THE REACTIONS OF STEROIDAL ENAMINES

by

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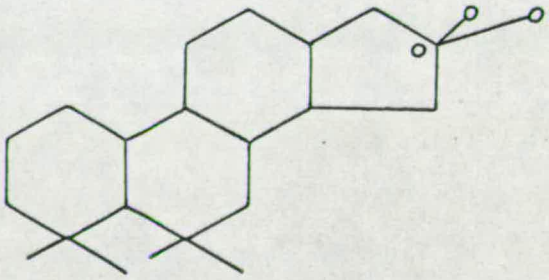
They said it couldn't be done,

So I went right to it,

And tackled that thing that "couldn't be done",

And couldn't do it.

TO MY PARENTS



DECLARATION

I declare that this thesis has been composed by myself and that the work described herein is my own.

ACKNOWLEDGEMENTS

Many thanks are due to Dr P.J. Sykes for his constant help during the course of this work and to Professor J.I.G. Cadogan for the provision of laboratory and library facilities. I must also thank the technical staff, whose assistance has, on very many occasions, been much more than working to rule.

CONTENTS

Section
Designation

GENERAL LEGEND TO DIAGRAMS

The configuration of the hydrogen atoms at the ring junctions will be 5α, 8β, 9α and 14α unless otherwise specified. Other configurations will be shown as follows:

(a) A solid line indicates a β-configuration

(b) A broken line indicates an α-configuration

(c) A wavy line indicates either unknown/unspecified configuration or a mixture of isomers.

ABSTRACT

Picrates of both the pyrrolidenamines of androstanolone acetate and D.H.A. acetate were prepared from the enamines in an analytically pure state, but the corresponding hydrochlorides could not be purified. Attempted regeneration of the enamines from these derivatives was at best only partially successful.

Attempts to methylate the pyrrolidenamines of 3-keto-steroids with methyl iodide were successful in giving the 2α-methyl derivative only in a high polarity solvent such as ethanol. Reaction with allyl bromide furnished 2α-allylandrostanolone acetate whilst ethyl crotonate failed to give a substitution product.

Methyl α-(bromomethyl)-acrylate, produced in situ by the action of triethylamine on methyl $\beta\beta'$-dibromoisobutyrate, reacted with cyclohexanone pyrrolidenamine to give either 2-(2-carbomethoxyprop-2-enyl)-cyclohexanone or the previously reported methyl 9-oxobicyclo [3,3,1] nonane-3α-carboxylate depending on reaction conditions. The pyrrolidenamine of trans-decal-2-one gave the analogous compounds 3α-(2-carbomethoxyprop-2-enyl)-trans-decal-2-one and 1,3-(2-endo-carbomethoxytrimethylene)-trans-decal-2-one, while that of 19-norandrostanolone acetate yielded the similar bridge system 17β-acetoxy-2α,4α-(2α-carbomethoxytrimethylene)-5α,10β-estran-3-one as well as the 2α-(2-carbomethoxyprop-2-enyl)-derivative of the starting ketone. Another bridged ring steroid, 17β-acetoxy-2β,4β-(2β-carbomethoxytrimethylene)-5β-androstan-3-one was obtained from 5β-androstanolone acetate as well as the 4β-alkylated starting material. Pyrrolidenamines of 3-keto-5α-steroids gave generally the 2α-substituted derivatives, though cholestan-3-one yielded the 2α,4α-dialkylated compound in addition. With 5α-androstanolone

acetate the major product proved to be the salt 17β-acetoxy-5'β-carbomethoxy-5α-androst-2-eno[3,2-b]1'-azoniaspiro[4,5]decane bromide. The 17β-acetyl and 17α-methyl-17-hydroxy-salts were similarly prepared. Mechanisms are proposed for these reactions and supporting evidence is given.

Reaction with ω-nitrostyrene produced no isolable product with steroidal enamines, whilst acryloyl chloride gave 3-(17β-acetoxy-5α-androstan-3-one-2α-yl) propanoic acid.

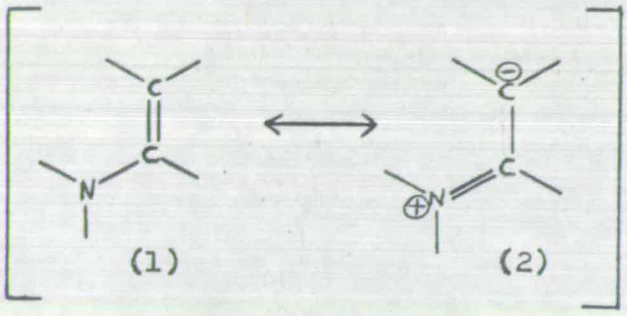
In contrast to this reaction acrolein failed to yield an isolable product with the steroidal enamine, but with the pyrrolidenamine of trans-decal-2-one, the compound 1,3-(1-pyrrolidinyltrimethylene)-trans-decal-2-one, analogous to the cyclohexanone product, was produced.

Salicylaldehyde reacted with the pyrrolidenamine of androstanolone acetate to yield 17β-acetoxy-3α-pyrrolidinyl-5α-androstano[3,2-b]2-H-benzopyran which was readily converted to the diene, 17β-acetoxy-5α-androst-3-eno[3,2-b]2-H-benzopyran.

The reaction of carboethoxyaziridine followed by hydrolysis gave 2-(17β-acetoxy-5α-androstan-3-one-2α-yl)-N-carboethoxyethylamine, whilst reaction followed by treatment with p-toluene sulphonic acid gave 17β-acetoxy-1'-N-carboethoxy-5α-androst-2-eno[3,2-b] dihydropyrrole.

The mechanism and stereochemistry of the above reactions are discussed in some detail.

Fig. 1.1 Enamine Structure



(1) (2)

Fig. 1.2 An Example of the Stork Reaction

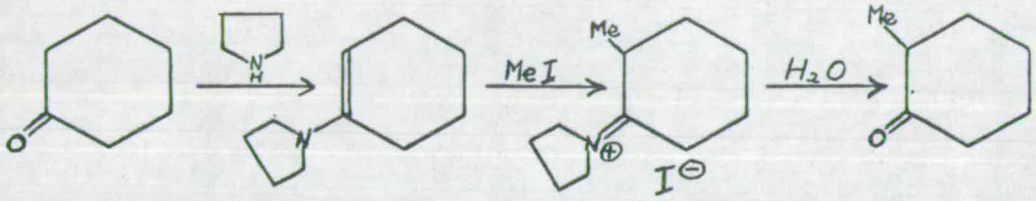


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Fig. 1.3 An Example of the $TiCl_4$ Synthesis

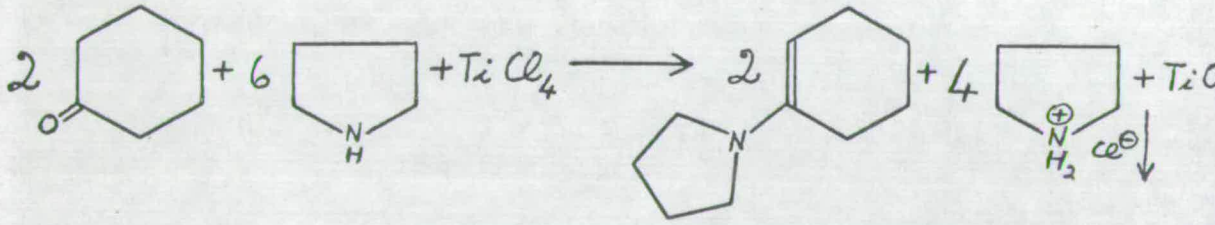
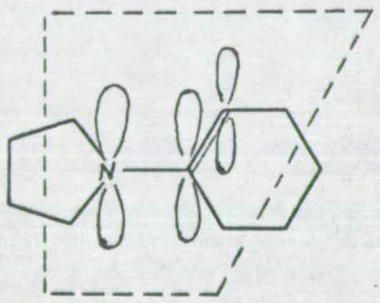


Fig. 1.4 Orbital Overlap for Enamine Delocalization



(4)

1. INTRODUCTION

1.1 Definitions

The term "enamine" is defined as synonymous with $\alpha\beta$-unsaturated amine (1) and "pyrrolidenamine" is equivalent to pyrrolidine enamine e.g. (3).

1.2 History

The word "enamine" was first introduced by Wittig and Blumenthal[1] in 1927, by analogy to the "enol" structure. The first general method of preparation, however, due to Mannich and Davidsen[2], was not reported until 1936. This method was somewhat improved by de Benneville and Macartney (1950)[3] and then much simplified by Herr and Heyl (1952)[4]. However, although enamines were well known, the synthetic possibilities inherent in the structure were not realized or exploited until as late as 1954, when Stork et al.[5] pointed out that the charge separated cannonical form (2) might be expected to make a marked contribution to the properties of these compounds, rendering them susceptible to electrophilic attack at the β carbon atom. The experimental trials made by these workers, of alkylation of pyrrolidenamines of simple ketones, such as cyclohexanone, with alkyl halides (e.g. Fig. 1.2) and also activated olefins, proved successful, thus confirming the supposition. Alkylation and acylation by the Stork reaction, with various modifications and extensions, provides the basis for most of the subsequent work. The rapid development of methods of characterization of the enamine system by Leonard and Gash (1954)[6] and also Witkop (1954)[7] proved invaluable to the development of enamine chemistry.

1.3 Note on Scope of Introduction

The subject matter of this introduction falls into two categories (a) properties of simple enamines and (b) reported reactions of steroidal enamines. The literature on simple enamines has already been ably reviewed[8-12,181]. Since, however, the experimental work and mechanistic discussion which constitute the bulk of this thesis builds upon that using simpler systems, a brief review of their more important and germane properties should not be omitted here.

Of the selection criteria applied to the literature on steroidal enamines to justify inclusion in this introduction a major consideration was preparative value, for example precedence was given to reactions with reasonable yield. Also an attempt was made to include examples of the major types of reaction, rather than detail every example. For the period 1954 to 1969 references to the reactions of steroidal enamines were obtained largely via two sources (a) the various indices of Chemical Abstracts and (b) the reviews noted above. From September 1969 to August 1975 the sub-section on enamines of the chapter "Steroid Properties and Reactions" in "Terpenoids and Steroids[182]" proved a valuable guide. Section 32 (Steroids) of Chemical Abstracts was surveyed for the following period to date (Vol.86, no 24, 1977).

1.4 Synthesis from Ketones

1.4(a) The most general method for the preparation of enamines of ketones (Herr and Heyl[4]) is that of refluxing a solution of the ketone in benzene, or some other water azeotroping solvent, with an excess of amine, using a trap to collect the water produced. The progress of reaction may be followed by the amount of water collected and reflux terminated when appropriate. The rate of reaction is very dependent on the nature of the ketone. Where necessary, due to the slowness of

the reaction, a small amount of an acid catalyst such as *p*-toluene sulphonic acid[13] may be added, or a higher boiling solvent such as toluene[14] may be employed. Many variations of procedure have been used to remove the generated water and drive the reaction forward, e.g. the mixture has been treated with molecular sieve[15] which catalyses[183] enamine formation as well as acting as dehydrating agent; also the distillate has been trickled through some dessicant such as calcium carbide[15] before being returned to the reaction flask. One modification which may be useful for certain pyrrolidenamines[15] consists merely of preparing an almost saturated solution of the steroid ketone in question, from which, on the addition of pyrrolidine, the enamine precipitates and may be filtered off. There is considerable selectivity for the different secondary amines in the carbonyl groups with which they will react[4,35,37,38,39], this being particularly noticeable in the steroid series; thus, for example, under the usual conditions pyrrolidine will react with a C-3 (or C-17) carbonyl function but not with a C-20 or C-11 ketone.

1.4(b) One water scavenging agent, which also promotes reaction by polarizing the carbonyl bond is the Lewis acid titanium tetrachloride[16], which reacts as in Fig. 1.3. Of particular importance is that some enamines which cannot be prepared by the more conventional methods, can easily be produced using this reagent under mild conditions (0-10°).

1.4(c) /

1.4(c) An interesting method for the preparation, not of an enamine, directly, but of the corresponding iminium salt[17] e.g. (18) consists of mixing solutions of the ketone and an amine salt, usually pyrrolidinium perchlorate, in an appropriate solvent, when the iminium salt precipitates and is filtered off.

1.5 Spectroscopic Properties

1.5(a) N.m.r.[18,19]

The olefinic proton appears about 5 to 4δ. The resonance is indicative of the extent of overlap between the electron pair on the nitrogen atom and the double bond, the greater the overlap the higher the field at which it appears. In simple pyrrolidenamines the four α-hydrogen atoms on the pyrrolidine ring give rise to a complex multiplet, which in the steroidal series becomes a characteristic hump about 3δ.

1.5(b) I.r.[6,20]

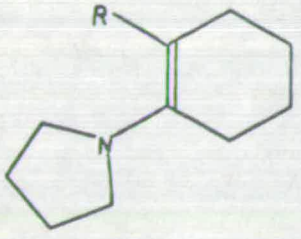
The double bond appears about 1630 to 1660cm^{-1} and shifts 20 to 50cm^{-1} towards higher frequency on conversion to the iminium salt by the addition of anhydrous acid.

1.6 Structure

1.6(a) Planarity

In order for the resonance delocalization previously ascribed to enamines to occur, it is necessary that the p orbitals of the nitrogen and of the double bond carbon atoms, overlap. For this

Fig. 1.5 Possible Structures of the Pyrrolidenamine of 2-Alkylcyclohexanone



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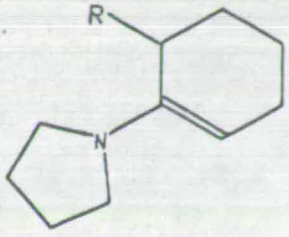

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Fig. 1.6 Steric Interference in the Tetrasubstituted Pyrrolidenamine of 2-Methylcyclohexanone

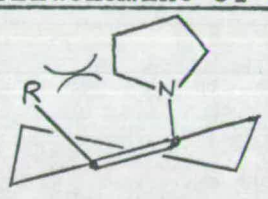

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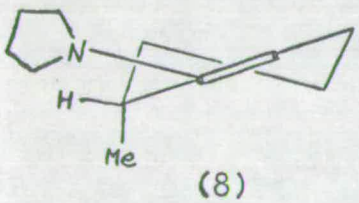
Fig. 1.7 Possible Conformations of the Trisubstituted Pyrrolidenamine of 2-Methylcyclohexanone



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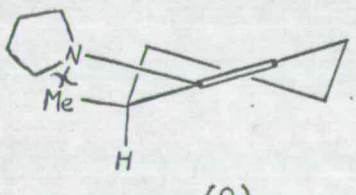

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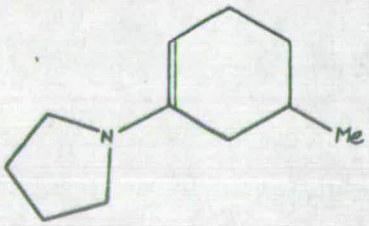
Fig. 1.8 Isomers of the Pyrrolidenamine of 3-Methylcyclohexanone



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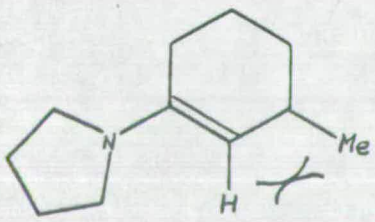


(11)

condition to be satisfied it is necessary that the seven atoms indicated (4), illustrated for the pyrrolidenamine of cyclohexanone, be approximately co-planar. The charge separated cannonical form may be regarded as the planar contribution and other factors being equal, the greater the stability of this form, the more planarity there will be. It is known, according to Brown's postulate[21,22], that a double bond exo to a five membered ring such as with pyrrolidine is more stable than a corresponding double bond exo to a six membered ring, as with morpholine or piperidine; so the charge separated cannonical form in the pyrrolidenamine case should make a larger contribution than in the six membered ring cases, i.e. pyrrolidenamines should be more planar (and delocalized) than the corresponding morpholine and piperidine enamines. In practice it is found from the resonance of the olefinic proton that there is indeed a considerable difference (ca. 25Hz at 60 MHz)[18,19] in the expected direction; thus some experimental support is available for the planarity of enamines, particularly pyrrolidenamines.

1.6(b) Structure of Enamines of 2-Substituted Cyclohexanone

1.6(b)(i) Position of the double bond

It has been shown by n.m.r. studies that the pyrrolidenamine of 2-methylcyclohexanone is largely (90-100%) the trisubstituted isomer (6)[14,18]. Also the pyrrolidenamine of 2-phenylcyclohexanone[23] fails to show any of the styrene type of absorption in the ultraviolet which would be expected for the tetrasubstituted isomer (5). This is readily understood in terms of the steric interaction between the substituent and the methylene group adjacent to the nitrogen atom in the tetrasubstituted isomer, if planarity is maintained, as

illustrated (7). This however does not hold true for all amines, as reflected in the isomer ratios shown in Table 1.

TABLE 1 - Isomer Distribution of the Enamines of 2-Methylcyclohexanone (after Cook[24])

Amine	% Tetrasubstituted	% Trisubstituted
Pyrrolidine	10	90
Morpholine	48	52
Piperidine	54	46
Diethylamine	75	25
N-Methylaniline	100	0

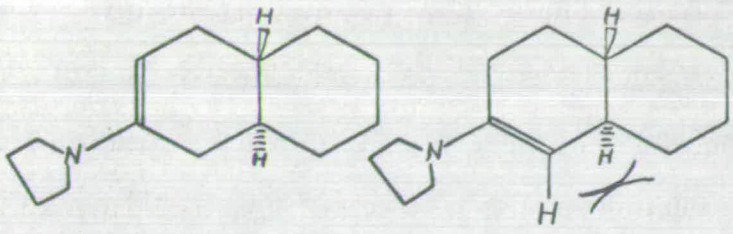
1.6(b)(ii) Conformation

The preferred conformation of a cyclohexene ring is the half chair[25]. Thus there are two possible conformations of the trisubstituted pyrrolidenamine of 2-methylcyclohexanone, with the methyl group a) quasi-axial (8) and b) quasi-equatorial (9). It is clear that of the two, the more stable is the quasi-axial, since in the other conformation there is considerable steric interference between the methyl and the methylene group adjacent to the nitrogen. This type of allylic steric effect has been generalized by Johnson and Malhotra[26,27] as $A^{(1,2)}$ strain. A number of experiments[28-32] substantiate this prediction of quasi-axial conformation.

1.6(c) Position of the Double Bond in Enamines of 3-Substituted Cyclohexanone, Trans-decal-2-one and Steroids

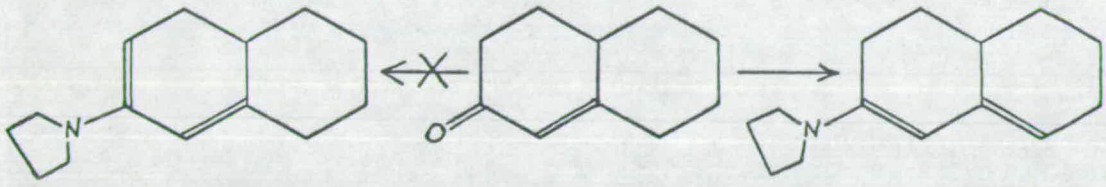
The pyrrolidenamine of 3-methylcyclohexanone has been shown by n.m.r. studies[33,34] to be predominantly (about 70%) the Δ^6 isomer (10). This is understood by the presence of $A^{(1,2)}$ strain

Fig. 1.9 Isomers of the Pyrrolidenamine of Trans-decal-2-on



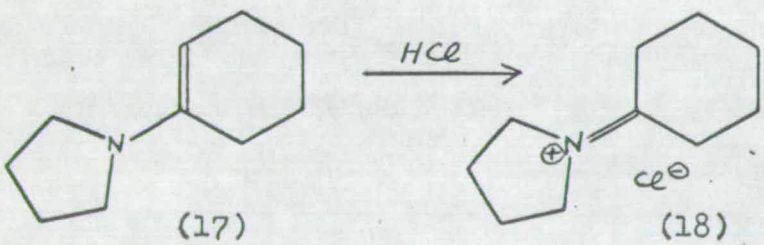
(12) (13)

Fig. 1.10 Examples of Dienamines



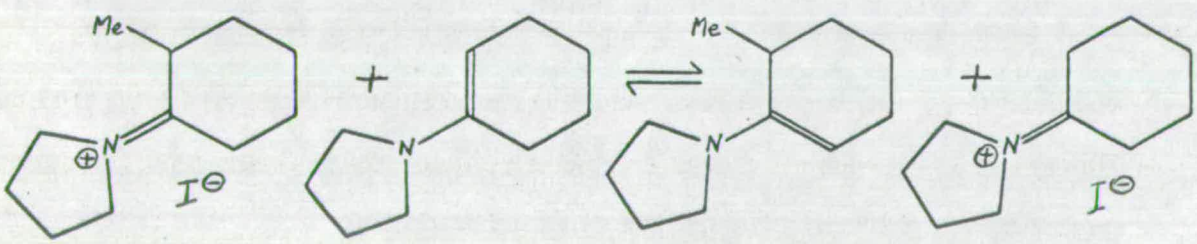
(16) (14) (15)

Fig. 1.11 Example of Iminium Salt Formation



(17) (18)

Fig. 1.12 Formation of the Monosubstituted Enamine in the Stork Reaction



(19) (20) (21)

between the equatorial methyl group and the olefinic hydrogen atom in the alternative Δ^1-isomer (11). The pyrrolidenamine of trans-decal-2-one, which bears considerable resemblance to the above, is found to behave similarly[33], about 72% being the Δ^2-isomer (12). In this case the disfavouring of the Δ^1-isomer (13) has been attributed to the analogous $A^{(1,2)}$ strain between the C-8 methylene group and the C-1 olefinic proton. For the same reasons the enamines of 3-keto-steroids are assigned the Δ^2-structure in the 5α and Δ^3 in the 5β - series[35,68,69].

1.6(d) Dienamines

Bicyclic α β -unsaturated ketones such as $\Delta^{1(9)}$-octal-2-one (14) give the heteroannular dienamine (15) rather than the homoannular compound (16) as shown by ultra-violet spectroscopy[36]. The same is true of the corresponding Δ^4-3-ketones of the steroid series[15,35], such as testosterone. Some reactions[184] of this type of compound, including the hydrolysis[185] have been compared with those of the corresponding dienol ethers.

1.7 Some Chemical Properties

1.7(a) Protonation

With the addition of an anhydrous acid to a solution of an enamine e.g. (17) the corresponding iminium salt e.g. (18) is formed[15]. These salts may be of considerable value in characterizing the parent enamine, as well as in purification procedures.

1.7(b) Hydrolysis

The rate of hydrolysis of enamines to the parent ketones depends greatly on whether the enamine is a simple one or a dienamine. Simple steroidal enamines generally react in the cold immediately on adding water but dienamines may require reflux for several hours in a sodium acetate-acetic acid buffer[35,185]. Steroidal enamines give the appearance of great water sensitivity because of the small amount of water required. Much care is required therefore to maintain anhydrous conditions.

1.7(c) The Stork Reaction

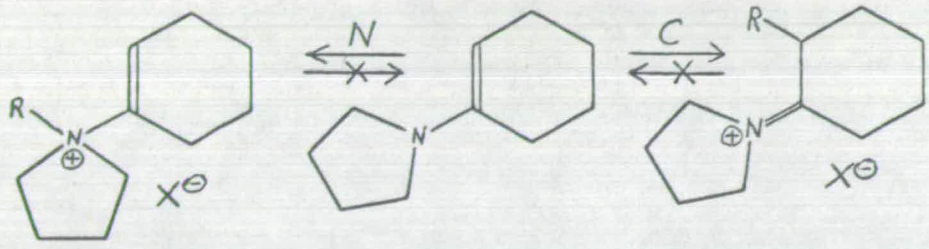
1.7(c)(i) Monosubstitution

The term 'Stork reaction' already mentioned in section 1.2 is a general term for the alkylation or acylation of a carbonyl compound through the enamine. This reaction on a ketone usually yields only the monosubstituted compound[14], or sometimes, under forcing conditions, the $\alpha\alpha'$-disubstituted ketone[14]. This is in marked contrast to the base catalysed alkylation of ketones[40], which reaction can generally only with some difficulty be made to produce a good yield of monosubstituted product. Further reaction yields the $\alpha\alpha$-disubstituted compound and indeed complete reaction may occur producing the tetrasubstituted derivative. Thus, effectively, the Stork reaction provides a two stage method for the synthesis of the α-monosubstituted derivative of the parent ketone.

It is of considerable practical importance and theoretical interest to investigate why monosubstitution should be the rule. Using the same example as before it is clear that the iminium salt (19) intermediate in the Stork reaction can give up HI to a competing base such as the original enamine (20) thus giving rise to a new

Fig. 1.13 Examples of C and N-Alkylation

(a) Alkyl Halides (RX)



(b) Activated Olefins ($>C=C<_{M}$: M = CN, COOR, COR etc.)

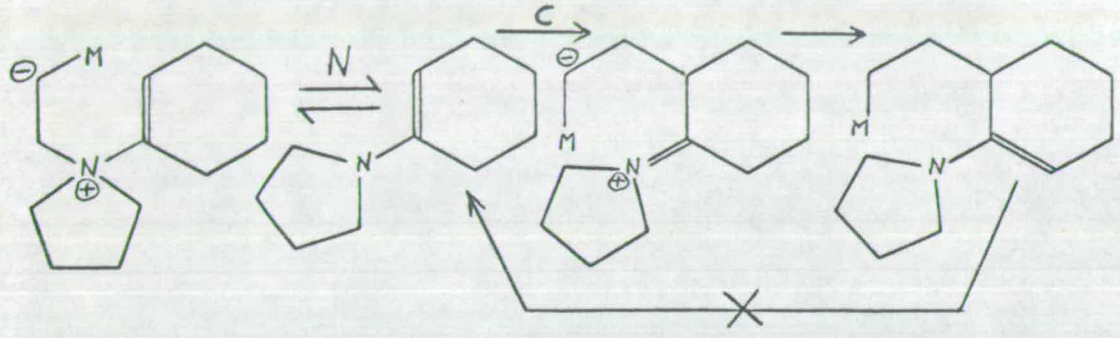
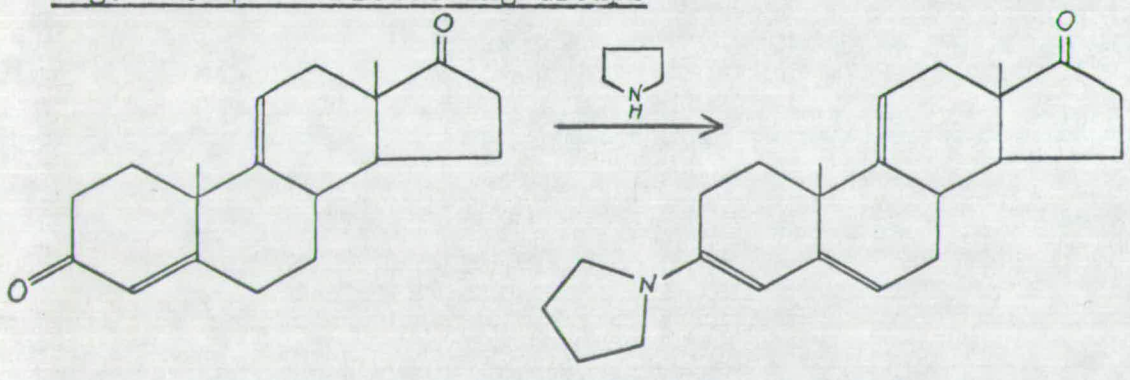
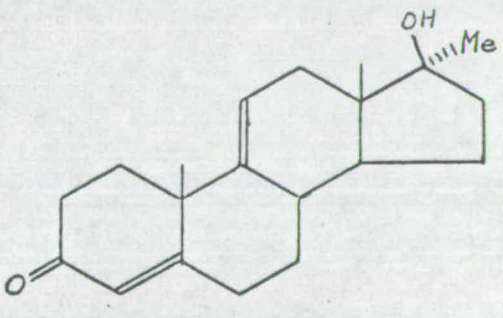


Fig. 1.14 Protecting Groups



(1) $MeMgBr$ (2) H_2O →



enamine (21), which might now be expected to alkylate again at the α'-position. Experimentally however it is found that if this enamine is made and refluxed for many hours with methyl iodide no further reaction will occur[14].

It has been shown in section 1.6(b)(ii) that the conformation of the enamine (21) is such that the methyl group is quasi-axial (8). It is clear then that the second alkylation, being subject to stereo-electronic control, would involve a severe 1,3-diaxial alkyl-alkyl interaction[41].

1.7(c)(ii) C versus N alkylation[14,41-45]

Of the two generally used alkylating agents i.e. alkyl halides and activated olefins, the latter usually produce considerably better yields of the C alkylated product. This is considered to be because in both cases either C or N alkylation is possible. However, N alkylation with activated olefins (Fig. 1.13(b)) is a reversible reaction unlike the corresponding C alkylation. The product of C alkylation is therefore formed at the expense of any initially produced N-alkyl compound in the case of alkylation by activated olefins. With alkyl halides however (Fig. 1.13(a)) both N and C alkylation are irreversible.

The enamines of simple ketones generally alkylate well, giving fair to good yields with alkyl halides. However the higher the molecular weight of the parent ketone, the less useful alkylation by this means becomes; so that with even moderate molecular weights, good yields are obtained only with strongly electrophilic halides.

1.7(c)(iii) Solvent Effect[14]

Increase in the polarity of the solvent generally enhances the Stork reaction, because of the stabilization of the charges appearing in the transition state.

Fig. 1.14 (cont.)

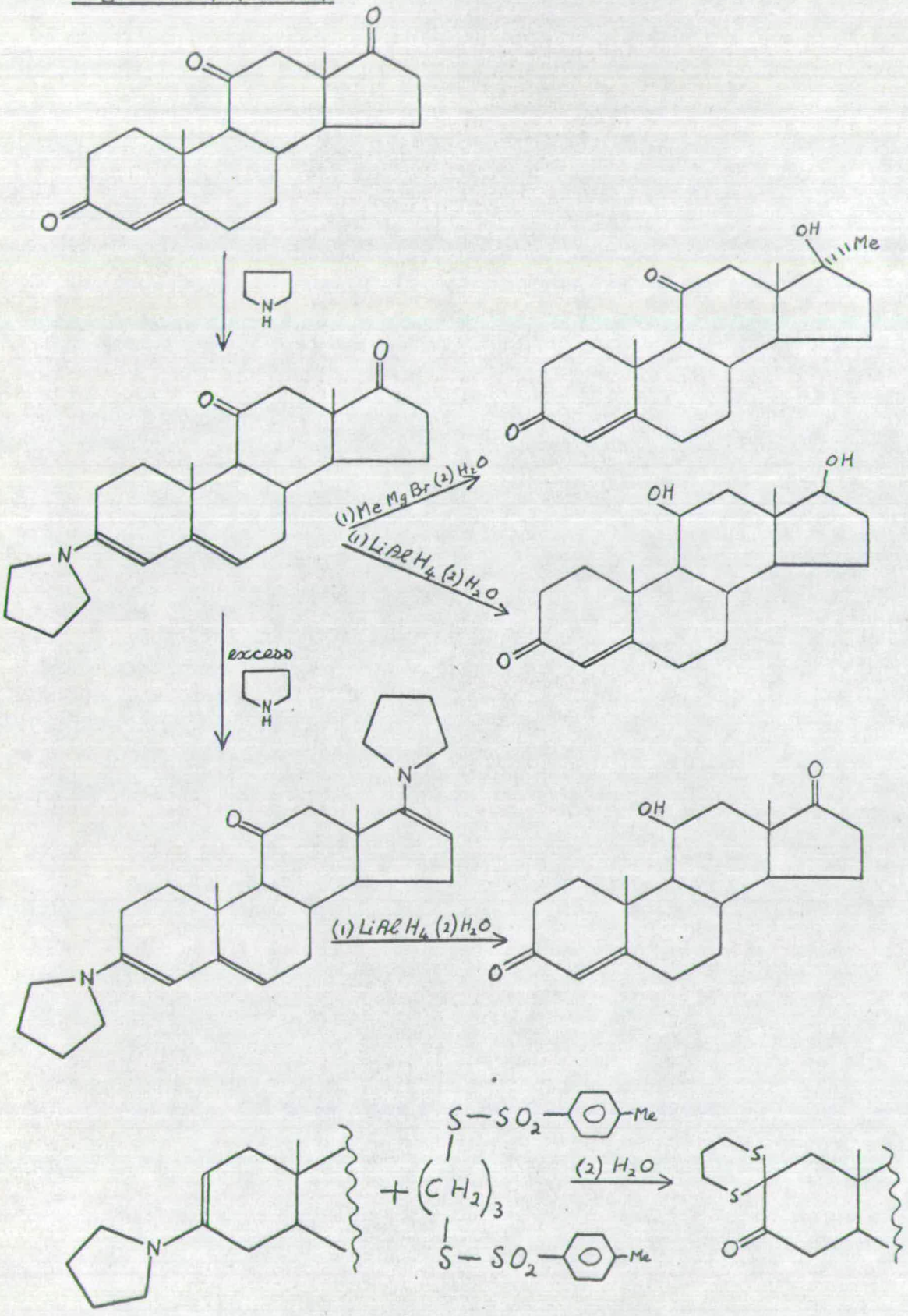
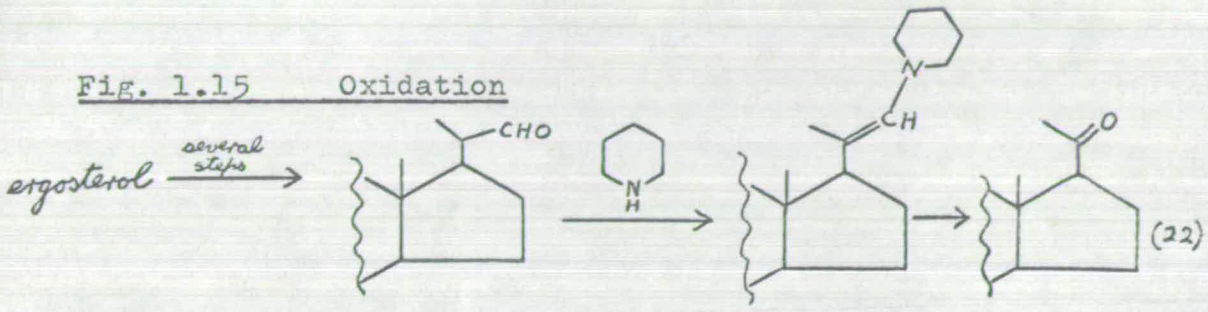
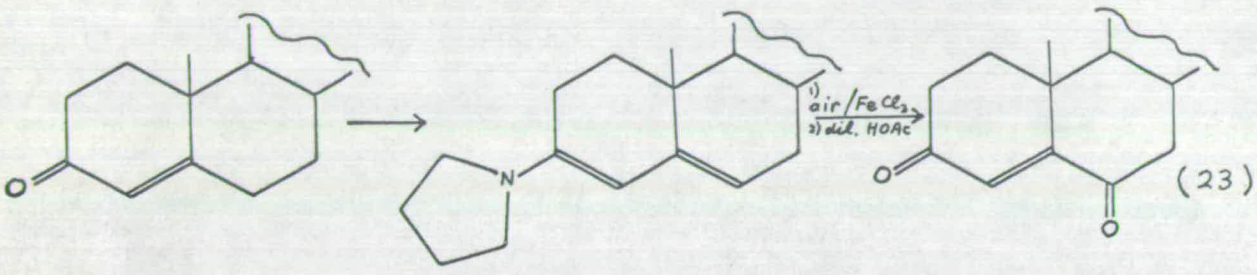
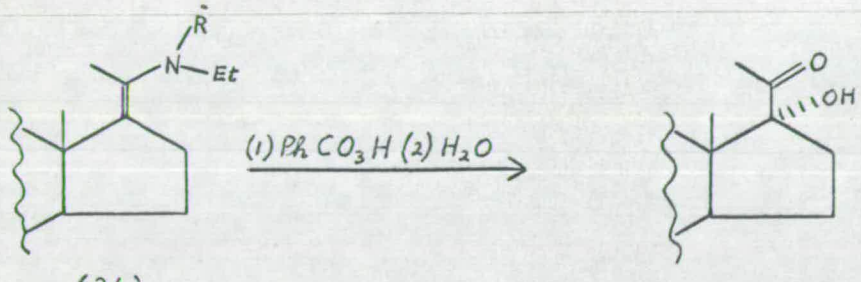

O
O
O
N
H
(1) Me Mg Br (2) H2O
(1) LiAlH4 (2) H2O
OH
Me
OH
OH
excess
N
H
N
N
O
OH
(1) LiAlH4 (2) H2O
S—SO2—Me
+ (CH2)3
S—SO2—Me
(2) H2O
S
S
O
N

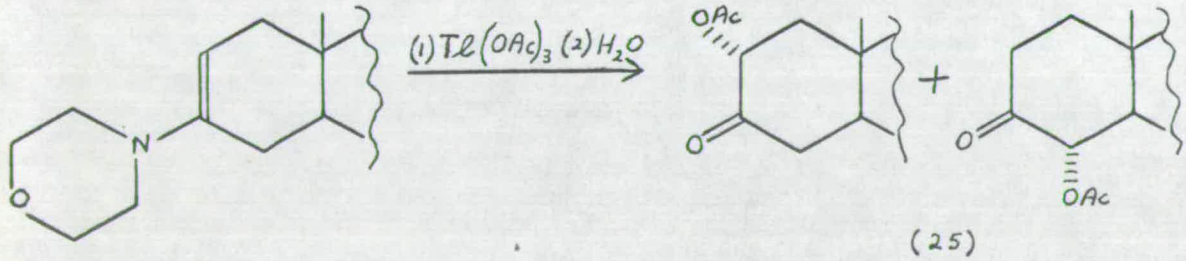
Fig. 1.15 Oxidation





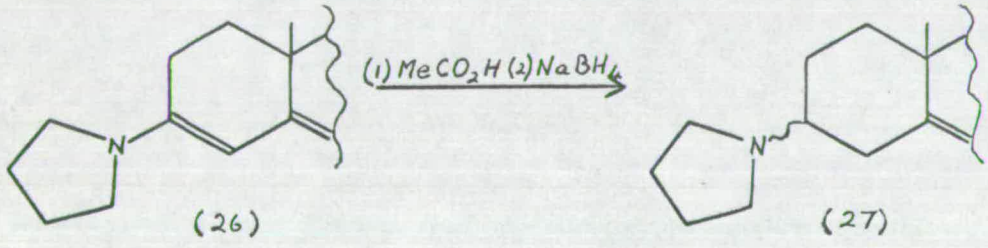


(24)



(25)

Fig. 1.16 Reduction



(26) (27)

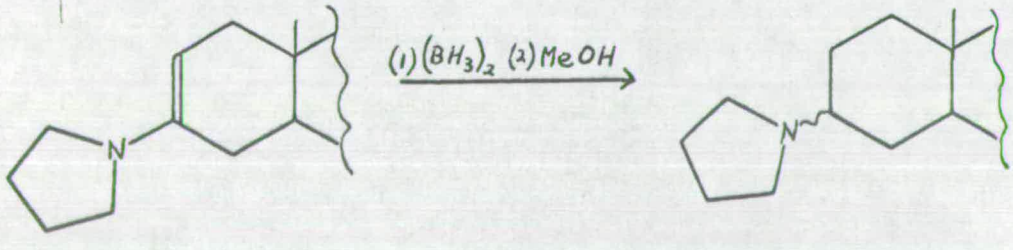
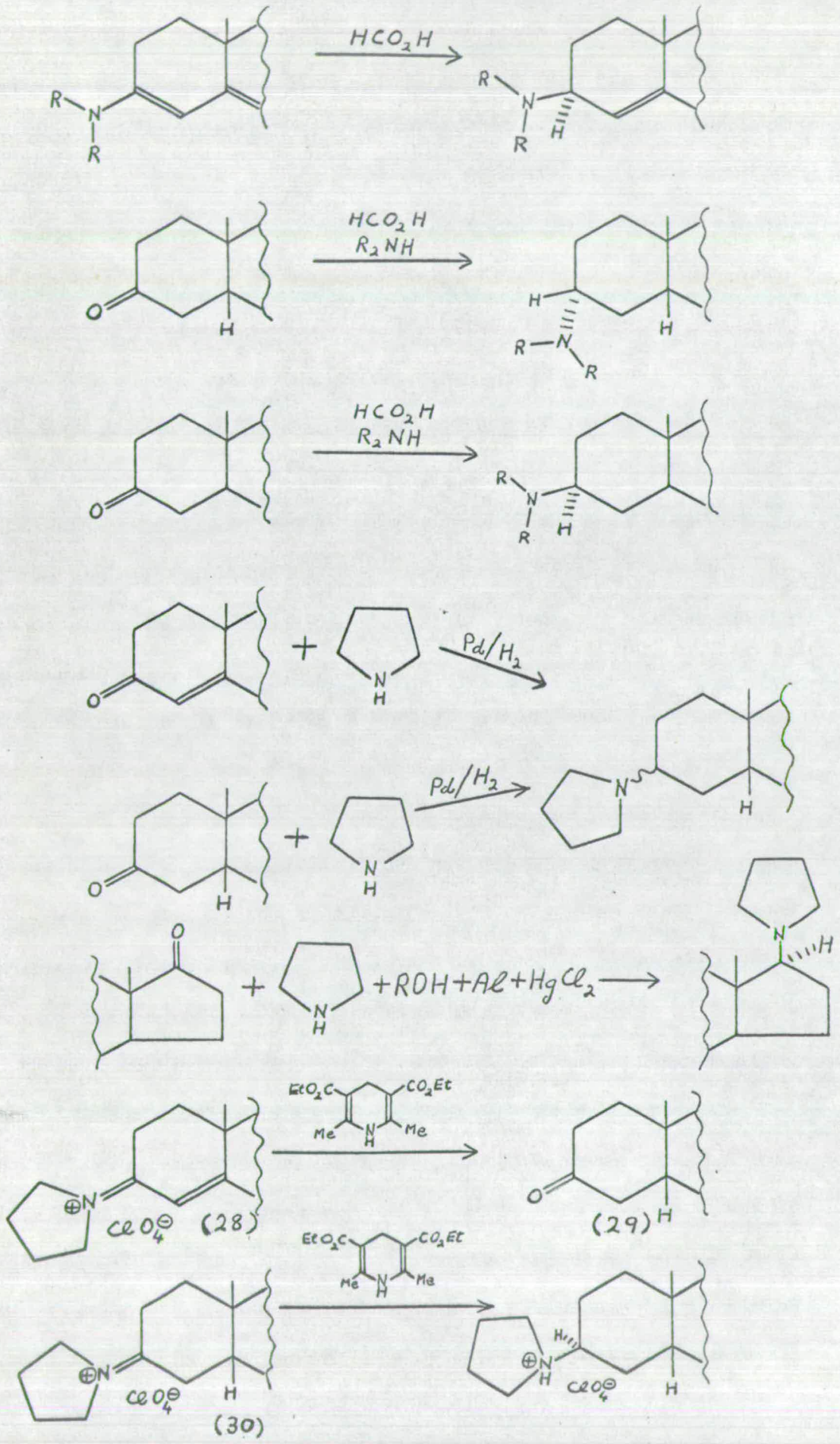


Fig. 1.16 (cont.)


HCO2H
HCO2H
R2NH
HCO2H
R2NH
Pd/H2
Pd/H2
+ROH+Al+HgCl2
EtO2C
CO2Et
Me
Me
ClO4⊖
(28)
(29)
(30)

1.8 Some Applications of Enamines in the Steroid Field

Enamines have found use as protecting groups in nucleophilic reactions since they do not, in the base form, react with anions. In polyfunctional molecules the previously mentioned selectivity of the various amines can be very useful. Some of these uses are illustrated in the syntheses of Fig. 1.14, using as nucleophiles Grignard reagents[48,70] and lithium aluminium hydride[47]. Enamines have also been used via reaction with trimethylene dithiotosylate[71,193] to introduce a thioketal function (Fig. 1.14), which has itself found use as a blocking group[72] in steroid syntheses. The thioketal is readily removed with Raney nickel.

Enamines have also been useful in the oxidative degradation of aldehyde-containing side chains[4,38,39]. Thus, progesterone (22) was prepared from ergosterol[38]. The same product was prepared in quantitative yield via reaction with singlet oxygen in a photo-oxygenation reaction[186]. Bubbling air through a solution of the dienamine from a Δ^4-3-ketosteroid in the presence of ferric chloride, cupric acetate or cupric chloride, followed by hydrolysis, produced a 64 to 75% yield of the Δ^4-3,6-diketosteroid (23). This autoxidation proceeds via a radical chain mechanism[187]. Oxygenation of the enamine system with perbenzoic acid[74,75] has been used with derivatives of 20-keto-steroids e.g. (24). The oxidation of enamines with thallic acetate[49] produced a 50:50 mixture of acetoxyketones (25) in yields ranging from 12 to 38%.

Enamines have been reduced to more saturated compounds, many of interesting stereochemistry. Thus, the borohydride[76-78,81,86] reduction of the dienamine (26) gives (27). Hydroboration[82] has also been used (Fig. 1.16). Reducing agents[79,83-85,87-90a] such as formic acid and catalytic hydrogenation produce products such as 3α-amino-5β and 3β-amino-5α-steroids (Fig. 1.16). Reductions of steroidal enamines

Fig. 1.17 Reductive Syntheses

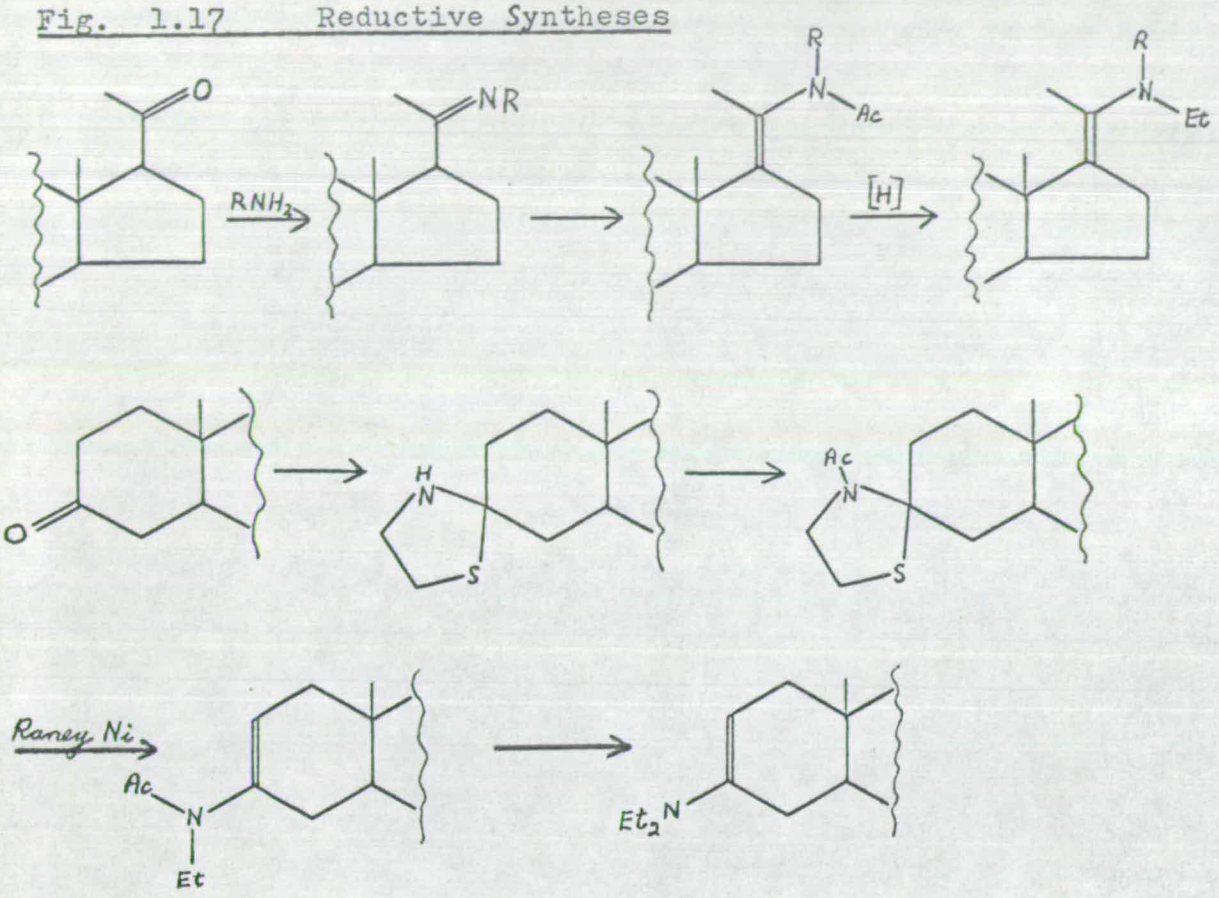


Fig. 1.18 Steroid Synthesis

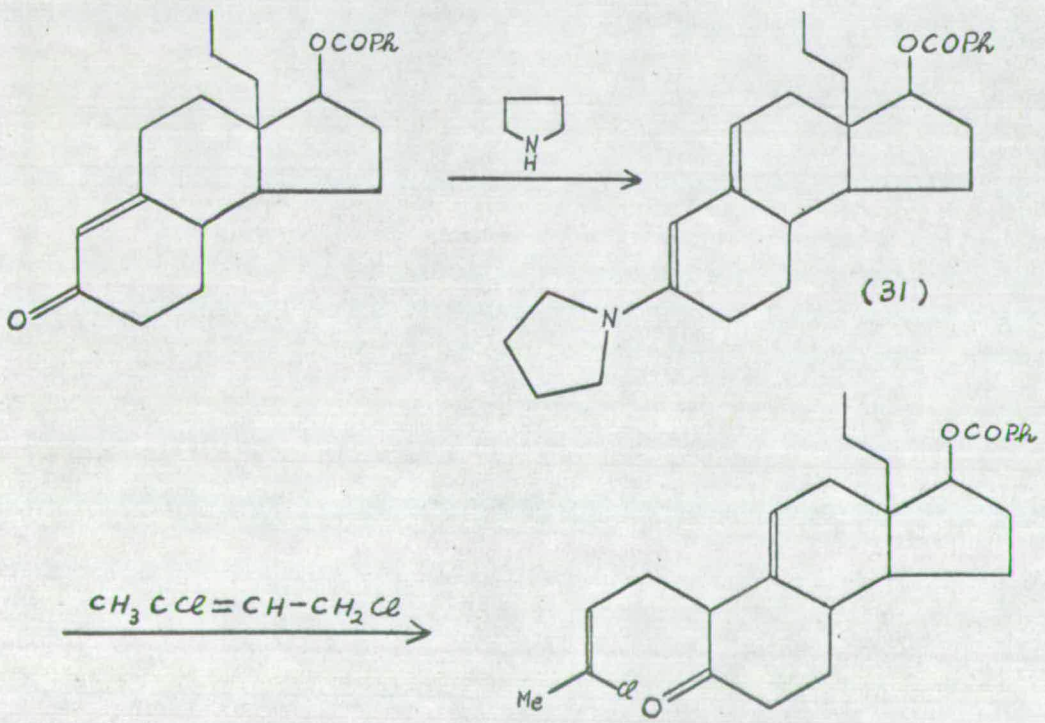


Fig. 1.18 (cont.)

