

128. *Experiments on the Synthesis of Purine Nucleosides. Part VII. Some Further Observations on the Synthesis of Pyrimidines from Esters and Malondiamidine.*

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Some experiments have been made to examine the scope of the pyrimidine synthesis from esters and malondiamidine described by Kenner, Lythgoe, Todd, and Topham (J., 1943, 574). Present results suggest that it is of limited value for, although ethyl benzoate, ethyl oxalate, ethyl carbonate, and ethyl chloroformate condense to give pyrimidine derivatives, this does not appear to be the case with esters of a number of other acids examined.

4 : 6-Diacetamido-2-methylpyrimidine is formed in good yield when malondiamidine dihydrochloride is heated with a mixture of acetic anhydride and sodium acetate.

In a previous communication (Kenner, Lythgoe, Todd, and Topham, J., 1943, 574) a synthesis of 4 : 6-diaminopyrimidine from ethyl formate and malondiamidine was described, and it was noted that by replacing the ethyl formate by ethyl acetate 4 : 6-diamino-2-methylpyrimidine could similarly be prepared. As this reaction of esters with malondiamidine represented a new synthesis of the pyrimidine ring system, it was desirable that the method should be further examined since it would, in theory at least, offer a means of preparing derivatives of 4 : 6-diaminopyrimidine bearing a variety of substituents in position 2. The purpose of this paper is to record the results of a brief survey of the applicability of the new synthesis. It is not claimed that a complete study of all the possibilities has been made, for our primary interest lay in the preparation of 2-substituted 4 : 6-diaminopyrimidines in which the group at position 2 would be of a type useful in our general scheme of nucleoside synthesis.

Despite the very ready reaction of ethyl formate and ethyl acetate, we were unable to isolate any pyrimidine derivative from the condensation of ethyl *n*-butyrate and malondiamidine, the major product of reaction being malondiamide. On the other hand, ethyl benzoate condensed as expected although the yield of 4 : 6-diamino-2-phenylpyrimidine was low. Ethyl carbonate reacted readily with malondiamidine to give 4 : 6-diamino-2-hydroxypyrimidine, and the same substance in the form of its *hydrochloride* was obtained when ethyl chloroformate was used. In the latter instance the chlorine atom appears to take part in the reaction rather than the carbonyl oxygen of the ester.

The case of ethyl oxalate was of interest since it seemed possible that it might react with 2 mols. of malondiamidine to give a tetra-aminodipyrimidyl. In fact no evidence for the formation of such a compound was obtained; only one of the ester groups reacted, the other being hydrolysed, and the sole product was 4 : 6-diaminopyrimidine-2-carboxylic acid, identified by decarboxylation to 4 : 6-diaminopyrimidine. No pyrimidine formation was observed when malondiamidine was heated with ethyl malonate, ethyl pyruvate, urethane, *N*-acetylurethane, phenylurethane or *NN*-dimethylurethane. In view of the greater reactivity of the dithioacids than of the corresponding carboxylic acids, it was of interest to examine the behaviour of methyl dithioacetate; although this ester reacted readily enough with malondiamidine, only red resinous products were formed.

Although further work on a variety of esters would be necessary to make an accurate assessment of its value, it would appear from the experiments so far carried out that the synthetic method, although useful in certain cases, is of limited applicability.

The synthesis of pyrimidines by this method bears an analogy to the synthesis of triazines from esters and biguanide described by Rackmann (*Annalen*, 1910, **376**, 180). According to that author, a mixture of sodium formate and formic acid may be used in place of ethyl formate in the reaction with biguanide, and a mixture of acetic anhydride and sodium acetate may similarly replace ethyl acetate. Efforts on our part to prepare 4 : 6-diaminopyrimidine by heating malondiamidine or its dihydrochloride with a mixture of sodium formate and formic acid were unsuccessful, but with acetic anhydride and sodium acetate a crystalline product was formed in good yield. This proved to be 4 : 6-diacetamido-2-methylpyrimidine, identical with the compound obtained on acetylating 4 : 6-diamino-2-methylpyrimidine.

#### EXPERIMENTAL.

*Ethyl Benzoate and Malondiamidine.*—Malondiamidine dihydrochloride (20 g.; Kenner, Lythgoe, Todd, and Topham, *loc. cit.*) was added to a solution of sodium (6 g.) in methanol (100 c.c.), the precipitated sodium chloride removed, and the solution evaporated under reduced pressure. To the resinous diamidine thus obtained, ethyl benzoate (50 c.c.) was added, and the mixture warmed on the steam-bath for 1 hour, during which time the contents of the flask set to a greenish semi-solid mass. After standing overnight, this product was extracted (Soxhlet) with boiling absolute alcohol. The residue, largely sodium benzoate, was discarded, and the extract evaporated and subjected to vacuum sublimation. At  $190^{\circ}/10^{-3}$  mm. 4 : 6-diamino-2-phenylpyrimidine sublimed as colourless needles. Recrystallised from alcohol, it had m. p.  $195\text{--}196^{\circ}$  (Found : C, 64.5; H, 5.3; N, 30.2.  $C_{10}H_{10}N_4$  requires C, 64.5; H, 5.4; N, 30.2%) (yield, 0.6 g.; 4%). The product was soluble in water and alcohol, but very sparingly so in common non-hydroxylic organic solvents; it appeared to be nitrosated (green colour) on treatment with sodium nitrite and dilute hydrochloric acid.

