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THE HYDROXYINDOLENINE DERIVATIVE OF VOACANGINE, A NEW INDOLE ALKALOID FROM *VOACANGA AFRICANA*

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Abstract—A new alkaloid from *Voacanga africana* was identified as the hydroxyindolenine derivative (**6**) of voacangine, and its structure was proven by synthesis. A rearrangement product of **6**, the pseudoindoxyl **9**, was also encountered and characterized. Two additional new alkaloids, the hydroxyindolenine (**7**) and pseudoindoxyl (**10**) derivatives of voacristine were synthesized. Mass spectra of all compounds are presented and interpreted.

ELEVEN indole alkaloids have previously been isolated from the tree bark of *Voacanga africana*, and structures have been assigned to many of these.[1] A re-examination of this species, using the very sensitive methods of gas chromatography and mass spectrometry, was considered likely to reveal the presence of many minor constituents which had as yet remained undetected. Thus a complete investigation was undertaken, leading to the isolation of twelve additional compounds.[2]

One of the new alkaloids (compound A) was isolated initially in small quantity by gas chromatography. Its mass spectrum (Fig. 5) indicated a mol wt of 384, and the presence of a OH and a carbomethoxyl group was shown by relatively intense peaks at M − 17 and M − 59. Additional mass spectral peaks at M − 15 and M − 29 were characteristic[3] of the Et side chain found in all the iboga alkaloids, the class to which many of the *Voacanga* alkaloids belong.

For a more detailed characterization, additional amounts of this new compound were obtained by repeated column chromatography over alumina. According to TLC and its mass spectrum, the material obtained by this method was a single compound, but when subjected to gas chromatography, two major peaks were always observed. The first of these proved to be compound A. The second substance (B) also had a mol wt of 384, but its mass spectrum (Fig. 2) had little resemblance to that of A. Especially revealing was the absence of an M − 17 peak, which was the major fragment peak in the spectrum of A. As described below, the identification of B as the pseudoindoxyl derivative (**9**) of voacangine (**2**) provided a key to the structure of A, subsequently proven to be the hydroxyindolenine derivative (**6**) of voacangine.

A similarity between B and the known alkaloid iboluteine (**8**),[4] originally apparent from the bright yellow color and intense fluorescence, was further demonstrated by a comparison of their UV spectra (B: λ_{max}^{MeOH} 228 mμ (log ε 4·44), shoulder 255 (3·89), 410 (3·51); iboluteine: λ_{max}^{MeOH} 226 mμ (log ε 4·44), shoulder 255 (3·90), 418 (3·48).) The difference in mol wts of these two compounds suggested that B was a carbomethoxyiboluteine (**9**), i.e. the pseudoindoxyl derivative of voacangine (**2**). Additional information which pointed to structure **9** was the ester absorption at 1720 cm^{-1} in

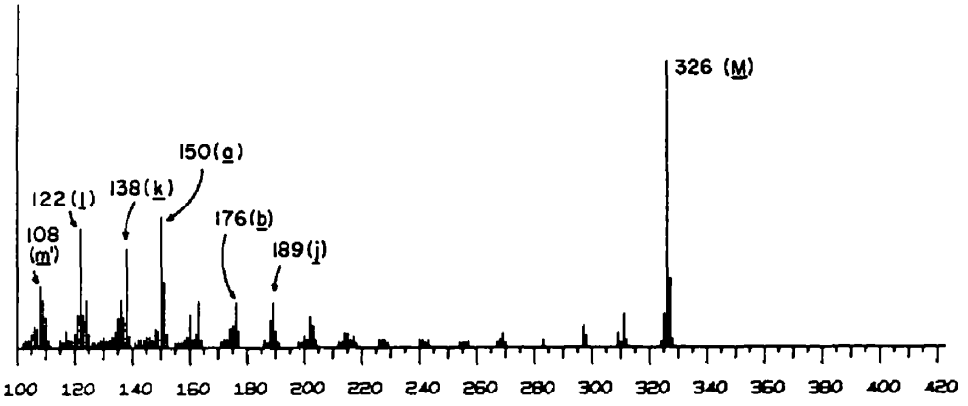


FIG. 1 Mass spectrum of iboluteine.

