

ALKALOID STUDIES.\*  
THE STRUCTURES OF STEMMADENINE AND CONDYLOCARPINE.

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AN earlier examination<sup>1</sup> of the alkaloids of Stemmadenia species led to the isolation of (+)-quebrachamine, a number of lboga-type bases<sup>2</sup> and a new alkaloid named stemmadenine (C<sub>21</sub>H<sub>26-28</sub>N<sub>2</sub>O<sub>3</sub>). The latter has also recently been encountered<sup>3</sup> in Diplorrhynchus condylocarpon together with a second new alkaloid, condylocarpine (C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>). We should now like to report the conversion of stemmadenine to condylocarpine as well as chemical, n.m.r. and mass spectral data, which limit the structures of these alkaloids to two possibilities (I (β→x) and V, or I (β→y) and VI).

Partial structure I for stemmadenine is based on the following observations. The recorded<sup>1,3</sup> ultraviolet and infrared spectra show the presence of a 2,3-disubstituted indole and of a non-conjugated carbomethoxy grouping. The n.m.r. spectrum<sup>4</sup> confirmed these conclusions (indole NH at 9.3δ, four aromatic protons

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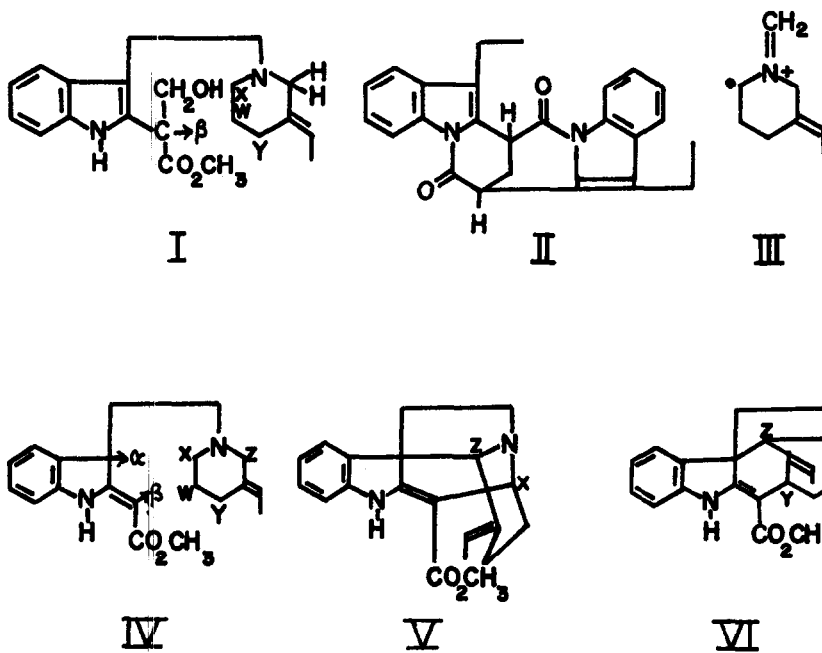
<sup>1</sup>F. Walls, O. Collera and A. Sandoval, Tetrahedron **2**, 173 (1958).

<sup>2</sup>For structures see M. F. Bartlett, D. F. Dickel and W. I. Taylor, J. Amer. Chem. Soc. **80**, 126 (1958).

<sup>3</sup>D. Stauffacher, Helv. Chim. Acta **44**, 2006 (1961).

<sup>4</sup>All spectra were measured with Varian A-60 (14.1 kilogauss) or HR-100 (23.5 kilogauss) spectrometers in CDCl<sub>3</sub> solution with added tetramethylsilane as internal standard; all chemical shifts are reported in ppm as δ values (cps/60).

centered at  $7.35\delta$ ,  $\text{CO}_2\text{CH}_3$  proton signals at  $3.79\delta$ ) and also revealed the existence of the ethylidene function (single olefinic proton as quartet at  $5.4\delta$  and methyl doublet centered at  $1.7\delta$ ). The empirical formula  $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_3$  (354) was confirmed by the mass spectrum (molecular ion at  $m/e$  354; shifted to  $m/e$  356 on catalytic hydrogenation), the most intense peak of which occurred at  $m/e$  123 consistent with ion III.<sup>5</sup> An important peak at  $m/e$  324 ( $M-30$ ) can be rationalized by the loss of formaldehyde, while a peak at  $m/e$  336 ( $M-\text{H}_2\text{O}$ ) represented the first evidence for the presence of a hydroxyl function. The primary nature of the hydroxyl group was demonstrated<sup>6</sup> by the isolation of formaldehyde (see below) and the n.m.r. signal at  $4.38\delta$  corresponding to the two methylene protons of the  $\text{CH}_2\text{OH}$  grouping.



