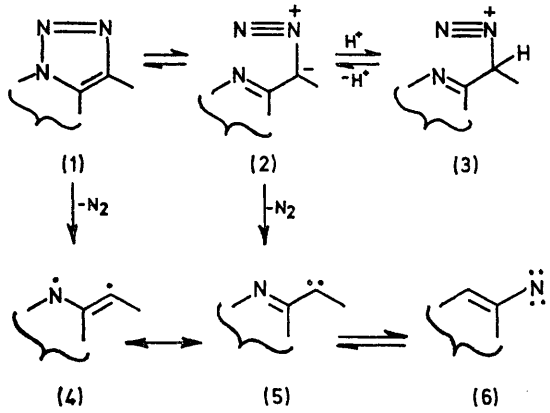
The Chemistry of Polyazaheterocyclic Compounds. Part V.[1] The Synthesis and Reactivity of the *v*-Triazolo[3,4-*a*]pyrimidine Ring System

By **D. R. Sutherland** and **G. Tennant,*** Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ

Heating the 4-substituted 5-amino-1*H*-1,2,3-triazoles (7a and b) and acetylacetone with piperidine in ethanol affords the *v*-triazolo[3,4-*a*]pyrimidine derivatives (9a and b) in high yield. Scission of the triazole ring in the triazolopyrimidine (9a) occurs in hot glacial acetic acid alone or in the presence of acetyl chloride, or in trifluoroacetic acid, yielding the 2-substituted pyrimidine derivatives (13a), (13c), and (13e), respectively. Condensation of the aminotriazole (7a) with acetylacetone in glacial acetic acid is accompanied by scission of the triazole ring to give the acetoxybenzylpyrimidine (13a). In contrast, heating the amide (7b) with acetylacetone in glacial acetic acid yields the *v*-triazolopyrimidine derivative (9b), which is stable to prolonged treatment with acetic or trifluoroacetic acid. The synthesis and scission of other *v*-triazolo[3,4-*a*]pyrimidine derivatives are described.

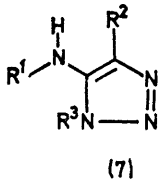
MOLECULES containing a fused 1,2,3-triazole nucleus of the type (1) are of potential value as substrates for the generation and study of a variety of reactive heterocyclic species. They often exhibit a marked 'diazo-character' in their chemical reactivity, manifested by homolytic [2-4] and heterolytic [5-8] ring scission to yield products by way of intermediate carbenes (5),[3] nitrenes (6),[3,4] or diazonium cations (3).[8] The construction of fused triazoles (1) from suitable triazole intermediates followed by scission of the triazole ring is also often a valuable method for the synthesis of otherwise inaccessible heterocyclic systems.[6,7] One of the implications of the 'diazo-character' of the nucleus (1) is the possible existence [6,7] of diazoalkylideneamine–triazole equilibria [(1) ⇌ (2)] analogous to the ring–chain tautomerism exhibited by fused tetrazoles.[9] Equilibria of the type [(1) ⇌ (2)] may be involved in the Dimroth rearrangement of amino-1,2,3-triazoles [1,10] and recently the equilibration of triazole and diazo-tautomers has been achieved for simple amino-1,2,3-triazoles.[11] Until recently [6,7] few heterocycles containing the nucleus (1) were known, and so far attempts [6,7] to detect the equilibrium [(1) ⇌ (2)] have been unsuccessful. As part of a general study of the synthesis and reactivity of heterocycles containing the nucleus (1), we now describe a synthesis of the *v*-triazolo[3,4-*a*]pyrimidine system. Acid-catalysed scission of *v*-triazolo[3,4-*a*]pyrimidine derivatives provides a new route to 2-substituted pyrimidines.[7]

The readiness with which tetrazolo[1,5-*a*]pyrimidines exhibit azide–tetrazole tautomerism [9] suggested that, in contrast to *v*-triazolo[1,5-*a*]quinazolines,[6a,c] *v*-triazolo[3,4-*a*]pyrimidines might be suitable substrates for the detection and study of the equilibrium [(1) ⇌ (2)]. Only one example of the *v*-triazolo[3,4-*a*]pyrimidine ring



system has been previously reported. Birr [12] briefly described the synthesis of the compound (8) by condensation of 4-amino-5-methyl-1*H*-1,2,3-triazole with ethyl acetoacetate. This method is analogous to the well documented [13] synthesis of *s*-triazolo[4,3-*a*]-pyrimidines from amino-1,2,4-triazoles. We have now investigated the scope of the synthesis of *v*-triazolo[3,4-*a*]pyrimidine derivatives by the condensation of β-dicarbonyl compounds with the amino-1,2,3-triazoles (7a and b).[14] The amines (7a and b) were readily available from the debenzylation [15] of the corresponding

