858. *An Examination of the Rutaceae of Hong Kong. Part VIII.* The Synthesis of the Alkaloid, Graveoline.*

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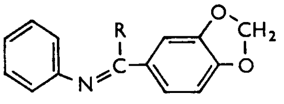
The alkaloid, graveoline [1-methyl-2-(3,4-methylenedioxyphenyl)-4-quinolone] (VI), from *Ruta graveolens* has been synthesised.

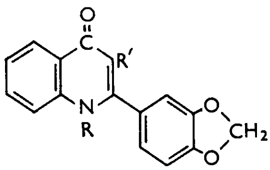
Ohta and Miyazaki[1] showed that the Japanese species of *Ruta graveolens* contained the alkaloids skimmianine and kokusaginine, and Ohta, Mori, Noda, and Aoki[2] later reported the presence of bergapten in the plant. In Part VI[3] it was reported that the Hong Kong species contained the alkaloids skimmianine and kokusaginine; this contained also a new alkaloid graveoline which was shown to be 1-methyl-2-(3,4-methylenedioxyphenyl)-4-quinolone by comparison with an authentic sample of this compound kindly sent to us by Dr. S. Goodwin who had prepared it in the course of her extensive work[4] on quinolone alkaloids but had not isolated it from a natural source.

Graveoline (VI) has now been synthesised also by us. Piperonylic acid was converted into its chloride and thence its anilide. The latter, on treatment with phosphorus pentachloride by the method of Elderfield *et al.*,[5] yielded an oily imidoyl chloride (I) which crystallised on storage at 0°. This crude product, with diethyl sodiomalonate,[5] yielded the diester (II) which was not isolated but on cyclisation afforded the pure quinolone ester (III). Alkaline hydrolysis gave the corresponding acid (IV) which was smoothly decarboxylated by copper powder in quinoline at 175—180°, to give 2-(3,4-methylenedioxyphenyl)-4-quinolone (V). Finally, *N*-methylation yielded graveoline (VI).



(I) R = Cl;

(II) R = $CH_2(CO_2Et)_2$



(V) R = R′ = H

(VI) R = Me, R′ = H

(III) R = H, R′ = CO_2Et

(IV) R = H, R′ = CO_2H

It is interesting that heating of the acid (IV) under reduced pressure in a cold-finger apparatus gave readily a sublimate which had a m. p. similar to that of the acid (IV) and was not depressed on admixture. Attempted decarboxylation with copper powder in boiling glycerol gave a solid (m. p. >300°) which when methylated did not yield graveoline and is believed to have lost the methylenedioxy-group. When boiling quinoline and copper powder were used decarboxylation took place, as shown by the infrared absorption spectrum, but again the product did not yield graveoline. However, by the quinoline method at 170—180°, the acid (IV) gave in 10 minutes an almost quantitative yield of the product (V) and during this reaction carbon dioxide was evolved. Although the quinolone (V) did not depress the m. p. of the acid (IV) it was clearly a new and decarboxylated product, as shown by its infrared spectrum and by its conversion into graveoline on methylation. We conclude that the sublimate of the acid (IV) referred to above is actually the decarboxylated quinolone (V) and that it did not depress the m. p. of the former because the acid becomes decarboxylated to a certain extent during the m. p. determination.

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* Part VII, *J.*, 1961, 3551.

[1] Ohta and Miyazaki, *J. Pharm. Soc. Japan*, 1958, **78**, 538.

[2] Ohta, Mori, Noda, and Aoki, *Chem. and Pharm. Bull.* (*Japan*), 1960, **8**, 377.

[3] Arthur and Cheung, *Austral. J. Chem.*, 1960, **13**, 510.

[4] Goodwin, Smith, and Horning, *J. Amer. Chem. Soc.*, 1957, **79**, 2239, and later papers.

[5] Elderfield, Gensler, Bembry, Kremer, Head, Brody, and Frohardt, *J. Amer. Chem. Soc.*, 1946, **68**, 1272.

Work is in progress to check this and to determine the nature of the other products obtained.

EXPERIMENTAL

Analyses are by Dr. K. W. Zimmermann, C.S.I.R.O. and University of Melbourne, Microanalytical Laboratory. M. P.s were taken on a gas-heated copper block except where otherwise stated. Infrared spectra were taken for Nujol mulls on a Perkin–Elmer Infracord (model 137) spectrophotometer. The alumina used for chromatography was of B.D.H. analysis grade.

