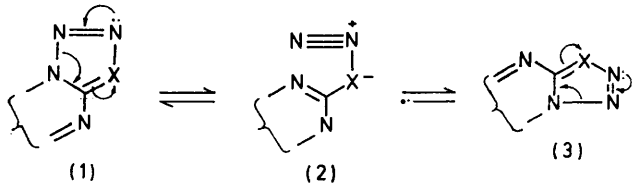
The Chemistry of Polyazaheterocyclic Compounds. Part VI.[1] Condensation Reactions of 5-Amino-1*H*-1,2,3-triazoles with Ethyl Acetoacetate and a New Type of Dimroth Rearrangement

By **Derek R. Sutherland, George Tennant,*** and **Robin J. S. Vevers,** Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ

Condensation of 5-amino-4-phenyl-1*H*-1,2,3-triazole (4a) with ethyl acetoacetate in the presence of piperidine affords mainly 5-methyl-3-phenyl-*v*-triazolo[3,4-*a*]pyrimidin-7(4*H*)-one (9a), which is also the major product of the piperidine-catalysed cyclisation of the triazole derivatives (5a) and (7a). The isomer (10a) was only a minor product of these reactions. In contrast, heating a mixture of the amino-1,2,3-triazolecarboxamide (4c) and ethyl acetoacetate, or the vinylaminotriazole (5c) with piperidine in ethanol affords an inseparable mixture of the isomeric *v*-triazolo[3,4-*a*]pyrimidinecarboxamides (9b) and (10b). The thermal conversion of the *v*-triazolopyrimidine (9a) into the isomer (10a) and its re-formation from the latter by heating with piperidine in ethanol constitutes a new type of reversible Dimroth rearrangement. The course of the reactions are discussed.

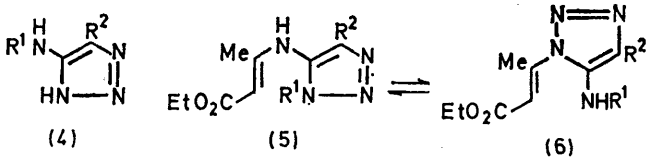
AZIDE–TETRAZOLE tautomerism [(1) ⇌ (2); X = N] and the attendant Dimroth-type rearrangements [(1) ⇌ (2) ⇌ (3); X = N] of fused tetrazoles are now well documented.[2] The analogous diazoalkylideneamine–triazole equilibrium has long been known for hydroxy-1,2,3-triazoles [3] and has been demonstrated recently for simple amino-1,2,3-triazoles [4] [*cf.* (1) ⇌ (2); X = CR]. Ring–Chain tautomerism of this type is almost certainly involved in the Dimroth rearrangements [5] of amino-



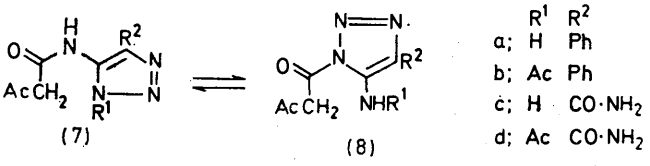
(1) (2) (3)

1,2,3-triazoles [*cf.* (1) ⇌ (2) ⇌ (3); X = CR] and in certain related processes.[6] So far, attempts [7] to detect equilibria of the type [(1) ⇌ (2); X = CR] in fused 1,2,3-triazoles have been unsuccessful. We now report further studies [1] of the synthesis and reactivity of the *v*-triazolo[3,4-*a*]pyrimidine ring system which were undertaken with the aim of demonstrating the hitherto unknown Dimroth-type rearrangement [(1) ⇌ (2) ⇌ (3); X = CR] in a fused 1,2,3-triazole.

Ethyl acetoacetate condensed readily with 5-amino-4-phenyl-1*H*-1,2,3-triazole (4a) in the presence of piperidine to give a product (X) which after drying at 140° and crystallisation, melted sharply and gave analytical data consistent with the molecular formula $C_{12}H_{10}N_4O$. The properties and transformations of this product are consistent with either of the possible *v*-triazolo[3,4-*a*]pyrimidine formulae (9a) or (10a). It showed broad i.r. absorption at 3100—2700 (>NH) and 1660 (>C=O) cm^{-1} attributable to a cyclic amide

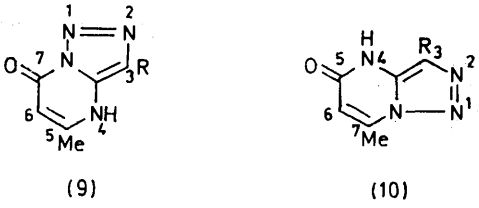


(4) (5) (6)

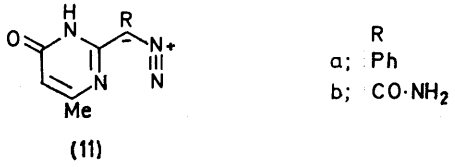


(7) (8)

a; R^1 = H, R^2 = Ph
b; R^1 = Ac, R^2 = Ph
c; R^1 = H, R^2 = CO·NH$_2$
d; R^1 = Ac, R^2 = CO·NH$_2$



(9) (10)



(11)

a; R = Ph
b; R = CO·NH$_2$

structure. The lack of diazo-absorption near 2000 cm^{-1} excludes the diazo-structure (11a). Its ^{1}H n.m.r. spectrum in [$^2H_6$]dimethyl sulphoxide contained a

[1] Part V, D. R. Sutherland and G. Tennant, *J. Chem. Soc.* (*C*), 1971, 2156.

[2] 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.

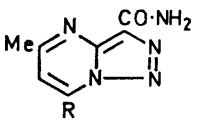
[3] B. R. Brown and D. L. Hammick, *J. Chem. Soc.*, 1947, 1384; M. Regitz and H. J. Geelhaar, *Chem. Ber.*, 1969, **102**, 1743.

[4] M. Regitz and H. Schwall, *Annalen*, 1969, **728**, 99; M. Regitz and G. Himbert, *Tetrahedron Letters*, 1970, 2823; *Chem. Ber.*, 1972, **105**, 2975, 2963; R. E. Harmon, F. Stanley, S. K. Gupta, and J. Johnson, *J. Org. Chem.*, 1970, **35**, 3444; *Chem. and Ind.*, 1970, 1021; A. C. Oehlschlager and L. H. Zalkow, *Canad. J. Chem.*, 1969, **47**, 461.

