Clarification of the Ring-closure of Certain 4,5-Diaminopyrimidines to 6-Substituted 8-Alkylpurines

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Acylation of 5,6-diaminopyrimidin-4(3*H*)-one (I) furnished the bisacylamino-derivatives (IIa—d). Contrary to previous reports, treatment of these diamides (IIa—d) with refluxing aqueous base did not furnish 8-alkylpurines, but the monoacylaminopyrimidinone derivatives (IIIa—d). The monoacylamino-derivatives (IIIa—d) are conveniently ring-closed to 8-alkyl-6-chloro-9*H*-purines with phosphoryl chloride. Acylation of 4,5,6-triaminopyrimidine (VI) gave monoacylamino-derivatives (VIIa and b) which underwent ready ring-closure to 8-alkyl-9*H*-adenines (VIIIa and b) in aqueous alkali.

RING-CLOSURE of aminopyrimidines to purines has been extensively studied, and formation of 8-alkylpurines has been the subject of several investigations beginning with Isay's synthesis of 8-methylpurine in 1906.[1]

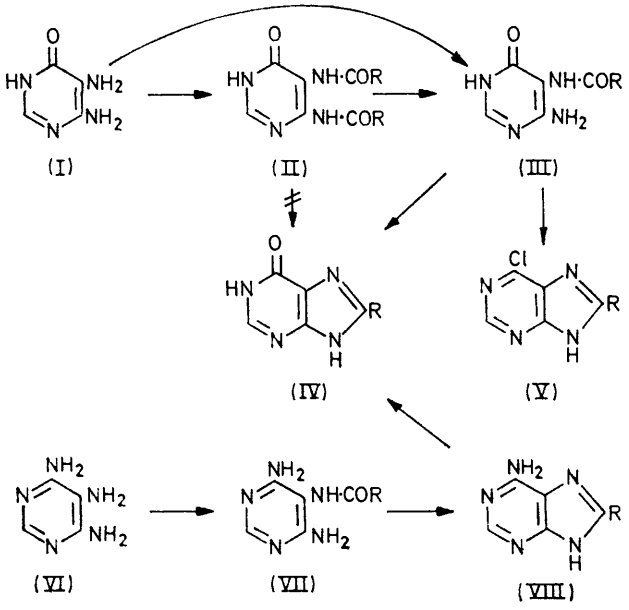
While preparing a number of 8-alkylpurine derivatives as potential antiviral agents, we repeated an earlier synthesis[2] of 8-methylhypoxanthine as well as the recently reported[3] synthesis of 8-hydroxymethylhypoxanthine. Treatment of 5,6-diaminopyrimidin-4(3*H*)-one (I) with acetic anhydride at reflux followed by refluxing base was claimed to give 8-methylhypoxanthine and treatment of the same diaminopyrimidine (I) with ethyl glycolate at reflux to give 8-hydroxymethylhypoxanthine. N.m.r. analyses clearly showed, however, that both products obtained (IIId and c, respectively) possessed an amino-group (δ 6·33 and 6·27).

[1] O. Isay, *Ber.*, 1906, **39**, 250.

[2] H. C. Koppel and R. K. Robins, *J. Org. Chem.*, 1958, **23**, 1457.

[3] A. Giner-Sorolla and D. M. Brown, *J. Chem. Soc.* (*C*), 1971, 126.

Since both compounds were reported [2,3] as monohydrates, and since no water of hydration was evident in the n.m.r. spectra, it was clear that (IIIc and d) were not the desired purines but were 5-acylaminopyrimidine



derivatives. Koppel and Robins [2] have reported that the compound (IIId) is converted by phosphoryl chloride into 6-chloro-8-methyl-9*H*-purine. Fu *et al.*[4] have stated that treatment of 6-amino-5-aroylaminopyrimidin-4(3*H*)-ones with phosphoryl chloride results in attack of chlorine at the 4-keto-group with *concomitant* dehydration and ring-closure to give an 8-aryl-6-chloro-9*H*-purine, which would explain why the failure of the acetic anhydride–base treatment to effect ring-closure of (I) went undetected.

