444. *The Conversion of Sucrose into Pyridazine Derivatives. Part III. Constitutional Studies on the Products of Chlorination of 2 : 6-Dimethyl-3-pyridazone.*

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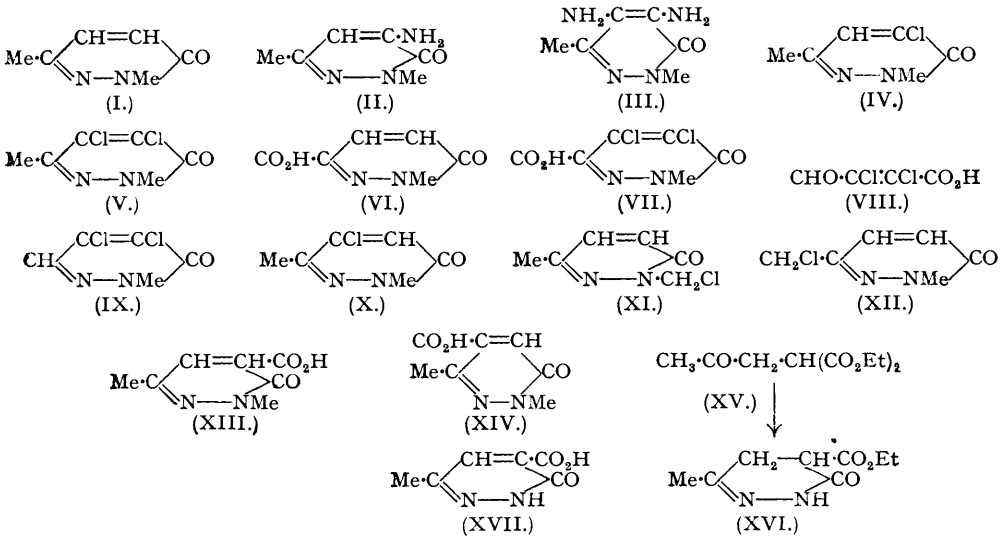
2 : 6-Dimethyl-3-pyridazone has been chlorinated and four different chlorine-containing substances isolated. Two of these have been shown to be 5-chloro- and 4 : 5-dichloro-2 : 6-dimethyl-3-pyridazone.

In continuation of studies on pyridazine derivatives obtained from sucrose through lævulic acid as the essential intermediate, we have studied the chlorination of 2 : 6-dimethyl-3-pyridazone (I). This was prepared from lævulic acid by conversion into 6-methyl-3-pyridazone (see Part I, Overend and Wiggins, *J.*, 1947, 239) followed by methylation. That the entering methyl group was attached to the nitrogen atom at position 2 was proved by synthesis of dimethylpyridazone from methylhydrazine and lævulic acid (Overend and Wiggins, unpublished work). It was envisaged that chlorination of 2 : 6-dimethyl-3-pyridazone might permit the introduction of new substituent groups at the unsubstituted carbon atoms remaining in the pyridazone nucleus. Particularly, the amino-derivatives, 4-amino- (II) and 4 : 5-diamino-2 : 6-dimethyl-3-pyridazone (III) were required for certain pharmacological tests and also for the preparation of sulphanilamido-derivatives, since preliminary chemotherapeutic trials have shown that several sulphanilamido-pyridazone and -pyridazine derivatives show marked promise as bacteriostatic agents.



Chlorination of 2 : 6-dimethyl-3-pyridazone (I) has already been described by Meyer (D.R.-P. 579,391, 1933), who claimed to have prepared 4-chloro-2 : 6-dimethyl-3-pyridazone (IV) and an unknown dichloro-derivative of 2 : 6-dimethyl-3-pyridazone, for which he gave no constants. These substances were not defined clearly in the patent, nor have they been described subsequently, and no proof of their constitution has been presented hitherto.

