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Isolation of a Tetramethoxylated Alkaloid from Demerara Greenheart

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The alkaloids in the bark of Demerara greenheart have been investigated. Following treatment with methyl iodide, mixed amorphous alkaloids from the bark yielded a crystalline compound. Chemical and physical properties of the latter, which was also characterized as its chloride and picrate, as well as by an O-methyl derivative, led to a tentative formula of $[C_{32}H_{25}O\{N(CH_3)_2\}_2(OCH_3)_4OH]^{++}I_2^{-}$. This new alkaloid derivative is named rodiasine dimethiodide.

The resistance of the tropical wood Demerara greenheart (*Ocotea rodiaei*)[2] to infection by molluscan and crustacean marine borers has been attributed[3] for some time to the presence in greenheart of the alkaloid bebeerine. Barger and Harrington[4] impregnated Baltic fir with an alcoholic extract of greenheart and found the treated wood superior to untreated controls. In 1922, Barger[5] reported the isolation from greenheart sawdust of an alkaloid "corresponding to bebeerine," which had been previously isolated from bark. The material was described as resinous and easily oxidized. Baldwin[6] attributes the resistance of greenheart to bebeerine, resinous tyloses and the texture of the wood. Van Iterson[7] in his studies of the resistance of greenheart to *Teredo* reported the presence, in extracts from greenheart, of material which inhibits bacterial growth. In addition, Howard[8] has commented on the general belief that greenheart is toxic and notes that workmen are very careful not to get splinters into their hands.

The early studies of Maclagan[9,10] point to the occurrence in greenheart of a number of alkaloids. The latter findings together with the paucity of information on precursors of bebeerine gave impetus to our investigation of greenheart alkaloids.

Greenheart bark from two different sources was extracted with acid, and the non-quaternary alkaloids were precipitated with alkali. An amorphous material was obtained which had the superficial characteristics of a bebeerine as described by Von Planta.[11]

In view of unrefuted claims of purity by Von Planta, who gave few details, other than a melting point 180°, and no optical rotation, and other existing claims that actual compounds had been obtained[11a,b] our material was characterized by analysis and optical rotation. The high methoxyl value of the product was clearly not that expected for the empirical formula of bebeerine, $C_{34}H_{32}O_4N_2(OCH_3)_2$. This, plus other factors, led to a careful consideration of the early literature in which bebeerine is mentioned.

Faltis and Neumann[12] have suggested that on etymological grounds the term bebeerine be used only for material derived from greenheart. These authors suggested that chondodendrine be used for the compound (commonly called "bebeerine") which in well-defined form is obtained from the *Chondrodendron* species. Unfortunately this suggestion has met little acceptance. Bebeerine has been continued as a term for the compound[13-16] which is called chondrodendrine and chonododendrine. A wide variety of other usage serves to complicate the matter. Bebeerine is defined[17] as an amorphous alkaloid obtained from the bark of the bebeeru (*Nectandra rodioei*). Commercial bebeerine is described[17] as a mixture of alkaloids which includes α-bebeerine, β-bebeerine, etc. Merck Index[18] defines bebeerine hydrochloride as the total alkaloids from the root of *Chondrodendron* spp. Henry[19] states that bebeerine has been described under various names: pelosine, chondrodendrine, chondodendrine and curine (for the *l*-form). Faltis and Neumann[12] have rejected the assertion of Flückiger,[20] who used the term bibirine,

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[2] Demerara greenheart in common usage is called greenheart. The systematic name *Ocotea rodiaei*,[2a] sometimes spelled *Ocotea rodioei*, is often given as *Nectandra rodioei*. Professor F. F. Wangaard of the Yale School of Forestry has informed us that there is little question concerning the correctness of the first named designation. The principal native names of the wood are given as bibiru and sipiri.[2b] A number of other woods,[2b-c] including *Tecoma leucoxylon* ("Surinam greenheart") on occasion enter the market as greenheart. Purveyors of Demerara greenheart refer to their commodity as the genuine greenheart; (a) D. B. Fanshawe, *Tropical Woods*, **92**, 25 (1947); (b) W. D. Brush, "Greenheart," Foreign Woods Series, U. S. Dept. of Agriculture, Washington, D. C., 1944; (c) D. A. Kribs, "Commercial Foreign Woods on the American Market," State College, Penna., 1950.

