161. *Akuamma Alkaloids. Part I. Akuammicine.*

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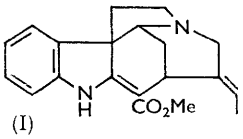
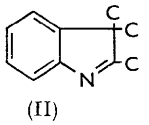
Some reactions of the product produced from akuammicine by loss of the methoxycarbonyl group are described. These lead to the partial structure (XI) for akuammicine.

Akuammicine, one of the alkaloids of *Picralima klaineana*, was first isolated by Henry and Sharp [1] and has recently been studied by Robinson and his co-workers,[2,3,4] who proved the presence in the alkaloid of the system Ar·NH·C:C·CO_2Me.[5] This, together with the formation of 3-ethylpyridine, skatole, and 3-ethylindole by dehydrogenation, and the assumption of a structural relation to the strychnine group of gases, enabled Robinson and Aghoramurthy [3] to propose structure (I) for akuammicine.

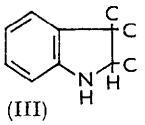
One of the reactions which suggested the relationship of the methoxycarbonyl group to the aromatic nitrogen atom was the acid hydrolysis [3,4] of akuammicine to a 3*H*-indole (indolenine) base, $C_{18}H_{20}N_2$, m. p. 147—148°. This base was stated to be very unstable, was obtained in only 3% yield, and was not studied further. By carrying out the hydrolysis in an evacuated sealed tube, we obtained a 3*H*-indole base, $C_{18}H_{20}N_2$, m. p. 80—84°, in practically quantitative yield. This product, in contrast to that obtained by the previous workers, is stable and shows no marked tendency to autoxidation. With



(I)



(II)



(III)

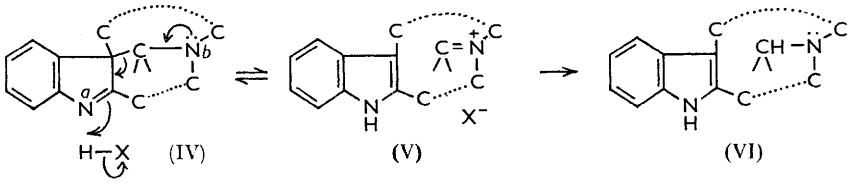
the intention of preparing the corresponding indoline base, involving the conversion of structure (II) into (III), we treated the indolenine base with methanolic potassium borohydride and quite unexpectedly obtained an indole base, $C_{18}H_{22}N_2$ (A), formed by the addition of two hydrogen atoms and isomeric with the expected indoline base. That this reaction does not involve the ethylidene double bond was demonstrated by hydrolysing dihydroakuammicine (in which the ethylidene group has been reduced to ethyl [4]) to the corresponding 3*H*-indole base, $C_{18}H_{22}N_2$, reduction of which with potassium borohydride in methanol gave an indole base, $C_{18}H_{24}N_2$ (B), identical with the product of catalytic hydrogenation of indole base A in ethanolic glacial acetic acid. Catalytic hydrogenation of the 3*H*-indole base $C_{18}H_{20}N_2$ in ethanol also gave the indolic base A.

The indoline base, $C_{18}H_{22}N_2$ (partial structure III), was however obtained from the 3*H*-indole base by catalytic hydrogenation in dry dioxan, or by reaction with lithium aluminium hydride in ether or with potassium borohydride in dilute aqueous hydrochloric acid. The evidence for the indoline nature of this base is spectroscopic [6] (see p. 794).

These results indicate the existence, in proton-donating solvents, of a reversible proton-catalysed equilibrium between the 3*H*-indole and a base containing an aromatic indole nucleus which must be formed by fission of one of the two C–C bonds at the β-position of the 3*H*-indole system. We formulate this equilibrium as the nitrogen equivalent of a reversible aldol condensation, (IV) ⇌ (V): this is, in fact, the reversible first step of a Mannich-type reaction, such as the condensation of indole with formaldehyde and dimethylamine to give gramine,[7] or the acid-catalysed dimerisation of indole.[8]

[1] Henry and Sharp, *J.*, 1927, 1950.
[2] Millson, Robinson, and Thomas, *Experientia*, 1953, **9**, 89; Robinson and Thomas, *J.*, 1955, 2049.
[3] Robinson and Aghoramurthy, *Tetrahedron*, 1957, **1**, 172.
[4] Aghoramurthy, D.Phil. Thesis, Oxford, 1956.
[5] See also Fritz, *Angew. Chem.*, 1959, **71**, 377.
[6] Hodson and Smith, *J.*, 1957, 1877.
[7] Liebermann and Wagner, *J. Org. Chem.*, 1949, **14**, 1001; Hellmann, Hallmann, and Lingens, *Chem Ber*, 1953, **86**, 1357.
[8] Smith, *Chem. and Ind.*, 1954, 1451.

