1,2,3-Triazoles. Part II.[1,2] 4-Amino-5-aminomethyl-1,2,3-triazoles †

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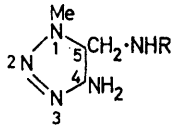
4-Amino-1-(and 2-)methyl-1,2,3-triazole-5-carbonitrile were made by acidic hydrolysis of 4-dimethylaminomethyleneamino-1-(and 2-)methyl-1,2,3-triazole-5-carbonitrile. These amino-nitriles, and also their known 3-methyl- and 3-benzyl-analogues, were hydrogenated to 4-amino-5-aminomethyl-1-methyl-1,2,3-triazole (1a) and its 2- and 3-methyl- and 3-benzyl analogues [(3a), (4a), and (4b), respectively]. Bis-(4-amino-3-benzyl-1,2,3-triazol-5-ylmethyl)amine (5), was obtained as a by-product. Nine *N*-acyl derivatives are described in which a formyl, acetyl, ethoxycarbonyl, (ethylthio)carbonyl, or ethoxalyl group substitutes the aminomethyl system, also four derivatives in which both amino-groups are monoacylated.

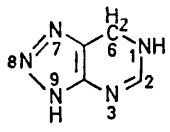
N.m.r., u.v., and i.r. data and ionization constants are reported and discussed. An estimate of the electron-attracting strength of the 1,2,3-triazole nucleus places it between benzene and pyrazine.

OUTSIDE the pyrimidine series, heteroaromatic compounds bearing an aminomethyl group *ortho* to an amino-group are rare; apparently the only known examples are 2-amino-3-aminomethyl-4-methylpyridine [3] and 2-amino-3-aminomethylpyrazine and its 5-methyl-derivative.[4] Several such compounds were required in the 1,2,3-triazole series [*e.g.* (1a)] in order to prepare derivatives of 1,6-dihydro-8-azapurine (2) (6,7-dihydro-*v*-triazolo[4,5-*d*]pyrimidine), alkylated, in turn, on each of the ring-nitrogen atoms.

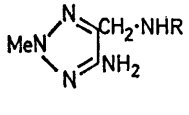


(1)

a; R = H
b; R = COMe
c; R = CO_2Et

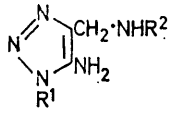


(2)



(3)

a; R = H
b; R = COMe
c; R = CO_2Et



(4)

a; R^1 = Me, R^2 = H
b; R^1 = $PhCH_2$, R^2 = H
c; R^1 = $PhCH_2$, R^2 = CHO
d; R^1 = $PhCH_2$, R^2 = CO_2Et
e; R^1 = $PhCH_2$, R^2 = CO·SEt
f; R^1 = $PhCH_2$, R^2 = CO·CO_2Et

After reduction of 4-aminotriazole-5-carboxamides with lithium aluminium hydride or sodium dihydrobis(2-methoxyethoxy)aluminate had failed, reduction was attempted of the appropriate 4-aminotriazole-5-carbonitriles. Of these nitriles, the 3-methyl [5] and 3-benzyl [6] derivatives were obtained, as before, by the combined action of phosphoryl chloride and dimethylformamide on the corresponding 4-aminotriazole-5-carboxamides, followed by acidic hydrolysis, without isolation, of the resulting amidine. This procedure also furnished the new analogues, 4-amino-1-(and 2-)methyl-1,2,3-triazole-5-carbonitrile, but only if the sensitive amidine intermediates [7] (*e.g.* 4-dimethylaminomethyleneamino-2-methyl-1,2,3-triazole-5-carbonitrile) were isolated and purified before hydrolysis. An improved preparation of 4-amino-3-methyl-1,2,3-triazole-5-carboxamide is given in the Experimental section.

Attempted reduction of these *o*-amino-nitriles with lithium aluminium hydride gave only poor yields of the required aminomethyl compounds [*e.g.* (1a)]; moreover, sodium and n-butanol only converted 4-amino-3-benzyl-5-carbonitrile into its known [6] dimer. However, hydrogenation of the amino-nitriles over Raney nickel gave good yields (60—80%) of the required 1-methyl- (1a), 2-methyl- (3a), 3-methyl- (4a), and 3-benzyl- (4b) derivatives of 4-amino-5-aminomethyl-1,2,3-triazole. The presence of ammonia was necessary to furnish a high proportion of primary to secondary amine [*e.g.* bis-(4-amino-3-benzyl-1,2,3-triazol-5-ylmethyl)amine (5)]. No other type of by-product was isolated.

The aminomethyl compounds were conveniently isolated and purified as phosphates. The liberated bases formed low-melting crystals with a waxy fracture. Two of them were deliquescent; chloroform extracted only the 3-benzyl derivative (4b) from water. All four absorbed carbon dioxide from the air giving, in one example (4b), a highly basic carbonate [$(base)_3H_2CO_3$]. Unlike 2-aminobenzylamine, which readily lost ammonia on storage,[8] these aminomethyltriazoles proved stable, remaining unchanged for at least a year at 4°.

