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Voacamine and Voacorine[1]

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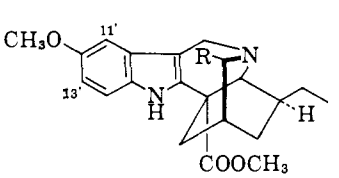
The structures of the two bisindole alkaloids named in the title were elucidated. Acid-catalyzed condensation of natural voacangine with vobasinol prepared from natural vobasine yielded voacamine and voacamidine. Analogous condensation of voacangarine with vobasinol furnished synthetic voacorine.

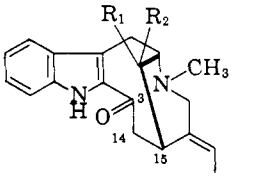
Recent investigations of the genus *Vocanga* have unearthed a quantity of new alkaloids biogenetically derived from tryptophan. One series of natural bases is characterized structurally by the presence of an isoquinuclidine ring and voacangine[4] (**1**) is the prototype of the entire group. Vobasine[5] (**3**) is representative of a second class of alkaloids containing the characteristic 2-acylindole grouping. Because of their apparent dimeric nature, a series of structurally unknown substances was classed together in a third family.

Voacamine, a prominent member of this group of "dimeric" *Voacanga* alkaloids, was first isolated from *Voacanga africana* Stapf,[6,7] and subsequently from other species[6,8] and other genera.[9,10] Its ultraviolet spectrum (λ_{max}^{EtOH} 225, 287, and 294 mμ; ε 52,600, 17,850, and 19,950) suggested the presence of a 5-methoxyindole chromophore and an equivalent weight of 698, obtained by potentiometric titration,[11] confirmed the "dimeric" nature of voacamine. Two of the four nitrogen atoms were found to be tertiary and basic (pK_a = 5.19 and 6.78),[11] whereas the remaining two were readily assigned as components of two indole rings. Early investigators[12,13] established the presence of one methoxy, one N-methyl, and two carbomethoxy groups in the molecule. Potash fusion of voacamine produced trimethylamine and 3-ethyl-5-methylpyridine, the latter being a characteristic transformation product of pentacyclic indole alkaloids containing the voacangine (**1**) skeleton. Saponification of voacamine furnished a salt of a dicarboxylic acid which on esterification with methanolic hydrochloric acid gave decarbomethoxy-*epi*-voacamine (**17**). Esterification with diazomethane yielded *epi*-voacamine (**15**)[11] which could also be obtained directly from voacamine by sodiumm ethoxide catalyzed epimerization.

The facile monodecarboxylation of the dicarboxylic acid, coupled with the aforementioned degradation to 3-ethyl-5-methylpyridine, led to the suggestion[13] that voacangine (**1**) might be a moiety of the voacamine molecule and this was subsequently established by acid-catalyzed cleavage of the dimer to voacangine (**1**).[14]



1, R = H_2
2, R = =O



3, R_1 = $COOCH_3$, R_2 = H
4, R_1 = H, R_2 = $COOCH_3$

We first considered the attachment of the as yet unknown moiety to the voacangine (**1**) unit. Cleavage of voacamine with 4 *N* hydrochloric acid in a mixture of deuterium oxide and methanol-O-*d* yielded, after recrystallization from methanol, trideuteriovoacangine. The n.m.r. spectrum of this material indicated that only the aromatic hydrogen atoms had been exchanged. This assignment was confirmed by a mass spectrum which exhibited a molecular ion at *m/e* = 371 (calcd. mol. wt. 371). The fragmentation pattern[15] again showed that the three deuterium atoms were located on the aromatic nucleus. This facile acid-catalyzed exchange of aromatic hydrogen atoms for deuterium atoms proved to be a general phenomenon[16] and was subsequently used to procure a variety of deuterated indole derivatives.

It became necessary to consider also part structure **5**. One can envision an acid-catalyzed cleavage of **5** initiated by protonation of the aromatic ring of the as yet unknown structural unit. Participation by the electron pair of the basic nitrogen atom results in the cleavage of the dimer (arrows in **5**). The resulting iminium intermediate **7** could cyclize to voacangine (**1**) by the sequence **7** → **8** → **9** → **1** without incorporating a deuterium atom into the aliphatic portion of the molecule. To test this hypothesis dihydrovoacamine[11] (*vide infra*) was oxidized with iodine[4] to a lactam, which on the basis of **5** would have part structure **6**,[17] in which the electron pair of the nitrogen atom is no longer able to participate in the formation of intermediate **7**. When this lactam was hydrolyzed with acid, voacangine lactam (**2**) was obtained, thus excluding part structure **5** from further consideration. The possible attachment of the voacangine (**1**) fragment to the unknown moiety by means of the indole nitrogen atoms was excluded

(1) A portion of the material discussed in this paper appeared in a Communication to the Editor: G. Büchi, R. E. Manning, and S. A. Monti, *J. Am. Chem. Soc.*, **85**, 1893 (1963).

(2) National Science Foundation Postdoctoral Fellow 1961–1962.

(3) National Science Foundation Predoctoral Fellow 1961–1964.

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

(5) (a) U. Renner and D. A. Prins, *Chimia* (Basel), **15**, 321 (1961); (b) U. Renner, D. A. Prins, A. L. Burlingame, and K. Biemann, *Helv. Chim. Acta*, **46**, 2187 (1963).

(6) M.-M. Janot and R. Goutarel, *Compt. rend. acad. sci.*, **240**, 1719 (1955).

(7) J. LaBarre and L. Gillo, *Bull. acad. roy. med. Belg.*, **20**, 194 (1955).

(8) F. Fish, F. Newcombe, and J. Poisson, *J. Pharm. Pharmacol.*, **12**, suppl. 41T (1960).

(9) F. Walls, O. Collera, and A. Sandoval, *Tetrahedron*, **2**, 173 (1958).

(10) M. Gorman, N. Neuss, N. J. Cone, and J. A. Deyrup, *J. Am. Chem. Soc.*, **82**, 1142 (1960).

(11) U. Renner and D. A. Prins, J. R. Geigy S.A., Basel, private communication.

(12) R. Goutarel, F. Percheron, and M.-M. Janot, *Compt. rend. acad. sci.*, **243**, 1670 (1956).

(13) F. Percheron, *Ann. chim.*, [13] **4**, 303 (1959).

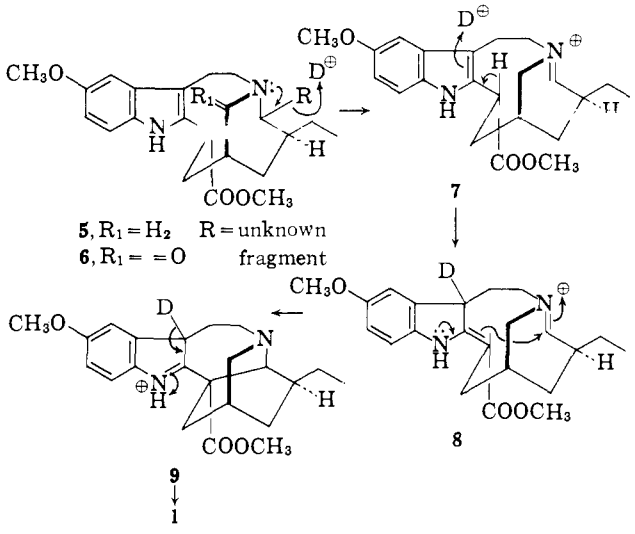
(14) W. Winkler, *Naturwiss.*, **48**, 694 (1961).

(15) (a) A. L. Burlingame and K. Biemann, unpublished results; (b) K. Biemann and M. Friedmann-Spitellel, *J. Am. Chem. Soc.*, **83**, 4805 (1961).

(16) In concentrated deuteriosulfuric acid N,N-dimethylaniline is converted to its polydeuterated analog: C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 303.

(17) *Cf.* the oxidation of ibogaine to ibogaine lactam (ref. 4).

for the following reasons. The aromatic region of the n.m.r. spectrum of hexadeuteriovoacamine[18] contained



two one-proton singlets at 7.48 and 7.78 δ,[19] which were shifted to 9.03 and 9.23 δ in acetone-d_6. The high-field indole N–H (7.48 δ) signal disappeared on exchange in deuterium oxide, whereas exchange of the low-field proton (7.78 δ) required acid catalysis. The n.m.r. spectrum of decarbomethoxy-*epi*-voacamine (**17**) showed indole N–H signals at 7.19 and 7.79 δ which demonstrated that the low-field, possibly hydrogen-bonded proton in voacamine was located in the unknown fragment. Clearly, the as yet obscure moiety in voacamine is linked to the aromatic ring of an intact voacangine (**1**) molecule.

Our original intention to deduce the structure of the unknown moiety from the products formed on acid-catalyzed cleavage of voacamine was thwarted by the appearance of a multitude of transformation products which we were unable to separate. Consequently it was necessary to investigate the nature of the unknown structural unit in the intact dimer.

An n.m.r. spectrum of voacamine revealed six aromatic protons and furthermore provided the first clue concerning the constitution of the second moiety. Signals at 1.66 (doublet, J = 7 c.p.s.) and 5.20 (quartet, J = 7 c.p.s.); 2.58 (singlet); 3.95 (singlet); 2.44 (singlet); and 3.61 δ (singlet) were assigned to ethylidene, N-methyl, O-methyl, and two carbomethoxy groupings. The high-field carbomethoxy group (2.44 δ) in voacamine (**14**) was shifted to 3.57 δ in *epi*-voacamine (**15**). This remarkable situation was also encountered in the n.m.r. spectra of vobasine (**3**) and *epi*-vobasine[5b] (**4**) and can be ascribed to the diamagnetic anisotropy effect of the indole nucleus.[20] These observations strongly suggested the presence of a vobasine-like skeleton in voacamine.[21] Treatment of voacamine (**14**) with methyl iodide in ether–methanol solution at room temperature furnished voacamine monomethiodide. The quaternary center presumably was located in the unknown moiety because voacangine (**1**) was recovered unchanged when subjected to identical reaction conditions. Sodium methoxide catalyzed Hofmann degradation of this methiodide gave voacamine methine (**10**). Its n.m.r. spectrum exhibited the expected signals for two carbomethoxy groups at 3.60 (singlet, six protons), one aromatic methoxy group at 3.85 (singlet), and two N-methyl groups at 2.12 δ (singlet, six protons). A two-proton multiplet at 4.52 δ was assigned to the methylene group of C-6 while a new, but somewhat obscured, one-proton signal was detected in the aromatic region. In the deuterated methine, prepared from hexadeuteriovoacamine, the new vinyl proton became visible at 7.4 δ (multiplet). When a similar sequence of reactions was carried out with dihydrovoacamine (**12**), available from voacamine by catalytic hydrogenation over platinum in acetic acid,[11] dihydrovoacamine methine (**13**) was secured. The 3-vinylindole grouping in **13** was revealed by the n.m.r. spectrum of the corresponding hexadeuteriomethine in which the two new vinyl protons appeared at 6.28 (quartet, $J \sim 10$ c.p.s.) and 7.00 δ (doublet, J = 11 c.p.s.). The absence of the characteristic 3-vinylindole type absorption[22] in the ultraviolet spectrum of dihydrovoacamine methine (**13**) is not surprising because the double bond is not coplanar with the indole ring.

