Pyridazines. Part IV.[1] Reaction of Alkoxydichloropyridazines and Dialkoxychloropyridazines with Amines

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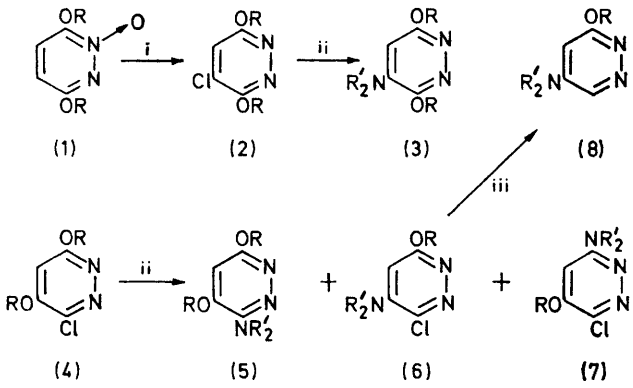
Nucleophilic attack by amines replaces chlorine in 3,6-dialkoxy-4-chloro- and 5- and 6-alkoxy-3,4-dichloropyridazines, but in 4-alkoxy-3,6-dichloro- and 4,6-dialkoxy-3-chloro-pyridazines replacement of an alkoxy-group may occur concurrently or preferentially.

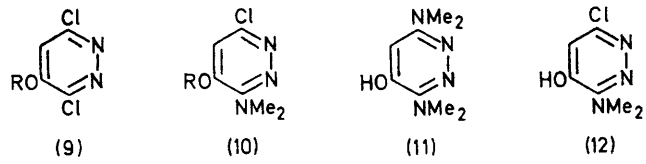
3,6-DIALKOXY-4-CHLOROPYRIDAZINES (2), which are conveniently made by reactions of 3,6-dialkoxypyridazine *N*-oxides (1) with phosphoryl chloride,[2] undergo normal nucleophilic displacements of chlorine by amines such as dimethylamine, piperidine, and morpholine giving 3,6-dialkoxy-4-dialkylaminopyridazines (3). The isomeric 4,6-dialkoxy-3-chloropyridazines (4), however, react with replacement either of chlorine (the main reaction) or of one or other of the alkoxy-groups. Thus compound (4; R = Bu) reacts with dimethylamine in methanol at 120° giving compounds (5)—(7) (R = Bu, R′ = Me). The structure of compound (6) was established by hydrogenolysis to give compound (8; R = Bu, R′ = Me), and its isomer (7; R = Bu, R′ = Me) has been obtained from 3,4-dichloro-6-dimethylaminopyridazine.[3] The reactions of compound (4; R = Bu) with morpholine and (4; R = EtO·[CH$_2$]$_2$) with dimethylamine also give mixtures, but only the dialkoxy-compounds (5) have been isolated in a pure state.



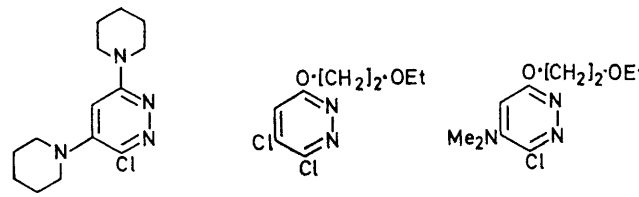
(1) (2) (3) (8) (4) (5) (6) (7)

Reagents: i, $POCl_3$; ii, R′$_2$NH; iii, H_2–Pd

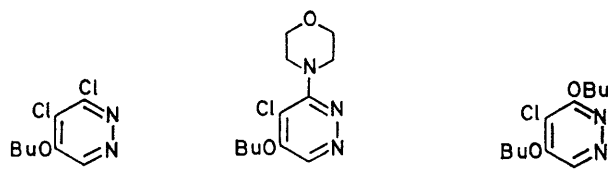
We have found that 3,4,6-trichloropyridazine, when treated with methanolic ammonia at room temperature, gives 3,6-dichloro-4-methoxypyridazine[4] (9; R = Me) whereas at temperatures above 100 °C the product is 4-amino-3,6-dichloropyridazine;[5] the latter compound is formed from (9; R = Me) and methanolic ammonia at higher temperatures (>100°). A similar displacement of an ethoxy-group in 3-chloro-4- or 5-ethoxypyridazine has been reported,[6] and Lederer[7] has found that (9; R = Me) with acetylsulphanilamide gave 4-*p*-acetamidophenylsulphonamido-3,6-dichloropyridazine. The reaction of compound (9; R = Me) with hydrazine in boiling methanol gives 3,6-dichloro-4-hydrazinopyridazine, which has also been obtained directly from 3,4,6-trichloropyridazine,[8] but with secondary aliphatic amines the main reactions are replacement of chlorine and



(9) (10) (11) (12)



(13) (14) (15)