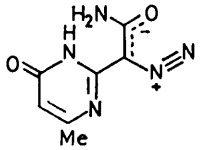
[5] D. R. Sutherland and G. Tennant, *J. Chem. Soc.* (*C*), 1971, 706.

[6] A. Albert and K. Tratt, *Angew. Chem. Internat. Edn.*, 1966, **5**, 587; D. J. Brown and M. N. Paddon-Row, *J. Chem. Soc.* (*C*), 1967, 1856; M. Regitz and A. Liedhegener, *Annalen*, 1967, **710**, 118; M. Regitz and H. Scherer, *Chem. Ber.*, 1969, **102**, 417; M. Begtrup, *Acta Chem. Scand.*, 1972, **26**, 1243; C. Temple, B. H. Smith, and J. A. Montgomery, *J.C.S. Chem. Comm.*, 1972, 52.

[7] G. Tennant, *J. Chem. Soc.* (*C*), 1966, 2290; 1967, 1279, 2658; D. R. Sutherland and G. Tennant, *Chem. Comm.*, 1969, 423.



(12) R
a; Me
b; Ph



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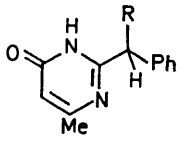


(14) R
a; H
b; OAc
c; $O_2C \cdot CF_3$
d; OH
e; Cl

poorly resolved quartet at τ 3·64 (1H) and a doublet at τ 7·31 (3H) in the ranges expected for H-6 and the protons of the methyl group in (9a) or (10a) by analogy with *s*-triazolo[1,5-*a*]pyrimidines of closely related structure.[8] The presence of a fused 1,2,3-triazole nucleus is supported by the mass spectrum, which exhibited an abundant fragment ion at $(M^+ - N_2)$ as well as a strong parent ion. Scission [1] in hot acetic acid or in acetic acid containing acetyl chloride gave the acetoxybenzylpyrimidine (14b) and the chlorobenzylpyrimidine (14e), respectively. Hydrogenolysis of both of these products yielded the known [9] 2-benzyl-6-methylpyrimidin-4(3*H*)-one (14a). Scission of the product (X) in trifluoroacetic acid occurred more slowly than for 5,7-dimethyl-3-phenyl-*v*-triazolo[3,4-*a*]pyrimidine.[1] Initially, the ^{1}H n.m.r. spectrum in trifluoroacetic acid (Table 1) shows a poorly resolved quartet at τ 3·07 (1H) and a doublet at τ 7·07 (3H) consistent with the presence of the ring-closed form (9a) or (10a). With time (Table 2) these signals diminish and are replaced by singlets at τ 2·79 (1H), 3·15 (1H), and 7·37 (3H) in the ranges expected [by analogy with the ^{1}H n.m.r. absorption of the acetoxybenzylpyrimidine (14b) (Table 2)] for H-5 and the benzylic and methyl protons of the trifluoroacetoxybenzylpyrimidine (14c). Ultimately (Table 2) the spectrum becomes identical with that of the alcohol (14d) derived by alkaline hydrolysis of the acetoxy-compound (14b). Gradual contamination of the trifluoroacetic acid solution by atmospheric moisture accounts for the observed hydrolysis [(14c) ⟶ (14d)].

With the object of establishing the precise structure of the product (X) the unambiguous synthesis of structures

TABLE 1

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

Compound	Solvent [b]	H-6	Me-5	Me-7	ArH	Others
(9a)	A	4·22	7·59			
(10a)	A	3·64 [c]		7·31 [d]	1·55—1·70 (m) [e] 2·05—2·35 (m) [f]	
	B [g]	3·07 [c]		7·07 [d]	2·28 (m)	
(9b) [h]	A	4·16 [c,i]	7·58 [j]			1·94br [k] 2·40br [k]
	B [l]	3·40 [c,m]	7·30 [j]			2·40br [k]
(10b) [h]	A	3·75 [c,i]		7·36 [n]		1·94br [k] 2·40br [k]
	B	3·30 [j]		7·08 [j]		2·40br [k]
(12a) [o]	A	2·75	7·35	7·14		

[a] Signals were sharp singlets unless otherwise designated. [b] A, $(CD_3)_2SO$; B, $CF_3 \cdot CO_2H$. [c] Becomes a poorly resolved quartet on expansion to 100 Hz. [d] Becomes a doublet (*J* 1·1 Hz) on expansion to 100 Hz. [e] 2H. [f] 3H. [g] Spectrum in trifluoroacetic acid run immediately. [h] Part spectrum of the mixture of (9b) and (10b). [i] *J* 0·4—0·5 Hz. [j] Not resolved on expansion to 100 Hz. [k] NH. [l] Spectrum unchanged after 8 days at room temperature. [m] *J* 1·0 Hz. [n] Becomes a doublet (*J* 0·4—0·5 Hz) on expansion to 100 Hz. [o] Signals are 0·37 p.p.m. upfield from reported values (*cf.* ref. 1) owing to an error in the position of the lock signal in spectra recorded previously (*cf.* ref. 1).

TABLE 2

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

Compound	Solvent [b]	H-5	Me-6	Benzylic H	ArH	Others
(14a)	A	3·80	7·70	6·05	2·48—2·80 (m)	
	B	3·31	7·45	5·50	2·42—2·70 (m)	
(14b)	A	3·83	7·73 (d) [c]	3·53	2·30—2·50 (m) [d] 2·50—2·72 (m)	7·76 [e]
	B	3·24	7·42 (d) [c]	2·86	2·42 (m)	7·59 [e]
(14c) [g,h]	B	3·15	7·37	2·79	2·23	
(14d)	B	2·75	6·36	2·26	1·46 (m)	
(14e)	A	3·77	7·68	4·13	2·30—2·47 (m) [d] 2·53—2·70 (m) [f]	
	B	3·22	7·35	3·61	2·40br (m)	

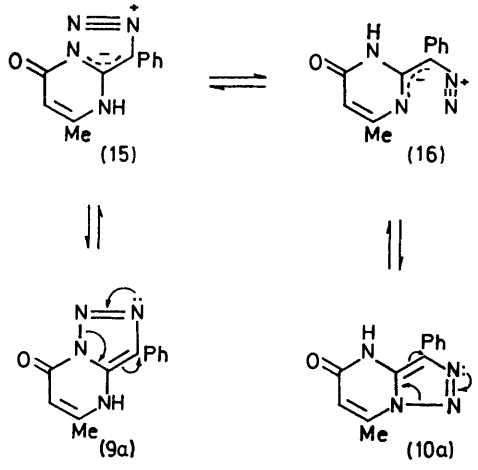
[a] Signals were sharp singlets unless otherwise designated. [b] A, $CDCl_3$; B, $CF_3 \cdot CO_2H$. [c] *J* 0·8 Hz. [d] 2H. OAc. [f] 3H. [g] Spectrum of compound (9a) run immediately, or of compound (10a) run after 2·0 h, in trifluoroacetic acid at room temperature. [h] After 48 h in trifluoroacetic acid, the spectrum becomes indentical with that of the alcohol (14d).

