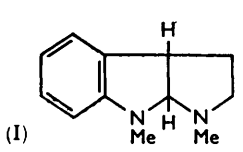
354. *The Structure of Folicanthine. Part II.*[1]

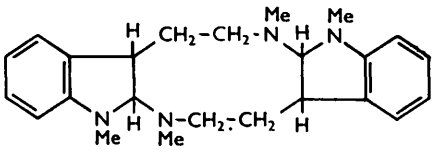
By H. F. Hodson and G. F. Smith.

The alkaloid folicanthine is shown to have structure (II).

The alkaloid folicanthine, first isolated from the leaves of *Calycanthus floridus* L. by Eiter and Svierak[2,3] in 0·34% yield, has now been isolated from the leaves of *C. occidentalis* Hook and Arn. in 0·14% yield. Earlier[1] we identified the main degradation products obtained by Eiter and Svierak[3] and discussed two possible structures, (I and II), for the

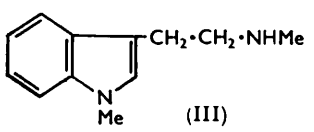


(I)

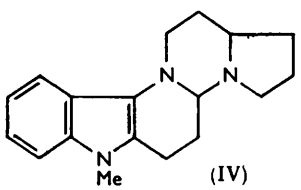


(II)

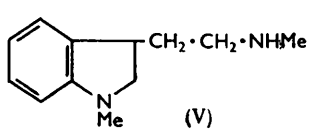
alkaloid. These structures are based mainly on the conversion of the alkaloid in 8N-hydrochloric acid[3] into 1-methyl-3-2′-methylaminoethylindole (III), the yield of which, being of the order of 50%, leaves open the possibility of the undetected loss of a non-indolic nitrogen-containing fragment, as indeed was postulated by Eiter[3] when he proposed structure (IV) for folicanthine.



(III)



(IV)



(V)

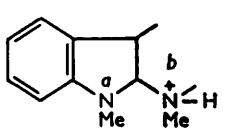
We now find that an excellent yield (86% as the pure dipicrate) of the indoline (V) is obtained from folicanthine by use of zinc and 5N-hydrochloric acid. This high yield rules out a structure such as (IV) containing three nitrogen atoms and clearly indicates that the structure must be made up of one or more dimethyltryptamine (III) units only.

Oxidation of folicanthine by silver acetate to 9-methylnorharman (XII)[1,3] suggests the presence of a hexahydro-β-carboline system: the ease of conversion of folicanthine into the indoles (III) and (V) cannot, however, be accounted for in terms of such a system, but follows naturally from a *gem*-diaminoeserine-like system. This is supported (Figs. 1—3) by the ultraviolet spectra. Folicanthine has an indoline-type spectrum, which is retained in acid solution though with hypsochromic shift of about 10 mμ for both bands (Fig. 1). Eserine and calycanthine behave in the same manner. In acid solution the absorbing species is a cation (VI), in which the formal positive charge on N(*b*) has rendered N(*a*) virtually non-basic: the N(*a*)-electron-pair is thus still able to resonate with the benzene ring, with retention of indoline-type absorption. The hypsochromic shift must be a result of the closeness of the positive charge on N(*b*) to the mesomeric system.

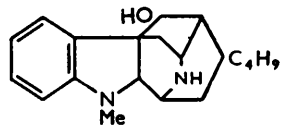
Deoxydihydroajmaline (VII) has a hexahydro-β-carboline type of structure; its ultraviolet absorption spectrum is also that of an indoline, but in this case acidification does not appreciably change the spectrum (Fig. 2). Here again we have a monoacidic base, N(*a*) having become practically non-basic as a result of the positive charge on N(*b*) in the cation: as a result, the indoline-type absorption is retained in acid solution. The

[1] The communication by Hodson and Smith, *Chem. and Ind.*, 1956, 740, is considered to be Part I.
[2] Eiter and Svierak, *Monatsh.*, 1951, **82**, 186.
[3] *Idem, ibid.*, 1952, **83**, 1453.