In the present work, the chlorination of (I) was found not to proceed in so clear-cut a manner as Meyer (*loc. cit.*) described. It has been found that on treating (I) in the fused state with chlorine in ordinary daylight at 100°, four, and not only two, products were isolated, namely: (*a*) m. p. 80°; (*b*) m. p. 116°; (*c*) m. p. 114—115°; and (*d*) a material of ill-defined melting point, b. p. 220°. The product (*a*) was clearly the same as Meyer's so-called 4-chloro-2 : 6-dimethyl-3-pyridazone, and the mixture of (*b*), (*c*), and (*d*) was what he described as crude dichloro-2 : 6-dimethyl-3-pyridazone. The substances (*c*) and (*d*) have not hitherto been described by other workers. It was also found that these chlorinated products of 2 : 6-dimethyl-3-pyridazone were formed in highly variable yields despite all efforts to ensure constancy of experimental conditions. Three of the four products (*a*, *b*, and *d*) were separated by differences in their

solubility in water, and one of them (*c*) was volatile in steam. It was found that (*d*) and (*a*) were monochloro-derivatives, and (*b*) and (*c*) contained two chlorine atoms in each pyridazone molecule. The constitution of (*a*) and (*b*) is discussed herein; the structure of (*c*) and (*d*) will be dealt with in a later paper.

Oxidation of the dichlorodimethylpyridazone (*b*) with potassium dichromate and sulphuric acid yielded a carboxylic acid still containing both chlorine atoms. This compound was found (see later) to be dichloromethylpyridazonecarboxylic acid. Since an *N*-methyl group would give on oxidation $N{\cdot}CO_2H$ which would be easily decarboxylated to NH, it was more likely to be the 6-methyl that had undergone oxidation to a carboxyl group. Some evidence for the supposition that the 6-methyl group is oxidised in preference to the *N*-methyl group is deduced from the fact that oxidation of 2 : 6-dimethyl-3-pyridazone leads to the formation of 2-methyl-3-pyridazone-6-carboxylic acid (VI). We have been able to allocate a precise structure to this compound (*b*) by the following synthetic approach. Mucochloric acid (VIII), which was obtained by Simonis (*Ber.*, 1899, **32**, 2085) from furfuraldehyde and chlorine, was condensed with methylhydrazine to give a dichloromethylpyridazone which from the method of preparation must be 4 : 5-dichloro-2-methyl-3-pyridazone (IX). The product of oxidation of (*b*) was then decarboxylated and gave, in high yield, a substance identical with (IX). Therefore the carboxylic acid produced by oxidation of (*b*) must be 4 : 5-dichloro-2-methyl-3-pyridazone-6-carboxylic acid (VII). It follows directly that (*b*) itself must be 4 : 5-dichloro-2 : 6-dimethyl-3-pyridazone (V).

The monochloro-derivative of 2 : 6-dimethyl-3-pyridazone (*a*) may have any of the structures (IV) or (X—XII). The possible formulæ (XI and XII) can be eliminated, however, because the monochloro-derivative (*a*) has been converted, by chlorination, into 4 : 5-dichloro-2 : 6-dimethyl-3-pyridazone in good yield; thus it follows that in (*a*) the chlorine atom must be attached to the pyridazone residue at either C_4 or C_5, and (*a*) is represented by either (IV) or (X). A decision between these two possibilities has been made by a synthetic procedure.

The chlorine atom in the monochloro-derivative (*a*) of 2 : 6-dimethyl-3-pyridazone was replaced by a carboxyl group by treatment with cuprous cyanide–potassium cyanide under pressure. The intermediate copper complex first isolated was decomposed to a carboxylic acid which had m. p. 183—185°, and behaved on potentiometric titration as a monobasic acid of K $1{\cdot}9 \times 10^{-4}$ in aqueous solution. This substance must be either 2 : 6-dimethyl-3-pyridazone-4-(XIII) or -5-carboxylic acid (XIV).

The intermediate copper complex first formed was a green crystalline solid which could be recrystallised from boiling water without decomposition. It dissolved in hot dilute hydrochloric acid without precipitation of cuprous chloride, so that copper is probably in the cupric state. The ratio of pyridazone residues to each copper atom was found by determination of copper to be 3·4 (gravimeteric) and 4·6 (polarographic). Despite the wide discrepancy between these two results it is fairly clear that four pyridazone residues are associated with one copper atom. The precise form in which this association takes place is not yet known, but will be studied. The complex was decomposed with nitric acid to give the carboxylic acid, m. p. 183—185°.

