Synthesis and Structure of Some Azolo[*a*]pyrimidines, 2,6,7,8-Tetrahydro-1*H*-cyclopenta[*e*]azolo[*a*]pyrimidines, 6,7-Dihydro-5*H*-cyclopenta[*f*]-azolo[*a*]pyrimidines, 7,8-Dihydro-6*H*-cyclopenta[*f*]-*s*-triazolo[4,3-*b*]pyridazine, 5,6,7,8-Tetrahydro-azolo[*b*]quinazolines, 6,7,8,9-Tetrahydro-azolo[*a*]quinazolines, and 7,8,9,10-Tetrahydro-*s*-triazolo[3,4-*a*]phthalazine

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The condensation of 3-amino-1,2,4-triazole (2), its 3-methyl (7) and 5-methylthio (23) derivatives, 3-amino-pyrazole (10) and its 4-cyano-derivative (27), 4-amino-1,2,4-triazole (13), 5-aminotetrazole (16), and 2-amino-benzimidazole (33) with 4,4-dimethoxybutan-2-one (1), 2-hydroxymethylenecyclohexanone (20), and 2-hydroxymethylenecyclopentanone (35) has been investigated. 7-Methyltetrazolo[1,5-*a*]pyrimidine (18) and not, as formerly claimed, 5-methyltetrazolo[1,5-*a*]pyrimidine (17) is shown to be the final product in the reaction of 5-aminotetrazole (16) and 4,4-dimethoxybutan-2-one (1). Most of the aminoazoles on condensation with the β-ketoacetal (1) or the β-ketoaldehyde (20) give mixtures of both possible fusion products, whereas the reaction of these aminoazoles with the β-ketoaldehyde (35) affords, in the main, angularly fused products. The linearly and angularly fused products are distinguished by ^{1}H n.m.r. and ^{13}C n.m.r. spectroscopy and independent synthesis. These same condensation products are again observed during the reactions between the aminoazoles and the β-ketoanils, 2-(2-acetylvinylamino)pyridine (40), 2-(2-pyridylaminomethylene)cyclohexanone (42), and 2-(2-pyridylaminomethylene)cyclopentanone (43). The mechanism of these condensation reactions is also discussed.

THE reaction between various aminoazoles and ethyl acetoacetate is known to produce 5-methyl-7-hydroxy-azolo[*a*]pyrimidines.[1a] However, the reactions of amino-azoles with β-keto-acetals and β-keto-aldehydes have not yet been fully exploited and we report in this paper structural and mechanistic investigations of compounds which are formed by the reaction of various aminoazoles with 4,4-dimethoxybutan-2-one (1), 2-hydroxymethyl-enecyclohexanone (20), and 2-hydroxymethylenecyclo-pentanone (35).

RESULTS AND DISCUSSION

It has been previously reported [2] that the reaction between 4,4-dimethoxybutan-2-one (1) and 3-amino-1,2,4-triazole (2) in refluxing xylene furnishes 5-methyl-*s*-triazolo[1,5-*a*]pyrimidine (3) as the sole reaction product in high yield. However, when we repeated this condensation by refluxing a solution of the β-keto-acetal (1) with the aminotriazole (2) in toluene in the presence of a small amount of toluene-*p*-sulphonic acid, we obtained 5-methyl-*s*-triazolo[1,5-*a*]pyrimidine (3) accompanied by the isomeric 7-methyl compound (4) and the self-condensation product 1,3,5-triacetylbenzene (5). The structures of the compounds (3) and (4) have already been adequately established by independent synthesis [3] and ^{1}H n.m.r. spectroscopy.[4] The formation of (5) has been previously observed [5] during the reaction of tryptamine hydrochloride and the β-ketoacetal (1). It is evident that compound (5) is formed by the self-condensation of three molecules of 4-hydroxybut-3-en-2-one (6; R = H), itself derived from the β-ketoacetal (1).

Under similar conditions, 4,4-dimethoxybutan-2-one (1) reacted with 3-amino-5-methyl-1,2,4-triazole (7) to give the two condensation products 2,5-dimethyl- (8) and 2,7-dimethyl-*s*-triazolo[1,5-*a*]pyrimidine (9), accompanied again by 1,3,5-triacetylbenzene (5). During the reaction of 5-aminopyrazole (10) with the β-keto-acetal (1), only two condensation products, 5- (11) and 7-methylpyrazolo[1,5-*a*]pyrimidine (12), were isolated. The pyrimidines (8) [6] and (11) [7] have been previously prepared by condensation of the corresponding amino-azoles with ethyl acetoacetate, followed by the removal of the residual oxygen atom from the intermediate condensation product by treatment with phosphorus oxychloride and subsequent hydrogenolysis. The pyr-imidines (9) [6] and (12) [7] have also been independently prepared from the reaction of the corresponding amino-azoles with ethyl 2-acetyl-3-ethoxyacylate followed by de-ethoxycarbonylation of the corresponding ethyl 7-methylazolo[*a*]pyrimidine-6-carboxylates. Under ana-logous conditions the condensation of 4-amino-1,2,4-triazole (13) with the β-keto-acetal (1) also gave two condensation products, 6- (14) and 8-methyl-*s*-triazolo-[4,3-*b*]pyridazine (15), contrary to the earlier reports [2,8] which indicate that only the single product (14) is formed in this reaction.

It has been reported [2] that 5-methyltetrazolo[1,5-*a*]-pyrimidine (17) is the condensation product finally formed in each of the following three syntheses: (*i*) re-action of 5-aminotetrazole (16) with ethyl acetoacetate, followed by treatment with phosphoryl chloride and subsequent hydrogenolysis; (*ii*) reaction of 4-methyl-2-hydrazinopyrimidine with nitrous acid; and (*iii*) re-action of 5-aminotetrazole (16) with 4,4-dimethoxy-butan-2-one (1). However, we observe that the spectroscopic properties of the condensation product are consistent with the structure (18) rather than structure (17). In the ^{1}H n.m.r. spectrum, the 7-methyl group signal (δ 3.50), is broadened by long-range coupling with 6-H, and the value of the coupling constant of the two doublets at δ 7.25 (6-H) and δ 8.90 (5-H) is found to be 4.00 Hz. If the product had structure (17), the methyl group would be expected to give a sharp singlet, and the value of the coupling constant of the two doublets would

be expected to be about 7.00 Hz.[1b] In the ^{13}C n.m.r. spectrum, the chemical shift of 5-C (158.44 p.p.m., Table 1) is found to be consistent with structure (18) [comparable with the chemical shift of 154.03 p.p.m. of 5-C in the triazolopyrimidine (4), discussed later]. In the alternative structure (17), the chemical shift of 7-C would be expected to be about 134 p.p.m., making it comparable with the chemical shift of 7-C in the triazolopyrimidine (3).

The ^1H n.m.r. spectrum of the compound (18) is further complicated by the fact that, in addition to the signals for the 7-methyl, the 6-H and the 5-H, a singlet at δ 2.50 and doublets at δ 6.97 and δ 8.50 (J 4.8 Hz) also appear, indicating that the compound (18) exists in equilibrium with the azido-form (19), the ratio of (18) : (19) being 3 : 1. The presence of the azido-form (19) is also confirmed by the appearance of an absorption band at 2 140 cm^{-1} in the i.r. spectrum.

