416. *Synthesis of Divicine (2 : 4-Diamino-5 : 6-dihydroxypyrimidine) and Other Derivatives of 4 : 5(5 : 6)-Dihydroxypyrimidine.**

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A number of 5-tetrahydropyran-2′-yloxypyrimidines have been prepared. On acid hydrolysis these afforded 5-hydroxypyrimidines in high yield. The compounds synthesised by this route include 2 : 4-diamino-5 : 6-dihydroxypyrimidine, shown to be the aglycone of the nucleoside vicine, and several 4 : 5 : 6-trihydroxypyrimidines, including dialuric acid. The ultraviolet spectra and structures of these compounds are discussed.

Divicine, the aglycone of the glucoside vicine isolated from vetch seeds, has recently been shown [1] to be 2 : 4-diamino-5 : 6-dihydroxypyrimidine (I; R = H), and the unsuccessful attempts at its synthesis exemplify the difficulties of preparing 5-hydroxypyrimidines; the parent compound and its simple derivatives, which might be expected to have the generally phenolic character of 3-hydroxypyridine, are unknown.

The usual methods for preparing hydroxy-compounds are not readily applicable to this series. Thus the readily available 5-halogenopyrimidines usually fail to react with acids or alkalis,[1] although one preparation of a 5-hydroxypyrimidine by this route has been

* A preliminary announcement of part of this work has been made (Bowman and Davoll, *Chem. and Ind.*, 1956, 138).

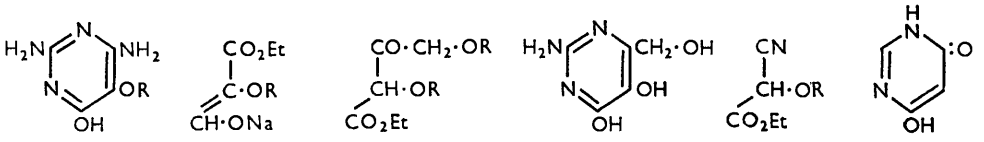
[1] Bendich and Clements, *Biochim. Biophys. Acta*, 1953, **12**, 462.

reported.[2] The 5-alkoxypyrimidines obtained by ring synthesis also show great stability to hydrolysis.[1] A few 5-hydroxypyrimidines have been prepared by acid hydrolysis of 5-amino-compounds;[3,4,5] and 5-aminopyrimidine reacts with nitrous acid with evolution of nitrogen,[6] but the other product of this reaction, possibly 5-hydroxypyrimidine, has not been isolated. Reduction of a 5-oxo-derivative is applicable only to the preparation of dialuric acid from alloxan. Compounds at first described as 2 : 4-diaryl-5-hydroxypyrimidines were reported,[7] but this structure was later disproved.[8] The colour reactions of a number of otherwise unknown 5-hydroxypyrimidines (including 2-amino-4 : 5 : 6-trihydroxypyrimidine and 4 : 5 : 6-trihydroxy-2-mercaptopyrimidine) have been described by Knott [9] without information about their method of preparation.

It appeared that the most versatile synthetical method would be one in which the potential 5-hydroxy-group was protected during the ring synthesis by some group which could be removed later under relatively mild conditions, and a synthesis of 2-amino-4 : 5-dihydroxypyrimidine was accomplished by condensation of guanidine with ethyl sodiobenzyloxyformylacetate (II; R = CH_2Ph) and subsequent hydrogenolysis of the benzyl group. This pyrimidine has previously been prepared from 2 : 5-diamino-4-hydroxypyrimidine.[4]

A far more convenient method, as regards both the preparation of intermediates and the ease of removal of the protecting group, was found in the use of tetrahydropyran-2-yl ethers, the products of ring synthesis being rapidly hydrolysed to 5-hydroxypyrimidines by cold dilute acid.

Ethyl tetrahydropyran-2-yloxyacetate, prepared from ethyl glycollate and 2 : 3-dihydropyran, reacted with ethyl formate in the presence of sodium to give the ester



(I) (II) (III) (IV) (V) (VI)

(II; R = tetrahydropyran-2-yl), which on condensation with guanidine gave 2-amino-4-hydroxy-5-tetrahydropyran-2′-yloxypyrimidine, hydrolysed by dilute acid to 2-amino-4 : 5-dihydroxypyrimidine. 4 : 5-Dihydroxy-2-methylpyrimidine [5] was similarly prepared by using acetamidine. Self-condensation of ethyl tetrahydropyran-2-yloxyacetate by sodium gave the acetoacetic ester derivative (III; R = tetrahydropyran-2-yl), which afforded the hydroxymethylpyrimidine (IV) by reaction with guanidine and subsequent acid hydrolysis.

