Position of Methylation of 2,3-Diaminopyridine and 3-Amino-2-methylaminopyridine

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Methylation of 3-amino-2-methylaminopyridine (III) with methyl iodide takes place exclusively at the 3-amino-group, unlike the cases of 2-methylaminopyridine and 3-aminopyridine where only ring methylation occurs. The position of methylation of 2,3-diaminopyridine (V) is solvent-dependent, with the ratio of ring to 3-amino-group methylation varying from 7·3:1 in acetonitrile to 1·1:1 in 4:1 2,2,2-trifluoroethanol–methanol. The diversion of methylation from the ring nitrogen atom to the 3-amino-group is attributed to a combination of steric and hydrogen-bonding effects.

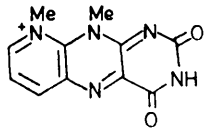
As part of a study of model compounds for oxidative co-enzymes [1] we wished to prepare the 8-azaflavin (I) and, in order to do so, we required the intermediate (II). Methylation of 3-amino-2-methylaminopyridine (III) appeared the obvious route to (II) since both 3-aminopyridine [2] and 2-methylaminopyridine [3] are

[1] J. M. McAndless and R. Stewart, *Canad. J. Chem.*, 1970, **48**, 263.

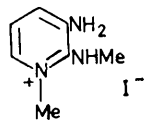
[2] N. F. Twritsyna and A. F. Vompe, *Doklady Akad. Nauk S.S.S.R.*, 1950, **74**, 509 (*Chem. Abs.*, 1951, **45**, 3846).

[3] A. E. Chichibabin, R. A. Konovalova, and A. A. Konovalova, *Ber.*, 1921, **54**, 814.

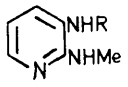
readily alkylated at the ring nitrogen atom. We found, however, that treatment of compound (III) with methyl iodide gave exclusively 2,3-bismethylaminopyridine (IV).



(I)



(II)



(III) R = H
(IV) R = Me

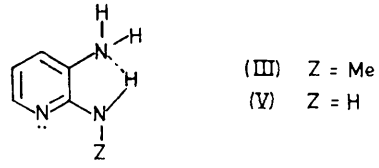
Other anomalies have been noted previously with regard to the position of alkylation of aminopyridines.[4] For example, although 2-aminopyridine, 2-methylaminopyridine, 3-dimethylaminopyridine, and 4-dimethylaminopyridine all undergo ring alkylation, 2-dimethylaminopyridine undergoes amino-group alkylation.[5,6] We now report a study of methylation of 2,3-diaminopyridine (V) and its 2-*N*-methyl derivative (III).

RESULTS AND DISCUSSION

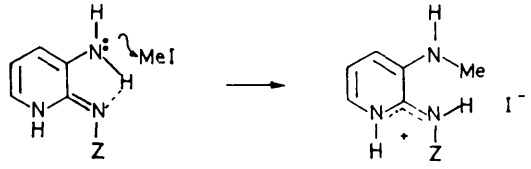
The product of methylation of compound (III) was shown to be the conjugate acid of (IV) by an unambiguous synthesis (see Experimental section). The n.m.r. spectrum of a sample of compound (II) synthesized by a different route (see Experimental section) showed the quaternary methyl group resonance at δ 4·0 p.p.m. No trace of such absorption was detected in the concentrated mother liquor remaining after the removal of the conjugate acid of (IV). Thus the amount of ring methylation of (III) must be extremely small.

Methylation of 2,3-diaminopyridine (V) occurs at both the ring nitrogen atom and the 3-amino-group. The product distribution is solvent-dependent, polar aprotic solvents favouring ring methylation more than hydrogen-bonding solvents. The figures in parentheses in the following list give the ratios (x : 1) of ring methylation to 3-*N*-methylation at room temperature: acetonitrile (7·3), acetone (3·8), tetrahydrothiophen dioxide (3·0), ethanol (2·3), methanol (2·2), no solvent (1·9), 1 : 1 methanol–phenol (1·5), 4 : 1 2,2,2-trifluoroethanol–methanol (1·1). The approximate reaction times were 4 h for the first five systems and 2—3 days for the last three. Refluxing the reaction mixtures reduced the amount of ring methylation in the case of acetonitrile but increased it in the case of the trifluoroethanol–methanol system. In all solvents studied the total yield of monomethylation product was nearly quantitative.

