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SYNTHESIS OF OXYAVICINE

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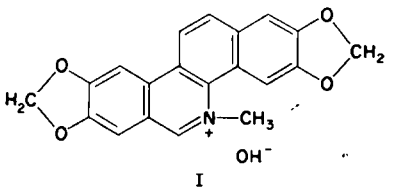
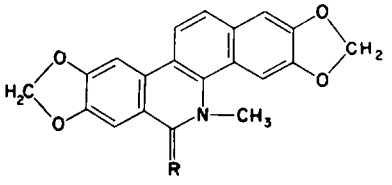
Abstract—The structure (I) assigned to the alkaloid avicine has been confirmed by a synthesis of oxyavicine (III).

ARTHUR *et al.*[1] isolated from the root bark of *Zanthoxylum avicennae* an alkaloid avicine, to which they assigned structure I. The alkaloid is isomeric with sanguinarine and was found to disproportionate to a mixture of dihydroavicine (II) and oxyavicine (III). The structure of avicine has now been confirmed by synthesis of oxyavicine along the Robinson–Bailey route starting from the tetralone (VIII) which had been prepared earlier in this laboratory[2] in connexion with other work.



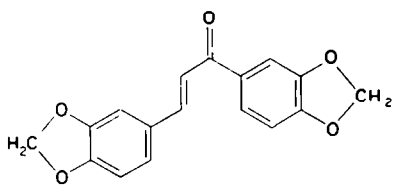
I



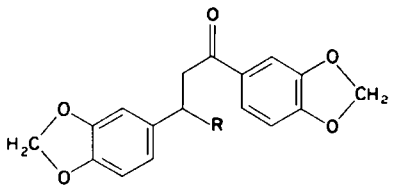
II: R = H_2
III: R = O

Condensation of acetopiperone with piperonal yielded 3,4:3′,4′-bismethylenedioxychalkone (IV). Addition of hydrogen cyanide gave the nitrile (V) which was hydrolysed to the amide (VI) with sulphuric acid. Further hydrolysis of the amide with alkali yielded the corresponding keto acid (VII). Reduction with hydrogen and palladium-charcoal in the presence of perchloric acid gave the substituted n-butyric acid which was cyclized with phosphorus oxychloride to yield 1,2,3,4-tetrahydro-6,7-methylenedioxy-2-(3,4-methylenedioxyphenyl)-1-oxonaphthalene (VIII). Leuckart reaction on this afforded a separable mixture of 3,4-dihydro-6,7-methylenedioxy-2-(3,4-methylenedioxyphenyl)-naphthalene and the 1-formamido derivative (IX). The former, on dehydrogenation, yielded 6,7-methylenedioxy-2-(3,4-methylenedioxyphenyl)naphthalene, identical with an authentic sample made by the method of Gopinath *et al.*[3] The formamide was cyclized with phosphorus oxychloride in toluene to 3,4,11,12-tetrahydro-6,7:2′,3′-bismethylenedioxy-1,2-benzophenanthtidine which was dehydrogenated to the benzophenanthridine (X). The methosulphate of this base, on oxidation with alkaline potassium ferricyanide, gave oxyavicine (III), identical in all respects (mixed m.p., ultra-violet and infra-red spectra) with a sample of the natural product. Oxyavicine has earlier been reduced[1] with lithium aluminium hydride to dihydroavicine.

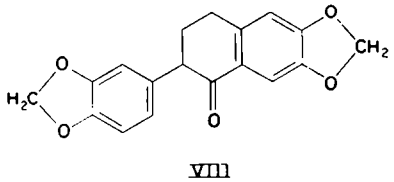
[1] H. R. Arthur, W. H. Hui and Y. L. Ng, *J. Chem. Soc.* 4007 (1959).
[2] N. Viswanathan, Ph.D. Thesis, Madras University (1959).
[3] K. W. Gopinath, T. R. Govindachari, K. Nagarajan and K. K. Purushothaman, *J. Chem. Soc.* 1144 (1957).