Bendich and Clements [1] converted ethoxymethyl cyanide by the method of Wallingford *et al.*[10] into the cyano-ester (V; R = Et), which reacted with guanidine to give 2 : 4-diamino-5-ethoxy-6-hydroxypyrimidine (I; R = Et); hydrolysis of this to divicine could not be effected. A similar synthesis using tetrahydropyran-2-yloxymethyl cyanide gave the analogous ester (I; R = tetrahydropyran-2-yl), which was converted into 2 : 4-diamino-5 : 6-dihydroxypyrimidine sulphate by hydrolysis with dilute sulphuric acid, hydrolysis with hot aqueous acetic acid giving the free base (I; R = H). The ultraviolet spectrum and colour reactions (see Table) of the sulphate were virtually identical with those of a sample of divicine sulphate prepared by acid hydrolysis of the glucoside vicine. The infrared spectra of the two preparations showed a number of differences; in view of the

[2] Bray, Lake, and Thorpe, *Biochem. J.*, 1951, **48**, 400.
[3] Behrend, *Annalen*, 1885, **229**, 39.
[4] Johnson and Johns, *Amer. Chem. J.*, 1905, **34**, 564.
[5] Huber and Hölscher, *Ber.*, 1938, **71**, 87.
[6] Whittaker, *J.*, 1951, 1565.
[7] Ekeley and Ronzio, *J. Amer. Chem. Soc.*, 1935, **57**, 1353; Ekeley and Elliott, *ibid.*, 1936, **58**, 163.
[8] Williams, Symonds, Ekeley, and Ronzio, *ibid.*, 1945, **67**, 1157.
[9] Knott, *J. Soc. Chem. Ind.*, 1940, **60**, 313.
[10] Wallingford, Jones, and Homeyer, *J. Amer. Chem. Soc.*, 1942, **64**, 576.

known difficulties of preparing the pure sulphate from vicine [1] it is considered that these may be due to impurities in the " natural " divicine sulphate. Insufficient of this material was available for more extensive purification.

Condensation of the ester (V; R = tetrahydropyran-2-yl) with urea, followed by acid hydrolysis, gave 4-amino-2 : 5 : 6-trihydroxypyrimidine (" isouramil " [11]), believed to be the aglycone of the glucoside convicine, also from vetch.

	Substituents [a]					$\lambda_{max.}$ ($\varepsilon \times 10^{-3}$) in			I_2 consumed [c]	Reactions *		
No.	2	4	5	6	pK_a' [b]	0·1N-HCl	Phosphate buffer, pH 6·8	0·1N-NaOH	(mole/mole)	A	B	C
1	Me	OH	OH	H	8·93	256 (9·3)	256 (9·3)	262 (7·6) 295 (7·9) [e]	0	+	−	+
2	Me	OH	OR	H	9·76	—	237 (5·6) 268 (5·7)	233 (7·4) 273 (5·9)	0	—	—	—
3 [f]	NH_2	OH	OH	H	4·06 9·60	234 (7·4) 276 (6·6)	235 (9·2) 278 (5·4) [e]	251 (5·1) 305 (4·6) [e]	*ca.* 0·4	+	+	+
4	NH_2	OH	OR	H	*ca.* 3·5 9·50	—	214 (13·1) 274 (3·7)	230 (6·9) 283 (5·1)	0	—	—	—
5	NH_2	OH	OR′	H	3·47 9·72	232 (9·1) 270 (6·7)	275 (4·1)	285 (6·0)	0	—	—	—
6 [f]	NH_2	OH	OH	CH_2·OH	4·00 9·78	238 (7·4) 278 (7·8)	215 (12·1) 281 (5·8)	—	*ca.* 0·4	+	+	+
7	NH_2	OH	OR	CH_2·OR	2·44 3·38 9·35	—	222(9·7) 293 (5·0)	285 (6·8)	0	—	—	—
8	NH_2	NH_2	OH	OH	*ca.* 3·8 *ca.* 9·2	281 (12·9)	—	—	1·05	+	+	+
9 [f,g]	NH_2	NH_2	OH	OH	—	280 (12·4)	—	—	—	+	+	+
10	NH_2	NH_2	OR	OH	*ca.* 3·0 >11·0	—	238 (3·8) 278 (12·0)	237 (4·0) 270 (8·8)	0·95	+	—	—
11	OH	NH_2	OH	OH	*ca.* 9·0	220 (s) (4·2) [h] 280 (13·6)	—	—	1·12	+	+	+
12	OH	NH_2	OR	OH	8·75	—	276 (14·8)	277 (13·5)	0·94	+	—	—
13	H	OH	OH	OH	— [i]	271 (9·0) [h]	—	—	— [i]	+	+	+
14	H	OH	OR	OH	6·44	—	261 (9·8)	260 (5·3)	1·15	+	—	—
15	Me	OH	OH	OH	6·41	272 (10·4)	270 (7·7) [e]	—	1·50	+	+	+
16	Me	OH	OR	OH	6·73	—	264 (10·8)	262 (9·7)	1·50	+	—	—
17	Ph	OH	OH	OH	6·57	232 (s) (8·2) 274 (8·8) 304 (s) (7·0)	223 (16·7) [e] 274 (7·7) 310 (4·5)	—	1·21	+	+	+
18	Ph	OH	OR	OH	6·40	—	263 (5·6) 300 (4·2)	270 (4·0) 292 (4·0)	1·51	+	—	—
19	NH_2	OH	OH	OH	2·93	273 (6·9) [h]	—	—	0·94	+	+	+
20	NH_2	OH	OR	OH	7·80	—	270 (12·5)	268 (9·2)	0·94	+	—	—
21	OH	OH	OH	OH	3·15	270 (3·2) (1% HCl) [d]	275 (16·5)	—	0·96	+	+	+
22	SH	OH	OH	OH	2·56	290 (7·3)	225 (9·9) 270 (9·4)	219 (4·7) 266 (18·6)	0·90	+	+	+
23	H	OH	H	OH	5·35	253 (8·3)	251 (7·1)	250 (3·6)	—	—	—	—
24	Me	OH	H	OH	6·55	252 (12·2)	252 (10·2)	252 (6·2)	—	—	—	—
25	Ph	OH	H	OH	6·54	250 (11·5) 283 (5·7)	230 (s) (18·6) 278 (s) (5·2)	278 (5·0)	—	—	—	—
26	NH_2	OH	H	OH	7·40	256 (9·5)	257 (13·9)	257 (8·6)	—	—	—	—