If one of the compounds (XIII) or (XIV) could be synthesised and proved to be identical or otherwise with the carboxylic acid, m. p. 183—185°, obtained from the monochloro-derivative (*a*), the constitution of (*a*) would automatically follow. We have now synthesised 2 : 6-dimethylpyridazone-4-carboxylic acid (XIII) in the following way. Ethyl acetonylmalonate (XV) was condensed with hydrazine to yield ethyl 6-methyl-3-pyridazinone-4-carboxylate (XVI) (Gault and Salomon, *Ann. Chim.*, 1924, **2**, 133). This gave on treatment with bromine in anhydrous acetic acid and by simultaneous de-esterification, *6-methyl-3-pyridazone-4-carboxylic acid* (XVII). The experimental conditions used were those found most favourable for the dehydrogenation of 6-methyl-3-pyridazinone to the corresponding pyridazone (Overend and Wiggins, *J.*, 1947, 239). Methylation of (XVII) with methyl iodide and sodium methoxide gave a product which must be 2 : 6-*dimethyl-3-pyridazone-4-carboxylic acid*. [Methylation of 6-methyl-3-pyridazone with these reagents has been found to yield 2 : 6-dimethylpyridazone (Overend and Wiggins, *loc. cit.*).] It had m. p. 150—153° and behaved as a monobasic carboxylic acid on potentiometric titration (K $1{\cdot}7 \times 10^{-4}$ in 20% aqueous alcohol). It was clearly different from the carboxylic acid, m. p. 183—185°, obtained from the monochloro-derivative (*a*). It follows that the carboxylic acid obtained from (*a*) is 2 : 6-*dimethyl-3-pyridazone-5-carboxylic acid* (XIV). The original monochloro-derivative (*a*) of 2 : 6-dimethyl-3-pyridazone is therefore 5-chloro-2 : 6-dimethyl-3-pyridazone (X).

Both the monochloro-derivative (*a*) and the dichloro-derivative (*b*) of 2 : 6-dimethyl-3-pyridazone showed absorption in the ultra-violet with a maximum at 3060 A. Also the original 2 : 6-dimethyl-3-pyridazone showed absorption with the head of the band in practically the same

position, at 2940 A. This shows that all three compounds have essentially the same type of structure.

An attempt to chlorinate 2 : 6-dimethyl-3-pyridazone with phosphorus pentachloride in a similar way to that in which 2-phenyl-6-methyl-3-pyridazone was converted into 4-chloro-2-phenyl-6-methyl-3-pyridazone (Overend and Wiggins, *J.*, 1947, 549) was not successful. It led to extensive demethylation at the nitrogen atom with formation of 6-methyl-3-pyridazone, and only a very small amount of a chlorine-containing product which has not yet been identified was isolated.

Experimental.

2 : 6-*Dimethyl*-3-*pyridazone*.—(*a*) Anhydrous 6-methyl-3-pyridazone (50 g.) was refluxed for 2 hours with methyl iodide (65 g.) and sodium (10·5 g.) in dry methyl alcohol (500 c.c.). A " drycold " cooled condenser fitted above the water condenser gave a marked improvement in yield. The mixture was evaporated to small bulk, diluted with water, and continuously extracted with ether. The extract was dried ($MgSO_4$), and on evaporation gave 2 : 6-dimethyl-3-pyridazone as a solid residue (40% yield) which distilled at 109—112°/16 mm., and after recrystallisation from ligroin had m. p. 50—51° in agreement with that found by Overend and Wiggins (forthcoming communication). The compound showed absorption at $\lambda_{max.}$ 2940 A. with $\varepsilon_{max.}^{7\cdot48\%}$ *ca.* 2460 in ethyl alcohol.

(*b*) Anhydrous 6-methyl-3-pyridazone (20 g.) was heated in an autoclave at 130° for 3½ hours with methyl iodide (25 g.) and sodium (4·3 g.) dissolved in dry methyl alcohol (200 c.c.). The mixture was diluted with water and evaporated to small bulk, and the residue was extracted with benzene. The extract was dried ($MgSO_4$) and evaporated to an oil which solidified on cooling and after recrystallisation from light petroleum (b. p. 40—60°) had m. p. 50—51°. Yield of 2 : 6-dimethyl-3-pyridazone 9 g. (48%).

(*c*) Anhydrous 6-methyl-3-pyridazone (4·5 g.) was added slowly during 2 hours with stirring to liquid ammonia (200 c.c.) (cooled in " drycold "–alcohol freezing mixture) containing sodium (0·95 g.) and methyl iodide (7 g.). The ammonia was allowed to evaporate and the residue was dissolved in water and extracted with benzene as above. 2 : 6-Dimethyl-3-pyridazone (2·1 g.; 40%) was obtained.

