612. *Esters of 2-Substituted 4,5-Diaminopyrimidine-6-carboxylic Acids and Some Related Purines.*

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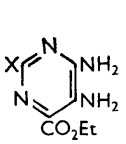
A number of 2-substituted ethyl 5,6-diaminopyrimidine-4-carboxylates (I; X = NH_2, NMe_2, OH, OEt, SH, or Cl) have been prepared and their ionisation constants and ultraviolet spectra measured. The diamines were used to prepare purines (II: R = H; X = NH_2, NMe_2, OH, or OEt), 8-mercaptopurines (II: R = SH; X = NH_2, NMe_2, or OEt), and related compounds.

4,5-Diaminopyrimidines are widely used in the synthesis of pteridines,[1] purines,[2] and other bicyclic heterocycles.[3] 4,5-Diaminopyrimidines with a carboxylic acid or ester substituent in the 2- or 6-position should lead to the rather inaccessible pteridines and purines with a carboxylic acid group in the pyrimidine ring. Derivatives of purine-6-carboxylic acid[4] aroused some interest as antitumour or antibacterial agents[5] and the acid function has been varied in many ways.[4,6] However, only a few examples of purine-6-carboxylic acid derivatives with an additional substituent are known[7,8] and only a few derivatives of pteridine-4-carboxylic acid have been described.[9] In the present work a series of 2-substituted ethyl 5,6-diaminopyrimidines-4-carboxylates (I; X = NH_2, NMe_2, OH, OEt, SH, or Cl) have been prepared and converted into the corresponding purines (II; R = H; X = NH_2, NMe_2, OH, or OEt) or related heterocycles.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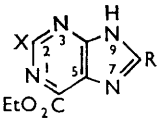
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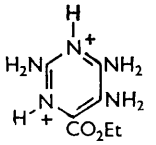
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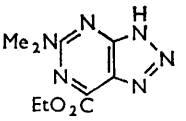
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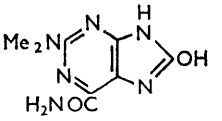
(V)

Ethyl 2,6-dichloro-5-nitropyrimidine-4-carboxylate[8] was treated with ammonia and the 2-chloro-atom of the product was replaced by an amino-, dimethylamino-, hydroxy-, ethoxy-, or mercapto-group by treatment with a suitable nucleophilic reagent. The nitro-compounds were reduced by sodium dithionite, or catalytically, to yield the corresponding diamines (I).

[1] Albert, *Quart. Rev.*, 1952, **6**, 225.
[2] Lister, *Rev. Pure Appl. Chem.* (*Australia*), 1961, **11**, 178.
[3] Brown, "The Pyrimidines," Interscience, New York and London, 1962, p. 333.
[4] Mackay and Hitchings, *J. Amer. Chem. Soc.*, 1956, **78**, 3511.
[5] Clarke, Elion, Hitchings, and Stock, *Cancer Res.*, 1958, **18**, 445; B.P. 799,384/1958.
[6] Cohen, Thom, and Bendich, *J. Org. Chem.*, 1962, **27**, 3545; Giner-Sorolla and Bendich, *J. Amer. Chem. Soc.*, 1958, **80**, 3932; Giner-Sorolla, Zimmerman, and Bendich, *ibid.*, 1959, **81**, 2515.
[7] Clark and Lister, *J.*, 1961, 5048.
[8] Clark and Ramage, *J.*, 1958, 2821.
[9] Clark and Layton, *J.*, 1959, 3411; Clark, Kernick, and Layton, preceding Paper.

The ionisation constants of these 2-substituted esters, together with ultraviolet absorption and fluorescence data are given in the Table. Ultraviolet spectra of the compounds whose second ionisation constant was determined fall into two groups, (a) those which exhibit a large hypsochromic shift on dication formation, and (b) those which exhibit a modest bathochromic shift. Compounds whose spectra are in group (b) (I; X = Me_2N or NH_2) contain two amidine systems, and their di-cations are probably formed by protonation of both hetero-atoms (III). The hypsochromic shift shown by the other compounds is typical of the change caused by protonation of an exocyclic amino-group, and the di-cations concerned are probably formed by protonation of the 3-nitrogen atom and the 5-amino-group.

