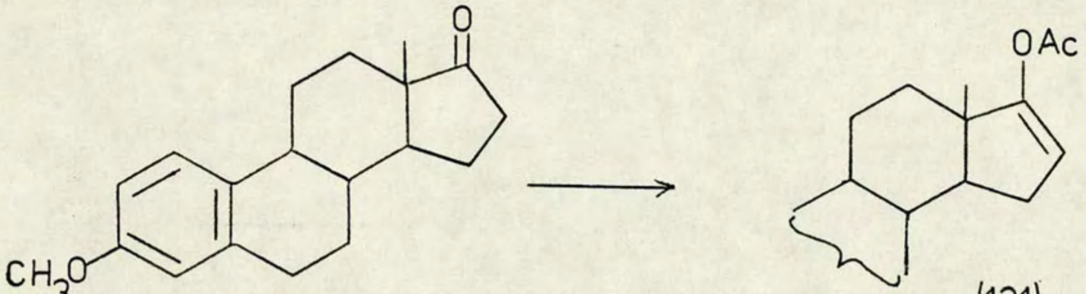
2.15 2α-Bromo-17β-hydroxy-17α-methyl-5α-androstan-3-one (117).
To a solution of 17β-hydroxy-17α-methyl-5α-androstan-3-one (3 g, 0.98×10^{-2} mole) in glacial acetic acid (25 ml) containing 5 drops of 48% hydrogen bromide in glacial acetic acid was added dropwise over a period of 30 min a solution of bromine (1.6 g, 0.98×10^{-2} mole) anhydrous sodium acetate (1.41 g) in glacial acetic acid (17 ml). The reaction mixture was diluted with water to precipitate the bromosteroid. The product was filtered, washed with water and dried. Recrystallisation

from ethanol gave white crystals (2 g, 53%), m. p. 194-196° (lit.[106] m. p. 203-206); i. r., γ_{max} 3600 (OH), 1720 cm^{-1} (C=O); ^{1}H n. m. r. (60 MHz), δ 0.92 (s, 3H, 18-CH$_3$), 1.15 (s, 3H, 19-CH$_3$), 1.22 (s, 3H, 17-CH$_3$) and 4.76 (dd, 1H, 2-H).

2.16 2α-Bromo-5α-cholestan-3-one (118). A solution of bromine (4.2 g, 2.6 x 10^{-2} mole) and 48% hydrobromic acid (0.3 ml) in glacial acetic acid (20 ml) was added over 10 min to a vigorously stirred solution of 5α-cholestan-3-one (10 g, 2.6 x 10^{-2} mole) in acetic acid (300 ml). After stirring for 2 min the resulting suspension was cooled to 10°, the bromoketone was filtered off and washed free of bromine with acetic acid. Recrystallisation from ethanol-acetone gave 2α-bromo-5α-cholestan-3-one (118) (72 g, 60%), m. p. 167-169° (lit.[107] m. p. 168-169°).

2.17 2α-Bromo-17β-hydroxyandrost-4-en-3-one (119) was prepared by treating 17β-hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4) (4 g, 1.27 x 10^{-2} mole), methanol (55 ml) and anhydrous potassium acetate (1.6 g) with bromine (2 g, 1.27 x 10^{-2} mole) dissolved in carbontetrachloride (8 ml). The reaction mixture was stirred for 50 min below 15°, refluxed 10 min with 2N methanol-sodium methoxide (8 ml), evaporated to dryness and the residue was recrystallised from methanol to give 2α-bromo-17β-hydroxyandrost-4-en-3-one (119) as light yellow crystals (2 g, 43%), m. p. 125-127° (lit.[108] m. p. 127-128°).

2.18 3-Methoxyoestra-1, 3, 5(10)-trien-17-one (120) was prepared by adding slowly, with vigorous stirring dimethylsulphate (30 ml) to a solution of d-oestrone (5 g, 1.58 x 10^{-2} mole). The temperature was



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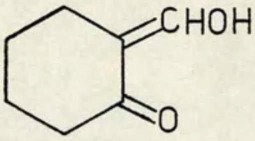

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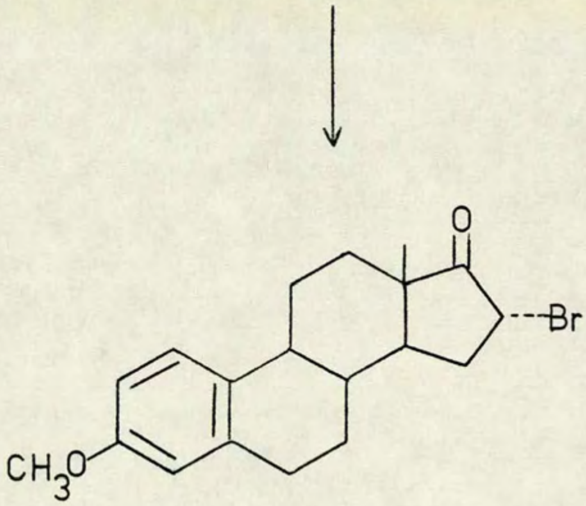

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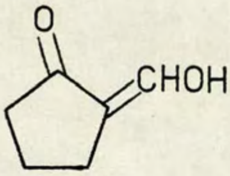

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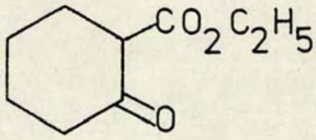

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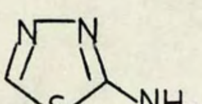


(77)

(83)

maintained at 25-30° and the solution was kept alkaline (to litmus) by frequent addition of 17% potassium hydroxide (ca. 100 ml altogether). After addition was complete (2. 5 h), ammonium hydroxide (20 ml) was added and stirring continued for 30 min. The finely divided precipitate which separated was filtered, washed with water and dried. Recrystallisation from ethanol gave 3-methoxyoestra-1, 3, 5(10)-trien-17-one (120) (4. 95 g, 94%), m. p. 167-169° (lit.[109] m. p. 168-169°).

2. 19 16-Acetoxy-3-methoxyoestra-1, 3, 5(10), 16-tetraene (121) was prepared as follows. A solution of 3-methoxyoestra-1, 3, 5(10)-trien-17-one (120) (5. 96 g, 2.1×10^{-2} mole) in isopropenyl acetate (90 ml, 8.1×10^{-2} mole) containing toluene-4-sulphonic acid (1 g) was distilled slowly (high reflux ratio) through a vigreux column to half of its volume over a period of 14 h. The solution was cooled, diluted with ether, washed with saturated sodium bicarbonate solution, water and dried over anhydrous magnesium sulphate. The residue obtained on evaporation of the solvent was adsorbed on a column of Florisil (90 g). Elution with petroleum ether (65-68°) gave crude enol acetate (5. 80 g) which on recrystallisation from petroleum ether (65-68°) afforded colorless plates (5. 51 g, 84%), m. p. 112-114° (lit.[110] m. p. 114. 5-115. 5°).

2. 20 16α-Bromo-3-methoxyoestra-1, 3, 5(10)-trien-17-one (122). A suspension of anhydrous potassium carbonate (0. 5 g) in a solution of the afore mentioned enol acetate (0. 77 g, 2.45×10^{-3} mole) in carbon tetrachloride (35 ml) was stirred at 0°, while a solution of bromine (0. 4 g, 2.45×10^{-3} mole) in carbon tetrachloride (10 ml) was added over 5 min. The colourless mixture was poured into water containing a little sodium

bisulphite, the aqueous layer was extracted with chloroform. The combined organic layers were dried over anhydrous magnesium sulphate. The residue obtained on evaporation of the solvent under reduced pressure was recrystallised from methanol to give white crystals of 16α-bromo-3-methoxyoestra-1, 3, 5(10)-trien-17-one (122) (0.790 g, 88.8%), m.p. 174-176° (lit.[110] m.p. 176-177).

2.21 <u>2-Hydroxymethylenecyclohexanone (123)</u>. A mixture of sodium hydride (12 g, 0.5 mole), dry ether (1000 ml), and ethyl alcohol (5 ml) was placed in a 3 l three necked flask equipped with a stirrer, dropping funnel and a vent tube. This reaction vessel was cooled by means of a cold water bath, and a solution of redistilled cyclohexanone (49 g, 0.5 mole) and ethyl formate (55 g, 0.75 mole) was added dropwise during half an hour. Stirring was continued for 6 h and the solution was allowed to stand overnight. After the addition of ethyl alcohol (15 ml), the mixture was stirred for 1 h. Water (100 ml) was added to the flask with stirring. The mixture was taken in a 3 l separating funnel, the upper ether layer separated and the aqueous layer collected. The ether layer was washed with water (25 ml) and the combined aqueous extracts were washed with ether (50 ml). The aqueous layer was acidified with 6N hydrochloric acid (80 ml) and the mixture extracted twice with ether (150 ml). The ether solution was washed with saturated sodium chloride solution (25 ml) and then dried over anhydrous magnesium sulphate. The drying agent was removed by filtration and the ether evaporated. The residue was distilled under reduced pressure. After a small fore-run 2-hydroxymethylenecyclohexanone (123) (40 g, 63%) was obtained, b.p. 85-90°/

15 mm (lit.[111a] b. p. 70-72°/5 mm); i. r., 1718 ($\gamma_{C=O}$, ketone and aldehyde), 1639 ($\gamma_{C=O-C=C}$) and 1607-1587 cm^{-1} ($\gamma_{C=O\quad H}$); ^{1}H n. m. r. (60MHz), δ 8. 61 (s, 2-CHO) and 14. 24 (s, enolic hydrogen).

2. 22 2-Hydroxymethylenecyclopentanone (124) was obtained from cyclopentanone (42 g, 0. 5 mole) by the procedure described for 2-hydroxymethylenecyclohexanone (123). The oil obtained was distilled under reduced pressure (12-16 mm). The product sublimed and was obtained as light yellow solid (124), m. p. 73-76° (18 g, 32%) (lit.[112] m. p. 76-77°) which was used as such without further purification. This substance gradually decomposes on standing at room temperature. I. r. 1748 ($\gamma_{C=O}$, ketone), 1724 ($\gamma_{C=O}$, aldehyde), 1675 ($\gamma_{C=C-C=O}$) and 1607 cm^{-1} ($\gamma_{C=O\quad H}$); ^{1}H n. m. r. (60MHz), δ 7. 34 (s, 2-CHO) and 11. 30 (s, enolic hydrogen).

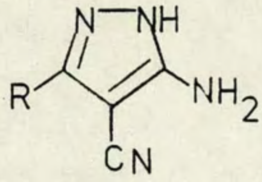
2. 23 2-Carbethoxycyclohexanone (125). A solution of sodium ethoxide was prepared from absolute ethanol (400 ml) and sodium (23 g, 1 mole). This solution was cooled to 0°, when a solution of cyclohexanone (98 g, 1 mole) in diethyl oxalate (146 g, 1 mole) at 0° was added over 30 min. When all the cyclohexanone and diethyl oxalate solution had been added, the mixture was stirred at 0° for a further 1 h, and then stirred at room temperature overnight. Concentrated sulphuric acid (28 ml) and ice (220 g) were added during which time the temperature of the mixture was not allowed to exceed 10°. The reaction mixture was then diluted to 2 l with ice and water, and the product separated. The aqueous layer was extracted with ether (4 x 250 ml) and the ether solutions were combined and dried. After evaporation of the ether under

reduced pressure, the crude product was distilled to afford ethyl-2-oxocyclohexylglyoxalate (130.6 g, 66%), b.p. 105-165°/12 mm.

Distillation of the above compound in the presence of finely ground glass (0.5 g) and a trace of iron powder, at 40 mm at a bath temperature of 165-185° gave 2-carbethoxycyclohexanone (125) (95 g, 56%), b.p. 125-140°/40 mm (lit.[113] b.p. 70-72°/0.4 mm).

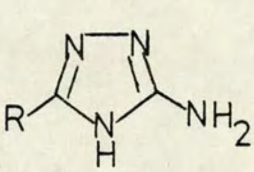
2.24 2-Amino-1,3,4-thiadiazole (77) was prepared by the method of Lauer and Zenchoff.[53] A solution of thiosemicarbazide (25 g, 0.27 mole) in 98% formic acid (180 ml) was refluxed for 15 h, evaporated to dryness in vacuo, , then refluxed for 2 h in 10% hydrochloric acid (250 ml). The resulting solution was then evaporated *in vacuo* to dryness again, the residue was dissolved in hot water (175 ml), made basic with 50% sodium hydroxide (40 ml), concentrated (to 50 ml) and filtered. The solid was washed with water, dissolved in hot methanol (400 ml), treated with activated charcoal, filtered and concentrated (to 75 ml). The product (16 g) was collected and dried, concentration of the mother liquors gave a second crop (1.5 g), for a total of 65% yield, m.p. 195-197° (lit.[53] m.p. 196-197°).

2.25 4-Amino-1,2,4-triazole (83). In a round bottom flask, equipped with an efficient water condenser, was placed ethyl formate (37 g, 0.5 mole) and ethanol (35 ml). Hydrazine hydrate (30 g, 0.5 mole) was added cautiously to this solution with shaking over a period of 10 min. After the reaction subsided, the solution was refluxed on a steam bath for 18 h. The bulk of the water and alcohol was then removed by evaporation under reduced pressure (until the volume in the flask was



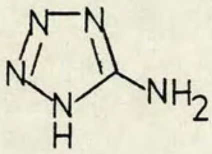
(92) R = CH_2CN

(126) R = H



(95) R = H

(127) R = CH_3



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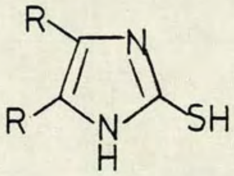
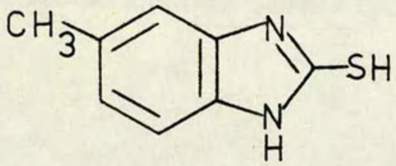


(128) R = H

(129) R = C_6H_5



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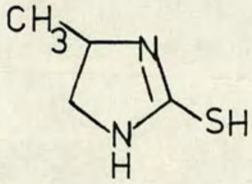

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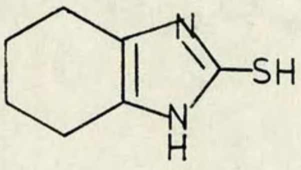

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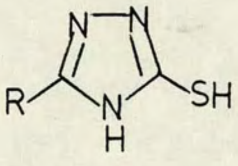


(133) R = H

(134) R = CH_3

about 40 ml). The resulting syrup, crude form hydrazide was heated under atmospheric pressure for 3 h, during which time the temperature of the bath was raised to 150-200°. After cooling to about 100°, the oil was taken up in 95% ethanol (15 ml) and activated charcoal (1.5 g) was added. The filtered solution was then diluted with ether (20 ml). After cooling the solution in ice, white crystals of 4-amino-1, 2, 4-triazole (83) (55 g, 65%), m.p. 76-78° (lit.[114a] m.p. 77-78°) were obtained.

2.26 <u>3-Amino-4-cyanopyrazole (126)</u> was prepared by carefully adding ethoxymethylenemalanonitrile (15 g, 0.12 mole) in small portions to hydrazine hydrate (8.5 g, 0.17 mole). After approximately one-half of the ethoxymethylenemalanonitrile had been added, the reaction mixture was cooled slightly in cold water and the remaining ethoxymethylenemalanonitrile added at such a rate that the contents of the flask boiled gently upon the addition of each 3 to 5 g portion. After all the ethoxymethylenemalanonitrile had been added, the reaction flask was heated for 1 h on the steam bath. To the solidified mass was added water (10 ml) and the solution was set aside in the refrigerator. The mushy solution was then filtered and the solid washed with 50 ml of cold water and sucked as dry as possible. The crude product was dried in a vacuo desiccator over calcium chloride. The crude yield of tan coloured material was 96% (9.7 g), m.p. 169-70°. Recrystallisation from water raised the m.p. to 172-174° (lit.[115] mp. 174-175°).

2.27 <u>3-Amino-4-cyano-5-cyanomethylpyrazole (92)</u>. To a solution of malanonitrile (16.5 g, 0.25 mole) in ethanol (45 ml) was added hydrazine hydrate (2 g) and the mixture was carefully heated to boiling. The remaining hydrazine hydrate (5 g, total 0.12 mole) was then added at such a rate that the reaction mixture continued to boil without external heating. Ammonia was continually evolved during this time. After all the hydrazine had been added, the reaction mixture was boiled for an additional 5 min and then quickly cooled to 0°. The light reddish tan crystals which had separated were collected by filtration and immediately recrystallised from glacial acetic acid with the addition of charcoal. A further recrystallisation from water yielded colourless long needles (7 g, 46%), m.p. 196-198° (lit.[116] m.p. 197-198°).

2.28 <u>3-Amino-1, 2, 4-triazole (95)</u> was prepared by the method described by Allen and Bell.[114b] To a solution of aminoguanidine bicarbonate (17 g, 0.12 mole) in a round bottom flask was added carefully cold dilute sulphuric acid (0.06 mole), made from concentrated sulphuric acid (sp. gr. 1.84, 6 g) and water (12 ml). After gas evolution subsided, the solution was heated for 1 h on a steam bath and then evaporated to dryness under reduced pressure.

To the white residue was added 98% formic acid (25 g) and 2, 3-drops of concentrated nitric acid. The mixture was heated for 24 h on a steam bath, the resulting syrup was dissolved in water (25 ml) and with temperature at 50°, was carefully treated with anhydrous sodium carbonate (6 g). The solution was then placed in an evaporating dish and evaporated to dryness on a steam bath. The residue was extracted by boiling with ethanol (2 x 50 ml) and the alcohol solution was filtered. The alcohol was removed by evaporation and the residue triturated with a mixture (25 ml) of equal parts of dry ethanol and dry ethyl ether, and collected on a filter. The yield of crude 3-amino-1, 2, 4-triazole (95) was 79% (8 g), and the m. p. was variable. The crude product was purified by dissolving it in boiling absolute alcohol (35 ml), treating it with activated charcoal (1 g) and filtering. To the filtrate was added ether (12 ml) and the solution was placed in a refrigerator for 48 h. The aminotriazole (95) was obtained as white crystals (5 g, 48%), m. p. 148-150° (lit.^{114b} m. p. 153°).

2. 29 3-Amino-5-methyl-1, 2, 4-triazole (127) was prepared by the above procedure except that formic acid was replaced by acetic acid and the crude 3-amino-5-methyl-1, 2, 4-triazole (127) was purified by extraction with ethyl acetate in a Soxhlet apparatus. 3-Amino-5-methyl-1, 2, 4-triazole (127), m. p. 145-147° (lit.^{117} m. p. 146-148°) was obtained in a quantitative yield.

2. 30 5-Aminotetrazole (100). A suspension of dicyandiamide (20. 5 g, 0. 25 mole) and sodium azide (29 g, 0. 45 mole) in water (50 ml) was warmed to 65° on a water bath under a reflux condenser and concentrated hydrochloric acid (37. 5 ml, 0. 45 mole) was added in small portions with frequent manual agitation. After complete addition of the acid, the mixture was kept at 65-70° on the water bath for 6 h during which time the product began to crystallize. The semi solid mass was allowed to stand overnight and was filtered off, and was washed with ice water. The crude 5-aminotetrazole (100) was recrystallized from boiling water as a monohydrate, m. p. 204-206° (33 g, 73%) (lit.^{118} m. p. 206. 5-207. 5).

2. 31 2-Mercaptoimidazole (128). An aqueous solution of aminoacetaldehyde

dimethyl acetal (10.5 g, 0.1 mole) and potassium thiocyanate (9.7, 0.1 mole) in water (50 ml) was boiled down to a syrup which was then heated in an oil bath at 140°. After hydrogen sulphide was given off, the solid formed was dissolved in ethanol, treated with charcoal and the solution was concentrated. 2-Mercaptoimidazole (128) was obtained as white crystals (5.3 g, 53%), m.p. 221-223° (lit.[119] m.p. 222°).

2.32 <u>4,5-Diphenyl-2-mercaptoimidazole (129)</u> was prepared by heating a solution of benzoin (5 g, 2.8×10^{-3} mole) and thiourea (1.8 g, 2.8×10^{-3} mole) in alcohol (15 ml) in a sealed tube, in an oil bath at a temperature of 120°. After 3 h, the solution was cooled down to room temperature and fine white crystals (4.5 g, 75%), m.p. >300 (lit.[120] m.p. >310°) were obtained.

2.33 <u>2-Mercapto-5-methylbenzimidazole (130)</u> was prepared by heating a mixture of 3,4-diaminotoluene (20 g, 0.16 mole) and thiourea (12 g, 0.16 mole) together in a round bottom flask on an oil bath at a temperature of 170-180°. The solids formed a melt which solidified to a hard cake after some time at this temperature. This solid cake was dissolved in warm sodium hydroxide and the solution was filtered. The filtrate was acidified with concentrated hydrochloric acid. The solid formed was filtered, dried and recrystallised from ethanol after charcoal treatment to give fine plates (13.7 g, 55%), m.p. 284-286° (lit.[121] m.p. 285°).

2.34 <u>2-Mercapto-4-methylimidazoline (131)</u> was prepared by adding dropwise 1,2-diaminopropane (37 g, 0.53 mole) to carbon disulphide (50 g, 0.65 mole) placed in a round bottom flask fitted with a reflux condenser

The reaction was found to be vigorous. After final addition of the amine, the mixture was carefully refluxed for 30 min and then cooled. The excess of carbon disulphide was poured off and the viscous reaction product was dissolved by warming in water (100 ml). Ring closure of the dithiocarbamate intermediate was easily accomplished by adding concentrated hydrochloric acid (15 ml) and finally refluxing the solution at 100° for 1 h. On cooling, a crystalline solid separated out which was filtered and was recrystallised from benzene to give 2-mercapto-4-methylimidazoline (131) (28 g, 34%), m. p. 96-98° (lit.[122] m. p. 100°).

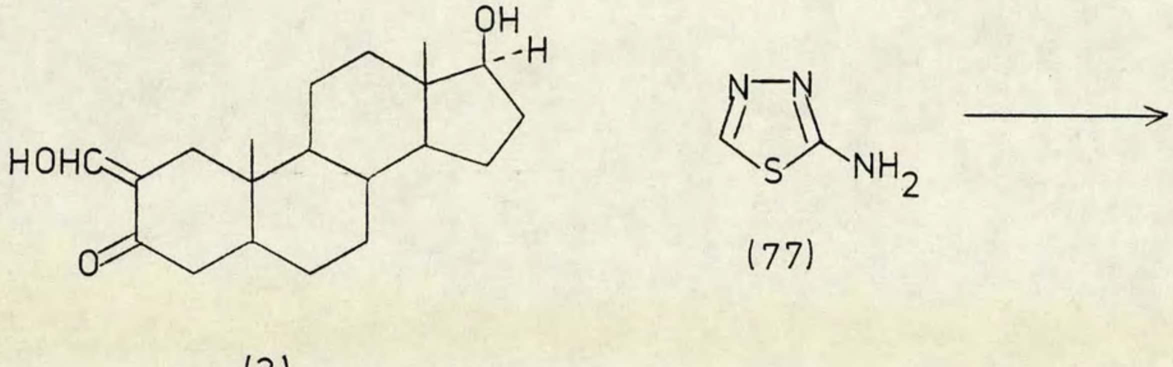
2.35 <u>2-Mercapto-4, 5, 6, 7-tetrahydrobenzimidazole (132).</u> A mixture of 2-aminocyclohexanone hydrochloride[123] (20 g, 0.13 mole) and potassium isothiocyanate (10.5 g, 0.13 mole) in water (100 ml) was heated on a steam bath for 7 h. A fine yellow powder began to fall out of solution within the first hour of heating. After chilling the mixture overnight, the precipitate was collected at the pump, washed well with water and dried. Recrystallisation from ethyl alcohol gave 2-mercapto-4, 5, 6, 7-tetrahydrobenzimidazole (132) (13.3 g, 65%), m. p. 279-281° (lit.[95] m. p. 282-283°).

2.36 <u>3-Mercapto-1, 2, 4-triazole (133)</u> was prepared by a two step synthesis.

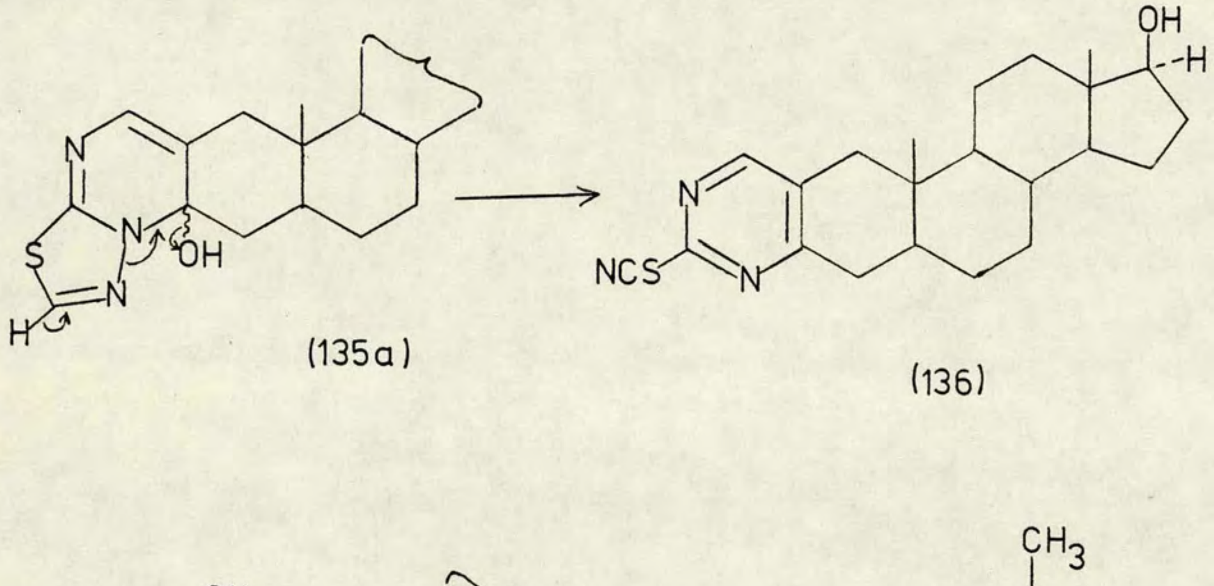
(a) <u>1-Formyl-3-thiosemicarbazide.</u> Formic acid (125 ml) contained in a round bottom flask was heated on a steam bath for 15 min and then thiosemicarbazide (61 g, 2 mole) was added. The mixture was swirled until the thiosemicarbazide had dissolved. The heating was continued for 30 min, during which time crystalline 1-formyl-3-thiosemicarbazide separated. Boiling water (200 ml) was added and the milky solution that resulted was filtered. After standing for 1 h, the filtrate was cooled in an ice bath for 2 h and the 1-formyl-3-thiosemicarbazide that separated was collected by filtration and air dried overnight, yield 56 g (71%), m.p. 177-178° dec.

(b) 3-Mercapto-1, 2, 4-triazole. A solution of 1-formyl-3-thiosemicarbazide (35.5 g, 0.3 mole) and sodium hydroxide (12 g, 0.3 mole) in water (60 ml) was heated on a steam bath for 1 h. The solution was cooled for 30 min in an ice bath and then treated with concentrated hydrochloric acid (30 ml). The reaction mixture was cooled in an ice bath for 2 h and the 3-mercapto-1, 2, 4-triazole which precipitated was collected by filtration. Recrystallisation from water gave white crystals (21 g, 72%), m.p. 219-21° (lit.[111b] m.p. 220-222°).

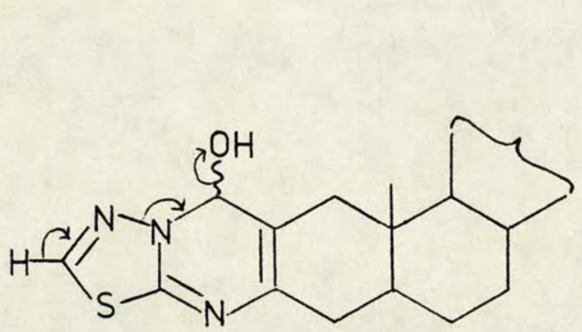
2.37 3-Mercapto-5-methyl-1, 2, 4-triazole (134) was also prepared by a two step synthesis. 1-Acetyl-3-thiosemicarbazide was prepared by the addition of acetyl chloride (39 g, 0.5 mole) to a stirred suspension of thiosemicarbazide (45 g, 0.5 mole) and dry pyridine (500 ml). The temperature was maintained between -5° and 0° throughout the addition. After standing at room temperature overnight most of the pyridine was removed by evaporation under reduced pressure. To effect cyclisation to 3-mercapto-5-methyl-1, 2, 4-triazole, the residue was dissolved in methanol (300 ml) and sodium methoxide (54 g, 1 mole) was added. The mixture was heated overnight on the steam bath and then the solvent was removed by evaporation under reduced pressure. The residue was dissolved in water (100 ml), the solution was decolorised with charcoal and concentrated hydrochloric acid (100 ml) was added. The solid formed was filtered, washed with water and air dried. Recrystallisation from water gave shining plates (44.5 g, 78%), m.p. 279-281° (lit.[124] m.p. 282-283°).



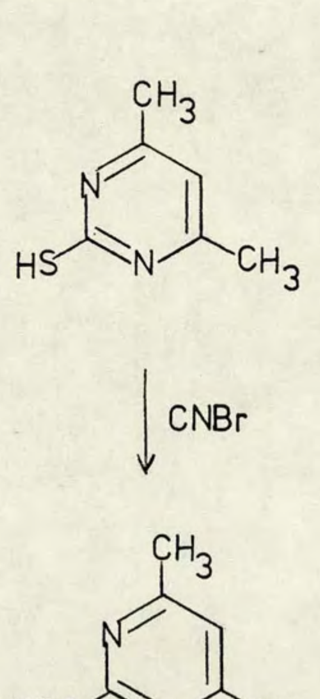
(3) (77)



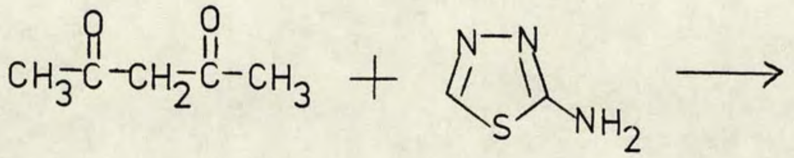
(135a) (136)



(135b)



(78)



3 The reaction of steroidal β-ketoaldehydes with 2-amino-1,3,4-thiadiazole.

3.1 The reaction of 17β-hydroxy-2-hydroxymethylene-5α-androstan-3-one (3) with 2-amino-1,3,4-thiadiazole (77).

A solution of 17β-hydroxy-2-hydroxymethylene-5α-androstan-3-one (3) and 2-amino-1,3,4-thiadiazole (77) in dry toluene containing a catalytic amount of toluene-4-sulphonic acid was refluxed overnight. On evaporation of the solvent, the residue was chromatographed over silica gel. Elution with methylene chloride-ethanol (95:5) followed by recrystallisation of the eluate from ethanol gave light yellow crystals (136), m.p. 213-215, in 60% yield.

Mass spectrometry and elemental analysis indicated that the product had a molecular formula of $C_{22}H_{29}N_3OS$. The i.r. spectrum showed absorptions at 3590, 2160, 1565, 1555 (inf), 1545 (inf), 1415, 1365 and 755 cm^{-1} and the ^1H n.m.r. spectrum exhibited signals at δ 0.76, δ 3.61 and δ 8.25.

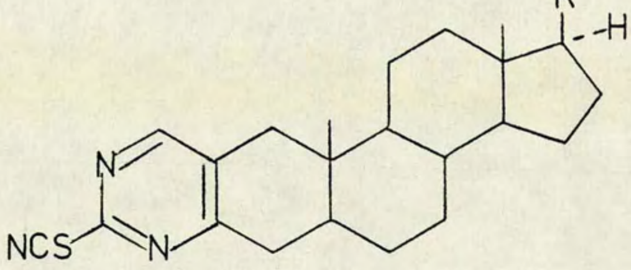
3.2 Discussion

The i.r. spectrum of the product obtained by the condensation of 17β-hydroxy-2-hydroxymethylene-5α-androstan-3-one (3) and 2-amino-1,3,4-thiadiazole (77) shows no carbonyl absorption but exhibits a strong absorption at 2160 cm^{-1} characteristic of a thiocyanate group and also absorptions at 1565, 1555 (inf), 1545 (inf), 1415, 1365 and 755 cm^{-1} characteristic of a pyrimidine ring. Thus the i.r. spectrum and the molecular formula $C_{22}H_{29}N_3OS$ obtained by mass spectroscopy and

and elemental analysis suggest that the product is 17β-hydroxy-2'-thiocyanato-5α-androst-2-eno[3, 2-d]pyrimidine (136). The presence of a signal at δ 8.25 in the ^{1}H n.m.r. spectrum confirms the 6'-H of the pyrimidine ring and therefore the structure (136).

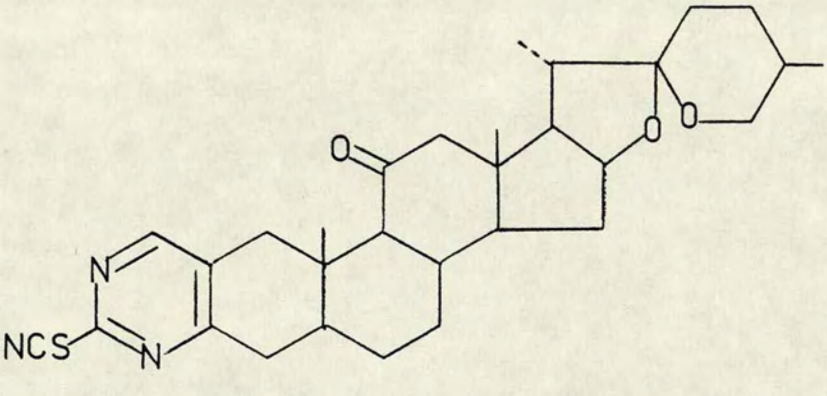
The thiocyanate group is known to isomerise to the isothiocyanate structure on refluxing in acetonitrile, benzene or toluene.[125] However no such isomerisation is observed in the above synthesis of the product (136), the 2'-thiocyanate group remaining intact even after prolonged heating in refluxing xylene. Absence of isomerisation to isothiocyanate is further confirmed in that the product fails to react with a primary amine.

Evidence has accumulated that aminoazoles (e.g. 3-amino-1, 2, 4-triazole, 3-aminopyrazole etc) react first with the aldehydic rather than the ketonic group of a β-ketoaldehyde.[80c] Thus the reaction of 2-amino-1, 3, 4-thiadiazole with 17β-hydroxy-2-hydroxymethylene-5α-androstan-3-one (3) would be expected to go through the intermediate (135a). Since this intermediate (135a) could not be isolated it is therefore possible that the intermediate might have an isomeric structure (135b) based upon the initial reaction of the amino group of the 1, 3, 4-thiadiazole and the 3-carbonyl of the steroidal β-ketoaldehyde (3). However, fission of the N-N bond in the rearrangement of either of the possible intermediates will yield the same product (136). A similar rearrangement has been reported during the reaction of 2-amino-1, 3, 4-thiadiazole and the simple 1, 3-dicarbonyl compound, acetylacetone, resulting in the formation of 2-thiocyanato-4, 6-dimethylpyrimidine (78).[53] The compound (78) has also been obtained[126] by the reaction of 2-mercapto-4, 6-

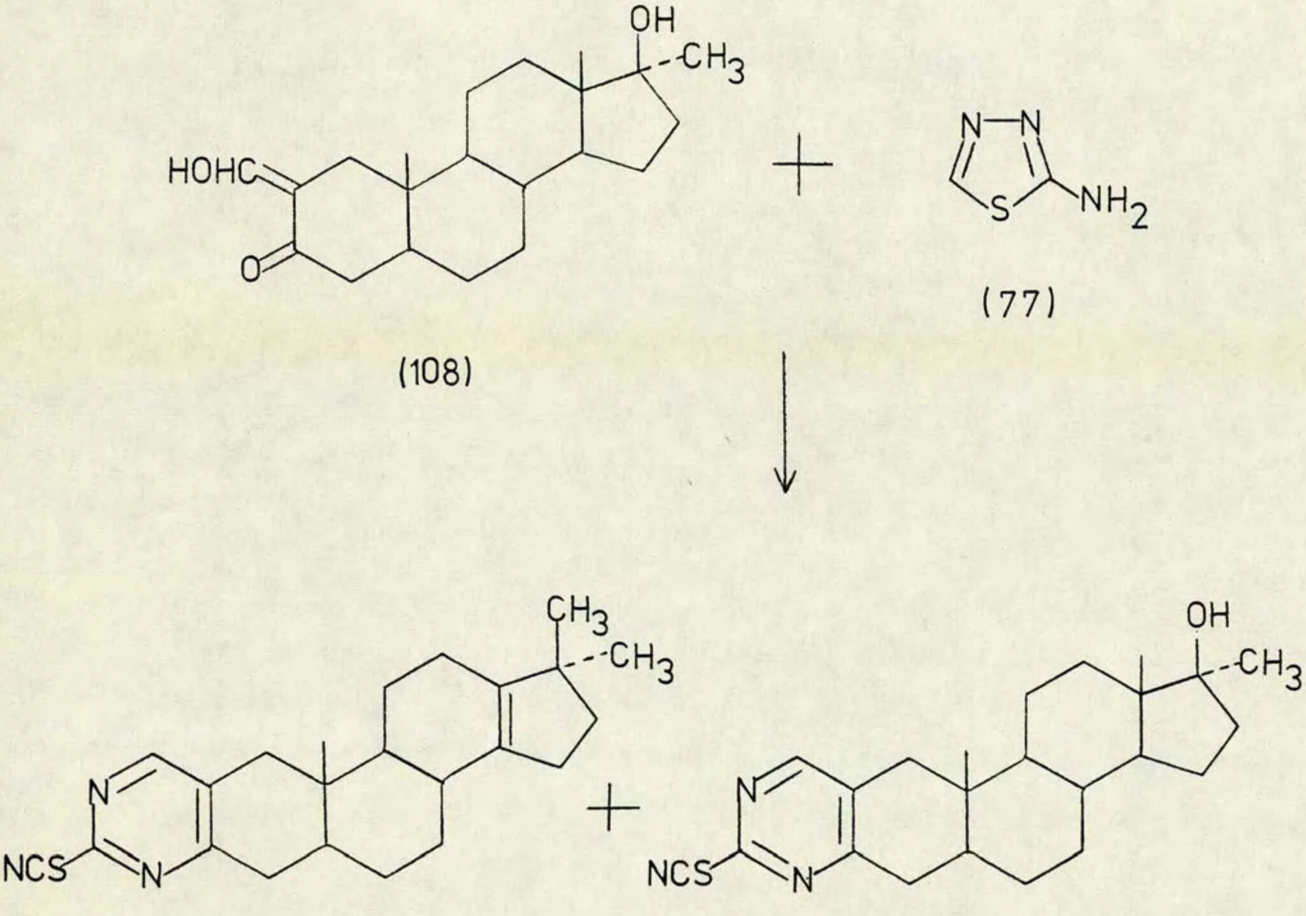


(137) R = H

(138) R = C_8H_{17}

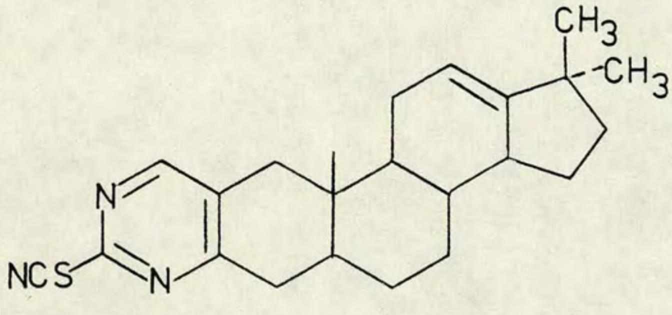


(139)

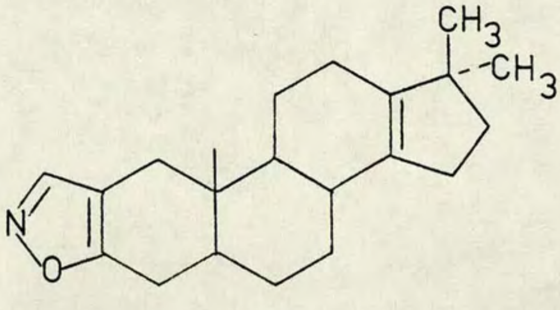


(140)

(141)



(140a)



(142)

dimethylpyrimidine with cyanogen bromide and this further supports the absence of isomerisation of the thiocyanate group into isothiocyanate during the condensation of 2-amino-1, 3, 4-thiadiazole with a β-dicarbonyl compound in refluxing toluene in the presence of a small amount of toluene-4-sulphonic acid.

In a similar manner, 2'-thiocyanato-5α-androst-2-eno[3, 2-d]-pyrimidine (137), 2'-thiocyanato-5α-cholest-2-eno[3, 2-d]pyrimidine (138) and 11-oxo-2'-thiocyanato-5α-spirost-2-eno[3, 2-d]pyrimidine (139) were prepared from 2-hydroxymethylene-5α-androstan-3-one (109), 2-hydroxymethylene-5α-cholestan-3-one (110) and 2-hydroxymethylene-5α-spirostan-3,11-dione (111) respectively.

3. 3 The reaction of 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108) with 2-amino-1, 3,4-thiadiazole (77).

A solution of 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108), 2-amino-1, 3, 4-thiadiazole (77) and a small amount of toluene-4-sulphonic acid in dry toluene was refluxed overnight. After evaporation of the solvent, the residue was chromatographed over silica gel. Elution with methylene chloride gave a white solid which recrystallised from ethanol as white crystals (140), m. p. 125-127°, in 11% yield. Further elution of the chromatogram with methylene chloride-ethanol (95 : 5) gave a yellow solid which upon recrystallisation from ethanol gave light yellow crystals (141), m. p. 172-173, in 85% yield.

Mass spectrometry and elemental analysis of the first product

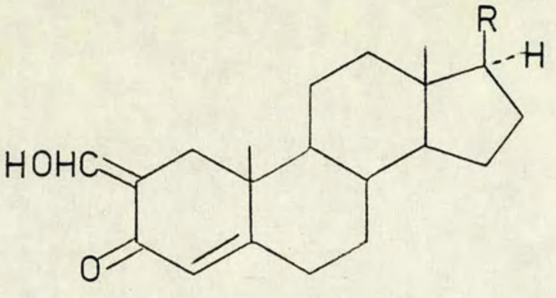
(m. p. 125-127°), give its molecular formula as $C_{23}H_{29}N_3S$ which shows that the product does not contain the hydroxyl group at the 17-position. The loss of hydroxyl group at the 17-position is further confirmed by the absence of any absorption around 3600 cm^{-1} in the i. r. spectrum which exhibits absorptions at 2160, 1565, 1540 (inf), 1440, 1415, 1365, 1350 and 755 cm^{-1}. The ^1H n. m. r. spectrum shows a signal at δ 8.30 which is assigned to the hydrogen on the pyrimidine ring. The absence of any other signal in the vinyl region eliminates the structure (140a) containing a double bond at the 12-position. However structure (140) is supported by the signal at δ 0.80 assigned to the gem dimethyl group at 17-C and the signal at δ 1.00 assigned to 19-methyl group. The yield of 17, 17-dimethyl-2'-thiocyanato-18-nor-5α-androst-2, 13-dieno[3, 2-d]pyrimidine (140) is found to be dependent upon the amount of toluene-4-sulphonic acid used in the condensation.

Acid-catalysed dehydration of tertiary alcohols is well known. Manson <u>et al.</u>[13] obtained 17, 17-dimethyl-18-nor-5α-androst-2, 13-dieno[2, 3-d]isoxazole (142) in high yield from the reaction of equimolar amounts of 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (3) and hydroxylamine hydrochloride in glacial acetic acid.

The structure of the compound (141), m. p. 172-173° follows by analogy with the structure of 17β-hydroxy-2'-thiocyanato-5α-androst-2-eno[3, 2-d]pyrimidine (136).

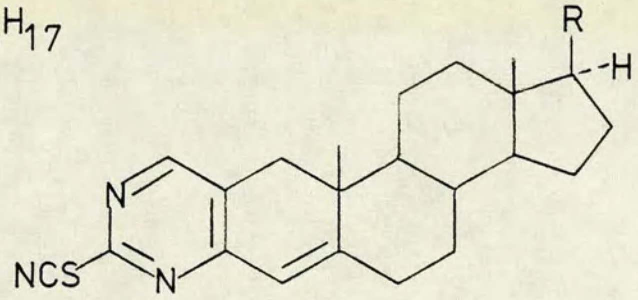
3.4 The reaction of 17β-hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4) with 2-amino-1, 3, 4-thiadiazole (77).

A solution of 17β-hydroxy-2-hydroxymethyleneandrost-4-en-3-one



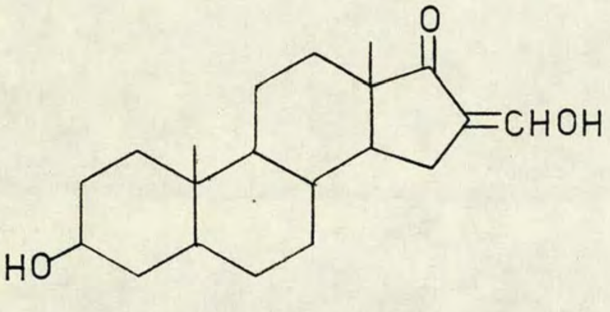
(4) R = OH

(112) R = C_8H_{17}

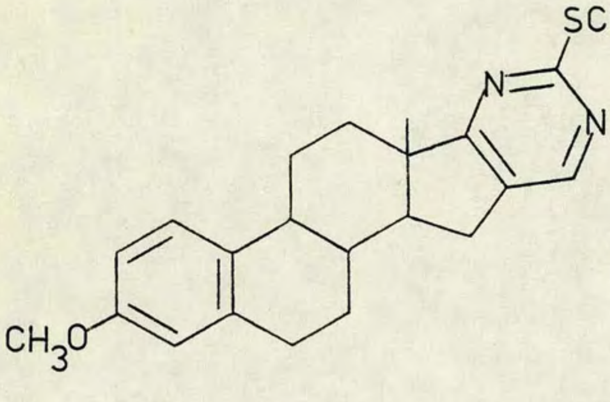


(143) R = OH

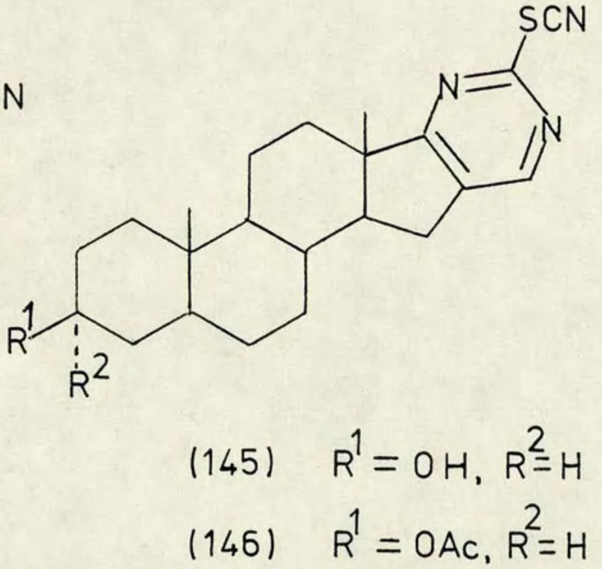
(144) R = C_8H_{17}



(7)



(148)



(145) R^1 = OH, R^2 = H

(146) R^1 = OAc, R^2 = H

(147) R^1R^2 = O

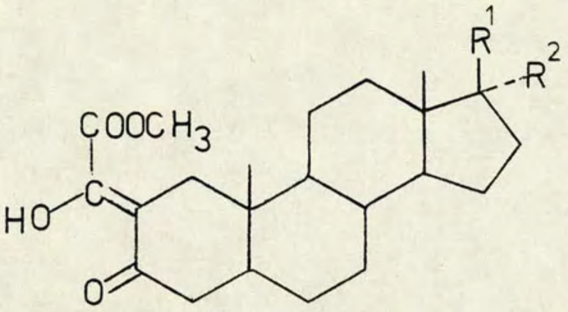
(4) and 2-amino-1, 3, 4-thiadiazole (77) in dry toluene containing a small amount of toluene-4-sulphonic acid was refluxed overnight. After usual work up of the reaction mixture a yellow solid was obtained, which was recrystallised from ethanol to give large yellow crystals (143), m. p. 185-187, in 41% yield.

Mass spectrometry and elemental analysis indicated that the product had a molecular formula of $C_{22}H_{27}N_3OS$. The i. r. spectrum exhibited absorptions at 3600 (OH), 2160 (SCN), 1565, and 755 cm^{-1} whilst ^1H n. m. r. spectrum showed signals at δ 0. 80 (s, 18-CH_3), 1. 00 (s, 19-CH_3), 3. 65 (m, 17-H), 6. 18 (s, 4-H) and 8. 20 (s, 6'-H). The product was assigned the structure, 17β-hydroxy-2'-thiocyanato-androst-2, 4-dieno[3, 2-d]pyrimidine (143) by analogy with the formation of 17β-hydroxy-2'-thiocyanato-5α-androst-2-eno[3, 2-d]pyrimidine (136) from 17β-hydroxy-2-hydroxymethylene-5α-androstan-3-one (3) and 2-amino-1, 3, 4-thiadiazole (77).

In an analogous manner 2'-thiocyanato-5α-cholest-2, 4-dieno[3, 2-d]pyrimidine (144) was obtained in 38% yield by the condensation of 2-hydroxymethylenecholest-4-en-3-one (112) and 2-amino-1, 3, 4-thiadiazole (77).

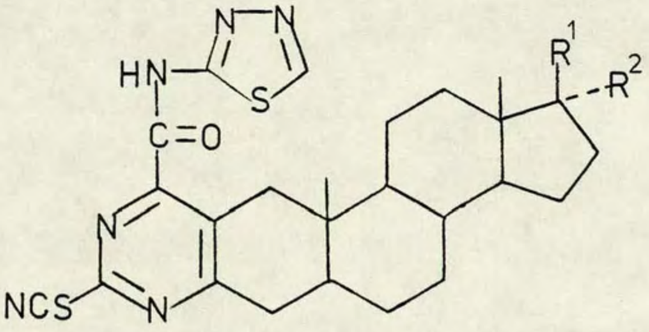
3. 5 The reaction of 3β-hydroxy-16-hydroxymethylene-5α-androstan-17-one (7) with 2-amino-1, 3, 4-thiadiazole (77).

Treatment of 3β-hydroxy-16-hydroxymethylene-5α-androstan-17-one (7) with 2-amino-1, 3, 4-thiadiazole (77) in the manner described for the synthesis of 17β-hydroxy-2'-thiocyanato-5α-androst-2-eno[3, 2-d]pyrimidine (136), gave a light yellow solid. Recrystallisation of this solid from ethanol gave white crystals of 3β-hydroxy-2'-thiocyanato-5α-androst-16-eno[17, 16-d]pyrimidine (145), m. p. 192-194°, in 75% yield.



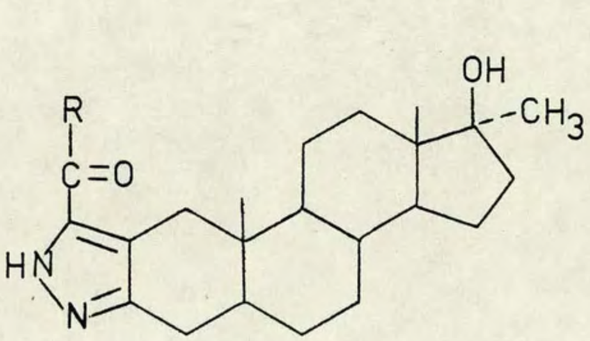
(113) $R^1 = OH$, $R^2 = CH_3$

(114) $R^1 = C_8H_{17}$, $R^2 = H$



(149) $R^1 = OH$, $R^2 = CH_3$

(151) $R^1 = C_8H_{17}$, $R^2 = H$



(150a) $R = OC_2H_5$

(150b) $R = NH-NH_2$

Mass spectrometry and elemental analysis were in agreement with the molecular formula $C_{22}H_{29}N_3OS$ of compound (145). The i. r. spectrum had absorptions at 3600 (OH), 2160 (SCN), 1580, 790 and 790 cm^{-1}, whilst ^{1}H n. m. r. spectrum exhibited signals at δ 0. 85 (s, 18-CH$_3$), 0. 97 (s, 19-CH$_3$), 402 (m, 3-H), 8. 35 (s, 6'-H).

Acetylation of the product (145) gave a monoacetate (146) identified by its i. r. spectrum as the 3β-acetate. Oxidation of product (145) by Jones reagent furnished the 3-oxo derivative (147).

In an analogous manner, the condensation of 2-amino-1,3,4-thiadiazole (77) with 16-hydroxymethylene-3-methoxyoestra-1,3,5(10)-trien-17-one (9) afforded 3-methoxy-2'-thiocyanato-oestra-1,3,5(10),16-tetraeno[17,16-d]pyrimidine (148).

3. 6 The reaction of 17β-hydroxy-2-methoxycarbonyl(hydroxy)methylene-17α-methyl-5α-androstan-3-one (113) with 2-amino-1,3,4-thiadiazole (77).

A solution of 17β-hydroxy-2-methoxycarbonyl(hydroxy)methylene-17α-methyl-5α-androstan-3-one (113) and 2-amino-1,3,4-thiadiazole (77) in dry toluene containing a small amount of toluene-4-sulphonic acid was refluxed overnight. After evaporation of the solvent, the residue was chromatographed over silica gel. Elution with methylene chloride-ethanol (95:5) followed by recrystallisation of the eluate from ethanol gave a light yellow solid (149), m. p. 244-246°, in 65% yield.

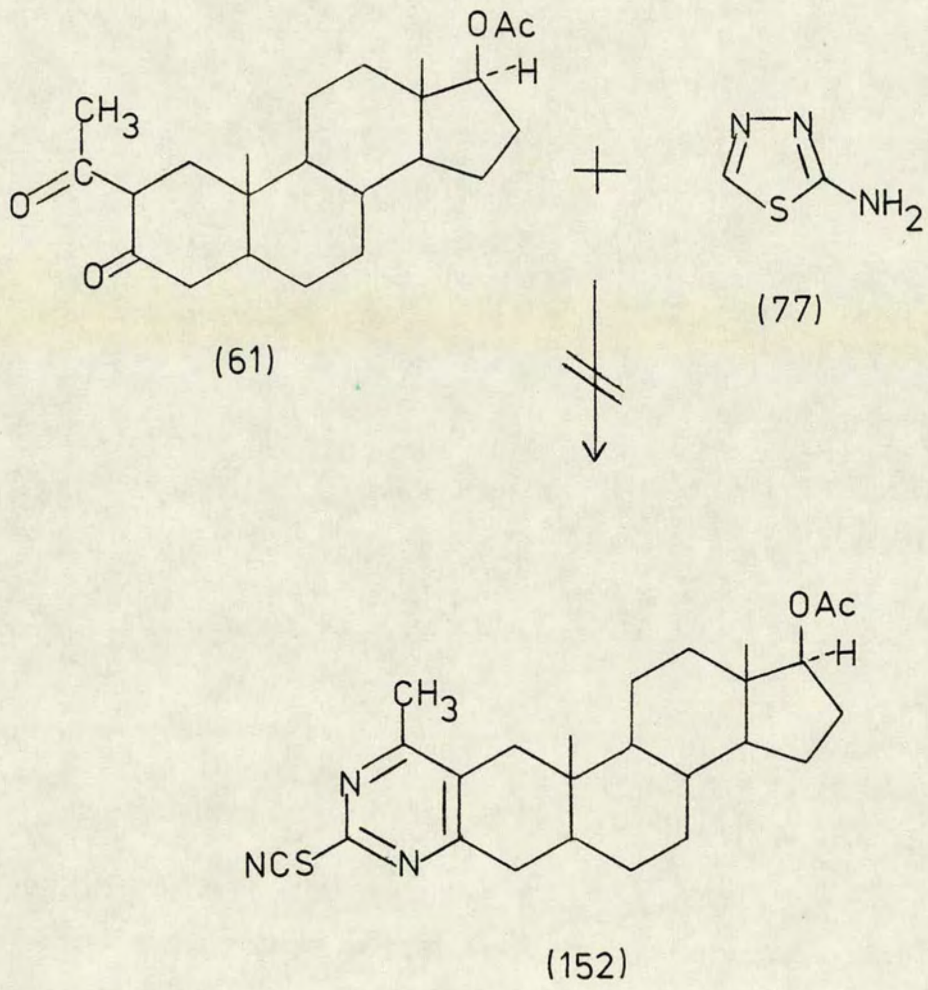
Mass spectrometry and elemental analysis showed that the product had a molecular formula of $C_{26}H_{32}N_6O_2S_2$. The i. r. spectrum exhibited absorptions at 3600, 3330, 2160, 1690, 1500 and 735 cm^{-1} whilst the

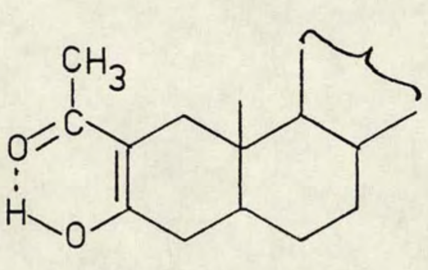
^{1}H n.m.r. spectrum showed two singlets at δ 8.90 and δ 12.00 apart from the usual signals for 17-, 18- and 19-methyl groups.

3.7 Discussion

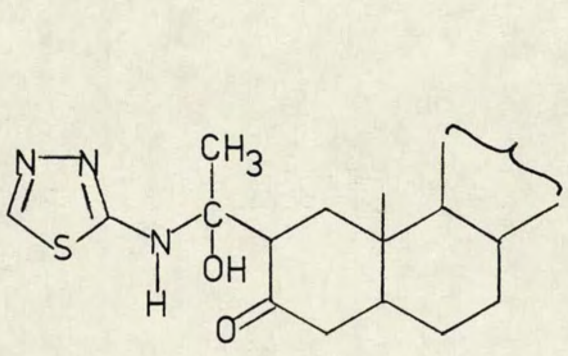
The presence of six nitrogen atoms and two sulphur atoms in the molecular formula $C_{26}H_{32}N_6O_2S_2$ of the product indicated that two moles of 2-amino-1, 3, 4-thiadiazole have reacted with one mole of the starting steroid (113). Ruggieri et al.[15] have shown that the reaction of hydrazine hydrate with 17β-hydroxy-2-ethoxycarbonyl(hydroxy)methylene-17α-methyl-5α-androstan-3-one gives 17β-hydroxy-17α-methyl-5α-androstan-[3, 2-c]-5'-carbethoxy pyrazole (150a) which when further allowed to react with hydrazine hydrate yields the corresponding hydrazide (150b). By analogy with these reactions, the product obtained by the condensation of 2-amino-1, 3, 4-thiadiazole and 17β-hydroxy-2-methoxycarbonyl-(hydroxy)methylene-17α-methyl-5α-androstan-3-one (113) is assigned structure (149) which is confirmed by i.r. and ^{1}H n.m.r. spectroscopy. The i.r. spectrum shows NH, SCN and CO groups by absorption bands at 3330, 2160 and 1690 cm^{-1} respectively, whilst the ^{1}H n.m.r. spectrum shows signals at δ 8.90 (5''-H) and δ 12.00 (NH), the latter signal disappears when the solution is shaken with deuterated water. All attempts to condense a single mole of 2-amino-1, 3, 4-thiadiazole with 3-keto oxalyl steroid (113) produced the same product (149).

Similarly the condensation of 2-methoxycarbonyl(hydroxy)methylene-5α-cholestan-3-one (114) with 2-amino-1, 3, 4-thiadiazole (77) afforded 6'-(1, 3, 4-thiadiazol-2-ylcarbonyl)-2'-thiocyanato-5α-cholest-2-eno-[3, 2-d]pyrimidine (151) in 71% yield.


OAc
H
CH3
O
O
(61)
N
N
S
NH2
(77)
OAc
H
CH3
N
NCS
N
(152)


CH3
C
O
H
O

(61a)


N
N
S
N
H
CH3
C
OH
O

(153)

3.8 The attempted reaction of 17β-acetoxy-2α-acetyl-5α-androstan-3-one (61) with 2-amino-1, 3, 4-thiadiazole (77).

A solution of 17β-acetoxy-2α-acetyl-5α-androstan-3-one (61) and 2-amino-1, 3, 4-thiadiazole (77) and a small amount of toluene-4-sulphonic acid in dry toluene was refluxed overnight. On evaporation of the solvent, the residue was taken up in chloroform which was washed with water, saturated sodium chloride solution and dried over anhydrous magnesium sulphate. On evaporation of the solvent, the residue was found to be 17β-acetoxy-2α-acetyl-5α-androstan-3-one (61), by its i.r. and ^{1}H n.m.r. spectra.

3.9 Discussion

By analogy with the formation of 17β-hydroxy-2'-thiocyanato-5α-androst-2-eno[3, 2-d]pyrimidine (136) from the condensation of 17β-hydroxy-2-hydroxymethylene-5α-androstan-3-one (3) and 2-amino-1, 3, 4-thiadiazole, the reaction of 17β-acetoxy-2α-acetyl-5α-androstan-3-one (61) with 2-amino-1, 3, 4-thiadiazole would be expected to give 17β-acetoxy-2'-thiocyanato-6'-methyl-5α-androst-2-eno[3, 2-d]pyrimidine (152). However, no such product was isolated from the above condensation reaction.

The i.r. spectrum of the 17β-hydroxy derivative of the compound (61) while having the characteristic broad β-diketone band at 1540-1640 cm^{-1} does not absorb in the "normal" carbonyl region from 1700 to 1750 cm^{-1}.[105] In contrast to this, acetylacetone[127] has an absorption of medium intensity in the region of 1700 cm^{-1} which from its position is attributable to the keto form. The i.r. spectrum of 17β-hydroxy-2-

hydroxymethylene-5α-androstan-3-one (3) exhibits an absorption of medium intensity at 1700 cm^{-1}. Furthermore the u.v. peak (290 nm)[105] arising from the cyclic hydrogen bonded enolic diketone in the 2-acetyl steroid occurs at a longer wavelength than that reported for 2-hydroxymethylene-3-keto steroids (ca. 282 nm)[7] or for simple β-diketones (ca. 270 nm).[127, 128] It would therefore appear that the cyclic hydrogen bonded enolic form (61a) is more stable than in 17β-hydroxy-2-hydroxymethylene-5α-androstan-3-one (3). This may be due to greater conformational lability in the latter compound, resulting in a greater tendency to open to the diketo form. Since acetyl acetone[53] and 17β-hydroxy-2-hydroxymethylene-5α-androstan-3-one (3) have been shown to react readily with 2-amino-1,3,4-thiadiazole in dry toluene to give 2-thiocyanato pyrimidines (78 and 136), the inability of 17β-acetoxy-2α-acetyl-5α-androstan-3-one (61) to condense readily with 2-amino-1,3,4-thiadiazole may be due in part to the fact that the cyclic hydrogen bonded enolic β-diketone is more stable in the 2-acetyl steroid than in the 2-hydroxymethylene steroid or the aliphatic β-diketone.

Another related reason for the slowness of the reaction is the probable steric hindrance caused by the methyl group of the 2-acetyl fragment. In anil formation, the carbon of the acetyl carbon will become tetrahedral in the transition state (153). In this transition state steric hindrance arises because of the close proximity of the methyl protons and the thiadiazole ring.

3.10 Experimental

General procedure for the condensation reaction

A solution of steroidal β-ketoaldehyde (0.001 mole), 2-amino-1,3,4-thiadiazole (77) (0.0015 mole) and toluene-4-sulphonic acid (20 mg) in dry toluene (50 ml) was refluxed and stirred overnight. The excess of solvent was removed under vacuo, the residue was chromatographed over silica gel (50 g, 80-200 mesh) using either methylene chloride or methylene chloride-ethanol (95:5) mixture and the product thus obtained was recrystallised from a suitable solvent.

3.10.i 17β-Hydroxy-2'-thiocyanato-5α-androst-2-eno[3,2-d]pyrimidine (136).

Starting β-ketoaldehyde: 17β-Hydroxy-2-hydroxymethylene-5α-androstan-3-one (3).

Silica gel chromatography (eluant methylene chloride-ethanol, 95:5) followed by recrystallisation from benzene gave white crystals of 17β-hydroxy-2'-thiocyanato-5α-androst-2-eno[3,2-d]pyrimidine (136) (60%), m.p. 213-215; i.r. γ_{max} 3590 (OH), 2160 (SCN), 1565, 1415, 1365 and 755 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.75 (s, 6H, 18-CH_3 and 19-CH_3), 3.62 (m, 1H, 17-H) and 8.26 (s, 1H, 6'-H) (Found: C, 69.02; H, 7.61; N, 11.11; M^+, 383.202537. $C_{22}H_{29}N_3OS$ requires C, 68.89; H, 7.63; N, 10.96; M, 383.203123).

3.10.ii 2'-Thiocyanato-5α-androst-2-eno[3,2-d]pyrimidine (137)

Starting β-ketoaldehyde: 2-Hydroxymethylene-5α-androstan-3-one (109).

Silica gel chromatography (eluant methylene chloride) followed by recrystallisation from benzene gave light yellow needles of 2'-thiocyanato-5α-androst-2-eno[3,2-d]pyrimidine (137) (85%), m.p. 210-212; i.r., γ_{max} 2160 (SCN), 1565, 1410, 1365, 1345 and 755 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ0.72 (s, 3H, 18-CH_3), 0.74 (s, 3H, 19-CH_3) and 8.28 (s, 1H, 6'-H) (Found: C, 71.72; H, 8.01; N, 11.67; M^+, 367.205933. $C_{22}H_{29}N_3S$ requires C, 71.89; H, 7.96; N, 11.44%; M, 367.207136).

3.10.iii 2'-Thiocyanato-5α-cholest-2-eno[3,2-d]pyrimidine (138).

Starting β-ketoaldehyde: 2-Hydroxymethylene-5α-cholestan-3-one (110).

Silica gel chromatography (eluant methylene chloride) followed by recrystallisation from ethanol gave yellow crystals of 2'-thiocyanato-5α-cholest-2-eno[3,2-d]pyrimidine (138) (70%), m.p. 159-160; i.r. γ_{max} 2160 (SCN), 1465, 1440, 1415, 1365, and 750 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.68, 0.74, 0.82 and 0.88 (methyl groups) and 8.28 (s, 1H, 6'-H). (Found: C, 75.32; H, 9.44; N, 8.57; M^+, 479.331357. $C_{30}H_{45}N_3S$ requires C, 75.10; H, 9.46; N, 8.76%; M, 479.333404).

3.10.iv 11-Oxo-2'-thiocyanato-5α-spirost-2-eno[3,2-d]pyrimidine (139).

Starting β-ketoaldehyde 2-Hydroxymethylene-5α-spirostan-3,11-dione (111)

Silica gel chromatography (eluant methylene chloride-ethanol, 95:5) followed by recrystallisation from ethanol gave white crystals of 11-oxo-2'-thiocyanato-5α-spirost-2-eno[3,2-d]pyrimidine (139) (68%), m.p. 241-243°; i.r., γ_{max} 2160 (SCN), 1695 (CO), 1565, 1450, 1415, 1365 and 755 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.76 (s, 3H, 18-CH_3), 0.96 (s, 3H, 19-CH_3), and 8.30 (s, 1H, 6'-H). (Found: C, 68.75;

H, 7.95; N, 8.10; M^+, 521.271406. $C_{30}H_{39}N_3SO_3$ requires C, 69.06; H, 7.54; N, 8.08%; M, 521.271198).

3.10.v 17,17-Dimethyl-2'-thiocyanato-18-norandrost-2,13-dieno[3,2-d]pyrimidine (140) and 17β-hydroxy-17α-methyl-2'-thiocyanato-5α-androst-2-eno[3,2-d]pyrimidine (141).

Starting β-ketoaldehyde: 17β-Hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108).

Silica gel chromatography (eluant methylene chloride) followed by recrystallisation from ethanol gave white crystals of 17,17-dimethyl-2'-thiocyanato-18-norandrost-2,13-dieno[3,2-d]pyrimidine (140) (11%) m.p. 125-127°; i.r., γ_{max} 2160 (SCN), 1565, 1415, 1365, and 755 cm^{-1}; ^1H n.m.r. (60 MHz), δ 0.80 (s, 6H, 17-gem dimethyl), 1.00 (s, 3H, 19-CH_3) and 8.30 (s, 1H, 6'-H) (Found: C, 72.75; H, 7.85; N, 10.5; M^+, 379.208494. $C_{23}H_{29}N_3S$ requires C, 72.78; H, 7.71; N, 10.71%; M, 379.208209).

Further elution of the chromatogram with methylene chloride-ethanol (95:5) followed by recrystallisation from ethanol gave light yellow crystals of 17β-hydroxy-17α-methyl-2'-thiocyanato[3,2-d]pyrimidine (141) (85%), m.p. 172-173°; i.r., γ_{max} 3600 (OH), 2160 (SCN), 1565, 1440, 1410, 1365 and 755 cm^{-1}; ^1H n.m.r. (60 MHz), δ 0.75 (s, 3H, 18-CH_3), 0.90 (s, 3H, 19-CH_3), 1.20 (s, 3H, 17-CH_3) and 8.20 (s, 1H, 6'-H) (Found: C, 69.50; H, 7.85; N, 10.95; M^+, 397.218722. $C_{23}H_{31}N_3OS$ requires C, 69.48; H, 7.86; N, 10.57%; M, 397.218773).

3.10.vi 17β-Hydroxy-2'-thiocyanatoandrost-2,4-dieno[3,2-d]pyrimidine (143)

Starting β-ketoaldehyde: 17β-Hydroxy-2-hydroxymethyleneandrost-4-en-

3-one (4).

Silica gel chromatography (eluant methylene chloride) followed by recrystallisation from ethanol gave yellow crystals of 17β-hydroxy-2'-thiocyanatoandrost-2, 4-dieno[3, 2-d]pyrimidine (143) (41%), m. p. 185-187; i. r., γ_{max} 3600 (OH), 2160 (SCN), 1620, 1575, 1535, 1430, 1415, 1350 and 750 cm^{-1}; ^{1}H n. m. r. (60 MHz), δ 0. 80 (s, 3H, 18-CH_3), 1. 00 (s, 3H, 19-CH_3), 3. 65 (m, 1H, 17-H), 6. 18 (s, 1H, 4-H) and 8. 20 (s, 1H, 6'-H) (Found: C, 68. 75; H, 7. 25; N, 10. 80; M^+, 381. 186086. $C_{22}H_{27}N_3OS$ requires C, 68. 25; H, 7. 13; N, 11. 02%; M, 381. 187474).

3. 10. vii 2'-Thiocyanato-5α-cholest-2, 4-dieno[3, 2-d]pyrimidine (144).

Starting β-ketoaldehyde: 2-Hydroxymethylene-cholest-4-ene-3-one (112).

Silica gel chromatography (eluant methylene chloride) followed by recrystallisation from ethanol gave yellow crystals of 2'-thiocyanato-5α-cholest-2, 4-dieno[3, 2-d]pyrimidine (144) (38%), m. p. 184-186°; i. r., γ_{max} 2160 (SCN), 1620, 1565, 1535, 1430, 1415, 1350 and 770 cm^{-1}; ^{1}H n. m. r. (100 MHz), δ 0. 70, 0. 82, 0. 88, and 0. 92 (methyl groups), 6. 16 (s, 1H, 4-H) and 8. 20 (s, 1H, 6'-H) (Found: C, 75. 25; H, 8. 90; N, 8. 50; M^+, 477. 316335. $C_{30}H_{43}N_3S$ requires C, 75. 42; H, 9. 08; N, 8. 80%; M, 477. 317754).

3. 10. viii 3β-Hydroxy-2'-thiocyanato-5α-androst-16-eno[17, 16-d]-pyrimidine (145).

Starting β-ketoaldehyde: 3β-Hydroxy-16-hydroxymethylene-5α-androstan-17-one (7).

Silica gel chromatography (eluant methylene chloride-ethanol, 95:5) followed by recrystallisation from ethanol gave 3β-hydroxy-2'-

thiocyanato-5α-anadrost-16-eno[17,16-d]pyrimidine (145) (75%), m.p. 192-194°; i.r., γ_{max} 3600 (OH), 2160 (SCN), 1580, 1535, 1445, 1410, 1370 and 790 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.85 (s, 3H, 18-CH$_3$), 0.97 (s, 3H, 19-CH$_3$), 4.02 (s, 1H, 3-H), and 8.35 (s, H, 6'-H) (Found: C, 69.10; H, 7.75; N, 10.95; M$^+$, 383.203289. $C_{22}H_{29}N_3OS$ requires C, 68.89; H, 7.63; N, 10.96%; M, 383.203123).

3.10.ix 3-Methoxy-2'-thiocyanato-oestra-1,3,5(10),16-tetraeno-[17,16-d]pyrimidine (148).

Starting β-ketoaldehyde: 16-Hydroxymethylene-3-methoxyoestra-1,3,5-(10)trien-17-one (9).

Silica gel chromatography (eluant methylene chloride-ethanol, 95:5) followed by recrystallisation from ethanol gave 3-methoxy-2'-thiocyanato-oestra-1,3,5(10),16-tetraeno[17,16-d]pyrimidine (148) (72%), m.p. 177-179°; i.r., γ_{max} 2160 (SCN), 1605, 1575, 1535, 1500, 1460, 1410 and 780 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 1.00 (s, 3H, 18-CH$_3$), 3.75 (s, 3H, 3-OCH$_3$), 6.60-7.25 (m, 3H, 1-H, 2-H and 4-H), 8.35 (s, 1H, 6'-H) (Found: C, 69.65; H, 6.25; N, 10.65; M$^+$, 377.154981. $C_{22}H_{23}N_3OS$ requires C, 69.99; H, 6.15; N, 11.13%; M, 377.156176).

3.10.x 17β-Hydroxy-17α-methyl-6'-(1,3,4-thiadiazol-2-ylcarbamoyl)-2'-thiocyanato-5α-androst-2-eno[3,2-d]pyrimidine (149).

Starting material: 17β-Hydroxy-2-methoxycarbonyl(hydroxy)methylene-17α-methyl-5α-androstan-3-one (113).

Silica gel chromatography (eluant methylene chloride-ethanol, 95:5) followed by recrystallisation from ethanol gave 17β-hydroxy-17α-methyl-6'-(1,3,4-thiadiazol-2-ylcarbamoyl)-2'-thiocyanato-5α-androst-2-eno[3,2-d]pyrimidine (149) (65%), m.p. 244-246°; i.r. γ_{max} 3595 (OH), 3330 (NH), 2160 (SCN), 1690 (CO), 1510, and 745 cm^{-1}; ^{1}H n. m. r. (100 MHz), δ 0. 77 (s, 3H, 18-CH_3), 0. 87 (s, 3H, 19-CH_3), 1. 20 (s, 3H, 17-CH_3), 8. 90 (s, 1H, 5''-H), and 12. 0 (bs, 1H, NH) (Found: C, 59. 70; H, 4. 20; N, 16. 20; M^+, 524. 204927. $C_{26}H_{32}N_6O_2S_2$ requires C, 59. 51; H, 4. 41; N, 16. 09%; M, 524. 202805).

3. 10. xi 6'-(1, 3, 4-Thiadiazol-2-ylcarbamoyl)-2'-thiocyanato-5α-cholest-2-eno[3, 2-d]pyrimidine (151).

Starting material: 2-Methoxycarbonyl(hydroxy)methylene-5α-cholestan-3-one (114).

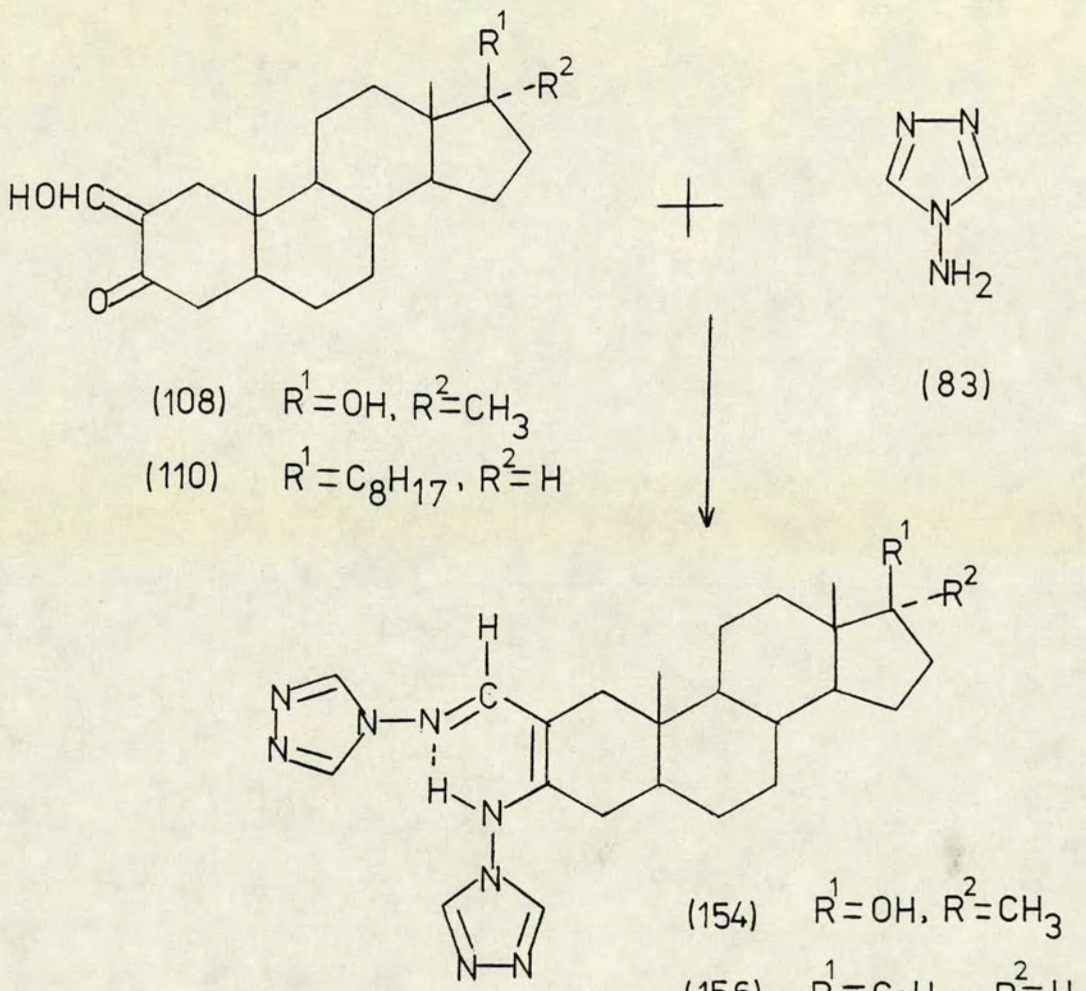
Silical gel chromatography (eluant methylene chloride-ethanol, 95:5) followed by recrystallisation from ethanol gave 6'-(1, 3, 4-thiadiazol-2-ylcarbamoyl)-2'-thiocyanato-5α-cholest-2-eno[3, 2-d]pyrimidine (151) (71%), m. p. 311-314°; i. r., γ_{max} 3330 (NH), 2160 (SCN), 1690 (CO), 1500, and 735; ^{1}H n. m. r. (100 MHz), δ 0. 72, 0. 82, 0. 90 and 0. 96 (methyl groups), 6. 16 (s, 1H, 6-H) and 8. 22 (s, 1H, 6'-H) (Found: C, 64. 95; H, 7. 5; N, 13. 5; M^+, 606. 317398. $C_{33}H_{46}N_6OS_2$ requires C, 65. 31; H, 7. 58; N, 13. 85%; M, 606. 317434).

3. 10. xii 3β-Acetoxy-2'-thiocyanato-5α-androst-16-eno[17, 16-d]-pyrimidine (146).

