THE SYNTHESIS OF 4,6-DIHYDROXY-2-METHOXYPYRIMIDINE AND DERIVED PYRIMIDINE INTERMEDIATES*

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4,6-Dihydroxy-2-methoxypyrimidine is a particularly useful intermediate for the synthesis of pyrimidines variously substituted in the 2-, 4-, and 6- positions, and purines with a variety of substituents in the 2- and 6- positions. A wide range of such compounds may be synthesized via the 4,6-dichloro- and 4,6-dichloro-5-nitro derivatives of 2-methoxypyrimidine. It is the purpose of this communication to report an improved synthesis of 4,6-dihydroxy-2-methoxypyrimidine, and its conversion to the abovementioned derivatives. The symmetry of these latter compounds is advantageous, as it reduces the need for separations which sometimes occur in similar pyrimidine syntheses.[1]

In their syntheses of 2-substituted ethers of barbituric acid, Basterfield and Powell[2] obtained poor overall yields due to the difficulty[3] of converting calcium cyanamide to *O*-alkylurea hydrochlorides.[4] We overcame this difficulty by preparing *O*-methylurea methosulphate by the method of Werner[5] (or as modified by Brown and Hoeger[6] for large-scale synthesis) and converting this directly to 4,6-dihydroxy-2-methoxypyrimidine. Three equivalents of sodium methoxide were necessary to effect the condensation (the methosulphate requires two for neutralization), much barbituric acid being formed when only two equivalents were used. In the nitration reaction, we found it advantageous to use freshly distilled anhydrous nitric acid, as smaller yields of less pure product were obtained when fuming nitric acid of uncertain composition was used.

Experimental

Melting points are corrected; analyses were performed by the Australian Microanalytical Service, Melbourne.

4,6-Dihydroxy-2-methoxypyrimidine

Urea (24 g) was converted into *O*-methylurea methosulphate by the method of Werner.[5] The reaction was carried out in four tubes with a slight modification of Werner's method.[5] It was found convenient to rapidly heat the tube contents to 105° and allow the exothermic reaction to proceed rapidly to between 150–160° before each tube was immersed in ice water. The temperature invariably rose to 170° and rapidly fell again. Cooling was stopped as the temperature fell below 140°. In this way the four tubes were treated in less than 15 min. Sodium (27·6 g) was converted to methoxide by reaction with anhydrous methanol (400 ml) and the methoxide solution was treated successively while still hot with diethyl malonate (64 g) and the four tubes

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[1] Winkelmann, W., *J. prakt. Chem.*, 1927, **115**, 292.

[2] Basterfield, S., and Powell, E. C., *Canad. J. Res.*, 1929, **1**, 261.

[3] Kurzer, F., and Lawson, A., *Org. Synth.*, 1954, **34**, 67.

[4] McKee, R. H., *J. Amer. Chem. Soc.*, 1901, **26**, 209.

[5] Werner, E. A., *J. Chem. Soc.*, 1914, **105**, 927.

[6] Brown, D. J., and Hoeger, E., *J. Appl. Chem.*, 1954, **4**, 283.

of *O*-methylurea methosulphate. Residues in these containers were washed into the reaction mixture with methanol (200 ml). The mixture was refluxed for 4 hr and stirred by a nitrogen bubbler to prevent bumping. It was filtered while still very hot, and the precipitate further extracted by boiling with two further quantities (300 ml and 100 ml) of methanol. The combined methanol solutions were evaporated on a rotary evaporator and the methanol replaced by water (300 ml). The aqueous solution was acidified to pH 3 (conc. HCl) and gave an immediate precipitate. Filtration after standing at 0° overnight yielded the required product (29 g). The mother liquor was reduced to approximately half volume to give another crop of crystals (9·0 g). Recrystallization from water (Basterfield[2] used ethanol) yielded white needles which melted on rapid heating (10° rise per minute) at 193–195°. Basterfield and Powell[2] reported a yellowing at 190°. Titration with 0·1N sodium hydroxide solution gave a curve having characteristic inflexions at pH 3·0 and 8·0. The ultraviolet spectrum had $\lambda_{max.}$ 257 mμ ($\epsilon_{max.}$ 8130), $\lambda_{max.}$ 225 mμ ($\epsilon_{max.}$ 2540), and $\lambda_{max.}$ 317 mμ ($\epsilon_{max.}$ 94) in ethanol; $\lambda_{max.}$ 254·5 mμ ($\epsilon_{max.}$ 11750) and $\lambda_{max.}$ 315 mμ ($\epsilon_{max.}$ 60) in borax buffer (pH 9·1); and $\lambda_{max.}$ 251 mμ ($\epsilon_{max.}$ 8320) in sulphuric acid (50% H_2SO_4 by weight).

