v-Triazolo[4,5-*d*]pyrimidines (8-Azapurines).† Part XI.[1] Preparation of 2-Benzyl-*v*-triazolo[4,5-*d*]pyrimidine (8-Benzyl-8-azapurine)

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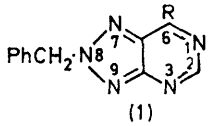
4-Formamido-1,2,3-triazole-5-carboxamide ‡ (2) (anion) on treatment with benzyl chloride gave the 2-benzyl derivative, which was converted by hot formamide into 2-benzyl-*v*-triazolo[4,5-*d*]pyrimidin-7(6*H*)-one (8-benzyl-8-azapurin-6-one) (3a). The latter, with phosphorus pentasulphide, produced the corresponding 7-thione (3b), which was desulphurised with nickel to give 2-benzyl-6,7-dihydro-*v*-triazolo[4,5-*d*]pyrimidine (8-benzyl-1,6-dihydro-8-azapurine) readily oxidised by potassium ferricyanide to 2-benzyl-*v*-triazolo[4,5-*d*]pyrimidine (8-benzyl-8-azapurine) (1a). The last-named was also prepared by oxidising 2-benzyl-7-hydrazino-*v*-triazolo[4,5-*d*]-pyrimidine (1c), obtained from hydrazine and the 7-methylthio-compound (1b), which was made by methylating the 7-thione (3b). ^{1}H N.m.r. spectra were recorded and assigned for all substances.

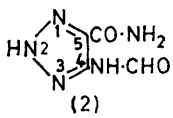
THIS paper reports two syntheses of 8-benzyl-8-azapurine (1a), a potentially useful intermediate for preparing 8-azapurines methylated in the pyrimidine ring on the assumption that there will be steric hindrance to methylation in the usually preferred [2] triazole ring.

It has been shown [3] that the anion of 4-formamido-1,2,3-triazole-5-carboxamide ‡ (2) can be methylated almost exclusively in the 2-position. In the present work, 2-benzyl-4-formamido-1,2,3-triazole-5-carboxamide was prepared similarly and converted by hot formamide into (chromatographically homogeneous) 8-benzyl-8-azapurin-6-one (3a). The latter and phosphorus pentasulphide gave the 6-thione (3b), which was methylated, with iodomethane in cold aqueous sodium hydroxide, to give the 6-methylthio-derivative (1b). Following the usual procedure,[3-5] this methylthio-compound was heated with hydrazine in methanol, and the resulting 6-hydrazino-derivative (1c) was oxidised with silver oxide. In the present case, this oxidative step did not proceed satisfactorily, so attention was turned to the removal of sulphur from the 6-thione (3b) by Raney nickel. In spite of previous failures [3,4] with this reagent in the 8-azapurine series, the reaction gave a high yield of a dihydro-derivative of 8-benzyl-8-azapurine. In the light of a comparison

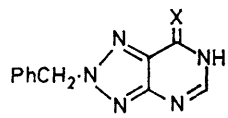


(1)

a; R = H
b; R = SMe
c; R = NH·NH$_2$



(2)



(3)

a; X = O
b; X = S

of its u.v. and n.m.r. spectra with those of other 1,6-dihydro-8-azapurines,[6] this compound was identified as the 1,6-dihydro-derivative. It was oxidised to 8-benzyl-8-azapurine (1a) by alkaline potassium ferricyanide in high yield (this is the first record of the successful oxidation of a dihydro-8-azapurine).

9-Benzyl-8-azapurine (m.p. 117°) [6] is a very weak base (pK_a −0·05); the u.v. spectrum of its cation ($\lambda_{max.}$ 262 nm) resembles that of the neutral species (263). The new isomer is a much stronger base (pK_a 3·31), and the main u.v. absorption of the cation ($\lambda_{max.}$ 256 nm) is markedly hypsochromic relative to that of the neutral species (273 nm); the ^{1}H n.m.r. signals for the hydrogen atoms on C-2 and C-6 undergo a large upfield shift when the molecule is converted into the cation. These data, which closely resemble the corresponding figures for 8-methyl-8-azapurine and its hydrated cation,[3] indicate that the cation of the 8-benzyl compound is also covalently hydrated across the 1,6-bond.

EXPERIMENTAL

The n.m.r. spectra were determined with a Perkin-Elmer model R10 instrument operating at 33·3° (unless specified otherwise) and 60 MHz; tetramethylsilane was the internal standard. Other physical data were obtained as before.[1] Except where otherwise stated, specimens for analysis were dried at 55—65° and 0·1mmHg.

