448. *Pyrimidine Reactions. Part I. Pyrimidines from Malondiamide.*

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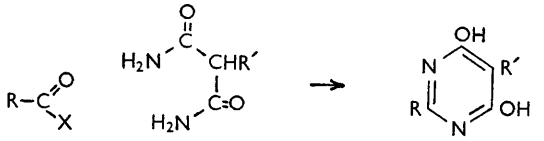
The Remfry–Hull synthesis of 4 : 6-dihydroxypyrimidines from malondiamides and esters is modified to permit inclusion of an alkylamino-group in position 5 or an alkyl group in position 2. Malondiamide is shown to self-condense in the presence of sodium ethoxide to give 2-carbamoylmethyl-4 : 6-dihydroxypyrimidine. Further, it reacts with other amides to give 4 : 6-dihydroxypyrimidine or its 2-alkyl derivatives. The conversion of one of the latter in several stages into 4 : 5-diamino-2-*n*-butylpyrimidine is described. Some 4 : 6-dihydroxypyrimidines are degraded readily to the corresponding malondiamides when boiled with damp piperidine.

4 : 6-Dihydroxypyrimidines (III) have usually been synthesized by condensing malonic esters with an amidine,[1,2] often difficult of access. The reverse type of reaction between a malondiamide (II) and an ester was first used by Remfry [3] to prepare indirectly 2 : 5-dialkyl-4 : 6-dihydroxypyrimidines, *e.g.*, (III; R = Me; R′ = Pr^n), and in Hull's synthesis [4] of 4 : 6-dihydroxypyrimidine and its 5-ethyl and 5-phenyl derivatives. The synthesis is now extended to 5-alkylamino- or 2-alkyl derivatives. Such a group in the 5-position cannot be otherwise readily introduced.

Thus α-bromomalondiamide [5] (II; R′ = Br) was converted into α-methylamino-malondiamide, and this cyclised with ethyl formate to 4 : 6-dihydroxy-5-methylamino-pyrimidine. Further, malondiamide reacted with ethyl *n*-butyrate or valerate (I; R = Bu^n, X = OEt) to give respectively 4 : 6-dihydroxy-2-*n*-propylpyrimidine and the



(I) (II) (III)

n-butyl homologue (III; R = Bu^n, R′ = H). The latter was nitrated in the 5-position, and phosphoryl chloride then gave 2-*n*-butyl-4 : 6-dichloro-5-nitropyrimidine. Mono-amination thereof produced 4-amino-2-*n*-butyl-6-chloro-5-nitropyrimidine, which with sodium hydrogen sulphide gave 4 : 5-diamino-2-*n*-butyl-6-mercaptopyrimidine. Raney-nickel desulphurization led to 4 : 5-diamino-2-*n*-butylpyrimidine, which was of use in pteridine and purine syntheses.

In the reaction of malondiamide with esters less reactive than ethyl formate, a second product was isolated. It proved to be 2-carbamoylmethyl-4 : 6-dihydroxypyrimidine (III; R = CH_2·CO·NH_2, R′ = H) formed by self-condensation of malondiamide (I; R = CH_2·CO·NH_2, X = NH_2) + (II; R′ = H). The same product was formed without ester present. It was identified with authentic material.[6] A logical extension of this reaction was condensation of malondiamide with other amides. Thus, for example, replacement of ethyl formate with formamide in Hull's synthesis improved the yield of 4 : 6-dihydroxypyrimidine, and gave comparable results with the 5-methylamino-derivative. Propionamide likewise gave the compound (III; R = Et, R′ = H) from malondiamide. This formally constitutes a new pyrimidine synthesis.

Unlike the isomeric uracils, 4 : 6-dihydroxypyrimidines are unstable to alkali: with

[1] Kenner, Lythgoe, Todd, and Topham, *J.*, 1943, 388.
[2] Dox and Yoder, *J. Amer. Chem. Soc.*, 1922, **44**, 361.
[3] Remfry, *J.*, 1911, **99**, 610.
[4] Hull, *J.*, 1951, 2214.
[5] Backes, West, and Whiteley, *J.*, 1921, **119**, 359.
[6] McElvain and Tate, *J. Amer. Chem. Soc.*, 1951, **73**, 2760.

boiling aqueous sodium hydroxide the parent substance gives ammonia and even potentiometric titration with alkali does not give self-consistent results in the alkaline region of the curve.[7] This behaviour is clarified by the action of piperidine on these pyrimidines. When 5-bromo-4 : 6-dihydroxypyrimidine [8] was boiled with damp piperidine, not the 5-piperidino-derivative, but α-piperidinomalondiamide was formed. It was identified by synthesis from α-bromomalondiamide. Similarly, piperidine and 4 : 6-dihydroxypyrimidine produced malondiamide.

