[CONTRIBUTION FROM THE CATEDRA DE QUIMICA BIOLOGICA, FACULTAD DE CIENCIAS MEDICAS
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STUDIES ON ARGENTINA PLANTS. XIV. N-METHYLISOCORYDINE, A QUATERNARY ALKALOID FROM THE BARK OF *FAGARA COCO* (GILL), ENGL.[1]

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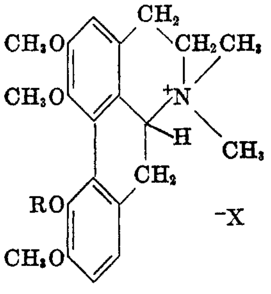
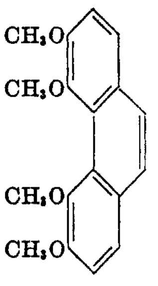
In *Fagara coco* (Gill), Engl., a tree of the Rutaceae family that grows wild in the central and northern part of Argentina, the leaves and twigs contain furoquinoline alkaloids (1) (γ-fagarine and skimmianine); bases of cryptopine type (2, 3) (*allo*cryptopine and fagarine II) besides fagarine III, an alkaloid of unknown structure (2). We have now found that the bark contains, as a major alkaloid N-methylisocorydine (I).

This work was already finished, when the isolation of N-methylisocorydine from the bark of some Australian plants was announced (4). Two of them, *Xanthoxylum brachyacanthum* and *X. veneficum* (F. Muell.) are also Rutaceae (4a) and as in *Fagara coco*, N-methylisocorydine is found together with *allo*cryptopine.

This alkaloid is obviously different from fagaridine, a quaternary base isolated also from *Fagara coco* by Stuckert (1, 5) and Fernández Bua (6). Stuckert (5) described fagaridine chloride as melting at 205–206°, laevorotatory and assigned to it the formula $C_{24}H_{28}NO_4 \cdot HCl$.



I



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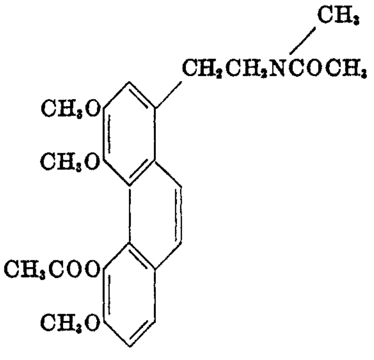

III

The identity of our alkaloid N-methylisocorydine was confirmed:

(a) by degradation to the active methine and reduction of the latter to the dihydroderivative that was found identical to the compounds described by Barger and Sargent (7) as derived from artabotrine, an alkaloid that Schlittler and Huber (8) showed was identical to isocorydine;

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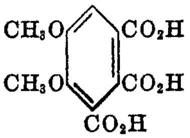
(b) by methylation of N-methylisocorydine to an O-methyl ether, whose chloride was identical to corytuberine dimethyl ether methochloride. By Hoffman degradation of its methiodide, the unknown 3,4,5,6-tetramethoxyphenanthrene was obtained (II).

Two further degradative reactions of N-methylisocorydine were studied. While treatment with acetic anhydride at low temperature afforded the expected O-acetyl derivative, boiling with the same reagent opened, as usual, with aporphine alkaloids, the heterocyclic ring and aromatized the phenanthrene structure forming compound (III). Methyl chloride was eliminated during the reaction.

A similar reaction was described by Robinson and Sugasawa (9) for the product of oxidation of laudanosoline (2,3,9,10-tetrahydroxydibenzo[*b*,*g*]tetrahydropyrrocoline methochloride). When heated with acetic anhydride and pyridine, methyl chloride was eliminated. At room temperature, Schöpf and Thierfelder (10) obtained the tetraacetyl derivative of the quaternary base.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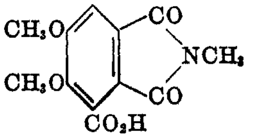
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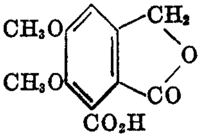
VI

Furthermore, strong permanganate oxidation in mild alkali of N-methylisocorydine, gave 4,5-dimethoxyhemimellitic acid (IV) and one of the methyl imides of this acid, to which we have assigned structure (V) although the position of the methylimino group is arbitrary.

Barger and Sargent (7), by permanganate oxidation of isocorydine (artabotrine in their paper) obtained a monocarboxylic acid lactone, to which structure (VI) was assigned.

