Tetrahedron Letters No. 19, pp. 36-42, 1960. Pergamon Press Ltd. Printed in Great Britain

ECHITAMINE

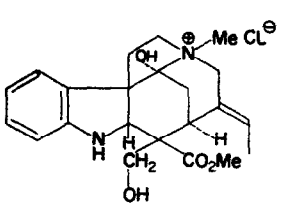
A. J. Birch, H. F. Hodson, B. Moore, H. Potts,

and G. F. Smith

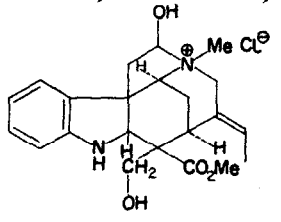
Department of Chemistry, University of Manchester

(Received 29 June 1960)

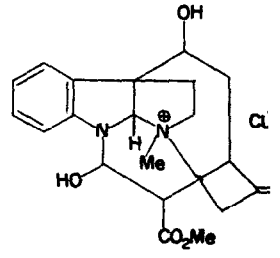
RECENT months have seen the proposal of three different structures for the alkaloid echitamine chloride: structure (I), proposed by Conroy et al.,[1] structure (II) proposed by Robinson, Chakravarti, Chakravarti and Ghose,[2]



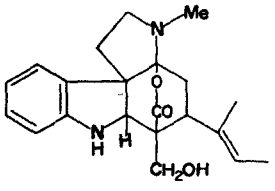
I



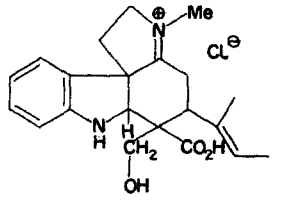
II



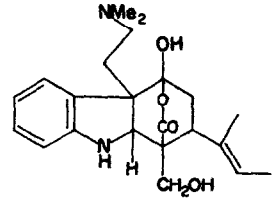
III



IV



VI



V

[1] H. Conroy, R. Bernasconi, P.R. Brook, R. Ikan, R. Kurtz and K.W. Robinson, Tetrahedron Letters No. 6, 1 (1960).

[2] D. Chakravarti, R.N. Chakravarti, R. Ghose and Sir Robert Robinson, Tetrahedron Letters No. 10, 10 (1960); Ibid. No. 11, 25 (1960).

and structure (III), proposed by Chatterjee, Ghosal and Ghosh Majundar.[3]

We wish in this communication to look at each of these structures critically in the light of the available evidence.

Structure (I) goes a long way towards interpreting the known reactions of the alkaloid, but fails on one important point. The Hofmann degradation of echitinolide (IV) should, on the basis of Conroy's formulation, lead to the unique structure (V) for the methine. This methine is described by Govindachari and Rajappa[4] as a base showing λ_{max} 245, 307 mμ (log ε 3.94, 3.54) in ethanol, changing to 240, 297 mμ (log ε 3.90, 3.49) on acidification. We have also studied the Hofmann degradation of echitinolide, but have found that the immediate product of the reaction is an as yet amorphous base $C_{22}H_{30}O_4N_2$ (base A), which has a C = O stretching frequency of 1740 cm^{-1}, OH-3630 cm^{-1}, NH-3455 cm^{-1} and which has λ_{max} 240, 296 mμ (ε 7450, 2820) unchanged on acidification; this base A is converted by being passed over alkaline alumina in benzene into a crystalline isomeric base B, m.p. 169-173°, which has a C = O stretching frequency of 1723 cm^{-1}, OH-3590 cm^{-1}, NH-3470 cm^{-1} and λ_{max} 247, 306 mμ (ε 9100, 3640) changed to 243, 302 mμ (ε 9200, 3550) on acidification. It is not possible to account for the production of two isomeric methines on the basis of structure (V). That the double bond of the isobutenyl group is not involved in this isomerization is shown by the fact that β-dihydroechitinolide undergoes the Hofmann degradation to give a completely analogous pair of methine bases (catalytic hydrogenation of echitinolide in glacial acetic acid gives two isomeric

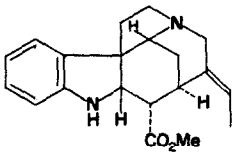
---

[3] A. Chatterjee, S. Ghosal and S. Ghosh Majundar, Chem. & Ind. 265 (1960).

