Reactions of Pyridine *N*-Oxides with 3,6-Dichloropyridazine

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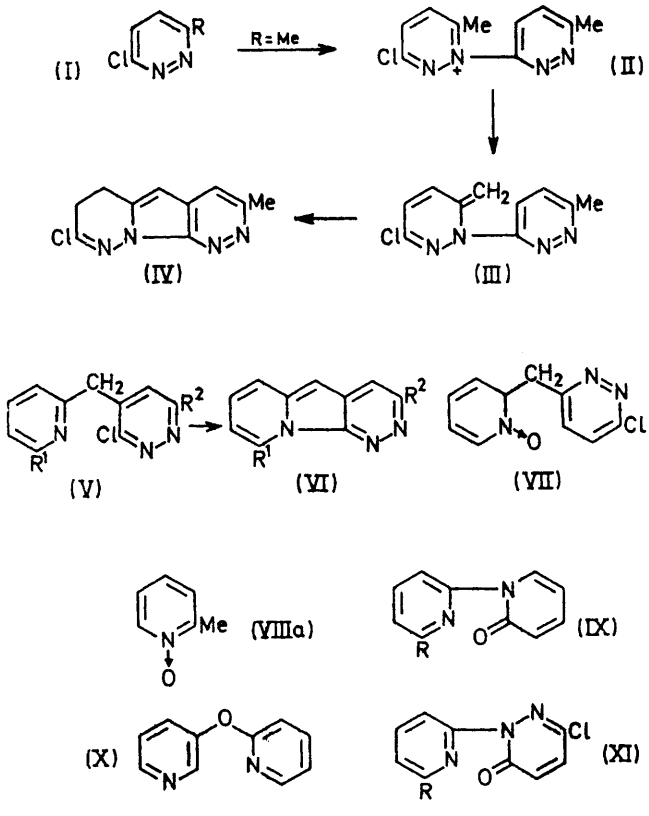
The main products of the reaction of 3,6-dichloropyridazine with 2-methylpyridine 1-oxide were 6-chloro-2-(2-pyridylmethyl)pyridazin-3(2*H*)-one (XII; R = H), 6-chloro-4-(2-pyridylmethyl)pyridazin-3(2*H*)-one (XIV; R = H), and 6-chloropyridazin-3-yl 2-pyridylmethyl ether (XVI). 2,6-Dimethylpyridine 1-oxide gave homologues corresponding to the pyridazinones (XII) and (XIV), and, in addition, 6-chloropyridazin-3-yl 2,6-dimethyl-3-pyridyl ether (XIX). No compound corresponding to the methyl ether (XVI) was isolated. The reactions are discussed in the light of earlier studies of the action of 2-bromopyridine on pyridine 1-oxide, and it is suggested that initial formation of a 1-(pyridazinyloxy)pyridinium salt is followed by loss of a proton to give an anhydro-base.

An earlier observation,[1] confirmed by subsequent and more detailed studies,[2] concerning the self-condensation of 3-chloro-6-methylpyridazine (I; R = Me) to give the tricyclic compound (IV), prompted a more deliberate attempt to synthesise bridgehead nitrogen ring systems of this type by less equivocal routes. It was reasonably assumed that the first step in this reaction involved formation of the cation (II), followed by the methylene compound (III). One new scheme envisaged a reaction



series in which quaternisation was the final step, and required the initial synthesis of compounds of type (V), for example, which would then readily be converted into the related tricyclic structures (VI). As a further alternative, it was considered that similar structures might result from the ring closure of an *N*-oxide such as (VII), and this paper is concerned with the interplay of these two approaches. Earlier work by one of us [3] in the pyrimidine series, suggested that a suitable route to the methane derivative (VII) might be through the interaction of the dichloropyridazine (I; R = Cl) and diethyl 2-pyridylmalonate, itself obtained in low yield from treatment of 2-methylpyridine 1-oxide (VIIIa) with diethyl carbonate in the presence of sodium hydride. Preliminary experiments were discouraging, and attention was turned to the direct action of dichloropyridazine on 2-methylpyridine *N*-oxide. Literature precedent for such a reaction was slight. 2-Bromopyridine and pyridine *N*-oxide are reported [4,5] to condense on fusion to give a mixture of compounds (IX; R = H) and (X), whereas the 2-methyl derivative (VIIIa) yielded compound (IX; R = Me). No substitution of the methyl group was recorded. 3,6-Dichloropyridazine and pyridine *N*-oxide were found by us to give the analogue (XI; R = H), but the *N*-oxides of 2- and 4-methylpyridines (VIIIa and b), and later of 2,6-dimethylpyridine (VIIIc), were shown to behave differently. The optimum conditions involved initial fusion of the components at 100—110° under nitrogen, and control of the violent exothermic reaction that ensued by addition of benzene or dioxan. Preliminary fractionation of the tarry products by solvent extraction, first at pH 11, then at pH 5, was followed by column chromatography (silica) of the extracts. The major product (20%) from 2-methylpyridine *N*-oxide (VIIIa) was unexpectedly the *N*-(pyridylmethyl)pyridazine (XII; R = H) which was differentiated readily by n.m.r. (methylene singlet at τ 4·58, pyridine 2-proton at τ 1·43) from the expected compound (XI; R = Me). Further confirmation for this structure was provided by treatment with phosphoryl chloride to give the pyridoimidazopyridazinium salt (XIII; R = H). The second isolated product (13%) was, even more unexpectedly, the isomeric chloropyridazinone (XIV; R = H). Solubility in dilute aqueous sodium hydroxide, the amidic carbonyl absorption (1660 cm^{-1}), and the n.m.r. data (methylene protons τ 6·025,

