The Chemistry of Polyazaheterocyclic Compounds. Part VII.[1] Extensions of a *v*-Triazolo[1,5-*a*]quinazoline Synthesis and a New Route to 4-Aminoquinazoline Derivatives

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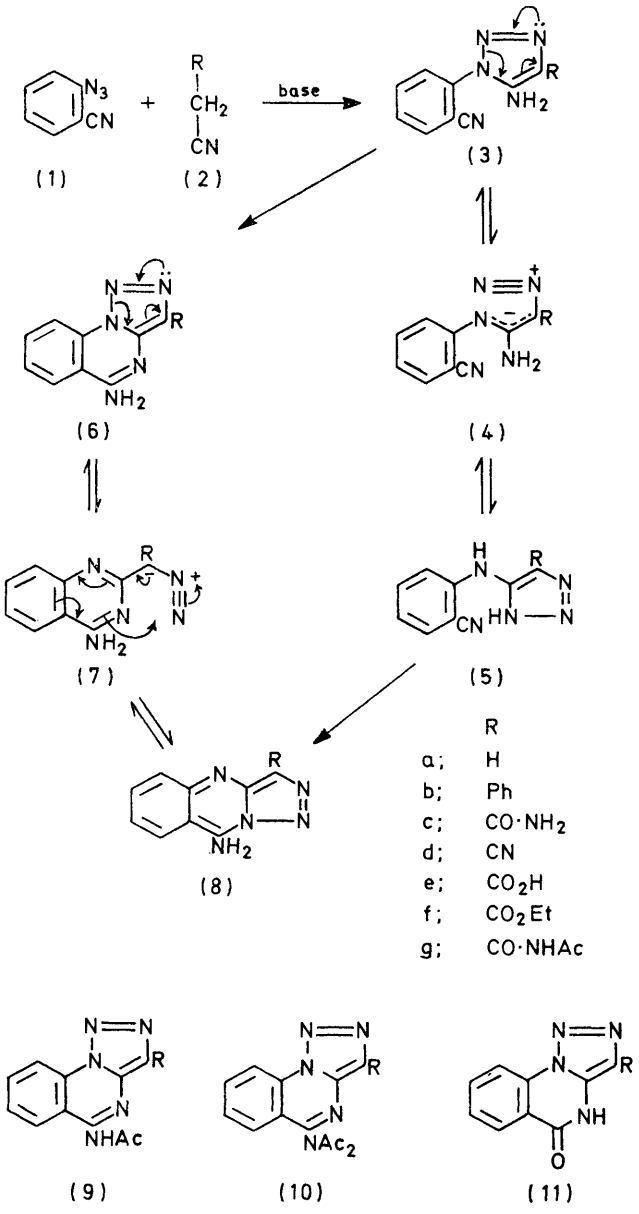
The base-catalysed condensation of *o*-azidobenzonitrile with active methylene compounds containing a cyano-group (phenylacetonitrile, cyanoacetic acid, ethyl cyanoacetate, cyanoacetamide, and malononitrile) gives high yields of 5-amino-*v*-triazolo[1,5-*a*]quinazolines (6). Breakdown of the triazole ring in these heterocycles occurs under a variety of acidic conditions affording new 4-aminoquinazoline derivatives.

FUSED *v*-triazoles containing a bridgehead nitrogen atom are of current interest as substrates for the *in situ* generation of a variety of reactive heterocyclic species, notably carbenes and nitrenes,[2] and diazonium cations.[3] The ' diazo-like ' reactivity of such fused triazoles can be explained in terms of diazoalkylideneamine–triazole ring–chain tautomerism, support for the existence of which has recently been presented.[1] As a continuation of these studies on the synthesis and reactivity of fused *v*-triazoles containing bridgehead nitrogen atoms, we now describe a synthetic route to 5-amino-*v*-triazolo-[1,5-*a*]quinazolines and their acid-catalysed conversion into relatively inaccessible 4-aminoquinazoline derivatives.[4]

o-Azidobenzoic acid condenses with phenylacetonitrile in the presence of base to afford[5] the *v*-triazolo[1,5-*a*]-quinazolone derivative (11b) in high yield. The readily available[6] *o*-azidobenzonitrile reacted similarly with phenylacetonitrile, cyanoacetamide, and malononitrile, in the presence of sodium methoxide to afford high-melting products whose properties and transformations are consistent with the amino-*v*-triazoloquinazoline structures (6b—d). The i.r. spectrum of the phenyl compound (6b) showed absorption due to a primary amino-group, but lacked bands attributable to a cyano-group thereby excluding the alternative[7] amino-*v*-triazole structure (3b). In accord with the primary amino-structure (6b), acetylation led to a readily separated mixture of the mono- and di-acetyl derivatives, (9b) and (10b). In the case of the nitrile (6d), the

[1] Part VI, D. R. Sutherland, G. Tennant, and R. J. S. Vevers, *J.C.S. Perkin I*, 1973, 943.
[2] W. D. Crow, M. N. Paddon-Row, and D. S. Sutherland, *Tetrahedron Letters*, 1972, 2239; R. Gleiter, C. Mayor, and C. Wentrup, *Helv. Chim. Acta*, 1972, **55**, 2628.
[3] 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.
[4] D. R. Sutherland and G. Tennant, *Chem. Comm.*, 1969, 423.
[5] G. Tennant, *J. Chem. Soc.* (*C*), 1966, 2290.
[6] M. O. Forster and H. M. Judd, *J. Chem. Soc.*, 1910, **97**, 254.
[7] O. Dimroth, *Annalen*, 1909, **364**, 183.

diacetyl derivative (10d) formed on acetylation was unstable and afforded the monoacetyl compound (9d) on attempted crystallisation. The amide (6c) gave a labile triacetyl product which is tentatively assigned



the structure (10g) on the basis of its i.r. and ^{1}H n.m.r. absorption and the known [8] capacity for a *v*-triazole carboxamide group to undergo acetylation. Partial hydrolysis of the triacetyl compound (10g) occurred in hydroxylic solvents giving a stable diacetyl product whose spectral properties are consistent with either of the possible structures (9g) and (10c).

