The Alkaloids of Picralima nitida, *Stapf, Th. and H. Durand. Part II.* Some Investigations concerning the Structure of* pseudo*Akuammigine.*

By Sir Robert Robinson and A. F. Thomas.

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The spectrographic properties of *pseudo*akuammigine, $C_{22}H_{26}O_3N_2$, from *Picralima nitida*, Stapf, indicate that it is a dihydroindole containing an ester group, $\cdot CO_2Me$. The latter has been reduced to $\cdot CH_2\cdot OH$ affording *pseudo*akuammigol, $C_{21}H_{26}O_2N_2,H_2O$. Nitration of *pseudo*akuammigine gives a nitro-compound, and nitrosation a green *C*-nitroso-compound. The best reconciliation of the somewhat conflicting evidence is obtained on the assumption that $\cdot CO_2Me$ is so close to N(*a*) that it can neutralise the normal activation of the benzene ring by the substituted amino-group. This theory is exemplified in a formula that also takes into account the nature of the congeners of the alkaloid.

*pseudo*Akuammigine and akuammicine hydrochlorides are obtained together on extraction of the crude alkaloid from *Picralima nitida* seeds with N-hydrochloric acid (cf. Henry, *J.*, 1932, 2759). A 50% mixture of the two alkaloids is often obtained as a well-defined crystalline substance with a sharp melting point, and it is best separated into its components by extraction of a benzene or chloroform solution with the amount of 0·1N-hydrochloric acid required to combine with all the akuammicine, this being slightly the stronger base and having a less soluble hydrochloride. The separation is conveniently followed by

* Part I, *J.*, 1954, 3479.

means of the optical rotation, which is −746° for akuammicine, and −35° for *pseudo*-akuammigine. The later fractions of the hydrochloric acid extraction of the crude base give a mixture of akuammigine and *pseudo*akuammigine, separated by the sparing solubility of akuammigine hydrochloride in water. The *pseudo*akuammigine is then easily purified through the hydriodide (cf. Henry, *loc. cit.*).

*pseudo*Akuammigine has the formula $C_{22}H_{26}O_3N_2$, containing one methoxyl, one methylimino-, and one *C*-methyl group. At first, it was believed that two of the latter groups were present (Millson, Robinson, and Thomas, *Experientia*, 1953, **9**, 89), but further analyses have not confirmed this, and Kuhn–Roth estimations in this group of alkaloids have been shown to be unreliable (Robinson and Thomas, Part I). The ultra-violet absorption spectrum is that of a dihydroindole (Raymond-Hamet, *Compt. rend.*, 1950, **230**, 1183), although the curve is not quite coincident with that of ajmaline (Anet, Chakravarti, Robinson, and Schlittler, *J.*, 1954, 1242).

The colour reactions of *pseudo*akuammigine are different from those of ajmaline or strychnidine. Thus nitric acid gives a brownish-yellow colour (Henry, *loc. cit.*); ferric chloride gives a feeble red colour only on warming, and no coupling to an azo-compound occurs with diazotised sulphanilic acid in acetic acid solution—very slow coupling occurs, however, in the presence of sodium acetate in *dilute* acetic acid. The basic strength of *pseudo*akuammigine is nearer to that of strychnine than that of strychnidine (cf. Prelog and Häfliger, *Helv. Chim. Acta*, 1949, **32**, 1851).

The infra-red spectrum of *pseudo*akuammigine shows that no NH or OH group is present; bands corresponding to C=O (probably in a saturated ester) and a 1 : 2-disubstituted benzene ring are observed.

The evidence of the failure of colour reactions suggests that the group :N(*a*)·CO· is present but the spectra do not support this hypothesis. Nitration and nitrosation occur readily, the nitroso-compound having the green colour characteristic of di-*N*-substituted *p*-nitroso-anilines. After reduction of the nitroso-compound, the product gives a blood-red colour with nitric acid, similar to that observed with akuammine (Henry and Sharp, *J.*, 1927, 1950).