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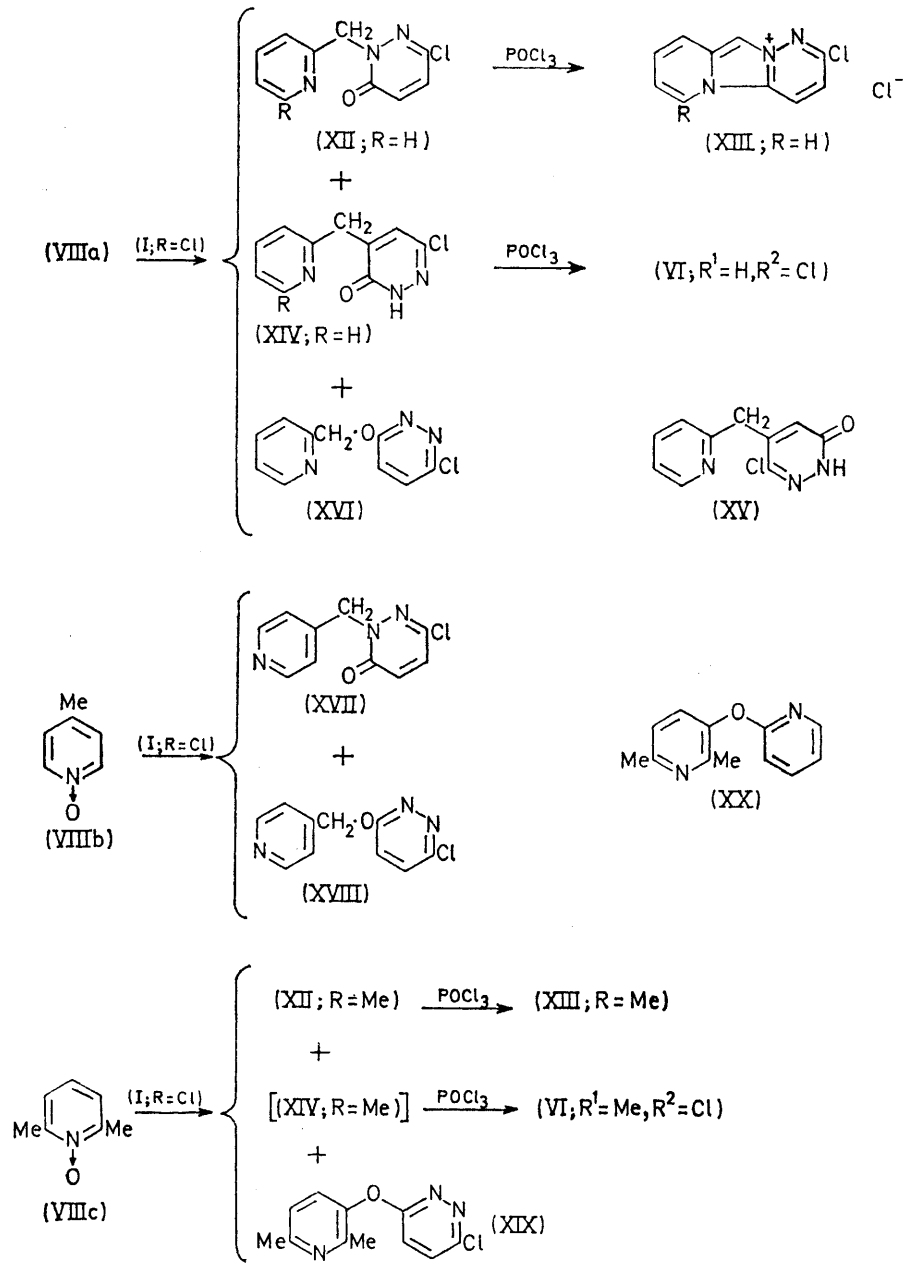
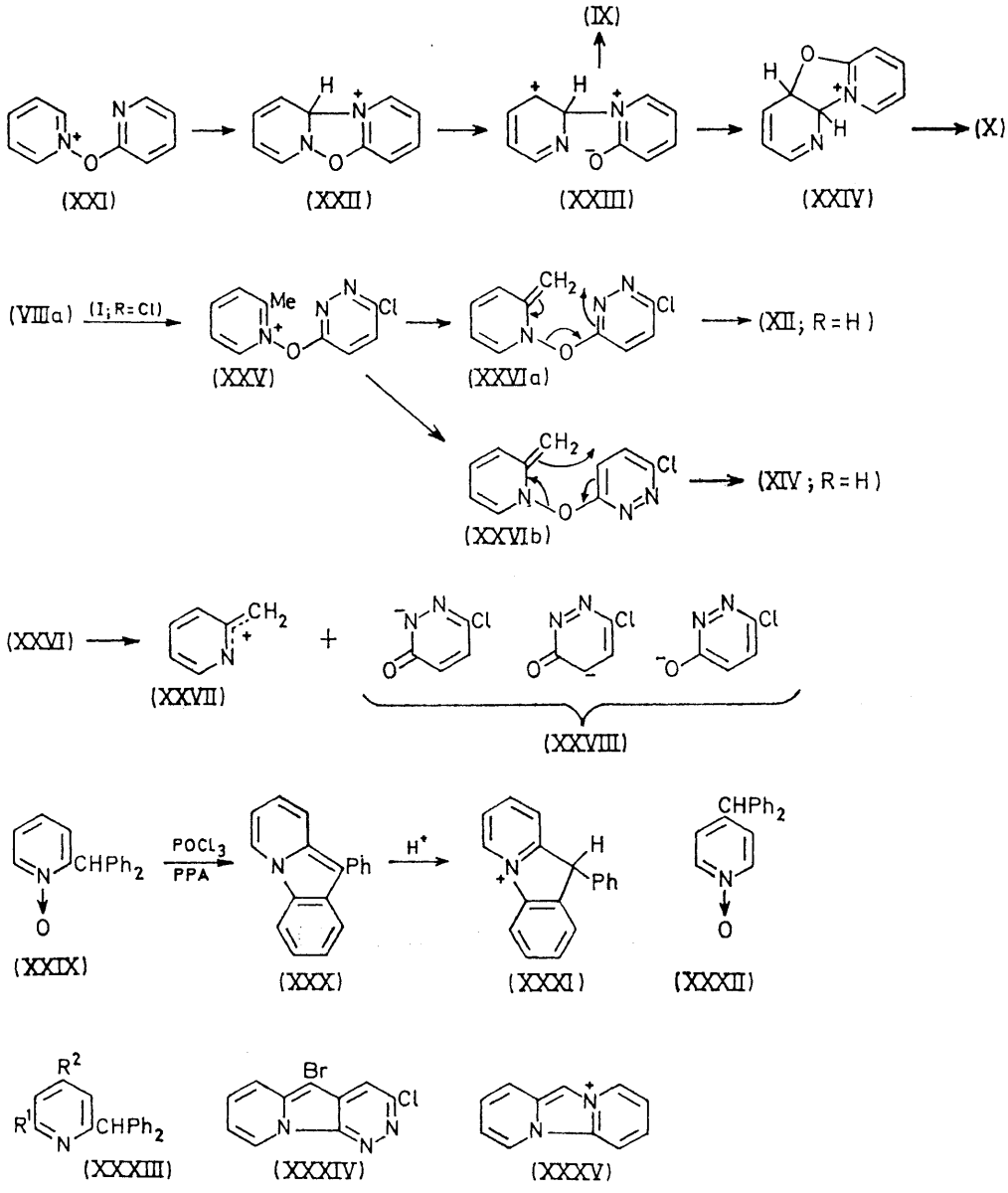
[1] N. K. Basu and F. L. Rose, *J. Chem. Soc.*, 1963, 5660.
[2] H. Lund and S. Gruhn, *Acta Chem. Scand.*, 1966, **20**, 2637.
[3] F. L. Rose, *J. Chem. Soc.*, 1954, 4116.
[4] F. Ramirez and P. W. von Ostwalden, *J. Amer. Chem. Soc.*, 1959, **81**, 156.
[5] S. Kadjihara, *Nippon Kagaku Zasshi*, 1965, **86**, 1060 (*Chem. Abs.*, 1966, **65**, 16,936).

pyridazine proton singlet τ 2·75), provided evidence for the structure. The action of phosphoryl chloride gave the pyridazinoindolizine (VI; $R^1 = H$, $R^2 = Cl$). The alternative structure (XV) was discounted both on mechanistic grounds and also in the light of the failure to effect ring closure in the absence of phosphoryl chloride. A third product (4%) isolated from the fusion reaction was assigned structure (XVI) on the basis of i.r. findings, a satisfactory correspondence with the expected n.m.r. of the pyridazine, pyridine, and methylene (τ 4·38) protons, and unequivocal synthesis from the action of the dichloropyridazine (I; R = Cl) on 2-pyridyl methanol.