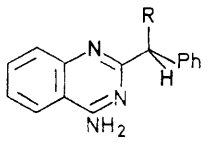
The angular structure (6b) for the phenyl compound {as opposed to the linear structure (8b), the end product of Dimroth rearrangement prior to [8] [(3) ⇌ (4) ⇌ (5)] or subsequent to [1] [(6) ⇌ (7) ⇌ (8)] cyclisation} was firmly established by its conversion by forcing alkaline hydrolysis into the known [5] triazoloquinazolone (11b). The angular structure of the amide (6c) and the nitrile (6d) follow from their similar conversion into the triazoloquinazolone (11c) of established constitution.[9] The hydrolysis of the amino-group involved in the transformations [(6b—d) ⟶ (11b or c)] is akin to the well known [10] hydrolysis of 4-aminoquinazolines to quinazolin-4(3*H*)-ones.

The ethoxide-catalysed condensation of ethyl cyanoacetate and cyanoacetic acid with *o*-azidobenzonitrile gave the same product, $C_9H_7N_5$, which showed i.r. absorption due to a primary amino-group, but lacked i.r. carbonyl absorption. Alkaline hydrolysis to the known [9] triazoloquinazolone (11a) identified this product as 5-amino-*v*-triazolo[1,5-*a*]quinazoline (6a). The ester (6f) and the acid (6e) are probable intermediates in the reactions of the azide (1) with ethyl cyanoacetate and cyanoacetic acid to give the amine (6a).

The absence of diazo-absorption at *ca.* 2200 cm^{-1} in the i.r. spectra of the triazoloquinazolines (6a—d) excludes the existence of ring–chain tautomerism [(6) ⇌ (7)], at least in the solid phase at room temperature. The insolubility of compounds (6a—d) precluded the study of their i.r. absorption in solution. However, as in *v*-triazolo[1,5-*a*]pyrimidines [1,11] and *v*-triazolo[1,5-*a*]quinazolones,[5] scission of the triazole ring in compounds (6a and b) occurred readily in acidic media. Heating the phenyl derivative (6b) in glacial acetic acid afforded a compound which could be crystallised unchanged from aprotic solvents and gave analytical data consistent with the molecular formula $C_{19}H_{19}N_3O_4$, corresponding to an acetic acid solvate of the expected [5] acetoxybenzylquinazoline scission product (12c). The spectral properties and transformations of the scission product are fully consistent with this structure. I.r. absorption at 3400—3200 and 1739 cm^{-1} can be attributed to a primary amino-group and an acetoxy carbonyl group, respectively; bands at 3100—2700 and 1695 cm^{-1} correspond to the hydroxy- and carbonyl-absorptions of acetic acid. The ^{1}H n.m.r. spectrum (solvent trifluoroacetic acid) contains signals at τ 3·02 and 7·57 assigned to the benzyl and acetoxy-groups, respectively, and a signal at τ 7·73 corresponds to the methyl absorption of acetic acid. Acetylation of the scission product yielded a monoacetyl derivative (13c), which was also the product when the acetamido-triazoloquinazoline (9b) was heated in acetic acid. Mild alkaline hydrolysis of the acetoxy-compound (12c) or of its acetyl derivative (13c) gave an amino-alcohol. The benzylic structure (12b) for this product follows from

[8] D. R. Sutherland and G. Tennant, *J. Chem. Soc.* (*C*), 1971, 706.
[9] G. Tennant, unpublished work.
[10] W. L. F. Armarego, in 'Quinazolines,' 'The Chemistry of Heterocyclic Compounds,' ed. A. Weissberger, Interscience-Wiley, New York, 1967, pp. 333—334.
[11] D. R. Sutherland and G. Tennant, *J. Chem. Soc.* (*C*), 1971, 2156.

its oxidation by manganese dioxide [12] to an amino-ketone (18a), which formed a monoacetyl derivative (18b), and was reconverted into the alcohol (12b) by



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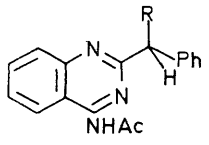

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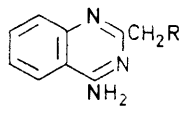

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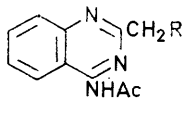
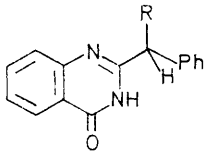


(15)

R	
a;	H
b;	OH
c;	OAc
d;	O·COCF$_3$
e;	Cl
f;	Br
g;	OEt



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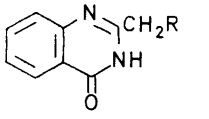
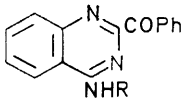
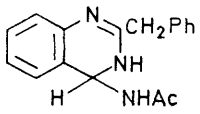


(17)

catalytic reduction. Catalytic reduction of the benzylic acetate (12c) resulted in its hydrogenolysis [5] to the



