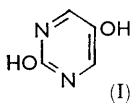
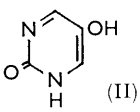
1311. *Pyrimidines. Part XIV.*[1] *Synthesis of 2,5-Dihydroxypyrimidine*

By D. T. Hurst, J. F. W. McOmie, and J. B. Searle

2,5-Dihydroxypyrimidine has been synthesised from 5-benzyloxy-4-hydroxy-2-mercaptopyrimidine. Its properties are compared with those of α- and β-isouracil which Tafel and Houseman had tentatively considered to be tautomeric forms of 2,5-dihydroxypyrimidine.

There are four possible dihydroxypyrimidines, of which three have been well-characterised, namely, 2,4-dihydroxy- (uracil), 4,5-dihydroxy-,[2] and 4,6-dihydroxy-pyrimidine.[3] The fourth isomer, 2,5-dihydroxypyrimidine, may have been prepared by Tafel and Houseman but in view of doubts concerning the identity of their material the present synthetic work was undertaken. In 1901 Tafel[4] reduced uric acid electrolytically and obtained a substance, $C_5H_8N_4O_2$ which he called " purone." When this was treated with acid or alkali it was irreversibly isomerised to " isopurone." Tafel and Houseman[5] oxidised the latter with bromine water and obtained two compounds, $C_4H_4N_2O_2$, which were isomeric with uracil. These they called α- and β-isouracil. α-Isouracil crystallised as needles, which carbonised without melting at about 350°, and with ferric chloride it gave a brown-violet colour which soon faded. It was more soluble in dilute acid or alkali than in water alone, and it was gradually decomposed by cold dilute acid or by hot water with the formation of a grey-green, amorphous, sparingly soluble precipitate. It did not react with phenylhydrazine in acetic acid, but on prolonged warming with an excess of this reagent in ethanol it gave an amorphous, osazone-like precipitate whose composition was not established. Tafel and Houseman tentatively suggested formulæ (I) or (II) for α-isouracil. The β-isomer was found to be very stable; it dissolved in alkali and could be recovered on acidification. Reaction with phenylhydrazine in acetic acid gave a crystalline product, but this was not fully investigated. Because of its apparent ketonic nature, β-isouracil was given the provisional structure (III). Attempts to interconvert the α- and β-isomers were unsuccessful.


(I)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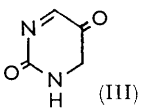
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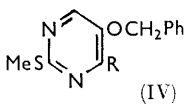
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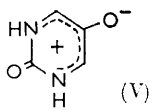
(V)

In the present work, authentic 2,5-dihydroxypyrimidine has been prepared starting from 5-benzyloxy-4-hydroxy-2-mercaptopyrimidine[6] which was first methylated to give the corresponding 2-methylthio-compound (IV; R = OH), and then treated with phosphoryl chloride to give 5-benzyloxy-4-chloro-2-methylthiopyrimidine (IV; R = Cl). When this was reduced with zinc dust and boiling water it yielded 5-benzyloxy-2-methylthiopyrimidine (IV; R = H); acid hydrolysis then gave 5-hydroxy-2-methylthiopyrimidine which resisted further hydrolysis. This compound has been made by Budesinsky *et al.*[7] by heating 5-methoxy-2-methylthiopyrimidine with 25% ammonia for 2 hr. at 200°. An indirect method of hydrolysis of the 2-methylthio-group had to be used, based on the

[1] Part XIII, J. H. Chesterfield, D. T. Hurst, J. F. W. McOmie, and M. S. Tute, *J.*, 1964, 1001.
[2] J. F. W. McOmie and A. B. Turner, *J.*, 1960, 5590.
[3] D. J. Brown, *J.*, 1956, 2312.
[4] J. Tafel, *Ber.*, 1901, **34**, 258.
[5] J. Tafel and P. A. Houseman, *Ber.*, 1907, **40**, 3743.
[6] J. H. Chesterfield, J. F. W. McOmie, and M. S. Tute, *J.*, 1960, 4590.
[7] Z. Budesinsky, V. Bydzovsky, J. Kopecky, A. Svab, and J. Vavrina, *Cesk. Farm.*, 1961, **10**, 241 (*Chem. Abs.*, 1961, **55**, 25,972).

work of Sprague and Johnson.[8] An aqueous suspension of 5-benzyloxy-2-methylthiopyrimidine was treated with chlorine and, without isolation, the resulting 5-benzyloxy-2-methylsulphonylpyrimidine was boiled with alkali, thereby giving 5-benzyloxy-2-hydroxypyrimidine. Similar treatment of 5-hydroxy-2-methylthiopyrimidine caused complete decomposition. The benzyl group proved unexpectedly difficult to remove from 5-benzyloxy-2-hydroxypyrimidine, thus the compound was recovered unchanged after being boiled with Raney nickel and on treatment with hydrogen in presence of palladium catalysts; it also resisted hydrolysis by hydrochloric acid. However, hydrolysis with boiling hydrobromic acid was successful and 2,5-dihydroxypyrimidine was obtained in good yield. It was characterised by conversion into the 5-acetate and 5-benzoate. On reaction with phosphoryl chloride it gave 2-chloro-5-hydroxypyrimidine which was also made by two other methods (see below).