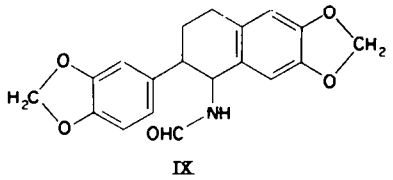
IV



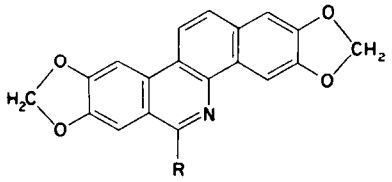
V . R = CN
VI . R = $CONH_2$
VII . R = COOH



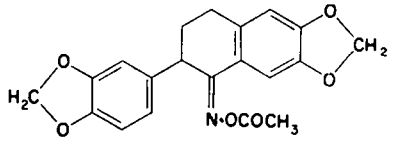
VIII



IX



X : R = H
XII : R = CH_3



XI

As in the case of other 2-aryl-1-tetralone oxime acetates investigated in this laboratory,[4] the oxime acetate (XI) made from the tetralone (VIII), on treatment with acetic acid, acetic anhydride and hydrogen chloride in a sealed tube, underwent an abnormal Schroeter reaction to furnish the substituted 9-methyl-1,2-benzophenanthridine (XII) in excellent yield.

EXPERIMENTAL

3,4:3′,4′-*Bismethylenedioxychalkone* (IV). A mixture of piperonal (10 g) and acetopiperone (10·6 g) in ethanol (50 ml) was treated with aqueous NaOH (10%; 14 ml) and left overnight. The precipitated *chalkone* (17 g) was collected, washed with water and crystallized from acetone to yield yellow needles, m.p. 174° (Found: C, 68·6; H, 3·8. $C_{17}H_{12}O_5$ requires: C, 68·9; H, 4·1%).

α,γ-*Bis*(3,4-*methylenedioxyphenyl*)γ-*oxobutyronitrile* (V). The chalkone (10 g) was dissolved in boiling 2-ethoxyethanol (70 ml) containing acetic acid (2·5 ml) and the solution transferred quickly to a water bath preheated to 100° to prevent crystallization of the chalkone. A solution of potassium cyanide (5 g) in water (9 ml) was added with stirring, during 3 min, and the heating continued for 15 min. Dilution with water gave the *nitrile* (10 g), which crystallized from ethanol as colourless needles, m.p. 141° (Found: C, 66·9; H, 4·2. $C_{18}H_{13}NO_5$ requires: C, 66·9; H, 4·0%).

α,γ-*Bis*(3,4-*methylenedioxyphenyl*)-γ-*oxobutyramide* (VI). A solution of the nitrile (6 g) in acetic acid (42 ml) was treated gradually with conc H_2SO_4 (6 ml) during 15 min. Addition of water yielded the *amide* (5·5 g) which crystallized from acetone as shining prisms, m.p. 164° (Found: C, 63·7; H, 4·4. $C_{18}H_{15}NO_6$ requires: C, 63·3; H, 4·4%).

α,γ-*Bis*(3,4-*methylenedioxyphenyl*)-γ-*oxobutyric acid* (VII). A mixture of the amide (10 g), ethanol (100 ml) and aqueous sodium hydroxide (7%; 160 ml) was refluxed for 7 hr and acidified to yield the *keto acid* (8 g), Crystallization from ethanol gave colourless needles, m.p. 169–170° (Found: C, 62·8; H, 4·4. $C_{18}H_{14}O_7$ requires: C, 63·2; H, 4·1%).