[3] W. G. Atwood and A. A. Johnson, "Marine Structures, Their Deterioration and Preservation," National Research Council, Washington, D. C., 1924, p. 85.

[4] G. Barger, in "Fourth (interim) Report of the Committee of the Institution of Civil Engineers," London, 1924, p. 25.

[5] G. Barger, in "Second (interim) Report of the Committee of the Institution of Civil Engineers," London, 1922, p. 33.

[6] C. E. Baldwin, *Dock and Harbour Authority*, **17**, 112 (1938).

[7] G. Van Iterson, Jr., *Proc. Fifth Pacific Sci. Congr., Canada*, 1933, **5**, 3907 (1934).

[8] A. L. Howard, "A Manual of Timbers of the World," The MacMillan Co., London, 1920.

[9] D. Maclagan, *Ann.*, **48**, 106 (1843).

[10] D. Maclagan and A. Gamgee, *Pharm. J.*, (ii) **11**, 19 (1869-1870).

[11] A. Von Planta, *Ann.*, **77**, 333 (1851).

[11] (a) D. Maclagan and T. G. Tilley, *J. prakt. Chem.*, **37**, 247 (1846); (b) *Ann.*, **55**, 105 (1845).

[12] F. Faltis and F. Neumann, *Monatsh.*, **42**, 311 (1921).

[13] M. Kulka, "Bisbenzylisoquinoline Alkaloids," in R. H. F. Manske and H. L. Holmes, "The Alkaloids," Vol. IV, Academic Press, Inc., New York, N. Y., 1954.

[14] F. A. L. Anet, G. K. Hughes and E. Ritchie, *Australian J. Sci. Research*, **3A**, 346 (1950).

[15] J. D. Dutcher, THIS JOURNAL, **68**, 419 (1946).

[16] H. King, *J. Chem. Soc.*, 1276 (1936).

[17] W. A. Neilson, editor, "Webster's New International Dictionary of the English Language," 2nd edition, G. and C. Merriam Co., Springfield, Mass., 1948.

[18] "The Merck Index of Chemicals and Drugs," 6th edition, Merck and Co., Rahway, N. J., 1952.

[19] T. A. Henry, "The Plant Alkaloids," 4th edition, The Blakiston Co., Inc., New York, 1949, p. 367.

[20] F. A. Flückiger, *Pharm. J.*, (ii) **11**, 192 (1869-1870).

that the greenheart bebeerine was identical with "*Pareira brava*" bebeerine. Earlier, Boedecker[21] reached similar conclusions on the basis of olfactory tests on pyrolysis products. Since much of the early literature embraces non-equivalent alkaloidal mixtures from various species, complete abandonment of the term bebeerine appears advisable. In addition no substantial evidence appears to support the belief that pure alkaloids of any type were, in the past, isolated from greenheart.

In consequence we abandoned, for the moment, attempts to match our greenheart alkaloids with those of the literature and sought means of obtaining crystalline derivatives. These studies were hampered by the instability of crude alkaloids. Analysis of this instability suggested oxidative phenomena, perhaps associated with free phenolic groups or tertiary nitrogen atoms.

Upon investigation it was found that partially purified material reacted readily with methyl iodide to yield an insoluble methiodide which was crystalline. The latter is designated rodiasine dimethiodide, m.p. 321° with decomposition.

Bark from another source yielded the same compound which melted seven degrees lower. The elementary analyses for the two methiodides appeared consistent with an empirical formula $C_{40}H_{50}O_6N_2^{++}$ for the positive ion—with some uncertainties as to the exact number of hydrogen atoms (arising from errors inherent in the combustion analysis).

