THE CHEMISTRY OF 1,2,3-TRIAZOLES AND RELATED HETEROCYCLES

by

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SUMMARY

The syntheses and reactivity of heterocycles containing a vicinal triazole ring have been studied. The condensation of 2-azidobenzonitrile with substituted acetonitriles in the presence of alkoxide ion affords the 5-amino-1,2,3-triazolo[1,5-a]quinazoline ring system, which when substituted in the 3-position with electron donating or weak electron withdrawing groups undergoes triazole scission to yield 2-substituted quinazolines. Triazole scission is observed to occur in trifluoroacetic acid at room temperature, and the reaction sequence is followed by proton magnetic resonance spectroscopy. Transformations of substituted benzylquinazolines are reported.

The triazolo[3,4-a]pyrimidine ring system is synthesised by the acid- or base-catalysed condensation of substituted 5-amino-1-H-1,2,3-triazoles with various β-dicarbonyl compounds. Intermediate acylated aminotriazoles are isolated, allowing study of the orientation of the condensation reactions. Isomerisation of triazolopyrimidines by a Dimroth rearrangement process is reported. Triazole scission and rearrangement of triazolopyrimidines are examined by proton magnetic resonance spectroscopy. Substituted benzylpyrimidines are prepared by the acid-catalysed triazole scission of triazolopyrimidines.

1,2,3-triazolo[5,1-c]benzo-1,2,4-triazines are synthesised by oxidation of 5-amino-1-(2-aminophenyl)-1,2,3-triazoles, and their stability towards acidic conditions

investigated. A new and simple route to halogenated 1,2,3-triazoles is presented.

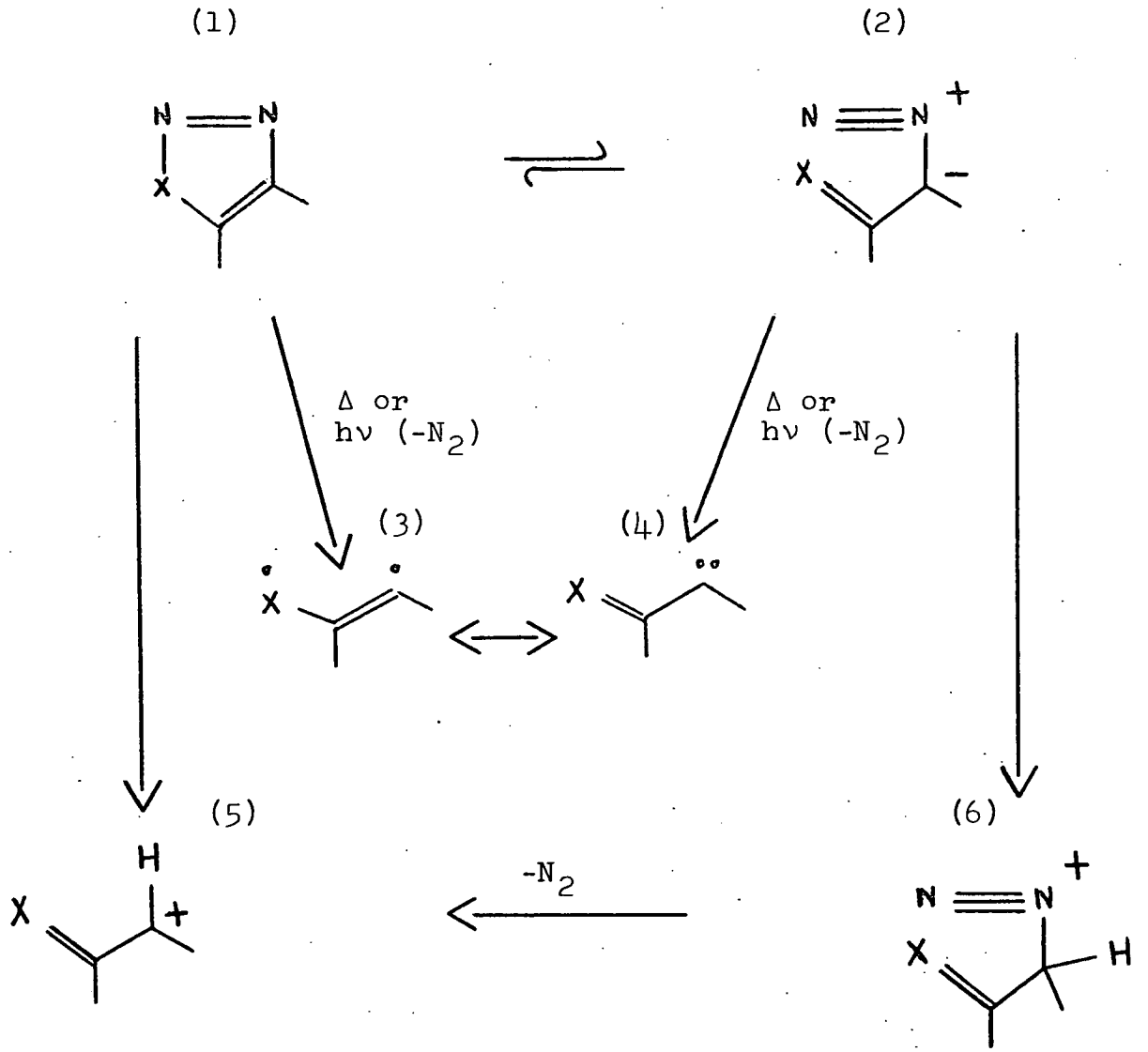
It is shown that 5-aminotriazoles undergo Dimroth rearrangement in polar and non-polar solvents. The acylation of aminotriazoles and acylated aminotriazoles in acetic anhydride is shown to involve a complex series of rearrangements, and gives an insight into the mechanism of the Dimroth rearrangement. The triazolo[4,3-d]pyrimidine ring system is synthesised by the action of aqueous alkali on suitably substituted aminotriazoles.

CONTENTS

PART 1

GENERAL INTRODUCTION

Heterocyclic nuclei of the general type (1) containing a pair of adjacent nitrogen atoms are potentially reactive by virtue of the driving force for loss of the stable nitrogen molecule. Compounds containing nuclei of

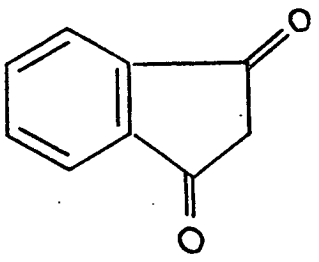


a) X = NR
b) X = O
c) X = S

Scheme 1

this type might therefore be expected to undergo ring scission to yield products derived from such reactive intermediates as diradicals (3), carbenes (4) or carbonium ions (5). Since it is conceivable that the loss of nitrogen may occur directly, or after ring opening, the study of the reactivity of such heterocyclic nuclei is also concerned with the possibility of ring-chain tautomerism [(1) $\rightleftharpoons$ (2)] and the intervention of diazo (2) and diazonium (6) intermediates. The study of certain of these aspects of chemical reactivity in compounds containing the vicinal triazole nucleus (1a) constitutes the subject material of the following thesis.

Ring-chain tautomerism has been observed in compounds of the general type (1). The diazotisation of unsymmetrically substituted aminoketones (7) gives only one product which is formulated as the diazoketone (8) rather than either of the two possible isomeric 1,2,3-oxadiazoles (9) or (10).[1] This result suggests that the equilibrium [(8) $\rightleftharpoons$ (9) or (10)] lies entirely in favour of the diazo form (8). Regitz and coworkers have prepared many diazoketones of the general type (8)[2] formulating them in the ring-opened form on the basis of the presence of the characteristic diazo absorption in the infra red (i.r.) These compounds were prepared by reacting an active methylene



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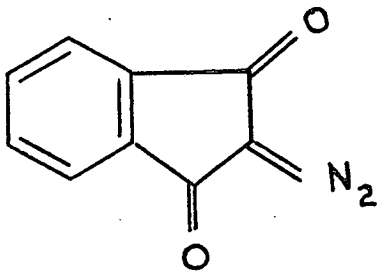

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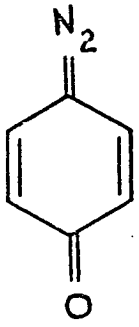

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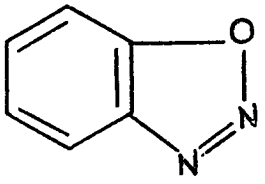

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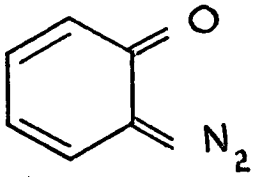

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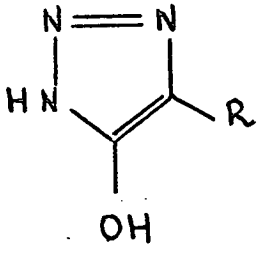

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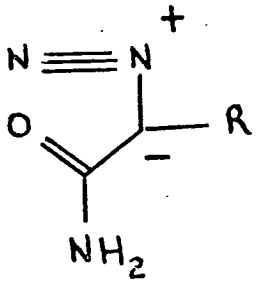

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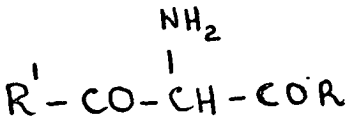

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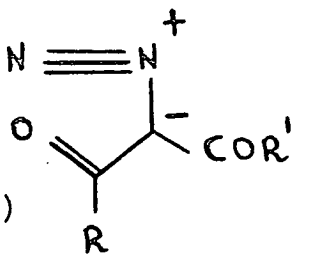

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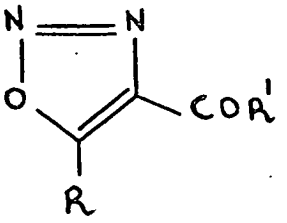

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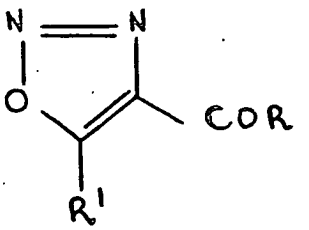
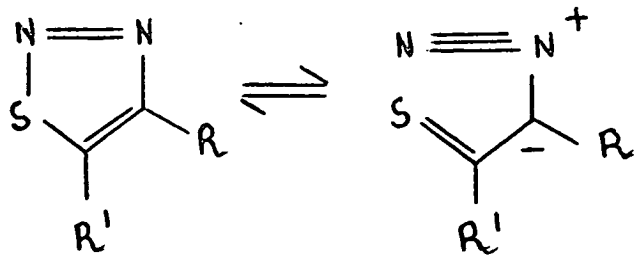


(10)

compound with p-toluenesulphonyl azide in the presence of base,[2] the two active hydrogens being replaced by a diazo group, giving the diazo compound and p-toluenesulphonamide. For example, indane-1,3-dione (11) yields 2-diazoindane-1,3-dione (12) by diazo transfer under basic conditions.[3] In studies of the absorption spectra and dipole moments of 1,2- and 1,4-diazophenols[4,5] it was concluded that 4-diazophenol (13) is quinonoid, and that 2-diazophenol is not bicyclic (14) but also probably quinonoid (15). In his classical studies[6,7,8] on 5-hydroxy-1,2,3-triazoles (16) Dimroth formulated these compounds as the ring-opened diazoamides (17), again indicating the preference for the open chain structure.

In contrast to 1,2,3-oxadiazoles, 1,2,3-thiadiazoles appear to exist in the cyclic form (18), rather than the diazothioketone form (19). This is demonstrated by their synthesis from unsymmetrically substituted diazoketones (8) by the action of phosphorus pentasulphide.[9,10] Both the expected products (20) and (21) are obtained. The

diazoketones (8) may also be converted into derivatives of 1,2,3-triazoles by reaction with amino compounds.



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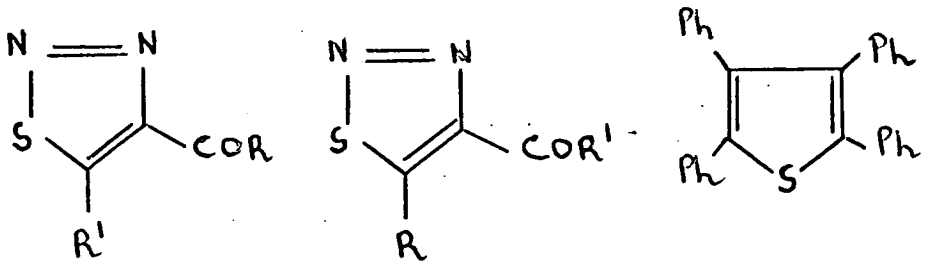
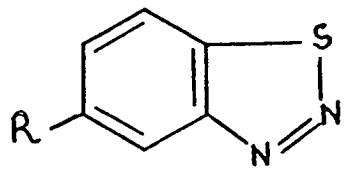


(20) (21) (22)

Although existing preferentially in the ring-closed form (18) 1,2,3-thiadiazoles exhibit reactions which may be attributed to the open-chain form (19). When 4,5-diphenyl-1,2,3-thiadiazole (18, $R=R^1=Ph$) was pyrolysed above 200° the only product isolated was tetraphenylthiophene (22)[11] which may have been formed from a radical species (3c) by initial ring-opening to the diazo form (2c) followed by loss of nitrogen. Alternatively formation of the diradical species (3c) may involve concerted elimination of nitrogen from the thiadiazole (1c). 1,2,3-benzothiadiazoles (23a) may be formed by diazotising 2-aminothiophenols (24),[12] and it is interesting to note that 5-amino-1,2,3-benzothiadiazole



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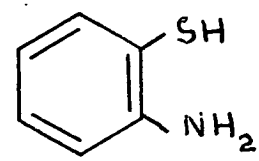


(24)

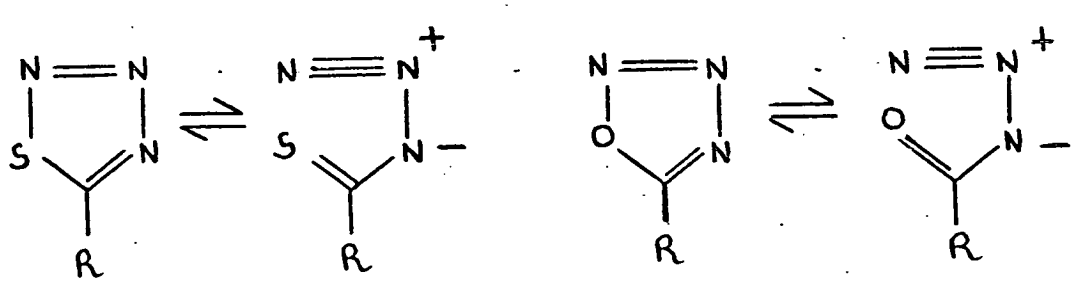
(a) R = H

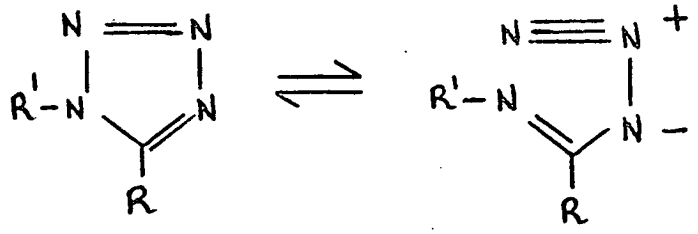
(b) R = NH_2

(23b) fails to undergo a double Sandmeyer reaction after diazotisation,[13,14] furnishing further evidence for the ring-closed structure. Also 1,2,3-benzooxadiazoles (14) readily undergo direct coupling with alkaline 2-naphthol, whereas 1,2,3-benzothiadiazoles do not react under similar conditions.[13,14] To explain the high degree of stability of the 1,2,3-thiadiazole ring it has been suggested that the ring system, like that of thiophene, may be stabilised by an aromatic sextet.[13,14]

The ring systems 1,2,3,4-oxatriazole (27) and 1,2,3,4-thiatriazole (25) again illustrate the tendency for the oxygen containing system to exist in the open-chain form (28), and the sulphur containing system to exist in the

(25) (26) (27) (28)





(29) (30)

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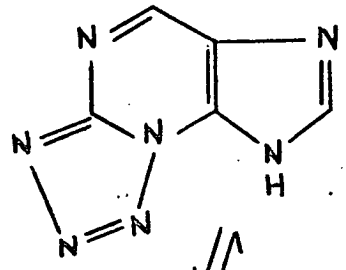

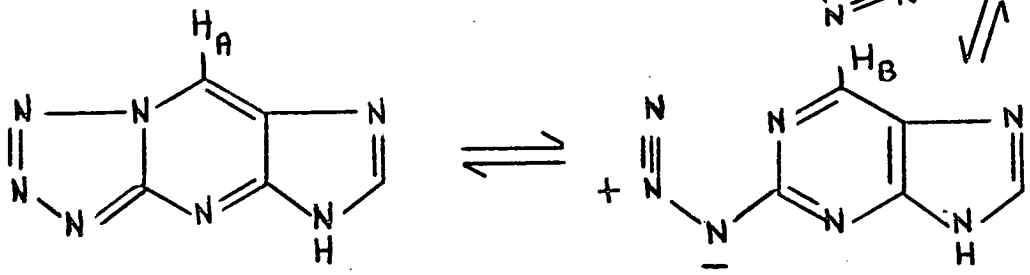

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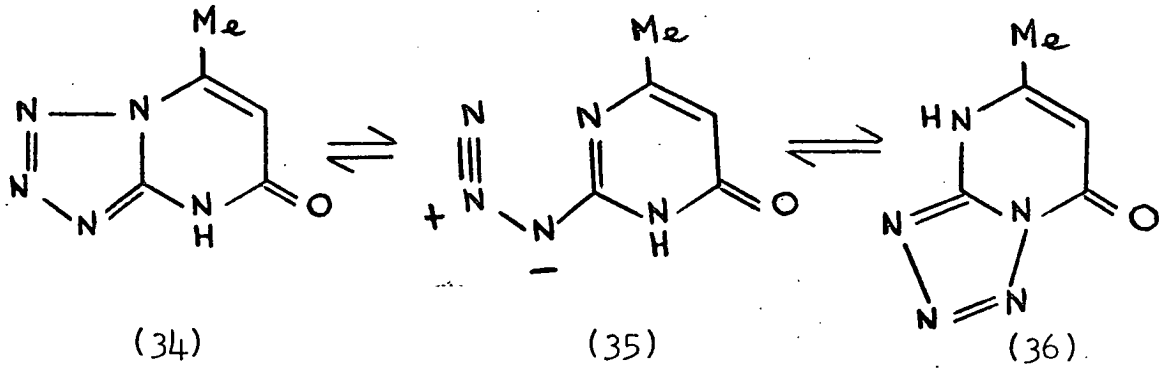
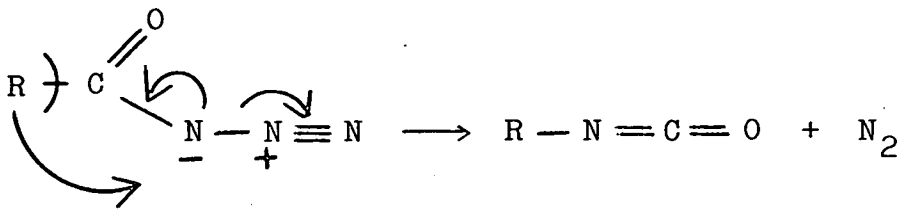


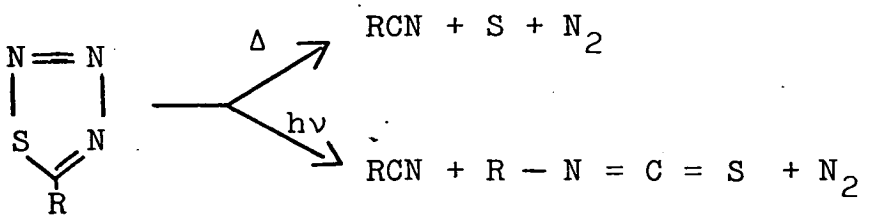
(34) (35) (36)

ring-closed form (25). The acylazide form (28) is very unstable, decomposing to the isocyanate with the loss of nitrogen, on mild pyrolysis (see scheme 2). This has



scheme 2

been explained by a synchronous mechanism involving a Curtius rearrangement (see scheme 2).[15] The existence of the 1,2,3,4-thiatriazole (25) in the ring-closed form is supported by the absence of diazo absorption in the i.r. spectrum.[16,17] 1,2,3,4-thiatriazoles however are relatively unstable, being readily decomposed by heat or light to give mixtures of nitriles, and elemental sulphur or isothiocyanates, (see scheme 3).[18,19]

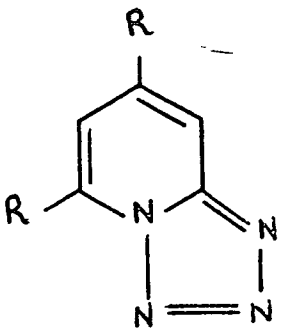


scheme 3

The tetrazole ring system can also exhibit ring-chain tautomerism of the type [(29) ⇌ (30)]. The existence of such azidoazomethine-tetrazole equilibria is now well established by the work of Montgomery and coworkers. These workers demonstrated[23] such equilibria in the tetrazolopurine ring system. Compound (31) was prepared by treatment of the corresponding hydrazine derivative with

nitrous acid,[20] and was shown to exist in the solid state as an equilibrium mixture of the azide (32) and the tetrazole (31). However in trifluoroacetic acid (TFA) or hydrochloric acid only the ring-opened azido form (32) was present, whereas in a solution of deuterated-dimethylsulphoxide (d_6-DMSO) containing TFA the presence of an equilibrium mixture of (31), (32) and the isomeric ring-closed form (33) could be demonstrated. The different species were detected by i.r. spectroscopy, the azide isomer showing a strong absorption at ca. 2100 $cm.^{-1}$, and by variations in the nuclear magnetic resonance (n.m.r.) of the ring protons. The ring proton (H_A) in the tetrazole (31) is more deshielded than the proton (H_B) in the azide form (32) because of the stronger electron withdrawing effect of the tetrazole ring. Similar ring-chain tautomerism was demonstrated in the tetrazolopyrimidines (34)[21] which formed an equilibrium mixture of (35), (36) and (34) in TFA, but existed solely in the ring-closed forms (34) and (36) in d_6-DMSO. In general, in the solid state fused tetrazoles exist mainly in the tetrazolo form as demonstrated by the absence of azide absorption in their solid state i.r. spectra. Azide bands may however be present when the compounds are examined in solution, their intensity depending on the solvent and the temperature. In some cases separation of the azide and tetrazole isomers may be achieved by paper chromatography.[23]

The existence of ring-chain tautomerism [(29) $\rightleftharpoons$ (30)] is also revealed by the reactions of fused tetrazoles, which can be attributed to the presence of the



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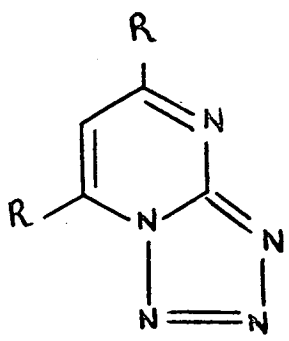

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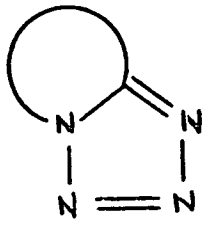

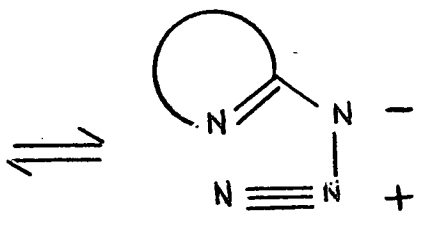

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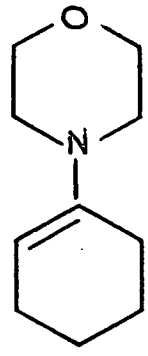

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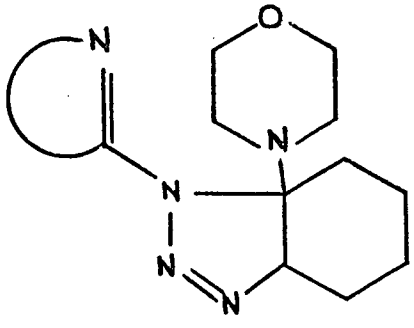

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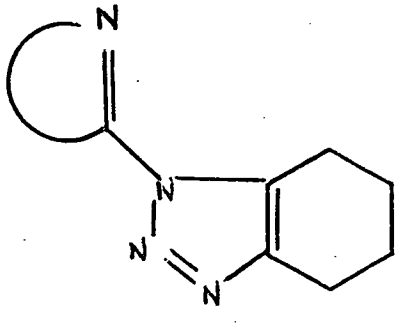

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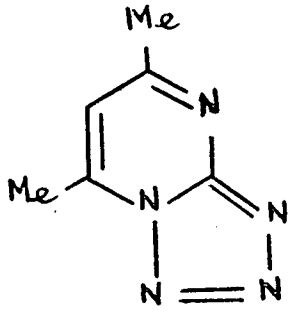
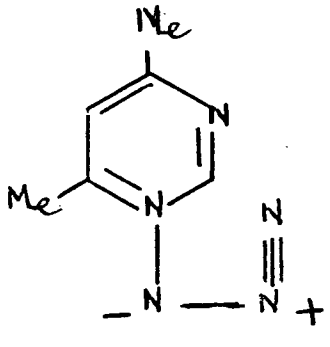
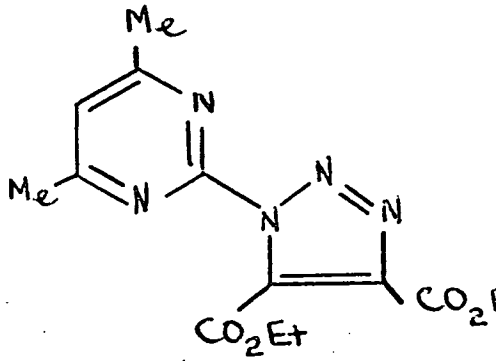




(38a) (44)

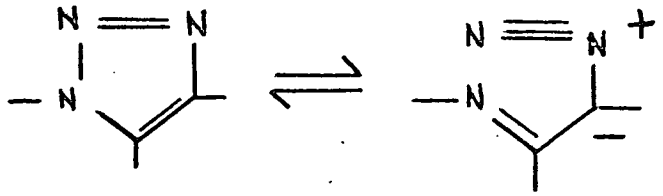


(45)

azide form (30). In particular tetrazolo[1,5-a]pyridines (37) and tetrazolo[1,5-a]pyrimidines (38) react with activated olefins and acetylenes to give adducts derived by addition of the azide dipole to the unsaturated system.[24-27] Considering the fused tetrazoles (37) and (38) as the general structure (39), which may exist as the azide form (40), reaction with α-cyclohexene-N-morpholine (41) afforded the addition compounds (42), which were decomposed into the corresponding fused 1,2,3-triazoles (43) by treatment with alkali.[27] Huisgen and coworkers[24-26] have observed cyclo-addition reactions of tetrazolopyridines (37) and tetrazolopyrimidines (38), which also may be considered to involve the azide tautomer of general form (40). For instance 5,7-dimethyltetrazolo[1,5-a]pyrimidine (38a) reacts with dimethylacetylene dicarboxylate to give the compound (45),[24] presumably by dipolar addition of the azide form (44) across the triple bond of the alkyne.

The existence of a molecule as an azidoazomethine tautomer (30) or as the tetrazole (29) is dependent on the character of the substituents. Compounds with an aryl grouping on carbon (30, R=aryl) and substituted with hydroxy, methoxy or benzoyl groups on nitrogen (30, R^1 = OH, OMe or COPh) exist as the azidoazomethines,[28,29] whereas those with hydrogen or phenyl on nitrogen (29, R^1 = H or Ph) exist as tetrazoles.[28]

The 1,2,3-triazole ring (46) incorporates three adjacent nitrogen atoms and so exhibits a potential for ring-chain tautomerism [(46) ⇌ (47)]. Recently the reaction



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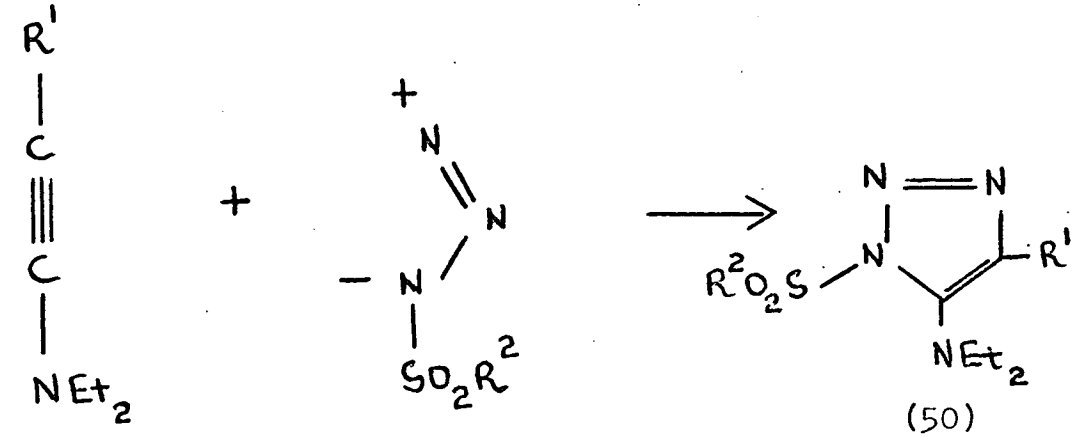

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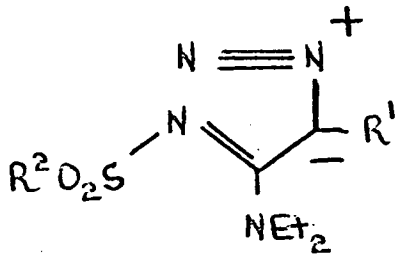

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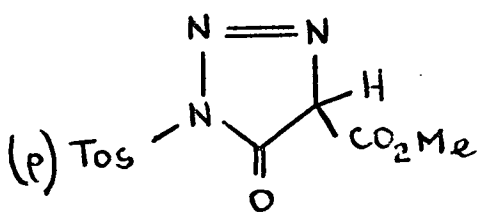

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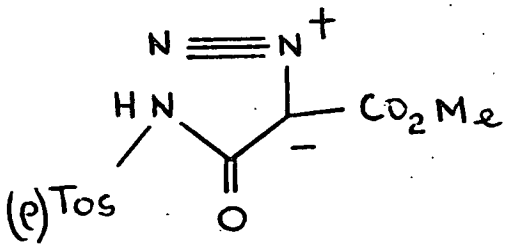
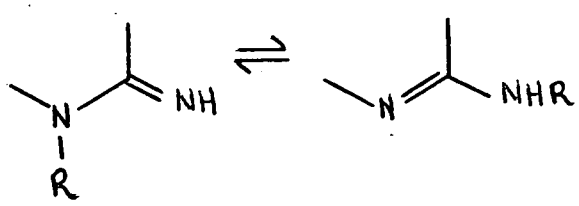


(53)

between the aminoalkyne (48) and the sulphonyl azide (49) has been shown to afford the 1,2,3-triazole (50), which appears to exist partially in the diazo form (51) as demonstrated by the presence of diazo absorption at ca. 2050 $cm.^{-1}$[31] Curtius observed[32] that the reaction between dimethyl malonate and p-toluenesulphonyl azide in the presence of methoxide ion yielded methyl diazomalonate toluene-p-sulphonamide (53), presumably via the triazolone (52).

In its simplest form the Dimroth rearrangement involves a transposition of the type [(54) ⇌ (55)]. The first example was reported by Rathke[33] who found that 4,6-diphenylamino-1,2-dihydro-2-imino-1-phenyl-1,3,5-triazine (56) treated with alcoholic ammonia gave 2,4,6-triphenyl-1,3,5-triazine (57). Later Dimroth[34,35] reported the



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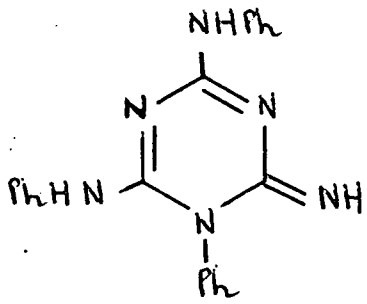

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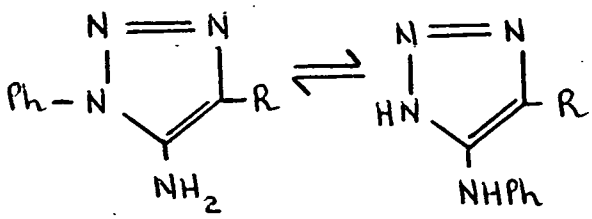

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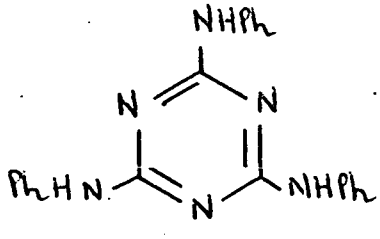
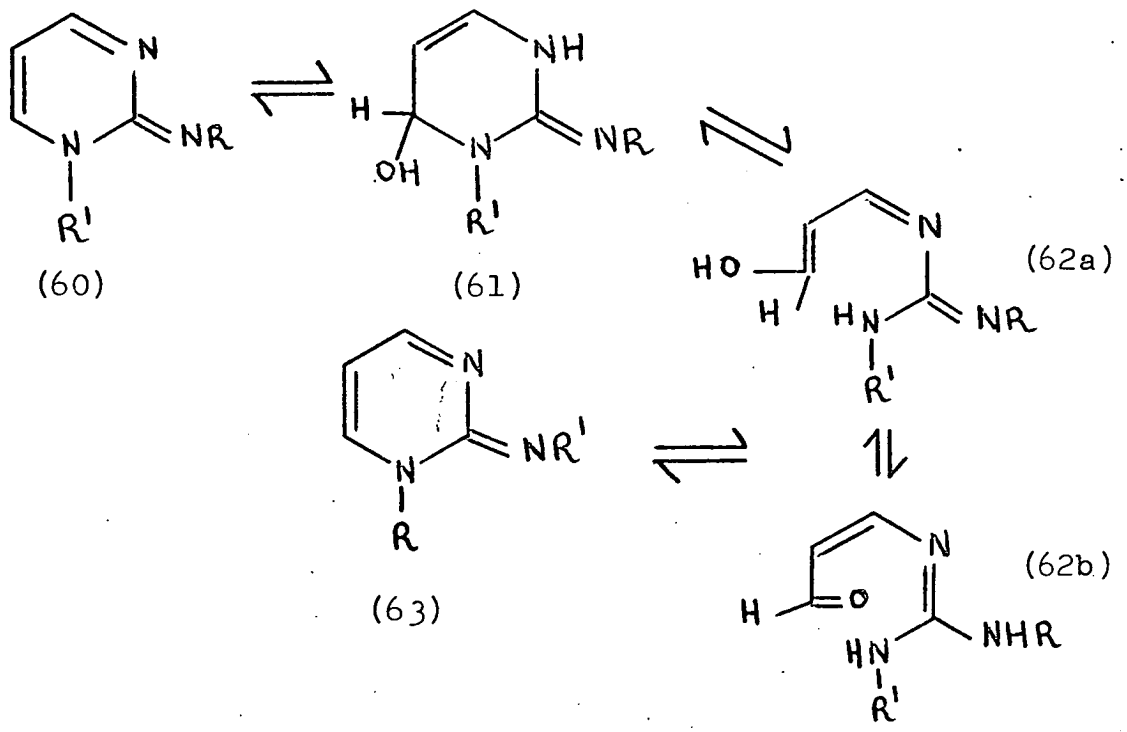


(57)

transformation of 4-substituted-5-amino-1-phenyl-1,2,3-triazoles (58) or 4-substituted-5-phenylamino-1-H-1,2,3-triazoles (59) into the same equilibrium mixtures when either was heated in water or pyridine, or in an homogeneous melt.

Brown, who coined[36] the phrase "Dimroth rearrangement", included both of these types of reaction in the classification, which is perhaps unfortunate as they involve different mechanisms. The process first investigated by Dimroth will henceforth be called the Dimroth rearrangement, and that discovered by Rathke and later extensively studied by Brown and coworkers[37] will be referred to as the pseudo-Dimroth rearrangement. As discussed in detail later ring-chain tautomerism of the type [(46) ⇌ (47)] is an integral feature of the Dimroth rearrangement of 1,2,3-triazoles.

Particular emphasis has been placed on the study of pseudo-Dimroth rearrangements of iminopyrimidines and pteridines. Brown and coworkers have postulated a mechanism[37] which involves hydration, followed by ring-opening to acyclic tautomeric intermediates and cyclisation. At one time[36] the first step of the pseudo-Dimroth rearrangement was thought to be a heterolytic fission but new evidence[38] suggests that the 2-iminopyrimidines (60) in aqueous solution are in rapid equilibrium with the hydrates (61). These reversibly give the acyclic tautomeric intermediates (62a) and (62b) of which part is cyclised to the rearranged product (63). The last step of the reaction sequence is irreversible if (63) is aromatic, i.e. where R = H.

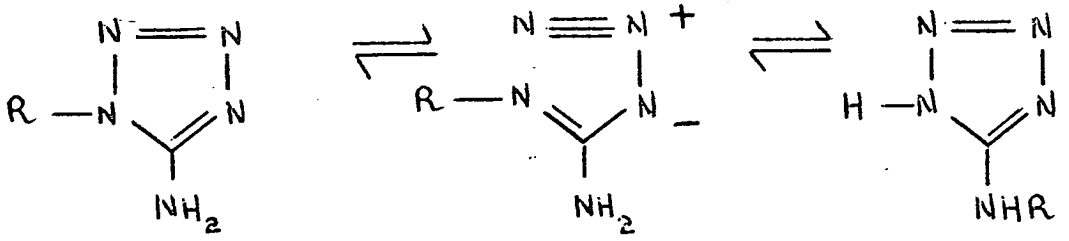


(60) (61) (62a) (63) (62b)

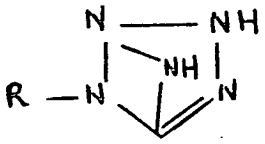
Some of the open-chain compounds (62) undergo degradation to give other products.[37] Strong nucleophiles favour the formation of the hydrates (61), which have been detected spectroscopically, and this reaction has been shown to be first-order. Other evidence for the initial hydration step is that the free amine (60) is stable in dry solvents until a little water is added, causing hydration. Several of the open-chain aldehydes (62b) have been isolated and characterised.[37] Recent results have shown that 1,2-dihydro-2-imino-1-methylpyrimidine (60, R = H, R^1 = Me) heated in dry diethylamine gives an adduct corresponding to (61), except that the nucleophilic attack is by $^-NEt_2$ (61) then ring opens to an enamine which eliminates diethylamine irreversibly to give 2-methylaminopyrimidine. The

formation of an aromatic species forces the equilibrium over to one side. However electronic effects due to substituents have a strong effect on the position of equilibrium when aromatisation cannot occur. It is found that electron withdrawing substituents, which will tend to increase the rate of hydration by reducing the electron density at the site of attack, prefer to reside on the exocyclic nitrogen.[37] In this way the equilibrium is shifted in favour of the isomer having the more electron withdrawing substituent on the side chain. Similarly, because of the reduction in steric strain bulky groups prefer to reside on the side chain. Conversely the more electron donating substituents show a preference for the ring nitrogen. The pyrimidine derivative (60, R = Me, R^1 = H) is stable in dry acetone, ether or dioxane, but in presence of water is converted into an equilibrium mixture in which the more stable isomer (63, R = Me, R^1 = H) predominates.[37]

The true Dimroth rearrangement (see above) as first observed by Dimroth[34] has also been observed for 5-amino-tetrazoles. Dimroth suggested that the reactions proceed through an acyclic diazo or azido intermediate (65), but other workers proposed a bridged bicyclic species (66).[39,40] However the bridged species does not account for the polar effects of substituents revealed by kinetic studies. In any case the high ring strain present in the structure (66) make it an unlikely intermediate.[41] The studies on the triazole isomerisation[41,47,48,53] will be discussed in a later section.

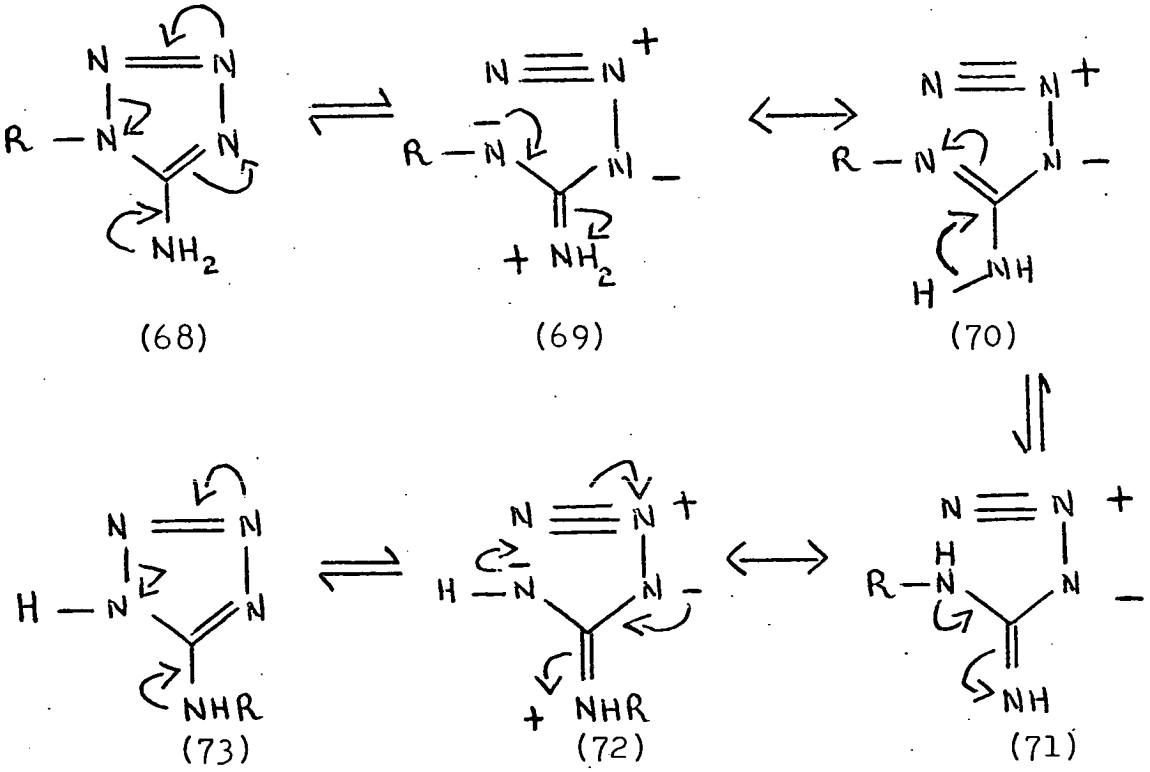


(64) (65) (67)



(66)

1-substituted-5-aminotetrazoles (64) and 5-substituted aminotetrazoles (67) are thermally unstable, and can be isomerised, without decomposition, in glycol or in homogeneous melts.[42] Lieber and coworkers studied the kinetics of this isomerisation, and found that it followed a first order rate law.[42] They showed that the rate of the forward reaction increased with increasing electronegativity of the 1-substituent, and conversely that of the reverse



(68) (69) (70)

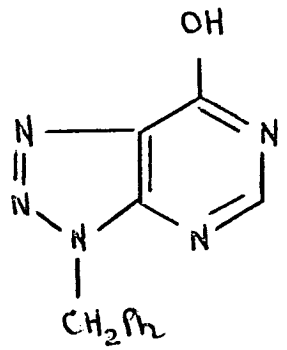
(73) (72) (71)

Scheme 4

reaction (retrogression) decreased with increasing electronegativity of the substituent on the 5-amino group. These substituent effects are in accord with the mechanism shown (scheme 4) for the Dimroth rearrangement of 5-aminotetrazoles. Thus electron withdrawal by the 1-substituent in (68) will stabilise the developing negative charge in the intermediate (69) thereby facilitating the forward process. Conversely electron withdrawal by the 5-substituted amino group in (73) will inhibit the development of the positive charge in (72) thereby retarding the retrogression. The rearrangement also involves proton transfer [(70) $\rightleftharpoons$ (71)].

The formation of an azidoazomethine intermediate (65) is further supported by the conversion of 1-phenyl-5-aminotetrazole (64, R = Ph) in hot aqueous alkali into a mixture of aniline, ammonia and carbonate ion. These are the products expected from the base-catalysed decomposition of phenylguanyl azide.[43,44]

Many other systems undergo Dimroth rearrangement, whether it be the true rearrangement observed for 5-aminotetrazoles or the pseudo rearrangement as exhibited by 2-iminopyrimidines. 1,2,4-triazolo[4,3-a]pyridine (74) when treated with dilute base at 100° is converted into 1,2,4-triazolo[1,5-a]-pyridine (75).[45] This pseudo-Dimroth rearrangement must occur by nucleophilic attack by hydroxide ion on the 4-position of (74) to form the covalent hydrate which ring opens and recyclises in the same manner as discussed above for the rearrangement of iminopyrimidines. Similarly 1,2,4-triazolo[4,3-a]pyrimidines (76) rearrange to



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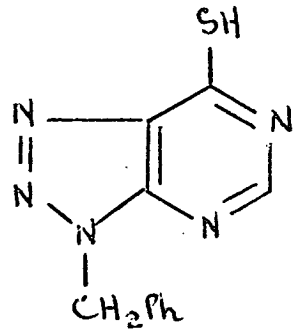

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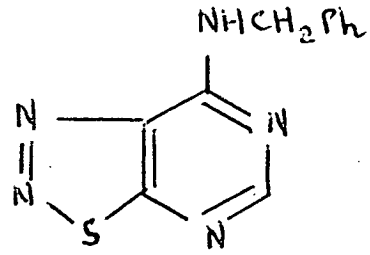

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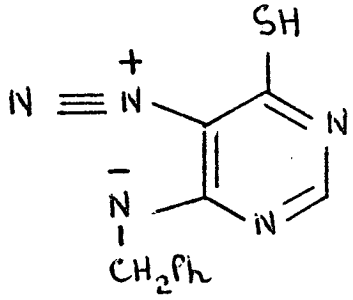
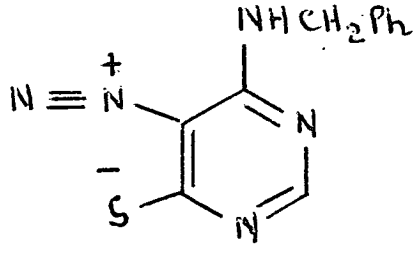
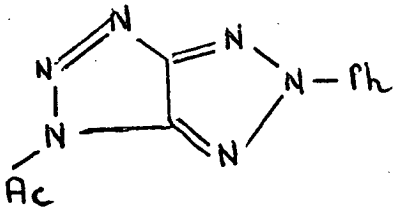


(79a)



(80a)



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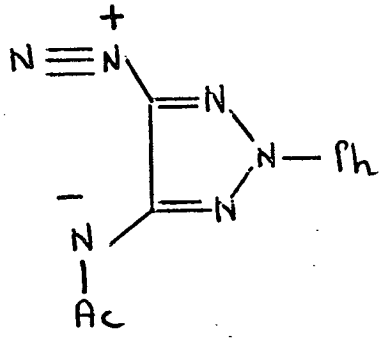

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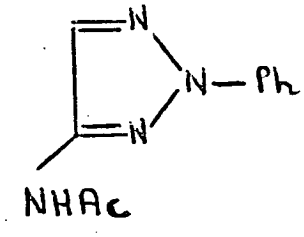
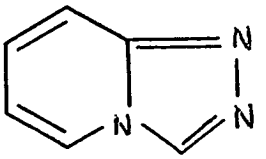


(83)

1,2,4-triazolo[1,5-a]pyrimidines (77),[46] the reaction again being initiated by nucleophilic attack at the 4-position.



