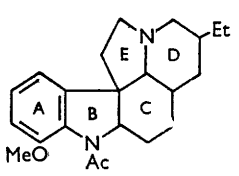
294. *The Constitution of Aspidospermine. Part IV.**

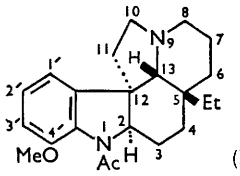
By G. F. Smith and J. T. Wróbel.

The pyridine base obtained by Witkop by dehydrogenation of aspidospermine is shown to be a mixture of 3-ethyl-5-methyl- and 3,5-diethylpyridine. The degradation of the alkaloid around N(*a*) is described. Steric hindrance at N(*b*) is discussed in the light of the structure proposed by Nyburg and Mills for aspidospermine *N*(*b*)-methiodide on the basis of *X*-ray crystallographic studies. Also, a synthesis of 2,3-diethylpyridine is described.

Aspidospermine, for which structure (I) had earlier been tentatively proposed [1,2] on the report by Witkop [3] of the formation of skatole, 3-ethylindole, and 3,5-diethylpyridine on



(I)



(II)

dehydrogenation with zinc dust, has recently been shown by Nyburg and Mills [4] to have structure (II) as the result of the *X*-ray crystallographic analysis of aspidospermine *N*(*b*)-methiodide. The identity of Witkop's dehydrogenation base with 3,5-diethylpyridine has for some time been considered not to be finally established, because of the large discrepancy

Picrate of	M. p.
(i) 3,5-Diethylpyridine (A)	158—162°
(ii) 3-Methyl-5-methylpyridine (B)	188—192
Mixtures of (A) and (B):	
(iii) 3 : 1	159—169
(iv) 1 : 1	170—179
(v) 1 : 3	178—184
(vi) Dehydrogenation base (C) [3,5]	180—182, sinters 168
(vii) Mixture of (A) and (C) [3]	182, sinters 168

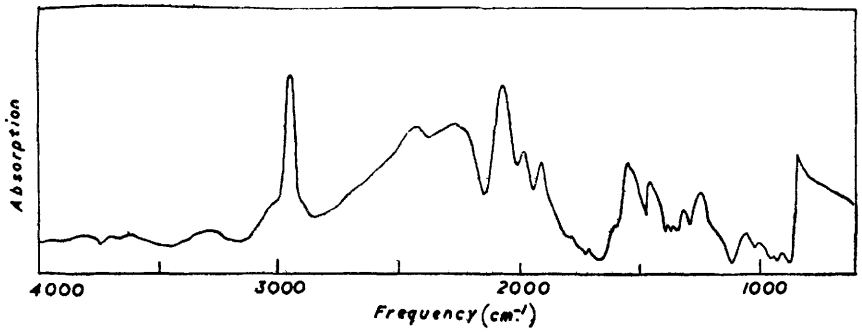
between the melting points of the picrates of the dehydrogenation product and of pure synthetic 3,5-diethylpyridine. Witkop himself later [5] suggested that the dehydrogenation product might be a mixture of 3,5-diethyl- and 3-ethyl-5-methyl-pyridine. We

* Part III, Everett, Openshaw, and Smith, *J.*, 1957, 1120.

[1] Openshaw, Smith, and Chalmers, 13th Internat. Congr. Pure and Appl. Chem., 1953, Abs., p. 223.
[2] Witkop and Patrick, *J. Amer. Chem. Soc.*, 1954, **76**, 5603.
[3] Witkop, *ibid.*, 1948, **70**, 3712.
[4] Mills and Nyburg, preceding paper.
[5] Witkop, *J. Amer. Chem. Soc.*, 1957, **79**, 3193.

have investigated this question experimentally, and find Witkop's suggestion to be correct. The picrate of 3-ethyl-5-methylpyridine does not in fact depress the melting point of 3,5-diethylpyridine picrate. The melting points in the annexed Table were determined on a Kofler block. In all cases, including the pure substances, there was considerable

Infrared spectrum of 3-*ethyl*-5-*methylpyridine hydrochloride in chloroform. Principal bands are at* 2950, 2435, 2280, 2070, 1990, 1905, 1550, 1455, 1320, 1255, 1060, 900, *and* 860 *cm.*$^{-1}$.