In neutral solution, 2,5-dihydroxypyrimidine probably exists mainly as a mixture of the tautomeric forms (II) and (V). It gave no crystalline product when treated with phenylhydrazine in acetic acid even after 3 hr. at 100°, and it therefore differs conclusively from Tafel's β-isouracil; under much milder conditions alloxan rapidly gives a beautifully crystalline, yellow phenylhydrazone. In several respects, 2,5-dihydroxypyrimidine resembles α-isouracil, *e.g.*, in its solubility, relative instability, and in giving with aqueous ferric chloride a transient mauve colour. Furthermore, after the dihydroxypyrimidine had been boiled for 8 hr. with phenylhydrazine in ethanol, dilution with water gave a yellow amorphous precipitate which could not be crystallised. Unfortunately, despite numerous attempts, we were unable to repeat Tafel and Houseman's work. In our hands, electrolytic reduction of uric acid was always very incomplete and we were unable to obtain any reduction products pure. The available evidence suggests that Tafel probably did obtain 2,5-dihydroxypyrimidine but in the absence of a direct comparison it is not possible to be certain.

Before the synthesis of 2,5-dihydroxypyrimidine by the foregoing sequence had been achieved, several other routes were explored. 2,4,5-Trihydroxy- and 5-acetoxy-2,4-dihydroxy-pyrimidine were treated with phosphoryl chloride and the resulting crude 2,4-dichloro-compound was reduced with zinc dust to give 2-chloro-5-hydroxypyrimidine. However, the latter could not be hydrolysed to 2,5-dihydroxypyrimidine using sodium acetate, hydrogen carbonate, or hydroxide, nor could the chlorine atom be displaced by reaction with sodium methoxide, sodium hydrosulphide, or with thiourea. Likewise, 5-bromo-2-hydroxypyrimidine [9] could not be hydrolysed (cf. the hydrolysis of 5-bromo-2,4-dihydroxypyrimidine [10]) nor could simultaneous hydrolysis and decarboxylation of 2-amino-5-bromopyrimidine-4,6-dicarboxylic acid [11] be effected. Attempts to effect selective thionation (cf. ref. 12) at position 4 of 2,4,5-trihydroxy- and 5-acetoxy-2,4-dihydroxypyrimidine resulted in tars. Oxidation of 2-hydroxypyrimidine with ammonium persulphate (cf. ref. 13) did not give the desired product.

Experimental

5-Benzyloxy-4-hydroxy-2-methylthiopyrimidine (IV; R = OH).—(*a*) Methyl sulphate (2·2 ml.) was added dropwise to a stirred solution of 5-benzyloxy-4-hydroxy-2-mercaptopyrimidine [6] (5 g.) and sodium hydroxide (1·4 g.) in water (20 ml.). After 30 min. the mixture was filtered and the solid (2·1 g.) was recrystallised from ethanol giving *1,6-dihydro-5-benzyloxy-1-methyl-2-methylthio-6-oxopyrimidine* as needles, m. p. 93—94° (Found: C, 59·4; H, 5·3; N, 10·8. $C_{13}H_{14}N_2O_2$ requires C, 59·5; H, 5·4; N, 10·7%). The filtrate was acidified with dilute hydrochloric acid and the precipitate (2·8 g.) was collected. After recrystallisation from ethanol

[8] J. Sprague and T. B. Johnson, *J. Amer. Chem. Soc.*, 1935, **57**, 2252.
[9] J. H. Chesterfield, J. F. W. McOmie, and E. R. Sayer, *J.*, 1955, 3478.
[10] S. Y. Wang, *J. Amer. Chem. Soc.*, 1959, **81**, 3768.
[11] H. G. Bray, H. J. Lake, and W. V. Thorpe, *Biochem. J.*, 1951, **48**, 400.
[12] G. Levin, A. Kalmus, and F. Bergmann, *J. Org. Chem.*, 1960, **25**, 1752.
[13] R. Hull, *J.*, 1956, 2033.

the *5-benzyloxy-4-hydroxy-2-methylthiopyrimidine* formed needles, m. p. 180—181° (Found: C, 58·2; H, 4·5; N, 11·7. $C_{12}H_{12}N_2O_2S$ requires C, 58·1; H, 4·9; N, 11·3%). Neither product gave a colour with ferric chloride.