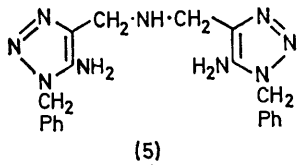
Because alkaline conditions were used during and after the reduction of 4-amino-3-benzyl-1,2,3-triazole-5-carbonitrile, a Dimroth rearrangement [6] could conceivably have occurred to give 5-aminomethyl-4-benzylamino-1,2,3-triazole. That this had not taken place was shown by the ^1H n.m.r. spectrum (Table 1) of the product, which gave a signal at τ 4·62 for CH_2Ph [*cf.* 4·5—4·6 for the 3-CH_2Ph group in other 1,2,3-triazoles, and 5·6 for the 4-NH·CH_2Ph group in the same triazoles after Dimroth rearrangement [6]]. Moreover rearrangement would create an acidic centre of pK_a *ca.* 9, on N-3, whereas the aminomethyl compound (4b) was readily and completely

† In this series, the amino-group of triazoles is consistently numbered 4, to facilitate comparisons.

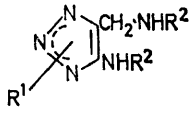
[1] Part I, A. Albert and H. Taguchi, preceding paper.
[2] Preliminary report, A. Albert, *Chem. Comm.*, 1970, 858.
[3] P. J. Vanderhorst and C. S. Hamilton, *J. Amer. Chem. Soc.*, 1953, **75**, 656.
[4] A. Albert and K. Ohta, *J. Chem. Soc.* (*C*), 1970, 1540.
[5] A. Albert, *J. Chem. Soc.* (*C*), 1969, 2379.
[6] A. Albert, *J. Chem. Soc.* (*C*), 1970, 230.
[7] A. Albert, *J.C.S. Perkin I*, 1972, 461.
[8] S. Gabriel, *Ber.*, 1887, **20**, 2224.

extracted by chloroform from an aqueous solution of pH 11. It is known [6] that equilibrium in the Dimroth reaction favours the secondary-amine isomer when an electron-attracting substituent is in the 5-position. The 5-aminomethyl compound (4b) exemplifies the converse of this rule: an attempt to effect a Dimroth rearrangement by boiling with N-sodium hydroxide for 4 h, left it completely unchanged. Previous experience [9] has shown that a Dimroth rearrangement is unlikely for a 3-methyl-1,2,3-triazole, and considerations of valence preclude it for the 1- and 2-methyl isomers.

Acyl derivatives of the 4-amino-5-aminomethyltriazoles were needed for the intended cyclizations. Unless



(5)



(6)

a; R^1 = 1-Me, R^2 = Ac
b; R^1 = 1-Me, R^2 = CO_2Et
c; R^1 = 3-$PhCH_2$, R^2 = CHO
d; R^1 = 3-$PhCH_2$, R^2 = CO_2Et

TABLE 1

^{1}H N.m.r. data (33·3°) for 1,2,3-triazoles. Chemical shifts (τ) [a] in $(CD_3)_2SO$

1,2,3-Triazole	τ
4-Amino-5-cyano-1-methyl	3·69 * (2H, NH_2), 5·94 (3H, Me)
4-Amino-5-cyano-2-methyl	3·83 * (2H, NH_2), 5·98 (3H, Me)
4-Amino-5-aminomethyl-1-methyl	5·50 *m,br (2H, 4-NH_2), 6·19 (3H, Me), 6·36 (2H, CH_2), 8·2 *br (2H, CH_2·NH_2)
4-Amino-5-aminomethyl-2-methyl	5·2 *br (2H, 4-NH_2), 6·21 (3H, Me), 6·39 (2H, CH_2), 8·15 *m,br (2H, CH_2·NH_2)
4-Amino-5-aminomethyl-3-benzyl	2·67 (5H, Ph), 4·54 *sharp (2H, 4-NH_2), 4·62 (2H, CH_2Ph), 6·30 (2H, CH_2·NH_2), 8·13 *sharp (2H, CH_2·NH_2)
5-Acetamidomethyl-4-amino-1-methyl	1·7 *br (1H, CO·NH), 5·37 *br (2H, 4-NH_2), 5·76 † (2H, d, J 6 Hz), 6·16 (3H, 1-Me), 8·18 (3H, Ac)
5-Acetamidomethyl-4-amino-2-methyl	1·7 *br (NH), 5·08 *br (2H, 4-NH_2), 5·89 † (2H, d, J 6 Hz), 6·18 (3H, 2-Me), 8·18 (3H, Ac)
5-Acetamidomethyl-4-amino-3-benzyl	1·6 *br (NH), 2·66 (5H, Ph), 4·41 * (2H, 4-NH_2), 4·62 (2H, CH_2Ph), 5·85 † (2H, d, J 6 Hz), 8·18 (3H, Ac)
4-Amino-3-benzyl-5-formamidomethyl	1·6 *br (NH), 1·86 (1H, CHO), 2·61 (5H, Ph), 4·39 * (2H, 4-NH_2), 4·59 (2H, CH_2Ph), 5·75 † (2H, d, J 5 Hz)
4-Amino-5-ethoxycarbonylaminomethyl-1-methyl	2·5 *br (NH),[b] 5·96 † (2H, d),[c] 6·13 (3H, 1-Me),[c] 8·84 (centre) (3H, t, J 7 Hz, Me of Et)
4-Amino-5-ethoxycarbonylaminomethyl-2-methyl	2·5 *vbr (NH), 5·13 * (4-NH_2), 5·89 † (2H, d),[c] 6·17 (3H, 2-Me),[c] 8·80 (3H, t, J 7 Hz, Me of Et)
4-Amino-3-benzyl-5-ethoxycarbonylaminomethyl	2·68 (5H, Ph), 4·52 * (2H, NH_2), 4·62 (2H, CH_2Ph), 5·82 † (2H, d),[c] 8·83 (3H, t, Me of Et)
4-Amino-3-benzyl-5-(ethylthio)carbonylaminomethyl	0·06 *br (1H, NH), 2·69 (5H, Ph), 4·5 *br (2H, 4-NH_2), 4·63 (2H, CH_2Ph), 5·76 † (2H, d, J 6 Hz), 7·17 (centre) (2H, q, J 7 Hz, CH_2 of Et), 8·78 (3H, t, J 8 Hz, CH_3 of Et)
4-Amino-3-benzyl-5-ethoxalylaminomethyl	0·6 *br (1H, NH), 2·70 (5H, Ph), 4·46 * (2H, 4-NH_2), 4·66 (2H, CH_2Ph), 5·75 (centre of complex signal from CH_2 of Et and CH_2·NH, slightly simplified by D_2O), 8·74 (centre) (3H, t, Me of Et)
3-Benzyl-4-formamido-5-formamidomethyl	1·66 (1H, 4-NH·CHO), 1·90slbr (2H, CH_2·NH·CHO superimposed; D_2O converts to 1H, CHO), 2·68 (5H, Ph), 4·52 (2H, CH_2Ph), 5·7 † (2H, d, J 6 Hz)
4-Acetamido-5-acetamidomethyl-1-methyl	0·01 *br (1H, 4-NH), 1·9 *br (1H, CH_2·NH), 5·67 † (2H, d), 6·02 (3H, 1-Me), 7·94 and 8·16 (each 3H, Ac)
4-Acetamido-5-acetamidomethyl-2-methyl	0·05 * slbr (1H, 4-NH), 1·9 *br (1H, CH_2·NH), 5·82 † (2H, d, J 6 Hz), 5·99 (3H, 2-Me), 7·97 and 8·18 (each 3H, Ac)
4-Ethoxycarbonylamino-5-ethoxycarbonylaminomethyl-1-methyl	0·80 * (1H, 4-NH), 2·6 * (1H, CH_2·NH), 5·73 † (2H, d, J 6 Hz),[c] 6·03 (3H, 1-Me),[c] 8·6—9·0 (6H, complex of 2 × t, Me of Et groups)
3-Benzyl-4-ethoxycarbonylamino-5-ethoxycarbonylaminomethyl	0·55 *br (1H, 4-NH), 2·67 [d] (5H, Ph), 4·52 (2H, CH_2Ph), 5·82 † (2H, d),[c] 8·81 (centre) (6H, t, Me of Et)

