

Alkaloids from *Apocynaceae*. II.¹ Ibogaline, a New Alkaloid from *Tabernanthe iboga* Baill

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As a result of our interest in the *Rauwolfia* alkaloids² we have undertaken in these laboratories a systematic study of other genera of the family *Apocynaceae*, in particular the members of the subfamily *Plumerioideae*. This subfamily contains several species which are known to be abundant in alkaloids.³ (e.g., *Aspidosperma*, *Tabernacmontana*, *Tabernanthe*, *Voacanga*, *Rauwolfia*, etc.)

Among the genera which were examined was the African hardwood *Tabernanthe iboga* Baill. This plant has been the subject of intensive investigations by several groups.⁴ More recently Taylor and co-workers have elucidated the structures of alkaloids occurring in this plant.⁵

The following alkaloids have been isolated from this plant: ibogaine,⁶ tabernanthine,⁶ ibogamine,⁶ iboluteine,⁷ iboquine,⁷ desmethoxyiboluteine,⁸ and hydroxyindolenine derivatives of ibogaine⁸ and ibogamine,⁸ voacangine,⁸ gabonine,⁸ kisanthine,⁸ and kimvuline.⁸

Of these the hydroxyindolenine derivatives as well as iboluteine, desmethoxyiboluteine, and iboquine could also be formed by the easy autoxidation of the parent alkaloids during the process of isolation.⁸

During the course of our investigation small amounts of a presumably new alkaloid,⁹ ibogaline, were isolated.

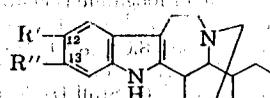
The commercial bark was processed by a scheme described in detail in the Experimental section, fractionation being accomplished by taking advantage of the solubility of ibogaine and congeners in ether. Ether-soluble alkaloids were

chromatographed on alumina. Elution with ether gave small amounts of ibogamine. Ether-chloroform mixtures and chloroform yielded small amounts of ibogaine followed immediately by an amorphous base which did not crystallize. The alkaloid was made into a crystalline hydrochloride salt, and the base was liberated and crystallized from aqueous methanol. This material, named ibogaline, gave analytical results compatible with a $C_{21}H_{28}N_2O_2$ formulation.

The ultraviolet spectrum of ibogaline is typical of a 2,3-dimethyl-5,6-dimethoxyindole,¹⁰ $\lambda_{\text{max}}^{\text{EtOH}}$ 227 m μ , (log a_M 4.40), 302 m μ , (log a_M 3.92).

Bands at 6.13, 6.28, 6.39, 6.74, and 11.96 μ in the infrared spectrum of ibogaline in chloroform solution occur at very nearly the same wave lengths and with about the same intensity in 2,3-dimethyl-5,6-dimethoxyindole¹⁰ (but are absent in the spectrum of ibogamine).

The major alkaloids of *Tabernanthe iboga* are represented by structures¹¹ I, II, and III for ibogamine, ibogaine, and tabernanthine, respectively.



$R' = R'' = H$; Ibogamine (I)
 $R' = OCH_3$; $R'' = H$; Ibogaine (II)
 $R' = H$; $R'' = OCH_3$; Tabernanthine (III)

On the basis of physical and analytical data as well as probable biogenesis of these alkaloids¹² it is reasonable to assume that ibogaline represents another congener of ibogamine with methoxyls placed at C₁₂ and C₁₃.

The scarcity of the material did not allow any degradative studies to prove the tentative assignment of the structure of ibogaline as 12,13-dimethoxy ibogamine.

EXPERIMENTAL

All melting points are uncorrected. The known alkaloids were identified by m.p., infrared spectra, and x-ray diffraction patterns with those of authentic samples.

Isolation of ibogaline. The ground root of *Tabernanthe iboga* (Hugo Frey, Belgium, 7.6 kg.) were mixed with 200 g. of sodium bicarbonate and exhaustively extracted with benzene until alkaloid test with Mayer's reagent was negligible. The benzene extract was evaporated to dryness *in vacuo*, and the residue dissolved in 5% sulfuric acid. After washing with Skelly F, the bases were liberated with aqueous ammonia and filtered (194 g.). The solids were dissolved in ether, and the ether-soluble material evaporated *in vacuo* (45 g.). This was dissolved in ether, passed quickly through 350 g. of deactivated alumina (acid-washed alumina, Merck), and the filtrate evaporated to dryness (23.5 g.). Crystallization from ethanol gave 10 g. of crystalline ibogaine still containing traces of another alkaloid

(10) N. Neuss, H. E. Boaz, and J. W. Forbes, *J. Am. Chem. Soc.*, **76**, 2463 (1954).

