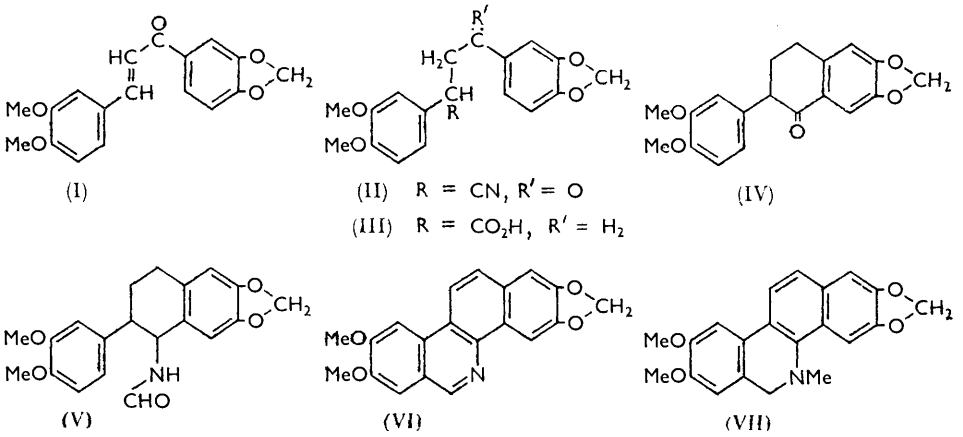
804. *An Examination of the Rutaceae of Hong Kong. Part IV.*[1a] *The Synthesis of Dihydronitidine.*

By H. R. Arthur and (Miss) Y. L. Ng.

Dihydronitidine has been synthesised and the structures for nitidine and oxynitidine proposed in our earlier work have been confirmed.

We reported in Part II [1b] the occurrence of oxynitidine and a salt of nitidine in the bark of *Zanthoxylum nitidum* and the elucidation of the structures of these alkaloids by their conversion into a known compound. The structures have now been confirmed by synthesis of dihydronitidine using the route designed by Robinson and his co-workers [2] for compounds of the chelidonine–sanguinarine type, and used recently by Bailey and Worthing,[3] who synthesised chelerythrine.

Acetopiperone (prepared as stated by Gopinath *et al.*[4]) and veratraldehyde on condensation gave the chalkone [2] (I), which was converted *via* the nitrile [2] (II) and the amide



into the corresponding keto-acid, which on reduction with hydrogen and palladium–charcoal in the presence of perchloric acid [3] gave the substituted n-butyric acid (III); cyclisation of this yielded a tetralone derivative (IV). Treatment with formamide and formic acid [2] afforded the substituted formamide (V) which on dehydration gave 3,4,11,12-tetrahydro-6,7-dimethoxy-4′,5′-methylenedioxy-1 : 2-benzophenanthridine; dehydrogenation to the benzophenanthridine (VI) was accomplished with 30% palladised charcoal.[5] The methosulphate of the base (VI), when reduced with zinc and hydrochloric acid, gave a product (VII) identical with dihydronitidine prepared from oxynitidine and nitidine acetate.[1b] Simple transformations by the methods [1b] used for dihydronitidine lead to syntheses of oxynitidine and nitidine acetate.

Experimental

Analyses were by Dr. Zimmermann, Melbourne. Unless otherwise stated, m. p.s were taken on a gas-heated copper block.

3,4-Dimethoxy-3′,4′-methylenedioxychalkone (I).—Acetopiperone (25 g.) and veratraldehyde (30 g.) were treated in ethanol (150 ml.) with 10% aqueous sodium hydroxide (30 ml.). The product, which slowly separated, was collected, and after crystallisation from ethanol was obtained as yellow needles (30 g.), m. p. 135°.

[1] (*a*) Part III, preceding paper; (*b*) Part II, *J.*, 1959, 1840.
[2] Richardson, Robinson, and Seijo, *J.*, 1937, 835.
[3] Bailey and Worthing, *J.*, 1956, 4535.
[4] Gopinath, Govindachari, Nagarajan, and Viswanathan, *J.*, 1957, 4760.
[5] Bailey, Robinson, and Staunton, *J.*, 1950, 227.

α-(3,4-*Dimethoxyphenyl*)-γ-(3,4-*methylenedioxyphenyl*)-γ-*oxobutyronitrile*.—To a solution of the chalkone (30 g.) in 2-ethoxyethanol (110 ml.) containing acetic acid (6·5 ml.) at 100° was added, during 3 min., potassium cyanide (12·5 g.) in water (45 ml.). Heating was continued for 10 min., then water (150 ml.) was added. The nitrile, which separated, was collected and after recrystallisation from ethanol was obtained as yellow needles (30 g.), m. p. 146°.

α-(3,4-*Dimethoxyphenyl*)-γ-(3,4-*methylenedioxyphenyl*)-γ-*oxobutyramide*.—A solution of the nitrile (30 g.) in acetic acid (200 ml.) was treated gradually with concentrated sulphuric acid (30 ml.). After dilution of the solution with water, the product separated; it was collected and crystallised from ethanol. The amide (25 g.) was obtained as needles, m. p. 177° (Found: C, 64·1; H, 5·4. Calc. for $C_{19}H_{19}O_6N$: C, 63·9; H, 5·4%).