[a] Tetramethylsilane was the internal standard; all peaks were singlets except where otherwise noted. [b] No recognizable signal for 4-NH_2. [c] Partly overlaps a quartet (CH_2 of Et). [d] Signal * for CH_2·NH coincident.

* Exchanged when D_2O was added. † 5-CH_2 coupled to NH·CO; collapsed to a singlet (2H) when D_2O was added.

the acylating agent was limited to a very few equivalents (and to *one* equivalent in the case of ethyl chloroformate) a substantial proportion of diacylated product was formed. That both amino-groups had reacted was shown by the acidic character generated in the 4-NH group (see *e.g.* 4-ethoxycarbonylamino-5-ethoxycarbonylaminomethyl-1-methyl-1,2,3-triazole, Table 2), and by the doublet (2H) n.m.r. signal for CH_2·NH which became a singlet on deuteriation (see Table 1). The monoacyl analogues were shown to be acylated on the stronger amino-group (CH_2·NH_2) by the large decline in basic strength that followed acetylation (see Table 2). Mono-formyl (4c), -acetyl [(1b) and (3b)], -ethoxycarbonyl [(1c), (3c), and (4d)], -(ethylthio)carbonyl (4e), and -ethoxalyl (4f) derivatives were made; also di-acetyl (6a), -ethoxycarbonyl (6b and d), and -formyl (6c) derivatives. The acyl derivatives were more readily extracted from water by chloroform than were the parent amines.

Physical Properties.—The assignments for n.m.r. chemical shifts (Table 1) of the 4-amino-5-aminomethyl-1,2,3-triazoles were facilitated by the following values assigned to 2-amino-3-aminomethylpyrazine: [4] τ 3·49 (2H, 2-NH_2), 6·13 (2H, CH_2), and 7·64 (2H, CH_2·NH_2).

[9] A. Albert, *J. Chem. Soc.* (*C*), 1969, 152.

Most previous values for a 4-NH_2 group in 1,2,3-triazoles fall between τ 3·0 and 5·4 (*cf.* ref. 1).

That the aminomethyl group is the strongest basic centre, as expected, was shown by the lack of change in the u.v. spectrum when the monocation was formed (Table 2). The bathochromic shift seen on formation of the dication denoted addition of the second proton to a ring-nitrogen atom.[10] The greater the basic strength of the aminomethyl group, the sharper was the n.m.r. signal near τ 8·1; this seemed to imply a correlation between hydrogen bonding (intramolecular), maximal with the 3-benzyl derivative (4b), and increase in basic strength.

The wide variation (251—283 nm) in $\lambda_{max.}$ among the *o*-amino-nitriles (Table 2) contrasts with the similarity of the values (238—241 nm) found [1,5,6] for analogues lacking the cyano-group. The latter is evidently conjugated with the ring, and most strongly so when a methyl group is in the 1-position.

In the i.r. spectra (Table 3), a tendency is seen for the main C=O stretching frequency to be low, strikingly so in 5-acetamidomethyl-4-amino-2-methyl-1,2,3-triazole. This effect is attributable to internal hydrogen bonding, and is less evident in the diacyl derivatives.