<sup>5</sup>See K. Biemann, M. Friedmann-Spiteller and G. Spiteller, Tetrahedron Letters 485 (1961).

<sup>6</sup>Acetate formation could not be employed as the substance decomposed upon attempted acetylation.

Palladium dehydrogenation (30 min., 245°) of stemmadenine furnished 3-ethylpyridine<sup>7</sup> (picrate,<sup>8</sup> 127-129°) as well as a crystalline solid, m.p. 244-245° ( $\lambda_{\text{max}}^{\text{CHCl}_3}$  5.88  $\mu$ ,  $\lambda_{\text{max}}^{\text{MeOH}}$  250, 283 and 319  $\mu$ ,  $\epsilon$  34200, 14700 and 15850) corresponding in empirical formula to  $\text{C}_{25}\text{H}_{22}\text{N}_2\text{O}_2$  (strong mass spectrometric molecular ion at  $m/e$  382), the n.m.r. spectrum of which uniquely established its constitution as the symmetrical structure II (integrated proton count (11)<sub>n</sub>). The two single aromatic protons closest to the carbonyl group were found at 8.33  $\delta$ , while the remaining six aromatic hydrogens exhibited signals in the 7.1 - 7.7  $\delta$  region. A multiplet at 4.43  $\delta$  (corresponding to half of an  $\text{A}_2\text{X}_2$  spectral pattern) is associated with the two angular hydrogens, the large downfield chemical shift being due to the adjacent carbonyl and indole double bond. A second multiplet at 2.78  $\delta$  represents the other half of the  $\text{A}_2\text{X}_2$  pattern required by the two symmetrically situated central methylene hydrogens. This multiplet is partially obscured by the methylene quartet (from the ethyl groups) but could be shifted into full view using pyridine as solvent. Finally, there is observed a triplet centered at 1.31  $\delta$  due to the six methyl hydrogens of the two ethyl groups. The structure of the "dimeric" dehydrogenation product II settles the location of the carbomethoxy and hydroxymethyl substituents; furthermore, its "monomeric" fragment together with 3-ethylpyridine accounts for all of the carbon atoms of stemmadenine and since the parent alkaloid does not possess a C-ethyl group (n.m.r. spectrum), the ethyl group of II must be connected in stemmadenine to the 3-ethylpyridine progenitor. The carbon atom bearing the carbomethoxy group cannot be connected to  $\text{N}_B$ , because condylocarpine (V or VI--see below) is not an enamine, thus requiring the biogenetically plausible tryptamine bridge shown in I as the connecting link between the indole and piperidine moieties of stemmadenine, a conclusion which is also fully consistent with the formation of the ion III ( $m/e$  123) as the principal product in the mass spectrometric fragmentation of stemmadenine. Only one bond (arrow  $\beta$  in I) needs to be completed to afford the complete structure of stemmadenine and we show below that positions  $\underline{x}$  and  $\underline{y}$  are the only possible termination points of this bond  $\beta$ .

When stemmadenine hydrochloride was oxidized in aqueous solution (5°) with potassium permanganate (oxidation with iodine gave inferior yields) and the resulting crude product heated in a nitrogen current at 90°, there was isolated formaldehyde

<sup>7</sup>3-Ethylpyridine is formed even on thermal treatment as shown by the appearance of a strong  $m/e$  107 peak when a sample of stemmadenine was heated for 1 hr. at 260° in the inlet system of the mass spectrometer.

<sup>8</sup>An authentic sample was kindly supplied by E. R. Wallsgrove, Midland Tar Distillers, Ltd., Staffs., England.