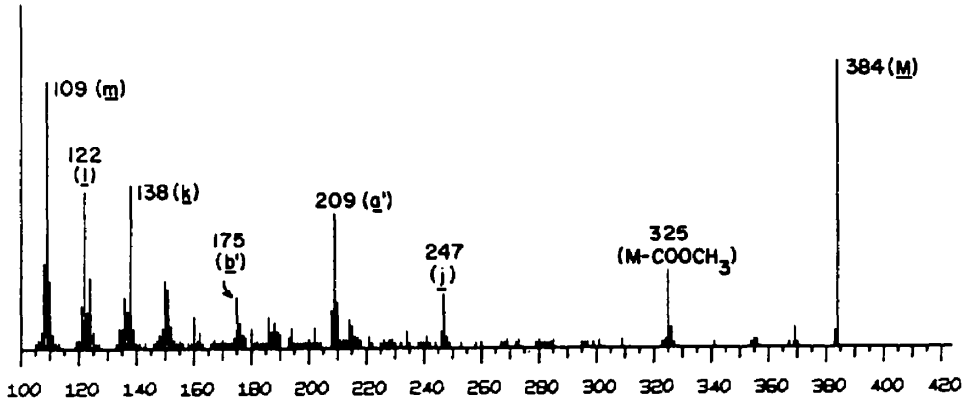


FIG. 2 Mass spectrum of voacangine pseudoindoxyl.

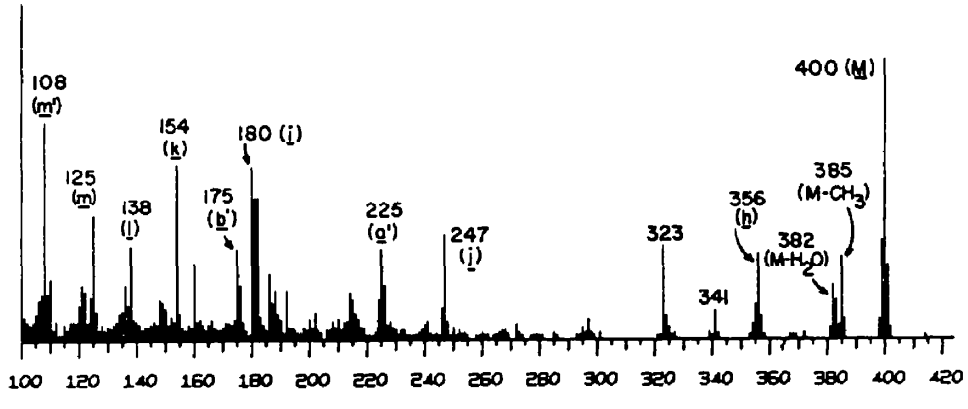


FIG. 3 Mass spectrum of voacristine pseudoindoxyl.

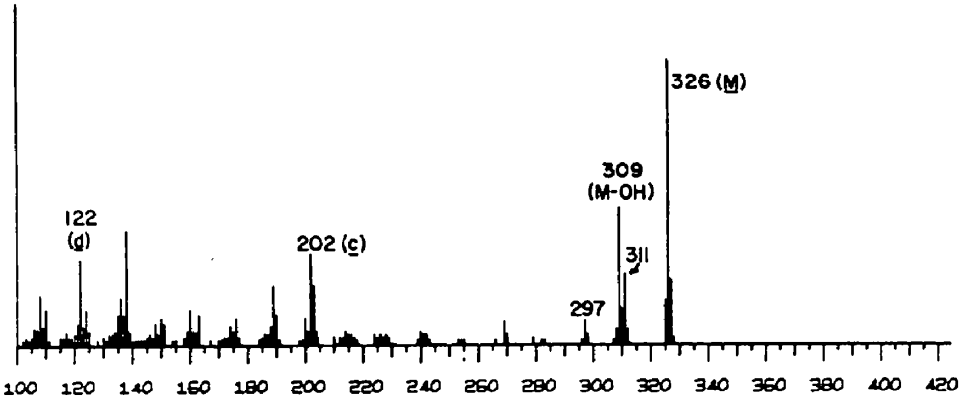


FIG. 4 Mass spectrum of ibogaine hydroxyindolenine.