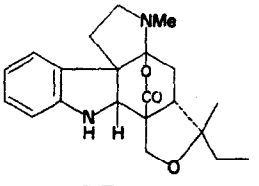
[4] T.R. Govindachari and S. Rajappa, Chem. & Ind. 1549 (1959).

dihydro derivatives whose I.R. spectra are identical: α-, with m.p. 120-124° partially recrystallizing to melt finally at 195-197°, β-, with m.p. 92-97° partially recrystallizing to melt finally at 112-117°.

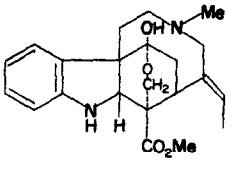
The following are further criticisms of structure (I) proposed by Conroy et al.: (a) The American authors believe the failure of N(a) in (I), (IV), and (V) to protonate in acid solution to be due to steric hindrance of the N(a) ammonium ion to solvation. We should like to point out that in 2,16-dihydroakuammicine (VII), in which there is the same order of steric hindrance around N(a), protonation of N(a) is complete in 0.5 N ethanolic HCL.[5] It is noteworthy that (i) neither echitamine chloride nor echitinolide



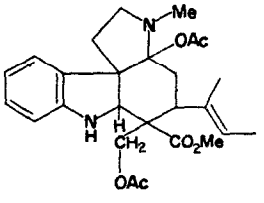
VII



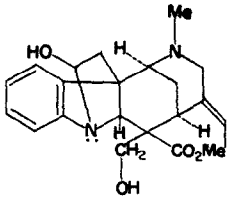
VIII



IX



X



XI

are protonated on N(a) even in concentrated hydrochloric acid and (ii) acetic anhydride and sodium acetate at the b.p. acetylate echitinolide cleanly on N(a).

---

[5] P.N. Edwards and G.F. Smith, In press.

(b) The U.V. spectrum of echitinolide (IV) undergoes a marked hypsochromic shift on acidification. This is accounted for by Conroy in terms of conversion of (IV) into an immonium carboxylic acid (VI), the spectral shift being held to be due to a conformational change caused by the opening of the lactone ring and involving N(a). We have hydrogenated diacetyl echitamine chloride to a di-O-acetyl base, $C_{26}H_{34}O_6N_2$, in which the carbomethoxy group is still present (Found: OMe, 6.15. Calc. for one OMe in $C_{26}H_{34}O_6N_2$, 6.6%). This base dissolves in 0.5 N aqueous HCl at room temperature and can be recovered unchanged on basification; it is hydrolysed to echtinolide by dilute methanolic sodium hydroxide at the boiling point. This diacetyl carbomethoxy base, which on Conroy's formulation should have structure (X), has λ_{max} 251, 308 (ε 7000, 2800), changed to 241, 297 mμ (ε 7500, 2800) on acidification. Since this base cannot undergo a reversible change of conformation of the type postulated by Conroy, the latter's argument concerning the spectral shift is invalidated. A further weakness of the lactone ring-opening hypothesis is that it fails to account for the resistance of echitinolide to reduction in acid solution, for the immonium ion in (VI) is not particularly sterically hindered (questions of steric hindrance were decided on by inspection of Stuart - Briegleb models). We feel that the β-N-C-N system still affords the simplest rationalization of the data,[6] though any system which brings a positively charged N(b) spatially very close to N(a) will give rise to the same effects. The observation that a 9 mμ hypsochromic

---

[6] A.J. Birch, H.F. Hodson and G.F. Smith, Résumé des Communications, Tome II, p. 207, XVIth Internat. Congr. Pure. Appl. Chem., Paris, 1957; Proc. Chem. Soc. 224 (1959); T.R. Govindachari and S. Rajappa, Ibid. 134 (1959).

shift of the acylarylamine type spectrum of O,N-diacetyl echitinolide occurs on acidification tends to support this.

