Pyridazines. Part V.[1] Preparation and Reactions of some Dialkylaminopyridazinones

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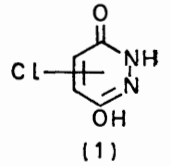
Reactions of 4(5)-chloro-6-hydroxypyridazin-3(2*H*)-one and of 4,5-dichloro- and 4,5,6-trichloropyridazin-3(2*H*)-ones with amines are described. 6-Butoxy-4- and 5-morpholinopyridazin-3(2*H*)-ones are obtained by alkylation of 6-hydroxy-4(or 5)-morpholinopyridazin-3(2*H*)-one and also from 6-butoxy-4- and 5-chloropyridazin-3(2*H*)-ones. They are *O*-alkylated by Meerwein's reagent.

DIALKOXYDIALKYLAMINOPYRIDAZINES have been investigated as anaesthetics,[2] and earlier papers in this series have described their preparation from polychloro-compounds by successive nucleophilic replacements. Alternative methods of preparation avoiding the use of tri- or tetra-chloropyridazines are based on dialkylaminopyridazinones, which are obtained by reaction of chloropyridazinones with amines. For example, 'chloromaleic hydrazide' [4- or 5-chloro-6-hydroxypyridazin-3(2*H*)-one] (1), when heated with aliphatic or cyclic secondary amines, affords 4- or 5-(substituted amino)-6-hydroxypyridazin-3(2*H*)-ones (2), which may be converted into the corresponding 4-amino-3,6-dichloropyridazines (3) by treatment with phosphoryl chloride.

Monoalkylation of 6-hydroxy-4(or 5)-morpholinopyridazin-3(2*H*)-one (4), with butyl bromide and sodium hydride in dimethylformamide, gave a mixture of the butoxypyridazinones (5) and (6), together with a small amount of an isomeric *N*-butyl derivative. A similar mixture of products was obtained when thallium(I) ethoxide was used as the base. The structures of the butoxy-compounds were assigned by converting (5) into 3-butoxy-6-chloro-4-morpholinopyridazine by treatment with phosphoryl chloride. Further evidence is supplied by the n.m.r. spectra, which show the aromatic proton next to the carbonyl group in compound (5) to be more deshielded than the aromatic proton in compound (6). Compound (5) and the analogous propoxy-compound have been isolated as by-products in the preparation of 3,6-dibutoxy(propoxy)-4-morpholinopyridazine hydrochlorides by the method described in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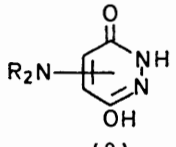
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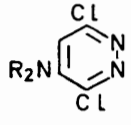
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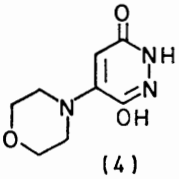
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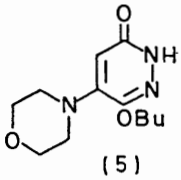
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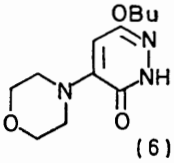
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Part III,[3] and they are thought to arise from the acid-catalysed hydrolysis of the dialkoxy-compounds.

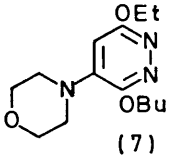
Alkylation of (5) and (6) by triethyloxonium fluoroborate gave the ethoxy-derivatives (7) and (8); the preparation of such compounds by successive replacements of chlorine in polychloro-compounds is not practicable because of the exchangeability of 3- and 6-alkoxy-groups.[3] Alkylation of 6-alkoxypyridazin-3(2*H*)-ones with less electrophilic alkylating agents gives *ON*-dialkyl derivatives.

During the preparation of 3,6-dibutoxy-4-chloropyridazine (9) from 3,6-dibutoxypyridazine 1-oxide, a

[1] Part IV, J. K. Landquist and Miss S. E. Meek, *J.C.S. Perkin I*, 1972, 2735.
[2] I.C.I. Limited, Belg.P. 770,569.
[3] R. S. Fenton, J. K. Landquist, and Miss S. E. Meek, *J.C.S. Perkin I*, 1972, 2323.

butoxychloropyridazinone of m.p. 155° was isolated.[1] This compound (10) and its isomer (11) have been obtained by hydrolysis of (9) by hydrogen chloride in acetic acid. When the hydrolysis was carried out with hydrogen bromide in acetic acid, appreciable amounts of the corresponding bromobutoxypyridazinones were formed and were identified by mass spectrometry. The structures of (10) and (11) were established by their ready conversion into (5) and (6), respectively, by treatment with morpholine.