N-*Phenylpiperonylamide*.—Piperonylic acid (10·0 g.) obtained from piperonaldehyde by the method given [6] for the disproportionation of benzaldehyde, was converted into piperonyl chloride by treatment with boiling thionyl chloride (6·0 ml.). The excess of thionyl chloride was removed and aniline (6·0 ml.) was added to the residue. The mixture was warmed on the steam-bath for ½ hr. The brown product was washed with dilute hydrochloric acid and aqueous sodium carbonate and then crystallised once from methanol and twice from benzene, giving colourless N-*phenylpiperonylamide* (15·1 g.), m. p. 144—145° (Found: C, 69·9; H, 4·6; N, 6·0. $C_{14}H_{11}NO_3$ requires C, 69·7; H, 4·6; N, 5·8%).

Ethyl 1,4-*Dihydro*-2-(3,4-*methylenedioxyphenyl*)-4-*oxoquinoline*-3-*carboxylate*.—The preceding amide (15·0 g.) was treated with phosphorus pentachloride (13·5 g.) at 110—115° for 1 hr. by the method of Elderfield *et al.*[5] for the preparation of imidoyl chlorides. Removal of phosphorus oxychloride at the pump left a yellow oil which at 0° gave crude crystalline *N*-phenylpiperonylimidoyl chloride. Sodium (1·6 g.) was dissolved in magnesium-dried ethanol (19·8 ml.). Diethyl malonate (9·9 ml.) was added. Removal of ethanol at the pump left a residue which was added in suspension in sodium-dried toluene (200 ml.) to the crude imidoyl chloride. The mixture was boiled under reflux for 3½ hr. Toluene was removed at the pump and the residue was extracted with water and ether. Distillation of the dried ethereal layer left a brown oil from which diethyl malonate was removed *in vacuo*. The brown semisolid residue was heated under reduced pressure at 150—170° for 3½ hr., then at 180—190° for ¾ hr. As much as possible of the residue was taken up in cold benzene (300 ml.) and applied to a column of alumina. Elution with benzene gave *N*-phenylpiperonylamide. Elution with chloroform gave a brown oil. Elution with methanol then gave the *ester* (III) which after crystallisation from ethanol was deposited as needles or prisms, m. p. 228° (Found: C, 67·9; H, 4·9; N, 4·2. $C_{19}H_{15}NO_5$ requires C, 67·7; H, 4·5; N, 4·2%). The portion of the residue insoluble in cold benzene was shown to consist entirely of this ester (total yield, 3·4 g.).

1,4-*Dihydro*-2-(3,4-*methylenedioxyphenyl*)-4-*oxoquinoline*-3-*carboxylic Acid*.—The preceding ester (1·5 g.) was boiled under reflux with 40% aqueous-ethanolic sodium hydroxide for 7 hr. The solution, on cooling, was acidified. The *acid* (IV) was collected and crystallised from 2-methoxyethanol as needles (0·9 g.), m. p. 291—292° (Found: C, 65·6; H, 4·0; N, 4·4. $C_{17}H_{11}NO_5$ requires C, 66·0; H, 3·6; N, 4·5%).

2-(3,4-*Methlenedioxyphenyl*)-4-*quinolone*.—The acid (IV) (0·9 g.) was heated in quinoline (5 ml.) containing a little copper powder at 175—180° for 10 min., then allowed to cool. The crystalline *quinolone* (V) (0·7 g.) that separated was collected and recrystallisated three times from ethanol, forming needles, m. p. 290—291° (Found: C, 72·8; H, 4·2; N, 4·8. $C_{16}H_{11}NO_3$ requires C, 72·4; H, 4·2; N, 5·3%).

1-*Methyl*-2-(3,4-*methylenedioxyphenyl*)-4-*quinolone* [*Graveoline* (VI)].—The quinolone (V) (0·7 g.) was treated in methanol (25 ml.) at 60° alternately with potassium hydroxide and drops of methyl sulphate for 1½ hr. The methanol was distilled off and water (250 ml.) was added. Crystals separated, which on recrystallisation from ethanol formed needles, m. p. 204—205° (Kofler block), that did not depress the m. p. of graveoline; its infrared spectrum was identical with that of the natural product (Found: C, 72·4; H, 4·9; N, 5·0. Calc. for $C_{17}H_{13}NO_3$: C, 73·1; H, 4·7; N, 5·0%).

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[6] Cohen, " Practical Organic Chemistry," 3rd Edn., Macmillan and Co. Ltd., London, 1949, p. 236.