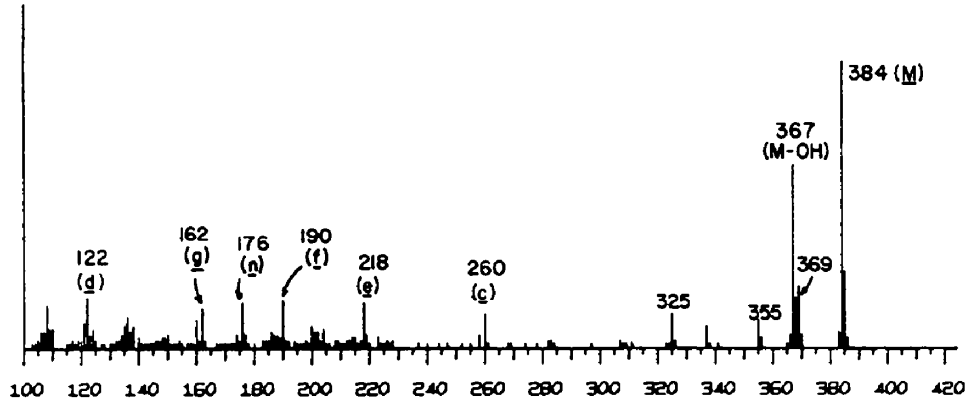


FIG. 5 Mass spectrum of voacangine hydroxyindolenine.

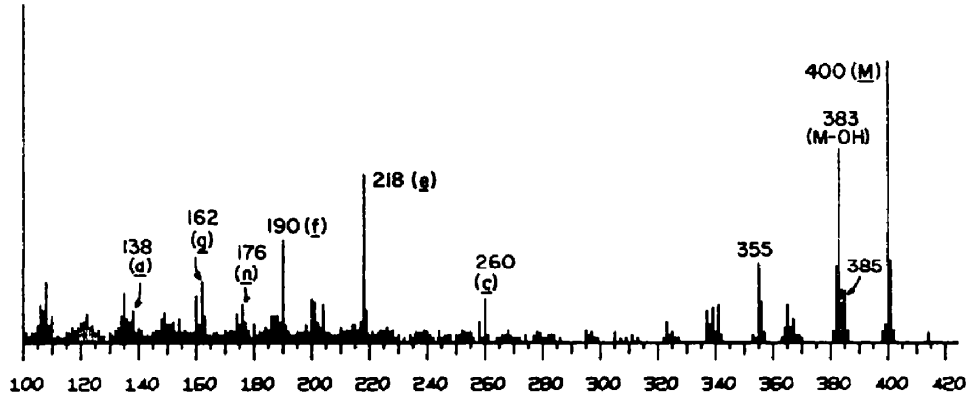
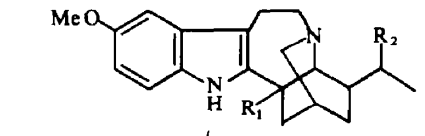
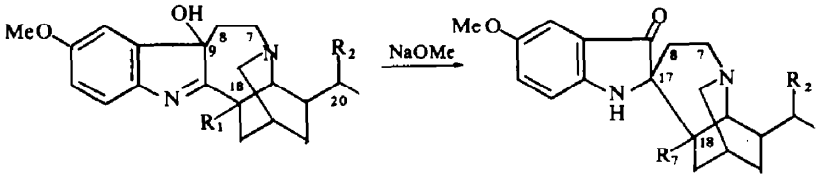


FIG. 6 Mass spectrum of voacristine hydroxyindolenine.

the IR spectrum, as well as a band at 1690 cm^{-1} from the pseudoindoxyl CO group. (We observed absorption of this CO at 1670 cm^{-1} in the spectrum of iboluteine.)



