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NMR SPECTRA OF GELSEMINE DERIVATIVES.
THE STRUCTURE AND BIOGENESIS OF THE ALKALOID GELSEMINE[1]

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THE hexacyclic alkaloid gelsemine, $C_{20}H_{22}O_2N_2$, of Gelsemium sempervirens, contains a vinyl side chain.[2] With the exception of the reaction leading to bromo-allo-gelsemine,[3] which shows that the olefinic center must be located within bonding distance of the carbonyl oxygen associated with the oxindole[4] nucleus, definitive information as to the site of attachment of this vinyl chain has been unavailable.

The 60 mc/sec NMR spectrum[5] of gelsemine shows the twelve strong lines of the ABC (approximately ABX) system,[6] $-CH_X=CH_AH_B$, which comprise three symmetrically split quartets centered at values of τ:[7] (X) 3.72, (A) 4.95 and (B) 5.10, with splittings: (X) 11.3 and 17.8 cps; (A) 1.5 and 11.3 cps and (B) 1.5 and 17.8 cps. Coupling between geminal protons A

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[1] Contribution numbered 1536 from the Department of Chemistry at Yale University.

[2] L. Marion and K. Sargeant, J. Amer. Chem. Soc. 78, 5127 (1956).

[3] R. Goutarel, M.-M. Janot, V. Prelog, R. P. A. Sneeden and W. I. Taylor, Helv. Chim. Acta 34, 1139 (1951).

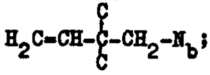
[4] M. Kates and L. Marion, J. Amer. Chem. Soc. 72, 2308 (1950); Canad. J. Chem. 29, 37 (1951).

[5] Spectra were determined in deuterochloroform (99.5%) by Dr. LeRoy Johnson, Applications Laboratory, Varian Associates, Palo Alto, California.

[6] H. J. Bernstein, J. A. Pople and W. G. Schneider, Canad. J. Chem. 35, 65 (1957).

[7] G. V. D. Tiers, J. Phys. Chem. 62, 1151 (1958).

and B within the trigonally hybridized methylene is expected to be small, as it is in styrene,[8] and small coupling is in consonance with the recently calculated variation of J with H-C-H bond angle.[9] The absence of any further splitting in the X set, i.e. the isolation from further spin-spin coupling to a fourth proton Y, requires either that (i) the vinyl group is substituted upon a quaternary carbon or (ii) that a J_{XY} is accidentally zero because of a special conformational relationship of X to Y. In the latter event any minor modification in the steric environment of the vinyl should increase multiplicity in the X spectrum, yet the indoline base, deoxogelsemine,[4] shows the same pattern except that the X multiplet has been shifted to center at $\tau = 3.93$. Acetylation of deoxogelsemine gave N_a-acetyldeoxogelsemine, m.p. 137-139° (Found: C, 75.59; H, 7.38; N, 8.23. $C_{22}H_{26}O_2N_2$ requires: C, 75.40; H, 7.48; N, 7.99.), osmium tetroxide-periodate oxidation of which gave the nor-aldehyde, m.p. 172-174° (Found: C, 71.41; H, 6.73; N, 7.82. $C_{21}H_{24}O_3N_2$ requires: C, 71.57; H, 6.86; N, 7.95.). The NMR spectrum of the aldehyde contains none of the foregoing twelve peaks, but instead a sharp singlet C-CHO resonance line at $\tau = 0.11$ (half-width 1 cps) in confirmation of the postulated quaternary substitution.

Biogenetic considerations suggested the presence of the system  $H_2C{=}CH{-}\overset{C}{\underset{C}{C}}{-}CH_2{-}N_b$; in this environment the N_b-methylene[10] should comprise

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[8] R. W. Fessenden and J. S. Waugh, Abstracts 132nd Meeting of the American Chemical Society, Sept., 1957, p. 72P.

[9] M. Karplus and H. S. Gutowsky, To be published.

[10] T. Habgood and L. Marion, Canad. J. Chem. 33, 604 (1955).

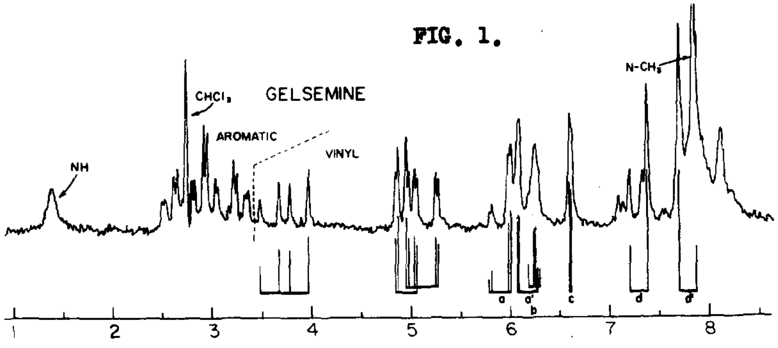

FIG. 1.