Although imidazole and pyrazole have π-excessive nuclei,[10] the presence of an extra doubly-bound nitrogen atom in 1,2,3-triazole may conceivably make it π-deficient. That this is so was indicated by the weakness as bases of the aminomethyltriazoles (Table 2) in comparison with benzylamine (pK_a 9·3). This suggestion was strengthened by comparison of the pK_a value of benzoic acid (4·12) with that of 1,2,3-triazole-4-carboxylic acid [11] (3·22), the latter being the stronger. However 1,2,3-triazole is not so electron-attracting as pyrazine, a typically π-deficient nucleus, as shown by the fact that pyrazine-2-carboxylic acid [12] is more acidic (pK_a 2·92) [compare also 1,2,3-triazole [13] (pK_a 1·17) with pyrazine [14] (0·65) (both nuclei unsubstituted)]. Similar comparisons have been made for time-dependent reactions.[15]

TABLE 2

Ionization constants and u.v. spectra.

		Ionization in water (20°)				Spectroscopy in water [c]		
1,2,3-Triazole	Species [a]	pK_a	Spread ±	Concn. (M)	A.w.l.[b] (nm)	$\lambda_{max.}$/nm	log ε	pH or H_0
4-Amino-5-cyano-1-methyl	0					*215*, 283	*3·76*, 3·74	E [d]
4-Amino-5-cyano-2-methyl	0					*216*, 269	*3·74*, 3·73	7·0
	+	−1·35	0·05	0·00007	270			
4-Amino-5-cyano-3-methyl [5] (for comparison)	0					225, 251	3·95, 3·78	M [e]
4-Amino-3-benzyl-5-cyano [6] (for comparison)	0					*216*, 228, 251	*3·96*, 3·95, 3·82	E [d]
4-Amino-5-aminomethyl-1-methyl	0					249	3·62	10·0
	+	7·65	0·02	0·01	P	249	3·56	4·0
	++	1·01	0·04	0·0001	246	266	3·46	−1·2
4-Amino-5-aminomethyl-2-methyl	0					250	3·81	11·0
	+	8·58	0·04	0·01	P	249	3·73	5·0
	++	0·70	0·05	0·0001	250			
4-Amino-5-aminomethyl-3-benzyl	0					244	3·70	11·0
	+	8·85	0·04	0·005	P	244	3·70	6·0
	++	−0·45	0·06	0·00004	275	266	3·65	−2·8
5-Acetamidomethyl-4-amino-1-methyl	0					248	3·63	7·0
	+	2·19	0·03	0·00004	250	264	3·54	0·5
5-Acetamidomethyl-4-amino-3-benzyl	0					*216*, 245	*3·86*, 3·76	7·0
	+	1·00 [f]	0·04	0·00004	270			
4-Ethoxycarbonylamino-5-ethoxycarbonylaminomethyl-1-methyl	0					220	3·65	7·0
	−	12·94	0·02	0·0001	250			

[a] Neutral species (0), cation (+), dication (++), anion (−). [b] Analytical wavelength for spectrometric determination when not marked P (potentiometric determination). [c] Shoulders in italics. [d] In ethanol. [e] In methanol. [f] No other pK_a up to 12.

TABLE 3

I.r. spectrometry [a]

1,2,3-Triazole	ν/cm^{-1}
4-Amino-5-cyano-1-methyl	3420, 3330, 3200 (NH_2 str.), 2220 (C⋮N str.), 1650 (C:N str.), 1585, and 1195 (all m)
4-Amino-5-cyano-2-methyl	3400, 3330, 3220 (NH_2), 2210 (C⋮N), 1640 (C:N), 1565, and 1300 (all m)
4-Amino-5-aminomethyl-1 methyl	3420s, 3260s (NH_2), 1655m, 1590s (NH in-plane bend), 1405m, 1180m, and 915s (NH out-of-plane bend)
4-Amino-5-aminomethyl-2-methyl	3400s, 3280s (NH_2), 1630m, 1540s (NH), 1325m, and 995m
4-Amino-5-aminomethyl-3-benzyl	3380m, 3250m (NH_2), 1645m, 1600m, 1310m, 1225mw, and 725m
5-Acetamidomethyl-4-amino-1-methyl	3280s, 3080m (NH), 1665s [b], and 1630br,s [b] (CO str.), 1595m, 1565s (amide II band), 1295m, 1185m, 830m, and 750br,m
5-Acetamidomethyl-4-amino-2-methyl	3410w, 3300s (NH), 1625s, (CO) 1550s, 1355m, 1300m, and 1225m

[10] A. Albert, 'Heterocyclic Chemistry,' 2nd edn., Athlone Press, London, 1968, pp. 56, 382.
[11] L. D. Hansen, B. D. West, E. J. Baca, and C. L. Blank, *J. Amer. Chem. Soc.*, 1968, **90**, 6588.
[12] J. W. Sausville and P. E. Spoerri, *J. Amer. Chem. Soc.*, 1941, **63**, 3153.
[13] A. Albert, *J. Chem. Soc.* (*C*), 1968, 2076.
[14] A. S. Chia and R. F. Trimble, *J. Phys. Chem.*, 1961, **65**, 863.
[15] G. B. Barlin, *J. Chem. Soc.* (*B*), 1967, 641.

