The Alkaloids of Picralima nitida, *Stapf, Th. and H. Durand. Part I. The Structure of Akuammigine.*

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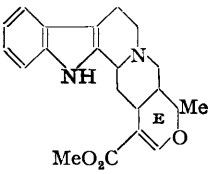
Akuammigine, an alkaloid from *Picralima nitida*, Stapf, has been shown to be an indole derivative containing the group, $MeO_2C{\cdot}C{:}C{\cdot}O$. Dehydrogenation with selenium affords alstyrine, and it is suggested that the substance is a stereoisomeride of δ-yohimbine.

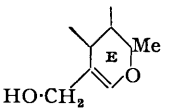
Extracts of *Picralima nitida*, Stapf (syn. *P. Klaineana*, Pierre) are employed by West African natives because of their alleged antipyretic and antimalarial properties, also as a remedy for chest complaints and as a fish poison. The drug has various local names, but apparently not "akuamma" (cf. Henry and Sharp, *J.*, 1927, 1950), a term used to denote the fruit of *Pentaclethra macrophylla*, Benth., and later extended to the *Picralima* extract in Accra (Dalziel, "The Useful Plants of West Tropical Africa, H.M.S.O., London, 1937, p. 220).

After the alkaloids had been shown to be inactive in avian and human malaria (Goodson, Henry, and Macfie, *Biochem. J.* 1930, **24**, 874; van den Branden, *Ann. Soc. Belg. Med. trop.*, 1930, **10**, 123), detailed chemical research on them was not pursued. A series of papers on the remarkable pharmacological properties of some of the alkaloids is due to Raymond-Hamet (a summary of these is to be found in *Rev. Int. Bot. app. Agric. trop.*, 1951, **31**, 465). Akuammigine, however, was found to be almost devoid of physiological activity (Raymond-Hamet, *Compt. rend.*, 1945, **221**, 699).

Akuammigine was first isolated by Henry (*J.*, 1932, 2759), and the formula was given as $C_{22}H_{26}O_3N_2$, which we propose to alter to $C_{21}H_{24}O_3N_2$. The presence of a methoxyl group, and absence of a methylimino-group have been confirmed. The ultra-violet spectrum is like that of a true aromatic indole (Raymond-Hamet, *loc. cit.*), with the flattening associated with $MeO_2C{\cdot}C{:}C{\cdot}O$ (Bader, *Helv. Chim. Acta*, 1935, **36**, 215; Millson, Robinson, and Thomas, *Experientia*, 1953, **9**, 89), and the infra-red spectrum has been shown to contain peaks due to the presence of OH (as water of crystallisation), C=O (unsaturated ester type) and C=C, with an extra peak in the carbonyl absorption region (Millson *et al.*, *loc. cit.*). This extra peak has now been shown to be caused by intramolecular hydrogen bonding, since it is not observed in the spectrum of a chloroform solution. Akuammigine has been said to resemble mayumbine (I) (Janot, Goutarel, and Massonneau, *Compt. rend.*, 1952, **234**, 850) on the ground that it contains one *C*-methyl group, unlike the α-type indole alkaloids with an alicyclic E-ring (Raymond-Hamet, *loc. cit.*). This fact has

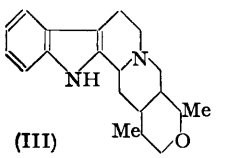
been confirmed, although values of about 120% are found in the Kuhn–Roth determination. A similar discrepancy was noted in the case of tetrahydroalstonine (Elderfield and Gray, *J. Org. Chem.*, 1951, **16**, 506).

(I) 

 (II)

The presumed ester group of akuammigine is not readily hydrolysed by alkali, a fact which tallies with the usual behaviour of dihydropyran esters of the alstonine type (Bader, *loc. cit.*; Schlittler and Hohl, *Helv. Chim. Acta*, 1952, **35**, 29). Reduction with lithium aluminium hydride gave an alcohol, akuammigol (II), corresponding to the tetrahydroalstonol obtained by Elderfield and Gray from tetrahydroalstonine (*loc. cit.*); this substance retains solvents of crystallisation tenaciously, and, again like tetrahydroalstonol, gives no crystalline salts with acids although, unlike the latter, both a methiodide and a normal *O*-acetate could be obtained.