(16) (17) (18)

demethylation. For example, compound (9; R = Me) when heated with dimethylamine in dry benzene at 120° gave 3-chloro-4-methoxy-6-dimethylaminopyridazine (7; R = R′ = Me), 6-chloro-4-methoxy-3-dimethylaminopyridazine (10; R = Me), 3,6-bis(dimethylamino)-4-hydroxypyridazine (11), 6-chloro-3-dimethylamino-4-hydroxypyridazine (12), and, probably, 3-chloro-6-dimethylamino-4-hydroxypyridazine. In the reaction of 4-butoxy-3,6-dichloropyridazine (9; R = Bu) with dimethylamine or morpholine dealkylation did not occur, and the products were the isomeric butoxychlorodimethylaminopyridazines (7; R = Bu, R′ = Me) and (10; R = Bu) and the analogous morpholinopyridazines. The reaction of compound (9; R = Me) with boiling piperidine, however,

[1] Part III, R. S. Fenton, J. K. Landquist, and Miss S. E. Meek, *J.C.S. Perkin I*, 1972, 2323.
[2] H. Igeta, *Chem. and Pharm. Bull.* (*Japan*), 1960, **8**, 368.
[3] R. S. Fenton, J. K. Landquist, and Miss S. E. Meek, *J. Chem. Soc.* (*C*), 1971, 1536.
[4] K. Eichenberger, R. Rometsch, and J. Druey, *Helv. Chim. Acta*, 1956, **39**, 1755; *cf.* T. Kuraishi, *Chem. and Pharm. Bull.* (*Japan*), 1958, **6**, 331.
[5] T. Kuraishi, *Pharm. Bull.* (*Japan*), 1956, **4**, 137.
[6] M. Yanai and T. Kinoshita, *J. Pharm. Soc. Japan*, 1962, **82**, 857.
[7] J. Lederer, *J. Org. Chem.*, 1961, **26**, 4462.
[8] T. Kuraishi, *Pharm. Bull.* (*Japan*), 1957, **5**, 376.

gave 4-hydroxy-3,6-dipiperidinopyridazine and 3-chloro-4,6-dipiperidinopyridazine (13). The structures of compounds (7), (10), and (12) were confirmed by reduction to the chlorine-free compounds.

Alkoxydichloropyridazines of two other series reacted with amines with substitution of a chlorine atom: 3,4-dichloro-6-(2-ethoxyethoxy)pyridazine (14) with dimethylamine gave the 4-dimethylamino-c ompound (15) and 5-butoxy-3,4-dichloropyridazine (16) with morpholine gave the 3-morpholino-derivative (17). Reduction of this gave 5-butoxy-3-morpholinopyridazine, which had also been obtained from (7; R = Bu, NR_2' = morpholino), thus confirming the structure of compound (16). With sodium butoxide compound (16) gave 3,5-dibutoxy-4-chloropyridazine (18). The reaction of 3,4,5-trichloropyridazine with 2 equiv. of sodium methoxide has been reported [9] to give both 3-chloro-4,5-dimethoxy- and 4-chloro-3,5-dimethoxy-pyridazine. It seems, therefore, that the reactions of compound (16) are controlled by steric hindrance, whereas (14) reacts at the position expected to give the most stable transition state. In the reactions of 4-alkoxy-3,6-dichloropyridazine (9) the nature of the attacking nucleophile is of greatest importance.

EXPERIMENTAL

3,6-Di-isopropoxypyridazine 1-Oxide (1; R = Pr^i).—3,6-Di-isopropoxypyridazine [10] (28 g) in chloroform (116 ml) was added to *m*-chloroperbenzoic acid (40 g) in chloroform (350 ml) and the mixture was stirred for 68 h; it was then concentrated, filtered from *m*-chlorobenzoic acid, and evaporated to dryness. The residual syrup was purified by chromatography on grade III alumina, with 7% methanol in chloroform as eluant, to give the *N*-oxide as a viscous oil (Found: C, 56·1; H, 7·5; N, 12·4. $C_{10}H_{16}N_2O_3$ requires C, 56·6; H, 7·6; N, 13·2%). Oxidation of 3,6-di-isopropoxypyridazine with hydrogen peroxide in acetic acid [11] (the method used for preparing other dialkyloxypyridazine *N*-oxides) gave mainly *3-isopropoxypyridazin-6(1H)-one*, m.p. 140—142° (from benzene) (Found: C, 54·9; H, 6·2; N, 17·9. $C_7H_{10}N_2O_2$ requires C, 54·5; H, 6·5; N, 18·2%), τ ($CDCl_3$) −2·4 (1H, s), 2·95 (2H, s), 4·95 (1H, q), and 8·65 (6H, d). A similar hydrolysis of 3,6-dibenzyloxypyridazine has been reported.[11]

3,6-Bis-(2-ethoxyethoxy)pyridazine 1-Oxide.— 3,6-Bis-(2-ethoxyethoxy)pyridazine [10] (26 g) was heated at 65—70° with glacial acetic acid (242 ml) and 30% hydrogen peroxide (52 ml). After 3 h, more hydrogen peroxide (26 ml) was added and heating was continued for 3 h. The solution was then evaporated under reduced pressure and the residue was neutralised with sodium hydrogen carbonate and extracted with chloroform. The extract was evaporated and the residual oil was shown by t.l.c. (silica GF; ethyl acetate) to consist of the *N*-oxide (R_F 0·16) and some unchanged bis-(2-ethoxyethoxy)pyridazine. It was purified by re-treatment with hydrogen peroxide–acetic acid and by column chromatography (alumina; 4 : 1 benzene–ethyl acetate) to give the *product* (22 g) as an oil (Found: C, 52·5; H, 7·6; N, 9·8. $C_{12}H_{20}N_2O_5$ requires C, 52·9; H, 7·4; N, 10·3%).