Deamination of 8-methyl- and 8-hydroxymethyl-9*H*-adenine (VIIId and c) with nitrous acid gave the corresponding hypoxanthine derivatives (IVd and c) which differed from (IIId and c).

To confirm the identity of compounds (IIIc and d) and add to our understanding of the purine ring-closure, the diaminopyrimidinone (I) was acylated with isobutyryl chloride (or pivaloyl chloride) in pyridine at room temperature. The product (IIa) [or (IIb)] was characterized by elemental analysis and n.m.r. spectra as 5,6-bisisobutyrylamino-(or 5,6-bispivaloylamino-)pyrimidin-4(3*H*)-one. Treatment of the bisacylamino-derivatives (IIa and b) with refluxing alkali gave the monoacylamino-derivatives (IIIa and b), which possessed correct elemental analyses, and n.m.r. spectra similar to those obtained from (IIIc and d). Treatment of the monoacylamino-derivatives (IIIa and b) with phosphoryl chloride gave 6-chloro-8-isopropyl-9*H*-purine (Va) and 6-chloro-8-isobutyl-9*H*-purine (Vb), respectively.

Similarly, treatment of (I) with glycolic acid,[5] by a modification of the fusion procedure of Bredereck *et al.*,[6] gave the 5-glycoloylamino-derivative (IIIc). The elemental analysis and spectral data for (IIIc) were identical with those of the product of the reaction of ethyl glycolate and (I) as described by Giner-Sorolla and Brown.[3] Treatment of (IIIc) with aqueous base gave, not the corresponding purine derivative, but only the starting material (I). Fusion of (IIIc) with potassium acetate at 200° gave a 30% yield of 8-hydroxymethyl-9*H*-hypoxanthine (IVc), identical with the product of the deamination of 8-hydroxymethyl-9*H*-adenine.

Acylation of 4,5,6-triaminopyrimidine (VI) with isobutyryl chloride or pivaloyl chloride (in pyridine at room temperature) gave the 5-*mono*acylated products (VIIa and b, respectively). The 5-amino-group of 4,5,6-triaminopyrimidine must therefore be much more basic than the 4- and 6-amino-groups, enabling the monoacyl product to be isolated without further reaction. Treatment of (VIIa and b) with aqueous base [2,7] gave 8-isopropyl-9*H*-adenine (VIIIa) and 8-t-butyl-9*H*-adenine (VIIIb), respectively.

The fact that the 5-acylamino-6-aminopyrimidin-4(3*H*)-ones (IIIa—d) do not ring-close to purine derivatives when treated with aqueous base and the 5-acylamino-4,6-diaminopyrimidines (VIIa and b) do ring-close under the same conditions must result from the greater basicity of the 4(6)-amino-group of (VIIa and b) when there is already one amino-group present in the molecule.[8]

EXPERIMENTAL

M.p.s were determined with a Thomas–Hoover apparatus. U.v. spectra were recorded on a Cary 15 spectrometer, i.r. spectra on a Perkin-Elmer 257 spectrophotometer (KBr pellets), and n.m.r. spectra with a Hitachi R20a spectrometer (sodium 2,2-dimethyl-2-silapentane-5-sulphonate as internal standard). Values for coupling constants (Hz) and chemical shifts (δ) are first-order. Microanalyses were performed by M-H-W-Laboratories, Garden City, Mich., and by Galbraith Laboratories, Inc., Knoxville, Tenn.

5,6-Bisisobutyrylaminopyrimidin-4(3H)*-one* (IIa).—5,6-Diaminopyrimidin-4(3*H*)-one (10 g, 80 mmol) was suspended in isobutyryl chloride (30 ml), and pyridine (14 ml) was added dropwise. Spontaneous exothermic reaction occurred. After 1 h the mixture was treated with ice–water. Filtration and washing (water and ethanol successively) gave tan crystals (16 g, 71%); recrystallization from water (charcoal) afforded crystalline *product* (IIa) (12 g, 56%), m.p. 239—240° (Found: C, 54·0; H, 6·8; N,

[4] S. C. J. Fu, E. Chinoporos, and H. Terzian, *J. Org. Chem.*, 1965, **30**, 1916.