TABLE 3 (*Continued*)

I.r. spectrometry [a]

1,2,3-Triazole	ν/cm^{-1}
5-Acetamidomethyl-4-amino-3-benzyl	3380m, 3220s, 3030m (NH), 1655s (CO), 1600m, 1565m, 1295m, and 1245m
4-Amino-5-ethoxycarbonylaminomethyl-1-methyl	3300br (NH), 1700s (CO str.),[c] 1650s, 1585s, 1540s, 1435m, 1300m, 1280s, 1245m, 1195m, 1015m, and 790m
4-Amino-5-ethoxycarbonylaminomethyl-2-methyl	3330s (NH), 1680s (CO), 1625m, 1530s, 1275s, 1150m, and 1045m
4-Amino-3-benzyl-5-ethoxyalylaminomethyl	3500w, 3410m, 3280m (NH), 1745s (CO, ester), 1690m, 1625s (CO, amide), 1540m, 1520m, 1305m, and (1235, 1220, 1205m, asym. and sym. str. ester)
3-Benzyl-4-formamido-5-formamidomethyl	3290br,s (NH), 1675vs (CO),[d] 1535s, and 1230m
4-Acetamido-5-acetamidomethyl-1-methyl	3360s, 3100m (NH), 1695s, and 1655s (CO str.), 1560br,s (amide II band), 1445m, 1275m, and 1100m
4-Acetamido-5-acetamidomethyl-2-methyl	3400m, 3250m (NH), 1655br,s (CO), 1570s, 1545s, 1305m, 1280m, and 760m
4-Ethoxycarbonylamino-5-ethoxycarbonylaminomethyl-1-methyl	3290s, 3210m (NH), 1715s,[c] 1680s,[c] 1535s, 1450m, 1240s, 1195m, 1135m, 1065s, and 1020m
3-Benzyl-4-ethoxycarbonylamino-5-ethoxycarbonylaminomethyl	3250s, 3080m (NH), 1735m,[c] 1680s,[c] 1565s, 1270s, 1225s, 1060m, and 1020m

[a] For Nujol mulls. [b] Possibly free and associated forms, respectively. [c] $\nu_{CO\ str.}$ of carbamate group usually occurs in range 1740—1690 cm^{-1}. [d] Only one CO str. peak, but exceptionally strong.

EXPERIMENTAL

^{1}H N.m.r. spectra were measured with a Perkin-Elmer model R10 instrument operating at 33·3° and 60 MHz. U.v. spectra were recorded with a Unicam SP 800 spectrophotometer; the wavelength and intensity of each maximum were then checked with a Unicam SP 500 (series 2) manual instrument. I.r. spectra were taken with a Unicam SP 200 spectrometer calibrated with polystyrene at 1603 cm^{-1}. Ionization constants were determined as in ref. 16. M.p.s were taken with a thermometer recalibrated with National Standards Laboratories standards. Identity of compounds prepared by different routes was established by i.r. spectral, paper chromatographic and, where applicable, mixed m.p. comparisons. Yields for substances without sharp m.p. refer to material giving only one spot on paper chromatograms developed in (*a*) aqueous 3% ammonium chloride and (*b*) butanol–5N-acetic acid (7 : 3) and viewed in u.v. light of λ (mainly) 254 nm.

4-Amino-1-(and 2-)methyl-1,2,3-triazole-5-carbonitriles.—4-Dimethylaminomethyleneamino-1-methyl-1,2,3-triazole-5-carbonitrile [7] (8·9 g, 0·05 mol) and N-hydrochloric acid (75 ml) were heated under reflux for 15 min and quickly chilled. The crystals were collected, pressed, washed with water (20 ml), and recrystallized from water (10 parts), giving *4-amino-1-methyl-1,2,3-triazole-5-carbonitrile* (90%), m.p. 187°, poorly soluble in boiling benzene [Found (material dried at 85° in air): C, 38·8; H, 4·1; N, 56·5. $C_4H_5N_5$ requires C, 39·0; H, 4·1; N, 56·9%]. 4-Dimethylaminomethyleneamino-2-methyl-1,2,3-triazole-5-carbonitrile [7] (3·6 g, 0·02 mol) was heated under reflux with 2N-hydrochloric acid (15 ml) for 15 min, and the mixture was refrigerated overnight. The crystals were filtered off, pressed, washed with ice–water (only a little because they were soluble) and dried at 85°. A second crop was obtained by heating the undiluted filtrate for a further 15 min. The combined crops were boiled with benzene (10 parts); the solution was cooled, filtered from a yellow deposit, and concentrated to give *4-amino-2-methyl-1,2,3-triazole-5-carbonitrile* (80%), m.p. 115° (Found: C, 38·9; H, 4·0; N, 56·8%).

4-Amino-3-methyl-1,2,3-triazole-5-carboxamide (*Preparation 5 Improved*).—*S*-Methyl-4-amino-3-methyl-1,2,3-triazole-5-carbothioate [5] (4 g) and 14N-ammonia (aqueous; 40 ml) were stirred at 20—25° for 4 h; the mixture was then slowly (6 h) brought to the boil under reflux. The product was concentrated (to 10 ml) *in vacuo* and chilled overnight. The crystals, dried at 110°, gave the carboxamide (88%), m.p. 244°, identical with authentic material.

