[CONTRIBUTION FROM THE LABORATORIO DE QUÍMICA ORGÁNICA, FACULTAD DE CIENCIAS EXACTAS, FISICAS Y NATURALES]

STUDIES ON ARGENTINE PLANTS. VII. THE STRUCTURE OF γ-FAGARINE

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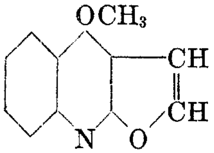
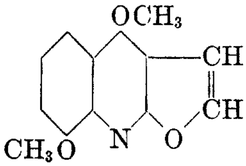
Two of the alkaloids found by Stuckert (1) in *Fagara coco* (Gill) Engl. were shown by Deulofeu, Labriola, and DeLanghe (2) to belong to the class possessing a furoquinoline structure. β-Fagarine was identified as skimmianine (III), which was found by Honda (3) in *Skimmia japonica.* γ-Fagarine yielded on degradation by a method similar to that applied to skimmianine by Asahina and Inubuse (4), a 2,4-dihydroxymethoxyquinoline, which showed γ-fagarine to be a methoxydictamine. Dictamine (I) itself has been found by Thoms (5) in *Dictamus albus* and by Asahina, Ohta, and Inubuse (6) in *Skimmia repens.*

To ascertain the position of the methoxyl group, it was necessary to synthesize the isomeric 2,4-dihydroxymethoxyquinolines. These were prepared by the method of Bischoff (7), by condensation of the chlorides of the isomeric methoxy-*o*-nitrobenzoic acids with ethyl malonate and simultaneous hydrolysis and reduction of the nitro group.

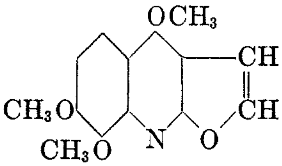
2,4-Dihydroxy-8-methoxyquinoline was found to be identical with that obtained from γ-fagarine. Their 3-nitroso derivatives were also identical, after a discrepancy in the melting point of the one obtained from the alkaloid was corrected by further purification. γ-Fagarine has, then, the structure (II), and it is interesting to point out that it is an intermediate step between dictamine and skimmianine.



I. Dictamine



II. γ-Fagarine



III. Skimmianine

EXPERIMENTAL

Preparation of the four isomeric methoxy-o-nitrobenzoic acids. 2-Methoxy-6-nitrobenzoic acid was prepared according to Buehler, Deebel, and Evans (8). From 25 g. of *m*-nitrocresol, 13–14 g. of the benzyl chloride was obtained in each batch, m.p. 134–140°. From this, 2-methoxy-6-nitrobenzyl chloride was obtained and oxidized to 2-methoxy-6-nitrobenzoic acid. To 4.25 g. of the chloride, dissolved in 125 cc. of water, 8 g. of potassium permanganate and 10 g. of potassium hydroxide were added, and the solution boiled under reflux for 2 hours. In the usual way 3 g. of crude acid was obtained, which melted at 182° after recrystallization from water.

3-Methoxy-2-nitrobenzoic acid was prepared according to Rieche (9), by nitration of *m*-methoxybenzaldehyde and further oxidation to the acid; m.p. 251°.

4-Methoxy-2-nitrobenzoic acid was obtained starting from *p*-toluidine, following the directions of Ullmann and Dootson (10); m.p. 199°.

3-Methoxy-6-nitrobenzoic acid was prepared by oxidation of 3-methoxy-6-nitrotoluene with potassium permanganate, as described by Ullmann and Dootson (10) for the above 4,2-isomer; m.p. 132°.

Preparation of the acid chlorides. The four chlorides were prepared by treating 2 g. of each acid with 20 cc. of thionyl chloride and heating to boiling for 2 hours. After distilling the thionyl chloride in a vacuum the remaining chlorides were employed without further purification. With the exception of the liquid chloride from 3-methoxy-6-nitrobenzoic acid, they were crystalline solids.

