152. *Experiments on the Synthesis of Purine Nucleosides. Part IV. 4 : 6-Diaminopyrimidine. A New Synthesis of Pyrimidine Derivatives.*

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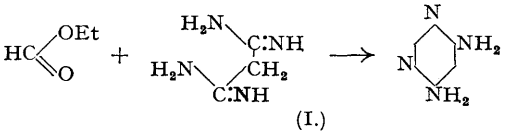
The preparation of 4 : 6-diaminopyrimidine, required as starting material for nucleoside synthesis, by the method of Büttner (*Ber.*, 1903, **36**, 2227), by amination of 4 : 6-*dichloropyrimidine* or from 4 : 6-diamino-2-thiolpyrimidine, is unsatisfactory. A convenient method has been found in the condensation of malondiamidine with ethyl formate. This route, also applied to the preparation of 4 : 6-diamino-2-methylpyrimidine, represents a new method of synthesising the pyrimidine nucleus.

In applying the experience of model experiments described in previous papers of this series (this vol., pp. 383, 386, preceding paper) to the synthesis of adenine-9-glycosides (*e.g.*, adenosine), the obvious starting material is 4 : 6-diaminopyrimidine. The alternative of starting with a 2-substituted 4 : 6-diaminopyrimidine and replacing the 2-substituent in the final nucleoside by hydrogen is complicated by the instability of the nucleosides under acid conditions. Although this alternative has not been neglected in our investigations, the route starting from 4 : 6-diaminopyrimidine seemed the more attractive for initial study.

4 : 6-Diaminopyrimidine has been described by Büttner (*Ber.*, 1903, **36**, 2227), who prepared it by an involved series of reactions from barbituric acid; the analytical data were rather unsatisfactory and the yield was recorded as " very small." We repeated Büttner's work with slight modifications in detail and confirmed the production of 4 : 6-diaminopyrimidine, but the overall yield was so low as to make the method useless for preparative purposes, and alternative methods were sought. An attempt to synthesise the substance directly by condensing formamidine with malononitrile led instead to 4-amino-5-cyanopyrimidine (Part II; Baddiley, Lythgoe, and Todd, this vol., p. 386), and replacement of the halogen atoms in 4 : 6-*dichloropyrimidine* by amino-groups required such drastic treatment with ammonia under pressure that the pyrimidine nucleus was largely destroyed in the process. The replacement of a 2-thiol group by hydrogen can frequently be accomplished in the pyrimidine series by the action of hydrogen peroxide in strong acid solution, but under these conditions 4 : 6-diamino-2-thiolpyrimidine was completely destroyed. Hydrogen peroxide in presence of acetic acid and sodium acetate did produce 4 : 6-diaminopyrimidine from the corresponding 2-thiol compound, but again the yield was extremely low.

The comparative failure of these experiments led us to examine the possibility of direct synthesis by new methods. It is known that diamino-1 : 3 : 5-triazines may be synthesised by the condensation of biguanide with esters (Rackmann, *Annalen*, 1910, **376**, 180). By analogy it seemed possible that ethyl formate might condense with malondiamidine (I) to give 4 : 6-diaminopyrimidine as indicated below :



(I.)

This proved to be the case. The hitherto undescribed malondiamidine (conveniently isolated as its *dihydrochloride*), prepared from malononitrile *via malondi-iminoether*, reacted readily with ethyl formate, giving 4 : 6-diaminopyrimidine in moderately good yield. In the same way ethyl acetate and malondiamidine yielded 4 : 6-diamino-2-methylpyrimidine. Apart from making 4 : 6-diaminopyrimidine readily accessible, this route is attractive as a potential general method for the synthesis of 2-substituted 4 : 6-diaminopyrimidines, and an investigation of it from this standpoint will be reported in due course.

Experimental.