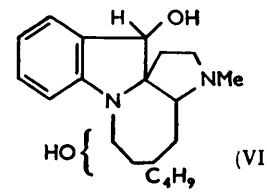
positive charge on N(*b*), however, is now no longer sufficiently close to the mesomeric system, and there is no appreciable shift of the bands. ε_1-Hexahydrofluorocurine (VIII), a hexahydro-β-carboline analogue, is reported to behave in the same manner.[4]



(VI)



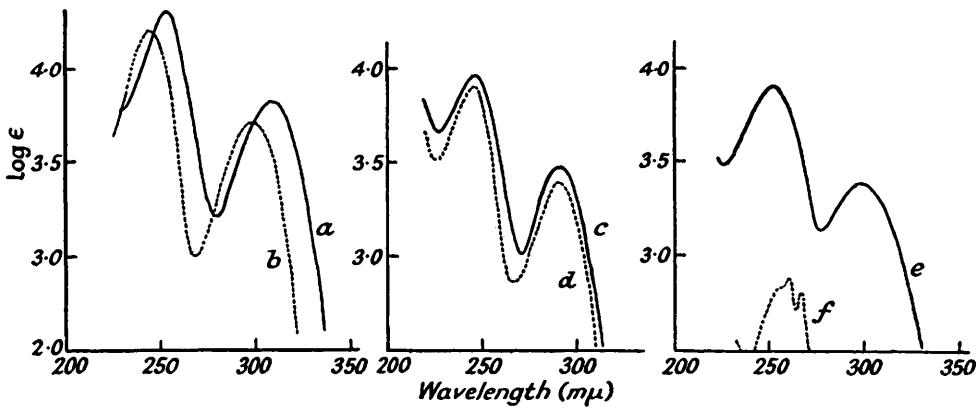
(VII)



(VIII)

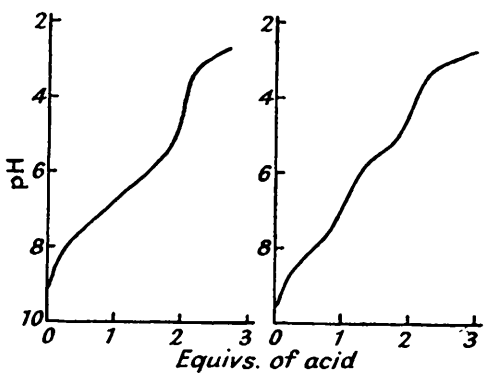
To complete the picture, the case of the indoline (V) may be mentioned. Its indoline-type absorption disappears in acid and is replaced by the benzenoid absorption of anilinium-

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



Absorption spectra of (Fig. 1) *folicanthine* (II) (*a*) *in* EtOH *and* (*b*) *in* HCl–EtOH, (Fig. 2) *deoxydihydro-ajmaline* (VII) (*c*) *in* EtOH *and* (*d*) *in* HCl–EtOH, *and* (Fig. 3) *1-methyl-3-2′-methylaminoethylindoline* (V) (*e*) *in* EtOH *and* (*f*) *in* HCl–EtOH.

FIG. 4. FIG. 5.