A solution of 3β-hydroxy-2'-thiocyanato-5α-androst-16-eno[17, 16-d]pyrimidine (145) (383 mg 1×10^{-3} mol) and a few drops of acetic anhydride in pyridine (20 ml) was refluxed for 2 h. The solvent was evaporated in vacuo and the residue taken up in chloroform. The chloroform solution was washed with water, 5% hydrochloric acid, saturated sodium chloride solution and dried over anhydrous magnesium sulphate. After removal of the solvent, the residue was recrystallised from ethanol to give 3β-acetoxy-2'-thiocyanato-5α-androst-16-eno[17,16-d]pyrimidine (146) (225 mg, 53%), m.p. 175-177; i.r., γ_{max} 2160 (SCN), 1720 (CO), 1580, 1540, 1450, 1410 and 900 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.90 (s, 3H, 18-CH_3), 1.00 (s, 3H, 19-CH_3), 2.00 (s, 3H, 3-$OCOCH_3$), 4.66 (m, 1H, 3-H) and 8.50 (s, 1H, 6'-H) (Found: C, 67.40; H, 7.00; N, 9.90; M^+, 425.214789. $C_{24}H_{31}N_3O_2S$ requires C, 67.73; H, 7.29; N, 9.87%; M, 425.213686).

3.10.xiii 3-Oxo-2'-thiocyanato-5α-androst-16-eno[17,16-d]pyrimidine (147).

3β-Hydroxy-2'-thiocyanato-5α-androst-16-eno[17,16-d]pyrimidine (145) (190 mg, 5 x 10^{-4} mole) in acetone (60 ml) was oxidised with 8N chromic acid (2 ml). The reaction was allowed to proceed for 4 min and the excess reagent was decomposed with methanol (10 ml). Water (30 ml) was added, the organic solvents removed under reduced pressure and the steroid was filtered, washed with water and dried. Recrystallisation of the crude product from ethanol gave white crystals of 3-oxo-2'-thiocyanato-5α-androst-16-eno[17,16-d]pyrimidine (147) (80%), m.p. 226-228°; i.r., γ_{max} 2160 (SCN), 1700 (CO), 1575, 1535, 1440, 1410 and 790 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 1.00 (s, 3H, 18-CH_3), 1.10 (s, 3H, 19-CH_3), and 8.40 (s, 1H, 6'-H) (Found: C, 68.95; H, 7.25; N, 10.75; M^+, 381.187281. $C_{22}H_{27}N_3OS$ requires C, 69.26; H, 7.14; N, 11.02%; M, 381.187474).



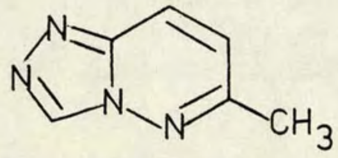
(108) $R^1 = OH$, $R^2 = CH_3$

(110) $R^1 = C_8H_{17}$, $R^2 = H$

(83)

(154) $R^1 = OH$, $R^2 = CH_3$

(156) $R^1 = C_8H_{17}$, $R^2 = H$



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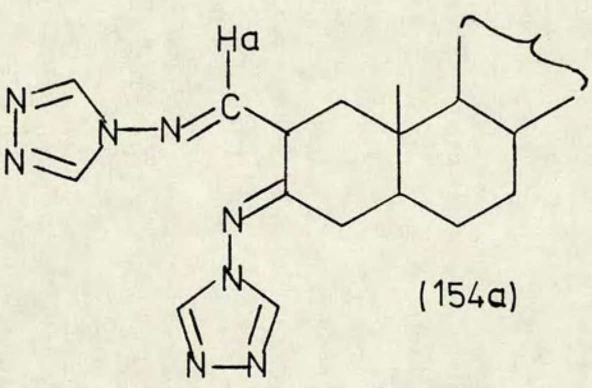
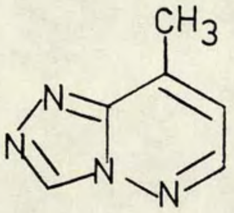


(154a)



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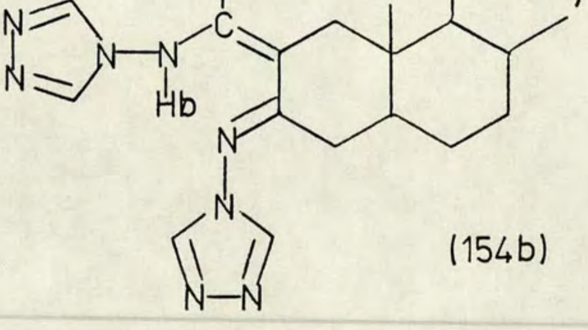

(154b)

4 The reaction of steroidal β-ketoaldehydes with 4-amino-1, 2, 4-triazole.

4. 1 The reaction of 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108) with 4-amino-1, 2, 4-triazole (83).

A solution of 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108) and 4-amino-1, 2, 4-triazole (83) in dry toluene containing a catalytic amount of toluene-4-sulphonic acid was refluxed overnight. After evaporation of the solvent under vacuo, the residue was chromatographed over alumina. Elution with chloroform-ethanol (9:1) mixture, followed by recrystallisation from chloroform-ethanol gave a white solid (154), m. p. 200-202, in 78% yield.

Elemental analysis indicated that the product had a molecular formula of $C_{25}H_{36}N_8O$ (mol. wt. 464) whilst its mass spectrum showed a molecular ion peak at m/e 395. The u. v. spectrum showed λ_{max} at 320 nm (log ε 4. 20) and the i. r. spectrum (in nujol) showed absorptions at 3400, 3100, 1630, 1555, 1500, 1460, 1375, 1190 and 1060 cm^{-1}. The ^{1}H n. m. r. spectrum exhibited absorptions at δ 0. 75 (3H), 0. 85 (3H), 1. 20 (3H), 7. 37 (1H), 8. 25 (2H), 8. 52 (1H), 8. 62 (1H) and 10. 5 (1H).

Similarly the reaction of 2-hydroxymethylene-5α-cholestan-3-one (110) with 4-amino-1, 2, 4-triazole afforded a product (156) in 80% yield which had properties similar to that of (154).

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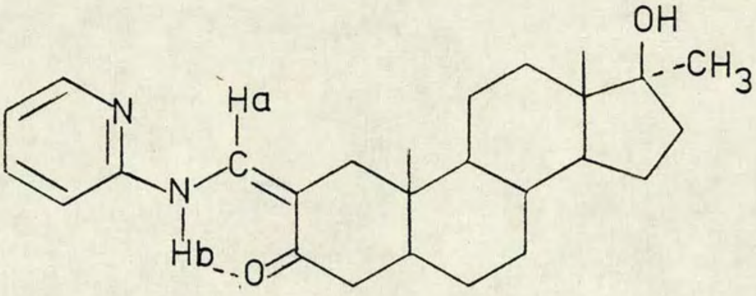
4.2 Discussion

The presence of eight nitrogens in the molecular formula $C_{25}H_{36}N_8O$ indicates that the product (154) arises from the condensation of two moles of 4-amino-1, 2, 4-triazole (83) with each mole of 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108). Condensation of the amino group of the triazole with each of the carbonyl groups in the steroid (108) leads to a bisanil 17β-hydroxy-17α-methyl-2(4N-methyleneamino-1, 2, 4-triazolyl)-3-(4N-amino-1, 2, 4-triazolyl)-5α-androst-2-ene (154). The i. r. spectrum (in nujol) of the steroid (154) exhibits absrptions at 3400 cm^{-1} and 3100 cm^{-1}. The absorption at 3400 cm^{-1} is assigned to the hydroxyl group at position 17. The absorption at 3100 cm^{-1} could not be definitely assigned, though it appears to be a characteristic of the 1, 2, 4-triazole ring system rather than a N-H vibration; 6-methyl-s-triazolo[4, 3-b]pyridazine (157) and 8-methyl-s-triazolo[4, 3-b]pyridazine (158) which contain no NH groups also exhibit a similar absorption at 3130 cm^{-1} (section 9, page 168). The N-H bond in the hydrogen bonded steroid (154) might have been broadened and lowered to around 3000 cm^{-1} where it would be hidden by the C-H bands. The structure (154) is supported by the ^1H n. m. r. spectrum which exhibits signals at δ7. 37 (s, -N=C$\underline{H}$-), δ 8. 25 (s, triazole 2H's), δ 8. 52 and δ 8. 62 (each s, triazole 2H's) and δ10. 50 (s, N$\underline{H}$). The signal at δ10. 50 disappears on addition of deuterated water which indicates that the product (154) has one labile hydrogen. The ^1H n. m. r. spectrum also shows that the bisanil exists preferentially in the form (154) rather than in the form (154a) or (154b). The structure (154a) does not have any hydrogen attached to nitrogen and therefore the bisanil would not be expected to give a signal at δ 10. 5 and the proton



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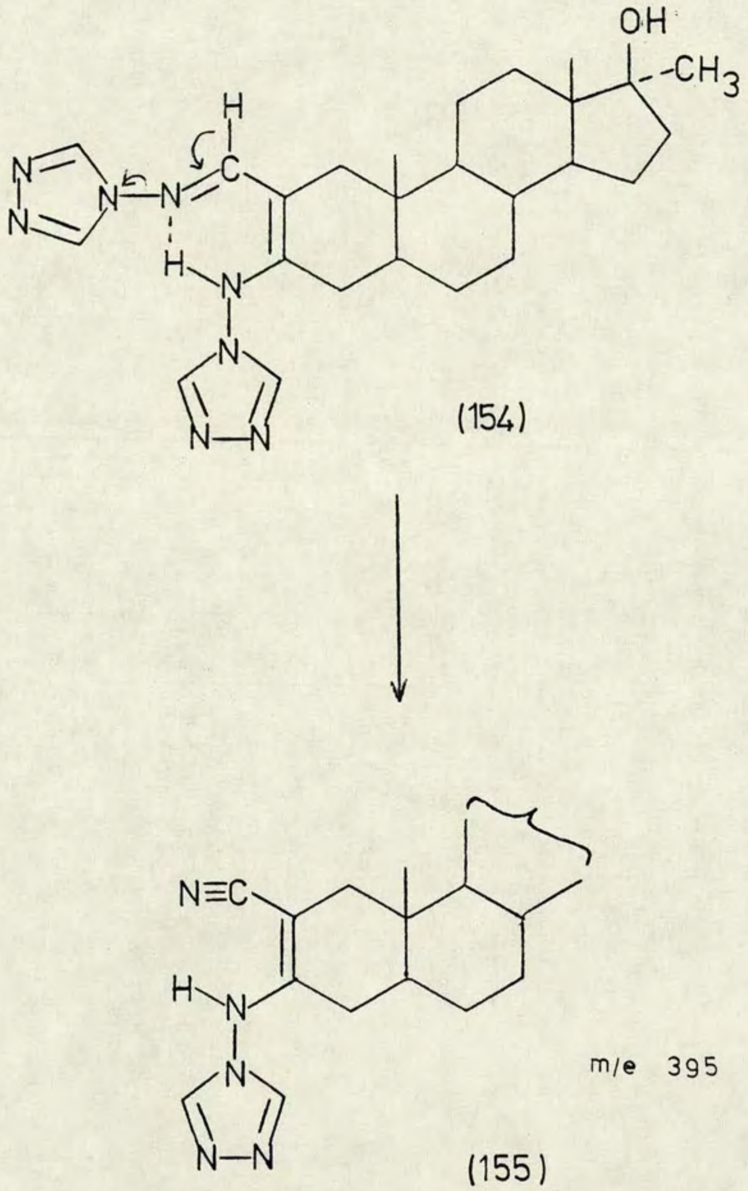


Ha would be expected to give a doublet around δ7.37 because of coupling with the proton at position 2. The structure (154b) would be expected to show two doublets around δ 7.82 and δ11.90 arising from the coupling of the two protons Ha and Hb as Burgess[51] has shown that 17β-hydroxy-17α-methyl-2(2'-pyridyl-aminomethylene)-5α-androstan-3-one (159) exhibits two doublets at δ 7.82 and δ11.88 each with a coupling constant, J = 11.5 Hz, corresponding to protons Ha and Hb respectively.

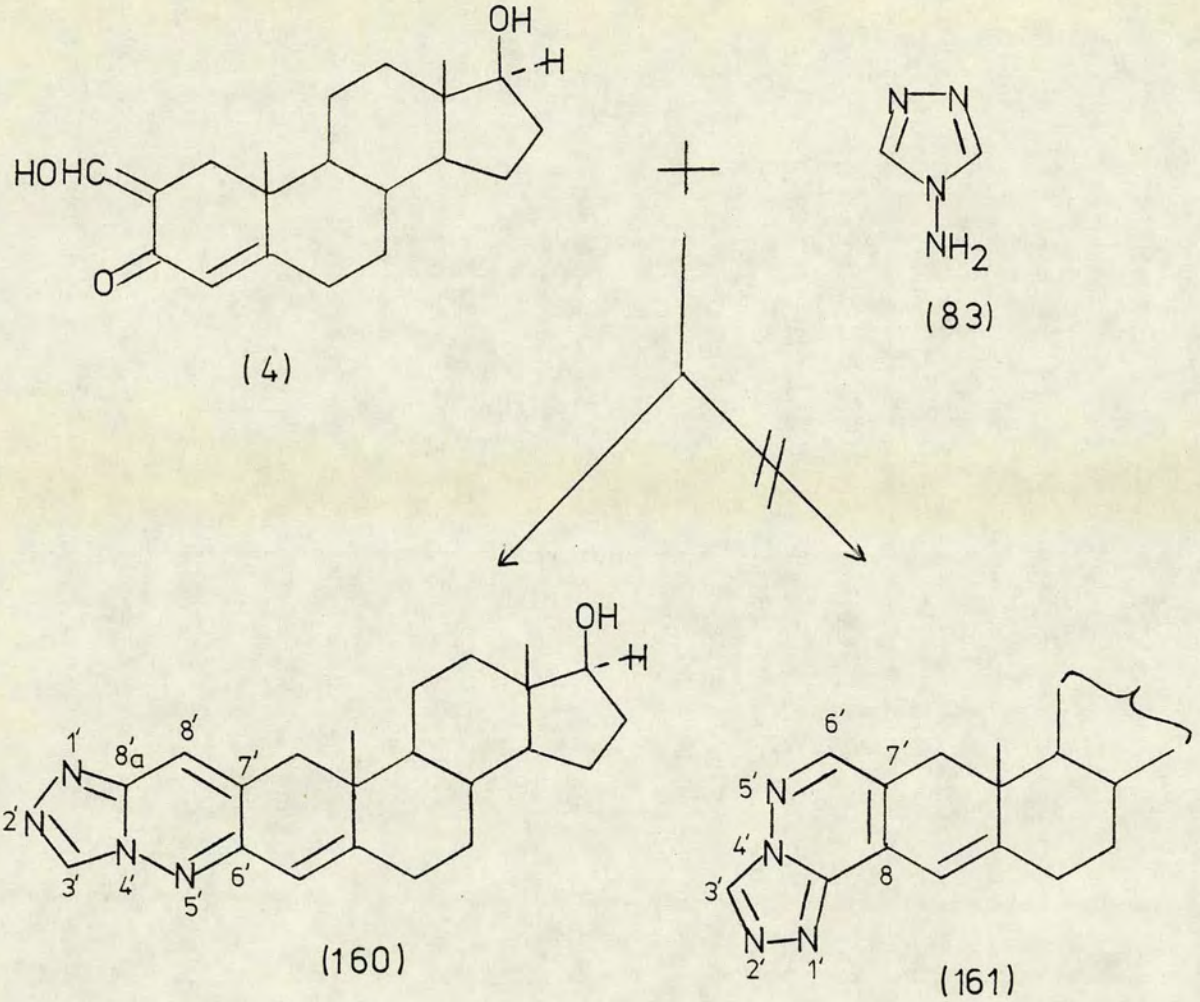
The mass spectrum does not show a peak corresponding to the molecular ion of the steroid (154) but indicates a molecular ion at m/e 395 due to the formation of the nitrile (155) which arises by the loss of a 1,2,4-triazole fragment from the bisanil (154).

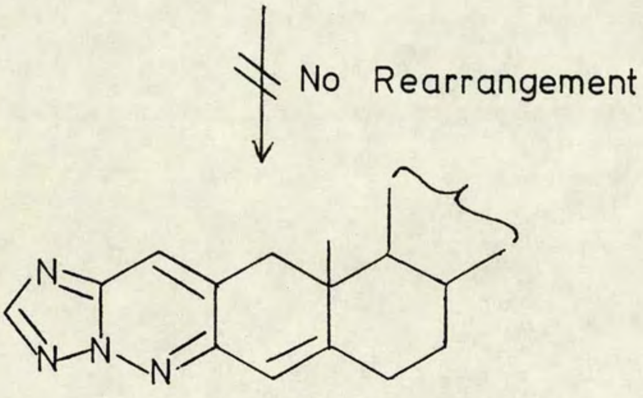
The system of conjugated double bonds extending to the two triazole rings is the longest chromophore in the molecule and can be expected to give the highest λ_{max} at 320 nm in the u.v. spectrum.

All attempts to cyclise the product (154) by heating it either in dimethyl formamide or in xylene for 12 h failed and the starting compound (154) was recovered in good yield.

4.3 The reaction of 17β-hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4) with 4-amino-1,2,4-triazole (83).

A solution of 17β-hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4) and 4-amino-1,2,4-triazole (83) in dry toluene containing a catalytic amount of toluene-4-sulphonic acid was refluxed overnight. The solvent was evaporated and the residue was chromatographed over alumina. Elution with chloroform followed by recrystallisation from ethanol gave





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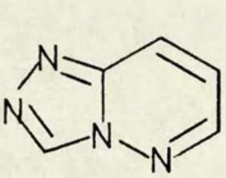

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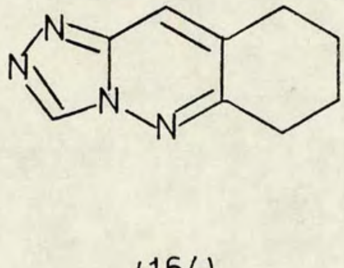

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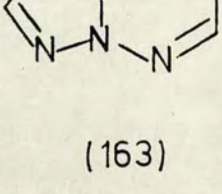

(163)

large yellow crystals (160), m.p. 243-245°, in 37% yield.

Mass spectrometry and elemental analysis showed that the product had a molecular formula of $C_{22}H_{28}N_4O$. The u.v. spectrum showed λ_{max} at 243, 250 and 288 nm (log ϵ 4.40, 4.42 and 3.95).

4.4 Discussion

The i.r. spectrum of the product obtained by the condensation of 4-amino-1,2,4-triazole with 17β-hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4) exhibits absorptions at 3130 (w), 1630, 1615, 1485, 1440 and 1375 cm^{-1} which resemble the absorptions in the i.r. spectra of 6-methyl- and 8-methyl-s-triazolo[4,3-b]pyridazines (157) and (158). Thus the condensation product appears from its i.r. spectrum and molecular formula $C_{22}H_{28}N_4O$ to be a derivative of s-triazolo[4,3-b]-pyridazine (67). In the condensation of 4-amino-1,2,4-triazole (83) with β-dicarbonyl compounds, ambiguity in the identity of the products arises from the two possible reaction sites. Therefore two possible structures (160) and (161) were postulated for the product obtained by the condensation of 4-amino-1,2,4-triazole with the β-ketoaldehyde (4). However, ^1H n.m.r. and ^{13}C n.m.r. spectroscopy show that the condensation product has structure (160).

The ^1H n.m.r. spectrum of the condensation product (160) shows signals at δ 0.85 (s, 18-CH_3), 1.05 (s, 19-CH_3), 3.70 (t, 17-H). 6.27 (s, 4H), 7.70 (s, 8'-H), and 8.90 (s, 3'-H), the assignment of the chemical shifts to 3'-H and 8'-H being based upon the earlier studies of s-triazolo[4,3-b]pyridazines.[129] Of particular interest in ^1H n.m.r.

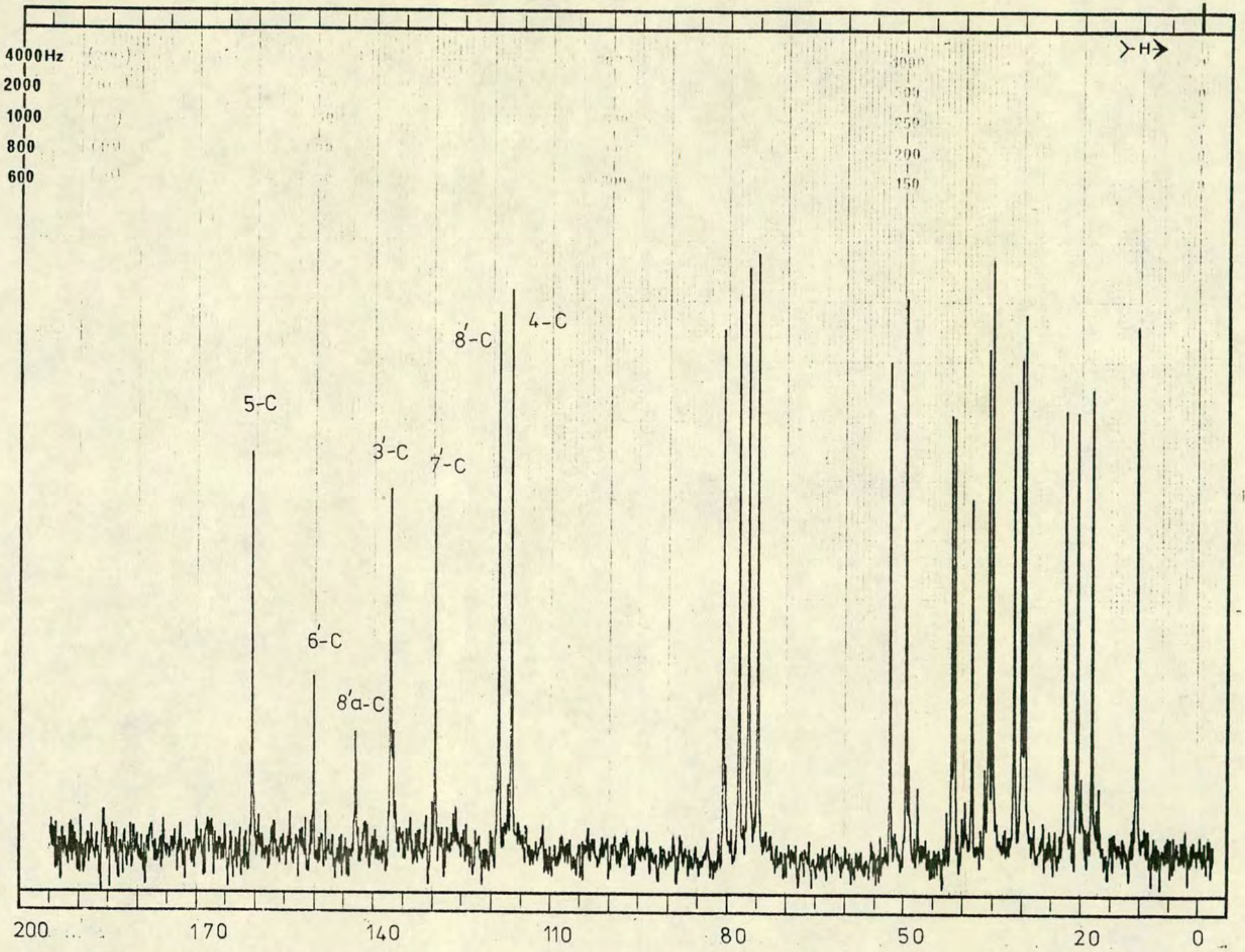

Fig. 1: ^{13}C n. m. r. spectrum of 17β-hydroxyandrost-4-eno[3, 2-f]-s-triazolo-[4, 3-b]pyridazine (160).

spectrum is the fact that the 8'-H singlet is broadened due to a small long range coupling with the 1-C methylene protons. This long range coupling was confirmed by double resonance experiments, irradiation at the frequency of the methylene protons sharpened the broad signal of the 8'-H. Similar long range coupling has been reported in s-triazolo-[4, 3-b]pyridazines[129] where it was observed that the methyl group protons at either positions 8 or 7 of s-triazolo[4, 3-b]pyridazine (67) are coupled with the 7-H or 8-H respectively (J = 1. 2Hz). Coupling between methyl protons at position 7 and the 6-H has not been observed,[129] therefore the alternative structure (161) for the condensation product is discounted since it would be expected to show a sharp singlet for the 6'-H due to the absence of long range coupling.

The structure (160) is also supported by the fact that the chemical shifts, δ 8. 90 and δ 7. 70 of 3'-H and 8'-H respectively in the ^{1}H n. m. r. spectrum of the condensation product (160) are identical with that of 3-H and 10-H in 6,7,8, 9-tetrahydro-s-triazolo[4, 3-b]cinnoline (164)[130] where the fusion of the heterocyclic system with the cyclohexane ring is similar to that in the steroid structure (160). The signal for the 10-H in the ^{1}H n. m. r. spectrum of the compound (164) was also found to be split into a triplet by a small long range coupling with the 9-C methylene protons (J = 1Hz).

The assignment for structure (160) is further supported by the ^{13}C n. m. r. spectrum (Fig. 1). The ^{13}C-chemical shifts of the aromatic ring carbons of the triazolopyridazine (160) are given in the Table 1 along with those of the two model compounds s-triazolo[4, 3-b]pyridazine (67)

Table 1

^{13}C-Chemical shifts of steroidal s-triazolo[4,3-b]pyridazines (p.p.m.)

Compound	3'-C	6'-C	7'-C	8'-C	8'a-C	Other carbons
(67)	139.04	146.57	121.20	124.61	143.31	
(160)	137.95	150.91	130.43	119.58	143.89	4-C, 117.44; 5-C, 161.24
(163)	152.50 (2-C)	144.55	123.04	125.92	144.05	
(170)	137.52	170.58*	138.31	118.68	144.05	C=O, 170.34*
(172)	137.38	170.44*	138.43	118.76	144.25	5-C, 140.14 6-C, 121.49 C=O, 170.14*

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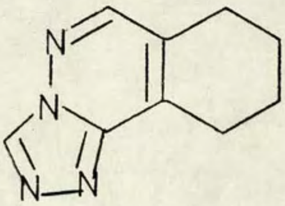
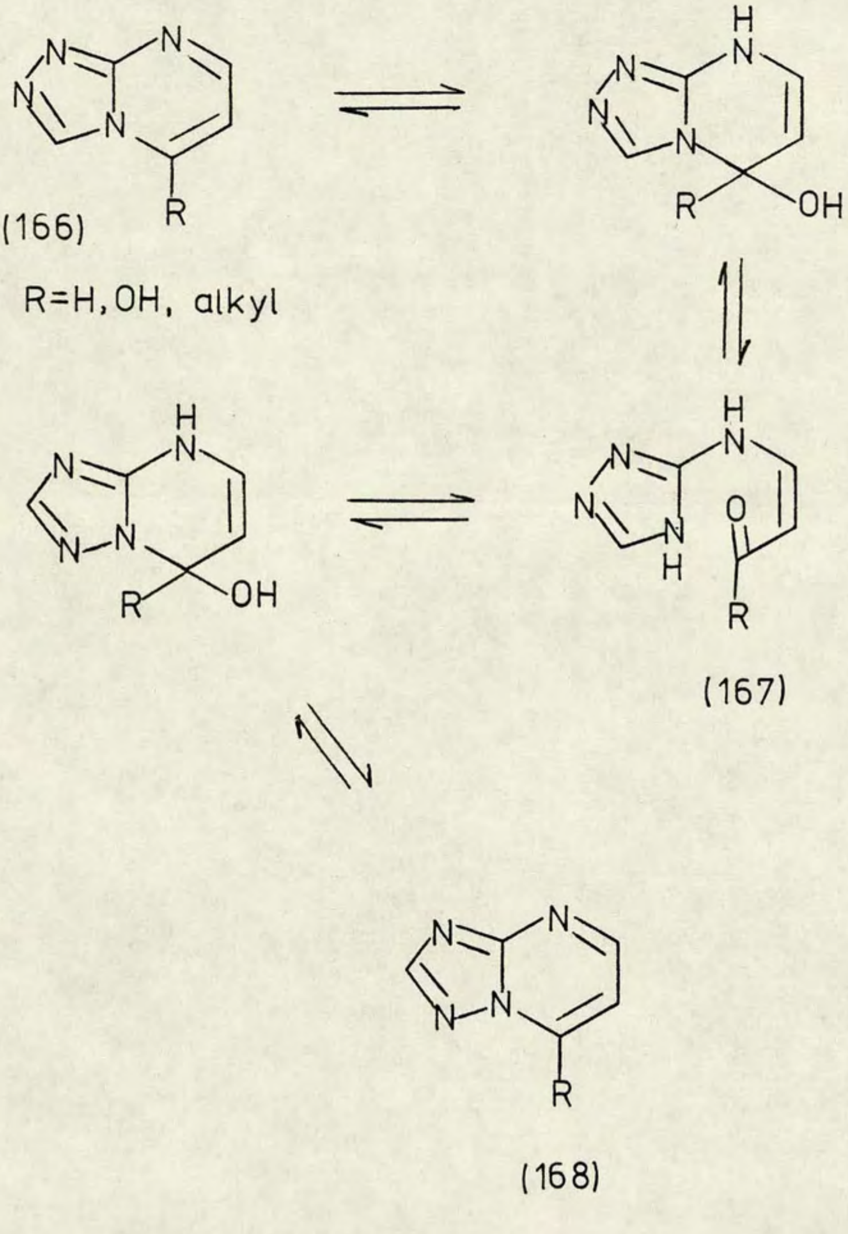
* These values could be interchanged.

and s-triazolo[1, 5-b]pyridazine (163).[131] The assignments quoted for the chemical shifts of the five carbons of the steroid (160) follow directly by analogy with the values allocated to the comparable ring system (67). The chemical shift of 8'-C (119. 58 p. p. m.) in the condensation product (160) is found to be in agreement with the chemical shift of 8-C (124. 61 p. p. m.) in the triazolopyridazine (67) thus confirming a linear fusion of the steroid to the heterocyclic system. If the condensation product had had the angular structure (161) the chemical shift of 6'-C would have been expected to appear in the region of 146. 57 p. p. m. , which is the value assigned to 6-C in the compound (67).

Isomerisation of fused triazoles by acid, base or heat has been reported.[132] However, no such transformation was encountered during the reaction of 4-amino-1, 2, 4-triazole with 17β-hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4) in refluxing toluene (24 h) and indeed the condensation product (160) was recovered unchanged after being heated with either formic acid for 12 h or pyridine for 3 h. The spectroscopic evidence quoted above which shows that the condensation product has structure (160) also excludes the isomeric structure (162). Reimlinger and Pieren[133] as well as Paudler and Helmic[76] have shown that, in a series of triazolopyrimidines, the triazole proton with N-4 of the triazole ring at a ring junction (as in 160) is deshielded in comparison with the triazole proton in the isomeric series with the triazole N-1 at the ring junction (as in 162). If the condensation product had had structure (162), the triazole proton would have had a chemical shift comparable to that of the corresponding proton at 2-C (δ 8. 38) in s-triazolo[1, 5-b]pyridazine (163).[134] The low field triazole proton



(165)



(166)

R=H,OH, alkyl

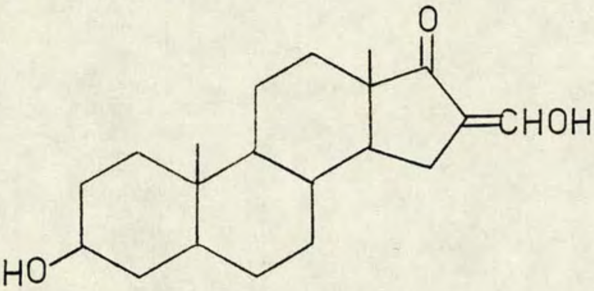
(167)

(168)

in the condensation product is in fact observed at δ 8.90. This corresponds closely to the chemical shift of the proton at 3-C (δ 9.15) in s-triazolo [4,3-b]pyridazine (67),[129] indicating that the structure (160) is correctly written with N-4 of the triazole ring occupying the bridgehead position.

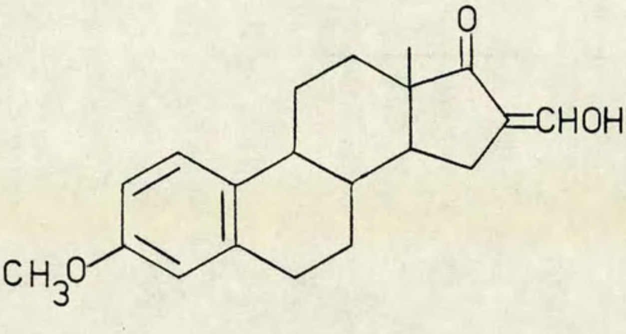
Conclusive support for the structure (160) rather than the isomeric structure (162) again comes from ^{13}C n.m.r. spectroscopy. One major difference between the carbon atom 2 of s-triazolo[1,5-b]pyridazine (163) and the carbon atom 3 of s-triazolo[4,3-b]pyridazine (67) is that 2-C of pyridazine (163) is bonded to two ring nitrogens whereas 3-C of pyridazine (67) is bonded to a ring nitrogen and a bridgehead nitrogen. For nitrogen heterocyclic systems, the carbons bonded to nitrogen atoms are known to be appreciably deshielded relative to benzene while β-carbons are shielded.[135] Nitrogen atoms at bridgehead positions, however have little deshielding effect on the adjacent carbon atoms due to the significant delocalisation of the lone pair of electrons.[136] Thus the chemical shift of 2-C in pyridazine (163) occurs further downfield (152.5 p.p.m.) as compared to the chemical shift of 3-C in pyridazine (67) which occurs at 139.04 p.p.m. In the ^{13}C n.m.r. spectrum of the steroidal triazolopyridazine, the chemical shift of 3'-C is found to be 137.95 p.p.m., consistent with the structure (160).

It has been accepted that the initial step of the base- and acid-catalysed Dimroth-type rearrangements involve an equilibrium-controlled covalent hydration process with the initial addition of $OH^{\ominus}$ at position 7 of the azaindolizine nucleus (166).[80e] This step is followed by a tautomeric ring opening of the 6-membered ring to a carbonyl intermediate analogous to (167). This species then cyclises to the rearranged azaindolizine

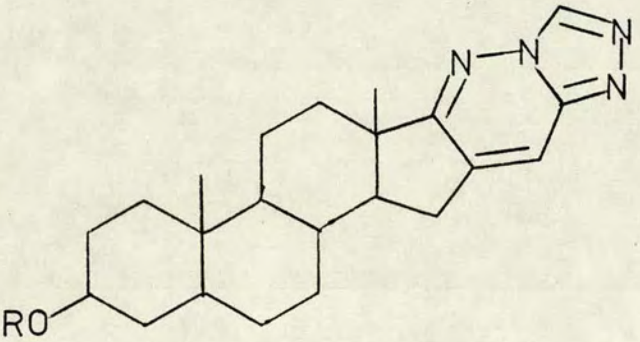


(7)

(8) Δ^5



(9)

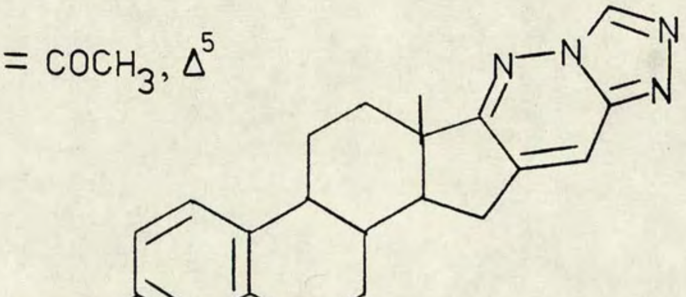


(169) R = H

(170) R = $COCH_3$

(171) R = H, Δ^5

(172) R = $COCH_3$, Δ^5



(173)

(168). Thus it is evident that the rearrangement of azaindolizine (166) to (168) involves the fission of bond 7-8 and this is unlikely to occur if position 7 is occupied by a nitrogen atom. This justifies the stabilities of s-triazolo[4, 3-b]pyridazines[80a] towards acids and bases.

Regardless of the nature of the aminoazole, most of the studies show that the exocyclic amino group of the aminoazole reacts preferentially with an aldehydic rather than a ketonic group.[80c] Obviously this is at variance with the formation of linearly fused product (160) from the reaction of 4-amino-1, 2, 4-triazole with 2-hydroxymethylene-3-oxo steroid (4). The mechanism of this condensation reaction leading to the formation of linearly fused product is discussed in section 10.

4.5 The reaction of 3β-hydroxy-16-hydroxymethylene-5α-androstan-17-one (7) and 4-amino-1, 2, 4-triazole (83).

A solution of 3β-hydroxy-16-hydroxymethylene-5α-androstan-17-one (7) and 4-amino-1, 2, 4-triazole (83) in dry toluene containing a catalytic amount of toluene-4-sulphonic acid was refluxed overnight. The solvent was evaporated in vacuo and the residue was chromatographed over alumina. Elution with chloroform followed by recrystallisation of the eluate from acetone gave white needles (169), m. p. 287-289°(dec), in 78% yield.

Mass spectrometry and elemental analysis indicated that the product had a molecular formula of $C_{22}H_{30}N_4O$. The u. v. spectrum showed λ_{max} 215 and 291 nm (log ε 427 and 396), whilst the i. r. spectrum showed absorptions at 3590, 1515, 1415 and 1375 cm^{-1}. The ^1H n. m. r. spectrum exhibited signals at δ7.80 and δ 8.95 in addition to the signals corresponding to the 18- and 19-methyl protons and the proton at 3-C.

4.6 Discussion

The i. r. and u. v. spectra of the condensation product do not correlate well with the i. r. and u. v. spectra of 17β-hydroxyandrost-4-eno[3, 2-f]-s-triazolo[4, 3-b]pyridazine (160) to be of any use in determining the structure of the condensation product. This is probably because of the presence of Δ^4 double bond which is conjugated with the aromatic system in the compound (160). However, the signals at δ 8.95 and δ 7.80 in the ^{1}H n. m. r. spectrum of the condensation product correlate very well with the signals for 3'-H (δ 8.90) and 8'-H (δ 7.80) in the ^{1}H n. m. r. spectrum of 17β-hydroxyandrost-4-eno[3, 2-f]-s-triazolo[4, 3-b]pyridazine (160). The signal at δ 7.80 is also found to be broadened by coupling with 15-C methylene protons.

Therefore on the basis of ^{1}H n. m. r. spectrum, the condensation product is formulated as 3β-hydroxy-5α-androstano[17, 16-f]-s-triazolo[4, 3-b]pyridazine (169). The structure is supported by ^{13}C n. m. r. spectroscopy. The condensation product (169), was not sufficiently soluble in deuterated chloroform to permit its ^{13}C n. m. r. spectrum to be obtained. However, in the ^{13}C n. m. r. spectrum of its acetyl derivative (170), the chemical shift of 8'-C (118. 68 p. p. m.) is found to be in agreement with the chemical shift of 8'-C (119. 58 p. p. m.) in the compound (160), thus confirming the linear fusion of the heterocyclic system to the steroid.

Under analogous conditions, the reaction of 4-amino-1, 2, 4-

triazole with 3-β-hydroxy-16-hydroxymethyleneandrost-5-en-17-one (8) and 16-hydroxymethylene-3-methoxyoestra-1, 3, 5(10)-trien-17-one (9) gave 3β-hydroxyandrost-5-eno[17, 16-f]-s-triazolo[4, 3-b]pyridazine (171) and 3-methoxyoestra-1, 3, 5(10)-trieno[17, 16-f]-s-triazolo[4, 3-b]pyridazine (173) respectively. Acetylation of the sterols (169) and (171) gave the corresponding acetyl derivatives (170) and (172).

The reaction mechanism of these condensation reactions leading to the formation of linearly fused products will be discussed in section 10.

It is interesting to note that the type of the product(s) formed is very much dependent upon the β-dicarbonyl compound employed in the reaction. For example the reaction of 4-amino-1, 2, 4-triazole with (i) 2-hydroxymethylenecyclohexanone gives a mixture of two products, 6, 7, 8, 9-tetrahydro-s-triazolo[4, 3-b]cinnoline (164) and 7, 8, 9, 10-tetrahydro-s-triazolo[3, 4-a]phthalazine (165) (section 9), (ii) 2-hydroxymethylene-3-oxo steroids (108) and (110) without a Δ^4 double bond gives the bisanils (154) and (156) respectively, (iii) 2-hydroxymethylene-3-oxo steroid (4) with Δ^4 double bond and 16-hydroxymethylene-17-oxo steroids (7), (8) and (9) gives the linearly fused products (160), (169), (171) and (173) respectively.

4.7 Experimental

General procedure for the condensation reaction.

A solution of the steroidal β-ketoaldehyde (1×10^{-3} mole), 4-amino-1, 2, 4-triazole (1.5×10^{-3} mole) and toluene-4-sulphonic acid (20 mg) in dry toluene (30 ml) was refluxed overnight. The reaction mixture was evaporated to dryness, the residue chromatographed over alumina (50 g) using either chloroform or 10% ethanol in chloroform as the eluant and the product was recrystallised from a suitable solvent.

For the synthesis of the compounds (154) and (156) an excess of 4-amino-1, 2, 4-triazole (2.3×10^{-3} mole) was used.

4.7 i 17β-Hydroxy-17α-methyl-2-(4N-aminomethylene-1, 2, 4-triazolyl)-3-(4N-amino-1, 2, 4-triazolyl)-5α-androst-2-ene (154).

Starting β-ketoaldehyde: 17β-Hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108).

General: Alumina chromatography (eluant 10% methanol in chloroform) followed by recrystallisation from methanol-benzene gave 17β-hydroxy-17α-methyl-2(4N-aminomethylene-1, 2, 4-triazolyl)-3-(4N-amino-1, 2, 4-triazolyl)-5α-androst-2-ene (154) (78%), m. p. 200-202°, m. s., m/e 395 (M^+ -69); u. v. λ_{max} 208 and 320 nm (log ε 3.95 and 4.20); i. r. (nujol), γ_{max} 3400 (OH), 3100 (NH), 1630, 1555, 1500, 1460, 1375, 1190 and 1060 cm^{-1}; ^1H n. m. r. (60 MHz), δ 0.75 (s, 3H, 18-CH_3), 0.85 (s, 3H, 19-CH_3), 1.20 (s, 3H, 17-CH_3), 7.37 (s, 1H, -N=C<u>H</u>-), 8.25 (s, triazole 2 H's), 8.52 and 8.62 (each s, triazole 2 H's) and 10.5 (s, N<u>H</u>, exchanges with D_2O) (Found: C, 64.28; H, 7.56; N, 23.95. $C_{25}H_{36}N_8O$ requires C, 64.65; H, 7.76; N, 24.13%).

4.7 ii The attempted cyclisation of 17β-hydroxy-17α-methyl-2(4N-methyleneamino-1, 2, 4-triazolyl)-3-(4N-amino-1, 2, 4-triazolyl)-5α-androst-2-ene (154).

(a) A suspension of 17β-hydroxy-17α-methyl-2(4N-methyleneamino-1, 2, 4-triazolyl)-3-(4N-amino-1, 2, 4-triazolyl)-5α-androst-2-ene (154) (0.425 g, 1×10^{-3} mole) and toluene-4-sulphonic acid (20 mg) in xylene (30 ml) was refluxed for 12 h. The excess of xylene was removed under vacuo and the residue was purified by chromatography over alumina using 10% ethanol in chloroform as the eluant. Recrystallisation of the eluate from chloroform-ethanol gave a white solid (275 mg, 65%) which was found to be the starting compound (154) by its ^{1}H n.m.r. spectrum.

(b) The above reaction was repeated using dimethyl formamide as the solvent. Again the starting compound (154) was recovered in 58% yield.

4.7 iii 2-(4N-Aminomethylene-1, 2, 4-triazolyl)-3-(4N-amino-1, 2, 4-triazolyl)-5α-cholest-2-ene (156).

Starting β-ketoaldehyde: 2-Hydroxymethylene-5α-cholestan-3-one (110).

General: Alumina chromatography (eluant 10% methanol in chloroform) followed by recrystallisation from ethanol-chloroform gave white crystals of 2-(4N-aminomethylene-1, 2, 4-triazolyl)-3-(4N-amino-1, 2, 4-triazolyl)-5α-cholest-2-ene (156) (80%), m. p. 243-245° (dec.); m. s., m/e 477 (M^+ -69); u. v., λ_{max} 207 and 321 (log ε 4.01 and 4.21); i. r. (nujol), γ_{max} 3110 (NH), 1630, 1570, 1460, 1380 and 1060 cm^{-1}. (Found: C, 69.63; H, 9.18; N, 20.14. $C_{32}H_{50}N_8$ requires C, 70.28; H, 9.22; N, 20.50%).

4.7 iv 17β-Hydroxyandrost-4-eno[3, 2-f]-s-triazolo[4, 3-b]pyridazine (160).

Starting β-ketoaldehyde: 17β-Hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4).

General: Alumina Chromatography (eluant chloroform) followed by recrystallisation from ethanol afforded yellow crystals of 17β-hydroxyandrost-4-eno[3, 2-f]-s-triazolo[4, 3-b]pyridazine (160) (37%), m. p. 243-245°; u. v., λ_{max} 243, 250 and 288 nm (log ε 4.40, 4.42 and 3.95); i. r., γ_{max} 3590 (OH), 1630, 1615, 1485, 1440 and 1375 cm^{-1}; ^{1}H n. m. r. (100 MHz), δ 0.85 (s, 3H, 18-CH_3), 1.05 (s, 3H, 19-CH_3), 3.70 (t, 1H, 17-H), 6.27 (s, 1H, 4-H), 7.70 (s, 1H, 8'-H), and 8.90 (s, 1H, 3'-H) (Found: C, 72.25; H, 7.82; N, 14.95; M^+, 364.2257. $C_{22}H_{28}N_4O$ requires C, 72.48; H, 7.68; N, 15.37%; M, 364.22600).

4.7 v 3β-Hydroxy-5α-androstano[17, 16-f]-s-triazolo[4, 3-b]pyridazine (169).

Starting β-ketoaldehyde: 3β-Hydroxy-16-hydroxymethylene-5α-androstan-17-one (7).

General: Alumina chromatography (eluant chloroform) followed by recrystallisation from acetone gave white needles of 3β-hydroxy-5α-androstano[17, 16-f]-s-triazolo[4, 3-b]pyridazine (169) (78%), m.p. 287-289° (dec.); u.v., λ_{max} 215 and 291 nm (log ε 4.27 and 3.56); i.r., γ_{max} 3590 (OH), 1515, 1415 and 1375 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.90 (s, 3H, 18-CH_3), 1.10 (s, 3H, 19-CH_3), 3.60 (m, 1H, 3-H), 7.80 (s, 1H, 8'-H) and 8.95 (s, 1H, 3'-H) (Found: C, 71.85; H; 8.30; N, 15.19; M^{+}, 366.241198. $C_{22}H_{30}N_4O$ requires C, 70.08; H, 8.25; N, 15.30%; M, 366.241949).

4.7 vi 3β-Hydroxyandrost-5-eno[17, 16-f]-s-triazolo[4, 3-b]pyridazine (171).

Starting β-ketoaldehyde: 3β-Hydroxy-16-hydroxymethyleneandrost-5-en-17-one (8).

General: Alumina chromatography (eluant chloroform) followed by recrystallisation from ethanol gave white needles of 3β-hydroxyandrost-5-eno[17, 16-f]-s-triazolo[4, 3-b]pyridazine (171) (83%), m.p. 245-247°; u.v., λ_{max} 215 and 291 nm (log ε 4.28 and 3.50); i.r., γ_{max} 3590 (OH), 1510, 1450, 1430 and 1375 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 1.07 (s, 3H, 18-CH_3), 1.10 (s, 3H, 19-CH_3), 3.55 (m, 1H, 3H), 5.40 (t, 1H, 6-H), 7.80 (s, 1H, 8'-H) and 8.90 (s, 1H, 3'-H) (Found: C, 72.25; H, 7.70; N, 14.99; M^{+}, 364.224701. $C_{22}H_{28}N_4O$ requires C, 72.48; H, 7.75; N, 15.38%; M, 364.226300).

4.7 vii 3-Methoxyoestra-1, 3, 5(10)-trieno[17, 16-f]-s-triazolo(4, 3-b]pyridazine (173).

Starting β-ketoaldehyde: 16-Hydroxymethylene-3-methoxyoestra-1, 3, 5(10)-trien-17-one (9).

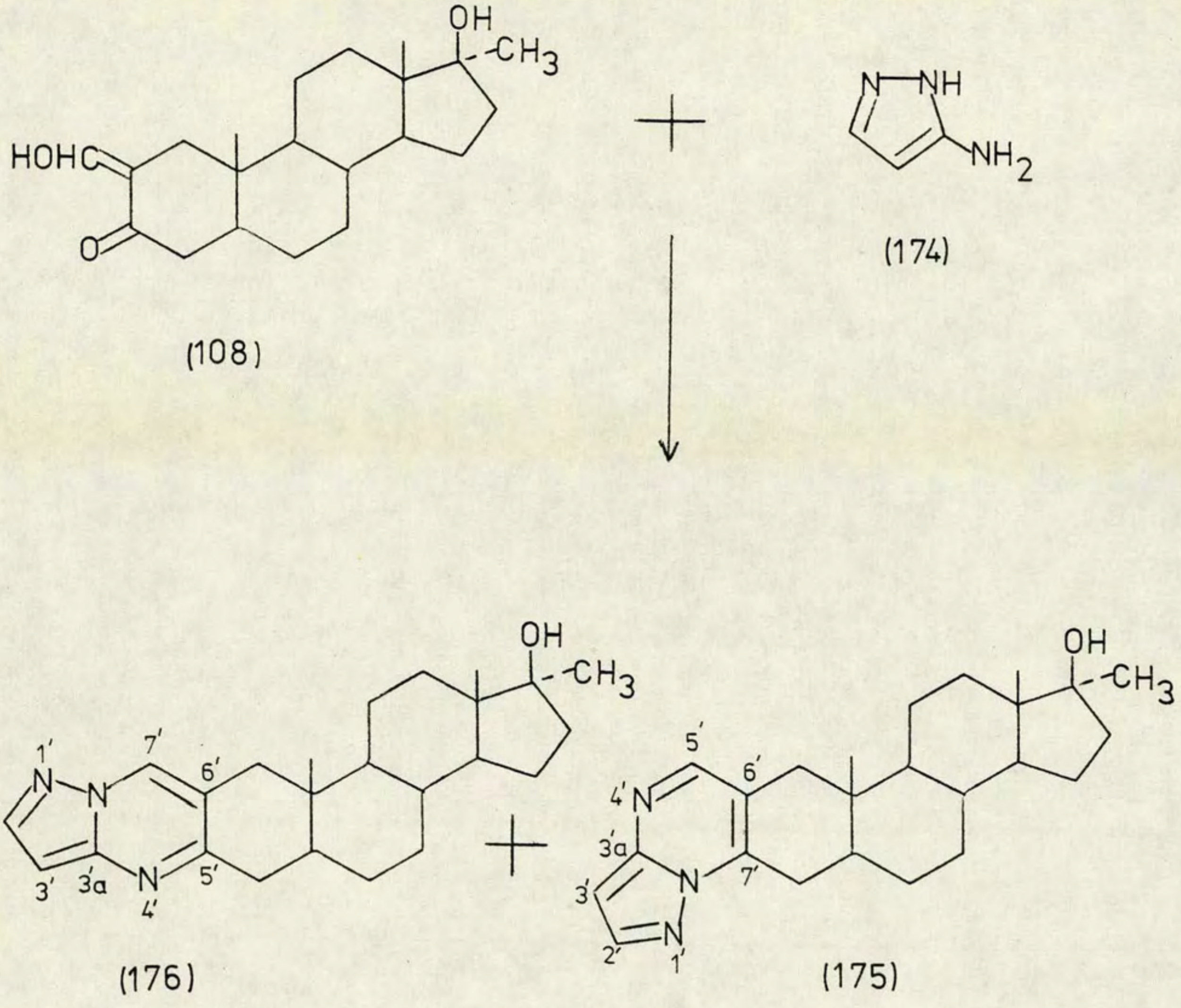
General: Alumina chromatography (eluant chloroform) followed by recrystallisation from ethanol gave white needles of 3-methoxyoestra-1,3,5(10)-trieno[17,16-f]-s-triazolo[4,3-b]pyridazine (173) (85%). m.p. 232-234°; i.r., γ_{max} 1605, 1500, 1450 and 1375 cm^{-1}; ^1H n.m.r. (100 MHz), δ 1.15 (s, 3H, 18-CH_3), 3.80 (s, 3H, 3-OCH_3), 6.57 - 7.30 (3H, 1-H, 2-H, 4-H), 7.80 (s, 1H, 8'-H) and 8.90 (s, 1H, 3'-H) (Found: C, 73.58; H, 6.65; N, 15.21; M^+, 360.193466. $C_{22}H_{24}N_4O$ requires C, 73.29; H, 6.76; N, 15.55%; M, 360.195001).

4.7 viii 3β-Acetoxy-5α-androstano[17,16-f]-s-triazolo[4,3-b]pyridazine (170).

A solution of 3β-hydroxy-5α-androstano[17,16-f]-2-triazolo-[4,3-b]pyridazine (169) (0.200 g, 5.14 x 10^{-4} mole) in dry pyridine (20 ml) containing a few drops of acetic anhydride was refluxed for 2 h. The solution was evaporated to dryness in vacuo. The residue was taken up in chloroform, washed with 5% hydrochloric acid solution, water and finally with saturated sodium chloride solution. The chloroform solution was dried over anhydrous magnesium sulphate, evaporated to dryness in vacuo and the residue was recrystallised from ethanol to give 3β-acetoxy-5α-androstano[17,16-f]-s-triazolo[4,3-b]pyridazine (170) (0.136 g, 61%), m.p. 311-313° (dec.); u.v., λ_{max} 214 and 293 nm (log ε 4.28 and 2.50); i.r., γ_{max} 1715 (CO), 1515, 1445 and 1350-1365 cm^{-1}; ^1H n.m.r. (100 MHz), δ 0.92 (s, 3H, 18-CH_3), 1.10 (s, 3H, 19-CH_3), 2.02 (s, 3H, 3-$OCOCH_3$), 4.70 (m, 1H, 3-H), 7.80 (s, 1H, 8'-H) and 9.00 (s, 1H, 3'-H) (Found: C, 70.46; H, 7.87; N, 13.50; M^+, 408.251875. $C_{24}H_{32}N_4O$ requires C, 70.54; H, 7.83; N, 13.71%; M, 408.252512).

4.7 ix 3β-Acetoxyandrost-5-eno[17,16-f]-s-triazolo[4,3-b]pyridazine (172).

Treatment of 3β-hydroxyandrost-5-eno[17,16-f]-s-triazolo-[4,3-b]pyridazine (170) (0.200 g, 5.4×10^{-4} mole) in the above described manner, followed by recrystallisation from methanol gave white needles of 3β-acetoxyandrost-5-eno[17,16-f]-s-triazolo[4,3-b]pyridazine (172) (67%), m.p. 293-295; i.r., γ_{max} 1720 (CO), 1510, 1450, 1430 and 1375 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 1.15 (s, 6H, 18-CH_3 and 19-CH_3), 2.07 (s, 3H, 3-$OCOCH_3$), 4.65 (m, 1H, 3-H), 5.50 (t, 1H, 6-H), 7.85 (s, 1H, 8'-H) and 9.00 (s, 1H, 3'-H) (Found: C, 70.02; H, 7.30; N, 13.35; M^+, 346 (M-60). $C_{24}H_{30}N_4O$ requires C, 70.93; H, 7.38; N, 13.79%; M, 406).



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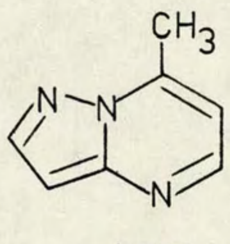

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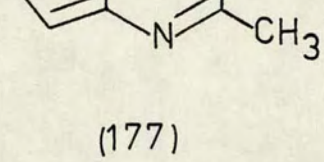

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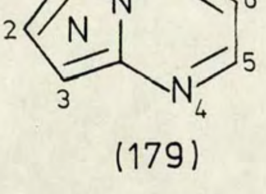


(179)

5 The reaction of steroidal β-ketoaldehydes with 3-aminopyrazole and its derivatives

5. 1 The reaction of 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108) and 3-aminopyrazole (174).

A solution of 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108) and 3-aminopyrazole (174) in absolute alcohol was refluxed overnight. The excess of solvent was removed under vacuo and the residue was chromatographed over alumina. Elution with ethyl acetate-ether (7:3) gave, in order of elution two products (175), m. p. 222-224° (34%) and (176), m. p. 186-188° (27%), both recrystallised from ethanol.

Mass spectrometry and elemental analysis indicated that both the products (175) and (176) had the same molecular formula $C_{24}H_{33}N_3O$.

The u. v. spectrum of the product (175) showed λ_{max} at 232 and 317 nm (log ε 4. 60 and 3. 40) whilst the i. r. spectrum showed absorptions at 3590, 1620, 1530, 1445, 925 and 770 cm^{-1}. The ^1H n. m. r. spectrum exhibited, in addition to the signals for 17-, 18- and 19-methyl protons, a singlet at δ 8. 15 and doublets at δ 6. 60 and δ 8. 0, each with spin coupling constant, J = 2 Hz.

The u. v. spectrum of the product (176) showed λ_{max} at 209, 235, 238 and 287 nm (log ε 4. 41, 4. 66, 4. 66 and 3. 27) whilst its i. r. spectrum exhibited absorptions at 3590, 1625, 1530, 1500, 1440, 1405, 925 and 765 cm^{-1}. The ^1H n. m. r. spectrum showed, in addition to the signals for three methyl groups, a singlet at δ 8.32 and doublets at δ 6.46 and δ 7.95 each with spin coupling constant, J = 2 Hz.

5.2 Discussion

In the condensation of 3-aminopyrazole (174), as in the condensation of 4-amino-1,2,4-triazole (83) (section 4), with unsymmetrical β-dicarbonyl compounds, ambiguity in the identity of the products results from the two possible reaction sites. The i.r. spectra of the two condensation products obtained by the reaction of 3-aminopyrazole (174) and 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108) show no carbonyl absorption. Therefore on the basis of the i.r. spectra and the molecular formula $C_{24}H_{33}N_3O$, the two condensation products were expected to be 17β-hydroxy-17α-methyl-5α-androst-2-eno[2,3-g]-pyrazolo[1,5-a]pyrimidine (175) and 17β-hydroxy-17α-methyl-5α-androstano-[3,2-f]pyrazolo[1,5-a]pyrimidine (176). Definite assignment of these structures can be made by comparison of the i.r., u.v., ^{1}H n.m.r. and ^{13}C n.m.r. spectra of the two products (175) and (176) with those of 5-methylpyrazolo[1,5-a]pyrimidine (177) and 7-methylpyrazolo[1,5-a]-pyrimidine (178), whose preparation and structure are reported in section 9 (page 167).

The i.r. spectrum of 5-methylpyrazolo[1,5-a]pyrimidine (177) is found to correlate well with that of isomer (176) whilst the i.r. spectrum of 7-methylpyrazolo[1,5-a]pyrimidine (178) correlates well with that of isomer (175). Of particular interest, in the i.r. spectra of these compounds is the region 1500-1630 cm^{-1}. The compounds (176) and 5-methylpyrazolo[1,5-a]pyrimidine (177) differ from the compounds (175)

Table 2

Characteristic i.r. absorption frequencies (cm^{-1})

Compound	γ_{max} (cm^{-1})	Compound	γ_{max} (cm^{-1})
(175)	$\left.\begin{matrix}1620\\1530\end{matrix}\right\}$ s	(176)	$\left.\begin{matrix}1625\\1525\\1500\end{matrix}\right\}$ s
(178)	$\left.\begin{matrix}1610\\1540\end{matrix}\right\}$ s	(177)	$\left.\begin{matrix}1625\\1535\\1505\end{matrix}\right\}$ s
(189)	$\left.\begin{matrix}1625\\1535\end{matrix}\right\}$ s		
(192)	$\left.\begin{matrix}1630\\1520\end{matrix}\right\}$ s		

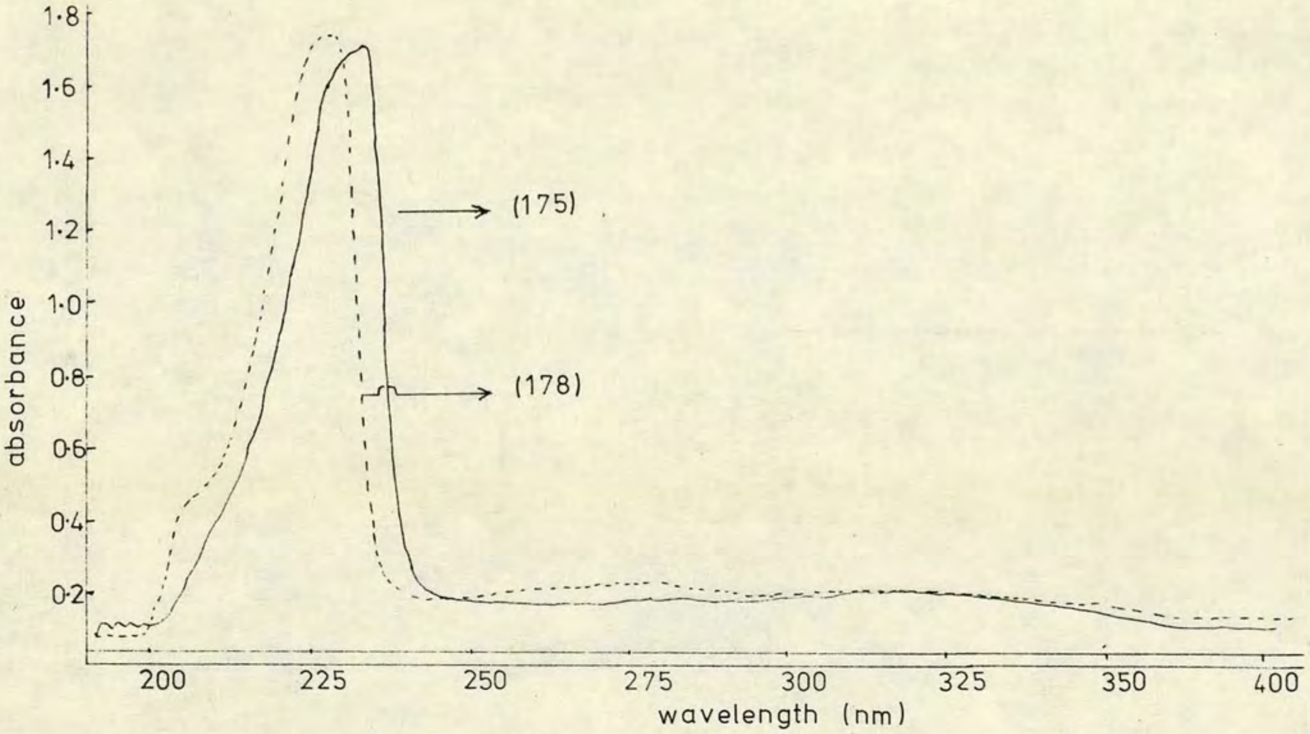


Fig. 2: u. v. Spectra of 17β-hydroxy-17α-methyl-5α-androst-2-eno-[2, 3-g]pyrazolo[1, 5-a]pyrimidine (175) and 7-methylpyrazolo-[1, 5-a]pyrimidine (178).

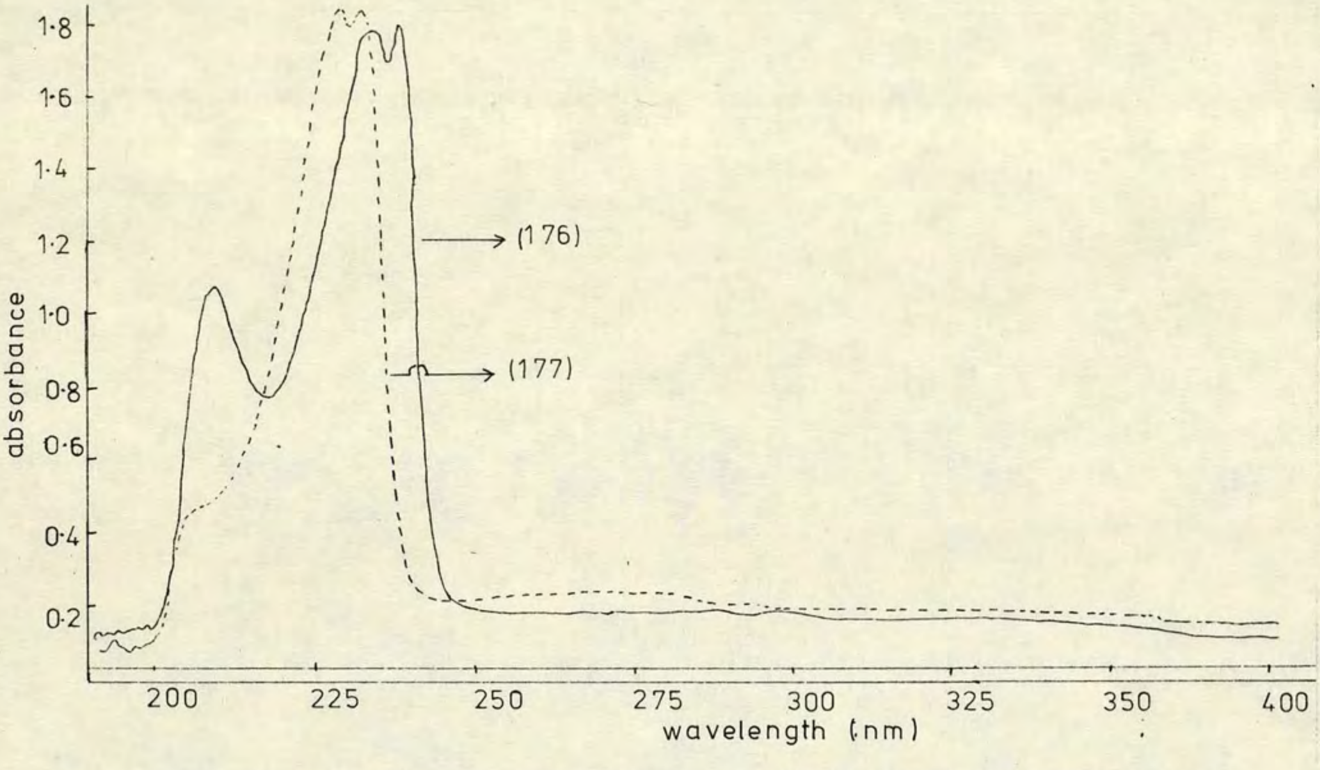


Fig. 3: u. v. Spectra of 17β-hydroxy-17α-methyl-5α-androstano-[3, 2-f]pyrazolo[1, 5-a]pyrimidine (176) and 5-methylpyrazolo[1, 5-a]pyrimidine (177).

and 7-methylpyrazolo[1,5-a]pyrimidine (178) in showing an extra absorption in the region 1500-1505 cm^{-1} (Table 2). Thus it is inferred from the i. r. spectra that the two products with m. p. 222-224° and 186-188° are 17β-hydroxy-17α-methyl-5α-androst-2-eno[2,3-g]pyrazolo[1,5-a]pyrimidine (175) and 17β-hydroxy-17α-methyl-5α-androstano[3,2-f]-pyrazolo[1,5-a]pyrimidine (176) respectively.

The two products (175) and (176) are also distinguished from their u. v. spectra. The u. v. spectra of the pyrazolopyrimidine (175) and 7-methylpyrazolo[1,5-a]pyrimidine (178) are found to show similar absorptions (Fig. 2), in contrast to the u. v. spectra of the steroid (176) and 5-methylpyrazolo[1,5-a]pyrimidine (177) which also show similar absorptions (Fig. 3). The compounds (176) and (177) differ from the compounds (175) and (178) in exhibiting an extra λ_{max} in the region 228-238 nm.

Assignment of these structures is further supported by ^1H n. m. r. spectroscopy. The ^1H n. m. r. spectrum of 17β-hydroxy-17α-methyl-5α-androst-2-eno[2,3-g]pyrazolo[1,5-a]pyrimidine (175) shows signals at δ 0.82 (s, 18-CH_3), 0.90 (s, 19-CH_3), 1.25 (s, 17-CH_3), 6.60 (d, J = 2Hz, 3'-H), 8.00 (d, 2'-H) and 8.15 (s, 5'-H) whilst the ^1H n. m. r. spectrum of 17β-hydroxy-17α-methyl-5α-androstano[3,2-f]pyrazolo-[1,5-a]pyrimidine (176) shows signals at δ 0.85 (s, 18-CH_3), 0.92 (s, 19-CH_3), 1.25 (s, 17-CH_3), 6.50 (d, J = 2Hz, 3'-H), 8.0 (d, 2'-H) and 8.37 (s, 7'-H). A number of authors have attempted to show that for related nitrogen heterocycles an empirical correlation exists between the chemical shifts and the electron densities. However, it has been pointed out that the observed chemical shifts are not a very reliable

Table 3

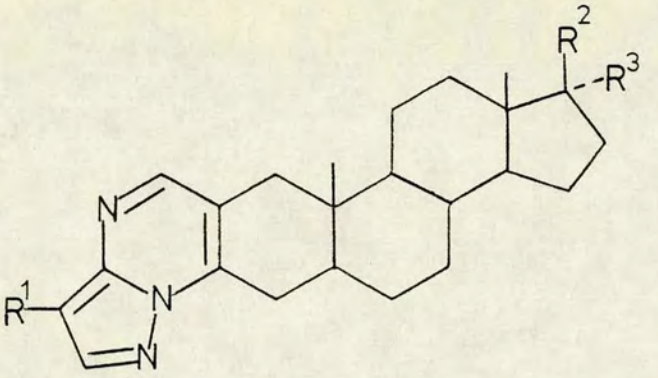
^{13}C-Chemical shifts of steroidal pyrazolo[1,5-a]pyrimidines (p.p.m.)

Compound	2'-C	3'-C	3'a-C	5'-C	6'-C	7'-C	Other Carbons
(175)	143.68	96.68	147.70	150.85	115.62	142.96	
(176)	144.48	94.73	147.61	158.98	117.38	133.10	
(177)	145.01	95.68	148.30	158.90	108.74	134.43	
(178)	144.39	96.97	148.91	148.91	107.42	146.13	
(184)	146.53	82.67	148.89	154.28	119.10	145.17	CN, 112.99
(185)	147.19	80.85	148.73	163.94	120.66	134.14	CN, 113.18
(189)	149.11	82.12	149.20	154.62	119.71	145.24	CN, 114.43 CH_2CN, 111.63
(191)	143.98	96.08	148.83	149.00	110.48	149.00	4-C, 110.73; 5-C, 162.33
(203)	144.71	96.04	149.38	147.06	120.06	157.01	C=O, 170.54

measure of π-electron density. Nevertheless, available spectral evidence from related azoloazines with bridgehead nitrogen,[77, 129, 137-139] postulate higher δ value for the proton at position 7' in the steroid (176) compared with the δ value for the proton at position 5' in the steroid (175). The chemical shift of 7'-H (δ 8. 37) in the steroid (176) is obviously higher than the chemical shift of 5'-H (δ 8. 15) in the steroid (175) and this further supports the structural assignment of the two compounds (175) and (176).

The most striking difference in the ^{1}H n. m. r. spectra of the compounds (175) and (176) is the fact that the signal of 7'-H of the compound (176) is broadened due to a small long range coupling with the protons at 1-C whereas 5'-H of the compound (175) gives a sharp signal because of the absence of any long range coupling. This long range coupling between 1-C protons and the 7'-H in the compound (176) possibly arises because of the higher bond order of the 6'-7' bond[80d] and was confirmed by double resonance experiments. Irradiation at the frequency of 1-C protons sharpened the signal of 7'-H. Similar long range coupling has been reported[77] in azolo[a]pyrimidines (179) where it was observed that the methyl group protons at either positions 6 or 7 are coupled with the 7-H or 6-H respectively (J = 1Hz). Coupling between the methyl protons at position 5 and the 6-H has not been observed.[77]

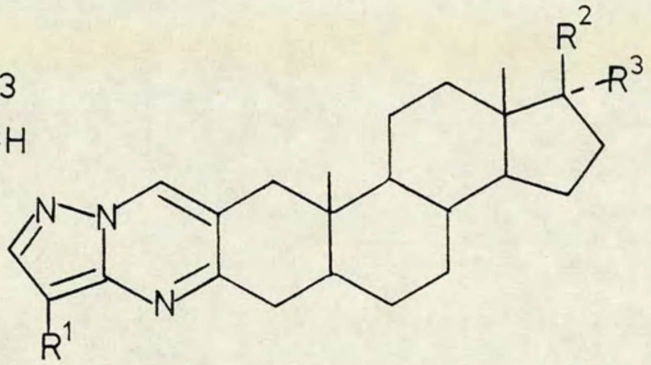
The assignments for structures (175) and (176) are also confirmed by ^{13}C n. m. r. evidence. The ^{13}C-chemical shifts of the aromatic ring carbons of the pyrazolopyrimidines (175) and (176) are given in the Table 3. The assignments quoted for the chemical shifts of the five carbons of the steroids (175) and (176) follow directly by analogy with



(180) R^1=H, R^2=C_8H_{17}, R^3=H

(184) R^1=CN, R^2=OH, R^3=CH_3

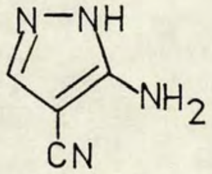
(186) R^1=CN, R^2=C_8H_{17}, R^3=H



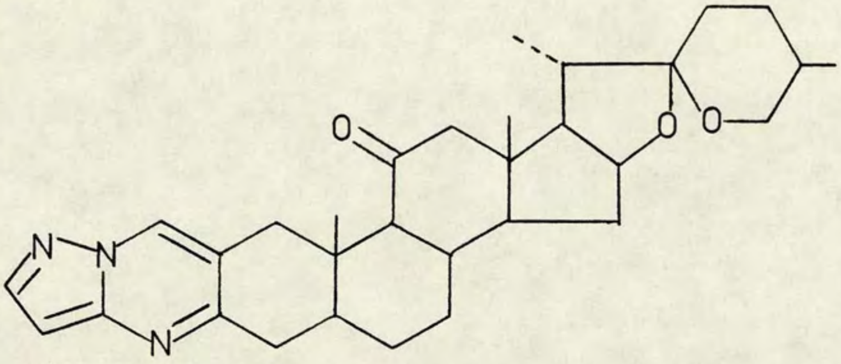
(181) R^1=H, R^2=C_8H_{17}, R^3=H

(185) R^1=CN, R^2=OH, R^3=CH_3

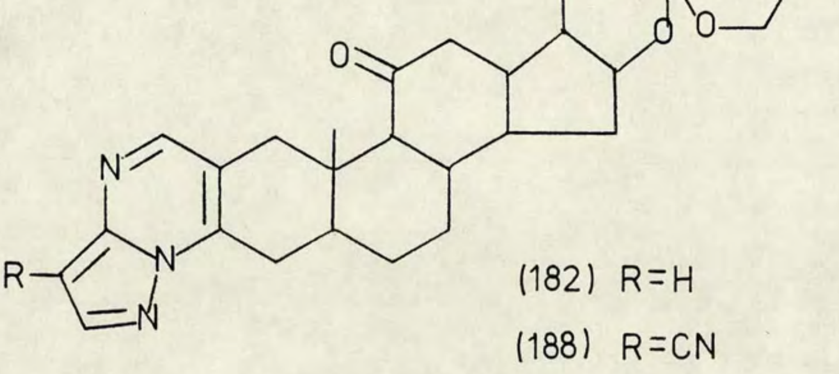
(187) R^1=CN, R^2=C_8H_{17}, R^3=H



(126)



(183)



(182) R=H

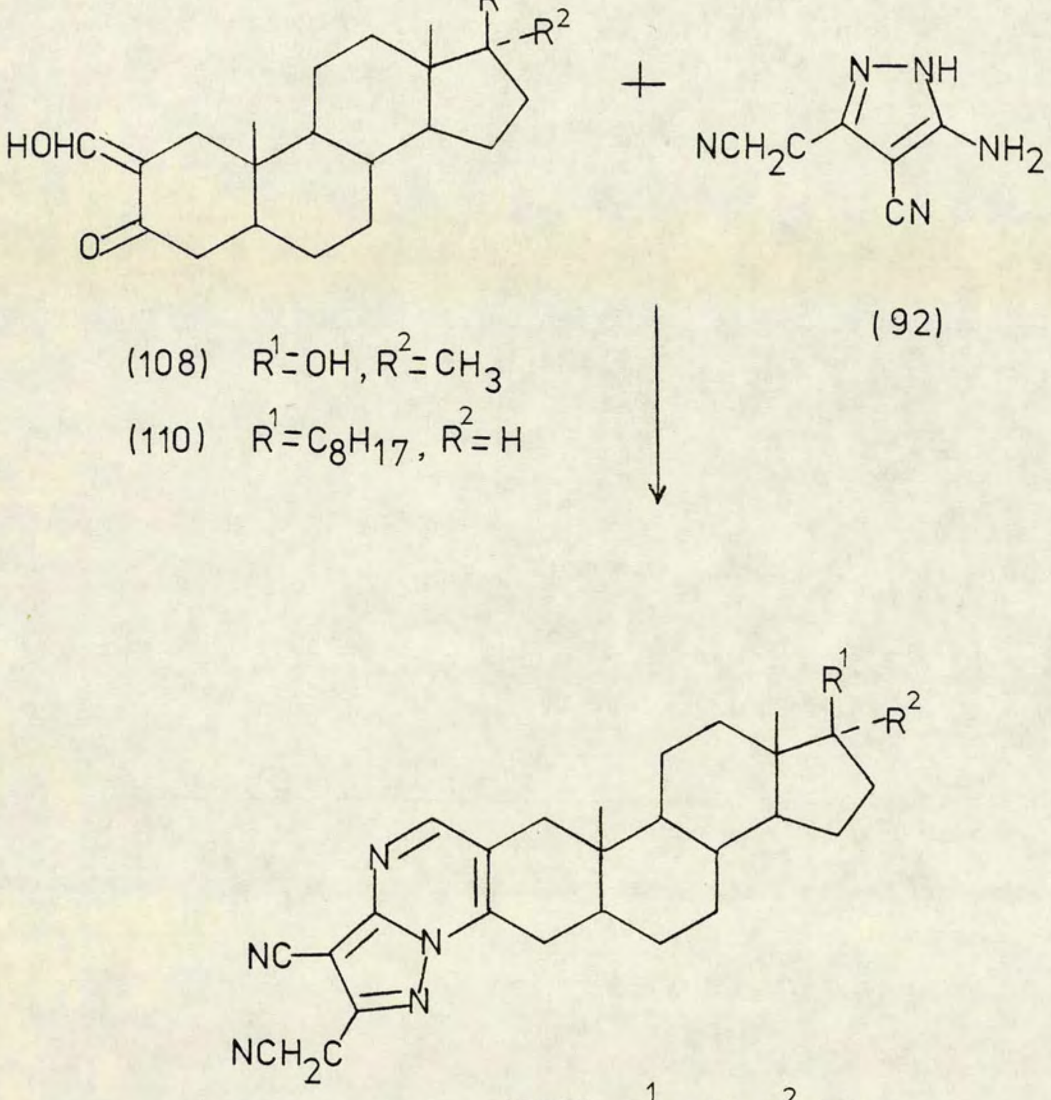
(188) R=CN

the values allocated to the model compounds (177) and (178) (section 9). The chemical shift of 5'-C (150.85 p.p.m.) in the condensation product (175) is found to be in good agreement with the chemical shift of 5-C (148.58 p.p.m.) in 7-methylpyrazolo[1,5-a]pyrimidine (178), confirming an angular fusion of the steroid to the heterocyclic system, whilst the chemical shift of 7'-C (133.10 p.p.m.) in the condensation product (176) is found to be in good agreement with the chemical shift of 7-C (134.43 p.p.m.) in 5-methylpyrazolo[1,5-a]pyrimidine (177) confirming a linear fusion of the steroid to the heterocyclic system.