*Ethyl Carbonate and Malondiamidine.*—Ethyl carbonate (30 c.c.) was added to malondiamidine (prepared from 20 g. of dihydrochloride by the method described above), the mixture heated for 1 hour on the steam-bath, and left overnight. The pale green solid which had separated was collected and recrystallised from water (charcoal). Colourless needles (4 g.; 44%) were obtained which did not melt below  $360^{\circ}$  and showed the general reactions of the expected 4 : 6-diamino-2-hydroxypyrimidine (Found : C, 38.2; H, 4.9; N, 44.3. Calc. for  $C_4H_6ON_4$  : C, 38.1; H, 4.8; N, 44.2%).

*Ethyl Chloroformate and Malondiamidine.*—A solution of ethyl chloroformate (30 c.c.) in dry ether was added dropwise to malondiamidine (prepared from 20 g. of dihydrochloride). Violent reaction occurred during the addition, and after standing for 1 hr. the greenish solid was collected. On recrystallisation from water (charcoal), colourless needles (4 g.; 33%) of 4 : 6-diamino-2-hydroxypyrimidine hydrochloride were obtained (Found : C, 30.0; H, 4.8; N, 35.3; Cl, by Volhard titration, 21.8.  $C_4H_7ON_4Cl$  requires C, 29.6; H, 4.3; N, 34.5; Cl, 21.8%). The substance had no m. p. and the free base had the reactions of the known 4 : 6-diamino-2-hydroxypyrimidine.

*Ethyl Oxalate and Malondiamidine.*—When ethyl oxalate (75 c.c.) was added to malondiamidine (prepared in the usual manner from 50 g. of the dihydrochloride) a violent reaction occurred with considerable evolution of heat. When it subsided the mixture was heated under reflux for 1 hour with dry ether (50 c.c.), and the solid product filtered off. Recrystallised from water, 4 : 6-diaminopyrimidine-2-carboxylic acid was obtained as colourless needles (50 g.) having no m. p. below  $360^{\circ}$  (Found : C, 38.3; H, 3.9; N, 35.6.  $C_5H_6O_2N_4$  requires C, 38.9; H, 3.9; N, 36.4%). The acid dissolved readily in sodium carbonate solution. It was sparingly soluble in water, and aqueous solutions gave with ferrous sulphate a red precipitate insoluble in dilute nitric acid. Although it did not appear to be decarboxylated when heated with quinoline at  $220^{\circ}$  in presence of copper bronze, it lost carbon dioxide readily when warmed in a tube over a free flame. The decarboxylated material which sublimed had m. p.  $263^{\circ}$  and was identified as 4 : 6-diaminopyrimidine by its properties and by mixed m. p. with an authentic specimen.

4 : 6-Diacetamido-2-methylpyrimidine.—A mixture of malondiamidine dihydrochloride (20 g.), fused sodium acetate (20 g.), and acetic anhydride (150 c.c.) was refluxed for 5–6 hours, cooled, and filtered. The filtrate yielded acetamide on evaporation, and the residue, extracted (Soxhlet) with boiling alcohol, gave a solution which on cooling deposited 4 : 6-diacetamido-2-methylpyrimidine. Recrystallised from alcohol, this formed colourless needles (20 g.; 84%), m. p.  $232^{\circ}$ . In this form it was hydrated, the water of crystallisation being removed only by drying for more than 12 hours at  $130^{\circ}/1$  mm. over phosphoric oxide (Found, in hydrated material : C, 47.8; H, 6.2; N, 25.3.  $C_9H_{12}O_2N_4 \cdot H_2O$  requires C, 47.8; H, 6.2; N, 24.8%). The substance (1 g.) was hydrolysed by heating under reflux for 1 hour with sulphuric acid (10 c.c. of 70%), the resulting solution being diluted to 50 c.c., neutralised with barium hydroxide, filtered, and concentrated. 4 : 6-Diamino-2-methylpyrimidine separated, m. p.  $298^{\circ}$  undepressed by an authentic specimen.

For final identification, a small sample of 4 : 6-diamino-2-methylpyrimidine was refluxed with acetic anhydride and fused sodium acetate for 5 hours. The product was identical in m. p. and mixed m. p. with that obtained from malondiamidine as described above (Found : C, 47.4; H, 6.2; N, 25.3. Calc. for  $C_9H_{12}O_2N_4 \cdot H_2O$  : C, 47.8; H, 6.2; N, 24.8%).

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