399. *Pyrimidines. Part I. The Synthesis of Some 5-Hydroxypyrimidines.*

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Certain pyrimidines, containing at least one electron-releasing group, react with persulphate to give 5-pyrimidyl hydrogen sulphates which are hydrolysed by acid to 5-hydroxypyrimidines.

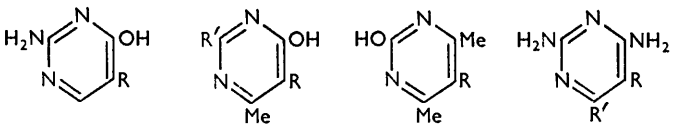
This paper describes a series of pyrimidines containing a 5-hydroxy-group,* which have been little investigated. They have generally been prepared as alkyl [1] or aryl [2] derivatives from substituted formylacetic esters and amidines, or less often by treatment of 5-bromopyrimidines with lead oxide [3] or barium hydroxide and copper bronze,[4] reduction of uric acid,[5] or treatment of a 5-nitropyrimidine with zinc and hydrochloric acid.[6]

The oxidation of monohydric phenols to dihydric compounds by persulphate discovered by Elbs [7] suggested that other compounds possessing similar activated centres might behave similarly. It is known that electron-releasing groups in the pyrimidine nucleus have a favourable effect on electrophilic substitution at $C_{(5)}$, affording workable yields in certain cases of coupling, halogenation, nitration, and nitrosation. The Elbs persulphate oxidation has now been successfully applied to a number of hydroxypyrimidines. Thus, the hydroxypyrimidines (I—IV; R = H) with alkaline ammonium persulphate gave the pyrimidyl hydrogen sulphates (I—IV; R = $O{\cdot}SO_3H$), as high-melting crystalline compounds readily soluble in sodium hydrogen carbonate solution and reprecipitated with mineral acid. Subsequent acid hydrolysis gave the corresponding 5-hydroxypyrimidines (I—IV; R = OH). These compounds gave typical phenolic reactions: a dark blue colour was obtained with ferric chloride; 2-amino-4 : 5-dihydroxy-6-methylpyrimidine (II; R = OH) gave a diacetyl and a monobenzoyl derivative; 2 : 5-dihydroxy-4 : 6-dimethylpyrimidine (IV; R = OH) gave the 5-acetoxy-derivative (IV; R = OAc).

* Patent pending.

[1] Johnson and McCollum, *J. Biol. Chem.*, 1906, **1**, 105, 437; *Amer. Chem. J.*, 1906, **36**, 136; Johnson and Heyl, *ibid.*, 1907, **38**, 247; Johnson and Jones, *ibid.*, 1908, **40**, 538.
[2] Falco, Russell, and Hitchings, *J. Amer. Chem. Soc.*, 1951, **73**, 3753.
[3] Levene and La Forge, *Ber.*, 1912, **45**, 616; Roberts and Visser, *J. Amer. Chem. Soc.*, 1952, **74**, 668.
[4] Bray, Lake, and Thorpe, *Biochem. J.*, 1951, **48**, 400.
[5] Tafel and Houseman, *Ber.*, 1907, **40**, 3743.
[6] Behrend, *Annalen*, **251**, 239.
[7] Elbs, *J. prakt. Chem.*, 1893, **48**, 179.

Experiments were made also with other 4-hydroxypyrimidines: in these cases the hydroxy-compound was not isolated, the ferric chloride colour being taken as an indication



(I) (II) $R' = NH_2$ (IV) (V)

(III) $R' = N\langle[CH_2]_5$

of reaction. Positive results were obtained in each experiment. It is of interest that with 4 : 6-dihydroxy-2-methylpyrimidine, having electron-releasing groups at positions 4 and 6, a red ferric chloride colour was obtained. Finally, persulphate reacted with pyrimidines

Reactions of some pyrimidines with ammonium persulphate with subsequent acid hydrolysis and addition of ferric chloride.

Substs.	2	NMe_2	NMe_2	NHMe	OH	NBu^n_2	$NHBu^n$	Me
	4	OH	OH	OH	OH	OH	OH	OH
	6	H	Me	Me	Me	Me	Me	OH
$FeCl_3$ colour	—	Blue	Blue	Blue	Blue	Blue	Blue	Red

containing amino- as the only electron-releasing group in the molecule: 2 : 4-diamino-6-methyl- and 2 : 4-diamino-pyrimidine (V; R = H, R′ = Me or H) gave the sulphuric esters which were hydrolysed to the hydroxy-compounds (V; R = OH, R′ = Me or H).