Under analogous reaction conditions, the condensation of 3-aminopyrazole (174) with 2-hydroxymethylene-5α-cholestan-3-one (110) gave 5α-cholest-2-eno[2,3-g]pyrazolo[1,5-a]pyrimidine (180) and 5α-cholestano-[3,2-f]pyrazolo[1,5-a]pyrimidine (181) whilst the condensation of 3-aminopyrazole (174) with 2-hydroxymethylene-5α-spirostan-3,11-dione (111) gave 11-oxo-5α-spirost-2-eno[2,3-g] pyrazolo[1,5-a]pyrimidine (182) and 11-oxo-5α-spirostano[3,2-f]pyrazolo[1,5-a]pyrimidine (183).

Similarly the reaction of 3-amino-4-cyanopyrazole (126) with 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108) gave 17β-hydroxy-17α-methyl-5α-androst-2-eno[2,3-g]-3'-cyanopyrazolo-[1,5-a]pyrimidine (184) and 17β-hydroxy-17α-methyl-5α-androstano-[3,2-f]-3'-cyanopyrazolo[1,5-a]pyrimidine (185), and with 2-hydroxymethylene-5α-cholestan-3-one (110) gave 5α-cholest-2-eno[2,3-g]-3'-cyanopyrazolo[1,5-a]pyrimidine (186) and 5α-cholestano[3,2-f]-3'-cyanopyrazolo[1,5-a]pyrimidine (187).

It is observed that the angularly fused product becomes the major product as 3-aminopyrazole (174) is replaced by 3-amino-4-cyano-



(108) $R^1 = OH, R^2 = CH_3$

(110) $R^1 = C_8H_{17}, R^2 = H$

(92)

(189) $R^1 = OH, R^2 = CH_3$

(190) $R^1 = C_8H_{17}, R^2 = H$

pyrazole (126). In one particular example, the reaction of 3-amino-4-cyanopyrazole (126) with 2-hydroxymethylene-5α-spirostan-3, 11-dione (111), only the angularly fused product, 11-oxo-5α-spirost-2-eno[2, 3-g]-3'-cyanopyrazolo[1, 5-a]pyrimidine (188) was isolated.

5.3 The reaction of 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108) with 3-amino-4-cyano-5-cyanomethylpyrazole (92).

A solution of 17β-hydroxy-2-hydroxymethylene-5α-androstan-3-one (108) and 3-amino-4-cyano-5-cyanomethylpyrazole (92) in absolute alcohol was refluxed overnight. The reaction mixture was allowed to cool to room temperature. The white crystals formed were filtered, washed with ethanol and dried to give a pure product (189), m. p. 265-267°, in 71% yield. Mass spectrometry indicated that the product had a molecular formula of $C_{27}H_{33}N_5O$. The u. v. spectrum showed λ_{max} at 207, 232 and 313 nm (log ε 4. 07, 4. 65 and 3. 76) and the i. r. spectrum had absorptions at 3600, 2220, 1625, 1535, 1490, 1440, 1405, 1380, 960, 930 and 760 cm^{-1}. The ^{1}H n. m. r. spectrum showed, apart from the signals for the methyl groups, a singlet at δ 4. 05 corresponding to two protons and another singlet at δ 8. 40 corresponding to one proton.

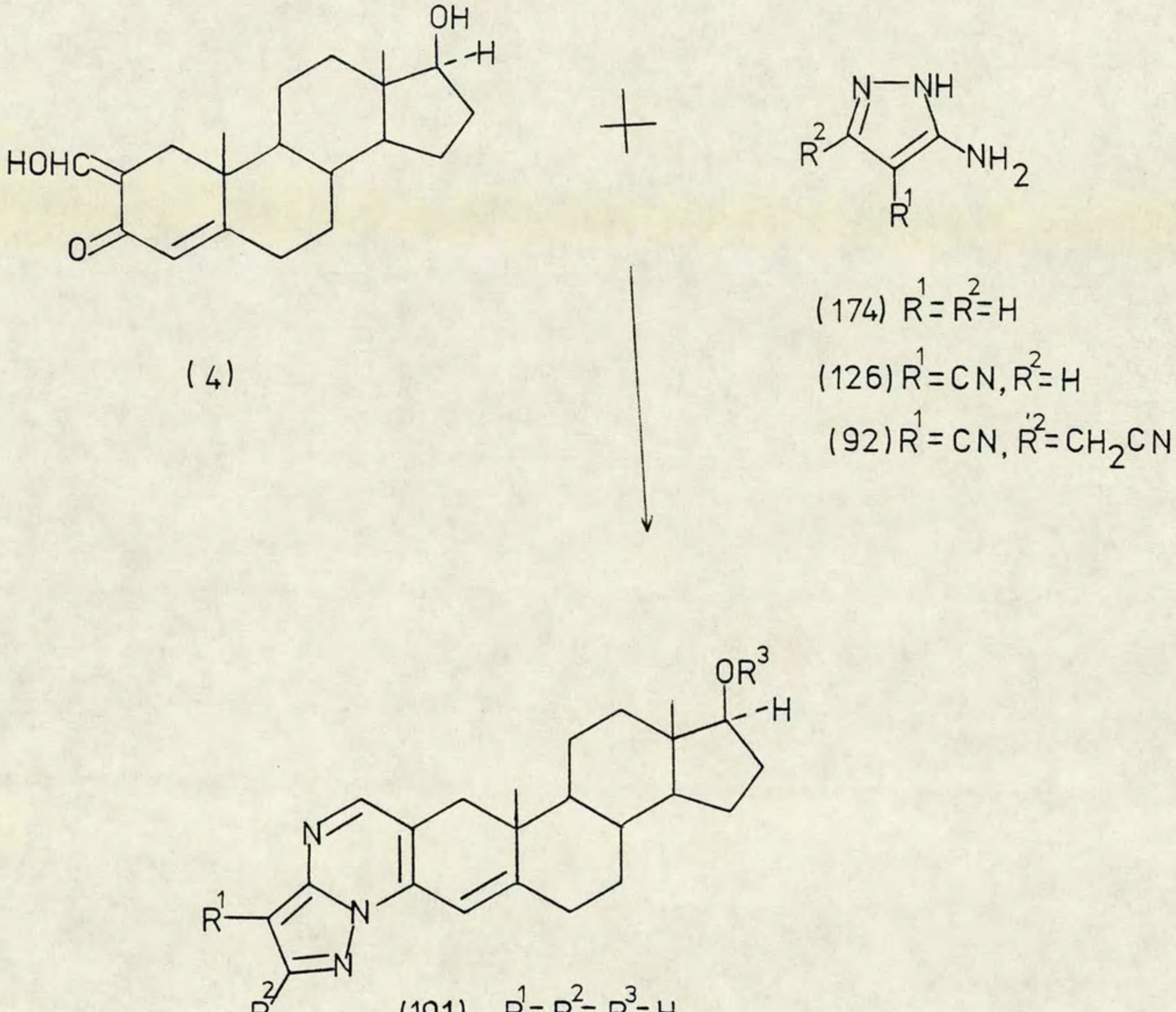
5.4 Discussion

U. v., i. r. ^{1}H n. m. r. and ^{13}C n. m. r. spectroscopy show that the condensation product of the reaction between 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108) and 3-amino-4-cyano-

5-cyanomethylpyrazole (92) is 17β-hydroxy-17α-methyl-5α-androst-2-eno[2,3-g]-3'-cyano-2'-cyanomethylpyrazolo[1,5-a]pyrimidine (189). The u.v. spectrum of the product (189) shows only one λ_{max} at 232 nm in the region 228-238 nm whilst the i.r. spectrum (Table 2) exhibits no absorption in the region 1500-1505 cm^{-1} but shows two absorptions at 1625 and 1535 cm^{-1} comparable to the absorptions at 1620 and 1530 cm^{-1} in the i.r. spectrum of the angularly fused compound (175). The ^{1}H n.m.r. spectrum shows two singlets at δ 4.05 and δ 8.40 which are assigned to 2'-CH_2CN and 5'-H, although a downfield shift of 0.25 p.p.m. is noticed for the latter resonance relative to the chemical shift of the corresponding resonance in 17β-hydroxy-17α-methyl-5α-androst-2-eno-[2,3-g]pyrazolo[1,5-a]pyrimidine (175). The singlet at δ 8.40 due to 5'-H is found to be sharp and this is in agreement with the assignment of angular structure (189). The structure (189) is further confirmed by the ^{13}C n.m.r. spectrum in which the chemical shift of 5'-C (154.62 p.p.m.) (Table 3) is found to agree with the chemical shift of 5'-C (150.85 p.p.m.) in 17β-hydroxy-17α-methyl-5α-androst-2-eno[2,3-g]pyrazolo-[1,5-a]pyrimidine (175).

Similarly the reaction of 3-amino-4-cyano-5-cyanomethylpyrazole (92) with 2-hydroxymethylene-5α-cholestan-3-one (110) gave 5α-cholest-2-eno[2,3-g]-3'-cyano-2'-cyanomethylpyrazolo[1,5-a]pyrimidine (190).

It is evident that the substituents on the pyrazole nucleus markedly influence the course of the condensation of 3-aminopyrazoles with 2-hydroxymethylene-3-oxo steroids. Thus the condensation of 3-aminopyrazole (174) with 2-hydroxymethylene-3-oxo steroids gives a mixture of a linearly and an angularly fused product and the percentage yield of angularly fused product is increased when 3-aminopyrazole (174) is replaced by



(4)

(174) $R^1 = R^2 = H$

(126) $R^1 = CN, R^2 = H$

(92) $R^1 = CN, R^2 = CH_2CN$

(191) $R^1 = R^2 = R^3 = H$

(192) $R^1 = CN, R^2 = R^3 = H$

(193) $R^1 = CN, R^2 = CH_2CN, R^3 = H$

(194) $R^1 = R^2 = H, R^3 = COCH_3$

(195) $R^1 = CN, R^2 = H, R^3 = COCH_3$

3-amino-4-cyanopyrazole (126). However, the reaction of 3-amino-4-cyano-5-cyanomethylpyrazole (92) with 2-hydroxymethylene-3-oxo steroids leads exclusively to the formation of angularly fused products.

5.5 The reaction of 17β-hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4) with 3-aminopyrazole (174).

A solution of 17β-hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4) and 3-aminopyrazole (174) in absolute alcohol was refluxed overnight. The excess of solvent was removed under vacuo and the residue was chromatographed over alumina. Elution with ethyl acetate followed by recrystallisation of the eluate from acetone gave yellow crystals (191), m. p. 230-232°, in 72% yield. Mass spectrometry indicated that the product had a molecular formula of $C_{23}H_{29}N_3O$. The u. v. spectrum showed λ_{max} at 209, 235 (sh), 242, 265 (sh) and 370 mn (log ϵ 3. 89, 4. 48, 4. 57 and 3. 98) and the i. r. spectrum had absorptions at 3595, 1630, 1590, 1520, 1460, 1060, 1045, 895, 860 and 770 cm^{-1}. The ^1H n. m. r. spectrum showed a singlet at δ 8. 25 and two doublets at δ 6. 70 and δ 8. 05 each with spin coupling constant, J = 2Hz.

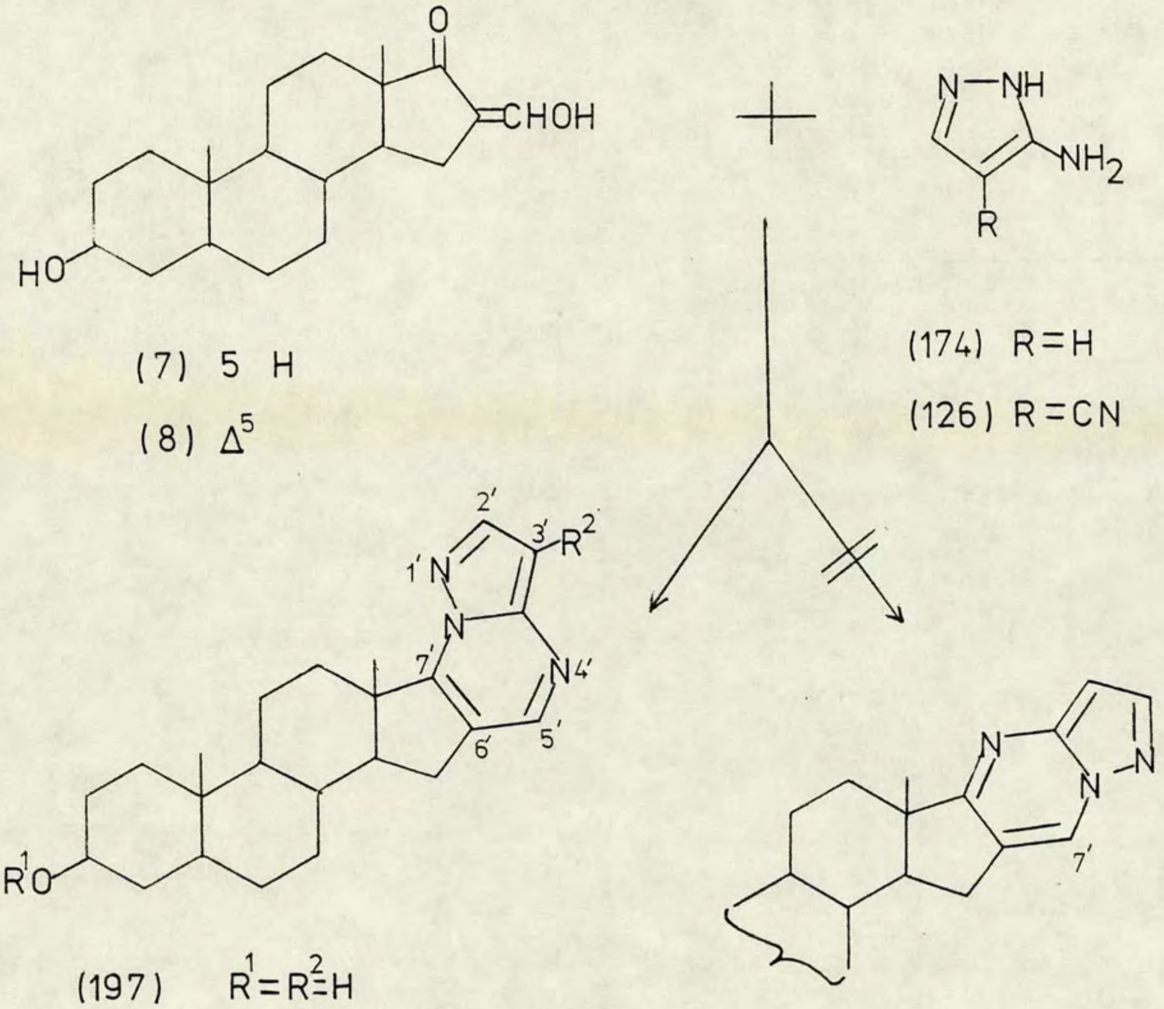
5.6 Discussion

The i. r., ^1H n. m. r. and ^{13}C n. m. r. spectra of the condensation product of the reaction between 17β-hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4) and 3-aminopyrazole (174) resemble closely the i. r., ^1H n. m. r. and ^{13}C n. m. r. spectra obtained for 17β-hydroxy-17α-methyl-5α-androst-2-eno[2,3-g]pyrazolo[1,5-a]pyrimidine (175), thus the product is formulated as 17β-hydroxyandrost-2,4-dieno[2,3-g]pyrazolo[1,5-a]-pyrimidine (191). The i.r. spectrum of the steroid (191) shows no absorption in the region 1500-1505 cm^{-1} (Table 2), but shows two absorptions at 1630 and 1520 cm^{-1} comparable to the absorptions at 1620 and 1530 cm^{-1} in the i.r. spectra of the angularly fused product (175). The i.r. spectrum also contains an additional absorption at 1590 cm^{-1} which arises because of Δ^4 double bond present in the steroid (191). In the ^{1}H n.m.r. spectrum, the two doublets at δ 6.70 and δ 8.05 are assigned to 3'-H and 2'-H respectively whilst the sharp singlet at δ 8.25 is assigned to 5'-H. In the ^{13}C n.m.r. spectrum, the chemical shift of 5'-C (149.00 p.p.m.) is found to be comparable with the chemical shift of 5'-C (150.85 p.p.m.) in 17β-hydroxy-17α-methyl-5α-androst-2-eno[2,3-g]pyrazolo[1,5-a]pyrimidine (175) (Table 3).

Under analogous conditions, the reaction of 17β-hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4) with 3-amino-4-cyanopyrazole (126) and 3-amino-4-cyano-5-cyanomethylpyrazole (92) gave 17β-hydroxy-androst-2,4-dieno[2,3-g]-3'-cyanopyrazolo[1,5-a]pyrimidine (192) and 17β-hydroxyandrost-2,4-dieno[2,3-g]-3'-cyano-2'-cyanomethylpyrazolo-[1,5-a]pyrimidine (193) respectively. The 17β-acetoxy derivatives (194) and (195) were obtained by acetylation of the steroids (191) and (192) respectively using acetic anhydride in pyridine.

5.7 The reaction of 3β-hydroxy-16-hydroxymethylene-5α-androstan-17-one (7) with 3-aminopyrazole (174).

A solution of 3β-hydroxy-16-hydroxymethylene-5α-androstan-17-one (7) and 3-aminopyrazole (174) in absolute alcohol was refluxed overnight.



(7) 5 H

(8) Δ^5

(174) R = H

(126) R = CN

(197) $R^1 = R^2 = H$

(198) Δ^5, $R^1 = R^2 = H$

(200) $R^1 = H$, $R^2 = CN$

(201) Δ^5, $R^1 = H$, $R^2 = CN$

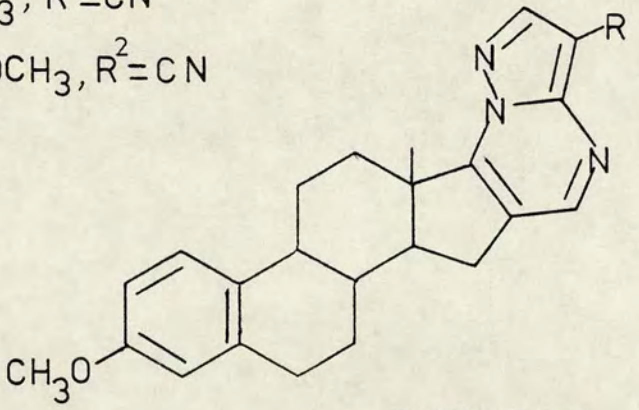
(203) $R^1 = COCH_3$, $R^2 = H$

(204) Δ^5, $R^1 = COCH_3$, $R^2 = H$

(205) $R^1 = COCH_3$, $R^2 = CN$

(206) Δ^5, $R^1 = COCH_3$, $R^2 = CN$

(196)



(199) R = H

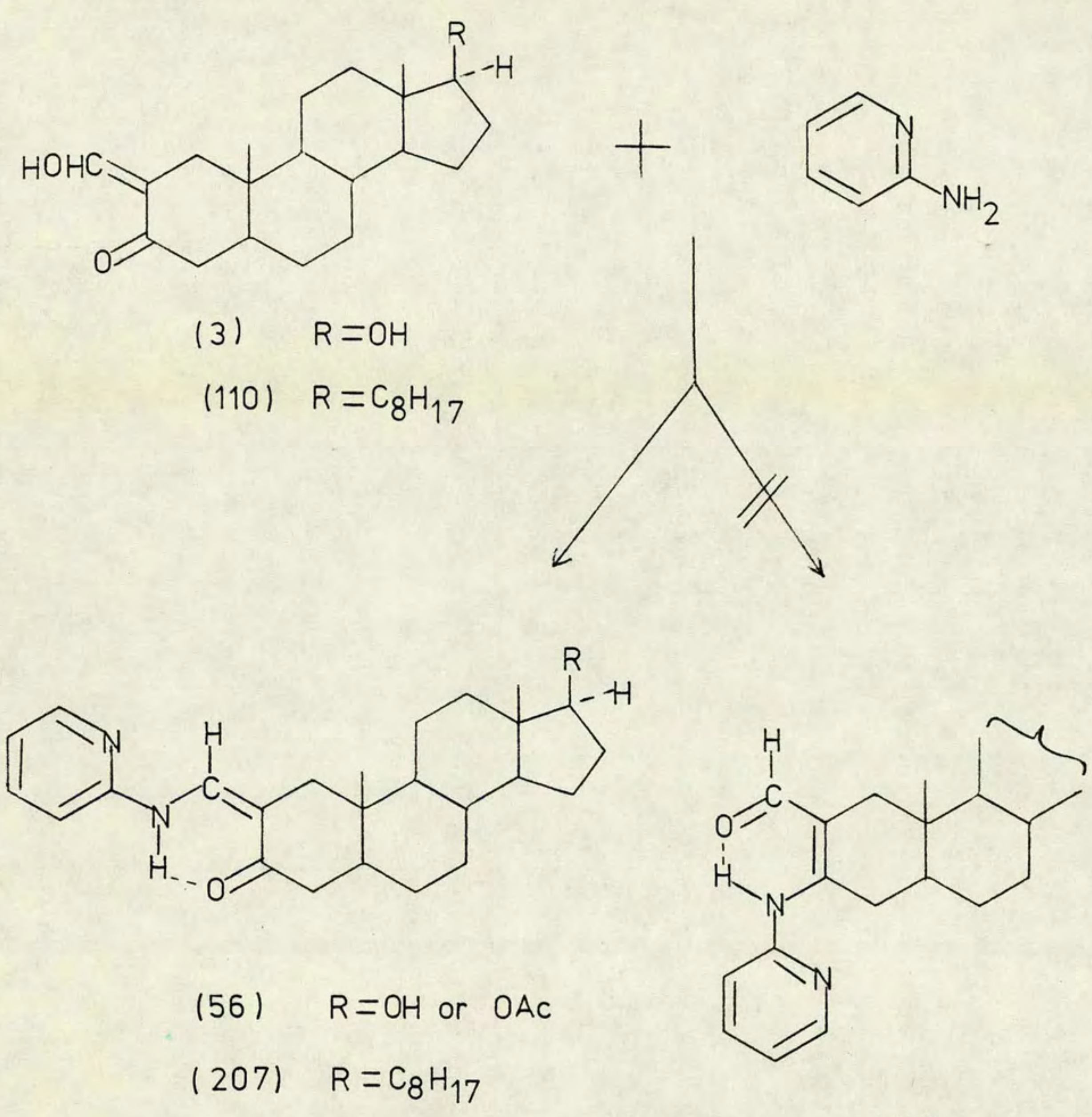
(202) R = CN

The excess of solvent was removed under vacuo and the residue was chromatographed over alumina. Elution with ethyl acetate followed by recrystallisation of the eluate from acetone gave white needles (197), m. p. 240-242°, in 91% yield. Mass spectrometry and elemental analysis indicated that the product had a molecular formula of $C_{23}H_{31}N_{3}O$. The u. v. spectrum showed λ_{max} at 236, and 327 nm (log ε 4. 51 and 3. 38) and the i. r. spectrum showed absorptions at 3590, 1600, 1545, 1510, 1455, 1345, 1030, 900 and 775 cm^{-1}. ^{1}H n. m. r. spectrum showed, apart from the signals for 18-CH_3, 19-CH_3 and 3-H, doublets at δ 6. 70 and δ 8. 15 each with spin coupling constant, J = 2Hz and a singlet at δ 8. 45.

5. 8 Discussion

The i. r. spectrum of the condensation product obtained by the reaction of 3β-hydroxy-16-hydroxymethylene-5α-androstan-17-one (7) and 3-aminopyrazole (174) exhibits absorptions at 1600, 1545 and 1510 cm^{-1} in the region 1500-1630 cm^{-1}, these compare well with the absorptions in the spectrum of 17β-hydroxy-17α-methyl-5α-androstano[3, 2-f]-pyrazolo[1, 5-a]pyrimidine (176) and thus it was predicted that the condensation product had structure (196). However, the condensation product is identified by its u. v., ^{1}H n. m. r. and ^{13}C n. m. r. spectra as 3β-hydroxy-5α-androst-16-eno[16, 17-g]pyrazolo[1, 5-a]pyrimidine (197). The u. v. spectrum of the condensation product (197) and that of 17β-hydroxy-17α-methyl-5α-androst-2-eno[2, 3-g]pyrazolo[1, 5-a]pyrimidine (175) both exhibit only one λ_{max} at 232 nm in the region 228-238 nm as compared to two $\lambda_{max's}$ at 235 nm and 238 nm in the u. v. spectrum of the linearly fused pyrazolopyrimidine (176). In the ^{1}H n. m. r. spectrum of the product (197), the 5'-H gives a sharp singlet at δ 8.45. In the alternative structure (196), the signal at δ8.45 would be expected to be broadened due to long range coupling between the 7'-H and the protons at position 15.[77] The structure (197) is further confirmed by ^{13}C n.m.r. evidence. In the ^{13}C n.m.r. spectrum of the acetyl derivative (203), the chemical shift of 5'-C (145.17 p.p.m.) (Table 3) agrees well with the chemical shift of 5-C (148.58 p.p.m.) in pyrazolopyrimidine (178) and the chemical shift of 5'-C (150-85 p.p.m.) in the angularly fused product (175). Therefore it is concluded from u.v., ^{1}H n.m.r. and ^{13}C n.m.r. evidence that the product obtained by the condensation of 3-aminopyrazole (174) and 3β-hydroxy-16-hydroxymethylene-5α-androstan-17-one (7) is 3β-hydroxy-5α-androst-16-eno-[16, 17-g]pyrazolo[1, 5-a]pyrimidine (197). This behaviour is parallel to the one observed in the reaction of 3-aminopyrazole (174) with 17β-hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4).

Under analogous reaction conditions, the condensation of 3-aminopyrazole (174) with 3β-hydroxy-16-hydroxymethyleneandrost-5-en-17-one (8) and 16-hydroxymethylene-3-methoxyoestra-1, 3, 5(10)-trien-17-one (9) gave 3β-hydroxyandrost-5-16-dieno[16, 17-g]pyrazolo[1, 5-a]pyrimidine (198) and 3-methoxyoestra-1, 3, 5(10), 16-tetraeno[16, 17-g]pyrazolo[1, 5-a]-pyrimidine (199) respectively. The compounds, 3β-hydroxy-5α-androst-16-eno[16, 17-g]-3'-cyanopyrazolo[1, 5-a]pyrimidine (200), 3β-hydroxy-androst-5, 16-dieno[16, 17-g]-3'-cyanopyrazolo[1, 5-a]pyrimidine (201) and 3-methoxyoestra-1, 3, 5(10), 16-tetraeno[16, 17-g]-3'-cyanopyrazolo-[1, 5-a]pyrimidine (202) were also obtained by the reaction of 3-amino-4-cyanopyrazole (126) with 16-hydroxymethylene-17-oxo steroids (7),



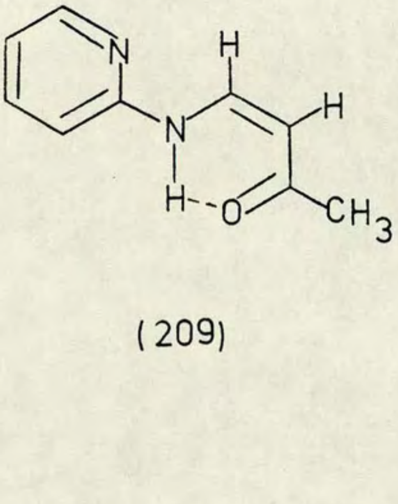
(3) $R = OH$

(110) $R = C_8H_{17}$

(56) $R = OH$ or OAc

(207) $R = C_8H_{17}$

(208)



(209)

(8) and (9) respectively.

The sterols (197), (198), (200) and (201) were acetylated using acetic anhydride in pyridine to give the corresponding 3β-acetyl derivatives (203)-(206).

The reaction mechanism of these condensations is discussed in detail in section 10, where it is shown that the formation of the linearly fused products, resulting from the reaction of 3-aminopyrazole (174) and its 4-cyano derivative (126) with 2-hydroxymethylene-3-oxo steroids without a Δ^4 double bond, is a two step reaction. Evidence for this two step reaction sequence comes from the condensation of 2(2'-pyridyl-aminomethylene)-5α-cholestan-3-one (207) with 3-aminopyrazole (174), which is discussed below.

5.9 The reaction of 2-hydroxymethylene-5α-cholestan-3-one (110) with 2-aminopyridine.

A solution of 2-hydroxymethylene-5α-cholestan-3-one (110) and 2-aminopyridine was allowed to stand at room temperature overnight. The product was recovered by evaporation of the solvent and extraction of the residue with chloroform. The crude product was chromatographed over alumina and recrystallisation of the eluate from acetone gave yellow crystals (207), m.p. 135-138°, in 60% yield.

Mass spectrometry and elementary analysis indicated that the product had a molecular formula of $C_{33}H_{50}N_2O$. The i.r. spectrum had absorptions at 1640, 1590, 1545, 1475, 1440, 1415, 1360 and 770 $cm.^{-1}$ The ^{1}H n.m.r. spectrum showed signals at δ6.60-6.95, δ7.50 and δ8.20 associated with the four hydrogens of a monosubstituted pyridine

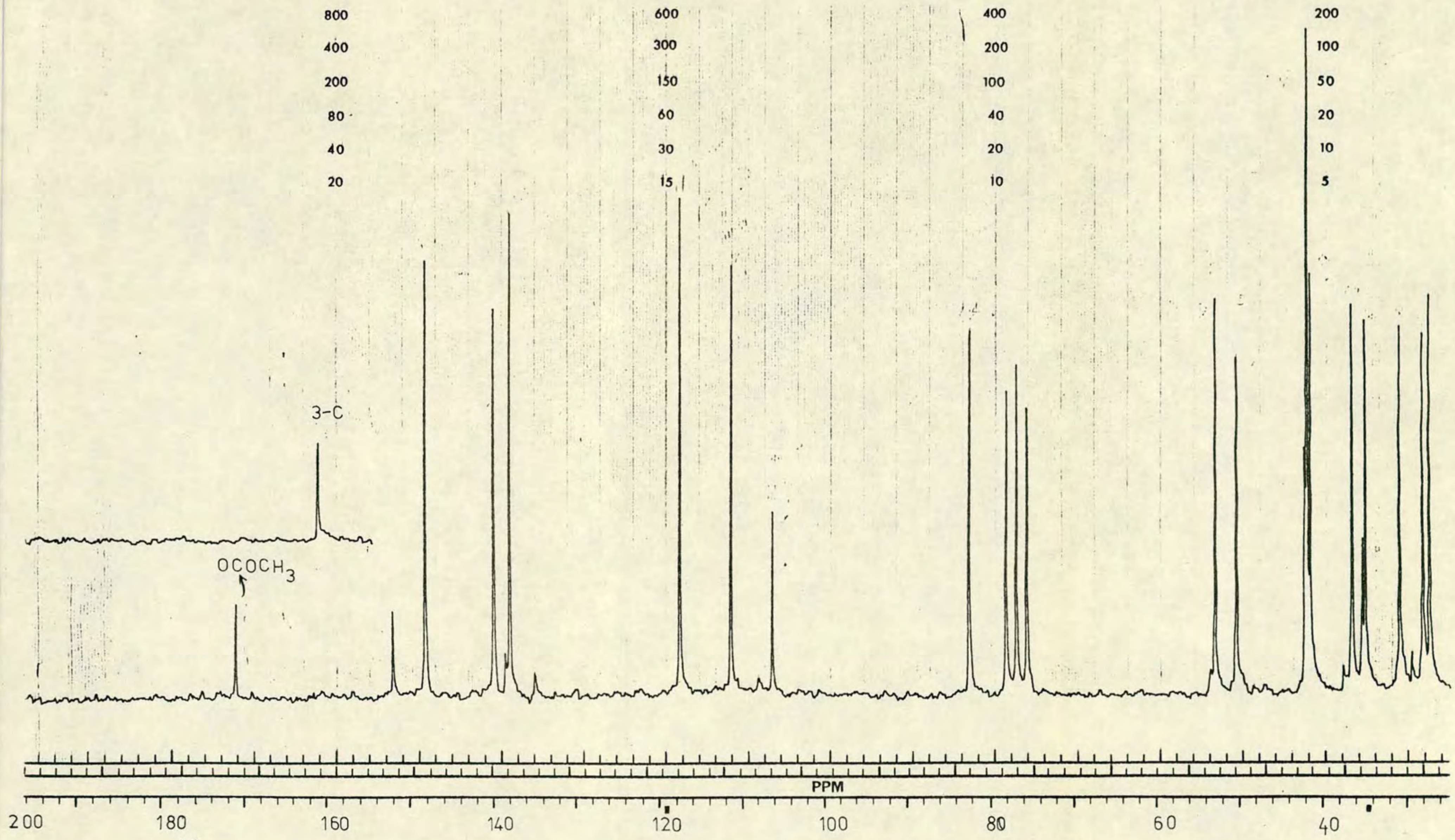


Fig. 4; ^{13}C n. m. r. (spin decoupled) spectrum of 17β-acetoxy-2(2'-pyridyl-aminomethylene)-5α-androstan-3-one (56).

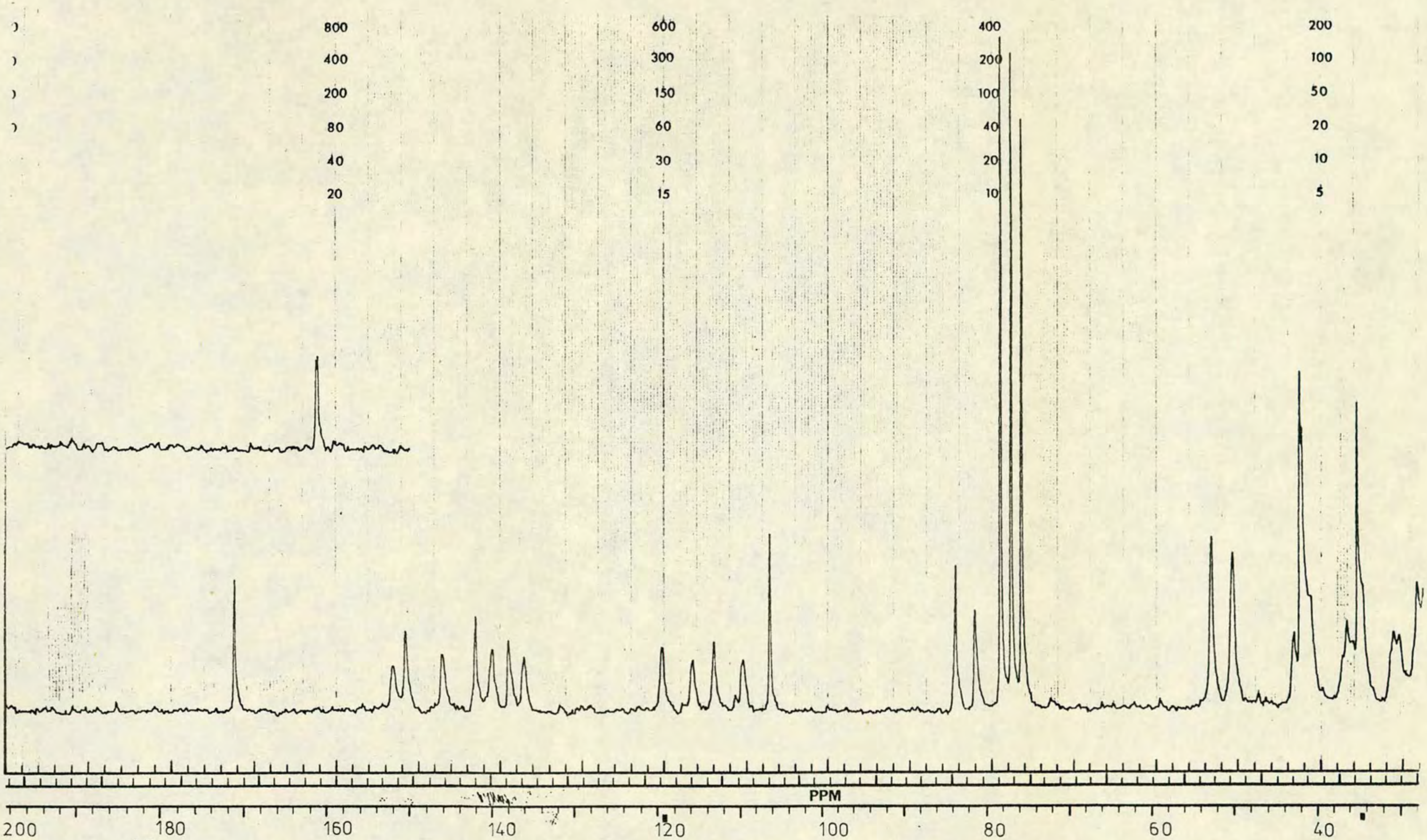


Fig. 5: ^{13}C n. m. r. (spin coupled) spectrum of 17β-acetoxy-2(2'-pyridylaminomethylene)-5α-androstan-3-one (56)

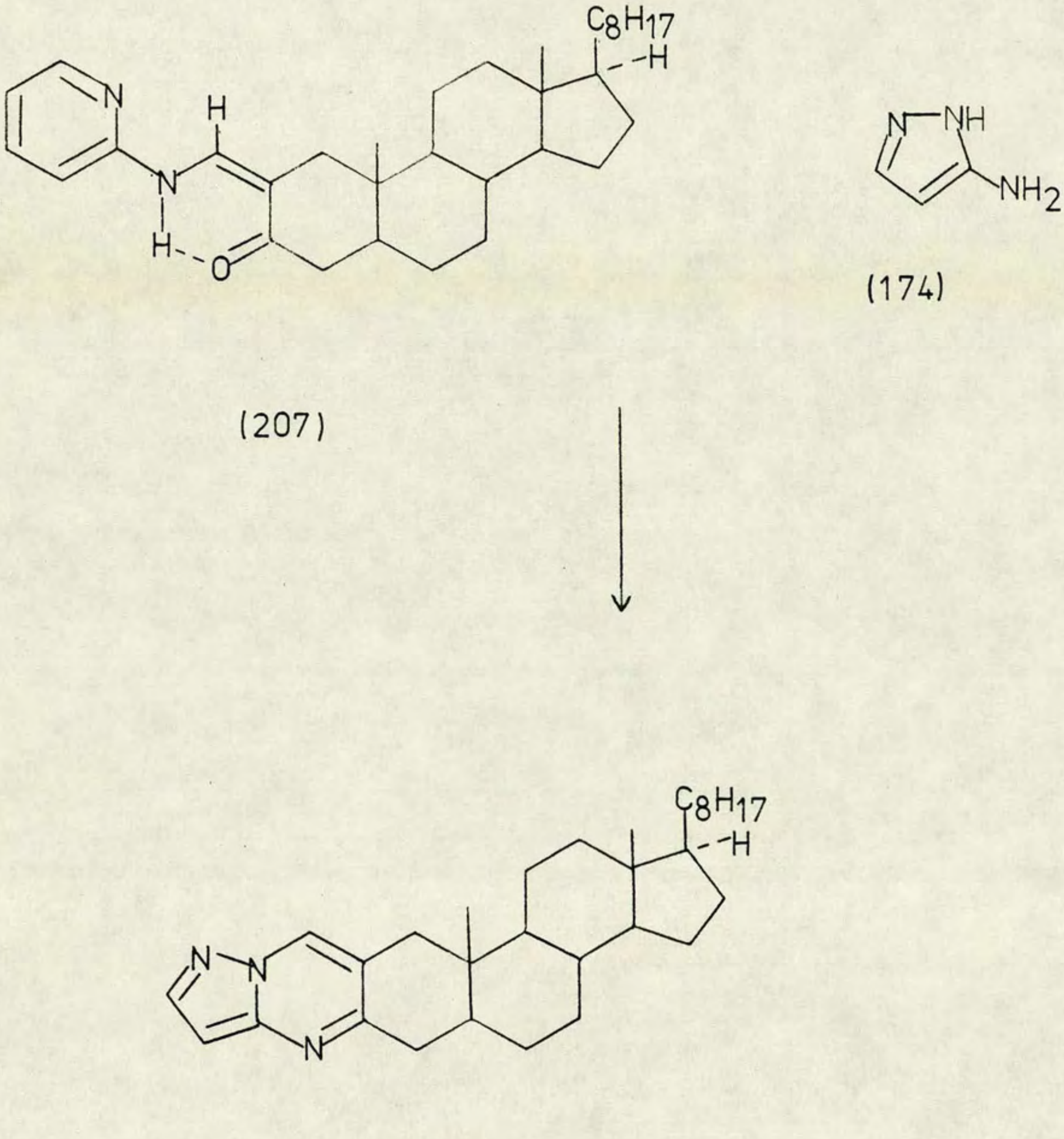
ring and doublets at δ7.82 and δ10.92 each with spin coupling constant, J = 11.5Hz.

5.10 Discussion

Burgess[51] has recently investigated the reaction of 2-aminopyridine with the steroidal β-ketoaldehydes and has shown with the help of i.r. and ^{1}H n.m.r. spectroscopy that the product obtained by the reaction of 2-aminopyridine and 17β-hydroxy-2-hydroxymethylene-5α-androstan-3-one (3), has the enaminone structure (56) and not (208).

Further support for structure (56) by ^{13}C n.m.r. spectroscopy is given here. In the ^{13}C n.m.r. spin-coupled spectra, the carbons attached with hydrogen atoms are readily distinguished, by their large C-H couplings, from the tetrasubstituted carbons which appear as singlets. In the ^{13}C n.m.r. spectrum (Fig.4) of the compound (56), the downfield signals at 170.99 p.p.m. and 200.78 p.p.m. are assigned to the carbon of the acetyl group at position 17 and 3-C respectively. It is noticed that the signal at 200.78 p.p.m. corresponding to 3-C remains a singlet in the spin-coupled spectrum (Fig. 5) and this is consistent with the assignment of enaminone structure (56). If the condensation product had had structure (208) the carbon of the aldehyde group at position 2 would be expected to appear as a doublet in the region of 200 p.p.m.

Thus by analogy with the structure of 17β-hydroxy-2(2'-pyridylaminomethylene)-5α-androstan-3-one (56), the product obtained by the condensation of 2-aminopyridine and 2-hydroxymethylene-5α-cholestan-3-one (110) is assigned structure (207). The doublets at δ7.82 and δ10.92 are assigned to a vinyl proton and an adjacent amino proton



(207) (174)

(181)

respectively. The coupling constant (J = 11.5Hz) between the two doublets is consistent with those reported for 17β-acetoxy-2(2'-pyridyl-aminomethylene)-5α-androstan-3-one (56)[51] and 2-(2-acetylvinylamino)-pyridine (209)[140] and indicates that the two protons are trans to one another.

5.11 The reaction of 2(2'-pyridyl-aminomethylene)-5α-cholestan-3-one (207) with 3-aminopyrazole (174).

A solution of 2(2'-pyridyl-aminomethylene)-5α-cholestan-3-one (207) and 3-aminopyrazole (174) in dry toluene containing a catalytic amount of toluene-4-sulphonic acid was refluxed for 7 h. The solvent was removed in vacuo and the residue was chromatographed over alumina. Elution with ethyl acetate followed by recrystallisation of the eluate from ethanol gave white crystals (60%), m.p. 138-140°, identical (m.p., i.r. and ^{1}H n.m.r.) with that of 5α-cholestano[3, 2-f]pyrazolo-[1, 5-a]pyrimidine (181).

The formation of 5α-cholestano[3, 2-f]pyrazolo[1, 5-a]pyrimidine (181) from 2(2'-pyridyl-aminomethylene)-5α-cholestan-3-one (207) and 3-aminopyrazole (174) shows that the condensation of 2-hydroxymethylene-3-oxo steroids with 3-aminopyrazole is a two step reaction. It also indicates that 3-aminopyrazole reacts first with the 2-formyl group of the steroid and not with the 3-carbonyl group as it might appear from the structure of the final condensation product (see section 10).

5.12 Experimental

General procedure for the condensation reaction

A solution of the steroidal β-ketoaldehyde (1.5 x 10^{-3} mole) and 3-aminopyrazole (174) or its derivative (92 or 126) (2 x 10^{-3} mole) in absolute alcohol (30 ml) was refluxed overnight. The reaction mixture was evaporated to dryness under vacuo, the residue was chromatographed over alumina (50 g) and the crude products thus obtained were recrystallised from suitable solvents.

5.12.i 17β-Hydroxy-17α-methyl-5α-androst-2-eno[2, 3-g]pyrazolo-[1, 5-a]pyrimidine (175) and 17β-hydroxy-17α-methyl-5α-androstano[3, 2-f]pyrazolo[1, 5-a]pyrimidine (176).

Source: 17β-Hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108) and 3-aminopyrazole (174).

General: Alumina chromatography (eluant ethyl acetate-ether, 7:3).

17β-Hydroxy-17α-methyl-5α-androst-2-eno[2, 3-g]pyrazolo[1, 5-a]-pyrimidine (175) was recrystallised from ethanol as long white needles (34%), m.p. 222-224°; u.v., λ_{max} 232 and 317 nm (log ε 4.60 and 3.40); i.r., γ_{max} 3590, 1620, 1530, 1445 and 770 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.84 (s, 3H, 18-CH_3), 0.90 (s, 3H, 19-CH_3), 1.24 (s, 3H, 17-CH_3), 6.62 (d, J=2Hz, 1H, 3'-H), 8.03 (d, J=2Hz, 1H, 2'-H) and 8.20 (s, 1H, 5'-H) (Found: C, 75.69; H, 8.70; N, 10.88; M^+, 379.261508. $C_{24}H_{33}N_3O$ requires C, 75.93; H, 8.77; N, 11.08%; M, 379.262349).

17β-Hydroxy-17α-methyl-5α-androstano[3, 2-f]pyrazolo[1, 5-a]pyrimidine (176) was recrystallised from ethanol as light brown crystals (27%), m. p. 186-188°; u. v., λ_{max} 209, 235, 238 and 287 nm (log ε 4.41, 4.66, 4.66 and 3.21); i. r., γ_{max} 3590 (OH) 1625, 1530, 1500, 1440, 1405 and 765 cm^{-1}; ^1H n. m. r. (100 MHz), δ 0.80 (s, 3H, 18-CH_3), 0.87 (s, 3H, 19-CH_3), 1.22 (s 3H 17-CH_3), 6.46 (d, J=2Hz, 1H, 3'-H), 7.95 (d, J=2Hz 1H, 2'-H) and 8.32 (s, 1H, 7'-H) (Found: C, 75.73; H, 8.87; N, 10.97; M^+ 379.261132. $C_{24}H_{33}N_3O$ requires C, 75.39; H, 8.77; N, 11.08%; M, 379.262349).

5.12.ii 5α-Cholest-2-eno[2, 3-g]pyrazolo[1, 5-a]pyrimidine (180) and 5α-cholestano[3, 2-f]pyrazolo[1, 5-a]pyrimidine (181).

Source: 2-Hydroxymethylene-5α-cholestan-3-one (110) and 3-aminopyrazole (174).

General: Alumina chromatography (eluant ether).

5α-Cholest-2-eno[2, 3-g]pyrazolo[1, 5-a]pyrimidine (180) was recrystallised from ethanol as white crystals (35%), m. p. 165-167° (dec.); u. v., λ_{max} 283 and 317 nm (log ε 4.59 and 3.19); i. r., γ_{max} 1620, 1530, 1450, 1440, 795 and 770 cm^{-1}; ^1H n. m. r. (100 MHz), δ 0.70, 0.80, 0.84, 0.90 (methyl groups), 6.62 (d, J=2Hz, 1H, 3'-H), 8.02 (d, J=2Hz, 1H, 2'-H) and 8.20 (s, 1H, 5'-H) (Found: C, 80.76; H, 10.08; N, 9.04; M^+, 461.376241. $C_{31}H_{47}N_3$ requires C, 80.63; H, 10.27; N, 9.11%; M, 461.376980).

5α-Cholestano[3, 2-f]pyrazolo[1, 5-a]pyrimidine (181) was recrystallised from ethanol as long yellow needles (18%), m. p. 138-140°; u. v., λ_{max} 206, 229, 233 and 280 nm (log ε 4.33, 4.76, 4.74 and 3.56); i. r.,

γ_{max} 1620, 1530, 1500, 1465, 1450, 1405 and 765 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.70, 0.80, 0.84, 0.90 (methyl groups), 6.47 (d, J=2Hz, 1H, 3'-H), 7.98 (d, J=2Hz, 1H, 2'-H) and 8.32 (s, 1H, 7'-H) (Found: C, 80.41; H, 10.35; N, 8.83; M$^+$, 461.376241. $C_{31}H_{47}N_3$ requires C, 80.63; H, 10.27; N, 9.11%; M, 461.376980).

5.12. iii <u>11-Oxo-5α-spirost-2-eno[2, 3-g]pyrazolo[1, 5-a]pyrimidine (182) and 11-oxo-5α-spirostano[3, 2-f]pyrazolo[1, 5-a]pyrimidine (183).</u>

Source: 2-Hydroxymethylene-5α-spirostan-3, 11-dione (111) and 3-aminopyrazole (174).

General: Alumina chromatography (eluant ethyl acetate-ether, 1:3).

11-Oxo-5α-spirost-2-eno[2, 3-g]pyrazolo[1, 5-a]pyrimidine (182) was recrystallised from acetone as white crystals (40%), m.p. 243-245°; u.v., λ_{max} 207, 227 and 314 nm (log ε 4.33, 4.62 and 3.96); i.r., γ_{max} 1700 (CO), 1620, 1530, 1450, 1380, 1350 and 770 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.78 (s, 3H, 18-CH$_3$), 1.04 (s, 3H, 19-CH$_3$), 6.63 (d, J=2Hz, 1H, 3'-H), 8.05 (d, J=2Hz, 1H, 2'-H) and 8.20 (s, 1H, 5'-H) (Found: C, 73.68; H, 8.27; N, 7.95; M$^+$, 503.312372. $C_{31}H_{41}N_3O$ requires C, 73.91; H, 8.21; N, 8.35%; M, 503.314775).

11-Oxo-5α-spirostano[3, 2-f]pyrazolo[1, 5-a]pyrimidine (183) was recrystallised from ethanol as yellow crystals (27%), m.p. 270-272°; u.v., λ_{max} 208, 231, 280 and 316 nm (log ε 4.22, 4.70, 3.57 and 3.53); i.r., γ_{max} 1695 (CO), 1620, 1500, 1445, 1405, 1380 and 765 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ0.78 (s, 3H, 18-CH$_3$), 1.02 (s, 3H, 19-CH$_3$), 6.45 (d, J=2Hz, 1H, 3'-H), 7.96 (d, J=2Hz, 1H, 2'-H) and 8.35 (s, 1H, 7'-H) (Found: C, 73.73; H, 8.22; N, 8.20; M$^+$, 503.312836. $C_{31}H_{41}N_3O_3$ requires C, 73.91; H, 8.21; N, 8.35; M, 503.314775).

5.12.iv <u>17β-Hydroxy-17α-methyl-5α-androst-2-eno[2,3-g]-3'-cyanopyrazolo[1,5-a]pyrimidine (184) and 17β-hydroxy-17α-methyl-5α-androstano[3,2-f]-3'-cyanopyrazolo[1,5-a]pyrimidine (185)</u>.

<u>Source</u>: 17β-Hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108) and 3-amino-4-cyanopyrazole (126).

<u>General</u>: Alumina chromatography (eluant ethyl acetate-ether, 3:2).

<u>17β-Hydroxy-17α-methyl-5α-androst-2-eno[2,3-g]-3'-cyanopyrazolo-[1,5-a]pyrimidine (184)</u> was recrystallised from ethanol as white crystals (24.7%), m.p. 246-248°; u.v., λ_{max} 206, 226 and 315 nm (log ε 3.91, 4.55 and 3.66); i.r., ν_{max} 3600 (OH), 2220 (CN), 1620, 1535, 1465, 1440, 1365 and 755 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.84 (s, 3H, 18-CH_3), 0.90 (s, 3H, 19-CH_3), 1.24 (s, 3H, 17-CH_3), 8.28 (s, 1H, 2'-H) and 8.42 (s, 1H, 5'-H) (Found: C, 73.93; H, 7.86; N, 13.49; M$^+$, 404.256375. $C_{25}H_{32}N_4O$ requires C, 74.21; H, 7.98; N, 13.86%; M, 404.256774).

<u>17β-Hydroxy-17α-methyl-5α-androstano[3,2-f]-3'-cyanopyrazolo[1,5-a]-pyrimidine (185)</u> was recrystallised from acetone as white crystals (18.5%), m.p. 212-215°; u.v., λ_{max} 207, 235, 240 and 315 nm (log ε 4.05, 4.66, 4.66 and 3.33); i.r., ν_{max} 3590 (OH), 2220 (CN), 1630, 1510, 1460, 1440, 1405 and 755 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.82 (s, 3H, 18-CH_3), 0.90 (s, 3H, 19-CH_3), 1.22 (s, 3H, 17-CH_3), 8.22 (s, 1H, 2'-H), and 8.42 (s, 1H, 7'-H) (Found:[141] M$^+$, 404.257598. $C_{25}H_{32}N_4O$ requires M, 404.256774).

5. 12. v 5α-Cholest-2-eno[2, 3-g]-3'-cyanopyrazolo[1, 5-a]pyrimidine (186) and 5α-cholestano[3, 2-f]-3'-cyanopyrazolo[1, 5-a]-pyrimidine (187).

Source: 2-Hydroxymethylene-5α-cholestan-3-one (110) and 3-amino-4-cyanopyrazole (126).

General: Alumina chromatography (eluant ethyl acetate-ether, 1:1).
5α-Cholest-2-eno[2, 3-g]-3'-cyanopyrazolo[1, 5-a]pyrimidine (186) was recrystallised from acetone as light yellow crystals (51%), m. p. 207-209^{o}; u. v., λ_{max} 232, 279 and 314 nm (log ϵ 4. 58, 3. 73 and 3. 77); i. r., γ_{max} 2220 (CN), 1625, 1535, 1465, 1440, 1375 and 775 cm^{-1}; ^{1}H n. m. r. (100 MHz), δ 0. 70, 0. 80, 0. 82, 0. 88, 0. 95 (methyl groups), 8. 27 (s, 1H, 2'-H), 8. 42 (s, 1H, 5'-H) (Found: C, 78. 95; H, 9. 53; N, 11. 54; M^{+}, 486. 373134. $C_{32}H_{46}N_4$ requires C, 78. 95; H, 9. 53; N, 11. 52%; M, 486. 372229).

5α-Cholestano[3, 2-f]-3'-cyanopyrazolo[1, 5-a]pyrimidine (187) was recrystallised from acetone as light yellow crystals (17%, m. p. 214-217^{o}; m. s., m/e 486; i. r., γ_{max} 2220 (CN), 1630, 1550, 1505, 1460, 1405 and 750 cm^{-1}; ^{1}H n. m. r. (60 MHz), δ 0. 70, 0. 80 and 0. 90 (methyl groups), 8. 25 (s, 1H, 2'-H) and 8. 45 (s, 1H, 7'-H).

5. 12. vi 11-Oxo-5α-spirost-2-eno[2, 3-g]-3'-cyanopyrazolo[1, 5-a]-pyrimidine (188).

Source: 2-Hydroxymethylene-5α-spirostan-3, 11-dione (111) and 3-amino-4-cyanopyrazole (126).

General: Alumina chromatography (eluant ethyl acetate) gave 11-oxo-5α-spirost-2-eno[2, 3-g]-3'-cyanopyrazolo[1, 5-a]pyrimidine (188) which was recrystallised methanol as yellow crystals (45%), m.p. 288-290°; u.v., λ_{max} 207, 227 and 314 nm (logϵ 4.33, 4.62 and 3.96); i.r., ν_{max} 2220 (CN), 1700 (CO), 1540, 1450, 1385, 1370 and 755 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.76 (s, 3H, 18-CH_3), 1.02 (s, 3H, 19-CH_3), 8.26 (s, 1H, 2'-H) and 8.42 (s, 1H, 5'-H) (Found: C, 72.45; H, 7.63; N, 10.36; M$^+$, 528.310046. $C_{32}H_{40}N_4O_3$ requires C, 72.69; H, 7.63; N, 10.60%; M, 528.310024).

5.12.vii 17β-Hydroxy-17α-methyl-5α-androst-2-eno[2, 3-g]-3'-cyano-2'-cyanomethylpyrazolo[1, 5-a]pyrimidine (189).

Source: 17β-Hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108) and 3-amino-4-cyano-5-cyanomethylpyrazole (92).

General: After cooling the reaction mixture to room temperature, 17β-hydroxy-17α-methyl-5α-androst-2-eno[2, 3-g]-3'-cyano-2'-cyanomethylpyrazolo[1, 5-a]pyrimidine (189) was obtained directly as white crystals (71%) m.p. 265-267°; u.v., λ_{max} 207, 232 and 313 nm (log ϵ 4.07, 4.65 and 3.76); i.r., ν_{max} 3600 (OH), 2220 (CN), 1625, 1535, 1490, 1440, 1405, 1380 and 760 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 0.85 (s, 3H, 18-CH_3), 0.90 (s, 3H, 19-CH_3), 1.25 (s, 3H, 17-CH_3), 4.05 (s, 2H, 2'-CH_2CN) and 8.40 (s, 1H, 5'-H) (Found: C, 72.95; H, 7.55; N, 15.69; M$^+$, 443.269215. $C_{27}H_{33}N_5O$ requires C, 73.09; H, 7.50; N, 15.79%; M, 443.268497).

5.12.viii 5α-Cholest-2-eno[2, 3-g]-3'-cyano-2'-cyanomethylpyrazolo-[1, 5-a]pyrimidine (190).

Source: 2-Hydroxymethylene-5α-cholestan-3-one (110) and 3-amino-

4-cyano-5-cyanomethylpyrazole (92).

General: Alumina chromatography (eluant chloroform) gave 5α-cholest-2-eno[2, 3-g]-3'-cyano-2'-cyanomethylpyrazolo[1, 5-a]pyrimidine (190) which was recrystallised from ethanol to give a white solid (28%), m.p. 260-262°; u.v., λ_{max} 208, 231 and 311 nm (log ε 4.05, 4.48 and 3.69); i.r., ν_{max} 2220 (CN), 1620, 1540, 1490, 1460, 1440, 1400, 1380 and 755 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.70, 0.80, 0.84 and 0.90 (methyl groups), 4.06 (s, 2H, 2'-CH_2CN), and 8.44 (s, 1H, 5'-H) (Found: C, 76.39; H, 8.91; N, 12.87; M$^+$, 525.382049. $C_{34}H_{47}N_5$ requires C, 77.66; H, 9.02; N, 13.33%; M$^+$, 525.38128).

5.12.ix 17β-Hydroxyandrost-2,4-dieno[2, 3-g]pyrazolo[1, 5-a]pyrimidine (191)

Source: 17β-Hydroxy-2-hydroxymethyleneandrost-4-ene-3-one (4) and 3-aminopyrazole (174).

General: Alumina chromatography (eluant ethyl acetate) gave 17β-hydroxyandrost-2,4-dieno[2, 3-g]pyrazolo[1, 5-a]pyrimidine (191) which was recrystallised from acetone as yellow crystals (72%), m.p. 230-232°; u.v., λ_{max} 209, 235 (sh), 242 and 370 nm (log ε 3.89, 4.48, 4.59 and 3.98); i.r., ν_{max} 3595 (OH), 1630, 1590, 1520, 1460 and 770 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.80 (s, 3H, 18-CH_3), 1.00 (s, 3H, 19-CH_3), 3.66 (m, 1H, 17-H), 6.56 (d, J=2Hz, 1H, 3'-H), 7.00 (s, 1H, 4-H), 8.05 (d, J=2Hz, 1H, 2'-H) and 8.18 (s, 1H, 5'-H) (Found: C, 75.82; H, 8.16; N, 11.44; M$^+$, 363.231059. $C_{23}H_{29}N_3O$ requires C, 75.98; H, 8.04; N, 11.56%; M, 363.231050).

5.12.x 17β-Hydroxyandrost-2,4-dieno[2,3-g]-3'-cyanopyrazolo-[1,5-a]pyrimidine (192).

Source: 17β-Hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4) and 3-amino-4-cyanopyrazole (126).

General: Alumina chromatography (eluant chloroform) gave 17β-hydroxyandrost-2,4-dieno[2,3-g]-3'-cyanopyrazole (192) which was recrystallised from ethanol to give yellow crystals (53%), m.p. 258-260°; u.v., λ_{max} 209, 239, 251, 313 and 364 (log ε 4.18, 4.50, 4.25, 3.59 and 3.94); i.r., γ_{max} 3600 (OH), 2220 (CN), 1630, 1595, 1530, 1480, 1375 and 760 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.82 (s, 3H, 18-CH$_3$), 1.04 (s, 3H, 19-CH$_3$), 3.68 (t, 1H, 17-H), 6.98 (s, 1H, 4-H), 8.26 (s, 1H, 2'-H) and 8.40 (s, 1H, 5'-H) (Found:[141] M$^+$, 388.225263. $C_{24}H_{28}N_4O$ requires M, 388.226300).

5.12.xi 17β-Hydroxyandrost-2,4-dieno[2,3-g]-3'-cyano-2'-cyanomethylpyrazolo[1,5-a]pyrimidine (193).

Source: 17β-Hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4) and 3-amino-4-cyano-5-cyanomethylpyrazole (92).

General: Alumina chromatography (eluant chloroform) gave 17β-hydroxyandrost-2,4-dieno[2,3-g]-3'-cyano-2'-cyanomethylpyrazolo[1,5-a]-pyrimidine (193) which was recrystallised from acetone as yellow crystals (23%), m.p. 268-270°; i.r., γ_{max} 3590 (OH), 2220 (CN), 1630, 1595, 1530, 1490, 1380 and 925 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 0.85 (s, 3H, 18-CH$_3$), 1.05 (s, 3H, 19-CH$_3$), 3.70 (m, 1H, 17-H), 4.10 (s, 2H, 2'-CH$_2$CN), 7.02 (s, 1H, 4-H) and 8.50 (s, 1H, 5'-H) (Found: C, 72.89; H, 6.81; N, 16.25; M$^+$, 427.235968. $C_{26}H_{29}N_5O$ requires C, 73.02;

H, 6.84; N, 16.39%; M, 427.237198).

5.12.xii 3β-Hydroxy-5α-androst-16-eno[16,17-g]pyrazolo[1,5-a]pyrimidine (197).

Source: 3β-Hydroxy-16-hydroxymethylene-5α-androstan-17-one (7) and 3-aminopyrazole (174).

General: Alumina chromatography (eluant ethyl acetate) gave 3β-hydroxy-5α-androst-16-eno[16,17-g]pyrazolo[1,5-a]pyrimidine (197) which was recrystallised from acetone as white fine crystals (91%), m.p. 240-241°; u.v., λ_{max} 236 and 327 nm (log ε 4.51 and 3.38); i.r., γ_{max} 3590 (OH), 1600, 1545, 1510, 1455, 1345 and 775 cm^{-1}; ^{1}H n.m.r. (60 MHz) δ 0.90 (s, 3H, 18-CH_3), 1.18 (s, 3H, 19-CH_3), 3.65 (m, 1H, 3-H), 6.70 (d, J=2Hz, 1H, 3'-H), 8.15 (d, J=2Hz, 1H, 2'-H) and 8.45 (s, 1H, 5'-H) (Found: C, 75.34; H, 8.63; N, 11.84; M^+, 365.245445. $C_{23}H_{31}N_3O$ requires C, 75.57; H, 8.55; N, 11.50%; M, 365.246700).

5.12.xiii 3β-Hydroxyandrost-5,16-dieno[16,17-g]pyrazolo[1,5-a] pyrimidine (198).

Source: 3β-Hydroxy-16-hydroxymethyleneandrost-5-en-17-one (8) and 3-aminopyrazole (174).

General: Alumina chromatography (eluant chloroform) gave 3β-hydroxyandrost-5,16-dieno[16,17-g]pyrazolo[1,5-a]pyrimidine (198) which was recrystallised from alcohol as white long needles (84%), m.p. 248-249°; u.v., λ_{max} 206, 234 and 330 nm (log ε 3.99, 4.58 and 3.53); i.r., γ_{max} 3595 (OH), 1600, 1545, 1510, 1455, 1370 and 755 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 1.12 (s, 3H, 18-CH_3), 1.25 (s, 3H, 19-CH_3), 3.55 (m, 1H, 3-H), 5.45 (t, 1H, 6-H), 6.70 (d, J=2Hz, 1H, 3'-H), 8.15 (d, J=2Hz, 1H, 2'-H) and 8.40 (s, 1H, 5'-H) (Found: C, 75.82; H, 8.10; N, 11.95; M^+, 363.229650. $C_{23}H_{29}N_3O$ requires C, 75.98; H, 8.04; N, 11.57%; M, 363.231050).

5.12.xiv 3-Methoxyoestra-1, 3, 5(10), 16-tetraeno[16, 17-g]pyrazolo-[1, 5-a]pyrimidine (199).

Source: 16-Hydroxymethylene-3-methoxyoestra-1, 3, 5(10)-trien-17-one (9) and 3-aminopyrazole (174).

General: 3-Methoxyoestra-1, 3, 5(10), 16-tetraeno[16, 17-g]pyrazolo-[1, 5-a]pyrimidine (199) crystallised directly as white needles upon cooling the reaction mixture (98%), m.p. 203-205° (dec); i.r., γ_{max} 1600, 1545, 1510, 1495, 1455, 1345, 775 and 755 cm^{-1}; ^1H n.m.r. (100 MHz), δ 1.20 (s, 3H, 18-CH_3), 3.74 (s, 3H, 3-OCH_3), 6.62-6.78 (m, 3H, 3'-H, 2-H and 4-H), 7.20 (d, 1H, 1-H), 8.06 (d, J=2Hz, 1H, 2'-H) and 8.33 (s, 1H, 5'-H) (Found: C, 76.64; H, 7.13; N, 11.98; M^+, 359.198064. $C_{23}H_{25}N_3O$ requires C, 76.84; H, 7.01; N, 11.69%; M, 359.199752).

5.12.xv 3β-Hydroxy-5α-androst-16-eno[16, 17-g]-3'-cyanopyrazolo[1, 5-a]pyrimidine (200).

Source: 3β-Hydroxy-16-hydroxymethylene-5α-androstan-17-one (7) and 3-amino-4-cyanopyrazole (126).

General: Alumina chromatography (eluant chloroform) gave 3β-hydroxy-5α-androst-16-eno[16, 17-g]-3'-cyanopyrazolo[1, 5-a]pyrimidine (200) which was recrystallised from ethanol as white crystals (40%), m.p.

316-318° (dec); u.v., λ_{max} 207, 234 and 323 nm (log ϵ 3.94, 4.41 and 3.74); i.r., γ_{max} 3590 (OH), 2220 (CN), 1610, 1555, 1520 and 770 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 0.92 (s, 3H, 18-CH_3), 1.18 (s, 3H, 19-CH_3), 4.70 (m, 1H, 3-H), 8.30 (s, 1H, 2'-H) and 8.55 (s, 1H, 5'-H) (Found: C, 73.70; H, 7.91; N, 14.15; M^{+}, 390.242024. $C_{24}H_{30}N_4O$ requires C, 73.80; H, 7.75; N, 14.35%; M, 390.241949).

5.12.xvi 3β-Hydroxyandrost-5,16-dieno[16,17-g]-3'-cyanopyrazolo[1,5-a]pyrimidine (201).

Source: 3β-Hydroxy-16-hydroxymethyleneandrost-5-en-17-one (8) and 3-amino-4-cyanopyrazole (126).

General: Alumina chromatography (eluant chloroform) gave 3β-hydroxyandrost-5,16-dieno[16,17-g]-3'-cyanopyrazolo[1,5-a]pyrimidine (201) which was recrystallised from ethanol as light yellow crystals (38%), m.p. 308-311° (dec); u.v., λ_{max} 207, 233 and 322 nm (log ϵ 4.12, 4.54 and 3.82); i.r., γ_{max} 3590 (OH), 2220 (CN), 1610, 1540, 1520, 1370 and 770 cm^{-1}; ^{1}H n.m.r. (MHz), δ 0.92 (s, 3H, 18-CH_3), 1.20 (s, 3H, 19-CH_3), 3.70 (m, 1H, 3-H), 8.42 (s, 1H, 2'-H) and 8.65 (s, 1H, 5'-H) (Found: C, 74.03; H, 7.24; N, 14.38; M^{+}, 388.223760. $C_{24}H_{28}N_4O$ requires C, 74.18; H, 7.27; N, 14.43%; M, 388.226300).

5.12.xvii 3-Methoxyoestra-1,3,5(10),16-tetraeno[16,17-g]-3'-cyanopyrazolo[1,5-a]pyrimidine (202).

Source: 16-Hydroxymethylene-3-methoxyoestra-1,3,5(10)-trien-17-one (9) and 3-amino-4-cyanopyrazole (126).

General: Alumina chromatography (eluant chloroform) gave 3-methoxyoestro-1,3,5(10),16-tetraeno[16,17-g]-3'-cyanopyrazolo[1,5-a]pyrimidine (202) which was recrystallised from ethanol-chloroform as white crystals (53%), m.p. 255-257°; i.r., γ_{max} 2220 (CN), 1610, 1520, 1500 and 955 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 1.22 (s, 3H, 18-CH_3), 3.76 (s, 3H, 3-OCH_3), 6.70-6.88 (m, 2H, 2-H, and 4-H), 7.30 (d, 1H, 1-H), 8.32 (s, 1H, 2'-H) and 8.58 (s, 1H, 5'-H) (Found: C, 74.73; H, 6.31; N, 14.66; M$^+$, 384.195502. $C_{24}H_{24}N_4O$ requires C, 74.96; H, 6.30; N, 14.58%; M, 384.195001).

5.12.xviii 17β-Acetoxyandrost-2,4-dieno[2,3-g]pyrazolo[1,5-a] pyrimidine (194).

A solution of 17β-hydroxyandrost-2,4-dieno[2,3-g]pyrazolo-[1,5-a]pyrimidine (192) (400 mg, 1.11x10^{-3} mole) in pyridine(25 ml)containing a few drops of acetic anhydride was refluxed for 2 h. The solvent was evaporated in vacuo and the residue taken up in chloroform. The chloroform solution was washed with water, 5% hydrochloric acid, saturated sodium bicarbonate solution and water again before being dried over anhydrous magnesium sulphate and was evaporated to dryness. The residue was chromatographed over alumina. Elution with chloroform gave 17β-acetoxyandrost-2,4-dieno[2,3-g]pyrazolo[1,5-a]pyrimidine (194) which was recrystallised from acetone as yellow crystals (290 mg, 65%), m.p. 185-187°; u.v., λ_{max} 206, 242 and 374 nm (log ε 4.08, 4.54 and 3.77); i.r., γ_{max} 1715 (C=O), 1625, 1585, 1520, 1455, 1420, 1370, 1355, 1245, 1035, 895, 860 and 770 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.84 (s, 3H, 18-CH_3), 1.00 (s, 3H, 19-CH_3), 2.04 (s, 3H, 17-$OCOCH_3$), 4.62 (t, 1H, 17-H), 6.58 (d, J=2Hz, 1H, 3'-H), 7.00 (s, 1H, 4-H), 8.00

(d, J=2Hz, 1H, 2'-H) and 8.20 (s, 1H, 5'-H) (Found: C, 74.22; H, 7.71; H, 10.55; M^+, 405.239142. $C_{25}H_{31}N_3O_2$ requires C, 74.03; H, 7.71; N, 10.37%; M, 405.241614).

Similarly treatment of the compounds (192), (197), (198), (200) and (201) with acetic anhydride in pyridine gave the corresponding acetyl derivatives (195), (203)-(206).

5.12.xix 17β-Acetoxyandrost-2,4-dieno[2,3-g]-3'-cyanopyrazolo-[1,5-a]pyrimidine (195) was recrystallised from ethanol as yellow crystals (54%), m.p. 235-237°; i.r., γ_{max} 2220 (CN), 1720 (C=O), 1628, 1595, 1520, 1575, 1370 and 760 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.86 (s, 3H, 18-CH_3), 1.04 (s, 3H, 19-CH_3), 2.04 (s, 3H, 17-$OCOCH_3$), 4.62 (m, 1H, 17-H), 6.96 (s, 1H, 4-H), 8.26 (s, 1H, 2'-H) and 8.40 (s, 1H, 5'-H) (Found: C, 72.29; H, 6.93; N, 12.81; M^+, 430.237711. $C_{26}H_{30}N_4O_2$ requires C, 72.52; H, 7.03; N, 13.02%; M, 430.236863).

5.12.xx 3β-Acetoxy-5α-androst-16-eno[16,17-g]pyrazolo[1,5-a]pyrimidine (203) was recrystallised from ethanol to give white needles (61%), m.p. 264-265°; u.v., λ_{max} 235 and 330 nm (log ε 4.58 and 3.56); i.r., γ_{max} 1720 (CO), 1600, 1545, 1510, 1460 and 775 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.90 (s, 3H, 18-CH_3), 1.16 (s, 3H, 19-CH_3), 2.00 (s, 3H, 3-$OCOCH_3$), 4.68 (m, 1H, 3-H), 6.63 (d, J=2Hz, 1H, 3-H), 8.04 (d, J=2Hz, 1H, 2'-H) and 8.33 (s, 1H, 5'-H) (Found: C, 73.82; H, 8.14; N, 10.35; M^+, 407.254023. $C_{25}H_{33}N_3O_2$ requires C, 73.66; H, 8.17; N, 10.32%; M, 407.257263).

5.12.xxi 3β-Acetoxyandrost-5,16-dieno[16,17-g]pyrazolo[1,5-a]-pyrimidine (204) was recrystallised from ethanol as long white needles (85%), m.p. 229-231°; u.v., λ_{max} 206, 234, 284 and 331 nm (log ε 3.84, 4.57, 3.16 and 3.33); i.r., ν_{max} 1720 (CO), 1600, 1545, 1510, 1460, 1445 and 775 cm^{-1}; ^1H n.m.r. (100 MHz), δ 1.12 (s, 3H, 18-CH_3), 1.20 (s, 3H, 19-CH_3), 2.02 (s, 3H, 3-$OCOCH_3$), 4.60 (m, 1H, 3-H), 5.42 (t, 1H, 6-H), 6.64 (d, J=2Hz, 1H, 3'-H), 8.06 (d, J=2Hz, 1H, 2'-H) and 8.34 (s, 1H, 5'-H) (Found: C, 74.16; H, 7.61; N, 10.65; M^+, 405.239518. $C_{25}H_{31}N_3O_2$ requires C, 74.03; H, 7.71; N, 10.37%; M, 405.241614).

5.12.xxii 3β-Acetoxy-5α-androst-16-eno[16,17-g]-3'-cyanopyrazolo-[1,5-a]pyrimidine (205) was recrystallised from ethanol as white crystals (58%), m.p. 335-337°; u.v., λ_{max} 207, 234 and 323 nm (log ε 4.11, 4.50 and 3.81); i.r., ν_{max} 2220 (CN), 1720 (CO), 1610, 1550, 1520, 1365 and 755 cm^{-1}; ^1H n.m.r. (100 MHz), δ 0.92 (s, 3H, 18-CH_3), 1.18 (s, 3H, 19-CH_3), 2.02 (s, 3H, 3-$OCOCH_3$), 4.70 (m, 1H, 3-H), 8.32 (s, 1H, 2'-H) and 8.56 (s, 1H, 5'-H) (Found: C, 72.36; H, 7.45; N, 12.92; M^+, 432.253011. $C_{26}H_{32}N_4O_2$ requires C, 72.18; H, 7.46; N, 12.96%; M, 432.252512).

5.12.xxiii 3β-Acetoxyandrost-5,16-dieno[16,17-g]-3'-cyanopyrazolo-[1,5-a]pyrimidine (206) was recrystallised from ethanol as white crystals (59%), m.p. 298-300° (dec); u.v., λ_{max} 208, 239 and 324 nm (log ε 4.07, 4.49 and 3.75); i.r., ν_{max} 2220 (CN), 1720 (CO), 1610, 1550, 1520, 1380 and 950 cm^{-1}; ^1H n.m.r. (100 MHz), δ 1.12 (s, 3H, 18-CH_3), 1.22 (s, 3H, 19-CH_3), 2.02 (s, 3H, 3-$OCOCH_3$), 4.58 (m, 1H, 3-H), 5.45 (t, 1H, 6-H), 8.32 (s, 1H, 3'-H) and 8.58 (s, 1H, 5'-H) (Found: C, 72.39; H, 6.99; N, 13.13; m/e, 370. $C_{26}H_{30}N_4O_2$ requires C, 72.52; H, 7.03; N, 13.02%; M^+-CH_3COOH, 370).

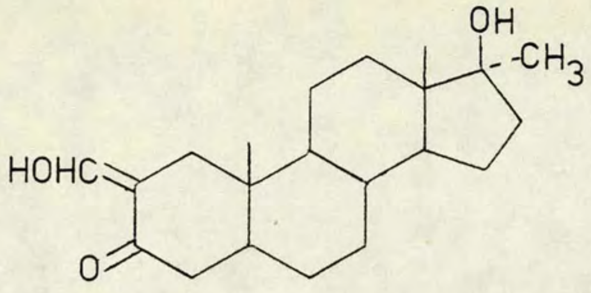
5.12.xxiv 2(2'-Pyridyl-aminomethylene)-5α-cholestan-3-one (207).

A solution of 2-hydroxymethylene-5α-androstan-3-one (110) (500 mg, 1.21 x 10^{-3} mole) and 2-aminopyridine (120 mg, 1.26 x 10^{-3} mole) in pyridine (5 ml) was allowed to stand at room temperature overnight. The solvent was removed in vacuo and the residue taken up in chloroform. The chloroform solution was washed with 5% hydrochloric acid and water. It was dried over anhydrous magnesium sulphate and the solvent was evaporated to dryness. Chromatography (eluant chloroform) of the residue followed by recrystallisation from acetone gave yellow crystals of 2(2'-pyridyl-aminomethylene)-5α-cholestan-3-one (207) (355 mg, 60%); m.p. 135-138°; i.r., ν_{max} 1640, 1590, 1545, 1475, 1440, 1415, 1360 and 770 cm^{-1}; ^1H n.m.r. (60 MHz), δ 0.65, 0.78, 0.82 and 0.92 (methyl groups), 6.60-6.95 (m, 2H, pyridine ring 3-H and 5-H), 7.50 (dd, 1H, pyridine ring, 4-H), 7.82 (d, J=11.5Hz, -NH-C$\underline{H}$=C-), 8.25 (d, 1H, pyridine ring 6-H) and 10.90 (d, J=11.5Hz, 1H, N-$\underline{H}$) (Found: C, 80.44; H, 10.14; N, 5.52; M^+ 490.393935. $C_{33}H_{50}N_2O$ requires C, 80.75; H, 10.19; N, 5.71%; M, 490.392294).

5.12.xxv The reaction of 2(2'-pyridyl-aminomethylene)-5α-cholestan-3-one (207) with 3-aminopyrazole (174).

A solution of 2(2'-pyridyl-aminomethylene)-5α-cholestan-3-one (207) (400 mg, 8.15 x 10^{-4} mole) and 3-aminopyrazole (174) (90 mg,

1.08×10^{-3} mole) in dry toluene containing a catalytic amount of toluene-4-sulphonic acid was refluxed for 7 h. The solvent was removed in vacuo and the residue was chromatographed over alumina (50 g). Elution with ethyl acetate followed by recrystallisation of the eluate from ethanol gave white crystals of 5α-cholestano[3, 2-f]pyrazolo-[1, 5-a]pyrimidine (181) (185 mg, 60%), m. p. 138-140° (identified by its m. p. , i. r. and ^{1}H n. m. r. spectra).