Chlorination of 2 : 6-*Dimethyl*-3-*pyridazone*.—Anhydrous 2 : 6-dimethyl-3-pyridazone (10 g.) was heated on a boiling water-bath and dry chlorine passed in at a rate of 10 l./hour for 1 hour. The crude melt after cooling was triturated with water (50 c.c.) and the insoluble material filtered off.

The filtrate was made strongly alkaline with 5N-sodium hydroxide. The solid 5-*chloro*-2 : 6-*dimethyl*-3-*pyridazone* (*a*) which separated (4·2 g.), m. p. 80°, showed absorption in the ultra-violet at $\lambda_{max.}$ 3060 A. and $\varepsilon_{max.}^{3\cdot89\%}$ *ca.* 3750 in ethyl alcohol (Found : C, 45·1; H, 4·3; N, 17·0. $C_6H_7ON_2Cl$ requires C, 45·4; H, 4·5; N, 17·7%).

The combined insoluble fraction from 7 chlorination experiments (28·5 g.) was extracted with boiling water (1 l.). The clear liquor was decanted from the insoluble oil. On cooling, crystals of 4 : 5-*dichloro*-2 : 6-*dimethyl*-3-*pyridazone* (*b*) (17·3 g.) were deposited, m. p. 116·5°, showing absorption band maximum at $\lambda_{max.}$ 3060 A. with $\varepsilon_{max.}^{4\cdot0\%}$ *ca.* 4000 (Found : C, 37·9; H, 3·2; N, 13·9. $C_6H_6ON_2Cl_2$ requires C, 37·3; H, 3·1; N, 14·5%).

The insoluble oily material gave on steam distillation crystals (1 g.) of a *dichloro*-derivative of 2 : 6-dimethyl-3-pyridazone, m. p. 114—115° (Found : C, 37·3; H, 3·2; N, 14·5%).

The filtrate from the 4 : 5-dichloro-2 : 6-dimethyl-3-pyridazone was extracted with chloroform, and the dried extract evaporated to an oil which solidified on cooling. This was a monochloro-derivative of 2 : 6-dimethyl-3-pyridazone (*d*) and was purified by distillation, b. p. 220°. It had, however, no definite m. p. and was probably a mixture of isomeric monochloro-compounds (Found : Cl, 22·7. Calc. for $C_6H_7ON_2Cl$: Cl, 22·4%).

Chlorination of 5-*Chloro*-2 : 6-*dimethyl*-3-*pyridazone*.—5-Chloro-2 : 6-dimethyl-3-pyridazone (2 g.) was fused at 100° and dry chlorine passed in at a rate of 5 l./hour for 1 hour. The melt, which solidified on cooling, gave, on crystallisation from water, 1·2 g. of material, m. p. 116°, alone or in admixture with 4 : 5-dichloro-2 : 6-dimethyl-3-pyridazone.

2 : 6-*Dimethyl*-3-*pyridazone*-5-*carboxylic Acid*.—5-Chloro-2 : 6-dimethyl-3-pyridazone (2 g.), potassium cyanide (2 g.), and cuprous cyanide (0·5 g.) were heated with ethyl alcohol (10 c.c.) and water at 200° in a sealed tube for 5½ hours. The mixture was acidified with sulphuric acid and continuously extracted with ether. The extract was dried ($MgSO_4$) and evaporated to a solid residue (50 mg.) which recrystallised from water as green needles, and had m. p. 317° (decomp.). An ash determination (as CuO) showed it to contain 10·0% of Cu, and a polarographic estimation gave 8·3% of Cu. The former indicated the presence of 3·4 units and the latter 4·6 units of the pyridazone molecule per copper atom. Treatment of the complex with dilute hydrochloric acid gave a clear green solution. No cuprous chloride was precipitated, indicating that the copper was present in the cupric state. After being boiled with dilute nitric acid the copper complex deposited colourless crystals of 2 : 6-*dimethyl*-3-*pyridazone*-5-*carboxylic acid*, m. p. 183—185°, which behaved as a monobasic carboxylic acid on potentiometric titration (in water) having K $1\cdot9 \times 10^{-4}$ (Found : C, 49·6; H, 4·54; equiv., 164. $C_7H_8O_3N_2$ requires C, 50·0; H, 4·77%; equiv., 168).

