1070. *Pyrimidines. Part XII.*[1] *Syntheses of 4-Amino-5-hydroxy- and 4,5-Dihydroxy-pyrimidine.*

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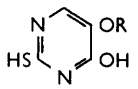
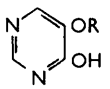
4-Amino-5-hydroxypyrimidine has been prepared from the corresponding 5-benzyloxy-4-hydroxy-2-mercapto-compound in five stages. 4,5-Dihydroxypyrimidine has been obtained by acid hydrolysis of nine disubstituted pyrimidines and by the action of Raney nickel on 5-benzyloxy-4-hydroxy-2-mercaptopyrimidine.

In continuation of our studies [1] of derivatives of 5-hydroxy-pyrimidine we have prepared 4-amino-5-hydroxy- and 4,5-dihydroxy-pyrimidine. The former is the fifth known isomer of the seven possible monoaminomonohydroxypyrimidines.[2]

[1] Part XI, Chesterfield, McOmie, and Tute, *J.*, 1960, 4590.
[2] Boarland and McOmie, *J.*, 1952, 4942.

The desulphurisation[1] of 5-benzyloxy-4-hydroxy-2-mercaptopyrimidine (I; R = CH_2Ph) by Raney nickel has been studied further. When the reaction is carried out in 0·2N-sodium hydroxide, the product is 5-benzyloxy-4-hydroxypyrimidine (II; R = CH_2Ph). In neutral or in very weakly alkaline solution the product is mainly 4,5-dihydroxypyrimidine (II; R = H) (see Experimental section), but if the Raney nickel has low reactivity then 5-benzyloxy-4-hydroxypyrimidine is the main product.[1] The conversion of 5-benzyloxy-4-hydroxypyrimidine into the corresponding chloropyrimidine proceeded satisfactorily only if the pure hydroxy-compound was used. 5-Benzyloxy-4-chloropyrimidine reacted readily with hydrazine, to give the corresponding hydrazinopyrimidine (III; R = CH_2Ph) which, on treatment with Raney nickel, gave 4-amino-5-benzyloxypyrimidine (IV; R = CH_2Ph). The benzyl group was removed from the latter by catalytic reduction, thereby giving 4-amino-5-hydroxypyrimidine (IV; R = H). This compound was converted into its *N*-acetyl and *N*-benzoyl derivatives, but neither of these could be cyclised with phosphoryl chloride to give oxazolopyrimidines. This is in contrast to the ready conversion of 5-benzamido-4-hydroxypyrimidine and its derivatives into oxazolopyrimidines.[2,3]


(I)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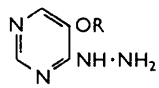
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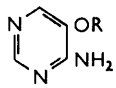
(IV)

A similar series of reactions was carried out starting from 4-hydroxy-2-mercapto-5-methoxypyrimidine (I; R = Me). This was first converted into 4-hydroxy-5-methoxy-2-methylthiopyrimidine and thence, through the 4-chloro-compound, into 4-hydrazino-5-methoxy-2-methylthiopyrimidine which, on treatment with Raney nickel, gave 4-amino-5-methoxypyrimidine (IV; R = Me). This amine was also obtained by the action of Raney nickel on 4-hydrazino-5-methoxypyrimidine (III; R = Me). Attempts to convert 4-amino-5-methoxypyrimidine into the corresponding 5-hydroxy-compound were unsuccessful since hydrolysis of the amino-group occurred simultaneously and the product was 4,5-dihydroxypyrimidine (II; R = H). This compound was first prepared by Dr. E. A. Falco,[4] who had kindly sent us details of its preparation by the acid hydrolysis of 5-benzamido-4-hydroxypyrimidine. We confirmed this observation (see Experimental section) and since then we have obtained 4,5-dihydroxypyrimidine by the acid hydrolysis of eight other compounds, namely, 4,5-diamino-, 5-amino-4-hydroxy-, 4-amino-, 4-benzamido-, and 4-hydroxy-5-benzyloxy-pyrimidine, also 4-amino-, 4-hydroxy-, and 4-mercapto-5-methoxypyrimidine. As noted above, we have also obtained it by the action of Raney nickel on 5-benzyloxy-4-hydroxy-2-mercaptopyrimidine in certain conditions. After the completion of this work, Chang and Chiang[5] described the preparation of 4,5-dihydroxypyrimidine by catalytic hydrogenolysis of 5-benzyloxy-4-hydroxypyrimidine. For preparative purposes we recommend the hydrolysis of 4-hydroxy-5-methoxypyrimidine.