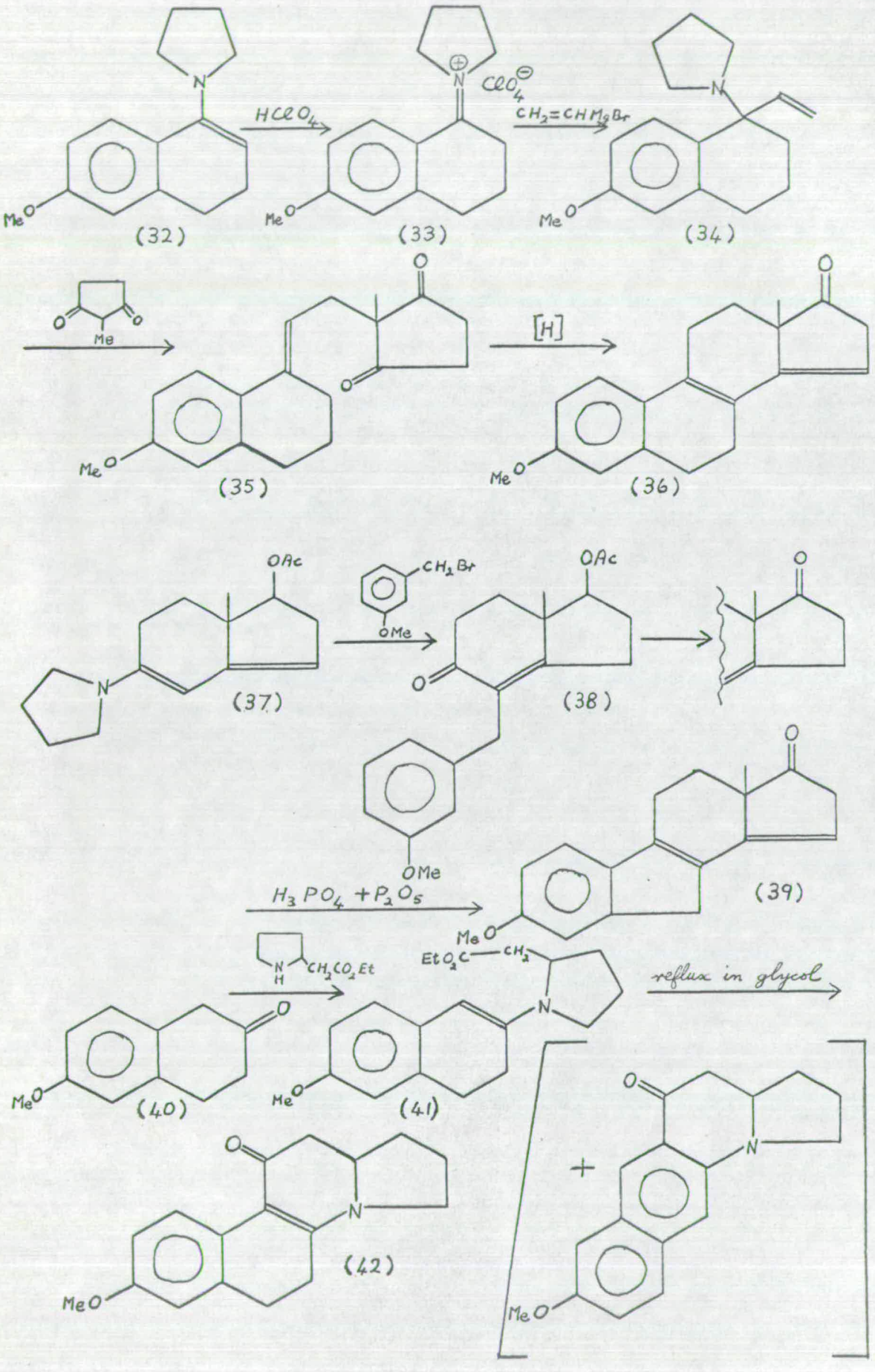
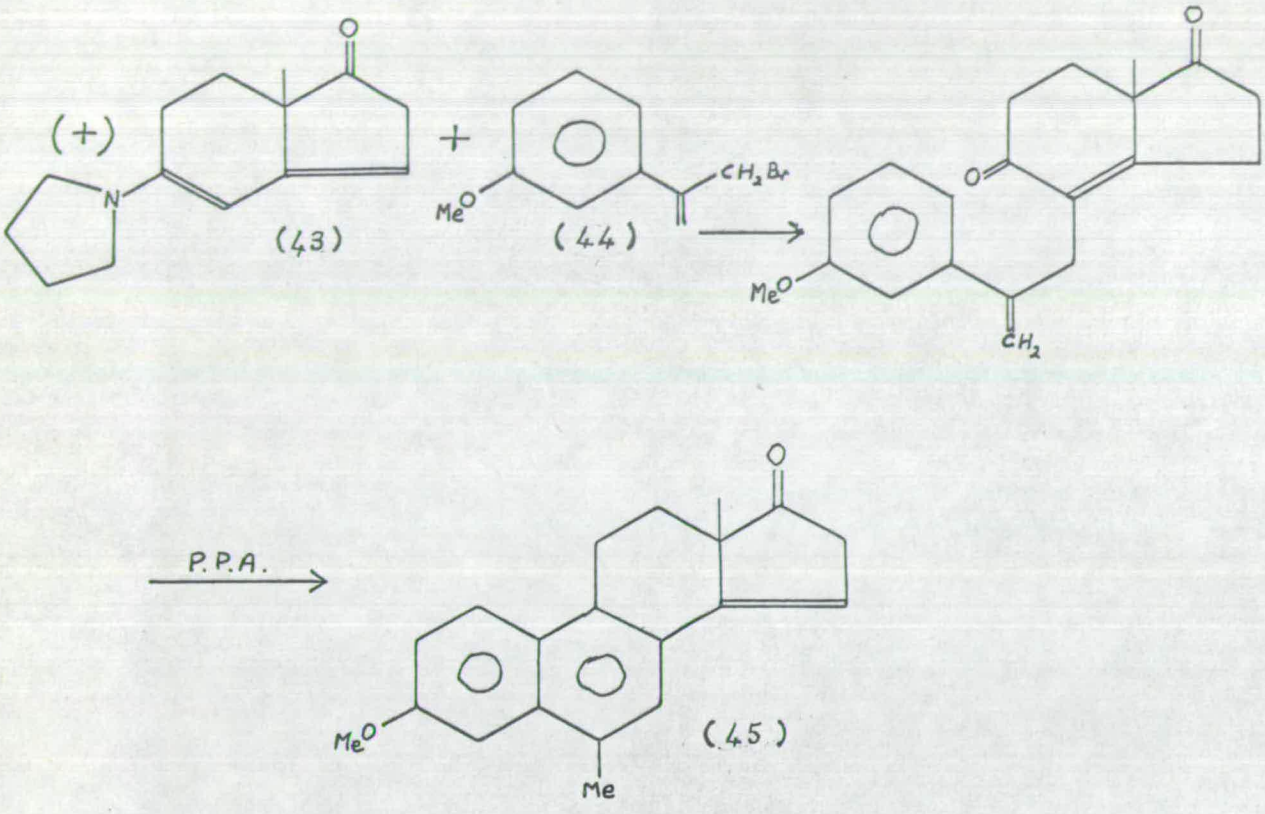

HClO4
ClO4
CH2=CHMgBr
MeO
(32)
(33)
(34)
Me
[H]
(35)
(36)
OAc
CH2Br
OMe
(37)
(38)
(39)
H3PO4 + P2O5
N
H
CH2CO2Et
EtO2C
CH2
reflux in glycol
(40)
(41)
(42)

Fig. 1.18 (cont.)



have also been performed with aluminium and mercuric chloride in ethanol[90b] (Fig. 1.16). The corresponding iminium salts have not escaped attention. Iminium perchlorates[91] from 3-keto-Δ^4-steroids (28) were reduced by Hantzsch ester to 5β-ketones (29). The iminium perchlorates corresponding to the latter (30) could be further reduced to the ammonium salts[92] in better than 90% yield.

While steroidal enamines are generally prepared by the direct reaction of the amine on the ketone, in some cases indirect methods may prove more apposite. For example, with methyl ketones poor yields of the enamine are generally obtained[93]; thus Schiff's bases have been alkylated or acylated and reduced[74] to produce enamines (Fig. 1.17). A similar method uses the formation and desulphurization of N-acylthiazoles[94,95] with subsequent reduction (Fig. 1.17).

Enamines have been used in the synthesis of steroids and analogues e.g. the chain to become an A-ring was added to the dienamine[96] (31) (Fig. 1.18). $\Delta^{8,14}$-steroids, such as 8,14-bisdehydro-estrone methyl ether (36) have been prepared through the 6-methoxytetralone enamine (32). This is converted to the iminium salt (33), which suffers nucleophilic attack by vinyl magnesium bromide. Reaction of the resulting olefin (34) with 2-methylcyclopentan-1,3-dione yields (35) which is reductively cyclized to give the final product[105]. An example of the synthesis of a B-norsteroid is illustrated in Fig. 1.18. The enamine (37) undergoes Stork reaction with m-methoxybenzyl bromide. The product (38), after conversion of the acetate function to carbonyl is cyclized to yield the B-norsteroid (39)[106]. A similar reaction of the (+)-isomer of enamine (43) with the substituted styrene (44), followed by cyclization of the product gives the optically active 13S,17S-dehydroequilenin derivative (45)[194].

Fig. 1.18 (cont.)

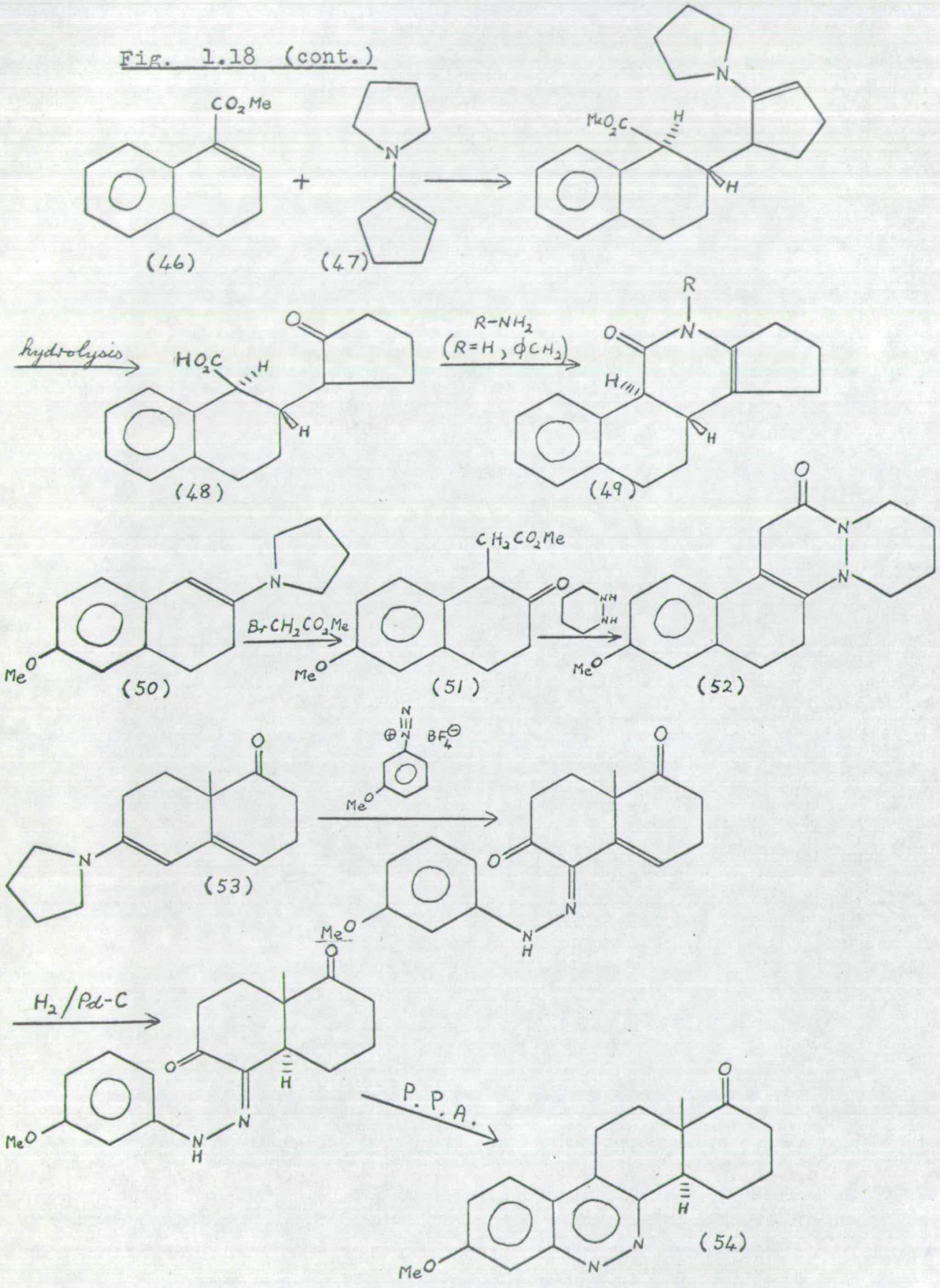

CO2Me
(46)
(47)
MeO2C
H
hydrolysis
HO2C
R-NH2
(R=H, φCH2)
(48)
(49)
CH2CO2Me
BrCH2CO2Me
(50)
(51)
(52)
(53)
BF4
H2/Pd-C
P.P.A.
(54)

Fig. 1.18 (cont.)

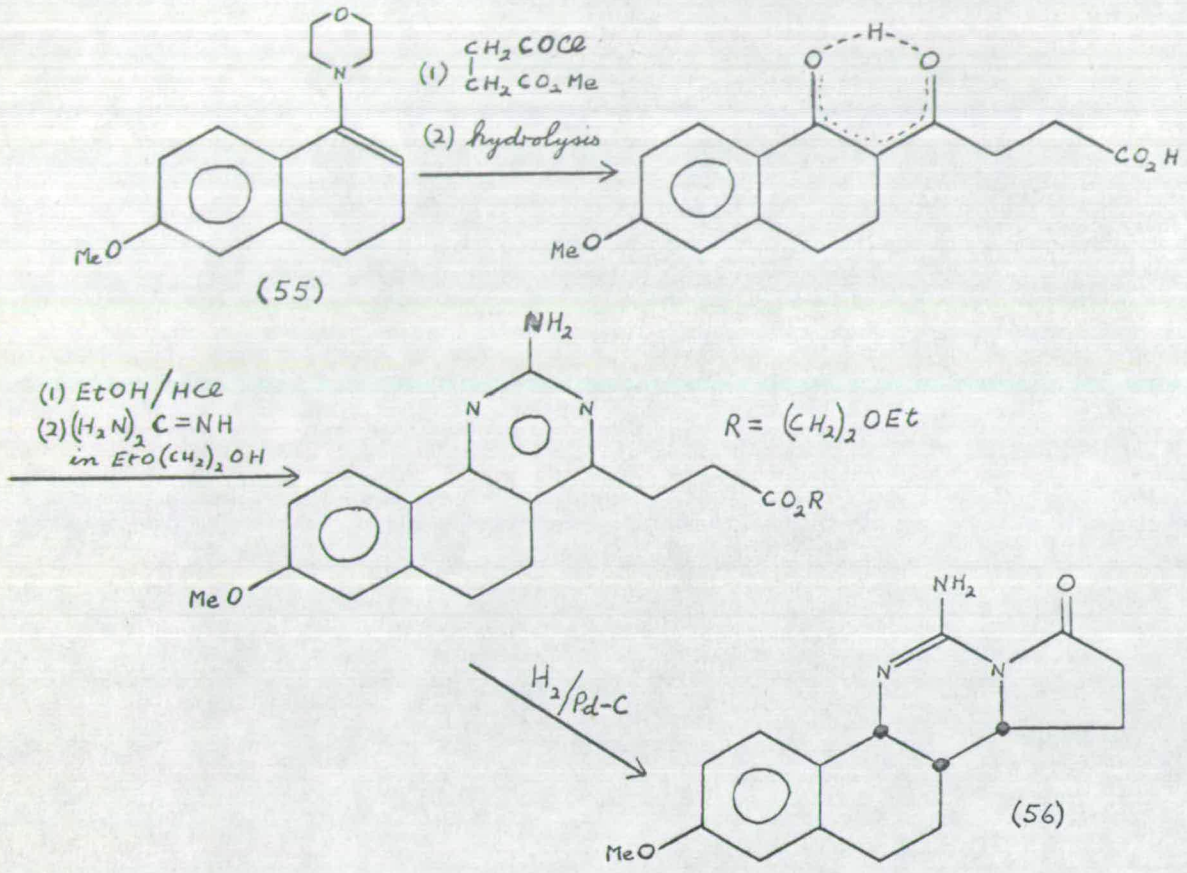


Fig. 1.19 Carbene Reactions

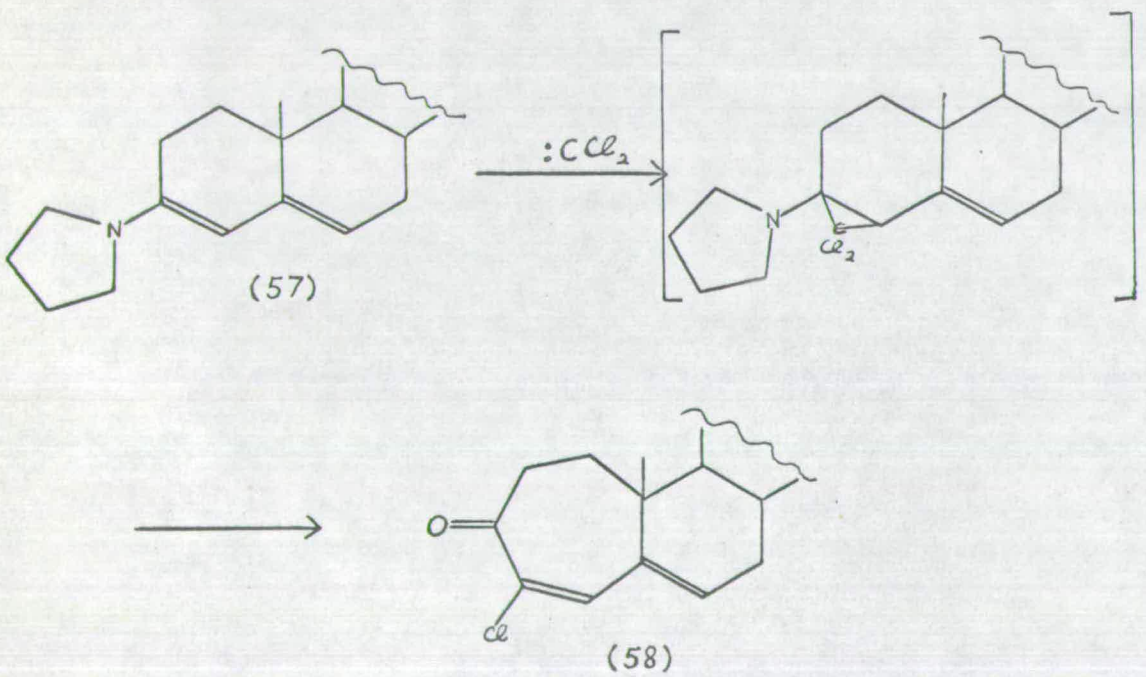
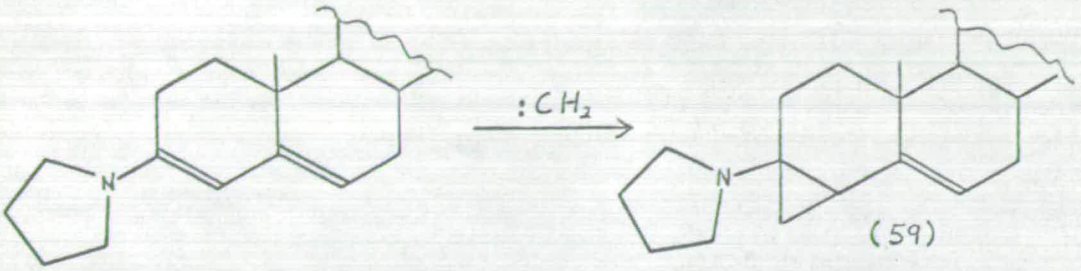
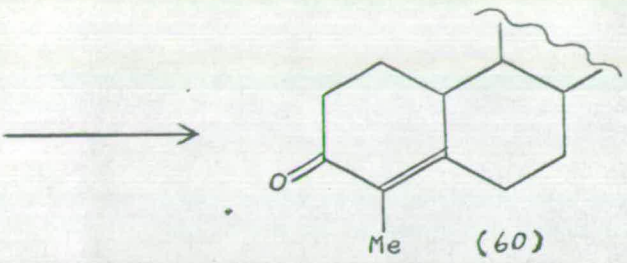


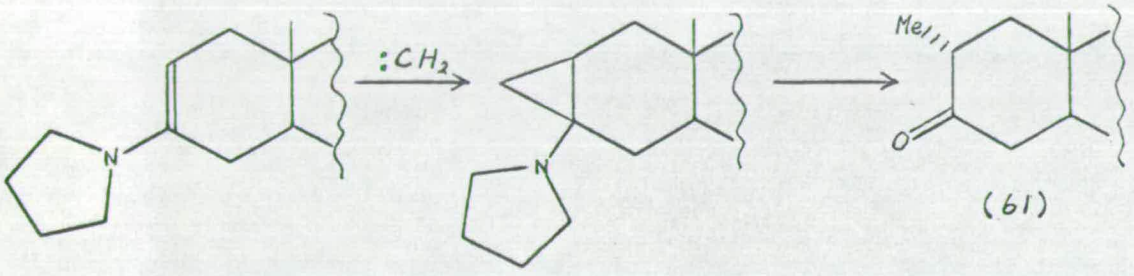
Fig. 1.19 (cont.)



(59)

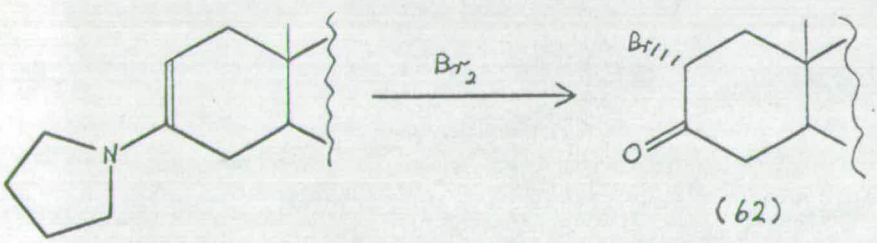


(60)

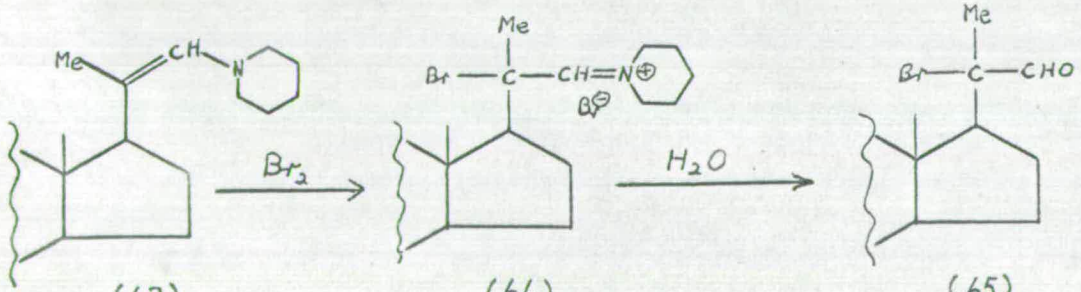


(61)

Fig. 1.20 Halogenation



(62)



(63) (64) (65)

Azasteroid synthesis has also involved enamines. The 14-aza-11-keto-steroid (42) has been prepared via the reaction of the 6-methoxytetralone (40) and ethyl 2-pyrrolidylacetate, to produce an enamine (41), followed by cyclization[107].

The reaction of the enamine 1-pyrrolidinocyclopentene (47) with methyl 3,4-dihydro-1-naphthoate (46), followed by hydrolysis of the product gives the compound (48) which on reaction with ammonia or benzylamine gives the 12-aza-11-keto-steroid (49)[108].

Diazasteroid syntheses using enamines have also been reported. Thus the 13,14-diazasteroid (52) has been prepared by the reaction of the enamine (50) and methyl bromoacetate to produce the compound (51), which is further reacted with a cyclic hydrazine[109].

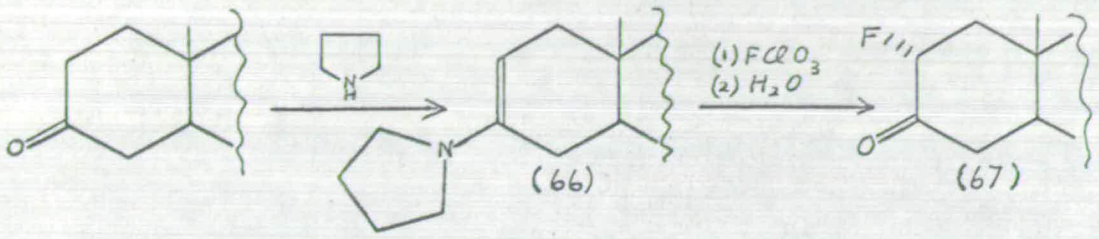
6,7-diazasteroids and 6,7-diazo-D-homo-steroids such as 6,7-diaza-D-homoequilenin methyl ether (54) have been produced by the reaction of the dienamine (53) with a diazonium salt, followed here by catalytic hydrogenation and cyclization with polyphosphoric acid[110,111,112].

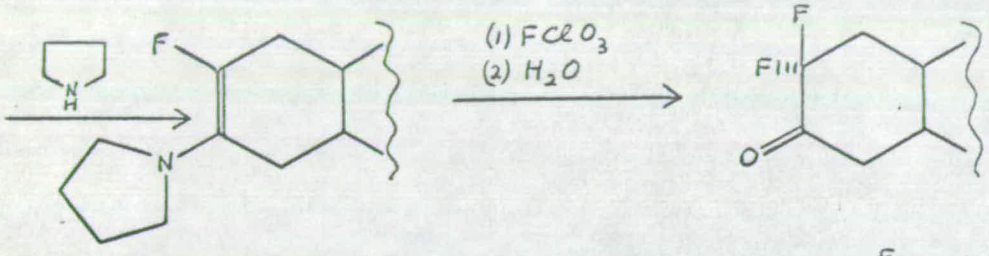
The 11,13-diazasteroid (56) was prepared via reaction of the morpholine enamine (55) with the acid chloride of monomethyl succinate, as illustrated in Fig. 1.18[113].

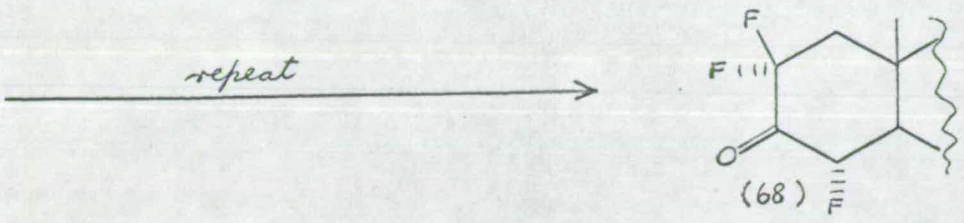
Some reactions of enamines with carbenes have been reported; thus the dienamine[97,188] (57) reacts with dichlorocarbene to give an A-homo-4-chloro product (58). Carbene itself, from either diethyl-zinc and di-iodomethane or diazomethane-copper (I) chloride, reacts with the same dienamine system to give a cyclopropylamine (59), which is readily converted by aqueous ethanol to the 4-methyl steroid[98] (60). The simple enamine system reacts similarly to give the 2α-methyl steroid[98] (61).

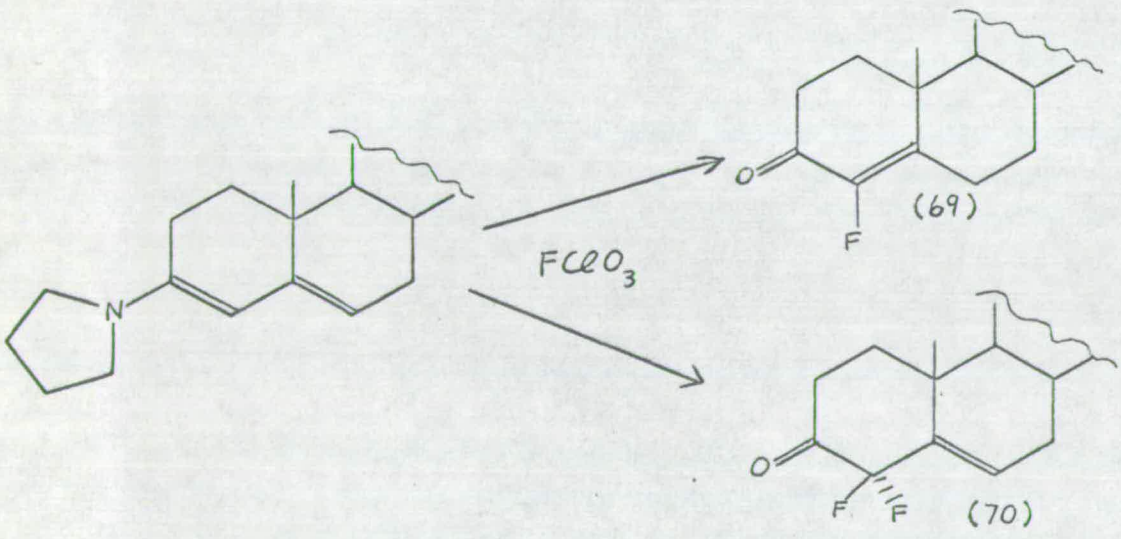
Interesting halogenation reactions have been developed. Bromine reacts with the pyrrolidenamine of cholestan-3-one to give the

Fig. 1.20 (cont.)









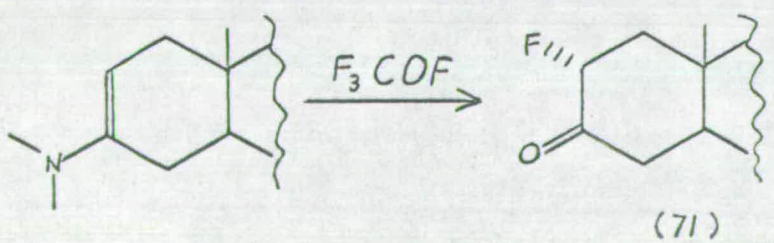
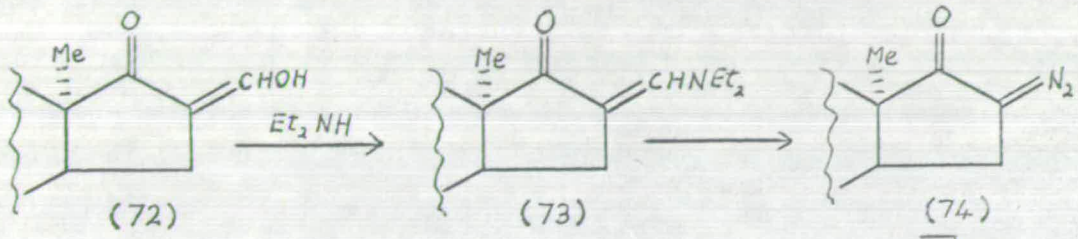
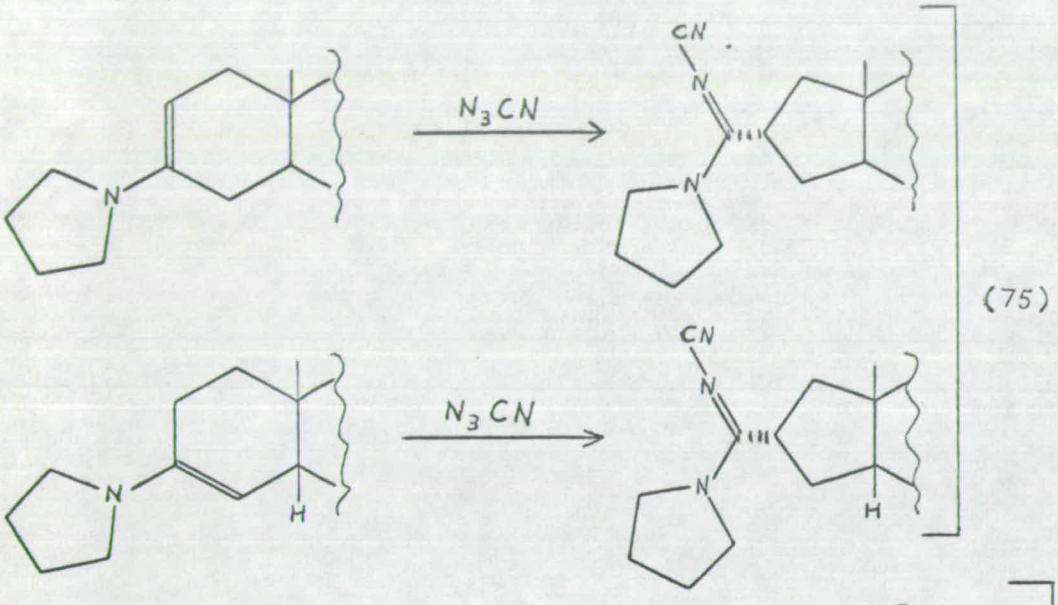


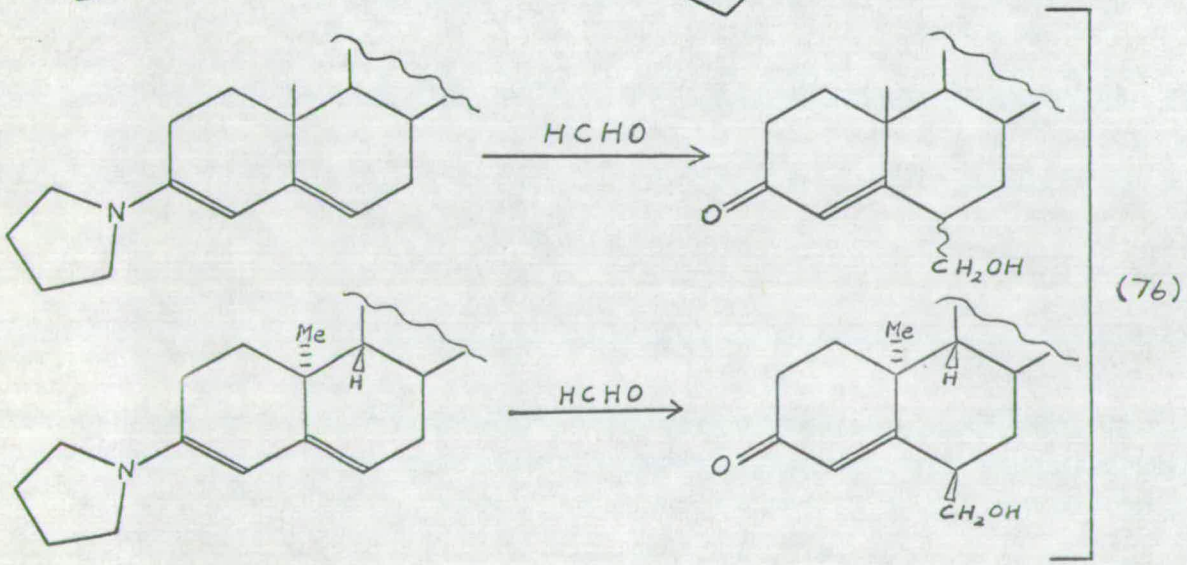
Fig. 1.21 Miscellaneous



(72) (73) (74)



(75)



(76)

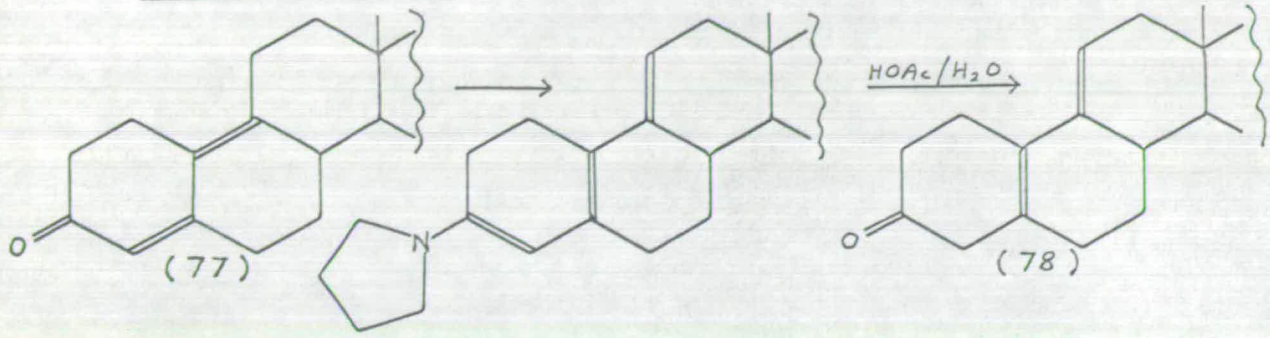
2α-bromocholestanone[49] (62). Treatment of the aldehyde-derived piperidine enamine[58] (63) with bromine, however, yields the β-bromoiminium bromide (64), which is readily hydrolysed to the α-bromoaldehyde (65). More useful are some methods of fluorination. Perchloryl fluoride can be used to achieve up to tri-fluorination with the pyrrolidenamines of 3-keto-5α-steroids[50-53]. Thus, the pyrrolidenamine of 5α-androstan-17β-ol-3-one acetate (66) on treatment with $FClO_3$ yields the 2α-fluoro derivative (67). Two repetitions of the process yields the trifluoro compound (68). The same reagent, with the dienamines of 3-keto-Δ^4-steroids[51,52,53], such as testosterone yields either the mono (69) or di-fluorinated compound (70) depending on reaction conditions. Fluorination with CF_3OF has also been done[55] with the enamines of 3-keto-5α-steroids to give similar 2α-fluoro derivatives (71).

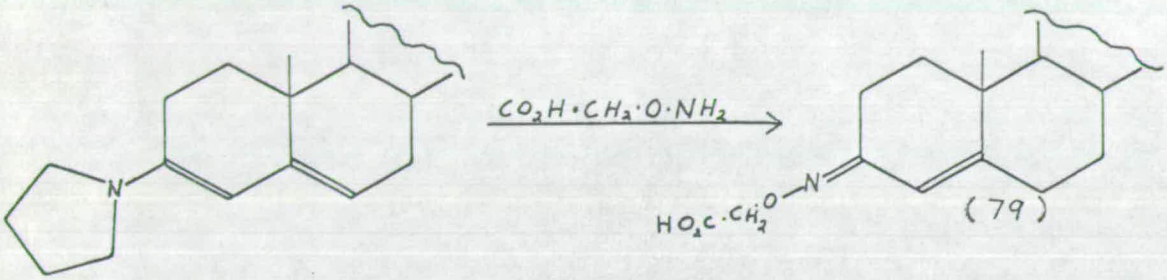
An enamine route to 16-diazo-17-keto-steroids has been used[99] where the usual chloramine oxidation of the oximino ketone gives low yield. The 16-aldehyde (72) which exists largely in the enol form was converted to the enamine (73) by the action of diethylamine. The enamine was further reacted with p-carboxybenzenesulphonyl azide to give the diazo compound (74).

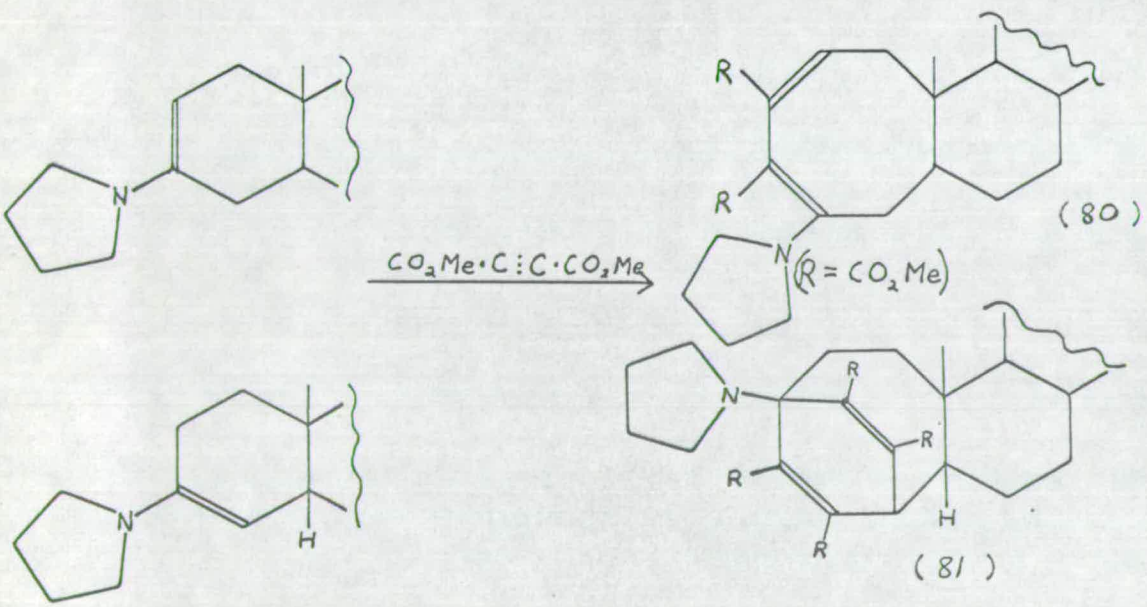
The reaction of cyanogen azide[69] on steroidal enamines has been found to yield the cyanoamidines (75) through a rearrangement in which the A-ring is contracted.

A-ring expansion has been achieved by the reaction of enamines with dimethyl acetylenedicarboxylate[68]. With the pyrrolidenamine of 5α-cholestan-3-one the bis-homosteroid (80) was produced in 75% yield, while with the 5β-steroid coprostan-3-one the double adduct (81) was formed.

Fig. 1.21 (cont.)


HOAc/H₂O
(77)
(78)


CO₂H·CH₂·O·NH₂
HO₂C·CH₂O
(79)


CO₂Me·C:C·CO₂Me
R = CO₂Me
(80)
(81)

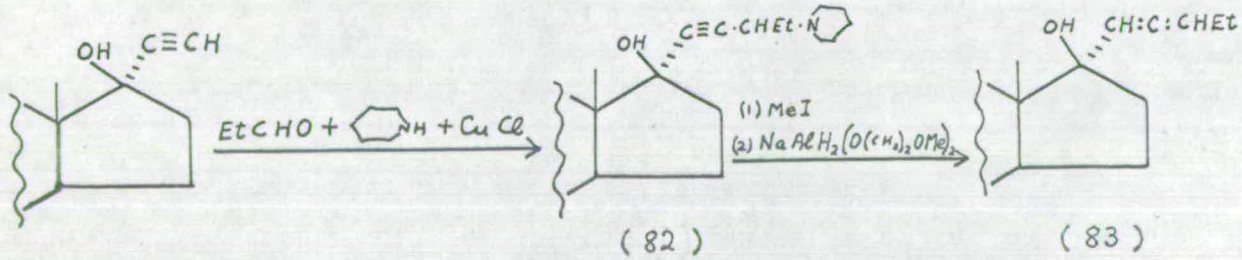

EtCHO +
Cu Cl
(1) MeI
(2) NaAlH₂(O(CH₂)₂OMe)₂
(82)
(83)

Fig. 1.22 Stork Reactions

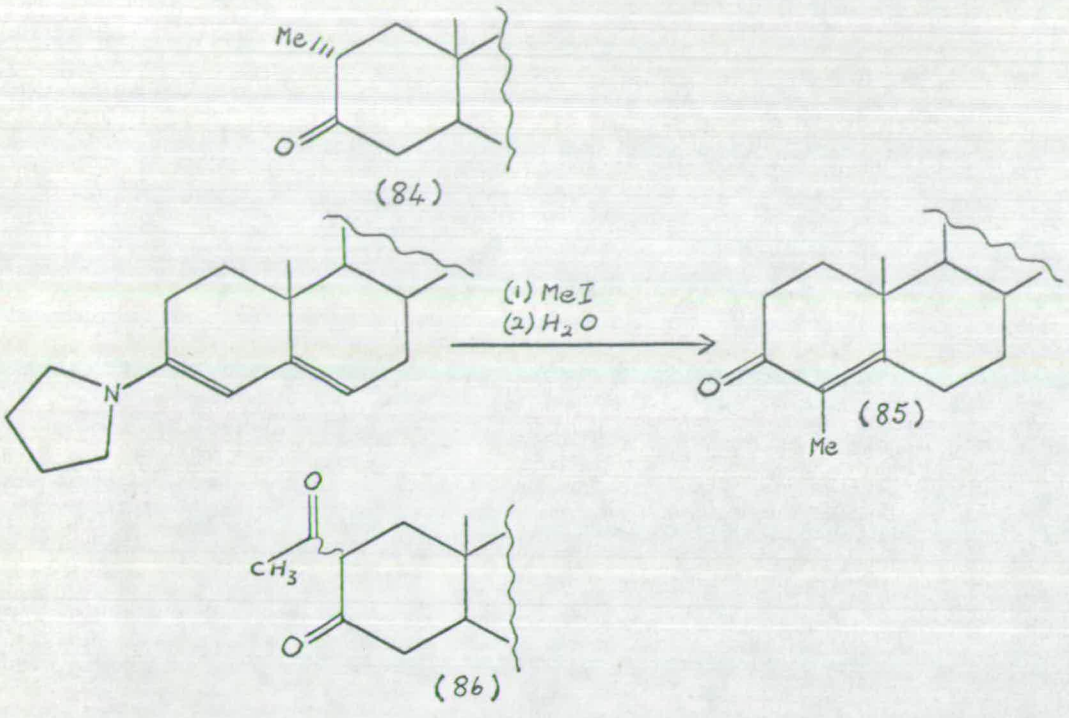
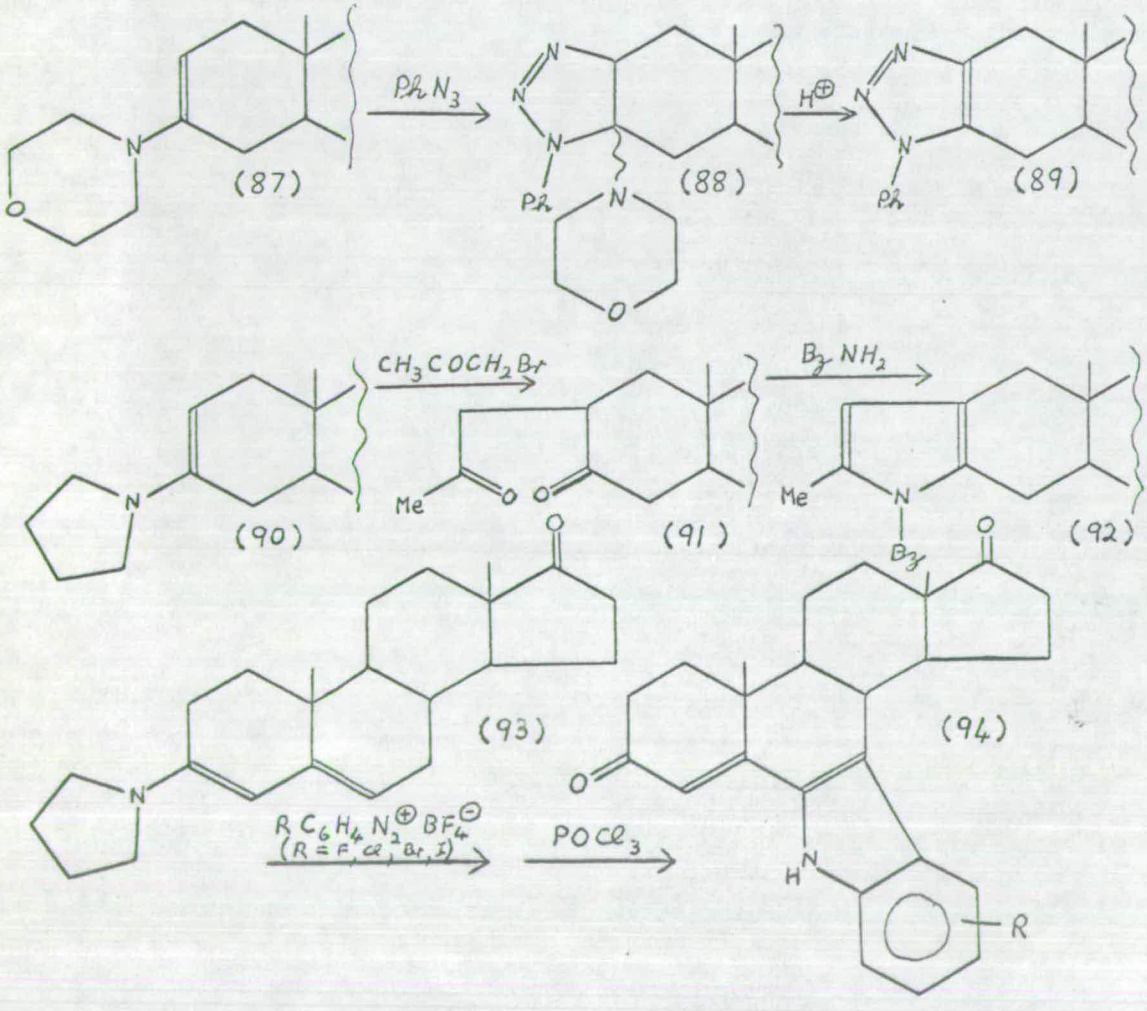


Fig. 1.23 Ring Addition



Formaldehyde has been reported to add at the 4-position to steroidal dienamines to yield alcohols[100] (76).

Deconjugation of the enamines of $\Delta^{4,9}$-dien-3-ones (77) by hydrolysis with acetic acid/water produces the $\Delta^{5(10),9(11)}$-dien-3-ones (78) in yields ranging from 19 to 75%[189].

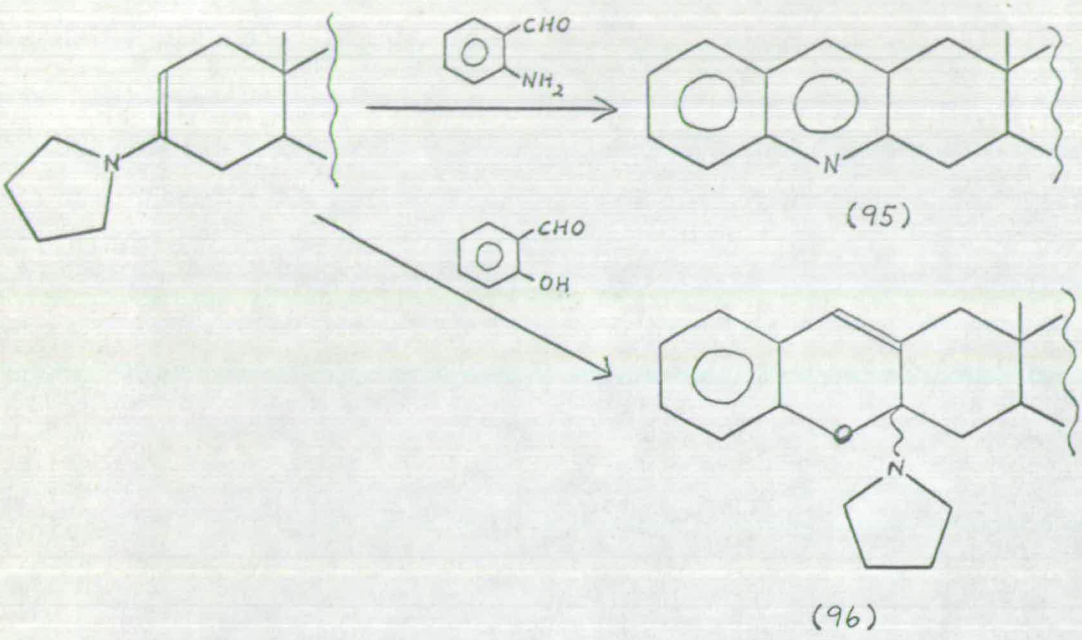
A preparation of a required 3-oxime (79) was reported, where the usual reaction of the steroid (here progesterone) with O-(carboxymethyl) hydroxylamine gave the 3,20-bis-oxime. The 3-pyrrolidenamine was readily prepared and this reacted to produce the desired product[190].

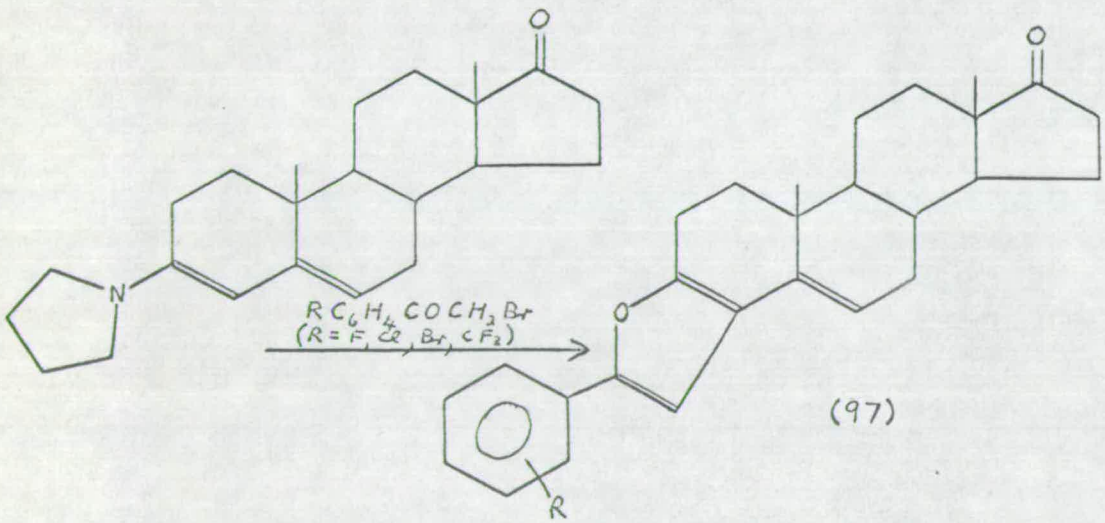
Allene-bearing steroids have been prepared by reaction of an acetylenic side-chain with the iminium form of an enamine formed in situ, followed by quaternization of the nitrogen and reductive elimination of the amine[195]. Thus, the acetylenic group was reacted with a mixture of EtCHO, piperidine and copper (I) chloride to give the amine (82), which was quaternized and reduced to the allene (83).