4-Chloro-3,6-diethoxypyridazine (2; R = Et).—3,6-Diethoxypyridazine 1-oxide (8·6 g) in chloroform (130 ml) was stirred and treated dropwise with phosphoryl chloride (17 ml) at 0°. The mixture was left at laboratory temp. for 4 h and was poured on to ice and neutralised with sodium carbonate. When hydrolysis of the excess of phosphoryl chloride was complete (3—4 h) the chloroform layer was separated, dried (Na_2SO_4), and evaporated. Crystallisation of the residue from aqueous ethanol gave the *chloro-compound* (6·5 g), m.p. 49° (Found: C, 47·4; H, 5·3; N, 13·6. $C_8H_{11}ClN_2O_2$ requires C, 47·4; H, 5·4; N, 13·8%).

The following were made similarly: *4-chloro-3,6-di-isopropoxypyridazine*, m.p. 19·5—22° [after chromatography on alumina (benzene–light petroleum)] (Found: C, 52·6; H, 6·6; Cl, 15·4; N, 12·1. $C_{10}H_{15}ClN_2O_2$ requires C, 52·1; H, 6·5; Cl, 15·4; N, 12·15%), τ ($CDCl_3$) 3·15 (1H, s), 4·7 (2H, m), and 8·6 (12H, 2d); *4-chloro-3,6-bis-(2-ethoxyethoxy)pyridazine*, m.p. 30·5—33° [from light petroleum (b.p. 30—40°)] (Found: C, 49·4; H, 6·5; N, 9·4. $C_{12}H_{19}ClN_2O_4$ requires C, 49·6; H, 6·5; N, 9·6%), τ ($CDCl_3$) 3·0 (1H, s), 5·5 (4H, m), 6·1—6·7 (8H, m), 8·8 (6H, t); *3,6-dibutoxy-4-chloropyridazine*, m.p. 13—14° [after chromatography on alumina (4 : 1 benzene–ethyl acetate)] (Found: C, 55·3; H, 7·4; N, 10·6. $C_{12}H_{19}ClN_2O_2$ requires C, 55·7; H, 7·3; N, 10·8%), τ ($CDCl_3$) 2·93 (1H, s), 5·35—5·6 (4H, m), 7·9—8·6 (8H, m), and 8·95 (6H, t). In an experiment in which the reaction mixture became acidic during hydrolysis of the phosphoryl chloride some of the product was hydrolysed to *6-butoxy-4-* or *5-chloropyridazin-3(2H)-one*, m.p. 155° (from cyclohexane) (Found: C, 47·6; H, 5·6; N, 13·7. $C_8H_{11}ClN_2O_2$ requires C, 47·4; H, 5·4; N, 13·8%), τ ($CDCl_3$) *ca.* −2 (1H), 2·9 (1H, s), 5·8 (2H, t), 8·1—8·8 (4H, m), and 9·03 (3H, t).

Reactions of 3,6-Dialkoxy-4-chloropyridazines with Amines.—4-Chloro-3,6-diethoxypyridazine (1 g) and morpholine (5 ml) were boiled under reflux for 2 h; excess morpholine was evaporated off under reduced pressure and the residue was shaken with aqueous sodium hydroxide and extracted with benzene. Evaporation of the extract gave *3,6-diethoxy-4-morpholinopyridazine*, m.p. 62—63° [from light petroleum (b.p. 60—80°)] (Found: C, 57·4; H, 7·7; N, 16·9. $C_{12}H_{19}N_3O_3$ requires C, 56·9; H, 7·6; N, 16·6%), τ ($CDCl_3$) 3·8 (1H, s), 5·5 (4H, m), 6·1 (4H, m), 6·8 (4H, m), and 8·6 (6H, 2t); *hydrochloride*, m.p. 144—145° (Found: C, 50·1; H, 6·9; N, 14·3. $C_{12}H_{19}N_3O_3$,HCl requires C, 49·7; H, 6·9; N, 14·5%).

The following were made similarly: *3,6-di-isopropoxy-4-morpholinopyridazine*, m.p. 102—104·5° [from light petroleum (b.p. 60—80°)] (Found: C, 59·9; H, 8·3; N, 15·1. $C_{14}H_{23}N_3O_3$ requires C, 59·8; H, 8·2; N, 14·9%), τ ($CDCl_3$) 4·0 (1H, s), 4·7 (2H, m), 6·25 (4H, m), 6·85 (4H, m), and 8·65 (12H, 2d); *3,6-dibutoxy-4-pyrrolidinopyridazine hydrochloride*, m.p. 138° (from butanone) (Found: C, 58·8; H, 8·9; N, 13·3. $C_{16}H_{27}N_3O_2$,HCl requires C, 58·3; H, 8·5; N, 12·75%); *3,6-bis-(2-ethoxyethoxy)-4-morpholinopyridazine hydrochloride*, m.p. 135° (from ethanol–ethyl acetate) (Found: C, 50·7; H, 7·4; Cl, 9·3; N, 11·1. $C_{16}H_{27}N_3O_5$,HCl requires C, 50·9; H, 7·4; Cl, 9·4; N, 11·1%); *3,6-bis-(2-ethoxyethoxy)-4-pyrrolidinopyridazine hydrochloride*, m.p. 109—111° (from ethyl acetate) (Found: C, 52·7; H, 7·5; Cl, 9·5; N, 11·9. $C_{16}H_{27}N_3O_4$,HCl requires C, 53·1; H, 7·75; Cl, 9·8; N, 11·6%); *3,6-bis-(2-ethoxyethoxy)-4-*

[9] T. Itai and S. Kamija, *Chem. and Pharm. Bull.* (*Japan*), 1963, **11**, 1059.