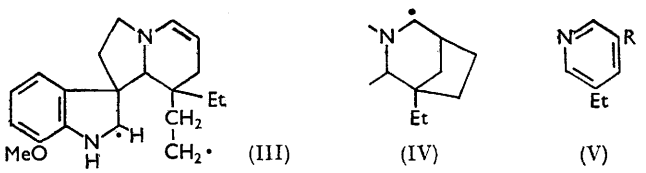


distillation of picric acid on to the cover slip: this, the result of some dissociation of the picrate, began to occur well below the actual melting point of the crystals, and complicated matters somewhat.

The last two m. p.s are Dr. Witkop's and are not incompatible with m. p.s (iv) and (v), this type of observation being so subject to personal variation. It is relevant that (A) and (B) strongly depress the m. p.s of 3-ethyl-4-methyl-, 5-ethyl-2-methyl-, 3-ethyl-2-methyl-, and 3,4-dimethyl-pyridine picrates.

A further observation perhaps of greater importance is that the infrared spectrum of 3-ethyl-5-methylpyridine hydrochloride in chloroform (Figure) is, if anything, more closely similar to that published [3] for the dehydrogenation base hydrochloride than is that of 3,5-diethylpyridine hydrochloride. We therefore conclude that the base isolated by Witkop is a mixture of 3-ethyl-5-methyl- and 3,5-diethyl-pyridine in which the former predominates.

The simple aromatisation of ring D in aspidospermine is prevented by the quaternary nature of $C_{(5)}$. In such cases aromatisation, if it occurs, is the result of either the elimination of one of the blocking groups or its migration to an adjacent ring atom. The aspidospermine case is special in that there is specific 1,3-migration. The only explanation which occurs to us is that the break-up of the molecule involves a stage such as (III), in which the ethylene radical swings round to form a bridged intermediate (IV), which subsequently aromatises to (V; R = Me or Et). Quebrachamine, another alkaloid



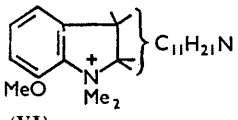
(III) (IV) (V)

present in *Aspidosperma quebracho blanco*, yields the same mixture of pyridines,[5] and is thus very likely to have structure (II) with no 12,13-bond and an aromatic ring B. The only other instance of 3,5-dialkylpyridine formation is the dehydrogenation of ibogaine, which yields pure 3-ethyl 5-methylpyridine: [6] this is formed without skeletal rearrangement.

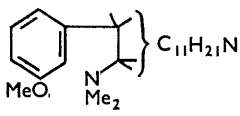
In the systematic degradation of aspidospermine, Dr. H. Conroy studied reactions

[6] Goutarel, Janot, Mathys, and Prelog, *Compt. rend.*, 1953, **237**, 1718.

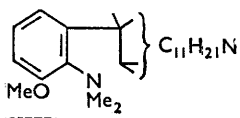
around N(*b*),[7] and we studied reactions around N(*a*). Deacetyl-1,1-dimethylaspidosperminium iodide (VI) (the *a*-methiodide) reacts very rapidly with sodium in dry liquid ammonia, to give a mixture of bases which inexplicably contained a variable and appreciable proportion of polymeric material. Up to 72% of a base A, $C_{22}H_{34}ON_2$, was however obtained and characterised as its crystalline perchlorate. The ultraviolet absorption of base A corresponds to that of anisole. This in itself was not sufficient to



(VI)



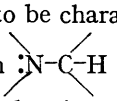
(VII)

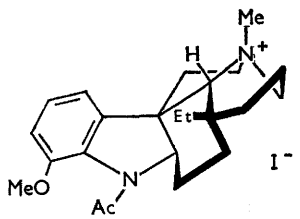


(VIII)

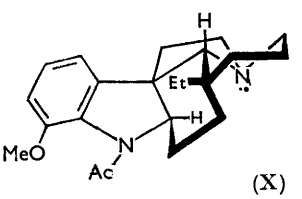
discriminate between the alternatives (VII) and (VIII), for the latter contains a highly sterically hindered dimethylamino-group, which would not be expected to conjugate with the methoxybenzene ring. Nor could a discrimination be achieved by pK_a measurements, for protonated N(*b*) might be expected to lower the basicity of the now aliphatic N(*a*) in (VII), and the N(*a*) in (VIII), not being in conjugation with the aromatic ring would be much more basic than in a normal arylamine. Prolonged heating of base A with methyl iodide at 100° led to the elimination of N(*a*) as tetramethylammonium iodide and the formation of an amorphous monomethiodide, which was converted by Hofmann degradation into base B, $C_{20}H_{27}ON$ or $C_{21}H_{29}ON$. This base did not give a crystalline derivative, but the addition of one mol. of hydrogen over Adams catalyst led to a base C, $C_{20}H_{29}ON$ or $C_{21}H_{31}ON$, characterised as the crystalline perchlorate. The easy elimination of N(*a*) from base A shows the latter to have structure (VII).

