substitution products) because the 3-hydrogen is the most acidic. With anilide ion, these steps approximate equilibria because aniline is a faster proton donor than ammonia. The rates of Br^- and I^- formation then depend on the respective equilibrium constants and on the rates of steps 2, 4 and 6. In the two cases, different factors determine which halide is expelled.

Acknowledgment.—We thank Professor John Neumer for stimulating discussions and the National Science Foundation and Army Research Office (Durham) for financial support.

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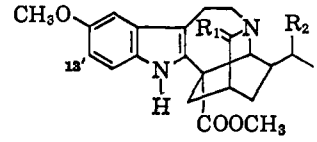
Voacamine

Sir:

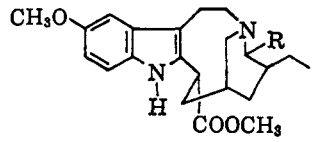
The indole alkaloid voacamine was first isolated from *Voacanga africana* Stapf.[1,2] Researches concerned with its structure established the presence in the molecule of one methoxy, one N-methyl and two carbomethoxy groups.[3,4] Molecular weight determinations indicated a molecule containing approximately twice as many atoms as the common indole alkaloids. Two of the four nitrogen atoms were found to be tertiary and basic whereas the remaining two were readily placed as components of two indole rings. Alkaline treatment furnished a dicarboxylic acid salt which on esterification with methanolic hydrochloric acid gave decarbomethoxy *epi*-voacamine (X). Esterification with diazomethane, however, yielded *epi*-voacamine (XI).[5] The facile decarboxylation of the dicarboxylic acid led to the suggestion[4] that voacangine (I) might be a moiety of the voacamine molecule and this was established by acid-catalyzed cleavage of the dimer to voacangine (I).[6] We now present further observations which establish structure IX for voacamine.

Cleavage of voacamine with 4 *N* hydrochloric acid in CH_3OD/D_2O (23 hr.) at reflux yielded, after recrystallization from methanol, trideuteriovoacangine identical with the product obtained by similar treatment of voacangine (I). All three deuterium atoms were located on the aromatic ring (mass spectra).[7] To exclude part structure IV, dihydrovoacamine,[5] m.p. 212–214° dec., was oxidized with iodine[8] to the corresponding lactam, m.p. 242–244° dec., convertible to voacangine lactam (II), m.p. 252–254°; $\nu_{max}^{CHCl_3}$ 1660, 1725 $cm.^{-1}$ by acid cleavage. The n.m.r. spectrum of voacamine (all in $CDCl_3$; chemical shifts in p.p.m. from tetramethylsilane) shows indole–NH signals at 7.48 and 7.70 δ, shifted to 9.03 and 9.23 δ in acetone-d_6. The voacangine proton at high field disappeared on exchange in D_2O whereas deuteration of the hydrogen bonded proton required acid catalysis. Clearly, the as yet obscure moiety in voacamine is linked to the aromatic ring of an intact voacangine (I) molecule.

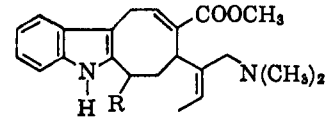
Proton spectra of voacamine did reveal only six aromatic protons and, furthermore, provided the first clue concerning the nature of the second moiety. Signals at 1.66 (doublet, J = 7 c.p.s.), 5.20 (quartet, J = 7 c.p.s.), 2.58 (singlet) and 2.44 δ (singlet) could be assigned to ethylidene, carbomethoxy and N-methyl groupings. In *epi*-voacamine (XI) the methyl ester protons appear at 3.57 δ. Substantially identical chemical shifts for these functionalities are found in the spectra of vobasinol (V)[9,10] and *epi*-vobasinol (VI)[11] and suggested the presence of these structural units in voacamine and *epi*-voacamine, respectively.



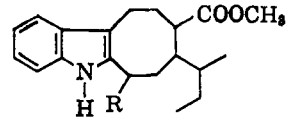
I. $R_1 = H_2$; R_2 = H
II. R_1 = O=; R_2 = H
III. $R_1 = H_2$; R_2 = OH



