

the hydroxy compound IX, oxidized on standing in the air to the ketone VIII.

6,6,11-Trimethyl-11-hydroxy-6,11-dihydrobenz(b)acridine (X).—A 1.0-g. (0.00356 mole) portion of VIII was extracted from the thimble of a Soxhlet apparatus into a 12 ml. of ether solution of methylmagnesium iodide made from 1.02 g. (0.0072 mole) of methyl iodide. The red colored complex was decomposed with a saturated ammonium chloride solution. From the ether solution 0.954 g. (91% yield) of crude tertiary carbinol X, m.p. 151–155°, resulted; recrystallized from petroleum ether, m.p. 156–158°; λ_{\max} 231, 273, 294, 300, 307, 313, 321 $m\mu$ ($\epsilon \times 10^{-3}$, 48.6, 4.3, 3.9, 3.9, 4.9, 4.0, 6.3); γ_{OH} , 3606/31, $\gamma_{C=C}$ and/or $C=N$, 1625/28, 1600/30.

Anal. Calcd. for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 83.30; H, 6.55; N, 4.92.

6,6-Dimethyl-11-oximino-6,11-dihydrobenz(b)acridine (XI) was not obtained by the usual methods for preparing

oximes. A solution of 0.698 g. (0.01 mole) of hydroxylamine hydrochloride and 2.37 g. of dry pyridine in 10 ml. of freshly prepared abs. ethanol was mixed with a solution of 1.0 g. (0.0036 mole) of VIII in 30 ml. of abs. ethanol and refluxed for 5 days during which time the alcohol and water were allowed to distil off slowly being replaced from time to time with fresh abs. ethanol. A 68% yield, 0.818 g., of crude oxime, m.p. 219–224°, was isolated; recrystallization from ethanol gave colorless flakes, m.p. 222–224°, λ_{\max} 244.5 $m\mu$ (ϵ 40,800).

Anal. Calcd. for $C_{19}H_{18}N_2O_2$: C, 79.14; H, 5.59; N, 9.72. Found: C, 79.10; H, 5.58; N, 9.81.

Catalytic hydrogenation of the oxime XI with Raney nickel in ethanol at 45 lb./in.² for 10 hours produced an oil from which no solid product was isolated.

LINCOLN, NEBR.

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Alkaloids from *Apocynaceae*. III.¹ Alkaloids of *Tabernaemontana* and *Ervatamia*. The Structure of Coronaridine, A New Alkaloid Related to Ibogamine²

BY MARVIN GORMAN, NORBERT NEUSS, NANCY J. CONE AND JAMES A. DEYRUP³

RECEIVED JULY 13, 1959

Six representative species of the genera *Ervatamia* and *Tabernaemontana* were investigated. The alkaloids ibogamine (Id), voacangine (Ia) and voacangine, common to the genera *Tabernanthe* and *Voacanga*, were isolated. In addition to these, four other alkaloids are described: olivacine (alkaloid "205"), dregamine, tabernaemontanine and coronaridine (Ic). The latter is shown by saponification and decarboxylation to be carbomethoxyibogamine (Id). Dregamine and tabernaemontanine are examples of 2-acylindole alkaloids.

In pursuing the study of different members of the family *Apocynaceae*, we became interested in botanical relatives of the African hardwood *Tabernanthe iboga* Baill.¹ This plant is a source of numerous alkaloids which have been studied by pharmacologists as potential stimulants.⁴ The structures of these alkaloids have been elucidated by Taylor.⁵

Another genus closely related botanically to *Tabernanthe* is *Voacanga*.⁶ The major alkaloid of *Voacanga africana*, voacangine (Ia), and that of *Tabernanthe iboga*, ibogaine (Ib), differ only in that the former contains an additional carbomethoxy function. The close relationship of these two alkaloids has been demonstrated by the conversion of voacangine to ibogaine.⁷ While these two compounds are quite similar chemically, their pharmacology is different⁸ in that voacangine lacks the stimulant properties of ibogaine.

