the product synthesized from this alkaloid and deuterated dregaminol exhibited two one-proton singlets at 6.75 and 7.03 $\delta$, 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]

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## Stereospecific Preparation of Epoxyketones by Photochemical Oxygenation

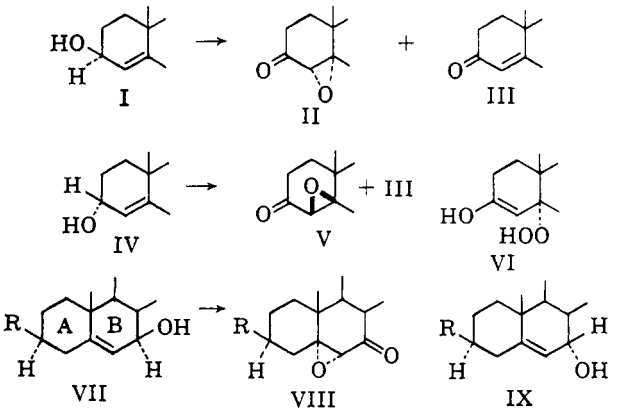
*Sir:*

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 $\alpha,\beta$-epoxyketones from allylic alcohols.

Photoöxygenation of $\Delta^4$-cholesten-3$\beta$-ol (partial structure I) in pyridine with hematoporphyrin produced 4$\alpha$,5-epoxy-5$\alpha$-cholestan-3-one[3] (II; 75%) along with some $\Delta^4$-cholesten-3-one (III; 16%). Similar irradiation of $\Delta^4$-cholesten-3$\alpha$-ol (IV) gave 4$\beta$,5-epoxy-5$\beta$-cholestan-3-one (V; 50%) along with some enone III (10%). In the 3$\alpha$-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 5$\alpha$-hydroperoxide VI is an expected intermediate in the reaction of I; and the corresponding 5$\beta$-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 $\pi$ 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 $\Delta^5$-cholesten-3$\beta$-7$\beta$-diol (VII; R = OH) proceeded readily and gave 56% of the 5$\alpha$,-6$\alpha$-epoxyketone VIII (R = OH) and about 15% of the corresponding enone, $\Delta^5$-cholesten-3$\beta$-ol-7-one. Similarly, oxygenation of a small sample of $\Delta^5$-cholesten-7$\beta$-ol (VII; R = H) gave products whose infrared and ultraviolet spectra were consistent with the presence of the $\alpha,\beta$-epoxyketone (VIII; R = H) and a small proportion (*ca.* 20%) of $\Delta^5$-cholesten-7-one. In this case the products were not isolated because of paucity of material. In contrast, each of the two 7$\alpha$-alcohols, $\Delta^5$-cholestene-3$\beta$,7$\alpha$-diol (IX; R = OH) and $\Delta^5$-cholesten-7$\alpha$-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 $\Delta^4$-cholestene and $\Delta^5$-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-

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(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 $\alpha,\beta$-epoxyketones to allylic alcohols. We confirmed their conversion of V to 5$\beta$-cholest-3-ene-5-ol and used their method to convert II to 5$\alpha$-cholest-3-ene-5-ol (m.p. 75–76°; $\alpha$ −14° in $CHCl_3$). Therefore our photochemical conversion followed by Wharton–Bohlen reduction of the derived $\alpha,\beta$-epoxyketones provides a two-step transformation of certain alcohols to their allylic isomers with net inversion of C–O configuration.

marized in Table I and show that either product can be made to predominate.[6]

TABLE I

| Sensitizer[a] | Fluorescence maximum, mμ[b] | Total % conversion | Ratio III/II |
|---|---|---|---|
| Chlorin $e_6$ | 670 | 85 | 1:4.5 |
| Hematoporphyrin | 630 | 80 | 1:4.5 |
| Rose Bengal | 580 | 88 | 1:1.2 |
| Erythrosin B | 578 | 71 | 1.6:1 |
| Eosin Y | 565 | 82 | 3.1:1 |
| Riboflavin[c] | 510 | 61 | 30:1 |

[a] Photoöxygenations were conducted in pyridine for 80 hr. [b] Measured in pyridine with an Aminco-Bowman Spectrofluorometer. [c] Owing to low solubility this run was in pyridine–methanol (4:1) for 110 hr. About the same product ratio was observed in pyridine alone but the total conversion was only 35%.

This finding has practical value for synthetic work and raises questions on the precise nature of the intermediates in sensitized oxygenations.[7] Interestingly, there is a rough parallelism between the trend in product ratio and the trend in fluorescence emission maximum for the different sensitizers.

(6) Control experiments showed that both products are stable to the conditions of photoöxygenation.

(7) An example of sensitizer control of product composition in a photochemical reaction not involving oxygen was reported recently [G. S. Hammond, N. J. Turro and A. Fischer, *J. Am. Chem. Soc.*, **83**, 4674 (1961)].