The results can be explained by assuming that the nucleophilicities of the various centres (as indicated by their equilibrium acidities) are modified by two factors: steric hindrance[7] and hydrogen bonding. If nucleophilicity were directly proportional to base strength, ring methylation would be expected to predominate over amino-methylation in all cases.[8] 2-Dimethylaminopyridine, but not 2-methylaminopyridine, is methylated at the amino-group rather than at the ring nitrogen atom and Frampton, Johnson, and Katritzky[6] have ascribed this to a combination of steric and electronic factors. The forced coplanarity of the *N*-methyl groups and the ring that results from the conjugative interaction between ring and side-chain nitrogen atoms screens the ring nitrogen atom from attack by methyl iodide. Our results show that a 3-amino-group greatly reduces the susceptibility of the ring nitrogen atom to substitution even when the 2-amino-group is unmethylated or monomethylated. We conclude that hydrogen-bonding interaction of the type illustrated locks the 2-*N*-methyl group in (III) in a position where the ring nitrogen atom is effectively screened. A similar but smaller effect presumably applies to the unmethylated compound (V).



(III) Z = Me
(V) Z = H



(VI)

Substitution occurs at the 3-position even though such hydrogen-bonding would be expected to impair the nucleophilicity of the 3-amino-group. An alternative explanation is that substitution occurs *via* the minor tautomer (VI), which could give the product directly.

EXPERIMENTAL

Materials.—2,3-Bismethylaminopyridine (IV) was prepared by the following four-step procedure. 3-Amino-2-chloropyridine was converted into its 3-*N*-*p*-tolylsulphonyl derivative, and thence into 2-chloro-3-*N*-methyl-*p*-tolylsulphonylaminopyridine and 2-chloro-3-methylaminopyridine in 52% overall yield.[9] The last compound (2 g) was heated with aqueous 40% methylamine (15 ml) and copper sulphate (0·5 g) at 160° for 20 h. The resulting solution was extracted with ether; the extract was evaporated and the resulting *solid* recrystallized from benzene–petroleum; yield 55%, m.p. 97·8—98·2° (Found: C, 61·1; H, 8·1; N, 30·8. $C_7H_{11}N_3$ requires C, 61·25; H, 8·1; N, 30·65%). The n.m.r. spectrum of this compound in D_2O was identical to that of the free base obtained from the

[4] G. B. Barlin and A. C. Young, *J. Chem. Soc.* (*B*), 1971, 1675, 2323.
[5] A. E. Chichibabin and R. A. Konovalova, *Ber.*, 1926, **59**, 2055.
[6] R. Frampton, C. D. Johnson, and A. R. Katritzky, *Annalen*, 1971, **749**, 12.
[7] J. Packer, J. Vaughan, and E. Wong, *J. Amer. Chem. Soc.*, 1958, **80**, 905; H. C. Brown and A. Cahn, *ibid.*, 1955, **77**, 1715.
[8] G. B. Barlin, *J. Chem. Soc.*, 1964, 2150.
[9] J. W. Clark-Lewis and M. J. Thompson, *J. Chem. Soc.*, 1957, 442.

product of the reaction of 3-amino-2-methylaminopyridine with methyl iodide.

The *hydriodide* of (IV) had m.p. 265—270° (decomp.) (Found: C, 31·65; H, 4·7; N, 16·05. $C_7H_{12}IN_3$ requires C, 31·7; H, 4·55; N, 15·85%), and was identical (n.m.r. spectrum and m.p.) with the product from 3-amino-2-methylaminopyridine.