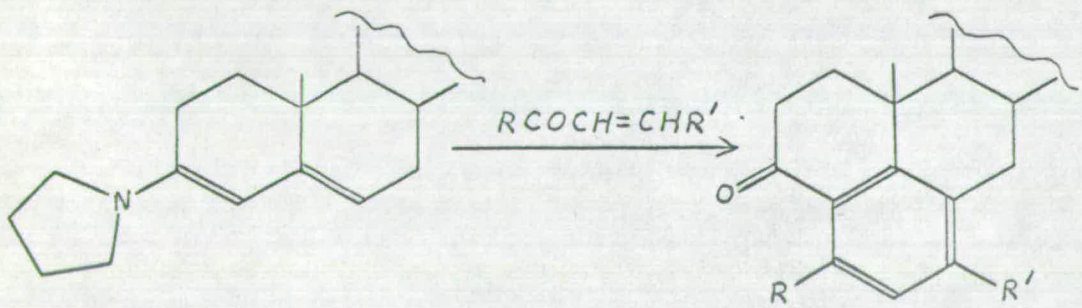
Of some interest is the methylation of steroidal enamines. Methyl iodide reacts with the pyrrolidenamine of cholestan-3-one in solvents of high polarity, such as ethanol, to produce a small amount (about 12%) of 2α-methylcholestan-3-one[59] (84). This, however, is a lower yield than is obtained by the corresponding base-catalysed reaction[65], which gives about 20%. It is noteworthy that the reaction of steroidal enamines with carbene, followed by cleavage of the cyclopropylamine (Fig. 1.19) has been reported to give the 2α-methyl-steroid in 69% overall yield[98]. The pyrrolidenamine of testosterone, in ethanol, reacts with methyl iodide to give the C-4 methyl derivative (85)[15,60-63]. 2-acetyl steroids (86) have also been made by the reaction of steroidal enamines with acetyl chloride[64,66].

Enamines have been used to add rings, usually heterocyclic, to steroids. The morpholine enamine (87) reacts with phenyl azide[202]

Fig. 1.23 (cont.)


CHO
NH2
N
(95)
CHO
OH
N
(96)

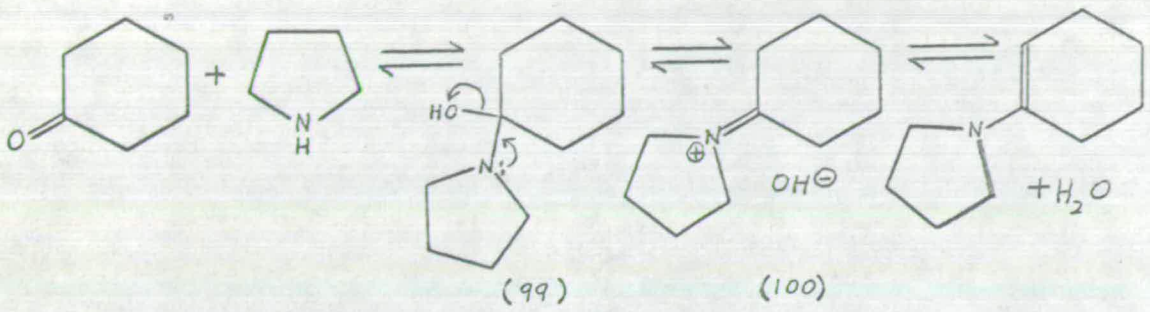

O
N
RC6H4COCH2Br
(R = F, Cl, Br, CF3)
O
O
R
(97)


N
RCOCH=CHR'
O
R
R'
(98)

to give an aminotriazole (88), from which the amine group is removed by treatment with acid to give a steroid with a [3,2-b] triazole ring (89). The pyrrolidenamine of androstan-17β-ol-3-one (90) reacts with bromoacetone[101] to give the diketone (91), which is then cyclized with benzylamine to give the [3,2-b] pyrrole (92). It will be recognised that the cyclization step is essentially an enamine synthesis. The dienamine system (93), on reaction with the substituted phenyl diazonium salt illustrated (Fig. 1.23), followed by cyclization with $POCl_3$, gives the [6,7-b] indole system (94)[102,191]. The pyrrolidenamine of a 3-keto-steroid reacts with *o*-aminobenzaldehyde to form a [3,2-b] quinole (95)[103], while the same enamine reacts with *o*-hydroxybenzaldehyde to give the [3,2-b] benzopyran (96)[103]. By reaction of dienamines with the substituted bromoketone shown [3,4-b] furan steroids (97) have been prepared[102,191]. Carbocyclic rings have also been added and compounds such as benz [4,5,6] androstanes (98) synthesized[104,191] as shown (Fig. 1.23).

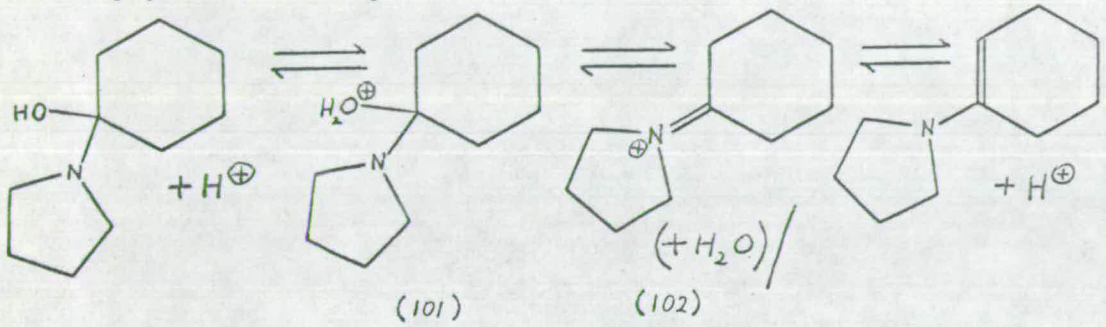
Fig. 2.1 Heyl and Herr Enamine Synthesis

(a) Non-catalysed



(99) (100)

(b) Acid-catalysed



(101) (102)

Fig. 2.2 (≡1.3) Titanium Tetrachloride Enamine Synthesis

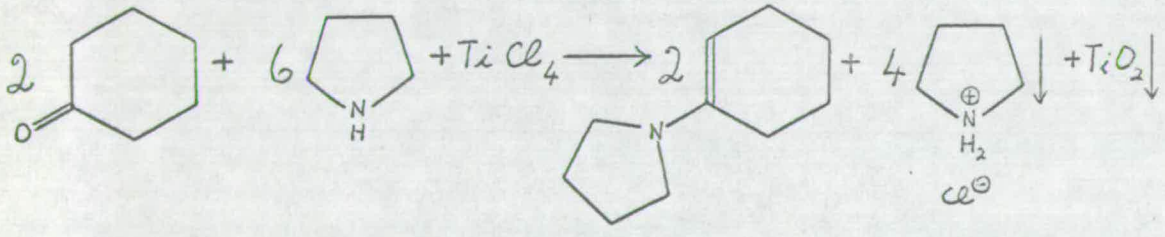
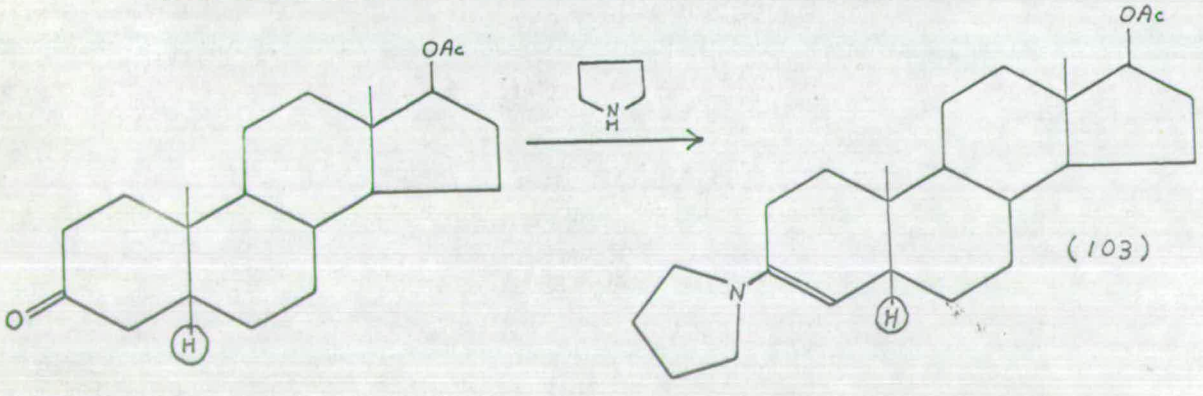


Fig. 2.3 Preparation of Steroidal Enamines

(i) Heyl and Herr Method



(103)

2. EXPERIMENTAL RESULTS AND DISCUSSION

2.1 STEROIDAL ENAMINES

2.1(a) Syntheses

Results

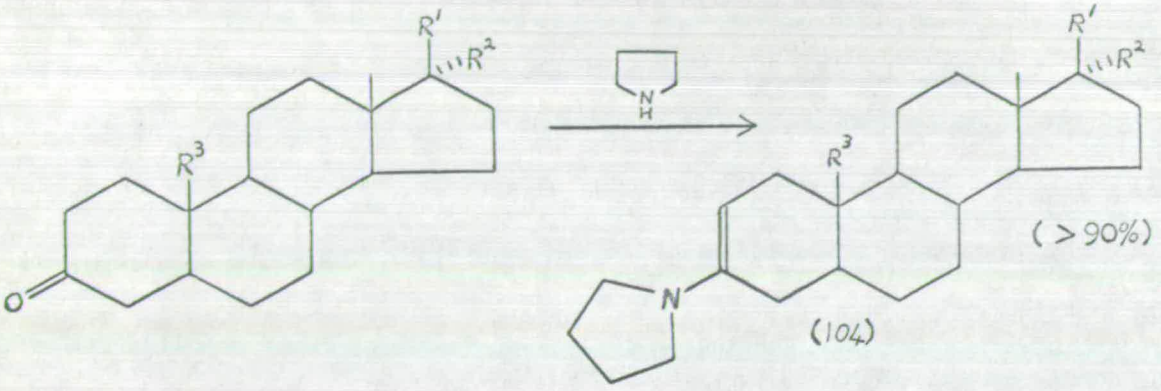
Five methods for the synthesis of steroidal enamines were explored.

The most generally useful was that of Heyl and Herr[35]. This procedure consists of refluxing a solution of the steroid ketone with excess of amine in the water-azeotroping solvent benzene, using a Dean and Stark trap between the flask and condenser. Reaction generally took about one hour and was monitored by the volume of water collected. It was found necessary on the small scale to use a trap with a small (1 ml) side-arm, otherwise the amine, in partitioning between the benzene in the flask and the comparable volume in the side-arm, became diluted and tended to starve the reaction mixture in the flask.

When reaction was terminated, solvent was removed as rapidly as possible, using a rotary evaporator. It was found that in general for steroidal enamines, attempts to purify the material at this stage by methods such as recrystallisation etc had the effect of making the material less pure, due to reaction with traces of water. Therefore, the crude enamine was kept in a stoppered flask and was used as soon as possible. The pyrrolidenamines were yellowish crystalline solids smelling of pyrrolidine. This procedure produced excellent yields of the pyrrolidenamines of the 3-keto-5α-steroids: androstanolone (104a), androstanolone acetate (104b), 17α-methylandrostanolone (104c), 19-norandrostanolone acetate (104d), cholestan-3-one (104e) and androstanolone 4-methylpentanoate (104f) (itself not previously described in the literature). Also, under these conditions only the

Fig. 2.3 (cont.) Preparation of Steroidal Enamines

(Cont.) Heyl and Herr Method

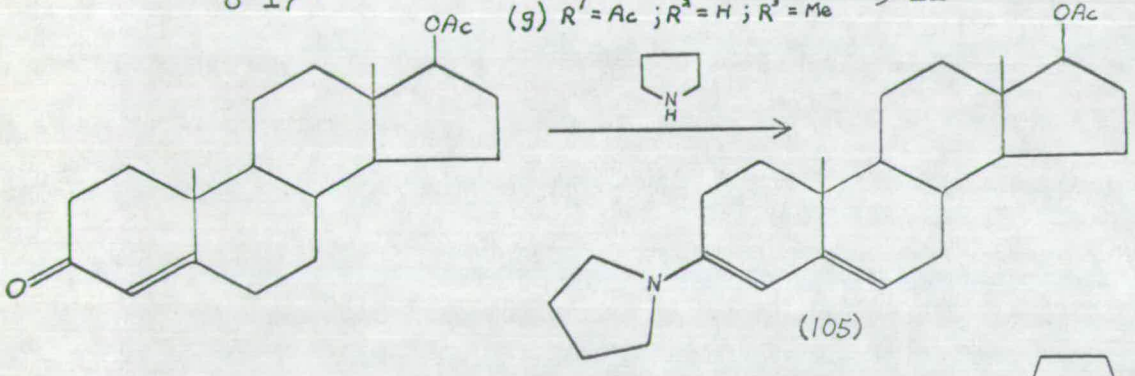


(a) $R' = OH$; $R^2 = H$; $R^3 = Me$ (b) $R' = OAc$; $R^2 = H$; $R^3 = Me$

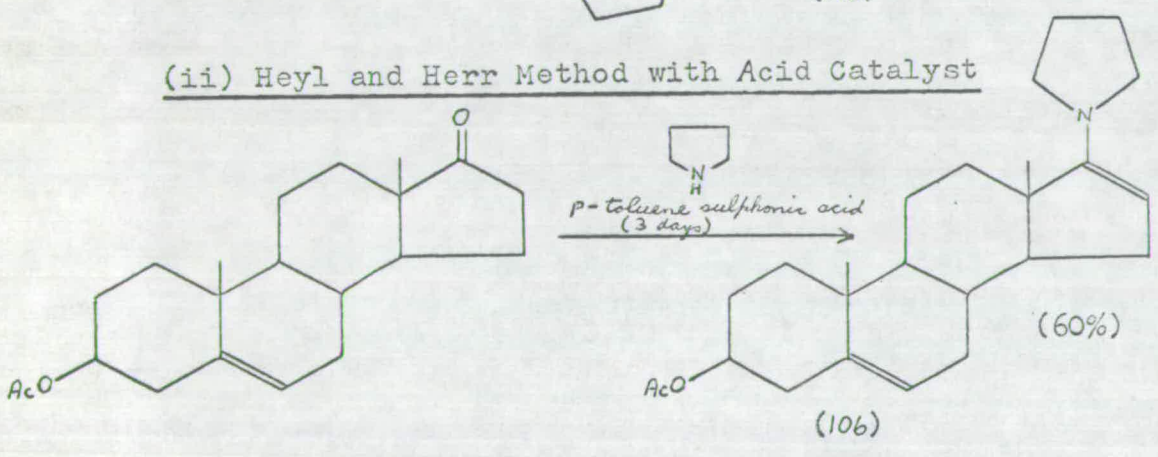
(c) $R' = OH$; $R^2 = Me$; $R^3 = Me$ (d) $R' = OAc$; $R^2 = H$; $R^3 = H$

(e) $R' = C_8H_{17}$; $R^2 = H$; $R^3 = Me$ (f) $R' = iso\text{-}C_5H_{11}COO$; $R^2 = H$; $R^3 = Me$

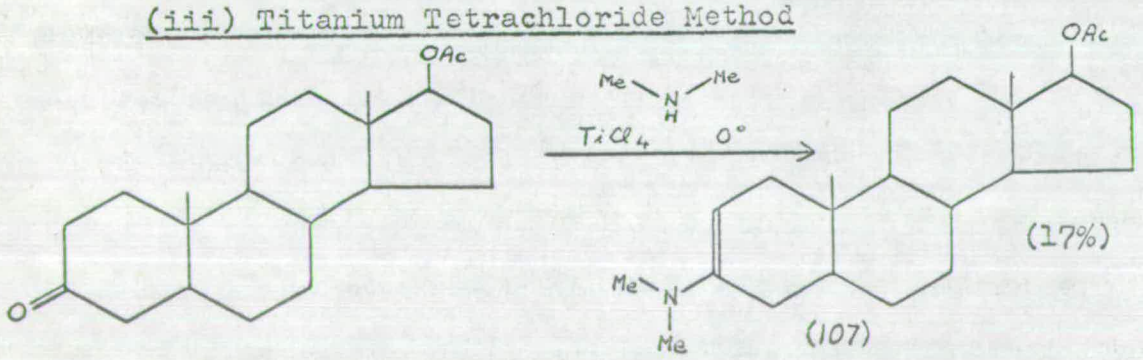
(g) $R' = Ac$; $R^2 = H$; $R^3 = Me$



(ii) Heyl and Herr Method with Acid Catalyst



(iii) Titanium Tetrachloride Method



mono-pyrrolidenamine (104g) was produced from 5α-pregnan-3,20-dione, as shown by the unchanged C-17 acetyl resonance in the n.m.r. spectrum. Similarly prepared were pyrrolidenamines of the 5β-compound 5β-androstanolone acetate (103) and the Δ^4-3-keto-steroid testosterone acetate (105).

The degree of conversion as calculated from the n.m.r. integral of the olefinic proton versus the C-17 proton (or other convenient peak) was better than 90%. Although with the pyrrolidenamines of 3-keto-5α-steroids the double bond absorption was discernable in the infra-red spectrum at about 1645cm^{-1}, the n.m.r. spectrum was more diagnostic. The olefinic proton resonance lies at about 4.13δ, clear of other peaks but near that of the C-17 proton when present. The ratio of the integrals of these peaks provides a useful measure of the purity of the enamine. Both the α-protons (about 2.97δ) and the β-protons on the pyrrolidine ring (about 1.82δ) are also readily discernable.

While, as previously noted, the enamines were generally used in a crude state, analytically pure pyrrolidenamine of androstanolone acetate was prepared, by multiple recrystallisation from rigorously dried solvents, as lustrous white plates melting with decomposition over a 12° range.

Harsher conditions than employed for the above compounds were required to produce the pyrrolidenamine of D.H.A. acetate (106). The addition of a catalytic amount of p-toluene sulphonic acid[35], as well as reflux for three days was necessary. Even then the enamine was quite impure (about 60% as estimated from the n.m.r. integral of the enamine C-18 methyl versus the corresponding resonance of unchanged D.H.A. acetate). The identity of the product was supported by exact mass measurement.

An attempt was made to effect the dehydration of a solution of androstanolone acetate and pyrrolidine in deuterochloroform at room

temperature, using calcium hydride. N.m.r. spectra were taken at intervals. After 15 minutes about 60% enamine was present, which increased to 66% only on leaving the mixture overnight.

A simple precipitation method[15] was also explored. In this a hot almost saturated solution of the steroid ketone is prepared, to which pyrrolidine is added. On cooling, the precipitated enamine is collected by filtration. Using androstanolone acetate a 60% yield of 83% pure enamine was obtained, while with testosterone acetate the precipitate consisted solely of starting material.

The method of White and Weingarten[16] was also investigated. In this, titanium tetrachloride in benzene is added to a benzene solution, under nitrogen, of the ketone and excess amine at ice temperature, then the mixture is stirred at room temperature for a further period. The precipitated titanium dioxide and amine hydrochloride are filtered off with an oven-dry sintered glass funnel and the solvent is rapidly removed on a rotary evaporator.

While some pyrrolidenamine of D.H.A. acetate was produced by this method, the purity of the product was extremely low and the acid-catalysed method of Heyl and Herr was therefore preferred for this compound. However, the dimethylamine enamine of androstanolone acetate, confirmed by i.r. and n.m.r. spectra, was produced in about 17% purity (integration of N-methyl versus acetate) (107).

Discussion

The mechanism of the synthesis of enamines from ketone and amine is illustrated for cyclohexanone and pyrrolidine as Fig. 2.1. For the non-catalysed reaction[14,139] the first step is the attachment of the pyrrolidine ring to give the carbinolamine (99). This loses a hydroxyl ion to yield the iminium hydroxide (100). The anion then

abstracts a proton to give the enamine and water. In the acid-catalysed case[142], however, the carbinolamine becomes protonated (101) and subsequently loses water to give the iminium cation (102) which, in its turn, loses the proton, yielding the enamine.

The method of Heyl and Herr and its modifications drives the reaction forward by removal of water. This forms an azeotrope with benzene, which condenses to two discrete phases. The water, being denser settles and is retained in the trap, while the benzene, saturated with water at the temperature of the trap returns to the reaction mixture. Some estimate of the residual water may be made from the known solubility of water in benzene (0.054g/100g at 26° [140]). Residual water is thus quite negligible. This is probably an optimistic figure, however, since the pyrrolidine in the distillate may be expected to increase the residual water. Nonetheless better than 90% yields are obtained.

That the harsher conditions of the acid-catalysed modification are required to prepare the pyrrolidenamine of D.H.A. acetate can be attributed to the relatively greater strain introduced by a double bond in the more conformationally constrained 5-membered D ring as compared to the 6-membered A ring.

In contrast to azeotroping, the chemical method of removing water with calcium hydride becomes much slower as the enamine formation proceeds and conditions become more anhydrous. The difference in rate between this and the method of Heyl and Herr is accentuated by the 60° temperature difference.

The titanium tetrachloride method also involves chemical dehydration and in addition promotes reaction by polarising the carbonyl bond[16]. The reaction is illustrated for cyclohexanone and pyrrolidine

as Fig. 2.2. The yields obtained were much lower than might have been expected. It seems likely, in spite of careful handling, that on the small scale used here, the extra manipulation involved in filtration allowed the absorption of sufficient water vapour from the air to decompose much of the enamine. Because of the low yield this method was used only for the dimethylamine enamine of androstanolone acetate, where the low boiling point of the amine (7^{o} [141]) precluded use of the method of Heyl and Herr.

The only synthesis which does not operate by removing water is the precipitation method. This disturbs the equilibrium instead by removing the enamine as a crystalline solid. In view of this relatively weaker driving force it is to be expected that yields will be poorer than with the Heyl and Herr procedure.

It has been noted in section 1.6(c) that the enamines of 3-keto-steroids are generally designated as predominantly the Δ^2-structure in the 5α and Δ^3 in the 5β- series. Examination of the n.m.r. spectra supports this assignment and in addition an estimate of the proportion of each isomer can be made. In a Δ^2-enamine the olefinic proton resonance is split by the two adjacent nearly equivalent C-1 protons and should therefore assume a 'triplet-like' form (strictly, a degenerate quadruplet). Conversely, for the Δ^3-isomer the single C-5 proton should give rise to a doublet. In practice both resonances are of somewhat indeterminate form, through three maxima can be discerned in some examples of the 5α- type. The resonance in the 5β-series is, however, considerably narrower than for 5α-enamines and it is therefore assigned as the narrower (degenerate doublet) of the two possibilities, corresponding to the Δ^3- structure, while the 5α-compounds have the wider resonance (degenerate quadruplet) of the Δ^2-isomer. In the 5α- series, in addition to the major olefinic

resonance (about 4.13 δ), a very small peak appears at slightly higher field (about 3.80 δ). Integration reveals that there are marginally more α-pyrrolidine protons than are accounted for on the basis of the major olefinic resonance alone, whereas when the minor peak integral is added to the major the figures tally quite well. The minor resonance is therefore considered to represent the olefinic proton of the minor Δ^3-isomer. Ratios of the integrals for some 5α-steroids reveal the presence of from 83 to 88% of the Δ^2 - compound: this can be compared with the literature value of 72% for the pyrrolidenamine of trans-decal-2-one[33]. The spectrum of the enol acetate 5α-androst-2-en-3,17β-diol diacetate also reveals a major (Δ^2) olefinic peak (5.27 δ) and a minute (Δ^3) resonance upfield (5.00 δ). This similarity to the enamine adds further support to the assignments above.

It is instructive to compare the spectra of 5α - and 5β-androstanolone acetate. The ketones are indistinguishable but the enamines are quite distinct. The major (Δ^3) resonance at 3.84 δ for the 5β - compound is matched by the minor (Δ^3) resonance at 3.80 δ for the 5α-isomer. Corresponding to the major (Δ^2) signal at 4.13 δ for the 5α- series is an extremely weak signal at 4.12 δ, equivalent to 5% of the total olefinic integral for the 5β- compound. It appears, then, that the enamine from the 5β - steroid is almost entirely (95%) the Δ^3-isomer.

Interestingly, the resonance corresponding to the Δ^2-proton appears at almost identical field in both the 5α- and 5β - series: the same is true of the Δ^3-proton. This value is determined by the electron density at the olefinic hydrogen. Considering the markedly differing geometry of the A-ring in the two series, it is tempting to suggest that the electron density is largely determined by the

inductive effect of the adjacent carbon and little by the rest of the molecule: thus the greater inductive effect of the tertiary carbon (C-5) in the Δ^3- compounds produces a higher electron density at C-4 than the secondary carbon (C-1) does at C-2 in the Δ^2- series. Whatever the truth of this speculation, it is to be expected that the greater electron density will render the Δ^3-enamines from 5β-steroids more reactive than the corresponding Δ^2-5α- compounds.

Conclusions

Only three of the methods proved of practical utility in preparative work (Fig. 2.3), the method of Heyl and Herr and its acid-catalysed modification, both of which have been widely used for steroidal enamines and the titanium tetrachloride method of White and Weingarten. The first was here used generally, while the second was useful for the pyrrolidenamine of D.H.A. acetate. The third was used only in the synthesis of the dimethylamine enamine of androstanolone acetate, for which the methods with better yield were not practicable.

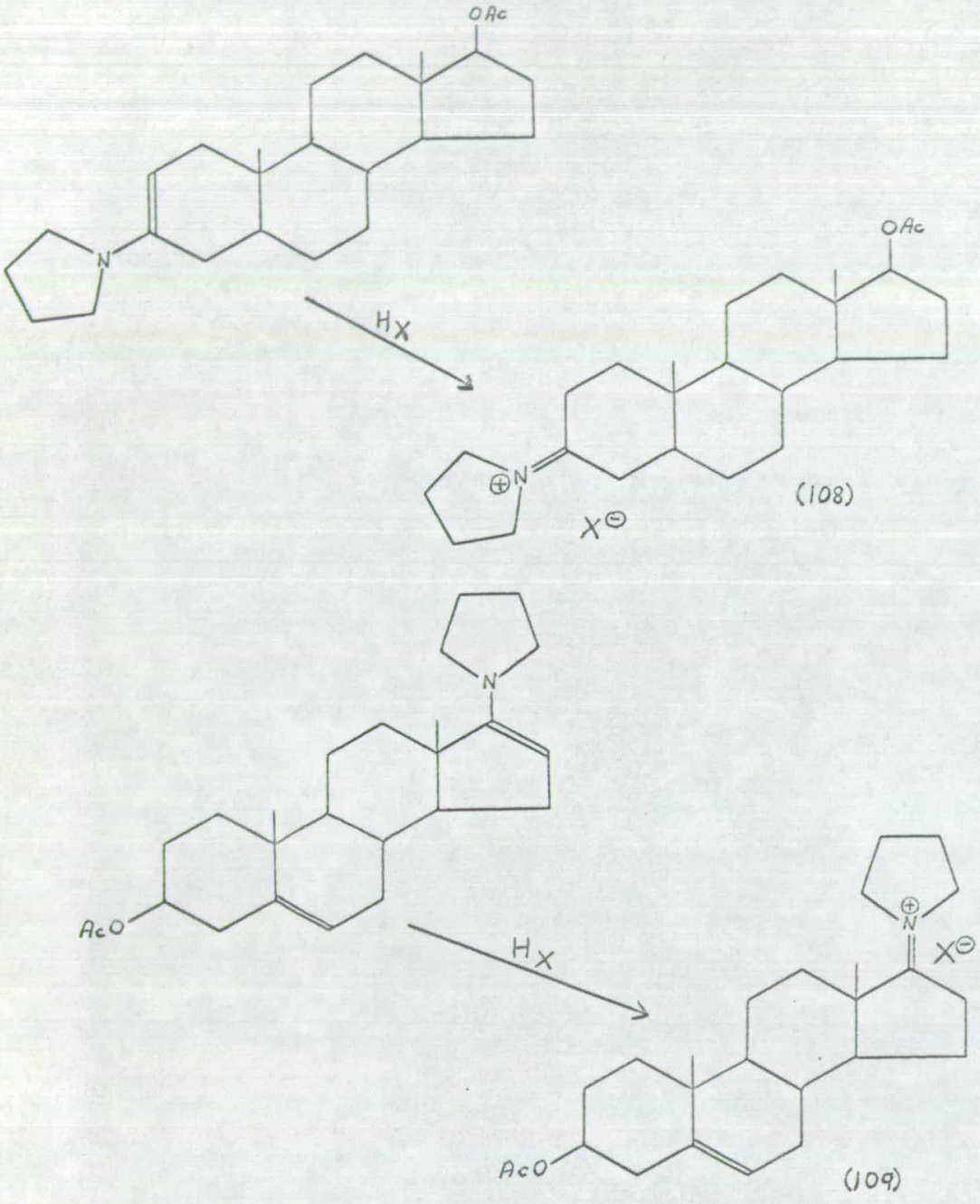
The n.m.r. spectra showed the pyrrolidenamines of 3-keto-5α-steroids to be predominantly (about 85%) the Δ^2-isomer, while the 5β- series consists almost entirely (about 95%) of the Δ^3- compound. The higher field resonance (by 0.29 δ) of the olefinic proton in the Δ^3- series suggests that the pyrrolidenamines of 5β-steroids may be more reactive towards electrophilic attack than the corresponding 5α- compounds.

2.1(b) Derivatives

Background

The hydrochlorides of the dienamines from a number of Δ^4-3-keto-steroids have been described in the literature[15]. The hydrochlorides were prepared by the dropwise addition of excess anhydrous ethereal

Fig. 2.4 Derivatives



(a) $X^{\ominus}$ = Chloride

(b) $X^{\ominus}$ = Picrate

hydrogen chloride to an ether or ether/benzene solution of the dienamine. The precipitate of hydrochloride was washed with ether, then dried and recrystallised to yield sharp-melting analytically pure material. It was reported, too, that the dienamine could be regenerated from the hydrochloride by the action of piperidine.

Accordingly it was considered worth while to investigate the potential of the hydrochlorides of steroidal mono-enamines for characterisation of the parent enamine and for purification of the enamine via compound formation.

Results

The pyrrolidiminium chlorides were prepared by the above method.

The crude pyrrolidenamine of androstanolone acetate (better than 90%) gave, on treatment with ethereal hydrogen chloride, a white precipitate (108a) which was shown by exact mass measurement to be some complex of the enamine; however, despite extensive efforts at recrystallisation from various solvents analytically pure material could not be produced. Regeneration of the enamine was attempted by stirring an ether suspension of the hydrochloride with dry piperidine. N.m.r. spectroscopy revealed about 50% (integral of olefinic versus C-17 proton) of regenerated enamine in the product.

The crude pyrrolidenamine of D.H.A. acetate (about 60%), on the other hand, did not give a white precipitate of hydrochloride but rather a brown/black semi-solid (109a) which exact mass measurement similarly showed to contain some complex of the enamine. Attempted regeneration of the enamine was here unsuccessful.

Picrates

In view of these unpromising results attention was turned to other derivatives. Many different salts[143] have been used for the

characterisation of non-steroidal enamines, in particular perchlorates, as well as hexachlorostannates, hexachloroantimonates, hydrochlorides, hydrobromides, tetraphenylborates and nitrates. Since picrates can readily be prepared under anhydrous conditions and have proved of considerable value in the characterisation of saturated amines it was decided to examine the pyrrolidiminium picrates.

These were prepared in the standard manner by making a hot saturated solution of the crude enamine in absolute ethanol and adding a cold saturated ethanolic solution of picric acid. Cooling and scratching afforded a crystalline precipitate of picrate.

With the crude pyrrolidenamine of androstanolone acetate (better than 90%) analytically pure picrate (108b) precipitated. Two attempts were made to regenerate the enamine: by stirring an ether suspension with pyrrolidine and by filtering a solution of the picrate through a small column of ultra-dry alumina. In both cases only androstanolone acetate was recovered.

With the crude pyrrolidenamine of D.H.A. acetate (about 60%) a crystalline precipitate of picrate (109b) formed although it was considerably less in quantity than in the above case. It was also less pure and it was necessary to recrystallise the picrate from ethanol.

Conclusion

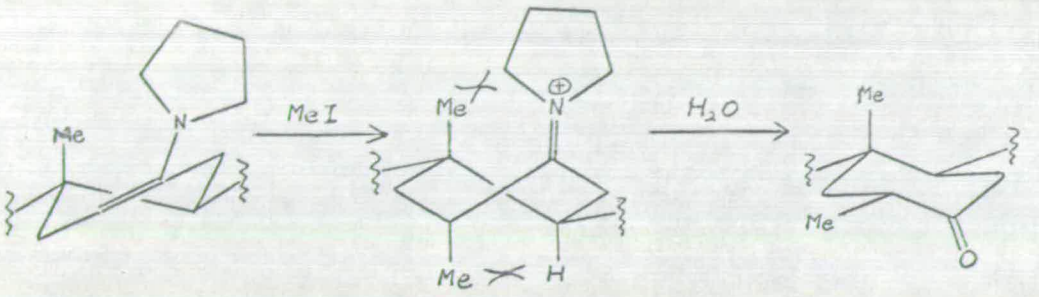
The pyrrolidiminium chlorides from keto-steroids are unsuitable for characterising the enamine, since it did not prove possible to prepare pure material. Further, attempted regeneration of the enamine produced, at best, only very impure material.

The picrates, however, were eminently suitable for characterisation, a crystalline solid forming even in the presence of considerable (40%) starting material. Nevertheless regeneration of the enamine

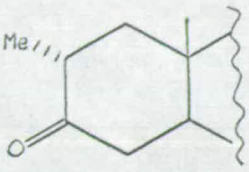
proved impracticable, despite vigorous attempts to maintain anhydrous conditions, because of the avidity of small quantities of the high molecular weight compounds for residual traces of water.

Fig. 2.5 Methylation

(a) mechanism



(110) (111)



(a) R = OH

(b) R = OAc; C_8

(b) experimental

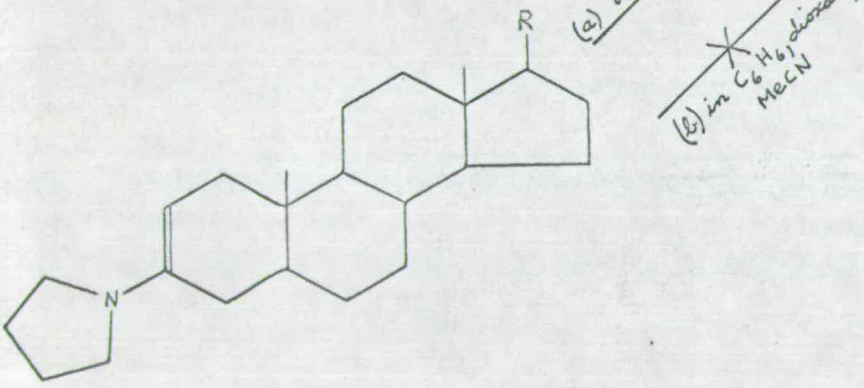
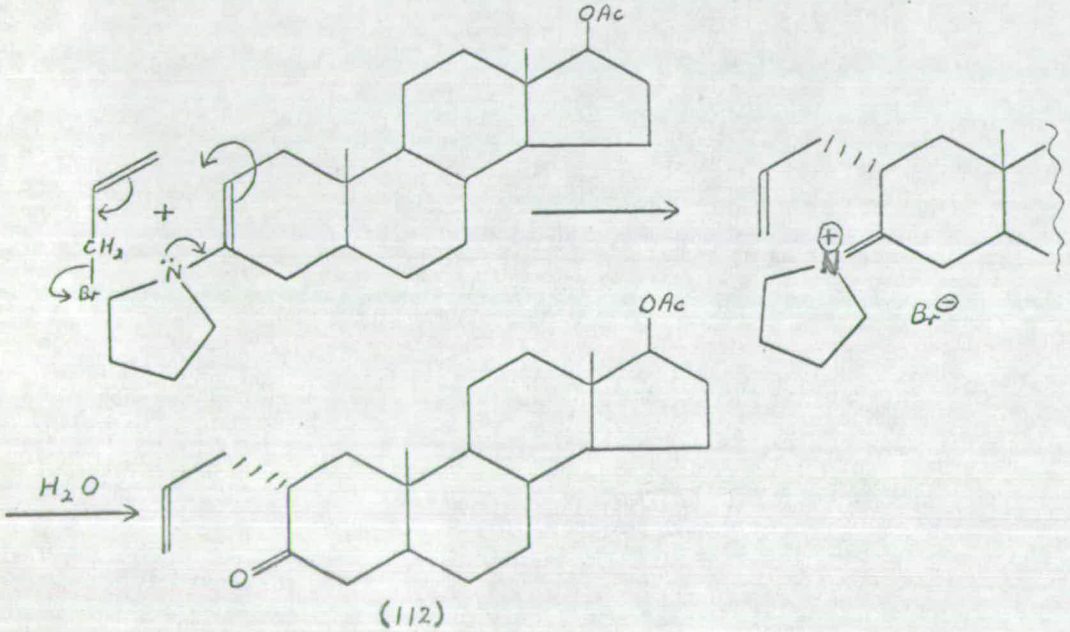


Fig. 2.6 Reaction with Allyl Bromide



(112)

2.2 METHYLATION

Previously Reported Experiments

Methylation of the pyrrolidenamine of cyclohexanone with methyl iodide was among the earliest reactions of enamines reported by Stork et al.[5]. When the reaction was performed in refluxing methanol, followed by hydrolysis of the iminium iodide, a 70% yield of 2-methyl-cyclohexanone was reported. In benzene, however, only 37% was obtained[144]. It has already been noted in section 1.7(c)(iii) that more polar solvents generally enhance alkylation by the Stork reaction, because of the stabilization of the charges appearing in the transition state.

The methylation of the pyrrolidenamines of 3-keto-steroids have also been investigated. In a series of patent applications the preparation, in better than 11% yield, of the 2α-methyl derivatives of androstanolone, 17α-methylandrostanolone and androstan-3,17-dione were reported[145,146,59]. 2α-methylcholestan-3-one was prepared in similar manner though the yield was not reported[147].

Stereochemistry

The stereochemistry of this reaction is of some interest. The substituent in the product is in the more stable (α) equatorial position: however it is known that in the methylation of cyclohexanone, the methyl group assumes the axial position in the iminium salt as in the enamine (section 1.6(b)(ii)). The methylation is under stereo-electronic control and thus, in the steroid, top-face attack would lead to a severe C-19 methyl/methyl (1,3-diaxial) interaction. With bottom-face attack, on the other hand, there is no comparable hindrance and although the A-ring becomes boat-like it seems probable that this

option will be favoured. The iminium salt likely assumes the twist boat conformation (110), thus minimizing the 1,4 interactions (C-19 methyl/pyrrolidinyl and methyl/C-5 hydrogen) in the two possible full boat forms. Nonetheless at least part of the large difference in yield between the steroid and the conformationally mobile cyclohexanone (70 against 12%) can confidently be attributed to the relatively greater strain in the iminium salt (110). Aqueous hydrolysis, in regenerating the ketone, removes the pyrrolidine ring and free of this the methyl in (110) would be expected to settle into the more stable equatorial (∝) position, while the A-ring resumes its customary chair conformation to give the 2∝-methyl-steroid (111).

Results (Fig. 2.5(b))

The methylation reaction was investigated in a variety of solvents. The pyrrolidenamine of androstanolone acetate, refluxed with methyl iodide in the relatively low polarity solvents benzene, dioxan and acetonitrile for periods ranging from 2 to 18 hours produced only recovered starting material as shown by n.m.r. The pyrrolidenamine of cholestan-3-one with methyl iodide and bromide in acetonitrile/dioxan mixture similarly failed to yield the methylated product.

In ethanol the principal reaction using androstanolone acetate was de-acetylation (base-catalysed transesterification) as determined by t.l.c.; however the enamine of androstanolone itself, after three hours at reflux, gave a crude mixture containing a small amount of the methylated product. Initial purification on alumina removed polar by-products and further chromatography on florisil followed by recrystallization gave pure 2∝-methylandrostanolone (111). The 2∝-methyl doublet was visible in the n.m.r. spectrum and the melting point was in agreement with the literature value.

Discussion

The results are consistent with the literature: a high polarity solvent (ethanol), as used by Babcock et al[145,146,59], was required to produce a discernable yield of methylated product. Not only is this concordant with the trend towards greater yields with increased polarity in the cyclohexanone series (above) but a similar effect has been noted with steroidal dienamines; thus reaction of the pyrrolidinyl dienamine from testosterone with methyl iodide produces the C-4 methylated product only in high polarity solvents[15,60-63].

2.3 REACTION WITH ALLYL BROMIDE

Previously Reported Experiments

Reaction of the pyrrolidenamine of cyclohexanone with one equivalent of allyl bromide in refluxing acetonitrile for 13 hours, followed by hydrolysis, is reported to give a yield of 67% of 2-allylcyclohexanone[150].

In the steroid field the pyrrolidenamine of androstanolone with excess of allyl bromide in refluxing D.M.F. for two hours is reported to have given a 14% yield of 2α-allylandrostanolone[138].

Results

The pyrrolidenamine of androstanolone acetate was refluxed with excess of allyl bromide in acetonitrile for four hours. Initial purification on alumina gave the crude allylated product as a yellow oil. Further chromatography on silica gel gave crystalline 2α-allylandrostanolone acetate (112) in 16% yield. Three recrystallizations gave a melting point in agreement with the literature value: the n.m.r. spectrum showed the olefinic protons and the double bond absorption was discernable in the infra-red. Exact mass measurement of the molecular ion proved satisfactory.

Discussion

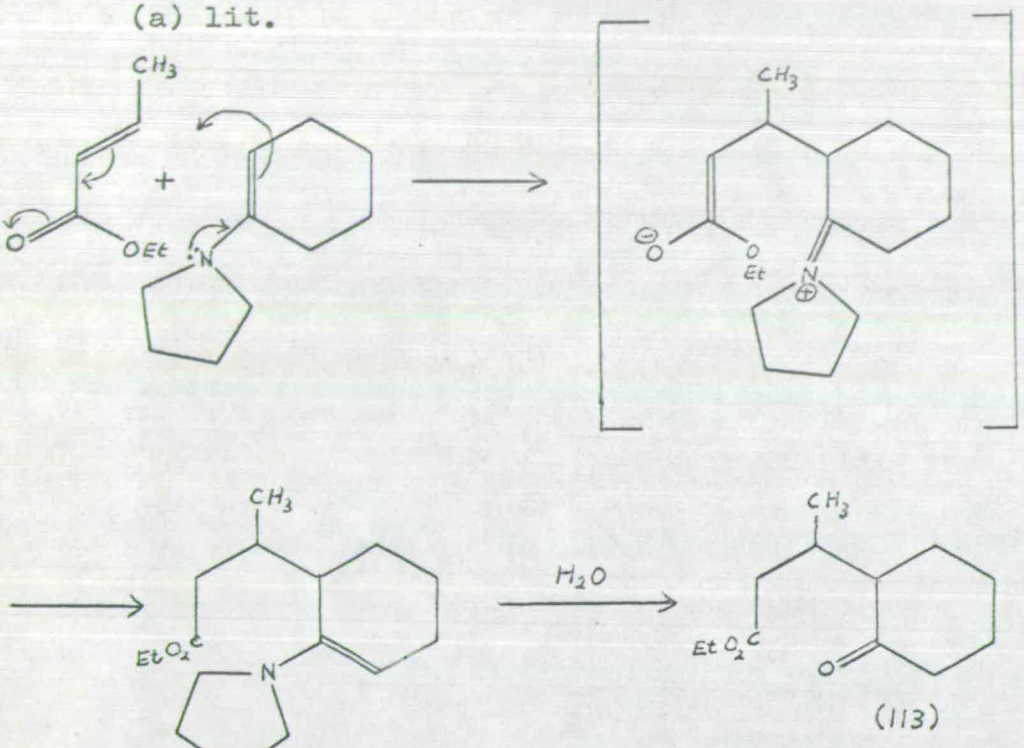
The result obtained was similar to that reported in the literature (in which androstanolone rather than the acetate was used), though the yield obtained here was marginally better (16 versus 14%). Miller and Christiansen[138] remark that in their case a large amount of oily by-product was produced which interfered with isolation. In the present instance, although the crude product was an oil, this seemed to be due to admixture with starting material: t.l.c. indicated that the only appreciable products were androstanolone acetate and the 2α-allyl

derivative. This apparent superiority may be due to the solvent used (acetonitrile versus D.M.F.) or possibly the presence here of the 17β-acetate function.

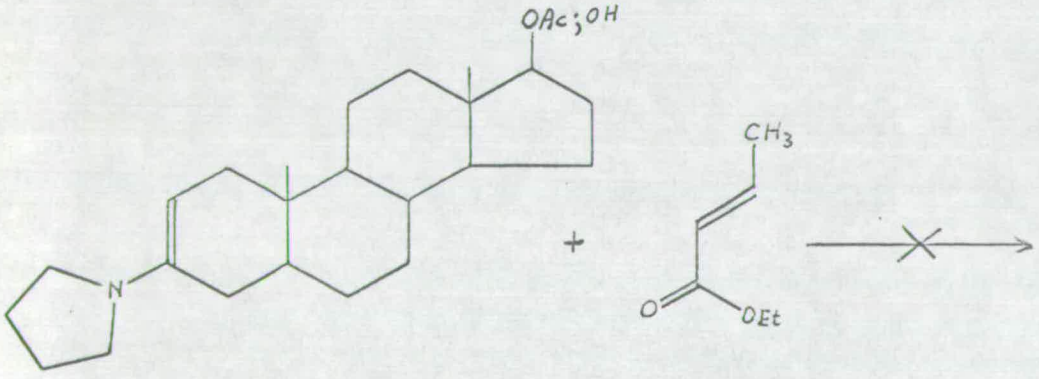
The greater yield with allylation than methylation is readily explained in terms of the more electrophilic nature of allyl bromide than methyl iodide.

Fig. 2.7 Reaction with Ethyl Crotonate

(a) lit.



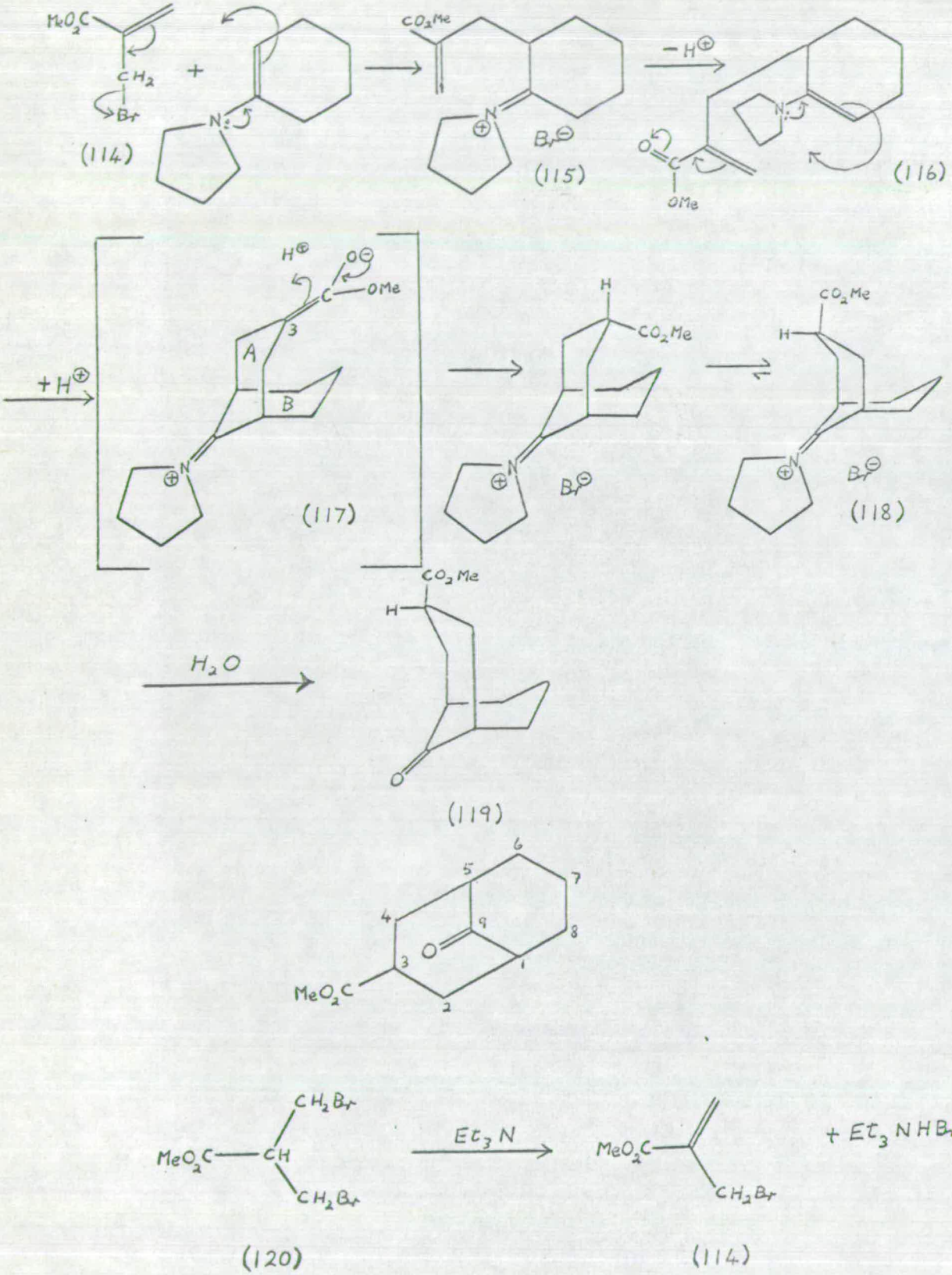
(b) experimental



2.4 REACTION WITH ETHYL CROTONATE

Ethyl crotonate (1.6 equivalents) and the pyrrolidenamine of cyclohexanone refluxed in D.M.F. for 36 hours is reported to have produced 56% of the monosubstituted compound (113)[151]. In view of this relatively low yield after extended reaction, even compared to methylation with methyl iodide, it was not surprising to find unchanged steroid ketone (n.m.r.) recovered after refluxing the pyrrolidenamine of androstanolone acetate with excess ethyl crotonate in acetonitrile for 18 hours. There was a similar lack of reaction (t.l.c.) in ethanol (with the pyrrolidenamine of androstanolone acetate (Fig. 2.7(b)).

Fig. 2.8 α,α'-Annelation Reaction (lit.)



