Calcutta, for the microanalyses and Prof. T. R. Govindachari, Presidency College, Madras, for the infrared spectra.

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Hawaiian Plant Studies. VIII.[1] Isolation of Chelerythrine and Dihydrochelerythrine from *Fagara semiarticulata*

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Fagara semiarticulata is an endemic Hawaiian rutaceous shrub. Its range is confined to the Koolau mountains on the island of Oahu and it was found to be rich in alkaloids.[2] The hexane extract of the root and trunk bark gave a positive test with Mayer's reagent; after removal of waxy material and of two neutral solids it was treated with 2% hydrochloric acid. A mixture of yellow salts formed at the interface during the extraction. The two major components of this mixture were identified as chelerythrine and dihydrochelerythrine chlorides.

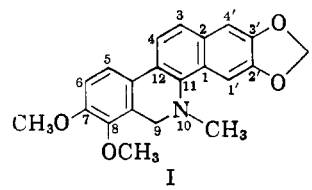
The free dihydro base could be isolated by dissolving and filtering the hot aqueous solution of chlorides. The weak dihydro base was hydrolyzed under these conditions and precipitated. It was recrystallized from methanol as colorless platelets, m.p. 161–165°. Addition of dilute nitric acid to the aqueous filtrate precipitated chelerythrine nitrate as a yellow amorphous solid. It was purified by crystallization from dilute nitric acid and absolute ethanol, m.p. 240°. Zinc-hydrochloric acid reduction of chelerythrine nitrate furnished dihydrochelerythrine, m.p. 160–162°, identical with the compound isolated from the plant. The dihydro plant base in turn, could be oxidized with mercuric acetate and the nitrate of the oxidation product was identical with our chelerythrine nitrate.

Analytical and ultraviolet spectral data indicated that the principal base was a naphthaphenanthridine alkaloid and its identity with chelerythrine was established as follows. A 9-ethyl ether of the free base, m.p. 239–242°, could be prepared by shaking a suspension of the nitrate in chloroform with ammonia and crystallizing the crude base from ethanol; and a pseudocyanide, m.p. 229–233°, by treatment of the free base in a solution of chloroform and methanol with aqueous potassium cyanide. Preparation of the 9-oxo compound, which is reported to proceed with ease in the case of chelerythrine[3] as well as sanguinarine,[4] was finally achieved, albeit in small yield, by heating at elevated temperature with alkaline ferricyanide, m.p. 199–201°.

The dioxymethylene ring of the dihydro base was cleaved with aluminum chloride in boiling benzene. The crude phenolic product upon treatment with diazomethane and purification yielded a product, m.p. 183–186°, in good agreement with the reported melting point range[5] of 182–192° for 7,8,2′,3′-tetramethoxy-9,10-dihydro-10-methyl-1,2-benzophenanthridine.

Finally, pyrolysis of our chelerythrine nitrate or chloride *in vacuo* furnished an *N*-norbase, m.p. 221–222°, which had an ultraviolet spectrum and Rf-value identical with those reported in the literature[6] for *N*-norchelerythrine. Mixture melting point of our norbase and an authentic sample obtained from Bailey[7] was undepressed.

Chelerythrine is of rather widespread occurrence in *Papaveraceae*.[8] It has been isolated as a minor constituent of several rutaceous plants, *Xanthoxylum rhetsa*,[9] *Zanthoxylum brachyacanthum*,[10] *Z. veneficum*[10] and *Toddalia aculeata*.[3] To our knowledge, this is the first instance of the isolation of dihydrochelerythrine. (I).



I

EXPERIMENTAL[11]

Isolation of chelerythrine nitrate and dihydrochelerythrine. The dried and ground bark (15.3 kg.) of the shrub *Fagara semiarticulata* was thoroughly extracted with hexane (9 l.,

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(5) A. S. Bailey, R. Robinson, and R. S. Staunton, *J. Chem. Soc.*, 2277 (1950).

(6) A. S. Bailey and C. R. Worthing, *J. Chem. Soc.*, 4535 (1956).

(7) We should like to thank Dr. A. S. Bailey for this comparison sample.