Tabernanthe and *Voacanga* are close botanical relatives, being found in the same family: (*Apo-*

cyneaceae), subfamily (*Plumeroideae*) and tribe (*Tabernaemontanoideae*).⁶

In view of the structural correlations found among the constituents of these genera, it was of interest to investigate other members of the same tribe in the hope of finding biogenetically related alkaloids. Such alkaloids were present.⁹

The tribe *Tabernaemontanoideae* contains, according to Pichon,¹⁰ twenty closely related genera. The largest of these are the genera *Tabernaemontana* with 140 species and *Ervatamia* with 92–96 species.¹¹ Of the remaining eighteen genera, eight are monotypic, and the rest range from two to twenty species.

We have chosen to investigate the two larger genera because of their broad distribution and availability. The following species were examined: *Ervatamia coronaria*, *E. divaricata*, *Tabernaemontana undulata*, *T. psychotriifolia*, *T. oppositifolia* and *T. australis*.

Ervatamia coronaria, syn. *Tabernaemontana coronaria*. This plant, an 8–10 foot tree, is cultivated throughout India both for the ornamental value of its fragrant white blossoms and as a medicinal. The leaves, bark and flowers of the plant are used in the Ayurvedic system for different ailments as a soothing agent.

(9) In the presentation of these results, Walls, Collera and Sandoval reported the isolation, from the genus *Stemmadenia*, of the new alkaloids (+)-quebrachamine, isovocangine, stemmadenine, as well as the known alkaloids voacangine, voacamine, tabernanthine and ibogamine. These alkaloids are characteristic constituents of the genus *Voacanga*. The presence of these alkaloids in *Stemmadenia* sp. indicates the relationship of this genus to those of *Tabernanthe*, *Voacanga* and *Tabernaemontana* (*Tetrahedron*, **2**, 173 (1958)).

(10) M. Pichon, *Mém. Mus. Nat. Paris*, **24**, 111 (1948), *et seq.*

(11) In some species these genera are synonymous.

(1) Alkaloids from Apocyanaceae, II, Norbert Neuss, *J. Org. Chem.*, **24**, 2047 (1959).

(2) Presented in part before the Organic Division of the 139th National Meeting of the American Chemical Society, San Francisco, Calif., April, 1958.

(3) On leave from the University of Illinois as a trainee in the summer employment program, 1958, of Eli Lilly and Co., Indianapolis, Ind.

(4) J. A. Schneider, *Ann. N. Y. Acad. Sci.*, **66**, Art. 3 (1957), March 14, and references cited therein.

(5) W. I. Taylor, *THIS JOURNAL*, **79**, 3298 (1957).

(6) K. Schumann, in A. Engler and K. Prantl, "Die natürlichen Pflanzenfamilien," Vol. 4, part 2, 1895, p. 109.

(7) F. Percheron, Alain Le Hir, R. Goutarel and M. W. Janot, *Compt. rend. acad. sci.*, **245**, 1141 (1957).

(8) R. C. Rathbun, Lilly Research Laboratories Pharmacology Division, private communication.

The isolation of alkaloids from this species has been reported by two groups.¹²⁻¹⁴

The earlier workers isolated two crystalline compounds, tabernaemontanine, a $C_{20}H_{26}O_3N_2$ compound, m.p. 208–210°, and coronarine, a yellow $C_{44}H_{56}O_6N_4$ compound, m.p. 196–198°. The more recent investigation¹³ yielded only tabernaemontanine of melting point 208–210°. Upon repeated recrystallization, the authors reported the substance as melting at 217–218°.

Since our material was grown in Florida by Menninger,¹⁵ it was of interest to determine whether the alkaloidal constituents would be of the same nature as those found in the Indian material.

Total alkaloids obtained by the extraction of stems were chromatographed on deactivated alumina. Elution with benzene yielded small amounts of a new alkaloid called coronaridine which could not be induced to crystallize. Treatment of the base with ethereal hydrochloric acid yielded an amorphous hydrochloride which could be crystallized from acetone. Analytical results were in good agreement with its formulation as a $C_{21}H_{26}O_2N_2$ compound.