Reduction of *pseudo*akuammigine with lithium aluminium hydride in ether gives the corresponding alcohol, *pseudo*akuammigol, confirming the presence of a methyl ester group in the alkaloid. *pseudo*Akuammigol gives the colour reactions of strychnidine, although the ferric chloride coloration is still reluctant. The ultra-violet spectrum is now identical with that of ajmaline.

*pseudo*Akuammigine could not be hydrolysed to a corresponding acid by 7 hours' boiling with aqueous-alcoholic 10% potassium hydroxide.

Neither *pseudo*akuammigine nor *pseudo*akuammigol could be reduced catalytically: indeed the only reason for assuming the presence of a double bond is the composition of the base. The formula $C_{22}H_{28}O_3N_2$ is not excluded by the analyses but $C_{22}H_{26}O_3N_2$ gives the better fit for the derivatives. Naturally it is possible that *pseudo*akuammigine is heptacyclic. However, it is very likely that the phenolic base, akuammine, is hydroxy*pseudo*akuammigine since, apart from the band due to hydroxyl, the infra-red spectra are very similar (Millson, Robinson, and Thomas, *loc. cit.*). In the case of akuammine the H_{26} formula was found much the better (*idem, ibid.*) and there was some evidence of catalytic hydrogenation.

The amount of *pseudo*akuammigine available has been very small and this precluded attempted degradation on the required scale.

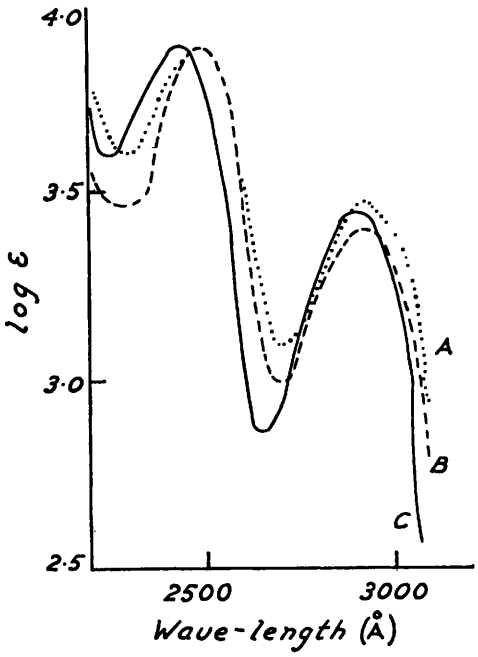
On the assumption of the suggested relation to akuammine we may take cognisance of the formation of 3-ethylpyridine from that base (*idem, ibid.*). Moreover akuammigine (Part I) affords alstyrine, and *pseudo*akuammigine contains a third oxygen atom which is present neither in a carbonyl nor in a hydroxyl group, and must be in a cyclic ether group.

These facts lead to the conclusion that the alkaloid is the result of a Woodward fission at some stage. But as it appears to be a dihydro-indole (ultra-violet spectrum) the simplest working hypothesis, and it is no more than this, can be based on the β-indole-alkaloid type.

The remarkable deactivation of the position *para* to N(*a*) cannot be due to the presence of :N(*a*)·CO· because (1) the ultra-violet spectrum would then be quite different from that

observed, and (2) the infra-red band for ·N·CO· should be noted, but is absent, and (3) the green nitroso-compound would not be formed. The deactivation may plausibly be regarded as due to neutralisation of a potentially basic, anionoid N(*a*) across space, and the only available group that could effect this is the carbonyl of $\cdot CO_2Me$ (cf. Anet, Bailey, and Robinson, *Chem. and Ind.*, 1953, 944).

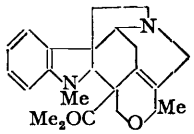
The formula suggested by Millson, Robinson, and Thomas (*loc. cit.*) is based on the arrangement of groups in yohimbine moved round one place clockwise so as to give a β-indole alkaloid instead of the α-type (yohimbine, corynantheine, akuammigine). However the proposed position of the double bond became untenable when Bader (*Helv. Chim. Acta*,

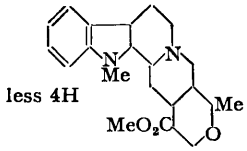


A, ..., pseudo*Akuammigol*.
B, – – – –, *Ajmaline*.
C, ———, pseudo*Akuammigine*.