Catalytic reduction of voacamine methine (**10**) over platinum in acetic acid gave a new compound whose n.m.r. spectrum indicated that it was still dimeric, containing no vinyl hydrogens and no N-methyl groupings but *three* C-methyl groups. It was formulated as **11** in which the dimethylamino group of the precursor (**10**) had been hydrogenolyzed prior to reduction of the ethylidine group. Acid-catalyzed cleavage of this substance **11** yielded voacangine (**1**), demonstrating that the basic nitrogen atom of the vobasine fragment is not required for cleavage. Consequently, the carbon–carbon link between the two monomers can originate only at C-3, C-14, or C-15 of the vobasine moiety. Of these alternative structures, **14** appeared most probable because the n.m.r. spectra of voacamine and its transformation products displayed a broad one-proton doublet in the 5-δ region. The carbomethoxy group of the vobasine (**3**) moiety influences the chemical shift of this proton. In voacamine the proton under discussion absorbs at 5.2 δ while in *epi*-voacamine (**15**) the signal is shifted to 4.7 δ. This implies that carbomethoxy group and hydrogen atom must be in proximity and the molecular model shows that this condition is satisfied in structure **14**. The "5-δ proton" in voacamine (**14**) was not replaced by deuterium under acid catalysis while the corresponding proton in the hydrogenolysis product (**11**) exchanged rapidly under identical conditions. These findings do not necessarily conflict with the structures proposed because the generation of the necessary methyleneindoline intermediate is sterically retarded in voacamine (**14**) but not in the ring-opened product (**11**).

Structure **14** also offered an explanation for the appearance of a low-field indole N–H signal in the n.m.r. spectrum of voacamine which might be caused by hydrogen bonding to the aromatic methoxy group. For spectral comparison with voacamine the model com-

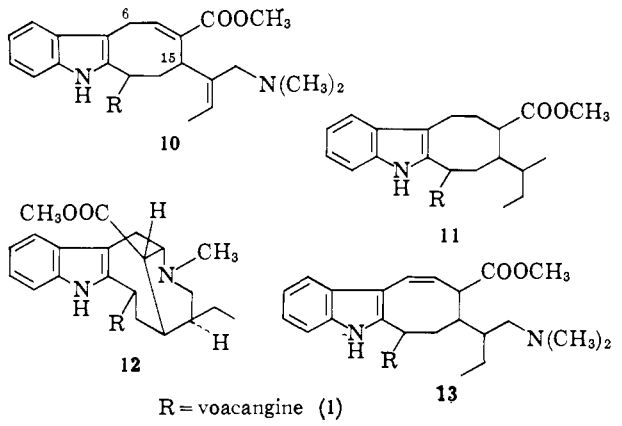
(18) Hexadeuteriovoacamine was prepared by exposure of voacamine to mineral acids in deuterated solvents. It could be separated from concomitantly formed cleavage products by chromatography.

(19) Chemical shifts are reported in p.p.m. downfield from tetramethylsilane.

(20) This has been discussed also by M. P. Cava, S. K. Talapatra, J. A. Weisbach, B. Douglas, and G. O. Dudek, *Tetrahedron Letters*, 53 (1963).

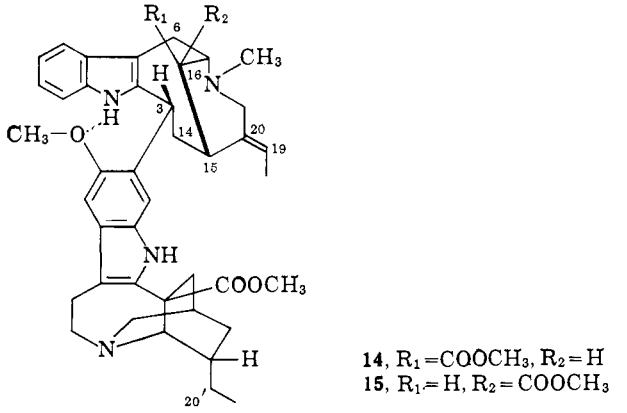
(21) The parallel behavior of voacamine and vobasine on base-catalyzed epimerization led to the tentative proposal that the latter alkaloid is related to a biogenetic precursor of voacamine: U. Renner, *Experientia*, **16**, 185 (1959).

(22) (a) E. Leete, *Tetrahedron*, **14**, 35 (1961); (b) W. E. Noland and R. J. Sundberg, *J. Org. Chem.*, **28**, 884 (1963).



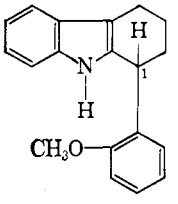
10 11 12 13

R = voacangine (1)



14, R_1=$COOCH_3$, R_2=H
15, R_1=H, R_2=$COOCH_3$

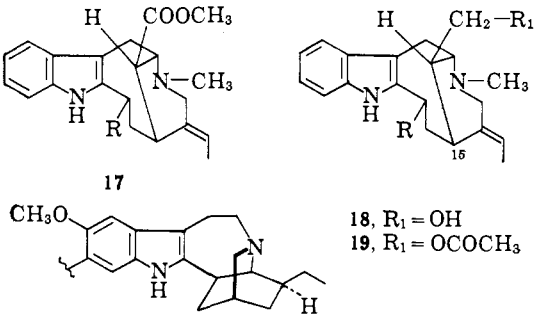
pound **16** was synthesized and its n.m.r. spectrum exhibited a triplet at 4.65 δ (C_1-proton) which was absent in the spectrum of the deuterated analog prepared by conventional acid-catalyzed hydrogen–deuterium exchange. In complete analogy to voacamine, the proton bonded to the indole nitrogen atom was exchanged for deuterium only under acid catalysis.



16

The evidence so far discussed indicated to us that voacamine might have structure **14**. Unfortunately, however, combustion analyses had resulted in the advancement of at least five different empirical formulas and the presence of an additional oxygen atom was strongly indicated by these findings. In order to settle this question, voacamine was submitted to mass spectral analysis.[23]

The initial mass spectrum of voacamine, obtained on a time-of-flight instrument, showed a molecular ion at m/e = 722 ± 4, whereas the calculated molecular weight of **14** is 704. Consequently we believed it necessary to place an additional oxygen atom in the vobasine portion of the molecule. Various cyclic ether structures were easily rejected on the basis of previously described evidence and a hydroxyl group was considered subsequently. The bridgehead carbon atom (C-15) appeared to be the most likely site of such a hydroxyl group because the mass spectrum of the hydrogenolysis product showed the anticipated molecular ion at m/e = 678 calculated for formula **11**. To explain the change in molecular composition, hydrogenolysis of the hydroxyl group in the methine (**10**, C_{15}-OH) had to be assumed. All efforts to confirm the presence of a hydroxyl group in voacamine failed. For example, reduction of decarbomethoxy-*epi*-voacamine (**17**) with lithium aluminum hydride yielded the corresponding alcohol **18** which did not give the anticipated cyclic carbonate (C_{15}→C_{17}) when treated with phosgene. We consequently were forced to assume that the peak at m/e = 722 ± 4 in the mass spectrum of voacamine did *not* correspond to the molecular weight of the alkaloid but to the molecular ion of some transformation product. The previously observed[13] formation of trimethylamine on pyrolysis of voacamine furnished the necessary clue to the nature of this artifact. Intermolecular methyl transfer and subsequent Hofmann elimination could occur thermally when voacamine was vaporized directly into the ion source and the molecular ion actually measured would be that of voacamine methine (**10**, mol. wt. 718). This hypothesis was shown to be correct. A mass spectrum of voacamine, obtained on a CEC 103 instrument, showed a molecular ion at m/e = 718 ± 0 and the spectrum of the acetate **19** which *lacks carbomethoxy groups*, necessary for methyl transfer, showed the anticipated molecular ion at m/e = 660. Consequently, voacamine contains only the five previously discussed oxygen atoms and can be assigned a molecular weight of 704 corresponding to the composition $C_{43}H_{52}N_4O_5$.



17

R =

18, R_1 = OH
19, R_1 = $OCOCH_3$

Examination of the peaks at high mass numbers in the spectrum of voacamine revealed the course of this methyl transfer reaction. Thus, the peak at m/e = 673 results from quaternization of voacamine methine (mass 718) followed by loss of trimethylamine. The initial methyl transfer produces a nonvolatile carboxylic acid anion which becomes protonated in the course of the Hofmann elimination. This amino acid (mass 690) is not detectable in the spectrum, possibly owing to its zwitterionic nature. It seems to lose carbon dioxide to produce a peak at m/e = 646. A peak at m/e = 660 could arise from methyl transfer to a mass 646 species followed by Hofmann elimination. A further methyl transfer followed by loss of trimethylamine gives m/e = 615. Utilization of the material with mass 615 as a source of methyl groups produces, after protonation, a carboxylic acid in which the basic vobasine nitrogen atom is no longer present. This substance is now volatile and detectable in the mass spectrum at m/e = 601.

In the course of pyrolysis, each transformation product containing a carbomethoxy group can serve as a

(23) Mass spectra were kindly measured by Professor K. Biemann and his collaborators at M.I.T.

