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STUDIES ON ARGENTINE PLANTS. VIII. ON THE CONSTITUTION OF α-FAGARINE

V. DEULOFEU, R. LABRIOLA, AND B. BERINZAGHI

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Of the three major alkaloids isolated by Stuckert (1) from the leaves and young twigs of *Fagara coco* (Gill) Engl., β-fagarine was identified by Deulofeu, Labriola, and De Langhe (2) as identical with skimmianine, and γ-fagarine as a methoxydictamine. Subsequent work by Berinzaghi, Muruzabal, Labriola, and Deulofeu showed that the methoxyl group is in position 8 of the nucleus (3).

α-Fagarine was described by Stuckert (1) as a base melting at 169° of formula $C_{19}H_{22}NO_4$, and was supposed to be identical with a base melting at 163° of formula $C_{19}H_{23}NO_5$ and named Fagarine I, which was isolated by Merck and Co. (Darmstadt, Germany), who carried out a large-scale preparation of the alkaloids of *Fagara coco* at Stuckert's request.

α-Fagarine has the very important pharmacological property of having a higher activity than quinidine in auricular flutter and auricular fibrillation (4).

In our first paper on the *Fagara coco* alkaloids (2), we proposed for α-fagarine the formula $C_{18}H_{21}NO_4$. It possesses two methoxyl groups, one dioxymethylene group, and one methylimino group. Further work has resulted in the preparation of a series of derivatives of this base, whose analyses agree, with the exception of the free base and the hydrochloride, with formula $C_{19}H_{23}NO_4$ that we accept in this paper as representing α-fagarine.

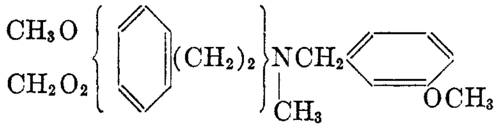
This base has very different properties from the other alkaloids of *Fagara coco.* α-Fagarine can be liberated from its salts only at *p*H 9. It is a tertiary base, does not react with nitrous acid, gives a methiodide, and a series of salts has been prepared. The existence of a dioxymethylene group has been confirmed, as the alkaloid gives a strong Labat's (5) test.

Fagarine can be distilled in a high vacuum without decomposition. It resists reduction by hydrogen at 4 atmospheres with Adams' platinum oxide catalyst and is recovered after treatment with ethanolic sodium hydroxide, with sodium ethoxide, or dilute hydrochloric acid. Heated with soda-lime, it yields methylamine.

Fagarine is oxidized by potassium permanganate in alkaline solution but no crystalline products could be isolated. In acid solution *m*-methoxybenzaldehyde and methanal were produced. Both were isolated and identified as 2,4-dinitrophenylhydrazones.

The production of *m*-methoxybenzaldehyde by oxidation can be interpreted as arising from a group $—CH_2C_6H_4OCH_3$ attached to the nitrogen atom, as no aliphatic double bond appears to be present in the molecule, and the lack of rotatory power excludes the existence of a series of cyclic structures. It follows that the remaining methoxyl and dioxymethylene groups are attached to another benzene ring.

Fagarine could be represented by the provisional structure:



which explains basicity, production of *m*-methoxybenzaldehyde, and lack of rotatory power, and although one is tempted to assign to it the structure of a substituted methylbenzylphenetylamine, further work is necessary to elucidate it in a complete form.

EXPERIMENTAL

The α-fagarine employed in this work was prepared by the acid extraction method described by us (2). Crude α-fagarine is best purified by one crystallization from acetone and recrystallization from ethanol (96%); well dried, it melts at 169–170°. The form with lower melting point described in our former papers contains solvent. Further purification can be carried out by distillation in a high vacuum (0.001 mm.) and at a bath temperature of 170–175°. Melting point of the distilled base, 169–170°.

For analysis, samples dried at constant weight were used (2 mm. vacuum and 120° for five hours).

Anal. Calc'd for $C_{19}H_{23}NO_4$: C, 69.30; H, 6.98; N, 4.25; M. W., 329.

Found: C, 68.39, 68.64; H, 6.26, 6.31; N, 4.33, 4.28; M. W. (11.6 mg. in 107.85 mg. camphor Δ, $-13.5°$), 321.

Dioxymethylene group. Two cubic centimeters of concentrated sulfuric acid was placed in a porcelain dish and 0.1 cc. of 5% ethanolic solution of α-fagarine and 0.1 cc. of 5% gallic acid solution added, and heated in a boiling water-bath. A green color developed that changed to blue. Piperonal was used as a positive control.

Tentative hydrogenation. Two hundred milligrams of base was shaken for two hours at 4 atmospheres pressure, with 50 mg. of Adams' platinum oxide. The base melting at 169–170° was recovered.

Action of alkalies. A small amount of α-fagarine was heated for 6 hours with 5% ethanolic solution of sodium hydroxide at 120°. The base melting at 169° was recovered.

The alkaloid was also recovered when boiled for one hour with absolute ethanol containing 2.5% dissolved sodium.

Action of hydrochloric acid. A small amount of α-fagarine was boiled for 3 hours with dilute hydrochloric acid (1:10) and recovered unchanged.

Hydrochloride. Three hundred milligrams of α-fagarine was suspended in 300 cc. of absolute ethanol and 0.1 cc. of concentrated hydrochloric acid added. The base dissolved, but immediately the hydrochloride crystallized out. Ether was added to complete crystallization and the solid hydrochloride filtered. After recrystallization from 96% ethanol, long prisms melting at 192–193° were obtained.

