v-Triazolo[4,5-*d*]pyrimidines (8-Azapurines). Part 18.[1] Three New Reactions for synthesizing 8-Azapurinethiones from 4-Amino-5-cyano-1,2,3-Triazoles †

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4-Amino-5-cyano-1,2,3-triazole (2d) and its 1-, 2-, and 3-methyl and 3-benzyl derivatives were, variously, subjected to (*a*) condensation with triethyl orthoformate followed by treatment with sodium hydrogen sulphide, (*b*) condensation with *O*-ethyl dithiocarbonate, and (*c*) condensation with phenyl isothiocyanate, to give (respectively) 8-azapurine-6-thiones (4), 8-azapurine-2,6-dithiones (6), and 6-anilino-8-azapurine-2-thiones (9). Several of the dithiones were characterized by di-*S*-methylation to give 2,6-bismethylthio-8-azapurines. The reversible isomerisation of 8-azapurine-2,6-dithione (6d) to 7-amino[1,2,3]thiadiazolo[5,4-*d*]pyrimidine-5-thione (7) was explored. I.r. and ^{1}H n.m.r. spectra are discussed.

SEVERAL sulphur-containing derivatives of purine are highly valued in clinical medicine. Of these, '6-mercaptopurine' (1a) has proved efficient in treating the acute leukaemias [2] and in immunosuppression, and the 2-amino-derivative (1b), known as 'thioguanine,' has special value in treating granulocytic leukaemia.[3] A third example 'azathioprine,' is the *S*-(1-methyl-4-nitroimidazol-5-yl) derivative of '6-mercaptopurine,' which it slowly releases in the body; it is much used in preventing rejection of organ transplants, particularly of the kidney.[4] With this background in mind, and conscious of a new interest in medical applications of 8-azapurines,[5] we have sought new reactions for the introduction of sulphur into this nucleus, because existing methods [6,7] are too restrictive.

Our starting materials were 4-amino-5-cyano-1,2,3-triazole [8] and its 1-, 2-, and 3-methyl [9] and 3-benzyl [10] derivatives (2), all readily available from 4-amino-3-benzyl-1,2,3-triazole-5-carboxamide.[11] Taylor *et al.*[12] discovered that *o*-amino-nitriles in the benzene and in some heterocyclic series formed a fused pyrimidine-4-thione ring when heated with triethyl orthoformate and then with sodium hydrogen sulphide. However, this procedure did not make our triazoles (2) undergo even the first step, namely the production of 5-cyano-4-ethoxymethyleneamino-1,2,3-triazoles (3). The π-deficient [13] character of the 1,2,3-triazole nucleus, greater than in any of the successful examples,[14] decreased electron density in the 4-amino-group sufficiently to inhibit the reaction. Fortunately, the required materials (3) were known from earlier work [7,15] in which acetic anhydride had been added to force this reaction. These

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

[1] Part 17, A. Albert, *J.C.S. Perkin I*, 1976, 291.

[2] G. H. Hitchings, G. B. Elion, E. A. Falco, P. B. Russell, M. B. Sherwood, and H. VanderWerff, *J. Biol. Chem.*, 1950, **183**, 1; J. H. Burchenal, M. L. Murphy, R. R. Ellison, D. A. Karnofsky, M. P. Sykes, T. C. Tan, L. A. Leone, L. F. Craver, H. W. Dargeon, and C. P. Rhodes, *Blood*, 1953, **8**, 965; G. Brulé, S. J. Eckhardt, T. C. Hall, and A. Winkler, 'Drug Therapy of Cancer,' World Health Organization, Geneva, 1973, pp. 46 and 74—99.

[3] B. D. Clarkson, *Cancer*, 1972, **30**, 1572.

[4] G. B. Elion, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, 1967, **26**, 898; G. B. Elion, S. W. Callahan, R. W. Rundles, and G. H. Hitchings, *Cancer. Res.*, 1963, **23**, 1207.

[5] A. Holland, D. Jackson, P. Chaplen, E. Lunt, S. Marshall, D. Pain, and K. Wooldridge, *European J. Medicin. Chem.*, 1975, **10**, 447; B. J. Broughton, P. Chaplen, P. Knowles, E. Lunt, S. M. Marshall, D. L. Pain, and K. R. H. Wooldridge, *J. Medicin. Chem.*, 1975, **18**, 1117.