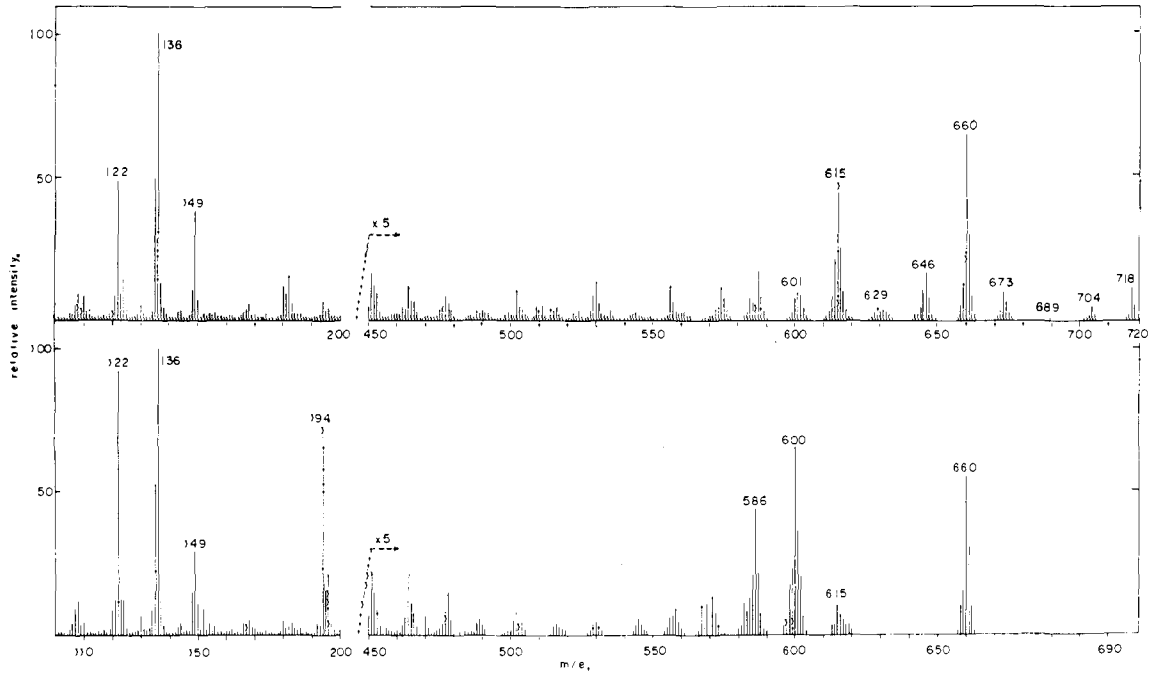


Fig. 1 (upper curve).—Voacamine (**14**). Fig. 2 (lower curve).—Acetate **19**. Doubly charged ions are the only significant fragments in the region m/e = 200–450. Peak intensities above m/e = 450 are magnified by a factor of five.

source of methyl groups and consequently masses 673 and 718 can give rise to masses 615 and 660, respectively. The pyrolytic origin of these transformation products is readily confirmed by the dependence of the peak intensities on time and temperature. At the time of the initial appearance of the spectrum the peaks at m/e = 615, 646, 660, 673, 704, and 718 are of comparable intensity. As the inlet temperature is increased, the intensity at mass 704 decreases while the others, especially masses 615 and 660, increase (spectrum shown in Fig. 1). As the pyrolysis proceeds the intensities of the peaks which contain two carbomethoxy groups (masses 673, 704, and 718) diminish considerably, whereas the intensity of mass 660 reaches a maximum. It subsequently decreases and mass 615 becomes the major high mass number peak while there is a definite increase in the intensity of mass 601. This behavior is precisely that anticipated for a pyrolysis, but it is not compatible with fragmentation in the ion source. If mass 615 were derived from mass 660 by electron impact, the intensity ratio of the two peaks would be independent of time and temperature. The low mass number region of the spectrum distinctly displays the isoquinuclidine fragments (m/e = 122, 136, and 149) of the voacangine moiety.[15] The spectrum of the acetate 19 shows the loss of acetic acid and methyl acetate at m/e = 600 and 586, respectively, while the isoquinuclidine fragments of the voacangine molecule as well as the intact aliphatic vobasine fragment (m/e = 194)[5] appear at low mass numbers.

Thus, after an appropriate period of confusion, the mass spectral data eventually supported the gross structural formula of voacamine (see also ref. 41) but it must be emphasized that misleading mass spectrometric molecular weights may be produced by substances of low volatility which are prone to undergo thermal reactions. More recently a similar situation was encountered with vinblastine and high resolution data[24] fully confirmed the explanation offered for voacamine.

The remaining aspect of the structure of voacamine (excluding stereochemistry) concerned the precise attachment of the "vobasine unit" to the aromatic ring of voacangine. Structure **14** was favored because the n.m.r. spectrum of voacamine showed a partly obscured one-proton singlet at 6.72 δ. More definitive evidence was provided by synthetic studies which will now be discussed.

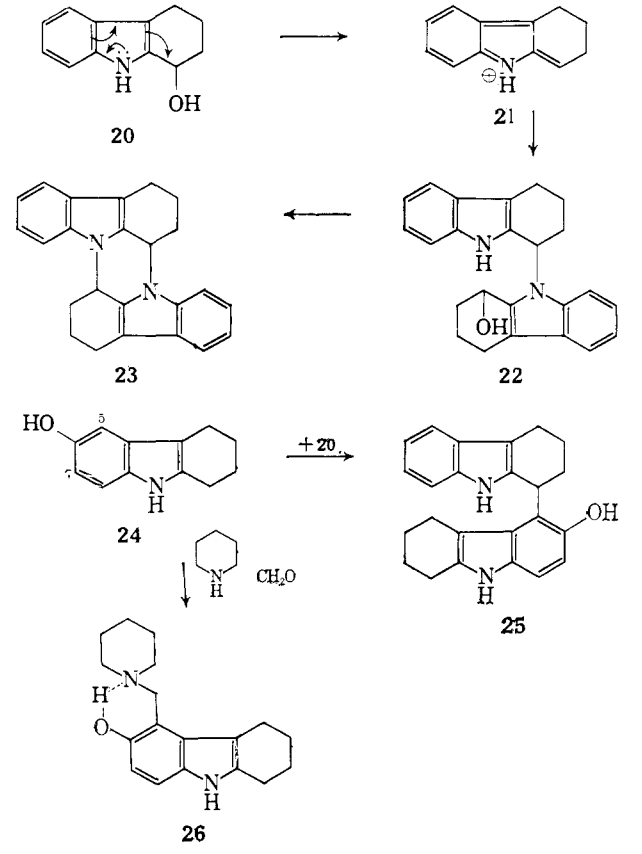
To effect a partial synthesis of voacamine (**14**) the cleavage reaction already discussed has to be reversed. This approach necessitates the generation of an electrophilic center at C-3 in a vobasine-type precursor which in turn should condense with voacangine (**1**). 1-Hydroxy-1,2,3,4-tetrahydrocarbazole (**20**) is known to undergo rapid self-condensation to the dimer **23** in the presence of dilute mineral acids.[25] The over-all process can be rationalized with ease by assuming the intermediacy of an iminium salt (**21**) which undergoes condensation with the nucleophilic nitrogen atom of the indole ring to yield a second intermediate (**22**). An intramolecular repetition of the same process leads to the dimer **23**. This case indicated that vobasinol (**42**) might serve as the precursor of the desired iminium salt and the question of whether a methoxyindole would undergo condensation on carbon or nitrogen was investigated next. Condensation of 6-hydroxy-1,2,3,4-tetrahydrocarbazole (**24**) with formaldehyde and piperidine gave the adduct **26**. Similarly, an equimolar mixture of the two isomeric hydroxytetrahydrocarbazoles **20** and **24** produced a condensation product (**25**).

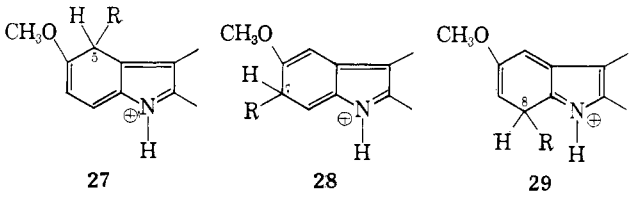
The n.m.r. spectrum of the tetradeuterio analog of **25** prepared from Ar-tetradeuterioalcohol **20** clearly showed that condensation had again taken place at C-5 whereas linkage to C-13′ of voacangine (**1**) seemed required in a synthesis of voacamine. A comparison of the relative stabilities of the three formally possible in-

(24) P. Bommer, W. McMurray, and K. Biemann, *J. Am. Chem. Soc.*, **86**, 1439 (1964).

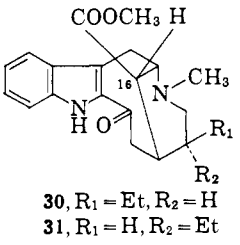
(25) S. G. P. Plant, R. Robinson, and M. Tomlinson, *Nature*, **165**, 928 (1950).

termediates resulting from addition of a 5-methoxyindole to an iminium salt indicated that condensation at C-5 should be favored. Electronically, intermediate **27** appears most stable because the oxygen atom of the methoxy group and the positively charged indole nitrogen atom are fully conjugated. Intermediate **28** leading to a C_7-substituted product still exhibits considerable conjugation, while in the third Mannich intermediate (**29**) delocalization between oxygen and nitrogen is no longer possible. Consequently, condensation at this position appears most unlikely and was in fact never observed. At the time we were ready to attempt a

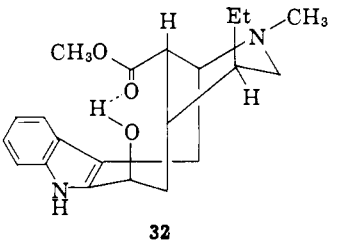




partial synthesis of voacamine no vobasine (**3**) was available to us and dihydrovoacamine (**12**) became the initial target. Reduction of natural dregamine (**30**) with sodium borohydride yielded dregaminol (**32**) which on condensation with equimolar amounts of voacangine (**1**) in dilute methanolic hydrochloric acid was converted to dihydrovoacamine (**12**) identical in all respects with a sample prepared from natural voacamine (**14**). Mannich condensation had clearly occurred at the C_{13}-position of voacangine (**1**) since the n.m.r. spectrum of deuterated **12** synthesized from Ar-tetradeuteriodregaminol exhibited two one-proton singlets at 6.75 and 7.03 δ. This partial synthesis of dihydrovoacamine established the composition of the original alkaloid as $C_{43}H_{52}N_4O_5$ which disagrees with all previous proposals based on combustion analyses. If it is assumed that sodium borohydride attacks the carbonyl group of dregamine (**30**) from the sterically less crowded side of the molecule, dregaminol (**32**) has the 3β-OH configuration and this was confirmed by its infrared spectrum. The shift of the ester carbonyl frequency from 1720 cm.$^{-1}$ in dregamine (**30**) to 1690 cm.$^{-1}$ in dregaminol (**32**) demands an intramolecular hydrogen bond between the carbonyl oxygen atom and the hydroxyl hydrogen atom in the alcohol **32**. Furthermore, the n.m.r. spectrum of dregaminol (**32**) revealed that the carbomethoxy group (2.40 δ) was again located above the indole nucleus and a molecular model demonstrates that only one conformation of dregaminol (that depicted by formula **32**) is consistent with these findings. Entirely parallel spectral phenomena were previously[5] observed with vobasine (**3**) and vobasinol (**42**).