[8] H. Reimlinger and M. A. Peiren, *Chem. Ber.*, 1970, **103**, 3266.

[9] A. Pinner, *Ber.*, 1889, **22**, 1612.

(9a) and (10a) by cyclisation of the condensates (5a) and (7a) was attempted. It has been shown [10] that condensation of an amino-1,2,4-triazole with the most electrophilic centre in a β-dicarbonyl compound under basic conditions involves initial attack at a ring N-atom, whereas mildly acidic media promote reaction at the primary amino-group. However, the general validity of these observations has been questioned.[11] In the present case, condensation of the amino-1,2,3-triazole (4a) with ethyl acetoacetate at room temperature under both basic and mildly acidic conditions yielded the same product, whose spectral properties are consistent with either of the vinylaminotriazole formulae (5a) or (6a). The former structure is established by the absence of a diazotisable centre and the formation of a monoacetyl derivative (5b) which shows i.r. carbonyl and ^{1}H n.m.r. absorption characteristic [5] of a 1,2,3-triazole ring *N*-acetyl group. Formation of the compound (5a) under basic conditions implies attack at the primary amino-group in preference to reaction at a ring N-atom and contrasts with the reported [10] behaviour of amino-1,2,4-triazoles. However, this apparent inconsistency in the reactivity of amino-1,2,3-triazoles is explained if initial attack at a ring N-atom to give (6a) is followed by base-catalysed Dimroth rearrangement [12] to the more stable isomer (5a).[5] The condensation of ethyl acetoacetate with the aminotriazole (4a) in refluxing toluene occurred between the ester group and the primary amino-group to afford the acetoacetylaminotriazole (7a). The side-chain position for the acetoacetyl group in this product is consistent with the absence of a diazotisable centre and the formation of a ring *N*-acetyl derivative (7b). The possibility of structural ambiguity due to the operation of Dimroth rearrangement [5] [*i.e.* (7a) ⇌ (8a) ⇌ (8b) or (7a) ⇌ (7b) ⇌ (8b)] concurrent with acetylation is excluded by the regeneration of the acetoacetylaminotriazole (7a) from the acetyl derivative (7b) by mild hydrolysis. Preferential condensation at the primary amino-group rather than at a ring N-atom is further demonstrated by the failure of the acetylaminotriazole (4b) [1] to condense with ethyl acetoacetate in refluxing toluene.

Both condensates (5a) and (7a) underwent piperidine-catalysed cyclisation to afford the same product, which, after purification, proved to be identical with the compound (X). This unexpected result is most readily explained in terms of Dimroth rearrangement prior to [(5a) ⇌ (6a) or (7a) ⇌ (8a)] or subsequent to [(9a) ⇌ (15) ⇌ (16) ⇌ (10a); *cf.* Scheme 1] cyclisation. Dissociation of either substrate (5a) or (7a) into the amino-1,2,3-triazole (4a) and ethyl acetoacetate (or an equivalent fragment) and subsequent recondensation at the alternative carbonyl centre in the latter is also a possible course (see later) which finds analogy in the condensation reactions of ethyl acetoacetate with aniline.[13] Rearrangement prior to cyclisation, though possible (see later), cannot be a major pathway since the formation of (X) by such a process would require the complete transformation under equilibrium conditions of one or other of the compounds (5a) or (7a) into the isomers (6a) or (8a), which are disfavoured on the grounds of lower stability (presence of an electron-withdrawing group on a ring N-atom [5]) and

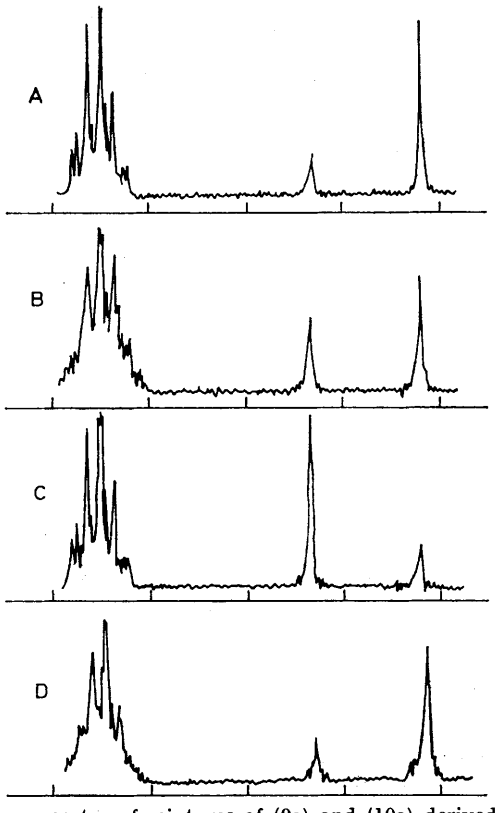


SCHEME 1

lower acidity (absence of triazole NH). However, the operation of rearrangement subsequent to cyclisation was revealed by a careful examination of the crude *v*-triazolopyrimidine product before purification. The ^{1}H n.m.r. spectrum in [$^2H_6$]dimethyl sulphoxide (Figure, A) of a sample *dried at room temperature* contained a poorly resolved quartet at τ 4·22 (1H) and a doublet at τ 7·59 (3H) at higher field than the proton resonances of H-6 and the methyl group in the pure compound (X), and attributable to a different species (Y). Compound (X) was also present to the extent of *ca.* 20% (as estimated from the integrated ratio of the H-6 signal in both species; *cf.* Figure, A), but increased in proportion (Figure, B) and ultimately became the predominant component (Figure, C) when the sample was heated at 140°. Attempted crystallisation of the impure sample of (Y) from ethanol also tended to promote the transformation (Y) ⟶ (X). On the other hand, heating for a short time with piperidine in ethanol reconverted the pure compound (X) mainly into compound (Y) (Figure, D), demonstrating the reversibility of the process (Y) ⇌ (X). The isomeric relationship of (Y) to (X) is supported by analytical and mass spectral data, and also by the reaction of (Y) with hot acetic acid or cold trifluoroacetic acid (*cf.* Tables 2 and 3) to afford the acetoxybenzyl- and trifluoroacetoxybenzyl-pyrimidines (14b and c), respectively. The interconversion of the compounds (X) and (Y) is most readily interpreted in terms of a new type of reversible Dimroth