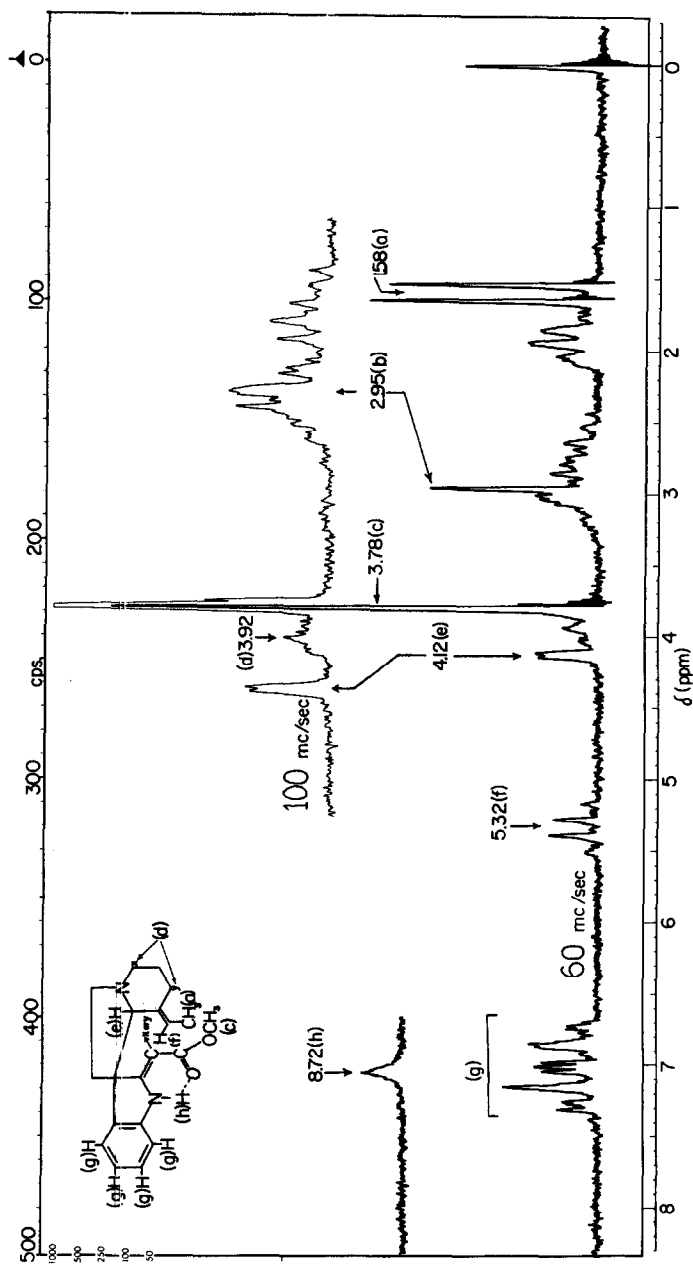


FIG. 1

Nuclear magnetic resonance spectra (60 and 100 mc) of condylocarpine.

as well as a crystalline product,  $C_{20}H_{22}N_2O_2$  (empirical formula confirmed by mass spectrometry) m.p. 167-168°,  $[\alpha]_D^{25} +87.6^\circ$ ,  $\lambda_{max}^{CHCl_3}$  2.98, 6.0 and 6.25  $\mu$ ,  $\lambda_{max}^{MeOH}$  229, 298 and 330  $\mu$ , which proved to be identical (mixture melting point, optical rotatory dispersion, i. r., n.m.r. and mass spectral comparison) with condylocarpine<sup>3</sup> kindly provided by Dr. Stauffacher. Condylocarpine thus must possess partial structure IV, the spectral properties (ref. 3 and present paper) and high rotation being typical of the  $\alpha$ -methylene indoline chromophore conjugated with a carbomethoxy group as has been found in akuammicine.<sup>9</sup> This conclusion is supported by the observation that the n.m.r. spectra of akuammicine and of condylocarpine are very similar in the 6.5 - 9.0  $\delta$  region. The formation of condylocarpine (V or VI) from stemmadenine (I) is mechanistically straight forward and appears to involve initial introduction of a double bond next to the piperidine nitrogen, followed by expulsion of formaldehyde and bond formation between the  $\beta$ -position of the indole system and a carbon atom  $\alpha$  to the piperidine nitrogen.

Precise definition of the termination points of bonds  $\alpha$  and  $\beta$  in partial structure IV would lead to the complete structure of condylocarpine and *ipso facto* of stemmadenine. As shown below, all but structures V and VI can be eliminated on the basis of the n.m.r. spectra at 60 mc/sec. and especially at 100 mc/sec.<sup>4</sup> of condylocarpine, the most prominent features being designated with the letters (a) to (h) in Fig. 1. The doublet (a) and the quartet (f) at 1.58  $\delta$  and 5.32  $\delta$  demonstrate the presence of the ethylidene function, while the singlet (c) at 3.78  $\delta$  (area = 3 protons) represents the carbomethoxy group. The signal (b) at 2.95  $\delta$  is quite sharp in the 60 mc. spectrum and it is tempting to interpret it as an isolated proton (no spin coupling to neighbors) whose signal is superimposed on a more complex multiplet; however, the 100 mc. spectrum shows that this signal is due to the accidental overlap of weaker lines and is thus without structural significance. Signals (d) and (e) at 3.92  $\delta$  and 4.12  $\delta$  each have integrated areas corresponding to one proton and neither shows the spin coupling characteristic of coupling between two *gem*-protons. Thus, there are two hydrogens on tertiary carbon atoms with rather similar chemical shifts in the vicinity of 3.9 - 4.1  $\delta$ .