* A, with phosphomolybdate; B, with 2 : 6-dichlorophenol-indophenol; C, with $FeCl_3$–NH_3 (see ref. 1.)

[a] R = tetrahydropyran-2-yl; R′ = benzyl. [b] Determined in 50% ethanol. [c] On titration in aqueous suspension with 0·1N-iodine. [d] Patterson, Lazarow, Lemm, and Levey, *J. Biol. Chem.*, 1949, **177**, 197. [e] Unstable. [f] Sulphate. [g] Prepared from vicine. [h] Determined by dissolving the tetrahydropyranyl derivative in 0·1N-hydrochloric acid. The trihydroxy-compounds were too insoluble to be dissolved without decomposition. [i] Too insoluble.

4 : 5 : 6-Trihydroxypyrimidines were prepared from dimethyl tetrahydropyran-2-yloxymalonate, obtained from dimethyl tartronate and dihydropyran. Condensation of the malonate with guanidine and hydrolysis of the product gave 2-amino-4 : 5 : 6-trihydroxypyrimidine, and dialuric acid was similarly obtained from urea although in this

[11] Davidson and Bogert, *Proc. Nat. Acad. Sci.*, 1932, **18**, 490.

case the intermediate tetrahydropyranyl ether was too unstable to be isolated. Treatment of the crude reaction product with dilute acid gave a solution which contained very little dialuric acid (according to iodometric titration), although addition of excess of sodium hydroxide followed by acetic acid gave a 36% yield of sodium dialurate. This suggests that hydrolysis of the tetrahydropyranyl ether liberates a tautomeric form of dialuric acid, possibly *iso*dialuric acid,[12] which is converted into sodium dialurate under similar conditions. Substitution of thiourea for urea in the above synthesis gave 4 : 5 : 6-trihydroxy-2-mercaptopyrimidine.

4 : 5 : 6-Trihydroxy-2-methyl- and -2-phenyl-pyrimidine were prepared by condensation of dimethyl tetrahydropyranyloxymalonate with the appropriate amidines, followed by acid hydrolysis, and 4 : 5 : 6-trihydroxypyrimidine itself by reaction of tetrahydropyranyloxymalondiamide with ethyl formate,[13] followed by hydrolysis of the tetrahydropyranyl ether thus obtained.

The reactions of the compounds with oxidising agents and with ferric chloride (cf. ref. 1) are given in the Table, together with their pK_a' values and ultraviolet absorption maxima; the range of pH values over which the latter could be determined was limited by the instability of most of the 5-hydroxypyrimidines in neutral and alkaline solution, and by the lability of the tetrahydropyranyl ethers in acid.

All the compounds with hydroxy-groups at both the 4- and the 5-position reduce alkaline phosphomolybdate, and if a 2-amino-group is also present (compounds 3 and 6) reduce Tillman's reagent (2 : 6-dichlorophenol-indophenol) and react slowly with iodine. The 6-amino-4 : 5-dihydroxy- and 4 : 5 : 6-trihydroxy-compounds give positive reactions with Tillman's reagent and phosphomolybdate, and react rapidly with iodine, consuming approximately one mol. per mol. if a 2-amino-, 2-hydroxy-, or 2-mercapto-group is present; otherwise, more extensive oxidation occurs. The 5-tetrahydropyranyl ethers of the 6-amino-4 : 5-dihydroxy- and 4 : 5 : 6-trihydroxy-compounds also react with phosphomolybdate and iodine, presumably with loss of the protecting group. All the 5-hydroxy-compounds give a blue ferric chloride reaction, except 4 : 5-dihydroxy-2-methylpyrimidine, which gives a reddish-violet colour.