In further experiments designed to elucidate the mechanism of formation of these three substances, similar condensations were effected, as already indicated, between the dichloropyridazine and the *N*-oxides of 4-methylpyridine and 2,6-dimethylpyridine. The reactions gave mainly tars, the major (pure) products isolated being, respectively, compounds (XVII) (10%) and (XVIII) (9%), and (XII; R = Me), (18%) and (XIX) (3%). 4-Methylpyridine *N*-oxide gave no trace of a derivative analogous to compound (XIV). The related homologue (XIV; R = Me) was, however, obtained from the dimethylpyridine experiment. It could not be separated completely from the pyridazine (I; R = OH) with which it was contaminated, but it was converted into the tricyclic structure (VI; R^1 = Me,



R^2 = Cl) by the action of phosphoryl chloride. The structure of the ether (XVIII) was proved definitively by synthesis from 4-pyridylmethanol. Only the formation of the ether (XIX) was out of line with the 2-methylpyridine results. The i.r., u.v., and n.m.r. data for this substance (two three-proton singlets, and two AB patterns) indicated that the ether linkage could only be in position 3 of the pyridyl residue. No such analogous



derivative was reported [4] to be formed when 2,6-dimethylpyridine 1-oxide and 2-bromopyridine were brought together at 100°, but repetition of this experiment at 120—130°, gave an 11% yield of the dipyridyl ether (XX), whose spectral data were as expected.

Two distinct reaction courses are indicated. In the first the methyl group of the pyridine residue remains intact, as in reactions with pyridine *N*-oxide itself, and in the second a methyl group becomes substituted by an *N*-, *O*-, or *C*-linked heterocycle. The former reactions have been considered [4,6] to involve primary nucleophilic attack by the *N*-oxide on, say, 2-bromopyridine to give the cation (XXI), which then condenses by acceptable electromeric shifts to the cyclic intermediate (XXII). Breakage of the N–O bond yields the carbonium structure (XXIII), which either loses a hydrogen ion and forms the bipyridyl (IX), or, through ring formation in a different mode, gives first the tricyclic intermediate (XXIV), and then again by proton loss and ring fission, the 3-substituted pyridine (X).

Substitution of a heterocyclic structure into a methyl group associated with an *N*-oxide does not seem to have

[6] S. Kadjihara, *Nippon Kagaku Zasshi*, 1965, **86**, 839 (*Chem. Abs.*, 1966, **65**, 16,935).

been recorded hitherto. It seems reasonable that the initial product from 2-methylpyridine *N*-oxide (VIIIa) and 3,6-dichloropyridazine is the cation (XXV), analogous to the pyridine derivative (XXI). Loss of a proton would then lead to the anhydro-base (XXVIa) [*cf.* structures (III)] which by the sigmatropic shift indicated would rearrange to the substituted methane (XII; R = H). The isomer (XIV; R = H) could arise from a related sigmatropic rearrangement of the anhydro-base formulated as in (XXVIb), followed by prototropic change to the more stable lactam. The production of the homologous compounds (XII; R = Me) and (XIV; R = Me) in the dimethylpyridine experiment would conform to the same hypothesis, as would also the complete failure to detect the 4-substituted isomer of (XIV; R = H) when 4-methylpyridine *N*-oxide was substituted for the 2-methyl derivative. The occurrence of the *N*-substituted pyridazine (XVII) in the latter instance, however, must throw some doubt on the exclusive nature of these explanations. An alternative general mechanism would be an indirect route operating through dissociation of the intermediate (XXVI) into the two separate ionic species (XXVII) and (XXVIII), which could then recombine to give the observed products, including the methylene ether (XVI). The same argument is applicable to the reaction involving 4-methylpyridine *N*-oxide, except that the absence of the 4-pyridylmethyl analogue of compound (XIV) now appears anomalous. One further possibility was the formation of the *N*-substituted derivatives (XII) and (XVII) from migration of the pyridylmethyl-residues in the corresponding pyridylmethoxypyridazinones (XVI) and (XVIII), respectively. All attempts, however, to realise this rearrangement, under a wide variety of experimental conditions, proved abortive. In general, the ethers were decomposed to unidentifiable tars above 140°; perhaps this instability was reflected to some extent in the poor yields obtained in the fusion reactions when the temperature was not sufficiently controlled.

The precise reaction courses remain equivocal in the face of existing evidence. The initial formation of the heteroaryloxyammonium salts (XXI) and (XXV) seems to be a prerequisite whatever the subsequent course of events, but attempts to isolate these products, or the anhydro-bases into which they are assumed to be converted, have failed. In this connection, it is well known that aromatic amine oxides react with alkyl halides to form unstable alkoxyammonium salts,[7] and there has been limited success in preparing acyloxyammonium derivatives, in that several *N*-acetoxypyridinium perchlorates have been prepared.[8] Since there was no spectroscopic evidence for the formation of an anhydro-base on conversion of perchlorate into acetate, Bodalski and Katritzky[9] reinvestigated the related acetic anhydride rearrangement of 2-alkylpyridine 1-oxides to 2-acetoxyalkylpyridines, and it was they who first postulated the involvement of an ion pair based on structure (XXVII), for example. As a more realisable model for the present investigation, it was considered that the introduction of one or two phenyl residues into the methyl group of the methylpyridine *N*-oxides might exert a stabilising influence on the hypothetical anhydro-bases, and the *N*-oxides (XXIX) and (XXXII) were accordingly prepared. The former was unchanged after fusion with 3,6-dichloropyridazine for 12 hr. at 100—110°, but no other conditions were examined since it was realised that there would be strong steric impediment to the reaction. The conditions employed with the 4-diphenylmethyl *N*-oxide were more varied, and concentrated on the use of acid-binding agents such as triethylamine, and of both the sodium and potassium salts, the latter obtained as a blood-red solution in dimethylformamide by the addition of potassium t-butoxide. There was no desired reaction at 20—25° (under nitrogen) in the presence of the organic base, and even after 4 days with the alkali metal salts, t.l.c. showed unchanged *N*-oxide still present. It did, however, demonstrate the production of four by-products. Column chromatography showed these to be benzophenone, 3-chloro-6-dimethylaminopyridazine, diphenyl-4-pyridylmethane, and diphenyl-4-pyridylmethanol. Again there was no positive evidence for anhydro-base formation. As an aside, the action of dehydrating agents on the 2-diphenylmethyl oxide (XXIX) was examined in the hope that the pyridoindole (XXX) might result. Treatment with phosphoryl chloride followed by t.l.c. showed three fractions. A yellow minor component fluoresced strongly, and was later shown to be the expected tricyclic compound (XXX). The other two fractions, separated on an alumina column, were the two isomeric chloropyridines (XXXIII; R^1 = H, R^2 = Cl, and R^1 = Cl, R^2 = H). The formation of these substances is in line with known pyridine *N*-oxide chemistry. Ultimately, the indolizine (XXX) was found to be best prepared by the action of polyphosphoric acid at 250°. Its u.v. spectrum agreed with that recorded by Wasserman and Waterfield,[10] who obtained the same substance by another route. It was an extremely weak base, but dissolved in concentrated hydrochloric acid to give a colourless non-fluorescent solution. The change in the u.v. spectrum suggested that the cation was now that of the pyridinium salt (XXXI).