[10] J. Druey, Kd. Meier, and K. Eichenberger, *Helv. Chim. Acta*, 1954, **37**, 121.

[11] T. Itai and S. Sako, *Chem. and Pharm. Bull.* (*Japan*), 1961, **9**, 149.

piperidinopyridazine hydrochloride, m.p. 98·5—100·5° (from ethyl acetate) (Found: C, 53·4; H, 7·7; Cl, 9·3; N, 11·0. $C_{17}H_{29}N_3O_4$,HCl,0·5H_2O requires C, 53·0; H, 8·05; Cl, 9·2; N, 10·9%); *3,6-bis-(2-ethoxyethoxy)-4-(hexamethyleneimino)pyridazine hydrochloride*, m.p. 146—147° (from butanone) (Found: C, 55·1; H, 8·4; N, 10·8. $C_{18}H_{31}N_3O_4$,HCl requires C, 55·5; H, 8·2; N, 10·8%); *4-(2-diethylaminoethylamino)-3,6-bis-(2-ethoxyethoxy)pyridazine oxalate*, m.p. 112° (from butanone–ethyl acetate) (Found: C, 48·3; H, 6·9; N, 10·9. $C_{18}H_{34}N_4O_4$,2$C_2H_2O_4$ requires C, 48·0; H, 6·9; N, 10·2%); *dipicrate*, m.p. 108—114° (from ether) (Found: C, 43·9; H, 5·0; N, 17·0. $C_{18}H_{34}N_4O_4$,2$C_6H_3N_3O_7$ requires C, 43·5; H, 4·8; N, 16·9%).

3,6-Dibutoxy-4-chloropyridazine (4·6 g) and dimethylamine (3·6 g) in benzene (35 ml) were heated in a sealed tube at 100° for 6 h, and the solution was filtered from dimethylamine hydrochloride and was evaporated. The residual oil was treated with hydrogen chloride in ether to precipitate 3,6-dibutoxy-4-dimethylaminopyridazine hydrochloride (4·9 g), which was crystallised from ethanol–ethyl acetate and was identical with an authentic sample [1] (m.p. and mixed m.p. 145—146°; i.r. spectra).

3-Chloro-4,6-dimethoxypyridazine (4; R = Me).—Crude 5,6-dichloropyridazin-3-yltrimethylammonium chloride [3] (8·2 g) was added to a solution of sodium (1·9 g) in methanol (80 ml); the mixture was boiled under reflux for 1·5 h, filtered from sodium chloride, and evaporated. Chromatography of the residue on silica, with 4 : 1 benzene–ethyl acetate as eluant, gave the dimethoxy-compound, m.p. 110° (Found: C, 41·5; H, 4·0; N, 15·5. Calc. for $C_6H_7ClN_2O_2$: C, 41·3; H, 4·0; N, 16·0%). (Schönbeck and Kloimstein [12] recorded m.p. 95° for the material prepared from 3,4,6-trichloropyridazine and sodium methoxide.) Further elution of the chromatogram with ethanol gave 3,4,6-trimethoxypyridazine, m.p. 121°.

4,6-Dibutoxy-3-chloropyridazine was prepared similarly (reaction temp. 95—100°); m.p. 48—50° [from light petroleum (b.p. 40—60°)] (Found C, 55·5; H, 7·4; Cl, 14·4; N, 10·7. $C_{12}H_{19}ClN_2O_2$ requires C, 55·7; H, 7·3; Cl, 13·7; N, 10·8%), τ ($CDCl_3$) 3·65 (1H, s), 5·5 (2H, t), 5·9 (2H, t), and 8·1—9·2 (14H, m).