2.5 REACTION WITH METHYL $\beta\beta'$-DIBROMOISOBUTYRATE ($+Et_3N$)

Previously Reported Experiments

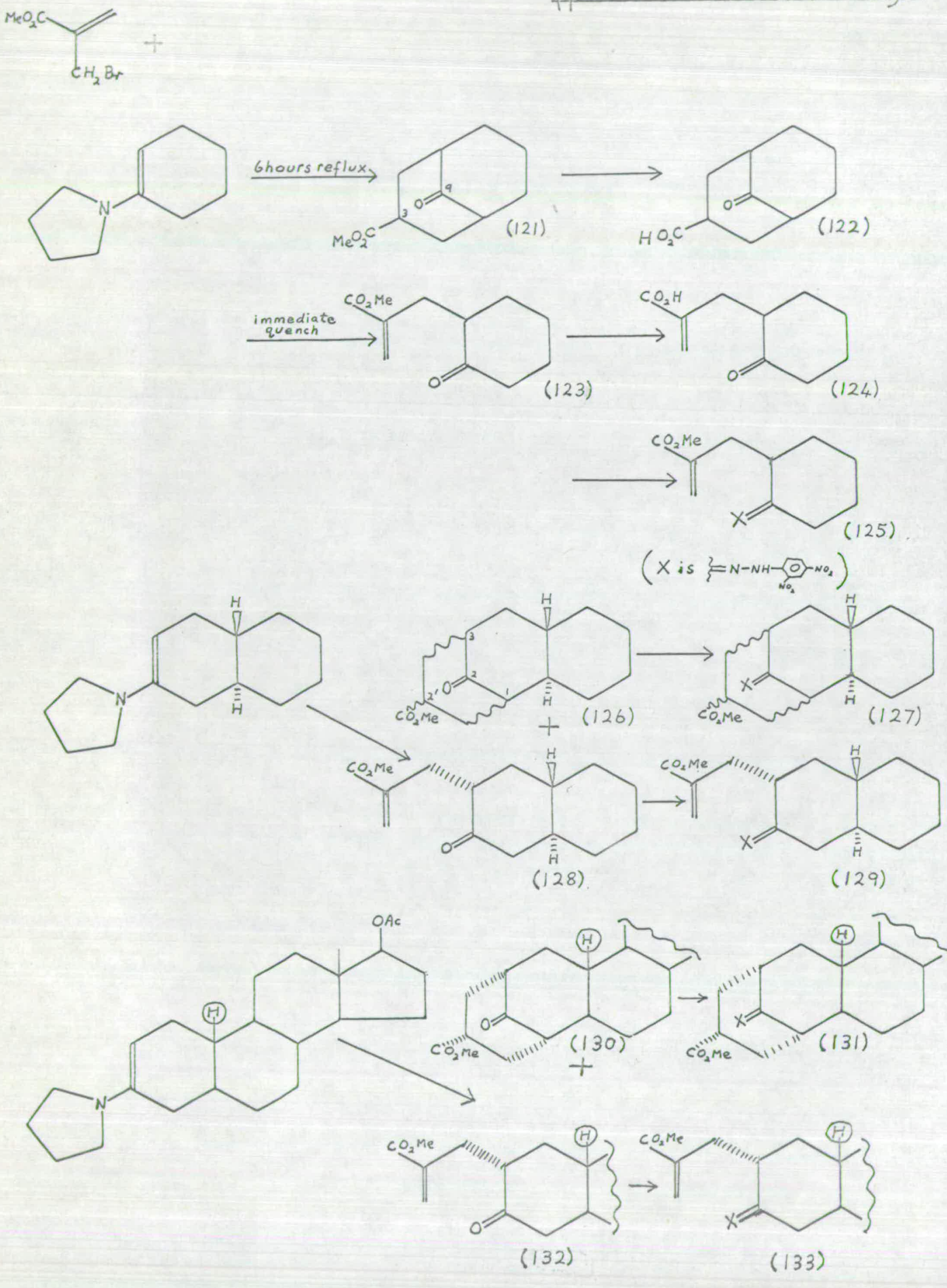
It is reported[130,196] that methyl α-(bromomethyl)-acrylate (114), prepared in situ by the action of triethylamine on methyl $\beta\beta'$-dibromoisobutyrate (120) was allowed to react with the pyrrolidenamine of cyclohexanone in refluxing acetonitrile for periods ranging from 3 to 13 hours. The three reactants were present in equimolar quantities. After hydrolysis, the reaction yielded methyl 9-oxobicyclo [3,3,1] nonane-3α-carboxylate (119). The mechanism proposed by the original workers for this "α,α'-annelation" reaction, slightly modified by subsequent work[196], is illustrated as Fig. 2.8. In the substituted iminium salt (115) the substituent is held axial, in which corresponding quasi-axial position it is possible for the double-bond end of the side-chain to react with the new enamine (116) formed by abstraction of a proton. The intermediate zwitterion (117) must give rise to the identified endo isomer (119): if it is assumed that the protonation involves attack from the least hindered side, then ring A (the new ring) must be chair-like, since a boat-like conformation gives rise to the wrong isomer. Only after protonation can ring A invert to give the more stable boat-chair iminium salt (118) which is hydrolysed to the ketone (119).

2.5(a) Methyl $\beta\beta'$-dibromoisobutyrate ($+Et_3N$) with the Pyrrolidenamine of Cyclohexanone

With a six hour reaction, followed by alumina chromatography the expected methyl 9-oxobicyclo [3,3,1] nonane-3α-carboxylate (121) was obtained in 24% yield as a colourless, odourless oil which crystallized to a low-melting white solid. The melting point (after recrystallizations), n.m.r. and i.r. spectra were consistent with reported values.

Fig. 2.9 Experimental Results with Methyl

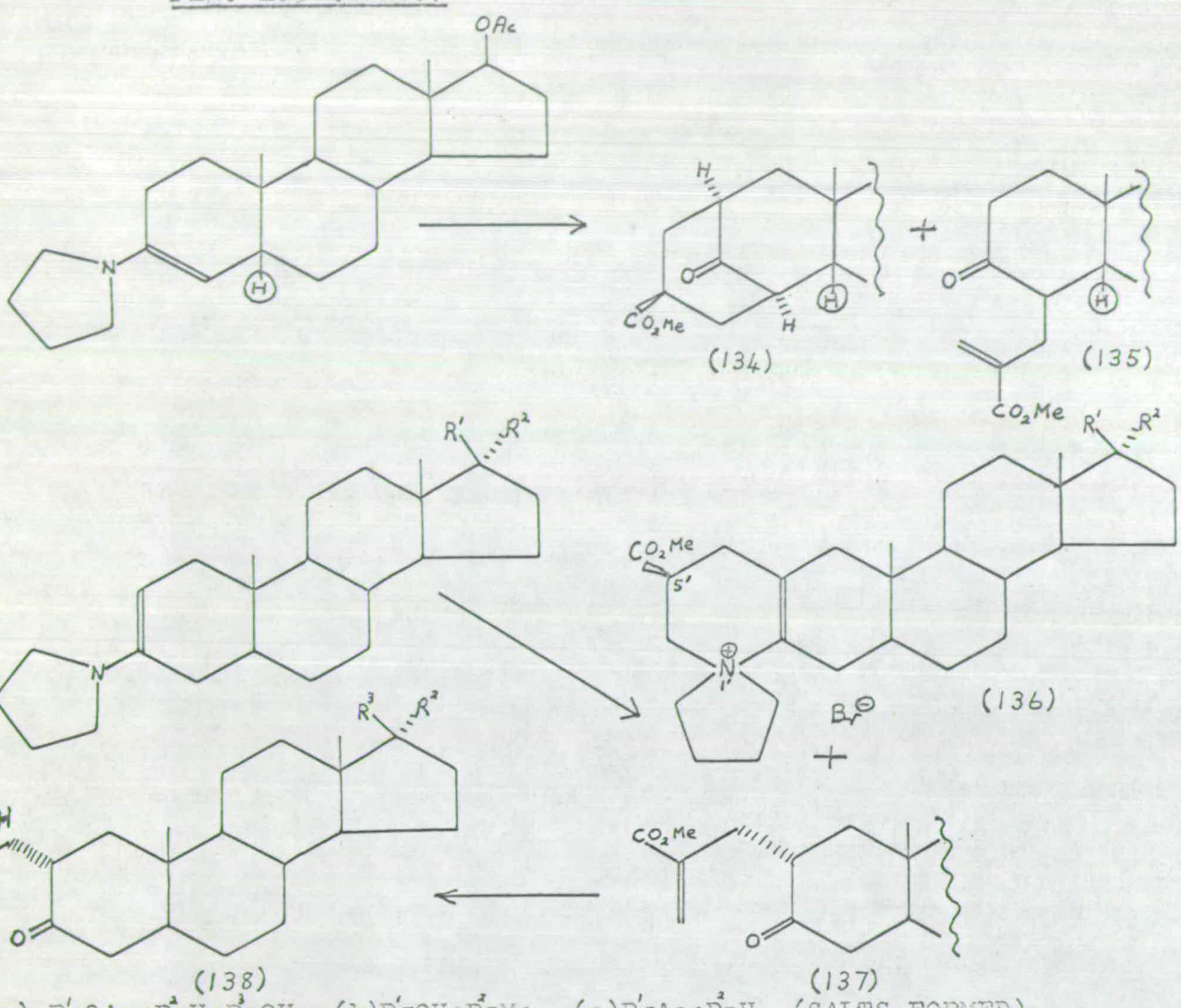
ββ′-dibromoisobutyrate (+Et_3N)



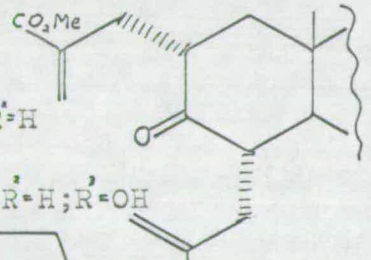
Hydrolysis of this ester with aqueous potassium hydroxide gave 9-oxobicyclo [3,3,1] nonane carboxylic acid (122) as a higher-melting white solid. The melting point (after recrystallization) was in agreement with the reported value and n.m.r. and i.r. spectra were consistent with the assigned structure. Thus the results obtained parallel those described in the literature. Additionally a minor by-product of the α,α'-annelation reaction, isolated from the column as a less polar fraction, proved to be identical (t.l.c. and n.m.r.) to 2-(2-carbomethoxyprop-2-enyl)-cyclohexanone prepared as described below.

When the reaction was quenched by the addition of dilute acetic acid to the mixture immediately after the methyl $\beta\beta'$-dibromoisobutyrate was added to the enamine solution, the major product was the previously unreported olefin 2-(2-carbomethoxyprop-2-enyl)-cyclohexanone (123) in 33% yield, a light yellow fragrant liquid with appropriate mass spectrum and exact mass. The double bond absorption could be seen in the infra-red spectrum and the two olefinic resonances and carbomethoxy peak in the n.m.r. spectrum integrated correctly against the methylene hump for the mono-substituted compound. Alkaline hydrolysis, as above, produced 2-(2-carboxyprop-2-enyl)-cyclohexanone (124). However this proved not to be a solid but a very pale yellow oil which gave appropriate n.m.r. and i.r. spectra. The 2,4-dinitrophenylhydrazone (125) was therefore prepared as (after recrystallizations) a felt of orange needles of sharp melting point. The isolation of the olefin (123) as the major product in the rapidly quenched reaction may be rationalized as the result of hydrolysis of the initially formed monosubstituted iminium salt (115)/enamine (116) and thus provides additional evidence supporting the reaction scheme of Fig. 2.8.

Fig. 2.9 (cont.)



(a) R'=OAc; R^2=H; R^3=OH (b) R'=OH; R^2=Me (c) R'=Ac; R^2=H (SALTS FORMED)

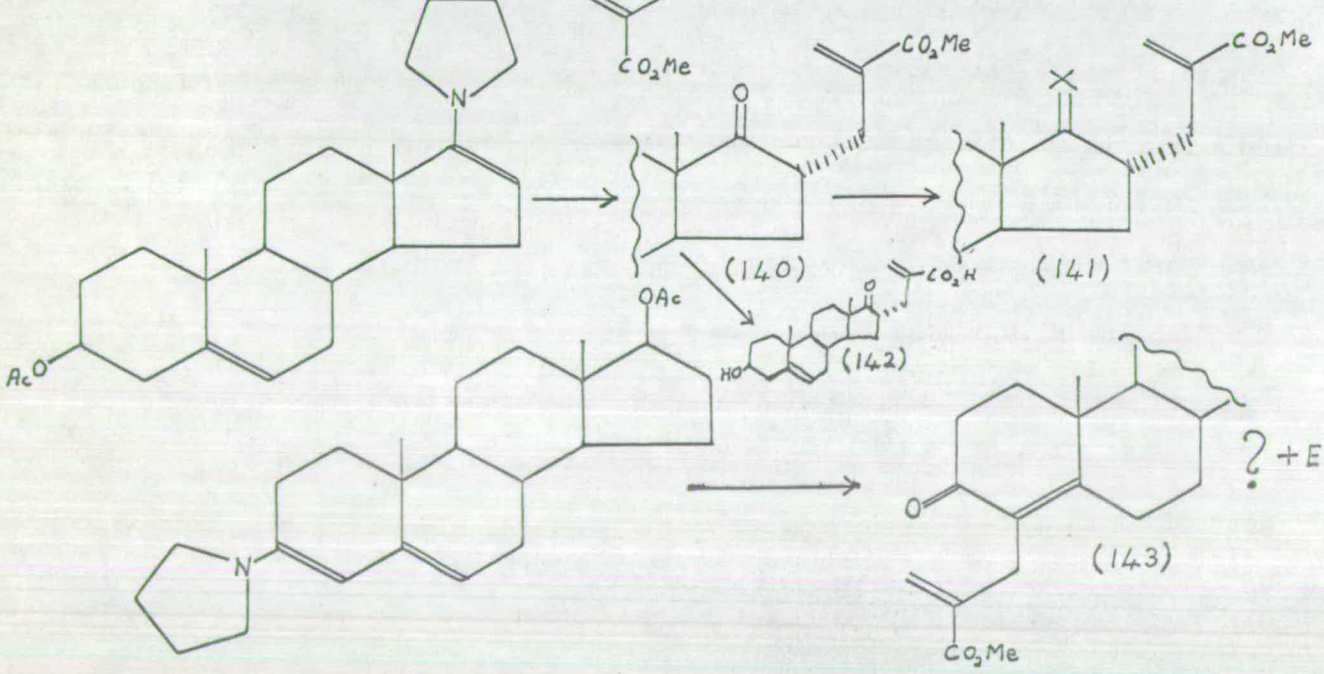


(139) isolated

(OLEFINS ONLY)

(d) R'= (C_8H_{17}); R^2=H

(e) R'= $(C_5H_{11}COO-)$; R^2=H; R^3=OH



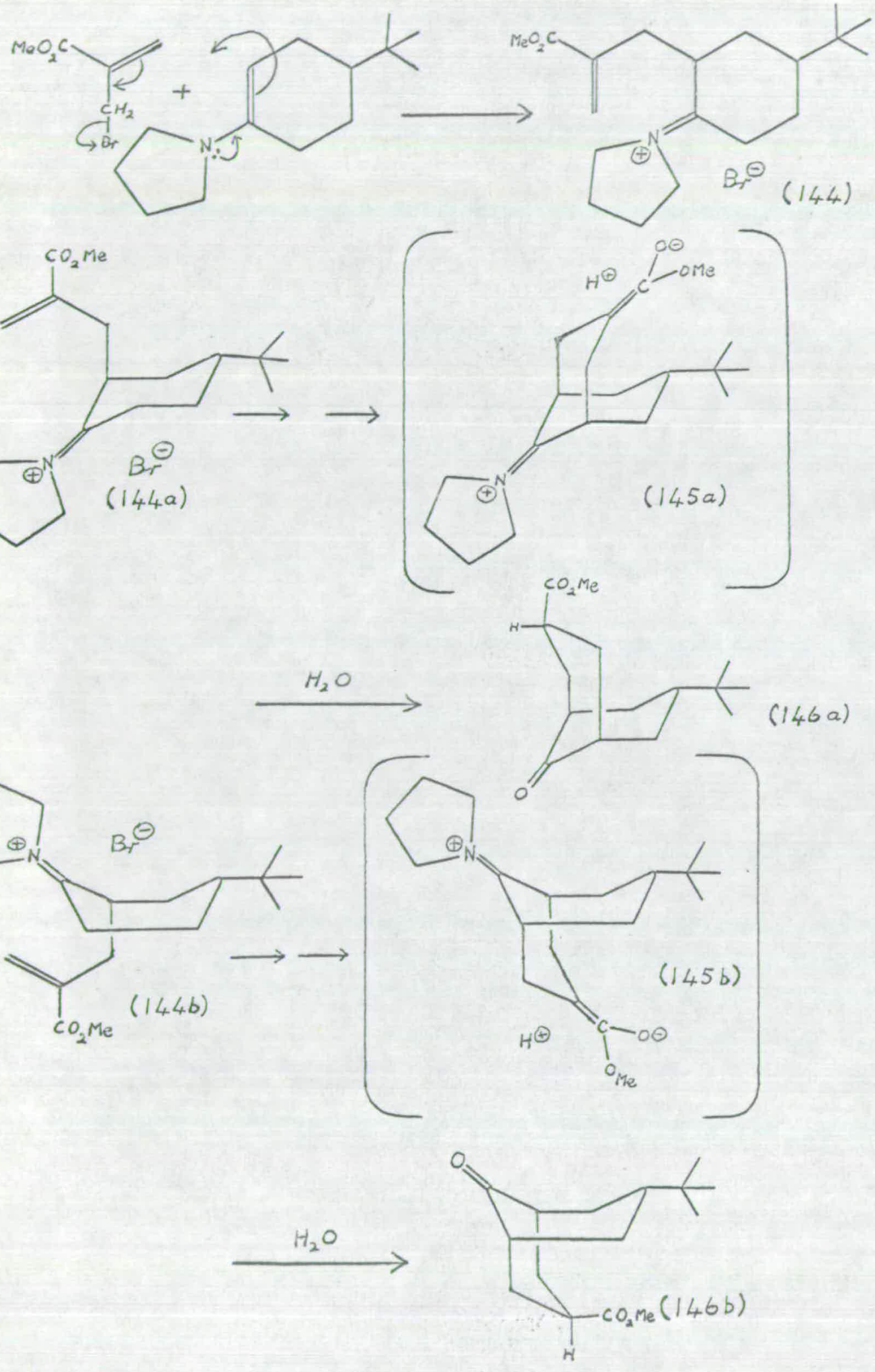
2.5(b) Methyl $\beta\beta'$-dibromoisobutyrate (+Et_3N) with the Pyrrolidenamine of Trans-decal-2-one

The reaction of equimolar quantities of methyl $\beta\beta'$-dibromoisobutyrate with the pyrrolidenamine of trans-decal-2-one in the presence of triethylamine for 13 hours in refluxing acetonitrile followed by chromatography on alumina gave two isolable products. The more polar proved to be the bicyclononane 1,3-(2-endo-carbomethoxytrimethylene)-trans-decal-2-one (126), an oil, in 7.3% yield. The n.m.r. spectrum had a carbomethoxy resonance but no olefinic peaks, while the infra-red spectrum showed only carbonyl absorptions. Although the compound was homogeneous to t.l.c., gas chromatography revealed two peaks of nearly equal area and the associated mass spectra both showed an abundant ion at m/e 250, corresponding to the molecular weight of the bicyclononane. Also the 2,4-dinitrophenyhydrazone (127) was prepared: this was repeatedly recrystallized until the quantity was too small (0.3 mg) to continue, but the melting range remained wide (100-120°). Despite this, the base peak of the mass spectrum corresponded to the expected molecular ion (with satisfactory exact mass) and the compound was homogeneous to t.l.c. using two different solvent systems. It was concluded that the bicyclononane was a mixture of isomers.

The less polar fraction from the column was the olefin 3α-(2-carbomethoxyprop-2-enyl)-trans-decal-2-one (128) an oil in 4.9% yield. N.m.r. showed the expected olefinic and carbomethoxy resonances and the double bond absorption was visible in the infra-red spectrum (in chloroform). The 2,4-dinitrophenyhydrazone (129) was prepared in low yield (11%) and after recrystallizations gave a felt of sharp melting yellow crystals comprising 0.9 mg. The compound was homogeneous to t.l.c. and gave satisfactory analysis and exact mass measurement.

Analogous reactions of the similarly conformationally frozen pyrrolidenamines of 4-substituted cyclohexanones have been described in

Fig. 2.10 α,α'-Annelation Reaction with Substituted Cyclohexanones (lit.)



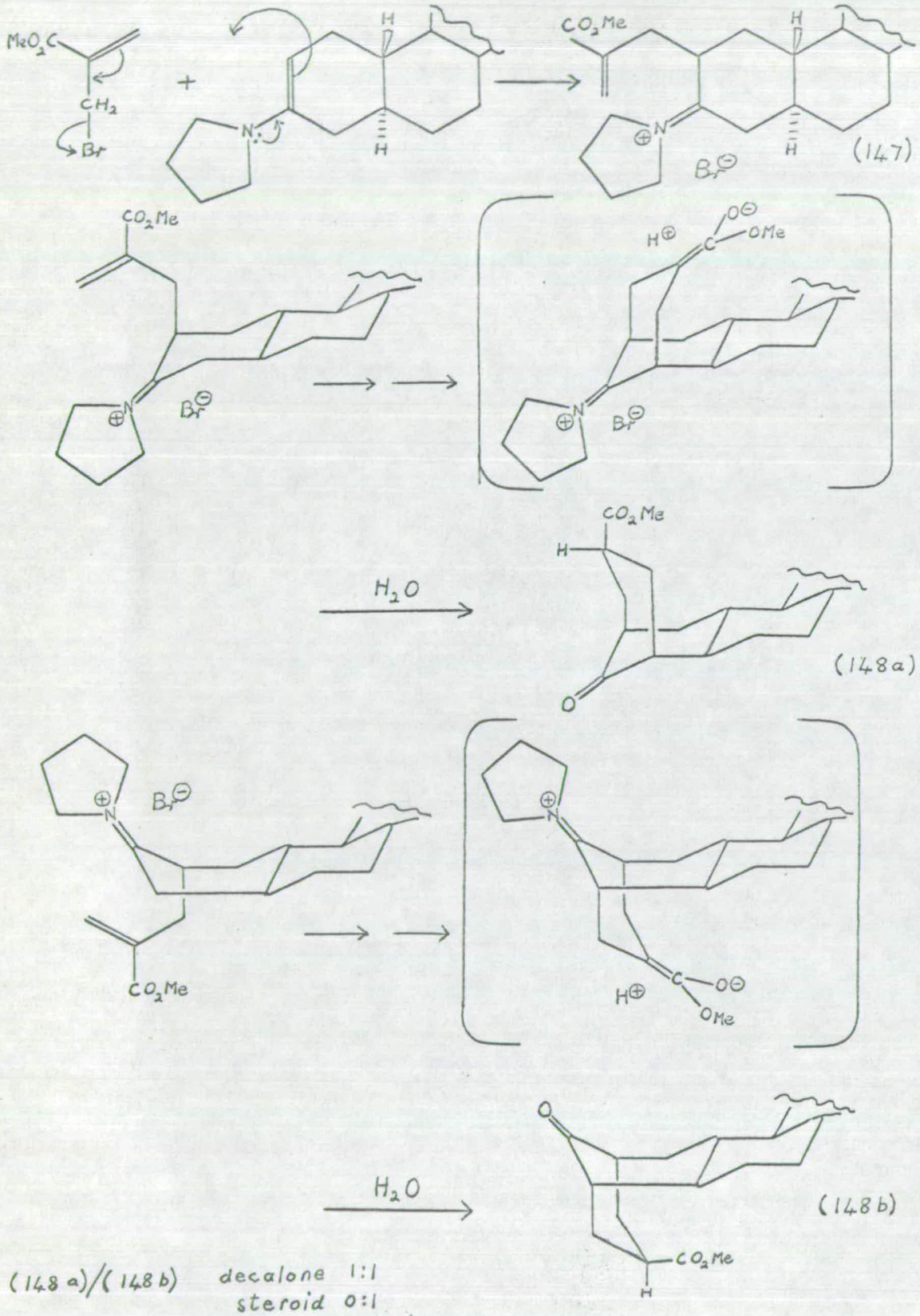
Ratio (146a)/(146b) is 3:2 for t-Bu (illust.); Me; i-Pr

the literature[196]. These give a mixture of the bicyclononane isomers (146a) and (146b) in the approximate ratio of 3 to 2 for R = Me, i-Pr and t-Bu. The authors explain the reaction by the scheme illustrated as Fig. 2.10, a slightly modified version of one proposed earlier by McEuen et al.[130]. There are two possible axial conformations of the initially formed iminium bromide (144). Of these the more stable is that with the ring chair-like (144a): this cyclizes to the zwitterion (145a) which after protonation and hydrolysis gives the preponderant bicyclononane isomer (146a): the boat-like iminium salt (144b) similarly yields the other isomer (146b).

It seems probable that the analogous scheme applies to the reaction of the pyrrolidenamine of trans-decal-2-one and this is illustrated as Fig. 2.11. In this case it must be assumed that the reaction paths are about equally favoured, producing roughly equal amounts of the "bridge-down" (148a) and the "bridge-up" isomer (148b).

The sharp melting point of the D.N.P. (129) from the olefin argues that this is a single isomer: moreover the melting point is very close (127.5-129.5° compared to 127.5-129.0°) to that for the D.N.P. (125) from the cyclohexanone-derived olefin. This suggests that the crystal packing is similar in the two cases. Given that the side-chain is equatorial in the cyclohexanone derivative it seems much more plausible that a comparable lattice would be possible with a similarly equatorial side-chain in the decalone case, rather than with an axial isomer. However, because of the considerable loss of material sustained in preparing the D.N.P. it is not possible to argue that the parent olefin (128) must also have been the α-isomer. Nonetheless the olefin is derived, as in the cyclohexanone reaction, by hydrolysis of the initially formed iminium bromide (147)/enamine

Fig. 2.11 Methyl ∝-(bromomethyl)-acrylate with the Pyrrolidenamines of Trans-decal-2-one and 19-norandrostanolone Acetate



and it would be expected that, once free of the pyrrolidine ring, any initially formed axially-substituted ketone would epimerize to the considerably more stable equatorial form. The olefin (128) is thus assigned the α (equatorial) structure.

2.5(c) Methyl $\beta\beta'$-dibromoisobutyrate (+Et_3N) with Steroidal Pyrrolidenamines

The reaction of equimolar quantities of methyl $\beta\beta'$-dibromoisobutyrate with the steroidal pyrrolidenamine, in the presence of triethylamine, was allowed to proceed in refluxing acetonitrile for 16 hours. An ether and a chloroform-soluble fraction were taken.

The reaction was performed on the pyrrolidenamines of the following nine steroids:

I
- 5α-androstanolone acetate
- 17α-methylandrostanolone
- pregnan-3,20-dione (3-mono-enamine)

II
- 19-norandrostanolone acetate
- 5β-androstanolone acetate

III
- 5α-cholestan-3-one
- androstanolone 4-methylpentanoate
- D.H.A. acetate
- testosterone acetate

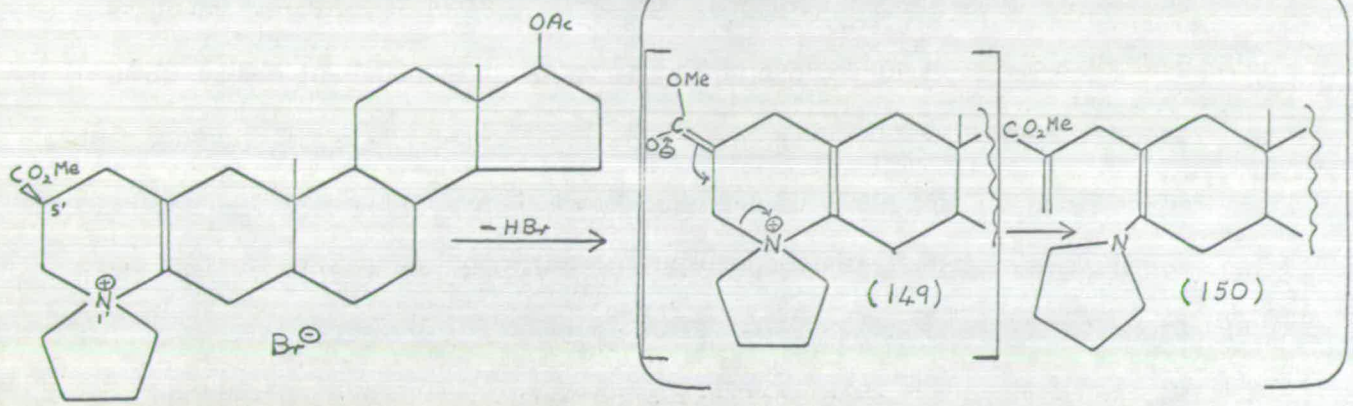
The three groups gave rise to distinct types of product: group I gave steroidal salts (contaminated with triethylamine hydrobromide) in the chloroform-soluble fractions as well as ether-soluble olefins. Steroidal bicyclononanes as well as olefins were isolated from group II, while the latter were obtained from all three groups. In the arrangement adopted for this section the salts (from group I) are covered first: these are followed by the bicyclononanes (and olefins) from group II, and finally the olefins from groups I and III. Within a group the reactions are treated in the order of the starting materials, above.

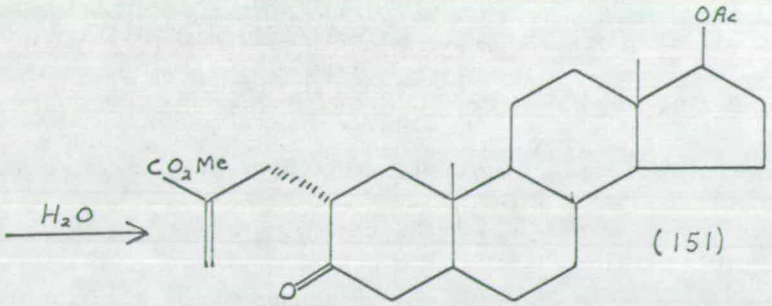
Salts (group I)

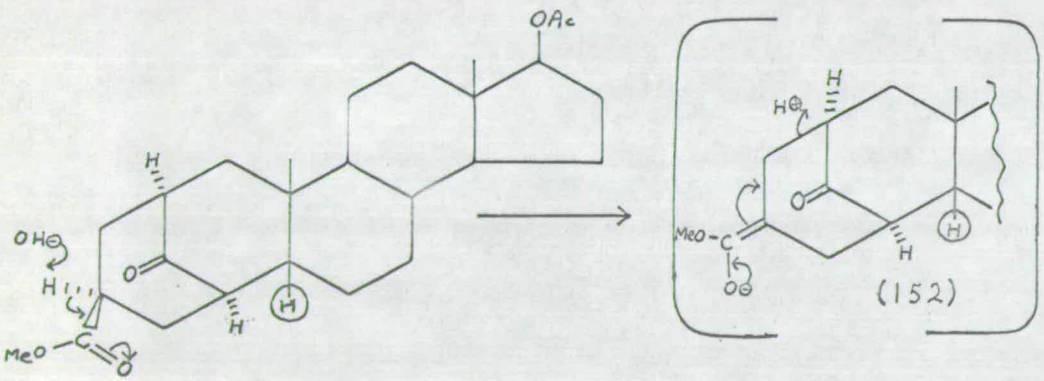
The three crude salts, from the chloroform-soluble fractions, 17β-acetoxy-5′β-carbomethoxy-5α-androst-2-eno [3,2-b] 1′-azoniaspiro [4,5] decane bromide (136a) (62%) from 5α-androstanolone acetate, 5′β-carbomethoxy-17β-hydroxy-17-methyl-5α-androst-2-eno [3,2-b] 1′-azoniaspiro [4,5] decane bromide (136b) (80%) from 17α-methylandrostanolone and 5′β-carbomethoxy-20-oxo-5α-pregn-2-eno [3,2-b] 1′-azoniaspiro [4,5] decane bromide (136c) (31%) from pregnan-3,20-dione, soluble in water and insoluble in ether, were purified by trituration with acetone or ethyl acetate and acetone to give white solids of satisfactory melting range. The salt (136a) from 5α-androstanolone acetate gave an analysis in agreement with the assigned molecular formula and exact mass measurement on the peak "salt minus HBr" was also consistent. The n.m.r. spectrum revealed the protons on each of the three new ring carbons as well as the carbomethoxy and α-pyrrolide protons. In addition a carbon-13 n.m.r. spectrum[152] disclosed both carbons of the tetrasubstituted double bond. The infra-red spectrum, too, revealed a double-bond absorption. N.m.r. and i.r. spectra of the other two salts (136b and 136c resp.) from 17α-methylandrostanolone and pregnan-3,20-dione were similar and mass spectra and exact mass measurements were consistent with the assigned structures.

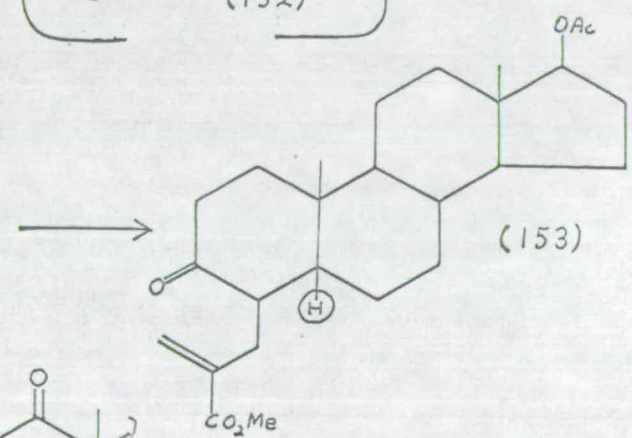
The presence of ionic bromide in the salt (136a) from 5α-androstanolone acetate was confirmed by the immediate formation of a precipitate of silver bromide and on removal of the ionic bromide no covalent bromine was detected by a sodium fusion test. A yellow colouration with tetranitromethane[134] was consistent with the presence of a tetrasubstituted double bond. The nitrogen was shown to be quaternary by the absence of a new methyl peak on treatment of the

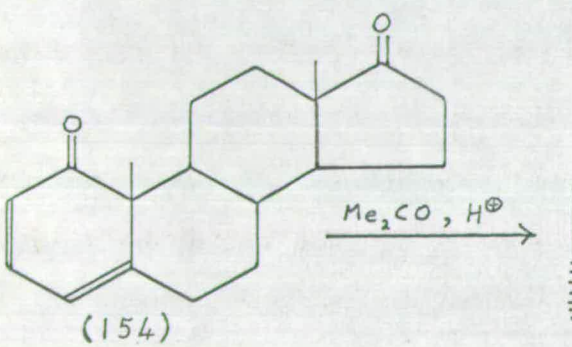
Fig. 2.12 Miscellaneous





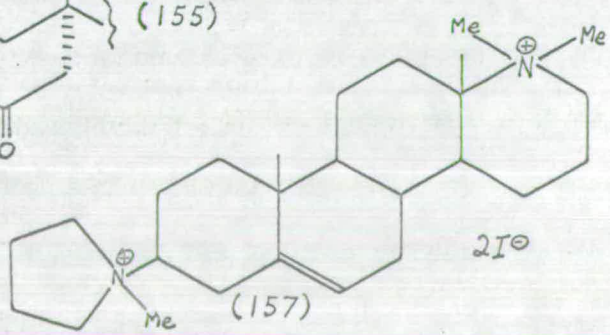






$\left[Me_3\overset{\oplus}{N}(CH_2)_2OAc\right]\overset{\ominus}{O}H$

(156)



hydroxide with methyl iodide. The salt proved refractory to acid hydrolysis, even on reflux with 50% conc. hydrochloric acid: with alkali, however, reaction was readily effected under mild conditions. A solution of the salt in chloroform, ethanol and water was stirred to an emulsion with saturated sodium bicarbonate solution for two days in a stoppered flask. Ether work-up gave the olefin 17β-acetoxy-2α-(2-carbomethoxyprop-2-enyl)-5α-androstan-3-one (151) (Fig. 2.12) as a yellow oil in 39% yield. Four recrystallizations gave the olefin as a white solid of narrow melting range. The identity of this compound with the same olefin prepared as described later was established by the melting point and an undepressed mixed melting point, as well as by comparison of the n.m.r. spectra.

Bicyclononanes (and olefins) (group II)
from 19-norandrostanolone acetate

The total crude material from 19-norandrostanolone acetate was first carefully chromatographed on alumina, then further separated by preparative t.l.c. on silica gel. The more polar compound was the bicyclononane 17β-acetoxy-2α,4α-(2α-carbomethoxytrimethylene)-5α,10β-estran-3-one (130), as a clear colourless oil in 2.1% yield. N.m.r. revealed a carbomethoxy resonance but no olefinic peaks and no double bond absorption was discernable in the infra-red. The 2,4-dinitrophenylhydrazone (131) was prepared in the standard manner, but although this gave an initially crystalline precipitate attempts to recrystallize it from hot ethanol gave a tar. The solid was therefore dissolved in ethanol and solvent was allowed to evaporate off slowly: filtration gave 4.3 mg of crystalline solid; however t.l.c. revealed that the compound was contaminated with the olefin D.N.P. (133). The material was therefore subjected to preparative t.l.c. on silica gel and the resultant 2 mg was recrystallized to give bright

yellow crystals. The amount of these crystals (0.8 mg, corresponding to a 2.8% yield from the crude bicyclononane) was insufficient for further recrystallization; however the melting range (7^{o}) was sufficiently narrow to indicate that the purified material consisted of a single isomer. The compound proved homogeneous to t.l.c. using two different solvent systems and the mass spectrum and exact mass measurement of the molecular ion were satisfactory.

The less polar material was the olefin 17β-acetoxy-2α-(2-carbomethoxyprop-2-enyl)-5α,10β-estran-3-one (132) as a yellow oil in 18% yield. The n.m.r. spectrum revealed olefinic resonances in addition to a carbomethoxy peak and a double bond absorption was discernable in the infra-red. The 2,4-dinitrophenylhydrazone (133) was prepared and five recrystallizations gave 4.8 mg of D.N.P., melting over a 5^{o} range. It was homogeneous to t.l.c. using two different solvent systems and the mass spectrum and exact mass measurement of the molecular ion proved satisfactory.

from 5β-androstanolone acetate

Examination of the n.m.r. spectrum of the chloroform-soluble fraction from 5β-androstanolone acetate suggested that it was a mixture of bicyclononane (134) and triethylamine hydrobromide. An attempt was made to remove the latter by washing a chloroform solution with sodium bicarbonate; however the n.m.r. spectrum showed that as well as removing the triethylamine hydrobromide the washing had largely hydrolysed the bicyclononane (134) to the olefin (153) (Fig. 2.12). The mixture was therefore combined with the similar ether-soluble fraction and the whole was carefully chromatographed on alumina, then further separated by preparative t.l.c. on silica gel.

The more polar material was the bicyclononane 17β-acetoxy-2β,4β-(2β-carbomethoxytrimethylene)-5β-androstan-3-one (134) in 0.54% yield, notable among the oils produced in this reaction in being a crystalline solid. Recrystallization gave 2.2 mg of sharp-melting white plates. The n.m.r. spectrum, run on the crude material from the column, was very noisy owing to the tiny quantity but it revealed the carbomethoxy peak and no olefinic resonances were visible. Similarly the infra-red spectrum disclosed no double bond. Analysis proved consistent with the assigned molecular formula and the mass spectrum and exact mass measurement of the molecular ion were satisfactory.

The less polar material was the olefin 17β-acetoxy-4β-(2-carbomethoxyprop-2-enyl)-5β-androstan-3-one (135) as an oil in 11% yield. This was recrystallized five times to give sharp-melting white needles. The n.m.r. spectrum revealed the characteristic olefinic (and carbomethoxy) resonances and the double bond absorption was discernable in the i.r. spectrum. Analysis and exact mass measurement of the molecular ion proved satisfactory.

Olefins (groups I and III)

from 5α-androstanolone acetate

The crude ether-soluble material from 5α-androstanolone acetate was twice chromatographed on alumina to give the olefin 17β-acetoxy-2α-(2-carbomethoxyprop-2-enyl)-5α-androstan-3-one (137a) as an oil in 1.4% yield. This was recrystallized four times to give a white solid of sharp melting point and satisfactory analysis and n.m.r. and i.r. spectra. A tiny sample of the olefin (137a) was also prepared from the crude ether-soluble material by gas chromatography: the mass spectrum and exact mass measurement of the molecular ion were satisfactory. The presence of the double bond in the olefin (137a)

was confirmed chemically by the decolourization of bromine water and of potassium permanganate solution.

The crude ether-soluble olefin mixture was hydrolysed with aqueous potassium hydroxide and the resultant very small quantity of the acid 2α-(2-carboxyprop-2-enyl)-5α-androstan-17β-ol-3-one (138a) gave an n.m.r. spectrum which, though noisy due to the small quantity, was consistent with the assigned structure. The material was recrystallized to give an off-white solid of narrow melting range. Mass spectrum and exact mass measurement of the molecular ion were satisfactory.

from 17α-methylandrostanolone

Careful alumina chromatography of the crude ether-soluble material from 17α-methylandrostanolone gave the olefin 2α-(2-carbomethoxyprop-2-enyl)-17α-methyl-5α-androstan-17-ol-3-one (137b) still contaminated with some starting material, as an oil. The quantity (12.9 mg) was insufficient to proceed with further purification. Spectroscopic properties showed that the mixture was largely the olefin (137b): the n.m.r. spectrum showed substantial olefinic and carbomethoxy resonances, the double bond absorption could be seen in the infra-red and in the mass spectrum the molecular ion (402) was the largest peak above m/e 304: exact mass measurement proved satisfactory.

from pregnan-3,20-dione

Although the quantity of ether-soluble material available was insufficient to proceed with purification the crude substance revealed tiny olefinic and carbomethoxy peaks in the n.m.r. spectrum, as expected of the olefin 2α-(2-carbomethoxyprop-2-enyl)-5α-pregnan-3,20-dione (137c). Furthermore, the mass spectrum showed the 414 peak corresponding to the molecular ion (with satisfactory exact mass) to be the largest above m/e 330.

from cholestan-3-one

Careful chromatography on alumina of the crude ether-soluble material from cholestanone gave an oil which was homogeneous to t.l.c. using two different solvent systems. However, the n.m.r. spectrum, in addition to the olefinic and carbomethoxy resonances expected for the olefin 2α-(2-carbomethoxyprop-2-enyl)-5α-cholestan-3-one (137d) showed two C-19 methyl peaks. This suggested the presence of two different olefins. Attempts to recrystallize the material from the usual hexane were unsuccessful since it proved too soluble but five recrystallizations from methanol gave the di-olefin 2α,4α-di-(2-carbomethoxyprop-2-enyl)-5α-cholestan-3-one (139) as 1.1 mg of white solid, melting over a 4° range. The infra-red spectrum showed the double bond absorption: the mass spectrum as well as exact mass measurement of the molecular ion were consistent with the assigned structure.

from androstanolone 4-methylpentanoate

The n.m.r. spectrum of the crude ether-soluble material from androstanolone 4-methylpentanoate was consistent (olefinic and carbomethoxy resonances) with the presence of a small quantity of the olefin 2α-(2-carbomethoxyprop-2-enyl)-5α-androstan-17β-ol-3-one 4-methylpentanoate (137e). Hydrolysis with aqueous potassium hydroxide gave an off-white solid which was recrystallized to give less than 1 mg of the acid 2α-(2-carboxyprop-2-enyl)-5α-androstan-17β-ol-3-one (138e). The melting point agreed with that of the same acid prepared (above) from 5α-androstanolone acetate: the mixed melting point was undepressed.

from D.H.A. acetate

The total crude material from D.H.A. acetate was twice chromatographed on alumina to give the olefin

3β-acetoxy-16α-(2-carbomethoxyprop-2-enyl)-androst-5(6)-en-17-one (140) as an oil in 1.2% yield. The n.m.r. and i.r. spectra were consistent with this assignment.

The 2,4-dinitrophenylhydrazone (141) was prepared and recrystallized to give an extremely poor yield (2.3%) of orange solid. This melted over a 20° range and t.l.c. showed that the compound was still impure. Further recrystallization could not, however, be done because of the small quantity (0.3 mg) of D.N.P. However, the mass spectrum showed the 608 peak corresponding to the molecular ion (with satisfactory exact mass) to be the largest above m/e 562.

Hydrolysis of the once-chromatographed crude olefin was performed with aqueous potassium hydroxide to give less than 1 mg of the acid 16α-(2-carboxyprop-2-enyl)-androst-5(6)-en-3β-ol-17-one (142) as a mid-brown solid. The mass spectrum showed the 372 peak corresponding to the molecular ion (with satisfactory exact mass) to be the largest above m/e 18.

from testosterone acetate

The total crude material from testosterone acetate was carefully chromatographed on alumina. Two fractions were obtained, each of which was subjected to preparative t.l.c. on silica gel. As a result three (about 10 mg) fractions of oil were obtained, homogeneous to t.l.c. However, n.m.r. showed that each was a mixture of several olefins: these proved intractable to further purification.

Preparative gas chromatography of the original crude material gave a fraction with mass spectrum consistent with testosterone acetate plus a single side-chain. The molecular ion 428 was the largest peak above m/e 149 and the exact mass measurement was satisfactory: this material may be 17β-acetoxy-4-(2-carbomethoxyprop-2-enyl)-testosterone (143) by analogy to the known major product of the reaction of the pyrrolidenamine of testosterone with methyl iodide[15,60-63].

Modifications and Additional Reactions

When the reaction of methyl $\beta\beta'$-dibromoisobutyrate with the pyrrolidenamine of androstanolone acetate was carried out with no triethylamine present, only the olefin (137a) was produced. Similarly when the reaction time was cut to 10 minutes only olefin could be isolated.

An attempt to prepare the olefin 2α-(2-carbomethoxyprop-2-enyl)-5α-androstan-17β-ol-3-one acetate (137a) by the alternative base-catalysed reaction led to a mixture of alkylated products. The n.m.r. spectrum of this mixture contained resonances corresponding to those of the olefin produced via the enamine and it was concluded that one of the components was the desired olefin.

Discussion of Steroid Reactions

Purification procedures

The salts (136a,b,c) were readily isolated from the chloroform-soluble fractions. Isolation of the other compounds, however, proved difficult. Repeated chromatography was generally needed to separate products from each other and starting material. The polarity differences were often so small that t.l.c. failed to resolve the compounds. Generally t.l.c. with two different solvent systems was required to monitor chromatographic fractions and even then it sometimes proved necessary to use n.m.r. spectroscopy in addition. This was useful in assaying the olefins; however the bicyclononanes have no characteristic resonances: the carbomethoxy peaks are coincident with those of the olefins formed in the same reactions; thus bicyclononanes could be monitored only by the discrepancy between olefinic and carbomethoxy integrals. Nonetheless the technical problems were in one way less serious with the bicyclononane-producing reactions (group II) since these produced at least one compound in more than 10% yield: the other

TABLE 2.1 Yields of New Reactions of Methyl -(bromomethyl)-acrylate with Pyrrolidenamines

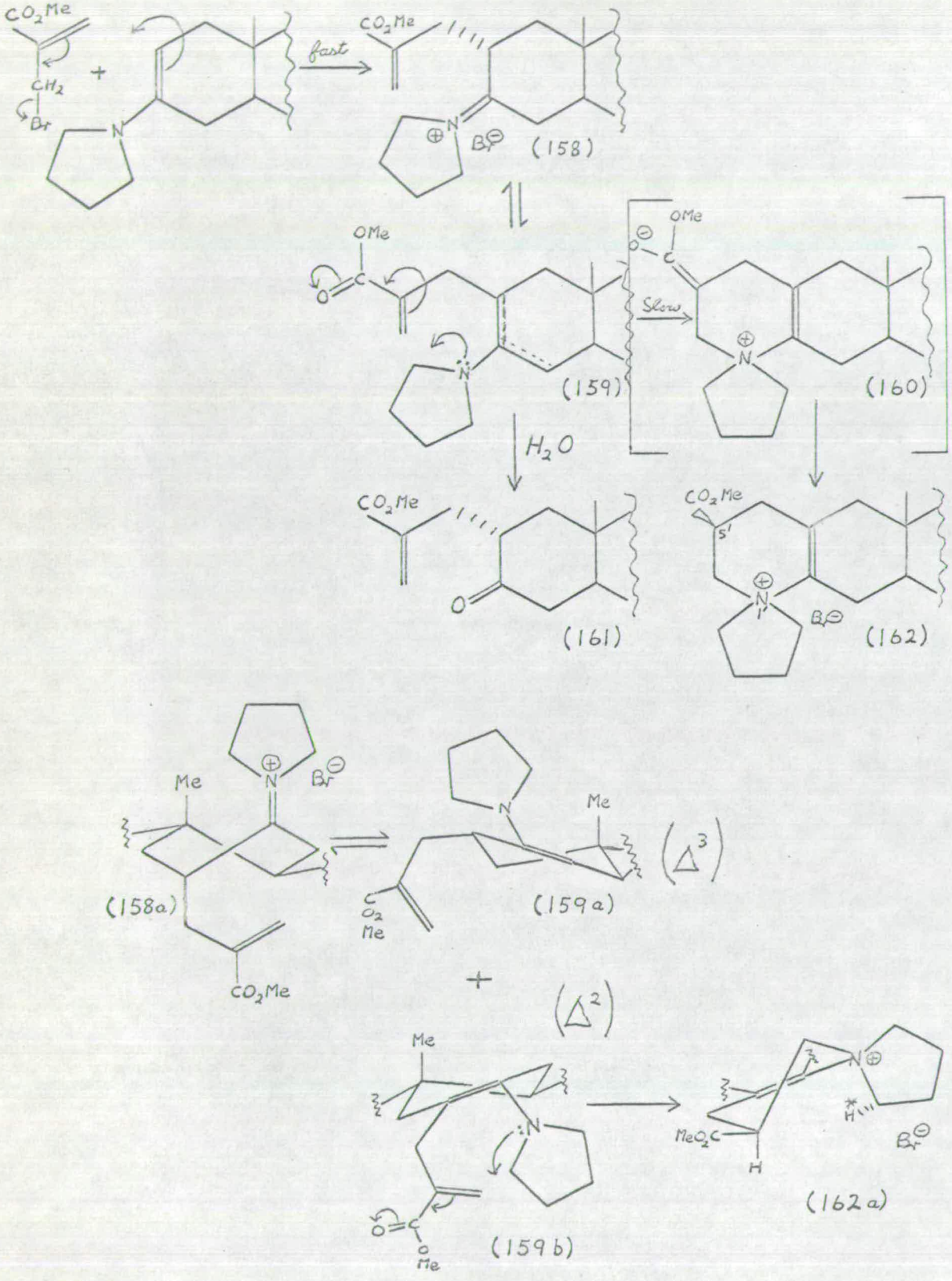
Starting Ketone	Product	Yield from Chromatography (%)	Purification Yield (%)	Overall Yield (%,(wt in mg))	
cyclohexanone	olefin	33	24	7.9	(46)
decal-2-one	bicyclo	7.3	recryst. to 0.3mg DNP	-	-
	olefin	4.9	2.6 of DNP	0.13	(0.9)
19-norandrostanolone acetate	bicyclo	2.1	2.8 of DNP	0.059	(0.8)
	olefin	18	3.0 of DNP	0.54	(4.8)
5β-androstanolone acetate	bicyclo	0.54 crystals	34	0.18	(2.2)
	olefin	11	13	1.4	(17.4)
5α-androstanolone acetate	olefin	1.4	10	0.14	(7.5)
17α-methylandrostanolone	olefin	0.95 impure	-	-	-
pregnan-3,20-dione	olefin	insufficient crude starting material		-	-
5α-cholestan-3-one	di-olefin	1.2 probable mixture	5.0	0.06	(1.1)
androstanolone 4-methylpentanoate	olefin	characterized via the acid		-	-
D.H.A. acetate	olefin	1.2	2.3 of DNP, slightly impure	0.028	(0.3)
testosterone acetate	olefin	none isolated	-	-	-

olefins (from groups I and III), however, were isolated in yields always less than 1.5%. Even on producing the compounds chromatographically in a substantially pure state the difficulties were not over since the crude substances were oils (reminiscent of the allylation reaction of Section 2.3) which could be induced to crystallize from hexane only by dint of considerable effort and multiple recrystallization was necessary to give sharp-melting material. This purification procedure reduced the already small yields by a further factor of about 10%. Another way adopted to characterize the compounds was by preparation and recrystallizations of the 2,4-dinitrophenylhydrazone derivative; however with steroids this method was even poorer, giving perhaps 3% yield of the pure D.N.P. from the oily ketone. Both methods gave rise to the manipulative problems involved in the recrystallization of milligram quantities. In the event, the olefins could be fully characterized only when an appreciable quantity (more than 700 mg) of crude starting material was available. The yields obtained, both with steroids and the simpler compounds, are summarized as Table 2.1. The steroid reactions will now be examined piece-meal and a unified discussion will be deferred till later.