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

[7] A. Albert, *J.C.S. Perkin I*, 1972, 461.

[8] A. Albert and H. Taguchi, *J.C.S. Perkin I*, 1973, 1629.

[9] A. Albert, *J.C.S. Perkin I*, 1973, 1634.

[10] A. Albert, *J. Chem. Soc.* (*C*), 1970, 230.

[11] J. R. E. Hoover and A. R. Day, *J. Amer. Chem. Soc.*, 1956, **78**, 5832.

[12] E. C. Taylor, A. McKillop, and S. Vromen, *Tetrahedron*, 1967, **23**, 885.

[13] A. Albert, 'Heterocyclic Chemistry,' Athlone Press, London, 2nd edn., 1968.

[14] E. C. Taylor and A. McKillop, 'The Chemistry of Cyclic Enaminonitriles and *o*-Aminonitriles,' Interscience, New York, 1970.

[15] A. Albert, *J.C.S. Perkin I*, 1973, 2659.

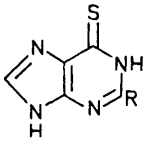
ethoxymethyleneamino-derivatives, when heated with sodium hydrogen sulphide, gave high yields of the *N*-alkylated 8-azapurine-6-thiones (4a—c).

This synthesis was also effected in reverse order. Hydrogen sulphide was combined with the nitrile (2a) to give 4-amino-3-benzyl-1,2,3-triazole-5-thiocarboxamide by a modification that greatly improved the published yield.[11] This thioamide, when condensed with triethyl orthoformate, gave the 8-azapurine-6-thione (4a), but the overall yield was less than in the alternative method. In neither approach is any of the isomeric 7-aminothiadiazolopyrimidine, *e.g.* (5), formed; such products complicated the original synthesis of 8-azapurine-6-thiones.[6]

Another reaction, in which *o*-amino-nitriles were condensed with carbon disulphide in pyridine to give fused pyrimidine-2,4-dithiones,[16] succeeded with two of our nitriles (2b and c), giving quantitative yields of *N*-alkylated 8-azapurine-2,6-dithiones (6b and c). The other three nitriles (2a, d, and e) responded to severer conditions in which carbon disulphide was made available at a much higher temperature by boiling the nitrile with potassium *O*-ethyl dithiocarbonate[17] in dimethylformamide. All four *N*-alkyl-8-azapurine-2,6-dithiones, being unstable, were characterized by quantitative conversion into *S*-methyl derivatives (*N*-alkyl-2,6-bismethylthio-8-azapurines) under mild conditions. The non-alkylated dithione (6d) was stable enough for microanalysis, but isomerized in boiling butanol to 7-amino[1,2,3]thiadiazolo[5,4-*d*]pyrimidine-5-thione (7), a reaction easily reversed by boiling with N-sodium hydroxide. This isomerization differs from the Christmas rearrangement and retrogression[18] [*e.g.* the transformation of the azapurines (4a, d, and e) into thiadiazolopyrimidines of type (5)] in that both equilibrating compounds are acids, so that the driving force of anion formation in the retrogression[18] does not apply here.

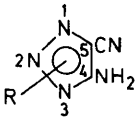
So far, 8-azapurine-2,6-dithiones had been prepared only by the fusion of *N*-alkylated 4-amino-1,2,3-triazole-5-carboxamides with urea, followed by treatment of the products with phosphorus pentasulphide.[19] The new reaction gives much better yields.