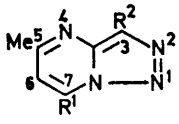
[1] Part IV, D. R. Sutherland and G. Tennant, *J. Chem. Soc.* (*C*), 1971, 706.
[2] J. H. Boyer and R. Selvarajan, *J. Heterocyclic Chem.*, 1969, **6**, 503.
[3] W. D. Crow and C. Wentrup, *Tetrahedron Letters*, 1968, 6149.
[4] C. Wentrup, *Chem. Comm.*, 1969, 1386.
[5] J. H. Boyer and L. T. Wolford, *J. Amer. Chem. Soc.*, 1958, **80**, 2741; J. H. Boyer and N. Goebel, *J. Org. Chem.*, 1960, **25**, 304.
[6] G. Tennant, *J. Chem. Soc.* (*C*), (*a*) 1966, 2290; (*b*) 1967, 1279, 2658; (*c*) D. R. Sutherland and G. Tennant, *Chem. Comm.*, 1969, 423.
[7] D. R. Sutherland and G. Tennant, *Chem. Comm.*, 1969, 1070.
[8] M. Regitz, *Chem. Ber.*, 1966, **99**, 2918; *Tetrahedron Letters*, 1965, 3287; M. Regitz and H. Schwall, *Annalen*, 1969, **728**, 99; G. Holt and D. K. Wall, *J. Chem. Soc.*, 1965, 1428.
[9] C. Temple, W. C. Coburn, M. C. Thorpe, and J. A. Montgomery, *J. Org. Chem.*, 1965, **30**, 2395; C. Temple, C. L. Kussner, and J. A. Montgomery, *ibid.*, 1966, **31**, 2210, and references cited therein.
[10] (*a*) E. Lieber, T. S. Chao, and C. N. R. Rao, *J. Org. Chem.*, 1957, **22**, 654; (*b*) R. A. Henry, W. G. Finnegan, and E. Lieber, *J. Amer. Chem. Soc.*, 1954, **76**, 88; A. Albert, *J. Chem. Soc.* (*C*), 1970, 230.
[11] R. E. Harmon, F. Stanley, S. K. Gupta, and J. Johnson, *J. Org. Chem.*, 1970, **35**, 3444; M. Regitz and G. Himbert, *Tetrahedron Letters*, 1970, 2823.
[12] E. J. Birr, *Z. wiss. Phot.*, 1952, **47**, 2 (*Chem. Abs.*, 1953, **47**, 2617).
[13] C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker, and J. A. Van Allan, *J. Org. Chem.*, 1959, **24**, 779; L. A. Williams, *J. Chem. Soc.*, 1962, 2222, and references cited therein.
[14] (*a*) M. Ruccia and D. Spinelli, *Gazzetta*, 1959, **89**, 1654 (*Chem. Abs.*, 1961, **55**, 4488); (*b*) H. El Khadem, M. A. E. Shaban, and M. A. M. Nassr, *J. Chem. Soc.* (*C*), 1970, 2167.
[15] J. R. E. Hoover and A. R. Day, *J. Amer. Chem. Soc.*, 1956, **78**, 5832.



(7)

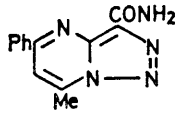
	R^1	R^2	R^3
a;	H	Ph	H
b;	H	CO·NH_2	H
c;	Ac	Ph	H
d;	Ac	CO·NH_2	H
e;	Ac	CO·NH_2	Ac
f;	H	Ph	CH_2Ph
g;	H	CO·NH_2	CH_2Ph

(8)

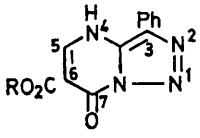


(9)

	R^1	R^2
a;	Me	Ph
b;	Me	CO·NH_2
c;	Ph	CO·NH_2
d;	Ph	Ph

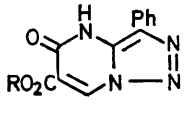


(10)



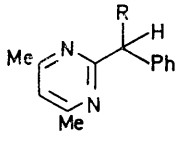
(11)

	R
a;	Et
b;	H



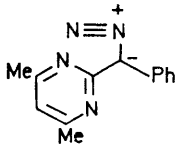
(12)

	R
a;	Et
b;	H

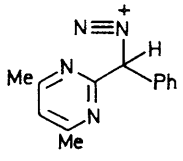


(13)

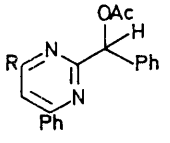
	R
a;	OAc
b;	OH
c;	Cl
d;	H
e;	O·CO·CF_3



(14)

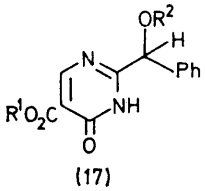


(15)



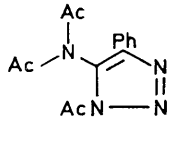
(16)

	R
a;	Me
b;	Ph

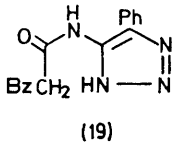


(17)

	R^1	R^2
a;	Et	CO·CF_3
b;	H	Ac
c;	H	CO·CF_3
d;	H	H



(18)



(19)

N-benzyltriazoles (7f and g).[10a,15,16] Condensation of the aminotriazole (7a) with acetylacetone occurred smoothly in the presence of aqueous sodium hydroxide or piperidine to give, in high yield, a single product which gave analytical data consistent with the formula $C_{13}H_{12}N_4$. The *v*-triazolo[3,4-*a*]pyrimidine structure (9a) is established by scission[6a] in hot acetic acid to yield the acetoxybenzylpyrimidine derivative (13a), $\nu_{max.}$ 1740 cm^{-1} (OAc), which on hydrogenolysis[6a] afforded the known[17] 2-benzylpyrimidine (13d). The presence of the diazo-structure (14), and hence the existence of the equilibrium [(9a) ⇌ (14)] either in the solid state or in solution, is excluded by the lack of significant i.r. absorption above 1600 cm^{-1} and by the presence of ^1H n.m.r. absorption attributable to two non-equivalent methyl groups in the condensation product. The ^1H n.m.r. spectrum of a solution in deuteriochloroform contains (Table 1) a singlet at τ 3·38 (1H) and two singlets (each 3H) at τ 7·18 and 7·40, which are shifted downfield in [$^2H_6$]dimethyl sulphoxide (Table 1) and are assigned to H-6 and the methyl groups respectively in the structure (9a). On expansion of the spectrum of the solution in [$^2H_6$]dimethyl sulphoxide to 250 Hz only the signal at τ 6·85 is resolved into a doublet. The singlet at τ 7·07 remains unsplit while the H-6 signal appears as a poorly resolved quartet. The assignment of the singlet at τ 6·85 to Me-7 and of that at τ 7·07 to Me-5 (Table 1) is based on the expectation that, owing to bond fixation in the structure (9a), the splitting associated with the benzylic-type Me(7)–H(6) coupling will be larger than that due to Me(5)–H(6) coupling.[18] The enhanced deshielding of a methyl group adjacent to a bridgehead nitrogen atom is also observed in the *s*-triazolo[4,3-*a*]-pyrimidine ring system.[19] The ^1H n.m.r. spectrum of the triazolopyrimidine (9a) in trifluoroacetic acid (run immediately) (Table 2) contains two singlets (each 1H) at τ 2·34 and 2·91 and a methyl singlet (6H) at τ 7·16. This spectrum is similar to that of the acetoxy-compound (13a) (Table 2), and demonstrates that scission of compound (9a) occurs almost instantaneously in trifluoroacetic acid at room temperature to yield the trifluoroacetate (13e). The species formed immediately from the triazolopyrimidine (9a) in trifluoroacetic acid cannot be the diazonium cation (15) since the benzylic proton signal in this structure should be shifted well downfield relative to that in the acetate (13a), owing to the powerful deshielding effect of the diazonium group. In this context, only the upper of the two low-field singlets in the ^1H n.m.r. spectra of the compounds (13a—c) (Table 2) shows the expected variation in chemical shift with change in the electron density at the benzyl side-chain. Consequently, the singlet at τ 3·2—4·2 (in deuteriochloroform) or at τ 2·9—3·7 (in trifluoroacetic acid) is assigned to the benzylic proton and that at *ca.* τ 3·1 (in deuteriochloroform) or at *ca.* τ 2·3 (in trifluoroacetic acid) to H-5. After 24 h the ^1H n.m.r. spectrum of the compound (9a) in trifluoroacetic acid was identical with that of the alcohol (13b) derived from the acetoxy-compound (13a) by alkaline hydrolysis. Formation of