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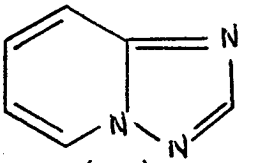

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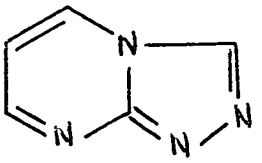

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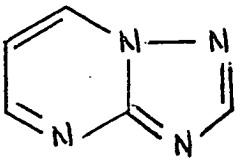
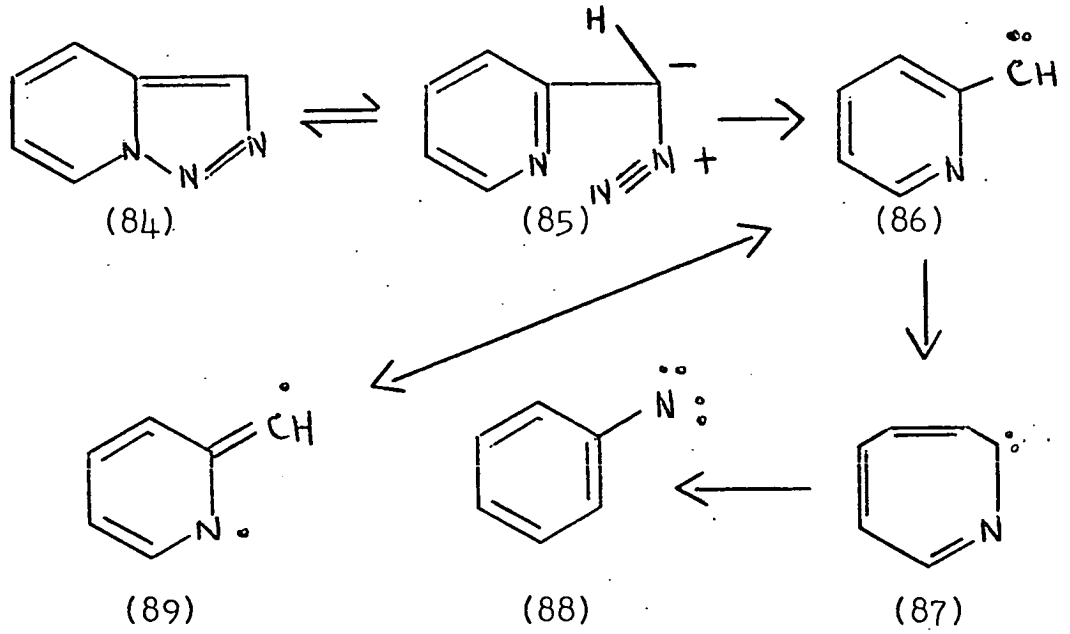


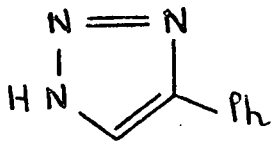
(77)

True Dimroth rearrangements have been observed in the azapurine series. By analogy with the azidoazomethine-tetrazole equilibrium discussed above for tetrazolopurines these rearrangements can be explained by a course involving ring opening to a diazo intermediate. Thus it has been shown[49] that treating 9-benzyl-6-hydroxy-8-azapurine (78) with phosphorus pentasulphide yields an equilibrium mixture of 9-benzyl-6-mercapto-8-azapurine (79) and 7-benzylamino-1,2,3-thiadiazolo[5,4-d]pyrimidine (80). When (80) was refluxed in dilute alkali it rearranged to the sodium salt of (79). Conversely heating the compound (79) in ethanol results in its retrogression to compound (80). The reactions may be explained by initial ring opening to the diazo intermediates (79a) and (80a), followed by subsequent ring closure. These reactions demonstrate the ability of thiadiazoles (80) and triazoles (79) to undergo Dimroth rearrangements, and lend further support to the formation of thiadiazo (80a) and diazoazomethine (79a) intermediates in

reactions of this type.[37,50]

The ready loss of nitrogen on pyrolysis or photolysis of heterocycles containing a pair of adjacent nitrogen atoms has already been discussed in the case of 1,2,3-thiadiazoles[(18, $R = R^1 = Ph$) ⟶ (22)] and 1,2,3,4-thiatriazoles (see scheme 3 above). Thermal and photochemical extrusion of nitrogen is also known in a variety of other heterocyclic ring systems. Pyrolysis of 1-acetyl-1,5-dihydro-5-phenyl-1,2,3-triazolo[4,5-d]-1,2,3-triazole (81) in alcohol occurs with the release of nitrogen and formation of 2-phenyl-4-acetylamino-1,2,3-triazole (83).[51] This reaction could occur by direct loss of nitrogen from the ring closed system (81), or from a ring opened intermediate of the type (82). The pyrolysis of 1,2,3-triazolo[1,5-a]-pyridines (84)[52] which results in the generation of a nitrene (88), presumably via the carbene (86), may proceed by





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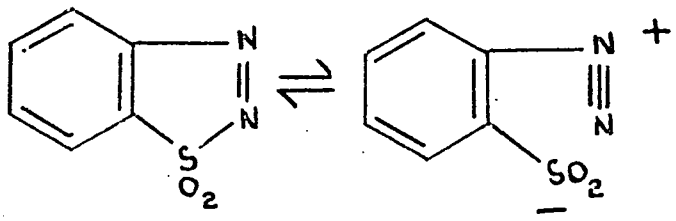

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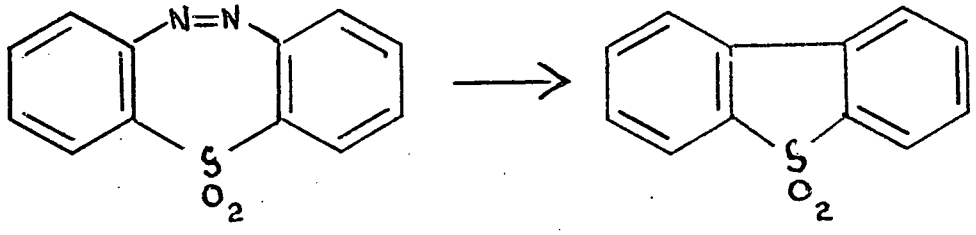
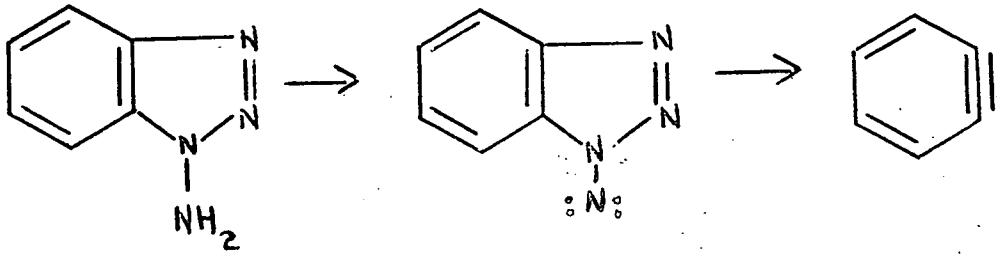


(93) (94)



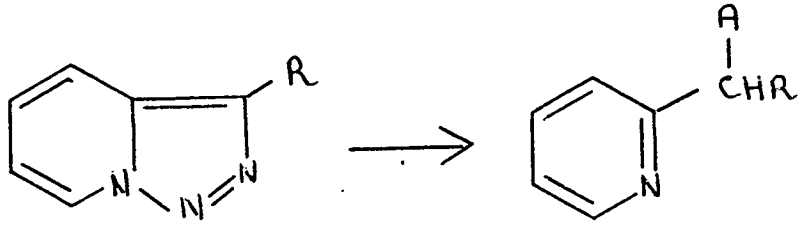
(95) (96) (97)

the initial formation of a diazo tautomer (85). The rearrangement [(86) ⟶ (88)] is thought to occur by carbene insertion into the 2,3-bond of the pyridine ring to give a seven membered ring (87), which then extrudes the pyridine nitrogen onto the 2-carbon affording the nitrene (88). The initial mechanistic stage may however involve the concerted loss of a nitrogen to give a diradical (89) which is a canonical form of the carbene (86). Recently the first example of photolytic cleavage of a 1,2,3-triazole ring with no substituents on the nitrogen atoms has been observed.[54] Photolysis of 4-phenyl-1-H-1,2,3-triazole (90) in methanol results in the loss of nitrogen and formation of phenylacetonitrile.

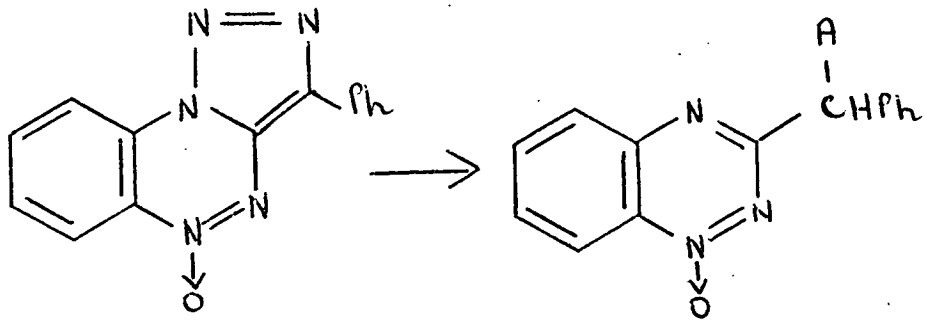
Diazotisation of 2-aminobenzenesulfinic acid does not lead to the diazo compound (92) but to the cyclic isomer (91), which shows no diazo absorption in the i.r.[55] (91) readily decomposes in inert solvents with the evolution of nitrogen and sulphur dioxide yielding benzyne. Azosulphones (91) are generally in equilibrium with the ring opened diazonium sulfinates (92),[56] which couple with alkaline 2-naphthol.[57] However the kinetics of the nitrogen evolution from (91) suggest that direct formation of benzyne is involved. There are only very small solvent and salt effects. It is interesting to note that when the azo group and the sulphone are separated as for instance in (93) the decomposition does not occur until 700°, giving (94) with the evolution of nitrogen.[58] Oxidation of 1-aminobenzotriazole (95) with lead tetraacetate or nickel peroxide in benzene

results in the evolution of nitrogen and generation of benzyne (97).[59] This reaction proceeds via the nitrene intermediate (96).

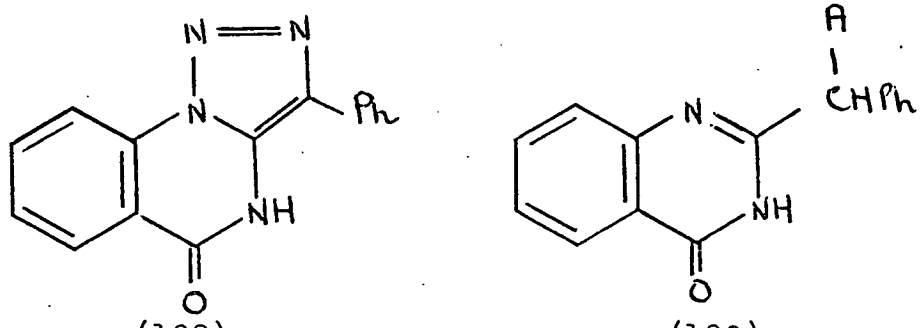
The loss of nitrogen may also occur by displacement of a diazonium group. Substituted 1,2,3-triazolo[3,4-a]-pyridines (98) are converted into 2-substituted pyridines (99) on treatment with acids,[60] although in contrast pyridotetrazoles appear to be stable under acidic conditions.



(98) (99)



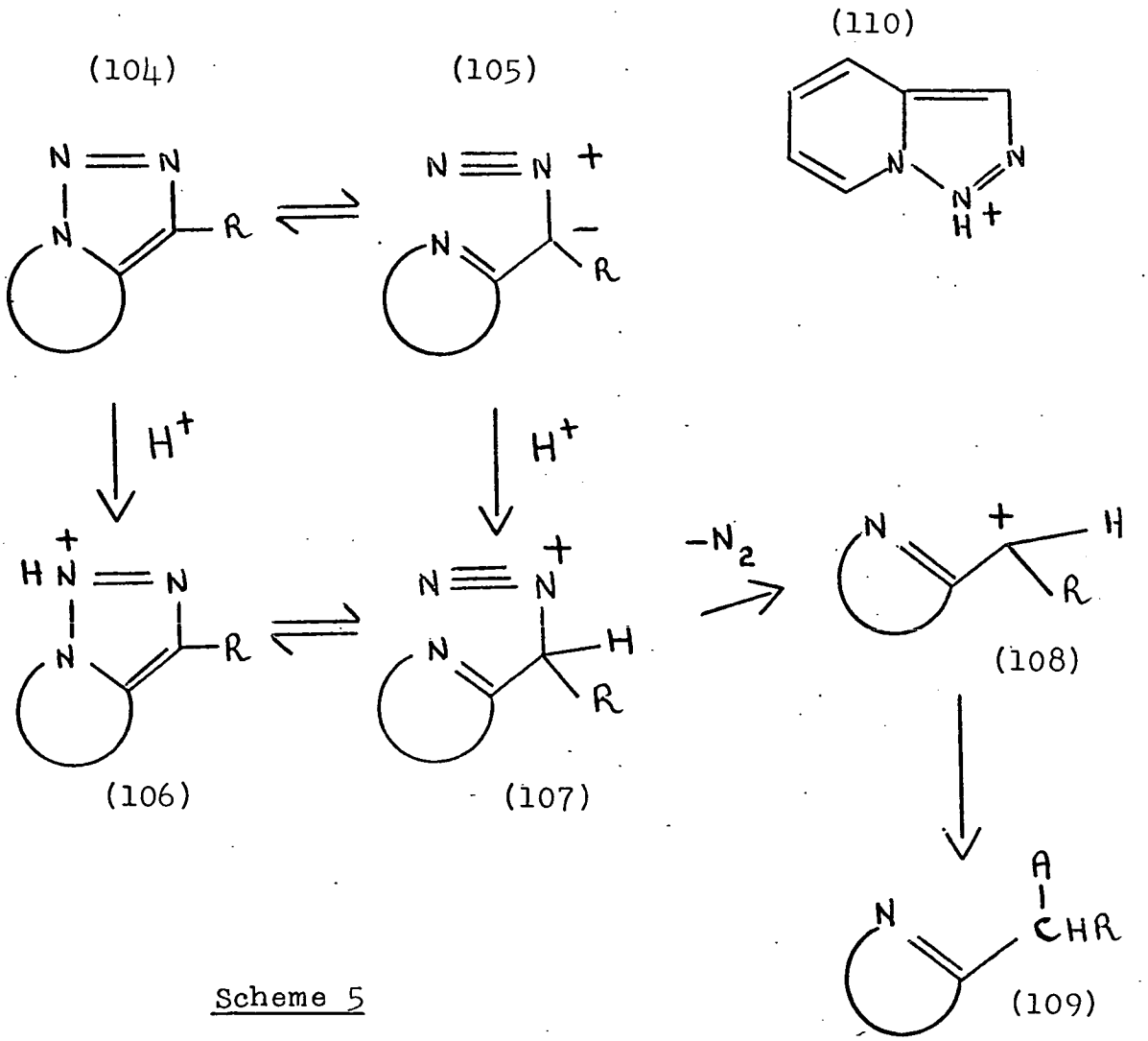
(100) (101)



(102) (103)

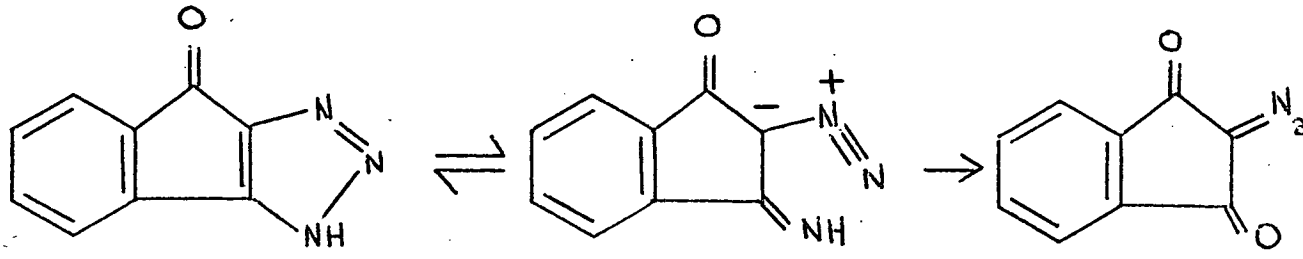
This type of process is also exemplified by the acid-catalysed (HA) conversion of 1,2,3-triazolo[5,1-c]benzo-1,2,4-triazines (100) into 3-substituted benzo-1,2,4-triazines

(101)[61,62] and of 1,2,3-triazolo[1,5-a]quinazolines (102) into 2-substituted quinazolines (103).[63] These reactions may occur via the diazo tautomer (105) (see scheme 5), followed by protonation to give the diazonium salt (107) and loss of nitrogen to yield the carbonium ion (108), which then reacts with the acid, affording the product (109). Alternatively direct ring opening to the diazonium cation (107) may occur without initial formation of the diazo intermediate (105) (see scheme 5). The formation of a conjugate acid (106) has been demonstrated.[60] Acidification of a neutral solution of the triazolopyridine (98) resulted in the disappearance of a band at 280 nm. in the ultra violet (u.v.) spectrum, and the appearance of a band at 267 nm. which has been assigned to the conjugate acid (110).



Scheme 5

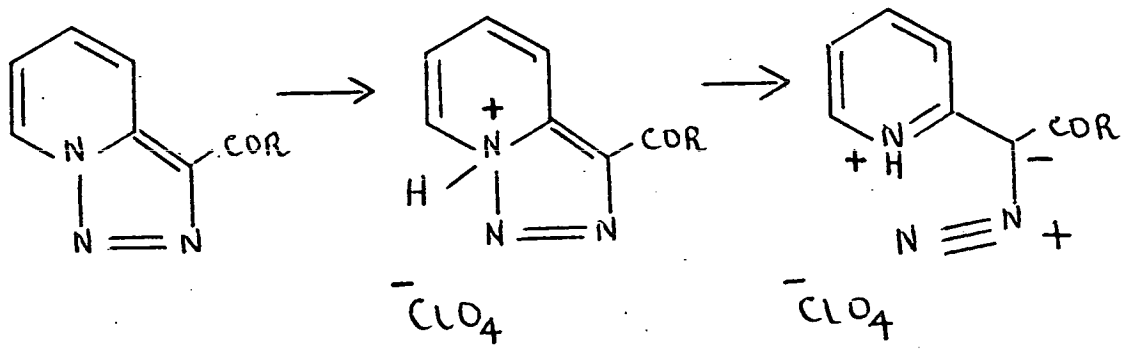
It is therefore possible that the acid-catalysed triazole scission follows the pathway [(104)→(106)→(107)→(108)→(109)] or the pathway [(104)→(105)→(107)→(108)→(109)]. The treatment of 8-oxoindeno[1,2-d]-1,2,3-triazole (111) with warm dilute acid affords 2-diazoindene-1,3-dione (113).[64] This may occur via the diazo species (112), which is then hydrolysed to the dione.



(111) (112) (113)

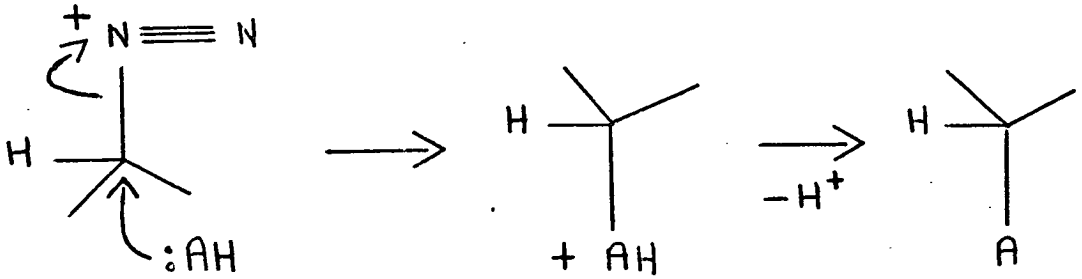
A diazonium cation of the type (115) thought to be involved in these processes as an intermediate has been isolated as the perchlorate. When 3-acyl-1,2,3-triazolo-[3,4-a]pyridine (114) is treated with perchloric acid in

(114) (115) (116)



dioxane a yellow perchlorate (116) is isolated, and can be recyclised in ethanol to the triazolopyridine (114).[65]

Although the acid-catalysed triazole scissions discussed above have been assumed to involve the intermediate formation of a carbonium ion (i.e. by an S_n1 type decomposition of the diazonium intermediate) there is no evidence to exclude the corresponding process involving



(117) (118) (119)

S_n2 displacement of the diazonium group [(117) → (119)].

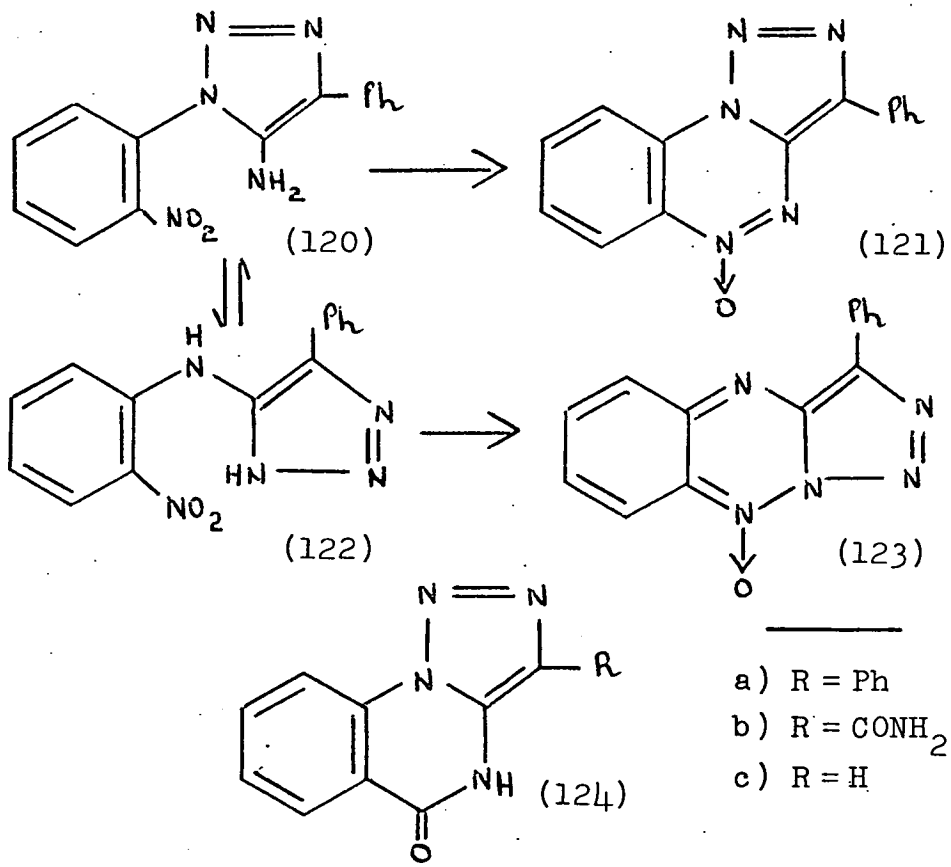
PART 2

DISCUSSION

Part 2. Section 1. (2.1)

The synthesis and reactivity of the 5-amino-1,2,3-triazolo[1,5-a]quinazoline ring system. A synthetic route to 2-substituted quinazolines.

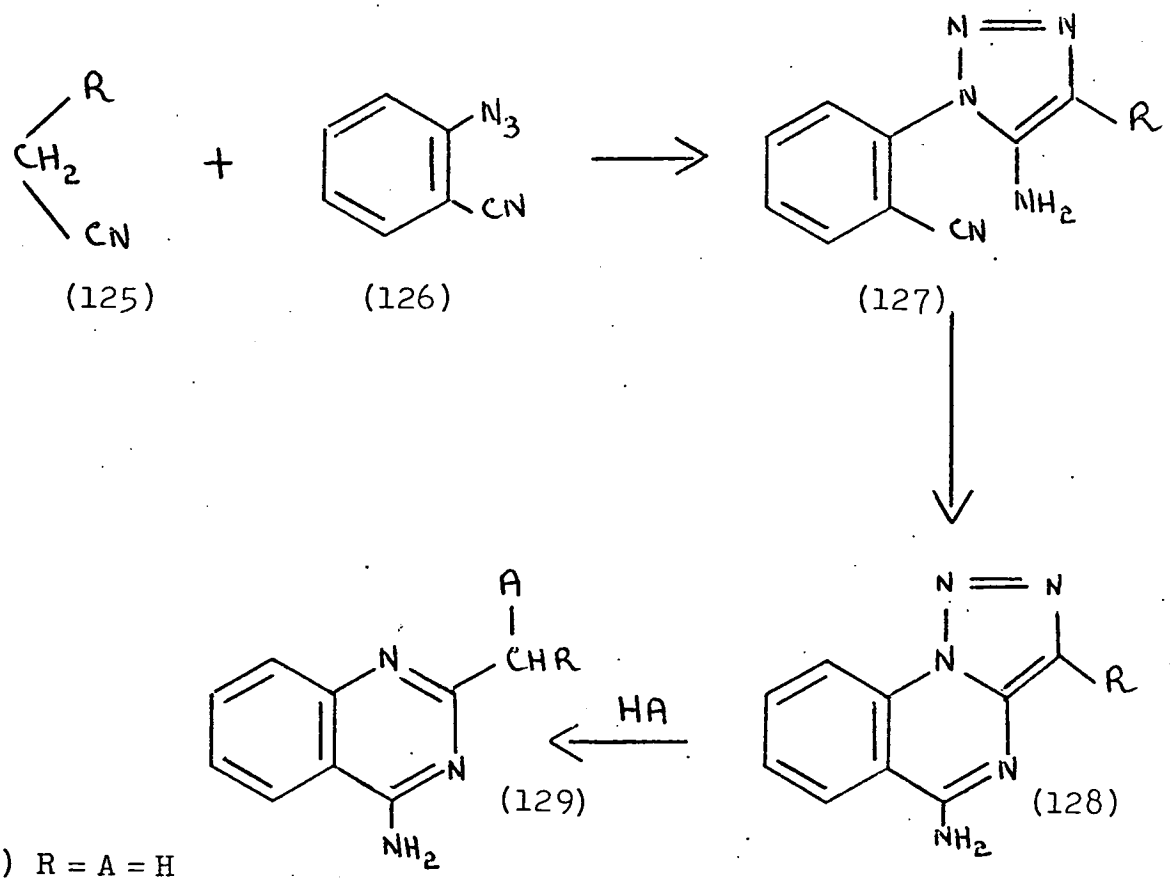
2-Nitrophenyl azide is known to react with phenylacetonitrile in the presence of methoxide ion to afford 3-phenyl-1,2,3-triazolo[5,1-c]benzo-1,2,4-triazine-5-oxide (121), rather than the linear isomer (123).[61,62] The isolation of the non-linear isomer (121) suggests that the intermediate (120) cyclises before Dimroth rearrangement



to (122) occurs. The isomer (122) would be expected to yield the linear compound (123) on cyclisation. The cyclisation of (120) must be rapid as the electron withdrawing nature of the 1-substituent on the triazole ring will make the basic isomer (120) less stable than the acidic isomer (122) (see part 2, Section 4).

2-azidobenzoic acid reacts similarly with phenylacetonitrile to yield 4,5-dihydro-5-oxo-3-phenyl-1,2,3-triazolo[1,5-a]quinazoline (124).[63]

Triazolobenzotriazines,[61,62] triazoloquinazolines[63] and triazolopyridines,[60] as already discussed (see General Introduction), undergo triazole scission under acidic conditions. As an extension of this work it was of interest to investigate the products of reactions between 2-azidobenzonitrile and substituted acetonitriles, and to study the acid-catalysed cleavage of the fused-triazole systems obtained. The reaction between 2-azidobenzonitrile (126) and a substituted acetonitrile (125) under base-catalysed

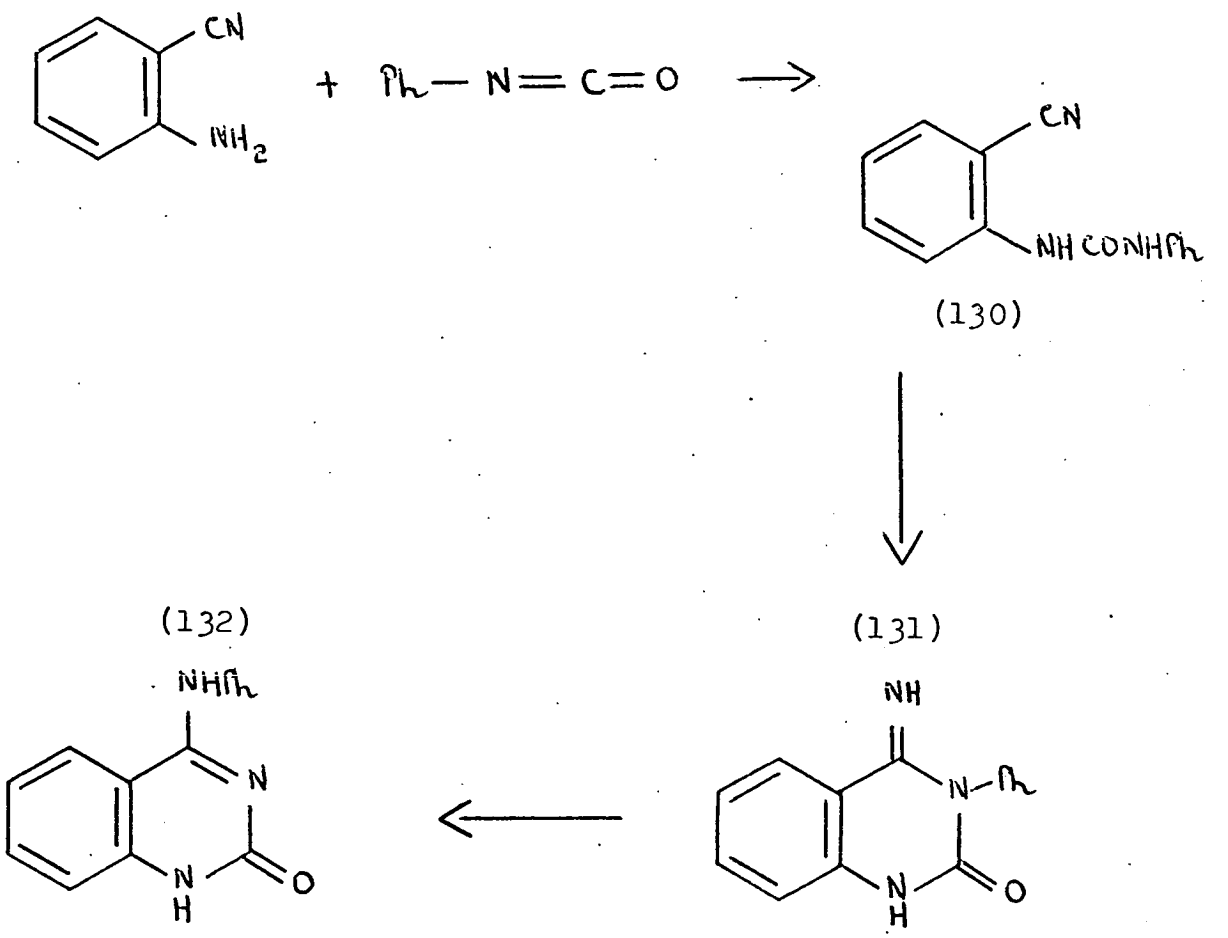


(125) (126) (127) (129) (128)

a) R = A = H

conditions, might be expected to yield a 3-substituted-5-aminotriazoloquinazoline (128), formed via the intermediate (127). The acid-catalysed (HA) triazole scission of this ring system (128) would lead to the formation of 2-substituted-4-aminoquinazolines (129). 4-Aminoquinazoline derivatives

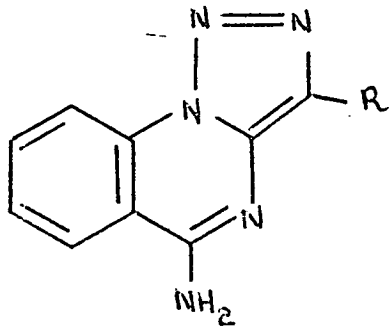
have been prepared by the reaction of 4-chloroquinazolines with amines. They may also be formed from 2-aminobenzonitrile, which, for example, reacts with acetonitrile in the presence of alcoholic ammonia to give 4-amino-2-methylquinazoline (129a).[67] Studies on the reactions of substituted acetonitriles with substituted 2-aminobenzonitriles indicated that the course of these reactions was governed by the ability of the cyano group to undergo nucleophilic attack, rather than by the basicity of the amino group.[67] When a mixture of 2-aminobenzonitrile was heated with phenyl isocyanate in boiling methanol the oxoquinazoline (131) was formed. Compound (131) on further



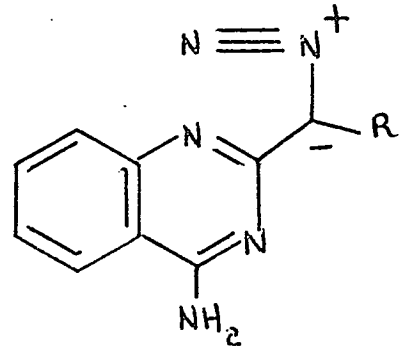
Scheme 6

heating rearranged to the isomer (132).[68] Presumably the reaction of 2-aminobenzonitrile with phenyl isocyanate proceeds via the intermediate (130) (see scheme 6).

It is known that 5-oxo-triazoloquinazolines (124) and triazolobenzotriazine-5-N-oxides (121) undergo triazole scission under acidic conditions (see General Introduction). However both these ring systems are substituted in the 5-position with electron withdrawing groups, and in the 3-position with a phenyl group. It was therefore of interest to prepare triazoloquinazolines with the electron donating 5-amino substituent, and a variety of 3-substituents, thus allowing a study to be made of the influence of these substituents on the stability of the ring system. The cation of quinazoline undergoes reversible addition of water across the 3,4-double bond. This covalent hydration is known to be inhibited by 4-substituents, due mainly to steric hindrance.[66] It is therefore unlikely that 4-aminoquinazolines will be susceptible to covalent hydration because electron donation by the amino group together with the steric effect will preclude attack by a nucleophylic species. The possibility of covalent hydration in the reactions discussed below is therefore excluded.

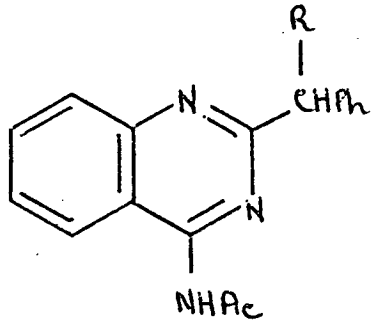


(133)



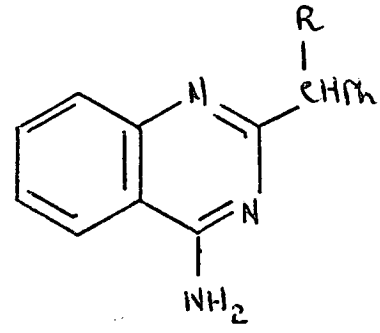
(134)

a) R = Ph
b) R = $CONH_2$
c) R = CN
d) R = H
e) R = CO_2Et



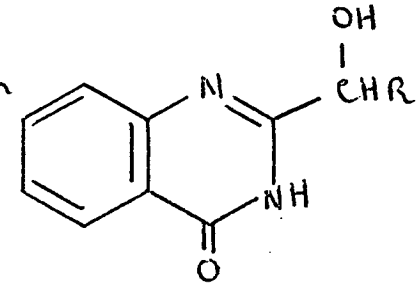
(137)

a) R = OAc
b) R = Cl
c) R = Br
d) R = H



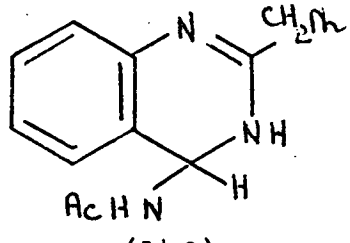
(138)

a) R = OH
b) R = H
c) R = OEt
d) R = OAc

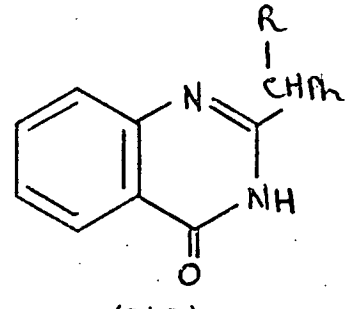


(139)

a) R = Ph
b) R = H

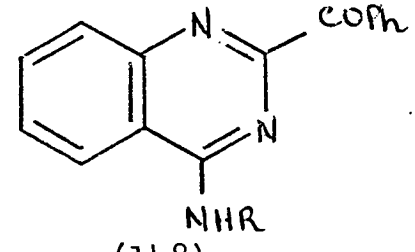


(140)



(141)

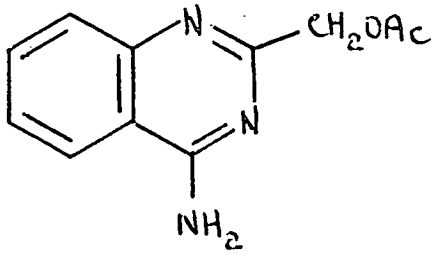
a) R = H
b) R = Br
c) R = Cl



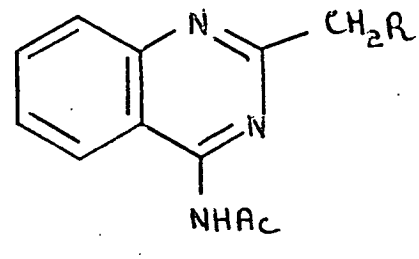
(148)

a) R = H
b) R = Ac

(149)



(150)

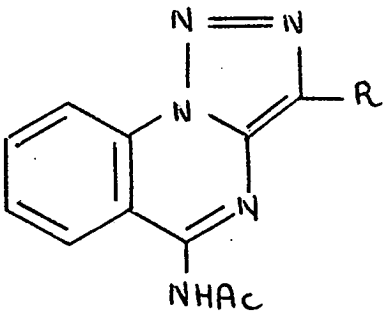


a) R = Cl
b) R = Br

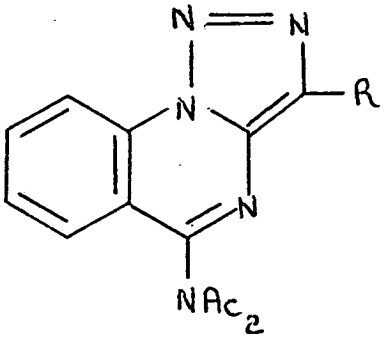
The condensation of 2-azidobenzonitrile with phenylacetonitrile, cyanoacetamide, malononitrile and ethyl cyanoacetate, in the presence of alkoxide ion, yielded the 3-phenyl, 3-carbamoyl, 3-cyano and 3-unsubstituted derivatives of the 5-amino-1,2,3-triazolo[1,5-a]quinazoline ring system (133a-d). The structures of these compounds are supported by spectral and chemical data. Bands due to cyano absorption were absent from the i.r. spectra of compounds (133a-b) and (133d). The cyano compound (133c) showed absorption at 2280 $cm.^{-1}$ due to the 3-cyano group. The i.r. spectra of the compounds (133a-d) likewise lacked azide absorption but contained bands at 3000-3500 $cm.^{-1}$ which could be assigned to a primary amino group. The i.r. spectrum of the amide (133b) was more complex in the region 3000-3400 $cm.^{-1}$ due to the presence of the primary amide group. The lack of absorption in the region ca. 2150 $cm.^{-1}$ excluded the possibility of the ring-opened diazo form (134a-d) being present in the solid state. Low solubility prevented studies on these compounds in solution. The 3-unsubstituted compound (133d) was the product obtained when ethyl cyanoacetate was condensed with 2-azidobenzonitrile. None of the expected ester (133e) was isolated. It is assumed that the ester (133e) is initially formed but suffers hydrolysis and decarboxylation during the reaction and/or work-up. As expected the compound (133d) shows no carbonyl absorption in the i.r. spectrum. The phenyl compound (133a) was converted into the known[63] 5-oxo compound (124a) when it was refluxed in 20% aqueous potassium hydroxide.

This reaction involves hydrolysis of the primary amino group (see below). The triazoloquinazolines (133b-d) were likewise convertible into known quinazoline derivatives (see below). Acetylation of the phenyl compound (133a) with acetic anhydride gave a mixture of monoacetyl and diacetyl derivatives, whose spectroscopic properties are consistent with the structures (135a) and (136a) respectively. In support of its acetylamino structure the monoacetyl compound (135a) shows a three proton methyl singlet in its p.m.r. spectrum and a single carbonyl

(135)



(136)



a) R = Ph
b) R = $CONH_2$
c) R = CN
d) R = H
e) R = CONHAc

absorption in its i.r. spectrum. The diacetylamino structure for the diacetyl product (136a) is likewise demonstrated by the presence of two carbonyl bands in its i.r. spectrum and a six proton methyl singlet in its p.m.r. spectrum indicating that both acetyl groups are in a similar environment. Treatment of the amide (133b) and the nitrile (133c) with acetic anhydride gave a triacetyl derivative and a diacetyl derivative respectively, both of which lose an acetyl group on attempted crystallisation. The p.m.r. spectrum of the triacetyl derivative of the amide (133b) shows

three methyl singlets, one of which is lost on crystallisation. Similarly the p.m.r. spectrum of the diacetyl derivative of the nitrile (133c) shows one methyl singlet representing six protons, indicating that both acetyl groups are in a similar environment. The diacetyl derivative of the nitrile (133c) is thus formulated as (136c), which on crystallisation forms the monoacetyl compound (135c), showing a three proton methyl singlet in its p.m.r. spectrum. The i.r. spectra of both acetyl derivatives of the nitrile (133c) contain a band at ca. 2300 $cm.^{-1}$ demonstrating the presence of an intact cyano group, and absorptions attributable to the acetyl carbonyl groups. The fact that the amide (133b) forms a triacetyl derivative suggests that the amide group itself has undergone acetylation. This phenomenon is also observed in the acetylation of 5-amino-4-carbamoyl-1-phenyl-1,2,3-triazole as will be discussed later (see Part 2, Section 4). The triacetyl compound is therefore formulated as (136e) which on crystallisation loses an acetyl group to afford (135e). The methyl signals in the p.m.r. spectrum of the triacetyl compound (136e) in TFA are at τ 7·20, 7·35 and 7·70, whilst in the diacetyl compound (135e) the signals are at τ 7·20 and 7·35. Therefore the signal at τ 7·70, which is in the acetylamino region, has been lost (see Section 2, part 4). This is in agreement with the assigned structures. Analytical data could not be obtained for compounds (136c) and (136e) due to their instability on attempted crystallisation.

However the mass spectra of the compounds showed peaks due to the parent ion corresponding in molecular weight to the assigned structures. The structures of the triazoloquinazolines (133b,c) were confirmed by their conversion into the known triazoloquinazolone (124b),[73] by refluxing with concentrated aqueous alkali (see below). The triazoloquinazoline (133d) was similarly converted into the known triazoloquinazolone (124c). The hydrolysis of the primary amino groups in these reactions is discussed below.

Triazole scission consistent with the assigned structure was exhibited by the phenyl compound (133a) and its acetyl derivative (135a). On refluxing in glacial acetic acid the acetyl compound (135a) gave a diacetyl product which showed carbonyl absorption at 1730 $cm.^{-1}$ attributable to an acetoxy group. The p.m.r. spectrum of the acetate in TFA contained a singlet at τ 2·95 assigned to a benzylic proton and singlets at τ 7·55 and τ 7·75 attributed to methyl groups. The acetate is therefore formulated as the acetylaminoquinazoline (137a). Treatment of (137a) with aqueous ethanolic sodium carbonate removed both the acetyl- and acetoxy groups, as demonstrated by the loss of carbonyl absorption in the i.r. spectrum and methyl absorption in the p.m.r. spectrum. The product was the hydroxy compound (138a), which shows a signal at τ 3·81 due to the benzylic proton and an OH absorption at 3110 $cm.^{-1}$ The presence of the primary amino group in compound (138a) is demonstrated by characteristic i.r. absorption in the region 3000 - 3500 $cm.^{-1}$ Hydrolysis of the acetate (137a) under strongly alkaline

conditions afforded the known[63] compound (139a), which is presumably formed via the hydroxy compound (138a). The hydrolysis of aminoquinazolines to oxo compounds with base is a well known reaction.[69-71]

Hydrogenolysis of the acetate (137a) yielded the benzyl compound (137d) together with a product formulated as 4-acetylamino-2-benzyl-3,4-dihydroquinazoline (140). The latter product shows a broad absorption centred at 3200 $cm.^{-1}$ and a carbonyl absorption at 1650 $cm.^{-1}$ The low frequency of the latter may be explained by slight intramolecular hydrogen bonding with the 3-NH group. Compound (140) is presumably formed by further reduction of the quinazoline (137d). Hydrogenolysis is a known route to 3,4-dihydroquinazolines.[72] In agreement with the assigned structure, the p.m.r. spectrum of the benzyl compound (137d) contains a two proton singlet at τ 5·30 (benzylic H) and a methyl singlet at τ 7·30, while carbonyl absorption is present at 1680 $cm.^{-1}$ in the i.r. spectrum. As expected the N-acetyl group was not removed by hydrogenation. However subjecting (137d) to mild alkaline hydrolysis afforded the deacetylated product (138b), which showed i.r. absorption typical of a primary amino group.

Triazole scission was also observed in the reactions of the triazoloquinazoline (133a) with acetyl chloride or acetyl bromide in acetic acid. The reaction with acetyl chloride resulted in both chlorination and acetylation to give the chloro compound (137b), which was easily hydrolysed by dilute aqueous acid to the hydroxy compound (138a), and

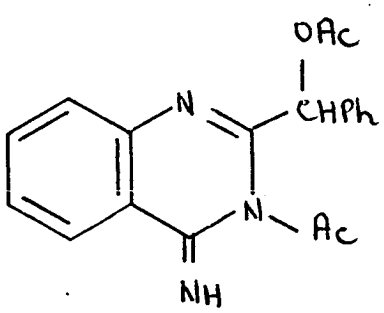
hydrogenated to a mixture of (137d) and (140). However treatment of the chloro compound (137b) with aqueous ethanolic sodium carbonate solution, yielded a compound formulated as the ether (138c) on the basis of its p.m.r. spectrum which contains a triplet centred at τ 8·60 and a quartet centred at τ 7·20, characteristic of an ethyl ether. The benzylic proton was evident at τ 4·25. The spectral data of the chloro compound (147b) was in agreement with the assigned structure. In particular it showed carbonyl absorption at 1690 $cm.^{-1}$, due to the acetyl group and the p.m.r. spectrum contained a methyl singlet at τ 7·30 and a benzylic proton signal at τ 3·50. The reaction of the triazoloquinazoline (133a) with acetyl bromide yielded the bromo compound (137c) and the benzyl compound (137d). The former, like the chloro compound (137b) and the acetate (137a) could be hydrolysed to the hydroxy compound (138a) and hydrogenated to a mixture of the benzyl compound (137d) and the dihydroquinazoline (140). The spectral data of the bromo compound was also in agreement with the assigned structure. The p.m.r. spectrum showed a methyl singlet at τ 7·05 and a benzylic proton singlet at τ 3·35. The acetyl carbonyl group absorbed at 1685 $cm.^{-1}$ Although the pure bromo-quinazoline (137c) was obtained from the crude mixture by fractional crystallisation the more soluble benzyl compound (137d) was contaminated with the bromo compound even after repeated crystallisation. The p.m.r. spectrum of the crude product indicated that it was a mixture of the above two products. Also the mass spectrum showed a signal at a

molecular ion weight equivalent to the benzyl compound (137d), as well as signals attributable to the bromo compound (137c). The formation of a benzyl derivative by the reaction of a fused triazole with acetyl bromide in acetic acid has been observed previously. The triazoloquinazoline (124a) reacts with acetyl bromide to give the quinazoline (141a).[63] It is thought that formation and reduction of the bromo compound (141b) is a possible course for the reaction. This course is supported by the fact that the chloro compound (141c) also gives the benzyl compound (141a) on treatment with acetyl bromide. Therefore by analogy it is assumed that the benzyl compound (137d) is formed by reduction of the initially formed bromo compound (137c). Treatment of the triazoloquinazoline (133a) with sulphuric acid also caused triazole scission affording a mixture of the hydroxy compound (138a), and the known hydroxyquinazolone (139a). Similar treatment for a longer period afforded only the quinazolone (139a). The isolation of the amine (138a) suggests that the triazole ring is cleaved before the amino group is hydrolysed. The conversion of aminoquinazolines into oxoquinazolines in the presence of acids is well known.[72]

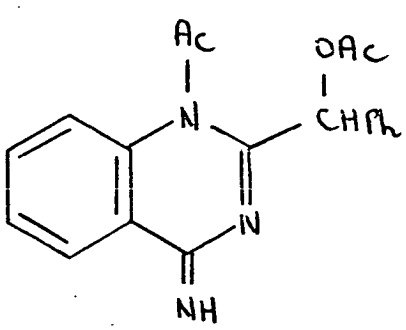
Acetic acid, which caused cleavage of the triazole ring in the monoacetyl compound (135a), also cleaves the ring in the parent compound (133a), affording a diacetyl derivative. This compound showed i.r. absorption at 1740 and 1685 $cm.^{-1}$ attributable to an acetoxy group and an N-acetyl group respectively. The possibility that it was a solvate with

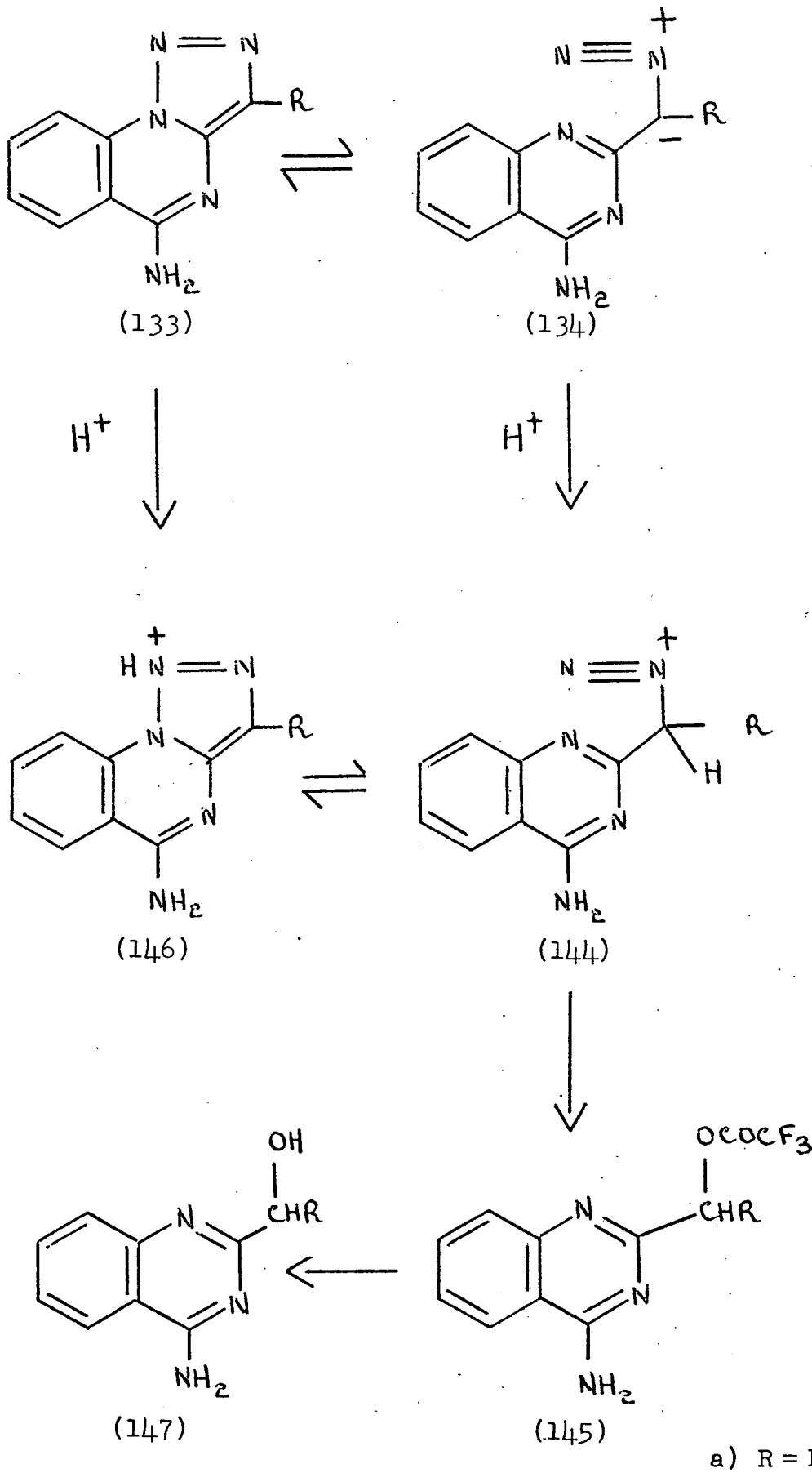
acetic acid was excluded when crystallisation from ethanol failed to alter the spectra. The assignments of the two acetyl groups are supported by the p.m.r. spectrum which contains methyl singlets at τ 7·55 and τ 7·75. A singlet at τ 2·95 can be attributed to a benzylic proton showing that triazole scission has occurred. The analytical data and molecular weight (obtained from the mass spectrum) of the product suggest an isomer of the diacetyl compound (137a), which is in fact obtained when the unknown diacetyl product is refluxed in acetic anhydride. Also, when hydrolysed under mildly basic conditions it affords the deacetylated compound (138a). However hydrogenation removed both acetyl groups yielding the aminoquinazoline (138b). The latter reaction excludes the presence of an acetylamino group (NHAc) since, as already discussed above, hydrogenation of (137a) left such a group intact. The unknown diacetyl compound is therefore tentatively formulated as 2-(α-acetoxybenzyl)-3-acetyl-3,4-dihydro-4-iminoquinazoline (142). However there is no reason to exclude the 1-acetyl

(142)



(143)





Scheme 7

isomer (143). As attempts to prepare the aminoacetate (138d) failed, because hydrolysis reactions always afforded the hydroxy compound (138a), the attempted preparation of the above diacetyl compound formulated as (142) by the reaction of (138d) with acetic acid was not possible.