4-Amino-5-aminomethyl-1-methyl-1,2,3-triazole (1b).—4-Amino-1-methyl-1,2,3-triazole-5-carbonitrile (2·46 g, 0·02 mol), ethanolic 3N-ammonia (125 ml), and Raney nickel (4 g; weighed wet) were hydrogenated for 4 h at 70° and 4 atm. The solid was filtered off and refluxed with ethanol (30 ml) for 15 min; the suspension was filtered hot. The combined filtrates were taken to dryness. The residue, dissolved in ethanol (25 ml), was mixed with ethanolic M-phosphoric acid (30 ml; 1·5 equiv.), and set aside overnight at 20—25°. The supernatant was decanted from the plastic mass, which was then stirred with ethanol (20 ml). Next day the *phosphate* had crystallized and was filtered off. For analysis, it was purified by dissolution in hot water (1 ml) and precipitation with boiling ethanol (9 ml); it melted at 188—190° with effervescence [Found (material dried at 80° and 0·01 mmHg): C, 21·3; H, 5·45; N, 31·2; P, 13·4. $C_4H_9N_5,H_3PO_4$ requires C, 21·3; H, 5·4; N, 31·1; P, 13·75%]. Alternatively, the phosphate was dissolved in water (5 ml), the pH was adjusted to 11 with 10N-sodium hydroxide (about 2·5 ml), and the mixture was taken to dryness at 60°. The product was powdered finely and extracted twice by boiling with ethanol (2 × 25 ml). The combined filtrates taken to dryness gave *4-amino-5-aminomethyl-1-methyl-1,2,3-triazole* in 81% yield based on the nitrile. For analysis it was recrystallized (2 crops) from 15 parts of benzene–ethanol (4 : 1). It had m.p. 125°, was very soluble in cold water, and was soluble in 230 parts of boiling benzene [Found (material dried at 100° and 0·01 mmHg): C, 37·8; H, 7·1; N, 55·05. $C_4H_9N_5$ requires C, 37·8; H, 7·1; N, 55·1%]. The hydrochloride is only slightly soluble in cold ethanol.

4-Amino-5-aminomethyl-2-methyl-1,2,3-triazole (3a).—4-Amino-2-methyl-1,2,3-triazole-5-carbonitrile, treated similarly, gave 80% of crystalline *phosphate*, m.p. 183° (efferv.) [Found (material dried at 110° in air): C, 21·3; H, 5·5; N, 30·8; P, 13·5%]. The deliquescent free *base*, liberated quantitatively as before and recrystallized from 30 parts of benzene–cyclohexane (1 : 1), had m.p. 48° [Found (material dried over P_2O_5 at 20° and 0·01 mmHg): C, 37·9; H, 7·4; N, 54·8%].

4-Amino-5-aminomethyl-3-methyl-1,2,3-triazole (4a).—4-Amino-3-methyl-1,2,3-triazole-5-carbonitrile [5] similarly gave 60% of the 1 : 1 *phosphate*, m.p. 197° (foams) [Found: C, 21·2; H, 5·6; N, 30·2; P, 13·1%]. The free base, m.p. *ca.* 97° (from benzene), was highly deliquescent.

[16] A. Albert and E. P. Serjeant, 'The Determination of Ionization Constants,' Chapman and Hall, London, 1971.

4-Amino-5-aminomethyl-3-benzyl-1,2,3-triazole (4b).—4-Amino-3-benzyl-1,2,3-triazole-5-carbonitrile [6] (4·8 g, 0·024 mol) and Raney nickel (9·6 g) were hydrogenated in ethanolic 3N-ammonia (180 ml) for 5 h, at 70° and 4 atm. The suspension was filtered, the solid was boiled with ethanol (50 ml), and the combined filtrates were taken to dryness at (finally) 60° and 25 mmHg. The resultant glass was homogenized in hot water (48 ml) and the suspension was refrigerated, then filtered from the secondary amine (5) (15%; see later for properties). The filtrate and washings were mixed, at 100°, with enough 0·5N-phosphoric acid to give pH 7·5. The suspension was chilled and filtered. The precipitate was washed, then suspended in boiling water (20 ml). 10N-Sodium hydroxide (*ca.* 2 ml) was added until pH 12 was reached and maintained. The cooled solution was shaken with chloroform (3 × 50 ml). The united extracts were dried (K_2CO_3) and evaporated, giving 66% of pure *4-amino-5-aminomethyl-3-benzyl-1,2,3-triazole*, m.p.* 105° (from 30 parts of benzene; two crops) [Found (material dried at 80° and 0·01 mmHg): C, 59·0; H, 6·3; N, 34·1. $C_{10}H_{13}N_5$ requires C, 59·1; H, 6·45; N, 34·45%].

The neutral *phosphate*, prepared as before, was recrystallized for analysis from 120 parts of 33% ethanol, m.p. 215—216° (foams) [Found (material dried in air of 110°): C, 47·8; H, 6·0; N, 27·65; P, 6·1. $(C_{10}H_{13}N_5)_2,H_3PO_4$ requires C, 47·6; H, 5·8; N, 27·8; P, 6·1%]. An *acid phosphate*, prepared from the diamine (0·2 g) and ethanolic 3N-phosphoric acid (1 ml), and recrystallized from 5 parts of water, had m.p. 197° (foams) [Found (for material dried in air at 120°): C, 39·9; H, 5·6; N, 23·1; P, 10·2. $C_{10}H_{13}N_5,H_3PO_4$ requires C, 39·9; H, 5·4; N, 23·25; P, 10·3%].

When exposed to air, the free base forms a basic *carbonate*, m.p. 135—138°, purified by trituration with cold ethanol in which it is poorly soluble [Found (for material dried at 20° and 25 mmHg): C, 55·5; H, 5·9; N, 30·9. $(C_{10}H_{13}N_5)_3,H_2CO_3$ requires C, 55·4; H, 6·15; N, 31·2%]. A monohydrochloride, decomposing sharply at 208° and only sparingly soluble in cold water, and a more soluble monoacetate, m.p. 154—156°, and citrate, m.p. 180°, were also prepared.