[16] E. Lieber, C. N. R. Rao, and T. V. Rajkumar, *J. Org. Chem.*, 1959, **24**, 134.
[17] A. Pinner, *Ber.*, 1893, **26**, 2122.
[18] H. Rottendorf and S. Sternhell, *Austral. J. Chem.*, 1964, **17**, 1315; S. Sternhell, *Quart. Rev.*, 1969, **23**, 236.
[19] H. Reimlinger and M. A. Peiren, *Ber.*, 1970, **103**, 3266.

the alcohol (13b) from (9a) in trifluoroacetic acid is presumably due to the slow solvolysis of the initially formed trifluoroacetate (13e) by atmospheric moisture. When the aminotriazole (7a) was refluxed with acetylacetone in glacial acetic acid, condensation was accompanied by scission of the triazole ring, giving the acetoxybenzylpyrimidine (13a) in high yield. As in the case of *v*-triazoloquinazolines,[6a,c] triazole ring scission also occurred when the compound (9a) was refluxed with acetylacetone in acetic acid. It was unexpected therefore when the ^{1}H n.m.r. spectrum of the triazolopyrimidine amide (9b) in trifluoroacetic acid showed a six-proton singlet for the methyl protons (Table 1). However the spectrum lacks absorption due to a benzylic proton. Consequently, coalescence of the Me-5 and Me-7 resonances cannot be the result of the conversion of the amide (9b) into the corresponding trifluoroacetoxypyrimidine (see before) and is probably due to a solvent effect. Significantly, the ^{1}H n.m.r. spectrum of the

absorptions of a primary amide group. Proton resonances at τ 2·38 and at 6·77 and 6·98 can be assigned likewise to H-6 and the C-7 and C-5 methyl groups, respectively. In accord with the stabilising effect of a carboxamide group,[6a] the amide (9b) was unaffected when it was heated under reflux in acetic acid. This stability to triazole ring scission was also apparent in the formation of the *v*-triazolopyrimidine (9b) in high yield when the aminotriazole (7b) was heated under reflux

TABLE 1

^{1}H N.m.r. signals (τ) of *v*-triazolo[3,4-*a*]pyrimidines [a]

Compd.	Solvent [b]	H-5	H-6	Me-5	Me-7	ArH	Others
(9a)	A		3·38	7·40	7·18 [c]	1·47—2·70(m)	
	B		2·57 [d]	7·07	6·85 [c]	1·23—2·38(m)	
	C		3·23	7·44	7·22	1·59—2·70(m)	
(9b)	B		2·38	6·98	6·77		
	C		2·94	7·30	7·08 [c]		
	D		2·69	← 7·21 [e] →			
(9c)	B		1·64	6·70		1·26—1·38(m), 1·98—2·08(m)	
	D		2·16	7·13 [f]		1·70—2·45(m)	
(11a)	B	1·12				1·65—2·15(m)	5·35(q), 8·33(t)
(11b)	B	1·09				1·62—2·27(m)	3·80—4·40 [g]

[a] Signals were sharp singlets unless otherwise designated. [b] A, $CDCl_3$; B, $(CD_3)_2SO$; C, $CD_3{\cdot}CO_2D$; D, $CF_3{\cdot}CO_2H$. [c] Becomes a doublet, J 2·3—2·5 Hz, on expansion to 250 Hz. [d] Becomes a poorly resolved quartet on expansion to 250 Hz. [e] Six-proton singlet assigned to overlapping Me-5 and Me-7; no change after 48 h. [f] Unsplit on expansion to 250 Hz. [g] Broad singlet (OH).

TABLE 2

^{1}H N.m.r. signals (τ) of 2-substituted pyrimidines [a]

Compd.	Solvent [b]	H-5	Me-5	Me-6	Benzylic H	ArH	Others
(13a)	A	3·12	← 7·45 →		3·28	2·35—2·75(m)	7·80 [c]
	B	2·25	← 7·10 →		2·92	2·35—2·55(m)	7·50 [c]
(13b)	A	3·15	← 7·58 →		4·22	2·40—2·80(m)	4·90 [d]
	B	2·30	← 7·13 →		3·69	2·57	
(13c)	A	3·10	← 7·52 →		3·90	2·25—2·75(m)	
	B	2·26	← 7·12 →		3·58	2·40—2·60(m)	
(13d)	A	3·15	← 7·55 →		5·75	2·50—2·80(m)	
	B	2·30	← 7·16 →		5·42	2·60—2·70(m)	
(13e) [e,f]	B	2·34	← 7·16 →		2·91	2·44—2·56(m)	
(16a)	A	2·68	7·52		3·20	1·48—2·80(m)	7·78 [c]
	B	1·85	7·09		2·90	1·62—1·72(m), 2·20—2·60(m)	7·58 [c]
(16b)	B	1·57			2·84	1·76—2·70(m)	7·54 [c]
(17a) [g]	B	0·83			2·94	2·30—2·50(m)	5·38(q), 8·53(t)
(17b)	B	0·88			2·98	2·51, 2·71	7·59 [c]
(17c) [h]	B	0·84			2·94	2·36—2·50(m)	
(17d) [i]	B	0·92			3·72	2·35—2·54(m)	