Recent studies of pyrimidine ultraviolet spectra[14,15] have shown that 2- and 4(6)-hydroxypyrimidines exist mainly or entirely in the pyrimidone form, while aminopyrimidines generally have the structure of true amino-compounds. The spectra listed in the Table indicate that the 5-hydroxy-group exists as such (except possibly in 4 : 5-dihydroxy-2-methylpyrimidine), since there is a close resemblance between the spectra of the hydroxy-compounds and their ethers. Comparison of these spectra with those of the corresponding pyrimidines unsubstituted at the 5-position shows that the 5-hydroxy-group causes a bathochromic shift of 16—21 mμ, and the ether group a rather smaller one.

In the same way, the spectra of compounds 13—22 are regarded as derived from that of 4 : 6-dihydroxypyrimidine. Stimson[16] reported the spectrum of this compound to have maxima at 270 (ε 5050—5120) and 328 mμ (ε 8160—9400) at pH 2·9—10·9. These values were inconsistent with those of related compounds, and a redetermination on material prepared by Hull's method[13] gave a single maximum at 250—253 mμ, hardly affected in position by change of pH (see Table). Three other 4 : 6-dihydroxypyrimidines (compounds 24—26) also showed little change in absorption with pH. The structure (VI) for 4 : 6-dihydroxypyrimidine receives support from the infrared spectrum,[17] and with a 5-hydroxy-substituent gives a carbonyl-conjugated enediol system which convincingly explains the reducing properties of these compounds.[1]

Polarography of the compounds yielded no definite results. Their infrared spectra were determined, and a detailed account will be submitted for publication elsewhere.

[12] Behrend and Roosen, *Annalen*, 1889, **251**, 235.
[13] Hull, *J.*, 1951, 2214.
[14] Marshall and Walker, *J.*, 1951, 1004; Boarland and McOmie, *J.*, 1952, 3716, 3722; Brown Hoerger, and Mason, *J.*, 1955, 211.
[15] Brown and Short, *J.*, 1953, 331.
[16] Stimson, *J. Amer. Chem. Soc.*, 1949, **71**, 1470.
[17] Short and Thompson, *J.*, 1952, 168.

Experimental

Unless otherwise stated, analytical samples were dried at 20°/1 mm.

2-Amino-5-benzyloxy-4-hydroxypyrimidine.—Ethyl benzyloxyacetate [18] (9·7 g.) was added to sodium wire (1·15 g.) in a mixture of dry ether (25 c.c.) and ethyl formate (3·7 g., 4 c.c.). After 2 hr. the clear brown solution was evaporated to dryness and the residue treated with guanidine (prepared from a hot solution of 4·8 g. of the hydrochloride in absolute ethanol by adding one equiv. of ethanolic sodium ethoxide and filtering) in absolute ethanol (80 c.c.). The mixture was boiled under reflux for 2 hr., then evaporated to dryness, and a filtered solution of the residue in water (60 c.c.) was acidified with glacial acetic acid (3 c.c.). The gum which separated crystallised rapidly, giving a tan-coloured powder (7·06 g., 65%). Crystallisation from 50% ethanol (800 c.c.) with charcoal gave the *benzyloxypyrimidine* (4·52 g.) as needles, m. p. 245—246° (decomp. >200°) (Found: C, 60·9; H, 5·2; N, 19·0. $C_{11}H_{11}O_2N_3$ requires C, 60·8; H, 5·1; N, 19·4%).

2-Amino-4:5-dihydroxypyrimidine Sulphate.—(*a*) A solution of the above compound (1·0 g.) in 50% acetic acid (30 c.c.) on hydrogenation at ordinary temperature and pressure in presence of 5% palladised charcoal rapidly absorbed 1 mol. of hydrogen. Addition of dilute sulphuric acid, evaporation to small volume, and addition of ethanol gave the sulphate (0·62 g., 76%) as colourless crystals [Found: N, 23·8. $(C_4H_5O_2N_3)_2H_2SO_4$ requires N, 23·9%]. Cf. (*b*) below.

Ethyl Tetrahydropyran-2-yloxyacetate.—To a mixture of ethyl glycollate (100 g.) and redistilled 2:3-dihydropyran (88 g.) was added a little toluene-*p*-sulphonic acid; the temperature rose rapidly to about 150°. After cooling, a solution of the product in ether was washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and distilled from a little sodium hydrogen carbonate, giving the *ester* (165 g., 83%), b. p. 88°/1 mm., n_D^{20} 1·4415 (Found: C, 57·8; H, 8·6. $C_9H_{16}O_4$ requires C, 57·4; H, 8·6%).