Bis-(4-amino-3-benzyl-1,2,3-triazol-5-ylmethyl)amine (5).—This secondary amine, formed in traces in the hydrogenation of 4-amino-3-benzyl-1,2,3-triazole-5-carbonitrile (see before), and in 85% yield if the ammonia was omitted, was recrystallized from 400 parts of water. The *product* had m.p. 186°, was soluble in ethanol and chloroform, and was almost insoluble in boiling benzene [Found (for material dried at 110° and 0·01 mmHg): C, 61·5; H, 5·9; N, 32·5. $C_{20}H_{23}N_9$ requires C, 61·7; H, 5·95; N, 32·4%]. The acetate (but not the hydrochloride) is soluble in cold water.

Formyl Derivatives.—Acetic formic anhydride (freshly prepared; 1·3 g, 3 equiv.) was added with stirring to 4-amino-5-aminomethyl-3-benzyl-1,2,3-triazole (4b) (1·0 g, 0·005 mol) in dry pyridine (10 ml) at 20°. The solution was set aside at 22° overnight. Water (7 ml) was added, and the solvent was removed *in vacuo* at 50°. The residue was stirred with water (5 ml) and the suspension was refrigerated and filtered, giving 80% of *4-amino-3-benzyl-5-formamidomethyl-1,2,3-triazole* (4c), m.p. 155° (from 9 parts of water), insoluble in cold N-sodium hydroxide, soluble in cold N-hydrochloric (but not acetic) acid [Found (material dried at 85° in air): C, 56·9; H, 5·75; N, 29·7. $C_{11}H_{13}N_5O$ requires C, 57·1; H, 5·7; N, 30·3%]. The primary amine (4b) (1 g) and acetic formic anhydride (10 ml) were set aside at 20° for 18 h. The solution was taken to dryness at 60° and 25 mmHg. The residual gum was dissolved in water (1 ml) and the solution, adjusted to pH 5 with 2N-sodium carbonate, deposited *3-benzyl-4-formamido-5-formamidomethyl-1,2,3-triazole* (6c) (60%), m.p. 120° (from 2 parts of ethanol or of water) [Found (material dried at 80° in air): C, 55·85; H, 5·0; N, 27·0. $C_{12}H_{13}N_5O_2$ requires C, 55·6; H, 5·05; N, 27·0%].

Monoacetyl Derivatives.—Acetic anhydride (0·20 g, 1 equiv.) was added dropwise to a solution of 4-amino-5-aminomethyl-1-methyl-1,2,3-triazole (0·25 g, 0·002 mol) in aqueous pyridine (constant-boiling mixture) (2 ml) stirred at 20°, then set aside overnight. The solution was taken to dryness at 60°. Water (2 ml) was added to the residue and the pH was adjusted to 7—8. The mixture was again taken to dryness, giving 55% of *5-acetamidomethyl-4-amino-1-methyl-1,2,3-triazole* (1b), m.p. 152° (from 6 parts of ethanol) [Found (for material dried at 85° in air): C, 42·8; H, 6·5; N, 41·65. $C_6H_{11}N_5O$ requires C, 42·6; H, 6·55; N, 41·4%]. The *2-methyl isomer* (3b), similarly prepared in 65% yield, had m.p. 122° (from 33 parts of benzene) (Found: C, 42·7; H, 6·5; N, 41·5%). Acetic anhydride (2 g, 4 equiv.) was similarly added to 4-amino-5-aminomethyl-3-benzyl-1,2,3-triazole (4b) (1·0 g, 0·005 mol) in dry pyridine (10 ml). Next day, ethanol (10 ml) was added and. after 3 h, volatile material was removed at 40° and 25 mmHg. Water (4 ml) was added. Chilling and filtration furnished 90% of *5-acetamidomethyl-4-amino-3-benzyl-1,2,3-triazole*, m.p. 199° (from 45 parts of water) [Found (material dried at 105° in air): C, 58·6; H, 6·2; N, 28·7. $C_{12}H_{15}N_5O$ requires C, 58·8; H, 6·2; N, 28·6%].

Diacetyl Derivatives.—Acetic anhydride (0·80 g, 4 equiv.) was added dropwise to 4-amino-5-aminomethyl-1-methyl-1,2,3-triazole (1a) (0·25 g) suspended in dry pyridine (2 ml). After 24 h, ethanol (2 ml) was added to the solution. After 7 h, volatile material was removed *in vacuo* at 50°. Water (2 ml) was added to the residue, and volatile material was removed *in vacuo* at 60°. The flask contents, recrystallized from 13 parts of ethanol gave 75% of *4-acetamido-5-acetamidomethyl-1-methyl-1,2,3-triazole* (6a), m.p. 192°, sparingly soluble in boiling benzene [Found (material dried at 110° in air): C, 45·3; H, 6·35; N, 33·6. $C_8H_{13}N_5O_2$ requires C, 45·5; H, 6·2; N, 33·2%]. The *2-methyl isomer*, m.p. 122°, was similarly prepared, but recrystallized from benzene [Found (material dried at 85° in air): C, 45·7; H, 6·4; N, 33·6%].