[a] Signals were sharp singlets unless otherwise designated. [b] A, $CDCl_3$; B, $CF_3{\cdot}CO_2H$. [c] OAc. [d] Broad singlet (OH). [e] Spectrum of compound (9a) run immediately in trifluoroacetic acid. [f] After 24 h in trifluoroacetic acid the spectrum becomes identical with that of the alcohol (13b). [g] Spectrum of the ester (11a) or (12a) run immediately in trifluoroacetic acid. [h] Spectrum of the acid (11b) or (12b) run immediately in trifluoroacetic acid. [i] Spectrum of the acid (11b) or (12b) run after 24 h in trifluoroacetic acid.

acetyl chloride in glacial acetic acid. The α-chlorobenzylpyrimidine structure (13c) for the product is in accord with its ^{1}H n.m.r. spectrum and its hydrogenolysis [6a] to the benzylpyrimidine (13d).

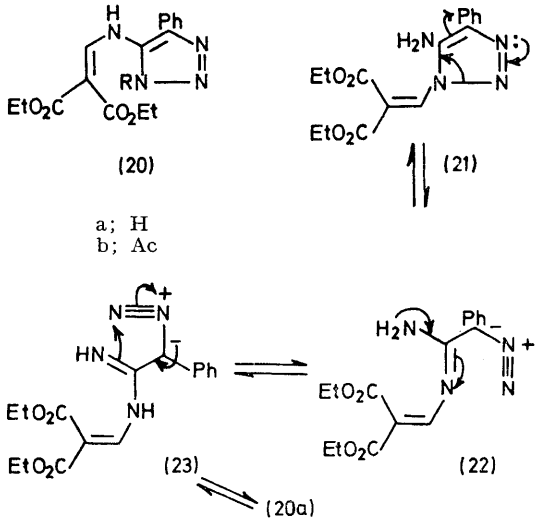
Acetylacetone also condensed readily with the triazole amide (7b) in the presence of piperidine to give a single product assigned the *v*-triazolo[3,4-*a*]pyrimidine structure (9b) on the basis of its elemental analysis and spectral properties. I.r. bands at 3450—3150 and 1680 cm^{-1} are attributable to the amino- and carbonyl

amide (9b) in [$^2H_4$]acetic acid (Table 1) contains singlets at τ 7·08 and 7·30, demonstrating the non-equivalence of the C-7 and C-5 methyl groups, respectively.

Attempts to extend the scope of the *v*-triazolo[3,4-*a*]-pyrimidine synthesis by use of other β-dicarbonyl compounds were only partially successful. Benzoylacetone and dibenzoylmethane did not condense with the aminotriazole (7a) in the presence of piperidine. However, condensation occurred smoothly in hot acetic acid to give the α-acetoxybenzylpyrimidine derivatives (16a and b) in high yield. The structures assigned to these products are based on elemental analysis and i.r. and ^{1}H n.m.r. spectra (Table 2). The corresponding *v*-triazolopyrimidine derivatives [*e.g.* (9d)] are presumably intermediates in the formation of the acetoxy-compounds (16a and b). In support of this contention, the amide (7b) condensed with benzoylacetone in hot acetic acid without triazole ring scission to yield the *v*-triazolopyrimidinecarboxamide (9c). The lack of any detectable splitting in the ^{1}H n.m.r. absorption of the methyl protons in this product demonstrates the absence of a C-7 methyl group (see before) and thereby excludes the alternative orientation (10). The exclusive formation of the product (9c) is consistent with preferential condensation between the primary amino-group in the aminotriazole (7b) and the more reactive acetyl group in benzoylacetone. Alternatively, formation of the compound (9c) might have occurred by initial condensation between the acetyl group and the triazole ring NH group to give, after ring closure, the compound (10) and thence, by a Dimroth type of rearrangement,[20] the isomer (9c). The latter course is unlikely since the presence of the carboxamide group, by stabilising the triazole ring (see before), will tend to inhibit the rearrangement step [(10) ⟶ (9c)]. 2-Amino-1,2,4-triazole derivatives are reported[21] to undergo preferential electrophilic attack at the primary amino-group under acidic conditions. In contrast to the aminotriazole (7a), the amide (7b) did not react with dibenzoylmethane in hot acetic acid but instead gave a diacetyl derivative which showed carbonyl i.r. absorption at 1760 and *ca.* 1700 cm^{-1} attributable to ring and side-chain *N*-acetyl groups, respectively.[1] The structure (7e) assigned to the diacetyl derivative is also consistent with the chemical shift[1] of the acetyl protons and the ready loss[1] of the ring *N*-acetyl group when crystallisation from water was attempted.

The aminotriazole (7a) did not condense with diethyl malonate or ethyl benzoylacetate in the presence of piperidine or in acetic acid. It was unchanged when heated under reflux with the active methylene compound and piperidine in ethanol, and in hot acetic acid it was converted into a monoacetyl derivative. The latter compound is assigned the acetylamino-structure (7c) rather than a ring *N*-acetyl structure[1] on the basis of the low carbonyl i.r. frequency of the acetyl group and the relatively high chemical shift of the acetyl protons.[1] In contrast, acetylation of the aminotriazole (7a) in hot acetic anhydride afforded a triacetyl derivative which showed carbonyl i.r. absorption at 1770, and 1740 and 1710 cm^{-1} in the ranges expected[1] for a ring *N*-acetyl group and a diacetylamino-group respectively. The assigned structure (18) is further supported by the ^{1}H n.m.r. spectrum, τ 7·16 (3H, s, ring NAc) and 7·68 (6H, s, NAc_2). Acetylation of the aminotriazole (7a) with acetyl chloride in pyridine was reported[14b] to yield an imino-acetate, though unequivocal support for the assigned structure was not presented. The aminotriazole (7a) also failed to condense thermally[13] with diethyl malonate in refluxing toluene. Ethyl benzoylacetate, on the other hand, yielded a product assigned the benzoylacetyl structure (19) on the basis of its elemental analysis and spectral properties. The side-chain position for the benzoylacetyl group in this product is consistent with the low carbonyl i.r. frequency of the amide-group (see before). Attempts to cyclise the triazole derivative (19) to the corresponding *v*-triazolopyrimidine derivative were unsuccessful. It was unchanged when heated under reflux with piperidine in ethanol, and in hot acetic acid it was converted with concomitant loss of the benzoylacetyl group into the *N*-acetylaminotriazole (7c).