Distillation of base A (VII) with zinc dust gave a 4% yield of indole, isolated as the picrate and as the 3-formyl derivative. The formation of indole is very surprising, for on the basis of structure (II) for aspidospermine one would have expected 7-ethyl- or 7-n-propyl-indole. Dehydrogenation of base B with zinc dust or selenium failed to give a homogeneous product. We had hoped that, after ring B had been opened, dehydrogenation would give valuable skeletal information. We had not reckoned with the presence of a second quaternary carbon atom which effectively prevented the straightforward dehydrogenations hoped for on the basis of structure (I).

All aspidospermine derivatives with a tertiary N(*b*) show a medium well-defined infrared band between 2750 and 2800 cm.$^{-1}$. This band, which has been shown to be characteristic of *N*-methyl groups,[8] is more generally characteristic of the system  in which the nitrogen *p*-electrons and the hydrogen are *trans* and coplanar with the nitrogen and the carbon.[9] The stereochemistry of aspidospermine *N*(*b*)-methiodide has been shown by Nyburg and Mills [4] to be (IX), in which ring C is a chair and ring D a boat



(IX)



(X)

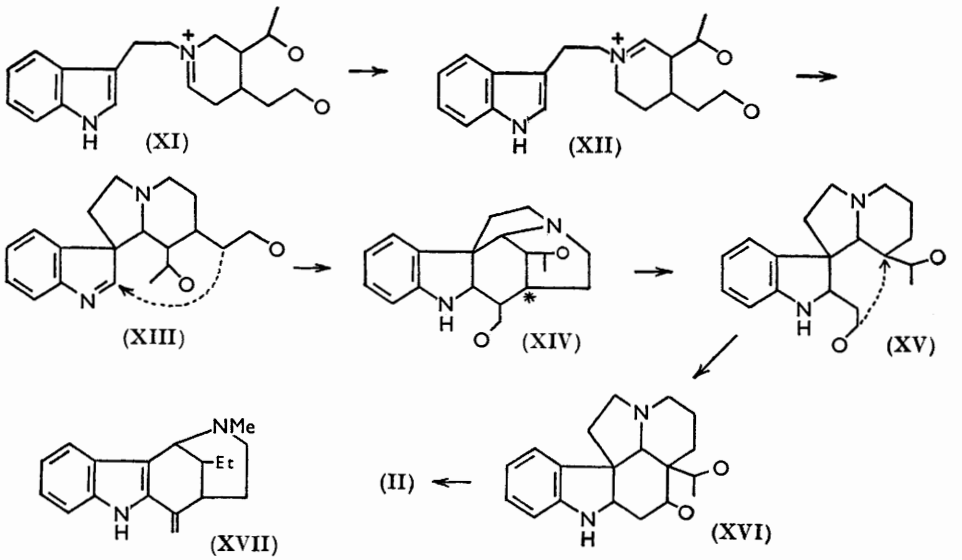
form, and the quaternary *N*(*b*)-methyl group is *cis* to the 13-hydrogen atom. If aspidospermine itself had the same stereochemistry, no band in the 1750—1800 cm.$^{-1}$ region

[7] Conroy, Brook, Rout, and Silverman, *J. Amer. Chem. Soc.*, 1958, **80**, 5178.
[8] Hill and Meakins, *J.*, 1958, 760; Braunholz, Ebsworth, Mann, and Sheppard, *ibid.*, p. 2780.
[9] Bohlmann, *Angew. Chem.*, 1957, **69**, 641; Wenkert and Roychaudhuri, *J. Amer. Chem. Soc.*, 1956, **78**, 6417.

would be expected. Simple inversion of N(*b*), however, leads to structure (X), in which both rings C and D are chair forms: in this structure the *p*-electrons on N(*b*) and the 13-hydrogen atom are in *trans*-relation. We therefore suggest that formula (X) represents the stereochemistry of aspidospermine. This structure explains the failure of the alkaloid to react with methyl iodide at room temperature, for a model shows the approach to the N(*b*) *p*-electrons to be sterically hindered, mainly by the axial 2-hydrogen atom. At a higher temperature, increased thermal energy renders possible a change to the less favoured conformation corresponding to (IX), in which ring D becomes a boat: in this conformation N(*b*) is no longer sterically hindered and reacts with methyl iodide to give the salt (IX).