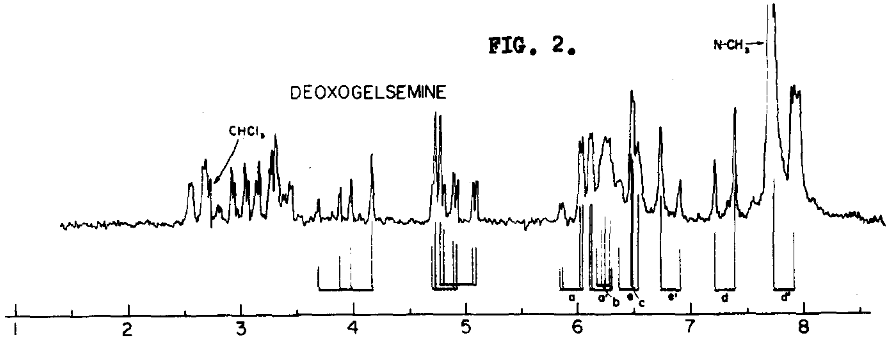

FIG. 2.

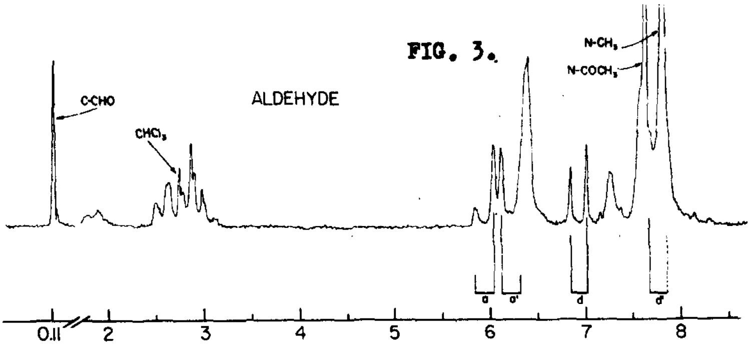

FIG. 3.

an isolated AB system[6] with NMR absorption predicted to be a symmetrical quartet of sharp lines. These appear in the spectra as the doublet pairs d and d', with J = 10.6 cps, with the intensity-spacing relationship in good accord with the theoretical requirement;[6] there is no additional splitting.

[Similarly the N_a-methylene present in deoxogelsemine (but not in gelsemine) appears as the doublet pairs e and e', with J = 10.2 cps, at lower fields because of the conjugation of N_a with the aromatic ring.] The N-methyl[11] appears at τ = 7.84 in the gelsemine curve and at corresponding positions in the other spectra.

The remaining peaks in the region τ = 6 - 7 represent other C-H protons adjacent to nitrogen or oxygen; the overall integrated intensity is in excellent agreement with four such protons. The sets a and a' form a symmetrical nonequivalence quartet, each member of which is further split into a close doublet, as in the AB segment of an ABX spectrum. The magnitude of the large splitting, 11.5 cps, requires geminal placement of the two protons (upon a saturated carbon); an O-methylene is indicated in view of the low resonance field. The smaller splittings, 0.9 and 1.6 cps, are then caused by coupling with one vicinal proton, as in $>\mathrm{CH{-}CH_2{-}O}$. The other multiplets, b and c, each with an area given by one proton, do not reveal the large coupling characteristic of the saturated methylene and so must represent separate tertiary protons, as in $\mathrm{O{-}CH}{<}^{\mathrm{C}}_{\mathrm{C}}$ and $\mathrm{N{-}CH}{<}^{\mathrm{C}}_{\mathrm{C}}$, respectively. Since neither multiplet appears fully resolved, we can deduce only the minimum number of vicinal protons present, as in $\mathrm{O{-}CH}{<}^{\mathrm{C}}_{\mathrm{CH_2{-}}}$ (or $\mathrm{O{-}CH}{<}^{\mathrm{CH<}}_{\mathrm{CH<}}$) and $\mathrm{N{-}CH}{<}^{\mathrm{C}}_{\mathrm{CH<}}$.