The diaminopyrimidines (I; X = NH_2, NMe_2, OH, or OEt) were converted into the corresponding 2-substituted ethyl purine-6-carboxylates (II: R = H; X = NH_2, NMe_2, OH, or OEt) by a mixture of formic acid and acetic anhydride. A second series of compounds was prepared by treating the diaminopyrimidines (I; X = NH_2, NMe_2, or OEt) with carbon disulphide in pyridine, to yield the purine esters (II: R = SH; X = NH_2, NMe_2, or OEt). The more weakly basic 2-chloro- and 2-hydroxy-diaminopyrimidines (I; X = Cl or OH) were not changed by similar treatment.

Ethyl 5,6-diamino-2-dimethylaminopyrimidine-4-carboxylate (I; X = NMe_2) was also converted into ethyl 5-dimethylamino-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine-7-carboxylate (IV) by nitrous acid, into ethyl 2-dimethylamino-8-methylpurine-6-carboxylate (II; R = Me, X = Me_2N) by refluxing with acetic anhydride, into ethyl 2-dimethylamino-8-hydroxypurine-6-carboxylate (II; R = OH, X = Me_2N) by refluxing with a mixture of pyridine and urea, and into 2-dimethylamino-8-hydroxypurine-6-carboxyamide (V) by fusion with urea.

Spectra (in water) and ionisation constants (in water at 20°) of ethyl 2-substituted 5,6-diaminopyrimidine-4-carboxylates (I).

X	pK_a	Concn. (M)	Species [a]	$\lambda_{max.}$ (mμ) [b]	log ε [b]	pH or H_0 [c]	Fluorescence [d]
Cl	1·18 ± 0·03 [e]		+	238, 286, 345	3·90, 3·74, 4·01	−3·0	
			0	232, 260, 344	3·89, 3·77, 3·90	5·2	P 3+
NH_2	−1·90 [e]		++	215, 251, 374	4·11, 3·91, 3·76	−3·9	B +
	6·54 ± 0·05 [f]	3 × 10^{-3}	+	243, 350	4·13, 3·88	4·0	B 3+
			0	235, 359	4·04, 3·84	9·0	G 4+
NMe_2	−2·03 [e]		++	235, *265*, 375	4·30, *3·87*, 3·39	−4·4	
	6·47 ± 0·01 [f]	5 × 10^{-3}	+	209, 252, 362	4·16, 4·25, 3·75	3·9	BG 3+
			0	254, 385	4·17, 3·69	9·0	G 2+
OH	−3·21 [e]		++	307	3·92	−4·9	B +
	3·22 [e]		+	234, 365	4·01, 3·91	0·0	G +
			0	235, 348	4·08, 3·89	6·3	B +
OEt	−3·06 [e]		++	218, 292	4·09, 3·83	−4·9	B +
	4·60 ± 0·03 [f]	10^{-3}	+	236, *250*, 343	3·96, *3·76*, 3·97	2·6	P +
			0	227, 346	3·98, 3·88	8·6	B +
SH	−4·66 [e,g]						
	2·11 [e]		+	234, 297, 402	3·83, 4·41, 3·63	−0·5	
			0	239, 285, 375	3·89, 4·41, 3·61	5·9	

[a] ++, dication; +, cation; 0, neutral molecule. [b] Inflexions in italics. [c] H_0 in sulphuric acid. [d] Fluorescence varies from + (weak fluorescence in ultraviolet light) to 5+ (strong fluorescence in daylight); B = blue, P = purple, G = green, BG = blue-green. [e] Determined spectrophotometrically. [f] Determined potentiometrically. [g] Approximate.

Experimental

Ethyl 6-Amino-2-chloro-5-nitropyrimidine-4-carboxylate.—2·4N-Ethanolic ammonia (38 ml.) was added during 1 hr. to a stirred solution of ethyl 2,6-dichloro-5-nitropyrimidine-4-carboxylate

(10·8 g.) in ether (25 ml.), maintained at 0—5°. Stirring was continued for 1 hr. and the *chloro-ester* (4·5 g.) (45%) was filtered off, washed with water, and crystallised from ethanol as needles, m. p. 171—172° (Found: C, 34·3; H, 3·1. $C_7H_7ClN_4O_4$ requires C, 34·1; H, 2·9%).

The filtrate was refluxed with an excess of 4N-ethanolic ammonia, cooled, and *ethyl 2,6-diamino-5-nitropyrimidine-4-carboxylate* (2·9 g.) was filtered off, needles, m. p. 186° (from water) (Found: C, 37·5; H, 3·7. $C_7H_9N_5O_4$ requires C, 37·0; H, 4·0%).