1: $R_1, R_2 = H$
2: $R_1 = COOMe; R_2 = H$
3: $R_1 = COOMe; R_2 = OH$
4: $R_1 = CH_2OH; R_2 = H$

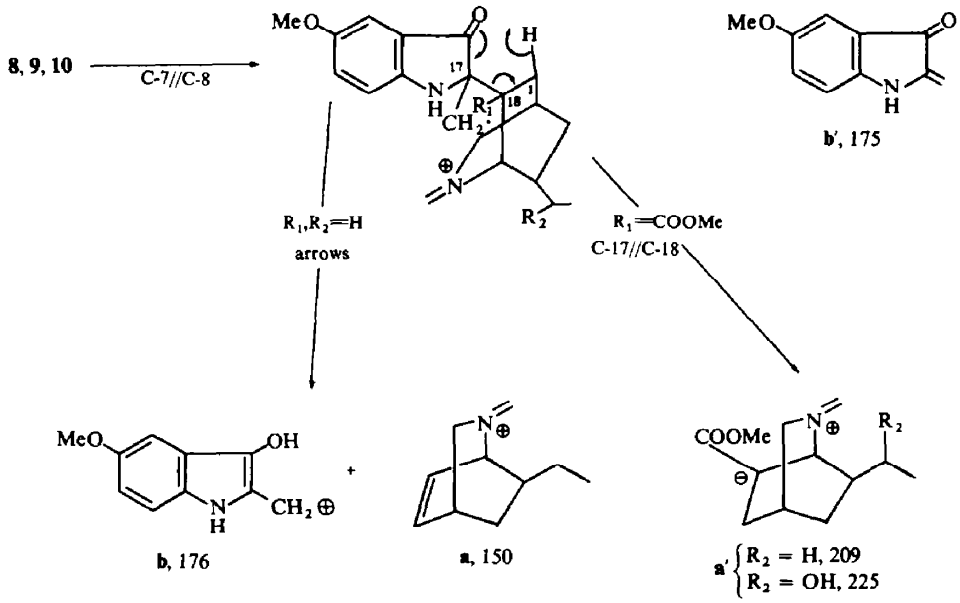


5: $R_1, R_2 = H$
6: $R_1 = COOMe; R_2 = H$
7: $R_1 = COOMe; R_2 = OH$

8: $R_1, R_2 = H$
9: $R_1 = COOMe; R_2 = H$
10: $R_1 = COOMe; R_2 = OH$

The mass spectrum of B (Fig. 2) also supported the suggested structure **9**. Mass spectra of very few pseudoindoxyl alkaloids had previously been discussed;[5] however a fragmentation scheme had been proposed[5b] to account for a few of the major peaks in the spectrum (Fig. 1) of iboluteine (**8**). As diagrammed in Scheme 1, cleavage at C-7, C-8 accompanied by a transfer of the C-1 hydrogen to the CO group leads to fragments **a** and **b**. However, the presence of a carbomethoxy group at C-18, as we had proposed for the new compound B, appeared to promote simple cleavage

SCHEME 1

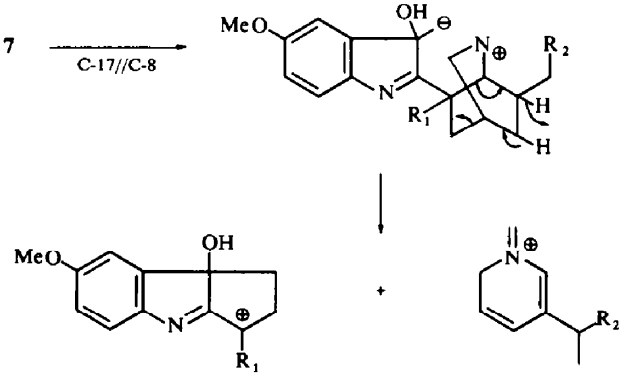


at C-17,C-18, and the resulting ions **a'** and **b'** differ from the iboluteine fragments by one H atom (with of course the additional carbomethoxyl group appearing in **a'**). The same effect of the carbomethoxyl group was also observed in the mass spectrum (Fig. 3) of the voacristine pseudoindoxyl (**10**, synthesis described later). The remaining major peaks of these mass spectra could be accounted for by the corresponding alkaloid structures, and are discussed in detail elsewhere.[2a]