Oxidation of the hydroxybenzylquinazoline (138a) with manganese dioxide afforded the ketone (148a). The structure of this compound is established by the presence of carbonyl absorption at 1680 $cm.^{-1}$ in its i.r. spectrum and absorption in the 3000 - 3500 $cm.^{-1}$ region attributable to a primary amino group. The presence of the latter group was demonstrated by acetylation with acetic anhydride to yield the acetyl derivative (148b). The latter showed carbonyl absorption at 1680 and 1670 $cm.^{-1}$ a methyl singlet at τ 7·25, and was hydrolysed back to compound (148a), by warming with dilute alkali. Hydrogenation of the benzoyl compound (148a) afforded the hydroxybenzylquinazoline (138a).

As the triazole scission of the phenyltriazoloquinazoline (133a) has been well demonstrated by chemical means it was of interest to examine the behaviour of the compound in TFA solution by means of p.m.r. The p.m.r. spectrum obtained on dissolution in TFA showed an aromatic multiplet and a one proton singlet at τ 2·94. The presence of this uncoupled singlet and the observation that nitrogen was evolved on dissolution of (133a) in TFA, was evidence for a ring-opened compound, which is assigned the trifluoroacetate structure (145a) (see scheme 7) by analogy with the triazole scission of triazolopyrimidines in TFA

(see Part 2, Section 2). The p.m.r. spectrum of compound (133a) in d_6-DMSO showed only an aromatic multiplet, thus excluding the formation of a ring-opened species in this solvent. After 24 hours in TFA the p.m.r. spectrum of (133a) showed signals due to the trifluoroacetate (145a), and a singlet at τ 3·81, corresponding to the formation of the hydroxy compound (147a). The formation of the hydroxy compound (147a) under these conditions is analogous to the formation of hydroxybenzylpyrimidines from triazolopyrimidines in TFA (see Part 2, Section 2). As discussed above (see General Introduction) the diazonium species (144a) may be formed via the diazo intermediate (134a) or from the protonated fused triazole (146a). The immediate detection of a benzylic proton signal in the p.m.r. spectrum of the triazoloquinazoline (133a) in TFA shows that ring-opening must occur rapidly.

The unsubstituted 5-aminotriazoloquinazoline (133d) also exhibits triazole scission. Treatment with glacial acetic acid afforded the acetoxymethylquinazoline (149) whose p.m.r. spectrum shows a two proton singlet at τ 4·45 assigned to the methylene protons, and a methyl singlet at τ 7·60. The i.r. spectrum of (149) shows absorptions at 1740 $cm.^{-1}$ due to the ester carbonyl group, and at 3300 $cm.^{-1}$ and 3100 $cm.^{-1}$ due to a primary amino group. The acetate (149) on treatment with dilute aqueous alkali gave a hydroxy compound (147d), whose p.m.r. spectrum showed a singlet at τ 4·76 due to the methylene protons. The i.r. spectrum contained absorption in the region 3000 - 3500 $cm.^{-1}$ assigned

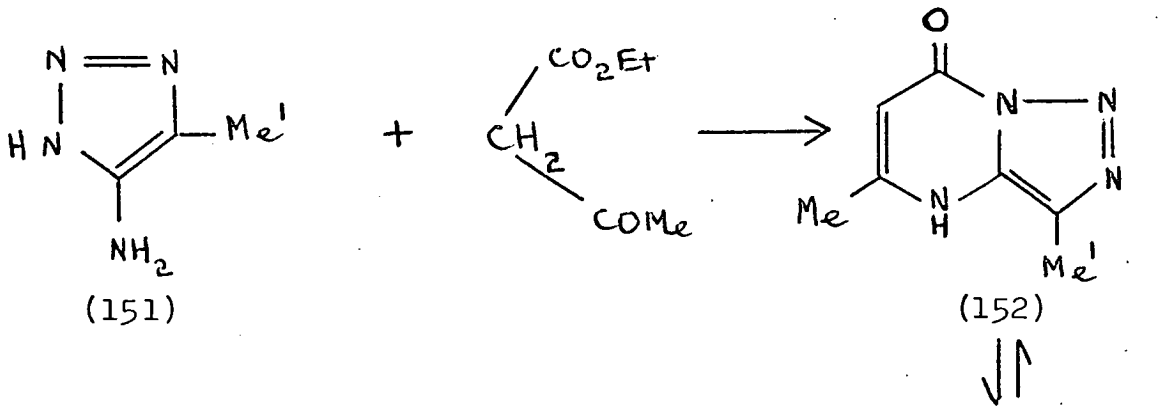
to the hydroxy and primary amino groups. Attempts to oxidise the alcohol (147d) with manganese dioxide or to catalytically reduce the acetate (149) were unsuccessful. The triazoloquinazoline (133d) also underwent triazole scission in mineral acid. Treated with dilute sulphuric acid it afforded the known quinazolone (139b)[73] presumably[72] by hydrolysis of the aminoquinazoline (147d). The structure of the acetate (149) was confirmed by its reaction with dilute sulphuric acid to afford the same quinazolone (139b). Treatment of the compound (133d) with acetyl chloride or acetyl bromide in acetic acid also resulted in triazole scission to give the chloro compound (150a) or bromo compound (150b), which could both be hydrolysed to the alcohol (147d). Compounds (150a) and (150b) showed carbonyl absorption at 1685 $cm.^{-1}$ and 1680 $cm.^{-1}$ respectively due to the N-acetyl group. The p.m.r. spectra showed methyl singlets due to the acetyl groups, and the expected methylene singlets. Triazole scission of (133d) was also evident in TFA. After one minute the p.m.r. spectrum in TFA showed a one proton singlet at τ 4·36 due to the methylene protons in the trifluoroacetate (145d). However after 24 hours re-examination of the spectrum revealed a new singlet τ 4·76 due to the alcohol (147d), as well as the signal due to the trifluoroacetate (145d). As discussed above ring-opening in TFA may proceed via the conjugate acid (146d) or the diazonium intermediate (134d) (see scheme 7). It is therefore obvious that the ease of triazole scission in triazoloquinazolines (133a-d) is affected by the nature of

the 3-substituent. The phenyl and unsubstituted compounds (133a,d) undergo triazole scission in refluxing acetic acid, acetyl chloride in acetic acid and acetyl bromide in acetic acid, or in TFA at room temperature. On the other hand the amide and nitrile (133b-d) are stable under these conditions, but undergo triazole scission when they are refluxed in dilute sulphuric acid. Both compounds yield the known quinazolone (139b).[73] However this is presumably the result of initial hydrolysis and decarboxylation to the unsubstituted triazoloquinazoline (133d) which then undergoes triazole scission and hydrolysis of the amino group (see above). It appears therefore that triazole scission in triazoloquinazolines is inhibited by the presence of electron withdrawing substituents in the 3-position. Presumably this is due to electron withdrawal lowering the basicity of the triazole ring, thus rendering it less liable to attack by acids. The 5-amino group which should increase the basicity of the triazole ring does not appear to overcome the electron withdrawal of the 3-substituent. The readily available 5-aminotriazolo[1,5-a]quinazoline ring system is a useful precursor for the synthesis of 2-substituted quinazolines which have hitherto been difficult to obtain. The use of p.m.r. spectroscopy provides a quantitative approach to the speed of ring opening of fused triazoles.

Part 2. Section 2. (2.2)

The synthesis and reactivity of the 1,2,3-triazolo[3,4-a]pyrimidine ring system. A new route to 2-substituted pyrimidines.

— Birr observed that the reaction between ethyl acetoacetate and 5-amino-4-methyl-1-H-1,2,3-triazole (151) gave the 1,2,3-triazolo[3,4-a]pyrimidine (152).[74] However no details of reaction conditions were reported. Apart from this brief record the 1,2,3-triazolo[3,4-a]pyrimidine ring system is unknown. Triazolopyrimidines of this type could possibly undergo triazole scission to yield substituted pyrimidines of the general structure (155). The ring opening of the isosteric tetrazolopyrimidines (34) to the corresponding azides (35) which may then recyclise in a



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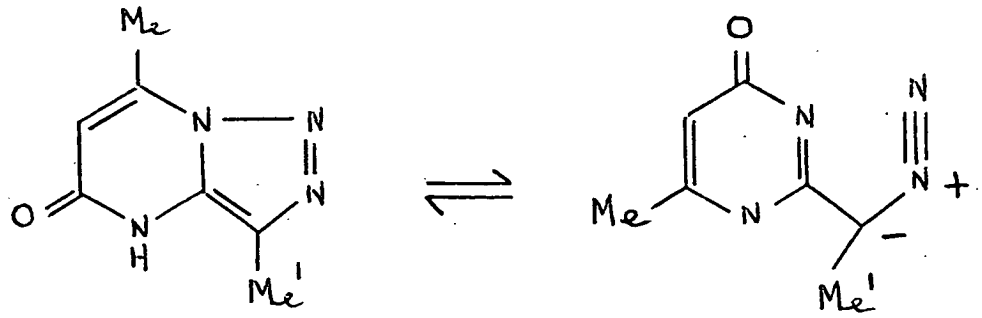

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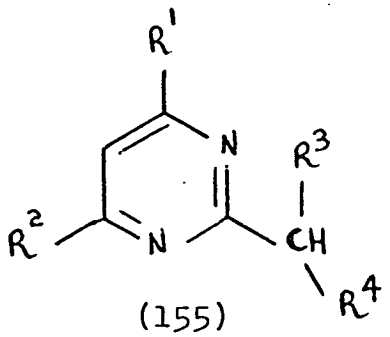
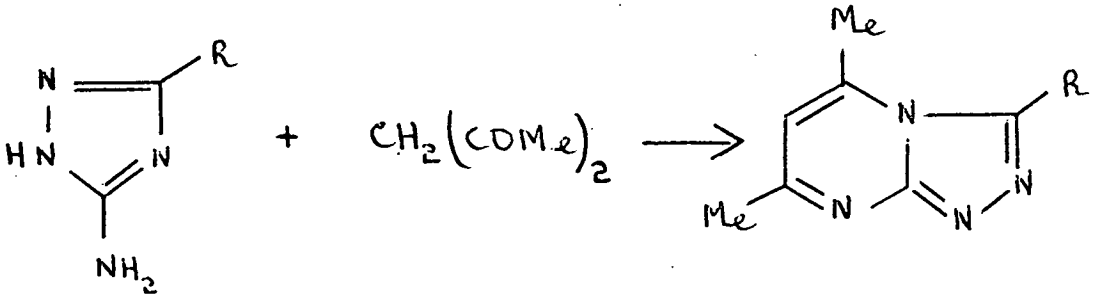


(155)

different direction to give the isomeric tetrazolopyrimidines (36) has already been discussed[21] (see General Introduction). By analogy triazolopyrimidines might undergo rearrangement of the type [(152) ⟶ (154)] via the diazo intermediate (153). As an extension of the general study of the synthesis and reactivity of fused triazoles it was decided to examine in detail the synthetic route to triazolopyrimidines described by Birr,[74] and to examine in general the potential for triazole scission of the 1,2,3-triazolo[3,4-a]pyrimidine ring system.

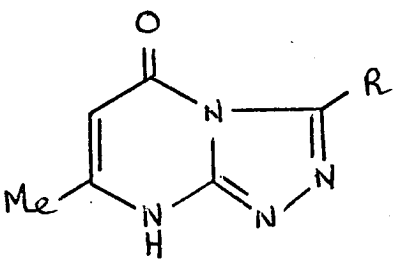
The reaction of 5-amino-1-H-1,2,4-triazoles (156) with acetylacetone in refluxing acetic acid or aqueous alkali is reported to yield 1,2,4-triazolopyrimidines (157).[75] It can be seen from the structure of the ring system that



(156) (157)

1,2,4-triazolopyrimidines cannot exist as stable open chain forms, and therefore cannot rearrange by the same mechanism as 1,2,3-triazolopyrimidines (see above). Other workers have reported[76] the formation of 1,2,4-triazolopyrimidines from the reaction of ethyl acetoacetate or ethyl ethoxymethylenemalonate with 5-amino-1,2,4-triazoles. The reactions were found to proceed in neutral solvents or in

excess carbonyl compound. It appears therefore that enolising conditions (e.g. acid or alkali) or non-polar conditions promote the reactions of β-dicarbonyl compounds with aminotriazoles. The existence of 1,2,4-triazolo-pyrimidines isomeric with respect to the pyrimidine ring has been studied by many workers.[76-81] It has been shown that reacting 5-amino-1,2,4-triazole with ethyl acetoacetate can afford either of the fused systems (158) or (159). It is well known that under mild acidic or alkaline conditions,



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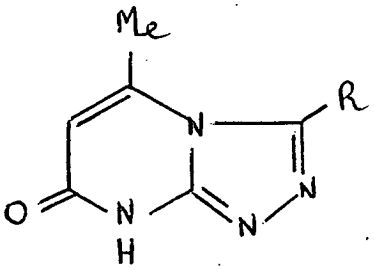
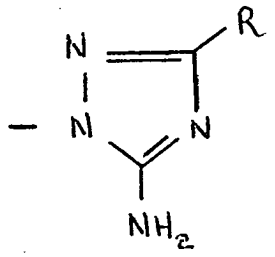


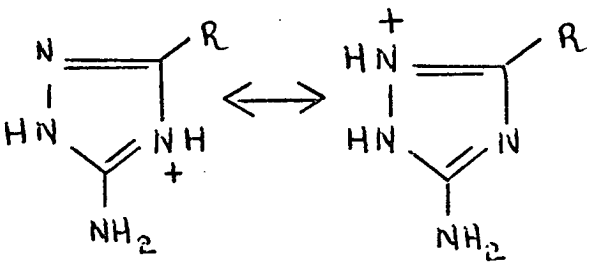
(159)

ethyl acetoacetate reacts with amines rapidly and exclusively at the ketonic carbonyl group.[82] The production of each isomer will depend on which of the amino centres of the triazole reacts with the carbonyl component. The nucleophilicity of the amino centres will of course vary with changing pH. Williams[79] considers that acidic conditions favour electrophilic attack at the 5-amino group of the 5-amino-1,2,4-triazole, whereas alkaline conditions favour attack at the 1-position of the ring. In base the 1,2,4-triazole may be considered to have ionised to the anion (160) thus rendering the 1-position most susceptible

to nucleophilic attack. Under acidic conditions protonation of the triazole ring (161) will result in preferential condensation between the 5-amino group and the carbonyl



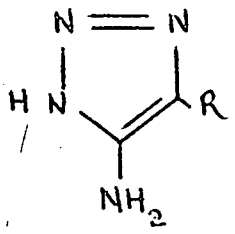
(160)



(161)

compound. Hence under acidic conditions the isomer (158) is the expected product whereas under alkaline conditions the product should be (159). However both isomers (158) and (159) can be isolated under mild basic and acidic conditions.[76-81] The situation is further complicated in the 1,2,4-triazole series by the possibility of pseudo-Dimroth rearrangement (see General Introduction).

The 5-amino-1-H-1,2,3-triazoles required as starting materials for the synthesis of 1,2,3-triazolo-[3,4-a]pyrimidines were available by debenzylating[83] the 1-benzyl compounds (163a,b), which were synthesised by the base catalysed condensation of benzyl azide[84-86] with cyanoacetamide or phenylacetonitrile. Debenzylation was accomplished using sodium in liquid ammonia.[83] The successful isolation of the phenyl compound (162a) was



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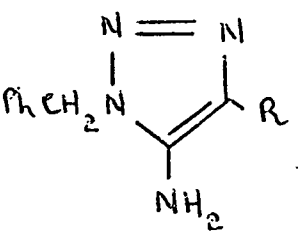

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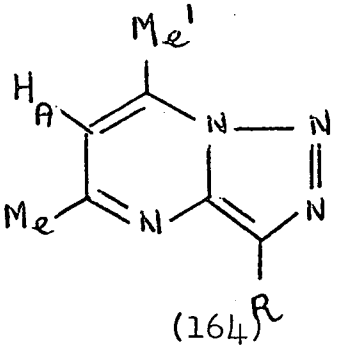

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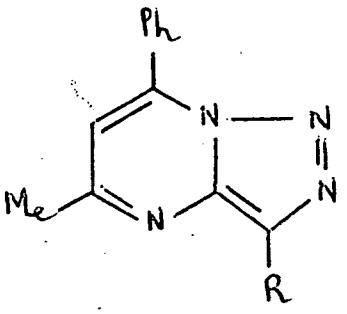

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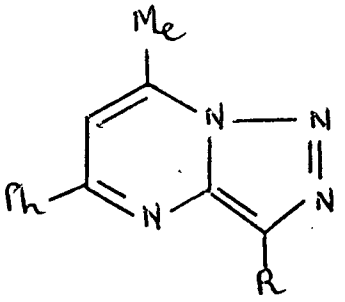
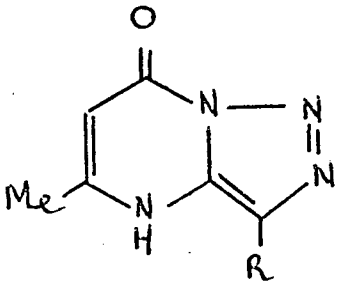


(166)

a) R = Ph
b) R = $CONH_2$



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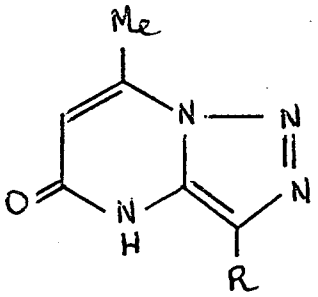

(168)

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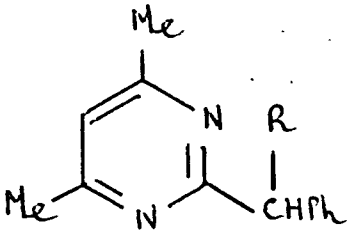
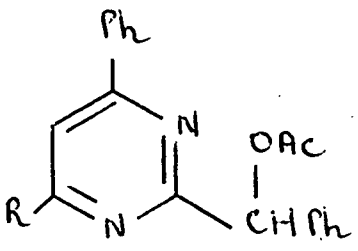
(175)



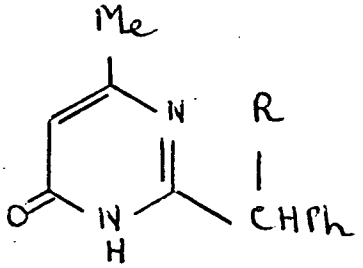
a) R = OAc
b) R = H
c) R = Cl
d) R = OH

(176)



a) R = Ph
b) R = Me

(177)



a) R = OAc
b) R = H
c) R = Cl
d) R = OH

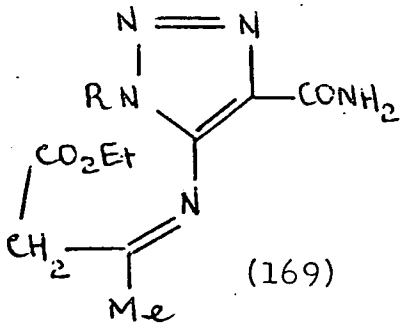
dependent on careful adjustment of the pH of the solution obtained after acidifying the reaction mixture. The amide (162b) precipitated from the reaction mixture on acidification.

5-Amino-4-carbamoyl-1-H-1,2,3-triazole (162b) was reacted with acetylacetone in refluxing acetic acid affording a high melting solid, m.p. 275°, whose molecular formula corresponded to the structure (164b). The presence of an intact amide group was supported by the presence of NH and carbonyl absorption in the i.r. spectrum. In accord with this structure the p.m.r. spectrum in d_6-DMSO exhibited two methyl signals, at τ 6·53 and τ 6·72. The former signal resolved to a doublet or expansion, suggesting that it represents the absorption of 7-Me^1 group which is split due to coupling with the olefinic proton H_A[see (164b)]. On expansion the pyrimidine proton (H_A) appears as a poorly resolved quartet centred at τ 2·02. It would appear therefore, that the 5-Me group in the triazolopyrimidine (164b) absorbs at higher field than the 7-Me^1 group, presumably due to the electron withdrawing effect of the triazole ring being more strongly felt at the neighbouring 7-position. In TFA the methyl absorptions collapse to a singlet, which integrates for six protons. However only the pyrimidine proton H_A (164b) is evident at lower field indicating that ring cleavage does not occur, since the ring opened form would show a second low field singlet due to the benzylic proton (see below). Collapse of the two methyl signals appears to be peculiar to the spectrum in TFA since

the p.m.r. spectrum of the amide (164b) in d_4-acetic acid shows the expected methyl doublet centred at τ 7·08, and a methyl singlet at τ 7·30, together with the pyrimidine proton (H_A) quartet at τ 2·94. The amide (164b) could also be synthesised by refluxing the aminotriazole (162b) with acetylacetone in ethanol in the presence of piperidine. The triazolopyrimidine amide (164b) was stable to prolonged refluxing in glacial acetic acid. This lack of triazole scission is expected since, as discussed previously (see Part 2, Section 1) electron withdrawal by the amide group will inhibit acid-catalysed attack on the triazole ring. Condensation of the triazole (162b) with benzoylacetone in refluxing acetic acid likewise gave the triazolopyrimidine (165b), which was also stable to prolonged acetic acid treatment. The p.m.r. spectrum of (165b) in TFA showed a methyl singlet at τ 7·12, and a signal at τ 2·17 attributable to the pyrimidine proton. The lack of splitting in the methyl signal provides evidence for the structure (165b) rather than the isomer (166b) since the methyl signal in the latter structure would be split into a doublet by the neighbouring olefinic proton. The isolation of the isomer (165b) rather than (166b) infers that the acetyl carbonyl group preferentially attacks the 5-amino group on the triazole ring, before the benzoyl carbonyl group. This is in accord with the greater carbonyl reactivity of an acetyl group compared to a benzoyl group. The p.m.r. spectrum of (165b) in d_6-DMSO confirmed the structure assignment, showing a pyrimidine proton signal at τ 1·60, and a methyl singlet at τ 6·66.

When the aminotriazole amide (162b) was refluxed in ethanol-piperidine with ethyl acetoacetate the product was a mixture of two compounds. All attempts to resolve this into its components, using fractional crystallisation or column chromatography, failed. The crude solid was soluble in aqueous alkali and reprecipitated by acid. The molecular formula suggested that the compound was either the triazolopyrimidine (167b) or its isomer (168b). It showed carbonyl absorption at 1690 $cm.^{-1}$ and 1670 $cm.^{-1}$, and NH absorption attributable to a primary amide group. The p.m.r. spectrum of the crude solid was unchanged by crystallisation or dry heat, or by altering the time of reflux in ethanol-piperidine used in the actual condensation. In TFA the spectrum of the mixture showed methyl doublets at τ 7·13 and τ 7·32, and poorly resolved pyrimidine proton quartets centred at τ 3·32 and τ 3·46. The spectrum was unchanged on being rerun after 48 hours. The presence of two methyl signals cannot be explained by ring-opening in a triazolopyrimidine structure because no absorption due to a benzylic proton could be detected in the spectrum. Also the p.m.r. spectrum in d_6-DMSO showed a similar absorption pattern, namely two methyl doublets and two pyrimidine proton quartets. The pattern and intensities of the signals suggest that the product is an almost equimolar mixture of the isomers (167b) and (168b). An identical equimolar mixture (based on p.m.r. evidence) was obtained when the aminotriazole (162b) was treated with ethyl acetoacetate in refluxing dimethylformamide-acetic acid, or in refluxing sodium ethoxide.

However when the triazole (162b) was refluxed with ethyl acetoacetate in benzene, containing glacial acetic acid, the main product was the uncyclised compound (169, R = H), the isomeric mixture (167b)/(168b) also being formed in minor amount. Acetylation of the uncyclised product afforded a monoacetyl derivative whose i.r. and p.m.r. spectra showed absorptions at 1750 $cm.^{-1}$ and τ 7·20, typical of a ring



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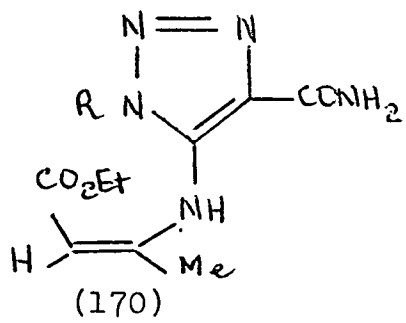

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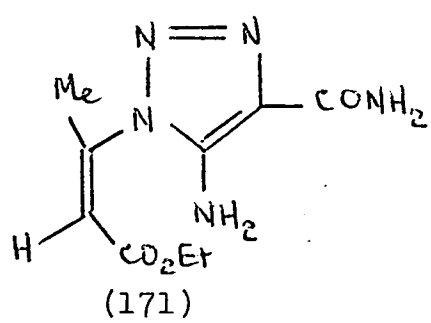
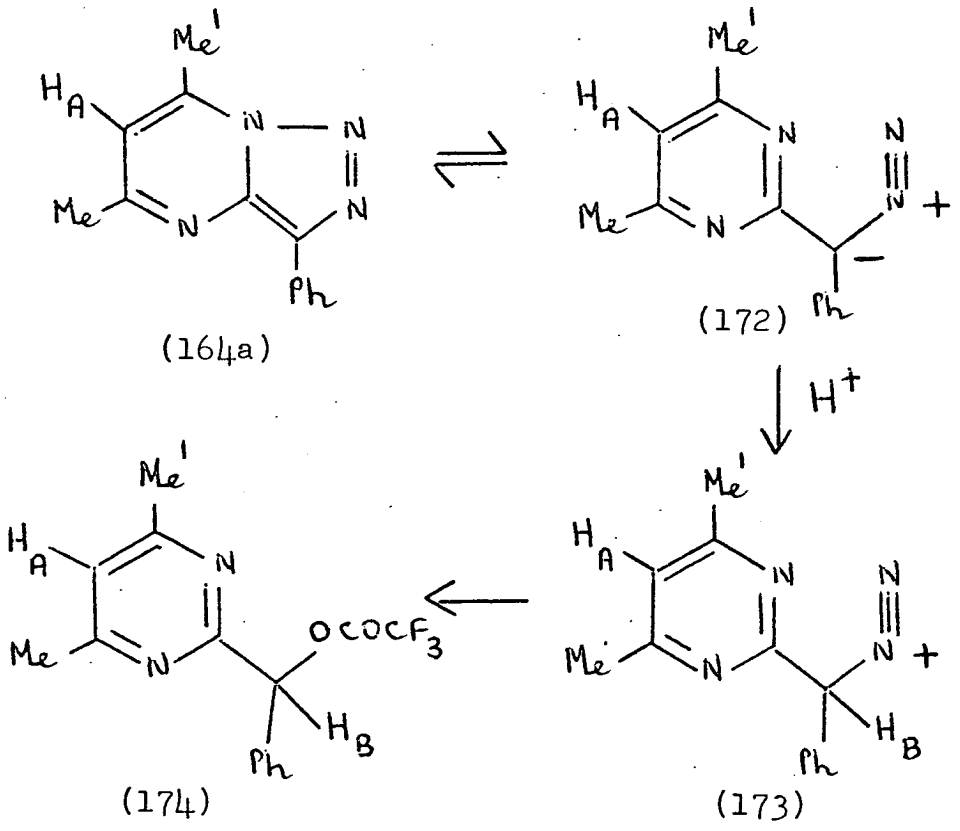


(171)

N-acetyl group, thus suggesting the structure (169, R = Ac). This supports the assignment of structure (169, R = H) to the uncyclised compound, and excludes the isomer (171). The possibility of isomerisation [(169, R = H) $\longrightarrow$ (171)] occurring during acetylation is excluded since it was found that hydrolysis of the acetyl compound (169, R = Ac) regenerated the amide (169, R = H). The i.r. spectrum of compound (169, R = H) suggests that it exists as the enamine tautomer (169, R = H) in the solid state as revealed by the presence of a conjugated ester carbonyl absorption at 1645 $cm.^{-1}$ In TFA, on the other hand, the p.m.r. spectrum contains a two proton singlet at τ 6·16 attributable to a methylene group which can only be explained by the presence of the anil structure (170, R = H). The acyltriazole (169, R = H) in refluxing piperidine-ethanol cyclised to the isomer mixture [(167b)/(168b)] obtained previously (see below).

The stability of the amide substituted triazolopyrimidine ring system to acid catalysed triazole scission has been demonstrated in both fully aromatic systems [(164b) and (165b)] and triazolopyrimidones [(167b) and (168b)]. This stability is exemplified by the p.m.r. spectra run in TFA, which show no change for periods up to 48 hours, and the lack of reaction with glacial acetic acid. However the phenyl substituted systems which lack the stabilising influence of the electron withdrawing amide group, might be expected to be unstable under acid conditions. This proved to be the case (see below).

Refluxing 5-amino-4-phenyl-1-H-1,2,3-triazole (162a) with acetylacetone and piperidine in ethanol yielded a product assigned the triazolopyrimidine structure (164a). The structure agreed with the observed p.m.r. spectrum, run in d_6-DMSO, which showed a methyl doublet centred at τ 6·85 due to the 7-Me[1] group (164a) which is split by the neighbouring pyrimidine hydrogen (H_A)(164a), and a methyl singlet at τ 7·07 assigned to the 5-Me group (164a). The pyrimidine proton was observed as a poorly resolved quartet, split by the 7-Me[1] group. However when the spectrum of (164a) was examined in TFA it was observed that the methyl signals had collapsed to a poorly resolved six proton doublet at τ 7·14, and that a one proton singlet at τ 2·91 was present at lower field together with a poorly resolved quartet of the pyrimidine proton. The presence of a one proton singlet suggests the presence of a ring-opened species, in which the afore-mentioned signal represents the benzylic proton H_B[(173) or (174)].



Scheme 8

The observation of ring opening was substantiated by the fact that the triazolopyrimidine (164a) reacted with hot glacial acetic acid to give 2-(α-acetoxybenzyl)-4,6-dimethylpyrimidine (175a), whose structure follows from its smooth hydrogenolysis to the known benzyl compound (175b).[87] The acetoxypyrimidine (175a) exhibits a carbonyl absorption at 1735 $cm.^{-1}$ in its i.r. spectrum, attributable to an acetoxy carbonyl group. The p.m.r. spectrum of (175a) in TFA showed a singlet at τ 2·95 assigned to the benzylic proton. Since (see below) in such systems the protons of a trifluoroacetoxymethyl group [e.g. (H_B)(174)] appear to absorb at lower field than those of an acetoxymethyl group, the singlet at τ 2·90 in the spectrum of the triazolopyrimidine (164a) in TFA must be the trifluoroacetate (174). The

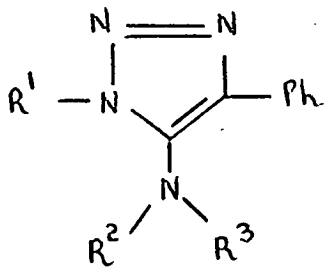
triazolopyrimidine (164a) also underwent ring cleavage when it was refluxed in a mixture of acetyl chloride and acetic acid, affording the chloro compound (175c), which on hydrogenolysis yielded the known benzyl compound (175b).[87] The p.m.r. spectrum of the chloro compound (175c) showed a six proton methyl signal at τ 7·13, and absorptions at τ 2·26 and τ 3·58 due to the pyrimidine and benzylic protons respectively. The hydroxy compound (175d) was formed by refluxing the acetate (175a) in aqueous ethanolic alkali. The i.r. spectrum of the hydroxy compound showed an absorption at 3400 $cm.^{-1}$ attributable to the OH group, and the p.m.r. spectrum contained a six proton methyl signal at τ 7·13, with single proton absorptions at τ2·30 and τ 3·68 due to the pyrimidine and benzylic protons respectively. When the aminotriazole (162a) was refluxed with acetylacetone in glacial acetic acid, the acetate (175a) was isolated in good yield. This reaction presumably occurs by the initial formation and triazole scission of the triazolopyrimidine (164a).

The use of aqueous alkali to catalyse the condensation of the aminotriazole (162a) with β-dicarbonyl compounds was successful in the reaction with acetylacetone, which afforded the expected triazolopyrimidine (164a). However the aqueous alkaline conditions did not cause reaction between the aminotriazole (162a), and dibenzoylmethane, diethyl malonate, ethyl acetoacetate or ethyl benzoylacetate, merely affording quantitative recovery of the aminotriazole (162a), presumably due to the decomposition

of the β-unsaturated compounds under the basic conditions involved. The reactions appeared to proceed satisfactorily in glacial acetic acid, as the aminotriazole (162a) refluxed with dibenzoylmethane, benzoylacetone or ethyl acetoacetate in the minimum of glacial acetic acid afforded the acetates (176a), (176b) and (177a) respectively. The structures (176a) and (176b) were confirmed by the spectral data. The i.r. spectra showed typical acetoxy absorptions at ca. 1740 $cm.^{-1}$ whilst the p.m.r. spectra showed benzylic proton and methyl absorptions attributable to the assigned structures (see experimental section). The acetate (177a) was convertible by hydrogenolysis into the benzyl compound (177b), whose p.m.r. spectrum showed a methyl signal at τ 7·45 and a two proton singlet at τ 5·50, attributable to the benzylic protons. The pyrimidine proton in the compound absorbed at τ 3·31. Treatment of the acetate (177a) with aqueous alkali afforded the hydroxy compound (177d), whose i.r. spectrum showed an OH absorption at 3400 $cm.^{-1}$ The p.m.r. spectrum of the hydroxy compound (177d) showed a methyl signal at τ 7·38, and single proton absorptions at τ 3·29 and τ 3·82 due to the pyrimidine and benzylic protons respectively verifying the correctness of the structure assignment. It was essential to carry out the condensations of 5-amino-1-H-1,2,3-triazoles with β—unsaturated compounds in a minimum of glacial acetic acid, otherwise the starting triazole is acetylated to give a monoacetyl compound. This monoacetyl compound exhibited a low carbonyl absorption at 1670 $cm.^{-1}$ and a fairly high field

methyl singlet at τ 7·51. These absorptions are not typical of a triazole ring N-acetyl group (see Part 2, Section 4), and therefore the compound is formulated as (178a). Also treatment of the aminotriazole (162a) with acetic anhydride afforded a triacetyl compound whose i.r. and p.m.r. spectra exhibit a carbonyl absorption at 1770 $cm.^{-1}$ and a methyl singlet at τ 7·16, both characteristic of a triazole ring N-acetyl group (see Part 2, Section 4). The triacetyl compound also showed carbonyl absorption at 1740 and 1710 $cm.^{-1}$ and a six proton methyl singlet at τ 7·67 attributable to an NAc_2 group, allowing its formulation

(178)

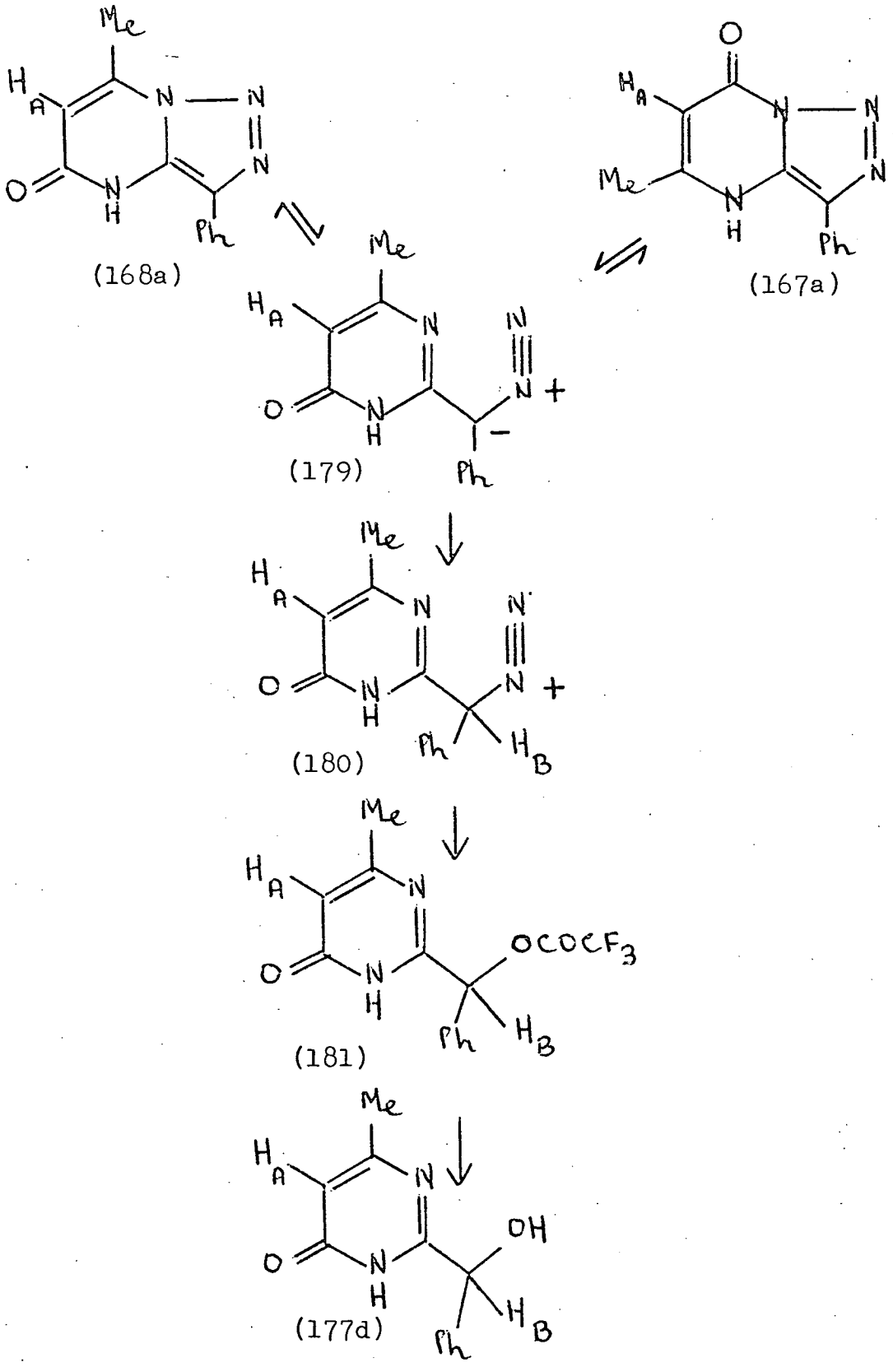


(a) $R^1 = R^2 = H$, $R^3 = Ac$

(b) $R^1 = R^2 = R^3 = Ac$

as (178b). The lower carbonyl absorption frequency of the acetylamino group in the monoacetyl compound (178a) compared with those in the triacetyl compound (178b) can be attributed to intramolecular hydrogen bonding between the acetyl group and the triazole ring NH. This is of course impossible in the triacetyl compound. Even by reducing the volume of glacial acetic acid to a minimum the reactions between diethyl malonate, ethyl benzoylacetate, or ethyl ethoxymethylene malonate and the aminotriazole (162a) afforded none of the expected pyrimidine derivatives, the acetyltriazole (178a) being the sole product.

The reaction between ethyl acetoacetate and the aminotriazole (162a) in refluxing ethanol in the presence of piperidine afforded a product whose molecular weight and acidic nature suggested a triazolopyrimidone structure. The i.r. spectrum of the crude solid contained NH and carbonyl absorption attributable to either of the isomeric triazolopyrimidines (167a) or (168a). However when the crude solid was heated at 140° or crystallised from ethanol the resulting crystalline solid showed a significantly different fingerprint region, and the loss of a carbonyl absorption, in its i.r. spectrum (see spectra 3 and 4). However the mass spectrum of the crystalline material was identical with that of the crude material. The p.m.r. spectrum of the crude solid in d_6-DMSO solution indicated that it was a mixture of the isomers (167a) and (168a) showing two unequal methyl doublets at τ 6·94 and τ 7·28 and two unequal poorly resolved pyrimidine proton quartets at τ 3·29 and τ 3·88. Since, as discussed above, a 5-methyl group is expected to absorb at higher field than a 7-methyl group, the signals at τ 7·28 and τ 3·88 of ratio 3:1 are assigned to isomer (167a). Correspondingly the signals at τ 6·94 and τ 3·29, again in a 3:1 ratio, are assigned to isomer (168a). By comparing the integrated ratios of the aromatic multiplet in each isomer, it was calculated that the crude product consisted of 10% of isomer (168a) and 90% of isomer (167a). However the d_6-DMSO spectrum of the material obtained by heating or crystallising the crude mixture, indicated that it was the single isomer (168a). These structure assignments are in agreement with the following triazole scission reactions,

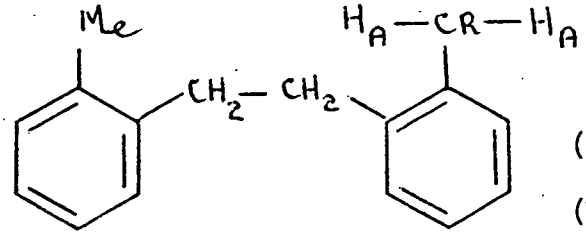

Me
H A
N
N
O
N H
Ph
(168a)
O
H A
N
N
Me
N H
Ph
(167a)
Me
H A
N
N
O
N H
N +
Ph
(179)
Me
H A
N
N
O
N H
N +
Ph
H B
(180)
Me
H A
N
O
N H
OCOCF3
Ph
H B
(181)
Me
H A
N
O
N H
OH
Ph
H B
(177d)

Scheme 9

which were carried out on both the crude isomeric mixture (167a)/(168a) and the pure compound (168a), although it was found that both solids gave identical products. Triazole scission was observed on treatment of the mixture (167a)/(168a) or the single isomer (168a) with acetic acid, affording the acetate (177a)(see above). Heating with a mixture of acetic acid and acetyl chloride, yielded the chloro compound (177c). The chloro derivative (177c) was convertible into the benzyl compound (177b) (see above), and its p.m.r. spectrum showed a methyl signal at τ 7·35, and signals at τ 3·22 and τ 3·60 attributable to the pyrimidine and benzylic protons respectively.

The spectrum of the triazolopyrimidine (168a) in TFA initially shows a methyl doublet at τ 7·08 and a poorly resolved quartet due to the pyrimidine proton (H_A) centred at τ 3·08, both attributable to the ring closed structure (168a). However after (168a) has been in solution for 12 hours the spectrum exhibits signals due to (168a), and a one proton singlet at τ 2·80, a one proton poorly resolved quartet at τ 3·18, together with another methyl doublet at τ 7·38. The proton giving rise to the singlet at τ 2·80 must be remote from the pyrimidine ring as it is not coupled to any other protons. Thus ring opening of the triazole must occur in TFA. The observations that the benzylic proton absorbs at τ 2·80, which is at slightly lower field than the benzylic proton signal in the acetate (177a), together with the observed evolution of nitrogen, suggest that the ring opened species is (181) (see scheme 9). It

is to be expected that protons adjacent to a trifluoroacetoxy group will be at lower field than those adjacent to an acetoxy group due to the stronger electron withdrawing effect of the trifluoromethyl group. This effect has been observed[88] in the di-σ-xylylenes (182). In the acetate (182a) the benzylic protons (H_A) absorb at τ 5·00 whilst in



(a) R = OAc

(b) R = $OCOCF_3$

(182)

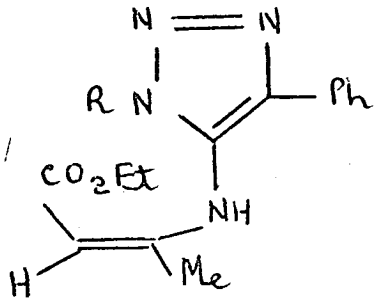
the trifluoroacetate (182b) they absorb at τ 4·83. The signals at τ 7·18 and τ 3·18 in the p.m.r. spectrum of (168a) in TFA after 12 hours, may therefore be assigned to the methyl and pyrimidine protons in the trifluoroacetate (181). The TFA solution of (168a) was allowed to stand for a further 12 hours, whence the spectrum no longer contained signals due to (168a) or (181), but instead showed a singlet at τ 3·82 due to the benzylic proton, a poorly resolved quartet at τ 3·29 due to the pyrimidine proton and a methyl doublet at τ 7·38. This spectrum was identical to that of the hydroxy compound (177d). However attempts to isolate the solid from the TFA solution gave only tarry material. The unexpected formation of the alcohol (177d) from the trifluoroacetate (181) presumably occurs due to contamination of the TFA solution with water on standing. The p.m.r.

spectrum of the crude mixture [(167a) and (168a)] run after 30 seconds in TFA showed signals due to the structures (167a), (168a) and (181). However it has already been shown that (168a) does not ring cleave in TFA as quickly as this, therefore the trifluoroacetate (181) present in solution must be derived from isomer (167a). If the integrals are summed and compared with the proportions of (167a) and (168a) in the crude solid (obtained from the d_6-DMSO spectrum where ring opening was not observed) it is again evident that isomer (168a) has not ring-opened after 30 seconds. Therefore it can be argued that isomer (167a) is less stable towards cleavage by acid than (168a)(see below). After 1 minute in solution the spectrum shows only signals attributable to (168a) and (181), whilst after two hours the spectrum demonstrates the presence of (168a), (181) and (177d) and after 24 hours only (177d) is evident. The methyl signals due to the trifluoroacetate (181) and the alcohol (177d) are inseparable even on expansion. However the integral clearly demonstrates that two distinct methyl groups are involved. The triazole scission of triazolo-pyrimidines in TFA presumably proceeds via the diazonium cation (180), although there is no evidence to exclude synchronous attack by trifluoroacetic acid and expulsion of nitrogen.

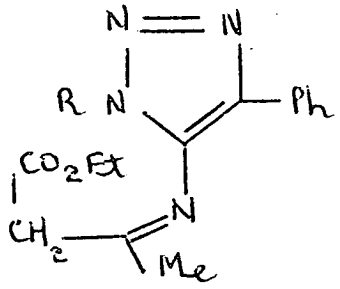
The isomer (167a) was not obtained pure; any attempts to purify it afforded the more stable isomer (168a). The isomerisation [(167a) $\rightleftharpoons$ (168a)] may be considered as a true Dimroth rearrangement presumably occurring via the

diazo intermediate (179). The adjacent carbonyl group in (167a) may aid the heterolysis of the nitrogen-nitrogen bond and thus enhance the rate of ring-opening in (167a) compared to the isomer (168a), in which the carbonyl group is remote from the site of ring scission. Although it appears that isomer (168a) is more stable under thermal and acidic conditions, it is isomerised to (167a) on refluxing with piperidine in ethanol. Presumably this is due to the preferential formation of the piperidine salt of (167a) (see below).