The formation of tricyclic compounds of types (VI) and (XIII) has already been mentioned as providing supporting evidence for the structures of the several precursors. Those of the former class were yellow highly fluorescent substances, but which dissolved in dilute hydrochloric acid to give cherry-red, non-fluorescent solutions, in these respects resembling closely the aromatic dehydro-derivative of compound (IV). The halogen substituent in compound (VI; R^1 = H, R^2 =

[7] E. Ochiai, 'Aromatic Amine Oxides,' Elsevier, Amsterdam, 1967, p. 178.
[8] C. W. Muth and R. S. Darlak, *J. Org. Chem.*, 1965, **30**, 1909.
[9] R. Bodalski and A. R. Katritzky, *J. Chem. Soc.* (*B*), 1968, 831.
[10] H. W. Wasserman and W. R. Waterfield, *Chem. and Ind.*, 1961, 1220.

Cl) was unexpectedly resistant to nucleophilic displacement; no reaction occurred for example with piperidine or hydrazine in alcohol under reflux. Prolonged treatment with boiling dilute hydrochloric acid gave a small yield of the corresponding hydroxy-derivative (VI; $R^1 = H$, $R^2 = OH$). By contrast, electrophilic attack on the same compound took place readily, as exemplified by the action of bromine in cold pyridine solution to yield the bromo-derivative (XXXIV), in line with the experimental findings and theoretical expectations with the related indolizine molecule.[11] The analogous ring structures (XIII; R = H and R = Me) were obtained as water-soluble chlorides from the phosphoryl chloride ring-closure of the precursors (XII; R = H and R = Me). The solutions in water were bright yellow, and again, fluoresced strongly. Structure assignment was based on n.m.r. observations, but also on the similarity of the u.v. spectra to that of the perchlorate of the related dipyrido-derivative (XXXV).[12] Bromination in cold acetic acid solution gave monobromo-derivatives, which were shown by i.r. and n.m.r. studies to have structures entirely analogous to compound (XXXIV).

EXPERIMENTAL

U.v. spectra were measured for methanolic solutions, unless otherwise stated, and i.r. spectra were obtained for Nujol mulls.

2-Diphenylmethylpyridine was obtained from pyridine-2-carbaldehyde by the reported [13] method; m.p. 54—58° (lit.,[14] 60°). 4-Diphenylmethylpyridine was similarly prepared from pyridine-4-carbaldehyde (48% yield); m.p. 121—124° (lit.,[14] 124—124·5°).

2-Diphenylmethylpyridine N-Oxide (XXIX).—2-Diphenylmethylpyridine (76·5 g.) in glacial acetic acid (190 ml.) containing hydrogen peroxide (30% w/v; 33 ml.) was stirred at 70—80° for 3 hr., then more hydrogen peroxide (23 ml.) was added. Heating was continued for a further 9 hr. Most of the acetic acid was distilled off under reduced pressure at 50—60°, and water (100 ml.) was added. Re-evaporation left a viscous, pale yellow gum, which solidified on addition of more water (100 ml.) and adjustment to pH 8—9 with sodium carbonate. Crystallisation from benzene gave the *N-oxide* (56 g.), m.p. 164—166° (Found: C, 83·4; H, 5·6; N, 5·4. $C_8H_{15}NO$ requires C, 82·7; H, 5·8; N, 5·4%), $\nu_{max.}$ 1240 cm.$^{-1}$ (N→O).

4-Diphenylmethylpyridine N-oxide, prepared similarly (82% yield), had m.p. 146—147° (Found: C, 82·4; H, 5·2; N, 5·4%), $\nu_{max.}$ 1250 cm.$^{-1}$ (N→O).

10-Phenylpyrido[1,2-a]*indole* (XXX).—Polyphosphoric acid (25 g.) was stirred at 250—260° and 2-diphenylmethylpyridine *N*-oxide (5·2 g.) was added. Heating was continued for 5 min. The temperature rose momentarily to *ca.* 280°. The mixture was cooled to 100° and added cautiously to water (250 ml.). After 0·5 hr., the crude product was filtered off and extracted into hot benzene (4 × 100 ml.). The benzene solution was washed (aqueous sodium hydrogen carbonate), dried ($MgSO_4$), and evaporated. Trituration of the residual gum (3·6 g.) with methanol gave 10-phenylpyrido[1,2-*a*]indole as a solid (1·75 g.), which formed golden yellow needles, m.p. 91—93° (from methanol) (lit.,[10] 94°) (Found: C, 88·4; H, 5·5; N, 5·7. Calc. for $C_8H_{13}N$: C, 88·9; H, 5·4; N, 5·8%), $\lambda_{max.}$ 257infl, 263, 300, 310infl, 325infl, 339, 419, 444infl, and 476infl nm. (ε 44,600, 55,500, 13,900, 13,200, 9490, 7300, 2640, 3440, 2900, and 1170), $\lambda_{max.}$ (M-$HClO_4$) 220infl, 282, and 312 nm. (ε 18,390, 12,730, and 5660).

6-Chloropyridazin-3-yl 2-Pyridylmethyl Ether (XVI).—Methylpyridine *N*-oxide was converted into 2-acetoxymethylpyridine [pale yellow oil, b.p. 118—122°/21 mm. (77%)] by treatment with acetic anhydride.[15] Hydrolysis with dilute sodium hydroxide then gave 2-pyridylmethanol, obtained as an oil, b.p. 116—118°/15 mm. (*cf.* ref. 16) (45%). A solution of the alcohol (14·1 g.) in dry tetrahydrofuran (25 ml.) was added dropwise to a stirred suspension of sodium hydride (50% dispersion; 6·21 g.) in dry tetrahydrofuran (75 ml.), under nitrogen. After 2 hr., 3,6-dichloropyridazine (19·3 g.) in tetrahydrofuran (75 ml.) was added (15 min.) at 15—20° and stirring was continued for 16 hr. The solvent was evaporated off *in vacuo* at 35° and the residue was treated with cold water (50 ml.). The insoluble solid was filtered off, washed with water, and dried (40—45° *in vacuo*) to give the crude *ether* (27 g.) which formed needles (23 g.), m.p. 103—105° [from benzene (charcoal)] (Found: C, 54·1; H, 3·6; Cl, 16·2; N, 19·1. $C_{10}H_8ClN_3O$ requires C, 54·2; H, 3·6; Cl, 16·0; N, 19·1%), $\nu_{max.}$ 1190 cm.$^{-1}$ (C–O–C), $\lambda_{max.}$ 254, 260, 266, and 284infl nm. (ε 4250, 4850, 4250, and 1820), τ 1·39 (1H, d, *J* 5·0 Hz, pyridine α-H), 2·59 and 2·97 (2H, ABd, *J* 9·4 Hz, pyridazine 4-H and 5-H), and 4·38 (2H, s, CH_2); picrate, m.p. 175—176° (decomp.) (yellow crystals from methanol).