These data at first suggested the possibility that rodiasine dimethiodide was derived from an alkaloid, originally present in the extraction liquor, with an empirical formula $C_{38}H_{42}O_6N_2$ consistent with that of the dimethyl ether of chondrodendrine or a structural isomer. This possibility, however, was tentatively eliminated on the basis of a positive Folin phenol reaction. The existence of a free phenolic group was confirmed through preparation of O-methyl derivatives. The O-methyl derivatives derived from the two dimethiodides corresponded in all physical properties, including X-ray powder diffraction.

In view of the general belief that so-called bebeerine is an important constituent of greenheart bark, it was of interest to compare the absorption spectra of material isolated from *Ocotea rodiaei* with a number of alkaloids and derivatives having the general chondrodendrine-type structure. In view of the diversity of physical constants recorded, our methods of preparation, where pertinent, are described briefly.

The ultraviolet absorption of O-dimethyl-*d*-tubocurarine iodide[22] and O-dimethyl-*d*-isochondrodendrine dimethiodide as well as *d*-tubocurarine iodide[23] and *d*-chondrocurine iodide,[23] all show a well-defined maximum at 225 or 226 mμ (log ε 4.80 to 4.89). These alkaloids or alkaloid derivatives are all members of the isochondrodendrine or chondrodendrine series of biscoclaurine compounds. Tomita[24] in his recent review of alkaloids from the *Menispermaceae* has listed both the tertiary and quaternary alkaloids of this series in his group IIb. Whether maxima in the 225 mμ region are typical of this group as a whole and whether other groups of biscoclaurine alkaloids also show similar maxima has not been established. Ochiai[25] has made determinations as far as 222 mμ but, unfortunately, the reported absorption spectra for other biscoclaurine alkaloids[26,27] show only the portion of the spectra above 240 mμ.

Rodiasine dimethiodide and its O-methyl derivative, which have almost identical spectra, do not show maxima at 225 mμ. A qualitative examination of this region with the Beckman DU Spectrophotometer with photomultiplier attachment revealed the absence of peaks as far out as 200 mμ. In the region above 240 mμ the absorption curves are not inconsistent with those reported for a number of biscoclaurine alkaloids.[25-27]

There is not, however, sufficient chemical or spectroscopic evidence to place rodiasine dimethiodide in the bisbenzylisoquinoline series. A minimum C_{40}, rather than a C_{20}, formula is indicated by the presence of one phenolic group for every forty carbon atoms, as shown by the formation of an O-methyl derivative, color tests and alkoxyl determinations. Involvement of four of the five remaining oxygens in methoxyl groups is shown by Zeisel determinations. Tests for methylenedioxy groups were negative. Involvement of the one remaining oxygen in an ether linkage is suggested by negative tests for ester, amide and carbonyl groups. If rodiasine is of the biscoclaurine series, the remaining oxygen forms a diphenyl ether linkage. The nitrogen of rodiasine is apparently present in tertiary amine groups. The instability in air of the mixed ether-soluble alkaloids, as a whole, is consistent with the presence of such groups, but such behavior could also be attributed to free phenolic groups.

From the previous consideration of the greenheart alkaloids, it appeared that further insight into their structure might be obtained by pharmacological investigation. In a collaborative study with Professors Harvey Haag, Paul S. Larson and J. K. Finnegan of the Medical College of Virginia, the ether-soluble alkaloids were assayed for curare-like activity by the head-drop method in the rabbit. The material had little or no curare-like activity. Following treatment with methyl iodide the material had marked activity. The dimethochloride of *rodiasine* had an activity approximately one-half that of a standard U.S.P. reference sample of tubocurarine chloride. Marked increase in activity following quaternization of nitrogen has been observed in many compounds.[28,29] Further details on the pharmacological investigation will be reported elsewhere.