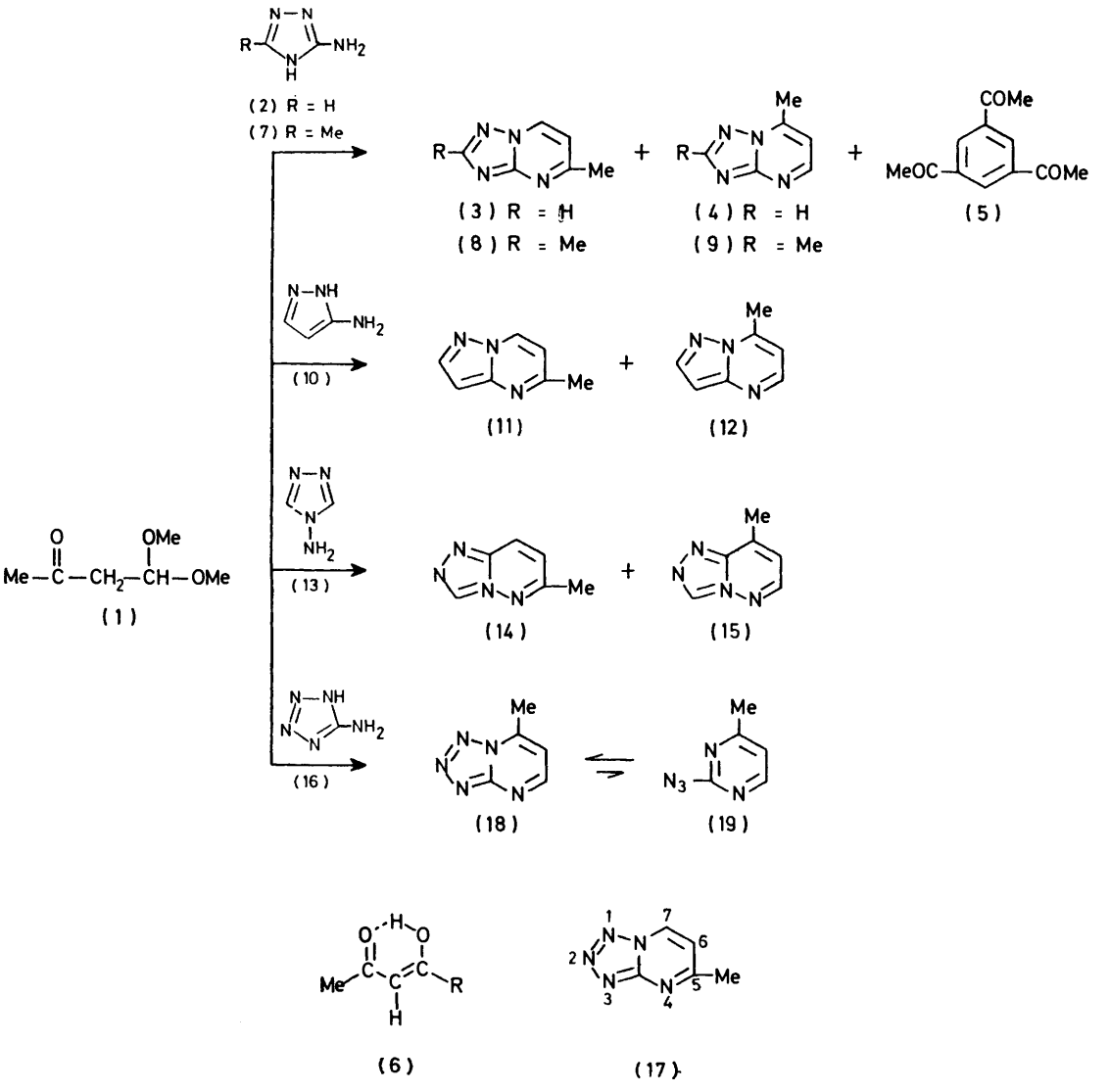


TABLE 1

^{13}C N.m.r. chemical shifts of azolo[*a*]pyrimidines (p.p.m.)

Compound	2-C	3-C	3a-C	5-C	6-C	7-C	5-Me	7Me
(3)	156.08		155.13	165.69	111.25	134.98	25.22	
(4)	155.56		155.96	154.03	110.06	148.15		17.20
(11)	145.01	95.68	148.30	158.90	108.74	134.43	24.77	
(12)	144.39	96.97	148.91	148.91	107.42	146.13		17.20
(18) [a]			158.91	158.44	112.42	146.84		16.63
(58) [b]	168.16		155.75	163.96	109.81	145.64	24.81	16.93
(59)	155.36		155.36	164.75	110.75	146.73	24.98	16.97

[a] Spectrum taken in $(CD_3)_2SO$. [b] 2-SMe at 13.95 p.p.m.

Rearrangements of this type have been previously reported.[1c]

The condensation of 2-hydroxymethylenecyclohexanone (20) with various aminoazoles proceeds in a manner analogous to the condensation of the aminoazoles with 4,4-dimethoxybutan-2-one (1), except that the triazole (7) reacts with the β-keto aldehyde (20) to give only the linear product (26), in contrast to the formation of two products (8) and (9) during the reaction with the ketoacetal (1). The compounds (21)[9a] and (32)[9b] have been previously prepared but no evidence has been given for the structure of these materials.

The condensation of various aminoazoles with 2-hydroxymethylcyclopentanone (35) is shown, however, to take a different course, in that the reaction of 3-amino-1,2,4-triazole (2), 3-amino-5-methylthio-1,2,4-triazole (23), and 3-amino-4-cyanopyrazole (27) with the β-ketoaldehyde (35) furnishes only angularly fused products, the cyclopentatriazolopyrimidines (36) and (37), and the cyclopentapyrazolopyrimidine (38), respectively. An exception to this behaviour is evidenced by the reaction between 4-amino-1,2,4-triazole (13) and the β-ketoaldehyde (35) where linear cyclopentatriazolopyridazine (39) is the only product isolated. The linearly fused condensation products (44), (45), and (46) are available from the condensation of the aminoazoles (2), (23), and (27), respectively, with 2-(2-pyridylaminomethylene)cyclopentanone (43).

The linear condensation products [*e.g.* (28)] can be readily distinguished from the angular condensation products [*e.g.* (29)] by ^1H and ^{13}C n.m.r. spectroscopy. For example, in the ^1H n.m.r. spectrum of the linear pyrazolo[5,1-*b*]quinazoline (28), the 9-H signal is broadened by long-range coupling with the 8-H protons, whilst 5-H in the pyrazolo[1,5-*a*]quinazoline (29) appears as a sharp singlet because of the absence of long-range coupling. The long-range coupling observed in the 9-H signal of the compound (28) was confirmed by double irradiation. Similar long-range coupling has been reported in azolo[*a*]pyrimidines, where it was observed that the methyl protons at 6-C are split into a doublet by coupling with 7-H, whilst no such coupling was observed between the methyl protons at 6-C and 5-H.[1b,4] In the ^{13}C n.m.r. spectrum of compound (28) (Table 3), the chemical shift of 9-C was found to be 133.30 p.p.m. [comparable with the chemical shift of 134.43 p.p.m. of 7-C in the pyrazolopyrimidine (11) (Table 1)], whilst the chemical shift of 5-C in compound