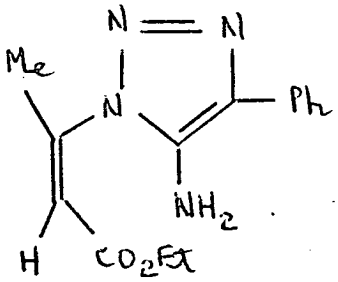
In contrast to the reaction of ethyl acetoacetate with the aminotriazole (162a) in glacial acetic acid which afforded the acetoxypyrimidine (177a)(see above) the reaction in benzene containing acetic acid yielded an uncyclised product formulated as (183a) on the basis of the following spectral and chemical evidence. On treatment with acetic anhydride compound (183a) afforded a monoacetyl compound with a high carbonyl absorption at 1740 $cm.^{-1}$ and a methyl singlet at τ 7·23. These values are both typical of a triazole ring N-acetyl group (see Part 2, Section 4), suggesting the formulation (183b). The possibility that isomerisation [(185) $\longrightarrow$ (183a)] may have occurred during the acetylation reaction was excluded because under mild hydrolysis using conditions which do not cause isomerisation, the acetyl derivative regenerated the compound (183a). The structure (183a) was preferred to the isomeric structure (184a) because the p.m.r. spectrum in deuterochloroform ($CDCl_3$) showed an olefinic methyl signal at τ 8·02, an



(183)



(184)

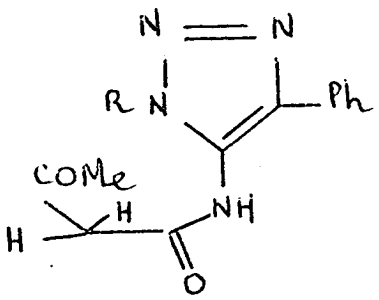


(185)

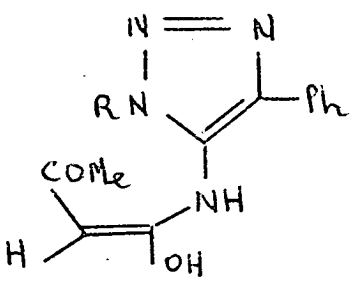
(a) R = H

(b) R = Ac

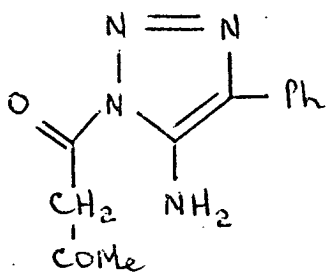
olefinic proton signal at τ 5·20, and characteristic ethyl absorptions (a quartet at τ 5·85, and a triplet at τ 8·75) due to the ester group. The ester carbonyl group absorption was at 1640 $cm.^{-1}$ in compound (183a) and at 1650 $cm.^{-1}$ in the acetyl derivative (183b). The low frequency absorption of the ester carbonyl group must be due to conjugation with the olefinic double bond, and thus lends support to the formulations (183a,b). The p.m.r. spectrum of (183b) in $CDCl_3$ also shows absorptions attributable to the formulated structure. Cyclisation of compound (183a) by refluxing it with piperidine in ethanol afforded a mixture of the triazolopyrimidines (167a) and (168a), identical with the mixture obtained by reacting the aminotriazole (162a) with ethyl acetoacetate under similar conditions. Refluxing the aminotriazole (162a) with ethyl acetoacetate in toluene also afforded an uncyclised product, which did not show the typical ethyl group absorptions in its p.m.r. spectrum. The i.r. spectrum showed bands at 1690 and 1700 $cm.^{-1}$ attributable to amide and ketonic carbonyl groups respectively. The relatively high frequency absorption of the ketonic carbonyl group and the presence of the amide carbonyl group



(186) (a) R = H
(b) R = Ac



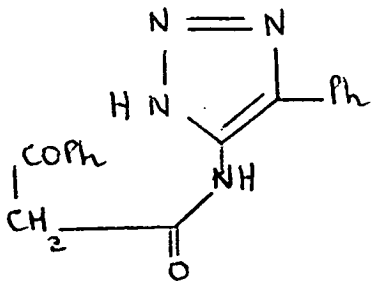
(187)



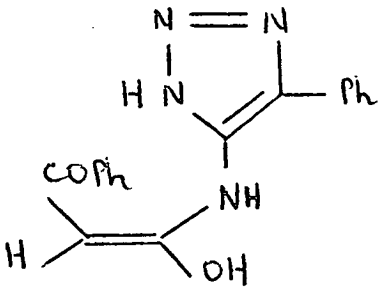
(188)

excludes the existence of the enolic isomer (187a), at least in the solid state. The ketone treated with acetic anhydride formed a monoacetyl derivative whose p.m.r. and i.r. spectra showed absorptions at τ 7·24 and 1730 $cm.^{-1}$ typical of a triazole ring N-acetyl group. The p.m.r. spectrum of the acetyl compound in $CDCl_3$ also showed a methylene signal at τ 6·31, and a methyl signal at τ 7·71, attributable to groups in the structure (186b). The possibility of rearrangement occurring during acetylation was excluded by hydrolysing the acetyl compound under conditions which do not cause isomerisation [(188) = (186a)]. The hydrolysis treatment regenerated the ketoamide (186a) which enolises under suitable conditions. Thus the spectrum in TFA showed a methylene signal at τ 5·90 and a methyl signal at τ 7·55, due to the presence of the ketoamide isomer (186a), and an olefinic proton signal at τ 6·50 and a methyl signal at τ 7·70 due to the enol form (187a). If the spectrum is run immediately after the compound is dissolved in TFA, the ketoamide (186a) to enol (187a) ratio is 2:3, but after leaving the solution for two hours only signals due to the enol form are evident in the spectrum. Cyclisation of compound (186a) by refluxing with ethanolic

piperidine gave an isomeric mixture of the triazolopyrimidines (167a) and (168a). The latter isomer is again present as the minor product. A similar condensation in toluene between ethyl benzoylacetate and the aminotriazole (162a) affords the ketoamide (189), whose i.r. spectrum shows



(189)



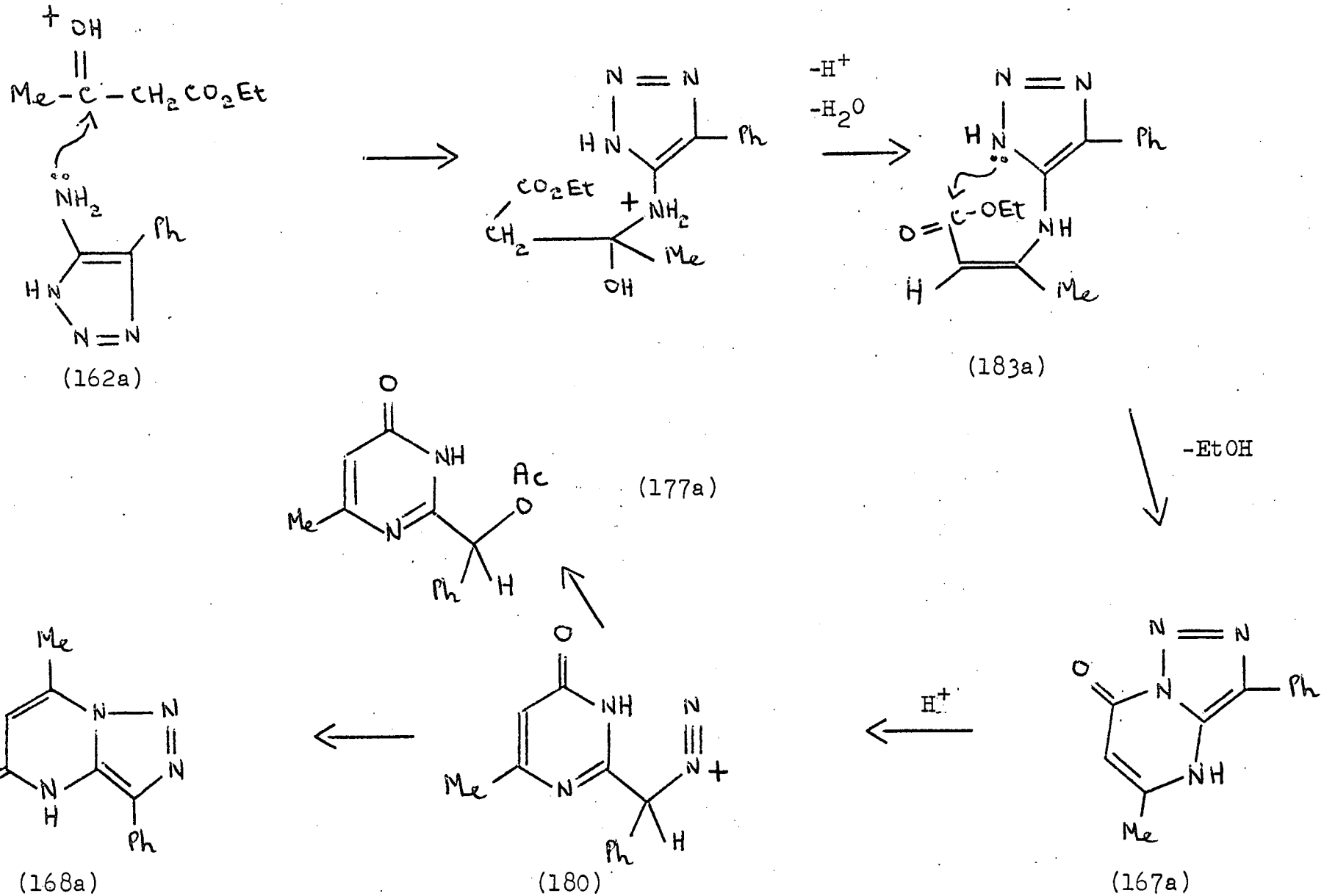
(190)

carbonyl absorption at 1675 and 1695 $cm.^{-1}$ The p.m.r. spectrum of (189) in TFA shows a methylene singlet at τ 5·37 which together with the i.r. spectrum indicates that the compound exists as the amide (189) rather than the enamine (190). Attempted cyclisation of (189) in refluxing ethanolic piperidine was unsuccessful, presumably due to the low reactivity of the benzoyl group (see previously). The reaction afforded a quantitative recovery of starting material.

It is known[82] that under mild acidic conditions ethyl acetoacetate reacts with amines rapidly and exclusively at the ketonic carbonyl group producing substituted aminocrotonates (see equation 1). Therefore

$$R_2NH + CH_3COCH_2CO_2Et \longrightarrow R_2N-\underset{\underset{Me}{|}}{C}=CHCO_2Et \quad \ldots\ldots\ldots \quad (1)$$

catalysts promoting enolisation favour the path to the crotonate rather than the amide, which is formed at higher



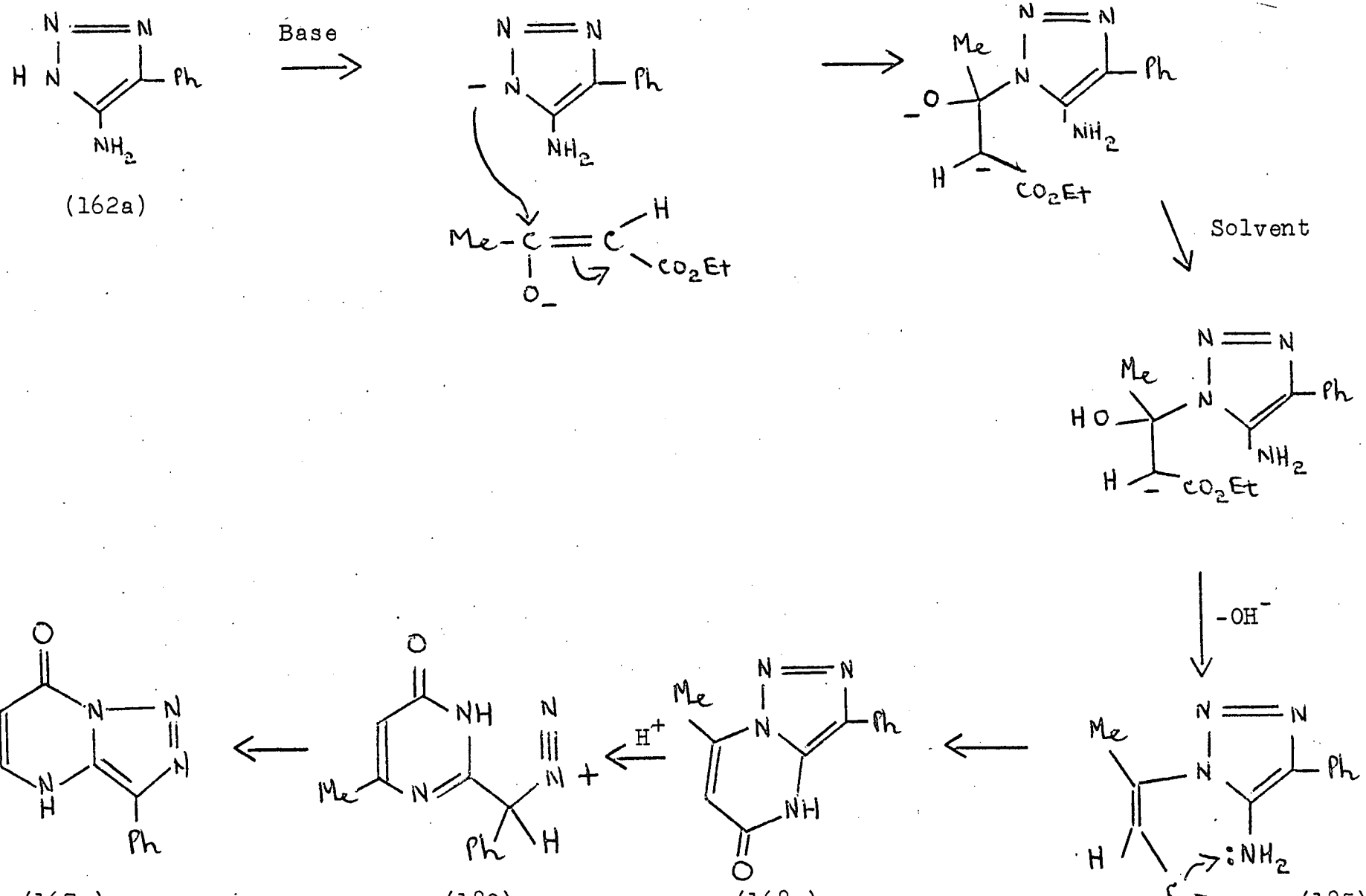
Scheme 10

temperatures (see equation 2). Hauser and coworkers consider that at higher

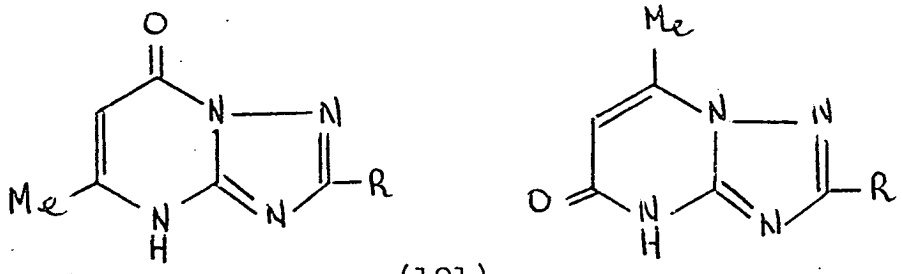
$$R_2NH + CH_3COCH_2COEt \longrightarrow R_2N-\underset{\underset{O}{\|}}{C}-CH_2COMe \quad \ldots\ldots\ldots \quad (2)$$

temperatures condensation takes place at the ester carbonyl group due to the lower volality of ethanol, which is eliminated during the reaction, compared with water, which is eliminated during the condensation at the ketonic carbonyl group.[82] Under mild acidic conditions nucleophilic attack by the more basic primary amino group in the triazole (162a) (see scheme 10) on the conjugate acid of ethyl acetoacetate will yield the enamine (183a). As discussed above the condensation of ethyl acetoacetate in benzene-acetic acid with the aminotriazole (162a) affords the uncyclised product (183a). However it was also observed that a similar condensation in neat acetic acid gave the acetate (177a), which must be formed via the diazo intermediate (180). Therefore cyclisation, presumably to isomer (167a), must have occurred. The p.m.r. spectra of (167a) and (168a) in TFA showed that the latter was more stable to acid attack (see above). It is therefore likely that triazole scission occurs on the isomer (167a) before rearrangement to isomer (168a) can occur.

On the other hand, under base-catalysed conditions the 1,2,3-triazole (162a) will exist as the anion (see scheme 11). The enolic ethyl acetoacetate (see scheme 11) will therefore condense at the more nucleophilic 1-position on the triazole ring to give the enamine (185), whence the


Base
Solvent
$-OH^-$
H^+
(162a)

free ester group will react with the primary amino group yielding the cyclic product (168a), with the elimination of ethanol. Williams[79] has shown that in the 1,2,4-triazolopyrimidine system (191), the isomer (191a) is preferentially formed to isomer (191b) in basic conditions because (191a) forms a pyridinium salt. By

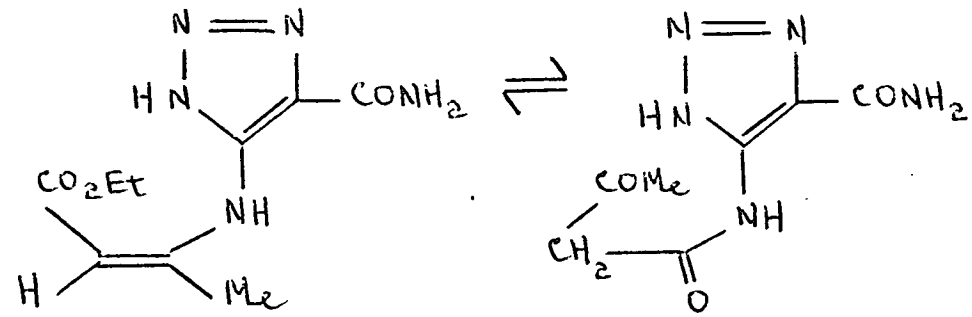


(191)

(a) (b)

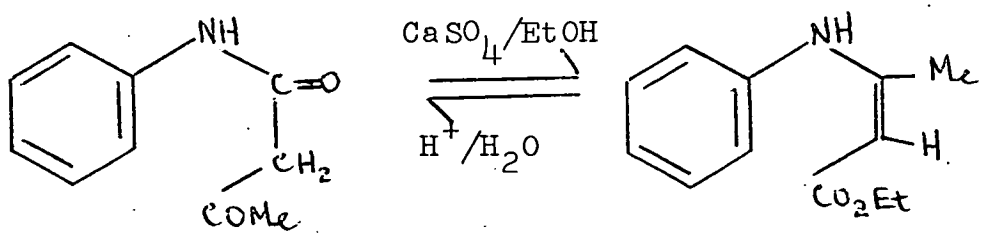
analogy one would expect isomer (167a) (see scheme 12) to be preferentially formed under basic conditions. In fact the condensation of ethyl acetoacetate with the amino-triazole (162a) under basic conditions (i.e. piperidine) afforded mainly the isomer (167a) in agreement with the above hypothesis. Since initial condensation under basic conditions occurs at the triazole ring (see scheme 11), the observed formation of the isomer (167a) under these conditions must thus involve triazole scission followed by recyclisation (see scheme 11). However when the amide (162b) was condensed with ethyl acetoacetate under basic conditions both isomers (167b) and (168b) were isolated. It was shown previously that (167b) and (168b) do not readily undergo triazole scission, and therefore a direct

rearrangement [(167b) ⇌ (168b)] cannot be invoked to account for the isolation of isomer (167b). However cyclisation in piperidine and ethanol of the semi-condensed products (183a), (186a) and (169, R = H) (see above) which yield triazolopyrimidine isomer mixtures (167a)/(168a) or (167b)/(168b) may be preceded by rearrangement, (e.g. see



(169, R = H)

Scheme 12



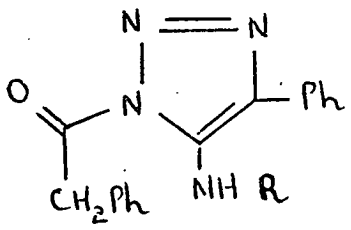
(192) (193)

scheme 12). This type of rearrangement has been observed by Hauser,[82] who found that the amide (192) and the enamine (193) were inconvertible. In particular the cyclisation of amide (169, R = H) which affords the triazolopyrimidine mixture [(167b)/(168b)] must be preceded by rearrangement

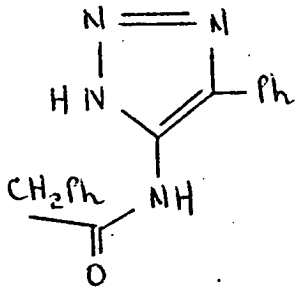
to allow formation of isomer (167b), because triazole scission is not possible (see above).

The reaction pathways may also be complicated by a competing thermal process, which will tend to cause initial reaction at the ester carbonyl group. This tendency was observed (see above) in the condensation of the aminotriazole (162a) with ethyl acetoacetate in refluxing toluene, which afforded the uncyclised product (186a).

The condensation of the aminotriazole (162a) with phenacyl bromide in the presence of sodium bicarbonate afforded an uncyclised phenacyl compound. The i.r. spectrum of the compound showed a carbonyl absorption at 1700 $cm.^{-1}$ and absorptions in the 3000-3500 $cm.^{-1}$ region attributable to a primary amino group, whilst the p.m.r. spectrum showed a methylene singlet at τ 4·92. The formulation of the



(194) (a) R = H
(b) R = Ac

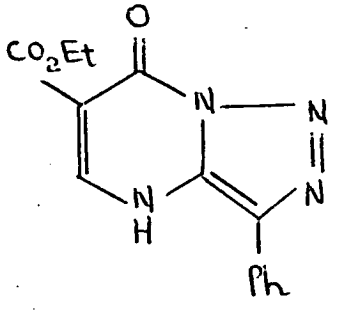


(195)

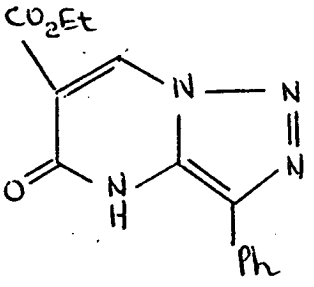
compound as (194a) rather than the isomer (195) is supported by its reaction with acetic anhydride, which afforded a monoacetyl compound whose i.r. and p.m.r. spectra showed absorptions at 1700 $cm.^{-1}$ and τ 7·63, attributable to an aminotriazole NHAc group (see Part 2, Section 4).

The acetyl derivative was thus formulated as (194b), and on hydrolysis regenerated the phenacyl compound (194a), which could not be cyclised by refluxing with piperidine in ethanol, or with acetic acid.

Ethyl ethoxymethylenemalonate and the phenyl aminotriazole (162a) reacted in ethanolic piperidine to yield a mixture of the triazolopyrimidone (196) and the diester (197a). The mixture was separable because (196)

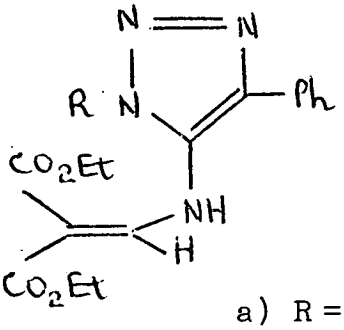


(a)



(b)

(196)

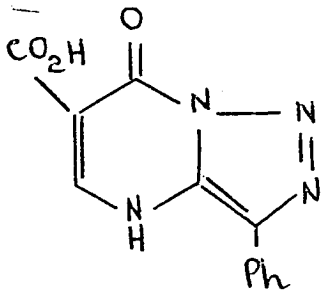


(197)

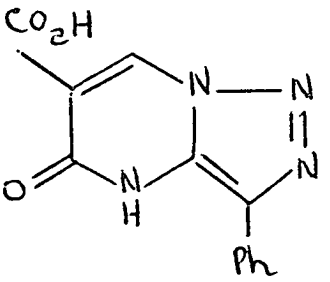
a) R = H
b) R = Ac

formed an insoluble sodium salt, whilst (197a) was soluble in aqueous alkali, and regenerated as the free compound on acidification. The diester (197a) was also formed when the aminotriazole (162a) was refluxed with ethyl ethoxymethylene-malonate in toluene, or in benzene containing acetic acid. The structure (197a) is supported by the p.m.r. and i.r. spectra. The former showed an olefinic signal at τ 1·16, and a four proton quartet at τ 5·72, which together with a six proton triplet at τ 8·61 are indicative of a diester. The low field position for the olefinic proton is presumably due to the strong deshielding effect of the adjacent diester group. Acetylation of the diester afforded a compound

formulated as (197b) on the basis of its p.m.r. and i.r. spectra which contained absorptions at τ 7·16 and 1770 $cm.^{-1}$ inferring the presence of a triazole ring N-acetyl group (see Part 2, Section 4). When the aminotriazole (162a) and ethyl ethoxymethylenemalonate, or the diester (197a) were refluxed in piperidine and ethanol for 7 days only the triazolopyrimidone (196) was isolated. The p.m.r. spectrum of (196) in d_6-DMSO exhibited a triplet centred at τ 8·35 and a quartet centred at τ 5·35, characteristic of an ethyl group. The pyrimidine proton absorbs as a singlet at τ 1·13. The low field position of this proton must be due to the deshielding effect of the neighbouring carbethoxy group. The i.r. spectrum of the triazolopyrimidine (196) shows carbonyl absorption at 1710 and 1700 $cm.^{-1}$ supporting the assigned structure. However the spectral data does not allow a distinction to be made between the isomeric structures (196a) or (196b), for the product. The fact that the product forms a piperidine salt suggests that by analogy with the argument for supporting the structure of the triazolopyrimidine (167a), structure (196a) is correct. However (167a) isomerised to (168a) on heating or crystallisation (see above), but no such change is observed in the carbethoxy compound (196). Therefore a choice between the two possible structures (196a,b) cannot be made on the basis of the evidence available. Aqueous alkaline hydrolysis of the ester (196) afforded the corresponding carboxylic acid. This compound is formulated as (198) on the basis of its i.r. spectrum which shows an acidic OH absorption at 2400 - 2800 $cm.^{-1}$ and carbonyl bands



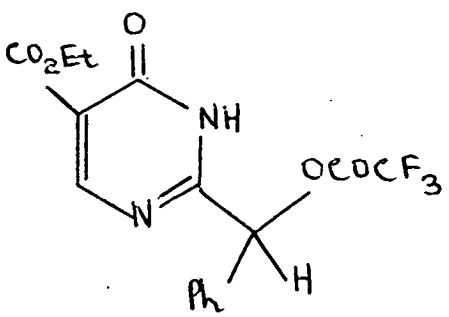
(a)



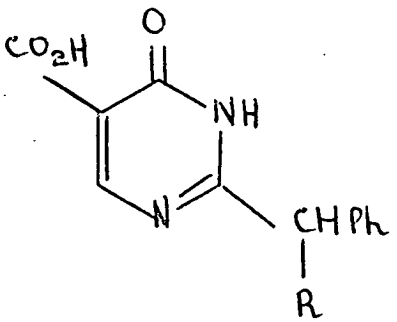
(b)

(198)

at 1720 and 1665 $cm.^{-1}$ The loss of the ester group was also demonstrated by the p.m.r. spectrum of the acid (198) in d_6-DMSO which showed only a singlet at τ 1·12 due to the pyrimidine proton. Again the available evidence fails to distinguish between the alternative structures (198a,b) for this compound. The ester (196) underwent triazole scission in TFA. The p.m.r. spectrum in TFA shows a one proton singlet at τ 2·73, which may be assigned to the benzylic proton in the ring opened species (199). The spectrum also shows a triplet at τ 8·55, which together with the quartet



(199)



(200)

a) R = OAc
b) R = $OCOCF_3$
c) R = OH

at τ 5·40 may be assigned to the ethyl group, and a signal at τ 0·85 assigned to the pyrimidine proton. The acid (198) reacted with acetic acid to afford a compound whose high frequency carbonyl absorption at 1745 $cm.^{-1}$ suggested that it was the acetate (200a). This structure assignment is verified by the p.m.r. spectrum of (200a) in TFA which showed singlets at τ 0·86, 2·97 and 7·58 attributable to the pyrimidine, benzylic and methyl protons respectively. The p.m.r. spectrum of the acid (198) in TFA also demonstrated triazole scission. Initially singlets were observed at τ 0·89 and 2·94 attributable to a pyrimidine and a benzylic proton respectively in a ring opened species, formulated as (200b) by analogy with the species formed from the triazolopyrimidines (167a) and (168a) in TFA (see above). On taking the spectrum of the acid (198) again after 24 hours it was observed that it contained singlets at τ 0·95 and τ 3·75, presumably due to formation of the hydroxy compound (200c)(see previously).

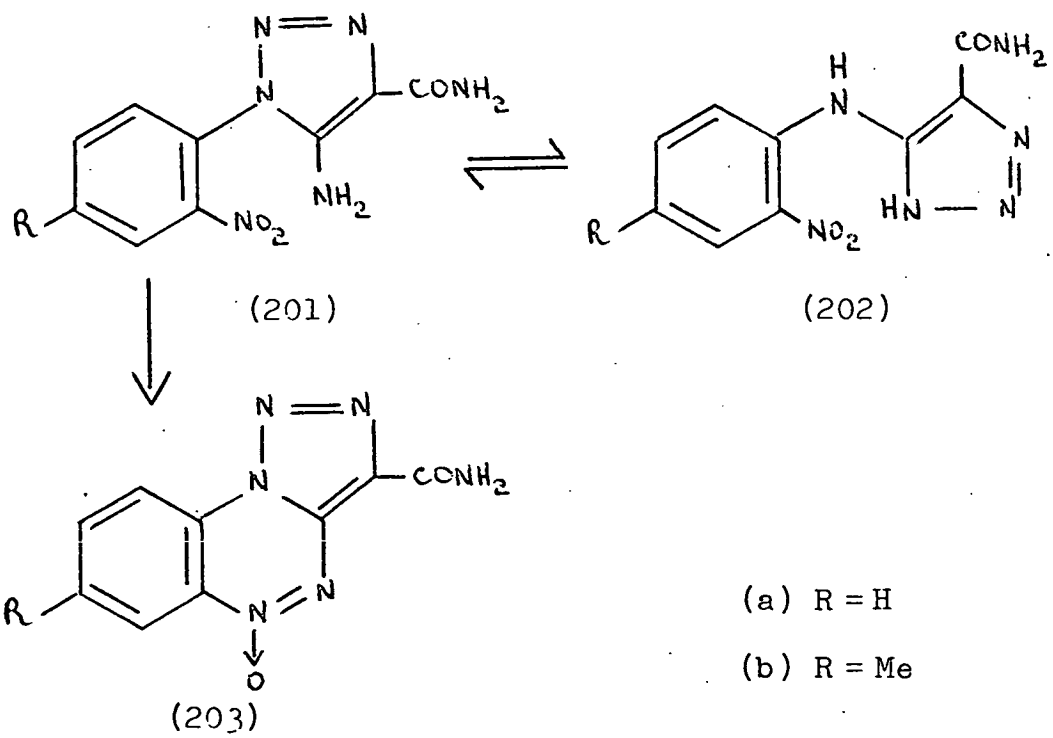
Part 2. Section 3. (2.3)

Synthetic routes to
1,2,3-triazolo[5,1-c]benzo-1,2,4-triazines.
The halogenation of substituted
5-amino-1,2,3-triazoles.

The observation (see Part 2, Section 1) that 5-amino-3-carbamoyl-1,2,3-triazolo[1,5-a]quinazoline (133b) and its cyano analogue (133c) were stable to glacial acetic acid, presumably due to the electron withdrawing characteristics of the 3-substituents lessening the basicity of the triazole ring, prompted investigations into the effect of negative groups on the stability of the 1,2,3-triazolo-[5,1-c]benzo-1,2,4-triazine ring system. Triazole scission, in glacial acetic acid and aqueous sulphuric acid, has been observed in the phenyl substituted triazolobenzotriazine (121), which was prepared by condensing 2-nitrophenyl azide with phenylacetonitrile in the presence of sodium methoxide.[61,62] This reaction presumably proceeds via the triazole (120) which then cyclises by an aldol type condensation, between the nitro and amino groups with the elimination of water. The triazole (120) was not isolated in these reactions.[61,62] Attempts were made therefore to synthesise the triazolobenzotriazines (203a,b) in order to study their chemical activity.

The reaction of 2-nitrophenyl azide with cyanoacetamide in the presence of sodium methoxide afforded three products, a colourless basic solid and two acidic solids, one of which was red and the other yellow. The yellow solid was soluble in saturated sodium bicarbonate

solution, and was reprecipitated by acid, whereas the red solid was only soluble in dilute alkali, again being reprecipitated by acid. Elemental analysis showed that the colourless solid had a molecular formula $C_9H_8N_6O_3$, and its i.r. spectrum showed nitro group absorption as well as bands in the NH region (3000 - 3500 $cm.^{-1}$) and a carbonyl absorption at 1640 $cm.^{-1}$ The insolubility of the colourless solid in dilute alkali was in agreement with its assigned structure (201a). On crystallisation from ethanol the colourless crystals became a faint red colour, and on prolonged refluxing in the solvent of crystallisation an insoluble red solid isomeric with the colourless compound was formed. This solid was identical with the red product obtained from the condensation of 2-nitrophenyl azide with cyanoacetamide. Its i.r. spectrum showed nitro, amide and



(201) (202)

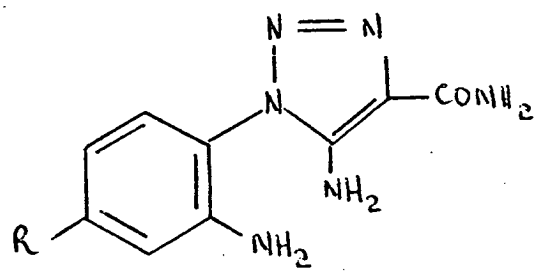
(203)

(a) R = H

(b) R = Me

NH absorption. It was readily soluble in aqueous alkali and reprecipitated by acidification. This behaviour is in accord with the 1-H-1,2,3-triazole structure (202a). The basic compound (201a) was also convertible into the isomer (202a) on dry heating at 140°. The p.m.r. spectrum of the compound (201a) in TFA showed an aromatic multiplet, which had changed into the aromatic multiplet of compound (202a) after 24 hours. This demonstrates that the rearrangement [(201a) ⟶ (202a)] occurs in acidic media at room temperature. The homologue (201b) of the triazole amide (201a) was prepared by condensing 4-methyl-2-nitrophenylazide with cyanoacetamide in the presence of sodium methoxide. This condensation also yielded the acidic isomer (202b) as a by-product and a yellow acidic solid homologous with that obtained from 2-nitrophenyl azide. The p.m.r. spectrum of the amide (201b) in TFA showed a methyl singlet at τ 7·38, but after 24 hours in solution this had shifted upfield to τ 7·45, and the complete spectrum was then identical to that of the acid isomer (202b). Therefore Dimroth rearrangement had again occurred in TFA at room temperature.

Hydrogenolysis of the nitro amines (201a) and (201b) afforded the diamines (206a) and (206b) respectively, whose



(206)

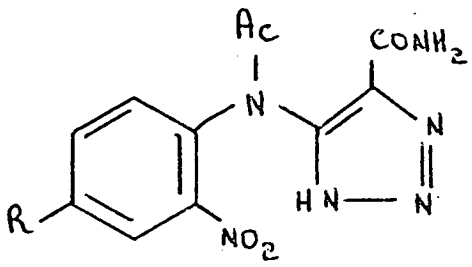
(a) R = H
(b) R = Me

structures are supported by elemental analysis and by their i.r. spectra which lack nitro absorption but contain absorption due to primary amino and amide groups. The diamines (206a,b) were not so susceptible to Dimroth rearrangement as the nitro compounds (201a,b). This was demonstrated by the lack of change in their p.m.r. spectra in TFA after 24 hours. For instance the methyl signal of the diamine (206b) at τ 7·43 shows no change in chemical shift after 24 hours. This lack of rearrangement is in accord with the electron donating effect of the 1-(2-amino-phenyl) substituent, which will stabilise the triazole ring in (201a,b) to Dimroth rearrangement, (see Part 2, Section 4). The structures assigned to the diamines are supported by their p.m.r. spectra. Thus the p.m.r. spectrum of (206b) in d_6-DMSO shows a methyl singlet at τ 7·40, an aromatic multiplet centred at τ 3·0 and broad singlets at τ 2·13 and 2·55 due to the amide NH protons. Significantly the spectrum also shows singlets at τ 3·69 and 4·66 which may be assigned to the primary amino groups in the molecule.

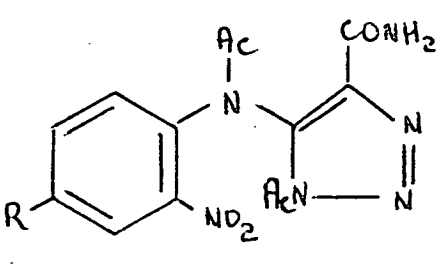
The yellow acidic solids obtained as by-products in the reactions of 4-methyl-2-nitrophenyl azide, and 2-nitrophenyl azide, with cyanoacetamide had molecular weights of 244 and 230, and analysed for $C_{10}H_8N_6O_2$ and $C_9H_6N_6O_2$ respectively. They were soluble in saturated aqueous sodium bicarbonate, thereby precluding N-oxide structures (203a) and (203b) which would otherwise satisfy the molecular weights and elemental analysis. The absence of an N-oxide group in the yellow solids was further

demonstrated by the observed lack of reaction with sodium dithionite. The assignment of structures to these yellow products awaits further experimental work.

The Dimroth rearrangements of the aminotriazoles (201a) and (201b)(see above) appears to be complete in refluxing ethanol and in TFA at room temperature. The product obtained after reflux in ethanol is completely soluble in dilute alkali, thus excluding the presence of equilibrium mixtures [(201a) $\rightleftharpoons$ (202a)] or [(201b) $\rightleftharpoons$ (202b)] containing the basic isomers (201a) and (201b) which are insoluble in dilute alkali. Refluxing the basic isomers (201a) and (201b) in cellosolve, dilute alkali or dilute acid also results in complete isomerisation to the acid isomers (202a)and (202b) respectively. Acetylation of the aminotriazoles (201a) and (201b) also caused Dimroth rearrangement. The aminotriazole (201a) and its anilino isomer (202b) formed the same monoacetyl and diacetyl derivatives when refluxed in acetic anhydride. Both acetyl derivatives hydrolyse to the anilinotriazole (202a), under conditions which do not form (202a) from the basic isomer (201a). An anilinotriazole nucleus in the acetyl compounds is therefore indicated. The p.m.r. spectrum of the monoacetyl compound shows a methyl singlet at τ 7·00, and the i.r. spectrum contains carbonyl absorption at 1760 $cm.^{-1}$ These features are typical of an acetyl group attached to a triazole ring nitrogen (see Part 2, Section 4). Likewise the p.m.r. spectrum of the diacetyl compound exhibits methyl singlets at τ 7·00 and τ 7·30, the latter being in



(204)



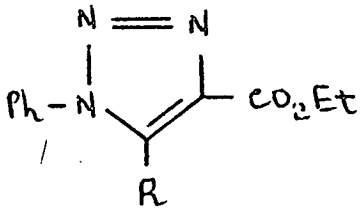
(205)

(a) R = H

(b) R = Me

the range attributable to an N-acetylamide group, (see Part 2, Section 4). Carbonyl absorptions at 1760 and 1700 $cm.^{-1}$ in the diacetyl product are in the ranges expected for ring N-acetyl and N-acetylamide groups. The mono- and diacetyl compounds are therefore assigned the structures (204a) and (205a) respectively. The aminotriazole (201b) and the anilinotriazole (202b) formed analogous acetyl derivatives, which are assigned the structures (204b) and (205b) on the basis of their i.r. spectra.

Attempts to cyclise the basic aminotriazoles (201a) and (201b) by refluxing them with ethanolic sodium ethoxide were unsuccessful. This treatment caused isomerisation to the anilinotriazoles (202a) and (202b), which failed to cyclise. Thus cyclisation of (201a) and (201b) appears to be difficult presumably due to rapid isomerisation to the Dimroth isomers (202a) and (202b) respectively. The rapid isomerisation is to be expected (see Part 2, Section 4) due to the electron withdrawing 2-nitrophenyl and 4-methyl-2-nitrophenyl substituents, which tend to destabilise the basic isomers (201a) and (201b).



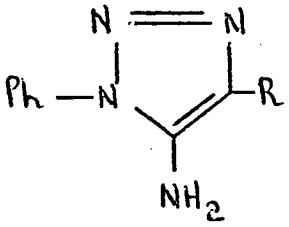
(209)

(a) R = NH_2

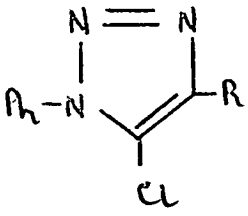
(b) R = N_3

(c) R = N:

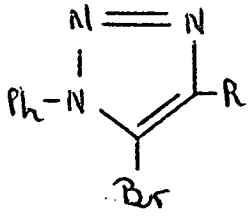
(d) R = Cl



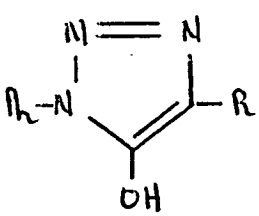
(213)



(214)



(215)



(216)

(a) R = Ph

(b) R = $CONH_2$

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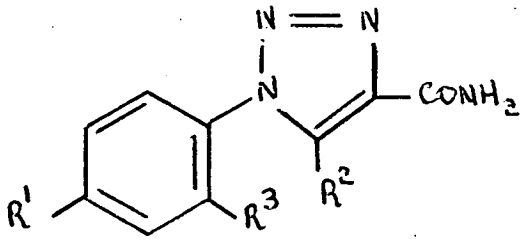
(217)



(a) R^1 = H, R^2 = R^3 = Cl

(b) R^1 = H, R^2 = R^3 = Br

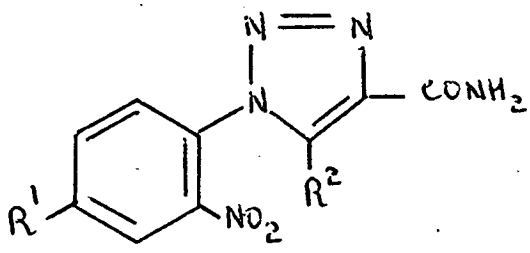
(c) R^1 = Me, R^2 = R^3 = Cl

(d) R^1 = Me, R^2 = R^3 = Br

(e) R^1 = Me, R^2 = Cl, R^3 = N_3

(f) R^1 = Me, R^2 = N_3, R^3 = Cl

(218)



(a) R^1 = H, R^2 = Cl

(b) R^1 = H, R^2 = Br

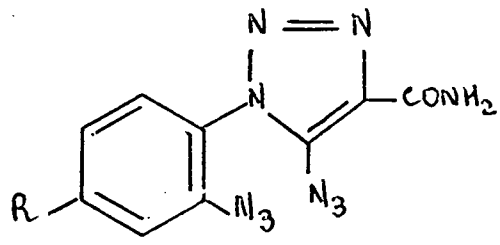
(c) R^1 = Me, R^2 = Cl

(d) R^1 = Me, R^2 = Br

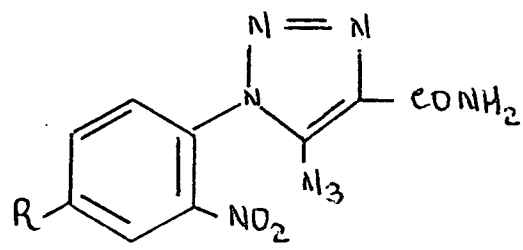
(e) R^1 = Me, R^2 = N_3

It was therefore desirable to develop other routes to the required derivatives of the triazolo[5,1-c]benzotriazine ring system.

A route to the triazolobenzotriazines (203a,b) was sought via the diazides (207a,b) and the monoazides (208a,b). It was considered that these compounds might cyclise on pyrolysis or photolysis via a nitrene intermediate. It is known that 5-azido-4-carbethoxy-1-phenyl-1,2,3-triazole (209b) on pyrolysis affords products which may be formed via the nitrene (209c).[89] Shemyakin and co-



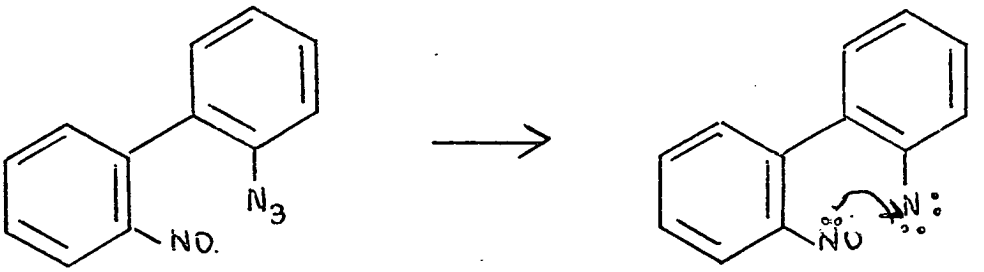
(207)



(208)

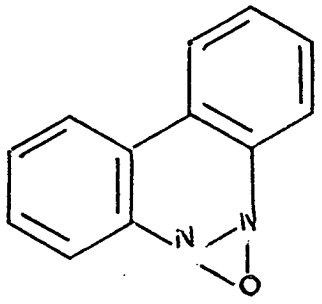
(a) R = H
(b) R = Me

workers[90] have reported that 1-azido-1'-nitrosobiphenyl (210) affords the N-oxide (212) on photolysis or pyrolysis. This reaction may proceed via the nitrene (211) in which the active hydrogen reacts with the nitroso group leading to (212), or to (212a), which then isomerises into (212). However during attempts to prepare the azides by the addition of sodium azide to the diazonium solutions of (201b) and (206b) the precipitation of chlorinated compounds was observed. Therefore using identical conditions, the amino-triazoles (213a,b) were diazotised in hydrochloric acid,

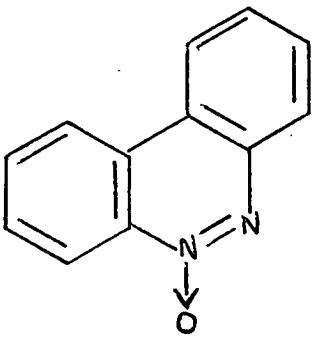


(210)

(211)



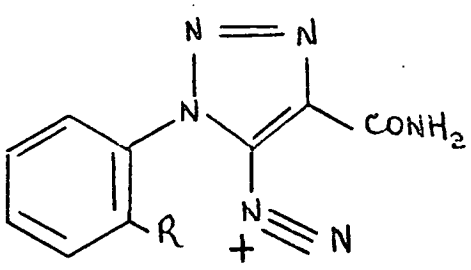
(212a)



(212)

yielding the chloro compounds (214a,b) respectively. To verify the structures of these products the chloro compound (214a) was compared with an authentic sample prepared by reacting the hydroxytriazole (216a) with phosphorus pentachloride and phosphorus oxychloride.[83] Using 50% hydrobromic acid as the acid medium for diazotisation of the amines (213a,b), the bromotriazoles (215a,b) were obtained. The bromo compound (215a) was convertible into the known hydroxytriazole (216a)[6] by treatment with aqueous alkali. In similar reactions diazotisation of the amines (201a,b)

and (206a,b) in hydrochloric and hydrobromic acids afforded the halogenated products, (217a-d) and (218a-d), whose structures are assigned by analogy. Formation of the dichloro (217a,c) and the dibromo (217b,d) compounds demonstrates that halogenation is not confined to an amino group on a triazole ring, but also occurs with an anilino amino group. Smith and his coworkers[89] used somewhat different conditions for the successful diazotisation of the amine (209a), and its conversion into the azide (209b). These authors did not observe the formation of an halogenated triazole. Consequently the amine (213a) was diazotised using Smith's conditions. In this case a diazonium solution was obtained (demonstrated by the formation of a red precipitate with alkaline 2-naphthol) but on the addition of water the chlorotriazole (214a) was precipitated in good yield. It appears therefore that the halogenotriazoles are formed via the diazonium salts and not directly from the aminotriazoles. The presence of the diazonium salt in solution prior to the precipitation of the halogenated triazoles could sometimes, but not always be detected by the development of a red colour with alkaline 2-naphthol. It appears, from the results using Smith's conditions, that the water concentration in the diazonium solution is the controlling factor. Varying the volume of acid and weight of sodium nitrite relative to the aminotriazoles did not inhibit the formation of the halogenated compounds on dilution with water. These reactions constitute a valuable route to halogenated triazoles which does not appear to be affected by the other substituent present. In



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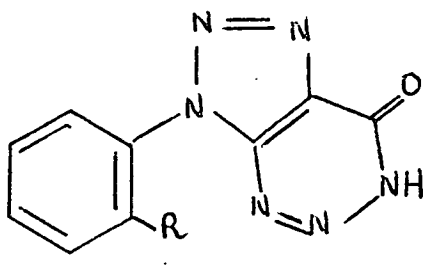
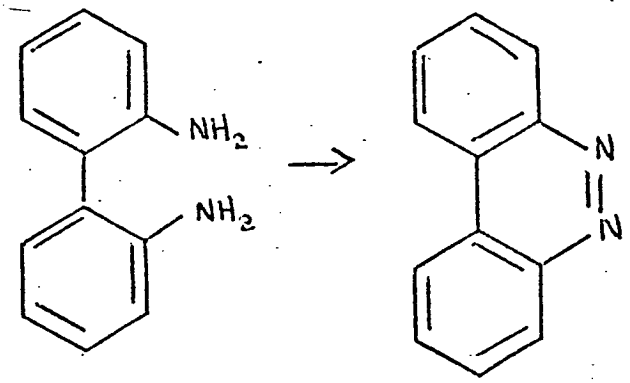


(220)

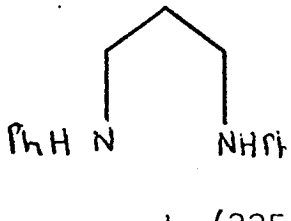
particular there appears to be no interference by the amide group which might have been expected to interact with the diazonium group on the triazole ring [(219) ⟶ (220)].