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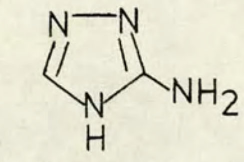

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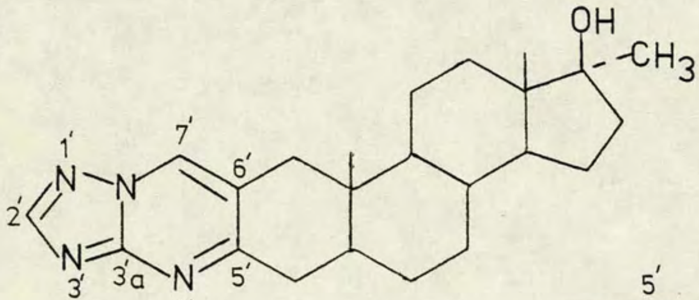

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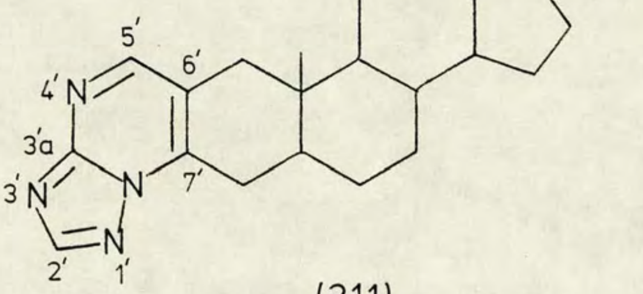

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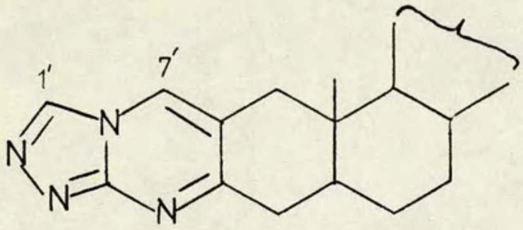

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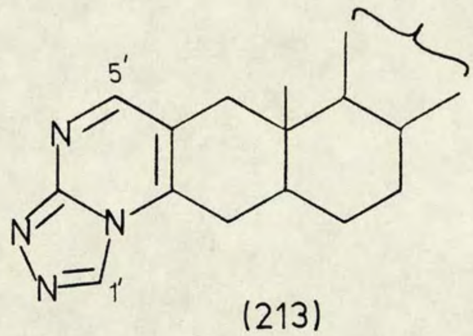

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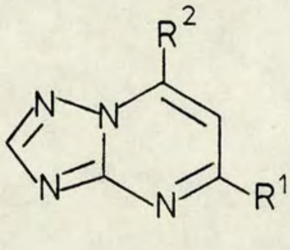

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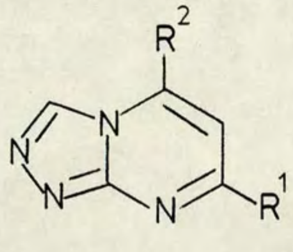

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6 The reaction of steroidal β-ketoaldehydes with 3-amino-1,2,4-triazole and its derivatives.

6.1 The reaction of 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108) with 3-amino-1,2,4-triazole (95).

A solution of 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108) and 3-amino-1,2,4-triazole (95) in absolute alcohol was refluxed overnight. The excess of solvent was removed under vacuo and the residue was chromatographed over alumina. Elution with benzene-chloroform (3:1) gave two products (210), m.p. 118-120°, in 45% yield and (211), m.p. 248-250°, in 25% yield.

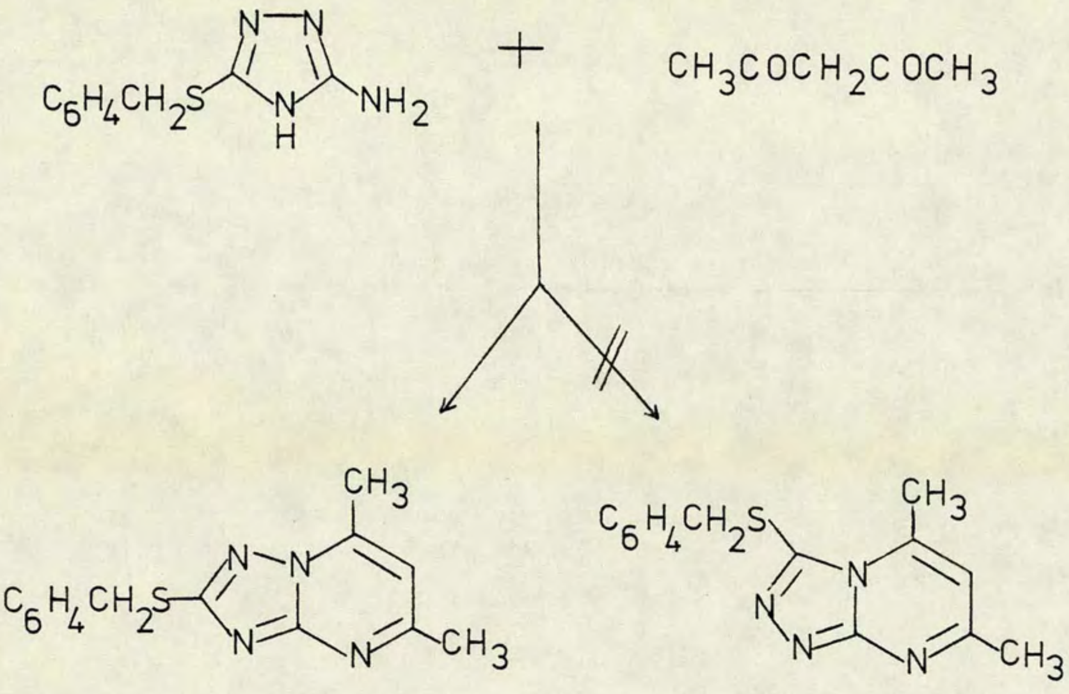
Mass spectrometry and elemental analysis indicated that both the products had the same molecular formula $C_{23}H_{32}N_4O$.

The u.v. spectrum of the product, m.p. 118-120°, showed λ_{max} at 220 and 283 nm (log ε 4.34 and 3.58) whilst the i.r. spectrum showed absorptions at 3600, 1620, 1510, 1440, 1405 and 775 cm^{-1}. The ^{1}H n.m.r. spectrum exhibited two singlets at δ 8.34 and δ 8.48, apart from the signals for the 17-, 18- and 19-methyl protons.

The u.v. spectrum of the product, m.p. 248-250°, showed λ_{max} at 218 and 283 nm (log ε 4.26 and 3.65) and the i.r. spectrum exhibited absorptions at 3600, 1620, 1545, 1520, 1445 and 775 cm^{-1}. The ^{1}H n.m.r. spectrum showed singlets at δ 8.40 and δ8.50 apart again from the signals for the 17, 18- and 19-methyl protons.

6.2 Discussion

The reaction of 3-amino-1,2,4-triazole (95) with the β-ketoaldehyde



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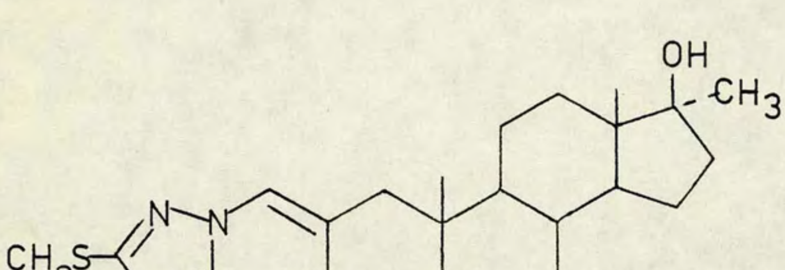

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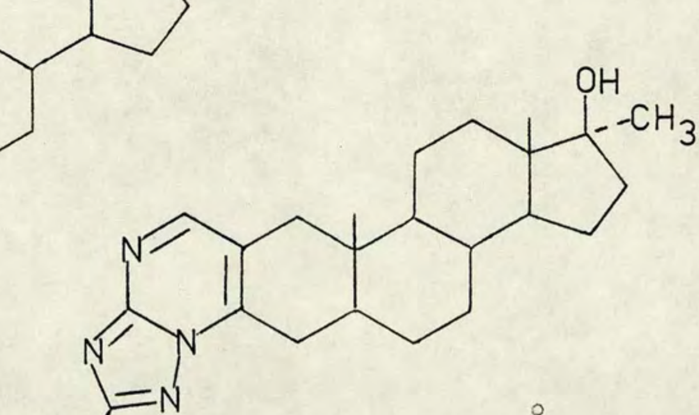


(226)

(108) can theoretically lead to four different s-triazolopyrimidine derivatives (210) - (213), depending upon the reaction site in the triazole part and upon the initial condensation step with the cyclic β-ketoaldehyde (108). However, in practice, only two products are formed whose structures follow from the evidence below.

(a) The alkyl-s-triazolo[4,3-a]pyrimidines (e.g. 99, $R^1=R^2=H$; λ_{max} 290 nm) are distinguished from the s-triazolo[1,5-a]pyrimidines (e.g. 98, $R^1=R^2=H$; λ_{max} 270 nm) by the absorption at longer wavelength of the former.[142] The two steroidal condensation products have almost identical u.v. spectra and thus these two products have structures either (210) and (211) or (212) and (213).

(b) The condensation of 3-amino-5-benzylthio-s-triazole with acetylacetone in refluxing acetic acid was reported by Okabe et al.[143] to have given 3-benzylthio-5,7-dimethyl-s-triazolo[4,3-a]pyrimidine (215). However, it was later established,[132] with the aid of ^{13}C n.m.r. spectroscopy and a modification of the original synthetic work that only 2-benzylthio-s-triazolo[1,5-a]pyrimidine (214) can be obtained by this method of condensation and this is found to be in agreement with the literature reported by Maury[80c] that s-triazolo[4,3-a]pyrimidines (99) have never been obtained by the reaction of β-ketoacetals, β-ketoaldehydes or β-diketones with 3-amino-1,2,4-triazoles. Thus it seems very unlikely that the two steroidal condensation products have structures (212) and (213).

(c) It has been demonstrated[132] in numerous examples that s-triazolo-[4,3-a]pyrimidines (99) rearrange very readily to s-triazolo[1,5-a]-pyrimidines (98) under basic, acidic or neutral conditions. The two steroidal condensation products, however, remain unchanged when heated in boiling pyridine or toluene for 12 h. The effect of acid on these products could not be investigated since the hydroxyl group at the 17 position is eliminated by a Wagner-Meerwein rearrangement. However, the two similar condensation products obtained by the reaction of 3-amino-1, 2, 4-triazole (95) with 2-hydroxymethylene-5α-cholestan-3-one (110) do not undergo any change when heated in boiling formic acid for 12 h. Therefore, it appears that the two products obtained by the condensation of 3-amino-1, 2, 4-triazole (95) with the β-ketoaldehyde (108) are s-triazolo[1, 5-a]pyrimidine derivatives (210) and (211) and not s-triazolo-[4, 3-a]pyrimidine derivatives (212) and (213).

(d) In the ^{1}H n. m. r. spectra (d^6-DMSO), the resonance of the triazole proton in the isomer, m. p. 118-120°, occurs at δ 8. 50 whilst in the isomer, m. p. 248-250°, it occurs at δ 8. 55. Reimlinger and Pieron[133] as well as Paudler and Helmic,[76] as stated earlier (section 4, page 56) have shown in a series of s-triazolopyrimidines that the triazole proton in s-triazolo[4, 3-a]pyrimidines (99) is deshielded and occurs at a lower field (>δ 9) in comparison with the triazole proton in the isomeric s-triazolo[1, 5-a]pyrimidines (98) which occurs at a higher field (<δ 9). Since the chemical shift of the triazole proton in both the isomers, m. p. 118-120° and m. p. 248-250°, is found to be less than δ 9, the structures (212) and (213) are rejected. This is further confirmed by the following ^{13}C n. m. r. evidence.

(e) The ^{13}C chemical shifts of 2'-C in s-triazolo[1, 5-a]pyrimidines (210) and (211) where the 2'-C atom is bonded to two ring nitrogens, are expected[135, 136a] to occur considerably further downfield compared to

Table 5

^{13}C-Chemical shifts of steroidal s-triazolo[1,5-a]pyrimidines (p.p.m.)

Compound	2'-C	3'a-C	5'-C	6'-C	7'-C	Other carbons
(210)	155.83	154.23	165.38	120.19	133.77	
(211)	155.94	154.23	155.35	118.59	144.99	
(216)	156.08	155.13	165.69	111.25	134.98	
(217)	155.56	155.96	154.03	110.06	148.15	
(225)	168.35	154.87	164.35	119.71	132.71	
(226)	168.34	154.86	154.86	117.77	144.07	
(232)	164.48*	154.86	166.08*	119.21	133.09	
(236)	155.29*	155.01	153.32*	112.90	140.52	4-C, 110.30; 5-C, 165.00
(237)	168.34	155.67	152.28	112.48	139.59	4-C, 110.36; 5-C, 165.32
(238)	164.59	152.46	152.64	112.36	139.85	4-C, 110.49; 5-C, 165.71
(244)	156.29	155.80	151.75	123.52	159.22	
	(1-C, 126.07)	(2-C, 111.66)	(3-C, 157.75)	(4-C, 113.94)	(5-C, 137.44)	(10-C, 131.61)

---

* These values could be interchanged.

the chemical shifts of 1'-C in s-triazolo[4,3-a]pyrimidines (212) and (213) where the 1'-C is bonded to a ring nitrogen and a bridgehead nitrogen. Since s-triazolopyrimidine and s-triazolopyridazine are both 10 π electron systems, it is reasonable to compare the chemical shifts of 2'-C in s-triazolo[1,5-a]pyrimidines (210) and (211) with that of 2-C in s-triazolo[1,5-b]pyridazine (163) and the chemical shifts of 1'-C in s-triazolo[4,3-a]pyrimidines (212) and (213) with that of 3-C in s-triazolo[4,3-b]pyridazine (67). The chemical shifts of the unsubstituted triazole carbon in the steroidal condensation products are found to be 155.83 p.p.m. and 155.94 p.p.m. (Table 5) which are in good agreement with the chemical shift of 2-C (152.04 p.p.m.) in s-triazolo-[1,5-b]pyridazine (163).[131] If the two condensation products had had structures (212) and (213), the chemical shifts of the unsubstituted triazole carbon would have been in the region of 139.04 p.p.m. which is the chemical shift of 3-C in s-triazolo[4,3-b]pyridazine (67).[131]

Under analogous reaction conditions, the condensation of 3-amino-5-methylthio-1,2,4-triazole (224) with 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108) gave two products (225) and (226) in which the chemical shifts of 2'-C (168.35 p.p.m. and 168.35 p.p.m.) are again found to resemble closely the chemical shift of 2-C (164.1 p.p.m.) in 2-benzylthio-5,7-dimethyl-s-triazolo[1,5-a]pyrimidine (214).[132] If the two condensation products had had structures like (212) and (213) then the chemical shifts of 1'-C in both the isomers would have been in agreement with the chemical shift of 1'-C (144.2 p.p.m.) in 5,7-dimethyl-s-triazolo[4,3-a]pyrimidine (215).[132]

In conclusion, the reaction of 2-hydroxymethylene-3-oxo steroid

Table 4

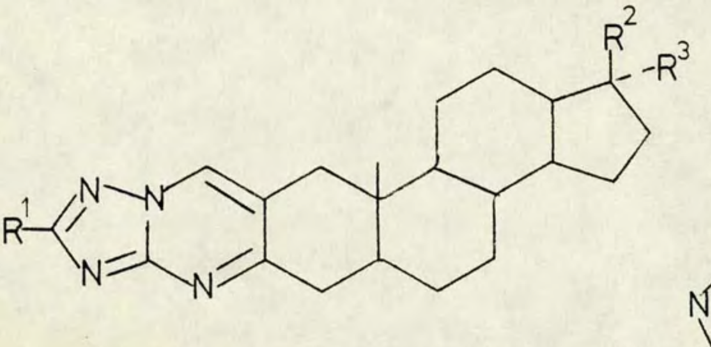
Characteristic i. r. absorption frequencies (cm^{-1})

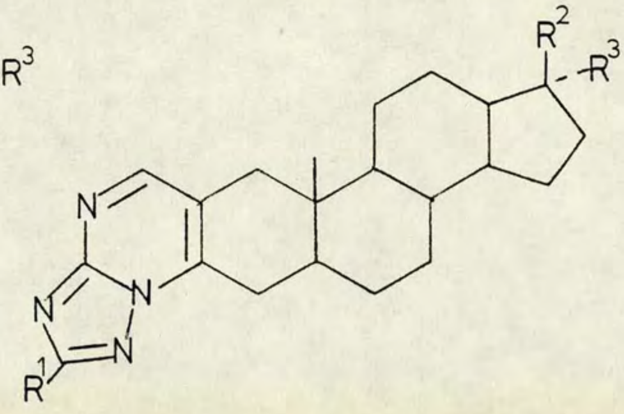
Compound	γ_{max} (cm^{-1})	Compound	γ_{max} (cm^{-1})
(210)	$\left.\begin{array}{l}1620\\1510\end{array}\right\}$ s 1405 s	(211)	$\left.\begin{array}{l}1620\\1545\\1520\end{array}\right\}$ s
(216)	$\left.\begin{array}{l}1615\\1530\end{array}\right\}$ s 1410 s	(217)	$\left.\begin{array}{l}1615\\1545\\1520\end{array}\right\}$ s
(233)	$\left.\begin{array}{l}1625\\1515\end{array}\right\}$ s 1415 s	(236)	$\left.\begin{array}{l}1630\\1550\\1510\end{array}\right\}$ s
		(241)	$\left.\begin{array}{l}1605\\1555\\1500\end{array}\right\}$ s

(108) with 3-amino-1, 2, 4-triazole (95) leads to the isomeric s-triazolo-[1, 5-a]pyrimidine derivatives (210) and (211) which are further distinguished as follows.

(f) The i. r. spectra of the two steroid isomers (210) and (211) which show some important differences when compared with each other also show some important similarities with the i. r. spectra of 5-methyl-s-triazolo[1, 5-a]pyrimidine (216) and 7-methyl-s-triazolo[1, 5-a]pyrimidine (217) (Table 4). The compound (211) and 7-methyl-s-triazolo[1, 5-a]-pyrimidine (217) differ from the compound (210) and 5-methyl-s-triazolo-[1, 5-a]pyrimidine (216) in showing an extra absorption band at 1545 cm^{-1} in the region 1500-1520 cm^{-1}. Secondly, the compound (210) and 5-methyl-s-triazolo[1, 5-a]pyrimidine (216) are distinguished by a strong absorption at 1405 or 1410 cm^{-1} which is absent in the i. r. spectra of the compound (211) and 7-methyl-s-triazolo[1, 5-a]pyrimidine (217).

(g) In the ^{1}H n. m. r. spectra, the chemical shifts of the 7'-H (δ 8.50) and the 5'-H (δ 8.48) in the triazolopyrimidines (210) and (211) respectively, are found to be almost identical. However, the most important difference is that the signal for 7'-H in the triazolo-pyrimidine (210) is broadened by a small long range coupling with the methylene protons at position 1 whilst the signal for 5'-H in the triazolo-pyrimidine (211) is found to be sharp. Thus, the assignment of structures (210) and (211) is consistent with the observation made by Makisumi <u>et al.</u>[77] that the methyl protons at position 6 of s-triazolo[1, 5-a]-pyrimidine (69) are coupled with the 7-H whilst no such coupling takes place between the methyl protons at position 6 and the 5-H.





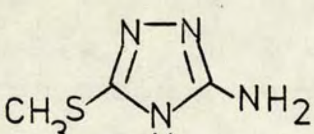
(218) $R^1=H=R^2=R^3$ (219)

(220) $R^1=H$, $R^2=C_8H_{17}$, $R^3=H$ (221)

(225) $R^1=SCH_3$, $R^2=OH$, $R^3=CH_3$ (226)

(227) $R^1=SCH_3$, $R^2=R^3=H$ (228)

(229) $R^1=SCH_3$, $R^2=C_8H_{17}$, $R^3=H$ (230)



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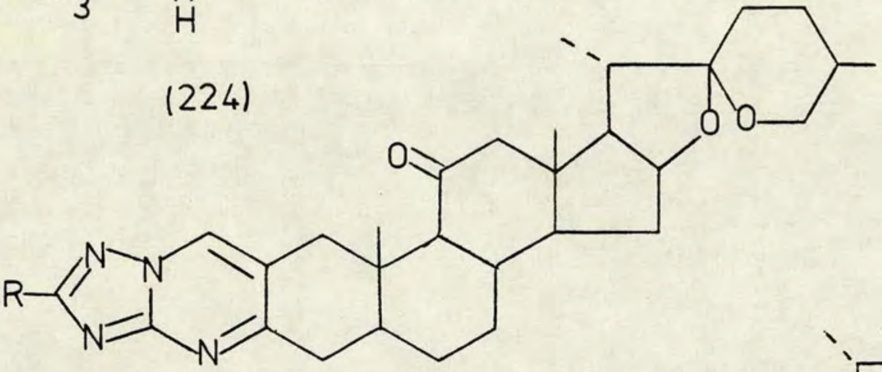
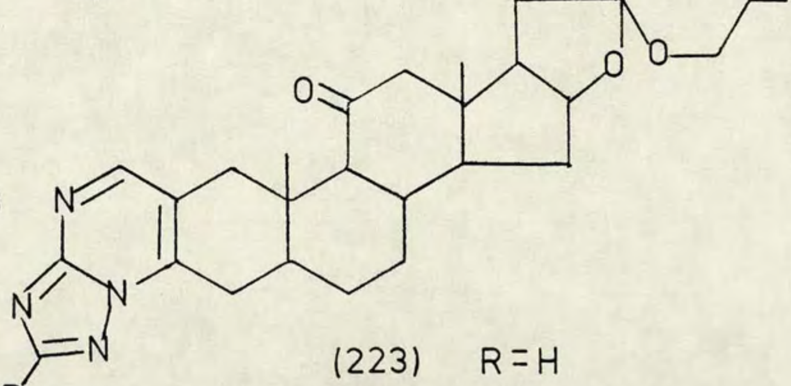


(222) R = H

(231) $R=SCH_3$



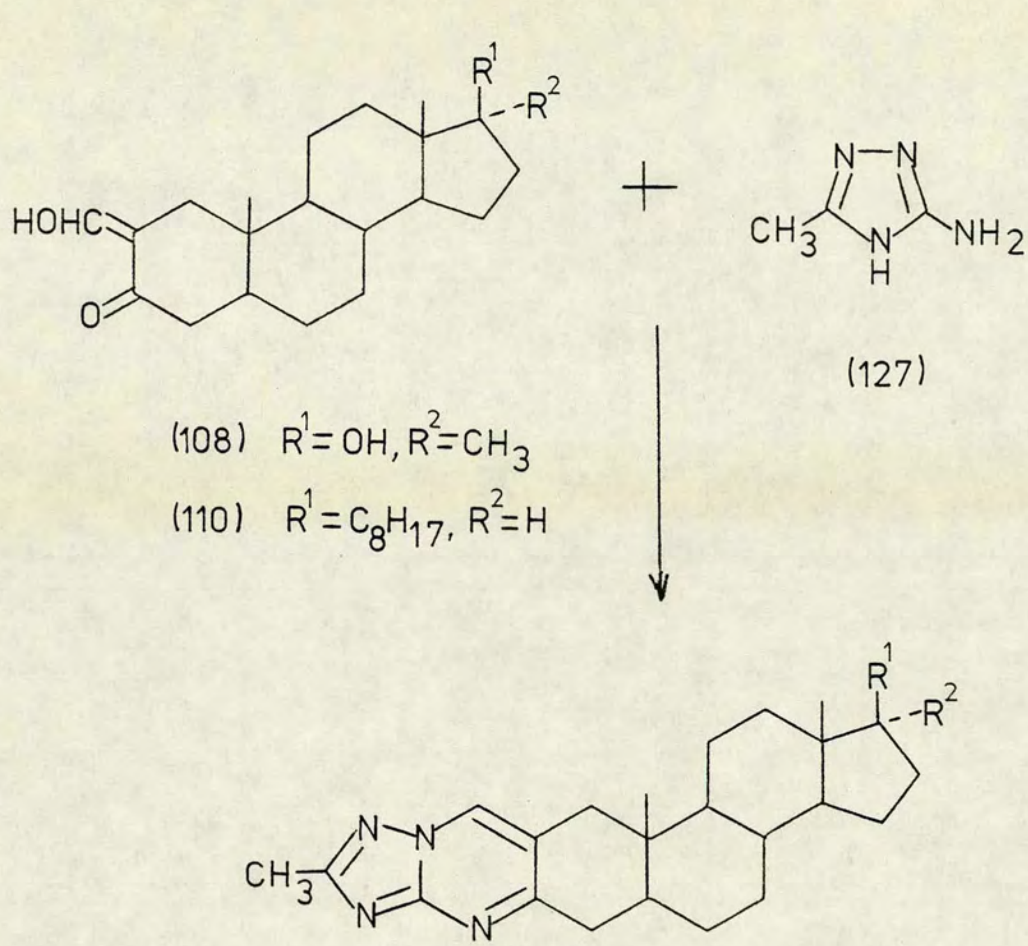
(223) R = H

(232) $R=SCH_3$

(h) Assignment of structures (210) and (211) is further supported by ^{13}C n. m. r. evidence. The ^{13}C-chemical shifts of the aromatic ring carbons of the triazolopyrimidines (210) and (211) are given in Table 5, along with those of the two model compounds (216) and (217). The assignments for the chemical shifts of the five carbons of the steroids (210) and (211) follow directly by analogy with the values allocated to triazolopyrimidines (216) and (217) (section 9). The chemical shift of 7'-C (133. 77 p. p. m.) in the triazolopyrimidine (210) is found to agree well with the chemical shift of 7-C (134. 98 p. p. m.) in 5-methyl-s-triazolo[1, 5-a]pyrimidine (216) thus confirming a linear fusion of the steroid to the heterocyclic system. The chemical shift of 5'-C (155. 35 p. p. m.) in the compound (211) is found to be in agreement with the chemical shift of 5-C (154. 03 p. p. m.) in 7-methyl-s-triazolo[1, 5-a]-pyrimidine (217) thus confirming an angular fusion of the steroid to the heterocyclic system.

Under analogous reaction conditions the condensation of 3-amino-1, 2, 4-triazole (95) with 2-hydroxymethylene-5α-androstan-3-one (109), 2-hydroxymethylene-5α-cholestan-3-one (110) and 2-hydroxymethylene-5α-spirostan-3, 11-dione (111) gave 5α-androstano[3, 2-f]-s-triazolo-[1, 5-a]pyrimidine (218) and 5α-androst-2-eno[2, 3-g]-s-triazolo[1, 5-a]-pyrimidine (219); 5α-cholestano[3, 2-f]-s-triazolo[1, 5-a]pyrimidine (220) and 5α-cholest-2-eno[2, 3-g]-s-triazolo[1, 5-a]pyrimidine (221); and 11-oxo-5α-spirostano[3, 2-f]-s-triazolo[1, 5-a]pyrimidine (222) and 11-oxo-5α-spirost-2-eno[2, 3-g]-s-triazolo[1, 5-a]pyrimidine (223) respectively.

Similarly the condensation of 3-amino-5-methylthio-1, 2, 4-triazole (224) with the β-ketoaldehydes (108)-(111) gave the 2'-methylthio derivatives



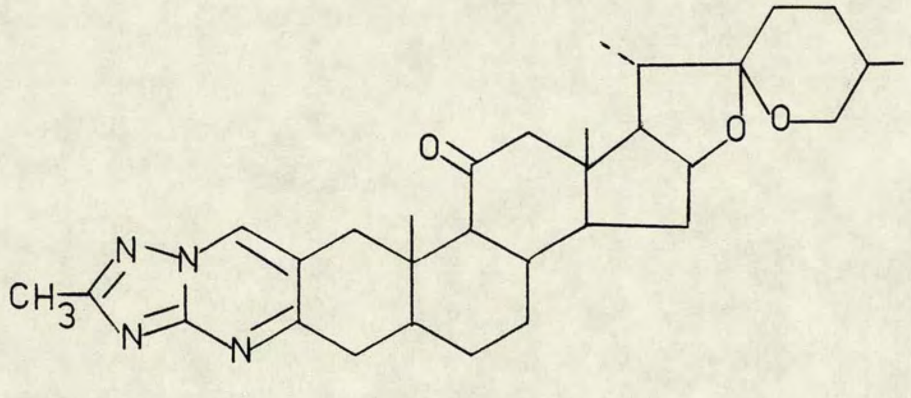
(127)

(108) $R^1 = OH, R^2 = CH_3$

(110) $R^1 = C_8H_{17}, R^2 = H$

(233) $R^1 = OH, R^2 = CH_3$

(234) $R^1 = C_8H_{17}, R^2 = H$



(235)

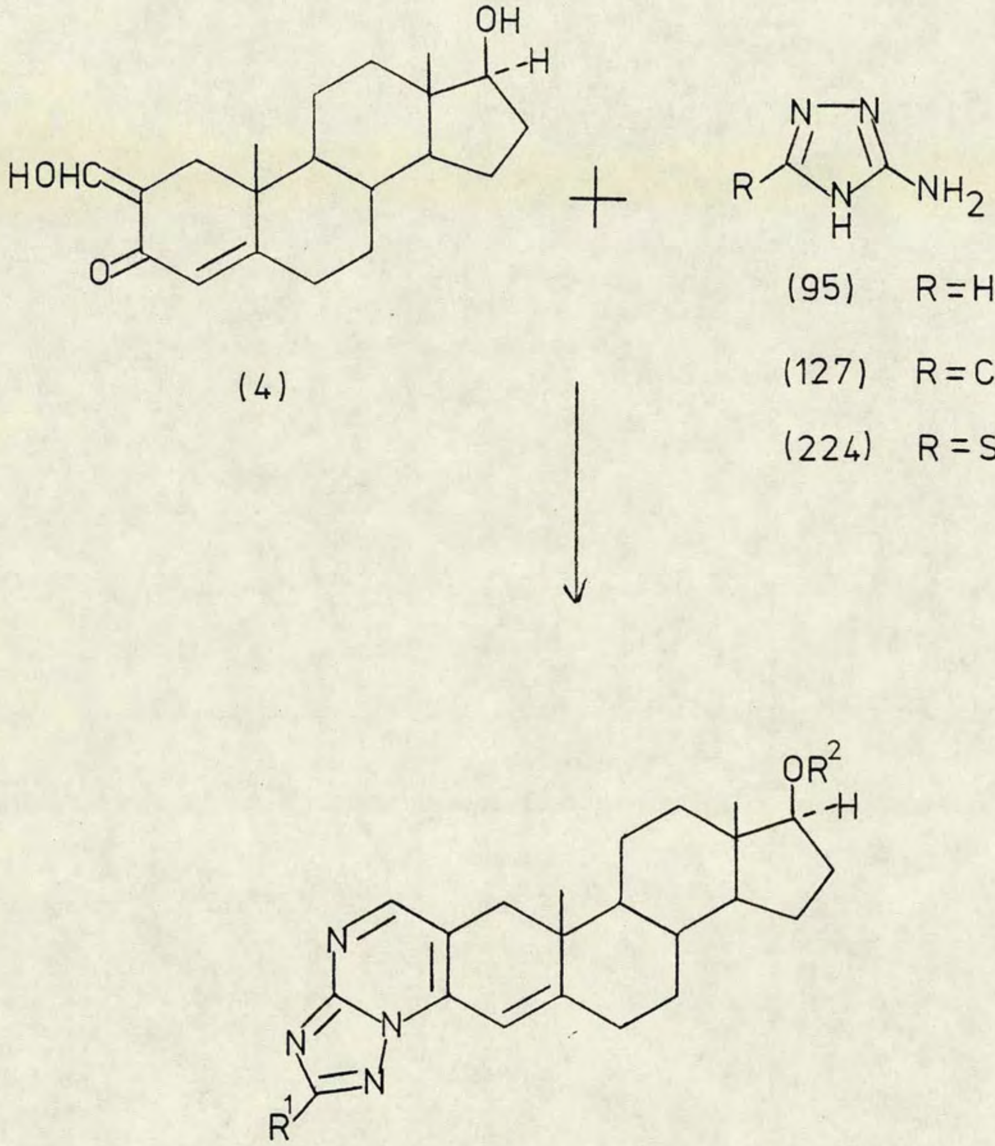
(225) and (226); (227) and (228); (229) and (230); and (231) and (232) respectively.

6.3 The reaction of 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108) with 3-amino-5-methyl-1, 2, 4-triazole (127).

A solution of 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108) and 3-amino-5-methyl-1, 2, 4-triazole (127) in absolute ethanol was refluxed overnight. The excess of solvent was removed under vacuo and the residue was chromatographed over alumina. Elution with chloroform followed by recrystallisation of the eluate from ethyl acetate gave white crystals (233), m. p. 232-234, in 68% yield.

Mass spectrometry and elemental analysis indicated that the product had a molecular formula of $C_{24}H_{34}N_4O$. The u. v. spectrum showed λ_{max} at 219 and 289 nm (log ε 4.51 and 3.77). The i. r. spectrum exhibiting absorptions at 3600, 1625, 1515, 1465, 1440, 1410, 1380 and 775 cm^{-1} compares well with the i. r. spectrum of 17β-hydroxy-17α-methyl-5α-androstano[3, 2-f]-s-triazolo[1, 5-a]pyrimidine (210). The ^1H n. m. r. spectrum showed a singlet at δ 8.32 (1H) which is broadened by coupling with the protons at position 1 and another singlet at δ 2.56 (3H), apart from the signals for the 17-, 18- and 19-methyl protons. All this evidence indicates that the steroid is 17β-hydroxy-17α-methyl-5α-androstano[3, 2-f]-2'-methyl-s-triazolo[1, 5-a]pyrimidine (233), and this structure is further confirmed by the ^{13}C - chemical shift of 7'-C (133.09 p. p. m.) which compares well with the chemical shift of 7'-C (133.77 p. p. m.) in the compound (210) (Table 5).

Similarly the reaction of 3-amino-5-methyl-1, 2, 4-triazole (127) with 2-hydroxymethylene-5α-cholestan-3-one (110), 2-hydroxymethylene-



(4)

(95) $R = H$

(127) $R = CH_3$

(224) $R = SCH_3$

(236) $R^1 = H = R^2$

(237) $R^1 = SCH_3$, $R^2 = H$

(238) $R^1 = CH_3$, $R^2 = H$

(239) $R^1 = SCH_3$, $R^2 = COCH_3$

5α-spirostan-3, 11-dione (111) gave 5α-cholestano[3, 2-f]-2'-methyl-s-triazolo[1, 5-a]pyrimidine (234) and 11-oxo-5α-spirostano[3, 2-f]-2'-methyl-s-triazolo[1, 5-a]pyrimidine (235) respectively.

6.4 The reaction of 17β-hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4) with 3-amino-1, 2, 4-triazole (95).

A solution of 17β-hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4) and 3-amino-1, 2, 4-triazole (95) in absolute alcohol was refluxed overnight, evaporated to dryness under vacuo and the residue was chromatographed over alumina. Elution with ethyl acetate followed by recrystallisation from ethanol gave yellow crystals (236), m. p. 252-254°, in 57% yield.

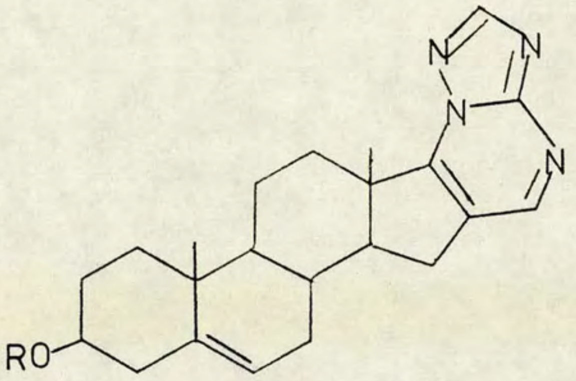
Mass spectrometry and elemental analysis indicated that the product had a molecular formula of $C_{22}H_{28}N_4O$. The u. v. spectrum of the product showed λ_{max} at 226 and 343 nm (log ε 4. 34 and 4. 21) whilst the i. r. spectrum had absorptions at 3600, 1630, 1590, 1550, 1510 and 780 cm^{-1}. The ^{1}H n. m. r. spectrum exhibited two sharp singlets at δ 8. 40 and δ 8. 52 corresponding to the proton on the triazole ring and the pyrimidine ring respectively. The i. r. spectrum, in which an absorption at 1550 cm^{-1} and the absence of any absorption at 1400 cm^{-1} are noteworthy (Table 4) and the ^{1}H n. m. r. spectrum which shows the pyrimidine ring proton as a sharp singlet at δ 8. 52, both correlate well with the i. r. and ^{1}H n. m. r. spectra of the compound (211) and indicate that the structure of the steroid is 17β-hydroxyandrost-2, 4-dieno[2, 3-g]-s-triazolo[1, 5-a]pyrimidine (236). This is confirmed by the ^{13}C-chemical shift observed for the 5'-C (155. 32 p. p. m.) which again agrees with the chemical shift of 5'-C (155.35 p.p.m.) in the compound (211) (Table 5).

Similarly the condensation of 17β-hydroxy-2-hydroxymethylene-androst-4-en-3-one (4) with 3-amino-5-methylthio-1, 2, 4-triazole (224) and 3-amino-5-methyl-1, 2, 4-triazole (127) gave 17β-hydroxyandrost-2, 4-dieno[2, 3-g]-2'-methylthio-s-triazolo[1, 5-a]pyrimidine (237) and 17β-hydroxyandrost-2, 4-dieno[2, 3-g]-2'-methyl-s-triazolo(1, 5-a]-pyrimidine (238) respectively.

It is interesting to note that the Δ^4 double bond in the steroid and the substituents on the triazole nucleus markedly influence the course of the condensation of 3-amino-1, 2, 4-triazoles with unsymmetrical β-dicarbonyl compounds. Thus, whilst the condensation of 3-amino-1, 2, 4-triazole (95) and 3-amino-5-methylthio-1, 2, 4-triazole (224) with 2-hydroxymethylene-3-oxo steroids without a Δ^4 double bond gives a mixture of linearly fused and angularly fused products, condensation with a 2-hydroxymethylene-3-oxo steroid with a Δ^4 double bond gives only angularly fused products. Further, the condensation of 3-amino-5-methyl-1, 2, 4-triazole (127) with 2-hydroxymethylene-3-oxo steroids without a Δ^4 double bond gives only linearly fused products whereas condensation with 2-hydroxymethylene-3-oxo steroids with a Δ^4 double bond gives only angularly fused products demonstrating that the Δ^4 double bond in the steroid nucleus overcomes the opposing effect of the methyl substituent of the triazole (127) on the course of the condensation reaction.

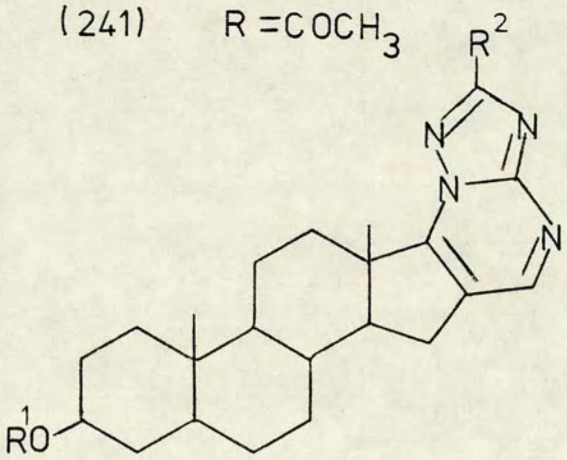
6.5 The reaction of 3β-hydroxy-16-hydroxymethyleneandrost-5-en-17-one (8) with 3-amino-1, 2, 4-triazole (95).

A solution of 3β-hydroxy-16-hydroxymethyleneandrost-5-en-17-one



(240) R = H

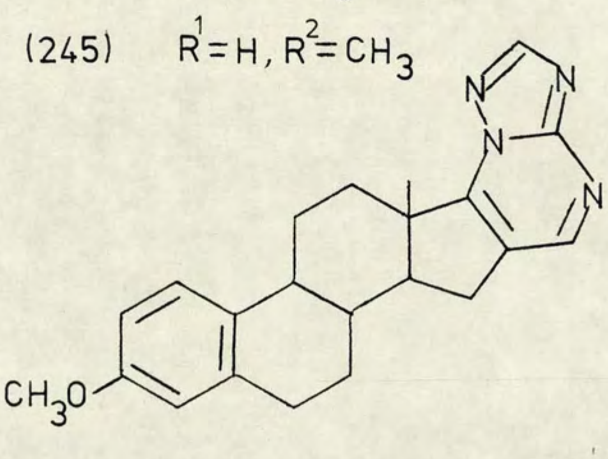
(241) R = $COCH_3$



(242) $R^1 = H = R^2$

(243) $R^1 = COCH_3$, $R^2 = H$

(245) $R^1 = H$, $R^2 = CH_3$



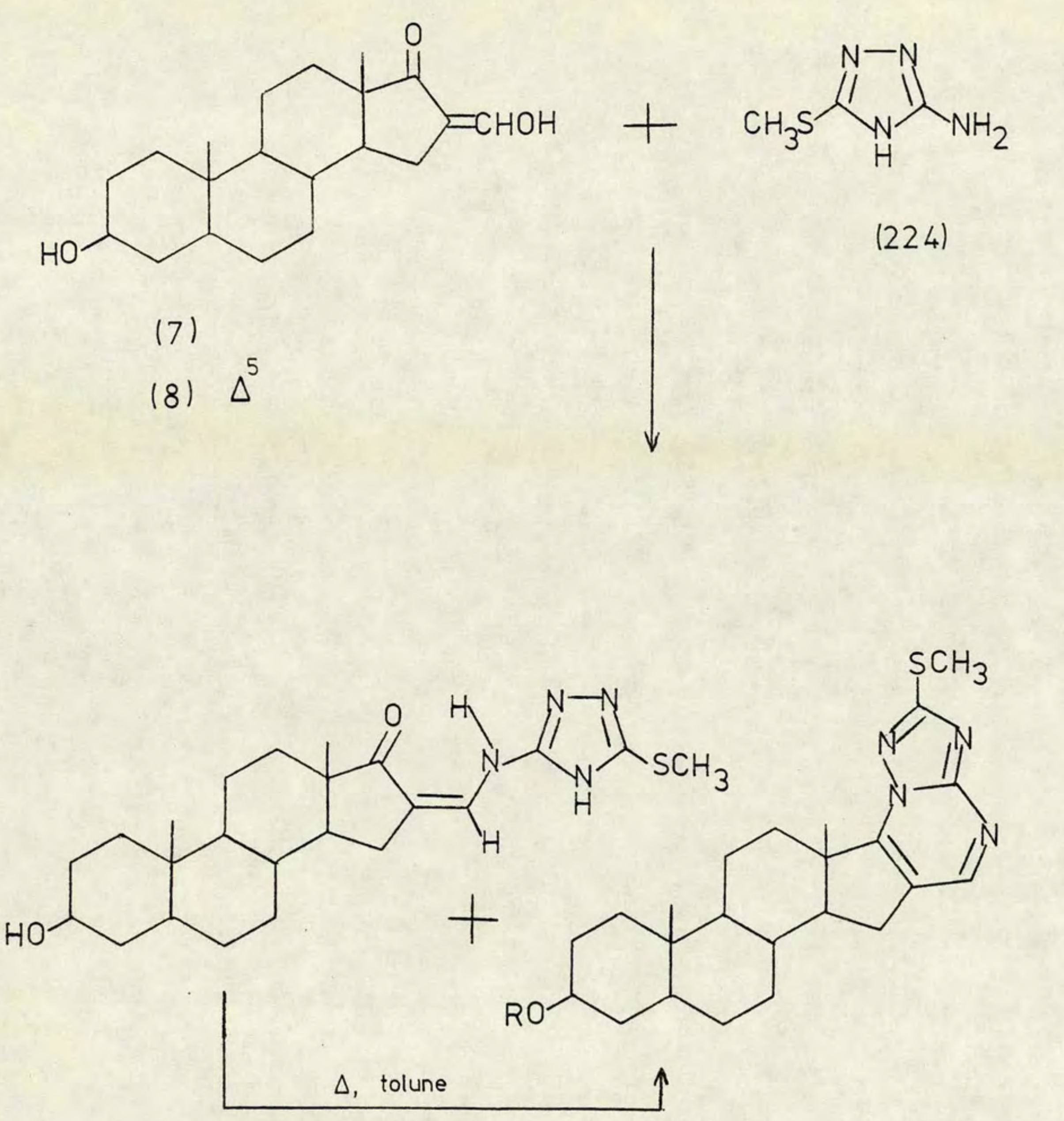
(244)

(8) and 3-amino-1,2,4-triazole (95) in absolute alcohol was refluxed overnight. The reaction mixture was diluted with water, the white precipitate was filtered, washed, dried and recrystallised from ethanol to give a white solid (240), m.p. 176-180° in 55% yield. Mass spectrometry indicated that the product had a molecular formula of $C_{22}H_{28}N_4O$. The product was not soluble in bromoform and deuterated chloroform, thus the i.r. and ^{1}H n.m.r. spectra could not be measured.

Acetylation of the product gave the 3β-acetate (241). The i.r. spectrum of the acetyl derivative showed absorptions at 1720 (C=O), 1605, 1550, 1500, 1450, 1370 and 780 cm^{-1}. The u.v. spectrum showed λ_{max} at 216 and 290 nm (log ε 4.36 and 3.74) whilst the ^{1}H n.m.r. spectrum exhibited two sharp singlets at δ 8.42 and δ 8.64 corresponding to the proton on the triazole ring and the proton on the pyrimidine ring respectively. The i.r., u.v. and ^{1}H n.m.r. spectra of this acetyl derivative resemble closely the i.r., u.v. and ^{1}H n.m.r. spectra of 17β-hydroxy-17α-methyl-5α-androst-2-eno[2,3-g]-s-triazolo[1,5-a]pyrimidine (211) and thus the product of the condensation of 3-amino-1,2,4-triazole (95) with 3β-hydroxy-16-hydroxymethyleneandrost-5-en-17-one (8) is formulated as 3β-hydroxyandrost-5,16-dieno[16,17-g]-s-triazolo[1,5-a]pyrimidine (24).

Similarly the condensation of 3-amino-1,2,4-triazole (95) with 3β-hydroxy-16-hydroxymethylene-5α-androst-17-one (7) and 16-hydroxymethylene-3-methoxyoestra-1,3,5(10)-trien-17-one (9) gave 3β-hydroxy-5α-androst-16-eno[16,17-g]-s-triazolo[1,5-a]pyrimidine (242) and 3-methoxyoestra-1,3,5(10),16-tetraeno[16,17-g]-s-triazolo[1,5-a]pyrimidine (244). The product (242) was also acetylated to give the acetyl derivative (243).

The condensation of 3-amino-5-methyl-1,2,4-triazole (127) with 3β-hydroxy-16-hydroxymethylene-5α-androstan-17-one (7) also leads to



(7)

(8) Δ^5

(224)

(247)

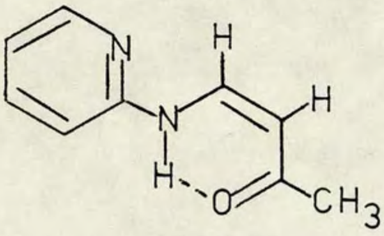
(249) Δ^5

(246) R = H

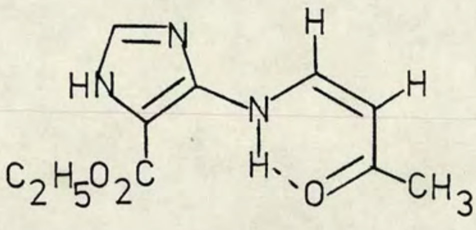
(250) Δ^5, R = H

(253) R = $COCH_3$

(254) Δ^5, R = $COCH_3$



(209)



(248)

the formation of an angularly fused product, 3β-hydroxy-5α-androst-16-eno[16,17-g]-2'-methyl-s-triazolo[1,5-a]pyrimidine (245) though in poor yield. It was noticed that the reaction of 16-hydroxymethylene-17-oxo steroids, like the reaction of 2-hydroxymethylene-Δ^4-3-oxo steroid with aminotriazoles (95), (127) and (224), gives only angularly fused products whereas the reaction of 2-hydroxymethylene-3-oxo-steroids without a Δ^4 double bond leads to linearly fused products or a mixture of linearly and angularly fused products, depending upon the amino-triazole employed in the reaction.

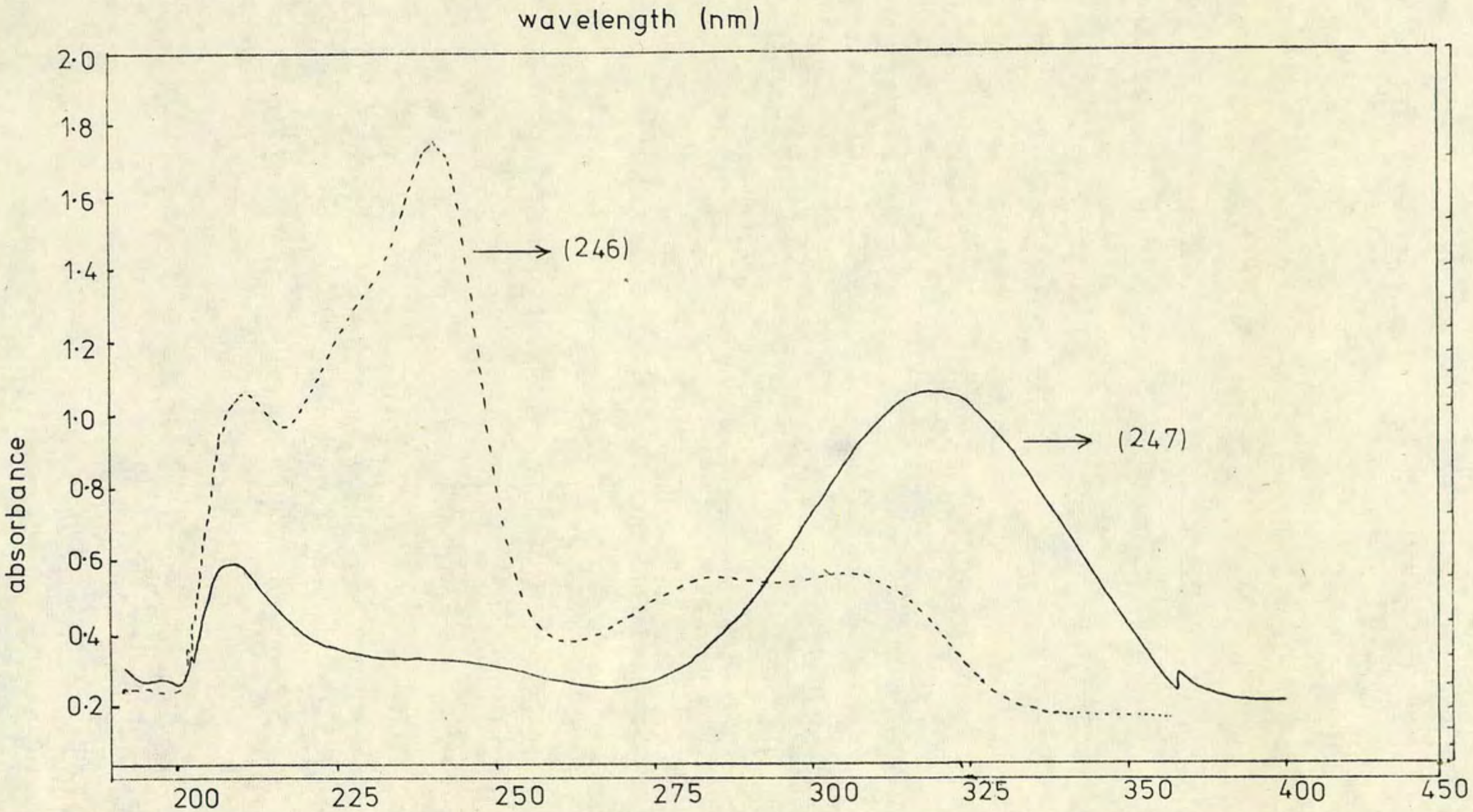
6.6 The reaction of 3β-hydroxy-16-hydroxymethylene-5α-androstan-17-one (47) with 3-amino-5-methylthio-1,2,4-triazole (224).

(a) In absolute alcohol.

A solution 3β-hydroxy-16-hydroxymethylene-5α-androstan-17-one (7) and 3-amino-5-methylthio-1,2,4-triazole (224) in absolute alcohol was refluxed overnight. The solution was evaporated to dryness under vacuo and the residue was chromatographed over alumina. Elution with chloroform gave a solid which recrystallised from alcohol as white needles (246), m.p. 244-246°, in 45% yield. Further elution of the column with 10% ethanol in chloroform gave a light yellow solid which was recrystallised from acetone to give white crystals (247), m.p. 181-185° in 22% yield.

(b) In toluene.

Only one product (246) was obtained in 77% yield when the above reaction was carried out in dry toluene.



<u>Fig. 6</u>: u. v. Spectra of 3β-hydroxy-5α-androst-16-eno[16, 17-g]-2'-methylthio-s-triazolo[1, 5-a]pyrimidine (246) and 3β-hydroxy-16[3'-(5-methylthio)-s-triazolyl-aminomethylene]androstan-17-one (247).

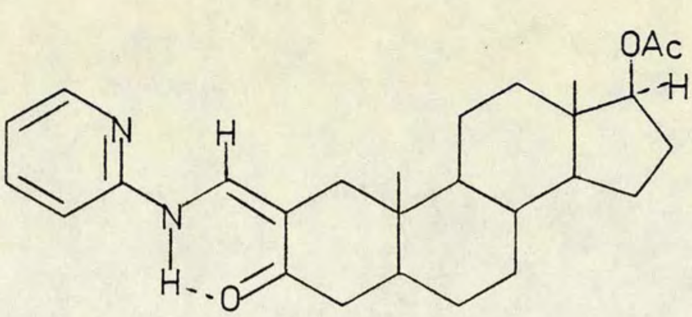
6.7 Discussion

Mass spectrometry and elemental analysis of the first product, m.p. 244-246°, showed that it had a molecular formula of $C_{23}H_{32}N_4OS$. The u.v. spectrum showed λ_{max} at 211, 241, 286 and 307 nm (log ϵ 4.25, 4.46, 3.85 and 3.87) whilst the i.r. spectrum exhibited absorptions at 3600 (OH), 1600, 1555, 1490, 1440, 1420, 1350 and 780 cm^{-1}. These absorptions in the u.v. and i.r. spectra of the product correlate well with that of 17β-hydroxy-17α-methyl-5α-androst-2-eno[2,3-g]-2'-methylthio-s-triazolo[1,5-a]pyrimidine (226) (see page 115) thereby indicating that this steroid has the structure, 3β-hydroxy-5α-androst-16-eno[16,17-g]-2'-methylthio-s-triazolo[1,5-a]pyrimidine (246). This structure is confirmed by the ^{1}H n.m.r. spectrum which shows the 2'-SCH_3 and the 5'-H, both as sharp singlets at δ 2.64 and δ 8.67 respectively.

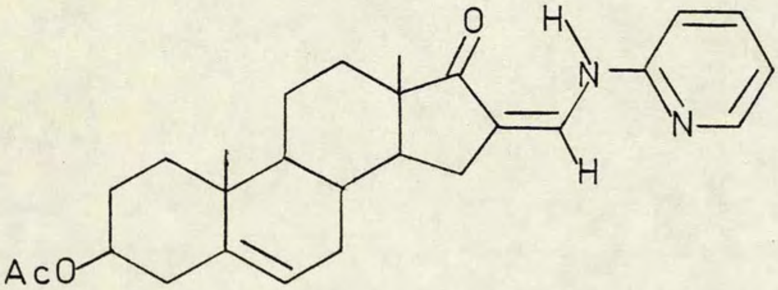
The u.v. spectrum of the second product, m.p. 181-185°, exhibiting λ_{max} at 208 and 320 nm (log ϵ 4.04 and 4.26) (Fig. 6) does not show any similarity with either of the analogous linearly or angularly fused products, and this must mean that the steroid is not a derivative of the s-triazolo[1,5-a]pyrimidine system (69). The λ_{max} at 320 nm shows that the steroid contains a highly conjugated chromophore. Furthermore, when this steroid is heated in dry toluene containing a small amount of toluene-4-sulphonic acid for 3 h, 3β-hydroxy-5α-androst-16-eno[16,17-g]-2'-methylthio-s-triazolo[1,5-a]pyrimidine (246) was obtained in 85% yield. It is, therefore, evident that the steroid must be an intermediate between the starting β-ketoaldehyde (7) and the final cyclized product (246) and the most obvious structure to choose is the enaminone (247).

The ^{1}H n.m.r. spectrum of the enaminone exhibited two doublets at δ 7.60 and δ 9.70 (J=12Hz) and a broad singlet at δ 13.18 which are assigned to the vinyl proton, the amino proton and the proton on the triazole ring respectively. The coupling between the first two protons was confirmed by double irradiation experiments. Sawyer and Wibberley[140] found that the ^{1}H n.m.r. spectrum of 2(2-acetylvinylamino)pyridine (209) where the enaminone system is similar to that in the steroid (247) showed two doublets at δ 7.93 and δ 11.69, each with spin coupling constant, J=12Hz. These signals were assigned to the vinyl proton and to the amino proton respectively. Similarly the ^{1}H n.m.r. spectrum of the enaminone (248) has also been reported[73] to exhibit two doublets at δ 7.56 and δ 11.90 (J=12Hz). The observed chemical shift of the vinyl proton in the steroidal enaminone and the coupling constant are in good agreement with the proposed structure (247). The magnitude of the coupling constant (12Hz) between the amino proton and the vinyl proton on the adjacent carbon is consistent with these two protons being trans to one another,[144] as shown in structure (247). The coupling constant, if the two protons had been cis would have been observed at the much lower value of 0-2Hz.[144]

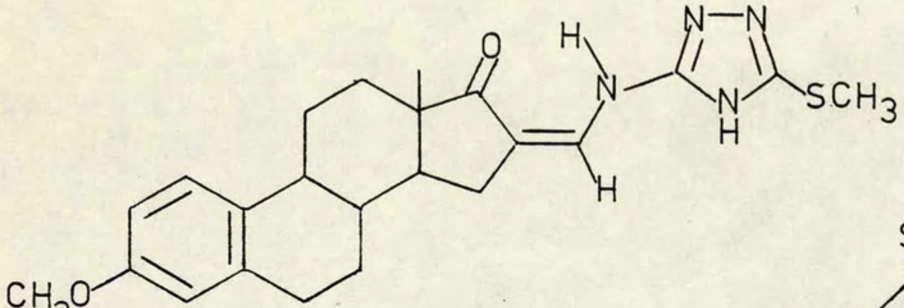
It is observed that the chemical shift of the amino proton in the steroidal enaminone (247) occurs at a higher field compared with the chemical shifts of the corresponding protons in the enaminones (209) and (248). This is attributed to the amino proton in the steroid (247) having a lower electron density in its vicinity because of the presence of only weak hydrogen bonding to the 17-ketone. The enaminones (209)[140] and (248)[73] on the other hand have been reported to have significant



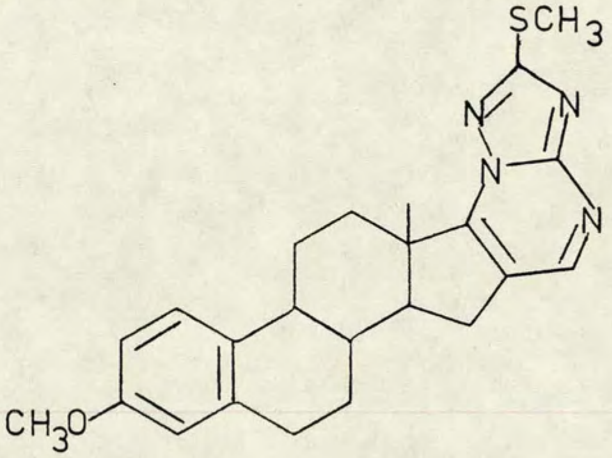
(56)



(58)



(251)

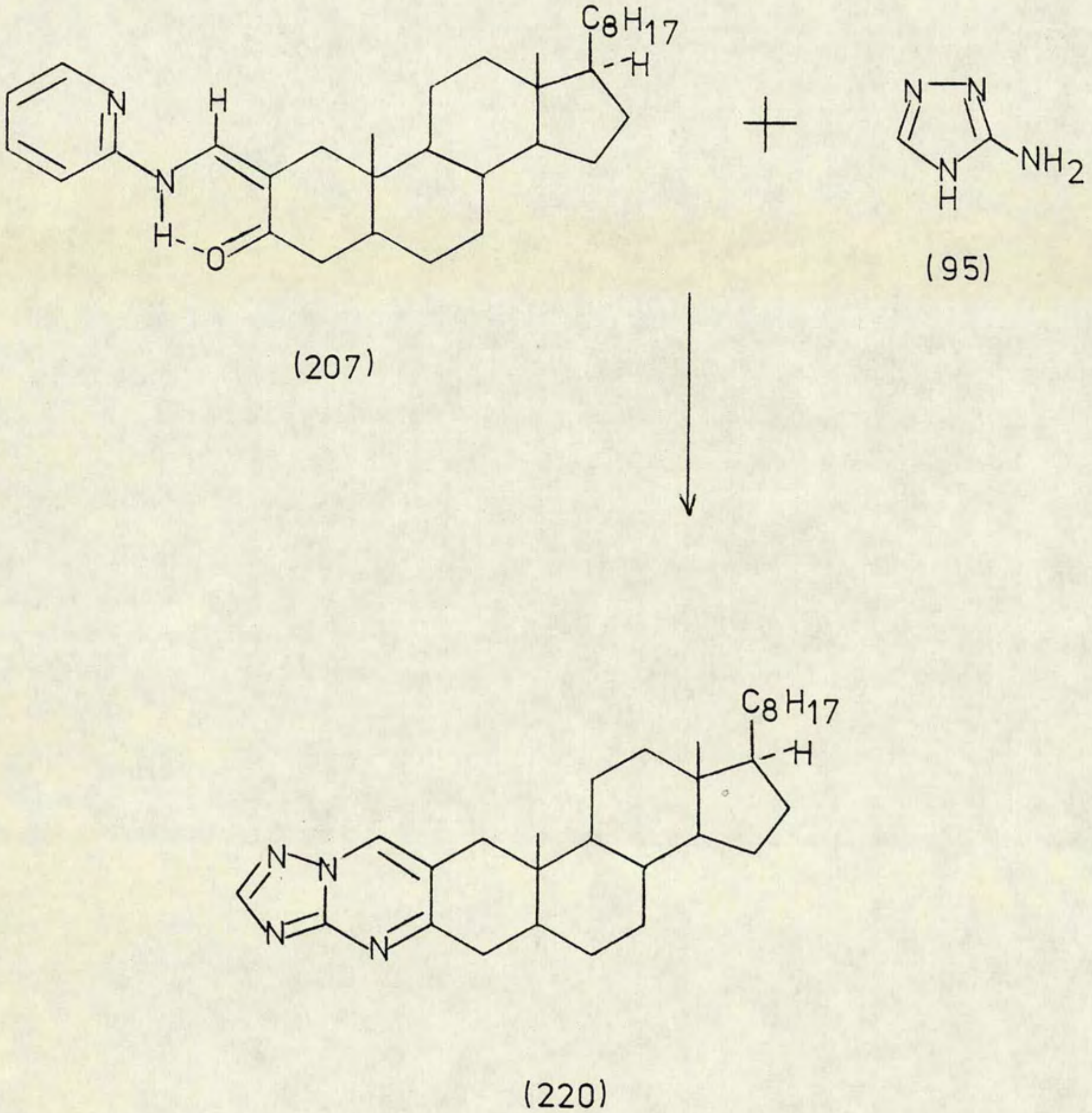


(252)

hydrogen bonding. The most likely reason for the absence of significant hydrogen bonding in the steroidal enaminone (247) appears to be that the adjacent five membered D-ring of the steroid imposes a conformation on the enaminone such that the carbonyl oxygen and the amino proton are not close enough to permit hydrogen bonding between them. Similarly, Burgess[51] observed an upfield chemical shift (δ 10.70) of the amino hydrogen in the ^{1}H n.m.r. spectrum of 3β-acetoxy-16(2'-pyridyl-aminomethylene)androst-5-en-17-one (58) relative to the corresponding chemical shift (δ 11.88) in 17β-acetoxy-2(2'-pyridyl-aminomethylene)-5α-androstan-3-one (56).

Under analogous reaction conditions, the condensation of 3-amino-5-methylthio-1,2,4-triazole (224) with the β-ketoaldehydes (8) and (9) gave 3β-hydroxy-16[3'-(5'-methylthio)-s-triazolyl-aminomethylene]androst-5-en-17-one (249) and 3β-hydroxyandrost-5,16-dieno[16,17-g]-2'-methylthio-s-triazolo[1,5-a]pyrimidine (250); and 3-methoxy-16[3'-(5'-methylthio)-s-triazolyl-aminomethylene]oestra-1,3,5(10) trien-17-one (251) and 3-methoxyoestra-1,3,5(10),16-tetraeno[16,17-g]-2'-methylthio-s-triazolo[1,5-a]pyrimidine (252) respectively. The enaminones (249) and (251) were also converted to the triazolopyrimidines (250) and (252) respectively upon heating in dry toluene in the presence of toluene-4-sulphonic acid. The sterols (246) and (250) were acetylated to give the corresponding 3β-acetates (253) and (254).

None of the enaminones (247), (249) and (251) showed peaks corresponding to their molecular ions in the mass spectrometry but exhibited peaks at m/e (M^{+}-18) corresponding to the triazolopyrimidines (246), (250) and (252) respectively.



(207)

(95)

(220)

Likewise the condensation of 3-aminopyrazoles (section 5), the condensation of 3-amino-1, 2, 4-triazoles with 2-hydroxymethylene 3-oxo steroids without a Δ^4 double bond resulting in the formation of linearly fused products is also a two step process. Evidence for this two step reaction sequence comes from the reaction of 2(2'-pyridyl-aminomethylene)-5α-cholestan-3-one (207) with 3-amino-1, 2, 4- triazole (95) which is reported below.

6.8 The reaction of 2(2'-pyridyl-aminomethylene)-5α-cholestan-3-one (207) with 3-amino-1, 2, 4-triazole (95).

A solution of 2(2'-pyridyl-aminomethylene)-5α-cholestan-3-one (207) and 3-amino-1, 2, 4-triazole (95) in dry toluene containing a catalytic amount of toluene-4-sulphonic acid was refluxed for 5 h. The excess of solvent was removed under vacuo and the residue was chromatographed over alumina. Elution with ethyl acetate followed by recrystallisation of the eluate from ethyl acetate gave white shining plates (68%), m. p. 170-173°, identical (m. p. , i. r. and ^{1}H n. m. r. spectra) with that of 5α-cholestano[3, 2-f]-s-triazolo[1, 5-a]pyrimidine (220).

The mechanism of these condensation reactions is discussed in detail in section 10.

6.9 Experimental

General procedure for the condensation reaction

A solution of the steroidal β-ketoaldehyde (1.5×10^{-3} mole) and 3-amino-1, 2, 4-triazole (95) or its derivative (127 or 224) (2×10^{-3} mole) in absolute alcohol was refluxed overnight. The reaction mixture was evaporated to dryness under vacuo, the residue was chromatographed over alumina (50 g) and the products thus obtained were recrystallised from suitable solvents.

6.9.i 17β-Hydroxy-17α-methyl-5α-androstano[3, 2-f]-s-triazolo[1, 5-a]-pyrimidine (210) and 17β-hydroxy-17α-methyl-5α-androst-2-eno-[2, 3-g]-s-triazolo[1, 5-a]pyrimidine (211).

Source: 17β-Hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108) and 3-amino-1, 2, 4-triazole (95).

General: Alumina chromatography (eluant benzene-chloroform, 3:1).

17β-Hydroxy-17α-methyl-5α-androstano[3, 2-f]-s-triazolo[1, 5-a]-pyrimidine (210) was recrystallised from chloroform-ether as white needles (45%), m.p. 118-120; u.v., λ_{max} 220 and 283 nm (log ε 4.34 and 3.58); i.r., γ_{max} 3600, 1620, 1510, 1440, 1405, 1370 and 775 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.82 (s, 3H, 18-CH_3), 0.88 (s, 3H, 19-CH_3), 1.22 (s, 3H, 17-CH_3), 8.34 (s, 1H, 2'-H) and 8.50 (s, 1H, 7'-H) (Found: C, 72.64; H, 8.58; N, 14.86; M^+, 380.255601. $C_{23}H_{32}N_4O$ requires C, 72.58; H, 8.48; N, 14.73%; M, 380.257598).

17β-Hydroxy-17α-methyl-5α-androst-2-eno[2, 3-g]-s-triazolo[1, 5-a]-

pyrimidine (211) was recrystallised from ether as white crystals (25%), m.p. 248-250°; u.r., λ_{max} 218 and 283 nm (log ϵ 4.26 and 3.65); i.r., ν_{max} 3600, 1620, 1545, 1520, 1445, 1370, 1355 and 775 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.82 (s, 3H, 18-CH$_3$), 0.90 (s, 3H, 19-CH$_3$), 1.24 (s, 3H, 17-CH$_3$), 8.40 (s, 1H, 2'-H) and 8.50 (s, 1H, 5'-H) (Found: C, 72.70; H, 8.54; N, 14.50; M$^+$, 380.255976. $C_{23}H_{32}N_4O$ requires C, 72.58; H, 8.48; N, 14.73%; M, 380.257598).

6.9.ii 5α-Androstano[3,2-f]-s-triazolo[1,5-a]pyrimidine (218) and 5α-androst-2-eno[2,3-g]-s-triazolo[1,5-a]pyrimidine (219).

Source: 2-Hydroxymethylene-5α-androstan-3-one (109) and 3-amino-1,2,4-triazole (95).

General: Alumina chromatography (eluant ethyl acetate). 5α-Androstano-[3,2-f]-s-triazolo[1,5-a]pyrimidine (218) was recrystallised from ethanol to give a single large crystal (46%), m.p. 174-176°; u.v., λ_{max} 220 and 285 nm (log ϵ 4.28 and 3.65); i.r., ν_{max} 1630, 1510, 1440, 1405 and 775 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.76 (s, 3H, 18-CH$_3$) 0.84 (s, 3H, 19-CH$_3$ 8.35 (s, 1H, 2'-H) and 8.50 (s, 1H, 7'-H) (Found: C, 75.23; H, 8.72; N, 15.85; M$^+$, 350.246730. $C_{22}H_{30}N_4$ requires C, 75.38; H, 8.63; N, 16.00%; M, 350.247035).

5α-Androst-2-eno[2,3-g]-s-triazolo[1,5-a]pyrimidine (219) was recrystallised from ethanol to give white crystals (21%), m.p. 272-273°; u.v., λ_{max} 218 and 282 nm (log ϵ 4.37 and 3.77); i.r., ν_{max} 1620, 1545, 1520, 1450 and 780 cm^{-1}; ^{1}H n.m.r. (60 MHz) δ 0.72 (s, 3H, 18-CH$_3$), 0.82 (s, 3H, 19-CH$_3$), 8.44 (s, 1H, 2'-H) and 8.54 (s, 1H, 5'-H) (Found: C, 75.19; H, 8.63; N, 15.80; M$^+$, 350.245612. $C_{22}H_{30}N_4$ requires C, 75.38; H, 8.63; N, 16.00%; M, 350.247035).

6.9.iii 5α-Cholestano[3, 2-f]-s-triazolo[1, 5-a]pyrimidine (220) and 5α-cholest-2-eno[2, 3-g]-s-triazolo[1, 5-a]pyrimidine (221).

Source: 2-Hydroxymethylene-5α-cholestan-3-one (110) and 3-amino-1, 2, 4-triazole (95).

General: Alumina chromatography (eluant ethyl acetate). 5α-Cholestano-[3, 2-f]-s-triazolo[1, 5-a]pyrimidine (220) was recrystallised from ethanol to give white crystals (48%), m.p. 170-173°; u.v., λ_{max} 221 and 284 nm (log ε 4.35 and 3.75); i.r., ν_{max} 1630, 1510, 1465, 1440, 1405 and 775 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 0.70, 0.80, 0.85 and 0.90 (methyl groups), 8.45 (s, 1H, 2'-H) and 8.55 (s, 1H, 7'-H) (Found: C, 78.10; H, 10.00; N, 11.97; M^{+}, 462.372602. $C_{30}H_{46}N_{4}$ requires C, 77.86; H, 10.03; N, 12.12%; M, 462.372229). 5α-Cholest-2-eno[2, 3-g]-s-triazolo[1, 5-a]pyrimidine (221) was recrystallised from ethanol to give white crystals (23%), m.p. 176-178°; u.v., λ_{max} 217 and 282 nm (log ε 4.23 and 3.58); i.r., ν_{max} 1620, 1545, 1515, 1440, 1380, 1355 and 775 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.70, 0.80, 0.82 and 0.90 (methyl groups), 8.40 (s, 1H, 2'-H) and 8.52 (s, 1H, 5'-H) (Found: C, 77.93; H, 9.97; N, 12.12; M^{+}, 462.371326. $C_{30}H_{46}N_{4}$ requires 77.86; H, 10.03; N, 12.12%; M, 462.372229).

6.9.iv 11-Oxo-5α-spirostano[3, 2-f]-s-triazolo[1, 5-a]pyrimidine (222) and 11-oxo-5α-spirost-2-eno[2, 3-g]-s-triazolo[1, 5-a]pyrimidine (223).

Source: 2-Hydroxymethylene-5α-spirostan-3, 11-dione (111) and 3-amino-1, 2, 4-triazole (95).

General: Alumina chromatography (eluant ethyl acetate). 11-Oxo-5αspirostano[3, 2-f]-s-triazolo[1, 5-a]pyrimidine (222) was recrystallised from ethanol to give white needles (37%), m.p. 217-219°; u.v., λ_{max} 221 and 285 nm (log ε 4.36 and 3.65); i.r., γ_{max} 1690 (C=O), 1625, 1510, 1450, 1405, 775 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.74 (s, 3H, 18-CH$_3$), 1.00 (s, 3H, 19-CH$_3$), 8.34 (s, 1H, 2'-H) and 8.48 (s, 1H, 7'-H) (Found: C, 70.98; H, 7.87; N, 10.82; M$^+$, 504.308274. C$_{30}$H$_{40}$N$_4$O$_3$ requires C, 71.38; H, 7.99; N, 11.11%; M, 504.310024).

11-Oxo-5α-spirost-2-eno[2, 3-g]-s-triazolo[1, 5-a]pyrimidine (223) was recrystallised from ethanol to give white crystals (18%), m.p. 176-179°; u.v., λ_{max} 217 and 282 nm (log ε 4.41 and 3.73); i.r., γ_{max} 1695 (C=O), 1625, 1545, 1520, 1365 and 775 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 0.75 (s, 3H, 18-CH$_3$), 1.03 (s, 3H, 19-CH$_3$), 8.50 (s, 1H, 2'-H) and 8.60 (s, 1H, 5'-H) (Found: C, 71.17; H, 8.15; N, 10.79; M,$^+$ 504.307597. C$_{30}$H$_{40}$N$_4$O$_3$ requires C, 71.38; H, 7.99; N, 11.11%; M, 504.310024).

6.9.v 17β-Hydroxy-17α-methyl-5α-androstano[3, 2-f]-2'-methylthio-s-triazolo[1, 5-a]pyrimidine (225) and 17β-hydroxy-17α-methyl-5α-androst-2-eno[2, 3-g]-2'-methylthio-s-triazolo[1, 5-a]pyrimidine (226).

Source: 17β-Hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108) and 3-amino-5-methylthio-1, 2, 4-triazole (224).

General: Alumina chromatography (eluant ethyl acetate-methylene chloride, 9:1).

17β-Hydroxy-17α-methyl-5α-androstano[3, 2-f]-2'-methylthio-s-triazolo-[1, 5-a]pyrimidine (225) was recrystallised from ethanol to give fine white crystals (52%), m.p. 207-208°; u.v., λ_{max} 212, 217, 237 and 315 nm (log ε 4.40, 4.40, 4.43 and 4.03); i.r., 3600 (OH), 1620, 1510, 1440, 1415, 1370, 1345 and 770 cm^{-1}; ^1H n.m.r. (100 MHz), δ 0.80 (s, 3H, 18-CH_3), 0.88 (s, 3H, 19-CH_3), 1.22 (s, 3H, 17-CH_3), 2.66 (s, 3H, 2'-SCH_3) and 8.30 (s, 1H, 7'-H) (Found: C, 67.31; H, 8.10; N, 12.79; M^+, 426.246147. $C_{24}H_{34}N_4OS$ requires C, 67.57; H, 8.04; N, 13.14%; M, 426.245320).

17β-Hydroxy-17α-methyl-5α-androst-2-eno[2, 3-g]-2'-methylthio-s-triazolo[1, 5-a]pyrimidine (226) was crystallised from acetone to give white needles (27%), m.p. 230-232°; u.v., λ_{max} 209, 239, 283 and 308 nm (log ε 4.26; 4.50, 3.89 and 3.91); i.r., γ_{max} 3600 (OH), 1615, 1545, 1515, 1440, 1400, 1360 and 770 cm^{-1}; ^1H n.m.r. (100 MHz), δ 0.80 (s, 3H, 18-CH_3), 0.90 (s, 3H, 19-CH_3), 1.24 (s, 3H, 17-CH_3), 2.70 (s, 3H, 2'- SCH_3) and 8.38 (s, 1H, 5'-H) (Found: C, 68.12; H, 8.22; N, 13.13; M^+, 426.245734. $C_{24}H_{34}N_4OS$ requires C, 67.57; H, 8.04; N, 13.14%; M, 426.245320).

6.9.vi 5α-Androstano[3, 2-f]-2'-methylthio-s-triazolo[1, 5-a]pyrimidine (227) and 5α-androst-2-eno[2, 3-g]-2'-methyl-s-triazolo[1, 5-a]-pyrimidine (228).

Source: 2-Hydroxymethylene-5α-androstan-3-one (109) and 3-amino-5-methylthio-1, 2, 4-triazole (224).

General: Alumina chromatography (eluant ether-ethyl acetate, 1:1).

5α-Androstano[3, 2-f]-2'-methylthio-s-triazolo[1, 5-a]pyrimidine (227) was recrystallised from acetone to give white shining crystals (55%), m.p. 182-183°; u.v., λ_{max} 213, 228, 237 and 316 nm (log ε 4.38, 4.38, 4.40 and 3.97); i.r., γ_{max} 1620, 1510, 1435, 1415, 1345 and 770 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.72 (s, 3H, 18-CH_3), 0.78 (s, 3H, 19-CH_3), 2.70 (s, 3H, 2'-SCH_3) and 8.38 (s, 1H, 7'-H) (Found: C, 69.42; H, 8.18; N, 14.07; M^+, 396.231886. $C_{23}H_{32}N_4S$ requires C, 69.66; H, 8.14; N, 14.14%; M, 396.234757).

5α-Androst-2-eno[2,3-g]-2'-methylthio-s-triazolo[1,5-a]pyrimidine (228) was recrystallised from ethanol as white fluffy crystals (32%), m.p. 216-217°; u.v., λ_{max} 210, 239, 281 and 307 nm (log ε 4.22, 4.40, 3.81 and 3.81); i.r., γ_{max} 1620, 1510, 1435, 1415, 1345 and 770 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.74 (s, 3H, 18-CH_3), 0.78 (s, 3H, 19-CH_3), 2.66 (s, 3H, 2-SCH_3) and 8.32 (s, 1H, 5'-H) (Found: C, 69.62; H, 8.35; N, 14.03; M^+, 396.232662. $C_{23}H_{32}N_4S$ requires C, 69.66; H, 8.14; N, 14.14%; M, 396.234757).

6.9.vii 5α-Cholestano[3,2-f]-2'-methylthio-s-triazolo[1,5-a]pyrimidine (229) and 5α-cholest-2-eno[2,3-g]-2'-methylthio-s-triazolo[1,5-a]-pyrimidine (230).

Source: 2-Hydroxymethylene-5α-cholestan-3-one (110) and 3-amino-5-methylthio-1,2,4-triazole (224).

General: Alumina chromatography (eluant ether-ethyl acetate, 1:1).

5α-Cholestano[3,2-f]-2'-methylthio-s-triazolo[1,5-a]pyrimidine (229) was recrystallised from ethyl acetate as white shining plates (42%), m.p. 192-193°; u.v., λ_{max} 213, 228, 237 and 316 nm (log ε 4.28, 4.31, 4.34 and 3.90); i.r., γ_{max} 1620, 1510, 1465, 1440, 1415, 1350 and 770 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.68, 0.78, 0.82 and 0.88 (methyl groups), 2.66 (s, 3H, 2'-SCH_3) and 8.30 (s, 1H, 7'-H) (Found: C, 72.91;

H, 9.56; N, 10.86; M^+, 508.356695. $C_{31}H_{48}N_4S$ requires C, 73.18; H, 9.52; N, 11.02%; M, 508.359951).