(11) W. I. Taylor, *J. Am. Chem. Soc.*, **79**, 3298 (1957).

(12) W. I. Taylor, *Experientia*, **13**, 454 (1957).

(1) Alkaloids from *Apocynaceae*, I. M. Gorman, N. Neuss, and N. J. Cone, 139th National Meeting of the American Chemical Society, San Francisco, Calif., April 1958.

(2) Norbert Neuss and Harold E. Boaz, *J. Org. Chem.*, **22**, 1001 (1957) and references cited therein.

(3) J. J. Willaman and B. G. Schubert, *Am. J. Pharm.*, **129**, 246 (1957).

(4) M. M. Janot, R. Goutarel, and R. P. A. Sneedon, *Helv. Chim. Acta*, **34**, 1205 (1951) and E. Schlittler, C. A. Burkhardt, and B. Gellert, *Helv. Chim. Acta*, **36**, 1337 (1953).

(5) M. F. Bartlett, D. F. Dickel, and W. I. Taylor, *J. Am. Chem. Soc.*, **80**, 126 (1958) and references cited therein.

(6) T. A. Henry, *The Plant Alkaloids*, J. A. Churchill Ltd., London, 1949, p. 768.

(7) R. Goutarel and M. M. Janot, *Ann. pharm. franc.*, **11**, 272 (1953).

(8) D. F. Dickel, C. L. Holden, R. C. Maxfield, L. E. Paszek, and W. I. Taylor, *J. Am. Chem. Soc.*, **80**, 123 (1958).

(9) We should like to thank Dr. W. I. Taylor for the samples of some of the rare *Iboga* alkaloids for the comparison with our alkaloid.

(paper chromatography). The mother liquor was evaporated to dryness to give 13.0 g. of a buff colored powder. This fraction was dissolved in 100 ml. of ether-benzene mixture (3:1) and chromatographed on 260 g. of deactivated acid-washed alumina. Elution with ether gave 350 mg. of crude ibogamine, which crystallized from methanol. When the solvent was changed to chloroform-ether mixtures, then to chloroform alone, 450 mg. of crude ibogaine were obtained. This fraction was followed by 520 mg. of a base which could not be induced to crystallize and gave a bright rose red color with Keller's reagent. The hydrochloride salt was prepared in the usual manner. After recrystallization from methanol-ether, 120 mg. of the hydrochloride were obtained, m.p. 264-266° (dec.).

Anal. Calcd. for $C_{21}H_{25}O_2N_2 \cdot HCl$: C, 66.91; H, 7.75; N, 7.43; Cl, 9.41; $OCH_3(2)$, 16.47. Found: C, 66.58; H, 7.86; N, 7.39; Cl, 9.40; OCH_3 , 16.75; 15.94.

The free base was liberated and crystallized from aqueous methanol, m.p. 141-143°. (The m.p. of the mixtures of ibogaline and ibogaine, and ibogaline and ibogamine were 112-119° and 113-123° respectively). $[\alpha]_D^{25} = -42.9^\circ$ ($CHCl_3$, $C = 1$).

Anal. Calcd. for $C_{21}H_{25}O_2N_2$: C, 74.08; H, 8.29; N, 8.23; $OCH_3(2)$, 18.24. Found: C, 73.87, 74.30; H, 8.33, 8.48; N, 8.21, 8.23; OCH_3 , 18.26. (The second analysis was obtained on material sublimed at 0.01 mm. pressure and 115°.)

The ultraviolet spectrum has the following bands: λ_{max}^{EtOH} 228 μ ($\log a_M$ 4.43), 304 μ ($\log a_M$ 4.01).