Ethyl 5,6-Diamino-2-chloropyrimidine-4-carboxylate.—A solution of ethyl 6-amino-2-chloro-5-nitropyrimidine-4-carboxylate (1·85 g.) in methanol (300 ml.) was shaken with Raney nickel (5 ml.; settled suspension) and hydrogen until the calculated uptake of hydrogen was reached (approximately 2·5 hr.). The spent catalyst was removed and the solution concentrated to 30 ml., to give the *ester* (1·05 g.), needles, m. p. 270° (from dioxan) (Found: C, 39·4; H, 4·1. $C_7H_9ClN_4O_2$ requires C, 38·8; H, 4·2%).

Ethyl 2,5,6-Triaminopyrimidine-4-carboxylate.—Sodium hydrogen carbonate (10 g.) in water (100 ml.) was added to a solution of ethyl 2,6-diamino-5-nitropyrimidine-4-carboxylate (2 g.) in acetone (75 ml.). The mixture was stirred during the addition (5 min.) of sodium dithionite (7 g.), then for a further 15 min. Insoluble matter was filtered off and washed with acetone. Acetone was evaporated from the combined mother-liquor and washings, and the *triamino-ester* (0·43 g.) filtered off. A further quantity (0·27 g.) was obtained by exhaustive extraction of the filtrate with ethyl acetate, needles which decomposed at 205—206° (from ethyl acetate) (Found: C, 39·6; H, 5·9. $C_7H_{11}N_5O_2,H_2O$ requires C, 39·1; H, 6·1%).

Ethyl 6-Amino-2-dimethylamino-5-nitropyrimidine-4-carboxylate.—26% Aqueous dimethylamine (5·6 ml.) in ethanol (15 ml.) was added dropwise to a stirred solution of ethyl 6-amino-2-chloro-5-nitropyrimidine-4-carboxylate (3·5 g.) in ethanol (100 ml.). After 30 min. water (150 ml.) was added and the *dimethylamino-ester* (3·4 g.) separated, blades, m. p. 183° (from ethanol) (Found: C, 39·8; H, 5·3. $C_9H_{13}N_5O_4,H_2O$ requires C, 39·6; H, 5·5%).

Ethyl 5,6-Diamino-2-dimethylaminopyrimidine-4-carboxylate.—A suspension of sodium hydrogen carbonate (10 g.) in water (40 ml.) was added to a well-stirred solution of the foregoing dimethylamino-ester (2 g.) in acetone (40 ml.). Sodium dithionite (10 g.) was added during 5 min. and, 1 min. later, water (100 ml.) was added. Acetone was evaporated under reduced pressure and the *diamino-compound* (1 g.) was filtered off. A further quantity (0·3 g.) was obtained by chloroform extraction of the filtrate. The product formed prisms, m. p. 165° (from ethyl acetate) (Found: C, 47·9; H, 6·5. $C_9H_{15}N_5O_2$ requires C, 48·0; H, 6·7%).

Ethyl 6-Amino-2-ethoxy-5-nitropyrimidine-4-carboxylate.—Ethyl 6-amino-2-chloro-5-nitropyrimidine-4-carboxylate (2 g.), ethanol (40 ml.), and pyridine (2 ml.) were heated under reflux for 3 hr. The hot solution was acidified with N-hydrochloric acid, diluted with water until precipitation started, cooled, and the *ester* filtered off, needles (1·6 g.), m. p. 120° [from ethyl acetate–light petroleum (b. p. 60—80°)] (Found: C, 42·7; H, 4·8. $C_9H_{12}N_4O_5$ requires C, 42·2; H, 4·7%).

Ethyl 5,6-Diamino-2-ethoxypyrimidine-4-carboxylate.—A suspension of sodium hydrogen carbonate (9·3 g.) in water (40 ml.) was added to a well-stirred solution of the foregoing ethoxy-ester (2 g.) in acetone (35 ml.). The mixture was stirred during the addition (5 min.) of sodium dithionite (9·3 g.), then for a further 20 min. Water (100 ml.) was added and the *diamino-compound* (1·3 g.) was filtered off, prisms, m. p. 201° (from ethyl acetate) (Found: C, 48·2; H, 6·2. $C_9H_{14}N_4O_3$ requires C, 47·8; H, 6·2%).