6-*Methyl*-3-*pyridazone*-4-*carboxylic Acid*.—Ethyl 6-methyl-3-pyridazinone-4-carboxylate (Gault and Salomon, *loc. cit.*) (1·1 g.) was dissolved in dry acetic acid (20 c.c.). Bromine (0·9 g.) was added slowly and the mixture allowed to stand for 24 hours. Water was added, and the solution evaporated to a syrup. Water was repeatedly distilled over this to remove as much hydrogen bromide as possible. The residue deposited some crystals of 6-*methyl*-3-*pyridazone*-4-*carboxylic acid* which were separated and recrystallised from water, m. p. 182—183° (Found : C, 47·1; H, 4·1; N, 18·3; equiv., 158. $C_6H_6O_3N_2$ requires C, 46·8; H, 3·9; N, 18·2%; equiv., 154). Yield 0·33 g.

The acid (0·2 g.) was refluxed with 2% methyl-alcoholic hydrogen chloride (10 c.c.) for 6 hours. The solution was neutralised with lead carbonate, filtered, and evaporated to dryness. The *methyl* ester,

recrystallised from water, had m. p. 161—162° (Found: N, 16·3. $C_7H_8O_3N_2$ requires N, 16·6%). Yield 40 mg.

2 : 6-*Dimethyl*-3-*pyridazone*-4-*carboxylic Acid.*—6-Methyl-3-pyridazone-4-carboxylic acid (103 mg.) was dissolved in dry methyl alcohol (3 c.c.) containing sodium (14·2 mg., 2 mols.) and methyl iodide (85 mg.). The solution was refluxed for 2 hours and then poured into water and acidified with hydrochloric acid. Extraction with ether gave 2 : 6-*dimethyl*-3-*pyridazone*-4-*carboxylic acid*; K, $1·7 \times 10^{-4}$ (in 20% aqueous alcohol), m. p. 150—153° (Found: N, 16·6; equiv., 167. $C_7H_8O_3N_2$ requires N, 16·6%; equiv., 168).

2-*Methyl*-3-*pyridazone*-6-*carboxylic Acid.*—Finely powdered potassium dichromate (28·40 g., 20% excess) was added slowly in portions, with constant stirring, to 2 : 6-dimethyl-3-pyridazone (5·0 g.) dissolved in concentrated sulphuric acid (50 c.c.). The temperature was at first kept at *ca.* 20°, but when about half of the dichromate had been added the water-bath was removed, and the mixture allowed to warm slowly until the reaction commenced as indicated by the development of a green coloration. The cold water-bath was then replaced, and the addition of dichromate continued. Thereafter the temperature was raised to 70° for 1 hour. After cooling, the dark green viscous liquid was extracted with ether, the ethereal extract was washed with water and dried ($MgSO_4$), and the ether was evaporated. The white crystalline residue recrystallised from water formed feathery needles (0·2 g.), m. p. 239°. After some time the mixture of residues and washings deposited crystals which were collected and recrystallised from water, giving needles (0·5 g.), m. p. 239° alone or in admixture with the product from the ether extract. The 2-*methyl*-3-*pyridazone*-6-*carboxylic acid* had K, $6·3 \times 10^{-4}$ (Found: C, 46·3; H, 4·0; N, 18·3; equiv., 157·7. $C_6H_6O_3N_2$ requires C, 46·7; H, 3·9; N, 18·2%; equiv., 154).

The acid (0·2 g.) was heated on a water-bath under reflux, with 2% methyl-alcoholic hydrogen chloride for 6 hours. After neutralisation with barium carbonate, filtration, and evaporation of the filtrate under reduced pressure, the residue was extracted with chloroform. Evaporation of the chloroform extract and recrystallisation of the residue from ligroin (b. p. 60—80°) gave long needles of *methyl* 2-*methyl*-3-*pyridazone*-6-*carboxylate* (0·2 g.), m. p. 103°, alone or in admixture with the compound obtained below by methylation of methyl 3-pyridazone-6-carboxylate (Found: C, 49·8; H, 4·76. $C_7H_8O_3N_2$ requires C, 50·0; H, 4·76%).

Methyl 3-*Pyridazone*-6-*carboxylate.*—3-Pyridazone-6-carboxylic acid (see following paper) (6·0 g.) was heated under reflux for 6 hours with 2% methyl-alcoholic hydrogen chloride (100 c.c.). After the mixture had been kept overnight fine needles separated which, on filtration and recrystallisation from methyl alcohol, gave *methyl* 3-*pyridazone*-6-*carboxylate* (6·45 g.; 98%), m. p. 188° (Found: C, 47·0; H, 3·8; N, 18·7. $C_6H_6O_3N_2$ requires C, 46·7; H, 3·9; N, 18·2%).