α-(3,4-*Dimethoxyphenyl*)-γ-(3,4-*methylenedioxyphenyl*)-γ-*oxobutyric Acid*.—A solution of the amide (25 g.) in 7% aqueous sodium hydroxide (350 ml.) and ethanol (200 ml.) was boiled under reflux for 10 hr. and then acidified. The *keto-acid* (22 g.), which separated on cooling, was obtained as needles, m. p. 172° (from ethanol) (Found: C, 62·9; H, 5·0. $C_{19}H_{18}O_7$ requires C, 63·7; H, 5·0%).

2-(3,4-*Dimethoxyphenyl*)-1,2,3,4-*tetrahydro*-6,7-*methylenedioxy*-1-*oxonaphthalene*.—The keto-acid (11 g.) in acetic acid (110 ml.) containing 70% perchloric acid (2 ml.) was hydrogenated at 60°/1 atm. in the presence of 5% palladium–charcoal (2 g.) during 2 hr. The catalyst was removed and then most of the solvent under reduced pressure. Water was added to the residue, and the oily product was extracted with benzene. This extract, having been washed with water, was dried (Na_2SO_4) and then distilled on the steam-bath. The brown oil [α-(3,4-dimethoxyphenyl)-γ-(3,4-methylenedioxyphenyl)butyric acid] (8 g.) obtained, was boiled with phosphoryl chloride (20 ml.) for 4 min., and the mixture, having cooled, was poured on ice. The solid which separated was dissolved in chloroform and the solution was washed with aqueous sodium hydroxide, then with water, dried (Na_2SO_4), and evaporated. The residue, crystallised from ethanol, gave prisms (6·5 g.) of *the tetralone*, m. p. 165° (Found: C, 69·5; H, 5·6. $C_{19}H_{18}O_5$ requires C, 69·9; H, 5·6%).

2-(3,4-*Dimethoxyphenyl*)-1-*formamido*-1,2,3,4-*tetrahydro*-6,7-*methylenedioxynaphthalene*.—To a solution of the tetralone (6 g.) in formamide (15 ml.) and formic acid (0·8 ml.) was added ammonium sulphate (0·8 g.). The mixture was heated at 180° for 3 hr., formic acid (0·8 ml.) being added hourly. The cooled mixture was diluted with water, then extracted with chloroform. The washed extract was dried. Removal of its solvent gave an oil which was triturated with methanol (6 ml.). The colourless crystals which appeared overnight were collected and washed with acetone (10 ml.). The residue (3·5 g.) on recrystallisation from dioxan–ethanol (9 : 1) yielded the *formamide*, m. p. 178° (Found: C, 67·3; H, 5·9. $C_{20}H_{21}O_5N$ requires C, 67·6; H, 6·0%).

3,4,11,12-*Tetrahydro*-6,7-*dimethoxy*-2′,3′-*methylenedioxy*-1,2-*benzophenanthridine*.—The formamide (1·5 g.) was boiled with phosphoryl chloride (3 ml.) in toluene (10 ml.) for 15 min. The yellow solid which was deposited was washed with hot toluene and then suspended in hot methanol (15 ml.). Basification of the methanol suspension with ammonia gave white crystals (1 g.) which on crystallisation from methanol separated as colourless needles of the *product*, m. p. 188—189° (Found: C, 70·7; H, 5·3. $C_{20}H_{19}O_4N$ requires C, 71·2; H, 5·7%).

6,7-*Dimethoxy*-2′,3′-*methylenedioxy*-1,2-*benzophenanthridine*.—The tetrahydro-compound (0·9 g.) was heated with 30% palladium–charcoal (0·2 g.) at 240° for 30 min. The resulting solid was extracted with chloroform (4 × 30 ml.). The residue obtained on removal of the solvent from this extract, yielded, on crystallisation from pyridine, colourless needles (0·6 g.) of the *benzophenanthridine*, m. p. 273° (Found: C, 71·7; H, 4·5. $C_{20}H_{15}O_4N$ requires C, 72·1; H, 4·5%).

A solution of this product (0·5 g.) in xylene (5 ml.) and nitrobenzene (10 ml.) was boiled for a few minutes with methyl sulphate (1 ml.). A yellow precipitate was formed. Ether was added to the cooled suspension, then the solid was collected, washed with ether, and recrystallised from aqueous ethanol. The yellow *methosulphate*, m. p. 306—307° (decomp.), of 6,7-dimethoxy-2′,3′-methylenedioxy-1 : 2-benzophenanthridine (0·5 g.), was obtained as needles (Found: C, 57·8; H, 4·8. $C_{22}H_{21}O_8NS$ requires C, 57·5; H, 4·6%).

Dihydronitidine.—A solution of the methosulphate (0·4 g.) in water (60 ml.) and concentrated hydrochloric acid (4 ml.) was boiled under reflux with zinc powder (8 g.) in an atmosphere of argon for 5 hr., more hydrochloric acid (3 ml.) being added after each hr. The clear solution was then cooled to 0—5° and sealed under argon for 12 hr. The solid which separated

was collected, washed with water, and shaken with chloroform and ammonia. The chloroform extract was washed, dried, and evaporated in an atmosphere of argon. Crystallisation of the residue from ethanol gave prisms (0·2 g.) of *dihydronitidine*, m. p. 208—211° alone or in admixture with a sample prepared from a nitidine salt isolated from *Zanthoxylum nitidum* (Found: C, 72·0; H, 5·4. $C_{21}H_{19}O_4N$ requires C, 72·2; H, 5·5%). The light absorption for the synthetic compound in ethanol solution agreed with that earlier recorded.[1b]

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