Experimental

Analyses were done by Mr. P. R. W. Baker, Wellcome Research Laboratories, Beckenham.

α-Methylaminomalondiamide.—α-Bromomalondiamide [5] (30 g.) was added during 10 min. to ethanolic methylamine (33% w/w; 300 ml.), the whole being ground in a mortar. After a further 30 min. the product was recrystallised from 0·2% ethanolic methylamine (120 parts), giving *α-methylaminomalondiamide* (23·2 g.), m. p. 200—201° (Found: N, 31·95. $C_4H_9O_2N_3$ requires N, 32·05%).

4 : 6-Dihydroxy-5-methylaminopyrimidine.—α-Methylaminomalondiamide (13 g.), sodium ethoxide solution (sodium, 4·7 g.; ethanol, 150 ml.), and ethyl formate (12·5 ml.) were refluxed for 2 hr. The residue obtained on removal of ethanol *in vacuo* was dissolved in water (30 ml.) and brought to pH 5. Recrystallisation from water (60 ml.) gave *4 : 6-dihydroxy-5-methylaminopyrimidine* (8·4 g.), m. p. 240° (decomp.) (Found: C, 42·5; H, 4·9; N, 30·0. $C_5H_7O_2N_3$ requires C, 42·55; H, 5·0; N, 29·8%). When formamide replaced ester, the yield was 5·2 g.

2-n-Butyl-4 : 6-dihydroxypyrimidine.—Malondiamide (184 g.), sodium ethoxide solution (sodium, 83 g.; ethanol, 2700 ml.), and ethyl *n*-valerate (410 ml.) were refluxed with stirring for 2 hr. After cooling overnight, the solid was filtered off (see below). The filtrate was evaporated *in vacuo* and the residue in water (450 ml.) brought to pH 2·5. The precipitate was recrystallised from ethanol (150 parts) to give needles (21 g.) of *2-n-butyl-4 : 6-dihydroxypyrimidine*, m. p. 300° (decomp.) (Found: C, 57·2; H, 7·3; N, 16·6. $C_8H_{12}O_2N_4$ requires C, 57·1; H, 7·2; N, 16·65%).

4 : 6-Dihydroxy-2-n-propylpyrimidine.—Prepared with ethyl *n*-butyrate as above and recrystallised from ethanol (135 parts), the *propyl homologue* formed needles, m. p. 296° (decomp.) (Found: C, 54·95; H, 6·3; N, 18·4. $C_7H_{10}O_2N_4$ requires C, 54·55; H, 6·5; N, 18·2%).

2-Carbamoylmethyl-4 : 6-dihydroxypyrimidine.—The sodium salt (see butyl compound above) in water (600 ml.) was brought to pH 2—3. Refrigeration and recrystallisation from water (30 parts) gave the amide (39 g.) as prisms, decomp. >200° (Found: C, 42·6; H, 4·2; N, 24·9. Calc. for $C_6H_7O_3N_3$: C, 42·6; H, 4·2; N, 24·85%). It was identical (infrared spectrum and chromatography) with authentic material.[6] When malondiamide (30·6 g.) was refluxed with sodium ethoxide solution (sodium, 13·8 g.), the same compound (8·2 g.) resulted.

2-n-Butyl-4 : 6-dihydroxy-5-nitropyrimidine.—*2-n*-Butyl-4 : 6-dihydroxypyrimidine (9·6 g.) was added during 15 min. with stirring to nitric acid (*d* 1·5; 12 ml.) and acetic acid (30 ml.) at 40—50°. After a further 30 min. the whole was added to ice and water (80 ml.), and the product (6·1 g.) recrystallised from ethanol (90 parts) giving colourless laths of *nitro-compound*, m. p. 265° (decomp.) (Found: C, 45·4; H, 4·85; N, 19·7. $C_8H_{11}O_4N_3$ requires C, 45·1; H, 5·2; N, 19·7%).

2-n-Butyl-4 : 6-dichloro-5-nitropyrimidine.—The above (4·25 g.), phosphoryl chloride (22 ml.), and diethylaniline (5·5 ml.) were refluxed for 1 hr. After removal of phosphoryl chloride (15 ml.) the residue was stirred with ice for 20 min. and extracted with ether (3 × 50 ml.). Evaporation and distillation gave *dichloro-compound* (3·8 g.) as a yellow oil, b. p. 142—143°/17 mm. (Found: C, 38·8; H, 3·6; Cl, 28·35. $C_8H_9O_2N_3Cl_2$ requires C, 38·4; H, 3·6; Cl, 28·35%).