(8) R. H. F. Manske in *The Alkaloids*, Vol. IV, R. H. F. Manske and H. L. Holmes, eds., Academic Press, New York, 1954, p. 253.

(9) A. Chatterjee, S. Bose, and C. Ghosh, *Tetrahedron*, **7**, 257 (1959).

(10) J. R. Cannon, G. K. Hughes, E. Ritchie, and W. C. Taylor, *Australian J. Chem.*, **6**, 86 (1953).

(11) All melting points were determined on a Kofler hot stage and are uncorrected. Infrared spectra were taken in potassium bromide on a Beckman IR-5 double-beam instrument. Analyses were performed by Dr. A. Bernhardt, Mülheim, Germany. All paper chromatograms were run on Whatman #1 paper in a system of n-butanol:water:acetic acid/63:27:10 by volume, which was equilibrated at room temperature for 48 hr. before use. The spots were visualized under long wave length ultraviolet light.

30 hr.), and the hexane extract concentrated to 4 l. and treated with 2% hydrochloric acid (2 × 2 l.). A mixture of chloride salts, precipitated at the hexane-acid interface, was isolated and extracted in a Soxhlet with carbon tetrachloride. An amount of the solid (2.1 g.) thus freed of waxy impurities was treated with hot water and filtered with suction. To the filtrate was added 6N nitric acid, precipitating chelerythrine nitrate (1.5 g.), which was recrystallized first from dilute nitric acid then from absolute ethanol to give a yellow salt, m.p. 240°, which showed a bright yellow fluorescence under ultraviolet light. Chelerythrine nitrate was also prepared from an authentic sample of cherlerythrine chloride,[12] m.p. 238°. A mixture melting point of both preparations of nitrate salts was undepressed.

Anal. Calcd. for $C_{21}H_{18}O_4N \cdot NO_3$: C, 61.46; H, 4.42; N, 6.83. Found: C, 61.13, 61.09; H, 4.70, 4.79; N, 6.67, 6.67.

The water-insoluble portion, a buff colored solid which contained dihydrochelerythrine, was dried (0.63 g.), ground with ether and filtered. Treatment with ether was repeated a number of times. The washes were combined and removal of the ether left a white solid which was recrystallized from methanol to give platelets of dihydrochelerythrine, m.p. 160–165°. Reported m.p. 167°.[3]

Anal. Calcd. for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48. Found: C, 72.10, 71.93; H, 5.56, 5.56.

Dihydrochelerythrine was prepared from chelerythrine nitrate by treatment with zinc dust and dilute hydrochloric acid in the usual manner.[13] The product was recrystallized from ethanol, m.p. 160–162°. Its infrared spectrum was identical with that of dihydrochelerythrine.

Anal. Calcd. for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48. Found: C, 72.68, 72.77; H, 5.59, 5.63.

Chelerythrine nitrate from dihydrochelerythrine. To a hot solution of dihydrochelerythrine (100 mg.) in 50% aqueous acetic acid (12 ml.) was added 0.5 g. of mercuric acetate. The mixture was heated on a boiling water bath for 2 hr., and the precipitated mercurous acetate was removed from the cooled reaction mixture by filtration. The filtrate was treated with hydrogen sulfide, filtered over Celite, and evaporated to dryness under vacuum. The residue, a dark brown liquid, was repeatedly treated with methanol and evaporated to dryness. The buff colored solid which formed, m.p. 240°, was crystallized once from ethanol then from dilute nitric acid to give a salt having an infrared spectrum and melting point identical with that of chelerythrine nitrate.

9-Ethoxychelerythrine was prepared by shaking a chloroform suspension of chelerythrine nitrate (107 mg.) in a separatory funnel with ammonia (10 ml.). The chloroform solution was dried over anhydrous sodium sulfate, filtered, and evaporated to dryness under vacuum. Repeated treatment of the residual oil with methanol and evaporating the solution to dryness produced a yellow-brown solid, which was recrystallized several times from absolute ethanol to give fine white crystals of 9-ethoxychelerythrine, m.p. 239–242°. R_f = 0.72.[11]

Anal. Calcd. for $C_{21}H_{18}NO_4 \cdot OC_2H_5$: C, 70.21; H, 5.89. Found: C, 70.78, 70.90; H, 5.87, 5.92.