[10] L. A. Williams, *J. Chem. Soc.*, 1961, 3046.
[11] E. C. Taylor and R. W. Hendess, *J. Amer. Chem. Soc.*, 1965, **87**, 1980.
[12] E. Lieber, T. S. Chao, and C. N. R. Rao, *J. Org. Chem.*, 1957, **22**, 654.
[13] C. R. Hauser and G. A. Reynolds, *J. Amer. Chem. Soc.*, 1948, **70**, 2402.

rearrangement [(9a) ⇌ (15) ⇌ (16) ⇌ (10a)] associated with a prototropic shift (*cf.* Scheme 1). The 7-oxo-structure (9a) is assigned to the base-stable isomer



^{1}H N.m.r. spectra of mixtures of (9a) and (10a) derived (a) by piperidine-catalysed condensation of ethyl acetoacetate with the aminotriazole (4a) followed by drying the product A, at room temperature; B, at 140° for 10 min; or C, at 140° for 60 min, or (b) by heating pure (10a) with ethanolic piperidine, followed by drying the product, D, at room temperature

[compound (Y)] in anticipation [10] of its greater acidity relative to the 5-oxo-isomer (10a). The assignment of the latter structure to the thermally stable isomer [compound (X)] is in accord with the expected [8] lower field position for the proton resonances of H-6 and the C-7 methyl group compared with those in the 7-oxo-structure (9a). The ^{1}H n.m.r. spectrum of impure (9a) in trifluoroacetic acid (Tables 2 and 3) shows immediate ring-opening to the trifluoroacetoxypyrimidine (14c), whereas scission of the contaminant (10a) occurs much more slowly. The greater rate of scission in the case of (9a) can be attributed to the greater destabilisation inherent in the direct attachment of a carbonyl group to a triazole ring N-atom and further supports the structures assigned to (9a) and (10a).

TABLE 3

Triazole scission of the *v*-triazolo[3,4-*a*]pyrimidines (9a) and (10a) in trifluoroacetic acid at room temperature [a]

Substrate composition (%) [b]		Product composition (%) [c]		
(9a)	(10a)	(9a)	(10a)	(14c)
80	20	0	14—17	83—86
52	48	0	46	54
0	100	0	77	23

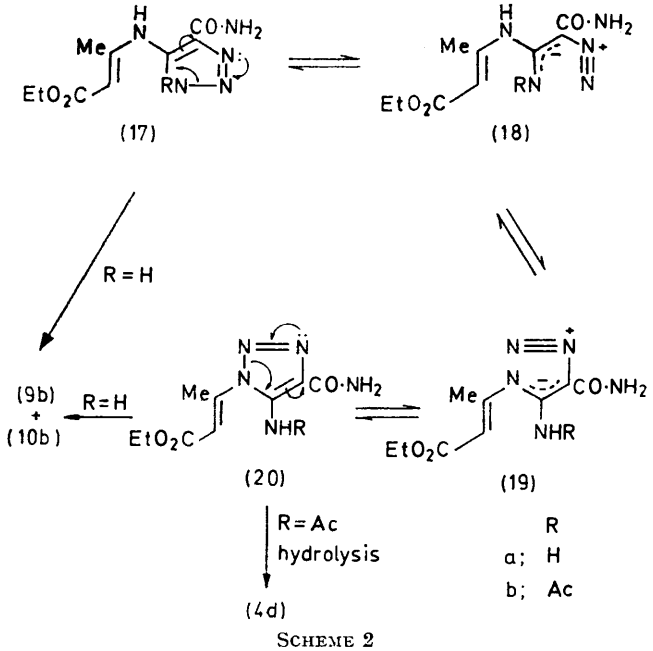
[a] Detected by the ^{1}H n.m.r. absorption at 100 MHz of a trifluoroacetic acid solution aged at room temperature for *ca.* 5 min. [b] Estimated from the integrated ratio of the Me-5 and Me-7 proton resonances of mixtures of (9a) and (10a), respectively. [c] Estimated from the integrated ratio of the Me-7 and Me-6 proton resonances of (10a) and (14c), respectively.

Piperidine in ethanol also catalysed the condensation of ethyl acetoacetate with the amino-1,2,3-triazolecarboxamide (4c). The product gave analytical and mass spectral data consistent with the formula $C_7H_7N_5O_2$ and showed i.r. absorption at 3350—3200 (>NH) and 1670 (>C=O) cm^{-1} in accord with either of the expected *v*-triazolo[3,4-*a*]pyrimidinecarboxamide structures (9b) and (10b). However, the ^{1}H n.m.r. spectrum in [$^2H_6$]-dimethyl sulphoxide showed poorly resolved quartets at τ 3·75 and 4·16 (each 1H) and a singlet and a doublet at τ 7·36 and 7·58 (each 3H) consistent with the presence of *both* isomers (9b) and (10b). Attempts to separate the mixture were unsuccessful. The isomer mixture was also formed when the amide (4c) was heated with ethyl acetoacetate in glacial acetic acid alone or in the presence of dimethylformamide. The acetylaminotriazolecarboxamide (4d) was a by-product of the former reaction. The lack of triazole scission under these conditions is in accord with the stabilising effect of the carboxamide group,[1] which also accounts for the stability of the isomer mixture to prolonged treatment with acetic and trifluoroacetic acids. The relative stability of the structures (9b) and (10b) to nitrogen loss is also demonstrated by the mass spectrum of the isomer mixture, which contains a strong molecular ion but lacks a fragment ion corresponding to ($M^+ - N_2$). Instead, the primary fragmentation process corresponds to the formation of an ion ($M^+ - 83$). The mass spectra of the *v*-triazolopyrimidine carboxamides (12a and b) [1] show similar primary fragment ions which may be formed by H-atom transfer and loss of the side-chain in radical cations derived from ring-opened structures of the type (13).