Further elution with a mixture of benzene-chloroform (3:1) yielded a second alkaloid, m.p. 207–209° (from ether). Recrystallization from methanol gave material melting at 217–219°. The double melting point of this alkaloid is in agreement with the melting points reported for the alkaloid tabernaemontanine.^{12,13} Our analytical data for this compound do not exclude the possibility of its formulation as a $C_{21}H_{26}O_3N_2$ compound rather than $C_{20}H_{26}O_3N_2$ as postulated by the previous investigators.

Continuing the elution with the same solvent system yielded minute amounts of a new alkaloid called dregamine.¹⁶

Ervatamia divaricata.—This plant is classified by some authors as synonymous with *E. coronaria* and is commercially available in India.¹⁷ Chromatography of the alkaloidal fraction yielded coronaridine as the only homogeneous material.

The following three species of *Tabernaemontana* were collected for us on Trinidad and neighboring islands where they are found both in natural and cultivated states.

Tabernaemontana undulata.—The results of a paper chromatogram of the alkaloidal fraction indicated the presence of at least three components. Repeated chromatography of this fraction has not yielded any crystalline material.

T. psychotrifolia.—The chromatography of the alkaloidal fraction obtained by the extraction of the root yielded upon elution with benzene coronaridine. The elution with benzene was then continued, yielding voacangine. Using benzene-

chloroform mixtures (3:1), voacamine was obtained. Later fractions, eluted with the same solvent mixture, gave a small amount of a crystalline yellow alkaloid, olivacine.¹⁸ The same alkaloid was obtained directly from the benzene extract of the plant by treating it with a tartaric acid solution, recrystallization of the tartrate and liberation of the free base.

This substance was shown to be a $C_{17}H_{14}N_2$ compound,¹⁸ isomeric with ellipticine, also a yellow alkaloid, first isolated by Goodwin from *Ochrosia elliptica*.¹⁹ The two compounds are characterized by very similar spectral and chemical properties. Thus, alkaloid "205" forms a methiodide which can be readily reduced with sodium borohydride to the corresponding tetrahydro compound.²⁰

T. oppositifolia.—Chromatography of the alkaloidal fraction prepared from the benzene extract of the root yielded several known alkaloids. Elution with benzene gave first crystalline ibogamine, (Id)⁶ then coronaridine, and, finally, voacangine. After elution with benzene-chloroform (1:1), voacamine was obtained.

T. australis.—This species was collected for us in northeastern Argentina. The alkaloids obtained were chromatographed to give voacangine, followed by voacamine.

The results described above are summarized in Table I.

The occurrences of the three alkaloids coronaridine (Ic), voacangine (Ia) and ibogamine (Id) in the same plant species (Table I) indicated a possible biogenetic relationship in their structures. An examination of the infrared spectra of the above alkaloids confirmed this speculation. The bands present in voacangine (Ia) and absent in coronaridine (Ic) could be attributed to a 5-methoxy indole moiety ($\lambda_{max}^{CS_2}$ 6.15, 9.65, 12.05, 12.55 μ)²¹ while those present in coronaridine (Ic) and absent in ibogamine (Id) were characteristic of a carbomethoxy function ($\lambda_{max}^{CS_2}$ 5.8 μ , 8.05 μ).

TABLE I
ALKALOIDS ISOLATED FROM SPECIES OF *Ervatamia* AND *Tabernaemontana*

Plants	Alkaloids			
	Coro- nari- dine	Voa- can- gine	Voa- ca- mine	Others
<i>E. coronaria</i>	+	—	—	Tabernaemontanine Dregamine
<i>E. divaricata</i>	+	—	—	
<i>T. undulata</i>	—	—	—	
<i>T. psychotrifolia</i>	+	+	+	Olivacine (alkaloid "205")
<i>T. oppositifolia</i>	+	+	+	Ibogamine
<i>T. australis</i>	—	+	+	

(18) This alkaloid was first thought to be a new compound and was referred to as alkaloid "205."¹² It has recently been identified as olivacine, reported by Schmutz from *Aspidosperma olivaceum* M. Arg. (J. Schmutz and F. Hunziker, *Pharm. Acta Helv.*, **33**, 341 (1958)). We should like to thank Dr. Schmutz for the direct comparison of our sample with that of authentic olivacine.

