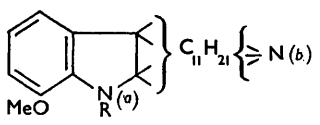
221. *The Constitution of Aspidospermine. Part III.* Reactivity at the Nitrogen Atoms, and Biogenetic Considerations.*

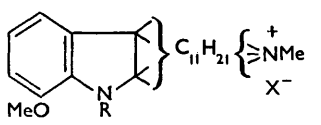
By A. J. Everett, H. T. Openshaw, and G. F. Smith.

Aspidospermine methiodide and deacetyl-*N*-methylaspidospermine dimethiodide have been prepared, and the nature of deacetyl-*N*-methylaspidospermine monomethiodide has been established. Thermodynamic dissociation constants of aspidospermine and several derivatives are recorded. A tentative structure for aspidospermine is discussed from the biogenetic aspect.

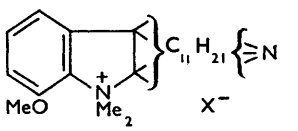
Aspidospermine (Ia) does not react with methyl iodide at room temperature,[1] and previous attempts to prepare a methiodide at elevated temperature have resulted only in ill-defined, amorphous products. However, a crystalline methiodide (IIa) has now been obtained by prolonged interaction of the components at 56°. The rather sluggish reactivity of the basic nitrogen atom, N(*b*), is most probably due to steric hindrance, since its basic strength (see Table) is comparable with that of strychnine, for example, which reacts readily with methyl iodide.



(I) a: R = Ac
b: R = H
c: R = Me



(II) a: R = Ac, X = I
b: R = Me, X = I
c: R = H, X = Br



(III) a: X = I
b: X = Br

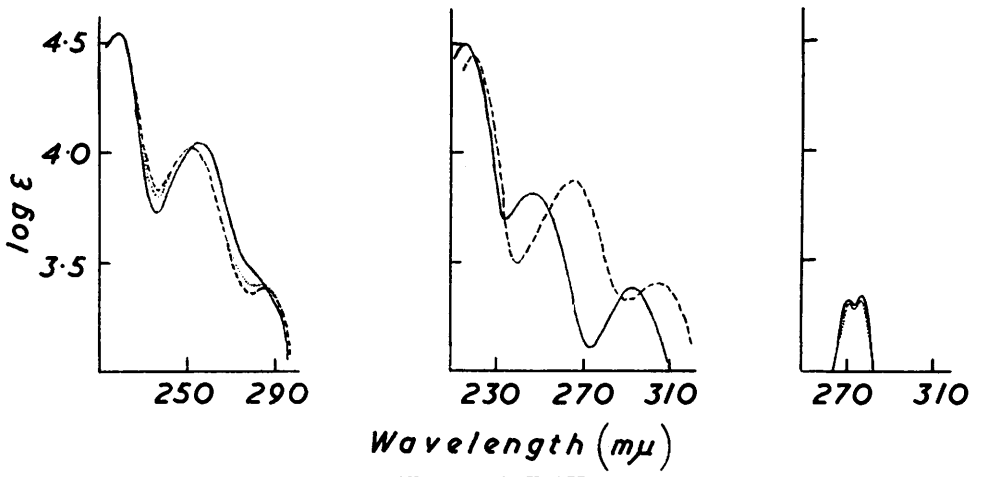
Deacetylaspidospermine (Ib), in contrast, reacts with methyl iodide in the cold to give deacetyl-*N*(*a*)-methylaspidospermine monomethiodide hydriodide (this product was wrongly described by Ewins [1] as a dimethiodide [2,3]). On treatment with alkali this gives the monomethiodide, which Witkop and Patrick [3] designated as deacetyl-*N*(*a*)-methylaspidospermine *N*(*b*)-methiodide (IIb) without any clear justification. In view of the

* Part II, preceding paper.