EXPERIMENTAL PART

N-Methylisocorydine chloride ($I, R = H, X^- = Cl^-$) *from the bark of Fagara coco.* The bark was dried in an industrial vacuum drier and ground to a coarse powder. This powder was extracted by covering it with 96% ethanol and keeping for a week at room temperature, with occasional agitation. The extraction was repeated three times, the extracts were combined and in portions equivalent to 10 kg. of bark, were evaporated in a vacuum to dryness. Then 700 ml. of water was added and the evaporation was repeated to eliminate all the ethanol. To the viscous dark residue, 4.5 liters of water were added and sufficient hydrochloric acid, to Congo Red acidity (140 ml.). By shaking, the bases passed into solution and an insoluble residue remained, that was reserved for further study.

After keeping for five days in a cold room, thus favoring coagulation of the insoluble particles, the suspension was filtered through a bed of 100 g. of Darco G-60 (charcoal), with the addition of Filter Cel. The filtrate was extracted with ethyl ether (14 times with 250 ml.), no residue being left by the ether in the last extraction.

The solution was carried to *p*H 11 with 10% sodium hydroxide. An insoluble portion appeared and was filtered off. The filtrate then was extracted with small portions of trichloroethylene (250 ml.) until the Mayer reaction in the extract was negative. Two extractions were finally made with 300 ml. each of chloroform. All the small amounts of tertiary bases present in the bark passed into the organic solvents. The water solution was again acidified to *p*H 2, and the volume was made up to 6 liters. To this solution 6 liters of a 5% solution of mercuric chloride in water were slowly added, with agitation. A voluminous yellow precipitate was produced and after one hour, was filtered, drained, and dried in a vacuum desiccator. The yield was 485 g. It was suspended in 4 liters of 96% ethanol, and a current of hydrogen sulfide was passed through the solution, until no yellow spots could be detected in the black precipitate of mercuric sulfide produced.

The suspension was filtered through a bed of 100 g. of Darco mixed with Filter Cel. The filtrate was concentrated in a vacuum to 500 ml. and left overnight in a refrigerator. A small amount of sodium chloride that precipitated was filtered and the filtrate was evaporated to dryness. A dark viscous oil (200 g.) remained; it was crystallized by dissolving in 440 ml. of warm absolute ethanol and cooling. When recrystallized from absolute ethanol, 56 g. of white crystals of N-methylisocorydine chloride, melting at 213–215° were obtained. By evaporation of the mother liquors, further crops were obtained, totaling 86 g. Yield from the bark 0.85%.

N-Methylisocorydine chloride was purified by several crystallizations from absolute ethanol. Product formed prisms, melting at 217–218° (dec. slow heating); 235° (quick heating). $[\alpha]_D^{20°}$ +168.6° (water, *c*, 0.22); $[\alpha]_D^{15°}$ +146.3° (chloroform, *c*, 0.17). It was very soluble in water, moderately soluble in absolute methanol, less in absolute ethanol. Upon warming the product dissolved appreciably in chloroform giving solutions from which it crystallized slowly as fine needles.

Anal. Calc'd for $C_{21}H_{26}ClNO_4$: C, 64.34; H, 6.68; N, 3.60; Cl, 9.04; $3CH_3O$, 23.75; $2CH_3(N)$, 7.67.

Found: C, 64.08; H, 6.78; N, 3.33; Cl, 9.24; CH_3O, 22.75; $CH_3(N)$, 7.24.

N-Methylisocorydine bromide. (I, R = H, $X^- = Br^-$) The chloride (500 mg.) was dissolved in 15 ml. of water and the solution was passed through a column of 1 ml. of Amberlite IRA-400, in the hydroxide state. The effluent (*p*H 11) was neutralized to *p*H 5 with hydrobromic acid. The solution was concentrated to dryness. The white solid residue was recrystallized four times from absolute ethanol. Prisms melting 218° (dec., slow heating) and 232–233° (quick heating); $[\alpha]_D^{17}$ +148.0° (water, *c*, 0.16).

Anal. Calc'd for $C_{21}H_{26}BrNO_4$: C, 57.80; H, 6.01; Br, 18.32; $3CH_3O$, 21.33; $2CH_3(N)$, 6.88.

Found: C, 57.82; H, 6.35; Br, 19.19; CH_3O, 21.94; $CH_3(N)$, 4.85.