4-Amino-2-n-butyl-6-chloro-5-nitropyrimidine.—Methanolic ammonia (10% w/v; 3 ml.) was added during 1 hr. with stirring to the dichloro-compound (2·5 g.) in ether (30 ml.). After a further 1 hr. the solid was filtered off and washed with hot ethyl acetate (10 ml.). The residue obtained on vacuum-evaporation of both filtrates was recrystallised from benzene (15 ml.) and after concentration gave colourless *amine* (1·5 g.), m. p. 132° (Found: C, 42·15; H, 4·9; N, 24·3. $C_8H_{11}O_2N_4Cl$ requires C, 41·7; H, 4·8; N, 24·3%).

4 : 5-Diamino-2-n-butyl-6-mercaptopyrimidine.—The above amine (1 g.) was heated at 95° for 1·5 hr. with aqueous 1·25M-sodium hydrogen sulphide (20 ml.). Adjustment to pH 5 and extraction of the cake with boiling water (60 ml.) gave a solid (0·6 g.; m. p. 184°) which from

[7] Albert and Phillips, *J.*, 1956, 1294.
[8] Chesterfield, McOmie, and Sayer, *J.*, 1955, 3478.

water formed needles of the *mercapto-compound*, m. p. 186—187° (Found : N, 28·5; S, 16·0. $C_8H_{14}N_4S$ requires N, 28·3; S, 16·15%).

4 : 5-*Diamino*-2-n-*butylpyrimidine*.—The above mercapto-derivative (1·5 g.) in hot aqueous 1·5N-ammonia (55 ml.) was vigorously refluxed with Raney nickel (*ca.* 6 g. wet) for 1 hr. The filtered solution was evaporated *in vacuo*, giving in 87% yield a material of m. p. 115°. Recrystallised from benzene it formed needles which obstinately retained solvent. Sublimation (105°/0·001 mm.) gave the *diamine*, m. p. 121—122° (Found : N, 33·8. $C_8H_{14}N_4$ requires N, 33·7%).

4 : 6-*Dihydroxypyrimidine*.—When this was prepared from malondiamide (10·2 g.) as in Hull's synthesis,[4] but with formamide (6·5 ml.) replacing ethyl formate, the yield was 5·8 g. (cf. 4·5 g.). It was identified by conversion into 4 : 6-dichloropyrimidine and 5-bromo-4 : 6-dihydroxypyrimidine.[8]

2-*Ethyl*-4 : 6-*dihydroxypyrimidine*.—Malondiamide (20·4 g.), propionamide (22 g.), and sodium ethoxide (sodium, 9·2 g.) treated as for the *n*-butyl homologue gave 2-carbamoylmethyl- and 2-*ethyl*-4 : 6-*dihydroxypyrimidine* (2·8 and 1·55 g. respectively). The latter recrystallised from water (40 parts) as plates, m. p. 294° (decomp.) (Found : C, 51·1; H, 5·5; N, 20·4. $C_6H_8O_2N_2$ requires C, 51·4; H, 5·7; N, 20·0%).

α-*Piperidinomalondiamide*.—(*a*) 5-Bromo-4 : 6-dihydroxypyrimidine (1 g.) was refluxed (oil-bath) with damp piperidine (2·5 ml.) for 2 hr. The solid (0·5 g.; m. p. 255°) formed on addition of water (5 ml.) was recrystallised from water (160 parts), giving α-*piperidinomalondiamide*, m. p. 257° (Found : C, 52·05; H, 7·85; N, 23·0. $C_8H_{15}O_2N_3$ requires C, 51·9; H, 8·15; N, 22·7%). (*b*) α-Bromomalondiamide[5] (1 g.) was heated at 100° with piperidine (5 ml.). The mixture was dissolved in boiling water (120 ml.); the product (0·8 g.; m. p. 257°) crystallised.

Malondiamide from 4 : 6-*Dihydroxypyrimidine*.—The pyrimidine (2 g.), piperidine (5 ml.), and water (0·3 ml.) were refluxed for 2 hr. The solid was washed with ethanol and recrystallised from methanol (40 ml.), giving, after concentration, plates (0·75 g.) of m. p. 168—171°, undepressed by authentic malondiamide.

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