Reaction of 4,6-Dibutoxy-3-chloropyridazine with Dimethylamine.—4,6-Dibutoxy-3-chloropyridazine (3 g), dimethylamine (5·2 g), and methanol (25 ml) were heated in a sealed tube for 6 h at 120 °C. The solution was evaporated and the residue was extracted with benzene, leaving dimethylamine hydrochloride. The benzene-soluble material, chromatographed on a silica column, gave unchanged dibutoxychloropyridazine (1·3 g; eluted with benzene) and a mixture (eluted with benzene–ethyl acetate) that was separated by preparative t.l.c. (silica GF with 4 : 1 benzene–ethyl acetate) giving three main bands: (*a*) 6-butoxy-3-chloro-4-dimethylaminopyridazine (0·55 g), τ ($CDCl_3$) 3·8 (1H, s), 5·55 (2H, t), 7·0 (3H, s), and 8·1—9·15 (7H, m); *picrate*, m.p. 99—100·5° (Found: C, 41·8; H, 4·2; Cl, 7·4; N, 18·2. $C_{10}H_{16}ClN_3O$,$C_6H_3N_3O_7$ requires C, 41·9; H, 4·1; N, 18·3; Cl, 7·7%), which on hydrogenation over 5% palladium–carbon gave 3-butoxy-5-dimethylaminopyridazine hydrochloride,[3] m.p. and mixed m.p. 143°; (b) 4,6-dibutoxy-3-dimethylaminopyridazine (0·6 g), τ ($CDCl_3$) 3·8 (1H, s), 5·6 (2H, t), 6·0 (2H, t), 7·0 (6H, s), 8·0—9·2 (14H, m); *picrate*, m.p. 75—76° (Found: C, 48·7; H, 5·7; N, 16·7. $C_{14}H_{25}N_3O_2$,$C_6H_3N_3O_7$ requires C, 48·4; H, 5·7; N, 16·9%); and (c) 4-butoxy-3-chloro-6-dimethylaminopyridazine (0·05 g), spectroscopically identical with an authentic sample.[3]

Similarly, the reaction of 3-chloro-4,6-bis-(2-ethoxyethoxy)pyridazine [3] with methanolic dimethylamine at 120° and purification by column chromatography (silica; benzene–ethyl acetate) gave 3-dimethylamino-4,6-bis-(2-ethoxyethoxy)pyridazine, τ ($CDCl_3$) 3·7 (1H, s), 5·45 (m), 5·9 (m) and 6·1—6·65 (12H in all), 7·0 (6H, s), and 8·8 (6H, t); *picrate*, m.p. 89—93° (Found: C, 45·1; H, 5·3; N, 16·0. $C_{14}H_{25}N_3O_4$,$C_6H_3N_3O_7$ requires C, 45·45; H, 5·3; N, 15·9%).

4,6-Dibutoxy-3-morpholinopyridazine.— 4,6-Dibutoxy-3-chloropyridazine (5 g) and dry morpholine (6·7 ml) were boiled under reflux for 3 h and the excess of morpholine was evaporated off under reduced pressure. The residue was extracted repeatedly with boiling light petroleum (b.p. 60—80°), the extracts were evaporated, and the oily product was purified by chromatography (alumina; 10 : 1 benzene–ethyl acetate) to give the *morpholino-compound*, m.p. 80—82·5° [from light petroleum (b.p. 40—60°)] (Found: C, 62·4; H, 8·8; N, 13·6. $C_{16}H_{27}N_3O_3$ requires C, 62·1; H, 8·8; N, 13·6%), τ ($CDCl_3$) 3·8 (1H, s), 5·6 (2H, t), 6·05 (2H, t), 6·2 (4H, t), 6·6 (4H, t), 8·0—8·7 (8H, m), and 9·05 (6H, t); *hydrochloride*, m.p. 122·5—124° (Found: C, 55·5; H, 8·1; Cl, 10·1; N, 12·5. $C_{16}H_{27}N_3O_3$,HCl requires C, 55·6; H, 8·1; Cl, 10·3; N, 12·2%). If the morpholine was not dried rigorously the product was *4-butoxy-3-morpholinopyridazin-6(1H)-one*, m.p. 168—170° (from water) (Found: C, 56·4; H, 7·6; N, 17·0. $C_{12}H_{19}N_3O_3$ requires C, 56·9; H, 7·6; N, 16·6%), τ ($CDCl_3$)—1·65 (1H), 3·85 (1H, s), 5·85—6·3 (6H, m), 6·8 (4H, m), 8—9·2 (7H, m). The alternative 6-butoxypyridazin-4-one structure was excluded [13] by the strong i.r. carbonyl band at 1655 cm^{-1}.

Reaction of 3,4,6-Trichloropyridazine with Methanolic Ammonia.—3,4,6-Trichloropyridazine (5 g) and methanolic ammonia (40 ml; saturated at 0° C) were mixed and left at room temperature for 4 days. The crystalline products (1·4 g) were filtered off and crystallised from benzene–light petroleum (b.p. 60—80°) giving ammonium chloride (0·45 g; insoluble) and 3,6-dichloro-4-methoxypyridazine (9; R = Me) (0·8 g), m.p. 130° (lit.,[4] 130—131°) (Found: C, 33·6; H, 2·7; N, 15·6. Calc. for $C_5H_4Cl_2N_2O$: C, 33·5; H, 2·2; N, 15·6%). At 105° (sealed tube) the same reaction mixture gave 4-amino-3,6-dichloropyridazine, m.p. 206—207° (from ethanol–water) (lit.,[12] 205°), and at 65° a mixture of amino- and methoxy-compounds was obtained. 3,6-Dichloro-4-methoxypyridazine (1 g), heated with methanolic ammonia (10 ml) at 105° for 5 h, gave 4-amino-3,6-dichloropyridazine; further treatment of this compound with methanolic ammonia (180° for 8 h) did not achieve further substitution.