6-Chloropyridazin-3-yl 4-Pyridylmethyl Ether (XVIII).—4-Acetoxymethylpyridine was prepared from 4-methylpyridine *N*-oxide and acetic anhydride, purified *via* its hydrogen oxalate salt,[17] and hydrolysed [15] to give 4-pyridylmethanol hydrochloride. The free base [needles from benzene, m.p. 58—60° (lit.,[17] 57·8—58·8°)] was condensed with 3,6-dichloropyridazine to give the *ether* as needles (from carbon tetrachloride), m.p. 95—97° (Found: C, 53·8; H, 4·2; Cl, 16·0; N, 18·8. $C_{10}H_8ClN_3O$ requires C, 54·2; H, 3·6; Cl, 16·0; N, 19·0%), $\nu_{max.}$ 1190 cm.$^{-1}$ (C–O–C), $\lambda_{max.}$ 258, 263infl, and 284 nm. (ε 4210, 3060, and 1840), τ 1·35 (2H, d, *J* 4·2 Hz, pyridine α-H), 2·53 and 2·95 (2H, ABd, *J* 9·0 Hz, pyridazine 4-H and 5-H), and 4·42 (2H, s, CH_2); picrate, pale yellow microneedles, m.p. 118° (decomp.) (from ethanol).

General Procedure for the Reaction of N-Oxides with Halogeno-heterocycles.—The reactants were stirred together under dry nitrogen, usually at 100—110°, in an oil-bath. Except when 2,6-dimethylpyridine *N*-oxide was used, the reactions became exothermic during heating, and either benzene or dioxan was added at such a rate as to maintain the temperature below 150°. After the evolution of heat had subsided, heating at 100—110° was recommenced to complete the reaction. Remaining solvents were removed under reduced pressure, and the residue was digested in

[11] W. L. Mosby, 'Systems with Bridgehead Nitrogen,' Part I, Interscience, New York, 1961, p. 252.
[12] B. R. Brown and J. Humphreys, *J. Chem. Soc.*, 1969, 2040.
[13] W. Mathes and A. Wolf, Ger.P. 1,198,366/1965 (*Chem. Abs.*, 1965, **63**, 14,825c).
[14] P. Ph. H. L. Otto, J. P. Wibaut, and G. W. J. M. Groenendaal, *Rec. Trav. chim.*, 1959, **78**, 446 (*Chem. Abs.*, 1960, **54**, 1512).
[15] V. Boekelheide and W. J. Linn, *J. Amer. Chem. Soc.*, 1954, **76**, 1286.
[16] O. H. Bullitt, jun. and T. J. Maynard, *J. Amer. Chem. Soc.*, 1954, **76**, 1370.
[17] J. A. Berson and J. Cohen, *J. Amer. Chem. Soc.*, 1955, **77**, 1281.

dilute hydrochloric acid. The solution so obtained was made alkaline (pH 11) with aqueous sodium hydroxide (40% w/v) and extracted well with benzene. The combined extracts were washed with water, dried ($MgSO_4$), and set aside after evaporation of the solvent for chromatography if required [fraction (A)]. The alkaline mother liquor was then treated with acetic acid (to pH 4—5) and re-extracted with chloroform ($MgSO_4$) [fraction (B)].

Pyridine N-*oxide and* 3,6-*dichloropyridazine*. A vigorous reaction was observed after *ca.* 10 min. when the *N*-oxide (4·75 g.) and the dichloropyridazine (8·25 g.) were fused together at 100—110°. Heating was continued for a further 1 hr. Fraction (A) was a reddish-brown solid (5·35 g.) that was extracted with boiling light petroleum (b.p. 100—120°; 4 × 50 ml.) to give, on cooling to 0°, a solid (2·9 g.) which separated from toluene as 6-*chloro*-2-(2-*pyridyl*)*pyridazin*-3(2H)-*one* (XI; R = H) (2·3 g.), m.p. 124·5—127° (Found: C, 52·0; H, 3·1; Cl, 16·8; N, 20·4. $C_9H_6ClN_3O$ requires C, 52·1; H, 2·9; Cl, 17·1; N, 20·0%), $\nu_{max.}$ 1675 cm.$^{-1}$ (C=O), $\lambda_{max.}$ 214, 233infl, 262, and 309 nm. (ε 14,300, 4470, 2650, and 4340), τ 1·39 (1H, d, *J* 5·2 Hz, pyridine α-H), 2·74 and 3·0 (2H, ABd, *J* 9·8 Hz, pyridazine 4-H and 5-H).

2-*Methylpyridine* N-*oxide and* 3,6-*dichloropyridazine*. The reaction between the *N*-oxide (16·5 g.) and the dichloropyridazine (24·75 g.) became exothermic after *ca.* 2 hr. at 100—110°, and the temperature was held at 140—150° by addition of benzene; excess of solvent was allowed to distil off. The mixture was finally kept at 100—110° for 45 min. Fraction (A) was a gum (14·75 g.), which was dissolved in chloroform and applied to a silica gel (450 g.; MFC) column. Elution with ether gave unchanged 3,6-dichloropyridazine, then 2-pyridylmethyl chloride (1·7 g.) (i.r. spectrum and formation of dimer,[18] identical with authentic specimen), and 6-*chloro*-2-(2-*pyridylmethyl*)*pyridazin*-3(2H)-*one* (XII; R = H) (ethyl acetate elution), obtained as a pale yellow viscous oil (6·9 g.) which slowly solidified. Crystallisation from benzene–light petroleum (b.p. 60—80°) afforded needles, m.p. 82—85° (Found: C, 54·3; H, 3·7; Cl, 15·7; N, 18·5. $C_{10}H_8ClN_3O$ requires C, 54·2; H, 3·5; Cl, 16·0; N, 19·0%), $\nu_{max.}$ 1650 cm.$^{-1}$ (C=O), $\lambda_{max.}$ 213, 232infl, 253infl, 260, 267infl, and 304 nm. (ε 15,600, 4410, 2650, 3200, 2800, and 2940), τ 1·43 (1H, d, *J* 5·2 Hz, pyridine α-H), 2·8 and 3·04 (2H, ABd, *J* 9·3 Hz, pyridazine 4-H and 5-H), and 4·58 (2H, s, CH_2). Fraction (B) was a solid (16·2 g.), which was transferred to a silica gel (480 g.; MFC) column in chloroform and eluted with chloroform–ethanol (10 : 1). Initial fractions contained a coloured product (0·15 g.) {presumed but not proved to be 3-chloro-5-(6-chloro-2,3-dihydro-3-oxopyridazin-4-yl)pyridazino-[4,3-*b*]indolizine} which crystallised from acetic acid in bright orange microneedles, m.p. 360° (decomp.) (Found: C, 50·8; H, 2·6; Cl, 20·5; N, 20·8. Calc. for $C_{14}H_7Cl_2N_5O$: C, 50·6; H, 2·2; Cl, 21·4; N, 21·1%), $\nu_{max.}$ 1665 cm.$^{-1}$, $\lambda_{max.}$ 216, 266, 284infl, 296, 312, 326infl, 343, 389, 442infl, 470infl, and 504infl nm. (ε 29,300, 33,500, 9330, 5940, 3620, 4150, 5940, 12,200, 5710, 5440, and 2860), τ 0·74 (1H, d, *J* 5·57 Hz, 9-H), 1·93 (s, 1H, pyridazine 5-H), and 2·37 (1H, s, 4-H). This product formed a sparingly soluble red sodio-derivative with aqueous sodium hydroxide. Continued elution of the column gave 6-chloropyridazin-3(2*H*)-one (9·55 g.), m.p. 139—141° (from benzene), followed by 6-*chloro*-3-(2-*pyridylmethyl*)*pyridazin*-3(2H)-*one* (XIV; R = H) (4·4 g.), m.p. 189—191° (from ethanol) (Found: C, 54·4; H, 3·7; Cl, 16·3; N, 18·7. $C_{10}H_8ClN_3O$ requires C, 54·2; H, 3·6; Cl, 16·0; N, 19·0%), $\nu_{max.}$ 1660 cm.$^{-1}$ (C=O), $\lambda_{max.}$ 209, 232, 253infl, 261, 267, and 296 nm. (ε 18,900, 45,450, 3160, 3870, 3490, and 2740), τ −3·16br (1H, pyridazine NH or OH), 1·5 (1H, d, *J* 5·0 Hz, pyridine α-H), 2·75 (1H, s, pyridazine 5-H), and 6·025 (2H, s, CH_2). The fusion experiment was repeated [*N*-oxide (16·5 g.) and dichloropyridazine (24·75 g.)] but the reaction was controlled by addition of dry dioxan (20 ml.), after which the temperature was kept at 100—110° for 6 hr. Fraction (A) similarly yielded the aforementioned 6-chloro-2-(2-pyridylmethyl)pyridazin-3(2H)-one (6·95 g.), m.p. 83—85° (from benzene–light petroleum). Elution with ether then gave 6-chloropyridazin-3-yl 2-pyridylmethyl ether (1·3 g.) as needles, m.p. 103—105° (from benzene) (Found: C, 54·1; H, 3·8; Cl, 16·1; N, 19·2. Calc. for $C_{10}H_8ClN_3O$: C, 54·2; H, 3·6; Cl, 16·0; N, 19·0%) identical (i.r., m.p. and mixed m.p.) with authentic material (see before). Fraction (B) afforded further samples of the pyridazino[4,3-*b*]indolizine (0·75 g.), m.p. 320° (decomp.), and compound (XIV; R = H) (2·73 g.), m.p. 187—190°.