[5] A. Albert, 'The Chemistry and Biology of Purines,' CIBA Foundation Symposium, eds. G. E. W. Wolstenholme and C. M. O'Connor, J. and A. Churchill, Ltd., London, 1957, p. 97.

[6] H. Bredereck, E. Siegel, and B. Fohlisch, *Chem. Ber.*, 1962, **95**, 403.

[7] V. M. Cherkason and L. K. Kurilenko, *Khim. geterotsikl. Soedinenii*, 1970, **6**, 1579.

[8] D. J. Brown, 'The Pyrimidines, Supplement 1,' Wiley-Interscience, New York, 1970, p. 368.

21·2. $C_{12}H_{18}N_4O_3$ requires C, 54·1; H, 6·8; N, 21·05%); δ [$(CD_3)_2SO$] 11·5br [1H, s, N(3)H], 9·82 [1H, s, C(6)NH], 8·68 [1H, s, C(5)NH], 8·09 (1H, s, 2-H), 3·0—2·3 (m, CH, overlapped by solvent peak), and 1·10 (12H, d, CH_3), $\lambda_{max.}$ (pH 1) 280 nm (ε 6100), $\lambda_{max.}$ (MeOH) 285 nm (ε 5700), $\lambda_{max.}$ (pH 11) 275 nm (ε 4800).

5,6-*Bispivaloylaminopyrimidin*-4(3H)-*one* (IIb).—Use of the foregoing procedure with 5,6-diaminopyrimidin-4(3*H*)-one (10·0 g) and pivaloyl chloride (30 ml) gave the product (IIb) (68%) as *crystals*, m.p. 251—253° (from water) (Found: C, 56·9; H, 7·6; N, 19·3. $C_{14}H_{22}N_4O_3$ requires C, 57·1; H, 7·55; N, 19·05%), δ [$(CD_3)_2SO$] 12·4br [1H, s, N(3)H], 9·50 [1H, s, C(6)NH], 8·31 [1H, s, C(5)NH], 8·08 (1H, s, 2-H), and 1·22 (18H, s, CH_3), $\lambda_{max.}$ (pH 1) 279 nm (ε 7400), $\lambda_{max.}$ (MeOH) 288 nm (ε 7400), $\lambda_{max.}$ (pH 11) 279 nm (ε 6100).

6-*Amino*-5-*isobutyrylaminopyrimidin*-4(3H)-*one* (IIIa).—The 5,6-bisisobutyrylamino-derivative (IIa) (4·0 g, 15 mmol) dissolved in 0·2N-sodium hydroxide (50 ml) was heated at 90—100° for 5 h and then cooled in an ice-bath. Acidification to pH 2 with conc. hydrochloric acid gave a white precipitate (2·6 g, 88%) which was recrystallized from water to give the *product* (IIIa) (2·2 g, 75%), m.p. 266—268° (Found: C, 48·75; H, 6·2; N, 28·35. $C_8H_{12}N_4O_2$ requires C, 48·95; H, 6·15; N, 28·55%); δ [$(CD_3)_2SO$] 11·8br [1H, s, N(3)H], 8·56br [1H, s, N(5)H], 6·02br (2H, s, NH_2), 2·90—2·10 (m, overlapped by solvent peak), and 1·10 (6H, d, CH_3), $\lambda_{max.}$ (pH 1) 258 nm (ε 7800), $\lambda_{max.}$ (MeOH) 260 nm (ε 6300), $\lambda_{max.}$ (pH 11) 255 nm (ε 5100).