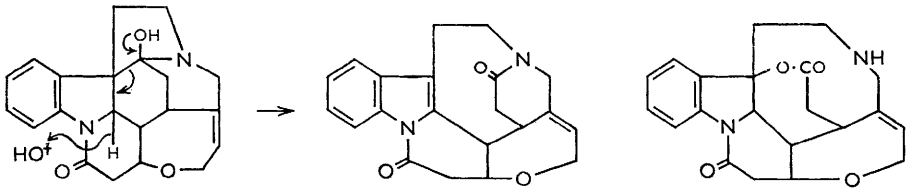
The reactions described above may thus be interpreted as follows: (*a*) The 3*H*-indole (IV) in dioxan, that is, in the absence of a proton donor, cannot be in equilibrium with (V); reduction therefore leads exclusively to the indoline base. (*b*) The ultraviolet spectrum in ethanol shows that in that solvent the 3*H*-indole (IV) is still predominant: the formation of the indole base A (VI) by reduction in ethanol shows that form (V) is much more



(IV) (V) (VI)

susceptible to reduction than is (IV), and that as fast as it is reduced it is replaced, by the operation of the equilibrium, until all has been converted into the indole base A. (*c*) In acid solution, the aliphatic nitrogen, N(*b*), will be almost completely protonated; the concentration of free 3*H*-indole base (IV) will be quite negligible. Now protonation of N(*b*) blocks the reversible ring opening to an indole, for the mechanism requires free *p*-electrons on N(*b*). Reduction thus leads to formation of the indoline base. It is interesting that reduction here competes successfully with decomposition of borohydride by the excess of mineral acid. Borohydride reduction of the 3*H*-indole base in a buffer at pH 6 leads to a mixture of indoline and indole bases.

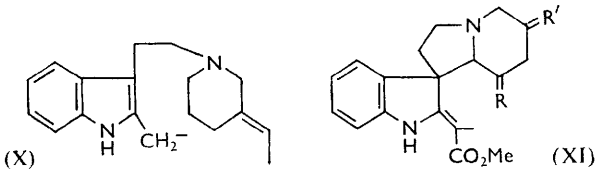
The equilibrium (IV) ⇌ (V) is also believed to operate [9] in the case of the compounds $C_{21}H_{20}O_3N_2$ and $C_{21}H_{20}O_4N_2$ isolated by Teuber and Fahrbach [10] by oxidation of isostrychnic acid with peroxidic reagents. The oxidation of ψ-strychnine (VII) to strychnone



(VII) (VIII) (IX)

by hydrogen peroxide in acetic acid [11] may well involve a similar reaction, designated by arrows in (VII): Woodward *et al.*[11] proposed a quite different route involving (IX) as an intermediate.

Distillation of the indole base A with zinc dust at 300° gave relatively high yields of 3-ethylpyridine and 3-ethyl-2-methylindole: these two products together account for all the carbon atoms of the indolic base, and, since akuammicine contains only one *C*-methyl group [3] and yields acetaldehyde on ozonolysis, they allow the expansion of formula (VI) to (X), in which the point of attachment of the indole α-CH_2 to the piperidine ring is not



(X) (XI)

defined. The corresponding expression for akuammicine then is (XI), in which R = H_2 and R′ = CHMe or *vice versa*. Attempts to discover the point of attachment of the CH_2

[9] Joule and Smith, *Proc. Chem. Soc.*, 1959, 322.
[10] Teuber and Fahrbach, *Chem. Ber.*, 1958, **91**, 713.
[11] Leuchs, Tuschen, and Mengelberg, *Ber.*, 1944, **77**, 405; Woodward, Brehm, and Nelson, *J. Amer. Chem. Soc.*, 1947, **69**, 2250.

to the piperidine ring in (X) have so far failed: these attempts included a full range of dehydrogenations; Hofmann degradation of the indole base B proceeded anomalously, and yielded no structural information.

Structure (I) is compatible with partial structure (XI), but cannot be yet regarded as proved.

Experimental

3H-*Indole Base* (II).—Akuammicine (200 mg.) in 20% aqueous hydrochloric acid (10 ml.) was heated at 115° for 2½ hr. in an evacuated sealed tube. Ether-extraction of the basified mixture yielded a pale yellow product which crystallised slowly; it had m. p. 80—84° (161 mg., 98%), $\lambda_{max.}$ 283, 224 mμ (ε 5320, 11,200 respectively) in ethanol, $\lambda_{max.}$ 276, 223 mμ (ε 3950, 8800 respectively) in ethanolic hydrochloric acid [cf. 1,2,3,4-tetrahydro-11-methylcarbazolenine: $\lambda_{max.}$ 255 mμ (ε 7030) in ethanol, $\lambda_{max.}$ 275, 231 mμ (ε 6300, 8000 respectively) in ethanolic hydrochloric acid]. The base was very soluble in all solvents except water and could not conveniently be crystallised. It was stable to autoxidation. It gave a crystalline *perchlorate*, as glossy blades (from water), m. p. 209—213° (decomp.) (Found: C, 59·9; H, 5·7; N, 7·55. $C_{18}H_{20}N_2,HClO_4$ requires C, 59·3; H, 5·8; N, 7·7%).