2-Benzyl-4-formamido-1,2,3-triazole-5-carboxamide.—The anhydro-dimer [3] of 4-formamido-1,2,3-triazole-5-carboxamide (8·76 g, 0·03 mol), dimethylformamide (60 ml), finely ground, dried potassium carbonate (5 g, 0·036 mol), and benzyl chloride (8·35 g, 1·1 equiv.) were stirred briefly at 20°, then for 3 h at 90°. Water (200 ml) and methanol (30 ml) were then added and the mixture was refrigerated to give the *2-benzyl derivative* (75%), m.p. 165° (from methanol) (Found: C, 53·6; H, 4·5; N, 28·85. $C_{11}H_{11}N_5O_2$ requires C, 53·9; H, 4·5; N, 28·6%), τ [$(CD_3)_2SO$; 60°] 0·16br (1H, NH), 1·35 (1H, s, CHO; signal not visible below 40°), 2·32br (2H, NH_2), 2·82 (5H, s, Ph), and 4·38 (2H, s, CH_2), $\lambda_{max.}$ (EtOH) 239 nm (log ε 3·95).

2-Benzyl-v-triazolo[4,5-d]*pyrimidin-7*(6H)*-one* (*8-Benzyl-8-azapurin-6-one*) (3a).—The foregoing triazole (3 g, 0·012 mol) was heated with formamide (12 ml) in an open vessel at 200° for 45 min. The mixture was cooled and water

† This series was previously entitled '1,2,3,4,6-Penta-azaindenes'.

‡ In this paper, and throughout this series, the amino-group of aminotriazoles is numbered 4 to facilitate comparisons.

[1] Part X, A. Albert, preceding paper.

[2] A. Albert, W. Pfleiderer, and D. Thacker, *J. Chem. Soc.* (*C*), 1968, 1084.

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

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

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

[6] A. Albert, *J. Chem. Soc.* (*B*), 1966, 427.

(24 ml) was added. The solid was filtered off and gave the *triazolopyrimidinone* (96%), m.p. 242° [from methanol (130 ml)] (Found: C 58·0; H, 4·25; N, 31·3. $C_{11}H_9N_5O$ requires C, 58·1; H, 4·0; N, 30·8%), τ [$(CD_3)_2SO$] 1·89 (1H, s, CH), 2·61 (5H, s, Ph), and 4·13 (2H, s, CH_2).

2-*Benzyl*-v-*triazolo*[4,5-d]*pyrimidin*-7(6H)-*thione* (8-*Benzyl*-8-*azapurine*-6-*thione*) (3b).—Redistilled phosphorus pentasulphide (12 g; Fluka) was heated under reflux for 1 h with a solution of the cyclic amide (3a) (3 g) (0·013 mol) in dried pyridine (40 ml). The mixture was cooled, water (80 ml) was added, and the product was filtered off. A second crop was obtained by evaporating the filtrate *in vacuo* and adding water (20 ml). The combined solids, gave the *thione* (3b) (82%), m.p. 244° [from ethanol (200 ml)] (Found: C, 54·5; H, 3·8; N, 28·8. $C_{11}H_9N_5S$ requires C, 54·3; H, 3·7; N, 28·8%), τ [$(CD_3)_2SO$] 1·83 (1H, s, CH), 2·61 (5H, s, Ph), and 4·11 (2H, s, CH_2).

2-*Benzyl*-7-*methylthio*-v-*triazolo*[4,5-d]*pyrimidine* (8-*Benzyl*-6-*methylthio*-8-*azapurine*) (1b).—To a solution of the thione (3b) (1 g, 0·004 mol) in 2N-sodium hydroxide (5 ml), cooled in ice, was added iodomethane (1 ml, 4 equiv.). The mixture was stirred vigorously for 1 h and filtered. The solid, well washed with water and recrystallised from methanol (200 ml), gave the *methylthio-derivative* (1b) (95%), m.p. 153° (Found: C, 55·5; H, 4·1; N, 27·4. $C_{12}H_{11}N_5S$ requires C, 56·0; H, 4·3; N, 27·2%), τ [$(CD_3)_2SO$] 1·07 (1H, s, CH), 2·60 (5H, s, Ph), 3·98 (2H, s, CH_2), and 7·29 (3H, s, Me).