As a model for a reaction between our aminocyanotriazoles (2) and phenyl isothiocyanate, it was noted that 2-aminobenzonitrile gave[20] the corresponding



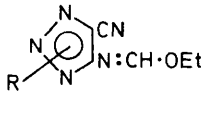
(1)

a; R = H
b; R = NH_2



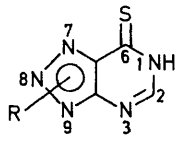
(2)

a; R = 3-CH_2Ph
b; R = 1-Me
c; R = 2-Me
d; R = H
e; R = 3-Me



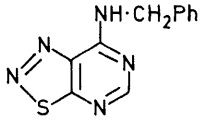
(3)

R as in (2a-c)

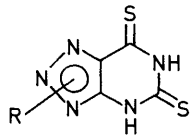


(4)

R as in (2a-c)

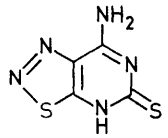


(5)

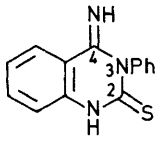


(6)

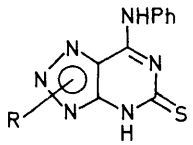
R as in (2a-e)



(7)

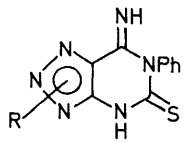


(8)



(9)

R as in (2a-d)



(10)

R as in (2)

[16] E. C. Taylor, A. McKillop, and R. N. Warrener, *Tetrahedron*, 1967, **23**, 891; R. J. Rousseau and L. B. Townsend, *J. Org. Chem.*, 1968, **33**, 2828.

[17] C. C. Price and G. W. Stacy, *Org. Synth.*, Coll. Vol. III, 1955, p. 668; H.-J. Kabbe, *Synthesis*, 1972, 268.

[18] A. Albert and K. Tratt, *Angew. Chem.*, 1966, **78**, 596.

[19] A. Albert and H. Taguchi, *J.C.S. Perkin I*, 1972, 449.

[20] E. C. Taylor and R. V. Ravindranathan, *J. Org. Chem.*, 1962, **27**, 2622.

phenylthiourea at 50 °C (no solvent), and boiling methanol converted this product into 3,4-dihydro-4-imino-3-phenylquinazoline-2-thione (8); this was then transformed by boiling (154 °C) dimethylformamide into 4-anilinoquinazoline-2-thione. Under these conditions, our amino-nitriles (2) gave hardly any of the expected alkali-soluble products (9) and (10). It was then discovered that boiling pyridine, alone of many solvents tried, specifically forced the reaction of the 1-methyl and 2-methyl amino-nitriles (2b and c), giving excellent yields of 6-anilino-7-(and 8-)methyl-8-azapurine-2-thione (9b and c). When this reaction was repeated at 24 °C, the same products were obtained, although in lower yields, which indicates that the imino-intermediates (10) are transformed by Dimroth rearrangement [21] as fast as they are produced. The constitution of the 6-anilino-products (9b and c) was established by acidic hydrolysis to the known [17] 2-mercapto-7-(and 8-)methyl-8-azapurin-6-one and aniline. The benzyl amino-nitrile (2a), reacting less readily with phenyl isothiocyanate, gavé a low yield of 6-anilino-9-benzyl-8-azapurine-2-thione (9a), which resisted acidic hydrolysis.

None of the amino-nitriles (2a—d) could be induced to react with methyl isothiocyanate, thioacetamide, or thiourea. However, it was shown, by degradation to 4-aminoquinazoline, that the product from 2-aminobenzonitrile and thiourea is 4-aminoquinazoline-2-thione and not the isomeric 2-amino-4-thione, an alternative orientation that had not been eliminated in this type of reaction.[14]

Physical Properties.—I.r. spectra, reported in the Experimental section for four thiones [(6d), (7), and (9a and c)], show typical strong C:S stretching bands in the 1 160—1 180 cm^{-1} region, and also strong C(:S)N bands at 1 560—1 585 cm^{-1} corresponding to the Amide II bands of oxygen analogues.[22] All show NH stretching in the 3 300—3 600 cm^{-1} region. 8-Azapurine-2,6-dithione has a curious strong and broad band, 2 873—3 088 cm^{-1}, similar to that for 8-azapurine-6-thione in a KBr disc,[6] and apparently the sulphur equivalent of an Amide I band. ^1H N.m.r. spectra, reported for five compounds, show typical [19] SMe signals at τ 7.2—7.4, the usual [15,19] NMe signals at 5.6—5.8, and the characteristic [15] benzyl signals at 2.6—2.8 and 4.2—4.3 (all singlets). Phenyl, when part of an anilino-group, afforded a complex multiplet in the 1.6—3.1 region.