3,6-Dichloro-4-hydrazinopyridazine.— 3,6-Dichloro-4-methoxypyridazine (5 g) and hydrazine hydrate (2·8 g) in methanol (35 ml) were boiled under reflux for 0·5—1 h. The solution was cooled and the hydrazino-compound (4 g), m.p. 195—197° (decomp.), was filtered off. Identical material was obtained from 3,4,6-trichloropyridazine and hydrazine in ethanol.[8] Repeated crystallisation from methanol raised the decomposition point to 213° (Found: C, 26·7; H, 2·3; Cl, 39·6; N, 31·0. Calc. for $C_4H_4Cl_2N_4$: C, 26·8; H, 2·2; Cl, 39·7; N, 31·3%).

Reaction of 3,6-Dichloro-4-methoxypyridazine (9; R = Me) *with Amines.*—(*a*) 3,6-Dichloro-4-methoxypyridazine (20 g)

[12] R. Schönbeck and E. Kloimstein, *Monatsh.*, 1968, **99**, 15.
[13] A. R. Katritzky and P. J. Taylor, 'Physical Methods in Heterocyclic Chemistry,' vol. 4, Academic Press, London and New York, 1971, p. 363.

and dimethylamine (12·5 g) in benzene (100 ml) were heated at 120° for 6 h (sealed tubes). The solid product was filtered off and treated with water, and the insoluble material (4·2 g) was crystallised from ethanol to give *6-chloro-3-dimethylamino-4-hydroxypyridazine* (10; R = H), plates, m.p. 239—244° (Found: C, 41·7; H, 4·7; Cl, 20·5; N, 23·7. $C_6H_8ClN_3O$ requires C, 41·5; H, 4·6; Cl, 20·4; N, 24·2%). The aqueous extract was made alkaline (pH 11) with potassium hydroxide and was concentrated until a solid (A) (2·6 g) separated. The solution was then extracted with ether and the extract was evaporated, giving an oil (B) (4 g). The benzene filtrate from the reaction mixture was evaporated and the residual oil (8 g) was extracted with cold water, leaving *3-chloro-6-dimethylamino-4-methoxypyridazine* (7; R = R′ = Me) (2·7 g), m.p. 159—160° (from water) (Found: C, 44·8; H, 5·6; Cl, 18·4; N, 22·1. $C_7H_{10}ClN_3O$ requires C, 44·8; H, 5·3; Cl, 18·9; N, 22·4%), τ ($CDCl_3$) 3·9 (1H, s), 6·1 (3H, s), and 6·85 (6H, s). The aqueous extract was made strongly alkaline with potassium hydroxide and was extracted eith ether, and the extract was evaporated. The residue (2·7 g) was combined with the oil (B) and was separated by column chromatography (alumina; benzene–ethyl acetate) into *6-chloro-3-dimethylamino-4-methoxypyridazine* (10; R = Me) (3·3 g), m.p. 70—71·5° (from cyclohexane) (Found: C, 45·0; H, 5·6; Cl, 19·0; N, 22·0%), τ ($CDCl_3$) 3·3 (1H, s), 6·1 (3H, s), and 6·9 (6H, s), and compound (7; R = R′ = Me). The solid (A) was extracted with dilute potassium hydroxide solution, leaving compound (7; R = R′ = Me) (0·5 g), and the extract was neutralised with hydrochloric acid and evaporated to give a solid (*ca.* 2 g), m.p. 218—223°, that appeared to be a mixture of 3-chloro-6-dimethylamino-4-hydroxypyridazine and 3,6-bis(dimethylamino)-4-hydroxypyridazine (analysis and n.m.r.). Attempts to separate these compounds were unsuccessful, and the mixture was treated with dimethylamine in ethanol (140°; 6 h) to give *3,6-bis(dimethylamino)-4-hydroxypyridazine* (11), m.p. 247—250° (from water) (Found: C, 52·9; H, 8·0; N, 30·8. $C_8H_{14}N_4O$ requires C, 52·7; H, 7·7; N, 30·75%), τ [$(CD_3)_2SO$] −1·5 (1H), 4·6 (1H, s), and 7·1 (12H, s). This compound was also obtained from 3,6-dichloro-4-hydroxypyridazine [12] (0·8 g) and dimethylamine (2·6 g) in benzene (25 ml) heated at 140° for 6 h.

(*b*) 3,6-Dichloro-4-methoxypyridazine (2 g) and piperidine (10 ml) were boiled under reflux for 3·5 h; the mixture was cooled and filtered, and the solid product was washed with benzene. Treatment of this product with water and crystallisation from ethanol gave *4-hydroxy-3,6-dipiperidinopyridazine*, m.p. 303° (decomp.) (Found: C, 63·9; H, 8·4; N, 20·9. $C_{14}H_{22}N_4O$ requires C, 64·1; H, 8·45; N, 21·4%), τ ($CF_3{\cdot}CO_2H$) 2·65 (1H, s), 5·9—6·3 (8H, m), and 7·5—8·3 (12H, m). The filtrate from the reaction mixture and the benzene washings were evaporated and the residue was purified by chromatography (alumina; 4 : 1 benzene–ethyl acetate) giving *3-chloro-4,6-dipiperidinopyridazine* (13) (0·6 g), m.p. 105—107° (from aqueous ethanol) (Found: C, 59·4; H, 7·3; Cl, 12·8; N, 19·9. $C_{14}H_{21}ClN_4$ requires C, 59·9; H, 7·5; Cl, 12·65; N, 20·0%), τ ($CDCl_3$) 3·78 (1H, s), 6·4 (4H, m), 6·85 (4H, m), and 8·05—8·5 (12H, m). Hydrogenation of this compound over 5% palladium–carbon in ethanol gave *3,5-dipiperidinopyridazine hydrochloride*, m.p. 215—217° (Found: C, 59·1; H, 8·0; Cl, 12·2; N, 19·5. $C_{14}H_{22}N_4$,HCl requires C, 59·5; H, 8·1; Cl, 12·6; N, 19·8%), τ ($CDCl_3$) 1·85 (1H, d), 3·8 (1H, d, *J* 2·5 Hz), 6·0—6·5 (8H), and 8·25 (12H).