Reaction of amines with 4,5-dichloropyridazin-3(2*H*)-one (12; R = H) usually occurs only at the 5-position, *e.g.* with dimethylamine only compound (14) was formed. However, 4,5-dichloro-2-(3,4-dichloro-2,5-dihydro-5-oxo-2-furyl)pyridazin-3(2*H*)-one (13) reacted with dimethylamine with cleavage of the furyl residue and formation of the isomeric chlorodimethylaminopyridazinones (14) and (15).[4] The *N*-methyl compound (12; R = Me) with dimethylamine also gave two isomeric chlorodimethylamino-compounds. Takahashi *et al.*[5] reported only one of these isomers, which they identified as (16) by an independent synthesis of its reduction product, 5-dimethylamino-2-methylpyridazin-3(2*H*)-one. The n.m.r. spectrum of the latter compound confirms this assignment.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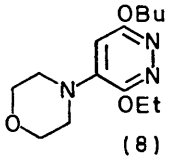
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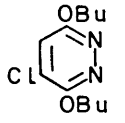
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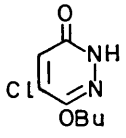
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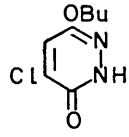
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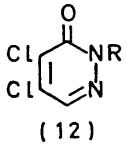
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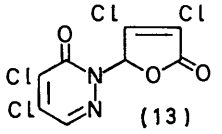
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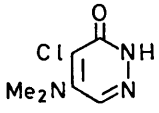
Morpholine also caused cleavage and substitution of compound (13), but the only pyridazine fragment was 4-chloro-5-morpholinopyridazin-3(2*H*)-one. This has also been obtained from (12; R = H).[6] It was hydrogenolysed to give 5-morpholinopyridazin-3(2*H*)-one, and was converted by phosphoryl chloride into 3,4-dichloro-5-morpholinopyridazine. Reaction of (15) with phosphoryl chloride gave 3,5-dichloro-4-dimethylaminopyridazine (17) together with some 3,4,5-trichloropyridazine. Both chlorine atoms in (17) were replaced by the action of sodium butoxide.

4,5,6-Trichloropyridazin-3(2*H*)-one (18) with dimethylamine gave two isomeric dichlorodimethylaminopyridazinones which were identified as the 5- and 4-dimethylamino-compounds (19) and (20) by hydrogenolysis to the chlorine-free compounds. These had also been obtained from (14) and (15).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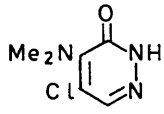
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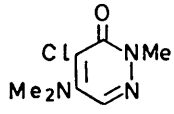
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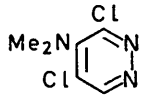
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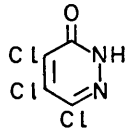
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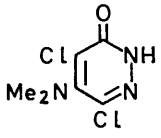
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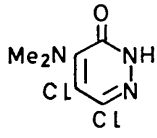
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EXPERIMENTAL

Reaction of Amines with Chloropyridazinones.—(*a*) ' Chloromaleic hydrazide ' (3 g) and piperidine (5 ml) were boiled under reflux for 1·5 h. The mixture was cooled and was triturated with dilute hydrochloric acid and the 6-*hydroxy*-4(*or* 5)-*piperidinopyridazin*-3(2H)-*one* (3·2 g) was filtered off, washed with water, and crystallised from dimethylformamide. Compounds made in this manner are shown in the Table (diethylamine required a sealed tube to permit a reaction temp. of 100°).