6-*Amino*-5-*pivaloylaminopyrimidin*-4(3H)-*one* (IIIb).—Hydrolysis of (IIb) (1·0 g) by the procedure for the preparation of (IIIa) gave (IIIb) as *crystals* (0·5 g, 70%), m.p. 242—243° (from water) (Found: C, 47·2; H, 6·85; N, 24·85. $C_9H_{14}N_4O_3,H_2O$ requires C, 47·35; H, 7·05; N, 24·55%); δ [$(CD_3)_2SO$] 11·75br [1H, s, N(3)H] 8·10 [1H, s, N(5)H], 7·80 (1H, s, 2-H), 5·98br (2H, s, NH_2), and 1·23 (6H, s, CH_3), $\lambda_{max.}$ (pH 1) 258 nm (ε 7600), $\lambda_{max.}$ (MeOH) 260 nm (ε 6100), $\lambda_{max.}$ (pH 11) 255 nm (ε 5000).

6-*Amino*-5-*glycoloylaminopyrimidin*-4(3H)-*one* (IIIc).—The pyrimidinone (I) (2·5 g, 2 mmol) and glycolic acid (3·6 g, 6 mmol) were finely ground and fused in a beaker at 150° (oil-bath) for 5 h. After cooling, the light brown solid was suspended in water and the insoluble product was filtered off (3·9 g). Two recrystallizations from water (charcoal) gave *crystals* of (IIIc) (1·8 g, 49%), m.p. 300° (decomp.) (Found: C, 39·05; H, 4·45; N, 30·45. $C_6H_8N_4O_3$ requires C, 39·15; H, 4·5; N, 30·45%), δ [$(CD_3)_2SO$] 11·85br [1H, s, N(3)H], 8·48br (1H, s, NHCO), 7·81 (1H, s, 2-H), 6·33br (2H, s, NH_2), 5·60 (1H, t, *J* 6 Hz, OH), and 3·98 (2H, d, CH_2), $\lambda_{max.}$ (pH 1) 258 nm (ε 8100), $\lambda_{max.}$ (pH 4·5) 258 nm (ε 7800), $\lambda_{max.}$ (pH 11) 255 nm (ε 5000).

6-*Amino*-5-*acetylaminopyrimidin*-4(3H)-*one* (IIId).—Prepared according to the procedure reported [3] for '8-methylhypoxanthine,' compound (IIId) had m.p. >300° (from water) (lit.,[3] >300°), δ [$(CD_3)_2SO$] 8·69br (1H, s, NHCO), 7·85 (1H, s, 2-H), 6·27br (2H, s, NH_2), and 2·01 (3H, s, CH_3), $\lambda_{max.}$ (pH 1) 260 nm (ε 6900), $\lambda_{max.}$ (pH 11) 257 nm (ε 8700).

8-*Hydroxymethyl*-9H-*hypoxanthine* (IVc).—*Method A*. 8-Hydroxymethyl-9*H*-adenine (VIIIc) (1·0 g, 6 mmol) was dissolved in aqueous 50% acetic acid (60 ml), and nitrous acid anhydride (N_2O_3) was passed through the solution until the starting material had been consumed [2 h, determined by t.l.c. in solvent E (see below)]. Evaporation of the solvent and excess of N_2O_3 under reduced pressure gave a brown solid which was suspended in a small amount of water and cooled to 5° for 18 h; filtration furnished yellowish *crystals* of (VIIIc) (0·9 g, 91%), m.p. >300° (Found: C, 43·2; H, 3·6; N, 33·7. $C_6H_6N_4O_2$ requires C, 43·35; H, 3·65; N, 33·75%), δ [$(CD_3)_2SO$–NaOD] 7·78 (1H, s, 2-H) and 4·61 (2H, s, CH_2), $\lambda_{max.}$ (pH 1) 249 nm (ε 12,300), $\lambda_{max.}$ (pH 4·5) 251 nm (ε 12,100), $\lambda_{max.}$ (pH 11) 261 nm (ε 12,800).

Method B. Compound (IIIc) (2 g, 11 mmol) and potassium acetate (1 g) were ground together and the mixture was fused (oil-bath at 200°) for 10 min. The dark solid material was suspended in water; decolorization and concentration of the resulting solution gave yellowish crystals (0·5 g, 30%), and recrystallization from water (with few drops of dimethylformamide) furnished tan crystals, m.p. >300°. The mixed m.p. of products of Methods A and B was >300°. U.v. and i.r. spectra of the two products were identical, and t.l.c. on silica gel using solvent E [ethyl acetate–propan-1-ol–water (4 : 1 : 2; upper layer)] showed both products to have the same mobility.