The known routes to chlorotriazoles involve classical methods such as treatment of the hydroxy compound with phosphorus pentachloride or phosphorus oxychloride,[83] or Sandmeyer reaction on the diazonium salt.[34] Lieber and coworkers report[91] that treatment of an ethanolic solution of the amine (209a), saturated with hydrogen chloride, with amyl nitrite afforded the chlorotriazole (209c).

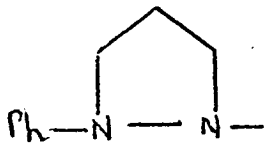
The solutions of the diazonium salts derived from the nitro compound (201b) and the diamine (206b) were prepared by ensuring that the volume of water used in the diazotisation was kept to a minimum. Both diazonium solutions gave positive tests with alkaline 2-naphthol, and on the addition of an aqueous solution of sodium azide solids were obtained. The mass spectra of the crude solids so obtained indicated the presence of both azide and chlorinated products. Compound (201b) yielded a solid whose mass spectrum showed strong peaks at 281 and 283 mass units in a ratio of 3:1



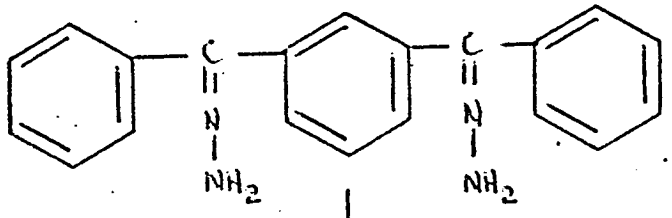
(221) (222)



(225



(226)



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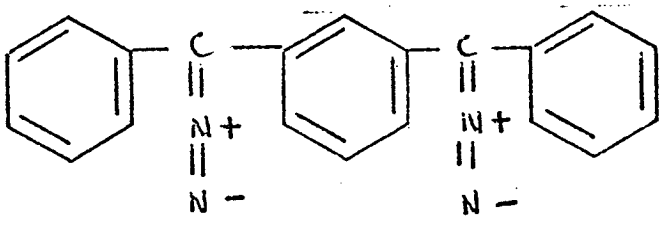
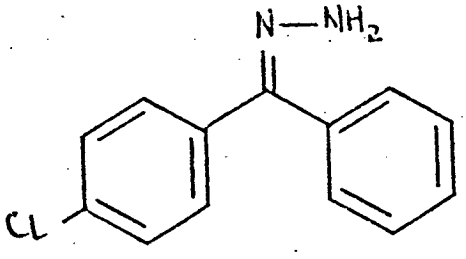


(224)



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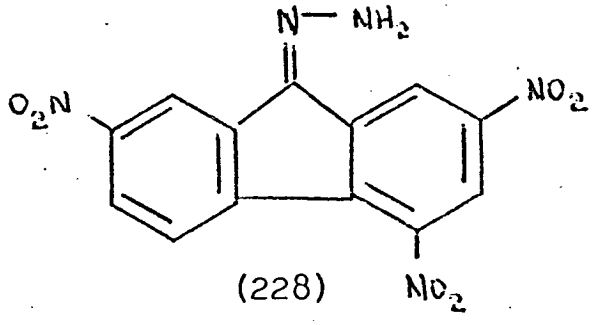
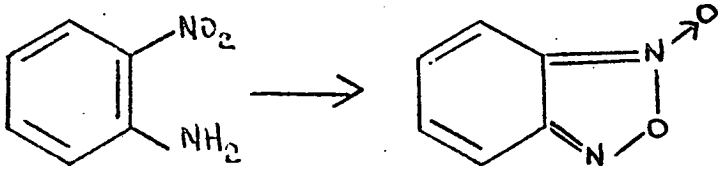


(228)

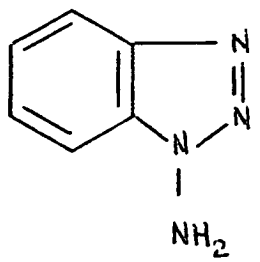


(229) (230)

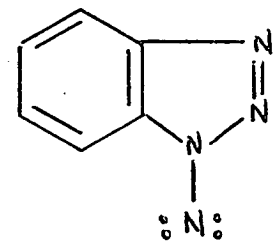
indicating the presence of a chloro compound, which can be assigned the structure (218c). This mass spectrum also showed a peak at 294 mass units which can be assigned to the azide (218e). The i.r. spectrum of the mixture showed an absorption at 2150 $cm.^{-1}$ attributable to an azide group. Separation of the mixture of (218c) and (218e) could not be achieved by fractional crystallisation, and the relative insolubility of the mixture precludes the use of chromatographic techniques. The diamine (206b) also afforded a mixture on diazotisation followed by treatment of the diazonium solution with aqueous sodium azide. The mass spectrum of the crude solid, which was not separable by crystallisation, showed peaks at 270 and 274 mass units, attributable to the dichloro compound (217c), and peaks at 283 and 285 mass units attributable to either of the chloro azides (217e) or (217f). Azide absorption was also evident in the i.r. spectrum of the mixture. Even reducing the volume of water, used to dissolve the sodium azide, to a minimum caused formation of the chloro compounds. It was therefore decided to examine another route to the required derivatives (203a,b) of the triazolo[5,1-c]benzo-1,2,4-triazine ring system.

It is known that 2,2'-diaminobiphenyl (221) is oxidised to benzo[c]cinnoline (222) by active manganese dioxide.[92] The same reagent converts the bishydrazone (223) into the purple diazo compound (224),[93] whereas mercuric oxide, the usual reagent used for such oxidations, gave very low yields of (224). N,N'-diphenylpyrazolidine (226) is

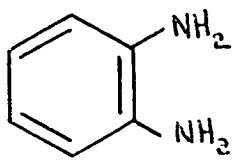
obtained by oxidation with active manganese dioxide of 1,3-dianilinopropane (225).[94,95] Silver oxide fails to oxidise hydrazones of the type (227)[96] or (228),[97] and is thus presumably a weaker oxidising agent than active manganese dioxide.[98] It has been reported that an alkaline solution of sodium hyprochlorite oxidises 2-nitroaniline (229) to benzofuroxan (230).[99] Lead tetraacetate has been used to oxidise 1-aminobenzotriazole (231) to benzyne,[59] the reaction proceeding via the nitrene (232). A nitrene



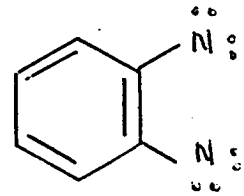
(231)



(232)



(233)



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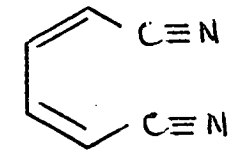
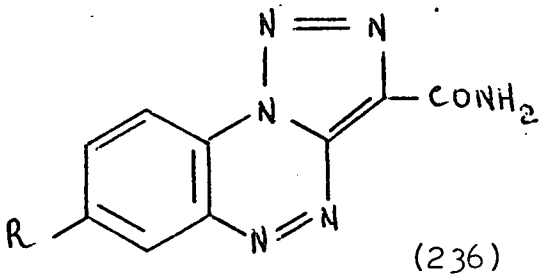


(235)

intermediate (234) is invoked to account for the lead tetraacetate oxidation of 2-aminoaniline (233) to muconononitrile (235).[100]

In the present work it was found that the diamines (206a,b) were unaffected by active manganese dioxide. However lead tetraacetate oxidation afforded compounds formulated as the triazolobenzotriazines (236a,b). The p.m.r. spectrum of (236b) in d_6-DMSO showed no evidence of primary amino group absorption, which were evident in the

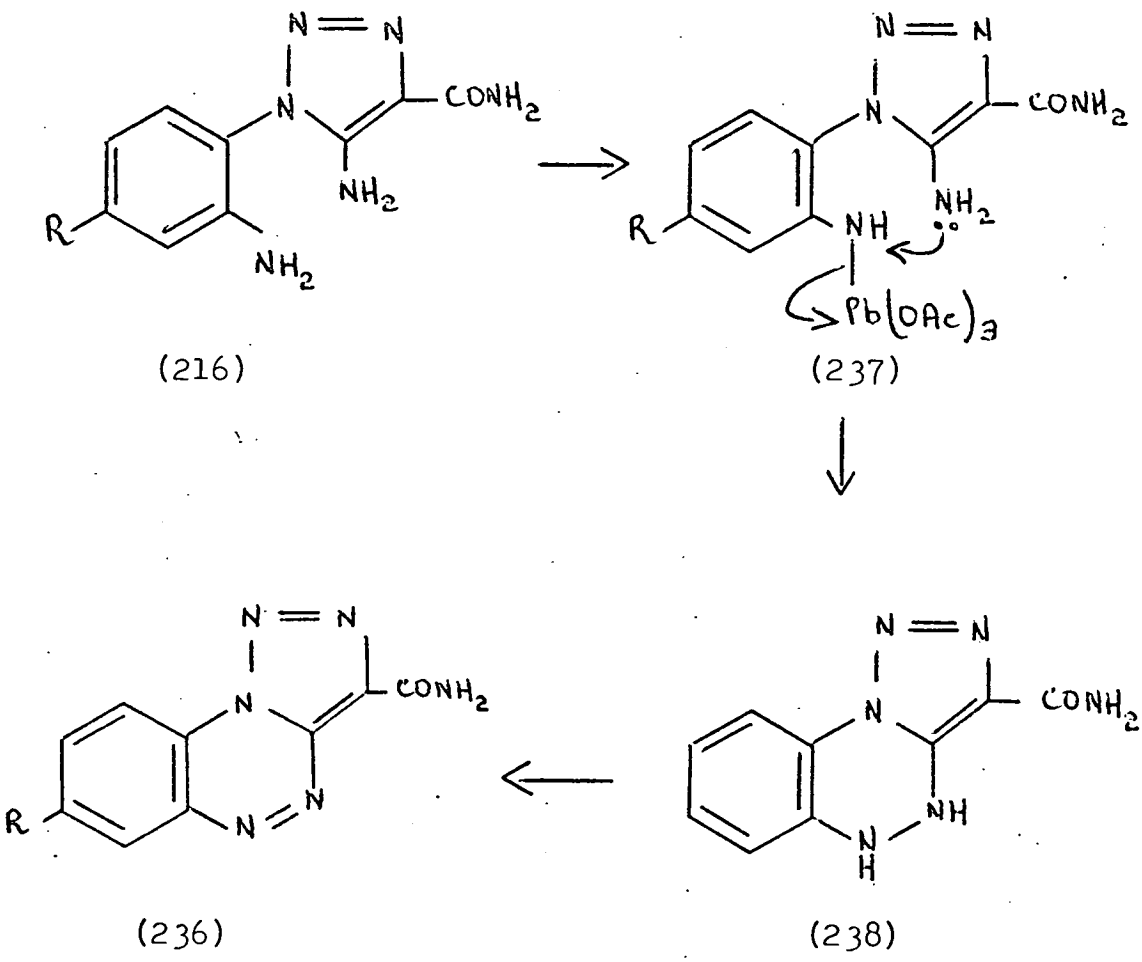


(236)

(a) R = H
(b) R = Me

diamine (206b) (see above). Also the molecular weight (228) of the product from oxidation of the diamine (206b) indicated a loss of 4 mass units. The presence of an amide group in the triazolobenzotriazine (236b) is supported by a characteristic i.r. absorption at 1675 $cm.^{-1}$ The spectral data of compound (236a) was also consistent with the assigned structure. Treatment of the compounds (236a,b) with acetic acid did not cause triazole scission, presumably due to the electron withdrawing effect of the amide group (see above). Also the p.m.r. spectra of the triazolobenzotriazines (236a,b) in TFA did not alter after 48 hours in solution.

The lead tetraacetate oxidation of the diamines (206a,b) to the triazolobenzotriazines (236a,b) can be explained by attack of a primary amino group with the $[^{+}Pb(OAc)_3]$ cation to form the intermediate (237). The lone pair on the remaining primary amino group will then

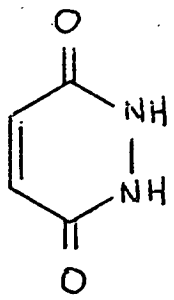


(216) (237) (238) (236)

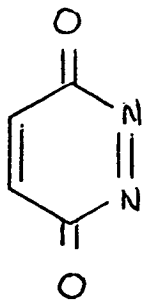
Scheme 13

insert (see scheme 13), affording the dihydro compound (238) which will be further oxidised to the triazolobenzotriazine (236). The latter step is feasible since 1,2-dihydro-pyridazine-3,6-dione (239) is known to be oxidised by lead tetraacetate to the dehydro product (240).[101,102] Although Nakagawa and Onue[100] have invoked a nitrene intermediate

for the transformation [(233) ⟶ (235)] (see above), other



(239)



(240)

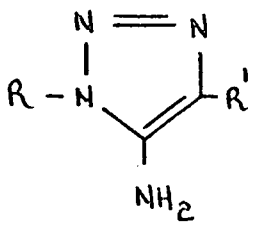
workers suggest the preferential formation of lead intermediates during lead tetraacetate oxidations.

Part 2. Section 4. (2.4)

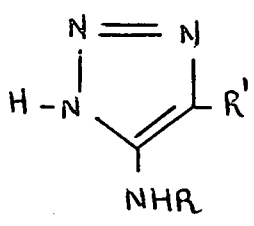
Dimroth rearrangements of

4-substituted-5-amino-1-phenyl-1,2,3-triazoles.

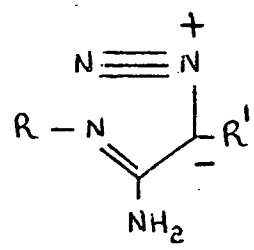
The Dimroth Rearrangement of substituted-5-amino-1,2,3-triazoles (241) and 5-substituted amino-1,2,3-triazoles (242) was first reported by Dimroth,[34,35] who postulated an acyclic diazo form (243) as an intermediate. Later workers[39] suggested a bridged intermediate (244), but this was disproved by kinetic studies.[22,48,53] Dimroth showed[34,35]



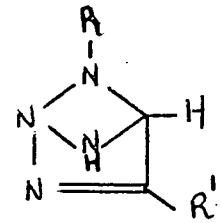
(241)



(242)

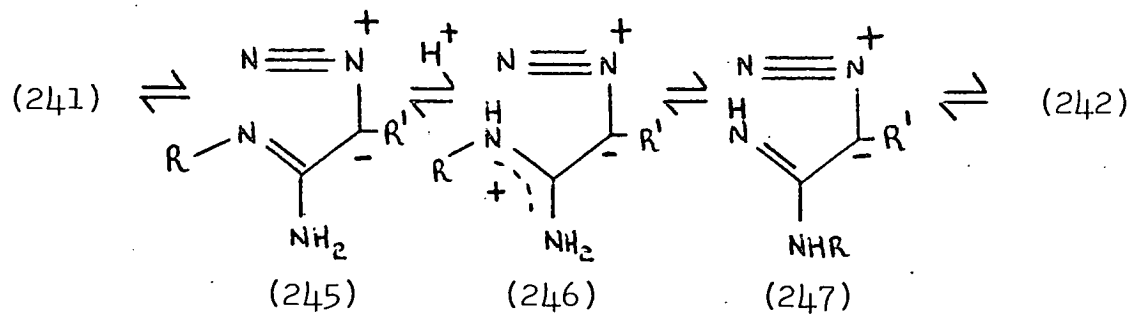


(243)



(244)

that heating either (241) or (242) in water, pyridine, or in a homogeneous melt yielded the same equilibrium mixture. The rate of isomerisation of 5-amino-4-carbethoxy-1-phenyl-1,2,3-triazole (241, R = Ph, R' = CO_2Et) in ethanol was studied by Hammick and coworkers.[53] By varying the groups on the para position of the 1-phenyl group they demonstrated that the instability of the basic isomer (241) was increased by electron withdrawing groups, and reduced by electron donating groups. A slow approach to equilibrium was observed in the absence of acid, but in the presence of trace amounts of picric acid a first order rate law was followed. From these results Hammick postulated a mechanism involving protonation of the acyclic diazo species, followed by rotation, deprotonation and recyclisation [(245) $\longrightarrow$ (247)]. This mechanism accounts for the facilitating effect of electron

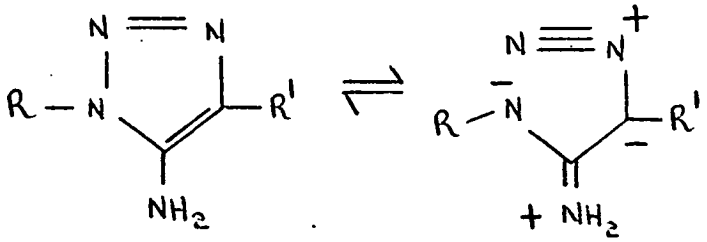


(245) (246) (247)

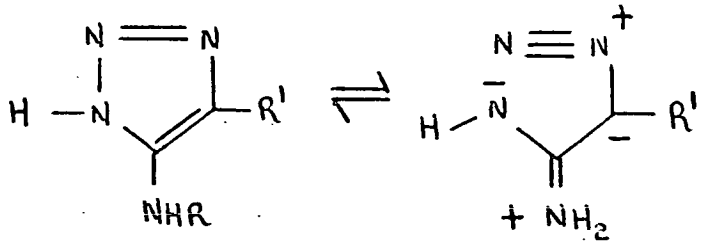
withdrawing groups on the 1-position on the forward reaction. Electron withdrawal by decreasing the resonance energy of the basic isomer and causing polarisation of the 1,2-bond will thereby aid formation of the acyclic diazo intermediate (245). However it does not explain why electron donating groups on the exocyclic nitrogen increase the instability of the acid isomer (242). Also, studies on the ring opening of fused triazoles have shown the preference for proton attack at the N(2) position before ring opening,[60] and protonation at the negatively charged C(4) position after ring opening.[61-63] Therefore the protonation step envisaged by Hammick [(245) ⇌ (246)] is rather unlikely.

Lieber and coworkers[48] investigated the kinetics of the thermal Dimroth rearrangements of aminotriazoles (241) and (242). They studied both the acid and basic isomers, the former being obtained by refluxing the basic isomer in pyridine. Under basic conditions the conversion of the basic isomer into the acid isomer is irreversible. It was found that electron withdrawing groups on the 1-nitrogen atom of the triazole ring again promoted the

forward reaction [(241) ⟶ (242)] whilst electron donating groups on the exocyclic nitrogen promoted the back reaction [(242) ⟶ (241)]. On examining both isomers in homogeneous melts a first order rate law was established. From these results Lieber argued[48] that, since the rate of the forward reaction was increased by increasing the electronegativity of the 1-substituent and the rate of reverse reaction was decreased by increasing the electronegativity of the exocyclic substituent, heterolysis of the nitrogen-nitrogen bond in the ring must occur so that the negative change in the diazo intermediate is on the nitrogen originally in the 1-position of the triazole ring. Therefore intermediates (248) and (249) were postulated.



(241) (248)

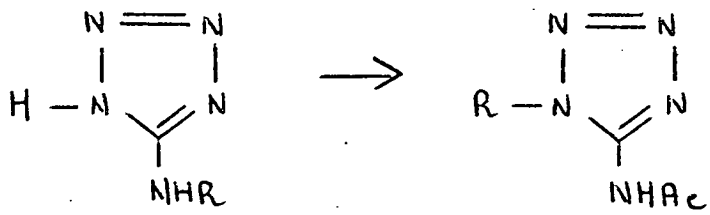


(242) (249)

It can be seen from this scheme that the mechanism accounts for the electronic effects of the substituents by demanding a shift of electrons from the exocyclic amino group into the ring causing heterolytic cleavage of the 1,2-bond. Cleavage of the 1,2-bond may be promoted by electron donation from the exocyclic substituent or by electron withdrawal by the 1-nitrogen substituent, and so the rate of isomerisation is dependent on the polarity of the substituents. It has been suggested that bulky substituents prefer to exist on the exocyclic position, thereby alleviating steric strain.[37] This has proved correct experimentally, but is a minor effect, easily overruled by electronic factors.

When treated under conditions which favour isomerisation 5-amino-1-phenyl-1,2,3-triazoles (241, R = Ph)[34,35,4] give an equilibrium mixture [(241) $\rightleftharpoons$ (242)] in which the acidic isomer (242) predominates. Therefore the phenyl residue must be exerting an electron withdrawing effect on the triazole ring due to the sp^1 hybridised state of the carbon atoms in the benzene ring. For example when the aminotriazole (241, R = R' = Ph) on its acid isomer (242, R = R' = Ph) was heated[41] in an homogeneous melt the product contained 75% of the acid isomer.

Acylation has been shown to cause Dimroth rearrangement in the tetrazole series,[40] as exemplified by the acetylation of 5-alkylaminotetrazoles (250) to give 5-acetylamino-1-alkyltetrazoles (251). This demonstrates the preference of the more electronegative group to be exocyclic, and the more electropositive group to be on the ring.



R = aryl or alkyl.

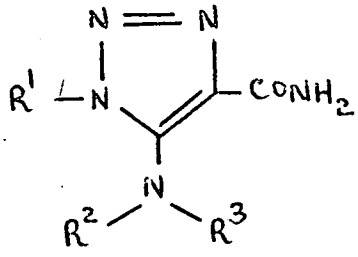
(250) (251)

The acetylation of substituted 5-amino-1,2,3-triazoles is also known to cause rearrangement. Heating the amide (241, R = Ph, R' = $CONH_2$)[103] or the ester (241, R = Ph, R' = CO_2Et) with acetic anhydride is reported to yield monoacetyl derivatives of the acid isomers (242, R = Ph, R' = $CONH_2$) and (242, R = Ph, R' = CO_2Et). However the positions of the acetyl groups in the products were not established. The rearrangement accompanying these acetylations is in contrast to the lack of rearrangement in the formylation[49] of 5-amino-1,2,3-triazoles, and in processes involving their acylation, which ultimately yield 1,2,3-triazolo[4,5-d]pyrimidine derivatives.[49,103,104]

The effect of the 4-substituent on the Dimroth rearrangement of 5-amino-1,2,3-triazoles has not yet been fully investigated, although it has been shown[41] that, for 4-substituted-5-amino-1-phenyl-1,2,3-triazoles (241, R = Ph) the acidic isomer is favoured in the order 4-phenyl > 4-H > 4-carbethoxy, when either the basic or acid isomer is heated in a melt at 184-185°. However Albert[105] has shown that the reverse reaction (retrogression), at equilibrium,

is less complete with a 4-carbamoyl or 4-carboxy substituent than with an unsubstituted 4-position. These results suggest that an electron withdrawing group on the 4-position enhances retrogression from the acidic isomer (242) to the basic isomer (241) and also enhances the forward reaction [(241) $\longrightarrow$ (242)]. This point therefore requires clarification.

The relatively electropositive benzyl group has been shown to exist preferentially on the ring. Indeed Albert[105] has demonstrated the retrogression of 5-benzylamino-1-H-1,2,3-triazole (242, R = CH_2Ph, R' = H) to the basic isomer (241, R = CH_2Ph, R' = H) by refluxing in ethanol. The rate of retrogression was enhanced by higher boiling solvents. It has also been observed[49] that 4-carbamoyl-5-methylamino-1-H-1,2,3-triazole (242, R = CH_3, R' = $CONH_2$) retrogresses to the basic isomer (241, R = CH_3, R' = $CONH_2$) when refluxed in cyclohexanol for one hour. These results demonstrate the reversibility of the Dimroth rearrangement of amino-1,2,3-triazoles. They also show that the course of rearrangement depends on the electronic effects of substituents. Rearrangement will always occur so as to place the more electron withdrawing substituent on the exocyclic nitrogen. However the apparent anomaly of the lack of rearrangement observed in the formylation of amino-1,2,3-triazoles compared with the ready rearrangement which occurs on acetylation, prompted a closer examination of reactions of this type.



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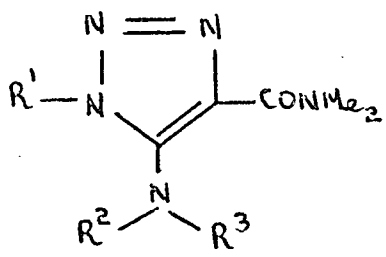

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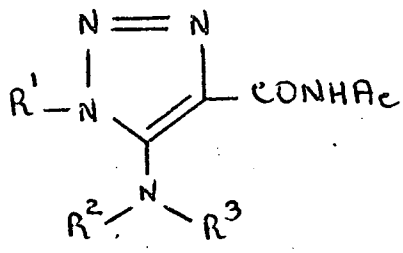

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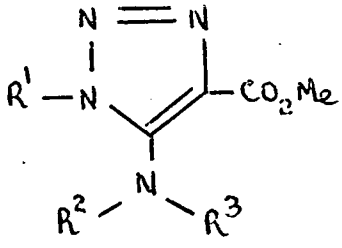

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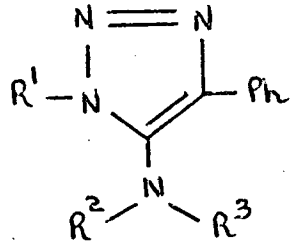
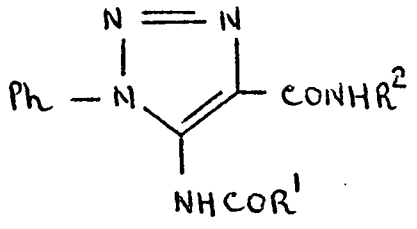


(256)

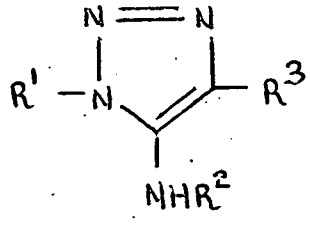
	R^1	R^2	R^3
(a)	Ph	H	H
(b)	Ph	H	Ac
(c)	Ph	Ac	Ac
(d)	H	H	Ph
(e)	Ac	H	Ph
(f)	Ac	Ac	Ph
(g)	$COCH_2Ph$	H	Ph

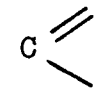
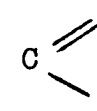
(257)



	R^1	R^2
(a)	Et	COEt
(b)	CH_2Ph	H
(c)	CH_2Ph	$COCH_2Ph$

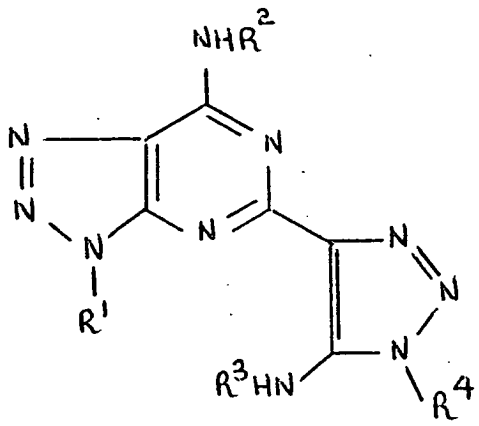
(258)



	R^1	R^2	R^3
(a)	Ph	H	CO_2H
(b)	H	Ph	CO_2H
(c)	Ph	H	CN
(d)	Ph	H	
(e)	H	Ph	

The aminotriazoles (252a), (253a), (255a) and (256a) studied were available by the base catalysed condensation of phenyl azide with the appropriate aceto-nitrile derivative. The acid (258a) was obtained as a by-product in the synthesis of the ester (255a) and was converted into the latter by esterification. The anilino isomers were synthesised by pyridine isomerisation of the corresponding 5-amino-1-phenyl-1,2,3-triazoles, the basic conditions allowing irreversible formation of the acidic (anilino) isomers. Treatment of the ester (255a) in this manner resulted in the formation of the known[34] decarboxylated product (274, $R^1=R^2=H$), as well as the rearranged ester (255d). The amide (252a) was also readily isomerised in hot aqueous or glacial acetic acid to yield an equilibrium mixture, in which the acidic isomer (252d) predominated. Isomerisation was also observed on heating the amide (252a) for a long period in strong aqueous alkali, the product being the carboxylic acid (258b), which was identified by esterification to the ester (255d). The nitrile (258c) is reported[103] as the product, m.p. 320°, obtained by condensing phenyl azide with malononitrile in the presence of sodium methoxide. Repetition of this reaction yielded a product identified as the iminoether (258d), from its p.m.r. spectrum, which showed a methyl singlet at τ 6·06, and its conversion, on hydrolysis, into the known ester (255a).[34] The high melting solid was also isolated, as was a compound whose molecular weight (from the mass spectrum) and analysis suggested it was the nitrile (258c). When the reaction was

repeated using sodium ethoxide as the catalyst only the high melting solid was isolated. The mass spectrum of this product indicated a molecular weight of 370 for the parent ion corresponding to a molecular formula $C_{18}H_{14}N_{10}$, and hence a dimer of the nitrile (258c). The analysis supports the formulation of this high melting solid as (260a). The dimer does not show cyano absorption in the



(260)

	R^1	R^2	R^3	R^4
(a)	Ph	H	H	Ph
(b)	Ph	H	Ph	H
(c)	H	Ph	H	Ph
(d)	H	Ph	Ph	H

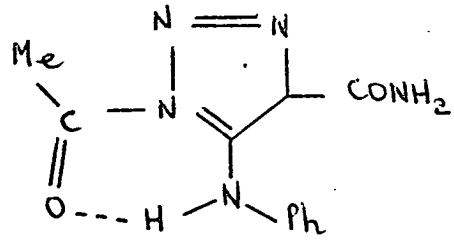
i.r. spectrum unlike the monomer (258c) which has an absorption at 2300 $cm.^{-1}$ but it does show i.r. absorptions at ca. 3250 $cm.^{-1}$ attributable to N-H bonds. A similar structure has been assigned[105] to the product of the base catalysed dimerisation of the nitrile (258c; CH_2Ph for Ph). The compound (260a) was similarly formed when the nitrile (258c) or the imino ether (258d) were refluxed with aqueous alkali. The formulation (260a) for the dimer is consistent with its basic properties (formation of a sparingly soluble salt in dilute sulphuric acid), and its insolubility in dilute alkali, inferring the absence of a triazole NH group. In accord with its 4-substituted-5-amino-1-phenyl-1,2,3-

triazole structure (260a), the dimeric compound readily rearranged to an isomeric compound when it was heated at 200°, or when it was refluxed in pyridine or glacial acetic acid. This isomer is tentatively assigned the structure (260b) on the basis of the Dimroth rearrangement implicit in its mode of formation, its amphoteric properties and its conversion in hot acetic anhydride into a diacetyl derivative, which was also formed from the basic dimer (260a) under similar conditions. Hydrolysis of the diacetyl derivative, under conditions which do not cause isomerisation, yielded the amphoteric dimer (260b). These properties do not exclude the alternative structures (260c) and (260d) for the isomer, but these structures are considered less likely than (260b) in view of the reported[49] failure of 7-amino-1,2,3-triazolo[4,5-d]pyrimidines to undergo Dimroth rearrangement. The transformation [(260a) ⟶ (260b)] will be favoured as it results in the replacement of the relatively electronegative phenyl group on the exocyclic amino group (see previously).

Heating the amide (252a) in acetic anhydride for 3 hours is reported[103] to yield a monoacetyl derivative, m.p. 185°. Repetition of this reaction afforded a product, m.p. 172°, which ran as two spots when chromotographed on alumina, demonstrating that it was a mixture. The p.m.r. spectrum showed two non-equivalent methyl singlets at τ 7·20 and τ 7·40. The former was resolved into a doublet on expansion of the spectrum. Three carbonyl absorptions were observed in the i.r. spectrum, one of which was

attributable to the amide group. Heating the amide (252a) briefly in acetic anhydride gave mainly a monoacetyl derivative, m.p. 161°, together with a small quantity of a diacetyl derivative, m.p. 185°, which was the major product when the amide (252a) or the monoacetyl derivative was refluxed in acetic anhydride for 6 hours. The same products were obtained when the isomeric anilino isomer (252d) was refluxed with acetic anhydride. Cocrystallisation of the pure mono- and diacetyl compounds gave the solid, m.p. 172°, confirming the heterogeneity of the initially isolated solid. The structures of the two acetyl derivatives (252e) and (254e) were assigned on the basis of the following evidence. Anilino structures may be inferred from the hydrolysis of both compounds, to the compound (252d) under conditions which fail to rearrange the aminotriazole (252a) to the acidic isomer (252d). Carbonyl absorption[106] at 1745 - 1760 $cm.^{-1}$ and methyl signals[107,108] at ca. τ 7·20 may be attributed to acetyl groups attached to a nitrogen atom of the triazole ring. The assignment of ring N-acetyl structures to both compounds is in accord with the ready loss of an acetyl group on briefly warming the acetyl compounds in aqueous acetic acid. Under these conditions the monoacetyl compound (252e) afforded the anilinotriazole (252d), whilst the diacetyl compound (254e) gave a monoacetyl derivative (254d) whose i.r. and p.m.r. spectra contained a low carbonyl absorption (table 3), and a methyl singlet in the range expected for an acetylamido group (table 4). The presence of an acetylamide group in

the diacetyl compound (254e) was therefore indicated, and was in agreement with the observed methyl and carbonyl absorptions (tables 3 and 4). It can be seen (table 3) that the ring carbonyl frequency in the monoacetyl and diacetyl compound [(252e) and (254e)] is much lower than that in the triacetyl compound (254f) (see below). This may be attributed to hydrogen bonding between the ring N-acetyl group and the anilino side chain, again demonstrating the absence of an acetyl group on the latter (see Fig. 1).



(252e)

Figure 1

The aminotriazoles (253a), (255a), (256a), and their anilino isomers (253d), (255d) and (256d) fail to form diacetyl derivatives of the acid isomer under conditions similar to the formation of (254e). This supports the position of the second acetyl group in (254e) on the amide group, as this position is not available in the other compounds. The aminotriazoles (253a), (255d), (256a), and their anilino isomers (253d), (255d) and (256d) do form monoacetyl derivatives which are assigned the structures (253e), (255e) and (256e) respectively, on the basis of the relatively low field methyl signals (ca. τ 7·10) (see table 4) and the high carbonyl absorptions

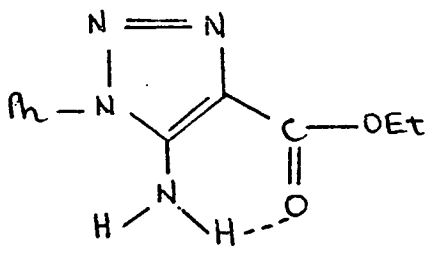
shown by the acetyl groups present in these compounds (see table 3). They are also hydrolysed to the anilino isomers under conditions, which will only hydrolyse triazole ring N-acetyl groups. The i.r. and p.m.r. absorptions of the ring acetyl groups in the compounds (252e), (253e), (254e), (255e) and (256e) are in the ranges expected[108] for 1-N-acetyl-1,2,3-triazoles rather than their 2-N-acetyl isomers. However as the effects of the other substituents on the acetyl absorptions are not known quantitatively, the assignment of the 1-N-acetyl structures to these compounds is purely tentative. Indeed it is known that 1-N-acetyl-1,2,3-triazoles can rearrange to 2-N-acetyl-1,2,3-triazoles when they are refluxed in acetic anhydride.[107,108]

The formation of acetyl derivatives of the acid isomers of aminotriazoles by acetylation of the basic isomers suggests that Dimroth rearrangement is occurring at some stage of the reaction sequence. It is well known that aminotriazoles rearrange thermally,[34,41,48] and under acid-catalysed[53] conditions. It was therefore of interest to investigate the acid-catalysed acetylation of aminotriazoles, and thereby determine whether the uncatalysed acetylations were caused by thermal rearrangement or by another process.

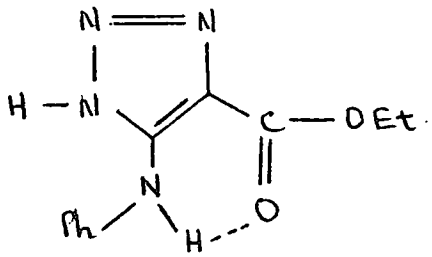
No reaction was observed at room temperature using acetic anhydride alone, but acetylation occurred at room temperature in the presence of concentrated sulphuric acid, to yield unrearranged acetylamino triazoles. Under these conditions the dimethylamide (253a), the ester (255a) and the diphenyltriazole (256a) yielded monoacetyl products on

treatment with acetyl chloride. These products were readily hydrolysed back to the aminotriazoles (253a), (255a) and (256a) under conditions which did not cause isomerisation of the unacetylated anilino isomers (253d), (255d) and (256d). The carbonyl absorptions, 1690 - 1710 $cm.^{-1}$ and the high field methyl signals at ca. τ 7·90, in these monoacetyl compounds are consistent with the structures (253b), (255b) and (256b) respectively. Treatment of the aminotriazoles (253a) and (256a) with acetic anhydride in the presence of concentrated sulphuric acid at room temperature also yielded the unrearranged monoacetyl compounds (253b) and (256b), but (255a) treated similarly afforded a diacetyl derivative, which showed carbonyl absorption at 1710 and 1680 $cm.^{-1}$ and a methyl absorption, representing six protons, at τ 7·80. The lone methyl signal implies equivalence of the two acetyl groups, whilst the chemical shifts of the methyl groups and carbonyl frequencies of the acetyl groups may be assigned to demonstrate the presence of a diacetylamino grouping. The assigned structure (255c) is supported by hydrolysis to the monoacetyl compound (255b) and the unacetylated aminotriazole (258a), the latter, presumably being formed by hydrolysis and dicarboxylation of the ester (255a), into which it is converted by esterification. The carbonyl absorption at 1730 $cm.^{-1}$ in the i.r. spectra of the compounds (255b) and (255c) may be attributed to the ester carbonyl group. The lower frequency of the carbonyl absorption in the unacetylated system (255a) may be explained

by intramolecular hydrogen bonding between the ester group and the unsubstituted amino group. The same effect is observed in the carbonyl frequency of the ester group in the anilino isomer (255d), which also has a relatively low carbonyl absorption frequency.



(255a)

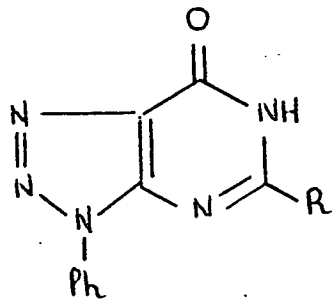


(255d)

Figure 2

Acetylation of the amide (252a) with acetyl chloride in concentrated sulphuric acid yielded a diacetyl compound, assigned the structure (254b) because of the acetylamino methyl signal at τ 7·90 and a methyl signal at τ 7·47, which is in the region appropriate[109] for an acetylamide group. When the compound (254b) was refluxed in acetic anhydride, or when the amide (252a) was treated with acetic anhydride in the presence of concentrated sulphuric, a triacetyl compound was obtained. A six proton methyl singlet at τ 7·75 inferred the presence of a diacetylamino grouping whilst the methyl signal at τ 7·45 was typical[109] of an acetylamide group. The structure (254c) assigned to this triacetyl derivative, and that of (254b) assigned to the diacetyl compound are supported by the carbonyl absorptions. The formation of N-acetylamides by acid catalysed acetylation of primary amides has recently been reported.[109]

Alkaline hydrolysis of the acetyl derivatives (254b) and (254c) failed to yield the parent triazole (252a), which might have been expected from previous results. The product in both cases was a high melting acidic compound

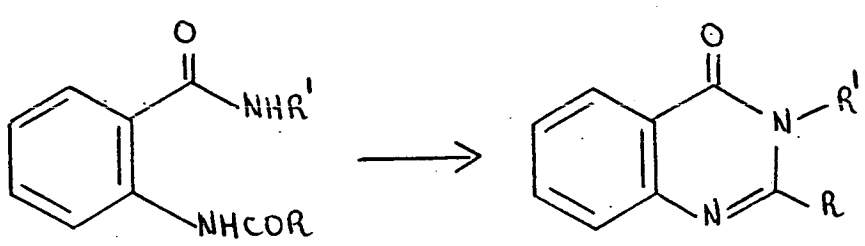


(259)

	R
(a)	H
(b)	Me
(c)	Et
(d)	CH_2Ph

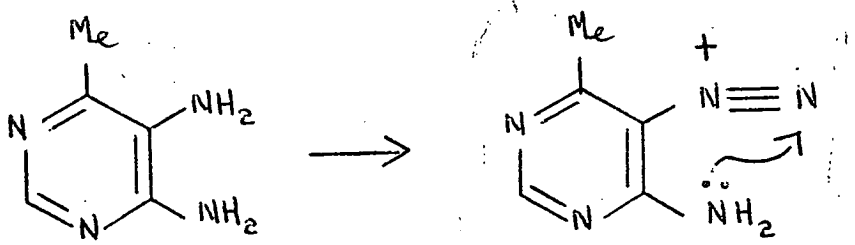
of molecular formula $C_{11}H_9N_5O$. The compound showed a three proton methyl singlet at τ 7·25, and is assigned the 1,2,3-triazolo[4,5-d]pyrimidine structure (259b) on the basis of its ultra violet (u.v.) spectrum, which is identical to that of the known compound (259a).[103] The formation of this compound from the acetyltriazoles [(254b) and (254c)] is analogous to the base-catalysed cyclisation

(261) (262)

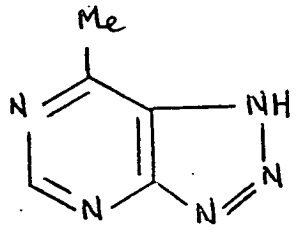


of 2-acylaminobenzamides (261) to quinazolones (262).[110] Acylation of 5-amino-4-carbamoyl-1,2,3-triazoles, followed by base catalysed cyclisation is potentially a valuable route to derivatives of the biologically important 1,2,3-triazolo[4,5-d]pyrimidine ring system.

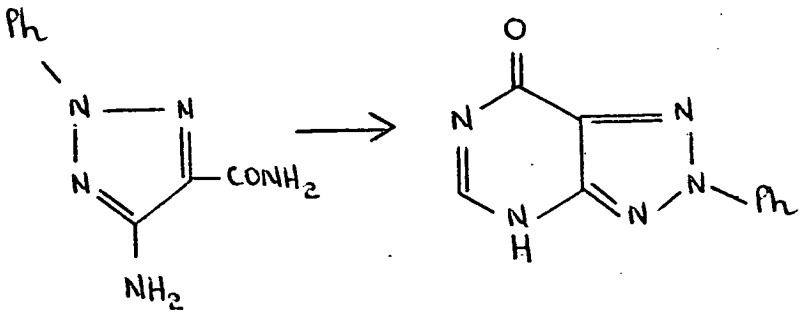
1,2,3-Triazolo[4,5-d]pyrimidines may also be prepared by direct ring closure of 5,6-diaminopyrimidines [e.g. (263) ⟶ (265)].[111] However Taylor and Richter have prepared the ring system from 1,2,3-triazoles.[112]



(263) (264)



(265)

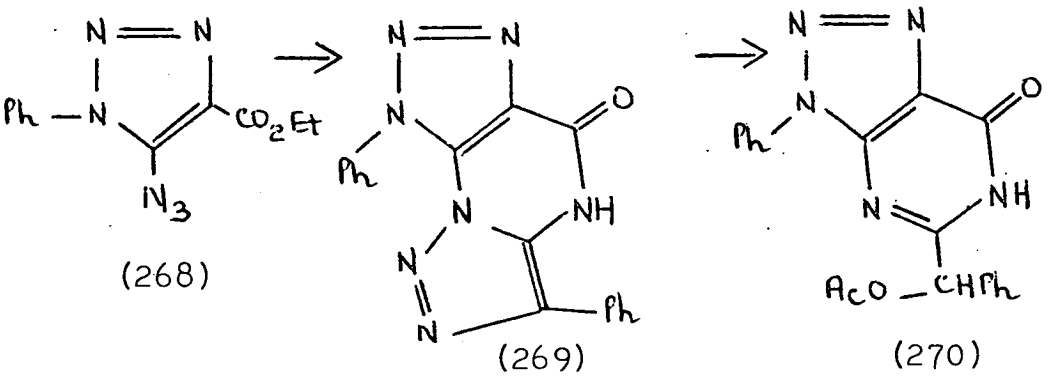


(266) (267)

5-amino-4-carbamoyl-2-phenyl-1,2,3-triazole (266) cyclised on treatment with ethyl orthoformate and acetic anhydride affording the triazolopyrimidine (267).[112] This synthesis was extended by reacting the aminotriazole (252a) or the anilino isomer (252d) with ethyl orthoformate and acetic anhydride to give the fused system (259a).[103] The fact that the anilinotriazole (252d) gave the compound (259a) infers that retrogression to the amino triazole (252a) or the acylated aminotriazole has occurred before cyclisation, otherwise the phenyl substituent would be present on the pyrimidine ring in the product. 1,2,3-triazolo[4,5-d]-pyrimidines are thought to affect nucleic acid metabolism, and are therefore of potential use in cancer chemotherapy.[83]

In the present work the amide (252a) reacted with propionyl chloride or phenylacetyl chloride, in the presence of concentrated sulphuric acid to yield (257a) or (257c). In the reaction with phenylacetyl chloride some of the monoacyl compound (257b) was also formed. The assignment of the structure (257b) to the monoacyl product is in agreement with the presence in its p.m.r. spectrum of a high field methylene singlet at τ 6·40, and the low frequency of the carbonyl absorption in its i.r. (table 3). On the other hand (257c) shows methylene singlets at τ 5·85, assignable to an acylamide group, and τ 6·35 which may be assigned to an acylamino group. (257c) also shows the high carbonyl absorption associated with an imide. Heating the acyl derivatives (257a) and (257d) in aqueous alkali afforded the triazolo[4,5-d]pyrimidines (259c) and

(259d) respectively, whose u.v. spectra were identical with the compound (259a). The assigned structures (259c) and (259d) were established by the unambiguous synthesis of the benzyltriazolopyrimidine (259d). The azide (268) was synthesised from the aminotriazole (255a) by conversion into the diazonium salt and treatment with sodium azide.



(268) (269) (270)

Treatment of the azide (268) with phenylacetonitrile in the presence of sodium methoxide yielded 4,5-dihydro-1,6-diphenyl-5-oxo-1,2,3-triazolo[1,5-a]-1,2,3-triazolo-[4,5-e]pyrimidine (269). Triazole scission of the latter compound in glacial acetic acid afforded the acetoxy compound (270), which yielded the benzyl compound (259d) on hydrogenolysis.

While investigating the reaction of phenylacetyl chloride with the amide (252a) it was found that under reflux in dry benzene the product was a monoacyl derivative, which on mild hydrolysis under conditions which did not cause isomerisation of aminotriazole (252a) or the anilinotriazole (252d), yielded the deacylated compound (252d). These results indicate the structure (252g) which is supported by the presence in the p.m.r. spectrum

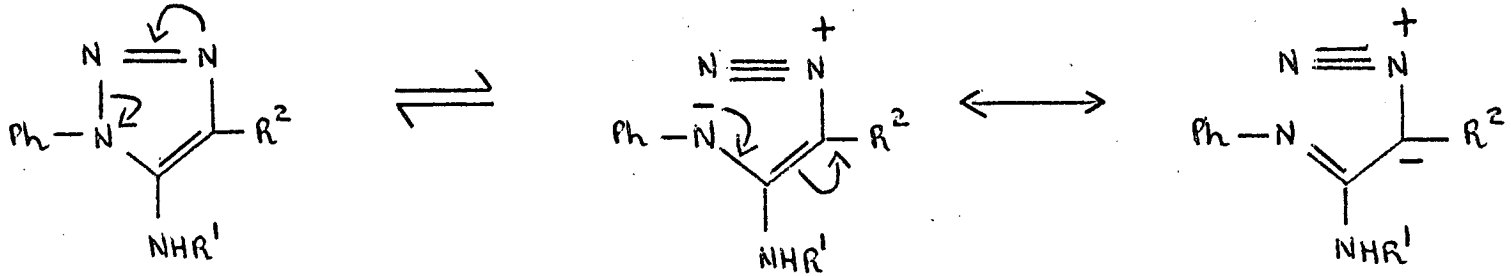
of a low field methylene singlet at τ 5·50, and the high frequency carbonyl absorption in the i.r. spectrum. The carbonyl absorption appears as a doublet. Thus the i.r. and p.m.r. data is consistent with the presence of a ring N-acyl group.

Acetylation of the anilino isomer (252d) in the presence of concentrated sulphuric acid at room temperature proceeded without retrogression of the Dimroth rearrangement. The product, a triacetyl derivative, was not identical to the triacetyl compound (254c), and was also formed when the anilino isomer (252d), the monoacetyl compound (252e) or the diacetyl compound (254e) were refluxed in acetic anhydride for 12 hours. The triacetyl derivative contained three non-equivalent acetyl groups, as demonstrated by the presence in the p.m.r. spectrum of methyl singlets at τ 7·22, τ 7·42, and τ 7·92 due to the most shielded ring N-acetyl group, an acetylamido group and an acetylamino group respectively. By analogy with previous assignments the carbonyl absorption in the i.r. spectrum at 1770, 1710 and 1730 $cm.^{-1}$ may be assigned to the ring N-acetyl group, the acetylamino group and the acetylamide group respectively.