(*b*) 4,5-Dichloro-2-methylpyridazin-3(2*H*)-one (1 g) and dimethylamine (1·5 g) in benzene (8 ml) were left in a closed flask at room temperature for several months. The solution was then filtered from dimethylamine hydrochloride (0·27 g) and was evaporated. The residual oil (1·1 g) was rubbed with light petroleum (b.p. 40—60°) and the solid (0·37 g; m.p. 67—73°) was collected. Crystallisation from cyclohexane gave 4-chloro-5-dimethylamino-2-methylpyridazin-3(2*H*)-one (16), m.p. 74—75° (lit.,[5] 75—76°) (Found: C, 44·8; H, 5·2; N, 22·2. Calc. for $C_7H_{10}ClN_3O$: C, 44·8; H, 5·3; N, 22·4%). The petrol-soluble fraction was purified by chromatography on alumina; elution with benzene gave 5-*chloro*-4-*dimethylamino*-2-*methylpyridazin*-3(2H)-*one* (0·44 g), m.p. 31·5—32·5° (Found: C, 45·3; H, 5·2; Cl, 18·8; N, 22·4. $C_7H_{10}ClN_3O$ requires C, 44·8; H, 5·3; Cl, 18·9; N, 22·9%). Further elution, with benzene–ethyl acetate (4 : 1), gave more of (16) (0·13 g). The isomers were distinguished by t.l.c. [silica GF; benzene–ethyl acetate (4 : 1); R_F 0·09 and 0·3]; the n.m.r. spectra were almost identical: τ ($CDCl_3$) 2·45 (1H, s), 6·25 (3H, s), and 6·85 (6H, s). Hydrogenation of (16) over 5% Pd–C in ethanol gave crude 5-dimethylamino-2-methylpyridazin-3(2*H*)-one hydrochloride, τ ($CDCl_3$) 2·15 (1H, d), 3·2 (1H, d, *J* 3 Hz), 6·25 (3H, s), and 6·9 (6H, s).

(*c*) 4,5-Dichloro-2-(3,4-dichloro-2,5-dihydro-5-oxo-2-furyl)pyridazin-3(2*H*)-one [4] (3·8 g) dissolved in dry benzene

[4] J. K. Landquist and Miss S. E. Meek, *Chem. and Ind.*, 1970, 688.

[5] T. Takahashi, Y. Maki, H. Kizu, M. Takaya, and T. Miki, *J. Pharm. Soc. (Japan)*, 1966, **86**, 1168.

[6] J. Bourdais, *Bull. Soc. chim. France*, 1969, 2124.

(50 ml) was treated with morpholine (16·75 ml). After 24 h the solution was filtered from morpholine hydrochloride (2·8 g) and was evaporated. The residue was extracted with water and the solid product (1·9 g) was crystallised from ethanol, giving 4-chloro-5-morpholinopyridazin-3(2*H*)-one (1·3 g), m.p. 230° (lit.,[6] 229°) (Found: C, 43·9; H, 4·3; N, 19·7. Calc. for $C_8H_{10}ClN_3O_2$: C, 44·5; H, 4·6; N, 19·5%). The aqueous extract was evaporated to small bulk and was made alkaline with potassium hydroxide to precipitate 3-*chloro*-2,5-*dihydro*-4,5-*dimorpholinofuran*-2-*one* (0·9 g), m.p. 197·5—199° (from ethyl acetate) (Found: C, 49·9; H, 5·9; Cl, 12·3; N, 9·7. $C_{12}H_{17}ClN_2O_4$ requires C, 49·9; H, 5·9; Cl, 12·3; N, 9·7%).

(*d*) 4,5,6-Trichloropyridazin-3(2*H*)-one[7] (4 g) and dimethylamine (18 g) in ethanol (50 ml) were boiled under reflux for 4 h and the solution was evaporated to dryness. The residue was extracted with ethyl acetate, leaving dimethylamine hydrochloride, and the soluble products (4 g) were separated by chromatography on silica. Elution with toluene–ethyl acetate (4 : 1) containing 4% triethylamine gave first 5,6-*dichloro*-4-*dimethylaminopyridazin*-3(2H)-*one* (1·3 g), m.p. 200° (from ethanol) (Found: C, 34·7; H, 3·4; Cl, 34·3; N, 20·5. $C_6H_7Cl_2N_3O$ requires C, 34·6; H, 3·4; Cl, 34·1; N, 20·2%), then a mixture (1·5 g), and then 4,6-*dichloro*-5-*dimethylaminopyridazin*-3(2H)-*one* (19) (1·1 g), m.p. 205° (from ethanol) (Found: C, 34·8; H, 3·4; Cl, 33·9; N, 19·9%). Reaction of 4,5-dichloropyridazin-3(2*H*)-one with dimethylamine in ethanol (room temperature, overnight) gave only 4-chloro-5-dimethylaminopyrazin-3(2*H*)-one (14), m.p. 203°.[4]