Since both A and B had the same elemental composition ($C_{22}H_{28}N_2O_4$, from high resolution mass spectral determinations), the conversion of A to B must occur by a thermally induced rearrangement in the injection port of the gas chromatograph. Because of this relationship of A and B, a structure considered likely to represent A was the hydroxyindolenine derivative (**6**) of voacangine. Other known hydroxyindolenines (e.g. from ibogamine and ibogaine) undergo a similar rearrangement to the pseudoindoxyl skeleton under the conditions of base catalysis.[4a]

Structure **6** received support from the ultraviolet spectrum of A (λ_{max}^{MeOH} 228 mμ (log ε 4·24), 272 (3·78), 286 (3·79), 293 (3·78), shoulder 313 (3·68)). The shape of this curve was distinctly different from the indole spectra of various iboga alkaloids, yet it was remarkably similar to the spectrum of the ibogaine derivative **5** (λ_{max} 223 mμ (log ε 4·14), shoulder 260, 283 (3·77), shoulder 290, 312–313 (3·55)[4b]).

Substantial support for the hydroxyindolenine structure **6** was also provided by the mass spectrum of A (Fig. 5). The significance of the pronounced losses of 15, 17, 29 and 59 mass units from the molecular ion has already been discussed. Cleavage between C-7 and C-8, followed by a rearrangement found to be general for the iboga skeleton,[3] leads to the important ions **c** and **d**.



c $\begin{cases} R_1 = H, m/e\ 202 \\ R_1 = COOMe, m/e\ 260 \end{cases}$ **d** $\begin{cases} R_2 = H, 122 \\ R_2 = OH, 138 \end{cases}$

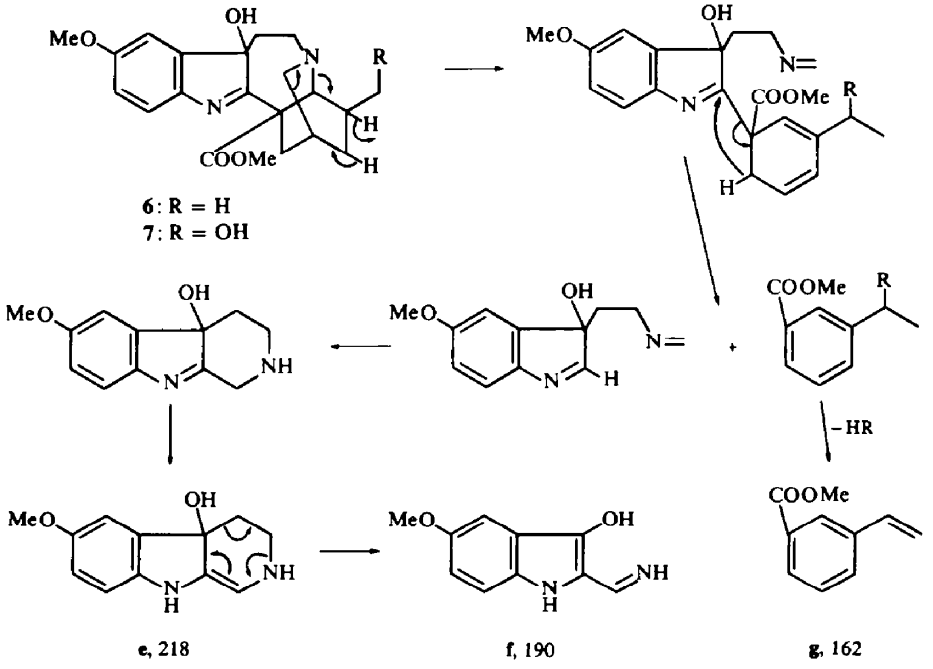
The ions at *m/e* 218 (**e**) and 190 (**f**), were similar in that they both contained the aromatic nucleus, two O atoms, and both nitrogens. In addition, a spectrum of **6** with a deuterated OH group showed the presence of the OH proton in these ions. The composition of **f** required that the alicyclic N be separated from the indole portion by only one C atom, whereas the structure **6** contains no fewer than two connecting carbons. The precursor of *m/e* 190 is most probably **e**, which loses ethylene by a retro-Diels-Alder rearrangement. The necessity to invoke a β-carboline

