## 803. *An Examination of the Rutaceae of Hong Kong. Part III.*[1] *The Alkaloid, Avicine, from* Zanthoxylum avicennae.

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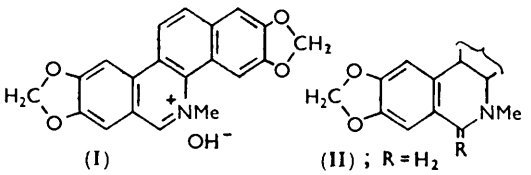
A new benzophenanthridine alkaloid, avicine, has been isolated from the root bark of *Zanthoxylum avicennae*. Avicine is related to nitidine in the same way as sanguinarine is related to chelerythrine. Hesperidin has been obtained from the leaves, and a mixture of hesperidin, diosmin, and, avicennin, from the root bark of this plant.

*Zanthoxylum avicennae* (Lam.) DC. (*Ying pu po*), an erect shrub with white flower, is used in the Colony against sore throat and jaundice. The bark was earlier reported to contain a mixture of hesperidin and diosmin [2] and a new yellow coumarin, avicennin.[3]

Hesperidin has now been obtained from the leaves, and a mixture of hesperidin, diosmin, and avicennin and also a new benzophenanthridine alkaloid, avicine (I), from the root bark.




(I)

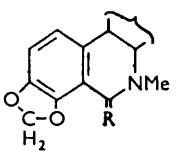



(II); R = $H_2$

(III); R = O


(IV); R = $H_2$

(VII); R = O




(V); R = $H_2$. (VI); R = O

Avicine was isolated from the methanol extract as a crude quaternary salt which yielded a mixture of dihydroavicine (II), and oxyavicine (III), when its aqueous solution was basified. (This disproportionation of avicine occurred less readily than that of

[1] Part II, *J.*, 1959, 1840.
[2] Arthur, Hui, and Ma, *J.*, 1956, 632.
[3] Arthur, "Proceedings of the Phytochemical Symposium, Kuala Lumpur," 1957, p. 123.

nitidine [1] isolated from *Zanthoxylum nitidum*.) Like dihydronitidine (IV), dihydroavicine was easily oxidised by air and so it was separated from oxyavicine under argon. The general chemical properties and ultraviolet absorption spectra of these two compounds suggested that they were benzophenanthridine derivatives. Oxyavicine, a substituted amide, did not form salts. It was converted into dihydroavicine by reduction and dihydroavicine was converted into oxyavicine by oxidation *via* the quaternary avicine acetate. Whilst dihydroavicine and oxyavicine were shown not to contain methoxyl groups, a positive Labat test indicated the presence of methylenedioxy-groups; and so it was clear that dihydroavicine was isomeric with, and contained the same functional groups as, dihydrosanguinarine (V) and that oxyavicine was similarly related to oxysanguinarine (VI).

Demethylenation of oxyavicine gave a tetrahydric phenol which on methylation yielded 6,7,2′,3′-tetramethoxy-10-methyl-1,2-benzophenanthridone previously obtained [1] from oxynitidine (VII). Hence it was clear that the methylenedioxy-groups of oxyavicine (and those of avicine and dihydroavicine) were present in the 6,7- and 2′,3′-positions of the benzophenanthridine skeleton; and that avicine is 6,7:2′,3′-bismethylenedioxy-10-methyl-1,2-benzophenanthridium hydroxide. Salts of this alkaloid and of dihydroavicine have been prepared.

Avicine, whose existence might have been predicted on biogenetic grounds particularly following the discovery of nitidine, is related to nitidine as sanguinarine is related to chelerythrine.

There was no evidence that oxyavicine (cf. oxynitidine [1]) occurred in the root bark.

## Experimental

Analyses were by Dr. Zimmermann, Melbourne. The alumina used was B.D.H. analysis grade. Unless otherwise stated m. p.s were taken on a Kofler block; where stated to have been taken on a gas-heated copper block the m. p.s are uncorrected.