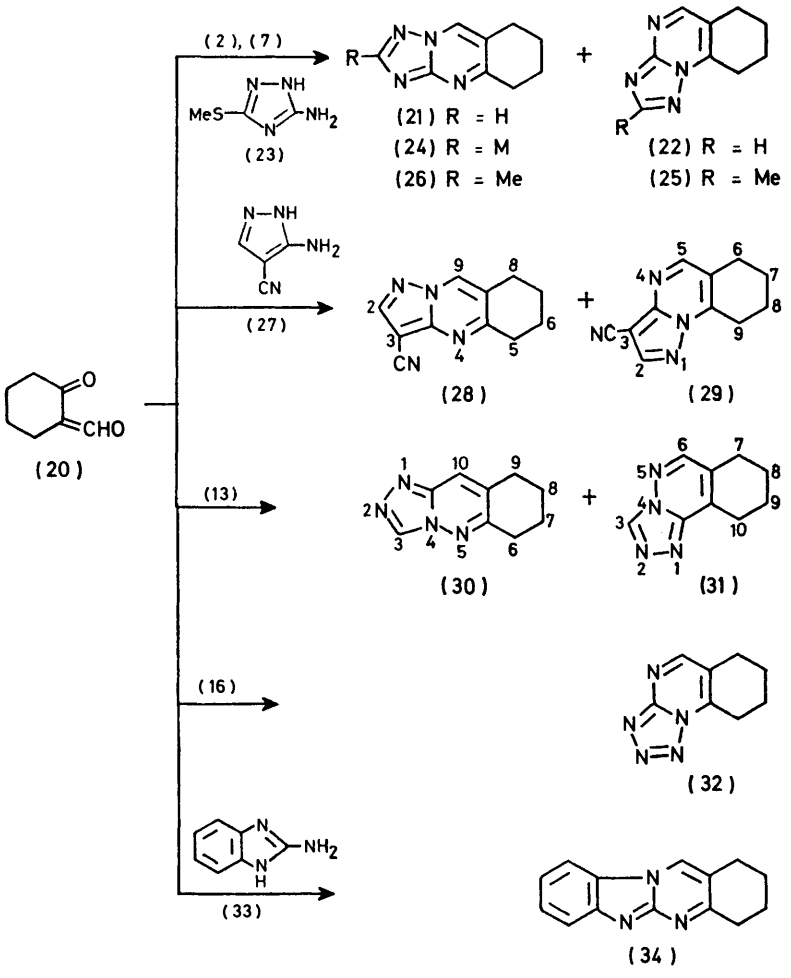


TABLE 2

^{13}C N.m.r. chemical shifts of *s*-triazolo[4,3-*b*]pyridazine derivatives (p.p.m.)

Compound	3-C	6-C	7-C	8-C	8a-C	Methyl or alicyclic carbons
(14)	138.41	155.01	122.81	124.14	143.08	21.64
(15)	139.10	145.64	118.86	137.31	145.43	16.46
(30)	137.48	155.85	132.61	121.04	143.68	(21.66—29.73)
		5a-C	9a-C	10-C	10a-C	
(31)	138.23	147.61	128.68	133.64	145.12	(20.50—25.47)
			6a-C	10a-C	10b-C	
(39)	138.03	164.67	138.41	117.43	143.99	(24.12—31.16)
		5a-C	8a-C	9-C	9a-C	

TABLE 3

^{13}C N.m.r. chemical shifts of 5,6,7,8-tetrahydroazolo[*b*]quinazolines (p.p.m.)

Compound	2-C	3-C	3a-C	4a-C	8a-C	9-C	Alicyclic carbons
(21)	155.38		153.76	165.81	120.51	132.84	(21.65—32.89)
(24)	168.09		154.32	164.84	119.42	131.84	(21.68—32.75)
(26)	165.91 *		154.01	165.14 *	119.73	132.33	(21.94—33.00)
(28)	146.69	80.27	148.23	164.48	121.09	133.30	(21.57—32.75) (CN, 112.88)

* These values could be interchanged.

TABLE 4

^{13}C N.m.r. chemical shifts of 6,7-dihydro-5*H*-cyclopenta[*f*]azolo[*a*]pyrimidines (p.p.m.)

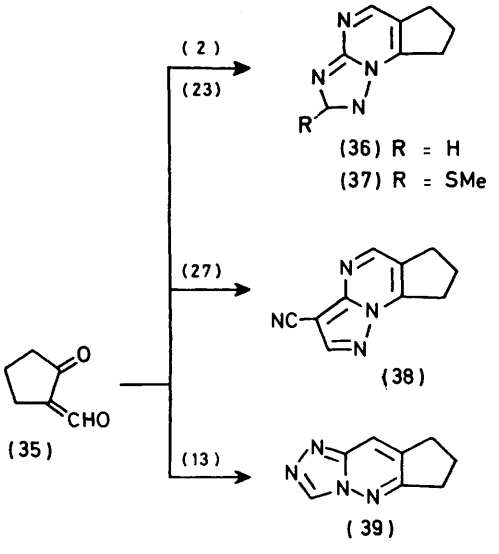
Compound	2-C	3-C	3a-C	4a-C	7a-C	8-C	Alicyclic carbons
(44)	155.12		155.84	175.08	125.56	129.61	(23.91—34.17)
(45)	167.46		155.47	174.05	124.35	128.64	(23.70—34.07)
(46)	146.36	81.14	149.62	173.41	126.25	130.19	(23.81—33.96)

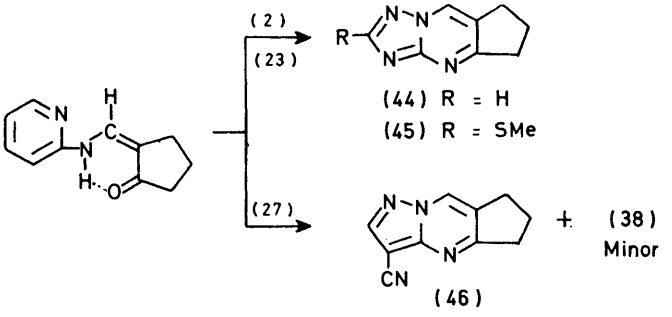
TABLE 5

^{13}C N.m.r. chemical shifts of azolo[*a*]quinazolines and cyclopenta[*e*]azolo[*a*]pyrimidines (p.p.m.)

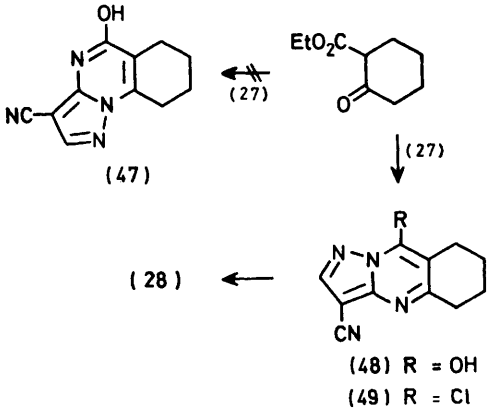
Compound	2-C	3-C	3a-C	5-C	5a-C	9a-C	Alicyclic carbons
(25)	167.75		154.66	154.14	118.42	144.88	(20.54—23.96)
(29)	146.04	82.27	149.01	153.61	119.82	144.08	(20.6—24.07) (CN, 112.74)
(32)			158.43	159.20	121.66	143 64	(20.21—23.90)
(36)	155.69		155.15	150.84	125.27	151.54 8a-C	(22.64—29.57)
(37)	168.69		155.64	149.66	124.50	150.46 8a-C	(22.63—29.49)
(38)	147.09	82.18	148.68	149.56	125.80	151.71 8a-C	(22.20—29.51) (CN, 112.81)

(29) was found to be 153.61 p.p.m. (Table 5) [comparable with the chemical shift of 148.91 p.p.m. of 5-C in the pyrazolopyrimidine (12) (Table 1)]. These values are also consistent with the observation that the carbons bonded to nitrogen atoms are appreciably deshielded relative to benzene, and occur further downfield compared with the carbons bonded to bridgehead nitrogens.[10,11] The structural assignment of compound (28) is further supported by the alternative synthesis outlined in Scheme 1.