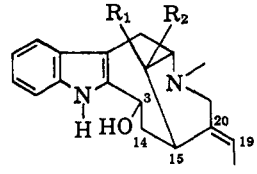
IV



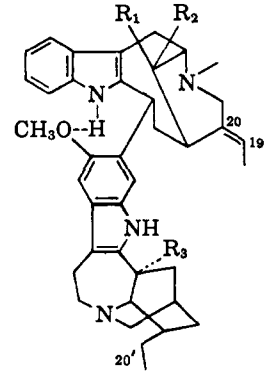
VII. R = voacangine



VIII. R = voacangine



V. R_1 = $COOCH_3$; R_2 = H
VI. R_1 = H; R_2 = $COOCH_3$



IX. $R_1 = R_3 = COOCH_3$; R_2 = H
X. $R_2 = COOCH_3$; $R_1 = R_3$ = H
XI. R_1 = H; $R_2 = R_3 = COOCH_3$

Sodium methoxide-catalyzed Hofmann degradation of voacamine monomethiodide gave the methine (VII),[5] m.p. 216–218° dec., $\gamma_{max}^{CHCl_3}$ 1710 $cm.^{-1}$, λ_{max}^{EtOH} 225, 286, 294 mμ (ϵ 62,700, 19,200, 19,400). In the deuterated methine, prepared from hexadeuteriovoacamine, the new vinyl proton became visible in the n.m.r. spectrum at 7.4 δ (multiplet) and the multiplet due to the adjacent methylene group appeared at 4.5 δ. The spectrum of the hydrogenolysis product (VIII), m.p. 252–255°, prepared by catalytic reduction of the methine over platinum in acetic acid revealed *three* C–methyl groups. Consequently, the carbon–carbon bond linking the two monomers can originate only at C-3, C-14 or C-15 of the vobasine fragment. Structure IX appeared most likely because the n.m.r. spectra of, *e.g.*, dihydrovoacamine (19,20-dihydro-IX) and *epi*-voacamine (XI) contained broad doublets due to a single proton at 5.00 and 4.74 δ, respectively. Condensation of equimolar amounts of dregaminol (19,20-dihydro-V)[9,10] and voacangine (I) in 1% HCl–CH_3OH (reflux, 1 hr.) yielded 50% of dihydrovoacamine (19,20-dihydro-IX), m.p. 213–215° dec., identical (infrared spectrum, R_f values, mixture melting point not depressed) with a sample prepared from natural (?) voacamine (IX). Mannich condensation occurred at the C-13′ position of voacangine (I) since the spectrum of

(1) M.-M. Janot and R. Goutarel, *Compt. rend. acad. sci.*, **240**, 1719 (1955).
(2) J. LaBarre and L. Gillo, *Bull. acad. roy. med. Belg.*, **20**, 194 (1955).
(3) R. Goutarel, F. Percheron and M.-M. Janot, *Compt. rend. acad. sci.*, **243**, 1670 (1956).
(4) F. Percheron, *Ann. chim.* (Paris), [13] **4**, 303 (1959).
(5) U. Renner and D. A. Prins, J. R. Geigy, S. A., Basel, private communication.
(6) W. Winkler, *Naturwiss.*, **48**, 694 (1961).
(7) K. Biemann and M. Friedmann-Spiteller, *J. Am. Chem. Soc.*, **83**, 4805 (1961).
(8) Method of M. F. Bartlett, D. F. Dickel and W. I. Taylor, *ibid.*, **80**, 126 (1958).
(9) U. Renner and D. A. Prins, *Experientia*, **17**, 209 (1961).
(10) U. Renner and D. A. Prins, *Chimia* (Basel), **15**, 321 (1961).
(11) The diamagnetically shifted carbomethoxy protons in vobasine were the subject of a recent communication by M. P. Cava, S. K. Talapatra, J. A. Weisbach, B. Douglas and G. O. Dudek, *Tetrahedron Letters*, **2**, 53 (1963).

the product synthesized from this alkaloid and deuterated dregaminol exhibited two one-proton singlets at 6.75 and 7.03 δ, respectively. 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 guesses. It does not reveal the configuration of the ethylidene side chain and does not distinguish between two diastereomeric formulations because the absolute configuration of neither monomer is established. The mass spectrum of voacamine caused much concern. It showed a peak at mass 718 (calcd. mol. wt. 704) whereas the spectra of the hydrogenolysis product (VIII) and of the primary acetate prepared from decarbomethoxyvoacamine (X) by hydride reduction and acetylation exhibited the anticipated molecular ion peaks (m/e = 678 and 660, respectively). In the case of voacamine (IX) intermolecular methyl transfer occurs thermally when vaporizing the sample directly into the ion source and the molecular ion actually measured is that of the methine (VII). Acid cleavage of voacorine[12] gives voacangarine (III)[13] and the former alkaloid most probably is 20′-hydroxyvoacamine. Voacamine (IX) is structurally related to the oncolytic vinca alkaloids whose structures were elucidated partially.[14]

Acknowledgment.—We are indebted to the National Institutes of Health for financial support (RG 9686), to Drs. D. A. Prins and U. Renner for generous samples of various alkaloids and unpublished information. Mass spectra were kindly measured by Professor K. Biemann and his collaborators.

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

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

(14) N. Neuss, M. Gorman, H. E. Boaz and N. Cone, *J. Am. Chem. Soc.*, **84**, 1509 (1962).

(15) National Science Foundation Postdoctral Fellow 1961–1962.

(16) National Science Foundation Predoctoral Fellow 1961–1963.