3-Amino-1-methyl-2-methylaminopyridinium iodide (II) was prepared by the following four-step sequence. 3-Amino-2-chloropyridine (10 g) was converted into its 3-*N*-acetyl derivative,[10] which was, in turn, converted into 3-acetylamino-2-chloro-1-methylpyridinium iodide by refluxing in methanol with methyl iodide. Recrystallization of the product from propan-2-ol containing a small amount of ether gave white *needles*, m.p. 144—146° (decomp.) (Found: C, 30·45; H, 3·05; N, 8·9. $C_8H_{10}ClIN_2O$ requires C, 30·7; H, 3·25; N, 8·95%). This compound (12 g) was dissolved in hydrochloric acid (1N; 30 ml) and warmed on a boiling water bath for 0·5 h; the solution was then evaporated to dryness to give 3-amino-2-chloro-1-methylpyridinium iodide (94%), white *needles* (from ethanol), m.p. 172—173° (decomp.) (Found: C, 26·4; H, 2·75; N, 10·15. $C_6H_8ClIN_2$ requires C, 26·6; H, 3·0; N, 10·35%). This product (3 g), dissolved in water (10 ml) and aqueous 40% methylamine (15 ml), was warmed on a water-bath for 1 h; the solution was then evaporated to dryness. Methylammonium iodide was removed by dissolving the residue in aqueous 10% sodium carbonate, evaporating the solution to dryness, and then adding ethanol (25 ml). The suspension was shaken well and then filtered. The filtrate was evaporated to dryness and the residue was recrystallized twice from ethanol–propan-2-ol to give white *needles* (2·2 g), m.p. 149—149·8° (76%) (Found: C, 31·9; H, 4·55; N, 15·9. $C_7H_{12}IN_3$ requires C, 31·7; H, 4·55; N, 15·85%), δ (D_2O) 3·20 (3H, s, 3-*N*-Me), 4·00 (3H, s, 1-Me), 6·93 (1H, q), 7·39 (1H, q), and 7·53 (1H, q).

2,3-Diamino-1-methylpyridinium iodide was prepared by bubbling ammonia through a solution of 3-amino-2-chloro-1-methylpyridinium iodide (3 g) in methanol (40 ml) for 1 h. Ammonium iodide was removed by sodium carbonate treatment as in the previous procedure and the product, crystallized from propan-2-ol, gave white *needles* (1·5 g, 64%), m.p. 121—123° (Found: C, 28·8; H, 4·0; N, 16·7. $C_6H_{10}IN_3$ requires C, 28·7; H, 4·0; N, 16·75%), δ (D_2O) 3·87 (3H, s), 6·80 (1H, q), 7·30 (1H, q), and 7·45 (1H, q).

2-Amino-3-methylaminopyridine[9] and its hydriodide (m.p. 191—192°) were obtained from 2-chloro-3-methylaminopyridine in a manner analogous to that used for the preparation of (IV) and its salt.

Reaction of 3-Amino-2-methylaminopyridine with Methyl Iodide.—3-Amino-2-methylaminopyridine (III)[10] (1·2 g) was stirred in methanol (1 ml) with excess of methyl iodide (2 g) for 15 h. Fractional crystallization yielded 2,2-bismethylaminopyridinium iodide (2·0 g, 85%), m.p. 265—270°. A solution of this compound (1 g) in water (10 ml) was made slightly basic with sodium carbonate, saturated with sodium chloride, and then extracted with ether. Evaporation, and recrystallization of the residue from benzene–petroleum gave white needles, m.p. 97·5—98°, of 2,3-bismethylaminopyridine (Found: C, 61·05; H, 8·35; N, 30·35%).

Reaction of 2,3-Diaminopyridine with Methyl Iodide.—2,3-Diaminopyridine (*ca.* 40 mg) and methyl iodide (200 mg) were stirred in the solvent (0·8 ml) for, in most cases, 4 h. After the solvent and excess methyl iodide had been removed by evaporation the residue was dissolved in D_2O and the n.m.r. spectrum of the solution was recorded. In all cases the product consisted of a mixture of the ring-methylated and 3-*N*-methylated products in almost quantitative yield, as shown by absorptions at δ 3·87 and 2·85 p.p.m. The absence of absorption at δ 3·13 showed that little, if any, 2-*N*-methylation had occurred. [All n.m.r. chemical shifts were measured from tetramethylsilane in organic solvents or from sodium 2,2-dimethyl-2-silapentane-5-sulphonate in deuterium oxide (internal references).]

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[10] O. V. Schickh, A. Binz, and A. Schulz, *Ber.*, 1936, **69**, 2593.