*Isolation of Products.*—Leaves (400 g.) were extracted with hot methanol (3 l.) for 20 hr. The extract was concentrated to 100 ml., and left for 2 days. The green solid (0·4 g.) which separated was extracted with light petroleum (b. p. 60—80°) and then with methanol. The pale brown residue was recrystallised twice from aqueous pyridine. Nearly colourless fine needles of hesperidin hydrate, m. p. 260° (decomp.; vac.; gas-heated copper block), were obtained.

Milled root bark (2·5 kg.) was extracted with hot methanol (16 l.) for 30 hr. The extract was concentrated to 1 l., then left for 3 days. The pale yellow crystals *A* (8·0 g.) were collected, and the filtrate concentrated to 0·5 l. and left for 3 more days. The crude bright yellow alkaloid salt *B*, (2·4 g.) was collected and then washed with methanol.

Material *A* (8·0 g.) was boiled with methanol, and from the extract avicennin [3] (1·1 g.), m. p. 141—142° alone or in admixture with an authentic sample, was obtained by recrystallisation. The methanol-insoluble fraction of *A* (investigated by Miss Y. L. Ng) on recrystallisation from aqueous pyridine gave diosmin hydrate, m. p. 275—276° (decomp.; vac.; gas-heated copper block) (Found: C, 53·9; H, 5·8. Calc. for $C_{28}H_{32}O_{15},H_2O$: C, 53·7; H, 5·4%); the aqueous pyridine mother-liquors gave, after concentration under reduced pressure, hesperidin hydrate, m. p. 257—260° (decomp.; vac.; gas-heated copper block) (Found: C, 53·9; H, 5·9. Calc. for $C_{28}H_{34}O_{15},H_2O$: C, 53·5; H, 5·7%); it was purified by recrystallisation from aqueous pyridine.

*Separation of Dihydroavicine* (II) *and Oxyavicine* (III).—Material *B* (4·8 g.) was boiled with water. After being filtered, the hot aqueous solution was basified with ammonia, and the buff-coloured precipitate (3·0 g.) was dried and then extracted with boiling benzene. The benzene extract was chromatographed on alumina (200 g.) under argon. Elution with benzene gave a product (0·7 g.) which, after recrystallisation from ethanol under argon, yielded colourless prisms of *dihydroavicine*, m. p. 211—212·5° (Found: C, 72·5; H, 4·5; N, 4·2; NMe, 8·3%; *M* 382. $C_{20}H_{15}O_4N$ requires C, 72·1; H, 4·5; N, 4·2; NMe, 8·7%; *M* 333); $\lambda_{max.}$ in ethanol (log ε) 322 (4·33), 278 (4·50), 232 mμ (4·60). (Dihydroavicine gave a blue fluorescence in ultraviolet light in the solid or in solution). Elution with benzene–chloroform (3 : 1) gave a product (0·65 g.) which after two recrystallisations from concentrated ethanol solution, separated as

prisms of *oxyavicine*, m. p. 257—259°, solidifying to needles, m. p. 275—277° (the needle form was also obtainable by crystallisation from a less concentrated solution) (Found: C, 69·4; H, 3·8; N, 4·0; NMe, 7·0. $C_{20}H_{13}O_5N$ requires C, 69·2; H, 3·8; N, 4·0; NMe, 8·3%); $\lambda_{max.}$ in ethanol (log ε) 332 (4·19), 322 (4·21), 289 (4·76), 278 (4·70), 248 mμ (4·50). (Oxyavicine gave a purple fluorescence in ultraviolet light in the solid or in solution.)

*Dihydroavicine from Oxyavicine.*—To oxyavicine (0·1 g.), dissolved in sodium-dried tetrahydrofuran (15 ml.), was added lithium aluminium hydride (0·07 g.). The mixture was boiled under reflux in argon for 3 hr. Dilute hydrochloric acid was then added, and the mixture, after dilution with water, gave a precipitate, which, after recrystallisation from ethanol, yielded elongated prisms (0·07 g.), m. p. 210—212° alone or in admixture with dihydroavicine.