The difficulty of condensing the aminotriazoles (7a and b) with active methylene compounds containing ethoxycarbonyl or benzoyl groups is a measure of the lower carbonyl reactivity of these substituents. The same effect was encountered in the condensation of the aminotriazole (7a) with ethyl ethoxymethylenemalonate. Heating under reflux with piperidine in ethanol for 40 h yielded a *v*-triazolopyrimidine derivative only in low yield. The main product was the ethylideneamino compound (20a), which was also formed in high yield when the aminotriazole (7a) was heated under reflux with the ethoxymethylene compound in toluene or in benzene con-



taining acetic acid. The structure (20a) rather than the alternative (21) is based on the ^{1}H n.m.r. absorption of

[20] D. R. Sutherland and G. Tennant, to be published.
[21] L. A. Williams, *J. Chem. Soc.*, 1961, 3046.

the olefinic proton, which appears as a doublet centred at τ 1·15. Splitting is readily explained by coupling between the olefinic and NH protons in the ethylideneamino-structure (20a) but cannot be accommodated by the structure (21), which lacks an NH proton. The side-chain position for the substituted ethylidene group is also supported by the conversion of the condensation product into a monoacetyl derivative whose ring *N*-acetyl structure (20b) is in accord with the high carbonyl i.r. frequency of the acetyl group and the low chemical shift of the acetyl protons (see before). The possibility that the condensation product does have the structure (21) but undergoes the Dimroth rearrangement [(21) ⇌ (22) ⇌ (23) ⇌ (20a)] prior to acetylation is excluded by the reconversion of the acetyl derivative (20b) into the condensation product [*i.e.* (20a)] by mild hydrolysis. Formation of the ethylideneamino compound (20a) rather than the isomer (21) implies the preferential condensation between the primary amino-group in the aminotriazole (7a) and the most electrophilic β-position [21] in ethyl ethoxymethylenemalonate under both acidic and basic conditions. This behaviour contrasts with that of 2-amino-1*H*-1,2,4-triazoles in which electrophilic attack at the amino-group is favoured by acidic media and that at a triazole nitrogen atom by basic conditions. This difference in behaviour can be rationalised by postulating that under basic conditions the isomer (21) is initially formed but is converted by the Dimroth rearrangement [(21) ⇌ (22) ⇌ (23) ⇌ (20a)] into the more stable isomer (20a) in which the electron-withdrawing ethylidene group is situated on the amino side-chain.[1] Prolonged heating of the ethylideneamino compound (20a) or of a mixture of the aminotriazole (7a) and ethyl ethoxymethylenemalonate with piperidine in ethanol afforded a single product in high yield, whose elemental analysis and spectral and chemical properties are consistent with either of the *v*-triazolopyrimidine structures (11a) and (12a). Since the ethylideneamino compound (20a) is stable to heating under reflux with piperidine in ethanol, Dimroth rearrangement [(20a) ⟶ (21)] and subsequent cyclisation to the structure (12a) is unlikely. Consequently formation of the *v*-triazolopyrimidine derivative from the aminocrotonate (20a) supports the structure (11a), but not unequivocally, since there is evidence [20] that structures of this type can undergo a Dimroth type of rearrangement [*e.g.* (11a) ⟶ (12a)] in the presence of piperidine. Attempts to effect triazole ring scission of the ester (11a) in hot acetic acid yielded only unidentified oils. Likewise, heating of the aminotriazole (7a) under reflux with ethyl ethoxymethylenemalonate in acetic acid yielded the acetylaminotriazole (7c) rather than the acetoxybenzylpyrimidine derivative (17a; Ac for $CO{\cdot}CF_3$). However, the derived acid (11b) was smoothly converted in hot acetic acid into the acetoxybenzylpyrimidine (17b), whose structure follows from its i.r. and ^{1}H n.m.r. spectra. Also, triazole ring scission of the compounds (11a and b) occurred readily in cold trifluoracetic acid; ^{1}H n.m.r. spectra run immediately in this solvent (Table 2) clearly demonstrate the presence of the trifluoroacetoxy-derivatives (17a) and (17c). After 24 h a solution of the acid (11b) showed ^{1}H n.m.r. absorption (Table 2) consistent with the presence of the alcohol (17d) (see before).

EXPERIMENTAL

I.r. and u.v. spectra were recorded for Nujol suspensions and ethanolic solutions, respectively, with Unicam SP 200 and SP 800 instruments. N.m.r. spectra were measured at 100 MHz for solutions in deuteriochloroform, [$^2H_6$]-dimethyl sulphoxide, [$^2H_4$]acetic acid, or trifluoroacetic acid, at 28°, with tetramethylsilane as internal standard, with a Varian HA 100 instrument. Molecular weights were measured with an A.E.I. MS 902 mass spectrometer.

Light petroleum had b.p. 60—80°.

5-Amino-1-benzyl-4-phenyl-1,2,3-triazole (7f).—A mixture of benzyl azide (80·0 g) and phenylacetonitrile (70·2 g, 69·0 ml) was heated under reflux with a solution of sodium (13·8 g) in methanol (300 ml) for 5 h. The solid which separated from the hot solution was collected on cooling and combined with material obtained by evaporation of the methanolic filtrate followed by trituration with water. Crystallisation of the crude product from hot ethanol–benzene, with filtration while hot to remove inorganic material, afforded the pure triazole (7f) (111 g), m.p. 157° (lit.,[16] 158°).