Experimental

Examination of Demerara Greenheart Source Material.—Bark and sawdust were obtained from two sources, desig-

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[21] C. Boedecker, *Ann.*, **69**, 37 (1849).

[22] Values are similar to those reported by R. V. Swann, *J. Pharm. and Pharmacol.*, **3**, 843 (1951).

[23] J. D. Dutcher, *Ann. New York Acad. Sci.*, **54**, 326 (1951).

[24] M. Tomita, *Fortschr. Chem. Org. Naturstoffe*, **9**, 175 (1952).

[25] E. Ochiai, *J. Pharm. Soc. Japan*, **49**, 425 (1929).

[26] I. R. C. Bick, E. S. Ewen and A. R. Todd, *J. Chem. Soc.*, 2767 (1949).

[27] I. R. C. Bick and A. R. Todd, *ibid.*, 1606 (1950).

[28] L. E. Craig, *Chem. Revs.*, **42**, 285 (1948).

[29] J. Hoppe, *Ann. N. Y. Acad. Sci.*, **54**, 395 (1951).

nated G and W. The sawdust was mixed material obtained directly from the mills. The bark similarly was mixed material obtained in a similar fashion. Dried bark W contained 0.83% nitrogen (Dumas) and 15.5% ash. Sawdust W (600 g.) (0.54% N based on the dry weight) was shaken with 2 l. of ethanol for 70 hours. The alcoholic extract contained by analysis 4.9 g. (0.82% based on the dry weight of sawdust) of solid, 1.6% N; Barger,[5] by exhaustively extracting sawdust with ethanol, obtained a 4.5% yield of solid.

Extraction of Greenheart Bark.—The methods employed for the extraction of alkaloids from bark were modified from the procedure used by King[30] for alkaloids of *Radix pareirae bravae:* After passage through a hammer mill, the bark was further ground in a Wiley mill to pass a 1 mm. screen. To 10 kg. of bark was added 17.5 l. of 1% aqueous *d*-tartaric acid. The mixture was stirred rapidly for 2.5 hours and then allowed to stand overnight. The supernatant liquid was filtered, concentrated to approximately one-fifth its original volume, and then refiltered. Sodium hydroxide was added to the cooled solution to a *p*H of 5. Saturated aqueous sodium carbonate was then added until a *p*H of 9. The solid was collected, washed with water and dried under diminished pressure over sodium hydroxide. Extraction of the bark was repeated with nine additional 7.5-l. portions of aqueous tartaric acid. The final extract was obtained by suction filtration. The total yield of crude alkaloid was 220–240 g. Some samples of bark were extracted by a percolation procedure. Similar yields were obtained.

Separation of the Ether-soluble Bases.—Crude bases from either the percolation or agitation-extraction procedure were placed in a Soxhlet thimble and extracted continuously with ether for 2–4 days. Maclagan[9] employed ether extraction to separate bebeerine from crude greenheart alkaloids, and others[30-32] have employed ether extraction to obtain partial purification of bebeerine. The ether-soluble material was dissolved in dilute hydrochloric acid and then washed profusely with ether. The base was reprecipitated by addition of ammonia water to *p*H 9. The yield of reprecipitated ether-soluble alkaloids was 33–40% of the weight of the crude mixed alkaloids.

Characterization of the Reprecipitated Ether-soluble Alkaloids.—The reprecipitated material contained nitrogen and gave negative tests for sulfur and halogen (sodium fusion). The test for phosphate was also negative. A Baeyer test for unsaturation was positive. The material gave a negative test for aldehydes with Schiff reagent and dimedon. Enol tests with both aqueous and alcoholic ferric chloride were negative. The indophenol reaction[33] was negative, but reactions with Folin phenol reagent[34] and Millon reagent[35] were positive. The absence of methylenedioxy groups was indicated by negative response in the test of Labat,[36] and the lack of ester groups by the ferric hydroxamate test.[37] The reprecipitated alkaloids were amorphous, almost without color, and melted in the region of 180–213°. In one run an amorphous material was obtained with an equivalent weight of 318 (by titration of the hydrochloride with 0.1 *N* NaOH), calculated 315 on the basis of the nitrogen content. Other properties of the material were consistent with those expected for "bebeerine" from greenheart. A methoxyl determination, however, indicated noncorrespondence with the compound "bebeerine." The material was soluble in sodium hydroxide and was reprecipitated by carbon dioxide; $[\alpha]^{20}\mathrm{D}$ +129° (*c* 1.01 in methanol).