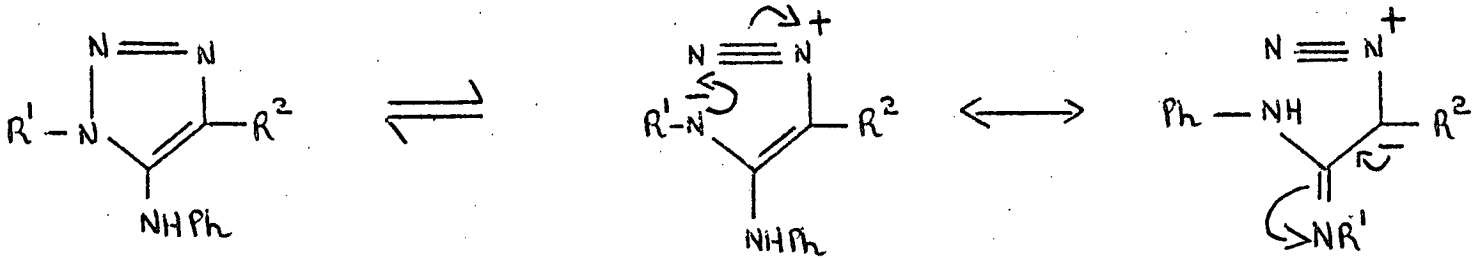
When the aminotriazoles (252a), (255a) or (256a) were refluxed in acetic anhydride for 12 hours the products were unexpectedly the unrearranged acetyl derivatives (254c), (255c) or (256c) respectively. The structure of (256c) follows from its p.m.r. spectrum which contains a singlet at τ 7·80 representing two equivalent methyl groups attached to a primary amino group. Also, it hydrolysed to

the monoacetyl compound (256b), and thence to the amino-triazole (256a). The triazole derivative (256c) could be reformed by refluxing (256b) in acetic anhydride. The structure of compounds (254c) and (255c) were discussed above. Since heating in acetic anhydride for periods up to six hours has already been shown to cause Dimroth rearrangement [(252a) ⟶ (252e) and (254e); (253a) ⟶ (253e); (255a) ⟶ (255e) and (256a) ⟶ (256e)], the results obtained by refluxing in acetic anhydride for twelve hours infer that retrogression has occurred in the course of prolonged treatment. In support of this contention it was found that heating the anilino isomers (255d) and (255e) or (256d) and (256e) in acetic anhydride for five to twelve hours afforded the diacetylaminotriazoles (255c) and (256c) respectively. However retrogression of the triacetyl compound (254f) to its isomer (254c) required a reflux period of 30 hours, and no retrogression was observed on refluxing the dimethylamides (253a), (253b) or (253d) in acetic anhydride for 12 hours, only the monoacetyl anilinotriazole (253e) being formed.

As noted in the introduction 5-amino-1,2,3-triazoles having an electronegative group on the 1-position readily undergo Dimroth rearrangement to yield isomers in which the electronegative group is on an exocyclic position. It was also pointed out that the phenyl residue must act as an electron withdrawing agent, since it prefers to exist exocyclically. This is demonstrated by the isomerisation of (252a) or (252d) into an equilibrium mixture



(271) (272)



(274) (273)

(a) R' = H

(b) R' = Ac

favouring the anilino isomer (252d). Therefore it can be seen that acetylation of 1-phenyl-5-amino-1,2,3-triazoles or their anilino isomers will result in the triazole being substituted by two negative groups, viz. acetyl and phenyl. There will therefore be two competing electronic effects in acetylated phenylaminotriazoles. As shown above acetylation of 5-amino-1,2,3-triazoles yields initially an acetylanilinotriazole, which may further acetylate, and/or retrogress to acetylaminotriazole derivatives. Therefore the acetylaminotriazole products appear to be more stable than the acetylanilinotriazoles. This is in accord with the placement of the more electronegative acetyl group on an exocyclic position.

However there still exists the problem of deciding whether acetylation precedes or follows rearrangement. The thermal[34,41,48] and acid catalysed[53] rearrangements are considered to involve a diazo intermediate, which may be formulated as (272) in the pathway [(271) ⇌ (274)], and the mechanism requires a proton shift from the exocyclic amino group to the triazole ring. This proton shift cannot occur in fully acetylated triazoles, as there will no longer be a proton available. Therefore in the rearrangement of polyacetyltriazoles, loss of one or more acetyl groups must occur before rearrangement may take place, followed by reacetylation.

On this basis two pathways may be envisaged for the rearrangement [(271a) ⟶ (274a)], and its retrogression [(274a) ⟶ (271a)]. Rearrangement may precede

[(271a) ⟶ (274a) ⟶ (274b)] or follow [(271a) ⟶ (271b) ⟶ (274b)] acetylation. Similarly retrogression may precede [(274a) ⟶ (271a) ⟶ (271b)] or follow acetylation [(274a) ⟶ (274b) ⟶ (271b)]. However as described above a monoacetyl compound of the type (271b) has not been observed to rearrange to (274b). This is in accord with the stability of (271b), which has the negative acetyl group on the exocyclic position. It is therefore unlikely that acetylation precedes rearrangement, suggesting the pathway [(271a) ⟶ (274a) ⟶ (274b)] for rearrangement and acetylation. Conversely it is unlikely that acetylation will be preceded by retrogression, as (274a) is more stable than (271a) because of the exocyclic phenyl group in (274a)(see above). Also deacetylation of the monoacetyl compound (252e) by heating in 2-ethoxyethanol does not result in a retrogression to (252a). Retrogression can therefore be explained by the pathway [(274a) ⟶ (274b) ⟶ (271b)], where (271b) is more stable than (274b), as discussed above.

The electronegativity of the 4-substituent in substituted 5-amino-1,2,3-triazoles has been shown to influence the speed of retrogression of the monoacetyl compounds (274b)(see above). The phenyl derivative (256e) retrogresses faster than the ester (255e) or the amides (252e) and (254e), which in fact further acetylate before retrogressing. The dimethylamide (253e) fails to retrogress to the basic isomer. These observations are in accord with the results obtained by Albert,[105] which were discussed previously.

It can now be seen that the acetyl compounds obtained by treatment with acetic anhydride in the presence of concentrated sulphuric acid are the more stable isomers, because the more electronegative group is then on an exocyclic position. The driving force behind rearrangement, i.e. to obtain a product with the electronegative group on an exocyclic position is therefore not activated. The initial rearrangement in refluxing acetic anhydride to the anilino isomer (274b) is therefore a thermally induced reaction.

PART 3

EXPERIMENTAL

I.r. and u.v. spectra were recorded for Nujol suspensions or ethanolic solutions respectively, using Unicam SP 200 and SP 800 instruments. Proton magnetic resonance (p.m.r.) spectra were measured at 60 or 100 MHz using a Perkin-Elmer R10 or Varian HA 100 instrument, in deuterochloroform ($CDCl_3$), trifluoroacetic acid (TFA), 6_6-dimethylsulphoxide (d_6-DMSO) or d_4-acetic acid, at 28°, using tetramethylsilane as internal standard. P.m.r. signals were expanded to 250 Hz where necessary. Aromatic signals were observed as multiplets (τ 1·9 - 3·2). Molecular weights were measured using an AEI MS 902 mass spectrometer. Melting points were recorded on a Kofler block, and are uncorrected. All identical products were compared by mixed m.p., i.r. and p.m.r. spectra, and in most cases by mass spectra. Petrol was light petroleum, b.p. 60 - 80°. Chloroform extracts were dried over anhydrous magnesium sulphate.

3.1.1 Preparation of 5-amino-1,2,3-triazolo[1,5-a]-quinazolines.

(a) 5-amino-3-phenyl-1,2,3-triazolo[1,5-a]quinazoline (133a)

2-Azidobenzonitrile (0·1 mole) and phenylacetonitrile (0·1 mole) were suspended in methanol (20 ml.), and treated with a solution of sodium (0·4 g. atom) in methanol (100 ml.). The solution was stirred at room temperature for 30 min., and the resulting solid collected then washed with methanol (300 ml.), followed by water (200 ml.). The yellow solid was identified as (133a)(84%), m.p. 267-268° (from acetic acid), $\nu_{max.}$ 3400, 3250 and 3150 (NH) $cm.^{-1}$, τ (d_6-DMSO) aromatic signal only, τ (TFA) after 1 min., 2·94 [1H, s, benzylic CH of (145a)], after 24 hr., 2·94 [1H, s, benzylic CH of (145a)](78%) and 3·81 [1H, s, benzylic CH of (138a)] (22%), (Found: C, 68·9; H, 4·2; N, 26·9. $C_{15}H_{11}N_5$ requires C, 69·0; H, 4·2; N, 26·8%).

(b) 5-amino-3-carbamoyl-1,2,3-triazolo[1,5-a]quinazoline (133b)

2-Azidobenzonitrile (0·1 mole) and cyanoacetamide (0·1 mole) were treated as above to yield (133b). Evaporation under reduced pressure at 30° and trituration of the residual gum with water gave a further crop of (133b), (total yield 91%), m.p. 310-312° (from acetic acid-dimethyl-formamide), $\nu_{max.}$ 3480, 3400, 3300 and 3200 (NH), and 1680 (CO) $cm.^{-1}$, τ (TFA - after 1 min.and 26 hr.) aromatic signal only, (Found: C, 52·4; H, 3·5; N, 36·9. $C_{10}H_8N_6O$ requires C, 52·6; H, 3·5; N, 36·8%).

(c) 5-amino-3-cyano-1,2,3-triazolo[1,5-a]quinazoline (133c)

2-Azidobenzonitrile (0·1 mole) and malononitrile (0·1 mole) were treated as above to yield (133c)(76%), m.p. 285-286° (from dimethylformamide), $\nu_{max.}$ 3400 and 3180 (NH), and 2280 (CN) $cm.^{-1}$, τ (TFA - after 1 min. and 26 hr.) aromatic signal only, (Found: C, 57·0; H, 2·9; N, 39·9. $C_9H_7N_5$ requires C, 57·1; H, 2·9; N, 40·0%).

(d) 5-amino-1,2,3-triazolo[1,5-a]quinazoline (133d)

2-Azidobenzonitrile (0·1 mole) and ethyl cyanoacetate (0·1 mole) were treated as above to yield (133d) (82%), m.p. 265-267° (from water-dimethylsulphoxide), $\nu_{max.}$ 3300 and 3100 (NH) $cm.^{-1}$, τ (TFA) after 1 min., 4·36[2H, s, benzylic CH_2 of (145d)], after 24 hr., 4·36[2H, s, benzylic CH_2 of (145d)] (20%) and 4·76[2H, s, benzylic CH_2 of (147d)] (80%), (Found: C, 58·9; H, 3·6; N, 37·7. $C_9H_7N_5$ requires C, 58·4; H, 3·8; N, 37·9%).

3.1.2 Reactions of 5-amino-3-phenyl-1,2,3-triazolo[1,5-a]-quinazoline (133a), or (135a)

(a) Acetic acid

The triazoloquinazoline (133a)(0·004 mole) was refluxed in glacial acetic acid (60 ml.) for 1-6 hr. The reaction mixture was evaporated to a yellow gum, which on trituration with ether yielded 2-(α-acetoxybenzyl)-3-acetyl-3,4-dihydro-4-iminoquinazoline (142) (89-94%), m.p. 169-170° (from ethanol), $\nu_{max.}$ 3400 (br.) and 3150 (NH), 1740 (OAc) and 1685 (Ac) $cm.^{-1}$, τ ($CDCl_3$) 3·30 (1H, s, benzylic CH), 7·75 (3H, s, Me) and 7·85 (3H, s, Me), (TFA) 2·95 (1H, s, benzylic CH), 7·55 (3H, s, Me) and 7·75 (3H, s, Me), (Found: C, 68·3; H, 5·0; N, 12·4. $C_{19}H_{17}N_3O_3$ requires C, 68·0; H, 5·1; N, 12·5%).

(b) Acetic anhydride

The triazoloquinazoline (133a)(0·002 mole) was refluxed in acetic anhydride (15 ml.) for 3 min. The reaction mixture was cooled and filtered to give the mono-acetyl compound (135a)(67%), m.p. 263-265° (from ethanol-dimethylformamide), $\nu_{max.}$ 3200 (NH) and 1680 (CO) $cm.^{-1}$, τ (TFA) 7·11 (3H, s, Me), (Found: C, 67·8; H, 4·3; N, 22·9. $C_{17}H_{13}N_5O$ requires C, 67·3; H, 4·3; N, 23·1%). The filtrate, on evaporation, yielded a gum which was triturated with ether and petrol to give the diacetyl derivative (136a) (16%), m.p. 183-184° (from benzene-petrol), $\nu_{max.}$ 1730 and 1685 (CO) $cm.^{-1}$, τ (TFA) 7·34 (6H, s, 2 Me), (Found: C, 66·3; H, 4·4; N, 20·3. $C_{19}H_{15}N_5O_2$ requires C, 66·1; H, 4·4; N, 20·3%).

(c) Acetyl chloride

The triazoloquinazoline (133a)(0·004 mole) or its monoacetyl derivative (135a)(0·004 mole) was refluxed in acetyl chloride (20 ml.) and acetic acid (20 ml.) for 90 min. The reaction mixture was evaporated, yielding a gum, which was treated with saturated aqueous sodium bicarbonate solution and chloroform. The chloroform extract on evaporation and trituration of the residual gum with ether-petrol yielded the chloro compound (137b)(90-93%), m.p. 173-174° (from benzene), $\nu_{max.}$ 3200 (NH) and 1690 (CO) $cm.^{-1}$, τ (TFA) 3·50 (1H, s, benzylic CH) and 7·30 (3H, s, Me), (Found: C, 65·3; H, 4·5; N, 13·8. $C_{17}H_{14}ClN_3O$ requires C, 65·5; H, 4·5; N, 13·5%).

(d) Acetyl bromide

The triazoloquinazoline (133a) (0·003 mole) or the monoacetyl derivative (135a) (0·003 mole) was refluxed in a mixture of acetyl bromide (20 ml.) and acetic acid (20 ml.) for 90 min. The reaction mixture was evaporated to give a gum which was treated with saturated aqueous sodium bicarbonate and chloroform. The chloroform extract, on evaporation and trituration of the residual gum with ether, yielded a solid. Fractional crystallisation from benzene afforded the less soluble bromo compound (137c) (34%), m.p. 202-203° (from benzene-ethanol), $\nu_{max.}$ 3200 (NH) and 1685 (CO) $cm.^{-1}$, τ (TFA) 7·05 (3H, s, Me) and 3·35 (1H, s, benzylic CH), τ ($CDCl_3$) 7·30 (3H, s, Me) and 3·70 (1H, s, benzylic CH), (Found: C, 58·0; H, 4·0; N, 11·7. $C_{17}H_{14}BrN_3O$ requires C, 58·0; H, 3·9; N, 11·7%). However the more

soluble component of the crude mixture could not be obtained pure due to contamination by the bromo compound (137c). The p.m.r. spectra of the mixture showed it to contain the bromo compound (137c) (40%) and the benzyl compound (137d)(see later)(60%), on comparison with the p.m.r. spectra of the pure compounds.

(e) Potassium hydroxide

The triazoloquinazoline (133a)(0·0004 mole) was refluxed in 20% w/v aqueous potassium hydroxide (2·0 ml.) and cellosolve (5·0 ml.) for 3 hr. The reaction mixture was cooled and starting material (133a)(23%) was collected. The filtrate was evaporated to give a gum which was dissolved in water and acidified with dilute aqueous sulphuric acid to give the quinazolone (124a)(71%), m.p. 258-259° (from dimethylformamide), identical with an authentic sample, (lit. m.p. 259°[63])

(f) Sulphuric acid

The triazoloquinazoline (0·0005 mole) was refluxed in 30% w/v aqueous sulphuric acid (7·5 ml.) and ethanol (7·5 ml.) for 30 min. The solvents were evaporated and the remaining oil diluted with water. The resulting solution was then basified with 10% w/v aqueous sodium hydroxide, and extracted with chloroform. Evaporation of the chloroform extract and trituration of the residual oil with ether-petrol yielded the hydroxy compound (138a) (46%), identical with a previously prepared sample. The aqueous fraction was made just acidic with acetic acid affording the

hydroxyquinazolone (139a) (33%), m.p. 206-208° (from ethanol) identical with an authentic sample, (lit. m.p. 208°[63]).

The reaction was repeated under identical conditions for 2 hr. to give the quinazolone (139a) (78%).

(g) Acetic acid

The monoacetyl compound (135a) (0·002 mole) was refluxed in acetic acid (40 ml.) for 2 hr. The reaction mixture on evaporation yielded a gum, which was triturated with ether to give the acetoxy compound (137a) (92%), m.p. 167-168° (from benzene-petrol), $\nu_{max.}$ 3200 (NH), 1730 (OAc) and 1690 (Ac) $cm.^{-1}$, τ (TFA) 2·76 (1H, s, benzylic CH), 7·27 (3H, s, Me) and 7·51 (3H, s, Me), (Found: C, 67·5; H, 5·0; N, 12·3. $C_{19}H_{17}N_3O_3$ requires C, 68·0; H, 5·1; N, 12·5%).

3.1.3 Reactions of 2-(α-acetoxybenzyl)-3-acetyl-3,4-dihydro-4-iminoquinazoline (142)

(a) The quinazoline (142) (0·002 mole) was refluxed in acetic anhydride (10 ml.) for 20 min. The solvent was evaporated and the residual gum triturated with ether to give the acetoxy compound (137a) (86%), m.p. 167-168°, identical with a previously prepared sample (see above).

(b) The quinazoline (142) (0·001 mole) was refluxed with N-aqueous sodium carbonate (10 ml.) in ethanol (7·0 ml.) for 20 min. The reaction mixture was evaporated, and the remaining gum dissolved in water, then extracted with chloroform. The chloroform extract was evaporated to give a gum which solidified on trituration with ether to yield the hydroxy derivative (138a) (81%), m.p. 172-173° (from benzene-ethanol), $\nu_{max.}$ 3275 (br.) and 3110 (NH and OH) $cm.^{-1}$, τ (TFA) 3·81 (1H, s, benzylic CH), (Found: C, 71·8; H, 5·1; N, 17·0. $C_{15}H_{13}N_3O$ requires C, 71·7; H, 5·2; N, 16·7%).

(c) The compound (142) (0·004 mole) was dissolved in ethanol (400 ml.) and hydrogenated over 10% palladium-on-charcoal (0·25 g.) for 4 hr. The suspension was filtered and the filtrate evaporated to yield a gum, which solidified in contact with ether to give the benzyl compound (138b) (87%), m.p. 220-221° (from benzene-ethanol), $\nu_{max.}$ 3230 and 3060 (NH) $cm.^{-1}$, τ (TFA) 5·40 (2H, s, benzylic CH_2), (Found: C, 76·5; H, 5·6; N, 17·7. $C_{15}H_{13}N_3$ requires, C, 76·6; H, 5·6; N, 17·9%).

3.1.4 Reactions of 2-substituted-benzylquinazolines

(a) The quinazolines (137a), (137b) or (137c) (0·002 mole) were dissolved in ethanol (200 ml.) and hydrogenated over 10% palladium-on-charcoal (0·19 g.) for 48 hr. The catalyst was removed by filtration and the filtrate evaporated leaving a gum which was triturated with ether to give the dihydroquinazoline (140) (72-74%), m.p. 139-140° (from benzene), $\nu_{max.}$ 3160-3280 (NH) and 1650 (br.)(CO) $cm.^{-1}$, τ (TFA) 5·80 (2H, s, benzylic CH_2) and 7·80 (3H, s, Me), (Found: C, 72·9; H, 6·3; N, 14·9. $C_{17}H_{17}N_3O$ requires C, 73·1; H,6·1; N, 15·0%). The ether mother liquors were evaporated and the remaining gum triturated with ether to give the benzylquinazoline (137d) (16-19%), m.p. 143-144° (from benzene-petrol), $\nu_{max.}$ 3280 (NH) and 1680 (CO) $cm.^{-1}$, τ (TFA) 5·30 (2H, s, benzylic CH_2) and 7·30 (3H,s, Me), τ ($CDCl_3$) 5·70 (2H, s, benzylic CH_2) and 7·55 (3H, s, Me), (Found: C, 73·5; H, 5·6; N, 15·3. $C_{17}H_{15}N_3O$ requires C, 73·6; H, 5·5; N, 15·2%).

The reaction was repeated for 60 hr. yielding the dihydro compound (140) (86%), and for 4 hr. yielding the quinazoline (137d) (82%).

(b) The chloro compound (137b) (0·001 mole) was refluxed with N-aqueous sodium carbonate solution (10 ml.) in ethanol (10 ml.). The solvents were evaporated, and the resulting gum dissolved in water, then extracted with chloroform. The chloroform extract was evaporated to yield 4-amino-2-(α-ethoxybenzyl)quinazoline (138c) (79%),

m.p. 195-197° (from benzene), $\nu_{max.}$ 3200 and 3060 (NH) $cm.^{-1}$, τ (TFA) 4·25 (1H, s, benzylic CH), 7·20 (2H, q, OCH_2) and 8·60 (3H, tr, Me), (Found: C, 73·0; H, 6·6; N, 15·1. $C_{17}H_{17}N_3O$ requires C, 73·1; H, 6·1; N, 15·0%).

(c) The acetoxy compound (137a) (0·001 mole) was treated as in (b) above to give the hydroxy compound (138a) (81%), m.p. 171-173°, identical with a sample prepared above.

(d) The acetyl derivative (137d) (0·001 mole) was treated as in (b) above to yield the benzylquinazoline (138b) (78%), m.p. 220-221°, identical with a previously prepared sample (see above).

(e) The chloro compound (137b) (0·003 mole) or its bromo analogue (137c) (0·003 mole) was refluxed in 10% w/v aqueous sulphuric acid (5·0 ml.) and ethanol (10 ml.) for 30 min. The reaction mixture was evaporated leaving an oil, which was extracted into chloroform. The chloroform extract on evaporation gave a gum, which was triturated with ether to yield the hydroxy derivative (138a) (81%), m.p. 172-173°, which was identical with a sample prepared above.

(f) The acetoxy compound (137a) (0·004 mole) was treated with 20% w/v potassium hydroxide (2·0 ml.) as above [see 3.1.2(e)] to give the quinazolone (139a) (82%) m.p. 206-208° (from ethanol) identical with a known sample (lit. m.p. 208°[63]).

(g) Treatment of the acetoxy compound (137a) (0·0005 mole) in ethanol (7·5 ml.) with 30% w/v sulphuric acid (7·5 ml.) under reflux for 30 min. afforded the hydroxy derivative (138a) (41%), identical with a sample prepared above. (138a) was isolated by evaporating the reaction mixture to give an oil which was diluted with water, then extracted with chloroform. On evaporation the chloroform extract yielded (138a). The aqueous fraction was made just acidic with acetic acid to give the quinazolone (139a) (36%), m.p. 206-208°, which was identical with an authentic sample prepared above.

3.1.5 Oxidation of 4-amino-2-(α-hydroxybenzyl)quinazoline (138a)

The quinazoline (138a) (0·003 mole) was dissolved in dry acetone (40 ml.) and refluxed with activated manganese dioxide (3·0 g.) for 5 min. The reaction mixture was filtered and the filtrate evaporated to give 4-amino-2-benzoylquinazoline (148a) (92%), m.p. 202-203° (from benzene-ethanol), $\nu_{max.}$ 3400 and 3200 (NH) and 1680 (CO) $cm.^{-1}$, (Found: C, 72·6; H, 4·3; N, 17·0. $C_{15}H_{11}N_3O$ requires C, 72·3; H, 4·5; N, 16·9%).

The benzoyl compound (148a) (0·0004 mole) was refluxed in acetic anhydride for 15 min. The solvent was evaporated to leave a gum, which on trituration with ether yielded the acetyl derivative (148b) (91%), m.p. 170-171° (from benzene), $\nu_{max.}$ 3200 (NH), 1680 and 1670 (CO) $cm.^{-1}$, τ (TFA) 7·25 (3H, s, Me), (Found: C, 70·3; H, 4·5; N, 14·9. $C_{17}H_{13}N_3O_2$ requires C, 70·1; H, 4·5; N, 14·4%).

The acetyl compound (148b) (0·001 mole) was refluxed in N-aqueous sodium carbonate solution (10 ml.) and ethanol (5·0 ml.) for 30 min. The reaction mixture was evaporated to a gum which was dissolved in water and extracted with chloroform. The chloroform extract, on evaporation yielded a gum which was treated with ether to give the benzoylquinazoline (148a) (78%), m.p. 202-203°, identical with a sample prepared above.

The benzoyl compound (148a) (0·0004 mole) was

dissolved in ethanol (50 ml.) and hydrogenated over 10% palladium-on-charcoal (0·03 g.) for 4 hr. The reaction mixture was filtered and the filtrate evaporated to give a gum, which on trituration with ether-petrol gave the hydroxybenzylquinazoline (138a) (82%), m.p. 172-173°, identical with a sample prepared above.

3.1.6 Reactions of 5-amino-3-carbamoyl-1,2,3-triazolo-[1,5-a]quinazoline (133b), and the 3-cyano compound (133c)

(a) Potassium hydroxide

The triazoloquinazolines (133b) and (133c) (0·002 mole) were refluxed with 20% w/v aqueous potassium hydroxide (10 ml.) in cellosolve (70 ml.) for 3 hr. The solvents were removed under reduced pressure, and the remaining gum dissolved in water, then acidified to give the triazoloquinazolone (124b) (81-86%), m.p. 294-295° (from ethanol) which was identical with an authentic sample (lit. m.p. 296°[73]).

(b) Sulphuric acid

The triazoloquinazolines (133b) and (133c) (0·004 mole) were refluxed with 30% w/v aqueous sulphuric acid (20 ml.) in cellosolve (80 ml.) for 4 hr. The solvents were removed under reduced pressure and the remaining gum dissolved in water. The solution was neutralised with saturated aqueous sodium bicarbonate solution and extracted with chloroform. The chloroform extract was evaporated to give a gum which solidified on treatment with ether to yield the quinazolone (139b) (61-67%), m.p. 222-224° (from ethanol), identical with an authentic sample (lit. m.p. 223°[73]).

(c) Acetic acid

The triazoloquinazolines (133b) and (133c) (0·002 mole) were refluxed with acetic acid (80 ml.) for

periods up to 24 hr. The reaction mixtures were evaporated to give gums, which were triturated with ether to give quantitative recoveries of starting materials (133b) or (133c).

(d) Acetic anhydride

i) The amide (133b) (0·003 mole) was refluxed in acetic anhydride (120 ml.) for 3 hr. The solvent was evaporated to give a gum which was triturated with ether to yield the triacetyl derivative (136e) (82%), m.p. 250-260° (crude), $\nu_{max.}$ 1720, 1700 (br.) and 1685 $cm.^{-1}$, τ (TFA) 7·20 (3H, s, Me), 7·35 (3H, s, Me) and 7·70 (3H, s, Me), $p(\frac{m}{e})$ 354. On crystallisation by heating in acetic acid or water-dimethylsulphoxide cooling yielded the diacetyl compound (135e) (81%), m.p. 285-287° (from water-dimethylsulphoxide), $\nu_{max.}$ 3300 and 3200 (w) (NH), 1735, 1710 and 1690 (CO) $cm.^{-1}$, τ (TFA) 7·20 (3H, s, Me) and 7·35 (3H, s, Me), (Found: C, 53·1; H, 3·8; N, 26·4. $C_{14}H_{12}N_6O_3$ requires C, 53·7; H, 3·8; N, 26·8%).

ii) The nitrile (133c) (0·003 mole) was refluxed in acetic anhydride (120 ml.) as above [see 3.1.6(d,i)], to give the diacetyl compound (136c) (86%), m.p. 230-239° (crude), $\nu_{max.}$ 2270 (CN), 1715 and 1700 (CO) $cm.^{-1}$, τ (TFA) 7·35 (6H, s, 2Me), $p(\frac{m}{e})$ 294, which on crystallisation from hot acetic acid or dimethylsulphoxide-water gave the monoacetyl compound (135c) (81%), m.p. 249-250° (from ethanol-dimethylformamide), $\nu_{max.}$ 3300 (NH), 2300 (CN) and 1700 (CO) $cm.^{-1}$, τ (TFA) 7·15 (3H, s, Me), (Found: C, 57·0; H, 3·2; N, 33·2. $C_{12}H_8N_6O$ requires C, 57·1; H, 3·2; N, 33·3).

3.1.7 Reactions of 5-amino-1,2,3-triazolo[1,5-a]quinazoline (133d), and the derived 3-substituted quinazolines (149) and (150)

(a) Potassium hydroxide

The triazoloquinazoline (133d) (0·005 mole) was refluxed with 20% w/v aqueous potassium hydroxide (20 ml.) for 4·5 hr. The reaction mixture was worked-up as above [see 3.1.6(a)] to yield the triazoloquinazolone (124c) (91%), m.p. 218-220° (from ethanol), which was identical with an authentic sample (lit. m.p. 220°[73]).

(b) Sulphuric acid

The triazoloquinazoline (133d) (0·004 mole) was refluxed with 30% w/v aqueous sulphuric acid (20 ml.) for 4 hr. The reaction mixture was worked-up as above [see 3.1.6(b)] to yield the quinazolone (139b) (63%), m.p. 222-224° (from ethanol) which was identical with an authentic sample (lit. m.p. 223°[73]).

(c) Acetic acid

The triazoloquinazoline (0·002 mole) was refluxed with acetic acid (50 ml.) for 3·5 hr. The solvent was evaporated leaving a gum, which on trituration with ether gave the acetoxy compound (149) (87%), m.p. 202-203° (from ethanol-benzene), $\nu_{max.}$ 3300 and 3100 (NH) and 1740 (CO) $cm.^{-1}$, τ (TFA) 4·45 (2H, s, CH_2) and 7·60 (3H, s, Me), (Found: C, 60·6; H, 5·0; N, 19·6. $C_{11}H_{11}N_3O_2$ requires C, 60·8; H, 5·1; N, 19·3%).

(d) Acetyl chloride or acetyl bromide

The triazoloquinazoline (0·002 mole) was refluxed with acetyl chloride (25 ml.) or acetyl bromide (25 ml.) in acetic acid (20 ml.) for 4 hr. The reaction mixtures were worked-up as above [see 3.1.2(c and d)] to give the chloro compound (150a), (73%), m.p. 197-199° (from benzene-petrol), $\nu_{max.}$ 3280 (NH) and 1685 (CO) $cm.^{-1}$, τ (TFA) 4·90 (2H, s, CH_2) and 7·15 (3H, s, Me), τ ($CDCl_3$) 5·20 (2H, s, CH_2) and 7·24 (3H, s, Me), (Found: C, 55·5; H, 4·1; N, 17·8. $C_{11}H_{10}Cl\,N_3O$ requires C, 56·1; H, 4·2; N, 17·8%) or the bromo compound (150b) (76%), m.p. 204-205° (from benzene-petrol), $\nu_{max.}$ 3280 (NH) and 1680 (CO) $cm.^{-1}$, τ (TFA) 5·10 (2H, s, CH_2) and 7·10 (3H, s, Me), τ ($CDCl_3$) 5·35 (2H, s, CH_2) and 7·25 (3H, s, Me), (Found: C, 47·1; H, 3·4; N, 15·0. $C_{11}H_{10}Br\,N_3O$ requires C, 47·2; H, 3·6; N, 15·0%).

(e) Acidic hydrolysis of the 2-substituted quinazolines

The halomethylquinazolines (150a) and (150b) and the acetoxy compound (149) (0·001 mole) were refluxed with N-aqueous sodium carbonate (10 ml.) in ethanol (7·0 ml.) for 20 min. The solvents were removed under reduced pressure to leave a gum, which was dissolved in water and extracted with chloroform. Evaporation of the chloroform extract left a gum which was treated with ether to give the hydroxymethylquinazoline (147d) (71-80%), m.p. 210-212° (from ethanol-benzene), $\nu_{max.}$ 3400 (br.) and 3100 (br.) (NH and OH) $cm.^{-1}$, τ (TFA) 4·76 (2H, s, CH_2), (Found: C, 61·6; H, 5·2; N, 23·9. $C_9H_9N_3O$ requires C, 61·7; H, 5·2; N, 24·0%).

3.2.1 The reactions of 5-amino-4-phenyl-1-H-1,2,3-triazole (162a) and the 4-carbamoyl compound (162b) with β-dicarbonyl compounds

(a) Reactions in ethanol-piperidine

i) 5-Amino-4-phenyl-1-H-1,2,3-triazole (162a) (0·0025 mole) was refluxed with ethyl acetoacetate (0·0028 mole) in ethanol (100 ml.) containing piperidine (0·7 ml.) for 12-48 hr. The resulting solution was evaporated to leave a gum which was dissolved in alkali, and the solution acidified to give a mixture of the isomeric triazolopyrimidones (167a) (76%) and (168a) (9%), m.p. 232-234° (crude), $\nu_{max.}$ 2650-2800 (NH), 1690 and 1670 (CO) $cm.^{-1}$ (see spectrum 3), τ (d_6-DMSO) 3·29 [1H, s → q on expansion, pyrimidine CH of (168a)], 6·94 [3H, s → d on expansion, Me of (168a)], 3·88 [1H, s → q on expansion, pyrimidine CH of (167a)] and 7·28 [3H, s → d on expansion, Me of (167a)], τ (TFA) see spectrum 1. When the crude product was crystallised from ethanol, or heated at 140° for 60 min. it was transformed into the isomer (168a), m.p. 239-240° (from ethanol), $\nu_{max.}$ 2600-2800 (NH) and 1670 (CO) $cm.^{-1}$ (see spectrum 4), τ (d_6-DMSO) 3·29 (1H, s → q on expansion, pyrimidine CH) and 6·94 (3H, s → d on expansion, Me), τ (TFA) see spectrum 2, (Found: C, 63·6; H, 4·5; N, 24·9. $C_{12}H_{10}N_4O$ requires C, 63·7; H, 4·5; N, 24·8%). The mass spectrum of the crude isomer mixture (168a/167a) was identical to that of the pure isomer (168a). All attempts to separate the isomer mixture by column chromatography were unsuccessful.

ii) The amide (162b) (0·0025 mole) was refluxed with ethyl acetoacetate (0·0028 mole) in ethanol (100 ml.) containing piperidine (0·7 ml.) for 24 hr. The reaction mixture was worked-up as above to give a mixture of the isomeric triazolopyrimidones (167b) (40%) and (168b) (41%) (the percentage yields were obtained on examination of the p.m.r. spectra - see below), m.p. 274-275° (mixture) (from ethanol-acetic acid), $\nu_{max.}$ 3450, 3150 and 2500-2700 (NH), 1690 and 1670 (CO) $cm.^{-1}$, τ (d_6-DMSO) 3·41 [1H, s → q on expansion, pyrimidine CH of (168b)], 7·05 [3H, s → d on expansion, Me of (168b)], 3·81 [1H, s → q on expansion, pyrimidine CH of (167b)] and 7·25 [3H, s → d on expansion, Me of (167b)], τ (TFA) 3·32 [1H, s → q on expansion, pyrimidine CH of (168b)], 7·13 [3H, s → d on expansion, Me of (168b)], 3·46 [1H, s → q on expansion, pyrimidine CH of (167b)] and 7·32 [3H, s → d on expansion, Me of (167b)], (Found: C, 43·4; H, 3·6; N, 36·4. $C_7H_7N_5O_2$ requires C, 43·5; H, 3·7; N, 36·3%). The crude mixture crystallised from ethanol-acetic acid or treated at 140° for 20 hr. remained as an equimolar mixture of the isomers (167b) and (168b) (p.m.r. spectrum evidence - see above). All attempts to separate the isomer mixture by fractional crystallisation or column chromatography were unsuccessful.

iii) The aminotriazole (162a) (0·0025 mole) was refluxed with ethyl ethoxymethylenemalonate (0·0028 mole) in ethanol (100 ml.) containing piperidine (0·7 ml.) for 40 hr. The reaction mixture was evaporated to leave a gum, which was treated with 10% w/v aqueous sodium hydroxide to

yield an insoluble salt, which was decomposed on treatment with dilute sulphuric acid to give the triazolopyrimidone (196) (15%), m.p. 235-237° (from ethanol-acetic acid), $\nu_{max.}$ 2600-2700 (NH), 1710 and 1700 (sh.) (CO) $cm.^{-1}$, τ (d_6-DMSO) 1·13 (1H, s, pyrimidine CH), 5·35 (2H, q, CH_2) and 8·35 (3H, tr, Me), τ (TFA) 0·85 [1H, s, pyrimidine CH of (199)], 2·73 [1H, s, benzylic CH of (199)], 5·40 [2H, q, CH_2 of (199)] and 8·55 [3H, tr, Me of (199)], (Found: C, 59·1; H, 4·2; N, 20·1. $C_{14}H_{12}N_4O_3$ requires C, 59·2; H, 4·3; N, 19·7%). The alkaline liquors were acidified to yield the diester (197a) (65%), m.p. 155-156° (from benzene), $\nu_{max.}$ 3100 and 2550-2700 (NH) and 1700 (br.)(CO) $cm.^{-1}$, τ ($CDCl_3$) 1·16 (1H, d, olefinic H), 5·72 (4H, q, 2 CH_2) and 8·61 (6H, tr, 2 Me), (Found: C, 57·8; H, 5·7; N, 16·9. $C_{16}H_{18}N_4O_4$ requires C, 58·2; H, 5·5; N, 17·0). When the aminotriazole (162a) was reacted with ethyl ethoxymethylene-malonate in refluxing piperidine-ethanol as above for 7 days the triazolopyrimidone (196) (79%) was isolated.

The ester (196) was refluxed with 10% w/v aqueous sodium hydroxide (10 ml.) in ethanol (30 ml.) for 15 min. The reaction mixture was evaporated to give a gum, which was dissolved in water, then acidified to give the acid (198) (71%), which was unchanged on heating at 150° for 3 hr. or by crystallisation, m.p. 243-244° (from acetic acid), $\nu_{max.}$ 2400-2800 (NH and OH), 1720 and 1665 (CO) $cm.^{-1}$, τ(d_6-DMSO) 1·12 (1H, s, pyrimidine CH), τ (TFA) after 1 min., 0·89 [1H, s, pyrimidine CH of (200b)] and 2·94 [1H, s, benzylic CH of (200b)], after 24 hr., 0·95 [1H, s, pyrimidine CH of (200c)] and 3·75 [1H, s, benzylic CH of

(200c)], (Found: C, 56·1; H, 3·6; N, 21·9. $C_{12}H_8N_4O_3$ requires C, 56·3; H, 3·2; N, 21·9%).

iv) The aminotriazole (162a) (0·0025 mole) was refluxed with diethyl malonate, ethyl benzoylacetate, malononitrile or benzoylmethane (0·0028 mole) with piperidine-ethanol as above for periods up to 7 days. Evaporation of the resulting solution and trituration of the residual gum with dilute sulphuric acid, followed by adjustment to pH 8 with concentrated ammonia solution yielded unchanged aminotriazole (162a) (85-89%).

v) The aminotriazole (162a) (0·0025 mole) was refluxed with acetylacetone (0·0028 mole) in ethanol (100 ml.) containing piperidine (0·7 ml.) for 24 hr. The reaction mixture was evaporated to give a gum which on treatment with ether-benzene yielded the triazolopyrimidine (164a) (79%), m.p. 159-160° (from benzene-petrol), τ (d_6-DMSO) 2·61 (1H, s, pyrimidine CH_A), 6·85 (3H, s → d on expansion, Me^1) and 7·07 (3H, s → s on expansion, Me), τ (TFA) 2·25 [1H, s → q on expansion, pyrimidine CH_A of (174)], 2·91 [1H, s → s on expansion, benzylic CH_B of (174)] and 7·14 [6H, s → d on expansion, Me and Me^1 of (174)].

vi) The aminotriazole (162b) (0·0025 mole) and acetylacetone (0·0028 mole) was refluxed in piperidine-ethanol as in (v) above to give the triazolopyrimidine (164b) (76%), m.p. 264-265° (from ethanol-acetic acid), $\nu_{max.}$ 3400 (w), 3320 and 3120 (NH), and 1690 (CO) $cm.^{-1}$,

τ (d_6-DMSO) 2·02 (1H, s → q on expansion, pyrimidine CH_A), 6·53 (3H, s → d on expansion, Me^1) and 6·72 (3H, s → s on expansion, Me), τ (TFA) 2·70 (1H, s → q on expansion, pyrimidine CH_A) and 7·20 (6H, s, Me and Me^1 - see discussion section), τ (CD_3CO_2D) 2·94 (1H, s → q on expansion, pyrimidine CH_A), 7·08 (3H, s → d on expansion, Me^1) and 7·30 (3H, s → s on expansion, Me), (Found: C, 49·8; H, 4·7; N, 36·7. $C_8H_9N_5O$ requires C, 50·3; H, 4·7; N, 36·6%).

(b) Reactions in benzene-acetic acid

i) The aminotriazole (162a) (0·0025 mole) and ethyl acetoacetate (0·0028 mole) were refluxed in benzene (70 ml.) containing acetic acid (0·7 ml.) for 24 hr. The reaction mixture was evaporated to leave a gum which after trituration with ether gave the ester (183a) (81%), m.p. 120-123° (from benzene-petrol), $\nu_{max.}$ 3140 and 2500-2700 (NH), and 1640 (CO) $cm.^{-1}$, τ ($CDCl_3$) 5·20 (1H, s, olefinic H), 5·85 (2H, q, OCH_2), 8·02 (3H, s, olefinic Me) and 8·75 (3H, tr, Me), (Found: C, 61·7; H, 5·8; N, 20·5. $C_{14}H_{16}N_4O_2$ requires C, 61·8; H, 5·9; N, 20·6%).

ii) The aminotriazole (162b) (0·0025 mole) and ethyl acetoacetate (0·0028 mole) were refluxed in benzene (100 ml.) containing acetic acid (1·5 ml.) for 24 hr. The reaction mixture was evaporated to leave a gum, which was treated with ether-benzene to give a solid. Fractional crystallisation of the solid from ethanol-acetic acid afforded the less soluble isomer mixture (167b/168b) (36%), m.p. 274-275°, identical with a sample prepared above, and the more soluble

ester (170) (41%), m.p. 185-187° (from ethanol-acetic acid), $\nu_{max.}$ 3460, 3350, 3200 (br.) and 3100 (NH), 1690 and 1645 (CO) $cm.^{-1}$, τ (TFA) after 2 hr. 5·6 (2H, q, OCH_2), 6·16 (2H, s, CH_2), 7·52 (3H, s, Me—C=N—) and 8·61 (3H, tr, Me), (Found: C, 45·8; H, 5·0; N, 29·4. $C_9H_{12}N_5O_3$ requires C, 45·8; H, 5·1; N, 29·7%).

iii) The aminotriazole (162a) (0·0025 mole) and ethyl ethoxymethylenemalonate (0·0028 mole) were refluxed in benzene (100 ml.) containing acetic acid (0·7 ml.) for 24 hr. as above to give the diester (197a) (78%), m.p. 155-156°, identical with a sample prepared above.

(c) Reactions in toluene

i) The aminotriazole (162a) (0·0025 mole) and ethyl acetoacetate (0·0025 mole) were refluxed in dry redistilled toluene (150 ml.) for 10 hr., the evolved ethanol being allowed to distil over with toluene (50 ml.). The reaction mixture was evaporated to leave a gum which was triturated with benzene to give the ketoamide (186a) (82%), m.p. 159-161° (from benzene-ethanol), $\nu_{max.}$ 3150 and 2500-2700 (NH) and 1700 (CO) $cm.^{-1}$, τ (TFA) shows a mixture of the isomers (186a) [5·90 (2H, s, CH_2) and 7·55 (3H, s, Me)] (41%) and 187a [6·50 (1H, s, olefinic H) and 7·70 (3H, s, Me)] (59%), (Found: C, 58·9; H, 4·9; N, 23·1. $C_{12}H_{12}N_4O_2$ requires C, 59·0; H, 5·0; N, 22·9%).

ii) The aminotriazole (162a) (0·0025 mole) and ethyl benzoylacetate (0·0025 mole) were refluxed in toluene

(150 ml.) as above to give the ketoamide (189) (79%), m.p. 193-194° (from benzene-ethanol), $\nu_{max.}$ 3250 and 2600-2700 (NH), 1695 and 1675 (CO) $cm.^{-1}$, τ (TFA) 5·37 (2H, s, CH_2), (Found: C, 66·9; H, 5·1; N, 19·0. $C_{17}H_{14}N_5O_2$ requires C, 66·7; H, 4·6; N, 18·3%).

iii) The aminotriazole (162a) (0·0025 mole) and ethyl ethoxymethylenemalonate (0·0025 mole) were refluxed in toluene (150 ml.) as above to yield the diester (197a) (82%), m.p. 155-156°, which was identical with a sample prepared above.

(d) Reactions in acetic acid

i) The aminotriazole (162a) (0·0025 mole) and acetylacetone (0·005 mole) were refluxed in glacial acetic acid (10 ml.) for 3·5 hr. The solution was evaporated to leave a gum which was triturated with ether to give the acetoxy compound (175a) (82%), m.p. 109-110° (from benzene-petrol), $\nu_{max.}$ 1735 (OAc) $cm.^{-1}$, τ (TFA) 2·32 (1H, s, pyrimidine CH), 2·95 (1H, s, benzylic CH), 7·15 (6H, s, 2 Me) and 7·61 (3H, s, Me), (Found: C, 70·2; H, 6·3; N, 11·2. $C_{15}H_{16}N_2O_2$ requires C, 70·3; H, 6·3; N, 10·9%).

ii) The aminotriazole (162a)(0·0025 mole) and dibenzoylmethane (0·005 mole) were refluxed in glacial acetic acid (2·5 ml.) for 2 days. The reaction mixture was worked-up as above to give the acetoxy compound (176a) (59%), m.p. 137-138° (from benzene-petrol), $\nu_{max.}$ 1740 (OAc) $cm.^{-1}$, τ (TFA) 7·53 (3H, s, Me), the other protons are hidden

in the aromatic multiplet, (Found: C, 79·3; H, 5·7; N, 7·2. $C_{25}H_{20}N_5O_2$ requires C, 78·9; H, 5·3; N, 7·4%). If the reaction was carried out in a larger volume of acetic acid (e.g. 10 ml.) the product obtained was a mixture of (176a) (10-15%) and the acetylaminotriazole (178a) (69-73%) based on the integrated ratios of the signals in the p.m.r. spectrum of the mixture.

iii) The aminotriazole (162a) (0·0025 mole) and ethyl acetoacetate (0·005 mole) were refluxed in glacial acetic acid (2·5 ml.) for 26 hr. The reaction mixture was evaporated and the remaining gum treated with warm benzene to give the acetoxy compound (177a) (82%), m.p. 186-187° (from benzene-petrol), $\nu_{max.}$ 2700 (NH), 1745 (OAc) and 1670 (CO) $cm.^{-1}$, τ (TFA) 2·86 (1H, s, pyrimidine CH), 3·24 (1H, s, benzylic CH), 7·53 (3H, s, Me) and 7·58 (3H, s, Me), (Found: C, 65·0; H, 5·8; N, 10·9. $C_{14}H_{14}N_2O_3$ requires C, 65·1; H, 5·5; N, 10·9%).

iv) The aminotriazole (162a) (0·0025 mole) and benzoylacetone (0·005 mole) were refluxed in glacial acetic acid (2·5 ml.) for 2·5 days. The solution was worked-up as above to give the acetoxy compound (176b) (82%), m.p. 134-135° (from benzene-petrol), $\nu_{max.}$ 1740 (OAc) $cm.^{-1}$, τ (TFA) 1·84 (1H, s, pyrimidine CH), 2·88 (1H, s, benzylic CH), 7·08 (3H, s, Me) and 7·55 (3H, s, Me), (Found: C, 75·3; H, 6·1; N, 8·7. $C_{20}H_{19}N_2O_2$ requires C, 75·5; H, 5·7; N, 8·8%).

v) The aminotriazole (162b) (0·0025 mole) and acetylacetone (0·005 mole) were refluxed in glacial acetic

acid (10 ml.) for 4 hr. The reaction mixture was worked-up as above to give the triazolopyrimidine amide (164b) (79%), m.p. 264-265° identical with a previously prepared sample (see above).

vi) The amide (162b) (0·0025 mole) and benzoylacetone (0·005 mole) were refluxed in glacial acetic acid (3·0 ml.) for 5 hr. The reaction mixture was evaporated to leave a gum, which was treated with benzene-ether to give the triazolopyrimidine (165b) (81%), m.p. 201-202° (from acetic acid), $\nu_{max.}$ 3400 (br.)(NH) and 1675 (CO) $cm.^{-1}$, τ (TFA) 2·17 (1H, s, pyrimidine CH) and 7·12 (3H, s → s on expansion, Me), τ (d_6-DMSO) 1·60 (1H, s, pyrimidine CH) and 6·66 (3H, s → s on expansion, Me), (Found: C, 61·6; H, 4·3; N, 27·7. $C_{13}H_{11}N_5O$ requires C, 61·7; H, 4·4; N, 27·7%).

vii) The aminotriazole (162a) (0·0025 mole) was refluxed in glacial acetic acid (2·5 ml.) with diethyl malonate, ethyl benzoylacetate or ethyl ethoxymethylene-malonate (0·005 mole) for periods up to 5 days. The reaction mixture worked-up as above afforded the acetylamino-triazole (178a) (69-76%), m.p. 217-219°, identical with a previously obtained sample (see below).