3-Amino-4-cyanopyrazole on condensation with 2-ethoxycarbonylcyclohexanone gave the pyrazolo[5,1-*b*]-pyrimidinol (48). The alternative structure, the pyrazolo[1,5-*a*]pyrimidinol (47), is ruled out since 3-amino-pyrazoles are known to react with ethyl acetoacetate to

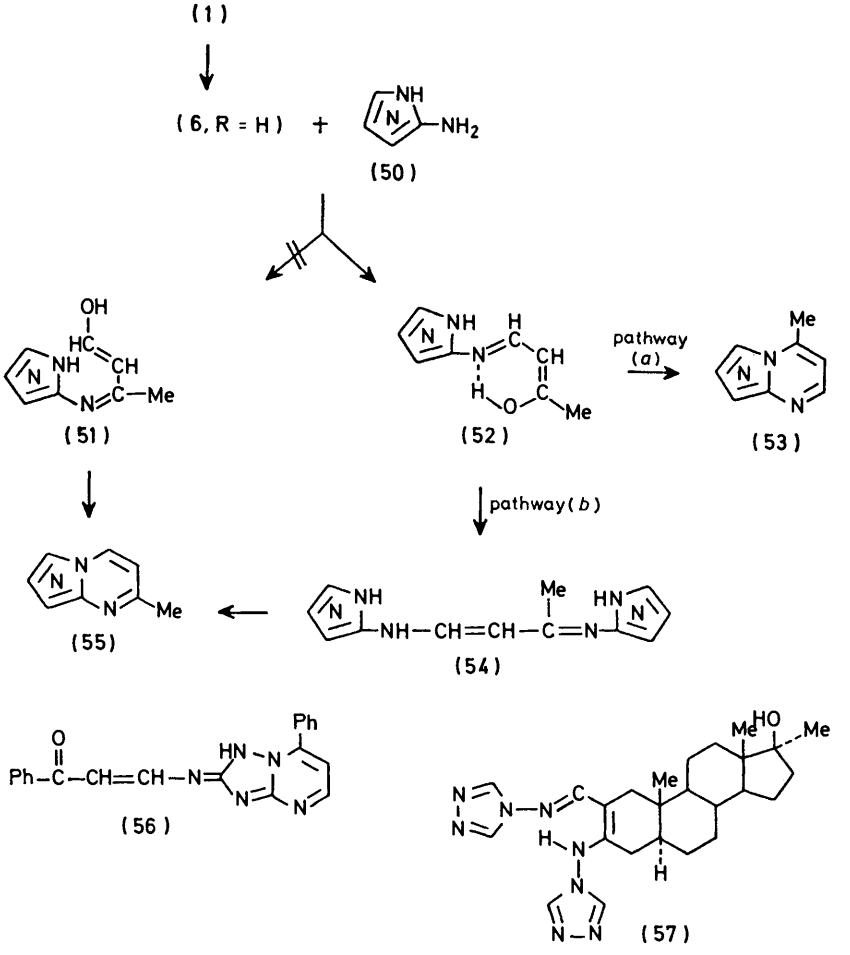


SCHEME 1

give 5-methylpyrazolo[1,5-*a*]pyrimidin-7-ols and not 7-methylpyrazolo[1,5-*a*]pyrimidin-5-ols.[1a] Subsequent reaction of the hydroxy group in the intermediate (48) with phosphoryl chloride, followed by hydrogenolysis, furnished a product identical in all respects with the pyrazolo[5,1-*b*]quinazoline (28).

It is interesting to note that the type of product obtained during these condensation reactions depends markedly on the β-ketoacetal or β-ketoaldehyde and the aminoazole actually used in the reaction. For example the triazole (7) reacts with the β-ketoacetal (1) to give two isomeric products [(8) and (9)], whilst only one product (26) was obtained from its reaction with 2-hydroxymethylenecyclohexanone (20). Secondly, most of the aminoazoles on reaction with the β-ketoacetal (1) or the β-ketoaldehyde (20) give two isomeric products, whereas these aminoazoles lead to the formation of only angular products on condensation with 2-hydroxymethylenecyclopentanone (35), with the exception of the triazole (13) which leads to the formation of only the linear product (39).

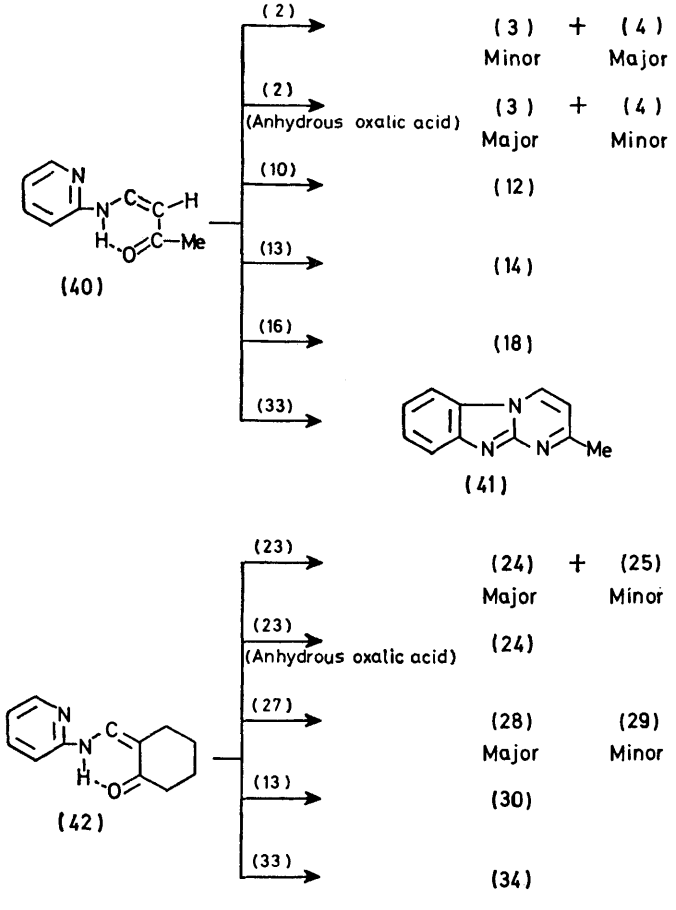
A reaction mechanism which allows for the formation of two products from each particular condensation reaction is outlined in Scheme 2. Due to the formation of 1,3,5-triacetylbenzene (5) as a byproduct of these condensation reactions it is inferred that the β-ketoacetal (1) is initially converted to 3-oxobutanal (6, R = H) by hydrolysis of the acetal (1) under the acidic reaction conditions. Support for the intermediacy of the β-ketoaldehyde (6, R = H) comes from ^{1}H n.m.r. spectroscopy. A solution of the acetal (1) in acetone containing small amounts of toluene-*p*-sulphonic acid and water, after