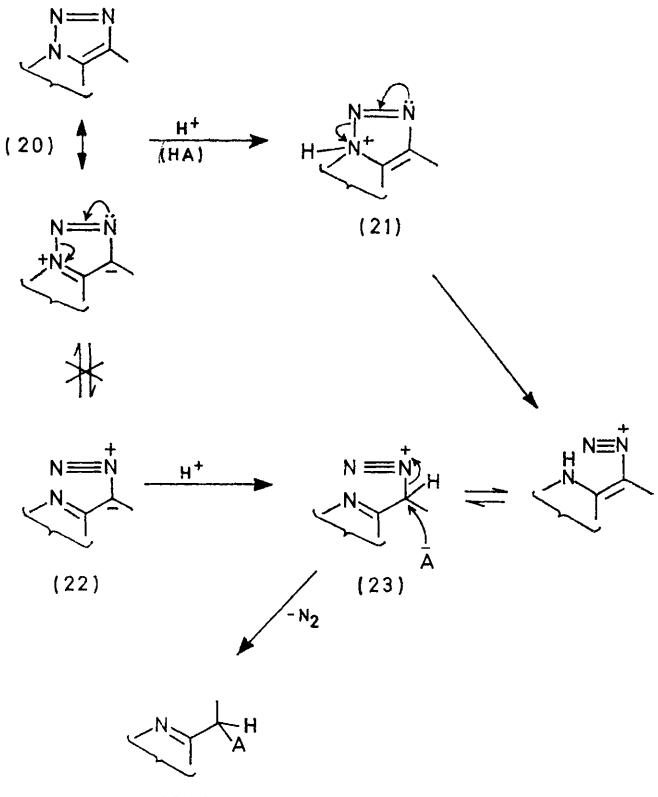
(18) R
a; H
b; Ac



(19)

aminobenzylquinazoline (12a). This compound was also obtained by hydrolysis of the acetamidoquinazoline (13a), the product of the hydrogenolysis of the acetoxybenzylquinazoline (13c). The latter reaction also gave a compound, $C_{17}H_{17}N_3O$, whose spectral properties are in accord with the 3,4-dihydroquinazoline structure (19). The catalytic reduction of 4-aminoquinazolines to 3,4-dihydro-derivatives is well known.[13] The structure of the acetyl compound (13c) [and hence that of the parent amine (12c)] was firmly established by forcing alkaline or acidic hydrolysis to the known [5] quinazolone (16b).

Triazole scission in the phenyl compound (6b) also occurred in trifluoroacetic acid at room temperature, but not so readily as in the cases of *v*-triazolo[1,5-*a*]pyrimidines.[1,11] The ^{1}H n.m.r. spectrum of a solution of the phenyl compound (6b) in trifluoroacetic acid left at room temperature for 1 h showed no signal due to a benzylic proton (Table 1), demonstrating the presence of the intact fused structure (6b). However, after 24 h the spectrum contained a singlet at τ 2·94 (Table 1) consistent with complete conversion into the trifluoroacetate (12d). After *ca.* 26 h the presence of a new signal at τ 3·78 indicated the presence of the alcohol (12b) produced by hydrolysis [1,11] of the ester (12d). In contrast to the phenyl compound (6b), the amide (6c) and the nitrile (6d) were unaffected by prolonged heating in glacial acetic acid, and the ^{1}H n.m.r. spectra of solutions in trifluoroacetic acid showed no sign of benzylic absorption after 27 h at room temperature. The reluctance of fused *v*-triazoles bearing electron-withdrawing groups at C-3 to undergo acid-catalysed scission has also been observed in the *v*-triazolo[1,5-*a*]pyrimidine ring system,[1,11] and may be reasonably explained in terms of destabilisation of the conjugate acid of the triazole [see Scheme; (21)], the probable species undergoing scission in acidic media. In support of this contention, the 3-unsubstituted aminotriazoloquinazoline (6a) was smoothly converted in hot glacial acetic acid into the amino-acetate (14c). The structure of this product was established by its hydrolysis under mild conditions to give the amino-alcohol (14b), and under



(20) (21) (22) (23) (24)

(A = OH, Cl, Br, OAc, or O·COCF$_3$)

SCHEME

forcing conditions to give the known [14] 2-hydroxymethylquinazolone (17b). In contrast to their more

[12] L. F. Fieser and M. Fieser in 'Reagents for Organic Synthesis,' Wiley, New York, 1967, p. 638.
[13] Ref. 10, pp. 398—399.
[14] M. Uskokovic, J. Iacobelli, V. Toome, and W. Wenner, *J. Org. Chem.*, 1964, **29**, 582.

reactive benzyl counterparts (12b and c), the alcohol (14b) and the derived acetate (14c) were inert to manganese dioxide oxidation and hydrogenolysis, respectively. The compound (6a) also underwent scission in trifluoroacetic acid. The ^{1}H n.m.r. spectrum of a solution of (6a) in trifluoroacetic acid kept at room temperature for 24 h showed a singlet of intensity equivalent to one proton at τ 4·75, attributable to the benzylic protons of the trifluoroacetate (14d).

Breakdown of the triazole ring in the triazoloquinazolines (6a and b) also occurred in the presence of acid halides [1,5,11] to afford 2-halogenoalkyl- or 2-halogenoaralkyl-quinazolines. Thus, heating the amine (6b) or its acetyl derivative (9b) with acetyl chloride in acetic acid afforded the chlorobenzylquinazoline (13e). The identification of this product is based on its hydrogenolysis to a mixture of the acetamido-compound (13a) and the dihydro-derivative (19), and on its acidic hydrolysis to the amino-alcohol (12b). Reaction of the chloro-compound (13e) with ethanolic sodium carbonate resulted in both hydrolysis and nucleophilic displacement to give the ether (12g). The amine (6b) also reacted with acetyl bromide in acetic acid to afford a product whose ^{1}H n.m.r. spectrum showed it to be a mixture of the benzyl compound (13a) and the bromobenzylquinazoline (13f), from which the latter was isolated by fractional crystallisation. Formation of the benzylquinazoline (13a) is explicable in terms of reduction of the bromo-compound (13f) by the hydrogen bromide produced by the interaction of acetyl bromide with acetic acid.[5] Reaction of the parent aminotriazoloquinazoline (6a) with acetyl chloride and acetyl bromide in acetic acid likewise gave the halogeno-compounds (15e and f), both of which were converted by acidic hydrolysis into the amino-alcohol (14b). The absence of 4-amino-2-methylquinazoline (14a) as a product of the reaction of the amine (6a) with acetyl bromide in acetic acid reflects the lower reactivity (towards reduction) of an alkyl bromide compared with an aralkyl bromide.