The positional change of the ethyl group in aspidospermine from position 7 to 5 calls for a revision of existing biogenetic schemes.[10,11] It is not easy to see how Wenkert's ingenious and important ideas involving transformations of prephenic acid and its derivatives at a very early stage of the biosynthesis [11] can be modified to produce a scheme for aspidospermine. We feel that the precursor (XI), common to so many indole alkaloids both of the yohimbine and the strychnine type, may also be the starting point for the formation of structure (II), and suggest the annexed scheme.

The change (XI) ⟶ (XII) is a simple reduction–oxidation sequence, and indeed an analogous change is invoked by Wenkert for the formation of ibogaine.[11; cf. 12] The changes (XII) ⟶ (XIV) follow Woodward's well-known strychnine scheme. Conversion of (XIV) into (XV) may be looked on as a reverse Michael reaction followed by reduction of the αβ-unsaturated ketone system, or, after introduction of oxygen at the carbon atom marked *, as a reverse aldol reaction. The latter device was employed in a previous biogenetic scheme [10] for structure (I). This particular sequence of changes was suggested by another *Aspidosperma* alkaloid, ulein, to which Büchi and Warnhoff [13] have assigned structure (XVII). This is seen to be very closely related to the intermediate (XIV).



During this work we had occasion to prepare aspidosine, the phenolic deacetyldemethylaspidospermine. By carrying out the hydrolysis with concentrated hydrobromic acid at 140° in an evacuated sealed tube the yield of apidosine was 73·5%, which is a very marked improvement on the previous highest yield of 25% reported by Witkop.[2]

[10] Everett, Openshaw, and Smith, *J.*, 1957, 1120.
[11] Wenkert, *Experientia*, 1959, **15**, 165.
[12] Taylor, *ibid.*, 1957, **13**, 454.
[13] Büchi, personal communication.

Whilst exploring the question of the identity of the dialkylpyridine picrate obtained from aspidospermine, we prepared the hitherto unknown 2,3-diethylpyridine, the last of the six isomers. The synthesis started from the known 3-ethyl-2-methylpyridine and followed an established sequence of reactions,[14] *i.e.*, condensation with formaldehyde to give 3-ethyl-2-2′-hydroxyethylpyridine, followed by dehydration to 3-ethyl-2-vinylpyridine, and catalytic hydrogenation.

Experimental

Base A (VII).—Deacetyl-1,1-dimethylaspidosperminium iodide (2 g.) in dry liquid ammonia (500 ml.) was treated with sodium until the blue colour persisted for a few minutes. Ammonium chloride was added, the ammonia boiled off, and the residue divided between water and ether–light petroleum (1 : 20). The organic phase yielded a colourless gum (1·45 g.) which on being distilled at 150° (bath-temp.)/0·01 mm. in a short-path apparatus gave *base A* as a colourless viscous liquid (1·05 g., 72%), $\lambda_{max.}$ 276, 282 mμ (ε 2240, 2020 respectively) (Found: C, 77·25; H, 9·75; N, 7·85. $C_{22}H_{34}ON_2$ requires C, 77·15; H, 10·0; N, 8·15%). The perchlorate crystallised from aqueous alcohol as prisms, m. p. 140—142° (Found: C, 47·4; H, 6·65; N, 5·15. $C_{22}H_{34}ON_2,2HClO_4,H_2O$ requires C, 47·1; H, 6·8; N, 5·0%).

Base B.—Base A (70 mg.) was heated in a sealed tube at 100° with methyl iodide (2 ml.) for 5 hr. The product was taken up in methanol, and the tetramethylammonium iodide (identified by its infrared spectrum) which crystallised was filtered off (21 mg.). The filtrate was evaporated, and the residue heated with methyl iodide (2 ml.) in a sealed tube at 100° for 5 hr. A further quantity of tetramethylammonium iodide (9 mg.) was obtained. The amorphous methiodide was converted into the quaternary hydroxide by means of silver oxide; distillation at 130°/0·01 mm. then yielded *base B* as a colourless liquid (50·6 mg., 86%) (Found: C, 80·75; H, 8·8; N, 4·75. $C_{20}H_{27}ON$ requires C, 80·75; H, 9·15; N, 4·7. $C_{21}H_{29}ON$ requires C, 81·0; H, 9·3; N, 4·5%).