1953, **36**, 215) found that substituted vinyl ethers show strong absorption in the region near 6·05 μ. This is not noted in the infra-red spectra of *pseudo*akuammigine and akuammine. Hence the small modification to (I) is necessary.

(I)





(II)

In order that the foregoing argument may be better understood we append the α-type structure (II) related to (I). Here the ester group is surprisingly more remote from N(*a*) than in (I); moreover αβ-disubstituted dihydroindoles have not yet been found among plant products.

The field of discussion is clearly widened considerably if we move the ester group from the yohimbine–corynantheine position, but there is no advantage to be gained by following this line of argument at the present stage. The structure (I) appears to present the greatest common measure of compliance with the requirements at this juncture and it is tentatively proposed as a basis for discussion.

EXPERIMENTAL

Fractional extraction of the crude alkaloid with N-hydrochloric acid gave a mixture of akuammicine and *pseudo*akuammigine (cf. Henry, *loc. cit.*), from which a crystalline perchlorate was obtained. This was recrystallised twice from water, then basified, and the base recrystallised from aqueous ethanol, glistening plates, m. p. 147—148°, $[\alpha]_D^{19}$ −347° (*c* 0·98 in EtOH), being obtained, corresponding to a mixture of akuammicine and *pseudo*akuammigine in nearly equimolecular proportion. The infra-red spectrum of this material showed sharp peaks due to the separate absorption by each alkaloid. Attempted separation by recrystallisation of the hydrobromides, perchlorates, and oxalates was unsuccessful. The solution of the mixture in chloroform was shaken with the quantity of 0·1N-hydrochloric acid found to be required to remove all the akuammicine, the organic solution was well washed with water (akuammicine hydrochloride being slightly soluble in chloroform), and the liberated bases recrystallised from aqueous ethanol. This gave, from the aqueous phase, akuammicine (88% pure; m. p. 166—168°, $[\alpha]_D^{18}$ −660°), and, from the organic phase, *pseudo*akuammigine (95% pure; m. p. 158°, $[\alpha]_D^{19}$ −56°). Recrystallisation of *pseudo*akuammigine to constant rotation from aqueous ethanol gave the pure base as colourless, square plates, or from benzene–light petroleum as thick prisms, m. p. 165°, $[\alpha]_D^{18}$ −35° (*c* 1·2 in EtOH), pK_a 7·35 (Found: C, 72·2; H, 7·2; N, 7·3; OMe, 9·8; NMe, 5·0; *C*-Me, 5·9, 5·8, 4·1; active H, 0·0. Calc. for $C_{22}H_{26}O_3N_2$: C, 72·1; H, 7·2; N, 7·6; OMe, 8·5; NMe, 7·9; *C*-Me, 4·1%).

The solution of the hydrochloride obtained from the later fractions of the extraction was heated to boiling, and a hot strong solution of potassium iodide was added. *pseudo*Akuammigine hydriodide crystallised gradually and separated from aqueous acetone containing a trace of sodium dithionite as lustrous colourless needles, m. p. 216° (decomp.), $[\alpha]_D^{19}$ −9° (*c* 1·4 in EtOH), −4° (*c* 1·8 in acetone). The salt was difficult to dry: after 5 hours at 100°/0·005 mm. about 0·5H_2O is still present (Found: C, 52·4, 52·5; H, 5·8, 5·9; I, 24·0, 26·3; OMe, 6·2; NMe, 5·8. Calc. for $C_{22}H_{26}O_3N_2$,HI,$\frac{1}{2}H_2O$: C, 52·5; H, 5·6; I, 25·3; OMe, 6·2; NMe, 5·8%).