The published u.v. spectrum of 8-methyl-6-methylthio-8-azapurine is amended in the Experimental section.

EXPERIMENTAL

The thermometer used for m.p. determinations was calibrated with the National Bureau of Standards set of specimens. I.r. spectra were obtained (for Nujol mulls, except where otherwise specified) with a Perkin-Elmer 567 grating instrument. ^1H N.m.r. spectra were taken with a Varian EM-360 spectrometer at 25 °C, with $(CD_3)_2SO$ as solvent and tetramethylsilane as internal standard. Specimens said to be identical were compared by (i) mixed m.p. where applicable, (ii) i.r. spectroscopy, and (iii) comparative chromatography on two Whatman No. 1 papers, developed in (*a*) 3% aqueous NH_4Cl and (*b*) butanol–5N-acetic acid (7 : 3). Compounds were dried for analysis mostly over phosphorus pentaoxide at 80—100 °C and 0.01 mmHg. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

The sodium hydrogen sulphide solutions were prepared by passing hydrogen sulphide (dried over $CaCl_2$) into a solution made from sodium and anhydrous ethanol, until phenolphthalein paper was no longer coloured (*ca.* 10 h). They were preserved in a refrigerator for up to 2 weeks.

8-*Azapurine-6-thiones.*—(*a*) *Preferred method.* 3-Benzyl-5-cyano-4-ethoxymethyleneamino-1,2,3-triazole [15] (0.10 g, 0.000 4 mol) and 0.075M-sodium hydrogen sulphide (8 ml, 1.5 equiv.) were heated under reflux for 10 h. The dark green solution was taken to dryness at 60 °C and 25 mmHg, and water (5 ml) was added. The pH was raised to 10 with N-sodium hydroxide and, after clarification, the filtrate was acidified (below 5 °C) to pH 2 with 5N-sulphuric acid. The precipitate, dried at 25 °C, gave 9-benzyl-8-azapurine-6-thione (83%), m.p. 150°, identical with authentic material.[6] Halving or doubling the reflux time lowered the yield to 50%.

(*b*) 4-Amino-3-benzyl-1,2,3-triazole-5-thiocarboxamide (see following) (0.05 g), triethyl orthoformate (2 ml), and acetic anhydride (0.17 ml), heated under reflux for 4 h and worked up as in (*a*), gave a 33% yield of the thione.

5-Cyano-4-ethoxymethyleneamino-1-(and 2-)methyl-1,2,3-triazole [7] (0.05 g, 0.000 28 mol) and ethanolic 0.2M-sodium hydrogen sulphide (2.8 ml, 2 equiv.) were heated under reflux for 10 h. The products, obtained as in (*a*) (in 90 and 97% yields, respectively), after recrystallization from water and drying at 110 °C, did not depress the m.p.s of authentic materials.[23,24]

4-*Amino*-3-*benzyl*-1,2,3-*triazole*-5-*thiocarboxamide.*— Dried hydrogen sulphide was bubbled for 4 h at 24 °C through a solution of 4-amino-3-benzyl-5-cyano-1,2,3-triazole [10] (0.20 g, 0.001 mol) and triethylamine (0.10 g) in dried pyridine (2 ml). Dilution with water precipitated the thioamide in 81% yield [m.p. 225—227° (from nitromethane)] (*cf.* 48% in the published method,[11] where ammonia was the only base).

8-*Azapurine*-2,6-*dithiones.*— 4-Amino-3-benzyl-5-cyano-1,2,3-triazole (0.05 g, 0.000 25 mol), potassium *O*-ethyl dithiocarbonate (0.08 g, 0.000 5 mol, 2 equiv.), and dimethylformamide (3 ml) were heated under reflux for 2 h. The solvent was removed *in vacuo*. The residue was dissolved in N-sodium hydroxide (4 ml), the solution was clarified, and the filtrate was stirred with iodomethane (0.15 g, 4 equiv.) at 24 °C for 1 h. The precipitate, dried and recrystallized from light petroleum (b.p. 60—80 °C), gave 9-*benzyl*-2,6-*bismethylthio*-8-*azapurine* (3-*benzyl*-5,7-*bismethylthio*-v-*triazolo*[4,5-d]*pyrimidine*) (93%), m.p. 93° (Found: C, 51.5; H, 4.5; N, 22.95. $C_{13}H_{13}N_5S_2$ requires C, 51.45; H, 4.3; N, 23.1%), τ 2.60 (5 H), 4.17 (2 H), and

[21] D. J. Brown in 'Mechanisms of Molecular Migrations,' ed. B. S. Thyagarajan, Interscience–Wiley, New York, 1968, vol. 1, p. 209 (review).