SCHEME 2

being heated in a boiling water-bath, exhibited two doublets at δ 5.55 and 7.85 (J 5 Hz). These correspond to the protons at C-2 and C-1, respectively, in 3-oxobutanal (6, R = H), and a signal observed at δ 9.75 is assigned to the aldehyde proton of the unenolized form. The chemical shift of the hydrogen at C-2 in the β-ketoaldehyde (6, R = H) is comparable to the chemical shift (δ 5.50) of the 3-H in acetylacetone (6, R = Me). The possibility that the acetal (1) might have been converted to methoxyvinyl ketone rather than the ketoaldehyde (6, R = H) was not considered likely, since the 1-H and 2-H signals belonging to methoxyvinyl ketone appear as doublets at δ 7.60 and 5.58 (J 13 Hz).[12]

Thus there are two possible sites for the condensation of the aminoazole (50) with the β-ketoaldehyde (6, R = H). However, it seems more likely that the amino-group of the azole (50) would react first with the aldehyde carbonyl to give the intermediate ketoanil (52) rather than with the keto-group to give the intermediate (51). The formation of the anil (52) is analogous to the formation of the (benzoylethylideneimino)triazolo[1,5-*a*]-pyrimidine (56) as a by-product during the reaction of



3,5-diamino-1,2,4-triazole with β,β-dimethoxypropiophenone.[2] Direct cyclisation of the intermediate (52) through pathway (*a*) affords 7-methylazolo[*a*]pyrimidine (53). However, during the formation of 5-methylazolo[*a*]pyrimidine (55) it is evident that some other intermediate must interpose between the ketoanil (52) and the final condensation product (55). Condensation of the ketoanil (52) with another molecule of aminoazole (50) provides just such an intermediate (54), pathway (*b*). This bisanil then spontaneously undergoes a cyclisation to yield the 5-methylazolo[*a*]pyrimidine (55).

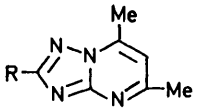
Support for the mechanism of pathway (*b*) comes from the study of the reaction of 4-amino-1,2,4-triazole (13) with 17β-hydroxy-2-hydroxymethylene-17α-methyl-5α-androstan-3-one,[13] where an attempt to condense 1 mol of the aminotriazole (13) with the above steroidal β-diketone produced the bisanil (57).

The reactions of the ketoanils 2-(2-acetylvinylamino)-pyridine (40), 2-(2-pyridylaminomethylene)cyclohexanone (42), and 2-(2-pyridylaminomethylene)cyclopentanone (43) with various aminoazoles have also been studied. It is observed that the reaction of 3-amino-1,2,4-triazole (2) with the ketoanil (40) catalysed by toluene-*p*-sulphonic acid furnishes a 20% yield of 5-methyl-*s*-triazolo[1,5-*a*]pyrimidine (3), which clearly results from the condensation reaction taking pathway (*b*) of Scheme 2, where the amino group of the triazole (2) condenses with the carbonyl of the ketoanil (40), prior to cyclisation and displacement of the 2-aminopyridine. However, it was interesting to note that 80% of the product isolated from this condensation was 7-methyl-*s*-triazolo[1,5-*a*]pyrimidine (4) which presumably arises by pathway (*a*) of Scheme 2, where the ketoanil (40) has undergone a preliminary retro-anil reaction to yield 3-oxobutanal (6, R = H) prior to condensation with the aminotriazole (2). In support of this novel route to compound (4), it was further observed that the ratio of (3) : (4) is dependent on the catalyst used for the condensation. When the ketoanil (40) is condensed with the aminotriazole (2) in the presence of anhydrous oxalic acid, the preliminary retro-anil reaction is suppressed and 5-methyl-*s*-triazolo[1,5-*a*]pyrimidine (3) becomes the predominant product (70%).

The condensation of the ketoanils (42) and (43) with aminoazoles proceeds in a manner similar to that of the ketoanil (40). It should be noted again that the condensation of the ketoanil (42) with the triazole (23) and the pyrazole (27), and the condensation of the ketoanil (43) with the aminoazole (27), affords a mixture of a linearly fused product (major) and an angularly fused product (minor). These condensations result respectively from pathways similar to (*b*) and (*a*) of Scheme 2. However, when the catalyst toluene-*p*-sulphonic acid was replaced by anhydrous oxalic acid in the condensation of the ketoanil (42) with the triazole (23), a high yield of the linearly fused compound (24) was the only product observed, indicating a preference for a pathway (*b*) type reaction under anhydrous conditions.

^{13}C *N.M.R. Spectra.*—The assignment of the various carbon resonances in the *s*-triazolo[1,5-*a*]pyrimidine system is based upon the comparison of the proton-coupled and proton-decoupled spectra of the triazolo-[1,5-*a*]pyrimidines (58), (59), (3), and (4). In the ^{13}C n.m.r. spectrum of compound (58), the 6-C resonance can

be easily identified from the large ^{13}C–^{1}H coupling, since this is the only ring carbon which has one hydrogen attached to it. By comparing the ^{13}C n.m.r. spectrum of the triazolopyrimidine (59) with that of (58), the chemical shift of 2-C in (59) and the chemical shifts of 2-C and SCH_3 in (58) can also be determined. Further



(58) R = SMe
(59) R = H

comparison of the spectra of compounds (58) and (59) with those of (3) and (4) enables the chemical shifts of all the ring carbons and methyl carbons of the compounds (3), (4), (58), and (59) to be assigned.

The chemical shifts of the various carbons in the tetrazolo[1,5-*a*]pyrimidine and pyrazolo[1,5-*a*]pyrimidine systems follow from the comparison with the chemical shifts of above-mentioned compounds (3) and (4), and of related systems.[12] The chemical shifts of the various *s*-triazolo[4,3-*b*]pyridazine derivatives follow from the comparison with the chemical shifts of the parent *s*-triazolo[4,3-*b*]pyridazine.[14] All the ^{13}C n.m.r. chemical-shift data are given in Tables 1—5.

EXPERIMENTAL

Melting points were determined on a Gallenkamp apparatus. I.r. spectra were recorded in bromoform on a Perkin-Elmer 157G spectrometer. ^{1}H N.m.r. spectra were recorded in $CDCl_3$ using $SiMe_4$ as internal standard on Nuclear Magnetic Resonance Ltd. EM 360 (60 MHz) or Varian HA100 (100 MHz) spectrometers. Mass spectrometry was carried out on A.E.I. MS 902 instrument. ^{13}C N.m.r. spectra in $CDCl_3$ (unless otherwise stated) were obtained on a CFT-20 spectrometer operating at 20—80 MHz in the Fourier-transform mode at a probe temperature of 30 °C.

The ^{13}C n.m.r. chemical shifts of various products are given in Tables 1—5 whilst the ^{1}H n.m.r., mass spectra, i.r. spectra, and elemental analyses are in Table 6.

2-(2-*Acetylvinylamino*)*pyridine* (40).—This was prepared by the method of Sawyer and Wibberley.[15] The following compounds were prepared by the same method.

2-(2-*Pyridylaminomethylene*)*cyclohexanone* (42) was prepared from 2-hydroxymethylenecyclohexanone (20) (3.78×10^{-2} mol) and 2-aminopyridine (2.82 g, 3×10^{-2} mol). Recrystallisation from methanol gave the title *compound* (42), m.p. 157—159 °C (56%) (Found: C, 72.7; H, 7.1; N, 14.05%; M^+, 202.110 485. $C_{12}H_{14}N_2O$ requires C, 72.69; H, 7.12; N, 14.14%; *M*, 202.110 607).