30, R_1 = Et, R_2 = H
31, R_1 = H, R_2 = Et



32

The configurations of the C_{20}-ethyl groups in the two naturally occurring epimeric alkaloids dregamine (**30**) and tabernaemontanine[5] (**31**) are based on the facile base-catalyzed epimerization of tabernaemontanine (**31**) to its C_{16}-epimer. Dregamine (**30**), on the other hand, was recovered unchanged when subjected to identical conditions. Epimerization at C-16 would result in a 1,3-diaxial arrangement of large substituents. In agreement with these observations, dihydrovoacamine (**12**), now known to contain the dregamine moiety, was also unaffected by conditions known to epimerize voacamine (**14**) to *epi*-voacamine (**15**).

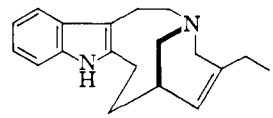
When vobasine (**3**) became available it was reduced to vobasinol (**42**) using the procedure developed for the reduction of perivine (**40**) (*vida infra*). Condensation of voacangine (**1**) with vobasinol (**42**) yielded voacamine (**14**) identical in all respects with natural material. It should be noted that a more highly acidic medium and a longer reaction time were required in the synthesis of voacamine (**14**) as compared to the analogous condensation leading to dihydrovoacamine (**12**). This difference in behavior can probably be attributed to a retardation of iminium salt formation in the case of vobasinol (**42**) which contains an additional trigonal carbon atom in the ten-membered ring. The partial synthesis of voacamine (**14**) has also been achieved in another laboratory.[26] Because the condensation of the monomers proceeds under relatively mild conditions, it was necessary to ask the question whether voacamine (**14**) might be an artifact formed from its progenitors in the course of isolation from natural sources. When a mixture of voacangine (**1**) and dregaminol (**32**) was processed in the manner recommended for the isolation of voacamine from plant material, dihydrovoacamine was not detectable and the monomers were recovered unchanged.

We now consider the absolute configuration of voacamine. At the time our structural findings were published in preliminary form the absolute configurations

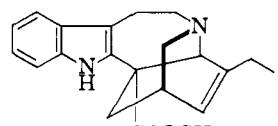
(26) U. Renner and H. Fritz, *Tetrahedron Letters*, 283 (1964).

of the two monomers were unknown but chemical evidence concerning this question is now complete. The absolute configuration of voacangine (**1**) follows directly from its relationship to cleavamine[27a] (**33**) whose absolute stereochemistry was determined using the X-ray technique of anomalous dispersion.[27b,28] Reductive decarbomethoxylation of catharanthine (**34**) was shown to yield cleavamine (**33**).[29,30]

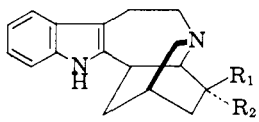
Secondly, catalytic hydrogenation of catharanthine (**34**) furnished *epi*-coronaridine (**35**)[29] which by means of hot hydrochloric acid was transformed to a mixture of *epi*-ibogamine (**37**) and ibogamine[30] (**36**). Thirdly, ibogaine (**38**) has been prepared from voacangine (**1**)[31] and the former has now been converted to ibogamine (**36**) by standard procedures (see Experimental section). Both ibogaine (**38**) and ibogamine (**36**) were previously transformed to the tricyclic ketone **39**. These transformations consequently correlate cleavamine (**33**) with voacangine (**1**) and the absolute configuration of the voacangine moiety of voacamine (**14**) is that already indicated in all formulas.[32]



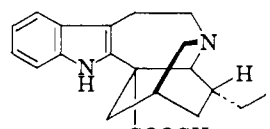
33



34



36, $R_1 = Et, R_2 = H$
37, $R_1 = H, R_2 = Et$



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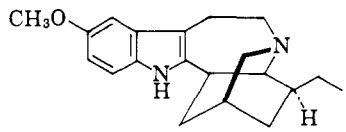

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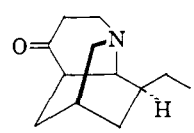
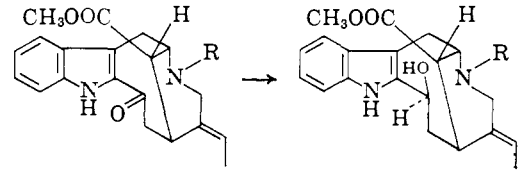


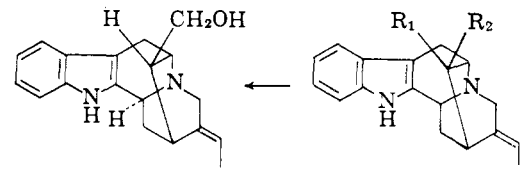
39

The absolute configuration of vobasine (**3**) was determined as follows. Reduction of perivine (**40**), recently shown to be des-N-methylvobasine,[33] with sodium borohydride at 0° in aqueous methanol saturated with carbon dioxide gas gave perivinol (**41**). The infrared spectral behavior of perivine (**40**) and perivinol (**41**) paralleled those of dregamine (**30**) and dregaminol (**32**), and perivinol (**41**) consequently has a 3β-OH configuration. Treatment of perivinol (**41**) with dilute methanolic hydrochloric acid or with *p*-toluenesulfonic acid in benzene, tetrahydrofuran, or dioxane gave no pentacyclic material. The secondary nitrogen atom is undoubtedly protonated under these conditions and consequently is no longer available for participation in the cyclization reaction. The desired transannular cyclization was effected, however, simply by refluxing the alcohol **41** in xylene which furnished ester **43** in excellent yield. The remaining transformations were unexceptional. Sodium methoxide catalyzed epimerization of the ester **43** gave the *epi*-ester **44** which was reduced with lithium aluminum hydride to give normacusine-B (**45**), identical in all respects with natural material. The absolute configuration of normacusine-B (**45**) is known[34-36] and this conclusion is already allowed for in all formulas presented in this paper. The remaining question of stereochemical detail concerns the geometry at C-3 in voacamine (**14**) and although no unambiguous evidence is available on this point it seems safe to assume that voacangine (**1**) adds to the vobasinol-derived iminium salt from the much less crowded α-side of the molecule thus dictating the configuration at C-3 already indicated in structure **14**. This assignment is in accord with the observed chemical shifts of the C_3-proton in voacamine (**14**) and *epi*-voacamine (**15**) (*vide supra*).



40, R = H
3, R = CH_3

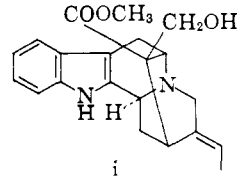
41, R = H
42, R = CH_3



45

43, $R_1 = COOCH_3, R_2 = H$
44, $R_1 = H, R_2 = COOCH_3$

Voacorine,[37,38] a second dimeric indole alkaloid of *Voacanga africana* Stapf., gives voacangarine[39,40] (**46**) on acid hydrolysis[41] and was previously postulated[13] to be 20′-hydroxyvoacamine.[42] This hypothesis has now been confirmed by a partial synthesis of voacorine from vobasinol (**42**) and voacangarine (**46**) using the procedure described for the partial synthesis of voacamine.



i

(27) (a) N. Neuss, M. Gorman, H. E. Boaz, and N. J. Cone, *J. Am. Chem. Soc.*, **84**, 1509 (1962); (b) J. P. Kutney, J. Troller, T. Tabata, A. Kerigan, and N. Camerman, *Chem. Ind.* (London), 648 (1963).

(28) J. M. Bijvoet, A. F. Peerdeman, and A. J. vanBommel, *Nature*, **168**, 271 (1951).

(29) N. Neuss and M. Gorman, *Tetrahedron Letters*, 206 (1961).

(30) M. Gorman and N. Neuss, Abstracts, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963, p. 38M.

(31) M.-M. Janot and R. Goutarel, *Compt. rend. acad. sci.*, **241**, 986 (1955).

(32) This assignment agrees with that of C. Djerassi (quoted in ref. 4) based on the optical rotatory dispersion curve of a ketonic degradation product of ibogaine.

(33) M. Gorman, Abstracts of Papers, IUPAC Symposium, Kyoto, Japan, 1964, p. 97. We are indebted to Dr. M. Gorman for informing us of his work prior to publication and for a generous supply of the alkaloid.

(34) A. R. Battersby and D. A. Yeowell, *Proc. Chem. Soc.*, 17 (1961).

(35) M. F. Bartlett, R. Sklar, W. I. Taylor, E. Schlittler, R. L. S. Amai, P. Beak, N. W. Bringi, and E. Wenkert, *J. Am. Chem. Soc.*, **84**, 622 (1962).

(36) The configuration of the ethylidine group in normacusine-B follows from its chemical relationship to akummidine (**5**), whose structure was determined by X-ray analysis: S. Silvers and A. Tulinsky, *Tetrahedron Letters*, 339 (1962).

(37) R. Goutarel and M.-M. Janot, *Compt. rend. acad. sci.*, **242**, 2981 (1956).

(38) J. LaBarre and L. Gillo, *Compt. rend. soc. biol.*, **150**, 1628 (1956).

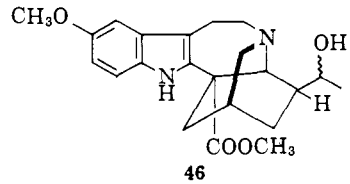
(39) U. Renner and D. A. Prins, *Experientia*, **17**, 106 (1961).

(40) K. Biemann and M. Friedmann-Spiteller, *Tetrahedron Letters*, **2**, 68 (1961).

(41) W. Winkler, *Arch. Pharm.*, **295**, 895 (1962).

(42) For mass spectrometric support of this structure, see H. Budzikiewicz, C. Djerassi, F. Puisieux, F. Percheron, and J. Poisson, *Bull. soc. chim. France*, 1899 (1963).

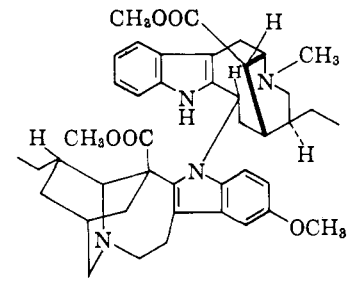
The synthetic material was identical with the natural alkaloid.