skeleton such as **e** created the serious question that the parent hydroxyindolenine might actually possess this, rather than an iboga, skeleton. The problem was solved by a hydride reduction[6] of A to an alcohol which showed all mass spectral fragmentations characteristic of the iboga alkaloids.[3] The product was identical (R_f and MS) with voacangol (**4**) obtained by hydride reduction of voacangine (**2**). Scheme 2 suggests one process by which these unusual ions may be formed, and the same process also can account for the origin of fragment **g**, unusual in its elemental composition ($C_{10}H_{10}O_2$; the high degree of unsaturation implies the presence of an aromatic ring which does not contain either of the nitrogens of the molecule).

To verify the suggested structures of A (**6**) and B (**9**), the synthesis of each from voacangine was attempted. One synthesis of the hydroxyindolenine derivative of voacangine by catalytic oxidation had been reported,[6a] but when this procedure was repeated, the desired product (**6**) was not obtained. A closer examination of the published IR spectrum of the compound reported to be **6** revealed that it was, in

SCHEME 2

(all structures represent radical ions; the customary brackets and +· notation has been omitted for simplicity's sake)

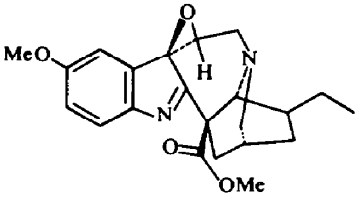


fact, voacangine lactam[7] rather than the hydroxyindolenine **6**. The authors had indeed expressed some doubt about the correctness of their structure assignment, because of the failure of their compound to undergo a base-catalyzed rearrangement characteristic of the hydroxyindolenines.

An alternative method, used successfully as the first step in the preparation of iboluteine, presumably *via* the intermediate **5**, involved the treatment of a benzene solution of the alkaloid with a stream of oxygen gas.[4c] This procedure, applied to voacangine (**2**); resulted in a good yield of the expected hydroxyindolenine derivative **6**, which was identical in every respect to A (UV, IR, and mass spectra, R_f).

The pseudoindoxyl derivative (**9**) of voacangine was prepared by the rearrangement of the synthetic hydroxyindolenine **6** in refluxing sodium methoxide. The product was identical in all spectral properties with the derivative obtained by thermal rearrangement of A. When **6** was treated with aqueous sodium hydroxide, hydrolysis of the ester group and subsequent decarboxylation accompanied the rearrangement. The resulting conversion to the known alkaloid iboluteine (**8**), identified by infrared and mass spectra, thus provided a confirmation of the structures of the voacangine derivatives.

Although the structure **6** seemed chemically well established, one unusual feature remained to be explained. The IR spectrum of **6** in chloroform has an intense peak at 1685 cm^{-1}, in addition to the expected ester band at 1735 cm^{-1}. This peak cannot be due to the indolenine C=N bond, because a similar absorption is entirely absent in the ibogaine hydroxyindolenine (**5**). Thus the peak seemed most likely to be associated with the ester group. Although the stereochemistry of the hydroxyindolenine alkaloids is unknown, one of the two possible C-9 epimers provides a relative stereochemistry which might account for the unusual IR absorption. In this epimer, two semi-rigid conformations may exist, indicated by structures **11** and **12**. The first of these will possess normal ester absorption. However, in the second conformer, the ester CO group is approximately one bond length from the H atom of the OH group, and its absorption may be shifted considerably to lower wavenumbers by a strong intramolecular hydrogen-bond. In solution, the two conformers may be in equilibrium, but in crystalline form only one of these should predominate. In agreement with this prediction, the infrared spectrum of **6** in potassium bromide shows a band at 1740 cm^{-1} of much greater intensity than the normal ester band of the solution spectrum. A very weak peak is also present at 1720 cm^{-1}, which may originate from a trace of a hydrogen-bonded conformer.