The inertness of the structures (9b) and (10b) to triazole scission implies a reluctance to undergo the ring opening [*cf.* Scheme 1; (9a; CO·NH$_2$ for Ph) ⇌ (15; CO·NH$_2$ for Ph)], which is a prerequisite of Dimroth rearrangement [(9b) ⇌ (10b)]. It was anticipated therefore, that the specific cyclisation of the condensates (5c) and (7c) to the structures (9b) and (10b) would be uncomplicated by their subsequent interconversion and so should provide a means for their unambiguous synthesis. Attempts to condense the amide (4c) with ethyl acetoacetate alone or in refluxing toluene either failed or gave the isomer mixture, thereby precluding the study of the acetoacetylaminotriazolecarboxamide (7c). In contrast, condensation of the amide (4c) with ethyl acetoacetate occurred smoothly in dimethylformamide at room temperature to give the vinylaminotriazole (5c), which was isolated as the hydrate. The structure of this product follows from its spectral properties and

from its conversion by acetylation into a ring *N*-acetyl derivative (5d). The attempted reconversion of this derivative by mild hydrolysis into the parent vinylaminotriazole (5c) resulted in complete degradation to the amide (4c). The structure (5c) is further supported by the failure of the acetylaminotriazole (4d) to condense with ethyl acetoacetate in the presence of acetic acid, demonstrating preferential attack on the primary amino-group under these conditions.[10]

Heating the vinylaminotriazole (5c) with piperidine in ethanol afforded not the single isomer (9b) but, contrary to expectations, the isomer mixture [(9b) + (10b)]. The isomer mixture was also the product when the compounds (5c and d) were heated under reflux with glacial acetic acid or when they were left in contact with cold aqueous alkali for a short time. Since Dimroth rearrangement before and after cyclisation is unlikely (see before), the formation of the isomer



SCHEME 2

mixture from the compound (5c) is most readily explained by a course involving dissociation–recombination (see before). Support for a dissociation–recombination mechanism is provided by reaction of the compound (5c) with acetylacetone alone, or in the presence of piperidine or glacial acetic acid, to give 5,7-dimethyl-*v*-triazolo[3,4-*a*]pyrimidine-3-carboxamide (12a),[1] which was also formed when the aminotriazolecarboxamide (4c) was heated in neat acetylacetone. The synthesis of (12a) from the amide (4c) and acetylacetone in piperidine–ethanol or acetic acid has already been described.[1] On the other hand, the observed formation of the isomer mixture from (5c) in the melt is difficult to reconcile with such a mechanism and indicates that rearrangement may become possible at elevated temperatures. Support for the operation of Dimroth rearrangement prior to cyclisation (*cf.* Scheme 2; R = H) under thermal conditions is provided by the conversion of the *pure* compound (5c) in refluxing toluene into a mixture of the starting compound and a component whose ^{1}H n.m.r. absorption is consistent with the isomeric structure (6c). Significantly, the observed ratio of (5c) to (6c) corresponds within experimental error to the proportions of (9b) and (10b) in the isomer mixture. The operation of a similar rearrangement process [(17b) ⇌ (18b) ⇌ (19b) ⇌ (20b)] before hydrolysis [(20b) ⇌ (4d)] provides a rationale for the conversion of the acetyl derivative (5d) in warm aqueous ethanol into a mixture of the acetamidotriazole (4d) and the parent amide (4c). However, in this case the acetyl group may play a crucial role [5] in promoting rearrangement.

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, or trifluoroacetic acid, at 28°, with tetramethylsilane as internal standard, with a Varian HA 100 instrument. Mass spectra were recorded at 70 eV and 150° (probe temperature) with an A.E.I. MS 902 spectrometer.

Light petroleum had b.p. 60—80°.

*5-Amino- and 5-Acetamido-*1H-1,2,3-*triazoles* (4).—5-Amino-4-phenyl-1*H*-1,2,3-triazole (4a) and 5-amino-1*H*-1,2,3-triazole-4-carboxamide (4c) were prepared as described previously.[1]

Heating the aminotriazolecarboxamide (4c) in glacial acetic acid gave the acetic acid solvate * of the monoacetyl compound (4d), m.p. 269—272° (from glacial acetic acid), $\nu_{max.}$ 3350, 3200br, and 2700br (OH, NH), 1710, and 1690 (CO), and 1670 cm^{-1}, τ [$(CD_3)_2SO$] −0·05br (1H, s, OH), 2·16br (1H, s, NH), 2·47 (1H, s, NH), 7·84 (3H, s, Ac), and 8·10 (3H, s, Ac), which was converted by crystallisation from water into the acetamidotriazolecarboxamide (4d), m.p. 270—273° (lit.,[14] 268°), $\nu_{max.}$ 3400, 3250, and 3100 (NH), and 1680 (CO) cm^{-1}, τ [$(CD_3)_2SO$] 2·18br (1H, s, NH), 2·49br (1H, s, NH), and 7·84 (3H, s, Ac).

*5-(2-Ethoxycarbonyl-1-methylvinylamino)-4-phenyl-*1H-1,2,3-*triazole* (5a).—(*a*) A solution of the aminotriazole (4a) (4·8 g, 0·03 mol) and ethyl acetoacetate (4·3 g, 4·2 ml, 0·033 mol) in anhydrous benzene (250 ml) was heated under reflux with glacial acetic acid (0·5 ml) for 18 h. Evaporation of the mixture gave an oil which afforded the solid product (5a) (5·6 g) in contact with benzene–light petroleum.

(*b*) The *vinylaminotriazole* (5a) was also formed (0·4 g) by heating a mixture of the aminotriazole (4a) (0·4 g, 0·0025 mol) and ethyl acetoacetate (0·7 g, 0·7 ml, 0·0054 mol) under reflux (24 h) with a solution of sodium (0·23 g) in absolute ethanol (10·0 ml). The mixture was evaporated, treated with water and dilute aqueous sulphuric acid, and neutralised with aqueous ammonia. The product had m.p. 123° (from benzene–light petroleum), $\nu_{max.}$ 3200 (NH), 1640 (CO), and 1620br (C=C) cm^{-1}, τ ($CDCl_3$) 2·13—2·28 (2H, m, ArH), 2·45—2·75 (3H, m, ArH), 5·17 (1H, d, *J* 0·8 Hz, olefinic CH), 5·80 (2H, q, *J* 7 Hz, CH_2), 8·01 (3H, d, *J* 0·8 Hz, Me), and 8·71 (3H, t, *J* 7 Hz, Me) (Found: C, 61·7; H, 5·8; N, 20·5%; M^+, 272. $C_{14}H_{16}N_4O_2$ requires

* This product was formulated previously (*cf.* ref. 1) as a diacetyl derivative.

[14] L. L. Bennett and H. T. Baker, *J. Org. Chem.*, 1957, **22**, 707.