<u>5α-Cholest-2-eno[2,3-g]-2'-methylthio-s-triazolo[1,5-a]pyrimidine</u> (<u>230</u>) was recrystallised from ethanol to give white crystals (30%), m.p. 189-191°; u.v., λ_{max} 211, 239, 282 and 308 nm (log ε 4.18, 4.49, 3.79 and 3.87); i.r., γ_{max} 1615, 1545, 1510, 1400, 1360 and 770 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.68, 0.76, 0.82 and 0.90 (methyl groups), 2.70 (s, 3H, 2'-SCH_3) and 8.38 (s, 1H, 5'-H) (Found: C, 72.94; H, 9.58; N, 10.78; M^+, 508.359951. $C_{31}H_{48}N_4S$ requires C, 73.18; H, 9.52; N, 11.02%; M, 508.359951).

6.9.viii <u>11-Oxo-5α-spirostano[3,2-f]-2'-methylthio-s-triazolo[1,5-a]-pyrimidine (231) and 11-oxo-5α-spirost-2-eno[2,3-g]-2'-methylthio-s-triazolo[1,5-a]pyrimidine (232)</u>.

<u>Source</u>: 2-Hydroxymethylene-5α-spirostan-3,11-dione (111) and 3-amino-5-methylthio-1,2,4-triazole (224).

<u>General</u>: Alumina chromatography (eluant ether-ethyl acetate, 2:3).

<u>11-Oxo-5α-spirostano[3,2-f]-2'-methylthio-s-triazolo[1,5-a]pyrimidine</u> (<u>231</u>) was recrystallised from ethanol to give white crystals (15%), m.p. 228-230°; u.v., λ_{max} 213, 228, 238 and 316 nm (log ε 4.33, 4.37, 4.40 and 3.97); i.r., γ_{max} 1690 (C=O), 1620, 1510, 1450, 1415, 1345 and 770 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.76 (s, 3H, 18-CH_3), 0.98 (s, 3H, 19-CH_3), 2.66 (s, 3H, 2'-SCH_3) and 8.34 (s, 1H, 7'-H) (Found: C, 67.39; H, 7.72; N, 10.20; M^+, 550.300342. $C_{31}H_{42}N_4O_3S$ requires C, 67.60; H, 7.69; N, 10.18%; M, 550.297746).

<u>11-Oxo-5α-spirost-2-eno[2,3-g]-2'-methylthio-s-triazolo[1,5-a]-</u>

pyrimidine (232) was recrystallised from ethanol to give white crystals (18%), m.p. 265-267°; u.v., λ_{max} 210, 239, 282 and 307 nm (log ε 4.20, 4.48, 3.77 and 3.82); i.r., γ_{max} 1695 (C=O), 1615, 1545, 1510, 1450, 1400, 1355 and 770 cm^{-1}; ^1H n.m.r. (100 MHz), δ 0.76 (s, 3H, 18-CH_3), 1.00 (s, 3H, 19-CH_3), 2.70 (s, 3H, 2'-SCH_3) and 8.38 (s, 1H, 5'-H) (Found: C, 67.05; H, 7.82; N, 9.90; M^+, 550.298728. $C_{31}H_{42}N_4O_3S$ requires C, 67.60; H, 7.69; N, 10.18%; M, 550.297746).

6.9.ix 17β-Hydroxy-17α-methyl-5α-androstano[3, 2-f]-2'-methyl-s-triazolo[1, 5-a]pyrimidine (233).

Source: 17β-Hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108) and 3-amino-5-methyl-1, 2, 4-triazole (127).

General: Alumina chromatography (eluant chloroform) gave 17β-hydroxy-17α-methyl-5α-androstano[3, 2-f]-2'-methyl-s-triazolo[1, 5-a]pyrimidine (233) which was recrystallised from ethyl acetate as long white needles (68%), m.p. 232-234; u.v., λ_{max} 219 and 289 nm (log ε 4.51 and 3.77); i.r., γ_{max} 3600 (OH), 1625, 1515, 1470, 1440, 1415, 1385 and 775 cm^{-1}; ^1H n.m.r. (100 MHz), δ0.80 (s, 3H, 18-CH_3), 0.88 (s, 3H, 19-CH_3), 1.24 (s, 3H, 17-CH_3), 2.56 (s, 3H, 2'-CH_3) and 8.34 (s, 1H, 7'-H) (Found: C, 72.89; H, 8.85; N, 13.85%; M^+, 394.272785. $C_{24}H_{34}N_4O$ requires C, 73.05; H, 8.69; N, 14.21%; M, 394.273247).

6.9.x 5α-Cholestano[3, 2-f]-2'-methyl-s-triazolo[1, 5-a]pyrimidine (234).

Source: 2-Hydroxymethylene-5α-cholestan-3-one (110) and 3-amino-5-methyl-1, 2, 4-triazole (127).

General: Alumina chromatography (eluant ether-ethyl acetate, 1:1) gave

5α-cholestano[3, 2-f]-2'-methyl-s-triazolo[1, 5-a]pyrimidine (234) which was easily recrystallised from acetone to give fine white needles (35%), m.p. 185-187°; u.v., λ_{max} 217 and 286 nm (log ϵ 4.59 and 3.84); i.r., ν_{max} 1625, 1510, 1465, 1410, 1380, 1360 and 770 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ0.70, 0.78, 0.84 and 0.90 (methyl groups), 2.56 (s, 3H, 2'-CH$_3$) and 8.34 (s, 1H, 7'-H) (Found: C, 78.36; H, 10.43; N, 11.77; M$^+$, 476.387943. $C_{31}H_{48}N_4$ requires C, 78.10; H, 10.15; N, 11.75%; M, 476.387878).

6.9.xi 11-Oxo-5α-spirostano[3, 2-f]-2'-methyl-s-triazolo[1, 5-a]-pyrimidine (235).

Source: 2-Hydroxymethylene-5α-spirostan-3, 11-dione (111) and 3-amino-5-methyl-1, 2, 4-triazole (127).

General: Alumina chromatography (eluant ethyl acetate) gave 11-oxo-5α-spirostano[3, 2-f]-2'-methyl-s-triazolo[1, 5-a]pyrimidine (235) which was recrystallised from acetone as white crystals (60%), m.p. 274-276; u.v., λ_{max} 217 and 287 nm (log ϵ 4.63 and 3.85); i.r., ν_{max} 1695 (C=O), 1625, 1515, 1450, 1410, 1380 and 775 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ0.75 (s, 3H, 18-CH$_3$), 1.20 (s, 3H, 19-CH$_3$), 2.60 (s, 3H, 2'-CH$_3$) and 8.40 (s, 1H, 7'-H) (Found: C, 71.60; H, 8.30; N, 10.62; M$^+$, 518.324335. $C_{31}H_{42}N_4O_3$ requires C, 71.77; H, 8.17; N, 10.81%; M, 518.325673).

6.9.xii 17β-Hydroxyandrost-2, 4-dieno[2, 3-g]-s-triazolo[1, 5-a]pyrimidine (236).

Source: 17β-Hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4) and

3-amino-1, 2, 4-triazole (95).

General: Alumina chromatography (eluant ethyl acetate) gave 17β-hydroxyandrost-2, 4-dieno[2, 3-g]-s-triazolo[1, 5-a]pyrimidine (236) which was recrystallised from ethanol as yellow crystals (57%), m. p. 252-254°; u. v., λ_{max} 226 and 343 nm (log ε 4. 34 and 4. 21); i. r., γ_{max} 3600 (OH), 1630, 1580, 1550, 1510, 1460, 1450 and 780 cm^{-1}; ^{1}H n. m. r. (100 MHz), δ 0. 84 (s, 3H, 18-CH_3), 1. 04 (s, 3H, 19-CH_3), 3. 50 (m, 1H, 17-H), 6. 94 (s, 1H, 4-H), 8. 40 (s, 1H, 2'-H) and 8. 52 (s, 1H, 5'-H) (Found: C, 72. 03; H, 7. 74; N, 15. 06; M^+, 364. 224701. $C_{22}H_{28}N_4O$ requires C, 72. 48; H, 7. 75; N, 15. 38%; M, 364. 226300).

6. 9. xiii 17β-Hydroxyandrost-2, 4-dieno[2, 3-g]-2'-methylthio-s-triazolo[1, 5-a]pyrimidine (237).

Source: 17β-Hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4) and 3-amino-5-methylthio-1, 2, 4-triazole (224).

General: Alumina chromatography (eluant ethyl acetate) gave 17β-hydroxyandrost-2, 4-dieno[2, 3-g]-2'-methylthio-s-triazolo[1, 5-a]-pyrimidine (237) which was recrystallised from ethanol as yellow crystals (58%), m. p. 226-228°; u. v., λ_{max} 215, 249 and 325 nm (log ε 4. 23, 4. 34 and 4. 16); i. r., γ_{max} 3600 (OH), 1630, 1590, 1550, 1505, 1410, 1350 and 775 cm^{-1}; ^{1}H n. m. r. (100 MHz), δ 0. 80 (s, 3H, 18-CH_3), 1. 00 (s, 3H, 19-CH_3), 2. 70 (s, 3H, 2'-SCH_3), 3. 70 (m, 1H, 17-H), 6. 80 (s, 1H, 4-H) and 8. 34 (s, 1H, 5'-H) (Found: C, 67. 25; H, 7. 34; N, 13. 42; M^+, 410. 212269. $C_{23}H_{30}N_4OS$ requires C, 67. 28; H, 7. 37; N, 13. 65%; M, 410. 214021).

6.9.xiv 17β-Hydroxyandrost-2,4-dieno[2,3-g]-2'-methyl-s-triazolo-[1,5-a]pyrimidine (238).

Source: 17β-Hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4) and 3-amino-5-methyl-1,2,4-triazole (127).

General: Alumina chromatography (eluant chloroform) gave 17β-hydroxyandrost-2,4-dieno[2,3-g]-2'-methyl-s-triazolo[1,5-a]pyrimidine (238) which was recrystallised from acetone-chloroform as light yellow crystals (28%), m.p. 248-250°; u.v., λ_{max} 207, 227 and 343 nm (log ε 4.10, 4.28 and 4.01); i.r., ν_{max} 3590 (OH), 1625, 1590, 1550, 1510, 1465, 1410 and 775 cm^{-1}; ^1H n.m.r. (60 MHz), δ 0.85 (s, 3H, 18-CH_3), 1.05 (s, 3H, 19-CH_3), 2.65 (s, 3H, 2'-CH_3), 3.70 (m, 1H, 17-H), 6.90 (s, 1H, 4-H) and 8.50 (s, 1H, 5'-H) (Found:[141] M^+, 378.240736. $C_{23}H_{30}N_4O$ requires M, 378.241949).

6.9.xv 17β-Acetoxyandrost-2,4-dieno[2,3-g]-2'-methylthio-s-triazolo-[1,5-a]pyrimidine (239).

A solution of 17β-hydroxyandrost-2,4-dieno[2,3-g]-2'-methylthio-s-triazolo[1,5-a]pyrimidine (237) (250 mg, 6.1×10^{-4} mole) in pyridine (25 ml) containing a few drops of acetic anhydride was refluxed for 2 h. The reaction mixture was evaporated to dryness under vacuo and the residue taken up in chloroform. The chloroform solution was washed with 5% hydrochloric acid, saturated sodium chloride solution and water, dried over anhydrous magnesium sulphate. The solution was evaporated to dryness and the residue purified by alumina chromatography (eluant ethyl acetate) followed by recrystallisation from ethanol to give 17β-acetoxyandrost-2,4-dieno[2,3-g]-2'-methylthio-s-triazolo[1,5-a]-

pyrimidine (239) (123 mg, 45%), m.p. 248-250°; u.v., λ_{max} 216, 248 and 325 nm (log ϵ 4.15, 4.28 and 4.09); i.r., γ_{max} 1710 (C=O), 1625, 1585, 1545, 1500, 1410 and 775 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.84 (s, 3H, 18-CH_3), 0.98 (s, 3H, 19-CH_3), 2.02 (s, 3H, 17-$OCOCH_3$), 2.68 (s, 3H, 2'-SCH_3), 4.60 (m, 1H, 17-H), 6.78 (s, 1H, 4-H) and 8.34 (s, 1H, 5'-H) (Found: C, 66.04; H, 7.22; N, 12.13; M^+, 452.221984. $C_{25}H_{32}N_4O_2S$ requires C, 66.34; H, 7.13; N, 12.38%; M, 452.224585).

6.9.xvi 3β-Hydroxyandrost-5,16-dieno[16,17-g]-s-triazolo[1,5-a]-pyrimidine (240).

Source: 3β-Hydroxy-16-hydroxymethyleneandrost-5-en-17-one (8) and 3-amino-1,2,4-triazole (95).

General: The crude material obtained by evaporating the reaction mixture (after it has been refluxed for 24 h) to dryness, directly recrystallised from ethanol to give white crystals of 3β-hydroxyandrost-5,16-dieno[16,17-g]-s-triazolo[1,5-a]pyrimidine (240) (53%), m.p. 176-180°.

6.9.xvii 3β-Acetoxyandrost-5,16-dieno[16,17-g]-s-triazolo[1,5-a]-pyrimidine (241).

Treatment of 3β-hydroxyandrost-5,16-dieno[16,17-g]-s-triazolo-[1,5-a]pyrimidine (240) (300 mg, 8.24 x 10^{-4} mole) with acetic anhydride in pyridine, in a manner described for the preparation of compound (239) gave 3β-acetoxyandrost-5,16-dieno[16,17-g]-s-triazolo[1,5-a]pyrimidine (241) (185 mg, 55%); m.p. 281-283°; u.v., λ_{max} 216 and 290 nm (log ϵ 4.36 and 3.74); i.r., γ_{max} 1720 (C=O), 1605, 1555, 1500, 1450, 1370, 1360 and 780 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 1.12 (s, 3H, 18-CH_3), 1.22 (s, 3H, 19-CH_3), 2.02 (s, 3H, 3-$OCOCH_3$), 4.60 (m, 1H, 3-H), 5.44 (m, 1H, 6-H), 8.44 (s, 1H, 2'-H) and 8.64 (s, 1H, 5'-H) (Found: C, 70.93; H, 7.55; N, 13.61; M^+-CH_3COOH, 346.215113. $C_{24}H_{30}N_4O_2$ requires 70.89; H, 7.44; N, 13.79%; M-60, 346.215736).

6.9.xviii <u>3β-Hydroxy-5α-androst-16-eno[16, 17-g]-s-triazolo[1, 5-a]-pyrimidine (242).</u>

<u>Source</u>: 3β-Hydroxy-16-hydroxymethylene-5α-androstan-17-one (7) and 3-amino-1, 2, 4-triazole (95).

<u>General</u>: The reaction mixture (after it has been refluxed for 24 h) on standing at room temperature overnight deposited a white solid of <u>3β-hydroxy-5α-androst-16-eno[16, 17-g]-s-triazolo[1, 5-a]pyrimidine (242)</u> (61%), m.p. 310-315°; M^+ 366.241902. $C_{22}H_{30}N_4O$ requires M, 366.241949.

6.9.xix <u>3β-Acetoxy-5α-androst-16-eno[16, 17-g]-s-triazolo[1, 5-a]-pyrimidine (243).</u>

3β-Hydroxy-5α-androst-16-eno[16, 17-g]-s-triazolo[1, 5-a]-pyrimidine (242) (275 mg, 7.5 x 10^{-4} mole) was acetylated using the method described for 17β-acetoxyandrost-2, 4-dieno[2, 3-g]-2'-methylthio-s-triazolo[1, 5-a]pyrimidine (239) to give its 3β-acetate. Recrystallisation of the crude product from ethanol gave <u>3β-acetoxy-5α-androst-16-eno-[16, 17-g]-s-triazolo[1, 5-a]pyrimidine (243)</u> (140 mg, 45%); m.p. 261-

263°; u.v., λ_{max} 219 and 278 nm (log ε 4.48 and 3.90); i.r., γ_{max} 1715 (C=O), 1605, 1550, 1500, 1450 and 780 cm^{-1}; ^1H n.m.r. (60 MHz), δ 0.95 (s, 3H, 18-CH_3), 1.20 (s, 3H, 19-CH_3), 2.05 (s, 3H, 3-$OCOCH_3$), 4.65 (m, 1H, 3-H), 8.50 (s, 1H, 2'-H) and 8.70 (s, 1H, 5'-H) (Found: C, 70.72; H, 8.08; N, 13.68; M^+, 408.251988; $C_{24}H_{32}N_4O_2$ requires C, 70.54; H, 7.90; N, 13.72%; M^+, 408.252512).

6.9.xx 3-Methoxy-oestra-1,3,5(10),16-tetraeno[16,17-g]-s-triazolo-[1,5-a]pyrimidine (244).

Source: 3-Methoxy-16-hydroxymethyleneoestra-1,3,5(10)-trien-17-one (9) and 3-amino-1,2,4-triazole (95).

General: Alumina chromatography (eluant chloroform) followed by recrystallisation of the crude product from ethanol gave white crystals of 3-methoxy-oestra-1,3,5(10),16-tetraeno[16,17-g]-s-triazolo[1,5,a]-pyrimidine (244) (63%); m.p. 239-241°; i.r., γ_{max} 1605, 1550, 1495, 1450, 800 and 785 cm^{-1}; ^1H n.m.r. (60 MHz), δ 1.25 (s, 3H, 18-CH_3), 3.80 (s, 3H, 3-OCH_3), 6.65-7.25 (m, 3H, 1-H, 2-H and 4-H), 8.45 (s, 1H, 2'-H) and 8.65 (s, 1H, 5'-H) (Found: C, 73.17; H, 6.65; N, 15.49; M^+, 360.195001. $C_{22}H_{24}N_4O$ requires C, 73.29; H, 6.72; N, 15.55%; M, 360.194522).

6.9.xxi 3β-Hydroxyandrost-5,16-dieno[16,17-g]-2'-methyl-s-triazolo-[1,5-a]pyrimidine (245).

Source: 3β-Hydroxy-16-hydroxymethyleneandrost-5-en-17-one (8) and 3-amino-5-methyl-1,2,4-triazole (127).

General: Alumina chromatography (eluant chloroform) followed by recrystallisation of the crude product from ethanol gave white crystals of 3β-hydroxyandrost-5,16-dieno[16,17-g]-2'-methyl-s-triazolo[1,5-a]-pyrimidine (245) (21%); m.p. 288-290; u.v., λ_{max} 217 and 283 nm (log ε 4.44 and 3.75); i.r., γ_{max} 3590 (OH), 1605, 1550, 1500, 1465, 1415, and 780 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 1.15 (s, 3H, 18-CH_3), 1.25 (s, 3H, 19-CH_3), 2.65 (s, 3H, 2'-CH_3), 3.55 (m, 1H, 3-H), 5.45 (m, 1H, 6-H) and 8.65 (s, 1H, 5'-H) (Found: C, 72.95; H, 8.22; N, 14.37; M^{+}, 378.242192. $C_{23}H_{30}N_4O$ requires C, 72.97; H, 7.99; N, 14.81%; M, 378.241949).

6.9.xxii 3β-Hydroxy-5α-androst-16-eno[16,17-g]-2'-methylthio-s-triazolo[1,5-a]pyrimidine (246) and 3β-hydroxy-16[3'-(5'-methylthio)-s-triazolyl-aminomethylene]-5α-androstan-17-one (247).

Source: 3β-Hydroxy-16-hydroxymethylene-5α-androstan-17-one (7) and 3-amino-5-methylthio-1,2,4-triazole (224).

General: Alumina chromatography (eluant chloroform) followed by recrystallisation of the eluant from acetone gave white needles of 3β-hydroxy-5α-androst-16-eno[16,17-g]-2'-methylthio-s-triazolo[1,5-a]-pyrimidine (246) (45%), m.p. 244-246°; u.v., λ_{max} 211, 241, 286 and 307 nm (log ε 4.25, 4.46, 3.85 and 3.87); i.r., γ_{max} 3600(OH), 1600, 1555, 1490, 1440, 1420, 1350 and 780 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.84 (s, 3H, 18-CH_3), 1.14 (s, 3H, 19-CH_3), 2.64 (s, 3H, 2'-SCH_3), 4.04 (m, 1H, 3-H) and 8.67 (s, 1H, 5'-H) (Found: C, 66.96; H, 7.91; N, 13.50; M^{+}, 412.229671. $C_{23}H_{32}N_4OS$ requires C, 66.95; H, 7.82; N, 13.59%; M, 412.227106).

Further elution of the column with 10% ethanol in chloroform followed by recrystallisation from acetone gave white crystals of 3β-hydroxy-16[3'-(5'-methylthio)-s-triazolyl-aminomethylene]-5α-androstan-17-one (247) (22%), m.p. 181-185°; u.v., λ_{max} 208 and 320 nm (log ε 4.04 and 4.26); ^{1}H n.m.r. (100 MHz), δ 0.74 (s, 6H, 18-CH_3 and 19-CH_3), 2.54 (s, 3H, 5'-SCH_3), 4.14 (m, 1H, 3-H), 7.60 (d, 1H, -NH-C<u>H</u>=C-), 9.70 (d, 1H, -N<u>H</u>-CH=C-) and 13.18 (bs, 1H, triazole-N<u>H</u>) (Found:[141] M^+, 412.229670. $C_{23}H_{34}N_4O_2S$ requires M (-H_2O), 412.229670).

The compound (246) was obtained as the sole product, in 77% yield, when the above condensation was carried out in dry toluene. The compound (246) was also obtained in 85% yield when a solution of the β-ketoanil (247) in dry toluene containing a small amount of toluene-4-sulphonic acid was refluxed for 4 h.

6.9.xxiii 3β-Hydroxyandrost-5,16-dieno[16,17-g]-2'-methylthio-s-triazolo[1,5-a]pyrimidine (250) and 3β-hydroxy-16[3'-(5'-methylthio)-s-triazolyl-aminomethylene]androst-5-ene-17-one (249).

Source: 3β-Hydroxy-16-hydroxymethyleneandrost-5-en-17-one (8) and 3-amino-5-methyl-1,2,4-triazole (224).

General: Alumina chromatography (eluant chloroform) followed by recrystallisation of the eluate from ethanol gave white needles of 3β-hydroxyandrost-5,16-dieno[16,17-g]-2'-methylthio-s-triazolo[1,5-a]-pyrimidine (250) (38%), m.p. 265-266°; u.v. λ_{max} 210, 241, 286 and 307 nm (log ε 4.11, 4.43, 3.91 and 3.93); i.r., γ_{max} 3590 (OH), 1600, 1555, 1490, 1450, 1415 and 780 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 1.10

(s, 3H, 18-CH_3), 1.18 (s, 3H, 19-CH_3), 2.70 (s, 3H, 2'-SCH_3), 3.50 (m, 1H, 3-H), 5.36 (m, 1H, 6-H) and 8.48 (s, 1H, 5'-H) (Found: C, 67.36; H, 7.47; N, 13.68; M^+, 410.212152. $C_{23}H_{30}N_4OS$ requires C, 67.28; H, 7.37; N, 13.65%; M, 410.214022).

Further elution of the column with 10% ethanol in chloroform gave 3β-hydroxy-16[3'-(5'-methylthio)-s-triazolyl-aminomethylene]androst-5-en-17-one (249) which was recrystallised from acetone as a white solid (42%), m.p. 100-110° u.v., λ_{max} 209 and 320 nm (log ε 4.06 and 4.34); ^{1}H n.m.r. (100 MHz), δ 0.80 (s, 3H, 18-CH_3), 0.98 (s, 3H, 19-CH_3), 2.54 (s, 3H, 5'-SCH_3), 3.50 (m, 1H, 3-H), 5.32 (m, 1H, 6-H), 7.64 (d, J=12Hz, 1H, -NH-C$\underline{H}$=C-), 9.72 (d, J=12Hz, 1H, -N$\underline{H}$-CH=C-) and 13.32 (bs, 1H, triazole -N$\underline{H}$) (Found:[141] M^+, 410.212559. $C_{23}H_{32}N_4O_2S$ requires M (-H_2O), 410.214022).

6.9.xxiv 3-Methoxyoestra-1, 3, 5(10), 16-tetraeno[16, 17-g]-2'-methylthio-s-triazolo[1, 5-a]pyrimidine (252) and 3-methoxy-16[3'-(5'-methylthio)-s-triazolyl-aminomethylene]oestra-1, 3, 5(10)trien-17-one (251).

Source: 3-Methoxy-16-hydroxymethyleneoestra-1, 3, 5(10)trien-17-one (9) and 3-amino-5-methylthio-1, 2, 4-triazole (224).

General: Alumina chromatography (eluant chloroform) followed by recrystallisation of the eluant from ethanol gave white needles of 3-methoxyoestra-1, 3, 5(10), 16-tetraeno[16, 17-g]-2'-methylthio-s-triazolo-[1, 5-a]pyrimidine (252) (27%), m.p. 184-186°; i.r., γ_{max} 1605, 1555, 1490, 1455, 1420, 1350 and 780 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 1.18 (s, 3H, 18-CH_3), 2.70 (s, 3H, 2'-SCH_3), 3.74 (s, 3H, 3-OCH_3), 6.64-7.20 (m, 3H, 1-H, 2-H and 4-H) and 8.52 (s, 1H, 5'-H) (Found: C, 67.81; H, 6.47; N, 13.51; M^+, 406.180323. $C_{23}H_{26}N_4OS$ requires C, 67.95; H, 6.45; N, 13.79%; M, 406.182723).

Further elution of the column with 10% ethanol in chloroform gave 3-methoxy-16[3'-(5'-methylthic)-s-triazolyl-aminomethylene]oestra-1,3,5(10)trien-17-one (251) (17 %), which resisted recrystallisation. ^{1}H n.m.r. (100 MHz), δ 0.78 (s, 3H, 18-CH_3), 2.56 (s, 3H, 5'-SCH_3), 3.68 (s, 3H, 3-OCH_3), 6.60-7.14 (m, 3H, 1-H, 2-H and 4-H), 7.66 (d, J=12Hz, 1H, -NH-C<u>H</u>=C-), 9.76 (d, J=12Hz, 1H, -N<u>H</u>-CH=C-) and 13.40 (bs, 1H, triazole-NH) (Found:^{141} $M^{=}$, 406.181231. $C_{23}H_{28}N_4O_2S$ requires M (-H_2O), 406.181723).

6.9.xxv 3β-Acetoxy-5α-androst-16-eno[16,17-g]-2'-methylthio-s-triazolo[1,5-a]pyrimidine (253).

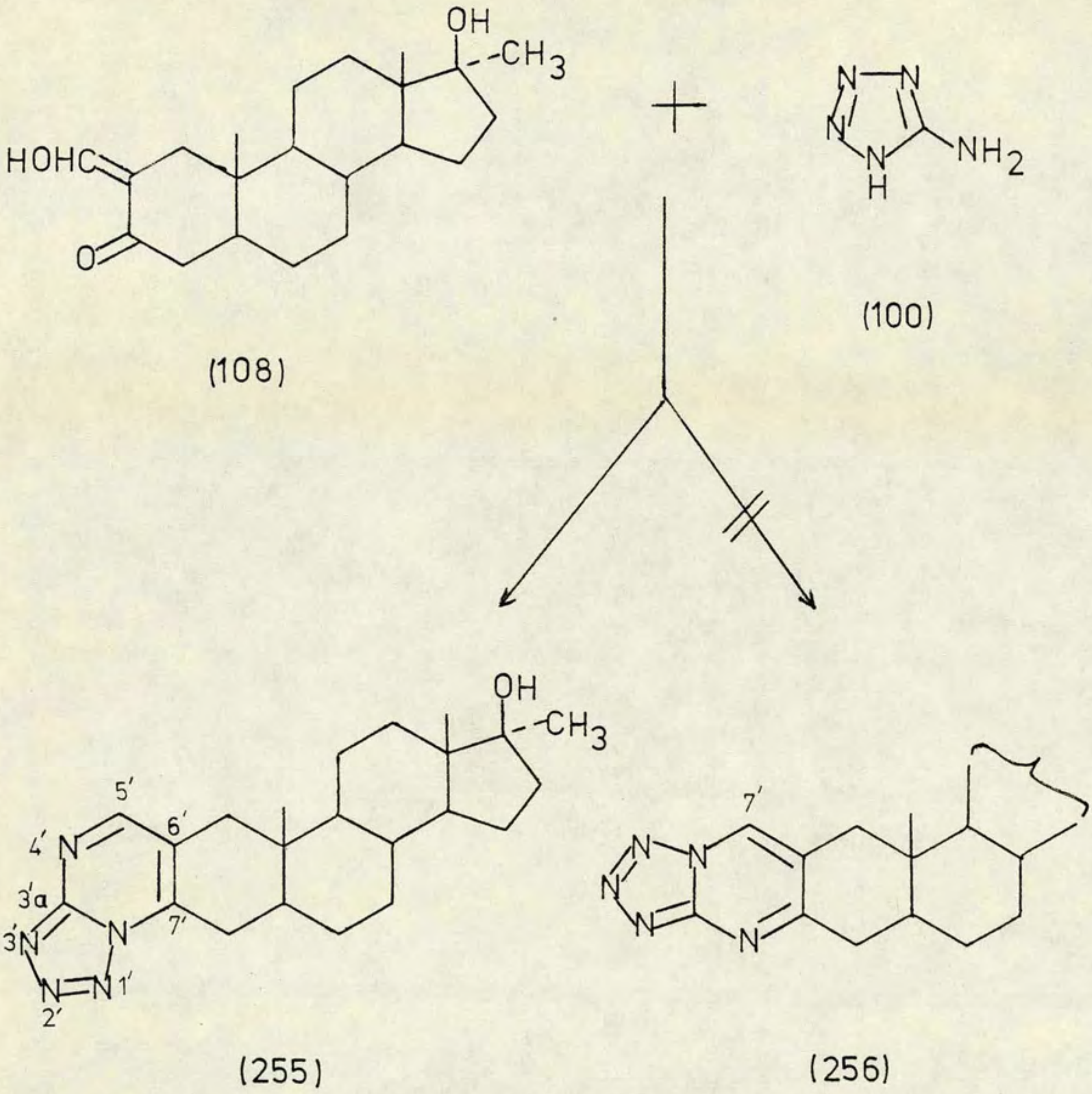
Treatment of 3β-hydroxy-5α-androst-16-eno[16,17-g]-2'-methylthio-s-triazolo[1,5-a]pyrimidine (246) (275 mg, 6.67 x 10^{-4} mole) with acetic anhydride in pyridine in a manner described for the preparation of 17β-acetoxyandrost-2,4-dieno[2,3-g]-2'-methylthio-s-triazolo[1,5-a]-pyrimidine (239) gave its 3β-acetate. Recrystallisation of the crude product from ethanol gave 3β-acetoxy-5α-androst-16-eno[16,17-g]-2'-methylthio-s-triazolo[1,5-a]pyrimidine (253) (166 mg, 55%); m.p. 191-192°; u.v., λ_{max} 212, 241, 285 and 306 nm (log ε 4.28, 4.70, 3.77 and 3.75); i.r., γ_{max} 1710 (C=O), 1600, 1555, 1490, 1420 and 780 cm^{-1}; ^{1}H n.m.r. (100 MHz, δ 0.84 (s, 3H, 18-CH_3), 1.10 (s, 3H, 19-CH_3), 2.02 (s, 3H, 3-$OCOCH_3$), 2.68 (s, 3H, 2'-SCH_3), 4.65 (m, 1H, 3-H), 8.48 (s, 1H, 5'-H) (Found: C, 66.23; H, 7.82; N, 12.01; M^+, 454.238562. $C_{25}H_{34}N_4O_2S$ requires C, 66.04; H, 7.54; N, 12.33%; M, 454.240235).

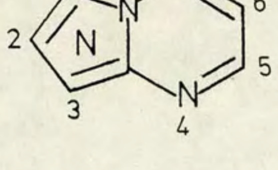
6.9.xxvi 3β-Acetoxyandrost-5,16-dieno[16,17-g]-2'-methylthio-s-triazolo[1,5-a]pyrimidine (254).

3β-Hydroxyandrost-5,16-dieno[16,17-g]-2'-methylthio-s-triazolo-[1,5-a]pyrimidine (250) (250 mg, 6.1×10^{-4} mole) was acetylated using the method described for 17β-acetoxyandrost-2,4-dieno[2,3-g]-2'-methylthio-s-triazolo[1,5-a]pyrimidine (239) to give its 3β-acetate. Recrystallisation of the crude product from ethanol gave white crystals of 3β-acetoxyandrost-5,16-dieno[16,17-g]-2'-methylthio-s-triazolo-[1,5-a]pyrimidine (254) (170 mg, 61%); m.p. 228-229°; u.v., λ_{max} 211, 241, 288 and 307 nm (log ε 4.11, 4.47, 3.82 and 3.85); i.r., γ_{max} 1715 (C=O), 1605, 1555, 1490, 1415, 1350 and 780 cm^{-1}; ^1H n.m.r. (100 MHz), δ 1.12 (s, 3H, 18-CH_3), 1.18 (s, 3H, 19-CH_3), 2.02 (s, 3H, 3-$OCOCH_3$), 2.70 (s, 3H, 2'-SCH_3), 4.62 (m, 1H, 3-H), 5.40 (m, 1H, 6-H) and 8.50 (s, 1H, 5'-H) (Found: C, 66.31; H, 7.21; N, 12.26; M^+, 452.223262. $C_{25}H_{32}N_4O_2S$ requires C, 66.34; H, 7.13; N, 12.38%; M, 452.224585).

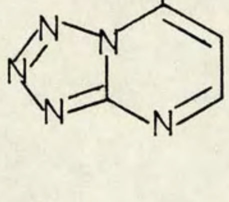
6.9.xxvii The reaction of 2(2'-pyridyl-aminomethylene)-5α-cholestan-3-one (207) with 3-amino-1,2,4-triazole (95).

A solution of 2(2'-pyridyl-aminomethylene)-5α-cholestan-3-one (207) (400 mg, 8.4×10^{-4} mole), 3-amino-1,2,4-triazole (95) (120 mg, 1.45×10^{-3} mole) and toluene-4-sulphonic acid (20 mg) in dry toluene (30 ml) was refluxed for 7 h. The excess of solvent was removed under vacuo and the residue was chromatographed over alumina. Elution with ethyl acetate followed by recrystallisation of the eluate from ethyl acetate gave white shining plates (265 mg, 68%); m.p. 170-173°, identical (m.p., i.r. and ^{1}H n.m.r. spectra) with that of 5α-cholestano[3,2-f]-s-triazolo[1,5-a]pyrimidine (220).


OH
CH_3
HOHC
O
(108)
N
N
N
N
H
NH_2
(100)
OH
CH_3
5′
6′
4′
N
3′a
3′N
N
7′
N
N 1′
2′
(255)
7′
N
N
N
N
N
(256)


1
7
6
2
N
5
3
N
4

(179)


CH_3
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N
N
N
N

(257)

7 The reaction of steroidal β-ketoaldehydes with 5-aminotetrazole

7.1 The reaction of 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108) with 5-aminotetrazole (100).

A solution of 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108) and 5-aminotetrazole (100) in absolute alcohol was refluxed overnight. On cooling the reaction mixture to room temperature, fine white crystals (255), m. p. 196-198°, in 84% yield were obtained.

Mass spectrometry and elemental analysis indicated that the product had a molecular formula of $C_{22}H_{31}N_5O$. The u. v. spectrum showed λ_{max} at 216 and 280 nm (log ε 4.31 and 3.72). The i. r. spectrum (in bromoform) exhibited absorptions at 3600, 2140, 1620, 1545, 1510, 1445, 1380, 1370, 930, and 780 cm^{-1} and the ^1H n. m. r. showed a singlet at δ 8.66 apart from the signals for the 17-, 18- and 19-methyl protons.

7.2 Discussion

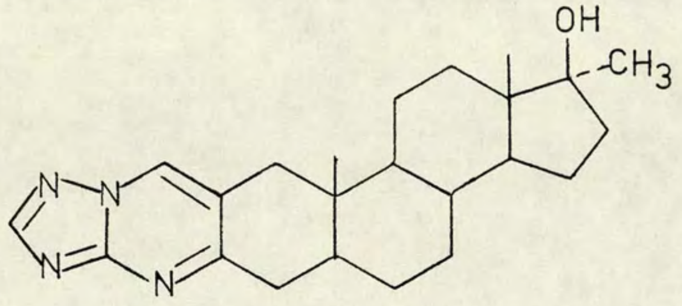
The i. r. spectrum of the product obtained by the condensation of 5-aminotetrazole with 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108) exhibits no carbonyl absorption. Thus the condensation product appears from its i. r. spectrum and the molecular formula $C_{22}H_{31}N_5O$ to be a derivative of the tetrazolo[1, 5-a]pyrimidine system. It was noted earlier (page 54, 68) that the condensation of an aminoazole

Table 6

^{13}C-Chemical shifts of steroidal tetrazolo[1, 5-a]pyrimidines (p. p. m.)

Compound	3'a-C	5'-C	6'-C	7'-C	Other carbons
(255)	154.17	159.79	120.92	142.76	
(257)	158.91	158.44	112.42	146.84	
(263a)*	154.77	167.64	120.78	129.54	4-C, 121.17; 5-C, 161.67
(268a)	153.06	179.81	128.93	126.12	

* Spectrum taken in d^6 DMSO



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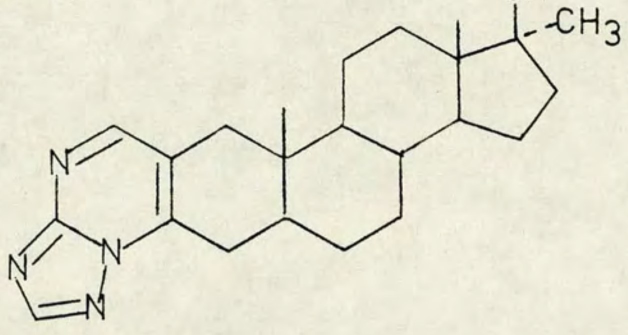
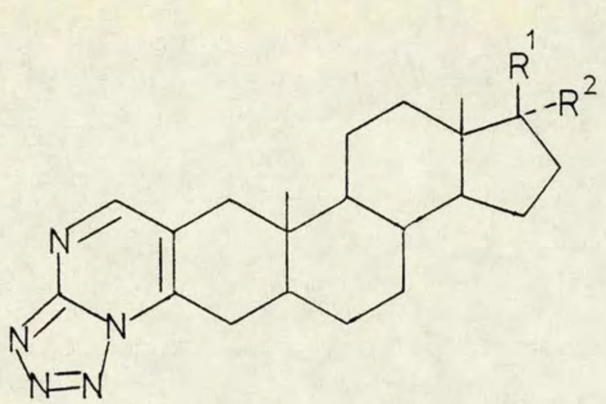


(211)

with an unsymmetrical β-ketoaldehyde can theoretically lead to two products. Therefore two possible structures (255) and (256) were postulated for the product obtained by the condensation of 5-aminotetrazole (100) with the β-ketoaldehyde (108). However, ^{1}H n.m.r. and ^{13}C n.m.r. spectroscopy show that the condensation product has structure (255).

The ^{1}H n.m.r. spectrum of this condensation product shows signals at δ 0.88 (s, 18-CH_3), 0.92 (s, 19-CH_3), 1.24 (s, 17-CH_3) and 8.67 (s, 5'-H). Of particular interest in the ^{1}H n.m.r. spectrum is the fact that the signal for the 5'-H is found to be sharp and this is consistent with the angular structure (255) assigned to the condensation product. It has been previously reported[77] that no long range coupling is observed between the methyl group protons at position 6 and the 5-H of azolo[a]pyrimidines (179). In contrast the methyl group protons at either position 7 or 6 of azolo[a]pyrimidines (179) have been found to couple with the 6-H or 7-H respectively (J = 0.4-1.0 Hz).[77] Therefore the alternative structure (256) is discounted, since the 7'-H would be expected to show a triplet or a broad singlet due to a small long range coupling with the methylene protons at position 1.

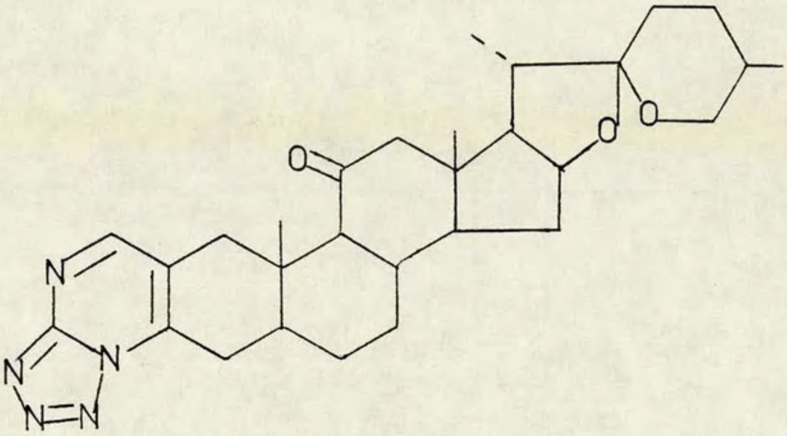
The assignment of structure (255) is further supported by ^{13}C n.m.r. evidence. The ^{13}C-chemical shifts of the aromatic ring carbons of the tetrazolopyrimidine (255) are given in Table 6. The assignments quoted for the chemical shifts of the aromatic ring carbons of the steroid (255) follow directly by analogy with the values allocated to the comparable ring system (257) (section 9). The chemical shift of 5'-C (159.79 p.p.m.) in the condensation product (255) is found to be in agreement with the chemical shift of 5-C (158.44 p.p.m.) in 7-methyltetrazolo[1,5-a]-pyrimidine (257) and 5'-C (155.94 p.p.m.) in 17β-hydroxy-17α-methyl-



(258) $R^1 = OH$, $R^2 = H$

(259) $R^1 = R^2 = H$

(260) $R^1 = C_8H_{17}$, $R^2 = H$



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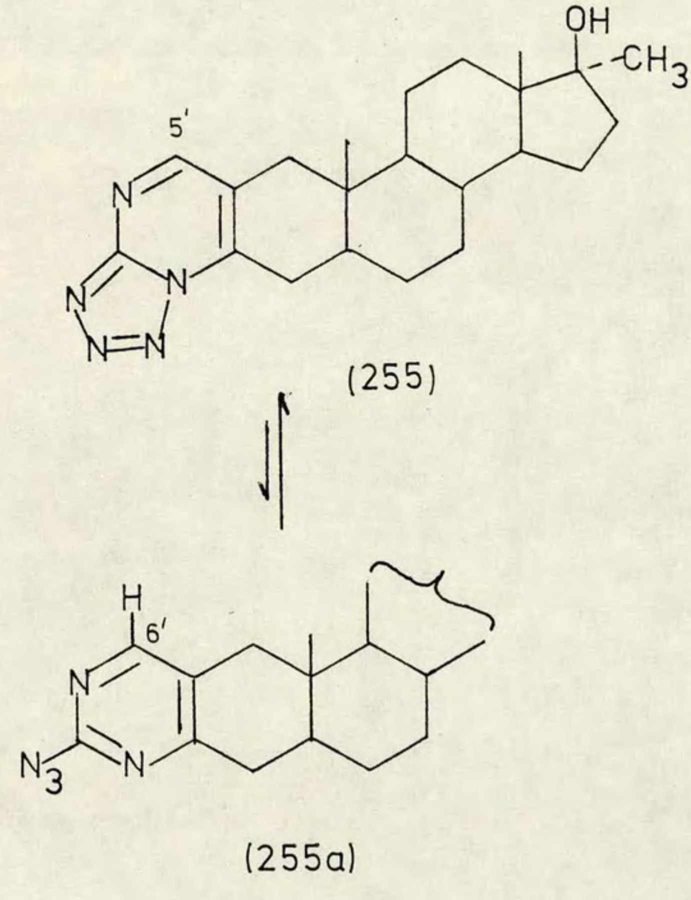
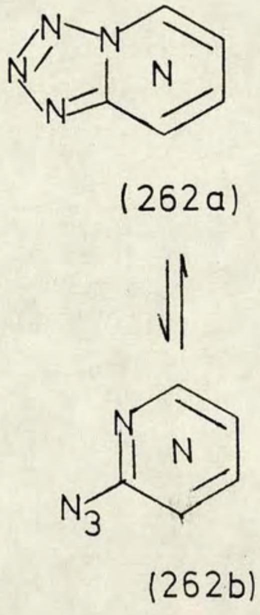


(255)

(255a)



(262a)

(262b)

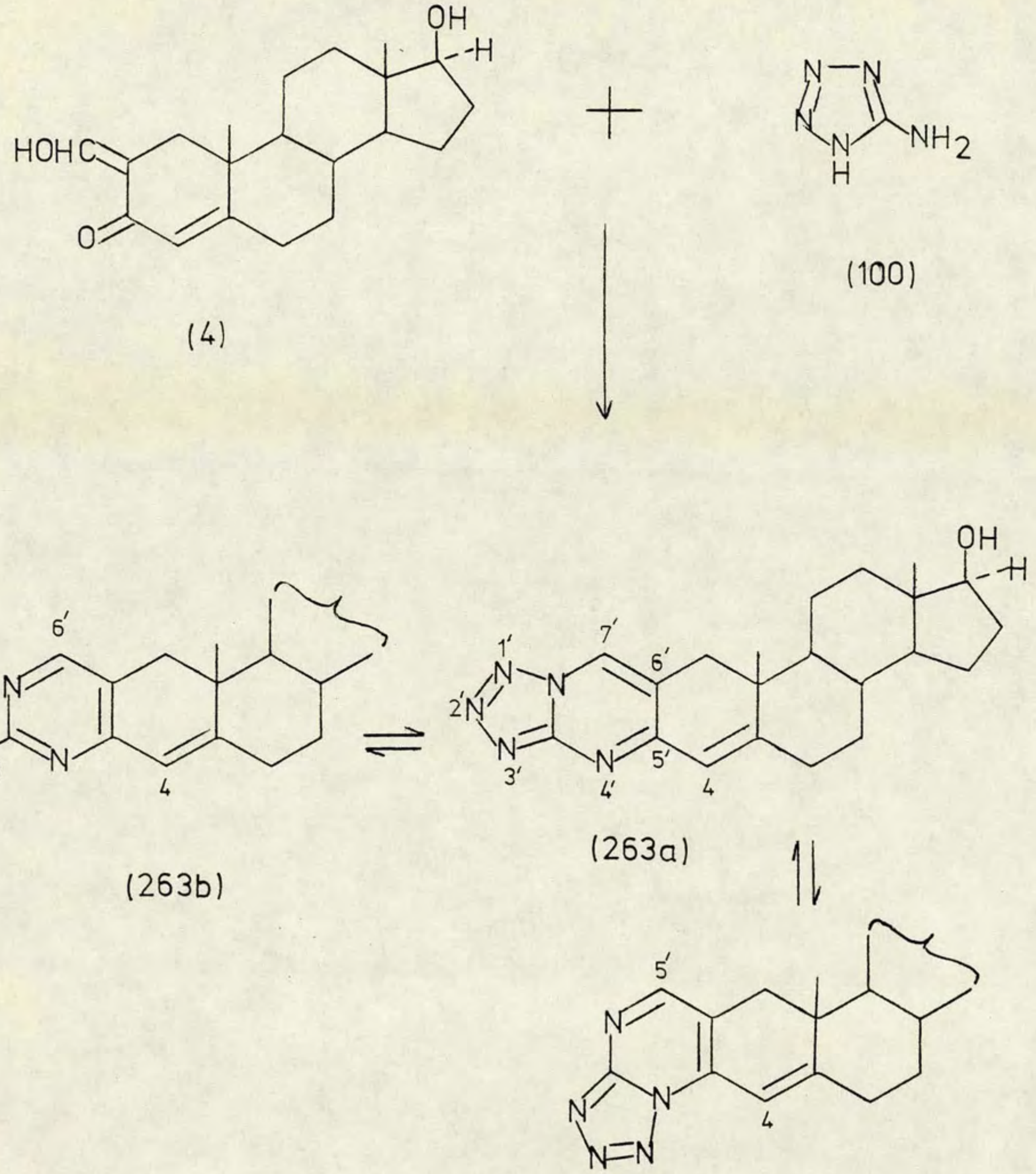
5α-androst-2-eno[2, 3-g]-s-triazolo[1, 5-a]pyrimidine (211). This confirms the angular fusion of the steroid to the heterocyclic system. If the condensation product had had the linear structure (256), the chemical shift of 7'-C would have been expected to appear in the region of 133. 77 p. p. m., which is the chemical shift of 7'-C in 17β-hydroxy-17α-methyl-5α-androstano[3, 2-f]-s-triazolo[1, 5-a]pyrimidine (210) (section 6, Table 5).

Under analogous reaction conditions, the condensation of 5-aminotetrazole (100) with 17β-hydroxy-2-hydroxymethylene-5α-androstan-3-one (3), 2-hydroxymethylene-5α-androstan-3-one (109), 2-hydroxymethylene-5α-cholestan-3-one (110) and 2-hydroxymethylene-5α-spirostan-3, 11-dione (111) gave 17β-hydroxy-5α-androst-2-eno[2, 3-g]tetrazolo-[1, 5-a]pyrimidine (258), 5α-androst-2-eno[2, 3-g]tetrazolo[1, 5-a]-pyrimidine (259), 5α-cholest-2-eno[2, 3-g]tetrazolo[1, 5-a]pyrimidine (260) and 11-oxo-5α-spirost-2-eno[2, 3-g]tetrazolo[1, 5-a]pyrimidine (261) respectively.

It is also noticed that the ^{1}H n. m. r. spectrum of the tetrazolopyrimidine (255) in deuterated chloroform also contains a small signal at δ 8. 20 in addition to the signal for the 5'-H at δ 8. 66. The small signal at δ 8. 20 persists even after further recrystallisation of the product from ethanol. This shows that the compound (255) exists in equilibrium with its azido form (255a) and this is confirmed by the i. r. spectrum of the compound in deuterated chloroform or in bromoform which exhibits a distinct azide absorption at 2140 cm^{-1}. The i. r. spectrum of the compound (255) in nujol does not show any azide absorption band in the 2100-2200 cm^{-1} region and the ^{1}H n. m. r. spectrum in d^6-DMSO shows no other signal in the aromatic region apart from the signal at δ 8.60 which corresponds to 5'-H in the tetrazolo form (255). These observations indicate that the condensation product exists solely in the tetrazolo form (255) in d^6-DMSO and in the solid state. However, in deuterated chloroform the tetrazolo form (255) is found to be in equilibrium with a small amount of the azido form (255a). It is also observed that the chemical shift of the 5'-H (δ 8.60) in the tetrazolo form (255) occurs at a lower field when compared with the chemical shift (δ 8.20) of the corresponding proton (6'-H) in the azido form (255a). This difference is attributed to the opposing effect[145] of the electron withdrawing tetrazole ring (deshielding) and the electron donating azido group (shielding).

Rearrangements of this type have been recently demonstrated in several tetrazoloazine series through the simultaneous applications of i.r. and ^{1}H n.m.r. spectroscopy.[82] It has been shown that regardless of the tetrazoloazine (262), the tetrazolo tautomer (262a) is generally favoured in the solid state or in dimethyl sulphoxide solution.[82, 146, 147] On the other hand the azido form (262b) is stabilised in trifluoroacetic acetic acid, presumably through protonation of an anular nitrogen and destabilisation of the tetrazoloazine tautomer.[82, 148] In other solvents both the forms (262a) and (262b) are usually detected.

Similarly the compounds (258)-(261) exist in equilibrium with their corresponding azido forms in deuterated chloroform or bromoform and in only their tetrazole forms in d^6-DMSO and in the solid state.



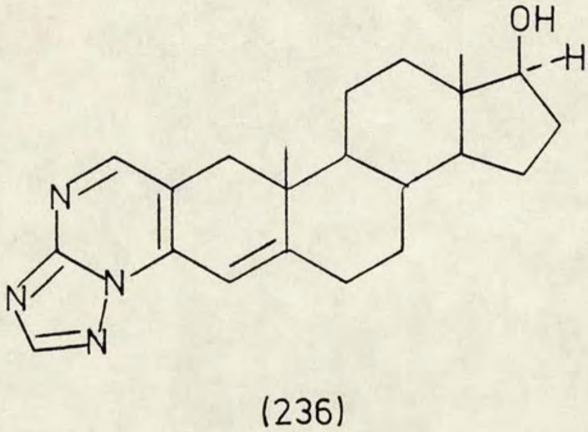
(4)

(100)

(263b)

(263a)

(263c)



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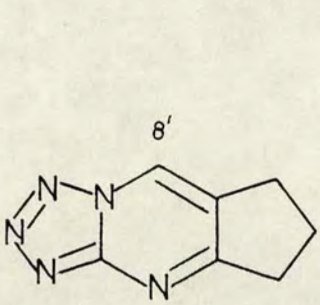


(268a)

7.3 The reaction of 17β-hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4) with 5-aminotetrazole (100).

A solution of 17β-hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4) and 5-aminotetrazole in absolute alcohol was refluxed overnight. The reaction mixture was concentrated and allowed to stand at room temperature for 24 h. Yellow crystals were obtained which were again recrystallised from ethanol to give fine yellow crystals (263), m.p. 143-145° in 37% yield.

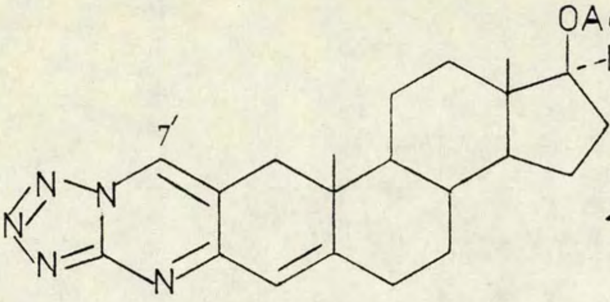
Mass spectrometry and elemental analysis indicated that the product had a molecular formula of $C_{21}H_{27}N_5O$. The u.v. spectrum showed λ_{max} at 213, 243 and 311 nm (log ε 4.15, 4.11 and 4.06). The i.r. spectrum showed absorption at 3600, 2140, 1620, 1500-1515, 1430, 1415, 1380 and 780 cm^{-1} whilst the ^1H n.m.r. spectrum exhibited signals at δ 0.80 (3H), 1.06 (3H), 3.70 (1H), 6.50 (1H) and 8.60 (1H).

7.4 Discussion

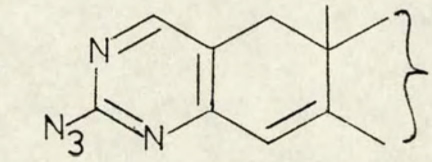
The i.r. spectrum of the condensation product obtained by the reaction of 17β-hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4) and 5-aminotetrazole does not correlate well with the i r. spectrum of 17β-hydroxy-17α-methyl-5α-androst-2-eno[2, 3-g]tetrazolo[1, 5-a]pyrimidine (255). However, it exhibits an absorption at 2140 cm^{-1} indicating the presence of the azido tautomer (263b) in bromoform solution. The ^1H n.m.r. spectrum of the condensation product (263) in deuteriochloroform initially indicates the presence of only one compound which is characterised as (263a), since the signal at δ 8.60 corresponding to 7'-H is found to be broadened by a small long range coupling with the methylene protons at position 1. After 10 minutes however, two additional small signals appear at δ 8.16 and δ 6.20. After 24 h this isomer reaches a concentration of about 40% as calculated from the ratio of the integrated intensities for the protons from the tetrazolo form to those of the new isomer. This new compound is characterised as the azido tautomer (263b) by the i.r. spectrum of the compound (263) in deuterated chloroform which shows an azide absorption at 2140 cm^{-1}. The signals at δ 8.16 and δ 6.20 in the ^1H n.m.r. spectrum are assigned to the 6'-H and the 4-H respectively in the tautomer (263b). After 24 h, the third tautomer (263c) is also found to be present (about 10%) in the ^1H n.m.r. sample tube and signals at δ 8.64 and δ 6.98 are assigned to the 7'-H and the 4-H respectively. The chemical shift of the 4-H (δ 6.98) in the tautomer (263c) correlates well with the chemical shift of the 4-H (δ 6.92) in 17β-hydroxyandrost-2,4-dieno[2,3-g]-s-triazolo[1,5-a]pyrimidine (236) and this supports the assignment of structure (263c). The chemical shifts of the 6'-H and the 4-H in the tautomer (263b) both occur at a higher field than the chemical shifts of the corresponding protons in the tautomers (263a) and (263b). This is again attributed to the deshielding and shielding effects[145] of the tetrazole ring and the azido group respectively.

In d^6-DMSO, only one isomer is detected and this is characterised as (263a) by its ^{13}C n.m.r. spectrum where the chemical shift of the 7'-C (129.53 p.p.m.) is found to agree well with the value observed for the 8-C (126.12 p.p.m.) in 6,7-dihydro-5H-cyclopento[d]tetrazolo[1,5-a]-pyrimidine (268a)(Table 6).

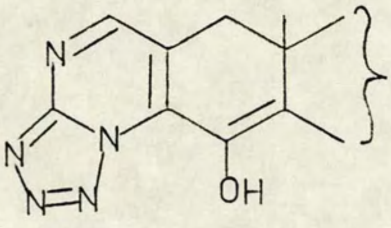
The effects of substituents on the tetrazoloazine equilibrium (262a $\rightleftharpoons$ 262b) have been investigated. In general, electron-attracting



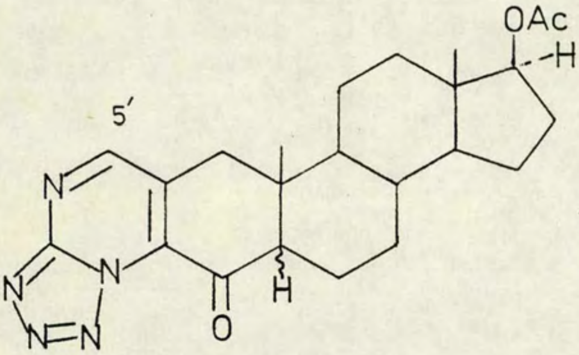
(264a)



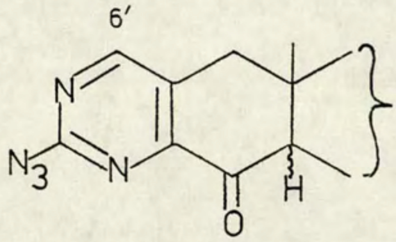
(264b)



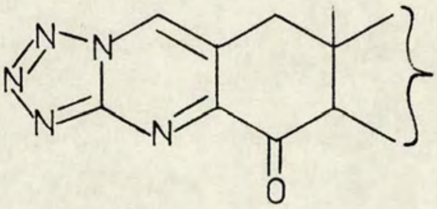
(265c)



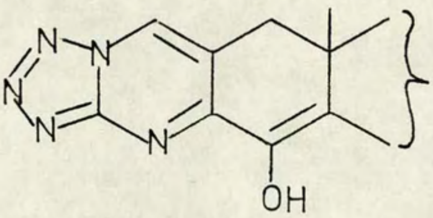
(265a)



(265b)



(265d)



(265e)

substituents stabilise the electron donating azido group, thereby favouring (262a) and destabilise the electron withdrawing tetrazole group and tautomer (262b). Electron donating substituents have the reverse effect.[80f]

7.5 Acetylation of 17β-hydroxyandrost-4-eno[3, 2-f]tetrazolo[1, 5-a]-pyrimidine (263a).

A solution of 17β-hydroxyandrost-4-eno[3, 2-f]tetrazolo[1, 5-a]-pyrimidine (263a) in pyridine containing a small amount of acetic anhydride was refluxed for 2 h. The solvent was evaporated in vacuo and the residue was taken up in chloroform. The chloroform solution was washed with water, 5% hydrochloric acid, saturated sodium bicarbonate solution and water again before being dried over anhydrous magnesium sulphate and evaporated to dryness. The residue was chromatographed over alumina. Elution with ethyl acetate gave a product which was recrystallised from ethanol to give a yellow solid (264) m. p. 217-219°, in 25% yield. Further elution of the column with chloroform gave another product which was recrystallised from ethanol to give a yellow solid (265), m. p. 235-237°, in 37% yield.

Mass spectrometry and elemental analysis of the first product, m. p. 217-219°, gave its molecular formula as $C_{23}H_{29}N_5O_2$. The u. v. spectrum showed λ_{max} 213, 243 and 311 nm (log ε 4.18, 4.22 and 4.19) and the i. r. spectrum exhibited absorptions at 2140, 1720, 1620, 1515, 1500, 1430, 1425, 1375 and 780 cm^{-1}. The ^1H n. m. r. spectrum showed a singlet (broadened due to a small long range coupling) at δ 8.60 corresponding to the proton of the pyrimidine ring.

Mass spectrometry and elemental analysis of the second product, m. p. 235-237°, indicated that it had a molecular formula of $C_{23}H_{29}N_5O_3$. The u. v. spectrum showed λ_{max} at 214, 249 and 287 nm (log ε 4. 13, 3. 98 and 3. 81). The i. r. spectrum exhibited absorptions of 2140, 1720, 1685, 1625, 1545, 1510, 1415, 1375 and 780 cm^{-1} whilst the ^1H n. m. r. spectrum exhibited a sharp singlet at δ 8. 65.

7. 6 Discussion

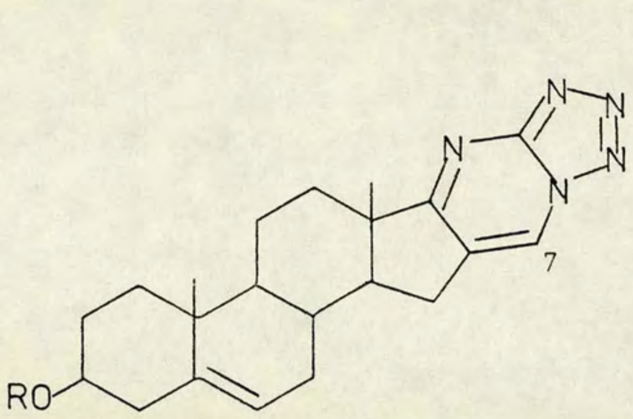
The i. r. and ^1H n. m. r. spectra obtained for the first product, m. p. 217-219°, resemble closely the i. r. and ^1H n. m. r. spectra obtained for its precursor 17β-hydroxyandrost-4-eno[3, 2-f]tetrazolo[1, 5-a]-pyrimidine (263a) so that the product, m. p. 217-219° can be formulated as 17β-acetoxyandrost-4-eno[3, 2-f]tetrazolo[1, 5-a]pyrimidine (264a). In the ^1H n. m. r. spectrum two small signals at δ 3. 15 and δ 6. 15 also appear whilst the i. r. spectrum exhibits an absorption of medium intensity at 2140 cm^{-1}, thus indicating that the compound (264a) exists in equilibrium with a small amount of the azido tautomer (264b).

The molecular formula $C_{23}H_{29}N_5O_3$ of the second product, m. p. 235-237°, indicate that it differs from that of 17β-acetoxyandrost-4-eno[3, 2-f]tetrazolo[1, 5-a]pyrimidine (264a) in having one extra oxygen atom but the product still has a characteristic u. v. spectrum of the tetrazolo[1, 5-a]pyrimidine moiety. It therefore appears that this steroid has been formed by the reaction of acetic anhydride-pyridine on the Δ^4 double bond of its precursor (264a). Epoxide formation can be eliminated on the grounds that the reaction conditions were not those normally associated with epoxide formation. The i. r. spectrum of the steroid shows no absorption around 3600 cm^{-1} thus excluding the enolic structures (265c) and (265e) however, it does exhibit absorptions at 1720 cm^{-1} and 1685 cm^{-1}. The absorption at 1720 cm^{-1} is assigned to the carbonyl of the 17β-acetyl group by analogy with 17β-acetoxyandrost-4-eno[3, 2-f]tetrazolo[1, 5-a]pyrimidine (264a) and the absorption at 1685 cm^{-1} is attributed to the presence of a new conjugated carbonyl group. Thus, it appears that the steroid has either structure (265a) or (265d). It has previously been noticed in sections 5 and 6 that the number and shape of the absorption bands in the region 1500-1630 cm^{-1} of heterocyclic steroids characterise the linear or the angular fusion of the heterocyclic system to the steroid nucleus. The absorptions at 1625, 1545 and 1510 cm^{-1} in the i. r. spectrum of this steroid differ significantly from the corresponding absorptions in the i. r. spectra of 17β-hydroxy- and 17β-acetoxyandrost-4-eno[3, 2-f]tetrazolo[1, 5-a]-pyrimidine (263a) and (264a) but are identical with the absorptions in the i. r. spectrum of 17β-hydroxy-17α-methyl-5α-androst-2-eno[2, 3-g]-tetrazolo[1, 5-a]pyrimidine (255). Therefore, the steroid, m. p. 235-237° is formulated as 17β-acetoxy-4-oxo-5α-androst-2-eno[2, 3-g]-tetrazolo[1, 5-a]pyrimidine (265a). This structure is further supported by ^{1}H n. m. r. spectroscopy where the signal for the 5'-H is found to be fairly sharp and this is consistent with the assignment of an angular structure (265a). If the product had had structure (265d), the signal for the 7'-H would have been broadened due to a small long range coupling with the methylene protons at position 1.[77] The i. r. spectrum of the steroid (265a) in bromoform shows an azide absorption at 2140 cm^{-1} whilst the ^{1}H n. m. r. spectrum in deuterated chloroform shows a small signal at δ 8.20 (6'-H in 265b) suggesting that the product exists in equilibrium with a small quantity of the azido tautomer (265b).

The assignment of angular structure (265a) is also found to be in accord with the following observation. The reaction of a Δ^4-unsaturated 2-hydroxymethylene-3-oxo steroid with an aminoazole affords the same type of product (linear or angular) as is obtained by the reaction of a 16-hydroxymethylene-17-oxo steroid with the same aminoazole. It will be seen shortly that the reaction of 16-hydroxymethylene-17-oxo steroids with 5-aminotetrazole leads to linearly fused products. Thus the reaction of 17β-hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4) with aminotetrazole should lead to 17β-hydroxyandrost-4-eno[3,2-f]-tetrazolo[1,5-a]pyrimidine (263a) and this has been confirmed. The product obtained by the reaction of a 2-hydroxymethylene-3-oxo steroid (e. g. 108) without a Δ^4 double bond with 5-aminotetrazole exists predominantly in the form in which the tetrazolopyrimidine system is fused angularly to the steroid nucleus (e. g. 255). Therefore, the steroid (265) which contains no Δ^4 double bond is expected to exist predominantly in the form (265a) and this is confirmed above by i. r. and ^{1}H n. m. r. spectroscopy. The mechanism for the formation of the steroid (265a) will be discussed in section 10.

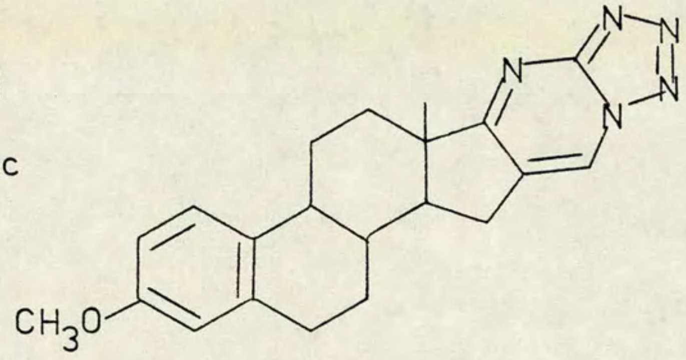
7. 7 The reaction of 3β-hydroxy-16-hydroxymethyleneandrost-5-en-17-one (8) with 5-aminotetrazole (100).

A solution of 3β-hydroxy-16-hydroxymethyleneandrost-5-en-17-one (8) and 5-aminotetrazole (100) in dry toluene was refluxed overnight. The reaction mixture was evaporated to dryness under vacuo and the residue was

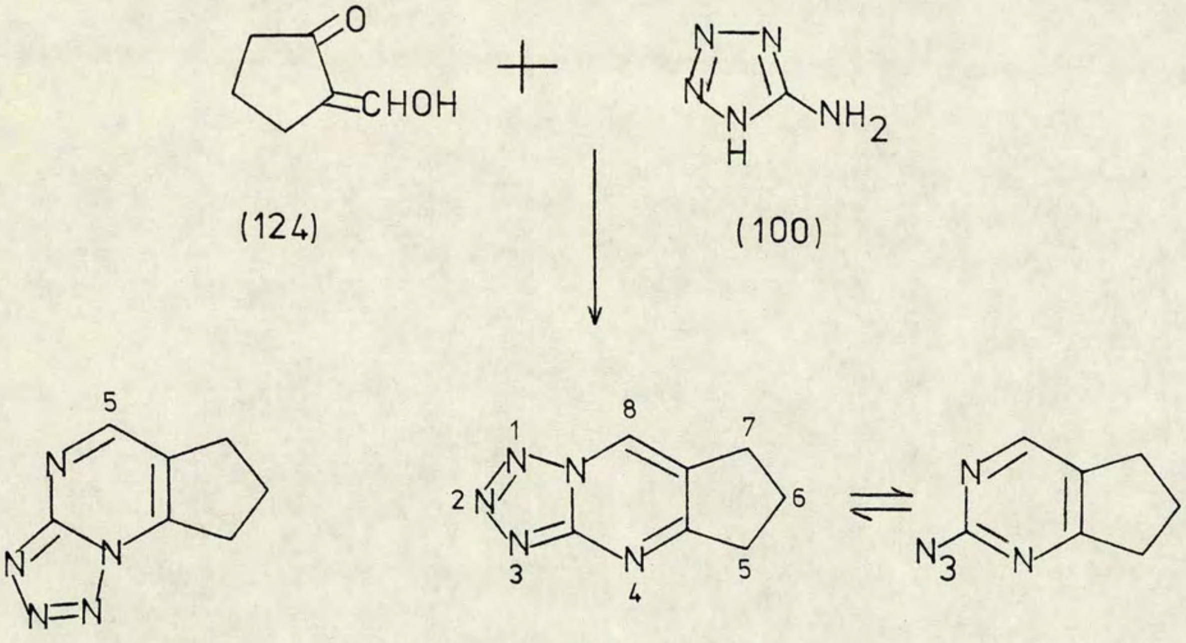


(266) R= H

(267) R = Ac



(269)



(124) (100)

(268c) (268a) (268b)

chromatographed over alumina. Elution with chloroform followed by recrystallisation from ethanol gave white crystals (266), m. p. 198-200°, in 54% yield. The same product was obtained in 30% yield when the reaction was carried out in absolute alcohol.

7.8 Discussion

Mass spectrometry and elemental analysis indicated that the product had a molecular formula of $C_{21}H_{27}N_5O$. The i. r. spectrum exhibited absorptions of 2140, 1645, 1540, 1500, 1465, 1455, 1405, 1375 and 790 cm^{-1} whilst the ^1H n. m. r. spectrum showed a singlet at δ 8.70 apart from the signals for the 18- and 19-methyl protons, 3-H and 6-H.

In 1950, Cook et al.[149b] reported that the condensation of 2-hydroxymethylenecyclopentanone (124) with 5-aminotetrazole (100) leads to the formation of 6, 7-dihydro-5H-cyclopenta[d]tetrazolo[1, 5-a]-pyrimidine (268c). The claim to this structure was presumably based upon the fact that the amino group of the tetrazole (100) reacts first with the aldehydic group and then the direct cyclisation of the intermediate keto anil gives the product (268c). The above reaction was repeated and it is established here with the aid of ^1H n. m. r. and ^{13}C n. m. r. spectroscopy that the product has, on the contrary, the linear structure (268a).

In the ^1H n. m. r. spectrum of the product (268a), the signal at δ 8.72 corresponding to the 8-H is found to be split into a triplet by a small long range coupling with the methylene protons at position 7. In the ^{13}C n. m. r. spectrum, the chemical shift of 8-C (126.12 p. p. m.) is found to be consistent with the linear structure (268a). If the product had had the previously reported structure (268c) then the signal for the 5-H in the ^{1}H n.m.r. spectrum would have been a sharp singlet and the chemical shift of the 5-C in the ^{13}C n.m.r. spectrum would have been in the region of 158.44 p.p.m. which is the chemical shift of the 5-C of 7-methyltetrazolo[1, 5-a]pyrimidine (257) (Table 6). The i.r. and ^{13}C n.m.r. spectroscopy also show that the product (268a) exists in equilibrium with the azido form (268b) in bromoform and deuterated chloroform solutions.

By analogy with the formation of 6, 7-dihydro-5H-cyclopenta[d]-tetrazolo[1, 5-a]pyrimidine (268a) from the reaction of 5-aminotetrazole (100) with 2-hydroxymethylenecyclopentanone (124), the product obtained by the condensation of 5-aminotetrazole (100) with the β-ketoaldehyde (8) is assigned structure (266). This structure is confirmed by the ^{1}H n.m.r. spectrum which shows a broad singlet at δ 8.70 corresponding to the 7'-H. The sterol (266) was acetylated using acetic anhydride in pyridine to give the 3β-acetate (267).

Under analogous reaction conditions, the condensation of 5-aminotetrazole (100) with 16-hydroxymethylene-3-methoxyoestra-1,3,5(10)-trien-17-one (9) gave 3-methoxyoestra-1,3,5(10)trieno[17,16-f]tetrazolo-[1,5-a]pyrimidine (269).

7.9 Experimental

General procedure for the condensation reaction.

A solution of the steroidal β-ketoaldehyde (1.5×10^{-3} mole) and 5-aminotetrazole (100) ($CH_3N_5 \cdot H_2O$, 2×10^{-3} mole) in absolute alcohol (30 ml) was refluxed overnight. The reaction mixture was cooled to room temperature and triturated. The precipitates formed were filtered and recrystallised from a suitable solvent.

7.9.i <u>17β-Hydroxy-17α-methyl-5α-androst-2-eno[2,3-g]tetrazolo[1,5-a]-pyrimidine (255)</u> was recrystallised from methanol as white crystals (84%), m.p. 196-198°; u.v., λ_{max} 216 and 280 nm (log ε 4.31 and 3.72); i.r., γ_{max} 3600 (OH), 2140 ($-N_3$), 1620, 1545, 1510, 1445, 1380, 1370, 930 and 780 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.88 (s, 3H, 18-CH_3), 0.92 (s, 3H, 19-CH_3), 1.24 (s, 3H, 17-CH_3) and 8.66 (s, 1H, 5'-H) (Found: C, 69.03; H, 8.27; N, 18.20; M^+, 381.251949. $C_{22}H_{31}N_5O$ requires C, 69.24; H, 8.19; N, 18.36%; M, 381.252847).

7.9.ii <u>17β-Hydroxy-5α-androst-2-eno[2,3-g]tetrazolo[1,5-a]pyrimidine (258)</u> was recrystallised from methanol as white needles (92%), m.p. 199-200°; u.v., λ_{max} 215 and 279 nm (log ε 4.29 and 3.73); i.r., γ_{max} 3600 (OH), 2140 ($-N_3$), 1625, 1545, 1510, 1385, 1050 and 780 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.80 (s, 3H, 18-CH_3), 0.88 (s, 3H, 19-CH_3), 3.68 (t, 1H, 17-H) and 8.68 (s, 1H, 5'-H) (Found: C, 68.72; H, 8.01; N, 19.24; M^+, 367.235799. $C_{21}H_{29}N_5O$ requires C, 68.62; H, 7.96; N, 19.06%; M, 367.237198).

7.9.iii <u>5α-Androst-2-eno[2,3-g]tetrazolo[1,5-a]pyrimidine (259)</u> was recrystallised from ethanol to give yellow fluffy crystals (77%), m.p. 195-197°; u.v., λ_{max} 215, 248 and 280 nm (log ε 4.26, 3.73 and 3.63); i.r., ν_{max} 2130 ($-N_3$), 1625, 1545, 1505, 1440, 1420, 1385, 820 and 780 cm^{-1}; ^1H n.m.r. (100 MHz), δ 0.74 (s, 3H, 18-CH_3), 0.86 (s, 3H, 19-CH_3) and 8.66 (s, 1H, 5'-H) (Found: C, 71.95; H, 8.51; N, 20.10; M^+, 351.240969. $C_{21}H_{29}N_5$ requires C, 71.75; H, 8.32; N, 19.93%; M, 351.242281).

7.9.iv <u>5α-Cholest-2-eno[2,3-g]tetrazolo[1,5-a]pyrimidine (260)</u> was recrystallised from methanol as white fluffy crystals (61%), m.p. 173-175°; u.v., λ_{max} 215 and 277 nm (log ε 4.32 and 3.68); i.r., ν_{max} 2140 ($-N_3$), 1625, 1540, 1510, 1460, 1445, 1380 and 780 cm^{-1}; ^1H n.m.r. (100 MHz), δ 0.72, 0.86, 0.90 and 0.96 (methyl groups), and 8.66 (s, 1H, 5'-H) (Found: C, 75.21; H, 9.95; N, 15.15; M^+, 463.364704. $C_{29}H_{45}N_5$ requires C, 75.10; H, 9.79; N, 15.11%; M, 463.367478).

7.9.v <u>11-Oxo-5α-spirost-2-eno[2,3-g]tetrazolo[1,5-a]pyrimidine (261)</u> was recrystallised from ethanol as a yellow solid (65%), m.p. 200-202°; u.v., λ_{max} 214 and 279 nm (log ε 4.32 and 3.70); i.r., ν_{max} 2140 ($-N_3$), 1700 (CO), 1630, 1545, 1510, 1450, 1390, 1050, 980, 920, 890 and 780 cm^{-1}; ^1H n.m.r. (100 MHz), δ 0.76 (s, 3H, 18-CH_3), 1.24 (s, 3H, 19-CH_3) and 8.68 (s, 1H, 5'-H) (Found: C, 68.82; H, 7.79; N, 13.73; M^+, 505.303706. $C_{29}H_{39}N_5O_3$ requires C, 68.87; H, 7.78; N, 13.85%; M, 505.305273).

7. 9. vi <u>17β-Hydroxyandrost-4-eno[3, 2-f]tetrazolo[1, 5-a]pyrimidine (263a)</u> was recrystallised from ethanol as yellow crystals (37%), m. p. 143-145°; u. v., λ_{max} 213, 243 and 311 nm (log ε 4. 15, 4. 11 and 4. 06); i. r., γ_{max} 3600 (OH), 2140 ($-N_3$), 1620, 1500-1515, 1430, 1415, 1380 and 780 cm^{-1}; ^{1}H n. m. r. (100 MHz), δ 0. 80 (s, 3H, 18-CH_3), 1. 06 (s, 3H, 19-CH_3), 3. 68 (t, 1H, 17-H), 6. 48 (s, 1H, 4-H) and 8. 60 (s, 1H, 7'-H) (Found: C, 68. 77; H, 7. 49; N, 19. 09; M^+, 361. 188867. $C_{21}H_{23}N_5O$ requires C, 68. 99; H, 7. 45; N, 19. 17%; M, 361. 190250).

7. 9 vii <u>The reaction of 17β-hydroxyandrost-4-eno[3, 2-f]tetrazolo[1, 5-a]-pyrimidine (263a) with acetic anhydride in pyridine.</u>

A solution of 17β-hydroxyandrost-4-eno[3, 2-f]tetrazolo[1, 5-a]-pyrimidine (263a) (450 mg, 1. 23 x 10^{-3} mole) in pyridine (25 ml) containing a few drops of acetic anhydride was refluxed for two hours. The excess of solvent was removed in vacuo and the residue was taken up in chloroform. The chloroform solution was washed with 5% hydrochloric acid, water and finally with saturated sodium chloride, dried over anhydrous magnesium sulphate and the solution was evaporated to dryness under vacuo. The residue thus obtained was chromatographed over alumina. Elution with methylene chloride followed by recrystallisation of the eluate from methanol gave yellow crystals of <u>17β-acetoxyandrost-4-eno[3, 2-f]-tetrazolo[1, 5-a]pyrimidine (264a)</u> (125 mg, 25%); m. p. 217-219°; u. v., λ_{max} 213, 243 and 311 nm (log ε 4. 18, 4. 22 and 4. 19); i. r., γ_{max} 2140 ($-N_3$), 1720 (C=O), 1615, 1515, 1505, 1430, 1420, 1375, 1360 and 780 cm^{-1}; ^{1}H n. m. r. (60 MHz), δ 0. 85 (s, 3H, 18-CH_3), 1. 05 (s, 3H, 19-CH_3), 2. 05 (s, 3H, 17-$OCOCH_3$), 4. 60 (s, 1H, 17-H), 6. 45 (s, 1H, 4-H) and

8.60 (s, 1H, 7-H) (Found: C, 67.48; H, 7.02; N, 16.80; M^+, 407.230336. $C_{23}H_{29}N_5O_2$ requires C, 67.78; H, 7.14; N, 17.20%; M, 407.232112).

