Tetrahedron Letters No. 6, pp. 1-9, 1960. Pergamon Press Ltd. Printed in Great Britain.

THE STRUCTURE OF ECHITAMINE[1]

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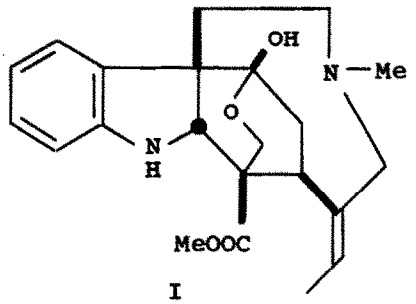
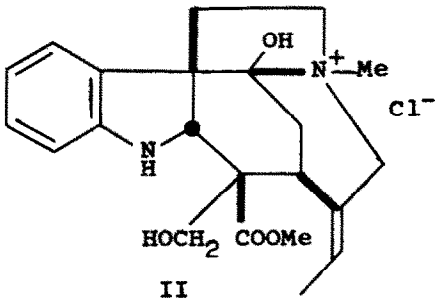
(Received 1 February 1960)

RECENT literature[2-5] indicates awakened interest in the constitution of the alkaloid echitamine, isolated nearly a century ago from Alstonia scholaris. We now point out that data accumulated elsewhere and in this Laboratory



I



II

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[1] Contribution 1599 from the Sterling Chemistry Laboratory at Yale University.

[2] T.R. Govindachari and S. Rajappa, Proc. Chem. Soc. 134 (1959).

[3] A.J. Birch, H.F. Hodson and G.F. Smith, Proc. Chem. Soc. 224 (1959).

[4] T.R. Govindachari and S. Rajappa, Chem. & Ind. 1154 (1959); Ibid. 1549 (1959).

[5] S. Ghosal and S.G. Majumder, Chem. & Ind. 19 (1960).

show singular compatibility with the expression (I), originally deduced by one of us from the tenets of the theory of alkaloid biogenesis. Indeed this structure very closely resembles those of certain intermediates long considered prominent in the scheme of natural elaboration of complex indole alkaloids, particularly of the strychnine-vomicine group.

Echitamine chloride (or hydrochloride), $C_{22}H_{29}O_4N_2Cl$,[6-8] for which we favor the expression (II), shows no infrared $\overset{+}{N}$-H peak and no absorption near 1680 cm^{-1} to be ascribed to $>C=\overset{+}{N}<$; the ester carbonyl appears at 1740 cm^{-1}. An aqueous solution of the salt is neutral, and titration shows an apparent pK_a near 11. The action of aqueous sodium hydroxide gives echitamine base, $C_{22}H_{28}O_4N_2$, previously obtained amorphous (ref. 7) ("base A")[3], but now readily crystallized as the benzene solvate, m.p. 139 - 140°

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6 O. Hesse, Liebigs Ann. 176, 326 (1875); Ibid. 203, 144 (1880).

7 J.A. Goodson and T.A. Henry, J. Chem. Soc. 127, 1640 (1925); J.A. Goodson, Ibid. 2626 (1932).

8 We reject the conslusion of Govindachari and Rajappa (ref. 4) that the empirical formula of echitamine chloride, long established as $C_{22}H_{29}O_4N_2Cl$, should be revised to $C_{22}H_{27}O_3N_2Cl + H_2O$. The Indian workers base their O_3 formulation on the composition of the derivative they call dihydroechitamine, which does contain only three oxygen atoms. But neither echitamine chloride nor echitamine base can be obtained "anhydrous" in this sense. We would be idle not to ask if the salt should crystallize from absolute methanol with a water molecule and a molecule of methanol of crystallization (ref. 7), or if the base should be obtained as a monohydrate, containing as well a molecule of benzene, from its solution in dry benzene. Certain very convincing experiments prove that the fourth oxygen is really part of the molecule; for example, Goodson and Henry (ref. 7) obtained from the chloride a diacetyl derivative ($C_{26}H_{33}O_6N_2Cl$), whose preparation and composition we have confirmed, which shows no amide or $\equiv\overset{+}{N}$-H absorption in the infrared. This derivative is clearly an O,O-diacetate and its formation requires that the two oxygen atoms aside from those in the carbomethoxyl group be present as hydroxyl group in echitamine chloride. We remain with the sole alternative

(Cont'd)