C, 61·8; H, 5·9; N, 20·6%; *M*, 272), and was converted by heating under reflux (15 min) with acetic anhydride into the *acetyl derivative* (5b) (96%), m.p. 115° (from benzene–light petroleum), $\nu_{max.}$ 3150 (NH), 1735 and 1665 (CO), and 1640 (C=C) cm^{-1}, τ ($CDCl_3$) 2·05—2·15 (2H, m, ArH), 2·35—2·50 (3H, m, ArH), 5·05 (1H, s, olefinic CH), 5·85 (2H, q, *J* 7 Hz, CH_2), 7·23 (3H, s, Ac), 7·60 (3H, s, Me), and 8·75 (3H, t, *J* 7 Hz, Me) (Found: C, 61·0; H, 5·7; N, 18·0. $C_{16}H_{18}N_4O_3$ requires C, 61·1; H, 5·7; N, 17·8%).

5-(2-*Ethoxycarbonyl*-1-*methylvinylamino*)-1H-1,2,3-*triazole*-4-*carboxamide* (5c).—A mixture of the amide (4c) (1·3 g, 0·01 mol) and ethyl acetoacetate (1·5 g, 1·5 ml, 0·011 mol) in dimethylformamide (7·0 ml) containing glacial acetic acid (1·0 ml) was stirred at room temperature for 16 h. The mixture was diluted with water (10·0 ml) and the precipitated solid was combined with a second crop obtained by evaporating the mother liquor and treatment with water, washed with ether, and crystallised to afford the *hydrate* of the vinylaminotriazole amide (5c) (1·4 g), m.p. 175° (from ethanol), $\nu_{max.}$ 3450, 3375, and 3150 (NH), 1660br (CO), and 1610 (C=C) cm^{-1}, τ [$(CD_3)_2SO$] 2·24br (1H, s, NH), 2·56br (1H, s, NH), 5·22 (1H, s, olefinic CH), 5·93 (2H, q, *J* 7 Hz, CH_2), 7·68 (3H, s, Me), and 8·82 (3H, t, *J* 7 Hz, Me) (M^+, 239. $C_9H_{13}N_5O_3$ requires *M*, 239) (Found: C, 42·0; H, 5·7; N, 27·7. $C_9H_{13}N_5O_3,H_2O$ requires C, 42·0; H, 5·8; N, 27·2%), which formed a sparingly soluble salt in dilute aqueous sodium hydroxide and was recovered unchanged on acidification. The hydrate of (5c) was converted in hot acetic anhydride into the *acetyl derivative* (5d) (83%), m.p. 196° (from ethyl acetate), $\nu_{max.}$ 3400, 3250, and 3200 (NH), and 1770, 1690, and 1670 (CO) cm^{-1}, τ [$(CD_3)_2SO$] 1·78br (1H, s, NH), 2·16br (1H, s, NH), 5·07 (1H, s, olefinic CH), 5·90 (2H, q, *J* 7 Hz, CH_2), 6·70 (3H, s, Me), 7·29 (3H, s, Ac), and 8·80 (3H, t, *J* 7 Hz, Me) (Found: C, 47·3; H, 5·3; N, 25·2. $C_{11}H_{15}N_5O_4$ requires C, 47·0; H, 5·3; N, 24·9%).

Heating the compound (5c) (0·48 g, 0·002 mol) under reflux in toluene (300 ml) for 2 or 18 h, followed by evaporation of the solution gave a solid (0·41 g) whose ^1H n.m.r. spectrum, τ [$(CD_3)_2SO$] 2·24br (s, NH), 2·56br (s, NH), 3·65 [s, olefinic CH of (6c)] 4·20br (s, NH), 5·20 [s, olefinic CH of (5c)], 5·91 [dq, overlapping CH_2 of (5c) and (6c)], 7·59 [s, olefinic Me of (6c)], 7·66 [s, olefinic Me of (5c)], and 8·80 [dt, overlapping Me of (5c) and (6c)], was consistent with a mixture of (5c) (80%) and (6c) (20%). Attempts to separate the mixture by fractional crystallisation or chromatography were unsuccessful.

The acetyl derivative (5d) (0·14 g) slowly dissolved when it was stirred at room temperature with a mixture of aqueous N-sulphuric acid (3·0 ml) and ethanol (5·0 ml). After 1 h the ethanol was evaporated off under reduced pressure at room temperature, and the solution filtered. The aqueous mother liquor was adjusted to pH 7 to afford the amide (4c) (0·03 g), m.p. 223° (from water), identical (mixed m.p. and i.r. spectrum) with an authentic sample.[1]

The compound (5d) (0·28 g) was heated under reflux in aqueous 75% w/v ethanol (10·0 ml) for 10 min. Concentration and dilution with water gave the acetamidotriazole (4d) (0·1 g), m.p. and mixed m.p. 270—273° (decomp.), identical (i.r. and ^1H n.m.r. spectra) with a sample prepared before. The colourless solid isolated by evaporating the aqueous filtrate was crystallised to yield the triazolecarboxamide (4c) (0·06 g), identified by comparison (m.p., mixed m.p., and i.r. spectrum) with an authentic sample.[1]

The amide (4d) (0·84 g, 0·0055 mol) was stirred with ethyl acetoacetate (0·72 g, 0·7 ml, 0·0055 mol) and glacial acetic acid (0·5 ml) in dimethylformamide (7·5 ml) at room temperature for 17 h. The mixture was evaporated and treated with water to give unchanged amide (4d) (77%).