Anal. Calcd. for $C_{32}H_{26}O_2N_2(OCH_3)_4$: C, 72.70; H, 6.44; N, 4.71; CH_3O, 20.8. Found: C, 72.79; H, 6.23; N, 4.45; CH_3O, 19.5.

Studies on the Stability of "Bebeerine" from Greenheart.—A 1% solution of "bebeerine" from greenheart bark (prepared as described above) was prepared by dissolving the precipitated ether-soluble alkaloids in 6 *N* hydrochloric acid and filtering to remove a small amount of insoluble material. The initial rotation, $[\alpha]^{21}\mathrm{D}$ 117.5° and $[\alpha]^{21}{}_{5461}$ +146°, was essentially unchanged after five days at room temperature or heating at 50° for 26 hours. In other experiments, a 1% solution of the alkaloid in 20% methanolic KOH was refluxed for 22 hours. The changes in rotation were negligible. A sample of alkaloid in methanol which was stored in the refrigerator for seven months changed its specific rotation from +125 to +73°. A sample with initial specific rotation of +120° was sealed in a polarimeter tube. After an initial drop to a specific rotation of +110°, which took place during the first month, the rotation remained unchanged for two additional months. Re-exposure to air caused the specific rotation to drop to +89° in a subsequent 2.5-week period. In contrast, a solution refluxed in methanol showed little change in rotation.

Reaction of the Alkaloids with Methyl Iodide.—By treating 3.511 g. of reprecipitated ether-soluble alkaloids with an excess of methyl iodide in methanol and evaporating to dryness, 5.092 g. of quaternary alkaloids was obtained. The material was amorphous and had the properties of a mixture. The uptake of methyl iodide corresponded to that of a tertiary amine with equivalent weight of 315. On the basis of the N determination (4.46%), the calculated value is 314.

Isolation of a Crystalline Quaternary Ammonium Compound.—The reprecipitated ether-soluble alkaloids from bark G (3.511 g.) were dissolved in 250 ml. of absolute methanol, and 14 ml. of methyl iodide was added. The mixture was allowed to stand for two days at room temperature and then concentrated to a volume of 70 ml. The solution deposited, upon cooling, 0.261 g. of colorless crystals. The latter, rodiasine dimethiodide, was recrystallized from methanol to constant melting point, 321° with decomposition (in an evacuated capillary; rate of heating, 4° per min.); $[\alpha]^{20}\mathrm{D}$ +68°, $[\alpha]^{20}{}_{5461}$ +83° (*c* 0.147 in water). For analysis the compound was dried at room temperature under diminished pressure in the presence of phosphoric acid anhydride. The melting point was unchanged. Recrystallization from water instead of methanol did not significantly alter the melting point. Absorption spectra[38]: λ (log ϵ) 220 (4.913), 225 (4.872) 259 min. (3.416), 283 max. (3.981).

Anal. Calcd. for $C_{32}H_{25}ON_2I_2(CH_3)_4(OH)(OCH_3)_4$: C, 52.87; H, 5.55; N, 3.08; I, 27.94; CH_3O, 13.66; N-CH_3, 6.62. Found[39]: C, 52.95; H, 5.17; N, 3.26; I, 28.08; CH_3O, 13.79; N-CH_3, 6.75.