Base C.—Base B (50 mg.) was hydrogenated in ethanol–glacial acetic acid (4 : 1). 1·1 mol. of hydrogen were taken up in 1·5 hr. Distillation of the product at 130—140° (bath-temp.)/0·1 mm. yielded a colourless liquid (41 mg.) which with two drops of concentrated perchloric acid gave, with difficulty, a crystalline perchlorate. One crystallisation from aqueous methanol yielded thick prisms, m. p. 215—217° (22·5 mg.), $\lambda_{max.}$ 274, 278 mμ (ε 2160, 2230 respectively) (Found: C, 60·3; H, 7·65. $C_{20}H_{29}ON,HClO_4$ requires C, 60·2; H, 7·5. $C_{21}H_{31}ON,HClO_4$ requires C, 60·9; H, 7·75%).

Dehydrogenation of Base A.—A mixture of base A (125 mg.) and zinc dust (4 g.) was heated under nitrogen in a sealed tube at 370° for 40 min., then extracted with boiling ethanol, and the extract divided into neutral and basic fractions. The latter failed to yield a crystalline salt. The neutral fraction was distilled at 140° (bath-temp.)/0·01 mm., a yellow viscous oil (20 mg.) being obtained which with ethanolic picric acid yielded a red picrate as needles, m. p. 112° with resolidification and remelting at 168°. This picrate did not depress the m. p. of indole picrate. The indole was recovered from the picrate and was formylated by dimethylformamide and phosphorus oxychloride to give a crystalline product, m. p. 194—198° (2·2 mg., 4% calc. on base A) alone or mixed with 3-formylindole of the same m. p.

Aspidosine.—Aspidospermine (942 mg.) in 48% hydrobromic acid (20 ml.) was heated in an evacuated sealed tube at 140° for 2·5 hr. The mixture was poured into water and basified with aqueous ammonia. The crude dried product crystallised from ethanol in two crops, to give brownish plates, m. p. 249—253° (583 mg., 73·5%).

3-Ethyl-2-2′-hydroxyethylpyridine.—3-Ethyl-2-methylpyridine (500 mg.) and paraformaldehyde (130 mg.) were heated in a sealed tube for 8 hr. at 140°. The product was distilled, and the fraction boiling below 100°/0·5 mm. (170 mg.) was again heated with paraformaldehyde (50 mg.) for 5 hr. at 140°. The products from this and the first run boiling above 100°/0·5 mm. were combined and redistilled: the 3-ethyl-2-2′-hydroxyethylpyridine distilled at about 110°/0·5 mm. (268 mg., 43%). The *picrate* formed yellow prisms (from ethanol), m. p. 114—115° (Found: C, 47·6; H, 4·3. $C_{15}H_{16}O_8N_4$ requires C, 47·4; H, 4·25%).

3-Ethyl-2-vinylpyridine.—The above pyridine (235 mg.) was treated with powdered potassium hydroxide (100 mg.), left overnight, and distilled under reduced pressure. 3-Ethyl-2-vinylpyridine boils at 85—90°/18 mm. (181 mg., 67%). The *picrate* crystallised from ethanol

[14] Frank, Blegen, Dearborn, Myers, and Woodward, *J. Amer. Chem. Soc.*, 1946, **68**, 1368.

as yellow needles, m. p. 115—117° (Found: C, 49·5; H, 3·85. $C_{15}H_{14}O_7N_4$ requires C, 49·7; H, 3·9%).

2,3-*Diethylpyridine*.—3-Ethyl-2-vinylpyridine (181 mg.) was hydrogenated in ethanol over Adams catalyst. One mol. of hydrogen was taken up in 30 min. The 2,3-diethylpyridine was not distilled, but was converted directly into its *picrate* which crystallised from ethanol as needles, m. p. 103—104° (410 mg., 83%) (Found: C, 49·5; H, 4·45. $C_{15}H_{16}O_7N_4$ requires C, 49·45; H, 4·45%).

We are grateful to Dr. T. White of the Forestal Land, Timber and Railways Co. Ltd. for a supply of *Aspidosperma quebracho palarosa* bark, to Professor M.-M. Janot and to Dr. B. Witkop for specimens of 3-ethyl-5-methyl- and 3,5-diethyl-pyridine picrates, to Dr. S. C. Nyburg and Mr. J. F. D. Mills for valuable collaboration in connection with the pyridine picrates, and to the Polish Ministry of Education for a grant (to J. T. W.).

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[*Received, July 14th*, 1959.]