5-*Acetoacetamido*-4-*phenyl*-1H-1,2,3-*triazole* (7a).—A mixture of the aminotriazole (4a) (3·2 g, 0·02 mol) and ethyl acetoacetate (2·6 g, 2·5 ml, 0·02 mol) in anhydrous toluene (500 ml) was heated under reflux for 7 h. The ethanol formed was allowed to distill through a short Vigreux column. The solution was concentrated to 250 ml and cooled, and the solid was collected, combined with a second crop obtained by evaporating the mother liquors, and crystallised to yield the *acetoacetamidotriazole* (7a) (3·1 g), m.p. 161° (from benzene–ethanol), $\nu_{max.}$ 3150 and 3050 (NH), and 1695 (CO) cm^{-1}, τ ($CDCl_3$) 2·51—2·85 (5H, m, ArH), 6·25 (2H, s, CH_2), and 7·65 (3H, s, Me) (Found: C, 58·9; N, 4·9; N, 23·1%; M^+, 244. $C_{12}H_{12}N_4O_2$ requires C, 59·0; H, 4·9; N, 23·0%; *M*, 244), which was converted in hot acetic anhydride into the *acetyl derivative* (7b) (90%), m.p. 182° (from benzene–light petroleum), $\nu_{max.}$ 3150 (NH), 1750, 1720, and 1680 (CO) cm^{-1}, τ ($CDCl_3$) 2·15—2·35 (2H, m, ArH), 2·42—2·62 (3H, m, ArH), 6·28 (2H, s, CH_2), 7·20 (3H, s, Ac), and 7·68 (3H, s, Ac) (Found: C, 59·0; H, 5·1; N, 20·3. $C_{14}H_{14}N_4O_3$ requires C, 58·7; H, 4·9; N, 19·6%). Hydrolysis of the compound (7b) by heating under reflux (0·5 h) with aqueous 10% w/v sodium hydroxide, and careful neutralisation with aqueous dilute sulphuric acid, gave the parent triazole (7a) (50%).

The triazole derivatives (4b) and (4c), heated under reflux with ethyl acetoacetate in anhydrous toluene as described before, were recovered unchanged (93—97%).

5-*Methyl*-3-*phenyl*-v-*triazolo*[3,4-a]*pyrimidin*-7(4H)-*one* (9a) *and* 7-*Methyl*-3-*phenyl*-v-*triazolo*[3,4-a]*pyrimidin*-5(4H)-*one* (10a).—(*a*) The amino-1,2,3-triazole (4a) (3·2 g, 0·02 mol) and ethyl acetoacetate (2·9 g, 2·8 ml, 0·022 mol) were heated under reflux with piperidine (0·5 ml) in ethanol (70·0 ml) for 27 h. Alternatively (*b*) the triazole derivative (5a) or (7a) (0·001 mol) was heated under reflux with piperidine (0·25 ml) in ethanol (10·0 ml) for 24 h. The gum obtained by evaporating the mixture was dissolved in warm water and acidified with dilute aqueous sulphuric acid. After drying *in vacuo* at room temperature, the ^1H n.m.r. spectrum [$(CD_3)_2SO$] (Figure, A) of the solid obtained (80—90%) showed it to be a mixture of the *v*-triazolopyrimidines (9a) (80%) and (10a) (20%), m.p. 232—234°, $\nu_{max.}$ 3100sh and 2700sh (NH), and 1660br (CO) cm^{-1} (Found: C, 63·8; H, 4·5; N, 24·7%; M^+, 226. $C_{12}H_{10}N_4O$ requires C, 63·7; H, 4·4; N, 24·8%; *M*, 226). Heating this solid at 140° for 2·0 h followed by crystallisation from ethanol gave the pure v-*triazolo*[3,4-a]*pyrimidine* (10a) (quant.), m.p. 240° (from ethanol), $\nu_{max.}$ 3150sh and 2700sh (NH), and 1665br (CO) cm^{-1}, $\lambda_{max.}$ 210, 243, 250sh, 276infl, 294infl, and 325 nm (log ε 4·22, 4·30, 4·28, 3·94, 3·62, and 3·39), *m/e* 226 (48%, M^+) and 198 (68, $M^+ - N_2$) (^1H n.m.r. data are shown in Table 1 and the Figure) (Found: C, 63·6; H, 4·5; N, 24·9. $C_{12}H_{10}N_4O$ requires C, 63·7; H, 4·4; N, 24·8%), which was reconverted into the isomer mixture of (9a) (80%) and (10a) (20%) (quant.) by heating with piperidine in ethanol and work-up as described before.

2-(α-*Acetoxybenzyl*)-6-*methylpyrimidin*-4(3H)-*one* (14b).—(*a*) A mixture of the aminotriazole (4a) (0·4 g) and ethyl acetoacetate (0·39 g, 0·38 ml) was heated under reflux in glacial acetic acid (5·0 ml) for 14 h. Alternatively (*b*) the *v*-triazolo[3,4-*a*]pyrimidine (10a) or the isomer mixture containing predominantly (9a) (see before) (0·0025 mol)

was heated under reflux in glacial acetic acid (25·0 ml) for 4 h. Evaporation gave a gum which was triturated with ether–light petroleum to yield the solid *acetoxybenzylpyrimidine* (14b) (60—90%), m.p. 187° (from benzene–light petroleum), $\nu_{max.}$ 3100sh and 2700sh (NH), and 1745 and 1660 (CO) cm^{-1} (^1H n.m.r. data in Table 2) (Found: C, 65·0; H, 5·8; N, 10·9. $C_{14}H_{14}N_2O_3$ requires C, 65·1; H, 5·4; N, 10·9%).

When reaction (*a*) was carried out for 3·5 h, the product was the acetamidotriazole (4b) (82%), m.p. 204° (from benzene–ethanol), identical (mixed m.p. and i.r. spectrum) with an authentic sample.[1]

2-(α-*Hydroxybenzyl*)-6-*methylpyrimidin*-4(3H)-*one* (14d).—The acetoxybenzylpyrimidine (14b) (0·8 g) was heated under reflux with aqueous 10% w/v sodium hydroxide (5·0 ml) in ethanol (20·0 ml) for 30 min. Evaporation of the mixture gave a gum which was dissolved in water, acidified (aqueous dilute sulphuric acid), and adjusted to pH 7 with solid sodium hydrogen carbonate. The solid *alcohol* (14d) was collected and crystallised (0·56 g), m.p. 199° (from benzene–light petroleum), $\nu_{max.}$ 3400, 3150, and 2750 (NH), and 1665 (CO) cm^{-1} (^1H n.m.r. data in Table 2) (Found: C, 66·4; H, 5·7; N, 13·3. $C_{12}H_{12}N_2O_2$ requires C, 66·7; H, 5·6; N, 13·0%).

2-(α-*Chlorobenzyl*)-6-*methylpyrimidin*-4(3H)-*one* (14e).—The *v*-triazolopyrimidine (10a) or the isomer mixture in which (9a) predominates (0·004 mol) was heated under reflux with a mixture of acetyl chloride (30·0 ml) and glacial acetic acid (10·0 ml) for 1·75 h. Evaporation gave an oil which afforded the solid *chlorobenzylpyrimidine* (14e) in contact with benzene–light petroleum (61%), m.p. 194° (from ethanol), $\nu_{max.}$ 3200sh and 2750sh (NH) and 1680 (CO) cm^{-1} (^1H n.m.r. data in Table 2) (Found: C, 61·6; H, 4·9; N, 12·2. $C_{12}H_{11}ClN_2O$ requires C, 61·3; H, 4·7; N, 11·9%).