4-*Methylpyridine* N-*oxide and* 3,6-*dichloropyridazine*. The *N*-oxide (4·4 g.) and the pyridazine (6·6 g.) were refluxed in dioxan (5 ml.) for 6 hr. (Omission of the solvent gave an uncontrollable explosive reaction.) Fraction (A), a gum (4·6 g.), was chromatographed through alumina (type H; 130 g.). Elution with ether gave 4-pyridylmethyl chloride as an orange oil (0·37 g.), i.r. spectrum identical with that of an authentic specimen; picrate,[19] m.p. 148—152°. Further elution [benzene–ethyl acetate (2 : 1)] gave 6-chloropyridazin-3-yl 4-pyridylmethyl ether (XVIII) (0·85 g.), needles, m.p. 93—95° (from cyclohexane) (Found: C, 53·7; H, 3·9; Cl, 15·7; N, 18·7. Calc. for $C_{10}H_8ClN_3O$: C, 54·2; H, 3·6; Cl, 16·0; N, 19·0%), identical (i.r. spectrum, m.p. and mixed m.p. of both base and picrate) with the product prepared from 4-pyridylmethanol. Finally, elution with ethyl acetate gave 6-*chloro*-2-(4-*pyridylmethyl*)*pyridazin*-3(2H)-*one* (XVII) (0·9 g.), which afforded needles, m.p. 122—124° (from cyclohexane) (Found: C, 54·2; H, 3·9; Cl, 16·0; N, 18·5. $C_{10}H_8ClN_3O$ requires C, 54·2; H, 3·6; Cl, 16·0; N, 19·0%), $\nu_{max.}$ 1650 cm.$^{-1}$ (C=O), $\lambda_{max.}$ 211, 231infl, 259, 266infl, and 305 nm. (ε 21,860, 5660, 2905, 2755, and 3210), τ 1·41 (2H, d, *J* 4·75 Hz, pyridine α-H), 2·75 and 3·08 (2H, ABd, *J* 9·5 Hz, pyridazine 4-H and 5-H), and 4·79 (2H, s, CH_2). Chromatography of fraction (B) through silica gel and elution with chloroform and then chloroform–ethanol resulted only in the isolation of 6-chloropyridazin-3(2*H*)-one and unchanged 4-methylpyridine *N*-oxide.

2,6-*Dimethylpyridine* N-*oxide and* 2-*bromopyridine*. The *N*-oxide (12·3 g.) and the bromopyridine (17·4 g.) were heated together at 120—130° for 8 hr. (no appreciable evolution of heat). Fraction (A), an oil (12·35 g.), was dissolved in chloroform and applied to a silica gel (360 g.; MFC) column. Elution with ethyl acetate removed unchanged 2-bromopyridine (5·3 g.), then 2,6-*dimethyl*-3-*pyridyl* 2-*pyridyl ether* (2·3 g.) (fawn-coloured needles from benzene), m.p. 51—52° (Found: C, 72·4; H, 6·0; N, 14·2. $C_{12}H_{12}N_2O$ requires C, 72·0; H, 6·0; N, 14·0%), $\nu_{max.}$ 1160 cm.$^{-1}$ (C–O–C), $\lambda_{max.}$ 218 and 270 nm. (ε 12,200 and 8660), τ 1·91 (1H, d, *J* 5·6 Hz, pyridine α-H), 2·75 and 3·1 (2H, ABd, *J* 8·0 Hz, pyridine 3-H and 4-H), 7·5 (3H, s, CH_3), 7·62 (3H, s, CH_3). Fraction (B) was a deep green gum

[18] T. Kato, Y. Goto, and Y. Yamamoto, *Yakugaku Zasshi*, 1964, **84**, 287 (*Chem. Abs.*, 1964, **61**, 638b).

[19] H. S. Mosher and J. E. Tessieri, *J. Amer. Chem. Soc.*, 1951, **73**, 4925.

(11·8 g.). Chromatography through silica gel (360 g.; MFC) in chloroform–ethanol (10 : 1) yielded 2-pyridone [20] (1·2 g.), m.p. 110°, and unchanged *N*-oxide. No material could be isolated which gave a fluorescent product when treated with boiling phosphoryl chloride.