4 : 6-*Dichloropyrimidine*.—4 : 6-Dihydroxypyrimidine (22 g.) (Kenner, Lythgoe, Todd, and Topham, this vol., p. 389) was refluxed with phosphoryl chloride (300 g.) and dimethylaniline (12 c.c.) until hydrogen chloride evolution ceased (*ca.* 3 hours). Unchanged phosphoryl chloride was removed in a vacuum, the residue poured on ice and extracted with ether, and the extract washed with sodium carbonate solution, dried, and evaporated. The *product* (15 g.) could be further purified by distillation (b. p. 176°) or by recrystallisation from light petroleum; it then had m. p. 67·5° (Found : C, 31·7; H, 1·5; Cl, 47·7. $C_4H_2N_2Cl_2$ requires C, 32·2; H, 1·4; Cl, 47·7%).

4 : 6-*Diaminopyrimidine from* 4 : 6-*Dichloropyrimidine*.—The above dichloro-compound (30 g.) was heated in an autoclave with alcoholic ammonia (750 c.c., saturated at 0°) at 170° during 8 hours. After evaporation the resulting mixture was extracted with *n*-butanol, and the extract agitated with two successive portions (250 g.) of aluminium oxide (activated by heating to 360°) and finally evaporated. The residue (11 g.), recrystallised from alcohol, gave yellowish crystals (3 g.), m. p. 260°; this material, after sublimation in a vacuum and a further recrystallisation from ethyl acetate–alcohol, gave colourless needles of 4 : 6-diaminopyrimidine, m. p. 267°, undepressed in admixture with material obtained by other methods described below (Found : C, 43·9; H, 5·5; N, 50·2. Calc. for $C_4H_6N_4$: C, 43·7; H, 5·5; N, 50·9%). The amination of the dichloro-compound was attempted under a variety of conditions both alcoholic ammonia and liquid ammonia being used, but no better results were obtained. When the temperature was raised above 200°, the sole product isolated was a liquid, b. p. 200°, apparently formoethylamide.

4 : 6-*Diaminopyrimidine from* 4 : 6-*Diamino-2-thiolpyrimidine*.—To sodium acetate (9·5 g.), dissolved in water (40 c.c.), a solution of 4 : 6-diamino-2-thiolpyrimidine (5 g.) in hot acetic acid (80 c.c.) was added. After cooling to 30°, hydrogen peroxide (17 c.c. of 100 vol., diluted to 40 c.c. with water) was added; the temperature rose slowly and was prevented by external cooling from exceeding 50°. After 1 hour the slightly turbid solution was evaporated in a vacuum, the residue taken up in water, and excess of aqueous picric acid added. The *picrate* was collected, dissolved in hot dilute sulphuric acid, and the solution cooled and extracted with nitrobenzene and then ether. The aqueous layer was neutralised with barium carbonate, filtered, and evaporated to dryness in a vacuum. Sublimation of the residue at 160°/10^{-2} mm. gave a small amount of 4 : 6-diaminopyrimidine in colourless needles, m. p. 269—271° (Found : C, 43·4; H, 5·4; N, 50·3%). A similar experiment, lead acetate being used in place of sodium acetate, failed to yield any of the desired product.

4 : 6-*Diaminopyrimidine from* 6-*Iodo*-4-*aminopyrimidine* (cf. Büttner, *loc. cit.*).—6-Iodo-4-aminopyrimidine (1·3 g.) was heated with alcoholic ammonia (1 g. of ammonia in 8 c.c. of alcohol) in a sealed tube at 180—200° during 2 hours; after cooling, the filtered solution was evaporated. The residual oil set on scratching to a pasty mass, which was extracted with ethyl acetate. A considerable proportion went into solution, but no product of definite m. p. could be obtained from the extract. The unextracted material could not be purified by recrystallisation, but sublimation in a vacuum at 160° gave colourless needles (0·22 g.), m. p. 268°, undepressed in admixture with 4 : 6-diaminopyrimidine prepared from 4 : 6-diamino-2-thiolpyrimidine.