(19) Sidney Goodwin, A. F. Smith and E. C. Horning, *THIS JOURNAL*, **81**, 1903 (1959).

(20) We should like to thank Dr. Goodwin for experimental conditions for the preparation of these derivatives prior to the publication of her results.

(21) N. Neuss, H. Boaz and J. W. Forbes, *THIS JOURNAL*, **76**, 2463 (1954).

(12) A. N. Ratnagiriswaran and K. Venkatochalom, *Quart. J. Pharm. and Pharmacol.*, **12**, 174 (1939).

(13) S. A. Warsi and Bashin Ahmed, *Pakistan J. Sci.*, **1**, 128 (1949).

(14) S. P. Raman and A. K. Barua, *J. Indian Chem. Soc.*, **34**, 912 (1957), have reported on the triterpene constituents of this plant.

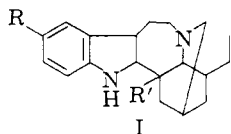
(15) E. A. Menninger, "What Flowering Tree Is That?" *Stuart Daily News*, Stuart, Florida, 1956.

(16) Dregamine was isolated as the main component of an alkaloidal extract prepared from the bark of the trunk of *Voacanga dregei* E. M.; N. Neuss and N. J. Cone, *Experientia*, **15**, 414 (1959).

(17) United Chemical Co. Ltd., Calcutta, India.

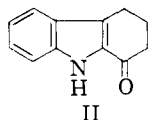
The proof that coronaridine (Ic) was indeed a desmethoxy voacangine was carried out in a manner analogous to that used in the conversion of voacangine (Ia) to ibogaine (Ib).⁷

The saponification of the base with ethanolic potassium hydroxide followed by decarboxylation in hydrochloric acid afforded ibogamine (Id), m.p. 160–162°.



I
Ia, R = OMe, R' = COOMe
Ib, R = OMe, R' = H
Ic, R = H, R' = COOMe
Id, R = H, R' = H

The ultraviolet spectrum ($\lambda_{\text{max}}^{\text{EtOH}}$ 237, 312 μ ; a_M 14,500, 17,500) of tabernaemontanine was similar to that of 1-keto-1,2,3,4-tetrahydrocarbazole²² (II) ($\lambda_{\text{max}}^{\text{EtOH}}$ 236, 309 μ ; a_M 15,900, 22,400), indicating that the absorbing chromophores were the same.



The infrared spectrum of tabernaemontanine also shows some similarities to that of compound II at the following wave lengths: $\lambda_{\text{max}}^{\text{CHCl}_3}$ 2.88, 3.00 (N-H), 6.06 (carbonyl) and 7.5 μ . The presence of a methyl ester is indicated by bands at $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.79 and 8.05 μ .

Thus tabernaemontanine would appear to be a member of a unique class of indole alkaloids—the 2-acylindoles. After presentation, in part, of this work,² Rao²³ reported the isolation of voacafrine and voacaficine from *Voacanga africana*; and more recently Renner²⁴ described the alkaloid vobasine from the same plant. These three compounds, as well as dregamine¹⁶ (*vide supra*), are probably also members of the 2-acylindole alkaloids since their ultraviolet spectra (Table II) are virtually identical to that of tabernaemontanine.

