The Position of the Aromatic Methoxyl Group in Falcatine

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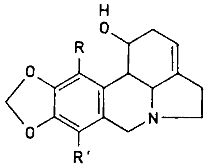
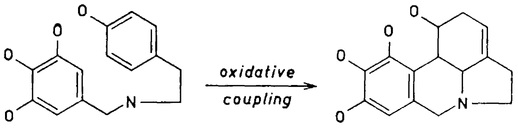
Degradative studies by Wildman *et al.*[1,2] have revealed structures I aor Ib for the alkaloid. The position of the methoxyl is still uncertain. Based on studies of ultra violet spectra of a number of *Amaryllidaceae* alkaloids Warnhoff and Wildman [3] assigned the aromatic methoxyl in undulatine II to position C_{10}. In the biogenetic scheme for the *Amaryllidaceae* alkaloids proposed by Barton and Cohen [4] falcatine and undulatine can be derived from a common precursor III. One would therefore predict that formula Ia is the most probable for falcatine.

From falcatine a degradation product IVa or IVb has been isolated [2]. Synthesis of one of these compounds will give conclusive evidence on the complete structure [5].

Methyl 2-hydroxy-3,4-methylenedioxy benzoate V is easily obtainable according to a recent method by Dallacker [6,7]. Methylation with dimethyl sulphate, hydrolysis and nitration gave VI. The isomeric acid VII seemed to be more difficult to prepare and therefore it was decided to synthesize IVb despite the fact that it was more likely that the other isomer IVa was the one derived from the natural product. The amide VIII, prepared *via* the acid chloride, was reduced catalytically, diazotized and cyclized. Chromatography on alumina of the crude product gave as a

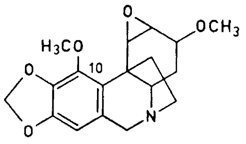


Ia: R = OCH_3; R' = H
Ib: R = H; R' = OCH_3

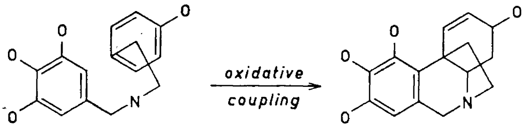


III

Ia

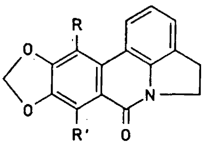


II

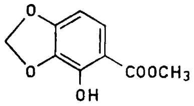


III

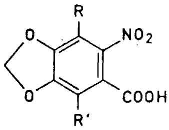
II



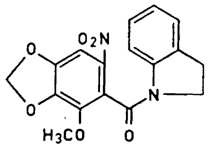
IVa: R = OCH_3; R' = H
IVb: R = H; R' = OCH_3



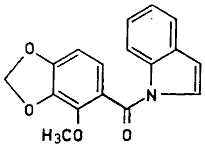
V



VI: R = H; R' = OCH_3
VII: R = OCH_3; R' = H



VIII



IX

first fraction the indole derivative IX and as a second fraction the phenanthridone IVb. Its melting point, 272—274°, differed markedly from the melting point reported in the literature, 198—201°, for the degradation product [2] and its UV spectrum, though essentially the same as the spectrum of the degradation product, showed around 300—350 mμ a slight shift to longer wave lengths (λ_{max} 251, 273 sh, 288 sh, 301 sh, 337 and 350; UV maxima for the degradation product [2]:λ_{max} 256, 273, 300 sh, 332 and 347). The compounds are obviously not identical. The structures Ia and IVa can therefore be assigned to falcatine and its degradation product, respectively. The assignment of the methoxyl in undulatine to C_{10} is further supported by this evidence.

Experimental. 2-Methoxy-3,4-methylenedioxy-6-nitro benzoic acid IV. Methyl 2-hydroxy-3,4-methylenedioxy benzoate [7] V (2.8 g) was dissolved in boiling 6 % sodium hydroxide (50 ml). The solution was cooled to room temperature and dimethyl sulphate (4 ml) was added slowly so that after every addition no unreacted dimethyl sulphate remained. The acid was precipitated with conc. hydrochloric acid, filtered, washed with cold water and dried. The finely divided crude product was added in portions to conc. nitric acid (28 ml) at 5—10° with stirring. 10 min after the last addition the mixture was poured into ice water (130 ml). The precipitate was filtered and crystallized from water-methanol (10:1). Yield 1.2 g. M.p. 190—193° (softening at 184°), lit.[8] 190—92°.

2,3-Dihydro-1-(2-methoxy-3,4-methylenedioxy-6-nitro benzoyl)indole VIII. The acid VI (1.35 g) was dissolved in thionyl chloride (3 ml). The excess was evaporated in vacuum. The yellow oil, which crystallized on cooling, was dissolved in chloroform (10 ml) and slowly added to a stirred water-cooled mixture of chloroform (5 ml), pyridine (0.7 ml) and indoline (1.4 g). After 15 min water was added, the aqueous phase was acidified with hydrochloric acid. The organic layer was separated, dried and the solvent evaporated. The residue was crystallized from ethanol. Yield 1.2 g, m.p. 156—158°. (Found: C 59.45; H 4.30. Calc. for $C_{17}H_{14}O_6N_2$(342.3): C 59.65; H 4.12).

2,3-Dihydro-1-(2-methoxy-3,4-methylenedioxy-6-amino benzoyl) indole. The corresponding nitro compound VIII (0.38 g) was catalytically reduced with Raney-Ni in ethyl acetate. The residue after evaporation of the solvent, was crystallized from ethanol. Yield 0.35 g, m.p. 190—191°. (Found: C 65.35; H 5.38. Calc. for $C_{17}H_{16}O_4N_2$ (312.3): C 65.37; H 5.16).