[1] Ewins, *J.*, 1914, **105**, 2738.
[2] Openshaw, Smith, and Chalmers, 13th Internat. Congr. Pure & Appl. Chem., 1955, Abs., p. 223.
[3] Witkop and Patrick, *J. Amer. Chem. Soc.*, 1954, **76**, 5603.

low reactivity of $N(b)$ in aspidospermine, the structure (IIIa) seemed to us more probable, and this is shown to be correct by a comparison of the ultraviolet absorption spectra of various aspidospermine derivatives. In agreement with expectation, Fig. 1 shows that protonation or quaternisation of $N(b)$ does not fundamentally alter the spectrum of aspidospermine. In contrast, the profound effect of protonation of $N(a)$ is shown by comparing the spectra of deacetylaspidospermine (Fig. 2) and its dihydrochloride (Fig. 3). Since the spectrum of deacetyl-$N(a)$-methylaspidospermine monomethobromide (derived from the

FIG. 1. FIG. 2. FIG. 3.



All spectra in EtOH.

FIG. 1. *Absorption spectra of aspidospermine* (——), *aspidospermine in* 0·1N-HCl (. . . .), *and aspidospermine methiodide* (– – – –).

FIG. 2. *Absorption spectra of deacetylaspidospermine* (——) *and deacetyl-*N(a)*-methylaspidospermine* (– – – –).

FIG. 3. *Absorption spectra of deacetyl-*N(a)*-methylaspidospermine* N(a)*-methobromide* (——) *and deacetylaspidospermine in* 0·1N-HCl.

methiodide) resembles that of deacetylaspidospermine dihydrochloride (Fig. 3), the structure (IIIa) is established for the monomethiodide.

The correctness of structure (IIIa) is confirmed by a consideration of the pK_a values of

pK_a *Values of aspidospermine and derivatives in aqueous solution.*

Compound	Basic centre	pK_a at 25°	Method
Aspidospermine (I*a*)	$N(b)$	7·63, 7·51	1, 2
Deacetylaspidospermine (I*b*)	$N(b)$	8·45, 8·48	1, 2
	$N(a)$	2·70	3
Deacetylaspidospermine $N(b)$-methobromide (II*c*)	$N(a)$	2·60 *	4
Deacetyl-$N(a)$-methylaspidospermine $N(a)$-methobromide (III*b*)	$N(b)$	6·13	1, 3
Hexahydro-8-methoxycarbazole	$N(a)$	5·43	4
Strychnine	$N(b)$	8·26	1

1, Titration in dilute solution (10^{-4}—10^{-5}M). 2, Precipitation titration. 3, Titration (10^{-1} and 10^{-2}M). 4, Spectroscopic. * At 21°.

The thermodynamic pK_a values were obtained by applying a correction, according to the Debye–Hückel equation, to pK_a' values derived from measurements in dilute aqueous solution. Deacetylaspidospermine $N(b)$-methobromide was titrated at ionic strengths ranging from 2×10^{-5} to 2×10^{-2} and the extrapolated pK_a was identical within the limits of measurement ($\pm$ 0·01 pK_a unit) with the values corrected according to the above method. Details of the experimental techniques will be published later.

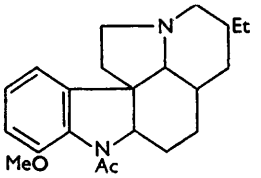
the compounds shown in the Table. The dissociation constant of the related methobromide (IIIb) corresponds to that of non-quaternised $N(b)$ in the environment of the positive charge on $N(a)$. By contrast, deacetylaspidospermine $N(b)$-monomethobromide

(IIc), prepared by the hydrolysis of aspidospermine methiodide, has a dissociation constant corresponding to the second dissociation constant of deacetylaspidospermine.

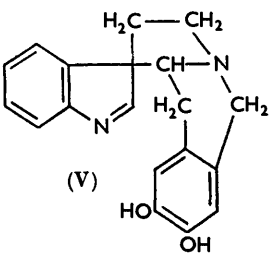
The difference between the pK_a of $N(a)$ in (IIc), or in deacetylaspidospermine, and the pK_a of hexahydro-8-methoxycarbazole ($\Delta pK_a = 2{\cdot}73$ and $2{\cdot}63$ respectively) can be attributed to the influence of the positive charge on $N(b)$. The effect on the pK_a of $N(b)$ of a positive charge on $N(a)$ is similar but somewhat smaller [compare (IIIb) with (Ib); $\Delta pK_a = 2{\cdot}32$]. Presumably this is because the positive charge on $N(a)$ is delocalised through polarisation of the attached methoxylated benzene ring.* Comparison of these pK_a differences with those recorded [4, 5] for the diamines, $H_2N{\cdot}[CH_2]_n{\cdot}NH_2$ ($n = 2$, $\Delta pK_a = 3{\cdot}0$; $n = 3$, $\Delta pK_a = 2{\cdot}0$), suggests that $N(a)$ and $N(b)$ in aspidospermine are separated by 2 or 3 carbon atoms. The greater compactness and rigidity of the aspidospermine structure probably increases the ΔpK_a value over that for an open-chain diamine, and the observed values are thus consistent with a separation of the nitrogen atoms by a chain of 3 carbon atoms.

