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ECHITAMINE

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THE constituents of Alstonia scholaris have been investigated by the present Indian authors[1] since 1955 and with special reference to the main alkaloidal constituent, namely echitamine chloride.

The results, anticipated in part by other workers, will be published later in detail and the present communication, the outcome of our discussions, has become necessary in view of papers contributed by three groups of investigators.[2,3,4] These concur in attributing an eserine-like constitution to the alkaloid, mainly on spectrographic evidence. The hypsochromic shift of the U.V. absorption on the addition of acid[5] is held to be characteristic of the part structure Ar - N (a) · C (b) - N : . We do not regard this argument as conclusive.

[1] Cf. R. Ghose, Ph.D. thesis, Calcutta University, 1957. Experimental results cited in the present memoir are due to the three first-named authors.

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

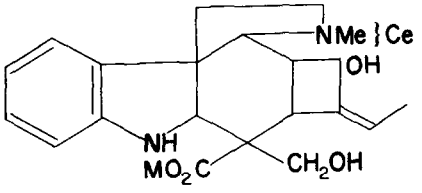
[3] A. J. Birch, H. F. Hodson and G. F. Smith, Proc. Chem. Soc. 224 (1959)

[4] A. Chatterjee, S. Ghosal and S. G. Majumdar, Chemistry and Industry 265 (1960).

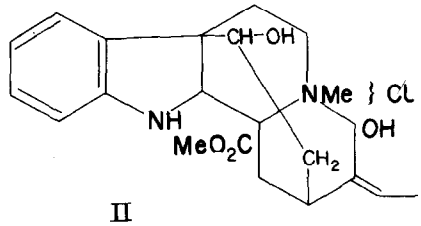
[5] Hodson and Smith, J. Chem. Soc. 1877 (1957).

The absorption is obviously due to the Ar N(a) conjugated system which can be modified by salt formation. The basic function of N(a) is in its turn influenced by the cationic charge on N(b) but it is a non sequitur to assume that this can only be effective in the group N(a) . C - N(b). Analogies from the chemistry of ajmaline[6] (III) akuammicine (IV) and pseudoakuammigine (V) combined with biogenetic considerations suggest the structures I or II for echitamine hydrochloride which serve to illustrate most of the chemistry of the alkaloid almost equally well.

On balance I is favoured since it provides, as shown below, an easier explanation of the formation of a degradation product obtained on distillation over zinc dust (Birch et al, loc. cit.).



I



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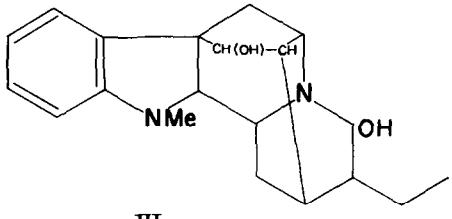
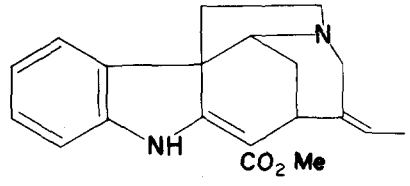
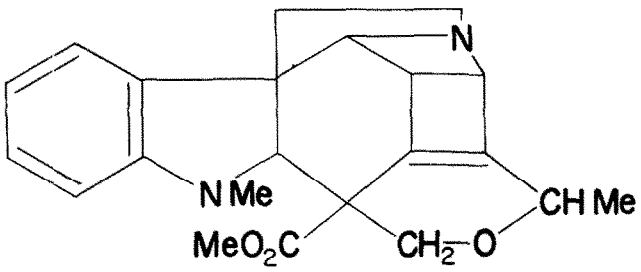


III



IV

[6] F.A.L. Anet, (Mrs.) D. Chakravarti, R. Robinson and E. Schlittler, J. Chem. Soc. 1242 (1954); F. C. Finch, J. D. Hobson, R. Robinson and E. Schlittler, Chemistry and Industry 653 (1955); R. Robinson Festschrift Arthur Stoll. Sandoz A.G., Basel, p. 457 (1957).