Further elution of the column with chloroform followed by recrystallisation of the eluate from ethanol gave 17β-acetoxy-4-oxo-5ξ-androst-2-eno[2,3-g]tetrazolo[1,5-a]pyrimidine (265a) (185 mg, 37%); m.p. 235-237°; u.v., λ_{max} 214, 249 and 287 nm (log ε 4.13, 3.98 and 3.81), i.r., γ_{max} 2140 ($-N_3$), 1720 (C=O, acetyl group), 1685 (C_4=O), 1625, 1545, 1510, 1430, 1415, 1370 and 780 cm^{-1}; ^1H n.m.r. (60 MHz), δ 0.85 (s, 6H, 18-CH_3 and 19-CH_3), 2.05 (s, 3H, 17-$OCOCH_3$), 4.65 (t, 1H, 17-H) and 8.65 (s, 1H, 5'-H) (Found: C, 65.28; H, 6.94; N, 16.23; M^+, 423.226596. $C_{23}H_{29}N_5O_3$ requires C, 65.21; H, 6.91; N, 16.54%; M, 423.227026).

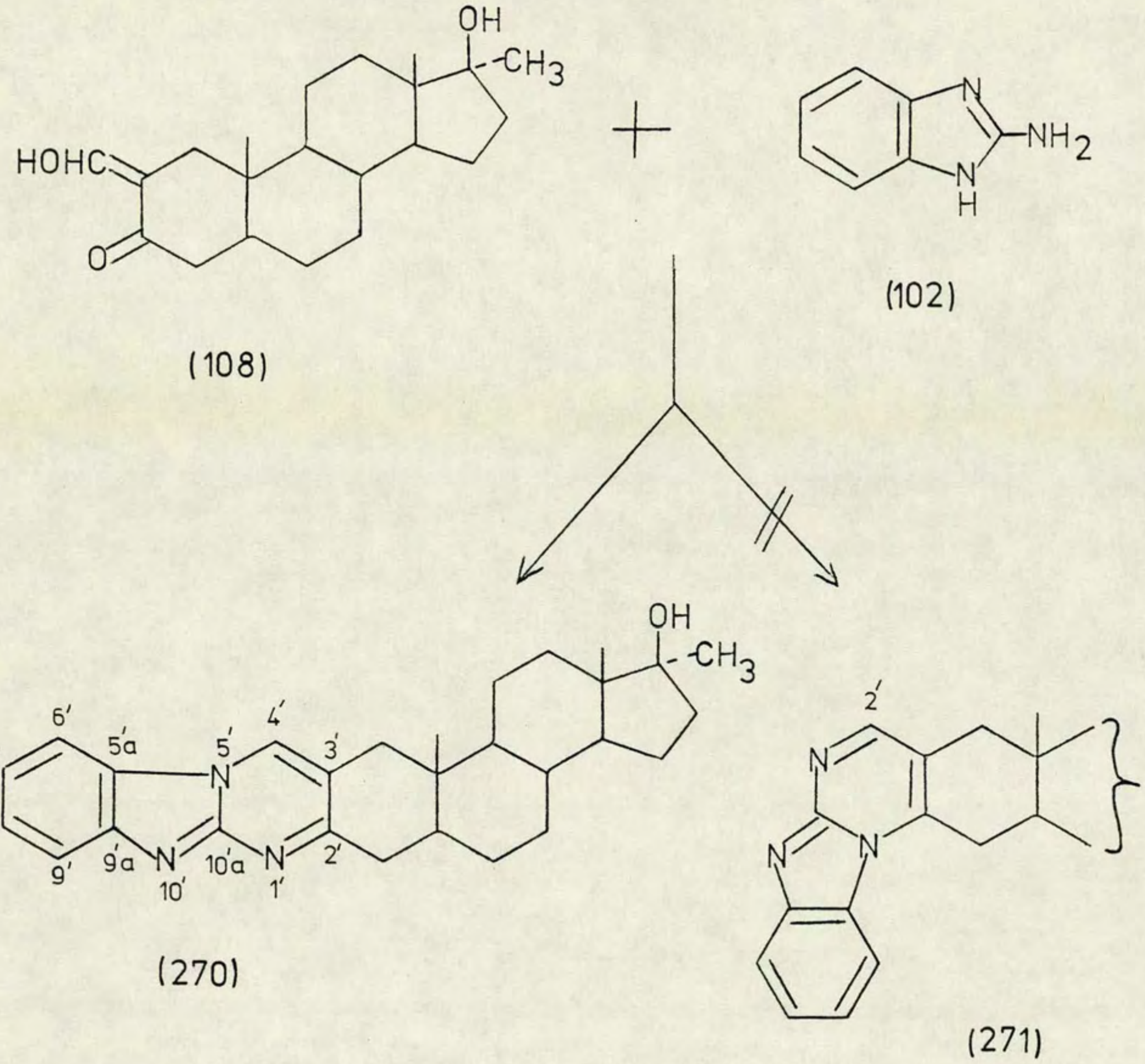
7.9.viii 3β-Hydroxyandrost-5-eno[17,16-f]tetrazolo[1,5-a]pyrimidine (266). Alumina chromatography (eluant chloroform) of the crude product followed by recrystallisation from ethanol gave white crystals of 3β-hydroxyandrost-5-eno[17,16-f]tetrazolo[1,5-a]pyrimidine (266) (54%); m.p. 198-200°; i.r., γ_{max} 3595 (OH), 2140 ($-N_3$), 1645, 1540, 1500, 1465, 1455, 1405, 1375 and 790 cm^{-1}; ^1H n.m.r. (60 MHz), δ 1.12 (s, 3H, 18-CH_3), 1.15 (s, 3H, 19-CH_3), 3.70 (m, 1H, 3-H), 5.40 (t, 1H, 6-H) and 8.70 (s, 1H, 7'-H) (Found: C, 68.77; H, 7.51; N, 19.16; M^+, 365.220461. $C_{21}H_{27}N_5O$ requires C, 68.99; H, 7.45; N, 19.17%; M, 365.221549).

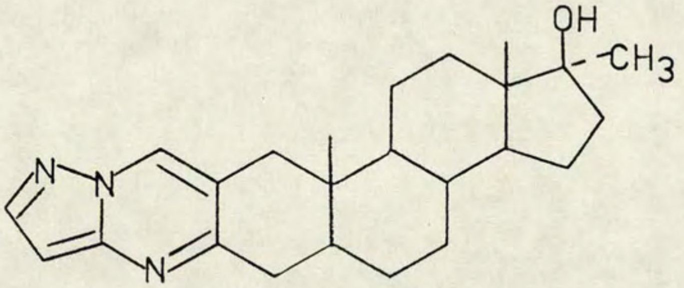
7.9.ix 3β-Acetoxyandrost-5-eno[17,16-f]tetrazolo[1,5-a]pyrimidine (267). 3β-Hydroxyandrost-5-eno[17,16-f]tetrazolo[1,5-a]pyrimidine

(266) (450 mg, 1.23 x 10^{-3} mole) was acetylated using the method described before for 17β-acetoxyandrost-4-eno[3, 2-f]tetrazolo[1, 5-a]-pyrimidine (264a) to give its 3β-acetate. Recrystallisation of the crude product from ethanol gave 3β-acetoxyandrost-5-eno[17, 16-f]tetrazolo-[1, 5-a]pyrimidine (267) (270 mg, 54%); m.p. 241-244°; i.r., γ_{max} 1725 (C=O), 1645, 1500, 1455, 1435, 1410, 1375, 790 cm^{-1}; ^1H n.m.r. (60 MHz), δ 1.12 (s, 6H, 18-CH_3 and 19-CH_3), 2.03 (s, 3H, 3-$OCOCH_3$), 4.60 (m, 1H, 3-H), 5.40 (t, 1H, 6-H) and 8.70 (s, 1H, 7'-H) (Found: C, 67.43; H, 7.01; N, 16.95; M^+-CH_3COOH, 347.209509. $C_{23}H_{29}N_5O_2$ requires C, 67.78; H, 7.14; N, 17.20%; M,-CH_3COOH, 347.210985).

7.9.x 3-Methoxyoestra-1, 3, 5(10)-trieno[17, 16-f]tetrazolo[1, 5-a]-pyrimidine (269) was recrystallised from ethanol as white crystals (92%), m.p. 235-237°; ^1H n.m.r. (d^6-DMSO) (100 MHz), δ 1.08 (s, 3H, 18-CH_3), 3.70 (s, 3H, 3-OCH_3), 6.60-7.22 (m, 3H, 1-H, 2-H and 4-H), 9.26 (s, 1H, 7-H) (Found:[141] M^+, 361.188867. $C_{21}H_{23}N_5O$ requires M, 361.190250).

7.9.xi 6, 7-Dihydro-5H-cyclopenta[d]tetrazolo[1, 5-a]pyrimidine (268a) was recrystallised from ethanol as white crystals (55%), m.p. 152-154° (lit[149b] m.p. 152-153°); i.r., γ_{max} 2140 (-N_3), 1655, 1635, 1530, 1500, 1405, 1345 and 775 cm^{-1}; ^1H n.m.r. (60 MHz), δ 2.35 (m, 2H, 6-H's), 3.15 (m, 4H, 5-H's and 7-H's) and 8.70 (t, 1H, 8-H).





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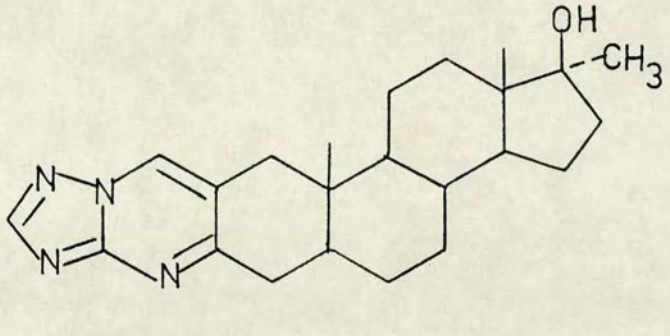


(210)

8 The reaction of steroidal β-ketoaldehydes with 2-aminobenzimidazole

8.1 The reaction of 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108) with 2-aminobenzimidazole (102).

A solution of 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108) and 2-aminobenzimidazole (102) in absolute alcohol was refluxed for 7 h. The reaction mixture was evaporated to dryness under vacuo and the residue was chromatographed over alumina. Elution with chloroform followed by recrystallisation of the eluate from ethanol gave yellow crystals (270), m.p. 268-270° (dec.) in 87% yield.

Mass spectrometry and elemental analysis indicated that the product had a molecular formula of $C_{28}H_{35}N_3O$. The i.r. spectrum of this product exhibited signals at 3600, 1635, 1605, 1510, 1450, 1415, 760 and 730 cm^{-1} and the ^1H n.m.r. spectrum showed, apart from the signals for the 17-, 18- and 19-methyl protons a multiplet at δ 7.14-δ 7.90 corresponding to four protons of the benzene ring and a singlet at δ 8.34 corresponding to one proton.

8.2 Discussion

The i.r. spectrum of the condensation product does not show any carbonyl absorption, thus it appears that the product has either structure (270) or (271), both consistent with the molecular formula $C_{28}H_{35}N_3O$. However, the ^1H n.m.r. and ^{13}C n.m.r. evidence favours structure (270), namely 17β-hydroxy-17α-methyl-5α-androstano[3, 2-b]benzimidazo-[1, 2-a]pyrimidine.

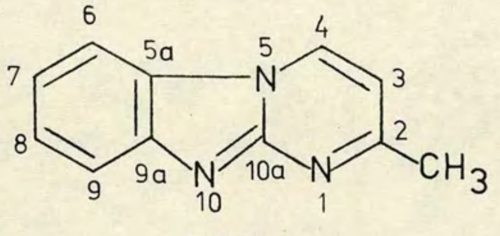
Table 7

^{13}C-Chemical shifts of the aromatic ring carbons (p.p.m.)

Compound	2'-C	3'-C	4'-C	5'a-C	9'a-C	10'a-C
(104)*	165.72	107.43	132.75	126.75	144.14	150.59
(270)**	165.90	115.80	130.65	126.39	144.28	150.28
(272)	150.94 (5-C)	109.41 (6-C)	136.04 (7-C)	112.66 (1-C)	135.14 (2-C)	148.86 (3a-C)

* ^{13}C-Chemical shifts of 6'-C - 9'-C 110.13, 120.17, 121.32 and 125.83 p.p.m.

** ^{13}C-Chemical shifts of 6'-C - 9'-C, 110.18, 119.84, 120.69 and 125.59 p.p.m.



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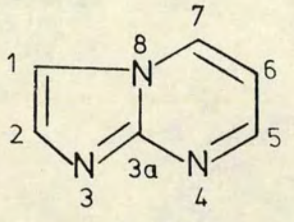
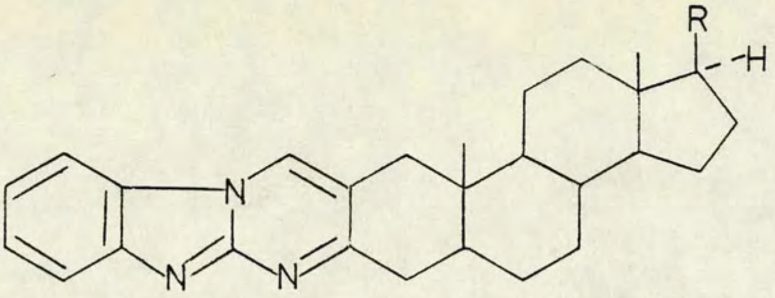


(272)

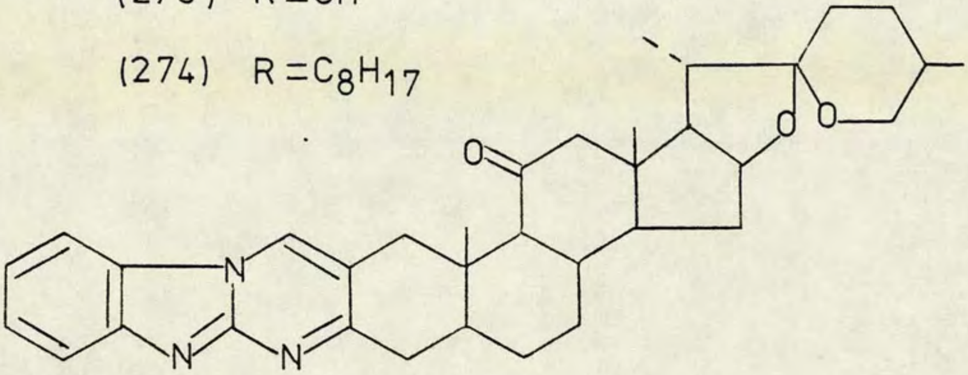
The ^{1}H n.m.r. spectrum of the condensation product (270) exhibits a fairly broad singlet at δ 8.34 which is assigned to the 4'-H. The assignment of linear structure (270) is consistent with the observations made in sections 5 and 6 that in the linearly fused pyrazolo[1, 5-a]-pyrimidines (e.g. 176) and s-triazolo[1, 5-a]pyrimidines (e.g. 210), the signal for the proton of the pyrimidine ring in the ^{1}H n.m.r. spectrum is broadened by a small long range coupling with the protons at position 1. The alternative structure (271) for the steroidal condensation product is discounted, since it would be expected to show a sharp singlet for the 2'-H due to the absence of any long range coupling.

The assignment of structure (270) is also supported by ^{13}C n.m.r. evidence. The ^{13}C-chemical shifts of the aromatic ring carbons of benzimidazopyrimidine (270) along with those of imidazo[1, 2-a]pyrimidine (272)[136a] and 2-methylpyrimido[1, 2-a]benzimidazole (104) are given in Table 7. The assignment of the chemical shifts for six of the ring carbons in the compounds (104) and (270) is based upon the comparison of the spectra of these two compounds and the ^{13}C-chemical shifts of imidazo[1, 2-a]pyrimidine (272).[136a] It is also noted that in nitrogen heterocyclic systems, the carbons bonded to nitrogen atoms are appreciably deshielded relative to benzene whilst the nitrogen atoms at bridgehead positions have little effect on the adjacent carbon atoms due to significant delocalisation of the lone pair of electrons.[136a] The specific assignment of the remaining 6'-C-9'-C carbon resonances although not important as far as the distinction of structure (270) from structure (271) is concerned, is not possible from the above information alone, however these carbon resonances can be readily distinguished from the



(273) R = OH

(274) R = C_8H_{17}



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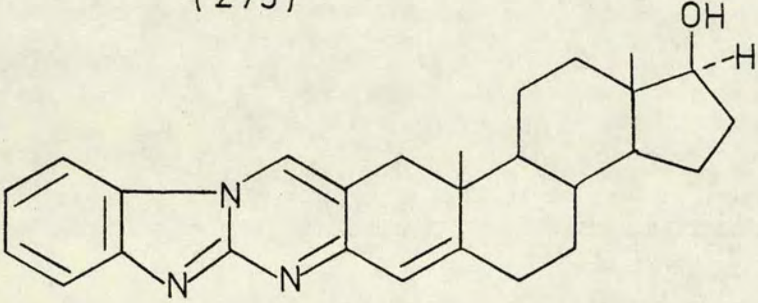
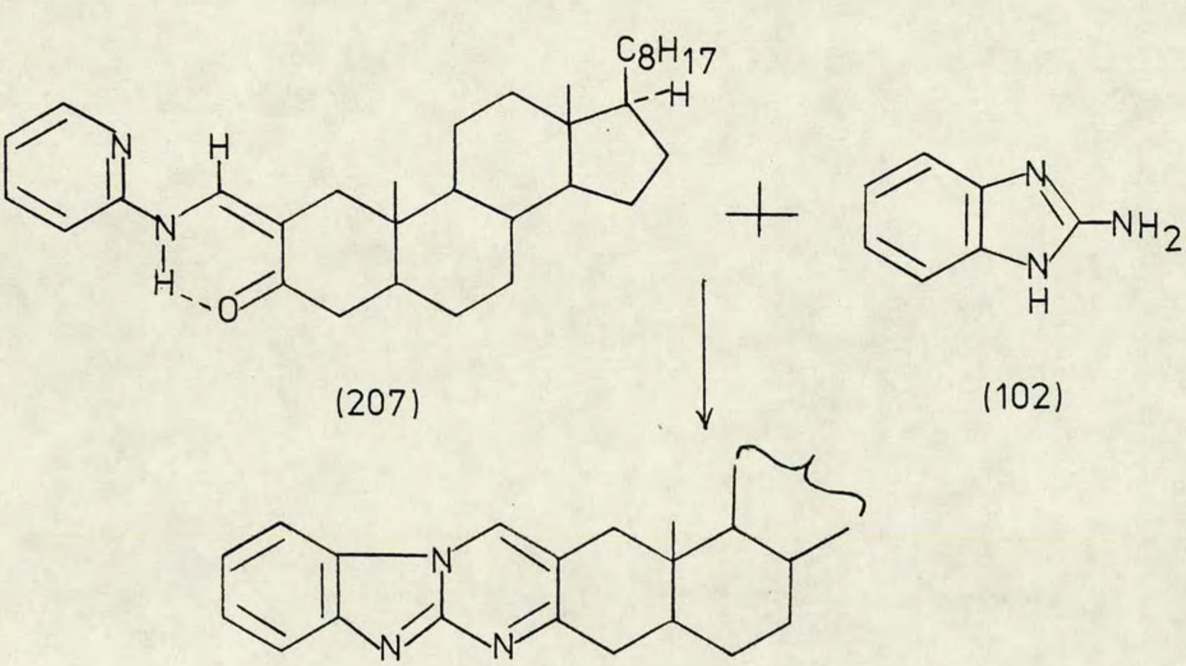


(276)



(207)

(102)

(274)

other carbon resonances. The chemical shift of 4'-C (130.65 p.p.m.) in the condensation product (270) correlates well with the chemical shift of 7-C (136.04 p.p.m.) in imidazo[1, 2-a]pyrimidine (272) and with the chemical shift of 4-C (132.75 p.p.m.) in 2-methylpyrimido[1, 2-a]-benzimidazole (104) thus confirming a linear fusion of the steroid to the heterocyclic system. If the condensation product had had the angular structure (271) the chemical shift of 2'-C would have been expected to be in the region of 150.94 p.p.m., which is the chemical shift of 5'-C in the imidazo[1, 2-a]pyrimidine (272).

Under analogous reaction conditions, the condensation of 2-aminobenzimidazole (102) with 17β-hydroxy-2-hydroxymethylene-5α-androstan-3-one (3), 2-hydroxymethylene-5α-cholestan-3-one (110), 2-hydroxymethylene-5α-spirostan-3, 11-dione (111) and 17β-hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4) gave 17β-hydroxy-5α-androstano[3, 2-b]-benzimidazo[1, 2-a]pyrimidine (273), 5α-cholestano[3, 2-b]benzimidazo-[1, 2-a]pyrimidine (274), 11-oxo-5α-spirostano[3, 2-b] benzimidazo[1, 2-a]-pyrimidine (275) and 17β-hydroxyandrost-4-eno[3, 2-b]benzimidazo-[1, 2-a]pyrimidine (276) respectively. The preparation of the compound (274) has been reported by Antaki and Petrow,[20] in 1951, but no spectroscopic evidence was given for its structure

8.3 The reaction of 2(2'-pyridyl-aminomethylene)-5α-cholestan-3-one (207) with 2-aminobenzimidazole (102).

A solution of 2(2'-pyridyl-aminomethylene)-5α-cholestan-3-one (207) and 2-aminobenzimidazole (102) in dry toluene containing a small amount of toluene-4-sulphonic acid was refluxed overnight. The reaction mixture was evaporated to dryness under vacuo and the residue was chromatographed over alumina. Elution with chloroform followed by recrystallisation of the eluate from ethanol-chloroform gave yellow crystals (72%), m. p. 290-292°, identical (m. p., i. r. and ^{1}H n. m. r.) with that of 5α-cholestano[3, 2-b]benzimidazo[1, 2-a]pyrimidine (274).

8.4 Experimental

General procedure for the condensation reaction

A solution of a 2-hydroxymethylene-3-oxo steroid (1×10^{-3} mole) and 2-aminobenzimidazole (102) (1.2×10^{-3} mole) in absolute alcohol (50 ml) was refluxed for 7 h. The reaction mixture was evaporated to dryness under vacuo and the residue was chromatographed over alumina. Elution with chloroform gave a yellow solid which was recrystallised from a suitable solvent.

8.4.i 17β-Hydroxy-17α-methyl-5α-androstano[3, 2-b]benzimidazo-[1, 2-a]pyrimidine (270) was recrystallised from chloroform-ethanol as fine yellow crystals (87%), m p. 268-270° (dec.); i. r., γ_{max} 3600 (OH), 1635, 1605, 1510, 1450, 1415, 925, 760 and 730 cm^{-1}; ^{1}H n m. r. (100 MHz), δ 0.80 (s, 3H, 18-CH_3), 0.90 (s, 3H, 19-CH_3), 1 24 (s, 3H, 17-CH_3), 7.14-7.90 (m, 4H, 6'-H, 7'-H, 8'-H and 9'-H) and 8.34 (s, 1H, 4'-H) (Found: C, 78.53; H, 8 40; N, 9.52; M^+, 429.277705. $C_{28}H_{35}N_3O$ requires C, 78.27; H, 8.22; N, 9.79%; M, 429.277998).

8.4.ii 17β-Hydroxy-5α-androstano[3, 2-b]benzimidazo[1, 2-a]pyrimidine (273) was recrystallised from acetone as yellow crystals (75%), m.p. 284-286° (dec.); i r., γ_{max} 3590 (OH), 1635, 1605, 1510, 1450, 1415, 1050, 760 and 730 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 0.80 (s, 6H, 18-CH_3 and 19-CH_3), 3.70 (m, 1H, 17-H), 7.18-8.05 (m, 4H, 6'-H, 7'-H, 8'-H and 9'-H) and 8.40 (s, 1H, 4'-H) (Found: C, 78.25; H, 8.17; N, 10.18; M^+, 415.262356. $C_{27}H_{33}N_3O$ requires C, 78.02; H, 8.01; N, 10.62%; M, 415.262349).

8.4.iii 5α-Cholestano[3, 2-b]benzimidazo[1, 2-a]pyrimidine (274) was recrystallised from chloroform-ethanol as yellow crystals (71%), m.p. $290-292^{\circ}$ (lit^{20} m.p. 295°); i.r., γ_{max} 1630, 1605, 1510, 1445, and 770 cm^{-1} (Found: C, 82.01; H, 9.46; N, 8.12; M^{+}, 511.392114. $C_{35}H_{49}N_{3}$ requires C, 82.13; H, 9.73; N, 10.17%; M, 511.392629).

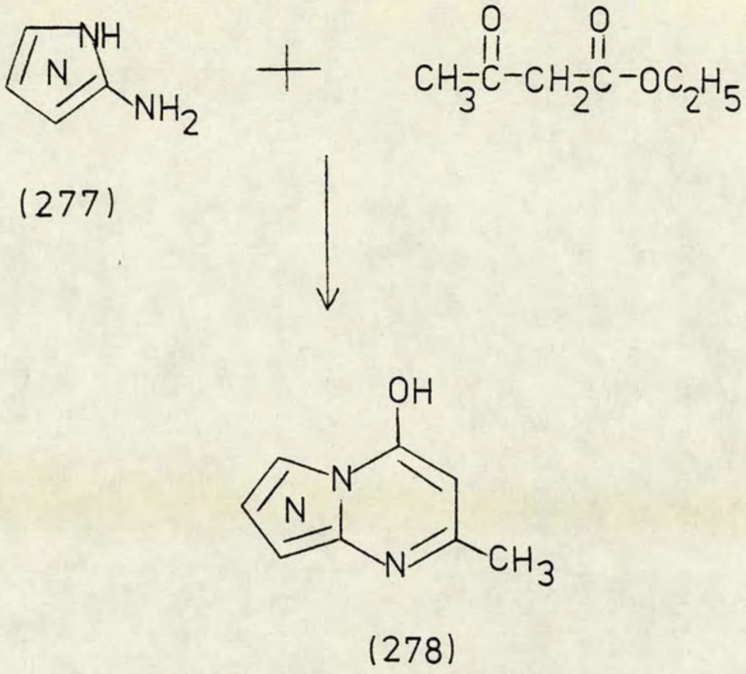
8.4.iv 11-Oxo-5α-androstano[3, 2-b]benzimidazo[1, 2-a]pyrimidine (275) was recrystallised from ethanol as yellow crystals (78%), m.p. $310-312^{\circ}$; i.r., γ_{max} 1695 (CO), 1635, 1610, 1510, 1450, 1420, 1045, 975, 915, 890, 760 and 730 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.74 (s, 3H, 18-CH_3), 1.00 (s, 3H, 19-CH_3), 7 20-8.94 (m, 4H, 6'-H, 7'-H, 8'-H and 9'-H) and 8.30 (s, 1H, 4'-H) (Found: C, 75.84; H, 7.87; N, 7.54; M^{+}, 553.329658. $C_{35}H_{43}N_{3}O_{3}$ requires C, 75.90; H, 7.83; N, 7.59%; M, 553.33024).

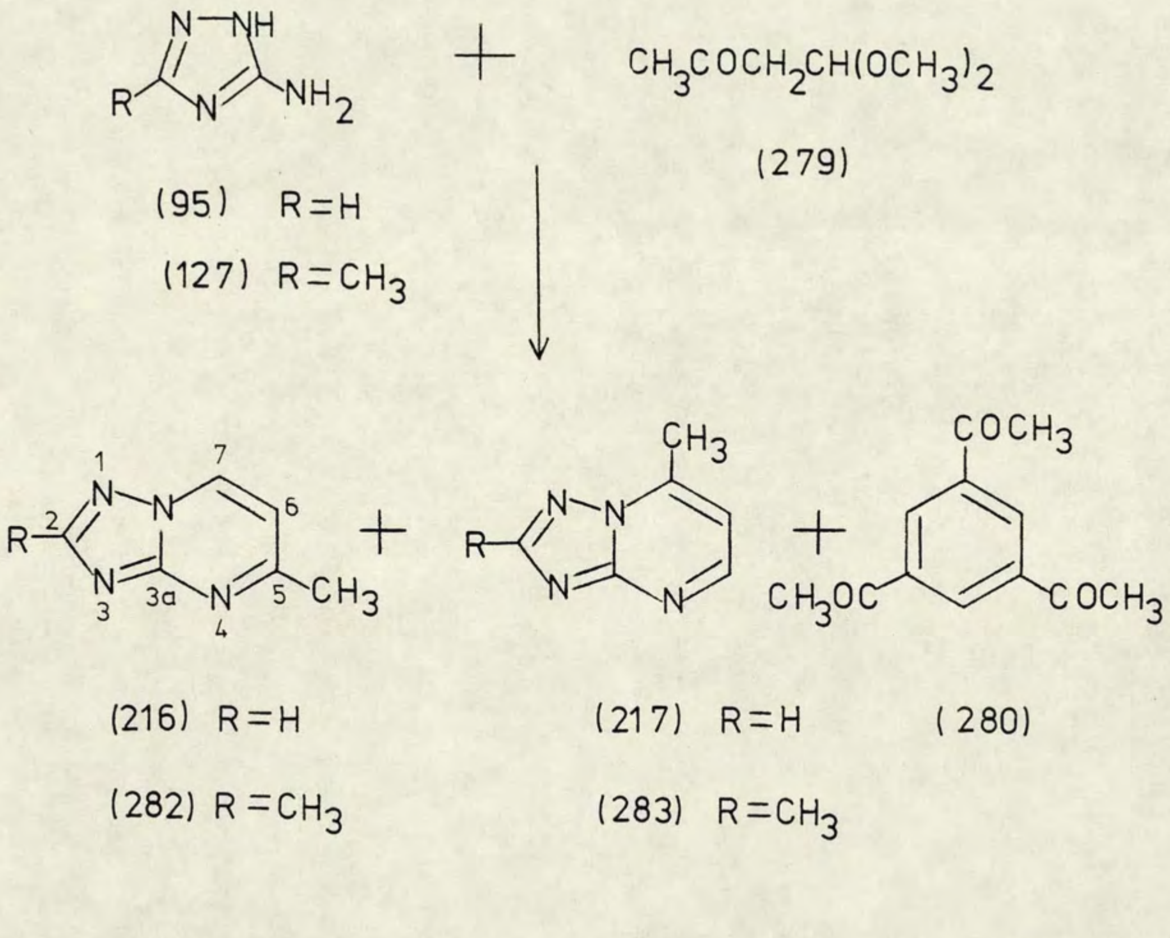
8.4.v 17β-Hydroxy-androst-4-eno[3, 2-b]benzimidazo[1, 2-a]pyrimidine (276) recrystallised from ethanol as yellow crystals (70%), m.p. $198-200^{\circ}$; i.r., γ_{max} 3590 (OH), 1635, 1580, 1505, 1450, 1430, 1215, 1060, 1040, 870, 765 and 735 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 0.82 (s, 3H, 18-CH_3), 1.05 (s, 3H, 19-CH_3), 3.65 (m, 1H, 17-H), 6.40 (s, 1H, 4-H), 7.10-8.96 (m, 4H, 6'-H, 7'-H, 8'-H and 9'-H) and 8.28 (s, 1H, 4'-H) (Found: C, 78.12; H, 7.60; N, 9.88; M^{+}, 413.246104. $C_{27}H_{31}N_{3}O$ requires C, 78.40; H, 7.56; N, 10.17%; M, 413.246700).

8.4.vi The reaction of 2(2'-pyridyl-aminomethylene)-5α-cholestan-3-one (207) and 2-aminobenzimidazole (102).

A solution of 2(2'-pyridylaminomethylene)-5α-cholestan-3-one

(207) (0.490 g, 1 x 10^{-3} mole) and 2-aminobenzimidazole (102) (0.158 g, 1.2 x 10^{-3} mole) in dry toluene (30 ml) containing p-toluenesulphonic acid (20 mg) was refluxed overnight. The reaction mixture was evaporated to dryness under vacuo and the residue chromatographed over alumina. Elution with chloroform and recrystallisation of the eluate from ethanol-chloroform mixture gave yellow crystals (0.360 g, 72%), m.p. 290-292°, identical (m.p., i.r. and ^{1}H n.m.r.) with that of 5α-cholestano[3, 2-b]-benzimidazo[1, 2-a]pyrimidine (274).


NH
N
NH2
O
O
CH3C-CH2C-OC2H5
(277)
OH
N
N
N
CH3
(278)

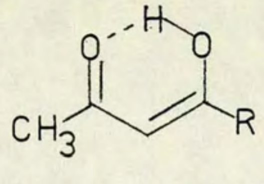

N
NH
R
N
NH2
CH3COCH2CH(OCH3)2
(279)
(95) R=H
(127) R=CH3
1
2
3
3a
4
5
6
7
N
N
N
N
R
CH3
CH3
R
N
N
N
N
COCH3
CH3OC
COCH3
(216) R=H
(282) R=CH3
(217) R=H
(283) R=CH3
(280)

9. The reaction of various aminoazoles with aliphatic β-ketoacetal, β-ketoaldehydes and β-ketoanils.

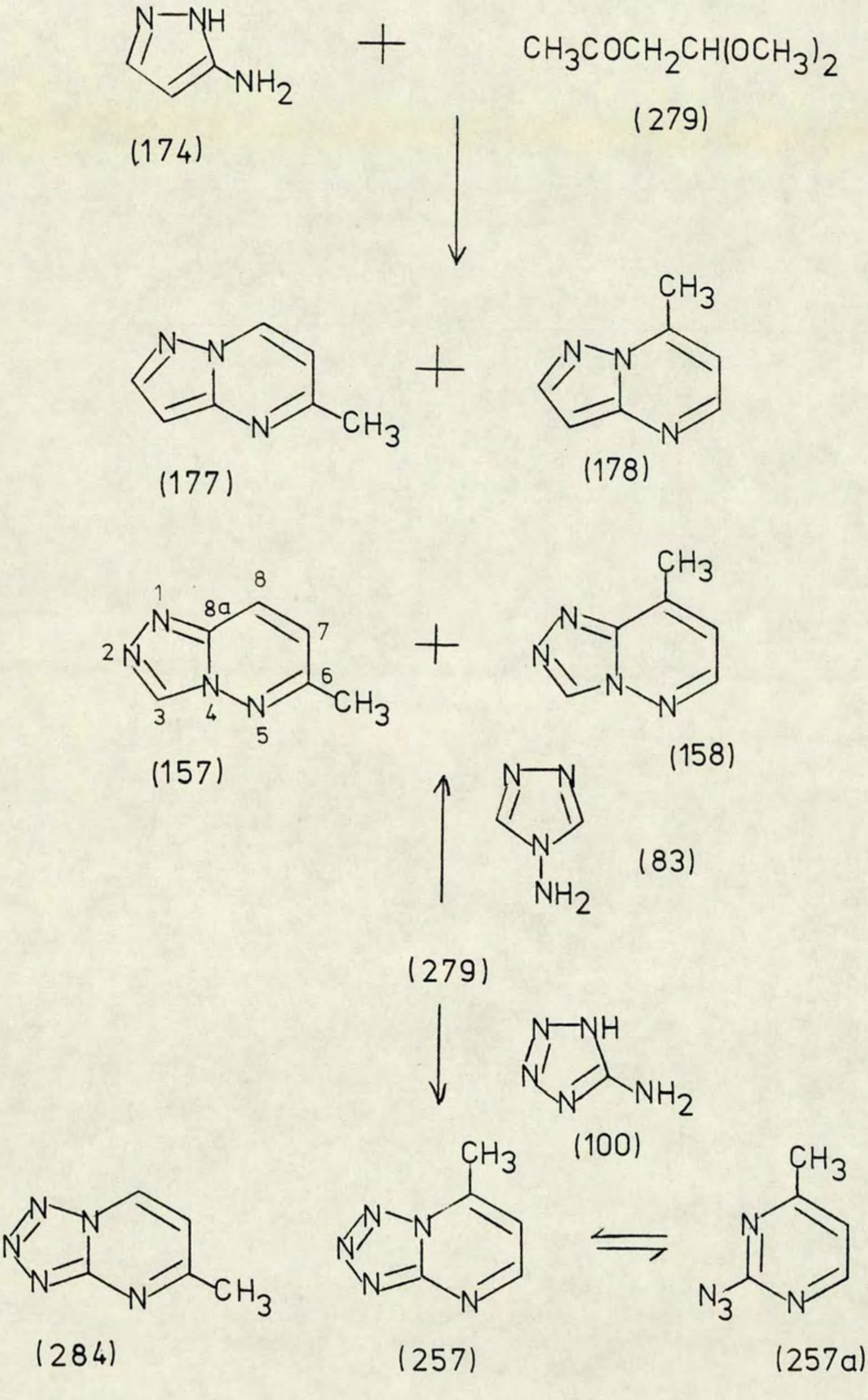
It is apparent from the preceeding sections that the reaction of aminoazoles with steroidal β-ketoaldehydes gives linearly and angularly fused products whose structures have been elucidated by correlating their spectra (u. v., i. r., ^{1}H n. m. r. and ^{13}C n. m. r.) with those of some simple model compounds. It is also well known that the reaction of an aminoazole (277) with a β-keto ester affords 5-alkyl-azolo[1, 5-a]-pyrimidine (278).[80b] However the reaction of aminozoles with unsymmetrical β-ketoaldehydes and β-diketones is not yet fully exploited. Thus, it was felt necessary firstly, to prepare some simple model compounds and secondly to investigate the reaction of various aminoazoles with some simple unsymmetrical β-ketoaldehydes and β-ketoanils.

9. 1 The reaction of 4, 4-dimethoxybutan-2-one with aminoazoles.

It has been previously reported[62d] that the reaction between 4, 4-dimethoxybutan-2-one (279) and 3-amino-1, 2, 4-triazole (95) in refluxing xylene furnishes 5-methyl-s-triazolo[1, 5-a]pyrimidine (216) as the sole reaction product in high yield. However, repetition of this condensation by refluxing a solution of the β-ketoacetal (279) with the aminotriazole (95) in toluene in the presence of a small amount of toluene-4-sulphonic acid afforded 5-methyl-s-triazolo[1, 5-a]pyrimidine (216), 7-methyl-s-triazolo[1, 5-a]pyrimidine (217) and the self condensation product 1, 3, 5-triacetylbenzene (280). The structures of the compounds (216) and (217) have already been adequately established by independent synthesis[146b] and ^{1}H n. m. r. spectroscopy.[77] The formation of 1, 3, 5-triacetylbenzene (280) has been previously observed[150] during the reaction of tryptamine



(281)



(174)
$CH_3COCH_2CH(OCH_3)_2$
(279)
(177)
(178)
1
2
3
4
5
6
7
8
8a
(157)
(158)
(83)
(279)
(100)
(284)
(257)
(257a)

hydrochloride and the β-ketoacetal (279). It is evident that the compound (280) is formed by the self condensation of three molecules of 3-ketobutanol (281, R=H), itself derived from the β-ketoacetal (279).

Under similar conditions, 4,4-dimethoxybutan-2-one (279) reacts with 3-amino-5-methyl-1,2,4-triazole (127) to give the two condensation products 2,5-dimethyl-s-triazolo[1,5-a]pyrimidine (282) and 2,7-dimethyl-s-triazolo[1,5-a]pyrimidine (283) accompanied again by 1,3,5-triacetylbenzene (280). During the reaction of 3-aminopyrazole (174) with the β-ketoacetal (279) only two condensation products, 5-methylpyrazolo[1,5-a]pyrimidine (177) and 7-methylpyrazolo[1,5-a]pyrimidine (178) were isolated. The 5-methylazolo[a]pyrimidines (177)[151b] and (282)[151a] have been previously prepared by the condensation of the corresponding aminoazole with ethyl acetoacetate, followed by the removal of the residual oxygen atom from the intermediate condensation product by treatment with phosphorus oxychloride and subsequent hydrogenolysis. The 7-methylazolo[a]pyrimidines (178)[151b] and (283)[151a] have also been independently prepared from the reaction of the corresponding aminoazole with ethyl 2-acetyl-3-ethoxyacrylate followed by decarbethoxylation of the corresponding ethyl 7-methylazolo[a]pyrimidine-6-carboxylates. Under analogous conditions, the condensation of 4-amino-1,2,4-triazole (83) with the β-ketoacetal (279) also gave two condensation products, 6-methyl-s-triazolo[4,3-b]pyridazine (157) and 8-methyl-s-triazolo[4,3-b]pyridazine (158), contrary to the earlier reports[54, 62d] which indicate that only a single product (157) is formed in this reaction.

It has been reported[62d] that 5-methyltetrazolo[1,5-a]pyrimidine (257) is the condensation product finally formed in each of the following three synthesis. Reaction of 5-aminotetrazole (100) with ethyl aceto-

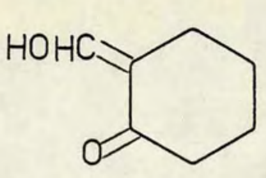
Table 8. ^{13}C N.m.r. Chemical Shifts of Azolo[a]pyrimidines (p.p.m.)

Compound	2-C	3-C	3a-C	5-C	6-C	7-C	5-CH_3	7-CH_3
(177)	145.01	95.68	148.30	158.90	108.74	134.43	24.77	-
(178)	144.39	96.97	148.91	148.58	107.42	146.13	-	17.20
(216)	156.08	-	155.13	165.69	111.25	134.98	25.22	-
(217)	155.56	-	155.96	154.03	110.06	148.15	-	17.20
(257)*	-	-	158.91	158.44	112.42	146.84	-	16.63
(306)	168.16	-	155.75	163.96	109.81	145.64	24.81	16.93 and 2-SCH_3 13.95
(307)	155.36	-	155.36	164.75	110.75	146.73	24.98	16.97

* spectrum taken in d^6 DMSO.

acetate followed by treatment with phosphorous oxychloride and subsequent hydrogenolysis; reaction of 4-methyl-2-hydrazinopyrimidine with nitrous acid and reaction of 5-aminotetrazole (100) with 4,4-dimethoxybutan-2-one (279). However, it is observed that the spectroscopic properties of the condensation product are consistent with the structure (257) rather than structure (284). In the ^{1}H n.m.r. spectrum the singlet at δ 3.50 for the 7-methyl group is found to be broadened by a small long range coupling with the 6-H and the value of the coupling constant of the two doublets at δ 7.25 (6H) and δ 8.90 (5-H) is found to be 4.00 Hz. If the product had structure (284), the methyl group would be expected to give a sharp singlet and the value of the coupling constant of the two doublets would be expected to be about 7.00 Hz.[80d] In the ^{13}C n.m.r. spectrum, the chemical shift of 5-C is found to be 158.44 p.p.m. [comparable with the chemical shift of 5-C (154.03 p.p.m.) in the triazolopyrimidine (217), discussed later] consistent with the structure (257). In the alternative structure (284), the chemical shift of 7-C would be expected to be about 134 p.p.m. making it comparable with the chemical shift of 7-C in the triazolopyrimidine (216) (Table 8).

The ^{1}H n.m.r. spectrum of the compound (257) is further complicated by the fact that, in addition to the signals for the 7-methyl, the 6-H and the 5-H, a singlet at δ 2.50 and doublets at δ 6.97 and δ 8.50 ($J = 4.8$ Hz) also appear indicating that the compound (257) exists in equilibrium with the azido form (257a), the ratio of the compound (257) to (257a) being 3:1. The presence of the azido form (257a) is also confirmed by the appearance of absorption band at 2140 cm^{-1} in the i.r. spectrum. Rearrangements of this type have been previously discussed in section 7.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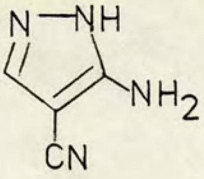
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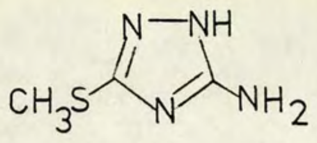
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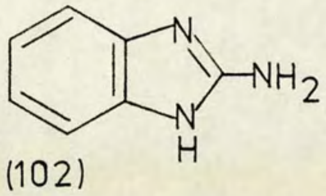
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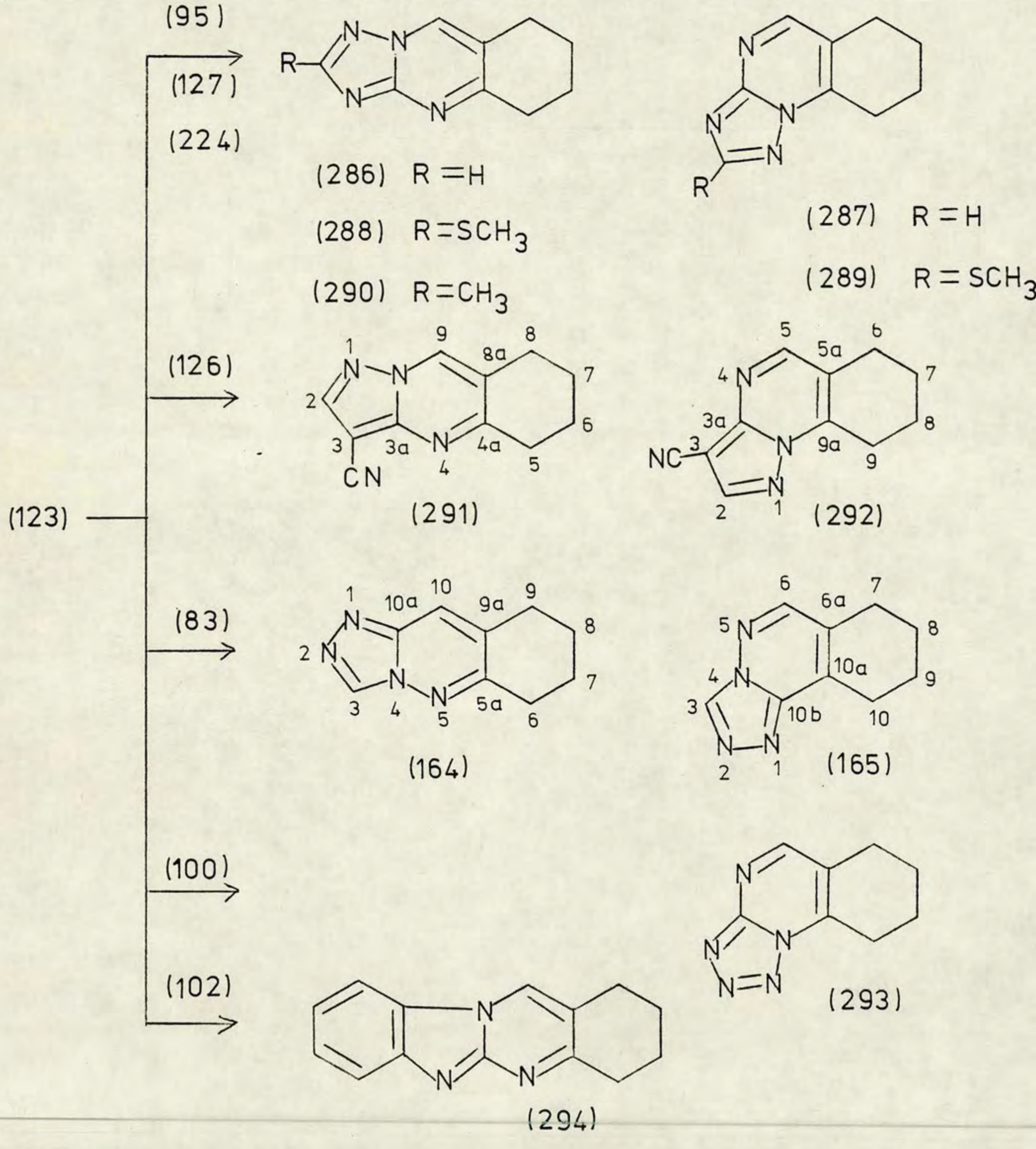


Due to the formation of 1, 3, 5-triacetylbenzene (280) as a by product of these condensation reactions it is inferred that the β-ketoacetal (279) is initially converted to 3-ketobutanal (281; R=H) by hydrolysis of the acetal (279) under the acidic reaction conditions. Support for the intermediacy of the β-ketoaldehyde (281; R=H) comes from ^{1}H n. m. r. spectroscopy. A solution of the acetal (279) in acetone containing small amounts of toluene-4-sulphonic acid and water after being heated on a boiling water bath exhibited two doublets at δ 5. 55 and δ 7. 85 (J = 5Hz). These correspond to the protons of 2-C and 1-C respectively in 3-ketobutanal (281; R=H) and a small signal observed at δ 9. 75 is ascribable to the aldehydic proton of the unenolized form. The chemical shift of the hydrogen at 2-C in the β-ketoaldehyde (281; R=H) is comparable to the chemical shift of 3-H (δ 5. 50) in acetylacetone (281; R=CH_3). The possibility that the acetal (279) might have been converted to methoxyvinyl ketone (285) rather than the β-ketoaldehyde (281; R=H) is not considered likely since, the signals for 1-H and 2-H belonging to methoxyvinyl ketone (285) appear as doublets at δ 7. 60 and δ 5. 58 with a coupling constant of 13Hz.[152]

9. 2 The reaction of 2-hydroxymethylenecyclohexanone (123) with aminoazoles.

The condensation of 2-hydroxymethylenecyclohexanone (123) with various aminoazoles proceeds in a manner analogous to the condensation of the aminoazoles with 4, 4-dimethoxybutan-2-one (279). The only exception is the reaction of 3-amino-5-methyl-1, 2, 4-triazole (127) with the β-ketoaldehyde (123) which affords the linear product (290) in contrast

Table 9. ^{13}C N. m. r. Chemical Shifts of 5,6,7,8-Tetrahydroazolo[b]quinazolines (p. p. m.)

Compound	2-C	3-C	3a-C	4a-C	8a-C	9-C	alicyclic carbons
(286)	155.38	-	153.76	165.81	120.51	132.84	(21.65 - 32.89)
(288)	168.09	-	154.32	164.84	119.42	131.84	(21.68 - 32.75)
(290)	165.91*	-	154.01	165.14*	119.73	132.33	(21.94 - 33.00)
(291)	146.69	80.27	148.23	164.48	121.09	133.30	(21.57 - 32.75)
							(CN, 112.88)

* These values could be interchanged.

Table 11. ^{13}C N. m. r. Chemical Shifts of 6,7-Dihydro-5H-cyclopenta[d]azolo[a]pyrimidines (p. p. m.)

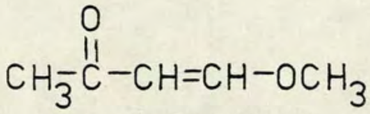
Compound	2-C	3-C	3a-C	4a-C	7a-C	8-C	alicyclic carbons
(303)	155.12	-	155.84	175.08	125.56	129.61	(23.91 - 34.17)
(304)	167.46	15	155.47	174.05	124.35	128.64	(23.70 - 34.07)
(305)	146.36	81.14	149.62	173.41	126.25	130.19	(23.81 - 33.96)

Table 10. ^{13}C N.m.r. Chemical Shifts of 6,7,8,9-Tetrahydro-azolo[a]quinazolines and 7,8-Dihydro-6H-cyclopenta[e]azolo[a]pyrimidines (p.p.m.)

Compound	2-C	3-C	3a-C	5-C	5a-C	9a-C	Alicyclic carbons
(289)	167.75	-	154.66	154.14	118.42	144.88	(20.54 - 23.96)
(292)	146.04	82.27	149.01	153.61	119.82	144.08	(20.6 - 24.07) (CN, 112.74)
(293)	-	-	158.43	159.20	121.66	143.64	(20.21 - 23.90)
(297)	155.69	-	155.15	150.84	125.27	151.54 8a-C	(22.64 - 29.57)
(298)	168.69	-	155.64	149.66	124.50	150.46 8a-C	(22.63 - 29.49)
(299)	147.09	82.18	148.68	149.56	125.80	151.71 8a-C	(22.20 - 29.51) (CN, 112.81)

Table 12. ^{13}C N.m.r. Chemical Shifts of s-Triazolo[4,3-b]pyridazine derivatives (p.p.m.)

Compound	3-C	6-C	7-C	8-C	8a-C	methyl or alicyclic carb
(157)	138.41	155.01	122.81	124.14	143.08	21.64
(158)	139.10	145.64	118.86	137.31	145.43	16.46
(164)	137.48	155.85	132.61	121.04	143.68	(21.66-29.7
		5a-C	9a-C	10-C	10a-C	
(165)	138.23	147.61	128.68	133.64	145.12	(20.50-25.4
			6a-C	10a-C	10b-C	
(300)	138.03	164.67	138.41	117.43	143.99	(24.12-31.1
		5a-C	8a-C	9-C	9a-C	

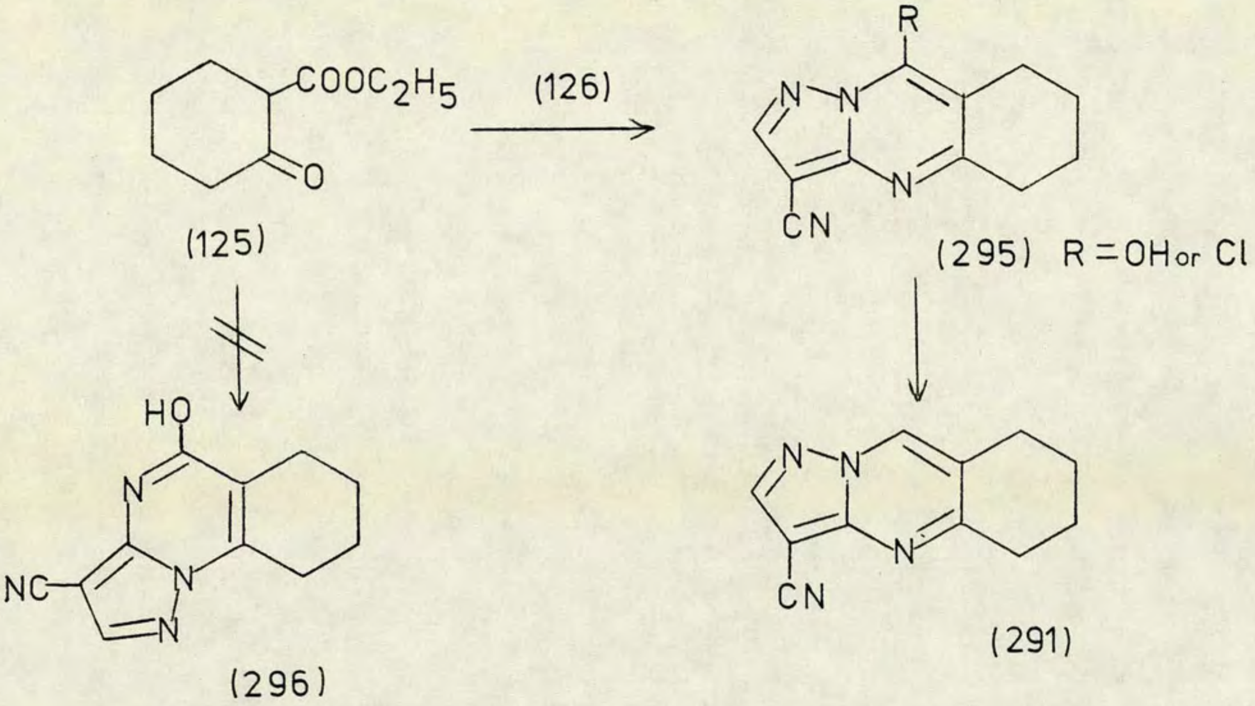


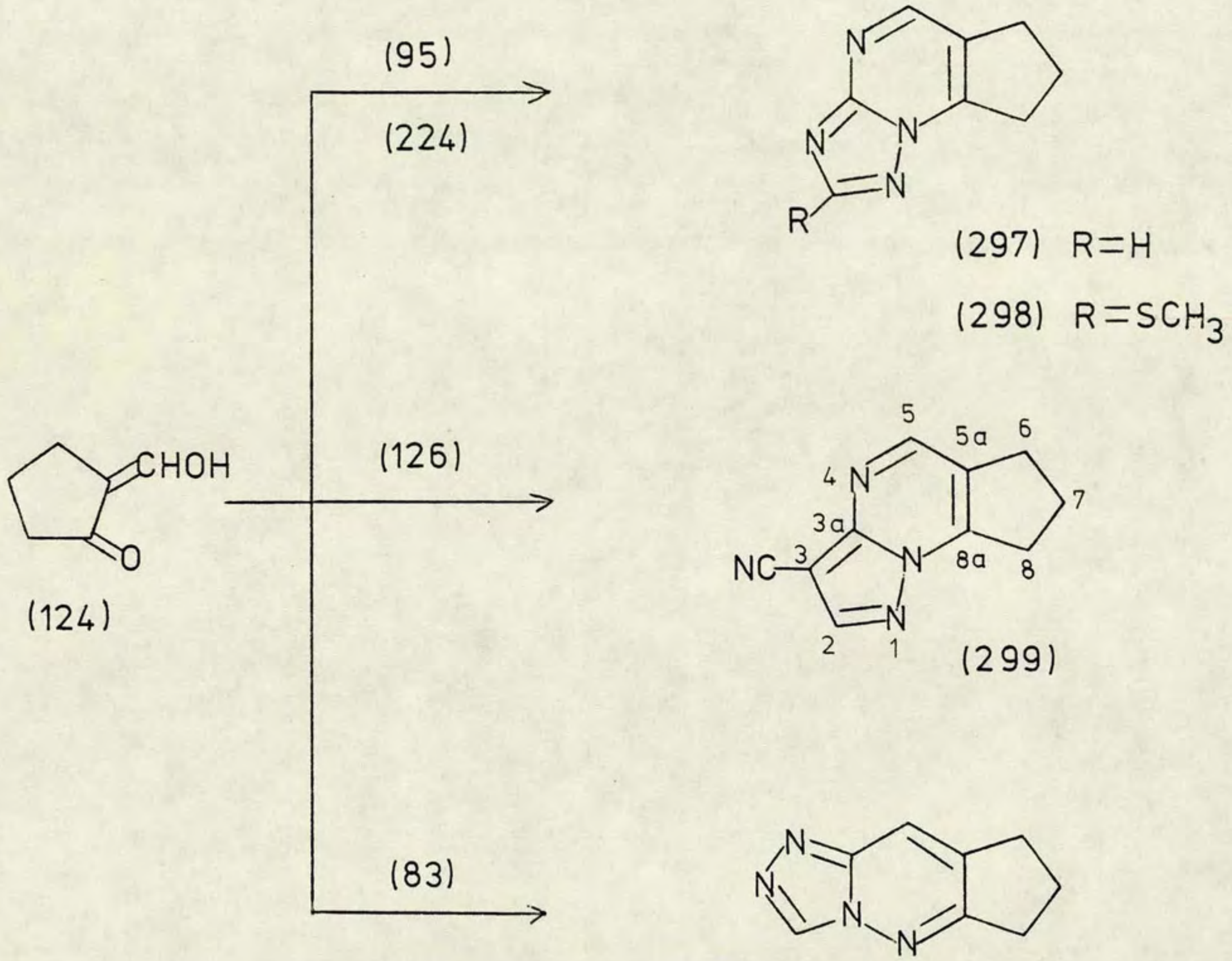
$CH_3-\overset{\overset{O}{\parallel}}{C}-CH=CH-OCH_3$

(285)

to the formation two products (282) and (283) during its reaction with the β-ketoacetal (279). The compounds (286)[149a] and(293)[149b] have been prepared before but no spectroscopic evidence has been given for the structure of these products. s-Triazolo[4, 3-b]cinnoline (164) has also been prepared by the reaction of 3-hydrazino-5, 6, 7, 8-tetrahydrocinnoline with formic acid. The ^{1}H n. m. r. spectrum of the compound (164) agrees with that recorded in the literature[130] but the melting point is 24° lower than previously recorded.

The linear condensation products (e. g. 291) can be readily distinguished from the angular condensation products (e. g. 292) by ^{1}H n. m. r. and ^{13}C n. m. r. spectroscopy. For example in the ^{1}H n. m. r. spectrum of the linear product 3-cyano-5, 6, 7, 8-tetrahydropyrazolo-[5, 1-b]quinazoline (291), the signal for the 9-H is broadened by a small long range coupling with the 8-H whilst the 5-H in 3-cyano-6, 7, 8, 9-tetrahydropyrazolo[1, 5-a]quinazoline (292) appears as a sharp singlet because of the absence of long range coupling. The long range coupling observed in the 9-H signal of the compound (291) was confirmed by double irradiation. Similar long range coupling has been observed,[77] as previously reported (sections 5 and 6) in azolo[a]pyrimidines (179) where it was observed that the methyl protons at 6-C are split into a doublet by coupling with the 7-H whilst no such coupling was observed between the methyl protons at 6-C and the 5-H.[77, 80d] In the ^{13}C n. m. r. spectra, the chemical shift of 9-C (133. 30 p. p. m.) (Table 9) in the compound (291) is found to be comparable with that of 7-C (134. 43 p. p. m.) (Table 8) in the pyrazolopyrimidine (177) whilst the chemical shift of 5-C (149.01 p. p. m.) (Table 10) in the compound (292) is found to agree well


COOC2H5
O
(125)
(126)
R
N
N
N
CN
(295) R = OH or Cl
HO
N
NC
N
N
(296)
N
N
N
CN
(291)


CHOH
O
(124)
(95)
(224)
(126)
(83)
N
N
N
N
R
(297) R=H
(298) R=SCH3
5
5a
6
4
N
7
3a
NC
3
N
8a
8
N
2
1
(299)
N
N
N
N
(300)

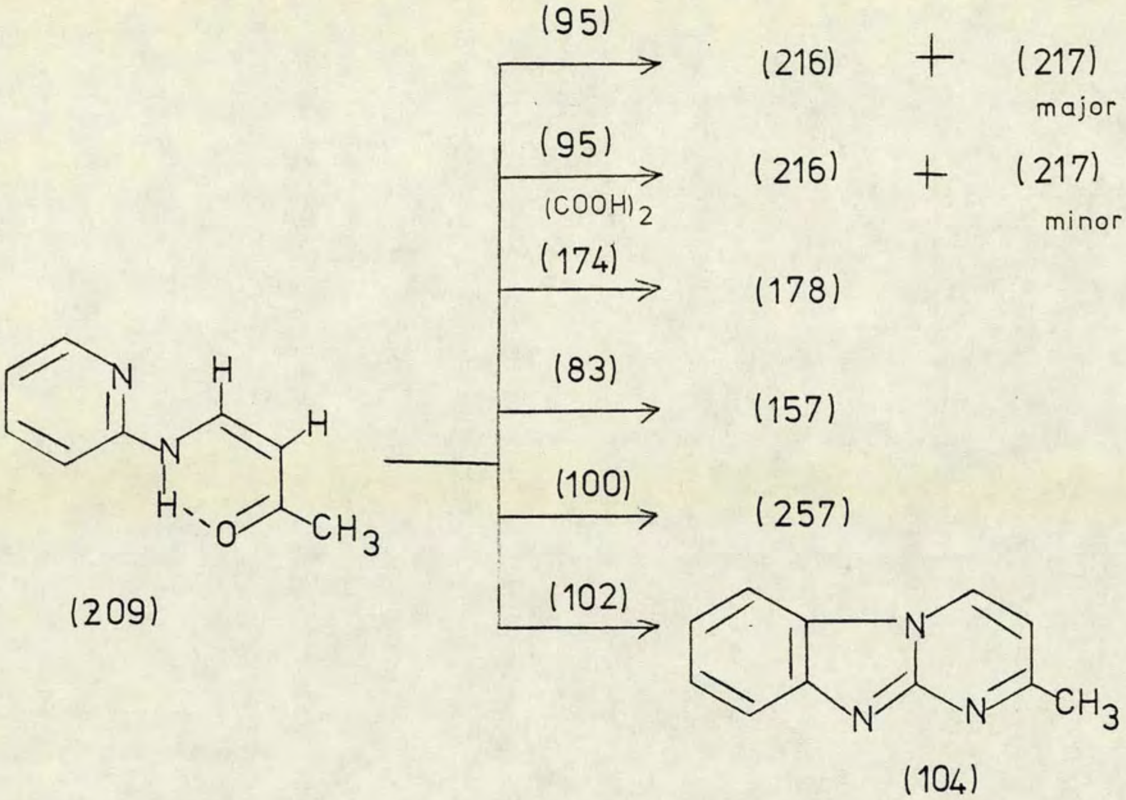
with the chemical shift of 5-C (148.58 p. p. m.) (Table 8) in the pyrazolopyrimidine (178). These values are also consistent with the observation that the carbons bonded to nitrogen atoms are appreciably deshielded relative to benzene and occur further downfield compared with the carbons bonded to bridgehead nitrogens.[135, 136a] The structural assignment of compound (291) is further supported by the following alternative synthesis.

3-Amino-4-cyanopyrazole (126) on condensation with 2-carbethoxycyclohexanone (125) gave 3-cyano-5, 6, 7, 8-tetrahydropyrazolo[5, 1-b]-pyrimidin-9-ol (295; R=OH). The possibility of the alternative structure 3-cyano-6, 7, 8, 9-tetrahydropyrazolo[1, 5-a]pyrimidin-5-ol (296) is ruled out since 3-aminopyrazoles are known to react with ethylacetoacetate to give 5-methylpyrazolo[1, 5-a]pyrimidine-7-ols and not 7-methylpyrazolo-[1, 5-a]pyrimidine-5-ols.[151c] Subsequent reaction of the hydroxyl group in the intermediate (295; R=OH) with phosphorus oxychloride followed by hydrogenolysis furnished a product identical in all respects with 3-cyano-5, 6, 7, 8-tetrahydropyrazolo[5, 1-b]quinazoline (291).

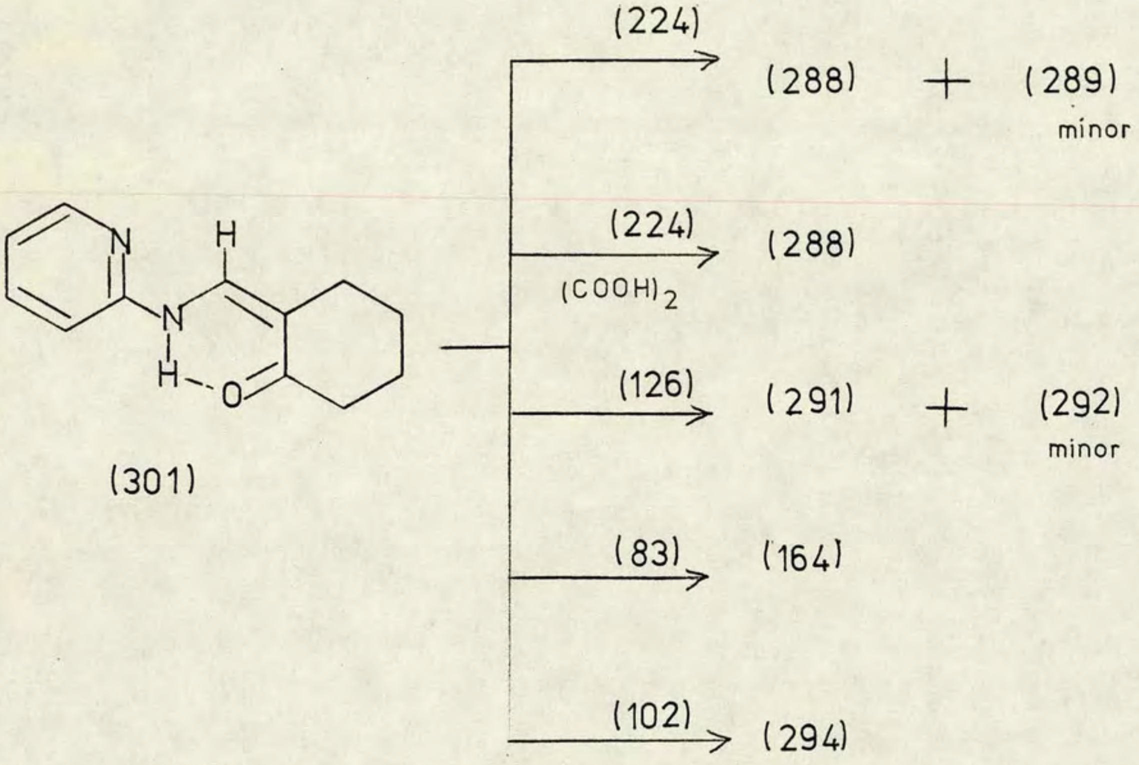
9. 3 The reaction of aminoazoles with 2-hydroxymethylenecyclopentanone.

The condensation of various aminoazoles with 2-hydroxymethylenecyclopentanone (124) is shown however, to take a different course, in that the reaction of 3-amino-1, 2, 4-triazole (95), 3-amino-5-methylthio-1, 2, 4-triazole (224) and 3-amino-4-cyanopyrazole (126) with the β-ketoaldehyde (124) furnishes only the angularly fused products, 7, 8-dihydro-6H-cyclopenta[e]-s-triazolo[1, 5-a]pyrimidine (297), 2-methylthio-7, 8-dihydro-6H-cyclopenta[e]-s-triazolo[1, 5-a]pyrimidine (298) and 3-cyano-7, 8-dihydro-6H-cyclopenta[e]pyrazolo[1, 5-a]pyrimidine (299) respectively.

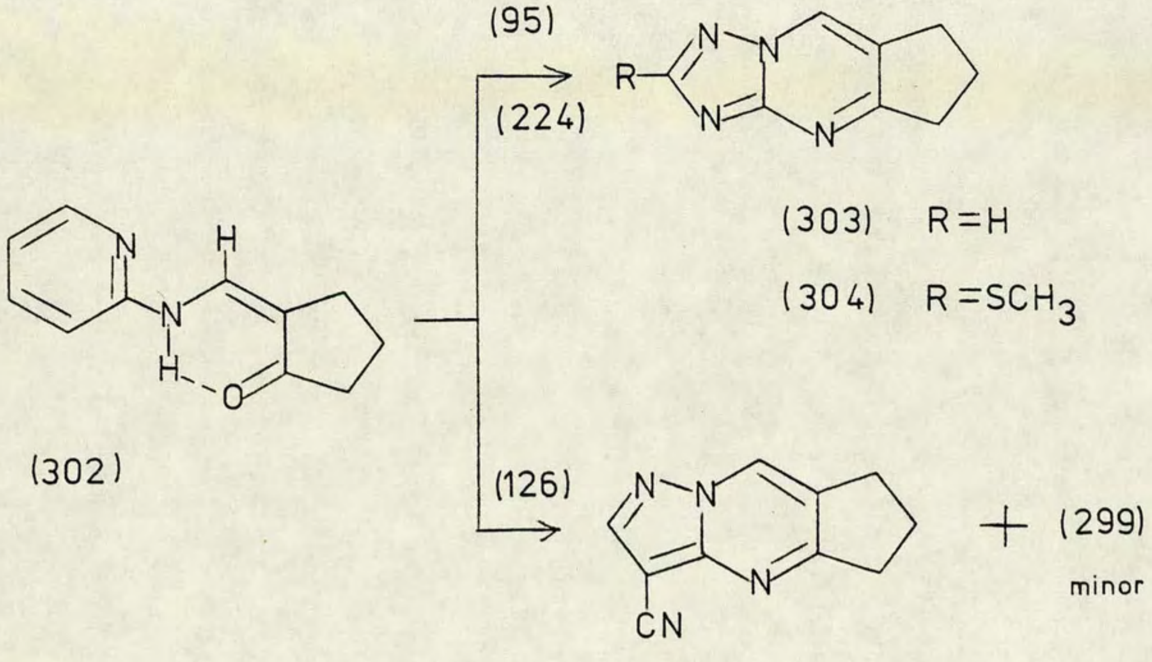
Scheme 1



Scheme 2



Scheme 3



An exception to this behaviour is evidenced by the reaction of 4-amino-1, 2, 4-triazole (83) with the β-ketoaldehyde (124) where the linear product 7, 8-dihydro-6H-cyclopenta[d]-s-triazolo[4, 3-b]pyridazine (300) is the only product isolated. The structures of the products were confirmed by ^{1}H n. m. r. and ^{13}C n. m. r. spectroscopy.

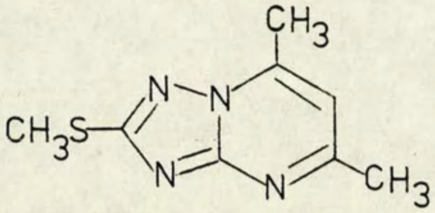
It is interesting to note that the type of the products obtained during these condensation reactions depends very much on the β-ketoacetal or the β-ketoaldehyde and the aminoazole actually used in the reaction. For example, 3-amino-5-methyl-1, 2, 4-triazole (127) reacts with the β-ketoacetal (279) to give two isomeric products (282) and (283) whilst only one product (290) was obtained from its reaction with 2-hydroxymethylene-cyclohexanone (123). Secondly, most of the aminoazoles on reaction with β-ketoacetal (279) or β-ketoaldehyde (123) give two isomeric products whereas these aminoazoles lead to the formation of only angular products on condensation with 2-hydroxymethylenecyclopentanone (124), with the exception of 4-amino-1, 2, 4-triazole (83) which leads to the formation of only linear product (300).

9.4 The reaction of various β-ketoanils with aminoazoles.

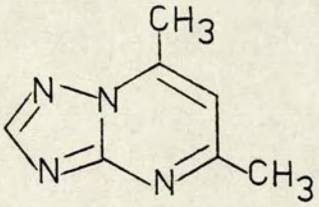
The reactions of the β-ketoanils, 2-(2-acetylvinylamino)pyridine (209), 2-(2'-pyridyl-aminomethylene)cyclohexanone (301) and 2-(2'-pyridyl-aminomethylene)cyclopentanone (302) with various aminoazoles have also been studied (Schemes 1-3). These β-ketoanils were prepared by the reaction of 2-aminopyridine with the respective β-ketoaldehydes or the β-ketoacetal. The structure of the β-ketoanil (209) has already been adequately established[140] with the help of ^{1}H n. m. r. and mass spectrometry. Structures of the β-ketoanils (301) and (302) are assigned by analogy with the structure of the β-ketoanil (209).

It is observed that the reaction of 3-amino-1, 2, 4-triazole (95) with the β-ketoanil (209) catalysed by toluene-4-sulphonic acid furnishes a 20% yield of 5-methyl-s-triazolo[1, 5-a]pyrimidine (216) which indicates that the amino group of the triazole (95) condenses with the carbonyl of the β-ketoanil (209) prior to cyclisation and displacement of the 2-aminopyridine. However, it is interesting to note that 80% of the product isolated from this condensation was 7-methyl-s-triazolo[1, 5-a]pyrimidine (217) which presumably arises by a preliminary reteroanil reaction of the β-ketoanil (209) to yield 3-ketobutanal (281; R=H) prior to condensation with the aminotriazole (95). It was further observed that the ratio of the compound (216) to (217) is dependent on the catalyst used for the condensation. When the β-ketoanil (209) is condensed with the aminotriazole (95) in the presence of anhydrous oxalic acid, the preliminary retroanil reaction is suppressed and 5-methyl-s-triazolo[1, 5-a]pyrimidine (216) becomes the predominant product (45%).

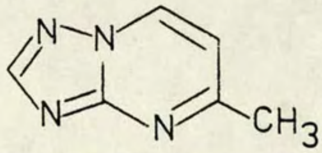
The condensation of the β-ketoanils (301) and (302) with aminoazoles proceeds in a manner similar to that of the β-ketoanil (209). It is noted again that the condensation of the β-ketoanil (301) with 3-amino-5-methylthio-1, 2, 4-triazole (224) and 3-amino-4-cyanopyrazole (126) and the condensation of the β-ketoanil (302) with the aminoazole (126) affords a mixture of a linearly fused product (major) and an angularly fused product (minor). However when the catalyst toluene-4-sulphonic acid was replaced by anhydrous oxalic acid in the condensation of the β-ketoanil (301) with 3-amino-5-methylthio-1, 2, 4-triazole (224), only the linearly fused compound (288) was the sole product obtained.



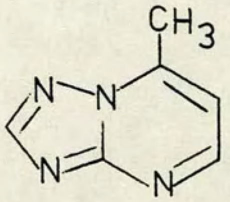
(306)



(307)



(216)



(217)

9.5 ^{13}C N.m.r. Spectra

The assignment of the various carbon resonances in the s-triazolo-[1, 5-a]pyrimidine system is based upon the comparison of the proton coupled and proton decoupled spectra of 2-methylthio-5, 7-dimethyl-s-triazolo[1, 5-a]pyrimidine (306), 5, 7-dimethyl-s-triazolo[1, 5-a]pyrimidine (307), 5-methyl-s-triazolo[1, 5-a]pyrimidine (216) and 7-methyl-s-triazolo[1, 5-a]pyrimidine (217). In the ^{13}C n.m.r. spectrum of the compound (306), the 6-C carbon resonance can be easily identified from the large carbon-13 proton coupling since this is the only ring carbon which has one hydrogen attached to it. By comparing the ^{13}C n.m.r. spectrum of the triazolopyrimidine (307) with that of traizolopyrimidine (306), the chemical shift of 2-C in (307) and the chemical shifts of 2-C and SCH_3 in (306) can also be determined. Further comparison of the spectra of compounds (306) and (307) with those of (216) and (217) enables the chemical shifts of all the ring carbons and methyl carbons of the compounds (216), (217), (306) and (307) to be assigned.

The chemical shifts of the various carbons in the tetrazolo[1, 5-a]-pyrimidine and pyrazolo[1, 5-a]pyrimidine systems follow from the comparison with the chemical shifts of above mentioned compounds (216), (217) and of related systems.[136a] The chemical shifts of the various s-triazolo[4, 3-b]pyridazine derivatives follow from the comparison with the chemical shifts of the parent s-triazolo[4, 3-b]pyridazine.[131] All the ^{13}C n.m.r. chemical shift data is given in Tables 8 to 12.

9.6 Experimental

9.6.i 2-(2-Acetylvinylamino)pyridine (209). A solution of 4,4-dimethoxybutan-2-one (279) (4 g, 3.03 x 10^{-2} mole) and 2-aminopyridine (3 g, 3.2 x 10^{-2} mole) in dry toluene (30 ml) was refluxed for 7 h. The reaction mixture was evaporated to dryness under vacuo and the residue was chromatographed over alumina (50 g). Elution with ethyl acetate followed by recrystallisation of the eluate from acetone gave yellow crystals of 2-(2-acetylvinylamino)pyridine (209) (2.8 g, 56%), m.p. 112-114° (lit,[140] m.p. 114-115°); i.r., ν_{max} 3250 (NH), 1645 (C=O), 1600, 1565 and 1515 cm^{-1}, ^{1}H n.m.r. (60MHz), δ 2.15 (s, 3H, $COCH_3$), 5.40 (d, J=8.6Hz, 1H, -NH-CH=C$\underline{H}$-), 6.60-7.00 (m, 2H, 3-H and 5-H), 7.55 (ddd, 1H, 4-H), 7.95 (dd, 1H, J=12Hz and 8.6Hz, -NH-C$\underline{H}$=CH-) 8.25 (d, 1H, 6-H) and 11.70 (d, 1H, exchanges with D_2O, N$\underline{H}$).

The following compounds were also prepared by the same method.

9.6.ii 2-(2'-Pyridyl-aminomethylene)cyclohexanone (301) was prepared from 2-hydroxymethylenecyclohexanone (123) (3.8 g, 3 x 10^{-2} mole) and 2-aminopyridine (2.82 g, 3 x 10^{-2} mole). Recrystallisation from methanol gave the title compound (301) (56%), m.p. 157-159° (Found: C, 72.71; H, 7.08; N, 14.06; M^+, 202.110485. $C_{12}H_{14}N_2O$ requires C, 72.69; H, 7.12; N, 14.14%; M, 202.110607).