Both 4-amino-5-hydroxy- and 4,5-dihydroxy-pyrimidine show phenolic properties. The former gives a deep red and the latter a deep reddish-purple with ferric chloride. The two compounds readily couple with diazotised *p*-nitroaniline. The structure of the resulting azopyrimidines will be discussed in Part XIII.

Experimental

Paper Chromatography.—The purity and identity of the pyrimidines described were studied by downward chromatography. The solvent consisted of the upper layer of a mixture of acetic acid, water, and ethyl acetate (1 : 2 : 3 v/v). The spots were detected by spraying the chromatograms with ferric chloride solution or with a modified Dragendorff's reagent.[6]

[3] Falco, Elion, Burgi, and Hitchings, *J. Amer. Chem. Soc.*, 1952, **74**, 4897.
[4] Dr. E. A. Falco, personal communication, June 18th, 1953.
[5] P. Chang and Kwei-che Chiang, *Sci. Sinica*, 1957, **6**, 293 (*Chem. Abs.*, 1958, **52**, 2023).
[6] Jentzsch, *Scientia Pharm.*, 1952, **20**, 216 (*Chem. Abs.*, 1953, **47**, 4552).

5-Benzyloxy-4-chloropyrimidine.—5-Benzyloxy-4-hydroxy-2-mercaptopyrimidine [1] (5 g.) and water-wet Raney nickel sludge [7] (15 g.) in 0·2N-sodium hydroxide (100 ml.) were boiled under reflux for 2 hr. with stirring. The hot solution was filtered and the filtrate and washings were neutralised with hydrochloric acid. 5-Benzyloxy-4-hydroxypyrimidine separated on cooling. A second crop was obtained on acidifying the solution to pH 4 and concentrating it to half its volume. The second crop was recrystallised from hot water. The total yield of the monohydrated pyrimidine was 2·8 g. (59%), m. p. 90—93°.

This pyrimidine (6 g.) and phosphoryl chloride (35 ml.) were boiled under reflux for 20 min., then the excess of reagent (*ca.* 15 ml.) was removed by distillation. The residue was added to ice (1 kg.), and the chloropyrimidine (5 g., 83%) was collected in ether. It was used directly for the next reaction.

4-Amino-5-benzyloxypyrimidine.—A solution of the above chloropyrimidine (5 g.) and 100% hydrazine hydrate (10 ml.) in ethanol (50 ml.) was warmed to 70° for a few minutes. The product, which separated on cooling, was collected and recrystallised from benzene, giving 5-benzyloxy-4-hydrazinopyrimidine (4·4 g., 86%) as needles, m. p. 122—123°. The hydrazine (5 g.) in ethanol (150 ml.) was stirred at the b. p. for 4 hr. with well-washed Raney nickel (20 g. of ethanol-wet sludge; the presence of alkali in the nickel lowered the yield of product). The hot mixture was filtered and the filtrate and washings were evaporated to dryness under reduced pressure. The residue was recrystallised from benzene, giving *4-amino-5-benzyloxypyrimidine* (3·3 g., 71%) as needles, m. p. 142—143° (Found: C, 65·6; H, 5·4; N, 20·5. $C_{11}H_{11}N_3O$ requires C, 65·7; H, 5·5; N, 20·9%).

The aminopyrimidine (0·5 g.) and benzoyl chloride (0·42 g.) in pyridine (5 ml.) were kept at 60° for 2 hr., affording *4-benzamido-5-benzyloxypyrimidine* (0·6 g., 80%), m. p. 176—178° (from ethanol) (Found: C, 70·8; H, 5·3. $C_{18}H_{15}N_3O_2$ requires C, 70·8; H, 4·95%).