Hot aqueous mineral acid also cleaved the triazole ring in the aminotriazoloquinazolines (6). Scission of the amino-compound (6b) in hot aqueous ethanolic sulphuric acid was accompanied by hydrolysis of the amino-group and gave the quinazolone (16b). Similar treatment of the unsubstituted aminotriazoloquinazoline (6a) likewise gave the quinazolone (17b), which was also the product of the forcing acidic hydrolysis of the amide (6c) and the nitrile (6d). In view of the stability of compounds (6c and d) to scission in acetic acid, their decomposition in aqueous mineral acid is best explained in terms of prior hydrolysis and decarboxylation to a 3-unsubstituted species, either (6a) or (11a), followed by scission.

The foregoing reactions demonstrate the viability of acid-catalysed scission of readily accessible 5-amino-*v*-triazolo[1,5-*a*]quinazolines as a synthetic route to 2-substituted 4-aminoquinazolines. In general, these reactions can be rationalised in terms of the solvolysis of a diazonium cation (23) produced by ring-opening of the conjugate acid of the triazole (21) (Scheme). The alternative formation of the cation (23) by protonation of a diazo-intermediate (22) (Scheme) is inconsistent with the stability of the amide (6c) and the nitrile (6d) to hot acetic acid, since electron-withdrawal at C-3 should promote ring-opening [(20) $\rightleftharpoons$ (22)] and hence acid-catalysed scission, rather than inhibit it as observed. On the other hand, the inertness of the amide (6c) and the nitrile (6d) is readily explained on the basis of destabilisation of the conjugate acid (21) by electron-withdrawal at C-3. The controlling influence of protonation on the course of the acid-catalysed reactions of the triazoloquinazolines (6) is further emphasised by the fact that their scission under electron impact without exception occurs by loss of nitrogen to give primary fragment ions of mass ($M^+ - 28$). These ions correspond to the base peaks in the mass spectra of compounds (6a, b, and d), whereas in the spectrum of the amide (6c), the peak at ($M^+ - 28$) is subsidiary to a peak at ($M^+ - 83$). The mass spectrum of the amide (11c) lacks a peak at ($M^+ - 28$); again the base peak corresponds to an ion of mass ($M^+ - 83$). Primary fragmentation to ions of mass ($M^+ - 83$) is also a feature of the mass spectra of *v*-triazolo[1,5-*a*]pyrimidine-3-carboxamides.[1]

EXPERIMENTAL

I.r. and u.v. spectra were recorded for Nujol suspensions and ethanolic solutions, respectively, with Unicam SP 200 and SP 800 instruments. ^{1}H N.m.r. spectra were measured at 60 and 100 MHz for solutions in deuteriochloroform or trifluoroacetic acid, at 28°, with tetramethylsilane as internal standard, with Perkin-Elmer R10 and Varian HA-100 instruments. ^{1}H N.m.r. data for triazoloquin-

TABLE 1

^{1}H N.m.r. signals (τ) of *v*-triazolo[1,5-*a*]quinazolines [a]

Compd.	Ac	Others	ArH
(6a) [b]		4·30 [c]	1·45—2·19(m) [d]
(6a) [b,e]		4·30, 4·75 [f]	1·30—2·30(m) [d]
(6b)			1·11—1·95(m) [d] 2·13—2·37(m) [g]
(6b) [e]		2·94 [f]	1·44—2·58(m) [h]
(6b) [i]		2·94 [f], 3·78 [f]	1·44—2·60(m) [h]
(6c)			1·08—2·16(m) [d]
(6d)			1·10—2·20(m) [d]
(9b)	7·12 [j]		1·09—1·85(m) [g] 2·23—2·35(m) [d]
(9d)	7·13 [j]		1·02—2·10(m) [d]
(10b)	7·34 [k]		1·63—1·83(m) [g] 2·21—2·35(m) [d]
(9g)/(10c) [b]	7·21, 7·36		1·10—2·10(m) [d]
(10d) [b]	7·37 [k]		0·90—1·95(m) [d]
(10g) [b]	7·21, 7·37, 7·72		1·05—2·10(m) [d]

[a] Spectra taken at 100 MHz on a Varian HA 100 instrument; solutions in trifluoroacetic acid at 28° with tetramethylsilane as internal standard. Signals were sharp singlets unless designated as m (multiplet). [b] Spectra taken at 60 MHz on a Perkin-Elmer R10 instrument. [c] H-3. [d] 4H. [e] Spectrum run after 24 h in trifluoroacetic acid. [f] Benzylic H. [g] 5H. [h] 9H. [i] Spectrum run after 26 h in trifluoroacetic acid. [j] NHAc. [k] NAc_2.

azolines and quinazolines are collected in Tables 1 and 2. Mass spectra were measured at 70 eV and 150° (probe

TABLE 2

^{1}H N.m.r. signals (τ) of 4-aminoquinazolines [a]

Compd.	H	NHAc	Others	ArH
(12a) [b]	7·15			1·00—2·05(m)
(12b)	3·80			2·55 [c]
(12c)	3·02		7·57 [d], 7·73 [e]	1·49—2·71(m)
(12g)	4·25		6·21(q) [f], 8·64(t)	1·55—2·10(m) [g]; 2·56 [h]
(13a)	5·30	7·30		1·30—2·10(m) [h]; 2·53 [g]
(13a) [b,i]	5·70	7·55		1·80—2·90(m) [c]
(13c)	2·76	7·29	7·53 [j]	1·33—1·97(m) [h]; 2·33—2·61(m) [g]
(13e)	3·51	7·30		1·61—1·73(m) [h]; 2·33—2·59(m) [g]
(13f)	3·44	7·27		1·30—1·80(m) [g]; 2·22—2·60(m) [h]
(14b)	4·84		5·92 [k]	1·48(dd) [l]; 1·73—2·19(m) [m]
(14c) [b]	4·45		7·57	1·35—2·15(m) [h]
(15e) [b]	4·88	7·15		1·18—2·00(m) [h]
(15e) [b,g]	5·20	7·25		1·80—2·50(m) [h]
(15f) [b,g]	5·35	7·25		1·85—2·61(m) [h]
(19)	5·82	7·84	1·17 [n], 1·81 [n], 3·33 [o]	2·32—2·86(m) [c]