O-Methylrodiasine (G) Dimethiodide.—The methiodide (182 mg.) was dissolved in 25 ml. of warm methanol. Methanolic potassium hydroxide (0.8 ml., 0.5 *N*) was added to the solution which was then treated with 0.08 ml. of methyl iodide. The mixture was refluxed for approximately one hour. A total of seven similar treatments was required to yield a phenol-free product, as adjudged by the Folin phenol reagent. The mixture was evaporated to dryness under diminished pressure, and the residue was dissolved in water. The colorless product was recrystallized from water to give a phenol-free product (74% of the calculated yield), m.p. 304° dec.; $[\alpha]^{20}\mathrm{D}$ +50°, $[\alpha]^{20}{}_{5461}$ +63° (*c* 0.255 in water). For analysis the compound was dried under diminished pressure in the presence of phosphoric acid anhydride. The melting point was unchanged.

Anal. Calcd. for $C_{32}H_{25}ON_2I_2(CH_3)_4(OCH_3)_5$: C, 53.37; H, 5.68; CH_3O, 16.82. Found: C, 53.39; H, 5.39; CH_3O, 16.50.

The same substance was obtained from bark W. The O-methyl methiodide, in common with parent dimethiodide from barks G and W, is unstable in the presence of light. Yellow coloration can be removed by treatment with copper[40] and recrystallization. It was noted throughout the studies that the melting point determinations of all the quaternary derivatives were influenced by rate of heating, particle size and variable interactions with air and light.

Rodiasine Dimethopicrate.—The rodiasine dimethiodide was readily converted to the picrate by treating a hot aqueous solution of the dimethiodide with a saturated aqueous

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(30) H. King, *J. Chem. Soc.*, 737 (1940).

(31) M. Scholtz, *Ber.*, **29**, 2054 (1896).

(32) M. Scholtz, *Arch. Pharm.*, **244**, 555 (1906).

(33) R. F. Milton and W. A. Waters, "Methods of Quantitative Microanalysis," Edward Arnold and Co., London, 1949, p. 340.

(34) *Ibid.*, p. 339.

(35) N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," Thomas Y. Crowell Co., New York, N. Y., 1947, p. 129.

(36) J. A. Labat, *Bull. soc. chim. biol.*, **15**, 1344 (1933).

(37) Reference 35, p. 121.

(38) Absorption spectra of all compounds were obtained in aqueous solution (10^{-4} to 10^{-5} *M*).

(39) The alkyl iodide in the alkoxyl determination was entirely methyl as determined by infrared spectra by the Clark Microanalytical Laboratories, Urbana, Ill.

(40) I. R. C. Bick and A. R. Todd, *J. Chem. Soc.*, 2170 (1948).

solution of picric acid. The halogen-free dipicrates were obtained in two forms and melted at 180 and 252° after vacuum drying over phosphoric acid anhydride. These values remained unchanged after further recrystallization from aqueous methanol. Recrystallization from aqueous methanol and seeding with the 252° dipicrate changed the melting point of the 180° material to 253°. By similar seeding with 180° dipicrate melting point of the 252° material was changed to 182°. These latter products failed to show a melting point depression with their respective seeding materials.

Anal. Calcd. for $C_{52}H_{54}O_{20}N_8$: C, 56.21; H, 4.90. Rodiasine dimethopicrate (m.p. 180°): Found: C, 56.23; H, 5.18. Rodiasine dimethopicrate (m.p. 252°): Found: C, 56.42; H, 4.74.

Rodiasine Dimethochloride.—Rodiasine dimethiodide (0.592 g.) in warm water was treated with an excess of silver chloride. The solution was filtered and concentrated to a small volume. The chloride was obtained from isopropyl alcohol–water as colorless needles, m.p. 284° dec. (0.365 g., or 77% of the calculated amount). For analysis the salt was recrystallized from isopropyl alcohol–water to give a product decomposing at 286°, $[\alpha]^{20}\mathrm{D}$ +81.5°, $[\alpha]^{20}{}_{5461}$ +100° (*c* 0.98 in water).