The infrared spectrum of ibogaline is characterized by the following prominent bands: $\lambda_{max}^{CHCl_3}$ 2.91 (indole NH), 6.13,¹² 6.28,¹³ 6.39,¹³ 6.74,¹³ 7.65, 8.64, 8.80, 9.79, and 11.96.¹³

ADDED IN PROOF: Since the submission of this paper, U. Renner, D. A. Prins and W. G. Stoll [*Helv. Chim. Acta*, 42, 1572 (1959)] have reported the isolation of an alkaloid, conopharyngine, from the bark of *Conopharyngia durissima* Stapf. A direct comparison of descarbomethoxy conopharyngine with our ibogaline has shown that, although the two compounds have different X-ray patterns, they are identical in all other respects (mixture m.p., optical rotation, and infrared spectrum in chloroform solution); therefore, conopharyngine is carbomethoxy ibogaline. We should like to thank Dr. Prins for the sample of descarbomethoxy conopharyngine.

Acknowledgment. The author wishes to thank Dr. H. E. Boaz for the infrared data, L. G. Howard for the ultraviolet spectra, W. L. Brown, G. M. Maciak, H. L. Hunter, and Miss G. Beckmann for microanalyses.

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(13) These bands occur at the same wave lengths in the infrared spectrum in chloroform solution of 2,3-dimethyl-5,6-dimethoxyindole and are absent in the spectrum of ibogamine.

Epoxidation of Diethyl Ethylidenemalonate by Alkaline Hydrogen Peroxide

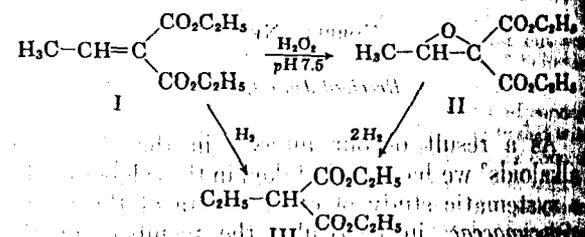
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The technique recently employed for the epoxidation of acrolein to glycidaldehyde¹ has also been successfully applied to an α,β -unsaturated diester,

(1) G. B. Payne, *J. Am. Chem. Soc.*, 80, 6461 (1958); 81, 4901 (1959).

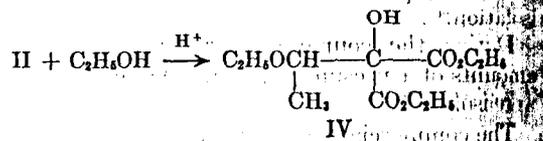
diethyl ethylidenemalonate (I). A solution of this ester in methanol containing 1.1 mol. equiv. of



50% hydrogen peroxide was treated dropwise with 1*N* aqueous alkali to effect the reaction over a 2-hr. period at 35-40° and pH 7.5-8. The product ethyl 2-carbethoxy-2,3-epoxybutyrate¹ (II) was readily isolated in 82% yield.

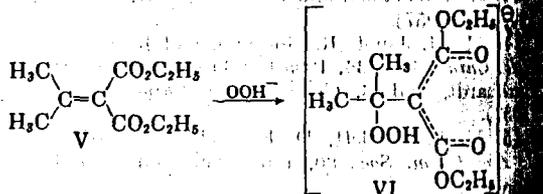
Hydrogenation of II proceeded with the absorption of 2 mol. of hydrogen to give diethyl ethylmalonate (III). The latter was also obtained from I to provide an authentic sample of ethylmalonic acid. When the hydrogenation of II was halted after 1 mol. uptake, only II and III were found.

Although II did not give the usual² titration for oxirane oxygen, the presence of that functional group was further indicated by reaction of II with hot acidic ethanol to give what was most likely the hydroxy ether IV, or the isomer having hydroxyl and ethoxyl groups reversed. The analysis of carefully fractionated IV was only fair; a low sapon-



ification equivalent, in particular, indicated the presence of an impurity.

The reaction of diethyl isopropylidenemalonate (V) with hydrogen peroxide proceeded to the extent of only 23% in 3 hr. at 45-50° and a higher pH (8-9) than used with I. Since alkali consumption was excessive during this period, the reaction was abandoned.



Failure of V to undergo epoxidation is in striking contrast to the facile reaction observed with I. This difference in reactivity is best rationalized on the basis of a steric inhibition of coplanarity

(2) J. L. Jungnickel, E. D. Peters, A. Polgar, and F. Weiss, *Organic Analysis*, Vol. I, Interscience Publishers, Inc., New York, N. Y., 1953, p. 135.

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