*5-Amino-4-phenyl-*1H-*1,2,3-triazole* (7a).—A suspension of 5-amino-1-benzyl-4-phenyl-1,2,3-triazole (60·0 g) in liquid ammonia (1500 ml) was stirred and treated with small pieces of sodium metal (total 13·8 g) until the transient blue-green colour produced initially became permanent. Ammonium chloride was added to discharge the blue-green colour and the mixture was allowed to evaporate at room temperature overnight. The crude solid obtained was stirred with water (250 ml) and the resulting suspension was filtered to remove unchanged benzyltriazole (7f) (2·1 g). The aqueous filtrate was made just acid with concentrated hydrochloric acid and then adjusted to pH 8 by the dropwise addition of concentrated aqueous ammonia. The solid which separated was collected and crystallised to yield the aminotriazole (7a) (22·6 g), m.p. 124° (from water) (lit.,[14a,b] 125°), $\nu_{max.}$ 3350, 3300, and 3200 (NH), and 1640 (NH def.) cm^{-1} (Found: C, 59·6; H, 5·4; N, 34·8. Calc. for $C_8H_8N_4$: C, 60·0; H, 5·0; N, 35·0%). The aminotriazole (7a) was converted in hot acetic anhydride into the *triacetyl derivative* (18), which formed needles, m.p. 115° (from benzene–light petroleum), $\nu_{max.}$ 1770, 1740, and 1710 (CO) cm^{-1}, τ ($CDCl_3$) 2·25—2·60 (5H, m, ArH), 7·16 (3H, s, ring NAc), and 7·68 (6H, s, NAc_2) (Found: C, 58·7; H, 5·1. $C_{14}H_{14}N_4O_3$ requires C, 58·7; H, 4·9%). Heated under reflux (4 h) in glacial acetic acid, the aminotriazole (7a) was converted into the monoacetyl derivative (7c) (80%), m.p. 204° (from benzene–ethanol), which was identical (mixed m.p. and i.r. spectrum) with a sample prepared as described later. The aminotriazole (7a) (0·01 mol) was unchanged (recovery >90%) when heated under reflux (48 h) with diethyl malonate, dibenzoylmethane, ethyl benzoylacetate, or benzoylacetone (0·01 mol) and piperidine (0·2 ml) in ethanol (60·0 ml), or when it was refluxed (2 h) with diethyl malonate (0·01 mol) in anhydrous toluene (50·0 ml) with provision for the removal of any ethanol formed (see later).

*5-Amino-*1H-*1,2,3-triazole-4-carboxamide* (7b).—The amide (7b), prepared by the method of Hoover and Day,[15] had m.p. 223° (from water) (lit.,[15] 225°), $\nu_{max.}$ 3350, 3200,

and 2700br (NH), and 1680 (CO), and 1650 (NH def.) cm^{-1}. Refluxed (4·5 h) in glacial acetic acid, the amide (7b) was converted into the *diacetyl derivative* (7e) (64%), which was identical (i.r. and ^1H n.m.r. spectra) with a sample prepared as described later.

5,7-*Dimethyl*-3-*phenyl*-v-*triazolo*[3,4-a]*pyrimidine* (9a).—A mixture of the aminotriazole (7a) (0·01 mol) and acetylacetone (0·01 mol) in ethanol (40·0 ml) was heated under reflux with aqueous 40% w/v sodium hydroxide solution (8·0 ml) for 10 min or with piperidine (0·2 ml) for 27 h. The ethanol was removed under reduced pressure and the gum obtained was treated with water or with ether–light petroleum to give the *triazolopyrimidine* (9a) (91%), m.p. 160° (from benzene–light petroleum), $\nu_{max.}$ 1620 cm^{-1}, $\lambda_{max.}$ 211, 231, 258, 279, 292, and 342 nm (log ε 4·25, 4·25, 4·16, 3·88, 3·75, and 3·67) (Found: C, 69·5; H, 5·3; N, 25·0%; M^+, 224. $C_{13}H_{12}N_4$ requires C, 69·6; H, 5·4; N, 25·0%; *M*, 224).

2-(*a-Acetoxybenzyl*)-4,6-*dimethylpyrimidine* (13a).—The *acetoxy-compound* (13a) was formed (70—90%) by heating the triazolopyrimidine (9a) (4·0 g) or a mixture of the aminotriazole (7a) (2·0 g) and acetylacetone (2·0 g) under reflux in glacial acetic acid (25·0 ml) for 4 h. Removal of the acetic acid under reduced pressure and crystallisation of the resulting oil from benzene–light petroleum gave needles, m.p. 103°, $\nu_{max.}$ 1740 (C·OAc) cm^{-1} (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%). Hydrogenated in ethanol over 10% palladium–charcoal, the acetate (13a) afforded 2-benzyl-4,6-dimethylpyrimidine (13d) (69%), m.p. 82° (from benzene–light petroleum) (lit.,[17] 80°), which was identified by comparison (mixed m.p. and i.r. spectrum) with a synthetic sample.[17]

2-(α-*Hydroxybenzyl*)-4,6-*dimethylpyrimidine* (13b).—The acetoxy-compound (13a) (0·8 g) was heated under reflux with aqueous 10% w/v sodium hydroxide (5·0 ml) in ethanol (10·0 ml) for 30 min. The ethanol was removed under reduced pressure and the aqueous residue was extracted with chloroform. The dried ($MgSO_4$) extract was evaporated to yield an oil which afforded the solid *alcohol* (13b) in contact with ether–light petroleum. Crystallisation gave needles (0·5 g), m.p. 80° (from benzene–light petroleum), $\nu_{max.}$ 3400 (OH) cm^{-1} (Found: C, 73·2; H, 6·8; N, 12·8. $C_{13}H_{14}N_2O$ requires C, 72·9; H, 6·6; N, 13·1%).