(e) Reactions in aqueous sodium hydroxide

i) The aminotriazole (162a) (0·0025 mole) and acetylacetone (0·005 mole) were refluxed with 40% w/v aqueous sodium hydroxide (2·0 ml.) in ethanol (10 ml.) for 10 min. The solvents were evaporated and the residual

gum triturated with water to give the triazolopyrimidine (164a) (69%), m.p. 159-160°, identical with a sample prepared above.

ii) The aminotriazole (162a) (0·0025 mole) refluxed with 40% w/v aqueous sodium hydroxide (2·0 ml.) in ethanol (10-15 ml.) with dibenzoylmethane, diethyl malonate, ethyl acetoacetate or ethyl benzoylacetate (0·005 mole) and the reaction mixture evaporated yielded a gum which afforded the starting triazole (162a) (69-78%) when it was dissolved in dilute acid and adjusted to pH 8 with concentrated ammonia.

(f) Reaction in ethanolic sodium ethoxide

The aminotriazole (162b) (0·0025 mole) and ethyl acetoacetate (0·005 mole) were refluxed with a solution of sodium (0·01 g. atom) in ethanol (20 ml.) for 24 hr. The reaction mixture was evaporated to give a gum which was dissolved in water, then acidified to yield the isomeric mixture [(167b)/(168b)] (61%), m.p. 274-275°, identical to a previously obtained sample.

(g) Reaction in acetic acid-dimethylformamide

The aminotriazole (162b) (0·0025 mole) and ethyl acetoacetate (0·005 mole) were refluxed in dimethylformamide (4·0 ml.) containing acetic acid (0·3 ml.) for 90 min. The dark reaction mixture was evaporated leaving a gum which on trituration with warm water gave an isomeric mixture [(167b)/(168b)](63%), m.p. 274-275°, identical with that prepared above.

3.2.2 Condensation of 5-amino-4-phenyl-1-H-1,2,3-triazole (162a) with phenacyl bromide

A solution of the aminotriazole (162a) (0·0025 mole) and phenacyl bromide (0·0025 mole) in ethanol (40 ml.) was refluxed with sodium bicarbonate (0·3 g.) for 12 hr. The suspension was cooled and the inorganic material removed by filtration. The filtrate was evaporated to give an oil, which on repeated trituration with ether gave the N-phenacyl triazole (194a) (77%), m.p. 178-179° (from benzene-ethanol), $\nu_{max.}$ 3380, 3310 and 3200 (NH) and 1700 (CO) $cm.^{-1}$, τ (TFA) 4·92 (2H, s, CH_2), (Found: C, 68·9; H, 5·2; N, 20·1. $C_{16}H_{14}N_4O$ requires C, 69·1; H, 5·1; N, 20·2%).

3.2.3 Base-catalysed cyclisation of the acylaminotriazoles (197a), (183a) or (185a)

(a) The diester (197a) (0·001 mole) was refluxed in ethanol (50 ml.) containing piperidine (0·3 ml.) for 7 days. The reaction mixture was evaporated and the remaining gum treated with dilute acid to give the triazolopyrimidine (196) (71%), m.p. 235-237°, identical with a previously prepared sample.

(b) The ester (183a) or the ketoamide (186a) was treated with ethanol-piperidine as above for 24 hr. to give the isomeric mixture [(167a)/(168a)] (79-81%), m.p. 232-234°, identical with the sample prepared previously.

3.2.4 Reactions of 5-amino-1-phenacyl-4-phenyl-1,2,3-triazole (194a)

(a) The N-phenacyl triazole (194a) (0·0025 mole) was refluxed with piperidine (0·7 ml.) in ethanol (80 ml.) for 24 hr. The reaction mixture was evaporated and the residual gum triturated with ether to yield the starting triazole derivative (194a) (83%).

(b) The triazole derivative (194a) (0·0025 mole) was refluxed in acetic anhydride (15 ml.) for 30 min. The reaction mixture was evaporated and the resulting gum treated with ether to yield the monoacetyl derivative (194b) (82%), m.p. 156-157° (from benzene-petrol), $\nu_{max.}$ 3400 (br.)(NH), 1700 (Ac) and 1685 (CO) $cm.^{-1}$, τ (TFA) 5·11 (2H, s, CH_2) and 7·63 (3H, s, Me), (Found: C, 68·2; H, 5·1; N, 17·9. $C_{18}H_{16}N_4O_2$ requires C, 67·5; H, 5·0; N, 17·5%).

(c) The N-phenacyl triazole (194a) (0·0025 mole) was refluxed in acetic acid (15 ml.) for 4 days. The reaction solution was evaporated to leave an oil which was triturated with ether to give 5-acetylamino-4-phenyl-1-H-1,2,3-triazole (178a) (77%), m.p. 217-219°, identical with a previously prepared sample.

3.2.5 Acetylation of 5-amino-4-phenyl-1-H-1,2,3-triazole (162a), and 5-acylamino derivatives

(a) The aminotriazole (162a) (0·0025 mole) was refluxed in glacial acetic acid (15 ml.) for 4 hr. The solution was evaporated to give a gum, which was triturated with ether to yield the monoacetyl derivative (178a) (86%), m.p. 217-219° (from benzene-ethanol), $\nu_{max.}$ 3150(w) and 2750 (NH), and 1670 (Ac) $cm.^{-1}$, τ (TFA) 7·51 (3H, s, Me), (Found: C, 59·6; H, 5·2; N, 27·8. $C_{10}H_{10}N_4O$ requires C, 59·4; H, 5·0; N, 27·7%).

(b) The aminotriazole (162a) or the acylaminotriazoles (183a), (186a) or (197a) (0·0025 mole) were refluxed in acetic anhydride (15 ml.) for 15 min. The reaction mixture was evaporated to leave a gum, which was triturated with ether to gum the following acetyl derivatives:-

(178b) (83%), m.p. 114-115° (from benzene-petrol), $\nu_{max.}$ 1770, 1740 and 1710 (Ac) $cm.^{-1}$, τ ($CDCl_3$) 7·16 (3H, s, Me), and 7·67 (6H, s, 2 Me), (Found: C, 58·7; H, 5·1; N, 19·7. $C_{14}H_{14}N_4O_3$ requires C, 58·7; H, 5·1; N, 19·6%).

(183b)(69%), m.p. 113-115° (from benzene-petrol), $\nu_{max.}$ 3200(w) (NH), 1740(Ac) and 1660 (CO) $cm.^{-1}$, τ ($CDCl_3$) 5·05 (1H, s, olefinic H), 5·85 (2H, q, $-OCH_2$), 7·23 (3H, s, Me), 7·6 (3H, s, olefinic Me), and 8·75 (3H, tr, Me), (Found: C, 61·0; H, 5·7; N, 18·0. $C_{16}H_{18}N_4O_3$ requires C, 61·1; H, 5·8; N, 17·8%).

(197b) (71%), m.p. 139-140° (from benzene-petrol), $\nu_{max.}$ 3150 (w)(NH), 1760 (Ac) and 1720 (CO) $cm.^{-1}$, τ ($CDCl_3$) 1·20 (1H, d, olefinic H), 5·71 (4H, q, 2·0 CH_2), 7·19 (3H, s, Me) and 8·7 (6H, tr, 2 Me), (Found: C, 58·0; H, 5·5; N, 15·2. $C_{18}H_{20}N_4O_5$ requires C, 58·1; H, 5·4; N, 15·1%).

(186b) (74%), m.p. 180-182° (from benzene-petrol, $\nu_{max.}$ 3400 (NH), 1730 (Ac) and 1685 (CO) $cm.^{-1}$, τ ($CDCl_3$) 6·31 (2H, s, CH_2), 7·24 (3H, s, Me) and 7·71 (3H, s, Me), (Found: C, 59·0; H, 5·1; N, 18·9. $C_{14}H_{14}N_4O_3$ requires C, 58·9; H, 4·9; N, 19·6%).

The acetyl derivatives (183b), (186b) or (197b) (0·0025 mole) were refluxed with N-aqueous sodium carbonate (5 ml.) in ethanol (10 ml.) for 20 min. The reaction mixtures were evaporated to leave gums which were dissolved in water, and acidified to give the acylaminotriazoles (183a), (186a) or (197a) respectively.

3.2.6 Reactions of substituted-1,2,3-triazolo[3,4-a]-pyrimidines

(a) Acetic acid

The substituted triazolopyrimidine (0·0025 mole) was refluxed in glacial acetic acid (15 ml.) for 4 hr. The solvent was removed under reduced pressure to give a gum, which was triturated with ether to afford the acetoxy compound (79-85%).

The isomeric mixture [(167a)/(168a)] or the compound (168a) yielded the acetoxy compound (177a), m.p. 186-187°, identical with a sample prepared above, whilst (164a) afforded the acetoxy derivative (175a), m.p. 109-110°, which was also identical with a sample obtained previously. The acid (198) gave the acetoxy compound (200a), m.p. 81-83° (from benzene), $\nu_{max.}$ 2500-2800 (NH and OH), 1745 (OAc) and 1700 (CO) $cm.^{-1}$, τ (TFA) 0·86 (1H, s, pyrimidine CH), 2·97 (1H, s, benzylic CH) and 7·58 (3H, s, Me), (Found: C, 58·6; H, 4·2; N, 9·7. $C_{14}H_{12}N_2O_5$ requires C, 58·3; H, 4·2; N, 9·7%).

Similar treatment of the isomer mixture [(167b)/(168b)], or the amides (164b) or (165b) with acetic acid afforded starting material (87-91%).

(b) Acetyl chloride

The triazolopyrimidine derivatives (164a) and (168a) (0·0025 mole) were refluxed in a mixture of acetyl chloride (30 ml.) and acetic acid (15 ml.) for 90 min. The

solvent was evaporated, and the gums obtained treated with ether to give the chloro compounds (175c) (69%), m.p. 111-112° (from benzene-petrol), τ (TFA) 2·26 (1H, s, pyrimidine CH), 3·58 (1H, s, benzylic CH) and 7·13 (6H, s, 2 Me), (Found: C, 67·5; H, 5·5; N, 12·3. $C_{13}H_{13}ClN_2$ requires C, 67·1; H, 5·6; N, 11·9%), and (175c) (72%), m.p. 193-194° (from ethanol), $\nu_{max.}$ 2600-2800 (NH) and 1690 (CO) $cm.^{-1}$, τ (TFA) 3·22 (1H, s, pyrimidine CH), 3·60 (1H, s, benzylic CH) and 7·35 (3H, s, Me), (Found: C, 61·6; H, 4·9; N, 12·2. $C_{12}H_{11}ClN_2O$ requires C, 61·4; H, 4·7; N, 11·9%).

3.2.7 Reactions of 2-(α-substituted benzyl)pyrimidines

(a) Hydrogenolysis

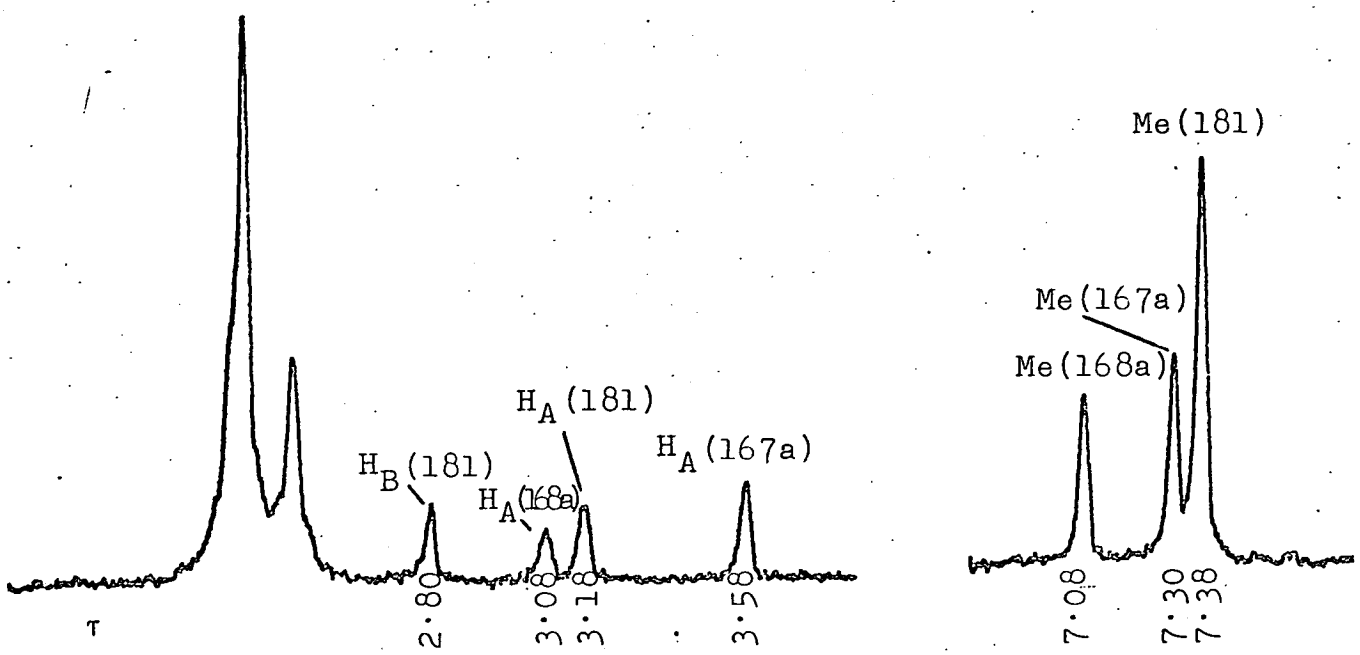
The 2-(α-substituted benzyl) pyrimidine (0·0025 mole) was dissolved in ethanol (100 ml.) and hydrogenated over 10% palladium-on-charcoal (0·1 g.). The suspension was filtered, the filtrate evaporated and the residual gum treated with ether-petrol to give the 2-benzylpyrimidine (79-84%). In this way the compounds (175a) and (175c) gave the known pyrimidine derivative[87] (175b), m.p. 78-79° (from benzene) (lit. m.p. 80°[87]), τ (TFA) 2·31 (1H, s, pyrimidine H), 5·41 (2H, s, benzylic CH_2) and 7·18 (6H, s, 2 Me), and (177a) and (177c) gave (177b), m.p. 165-166° (from benzene), $\nu_{max.}$ 2600-2700 (NH) and 1675 (CO) $cm.^{-1}$, τ (TFA) 3·31 (1H, s, pyrimidine CH), 5·50 (2H, s, benzylic CH) and 7·45 (3H, s, Me), (Found: C, 72·1; H, 6·2; N, 13·9. $C_{11}H_{12}N_2O$ requires C, 72·0; H, 6·0; N, 14·0%).

(b) Hydrolysis

The 2-(α-acetoxybenzyl)pyrimidine (175a) or (177a) (0·0025 mole) was refluxed with N-aqueous sodium carbonate (50 ml.) in ethanol (15 ml.) for 30 min. The reaction mixture was evaporated to give a gum which was treated with dilute sulphuric acid and chloroform. The chloroform extract was evaporated to leave a gum, which was triturated with petrol to give the hydroxy compound (175b) (69%), m.p. 78-79° (from benzene-petrol), $\nu_{max.}$ 3400 (OH) $cm.^{-1}$,

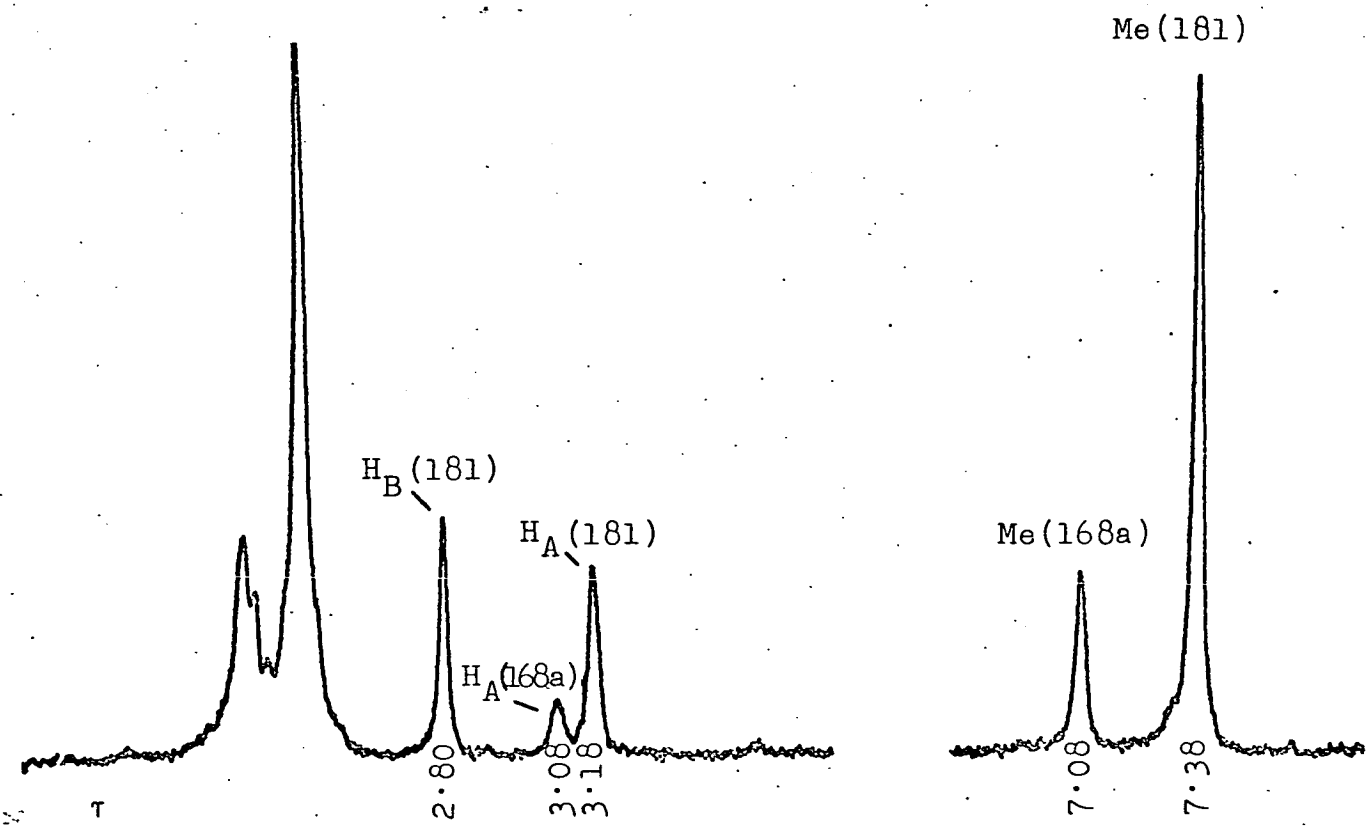
τ (TFA) 2·30 (1H, s, pyrimidine CH), 3·68 (1H, s, benzylic CH) and 7·13 (6H, s, 2 Me), (Found: C, 73·3; H, 6·8; N, 12·8. $C_{13}H_{14}N_2O$ requires C, 72·9; H, 6·6; N, 13·1%) or (177b) (73%), m.p. 197-199° (from benzene), $\nu_{max.}$ 3400 (OH), 2700 (NH) and 1670 (CO) $cm.^{-1}$, τ (TFA) 3·29 (1H, s, pyrimidine CH), 3·82 (1H, s, benzylic CH) and 7·38 (3H, s, Me), (Found: C, 69·4; H, 6·1; N, 12·7. $C_{12}H_{12}N_2O_2$ requires C, 69·1; H, 6·0; N, 12·9%).

(see scheme 9) Spectrum 1



Spectrum 1a.

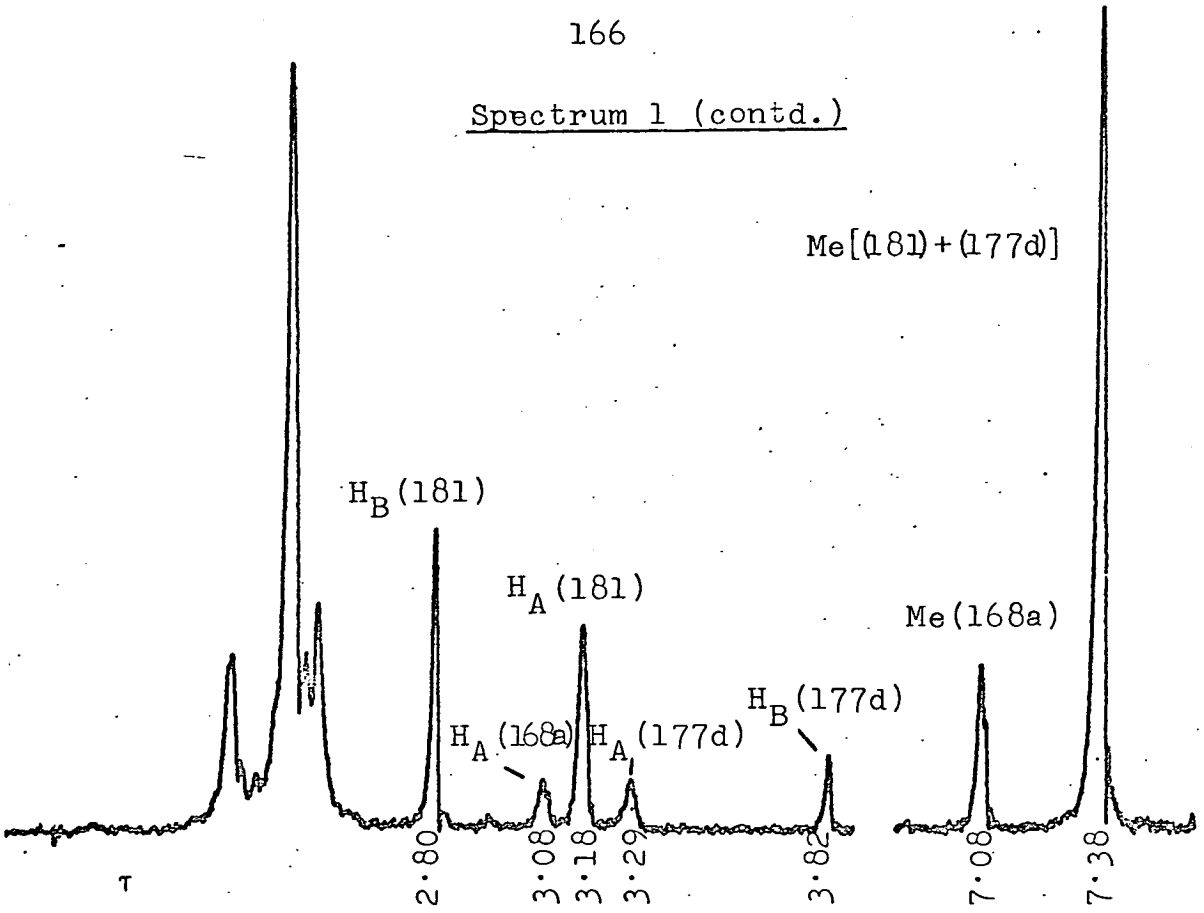
Mixture of (167a) and (168a) in TFA, run after 30 sec.



Spectrum 1b.

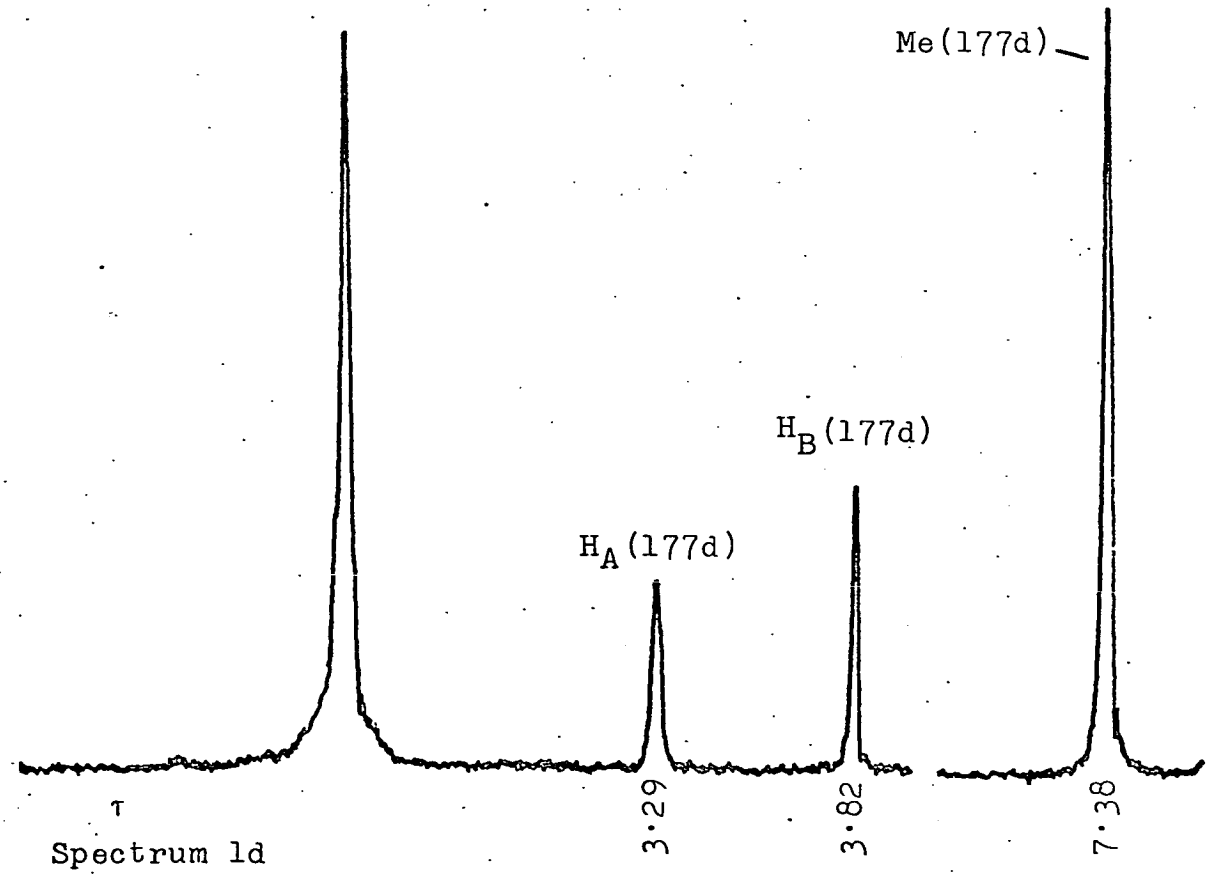
Mixture of (167a) and (168a) in TFA, run after 1 min.

Spectrum 1 (contd.)



Spectrum 1c

Mixture of (167a) and (168a) in TFA, run after 2 hr.

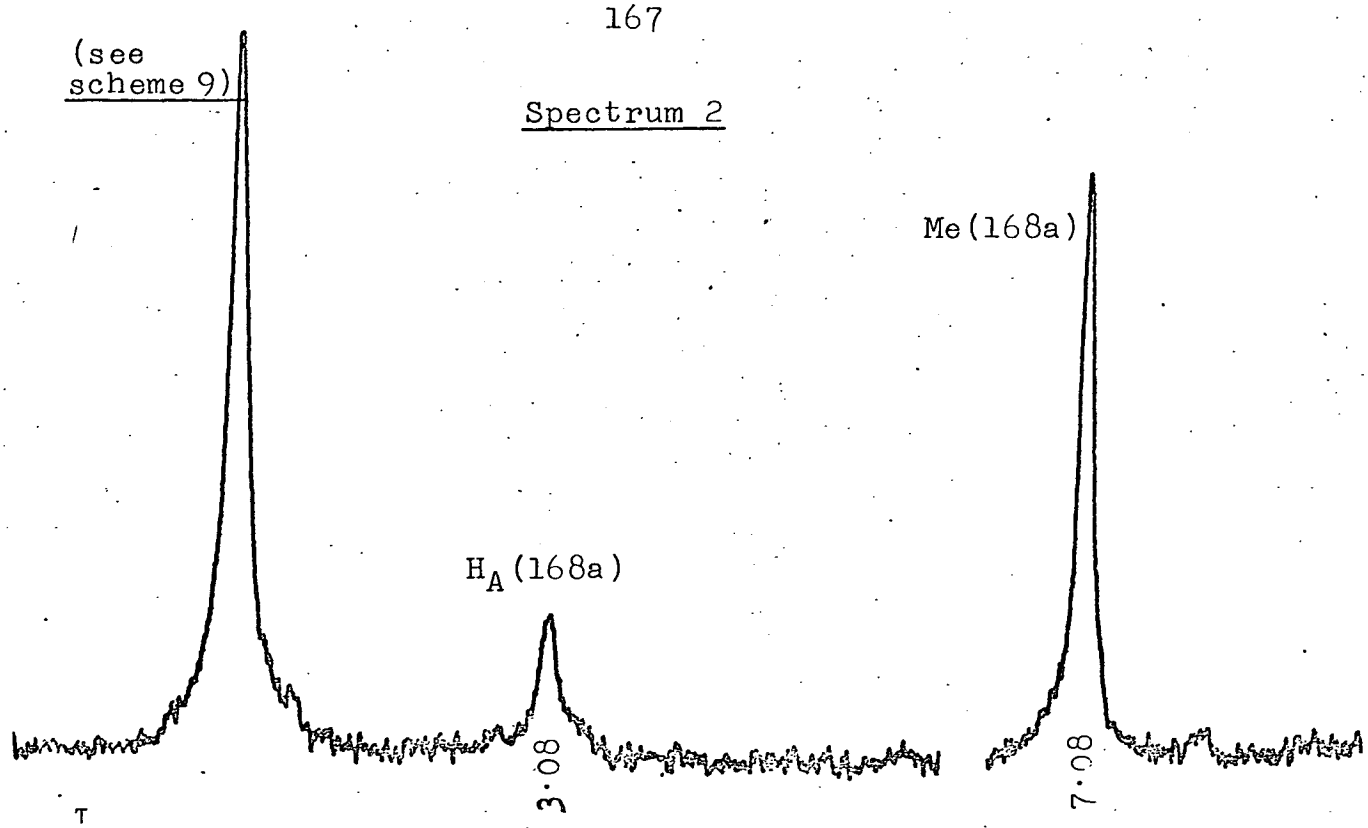


Spectrum 1d

Mixture of (167a) and (168a) in TFA, run after 24 hr.

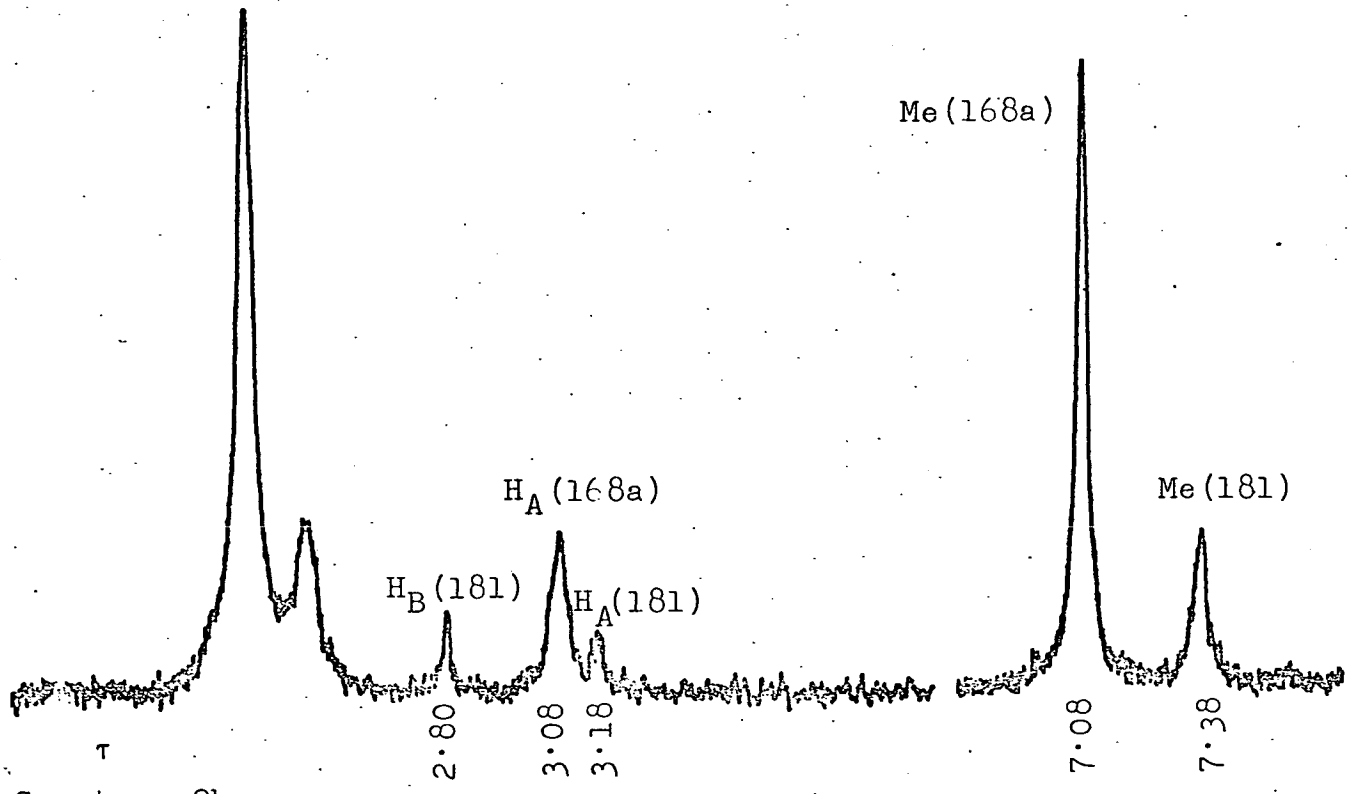
(see scheme 9)

Spectrum 2



Spectrum 2a

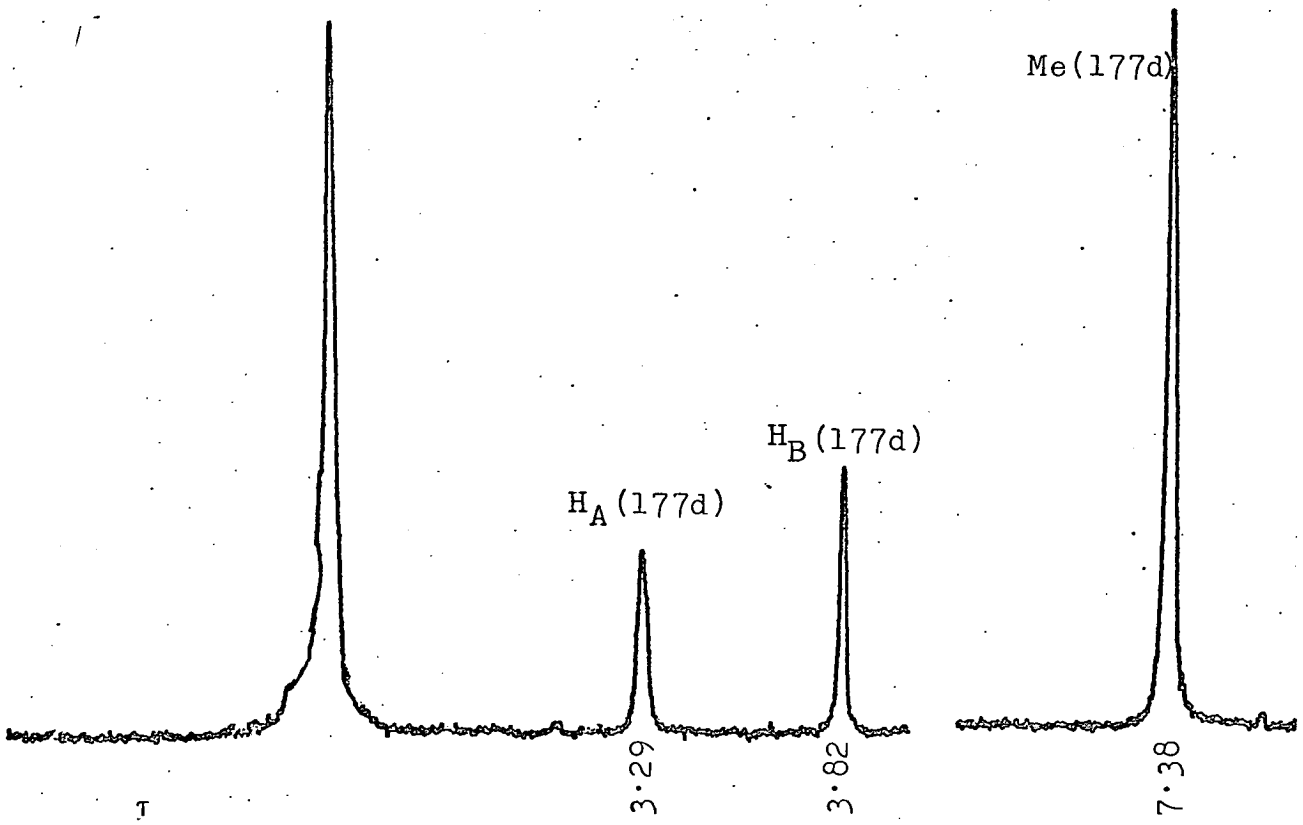
(168a) in TFA after 1 min.



Spectrum 2b

(168a) in TFA after 12 hr.

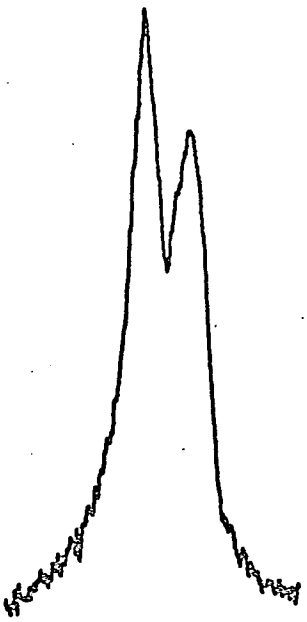
Spectrum 2 (contd.)



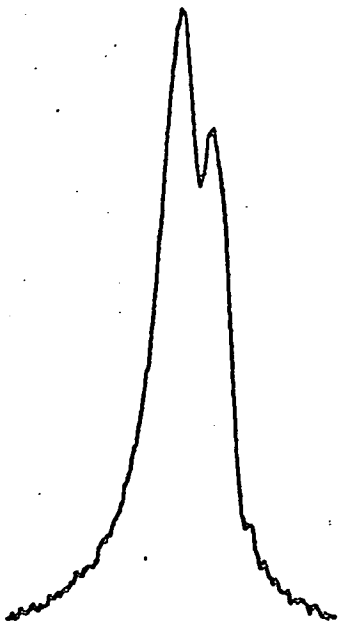
Spectrum 2c

(168a) in TFA after 24 hr.

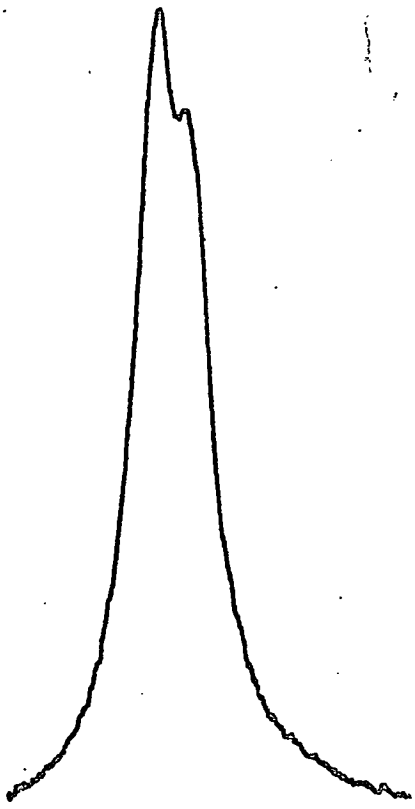
Expansions (250Hz) of signals shown in Spectra 1 and 2



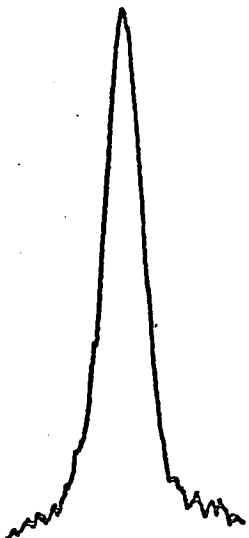
Me(167a)



Me (168a)

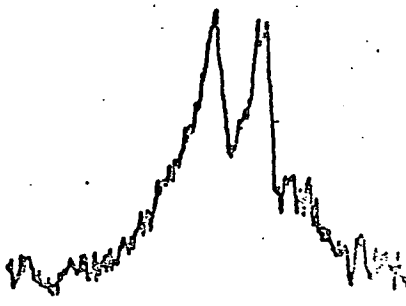


Me(181)
or
Me(177d)



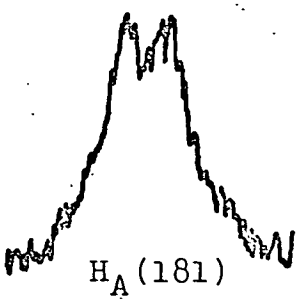
H_B(181)

H_B(177d)

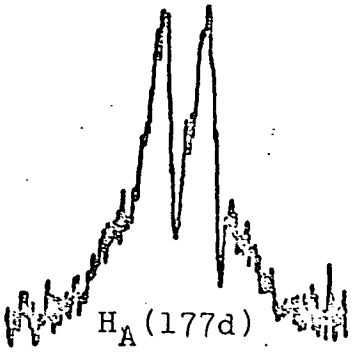


H_A(167a)

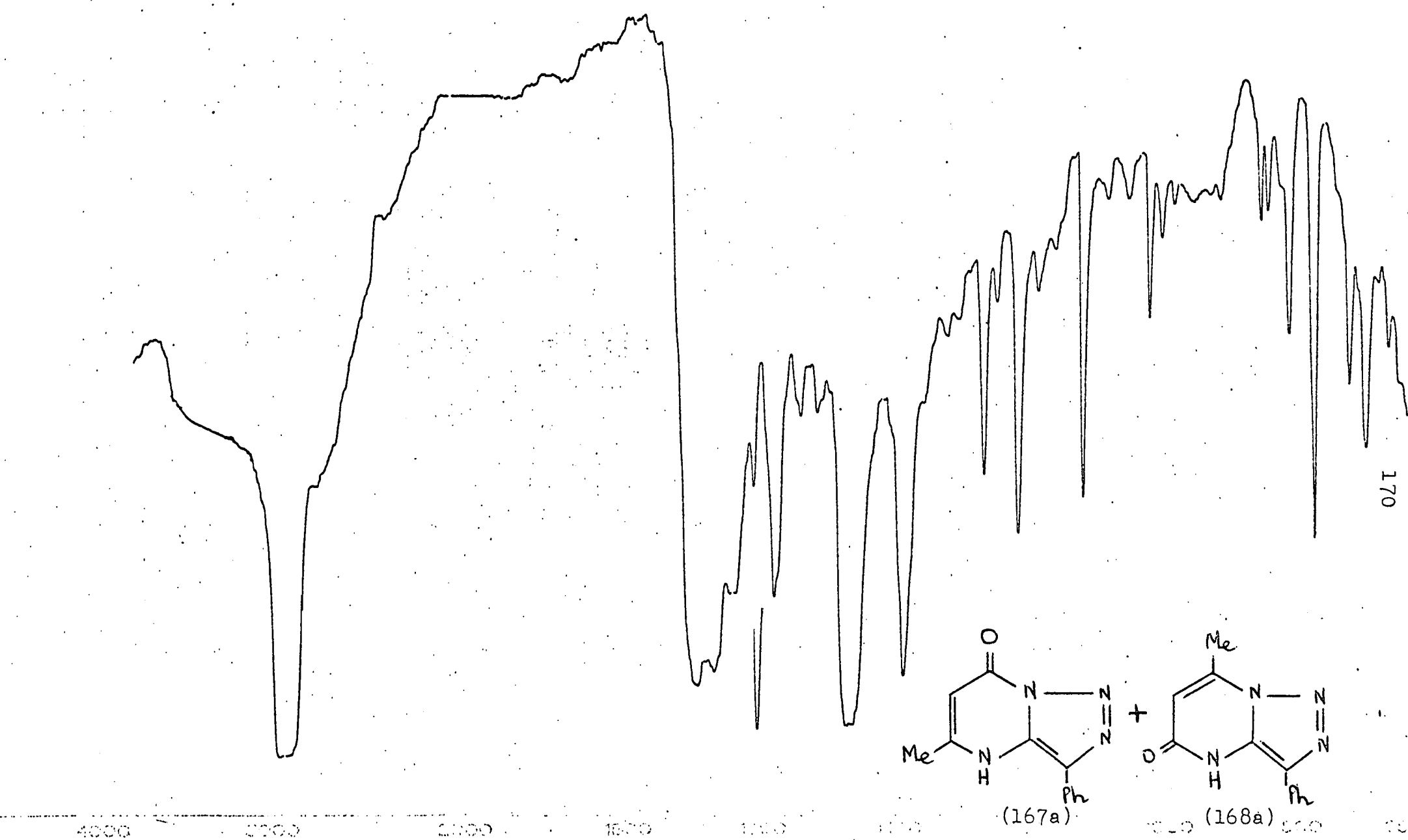
H_A(168a)



H_A(181)



H_A(177d)

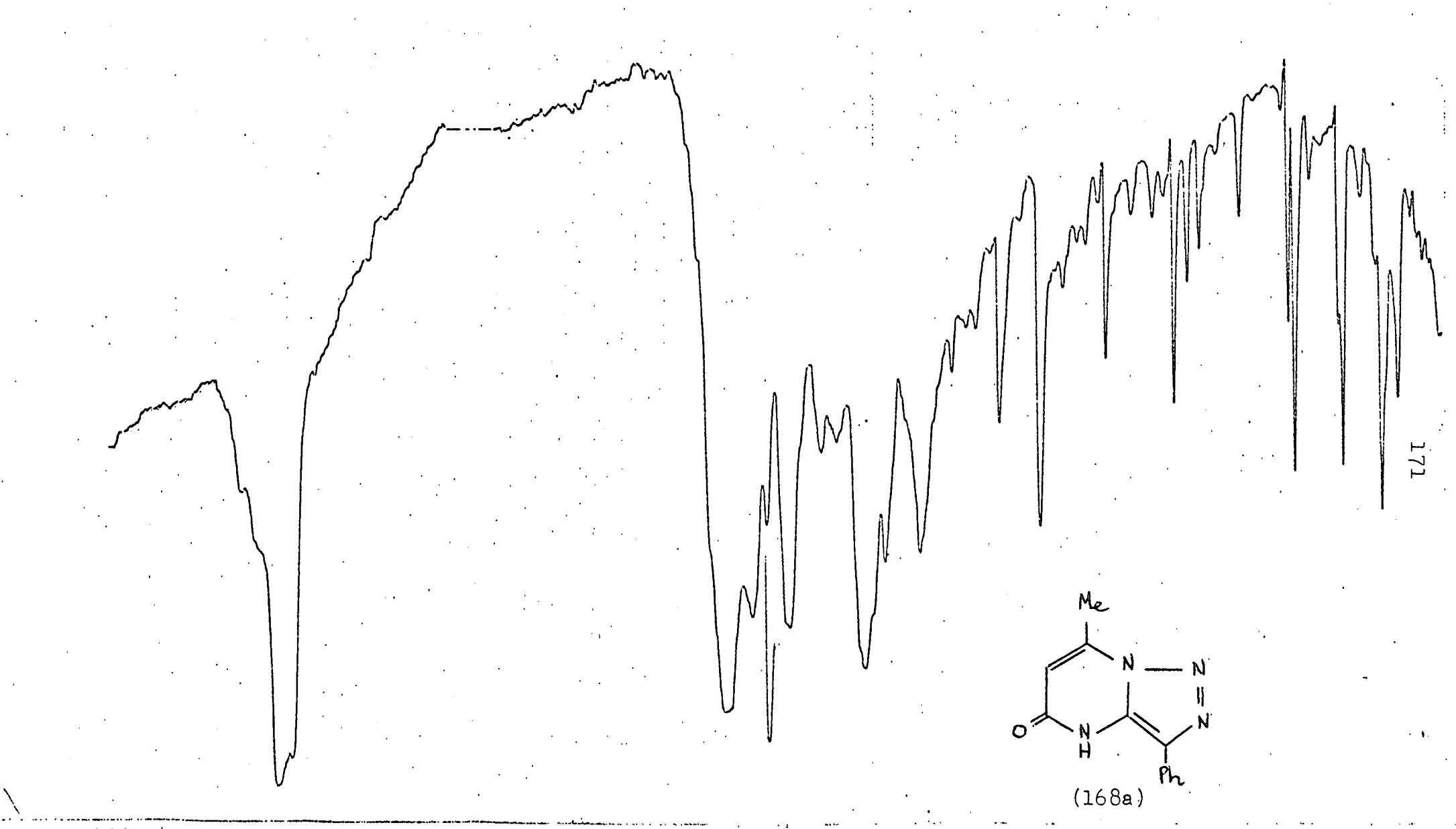


(167a)

+

(168a)

Spectrum 3



(168a)

Spectrum 4

3.3.1 Preparation of substituted 1-(2-nitrophenyl)-1,2,3-triazoles.

(a) 5-amino-4-carbamoyl-1-(2-nitrophenyl)-1,2,3-triazole(201a).