The infrared spectrum had peaks at 690, 713, 758, 800, 900, 940, 984, 1030, 1105, 1210, 1265, 1330, 1370, 1455, 1600–1630 (broad twin), 2300–3300 (broad H-bonding) and 3500 cm^{-1} in Nujol mull (Found: C, 42·4; H, 4·3; N, 19·7; OCH_3, 21·9%. Calc. for $C_5H_6N_2O_3$: C, 42·25; H, 4·2; N, 19·7; OCH_3, 21·8%).

*4,6-Dichloro-2-methoxypyrimidine**

A mixture of redistilled phosphorus oxychloride (16 ml) and redistilled dimethylaniline (4·0 ml) was added dropwise to 4,6-dihydroxy-2-methoxypyrimidine (2·6 g). After the initial reaction had subsided, the mixture was refluxed for 1½ hr, cooled, and poured onto ice. The product was extracted by ether and the ether washed with bicarbonate solution. On evaporation of the ether, the product was extracted from the residue with boiling light petroleum (b.p. 40–70°) and finally sublimed several times at the pressure of the water pump and 60–70°. The pure 4,6-dichloro-2-methoxypyrimidine (yield 75%) was colourless and had m.p. 59–60°. Purification could also be effected by distillation (b.p. 130–132°/75 mm) or recrystallization from aqueous alcohol (Found: C, 33·9; H, 2·3; Cl, 39·8%. Calc. for $C_5H_4Cl_2N_2O$: C, 33·5; H, 2·2; Cl, 39·7%).

4,6-Dihydroxy-2-methoxy-5-nitropyrimidine

Freshly distilled anhydrous nitric acid (20 ml) was cooled in ice and 4,6-dihydroxy-2-methoxypyrimidine (10 g) was added over half an hour with stirring. Stirring was continued for 1½ hr, during which time the temperature increased to 20°. A granular crystalline precipitate (*c.* 5 g) separated as the reaction proceeded. This precipitate was probably a nitric acid salt of the required product, as it decomposed in water to give the free base in a purer form than that obtained by dilution of the reaction mixture. The reaction mixture was diluted with water (200 ml), cooled, and filtered. The combined product (8·5 g) was recrystallized from ethyl acetate (water or ethanol were not as satisfactory) to give white needles of *4,6-dihydroxy-2-methoxy-5-nitropyrimidine* which melted with decomposition on rapid heating at 185° (Found: C, 31·8; H, 3·1; N, 22·2; OCH_3, 16·3%. Calc. for $C_5H_5N_3O_5$: C, 32·1; H, 2·8; N, 22·5; OCH_3, 16·6%).

4,6-Dichloro-2-methoxy-5-nitropyrimidine

A mixture of redistilled phosphorus oxychloride (23·0 ml) and redistilled dimethylaniline (5·75 ml) was added dropwise to 4,6-dihydroxy-2-methoxy-5-nitropyrimidine (5·0 g), care being taken during the initial vigorous reaction. After all the reagent was added, the reaction mixture was refluxed for a further 2 hr, then poured onto ice (after cooling) and the whole rapidly extracted with ether several times. The product obtained on evaporation of the ethereal extract recrystallized from light petroleum (b.p. 40–70°) to give *4,6-dichloro-2-methoxy-5-nitropyrimidine* as pale yellow leaflets, m.p. 73–75° (Found: C, 27·1; H, 1·7; Cl, 31·3%. Calc. for $C_5H_3Cl_2N_3O_3$: C, 26·8; H, 1·3; Cl, 31·7%).

* Bretschneider *et al.*[7] list this compound together with many others for which no analytical figures or physical constants are recorded.

[7] Bretschneider, H., *et al.*, *Mh. Chem.*, 1961, **92**, 75.