Salts

A scheme consistent with the reaction of methyl α-(bromomethyl)-acrylate with the pyrrolidenamines of 5α-androstanolone acetate, 17α-methylandrostanolone and pregnan-3,20-dione is presented as Fig. 2.13. On losing a proton the iminium bromide (158) produced by the primary alkylation, gives rise to the new enamine (159). Evidence has been presented in section 1.6(b)(i) that a trisubstituted enamine (here the Δ^3) is preferred to the tetrasubstituted (Δ^2) and it has been noted that this is because in the trisubstituted isomer the substituent can assume the quasi-axial position, away from interaction

Fig. 2.13 Reaction of Methyl ∝-(bromomethyl) Acrylate with Pyrrolidenamine of 5∝-Androstanolone Acetate etc.



with the pyrrolidine ring. In this case, however, as has been argued for methylation (section 2.2) the iminium salt (158a) is the product of bottom-face attack because of the influence of the angular C-19 methyl. Thus, the substituent in the Δ^3-enamine cannot assume a quasi-axial position but is quasi-equatorial and of correspondingly higher energy. With the Δ^3-isomer destabilized in this way an appreciable equilibrium population of the Δ^2-enamine must occur. In such a strained environment the pyrrolidine ring might be expected to turn out of conjugation to relieve the interaction, in which position N-alkylation by the activated olefin side chain is facilitated. However this should be a difficult step and consequently a slow one. In the short-term, hydrolysis of the rapidly produced iminium salt (158) and the enamine (159) give rise to the olefin (161). Protonation of the zwitterion (160) would by analogy to previously discussed reactions be considered a kinetically controlled process. In the present case, however, the 5′-hydrogen will be much more acidic due to the electron withdrawing effect of the quaternary nitrogen. This is supported by the low field resonance of this proton (3.46 δ) in the n.m.r. spectrum. Thus it seems likely that protonation might here be under thermodynamic control. Inspection of models of the salt (162) reveals that the more stable conformation of the new ring is that half chair represented by (162a) rather than the alternate half chair in which there is considerable steric interaction between the pyrrolidinyl hydrogen starred and the steroid C-4 α-hydrogen. The carbomethoxy group is assigned the more stable quasi-equatorial (β) position (162a).

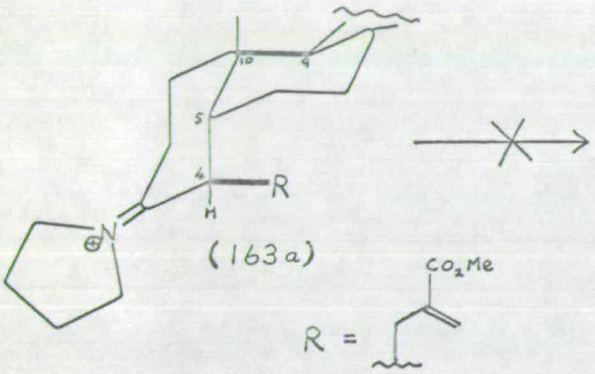
The failure of the reaction to produce a salt in a more acidic environment (no triethylamine) is consistent with the reaction proceeding as shown by proton abstraction from the initial iminium bromide (158) to yield the new enamine (159). Support for the postulated

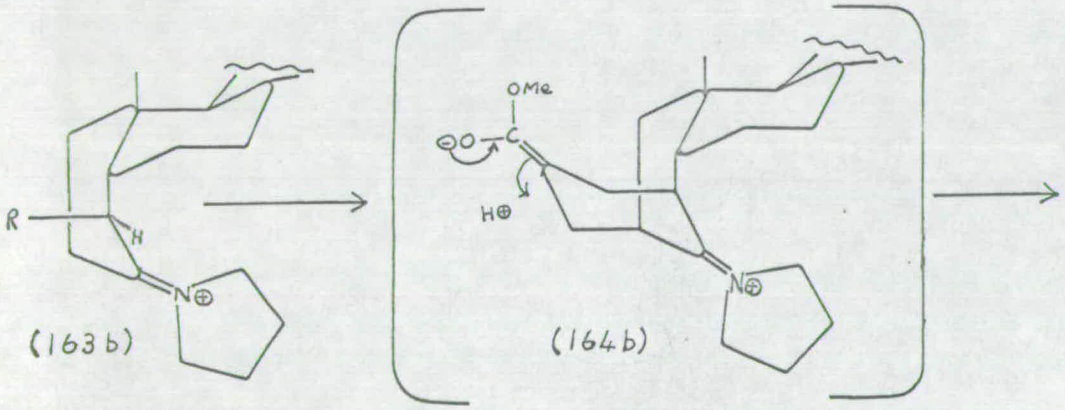
formation of the salt from the enamine (159) is provided by the production of the olefin (151) on gentle alkaline hydrolysis of the salt (136a). A possible mechanism for the reaction is presented in Fig. 2.12. The initial loss of the acidic 5'-proton to yield (149) initiates the decomposition of the new ring to give the enamine (150), which subsequently hydrolyses to the olefin (151). Not only is this a plausible mechanism but it will be noted that the sequence (salt $\longrightarrow$ (149) $\longrightarrow$ (150)) is just the reverse of that posited for the formation of the salt ((159) $\longrightarrow$ (160) $\longrightarrow$ (162)). Of course the intermediate (149) may not exist: the reaction may be concerted, but this is equally true of the forward reaction.

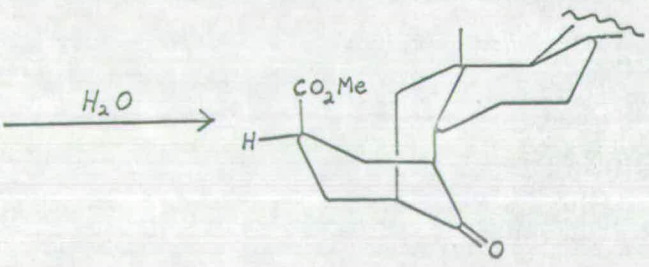
Bicyclononanes

The reaction of the pyrrolidenamine from 19-norandrostanolone acetate with methyl α-(bromomethyl)-acrylate is analogous to the similar reaction of the pyrrolidenamine from trans-decal-2-one. In contrast to the latter, however, the purified 2,4-dinitrophenylhydrazone (131) of the bicyclononane was a single compound. While it melted over 7° this was the result of the only recrystallization possible of the chromatographically pure D.N.P.: this can be compared with the 5° melting range of the D.N.P. (133) from the olefin. It is not possible to argue directly that because the D.N.P. derivative is a single isomer then this must also be true of the parent bicyclononane, since considerable material (97%) was lost in the preparation. However the contrary argument that losses were high because two isomers were present is not supported by the size of the yield (2.8%) which is quite typical of these D.N.P. preparations (Table 2.1). It should be noted too that repeated recrystallization did not succeed in isolating a single isomer from the equal mixture of D.N.P.s (127) of the bicyclononane from decal-2-one and it might be asked why this procedure

Fig. 2.14 Possible Reactions of Methyl ∝-(bromomethyl)-acrylate with the Pyrrolidenamine of 5β-Androstanolone Acetate







succeeded here if the steroid produced a similar mixture. The only answer could be that the properties of the two steroids must be more different than the simpler compounds. If this were so it is probable, though not certain, that the compounds would also behave differently to t.l.c., but empirically the steroid bicyclononane and D.N.P. were homogeneous to t.l.c. with two different solvent systems. This procedure is certainly capable of distinguishing ring junction isomers of an apparently similar degree of structural disparity, for example 5α-androstanolone acetate can be resolved from the 5β-isomer using similar solvents. Examination of the two reaction paths (Fig. 2.11) reveals that the "bridge-down" isomer (148a) is the product of top-face attack, while the other (148b) results from bottom-face reaction. The steroid is asymmetric and in particular both the angular C-18 methyl and C-17 acetate reside on the top face. This, together with associated solvation is likely to shield, to some degree, the approach of reagents from the top and therefore steer the reaction, which was fairly evenly balanced for the decalone, towards bottom-face attack. The combined weight of these arguments leads to the provisional assignment of the bicyclononane as (predominantly) the "bridge-up" 2α,4α-isomer (148b).

Possible reactions of methyl α-(bromomethyl)-acrylate with the pyrrolidenamine of 5β-androstanolone acetate are illustrated as Fig. 2.14. If it is assumed that the initial attack comes from the least hindered side then the two possible axial iminium salts are (163a) with the A-ring chair-like and (163b) with a boat-like A-ring. The former (163a) will probably be the less stable since the new side-chain suffers considerable 1,3-diaxial interaction with the C-9 methylene group. Cyclization would, in any case, be severely disfavoured by the introduction of yet another 1,3-diaxial interaction in the transition state. On the other hand no such difficulty is experienced by (163b)

in cyclizing to (164b). Protonation of this zwitterion, again from the least hindered side, gives rise to the A-ring-boat/new-ring-chair structure (165b) which is analogous to the bicyclononane (148b) from 19-norandrostanolone acetate. In the current case the bicyclononane was clearly a single isomer since chromatography gave it as a white crystalline solid and a single recrystallization sufficed to produce a sharp melting point. The n.m.r. spectrum shows that the angular C-19 methyl has a considerably changed electronic environment in the bicyclononane (0.72 δ) as compared to the starting ketone (1.03 δ). This cannot be attributed to a general inductive effect due to electron release since not only would the added bridge actually tend to withdraw electrons but the C-18 methyl resonance moves marginally downfield. Nor does it seem likely that the change is due to a through-space effect from the carbomethoxy group for it is free to rotate, thus partially cancelling any such result and the C-19 methyl resonance in the olefin (135) from 5β-androstanolone acetate is not shifted by more than 0.02 δ. The most plausible possibility is that the large change is due to the through-space effect of the C-3 carbonyl, the orientation of which is altered relative to the C-19 methyl as the A-ring changes from a chair in the starting ketone to a boat in the bicyclononane (165b). Examination of models in light of the known magnetic anisotropies of the carbonyl group[198] is consistent with this possibility: in the chair A-ring of 5β-androstanolone acetate the C-19 methyl lies within the de-shielding cone coaxial with the carbonyl bond, while in the boat bicyclononane it lies nearer to the perpendicular shielding cone. The net effect expected is therefore an upfield shift of the C-19 methyl resonance, as is observed in practice.

Olefins

In general the olefins which were isolated were the (2-carbomethoxyprop-2-enyl)-monosubstituted derivatives of the starting

ketones, produced by hydrolysis of the initially produced iminium salt (e.g. 158). With cholestan-3-one, however, the di-olefin (139) was isolated. In the course of purification two olefins were detected while only the one was prepared pure. By analogy it seems likely that the other was the mono-olefin (137d). This probability is strengthened by the isolation of the acid (138e) corresponding to the mono-olefin from the reaction with the analogous androstanolone 4-methypentanoate.

With testosterone acetate a mixture of olefins was obtained. The dienamine system is capable of reaction at C-6 as well as C-4: furthermore in the latter instance the residual 5(6)-double bond may or may not move back into conjugation (Δ^4) on mild hydrolysis. The main product, however, is likely to be the 4-substituted testosterone (143) by analogy to the methylation[15,60-63].

General Discussion

Unified reaction scheme

The reactions of methyl α-(bromomethyl)-acrylate with the pyrrolidenamines of the following 11 ketones have been examined piecemeal and mechanisms have been proposed to account for the empirical findings: cyclohexanone; decal-2-one; 19-norandrostanolone acetate; 5β-androstanolone acetate; 5α-androstanolone acetate; 17α-methylandrostanolone; pregnan-3,20-dione; cholestan-3-one; androstanolone 4-methylpentanoate; D.H.A. acetate and testosterone acetate. Three of these are stereochemically distinct from the others and 5β-androstanolone acetate, D.H.A. acetate and testosterone acetate will therefore be discussed separately. For the remaining compounds what remains to be explored is why one gives a bicyclononane in addition to the olefin and three yield salts as well as olefins. A combined reaction scheme appears as Fig. 2.15. The path leading to the bicyclononane is written almost as before: the first step gives the

Fig. 2.15 A Combined Reaction Scheme

monosubstituted iminium bromide (166). In compounds with an angular methyl the substituent, as previously argued, has the α-orientation. The iminium salt gives rise to a mixture of Δ^2 (167) and Δ^3-enamines (168). It has been noted previously that one effect of the angular methyl is to shift this equilibrium somewhat in the direction of the Δ^2-isomer from which the zwitterion (172) and salt (173) are formed. The Δ^3-enamine, on the other hand, cyclizes to the bicyclononane zwitterion (169) and protonates to give an iminium salt which is hydrolysed to the bicyclononane (171). For compounds with an angular methyl group this cyclization would cause severe steric compression between it and the pyrrolidine as the A-ring is pushed up into a boat. In practice no discernable amount of bicyclononane is formed from starting materials with an angular methyl group.

In summary the picture that emerges is a simple one. The basic reaction is the production of bicyclononane but where this path is blocked for steric reasons by an angular methyl group the equilibrium between the Δ^2 and Δ^3-enamines assumes importance. If the Δ^2-isomer with the pyrrolidine ring turned out of conjugation is present to an appreciable degree the salts will be formed. This equilibrium may, however, be delicately balanced. In practice no salt was formed from 5α-cholestan-3-one: instead the di-olefin (139) was obtained in 1.2% yield, though this was almost certainly (as argued above) accompanied by the mono-olefin (137d). The di-alkylation here strongly argues that in the cholestanone case the equilibrium favoured the Δ^3-enamine (168). Differences between androstanes and cholestanes are well known and have been attributed to transmitted conformational distortion[157-160] from the bulky C-17 chain. The picture has been further refined by molecular orbital calculations into two component parts, "conformational steric transmission" (C.S.T.) which corresponds to the classical idea

and variations in electron distribution due to the conformational changes, "conformational electronic transmission" (C.E.T.), which may generally be more important[199]. It was noted that the proportion of the unsubstituted Δ^3-isomer is marginally greater for the pyrrolidenamine of cholestan-3-one (17%) than 5α-androstanolone acetate (12%), as determined by n.m.r. integrals (section 2.1(a)). While the difference is small, if it is real the corresponding free energy difference might have a decisive effect in favouring the Δ^3-isomer in the more equally balanced situation with the substituted enamines: nonetheless little weight can be placed on this observation because of the considerable errors associated with the n.m.r. measurements. With the similarly bulky C-17 chain of androstanolone 4-methylpentanoate again no salt was formed, although only the mono- and not the di-olefin was detected (via the acid (138e)). The general principles outlined above are also applicable to the other compounds. Where, because of the orientation of the A-ring there is no interference from the angular methyl the bicyclononane is formed in addition to the olefin, as for example with 5β-androstanolone acetate. With D.H.A. acetate, on the other hand, the C-18 angular methyl inhibits cyclization to the bicyclononane and since the D-ring conformation is quite different to the A-ring no salt is formed; thus only the olefin (140) was isolated. In the case of testosterone acetate with quite different stereochemistry a mixture of mono-olefins was obtained.

Further comments

Probably the most important compounds mentioned in this chapter are the salts (136). They have already been discussed extensively from a chemical viewpoint: biologically too they are of interest. Quaternary ammonium salts play important roles in naturally occurring compounds such as acetylcholine (156), a "transmitter substance" in

the nervous system. Steroidal quaternary ammonium salts have found pharmacological application as neuromuscular-blocking agents, for example the bisquaternary chandonium iodide (157) "appears to be the most potent short-acting non-depolarising drug so far reported[201]". The salts described here are currently undergoing biological testing.

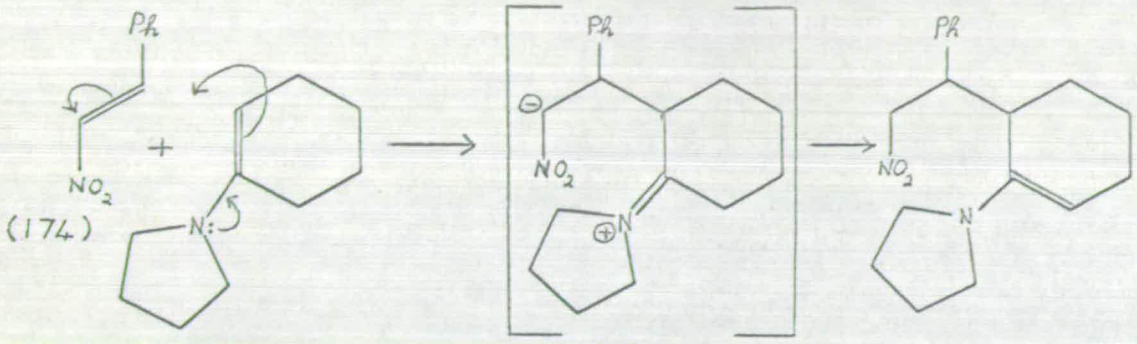
Another interesting class of compounds is that containing the bicyclo [3,3,1] nonane bridged-ring system. A single example of a bicyclo [3,3,1] nonane built on a steroid A-ring has been reported in the literature[197]: in this case the new ring bridged C-3 and C-5. This compound 3α,5α-(2-oxotrimethylene)-androstan-1,17-dione (155) was prepared by the facile reaction of the 2,4-diene-1-one system (154) with acetone in the presence of acid. Of the bicyclononane-producing reactions reported in this chapter the yields of crude material decrease markedly from the cyclohexanone (121) (24%) to the decalone (126) (7.3%) to the 19-norandrostanolone (130) (2.1%). However, no attempt was made to optimize reaction conditions and it may be that a considerably higher yield of 17β-acetoxy-2α,4α-(2α-carbomethoxytrimethylene)-5α,10β-estran-3-one (130) could be achieved. This prospect is even brighter for 17β-acetoxy-2β,4β-(2β-carbomethoxytrimethylene)-5β-androstan-3-one (134) from the 5β-steroid, since although it was finally isolated in only 0.54% yield, a very much larger quantity was earlier detected in the chloroform-soluble fraction.

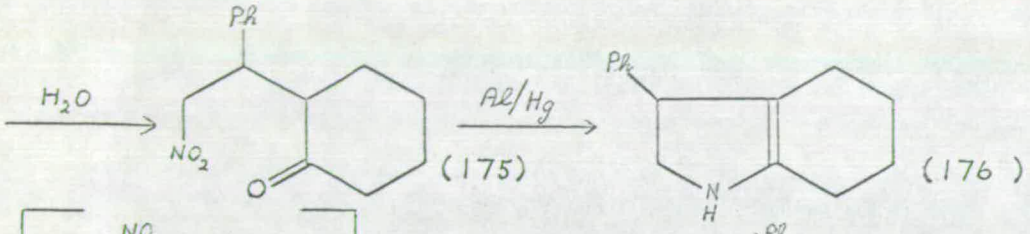
Addendum

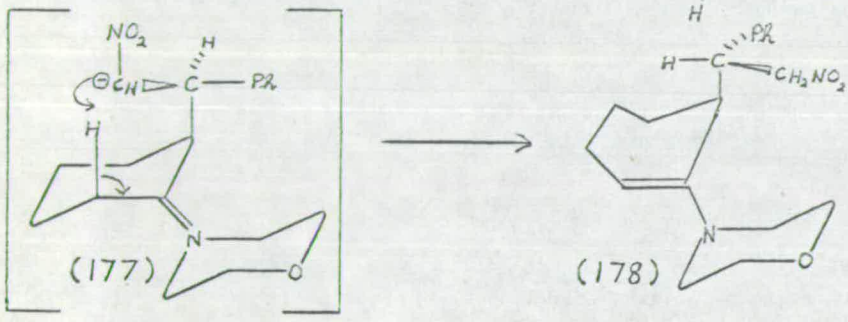
The 5β-androstanolone acetate used in the reaction with methyl α-(bromomethyl)-acrylate was prepared by the method of Pandit et al.[91]. These workers reported that the reaction of the iminium perchlorate of the pyrrolidenamine from testosterone acetate with Hantzsch ester gave completely stereospecific reduction to 5β-androstanolone acetate.

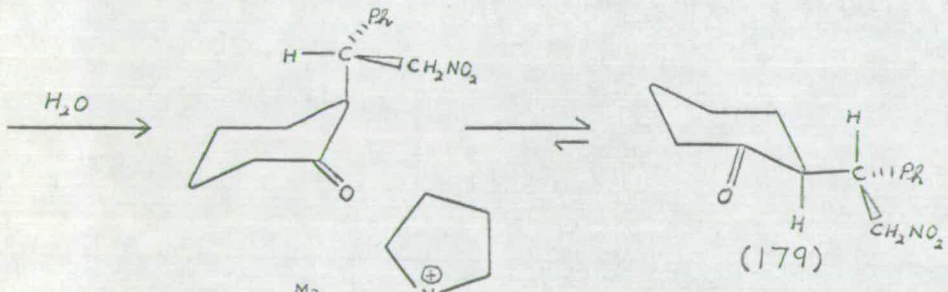
This conclusion was based upon n.m.r. spectra of the crude reaction product. In the present instance, however, although recrystallization gave the pure 5β-compound, t.l.c. of the crude mixture, using 15% ethyl acetate in hexane, revealed a small amount of the 5α-isomer (R_f = 0.21 chars brown) in addition to the major 5β-ketone (R_f = 0.17 chars yellow). This result is not inconsistent with the experimental results of Pandit et al. but may indicate only the greater sensitivity of the assay technique used here.

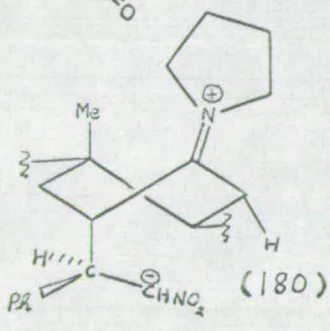
Fig. 2.16 Reactions of ω-nitrostyrene (lit.)

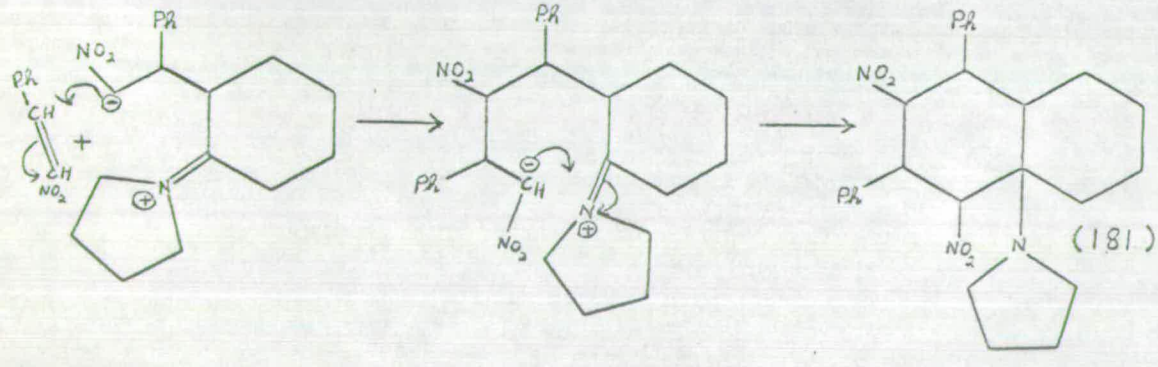












2.6 REACTION WITH ω-NITROSTYRENE

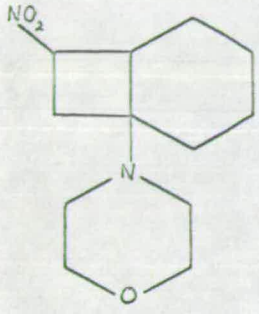
Previously Reported Experiments

The reaction of ω-nitrostyrene (174) with the pyrrolidenamine of cyclohexanone has been reported to give largely the monosubstituted ketone (175)[161,162], which in turn yields the indole derivative (176) on reductive cyclization with aluminium amalgam[162]. The stereochemistry of the analogous reaction with the morpholine enamine[163] has been explained as follows[164]. Intermediate zwitterion (177) exists with the substituent axial and furthermore the phenyl group lies anti to the ring. In this conformation the negative carbon atom is near enough to the hydrogen depicted for intramolecular hydrogen transfer to occur, producing the new enamine (178) with the substituent quasi-axial. It is only after hydrolysis that this can attain the more stable equatorial position in ketone (179), with the erythro configuration.

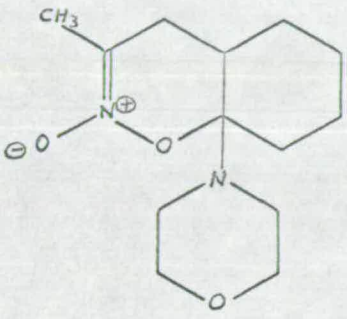
Results

An attempt was made to react the pyrrolidenamine of androstanolone acetate with an equimolar quantity of ω-nitrostyrene in dioxan at room temperature for two days. The product, however, did not contain any appreciable amount of the expected monosubstituted compound but did comprise considerable high molecular weight material (mass spectrum). Since thin layer chromatography showed the product to consist of starting material and a probable mixture of compounds (diffuse streak) of higher polarity than androstanolone acetate, the reaction product was not further investigated.

Fig. 2.16 (cont.)



(182)



(183)

Another attempt was made in which a solution of ω-nitrostyrene in dioxan was added to a solution of androstanolone pyrrolidenamine at 0°. The mixture was allowed to warm to room temperature for three hours and was then refluxed under nitrogen for one hour. The product of ether work-up was chromatographed on alumina and the bulk of this proved to be a brown tar which eluted only with a chloroform mixture. A yellow glass which came through with ethyl acetate was further chromatographed on florisil but the only material which could be isolated was unchanged androstanolone, identified by t.l.c. and n.m.r.

Similar results were obtained when the reaction was carried out in anhydrous ethanol.

Discussion

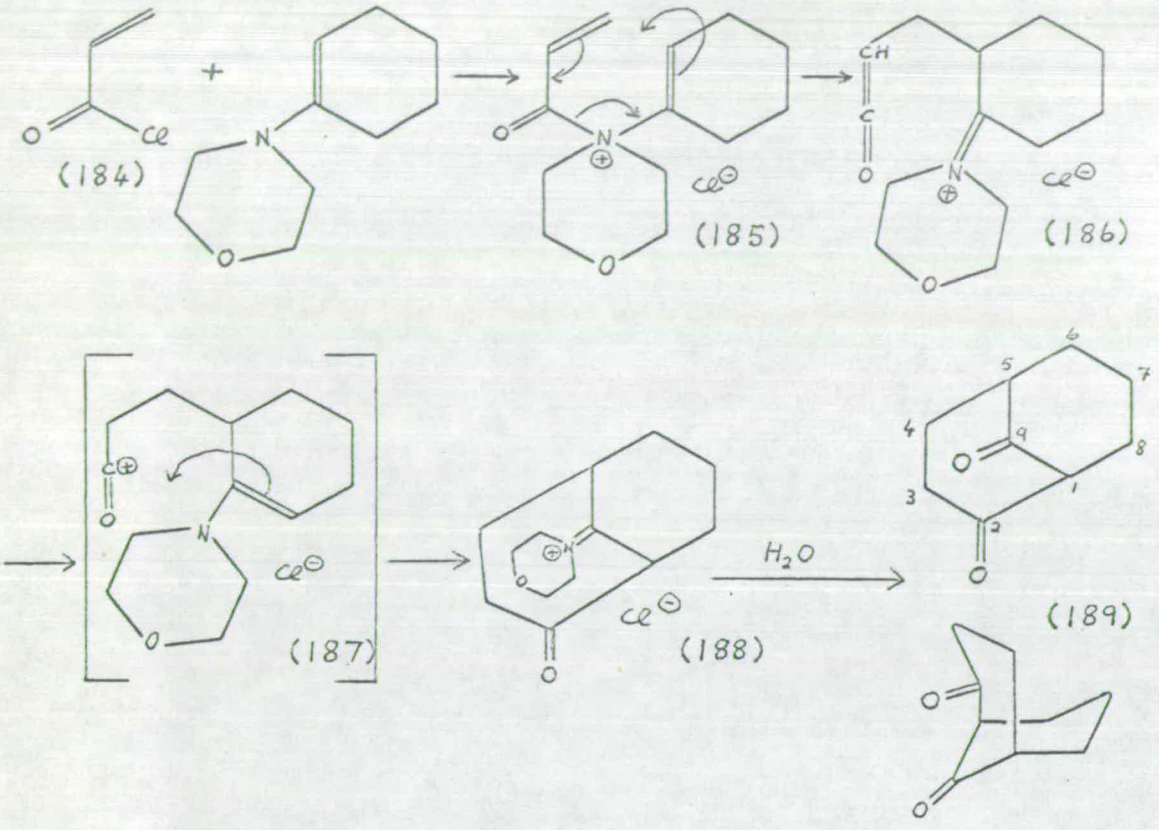
ω-nitrostyrene reacts vigorously with enamines. For example, ω-nitrostyrene gave better than 80% yield of the cyclohexanone derivative (175) after being allowed to react in dioxan at room temperature for one day[162]. In comparison allyl bromide[150] gave only 67% of 2-allylcyclohexanone after reaction in refluxing acetonitrile for 13 hours. It therefore seems likely that the primary alkylation step to yield the zwitterion (180) proceeds readily enough. However, in the skew-boat form (180) previously ascribed to 2-substituted 3-iminium steroids (section 2.2) the substituent is no longer in so favourable a position for intramolecular hydrogen transfer. In lieu of this a variety of reactions may be expected of the zwitterion. For example, it may react with more ω-nitrostyrene. This behaviour is not unknown even in the case of the pyrrolidenamine of cyclohexanone, with which excess of ω-nitrostyrene is reported[165] to have given the bis-adduct (181) formed from the zwitterion as illustrated. Other products too have been obtained in similar reactions of nitro-olefins with enamines e.g. the cyclobutane compound (182)[161] and the interesting stable

(below 0°) oxazine derivative (183)[166].

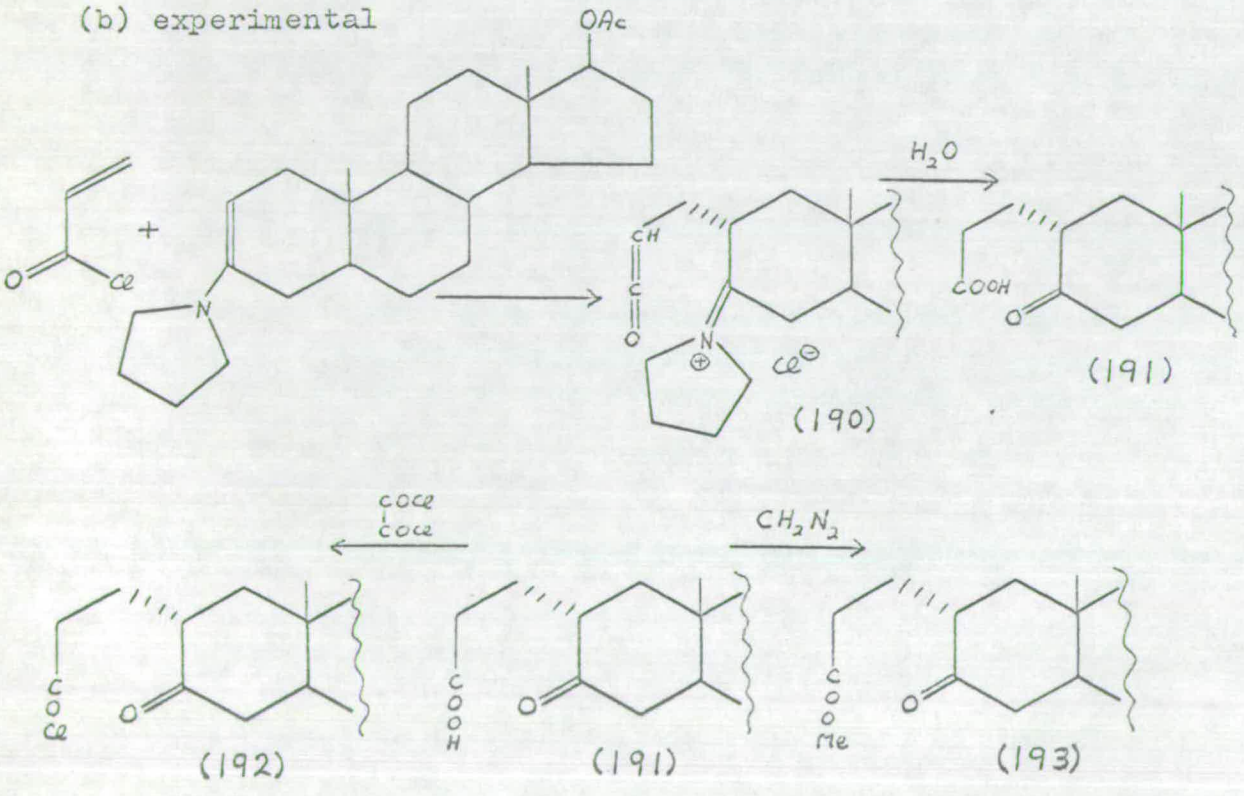
In summary, it seems likely that in the steroid case a number of compounds are formed from the intermediate (180) owing to the difficulty here, for steric reasons, of transannular hydrogen transfer, which with the cyclohexanone leads to the monosubstituted compound.

Fig. 2.17 Reactions of Acryloyl Chloride

(a) lit.



(b) experimental



2.7 REACTION WITH ACRYLOYL CHLORIDE

Previously Reported Experiments

Reaction of acryloyl chloride (184) with the morpholine enamine of cyclohexanone has been reported[167,168] to give the bridged iminium salt (188), which is converted on gentle hydrolysis with warm water to bicyclo [3,3,1] 2,9-dione (189). The pyrrolidenamine has also been used but under similar conditions this gave 17% yield as compared to 67% for morpholine[170]. Further studies to elucidate mechanistic details have also been performed[169,170,171]. In brief the mechanism proposed is a kinetic N-acylation to give (185), which undergoes [3,3] sigmatropic rearrangement to give the C-substituted ketene (186). Hydrogen migration then gives the acylium ion (187) which cyclizes to the 9-iminium chloride (188) of bicyclo [3,3,1] 2,9-dione (189). An unfamiliar feature of this scheme is the initial N-acylation and this is well-established, since not only have such compounds as (185) actually been isolated[169], but the reaction yield has been shown to depend on steric conditions at the nitrogen rather than electron density changes with different amines[170].

Results

Acryloyl chloride was added to a boiling benzene solution of the pyrrolidenamine from androstanolone acetate and reflux was maintained for 21 hours. The white precipitate was gently hydrolysed with water to yield 3-(17β-acetoxy-5α-androstan-3-one-2α-yl) propanoic acid (191). This compound dissolved in hot sodium hydroxide solution and the acid proton could be discerned in the n.m.r. spectrum. Exact mass measurement of the molecular ion confirmed the identification. Despite homogeneity to thin layer chromatography it remained possible that some bicyclo [3,3,1] nonan-dione steroid was present. Since the acid proton

could not readily be accurately integrated against another resonance the methyl ester (193) was prepared with diazomethane. Integration of carbomethoxy versus the C-17 proton showed that the ester and hence the acid comprised the whole (more than 95%) of the product. It may therefore be concluded that no detectable amount of bicyclo [3,3,1] nonandione steroid was formed in the reaction of acryloyl chloride with the pyrrolidenamine of androstanolone acetate.

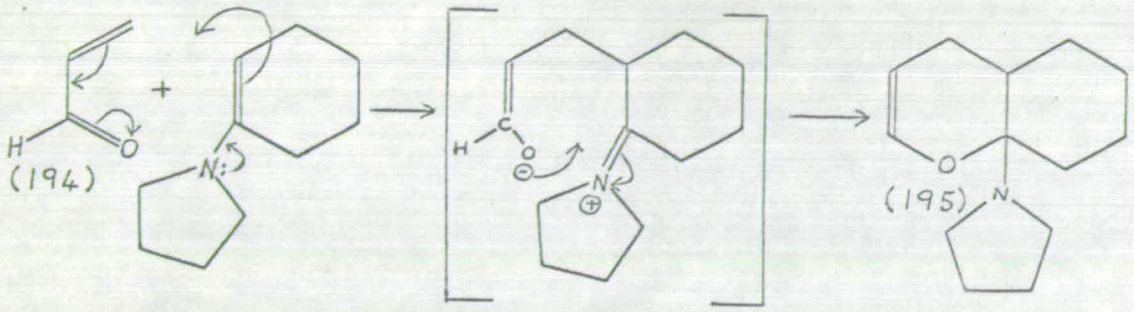
A trial was made to prepare the steroidal bicyclo [3,3,1] nonandione. The acid chloride (192) was produced by reaction of the acid (191) with oxalyl chloride in the presence of pyridine. Attempted cyclization of the acid chloride with stannic chloride was unsuccessful: the only effect was to remove the side-chain, returning androstanolone acetate, identified by thin layer chromatography.

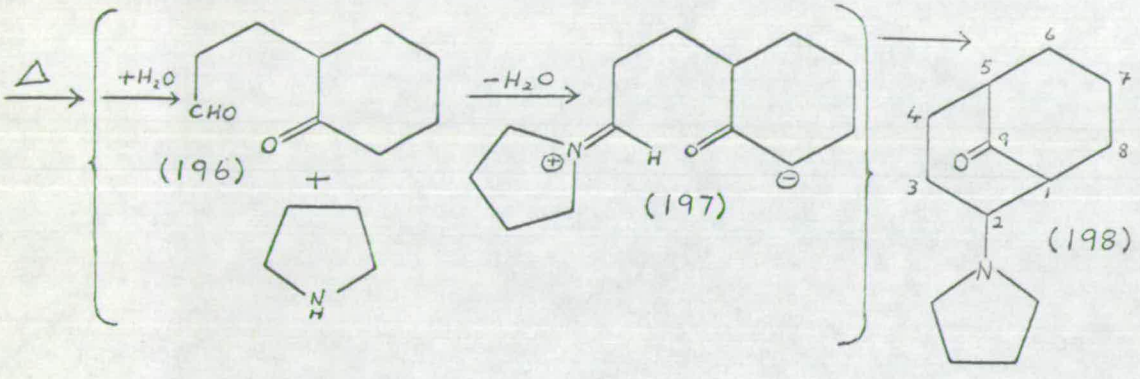
Discussion

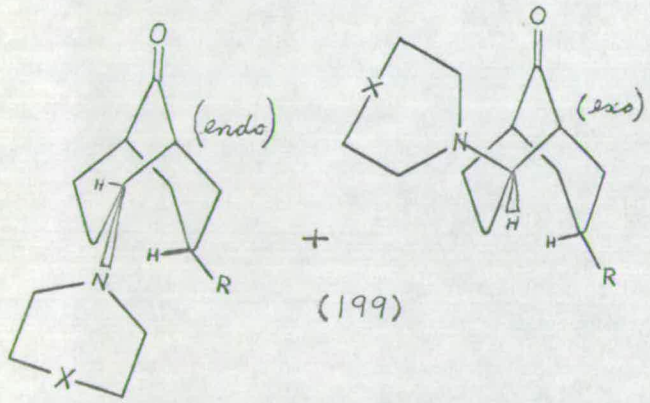
It seems likely that in the steroid case reaction proceeds smoothly as far as the ketene (190). However it has already been argued (section 2.6) that the skew-boat conformation in the steroid renders difficult any transannular hydrogen transfer to give a new enamine of type (187), thus any intramolecular transfer of this type is unlikely in the steroid. Furthermore it has been shown (section 2.5(c)) that the Δ^3-enamine is much more strained and is therefore present to a lesser extent than in the corresponding cyclohexanone case. In addition, perhaps most important, cyclization of (190) to give a bridged compound of type (188) would involve severe steric compression between the pyrrolidine ring and the angular C-19 methyl as the A-ring is forced into a boat by the α-substituent. It seems probable that the precipitate of steroid is the ketene iminium chloride (190) which hydrolyses readily to the acid (191).

Fig. 2.18 Reactions of Acrolein

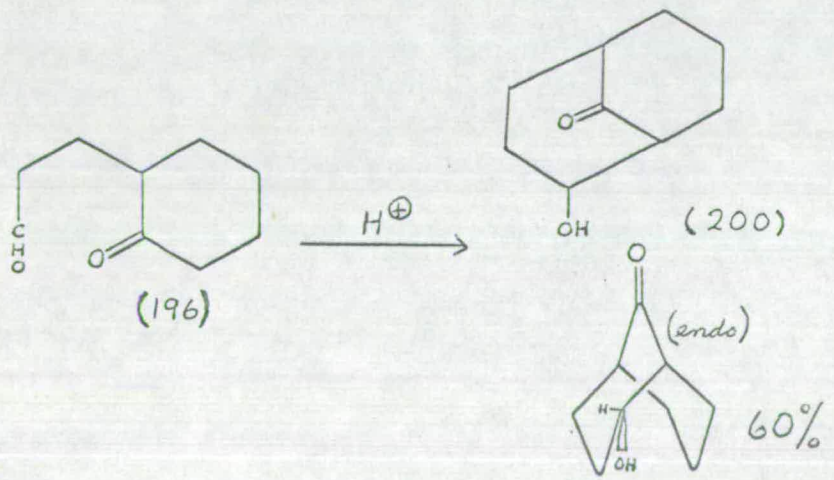
(a) lit.







	Endo (%)
(a) R = Me; X = -	50
(b) R = Bu^t; X = -	71
(c) R = H; X = NPh	>75
(d) R = H; X = O	75



2.8 REACTION WITH ACROLEIN

Previously Reported Experiments

Acrolein (194) is reported to react with one equivalent of the pyrrolidenamine of cyclohexanone in dioxan, initially at 0° to give on distillation a 75% yield of 2-pyrrolidinyl-bicyclo [3,3,1] nonan-9-one (198)[136]. The corresponding morpholine enamine gives similar results[172]. The stereochemistry of the products (199a,b,c,d) has been investigated. When the amine substituent is large (199c,d)[174,200] or the original ring has little conformational freedom (199b)[175], the endo configuration in which the amine lies in the more stable equatorial position is considerably favoured; however when neither of these conditions obtains (199a)[175] a more equal distribution of the isomers is obtained.

Although the reaction mechanism had earlier been partially described, the intermediacy of the hexahydrobenzopyran (type 195) was discovered only somewhat later. The reaction between the morpholine enamine of cyclohexanone and acrolein in benzene at 0° gave the pyran, which was isolated: this was converted to the bicyclononane by vacuum distillation or treatment with triethylamine in D.M.F. at 75° [174]. The intermolecular water-catalysed pyrrolidine transfer mechanism illustrated has been proposed to account for the product[176,175]. A number of pyrans were isolated from the acrolein reaction under the conditions above, for example with the 4-phenylpiperazine enamine of cyclohexanone; but the bicyclononanes were obtained directly with the corresponding enamines of cyclopentanone and cycloheptanone[174].

One modification of the reaction employs freshly distilled enamine and acrolein in ether solution at low temperature (-12°) for one hour[173]. Immediate hydrolysis of the mixture produced in 28 to 35% yield the

aldehyde (196) which could in turn be cyclized with acid to the bicyclic alcohol (200) of which 60% was the endo-isomer shown.

Results and Discussion

The reaction of acrolein and the pyrrolidenamine of cyclohexanone in anhydrous dioxan was studied using three different reaction conditions/work-up procedures. In each case the solution of enamine was initially chilled to 0^{o} before the addition of acrolein and was then allowed to warm to room temperature for one hour.

(A) Ether/aqueous work-up gave an oil which was fractionally distilled at reduced pressure (0.5 mm).

(B) Reflux for 30 minutes under an atmosphere of dry nitrogen was followed by removal of the solvent on a rotary evaporator. After removal of ether-insoluble material the oil was chromatographed on alumina.

(C) A further 30 minutes at room temperature was followed by chloroform/aqueous work-up. The resultant tar was chromatographed on alumina.

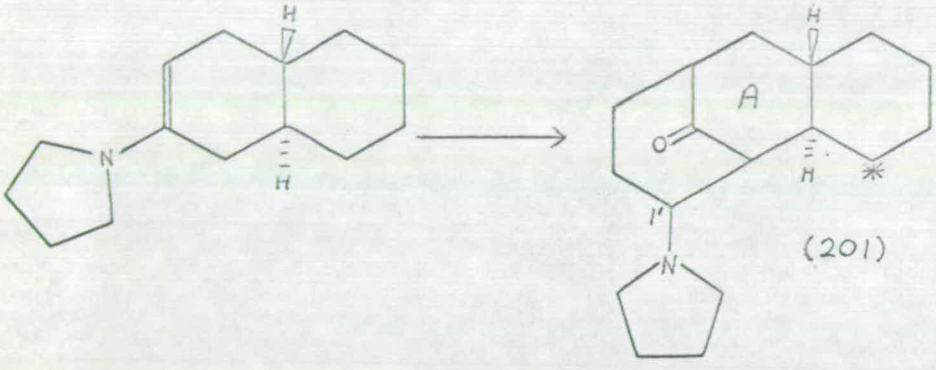
Each of these procedures gave the expected 2-pyrrolidinyl-bicyclo [3,3,1] nonan-9-one (198). The preferred chromatographic work-up (B) yielded the amine as a very pale-yellow viscous oil in 41% yield. The n.m.r. spectrum showed only a methylene hump and the i.r. a carbonyl absorption. The picrate, after recrystallization, had a melting point in agreement with the literature value. N.m.r. and i.r. spectra of the derivative were also consistent with the assigned structure.

It is notable that even with the mild (room temperature) conditions employed in method (C) only the bicyclononane was isolated and no pyran was detected.

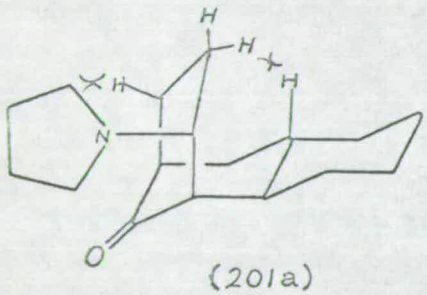
A procedure similar to (B) was followed for the reaction between acrolein and the pyrrolidenamine of trans-decal-2-one. Preliminary

Fig. 2.18 (cont.)

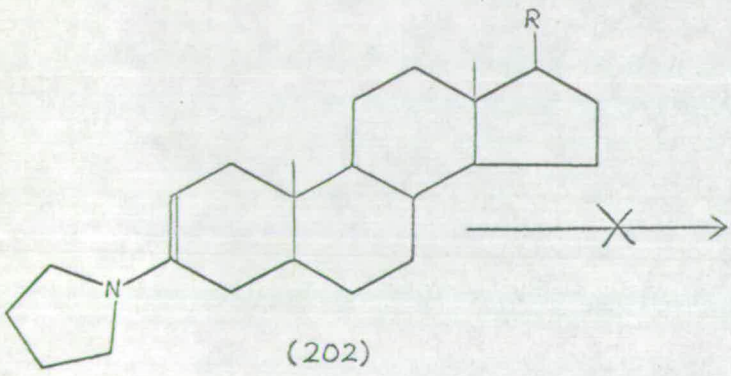
(b) experimental



(201)



(201a)



(202)

(a) $R = C_8H_{17}$

(b) R = OH

(c) R = OAc

purification on alumina gave an oil which t.l.c. revealed contained at least five compounds as well as decalone. Careful chromatography on florisil followed and the resultant 20 fractions were pooled to seven on the basis of t.l.c. Neither n.m.r. nor i.r. spectra were useful in determining the nature of the products since all fractions showed only methylene hump and carbonyl absorption. However, the fraction which was to prove to be the crude bicyclononane 1,3-(1-pyrrolidinyltrimethylene)-trans-decal-2-one (201) was a viscous pale-yellow oil in 9.8% yield. Since the spectra were of no use in identifying the amine, resort was had to chemical properties. Saturated ethanolic picric acid was added to all seven fractions. After standing for two days only the one gave a crystalline precipitate in poor yield (18%). After recrystallizations the picrate (by then 3 mg) melted over a 2° range. The infra-red spectrum of this picrate was quite similar to the picrate of (198) and to settle matters the abundant ion corresponding to the parent amine had an exact mass in agreement with the expected value.

It is interesting that the melting point of the picrate ($170-172^{\circ}$) was so close to that for the simpler system ($171.0-173.5^{\circ}$). One example has already been given in this thesis of a similar m.p. for a trans-decal-2-one (129) and a cyclohexanone derivative (125). It is easy to see that the stacking of molecules in the crystal may be similar for cyclohexanones and trans-decal-2-ones; furthermore it is probable that the intermolecular forces are determined principally by the polar substituents rather than by the hydrocarbon skeleton.

Examination of models reveals severe steric interference between the pyrrolidinyl α-protons and the methylene group starred (201) if the product is the endo-isomer of similar structure to the

conformationally frozen t-butyl-compound (199b). In the alternate exo form the only appreciable new interaction is that between the pyrrolidinyl α-protons and the axial C-4 proton. It seems likely therefore that the exo-compound will be the result of the thermodynamically controlled pyrrolidine transfer, though the new ring may be somewhat flattened as illustrated (201a) to relieve both the α-pyrrolide/C-4 axial proton and C-3/C-7 proton interactions.

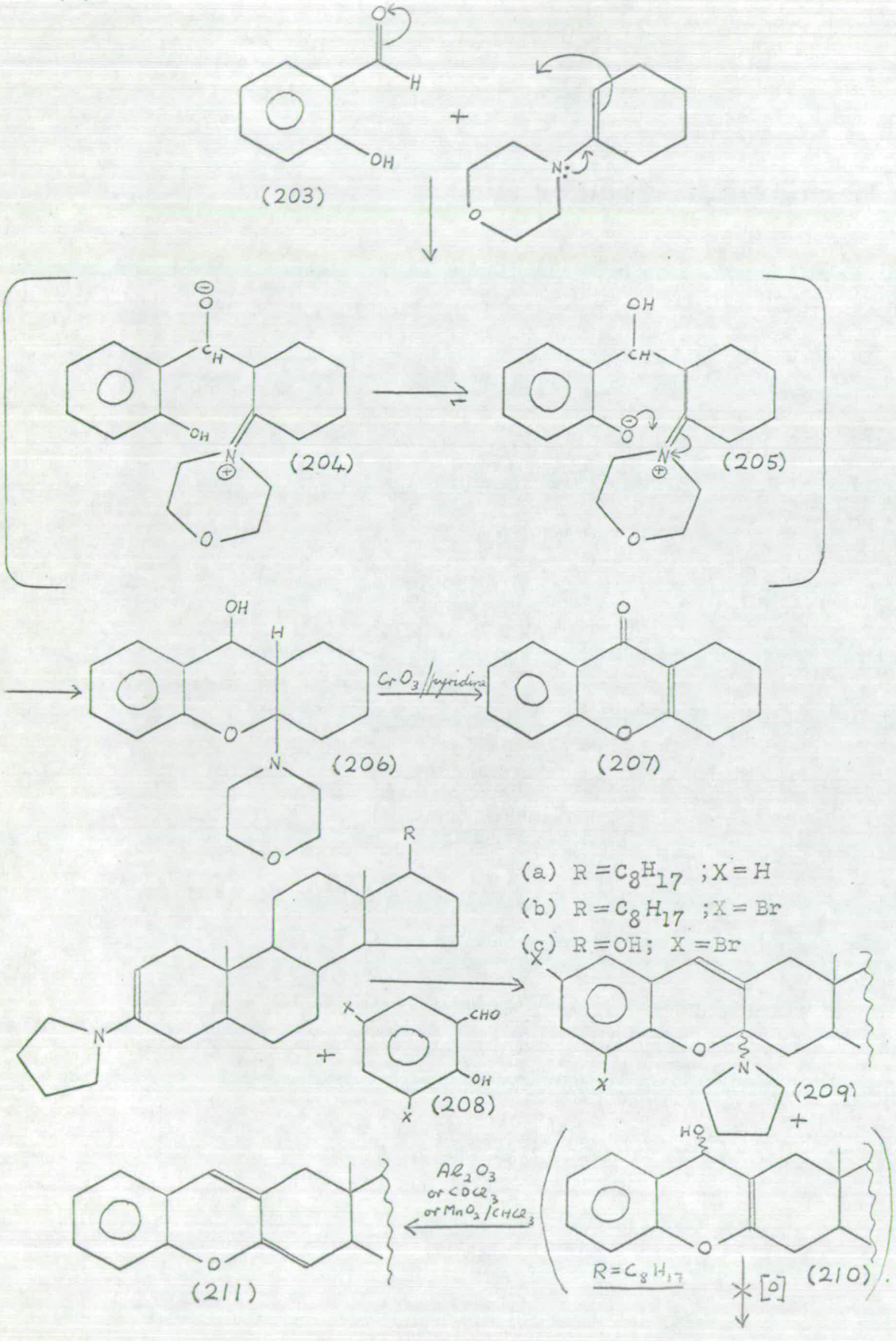
The reaction of acrolein with the pyrrolidenamines of the steroids cholestan-3-one (202a), androstanolone (202b) and androstanolone acetate(202c) was attempted in anhydrous dioxan at room temperature. Mass spectroscopy of the crude products failed to reveal a peak corresponding to the expected product and alumina chromatography gave only starting material as well as highly polar tar. Also using the two latter steroids, when the initial reaction period was followed by reflux similar results were obtained. Finally the reaction was carried out with reflux in anhydrous ethanol. Alumina chromatography gave roughly equal quantities of androstanolone and intractable material which eluted only with methanol. Picric acid was added to all 20 fractions but in no instance did a crystalline precipitate separate on standing.