(c) We have found both echitinolide and isoechitinolide not to be reduced by lithium aluminium hydride in ether at room temperature and only slowly at the boiling point. This would seem to indicate very considerable steric hindrance to approach of the reagent to the carbonyl carbon. This is not at all evident in (IV), and even less so in isoechitinolide, formulated by Conroy as (VIII). [We have found isoechitinolide to crystallize from ether as plates; m.p. 182-184° (cf. m.p. 149-154° quoted in reference 1)].

(d) Echitamine base, which we have also and independently obtained in the form of a crystalline benzene solvate, does not give any trace of acetaldehyde on ozonolysis in CCl_4, but gives formaldehyde in 40% yield. This is not easily reconcilable with structure (IX). We also differ from the American authors on the question of the speed with which echitamine reverts to echitamine hydroxide (I, OH^- instead of Cl^-): we find this conversion to occur very rapidly, for we observe echitamine to dissolve in water to give a solution the pH of which rises in less than one minute to a value correspondong to complete ionization as the quaternary hydroxide. We are of the opinion that the U.V. spectrum of (II) cannot be measured in ethanol, the spectrum observed being that of the quaternary hydroxide. The U.V. spectrum of echitamine in petrol has λ_{max} 227, 283 mμ (ε 10,000, 2360).

In support of the formulation of echitinolide as a lactone,[1] the molecular weight has been found to be 354 by the mass-spectrographic method (We are indebted to Dr. A.E. Williams, of the I.C.I. Dyestuffs Division, for this measurement); furthermore, we have shown that hydrogenolysis of

echitamine iodide ethyl ester (produced by the action of ethyl iodide on echitamine betaine, cf.[7]) also yields echitinolide.

With regard to structure (II) proposed by Robinson et al.[2] for echitamine chloride, we wish to point out that it suffers from many of the disadvantages of structure (I). In addition, the potential aldehyde group makes the failure of echitamine to be reduced by borohydride in alkaline methanol difficult to understand. Echitamine would have to have structure XI, and this would be expected to have benzenoid type of ultra-violet absorption, the p-electrons on N(a) being sterically unable to conjugate with the benzene ring.

With regard to structure (III),[3] N(a) being practically non-basic as a result of the formal positive charge on N(b), it would not be expected to form a carbinolamine system. Even if it did, being part of an eight-membered ring, one would expect it to dissociate very readily to give an α-formyl ester which should either form a carbonyl derivative or lose formic acid very easily. Similar difficulties are encountered in the formulation of echitinolide and further degradation products on the basis of (III). In a recent publication,[8] Chatterjee et al. discuss the C-nitrosation of echitamine chloride, and put forward this as further evidence for the tertiary nature of the aromatic nitrogen. In a quaternary gem-diamino system, however, the closeness of the positively charged N(b) to N(a) would afford a satisfactory explanation of the failure of a secondary N(a) to nitrosate.

We cannot yet propose a structure for echitamine which satisfactorily

---

[7] J.A. Goodson, J. Chem. Soc. 2626, (1932).

[8] A. Chatterjee and S. Ghosal, Naturwissenschaften 47, 234 (1960).

explains all the observed reactions and properties of this alkaloid. The alleged isolation of indoleacetaldehyde by periodate oxidation of echitamine chloride[3] is, for example, very difficult to reconcile with our isolation of an α,β-disubstituted indole, characterized as the crystalline methyl ester, $C_{21}H_{29}O_4N$, m.p. 142-143°, by the action of sodium in liquid ammonia on des-N-echitinolide, $C_{20}H_{23}O_4N$, m.p. 172-174°, the product of two Hofmann degradations of echitinolide. The final solution of this fascinating and complex structural problem awaits further experimental work.