2-*Benzyl*-7-*hydrazino*-v-*triazolo*[4,5-d]*pyrimidine* (8-*Benzyl*-6-*hydrazino*-8-*azapurine*) (1c).—Hydrazine hydrate (2 ml) was added to the methylthio-compound (1b) (0·8 g, 0·003 mol) in boiling methanol (75 ml), and refluxing was continued for 25 min. The refrigerated mixture was filtered and the product, washed with water (10 ml), gave the analytically pure *hydrazino-derivative* (1c) (90%), m.p. 270° (after turning orange near 210° and slow evolution of gas) [Found (material dried at 25° and 0·01 mmHg): C, 54·9; H, 4·65; N, 40·95. $C_{11}H_{11}N_7$ requires C, 54·8; H, 4·6; N, 40·6%], τ [$(CD_3)_2SO$] 1·70 (1H, s, CH), 2·60 (5H, s, Ph), and 4·12 (2H, s, CH_2).

2-*Benzyl*-6,7-*dihydro*-v-*triazolo*[4,5-d]*pyrimidine* (8-*Benzyl*-1,6-*dihydro*-8-*azapurine*).—A suspension of the thione (3b) (0·8 g), methanol (100 ml), and Raney nickel (5 g wet weight) was heated under reflux for 2 h, then filtered. From the filtrate, concentrated *in vacuo*, a little water precipitated the *dihydrotriazolopyrimidine* (75%), m.p. 153° (from dilute methanol) (Found: C, 62·45; H, 5·45; N, 33·2. $C_{11}H_{11}N_5$ requires C, 62·0; H, 5·2; N, 32·85%), τ ($CDCl_3$) 2·68 (5H, s, Ph), 2·93 (1H, d, *J* 5 Hz, CH), 3·9—4·1 (1H, NH), 4·60 (2H, s, PhCH_2), and 5·12 (2H, s, CH_2), pK_a (basic) 5·62 ± 0·04 (concn. 0·0001M), $\lambda_{max.}$ (neutral species in water) 284 nm (log ε 4·03), (cation) 267 nm (log ε 3·93).

2-*Benzyl*-v-*triazolo*[4,5-d]*pyrimidine* (8-*Benzyl*-8-*azapurine*) (1a).—(*a*) (preferred method). To the finely ground dihydro-derivative (0·213 g, 0·01 mol) suspended in benzene (30 ml) were added 2N-potassium hydroxide (5 ml), then 0·4M-potassium ferricyanide (5·5 ml) in one portion. The mixture was stirred vigorously for 30 min and the benzene layer was separated. More benzene (15 ml) was added and the mixture was stirred and separated as before. The combined benzene solutions were washed with water (2 × 10 ml), dried ($MgSO_4$), evaporated to low bulk, and diluted with light petroleum (b.p. 80—100°) until just opalescent. The solution was set aside at 20°, then filtered, and the crystals, either recrystallised from water or sublimed at 90° and 0·01 mmHg, furnished the *triazolopyrimidine* (1a) (70—80%), m.p. 99° (Found: C, 62·2; H, 4·4; N, 33·4. $C_{11}H_9N_5$ requires C, 62·55; H, 4·3; N, 33·2%), τ ($CDCl_3$) 0·48 (1H, s, 7-H), 0·73 (1H, s, 5-H), 2·61 (5H, s, Ph), and 4·05 (2H, s, CH_2), τ (N-DCl) 1·47 (1H, s, 7-H), 2·63 (5H, s, Ph), 3·33 (1H, s, 5-H), and 4·36 (2H, s, CH_2), pK_a (basic) 3·31 ± 0·04 (concn. 0·00002M), $\lambda_{max.}$ (neutral species in water) 273 nm (log ε 4·11), (cation) 256 nm (log ε 4·08). It is slowly decomposed by cold N-hydrochloric acid.

(*b*) 2-Benzyl-7-hydrazino-*v*-triazolo[4,5-*d*]pyrimidine (1c), dissolved in the minimum amount of propan-2-ol, was heated under reflux with silver oxide (1·5 equiv.; Fluka puriss.) with stirring for 1 h. A small amount of kieselguhr was added and the hot solution was filtered. The solvent was removed at 40° and the product sublimed to give the triazolopyrimidine (1a) (*ca.* 25%).

Microanalyses were performed by Dr. J. E. Fildes and her staff; u.v. spectra were determined by Mr. J. Lazdovskis under the supervision of Dr. E. Spinner, and n.m.r. spectra by Mr. S. E. Brown under Dr. T. J. Batterham, all of whom we thank.

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