Either bond  $\alpha$  or  $\beta$  must terminate at  $\underline{z}$  in IV, since no methylene signal appears in the spectrum with a chemical shift of 3.3 - 4.0  $\delta$ ;<sup>10</sup> consequently, the single

<sup>9</sup>K. Aghoramurthy and R. Robinson, *Tetrahedron* **1**, 172 (1957); G. F. Smith and J. T. Wrobel, *J. Chem. Soc.* 793 (1960); K. Bernauer, W. Arnold, C. Weissmann, H. Schmid and P. Karrer, *Helv. Chim. Acta* **43**, 717 (1960); J. Levy, J. Le Men and M.-M. Janot, *Bull. Soc. Chim. France* 979 (1960).

<sup>10</sup>1,2,5,6-Tetrahydropyridine (spectrum 115 in "NMR Spectra Catalog" by N. S. Bhacca, L. F. Johnson and J. N. Shoolery, Varian Associates, Palo Alto, California, 1962) shows this signal at 3.33  $\delta$  while the model alkaloid akuammicine (ref. 9) shows a signal assignable to such a group of 4.0  $\delta$ .

hydrogen attached to position  $\underline{z}$  is responsible for the peak at  $4.12 \delta$ .<sup>11</sup> If  $\beta$  terminated at  $\underline{z}$ , this peak would have been expected to have an even larger  $\delta$ -value since the proton shift would be influenced by two adjacent double bonds and the nitrogen atom. Furthermore, if bond  $\alpha$  were connected to either  $\underline{w}$ ,  $\underline{x}$ , or  $\underline{y}$ , the chemical shift for the proton at  $3.92 \delta$  cannot be accounted for, since it would have to arise from only an adjacent nitrogen or one double bond. Thus,  $\alpha$  must terminate at  $\underline{z}$ , leaving only positions  $\underline{x}$  or  $\underline{y}$  for the  $\beta$  bond, as  $\beta$  cannot terminate at  $\underline{w}$  and account for the signals at  $3.92 \delta$ . Only two structural alternatives are left for condylocarpine, namely V (IV with  $\alpha$ - $\underline{z}$  and  $\beta$ - $\underline{x}$  bonds) and VI (IV with  $\alpha$ - $\underline{z}$  and  $\beta$ - $\underline{y}$  bonds), which in turn lead to expression I ( $\beta$ - $\underline{x}$  or  $\beta$ - $\underline{y}$  bond) for stemmadenine.

The n.m.r. data listed above do not differentiate rigorously between structures V and VI for condylocarpine and in each structure, the  $4.12 \delta$  signal<sup>11</sup> can be assigned to the  $\underline{z}$  proton, while the  $3.92 \delta$  multiplet is attributed to the  $\underline{x}$  proton in V and the  $\underline{y}$  hydrogen in VI. The upfield shift of the  $4.12 \delta$  signal upon hydrogenation is equally accommodated by V or VI. The appearance (in dihydrocondylocarpine) of the ethyl signals at abnormally high field is compatible with either structure, since the ethyl group would then lie above the aromatic ring (V) or the acrylic ester system (VI) and thus be exposed to increased shielding.

Lack of material precluded further chemical studies to differentiate securely between these two structural alternatives. It should be noted that one of the two possible stemmadenine structures (I with  $\beta$ - $\underline{y}$  bond) contains the complete carbon skeleton of Wenkert's<sup>12</sup> postulated key intermediate in the biosynthesis of the Iboga and Aspidosperma alkaloids, while the other one (I with  $\beta$ - $\underline{x}$  bond) can be formulated via an intermediate such as XXXV in ref. 12. It should also be noted that one (VI) of the two possible condylocarpine structures represents an interesting biosynthetic variant of the aspidospermatine,<sup>5</sup> akuammicine<sup>9</sup> and vincadiffomine<sup>13</sup> alkaloid types and that it should lend itself to possible chemical conversion to aspidospermatine.

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<sup>11</sup>This peak is a doublet corresponding to a spin coupling of approximately 2 cps. Since this proton has no immediate neighbors, the splitting is attributed to a long-range coupling.

<sup>12</sup>E. Wenkert, J. Amer. Chem. Soc. **84**, 98 (1962), formula XXVI.

<sup>13</sup>C. Djerassi, H. Budzikiewicz, J. M. Wilson, J. Gosset, J. Le Men and M.-M. Janot, Tetrahedron Letters 235 (1962).