N-Methylisocorydine iodide (I, R = H, $X^- = I^-$) The chloride (250 mg.) was dissolved in 2 ml. of water and 100 mg. of solid sodium iodide was added, when a crystalline precipitate was formed. It was recrystallized from water. Prisms, m.p. 219° (dec., slow-heating); 231–232° (quick heating); $[\alpha]_D^{28}$ +139.9° (water, *c*, 0.18), λ_{max}: 2700 Å (log ε, 4.161) and 3025 Å (log ε, 3.805). Gadamer (11) gives m.p. 224–225° $(\alpha)_D$ + 143.5° (water).

Anal. Calc'd for $C_{21}H_{26}INO_4$: C, 52.18; H, 5.42; N, 2.90; I, 26.25; $3CH_3O$, 19.28; $2CH_3(N)$, 6.22.

Found: C, 52.96; H, 5.54; N, 3.29; I, 27.70; CH_3O, 19.75; $CH_3(N)$, 4.76.

This compound was found identical with two samples of isocorydine methiodide, kindly supplied by Dr. Manske (Guelph, Ontario) and Dr. L. Marion (Ottawa), m.p. 222°, showing no depression with the iodide of the alkaloid from *Fagara coco.* Ultraviolet and infrared spectra were identical.

Picrate. To 500 mg. of the chloride dissolved in 15 ml. of water, 200 mg. of sodium carbonate was added and dissolved. An addition of 400 mg. of picric acid then was made to the clear solution. A precipitate was formed. The suspension was heated to boiling, cooled, and filtered. The collected precipitate was suspended in 10 ml. of water, 100 mg. of sodium carbonate was added, heated again to boiling, cooled, filtered and well washed with water. The crude picrate was recrystallized from 96% ethanol, when long prismatic needles melting at 202–204° were obtained; $[\alpha]_D^{31}$ +90.9°, (acetone, *c*, 0.78).

Anal. Calc'd for $C_{21}H_{26}NO_4 \cdot C_6H_2N_3O_7$: C, 55.47; H, 4.83; N, 9.58; $3CH_3O$, 15.93; $2CH_3(N)$, 5.14; N basic, 2.37.

Found: C, 55.93; H, 4.83; N, 9.54; CH_3O, 14.85; $CH_3(N)$, 4.75; N basic, 2.51.

Color reactions of N-methylisocorydine chloride. Concentrated nitric acid produced a red-brown color. A concentrated solution reduced gold chloride. Frohde's reagent gave a blue color that turned green; Mandelin's a dark brown that turned violet; Marquis's a green color that turned green-brown, and Erdman's a stable red color. Pellagri's reaction (12) was negative.

Isocorydine methine and dihydroisocorydine methine. The methine was prepared according to Barger and Sargent (7) m.p. 124–124.5°; $[\alpha]_D^{28}$ −194.6° (absolute ethanol). Reduced with Adams platinum oxide, the *dihydroderivative* was obtained, m.p. 81–82°; $[\alpha]_D^{26}$ −224.5° (Barger and Sargent gives m.p. 122–123°; $[\alpha]_D^{18}$ −183° for the methine and m.p. 80–81° for the dihydroderivative).

O-Methyl-N-methylisocorydine chloride (I, R = CH_3, $X^- = Cl^-$). N-methylisocorydine chloride (1.5 g.) was dissolved in 7.5 ml. of methanol and an ethereal solution of diazomethane was added to a permanent yellow color. After remaining 12 hours in the cold room, ethyl ether was added to permanent turbidity and again the mixture was left in the cold room. Next day 560 mg. of a crystalline precipitate was collected and purified by recrystallization from ethanol and ethanol-ether. Needles, melting 230–232° (slow heating); 258° (quick heating); $[\alpha]_D^{20}$ +198.3° (water, *c*, 0.06). Gadamer (13) gives m.p. 234–237°; $[\alpha]_D^{20}$ +197.4°.

Anal. Calc'd for $C_{22}H_{28}ClNO_4$: C, 65.02; H, 6.65; N, 3.44; $4CH_3O$, 30.54; $2CH_3(N)$, 7.38.

Found: C, 65.13; H, 6.77; N, 3.48; CH_3O, 30.00; $CH_3(N)$, 6.16.

Hoffman degradation of O-methyl-N-methylisocorydine iodide. (I, R = CH_3, $X^- = I^-$) This procedure was carried out following Gadamer (13). An easy separation of the methines was obtained by chromatography on aluminium oxide. Benzene-chloroform (9:1) eluted a first fluorescent band that contained the active methine. Rectangular plates from 50% ethanol, m.p. 75–76°. Cooke and Haynes (4c) give m.p. 75–76°. *Methiodide:* prisms from ethanol, sintering from 165°, m.p. 280°; $[\alpha]_D^{20}$ −210.4° (*c*, 0.09, ethanol). Gadamer (13) gave m.p. above 260° and no rotation was reported.