Ethyl 6-Amino-2-hydroxy-5-nitropyrimidine-4-carboxylate.—Ethyl 6-amino-2-chloro-5-nitropyrimidine-4-carboxylate (1 g.), sodium acetate (1 g.), glacial acetic acid (2 ml.), and water (2 ml.) were heated under reflux for 30 min. The *hydroxy-ester* (0·72 g.) was filtered off from the cooled solution, washed with water, and crystallised from aqueous ethanol, needles, m. p. 240° (decomp.) (Found: C, 35·3; H, 3·5. $C_7H_8N_4O_5,\frac{1}{2}H_2O$ requires C, 35·5; H, 3·8%).

Ethyl 5,6-Diamino-2-hydroxypyrimidine-4-carboxylate.—The foregoing hydroxy-pyrimidine (2 g.), sodium hydrogen carbonate (6 g.), and water (60 ml.) were heated to 50° and stirred during the addition (5 min.) of sodium dithionite (6 g.). The mixture was stirred for 1 hr. at 20°, and the *diamino-ester* (1·45 g.) was filtered off, needles, m. p. 234° (decomp.) (from ethyl acetate) (Found: C, 38·8; H, 5·4. $C_7H_{10}N_4O_3,H_2O$ requires C, 38·9; H, 5·6%).

Ethyl 6-Amino-2-mercapto-5-nitropyrimidine-4-carboxylate.—Ethyl 6-amino-2-chloro-5-nitropyrimidine-4-carboxylate (0·85 g.), sodium sulphide nonahydrate (1 g.), sodium hydrogen carbonate (0·3 g.), and water (33 ml.) were stirred for 3 hr. The mixture was filtered and any unchanged starting material removed from the filtrate by ether extraction. The aqueous

solution was acidified with concentrated hydrochloric acid and again extracted with ether. The ether extract was washed with water, dried (Na_2SO_4), and evaporated to dryness, to yield the *mercapto-ester* (0·3 g.), needles, m. p. 202—204° (decomp.) (from ethanol) (Found: C, 34·7; H, 3·3. $C_7H_8N_4O_4S$ requires C, 34·4; H, 3·3%).

Ethyl 5,6-Diamino-2-mercaptopyrimidine-4-carboxylate.—A solution of ethyl 6-amino-2-chloro-5-nitropyrimidine-4-carboxylate (3 g.) in acetone (3 ml.) was treated with sodium hydrogen carbonate (6 g.) in water (50 ml.) and then sodium sulphide nonahydrate (4 g.) in water (80 ml.). The mixture was stirred for 3 hr., to give a clear solution. Sodium hydrogen carbonate (12 g.) was added in one portion, then sodium dithionite (13 g.) during 10 min., and the mixture set aside overnight to give the *mercapto-ester* (1·78 g.), needles, m. p. 202° (decomp.) (from ethanol) (Found: C, 39·3; H, 5·0. $C_7H_{10}N_4O_2S$ requires C, 39·2; H, 4·7%).

Ethyl 2-Aminopurine-6-carboxylate.—Ethyl 2,5,6-triaminopyrimidine-4-carboxylate (1 g.), formic acid (98—100%; 10 ml.), and acetic anhydride (5 ml.) were heated under reflux for 4 hr. The mixture was evaporated to dryness under reduced pressure, treated with ether, and filtered, giving the *ester* (0·95 g.), needles, m. p. 267° (decomp.) (from 2-ethoxyethanol) (Found: C, 46·8; H, 4·4. $C_8H_9N_5O_2$ requires C, 46·4; H, 4·4%).

Ethyl 2-dimethylaminopurine-6-carboxylate (0·87 g.), similarly prepared from ethyl 5,6-diamino-2-dimethylaminopyrimidine-4-carboxylate (1 g.), formed needles, m. p. 216° (from chloroform) (Found: C, 50·7; H, 5·4. $C_{10}H_{13}N_5O_2$ requires C, 51·0; H, 5·6%).

Ethyl 2-hydroxypurine-6-carboxylate (0·72 g.), prepared from ethyl 5,6-diamino-2-hydroxypyrimidine-4-carboxylate (1 g.) as for the corresponding 2-amino-compound except that the residue after evaporation was treated with ethanol, formed needles, m. p. 243° (from dimethylformamide) (Found: C, 45·8; H, 3·9. $C_8H_8N_4O_3$ requires C, 46·2; H, 3·9%).

Ethyl 2-ethoxypurine-6-carboxylate (0·27 g.), prepared from ethyl 5,6-diamino-2-ethoxypyrimidine-4-carboxylate (0·5 g.) as for the corresponding 2-amino-compound, except that the residue from evaporation was treated with water (2 ml.) before filtration, formed needles, m. p. 162° (from benzene) (Found: C, 51·2; H, 5·1. $C_{10}H_{12}N_4O_3$ requires C, 50·8; H, 5·1%).