1,2,3,4-*Tetrahydro*-6,7-*methylenedioxy*-2-(3, 4-*methylenedioxyphenyl*)-1-*oxonapathalene* (VIII). The

[4] K. W. Gopinath, T. R. Govindachari and N. Viswanathan, *Curr. Sci.* **28**, 241 (1959).

keto acid (2 g) in acetic acid (25 ml) and perchloric acid (70%; 0·5 ml) was reduced with hydrogen at a pressure of 15 lbs/in² at 60°, using palladized charcoal catalyst (5%; 0·6 g) during 2 hr. The catalyst was filtered off and the solvent removed under reduced press. Water was added and the product extracted with chloroform. The chloroform extract was dried (Na_2SO_4) and the solvent distilled to yield α,γ-bis(3,4-methylenedioxyphenyl)butyric acid (1·8 g) as a brownish oil. This was heated at 100° for 15 min with phosphorus oxychloride (4 ml). The mixture was cooled, poured on ice and the product extracted with chloroform. The chloroform extract was washed with Na_2CO_3 solution and then with water, dried (Na_2SO_4) and the solvent removed by distillation. Chromatography of the residue in benzene over alumina yielded the *tetralone* (0·7 g) which crystallized from ethyl acetate–ethanol as needles, m.p. 170–171° (Found: C, 69·7; H, 4·6. $C_{18}H_{14}O_5$ requires: C, 69·7; H, 4·5%).

1-*Formamido*-1,2,3,4-*tetrahydro*-6,7-*methylenedioxy*-2-(3,4-*methylenedioxyphenyl*)*naphthalene* (IX). The tetralone (2 g) was heated under reflux at 180° for 3 hr with formamide (5 ml), formic acid (0·25 ml) and ammonium sulphate (0·25 g), formic acid (0·25 ml) being added every 1 hr. The mixture was cooled, diluted with water and extracted with chloroform. The dried (Na_2SO_4) chloroform extract gave, on removal of the solvent, a brownish gum which was chromatographed in benzene over alumina. The initial fractions of the eluate which had a violet fluorescence yielded, on evaporation, 3,4-*dihydro*-6,7-*methylenedioxy*-2-(3,4-*methylenedioxyphenyl*)*naphthalene* (0·2 g) which crystallized from methanol as needles, m.p. 155°, λ_{max} 225, 335 mμ (log ε 4·03, 4·04) (Found: C, 73·7; H, 5·1. $C_{18}H_{14}O_4$ requires: C, 73·5; H, 4·8%). Further elution of the column with benzene and then with benzene containing 1% ethanol gave the *formamide* (0·8 g). Crystallization from alcohol gave needles, m.p. 169–170° (Found: C, 67·6; H, 5·3. $C_{19}H_{17}NO_5$ requires: C, 67·3; H, 5·0%).

6,7-*Methylenedioxy*-2-(3,4-*methylenedioxyphenyl*)*naphthalene*. A mixture of the dihydronaphthalene (0·4 g) and palladized charcoal catalyst (30%; 0·2 g) was heated at 240–250° for 10 min and the product sublimed *in vacuo* (0·2 mm). The solid sublimate, on crystallization from acetic acid, gave the *naphthalene* (0·3 g) as plates, m.p. 200°, undepressed by admixture with an authentic sample[3] (Found: C, 74·1; H, 4·0. $C_{18}H_{12}O_4$ requires: C, 74·0; H, 4·1%). The ultra-violet and infra-red absorption spectra of the two compounds were identical.

3,4,11,12-*Tetrahydro*-6,7:2′,3′-*bismethylenedioxy*-1,2-*benzophenanthridine*. The formamide (1 g) in dry toluene (10 ml) was refluxed gently for 30 min with phosphorus oxychloride (3 ml). The precipitated hydrochloride was filtered, washed with ether, and basified with ammonia, to yield the *tetrahydrobenzophenanthridine* (0·6 g). Crystallization from pyridine–ethanol gave needles, m.p. 235–236°, λ_{max} 230, 292 mμ (log ε 4·27, 3·69), λ_{infl} 315 mμ (log ε 3·61) (Found: C, 71·3; H, 4·5. $C_{19}H_{15}NO_4$ requires: C, 71·1; H, 4·7%).