Malondi-iminoether Dihydrochloride.—A rapid stream of dry hydrogen chloride was passed into a well-cooled and stirred solution of malononitrile (7·9 g.) in absolute alcohol (13·9 c.c.) and dry ether (150 c.c.) until saturated. Stirring was continued for 2 hours, by which time separation of the *iminoether dihydrochloride* was complete; it was collected (27 g.), washed thoroughly with dry ether, and dried in a desiccator over potassium hydroxide (Found by Volhard titration : *M*, 236. $C_7H_{14}O_2N_2$,2HCl has *M*, 231). This preparation can be conveniently carried out on 200 g. portions of malononitrile, the yield being nearly theoretical. A similar method for preparing this compound is given in Houben–Weyl, " Die Methoden der Organischen Chemie," 2nd Edn., IV, 312, reference being made to a private communication from Houben and Blaise. No analysis of the substance is given, nor have we found any other mention of it in the literature.

Malondiamidine Dihydrochloride.—The above iminoether dihydrochloride (25 g.) was added to cold alcoholic ammonia (100 c.c. of alcohol saturated at 0° and diluted with 100 c.c. of alcohol), and the mixture kept for 2 days. The *malondiamidine dihydrochloride* which separated (11 g.) was collected, washed with ether, and dried (Found by Volhard titration : *M*, 172. $C_3H_8N_4$,2HCl has *M*, 172). A further amount of the same substance could be obtained by concentrating the mother-liquors. By treatment of an absolute alcoholic solution of the dihydrochloride with 2 equivs. of sodium ethoxide, filtration and evaporation, malondiamidine was obtained as a deliquescent crystalline mass. For the preparation of large quantities of the dihydrochloride, 650 g. of the iminoether dihydrochloride, kept for 2 days with 3 l. of alcoholic ammonia (saturated at 0°), gave in a yield of 80% a product sufficiently pure (90%) for most purposes.

4 : 6-*Diaminopyrimidine*.—An ice-cold solution of sodium (38 g.) in dry methanol (500 c.c.) was added to malondiamidine dihydrochloride (140 g.), precipitated sodium chloride removed, and the solution evaporated at 30° in a vacuum. After the residual amidine had been washed with dry benzene (150 c.c.) by decantation, ethyl formate (500 c.c.) was added. After the initial violent reaction subsided, the mixture was refluxed for several hours and then evaporated. The crude product (88 g.) was not readily purified by simple recrystallisation, and sublimation, effective on a small scale, was inconvenient; after various trials the following procedure was adopted. The crude material (1 part), dissolved in alcohol, was allowed to flow through a column of aluminium oxide (20 parts, activated by heating to 360°), the column being well washed with alcohol; the combined filtrate and washings were evaporated, and the residue recrystallised from alcohol, giving colourless needles (39 g.), m. p. 267—268°, undepressed in admixture with 4 : 6-diaminopyrimidine prepared by other routes (Found : N, 51·2. Calc. for $C_4H_6N_4$: N, 50·9%). The substitution of ethyl orthoformate for ethyl formate in the above reaction gave much lower yields, and formamidine or a mixture of formic acid and sodium formate, heated with malondiamidine, gave at most only traces of the desired product.

4 : 6-*Diamino*-2-*methylpyrimidine*.—In the course of some other experiments ethyl acetate (500 c.c.) was added to malondiamidine (from 250 g. of crude dihydrochloride). There was immediate reaction, and the solid which separated was collected and extracted (Soxhlet) with alcohol. The extract on concentration yielded 4 : 6-diamino-2-methylpyrimidine; recrystallised from water, it had m. p. 296—297°, undepressed in admixture with an authentic specimen, m. p. 295° (Part I; Baddiley, Lythgoe, McNeil, and Todd, this vol., p. 383). The total yield (*ca.* 13 g.) was low, but subsequent experiments, carried out by the procedure used above in the analogous case of 4 : 6-diaminopyrimidine, have shown that yields of 40% are readily obtainable.

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