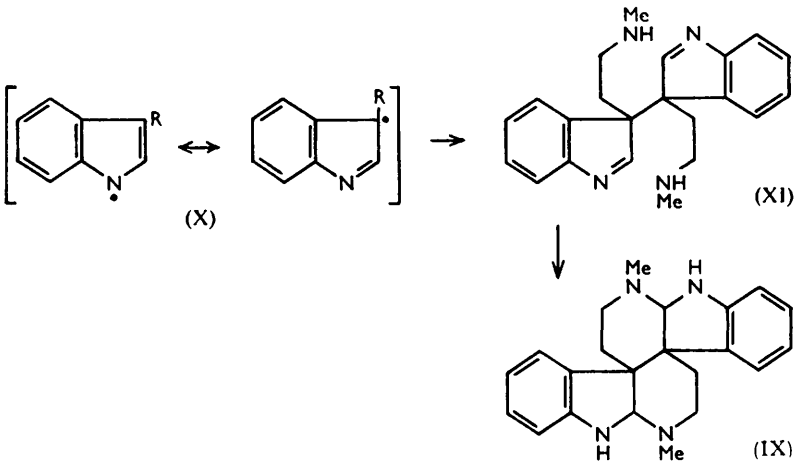
Potentiometric titration curve of (Fig. 4) *folicanthine and* (Fig. 5) *calycanthine in* 60% *aqueous ethanol.*

type ions (Fig. 3). In (V) the positive charge on the protonated N(*b*) is sufficiently far away from N(*a*) not to prevent it from being protonated in dilute aqueous acid. In contrast with (VI), (VII), (VIII), the base (V) is thus diacidic in dilute aqueous acid, and it forms a dipicrate.

[4] Bickel, Schmid, and Karrer, *Helv. Chim. Acta*, 1955, **38**, 654.

We are thus left with the alternatives (I) and (II) for folicanthine. Eiter and Svierak [3] reported a molecular weight of 297 by Rast's method in bornylamine: this falls between 188 for (I) and 376 for (II). In triplicate determinations by Rast's method in camphor, we obtained values of 384, 376, and 379; in addition, one determination by Barger's isothermal distillation method in benzene gave a value of 375. These results lead us to propose structure (II) for folicanthine.

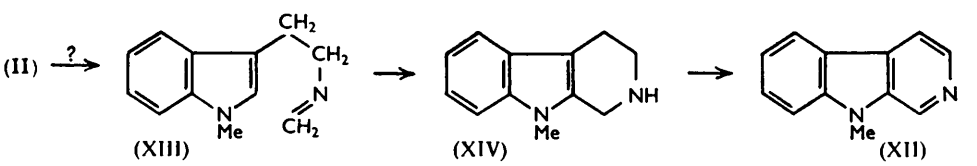
Attempts to prove structure (II) chemically by preparing a monosalt or a monosubstitution product have failed. The titration curve of folicanthine (Fig. 4), however, provides convincing evidence in favour of structure (II). The curve is not that expected of a monoacidic base, but falls into the category of diacidic bases and dibasic acids with a ΔpK_a of the order of 1·2. This conclusion is based on Auerbach and Smolczyk's work,[5] who made a thorough theoretical and experimental study of the change in shape of the titration curve of dibasic acids with change of ΔpK_a. For folicanthine the ΔpK_a is of the order of 1·4 (all titrations were carried out in 60% ethanol). The much stronger base putrescine has ΔpK_a 1·3, and its titration curve is almost identical with that of folicanthine.



Calycanthine (IX), with the larger ΔpK_a (about 2·2), has a titration curve with two inflexions (Fig. 5).

That the ΔpK_a of calycanthine is greater than that of folicanthine is probably due to the fact that structure (IX) requires the two basic centres to be closer together than in structure (II).

Folicanthine is thus seen to be very closely related structurally to calycanthine [6] (IX). The main difference is the absence in folicanthine of a bond uniting the β-positions of the two indole nuclei; the other difference is that the N(*a*) atoms of folicanthine are methylated. If we accept the view [7] that the biogenesis of calycanthine involves a free-radical dimerisation of two tryptamine units as portrayed in (X) ⟶ (XI), we can see a possible reason



for the non-existence of a ββ-link in folicanthine in the inability of a precursor carrying a methyl group on the indole nitrogen [say (III)] to form a free radical of type (X).

[5] Auerbach and Smolczyk, *Z. phys. Chem.*, 1924, **110**, 65.
[6] Robinson and Teuber, *Chem. and Ind.*, 1954, 783.
[7] Harley-Mason, personal communication.