[a] Unless otherwise stated, spectra were taken at 100 MHz on a Varian HA 100 instrument; solutions in trifluoroacetic acid at 28° with tetramethylsilane as internal standard. Signals were sharp singlets unless otherwise designated. [b] Spectra taken at 60 MHz on a Perkin-Elmer R10 instrument. [c] 9H. [d] OAc. [e] Methyl protons of acetic acid. [f] OEt, J 7 Hz. [g] 5H. [h] 4H. [i] Solution in deuteriochloroform. [j] OAc. [k] NH. [l] 1H. [m] 3H. [n] NH, poorly resolved doublet. [o] H-4, multiplet

temperature) with an A.E.I. MS 902 spectrometer. Light petroleum had b.p. 60—80°. Unless otherwise stated, chloroform extracts were washed (aqueous sodium hydrogen carbonate and water) and dried ($MgSO_4$) prior to evaporation under reduced pressure.

5-*Amino*-v-*triazolo*[1,5-a]*quinazolines* (6).—(*a*) A mixture of *o*-azidobenzonitrile (14·4 g, 0·1 mol) and phenylacetonitrile, cyanoacetamide, or malononitrile (0·1 mol) in methanol (150·0 ml) was mixed with a solution of sodium (9·2 g) in methanol (150·0 ml). A solid separated from the originally homogeneous mixture and the suspension was stirred at room temperature for 30 min. The solid was collected, washed with methanol (50·0 ml) and water (100·0 ml), and combined with solid material recovered from the methanolic filtrate and washings by evaporation and treatment with water. Crystallisation afforded the pure 5-*amino*-3-*phenyl*-v-*triazolo*[1,5-a]*quinazoline* (6b) (82%), m.p. 268° (from glacial acetic acid), $\nu_{max.}$ 3400, 3250, and 3150 (NH), and 1640 (NH def.) cm^{-1}, $\lambda_{max.}$ 215, 230sh, 254sh, 260, 273, 284, 295sh, and 347 nm (log ε 4·46, 4·33, 4·35, 4·37, 4·28, 4·27, 4·02, and 3·82), *m/e* 261 (12%, M^+) and 233 (100%, $M^+ - N_2$) (Found: C, 69·1; H, 4·3; N, 26·9. $C_{15}H_{11}N_5$ requires C, 69·0; H, 4·2; N, 26·8%); the 3-*carboxamide* (6c) (81%), m.p. 312° (from glacial acetic acid–dimethylformamide), $\nu_{max.}$ 3450, 3400, and 3150 (NH), and 1685 (CO) cm^{-1}, *m/e* 228 (63%, M^+), 200 (26%, $M^+ - N_2$), and 145 (100%, $M^+ - 83$) (Found: C, 52·4; H, 3·2; N, 36·9. $C_{10}H_8N_6O$ requires C, 52·6; H, 3·5; N, 36·8%); and the 3-*carbonitrile* (6d) (quant.), m.p. 286° (decomp.) (from glacial acetic acid–dimethylformamide), $\nu_{max.}$ 3400, 3350sh, and 3150 (NH), 2250 (CN), and 1650 (NH def.), $\lambda_{max.}$ 219infl, 229sh, 234, 248sh, 271sh, 280, and 310 nm (log ε 4·49, 4·62, 4·63, 4·32, 3·96, 4·01, and 3·97), *m/e* 210 (56%, M^+) and 182 (100%, $M^+ - N_2$) (Found: C, 57·0; H, 2·9; N, 39·9. $C_{10}H_6N_6$ requires C, 57·1; H, 2·9; N, 40·0%).

(*b*) A solution of *o*-azidobenzonitrile (14·4 g, 0·1 mol) and ethyl cyanoacetate or cyanoacetic acid (0·1 mol) in absolute ethanol (200·0 ml) was treated with a solution of sodium (9·2 g) in absolute ethanol (200·0 ml), added in one portion. A gelatinous solid separated from the initially homogeneous solution, and the mixture was stirred at 80° for 2·5 h. The crude salt was collected, augmented with further material obtained by concentrating the ethanolic mother liquors, washed with ethanol, and stirred with 50% v/v aqueous acetic acid (250·0 ml) at room temperature for 3 h to afford 5-*amino*-v-*triazolo*[1,5-a]*quinazoline* (6a) (quant.), m.p. 266° (decomp.) (from dimethylformamide–water), $\nu_{max.}$ 3350 and 3150 (NH), and 1680 (NH def.) cm^{-1}, *m/e* 185 (100%, M^+) and 157 (100%, $M^+ - N_2$) (Found: C, 58·8; H, 3·6; N, 37·7. $C_9H_7N_5$ requires C, 58·4; H, 3·8; N, 37·8%).