The monomethiodide (IIIa) does not react with methyl iodide in the cold, but does so readily at 100°, giving deacetyl-$N(a)$-methylaspidospermine dimethiodide. Preliminary observations indicate that both this compound and aspidospermine methiodide (IIa) are susceptible to Hofmann degradation; in contrast, and in agreement with the assigned structure, the quaternary hydroxide derived from the monomethiodide (IIIa) does not undergo ring-fission but gives deacetyl-$N(a)$-methylaspidospermine (Ic) on pyrolysis.[2, 3]

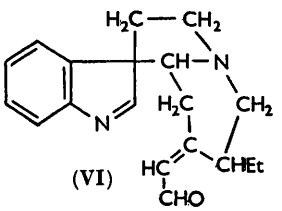
Failure to dehydrogenate aspidospermine or its derivatives to indole derivatives by



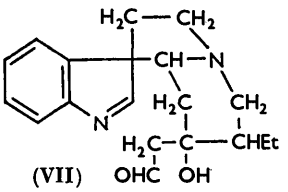
(IV)



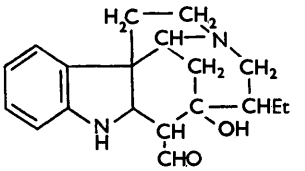
(V)



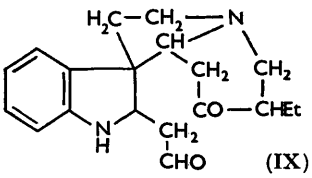
(VI)



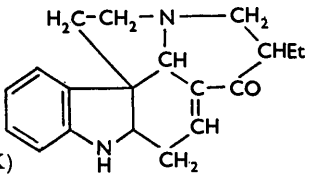
(VII)



(VIII)



(IX)



(X)

means of mild oxidising agents such as mercuric acetate indicates the presence of a blocked dihydroindole structure, and suggests that aspidospermine belongs biogenetically to the "β-indole series." [6] The structure (IV) has been proposed [2, 3, 7] because it accounts well

* The pK_a of $N(b)$ in aspidospermine is lowered similarly, but to a lesser extent, by the influence of the dipolar $CH_3{\cdot}CO{\cdot}N(a)$ group.

[4] Rometsch, Marxer, and Miescher, *Helv. Chim. Acta*, 1951, **35**, 1611.
[5] Schwarzenbach and Epprecht, *ibid.*, 1936, **19**, 169.
[6] Robinson, "The Structural Relations of Natural Products," Clarendon Press, Oxford, 1955, p. 119.
[7] Smith, Ph.D. Thesis, St. Andrews, 1949.

for the formation of 3-ethylindole and 3 : 5-diethylpyridine on distillation with zinc dust,[8] but it was not at first apparent how such a structure could be reconciled with Woodward's biogenetic scheme.[9] If, however, the supposed biogenetic intermediate (V) is assumed to be converted into (VI), hydration of the αβ-unsaturated carbonyl system could lead to (VII) which [unlike (VI)] could undergo the typical cyclisation to (VIII). By a reversal of an aldol condensation, (VIII) may then suffer ring-opening to (IX), which by cyclisation involving the keto-methylene group gives the desired skeleton (X).

It is difficult to envisage any other series of processes which would provide the required 3 : 5-diethylpyridine moiety. The presence of a *C*-ethyl group in aspidospermine has been confirmed by the application of Bickel, Schmid, and Karrer's [10] modification of the Kuhn–Roth method.