Monoethoxycarbonyl Derivatives.—Ethyl chloroformate (0·22 g, 1 equiv.) was dropped into a stirred solution of 4-amino-5-aminomethyl-1-methyltriazole (1a) (0·25 g, 0·002 mol) in N-sodium carbonate (2 ml) at 20°. After 6 h, the solution was taken to dryness. The residual paste was boiled with benzene (2 × 40 ml). The concentrated extracts deposited 75% of *4-amino-5-ethoxycarbonylaminomethyl-1-methyl-1,2,3-triazole* (1c), m.p. 124° (from 100 parts of benzene), very soluble in water [Found (material dried at 85° in air): C, 42·3; H, 6·5; N, 35·2. $C_7H_{13}N_5O_2$ requires C, 42·2; H, 6·6; N, 35·2%]. Ethyl chloroformate (0·24 g, 1·1 equiv.) in ethanol (1 ml) was slowly added to a solution of 4-amino-5-aminomethyl-2-methyl-1,2,3-triazole (0·25 g) in N-sodium hydroxide (2 ml). Next day the solution was taken to dryness at 60°. Water (1 ml) was added, and the pH (9) was adjusted to >12 with 10N-sodium hydroxide. The crystals were filtered off, after refrigeration, giving 70%

* The presence of a little carbonate prevents complete melting.

of 4-*amino*-5-*ethoxycarbonylaminomethyl*-2-*methyl*-1,2,3-*triazole* (3c), m.p. 109·5° (from 3 parts of water or 20 parts of benzene–cyclohexane, 1 : 1), soluble in 35 parts of cold water (Found: C, 42·0; H, 6·5; N, 35·4%). Ethyl chloroformate (0·55 g, 1 equiv.) in chloroform (5 ml) was added dropwise to a stirred solution of 4-amino-5-aminomethyl-3-benzyl-1,2,3-triazole (1·0 g, 0·005 mol) in dry pyridine (10 ml) at 20°. After 3 h, water (8 ml) was added. Volatile material was removed *in vacuo* at 50°. Water (5 ml) was added and the suspension refrigerated and filtered giving 71% of 4-*amino*-3-*benzyl*-5-*ethoxycarbonylaminomethyl*-1,2,3-*triazole* (4d), m.p. 144° (from 24 parts of benzene) [Found (material dried at 110° in air): C, 56·4; H, 6·15; N, 25·2. $C_{13}H_{17}N_5O_2$ requires C, 56·7; H, 6·2; N, 25·4%).

Diethoxycarbonyl Derivatives.—Ethyl chloroformate (0·88 g, 4 equiv.) was slowly added to a solution of 4-amino-5-aminomethyl-1-methyltriazole (1a) (0·25 g) in 2N-sodium carbonate (5 ml). After being stirred for 12 h, the suspension was refrigerated and filtered, giving 70% of 4-*ethoxycarbonylamino*-5-*ethoxycarbonylaminomethyl*-1-*methyl*-1,2,3-*triazole* (6b), m.p. 125° (from 25 parts of benzene–cyclohexane, 1 : 1, or 27 parts of water); mixed m.p. with the monoacylated analogue (1c) (which melts at 124°) 101°. A metastable form of compound (6b), m.p. 107°, was also encountered [Found (for material dried at 80° in air): C, 44·3; H, 6·4; N, 26·1. $C_{10}H_{17}N_5O_4$ requires C, 44·3; H, 6·3; N, 25·8%]. Ethyl chloroformate (0·66 g, 3 equiv.) was dropped into a stirred solution of 4-amino-5-aminomethyl-3-benzyltriazole (0·40 g) in dry pyridine (4 ml) at 20°. After 30 min, water (3 ml) was added and the solution taken to dryness at 75° and 25 mmHg. To the cooled residue, N-sodium hydroxide (6 ml) was added, and the suspension was filtered from a trace of monoacylated product. The filtrate, adjusted to pH 6 with acetic acid, deposited 50% of 3-*benzyl*-4-*ethoxycarbonylamino*-5-*ethoxycarbonylaminomethyl*-1,2,3-*triazole* (6d), m.p. 111° (from 9 parts of benzene–cyclohexane, 1 : 1) [Found (material dried at 85°): N, 20·2. $C_{16}H_{21}N_5O_4$ requires N, 20·2%].

4-*Amino*-3-*benzyl*-5-(*ethylthio*)*carbonylaminomethyl*-1,2,3-*triazole* (4e).—*S*-Ethyl chlorothioformate (0·124 g, 1 equiv.) in chloroform (1 ml) was dropped into a solution of 4-amino-5-aminomethyl-3-benzyltriazole (4b) (0·2 g) in dry pyridine (2 ml) at 20°. After 2 h, water (2 ml) was added, and the mixture was taken to dryness at 60°. Water (1 ml) was added to the residue, which rapidly solidified; the solid was filtered off giving 83% of the *ethylthio-compound*, m.p. 162·5° (from 50 parts of benzene) (Found: C, 53·5; H, 5·7; N, 24·0; S, 10·7. $C_{13}H_{17}N_5OS$ requires C, 53·6; H, 5·9; N, 24·0; S, 11·0%).

4-*Amino*-3-*benzyl*-5-*ethoxalylaminomethyl*-1,2,3-*triazole* (4f).—The 3-benzyl amine (4b) (0·20 g), diethyl oxalate (0·75 g, 5 equiv.), and ethanol (10 ml) were heated under reflux for 1 h. The ethanol was distilled off and the residue rubbed with benzene (2 ml) to remove unchanged ester, giving 87% of the *ethoxalylaminomethyl* compound, m.p. 150° (from 13 parts of ethanol) [Found (for material dried at 110° in air): C, 55·3; H, 5·7; N, 23·25. $C_{14}H_{17}N_5O_3$ requires C, 55·4; H, 5·65; N, 23·1%].

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