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RECEIVED APRIL 19, 1963

Stereospecific Preparation of Epoxyketones by Photochemical Oxygenation

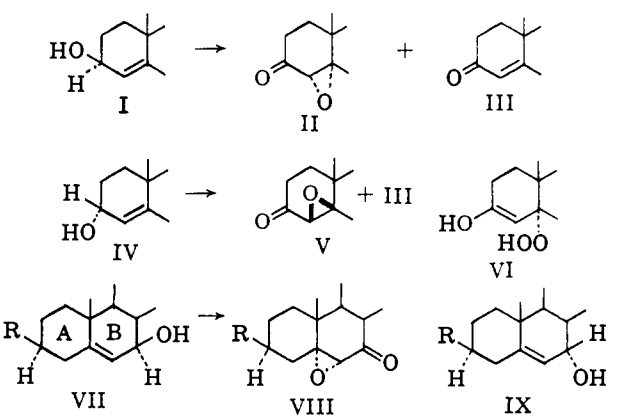
Sir:

Photosensitized oxygenation of monoölefins gives allylic hydroperoxides[1] with a rearranged double bond and for cyclohexenoid systems requires a *cis* relationship between the C–H bond cleaved and the C–O bond formed.[2] When applied to olefins having nearby functional groups the oxygenation reaction has considerable potential as a synthetic tool and can also yield information on conformational, electronic, and other factors that might influence sensitized photochemical processes. We now report adaptation of the reaction to a one-step stereospecific synthesis of α,β-epoxyketones from allylic alcohols.

Photoöxygenation of Δ⁴-cholesten-3β-ol (partial structure I) in pyridine with hematoporphyrin produced 4α,5-epoxy-5α-cholestan-3-one[3] (II; 75%) along with some Δ⁴-cholesten-3-one (III; 16%). Similar irradiation of Δ⁴-cholesten-3α-ol (IV) gave 4β,5-epoxy-5β-cholestan-3-one (V; 50%) along with some enone III (10%). In the 3α-ol case the reaction proceeded more slowly[4] and was less complete; the yields of V and III were 75 and 15%, respectively, when corrected for recovered starting material. From the known *cis* stereochemistry for the oxygenation reaction[2] the 5α-hydroperoxide VI is an expected intermediate in the reaction of I; and the corresponding 5β-hydroperoxide would be expected from IV. Collapse of these intermediates to their respective epoxyketones accounts for the observed stereospecificity.[5]

The faster oxygenation of I over IV is of interest and suggests a stereoelectronic effect as one of the relevant factors in cleavage of the C-3 carbon–hydrogen bond, which is *quasi*-axial in I and probably *quasi*-equatorial in IV. Conformational inversion or distortion in IV would be necessary to bring this C–H bond into optimum alignment with the adjacent π electrons. Further illustrations of epoxyketone formation and of retardation by unfavorable geometric factors were obtained with allylic alcohols in ring B, which has less conformational flexibility than ring A.

Photoöxygenation of Δ⁵-cholesten-3β-7β-diol (VII; R = OH) proceeded readily and gave 56% of the 5α,-6α-epoxyketone VIII (R = OH) and about 15% of the corresponding enone, Δ⁵-cholesten-3β-ol-7-one. Similarly, oxygenation of a small sample of Δ⁵-cholesten-7β-ol (VII; R = H) gave products whose infrared and ultraviolet spectra were consistent with the presence of the α,β-epoxyketone (VIII; R = H) and a small proportion (*ca.* 20%) of Δ⁵-cholesten-7-one. In this case the products were not isolated because of paucity of material. In contrast, each of the two 7α-alcohols, Δ⁵-cholestene-3β,7α-diol (IX; R = OH) and Δ⁵-cholesten-7α-ol (IX; R = H) reacted with oxygen only very slowly. Prolonged treatment still left a considerable amount of starting material, as well as some of the corresponding enone (13–20%) and a complex mixture from which no definite compounds were isolated.



That an allylic hydroxyl group deactivates the olefinic unit toward photosensitized oxygenation was shown by comparative studies with the parent olefins Δ⁴-cholestene and Δ⁵-cholestene, each of which reacted much more rapidly than did any of the allylic alcohols. This deactivation is increased by esterification because the acetate and benzoate esters of the alcohols were unchanged even on prolonged oxygenation. Consequently, esterification provides a simple way to protect an allylic alcohol unit should selective oxygenation at another site in a molecule be desired.

We found that the ratio of enone to epoxyketone could be altered markedly by varying the sensitizing dye. Some results from oxygenation of I are sum-

(1) For a review, see G. O. Schenck, *Angew. Chem.*, **69**, 579 (1957).

(2) A. Nickon and J. F. Bagli, *J. Am. Chem. Soc.*, **83**, 1498 (1961).

(3) Products were identified by direct comparison (m.p., infrared, etc.) with authentic samples prepared by reported methods.

(4) Competitive photoöxygenation of a 1:1 mixture of I and IV showed that after 40 hr. about twice as much of I had undergone conversion as had IV.

(5) Recently P. S. Wharton and D. H. Bohlen [*J. Org. Chem.*, **26**, 3615 (1961)] reported a procedure for direct reduction of α,β-epoxyketones to allylic alcohols. We confirmed their conversion of V to 5β-cholest-3-ene-5-ol and used their method to convert II to 5α-cholest-3-ene-5-ol (m.p. 75–76°; α −14° in $CHCl_3$). Therefore our photochemical conversion followed by Wharton–Bohlen reduction of the derived α,β-epoxyketones provides a two-step transformation of certain alcohols to their allylic isomers with net inversion of C–O configuration.