2-Amino-4-hydroxy-5-tetrahydropyran-2′-yloxypyrimidine.—The above ester (37·6 g.) was added to sodium wire (4·6 g.) and ethyl formate (14·8 g., 16 c.c.) in dry ether (100 c.c.), under a reflux condenser. After 4 hr. guanidine (from 19·1 g. of hydrochloride) in absolute ethanol (200 c.c.) was added to the spongy mass of sodium derivative, and most of the ether was distilled off. The remaining solution was boiled for 2 hr. and the product (24·7 g., 58%) isolated as described for the benzyloxy-compound. Rapid recrystallisation from 50% ethanol (1 l.) with charcoal gave the *tetrahydropyranyloxypyrimidine* (16·6 g.) as needles, m. p. 196° (decomp.) (Found: C, 51·1; H, 6·5; N, 19·9. $C_9H_{13}O_3N_3$ requires C, 51·2; H, 6·2; N, 19·9%). Prolonged heating during recrystallisation caused loss of the tetrahydropyranyl group.

2-Amino-4:5-dihydroxypyrimidine Sulphate.—(*b*) The above ether (9 g.) and 2N-sulphuric acid (70 c.c.) were shaken together for 1 hr. Collected after cooling to 0° and washed with ethanol, the sulphate (6·9 g., 92%) formed crystals identical spectroscopically with the preparation described above [Found: C, 27·0; H, 3·7; N, 24·1. Calc. for $(C_4H_5O_2N_3)_2H_2SO_4$: C, 27·3; H, 3·4; N, 23·9%].

The free base (1·16 g., 91%) was obtained by acidifying a solution of the sulphate (1·76 g.) in 2N-sodium hydroxide (10 c.c.) with acetic acid. It formed colourless needles (from water), decomp. >300° (Found: C, 37·3; H, 4·2; N, 33·4. Calc. for $C_4H_5O_2N_3$: C, 37·8; H, 4·0; N, 33·1%).

4-Hydroxy-2-methyl-5-tetrahydropyran-2′-yloxypyrimidine.—The procedure was as described for the 2-amino-compound, except that acetamidine was used, and refluxing was for 3 hr. The compound did not separate on neutralisation of a solution of its sodium salt and was extracted with ethyl acetate (3 × 60 c.c.). Evaporation of the dried (Na_2SO_4) extract and trituration with dry ether (100 c.c.) gave the *tetrahydropyranyl compound* (17·5 g., 42%), needles, m. p. 141—143° (with gas evolution and resolidification at a slightly higher temperature), unchanged by recrystallisation from benzene (Found: C, 57·4; H, 7·0; N, 13·1. $C_{10}H_{14}O_3N_2$ requires C, 57·1; H, 6·7; N, 13·3%).

4:5-Dihydroxy-2-methylpyrimidine.—The above ether (10 g.) and N-sulphuric acid (100 c.c.) were shaken together for 1½ hr. and the dihydroxypyrimidine (5·23 g., 87%) collected after dilution with ethanol (100 c.c.). It crystallised from water in prisms, m. p. *ca.* 310° (decomp.) (Found: C, 47·9; H, 5·0; N, 22·4. Calc. for $C_5H_6O_2N_2$: C, 47·6; H, 4·8; N, 22·2%). Huber and Hölscher [5] give m. p. 231°. As described by them, the aqueous solution of the compound is acid to litmus and gives a light green precipitate with aqueous cupric acetate.

[18] Rothstein, *Bull. Soc. chim. France*, 1932, **51**, 691.

2-Amino-4-hydroxy-5-tetrahydropyran-2'-yloxy-6-tetrahydropyran-2'-yloxymethylpyrimidine.—Sodium wire (1·15 g.) was added to ethyl tetrahydropyran-2-yloxyacetate (18·8 g.) in dry ether (50 c.c.). After 6 hr. the red solution was evaporated under reduced pressure and the residue treated with guanidine (from 4·8 g. of hydrochloride) in absolute ethanol (60 c.c.). The mixture was boiled under reflux for 2 hr., then evaporated, and a solution of the residue in water (80 c.c.) washed with ether and treated with glacial acetic acid (3 c.c.). The product (7·18 g., 44%) was crystallised rapidly from 80% ethanol (600 c.c.) to give the *pyrimidine* (4·32 g.) which contracted at 203—207° (Found : C, 55·4; H, 7·1; N, 13·0. $C_{15}H_{23}O_5N_3$ requires C, 55·4; H, 7·1; N, 12·9%).