*pseudo*Akuammigine hydrochloride crystallised from water or ethanol as colourless, flat needles, m. p. 215—220° (decomp.), $[\alpha]_D^{19}$ −23° (*c* 1·2 in EtOH) (Found: loss at 100°, 4·2; C, 62·8; H, 6·7; N, 6·7; Cl, 8·3; *C*-Me, 3·5. Calc. for $C_{22}H_{26}O_3N_2$,HCl,H_2O: C, 62·8; H, 6·5; N, 6·7; Cl, 8·4; *C*-Me, 3·6; 1H_2O, 4·3. Found, in anhydrous material: C, 65·3; H, 6·7; N, 7·0. Calc. for $C_{22}H_{26}O_3N_2$,HCl: C, 65·7; H, 6·7; N, 7·0%).

pseudo*Akuammigine hydrobromide*, made from the hydrochloride by addition of aqueous potassium bromide, crystallised from water as clusters of needles having a trace of colour that was difficult to remove. The salt had m. p. 185°, $[\alpha]_D^{19}$ −23° (Found: C, 56·7; H, 6·2; N, 5·7; Br, 17·5. $C_{22}H_{26}O_3N_2$,HBr,H_2O requires C, 56·7; H, 6·3; N, 6·0; Br, 17·2%).

The *perchlorate* formed colourless needles (from water), m. p. 196° (Found: C, 56·5; H, 5·8; N, 6·3; Cl, 7·7. $C_{22}H_{26}O_3N_2$,$HClO_4$ requires C, 56·6; H, 5·8; N, 6·0; Cl, 7·6%).

The *oxalate* formed long plates (from water), m. p. 166° (Found: C, 60·5; H, 5·7; N, 5·8. $C_{22}H_{26}O_3N_2$,$C_2H_2O_4$,H_2O requires C, 61·0; H, 6·1; N, 5·9%).

Attempted Catalytic Reduction of pseudo*Akuammigine*.—A solution of *pseudo*akuammigine (210 mg.) in ethanol (30 c.c.), with 10% palladised charcoal (50 mg.), was shaken under hydrogen. No significant absorption took place in 2 hr. With Adams catalyst in acetic acid (60%; 30 c.c.), a very slow uptake of hydrogen occurred; after 48 hr., a gum was isolated by filtration and basification, which, after recrystallisation from aqueous ethanol, had m. p. 162° and gave a bright red colour with concentrated nitric acid. Two further recrystallisations from the same solvent gave *pseudo*akuammigine, m. p. and mixed m. p. 164°.

Attempted Hydrolysis of pseudo*Akuammigine*.—The alkaloid (115 mg.) was heated under reflux for 7 hr. with ethanolic potassium hydroxide (15 c.c. of 10%). Concentration and dilution gave *pseudo*akuammigine (105 mg.), m. p. undepressed by an authentic sample.

Reduction of pseudo*Akuammigine with Lithium Aluminium Hydride*.—The alkaloid (1·8 g.) in ether (100 c.c.) was treated with lithium aluminium hydride (0·4 g.) in ether. After 2 hr. the excess of hydride was decomposed with a little water and the precipitated hydroxides were removed by filtration, the residue being washed with chloroform. Evaporation of the solvent gave a glass which crystallised when rubbed with ether–chloroform. Recrystallisation from the same solvent afforded colourless needles of *pseudo*akuammigol, m. p. 201°, $[\alpha]_D^{18}$ −174° (*c*, 2·3 in EtOH), pK_a 8·22. The base could not be obtained anhydrous without decomposition. After drying at 100°/0·01 mm. for 3 hr., the *monohydrate* was obtained (Found: C, 71·2; H, 8·1; N, 7·5. $C_{21}H_{26}O_2N_2$,H_2O requires C, 70·9; H, 7·9; N, 7·8%).