The formation of 9-methylnorharman (XII) by oxidation of folicanthine with silver acetate in boiling 1% aqueous acetic acid remains to be accounted for. The tryptamine (III) is completely resistant to this reagent, so that preliminary breakdown of folicanthine to (III) must be ruled out. Whatever mechanism operates, it is evident that the *N*(*b*)-methyl group becomes the $C_{(1)}$ of the harman system, probably by way of (XIII) and (XIV).

Experimental

M. p.s are corrected.

Extraction of Calycanthus occidentalis *Leaves.*—The dry, powdered leaves (740 g.) were extracted continuously with light petroleum (b. p. 60—80°) for 36 hr., the petroleum then distilled off, and the residue dissolved in ether (3 l.). The solution was extracted three times with 5% aqueous tartaric acid (120, 60, 60 c.c.), and the combined acid extracts were washed with ether, basified with aqueous sodium hydroxide, and repeatedly extracted with ether. The dried (K_2CO_3) ether extracts yielded practically pure folicanthine, m. p. 116—119° (677 mg.). After passage through a short alumina column in ether to remove traces of colour, the base was twice crystallised from ether–light petroleum (b. p. 30—40°), then forming colourless prisms, m. p. 118—120°. The extraction of the leaves was continued for 48 hr. after basification with triethylamine (20 c.c.). The extract was worked up as above and yielded a further quantity of fairly pure folicanthine (403 mg.). The total yield of alkaloid was 1·08 g., 0·144%. Light absorption : $\lambda_{max.}$ 2540 (log ε 4·249), 3110 Å (log ε 3·826).

Reduction of Folicanthine.—A solution of folicanthine (96 mg.) in 5N-hydrochloric acid (15 c.c.) was treated on the steam-bath with granulated zinc (5 g.) at a rate sufficient to maintain a vigorous evolution of hydrogen. After 1½ hr. the cooled solution was filtered, diluted to 30 c.c., basified with aqueous ammonia, and extracted with ether (4 × 20 c.c.); the combined dried extracts yielded a colourless viscous oil (94·4 mg.). This oil, with picric acid (250 mg.) in methanol (5 c.c.), gave the *dipicrate*, m. p. 161—165° (272 mg.). Concentration of the mother-liquor yielded a further 6 mg. (total, 86%). One crystallisation from acetone gave yellow prisms, m. p. 162—165°, unchanged by further crystallisation and undepressed by synthetic 1-methyl-3-2′-methylaminoethylindoline picrate (Found : C, 44·9; H, 4·2; N, 17·5. $C_{12}H_{18}N_2,2C_6H_3O_7N_3$ requires C, 44·5; H, 3·7; N, 17·3%). The free base, recovered from the picrate and distilled at 80—100° (oil bath)/5 × 10^{-5} mm., had ultraviolet (in absolute ethanol) and infrared (liquid film) spectra identical with those of synthetic 1-methyl-3-2′-methylaminoethylindoline.

1-*Methyl*-3-2′-*methylaminoethylindoline* (V).—1-Methyl-3-2′-methylaminoethylindole (23·0 mg.) was reduced by zinc and acid as described above. The product was a colourless oil (22·5 mg.), converted by picric acid (56 mg.) in methanol (1 c.c.) into 1-methyl-3-2′-methylaminoethylindoline dipicrate (57·5 mg., and second crop of 5 mg.) which crystallised from acetone as yellow prisms, m. p. 164—166° unchanged on further crystallisation (Found : C, 44·8; H, 4·1%). Light absorption of the free base in ethanol : $\lambda_{max.}$ 2540 (log ε 3·902), 3000 Å (log ε 3·388).

The authors are indebted to the Curator of the Royal Botanic Gardens, Kew, Mr. W. M. Campbell, for supplying leaves of *Calycanthus occidentalis*. The work was carried out during the tenure of a grant from the Schunck Fund of the University of Manchester (H. F. H.).

The University, Manchester. [*Received, December 13th,* 1956.]