Acetylation of the 5-*Amino*-v-*triazolo*[1,5-a]*quinazolines* (6).—(*a*) The 3-phenyl derivative (6b) (0·5 g) was heated under reflux in acetic anhydride (15·0 ml) for 5 min. The mixture was filtered hot to give the 5-N-*acetyl derivative* (9b) (0·4 g), m.p. 265° (from ethanol–dimethylformamide), $\nu_{max.}$ 3250 (NH) and 1685 (CO) cm^{-1}, $\lambda_{max.}$ 209, 227sh, 232, 255, 275sh, 290sh, and 356 nm (log ε 4·42, 4·46, 4·48, 4·41, 4·26, 4·04, and 3·87) (Found: C, 67·8; H, 4·2; N, 22·8%; M^+, 303. $C_{17}H_{13}N_5O$ requires C, 67·3; H, 4·3; N, 23·1%; M, 303). Evaporation of the acetic anhydride mother liquors gave a gum which yielded the solid 5,5-*di*-N-*acetyl derivative* (10b) (0·11 g) in contact with ether, m.p. 186° (from benzene–light petroleum), $\nu_{max.}$ 1730 and 1690 (CO) cm^{-1}, $\lambda_{max.}$ 208, 224, 254, 273sh, 286sh, 312sh, and 326sh nm (log ε 4·52, 4·47, 4·39, 4·25, 4·03, 3·67, 3·61, and 3·87) (Found: C, 66·8; H, 4·3; N, 20·0%; M^+, 345. $C_{19}H_{15}N_5O_2$ requires C, 66·5; H, 4·4; N, 20·4%; M, 345).

(*b*) The amino-compounds (6c and d) (0·4 g) were heated under reflux in acetic anhydride (80·0 ml) for 2 h. The gums obtained by evaporating the mixtures solidified on treatment with ether to give the triacetyl derivative (10g) (0·4 g), $\nu_{max.}$ 3300 (NH), and 1710, 1680, and 1660 (CO) cm^{-1}, or the diacetyl derivative (10d) (0·4 g), $\nu_{max.}$ 2250 (CN) and 1710 and 1690 (CO) cm^{-1} respectively, which were converted by heating with glacial acetic acid or by crystallisation, into the di-*N*-acetyl derivative (9g) or (10c), m.p. 287° (from dimethylformamide–water), $\nu_{max.}$ 3350, 3250, and 3150 (NH) and 1730, 1710, and 1680 (CO) cm^{-1}, $\lambda_{max.}$ 231, 270sh, 281sh, and 314 nm (log ε 4·34, 3·86, 3·79, and 3·85) (Found: C, 53·2; H, 4·0; N, 26·4%; M^+, 312. Calc. for $C_{14}H_{12}N_6O_3$: C, 53·8; H, 3·9; N, 26·9%; M, 312), or the *mono*-N-*acetyl derivative* (9d), m.p. 250° (from glacial acetic acid), $\nu_{max.}$ 3250 (NH), 2250 (CN), and 1690 (CO) cm^{-1}, $\lambda_{max.}$ 230, 263sh, 270sh, and 314 nm (log ε 4·46, 4·10, 3·95, and 3·92) (Found: C, 57·0; H, 3·2; N, 33·2%; M^+, 252. $C_{12}H_8N_6O$ requires C, 57·1; H, 3·2; N, 33·3%; M, 252).

v-*Triazolo*[1,5-a]*quinazolin*-5(4H)-*ones* (11).—The aminotriazoloquinazolines (6a—d) (0·002 mol) were heated under reflux with aqueous 20% w/v potassium hydroxide (10·0 ml) in 2-ethoxyethanol (60·0 ml) for 3 h. Removal of the solvent under reduced pressure afforded gums which were dissolved in the minimum of water and acidified (dilute aqueous sulphuric acid) to give the triazoloquinazolones (11a) (50%), m.p. 293° (from dimethylformamide), (11b) (91%), m.p. 259° (from dimethylformamide), and (11c)

[89 and 91% respectively from (6c) and (6d)], m.p. 296° (from dimethylformamide), *m/e* 229 (49%, M^+) and 146 (100%, $M^+ - 83$), which were identified by comparison (mixed m.p. and i.r. spectra) with authentic samples.[5,9]

2-Acetoxymethyl- and 2-(α-Acetoxybenzyl)-quinazolines (12c), (13c), *and* (14c).—The aminotriazoloquinazolines (6a and b) and (9b) (0·004 mol) were heated under reflux in glacial acetic acid (60·0 ml) for 2·5 h. The gums obtained by evaporating the acetic acid solidified when treated with ether to yield the *acetoxy-compounds* (14c) (87%), m.p. 203° (from ethanol–benzene), $\nu_{max.}$ 3250 and 3100 (NH), 1730 (CO), and 1660 (NH def.) cm^{-1} (Found: C, 60·1; H, 5·0; N, 19·6. $C_{11}H_{11}N_3O_2$ requires C, 60·8; H, 5·1; N, 19·4%); (12c) (acetic acid solvate) (98%), m.p. 102° (from benzene–light petroleum), $\nu_{max.}$ 3400, 3300, 3100, and 2700br (NH,OH), 1735 and 1695 (CO), and 1660 (NH def.) cm^{-1} (Found: C, 64·1; H, 5·4; N, 12·1%; M^+, 293. $C_{17}H_{15}N_3O_2,CH_3CO_2H$ requires C, 64·6; H, 5·4; N, 11·9%; *M*, 293); and (13c) (75%), m.p. 168° (from benzene–light petroleum), $\nu_{max.}$ 3250 (NH), 1730 and 1695 (CO), and 1570 (NH def.) cm^{-1} (Found: C, 67·5; H, 5·0; N, 12·3. $C_{19}H_{17}N_3O_3$ requires C, 68·0; H, 5·1; N, 12·5%). The acetic acid solvate of the acetoxy-amine (12c) was converted in hot acetic anhydride into the acetyl derivative (13c) (77%), identical (mixed m.p. and i.r. spectrum) with a sample prepared before).

The aminotriazoloquinazolines (6c and d) when heated under reflux with glacial acetic acid as described before, were unchanged (recovery 84%).