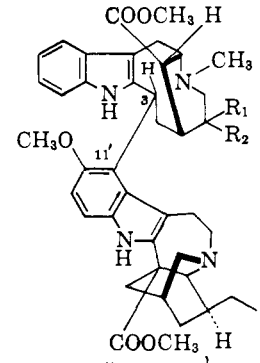
46

The condensation of dregaminol (**32**) with voacangine (**1**) described above yields more than one condensation product. Chromatographic purification of the mother liquors produced in the crystallization of dihydrovoacamine (**12**) led to the isolation of an amorphous but seemingly homogeneous base whose n.m.r. spectrum revealed the presence of the N-methyl and the carbomethoxy groups of the vobasine moiety (signals at 2.68 and 2.46 δ). Additional singlets at 3.80 and 3.08 δ were attributed to the two O-methyl groups in the voacangine (**1**) fragment and the remaining significant one-proton absorption at 5.51 δ was ascribed to the C_3-hydrogen atom of the vobasine portion. The presence of *two* shielded methoxy groups and a deshielded hydrogen atom on C-3 can be reconciled with either of the two structures, **47** and **49**. The carbomethoxy group in the voacangine portion is located above the indole ring of the "vobasine" portion in structure **47** and the deshielding of the C_3-proton could be caused by the neighboring indole nitrogen atom. The alternative structure **49** results from a condensation at the electronically more favorable but sterically hindered C_{11}'-position. The n.m.r. spectrum of the deuterated isomer of dihydrovoacamine prepared by condensation of Ar-tetradeuteriodregaminol with voacangine (**1**) showed a two-proton AB quartet centered at 6.88 and 7.18 δ (J = 8.5 c.p.s.). This absorption pattern is only compatible with structure **49**. Structure **48** was very recently assigned[26] to voacamidine,[43] a third bisindole alkaloid isolated from *Voacanga africana*. The n.m.r. spectrum of voacamidine (**48**) also contains *two* shielded methoxy groupings at 2.58 and 3.08 δ[26] and a one-proton multiplet for the C_3-hydrogen atom at 5.50 δ.[44]

Molecular models show that rotation about the C_3-C_{11}' bond is sterically inhibited and that in the more stable conformation the aromatic methoxy group of the voacangine unit is situated above the indole ring of the vobasine fragment. The three-proton singlet at 3.08 δ consequently was attributed to this shielded O-methyl group.[26] The restricted rotation about the C_3-C_{11}' bond also places the C_3-hydrogen atom in the plane of the voacangine nucleus and it is magnetically deshielded by the ring current of the indole nucleus.[44,45] After the structure of voacamidine (**48**) was announced, we reexamined the partial synthesis of voacamine and isolated minor amounts of a second bisindole which was purified as its highly crystalline hydrobromide salt. The infrared spectrum of this salt was different from that of voacamine hydrobromide but superimposable on that of voacamidine hydrobromide. Consequently, Mannich condensation with voacangine (**1**) occurs at both C_{11}' and C_{13}', and if sufficiently mild conditions are employed both voacamine (**14**) and voacamidine (**48**) are isolable. In more highly acidic media the latter alkaloid is isomerized to the more stable voacamine (**14**).[26]



47



48, R_1, R_2 =

49, R_1 = Et, R_2 = H

Experimental[46]

Voacamine dipotassium salt was prepared by the method of Percheron[13] in 85% yield.

Decarbomethoxy-*epi*-voacamine (**17**) was prepared by the method of Percheron.[13] Crystallization from methylene chloride–methanol yielded pure **17**, m.p. ~230° dec.,[47] $[\alpha]D$ −46° (c 6.84, chloroform); λ_{max}^{EtOH} 227, 287, and 294 mμ (ϵ 45,600, 14,500, and 15,100, respectively); $\nu_{max}^{CHCl_3}$ 3450, 3000, 2925, 2850, 2780, 1720, 1615, 1575, 1465, 1455, 1425, 1355, 1330, 1320, 1285, 1250, 1210, 1163, 1133, 1120, 1100, 1035, 1025, 1008, 975, 930, 880, 865, and 820 cm.$^{-1}$.

***epi*-Voacamine** (**15**).—(a) A solution of voacamine dipotassium salt (358 mg.) in a mixture of methanol (2 ml.) and ether (10 ml.) was cooled to 0° and excess ice-cold methanolic hydrochloric acid was added. An ethereal solution of diazomethane was immediately added and the yellow solution was allowed to stand at room temperature for 15 hr. Dilute acetic acid in ether was added and the solvent was removed *in vacuo* to yield a white solid. This material was suspended in aqueous sodium carbonate, extracted with methylene chloride, and, after drying (sodium sulfate), the organic phase was evaporated to yield 118 mg. of solid. Recrystallization from ether–methanol yielded **15**, m.p. 249–251° dec.,[47] $[\alpha]D$ −29° (c 7.20, chloroform); λ_{max}^{EtOH} 226, 287, and 294 mμ (ϵ 59,950, 18,600, and 19,300, respectively); $\nu_{max}^{CHCl_3}$ 3450, 3000, 2950, 2850, 2780, 1710, 1600, 1470, 1460, 1440, 1430, 1365, 1335, 1315, 1278, 1250, 1210, 1168, 1130, 1125, 1110, 1075, 1030, 1005, 935, and 825 cm.$^{-1}$.

(b) Voacamine (500 mg.) was added to a solution of sodium (530 mg.) dissolved in methanol (30 ml.) and dioxane (35 ml.) to give a clear solution which was heated under reflux for 15 hr. in a nitrogen atmosphere. The reaction mixture was diluted with water (60 ml.) and extracted with methylene chloride. The organic phase was dried (sodium sulfate) and evaporated to yield 495 mg. of solid. Recrystallization from ether–methanol yielded **15**, identical with that prepared above by infrared spectrum and R_f on thin layer chromatography.

Cleavage of Voacamine in Deuterium Oxide. Voacangine-d_3.—A solution of voacamine (500 mg.) in methanol-O-*d* (7 ml.), deuterium oxide (7 ml.), and deuterium oxide saturated with

(43) U. Renner, *Experientia*, **13**, 468 (1957).

(44) U. Renner, private communication.

(45) For a similar example see Y. Gaoni and R. Mechoulam, *J. Am. Chem. Soc.*, **86**, 1646 (1964).

(46) Melting points were observed on a Kofler micro hot stage and are corrected. Ultraviolet spectra were measured on a Cary recording spectrophotometer, Model 14, and infrared spectra were recorded on a Perkin–Elmer Model 237 grating infrared spectrophotometer. Optical rotations were determined on a Zeiss photoelectric polarimeter and $[\alpha]D$ was calculated from the observed $\alpha_{546\ m\mu}$ and $\alpha_{578\ m\mu}$ by means of the first approximation of Drude's formula for normal rotational dispersion. The n.m.r. spectra were taken in deuteriochloroform on a Varian Associates Model A-60 n.m.r. spectrometer and the chemical shifts are reported in p.p.m. (δ) downfield from an internal tetramethylsilane reference. Woelm alumina was used as a chromatographic adsorbent. Microanalyses were performed by the Scandinavian Microanalytical Laboratory, Copenhagen S., Denmark.

(47) The melting points of voacamine, many of its derivatives, and several companion alkaloids are, in reality, only broad decomposition ranges (attributable undoubtedly to pyrolytic transformations reminiscent of those observed in the mass spectrometer) and are not accurate criteria of purity or identity. Routinely the purity and identity of these compounds were determined by thin layer chromatography and infrared spectroscopy.

hydrogen chloride gas (7 ml.) was heated under reflux for 23 hr. After partial evaporation, water, sodium carbonate, and ether were added. The ether phase was washed with water, dried (sodium sulfate), and evaporated. The residue was purified by chromatography on alumina (activity III) and the appropriate fractions recrystallized from methanol to give pure voacamine-d_6 and pure voacangine-d_3. Under these prolonged cleavage conditions the major product is voacangine-d_3.

Dihydrovoacamine Lactam.—A solution of iodine (998 mg.) in tetrahydrofuran (16 ml.) was added dropwise to a stirred mixture of a solution of dihydrovoacamine (800 mg.) in tetrahydrofuran (20 ml.) and sodium bicarbonate (1.12 g.) in water (16 ml.). After stirring for 3 hr., water and methylene chloride were added. The organic phase was washed successively with sodium thiosulfate solution and water, dried (sodium sulfate), and evaporated. The residue was chromatographed on alumina (activity III). Recrystallization of the appropriate fractions from methanol yielded pure dihydrovoacamine lactam (225 mg.), m.p. 242–244 dec.; $\nu_{max}^{CHCl_3}$ 3450, 3000, 2950, 2925, 2865, 1720, 1660, 1470, 1465, 1445, 1430, 1380, 1330, 1315, 1285, 1260, 1230, 1150, 1145, 1125, 1105, 1080, 1050, 1035, 1005, 980, 930, 855, 830, and 800 cm.$^{-1}$.

Acid Cleavage of Dihydrovoacamine Lactam.—Dihydrovoacamine lactam (200 mg.) dissolved in methanol (10 ml.) and concentrated hydrochloric acid (5 ml.) was heated under reflux for 24 hr. Sodium carbonate solution and methylene chloride were added and the organic phase was washed with water, dried (sodium sulfate), and evaporated. The residue was chromatographed on alumina (activity III) to afford pure voacangine lactam (**2**), m.p. 250–252° after recrystallization from methanol. Mixture melting point with authentic voacangine lactam, m.p. 252–253.5°, was 250–253°. The infrared spectra of the two specimens were identical.

Voacangine Lactam (2).—A solution of iodine (745 mg.) in tetrahydrofuran (12 ml.) was added dropwise to a stirred mixture of a solution of voacangine (600 mg.) in tetrahydrofuran (15 ml.) and sodium bicarbonate (810 mg.) in water (12 ml.). After stirring for 2 hr., water and methylene chloride were added. The organic phase was washed successively with sodium thiosulfate solution and water, dried (sodium sulfate), and evaporated. A solution of the residue in methylene chloride was washed twice with 2 *N* sulfuric acid and once with sodium bicarbonate solution, dried (sodium sulfate), and evaporated. The residue was chromatographed on alumina (activity III) to give pure voacangine lactam (**2**), m.p. 252–253.5° after recrystallization from methanol; $\nu_{max}^{CHCl_3}$ 3450, 3000, 2950, 2875, 2830, 1725, 1660, 1625, 1585, 1485, 1450, 1380, 1355, 1335, 1295, 1255, 1230, 1200, 1155, 1145, 1110, 1055, 1030, 1020, 1005, 975, 950, 925, 910, 880, 855, 830, and 800 cm.$^{-1}$.

Voacamine (14): m.p. 227–229° dec.,[47] $[\alpha]D$ −41° (*c* 7.89, chloroform); λ_{max}^{EtOH} 225, 287, and 294 mμ (ε 52,600, 17,850, and 19,950, respectively); $\nu_{max}^{CHCl_3}$ 3450, 3000, 2940, 2860, 1710, 1600, 1470, 1460, 1440, 1430, 1380, 1365, 1330, 1310, 1270, 1250, 1210, 1160, 1150, 1110, 1075, 1030, 1010, 935, 878, and 840 cm.$^{-1}$; $pK_a^* = (MCS)^{11}$ 5.19 and 6.78.