(*b*) Methyl iodide (6·1 g.) was added dropwise to a stirred solution of 5-benzyloxy-4-hydroxy-2-mercaptopyrimidine (5 g.) in N-sodium hydroxide (20 ml.). When the addition was complete (*ca.* 10 min.) the solid was collected and recrystallised from ethanol giving the required pyrimidine (4·0 g., 75%), m. p. 180—181°.

5-Benzyloxy-4-chloro-2-methylthiopyrimidine (IV; R = Cl).—The above pyrimidine (4·0 g.) was boiled under reflux with phosphoryl chloride (50 ml.) and dimethylaniline (15 ml.) for 1·5 hr. Some of the phosphoryl chloride (*ca.* 20 ml.) was removed by distillation under reduced pressure and then the mixture, when cool, was poured on ice (300 g.). Extraction with ether, followed by crystallisation from light petroleum (b. p. 40—60°) gave the *chloropyrimidine* (3·7 g. 81%) as needles, m. p. 80—81° (Found: C, 53·9; H, 3·8; N, 10·0. $C_{12}H_{11}ClN_2OS$ requires C, 54·0; H, 4·1; N, 10·5%).

5-Benzyloxy-2-methylthiopyrimidine (IV; R = H).—The above chloropyrimidine (3·0 g.) was dissolved in the minimum volume of hot ethanol and precipitated by addition of water (200 ml.). Zinc dust (6·0 g.) was added and the mixture was boiled under reflux for 2·5 hr. The hot solution was filtered and extracted continuously with ether thereby giving a brown solid which on recrystallisation from petroleum (b. p. 40—60°) gave *5-benzyloxy-2-methylthiopyrimidine* (1·5 g., 58%) as pale yellow needles, m. p. 69—70·5° (Found: C, 62·4; H, 5·3; N, 12·3. $C_{12}H_{12}N_2OS$ requires C, 62·1; H, 5·2; N, 12·1%).

5-Hydroxy-2-methylthiopyrimidine.—5-Benzyloxy-2-methylthiopyrimidine (1·0 g.) was boiled with 5N-hydrochloric acid (30 ml.) for 5 hr. The reaction mixture was allowed to cool, and was then extracted continuously with ether, thereby giving a solid which on recrystallisation from benzene gave 5-hydroxy-2-methylthiopyrimidine (0·3 g., 49%) as needles, m. p. 168—169° (lit.,[7] 176—177°; a redetermination [14] on a Kofler hot-stage apparatus gave m. p. 170·5°) (Found: C, 42·1; H, 4·0. Calc. for $C_5H_6N_2OS$: C, 42·2; H, 4·3%).

5-Benzyloxy-2-hydroxypyrimidine.—Water (150 ml.) was added to a solution of 5-benzyloxy-2-methylthiopyrimidine (3·0 g.) in the minimum volume of hot ethanol. The resulting suspension was cooled to 0° and chlorine was bubbled through it for 1 hr. The solution was then aerated to remove excess of chlorine, and the crude 5-benzyloxy-2-methylsulphonylpyrimidine was collected by filtration. It was boiled with 2N-sodium hydroxide (60 ml.) for 30 min. The solution was cooled and the resulting solid was collected, then dissolved in water and the solution was acidified with hydrochloric acid. On cooling to 0°, a crystalline solid was obtained which was recrystallised from ethanol–petroleum (b. p. 60—80°) thereby giving *5-benzyloxy-2-hydroxypyrimidine* (1·65 g., 65%) as needles, m. p. 195—196° (decomp.) with darkening from 170° (Found: C, 65·6; H, 4·9; N, 13·9. $C_{11}H_{10}N_2O_2$ requires C, 65·3; H, 5·0; N, 13·9%).