2-(α-Hydroxybenzyl)quinazolin-4(3H)-one (16b).—(*a*) The aminotriazoloquinazoline (6b) (0·15 g) was heated under reflux with aqueous 30% w/v sulphuric acid (7·5 ml) in ethanol (7·5 ml) for 30 min. The ethanol was distilled off under reduced pressure and the residue was treated with dilute aqueous sodium hydroxide, and extracted with chloroform to give a gum, which was crystallised to yield the amino-alcohol (12b) (0·07 g), m.p. 173° (from benzene–ethanol), identical (mixed m.p. and i.r. spectrum) with a sample prepared later. Acidification of the alkaline extract with glacial acetic acid afforded the alcohol (16b) (0·05 g), m.p. 208° (from ethanol), identical (mixed m.p. and i.r. spectrum) with an authentic sample.[5]

(*b*) The quinazolone (16b) was also obtained (70—90%) when the aminotriazoloquinazoline (6b) or the acetoxybenzylquinazoline (13c) was heated under reflux with aqueous 30% w/v sulphuric acid in ethanol for 2 h, or when the compound (13c) was heated under reflux (3h) with aqueous 20% w/v potassium hydroxide. Work-up was carried out by evaporation of the mixtures under reduced pressure, treatment with water, neutralisation, and extraction with chloroform.

2-Hydroxymethylquinazolin-4(3H)-one (17b).—(*a*) Solutions of the amines (6a) or (6c and d) (0·005 mol) in 2-ethoxyethanol (80·0 ml) were heated under reflux with aqueous 30% w/v sulphuric acid (20·0 ml) for 4 h. Alternatively (*b*) the aminoquinazoline(14c) (0·5 g) in ethanol (50·0 ml) was heated under reflux with aqueous 20% w/v potassium hydroxide (15·0 ml) for 3 h. The mixtures were evaporated under reduced pressure, treated with water, and adjusted to neutral pH. Extraction with chloroform gave gums which were triturated with ether to yield the alcohol (17b) (60—90%), m.p. 214° (from ethanol) (lit.,[14] 214°), $\nu_{max.}$ 3200—2700br (OH, NH) and 1670br (CO) cm^{-1} (Found: C, 61·6; H, 4·8; N, 15·5. $C_9H_8N_2O_2$ requires C, 61·4; H, 4·5; N, 15·9%).

4-Acetamido-2-(α-chlorobenzyl)quinazoline (13e).—The aminotriazoloquinazoline (6b) or its acetyl derivative (9b) (0·004 mol) was heated under reflux with acetyl chloride (20·0 ml) and glacial acetic acid (20·0 ml) for 1·5 h. The mixture was evaporated under reduced pressure, treated with saturated aqueous sodium hydrogen carbonate, and extracted with chloroform. Evaporation of the extract gave a gum which solidified when triturated with ether to yield the *chlorobenzylquinazoline* (13e) (75—80%), m.p. 174° (from benzene), $\nu_{max.}$ 3250 (NH), 1680br (CO), and 1570 (NH def.) cm^{-1} (Found: C, 65·3; H, 4·4; N, 13·8. $C_{17}H_{14}ClN_3O$ requires C, 65·4; H, 4·5; N, 13·5%).

The chloro-compound (13e) (0·15 g) was heated under reflux with aqueous N-sodium carbonate (7·5 ml) and ethanol (7·5 ml) for 20 min. The mixture was evaporated and the residue was treated with water and extracted with chloroform to yield the *ether* (12g) (0·1 g), m.p. 197° (from benzene), $\nu_{max.}$ 3350—3000br (NH), 1670 (CO), and 1560 cm^{-1} (Found: C, 73·0; H, 6·6; N, 14·7%; M^+, 279. $C_{17}H_{17}N_3O$ requires C, 73·1; H, 6·1; N, 15·0%; *M*, 279).

4-Acetamido-2-chloromethylquinazoline (15e).—The amino-compound (6a) (0·5 g) was heated under reflux with a mixture of acetyl chloride (75·0 ml) and glacial acetic acid (50·0 ml) for 4 h. The gum obtained by evaporating the mixture solidified in contact with ether–light petroleum to afford the *chloromethylquinazoline* (15e) (0·4 g), m.p. 199° (from benzene–light petroleum), $\nu_{max.}$ 3250 (NH) and 1690br (CO) cm^{-1} (Found: C, 55·5; H, 4·0; N, 17·6. $C_{11}H_{10}ClN_3O$ requires C, 56·1; H, 4·2; N, 17·8%).

4-Acetamido-2-(α-bromobenzyl)quinazoline (13f).—The aminotriazoloquinazoline (6b) (1·0 g) was heated under reflux with a mixture of freshly distilled acetyl bromide (20·0 ml) and glacial acetic acid (20·0 ml) for 1·5 h. The mixture was evaporated, treated with saturated aqueous sodium hydrogen carbonate, and extracted with chloroform to give a gum which was triturated with ether to yield a solid mixture (0·8 g), m.p. 115—123°, of the acetamidoquinazolines (13a) and (13f), τ ($CDCl_3$) 1·85—2·85 (m, (ArH), 3·69 (s, CH), 5·69 (s, CH_2), 7·28 (s, Ac), and 7·51 (s, Ac), in the ratio 3 : 2 as estimated from the integrated intensities of the n.m.r. acetyl signals. Repeated crystallisation of the mixture afforded the pure *bromobenzylquinazoline* (13f), m.p. 178° (from benzene–light petroleum), $\nu_{max.}$ 3250 (NH) and 1680br (CO) cm^{-1} (Found: C, 58·0; H, 4·0; N, 11·7. $C_{17}H_{14}BrN_3O$ requires C, 57·3; H, 3·9; N, 11·8%).