2-(2-*Pyridylaminomethylene*)*cyclopentanone* (43) was prepared from 2-hydroxymethylenecyclopentanone (35) (3.36 g, 3×10^{-2} mol) and 2-aminopyridine (2.82 g, 3×10^{-2} mol). Recrystallisation from methanol gave the title *compound* (43), m.p. 163—165 °C (60%) (Found: C, 71.15; H, 6.5; N, 15.0%; M^+, 188.095 346. $C_{11}H_{12}N_2O$ requires C, 71.70; H, 6.57; N, 15.21%; *M*, 188.094 958).

General Procedure for the Condensation Reactions.—*Method A.* A solution of the β-ketoacetal or β-ketoaldehyde (4×10^{-3} mol), the aminoazole (4×10^{-3} mol) and toluene-*p*-sulphonic acid (30 mg) in dry toluene (50 ml) was refluxed overnight. After cooling, the reaction mixture was evaporated to dryness and the residue was chromatographed over alumina (40 g, activity II).

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

5-*Methyl*-s-*triazolo*[1,5-a]*pyrimidine* (3), 7-*Methyl*-s-*triazolo*[1,5-a]*pyrimidine* (4), *and* 1,3,5-*Triacetylbenzene* (5).—*Method A.* Alumina chromatography (eluant ether) gave 1,3,5-triacetylbenzene which was recrystallised from benzene as long needles, m.p. 158—160 °C (5%) (lit.,[5] m.p. 161—163 °C). Further elution of the column gave a mixture of compounds (3) and (4), which were separated by fractional recrystallisation from benzene. 5-Methyl-*s*-triazolo[1,5-*a*]-pyrimidine (3) crystallised first as long white needles, m.p. 180—182 °C (45%) (lit.,[2] m.p. 181—182.5 °C). Concentration of the mother liquors gave 7-methyl-*s*-triazolo-[1,5-*a*]pyrimidine, m.p. 134—135 °C (15%) (lit.,[3] m.p. 136—138 °C).

Method B. The two products (3) and (4) were obtained in 17 and 62% yields, respectively. However, when the toluene-*p*-sulphonic acid catalyst was replaced by anhydrous oxalic acid, the two products (3) and (4) were obtained in 45% and 16% yields, respectively.

2,5-*Dimethyl*-s-*triazolo*[1,5-a]*pyrimidine* (8), 2,7-*Dimethyl*-s-*triazolo*[1,5-a]*pyrimidine* (9), *and* 1,3,5-*Triacetylbenzene* (5). *Method A.* Chromatography of the crude reaction product over alumina using ether as the eluant gave 1,3,5-triacetylbenzene (5), m.p. 158—160 °C (4.5%) (lit.,[5] m.p. 161—163°). Further elution with ether–ethyl acetate (1 : 1) gave the two condensation products, 2,5-dimethyl-*s*-triazolo[1,5-*a*]pyrimidine (8) which was recrystallised from n-hexane, m.p. 82—83 °C (48%) (lit.,[6] m.p. 86—88 °C), and 2,7-dimethyl-*s*-triazolo[1,5-*a*]pyrimidine (9), also recrystallised from n-hexane, m.p. 157—159 °C (25%) (lit.,[6] m.p. 161—162 °C).

5-*Methylpyrazolo*[1,5-a]*pyrimidine* (11) *and* 7-*Methylpyrazolo*[1,5-a]*pyrimidine* (12).—*Method A.* Alumina chromatography (eluant ethyl acetate) gave the two isomeric compounds, 5-methylpyrazolo[1,5-*a*]pyrimidine (11) which was recrystallised from n-hexane, m.p. 122—124 °C (27%) (lit.,[7] m.p. 122—123 °C), and 7-methylpyrazolo[1,5-*a*]pyrimidine (12), crystallised from n-hexane–benzene, m.p. 59—60 °C (16%) (lit.,[7] m.p. 59—60 °C).

Method B. 7-Methylpyrazolo[1,5-*a*]pyrimidine (12) was obtained in 75% yield as the only reaction product.

6-*Methyl*-s-*triazolo*[4,3-b]*pyridazine* (14) *and* 8-*Methyl*-s-*triazolo*[4,3-b]*pyridazine* (15).—*Method A.* Alumina chromatography [eluant ethyl acetate–ether (1 : 1)] gave 6-methyl-*s*-triazolo[4,3-*b*]pyridazine (14), which was recrystallised from benzene, m.p. 168—170 °C (58%) (lit.,[2] m.p. 168—169 °C), and 8-methyl-*s*-triazolo[4,3-*b*]pyridazine (15), which was recrystallised from n-hexane, m.p. 124—126 °C (20%) (lit.,[16] m.p. 126—127 °C).

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

7-*Methyltetrazolo*[1,5-a]*pyrimidine* (18).—*Method A.* Alumina chromatography [eluant methylene chloride–ethyl acetate (9 : 1)] followed by recrystallisation from benzene gave the title compound (18), m.p. 129—131 °C (70%) (lit.,[2] m.p. 130—132.5 °C); $\nu_{max.}$ 2 140 (N_3), 1 625, 1 585 1 540, 1 510, 1 440, 1 365, and 1 350 cm^{-1}; δ 3.50 (3 H, br s 7-Me), 7.25 (1 H, d, *J* 4.0 Hz, 6-H), and 8.90 (1 H, d, 5-H)