Experimental

Aspidospermine Methiodide (IIa).—Aspidospermine (481 mg.) and methyl iodide (5 ml.) were heated in a sealed tube at the b. p. of acetone (56°) for 4 days. The pure product (632 mg., 95%) which crystallised was collected and washed with a little ethanol. *Aspidospermine methiodide* crystallised from ethanol as colourless prisms which decomposed with complete volatilisation between 280° and 290°, $\lambda_{max.}$ 254, 285 mμ (ε 10,800, 3200 respectively) (Found : C, 55·45; H, 6·75; N, 5·85. $C_{23}H_{33}O_2N_2I$ requires C, 55·65; H, 6·7; N, 5·65%). At 300°/0·01 mm. the methiodide (25·3 mg.) decomposed to give almost pure aspidospermine, m. p. 207—210°, in the form of a sublimate (18·6 mg. Calc. for loss of CH_3I : 18·2 mg.).

Deacetyl-N(a)-*methylaspidospermine* N(a)-*Methobromide* (IIIb).—A solution of deacetyl-*N*(*a*)-methylaspidospermine *N*(*a*)-methiodide (IIIa) (1·40 g.) in water (150 ml.) was shaken with excess of freshly precipitated silver oxide for 6 hr. in the dark. The clear halogen-free filtrate was treated with 0·76N-hydrobromic acid (5·0 ml.), concentrated *in vacuo* to a small volume, treated with aqueous sodium carbonate, and extracted with chloroform. Evaporation of the chloroform solution yielded the pure crystalline methobromide (1·18 g.). One crystallisation from benzene–ethanol yielded analytically pure *deacetyl*-N(a)-*methylaspidospermine* N(a)-*methobromide*, $\lambda_{max.}$ 271, 278 mμ (ε 2070, 2120), which decomposed with evolution of methyl bromide at about 170° depending on the rate of heating (Found, in air-dried product : C, 61·15, 61·3; H, 7·7, 7·8; N, 6·2, 6·45; Br, 18·5. $C_{22}H_{33}ON_2Br,\frac{1}{2}H_2O$ requires C, 61·35; H, 7·95; N, 6·5; Br, 18·55%).

The methobromide (51·1 mg.) was heated to melting at 180°, kept at that temperature for 1 min., and the tube then evacuated to 10 mm. for 1 min. The residue was completely soluble in light petroleum and weighed 39·9 mg. (Calc. for loss of $CH_3Br,\frac{1}{2}H_2O$: 38·8 mg.).

Deacetyl-N(a)-*methylaspidospermine Dimethiodide* (with J. R. Chalmers).—Deacetyl-*N*(*a*)-methylaspidospermine monomethiodide (IIIa) (370 mg.) in methyl iodide (3 ml.) was heated in a sealed tube at 100° for 2 hr. The *dimethiodide* (420 mg., 87%) which had crystallised was collected, washed with anhydrous ether, and dried; it had m. p. 195—196° (Found : C, 45·3; H, 6·2; I, 42·6. $C_{23}H_{36}O_2N_2I$ requires C, 45·3; H, 5·9; I, 41·6%). Recrystallisation from moist acetone gave the monohydrate, m. p. 172°, which was not dehydrated at 100° over phosphoric oxide in a vacuum (Found : C, 43·7; H, 5·9; N, 4·3. $C_{23}H_{36}O_2N_2I_2,H_2O$ requires C, 43·9; H, 6·0; N, 4·5%).

Deacetylaspidospermine N(b)-*Methobromide Hydrobromide*. (IIc)—Aspidospermine methiodide (800 mg.) was shaken with a suspension of excess of silver oxide in water (70 ml.), and the filtered iodide-free solution was concentrated under reduced pressure, and treated with pure 5N-hydrobromic acid (50 ml.). The solution was heated to 100° in an evacuated sealed tube for 7 hr., then evaporated to dryness under reduced pressure. The residual colourless gum of deacetylaspidospermine *N*(*b*)-methobromide hydrobromide (812 mg.) did not crystallise. The derived deacetylaspidospermine *N*(*b*)-methobromide (IIc), $\lambda_{max.}$ 248, 292 mμ (ε 6450, 2200), was also amorphous.

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The Wellcome Research Laboratories, Beckenham, Kent. [*Received, October 26th*, 1956.]

[8] Witkop, *J. Amer. Chem. Soc.*, 1948, **70**, 3712.
[9] Woodward, *Nature*, 1948, **162**, 155.
[10] Bickel, Schmid, and Karrer, *Helv. Chim. Acta*, 1955, **38**, 649.