4-Acetamido-2-bromomethylquinazoline (15f).—The triazoloquinazoline (6a) (1·0 g) was heated under reflux with a mixture of acetyl bromide (30·0 ml) and glacial acetic acid (30·0 ml) for 4 h. The mixture was evaporated under reduced pressure and the gum obtained was stirred with saturated aqueous sodium hydrogen carbonate to give the solid product, more of which was recovered by extracting the aqueous mother liquor with chloroform (total 1·1 g). Crystallisation yielded the pure *bromomethyl compound* (15f), m.p. 205° (from benzene–light petroleum), $\nu_{max.}$ 3250 (NH) and 1680 (CO) cm^{-1} (Found: C, 47·1; H, 3·4; N, 15·3. $C_{11}H_{10}BrN_3O$ requires C, 47·2; H, 3·6; N, 15·0%).

4-Amino-2-(α-hydroxybenzyl)quinazoline (12b).—(*a*) Solutions of the acetic acid solvate of (12c) and the acetoxy-compound (13c) (0·001 mol) in ethanol (10·0 ml) were heated under reflux with aqueous N-sodium carbonate (10·0 ml) for 20 min. Alternatively (*b*), the chlorobenzylquinazoline (13e) (0·001 mol) in ethanol (20·0 ml) was heated under reflux with aqueous 2N-sulphuric acid (10·0

ml) for 30 min. The mixtures were concentrated under reduced pressure and extracted with chloroform to give gums which were triturated with ether to yield the solid *amino-alcohol* (12b) (80—90%), m.p. 173° (from benzene–ethanol), $\nu_{max.}$ 3350 and 3200 (NH) and 1650 (NH def.) cm^{-1} (Found: C, 71·0; H, 5·1; N, 16·9. $C_{15}H_{13}N_3O$ requires C, 71·7; H, 5·2; N, 16·7%).

4-*Amino*-2-*hydroxymethylquinazoline* (14b).—Hydrolysis of the acetoxymethylquinazoline (14c) with hot aqueous ethanolic sodium carbonate or of the halogenomethylquinazolines (15e and f) with hot aqueous ethanolic sulphuric acid, as described before, gave the *amino-alcohol* (14b) (50—80%), m.p. 212° (from ethanol–benzene), $\nu_{max.}$ 3350 and 3100 (NH, OH) and 1670 (NH def.) cm^{-1} (Found: C, 61·6; H, 5·2; N, 23·9. $C_9H_9N_3O$ requires C, 61·7; H, 5·2; N, 24·0%).

4-*Amino*-2-*benzoylquinazoline* (18a).—The amino-alcohol (12b) (0·4 g) was heated under reflux with activated manganese dioxide [12] (1·6 g) in anhydrous acetone (20·0 ml) for 5 min. The filtered, evaporated mixture afforded a gum which solidified in contact with ether to yield the *ketone* (18a) (0·33 g), m.p. 203° (from benzene–light petroleum), $\nu_{max.}$ 3500 and 3300 (NH), 1680 (CO), and 1645 (NH def.) cm^{-1} (Found: C, 72·6; H, 4·3; N, 17·0. $C_{15}H_{11}N_3O$ requires C, 72·3; H, 4·5; N, 16·9%). The amino-ketone (18a) was converted in hot acetic anhydride into the *acetyl derivative* (18b), m.p. 171° (from benzene), $\nu_{max.}$ 3300 (NH) and 1685 and 1675 (CO) cm^{-1} (Found: C, 70·3; H, 4·6; N, 14·9. $C_{17}H_{13}N_3O_2$ requires C, 70·1; H, 4·5; N, 14·4%), and when hydrogenated in ethanol over 10% palladium–charcoal it afforded the amino-alcohol (12b) (80%), m.p. 173° (from benzene–ethanol), identical (mixed m.p. and i.r. spectrum) with a sample prepared before.

The amino-alcohol (14b) was unchanged (85%) when heated with activated manganese dioxide in anhydrous acetone as described before.

4-*Amino*-2-*benzylquinazoline* (12a).—Hydrogenation of the acetoxybenzylquinazoline (12c) (acetic acid solvate) in ethanol over 10% palladium–charcoal yielded the *amine* (12a) (quant.), m.p. 221° (from benzene–ethanol), $\nu_{max.}$ 3300 and 3150 (NH) and 1660 (NH def.) cm^{-1} (Found: C, 76·5; H, 5·7; N, 17·7. $C_{15}H_{13}N_3$ requires C, 76·6; H, 5·6; N, 17·9%). The acetoxy-compound (14c) was unchanged (90%) after attempted hydrogenation in ethanol over 10% palladium–charcoal.

4-*Acetamido*-2-*benzylquinazoline* (13a) *and its Dihydro-derivative* (19).—Hydrogenolysis of the acetamidoquinazolines (13c and e) (0·001 mol) in ethanol over 10% palladium–charcoal gave gums which were treated with ether to give the insoluble *dihydro-compound* (19) (0·22 g), m.p. 140° (from benzene), $\nu_{max.}$ 3250 (NH), 1665 (CO), and 1645 (NH def.) cm^{-1} (Found: C, 72·9; H, 6·3; N, 14·9. $C_{17}H_{17}N_3O$ requires C, 73·1; H, 6·1; N, 15·1%). Evaporation of the ether extract yielded the *acetamidoquinazoline* (13a) (0·08 g), m.p. 145° (from benzene–light petroleum), $\nu_{max.}$ 3250 (NH), 1680 (CO), and 1570 (NH def.) cm^{-1} (Found: C, 73·5; H, 5·6; N, 15·3. $C_{17}H_{15}N_3O$ requires C, 73·6; H, 5·5; N, 15·2%). The acetamidoquinazoline (13a) was hydrolysed with aqueous N-sodium carbonate in ethanol as described before to afford 4-amino-2-benzylquinazoline (12a) (82%), m.p. 221° (from benzene–ethanol), identical (mixed m.p. and i.r. spectrum) with a sample prepared before.

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

[3/2147 *Received*, 19*th October*, 1973]