TABLE 6

Hydrogen-1 n.m.r., mass, and i.r. spectra, and elemental analysis

Compd.	^{1}H N.m.r. spectrum (δ) Alicyclic protons Aromatic protons	High-resolution mass spectrum Found	Calculated	ν_{max}/cm^{-1}	Analysis (%) Found C	H	N	Calculated C	H	N
(21)	6-H, 7-H, 1.97m; 2-H, 8.40s; 5-H, 8-H, 3.00m; 9-H, 8.55br s	174.091 873	174.090 932	1 630, 1 510, 1 430, 1 420, 1 405, 1 350	62.10	5.89	32.00	62.04	5.79	32.17
(22)	7-H, 8-H, 1.95m; 2-H, 8.35s; 6-H, 9-H, 2.95m; 5-H, 8.40s	174.092 761	174.090 932	1 625, 1 545, 1 510, 1 435, 1 420, 1 405, 1 355	61.95	5.70	32.35	62.04	5.79	32.17
(24)	6-H, 7-H, 1.90m; 2-SMe, 2.77s; 5-H, 8-H, 2.95m; 9-H, 8.35br s	220,079 812	220.078 264	1 625, 1 510, 1 450, 1 435, 1 425, 1 370, 1 350	54.34	5.40	25.31	54.52	5.49	25.46
(25)	7-H, 8-H, 1.90m; 2-SMe, 2.70s; 6-H, 9-H, 3.00m; 5-H, 8.30s	220.077 244	220.078 264	1 615, 1 550, 1 515, 1 450, 1 435, 1 405, 1 365, 1 340	54.61	5.51	25.57	54.52	5.49	25.45
(26)	6-H, 7-H, 1.90m; 2-Me, 2.55s; 5-H, 8-H, 2.90m; 9-H, 8.35br s	188.104 757	188.106 191	1 630, 1 515, 1 470, 1 450, 1 440, 1 415, 1 385, 1 365, 1 355	63.38	6.37	29.59	63.79	6.43	29.78
(28)	6-H, 7-H, 1.95m; 2-H, 8.27s; 5-H, 8-H, 3.00m; 9-H, 8.42br s	198.090 620	198.090 542	2 220 (CN), 1 630, 1 550, 1 505, 1 460, 1 405	66.78	5.10	28.53	66.64	5.09	28.28
(29)	7-H, 8-H, 2.03m; 2-H, 8.35 s 6-H, 9-H, 3.05m; 5-H, 8.50s	198.091 372	198.090 542	2 220 (CN), 1 620, 1 530, 1 470, 1 370, 1 350	66.44	5.12	28.35	66.64	5.09	28.28
(30)	7-H, 8-H, 1.90m; 10-H, 7.70br s 6-H, 9-H, 2.95m; 3-H, 8.90s	174.090 423	174.090 542	3 140, 1 525, 1 485, 1 425, 1 340	61.88	5.79	32.47	62.07	5.72	32.17
(31)	8-H, 9-H, 1.92m; 6-H, 8.02s; 7-H, 10-H, 2.90m; 3-H, 8.97s	174.090 761	174.090 542	3 140, 1 620, 1 545, 1 500, 1 450, 1 430, 1 405, 1 345	61.96	5.80	32.18	62.07	5.72	32.17
(32)	7-H, 8-H, 2.07m; 5-H, 8.65s; 6-H, 9-H, 3.15m	175.083 652	175.085 742	2 145 ($-N_3$), 1 625, 1 545, 1 510, 1 450, 1 435, 1 420, 1 365, 1 355	54.95	5.10	40.17	54.82	5.18	39.99
(34)	2-H, 3-H, 1.86m; 7-H, 8-H, 9-H, 1-H, 4-H, 2.90m; 10-H, 7.15—7.95; 12-H, 8.20br s	223.112 482	223.110 942	1 640, 1 610, 1 585, 1 515, 1 490, 1 450, 1 435, 1 425, 1 410, 1 360	75.42	5.91	18.79	75.30	5.87	18.83
(36)	7-H, 2.45m; 2-H, 8.42s; 6-H, 8-H, 3.35m; 5-H, 8.65s	160.074 003	160.074 892	1 625, 1 545, 1 510, 1 455, 1 425, 1 400, 1 350, 1 340	60.28	5.14	34.78	59.97	5.04	34.99
(37)	7-H, 2.35m; 2-SMe, 2.68s; 6-H, 8-H, 3.20m; 5-H, 8.45s	206.061 356	206.062 615	1 610, 1 560, 1 500, 1 415, 1 350, 1 330	52.24	4.80	27.14	52.41	4.89	27.18
(38)	7-H, 2.48m; 2-H, 8.40s; 6-H, 8-H, 3.35m; 5-H, 8.65s	184.073 050	184.074 892	2 220 (CN), 1 625, 1 550, 1 530, 1 480, 1 425	65.19	4.40	30.81	65.19	4.38	30.43
(39)	7-H, 2.35m; 3-H, 9.00s; 6-H, 8-H, 3.00m; 9-H, 7.85bs	160.074 115	160.074 892	3 140, 1 545, 1 510, 1 445, 1 420, 1 380, 1 320	59.86	5.03	35.00	60.00	5.00	35.00
(44)	6-H, 2.35m; 2-H, 8.40; 5-H, 7-H, 3.15m; 8-H, 8.65	160.073 182	160.074 892	1 660, 1 645, 1 525, 1 435, 1 415, 1 410, 1 310, 1 280	59.84	5.01	35.20	59.97	5.04	34.99
(45)	6-H, 2.28m; 2-SMe, 2.68s; 5-H, 7-H, 3.10m; 8-H, 8.42dd	206,062 296	206.062 615	1 635, 1 515, 1 435, 1 420, 1 360, 1 350, 1 310, 1 290	52.20	4.90	27.10	52.41	4.89	27.18
(46)	6-H, 2.30m; 2-H, 8.26s; 5-H, 7-H, 3.08m; 8-H, 8.50dd	184.073 703	184.074 892	2 220 (CN), 1 645, 1 565, 1 525, 1 460, 1 440, 1 420, 1 405	64.99	4.37	30.56	65.19	4.38	30.43
(48)	6-H, 7-H, 1.90m; 2-H, 8.25s; 5-H, 8-H, 2.50m; NH, 13.05 br s	214.087 158	214.085 456	2 220 (CN), 1 680, 1 640, 1 585, 1 500, 1 460, 1 375	61.95	4.69	25.92	61.66	4.71	26.16
(49)	6-H, 7-H, 1.97m; 2-H, 8.35s; 5-H, 8-H, 3.05m	232.051 570 and 234.048 200	232.051 350 and 234.048 200	2 220 (CN), 1 610, 1 540, 1 475, 1 415, 1 380, 1 350	56.87	4.13	23.89	56.77	3.87	24.08

Method B. 7-Methyltetrazolo[1,5-*a*]pyrimidine (18) was obtained as the sole reaction product in 63% yield.

2-*Methylpyrimido*[1,2-a]*benzimidazole* (41).—*Method B.* Alumina chromatography (eluant ethyl acetate) gave the title compound (41) in 64% yield, m.p. 230—232 °C (lit.,[17] m.p. 229—232 °C).

5,6,7,8-*Tetrahydro*-s-*triazolo*[5,1-b]*quinazoline* (21) *and* 6,7,8,9-*Tetrahydro*-s-*triazolo*[1,5-a]*quinazoline* (22). *Method A.* The two condensation products were separated by shaking the mixture with light petroleum (60—80 °C). The insoluble material, on recrystallisation from benzene–n-hexane, gave pure 5,6,7,8-tetrahydro-*s*-triazolo[5,1-*b*]-quinazoline (21), m.p. 121—123 °C (55%) (lit.,[9a] m.p. 125—126 °C). The light petroleum fraction was evaporated to dryness and the residue was recrystallised from n-hexane to give 6,7,8,9-*tetrahydro*-s-*triazolo*[1,5-a]*quinazoline* (22), m.p. 87—89 °C (37%).

5,6,7,8-*Tetrahydro*-2-*methylthio*-s-*triazolo*[5,1-b]*quinazoline* (24) *and* 6,7,8,9-*Tetrahydro*-2-*methylthio*-s-*triazolo*[1,5-a]-*quinazoline* (25).—*Method A.* Alumina chromatography (eluant–ethyl acetate) gave two products, 5,6,7,8-*tetrahydro*-2-*methylthio*-s-*triazolo*[5,1-b]*quinazoline* (24), which was re-

crystallised from methanol, m.p. 106—108 °C (63%); and 6,7,8,9-*tetrahydro*-2-*methylthio*-s-*triazolo*[1,5-a]*quinazoline* (25), recrystallised from acetone, m.p. 139—141 °C (26%).

Method B. The two products (24) and (25) were obtained in 48% and 16% yields respectively. When the toluene-*p*-sulphonic acid catalyst was replaced by anhydrous oxalic acid, only product (24) was obtained (60%).

5,6,7,8-*Tetrahydro*-2-*methyl*-s-*triazolo*[5,1-b]*quinazoline* (26).—*Method A.* Alumina chromatography (eluant ethyl acetate) followed by recrystallisation from n-hexane gave long white needles of *compound* (26), m.p. 132—133 °C (56%).