V

The composition of echitamine chloride, $C_{22}H_{29}O_4N_2Cl$ (including CO_2Me and (Me)N) indicates an α - or β -indole alkaloidal skeleton with C_{19} (C_{10} + C_8 + C, the so-called berberine bridge carbon atom).

The biogenesis of II can be contemplated along the usual lines for indole alkaloids in cases involving a Woodward fission. The carbomethoxy group is here in the position of the terminal carboxyl of the hypothetical hydroxylated phenylalanine precursor. On the other hand this confers no advantage over I, because the carbomethoxy group in the β -indole alkaloid structure is in precisely the same relative position with respect to the presumed amino-acid precursor as it occurs in yohimbine or corynantheine which belong to this α-indole alkaloid type. Hence the biogenetic arguments cancel, but whichever structure we take, an interesting biogenetic origin of the ester group is revealed.

The comparison of I and II is developed further below, but we now turn to the features common to the two structures. The ethylidene group is established by ozonisation of echitamine with formation of acetaldehyde. Birch, Hodson and Smith[3] extended a device that had been used in the ajmaline group (cf. Stoll Festschrift[6]) and showed

that a catalytically reduced echitamine could be oxidised in a modified Kuhn-Roth process to a mixture of acetic and α -methylbutyric acids. We have found that echitamine is converted by hot 16% hydrochloric acid into the hydrochloride, m.p. 250-252°, of a t-base termed iso-echitamine. This affords formaldehyde instead of acetaldehyde on ozonisation. The explanation of the change is not clear. The colour reactions and reducing properties are also modified and something more profound than the simple shift of a bond -

$$\text{>C} = \text{CH} - \text{CH}_3 \longrightarrow \text{>CH} - \text{CH} = \text{CH}_2$$

has probably occurred. The liberation of an aldehyde function is also involved. The formation of dimethylechitamine by facile hydrolysis of echitamine, and its betaine-like character, has been recognised since the early work of Goodson[7] as evidence of a $\cdot CO_2Me$ group.

A diacetyl derivative affords evidence of :NH(a) and a hydroxyl group. The substance was prepared by the action of acetic anhydride on a pyridine solution of echitamine chloride at 100°. It crystallized from methanol-ether, m.p. 252°, $[\alpha]_D^{19}$ - 49.65. The analyses showed 2 Ac and agreed somewhat better with an anhydro-diacetyl derivative but the substance can be hydrolysed with regeneration of echitamine. The postulation of :N(a)Ac in this substance is based on the change of the colour reaction with nitric acid from red (echitamine) to violet and also by the change in U.V. absorption which resembles that between deacetylspermostrychnine (corresponding to echitamine) and spermostrychnine[8] (corresponding to diacetylechitamine). It appears therefore that echitamine contains only one hydroxyl group that can be acetylated under the conditions employed.

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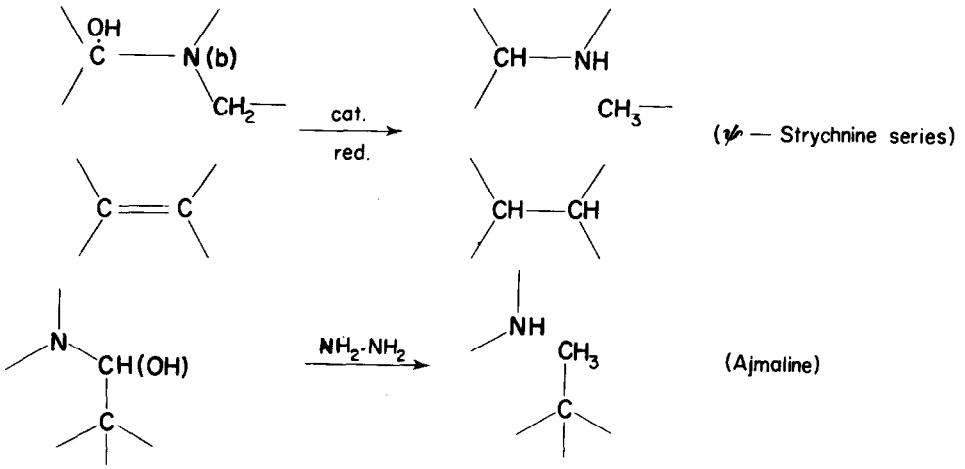
7 J. M. Goodson and T. Henry, J. Chem. Soc. 127, 1640 (1925); Goodson, ibid. 2626 (1932).