Voacamine-d_6.—A solution of voacamine (1.00 g.) in deuterium oxide (8 ml.), methanol-O-*d* (8 ml.), and deuterium oxide saturated with anhydrous hydrogen chloride gas (8 ml.) was heated under reflux for 9 hr. in a nitrogen atmosphere. The reaction mixture was neutralized with sodium carbonate, extracted with methylene chloride, and, after drying (sodium sulfate), the organic phase was evaporated to yield 950 mg. of solid. This material was chromatographed on alumina (activity III) to yield, after recrystallization from ether–methanol, 720 mg. of product. The n.m.r. spectrum of this material indicated that the aromatic hydrogen atoms had been exchanged for deuterium atoms to the extent of 70% while the spectrum above 6.0 δ was identical with that of voacamine.

Deuterium Exchange for N.m.r. Spectra.—(a) Neutral conditions: a 30–50-mg. sample of material was dissolved in 250 μl. of deuteriochloroform and an equal volume of deuterium oxide was added. The two-phase solution was then shaken continuously for 1 hr. The organic phase was removed with a pipet and filtered through a bed of anhydrous sodium sulfate directly into the n.m.r. probe.

(b) Acidic conditions: a 30–50 mg. sample of material was dissolved in 250 μl. of deuteriochloroform and an equal volume of deuterium oxide containing a trace of anhydrous hydrogen chloride gas was added. This mixture was then shaken for 2–7 min. during which time a heavy white precipitate always formed. The acid was neutralized with solid anhydrous potassium carbonate and the clear, two-phase solution was briefly shaken. The organic phase was then transferred to the n.m.r. probe as described above.

Voacamine Monomethiodide.—Excess methyl iodide (3 ml.) was added to a solution of voacamine (500 mg.) in ether (20 ml.). Methanol (10 ml.) was gradually added and the resulting clear solution was allowed to stand 15 hr. at room temperature. The residue obtained by evaporation was recrystallized from acetone–methanol to yield 470 mg. of product, m.p. 228–231° dec.[47]

Voacamine-d_6 Monomethiodide.—Using the procedure described for voacamine, voacamine-d_6 (610 mg.) yielded, after recrystallization from methylene chloride–methanol, 700 mg. of product.

Voacamine Methine (10).—A suspension of voacamine monomethiodide (250 mg.) in methanol (5 ml.) was added to a filtered solution of sodium (600 mg.) in methanol (25 ml.) and the mixture was heated under reflux for 1 hr. in a nitrogen atmosphere. The solution became homogeneous after 15 min. The final reaction mixture was concentrated to half volume, diluted with water (15 ml.), and extracted with methylene chloride. The organic phase was dried (sodium sulfate) and evaporated to yield, after recrystallization from methylene chloride–methanol, 180 mg. of product, m.p. 216–218° dec., $[\alpha]D$ +162° (*c* 11.00, chloroform); λ_{max}^{EtOH} 225, 286, and 294 mμ (ε 62,700, 19,200, and 19,400, respectively); $\nu_{max}^{CHCl_3}$ 3450, 2990, 2920, 2840, 2750, 1710, 1635, 1580, 1475, 1465, 1440, 1365, 1340, 1320, 1287, 1255, 1235, 1172, 1140, 1115, 1078, 1025, and 850 cm.$^{-1}$.

Voacamine-d_6 Methine.—Using the procedure described above, voacamine-d_6 monomethiodide (700 mg.) yielded 415 mg. of crystalline product. The n.m.r. spectrum revealed the new vinyl proton at 7.4 δ while the spectrum above 6.0 δ was identical with that of **10**.

Dihydrovoacamine (12).—Voacamine (500 mg.) in glacial acetic acid (30 ml.) was hydrogenated over platinum oxide (100 mg.) at 25° and atmospheric pressure. Hydrogen uptake (1 equiv.) was complete within 1.5 hr. The catalyst was removed by filtration and the solution was concentrated *in vacuo*. The resulting dark residue was diluted with water (50 ml.), neutralized with sodium carbonate, and extracted with methylene chloride. After drying (sodium sulfate), the organic phase was filtered through alumina (activity III) and the residue obtained by evaporation was recrystallized from methanol to yield 438 mg. of product, m.p. 212–214° dec., $[\alpha]D$ +35° (*c* 8.12, chloroform); λ_{max}^{EtOH} 226, 287, and 295 mμ (ε 56,500, 18,400, and 18,800, respectively); $\nu_{max}^{CHCl_3}$ 3450, 3000, 2930, 2855, 2800, 1710, 1620, 1575, 1470, 1460, 1440, 1430, 1365, 1330, 1315, 1275, 1250, 1225, 1160, 1145, 1128, 1110, 1078, 1035, 1008, 970, 930, 865, and 845 cm.$^{-1}$.

Dihydrovoacamine-d_6.—Dihydrovoacamine (844 mg.) yielded 400 mg. of product when the procedure described for the preparation of voacamine-d_6 was followed. The n.m.r. spectrum of this material showed that a 90% exchange of aromatic hydrogen atoms for deuterium atoms had taken place. The spectrum above 6.0 δ was identical with that of **12**.

Dihydrovoacamine Monomethiodide.—Dihydrovoacamine (500 mg.) was converted to its methiodide by use of the procedure described for voacamine monomethiodide. The residue (590 mg.) obtained on evaporation of the final reaction mixture would not crystallize but was shown to be homogeneous by thin layer chromatography.

Dihydrovoacamine-d_6 Monomethiodide.—Dihydrovoacamine-d_6 (463 mg.) yielded 540 mg. of noncrystalline product by use of the above-described procedure. This material was homogeneous (t.l.c.) and was not further purified.

Dihydrovoacamine Methine (13).—When the method described for voacamine methine was used, dihydrovoacamine monomethiodide (590 mg.) yielded, after recrystallization from ether–methanol, 240 mg. of product, m.p. 234–235° dec., $[\alpha]D$ +132° (*c* 7.00, chloroform); λ_{max}^{EtOH} 225, 284, and 294 mμ (ε 61,500, 20,600, and 20,200, respectively); $\nu_{max}^{CHCl_3}$ 3450, 3005, 2950, 2885, 2790, 1720, 1615, 1575, 1460, 1430, 1395, 1360, 1325, 1315, 1250, 1210, 1170, 1148, 1125, 1110, 1025, 1005, and 850 cm.$^{-1}$.

Dihydrovoacamine-d_6 Methine.—The procedure described for voacamine methine, when carried out on dihydrovoacamine-d_6 monomethiodide (540 mg.), yielded, after recrystallization from methylene chloride–methanol, 213 mg. of product.

Hydrogenolysis Product (11).—Voacamine methine (700 mg.), platinum oxide (65 mg.), and glacial acetic acid (20 ml.) were stirred under hydrogen at atmospheric pressure for 2 days and catalyst was removed by filtration. The filtrate was made basic with sodium carbonate solution and extracted with methylene chloride. The extracts were washed with water, dried (sodium sulfate), and evaporated. The resultant residue was chromatographed on alumina (activity III). Elution with benzene–hexane (1:1) afforded pure hydrogenolysis product (200 mg.), m.p. 252–255°; $[\alpha]D$ +69° (*c* 3.60, chloroform) after recrystallization from methanol; λ_{max}^{EtOH} 225, 287, 294, and 300 mμ (ε 67,000, 21,200, 21,500, and 19,300); $\nu_{max}^{CHCl_3}$ 3450, 3000, 2950, 2860, 1710, 1610, 1575, 1468, 1455, 1428, 1375, 1355, 1325, 1275, 1210, 1168, 1140, 1110, 1075, 1050, 1025, 1000, 920, and 850 cm.$^{-1}$.

Acid Cleavage of the Hydrogenolysis Product 11.—A solution of the hydrogenolysis product (300 mg.) in methanol (10 ml.) and concentrated hydrochloric acid (5 ml.) was heated under reflux for 24 hr. A small amount of precipitate was removed by filtration. The filtrate was treated with sodium carbonate solution, extracted with methylene chloride, and the organic phase dried (sodium sulfate) and evaporated. Voacangine (1), isolated from the residue by chromatography on alumina (activity III), had m.p. 138–139° pure and mixed with authentic voacangine. The infrared spectrum was identical with that of an authentic sample.

Deuteration of the Hydrogenolysis Product 11.—A solution of the hydrogenolysis product (200 mg.) in methanol-O-*d* (5 ml.), deuterium oxide saturated with hydrogen chloride gas (5 ml.), and dioxane (4 ml.) was heated under reflux for 7.5 hr. The reaction mixture was made basic with sodium carbonate solution and extracted with methylene chloride. The combined extracts were washed with water, dried (sodium sulfate), and evaporated. The residue was chromatographed on alumina (activity III). Fractions containing recovered starting material were combined and crystallized from methanol to give deuterated hydrogenolysis product (20 mg.), m.p. 249–252°, m.m.p. with authentic hydrogenolysis product, 249–253°. The n.m.r. spectrum of this material showed partial exchange of the aromatic protons and complete exchange of the proton present in the nondeuterated material at 4.72 δ.

2-(*o*-Anisyl)cyclohexanone was prepared from 1-(*o*-anisyl)-cyclohexene[48] by the method of Gutsche and Fleming[49] in 64% yield, b.p. 111–117° (0.2 mm.), m.p. 73.8–74.2°, $\nu_{max}^{CHCl_3}$ >C=O 1715 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.29; H, 7.85.

1-(*o*-Anisyl)-1,2,3,4-tetrahydrocarbazole (16).—A mixture of 1-(*o*-anisyl)cyclohexanone (4.00 g., 19.6 mmoles) and phenylhydrazine (2.12 g., 19.6 mmoles) was heated on a steam bath for 30 min., then under reduced pressure to remove the water formed, and, on cooling, the resulting orange oil solidified. A solution of concentrated sulfuric acid (4 ml.) and water (36 ml.) was added to this solid, the two-phase system was heated under reflux for 30 min., and was then extracted with ether. The organic phase, after washing with dilute sulfuric acid, water, aqueous sodium carbonate, and water, was evaporated to give a viscous oil. This material was chromatographed on alumina (activity I) to yield, after several crystallizations from methanol–ether, 2.21 g. of product, m.p. 132–132.5°.

Anal. Calcd. for $C_{19}H_{19}NO$: C, 82.28; H, 6.91; N, 5.05. Found: C, 82.08; H, 6.71; N, 4.96.

Deuterium Exchange of 16.—A sample of **16** (258 mg.) in a mixture of deuterium oxide (5 ml.), methanol-O-*d* (8 ml.), tetrahydrofuran (5 ml.), and deuterium oxide saturated with anhydrous hydrogen chloride gas (5 ml.) was heated under reflux for 23 hr. in a nitrogen atmosphere. The reaction mixture was concentrated to half volume and extracted with methylene chloride. Recrystallization from methylene chloride–methanol gave 200 mg. of product. The n.m.r. spectrum of this material showed no signal at 4.65 δ, whereas approximately five aromatic hydrogen atoms were present.