Anal. Calc'd for $C_{19}H_{23}NO_4 \cdot HCl + 0.5\ H_2O$: C, 60.80; H, 6.66.

Found: C, 60.95; H, 6.59.

Hydrobromide. To 500 mg. of α-fagarine suspended in 1.5 cc. of absolute ethanol, 0.5 cc. of hydrobromic acid (*d.* 1.38) was added. The base dissolved, ether was added to permanent turbidity, and the solution was kept cold until the hydrobromide crystallized out. It was recrystallized from 96% ethanol; long prisms melting at 186–188° (decomp.).

Anal. Calc'd for $C_{19}H_{23}NO_4 \cdot HBr$: C, 55.61; H, 5.85.

Found: C, 55.59; H, 6.20.

Hydriodide. Two hundred twenty-five milligrams of sodium iodide was dissolved in 2 cc. of absolute ethanol, 90 mg. of acetic acid added, and then 330 mg. of α-fagarine. The base dissolved, and after standing, the hydriodide crystallized out. After recrystallization from absolute ethanol, it was obtained as long prisms melting at 190–192° (decomp.).

Anal. Calc'd for $C_{19}H_{23}NO_4 \cdot HI$: C, 49.89; H, 5.25.
Found: C, 49.63; H, 5.30.

Picrate. Three hundred milligrams of α-fagarine dissolved in 5 cc. of absolute ethanol was mixed with 300 mg. of picric acid in 5 cc. of absolute ethanol. The picrate crystallized immediately; by recrystallization from the same solvent, yellow plates melting at 208–209° were obtained.

Anal. Calc'd for $C_{19}H_{23}NO_4 \cdot C_6H_3N_3O_7$: C, 53.76; H, 4.65; N, 10.03.
Found: C, 53.95; H, 4.42; N, 9.82.

Methiodide. Five hundred milligrams of α-fagarine was boiled for three hours with 3 cc. of methyl iodide in 10 cc. of acetone. The methiodide crystallized, and was purified from 96% ethanol; long needles melting at 205° (decomp.).

Anal. Calc'd for $C_{20}H_{26}INO_4$: C, 50.95; H, 5.52.
Found: C, 50.93; H, 5.58.

Oxidation. Characterization of m-methoxybenzaldehyde. Five hundred milligrams of α-fagarine was dissolved in 30 cc. of dilute sulfuric acid (1:1) and at room temperature a solution of 1.3 g. of potassium permanganate in water added slowly. The permanganate was decolorized immediately. When the addition was finished, the resulting solution was distilled with steam and the distillate extracted with ether. On evaporation, the ether left a residue that, treated with a hydrochloric acid solution of 2,4-dinitrophenylhydrazine, gave a crystalline orange precipitate melting at 210°. After recrystallization from acetic acid it melted at 220° and no depression was obtained with an authentic sample of *m*-methoxybenzaldehyde 2,4-dinitrophenylhydrazone that also melted at 220°.

Anal. Calc'd for $C_{14}H_{12}N_4O_5$: C, 53.16; H, 3.79.
Found: C, 53.01; H, 4.00.

Characterization of methanal. By adding a hydrochloric acid solution of 2,4-dinitrophenylhydrazine to the water solution left after the *m*-methoxybenzaldehyde had been extracted with ether, a yellow crystalline precipitate was obtained, which after crystallization from ethanol melted at 165–166° and gave no depression with a pure sample of methanal dinitrophenylhydrazone.

Anal. Calc'd for $C_7H_6N_4O_4$: N, 26.66. Found: N, 26.36.

Action of soda-lime. Characterization of methylamine. Five hundred milligrams of α-fagarine was mixed with an excess of soda-lime and slowly heated. The gases were collected in dilute hydrochloric acid (1:10) and the heating was stopped when no more gases were evolved.

The acid solution was extracted with ether, alkalified, and distilled, collecting the distillate in an ethanolic solution of 2,4-dinitrochlorobenzene (6). On standing, a precipitate appeared, which after recrystallization from ethanol melted at 176°, and gave no depression with a pure sample of 2,4-dinitromethylaniline.

SUMMARY

1. α-Fagarine, one of the major alkaloids of *Fagara coco* (Gill) Engl. has been characterized as a tertiary base and a series of derivatives prepared.

2. Oxidation of α-fagarine with potassium permanganate in acid medium has yielded *m*-methoxybenzaldehyde and methanal.

3. A preliminary structure for α-fagarine is proposed.

Buenos Aires, Argentina

REFERENCES

(1) Stuckert, "Investigaciones del Laboratorio de Química Biológica de Córdoba, Argentina", Vol. I, **1933**, and Vol. II, **1938**.

(2) Deulofeu, Labriola, and De Langhe, *J. Am. Chem. Soc.*, **64**, 2326 (1942).

(3) Berinzaghi, Muruzabal, Labriola, and Deulofeu, *J. Org. Chem.*, **10**, 181 (1945).

(4) Deulofeu, Labriola, Orias Moisset de Españes, and Taquini, *Science*, **102**, 6 (1945); *Ciencia Investig.*, **1**, 527 (1945).

(5) Labat, *Bull. soc. chim. biol.*, **15**, 1344 (1933).

(6) Valton, *J. Chem. Soc.*, 40 (1925).