An authentic sample of chelerythrine nitrate, m.p. 238°, prepared from chelerythrine chloride,[14] was treated in the manner described above. The base obtained was identical with our 9-ethoxychelerythrine, R_f = .72,[11] m.p. 233–236° mixture m.p. 234–236°.

This compound has a complex melting point, which apparently has not previously been noted in the literature. There is an initial fusion and resolidification which occurs between 175–200°, followed by a final melting at the higher temperatures reported.

Chelerythrine pseudocyanide. A solution in which 9-ethoxychelerythrine was barely dissolved in chloroform was diluted with methanol and heated. To the warmed solution was added aqueous potassium cyanide, and the mixture was boiled for 15 min. Methanol and chloroform were removed under vacuum, and the aqueous solution filtered. The collected solid was washed with dilute acid, dried and recrystallized from acetone to give the white pseudocyanide, m.p. 229–233°. Reported m.p. 248°.[13]

Anal. Calcd. for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85. Found: C, 70.22, 70.26; H, 5.21, 5.08.

9-Oxochelerythrine. To chelerythrine nitrate (121 mg.) in boiling water (10 ml.) was added a warm solution of potassium ferricyanide (400 mg.) in 2% aqueous potassium hydroxide (10 ml.). The mixture was heated under reflux for 4 hr., cooled and filtered. The solid was dried (70 mg.), dissolved in ethanol, and the inorganic contaminant removed by filtration. From the filtrate was obtained 45 mg. of a solid. This was treated with 1% hydrochloric acid on a hot water bath for 4 hr. The crude acid-insoluble 9-oxochelerythrine (26 mg.) was collected, dried, and crystallized from methanol, m.p. 199–201°. Reported m.p. 199°.[3]

7,8,2′,3′-Tetramethoxy-9,10-dihydro-10-methyl-1,2-benzophenanthridine from dihydrochelerythrine. Dihydrochelerythrine (60 mg.) in anhydrous benzene (15 ml.) was heated under reflux with 0.6 g. of aluminum chloride for 8 hr. The ice-cooled reaction mixture was acidified with 6N hydrochloric acid, and the crude phenolic product was isolated by filtration (52 mg.). This gave a purple color with aqueous ferric chloride, and was unstable to base. It was not further purified, but was treated directly with an excess of diazomethane in ether for 12 hr. Removal of the ether left a mixture of solids, which was separated into an ether-soluble yellow glass and a red insoluble powder by repeated stirring with small amounts of ether and filtering. Neither substance gave any color with ferric chloride. The ether soluble compound was purified by sublimation at 210°/10^{-3} mm. Crystallization of the sublimate from methanol yielded fine white needles of 7,8,2′,3′-tetramethoxy-9,10-dihydro-10-methyl-1,2-benzophenanthridine, m.p. 183–186°. Reported m.p. 183.5–185°.[5]

N-Norchelerythrine. Chelerythrine nitrate (41.7 mg.) was pyrolyzed at 240°/10^{-3} mm. in a sublimation apparatus. The crude solid (23.4 mg.) which collected on the cold finger was crystallized twice from pyridine-methanol to give 10.7 mg. of *N*-norchelerythrine, m.p. 221.5–222.5°, R_f = 0.88.[11] Reported m.p. 212–214°,[6] R_f = 0.87.[6,14] Its ultraviolet spectrum was identical with that reproduced in the literature,[6] and a mixture melting point with an authentic sample of *N*-norchelerythrine,[7] m.p. 220–222°, showed no depression.

Anal. Calcd. for $C_{20}H_{15}NO_4$: C, 72.06; H, 4.54. Found: C, 71.77, 71.77; H, 4.68, 4.72.

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(12) We should like to thank Dr. R. H. F. Manske for this sample.

(13) P. Karrer, *Ber.*, **50**, 212 (1917).

(14) These reported R_f values were obtained in a system of *n*-butyl alcohol:acetic acid:water/4:1:5 by volume. There is no difference between this and the system described in footnote 11; the latter is merely more economically prepared, *cf.* P. N. Campbell, B. Wock, and E. Mellanby, *Biochem. J.*, **48**, 109 (1951).