TABLE II

Compound	$\lambda_{\text{max}}^{\text{EtOH}}$, μ		a_M	
	237	312	14,500	17,500
Tabernaemontanine	237	312	14,500	17,500
Dregamine ¹⁶	239	316	15,200	18,600
Voacaficine ²³	240	315	17,070	20,670
Voacafrine ²³	238	315	16,570	22,500
Vobasine ²⁴	239.5	315	15,500	18,600
1-Keto-1,2,3,4-tetrahydrocarbazole	236	309	15,900	22,400

It is hoped that the eventual structure elucidation of this interesting group of compounds will help in the understanding of the biogenesis of indole alkaloids.

Acknowledgment.—We should like to express our appreciation to the following individuals for their assistance in this investigation: Plant pro-

urement: Dr. F. J. Simmonds, Imperial College of Tropical Agriculture, St. Augustine, Trinidad, B.W.I.; Dr. Rolf Singer, Head, Department of Botany, Fundacion Miguel Lillo, Tucuman, Argentina; Mr. E. A. Menninger, "Flowering Tree Man," Stuart, Fla. Plant taxonomy: Dr. Julian A. Steyermark, Research Associate, Missouri Botanical Gardens, 494 North Hill Drive, Barrington, Ill. Microanalyses: Messrs. W. L. Brown, G. M. Maciak, H. L. Hunter, R. Hughes and Miss G. Beckmann. Physical data: Dr. H. E. Boaz, Messrs. P. Landis, L. Howard and Miss Ann Van Camp.

Experimental

Identification of Known Alkaloids.—All known alkaloids isolated above were identified by comparison of mixture m.p., infrared spectra and X-ray diffraction patterns with those of authentic specimens.²⁵ The melting points were determined on a Kofler micro-stage.

The alkaloids contained in these plants were isolated using the following procedure:

The ground plant was defatted with hexane, moistened with dilute aqueous ammonia and repeatedly extracted with benzene. When the benzene extracts no longer gave a positive reaction with Mayer reagent, the marc was extracted twice with 95% ethanol. The ethanolic extracts gave positive alkaloid tests, but in no case yielded characterizable products. The benzene extracts were concentrated *in vacuo*, and the alkaloids removed by acid extraction. The acid solution on basification with ammonia and extraction with chloroform yielded the crude alkaloid mixture. This material, obtained as an amorphous powder, was subsequently chromatographed on deactivated alumina using benzene, then benzene-chloroform mixtures, chloroform, and, finally, chloroform-methanol mixtures as eluents. Fractions were collected, evaporated *in vacuo* and combined, where indicated by infrared spectroscopy. The purified alkaloids were crystallized from a suitable solvent or converted to an appropriate salt.

Ervatamia coronaria: Coronaridine and Tabernaemontanine.—The stems (2.2 kg.) were treated as described above, and the total alkaloids (8 g.) chromatographed. Elution with benzene yielded 140 mg. of coronaridine. Treatment of the base with ethereal hydrochloric acid gave an amorphous hydrochloride which crystallized (110 mg.) from acetone, m.p. 235° dec., $[\alpha]_{\text{D}}^{25}$ -8.5° (methanol, *c* 1).

Anal. Calcd. for $\text{C}_{21}\text{H}_{26}\text{O}_2\text{N}_2\cdot\text{HCl}$: C, 67.29; H, 7.23; N, 7.47; O, 8.54; OCH_3 , 8.28. Found: C, 67.54; H, 7.30; N, 7.30; O, 8.49; OCH_3 , 8.41.

Further elution with a mixture of benzene-chloroform (3:1) yielded tabernaemontanine (348 mg.), m.p. 207–209° (from ether). Recrystallization from methanol gave material melting at 217–219°, $[\alpha]_{\text{D}}^{25}$ -57.5° (CHCl_3 , *c* 1), pK_a 6.8 (66% DMF), av. mol. wt., 365.

Anal. Calcd. for $\text{C}_{21}\text{H}_{28}\text{O}_3\text{N}_2$: C, 70.76; H, 7.92; mol. wt., 356.45. Found: C, 70.98; H, 7.50; mol. wt. Rast, 350.4.

The hydrochloride was prepared in the usual manner and recrystallized from acetone, m.p. 230–233° dec.