2-*Benzyl*-6-*methylpyrimidin*-4(3H)-*one* (14a).—The pyrimidine derivative (14b) or (14e) (0·001 mol), hydrogenolysed in ethanol over 10% palladium–charcoal, gave 2-benzyl-6-methylpyrimidin-4(3*H*)-one (14a) (62—82%), m.p. 175° (from water), $\nu_{max.}$ 3050sh and 2700sh (NH) and 1680 (CO) cm^{-1}, identical (mixed m.p. and i.r. spectrum) with an authentic sample.[9]

4,7-*Dihydro*-5-*methyl*-7-*oxo*-v-*triazolo*[3,4-a]*pyrimidine*-3-*carboxamide* (9b) *and* 4,5-*Dihydro*-7-*methyl*-5-*oxo*-v-*triazolo*-[3,4-a]*pyrimidine*-3-*carboxamide* (10b).—The isomer mixture (9b) and (10b) was formed (60—90%), (*a*) when the vinylaminotriazole (5c) (12·0 g, 0·05 mol) or a mixture of the aminotriazolecarboxamide (4c) (6·4 g, 0·05 mol) and ethyl acetoacetate (7·0 g, 6·8 ml, 0·054 mol) was heated under reflux with piperidine (2·5 ml) in ethanol (600 ml) for 24 h, or in glacial acetic acid (200 ml) for 4 h, and the mixture then evaporated and treated with aqueous dilute sulphuric acid or water, (*b*) when the vinylaminotriazole (5c) or (5d) (0·0005 mol) was stirred at room temperature for 5 min in aqueous N-sodium hydroxide (1·0 ml), and the solution obtained acidified (aqueous dilute sulphuric acid), (*c*) when the amide (4c) (0·32 g) and ethyl acetoacetate (0·4 g, 0·39 ml) were heated under reflux in dimethylformamide (4·0 ml) containing glacial acetic acid (0·25 ml) for 1·5 h, and the mixture was evaporated and treated with water, (*d*) when a mixture of the amide (4c) (0·64 g) and ethyl acetoacetate (15·0 ml) was heated under reflux for 4 h, concentrated, and diluted with ether, or (*e*) when the ethylideneaminotriazole (5c) (0·1 g) was melted at 180° on a Kofler block, and the solid which crystallised in the melt was purified. The isomer mixture had the composition (9b) (72%), (10b) (28%) as estimated from the integrated ratio of the H-6 signal in the ^1H n.m.r. spectrum (Table 1) of the mixture in [$^2H_6$]dimethyl sulphoxide; m.p. 274—275° (from glacial acetic acid–ethanol), $\nu_{max.}$ 3350, 3250br, and 3200br (NH), 1670 (CO), and 1640 (NH def.) cm^{-1}, $\lambda_{max.}$ 210, 243, 250sh, 276infl, 294infl, and 325 nm (log ε 4·22, 4·30, 4·28, 3·94, 3·62, and 3·39), *m/e* 193 (75%, M^+) and 110 (75, $M^+ - 83$) (Found: C, 43·4; H, 3·6; N, 36·4. Calc. for $C_7H_7N_5O_2$: C, 43·5; H, 3·7; N, 36·3%). The mixture was unchanged (m.p., and i.r. and ^1H n.m.r. spectra) after heating under reflux with glacial acetic acid or ethanolic piperidine for 8 days.

Evaporation of the aqueous filtrate from the acetic acid-catalysed reaction of the compound (5c) in (*a*) gave a solid which was crystallised to afford the triazole amide (4c) (21%).

The solution obtained by heating the acetyl compound (5d) (0·28 g) under reflux (3 h) in glacial acetic acid (5·0 ml), on cooling deposited the acetamidotriazole (4d) (80%), identical (m.p., mixed m.p., and i.r. spectrum) with an authentic sample. Evaporation of the acetic acid mother liquor and treatment with ether gave the isomer mixture of (9b) and (10b) (0·05 g).

5,7-*Dimethyl*-v-*triazolo*[3,4-a]*pyrimidine*-3-*carboxamide* (12a).—(*a*) The aminotriazolecarboxamide (4c) (0·64 g, 0·005 mol) was heated under reflux in acetylacetone (15·0 ml) for 2·5 h. The mixture was cooled and the precipitated solid was combined with a second crop obtained by evaporating the filtrate and treatment with ether to give the *v*-triazolo[3,4-*a*]pyrimidine (12a) (0·91 g).

(*b*) The vinylaminotriazole (5c) (3·0 g, 0·0125 mol) was heated under reflux with acetylacetone (5·0 g, 5·2 ml, 0·05 mol) in glacial acetic acid (50·0 ml) for 4 h. Evaporation of the mixture gave a solid which was treated with water and ether, washed (ethanol then ether), and dried to give the product (12a) (0·73 g).

(*c*) The vinylaminotriazole (5c) (0·6 g, 0·0025 mol) was heated under reflux in acetylacetone (8·0 ml) for 4 h, or with acetylacetone (1·02 g, 1·0 ml, 0·01 mol) in the presence of piperidine (0·6 ml) in ethanol (25·0 ml) for 24 h. The mixture was evaporated and treated with ether, and the resulting solid (0·28—0·35 g) was suspended in water (3·0 ml), treated with piperidine (0·25 ml), and filtered off to yield the *v*-triazolopyrimidine (12a) (0·11—0·23 g). Acidification of the aqueous filtrate with aqueous dilute sulphuric acid gave the isomer mixture of (9b) and (10b) (0·08—0·17 g), identified by comparison (m.p., and i.r. and ^1H n.m.r. spectra) with a sample prepared before.

The *v*-triazolopyrimidine (12a) had m.p. 265° (from ethanol–acetic acid), *m/e* 191 (55%, M^+) and 108 (100, $M^+ - 83$) (^1H n.m.r. data in Table 1), and was identified by comparison (m.p., mixed m.p., and i.r. spectrum) with an authentic sample.[1]

Mass Spectral Data for v-*Triazolo*[3,4-a]*pyrimidines*.—The *v*-triazolopyrimidine (12a; Ph for $CO{\cdot}NH_2$) had *m/e* 224 (28%, M^+) and 196 (100, $M^+ - N_2$); compound (12b) had *m/e* 253 (100%, M^+) and 170 (100, $M^+ - 83$).

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