9.6.iii 2-(2'-Pyridyl-aminomethylene)cyclopentanone (302) was prepared from 2-hydroxymethylenecyclopentanone (124) (3.36 g, 3 x 10^{-2} mole) and 2-aminopyridine (2.82 g, 3 x 10^{-2} mole). Recrystallisation from methanol gave the title compound (302) (60%), m.p. 163-165° (Found: C, 71.16; H, 6.50; N, 14.98; M^+, 188.095346. $C_{11}H_{12}N_2O$ requires

C, 71.70; H, 6.57; N, 15.21%; M, 188.094958).

General procedure for the condensation reactions

Method-A: A solution of β-ketoacetal or β-ketoaldehyde (4×10^{-3} mole), the aminoazole (4×10^{-3} mole) and toluene-4-sulphonic acid (30 mg) in dry toluene (50 ml) was refluxed overnight. After cooling, the reaction mixture was evaporated to dryness and the residue was chromatographed over alumina (40 g).

Method-B: Method A was modified by employing the corresponding β-ketoanil (4×10^{-3} mole) instead of the β-ketoacetal or β-ketoaldehyde in the condensation reaction.

9.6.iv 5-Methyl-s-triazolo[1, 5-a]pyrimidine (216), 7-methyl-s-triazolo-[1, 5-a]pyrimidine (217) and 1, 3, 5-triacetylbenzene (280).

Method-A. Alumina chromatography (eluant ether) gave 1, 3, 5-triacetylbenzene (280) which was recrystallised from benzene as white long needles (5%), m.p. 158-160 (lit,[150] m.p. 161-163°). Further elution of the column with ether gave a mixture of two compounds which were separated by fractional crystallisation from benzene. 5-Methyl-s-triazolo[1, 5-a]-pyrimidine (216) crystallised out first as white long needles (45%), m.p. 180-182° (lit,[62d] m.p. 181-182.5°); i.r., γ_{max} 1635, 1615, 1530, 1410, 800 and 775 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 2.75 (s, 3H, 5-CH_3), 7.05 (d, J=7Hz, 1H, 6-H), 8.45 (s, 1H, 2-H) and 8.75 (d, J=7Hz, 1H, 7-H). Concentration of the mother liquor gave long white needles of 7-methyl-s-triazolo[1, 5-a]pyrimidine (217) (15%), m.p. 134-135° (lit,[146b] m.p. 136-138°); i.r., γ_{max} 1615, 1545, 1520, 1450, 1430, 1375, 1355 and

780 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 2.90 (s, 3H, 7-CH$_3$), 7.04 (d, J=4.5Hz, 1H, 6-H), 8.50 (s, 1H, 2-H) and δ.70 (d, J=4.5Hz, 1H, 5-H).

Method-B. The two products (216) and (217) were obtained in 17% and 62% respectively. However, when toluene-4-sulphonic acid catalyst was replaced by anhydrous oxalic acid, the two products (216) and (217) were obtained in 45% and 16% respectively.

9.6.v 2,5-Dimethyl-s-triazolo[1,5-a]pyrimidine (282), 2,7-dimethyl-s-triazolo[1,5-a]pyrimidine (283) and 1,3,5-triacetylbenzene (280).

Method-A. Alumina chromatography (eluant ether) gave 1,3,5-triacetylbenzene (280) which was recrystallised from benzene as long white needles (4.5%), m.p. 158-160° (lit.[150] m.p. 161-163°). Further elution of the column with ether-ethyl acetate (1:1) gave 2,5-dimethyl-s-triazolo-[1,5-a]pyrimidine (282) which recrystallised from n-hexane as white crystals (48%), m.p. 82-83° (lit.[151a] m.p. 86-88°); ^{1}H n.m.r. (60MHz), δ 2.60 (s, 3H, 2-CH$_3$), 2.68 (s, 3H, 5-CH$_3$), 6.85 (d, J=7Hz, 1H, 6-H) and 8.58 (d, J=7Hz, 1H, 7-H); and 2,7-dimethyl-s-triazolo[1,5-a]-pyrimidine (283) which was also recrystallised from n-hexane to give white crystals (25%), m.p. 157-159° (lit.[151a] m.p. 161-162°); ^{1}H n.m.r. (100 MHz), δ 2.62 (s, 3H, 2-CH$_3$), δ 2.80 (bs, 3H, 7-CH$_3$), 6.90 (d, J=4.5, 6-H) and 8.62 (d, J=4.5, 5-H).

9.6.vi 5-Methylpyrazolo[1,5-a]pyrimidine (177) and 7-methylpyrazolo-[1,5-a]pyrimidine (178).

Method-A. Alumina chromatography (eluant ethyl acetate) gave the two isomeric compounds, 5-methylpyrazolo[1,5-a]pyrimidine (177) which was recrystallised from n-hexane as white needles (27%), m.p. 122-124° (lit.[151b] m.p. 122-123°); i.r, γ_{max} 1625, 1610, 1535, 1510, 1405, 790 and 770 cm^{-1}; ^1H n.m.r. (60 MHz) δ 2.60 (s, 3H, 5-CH_3) 6.60 (d, J=2Hz, 1H, 3-H), 6.65 (d, J=7.5 Hz, 6-H), 8.15 (d, J=2Hz, 1H, 2-H) and 8.60 (d, J=7.5Hz, 1H, 7-H); and 7-methylpyrazolo[1, 5-a]pyrimidine (178) which was recrystallised from n-hexane-benzene to give white crystals (16%), m.p. 59-60 (lit.[151b] m.p. 59-60°); i.r., γ_{max} 1610, 1540, 1445, 1430, 1385, 810 and 770 cm^{-1}; ^1H n.m.r. (60 MHz), δ 2.80 (bs, 3H, 7-CH_3), 6.60 (d, J=4.4 Hz, 1H, 6-H), 6.75 (d, J=2Hz, 1H, 3-H), 8.20 (d, J=2Hz, 1H, 2-H) and 8.45 (d, J=4.4 Hz, 1H, 5-H).

Method-B. 7-Methylpyrazolo[1, 5-a]pyrimidine (178) was obtained in 75% yield as the sole reaction product.

9.6.vii 6-Methyl-s-triazolo[4, 3-b]pyridazine (157) and 8-methyl-s-triazolo[4, 3-b]pyridazine (158).

Method-A. Alumina chromatography (eluant ethyl acetate-ether, 1:1) gave 6-methyl-s-triazolo[4, 3-b]pyridazine (157) which was recrystallised from benzene to give white needles (58%), m.p. 168-170° (lit.[62d] m.p. 168-169°); i.r., γ_{max} 3140, 1620, 1540, 1500, 1445, 1425, 1390, 1375, 1355 and 805 cm^{-1}; ^1H n.m.r. (60 MHz), δ 2.62 (s, 3H, 6-CH_3), 7.05 (d, J=9.5Hz, 1H, 7-H), 8.05 (d, J=9.5Hz, 1H, 8-H) and 9.05 (s, 1H, 3-H); and 8-methyl-s-triazolo[4, 3-b]pyridazine (158) which was recrystallised from n-hexane to give white crystals (20%), m.p. 124-126° (lit.[129] m.p. 126-127°); i.r., γ_{max} 3140, 1610, 1565, 1490, 1430, 1385, 1370, 1345 and 805 cm^{-1}; ^1H n.m.r. (60 MHz), δ 2.75 (d, J=0.8 Hz, 3H, 8-CH_3), 6.92 (dd, J=0.8 and 5 Hz, 1H, 6-H), 8.25 (d, J=5Hz, 1H, 5-H) and 9.08 (s, 1H, 3-H).

Method-B. 6-Methyl-s-triazolo[4, 3-b]pyridazine (157) was obtained in 25% yield as the only reaction product.

9.6.viii 7-Methyltetrazolo[1, 5-a]pyrimidine (257).

Method-A. Alumina chromatography (eluant methylene chloride-ethyl aceyate, 9:1) followed by recrystallisation of the eluate from benzene gave 7-methyltetrazolo[1, 5-a]pyrimidine (257) as white needles (70%), m.p. 129-131^{o} (lit.[62d] m.p. 130-132.5^{o}); i.r., γ_{max} 2140 (-N_3), 1625, 1585, 1540, 1510, 1440, 1365 and 1350 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 3.50 (bs, 3H, 7-CH_3), 7.25 (d, J=4.0 Hz, 1H, 6-H) and 8.90 (d, 1H, 5-H).

Method-B. 7-Methyltetrazolo[1, 5-a]pyrimidine (257) was obtained as the sole reaction product in 63% yield.

9.6.ix 2-Methylpyrimido[1, 2-a]benzimidazole (104).

Method-B. Alumina chromatography (eluant ethyl acetate) gave the 2-methylpyrimido[1, 2-a]benzimidazole (104) which was recrystallised from ethanol to give light yellow crystals (64%), m.p. 230-232^{o} (lit.[85] m.p. 229-232^{o}); i.r., γ_{max} 1630, 1610, 1515, 1460, 1440, 780, 765 and 735 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 2.62 (s, 3H, 2-CH_3), 6.75 (d, J=7Hz, 1H, 3-H), 7.20-8.05 (m, 4H, 6-9H's) and 8.60 (d, J=7Hz, 1H, 4-H).

9.6.x 5, 6, 7, 8-Tetrahydro-s-triazolo[5, 1, b]quinazoline (286) and 6, 7, 8, 9-tetrahydro-s-triazolo[1, 5-a]quinazoline (287).

Method-A. The two condensation products were separated by shaking the mixture with petroleum-ether (60-80^{o}). The insoluble material on recrystallisation from n-hexane-benzene gave 5, 6, 7, 8-tetrahydro-s-triazolo-

[5, 1-b]quinazoline (286) (55%); m. p. 121-123° (lit.[149a] m. p. 125-126°); i. r., γ_{max} 1630, 1510, 1430, 1420, 1405, 1350 and 770 cm^{-1}; ^{1}H n. m. r. (60MHz), δ 1.97 (m, 2H, 6-H and 7-H), 3.00 (m, 2H, 5-H and 8-H), 8.40 (s, 1H, 2-H) and 8.55 (bs, 1H, 9-H) (Found: C, 62.10; H, 5.89; N, 32.00; M$^+$, 174.091873. $C_9H_{10}N_4$ requires C, 62.04; H, 5.79; N, 32.17%; M, 174.090932).

The petroleum-ether fraction was evaporated to dryness and the residue was recrystallised from n-hexane to give 6, 7, 8, 9-tetrahydro-s-triazolo[1, 5-a]quinazoline (287) (37%); m. p. 87-89°; i. r., γ_{max} 1625, 1545, 1510, 1435, 1420, 1405, 1355 and 770 cm^{-1}; ^{1}H n. m. r. (60 MHz), δ 1.95 (m, 2H, 7-H and 8-H), 2.95 (m, 2H, 6-H and 9-H), 8.35 (s, 1H, 2-H) and 8.40 (s, 1H, 5-H) (Found: C, 61.95; H, 5.70; N, 32.35; M$^+$, 174.092761. $C_9H_{10}N_4$ requires C, 62.04; H, 5.79; N, 32.17%; M, 174.090932).

9.6.xi 2-Methylthio-5, 6, 7, 8-tetrahydro-s-triazolo[5, 1-b]quinazoline (288) and 2-methylthio-6, 7, 8, 9-tetrahydro-s-triazolo[1, 5-a]quinazoline (289).

Method-A. Alumina chromatography (eluant ethyl acetate) gave the two title products.

2-Methylthio-5, 6, 7, 8-tetrahydro-s-triazolo[5, 1-b] quinazoline (288) was recrystallised from ethanol to give white crystals (63%), m. p. 106-108°; i. r., γ_{max} 1625, 1510, 1450, 1435, 1425, 1370, 1350 and 770 cm^{-1}; ^{1}H n. m. r. (60 MHz), δ 1.90 (m, 2H, 6-H and 7-H), 2.77 (s, 3H, 2-SCH$_3$), 2.95 (m, 2H, 5-H and 8-H) and 8.35 (bs, 1H, 9-H) (Found: C, 54.34; H, 5.40; N, 25.31; M$^+$, 220.079812. $C_{10}H_{12}N_4S$ requires C, 54.52; H, 5.49; N, 25.46%; M, 220.078264).

2-Methylthio-6, 7, 8, 9-tetrahydro-s-triazolo[1, 5-a]pyrimidine (289) was recrystallised from acetone to give large white crystals (26%), m.p. 139-141°; i.r., γ_{max} 1615, 1550, 1515, 1450, 1435, 1405, 1365 and 770 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 1.90 (m, 2H, 7-H and 8-H), 2.70 (s, 3H, 2-SCH$_3$), 3.00 (m, 2H, 6-H and 9-H) and 8.30 (s, 1H, 5-H) (Found: C, 54.61; H, 5.51; N, 25.57; M$^+$, 220.077244. $C_{10}H_{12}N_4S$ requires C, 54.52; H, 5.49; N, 25.46%; M, 220.078264).

Method-B. The two products (288) and (289) were obtained in 48% and 16% yields respectively. When toluene-4-sulphonic acid catalyst was replaced by anhydrous oxalic acid, only product (288) was obtained in 60% yield.

9.6.xii 2-Methyl-5, 6, 7, 8-tetrahydro-s-triazolo[5, 1-b]quinazoline (290).

Method-A. Alumina chromatography (eluant ethyl acetate) followed by recrystallisation from n-hexane gave long white needles of 2-methyl-5, 6, 7, 8-tetrahydro-s-triazolo[5, 1-b]quinazoline (290) (56%), m.p. 132-133°; i.r., γ_{max} 1630, 1515, 1470, 1450, 1440, 1415, 1385, 1365 and 775 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 1.90 (m, 2H, 6-H and 7-H), 2.55 (s, 3H, 2-CH$_3$), 2.90 (m, 2H, 5-H and 8-H) and 8.35 (bs, 1H, 9-H) (Found: C, 63.38; H, 6.37; N, 29.59; M$^+$, 188.104757. $C_{10}H_{12}N_4$ requires C, 63.79; H, 6.43; N, 29.78%; M, 188.106191).

9.6.xiii 3-Cyano-5, 6, 7, 8-tetrahydropyrazolo[5, 1-b]quinazoline (291) and 3-cyano-6, 7, 8, 9-tetrahydropyrazolo[1, 5-a]quinazoline (292).

Method-A. Alumina chromatography (eluant ethyl acetate) gave the two title products.

3-Cyano-5, 6, 7, 8-tetrahydropyrazolo[5, 1-b]quinazoline (291) was recrystallised from methanol to give white crystals (30%), m.p. 110-111°; i.r., γ_{max} 2220 (CN), 1630, 1550, 1505, 1460, 1405 and 750 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 1.95 (m, 2H, 6-H and 7-H), 3.00 (m, 2H, 5-H and 8-H), 8.27 (s, 1H, 2-H), and 8.42 (bs, 1H, 9-H) (Found: C, 66.78; H, 5.10; N, 28.53; M^+, 198.090620. $C_{11}H_{10}N_4$ requires C, 66.64; H, 5.09; N, 28.28%; M, 198.090542).

3-Cyano-6, 7, 8, 9-tetrahydropyrazolo[1, 5-a]quinazoline (292) was recrystallised from methanol to give white crystals (15%), m.p. 116-118°; i.r., γ_{max} 2220 (CN), 1620, 1530, 1470, 1370, 1350 and 750 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 2.03 (m, 2H, 7-H and 8-H), 3.05 (m, 2H, 6-H and 9-H), 8.35 (s, 1H, 2-H) and 8.50 (s, 1H, 5-H) (Found: C, 66.44; H, 5.12; N, 28.35; M^+, 198.091372. $C_{11}H_{10}N_4$ requires C, 66.64; H, 5.09; N, 28.28%; M, 198.090542).

Method-B. The two products (291) and (292) were obtained in 50% and 12% yields respectively.

9.6.xiv 6, 7, 8, 9-Tetrahydro-s-triazolo[4, 3-b]cinnoline (164) and 7, 8, 9, 10-tetrahydro-s-triazolo[3, 4-a]phthalazine (165).

Method-A. Alumina chromatography (eluant ethyl acetate-ether, 3:2) gave the two title products.

6, 7, 8, 9-Tetrahydro-s-triazolo[4, 3-b]cinnoline (164) was recrystallised from n-hexane to give white needles (20%), m.p. 95-97° (lit.[130] m.p. 120°); i.r., γ_{max} 3140, 1525, 1485, 1425, 1340 and 800 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 1.90 (m, 2H, 7-H and 8-H), 2.95 (m, 2H, 6-H and 9-H), 7.70 (bs, 1H, 10-H) and 8.90 (s, 1H, 3-H) (Found: C, 61.88; H, 5.79;

N, 32.47; M^+, 174.090423. $C_9H_{10}N_4$ requires C, 62.07; H, 5.72; N, 32.17; M, 174.090542).

7, 8, 9, 10-Tetrahydro-s-triazolo[3, 4-a]phthalazine (165) was recrystallised from n-hexane to give white crystals (60%), m.p. 157-159°; i.r., γ_{max} 3140, 1620, 1545, 1500, 1450, 1430, 1405, 1345 and 775 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 1.92 (m, 2H, 8-H and 9-H), 2.90 (m, 2H, 7-H and 10-H), 8.02 (s, 1H, 6-H) and 8.97 (s, 1H, 3-H) (Found: C, 61.95; H, 5.80; N, 32.18; M^+, 174.090761. $C_9H_{10}N_4$ requires C, 62.07; H, 5.72; N, 32.17%; M, 174.090542).

Method-B. 6.7.8.9-Tetrahydro-s-triazolo[4, 3-b]cinnoline (164) was obtained in 15% yield.

9.6.xv 6, 7, 8.9-Tetrahydrotetrazolo[1, 5-a]quinazoline (293).

Method-A. 6, 7, 8, 9-Tetrahydrotetrazolo[1, 5-a]quinazoline (293) crystallised directly from the reaction mixture, further recrystallisation from ethanol gave white crystals (73%), m.p. 121-123° (lit.[149b] m.p. 122-123°); i.r., γ_{max} 2145 ($-N_3$), 1625, 1545, 1510, 1450, 1435, 1420, 1365, 1355 and 775 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 2.07 (m, 2H, 7-H and 8-H), 3.15 (m, 2H, 6-H and 9-H) and 8.65 (s, 1H, 5-H) (Found: C, 54.95; H, 5.10; N, 40.17; M^+, 175.083652. $C_8H_9N_5$ requires C, 54.82; H, 5.18; N, 39.99; M, 175.085742).

9.6.xvi 1, 2, 3, 4-Tetrahydrobenzimidazo[2, 1-b]quinazoline (294).

Method-A. Alumina chromatography (eluant ethyl acetate) followed by recrystallisation from acetone gave yellow needles of 1, 2, 3, 4-tetrahydrobenzimidazo[2, 1-b]quinazoline (294) (51%), m.p. 228-230°; i.r., γ_{max} 1640, 1610, 1585, 1515, 1490, 1450, 1435, 1425, 1410, 1360, 760 and 730 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 1.86 m (m, 2H, 2-H and 3-H), 2.90 (m, 2H, 1-H and 4-H), 7.15-7.95 (m, 4H, 7-H, 8-H, 9-H and 10-H) and 8.20 (bs, 1H, 12-H) (Found: 75.42; H, 5.91; N, 18.79; M^+, 223.112482. $C_{14}H_{13}N_3$ requires C, 75.30; H, 5.87; N, 18.33%; M, 223.110942).

Method-B. 1, 2, 3, 4-Tetrahydrobenzimidazo[2, 1-b]quinazoline (294) was obtained in 75% yield.

9.6.xvii 7, 8-Dihydro-6H-cyclopenta[e]-s-triazolo[1, 5-a]pyrimidine (297) and 6, 7-dihydro-5H-cyclopenta[d]-s-triazolo[1, 5-a]pyrimidine (303).

Method-A. Alumina chromatography (eluant ethyl acetate) followed by recrystallisation from petroleum-ether (100-120°) gave white needles of 7, 8-dihydro-6H-cyclopenta[e]-s-triazolo[1, 5-a]pyrimidine (297) (72%), m.p. 121-122; i.r., γ_{max} 1625, 1545, 1510, 1455, 1425, 1400, 1350, and 770 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 2.45 (m, 1H, 7-H), 3.35 (m, 2H, 6-H and 8-H), 8.42 (s, 1H, 2-H) and 8.65 (s, 1H, 5-H) (Found: C, 60.28; H, 5.14; N, 34.78; M^+, 160.074003. $C_8H_8N_4$ requires C, 59.97; H, 5.04; N, 34.99%; M, 160.074892).

Method-B. Alumina chromatography (eluant ethyl acetate) followed by recrystallisation from n-hexane gave white crystals of 6, 7-dihydro-5H-cyclopenta[d]-s-triazolo[1, 5-a]pyrimidine (303) (61%), m.p. 207-208° (lit.[149a] m.p. 207-208°); i.r., γ_{max} 1660, 1645, 1525, 1435, 1415, 1410 and 775 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 2.35 (m, 1H, 6-H), 3.15 (m, 2H, 5-H and 7-H), 8.40 (s, 1-H, 2-H) and 8.65 (bs, 1H, 8-H) (Found: C, 59.84; H, 5.01; N, 35.20; M^+, 160.073182. $C_8H_8N_4$ requires C, 59.97; H, 5.04; N, 34.99%; M, 160.074892).

9.6.xviii 2-Methylthio-7,8-dihydro-6H-cyclopenta[e]-s-triazolo[1,5-a]pyrimidine (298) and 2-methylthio-6,7-dihydro-5H-cyclopenta[d]-s-triazolo[1,5-a]pyrimidine (304).

Method-A. Alumina chromatography (eluant ethyl acetate) followed by recrystallisation from methanol gave white crystals of 2-methylthio-7,8-dihydro-6H-cyclopenta[e]-s-triazolo[1,5-a]pyrimidine (298) (81%), m.p. 128-129°; i.r., γ_{max} 1610, 1560, 1500, 1415, 1350 and 765 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 2.35 (m, 1H, 7-H), 2.68 (s, 3H, 2-SCH$_3$), 3.20 (m, 2H, 6-H and 8-H) and 8.45 (s, 1H, 5-H) (Found: C, 52.24; H, 4.80; N, 27.14; M$^+$, 206.061356. $C_9H_{10}N_4S$ requires C, 52.41; H, 4.89; N, 27.81%; M, 206.062615).

Method-B. Alumina chromatography (eluant ethyl acetate)followed by recrystallisation from methanol gave white lusterous crystals of 2-methylthio-6,7-dihydro-5H-cyclopenta[d]-s-triazolo[1,5-a]pyrimidine (304) (51%), m.p. 154-157°; i.r., 1635, 1515, 1435, 1420, 1360, 1350 and 765 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 2.28 (m, 1H, 6-H), 2.68 (s, 3H, 2-SCH$_3$), 3.10 (m, 2H, 5-H and 7-H) and 8.42 (dd, 1H, 8-H) (Found: C, 52.20; H, 4.90; N, 27.10; M$^+$, 206.062296. $C_9H_{10}N_4S$ requires C, 52.41; H, 4.89; N, 27.18%; M, 206.062615).

9.6.xix 3-Cyano-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine (299) and 3-cyano-6,7-dihydro-5H-cyclopenta[d]pyrazolo[1,5-a]pyrimidine (305).

Method-A. Alumina chromatography (eluant chloroform) followed by recrystallisation from methanol gave white crystals of 3-cyano-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine (299) (67%), m.p. 147-149°; i.r., γ_{max} 2220 (CN), 1625, 1550, 1530, 1480, 1425 and 750 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 2.48 (m, 1H, 7-H), 3.35 m (m, 2H, 6-H and 8-H), 8.40 (s, 1H, 2-H) and 8.65 (s, 1H, 5-H) (Found: C, 65.19; H, 4.40; N, 30.81; M^+, 184.073050. $C_{10}H_8N_4$ requires C, 65.19; H, 4.38; N, 30.43%; M, 184.074892).

Method-B. The following two products were obtained.

3-Cyano-7,8-dihydro-6H-cyclopenta[e]pyrazolo[1,5-a]pyrimidine (299) (17%).

3-Cyano-6,7-dihydro-5H-cyclopenta[d]pyrazolo[1,5-a]pyrimidine (305) (58%), m.p. 148-150°; i.r., γ_{max} 2220 (CN), 1645, 1565, 1525, 1460, 1440, 1420, 1405 and 755 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 2.30 (m, 1H, 6-H), 3.08 (m, 2H, 5-H and 7-H), 8.26 (s, 1H, 2-H) and 8.50 (dd, 1H, 8-H) (Found: C, 64.99; H, 4.37; N, 30.56; M^+, 184.073703. $C_{10}H_8N_4$ requires C, 65.19; H, 4.38; N, 30.43%; M, 184.074892).

9.6.xx 7,8-Dihydro-6H-cyclopenta[d]-s-triazolo[4,3-b]pyridazine (300).

Method-A. Alumina chromatography (eluant ethyl acetate) followed by recrystallisation from benzene gave white crystals of 7,8-dihydro-6H-cyclopenta[d]-s-triazolo[4,3-b]pyridazine (300) (60%), m.p. 139-140°; i.r., γ_{max} 3140, 1545, 1510, 1445, 1420 and 780 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 2.35 (m, 1H, 7-H), 3.00 (m, 2H, 6-H and 8-H), 7.85 (bs, 1H, 9-H) and 9.00 (s, 1H, 3-H) (Found: C, 59.86; H, 5.03; N, 35.00; M^+, 160.074115. $C_8H_8N_4$ requires C, 60.00; H, 5.00; N, 35.00%; M, 160.074892).

9.6.xxi 3-Cyano-5, 6, 7, 8-tetrahydropyrazolo[5, 1-b]quinazolin-9-ol (295, R=OH).

3-Amino-4-cyanopyrazole (126) (0.75 g, 7. x 10^{-3} mole) and 2-carbethoxycyclohexanone (125) (1.2 g, 7 x 10^{-3} mole) were refluxed together in glacial acetic acid (30 ml) for 4 h. During refluxing, the product crystallised out as fine yellow needles. After cooling the reaction mixture, the crystals were filtered, washed with glacial acetic acid, dried to give 3-cyano-5, 6, 7, 8-tetrahydropyrazolo[5, 1-b]quinazolin-9-ol (295, R=OH) (1.02 g, 75%), m.p. >310°; i.r., γ_{max} 2220 (CN), 1680, 1640, 1585, 1500, 1460, 1375, 750 and 705 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 1.90 (m, 2H, 6-H and 7-H), 2.50 (m, 2H, 5-H and 8-H), 8.25 (s, 1H, 2-H) and 13.05 (bs, 1H, N<u>H</u>) (Found: C, 61.95; H, 4.69; N, 25.92; M^{+}, 214.087158. $C_{11}H_{10}N_4O$ requires C, 61.66; H, 4.71; N, 26.16; M, 214.085456).

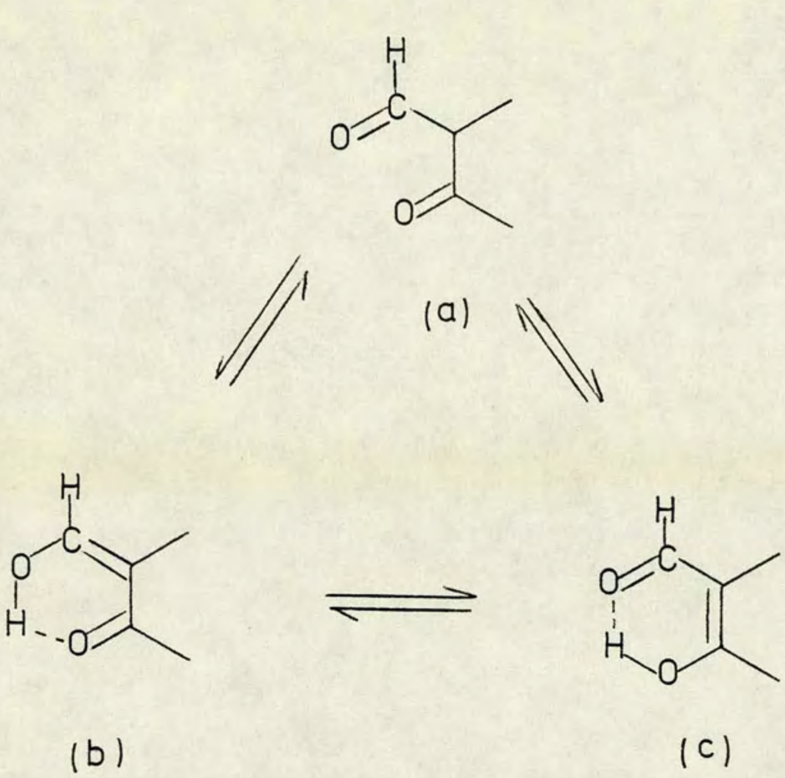
9.6.xxii 9-Chloro-3-cyano-5, 6, 7, 8-tetrahydropyrazolo[5, 1-b]quinazoline (295, R=Cl).

A solution of 3-cyano-5, 6, 7, 8-tetrahydropyrazolo[5, 1-b]quinazolin-9-ol (295, R=OH) (0.64 g, 3 x 10^{-3} mole) in phosphoryl chloride (30 ml) was boiled for 3 h and the excess of phosphoryl chloride was removed under vacuo. Ice was added to the residue, and the solution was neutralised with ammonium hydroxide. The brown precipitate was collected, washed with water, dried and purified by chromatography over alumina (eluant ethyl acetate). Recrystallisation of the eluate from petroleum-ether (60-80°) gave white needles of 9-chloro-3-cyano-5, 6, 7, 8-tetrahydropyrazolo-[5, 1-b]quinazoline (295, R=Cl) (0.57 g, 64%), m.p. 139-140°; i.r.,

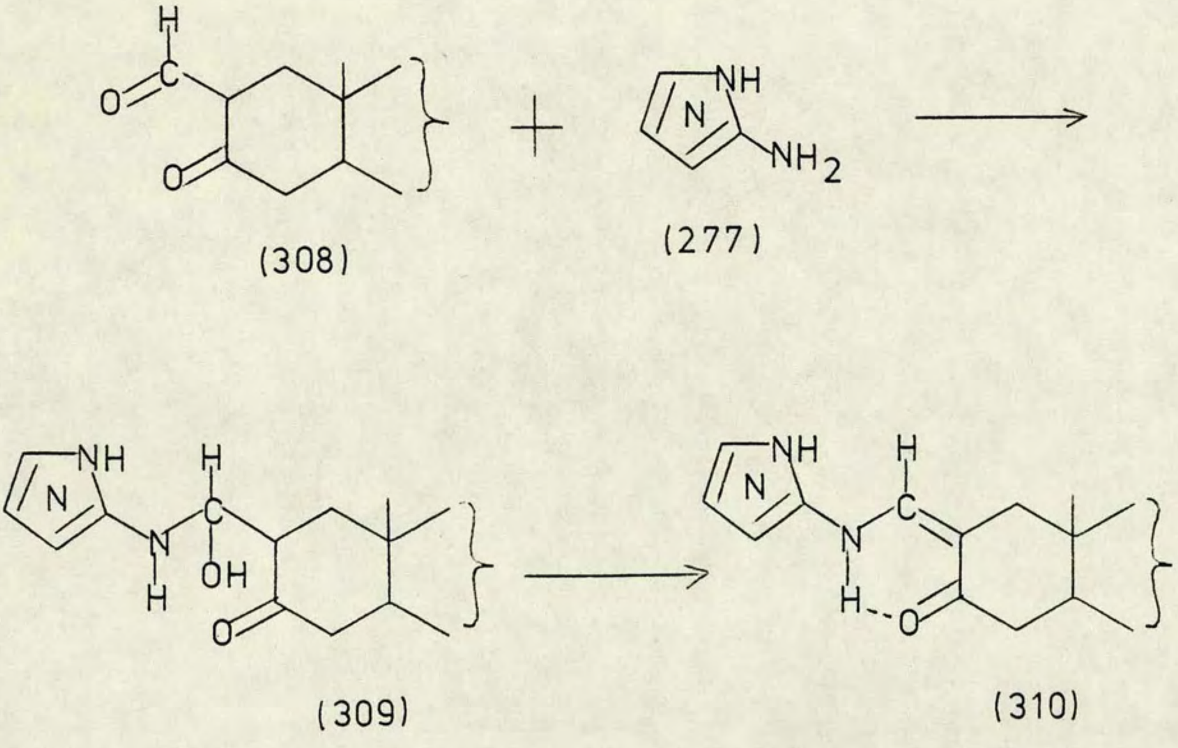
γ_{max} 2220 (CN), 1610, 1540, 1475, 1415, 1380 and 730 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 1.97 (m, 2H, 6-H and 7-H), 3.05 (m, 2H, 5-H and 8-H) and 8.35 (s, 1H, 2-H) (Found: C,56.87; H, 4.13; N, 23.89; M^{+}, 232.051570 and 234.048200. $C_{11}H_{9}N_{4}Cl$ requires C, 56.77; H, 3.87; N, 24.08%; M, 232.051350 and 234.048200).

9.6.xxiii 3-Cyano-5,6-7,8-tetrahydropyrazolo[5,1-b]quinazoline (291).

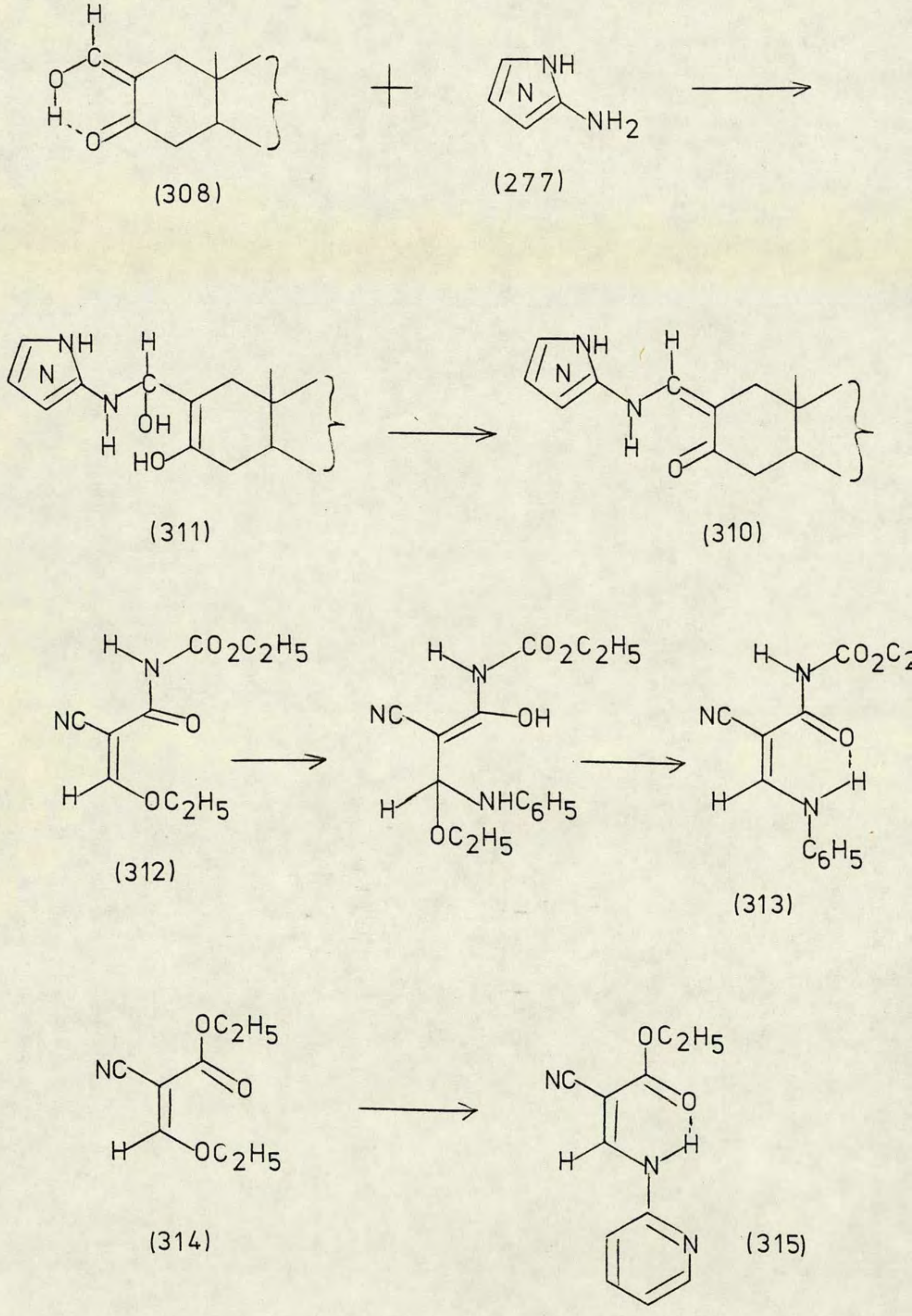
A solution of 9-chloro-3-cyano-5,6,7,8-tetrahydropyrazolo[5,1-b]-quinazoline (295, R=Cl) (0.464 g, 2 x 10^{-3} mole) in absolute alcohol (30 ml) was dehalogenated by shaking with hydrogen and 5% palladium on carbon catalyst (0.7 g). Recrystallisation of the crude product from methanol gave white crystals (0.217 g, 55%), m.p. 110-112° alone or mixed with a specimen prepared from 2-hydroxymethylenecyclohexanone (123).



Scheme 4



Scheme 5



10 Reaction mechanism of the condensation of steroidal β-keto-aldehydes with aminoazoles

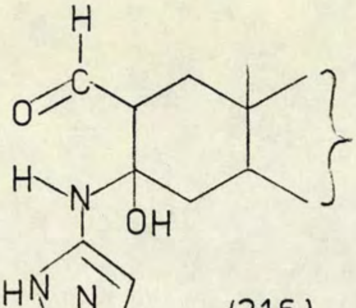
10.1 Anil formation.

It has been shown[152] with the help of ^{1}H n.m.r. spectroscopy that 2-formyl-3-oxo steroids (308) exist predominantly in the enolic forms (b and c). However, the i.r. spectra of 2-formyl-3-oxo steroids (without a Δ^4 double bond) do exhibit an absorption of medium intensity around 1700 cm^{-1} which can be attributed to the formyl keto form (a). Consequently two mechanisms for anil formation are shown in schemes 4 and 5.

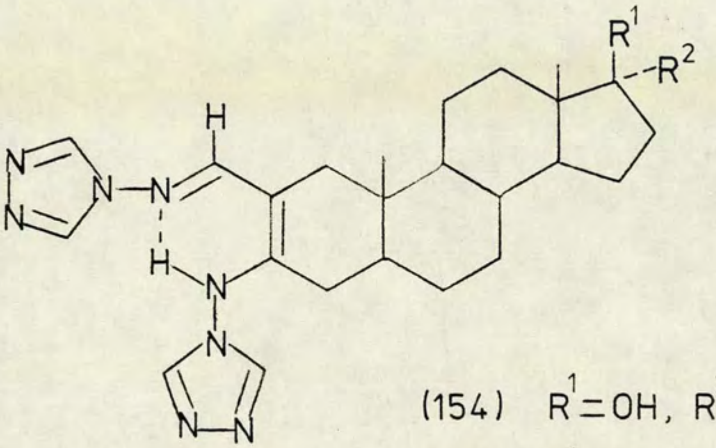
Scheme 4 illustrates the conventional nucleophilic addition reaction to the formyl group followed by elimination of water and rearrangement to yield the most stable enaminone form (310).

The mechanism shown in scheme 5 indicates 1,4-addition of the nucleophile to the conjugated carbonyl group followed by elimination of water to yield the same enaminone (310). Overall the reaction is seen as a displacement of the hydroxyl group from the enol by the incoming nucleophile. A similar mechanism has been observed[153] during the formation of ethyl 2-cyano-3-anilinoacryloyl-carbamate (313) from ethyl 2-cyano-3-ethoxy-acryloyl-carbamate (312) and aniline in cold ethanol, where the anilino group has displaced an ethoxy group. The formation of ethyl N(2-pyridyl)-aminomethylene-cyanoacetate (315) by the reaction of ethyl ethoxymethylene cyanoacetate (314) and 2-aminopyridine has also been reported.[154]

The reason for the condensation of the aminoazole (277) taking place at the formyl carbonyl rather than at the keto carbonyl is that the

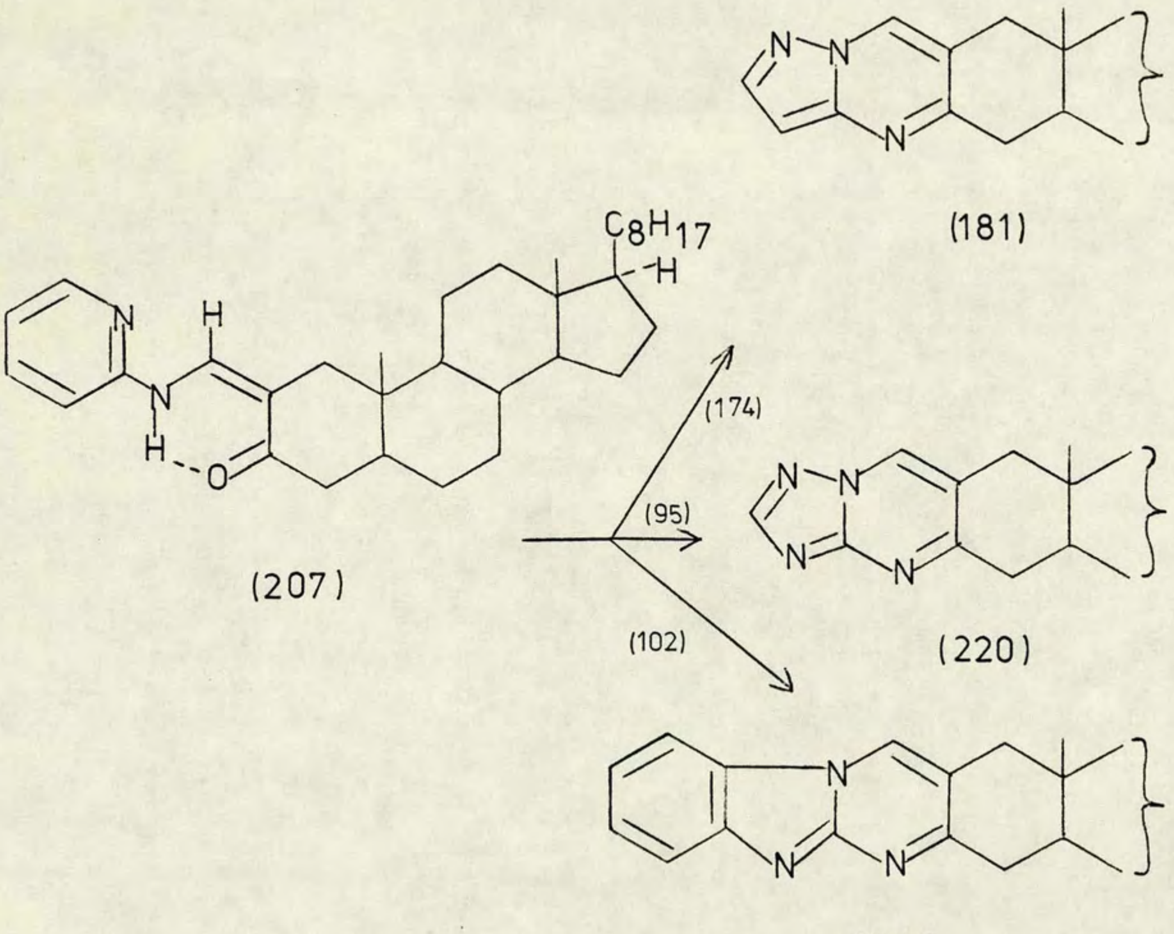


(316)



(154) $R^1 = OH$, $R^2 = CH_3$

(156) $R^1 = C_8H_{17}$, $R^2 = H$

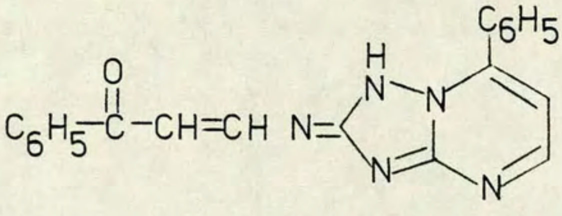


(181)

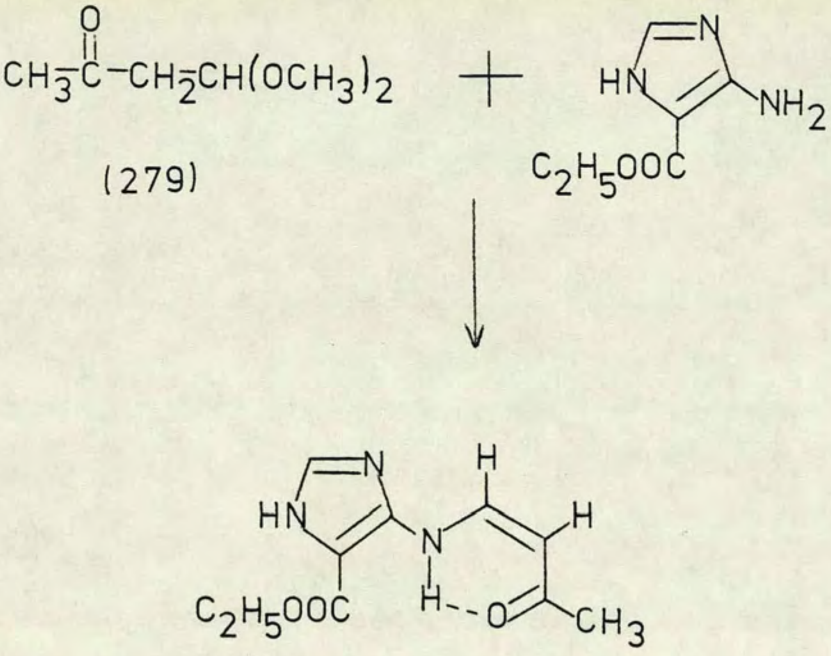
(207)

(220)

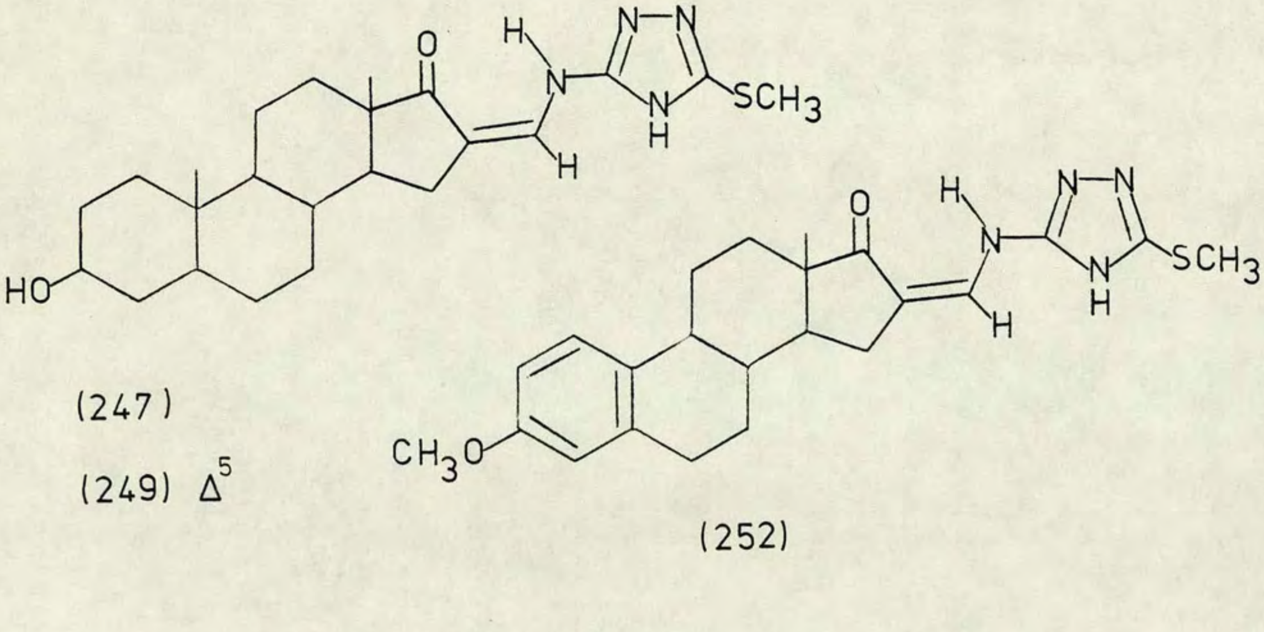
(274)



(317)



(248)



(247)

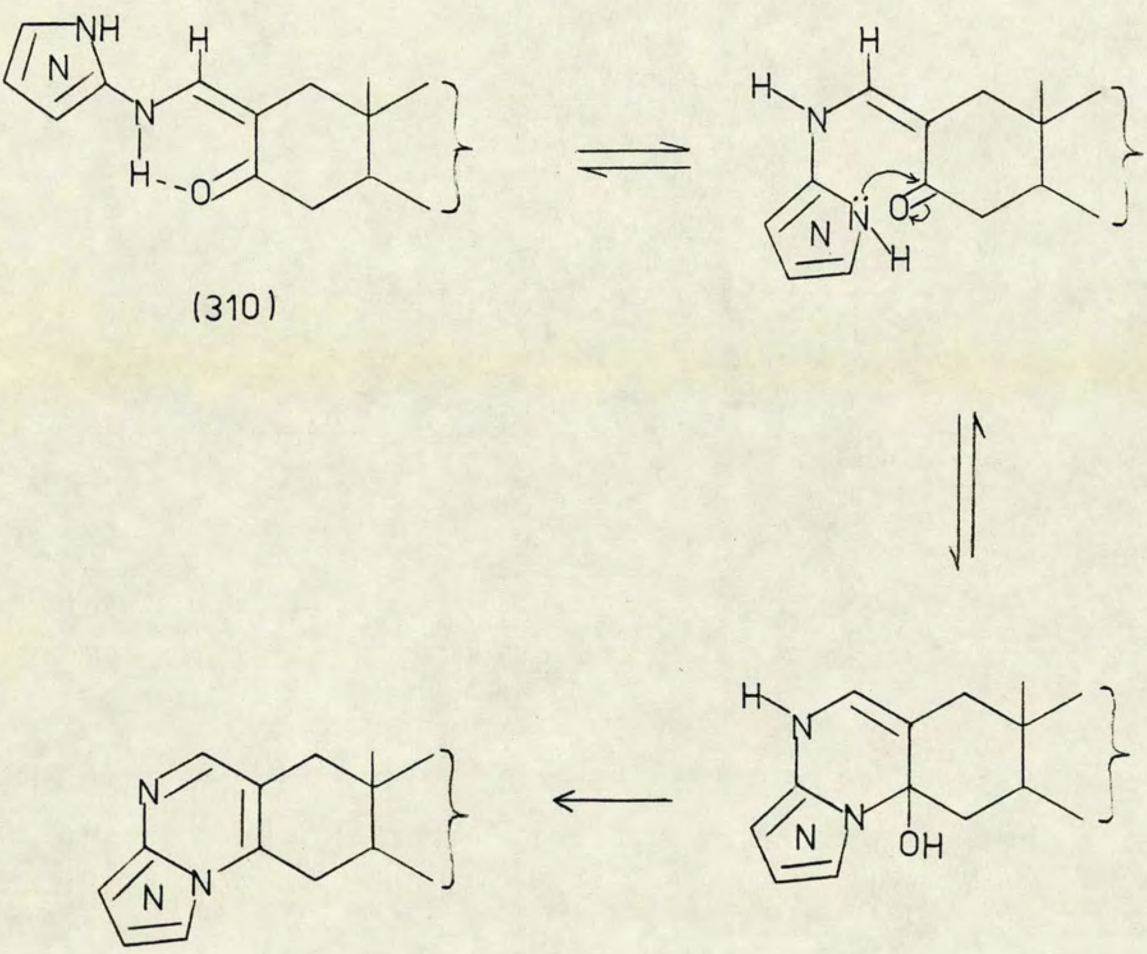
(249) Δ^5

(252)

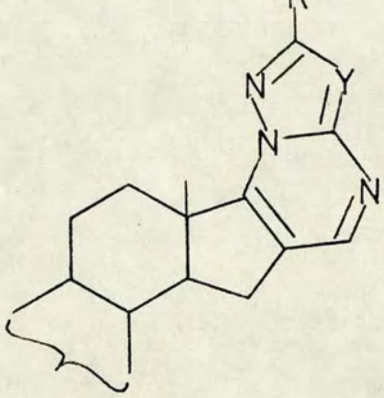
carbon atom of the formyl group is more electropositive. This difference in reactivity reflects the relative number of inductive effects of neighbouring carbon atoms. A possible reason which might be considered to explain this observed order of reactivity is the extra steric hindrance which would be encountered in the formation of an intermediate of type (316) as compared with the intermediates (309) and (311). However, this is not considered to be a very likely explanation since the products (154) and (156) arise from the reaction of 4-amino-1, 2, 4-triazole (83) with 2-hydroxymethylene-3-oxo steroids (108) and (110) respectively, where the relevant tetrahedral intermediates at carbon-3 are seen to be even more sterically demanding. Again, the formation of the linearly fused products, 5α-cholestano[3, 2-f]pyrazolo[1, 5-a]pyrimidine (181), 5α-cholestano[3, 2-f]-s-triazolo[1, 5-a]pyrimidine (220) and 5α-cholestano[3, 2-b]benzimidazo[1, 2-a]-pyrimidine (274) from the condensation of 2(2'-pyridyl-aminomethylene)-5α-cholestan-3-one (207) and the corresponding aminoazoles shows that the aminoazole can indeed react with the 3-carbonyl group.

The formation of the β-ketoanil (310) is in accord with the observations that (i) 2(2-benzoylethylideneamino)-5-phenyl-s-triazolo[1, 5-a]pyrimidine (317) was isolated as a by-product during the reaction of 3, 5-diamino-1, 2, 4-triazole and β, β-dimethoxypropiophenone[62d] and (ii) the reaction of 4-amino-5-carbethoxyimidazole with 4, 4-dimethoxybutan-2-one (279) yields the intermediate (248) which has been isolated and characterised by i. r. and ^{1}H n. m. r. spectroscopy.[130] Finally the condensation of an aminoazole with the aldehydic carbonyl group in steroidal β-ketoaldehydes is justified by the isolation of the β-ketoanils (247), (249) and (252) during the reaction of 16-hydroxymethylene-17-oxo steroids with 3-amino-5-methylthio-s-triazole (224) (section 7).

Scheme 6


(310)

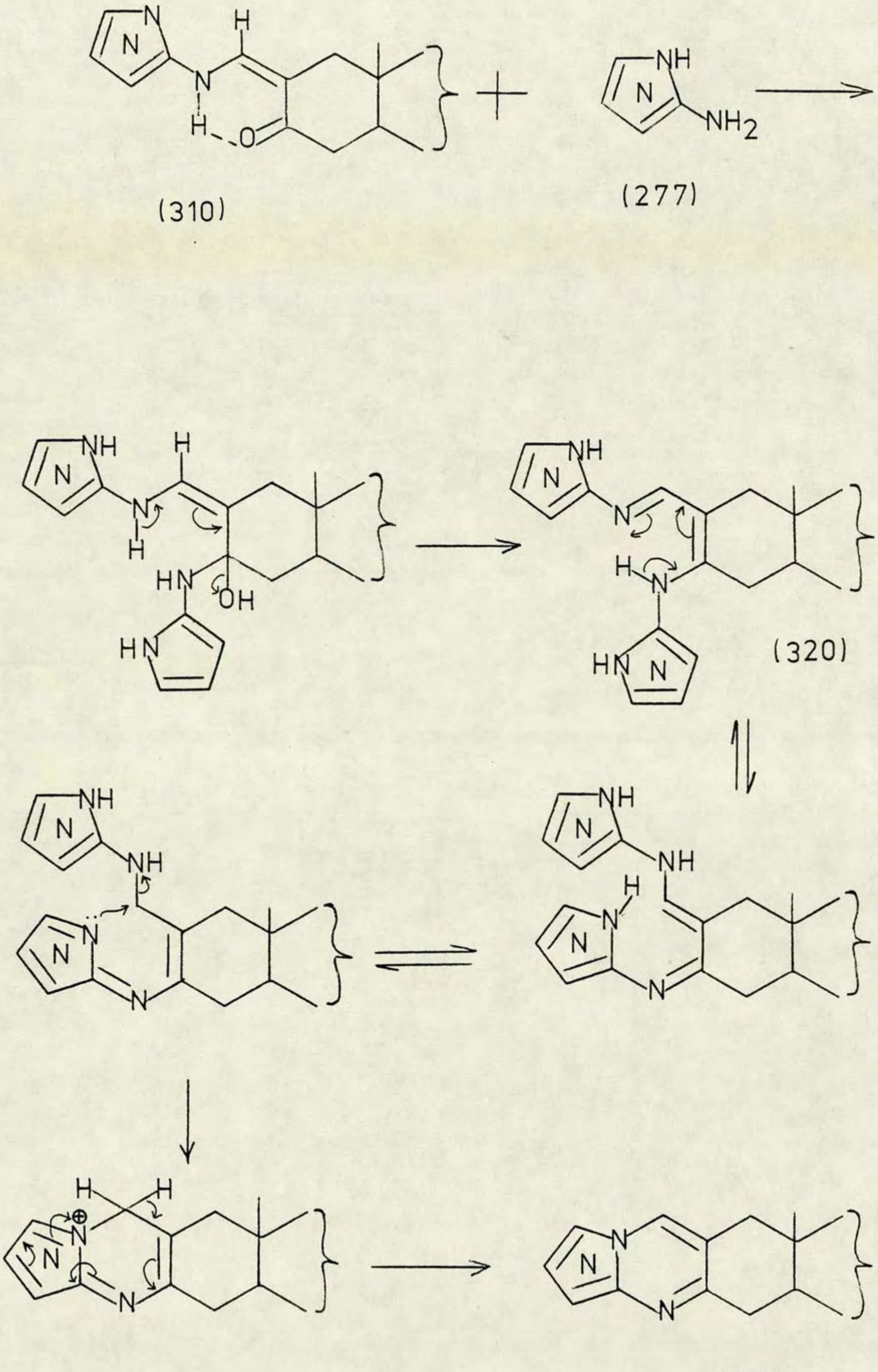
(318)



(319) (a) Y = N, R = H or CH_3 or SCH_3

(b) Y = CH or C–CN, R = H

Scheme 7



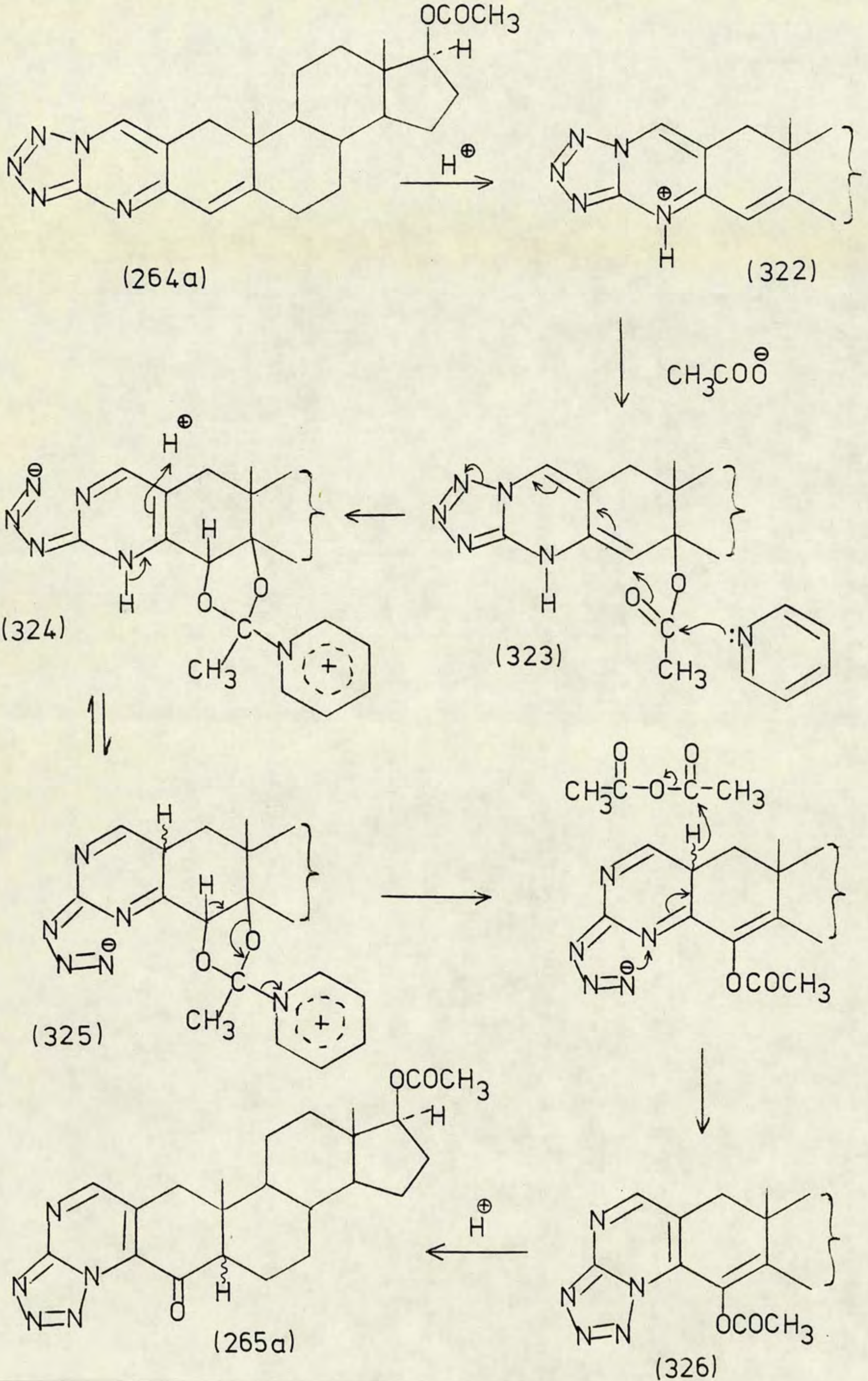
10. 2 Mechanism of cyclization of the 2(2'-azolyl-aminomethylene)-3-oxo system.

It was noted earlier (sections 4-8) that the condensations of aminoazoles with 2-hydroxymethylene-3-oxo steroids lead to linearly and/or angularly fused products. Schemes 6 and 7 show the mechanisms by which 2(2'-azolyl-aminomethylene)-3-oxo steroids may cyclize to afford linearly fused and angularly fused steroids respectively.

In the mechanism shown in scheme 6 rotation about the C-N bond must occur whilst the molecule is in enaminone form (310) so as to bring the azole ring nitrogen into the proximity of the carbonyl group. This involves the destruction of the hydrogen bonded six membered ring with the associated loss of free energy. Cyclization then occurs through the formation of a bond between the azole ring nitrogen and the carbon-3 of the steroid followed by loss of a molecule of water to give the aromatic system (318). The same mechanism can be used to explain the formation of the angularly fused products (319) which are obtained from the reaction of 16-hydroxymethylene-17-oxo steroids and 3-amino-1, 2, 4-triazoles and 3-aminopyrazoles, in these particular syntheses the primary condensation products (247), (249) and (252) are isolated.

Scheme 7 illustrates the mechanism which allows the formation of linearly fused condensation products. A second molecule of the aminoazole (277) is shown to attack the residual 3-carbonyl group to give the bisanil (320) which then spontaneously cyclises with the displacement of an aminoazole molecule to afford the observed linearly fused steroids (321).

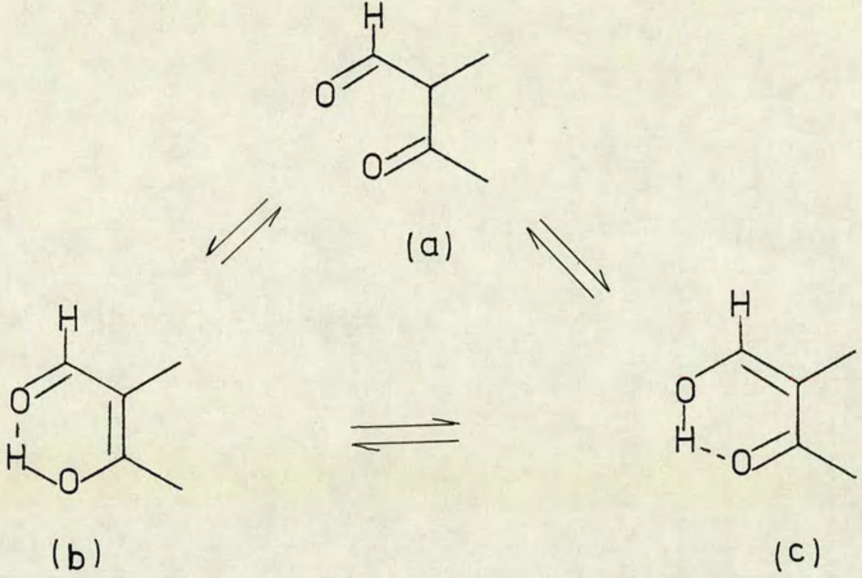
Scheme 8

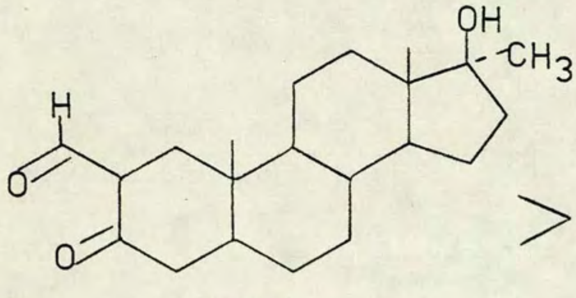

OCOCH$_3$
H
(264a)
H$^\oplus$
(322)
CH$_3$COO$^\ominus$
(323)
(324)
H$^\oplus$
CH$_3$
(325)
CH$_3$C–O–C–CH$_3$
OCOCH$_3$
(326)
H$^\oplus$
(265a)

Support for the intermediate (320) comes from the reaction of 4-amino-1,2,4-triazole (83) with 2-hydroxymethylene-3-oxo steroids (108) and (110) where the bisanils (154) and (156) were isolated as the sole products in high yields (section 4). Again, the overall mechanism shown in scheme 7 is supported by the formation of high yields of linearly fused products (181), (220) and (274) from the reactions of various aminoazoles with the independently prepared enaminone 2(2'-pyridyl-aminomethylene)-5α-cholestan-3-one (207). These syntheses clearly indicate that the amine which first functionalises the formyl carbonyl group becomes the leaving group in the final stage of cyclisation.

10.3 The formation of 4-oxo-17β-acetoxy-5ξ-androst-2-eno[2,3-g]-tetrazolo[1,5-a]pyrimidine (265a).

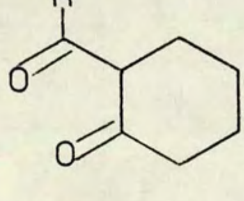
It was noted in section 7 that acetylation of 17β-hydroxyandrost-4-eno[3,2-f]tetrazolo[1,5-a]pyrimidine (263a) using acetic anhydride in pyridine gave 4-oxo-17β-acetoxy-5ξ-androst-2-eno[2,3-g]tetrazolo[1,5-a]-pyrimidine (265a) as the unexpected product along with the normal 17β-acetyl derivative (264a). A possible mechanism for the formation of the compound (265a) is illustrated in scheme 8. The primary acetylation product becomes protonated at the 4'-nitrogen and an acetate ion, which is produced by the reaction of pyridine with acetic anhydride attacks the potential electrophilic centre carbon-5 in the intermediate (322) to give the 5ξ-acetoxy derivative (323). The reaction of pyridine with the intermediate (323) results in fission of the tetrazole ring to give the intermediate (324) which could exist in equilibrium with the tautomeric intermediate (325). Loss of a proton from carbon 4 and a pyridine





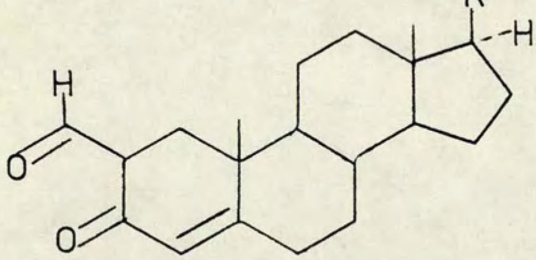
(108)

> 99 % enol ----- 78 % (b), 22 % (c)



(123)

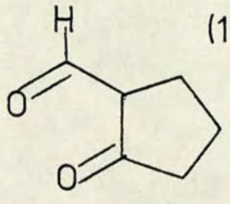
> 99 % enol ---- 76 % (b), 24 % (c)



(4) $R=C_8H_{17}$

(112) $R=OH$

----- 25 % (b), 75 % (c)



(124)

89 % enol ---- 22 % (b), 78 % (c)

11 % keto (a)

molecule followed by recyclisation of the tetrazole ring leads to the enol acetate (326) which in acidic conditions undergoes hydrolysis and rearrangement to afford the product (265a).

It is interesting to note that acetylation of 17β-hydroxyandrost-2,4-dieno[2,3-g]pyrazolo[1,5-a]pyrimidine (191) and 17β-hydroxyandrost-2,4-dieno[2,3-g]-2'-methylthio-s-triazolo[1,5-a]pyrimidine (237) gave only the expected 17β-acetyl derivatives (194) and (239) respectively. These observations indicate that the tetrazolo-azidopyrimidine equilibrium is responsible for the formation of the 4-oxo-steroid (265a).

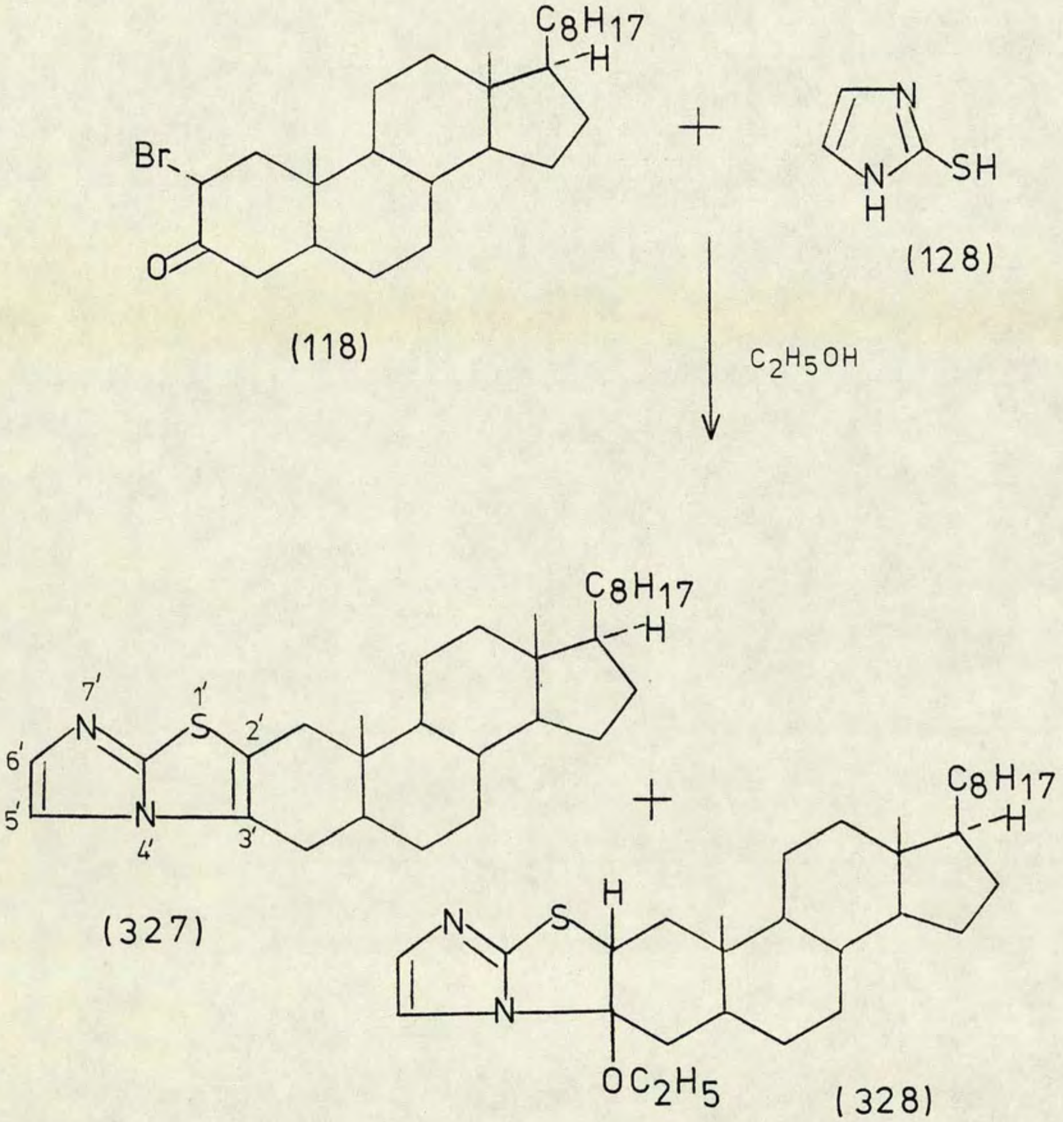
10.4 A correlation between β-dicarbonyl structure and condensation products.

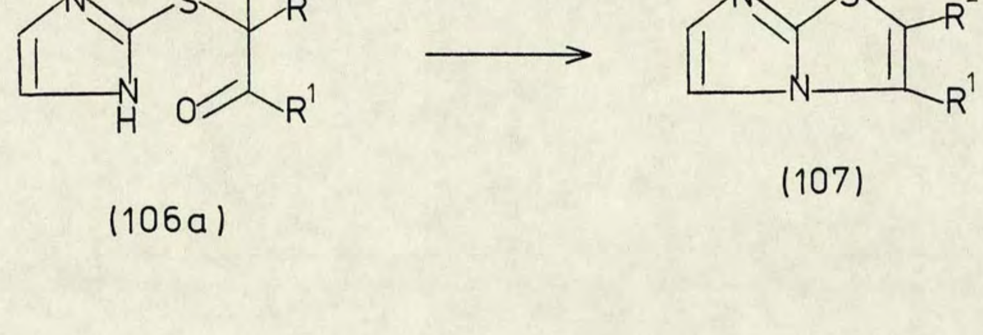
It can be seen by comparing sections 4-8 with section 9 that the reaction of aminoazoles with 2-hydroxymethylene-3-oxo steroids and 2-hydroxymethylenecyclohexanone yields the same type (linear and/or angular) of products whilst the reaction of aminoazoles with 2-hydroxymethylene-Δ^4-3-oxo steroids and 16-hydroxymethylene-17-oxo steroids proceeds in a manner analagous to the condensation of aminoazoles with 2-hydroxymethylenecyclopentanone. This correlation can best be explained as follows.

It has been shown[155] that the direction of enolisation of cyclic β-ketoaldehydes is strongly dependent upon structure and the trends may be rationalised in terms of the strain in double bonds (π strain). The application by Bhacca and Williams[152] of the method devised by Gabrish[155] to the ^{1}H n. m. r. spectrum of 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108), determined in deuterated chloroform, showed that the steroid (108) is greater than 99% enolised and exists as a mixture of 22% hydroxymethylene-ketone (c) and 78% formyl-enol (b). This is consistent with the observation that tautomers with double bonds in six membered rings are, in general, favoured in comparison with those with semicyclic double bonds.[156] Similarly 2-formylcyclohexanone has been shown[157] to exist to the extent of more than 99% in the enol form, 24% hydroxymethylene-ketone (c) and 76% formyl-enol (b).

2-Formylcyclopentanone (124) has likewise been shown[157] to be only 89% enolised, in the proportion 22% formyl-enol (b) and 78% hydroxymethylene-ketone (c). The application by Huynh and Julla[158] of the method devised by Gabrish[155] to the ^{1}H n. m. r. spectrum of 2-hydroxymethylenecholest-4-en-3-one (112), determined in deuterated chloroform solution, showed that the steroid existed in solution as a mixture of 75% hydroxymethylene-ketone (c) and 25% formyl-enol (b). The chemical shifts for the "aldehydic" protons in 2-hydroxymethylenecholest-4-en-3-one (112) and 17β-hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4) are identical and thus it is reasonable to assume that the equilibrium between the hydroxymethylene-ketone and formyl-enol tautomers is the same in both steroids. The equilibrium between the two tautomeric forms in 17β-hydroxy-2-hydroxymethyleneandrost-4-en-3-one (4) is thus the same as that observed for the simple formyl ketone (124) whereas a converse ratio is observed in the equilibrium between the tautomers of 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (108). This difference is due to the stability conferred on the hydroxymethylene-ketone tautomer by the Δ^4 double bond.

Thus it can be seen that a similarity in the initial composition of the mixture of the tautomeric forms (b and c) at equilibrium correlates well with the observed similarities in the type of products obtained by the condensation of an aminoazole with a β-dicarbonyl compound. It is not however possible to predict the structure (linear or angular) of the specific condensation product from the initial composition of the tautomeric forms of the β-dicarbonyl compound since the final outcome of any particular condensation seems to be dependent upon the actual aminoazole employed.


C8H17
H
Br
O
(118)
N
SH
H
(128)
C2H5OH
C8H17
H
7′
N
S
1′
2′
6′
5′
N
4′
3′
(327)
C8H17
H
N
S
H
N
OC2H5
(328)


N
S
H
R2
N
H
O
R1
(106a)
N
S
R2
N
R1
(107)

11 The reaction of steroidal α-bromo ketones with 2-mercapto imidazoles and 3-mercapto-1, 2, 4-triazoles.

11. 1 The reaction of 2α-bromo-5α-cholestan-3-one (118) with 2-mercapto imidazole (128).

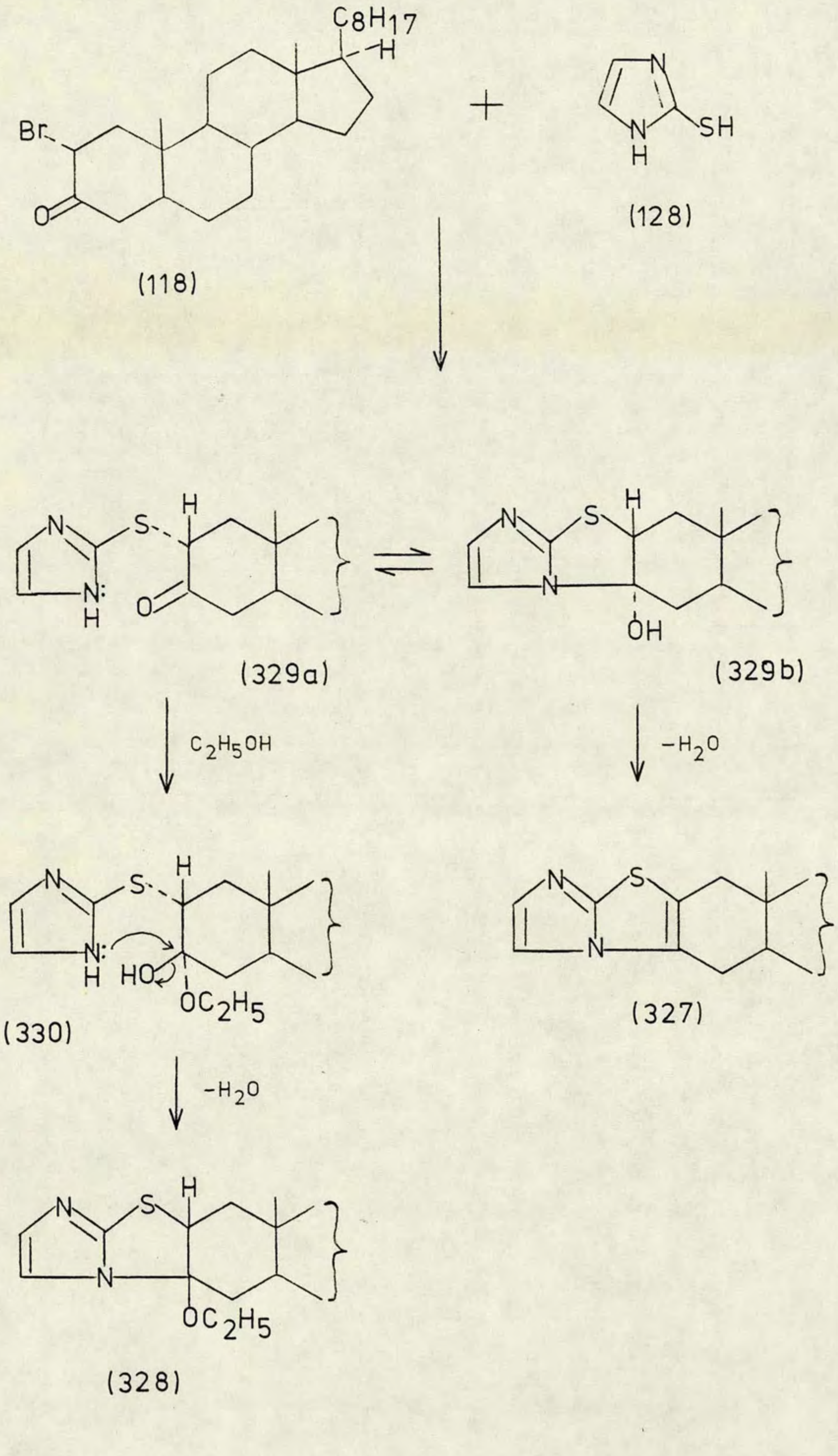
A solution of 2α-bromo-5α-cholestan-3-one (118) and 2-mercaptoimidazole (128) was refluxed in absolute alcohol for 24 h. The reaction mixture was concentrated under vacuo, diluted with water and neutralised with 28% ammonium hydroxide solution. The white precipitates formed were filtered, washed with water and dried. Alumina chromatography of this white solid gave two products, (327), m. p. 205-207°, in 26% yield and (328), m. p. 150-151°, in 35% yield.