[22] K. Nakanishi, 'Infrared Absorption Spectroscopy,' Holden–Day, San Francisco, 1962.

[23] A. Albert and K. Tratt, *J. Chem. Soc.* (*C*), 1968, 344.

[24] A. Albert, *J. Chem. Soc.* (*C*), 1968, 2076.

7.28 and 7.38 (each 3 H). Similarly, 4-amino-5-cyano-3-methyl-1,2,3-triazole [25] (0.031 g, 0.000 25 mol) gave 9-*methyl*-2,6-*bismethylthio*-8-*azapurine* (3-*methyl*-5,7-*bismethylthio*-v-*triazolo*[4,5-d]*pyrimidine*) (93%), m.p. 130° [from ethanol–water (1 : 9)] (Found: C, 37.1; H, 3.9; N, 30.8. $C_7H_9N_5S_2$ requires C, 37.0; H, 4.0; N, 30.8%), τ 5.8 (3 H) and 7.2 and 7.3 (each 3 H).

4-Amino-5-cyano-2-methyl-1,2,3-triazole [9] (0.05 g, 0.000 4 mol), carbon disulphide (0.5 ml), and dried pyridine (0.5 ml) were heated under reflux (bath temp. 115 °C) for 2 h. Volatile materials were removed at 90 °C and 25 mmHg. The residue was triturated with N-sodium hydroxide (4 ml), the solution was clarified, and the filtrate was stirred at 24 °C for 1 h with iodomethane (0.23 g, 4 equiv.). The yellow precipitate of 8-methyl-2,6-bismethylthio-8-azapurine, dried at 110 °C (overall yield 96%), was identical with authentic material.[19] 7-Methyl-2,6-bismethylthio-8-azapurine, made similarly in 95% overall yield from 4-amino-5-cyano-1-methyl-1,2,3-triazole,[9] did not depress the m.p. of authentic material.[19]

4-Amino-5-cyano-1,2,3-triazole [8] (0.05 g, 0.000 46 mol), potassium *O*-ethyl dithiocarbonate (0.074 g, 2 equiv.), and dimethylformamide (3 ml) were heated under reflux for 3 h. The solvent was removed at 110 °C and 25 mmHg, and the residue was dissolved in N-sodium hydroxide. The solution was clarified and the product, reprecipitated with sulphuric acid, gave yellow 8-*azapurine*-2,6-*dithione* (v-*triazolo*[4,5-d]*pyrimidine*-5,7-*dithione*) (88%) for which no recrystallizing solvent could be found. It remained unmelted at 300 °C, and gave a single yellow fluorescing spot on a paper chromatogram (R_F 0.30 in NH_4Cl) (Found: C, 26.05; H, 1.8; N, 37.6. $C_4H_3N_5S_2$ requires C, 25.9; H, 1.6; N, 37.8%), $\nu_{max.}$ 3 600s, 3 410s, 1 560br,s, 1 310s, and 1 163m cm^{-1} (also an extra band in hexachlorobutadiene mull at 2 873—3 088s cm^{-1}).

7-*Amino*[1,2,3]*thiadiazolo*[5,4-d]*pyrimidine*-5-*thione* (7).—A suspension of the dithione (6d) (0.015 g) in butanol (2 ml), heated under reflux for 1 h and cooled, deposited the *thiadiazolopyrimidine isomer* (7) quantitatively. It remained unmelted at 300°, was soluble in alkali, and gave a single dark (absorption) spot on a paper chromatogram (R_F 0.40 in NH_4Cl) (Found: C, 26.1; H, 1.6; N, 37.6%), $\nu_{max.}$ 3 353s, 1 648m, 1 560s, 1 523s, and 1 176m cm^{-1}.