Lithium Aluminum Hydride Reduction of Decarbomethoxy-*epi*-voacamine. Alcohol 18.—A solution of lithium aluminum hydride (200 mg.) in ether (25 ml.) was added to a solution of decarbomethoxy-*epi*-voacamine (95 mg.) in ether (20 ml.) and the mixture was heated under reflux for 6 hr. A little water was added and the ether layer was decanted, washed with water, dried (sodium sulfate), and evaporated. The residue was crystallized from methanol to give pure alcohol **18**, m.p. 220°, $[\alpha]D$ −78° (*c* 1.30, chloroform); λ_{max}^{EtOH} 226, 288, 295, and 308 mμ (ε 55,200, 17,300, 18,100, and 12,200); $\nu_{max}^{CHCl_3}$ 3455, 3050, 3000, 2935, 2855, 2790, 1625, 1575, 1470, 1460, 1425, 1375, 1360, 1330, 1285, 1250, 1210, 1152, 1140, 1125, 1110, 1100, 1030, 1008, 975, 960, 902, 860, and 820 cm.$^{-1}$.

Acetate 19.—A solution of the alcohol **18** (187 mg.) in acetic anhydride (0.5 ml.) and pyridine (0.2 ml.) was heated for 3 hr. Methanol was added and the solution evaporated. The residue was dissolved in methylene chloride and sodium carbonate solution, the organic phase dried (sodium sulfate), and evaporated. Crystallization of the resultant solid from methanol gave the pure acetate **19**, m.p. 211° dec., $[\alpha]D$ −62° (*c* 1.24, chloroform). λ_{max}^{EtOH} 226, 287, 295, and 308 mμ (ε 57,000, 18,300, 19,100, and 13,000); $\nu_{max}^{CHCl_3}$ 3450, 3000, 2940, 2850, 2780, 1725, 1625, 1575, 1475, 1460, 1425, 1360, 1335, 1280, 1250, 1230, 1140, 1125, 1100, 1030, 1008, 975, 960, 920, 860, and 822 cm.$^{-1}$.

1-Oxo-1,2,3,4-tetrahydrocarbazole-d_6.—A mixture of 1-oxo-1,2,3,4-tetrahydrocarbazole (2.00 g.),[50] dioxane (20 ml.), and deuterium oxide saturated with anhydrous hydrogen chloride (50 ml.) was heated under reflux for 8 hr. in a nitrogen atmosphere. The reaction mixture was diluted with water (40 ml.) and extracted with methylene chloride. The organic phase was washed with aqueous sodium carbonate and the residue obtained from evaporation was chromatographed on alumina (activity III) to give 2.00 g. of crude product. Recrystallization from dioxane–hexane yielded 1.72 g. of product. The n.m.r. spectrum showed *ca.* 80% exchange of the aromatic hydrogen atoms and complete exchange of the C_2-hydrogen atoms for deuterium atoms.

1-Hydroxy-1,2,3,4-tetrahydrocarbazole (20).—Sodium borohydride (2.0 g.) was slowly added to a suspension of 1-oxo-1,2,3,4-tetrahydrocarbazole[50] (2.00 g.) in methanol (50 ml.) and the resulting clear solution was heated under reflux for 15 min. An additional portion of sodium borohydride (1.0 g.) was added and the mixture was refluxed for 15 min. Acetone (5 ml.) was added to the reaction mixture and the solution was concentrated to half volume. An equivalent volume of hot water was added and, after cooling, the crystalline product (1.82 g.), m.p. 114–116° (lit.[25] m.p. 113–115°), was collected.

1-Hydroxy-1,2,3,4-tetrahydrocarbazole-d_6 was prepared from 1-oxo-1,2,3,4-tetrahydrocarbazole-d_6 in an analogous manner. The C_1-hydrogen atom appeared as a broad singlet at 4.80 δ in the n.m.r. spectrum.

6-Hydroxy-1,2,3,4-tetrahydrocarbazole (24) was prepared by the method of Milne and Tomlinson.[51] The crude product was purified by sublimation at 0.5 mm. and 165° to yield white crystals, m.p. 170–172° (lit.[51] m.p. 172°).

Mannich Adduct 26.—A mixture of piperidine (85 mg., 1.0 mmole) and paraformaldehyde (26 mg., 1.0 mmole) in ethanol (1 ml.) was warmed on a steam bath until the solution became homogeneous. This solution was cooled and 6-hydroxy-1,2,3,4-tetrahydrocarbazole (185 mg., 1.0 mmole) was added. The resulting pale yellow solution was allowed to stand at room temperature for 1.5 hr. and was then heated under reflux for 2 hr. in a nitrogen atmosphere. The reaction mixture crystallized on cooling to give 213 mg. of product, m.p. 163.5–164.5°; λ_{max}^{EtOH} 232, 285, and 295 (shoulder) mμ (ε 22,900, 9100, and 8250, respectively). The n.m.r. showed the expected aromatic AB quartet at 6.70 (doublet, J = 8.5 c.p.s.) and 7.05 δ (doublet, J = 8.5 c.p.s.) and the isolated methylene group appeared as a sharp singlet at 4.09 δ.

Anal. Calcd. for $C_{18}H_{24}N_2O$: C, 76.02; H, 8.51; N, 9.85. Found: C, 76.24; H, 8.53; N, 9.80.

Tetrahydrocarbazole Dimer 25.—A solution of 1-hydroxy-1,2,3,4-tetrahydrocarbazole (400 mg.) and 6-hydroxy-1,2,3,4-tetrahydrocarbazole (400 mg.) in 5% acetic acid–ethanol (15 ml.) was heated under reflux for 3 hr. in a nitrogen atmosphere. The reaction mixture was neutralized with sodium carbonate and evaporated to dryness. The residue was chromatographed on alumina (activity III) to yield the product **25**. This material was finally recrystallized from dioxane–ether as a solvate since after drying for 72 hr. at 50° and 0.5 mm. its n.m.r. spectrum contained a strong dioxane signal.

(48) D. Ginsburg and R. Pappo, *J. Chem. Soc.*, 516 (1951).

(49) C. D. Gutsche and F. A. Fleming, *J. Am. Chem. Soc.*, **76**, 1771 (1954).

(50) A. Kent, *J. Chem. Soc.*, 976 (1935).

(51) A. H. Milne and M. L. Tomlinson, *ibid.*, 2789 (1952).

In an analogous fashion, hexadeuterio-**25** was prepared from **24** and hexadeuterio-**20**. The n.m.r. spectrum of this material showed an aromatic AB quartet at 6.63 (doublet, J = 9 c.p.s.) and 6.95 δ (doublet, J = 9 c.p.s.) and a one-proton singlet at 5.00 δ.

Deuteriodregamine.—A solution of dregamine (1.00 g.) in methanol-O-*d* (10 ml.) and deuterium oxide saturated with hydrogen chloride gas (10 ml.) was heated under reflux for 23 hr. in a nitrogen atmosphere. The reaction mixture was neutralized with sodium carbonate and extracted with methylene chloride. The residue obtained on evaporation was recrystallized from ether to yield 950 mg. of product. The n.m.r. spectrum of this material indicated *ca.* 50% of the aromatic hydrogen atoms had been exchanged for deuterium atoms and the carbomethoxy group (2.67 δ) had not epimerized. Increasing the reflux period or the acid concentration did not alter the percentage exchange of aromatic protons.

Dregaminol (32).—Sodium borohydride (500 mg.) was slowly added to a suspension of dregamine (850 mg.) in methanol (30 ml.). This mixture was heated under reflux for 10 min. to give a homogeneous solution; an additional portion of sodium borohydride (500 mg.) was added and this was refluxed another 10 min. The reaction mixture was reduced to half volume and slowly diluted with hot water (30 ml.). The mixture crystallized on cooling to give 680 mg. of product, m.p. 203–204° (lit.[5] m.p. 210–212°).

Deuteriodregaminol was prepared from deuteriodregamine in an analogous manner.

Synthetic Dihydrovoacamine (12).—A mixture of dregaminol (106 mg.) and voacangine (110 mg.) in 1% methanolic hydrochloric acid (10 ml.) was heated under reflux for 1 hr. in a nitrogen atmosphere. The reaction mixture was diluted with water (15 ml.) and neutralized with sodium carbonate to give a heavy white precipitate. This was extracted with methylene chloride and the residue obtained on evaporation was crystallized from ether–methanol to yield 80 mg. of product, m.p. 213–215°, m.m.p. 212–214°; $[\alpha]D$ +44° (c 6.25, chloroform); the infrared spectrum was superimposable on that of authentic dihydrovoacamine.

The above sequence was repeated with deuteriodregaminol and voacangine to yield deuteriodihydrovoacamine, m.p. 213–215°, which showed two singlets in the n.m.r. spectrum at 6.75 and 7.03 δ.

Conversion of Ibogaine (38) to Ibogamine (36).—A solution of the amorphous ibogaine phenol[4] (26 g.) in pyridine (260 ml.) was treated with *p*-toluenesulfonyl chloride (45 g.) in portions. After standing for 2 days, the reaction mixture was treated successively with water, sodium carbonate solution, and chloroform; the chloroform layer was washed with water, dried (sodium sulfate), and evaporated. A solution of the residue in benzene was filtered through alumina (activity III) to give the tosylate as an amorphous solid (35 g.).

A solution of the tosylate (5 g.) in ethanol (200 ml.) was heated under reflux with Raney nickel (20 ml.) for 3 hr. The reaction mixture was filtered and the filtrate evaporated and dissolved in sodium carbonate solution and methylene chloride. The organic phase was washed with water, dried (sodium sulfate), and evaporated to give 2.5 g. of crude residue which was shown by thin layer chromatography to be a mixture of tosylate and ibogamine. Two crystallizations from methanol gave pure ibogamine (1.2 g.), m.p. 162–163°, $[\alpha]D$ −36° (c 3.00, chloroform) (lit.[52] m.p. 162–163°, $[\alpha]D$ −36° (chloroform)), identical with authentic ibogamine by mixture melting point (m.m.p. 162–163°) and infrared spectrum.

Perivine (40) was obtained as its sulfate salt. Neutralization of an aqueous suspension of the salt with potassium carbonate, extraction with methylene chloride, and evaporation of the resulting extract (after drying) furnished the free base. Crystallization from methanol gave pure material, m.p. 178–180°; $\nu_{max}^{CHCl_3}$ 1725 and 1640 cm.$^{-1}$ (>=O).