Preparation of the 2,4-dihydroxymethoxyquinolines. Two grams of ethyl malonate and the chloride obtained from 2 g. of the acid were dissolved in 40 cc. of anhydrous ether. One and one-half grams of well dried (120°, vacuum) and finely powdered sodium ethoxide was added, some heat being evolved. The suspension was shaken for 30 minutes, 20 cc. of water added, the aqueous layer decanted, and the ether washed twice with the same amount of water. The united water extracts were acidified with hydrochloric acid and extracted with ether. The ether was evaporated and an oily residue consisting of the benzoylmalonate was left.

TABLE I

PROPERTIES OF THE 2,4-DIHYDROXYMETHOXYQUINOLINES AND THEIR NITROSO DERIVATIVES

COMPOUND	M.P., °C	FOUND[a] N %	M.P. NITROSO DERIV., °C.	COLOR NITROSO DERIV.	FOUND[b] N %
2,4-Dihydroxy-5-methoxyquinoline	255–256	7.33	246	brick yellow	12.82
2,4-Dihydroxy-6-methoxyquinoline	318–319	7.59	254	dark red	12.33
2,4-Dihydroxy-7-methoxyquinoline	339–340	7.00	240	yellow	12.32
2,4-Dihydroxy-8-methoxyquinoline	245–246	6.98	227–228	dark red	12.45
From γ-fagarine	249–250	7.50	225–226	dark red	12.62

[a] Calc'd for $C_{10}H_9NO_3$: N, 7.33. [b] Calc'd for $C_{10}H_8N_2O_4$: N, 12.72.

This residue was dissolved in a mixture of 20 cc. of ethanol and 20 cc. of concentrated (*d*, 1.19) hydrochloric acid and 10 g. of tin added. The mixture was left overnight and then boiled under reflux for seven hours. The remaining tin was filtered and the solution evaporated to dryness. Fifty cubic centimeters of cold water was added to the residue and a water-insoluble portion, consisting of a double salt of tin and quinoline collected. It was dissolved in a mixture of 35 cc. of ethanol and 10 cc. of diluted hydrochloric acid (1:10) and the tin removed with hydrogen sulfide. After filtering, the solution was again evaporated to dryness, giving a residue consisting of the expected quinoline.

With the exception of the 2,4-dihydroxy-7-methoxyquinoline, which was very insoluble and had to be purified by recrystallizing from glacial acetic acid, the compounds were recrystallized from 50% ethanol. All four gave fine needles, insoluble in water. Table I gives melting points and analyses.

Nitroso derivatives. The 3-nitroso derivatives of the four synthetic 2,4-dihydroxymethoxyquinolines were prepared by dissolving 100 mg. of the quinoline and 100 mg. of sodium nitrite in 2–3 cc. of 8% aqueous sodium hydroxide solution, and pouring into an excess of cooled 10% sulfuric acid. The insoluble nitroso derivative was then filtered and recrystallized from glacial acetic acid. All were obtained as fine needles of variable color. Table I gives melting points and analyses.

2,4-Dihydroxy-8-methoxyquinoline from γ-fagarine. The degradation was carried out according to the already described method (2). A sample of this quinoline of m.p. 249–250°, mixed with synthetic 2,4-dihydroxy-8-methoxyquinoline of m.p. 245–246° showed the melting point 245–248°. The mixture with 2,4-dihydroxy-5-methoxyquinoline melting at 255–

256° had the m.p. 215–219°. This last quinoline mixed with synthetic 2,4-dihydroxy-8-methoxyquinoline gave the melting point 216–220°.

Nitroso derivative. The nitroso derivative of the natural 2,4-dihydroxy-8-methoxyquinoline melted originally when recrystallized from acetic acid at 216–217° (2). When recrystallized from glacial acetic acid and 50% acetic acid alternately the melting point 225–226° was attained. This sample mixed with the synthetic nitroso derivative melting at 227–228° showed the m.p. 225–227°.

SUMMARY

The 2,4-dihydroxymethoxyquinoline obtained by degradation of γ-fagarine has been shown by synthesis to be 2,4-dihydroxy-8-methoxyquinoline.

This establishes the position of the methoxyl group in γ-fagarine, and completes the determination of structure of this alkaloid.

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