(transition at 98 - 101°) (Found, for an air-dried sample: C, 72.43; H, 7.41; N, 6.22. $C_{22}H_{28}O_4N_2 \cdot C_6H_6$ requires: C, 72.70; H, 7.41; N, 6.06.). The 60 mc high resolution NMR spectrum of echitamine in deuteriochloroform fully supports previous conclusions with regard to the more obvious functional groupings; thus the O-methyl and N-methyl are clearly visible as intense singlets at τ = 6.30 and 7.76, respectively. The position of this N-methyl peak is quite normal for methyl bonded to tertiary nitrogen and indicates conclusively that echitamine is not a quaternary ammonium hydroxide. The allylic C-methyl appears as a doublet[9] (J = 6.4 cps) centered at τ = 8.39, consistent with its proximity to a singlet olefinic proton in the ethylidene group[10]; the olefinic proton appears as a 1:3:3:1 symmetrical quartet (J = 6.4 cps) centered at 4.56. The one-proton singlet near 5.1 is solely, but markedly, concentration dependent and is ascribed to a single hydroxyl in echitamine base.

Normal behavior as a tertiary base was further indicated in the formation of echitamine α-methiodide, with two N-methyl groups, just one of several crystalline salts isolated from reactions with methyl iodide. (Crystals from absolute ethanol, m.p. 226 - 229°, dec. Found: C, 52.22; H, 5.99; N, 5.30; OMe, 5.94; NMe, 9.05. $C_{23}H_{31}O_4N_2I$ requires: C, 52.46, H, 5.94; N, 5.32; OMe, 5.89; two NMe, 11.03.). The reconversion of echitamine to

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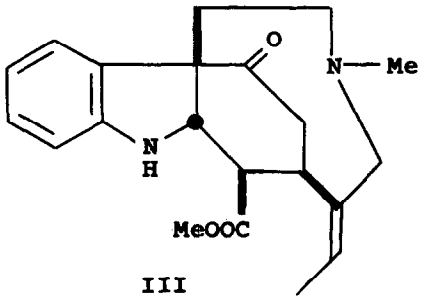
to the proposition of ref. 4, namely that the proximate product of hydrogenation is so remarkably constituted that it can lose one of its oxygen atoms spontaneously.

9 Under highest resolution, each member of the doublet is found to be further split, with about 0.5 cps separation, through longer range coupling with one or more of the other allylic protons.

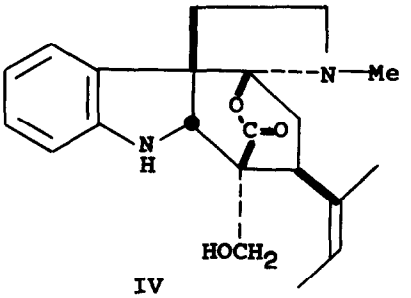
10 The presence of the ethylidene group was shown previously (ref. 3) as was the presence of the sec-butenyl group in "base B" of ref. 3; chromic acid oxidation of the reduction product, "base C", gave α-methylbutyric acid.

echitamine chloride, accomplished readily enough at 100°, is sufficiently slow at 25° so that titration of the base gives a different Pk_a (7.8; 60% aqueous ethanol); this hysteresis in the interconversion of the quaternary chloride (with two hydroxyl groups)[8] into the tertiary base (with only one hydroxyl) is well accommodated by the equilibrium I ⇌ II.

The reaction of echitamine chloride with potassium t-butoxide in absolute t-butyl alcohol yields, among other products, a substance we call alloechitamine, m.p. 191° from methanol (Found: C, 71.16; H, 7.65; N, 7.85; M.W. (Rast) 327. $C_{21}H_{26}O_3N_2$ requires: C, 71.16; H, 7.39; N, 7.90; M.W. 354), whose composition indicates the loss of the elements of hydrogen chloride and



III

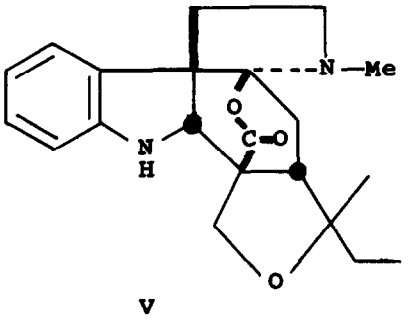


IV

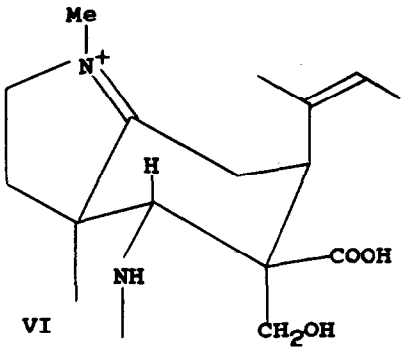
of formaldehyde. The easy removal of one carbon, by dealdolization, constitutes significant evidence for the presence of the system $HOCH_2$-C-COOMe in II. The ketonic carbonyl, masked in other echitamine derivatives, appears in the infrared spectrum of alloechitamine as a strong peak at 1689 cm^{-1}, in addition to that at 1736 cm^{-1}, associated with the ester; there is no hydroxyl absorption. The ultraviolet spectrum shows little change from that of echitamine base, and the NMR spectrum shows that the O-methyl, N-methyl and ehtylidene groups are still present. We consider alloechitamine to be III. The 1689 cm^{-1} carbonyl peak vanishes in the spectrum of alloechitamine

methiodide, containing the grouping $[MeO-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{N}}-Me]^+$; we recall similar evidence of transannular interaction in the formation of the methoperchlorate of N-methylpseudostrychnine.[11]