6-*Chloro*-8-*isopropyl*-9H-*purine* (Va).—Compound (IIIa) (5·2 g, 26 mmol) was suspended in phosphoryl chloride (30 ml) and heated at reflux for 7 h. Excess of phosphoryl chloride was removed by distillation under reduced pressure and the residue was cooled. Addition of crushed ice (~50 g) afforded a dark solution, which was made alkaline (pH 14) with aqueous sodium hydroxide and set aside for 20 min at room temperature. The resultant solution was acidified to pH 2 with conc. hydrochloric acid and extracted with ether (6 × 200 ml). Evaporation of the extract gave yellowish crystals (2·2 g, 42%), m.p. 157—160°, and recrystallization from ether furnished *crystals* of (Va), m.p. 158—160° (Found: C, 48·85; H, 4·55; N, 28·5. $C_8H_9ClN_4$ requires C, 49·0; H, 4·6; N, 28·5%), δ [$(CD_3)_2SO$] 8·70 (1H, s, 2-H), 3·30 (1H, septet, CH), and 1·43 (6H, d, CH_3), $\lambda_{max.}$ (pH 1) 267 nm (ε 11,800), $\lambda_{max.}$ (MeOH) 268 nm (ε 11,200), $\lambda_{max.}$ (pH 11) 278 (ε 11,400).

6-*Chloro*-8-*t-butyl*-9H-*purine* (Vb).—Use of the procedure for the preparation of (Va) with compound (IIIb) (3·0 g, 14 mmol) gave yellowish crystals of (Vb) (1·4 g, 47%), m.p. 234—237°; recrystallization from ether gave *crystals*, m.p. 236—237° (Found: C, 51·25; H, 5·1; Cl, 16·85; N, 26·5. $C_9H_{11}ClN_4$ requires C, 51·35; H, 5·2; Cl, 16·85; N, 26·6%), δ ($CDCl_3$) 11·73br (1H, s, NH), 8·77 (1H, s, 2-H), and 1·65 (9H, s, CH_3), $\lambda_{max.}$ (pH 1) 267 nm (ε 12,400), $\lambda_{max.}$ (MeOH) 268 nm (ε 11,400), $\lambda_{max.}$ (pH 11) 263 nm (ε 11,800).

4,6-*Diamino*-5-*isobutyrylaminopyrimidine* (VIIa).—A mixture of 4,5,6-triaminopyrimidine (VI) (1 g, 8 mmol), isobutyryl chloride (10 ml), and pyridine (2 ml) was heated at reflux for 2·5 h. Cooling and filtration of the mixture furnished grey crystals (1 g, 71%), which were recrystallized from water (charcoal) to give *needles* of (VIIa) (0·8 g), m.p. 288° (decomp.) (Found: C, 49·35; H, 6·7; N, 36·9. $C_8H_{13}N_5O$ requires C, 49·2; H, 6·7; N, 35·9%), δ [$(CD_3)_2SO$] 9·07 [1H, s, C(5)NH], 8·26 (1H, s, 2-H), 7·50br (4H, s, NH_2), 3·10—2·40 (m, CH overlapped by solvent peak at 2·56), and 1·19 (6H, d, *J* 7 Hz, CH_3), $\lambda_{max.}$ (pH 1) 264 nm (ε 9800), $\lambda_{max.}$(MeOH) 264 nm (ε 7000), $\lambda_{max.}$ (pH 11) 257 nm (ε 4100).