Ethyl 2-Amino-8-mercaptopurine-6-carboxylate.—Ethyl 2,5,6-triaminopyrimidine-4-carboxylate (0·4 g.) was refluxed for 4·5 hr. with carbon disulphide (2 ml.) and pyridine (4 ml.). The cooled solution was poured into water (20 ml.) and neutralised by dropwise addition of concentrated hydrochloric acid. The *ester* (0·45 g.) was filtered off, washed with acetone, and crystallised from aqueous dimethylformamide as needles, which gradually decomposed at 275° (Found: C, 40·7; H, 4·2; N, 29·2. $C_8H_9N_5O_2S$ requires C, 40·2; H, 3·8; N, 29·3%).

Ethyl 2-dimethylamino-8-mercaptopurine-6-carboxylate (0·42 g.), prepared from ethyl 5,6-diamino-2-dimethylaminopyrimidine-4-carboxylate (0·4 g.) as described for the corresponding 2-amino-compound, except that the period of reflux was 7 hr., was washed with ethanol and crystallised from dioxan as needles, m. p. 246—248° (Found: C, 45·4; H, 5·1; N, 24·1. $C_{10}H_{13}N_5O_2S,\frac{1}{4}C_4H_8O_2$ requires C, 45·7; H, 5·2; N, 24·2%).

Ethyl 2-ethoxy-8-mercaptopurine-6-carboxylate (0·32 g.), prepared from ethyl 5,6-diamino-2-ethoxypyrimidine-4-carboxylate (0·4 g.) as described for the corresponding 2-dimethylamino-compound, was washed with water and crystallised from aqueous dioxan as needles, m. p. 244—246° (Found: C, 45·2; H, 4·6; N, 21·2. $C_{10}H_{12}N_4O_3S$ requires C, 44·8; H, 4·5; N, 20·9%).

Ethyl 5-Dimethylamino-3H-1,2,3-triazolo[4,5-d]pyrimidine-7-carboxylate.—Sodium nitrite (0·4 g.), in water (6 ml.), was added to an ice-cold solution of ethyl 5,6-diamino-2-dimethylaminopyrimidine-4-carboxylate (1 g.) in 0·5N-hydrochloric acid (20 ml.). Next day the *triazolopyrimidine* (0·7 g.) was filtered off, and formed needles, m. p. 215—217° (from benzene) (Found: C, 46·0; H, 5·5; N, 35·6. $C_9H_{12}N_6O_2$ requires C, 45·7; H, 5·1; N, 35·6%).

Ethyl 2-Dimethylamino-8-methylpurine-6-carboxylate.—Ethyl 5,6-diamino-2-dimethylaminopyrimidine-4-carboxylate (1 g.) was refluxed for 2 hr. with acetic anhydride (20 ml.). The mixture was evaporated to dryness under reduced pressure, to give the *purine* (0·4 g.), needles, m. p. 158° (from water) (Found: C, 51·2; H, 6·1. $C_{11}H_{15}N_5O_2,\frac{1}{2}H_2O$ requires C, 51·1; H, 6·3%).

Ethyl 2-Dimethylamino-8-hydroxypurine-6-carboxylate —A mixture of ethyl 5,6-diamino-2-dimethylaminopyrimidine-4-carboxylate (0·2 g.) and urea (0·2 g.) was refluxed in pyridine (4 ml.) for 7 hr. The cooled solution was poured into water (15 ml.) and the *hydroxypurine* (0·12 g.) was filtered off and crystallised from dimethylformamide as needles, m. p. 303—305° (decomp.) (Found: 48·0; H, 5·2; N, 27·9. $C_{10}H_{13}N_5O_3$ requires C, 47·8; H, 5·2; N, 27·9%).

2-Dimethylamino-8-hydroxypurine-6-carboxyamide.—Ethyl 5,6-diamino-2-dimethylaminopyrimidine-4-carboxylate (0·5 g.) was fused at 180° with urea (2·5 g.), for 15 min. The melt

was poured into water (15 ml.) and the *carboxyamide* (0·32 g.) was filtered off and crystallised from aqueous dimethylformamide as reddish-brown needles which gradually decomposed at 311—316° (Found: C, 39·5; H, 5·1; N, 35·3. $C_8H_{10}N_6O_2,H_2O$ requires C, 40·0; H, 5·0; N, 35·0%).

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