Catalytic hydrogenation of dihydropyran esters is known to be difficult (cf. Bader, *loc. cit.*), and hydrogenation of akuammigol could not be effected under conditions similar to those used by Elderfield and Gray (*loc. cit.*) in the case of tetrahydroalstonine. A product in the latter example was a substance, $C_{20}H_{26}ON_2$, presumably (III) and possibly the result of rearrangement and hydrogenolysis of (II). Furthermore no reaction was observed when akuammigol was treated with sodium in liquid ammonia.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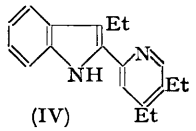
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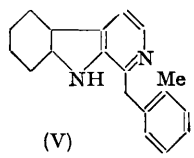

(V)

Selenium dehydrogenation of akuammigine gave alstyrine (IV), identified with a specimen from corynantheine (Karrer and Enslin, *Helv. Chim. Acta*, 1949, **32**, 1390; Janot and Goutarel, *Bull. Soc. chim.*, 1951, 588). This supports the formulation of akuammigine as a stereoisomeride of δ-yohimbine, since alicyclic α-type indole alkaloids give yobyrine (V) on dehydrogenation with selenium (Le Men, *Compt. rend.*, 1952, **234**, 1559). The known alkaloids to which structure (I) has been attributed are shown in the accompanying table.

δ-Yohimbine and its Stereoisomerides.

Alkaloid	Source	Reference: isolation	Reference: structure
δ-Yohimbine	*Pausinystalia yohimba*	1	2
(Ajmalicine)	*Rauwolfia serpentina*	3	4
	Reduction of serpentine from *R. serpentina*	5	5, 4
Tetrahydroalstonine	Reduction of alstonine from *Alstonia constricta*	6	7
	Pyrolysis of melinonine-A from *Strychnos melinoniana*	8	8
Mayumbine	*Pseudocinchona mayumbensis*	9	10
Akuammigine	*Picralima nitida*	11	12

References: 1, Heinemann, *Ber.*, 1934, **67**, 15. 2, Goutarel and Le Hir, *Bull. Soc. chim.*, 1951, 909. 3, Popelak, Spingler, and Kaiser, *Naturwiss.*, 1953, **40**, 625. 4, Weisenborn, Moore, and Diassi, *Chem. and Ind.*, 1954, 375; Hofmann, *Helv. Chim. Acta*, 1954, **37**, 849; Klohs, Draper, Keller, Malesh, and Petracek, *J. Amer. Chem. Soc.*, 1954, **76**, 1332. 5, Schlittler and Schwarz, *Helv. Chim. Acta*, 1950, **33**, 1463. 6, Sharp, *J.*, 1938, 1353. 7, Elderfield and Gray, *J. Org. Chem.*, 1951, **16**, 506. 8, Schlittler and Hohl, *Helv. Chim. Acta*, 1952, **35**, 29. 9, Raymond-Hamet, *Compt. rend.*, 1951, **232**, 2354. 10, Janot, Goutarel, and Massonneau, *ibid.*, 1952, **234**, 850. 11, Henry, *J.*, 1932, 2759. 12. Present communication.

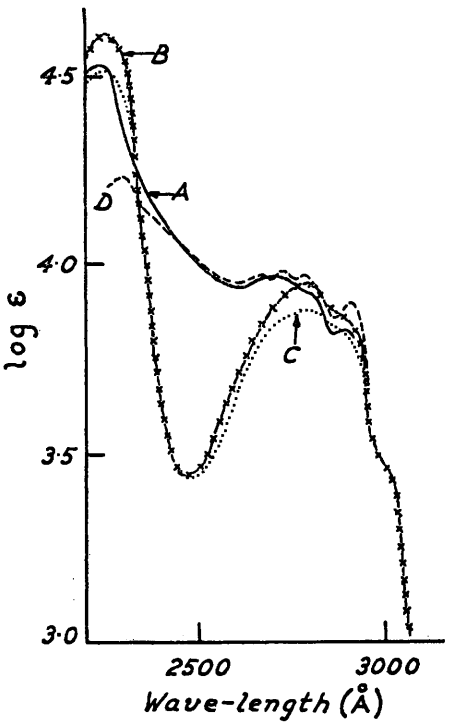
Experimental

Akuammigine hydrochloride was obtained as the least soluble fraction during extraction of the crude alkaloid mixture with N-hydrochloric acid (Henry, *loc. cit.*). It crystallises from aqueous methanol as colourless prisms, m. p. 285—290° (decomp.; dependent on the rate of heating), $[\alpha]_D^{23}$ −44° (*c*, 0·7 in MeOH) (Found: C, 64·8, 64·7, 64·9; H, 6·6, 6·5, 6·4; N, 7·0, 7·2;

Cl, 9·4, 9·2; OMe, 8·1; NMe, 1·1; *C*-Me, 4·9, 4·5. $C_{21}H_{24}O_3N_2$,HCl requires C, 64·8; H, 6·5; N, 7·2; Cl, 9·1; 1OMe, 8·0; 1*C*-Me, 3·9%).