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## The Synthesis of a Biologically Active Pentadecapeptide Corresponding to an Altered Sequence in the Adrenocorticotropin (ACTH) Structure

*Sir:*

Since the synthesis[1] of a nonadecapeptide corresponding to the $NH_2$-terminal 19-amino acids in the 39-amino acid chain of ACTH structures, several investigators[2-6] have reported the synthesis of various chain lengths. We wish to describe herein the synthesis of a pentadecapeptide with a structure consisting of the first ten $NH_2$-terminal residues linked with a sequence of positions 15 to 19 in ACTH structures; namely, L-seryl-L-tyrosyl-L-seryl-L-methionyl-L-glutamyl-L-histidyl-L-phenylalanyl-L-arginyl-L-tryptophyl-glycyl-L-lysyl-L-lysyl-L-arginyl-L-arginyl-L-proline. This synthetic product, designated as $\alpha^{(1-10)+(15-19)}$-ACTH, was shown to have an ACTH potency of approximately 1 U.S.P. unit per mg., as estimated by *in vitro*[7] and *in vivo*[8] methods in the rat. The product was found to exhibit the full lipolytic potency of the natural[9] $\alpha_s$-ACTH, when assayed[10] *in vitro* with perirenal adipose tissues of the rabbit. By the *in vivo* hypophysectomized frog assay,[11] the synthetic peptide had only one hundredth of the melanocyte-stimulating activity of the native hormones. Recent studies[10] with various synthetic peptides related to ACTH appeared to show that the same amino acid sequence may be important for both lipolytic and melanocyte-stimulating activities. It is further noted that the decapeptide ($\alpha^{1-10}$-ACTH) possesses approximately one tenth of the lipolytic[10] and the melanocyte-stimulating[12] activities of the natural hormone whereas the pentapeptide[13] ($\alpha^{15-19}$-ACTH) has none. The synthetic pentadecapeptide described herein is the first instance where a separation of these two activities has been achieved. Moreover, as far as we are aware this report represents the first synthesis of a biologically active peptide in which the natural sequence of the ACTH structure has been altered.

$N^{\alpha}$-Carbobenzoxy-$N^{G}$-tosyl-L-arginine[14] (I) was condensed with L-proline-*t*-butyl ester[15] by N-ethyl-5-phenyl isoxazolium-3′-sulfonate[16] (II) to give the crystalline protected dipeptide (III). III was hydrogenated and allowed to react with I, again with the aid of II. The protected tripeptide was converted to the pentapeptide $N^{\alpha}$-carbobenzoxy-$N^{\epsilon}$-*t*-butyloxycarbonyl-L-lysyl-$N^{\epsilon}$-*t*-butyloxycarbonyl-L-lysyl-$N^{G}$-tosyl-L-arginyl-$N^{G}$-tosyl-L-arginyl-L-proline-*t*-butyl ester (IV) by stepwise reaction of the tripeptide base with $N^{\alpha}$-carbobenzoxy-$N^{\epsilon}$-*t*-butyloxycarbonyl-L-lysine *p*-nitrophenyl ester.[17] IV was purified by countercurrent distribution in the toluene system[1] ($K = 0.25$); m.p. 105–110°; $[\alpha]^{25}D$ −36° (*c* 1, methanol). *Anal.* Calcd.: C, 56.4; H, 7.22; N, 13.2; S, 4.64. Found: C, 56.2; H, 7.33; N, 13.0; S, 4.69.

IV was hydrogenated to yield the pentapeptide base (V) which was purified by countercurrent distribution in the toluene system[1] ($K = 0.73$); m.p. 112–117°; $[\alpha]^{25}D$ −33.7° (*c* 1, methanol). *Anal.* Calcd.: C, 54.8; H, 7.51; N, 14.6. Found: C, 54.5; H, 7.72; N, 14.4.

V was treated with crystalline carbobenzoxy-L-seryl-L-tyrosyl-L-seryl-L-methionyl-γ-benzyl-L-glutamyl-L-histidyl-L-phenylalanyl-$N^{G}$-tosyl-L-arginyl-L-tryptophyl-glycine[5] in the presence of II to give the protected pentadecapeptide (VI). VI was purified by countercurrent distribution in the carbon tetrachloride system[1] followed by washing with methanol; m.p. 225–230° dec.; $[\alpha]^{25}D$ −51.5° (*c* 2.4, dimethylformamide). *Anal.* Calcd.: C, 57.0; H, 6.48; N, 14.0. Found: C, 56.6; H, 6.17; N, 13.8.

VI was treated with trifluoroacetic acid and then with sodium in liquid ammonia[18] to remove all the protecting groups. The crude pentadecapeptide was desalted and purified by chromatography in a carboxymethyl cellulose[19] column. The purified $\alpha^{(1-10)+(15-19)}$-ACTH was found to be homogeneous in paper and polyacrylamide gel[20] electrophoresis. Amino acid analysis of an acid hydrolysate of the synthetic pentadecapeptide both by the chromatographic method of

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