Anal. Calcd. for $C_{40}H_{50}O_6N_2Cl$: C, 66.20; H, 6.94. Found: C, 66.06; H, 6.70.

The product gave a negative Millon test in common with the iodide salt and in contrast to the alkaloid mixture which served as starting material. Millon tests on the iodide salt are difficult to interpret on account of interference of the iodide ion.

X-Ray Diffraction Studies.—X-Ray powder diffraction studies were carried out to compare rodiasine and dimethiodides from two different bark sources. The photographs showed no difference between the two materials. Similar analyses of the O-methyl derivatives showed no difference.

***d*-Isochondrodendrine.**—A sample of commercial "Bebeerine Hydrochloride" was converted to the free alkaloid by treatment with aqueous sodium carbonate. The material did not correspond to bebeerine. The manufacturer, on the basis of questioning, stated that the bebeerine content was "to the order of 89.1%, hydrochloride content 12.9% (*sic*)" and that the material comprised the total alkaloids of *pareira brava*. The alkaloids were then exhaustively extracted with chloroform. The chloroform extract was evaporated to dryness. The residue was recrystallized from chloroform–methanol to yield *d*-isochondrodendrine. The yield was 9% of the weight of the alkaloid obtained from fresh samples of the hydrochloride. After several months storage at room temperature the same alkaloid hydrochloride yielded an amorphous material under similar conditions. The purified *d*-isochondrodendrine from the fresh samples melted at 309°, $[\alpha]^{21}\mathrm{D}$ +49° (*c* 0.588 in pyridine), $[\alpha]^{21}\mathrm{D}$ +118° (*c* 0.330 in 0.1 *N* HCl). The melting point of *d*-isochondrodendrine is variously reported[14,15,30,41,42] from 290 to 316°.

Anal. Calcd. for $C_{36}H_{38}O_6N_2$: C, 72.70; H, 6.44; N, 4.71. Found: C, 72.52; H, 6.50; N, 4.83.

***d*-Isochondrodendrine Dimethiodide.**—The alkaloid was methylated with methyl iodide according to the procedure of Dutcher. The anhydrous product melted at 278–280°, $[\alpha]^{24}\mathrm{D}$ +85° (*c* 0.800 in water). The melting point is variously reported[14,15,30,42,43] from 275 to 287°.

***d*-Isochondrodendrine Dimethyl Ether Dimethiodide.**—The dimethyl ether dimethiodide was prepared from *d*-isochondrodendrine according to the procedure employed by Dutcher.[15] The product was recrystallized from water to give colorless needles which were dried *in vacuo* over phosphoric acid anhydride, m.p. 300° (evac. cap.). The melting point reported by Dutcher[15] is 302°. Scholtz and Koch[43] reported a melting point of 294°. The same compound is reported[14,30] to melt at approximately 312° after crystallization from methanol.

Anal. Calcd. for $C_{40}H_{48}O_6N_2I_2$: C, 52.99; H, 5.34. Found: C, 53.04; H, 5.24. λ (log ϵ): 226 max. (4.886), 263 min. (3.459), 273 max. (3.564).

Dimethyl Ether of *d*-Tubocurarine Iodide.—*d*-Tubocurarine chloride was methylated according to the procedure of Dutcher.[15] The identity of the starting material was confirmed by pharmacological test[44] and chemical degradation.[45] The resultant dimethyl ether iodide was recrystallized from water to yield a product with physical properties in agreement with the reported values[15,45]: λ (log ϵ): 226 max. (4.880), 257 min. (3.420), 280 max. (3.831).

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(41) F. Faltis, *Monatsh.*, **33**, 873 (1912).

(42) M. Scholtz, *Arch. Pharm.*, **251**, 136 (1913).

(43) M. Scholtz and O. Koch, *ibid.*, **252**, 513 (1914).

(44) "The Pharmacopoeia of the United States of America," 14th revision, Easton, Penna., 1950.

(45) H. King, *J. Chem. Soc.*, 1381 (1935).