Perivinol (41).—Carbon dioxide gas was continuously bubbled into a stirred suspension of perivine (500 mg.) in 80% methanol–water (20 ml.) which was cooled with an external ice bath; sodium borohydride (3 g.) was added in small portions. The pH of the solution did not go above eight during the addition and a pasty, white precipitate was present at the end of the reaction. The reaction mixture was diluted with water (30 ml.) and extracted with methylene chloride. The organic phase was dried (sodium sulfate) and evaporated to yield 465 mg. of product. This material was homogeneous on thin layer chromatography and was not further purified; $\nu_{max}^{CHCl_3}$ 1690 cm.$^{-1}$ (>=O).

Cyclization of Perivinol (41) to Ester 43.—A solution of perivinol (369 mg.) in xylene (40 ml.) was heated under reflux in a nitrogen atmosphere for 8 hr. After cooling, the xylene solution was extracted several times with 5% hydrochloric acid. The aqueous phase was then washed with benzene, neutralized with potassium carbonate, and extracted with methylene chloride. The organic phase was dried (sodium sulfate) and evaporated to yield 340 mg. of material which crystallized on trituration with methanol or methylene chloride. Recrystallization from ethanol yielded 239 mg. of product, m.p. 229–231°, with a change in crystalline form (plates to needles) at 215°, $[\alpha]D$ +3.8° (c 1.6, chloroform); $\nu_{max}^{CHCl_3}$ 3450, 3000, 2925, 2850, 1720, 1615, 1465, 1447, 1428, 1375, 1345, 1325, 1304, 1225, 1160, 1140, 1115, 1090, 1075, 1015, 1012, 995, 940, 920, and 840 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.42; H, 6.91; N, 8.74.

Epimerization of Ester 43 to Ester 44.—Ester **43** (176 mg.) was added to a solution of sodium (200 mg.) in methanol (10 ml.) and the mixture was refluxed under nitrogen for 4 hr. The reaction mixture was diluted with water and extracted with a large volume of methylene chloride. The residue obtained on evaporation of the dried organic phase was crystallized from ethanol to yield 111 mg. of product, m.p. 229–231°, with a change in crystalline form (prisms to needles) at 189°; mixture melting point with ester **43**, 205–224°, $[\alpha]D$ +3.6° (c 1.00, methanol). The crystalline material was insoluble in chloroform; however, its Nujol mull infrared spectrum was different from the Nujol mull spectrum of ester **43**; ν_{max}^{Nujol} 1720, 1670, 1375, 1340, 1305, 1298, 1260, 1230, 1205, 1075, 1050, 1020, and 740 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.63; H, 7.12; N, 8.41.

Conversion of Ester 44 to Normacusine-B (45).—A solution of ester (80 mg.), lithium aluminum hydride (250 mg.), and tetrahydrofuran (15 ml.) was heated under reflux for 3 hr. in a nitrogen atmosphere. The excess hydride was decomposed with ethyl acetate and the reaction mixture was carefully diluted with water. The organic phase was decanted and the remaining white solid was washed with hot methylene chloride. The combined organic phases were evaporated and the residue was crystallized from chloroform to yield 71 mg. of material, m.p. 240–241° after drying at 0.01 mm. and 100° for 12 hr. The tenaciously held solvent was removed by sublimation at 220° and 0.05 mm. (80% weight recovery) to yield pure normacusine-B, m.p. 272–275° with change in crystalline form (prisms to needles) at 239–242° (lit.[35] 245°, 270–272°), $[\alpha]D$ +38° (c 0.82, methanol) (lit.[35] $[\alpha]D$ +36° methanol). The Nujol mull infrared spectrum of the sublimed material was identical in all respects with the published spectrum of the natural material.

Vobasinol (42).—Following the procedure described for the preparation of perivinol, vobasine (250 mg.) yielded, after crystallization from ether, 141 mg. of vobasinol, m.p. 109–111° dec.[47] (lit.[5] m.p. 100–102°); infrared spectrum identical with that of authentic material.

Synthetic Voacamine (14).—A solution of vobasinol (50 mg.) and voacangine (53 mg.) in 1.5% methanolic hydrochloric acid (5 ml.) was heated under reflux in a nitrogen atmosphere for 7 hr. The reaction mixture was diluted with water (15 ml.), neutralized with solid potassium carbonate, and extracted with methylene chloride. The residue obtained from evaporation of the solvent was crystallized three times from ether–methanol to yield 14 mg. of voacamine, $[\alpha]D$ −41° (c 5.00, chloroform). The infrared spectrum was superimposable with that of natural material. If a shorter reaction time or more dilute acid was used, considerable starting material was recovered.

Synthetic Voacorine.—Using the procedure described for the synthesis of voacamine, vobasinol (75 mg.) and voacangarine (81 mg.) yielded, after chromatography on alumina (activity III) and repeated recrystallization from ether–methanol, 25 mg. of voacorine, $[\alpha]D$ −32° (c 5.70, chloroform), whose infrared spectrum was superimposable on that of natural material.

Dihydrovoacamidine (49).—The mother liquors from the dihydrovoacamine synthesis were chromatographed on alumina (activity III). Elution with hexane–benzene (1:1) furnished pure voacangine while the methylene chloride eluent contained

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

a mixture of the two dimers. Crystallization of the latter fraction from methanol, using a seed of dihydrovoacamine, yielded an additional quantity of the latter alkaloid. Thin layer chromatography indicated that the resulting mother liquors contained essentially uncontaminated dihydrovoacamidine. This material was converted to its hydrobromide salt which was crystallized from acetone; m.p. >300°.

Voacamidine (48) Hydrobromide.—The mother liquors from the voacamine synthesis were purified as described above. The hydrobromide salt was crystallized from acetone, m.p. >300°. Its Nujol mull infrared spectrum was identical with that of the hydrobromide salt of natural material.

Artifact Experiments.—A mixture of dreganinol (30 mg.) and voacangine (30 mg.) in methanol (3 ml.) was heated under reflux for 3 hr. and then evaporated to dryness on a steam bath. The residue was dissolved in ethyl acetate and extracted twice with 5% aqueous acetic acid. Both fractions were neutralized with potassium carbonate, the aqueous phase was extracted with methylene chloride, and both organic phases were taken to dryness. Recrystallization of the ethyl acetate residue from methanol–ether yielded pure voacangine (**1**) (infrared). Chromatography of the acetic acid residue on alumina (activity III) yielded pure voacangine (**1**) (infrared) and pure degraminol (**32**) (infrared). Thin layer chromatography of the crude mixtures showed only voacangine and dregaminol.

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Structures of Sultones from Proton Magnetic Resonance Spectra

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Proton magnetic resonance spectroscopy has been used to confirm structure assignments for eighteen sultones.

The degradative method for structure proof for a sultone is particularly difficult since it inevitably requires isolation of the salts of sulfonic acids, and these are hard to separate and to characterize. As a result, rigorous structure assignments for most sultones have not been made. The present study has shown that proton magnetic resonance (p.m.r.) spectra can often be used to make unambiguous structure assignments to these compounds. Eighteen sultones have been characterized in this way. Many of these were prepared by the sulfonation of alkenes, a reaction involving skeletal rearrangement.[3] In every instance the structure proved to be that expected on the basis of the reaction course assumed previously.[3]

Experimental

Sources of Sultones.—The method of preparation for most of these sultones has been given in previous publications.[3,4] Sultones **9**, **11**, and **12** were obtained from the Shell Development Co., Emoryville, Calif., through the courtesy of Dr. Curtis Smith. The preparation of sultones **13**–**18** will be described in a separate publication.

Spectra.—The p.m.r. spectra were taken at 25 ± 2° with a Varian high-resolution spectrometer at 40 and/or 60 Mc./sec. Pyrex tubes (5-mm. o.d.) were filled to a height of approximately 8 cm. with chloroform solutions of the sultones. Two solutions of each sultone were prepared, one at approximately 4% concentration (by weight), and one at approximately 25%. The chemical shift data given in Table I and in the following section are from the 4% solutions. The variation of chemical shift with concentration over the 4 to 25% range was no more than 0.1 p.p.m. Chemical shifts were measured by the conventional side-band technique for all sultones relative to chloroform. The positive numbers in Table I refer to resonance at higher magnetic field, relative to the chloroform resonance; the line positions are accurate to within ±1 c.p.s. for δ's given to three significant figures.

Results and Discussion

It was anticipated that sultones **1**, **2**, and **3** would have simple spectra, since in the structures assigned no two adjacent carbon atoms hold hydrogen atoms, and the possibility of proton spin coupling is thereby precluded. The appearance of three sharp peaks in the spectrum of **1** and of **3**, and of four sharp peaks in the spectrum of **2**, bears out this expectation. Judging from bond distances, one would expect five-membered sultone rings to be somewhat larger than cyclopentane rings. In sultones **1** and **3**, as well as in **2**, the hydrogen atoms, methyl groups, and oxygen atoms attached to adjacent ring atoms (carbon or sulfur) must then be staggered with respect to one another. The single sharp peaks in the spectra of **1**, **2**, and **3** are evidently average signals resulting from molecules undergoing rapid chair–chair interconversions.

The signals for the three types of methylene groups possible for five-membered ring sultones appear in distinctly different regions of the spectrum and are useful for structure assignment. Thus, the average methylene signal for protons on the carbon atom α to oxygen ($-CH_2OSO_2-$) appears at 2.79 p.p.m., whereas the average signal for the protons on the carbon atom α to sulfur ($-CH_2SO_2O-$) is at 4.05 p.p.m., and that for the protons on the carbon atom β to oxygen (or sulfur; $-CH_2-C-OSO_2-C-$) is at 4.8 p.p.m. The average signals for the corresponding methine protons for these three positions are 2.54, 3.98, and 4.96, respectively. For methyl groups the average values are 5.80, 5.85, and 6.12, respectively. The assignments are summarized in Fig. 1. (Compounds containing halogen or phenyl groups are not included in arriving at these averages.)

Reference to Table I will show that a relatively large number of values are available for methylene groups α to sulfur, and for methyl groups on carbon atoms α or β to oxygen. The other values are less reliable. The chemical shifts for the corresponding methylene and methyl groups in the two six-membered ring sultones **2** and **12** are of comparable magnitude.

When one of the hydrogen atoms in one methyl of a *gem*-dimethyl group is replaced by a bromine or chlorine atom, as in **4**, **14**, **15**, **16**, or **18**, the CH_2X signal is shifted downfield from that of the parent sultone (**3**, **13**, or **17**) to an extent anticipated on the basis of

(1) Abstracted in part from the M.S. Thesis of R. W. Ohline, Northwestern University, August, 1958.

(2) Alfred P. Sloan Research Fellow.

(3) F. G. Bordwell, R. D. Chapman, and C. E. Osborne, *J. Am. Chem. Soc.*, **81**, 2002 (1959).

(4) F. G. Bordwell, C. E. Osborne, and R. D. Chapman, *ibid.*, **81**, 2698 (1959).