2-Nitrophenyl azide (0·16 mole) and cyanoacetamide (0·16 mole) were suspended in dry ether (200 ml.) and cooled to 0° in an ice-salt bath. A solution of sodium (0·16 g. atom) in methanol (80 ml.) was added dropwise, with stirring, over 3 hr. The suspension was then stirred for a further 24 hr., the ice-salt bath being allowed to melt. The reaction mixture was filtered and the solid washed with methanol (150 ml.) and ether (200 ml.). After the solid was dried at the pump it was washed with 10% w/v aqueous sodium hydroxide (50 ml.) and water (200 ml.), and then dried at room temperature under vacuum. Fractional crystallisation from ethanol, ensuring a short contact time in the solvent, gave the aminotriazole (201a) (17%), m.p. 258-260° (from ethanol) [during heating the solid isomerised to (202a)], $\nu_{max.}$ 3400, 3250 and 3120 (NH), 1640 (CO), 1540 and 1350 (NO_2) $cm.^{-1}$, (Found: C, 43·4; H, 3·5; N, 34·0. $C_9H_8N_6O_3$ requires C, 43·5; H, 3·2; N, 33·8%), and the anilinotriazole (202a) (11%), m.p. 259-260° (from acetic acid), $\nu_{max.}$ 3410 and 3150-3300 (NH), 1660 (CO), 1545 and 1360 (NO_2) $cm.^{-1}$, (Found: C, 43·2; H, 3·6; N, 33·8. $C_9H_8N_6O_3$ requires C, 43·5; H, 3·2; N, 33·8%). The ethanolic crystallisation liquors were evaporated to give a gum which was dissolved in the aqueous alkaline liquors from above, then acidified to give an unidentified

yellow solid (12%), m.p. 165-166° (from acetic acid), $\nu_{max.}$ 1630 (w) $cm.^{-1}$, p($\frac{m}{e}$) 230, (Found: C, 47·6; H, 2·7; N, 36·1. $C_9H_6N_6O_2$ requires C, 47·0; H, 2·6; N, 36·5%). The yellow solid was soluble in saturated aqueous sodium bicarbonate solution, and was reprecipitated by acidification. The methanol-ether mother liquors from above were evaporated to leave a gum, which was treated with water and chloroform. The chloroform extract on evaporation gave 1-nitroaniline (19%) whilst the aqueous fraction was acidified to give a further crop of the anilinotriazole (202a) (19%) (see above).

(b) 5-amino-4-carbamoyl-1-(4-methyl-2-nitrophenyl)-1,2,3-triazole (201b)

4-Methyl-2-nitrophenyl azide (0·16 mole) and cyanoacetamide (0·16 mole) were reacted together in methanolic sodium methoxide as in (a) above to give the aminotriazole (201b) (23%), m.p. 277-278° (from methanol) [during heating the solid isomerises to (202b)], $\nu_{max.}$ 3410, 3300 and 3150 (NH), 1675 (CO), 1360 and 1530 (NO_2) $cm.^{-1}$, τ (TFA) after 1 min. 7·38 (3H, s, Me), after 24 hr. 7·45 [3H, s, Me of (202b)], (Found: C, 45·8; H, 4·0; N, 31·8. $C_{10}H_{10}N_6O_3$ requires C, 45·8; H, 3·8; N, 32·0%), the anilinotriazole (202b) (21%), m.p. 279-280° (from acetic acid), $\nu_{max.}$ 3440 and 3250 (br.) (NH), 1680 (CO), 1530 and 1360 (NO_2) $cm.^{-1}$, τ (TFA) 7·45 (3H, s, Me), (Found: C, 45·8; H, 4·2; N, 31·8. $C_{10}H_{10}N_6O_3$ requires C, 45·8; H, 3·8; N, 32·0%) and a yellow acidic solid (16% - based on molecular

weight), m.p. 176-179° (from acetic acid-dimethylformamide), $\nu_{max.}$ 1620 (w) $cm.^{-1}$, τ (TFA) 7·69 (3H, s, Me), p($\frac{m}{e}$) 244, (Found: C, 48·8; H, 2·8; N, 34·9. $C_{10}H_8N_6O_2$ requires C, 49·2; H, 3·3; N, 34·4%). 4-methyl-2-nitroaniline (16%) was isolated in the same manner as 2-nitroaniline was obtained from reaction (a) above.

The nitro compounds (201a,b) when refluxed in cellosolve, ethanol, ethanolic sodium ethoxide, 20% w/v aqueous sulphuric acid or 40% w/v aqueous sodium hydroxide for 3-6 hr. afforded the anilino isomers (202a,b) (79-88%), identified by comparison with the samples prepared above.

3.3.2 Acetylation of substituted-1-(2-nitrophenyl)-1,2,3-triazoles

(a) The aminotriazole (201a), or the anilinotriazole (202a), (0·0025 mole) was refluxed in acetic anhydride (10 ml.) for 15 min. The reaction mixture was evaporated to leave a gum, which was triturated with ether to give the monoacetyl compound (204a) (81%), m.p. 215-218° (from acetic acid), $\nu_{max.}$ 3490, 3300 and 3190 (NH), 1750 (Ac) and 1690 (CO) $cm.^{-1}$, τ (TFA) 7·00 (3H, s, Me), (Found: C, 45·9; H, 3·8; N, 29·0. $C_{11}H_{11}N_6O_4$ requires C, 46·0; H, 3·5; N, 29·3%). When the reaction was repeated under identical conditions for 2 hr. the product was a diacetyl compound (205a) (77%), m.p. 226-227° (from glacial acetic acid), $\nu_{max.}$ 3460 and 3220 (NH), 1760 and 1700 (Ac), and 1680 (CO) $cm.^{-1}$, τ (TFA) 7·00 (3H, s, Me) and 7·30 (3H, s, Me), (Found: C, 43·9; H, 4·1; N, 25·3. $C_{12}H_{13}N_6O_5$ requires C, 43·5; H, 3·9; N, 25·3%).

The acetyl derivatives (204a) and (205a) (0·002 mole) in ethanol (20 ml.) were warmed with 10% w/v aqueous sodium hydroxide (5·0 ml.) for 2 min. The reaction mixture was evaporated to give a gum which on treatment with dilute acid gave the anilinotriazole (202a) (79%), m.p. 259-260°, identical with the sample prepared above. The aminotriazole (201a) treated in an identical manner afforded the starting triazole (201a) (91%).

(b) The aminotriazole (201b), or the anilino isomer (202b), was treated with acetic anhydride as in (a) above to yield the monoacetyl derivative (204b) (81%), m.p. 212-214° (from acetic acid), $\nu_{max.}$ 3400, 3300 and 3220 (NH), 1765 (Ac) and 1690 (CO) $cm.^{-1}$, τ (TFA) 7·00 (3H, s, Me), (Found: C, 47·4; H, 4·1; N, 27·8. $C_{12}H_{13}N_6O_4$ requires C, 47·8; H, 4·0; N, 27·6%), and the diacetyl compound (205b) (79%), m.p. 226-228° (from glacial acetic acid), $\nu_{max.}$ 3410 and 3260 (NH), 1765 and 1700 (Ac), and 1690 (CO) $cm.^{-1}$

3.3.3 Catalytic reduction of the nitrophenyltriazoles (201a,b)

(a) The nitro compound (201b) (0·002 mole) in ethanol (250 ml.) was hydrogenated over 10% palladium-on-charcoal (0·15 g.). The catalyst was filtered off and the filtrate evaporated to give a gum, which on trituration with ether-petrol gave the diamine (206b) (86%), m.p. 190-191° (from ethanol), $\nu_{max.}$ 3400, 3200 and 3130 (sh.)(NH), and 1650 (CO) $cm.^{-1}$, τ (d_6 DMSO) 2·15 and 2·47 (1H, s, NH of amide), 3·69 and 4·68 (2H, s, NH_2), and 7·46 (3H, s, Me), (Found: C, 51·8; H, 5·1; N, 36·2. $C_{10}H_{12}N_6O$ requires C, 51·7; H, 5·2; N, 36·2%).

(b) Similar treatment of the nitro compound (201a) gave the diamine (206a) (87%), m.p. 194-195° (from ethanol), $\nu_{max.}$ 3400 and 3120-3320 (NH), and 1655 (CO) $cm.^{-1}$, (Found: C, 49·4; H, 4·8; N, 38·9. $C_9H_{10}N_6O$ requires C, 49·5; H, 4·6; N, 38·5%).

3.3.4 Lead tetraacetate oxidation of the diamines (206a,b)

The diamine (206a,b) (0·001 mole) was refluxed with dry lead tetraacetate (0·002 mole) in anhydrous benzene (250 ml.) for 6 hr. Inorganic material was removed by filtration and the filtrate evaporated to give a gum, which was treated with ether-petrol to give the triazolobenzotriazine (236a,b) (67-74%).

(236a), m.p. 225-226° (from acetic acid-ethanol), $\nu_{max.}$ 3450, 3330 and 3250 (NH), and 1675 (CO) $cm.^{-1}$, (Found: C, 50·9; H, 2·9; N, 38·8. $C_9H_{10}N_6O$ requires C, 50·4; H, 2·8; N, 39·3%).

(236b), m.p. 238-239 (from acetic acid-ethanol), $\nu_{max.}$ 3400 and 3200 (NH), and 1675 (CO) $cm.^{-1}$, τ (TFA) 7·61 (3H, s, Me), (Found: C, 52·4; H, 3·3; N, 37·2. $C_{10}H_{10}N_6O$ requires C, 52·6; H, 3·5; N, 36·8%).

The triazolobenzotriazines (206a,b) were refluxed in acetic acid (15 ml.) for periods up to 6 hr. The reaction mixtures were evaporated and the residual gums treated with ether to give the unchanged compounds (206a,b) (81-87%).

3.3.5 Halogenation of 1,4-substituted-5-amino-1,2,3-triazoles

(a) The 5-aminotriazole (0·001 mole) was dissolved in concentrated hydrochloric acid (10 ml.) or 50% hydrobromic acid (10 ml.) and cooled to 0° in an ice-salt bath. A solution of sodium nitrite (0·5 g.) in water (10 ml.) was added dropwise with stirring over 5 min. The solution was stirred for a further 10 min., then removed from the ice-salt bath and stirred for 10 min. at room temperature. The solid was collected and combined with the material obtained by diluting the filtrate with water (50-70 ml.) to give the halogenated triazole (80-87%).

The amide (213b) yielded the chlorotriazole (214b), m.p. 181-182° (from ethanol), $\nu_{max.}$ 3450 and 3290 (NH), and 1690 (CO) $cm.^{-1}$, (Found: C, 49·0; H, 3·2; N, 25·6. $C_9H_7ClN_4O$ requires C, 48·5; H, 3·1; N, 25·2%), or the bromotriazole (215b), m.p. 195-196° (from ethanol), $\nu_{max.}$ 3450, 3300 (w) and 3200 (NH), and 1690 (CO) $cm.^{-1}$, (Found: C, 40·4; H, 2·4; N, 20·7. $C_9H_7BrN_4O$ requires C, 40·5; H, 2·6; N, 21·0%).

The diphenyltriazole (213a) yielded the known chlorotriazole (214a), m.p. 137-138° (from benzene-ethanol) (lit.[34] m.p. 137°), identical with a sample prepared by a known route,[83] or the bromo compound (165a), m.p. 195-196° (from ethanol), (Found: C, 55·8; H, 3·2; N, 13·9. $C_{14}H_{10}BrN_3$ requires C, 56·0; H, 3·3; N, 14·0%). The bromo compound (215a) (0·001 mole) was refluxed with 20% w/v aqueous potassium hydroxide (5 ml.) in ethanol (10 ml.) for 30 min. The

reaction mixture was evaporated to leave a gum which was treated with chloroform and dilute sulphuric acid. The chloroform extract was evaporated and the residual gum treated with ether to give the hydroxytriazole (216a) (79%), m.p. 149-151° (from ethanol) (lit. m.p. 151°), identical with an authentic sample.

Halogenation (as above) of the nitro compound (201a) gave the chlorotriazole (218a), m.p. 192-194° (from ethanol), $\nu_{max.}$ 3420, 3300 and 3150 (NH), 1685 (CO), 1540 and 1350 (NO_2) $cm.^{-1}$, (Found: C, 40·7; H, 2·2; N, 26·3. $C_9H_6ClN_5O_3$ requires C, 40·4; H, 2·2; N, 26·3%) or the bromotriazole (218b), m.p. 179-180° (from ethanol-acetic acid), $\nu_{max.}$ 3420, 3290 (w) and 3150 (NH), 1685 (CO), 1540 and 1350 (NO_2) $cm.^{-1}$, (Found: C, 34·8; H, 1·9; N, 22·7. $C_9H_6BrN_5O_3$ requires C, 34·6; H, 1·9; N, 22·4%). Similarly the nitro compound (201b) gave the chlorotriazole (218c), m.p. 200-201° (from ethanol-acetic acid), $\nu_{max.}$ 3400 and 3200 (NH), 1690 (CO), 1540 and 1360 (NO_2) $cm.^{-1}$, (Found: C, 42·6; H, 2·7; N, 24·7. $C_{10}H_8ClN_5O_3$ requires C, 42·6; H, 2·9; N, 24·9%), or the bromotriazole (218d), m.p. 179-180° (from ethanol-acetic acid), $\nu_{max.}$ 3450 and 3320 (NH), 1685 (CO), 1540 and 1360 (NO_2) $cm.^{-1}$, (Found: C, 36·4; H, 2·2; N, 21·7. $C_{10}H_8BrN_5O_3$ requires C, 36·8; H, 2·5; N, 21·5%).

The diamino compound (206a) gives the dichlorotriazole (217a), m.p. 189-190° (from ethanol), $\nu_{max.}$ 3370 and 3190 (NH), and 1690 (CO) $cm.^{-1}$, (Found: C, 41·9; H, 2·2; N, 21·7.

$C_9H_6Cl_2N_4O$ requires C, 42·0; H, 2·3; N, 21·8%), and the diamine (206b) gives the dichloro compound (217c), m.p. 189-190° (from ethanol), $\nu_{max.}$ 3450, 3300 (w) and 3200 (NH), and 1690 (CO) $cm.^{-1}$, (Found: C, 44·9; H, 2·8; N, 20·6. $C_{10}H_8Cl_2N_4O$ requires C, 44·3; H, 3·0; N, 20·7%).

(b) The aminotriazole (213a) (0·002 mole) was suspended in concentrated hydrochloric acid (15 ml.), and cooled to 0° in an ice-salt bath. A solution of sodium nitrite (0·25 g.) in water (1·0 ml.) was added with stirring. The reaction mixture was stirred at 0° for 90 minutes,[89] and then the diazonium solution (positive test with alkaline 2-naphthol) was treated with water (100 ml.). The resulting suspension was stirred at room temperature for 1 hr. and the solid collected to give the chlorotriazole (214a) (81%) identical with the sample prepared as described in (a) above.

3.4.1 Synthesis and isomerisation of 4-substituted-5-amino-1-phenyl-1,2,3-triazoles

(a) 5-amino-1,4-diphenyl-1,2,3-triazole (256a)

The triazole (256a) was prepared by a known method[114] to yield (87%), m.p. 171-173° (from ethanol) (lit. m.p. 179°, 170°[34,114]), $\nu_{max.}$ 3400 (NH) $cm.^{-1}$, and was isomerised by the known route[114] to give the anilino compound (256d) (79%), m.p. 166-167° (from ethanol) (lit. m.p. 167°[114]), $\nu_{max.}$ 3250 and 3200 (sh)(NH) $cm.^{-1}$

(b) 5-amino-4 carbamoyl-1-phenyl-1,2,3-triazole (252a)

The triazole (252a) was prepared by a known method[103] to yield (80%), m.p. 166-167° (from ethanol) (lit. m.p. 167°[103]), $\nu_{max.}$ 3400, 3350 and 3200 (NH), and 1660 (CO) $cm.^{-1}$, and was isomerised[103] to the anilino isomer (252d) (79%), m.p. 197-199° (from ethanol) lit. m.p. 202°[103]). The amide (252a) was refluxed in 70% v/v aqueous acetic acid (15 ml.) for 6·5 hr. The solvent was removed under reduced pressure to yield the isomer (252d) (93%).

(c) 5-amino-4 N,N-dimethylcarbamoyl-1-phenyl-1,2,3-triazole (253a)

A mixture of phenyl azide (0·1 mole) and N,N-dimethylcyanoacetamide (0·1 mole)[113] in anhydrous ether (70 ml.) was cooled to 0° in an ice-salt bath, then stirred and dropwise treated with a solution of sodium

(0·1 g. atom) in methanol (50 ml.). The reaction mixture was stirred in a melting ice-salt bath for 24 hr. The solid product was collected washed with methanol (50 ml.) and water (20 ml.) and combined with material obtained by evaporating the combined ether-methanol filtrate and methanol washings followed by trituration with water, to give the triazole (253a) (79%), m.p. 158-161° (from ethanol), $\nu_{max.}$ 3350, 3250 and 3150 (NH), and 1610 (br.) (CO) $cm.^{-1}$, τ (TFA) 6·60 (6H, s, Me_2), (Found: C, 57·1, H, 5·9; N, 30·7. $C_{11}H_{13}N_5O$ requires C, 57·1; H, 5·6; N, 30·3%).

The dimethylamide (253a) (0·01 mole) was refluxed in dry redistilled pyridine (35 ml.) for 24 hr. Distillation of the pyridine under reduced pressure left a gum which on treatment with dilute sulphuric acid gave the isomer (253d) (84%), m.p. 216-217° (from ethanol), $\nu_{max.}$ 3300 and 3150 (NH), and 1610 (CO) $cm.^{-1}$, τ (TFA) 6·78 (6H, s, Me_2), (Found: C, 57·4; H, 5·4; N, 30·8. $C_{11}H_{13}N_5O$ requires C, 57·1; N, 5·4; N, 30·8%).

(d) 5-amino-4 carbomethoxy-1-phenyl-1,2,3-triazole (255a)

Phenyl azide likewise (see above) condensed with ethyl cyanoacetate resulting in ester exchange to give the ester (255a) (68%), m.p. 170-171° (from ethanol) (lit. m.p. 173°[34]), $\nu_{max.}$ 3450 and 3300 (NH), and 1690 (CO) $cm.^{-1}$, τ ($CDCl_3$) 6·00 (3H, s, Me), and the acid (258a) (17%), m.p. 141-142° (from ethanol) (lit. m.p. 142°[34]), $\nu_{max.}$ 3450 and 3200 (NH), 2500-2700 (OH) and 1670 (CO) $cm.^{-1}$

The ester (225a) was refluxed in pyridine for 24 hr. as in (c) above. The pyridine was evaporated to give a gum which was dissolved in dilute sulphuric acid and chloroform. The acidic aqueous fraction was neutralised with saturated aqueous sodium bicarbonate to give the anilinotriazole (274a, $R^1 = R^2 = H$)(61%), m.p. 135-137° (from benzene)(lit. m.p. 139°[34]), $\nu_{max.}$ 2350, 3310 and 3200 (NH) $cm.^{-1}$, τ ($CDCl_3$) 2·57 (1H, s, CH). The chloroform extract was evaporated to yield the ester (255d) (19%), m.p. 151-152° (from methanol-water) (lit. m.p. 154°[34]), $\nu_{max.}$ 3450 and 3250 (NH), and 1710 (CO) $cm.^{-1}$, τ ($CDCl_3$) 5·92 (3H, s, Me). Heating the ester (255a) in pyridine for 3 hr. afforded the ester (255d) (81%). The acid (258b) (81%) was formed when the ester (255d) was warmed in 10% w/v aqueous sodium hydroxide, m.p. 151-152° (from methanol) (lit. m.p. 153°[34]), $\nu_{max.}$ 3400 and 3250 (NH), 2500-2650 (OH), and 1700 (br.) (CO) $cm.^{-1}$

The acid (258b) was also formed in good yield (79%) when the amide (252a) (0·001 mole) was refluxed in ethanol (15 ml.) with 20% w/v aqueous potassium hydroxide (10 ml.) for 2 hr.

(e) 5-amino-4-cyano-1-phenyl-1,2,3-triazole (258c)

Malononitrile (0·1 mole) and phenyl azide (0·1 mole) in methanol (50 ml.), at 0°, were stirred with a solution of sodium (0·1 g. atom) in methanol (50 ml.), which was added dropwise over 60 min., for 12 hr. The ice-

salt bath was then removed and the reaction stirred at room temperature for 2 hr. The solid was collected and washed with methanol (50 ml.) and water (50 ml.) to yield the dimer (260a) (55%) (see below). The methanol filtrate and washings were combined and evaporated to leave a gum which was treated with dilute acid to give the inimoether (258d) (11%), m.p. 140-141° (from ethanol), $\nu_{max.}$ 3400 and 3250 (br.) (NH), and 1660 (CN) $cm.^{-1}$, τ ($CDCl_3$) 6·05 (3H, s, Me). (Found: C, 55·1; H,5·1; N, 32·4. $C_{10}H_{11}N_5O$ requires C, 55·3; H, 5·1; N, 32·3%). The acidic liquors and the aqueous washings were combined and extracted with chloroform. The chloroform extract was evaporated to leave a gum, which on trituration with ether gave the nitrile (258c) (13%), m.p. 126-127° (from benzene), $\nu_{max.}$ 3400, 3300 and 3200 (NH), and 2250 (CN) $cm.^{-1}$, (Found: C, 58·3; N, 3·9; H, 37·8. $C_9H_7N_5$ requires C, 58·4; H, 3·8; N, 37·8%).

The iminoether (258d) was refluxed in pyridine for 24 hr. as above to give the anilino isomer (258e) (82%), m.p. 146-147° (from ethanol-water), $\nu_{max.}$ 3400 and 3100 (NH) $cm.^{-1}$, (Found: C, 55·2; H, 5·0; N, 32·4. $C_{11}H_{13}N_5O$ requires C, 55·3; H, 5·1; N, 32·3%). The iminoether (258d) (0·001 mole) was refluxed in 70% v/v aqueous acetic acid (10 ml.) for 2·5 hr. The solvent was evaporated to leave a gum which on treatment with benzene-ether yielded the ester (255a) (79%).

If the condensation of malononitrile with phenyl azide (see above) was repeated over a period of 24 hr. the dimer (260a) (81%) was obtained, m.p. 333-334° (from methanol),

$\nu_{max.}$ 3500, 3400 and 3300 (NH) $cm.^{-1}$, P($\frac{m}{e}$) 370, (Found: C, 58·4; H, 3·8; N, 37·8. $C_{18}H_{14}N_{10}$ requires C, 58·4; H, 3·8; N, 37·8%). The dimer (260a) afforded a sparingly soluble salt in dilute aqueous sulphuric acid and was recovered on careful neutralisation with saturated aqueous sodium bicarbonate.

The nitrile (258c) on the iminoether (258d) (0·001 mole) refluxed in 20% w/v aqueous potassium hydroxide (15 ml.) for 4 hr. afforded the dimer (260a) (79-83%) on cooling the reaction mixture.

3.4.2 Reactions of 6-amino-2-(4-amino-3-phenyl-1,2,3-triazol-4-yl)-9-phenyl-8-azapurine (260a)

(a) The dimer (260a) (0·002 mole) was refluxed with acetic acid (50 ml.) for 3 hr. The suspended yellow solid slowly dissolved, then a yellow solid separated out. The reaction mixture was cooled and filtered to yield the isomer (260b) (96%), m.p. 335-338° (from dimethylformamide-water), $\nu_{max.}$ 3350 and 3200 (NH) $cm.^{-1}$, (Found: C, 58·5; H, 3·7; N, 37·8. $C_{18}N_{14}N_{10}$ requires C, 58·4; H, 3·7; N, 37·8%). The dimer (260b) formed sparingly soluble salts in dilute aqueous sodium hydroxide and dilute aqueous sulphuric acid from which it could be recovered on careful neutralisation. It was also obtained by refluxing the basic dimer (260a) (0·002 mole) in pyridine (20 ml.) for 2 hr., or with 10% w/v aqueous sodium hydroxide (20 ml.) in cellosolve (80 ml.) for 20 min., followed by removal of the solvent under reduced pressure, treatment with water, and careful neutralisation with dilute aqueous sulphuric acid, or by heating the dimer (260a) at 200° (oil bath) for 2 hr. (quantitative).

(b) The basic dimer (260a) or the amphoteric dimer (260b) (0·002 mole) was refluxed in acetic anhydride (20 ml.) for 3 hr. The suspension was allowed to cool to give a diacetyl derivative (93%), m.p. 282-284° (from dimethylformamide), $\nu_{max.}$ 3300 (NH) and 1720 (br.) (Ac) $cm.^{-1}$, (Found: C, 58·1; H, 3·9; N, 30·8. $C_{22}H_{18}N_{10}O_2$ requires C, 58·2; H, 4·0; N, 30·8%). When the diacetyl compound

(0·002 mole) was refluxed for 15 min. with 10% w/v aqueous sodium hydroxide (50 ml.) in cellosolve (150 ml.) it was reconverted into the amphoteric dimer (260b) (82%), which was identified by comparison with a sample prepared above.

3.4.3 Acylation of 4-substituted-5-amino- and 4-substituted-5-anilino-1,2,3-triazoles

Method A

A suspension of the triazole (0·005 mole) (table 1) in the appropriate acid chloride (7·5 ml.) was treated dropwise with stirring at 0° with concentrated sulphuric acid (0·75 ml.). The resulting solution was stirred for 24 hr. at room temperature, then poured onto ice and stirred for 60 min. The solid which separated was combined with the material obtained by evaporation and trituration with water, to give the crude acetyl derivative.

Method B

The triazole (0·005 mole) (table 1) was suspended in acetic anhydride (7·5 ml.) and treated dropwise, with stirring at 0°, with concentrated sulphuric acid (0·75 ml.). The solution was stirred for 24 hr. at room temperature then worked up as in Method (A) above to give the crude acetyl derivative (see table 1)

Method C

The triazole derivative (0·005 mole) was refluxed with acetic anhydride (15-20 ml.) for the time shown (table 2). The reaction mixture was evaporated to give a gum, which was triturated with ether to yield the crude acetyl compound (table 1). Mixtures were separated by fractional crystallisation.

Method D

The triazole derivative (0·005 mole) and phenylacetyl chloride (0·01 mole) were refluxed in dry benzene (100 ml.) for 3 days. Evaporation of the reaction mixture gave an oil which solidified on treatment with ether to give the acetyl derivative (see table 1).

Method E

The triazole (0·005 mole) was suspended in phenylacetyl chloride (10 ml.) containing concentrated sulphuric acid (1·0 ml.) and stirred at room temperature for 12 hr. Saturated aqueous sodium bicarbonate solution and chloroform were added to the resulting solid cake, and the suspension stirred for 20 min. The chloroform extract was evaporated to an oil which was fractionally crystallised from benzene to give the acetyl derivatives (see table 1).

The crude acetyl derivatives obtained by methods (A)-(E) were purified by crystallisation from ethanol or benzene. Yields and analytical data are shown in tables 1 and 2. I.r. and p.m.r. data are shown in tables 3 and 4 respectively.

3.4.4. Deacetylation of acylated aminotriazoles and anilinotriazoles (see table 5)

Method F

The acyl compound (0·001 mole) was refluxed in 50% v/v aqueous acetic acid (10 ml.) for 20 min. The gum which remained after evaporation was treated with water to give the product (see tables 1 and 5).

Method G

The acyl compound (0·001 mole) was refluxed in ethanol (10 ml.) with 10% w/v aqueous sodium hydroxide (5 ml.) for 30 min. The reaction mixture was evaporated to give a gum which on treatment with water gave the basic products and with dilute sulphuric acid gave the acidic products (see table 5).

Method H

The acyl derivative (0·001 mole) was refluxed in ethanol (10 ml.) with 20% w/v aqueous potassium hydroxide (5 ml.) for 20 min., and worked up as in method G above to give the deacylated products (see table 5).

The aminotriazoles (252a), (253a), (255a) or (256a) or the anilinotriazoles (252d), (253d), (255d) or (256d) treated as in methods F-H above afforded quantitative recovery of starting material.

The acetyltriazole (252e) (0·001 mole) was refluxed in cellosolve (10 ml.) for 24 hr. Evaporation of the solution

and trituration of the residual gum with ether gave the anilinotriazole (252d) (91%) which was identical with a previously prepared sample.

The crude products obtained by methods (F)-(H) are shown in table 5, and were crystallised and compared with previously prepared samples.

Table 1

Acylated 1,2,3-triazoles

Compd.	Method	Prod.	Yield(%)	M.p.[h]	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
(252a)	A	(254b)	68	179°[a]	54·4	4·8	24·3	$C_{13}H_{13}N_5O_3$	54·4	4·6	24·4
(252a)	B	(254c)	54-97	139[a]	54·8	4·7	21·3	$C_{15}H_{15}N_5O_4$	54·7	4·6	21·3
(252a)	A	(257a)	69	163[b]	57·0	5·4	22·2	$C_{15}H_{17}N_5O_3$	57·1	5·4	22·2
(252a)	E	(257b)	8	156[c]	63·4	4·8	21·6	$C_{17}H_{15}N_5O_2$	63·5	4·7	21·8
		(257c)	41	90[d]	68·7	4·9	16·4	$C_{25}H_{21}N_5O_3$	68·3	4·8	16·0
(252a)	C	(252e)	g	161[a]	54·0	4·9	28·2	$C_{11}H_{11}N_5O_2$	53·9	4·5	28·6
		(254e)	g	185[e]	54·3	4·6	24·3	$C_{13}H_{13}N_5O_3$	54·4	4·6	24·4
(252d)	B	(254f)	81	155[d]	54·0	4·6	21·3	$C_{15}H_{15}N_5O_4$	54·7	4·6	21·3
(253a)	A	(253b)	80	192[a]	56·5	5·5	25·7	$C_{13}H_{15}N_5O_2$	57·1	5·5	25·6
(253a)	B	(253b)	81	-	-	-	-	-	-	-	-
(253a)	C	(253e)	g	152[d]	57·2	5·5	25·6	$C_{13}H_{15}N_5O_2$	57·1	5·5	25·6
(254e)	F	(254d)	88	198[e]	54·0	4·8	28·3	$C_{11}H_{11}N_5O_2$	53·9	4·5	28·6
(254b)	B	(254c)	97	-	-	-	-	-	-	-	-
(255a)	A	(255b)	72[f]	128[c]	55·4	4·9	21·5	$C_{12}H_{12}N_4O_3$	55·4	4·7	21·5
(255a)	B	(255c)	46-89	140[a]	55·3	4·4	18·6	$C_{14}H_{14}N_4O_4$	55·6	4·7	18·5
(255a)	C	(255e)	g	161[a]	54·8	4·7	21·4	$C_{12}H_{12}N_4O_3$	55·4	4·6	21·5

[Contd.

Table 1 (contd.)

Compd.	Method	Prod.	Yield(%)	M.p.[h]	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
(256a)	A	(256b)	92[f]	167[c]	68·6	5·1	19·9	$C_{16}H_{14}N_4O$	69·1	5·1	20·1
(256a)	B	(256b)	58	-	-	-	-	-	-	-	-
(256a)	C	(256c)	g	186[a]	67·4	5·2	17·6	$C_{18}H_{16}N_4O_2$	67·5	5·0	17·5
(256a)	C	(256e)	g	147[b]	69·0	5·2	20·1	$C_{16}H_{14}N_4O$	69·1	5·1	20·1
(252a)	D	(252g)	69	150[b]	63·4	4·8	21·7	$C_{17}H_{15}N_5O_2$	63·6	4·7	21·8

[a] Crystallised from ethanol.

[b] Crystallised from benzene.

[c] Crystallised from benzene-ethanol.

[d] Crystallised from benzene-petrol.

[e] Crystallised from glacial acetic acid.

[f] Yield based on recovered starting material.

[g] See Table 2.

[h] Highest value of melting point range.

Table 2

Substrate	Time of Reflux	Product	Yield(%)
(252a)	12 hr.	(254c)	56
(252a)	20 min.	((252e)	(70
		(	(
		((254e)	(15
(252d)	3 or 6 hr.	((252e	(8
		(	(
		((254e)	(86
(252d)	20 min.	((252e	(59
		(	(
		((254e)	(5
(252d)	12 hr.	(254f)	63
(252e)	12 hr.	(254f)	79
(253a)	15 min. or 12 hr.	(253e)	92
(253b)	3 hr.	(253e)	quant.
(253d)	20 min.	(253e)	67
(254b)	6 hr.	(254c)	86
(254e)	12 hr.	(254f)	quant.
(254f)	30 hr.	(254c)	75
(255a)	12 hr.	(255c)	65
(255a)	3 hr.	(255e)	61
(255b)	6 hr.	(255c)	95
(255d)	12 hr.	(255c)	73
(255e)	12 hr.	(255c)	quant.
(256a)	4 hr.	(256c)	92
(256a)	20 min.	((256c)	(73
		(	(
		((256e)	(5
(256b)	6 hr.	(256c)	83
(256d)	12 hr.	(256c)	77
(256e)	5 hr.	(256c)	81

Table 3

Carbonyl stretching frequencies ($cm.^{-1}$) of acylated 1,2,3-triazoles

Compd.	Acetyl groups					
	N.Ac	Ph.N.Ac	$N.Ac_2$	NH.Ac	CO.NH.Ac	Others
(252e)	1745	-	-	-	-	1680
(253b)	-	-	-	1710	-	1630
(253e)	1745	-	-	-	-	1640
(254b)	-	-	-	1700	1745	1680
(254c)	-		(1720 (1710	-	1740	1690(sh)
(254d)	-	-	-	-	←1700-1600→	
(254e)	1760	-	-	-	1710	1680
(254f)	1770	1710	-	-	1730	1680
(255b)	-	-	-	1690	-	1730
(255c)	-	-	(1710 (1680	-	-	1730
(255e)	1745	-	-	-	-	1695
(256b)	-	-	-	1700	-	-
(256c)	-	-	(1730 (1710	-	-	-
(256e)	1740	-	-	-	-	-
(257a)	-	-	-	-	-	(1740 (1695
(257b)	-	-	-	-	-	(1680 (1670
(257c)	-	-	-	-	-	(1745 (1700 (1680
(252g)	-	-	-	-	-	(1720 (1725 (1685

Table 4

Assignments[a] (τ) of p.m.r.spectra signals of acylated 1,2,3-triazoles

Compd.	Acetyl protons					Others
	N·Ac	Ph·N·Ac	$N·Ac_2$	NH·Ac	CO·NH·Ac	
(252e)	7·20	-	-	-	-	-
(253b)	-	-	-	8·00	-	(6·90 (6·50
(253e)	7·22	-	-	-	-	(6·43 (6·85
(254b)	-	-	-	7·90	7·47	-
(254c)	-	-	7·75	-	7·45	-
(254d)[b]	-	-	-	-	7·60	-
(254e)	7·20	-	-	-	7·40	-
(254e)[b]	7·20	-	-	-	7·60	-
(254f)	7·22	7·92	-	-	7·42	-
(255b)	-	-	-	7·90	-	6·10
(255c)	-	-	7·80	-	-	6·05
(255e)	7·20	-	-	-	-	5·99
(256b	-	-	-	8·00	-	-
(256c)	-	-	7·80	-	-	-
(256e)	7·27	-	-	-	-	-
(257a)	-	-	-	-	-	(7·10q (7·60q (8·30-9·43m
(257b)	-	-	-	-	-	6·40
(257c)	-	-	-	-	-	(5·85 (6·35
(252g)	-	-	-	-	-	5·50

[a] Unless otherwise stated, p.m.r. spectra were recorded for solutions in deuterochloroform. Resonance signals were sharp singlets unless designated as q = quartet or m = multiplet.

[b] Spectra recorded in d_6-dimethyl sulphoxide.

Table 5

Substrate	Method	Product	Yield (%)
(252e)	F	(252d)	81
(253b)	G	(253a)	79
(253e)	G	(253d)	76
(255b)	G	(258a)	71
(255c)	G	(258a)	73
(255c)	F	(255b)	89
(255e)	G	(258b)	79
(256b)	G	(256a)	91
(256c)	G	(256b)	89
(256c)	H	(256a)	75
(256e)	F	(256d)	77
(256e)	G	(256d)	81
(252g)	F	(252d)	79

3.4.5 Preparation of 1,2,3-triazolo[4,5-d]pyrimidines (259)

Solutions of the acylaminotriazoles (254b,c) or (257a,c) (0·005 mole) in ethanol (10 ml.) were refluxed with 10% w/v aqueous sodium hydroxide (5·0 ml.) for 30 min. The ethanol was evaporated to leave a solution which was acidified to give the triazolopyrimidines (259b) (83%), m.p. 267-268° (from acetic acid), $\nu_{max.}$ 3100-2700 (br.) (OH and NH) and 1720-1660 (br.) (CO) $cm.^{-1}$, $\lambda_{max.}$ 209, 229 and 266 nm. (log ε 4·07, 4·08 and 3·90), τ (TFA) 7·25 (3H, s, Me), (Found: C, 58·6; H, 4·1; N, 31·3. $C_{11}H_9N_5O$ requires C, 58·2; H, 4·0; N, 30·8%), (259c) (96%), m.p. 270-271° (from acetic acid), $\nu_{max.}$ 3100-2700 (br.) (NH and OH), and 1720-1660 (br.) (CO) $cm.^{-1}$, $\lambda_{max.}$ 208, 229 and 271 nm. (log ε 4·12, 4·09 and 3·96), τ (TFA) 6·93 (2H, q, CH_2) and 8·46 (3H, tr, Me), (Found: C, 59·9; H, 4·7; N, 28·9. $C_{12}H_{11}N_5O$ requires C, 59·8; H, 4·6; N, 29·0%), or (259d) (93%), m.p. 280-281° (from acetic acid), $\nu_{max.}$ 3100-2700 (br.) (OH and NH), and 1720-1660 (br.) (CO) $cm.^{-1}$, $\lambda_{max.}$ 210, 228 and 274 nm. (log ε 4·33, 4·28 and 4·04), τ (TFA) 5·65 (2H, s, CH_2), (Found: C, 67·2; H, 4·3; N, 23·2. $C_{17}H_{13}N_5O$ requires C, 67·3; H, 4·3; N, 23·1%).

The triazolopyrimidine (259a) was prepared by the method of Dornow and Helberg,[103] m.p. 279° (from ethanol) (lit. m.p. 279°), $\nu_{max.}$ 3250-3100 (br.) (OH and NH), 1735 and 1690 (CO) $cm.^{-1}$, $\lambda_{max.}$ 210, 227 and 270 nm. (log ε 4·13, 4·17 and 3·94), τ (TFA) 1·30 (1H, s, CH).

3.4.6 The synthesis and structure of 4,5-dihydro-1,6-diphenyl-5-oxo-1,2,3-triazolo[1,5-a]-1,2,3-triazolo-[4,5-e]pyrimidine (269)

(a) Synthesis

i) 5-Amino-4-carbomethoxy-1-phenyl-1,2,3-triazole (255a) (0·022 mole) was dissolved in concentrated hydrochloric acid (150 ml.) and cooled in an ice-salt bath to 0°, with stirring. A solution of sodium nitrite (2·4 g.) in water (10 ml.) was added dropwise, over 20 min., to the stirred solution. After filtration the yellow filtrate was treated dropwise, with cooling and stirring, with a solution of sodium azide (2·4 g.) in water (15 ml.). The ice-salt bath was allowed to melt and the resulting suspension stirred for 16 hr. Filtration yielded crude 5-azido-4 carbomethoxy-1-phenyl-1,2,3-triazole (268) (49%), m.p. 65-75° (crude), $\nu_{max.}$ 2150 (NN) and 1710 (CO) $cm.^{-1}$ The filtrate was extracted with chloroform, and the extract evaporated to give an oil (2·06 g.) with an i.r. spectrum identical to the crude solid azide. The oil, after repeated trituration with ether yielded starting triazole (6%). The oil, obtained by evaporating the trituration liquors and the crude solid azide were combined and used in the next stage.

ii) Crude azide (268) (0·002 mole) and phenylaceto-nitrile (0·002 mole) were refluxed with a solution of sodium (0·0024 g. atom) in methanol (10 ml.). Cooling the reaction mixture gave the product (269) as a yellow solid (31%), m.p. 326-329° (from methanol), $\nu_{max.}$ 3150-3400 (br.) (NH), 1665 (CO) $cm.^{-1}$ (Found: C, 62·3; H, 3·4;

N, 29·7. $C_{17}H_{13}O_7$ requires C, 62·0; H, 3·3; N, 29·8%).

The filtrate, on evaporation, gave a red oil, which was dissolved in water and the solution acidified with dilute sulphuric acid. Extraction with chloroform and evaporation of the chloroform extract yielded a red oil (0·39 g.), $\nu_{max.}$ (liquid film) 3350 (w), 3100, 2990, 2300 (w), 2190, 1720, 1710 and 1690 (sh) $cm.^{-1}$
The oil was triturated with various solvents but failed to solidify, however the i.r. spectrum indicated that it was a mixture of the starting azide (268) and phenylacetonitrile.

(b) Reactions

The fused triazole (269) (50 mg.) was refluxed in acetic acid (1 ml.) for 1 min. On cooling a white crystalline solid separated and was collected to give the acetoxy compound (270) (91%), m.p. 236-237° (from acetic acid-ethanol), $\nu_{max.}$ 3050 (br.) (OH and NH), 1740 (OAc) and 1710-1690 (CO) $cm.^{-1}$, τ (TFA) 3·05 (1H, s, benzylic CH) and 7·50 (3H, s, Me), (Found: C, 63·3; H, 4·2; N, 19·6. $C_{19}H_{15}N_5O_3$ requires C, 63·2; H, 4·3; N, 19·4%).
Hydrogenated in ethanol (200 ml.) over 10% palladium-on-charcoal (0·03 g.) the acetoxy compound (270) (0·0003 mole) yielded the benzyl derivative (259d) (92%) which was identical with a sample prepared above.

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CHEMICAL COMMUNICATIONS, 1969

Triazole Scission in 5-Amino-1,2,3-triazolo[1,5-*a*]quinazolines. A New Route to 4-Aminoquinazoline Derivatives

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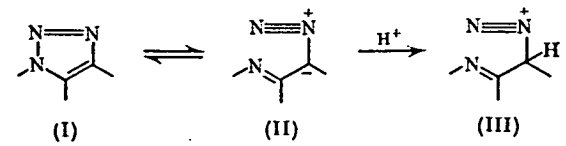
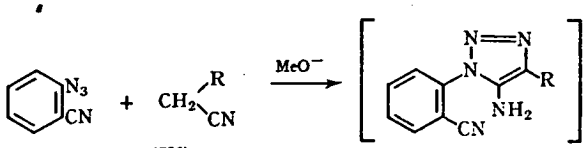
ortho-AZIDOBENZOIC ACID and 2-nitrophenyl azide condense with phenylacetonitrile in the presence of methanolic sodium methoxide yielding derivatives of 1,2,3-triazolo-[1,5-*a*]quinazoline[1] and 1,2,3-triazolo[5,1-*a*]benzo-1,2,4-triazine.[2] The triazole ring (I) in these compounds is readily cleaved by acidic reagents to give products derivable from the corresponding diazonium cation (III).[3] The cation (III) may be formed directly by ring-opening of the protonated triazole or by initial equilibration of the triazole with the diazo-tautomer (II) followed by protonation of the latter. The diazoalkylazomethine–triazole tautomerism [(I) ⇌ (II)] implied by the latter mode of triazole scission would then be analogous to the azidoazomethine–tetrazole equilibria whose existence is now well documented.[3] We have now synthesised 5-amino-1,2,3-triazolo[1,5-*a*]quinazolines (VI). Acid-catalysed triazole scission in these compounds provides

a convenient new route to 4-aminoquinazoline derivatives [*e.g.* (IX)].

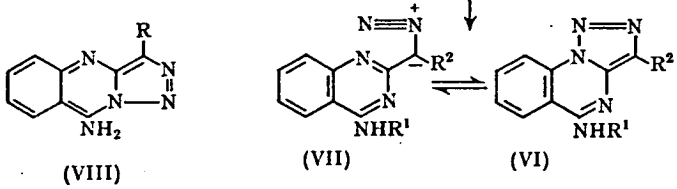
ortho-Azidobenzonitrile[4] when heated with phenylacetonitrile (IV; R = Ph) under reflux in the presence of methanolic sodium methoxide gave (VI; R^1 = H, R^2 = Ph) (90%). The structure of this product is supported by spectral and chemical evidence. Bands due to cyano-group and azide absorption were absent from its i.r. spectrum, but absorption at 3200—3450 cm.$^{-1}$ could be attributed to the presence of a primary amino-group. Hydrolysis of the amino-group occurred when the amine (VI; R^1 = H, R^2 = Ph) was heated under reflux with aqueous alkali to yield the 5-oxo-derivative (X) of known structure.[1]



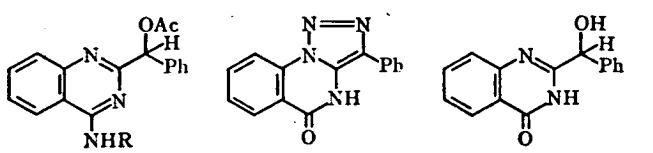
(I) (II) (III)



(IV) (V)



(VIII) (VII) (VI)



(IX) (X) (XI)

In similar reactions *ortho*-azidobenzonitrile smoothly condensed with cyanoacetamide (IV; R = $CONH_2$) or malononitrile (IV; R = CN) to give the triazoloquinazolines (VI; R^1 = H, R^2 = $CONH_2$ or CN) (85—95%). The corresponding 5-amino-(*o*-cyanophenyl)triazole (V) is a probable intermediate in these reactions. No products [*e.g.* (VIII)] formed by Dimroth rearrangement[5] of the intermediates (V) prior to cyclisation could be detected.

The amine (VI; R^1 = H, R^2 = Ph) when warmed with aqueous mineral acid underwent triazole scission[1] and hydrolysis of the amino-group affording the known compound (XI).[1] Under milder conditions acid-catalysed breakdown of the triazole ring occurred without loss of the amino-group to give 4-aminoquinazolines. In typical reactions the amine (VI; R^1 = H, R^2 = Ph) or its acetyl-derivative (VI; R^1 = Ac, R^2 = Ph) were smoothly converted by heating them under reflux with glacial acetic acid into the acetoxy-compounds (IX; R = H or Ac). Despite the ready cleavage of the triazole ring, the absence of diazo-absorption from the i.r. spectra of the triazoloquinazolines (VI; R^1 = H, R^2 = Ph, $CONH_2$, or CN) precludes the presence of the diazo-tautomer (VII) at least in the solid state. However the attainment of a diazoalkylazomethine–triazole equilibrium in solution cannot be excluded.

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The Synthesis and Reactivity of the 1,2,3-Triazolo[3,4-*a*]pyrimidine Ring System. A New Route to 2-Substituted Pyrimidines

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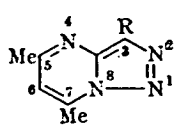
Summary Derivatives of the 1,2,3-triazolo[3,4-*a*]pyrimidine ring system are formed by condensing 5-amino-1*H*-1,2,3-triazoles with acetylacetone or ethyl acetoacetate in the presence of piperidine.

THE triazole ring in certain fused triazoles is readily cleaved by acidic reagents providing convenient synthetic routes to a variety of heterocycles.[1,2] We now report the synthesis and acid-catalysed triazole scission of 1,2,3-triazolo-[3,4-*a*]pyrimidines. These reactions constitute a convenient new route to 2-substituted pyrimidines [*e.g.* (IIIa)].

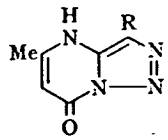
Heating 5-amino-4-phenyl-1*H*-1,2,3-triazole (obtained by

debenzylating[3] the 1-benzyl derivative[4]) with acetylacetone in the presence of piperidine afforded the triazolopyrimidine derivative (Ia). This compound was converted by hot glacial acetic acid into the acetoxypyrimidine (IIIa) whose structure follows from its smooth hydrogenolysis[1] to the known[5] pyrimidine derivative (IIIb). The acetoxy-compound (IIIa) was also formed by heating a mixture of 5-amino-4-phenyl-1*H*-1,2,3-triazole and acetylacetone in glacial acetic acid, the triazolopyrimidine (Ia) being a probable intermediate. Similar findings were obtained for the triazolopyrimidines (Ib), (IIa), and (IIb).

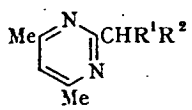
The reactivity of the triazole ring in fused triazoles towards acidic reagents can be explained[1,2] by the formation of a diazonium cation [*e.g.* (IIIc)] and reaction of the derived carbonium ion with the solvent. Conversion of the triazolopyrimidine (Ia) in acidic media into ring-opened species is indicated by ^{1}H n.m.r. measurements. Thus, the methyl absorption of the compound (Ia) changes from a pair of singlets at τ 7·21 and 7·44 in deuteriochloroform due to the nonequivalent C-5 and C-7 methyl-groups, to a single absorption at τ 7·15 in trifluoroacetic acid, indicating the formation of a structure in which the methyl groups become equivalent. Similar changes in methyl absorption in the ^{1}H n.m.r. spectra of tetrazolopyrimidines are attributed[6] to ring-opening to the azide form. Formation of the diazonium cation may occur[7] by ring-opening of the protonated triazole or by protonation of a diazoalkyl tautomer present in an initially established equilibrium. Equilibria of this type are probably involved in the Dimroth rearrangement of aminotriazoles[4,8] and find analogy in the azido-azomethine–tetrazole equilibria observed[9,10] in tetrazolopyrimidines and other fused tetrazoles.[11] The existence



(I) a; R=Ph
b; R=CONH$_2$



(II) a; R=Ph
b; R=CONH$_2$



(III) a; R^1=Ph, R^2=OAc
b; R^1=Ph, R^2=H
c; R^1=Ph, R^2=$\overset{+}{N}\equiv N$

of diazoalkylazomethine–triazole equilibria in triazolopyrimidines and related[1,2] fused triazoles is being investigated both chemically and by a detailed study of their i.r. and ^{1}H n.m.r. spectra.

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