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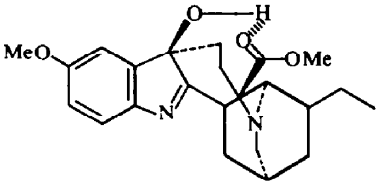

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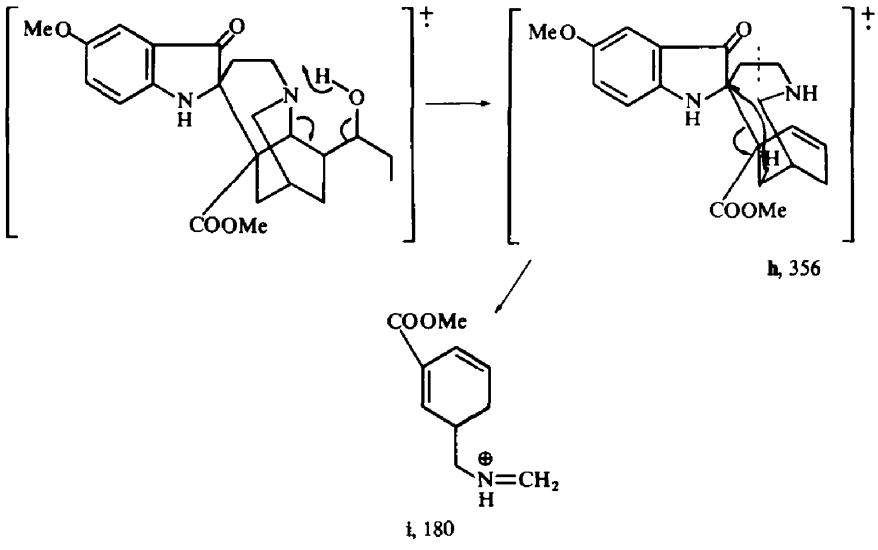
Although the iboga alkaloids ibogaine (**1**) and voacristine (**3**) are abundant in *V. africana*, the presence of their hydroxyindolenine derivatives in that plant was not detected. To aid in the comparison and interpretation of spectral and chemical data for this class of compound, these derivatives, **5**[4c] and **7**[8], were also prepared. Their mass spectra (Figs 4 and 6) are quite analogous to the spectrum of the voacangine derivative (Fig. 5), and the anomalous IR ester absorption discussed above for

the voacangine hydroxyindolenine (**6**) was also observed for the voacristine derivative **7** ($\nu_{max}^{CHCl_3}$ 1735, 1695 cm^{-1}).

The pseudoindoxyl derivative (**10**) of voacristine was obtained by treatment of **7** with base, followed by esterification with diazomethane.* The mass sepctrum of this product (Fig. 3) was completely analogous to that of voacangine pseudoindoxyl (Fig. 2). However, the additional ions at *m/e* 356 and 180 result from participation of the OH group in an interesting rearrangement (diagrammed below) and thus do not appear in the spectra of **8** and **9** which do not have a C-20 OH group.



Since the hydroxyindolenine and pseudoindoxyl derivatives are oxidation products of major alkaloids of *V. africana*, it is not certain that they exist as such in the plant. It is equally possible, in view of the ease of preparation in the laboratory, that these compounds were formed by air oxidation during the extraction and isolation processes. The apparent absence of the voacristine and ibogaine derivatives could also be in accord with this suggestion, since the *in vitro* oxidation of voacristine was found to proceed at a slower rate than that of voacangine, and the hydroxyindolenine of ibogaine is very unstable and would be expected to rearrange to iboluteine, which was isolated.

EXPERIMENTAL

The isolation of the alkaloids of *Voacanga africana* is described in greater detail elsewhere.[2] The voacangine hydroxyindolenine (**6**) was obtained by chromatography of the crude bases on alumina, from which it was eluted after voacangine and before voacristine. Further purification was effected by TLC on silica gel H. Mass spectra were determined with a Hitachi Perkin–Elmer RMU-6D mass spectrometer using a 70 eV ionizing potential. UV spectra were determined with a Cary Model 14 recording spectrophotometer, and IR spectra with a Perkin–Elmer Model 337 spectrophotometer.