8 F.A.L. Anet and R. Robinson, J. Chem. Soc. 2253 (1955).

The catalytic hydrogenation of echitamine has been studied under various conditions. It was found that hydrogenolysis occurred, with or without saturation of the double bond. Hydrogenation of echitamine hydrochloride with Adams' PtO_2 catalyst in acetic acid medium gives a mixture of products from which deoxydihydro-echitamine, $C_{22}H_{30}O_3N_2$, m.p. 158-160° after shrinking at 130°, has been isolated.

In methanol the main product was a t-base, $C_{22}H_{28}O_3N_2$, which collapsed at 160° to an opaque mass clearing at 183-186°. This latter base furnished acetaldehyde on ozonolysis. The processes recalled the course of reduction of certain pseudo-strychnine and ajmaline derivatives in which we observe the changes:-



As in some of these cases (e.g. ajmaline) the hydrogenolysis results in formation of a new !CMe group. Deoxydihydro-echitamine is a t-base which does not give a red colouration with nitric acid. The simplest explanation of this curious property is that the ring fission has released strain and brought the $-CO_2Me$ group into closer relation

with N(a). Pseudo-akuammigine is doubtless a dihydro-indole and its failure to exhibit oxidation colour reactions can only be due to such association, a point which has already been made.[9]

Chatterjee et al[4] recognise the :N·C(OH):group but consider that the nitrogen concerned is N(a). This hypothesis is untenable because N(b) must in any case be quaternary and hence must suffer Emde reduction. Thus the N(a) CHOH theory requires fission at N(b) and deoxidation in the group attached to N(a). Thus all the relevant analogies are set aside. In addition we have adduced evidence that N(a) occurs as :NH, which can be acetylated and recovered on hydrolysis.

Furthermore the pka of echitamine hydrochloride is 9·1 which is the value noted for methylajmaline hydrochloride. This shows that methylajmaline and echitamine are notably stronger than ordinary t-bases, similar in structure, and also weaker than quaternary salts with usual reduced alkyl-type substituents. This special intermediate strength of the bases is evidently characteristic and is attributed to the group $\rangle\overset{+}{N}Me$ - CH(6H) -. Fission to $\rangle NMe$ O:CH· is not facile; there is pseudo-quaternary character; but it occurs at a lower pH than the Hofmann elimination, which of course may not occur at any pH. These facts find no explanation on the suggestion of Chatterjee et al. These authors state that the U.V. absorption spectrum of echitamine is that of an indoline base of eserine type. Actually it closely resembles the spectrum of various dihydroindole alkaloids as may be seen from the annexed comparison with pseudo-akuammigine and ajmaline.

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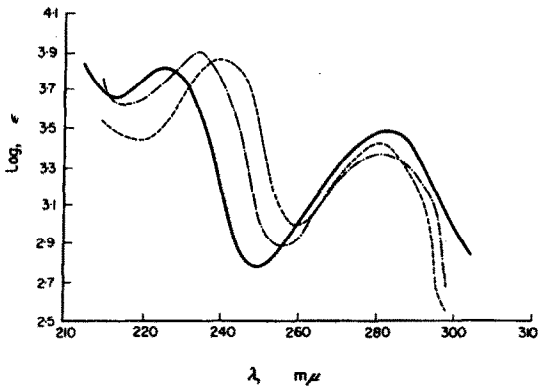
9 R. Robinson and A. F. Thomas, J. Chem. Soc. 3479 and 3522 (1954)