Hydrogenation of compound (20) over 5% Pd–C in ethanol gave 4-dimethylaminopyridazin-3(2*H*)-one, identical with an authentic sample[4] (n.m.r., t.l.c., and mixed m.p.). Similarly, hydrogenation of compound (19) gave 5-*dimethylaminopyridazin*-3(2H)-*one hydrochloride*, m.p. *ca.* 235° (decomp.) (Found: C, 40·2; H, 5·6; Cl, 19·9; N, 23·8. $C_6H_7N_3O$,HCl requires C, 41·0; H, 5·7; Cl, 20·2; N, 23·9%), τ [$(CD_3)_2SO$] 1·68 (1H, d), 3·75 (1H, d, *J* 3 Hz), and 6·9 (6H, s). This compound was also obtained by hydrogenating 4-chloro-5-dimethylaminopyridazin-3(2*H*)-one.[4]

Alkylation of 6-*Hydroxy*-4(*or* 5)-*morpholinopyridazin*-3(2H)-*one*.—Sodium hydride (60% dispersion; 1·2 g) was washed with light petroleum (b.p. 60—80°) under nitrogen, 6-hydroxy-4(or 5)-morpholinopyridazin-3(2*H*)-one (5 g) in dimethylformamide (40 ml) was added, and the mixture was stirred at room temperature for 1·5 h. n-Butyl bromide (4·2 g) was added and the mixture was heated on a steam-bath under nitrogen for 8 h. The solid which separated on cooling was dissolved in chloroform and washed with water and saturated sodium chloride solution. Evaporation of the dried (Na_2SO_4) solution gave 6-*butoxy*-5-*morpholinopyridazin*-3(2H)-*one* (2·5 g), m.p. 221—222° (from benzene) (Found: C, 56·9; H, 7·4; N, 16·6. $C_{12}H_{19}N_3O_3$ requires C, 56·9; H, 7·5; N, 16·6%), τ [$CDCl_3$] 3·96 (1H, s), 5·78 (2H, t), 6·13 (4H, m), and 6·73 (4H, m); $\nu_{max.}$ ($CHCl_3$) 1645vs and 1595ms cm^{-1}. The filtrate from the reaction was evaporated at 55° under reduced pressure and the residue was extracted with chloroform, leaving an insoluble residue of starting material (550 mg). The chloroform solution was washed with dilute sodium hydroxide solution. The sodium hydroxide layer was extracted with chloroform and the combined chloroform solutions were washed with water, dried (Na_2SO_4), and evaporated, giving a mixture (2 g) of 6-butoxy-5-morpholinopyridazin-3(2*H*)-one and its isomer. Chromatography on silica gel with 2% methanol in chloroform afforded 6-*butoxy*-4-*morpholinopyridazin*-3(2H)-*one* (0·9 g), m.p. 183° (from benzene–cyclohexane) (Found: C, 57·0; H, 7·6; N, 16·4%), τ ($CDCl_3$) 4·13 (1H, s), 5·97 (2H, t), 6·25 (4H, m), and 6·55 (4H, m); $\nu_{max.}$ ($CHCl_3$) 1650ms, 1590vs, and 1570sh cm^{-1}. The aqueous sodium hydroxide extract was neutralised with acetic acid and extracted with chloroform to give 2-*butyl*-6-*hydroxy*-4-*morpholinopyridazin*-3(2H)-*one* (200 mg), m.p. 130—131° (from benzene–cyclohexane) (Found: C, 57·1; H, 7·5; N, 16·8%), τ ($CDCl_3$) 4·14 (1H, s), 6·15 (2H, t), 6·2 (4H, m), and 6·55 (4H, m); $\nu_{max.}$ 1653w and 1604vs cm^{-1}.