6-*Anilino*-8-*azapurine*-2-*thiones*.—4-Amino-5-cyano-1-methyl-1,2,3-triazole (0.05 g, 0.000 4 mol), phenyl isothiocyanate (0.054 g, 0.000 4 mol), and dried pyridine (5 ml) were heated under reflux for 4 h. The pyridine was removed *in vacuo*. The residue, recrystallized from 6 parts of dimethylformamide–water (1 : 1), gave 6-*anilino*-7-*methyl*-8-*azapurine*-2-*thione* (7-*anilino*-1-*methyl*-v-*triazolo*[4,5-d]*pyrimidine*-5-*thione*) (95%), m.p. 253° (Found: C, 51.0; H, 4.0; N, 32.7. $C_{11}H_{10}N_6S$ requires C, 51.15; H, 3.9; N, 32.5%), τ 2.32—3.10 (6 H, NHPh) and 5.62 (3 H). Hydrolysis in boiling N-hydrochloric acid for 4 h gave, quantitatively, 2-mercapto-7-methyl-8-azapurin-6-one, which did not depress the m.p. of authentic material.[19] 6-*Anilino*-8-*methyl*-8-*azapurine*-2-*thione* (7-*anilino*-2-*methyl*-v-*triazolo*[4,5-d]*pyrimidine*-5-*thione*), m.p. 254—256° (from 9 parts of 1 : 1 dimethylformamide–water), was similarly prepared in 85% yield (Found: C, 51.0; H, 3.8; N, 32.5%), τ 1.66—2.93 (6 H, NHPh) and 5.60 (3 H), $\nu_{max.}$ 3 483s, 3 381s, 2 740s, 1 638m, 1 580m, and 1 180m cm^{-1}.

4-Amino-3-benzyl-5-cyano-1,2,3-triazole (0.10 g, 0.000 5 mol), phenyl isothiocyanate (0.068 g), and pyridine (5 ml) were heated under reflux for 4 h. The solvent was removed *in vacuo*. The residue was ground with N-sodium hydroxide (20 ml) and the solution filtered from much insoluble material. The filtrate, acidified to pH 2, deposited unstable material, m.p. *ca.* 150° (possibly 9-benzyl-1,6-dihydro-6-imino-1-phenyl-8-azapurine-2-thione) (10a), which was converted by refluxing with methanol for 2 h into 6-*anilino*-9-*benzyl*-8-*azapurine*-2-*thione* (7-*anilino*-3-*benzyl*-v-*triazolo*[4,5-d]*pyrimidine*-5-*thione*), m.p. 263° (from dimethylformamide–water, 1 : 1), in 20% overall yield (Found: C, 61.1; H, 4.1; N, 25.15. $C_{17}H_{14}N_6S$ requires C, 61.1; H, 4.2; N, 25.1%), M^+ 334, τ 1.90—3.20 (7 H, NH and NHPh), 2.80 (5 H, CH_2Ph), and 4.28 (2 H), $\nu_{max.}$ 3 333s, 1 630m, 1 585m, 1 355m, and 1 174 cm^{-1}.

4-*Aminoquinazoline*-2-*thione*.—2-Aminobenzonitrile (2.0 g, 0.017 mol) and thiourea (1.4 g, 1.1 equiv.) were heated at 190 °C for 2 h. The cooled melt was triturated with N-sodium hydroxide (20 ml). The filtrate, acidified to pH 5.5, deposited a solid which, recrystallized from ethanol, furnished a 30% yield of the thione, m.p. 301° (lit.,[26] 300°) (Found: C, 54.6; H, 4.1; N, 23.6. Calc. for $C_8H_7N_3S$: C, 54.8; H, 3.9; N, 23.7%). When heated under reflux with Raney nickel in ethanol it was converted into 4-aminoquinazoline, identical with authentic material.[27]

8-*Methyl*-6-*methylthio*-8-*azapurine*.—The published u.v. spectrum [24] requires amendment to $\lambda_{max.}$ 217 (log ε 4.07), 262 (3.73), 270 (3.74), and 3.15 nm (4.15) at pH 7.

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