382. *An Anomalous Reaction of* 4 : 6-*Dichloro*-5-*nitropyrimidine.*

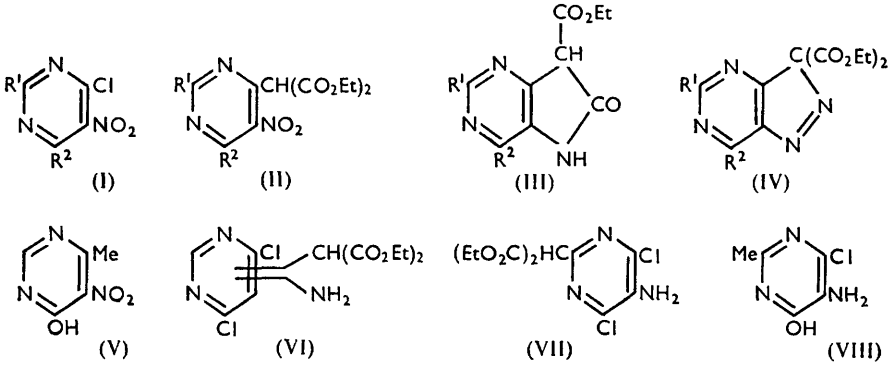
By F. L. Rose and D. J. Brown.

The condensation of 4 : 6-dichloro-5-nitropyrimidine with excess of diethyl malonate, previously described by analogy with closely related reactions as affording diethyl 4-chloro-5-nitro-6-pyrimidinylmalonate, has now been shown to give unexpectedly diethyl 5-amino-4 : 6-dichloro-2-pyrimidinylmalonate as a major product. Ethyl acetoacetate and acetylacetone react in a similar anomalous manner.

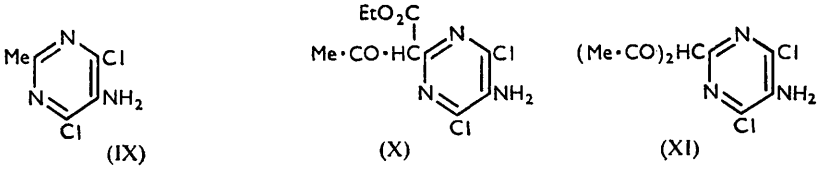
A previous communication [1] described the reaction of several chloronitropyrimidines of type (I) (R^1 = Me, R^2 = Cl; R^1 = Cl, R^2 = Me; and R^1 = NH_2, R^2 = Me) with excess of diethyl malonate, usually dissolved in organic solvents, and with aqueous sodium hydroxide as the condensing agent, to give the corresponding nitropyrimidinylmalonic esters (II). The structure of the latter compounds was established by elementary analysis, by destructive hydrolysis of the malonyl residue to methyl, and by reduction of the nitro- to the amino-group followed by intramolecular condensation to give the triazaindan-2-ones (III), or, through diazotisation, the tetra-azaindene-3 : 3-dicarboxylic esters (IV). A single experiment was included in which diethyl malonate was caused to react with the 5-nitropyrimidine (I; R^1 = H, R^2 = Cl), unsubstituted in the 2-position. The product had the usual low melting point, and elementary analysis for carbon, hydrogen, and nitrogen agreed approximately with those for the expected substance (II; R^1 = H, R^2 = Cl). In addition, hydrolysis with hydrochloric acid gave an alkali-soluble derivative which showed tolerable analytical accord with the hydroxymethylpyrimidine (V), isolated as the mono-hydrochloride monohydrate. No further investigation of these substances was made at

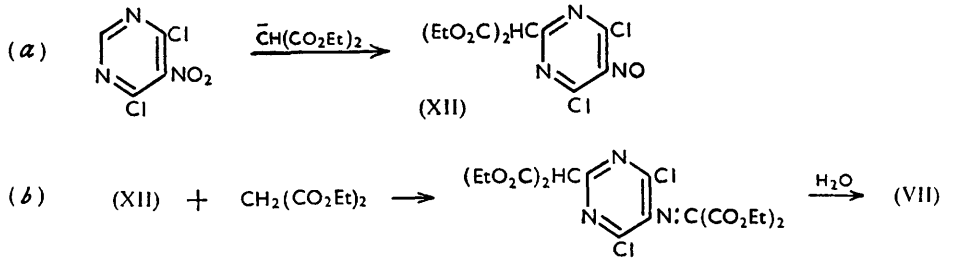
[1] Rose, *J.*, 1954, 4116.