2-(α-*Chlorobenzyl*)-4,6-*dimethylpyrimidine* (13c).—A suspension of the triazolopyrimidine (9a) (0·8 g) in a mixture of acetyl chloride (25·0 ml) and glacial acetic acid (15·0 ml) was heated under reflux for 2·5 h. The suspended solid slowly dissolved on heating. The mixture was evaporated to give a gum which was crystallised to yield the *chloro-compound* (0·7 g), m.p. 112° (from benzene–light petroleum) (Found: C, 67·5; H, 5·5; N, 12·2. $C_{13}H_{13}ClN_2$ requires C, 67·1; H, 5·6; N, 11·9%). Hydrogenated in ethanol over 10% palladium–charcoal, the chloro-compound (13c) yielded the benzylpyrimidine (13d) (80%), identical (m.p., mixed m.p., and i.r. spectrum) with an authentic sample.[17]

5,7-*Dimethyl*-v-*triazolo*[3,4-a]*pyrimidine*-3-*carboxamide* (9b).—(*a*) The triazole amide (7b) (1·3 g) and acetylacetone (1·1 g) were heated under reflux with piperidine (1·0 ml) in ethanol (200 ml) for 22 h. The solid was collected from the cooled mixture, combined with material obtained by evaporating the filtrate, and crystallised to yield the amide (9b) (79%).

(*b*) The triazole amide (7b) (6·4 g) and acetylacetone (10·0 g) were heated under reflux in glacial acetic acid (150 ml) for 3 h and the gum obtained by evaporating the mixture was treated with ether to give the solid *amide* (9b) (90%), which crystallised as needles, m.p. 265° (from ethanol–acetic acid), $\nu_{max.}$ 3450, 3400, 3300, and 3150 (NH), and 1680 (CO) cm^{-1}, $\lambda_{max.}$ 219, 262sh, 270, 280, and 305 nm (log ε 4·12, 3·56, 3·65, 3·66, and 3·61) (Found: C, 49·8; H, 4·9; N, 36·7%; M^+, 191. $C_8H_9N_5O$ requires C, 50·3; H, 4·7; N, 36·7%; *M*, 191).

2-(α-*Acetoxybenzyl*)*pyrimidines* (16a) *and* (16b).—The aminotriazole (7a) (0·8 g) and benzoylacetone (1·6 g) or dibenzoylmethane (2·2 g) were heated under reflux in glacial acetic acid (10·0 ml) for 60 h. The mixture was evaporated to give an oil which was triturated with ether to yield the solid *pyrimidine derivative* (16a) (1·3 g), m.p. 135° (from benzene–light petroleum), $\nu_{max.}$ 1740 (C·OAc) cm^{-1} (Found: C, 75·3; H, 6·1; N, 8·7. $C_{20}H_{18}N_2O_2$ requires C, 75·5; H, 5·7; N, 8·8%), or (16b) (1·6 g), m.p. 138° (from benzene–light petroleum), $\nu_{max.}$ 1740 (OAc) cm^{-1} (Found: C, 79·3; H, 5·7; N, 7·2. $C_{25}H_{20}N_2O_2$ requires C, 78·9; H, 5·3; N, 7·4%).

5-*Methyl*-7-*phenyl*-v-*triazolo*[3,4-a]*pyrimidine*-3-*carboxamide* (9c).—The triazole amide (7b) (1·3 g) and benzoylacetone (3·2 g) were heated under reflux in glacial acetic acid (10·0 ml) for 4·5 h. The solid was collected from the cooled mixture and combined with a second crop obtained by evaporating the filtrate and triturating the oil with ether–methanol. The *triazolopyrimidine* (9c) formed needles (1·4 g), m.p. 202° (from acetic acid), $\nu_{max.}$ 3400 and 3300sh (NH), and 1670 (CO) cm^{-1}, $\lambda_{max.}$ 213, 265, 285sh, 309sh, and 325 nm (log ε 4·26, 4·42, 4·03, 3·74, and 3·73) (Found: C, 61·6; H, 4·3; N, 27·7%; M^+, 253. $C_{13}H_{11}N_5O$ requires C, 61·7; H, 4·4; N, 27·7%; *M*, 253).

5-(α-*Benzoylacetamido*)-4-*phenyl*-1H-1,2,3-*triazole* (19).—The aminotriazole (7a) (2·6 g) and ethyl benzoylacetate (3·1 g) were heated under reflux in anhydrous toluene (250 ml) for 10 h. The ethanol formed was allowed to distil through a short Vigreux column. The solid product was collected from the cooled solution and combined with a second crop obtained by working up the toluene mother liquors, and crystallised to give the *benzoylacetamidotriazole* (19) (68%), m.p. 194° (from benzene–ethanol), $\nu_{max.}$ 3300 and 2800—2600br (NH), and 1690 and 1670 (CO) cm^{-1}, τ (CF_3·CO_2H) 1·90—2·50 (10H, m, ArH) and 5·38 (2H, s, CH_2) (Found: C, 66·9; H, 5·1; N, 19·0. $C_{17}H_{14}N_4O_2$ requires C, 66·7; H, 4·6; N, 18·3%). The benzoylacetamidotriazole (19), heated under reflux (60 h) with piperidine in ethanol as described before, was unchanged (recovery 80%). Heated under reflux (96 h) in glacial acetic acid it afforded the acetamidotriazole (7c) (95%), m.p. and mixed m.p. 204°, identical (i.r. spectrum) with a sample prepared as described later.

Condensation Reactions of the Aminotriazole (7a) *with Ethyl Ethoxymethylenemalonate.*—(*a*) The aminotriazole (7a) (0·0025 mol) and ethyl ethoxymethylenemalonate (0·0025 mol) were heated under reflux with glacial acetic acid (0·1 ml) in anhydrous benzene (40·0 ml) for 30 h, or in anhydrous toluene (100 ml) for 3 h as described before. The gum obtained by evaporating the mixture was treated with ether and crystallised to give the ethylideneamino compound (20a) (64—89%).