6,7:2′,3′-*Bismethylenedioxy*-1,2-*benzophenanthridine* (X). The tetrahydrobenzophenanthridine (0·3 g) was heated with palladized charcoal catalyst (30%; 0·3 g) at 230–240° for 40 min in an atmosphere of nitrogen. The product was thoroughly extracted with chloroform. Removal of the solvent by distillation and crystallization of the product from pyridine gave the *benzophenanthridine* (0·15 g) as needles, m.p. 325° (decomp), λ_{max} 230, 275, 370 mμ (log ε 4·59, 4·86, 3·50), λ_{infl} 327 mμ (log ε 4·26) (Found: C, 71·5; H, 3·9. $C_{19}H_{11}NO_4$ requires: C, 71·9; H, 3·5%).

Oxyavicine (III). A solution of the above benzophenanthridine (0·1 g) in xylene (3 ml) and nitrobenzene (5 ml) was boiled for 5 min and dry methyl sulphate (0·3 ml) added to the boiling solution. A yellow precipitate rapidly appeared and after 5 min the solution was cooled and diluted with ether (15 ml). The precipitate was collected and washed with ether to yield the methosulphate (100 mg) which did not melt below 360°. A solution of the methosulphate (0·1 g) in water (30 ml) was heated on a water bath to 70° and treated dropwise with stirring with a hot solution of potassium ferricyanide (0·4 g) and potassium hydroxide (0·2 g) in water (20 ml). The mixture was stirred vigorously for 20 min at 80°, cooled and extracted with benzene. The benzene extract was washed with dil HCl, then with water and dried (Na_2SO_4). Removal of the solvent and chromatography of the residue in chloroform over alumina yielded *oxyavicine* (20 mg) as needles from ethanol, m.p. 276–277°, undepressed by admixture with a sample of the natural product. The ultra-violet and infra-red spectra of the two samples were identical (Found: C, 68·9; H, 4·2. $C_{20}H_{13}NO_5$ requires: C, 69·2; H, 3·8%).

1,2,3,4-*Tetrahydro*-1-*hydroxyimino*-6,7-*methylenedioxy*-2-(3,4-*methylenedioxyphenyl*)*naphthalene*. A solution of the tetralone (VIII, 1 g) and hydroxylamine hydrochloride (1 g) in pyridine (4 ml) was heated at 100° on a steam bath for 5 hr and poured into water. Crystallization of the product from ethanol yielded the *oxime* (0·8 g) as needles, m.p. 191° (Found: C, 66·7; H, 4·4. $C_{18}H_{15}NO_5$ requires: C, 66·5; H, 4·6%). The oxime (0·8 g) was heated on a water bath for 1 hr with acetic anhydride (2 ml)

and pyridine (2 ml) and the solution left overnight at room temp. Dilution with water and crystallization of the product from ethanol gave the *acetate* (XI; 0·6 g) as prisms. m.p. 162° (Found: C, 65·5; H, 4·8. $C_{20}H_{17}NO_6$ requires: C, 65·4; H, 4·6%).

9-*Methyl*-6,7:2′,3′-*bismethylenedioxy*-1,2-*benzophenanthridine* (XII). A solution of the above oxime acetate (0·5 g) in acetic acid (2 ml) and acetic anhydride (3 ml) was saturated with dry hydrogen chloride at 0° and heated at 95–100° in a sealed tube for 8 hr. The contents were poured on ice and the brownish solid obtained was collected, washed with aqueous alcohol and basified with ammonia. Crystallization of the product from pyridine gave the *benzophenanthridine* (0·2 g) as needles, m.p. 299°, λ_{max} 230, 280, 350, 365 mμ (log ε 4·35, 4·70, 3·55, 3·35) (Found: C, 72·5; H, 4·1. $C_{20}H_{13}NO_4$ requires: C, 72·5; H, 3·9%).

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