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PRELIMINARY COMMUNICATIONS

The chemistry of akuammicine

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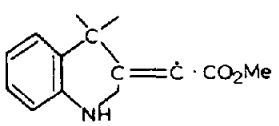
THE alkaloids of the seeds of *Picralima Klaineana* Pierre were first isolated and studied by Henry and Sharp[1] and Henry,[2] and later by Millson, Robinson, and Thomas,[3] who used seeds of *Picralima nitida* Stapf. (= Klaineana; the genus has only one species) obtained through the good offices of the Colonial Products Research Council.

The present authors have worked up a second batch of seeds from the same source, and are grateful to Dr. R. A. Galley for the provision of this material. Akuammicine is found among the bases soluble in light petroleum, and *n*-hexane was used in the present work. It is of special interest because of its high specific rotatory power, −737·7°, and it exhibits a number of very characteristic colour reactions. Raymond Hamet[4] has shown that the ultra-violet absorption of akuammicine is of indoline type and very similar to that of echitamidine, which also has an abnormally high rotatory power.

Henry's formula for akuammicine was $C_{19}H_{20}O_2N_2$, but Robinson and Thomas[5] proposed to change this to $C_{20}H_{20}O_2N_2$. We have confirmed the C_{20} formula by repeated analyses, especially of the methiodide and *picrate*.

Akuammicine is a strong base, pK_a, 7·45;[4] it contains 1 Me(C) and 1 Me(O) and affords on catalytic hydrogenation a dihydro-derivative which exhibits the same ultra-violet absorption as the parent base. Infra-red absorption indicates an *o*-disubstituted benzene nucleus, an –NH· group, and includes a strong band at 6·03 Å which was at first thought to be due to :N·CO.

This hypothesis was later found to be untenable, though it was the chemical evidence which led us to the realisation that the alkaloid probably contains the group.

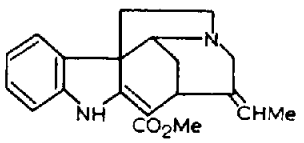


Confirmation was then available in the fact that the ester, Ph·NH·CMe=CH·CO_2Et, absorbs at 6·03 Å.

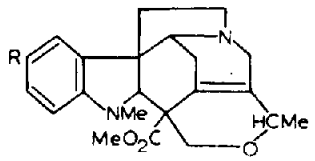
Robinson and Thomas found that akuammicine was resistant to lithium aluminium hydride, but, working under more vigorous conditions, we found that reduction could be effected by this reagent and the product was a crystalline base, $C_{19}H_{22}N_2$, showing typical indoline absorption and reactions. With Ehrlich's reagent it gave an intense orange-yellow coloration, which is a characteristic reaction for *sec*-aromatic amines. The composition change could be explained as $-CO_2Me \rightarrow CH_3$, and the new base did not contain methoxyl. The Me(C) content was augmented, but the values found were low both for akuammicine and the reduction product. These deductions were confirmed by the results of hydrolysis. With methanolic potassium hydroxide the methoxyl is removed, but the product is an intractable amino-acid. Careful acid hydrolysis afforded a base, $C_{18}H_{20}N_2$, which was oxidised readily on exposure to the air. The loss of CO_2 as well as Me is readily understood, on the basis that ϕ·NH·Ċ = Ċ·CO_2Me is a vinylogue of ϕ·NH·CO_2Me.

[1] T. A. Henry and T. M. Sharp *J. Chem. Soc.* 1950 (1927).
[2] T. A. Henry *J. Chem. Soc.* 2767 (1932).
[3] M. F. Millson, R. Robinson, and A. F. Thomas *Experientia* IX/3, 89, (1953).
[4] Raymond Hamet *Compt. Rend.* **211,** 125 (1940); **221,** 69, 699, (1945); **230,** 1183 (1950); **233,** 560 (1951); *Arch. Exp. Path. Pharm.* **199,** 399 (1942); *Compt. Rend. Soc. Biol.* **137,** 404 (1943); **138,** 199 (1944); **148,** 458 (1954); *Rev. Int. Bot. App. Agric. trop.* **31,** 465 (1951); *Bull. Soc. Pharm. Bordeaux* **90,** 178 (1952);
[5] R. Robinson and A. F. Thomas *J. Chem. Soc.* 2049 (1955).

On the biogenetic grounds generally accepted as applicable to the indole alkaloids, we developed the structure of akuammicine to (I).



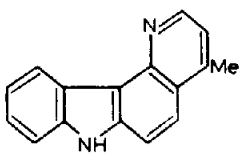
I



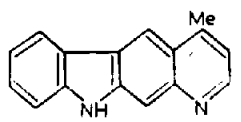
II

It is thus assigned to the β-series of indole alkaloids and the position of the $-CO_2Me$ is the same as that proposed for akuammine (II, R = OH) and *pseudo*-akuammigine (II, R = H) quite independently and on different grounds.[6] It was already known that akuammine affords β-ethylpyridine on distillation over zinc dust,[3] and we have found that *pseudo*-akuammigine behaves in the same way; also that carbazole is produced in the former reaction. The zinc-dust distillation of akuammicine also yields β-ethylpyridine, along with simple but unidentified indole derivatives.

The degradation by heating with selenium gave skatole and β-ethylindole (isolated as a mixture of their picrates) and a new base, $C_{18}H_{12}N_2$, which we propose to name *akuammicyrine*. The most natural structure that could be assigned to this substance is III



III



IV

Syntheses of the indolo-lepidines (III) and (IV) have been effected. 7-Hydrazino-4-methylquinoline was submitted to Fischer indole synthesis with *cyclo*hexanone and the product dehydrogenated to III. The linear isomeride (IV) was made from 7-hydrazino-4-methyl-2-quinolone by the Fischer reaction with *cyclo*hexanone followed by chlorination of the product with phosphoryl chloride hydrogenation in presence of Raney nickel and potassium hydroxide in ethanol, and dehydrogenation by means of palladised charcoal in boiling cymene.

The base (III) is closely similar to akuammicyrine in ultra-violet absorption. The behaviour of mixtures of the picrates on heating neither proves nor disproves identity, and the matter will be further investigated. Meanwhile the ultra-violet absorption curves are so similar that there can be little doubt but that akuammicyrine contains the basic skeleton of III. Conceivably the methyl group is differently sited or perhaps partly eliminated.

The composition, $C_{20}H_{26}O_3N_2$, was assigned to echitamidine,[7] which is akuammicine plus 4H and O. It is not easy to modify the structure (I) to fit this in view of the hypothesis that the high rotatory power is associated with unsaturation.

If the base were $C_{20}H_{24}O_3N_2$ (C analysis, 1% low), it could be a hydroxy-dihydro-akuammicine.

Half of its (N) or (O) methyl is given as methoxyl and half as methylimino. Goodson thought the labile Me(N) choice the better, but we suggest that a $-CO_2Me$ is present and the cause of the curious analytical results may be that a part of the methyl content wanders from O to N during the Zeisel operation. Analogies for this supposition are readily accessible.

Tabersonine[8] is probably a third member of this small group of alkaloids.

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[6] R. Robinson and A. F. Thomas *J. Chem. Soc.* 3552 (1954); cf. F. E. Bader *Helv. Chim. Acta* **36**, 215 (1953).
[7] J. H. Goodson *J. Chem. Soc.* 2626 (1932).
[8] M. M. Janot, R. Goutarel and J. Le Men *Bull. Soc. Chim. (France)* 707 (1954).