4-Amino-5-hydroxypyrimidine.—The above pyrimidine (0·5 g.) in ethanol (25 ml.) was shaken with hydrogen in presence of 10% palladium–charcoal (0·2 g.). Uptake of hydrogen ceased after 6 hr. The solution was filtered and evaporated to dryness. The residue was sublimed, giving the *hydroxypyrimidine* (0·2 g., 72%), m. p. >250° (Found: C, 43·4; H, 5·0; N, 37·4. $C_4H_5N_3O$ requires C, 43·2; H, 4·5; N, 37·8%). The compound gave a deep red colour with aqueous ferric chloride and with diazotised *p*-nitroaniline gave a red dye. When the compound was boiled with acetic anhydride for 30 min. it gave *4-acetamido-5-hydroxypyrimidine*, m. p. 179—180° (from benzene) (Found: C, 47·4; H, 4·7. $C_6H_7N_3O_2$ requires C, 47·1; H, 4·6%). The compound gave a red-brown colour with ferric chloride and is, therefore, the *N*- rather than the *O*-acetyl derivative.

Benzoylation of 4-Amino-5-hydroxypyrimidine.—A mixture of the pyrimidine (0·3 g.), pyridine (20 ml.), and benzoyl chloride (0·42 g.) was kept at 70° for 1 hr. After removal of the excess of pyridine, the mixture was poured into water (25 ml.), and the precipitate was recrystallised from ethanol, giving *4-benzamido-5-benzoyloxypyrimidine* (0·2 g., 23%), m. p. 188—191°, raised to 194—195° by two more recrystallisations (Found: C, 67·3; H, 4·2; N, 13·5. $C_{18}H_{13}N_3O_3$ requires C, 67·7; H, 4·1; N, 13·2%). It gave no colour with ferric chloride. Concentration of the pyridine–water filtrate gave *4-benzamido-5-hydroxypyrimidine* (0·17 g., 31%), m. p. 156—158°, raised to 159—160° by recrystallisation from benzene (Found: C, 60·8; H, 4·2; N, 19·8. $C_{11}H_9N_3O_2$ requires C, 61·4; H, 4·2; N, 19·5%). The compound gave a weak red-brown colour with ferric chloride.

4-Hydroxy-5-methoxy-2-methylthiopyrimidine.—4-Hydroxy-2-mercapto-5-methoxy-pyrimidine [1] (4 g.) and sodium hydroxide (1·75 g.) in water (150 ml.) were stirred with methyl sulphate (3·2 g.) for 1 hr. After being filtered, the solution was acidified with hydrochloric acid, and the precipitated 2-methylthiopyrimidine (3·1 g., 75%) was collected. A sample, recrystallised from ethanol, had m. p. 191—192° (lit.,[8] 197—198°) (Found: C, 41·5; H, 5·0. Calc. for $C_6H_8N_2O_2S$: C, 41·8; H, 4·7%).

4-Hydrazino-5-methoxy-2-methylthiopyrimidine.—The above pyrimidine (3·5 g.) and phosphoryl chloride (20 ml.) were boiled under reflux for 1½ hr. and the 4-chloro-5-methoxy-2-methylthiopyrimidine (2·6 g., 67%) was isolated in the usual way. A sublimed sample had m. p. 72—73° (lit.,[8] 81—82°) (Found: C, 38·1; H, 3·9; N, 14·5. Calc. for $C_6H_7ClN_2OS$: C, 37·8; H, 3·7; N, 14·7%).

[7] Brown, *J. Soc. Chem. Ind.*, 1950, **69**, 353.

[8] Budesinsky, Bydzovsky, Kopecky, Svab, and Vavrina, *Cesk. Farm.*, 1961, **10**, 241 (*Chem. Abs.*, 1961, **55**, 25,974).

A mixture of the crude chloropyrimidine (1·9 g.) and 100% hydrazine hydrate (2 ml.) in ethanol (10 ml.) was boiled for a few minutes. The product, which separated on cooling, was recrystallised from ethanol, giving the *hydrazinopyrimidine* (1·6 g., 85%) as needles, m. p. 114° (Found: N, 30·0. $C_6H_{10}N_4OS$ requires N, 30·1%).

4-Amino-5-methoxypyrimidine.—(*a*) Raney nickel (10 g.) was saturated with hydrogen at atmospheric pressure (*ca.* 60 ml. was absorbed) and was added to the above hydrazinopyrimidine (1·86 g.) in ethanol (75 ml.). The mixture was boiled under reflux for 3 hr. with stirring. After being filtered, the hot solution and washings were evaporated to dryness under reduced pressure. Extraction of the residue with benzene gave *4-amino-5-methoxypyrimidine* (0·5 g., 40%) as needles, which after sublimation had m. p. 118° (Found: C, 47·9; H, 5·9; N, 33·7. $C_5H_7N_3O$ requires C, 48·0; H, 5·6; N, 33·6%).