We turn now to a more detailed biogenetic argument. The proposed precursor (III) which bears the same essential relation (N_b-dehydrogenation-N_b-methylation) to corynoxeine (I)[12] or rhyncophylline (II)[13] as does

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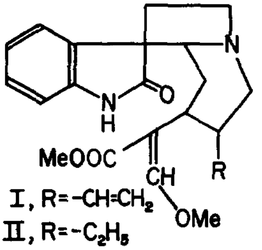
[11] B. Witkop, *J. Amer. Chem. Soc.* **70**, 1424 (1948).

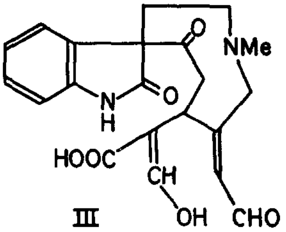
[12] N. An Cu, R. Goutarel and M.-M. Janot, *Bull. Soc. Chim. Fr.* 1292 (1957).

[13] J. C. Seaton and L. Marion, *Canad. J. Chem.* **35**, 1102 (1957).

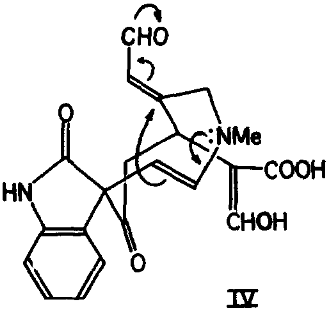


I, R=-CH=CH$_2$

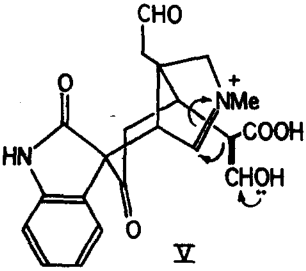
II, R=-C$_2$H$_5$



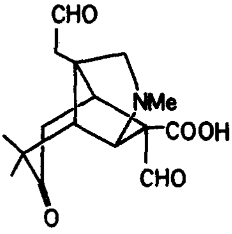
III



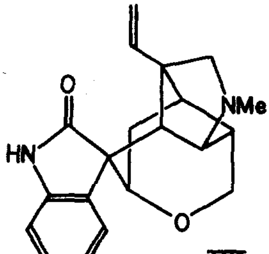
IV



V



VI



VII

vomicine to strychnine, may be derived from equivalents of tryptamine and 3,4-dioxyphenylalanine according to accepted principles.[14] Further dehydrogenation at N$_b$ gives IV; Michael addition of the enamine to the conjugated system establishes the quaternary carbon and forms the five-membered ring[10] enclosing N$_b$. The intermediate (V) is disposed to internal Mannich condensation, to give VI, whence decarboxylation, completion of the oxide ring and adjustment of oxidation state results in VII, as a

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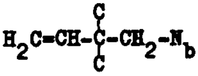
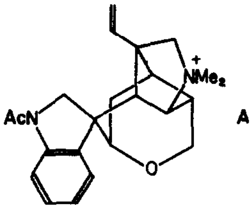
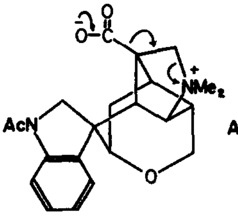
[14] Cf. R. Robinson, Structural Relations of Natural Products, Oxford University Press (1955); J. E. Saxton, Quart. Rev. **10**, 120 (1956); for an early application to the biogenesis of strychnine, Cf. R. B. Woodward, Nature, Lond. **162**, 155 (1948); for a discussion of the related biogenesis of corynantheine, Cf. M.-M. Janot and R. Goutarel, Bull. Soc. Chim. Fr. [5] **18**, 588 (1951).

structure for gelsemine.[15] We note that the bond formed in the Mannich reaction (V ⟶ VI) is identical in principle to linkages characteristic of sarpagine, ajmaline and others, but that the bond formed in the Michael change (IV ⟶ V) is, as yet, unique.

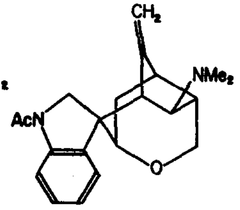
The following new degradative sequence provides rigorous proof of the presence in gelsemine of the chain  $H_2C{=}CH{-}\overset{C}{\underset{C}{C}}{-}CH_2{-}N_b$, and is otherwise fully consistent with the structure VII. N_a-acetyldeoxogelsemine gave N_a-acetyldeoxogelsemine N_b-methiodide, m.p. 297-299°, dec. (Found: C, 56.30; H, 6.05; N, 5.65. $C_{23}H_{29}O_2N_2I$ requires: C, 56.10; H, 5.94; N, 5.69.). Oxidation of the corresponding N_b-methohydroxide (VIII) (alkaline permanganate) provided the betaine (IX) with $\nu_{max} = 1597$ cm^{-1}. Concerted decarboxylation-β-elimination in dilute (0.1%) solution[16] in boiling dimethylformamide gave the basic