Akuammigine crystallised from aqueous ethanol as colourless square plates, m. p. 113°, $[\alpha]_D^{18\cdot5}$ −42° (*c*, 1·6 in EtOH), +1° (*c*, 2·4 in pyridine), pK_a 6·58 (Found: C, 68·0; H, 7·1; N, 7·5. $C_{21}H_{24}O_3N_2,H_2O$ requires C, 68·1; H, 7·0; N, 7·6%). Attempted removal of the solvent caused decomposition. A solution of akuammigine in chloroform slowly decomposes in air, but a solution in aqueous alcohol is stable. Henry (*loc. cit.*; 1932) gives the m. p. 127° for akuammigine but we found the lower value cited, unchanged after several recrystallisations, and rather sharp.

The *hydrobromide* separated when a hot, concentrated solution of potassium bromide was added to a saturated solution of the hydrochloride in boiling water; it was recrystallised with difficulty from water, forming colourless prisms, m. p. 248—250° (decomp.) (Found: C, 58·1; H, 5·8; Br, 19·1. $C_{21}H_{24}O_3N_2$,HBr requires C, 58·2; H, 5·8; Br, 18·5%). The *perchlorate* crystallised from water in clusters of needles, m. p. 75° (air-dry), m. p. 204° (dry; decomp.); $[\alpha]_D^{19}$ −39° (*c*, 1·1 in EtOH) [Found, in material dried at 120°/0·005 mm. for 15 hr. (loss, 10·6): C, 55·4; H, 5·7; N, 6·2; Cl, 7·6. $C_{21}H_{24}O_3N_2,HClO_4,3H_2O$ requires $3H_2O$, 10·7; $C_{21}H_{24}O_3N_2,HClO_4$ requires C, 55·7; H, 5·6; N, 6·2; Cl, 7·5%]. The *picrate* separated from ethanol as bright yellow rods of the *monohydrate*, m. p. 173° (Found: C, 53·8; H, 5·1; N, 11·4. $C_{21}H_{24}O_3N_2,C_6H_3O_7N_3,H_2O$ requires C, 54·0; H, 5·0; N, 11·7%). This salt is sometimes obtained in the same way as anhydrous pale yellow rods, m. p. 240° (decomp.) (Found: C, 55·7 H, 4·8; N, 12·2. $C_{21}H_{24}O_3N_2,C_6H_3O_7N_3$ requires C, 55·7; H, 4·8; N, 12·0%)



A, *Akuammigine*.
B, *Akuammigol*.
C, *Akuammigol acetate*.
D, *Mayumbine* (*Raymond-Hamet*, Compt. rend., 1951, **232**, 2354).

Akuammigine and all its salts and derivatives give a bright yellow colour with concentrated nitric acid. No colour is developed by ferric chloride in very dilute hydrochloride acid solution. The Adamkiewicz–Hopkins–Cole reaction (carried out according to Brustlier, Bourbon, and Vignes, *Bull. Soc. chim.*, 1950, 113) give a violet colour (indole reaction).

Akuammigine was not hydrolysed by 10% potassium hydroxide in methanol in 1 hr., nor was any change observed when it was heated with 2 : 4-dinitrophenylhydrazine in ethanolic hydrochloric acid for 1 hr. (contrast the behaviour of alstonine, Elderfield, and Gray, *loc. cit.*).

Reduction of Akuammigine with Lithium Aluminium Hydride.—Akuammigine (200 mg.) was reduced with lithium aluminium hydride (200 mg.) in ether (60 c.c.) for 2 hr. on the steam-bath. Excess of the reagent was decomposed with moist ether, and the filtered solution evaporated until crystallisation started. Akuammigol was recrystallised from ether as flattened rods of the *hemihydrate*, m. p. 211—213° (Found: C, 72·0; H, 7·8; N, 8·4. $C_{20}H_{24}O_2N_2,\frac{1}{2}H_2O$ requires C, 72·0; H, 7·6; N, 8·3%). *Akuammigol* separated from chloroform in crystals with $\frac{1}{3}$ molecule of the solvent, then having m. p. *ca.* 170°, solidifying at once and remelting at 213° (decomp.), $[\alpha]_D^{18}$ −60° (calc. on solvent-free base) [Found: C, 67·3, 66·9; H, 6·9, 6·8; N, 7·9; Cl, 9·4. $(C_{20}H_{24}O_2N_2)_3,CHCl_3$ requires C, 67·0; H, 7·6; N, 7·7; Cl, 9·7%]. After drying to constant weight (120°/0·005 mm. for 5 hr.) the substance still contained about 5·7% of chloroform (Found: C, 70·0; H, 7·2; N, 7·9%) and, to show that it was not a hydrochloride, a potentiometric titration was carried out against 0·1N-hydrochloric acid; this gave pK_a 7·04. Akuammigol dissolves in hot pyridine, but crystallises almost immediately with $1C_5H_5N$, and the pyridine is not lost at 120°/0·01 mm. during 5 hr. Thus dried, it had m. p. 175° (smell of pyridine), remelting at 213° (decomp.) (Found: C, 74·1; H, 7·1; N, 10·3. $C_{20}H_{24}O_2N_2,C_5H_5N$ requires C, 74·4; H, 7·2; N, 10·4%).