2-Amino-4 : *5-dihydroxy-6-hydroxymethylpyrimidine Sulphate.*—The above compound (1 g.) was shaken with 2N-sulphuric acid (7 c.c.) for 1 hr. Collected and washed with ethanol, the *sulphate* (0·58 g., 92%) formed prisms [Found : C, 28·9; H, 4·1; N, 20·6. $(C_5H_7O_3N_3)_2H_2SO_4$ requires C, 29·1; H, 3·9; N, 20·4%].

Tetrahydropyran-2-yloxymethyl Cyanide.—Glycollonitrile (134 g., prepared from a commercial 70% aqueous solution by azeotropic removal of water with benzene, followed by vacuum-distillation) in dry ether (400 c.c.) containing a little toluene-*p*-sulphonic acid was treated with redistilled 2 : 3-dihydropyran (198 g.) with stirring at such a rate that the mixture boiled gently. After 2 hr. at room temperature the solution was washed with aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated, and the residue distilled from a little sodium hydrogen carbonate, giving the *cyanide* (288 g., 87%), b. p. 76°/1 mm., n_D^{20} 1·4453 (Found : C, 59·4; H, 7·9; N, 10·2. $C_7H_{11}O_2N$ requires C, 59·6; H, 7·9; N, 9·9%).

2 : 4-Diamino-6-hydroxy-5-tetrahydropyran-2'-yloxypyrimidine.—A mixture of the above cyanide (28·2 g.) and ethyl carbonate (194 c.c.) was added to " foamed " sodium ethoxide (from 4·6 g. of sodium) and heated with stirring under a 6" Fenske column with a reflux ratio head until the temperature of the distillate reached 125° (1 hr.). The mixture was evaporated to dryness under reduced pressure and the residue heated under reflux for 2 hr. with guanidine (from 19·1 g. of hydrochloride) in absolute ethanol (200 c.c.). After evaporation, a solution of the residue in water (100 c.c.) was washed with ether and treated with glacial acetic acid (12·5 c.c.). The brown powder (25·5 g.) which separated was recrystallised rapidly from very dilute sodium hydrogen carbonate solution (500 c.c.), with charcoal, giving the *tetrahydropyranyl ether* (12·3 g., 27%) as needles, sintering at 121—123° (Found : C, 47·8; H, 6·4; N, 24·8. $C_9H_{14}O_3N_4$ requires C, 47·8; H, 6·2; N, 24·8%).

2 : 4-Diamino-5 : 6-dihydroxypyrimidine.—The above ether (1 g.) and 5% acetic acid (20 c.c.) were boiled together for 10 min. The *diaminodihydroxypyrimidine* (0·38 g., 61%) was collected after cooling and recrystallised from water, giving brownish needles, decomp. >280° (Found : C, 33·6; H, 4·3; N, 39·6. $C_4H_6O_2N_4$ requires C, 33·8; H, 4·3; N, 39·4%). The *sulphate*, prepared by hydrolysis of the tetrahydropyranyl ether with sulphuric acid in the usual way (91% yield), was microcrystalline and darkened slowly [Found : C, 25·3; H, 3·9; N, 28·9. Calc. for $(C_4H_6O_2N_4)_2H_2SO_4$: C, 25·1; H, 3·7; N, 29·3%].

2 : 4-Diamino-5 : 6-dihydroxypyrimidine Sulphate from Vicine.—Vicine (20 mg.) and 2N-sulphuric acid (0·2 c.c.) were heated together in a sealed tube at 100° for 15 min. After cooling and addition of ethanol (0·5 c.c.) the crystalline material was collected by centrifugation, washed with ethanol (2 × 0·5 c.c.), and dried *in vacuo* at room temperature.

4-Amino-2 : 6-dihydroxy-5-tetrahydropyran-2'-yloxypyrimidine.—Tetrahydropyran-2-yloxymethyl cyanide (14·1 g.) was converted into the cyano-ester as described above and the product boiled under reflux for 6 hr. with urea (6 g.) in absolute ethanol (150 c.c.). Isolated in the usual way, the *pyrimidine* (5·66 g., 25%) formed prisms (from 50% ethanol), m. p. >300° (Found : C, 47·3; H, 6·1; N, 18·4. $C_9H_{13}O_4N_3$ requires C, 47·6; H, 5·8; N, 18·5%).

4-Amino-2 : 5 : 6-trihydroxypyrimidine (" *Isouramil* ").—Obtained by hydrolysis of the above compound with cold 2N-sulphuric acid (87% yield) and crystallised from 50% ethanol the compound rapidly became pink (Found : C, 33·5; H, 4·0; N, 29·3. Calc. for $C_4H_5O_3N_3$: C, 33·6; H, 3·5; N, 29·4%).