(*b*) The aminotriazole (7a) (5·4 g) and ethyl ethoxymethylenemalonate (8·0 g) were heated under reflux with piperidine (1·0 ml) in ethanol (150 ml) for 40 h. The mixture was evaporated and the gum obtained was treated with water and crystallised to yield the *ethylideneamino compound* (20a) as needles (5·3 g), m.p. 156° (from benzene), $\nu_{max.}$ 3400 and

3200 (NH), 1710 and 1690 (CO), and 1660 (NH def.) cm^{-1}, τ ($CDCl_3$) 1·15 (1H, d, olefinic CH), 2·20—2·70 (5H, m, ArH), 5·50—5·80 (4H, m, CH_2), and 8·55—8·78 (6H, m, Me) (Found: C, 57·9; H, 5·7; N, 16·9. $C_{16}H_{18}N_4O_4$ requires C, 58·2; H, 5·5; N, 17·0%). Acidification of the aqueous mother liquor with dilute aqueous sulphuric acid gave the triazolopyrimidine derivative (11a) (0·05 g) which was identical (m.p., mixed m.p., and i.r. spectrum) with a sample prepared as described in (*c*). The ethylideneamino compound (20a) was converted in warm acetic anhydride into the *monoacetyl derivative* (20b) (95%), m.p. 115° (from benzene–light petroleum), $\nu_{max.}$ 1760, 1730, and 1660 (CO) cm^{-1}, τ ($CDCl_3$) 1·20 (1H, d, olefinic CH), 2·10—2·50 (5H, m, ArH), 5·70 (4H, sextet, CH_2), 7·18 (3H, s, Ac), and 8·65 (6H, m, 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%).

(*c*) The aminotriazole (7a) and ethyl ethoxymethylenemalonate were heated under reflux with piperidine in ethanol as in (*b*) for 96 h. The solid piperidine salt was collected from the cooled mixture and treated with dilute aqueous sulphuric acid to give *ethyl* 4,7-*dihydro*-7-*oxo*-3-*phenyl*-v-*triazolo*[3,4-a]*pyrimidin*-6-*carboxylate* (11a), which formed needles (2·5 g), m.p. 237° (from ethanol–acetic acid), $\nu_{max.}$ 3200 and 2800—2600br (OH), and 1760 and 1740—1700br (CO) cm^{-1} (Found: C, 59·1; H, 4·2; N, 20·1%; M^+, 284. $C_{14}H_{12}N_4O_3$ requires C, 59·2; H, 4·3; N, 19·7%; *M*, 284). The ester (11a) was also obtained (95%) when the aminocrotonate (20a) (5·0 g) was heated under reflux with piperidine (1·0 ml) in ethanol (150 ml) for 168 h and the mixture worked up as described before. Heating the triazolopyrimidine (11a) under reflux in glacial acetic acid (alone or containing acetyl chloride) yielded unidentified oils.

4,7-*Dihydro*-7-*oxo*-3-*phenyl*-v-*triazolo*[3,4-a]*pyrimidin*-6-*carboxylic Acid* (11b).—The ester (11a) (2·0 g) was heated under reflux with aqueous 10% w/v sodium hydroxide (10·0 ml) and water (25·0 ml) in ethanol (50·0 ml) for 15 min. The mixture was evaporated, treated with water, and acidified with dilute aqueous sulphuric acid to yield the *acid* (11b) (1·6 g), m.p. 244° (from acetic acid), $\nu_{max.}$ 3200—3100br and 2800—2600br (OH), and 1720 (CO) cm^{-1}, $\lambda_{max.}$ 210, 252, and 320 nm (log ε 4·41, 3·98, and 4·12) (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%).

2-(α-*Acetoxybenzyl*)-3,4-*dihydro*-4-*oxo*-*pyrimidin*-5-*carboxylic Acid* (17b).—The acid (11b) (0·5 g) was heated under reflux in glacial acetic acid (100 ml) for 4·5 h. The oil obtained by evaporating off the acetic acid crystallised to yield the *acetoxybenzylpyrimidine* (17b) (0·5 g), m.p. 83°, $\nu_{max.}$ 2800—2500br (OH), 1750—1720br (CO), and 1640 cm^{-1} (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%).

5-*Acetamido*-4-*phenyl*-1H-1,2,3-*triazole* (7c).—The aminotriazole (7a) (0·0025 mol) and diethyl malonate, ethyl benzoylacetate, or ethyl ethoxymethylenemalonate (0·005 mol) were heated under reflux in glacial acetic acid (3·0 ml) for 46 h. Work-up as before gave an oil which crystallised from benzene–ethanol to yield the *acetamidotriazole* (7c) (78—84%), m.p. 204°, $\nu_{max.}$ 3200 and 2700—2500br (NH), and 1670 (CO) cm^{-1}, τ ($CF_3{\cdot}CO_2H$) 2·35 (5H, s, ArH) and 7·52 (3H, s, Ac) (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%).

5-*Acetamido*-1-*acetyl*-1,2,3-*triazole*-4-*carboxamide* (7e) *and* 5-*Acetamido*-1H-1,2,3-*triazole*-4-*carboxamide* (7d).—The triazole amide (7b) (1·3 g) and dibenzoylmethane (4·5 g) were heated under reflux in glacial acetic acid (10·0 ml) for 120 h. The mixture was worked up as described before to yield the diacetyltriazole (7e) (1·1 g), $\nu_{max.}$ 3350, 3250—3150br, and 2650br (NH), and 1760 and 1710—1660 (CO) cm^{-1}, τ ($CF_3{\cdot}CO_2H$) 7·44 (3H, s, ring NAc) and 7·74 (3H, s, NHAc). Crystallisation from water gave the *monoacetyl triazole* (7d), m.p. 269° (from acetic acid), $\nu_{max.}$ 3450, 3350, 3250, and 3150 (NH), and 1700—1660br (CO) cm^{-1} (Found: C, 35·4; H, 4·8; N, 41·3. $C_5H_7N_5O_2$ requires C, 35·4; H, 4·2; N, 41·4%).

We thank the S.R.C. for a research studentship (to D. R. S.).

[1/139 *Received, February 8th*, 1971]