2,5-Dihydroxypyrimidine.—5-Benzyloxy-2-hydroxypyrimidine (0·9 g.) was boiled with 48% hydrobromic acid (10 ml.) for 3 min., and was then allowed to cool. After being extracted with ether (25 ml.), the solution was cooled to 0° and the crystals of 2,5-dihydroxypyrimidine hydrobromide were collected and immediately shaken with a dilute solution of sodium hydrogen carbonate, thereby giving *2,5-dihydroxypyrimidine* (0·35 g., 70%) as needles which darkened above 200° but did not melt up to 300° (Found, in a sample dried at 20°/0·01 mm. for 24 hr.: C, 42·65; H, 3·95; N, 24·86. $C_4H_4N_2O_2$ requires C, 42·9; H, 3·6; N, 25·0%). The compound could be recrystallised from *NN*-dimethylformamide (80% recovery) in the anhydrous form but when recrystallised from hot water it gave *2,5-dihydroxypyrimidine hydrate* as a hygroscopic powder (50% recovery) which was dried at 55°/0·01 mm. for 24 hr. (Found: C, 36·9; H, 4·9; N, 21·4. $C_4H_4N_2O_2,H_2O$ requires C, 36·9; H, 4·65; N, 21·5%).

2,5-Dihydroxypyrimidine is gradually decomposed by boiling water and is completely destroyed by boiling with 48% hydrobromic acid for 10 min. It dissolves in alkali to give a yellow solution from which some crude dihydroxypyrimidine can be obtained on acidification. An ice-cold solution of 2,5-dihydroxypyrimidine in very dilute sodium hydroxide gave a green colour with diazotised *p*-nitroaniline (cf. 4,5-dihydroxypyrimidine which gives a red colour [1]).

When 2,5-dihydroxypyrimidine was boiled with acetic anhydride it gave *5-acetoxy-2-hydroxypyrimidine*, m. p. 179—180° after being twice sublimed (125°/0·05 mm.) (Found: C, 47·0; H, 4·1; N, 18·2. $C_6H_6N_2O_3$ requires C, 46·75; H, 3·9; N, 18·1%). Similarly, when the dihydroxypyrimidine was boiled with benzoyl chloride it gave *5-benzoyloxy-2-hydroxypyrimidine*

[14] Z. Budesinsky, personal communication, February 1962.

[recrystallised from benzene–petroleum (b. p. 60—80°)] which melted with decomposition at 195° after darkening from 170° (Found: C, 61·2; H, 4·1; N, 12·75. $C_{11}H_8N_2O_4$ requires C, 61·1; H, 3·75; N, 13·0%).

2-*Chloro*-5-*hydroxypyrimidine*.—(*a*) A mixture of 2,4,5-trihydroxypyrimidine [15] (4·0 g.), phosphoryl chloride (40 ml.), and dimethylaniline (10 ml.) was boiled under reflux for 4 hr. When cool, the mixture was added to ice (300 g.) and it was then extracted continuously with ether, thereby giving 2,4-dichloro-5-hydroxypyrimidine (8·4 g.) as a yellow, viscous oil. This oil (8·4 g.) was boiled with water (410 ml.) and zinc dust (8·4 g.) for 4 hr. The solution, after being filtered, was extracted continuously with ether and thereby gave a solid which was recrystallised from ethanol–benzene giving 2-*chloro*-5-*hydroxypyrimidine* (0·92 g., 29% overall) as plates, m. p. 195—196° (decomp.) (Found: C, 36·75; H, 2·4; N, 21·25. $C_4H_3ClN_2O$ requires C, 36·7; H, 2·3; N, 21·4%).

(*b*) A mixture of 5-acetoxy-2,4-dihydroxypyrimidine [16] (7·0 g.), phosphoryl chloride (60 ml.), and dimethylaniline (15 ml.) was boiled under reflux for 30 min. The product (4·0 g.) was worked up as above, and then some (3·0 g.) of it was reduced with zinc dust (3·0 g.) and boiling water (150 ml.) during 1·5 hr., thereby giving 2-chloro-5-hydroxypyrimidine (0·3 g., 8% overall), m. p. 195—196° (decomp.) (Found: C, 37·5; H, 2·3; N, 21·4%).

(*c*) 2,5-Dihydroxypyrimidine (0·1 g.) was boiled under reflux with phosphoryl chloride (3·0 ml.) and dimethylaniline (1·0 ml.). The cooled mixture was poured on crushed ice and the product was isolated by continuous extraction with ether. Removal of the ether, followed by sublimation under reduced pressure gave the chloropyrimidine (0·01 g., 8%), m. p. 194—195° whose infrared spectrum was identical with those of samples made by methods (*a*) and (*b*).

2-Chloro-5-hydroxypyrimidine gave a red colour with ferric chloride.

THE UNIVERSITY, BRISTOL.

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[15] D. Davidson and O. Baudisch, *Ber.*, 1925, **58**, 1680.
[16] R. Behrend and O. Roosen, *Annalen*, 1889, **251**, 235.