Mass spectrometry and elemental analysis of the first product, m. p. 205-207° showed that it had a molecular formula of $C_{30}H_{46}N_2S$. The i. r. spectrum exhibited absorptions at 1465, 1440 and 1380 cm^{-1} whilst the ^1H n. m. r. spectrum showed a singlet at δ 7. 25 corresponding to two protons apart from the signals for the methyl groups.

Mass spectrometry and elemental analysis of the second product, m. p. 150-151° indicated that it had a molecular formula of $C_{32}H_{52}N_2OS$. The i. r. spectrum showed absorptions at 1495, 1460, 1445, 1365, 1065 and 905 cm^{-1} whilst the ^1H n. m. r. spectrum exhibited a singlet at δ 7. 05 (2H), a doublet of doublets at δ 4. 02 (1H) and a quartet at δ 3. 35 (2H), apart from the signals for the methyl groups.

11. 2 Discussion

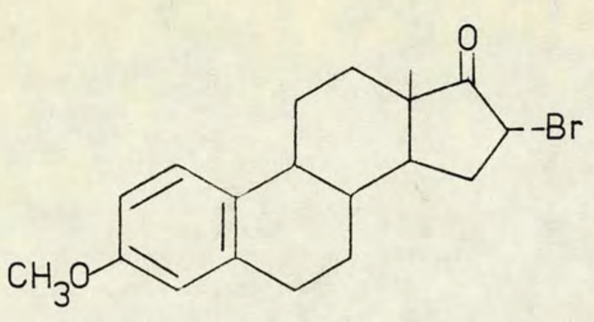
The reaction of 2-mercaptoimidazoles with α-halo ketones as mentioned in section 1 (page 16) affords the S-alkylated products (106a)


C8H17
H
Br
O
N
N
H
SH
(118)
(128)
N
S
H
N:
H
O
(329a)
N
S
H
N
OH
(329b)
C2H5OH
-H2O
N
S
H
N:
H
HO
OC2H5
(330)
N
S
N
(327)
-H2O
N
S
H
N
OC2H5
(328)

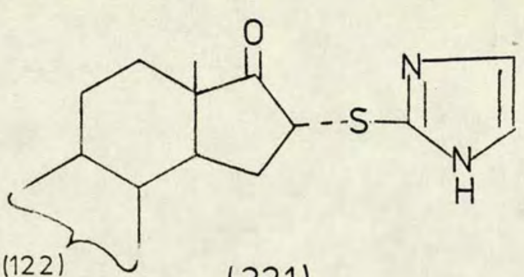
which on dehydration give imidazo[2, 1-b]thiazoles (107). Since the i. r. spectrum of the first steroidal condensation product, m. p. 205-207°, shows no carbonyl absorption, the product was assigned structure, 5α-cholest-2-eno[2, 3-b]imidazo[2, 1-b]thiazole (327), consistent with the molecular formula $C_{30}H_{46}N_2S$. In the ^{1}H n. m. r. spectrum, both the protons 5'-H and 6'-H were found to have the same chemical shift, δ 7.25.

The molecular formula, $C_{32}H_{52}N_2OS$ of the second product, m. p. 150-151° indicates that it differs from the molecular formula of 5α-cholest-2-eno[2, 3-b]imidazo[2, 1-b]thiazole (327) by C_2H_6O. It appears that this steroid has been formed by the reaction of ethanol with the precursor (329a) of the first product (327). The possibility of a hydroxyl group or a carbonyl group in the second product is ruled out since, the i. r. spectrum exhibits no absorption above 1495 cm^{-1}. The above evidence suggests that the steroid is 5α-cholestano[2, 3-b]-3β-ethoxy-2', 3'-dihydroimidazo[2, 1-b]-thiazole (328). This structure is supported by ^{1}H n. m. r. spectrum which exhibits a singlet at δ 7. 05 (5'-H and 6'-H), a doublet of doublets at δ 4. 02 (2'-H) and a quartet at δ 3. 35 ($3'$-O-C$\underline{H}_2$-CH_3). The triplet corresponding to the methyl protons of ethoxy group overlaps with the signals of the angular and side chain methyl groups of the steroid.

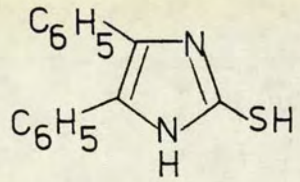
It is known from the general reactions of α-bromo ketones with 2-mercaptoimidazole that the initial product from the reaction of the steroid (118) with this reagent (128) will first be the S-alkylated product which may exist either in the acyclic form (329a) or the cyclic form (329b). Dehydration of the intermediate (329b) leads to the fully aromatic system (327). However, if the intermediate (329a) reacts first with ethanol present in the reaction mixture, then hemi-ketal (330) results. Ring closure finally results in the product (328) where the probable stereiochemistry



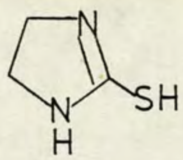
(122)



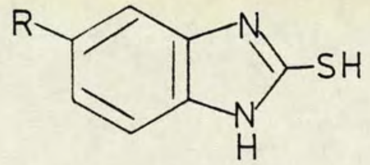
(331)



(129)

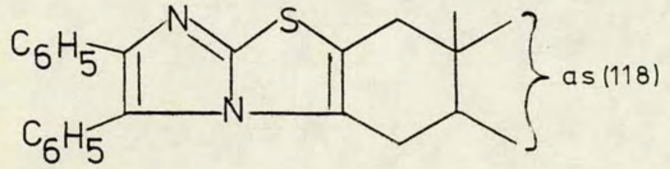


(332)



(130) $R = CH_3$

(333) $R = H$



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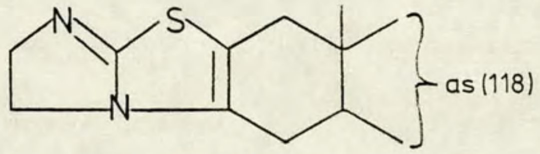

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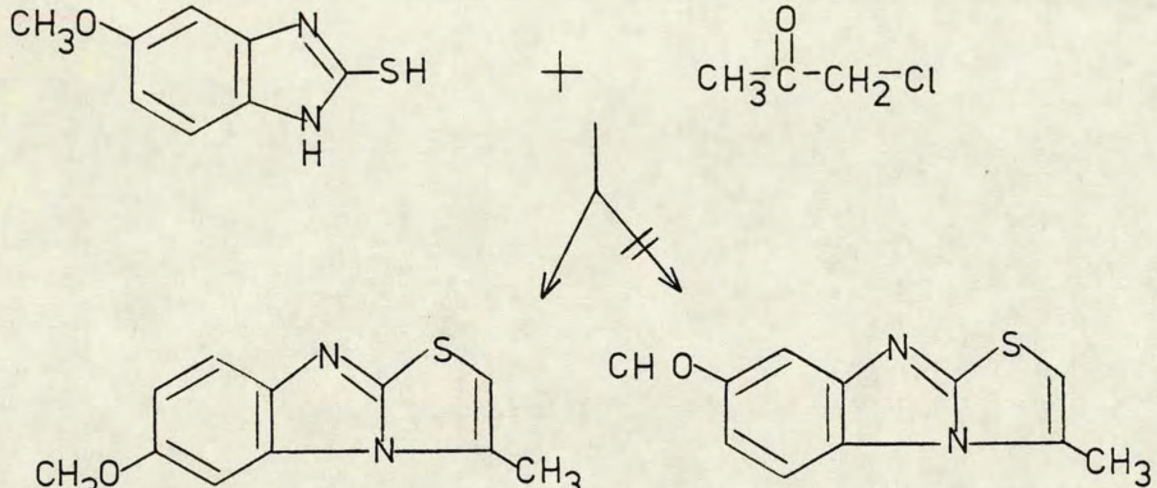
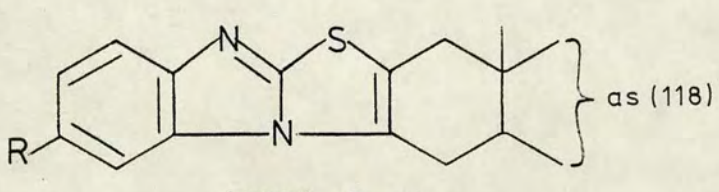


(337)



(336) $R = H$

(338) $R = CH_3$

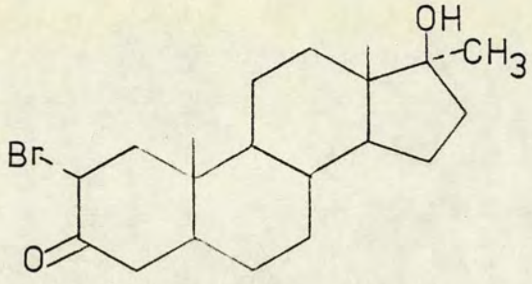
of the ethoxy group precludes its elimination.

The reaction of 2-mercaptoimidazole (128) with 16α-bromo-3-methoxyoestra-1,3,5(10)-trien-17-one (122) affords 16α-(imidazo-2-thiol)-3-methoxyoestra-1,3,5(10)-trien-17-one (331). The structure (331) is confirmed by the i.r. spectrum which exhibits absorptions at 1720 cm^{-1} (C=O) and 3300 cm^{-1} (NH) and the ^{1}H n.m.r. spectrum which shows signals at δ 0.87 (s, 18-CH_3), δ 3.75 (s, 3-OCH_3), δ 6.66-7.20 (m, 1-H, 2-H and 4-H) and δ 7.00 (s, 4'-H and 5'-H) and δ 7.70 (bs, N$\underline{H}$). Intermediates of type (331) as previously remarked in the introduction (page 16) have been isolated and characterised and are shown to exist in acyclic and cyclic forms.

Under analogous conditions, the condensation of 2α-bromo-5α-cholestan-3-one (118) with 2-mercapto-4,5-diphenylimidazole (129), 2-mercapto-4,5-dihydroimidazole (332) and 2-mercaptobenzimidazole (333) gave 5α-cholest-2-eno[3,2-b]-5',6'-diphenylimidazo[2,1-b]thiazole (334) 5α-cholest-2-eno[2,3-b]-5',6'-dihydroimidazo[2,1-b]thiazole (335) and 5α-cholest-2-eno[2,3-b]thiazolo[3,2-a]benzimidazole (336) respectively.

Mohan and Pajari[92] have assigned structure (337), on the basis of ^{1}H n.m.r. spectroscopy, for the product obtained by the reaction of 2-mercapto-5-methoxybenzimidazole and chloroacetone. Since the methoxy group (in compound 337) and the methyl group (in compound 338) are both electron donating groups, the product obtained by the condensation of 2α-bromo-5α-cholestan-3-one (118) and 2-mercapto-5-methylbenzimidazole (130) is by analogy assigned structure (338).

Similarly the reaction of 2α-bromo-17β-hydroxy-17α-methyl-5α-androstan-3-one (117) with 2-mercapto-4,5-diphenylimidazole (129), 2-



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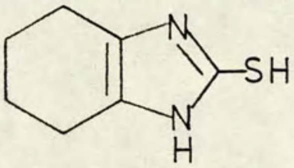

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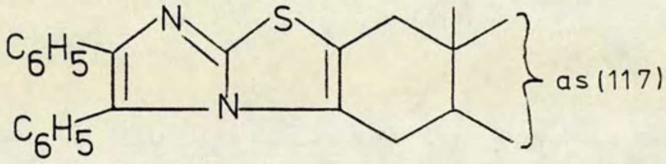

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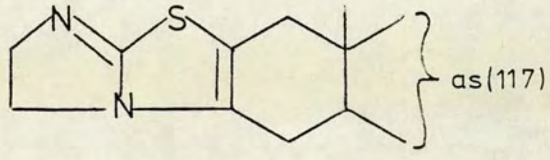

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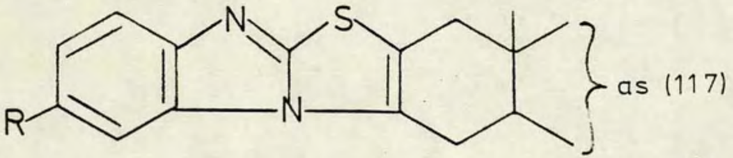
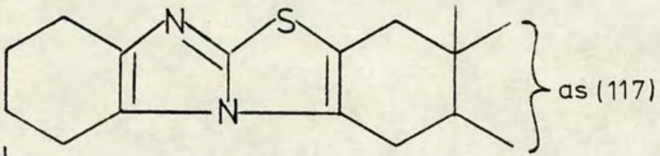


(342) R=H

(343) R=CH_3



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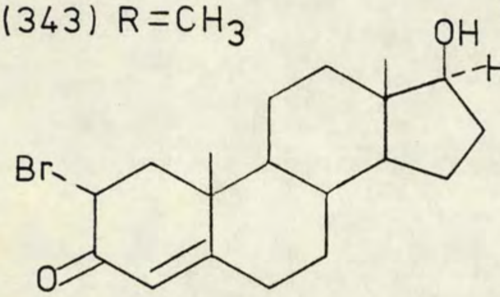

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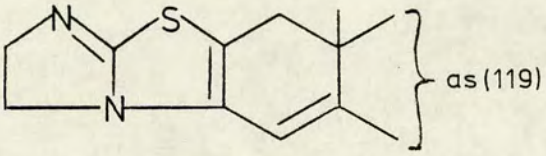

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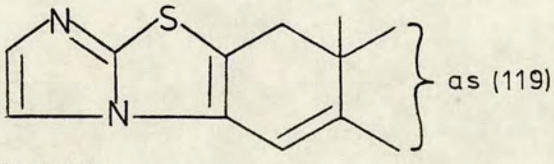

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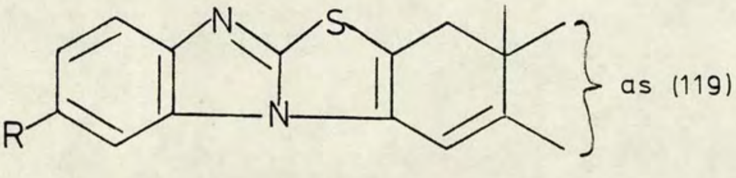


(346) R=H

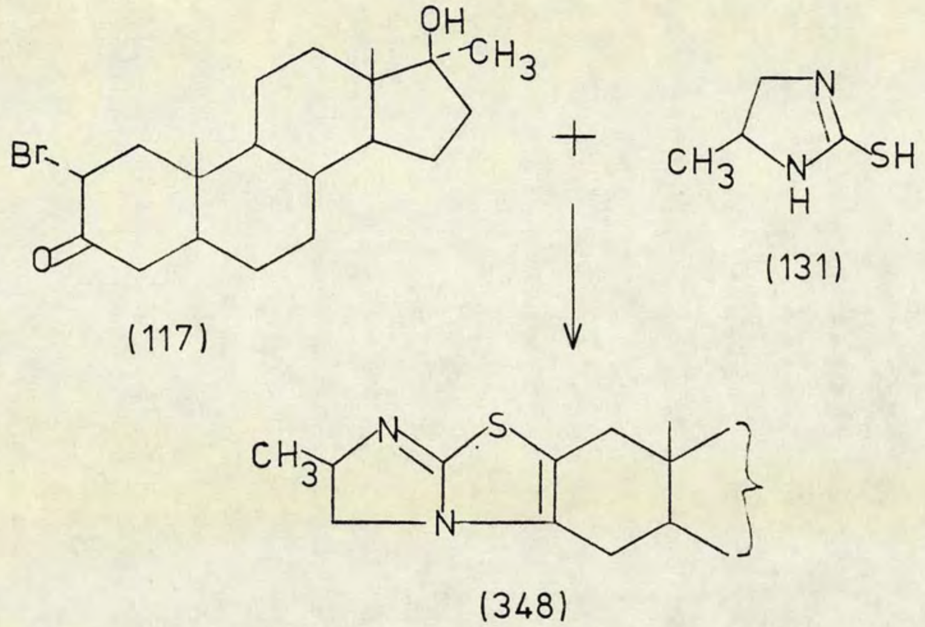
(347) R=CH_3

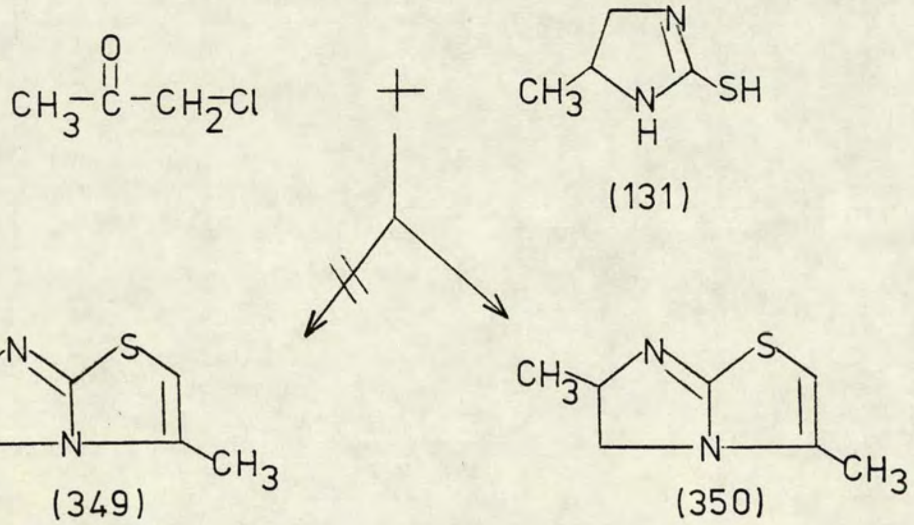
mercapto-4, 5-dihydroimidazole (332), 4, 5, 6, 7-tetrahydrobenzimidazole (132), 2-mercaptobenzimidazole (333) and 2-mercapto-5-methylbenzimidazole (130) gave 17β-hydroxy-17α-methyl-5α-androst-2-eno[2, 3-b]-5', 6'-diphenylimidazo[2, 1-b]thiazole (339), 17β-hydroxy-17α-methyl-5α-androst-2-eno[2, 3-b]-5', 6'-dihydroimidazo[2, 1-b]thiazole (340), 17β-hydroxy-17α-methyl-5α-androst-2-eno[2, 3-b]-5, 6, 7, 8-tetrahydrothiazolo-[3, 2-a]benzimidazole (341), 17β-hydroxy-17α-methyl-5α-androst-2-eno-[2, 3-b]thiazolo[3, 2-a]benzimidazole (342) and 17β-hydroxy-17α-methyl-5α-androst-2-eno[2, 3-b]-6'-methylthiazolo[3, 2-a]benzimidazole (343) respectively.

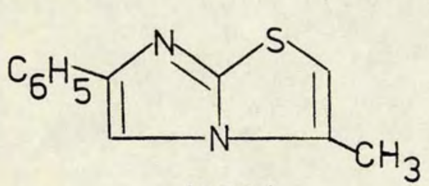
The reaction of 2-mercaptoimidazoles with 2α-bromo-17β-hydroxy-androst-4-en-3-one (119) has also been studied. However, the products were obtained in relatively poor yield. Thus, the condensation of 2α-bromo-17β-hydroxyandrost-4-en-3-one (119) with 2-mercaptoimidazole (128), 2-mercapto-4, 5-dihydroimidazole (332), 2-mercaptobenzimidazole (333) and 2-mercapto-5-methylbenzimidazole (130) afforded 17β-hydroxy-androst-2, 4-dieno[2, 3-b]imidazo[2, 1-b]thiazole (344), 17β-hydroxyandrost-2, 4-dieno[2, 3-b]-5', 6'-dihydroimidazo[2, 1-b]thiazole (345), 17β-hydroxy-androst-2, 4-dieno[2, 3-b]thiazolo[3, 2-a]benzimidazole (346) and 17β-hydroxy-androst-2, 4-dieno[2, 3-b]-6'-methylthiazolo[3, 2-a]benzimidazole (347) respectively.

11. 3 The reaction of 2α-bromo-17β-hydroxy-17α-methyl-5α-androstan-3-one (117) with 2-mercapto-4-methyl-4, 5-dihydroimidazole (131).

A solution of 2α-bromo-17β-hydroxy-17α-methyl-5α-androstan-3-one (117) and 2-mercapto-4-methyl-4, 5-dihydroimidazole (131) in absolute






(352)

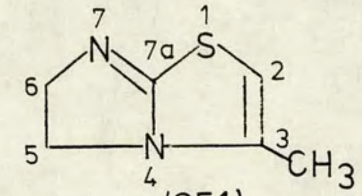

(351)

Table 13. ^{13}C-Chemical shifts of 5,6 dihydroimidazo[2,1-b]thiazoles (p.p.m.)

Compound	2-C	3-C	5-C	6-C	7a-C	3-CH_3	5-CH_3
(350)	94·13	132·06	52·33	68·22	168·31	13·78	22·44
(351)	92·79	130·76	44·07	58·84	168·06	12·25	–

alcohol was refluxed for 24 h. The reaction mixture was concentrated under vacuo, diluted with water and neutralised with 28% ammonium hydroxide. The white solid which precipitated was filtered and dried and recrystallised from ethanol to give white fluffy crystals (348), m. p. 220-222° in 42% yield.

Mass spectrometry and elemental analysis of the product indicated that it had a molecular formula of $C_{24}H_{36}N_2OS$. The i. r. spectrum exhibited absorptions at 3570, 1635, 1555, 1435 cm^{-1} whilst the ^1H n. m. r. spectrum showed multiplets at δ 4. 05 (1H), δ 3. 80 (1H), δ 3. 18 (1H) and a doublet at δ 1. 35 (3H), apart from the signals for the 17-, 18- and 19-methyl groups.

11. 4 Discussion

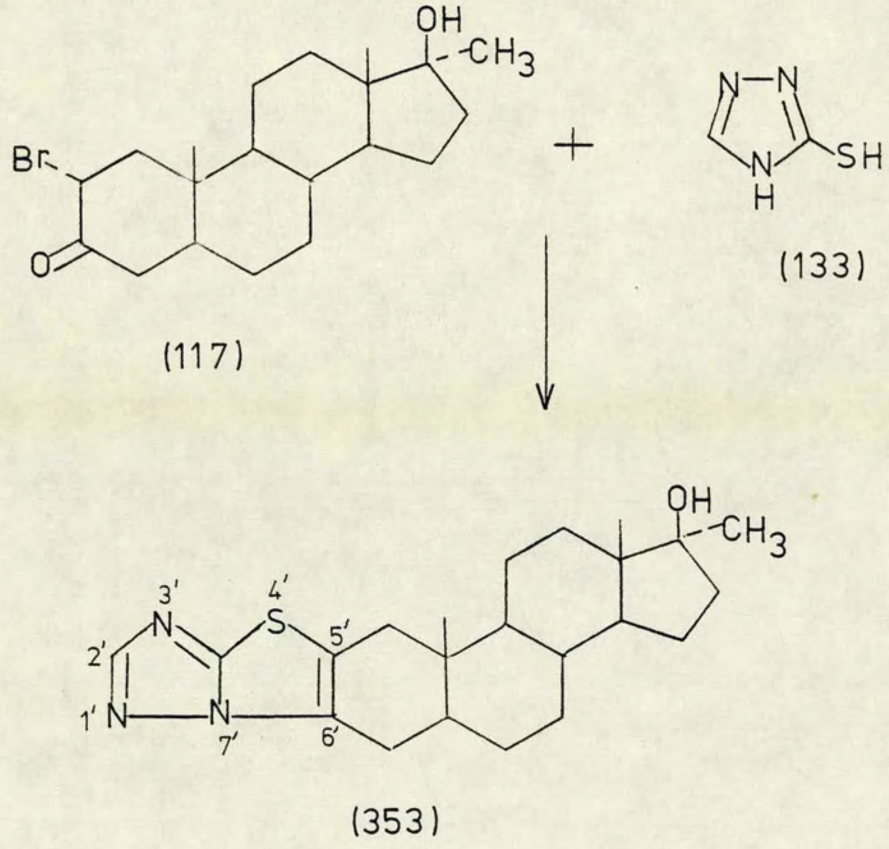
To establish the structure of the steroidal condensation product, the reaction of 2-mercapto-4-methyl-4, 5-dihydroimidazole (131) with chloroacetone,[159] which can theoretically give two products (349) and (350), was reinvestigated. ^{13}C N. m.r. spectroscopy shows that the product obtained by the above reaction has structure (350). The ^{13}C-chemical shifts of the various carbons in the compounds (350) and (351) are given in Table 13. The compound (351) was prepared by the reaction of chloroacetone with 2-mercapto-4, 5-dihydroimidazole (332).

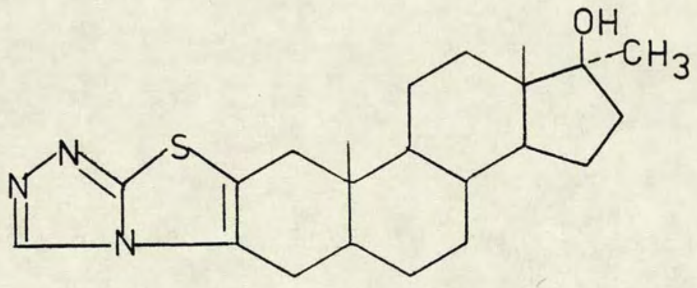
In the ^{13}C n. m. r. spin-coupled spectrum of the compound (351), the carbons 3 and 7a are easily distinguished from the other carbons as they remain singlets. Since the bridgehead carbon is expected to have the largest relaxation time (lowest intensity peak), the down field signal at 168. 06 p. p. m. was assigned to 7a-C. The other down field signal at

130.76 p.p.m. was therefore assigned to 3-C. The signal at 92.79 p.p.m. was attributed to 2-C without ambiguity as 2-C appears as a doublet in the spin-coupled spectrum in contrast to 5-C and 6-C which appear as triplets. Out of the remaining two carbon resonances, the low field signal (58.84 p.p.m.) was assigned to 6-C whilst the high field signal (44.07 p.p.m.) was assigned to 5-C by analogy with the observation[136] that in nitrogen heterocyclic compounds, the carbons bonded to ring nitrogens are deshielded and occur further downfield compared with the carbons bonded to bridgehead nitrogens.

In the ^{13}C n.m.r. spectrum of the compound (350), the chemical shifts of 2-C, 3-C and 7a-C are easily assigned by comparing its spectrum with that of the compound (351). It is known[160] that replacement of a proton by a methyl group on a sp^3 carbon causes the latter to become more deshielded by 6-10 p.p.m. Consequently the shift of 58.84 p.p.m. in the compound (351) to 68.22 p.p.m. in its 6-methyl derivative (350) identifies this signal as arising from the 6-carbon. However, it is noticed that the chemical shift of the 5-C is also shifted down field by 8.26 p.p.m. If the compound, however, had structure (349), this would mean that the carbons 5-C and 6-C would have chemical shifts of 68.22 p.p.m. and 52.33 p.p.m. respectively. This possibility is ruled out since by substituting a hydrogen at 5-C in structure (351) by a methyl group, the chemical shift of 5-C could not be expected to increase by 24.15 p.p.m. nor could the chemical shift of 6-C decrease by 6.51 p.p.m.

Further confirmation of structure (350) is based on an analogy with the work of Kochergin and Shchukin[90a] on the synthesis of 3-methyl-6-phenylimidazo[2,1-b]thiazole (352) in which the phenyl group at position 6





(354)

was established by an unambiguous synthesis.

By analogy with the structure (350), the product obtained by the condensation of 2-mercapto-4-methyl-4,5-dihydroimidazole (131) and 2α-bromo-17β-hydroxy-17α-methyl-5α-androstan-3-one (117) is assigned structure (348). In the ^{1}H n.m.r. spectrum, the multiplet at δ 4.05 was assigned to 6'-H, the two multiplets at δ 3.18 and 3.80 were assigned to two protons at 5'-C and the doublet at δ 1.35 was attributed to 6'-methyl protons.

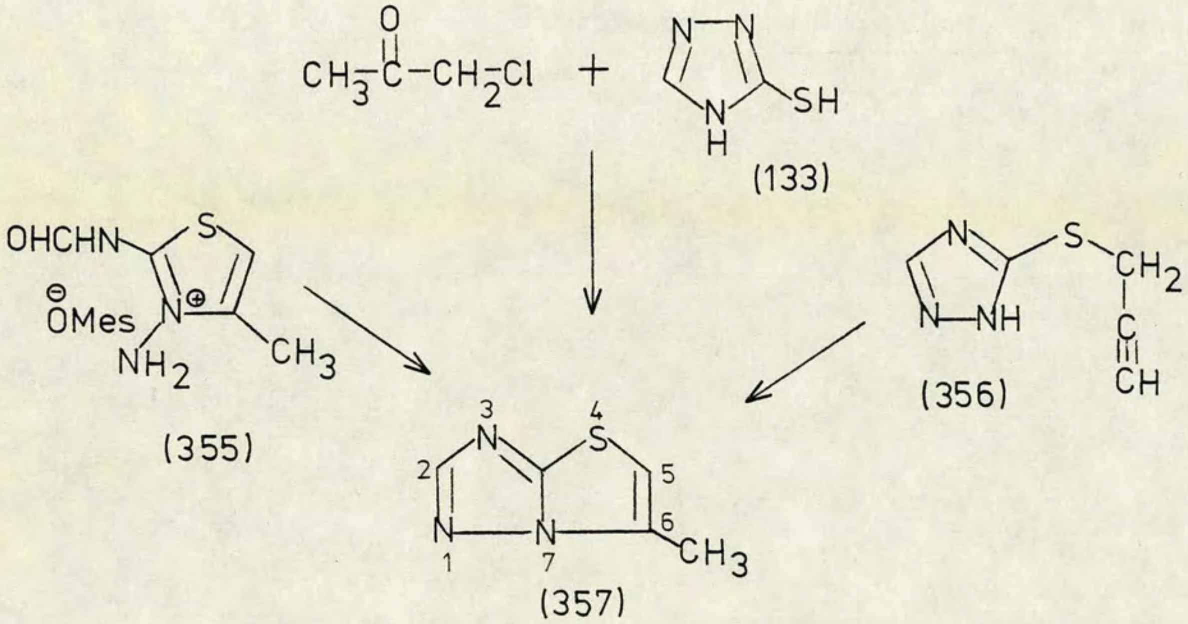
11.5 The reaction of 2α-bromo-17β-hydroxy-17α-methyl-5α-androstan-3-one (117) with 3-mercapto-1,2,4-triazole (133).

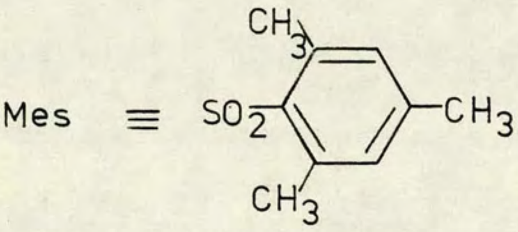
A solution of 2α-bromo-17β-hydroxy-17α-methyl-5α-androstan-3-one (117) and 3-mercapto-1,2,4-triazole (133) in absolute alcohol was refluxed for 24 h. The reaction mixture was concentrated under vacuo, diluted with water and neutrallised with 28% ammonium hydroxide. The white solid formed was filtered, dried and chromatographed over alumina. Elution with chloroform followed by recrystallisation of the eluate from ethanol gave white crystals (353), m.p. 115-118° in 23% yield.

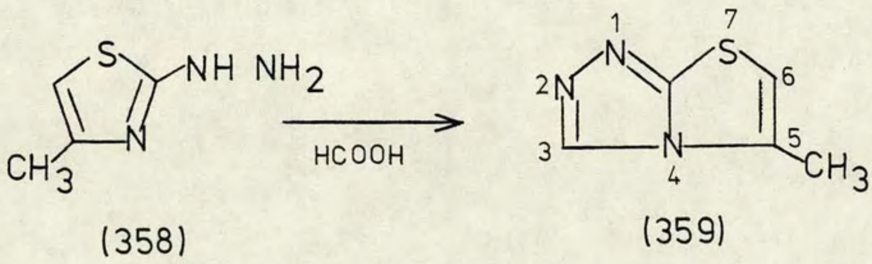
Mass spectrometry and elemental analysis showed that the product had a molecular formula of $C_{22}H_{31}N_3OS$. The i.r. spectrum exhibited absorptions at 3590, 1465, 1440, 1420 and 1355 cm^{-1} whilst the ^{1}H n.m.r. spectrum showed a singlet at δ 8.07 apart from the signals for the 17-, 18- and 19-methyl protons.

11.6 Discussion

The reaction of 3-mercapto-1,2,4-triazole (133) with an α-halo


CH3-C(O)-CH2Cl
+
SH
(133)
OHCHN
S
⊖OMes
N⊕
NH2
CH3
(355)
S
CH2
C
CH
N-NH
(356)
3
4
2
5
1
7
6
CH3
(357)

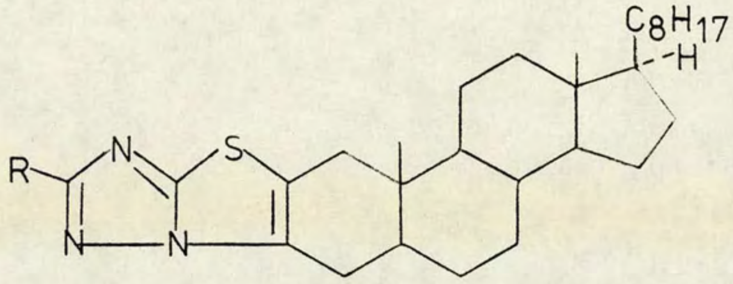

Mes ≡
SO2
CH3
CH3
CH3


S
NH NH2
N
CH3
(358)
HCOOH
1
7
2
6
3
5
4
CH3
(359)

ketone can theoretically lead to two products depending upon the mode of cyclisation. Therefore two structures (353) and (354) both consistent with the molecular formula $C_{22}H_{31}N_3OS$ were proposed. The i. r. spectrum is not of much help in distinguishing the two structures.

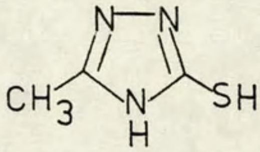
6-Methylthiazolo[3, 2-b]-s-triazole (357) has been prepared by the reaction of 3-mercapto-1, 2, 4-triazole (133) and chloroacetone[161] and by the cyclisation 3-(2-propynylthio)-1, 2, 4-triazole (356) with sodium ethoxide.[162] However, the structure of the compound (357) was assigned without ambiguity by Tamura and co-workers,[163] who prepared this compound in 90% yield by dehydrocyclisation with polyphosphoric acid of 3-amino-2-formamido-4-methylthiazolium mesitylenesulphonate (355) which in turn was readily obtained by the reaction of 2-formamidothiazole with O-mesitylenesulphonylhydroxylamine. The analogous isomer, 5-methylthiazolo[2, 3-c]-s-triazole (359) has been obtained by the reaction of 2-hydrazino-4-methylthiazole with formic acid.[161] Further, the two isomeric compounds (357) and (359) are distinguished by ^{1}H n. m. r. spectroscopy. The triazole proton 3-H in 5-methylthiazolo[2, 3-c]-s-triazole (359) is deshielded and occurs at a lower field (δ 8. 60)[161] in contrast to the triazole proton 2-H in 6-methylthiazolo-[3, 2-b]-s-triazole (357) which occurs at δ 8. 13.[163]

Thus by analogy with the formation of 6-methylthiazolo[3, 2-b]-s-triazole (357) by the reaction of chloroacetone with the thiol (133), the product obtained by the condensation of 2α-bromo-17β-hydroxy-17α-methyl-5α-androstan-3-one (117) and 3-mercapto-1, 2, 4-triazole (133) is assigned structure (353). This structure is supported by the ^{1}H n. m.r. spectrum in which the chemical shift (δ 8. 07) of the triazole proton correlates well with the chemical shift of 6-H (δ 8. 13) in 6-methylthiazolo[3, 2-b]-s-triazole (357).

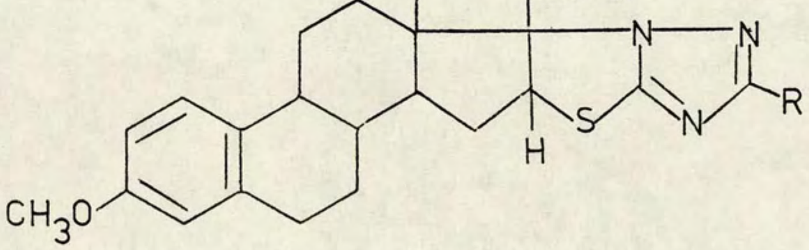


(360) R = H

(361) R = CH_3



(134)



(362) R = H

(363) R = CH_3

Similarly the reaction of 2α-bromo-5α-cholestan-3-one (118) with 3-mercapto-1, 2, 4-triazole (133) and 3-mercapto-5-methyl-1, 2, 4-triazole (134) gave 5α-cholest-2-eno[2, 3-f]thiazolo[3, 2-b]-s-triazole (360) and 5α-cholest-2-eno[2, 3-f]-2'-methylthiazolo[3, 2-b]-s-triazole (361) respectively. However, under analogous conditions the reaction of 16-α-bromo-3-methoxyoestra-1, 3, 5(10)trien-17-one (122) with 3-mercapto-1, 2, 4-triazole (133) and its 5-methyl derivative (134) gave only 3-methoxyoestra-1, 3, 5(10)trieno[16, 17-f]-17β-ethoxy-5', 6'-dihydrothiazolo[3, 2-b]-s-triazole (362) and 3-methoxyoestra-1, 3, 5(10)trieno[16, 17-f]-17β-ethoxy-2'-methyl-5', 6'-dihydrothiazolo[3, 2-b]-s-triazole (363) respectively. The structures of the products were identified by ^{1}H n. m. r. spectroscopy.

11.7 Experimental

General procedure for the condensation reactions

A solution of the steroidal α-bromo ketone (1×10^{-5} mole) and mercaptoazole (1.5×10^{-5} mole) in absolute alcohol (40 ml) was refluxed for 24 h. The reaction mixture was concentrated under vacuo, diluted with water and neutralised with 28% ammonium hydroxide. The white solid formed was filtered, washed with water and dried. The crude product was either directly recrystallised from a suitable solvent or chromatographed over alumina (40 g) before recrystallisation.

11.7.i 5α-Cholest-2-eno[2, 3-b]imidazo[2, 1-b]thiazole (327) and 5α-cholestano[2, 3-b]-3β-ethoxy-2', 3'-dihydro[2. 1-b]thiazole (328).

Source: 2α-Bromo-5α-cholestan-3-one (118) and 2-mercaptoimidazole (128).

General: Alumina chromatography (eluant ethyl acetate) followed by recrystallisation of the eluate from ethanol gave white shining flakes of *5α-cholestano-[2, 3-b]-3β-ethoxy-2', 3'-dihydroimidazo[2, 1-b]thiazole (328)* (35%), m.p. 150-151°, i.r., γ_{max} 1495, 1465, 1455, 1365 and 1065 cm^{-1}; ^1H n.m.r. (100 MHz), δ 0.62, 0.80 and 0.90 (methyl groups), 3.35 (q, 2H, $3'\text{-O-C}\underline{\text{H}}_2\text{-CH}_3$), 4.02 (dd, 1H, 2'-H) and 7.05 (s, 2H, 5'-H and 6'-H) (Found: C, 74.77; H, 10.27; N, 5.30; M^+-S, 480.406916. $C_{32}H_{52}N_2OS$ requires C, 74.94; H, 10.23; N, 5.46%; M-S, 480.407944).

Further elution of the column with chloroform followed by recrystallisation of the eluate from ethanol gave white crystals of *5α-cholest-2-eno[2, 3-b]-imidazo[2, 1-b]thiazole (327)* (26%), m.p. 205-207°; i.r. γ_{max} 1465, 1440 and 1380 cm^{-1}; ^1H n.m.r. (60MHz), δ 0.70, 0.80, 0.87 and 0.92 (methyl groups) and 7.25 (s, 2H, 5'-H and 6'-H) (Found: C, 76.69; H, 10.00; N, 5.80; M^+, 466.338027. $C_{30}H_{46}N_2S$ requires C, 77.19; H, 9.94; N, 6.00%; M, 466.338155).

11.7.ii <u>16α-(Imidazo-2-thiol)-3-methoxyoestra-1, 3, 5(10)-trien-17-one (331)</u>.

<u>Source:</u> 16α-Bromo-3-methoxyoestra-1, 3, 5(10)trien-17-one (122) and 2-mercaptoimidazole (128).

<u>16α-(Imidazo-2-thiol)-3-methoxyoestra-1, 3, 5(10)-trien-17-one (331)</u> was recrystallised from ethanol to give white crystals (47%), m.p. 150-153; i.r., γ_{max} 3300 (NH), 1720 (C=O), 1605, 1575, 1520, 1500, 1460, and 1380 cm^{-1}; ^1H n.m.r. (60 MHz), δ 0.87 (s, 3H, 18-CH_3), 3.75 (s, 3H, 3-OCH_3), 6.60-7.20 (m, 3H, 1-H, 2-H and 4-H), 7.05 (s, 2H, 4'-H and 5'-H) and 7.70 (bs, 1H, N<u>H</u>) (Found;[141] m/e 382. $C_{22}H_{26}N_2O_2S$ requires M, 382).

11.7.iii <u>5α-Cholest-2-eno[2, 3-b]-5', 6'-diphenylimidazo[2, 1-b]-thiazole (334)</u>.

<u>Source:</u> 2α-Bromo-5α-cholestan-3-one (118) and 2-mercapto-4, 5-diphenylimidazole (129).

<u>General</u>: Alumina chromatography (eluant ethyl acetate) followed by recrystallisation from acetone gave white crystals of <u>5α-cholest-2-eno-[2, 3-b]-5', 6'-diphenylimidazo[2, 1-b]thiazole (334)</u> (45%), m.p. 237-239°; i.r., γ_{max} 1600, 1500, 1465, 1440 and 1380 cm^{-1}; ^1H n.m.r. (100 MHz), δ 0.64, 0.79, 0.82 and 0.88 (methyl groups) and 7.06-7.64 (aromatic protons) (Found: C, 81.44; H, 8.62; N, 4.45; M^+, 618.399477.

$C_{42}H_{54}N_2S$ requires C, 81.50; H, 8.80; N, 4.56%; M, 618.400752).

11.7.iv <u>5α-Cholest-2-eno[2,3-b]-5',6'-dihydroimidazo[2,1-b]thiazole (335)</u>.

<u>Source:</u> 2α-Bromo-5α-cholestan-3-one (118) and 2-mercapto-4,5-dihydroimidazole (128).

<u>General:</u> Alumina chromatography (eluant chloroform) followed by recrystallisation from ethanol gave fine brown crystals of <u>5α-cholest-2-eno[2,3-b]-5',6'-dihydroimidazo[2,1-b]thiazole (335)</u> (41%), m.p. 211-213°; i.r., γ_{max} 1640, 1560, 1440-1460, 1400 and 1380 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.66, 0.80 and 0.87 (methyl groups), 3.63 and 4.12 (each s, 4H, 5'-H's and 6'-H's) (Found: C, 76.65; H, 10.33; N, 5.78; M^+, 468.3538764). $C_{30}H_{48}N_2S$ requires C, 76.84; H, 10.32; N, 5.98%; M, 468.353804).

11.7.v <u>5α-Cholest-2-eno[2,3-b]thiazolo[3,2-a]benzimidazole (336)</u>.

<u>Source</u>: 2α-Bromo-5α-cholestan-3-one (118) and 2-mercaptobenzimidazole (333).

<u>General</u>: Alumina chromatography (eluant chloroform) followed by recrystallisation from chloroform-ether gave a white solid of <u>5α-cholest-2-eno[2,3-b]thiazolo[3,2-a]benzimidazole (336)</u> (47%); m.p. 250-252; i.r., γ_{max} 1480, 1465 and 1380 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.58, 0.68, 0.82 and 0.90 (methyl groups) and 7.14-7.78 (aromatic protons) (Found: C, 78.71; H, 9.30; N, 5.43; M^+, 516.357110. $C_{34}H_{48}N_2S$ requires C, 79.01; H, 9.37; N, 5.42%; M, 516.353804).

11.7.vi 5α-Cholest-2-eno[2, 3-b]-6'-methylthiazolo[3, 2-a]benzimidazole (338).

Source: 2α-Bromo-5α-cholestan-3-one (118) and 2-mercapto-5-methylbenzimidazole (130).

General: Alumina chromatography (eluant ethyl acetate) followed by recrystallisation from ethanol gave white crystals of 5α-cholest-2-eno-[2, 3-b]-6'-methylthiazolo[3, 2-a]benzimidazole (338) (25%), m.p. 227-229; i.r., γ_{max} 1480, 1460, 1380 and 1270 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.66, 0.82 and 0.90 (methyl groups), 2.45 (d, 3H, 6'-CH_3), 6.94 and 7.48 (m, 3H, 5'-H, 7'-H and 8'-H) (Found: C, 79.05; H, 9.34; N, 5.19; M^{+}, 530.370136. $C_{35}H_{50}N_2S$ requires C, 79.19; H, 9.50; N, 5.28%; M, 530.369453).

11.7.vii 17β-Hydroxy-17α-methyl-5α-androst-2-eno[2, 3-b]-5', 6'-diphenylimidazo[2, 1-b]thiazole (339).

Source: 2α-Bromo-17β-hydroxy-17α-methyl-5α-androstan-3-one (117) and 2-mercapto-4, 5-diphenylimidazole (129).

Recrystallisation of the crude product from acetone gave white crystals of 17β-hydroxy-17α-methyl-5α-androst-2-eno[2, 3-b]-5', 6'-diphenylimidazo[2, 1-b]thiazole (339) (62%), m.p. 255-257%; i.r., γ_{max} 3570 (OH), 1590, 1495, 1465, 1455, 1435 and 1375 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 0.85 (s, 6H, 18-CH_3 and 19-CH_3), 1.20 (s, 3H, 17-CH_3), 7.05-7.45 (m, 10H, aromatic protons) (Found: C, 78.57; H, 7.39; N, 5.15; M^{+}, 536.284862. $C_{35}H_{40}N_2OS$ requires C, 78.36; H, 7.52; N, 5.23%; M, 536.286121).

11. 7. viii 17β-Hydroxy-17α-methyl-5α-androst-2-eno[2, 3-b]-5', 6'-dihydroimidazo[2, 1-b]thiazole (340).

Source: 2α-Bromo-17β-hydroxy-17α-methyl-5α-androstan-3-one (117) and 2-mercapto-4, 5-dihydroimidazole (332).

Recrystallisation of the crude product from benzene gave white crystals of 17β-hydroxy-17α-methyl-5α-androst-2-eno[2, 3-b]-5', 6'-dihydroimidazo[2, 1-b]thiazole (340) (38%), m. p. 263-265°; i. r., γ_{max} 3590 (OH), 1645, 1565, 1445 and 1400 cm^{-1}; ^1H n. m. r. (60 MHz), δ 0.90 (s, 6H, 18-CH_3 and 19-CH_3), 1.25 (s, 3H, 17-CH_3) and 3.65-4.25 (m, 4H, 5'-H's and 6'-H's) (Found: C, 71.28; H, 8.82; N, 7.02; M^+, 386.238205. $C_{23}H_{34}N_2OS$ requires C, 71.50; H, 8.88; N, 7, 26%; M, 386.239173).

11. 7. ix 17β-Hydroxy-17α-methyl-5α-androst-2-eno[2, 3-b]-5', 6', 7', 8'-tetrahydrothiazolo[3, 2-a]benzimidazole (341).

Source: 2α-Bromo-17β-hydroxy-17α-methyl-5α-androstan-3-one (117) and 2-mercapto-4, 5, 6, 7-tetrahydrobenzimidazole (132).

Recrystallisation of the crude product from ethanol gave white crystals of 17β-hydroxy-17α-methyl-5α-androst-2-eno[2, 3-b]-5', 6', 7', 8'-tetrahydrothiazolo[3, 2-a]benzimidazole (341) (26%), m. p. 285-287°; i. r., γ_{max} 3570 (OH), 1625, 1460, 1440, 1390, 1375 and 1365 cm^{-1}; ^1H n. m. r. (60 MHz), δ 0.90 (s, 6H, 18-CH_3 and 19-CH_3) and 1.25 (s, 3H, 17-CH_3) (Found: C, 74.18; H, 8.71; N, 6.21; M^+, 438.270369. $C_{27}H_{38}N_2OS$ requires C, 73.97; H, 8.74; N, 6.39%; M, 438.270471.

11. 7. x 17β-Hydroxy-17α-methyl-5α-androst-2-eno[2, 3-b]thiazolo-[3, 2-a]benzimidazole (342).

Source: 2α-Bromo-17β-hydroxy-17α-methyl-5α-androstan-3-one (117) and 2-mercaptobenzimidazole (333).

Recrystallisation of the crude product from ethanol gave white crystals of 17β-hydroxy-17α-methyl-5α-androst-2-eno[2, 3-b]thiazolo-[3, 2-a]benzimidazole (342) (52%), m.p. 224-226°; i.r., γ_{max} 3590 (OH), 1595, 1520, 1480 and 740 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.90 (s, 3H, 18-CH$_3$), 0.94 (s, 3H, 19-CH$_3$), 1.24 (s, 3H, 17-CH$_3$) and 7.42-7.98 (m, 4H, aromatic protons) (Found: C, 74.44; H, 7.80; N, 6.23; M$^+$, 434.2389164. $C_{27}H_{34}N_2OS$ requires C, 74.65; H, 7.895; N, 6.45%; M, 434.239173).

11.7.xi 17β-Hydroxy-17α-methyl-5α-androst-2-eno[2, 3-b]-6'-methylthiazolo[3, 2-a]benzimidazole (343).

Source: 2α-Bromo-17β-hydroxy-17α-methyl-5α-androstan-3-one (117) and 2-mercapto-5-methylbenzimidazole (130).

Recrystallisation of the crude product from benzene gave white crystals of 17β-hydroxy-17α-methyl-5α-androst-2-eno[2, 3-b]- 6'-methylthiazolo[3, 2-a]benzimidazole (343) (49%); m.p. 158-160°; i.r., γ_{max} 3570 (OH), 1625, 1480, 1460, 1420, 1375 and 1365 cm^{-1}; ^{1}H n.m.r. (60 MHz), 0.90 (s, 6H, 18-CH$_3$ and 19-CH$_3$), 1.25 (s, 3H, 17-CH$_3$), 2.45 (s, 3H, 6'-CH$_3$) and 6.85-7.50 (m, 3H, aromatic protons) (Found: C, 74.78; H, 7.84; N, 5.96; M$^+$, 448.254856. $C_{28}H_{36}N_2OS$ requires C, 75.00; H, 8.09; N, 6.25%; M, 448.254823).

11.7.xii 17β-Hydroxyandrost-2, 4-dieno[2, 3-b]imidazo[2, 1-b]thiazole (344)

Source: 2α-Bromo-17β-hydroxyandrost-4-en-3-one (119) and 2-

mercaptoimidazole (128).

Recrystallisation of the crude product from acetone gave yellow crystals of 17β-hydroxyandrost-2,4-dieno[2,3-b]imidazo[2,1-b]thiazole (344) (18%), m.p. 158-160°; ^{1}H n.m.r. (60 MHz), δ 0.80 (s, 3H, 18-CH_3), 1.10 (s, 3H, 19-CH_3), 3.63 (t, 1H, 17-H), 5.97 (s, 1H, 4-H), 7.20 and 7.30 (each singlet, 2H, 5'-H and 6'-H) (Found:^{141} M^+, 368.189773. $C_{22}H_{28}N_2OS$ requires M, 368.192225).

11.7.xiii 17β-Hydroxyandrost-2,4-dieno[2,3-b]-5',6'-dihydroimidazo-[2,1-b]thiazole (345).

Source: 2α-Bromo-17β-hydroxyandrost-4-en-3-one (119) and 2-mercapto-4,5-dihydroimidazole (332).

Recrystallisation of the crude product from ethanol gave a yellow solid of 17β-hydroxyandrost-2,4-dieno[2,3-b]-5',6'-dihydroimidazo[2,1-b]-thiazole (345) (15%), m.p. 255-257° (dec.); i.r., γ_{max} 3560 (OH), 1620, 1580, 1550, 1440 and 1420 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 0.80 (s, 3H, 18-CH_3), 1.08 (s, 3H, 19-CH_3), 3.70 (m, 3H, 6'-H's and 17-H), 4.15 (m, 2H, 5'-H's) and 5.55 (s, 1H, 4-H) (Found: C, 71.58; H, 7.96; N, 7.43; M^+-S, 338.234517. $C_{22}H_{30}N_2OS$ requires C, 71.31; H, 8.17; N, 7.57%; M-S, 338.235801).

11.7.xiv 17β-Hydroxyandrost-2,4-dieno[2,3-b]thiazolo[3,2-a]-benzimidazole (346).

Source: 2α-Bromo-17β-hydroxyandrost-4-en-3-one (119) and 2-mercaptobenzimidazole (333).

Recrystallisation of the crude product from a large excess of ethanol gave a brown solid of 17β-hydroxyandrost-2,4-dieno[2,3-b]thiazolo[3,2-a]-

benzimidazole (346) (27%), m.p. 275-279; i.r., γ_{max} 3560 (OH), 1615, 1470, 1460 and 1450 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 0.85 (s, 3H, 18-CH_3), 1.15 (s, 3H, 19-CH_3), 3.73 (t, 1H, 17-H), 6.54 (s, 1H, 4-H), and 7.20-7.90 (m, 4H, aromatic protons) (Found: C, 74.38; H, 7.18; N, 6.53; M$^+$, 418.206584. $C_{26}H_{30}N_2OS$ requires C, 74.60; H, 7.23; N, 6.70%; M, 418.207154).

11.7.xv 17β-Hydroxyandrost-2,4-dieno[2,3-b]-6'-methylthiazolo[3,2-a]-benzimidazole (347).

Source: 2α-Bromo-17β-hydroxyandrost-4-en-3-one (119) and 2-mercapto-5-methylbenzimidazole (130).

Recrystallisation of the crude product from acetone gave a white solid of 17β-hydroxyandrost-2,4-dieno[2,3-b]-6'-methylthiazolo[3,2-a]-benzimidazole (347) (22%), m.p. 245-247°; i.r., γ_{max} 3560 (OH), 1610, 1455 and 1360 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 0.80 (s, 3H, 18-CH_3), 1.10 (s, 3H, 19-CH_3), 2.50 (s, 3H, 6'-CH_3), 3.68 (t, 1H, 17-H), 6.45 (s, 1H, 4-H) and 6.98-7.75 (m, 3H, aromatic protons) (Found: C, 74.73; H, 7.40; N, 6.29; M$^+$-S, 400.247712. $C_{27}H_{32}N_2OS$ requires C, 75.00; H, 7.47; N, 6.48%; M-S, 400.251451).

11.7.xvi 17β-Hydroxy-17α-methyl-5α-androst-2-eno[2,3-b]-6'-methyl-5',6'-dihydroimidazo[2,1-b]thiazole (348).

Source: 2α-Bromo-17β-hydroxy-17α-methyl-5α-androstan-3-one (117) and 2-mercapto-4-methyl-4,5-dihydroimidazole (131).

Recrystallisation of the crude product from ethanol gave white crystals of 17β-hydroxy-17α-methyl-5α-androst-2-eno[2,3-b]-6'-methyl-5',6'-dihydroimidazo[2,1-b]thiazole (348) (42%), m.p. 220-222° (dec.);

i.r., γ_{max} 3570 (OH), 1635, 1555, 1435, 1395, 1375 and 1365 cm^{-1}; ^1H n.m.r. (60 MHz), δ 0.85 (s, 6H, 18-CH_3 and 19-CH_3), 1.20 (s, 3H, 17-CH_3), 1.35 (d, J=6Hz, 3H, 6'-CH_3), 3.18 and 3.80 (each m, 2H, 5'-H's) and 4.05 (m, 1H, 6'-H) (Found: C, 71.85; H, 9.55; N, 7.10; M^+, 400.252081. $C_{24}H_{36}N_2OS$ requires C, 71.95; H, 9.57; N, 6.99%; M, 400.252821).

11.7.xvii <u>17β-Hydroxy-17α-methyl-5α-androst-2-eno[2,3-f]thiazolo-[3,2-b]-s-triazole (353)</u>.

<u>Source</u>: 2α-Bromo-17β-hydroxy-17α-methyl-5α-androstan-3-one (117) and 3-mercapto-1,2,4-triazole (133).

<u>General</u>: Alumina chromatography (eluant chloroform) followed by recrystallisation from ethanol gave white crystals of <u>17β-hydroxy-17α-methyl-5α-androst-2-eno[2,3-f]thiazolo[3,2-b]-s-triazole (353)</u> (23%), m.p. 115-118; i.r., γ_{max} 3590 (OH), 1465, 1445, 1420, 1355 and 1240 cm^{-1}; ^1H n.m.r. (60 MHz), δ 0.90 (s, 3H, 18-CH_3), 0.95 (s, 3H, 19-CH_3), 1.23 (s, 3H, 17-CH_3) and 8.07 (s, 1H, 2'-H) (Found: C, 68.23; H, 7.95; N, 10.66; M^+, 385.215538. $C_{22}H_{31}N_3OS$ requires C, 68.53; H, 8.11; N, 10.99%; M, 385.218773).

11.7.xviii <u>5α-Cholest-2-eno[2,3-f]thiazolo[3,2-b]-s-triazole (360)</u>.

<u>Source</u>: 2α-Bromo-5α-androstan-3-one (118) and 3-mercapto-1,2,4-triazole (133).

<u>General</u>: Alumina chromatography (eluant chloroform) followed by recrystallisation from ethanol gave white needles of <u>5α-cholest-2-eno-[2,3-f]thiazolo[3,2-b]-s-triazole (360)</u> (32%), m.p. 188-190°; i.r.,

γ $_{max}$ 1465, 1440, 1420, 1380 and 1355 cm^{-1}; ^{1}H n.m.r. (60 MHz), δ 0.69, 0.83 and 0.89 (methyl groups) and 8.02 (s, 1H, 2'-H) (Found: C, 74.31; H, 9.63; N, 8.70; M$^+$, 467.333948. $C_{29}H_{45}N_3S$ requires C, 74.46; H, 9.70; N, 8.99%; M, 467.333404).

11.7.xix <u>5α-Cholest-2-eno[2, 3-f]-2'-methylthiazolo[3, 2-b]-s-triazole (361)</u>.

<u>Source:</u> 2α-Bromo-5α-cholestan-3-one (118) and 3-mercapto-5-methyl-1, 2, 4-triazole (134).

<u>General</u>: Alumina chromatography (eluant chloroform followed by recrystallisation from methanol gave a white solid of <u>5α-cholest-2-eno[2, 3-f]-2'-methylthiazolo[3, 2-b]-s-triazole (361)</u> (37%), m.p. 117-120°; i.r. γ $_{max}$ 1470, 1440 and 1380 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.67; 0.82, 0.84 and 0.90 (methyl groups) and 2.48 (s, 3H, 2'-CH_3) (Found: C, 74.57; H, 9.81; N, 8.40; M$^+$, 481.348292. $C_{30}H_{47}N_3S$ requires C, 74.79; H, 9.84; N, 8.73%; M, 481.349053).

11.7.xx <u>3-Methoxyoestra-1, 3, 5(10)-trieno[16, 17-f]-17β-ethoxy-5', 6'-dihydrothiazolo[3, 2-b]-s-triazole (362)</u>.

<u>Source</u>: 16α-Bromo-3-methoxyoestra-1, 3, 5(10)-trien-17-one (122) and 3-mercapto-1, 2, 4-triazole (134).

<u>General</u>: Alumina chromatography (eluant ethyl acetate) followed by recrystallisation from methanol gave white crystals of <u>3-methoxyoestra-1, 3, 5(10)-trieno[16, 17-f]-17β-ethoxy-5', 6'-dihydrothiazolo[3, 2-b]-s-triazole (362)</u> (50%), m.p. 195-197°; i.r., γ $_{max}$ 1605, 1570, 1495, 1475, 1450, 1420, 1380 and 1365 cm^{-1}; ^{1}H n.m.r. (100 MHz), δ 0.52 (s, 3H, 18-CH_3), 1.40 (t, 3H, 17-O-CH_2-C$\underline{H}_3$), 3.12 (q, 2H, 17-O-C$\underline{H}_2$-

CH_3), 3.72 (s, 3H, 3-OCH_3), 4.50 (t, 1H, 5'-H), 6.60, 6.74 and 7.20 (m, 3H, 1-H, 2-H and 4-H) and 7.90 (s, 1H, 2'-H) (Found: C, 67.00; H, 7.06; N, 10.02; M^+, m/e 411. $C_{23}H_{29}N_3O_2S$ requires C, 67.15; H, 7.11; N, 10.22%; M, 411).

11.7.xxi 3-Methoxyoestra-1, 3, 5(10)-trieno[16, 17-f]-17β-ethoxy-2'-methyl-5', 6'-dihydrothiazolo[3, 2-b]-s-triazole (363).

Source: 16α-Bromo-3-methoxyoestra-1, 3, 5(10)-trien-17-one (122) and 3-mercapto-5-methyl-1, 2, 4-triazole (134).

General: Alumina chromatography (eluant ethyl acetate) followed by recrystallisation from methanol gave white crystals of 3-methoxyoestra-1, 3, 5(10)-trieno[16, 17-f]-17β-ethoxy-2'-methyl-5', 6'-dihydrothiazolo[3, 2-b]-s-triazole (363) (49%), m.p. 193-195°; i.r., γ_{max} 1605, 1570, 1500, 1430, 1380 and 1370 cm^{-1}; ^1H n.m.r. (60 MHz), δ0.60 (s, 3H, 18-CH_3), 1.23 (t, 3H, 3'-O-CH_2-$C\underline{H}_3$), 2.40 (s, 3H, 2'-CH_3), 3.30 (q, 2H, 17-O-$C\underline{H}_2$-CH_3) 3.75 (s, 3H, 3-OCH_3), 4.50 (t, 1H, 5'-H) and 6.65-7.30 (m, 3H, 1-H, 2-H and 4-H) (Found: C, 67.55; H, 7.29; N, 9.78; M^+, 425.214102. $C_{24}H_{31}N_3O_2S$ requires C, 67.73; H, 7.35; N, 9.88%; M, 425.213687).

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Steroidal Heterocycles: 2′-Thiocyanatoandrosteno-[3,2-*d*]pyrimidines and -[17,16-*d*]pyrimidines

By **Joginder S. Bajwa** and **Peter J. Sykes,*** Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ

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Steroidal Heterocycles: 2′-Thiocyanatoandrosteno-[3,2-*d*]pyrimidin and -[17,16-*d*]pyrimidines

By **Joginder S. Bajwa** and **Peter J. Sykes,*** Department of Chemistry, University of Edinburgh, West Ma
Road, Edinburgh EH9 3JJ

The preparation of steroidal heterocycles containing the 2′-thiocyanatopyrimidine ring fused to the 2,3-positio 16,17-position of the steroid nucleus is described. These are prepared by the reaction of 2-amino-1,3,4-th diazole with 2-hydroxymethylene-3-oxo-steroids and 16-hydroxymethylene-17-oxo-steroids.

IT was of interest to prepare fused steroidal pyrimidines since other heterocyclic fused steroids have been shown to exhibit modified or accentuated hormonal activities.[1] Various pyrimidine bases in the steroid series have already been obtained by reactions involving the condensation of 2-hydroxymethylene-3-oxo-steroids with guanidine, urea, and thiourea [2] or by the treatment of ketones with trisformylaminomethane [3] and cyanoguanidine.[4] 2α-Cyano-3-oxo-steroids and their enol ethers have also been used as starting materials for the preparation of pyrimidine bases.[2] This paper describes another convenient synthesis of some androsteno-[3,2-*d*]pyrimidines and androsteno[17,16-*d*]pyrimidines by the reaction of 2-amino-1,3,4-thiadiazole (1) with steroidal β-diketones.

The condensation of 17β-hydroxy-2-hydroxymethylene-5α-androstan-3-one (2) with 2-amino-1,3,4-thiadiazole (1) in refluxing toluene in the presence of a catalytic amount of toluene-*p*-sulphonic acid gave 17β-hydroxy-2′-thiocyanato-5α-androst-2-eno[3,2-*d*]pyrimidine (4) in 60% yield. The i.r. spectrum of this compound exhibited a strong band at 2 160 cm^{-1} indicative a thiocyanate group and also bands at 1 565, 1 555i 1 545infl, 1 415, 1 365, and 755 cm^{-1} characteristic o pyrimidine ring. The ^{1}H n.m.r. spectrum showec singlet at δ 8.25 confirming the 6′-hydrogen of pyrimidine ring.

It is apparent that the final dehydration of the ini condensation product (3) results in a rearrangem furnishing the thiocyanato-pyrimidine ring syst Indeed a similar rearrangement has been report during the reaction between 2-amino-1,3,4-thiadia and the simple 1,3-dicarbonyl compound, acetylaceto resulting in the formation of 2-thiocyanato-4,6-dimet pyrimidine.

The intermediate condensation product (3) could be isolated and it is, therefore, possible that it might h an isomeric structure based upon an initial react between the amino-group of (1) and the 3-carbonyl gr of the steroid. However fission of the N–N bond in dehydration step of either of the possible intermedi will yield the same product.

The thiocyanate group is known to isomerise to isothiocyanate structure on refluxing in acetonit

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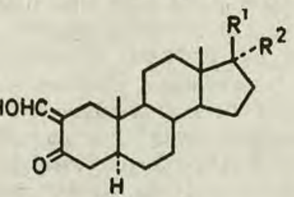
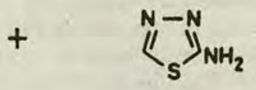
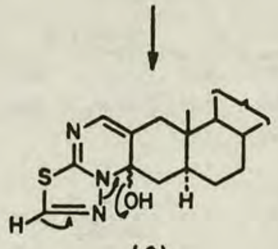
enzene, and toluene.[6] However, no such isomerisation vas observed in the above synthesis, the 2′-thiocyanate roup remaining intact even after prolonged heating in efluxing xylene. Absence of isomerisation to isothio-yanate was confirmed in that the product failed to react ith a primary amine.



(2) $R^1 = OH$, $R^2 = H$
(5) $R^1 = R^2 = H$
(7) $R^1 = C_8H_{17}$, $R^2 = H$
(10) $R^1 = OH$, $R^2 = Me$



(1)



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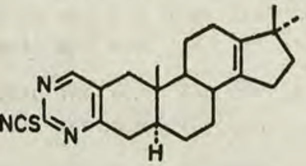

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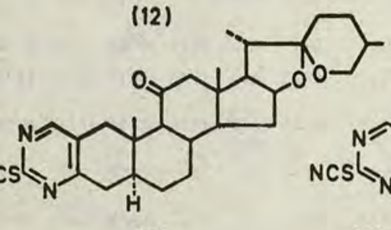

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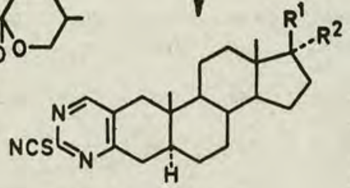
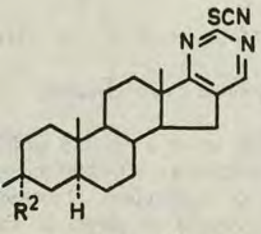
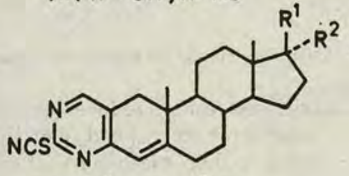


(4) $R^1 = OH$, $R^2 = H$
(6) $R^1 = R^2 = H$
(8) $R^1 = C_8H_{17}$, $R^2 = H$
(11) $R^1 = OH$, $R^2 = Me$



(15) $R^1 = OH$, $R^2 = H$
(16) $R^1 = OAc$, $R^2 = H$
(18) $R^1R^2 = O$



(13) $R^1 = OH$, $R^2 = H$
(14) $R^1 = C_8H_{17}$, $R^2 = H$

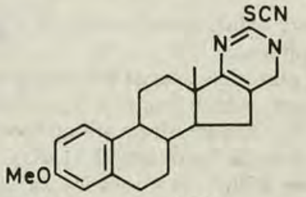
In a similar manner 2′-thiocyanato-5α-androst-2-eno-3,2-*d*]pyrimidine (6), 2′-thiocyanato-5α-cholest-2-eno-3,2-*d*]pyrimidine (8), and 11-oxo-2′-thiocyanato-5α-pirostan-2-eno[3,2-*d*]pyrimidine (9) were prepared from ne corresponding 2-hydroxymethylene-3-oxo-steroids 5), (7), and 2-hydroxymethylene-5α-spirostane-3,11-ione respectively.

Using the reaction conditions necessary for the con-ensation reaction, a 2-hydroxymethylene-3-oxo-steroid aving a tertiary hydroxy-group at C-17, also undergoes Wagner–Meerwein rearrangement. For example, 17β-ydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one (10) gave the expected 2′-thiocyanatopyrimidine (11) accompanied by a variable amount of 17,17-dimethyl-2′-thiocyanato-18-norandrost-2,13-dieno-[3,2-*d*]pyrimidine (12) depending upon the quantity of toluene-*p*-sulphonic acid used in the reaction.

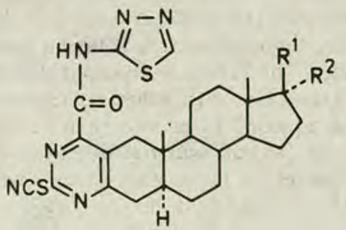
The reaction was also successfully applied to two steroids with a Δ^4-double bond, namely 17β-hydroxy-2-hydroxymethyleneandrost-4-en-3-one and 2-hydroxy-methylenecholest-4-en-3-one, but the yields of the products, 17β-hydroxy-2′-thiocyanatoandrost-2,4-dieno-[3,2-*d*]pyrimidine (13) and 2′-thiocyanatocholest-2,4-dieno[3,2-*d*]pyrimidine (14) were lower, being in the range 35—40%. Analogously fused 3β-hydroxy-2′-thiocyanato-5α-androst-16-eno[17,16-*d*]pyrimidine (15), and 3-methoxy-2′-thiocyanato-oestra-1,3,5(10),16-tetra-eno[17,16-*d*]pyrimidine (17) were prepared from 3β-hydroxy-16-hydroxymethylene-5α-androstan-17-one and 16-hydroxy-methylene-3-methoxyoestra-1,3,5(10)-trien-17-one respectively. Acetylation of the 3-hydroxy-steroid (15) gave the corresponding acetyl derivative (16) whilst oxidation by Jones reagent furnished the 3-oxo derivative (18).

The reaction of 17β-hydroxy-2-ethoxycarbonyl-(hydroxy)methylene-17α-methyl-5α-androstan-3-one with (1) under the same conditions furnished the expected 17β-hydroxy-17α-methyl-6′-(1,3,4-thiadiazol-2-ylcarbamoyl)-2′-thiocyanato-5α-androst-2-eno[3,2-*d*]-pyrimidine (19). A further example of this reaction was illustrated by the conversion of 2-ethoxycarbonyl-(hydroxy)methylene-5α-cholestan-3-one into 6′-(1,3,4-thiadiazol-2-ylcarbamoyl)-2′-thiocyanato-5α-cholest-2-eno[3,2-*d*]pyrimidine (20).

Under the same reaction conditions 2α-acetyl-17β-hydroxy-5α-androstan-3-one failed to yield any condensation product, probably because ketones, in this case the 2α-acetyl group, generally react with amines



(17)



(19) $R^1 = OH$, $R^2 = Me$
(20) $R^1 = C_8H_{17}$, $R^2 = H$

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[6] U. Tonellato, O. Rossetto, and A. Fava, *J. Org. Chem.*, 1969, **34**, 4032.

much more slowly than aldehydes (the 2-formyl group) to yield Schiff's bases.[7]

EXPERIMENTAL SECTION

M.p.s were determined on Gallenkamp apparatus and are uncorrected. I.r. spectra were recorded in bromoform on a Perkin–Elmer 157 G Spectrometer. ^{1}H N.m.r. spectra were recorded in deuteriated chloroform using tetramethylsilane as an internal standard on a Nuclear Magnetic Resonance Ltd EM360 (60 MHz) or a Varian HA 100 (100 MHz) spectrometer. Mass spectrometry was carried out on AEI MS 902 instrument.

Compd.	Mol. Formula	Yield (%)	M.p. (°C)	High resolution mass spectrum Found	Calculated	Characteristic i.r. abs (ν/cm^{-1})	^{1}H N.m.r. (δ) 6′-H	18-CH$_3$	19-CH$_3$	Analysis Found (%) C	H	N	Calculated (%) C	H	N
(4) [b]	$C_{22}H_{29}N_3OS$	60	213—215	383.202 537	383.203 123	2 160 (SCN), 1 565, 755	8.20	0.75	0.75	69.0	7.6	11.1	68.89	7.63	10.9
(6) [a]	$C_{22}H_{29}N_3S$	85	210—212	367.205 933	367.207 136	2 160 (SCN), 1 565, 755	8.30	0.70	0.75	71.7	8.0	11.65	71.89	7.96	11.4
(7) [a]	$C_{30}H_{45}N_3S$	70	159—160	479.331 357	479.333 404	2 160 (SCN), 1 565, 755	8.30			75.3	9.45	8.55	75.10	9.46	8.7
(9) [b]	$C_{30}H_{39}N_3SO_3$	68	241—243	521.271 406	521.271 198	2 160 (SCN), 1 695 (CO), 1 565, 755	8.30			68.75	7.95	8.1	69.06	7.54	8.0
(12) [a]	$C_{23}H_{29}N_3S$	11	125—127	379.208 494	379.308 209	2 160 (SCN), 1 565, 755	8.30	0.80 17-gem dimethyl	1.00	72.75	7.85	10.5	72.78	7.71	10.7
(13) [a]	$C_{22}H_{27}N_3SO$	41	185—187	381.186 086	381.187 474	2 160 (SCN), 1 620, 1 575, 750	8.20	0.80	1.00	68.75	7.25	10.8	68.25	7.13	11.0
(14) [a]	$C_{30}H_{43}N_3S$	38	184—186	477.316 335	477.317 754	2 160 (SCN), 1 620, 1 565, 770	8.20			75.25	8.9	8.5	75.42	9.08	8.8
(15) [b]	$C_{22}H_{29}N_3SO$	75	192—194	383.203 289	383.203 123	2 160 (SCN), 1 580, 790	8.35	0.85	0.97	69.1	7.75	10.95	68.89	7.63	10.9
(17) [b]	$C_{22}H_{23}N_3SO$	72	177—179	377.154 981	377.156 176	2 160 (SCN), 1 605, 1 575, 780	8.35	1.00		69.65	6.25	10.65	69.99	6.15	11.
(18)	$C_{22}H_{27}N_3SO$	80	226—228	381.187 281	381.187 474	2 160 (SCN), 1 700 (CO), 1 575, 790	8.50	1.00	1.10	68.95	7.25	10.75	69.26	7.14	11.0
(16)	$C_{24}H_{31}N_3SO_2$	53	175—177	425.214 789	425.213 686	2 160 (SCN), 1 720 (CO), 1 580, 900	8.50	0.90	1.00	67.4	7.0	9.9	67.73	7.29	9.8
(19) [b]	$C_{26}H_{32}N_6S_2O_2$	65	244—246	524.204 927	524.202 805	3 330 (NH), 2 160 (SCN), 1 690 (CO), 1 510, 745	8.90 (5″-H), 12.0 (NH)	0.77	0.87 (1.20, 17-Me)	59.7	4.2	16.2	59.51	4.41	16.0
(20) [b]	$C_{33}H_{46}N_6S_2O$	71	311—314	606.317 398	606.317 434	3 330 (NH), 2 160 (SCN), 1 690 (CO), 1 500, 735	8.90 (5″-H) 12.00 (NH)			64.95	7.5	13.5	65.31	7.58	13.8
(11) [b]	$C_{23}H_{31}N_3SO$	85	172—173	397.218 722	397.218 773	2 160 (SCN), 1 565, 755	8.20	0.75	0.90 (1.20 17-Me)	69.5	7.85	10.95	69.48	7.86	10.5

[a] Methylene chloride was used for the elution of these compounds over silica gel. [b] Methylene chloride–ethanol (95 : 5) was used for elution of these compounds.

All the starting materials except 2-hydroxymethylene-5α-spirostane-3,11-dione, which has not been reported so far, were prepared by the known literature methods.

2-Hydroxymethylene-5α-spirostane-3,11-dione.— Sodium hydride (1.5 g) was added to a solution of 5α-androstane-3,11-dione (5 g) in benzene (100 ml) and ethyl formate (5 ml) and the reaction mixture was set aside under nitrogen for one day. Methanol (10 ml) was added to decompose the excess of sodium hydride and the solution was diluted with water (300 ml). The layers were separated and the basic solution was extracted with ether to remove the neutral material. The aqueous layer was then acidified with 3M-hydrochloric acid (40 ml) and the liberated enol extracted with ether. The ether layer was washed with water and saturated sodium chloride solution, dried ($MgSO_4$), and evaporated to dryness. The crude product was recrystallised from ethanol to give *2-hydroxymethylene-5α-spirostane-3,11-dione* (3.5 g, 66%), m.p. 165—166. I.r. (CHBı
$\nu_{max.}$ 2 930, 2 870, 1 700 (C=O), 1 640, 1 585 (COC=CHOH
1 450, 1 385, and 1 375 cm^{-1}; ^{1}H n.m.r. δ 0.72, 0.82, 0.9
1.00 (methyl groups), and 8.60 (s, 1 H, 2=CHO) (Found:
73.20; H, 8.91. Calc. for $C_{28}H_{40}O_5$: C, 73.68; H, 8.77%

General Procedure for the Condensation Reaction.—
solution of steroidal β-diketone (0.001 mol), 2-amino-1,3,
thiadiazole (0.0015 mol), and toluene-*p*-sulphonic acid (
mg) in dry toluene (50 ml) was refluxed and stirred overnigh
The reaction mixture was cooled and the solvent w
removed under reduced pressure to leave a residue whi
was chromatographed over silica gel (50 g; 80—200 mes
using either methylene chloride or methylene chlorid
ethanol (95 : 5). A summary of results is given in t
Table. Compounds (4) and (6) were recrystallised fro
benzene and acetone respectively whilst all other produc
were recrystallised from ethanol.

17β-*Hydroxy*-17α-*methyl*-2′-*thiocyanato*-5α-*androst*-2-*eno*-
[3,2-d]-*pyrimidine* (11) and 17,17-*Dimethyl*-2′-*thiocyana*
18-*norandrost*-2,13-*dieno*[3,2-d]*pyrimidine* (12).—The cru
product from the condensation reaction was chromat
graphed over silica gel. Elution with methylene chlori
gave the rearranged steroid (12) which was recrystallis
from ethanol whilst further elution with methylene chlorid
ethanol (95 : 5) mixture gave the expected condensati
product (11) which was recrystallised from ethanol.

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[7] R. W. Hayes, *Chem. Rev.*, 1963, **63**, 489.