4(5)-Dialkylamino-6-hydroxypyridazin-3(2*H*)-ones

4(5)-Substituent	M.p. (°C)	Solvent	Formula	Found (%) C	H	N	Required (%) C	H	N
Piperidino	279—280	Me_2N·CHO	$C_9H_{13}N_3O_2$	55·0	7·1	21·9	55·4	6·7	21·5
Diethylamino	237—239	EtOH	$C_8H_{13}N_3O_2$	52·7	7·2	23·0	52·45	7·1	22·95
Pyrrolidino	315	EtOH	$C_8H_{11}N_3O_2$	52·8	6·0	23·0	53·0	6·1	23·2
Morpholino	298—299	Me_2N·CHO	$C_8H_{11}N_3O_3$	48·7	5·6	21·4	48·8	5·6	21·3
2-Hydroxyethyl(methyl)amino	231—232	EtOH	$C_7H_{11}N_3O_3$	44·9	5·9	22·6	45·4	5·9	22·7

6-Butoxy-5-morpholinopyridazin-3(2*H*)-one was isolated from the mother liquors from the crystallisation of 3,6-dibutoxy-4-morpholinopyridazine hydrochloride[3] from butanone. 5-*Morpholino*-6-*propoxypyridazin*-3(2H)-*one*, m.p. 164° (from cyclohexane), was obtained similarly (Found: C, 55·7; H, 7·0; N, 17·9. $C_{11}H_{17}N_3O_3$ requires C, 55·2; H, 7·1; N, 17·6%).

6-Butoxy-5-morpholinopyridazin-3(2*H*)-one (2·0 g) was treated with phosphoryl chloride (16 ml) and heated slowly (0·75 h) to the boiling point. The mixture was then heated under reflux for 0·5 h, cooled, and evaporated under reduced pressure. The residue was poured onto ice and after neutralisation with sodium hydroxide the product was extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated, and the residual oil (1·3 g) was purified by chromatography on silica gel. Elution with 5% ethyl acetate in benzene gave 3-butoxy-6-chloro-4-morpholinopyridazine, m.p. and mixed m.p. 65—68°, identical (t.l.c. and i.r.) with an authentic sample.[3]

Alkylation of Butoxymorpholinopyridazinones.—6-Butoxy-5-morpholinopyridazin-3(2*H*)-one (1·5 g) in methylene dichloride (50 ml) was treated under nitrogen with 2·5M-triethyloxonium fluoroborate in methylene chloride (3·5 ml) and stirred at room temperature for 18 h. The methylene chloride solution was then washed with aqueous sodium hydrogen carbonate and sodium chloride solution, dried (Na_2SO_4), and evaporated to give 3-*butoxy*-6-*ethoxy*-4-*morpholinopyridazine* as an oil, τ ($CDCl_3$) 3·90 (1H, s), 5·58 (2H, t), 5·61 (2H, q), 6·2 (4H, m), 6·8 (4H, m), 8·1—8·7 (4H, m), 8·64 (3H, t), and 9·05 (3H, t). Treatment of the base with ethereal hydrogen chloride gave the hygroscopic *hydrochloride* (1 g), m.p. 125—126° (Found: C, 52·8; H, 7·8; N, 13·4. $C_{14}H_{23}N_3O_3$,HCl requires C, 52·9; H, 7·6; N, 13·2%).

[7] R. Schönbeck and E. Kloimstein, *Monatsh.*, 1968, **99**, 15.

Similarly, 6-butoxy-4-morpholinopyridazin-3(2*H*)-one gave *6-butoxy-3-ethoxy-4-morpholinopyridazine*, as an oil, τ ($CDCl_3$) 3·86 (1H, s), 5·50 (2H, q), 5·63 (2H, t), 6·15 (4H, m), 6·75 (4H, m), 8·1—8·7 (4H, m), 8·58 (3H, t), and 9·05 (3H, t); *hydrochloride*, m.p. 126° (hygroscopic) (Found: C, 52·6; H, 7·7; N, 13·2%).