*Oxyavicine from Dihydroavicine* (via *Avicine Acetate*).—Dihydroavicine (0·35 g.) was dissolved in hot 50% acetic acid (30 ml.). Mercuric acetate (1·7 g.) was added, and the mixture was heated on the steam-bath for 2 hr. The precipitate was removed, and hydrogen sulphide was passed into the mother liquor. The black precipitate was discarded and the filtrate concentrated; it deposited bright yellow needles of *avicine acetate* (0·22 g.) which on recrystallisation from ethanol had m. p. 160° (decomp.; vac.; gas-heated copper block) (Found: C, 62·2; H, 4·9; N, 3·1. $C_{22}H_{17}O_6N,2H_2O$ requires C, 61·8; H, 5·0; N, 3·3%). To a solution of avicine acetate (0·1 g.) in hot water (20 ml.), was added a hot aqueous solution (10 ml.) containing potassium ferricyanide (0·2 g.) and potassium hydroxide (0·1 g.). The precipitate (0·08 g.) was collected and recrystallised from ethanol. Crystals, m. p. 257—259° (gradually re-solidifying to needles, m. p. 275—277°) alone or in admixture with oxyavicine, were obtained.

*Salts of Avicine and Dihydroavicine.*—(a) *Avicine ψ-cyanide.* To a solution of avicine acetate (0·1 g.) in water aqueous potassium cyanide was added. The precipitate (0·08 g.) was recrystallised from ethanol, giving needles of the *ψ-cyanide*, m. p. >340° (Found: C, 70·3; H, 4·1; N, 8·3. $C_{21}H_{14}O_4N_2$ requires C, 70·4; H, 3·9; N, 7·8%). (b) *Dihydroavicine hydrochloride.* Dihydroavicine (0·1 g.) was dissolved in chloroform (5·0 ml.), and concentrated hydrochloric acid (1·0 ml.) added. Removal of the chloroform under argon left a product which, when washed with alcohol under argon, gave the *hydrochloride* (0·11 g.), m. p. 255—258° (vac.; gas-heated copper block) (Found: C, 64·0; H, 4·4; Cl, 9·0. $C_{20}H_{15}O_4N,HCl$ requires C, 64·9; H, 4·4; Cl, 9·6%).

*6,7,2′,3′-Tetrahydroxy-10-methyl-1,2-benzophenanthridone.*—Oxyavicine (0·44 g.) was dissolved in boiling sodium-dried benzene (100 ml.). Anhydrous aluminium chloride (5 g.) was added and the mixture boiled under reflux for 7 hr. Addition of dilute hydrochloric acid gave a brownish precipitate (0·4 g.) which was recrystallised from ethanol. *6,7,2′,3′-Tetrahydroxy-10-methyl-1,2-benzophenanthridone* separated as pale brown crystals, m. p. 340° (Found: C, 67·0; H, 4·4; N, 4·1. $C_{18}H_{13}O_5N$ requires C, 66·9; H, 4·1; N, 4·3%). It gave a dark greyish-green colour with ferric chloride solution; a negative reaction was obtained in the Labat test. (Attempts to remove methylene groups from oxyavicine or dihydroavicine with phloroglucinol and sulphuric acid failed.)

*6,7,2′,3′-Tetramethoxy-10-methyl-1,2-benzophenanthridone.*—The above product (0·1 g.), suspended in ether, was treated with diazomethane in ether for 16 hr. A product separated as fine needles (0·09 g.), which after recrystallisation from ethanol had m. p. 251—253°, alone or in admixture with authentic 6,7,2′,3′-tetramethoxy-10-methyl-1,2-benzophenanthridone obtained from oxynitidine [1] (Found: C, 69·5; H, 5·5; N, 3·8; OMe, 32·5%. Calc. for $C_{22}H_{21}O_5N$: C, 69·6; H, 5·6; N, 3·7; 4OMe, 32·7%); $\lambda_{max.}$ in ethanol (log ε) 326 (4·22), 321 (4·26), 286 (4·84), 277 (4·75), 267 (4·72). (These values agree with those found for a sample of the product from oxynitidine.)

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