It is clear that in the steroid the influence of the angular C-19 methyl will cause the new chain to assume the α-orientation characteristic of bottom-face attack, thus any bicyclononane formed would have a boat-like A-ring rather than the chair forms for the simpler compounds. It is probable that cyclization would be much more difficult in this case because of the increased strain in the transition state; thus the enolate anion is free to undergo alternate condensation reactions to produce a mixture of products. If the strain in the bicyclononane is the critical factor, as postulated, then the

decalone should be intermediate between the cyclohexanone and the steroid since, as has been argued, the bicyclononane (201a) is somewhat more strained than in the former but less than in the latter case. In practice the decalone provides a transitional case nicely in line with this reasoning, for not only was the yield of bicyclononane (201a) considerably less (9.8%) than the corresponding cyclohexanone derivative (198) (41%) but t.l.c. revealed the presence of small amounts of at least four other products.

Fig. 2.19 Reactions of Salicylaldehyde and Analogues

(a) lit.



2.9 REACTION WITH SALICYLALDEHYDE AND ANALOGUES

Previously Reported Experiments

Reaction of the morpholine enamine of cyclohexanone and salicylaldehyde (203) is reported to give the benzopyran derivative (206) in quantitative yield[177,178]. This reaction was designed to exploit the known relative basicity of alkoxide and phenoxide ions. The alkoxide ion (204), produced by reaction of the enamine with the aldehyde function is in equilibrium with the phenoxide ion (205). The latter may be presumed to be favoured. This reacts further to give the cyclized product (206). On Sarett oxidation (chromium trioxide/pyridine) this in turn yielded the chromone (207).

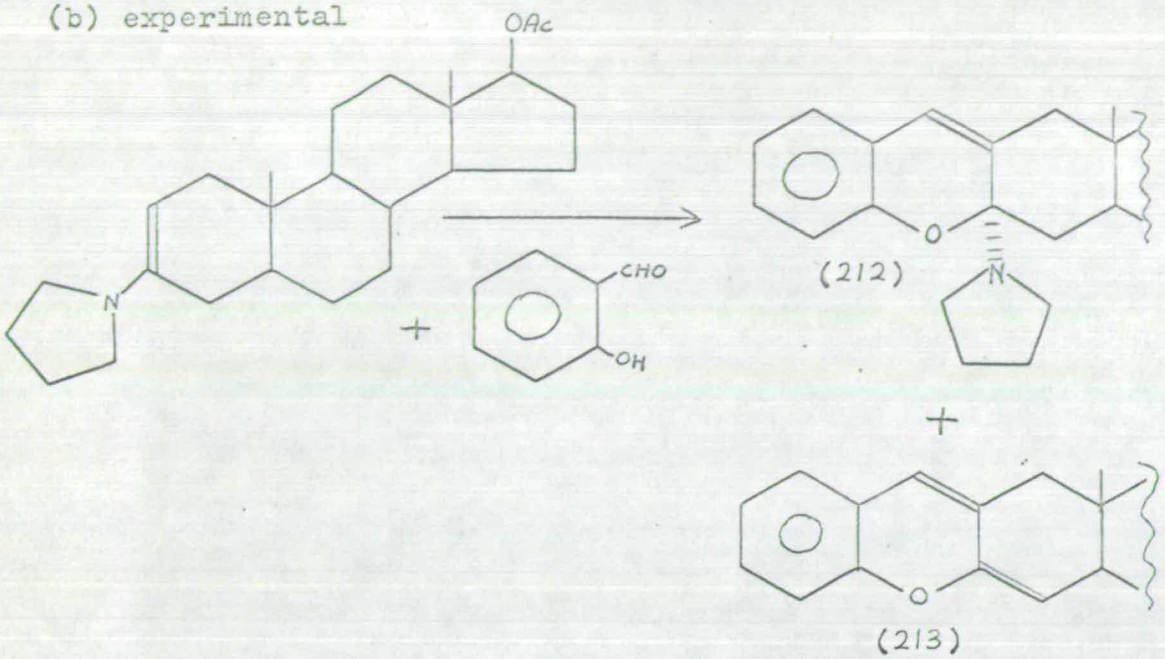
In the steroid field Manhas and McCoy[103] have reported the reaction of salicylaldehyde with the pyrrolidenamine of cholestan-3-one. Reflux in benzene for three days produced an excellent yield of the amine (209a) accompanied by about 25% of the pyrrolidine-eliminated alcohol (210). The latter proved resistant to oxidation to the chromone but readily decomposed on standing on alumina overnight, 24 hours in deuterochloroform or treatment with manganese dioxide in chloroform, to give the diene (211). Under the same conditions the pyrrolidenamine of androstanolone did not react with salicylaldehyde. However on using 3,5-dibromosalicylaldehyde (208b,c) with which the electron withdrawing bromine atoms tend to stabilize the phenoxide ion, reaction proceeded smoothly with the pyrrolidenamines of both cholestanone and androstanolone giving the analogous amines (209b,c).

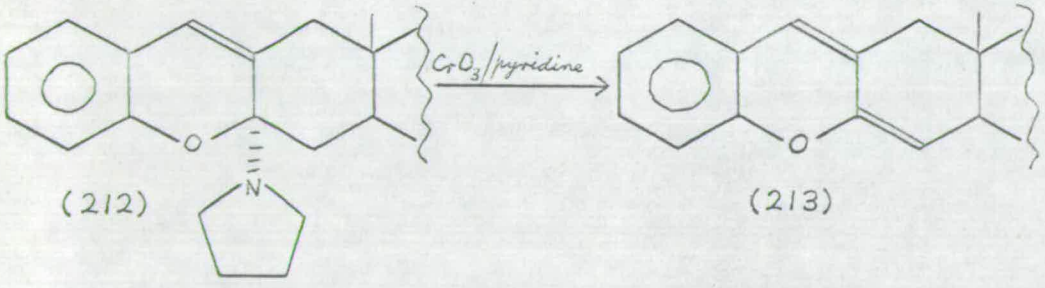
Results

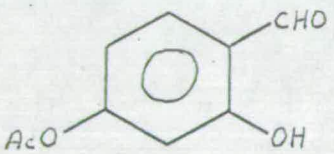
It was initially thought possible that the difference in the products of the cyclohexanone (206) and the steroid (209) was due to dehydration of the steroidal alcohol (type 206) at the reflux

Fig. 2.19 (cont.)

(b) experimental







(214)

temperature used by Manhas and McCoy. Thus the pyrrolidenamine of androstanolone acetate and salicylaldehyde were allowed to react in benzene at room temperature for two days. After removal of solvent three successive recrystallizations from ethanol yielded the amine 17β-acetoxy-3α-pyrrolidinyl-5α-androstano [3,2-b] 2-H-benzopyran (212) analogous to (209). Infra-red, ultra-violet and n.m.r. spectra were consistent with this identification and the identity was confirmed by exact mass measurement. This compound was contaminated by about 22% of the diene 17β-acetoxy-5α-androst-3-eno [3,2-b] 2-H-benzopyran (213) analogous to (211), as determined from integrals of the 4′ protons of the two compounds. No alcohol corresponding to (210) was detected, though this may be due to the method of isolation used here, crystallization versus chromatography for Manhas and McCoy.

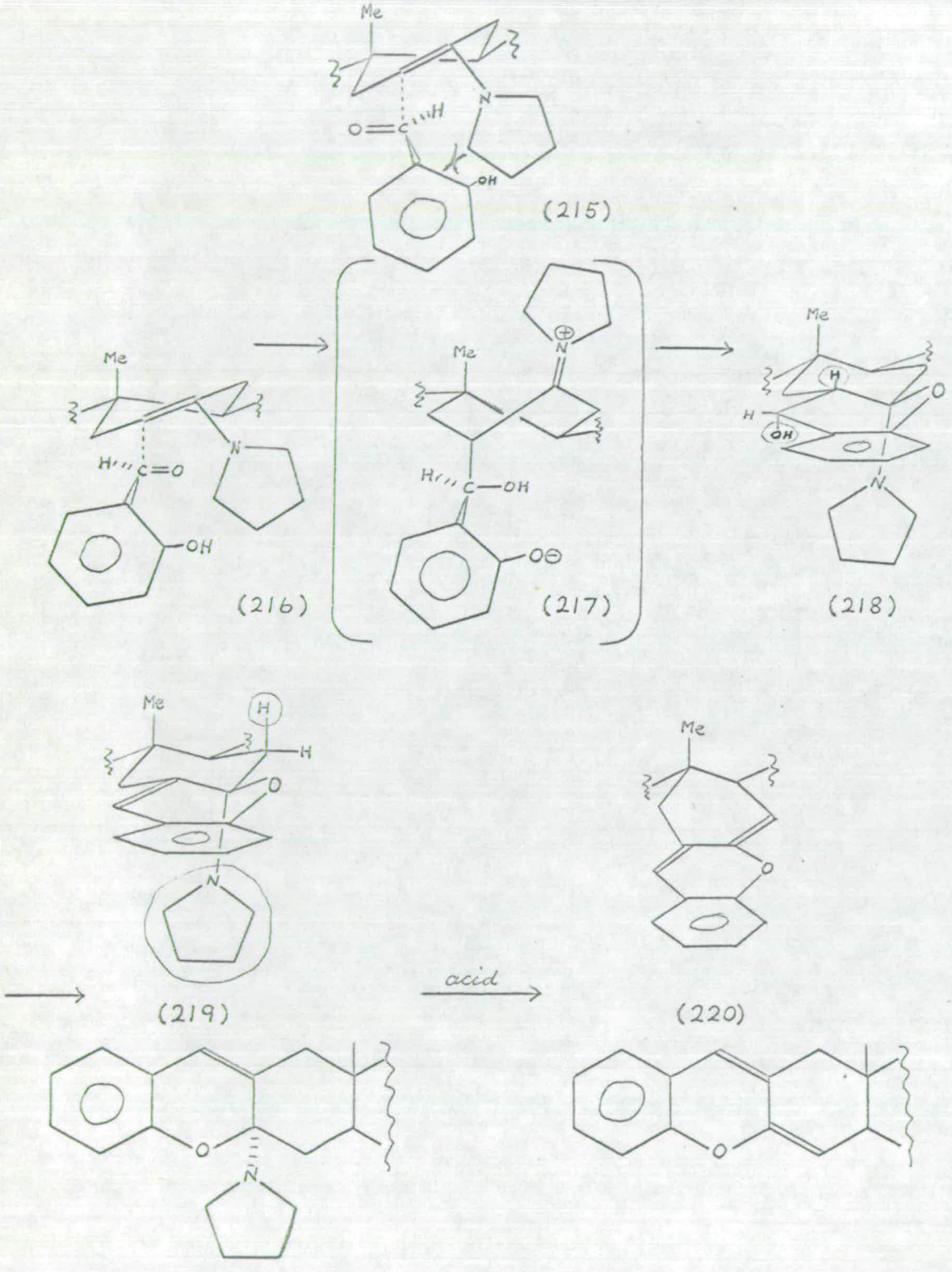
Attempted Sarett oxidation of the amine (212) gave not the expected chromone but the diene (213). The identity of the twice recrystallized compound was established by n.m.r., i.r. and u.v. spectra together with exact mass measurement. An attempt was made to react 4-acetoxy-2-hydroxybenzaldehyde (214) (itself surprisingly not previously described in the literature) with the pyrrolidenamine of androstanolone acetate. However, on work-up thin layer chromatography revealed a mixture of at least eight components, none except androstanolone acetate in any quantity. The mixture was therefore not further investigated.

Discussion

While, despite the temperature difference, the product types were the same as in the earlier steroid work one contrast is apparent. Manhas and McCoy reported the failure of the pyrrolidenamine of androstanolone to react with salicylaldehyde and reaction occurred only with 3,5-dibromosalicylaldehyde. In the present work, however,

Fig. 2.19 (cont.)

(c) proposed mechanism

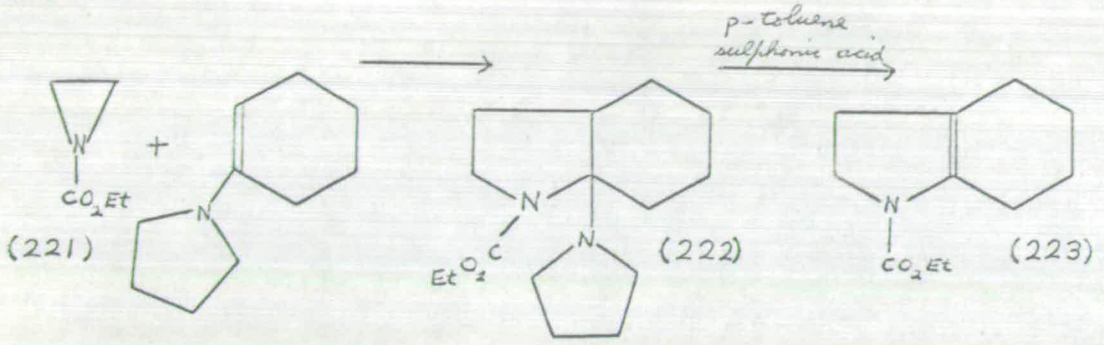


the reaction with salicylaldehyde went smoothly when the acetate of androstanolone was used, thus eliminating any possible involvement of the C-17 alcohol in the alkoxide/phenoxide equilibrium.

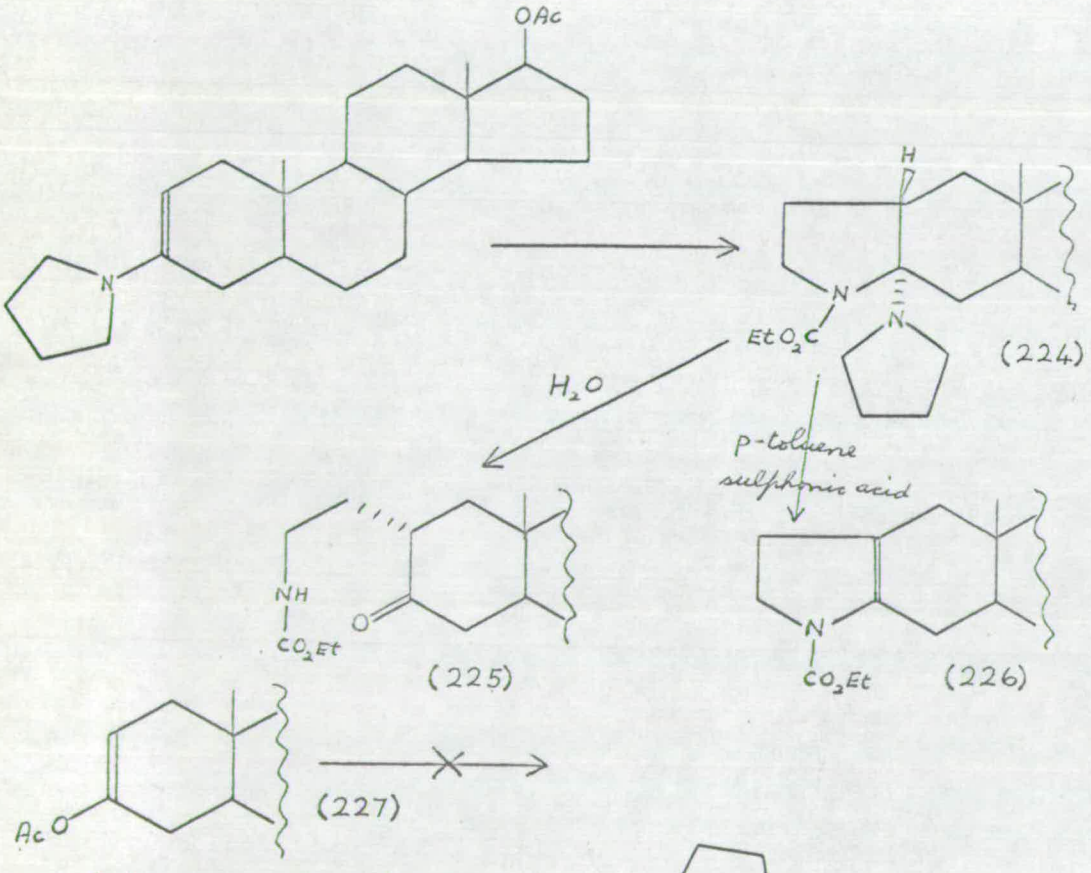
In the transition state of the reaction between enamine and aldehyde the enamine double bond and the carbonyl function must lie approximately parallel to each other in order to allow overlap of the p-orbitals. From examination of models it becomes apparent that the transition state illustrated (216) suffers from much less steric interaction between the incipient substituent and the pyrrolidinyl ring than does the antiparallel alternative (215). In the intermediate (217) the substituent lies axial, while the steroid A-ring is boat-like (section 2.2). If the cyclization step involves bottom-face attack on C-3 a severe steric interaction is to be expected between the pyrrolidinyl ring and the axial C-19 methyl. It is therefore proposed that the ring closure results in the thermodynamically stable isomer (218). In this alcohol (218) the hydroxyl and C-2 proton lie anti-periplanar to each other. Elimination of water to give the amine (219) is therefore likely to be facile[179]. Similarly, the elimination of pyrrolidine to give the diene (220) is to be expected under mild conditions.

Fig. 2.20 Reactions of Carboethoxyaziridine

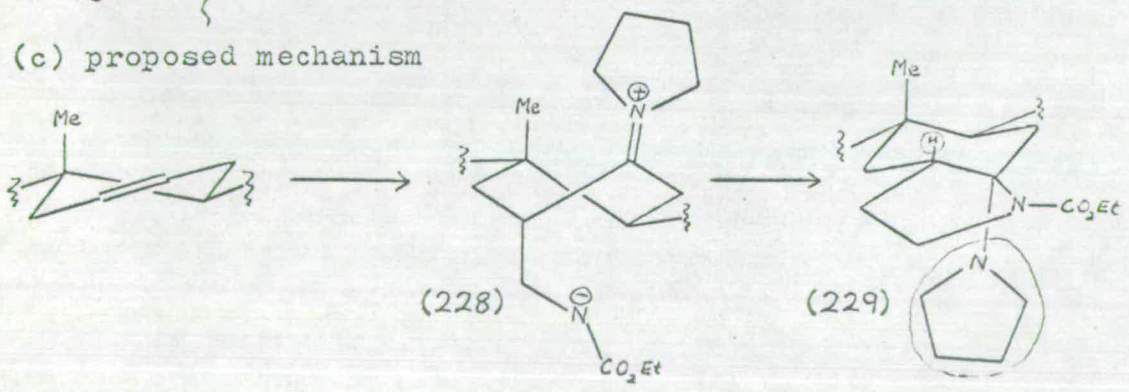
(a) lit.



(b) experimental



(c) proposed mechanism



2.10 REACTION WITH CARBOETHOXYAZIRIDINE

Previously Reported Experiments

The reaction of carboethoxyaziridine (221) with the pyrrolidenamine of cyclohexanone in refluxing p-xylene overnight has been reported to give a 65% yield of the octahydroindole (222)[180]. On treatment with p-toluenesulphonic acid this, in turn, gave the amine-eliminated compound (223)[180].

Results

Reaction of carboethoxyaziridine with the pyrrolidenamine of androstanolone acetate gave 17β-acetoxy-1'-N-carboethoxy-2β-H-3α-pyrrolidinyl-5α-androstano [3,2-b] tetrahydropyrrole (224) in the crude mixture, the presence of which was confirmed by exact mass measurement. Aqueous work-up, followed by alumina chromatography and crystallization gave the monosubstituted steroid 2-(17β-acetoxy-5α-androstan-3-one-2α-yl)-N-carboethoxyethylamine (225). Both the amine proton and the adjacent methylene peaks were visible in the n.m.r. spectrum as well as ethyl resonances. Exact mass measurement confirmed the identification.

An attempt to separate the tetrahydropyrrole (224) from the crude reaction mixture by preparative gas chromatography on an OV-1 column at 300° gave instead the pyrrolidine-eliminated compound (226) which was identified by the close resemblance of the infra-red spectrum to that of a sample made as follows.

17β-acetoxy-1'-N-carboethoxy-5α-androst-2-eno [3,2-b] dihydropyrrole (226) was prepared by the addition, after the mixture had been allowed to reflux overnight as before, of p-toluenesulphonic acid. The solution was refluxed for a further two hours. Ethyl

resonances and that due to CH_2N were discernable in the n.m.r. spectrum of the twice recrystallized compound and a double bond absorption was visible in the infra-red. The identification was confirmed by exact mass measurement. An attempt was made to react the enol acetate, androst-2-en-3, 17β-diol diacetate (227) analogous to the enamine, with carboethoxyaziridine, but thin layer chromatography revealed only recovered starting material.

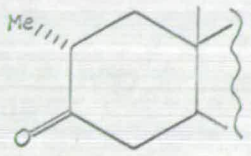
Discussion

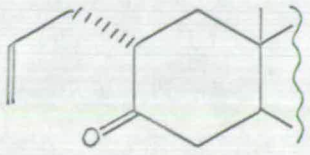
The mechanism proposed involves the familiar alkylation at C-2 to give zwitterion (228). This then collapses to the more thermodynamically stable isomer of tetrahydropyrrole (229), which can readily be induced to eliminate pyrrolidine due to the anti-periplanar arrangement shown (229).

Failure of the enol acetate to react in the stead of the enamine can be seen as a consequence of the much lesser ability of the acetate function to accommodate a positive charge.

Fig. 2.21 Summary of Investigated Reactions

MeI

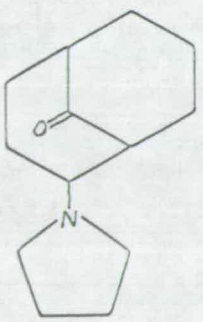


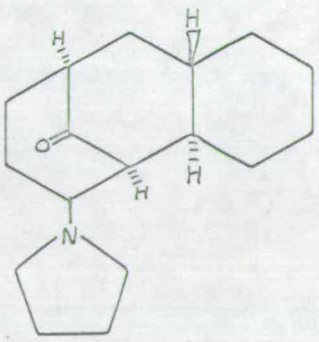


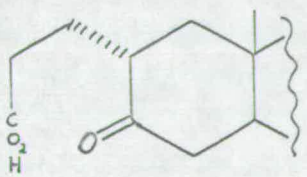
No reaction with 3-keto-5α-steroids

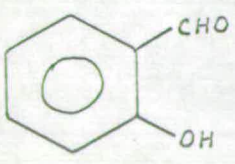
No isolable pdt. with 3-keto-5α-steroids

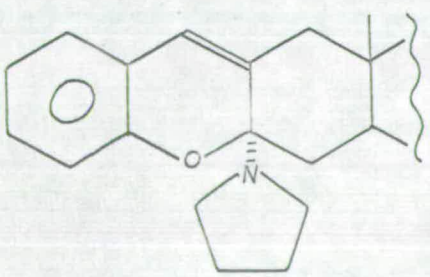
No isolable pdt. with 3-keto-5α-steroids

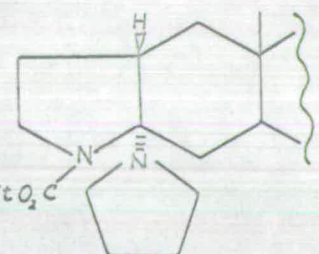












2.11 GENERAL DISCUSSION

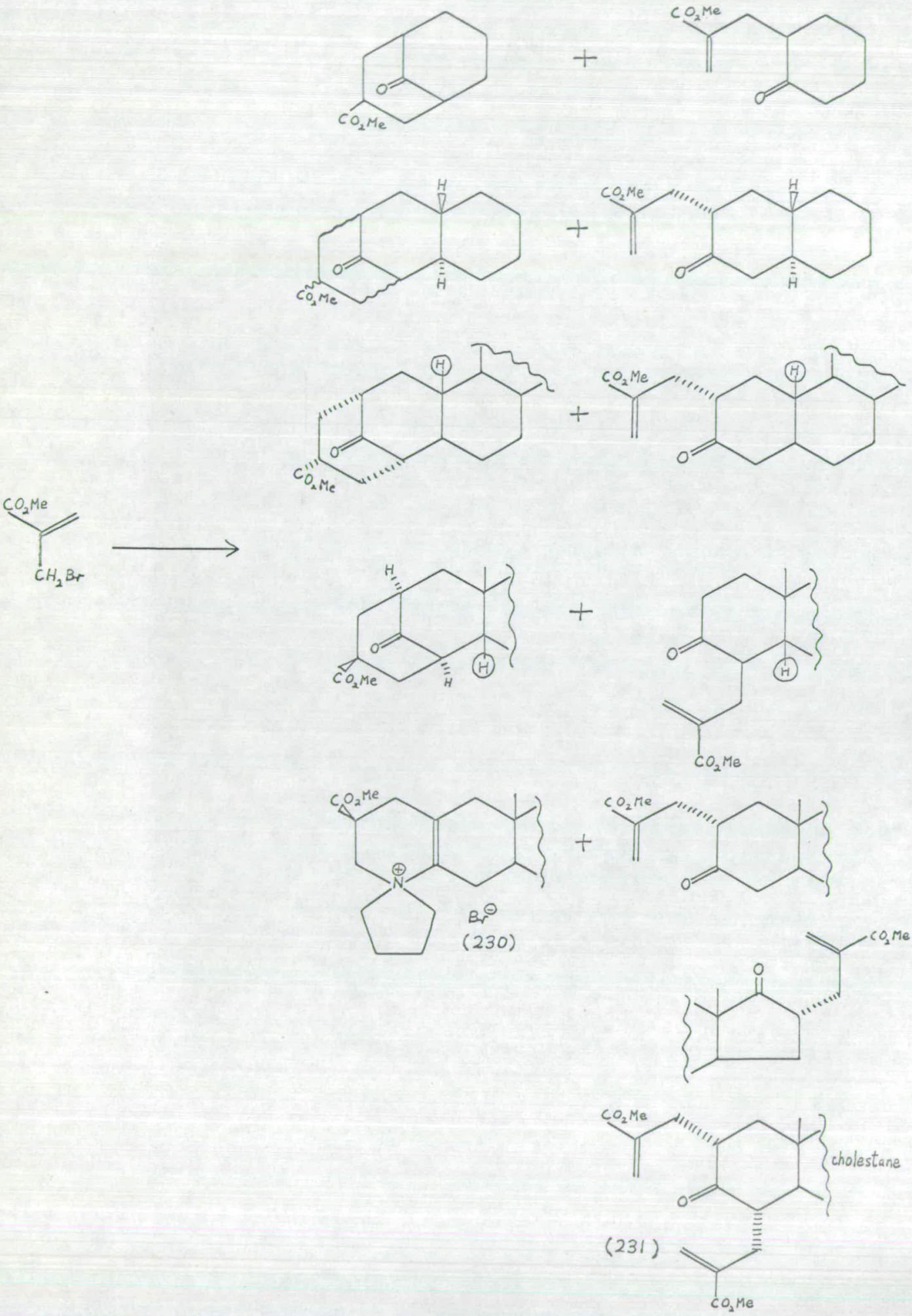
For convenience the reagents and primary products of the investigated reactions are summarized as Fig. 2.21.

The bulk of the work described in preceding sections concerns the reactions of the pyrrolidenamines of 3-keto-5α-steroids. Generally the initial reaction consists of attachment of reagent at the nucleophilic C-2. In only one case, that of acryloyl chloride (section 2.7), is there reason to assert (by analogy to the cyclohexanone) that initial N-alkylation is followed by rearrangement to give the C-substituted compound. It is, of course, possible that similar reactions occur with other of the reagents, for example allyl bromide, but there is no evidence in these cases.

In the steroid, the angular C-19 methyl exerts considerable influence upon the course of reaction. Initially, by inhibiting top face reaction, ring A boat-like forms are produced by attack from below (section 2.2). Thus, the substituent in the final product is attached at 2α. The pyrrolidenamine of the 17-keto-steroid D.H.A. acetate alkylates at 16α, for similar reasons involving the C-18 methyl group. The higher energy boat-like form required in the steroid as compared to the chair-like conformation in the corresponding reactions of cyclohexanone enamines must be considered as an important contribution to the lesser yields with the larger molecule in cases where the analogous product is formed: using ethyl crotonate, no discernable reaction occurred with the steroid.

This is not the only effect of the angular methyl: the steric constraints introduced by it may change the nature of the product (acryloyl chloride; methyl α-(bromomethyl)-acrylate) or by default of the reaction path followed by the cyclohexanone may allow multiple

Fig. 2.21 (cont.)



reactions (ω-nitrostyrene; acrolein), producing intractable mixtures. The three reactions (acryloyl chloride; acrolein; α-(bromomethyl)-acrylate), which with the cyclohexanone produce the bicyclo [3,3,1] nonane system are particularly instructive: in all cases cyclization was inhibited with the C-19 methyl-steroid. The latter two reactions were investigated using the trans-decalone system which has no angular methyl: in both instances bridged ring compounds analogous to those from the cyclohexanone were produced. The reaction of methyl α-(bromomethyl)-acrylate provides further evidence on the critical role of the C-19 methyl since bicyclononanes were produced both when a 19-norsteroid was used and when the A-ring bore a very different steric relationship to the angular methyl in the 5β-steroid. An alternative cyclization path leading to the salts (230) is available to some 19-methyl-5α-steroids where the bicyclononane route is blocked.

There are three general reaction paths which zwitterion (232), formed by the initial reaction at C-2, may follow (Fig. 2.22).

I. A negative ion may be expelled to give an iminium salt. This can be stable as with allyl bromide (section 2.3) or may react further. For example, in the reaction of methyl α-(bromomethyl)-acrylate with the pyrrolidenamine of androstanolone acetate (section 2.5(c)) the salt (230) is formed.

II. The negative centre may react with the electrophilic C-3 in a cycloaddition as with salicylaldehyde (section 2.9) and carboethoxyaziridine (section 2.10).

III. A further possibility is that intra, or possibly intermolecular hydrogen transfer might occur producing a new enamine capable of further reaction. While this reaction scheme must be invoked to account for a number

Fig. 2.22 Further Reactions of the Initial Zwitterion

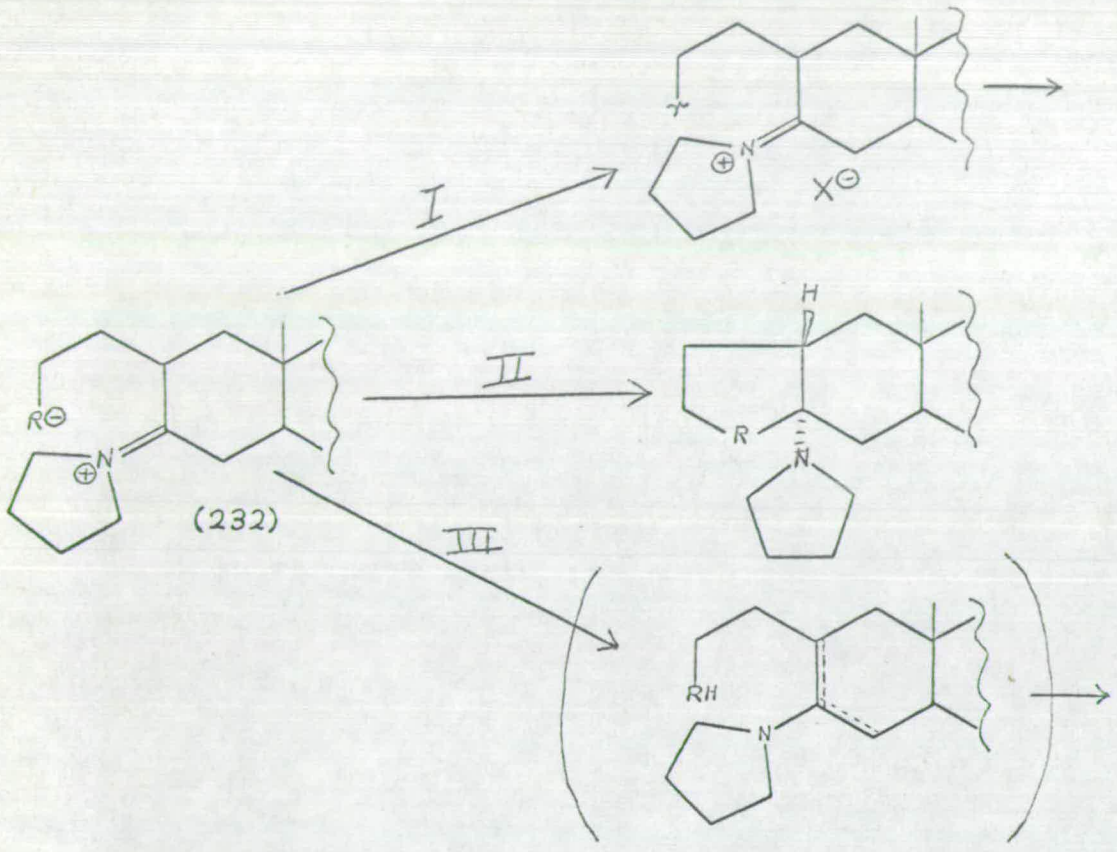
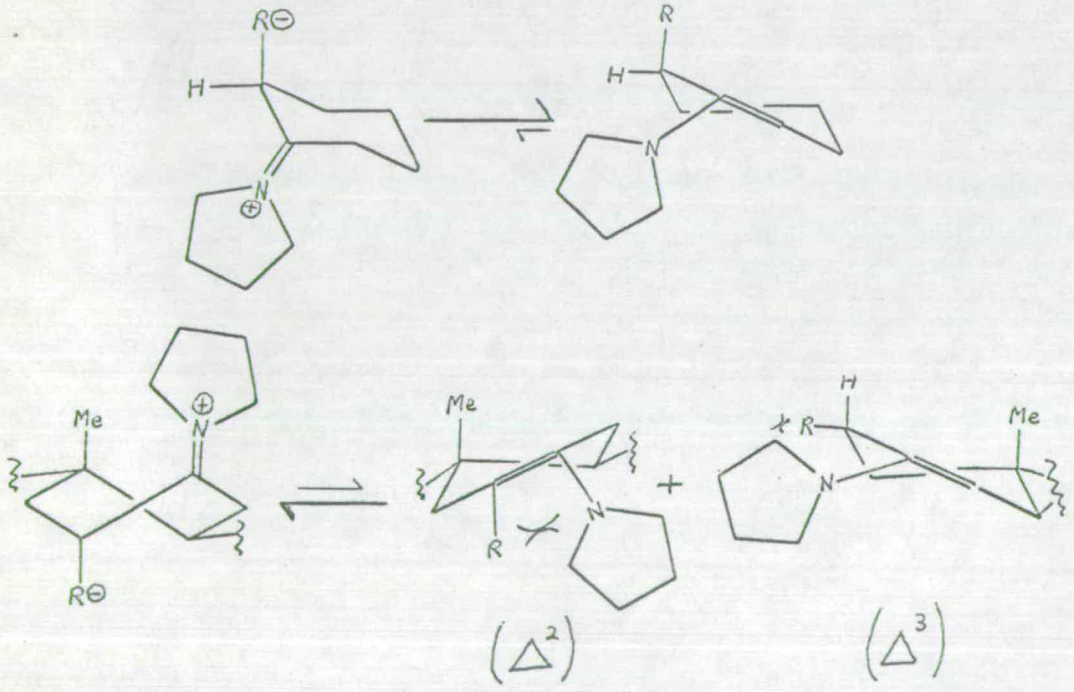


Fig. 2.23 Enamine Regeneration



of the reactions of cyclohexanone enamines, it seems this does not generally happen in the 5α-steroid with an angular C-19 methyl.

Notably in the three examples investigated (ethyl crotonate; ω-nitrostyrene; acryloyl chloride) in which the cyclohexanone reaction requires such an enamine regeneration, the product of the steroid reaction in no case bears evidence of the completion of this step. It is only with methyl α-(bromomethyl)-acrylate and in the presence of added base (triethylamine) that the structure of any of the products indicates the intermediacy of a regenerated enamine, Δ^3 for the disubstituted cholestanone (231) and the Δ^2-isomer for the salts (230).

It has previously been proposed that intramolecular hydrogen transfer from C-4 may not be favoured in the steroid because of the geometry of the intermediate (section 2.6). Also it was argued that in contrast to the cyclohexanone where the more stable trisubstituted enamine is produced, in the steroid the Δ^3-enamine is relatively more strained as compared to the Δ^2-isomer (section 2.5(c)). Thus, regardless of which enamine is produced from the iminium compound it is more strained than the corresponding cyclohexanone. If this were the only factor involved it could be immediately concluded that the reaction of iminium compound to enamine is less favourable in the steroid. However, the boat-like steroidal iminium compound is also less stable than the chair-like cyclohexanone. Nonetheless, examination of models suggests that it is more difficult to produce a new enamine from an iminium compound for a steroid than for the cyclohexanone (Fig. 2.23).

In practice little or no steroidal enamine must be regenerated in the absence of additional base (or if formed it must be practically

inert to further reaction). The former possibility is supported by the readiness of the cyclization reactions of salicylaldehyde and carboethoxyaziridine which proceed via the iminium ion.

3. EXPERIMENTAL SECTION

3.1 General Procedures

The following were generally adhered to but were modified where necessary, as noted in the text.

3.1(a)

Melting Points were determined on a Kofler hot block and are corrected.

Infra-red Spectra were recorded for carbon disulphide solution, using 0.5mm cells, on a Unicam SP 200 spectrometer. All values of infra-red maxima (ν max.) are quoted in cm^{-1}.

Ultra-violet Spectra were recorded on a Unicam SP 800 spectrometer. All values of ultra-violet maxima (λ max.) are quoted in nanometres.

N.m.r. Spectra were recorded in deuterochloroform solution, using tetramethylsilane as internal standard, on a Perkin Elmer R 10 spectrometer or a Nuclear Magnetic Resonance Ltd EM-360 (both 60 MHz) or a Varian HA 100 (100 MHz) spectrometer. Resonances are quoted as δ values.

Mass Spectra and Exact Mass Determinations were carried out on an AEI MS 902 instrument operated by Mr D. Thomas.

Analyses were determined on a Perkin Elmer model 240 instrument.

3.1(b) /

3.1(b)

Thin Layer Chromatography was performed on Merck silica gel GF_{254}. The eluting system was benzene/ethanol (9:1 by volume). The plates were developed by spraying with ethanolic sulphuric acid (5%) and subsequent heating on a hot plate.

Silver (I) impregnated plates[137] were prepared by spraying normal plates with a saturated ethanolic solution of silver nitrate.

Preparative Column Chromatography was performed on Spence type H alumina of Brockman activity 2.

Drying of solutions was carried out with anhydrous magnesium sulphate.

Compounds not previously described in the literature are underlined on first mention.

3.2 Starting Materials

3.2(a) Steroidal Starting Materials

Cholestan-3β-ol[114]

Cholesterol (120g) in ethyl acetate, was reduced by catalytic hydrogenation over 10% palladium on charcoal catalyst, at 30° and one atmosphere pressure. Perchloric acid (8 drops) was added as promoter. The acid was neutralised with solid sodium hydroxide and the catalyst was filtered off, using a celite pad. The volume of solvent was reduced and cooling afforded crystalline cholestan-3β-ol (94.1g; 78%); m.p. 141-142° (lit.[114] 139-141°).

Cholestan-3-one

Cholestan-3β-ol (30g) in acetone (2l) was oxidised with 8N chromic acid (Jones reagent[116]) (60ml). The reaction was allowed to proceed for 4 minutes, when excess reagent was decomposed with methanol (200ml). Water (200ml) was added, the acetone was removed under reduced pressure and the steroid was extracted into ether. The ethereal solution was washed with dilute hydrochloric acid, then water until the washings were neutral and finally with saturated sodium chloride solution. The ether layer was dried and the solvent was removed to give cholestan-3-one, which was recrystallized from acetone, to give needles (28g; 94%); m.p. 126-128° (lit.[115] 127-128°).

5α-Androstan-17β-ol-3-one (Androstanolone)[117]

Testosterone (10g) in dioxan (100ml) and ether (100ml) was added over 10 minutes to a solution of lithium (1.2g) in liquid ammonia (1.2 l). The solution was stirred for 30 minutes, during which the initial blue colour disappeared. Ammonium chloride (8g) was added and then water (200ml). When the remaining ammonia had evaporated,

the steroid was extracted into chloroform. This solution was washed with dilute hydrochloric acid and water before being dried and the solvent removed. The crude product was recrystallized from ethyl acetate/petrol to give 5α-androstan-17β-ol-3-one (8.7g; 87%); m.p. 182-184° (lit.[117] 184-185°); ν max. 1710cm^{-1} (carbonyl).

5α-Androstan-17β-ol-3-one Acetate (Androstanolone Acetate)

Androstanolone (10g) was dissolved in pyridine (50ml) and acetic anhydride (10ml) added. The solution was allowed to stand overnight. Water (10ml) was then added to destroy excess acetic anhydride and the mixture allowed to stand for a further 30 minutes. The steroid was then extracted into chloroform (300ml), the extract was washed with dilute hydrochloric acid (300ml x 3) and then water until neutral. The solution was dried and the solvent was removed to give a mass of microcrystalline androstanolone acetate, homogeneous to t.l.c. (10.1g; 89%); m.p. 160-163° (lit.[118] 157°); n.m.r. (60) δ 2.00 (acetate); ν max. 1731cm^{-1} (acetate carbonyl).

Testosterone Acetate

A similar procedure to that for androstanolone acetate (above) was carried out (11.3g; 98%); m.p. 145-147° (lit.[119] 140-141°); n.m.r. (60) δ2.01 (acetate); ν max. 1733cm^{-1} (acetate carbonyl).

Androst-5(6)-en-3β-ol-17-one Acetate (D.H.A. Acetate)

A similar procedure to that for androstanolone acetate was followed (10.8g; 94%); m.p. 168-169.5° (lit.[119] 171-172°); n.m.r. (60) δ 2.01 (acetate).

5α-Androstan-17β-ol-3-one 4-methyl-pentanoate

4-methyl pentanoyl chloride (1.5ml) was added to a solution of 5α-androstan-17β-ol-3-one (1.5g) in chloroform (15ml), containing

one potassium hydroxide pellet. After 30 minutes another potassium hydroxide pellet was added and the mixture was allowed to stand overnight. Chloroform (150ml) was added and the solution was washed with water containing a little pyridine (150ml x 3) and then with dilute hydrochloric acid (150ml x 2). The crude material was chromatographed to yield the ester as a white solid (0.98g; 49%); m.p. 173-5°; m/e 388.297 076 ($C_{25}H_{40}O_3$ = 388.297 728); t.l.c. homogeneous, R_f = 0.74; ν max. 1730 (ester carbonyl), 1712 (C-3 carbonyl), 1180cm^{-1}.

5β-Androstan-17β-ol-3-one Acetate[91]

Crude pyrrolidenamine from testosterone acetate (10g) was dissolved in the minimum (ca. 10ml) of glacial acetic acid (previously rigorously dried by the addition of 2% of acetic anhydride). Perchloric acid (72% aq.; 2.2ml = 0.8 equivalents) was added and the perchlorate was precipitated by the addition of anhydrous ether (250ml). The mixture was filtered with an oven-dry sintered glass funnel and washed with more ether to give the perchlorate as a white crystalline solid (5.31g; 36% from testosterone acetate); m.p. (250° softens) 254-261° dec. (lit[91] 254-261°).

(Excess saturated sodium bicarbonate solution was added to the mother liquor and the mixture was allowed to hydrolyse for some hours. It was then extracted with ether and the ether solution was washed with more bicarbonate, then with water. On drying and removal of the solvent unreacted testosterone acetate was recovered (5.99g; 94% of the unaccounted steroid).)

A solution of commercial Hantzsch ester in acetone was filtered to remove an insoluble impurity. Solvent was then removed and the ester was dessicated. Steroidal perchlorate (5.31g) and Hantzsch ester (6.25g = 1.5 equivalents) in calcium hydride dried acetonitrile (130ml) were heated to reflux, when the solids dissolved to give a clear orange solution. Reflux under dry nitrogen was maintained for 21 hours, when

a small sample was removed. This sample was hydrolysed by the addition of water and t.l.c. revealed largely a single spot of the product (R_f = 0.52), with no sign of testosterone acetate (R_f = 0.47). The reaction was therefore terminated and the acetonitrile was cautiously removed by rotary evaporator at a bath temperature less than 70°. The solid material was extracted with portions (100ml) of anhydrous ether to remove ether-soluble by-products. The material was thoroughly triturated with the first portion and the whole was then carefully refluxed (under nitrogen). The solid was then extracted with three more portions at room temperature and the residual ether was cautiously removed. The solid was then hydrolysed by solution in acetone (25ml) to which water (5ml) was added. This gave a clear brown solution on warming and was left at room temperature for a further 30 minutes. Ether (250ml) and bicarbonate (100ml) were then added and the precipitate which appeared was filtered off and discarded. The ether solution was washed with bicarbonate, dilute hydrochloric acid (x 5) and water (x 3). Drying, filtering and removal of solvent gave a low-melting yellow solid, which proved to be a mixture of steroid and substituted pyridine by-product.

Chromatography on alumina with ether gave crude 5β-androstan-17β-ol-3-one acetate as a white solid (1.55g; 42% from perchlorate); m.p. 101-135°. T.l.c. with the usual 9:1 benzene/ethanol solvent system versus the 5α-isomer revealed no polarity difference but the two materials charred yellow and brown respectively. With the solvent system 15% ethyl acetate in hexane, however, the product could be seen to consist of the 5β-compound (R_f = 0.17, yellow) contaminated with the 5α-isomer (R_f = 0.21, brown). Crude material (1.85g) was recrystallized (x 3) from hexane (typical recovery 80%) to give pure 5β-androstan-17β-ol-3-one acetate, homogeneous to t.l.c. (0.98g;

53% overall recovery); m.p. 145-150° (lit.[192] 140-145°), cf. 160-163° for the 5α-isomer; mixed m.p. with 5α-isomer depressed (90-145°); n.m.r. (60) δ 4.60 (C-17 proton); 2.04 (acetate); 1.03 (C-19 methyl); 0.82 (C-18 methyl), indistinguishable from the 5α-isomer; $\nu_{max.}$ 1741 (acetate carbonyl); 1719 (C-3 carbonyl); 1242cm^{-1}, indistinguishable from the 5α-isomer.

Oestrone Methyl Ether[121]

Oestrone (3g) was dissolved in 5% methanolic potassium hydroxide solution (60ml) and was stirred at 35° for one hour, over which dimethyl sulphate (6ml) was added. The solution was maintained at 35° for one hour more, during which a white precipitate formed. The steroid was extracted into chloroform (300ml) and was washed with dilute sodium hydroxide solution (300ml x 3), then with dilute hydrochloric acid (300ml x 2) and finally with water until neutral. The solution was dried and the solvent was removed to give pale brown crystals of oestrone methyl ether (2.89g; 91%); m.p. 159-165° (lit.[121] 163-167°); n.m.r. (60) δ 3.77 (C-3 methoxy).

3,17β-Estradiol 3-Methyl Ether[121]

Oestrone methyl ether (2.89g) in anhydrous ether (150ml) and lithium aluminium hydride (0.57g) were stirred for four hours at room temperature, then warmed to 30° for 30 minutes. Excess lithium aluminium hydride was decomposed by carefully and slowly adding water (10ml). Then enough 10% sulphuric acid was added to give two clear layers. Water (75ml) was added and the ether layer

separated. This was washed twice with saturated sodium bicarbonate solution, then with water until the washings were neutral. The solution was dried and the solvent was removed to give a semi-solid. This was recrystallized from ethanol to give white crystals of 3,17β-estradiol 3-methyl ether (2.21g; 76%); m.p. 117-119° (lit.[121] 120.5-121.5°); no carbonyl in i.r.

1,4-Dihydro-3,17β-Estradiol 3-Methyl Ether[121]

3,17β-estradiol 3-methyl ether (2.21g), liquid ammonia (224ml), lithium metal (2.24g) and anhydrous ether (176ml) were stirred together until the solution was homogeneous. Absolute ethanol (25.6ml) was then added dropwise over 20 minutes. The ammonia was allowed to evaporate, water (200ml) was added and the ether layer augmented to 200ml. The ether layer was separated and washed with portions (100ml) of saturated sodium bicarbonate solution, followed by saturated sodium chloride solution. The ether layer was then dried and the solvent was removed to yield a semi-solid, which was recrystallized from ethanol/petrol (60/80°) 1:4 to give 1,4-dihydro-3,17β-estradiol 3-methyl ether (1.52g; 68%); m.p. 118-119° (lit.[121] 118-119.5°); ν max. 1663, 1689cm^{-1} (d.b.).

19-Nortestosterone[121]

To a solution of 1,4-dihydro-3,17β-estradiol 3-methyl ether (1.5g) in methanol (75ml) maintained at 60° was added 3N aqueous hydrochloric acid (45ml) and the clear solution was kept at this temperature for 15 minutes. It was then cooled and water (100ml) and ether (200ml) were added. The ether layer was separated and washed with saturated sodium bicarbonate solution, then saturated sodium chloride solution, back extracting each time with ether (50ml).

The solution was dried and the solvent was removed to give a semi-solid. This was recrystallized from ether, with some difficulty to give crystals of 19-nortestosterone (0.85g; 57%); m.p. 120-123° (lit.[121] 123.8-124.6°); n.m.r. (60) δ 5.81 (olefin); ν max. 1674cm^{-1} (conj. carbonyl).

5α,10β-Estran-17β-ol-3-one (19-Norandrostanolone)

This was prepared by lithium/liquid ammonia reduction of 19-nortestosterone using the same method as was used earlier to prepare androstanolone (q.v.) from testosterone. The product was a semi-solid, which could not be induced to crystallize. It was therefore chromatographed, to give, on elution with ether, white crystals of 19-norandrostanolone (0.76g from 0.85g; 90%); m.p. 108-112° (lit.[122] 111-112°); ν max. 1710cm^{-1} (carbonyl).

19-Norandrostanolone Acetate

This was prepared in the same way as was androstanolone acetate (above) (0.72g from 0.76g; 95%); m.p. 133-135° (lit.[122] 132-134°); n.m.r. (60) δ 4.57 (C-17 proton); 2.02 (acetate); 0.79 (C-18 methyl).

Androst-2-en-3,17β-diol Diacetate

Androstanolone (1.60g) in carbon tetrachloride (25ml) with acetic anhydride (3ml) and 72% perchloric acid (5 drops) was allowed to react for 75 minutes. Chloroform (125ml) was added and the solution was washed with water (100ml x 2), dried and the solvent was removed to give slightly yellow crystals of androst-2-en-3,17β-diol diacetate (2.02g; 98%); m.p. 170-173° (lit.[123] 172-173°); n.m.r. (60) δ 5.27 (Δ^2-olefin); 5.00 very small (Δ^3-olefin); 2.10 (C-3 acetate); 2.03 (C-17 acetate); 0.84 (C-19 methyl); 0.80 (C-18 methyl).

3.2(b) Non-Steroid Starting Materials

1-N-Pyrrolidino-cyclohex-1-ene[124]

Cyclohexanone (21ml) in benzene (300ml) with pyrrolidine (21ml) was refluxed for 2 hours using a Dean and Stark water trap. Solvent was then removed to yield a brown oil. This was distilled under reduced pressure (b.p. 70-76°/1mm; lit.[124] b.p. 110-112°/12mm) to give 1-N-pyrrolidino-cyclohex-1-ene (20.0g; 51%); ν max. 1641cm^{-1} (d.b.).

Decal-1(9)-en-2-one[125]

1-N-pyrrolidino-cyclohex-1-ene (20g) was dissolved in anhydrous dioxan (200ml) and methyl vinyl ketone (10.7ml) in anhydrous dioxan (50ml) added. The mixture was left at room temperature for 4 hours. Using a rotary pump, the dioxan was removed at less than 50°. To the residue, sodium acetate (30g), water (30ml), glacial acetic acid (20ml) and methanol (150ml) were added and the mixture was refluxed for four hours. It was then extracted into ether, washed with saturated sodium bicarbonate solution and then with water to give an oil which was distilled under reduced pressure (b.p. 98-102°/0.5mm; lit.[119] b.p. 140-141°/14mm) affording decal-1(9)-en-2-one as a brown oil (9.34g; 47%); n.m.r. (60) δ 5.80 (olefin); ν max. 1675cm^{-1} (conj. carbonyl).

Trans-decal-2-one[127]

(a) Decal-1(9)-en-2-one (9.38g) in ether (85ml) was added to liquid ammonia (350ml). To this was added lithium metal (0.5g) in small pieces. The solution was stirred for 75 minutes; then ammonium chloride (14g) was added and the ammonia was allowed to evaporate

overnight. The solid residue was mixed with water (100ml) and extracted with ether (100ml x 2). The ether solution was then washed with 3N hydrochloric acid (100ml x 3), followed by water (100ml x 2) and finally with saturated sodium chloride (100ml). It was then dried, filtered and the solvent was evaporated to yield an oil. This was distilled under reduced pressure (b.p. 58-63°/0.5mm; lit.[127] b.p. 127-128°/28mm) to yield trans-decal-2-one as a brown oil (4.43g; 47%). This was chromatographed on alumina, eluting with ether to give the product as a clear colourless liquid homogeneous to t.l.c. R_f = 0.64; $\nu_{max.}$ 1710cm^{-1} (carbonyl).