3,4-Dichloro-6-dimethylaminopyridazine (3 g) and sodium methoxide [from sodium (0·36 g)] in methanol (25 ml) were boiled under reflux for 6 h and the solution was evaporated. The residue was extracted with ethyl acetate, giving 3-chloro-6-dimethylamino-4-methoxypyridazine (1·9 g), m.p. 159—160°. Hydrogenation of this over 5% palladium–carbon in ethanol gave *3-dimethylamino-5-methoxypyridazine hydrochloride*, m.p. 167—168° (Found: C, 44·4; H, 6·3; Cl, 18·6; N, 21·9. $C_7H_{11}N_3O$,HCl requires C, 44·4; H, 6·35; Cl, 18·7; N, 22·2%), τ [$(CD_3)_2SO$] 1·75 (1H, d), 3·05 (1H, d, *J* 2·7 Hz), 6·0 (3H, s), and 6·7 (6H, s). Similarly, hydrogenation of 6-chloro-3-dimethylamino-4-methoxypyridazine gave *3-dimethylamino-4-methoxypyridazine hydrochloride*, m.p. 138—139° (Found: C, 44·3; H, 6·7; Cl, 18·5; N, 22·1%), τ ($CDCl_3$) 1·15 (1H, d), 2·3 (1H, d, *J* 6 Hz), 5·7 (3H, s), and 6·7 (6H, s). Hydrogenation of 6-chloro-3-dimethylamino-4-hydroxypyridazine over 5% palladium–carbon in glacial acetic acid gave a product that approximated in composition to a hemihydrochloride of 3-dimethylamino-4-hydroxypyridazine, m.p. 140—143° (from butanone) (Found: C, 44·5; H, 5·9; Cl, 11·8; N, 26·2. $C_6H_9N_3O$,0·5HCl requires C, 45·8; H, 6·0; Cl, 11·3; N, 26·7%), τ [$(CD_3)_2SO$] 1·65 (1H, d), 3·3 (1H, d, *J* 7 Hz), and 6·95 (6H, s).

Reactions of 4-Butoxy-3,6-dichloropyridazine with Amines.—(*a*) 4-Butoxy-3,6-dichloropyridazine (14 g) and dimethylamine (8·5 g) in benzene (60 ml) were heated in sealed tubes at 120° for 6 h. The solution was filtered from dimethylamine hydrochloride and was evaporated. Chromatography of the residual oil on alumina, with benzene and then benzene–ethyl acetate as eluants, gave *6-chloro-4-butoxy-3-dimethylaminopyridazine* (5·4 g), m.p. 45—47° [from light petroleum (b.p. 40—60°)] (Found: C, 52·1; H, 7·0; Cl, 15·5; N, 18·0. $C_{10}H_{16}ClN_3O$ requires C, 52·3; H, 6·95; Cl, 15·5; N, 18·3%), τ ($CDCl_3$) 3·35 (1H, s), 5·95 (2H, t), 6·9 (6H, s), and 8·0—9·1 (7H, m), and then 4-butoxy-3-chloro-6-dimethylaminopyridazine (5·7 g), m.p. and mixed m.p. 58—59°.

(*b*) 4-Butoxy-3,6-dichloropyridazine (2 g) and morpholine (4 ml) were heated on a steam-bath for 0·5 h; the mixture was diluted with benzene and filtered from morpholine hydrochloride (1·2 g). The filtrate was evaporated and the residue was extracted repeatedly with boiling light petroleum (b.p. 60—80°), leaving *4-butoxy-3-chloro-6-morpholinopyridazine* (0·8 g), m.p. 134—135·5° (from cyclohexane) (Found: C, 53·2; H, 6·6; Cl, 13·0; N, 15·6. $C_{12}H_{18}ClN_3O_2$ requires C, 53·0; H, 6·6; Cl, 13·1; N, 15·5%). The combined extracts were evaporated and the residue was purified by chromatography (alumina; benzene–ethyl acetate) to give *4-butoxy-6-chloro-3-morpholinopyridazine* (0·25 g), m.p. 77—78° [from light petroleum (b.p. 40—60°)] (Found: C, 53·2; H, 6·5; Cl, 13·1; N, 15·2%), and a mixed fraction (1 g) containing both isomers.

Hydrogenation of 4-butoxy-3-chloro-6-morpholinopyridazine over 5% palladium–carbon in ethanol gave *5-butoxy-3-morpholinopyridazine hydrochloride*, m.p. 154·5—156° (from butanone) (Found: C, 52·8; H, 7·4; Cl, 12·8; N, 15·2. $C_{12}H_{19}N_3O_2$,HCl requires C, 52·65; H, 7·3; Cl, 13·0; N, 15·35%), τ ($CDCl_3$) 1·95 (1H, d), 2·65 (1H, d, *J* 2·5 Hz), 5·35—6·2 (10H), and 7·95—9·15 (7H).

