Synthesis of Evolitrine, an Alkaloid of Evodia littoralis

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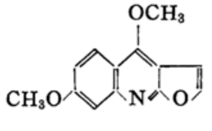
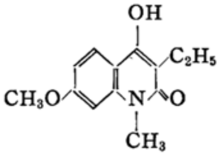
The structure of evolitrine was determined by Cook et al.[1] to be 7-methoxydictamnine (I). The position of the extra methoxyl group was unambigously determined by comparing the degration product II with the product obtained from the reaction between 4-methoxy-2-nitrobenzoyl chloride III and diethyl ethoxymagnesiumethylmalonate, followed by the reduction of nitro group, cyclization and *N*-methylation.



I



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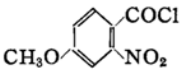
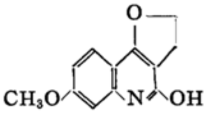


III



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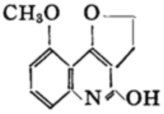

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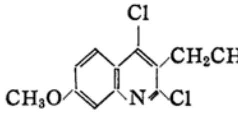
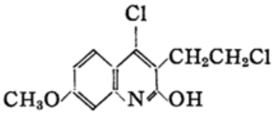


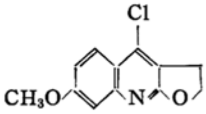
VI

In connection with our spectroscopic study of quinoline derivatives[2], we were obliged to determine which of the two possible products IV or V resulted in fact from the condensation of *m*-anisidine and diethyl β-methoxyethylmalonate. By synthesizing evolitrine starting with this condensation product[3,4] we identified it as IV, thus affirming the structure of evolitrine.

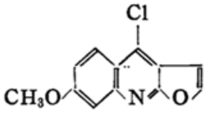
When *m*-anisidine and diethyl β-methoxyethylmalonate were refluxed in diphenyl ether IV was obtained. In search of another possible isomer V, the mother liquor was subjected to repeated purification, but the substance isolated was a small amount of white crystals which had a different and unidentified structure. Treatment of the compound IV with phosphorus oxychloride gave the trichloro derivative VI gave a white solid which was supposed to be a mixture of 2-hydroxy derivative VII and dihydrofuroquinoline derivative VIII in view of the experience gained from our dictamnine synthesis[3]. This mixture afforded the dihydrofuroquinoline derivative VIII on treatment with alkali. When the trichloro derivative VI was hydrolysed with acid according to the method of Grundon[4], the intermediate product VII was isolated, which was also cyclized to VIII by alkali. Treatment of VIII with *N*-bromosuccinimide in the presence of a small amount of benzoyl peroxide, and successive treatment with dimethylaniline afforded the chloro-furoquinoline derivative IX. This was converted by sodium methoxide into evolitrine I. The synthetic evolitrine was shown to be identical with the natural product by comparing their melting points, ultraviolet spectra and melting points of their picrates.



VII



VIII



IX

Experimental

2-Hydroxy-3-(β-chloroethyl)-4-chloro-7-methoxyquinoline (VII).—A mixture of trichloro derivative VI[2] (0.28 g.), 6N-hydrochloric acid (8 cc.) and dioxane (6.5 cc) was heated under reflux for 3 hours. Additon of water gave a white solid which was recrystallized from dilute methanol. m. p. 193°.

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[1] R. G. Cook and H. F. Hyne, *Austral. J. Chem.*, **7**, 273 (1954).

[2] T. Sato and M. Ohta, This Bulletin, **31**, 157 (1958).

[3] T. Sato and M. Ohta, ibid, **30**, 708 (1957).

[4] M. F. Grundon et al., *J. Chem. Soc.*, **1957**, 2177.

Anal. Found: N, 5.24, Calcd. for $C_{12}H_{11}O_2NCl_2$: N, 5.15%.

4-Chloro-7-methoxy-2, 3-dihydrofuro[2, 3-b]quinoline (VIII)—a) To a solution of VII (0.3 g.) of methanol (2 cc.) was added 10% methanolic sodium hydroxide and the solution was kept at 50—60° for 30 min. Addition of water gave a white solid which was recrystallized from dilute methanol m. p. 158°.

Anal. Found: C, 60.63; H, 4.61; N, 5.86. Calcd. for $C_{12}H_{10}O_2NCl$: C, 61.01; H, 4.23; N, 5.94%.

b) A solution of trichloro derivative VI (0.3 g) in glacial acetic acid (3 cc.) was heated under reflux for 1.5 hours. Addition of water gave a white solid which was treated with methanolic sodium hydroxide in the same way as described in a). m. p. and mixed m. p. 158°.

4-Chloro-7-methoxyfuro[2, 3-b]quinoline (IX).—A mixture of dihydrofuroquinoline derivative VIII (0.45 g.), N-bromosuccinimide, (0.45 g) a trace of benzoyl peroxide and carbon tetrachloride (15 cc.) was heated under reflux for 2 hours. Succinimide was filtered off and carbon tetrachloride evaporated in vacuo. The resulting residual oil, after dilution with dimethylaniline (4.5 cc.) was heated under reflux for 3 hours. After cooling the mixture was added to 3N-hydrochloric acid (45 cc.). The solid thus formed was collected, and recrystallized from dilute methanol. m. p. 169°. The compound was a semihydrate.

Anal. Found: C, 59.72; H, 3.71; N, 6.04. Calcd. for $C_{24}H_{18}O_5N_2Cl_2$: C, 59.32; H, 3.71; N, 5.77%.

Evolitrine (I).—To the chloro derivative IX (0.1 g) was added methanolic sodium methoxide (5 cc.), containing sodium (0.15 g). The mixture was heated under reflux for 3 hours, and allowed to stand overnight. Sodium chloride was filtered off and the filtrate, after partial evaporation of methanol, was treated with water. Recrystallization from dilute methanol gave pure evolitrine. m. p. 114°.

Anal. Found: C, 67.70; H, 5.22; N, 6.30. Calcd. for $C_{13}H_{11}O_3N$: C, 68.11; H, 4.84; N, 6.11%.

The ultraviolet spectrum in ethanol was also identical with the reported one. The picrate was prepared and recrystallized from methanol. m. p. 192—4°.

Anal. Found: N, 12.50. Calcd. for $C_{19}H_{14}O_{10}N_4$: N, 12.23%.

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