Gas chromatography on 5% N.P.G.S. at 150° demonstrated the identity of the product with one of the components of commercial cis/trans decal-2-one.

(b) A small amount of trans-decal-2-one was also prepared from the commercial mixture by preparative gas chromatography on 25% polyphenyl ether at 200°. The identity of the product was confirmed by gas chromatography as above.

2-N-Pyrrolidino-trans-decal-2-ene[35]

Trans-decal-2-one (0.76g) was refluxed with pyrrolidine (2.5ml) in benzene (12ml) for 90 minutes, with the use of a Dean and Stark water trap. The solvent was removed and the crude enamine was used without further purification.

4-Methyl-pentanoyl Chloride

A mixture of 4-methyl pentanoic acid (4.3ml) and thionyl chloride (3.6ml) was refluxed for two hours. The mixture was then fractionally distilled and the fraction 137-146° (lit.[119] b.p. 144-145°) collected.

$\nu_{max.}$ (liq.) 1800cm^{-1} broad.

Diethyl-bis (hydroxymethyl) Malonate[128]

To 40% w/v formaldehyde solution (320ml) and powdered potassium bicarbonate (17.1g) was added diethyl malonate (320ml) over 35 minutes. The solution was maintained at 25-30°. Stirring was continued for a further hour. Saturated ammonium sulphate solution (640ml) was then added and the mixture was extracted with ether (640ml). The solution was dried, filtered and the solvent removed to yield a glycerol-like oil. On adding isopropyl ether (1 litre) and seeding, a thick crop of white crystals formed, which after chilling the solution, were filtered off. The material was then recrystallized from isopropyl ether yielding diethyl-bis (hydroxymethyl) malonate (257g; 58%); m.p. 49-50° (lit.[128] 52°); ν max. 3570 (hydroxy), 1715cm^{-1} (carbonyl).

$\beta\beta'$-dibromoisobutyric Acid[129]

Diethyl-bis (hydroxymethyl) malonate (257g) was added to concentrated hydrobromic acid (1.7 litres). Liquid (600ml) was slowly distilled off over 2 hours and the remainder was refluxed for 6 hours. The solution was chilled, the precipitated solid was filtered off and was washed with water. The distillation and following procedures were repeated on the remaining mother liquor and the two crops of solid combined. The product, which was not further purified, was dried between filter papers and then dessicated (146g; 51%); ν max. 3000cm^{-1} broad (acid).

Methyl $\beta\beta'$-dibromoisobutyrate[130]

A solution of $\beta\beta'$-dibromoisobutyric acid (146g), methanol (72ml) and concentrated sulphuric acid (2.9ml) in 1,2-dichloroethane (180ml) was refluxed for 19 hours. The solution was then washed

successively with water, saturated sodium bicarbonate and saturated sodium chloride, then dried, filtered and the solvent was removed. The resulting oil was distilled at reduced pressure (60-70°/0.4-1.0mm; lit. b.p.[130] 60-62°/0.4mm) (110g; 71%); ν max. ($CHCl_3$) 1740cm^{-1} (carbonyl) (lit.[130] 1740cm^{-1}).

Acryoyl Chloride[119]

Acrylic acid (15ml) and thionyl chloride (14.3ml) were refluxed together for 4 hours. The product was then distilled b.p. 60-65° (lit. b.p.[119] 75°); (8.17g; 45%); ν max. 1752cm^{-1} (acid chloride).

Carboethoxyaziridine[131]

To a solution of ethylene imine (4.6g) and triethylamine (14.3ml) in benzene (40ml) a solution of ethyl chloroformate (10.8g) in benzene (10ml) was slowly added over one hour. The temperature was maintained at 0° throughout. The precipitate of triethylamine hydrochloride was filtered off and the solvent was removed. The oil was distilled under reduced pressure from a water pump b.p. 78-83°/30mm (lit. b.p.[131] 60-63°/21mm); n.m.r. (60) δ 4.15 quartet $\underline{2H}$ (CH_2 of Et); 2.18 $\underline{4H}$ (ring CH_2); 4.27 triplet $\underline{3H}$ (CH_3 of Et); ν max. (liq.) 1720cm^{-1} broad (carbonyl).

Diazomethane (ether/ethanol solution)[132]

To a solution of potassium hydroxide (1.7g) in water (2.7ml) and ethanol (8.3ml) maintained at 65° in a distillation apparatus was added over 25 minutes a solution of p-toluenesulphonyl-methylnitrosamide ("Diazald") (7.13g) in ether (43.3ml), then more ether (6.3ml) was added. The liquid which distilled was collected in a chilled

receiver. The solution was redistilled and the early portion, rich in diazomethane, was collected and used immediately.

Silver (I) Oxide[133]

A solution of silver nitrate (1g) in water (10ml) was heated to 85° and an equally hot solution of sodium hydroxide (0.23g) in water (10ml) was added. The precipitate of silver (I) oxide was thoroughly washed with hot water and kept wet until use.

3.3 STUDIED REACTIONS

3.3(a) Steroidal Enamines

3.3(a)(i) Preparation

Method of Heyl and Herr[35]

Pyrrolidenamines of the following steroids were prepared:

(A) 5α-androstan-17β-ol-3-one (androstanolone)

(B) 5α-androstanolone acetate [preferred method]

(C) 5α-androstan-17α-methyl-17-ol-3-one
(17α-methyl androstanolone)

(D) 5α,10β-estran-17β-ol-3-one acetate
(19-norandrostanolone acetate)

(E) androstanolone 4-methylpentanoate

(F) cholestan-3-one

(G) testosterone acetate

(H) 5α-pregnan-3,20-dione (under these conditions only the 3-mono-enamine was produced; see n.m.r.)

(I) 5β-androstanolone acetate

The steroid ketone (1.66g) and pyrrolidine (3ml) in benzene (25ml) were refluxed for one hour, or until reaction had ceased, using a Dean and Stark water trap with a small (1 ml) side-arm. Solvent was rapidly removed under reduced pressure and the crude enamine used as soon as possible after preparation, without further purification. The degree of conversion as calculated from the n.m.r. integral of the double bond proton versus the C-17 proton (or other convenient resonance) was typically 95%.

An analytical sample of the pyrrolidenamine of 5α-androstanolone acetate was also prepared. The crude enamine (95% pure; m.p.68-108° dec.)

was recrystallized successively from the following thoroughly dried solvents: acetone; petrol (60/80°); methanol plus a little acetone and finally methanol to yield lustrous white plates of 3-pyrrolidinyl-5α-androst-2-en-17β-ol acetate; m.p. 81-93° dec. (lit.[64] 100-105°);

m/e 385.296 750 ($C_{25}H_{39}NO_2$ = 385.298 063);

(Found: C, 78.5; H, 10.5; N, 3.85. $C_{25}H_{39}NO_2$ requires C, 77.9; H, 10.1; N, 3.64%);

n.m.r. see below;

$\nu_{max.}$ 1643cm^{-1} (d.b.).

Selected n.m.r. Spectra (60MHz) of Steroidal Pyrrolidenamines (δ-values)

Parent Ketone	5α-cholestan-3-one	5α-pregnan-3,20-dione	5α-androstanolone	5α-androstanolone acetate	5β-androstanolone acetate
Δ^2 olefinic proton	4.12 (rounded)	4.13 (triplet-like)	4.13 (triplet-like)	4.13 (rounded)	4.12 (possible minute resonance)
Δ^3 olefinic proton (minute for 5α-series)	3.83	3.81	3.80 (merges into C-17)	3.80	3.84 (narrow)
Ratio of integrals Δ^2: Δ^3	83:17	85:15 (total 1H)	84:16	88:12	5:95
C-17 proton	-	-	3.57	4.57	4.57
α-pyrrolide	2.96	2.98 (4H)	2.95	2.98	3.00
β-pyrrolide	1.81	1.83	1.82	1.82	1.83
C-18 methyl	0.81	0.77	0.78	(0.78)	0.78
C-19 methyl	0.77	0.62	0.73	(0.78)	0.94
Other resonances	0.91 ($CHMe_2$); 0.67 (C-21 Me)	2.11 (acetyl)(3H)	-	2.02 (acetate)	2.02 (acetate); 1.29 (accidental degeneracy)

Method of Heyl and Herr with Acid Catalyst[35]

Pyrrolidenamine of D.H.A. acetate (preferred method)

The procedure above was employed with the modification of the addition of a catalytic amount of p-toluene sulphonic acid (50mg) to the reaction mixture, which was refluxed for three days. Solvent was then removed to yield crude 3β-acetoxy-17-pyrrolidinyl-androst-5(6),16-diene.

m/e 383.281 869 ($C_{25}H_{37}NO_2$ = 383.282 414);

n.m.r. (60) δ0.99 (C-18 methyl) /C-18 methyl of D.H.A. acetate is at δ0.87/;

integral of enamine C-18 methyl to ketone C-18 methyl is 30:19, corresponding to approx. 60% enamine.

Precipitation Method[15]

Pyrrolidenamine of androstanolone acetate (non-preferred method)

To a hot saturated solution of androstanolone acetate (0.2g) in dry acetone, pyrrolidine (0.1 ml) was added, the solution was chilled and the precipitate was filtered off (0.14g; 60%). The purity of the product as calculated from the n.m.r. integral of the double bond proton versus the C-17 proton was 83%. The method of Heyl and Herr was therefore preferred.

The same method was attempted with testosterone acetate; but although a precipitate formed n.m.r. showed no enamine content.

Titanium Tetrachloride Method[16]

Pyrrolidenamine of D.H.A. acetate (non-preferred method)

and

Dimethylamine enamine of androstanolone acetate

Using a flask fitted with a dropping funnel and nitrogen line, titanium tetrachloride (0.30ml) in sodium-dried benzene (5ml) was added with stirring over 20 minutes, to a solution of the steroid ketone (1.66g) and the amine (3ml) in dry benzene (25ml). The mixture was maintained at 0-10° during the addition and then stirred at room temperature for three hours. It was then filtered through an oven-dry sintered glass funnel and the solvent rapidly removed under reduced pressure. Crude enamine from this reaction was used without further purification.

This procedure was found to be much inferior for D.H.A. acetate to the previously described acid catalysed method, which was therefore preferred.

The dimethylamine enamine of androstanolone acetate could, however, only be prepared using this method, though in a very impure state.

n.m.r. (60) δ 4.30 (olefinic proton), partly obscured by C-17 proton; 2.54 (N-methyl):

Integration of N-methyl against acetate revealed about 17% enamine.

ν max. 1646cm^{-1} (d.b.).

Calcium Hydride Dehydration

Androstanolone acetate (0.36g) and pyrrolidine (0.36ml) were dissolved in deuterochloroform (1ml). Calcium hydride was added and n.m.r. spectra taken at intervals. After 15 minutes about 60% enamine was present, which increased to 66% only on leaving the mixture overnight.

3.3(a)(ii) Derivatives

Pyrrolidiminium chloride of androstanolone acetate[15]

The parent crude pyrrolidenamine (570mg) was dissolved in sodium-dry ether (25ml), filtered and excess of a dry solution of hydrogen chloride in ether added. The precipitate was washed with anhydrous ether (30ml) and dried. Despite extensive efforts at recrystallization from various solvents analytical figures remained low. That the solid contained some complex of the enamine was demonstrated by exact mass measurement:

m/e 385.296 373 ($C_{25}H_{39}NO_2$ = 385.298 063).

Regeneration[15] of the enamine was attempted. The solid (100mg) in anhydrous ether (5ml) was stirred with dry piperidine (3 drops) for 15 minutes, the solution was filtered and the solvent was removed to yield a brown oil (80mg). The n.m.r. spectrum revealed about 50% of regenerated enamine:

n.m.r. (60) δ 4.13 [0.5H] (olefinic proton);

4.57 [1H] (C-17 proton).

Attempted purification of the pyrrolidenamine of D.H.A. acetate via the iminium chloride

The whole of the crude enamine from 1.66g of D.H.A. acetate was dissolved in sodium-dried benzene (20ml) and dry hydrogen chloride in ether was slowly added dropwise with stirring until the solution became acid to indicator paper. Stirring was continued for 15 minutes, when a black oil settled to the bottom. This oil was washed with dry benzene (20ml x 2) and ether (20ml). Residual solvent was then removed to yield a brown semi-solid. Exact mass measurement supported the presence of some complex of the enamine:

m/e 383.282 621 ($C_{25}H_{37}NO_2$ = 383.282 414).

This substance was suspended in a small quantity of dry ether (15ml) and anhydrous piperidine (5ml) was added. The mixture was stirred for 15 minutes, filtered and the solvent was removed. The product was extracted with dry ether and solvent was then removed. The n.m.r. spectrum of the resulting brown tar showed the major product to be D.H.A. acetate. No enamine was apparent.

Pyrrolidiminium picrate of androstanolone acetate

Crude enamine (1g) was dissolved in the minimum of hot absolute ethanol (ca. 5ml) and a saturated anhydrous ethanolic solution of picric acid (10ml) was added. This was chilled for one hour and scratched. The precipitate of picrate was filtered off and was washed with cold ethanol (1.26g; 79%) m.p. 166-171° dec., not improved by recrystallization. Exact mass measurement showed the compound to be a complex of the pyrrolidenamine:

m/e 385.298 630 ($C_{25}H_{39}NO_2$ = 385.298 063).

(Found: C, 60.3; H, 6.93; N, 8.99. $C_{31}H_{42}N_4O_9$ requires C, 60.6; H, 6.84; N, 9.13%);

n.m.r. (60) δ 8.71 [2H] (aromatic); 4.55 'triplet' [1H] (C-17 proton); 3.06 [4H] (α-pyrrolide); 2.76 [4H] (β-pyrrolide); 2.01 (acetate); 0.89 (C-19 methyl); 0.78 (C-18 methyl);

ν max. ($CHBr_3$) 1719cm^{-1} (acetate carbonyl).

Two attempts were made to regenerate the parent enamine.

(a) To a suspension of the picrate (100mg) in sodium-dried ether (5ml), dry pyrrolidine (1ml) was added and the mixture was stirred for one hour, filtered and the solvent was removed. The solid was extracted with dry ether, which on evaporation yielded a yellow glass (40mg). The n.m.r. revealed no enamine but was consistent with androstanolone acetate.

(b) Alumina was dried by heating under high vacuum on a sand-bath at 200°. A small (2cm long) column was then made with the alumina, on which the picrate (100mg) was eluted with sodium-dried ether. The product consisted of white crystalline material (50mg) which was shown by n.m.r. spectroscopy to be androstanolone acetate.

Pyrrolidiminium picrate of D.H.A. acetate

Crude enamine (0.81g) was dissolved in the minimum of hot absolute ethanol and anhydrous ethanolic picric acid solution (9ml) added, when a dark brown solid precipitated. This was washed with cold ethanol and was then dissolved in ethanol (ca. 20ml) at boiling point. The solution was cooled and scratched to yield yellow-brown crystals (10mg). This solid was then recrystallized from absolute ethanol, discarding the initial precipitate of brown oil to yield yellow crystals of the picrate (1mg). That the compound was a complex of the pyrrolidenamine was shown by exact mass measurement:

m/e 381.267 741 ($C_{25}H_{35}NO_2$ = 381.266 765) [enamine minus 2H].

3.3(b) Methylation

Attempted preparations of 2α-methyl-5α-androstan-17β-ol-3-one acetate (2α-methylandrostanolone acetate)

In benzene

Crude pyrrolidenamine (2.30g) of androstanolone acetate and methyl iodide (0.75ml) in anhydrous benzene (50ml) were refluxed for two hours. The reaction mixture was then allowed to stand for two days, during which time a precipitate formed. Reflux was resumed for a further hour and water (4ml) and acetone (4ml) were added, after which the precipitate redissolved. Water was added and the steroid extracted into chloroform/ether. The solution was washed, dried and the solvent removed. N.m.r. spectroscopy showed the product to be slightly impure androstanolone acetate.

In dioxan

The crude pyrrolidenamine from androstanolone acetate (1g) and

methyl iodide (0.5ml) in anhydrous dioxan (25ml) were refluxed overnight, a precipitate appearing. Water was added and the steroid extracted into chloroform. N.m.r. spectroscopy showed the product to be androstanolone acetate.

In acetonitrile

Both the acetonitrile solvent and the methyl iodide were dried over calcium hydride for 5 days. A solution of crude enamine (1.14g) and methyl iodide (0.5ml) in acetonitrile (35ml) was refluxed for 18 hours, using a guard tube to prevent the ingress of water. Water (5ml) was added and the solution was allowed to stand for 30 minutes. Water (60ml) was then added and the steroid was extracted into ether (100ml). The aqueous layer was back extracted with ether (50ml) and the two ether solutions combined. This was washed with water (100ml x 3), dried and the solvent was removed to yield a brown crystalline solid. N.m.r. spectroscopy showed the product to be androstanolone acetate.

In ethanol

Both the ethanol and methyl iodide were dried over calcium hydride for 5 days. A solution of crude enamine (1.10g) and methyl iodide (0.5ml) in ethanol (25ml) was refluxed for 16 hours, using a calcium chloride tube to prevent ingress of water vapour. Water (5ml) was added and the solution was allowed to stand for 30 minutes. Water (60ml) was then added and the steroid was extracted into ether (100ml). The aqueous layer was back extracted with ether (35ml) and the two ether fractions combined. The ether layer was washed with water (100ml x 2), dried and the solvent was removed to yield a low-melting semi-crystalline solid. Examination of the n.m.r. spectrum suggested that the product was largely a mixture of androstanolone and

androstanolone acetate. T.l.c. against authentic samples confirmed the identification.

Preparation of 2α-methyl-5α-androstan-17β-ol-3-one (2α-methylandrostanolone)[145,146,59]

In ethanol

Both the ethanol and methyl iodide had been thoroughly dried with calcium hydride: glassware was oven dry. A solution of the crude pyrrolidenamine from androstanolone (1.6g) in ethanol (10ml) was refluxed with methyl iodide (2.5ml) under an atmosphere of dry nitrogen. Reflux was maintained for three hours, during which time a white precipitate appeared. Solvents were then removed on a rotary evaporator and sodium hydroxide solution (10%; 10ml) and methanol (20ml) were added. The solution was refluxed for 25 minutes and then most of the methanol was taken off, leaving a semi-solid precipitate which was removed with a glass rod and dessicated. T.l.c. revealed a reaction product of marginally lower polarity than starting material, just resolved (R_f = 0.49) from androstanolone (R_f = 0.43). The resultant brittle brown solid was crushed to a powder, which was extracted well with ether and the residual solid was filtered off. The ether solution was evaporated and the semi-crystalline material was crudely chromatographed on an alumina column with ethyl acetate to remove polar by-products. Careful chromatography on florisil with 15% acetone in hexane gave two fractions. The first consisted of the reaction product 2α-methylandrostanolone (homogeneous to t.l.c.) (117 mg; 7.0% from androstanolone), while the second (297 mg) was a mixture with starting material. The product was recrystallized twice from ethyl acetate/hexane (ca. 70% recovery per recryst.) to give pure 2α-methylandrostanolone (56mg; 48% overall recovery); m.p. ca. 140° the crystals of undefined form started to change to rods, which

continued to grow coarser till melting at 174-5° (lit.[145,146,59] 174-6°).

N.m.r. (60) δ 1.06 (C-19 methyl);

1.02 centre, J = 12Hz doublet (i.e. 0.92, 1.12) (2α-methyl);

0.74 (C-18 methyl).

Attempted preparation of 2α-methyl-5α-cholestan-3-one

In acetonitrile/dioxan

Crude pyrrolidenamine from 5α-cholestan-3-one (0.73g) with methyl bromide (0.5ml) and methyl iodide (0.5ml) in a mixture of anhydrous acetonitrile (30ml) and dioxan (10ml) was refluxed overnight. Water (1 ml) was then added and the mixture refluxed for a further hour. The steroid was extracted into chloroform (200ml) and this washed with water (200ml x 3). N.m.r. spectroscopy showed the product to be unchanged cholestanone.

3.3(c) Reaction with Allyl Bromide

Both the acetonitrile and allyl bromide had been thoroughly dried with calcium hydride: glassware was oven dry. A solution of the crude pyrrolidenamine from androstanolone acetate (1g) in acetonitrile (25ml) was refluxed with allyl bromide (1.5ml) under an atmosphere of dry nitrogen. Reflux was maintained for four hours, during which time the initially yellow solution had changed to red/brown. The reaction mixture was then allowed to stand overnight in a stoppered flask. Water (5ml) was added to the solution, which was allowed to stand for 30 minutes. Chloroform (100ml) was added and this solution was successively washed with water, dried, filtered and the solvent was removed to yield a brown semi-solid. T.l.c. revealed a reaction

product of somewhat lower polarity (R_f = 0.71) than starting material as well as androstanolone acetate (R_f = 0.64). The n.m.r. spectrum (:CH_2 versus C-17 proton) was consistent with about 25% 2α-allylandrostanolone acetate. Crude chromatography on an alumina column, eluting with ether, removed polar material, leaving the reaction product mixture as a yellow oil. Careful chromatography of this on silica gel with 20% ether in hexane gave two crystalline fractions. T.l.c. showed the first to consist of 2α-allylandrostanolone acetate (174mg; 16% from androstanolone acetate), while the second fraction was a mixture with starting material. The product was recrystallized three times from hexane to give pure 2α-allylandrostanolone acetate (40mg; 23% recovery); m.p. 129-131° (lit.[138] 130-1°);

m/e 372.268 177 ($C_{24}H_{36}O_3$ = 372.266 430);

n.m.r. (60) δ 5.05(:CH_2); 4.82(:CH); 4.55(C-17 proton); 2.01 (acetate); 1.05(C-19methyl); 0.79(C-18 methyl);

$\nu_{max.}$ 1640cm^{-1} weak (d.b.).

3.3(d) Reaction with Ethyl Crotonate

In acetonitrile

The ethyl crotonate and acetonitrile solvent were dried over calcium hydride for five days. A solution of the crude pyrrolidenamine of androstanolone acetate (1.4g) and ethyl crotonate (0.4ml) in acetonitrile (35ml) was refluxed for 18 hours, using a calcium chloride tube to prevent the ingress of water vapour. Water (5ml) was then added to the solution which was allowed to stand for 30 minutes. Water (80ml) was then added and the solution extracted with ether (120ml). The aqueous layer was back extracted with ether (35ml) and the ether portions combined. This was washed with water (100ml x 2),

dried and the solvent was removed to give a semi-crystalline brown solid. Identity of the n.m.r. spectra showed the product to be androstanolone acetate (1.15g; 95% recovery).

In ethanol

A solution of the crude pyrrolidenamine of androstanolone (591mg) and ethyl crotonate (0.5ml) in anhydrous ethanol (10ml) was refluxed for five hours under an atmosphere of dry nitrogen. Ether work-up of the reaction mixture produced a brown crystalline solid which t.l.c. showed to be only recovered androstanolone.

3.3(e) Reactions of Methyl $\beta\beta'$-dibromoisobutyrate ($+Et_3N$)

3.3(e)(i) with 1-N-pyrrolidino-cyclohex-1-ene (pyrrolidenamine of cyclohexanone)

(A) Long reaction time[130,196]

The acetonitrile and triethylamine used had been rigorously dried with calcium hydride: glassware was oven dry. Crude pyrrolidenamine freshly prepared from cyclohexanone (1ml) was dissolved in acetonitrile (12ml) with triethylamine (1.36ml) and a solution of anhydrous methyl $\beta\beta'$-dibromoisobutyrate (1.40ml) in acetonitrile (8ml) was slowly added. Considerable heat was evolved by the reaction and on cooling to room temperature a mass of white needles was deposited. The mixture was refluxed for six hours under an atmosphere of dry nitrogen. Dilute acetic acid (5%; 1ml) was added and the reflux was continued for a further hour. Water (30ml) was then added to the reaction mixture which was extracted with portions of ether (50ml x 3). The ether solution was washed with water (100ml x 3), dried, filtered and the solvent was removed to yield crude methyl 9-oxobicyclo [3,3,1] nonane-3α-carboxylate as a yellow oil (1.45g). Subsequently the aqueous solution was saturated with sodium chloride and extracted with

chloroform (50ml x 3). The chloroform extract was washed with saturated sodium chloride solution (100ml), dried, filtered and the solvent was removed to yield a brown solid (0.36g) which n.m.r. revealed was triethylamine hydrobromide.

The crude bicyclononane was chromatographed on alumina, eluting with ether: fractions were examined by t.l.c. Initially a little yellow oil was collected which proved to be the olefin 2-(2-carbomethoxyprop-2-enyl)-cyclohexanone identical (t.l.c. and n.m.r.) with material prepared as described later. The main fraction was then collected as a colourless, odourless oil which slowly crystallized to give methyl 9-oxobicyclo [3,3,1] nonane-3α-carboxylate as a white solid (0.46g; 24% from cyclohexanone). This was twice recrystallized from hexane and the melting point was determined;

m.p. 42-43° (lit.[196] 41-42°);

t.l.c. R_f = 0.38 does not char well (olefin R_f = 0.51);

n.m.r. (100) [C_6H_6] δ 3.29 (carbomethoxy); 2.5-0.8 (methylene hump),

(lit.[130] n.m.r.(100) [C_6H_6] δ 3.33 and 3.6-0.8 respectively);

n.m.r. (60) [$CDCl_3$] δ 3.71 [3H] (carbomethoxy); 2.9-1.1 [13H]

(Methylene hump, principal maximum 1.95);

ν max. ($CHCl_3$) 1720cm^{-1} (carbonyls) (lit. ν max.[130] 1720cm^{-1}).

Acid

The methyl ester (200mg) was refluxed with potassium hydroxide solution (2N; 10ml) for 30 minutes. The solution was made acid to litmus with concentrated hydrochloric acid added dropwise. On chilling a white precipitate appeared, which was filtered off, washed with water and dried to give 9-oxobicyclo [3,3,1] nonane-3α-carboxylic acid (111mg; 60%). Most of this (107mg) was recrystallized from ethyl acetate (76mg; 68% recovery); m.p. 131-133° (lit.[196] 134-135°);

n.m.r. (60) δ 10.61 (acid); 3.0-1.2 (methylene hump, pattern similar to the ester, principal maximum 1.95);

ν max. ($CHBr_3$) 3480,3080,2620 multiple, broad(acid); 1704cm^{-1} broad (carbonyls).

(B) Rapidly quenched reaction

The reaction was carried out as in (A) above except that it was quenched with dilute acetic acid immediately after the addition of the methyl $\beta\beta'$-dibromoisobutyrate reagent to the enamine solution. The yellow oil (1.49g) from the ether work-up was chromatographed on alumina, eluting with ether: fractions were examined by t.l.c. The initial and major material was the olefin 2-(2-carbomethoxyprop-2-enyl)-cyclohexanone, a light-yellow fragrant liquid (0.63g; 33% from cyclohexanone). (Subsequently a small amount of the bicyclononane (above) was eluted.)

m/e 196.110 255 ($C_{11}H_{16}O_3$ = 196.109 937);

t.l.c. R_f = 0.51 (bicyclononane R_f = 0.38);

n.m.r.(60) δ 6.20 /1H/ (olefin); 5.59 /1H/ (olefin); 3.76 /3H/ (carbomethoxy); 3.2-1.0 /11H/ (featureless methylene hump);

$\nu_{max.}$ (CS_2) 1716 (carbonyls); 1637cm^{-1} weak (d.b.);

$\nu_{max.}$ ($CHCl_3$) 1708 (carbonyls); 1633cm^{-1} strong (d.b.).

Acid

The methyl ester (200mg) was refluxed with potassium hydroxide solution (2N; 10ml) for 30 minutes. The solution was extracted with ether which was discarded to remove ether-soluble material. The aqueous solution was then saturated with sodium chloride and made acid to litmus with concentrated hydrochloric acid added dropwise. The solution was extracted with chloroform and the organic layer was dried, filtered and solvent was removed to give the acid 2-(2-carboxyprop-2-enyl)-cyclohexanone as a very pale yellow oil (157mg; 85%).

N.m.r. (60) δ 11.33 (acid); 6.37 (olefin); 5.72 (olefin); 3.2-0.6 (methylene hump);

$\nu_{max.}$ ($CHBr_3$) 3670, 3500, 3300, 2600 multiple, broad (acid); 1695 broad (carbonyls); 1619cm^{-1} (d.b.).

D.N.P.

To the methyl ester (100mg) was added Brady's reagent (4ml). The oil which first precipitated crystallized after heating and then chilling the mixture: the solid was filtered off and dried (64mg; 33%). Two recrystallizations from ethanol gave the 2,4-dinitrophenylhydrazone (46mg; 72% overall recovery) as a felt of orange needles;

m.p. 127.5-129.0°;

t.l.c. homogeneous R_f = 0.73;

$\nu_{max.}$ 3323 (NH); 1723 (conj. carbonyl; N = C); 1332 (conj. NO_2);

d.b. not discernable in CS_2.

3.3(e)(ii) with the pyrrolidenamine of trans-decal-2-one

The acetonitrile and triethylamine used had been rigorously dried with calcium hydride: glassware was oven dry. Crude pyrrolidenamine freshly prepared from trans-decal-2-one (0.24ml) was dissolved in acetonitrile (5ml) with triethylamine (0.24ml) and a solution of anhydrous methyl $\beta\beta'$-dibromoisobutyrate (0.24ml) in acetonitrile (2ml) was added. The solution became warm and on cooling white needles were deposited. The mixture was refluxed for 13 hours under an atmosphere of dry nitrogen. Dilute acetic acid (5%; 0.5ml) was added and the reflux was continued for a further hour. Water (15ml) was then added to the reaction mixture which was extracted with portions of ether (25ml x 3). The ether solution was washed with water (50ml x 3), dried, filtered and the solvent was removed to yield a light brown oil (356mg). Subsequently the aqueous solution was saturated with sodium chloride and extracted with chloroform (25ml x 3). The chloroform extract was washed with saturated sodium chloride solution (50ml), dried, filtered and the solvent was removed to yield a brown solid (76mg) which n.m.r. revealed was triethylamine hydrobromide.

The oil was carefully chromatographed on alumina, eluting with 10% hexane in ether to produce about 20 fractions (50ml). T.l.c. allowed the pooling of these to three products plus unchanged trans-decal-2-one. The first product to elute was the olefin 3α-(2-carbomethoxyprop-2-enyl)-trans-decal-2-one as an oil (20mg; 4.9% from decalone). This was followed by the bicyclononane 1,3-(2-endo-carbomethoxytrimethylene)-trans-decal-2-one, another oil (30mg; 7.3% from decalone). A third compound of identical t.l.c. polarity to the olefin above was detected in a later fraction but in so minute a quantity that further investigation was impracticable.

1,3-(2-endo-carbomethoxytrimethylene)-trans-decal-2-one(bicyclononane)

T.l.c. R_f = 0.71 chars poorly (just resolved from olefin R_f = 0.77); n.m.r. (60) δ 3.76 (carbomethoxy); no olefinic protons; 3.0-0.5 (methylene hump);

$\nu_{max.}$ 1733cm^{-1} (carbonyls).

Gas chromatography on N.P.G.S. (5%) at 200° revealed two nearly equal peaks. G.l.c./m.s. examination showed that both were associated with molecular ions of m/e 250.

D.N.P.

To the bicyclononane (30mg) was added Brady's reagent (1.6ml) and after chilling in ice the precipitate of 2,4-dinitrophenylhydrazone was filtered off and dried (20mg; 39%). This was dissolved in excess ethanol and the solvent was allowed to evaporate slowly overnight. Filtration gave material (8mg) of broad melting range. The compound was recrystallized (three times) from ethanol until the quantity (0.3mg) was too small to continue, but the melting point did not improve; m.p. 100-120°;

m/e 430.185 742 base peak ($C_{21}H_{26}N_4O_6$ = 430.185 221);

t.l.c. (10% ethanol/benzene) homogeneous R_f = 0.74;

t.l.c. (20% ethyl acetate/hexane) homogeneous R_f = 0.28;

νmax. 3180 broad (NH); 1738 (carbonyl; N = C); 1331cm^{-1} (conj. NO_2).

3α-(2-carbomethoxyprop-2-enyl)-trans-decal-2-one (olefin)

T.l.c. R_f = 0.77 chars blue (just resolved from bicyclononane R_f = 0.71 and overlapping decalone R_f = 0.75 chars yellow);

n.m.r. (60) δ 6.18 $\overline{1}$ H (olefin); 5.56 $\overline{1}$ H (olefin); 3.74 $\overline{3}$ H (carbomethoxy); 3.0-1.5 (methylene hump);

νmax. (CS_2) 1719cm^{-1} (carbonyls); d.b. not discernable in CS_2;

νmax ($CHCl_3$) 1722 (carbonyls); 1633cm^{-1} weak (d.b.).

D.N.P.

To the olefin (20mg) was added Brady's reagent (0.8ml). The semi-solid which precipitated was collected on a spatula and was, with difficulty, recrystallized from ethanol to give the 2,4-dinitrophenylhydrazone as a yellow solid (3.8mg; 11%). Most of this was twice recrystallized from ethanol to give a felt of yellow needles (0.9mg; typically 80% recovery per recryst.); m.p.127.5-129.5°;

m/e 430.184 464 ($C_{21}H_{26}N_4O_6$ = 430.185 221);

(Found: C, 54.29; H, 5.33; N, 14.88. $C_{17}H_{20}N_4O_6$ requires C, 54.25; H, 5.36; N, 14.89);

t.l.c. homogeneous R_f = 0.76;

νmax. 3322 (NH); 1720 (conj. carbonyl; N = C); d.b. not discernable in CS_2; 1331cm^{-1} (conj. NO_2).

3.3(e)(iii) with steroidal enamines

General Method

The acetonitrile and triethylamine used had been rigorously dried with calcium hydride: glassware was oven dry. Crude pyrrolidenamine from the steroidal ketone (1g for M.W. = 332) was dissolved, if possible, in acetonitrile (30ml) with triethylamine (0.42ml) and a solution of anhydrous methyl $\beta\beta'$-dibromoisobutyrate (0.44ml) in acetonitrile (5ml) was added. The mixture was then refluxed for 16 hours under an atmosphere of dry nitrogen. Dilute acetic acid (5%; 0.5ml) was added and the reflux was continued for a further hour. Water (30ml) was then added to the reaction mixture which was extracted with portions of ether (50ml x 3). The ether solution was washed with water (100ml x 3), dried, filtered and the solvent was removed to yield the ether-soluble fraction. Subsequently the aqueous solution was saturated with sodium chloride and extracted with chloroform (50ml x 3). The chloroform extract was washed with saturated sodium chloride solution (100ml), dried, filtered and the solvent was removed to yield the chloroform-soluble fraction.

The reaction was performed on the pyrrolidenamines of the following nine steroids:

I
- 5α-androstanolone acetate
- 17α-methylandrostanolone
- pregnan-3,20-dione (3-mono-enamine)

II
- 19-norandrostanolone acetate
- 5β-androstanolone acetate

III
- cholestan-3-one
- androstanolone 4-methylpentanoate
- D.H.A. acetate
- testosterone acetate

The three groups gave rise to distinct types of product: thus group I gave steroidal salts (contaminated with triethylamine hydrobromide) in

the chloroform-soluble fractions. Steroidal bicyclonanes as well as olefins were isolated from group II, while the latter were obtained from all three groups. In the arrangement of this section the salts (from group I) are covered first: these are followed by the bicyclononanes (and olefins) from group II and finally the olefins from groups I and III. Within a group the compounds are considered in the order of the starting materials above. When, in the following, the chloroform-soluble fraction is not explicitly mentioned only triethylamine hydrobromide (n.m.r.) was found in it.

Modifications (using the pyrrolidenamine of 5α-androstanolone acetate)

(a) On the omission of triethylamine only olefin was produced.

(b) The reaction time was reduced to ten minutes, when only olefin was produced.

Salts

(A) 17β-acetoxy-5'β-carbomethoxy-5α-androst-2-eno [3,2-b] 1'-azoniaspiro [4,5] decane bromide

Yield 4.19g from 4g 5α-androstanolone acetate (62%). Since no suitable recrystallization solvent was found, a trituration procedure was adopted for purification. The salt (4.19g) was refluxed in acetone (67ml) for 15 minutes, the solution cooled, filtered and the filtrate washed with ice-cold acetone (13ml). The procedure was repeated to yield the salt as a white solid (2.76g; 66% recovery); m.p. 225-(27-31)° dec.; soluble in water, insoluble in ether.

Exact mass (on ion "salt minus HBr" i.e. $C_{30}H_{45}NO_4$)

m/e 483.333 348 ($C_{30}H_{45}NO_4$ = 483.334 840);

(Found: C, 64.1; H, 8.04; N, 2.56; Br 13.9.

$C_{30}H_{46}NO_4Br$ requires C, 63.8; H, 8.21; N, 2.48; Br 14.2%);

n.m.r. (100) δ 4.50 (CH_2N and C-17 proton);

4.06 (CH_2C = C); 3.74 (carbomethoxy);

3.46 ($CHCO_2$); 2.88 (α-pyrrolide);

2.00 (acetate); 0.72 (C-18 methyl);

0.60 (C-19 methyl);

^{13}C n.m.r. spectrum[152]: 16.7 p.p.m. (acetate carbonyl);

40.6 p.p.m. (carbomethoxy carbonyl);

45.3 p.p.m. (*C = C-N);

133.4 p.p.m. (C = C*-N);

ν max. ($CHBr_3$) 1720 (carbonyls); 1662cm^{-1} (d.b.).

(B) 5'β-carbomethoxy-17β-hydroxy-17-methyl-5α-androst-2-eno [3,2-b] 1'-azoniaspiro [4,5] decane bromide

Yield 1.40g from 0.99g ketone (80%). The salt (1.40g) was refluxed in acetone (20ml) for 15 minutes and the filtrate was washed with ice-cold acetone (4ml). The procedure was repeated to yield the salt as a white solid (0.95g; 68% recovery); m.p. 225-228° dec.; soluble in water, insoluble in ether.

Exact mass (on ion "salt minus HBr" i.e. $C_{29}H_{45}NO_3$)

m/e 455.341 844 (theory 455.339 926);

n.m.r. (100) δ 4.48 (CH_2N); 4.02 ($CH_2C=C$); 3.74 (carbomethoxy); 3.47 ($CHCO_2$); 2.82 (α-pyrrolide); 1.20 (C-17 methyl); 0.80 (C-18 methyl); 0.62 (C-19 methyl);

ν max. ($CHBr_3$) 1720 (carbonyls); 1660cm^{-1} (d.b.).

(C) 5'β-carbomethoxy-20-oxo-5α-pregn-2-eno [3,2-b] 1'-azoniaspiro [4,5] decane bromide

Yield 450mg crude salt from 840mg pregnan-3,20-dione (31%). The salt (450mg) was refluxed in ethyl acetate (13ml) for 30 minutes and the salt was filtered off to give an off-white solid (311mg; 69% recovery). The procedure was repeated with ethyl acetate (10ml) plus acetone (40 drops) to give the salt (252mg; 81% recovery); m.p. 218-219° dec.

Exact mass (on ion "salt minus HBr" i.e. $C_{30}H_{45}NO_3$)

m/e 467.339 980 (theory 467.339 926);

n.m.r. (60) δ 4.40 (CH_2N); 4.01 ($CH_2C=C$); 3.74 (carbomethoxy); $CHCO_2$ obscured; 2.98 (-pyrrolide); 2.11 (acetyl); 0.61 (C-18 methyl); 0.59 (C-19 methyl);

ν max. ($CHBr_3$) 1722 (carbomethoxy carbonyl); 1698 (acetyl carbonyl); 1665 (d.b.).

Reactions of Salt (A) (from 5α-androstanolone acetate)

The presence of ionic bromide was confirmed by the immediate formation of a yellow/white precipitate on the addition of silver nitrate solution to an acidified (HNO_3) solution of the salt.

The salt (100mg) was warmed with sodium hydroxide solution (2N). The bromide-free precipitate was filtered off and washed with more sodium hydroxide solution. A sodium fusion test was performed on the product. No covalent bromine was found.

A dilute solution of tetranitromethane[134] was added to a chloroform solution of the salt and the mixture warmed in a water bath. The appearance of a yellow colour was consistent with the presence of a tetrasubstituted double bond.

Attempted methylation

The salt (100mg) in water (5ml) was stirred with freshly prepared silver (I) oxide (200mg), overnight. The mixture was then put into chloroform (100ml), the water was removed, the solution was filtered and the solvent was removed to yield the product (70mg). This was dissolved in absolute ethanol (10ml) and was refluxed with methyl iodide (1 ml) for 45 minutes. No new methyl peak appeared in the n.m.r. spectrum.

Hydrolysis

(a) The salt (1.13g) was dissolved in acetonitrile (4ml) and dilute acetic acid (5%; 0.2ml) added. The mixture was refluxed for three hours. No material could then be extracted into ether.

(b) The salt (1g) was dissolved in dilute hydrochloric acid (5%; 15ml) and refluxed overnight. On cooling the material came down as a white precipitate insoluble in ether.

(c) Salt (1g) was refluxed for three hours with hydrochloric acid (25ml conc. + 25ml water). No material could then be extracted into ether.

(d) Salt (204mg) and saturated sodium bicarbonate solution (5ml) with ethanol (5ml), chloroform (5ml) and water (5ml) were stirred together to an emulsion in a stoppered flask for 49 hours. The product was extracted into ether (100ml) and the ether solution was washed with water (100ml x 3). The solution was dried, filtered and solvent was removed to yield 17β-acetoxy-2α-(2-carbomethoxyprop-2-enyl)-5α-androstan-3-one as a yellow oil (60mg; 39%). This was dissolved in excess hexane and insoluble material was filtered off and discarded. After removal of solvent the oil was, with considerable difficulty, recrystallized from hexane as a white solid. Three further recrystallizations (typical recovery per recryst. 60%) gave the pure olefin (9mg; 15% overall recovery; 5.9% from salt); m.p. 85-88°. The full characterization of this olefin, prepared in a different manner (m.p. 86-88°) is given later. The identity of the two compounds was established by mixed melting point (86-88° undepressed) as well as by comparison of the n.m.r. spectra.

Bicyclononanes and Olefins

(a) from 19-norandrostanolone acetate

The total crude material (738mg) from 19-norandrostanolone acetate (720mg) was carefully chromatographed on alumina, eluting with ether: 13 fractions (50ml) were collected. Further elution with 50% ether in ethyl acetate gave unchanged starting material. The first six and the last contained little material and were therefore rejected, leaving six fractions of colourless oil. T.l.c. with 10% ethanol in benzene as solvent system did not resolve the mixture from starting material (R_f = 0.73): with 20% ethyl acetate in hexane, however, the fractions could be seen to contain no starting material (R_f = 0.46) and consisted of two components, the olefin (R_f = 0.37)

and the bicyclononane (R_f = 0.24 chars bright red). The first three fractions were mostly olefin and were therefore combined: the other three were richer in bicyclononane and were also pooled (88mg). This latter mixture was subjected to preparative t.l.c. on silica gel with 20% ethyl acetate in hexane and produced crude bicyclononane 17β-acetoxy-2α,4α-(2α-carbomethoxytrimethylene)-5α,10β-estran-3-one (20mg; 2.1% from 19-norandrostanolone acetate) as a clear colourless oil. The olefin from the plate was combined with that from the column to give crude 17β-acetoxy-2α-(2-carbomethoxyprop-2-enyl)-5α,10β-estran-3-one (167mg; 18% from 19-norandrostanolone acetate) as a yellow oil.

17β-acetoxy-2α,4α-(2α-carbomethoxytrimethylene)-5α,10β-estran-3-one (bicyclononane)

N.m.r. (60) δ 4.57 (C-17 proton); 3.74 (carbomethoxy);
2.03 (acetate); 0.77 (C-18 methyl);

$\nu_{max.}$ 1738 (shoulder 1727) (carbonyls); 1240cm^{-1}.

D.N.P.

The crude bicyclononane (20mg) was dissolved in the minimum of methanol and Brady's reagent (0.8ml) was added. On chilling in ice a precipitate formed which was filtered off (20.3mg; 71%). Attempts to recrystallize this material from ethanol succeeded only in giving a semi-solid. It was therefore dissolved in excess ethanol which was allowed to evaporate slowly overnight: filtration produced a solid (4.3mg). T.l.c. revealed that this was contaminated with the olefin D.N.P. The material was therefore subjected to preparative t.l.c. on silica gel, using 20% ethyl acetate in hexane as the solvent system. The resultant 2mg of t.l.c. - homogeneous material was recrystallized from acetone/hexane with very considerable difficulty to give the 2,4-dinitrophenylhydrazone as bright yellow crystals (0.8mg; 2.8% from

crude bicyclononane; 0.059% from 19-norandrostanolone acetate);

m.p. 198-205°;

m/e 596.288 644 ($C_{31}H_{40}N_4O_8$ = 596.284 592);

t.l.c. (10% ethanol/benzene) R_f = 0.70 (same as olefin DNP);

t.l.c. (20% ethyl acetate/hexane) homogeneous R_f = 0.15 (olefin DNP R_f = 0.20).

17β-acetoxy-2α-(2-carbomethoxyprop-2-enyl)-5α,10β-estran-3-one (olefin)

N.m.r. (60) δ 6.17 [1 H] (olefin); 5.57 [1 H] (olefin);
4.58 [1 H] (C-17 proton); 3.74 [3 H] (carbomethoxy);
2.04 (acetate); 0.83 (C-18 methyl);

$\nu_{max.}$ 1738, 1720 (carbonyls); 1630 extremely weak (d.b.); 1240cm^{-1}.

Attempts to crystallize the crude olefin from hexane were discouraging: at best a sticky solid was obtained. The D.N.P. was therefore prepared.

D.N.P.

Crude olefin (110mg) was dissolved in the minimum of methanol and Brady's reagent (4ml) was added. On chilling the precipitated oil crystallized and it was filtered off (130mg; 82%). This was recrystallized five times from ethanol (typical recovery 50%) to give the pure 2,4-dinitrophenylhydrazone (4.8mg; 3.0% from crude olefin; 0.54% from 19-norandrostanolone acetate); m.p. 175-180°;

m/e 596.284 612 ($C_{31}H_{40}N_4O_8$ = 596.284 592);

t.l.c. (10% ethanol/benzene) R_f = 0.70 (same as bicyclononane DNP);

t.l.c. (20% ethyl acetate/hexane) homogeneous R_f = 0.20 (bicyclononane DNP R_f = 0.15).

(b) from 5β-androstanolone acetate

5β-androstanolone acetate (920mg) gave rise to semi-solid brown material (462mg) from the chloroform-soluble fraction. The n.m.r. spectrum suggested that it was a mixture of bicyclonane and triethylamine hydrobromide. An attempt was made to remove the latter by washing a solution in chloroform (100ml) with saturated sodium bicarbonate (50ml x 3) and then with dilute hydrobromic acid (10%; 50ml). After drying, filtration and removal of the solvent n.m.r. revealed that as well as removing the triethylamine hydrobromide the washing had hydrolysed the bicyclononane to the olefin. The mixture was therefore combined with the similar (t.l.c. and n.m.r.) ether-soluble fraction (221mg) to give crude material (551mg). This was chromatographed on alumina, eluting with ether: 20 fractions (50ml) were collected. All but six of these contained negligible amounts and were therefore discarded. Of the six retained fractions (9-14) the first and last were crystalline, while the other four were oils. T.l.c. using 10% ethanol in benzene as solvent system showed that the first two fractions were mostly unchanged 5β-androstanolone acetate (R_f = 0.59) while the next two were largely olefin (R_f = 0.66): the last two fractions gave predominantly a single spot corresponding to the olefin with this solvent system; however use of 20% ethyl acetate in hexane showed that as well as olefin (R_f = 0.22 same as 5β-androstanolone acetate) these last two fractions contained some bicyclononane (R_f = 0.10). The first two fractions were discarded and the second two were pooled to give crude olefin 17β-acetoxy-4β-(2-carbomethoxyprop-2-enyl)-5β-androstan-3-one as an oil (135mg; 11% from 5β-androstanolone acetate). The last two were also pooled and subjected to preparative t.l.c. on silica gel, running the plate twice with 20% ethyl acetate in hexane: this gave the

bicyclononane 17β-acetoxy-2β,4β-(2β-carbomethoxytrimethylene)-5β-androstan-3-one as white crystals (6.4mg; 0.54% from 5β-androstanolone acetate).

17β-acetoxy-2β,4β-(2β-carbomethoxytrimethylene)-5β-androstan-3-one (bicyclononane)

The bicyclononane (6.4mg) was, with some difficulty, recrystallized from acetone to give white plates (2.2mg; 34% recovery; 0.18% from 5β-androstanolone acetate); m.p. 215-218°;

m/e 430.271 363 ($C_{26}H_{38}O_5$ = 430.271 907);

(Found: C, 72.69; H, 8.96. $C_{26}H_{38}O_5$ requires C, 72.53; H, 8.90%);

n.m.r. (60) (run on crude material from column - very noisy spectrum due to tiny quantity) δ no olefinic resonance; 4.50 (C-17 proton); 3.73 (carbomethoxy); 2.00 (acetate); 0.88 (C-19 methyl); 0.72 (C-18 methyl);

$\nu_{max.}$ ($CHBr_3$) 1720 (carbonyls); no d.b.; 1247cm^{-1}.

17β-acetoxy-4β-(2-carbomethoxyprop-2-enyl)-5β-androstan-3-one (olefin)

The crude olefin (135mg oil) was recrystallized from hexane as a white solid which was recrystallized (typical recovery per recryst. 70%) four more times to give the olefin as white needles (17.4mg; overall recovery 13%; 1.4% from 5β-androstanolone acetate); m.p. 111-113°;

m/e 430.270 937 ($C_{26}H_{38}O_5$ = 430.271 907);

(Found: C, 72.35; H, 8.96. $C_{26}H_{38}O_5$ requires C, 72.53; H, 8.90%);

n.m.r. (60) δ 6.14 $\overline{1}$ H (olefin); 5.56 $\overline{1}$ H (olefin); 4.58 $\overline{1}$ H (C-17 proton); 3.72 $\overline{3}$ H (carbomethoxy); 2.04 (acetate); 1.01 (C-19 methyl); 0.81 (C-18 methyl);

$\nu_{max.}$ 1738; 1718 (carbonyls); 1631 very weak (d.b.); 1240cm^{-1}.

(c) from 5α-androstanolone acetate

The crude ether-soluble material (800mg) from 5α-androstanolone acetate (4g) was roughly chromatographed on alumina. Elution with ether gave recovered crystalline starting material (334mg): with ethyl acetate a crude olefin mixture (278mg) was obtained as an oil. On t.l.c. starting material (R_f = 0.62) was not resolved from the olefin (R_f = 0.67) but the two compounds could be distinguished by what difference there was together with differential charring behaviour. Further careful chromatography on alumina with 20% ethyl acetate in ether gave more crystalline starting material, then crude olefin as an oil (75mg; 1.4% from 5α-androstanolone acetate). The oil was, with some difficulty, recrystallized from hexane as a white solid. This was recrystallized from hexane (typical recovery per recryst. 55%) three more times to give pure 17β-acetoxy-2α-(2-carbomethoxyprop-2-enyl)-5α-androstan-3-one (7.5mg; overall recovery 10%; 0.14% from 5α-androstanolone acetate); m.p. 86-88°;

(Found: C, 72.44; H, 8.91. $C_{26}H_{38}O_5$ requires
C, 72.53; H, 8.90%);

(A tiny sample of the olefin was also prepared from the crude ether-soluble material by preparative gas chromatography on a Perkin-Elmer 801 instrument. The OV-1 column was held at 300°:

m/e 430.270 937 ($C_{26}H_{38}O_5$ = 430.271 907));

n.m.r. (60) δ 6.15 (1 H) (olefin); 5.54 (1 H) (olefin);
4.56 (1 H) (C-17 proton); 3.73 (3 H) (carbomethoxy);
2.03 (acetate); 1.05 (C-19 methyl); 0.81 (C-18 methyl);

$\nu_{max.}$ 1720 broad (carbonyls); 1626 extremely weak (d.b.); 1240cm^{-1};

the presence of the double bond was confirmed chemically by the decolourization of bromine water and of potassium permanganate solution.

Acid

(Hydrolysis procedure) The crude ether-soluble material (0.1g) was dissolved in ethanol (10ml). A few drops of water and potassium hydroxide (0.5g) were added and the solution was refluxed for 30 minutes. It was then added to ether (25ml) and sodium hydroxide solution (2N; 25ml). After shaking, the aqueous layer was separated. The ether layer was extracted again with a further portion of sodium hydroxide solution. The combined aqueous extract was acidified dropwise with concentrated hydrochloric acid, with which a precipitate appeared. This was extracted into chloroform (75ml x 3). The solution was then dried, filtered and the solvent was removed to yield the crude acid.