Echitamine hydrochloride _____

Pseudo-akuammigine .-.-.-.-.-.-.-

Ajmaline ----------

In view of this conclusion the failure or reluctance of some colour reactions of echitamine and its derivatives (oxidation reaction with ferric chloride; coupling with diazobenzenesulphonic acid) poses the same problem as did pseudo-akuammigine. The only structural factor which provides some resource in this matter is the CO_2Me group, the position of which may facilitate a sufficient neutralisation of N(a). The structure of pseudo-akuammigine was formulated with this requirement in view. But in the case of the congeneric akuammicine the same position of the CO_2Me was indicated on quite independent grounds, namely that the base clearly contained the group

$$Ar\dot{N}(a)\cdot\dot{C}=\dot{C}-CO_2Me.$$

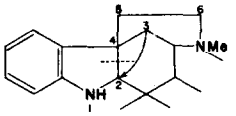
Karrer et al (loc. cit.) formulate a hydrogen bond between $\diagdown\!\!\diagup$NH(a) and oxygen of carbonyl; we are not clear that this should supply the observed neutralisation of N(a).

The suggested constitution of akuammicine[10] has now been confirmed

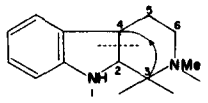
[10] K. Aghoramurthy and R. Robinson, Tetrahedron I, 172 (1957).

by Professor P. Karrer (private communication) in that a Nb-methyl-akuammicine salt and flavocurarine[11] yield a salt of one and the same base on hydrolysis by elimination of CO_2Me and CHO, respectively. Thus the position selected for the $-CO_2Me$ group in I and II has been found to be correct for another indole alkaloid.

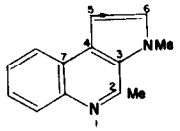
Finally, we note the structural changes required to derive 1'-methyl-pyrrolo (2':3'-3:4) quinoline (VI) from I and II. Actually it was a reduced t-base (hydrogenolysis and Emde reduction, but double bond intact) which was used by Birch, Hodson and Smith (loc. cit.). The same or a closely similar base had also been obtained in a similar manner by Govindachari and Rajappa (loc. cit.). Birch et al synthesised the substance.



Part of I



Part of II



VI

In both cases the αβ position in the indole nucleus suffers fission. It will be seen that I does leave a carbon atom attached to position 2, even though it be a heavily substituted one. On the other hand, II provides no such source of the 2-methyl group of VI which would need to be introduced by migration.

11 W. von Philipsborn, K. Bernauer, H. Schmidt and P. Karrer, Helv. Chim. Acta. XLII, 461 (1959).

After this note had been prepared for publication we read the communication of Conroy et al[12] on this topic and, as will be seen from the foregoing, find ourselves in agreement with most of the conclusions of these authors.

However, we greatly prefer the formula we have proposed on the methylajmaline model to that which the American workers adopt on the methyl-ψ-strychnine model.

In the first place it is not our experience that N(b) methyl-ψ-strychninum salts are so strongly quaternary as is echitamine. The former salts yield the keto-bases with weak alkalis.

An even more cogent argument is provided by the powerful reducing properties of echitamine base and of iso-echitamine. The latter base reduces ammoniacal silver solutions and Fehling's solution with great ease and echitamine itself exhibits the same property somewhat less readily. In this respect they resemble N(b) methylajmaline and oxo-dihydro-allostrychnine.[13] The ψ-strychnines do not exhibit strong reducing properties (cf. their preparation by means of oxidation[14]) which are evidently due to the aldehyde group liberated in alkaline solution from echitamine and ajmaline derivatives.

The formula I was foreshadowed in the Ph.D. (Calcutta) thesis of one of us[1] and it should also be pointed out that the akuammicine structure was clearly indicated[10] in 1957.

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

13 R.N. Chakravarti, K.H. Pausacker and R. Robinson, J. Chem. Soc. 1555 (1947), cf.

14 A.S. Bailey and R. Robinson, J. Chem. Soc. 703 (1948). Cf. Nature Lond. 160, 18 (1947).

Dr. G.F. Smith (private communication) has informed us that he has been able to relate akuammicine to the Wieland-Gumlich aldehyde by conversion into one and the same substance, without loss of carbon, thus affording an elegant constitutional proof.