4,6-*Diamino*-5-*pivaloylaminopyrimidine* (VIIb).—Use of the procedure for the preparation of (VIIa) with 4,5,6-triaminopyrimidine (1·0 g) and pivaloyl chloride (10 ml) gave product (1·3 g, 81%), m.p. 290—297°, recrystallized from aqueous ethanol to give a *sample* of (VIIb), m.p. >300° (Found: C, 51·7; H, 7·05; N, 33·45. $C_9H_{15}N_5O$

requires C, 51·65; H, 7·25; N, 33·45%), δ [$(CD_3)_2SO$] 8·70 [1H, s, C(5)NH], 8·28 (1H, s, 2-H), 7·45br (4H, s, NH_2), and 1·30 (9H, s, CH_3), $\lambda_{max.}$ (pH 1) 266 nm (ε 16,100), $\lambda_{max.}$ (~pH 4·5) 261 nm (ε 15,900), $\lambda_{max.}$ (pH 11) 266 nm (ε 14,400).

8-*Isopropyl*-9H-*adenine* (VIIIa).—Sodium hydroxide solution (1·5M; 10 ml) containing (VIIa) (0·75 g, 4 mmol) was heated at reflux for 1 h, and the solution was cooled to 4° and acidified to pH 4. Storing the solution in the refrigerator overnight deposited a solid which was filtered off and washed with water (0·6 g, 88%), m.p. 240—245°. Recrystallization from water gave *crystals* of (VIIIa), m.p. 262° (structure change at 245°) (Found: C, 54·25; H, 6·9; N, 39·4. $C_8H_{11}N_5$ requires C, 54·2; H, 6·25; N, 39·5%), δ [$(CD_3)_2SO$] 12·35br (1H, s, NH), 9·13br (2H, s, NH_2), 8·61 (1H, s, 2-H), 3·30 (1H, septet, *J* 7 Hz, CH), and 1·45 (6H, d, CH_3), $\lambda_{max.}$ (pH 1) 267 nm (ε 14,500), $\lambda_{max.}$ (MeOH) 261 nm (ε 14,900), $\lambda_{max.}$ (pH 11) 267 nm (ε 13,300).

8-*t-Butyl*-9H-*adenine* (VIIIb).—Use of the procedure for the preparation of (VIIIa) with (VIIb) (1·0 g) gave (VIIIb) (0·8 g, 88%), m.p. >300° (Found: C, 56·1; H, 6·9; N, 36·4. $C_9H_{13}N_5$ requires C, 56·5; H, 6·85; N, 36·65%), δ [$(CD_3)_2SO$] 8·16 (1H, s, 2-H), 6·97br (2H, s, NH_2), and 1·45 (9H, s, CH_3), $\lambda_{max.}$ (pH 1) 267 nm (ε 13,600), $\lambda_{max.}$ (MeOH) 261 nm (ε 13,600), $\lambda_{max.}$ (pH 11) 265 nm (ε 12,200).

8-*Hydroxymethyl*-9H-*adenine* (VIIIc).—4,5,6-Triaminopyrimidine (8 g, 64 mmol) was suspended in ethyl glycolate * (35 ml) and heated at reflux for 5 h. Evaporation afforded a semi-solid. Addition of water and cooling (at 4°) for 18 h caused precipitation of tan crystals, which were dissolved in sodium hydroxide (1·5 N; 70 ml) and heated at reflux for 1 h. The solution was cooled and the pH was adjusted to 4 with hydrochloric acid. The product precipitated and was filtered off (6 g, 60%), m.p. 298—300° (decomp.). Recrystallization from water (charcoal) furnished crystals of (VIIIc), m.p. >300° (decomp.) [lit.,[3] 320—322° (decomp.)], δ [$(CD_3)_2SO$] 8·20 (1H, s, 2-H), 7·20br (2H, s, NH_2), 6·78br (1H, s, OH), and 4·73 (2H, s, CH_2), $\lambda_{max.}$ (pH 1) 265 nm (ε 12,500), $\lambda_{max.}$ (pH 4·5) 262 nm (ε 12,200), $\lambda_{max.}$ (pH 11) 270 nm (ε 11,600).

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* Samples of ethyl glycolate from some commercial suppliers were low-boiling (90—110°) and did not function in the ring-closure reaction. Gallard–Schlesinger Corp. offers ethyl glycolate (b.p. 160°) which works well.