the time. More recently, the 6-chloropyrimidine corresponding to (V) was required, but analysis of the compound obtained by the action of phosphoryl chloride indicated that it might be an aminodichloromethylpyrimidine. The entire chlorine content was non-ionic. More complete analysis of the hydrolysis product, allegedly (V), agreed with an aminochlorohydroxymethylpyrimidine structure, while a similar re-investigation of the primary condensation product of the chloride (I; $R^1 = H$, $R^2 = Cl$) with diethyl malonate indicated



the presence of one amino- and one diethyl malonate residue and two (non-ionic) chlorine atoms, associated with the pyrimidine nucleus (cf. VI). Addition of sodium nitrite to an acidified solution of this compound (VI) in acetone gave a solution from which a red colour was obtained with alkaline R-salt, thus establishing the almost certain presence of a diazotisable amino-group in position 5, and from which it followed that the malonyl group must occupy the remaining position 2, as in (VII). The hydrolysis product therefore had the structure (VIII), and the corresponding dichloropyrimidine had structure (IX). This presumed orientation was confirmed by proving the identity of the amines (VIII) and (IX) with authentic materials prepared from acetamidine.[2]





The compound (I; $R^1 = H$, $R^2 = Cl$) has now been shown to react in the same unexpected manner with ethyl acetoacetate and acetylacetone in the presence of aqueous sodium hydroxide giving dichloropyrimidines which contained diazotisable amino-groups and gave analyses correct for structures (X) and (XI) respectively. On the other hand, no such reaction occurred between diethyl malonate and 5-amino-4 : 6-dichloro-, 4 : 6-dimethoxy-5-nitro-, or 4 : 6-dihydroxy-5-nitro-pyrimidine.

[2] Albert, Brown, and Wood, *J.*, 1954, 3832.

From the above investigations it seemed evident that the apparently anomalous behaviour of the 4 : 6-dichloro-5-nitropyrimidine was primarily due to the suceptibility of the 2-position to nucleophilic attack, mediated through electron-withdrawal at that point by the ring-nitrogen atoms and reinforced by the nitro-group. The inductive influence of the chlorine atoms in position 4 and 6 would also contribute. In the presence of sodium hydroxide, substitution might therefore be expected by the diethyl malonate anion, and in such a case the preferred mechanism would be by simultaneous intramolecular reduction of the nitro- to a nitroso-group [3] (reaction *a*). Further reduction of the nitroso- to an amino-group then seems not unreasonable through the reaction series (*b*), the final stage occurring on acidification. That direct nucleophilic substitution of the 2-position should be preferred to reaction with an active chlorine atom is not unknown, since, for example,[4] 4-chloro-6-methoxyquinoline reacts with *m*-chlorophenyl-lithium at position 2. When, however, the positive nature of the 2-position of the pyrimidine (I; $R^1 = H$, $R^2 = Cl$) is sharply decreased by substituting hydroxy-groups for chlorine atoms, the nucleophilic reaction might be expected to fail, in accord with experimental observation. It also fails when the chlorine atoms are replaced by methoxyl groups.

Experimental

Diethyl 5-Amino-4 : 6-dichloro-2-pyrimidinylmalonate.—The experiment described in the previous communication [1] was repeated. The *product* (previously described as diethyl 4-chloro-5-nitro-6-pyrimidinylmalonate) had m. p. 101—103° and showed one spot on a butanol–acetic acid paper chromatogram in ultraviolet light [Found : C, 41·0; H, 4·0; O, 19·7; N, 12·9; Cl (non-ionic), 22·15. $C_{11}H_{13}O_4N_3Cl_2$ requires C, 41·0; H, 4·1; O, 19·9; N, 13·0; Cl, 22·0%].

Rose [1] found for the same product : C, 40·9; H, 4·1; N, 13·6%. A solution in acetone, when treated successively with dilute hydrochloric acid and sodium nitrite, gave a strong red colour with alkaline R-salt.

5-Amino-4-chloro-6-hydroxy-2-methylpyrimidine.—(a) *From the above ester.* Ester (2·5 g.), concentrated hydrochloric acid (7·5 ml.), and water (5 ml.) were refluxed for 90 min. The hydrochloride remaining after vacuum-evaporation was suspended in water (5 ml.). The pH was adjusted to 4, and the precipitate twice recrystallised (carbon) from water (15 parts), to give a faintly yellow *product* (1·0 g.), m. p. 231—233° [Found : C, 37·3; H, 3·7; O, 10·4; N, 26·1; Cl (non ionic), 22·45. $C_5H_6ON_3Cl$ requires C, 37·6; H, 3·8; O, 10·0; N, 26·3; Cl, 22·2%).