Returning to formula (II), we see that no conceivable cyclization of the δ-hydroxy ester system, with expulsion of methanol, is sterically feasible. But this geometrical impediment to lactonization (e.g., to IV) is removed in (one epimer of) the carbinolamine in which the allylic C-N bond has been broken by hydrogenolysis. Catalytic reduction of echitamine with platinum in ethanol gave in high yield, without further treatment, a lactone, m.p. 140 - 144° (from ether), m.p. 154 - 157° (from benzene) (Found: C, 71.25; H, 7.46; N, 7.96; C-Me, 5.74; OMe, 0.16. $C_{21}H_{26}O_3N_2$ requires: C, 71.16; H, 7.39; N, 7.90; two C-Me, 8.48; OMe, 0.00.) after the absorption of one mole of hydrogen. The properties of this reduction



V



VI

[11] F. A. L. Anet, A. S. Bailey and R. Robinson, Chem. & Ind. 944 (1953).

product,[12] for which we adopt the denomination echitinolide, are indeed fully consonant with the expression (IV). The NMR spectrum is characterized by the absence of any O-methyl peak near $\tau = 6.3$, but the following features are readily distinguished: N-methyl (singlet at 7.53), C-methyl (broader singlet at 7.76) and a second C-methyl (doublet at 8.48; J = 6.6 cps). The infrared spectrum includes sharp OH and NH maxima, as well as a carbonyl peak at 1742 cm^{-1}, increasing to 1754 in the O-monoacetate, m.p. 210 - 214°, (Found: C, 70.03; H, 7.30; N, 7.27. $C_{23}H_{28}O_4N_2$ requires: C, 69.67; H, 7.12; N, 7.07.) (sharp NH but no OH infrared peak) obtained with acetic anhydride-pyridine under mild conditions. The much lower pK_a (5.4; 60% ethanol) of IV is consistent with the proximity of acyloxy and tertiary amino functions.

An isomer, isoechitinolide (V), m.p. 149 - 154° (from ether) (Found: C, 70.89; H, 7.15; N, 7.90), with ν_{max} 1754 cm^{-1}, containing no hydroxyl and no double bond, is formed when IV is heated with hydrochloric acid. Probably the sec-butenyl residue epimerizes prior to ring closure; with the intact system (II) the corresponding cyclization can be shown to be sterically completely prohibited, and we note that echitamine chloride is entirely stable to aqueous acid under these conditions.

Echitamine shows ultraviolet absorption almost identical with that of echitamine chloride [$\lambda\lambda_{max}$ 235 mμ (3.93); 295 mμ (3.55)], even in strongly alkaline solution, where any basic ionization is repressed. The α-methiodide

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[12] Echitinolide may well be and probably is identical with 'dihydroechitamine' (ref. 4; no m.p. or analytical data reported) and in this event the latter has been incorrectly formulated as $C_{22}H_{28}O_3N_2$. We prefer to reserve the name dihydroechitamine for the derivative otherwise identical with echitamine but with ethyl in place of ethylidene. Very probably echitinolide is also identical with 'base B' of ref. 3, also then incorrectly formulated.

gives a very similar spectrum, if allowance is made for the absorption of iodide ion. Echitinolide (IV) absorbs at longer wavelengths [$\lambda\lambda_{max}$ 248 mμ (3.91); 309 mμ (3.55)] as does isoechitinolide (V), but acidification of the solution causes downward displacement of the maxima in each case. Some of the previous authors (refs. 2 - 4) have sought to identify the hypsochromic shift in acid with the accumulation of positive charge on N_b in an eserine-like system[13] (N_a-C-N_b); this suggestion is notable in its failure to extend to the parent substance, echitamine, uncharged but with the same 'shifted' spectrum. We believe it to be more than coincidental that all of the compounds with low wavelength absorption have N_a equatorial (with respect to the six-membered carbocyclic ring C), on the basis of the structures proposed, while absorption appearing above 240 mμ (and above 300 mμ) can be consistently correlated with structures in which N_a has an axial conformation. Thus the cation of IV may exist in an open form, as in VI, with equatorial N_a, and this view is supported by the infrared spectrum of echitinolide hydrochloride, with characteristic broad carboxylic hydroxyl absorption at 2860 - 3450 cm^{-1}.