Dimethyl Tartronate.—Diethyl acetoxymalonate was prepared by the following modification of Dimroth and Schweizer's method[19] which avoids the isolation of lead tetra-acetate. To a mixture of glacial acetic acid (1260 c.c.), acetic anhydride (320 c.c.), and diethyl malonate (160 g.) at 90° was added red lead (820 g.) with stirring, so as to keep the temperature at 95—105°. The mixture was then kept for 3 hr. at 100°, cooled to 70°, and added to ice and water (3 l.). The solution was extracted with 1 : 1 benzene–ethyl acetate (5 × 400 c.c.) and the extract washed

[19] Dimroth and Schweizer, *Ber.*, 1923, **56**, 1375.

twice with water and with aqueous sodium carbonate, dried (Na_2SO_4), and distilled, giving diethyl malonate (38 g.), and diethyl acetoxymalonate (118 g., 59%), b. p. 130—133°/12 mm. This was converted into dimethyl tartronate as described by Bak.[20]

Dimethyl Tetrahydropyran-2-yloxymalonate.—To a mixture of dimethyl tartronate (43 g.) and redistilled 2 : 3-dihydropyran (24·3 g.) was added a little toluene-*p*-sulphonic acid; the temperature rose to 80°. After 1 hr. ether was added and the mixture worked up in the usual way, giving the *ester* (46·6 g., 69%), b. p. 126—130°/1·5 mm., n_D^{26} 1·4470 (Found: C, 52·2; H, 7·1. $C_{10}H_{16}O_6$ requires C, 51·7; H, 6·9%).

Tetrahydropyran-2-yloxymalondiamide.—The above ester (2·32 g.) and aqueous ammonia (*d* 0·88; 10 c.c.) were shaken together. The *diamide* (1·53 g., 76%) rapidly separated; it formed colourless needles (from ethanol), m. p. 160—163° (with evolution of gas) (Found: C, 47·7; H, 7·2; N, 14·1. $C_8H_{14}O_4N_2$ requires C, 47·5; H, 7·0; N, 13·9%).

2-Amino-4 : 6-dihydroxy-5-tetrahydropyran-2′-yloxypyrimidine.—To dimethyl tetrahydropyranyloxymalonate (11·6 g.) was added ethanolic sodium ethoxide (from 1·15 g. of sodium in 50 c.c. of absolute ethanol), followed by guanidine (from 4·8 g. of hydrochloride) in absolute ethanol (50 c.c.). The mixture, from which solid rapidly separated, was boiled under reflux for 4 hr. Isolated in the usual way, the *pyrimidine* (8·1 g., 71%) separated as a microcrystalline powder, decomp. >290°, on treatment of its solution in dilute sodium hydroxide with acetic acid (Found: C, 47·2; H, 6·0; N, 18·7. $C_9H_{13}O_4N_3$ requires C, 47·6; H, 5·8; N, 18·5%).

2-Amino-4 : 5 : 6-trihydroxypyrimidine.—The *trihydroxy-compound* separated as small brownish prisms (74% yield), decomp. >300°, when the above ether was shaken with 2N-sulphuric acid (Found: C, 29·7; H, 4·4; N, 26·6. $C_4H_5O_3N_3,H_2O$ requires C, 29·8; H, 4·4; N, 26·1%).

2 : 4 : 5 : 6-Tetrahydroxypyrimidine (Dialuric Acid).—Urea (1·5 g.) in hot absolute ethanol (50 c.c.) was added to the sodium derivative of dimethyl tetrahydropyranyloxymalonate (from 5·8 g. of ester) in absolute ethanol (25 c.c.). The gelatinous mass was kept for 6 hr. at 75—80° and evaporated to dryness. The residue was shaken for 20 min., with exclusion of air, with 2N-sulphuric acid (20 c.c.), then treated with 10N-sodium hydroxide (5 c.c.), followed after 10 min. by glacial acetic acid (3 c.c.) and ethanol (30 c.c.). The precipitate was collected after 3 days at 0° and shaken with water (60 c.c.), giving sodium dialurate (1·51 g., 36%), which was shaken 10 min. with 2N-sulphuric acid (10 c.c.), with exclusion of air, to give *dialuric acid* monohydrate (1·15 g., 28% overall yield) as rods, which gave the anhydrous compound when dried at room temperature in a high vacuum (Loss in wt., 10%. Calc. for $C_4H_4O_4N_2,H_2O$: 11·1%. Found: C, 33·1; H, 3·1; N, 19·3. $C_4H_4O_4N_2$ requires C, 33·3; H, 2·8; N, 19·4%). When heated slowly from an initial temperature of 150° the monohydrate became red above 180° but as described by Tipson and Cretcher,[21] did not melt up to 350°. When heated rapidly from an initial temperature of 200° the compound melted with decomposition at 210—215°; this m. p. is the one usually given in the literature. On titration with 0·1N-iodine the compound reacted with 0·96 mol. per mol.