The resultant very small quantity of the acid 2α-(2-carboxyprop-2-enyl)-5α-androstan-17β-ol-3-one gave a noisy n.m.r. spectrum:

n.m.r. (60) δ 6.32 (olefin); 5.70 (olefin); 4.73 (C-17 proton plus acid); 1.07 (C-19 methyl); 0.77 (C-18 methyl).

This material was recrystallized from ethyl acetate/hexane to give an off-white solid; m.p. 187-190°;

m/e 374.246 048 ($C_{23}H_{34}O_4$ = 374.245 695).

(d) from 17α-methylandrostanolone

The crude ether-soluble material (128mg) from 17α-methylandrostanolone (990mg) was chromatographed on alumina. Elution with 50% ethyl acetate in hexane gave three fractions containing (just) noticeable quantities of oil: further elution with ethyl acetate gave a large amount of unreacted crystalline starting material. T.l.c. of the three fractions with 10% ethanol in benzene showed the last two to consist of olefin (R_f = 0.56) as well as some starting

material (R_f = 0.51). With this solvent system the first fraction had the same polarity as the olefin: with 20% ethyl acetate in hexane, however, it was revealed as another compound (R_f = 0.19) and not olefin (R_f = 0.12 same as starting material). This first fraction constituted only 3.3mg of oil; thus it was not possible to characterize it further; however a very slowly run and heavily filtered n.m.r. spectrum (in CCl_4) suggested that it did not contain olefinic resonances but did show a carbomethoxy peak (3.68 δ). The two other (olefin-containing) fractions were combined but even here the quantity of oil (12.9mg) was insufficient to proceed with further purification. Spectroscopic properties, however, were consistent with this material's being the impure olefin 2α-(2-carbomethoxyprop-2-enyl)-17α-methyl-5α-androstan-17-ol-3-one.

m/e 402.276 349 ($C_{25}H_{38}O_4$ = 402.276 993), 402 is the largest peak above 304;

n.m.r. (60) (CCl_4) (very noisy due to the small quantity) δ 6.07 (olefin); 5.55 (olefin); 3.70 (carbomethoxy); 1.15 (C-17 methyl); 1.11? (C-19 methyl); 0.82 (C-18 methyl);

$\nu_{max.}$ 1718 broad (carbonyls); 1630cm^{-1} weak (d.b.).

(e) from pregnan-3,20-dione

232mg of crude ether-soluble material was obtained from pregnan-3,20-dione (840mg). The n.m.r. spectrum suggested that it contained a small amount of olefin and t.l.c. showed the compound was not resolved from starting material (R_f = 0.59). The typical yield of the olefins from groups I and III (about 1.5%) forcefully suggested that the amount of crude material available was insufficient to allow the isolation of 2α-(2-carbomethoxyprop-2-enyl)-5α-pregnan-3,20-dione, hence the mixture was not further investigated.

m/e 414.277 059 ($C_{26}H_{38}O_4$ = 414.276 993), 414 is largest peak above 330;

n.m.r. (60) (small resonances in addition to those from starting material) δ 6.14 (olefin); 5.52 (olefin); 3.72 (carbomethoxy).

(f) from 5α-cholestan-3-one

The crude ether-soluble material (1.32g) from 5α-cholestanone (1.27g) was chromatographed on alumina. Elution with 20% hexane in ether gave crystalline starting material followed by three fractions of oil. T.l.c., using 10% ethanol in benzene failed to resolve starting material and product; however 20% ethyl acetate in hexane showed the first fraction to be largely starting material (R_f = 0.62) and it was therefore discarded. The two later fractions gave predominantly a single spot (R_f = 0.56) and were combined to yield an oil (22.1mg). The presence of two C-19 methyl resonances in the n.m.r. spectrum of this crude material, however, suggested the presence of two different olefins:

n.m.r. (60) δ 6.20 (olefin); 5.57 (olefin); 3.76 (carbomethoxy); 1.27, 1.72 (two C-19 methyls); 0.92 ($CHMe_2$); 0.83 (C-18 methyl); 0.67 (C-21 methyl).

The oil proved too soluble to effect recrystallization from hexane; however a white solid was, with difficulty, obtained with poor (39%) recovery from methanol. Four more recrystallizations from methanol (typical recovery per recryst. 70%) gave the di-olefin 2α,4α-di-(2-carbomethoxyprop-2-enyl)-5α-cholestan-3-one as a slightly sticky white solid (1.1mg; 5.0% overall recovery; 0.06% from cholestanone); m.p. 75-79°, dependent on heating rate;

m/e 582.430 856 ($C_{37}H_{58}O_5$ = 582.428 397);

$\nu_{max.}$ (CS_2) 1724 (carbonyls); 1626cm^{-1} weak (d.b.);

$\nu_{max.}$ ($CHBr_3$) 1720 (carbonyls); 1630cm^{-1} weak (d.b.).

(g) from androstanolone 4-methylpentanoate

The n.m.r. spectrum of the crude ether-soluble material was consistent with the presence of a small quantity of the olefin 2α-(2-carbomethoxyprop-2-enyl)-5α-androstan-17β-ol-3-one 4-methylpentanoate:

n.m.r. (60) (small resonances in addition to those from starting material) δ 5.17 (olefin); 5.57 (olefin); 3.72 (carbomethoxy).

Acid

Hydrolysis by the procedure outlined in (c) above gave the acid as an off-white solid (3mg). This was recrystallized from ethyl acetate/hexane to give less than 1 mg of pure acid; m.p. 185-190°. The mixed melting point with the acid (m.p. 187-190°) prepared from 5α-androstanolone acetate as described in (c) was undepressed; m.p. 186-190°.

(h) from D.H.A. acetate

The total crude semi-solid material (1.36g) from D.H.A. acetate (1.5g) was roughly chromatographed on alumina, eluting with 25% chloroform in ether, to give a semi-crystalline solid (630mg). This material (244mg) was carefully re-chromatographed, using ether then 10% ethyl acetate in hexane: 20 fractions (50ml) were collected. Neither t.l.c. solvent system resolved olefin adequately from starting material, but with 10% ethanol in benzene the olefin (R_f = 0.73) was less polar than starting material (R_f = 0.69); while with 20% ethyl acetate in hexane it was more polar (R_f = 0.35; DHA acetate R_f = 0.37). This difference was sufficient to indicate that the oil of the eleventh fraction was the olefin

3β-acetoxy-16α-(2-carbomethoxyprop-2-enyl)-androst-5(6)-en-17-one

(9.2mg; corr. to 1.2% from D.H.A. acetate);

n.m.r. (60) (CCl_4) (noisy due to small quantity) δ 6.08 (olefin); 5.50 (olefin) not entirely resolved from 5.37 (C-6 olefinic proton); 4.46 (C-3 proton); 3.72 (carbomethoxy); 1.96 (acetate); 1.26 (C-18 methyl); 1.04 (C-19 methyl);

$\nu_{max.}$ 1740 broad (carbonyls); 1676 barely discernable ($\Delta^{5(6)}$ d.b.); 1630 (side-chain d.b.); 1237cm^{-1}.

D.N.P.

The addition of Brady's reagent gave an oil which was recrystallized from ethanol to give the 2,4-dinitrophenylhydrazone as an orange solid (0.3mg; 2.3%; 0.028% from D.H.A. acetate); m.p. broad 108-128°;

t.l.c. virtually homogeneous R_f = 0.78;

m/e 608.283 176 ($C_{32}H_{40}N_4O_8$ = 608.284 592), 608 is the largest peak above 562.

Acid

Hydrolysis of the roughly chromatographed crude olefin mixture using the procedure outlined in (c) above gave the crude acid 16α-(2-carboxyprop-2-enyl)-androst-5(6)-en-3β-ol-17-one as less than 1mg of mid-brown solid:

m/e 372.229 958 ($C_{23}H_{32}O_4$ = 372.230 045), 372 is the largest peak above 18.

(i) from testosterone acetate

875mg of the total crude material (1.35g) from testosterone acetate (1g) was carefully chromatographed on alumina, eluting with 10% ethyl acetate in ether: 18 fractions (50ml) were collected. The first compound to elute was crystalline testosterone acetate: this was followed by some fractions of oil. T.l.c. allowed the pooling of the oil to two fractions: the first was a mixture of testosterone acetate

and another material less polar to t.l.c., while the second fraction (41mg) showed two spots more polar than starting material. The first fraction was subjected to preparative t.l.c. on silica gel, using 10% ethanol in benzene as solvent system. This cleanly separated the product (33mg) from testosterone acetate, t.l.c. showing only a single spot; however the n.m.r. spectrum revealed the presence of at least three compounds (three C-19 methyl resonances as well as a number of olefinic peaks and a single large carbomethoxy resonance). The mixture was again subjected to preparative t.l.c. and a number of fractions were derived from closely spaced zones; however n.m.r. spectroscopy revealed that this had failed to separate the constituents to any appreciable degree.

Attention was then turned to the second fraction (above). The two constituent spots were isolated by preparative t.l.c. but again the two products, each homogeneous to t.l.c., proved to be intractable mixtures of olefins (n.m.r.).

The original crude material was subjected to preparative gas chromatography on an OV-1 column at 300°. The major fraction (other than starting material) proved to correspond to testosterone acetate with a single 2-carbomethoxyprop-2-enyl side-chain:

m/e 428.256 629 ($C_{26}H_{36}O_5$ = 428.256 258), 428 is the largest peak above 149.

Attempted preparation /

Attempted preparation of 2α-(2-carbomethoxyprop-2-enyl)-5α-androstan-17β-ol-3-one acetate (olefin from androstanolone acetate) via base catalysed reaction[65]

To a boiling solution of androstanolone acetate (0.22g) in benzene (2.5ml) and butanol (1.25ml), under a nitrogen atmosphere, a solution prepared by the addition of potassium (40mg) to butanol (1ml) was added. Methyl ββ′-dibromoisobutyrate (1.0g) was then added, followed by more potassium (160mg) 'dissolved' in butanol (4ml). A white precipitate appeared and the solution was refluxed for a further 10 minutes. Ice was added to the reaction mixture, which was extracted with ether (25ml x 3). This was washed with water (75ml x 3), dried and the solvent removed. The product proved to be a mixture of at least four components, which were not further separated. However the n.m.r. spectrum revealed the presence of (inter alia) resonances at δ 6.20 (olefin); 5.56 (olefin); and 3.73 (carbomethoxy) corresponding to resonances in the spectrum of the crude olefin mixture.

3.3(f) Attempted Reaction of ω-nitrostyrene with Pyrrolidenamines of Androstanolone and Acetate

In dioxan-room temperature

Crude pyrrolidenamine from androstanolone acetate (1g) and ω-nitrostyrene (0.45g) were dissolved in anhydrous dioxan (15ml) with gentle warming. The solution was left in a stoppered flask for two days. Water (3ml) was added and the mixture was allowed to stand for 25 minutes. Chloroform (300ml) was then added and the solution was washed with water (x 3). The chloroform layer was then dried and the solvent was removed to yield a brown glass.

Mass spectroscopy revealed no major peak corresponding to the molecular ion of the expected product, but instead showed ions up to at least m/e 660. The n.m.r. spectrum of this crude material revealed aromatic protons (7.25 δ) and t.l.c. disclosed a diffuse band of higher polarity than starting material, as well as androstanolone acetate. The mixture was not further investigated.

In dioxan-reflux

A chilled solution of dry α-nitrostyrene (250mg) in anhydrous dioxan (5ml) was added to a solution of crude androstanolone pyrrolidenamine (591mg) in anhydrous dioxan (10ml) at 0°. The mixture was allowed to warm to room temperature for three hours in a stoppered flask and was then refluxed under an atmosphere of dry nitrogen for one hour. Water (1ml) was added and the mixture was allowed to stand for 30 minutes. After addition of water (100ml) the whole was extracted with ether (100ml x 3), dried, filtered and the solvent was removed. T.l.c. showed a spot corresponding to androstanolone and a diffuse band of higher polarity. On alumina chromatography the bulk of the material (a dark brown tar) eluted only with a chloroform mixture. The less polar yellow glass, which came through with ethyl acetate, was carefully chromatographed on florisil, but the only compound which could be isolated was unchanged androstanolone (t.l.c. and n.m.r.).

In ethanol-reflux

The same procedure was followed using ethanol (7 and 20ml respectively) as solvent, with similar results.

3.3(g) Reaction of Acryloyl Chloride with Pyrrolidenamine of Androstanolone Acetate

Acryloyl chloride (0.88ml) in anhydrous benzene (15ml) was added dropwise to a refluxing solution of crude pyrrolidenamine of androstanolone acetate (4.25g) in anhydrous benzene (60ml). A white precipitate formed rapidly and reflux was maintained for 21 hours. The reaction mixture was then cooled in ice and the precipitate was filtered off and washed with anhydrous benzene (10ml). The solid was shaken with ice-cold water (50ml), allowed to stand in ice for three hours and then was warmed up to room temperature. The aqueous solution was then extracted with ether (100ml). The ethereal solution was dried and the solvent was removed to yield a white solid. This was then recrystallized from a mixture of petrol (60/80°) and acetone to yield:

3-(17β-acetoxy-5α-androstan-3-one 2α-yl)-propanoic acid

(0.44g; 9.9% from enamine); m.p. 168-173°; soluble in hot sodium hydroxide solution;

m/e 404.256 102 ($C_{24}H_{36}O_5$ = 404.256 258);

t.l.c. homogeneous R_f = 0.21;

n.m.r. (100) δ 9.70 (acid); 4.58 'triplet' (C-17 proton); 2.01 (acetate); 1.04 (C-19 methyl); 0.77 (C-18 methyl);

ν max. 1734 (acetate carbonyl); 1704cm^{-1} strong (C-3 and acid carbonyls).

Esterification

To the acid (50mg) in anhydrous ether (3ml) was added dropwise a solution of diazomethane until the yellow colour was no longer discharged. The solution was allowed to stand for 30 minutes. Solvent was then removed.

N.m.r. /

N.m.r. (100) δ4.58 'triplet' (C-17 proton);

3.64 (carbomethoxy); 2.02 (acetate); 1.06 (C-19 methyl);

0.89 (C-18 methyl).

Integration (C-17 proton versus carbomethoxy) showed the ester to be the sole (more than 95%) product.

Attempted cyclization

To the acid (202mg) in anhydrous benzene (50ml) with pyridine (1 drop) was added oxalyl chloride (0.1ml). A white precipitate formed. The solution was allowed to stand at room temperature for two hours and was then refluxed for ten minutes. The solvent was removed to yield the acid chloride (219mg).

νmax. 1759 (acid chloride); 1730cm^{-1} (C-3 and acetate carbonyls).

To a solution of the acid chloride (219mg) in dry chloroform (12ml) was added stannic chloride (0.07 ml) and the whole allowed to stand overnight. The chloroform solution was extracted with dilute hydrochloric acid (20ml). The aqueous layer was then itself extracted with hexane and the hexane and chloroform fractions combined. This solution was washed with saturated sodium bicarbonate solution (25ml) and then with water (35ml x 4). The solution was dried and the solvent was removed.

Chromatography on alumina produced androstanolone acetate (identified by t.l.c.) as the only isolable product.

3.3(h) Reactions of Acrolein

3.3(h)(i) with pyrrolidenamine of cyclohexanone

(A) Room temperature-distillation work-up[136]

To a solution of the crude pyrrolidenamine produced from cyclohexanone (12.4ml), dissolved in anhydrous dioxan (25ml) and maintained at 0°, was added acrolein (2.2ml). The mixture was then allowed to warm to room temperature and left for one hour. The reaction mixture was dissolved in ether (300ml) and repeatedly washed with water. The ether layer was dried and the solvent was removed to yield a brown oil (8.5g). This oil (6.29g) was fractionally distilled at 0.5mm pressure. The product 2-pyrrolidinyl-bicyclo [3,3,1] nonan-9-one was collected at 100-120° (1.26g; corr. to 25% from acrolein).

N.m.r. (60) principal maxima δ 2.50; 2.01; 1.77 (methylene hump);

νmax. 1720cm^{-1} (carbonyl).

Picrate

Amine (0.2g) was dissolved in the minimum of hot ethanol and a cold saturated ethanolic solution of picric acid (2ml) added. The precipitate was filtered off and recrystallized twice from ethanol; m.p. 170-172° (lit.[136] 171-172°);

n.m.r. (60) (almost saturated soln.) δ 8.88 (aromatic); 7.23 (NH); maximum 2.00 (methylene hump);

i.r. ($CHBr_3$) 1717 weak (carbonyl); 1610; 1564, 1312cm^{-1} broad.

(B) Reflux-chromatographic work-up

The dioxan had been rigorously dried with calcium hydride: glassware was oven dry: the acrolein was freshly distilled. Crude pyrrolidenamine from cyclohexanone (1 ml) was dissolved in dioxan (10ml)

and the light yellow solution was chilled to 0°. Acrolein (0.65ml) was added and the stoppered flask was allowed to warm to room temperature for one hour. The mixture was then refluxed for 30 minutes under an atmosphere of dry nitrogen. Solvent was removed on a rotary evaporator. The product was refluxed with ether for 30 minutes and the mixture was filtered through a celite pad to remove ether-insoluble material: solvent was removed to yield a red/brown oil (1.72g). This was chromatographed on alumina, eluting with ether: 50ml fractions were collected. Fractions two and three comprised an oil, samples of which gave yellow crystalline precipitates on the addition of ethanolic picric acid. T.l.c. did not reveal a single spot but a characteristic streak caused by reaction of the amine with the acidic silica gel. The identical behaviour of the two fractions on t.l.c., slowly charring from brown to scarlet, allowed them to be pooled. This gave 2-pyrrolidinyl-bicyclo [3,3,1] nonan-9-one as a very pale-yellow viscous oil (827mg; 41% from cyclohexanone;

n.m.r. and i.r. as above.

Picrate

The picrate was prepared from the amine (400mg) by the method outlined above. It (330mg; 39%) was recrystallized from ethanol (about 50ml) to give the pure picrate (210mg; 64% recovery); m.p. 171.0-173.5° (lit.[136] 171-172°).

(C) Room temperature - chromatographic work-up

The procedure in (B) above was followed: the reaction mixture was, however, not refluxed but simply allowed to stand at room temperature for a total of 90 minutes. After the addition of chloroform (100ml) the organic layer was washed with water (100ml x 5), dried, filtered and solvent was removed. This yielded a brown tar which was chromatographed on alumina with results similar to (B) above.

3.3(h)(ii) with pyrrolidenamine of trans-decal-2-one

The dioxan had been rigorously dried with calcium hydride: glassware was oven dry: the acrolein was freshly distilled. Crude pyrrolidenamine from trans-decal-2-one (0.24ml) was dissolved in dioxan (2.5ml) and the solution was chilled to 0°. Acrolein (0.08ml) was added and the stoppered flask was allowed to warm to room temperature for one hour. The mixture was then refluxed for 15 minutes under an atmosphere of dry nitrogen. Solvent was removed on a rotary evaporator to give a brown oil (386mg). This was roughly chromatographed on alumina, eluting with ethyl acetate to give a light brown liquid (259mg) smelling of decalone. T.l.c. revealed the presence of at least six compounds, two of lower polarity than starting material, one corresponding to decalone (R_f = 0.77) and another more polar (R_f = 0.58) as well as two further spots of even higher polarity. The crude material was carefully chromatographed on florisil with solvent mixtures of increasing polarity: twenty (50ml) fractions were collected. T.l.c. allowed pooling to seven fractions. After decalone a pale yellow liquid eluted with 50% ether in hexane which corresponded to the R_f = 0.58 spot. This material was the crude bicyclononane 1,3-(1-pyrrolidinyltrimethylene)-trans-decal-2-one, a viscous pale-yellow oil (42mg; 9.8% from decalone);

n.m.r. (60) principal maxima δ 2.52, 1.71 (methylene hump);

i.r. 1729cm^{-1} (carbonyl).

Picrate

A cold saturated ethanolic solution of picric acid was added to solutions of the seven fractions in the minimum of hot ethanol. On standing for two days the fraction noted above was the only one to furnish a crystalline precipitate (14mg; 18%; 1.7% from decalone). This was twice recrystallized from ethanol (about 50% recovery per

recryst.) to give the pure picrate (3.0mg; 21% overall recovery); m.p. 170-172°.

Exact mass on abundant ion corresponding to parent amine:

m/e 261.208 701 ($C_{17}H_{27}NO$ = 261.209 254);

i.r. ($CHBr_3$) 1718 weak (carbonyl); 1604; 1565; 1318cm^{-1} broad.

3.3(h)(iii) with steroids

The reaction was carried out with pyrrolidenamines of:

(a) cholestan-3-one

(b) androstanolone

(c) androstanolone acetate.

General

The crude enamine (1.5g) was dissolved in anhydrous dioxan (25ml) and keeping the mixture at 0°, acrolein (0.15ml) was added. The whole stood overnight at room temperature. The steroid was then extracted into chloroform, this was washed with water and the solvent was removed. Chromatography on alumina failed to separate the desired product; nor did attempted picrate formation fare better. Mass spectroscopy revealed no peak corresponding to the expected amine.

Modifications

(A) Using androstanolone and androstanolone acetate, the addition was carried out (as above) at ice temperature; but the solution was then refluxed for two hours. On work-up none of the desired product was detected.

(B) Using androstanolone the reaction was carried out as above, but in rigorously anhydrous ethanol. The product was worked up in two ways with similar results - (i) chloroform extraction, (ii) removal of the solvent on a rotary evaporator. The products were carefully chromatographed on alumina, eluting with solvent mixtures of increasing polarity.

About 20 fractions were collected, none except the following in any quantity: ethyl acetate gave unchanged androstanolone (t.l.c.) and methanol yielded considerable (176mg) brown tar. Saturated ethanolic picric acid was added to each fraction but in no instance did a crystalline picrate separate on standing.

3.3(i) Reactions of Salicylaldehyde and Analogues

3.3(i)(i) Salicylaldehyde with the pyrrolidenamine of androstanolone acetate

To a solution of the crude pyrrolidenamine from androstanolone acetate (1g) in anhydrous benzene (10ml) was added a solution of salicylaldehyde (0.32ml) in anhydrous benzene (10ml). The solution, which immediately became orange, was left for two days. Solvent was then removed. The product was recrystallized three times from ethanol to yield 17β-acetoxy-3α-pyrrolidinyl-5α-androstano [3,2-b] 2-H-benzopyran as a white solid (0.17g; 12% from androstanolone acetate); m.p. (161° softens) 168-172°;

m/e 489.325 389 ($C_{32}H_{43}NO_3$ = 489.324 276);

t.l.c. R_f = 0.66, fluoresces blue under near ultra-violet illumination: this is accompanied by the pyrrolidine-eliminated compound (following) 17β-acetoxy-5α-androst-3-eno [3,2-b] 2-H-benzopyran R_f = 0.77;

n.m.r. (100) δ 7.1-6.4 complex multiplet [4 H] (aromatic); 6.13 [1 H] (olefin); 4.59 [1 H] (C-17 proton); 2.84 [4 H] broad multiplet (α-pyrrolide); 2.03 (acetate); 1.65 (β-pyrrolide); 0.82, 0.79 (C-18 and C-19 methyls); in addition to the spectrum of the compound per se, the deuterochloroform solution contains a small amount (22% by integral of the 3.63 δ resonance versus the olefinic proton in

the amine) of the amine-eliminated compound (following).

$\nu_{max.}$ 1718 (carbonyl); 1600 and 1576 (d.b.); 1258cm^{-1};

$\lambda_{max.}$ (n-hexane) 227 (ε 29,300); 311nm (ε 4,000).

Sarett oxidation of the amine 17β-acetoxy-3α-pyrrolidinyl-5α-androstano [3,2-b] 2-H-benzopyran

The oxidizing complex was prepared by the addition of chromium trioxide (60mg) to pyridine (3ml). The temperature was held at 15-20° and continuous stirring was maintained until complete solution had occurred. At 0° a solution of the amine (50mg) in pyridine (5ml) was added and the solution stirred for a further two hours in the cold, then overnight at room temperature. The mixture was then poured into water and extracted with ether. The ether layer was dried and the solvent was removed. The yellow product was twice recrystallized from ethanol to yield 17β-acetoxy-5α-androst-3-eno [3,2-b] 2-H-benzopyran as a white solid (20mg; 45%); m.p. 173-222°, decomposes slowly);

m/e 418.249 344 ($C_{28}H_{34}O_3$ = 418.250 781);

t.l.c. homogeneous R_f = 0.79, fluoresces green under near ultra-violet illumination;

n.m.r. /

n.m.r. (100) δ 7.2 - 6.7 complex multiplet [4 H] (aromatic);
6.36 [1 H] (4 -H); 4.59 [1 H] (C-17 proton);
3.40 [2 H] multiplet (4-H and 5-H); 2.02 (acetate);
1.25, 1.18, 1.11, 1.04 [4 H] quartet-like (accidental
6-Hs and 7-Hs); 0.79 (C-18 and C-19 methyls);

ν max. 1732 (carbonyl); 1645 (d.b.); 1242cm^{-1};

λ max. (EtOH) 227 (ε 43,900); shoulder 260 (ε 14,400);
310nm (ε 8,300).

3.3(i)(ii) 4-acetoxy-2-hydroxybenzaldehyde with the pyrrolidenamine of androstanolone acetate

(a) Preparation of 4-acetoxy-2-hydroxybenzaldehyde

To 2,4-dihydroxybenzaldehyde (7g) in pyridine (50ml) was added acetic anhydride (4.8ml). The mixture, which immediately became hot, was left overnight. Most of the pyridine was then distilled off at low pressure. The residue was dissolved in chloroform (200ml). This was washed with saturated sodium chloride solution (50ml) with a little added concentrated hydrochloric acid (3ml). It was washed again with saturated salt solution (50ml x 4). The solution was dried and the solvent removed to give a liquid (9.26g) consisting of a mixture of the 2 and 4-acetates, the latter in excess (80 : 20 by g.l.c.).

N.m.r. (60) δ 10.04 (aldehyde of 2-acetate); 9.89 (aldehyde of 4-acetate); 2.33 (acetate of 2-acetate); 2.26 acetate of 4-acetate).

The liquid was fractionally distilled at low pressure and the more volatile material collected (118-124°/0.6mm). The separated 4-acetate (about 95% by g.l.c.) crystallized to a solid (5.89g). This was recrystallized from a mixture of petrol (40/60°) (25ml) and ether (15ml). Two further recrystallizations yielded 4-acetoxy-2-hydroxybenzaldehyde (1.08g; 12%); m.p. 61.5-63°;

m/e 180.042 361 ($C_9H_8O_4$ = 180.042 254);

n.m.r. (60) δ 11.12 (hydroxy); 9.82 (aldehyde);

7.7 - 6.6 (aromatic); 2.29 (acetate).

(b) Reaction of 4-acetoxy-2-hydroxybenzaldehyde with pyrrolidenamine of androstanolone acetate

To the crude pyrrolidenamine from androstanolone acetate (1g) in dry benzene (10ml) was added a solution of 4-acetoxy-2-hydroxybenzaldehyde (0.54g) in dry benzene (10ml). The reaction mixture, which immediately turned red, was left overnight. On working the mixture up in the same way as was the corresponding salicylaldehyde reaction mixture, t.l.c. revealed a complex mixture of at least eight components, none except androstanolone acetate in any quantity. The mixture was therefore not further investigated.

3.3(j) Reactions of Carboethoxyaziridine

3.3(j)(i) with pyrrolidenamine of androstanolone acetate followed by hydrolysis

The crude pyrrolidenamine from androstanolone acetate (1.66g) and carboethoxyaziridine (1.15g) were refluxed together in dry p-xylene (25ml) overnight, under a nitrogen atmosphere. The reaction mixture was added to ether (150ml) and washed with water

(100ml x 3). The solution was dried and the solvent removed to yield a pale brown glass. This was chromatographed on alumina to yield crystalline product (0.56g). No satisfactory recrystallization solvent was found; therefore the compound was suspended in petrol (60/80°) and ether added until it dissolved. Most of the ether was allowed to evaporate off and the precipitated solid was collected by filtration. The process was repeated to yield 2-(17β-acetoxy-5α-androstan-3-one-2α-yl)-N-carboethoxyethylamine as an off-white crystalline solid (80mg; 3.6% from androstanolone acetate); m.p. 114-125°;

m/e 447.298 547 ($C_{26}H_{41}NO_5$ = 447.298 455);

t.l.c. homogeneous R_f = 0.63;

n.m.r. (60) δ 5.04 (NH); 4.59 'triplet' (C-17 proton);

4.11 quartet (CH_2 of ethyl); 3.20 'quartet' (CH_2-N);

2.02 (acetate); 1.21 triplet (CH_3 of ethyl);

1.05 (C-19 methyl); 0.89 (C-18 methyl);

ν max. 3420 (NH); 1723 (carbonyls); 1250cm^{-1}.

An attempt to separate the compound from the crude material by preparative gas chromatography was made using an OV-1 column at 300°. Infra-red spectroscopy showed the compound to have cyclized on the column to yield 17β-acetoxy-1'-N-carboethoxy-5α-androst-2-eno [3,2-b] dihydropyrrole as deduced from the identity of the spectrum with that of a sample of the compound prepared as follows.

3.3(j)(ii) with pyrrolidenamine of androstanolone acetate, followed by elimination of pyrrolidine

The crude pyrrolidenamine from androstanolone acetate (1.66g) and carboethoxyaziridine (1.15g) were refluxed together in dry p-xylene (25ml) overnight, under a nitrogen atmosphere. A sample of

the solution was taken and solvent was removed. Mass spectroscopy revealed the presence of the amine, 17β-acetoxy-1'-N-carboethoxy-2β-H-3α-pyrrolidinyl-5α-androstano [3,2-b] tetrahydropyrrole, in the crude mixture.

m/e 500.360 562 ($C_{30}H_{48}N_2O_4$ = 500.361 387).

To the remainder of the reaction mixture was added p-toluene sulphonic acid monohydrate (2.0g) and the solution was refluxed for two hours. The mixture was then added to chloroform and washed with water till neutral. The solution was dried and the solvent removed. It was twice recrystallized from acetone to yield 17β-acetoxy-1'-N-carboethoxy-5α-androst-2-eno [3,2-b] dihydropyrrole as white crystals (60mg; 4.0% from androstanolone acetate) m.p. 169-171°; slightly fluorescent under short-wave ultra-violet light;

m/e 429.287 143 ($C_{26}H_{39}NO_4$ = 429.287 892);

t.l.c. homogeneous R_f = 0.70;

n.m.r. (60) δ 4.60 'triplet' (C-17 proton);

4.13 (CH_2 of ethyl); 3.74 'triplet' (CH_2-N);

2.02 (acetate); 1.25 triplet (CH_3 of ethyl);

0.79 (C-18 methyl); 0.74 (C-19 methyl);

ν max. 1734 (acetate carbonyl); 1707 (carboethoxy carbonyl);

1692 (d.b.); 1252cm^{-1}.

3.3(j)(iii) with androst-2-en-3,17β-diol diacetate

The reaction of carboethoxyaziridine with the corresponding enol acetate was attempted. The enol acetate (2.12g) and carboethoxyaziridine (1.25g) were refluxed together in p-xylene (25ml) overnight, under a nitrogen atmosphere. Thin layer chromatography of the reaction mixture revealed only starting material.

4. BIBLIOGRAPHY

1) G. Wittig and H. Blumenthal, Chem. Ber., 1927, 60, 1085

2) C. Mannich and H. Davidsen, Chem. Ber., 1936, 69, 2106

3) P.L. de Benneville and J.H. Macartney, J.Amer.Chem.Soc., 1950, 72, 3073

4) M.E. Herr and F.W. Heyl, J.Amer.Chem.Soc., 1952, 74, 3627

5) G. Stork, R. Terrell and J. Szmuszkovicz, J.Amer.Chem.Soc., 1954, 76, 2029

6) N.J. Leonard and V.W. Gash, J.Amer.Chem.Soc., 1954, 76, 2781

7) B. Witkop, J.Amer.Chem.Soc., 1954, 76, 5597

8) J. Klaubek, Chem. Listy, 1959, 53, 821

9) H. Hellman and G. Opitz, α-Aminoalkylierung, Verlag Chemie, Weinheim, (1960), quoted in ref.12 p169

10) J. Szmuszkovicz, Advances in Organic Chemistry: Methods and Results, Vol. 4, (Raphael, Taylor and Wynberg, Eds.), Wiley, pplff, Interscience, New York and London, (1963)

11) K. Bláha and O. Červinka, Advan.Heterocyclic Chem., 1966, 6, 147

12) A.G. Cook, Ed., Enamines: Synthesis, Structure and Reactions, Marcel Dekker, New York and London, (1969)

13) A. Mondon, Chem. Ber., 1959, 92, 1461

14) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz and R. Terrell, J.Amer.Chem.Soc., 1963, 85, 207

15) J.L. Johnson, M.E. Herr, J.C. Babcock, A.E. Fonken, J.E. Stafford and F.W. Heyl, J.Amer.Chem.Soc., 1956, 78, 430

16) W.A. White and H. Weingarten, J.Org.Chem., 1967, 32, 213

17) N.J. Leonard and J.V. Paukstelis, J.Org.Chem., 1963, 28, 3021

18) W.D. Gurowitz and M.A. Joseph, Tetrahedron Letters, 1965, 4433

19) W.D. Gurowitz and M.A. Joseph, J.Org.Chem., 1967, 32, 3289

20) G. Opitz, H. Hellman and H.W. Schubert, Annalen, 1959, 623, 112

21) H.C. Brown, J.H. Brewster and H. Schechter, J.Amer.Chem.Soc., 1954, 76, 467

22) H.C. Brown, J.Org.Chem., 1957, 22, 439

23) M.E. Kuehne, J.Amer.Chem.Soc., 1959, 81, 5400

24) Ref.12 p8

25) G.H. Whitham, Alicyclic Chemistry p62, Macdonald and Co., London, 1963

26) F. Johnson and S.K. Malhotra, J.Amer.Chem.Soc., 1965, 87, 5492

27) F. Johnson, Chem.Rev., 1968, 68, 375

28) F. Johnson and A Whitehead, Tetrahedron Letters, 1964, 3825

29) J.W. Lewis and P.P. Lynch, Proc.Chem.Soc., 1963, 19

30) S.K. Malhotra and F. Johnson, Tetrahedron Letters, 1965, 4027

31) J.P. Schaefer and D.S. Weinberg, Tetrahedron Letters, 1965, 1801

32) S. Karady, M. Lenfant and R.E. Wolff, Bull.Soc.Chim.France, 1965, 2472

33) S.K. Malhotra, D.F. Moakley and F. Johnson, Chem.Commun., 1967, 448

34) H.J. Jakobsen, S.O. Lawesson, J.T.B. Marshall, G. Schroll and D.H. Williams, J.Chem.Soc.(B), 1966, 940

35) F.W. Heyl and M.E. Herr, J.Amer.Chem.Soc., 1953, 75, 1918

36) G. Stork and G. Birnbaum, Tetrahedron Letters, 1961, 313

37) F.W. Heyl and M.E. Herr, J.Amer.Chem.Soc., 1955, 77, 488

38) D.A. Shepherd, R.A. Donia, J.A. Campbell, B.A. Johnson, R.P. Holysz, G. Slomp, J.E. Stafford, R.L. Pederson and A.C. Ott, J.Amer.Chem.Soc., 1955, 77, 1212

39) G. Slomp, Y.F. Shealy, J.L. Johnson, R.A. Donia, B.A. Johnson, R.P. Holysz, R.L. Pederson, A.C. Jensen and A.C. Ott, J.Amer.Chem.Soc., 1955, 77, 1216

40) Ref.12 p347

41) W.R.N. Williamson, Tetrahedron, 1958, 3, 314

42) A.T. Blomquist and E.J. Moriconi, J.Org.Chem., 1961, 26, 3761

43) E. Elkik, Bull.Soc.Chim.France, 1960, 972

44) G. Opitz and H. Mildenberger, Angew.Chem., 1960, 72, 169 and Annalen, 1961, 649, 26

45) G. Opitz, H. Mildenberger and H. Suhr, Annalen, 1961, 649, 47

46) R.E. Wolff, Bull.Soc.Chim.France, 1965, 2472

47) M.E. Herr and F.W. Heyl, J.Amer.Chem.Soc., 1953, 75, 5927

48) M.E. Herr, J.A. Hogg and R.H. Levin, J.Amer.Chem.Soc., 1956, 78, 500

49) M.E. Kuehne and T.J. Giacobbe, J.Org.Chem., 1968, 33, 3359

50) R.B. Gabbard and E.V. Jensen, J.Org.Chem., 1958, 23, 1406; ref.12 p416

51) B.J. Magerlein and F. Kagan, U.S. Patent 3,232,960; C.A., 1966, 64, 11287

52) S. Nakanishi, R.L. Morgan and E.V. Jensen, Chem. and Ind., 1960, 1136

53) R. Joly and J. Warnant, Bull.Soc.Chim.France, 1961, 569

54) S. Nakanishi and E.V. Jensen, J.Org.Chem., 1962, 27, 702

55) D.H.R. Barton, L.S. Godinho, R.H. Hesse and M.M. Pechet, Chem.Commun., 1968, 804

56) E. Biekert and H. Kössel, Annalen, 1963, 662, 93

57) R. Tiolais, H. Bouget, J. Huet and A. LePennec, Bull.Soc.Chim. France, 1964, 1205

58) R.L. Pederson, J.L. Johnson, R.P. Holysz and A.C. Ott, J.Amer.Chem.Soc., 1957, 79, 1115

59) J.C. Babcock, J.A. Campbell and R.L. Pederson, U.S. Patent 3,098,850; C.A., 1963, 59, 14067b

60) British Patent 885,756)
)
61) British Patent 887,080)
) ref.10 p86
62) U.S. Patent 2,990,400)
)
63) U.S. Patent 3,019,237)

64) G.I. Fujimoto and R.W. Ledeen, J.Org.Chem., 1964, 29, 2059

65) Y. Mazur and F. Sondheimer, J.Amer.Chem.Soc., 1958, 80, 5220

66) M.E. Kuehne, Synthesis, 1970, 510

67) M.S. Manhas and J.R. McCoy, J.Amer.Chem.Soc.(C), 1969, 1419

68) A.K. Bose, G. Mina, M.S. Manhas and Rzucidlo, Tetrahedron Letters, 1963, 1467

69) R.M. Scribner, Tetrahedron Letters, 1967, 4737

70) R. Huettenrauch, Pharmazie, 1967, 22, 179; C.A. 67, 43999h

71) R.B. Woodward, I.J. Pachter and M.L. Scheinbaum, J.Org.Chem., 1971, 36, 1137

72) R.B. Woodward, A.A. Patchett, D.H.R. Barton, D.A.J. Ives and R.B. Kelly, J.Chem.Soc., 1957, 1131

73) G.K. Trivedi, P.S. Kalsi and K. Chakravarti, Tetrahedron, 1964, 20, 2631

74) W. Fritsch, J. Schmidt-Thomé, H. Ruschig and W. Haede, Chem.Ber., 1963, 96, 68

75) J. Schmidt-Thomé and W. Fritsch, Annalen, 1963, 662, 27

76) J.A. Marshall and W.S. Johnson, J.Org.Chem., 1963, 28, 421

77) W.S. Johnson, V.T. Bauer and R.W. Franck, Tetrahedron Letters, 1961, 72

78) A.P. Shroff, J.Med.Chem., 1965, 8, 881; C.A. 1965, 63, 18199

79) M. Davis, E.W. Parnell and D. Warburton, J.Chem.Soc.(C), 1966, 1688

80) Ibid, 1966, 1698

81) M. Davis, E.W. Parnell and J. Rosenbaum, J.Chem.Soc.(C), 1966, 1983

82) J. Gore and J.J. Barieux, Tetrahedron Letters, 1970, 2849

83) J.J. Panouse, J. Schmitt, P.J. Cornu, A. Hallot, H. Pluchet and P. Comoy, Bull.Soc.Chim.France, 1963, 1753

84) Ibid, 1963, 1761

85) Ibid, 1963, 1767

86) J. Schmitt, J.J. Panouse, P. Comoy, P.J. Cornu, A. Hallot and H. Pluchet - ibid, 1963, 798

87) J. Schmitt, J.J. Panouse, A. Hallot, P.J. Cornu and H. Pluchet - ibid, 1963, 807

88) J. Schmitt, J. J. Panouse, A. Hallot, H. Pluchet, P. Comoy and P.J. Cornu - ibid, 1963, 816

89) F. Kasper, Z.Chem., 1965, 5, 53, quoted in ref. 12 p430

90a) J. Schmitt, J.J. Panouse, P.J. Cornu, H. Pluchet, A. Hallot and P. Comoy - Bull.Soc.Chim.France, 1964, 753

90b) J. Schmitt, J.J. Panouse, H. Pluchet, P. Comoy and P.J. Cornu - ibid, 1964, 771

91) U.K. Pandit, F.R. MasCabre, R.A. Gase, M.J. De Nie-Sarink, Chem.Comm., 1974, 627

92) U.K. Pandit, R.A. Gase, F.R. MasCabre, M.J. De Nie-Sarink, Chem.Comm., 1975, 211

93) Ref. 12 p321

94) C. Djerassi, N. Crossley and M.A. Kielczevski, J.Org.Chem., 1962, 27, 1112

95) N.S. Crossley, C. Djerassi and M.A. Kielczevski, J.Chem.Soc., 1965, 6253

96) L. Velluz, G. Nominé, R. Bucourt, A. Pierdet and Ph. Dufay, Tetrahedron Letters, 1961, 127

97) U.K. Pandit and S.A.G. de Graaf, Chem.Comm., 1970, 381

98) M.E. Kuehne and J.C. King, J.Org.Chem., 1973, 38, 304

99) J. Meinwald and A.J. Taggi, J.Amer.Chem.Soc., 1973, 95, 7663

100) F. Schneider, A. Boller, M. Mueller, P. Mueller and A. Fuerst, Helv.Chim.Acta, 1973, 56, 2396

101) R.G. Christiansen (Sterling Drug Co.), U.S. Patent 3,287,355; C.A., 1967, 66, P38145b

102) M.S. Manhas, J.W. Brown and U.K. Pandit, Heterocycles, 1975, 117

103) M.S. Manhas and J.R. McCoy, J.Chem.Soc.(C), 1969, 1419

104) P. Houndewind, J.C.L. Armande and U.K. Pandit, Tetrahedron Letters, 1974, 591

105) U.K. Pandit, F.A. van der Vlugt and A.C. van Dalen, Tetrahedron Letters, 1969, 42, 3697

106) U.K. Pandit, K. de Jonge, K. Erhart and H.O. Huisman, Tetrahedron Letters, 1969, 15, 1207

107) U.K. Pandit, K. de Jonge, G.J. Koomen and H.O. Huisman, Tetrahedron Letters, 1967, 36, 3529

108) U.K. Pandit and H.O. Huisman, Tetrahedron Letters, 1967, 40, 3901

109) U.K. Pandit, K. de Jonge and H.O. Huisman, Rec.Trav.Chim., 1969, 88, 149

110) U.K. Pandit, M.J.M. Pollmann and H.O. Huisman, Chem.Comm., 1969, 527

111) M.J.M. Pollmann, H.R. Reus, U.K. Pandit and H.O. Huisman, Rec.Trav.Chim., 1970, 929

112) M.J.M. Pollman, U.K. Pandit and H.O. Huisman, Rec.Trav.Chim., 1970, 941

113) U.K. Pandit, F.A. van der Vlugt, A.C. van Dalen, A.H. Joustra and H. Schenk, Tetrahedron Letters, 42, 1969, 3693

114) E.B. Hershberg, E. Oliveto, M. Rubin, H. Staeudle and L. Kuhlen, J.Amer.Chem.Soc., 1951, 73, 1144

115) L.F. Fieser and X.A. Dominquez, J.Amer.Chem.Soc., 1953, 75, 1704

116) K. Bowden, I.M. Heilbron, E.R.H. Jones and B.C.L. Weedon, J.Chem.Soc., 1946, 39

117) F.L. Weisenborn and H.E. Applegate, J.Amer.Chem.Soc., 1959, 81, 1960

118) A. Butenandt, K. Tscherning and G. Hanisch, Ber., 1935, 68, 2097

119) "Dictionary of Organic Compounds", 1965, Eyre and Spottiswoode, London

120) A. Butenandt, H. Dannenbaum, G. Hanisch and H. Kudszus, Z.Physiol.Chem., 1935, 237, 57

121) A.L. Wilds and N.A. Nelson, J.Amer.Chem.Soc., 1953, 75, 5366

122) C. Chen, Tetrahedron, 1958, 3, 43

123) R.D. Youssefyeh, J.Amer.Chem.Soc., 1963, 85, 3901

124) Ref. 10, p98 (taken from H.K. Landesman, Ph.D. thesis, Columbia University, 1956, p46

125) G. Stork, H.K. Landesman, J.Amer.Chem.Soc., 1956, 78, 5128

126) A.J. Birch, J.Chem.Soc., 1944, 430

127) R.L. Augustine, J.Org.Chem., 1958, 23, 1853

128) P. Block, Organic Syntheses, 1960, 40, 27

129) A.F. Ferris, J.Org.Chem., 1955, 20, 780

130) J.M. McEuen, R.P. Nelson and R.G. Lawton, J.Org.Chem., 1970, 35, 690

131) H. Bestian, Annalen, 1949, 566, 210

132) L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis" (vol. 1), John Wiley, 1967

133) "Organic Reactions (vol. 11)", p380, John Wiley, London, 1960

134) I. Ostromisslensky, J.Prakt.Chim., 1911, 84, 489

135) Y. Mazur and F. Sondheimer, J.Amer.Chem.Soc., 1958, 80, 5220

136) G. Stork and H.K. Landesman, J.Amer.Chem.Soc., 1956, 78, 5129

137) L.J. Morris, Chem. and Ind. 1962 (Pt. 2), 1238

138) T.C. Miller and R.G. Christiansen, J.Org.Chem., 1964, 29, 3612

139) Ref. 10, p10

140) Weissberger, Proskauer, Riddich and Toops "Organic Solvents" (2nd ed.), 1955, Interscience, New York and London

141) J. Timmermans "Physico-Chemical Constants of Pure Organic Compounds", 1950, Elsevier, Amsterdam

142) J.S. Marchese, Ph.D. thesis, 1964, University of Maryland, College Park, cited in ref. 12, p62

143) Ref. 12, p118

144) A.A. Brizzolara, Ph.D. thesis, 1960, Columbia University, cited in ref. 10, p28

145) J.C. Babcock, J.A. Campbell and R.L. Pederson (to Upjohn Co.) British Patent 889 330; C.A., 1962, 57, P2289b

146) Ibid. - German Patent 1 117 114; C.A., 1962, 57, P15 192c

147) B. Fuchs and H.J.E. Loewenthal, Tetrahedron, 1960, 11, 199

148) M. Mousseron, F. Winternitz, A.C. de Paulet, Compt.Rend., 1957, 245, 1859

149) O. Engelfried and M. Schenck, German Patent 1, 117, 112 (May 17, 1962)

150) S.K. Malhotra, Ph.D. thesis, 1961, Columbia University, cited in ref. 10, p29

151) H.K. Landesman, Ph.D. thesis, 1956, Columbia University, cited in ref. 10, p37

152) J.B. Stothers, "Carbon-13 NMR Spectroscopy", 1972, Academic Press, New York and London

153) British Patent 885,756

154) British Patent 887,080

155) U.S. Patent 2,990,400

156) U.S. Patent 3,019,237

157) P. Toft and A.J. Liston, Tetrahedron, 1971, 27, 969

158) D.H.R. Barton and A.J. Head, J.Chem.Soc., 1956, 932

159) D.H.R. Barton, A.J. Head and P.J. May, J.Chem.Soc., 1957, 935

160) D.H.R. Barton, J. McCapra, P.J. May and F. Thudium, J.Chem.Soc., 1960, 1297

161) M.E. Kuehne and L. Foley, J.Org.Chem., 1965, 30, 4280

162) H. Feuer, A. Hirschfeld and E.D. Bergmann, Tetrahedron, 1968, 24, 1187

163) A. Risaliti, S. Fatutta, M. Forchiassin and E. Valentin, Tetrahedron Letters, 1966, 17, 1821

164) A. Risaliti, M. Forchiassin and E. Valentin, Tetrahedron Letters, 1966, 51, 6331

165) A. Risaliti, L. Marchetti and M. Forchiassin, Ann.Chim.Rome, 1966, 56, 317, quoted in ref. 164

166) A. Risaliti, M. Forchiassin and E. Valentin, Tetrahedron, 1968, 24, 1889

167) P.W. Hickmott, Proc.Chem.Soc., 1964, 287

168) J.R. Hargreaves and P.W. Hickmott, Tetrahedron Letters, 1966, 35, 4173

169) P.W. Hickmott and J.R. Hargreaves, Tetrahedron, 1967, 23, 3151

170) P.W. Hickmott, G.J. Miles, G. Sheppard, R. Urbani, C.T. Yoxall, J.Chem.Soc. (Perkin I), 1973, 1514

171) P.W. Hickmott, P.J. Cox and G.A. Sim, J.Chem.Soc. (Perkin I), 1974, 2544

172) J.P. Schaefer, J.C. Lark, C.A. Flegal and L.M. Honig, J.Org.Chem., 1967, 32, 1372

173) A.C. Cope, D.L. Neally, P. Scheiner, G. Wood, J.Amer.Chem.Soc., 1965, 87, 3130

174) R.N. Schut and T.M.H. Liu, J.Org.Chem., 1965, 30, 2845

175) R.A. Appleton, K.H. Baggeley, C. Egan, J.M. Davies, S.H. Graham, D.O. Lewis, J.Chem.Soc.(C), 1968, 2032

176) K.G. Untch, Ph.D thesis, 1959, Columbia University, cited in ref. 10, p38

177) L.A. Paquette, Tetrahedron Letters, 1965, 1291

178) L.A. Paquette and H. Stucki, J.Org.Chem., 1966, 31, 1232

179) Ref. 25, p70

180) J.E. Dolfini and J.D. Simpson, J.Amer.Chem.Soc., 1965, 87, 4381.

181) S.F. Dyke, Chemistry of Enamines, Cambridge University Press (1973)

182) Terpenoids and Steroids Vol. 1 (1971) - Vol. 6 (1976), The Chemical Society

183) K. Taguchi and F.H. Westheimer, J.Org.Chem., 1971, 36, 1570

184) M.E. Kuehne and G. Di Vincenzo, J.Org.Chem., 1972, 37, 1023

185) P. Bolla and M. Legrand, Bull.Soc.Chim.France, 1973, 2143

186) J.E. Huber, Tetrahedron Letters, 1968, 3271

187) S.K. Malhotra, J.J. Hostynek and A.F. Lundin, J.Amer.Chem.Soc., 1968, 90, 6565

188) S.A.G. De Graaf and U.K. Pandit, Tetrahedron, 1974, 30, 1115

189) R. Bücourt and J. Dubé, Bull.Soc.Chim.France, 1974, 479

190) A.H. Janoski, F.C. Shulman and G.E. Wright, Steroids, 1974, 23, 49, quoted in ref. 182, vol. 5

191) M.S. Manhas, J.W. Brown, U.K. Pandit and P. Houndewind, Tetrahedron, 1975, 31, 1325

192) S. Schwartz, W. Pohnert, A. Stachowisk and D. Onken, Experientia, 1963, 19, 128, quoted in ref. 91

193) M.E. Kuehne, J.Org.Chem., 1963, 28, 2124

194) U.K. Pandit and H. Bieraugel, Rec.Trav.Chim., 1976, 95, 223

195) I. Basco, U.S. Patent 3978048; CA, 1977, 86, 29998t

196) J.A. Peters, J.M. Van Der Toorn and H. Van Bekkum, Tetrahedron, 1974, 30, 633

197) J.R. Hanson and T.D. Organ, J.Chem.Soc.(C), 1970, 1065

198) J.W. Ap Simon, P.V. Demarco, D.W. Mathieson, W.G. Craig, A. Karim, L. Saunders and W.B. Whalley, Tetrahedron, 1970, 26, 119

199) P.A. Kollman, D.D. Giannini, W.L. Duax, S. Rothenberg and M.E. Wolff, J.Amer.Chem.Soc., 1973, 95, 2869

200) C.S. Dean, J.R. Dixon, S.H. Graham and D.O. Lewis, J.Chem.Soc.(C), 1968, 1491

201) H. Singh and D. Paul, J.Chem.Soc. (Perk. I), 1974, 1475

202) G. Nathansohn, E. Testa, N. Di Mola, Experientia, 1962, 18, 57, quoted in ref. 12 p441.