3-*Cyano*-5,6,7,8-*tetrahydropyrazolo*[5,1-b]*quinazoline* (28) *and* 3-*Cyano*-6,7,8,9-*tetrahydropyrazolo*[1,5-a]*quinazoline* (29).—*Method A.* Alumina chromatography (eluant ethyl acetate) gave two products, 5,6,7,8-*tetrahydro*-3-*cyanopyrazolo*[5,1-b]*quinazoline* (28), which was recrystallised from methanol, m.p. 110—111 °C (30%); and 6,7,8,9-*tetrahydro*-3-*cyanopyrazolo*[1,5-a]*quinazoline* (29), recrystallised from methanol, m.p. 116—118 °C (15%).

Method B. The two products (28) and (29) were obtained in 50 and 12% yield, respectively.

6,7,8,9-*Tetrahydro*-s-*triazolo*[4,3-b]*cinnoline* (30) *and* 7,8,9,10-*Tetrahydro*-s-*triazolo*[3,4-a]*phthalazine* (31).—*Method A.* Alumina chromatography [eluant ethyl acetate–ether (3 : 2)] gave two compounds, 6,7,8,9-tetrahydro-*s*-triazolo[4,3-*b*]cinnoline (30) which was recrystallised from n-hexane, m.p. 95—97 °C (20%) (lit.,[18] m.p. 120 °C); and 7,8,9,10-*tetrahydro*-s-*triazolo*[3,4-a]*phthalazine* (31), recrystallised from n-hexane, m.p. 157—159 °C (60%).

Method B. 6,7,8,9-Tetrahydro-*s*-triazolo[4,3-*c*]cinnoline (30) was obtained in 15% yield, accompanied by the starting ketoanil (42).

6,7,8,9-*Tetrahydrotetrazolo*[1,5-a]*quinazoline* (32).—*Method A.* The product crystallised directly from the reaction mixture; further recrystallisation from ethanol gave white crystals of the title compound (32), m.p. 121—123 °C (73%) (lit.,[9b] m.p. 122—123 °C).

1,2,3,4-*Tetrahydrobenzimidazo*[2,1-b]*quinazoline* (34).—*Method A.* Alumina chromatography (eluant ethyl acetate) followed by recrystallisation from acetone gave yellow needles of the title *compound* (34), m.p. 228—230 °C (51%).

Method B. The title compound (34) was obtained in 75% yield.

2,6,7,8-*Tetrahydro*-1H-*cyclopenta*[e]-s-*triazolo*[1,5-a]*pyrimidine* (36) *and* 6,7-*Dihydro*-5H-*cyclopenta*[f]-s-*triazolo*-[1,5-a]*pyrimidine* (44).—*Method A.* Alumina chromatography (eluant ethyl acetate) followed by recrystallisation from light petroleum (100—120 °C) gave 2,6,7,8-tetrahydro-1*H*-cyclopenta[*e*]-*s*-triazolo[1,5-*a*]pyrimidine (36) as white needles (72%), m.p. 121—122 °C (lit.,[9a] m.p. 133—134 °C).

Method B. Alumina chromatography (eluant ethyl acetate) followed by recrystallisation from n-hexane gave 6,7-dihydro-5*H*-cyclopenta[*f*]-*s*-triazolo[1,5-*a*]pyrimidine (44) in 61% yield, m.p. 207—208 °C (lit.,[9a] m.p. 207—208 °C).

2,6,7,8-*Tetrahydro*-2-*methylthio*-1H-*cyclopenta*[e]-s-*triazolo*[1,5-a]*pyrimidine* (37) *and* 6,7-*Dihydro*-2-*methylthio*-5H-*cyclopenta*[f]-s-*triazolo*[1,5-a]*pyrimidine* (45).—*Method A.* Alumina chromatography (eluant ethyl acetate) followed by recrystallisation from methanol gave 2,6,7,8-*tetrahydro*-2-*methylthio*-1H-*cyclopenta*[e]-s-*triazolo*[1,5-a]*pyrimidine* (37) as white crystals, m.p. 128—129 °C (81%).

Method B. Alumina chromatography (eluant ethyl acetate) followed by recrystallisation from methanol gave 6,7-*dihydro*-2-*methylthio*-5H-*cyclopenta*[f]-s-*triazolo*-[1,5-a]*pyrimidine* (45) as white lustrous crystals, m.p. 154—157 °C (51%).

3-*Cyano*-7,8-*dihydro*-6H-*cyclopenta*[g]*pyrazolo*[1,5-a]*pyrimidine* (38) *and* 3-*Cyano*-6,7-*dihydro*-5H-*cyclopenta*[f]*pyrazolo*[1,5-a]*pyrimidine* (46).—*Method A.* Alumina chromatography (eluant chloroform) furnished 3-*cyano*-7,8-*dihydro*-6H-*cyclopenta*[g]*pyrazolo*[1,5-a]*pyrimidine* (38), which was recrystallised from methanol to give white crystals, m.p. 147—149 °C (67%).

Method B. Two products, the above-mentioned compound (38) and 3-*cyano*-6,7-*dihydro*-5H-*cyanopenta*[d]*pyrazolo*[1,5-a]*pyrimidine* (46), m.p. 148—150 °C, were obtained in 17 and 58% yields respectively; both were recrystallised from methanol.

7,8-*Dihydro*-6H-*cyclopenta*[f]-s-*triazolo*[4,3-b]*pyridazine* (39).—*Method A.* Alumina chromatography (eluant ethyl acetate) followed by recrystallisation from benzene gave the title *compound* (39) in 60% yield, m.p. 139—140 °C.

3-*Cyano*-5,6,7,8-*tetrahydropyrazolo*[5,1-b]*quinazolin*-9-*ol* (48).—3-Amino-4-cyanopyrazole (27) (0.75 g, 7×10^{-3} mol) and 2-ethoxycarbonylcyclohexanone (1.20 g, 7×10^{-3} mol) were refluxed together in glacial acetic acid (30 ml) for 4 h. During refluxing, the product crystallised as fine yellow needles. After cooling the reaction mixture, the crystals were filtered off, washed with glacial acetic acid, and dried to give the title *compound* (48) (1.02 g, 75%), m.p. >310 °C.

9-*Chloro*-3-*cyano*-5,6,7,8-*tetrahydropyrazolo*[5,1-b]*quinazoline* (49).—A solution of the 9-hydroxy-compound (48) (0.64 g, 3×10^{-3} mol) in phosphoryl chloride (30 ml) was boiled for 3 h and the excess of phosphoryl chloride was removed *in vacuo*. Ice was added to the residue, and the solution was neutralised with ammonium hydroxide. The brown precipitate was collected, washed with water, dried, and purified by chromatography over alumina (eluant ethyl acetate), and recrystallised from light petroleum (60—80 °C) to give the title *compound* as fine white needles (0.57 g, 64%), m.p. 139—140 °C.

3-*Cyano*-5,6,7,8-*tetrahydropyrazolo*[5,1-b]*quinazoline* (28).—A solution of the chloro-compound (49) (0.464 g, 2×10^{-3} mol) in absolute alcohol (30 ml) was dehalogenated by shaking with hydrogen and 5% palladium–carbon catalyst (0.7 g). After crystallising the product from methanol, colourless crystals were obtained (0.217 g, 55%), m.p. 110—112 °C, mixed m.p. with a specimen prepared from 2-hydroxymethylenecyclohexanone (20) the same.

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