The *hydrochloride* separated from ethanol, in which it is sparingly soluble in the cold, as

colourless stumpy needles, m. p. 282—284° (decomp.) (Found, in air-dried material: loss at 120°/0·002 mm. in 15 hr., 2·5; C, 63·9; H, 8·0; OMe, 4·6; NMe, 5·6 $C_{21}H_{26}O_2N_2,HCl,H_2O$ requires C, 64·1; H, 7·4; OMe, 7·9; NMe, 7·4; H_2O, 2·3%. Found, in dried material: C, 65·7; H, 7·7; N, 7·6; Cl, 9·7. $C_{21}H_{26}O_2N_2,HCl,\frac{1}{2}H_2O$ requires C, 65·7; H, 7·4; N, 7·3; Cl, 9·7%). This hydrochloride coupled slowly with diazobenzenesulphonic acid in aqueous acetic acid in the presence of sodium acetate. The brownish-yellow solution became crimson on the addition of hydrochloric acid.

The *perchlorate* crystallised from water as lustrous needles, m. p. 258—262° (decomp.) (Found, in material dried for 12 hr. at 100° *in vacuo*: C, 57·2; H, 6·6; N, 6·1; Cl, 7·7. $C_{21}H_{26}O_2N_2,HClO_4$ requires C, 57·5; H, 6·2; N, 6·4; Cl, 8·1%).

There was no significant uptake of hydrogen on shaking a methanol solution of the base with Adams catalyst of known activity under hydrogen for 2 hr.

By the procedure employed in the reduction of akuammigine (Part I) with sodium and liquid ammonia in the presence of ethanol, *pseudo*akuammigine gave a red tar from which no crystalline product was isolated. *pseudo*Akuammigol gave a similar result: a small amount of *pseudo*-akuammigol hydrochloride was recovered.

Nitrosation of pseudo*Akuammigine*.—Sodium nitrite (0·3 g.) in water (5 c.c.) was added to a stirred solution of *pseudo*akuammigine (1·2 g.) in concentrated hydrochloric acid (15 c.c.) and water (15 c.c.) below 5°. The resulting red-brown solution was kept at 0° for 5 min., then diluted with an equal volume of water and neutralised rapidly with ammonia (*d* 0·88) and ice. Isolation of the product with ether, and recrystallisation from ether–light petroleum (b. p. 40—60°), gave bright green rods of *nitroso*pseudo*akuammigine*, m. p. 204° (decomp. to red liquid) (0·8 g.) (Found: C, 66·8; H, 6·4; N, 10·8. $C_{22}H_{25}O_4N_3$ requires C, 66·8; H, 6·4; N, 10·6%).

Nitroso*pseudo*akuammigine absorbed 2 mols. of hydrogen in 30 min. when shaken in methanol with 10% palladised charcoal under hydrogen (microhydrogenation apparatus). The product oxidised rapidly in methanol solution in air, and gave a bright red colour with concentrated nitric acid.

Nitration of pseudo*Akuammigine*.—*pseudo*Akuammigine (0·5 g.) was added portionwise to a mixture of concentrated nitric acid (10 c.c.) and water (10 c.c.) at 0°. The yellow solution was allowed to reach the toom temperature during 5 min., the colour deepening; if allowed to stand too long, the solution became brown and the yield was considerably lower. The solution was basified with ammonia and the yellow *nitro*pseudo*akuammigine* was collected. After recrystallisation (with difficulty) from ether–light petroleum (as rods) or from aqueous acetone (as rectangular plates), the nitro-compound had m. p. 210° (decomp.). The crude product was often contaminated with a brown sludge, but was easily separated by dissolution in acetone in which the impurity was insoluble (Found: C, 64·3; H, 6·1; N, 10·1. $C_{22}H_{25}O_5N_3$ requires C, 64·2; H, 6·1; N, 10·2%).

Infra-red data (*Nujol suspensions*).—*pseudo*Akuammigine: 5·76 [C=O (unconjugated ester)], 6·23 [C=C (aromatic)], and 13·26 μ (1 : 2-disubstituted benzene ring). *pseudo*Akuammigol hydrochloride: many bands in OH and NH stretching region; 6·25 [C=C (aromatic)] and 13·34 μ (1 : 2-disubstituted benzene ring). Except for the absence of bands at 3·06 μ (OH) and at 12·33 μ (1 : 2 : 4-trisubstituted benzene) the curve for *pseudo*akuammigine closely resembles that observed for akuammine.

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THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, June 8th*, 1954.]