Chloroform eluted a second fluorescent band and by evaporation the inactive methine was obtained as an oil. Its methiodide crystallized from ethanol, as needles, m.p. 280°. Cannon, *et al.* (4a), give m.p. 278–280°. For the next Hoffman degradation, the methines were transformed without separation into methiodides. The crude 3,4,5,6-tetramethoxy-1-vinylphenanthrene was oxidized to 3,4,5,6-tetramethoxyphenenthrene-1-carboxylic acid, m.p. 165–166° (quick heating). Gadamer (13) gives m.p. 154–167°, according to the rate of heating.

3,4,5,6-Tetramethoxyphenanthrene (II). One gram of the former acid was mixed with 3 g. of Adkins copper-chromite catalyst, 10 ml. of quinoline was added, and the whole was boiled for three hours.

After cooling, 15 ml. ethyl ether was added and the suspension was filtered. The ether filtrate was collected separatedly and the solid remaining in the funnel was well washed with 10% hydrochloride acid. The ether filtrate was washed with hydrochloric acid, 5% sodium hydroxide, and water. The acid filtrate was extracted with ether and the ether extracts were combined with the washed ether filtrate.

After drying, the combined ether solutions gave 586 mg. of a crystalline residue, that after four crystallizations from methanol (Darco) gave prisms, melting at 114–115.5°.

Anal. Calc'd for $C_{18}H_{18}O_4$: C, 72.48; H, 6.05; $4CH_3O$, 41.60.

Found: C, 72.55; H, 5.99; CH_3O, 40.60.

O-Acetyl-N-methylisocorydine iodide. To 250 mg. of N-methylisocorydine chloride, 10 ml. of acetic anhydride and 0.25 ml. of dried pyridine were added with occasional shaking. The suspension was left at room temperature overnight and next morning the chloride had dissolved. The solution was evaporated at room temperature in a vacuum desiccator, when a white solid melting at 246° was obtained. This was dissolved in 2 ml. water, some insoluble particles were filtered, and solid sodium iodide was added to the solution. A crystalline precipitate was produced that was filtered and recrystallized five times from water. Prisms melting 260–265°; $[\alpha]_D^{28}$ +112.6° (water, *c*, 0.06).

Anal. Calc'd for $C_{23}H_{28}INO_5$: C, 52.57; H, 5.37; N, 2.67; I, 24.14; $3CH_3O$, 17.71; $2CH_3(N)$, 5.72; CH_3CO, 11.24.

Found: C, 52.85; H, 5.59; N, 2.95; I, 24.97; CH_3O, 15.27; $CH_3(N)$, 5.91; CH_3CO, 10.11.

β-[4-Acetoxy-3,5,6-trimethoxy phenanthryl-8]-N,N'-acetylmethylethylamine (III). One gram of N-methylisocorydine chloride was suspended in 20 ml. of acetic anhydride and boiled for four hours. The salt dissolved during the first 20 minutes and the solution turned brown slowly. Then it was concentrated in a desiccator to 6 ml. and poured into 100 ml. of ice water. The oily precipitate crystallized easily. It was filtered (220 mg.) and recrystallized once from benzene-petroleum ether and six times from 25% ethanol. Needles melting 165°; $[\alpha]_D^{15}$ ±0° (ethanol, *c*, 0.10).

Anal. Calc'd for $C_{24}H_{27}NO_6$: C, 67.75; H, 6.40; N, 3.29; $3CH_3O$, 21.88; $CH_3(N)$, 3.56; $2CH_3CO$, 20.20.

Found: C, 67.56; H, 6.04; N, 3.96; CH_3O, 22.64; $CH_3(N)$, 2.49; CH_3CO, 21.22.

Permanganate oxidation of N-methylisocorydine chloride. Methylimide of 4,5-dimethoxybenzene-1,2,3-tricarboxylic acid (V). Two grams of N-methylisocorydine chloride were dissolved in 50 ml. of water and solid potassium carbonate was added to alkalinity. The solution was heated to boiling and a 5% solution of potassium permanganate in water was added slowly, until the color persisted for 15 minutes (320 ml.).