Pschorr cyclisation of the amine. The amine was cyclized according to the method of Humber *et al.*[9] The chloroform extract from the reaction mixture (0.30 g amine) was chromatographed over alumina. The first fraction (benzene) yielded 60 mg of pale yellow crystals, which proved to be 1-(2-methoxy-3,4-methylenedioxy benzoyl) indole, m.p. 133°, from ethanol, λ_{max} 246, 302 (log ε 3.99, 4.36). (Found: C 69.06; H 4.45; N 4.91. Calc. for $C_{17}H_{13}O_4N$ (295.3): C 69.14; H 4.43; N 4.75). With chloroform-benzene (1:1) a reddish band was eluted, which gave 13 mg of the phenanthridone IVb, m.p. 272—274°, from nitromethane, pale yellow prisms. λ_{max} 251, 273sh, 288sh, 301, 337, 350 (log ε 4.53, 4.23, 3.98. 3.89, 3.85, 3.87). (Found: C 68.50; H 4.27. Calc. for $C_{17}H_{13}O_4N$ (295.3): C 69.14; H 4.43).

Added in proof. Recently Wildman *et al.* (*Tetrahedron Letters* **1961** p. 105) reinvestigated the structure of undulatine. They revised its structure and assigned the methoxyl group to C_7, which is in disagreement with the biogenetic scheme and also with the conclusion drawn above. This prompted us to synthesize the other isomer IVa. Dallacker *et al.* (*Monatsh. Ch.* **91** (1960) 1089) recently prepared the methylester of VII and they very kindly provided us with a sample of this compound. After hydrolysis with aqueous sodium hydroxide it was transformed into IVa according to the methods outlined above for VI. Our compound analyzed correctly for IVa and its physical constants agree excellently with the data reported for the degradation product. M.p. 196—199° (from ethanol-water); λ_{max} 256, 273, 295sh, 332, 347 mμ. Found: C 69.34; H 4.44; Calc. for $C_{17}H_{13}O_4N$ (295.3): C 69.14; H 4.43. It is therefore no doubt that Ia represents the correct structure for falcatine.

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Preparation of Benzonitrile, Isotopically Labelled in the Cyanide Group

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As a pre-requisite for the study of infrared and microwave spectra of benzonitrile(I), species isotopically labelled in the cyanide group were prepared.

$C_6H_5{}^{13}CN$. 2.65 g (0.0134 mole) of commercial $BaCO_3$ (52 % enriched in ^{13}C) was converted to carbon dioxide(II), which was distilled at −80°C for purification. Bromobenzene (2.62 g, 0.0167 mole) was converted to phenylmagnesium bromide and afterwards to benzoic acid (III) by addition of (II), roughly following Ref.[1] For the present purpose it was found useful to omit the prescribed extraction of (III) by ether. The yield of (III), contaminated by a small amount of inorganic substance, was 1.70 g. Refluxing for 3 h of (III) with 13 ml dry benzene and 2.3 ml $SOCl_2$ produced a quantity of benzoyl chloride (IV), mixed with traces of benzene and $SOCl_2$ after its distillation. (IV) was converted to benzamide (V), following the indications by Swan and Kelly [2], but using concentrated ammonium hydroxide in excess instead of NH_4NO_3 and base. Yield 1.02 g (0.0084 mole). The infrared absorption curve showed the substance to be pure. Following Ref.[1], (V) was converted to (I). The problem of removing the last traces of HCl in samples of the present magnitude was solved by pumping off the vapors in equilibrium with the liquid phase at room temperature six times with 2 h intervals after which the vapor pressure became normal. The infrared absorption curve of the undiluted sample showed that it consisted of the expected mixture of 52 % $C_6H_5{}^{13}CN$ and 48 % C_6H_5CN as evidenced by the relative intensity of the bands at 2 180 cm^{-1}($C_6H_5{}^{13}CN$) and at 2 230 cm^{-1}(C_6H_5CN). This disclosed that the weak line observed in non-enriched benzonitrile at 2 180 cm^{-1} is due to the presence of 1 % $C_6H_5{}^{13}CN$. The yield of (I) obtained was 0.566 g (0.0055 mole) or 41 % with respect to the enriched $BaCO_3$ applied.

$C_6H_5C^{15}N$. Following Ref.[2], 720 mg (0.0090 mole) of commercial NH_4NO_3 (33 % enriched in ^{15}N), dissolved in 30 ml of water, was treated with 1.35 g benzoyl chloride (0.0096 mole), dissolved in 70 ml chloroform, and 0.0190 mole of 1 N NaOH aq. for 1 h at room temperature under vigorous shaking. On evaporation of the chloroform layer and the small portions of chloroform used for extraction of the aqueous phase, a residue of 860 mg (0.0071 mole) enriched benzamide (VI) was obtained. The infrared spectrum showed (VI) to be pure. Hence, the suggested extraction by petrol ether is unnecessary, at least for the present purpose. (VI) was converted to ^{15}N-enriched benzonitrile(VII) by the same procedure as above, the yield being 540 mg (0.0052 mole) or 58 % with respect to enriched NH_4NO_3. The infrared absorption curve of the undiluted sample showed it to consist of the expected mixture of 33 % $C_6H_5C^{15}N$ (absorbing at 2 200 cm^{-1}) and 67 % C_6H_5CN (absorbing at 2 230 cm^{-1}). The spectral isotope effect of ^{15}N as compared to ^{13}C in benzonitrile is only 2/3. In natural abundance (1/3 %), ^{15}N in benzonitrile may still give rise to observable absorption at 2 200 cm^{-1}, if sufficient spectroscopic power of resolution is available.

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