3-Chloro-4-dimethylamino-6-(2-ethoxyethoxy)pyridazine (15).—3,4-Dichloro-6-(2-ethoxyethoxy)pyridazine [3] (3·4 g) in dry benzene (20 ml) was treated during 3 h with a slow stream of dimethylamine. The temperature rose to 40° and then fell. The solution was filtered from dimethylamine hydrochloride and was evaporated, and the crude dimethylamino-compound (3·6 g) was purified by chromatography

(alumina; benzene–ethyl acetate) and was isolated as the *hydrochloride*, m.p. 144° (from butanone) (Found: C, 43·2; H, 5·9; Cl^-, 12·3; N, 14·8. $C_{10}H_{16}ClN_3O_2$,HCl requires C, 42·6; H, 6·0; Cl^-, 12·6; N, 14·9%). Hydrogenation of this compound gave *5-dimethylamino-3-(2-ethoxyethoxy)-pyridazine hydrochloride*, m.p. 136·5—138·5 (from butanone) (Found: C, 48·2; H, 7·3; Cl, 14·3; N, 16·8. $C_{10}H_{17}N_3O_2$,HCl requires C, 48·5; H, 7·3; Cl, 14·3; N, 17·0%), τ ($CDCl_3$) 1·4 (1H, d), 3·5 (1H, d, *J* 2·5 Hz), 5·3 (2H, m), 6·2 (2H, m), 6·45 (2H, q), 6·7 (6H, s), and 8·8 (3H, t).

Reactions of 5-Butoxy-3,4-dichloropyridazine (16) (experiments by R. S. Fenton).—3,4,5-Trichloropyridazine (2·0 g) was boiled under reflux with a solution of sodium (0·25 g) in butanol (25 ml). After 5 h the solution was evaporated under reduced pressure and the residue was crystallised three times from light petroleum (b.p. 60—80°) to give *5-butoxy-3,4-dichloropyridazine*, m.p. 49—51° (Found: C, 43·5; H, 4·6; N, 12·6. $C_8H_{10}Cl_2N_2O$ requires C, 43·4; H, 4·5; N, 12·7%).

5-Butoxy-3,4-dichloropyridazine (0·5 g) and morpholine (10 ml) were heated on a steam-bath for 24 h, and the solution was then evaporated under reduced pressure. The residue was extracted with boiling light petroleum (b.p. 80—100°); the extract was evaporated, and the residual oil was purified by chromatography (silica; benzene–ethyl acetate), giving *5-butoxy-4-chloro-3-morpholinopyridazine* (17) (0·16 g), m.p. 73—74° (from light petroleum) (Found: C, 53·0; H, 6·7; N, 15·4. $C_{12}H_{18}ClN_3O_2$ requires C, 53·0; H, 6·6; N, 15·5%). Hydrogenation gave 5-butoxy-3-morpholinopyridazine hydrochloride, identical with the material already described.

3,5-Dibutoxy-4-chloropyridazine (18).—3,4,5-Trichloropyridazine (15 g) in xylene (40 ml) was added to a dispersion of sodium butoxide [from sodium (1·9 g) and butanol (8 ml)] in boiling xylene (100 ml). The mixture was stirred and refluxed for 12 h and the xylene was evaporated off; t.l.c. showed that unchanged trichloropyridazine was present. More sodium butoxide [sodium (2·0 g), butanol (100 ml)] was added and heating was continued for 5 h; the butanol was evaporated off and the residue was dissolved in water and extracted with chloroform. The chloroform-soluble material was purified by chromatography (alumina; benzene), giving a little *5-butoxy-4-chloropyridazin-3(2H)-one*, m.p. 203° (from ethyl acetate) (Found: C, 47·3; H, 5·5; Cl, 17·4; N, 14·1. $C_8H_{11}ClN_2O_2$ requires C, 47·4; H, 5·4; Cl, 17·5; N, 13·8%), and then 3,5-dibutoxy-4-chloropyridazine (12 g), an oil giving a solid *hydrochloride*, m.p. 114—118° (from butanone) (Found: C, 49·2; H, 6·8; N, 9·7. $C_{12}H_{19}ClN_2O_2$,HCl requires C, 48·8; H, 6·8; N, 9·5%), τ ($CDCl_3$) 0·3 (1H, s), 5·4 (4H, q), and 7·9—9·2 (14H, m). Hydrogenation of the dibutoxy-compound gave *5-butoxypyridazin-3(2H)-one*, m.p. 158° [from light petroleum (b.p. 80—100°)] (Found: C, 56·8; H, 7·1; N, 16·3. $C_8H_{12}N_2O_2$ requires C, 57·1; H, 7·2; N, 16·7%), τ ($CDCl_3$) 2·45 (1H, d), 3·9 (1H, d, *J* 3 Hz), 6·05 (2H, t), and 8—9·1 (7H, m), $\nu_{max.}$ (Nujol) 1660s, 1615ms, and 1555w cm^{-1} (confirming [13] the pyridazin-3-one structure).

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