(b) *From 5-amino-4 : 6-dichloro-2-methylpyrimidine.* The dichloro-compound [2] (0·5 g.) was refluxed for 1 hr. with 24% hydrochloric acid. Treatment as above gave the same yellow product (0·25 g.), m. p. and mixed m. p. 231°.

5-Amino-4 : 6-dichloro-2-methylpyrimidine.—The above hydroxy-compound (1 g.), phosphoryl chloride (5 ml.), and diethylaniline (1·0 ml.) were refluxed for 1 hr. About 3 ml. of phosphoryl chloride were distilled off in a vacuum and the residue stirred with ice and water for 20 min. The solution was extracted with ether (3 × 20 ml.), adjusted in pH to 3, and re-extracted. The residue after evaporation of all extracts was boiled with water (2 ml.), then cooled, and the dried crystalline product was sublimed (60°/0·1 mm.), giving 0·15 g. of the dichloro-compound, m. p. and mixed m. p. 70—71° (Found : C, 33·75; H, 2·65; N, 23·5; Cl, 40·15. Calc. for $C_5H_5N_3Cl_2$: C, 33·75; H, 2·8; N, 23·6; Cl, 39·85%).

Ethyl α-(5-Amino-4 : 6-dichloro-2-pyrimidinyl)acetoacetate.—4 : 6-Dichloro-5-nitropyrimidine (4·8 g.) was dissolved in ethyl acetoacetate (10 ml.) at 40°. Water (50 ml.) was added, followed during 3 min. by 11N-sodium hydroxide (15 c.c.) with vigorous stirring, at 30—35°. After a further 10 min. the solution was adjusted to pH 4 with concentrated hydrochloric acid. The semisolid *ester* hardened when shaken with light petroleum (b. p. 60—80°) to remove excess of ethyl acetoacetate, and was collected (2·1 g.; m. p. 93—95°). It gave very pale yellow crystals, m. p. 102—104°, when crystallised successively from benzene–light petroleum and methanol (Found : C, 41·5; H, 3·9; N, 13·5; Cl, 23·6. $C_{10}H_{11}O_3N_3Cl_2$ requires C, 41·1; H, 3·8; N, 14·4; Cl, 24·3%). The product was freely soluble in cold benzene, chloroform, ethanol, methanol, and acetone. A solution in the last solvent could be diazotised and coupled with alkaline R-salt.

3-(*5-Amino-4 : 6-dichloro-2-pyrimidinyl*)*acetylacetone.*—11N-Sodium hydroxide (15 ml.) was added during 5 min. with vigorous stirring to a solution of 4 : 6-dichloro-5-nitropyrimidine (4·8 g.) in acetylacetone (8 ml.) and ether (30 ml.) at 30—32°. After a further 7 min. the aqueous

[3] Bunnett and Zahler, *Chem. Rev.*, 1951, **49**, 273.
[4] Gilman and Spatz, *J. Amer. Chem. Soc.*, 1944, **66**, 62.

layer was separated and made acid with acetic acid. The precipitated crude *diketone* (1 g.) crystallised from toluene in large very pale yellow plates, m. p. 181—183° (Found: C, 41·2; H, 3·9; N, 16·1; Cl, 27·4. $C_9H_9O_2N_3Cl_2$ requires C, 41·2; H, 3·4; N, 16·0; Cl, 27·1%). The presence of a diazotisable group was demonstrated as described above (violet coloration).

4 : 6-*Dimethoxy-5-nitropyrimidine*.—4 : 6-Dichloro-5-nitropyrimidine (4·8 g.) in methanol (40 ml.) was added portionwise, at 28—32°, to methanol (50 ml.) in which sodium (2·3 g.) had been dissolved. The *nitropyrimidine* (4 g.) crystallised and was collected and washed with water. It formed pale yellow needles (from butanol), m. p. 173—174° (Found: C, 38·5; H, 3·8; N, 22·9. $C_6H_7O_4N_3$ requires C, 38·9; H, 3·8; N, 22·7%).

One of the authors (D. J. B.) thanks Mr. P. R. W. Baker, Beckenham, for some of the analyses.

Imperial Chemical Industries Limited, Hexagon House,
Blackley, Manchester, 9.

Australian National University,
183, Euston Road, London, N.W.1.

[*Received, January 4th*, 1956.]