Akuammigol methiodide was made from its generators in ethanol and separated as clusters of colourless prisms. After being washed with ethanol, and ether, and dried, it had m. p. 282—284° (decomp.; dependent on rate of heating) (Found: C, 53·2; H, 6·0; I, 28·2. $C_{20}H_{24}O_2N_2,CH_3I,\frac{1}{2}H_2O$ requires C, 53·1; H, 5·9; I, 27·7%).

Attempts to prepare the hydrochloride of akuammigol in various ways afforded only oils.

O-*Acetylakuammigol*.—A solution of akuammigol (200 mg.) in dry pyridine (5 c.c.) and redistilled acetic anhydride (0·5 c.c.) was heated on the steam-bath for 2 min. The mixture was cooled and light petroleum (b. p. 40—60°) added until crystallisation began. In this way, crude acetylakuammigol (120 mg.) was obtaned. After recrystallisation from ether, it was obtained as plates of the *pentahydrate*, m. p. 155° (Found: C, 58·2; H, 7·6; N, 5·9. $C_{22}H_{26}O_3N_2,5H_2O$ requires C, 57·9; H, 8·0; N, 6·1%), or sometimes as needles of a monohydrate, m. p. 155°, which were never free from the pentahydrate; $[\alpha]_D^{19}$ for the pentahydrate was −59° (*c*, 1·2 calc. on dry base, in EtOH). The pentahydrate, when dried to constant weight, gave the *monohydrate* (Found: loss 18·5. Found, in the dried sample: C, 69·2; H, 7·2. $C_{22}H_{26}O_3N_2,5H_2O$ requires $4H_2O$,18·7. $C_{22}H_{26}O_3N_2,H_2O$ requires C, 68·7; H, 7·3%).

No uptake of the gas was observed on shaking akuammigol under hydrogen in aqueous methanol (50%) with 10% palladised charcoal or with glacial acetic acid and Adams catalyst, even on addition of a few drops of concentrated hydrochloric acid (cf. Elderfield and Gray, *loc. cit.*

After attempted reduction with sodium in liquid ammonia, in the presence of alcohol, akuammigol was recovered to the extent of 90% after 1 hr.

Dehydrogenation of Akuammigine with Selenium.—A mixture of akuammigine (450 mg.) with powdered selenium (1 g.) was heated at 250° (metal-bath), and the temperature raised during 15 min. to 280°; the product was cooled, mixed with clean sand, and extracted with methanol for 4 hr. (Soxhlet), and the solution thus obtained was mixed with that of the red oil, which had collected in the condenser during the reaction, in benzene–methanol. The combined extracts were concentrated *in vacuo*, and the residue dissolved in chloroform (25 c.c.), washed twice with aqueous sodium hydrogen carbonate (10%), dried, and evaporated to dryness. The oil was dissolved in benzene (10 c.c.) and passed through an alumina column, the first two fractions (50 c.c. each) of eluate being collected. From these fractions, an orange oil was obtained, the solution of which in light petroleum (b. p. 40—60°) slowly deposited crystals (34 mg.) at 0°. Three recrystallisations from the same solvent gave four- and six-sided plates (21 mg.), m. p. 116—117°. The infra-red and ultra-violet spectra of these crystals were identical with those of alstyrine (Found: C, 81·9; H, 7·7; N, 10·4. Calc. for $C_{19}H_{22}N_2$: C, 82·0; H, 8·0; N, 10·1%). We are very grateful to Professor P. Karrer for a specimen of corynanthyrine (*syn.* alstyrine). From the mother-liquors of these fractions, the picrate, m. p. 210—212°, was obtained, though in very small amount.

Infra-red data (*Nujol suspension unless otherwise stated*).

	Maxima (cm.$^{-1}$)	Interpretation
Akuammigine	3546	OH and NH bands
	3333	
	3049	
	1707	
	1683	Conjugated ester C=O
	1629	Asymmetric C=C (conjugated)
	741	1 : 2-Disubstituted benzene ring
,, in $CHCl_3$	1689	Conjugated ester C=O
	1621	Asymmetric C=C (conjugated)
Akuammigol (+$\frac{1}{3}CHCl_3$)	3195	OH and NH bands
	3049	
	1656	Asymmetric C=C (unconjugated)
	738	1 : 2-Disubstituted benzene ring
Akuammigol acetate	3356	(broad) OH and NH absorption
monohydrate	1712	Unconjugated ester C=O
	1656	Asymmetric C=C

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