2,6-*Dimethylpyridine* N-*oxide and* 3,6-*dichloropyridazine*. The reactants [*N*-oxide (19·25 g.) and dichloropyridazine (25·8 g.)] were heated together at 120—130° for 12 hr. without addition of solvent. No exothermic reaction was observed. Fraction (A), black gum (23·4 g.), was chromatographed through silica gel (700 g.). Elution with carbon tetrachloride gave 2,6-dimethylpyridine (1·4 g.) (picrate,[21] m.p. 163—166°). Further elution (ether) removed unchanged dichloropyridazine (7·7 g.), m.p. 63—66°, and then 6-*chloropyridazin*-3-*yl* 2,6-*dimethyl*-3-*pyridyl ether* (XIX) (1·29 g.), which crystallised from cyclohexane (charcoal) in needles, m.p. 126—128° (Found: C, 56·1; H, 4·3; Cl, 15·2; N, 17·4. $C_{11}H_{10}ClN_3O$ requires C, 56·05; H, 4·3; Cl, 15·05; N, 17·8%), $\nu_{max.}$ 1180 cm.$^{-1}$ (C–O–C), $\lambda_{max.}$ 218 and 271 nm. (ε 15,400 and 6850), τ 2·58 and 2·86 (2H, ABd, *J* 9·1 Hz, pyridine 4-H and 5-H), 2·78 and 2·99 (2H, d, *J* 8·5 Hz, pyridazine 4-H and 5-H), 7·54 (3H, s, CH_3), and 7·69 (3H, s, CH_3). Finally, elution with benzene–ethyl acetate (1 : 1) gave 6-*chloro*-2-(6-*methyl*-2-*pyridylmethyl*)-*pyridazin*-3(2H)-*one* (XII; R = Me) as a yellow, viscous gum (6·75 g.), which was stirred in benzene (100 ml.) with silica gel (50 g.; MFC) for 2 hr. at room temperature. Decantation and evaporation gave a residue which crystallised from hexane in needles, m.p. 78—82° (Found: C, 55·9; H, 4·7; Cl, 15·0; N, 18·0. $C_{11}H_{10}ClN_3O$ requires C, 56·05; H, 4·3; Cl, 15·05; N, 17·8%), $\nu_{max.}$ 1650 cm.$^{-1}$ (C=O), $\lambda_{max.}$ 214, 233infl, 266, 273infl, and 303 nm. (ε 13,700, 4090, 4300, 3690, and 2930), τ 2·78 and 3·01 (2H, ABd, *J* 9·3 Hz, pyridazine 4-H and 5-H), 4·69 (2H, s, CH_2) 7·45 (3H, s, CH_3). Fraction (B) (6·0 g.) was chromatographed twice through silica gel (180 and 100 g.) in chloroform–ethanol (10 : 1) to yield 6-chloropyridazin-3(2*H*)-one (14 g.), and the same product as a minor impurity in 6-chloro-4-(6-methyl-2-pyridylmethyl)pyridazin-3(2*H*)-one (XIV; R = Me) (1·6 g.). The latter compound (1·6 g.) and phosphoryl chloride (16 ml.), were refluxed for 1 hr. Excess of phosphoryl chloride was removed under reduced pressure at 60° and the residue was added to cold water (25 ml.). The acidic solution was basified (pH 9) with sodium carbonate and extracted with ether. The yellow solid (1·2 g.) left after evaporation of the dried extract was dissolved in benzene and chromatographed through silica gel (30 g.; MFC). Elution with benzene gave 3,6-dichloropyridazine (0·1 g.). Further elution, with ethyl acetate, gave 3-*chloro*-9-*methylpyridazino*[4,3-b]*indolizine* (VI; R^1 = Me, R^2 = Cl) (0·6 g.), which crystallised from xylene in orange needles, m.p. 201—203° (Found: C, 60·2; H, 3·9; Cl, 16·5; N, 19·0. $C_{11}H_{18}ClN_3$ requires C, 60·7; H, 3·7; Cl, 16·3; N, 19·0%), $\lambda_{max.}$ 212, 226, 260, 267, 316infl, 328, 342, 431infl, 455, and 488infl nm. (ε 17,200, 14,600, 41,200, 43,200, 2500, 3520, 5180, 5850, and 3550), τ 2·35 (1H, s, H-4), 2·5—2·95 (2H, m, H-6, H-7), 3·49 (1H, d, H-8), 3·58 (1H, s, H-5), and 6·75 (3H, s, CH_3).

3-*Chloropyridazino*[4,3-b]*indolizine* (VI; R^1 = H, R^2 = Cl).—Prepared from 6-chloro-4-(2-pyridylmethyl)pyridazin-3(2*H*)-one (3·3 g.) and phosphoryl chloride (35 ml.) as already described, the product (2·7 g.) crystallised from benzene as orange-yellow needles, m.p. 169—170° (Found: C, 59·1; H, 3·3; Cl, 17·4; N, 20·3. $C_{10}H_6ClN_3$ requires C, 59·0; H, 3·0; Cl, 17·4; N, 20·6%), $\lambda_{max.}$ 260, 265, 316, 329, 343, 438, 462, and 494 nm. (ε 15,630, 12,390, 40,400, 46,300, 2910, 3110, 3640, 4620, 4840, and 2690), τ 1·05 (1H, d, H-9), 2·33 (1H, s, H-4), 2·4—3·0 (2H, m, H-6, H-7), 3·29 (1H, m, H-8), 3·65 (1H, s, H-5). The base in chloroform fluoresced yellow. In dilute hydrochloric acid it gave a cherry red, non-fluorescing solution, and formed a cherry-red picrate, m.p. 172—173° (decomp.) (from ethanol).

Pyridazino[4,3-b]*indolizin*-3(2H)-*one*.— 3-Chloropyridazino[4,3-*b*] indolizine (100 mg.) in hydrochloric acid (5N; 4 ml.) was heated under reflux for 10 hr. The solution was basified (pH > 11) with 5N-sodium hydroxide, and extracted with ether to remove unchanged starting material. It was made slightly acidic (pH 4—5) with glacial acetic acid and re-extracted with chloroform (4 × 25 ml.). The dried ($MgSO_4$) solvent layer was evaporated to leave a dark red solid (180 mg.), which was dissolved in ethanol (5 ml.) (charcoal) and applied to a silica gel (4 g.; MFC) column. Elution with chloroform–ethanol (10 : 1) removed the *pyridazinoindolizinone* (wine-red band) (28 mg.), which crystallised from ethanol in dark red microneedles, m.p. 294° (decomp.) (Found: C, 65·0; H, 4·3; N, 22·4. $C_{10}H_7N_3O$ requires C, 64·9; H, 3·8; N, 22·7%), $\nu_{max.}$ 1610 cm.$^{-1}$ (C=O).

5-*Bromo*-3-*chloropyridazino*[4,3-b]*indolizine* (XXXIV).—3-chloropyridazino[4,3-*b*]indolizine (150 mg.) was dissolved in the minimum volume of pyridine at room temperature. Bromine (0·16 g.) in pyridine (2 ml.) was added dropwise, and the resulting orange suspension was stirred at room temperature for a further 15 min. The *product* was filtered off and washed with water and acetone. It crystallised from methanol in orange microneedles (0·15 g.), m.p., 223—225° (Found: C, 42·5; H, 2·0; Br, 28·0; Cl, 12·7; N, 14·5. $C_{10}H_5BrClN_3$ requires C, 42·5; H, 1·8; Br, 28·3; Cl, 12·55; N, 14·9%), τ 0·78 (1H, d, H-9), 2·02 (1H, s, H-4), and 2·35—3·05 (3H, m, H-6, H-7, H-8).