Hydrolysis of 3,6-*Dibutoxy-4-chloropyridazine*.—The dibutoxy-compound (3·4 g) and glacial acetic acid (6 ml) saturated with hydrogen chloride were heated on a steam-bath for 0·5 h; the mixture was then evaporated under reduced pressure. The residue was treated with 2N-sodium carbonate solution and the product was extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated, and the residue was crystallised from cyclohexane and then from ethanol, to give 6-butoxy-5-chloropyridazin-3(2*H*)-one (1 g), m.p. 153°, identical with material previously described.[1] The mother liquors were evaporated and the residue was purified by chromatography (alumina; 10% ethanol in ethyl acetate) to give *6-butoxy-4-chloropyridazin*-3(2H)-*one* (0·6 g), m.p. 107° [from light petroleum (b.p. 60—80°)] (Found: C, 47·4; H, 5·3; N, 13·8. $C_8H_{11}ClN_2O_2$ requires C, 47·4; H, 5·4; N, 13·8%), τ ($CDCl_3$) 2·78 (1H, s), 5·83 (2H, t), 8·2—8·8 (4H, m), and 9·05 (3H, t).

6-Butoxy-5-chloropyridazin-3(2*H*)-one (2 g) and morpholine (5 ml) were dissolved in dry benzene (20 ml) and set aside for 2 days. The solid product (2·8 g) was filtered off and washed with benzene and then with water, and the residue was crystallised from ethanol to give 6-butoxy-5-morpholinopyridazin-3(2*H*)-one (1·8 g), m.p. and mixed m.p. 221°. Under the same conditions 6-butoxy-4-chloropyridazin-3(2*H*)-one gave 6-butoxy-4-morpholinopyridazin-3(2*H*)-one, m.p. and mixed m.p. 183°.

6-Hydroxy-4(or 5)-piperidinopyridazin-3(2*H*)-one (7·5 g) and phosphoryl chloride (35 ml) were boiled under reflux for 15—30 min; half the phosphoryl chloride was then distilled off under reduced pressure. The residue was poured onto ice and made alkaline with aqueous potassium hydroxide. The product was extracted with benzene (2 × 200 ml); the extracts were dried (Na_2SO_4) and evaporated and the residue was crystallised from light petroleum (b.p. 80—100°) (carbon treatment) to give 3,6-*dichloro-4-piperidinopyridazine*, m.p. 80° (Found: C, 46·6; H, 4·9; N, 17·9. $C_9H_{11}Cl_2N_3$ requires C, 46·55; H, 4·7; N, 18·1%). The yield was variable and was less with prolonged reaction times. Under the same conditions compound (2; R_2N = morpholino), compound (14), and 4-chloro-5-morpholinopyridazin-3(2*H*)-one gave the corresponding dichloro-compounds, but compound (15) (3 g) gave a mixture [separated by chromatography (alumina; benzene)] of 3,4,5-trichloropyridazine (0·4 g) and 3,5-*dichloro-4-dimethylaminopyridazine* (1·6 g), m.p. 43·5—45° (Found: C, 37·6; H, 3·9; Cl, 37·0; N, 21·4. $C_6H_7Cl_2N_3$ requires C, 37·5; H, 3·6; Cl, 37·0; N, 21·9%), τ ($CDCl_3$) 1·15 (1H, s) and 6·9 (6H, s).

3,6-Dichloro-4-piperidinopyridazine was hydrogenated over 5% palladium–carbon in ethanol to give *4-piperidinopyridazine hydrochloride*, m.p. 181—183° (from ethanol–ethyl acetate) (Found: C, 53·8; H, 6·6; N, 20·5. $C_9H_{13}N_3$,HCl requires C, 54·0; H, 7·0; N, 21·0%).

3,5-Dichloro-4-dimethylaminopyridazine (1·5 g) was boiled under reflux with a solution of sodium (0·54 g) in butanol (25 ml). After 5 h the solution was evaporated and the residue was treated with water and extracted with ether. Evaporation of the extract left 3,5-*dibutoxy-4-dimethylaminopyridazine* (2 g), an oil that was purified by chromatography on alumina (benzene–ethyl acetate); τ ($CDCl_3$) 1·5 (1H, s), 5·5 (2H, t), 5·9 (2H, t), 7·05 (6H, s), 7·9—9·2 (14H, m); *picrate*, m.p. 77—80° (Found: C, 48·4; H, 5·8; N, 16·8. $C_{14}H_{25}N_3O_2$,$C_6H_3N_3O_7$ requires C, 48·4; H, 5·65; N, 16·95%).

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