Methyl 2-*Methyl*-3-*pyridazone*-6-*carboxylate.*—To methyl 3-pyridazone-6-carboxylate (4·0 g.) in dry methyl alcohol was added a dry methyl-alcoholic solution of sodium methoxide (1·4 g.) and methyl iodide (5 c.c.). The mixture was heated under reflux on a water-bath for 1 hour. The yellow solution was evaporated nearly to dryness under reduced pressure, water (about 20 c.c.) was added, and the mixture extracted with benzene. The benzene extract was dried ($MgSO_4$) and the solvent removed. A white crystalline solid remained which, recrystallised from ligroin (b. p. 60—80°), formed long needles of methyl 2-methyl-3-pyridazone-6-carboxylate (2·75 g.; 63·5%), m. p. 103°.

5-*Chloro*-2-*methyl*-3-*pyridazone*-6-*carboxylic Acid.*—2 : 6-Dimethyl-5-chloro-3-pyridazone (2·5 g.) was dissolved in concentrated sulphuric acid, and finely powdered potassium dichromate (11·16 g., 2·2 mols.) was added slowly at 0° with continuous stirring. When nearly half of the dichromate had been added the ice-bath was removed and the flask allowed to warm gradually. When the reaction began to progress too rapidly, the ice-bath was replaced and the rest of the dichromate added. The temperature was then raised to 60° for 1 hour, and the mixture cooled and extracted with ether. The ethereal extract was washed with water, dried ($MgSO_4$), and evaporated to dryness. The residue was recrystallised several times from acetone–ligroin (b. p. 40—60°), and was obtained in feathery needles (0·15 g.), m. p. 188°. The 5-*chloro*-2-*methyl*-3-*pyridazone*-6-*carboxylic acid* had K, $2·2 \times 10^{-3}$ (Found: C, 38·2; H, 2·8; N, 15·1; Cl, 19·7; equiv., 188·8. $C_6H_5O_3N_2Cl$ requires C, 38·2; H, 2·6; N, 14·9; Cl, 18·8%; equiv., 188·5).

4 : 5-*Dichloro*-2-*methyl*-3-*pyridazone* 6-*Carboxylic Acid.*—To 4 : 5-dichloro-2 : 6-dimethyl-3-pyridazone (2·5 g.) in concentrated sulphuric acid (15 c.c.) finely powdered potassium dichromate (7·7 g.) was slowly added, with continuous stirring. The reaction was allowed to proceed at room temperature with periodic cooling to prevent the reaction from becoming too vigorous. The mixture was then cooled to 0°, poured on crushed ice, and exhaustively extracted with ether. The extract was washed with water, dried ($MgSO_4$), and evaporated to dryness. Repeated recrystallisation of the residue from water gave 4 : 5-*dichloro*-2-*methyl*-3-*pyridazone*-6-*carboxylic acid* (0·5 g.); this had K, $2·5 \times 10^{-3}$, and m. p. 203—204° (Found: C, 32·4; H, 2·2; N, 12·4; Cl, 32·7; equiv., 228·0. $C_6H_4O_3N_2Cl_2$ requires C, 32·2; H, 1·8; N, 12·6; Cl, 31·8%; equiv., 223·0).

4 : 5-*Dichloro*-2-*methyl*-3-*pyridazone.*—(*a*) 4 : 5-Dichloro-2-methyl-3-pyridazone-6-carboxylic acid (0·5 g.) was heated to above its melting point; carbon dioxide was evolved and the product distilled and immediately solidified. Recrystallisation from aqueous alcohol gave 4 : 5-dichloro-2-methyl-3-pyridazone in quantitative yield, m. p. 90—91° (alone or in admixture with the product obtained in (*b*) below).

(*b*) Methylhydrazine sulphate (0·85 g.) was dissolved in water (10 c.c.) containing sodium hydroxide (0·24 g., 1 mol.), and mucochloric acid (1·0 g.), prepared according to the method of Simonis (*loc. cit.*), in ethyl alcohol (10 c.c.) was then added and the solution refluxed for 2 hours. On cooling, crystals of 4 : 5-*dichloro*-2-*methyl*-3-*pyridazone* separated (0·95 g.; 97%) and were collected and recrystallised from aqueous alcohol, m. p. 91° (Found: C, 33·4; H, 2·2; N, 15·6. $C_5H_4ON_2Cl_2$ requires C, 33·6; H, 2·2; N, 15·7%).

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