2-*Chloropyrido*[1′,2′:3,4]*imidazo*[1,2-b]*pyridazinium Chloride* (XIII; R = H).—6-Chloro-2-(2-pyridylmethyl)-pyridazin-3(2*H*)-one (6·9 g.), and phosphoryl chloride (75 ml.) were heated together under reflux for 1 hr. The excess of chloride was distilled off under reduced pressure at 60°, and the residue was added to ice–water (50 g.). The resultant fluorescent solution was adjusted to pH 4—5 (Na_2CO_3) and the suspension so formed was evaporated to dryness at 50° under reduced pressure. The residue was extracted with boiling chloroform (3 × 50 ml.), to remove non-ionic impurities, and then with boiling ethanol (4 × 100 ml.). The combined alcoholic extracts were evaporated and the residue of the crude *pyridazinium chloride* (6 g.) was crystallised from propanol to give clusters of yellow needles, m.p. 320° (decomp.) (Found: C, 50·6; H, 2·6; Cl, 28·8; N, 17·3. $C_{10}H_7Cl_2N_3$ requires C, 50·0; H, 2·9; Cl, 29·5; N, 17·5%), $\lambda_{max.}$ 218, 244, 252infl, 302infl, 316, 331, 384infl, 403, and 431infl nm. (ε 30,400, 17,200, 14,700, 3050, 6580, 7080, 6580, 7080, and 4030), τ 1·05 (1H, d, H-3), 1·1 (1H, d, H-6), 1·3 (1H, s, H-10), 1·95 (1H, d, H-9), 2·22 (1H, d, H-4), 2·3 (1H, m, H-8), and 2·58 (1H, t, H-7). The *bromide* (from a solution in water and potassium bromide) formed glistening yellow plates, m.p. 325° (decomp.) (from aqueous ethanol) (Found: C, 42·0; H, 2·5; Br, 28·6; Cl, 12·8; N, 14·7. $C_{10}H_7BrClN_3$ requires C, 42·2; H, 2·5; Br, 28·1; Cl, 12·5; N, 14·8%). The *iodide*, similarly prepared,

[20] ' Pyridine and Derivatives,' part 3, ed. E. Klingsberg, Interscience, New York, 1962, p. 720.

[21] ' Pyridine and Derivatives,' part 2, ed. E. Klingsberg, Interscience, New York, 1961, p. 232.

formed yellow crystals, m.p. 315° (decomp.) (from aqueous methanol) (Found: C, 36·0; H, 2·2; Cl, 11·0; I, 38·7; N, 12·5. $C_{10}H_7ClIN_3$ requires C, 36·2; H, 2·1; Cl, 10·7; I, 38·3; N, 12·7%).

2-*Chloro*-6-*methylpyrido*[1′,2′:3,4]*imidazo*[1,2-b]*pyridazinium Chloride* (XIII; R = Me).—Prepared similarly from 6-chloro-2-(6-methyl-2-pyridylmethyl)pyridazin-3(2*H*)-one (1·5 g.) and phosphoryl chloride (17·5 ml.), the crude *product* (1·2 g.) crystallised from propanol in large yellow crystals of the monohydrate, m.p. 300° (decomp.) (Found: C, 48·7; H, 3·8; Cl, 26·3; N, 15·1. $C_{11}H_9Cl_2N_3,H_2O$ requires C, 48·5; H, 4·1; Cl, 26·1; N, 15·4%), $\lambda_{max.}$ 222, 246, 267infl, 381infl, 291, 304infl, 319, 334, 384infl, 405, and 432infl nm. (ε 33,750, 17,460, 7460, 3730, 3430, 4000, 7720, 8710, 7020, 8460, and 5300), τ 0·97 (1H, d, H-3), 1·2 (1H, s, H-10), 2·0 (1H, d, H-9), 2·24 (1H, d, H-4), 2·3—2·4 (1H, m, H-8), 2·67 (1H, d, H-7), 6·8 (3H, s, CH_3). The *bromide* and *iodide* were prepared similarly. The former crystallised from methanol in yellow irregular plates, m.p. 305° (decomp.) (Found: C, 44·0; H, 3·0; Br, 27·0; Cl, 11·9; N, 13·9. $C_{11}H_9BrClN_3$ requires C, 44·2; H, 3·0; Br, 26·8; Cl, 11·9; N, 14·1%). The latter afforded yellow crystals, m.p. 300° (decomp.) (from water) (Found: C, 38·1; H, 3·5; Cl, 10·8; I, 36·2; N, 12·0. $C_{11}H_9ClIN_3$ requires C, 38·2; H, 3·75; Cl, 10·3; I, 36·7; N, 12·2%).

10-*Bromo*-2-*chloro*-6-*methylpyrido*[1′,2′:3,4]*imidazo*[1,2-b]-*pyridazinium Bromide*.—A solution of bromine (0·35 g.) in glacial acetic acid (2·5 ml.) was added dropwise to a solution of 2-chloro-6-methylpyrido[1′,2′:3,4]imidazo[1,2-*b*]pyridazinium chloride monohydrate (0·25 g.) in acetic acid (5 ml.). The resulting orange-yellow suspension was stirred for 15 min. The solid was filtered off and washed first with acetic acid and finally with ether. Crystallisation from aqueous dimethyl sulphoxide gave yellow needles (0·29 g.), m.p. 320° (decomp.), of the *bromo-bromide* (Found: C, 35·0; H, 2·0; Br, 42·2; Cl, 9·5; N, 11·2. $C_{11}H_8Br_2ClN_3$ requires C, 35·0; H, 2·1; Br, 42·3; Cl, 9·4; N, 11·1%), $\lambda_{max.}$ 226, 252, 260infl, 288infl, 300, 316infl, 331, 347, 392infl, 442, and 448infl nm. (ε 31,620, 14,790, 12,020, 3470, 3800, 4790, 9120, 10,230, 6920, 8710, and 6460), τ 0·95 (1H, d, H-3), 2·05 (1H, d, H-9), 2·21 (1H, d, H-4), 2·15—2·35 (1H, m, H-8), 2·68 (1H, d, H-7), and 6·81 (3H, s, CH_3).

10-*Bromo*-2-*chloropyrido*[1′,2′:3,4]*imidazo*[1,2-]*pyridazinium Bromide*.—Prepared from 2-chloropyrido[1′,2′:3,4]-imidazo[1,2-*b*]pyridazinium chloride as described for the 6-methyl analogue, the *bromide* formed yellow crystals, m.p. 320° (decomp.) (from dimethyl sulphoxide–ethanol) (Found: C, 33·0; H, 1·9; Br, 43·7; Cl, 10·3; N, 11·4. $C_{10}H_6Br_2ClN_3$ requires C, 33·0; H, 1·7; Br, 44·0; Cl, 9·8; N, 11·6%), $\lambda_{max.}$ 223, 252, 259infl, 285infl, 313infl, 329, 344, 396infl, 421, and 452infl nm. (ε 30,900, 17,380, 12,880, 3550, 4270, 8320, 8710, 6170, 7240, and 4170).

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