Indoline Base (III).—(*a*) An ether solution of 3*H*-indole base (II) was added to an excess of lithium aluminium hydride in ether, and the mixture refluxed for 15 min. The product crystallised from di-isopropyl ether as colourless needles, m. p. 187—189° (152 mg., 92%) (Found: C, 81·0; H, 8·2; N, 10·55%; equiv. by electrometric titration, 264. $C_{18}H_{22}N_2$ requires C, 81·15; H, 8·35; N, 10·5%; equiv., 266), $\lambda_{max.}$ 297, 245 mμ (ε 3150, 8700 respectively) in ethanol, $\lambda_{max.}$ 268, 259 mμ (ε 975, 1410 respectively) in ethanolic hydrochloric acid.

(*b*) A solution of the 3*H*-indole base (II) (6 mg.) in dioxan (2 ml.) was hydrogenated over Adams catalyst for 3 hr. The product had m. p. 185—188°, undepressed by indoline base (III).

(*c*) A solution of the 3*H*-indole base (II) (10 mg.) in 0·02N-aqueous hydrochloric acid was treated with excess of sodium borohydride. The basic product, after one crystallisation from di-isopropyl ether, had m. p. 183—186°, undepressed by indoline base (III).

Dihydroindoline Base.—A solution of indoline base (III) (37 mg.) in 20% glacial acetic acid in ethanol (2 ml.) was hydrogenated in the presence of Adams catalyst (20 mg.). The hydrogen uptake had slowed considerably after 2 hr. and hydrogenation was stopped (1·1 mol.). The *product* crystallised from ether as long needles, m. p. 175—177° (31 mg.) (Found: C, 79·85, 80·2; H, 9·0, 9·1. $C_{18}H_{24}N_2$ requires C, 80·55; H, 9·0%).

Indole Base (VI).—Akuammicine (250 mg.) was hydrolysed as above, and the product added to an excess of methanolic potassium hydroxide. The alkaline mixture was treated with excess of potassium borohydride and boiled for 10 min. The methanol was then boiled off under reduced pressure and the residue partitioned between ether and water. The ether-soluble product crystallised from methanol with solvent of crystallisation, and had m. p. 100—110° (214 mg.). After several days at 60°/0·01 mm. the m. p. was 125—150°, with solidification and remelting at 160—162° (Found: C, 81·0; H, 8·3; N, 10·25. $C_{18}H_{22}N_2$ requires C, 81·15; H, 8·35; N, 10·5%), $\lambda_{max.}$ 291, 284, 228 mμ (ε 5750, 6020, 26,000 respectively) in ethanol, unchanged by acid.

Dihydroindole Base.—(*a*) The indole base (VI) (122 mg.) was hydrogenated in 20% acetic acid in ethanol over freshly prepared Adams catalyst (120 mg.). There was a rapid uptake of 1·07 mol. of hydrogen. The *product* crystallised from methanol as fine needles, m. p. 65—75° (99 mg., 81%) (Found, after prolonged drying over P_2O_5 at 60°/0·01 mm.: C, 80·7; H, 8·7. $C_{18}H_{24}N_2$ requires C, 80·55; H, 9·0%).

(*b*) Dihydroakuammicine, m. p. 169—171° (20 mg.) (Robinson and Aghoramurthy [3] give m. p. 171—173°), was hydrolysed with 20% aqueous hydrochloric acid in an evacuated sealed tube at 115° for 2½ hr., the solution poured into an excess of methanolic potassium hydroxide, and the mixture reduced with excess of potassium borohydride. The ether-soluble product crystallised from methanol as fine needles, m. p. 65—75°, identical with the product obtained as under (*a*) (17 mg.).

Dehydrogenation of the Indole Base A.—The indole base A (17·4 mg.) was passed over zinc dust at 300° in nitrogen. Two fractions were obtained: the more volatile formed 3-ethylpyridine picrate, m. p. and mixed m. p. 126—128° (4·6 mg.); the less volatile gave neutral material (1·4 mg.) which gave 3-ethyl-2-methylindole picrate, m. p. and mixed m. p. 147—150°.

Ozonolysis of Akuammicine.—A solution of akuammicine (53 mg.) in chloroform (5 ml.) was

ozonised at 0° for 2·5 hr. After removal of chloroform *in vacuo*, the product was treated with water, and the solution distilled into a saturated solution of dinitrophenylhydrazine in 2% aqueous hydrochloric acid. Acetaldehyde dinitrophenylhydrazone which separated had m. p. and mixed m. p. 146—160° (20·2 mg., 51%).

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