Anal. Calcd. for $\text{C}_{21}\text{H}_{28}\text{O}_3\text{N}_2\cdot\text{HCl}$: C, 64.18; H, 7.44; O, 12.21; N, 7.13; Cl, 9.02; OCH_3 , 7.91. Found: C, 63.72; H, 7.19; O, 12.92; N, 6.80; Cl, 8.98; OCH_3 , 7.61.

Further elution with the same solvent system gave 25 mg. of dregamine, m.p. 180–182°.

E. divaricata.—Eleven kg. of stems gave 16 g. of alkaloids which yielded only coronaridine (325 mg.) on chromatography.

T. psychotrifolia.—A. From 1.2 kg. of the ground root, there were obtained 11.9 g. of total alkaloids. The chromatography of the alkaloidal fraction yielded upon elution of benzene 0.32 g. of crude coronaridine, followed by 0.5 g. of crude voacangine. The latter was recrystallized from methanol to give 250 mg. of pure alkaloid. Using benzene-chloroform mixtures (3:1), 250 mg. of crude voacamine were

(22) R. A. Abramovitch and O. Shapiro, *J. Chem. Soc.*, 4589 (1956).

(23) K. V. Rao, *J. Org. Chem.*, 23, 1455 (1958).

(24) U. Renner, *Experientia*, 15, 185 (1959).

(25) N. Neuss, "Collection of Physical Data of Indole and Dihydroindole Alkaloids," Eli Lilly and Co., Indianapolis, Ind., 1959 (3rd Ed.).

obtained. Recrystallization from methanol gave 120 mg. of crystalline alkaloid.

B. Olivacine.—A larger batch of ground root (4.7 kg.) was extracted with benzene and 55 g. of alkaloidal residue obtained. Repeated extraction with 5% tartaric acid solution, followed by dissolving the insoluble portion in glacial acetic acid and water gave upon standing in the cold a yellow precipitate. Recrystallization from ethanol gave 1.6 g. of olivacine tartrate. For analysis, the material was recrystallized repeatedly from ethanol, m.p. 209–211° dec.

Anal. Calcd. for $C_{21}H_{20}O_6N_2$: C, 63.63; H, 5.09; N, 7.07. Found: C, 63.45; H, 5.17; N, 7.19.

The base was liberated from the tartrate and recrystallized two times from methanol; prisms, m.p. 317–325° dec.

Anal. Calcd. for $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37. Found: C, 83.16; H, 5.85; N, 11.30.

Base Methiodide.—A solution of the base (180 mg.) in warm acetone (100 ml.) was treated with excess (10 ml.) of freshly distilled methyl iodide. After standing for 6 hours, the crystals of methiodide were collected and recrystallized from boiling methanol (120 mg.), m.p. <270°.

Anal. Calcd. for $C_{18}H_{17}N_2I$: C, 55.68; H, 4.41; N, 7.22; I, 32.69. Found: C, 55.76; H, 4.63; N, 6.90; I, 32.27.

Sodium Borohydride Reduction of Base Methiodide.—To 150 mg. of methiodide in ethanol was added a solution of 250 mg. of $NaBH_4$ in 8 ml. of water. The yellow solution was allowed to stand overnight at room temperature. After this time, the solution became colorless. After the usual workup, 140 mg. of the reduced base was obtained. Recrystallization from acetone yielded 110 mg. of crystalline material, m.p. 218–221° dec. The ultraviolet spectrum of

olivacine is characterized by the following bands: λ_{max}^{EtOH} 222, 236 $m\mu$ ($\log a_M$ 4.39, 4.30), 266, 275, 285, 292 $m\mu$ ($\log a_M$ 4.50, 4.66, 4.84, 4.81), 312, 327, 342 $m\mu$ ($\log a_M$ 3.58, 3.70, 3.50), 375, 392 $m\mu$ ($\log a_M$ 3.54, 3.51).

Anal. Calcd. for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60. Found: C, 81.75; H, 7.41; N, 10.35.