Voacangine hydroxyindolenine (**6**). O_2 was bubbled through a soln of 400 mg voacangine in 4 ml benzene

* The carbomethoxyl group of **7** was quantitatively converted to the acid salt by the basic conditions, whereas the esters of **2**, **3**, and **6** remained intact after the same treatment. This facile hydrolysis is probably assisted by intramolecular participation of the C-20 oxygen of **7**.

for 4·5 hr under UV illumination (8 watts, long-wave). Upon chromatography on alumina, activity II, benzene eluted 75 mg of derivative **6** of voacangine, as well as considerable amounts of unchanged voacangine. The crystalline product, which formed by the slow evaporation of an ether soln of **6**, melted at 135–137°. The following data, including R_f, were identical with those of the natural alkaloid: λ_{max}^{MeOH} 228 mμ (log ε 4·44), 272 (3·78), 286 (3·79), 293 (3·78), shoulder 313 (3·68); $\nu_{max}^{CHCl_3}$ 1475, 1550, 1600, 1685, 1735, 3440, 3560 cm^{-1}; ν_{max}^{KBr} 1470, 1550, 1600, 1720, 1740, 3470 cm^{-1}; mass spectrum, Fig. 5.

Voacangine pseudoindoxyl (**9**). Compound **6**, 32 mg, was refluxed for 15 min in 5 ml of MeOH–MeONa. After the addition of 5 ml of water, two $CHCl_3$ extractions of 20 ml each yielded 27 mg of crystalline **9**. Recrystallization from MeOH gave yellow needles: m.p. 205–208°; λ_{max}^{MeOH} 228 mμ (log ε 4·44), shoulder 255 (3·89), 410 (3·51); $\nu_{max}^{CHCl_3}$ 1495, 1590, 1625, 1690, 1720, 3400 cm^{-1}; mass spectrum, Fig. 2.

Ibogaine hydroxyindolenine (**5**).[4c] Ibogaine (71 mg in 5 ml EtOAc), together with 36 mg of prereduced PtO_2, was treated with O_2 at room temp and press for 6 hr. The soln was flushed with N_2 and then reduced with H_2 gas for 45 min, again at room temp and press. Chromatography of the product on 3 g of alumina, activity II, yielded 26 mg of **5**. Two recrystallizations from acetone gave: m.p. 117–130°; λ_{max}^{MeOH} 224, 282, shoulders at 262, 292, and 313 mμ; $\nu_{max}^{CHCl_3}$ 1470, 1560, 1600, 3110, 3560 cm^{-1}; ν_{max}^{KBr} 1465, 1575, 1600, 3150 cm^{-1}; mass spectrum, Fig. 4.

Iboluteine (**8**). Compound **6** (12 mg) was suspended in 5 ml of 6N aq NaOH and refluxed for 30 min. Extraction with $CHCl_3$, and purification by TLC provided **8**: λ_{max}^{MeOH} 226 mμ (log ε 4·44), shoulder 255 (3·90), 418 (3·48); $\nu_{max}^{CHCl_3}$ 1480, 1590, 1620, 1670, 3400 cm^{-1}; mass spectrum, Fig. 1.

Iboluteine was also obtained by the treatment of **5** with refluxing methanolic NaOH.

Voacristine hydroxyindolenine (**7**).[8] Oxidation of 500 mg of **3**, using the same procedure as in the preparation of **6**, yielded 116 mg of amorphous **7** after purification by column and TLC; mass spectrum, Fig. 6.

Voacristine pseudoindoxyl (**10**). Compound **7** (10 mg) was refluxed for 15 min in 0·5 ml MeONa–MeOH. The total mixture was chromatographed on Sephadex LH-20 in MeOH, which gave the acid salt of **10**. Esterification with diazomethane yielded **10**; mass spectrum, Fig. 3.

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