VIII



IX



X

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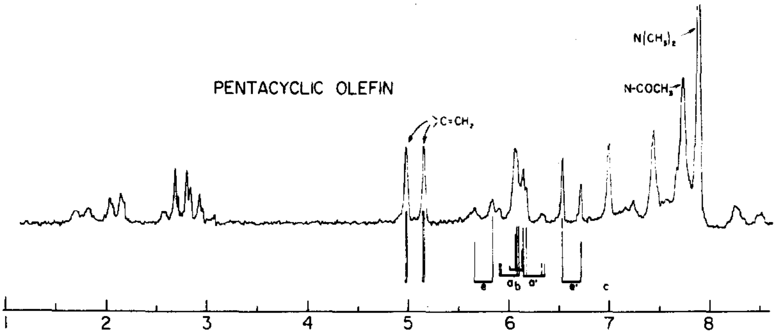
[15] The structure (VII) is consistent with all other previous results, of which the more significant include (i) the participation of the oxindole oxygen in bromination at the vinyl,[5] accountable in terms of the proximity of these groups, and (ii) the failure of Hofmann elimination with gelsemine methohydroxide [R. Goutarel, M.-M. Janet, V. Prelog and R. P. A. Sneeden, Helv. Chim. Acta 34, 1962 (1951); T. Habgood, L. Marion and H. Schwarz, Ibid. 35, 638 (1952); V. Prelog, J. B. Patrick and B. Witkop, Ibid. 35, 640 (1952)], a result of the steric impossibility of any olefinic product. Witkop[11] has reported the isolation of a base $C_{11}H_{11}N$, from the zinc dust degradation of gelsemine, which he regarded as a dimethyl- or ethyl- quinoline or isoquinoline. The 4,7-dimethylisoquinoline skeleton is present intact in VII.

[16] Bimolecular reaction, leading to the methyl ester of the corresponding tertiary base, occurred to the exclusion of the desired intramolecular elimination when the betaine (IX) was merely heated

pentacyclic olefin (X), m.p. 130° (Found: C, 74.25; H, 7.47; N, 8.26. $C_{21}H_{26}O_2N_2$ requires: C, 74.52; H, 7.74; N, 8.28.), further characterized by its methiodide (XI), m.p. 273-275° (from aqueous methanol) (Found: C, 54.09; H, 6.15; O, 7.44; N, 5.76; I, 26.40. $C_{22}H_{29}O_2N_2I.\frac{1}{2}H_2O$ requires: C, 54.10; H, 5.99; O, 8.19; N, 5.74; I, 25.99.). The 60 mc/sec NMR spectrum[5] of X shows a symmetrical pair of peaks in the $C=CH_2$ region, at τ = 4.98 and 5.15 (area of each = 1 proton) and agrees with the other features implied.[17] Microhydrogenation (platinum-acetic acid) of X gave the dihydro derivative, m.p. 165-167°, which contains an additional C-methyl (Found: C-Me, 7.09. $C_{21}H_{28}O_2N_2$ requires: one C-Me, 4.42; two C-Me, 8.83.), after absorption of 1.0 mole of hydrogen. Oxidation[18] (osmium tetroxide-periodate)



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in vacuo in the absence of any diluent. In sufficiently dilute solution, as would be expected, the unimolecular reaction predominates over the bimolecular transmethylation.

[17] The spectrum in the exo-methylene region is that expected of the AB system[6] when $J_{AB} \cong 0$; the weak coupling within the trigonal methylene has been mentioned (*vide supra*). The spectrum of X does not contain the N_b-methylene nonequivalence quartet of the precursors. The other multiplets (a,a', b, c, e and e') are assigned as in the previous spectra.

[18] The oxidations yielded as well a neutral fraction with ν_{max} =1720 cm^{-1}, believed to arise *via* (reverse Mannich) decomposition of the five-membered keto-base.

of X gave a keto-base with ν_{max} = 1748 cm^{-1}, evidence for substitution of the exo-methylene at the five-membered ring.

We were delighted to learn recently that the structure (VII) for gelsemine, which we had deduced on the basis of these arguments, and which is fully consonant with, though not proved in all details by, the evidence given in this communication, is identical with that entirely independently deduced by Lovell, Pepinsky and Wilson from elegant X-ray crystallographic studies, which are described in an accompanying communication. We are grateful to Professor Pepinsky for the opportunity to read his manuscript in advance of publication.

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