Experimental

2-Amino-4-hydroxy-6-methyl-5-pyrimidyl Hydrogen Sulphate.—Ammonium persulphate (34·2 g.) in water (70 ml.) was added dropwise to a stirred ice-cold solution of 2-amino-4-hydroxy-6-methylpyrimidine[8] (12·5 g.) in 3N-sodium hydroxide (220 ml.) during 1 hr. After being stirred overnight, the solution was acidified with concentrated hydrochloric acid and the product (14·5 g.) collected [m. p. 297° (decomp.)]. Recrystallisation from water gave the *sulphate* as colourless prismatic needles, m. p. 311° (decomp.) (Found: C, 27·1; H, 3·7; S, 14·0. $C_6H_7O_5N_3S$ requires C, 27·15; H, 3·2; S, 14·45%). The compound was soluble in sodium hydrogen carbonate solution, was reprecipitated with mineral acid, and gave no colour with ferric chloride.

2-Amino-4 : 5-dihydroxy-6-methylpyrimidine.—2-Amino-4-hydroxy-6-methyl-5-pyrimidyl hydrogen sulphate (76 g.) was heated under reflux in 5N-hydrochloric acid (208 ml.) during 30 min. The solution was cooled and the 5-hydroxypyrimidine hydrochloride collected, made into a slurry with sodium hydrogen carbonate solution, and refiltered. The *base* (39 g.) crystallised from water in colourless prismatic needles, m. p. >310° (Found: C, 39·8; H, 5·5; N, 28·5. $C_5H_7O_2N_3,0{\cdot}5H_2O$ requires C, 40·0; H, 5·35; N, 28·0%). The compound gave a deep blue colour with ferric chloride. Further evaporation of the filtrates from the hydrochloride gave a further 11 g. of the hydrochloride.

The 5-O-*benzoyl derivative*, crystallised from aqueous 2-ethoxyethanol, had m. p. 227—228° (Found: C, 56·8; H, 4·8; N, 17·1. $C_{12}H_{11}O_3N_3,0{\cdot}5H_2O$ requires C, 56·7; H, 4·4; N, 16·6%).

2-Acetamido-5-acetoxy-4-hydroxy-6-methylpyrimidine.—2-Amino-4 : 5-dihydroxy-6-methylpyrimidine (5 g.) and acetic anhydride (15 ml.) were heated under reflux during 1 hr. Next morning the *diacetyl derivative* (2·35 g.) was collected and washed with ethanol. Recrystallisation from ethanol gave prismatic needles, m. p. 232—233° (Found: C, 48·5; H, 5·2; N, 18·8. $C_9H_{11}O_4N_3$ requires C, 48·0; H, 4·9; N, 18·65%), which gave no colour with ferric chloride.

2-Amino-4-hydroxy-5-pyrimidyl Hydrogen Sulphate.—Prepared similarly from *iso*cytosine (11·1 g.), the crude *product* (9·95 g.) crystallised from water as pale yellow prismatic needles, m. p. >300° (Found: C, 22·8; H, 2·4; S, 15·9. $C_4H_5O_5N_3S$ requires C, 23·2; H, 2·4; S, 15·5%).

2-Amino-4 : 5-dihydropyrimidine.—Prepared from 2-amino-4-hydroxy-5-pyrimidyl hydrogen

[8] Michael, *J. prakt. Chem.*, 1894, **49**, 41.

sulphate (3·2 g.), the crude *hydrochloride* (1·8 g.), m. p. 323° (decomp.) (Found: Cl, 21·5. $C_4H_5O_2N_3$,HCl requires Cl, 21·7%), gave, after neutralisation with sodium hydrogen carbonate solution, 2-amino-4 : 5-dihydroxypyrimidine, which crystallised from water in needles, m. p. >300° (Found: C, 37·5; H, 4·2. Calc. for $C_4H_5O_2N_3$: C, 37·8; H, 3·95%). Johnson and Johns [9] give m. p. >300°.

4-Hydroxy-6-methyl-2-piperidino-5-pyrimidyl Hydrogen Sulphate.—Prepared similarly from 4-hydroxy-6-methyl-2-piperidinopyrimidine [10] (19·3 g.), the crude *product* crystallised from water in prisms (7·5 g.), m. p. 151° (Found: C, 41·0; H, 5·7; S, 10·9. $C_{10}H_{15}O_5N_3S$ requires C, 41·5; H, 5·2; S, 11·1%).

4 : 5-Dihydroxy-6-methyl-2-piperidinopyrimidine.—4-Hydroxy-6-methyl-2-piperidino-5-pyrimidyl hydrogen sulphate (47 g.) was heated under reflux in 5N-hydrochloric acid (110 ml.) under nitrogen during 30 min. 11N-Sodium hydroxide (70 ml.) was added to the cooled solution, followed by ammonia to pH 6. The crude *product* [34 g.; m. p. 289° (decomp.)] crystallised from aqueous ethanol in pale violet needles, m. p. 292° (decomp.) (Found: C, 57·6; H, 7·0; N, 19·2. $C_{10}H_{15}O_2N_3$ requires C, 57·4; H, 7·2; N, 20·1%).