T. oppositifolia.—Chromatography of 3.5 g. of alkaloids obtained from the benzene extract of the root (1.2 kg.) yielded 300 mg. of crystalline ibogamine, 70 mg. of coronaridine and, finally, 75 mg. of voacangine. Following elution with benzene-chloroform (1:1), 100 mg. of voacamine was obtained.

T. australis.—From the Skelly B extract prepared from 3.5 kg. of stems, there was obtained 2.0 g. of alkaloids. The chromatography of this material gave 1.7 g. of crystalline voacangine followed by 100 mg. of voacamine. Chromatography of the alkaloids prepared from the benzene extract yielded by elution with benzene 180 mg. of voacangine followed by 450 mg. of crystalline voacamine (benzene-chloroform mixture, 2:1).

T. undulata.—The alkaloids (1.83 g.) from the stems (1.3 kg.) gave no crystalline materials on repeated chromatography.

Ibogamine from Coronaridine.—A solution of 30 mg. of coronaridine in 8 ml. of 60% ethanol containing 0.5 g. of KOH was refluxed for 6 hours. Evaporation of the ethanol *in vacuo* and addition of 5 N hydrochloric acid (10 cc.) at 0° gave a clear solution of coronaridic acid. The acid solution was warmed on a steam-bath for 30 minutes, made basic with ammonia and extracted with ether. Crystallization of the residue from methanol yielded 21 mg. of material, m.p. 160–162°, identified as ibogamine (Id).

INDIANAPOLIS 6, IND.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

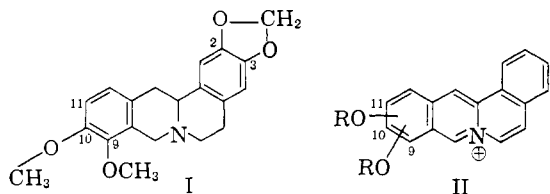
Aromatic Cyclodehydration. XLIII.^{1,2} Synthesis of Tetrahydroberberine and Some Dehydroberberine Analogs

BY C. K. BRADSHER AND N. L. DUTTA

RECEIVED JULY 13, 1959

6,7-Methylenedioxyisoquinoline-1-aldehyde (IV) and its oxime V have been synthesized, and used to prepare dehydroberberine (VI) and some of its analogs (VII–IX). The catalytic reduction of dehydroberberine gave the known tetrahydroberberine (I).

Berberine is perhaps the most important member of a group of alkaloids which bear the generic name. Although Perkin^{3,4} and his associates effected an



elegant and unequivocal synthesis of tetrahydroberberine (I), there has remained a need for a simple synthetic method suitable for the convenient preparation of tetrahydroberberine and its analogs.

In earlier work⁵ it was shown that benzo[a]acri-

(1) For the preceding communications of this series, see C. K. Bradsher and K. B. Moser, *J. Org. Chem.*, **24**, 592 (1959).

(2) This research was supported by a research grant (H-2170) from the National Heart Institute of the National Institutes of Health.

(3) (a) W. H. Perkin, J. N. Ray and R. Robinson, *J. Chem. Soc.*, **127**, 740 (1925); (b) R. D. Haworth, W. H. Perkin and H. S. Pink, *ibid.*, **127**, 1709 (1925); (c) R. D. Haworth, J. B. Koepfli and W. H. Perkin, *ibid.*, 548 (1927).

(4) Cf. I. K. Jezo and D. Rybár, *Chem. Zvesti.*, **8**, 14 (1954); C. A., **50**, 373 (1956).

(5) C. K. Bradsher and J. H. Jones, *J. Org. Chem.*, **23**, 430 (1958).

dizinium derivatives (II) having alkoxy substituents in one terminal ring (9- and 10-positions) could be prepared by cyclization of quaternary salts obtained by the reaction of suitable alkoxybenzyl halides with isoquinoline-1-aldehyde. It seemed very likely that if 6,7-methylenedioxyiso-