For comparison, sodium dialurate was prepared from a solution of commercial dialuric acid in excess of aqueous sodium hydroxide by addition of acetic acid, and was converted into dialuric acid as described above. The product showed the same m. p. behaviour, alone or in admixture, and consumed 0·97 mol. of iodine per mol. The infrared spectra of the two samples were virtually identical, and closely resembled that given by Tipson and Cretcher.

4 : 5 : 6-Trihydroxy-2-mercaptopyrimidine.—Prepared by substituting thiourea for urea in the above synthesis, the *mercaptopyrimidine* separated as a yellow powder (24%), decomposing slowly above 200° (Found: C, 30·0; H, 2·9; N, 17·1. $C_4H_4O_3N_2S$ requires C, 30·0; H, 2·5; N, 17·5%).

4 : 6-Dihydroxy-2-methyl-5-tetrahydropyran-2′-yloxypyrimidine.—Prepared from acetamidine as described for the corresponding 2-amino-compound, except that heating was for 2 hr., the *pyrimidine* (75% yield) separated as a microcrystalline powder on neutralisation of its solution in N-sodium hydroxide with acetic acid; it did not melt (Found: C, 52·8; H, 6·4; N, 12·5. $C_{10}H_{14}O_4N_2$ requires C, 53·1; H, 6·2; N, 12·4%).

4 : 5 : 6-Trihydroxy-2-methylpyrimidine.—After hydrolysis of the above ether by boiling 10% acetic acid (30 c.c. per g.) for 30 min., the *trihydroxypyrimidine* separated on cooling as parallelograms (82%) with no m. p. (Found: C, 41·8; H, 4·6; N, 19·5. $C_5H_6O_3N_2$ requires C, 42·3; H, 4·3; N, 19·7%).

[20] Bak, *Annalen*, 1939, **537**, 291.
[21] Tipson and Cretcher, *J. Org. Chem.*, 1951, **16**, 1091.

4 : 6-*Dihydroxy-2-phenyl-5-tetrahydropyran-2'-yloxypyrimidine*.—Prepared from benzamidine, with heating under reflux for 16 hr., the *pyrimidine* (30% yield) separated as a yellow microcrystalline powder, m. p. 165° (decomp.), on neutralisation of its solution in N-sodium hydroxide with acetic acid (Found : C, 62·8; H, 5·5; N, 10·2. $C_{15}H_{16}O_4N_2$ requires C, 62·5; H, 5·6; N, 9·7%).

4 : 5 : 6-*Trihydroxy-2-phenylpyrimidine*.—Prepared by hydrolysis of the above ether with boiling 10% acetic acid (15 c.c. per g.; 30 minutes' heating) the *trihydroxyphenylpyrimidine* was obtained as yellow rods (94%) (from ethanol), decomp. >230° (Found : C, 56·9; H, 4·5; N, 13·2. $C_{10}H_8O_3N_2,\frac{1}{2}H_2O$ requires C, 56·3; H, 4·3; N, 13·1%).

4 : 6-*Dihydroxy-5-tetrahydropyran-2'-yloxypyrimidine*.—To a solution of sodium ethoxide prepared from sodium (4·6 g.) and absolute ethanol (150 c.c.) were added tetrahydropyran-2-yloxymalondiamide (20·2 g.) and ethyl formate (11 g.). The mixture was heated under reflux for 2½ hr., cooled, and diluted with water (200 c.c.). After evaporation under reduced pressure to about 100 c.c., the solution was washed with ether and treated with glacial acetic acid (12 c.c.), giving the *pyrimidine* (13·5 g., 64%) which was purified by neutralisation of its alkaline solution with acetic acid and did not melt (Found : C, 50·9; H, 5·9; N, 13·1. $C_9H_{12}O_4N_2$ requires C, 50·9; H, 5·7; N, 13·2%).

4 : 5 : 6-*Trihydroxypyrimidine*.—Hydrolysis of the above ether by boiling 10% acetic acid (40 c.c. per g.) for 30 min. gave 4 : 5 : 6-*trihydroxypyrimidine* (56% yield) as a microcrystalline buff powder, with no m. p. (Found : C, 37·4; H, 3·6; N, 21·3. $C_4H_4O_3N_2$ requires C, 37·5; H, 3·2; N, 21·9%).

The authors thank Dr. R. E. Bowman for suggesting the application of tetrahydropyranyl ethers to the synthesis of 5-hydroxypyrimidines, and for many helpful discussions. They are also indebted to Dr. Aaron Bendich of the Sloan-Kettering Institute, New York, for a sample of vicine, and to Miss E. M. Tanner for the measurements of absorption spectra and potentiometric titrations. Microanalyses are by Mr. A. J. Durre.

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[*Received, December 28th*, 1956.]