2-Hydroxy-4 : 6-dimethyl-5-pyrimidyl Hydrogen Sulphate.—Prepared similarly from 2-hydroxy-4 : 6-dimethylpyrimidine hydrochloride (32 g.), the crude *product* (21 g.) crystallised from water as pale yellow needles, m. p. 264° (decomp.) (Found: C, 33·0; H, 3·9; N, 12·5; S, 14·3. $C_6H_8O_5N_2S$ requires C, 32·75; H, 3·6; N, 12·7; S, 14·55%).

2 : 5-Dihydroxy-4 : 6-dimethylpyrimidine.—The preceding sulphate (80 g.) was heated under reflux in 5N-hydrochloric acid (200 ml.) under nitrogen during 20 min. After cooling, 11N-sodium hydroxide (130 ml.) and ammonia were added to pH 4. The crude *product* crystallised from water as pale yellow needles (30 g.), m. p. >300° (Found: C, 51·4; H, 5·7; N, 19·9. $C_6H_8O_2N_2$ requires C, 51·4; H, 5·7; N, 20·0%).

This (1·5 g.) and acetic anhydride (4 ml.) were heated under reflux during 30 min. The cooled solution was poured into water and evaporated to a small volume. The *5-acetyl derivative* (2·0 g.) was collected and crystallised from dioxan as colourless prismatic needles, m. p. 216—217° (Found: C, 52·9; H, 5·9; N, 15·0. $C_8H_{10}O_3N_2$ requires C, 52·75; H, 5·5; N, 15·4%).

2 : 4-Diamino-6-methyl-5-pyrimidyl Hydrogen Sulphate.—Ammonium persulphate (102 g.) in water (150 ml.) was added dropwise during 4½ hr. to a stirred suspension of 2 : 4-diamino-6-methylpyrimidine [11] (37 g.) in 5N-sodium hydroxide (445 ml.) below 15°. The solution was stirred overnight, a small quantity of insoluble material was removed, and the filtrates were cooled to 10° and acidified with concentrated hydrochloric acid. The *pyrimidyl hydrogen sulphate* (53 g.), m. p. 281—283° (decomp.), was collected and washed with ice-water. Recrystallisation from water gave colourless prismatic needles, m. p. >300° (Found: C, 27·5; H, 3·8; S, 15·4. $C_5H_8O_4N_4S$ requires C, 27·3; H, 3·65; S, 14·6%).

2 : 4-Diamino-5-hydroxy-6-methylpyrimidine.—2 : 4-Diamino-6-methyl-5-pyrimidyl hydrogen sulphate (28 g.) was hydrolysed in the usual manner and gave the 5-hydroxypyrimidine dihydrochloride (19·5 g.), m. p. 278° (decomp.), on cooling. The *monohydrochloride*, obtained by the addition of sodium hydrogen carbonate to a solution of the dihydrochloride to about pH 4, crystallised from water as needles, m. p. >300° (Found: C, 32·6; H, 5·6; N, 29·4. $C_5H_8ON_4$,HCl,0·5H_2O requires C, 32·3; H, 5·4; N, 30·2%). The *picrate* crystallised from aqueous alcohol as yellow prisms, m. p. >300° (Found: C, 36·1; H, 2·7; N, 26·2. $C_5H_8ON_4$,$C_6H_3O_7N_3$ requires C, 35·8; H, 3·0; N, 26·55%).

2 : 4-Diamino-5-pyrimidyl Hydrogen Sulphate.—Prepared similarly from 2 : 4-diaminopyrimidine sulphate [12] (8·65 g.), the crude *product* (6·3 g.) crystallised from water in pale yellow needles, m. p. 276° (decomp.) (Found: C, 23·1; H, 3·1; S, 14·4. $C_4H_6O_4N_4S$ requires C, 23·3; H, 2·9; S, 15·5%).

2 : 4-Diamino-5-hydroxypyrimidine.—Prepared in the usual manner from 2 : 4-diamino-5-pyrimidyl hydrogen sulphate (1·7 g.), the crude *2 : 4-diamino-5-hydroxypyrimidine hydrochloride* (0·85 g.) crystallised from aqueous ethanol in prismatic needles, m. p. >300° (Found: C, 29·6; H, 4·0; N, 34·6; Cl, 21·0. $C_4H_6ON_4$,HCl requires C, 29·55; H, 3·7; N, 34·45; Cl, 20·8%). The *picrate* crystallised from aqueous ethanol in yellow needles, m. p. 250° (decomp.) (Found: C, 33·8; H, 2·7; N, 27·9. $C_4H_6ON_4$,$C_6H_3O_7N_3$ requires C, 33·8; H, 2·5; N, 27·6).

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[10] Hull, Lovell, Openshaw, Payman, and Todd, *J.*, 1946, 361.
[11] Gabriel and Colman, *Ber.*, 1901, **34**, 1253.
[12] U.S.P. 2,416,617.