(*b*) A mixture of 4-hydrazino-5-methoxypyrimidine [1] (2·8 g.) and Raney nickel (10 g.) in ethanol (50 ml.) was stirred for 3 hr. at the b. p. The product (1·8 g., 72%), m. p. 118°, was isolated as in (*a*).

4,5-Dihydroxypyrimidine.—(*a*) (Method of Dr. E. A. Falco [4]). 5-Benzamido-4-hydroxypyrimidine [2,3] (0·37 g.) was boiled for 4 hr. with 6N-hydrochloric acid. The solution was evaporated to dryness and extracted with hot ethanol to remove benzoic acid. The insoluble portion was then recrystallised from hot water, giving 4,5-dihydroxypyrimidine as needles, which blackened at about 260° and melted at about 300° [lit.,[5] 268—269° (decomp.)] (Found: 43·0; H, 3·4; N, 25·0. Calc. for $C_4H_4N_2O_2$: C, 42·9; H, 3·6; N, 25·0%).

(*b*) (With Dr. M. P. V. Boarland). Hydrolysis of 5-amino-4-hydroxy- [2] and 4,5-diamino-pyrimidine [9] with 6N-hydrochloric acid as above gave 4,5-dihydroxypyrimidine in 75% and 95% yield, respectively.

(*c*) (With Dr. J. H. Chesterfield). Hydrolysis of 5-benzyloxy-4-hydroxypyrimidine with 6N-hydrochloric acid for 20 min. gave the dihydroxypyrimidine in 68% yield.

(*d*) When 4-amino-5-benzyloxy- and 4-benzamido-5-benzyloxy-pyrimidine had been boiled with 3N-hydrochloric acid for 60 and 30 min., respectively, the products were shown by chromatography to be a mixture of starting material and 4,5-dihydroxypyrimidine.

(*e*) (With Dr. J. H. Chesterfield). 4-Hydroxy-5-methoxypyrimidine [1] (1·3 g.) was boiled with 48% hydrobromic acid (3·5 ml.) for 2 hr. The solid which separated on cooling recrystallised from 48% hydrobromic acid, giving *4,5-dihydroxypyrimidine hydrobromide* (1·6 g., 73%) as needles, m. p. >270° (decomp.) (Found: C, 25·0; H, 2·5; N, 14·5. $C_4H_4N_2O_2$,HBr requires C, 24·9; H, 2·6; N, 14·5%). A solution of this salt (0·8 g.) in water (10 ml.) was neutralised with sodium hydrogen carbonate, and the precipitated *4,5-dihydroxypyrimidine hydrate* (0·45 g.) was collected and dried at room temperature (Found: C, 36·7; H, 4·6. $C_4H_4N_2O_2$,H_2O requires C, 36·9; H, 4·6%). The anhydrous pyrimidine was obtained by sublimation at 210°/25 mm. Similar hydrolysis of 4-mercapto-5-methoxypyrimidine [1] gave a low yield of the dihydroxy-compound.

(*f*) 4-Amino-5-methoxypyrimidine, when boiled with hydrobromic acid, similarly gave the dihydroxy-compound in 80% yield.

(*g*) (With Dr. E. R. Sayer). When an aqueous solution of 5-benzyloxy-4-hydroxy-2-mercaptopyrimidine [1] was boiled for 1 hr. with an equal weight of freshly prepared Raney nickel it yielded 4,5-dihydroxypyrimidine.

In all the hydrolyses above, 4,5-dihydroxypyrimidine is first obtained as the hydrochloride or hydrobromide which, on recrystallisation from water (preferably after neutralisation of the solution), gives the free base as the monohydrate.

4,5-Dihydroxypyrimidine gives a deep reddish-purple colour with ferric chloride, which becomes deep red on addition of a little ammonia; an excess of ammonia gives a brown colour, as recorded by Chang and Chiang.[5] This pyrimidine couples with diazotised *p*-nitroaniline to give a deep red colour.

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[9] Albert, Brown, and Cheeseman, *J.*, 1951, 482.