The methine[4,14] obtained in the 'facile Hofmann degradation' with echitinolide ('dihydroechitamine')[12] methiodide, should be VII, and the empirical formula of this methine must then be revised from $C_{23}H_{32}O_4N_2$ to $C_{22}H_{30}O_4N_2$. The zinc-hydrochloric acid reduction product, 'deoxy<u>neo</u>dihydroechitamine-methine'[4], is still a lactone, with structure (VIII); there is

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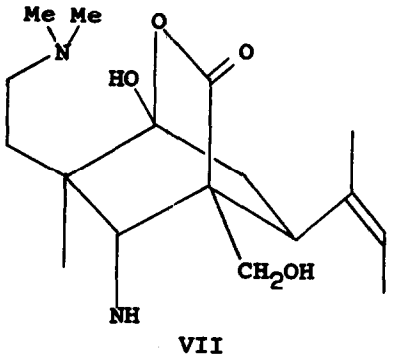
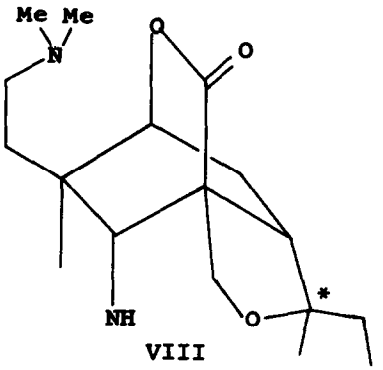
[13] Cf. H. F. Hodson and G. F. Smith, <u>J. Chem. Soc.</u> 1877 (1957).

[14] This 'dihydroechitamine-methine' was originally described as a 2-hydroxyindoline (ref. 4). The chemical literature contains no authenticated example of an N-unsubstituted 2-indolinol and we think it unlikely that any such system would be capable of existence independently of the corresponding indolenine.

now no opportunity for conformational inversion in the conjugate acid, so the ultraviolet spectrum [$\lambda\lambda_{max}$ 247 mμ (3.97); 307 mμ (3.59)] of this derivative is unchanged in acidic solution.[15]



VII



VIII

The zinc dust and selenium degradations leading to echitamyrine[4] and the dimethylpyrrolc(2′:3′-3:4)quinoline[3] might proceed via the intermediate (IX), which could arise from the iminium cation (VI) of IV by 1,2 migration of the indoline α carbon. We suggest that the specific biogenetic derivation og echitamine involves the precursor (X) in Mannich cyclization; the species (X) differs only in the most trivial sense from one already considered to account for the formation of the alkaloid gelsemine.[16] A close relationship to the quaternary alkaloid C-fluorocurarine[17] is apparent, while the system

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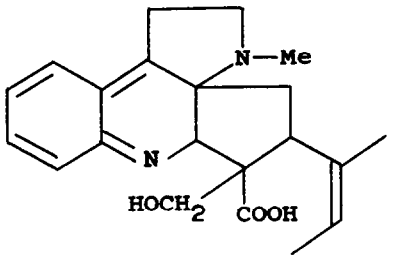
* No configurational representation at the starred atom intended.

15 N_a appears never to be protonated in these acidic solutions, probably because of steric hindrance to solvation of the ion; the steric block is also responsible for the unusual difficulty of N_a-acetylation of many of these derivatives.

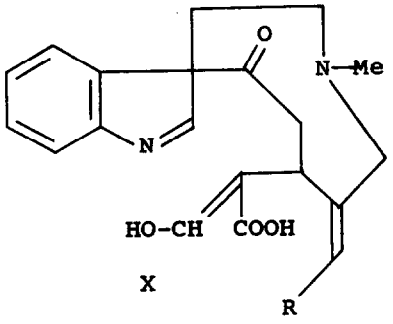
16 H.Conroy and J.K. Chakrabarti, Tetrahedron Letters No. 4, 6 (1959).

17 W. von Philipsborn, K. Bernauer, H. Schmid and P. Karrer, Helv. Chim. Acta 42, 461 (1959) and earlier references cited.

not cyclized, but retaining the carboxyl residue, is found in the alkaloids corynoxeine and rhyncophylline.[18,19]



IX



X

Acknowledgments - This research is supported by generous grants from the National Science Foundation (NSF-G6586) and from the National Institutes of Health (RG-6190C1 and CY-3722C1). Microanalyses are by Dr. S. M. Nagy (M. I. T.) and the Schwarzkopf Microanalytical Laboratory. We are greatly indebted to Dr. D. Dickel of CIBA (Summit) for the preparation of the echitamine.

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

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