The excess permanganate was destroyed by adding ethanol and the precipitated manganese dioxide was dissolved by passing in sulfur dioxide. The resulting solution was concentrated to 100 ml. and an inorganic precipitate that appeared was filtered and discarded. The filtrate was acidified to Congo Red with hydrochloric acid and was extracted with ethyl ether, in a continuous extractor, for 72 hours.

The ether extract was dried with sodium sulfate and evaporated. The residue (780 mg.) was dissolved in absolute ethanol when crystallization took place. Recrystallization from ethanol yielded needles, melting 208–209°. The could be sublimed in a vacuum without decomposition.

Anal. Calc'd for $C_{12}H_{11}NO_6$: C, 54.34; H, 4.18; N, 5.28; $2CH_3O$, 23.40; $1CH_3(N)$, 5.66. Equivalent weight, 255.

Found: C, 54.57; H, 4.21; N, 4.62; CH_3O, 19.24; $CH_3(N)$, 4.46. Equivalent weight, 265.

4,5-Dimethoxybenzene-1,2,3-tricarboxylic acid (IV). The ethanolic mother liquors of crystallization of the methylimide (V) were made alkaline by adding 25 ml. of 10% ethanolic potassium hydroxide solution; 10 ml. of water was added and the solution was boiled for five hours. After boiling, 40 ml. of water was added, the ethanol was evaporated, and the solution was acidified with 5 ml. of concentrated hydrochloric acid and extracted with ether during 24 hours. The dried ether was evaporated to dryness and the solid residue was ground with 10 ml. of anhydrous ethyl ether. After cooling, it was filtered and 100 mg. of a white solid melting at 164° was collected; after cooling this solidified and melted again at 170° (anhydride).

The crude acid was transformed into its methyl ester by treatment with diazomethane. The ester was purified by sublimation at 70° (bath temperature) and 0.005 mm. pressure and was recrystallized from ethyl ether-petroleum ether. It melted at 85–86.5°. Faltis and Kloiter (15) give m.p. 162° for the acid and 86–87° for the trimethyl ester.

Anal. Calc'd for $C_{14}H_{16}O_8$: C, 53.84; H, 5.16.

Found: C, 53.90; H, 5.10.

The same ester, melting at 82–83° and giving no depression with the ester prepared by treatment of the mother liquors, was obtained by alkaline hydrolisis of the imide.

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SUMMARY

N-Methylisocorydine has been isolated from the bark of *Fagara coco* (Gill), Engl.

Different degradation and oxidation reactions of the base have been studied in detail.

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BIBLIOGRAPHY

(1) STUCKERT, *Investigaciones Lab. Quimica Biológica*, Vol. I, Córdoba, 1933; DEULOFEU, LABRIOLA, AND DE LANGHE, *J. Am. Chem. Soc.*, **64**, 2326 (1942).
(2) REDEMANN, WISEGARVER, AND ALLES, *J. Am. Chem. Soc.*, **71**, 1030 (1949).
(3) DEULOFEU, LABRIOLA, AND BERINZAGHI, *Anales asoc. quím. argentina*, **37**, 268 (1949).
(4) (a) CANNON, HUGHES, RITCHIE, AND TAYLOR, *Australian J. Chem.*, **6**, 86 (1953);
(b) HUGHES, KAISER, MATHESON, AND RITCHIE, *Australian J. Chem.*, **6**, 90 (1953);
(c) COOKE, AND HAYMES, *Australian J. Chem.*, **7**, 99 (1954).
(5) STUCKERT, *Investigaciones Lab. Química Biológica*, Vol. II, Córdoba, 1938.
(6) FERNANDEZ BUA, *El alcaloide de la corteza Fagara coco.* La Fagaridina. Córdoba, 1933.
(7) BARGER AND SARGENT, *J. Chem. Soc.*, 991 (1939).
(8) SCHLITTLER AND HUBER, *Helv. Chim. Acta*, **35**, 111 (1952).
(9) ROBINSON AND SUGASAWA, *J. Chem. Soc.*, 789 (1932).
(10) SCHÖPF AND THIERFELDER, *Ann.*, **497**, 22 (1932).
(11) GADAMER. *Arch. Pharm.*, **249**, 669 (1911).
(12) PELLAGRI, *Gazz. chim. ital.*, **7**, 297 (1877).
(13) GADAMER, *Arch. Pharm.*, **249**, 641 (1911).
(14) SPÄTH AND HROMATKA, *Ber.*, **61**, 1692 (1928).
(15) FALTIS AND KLOITER, *Ber.*, **62**, 1041 (1929).