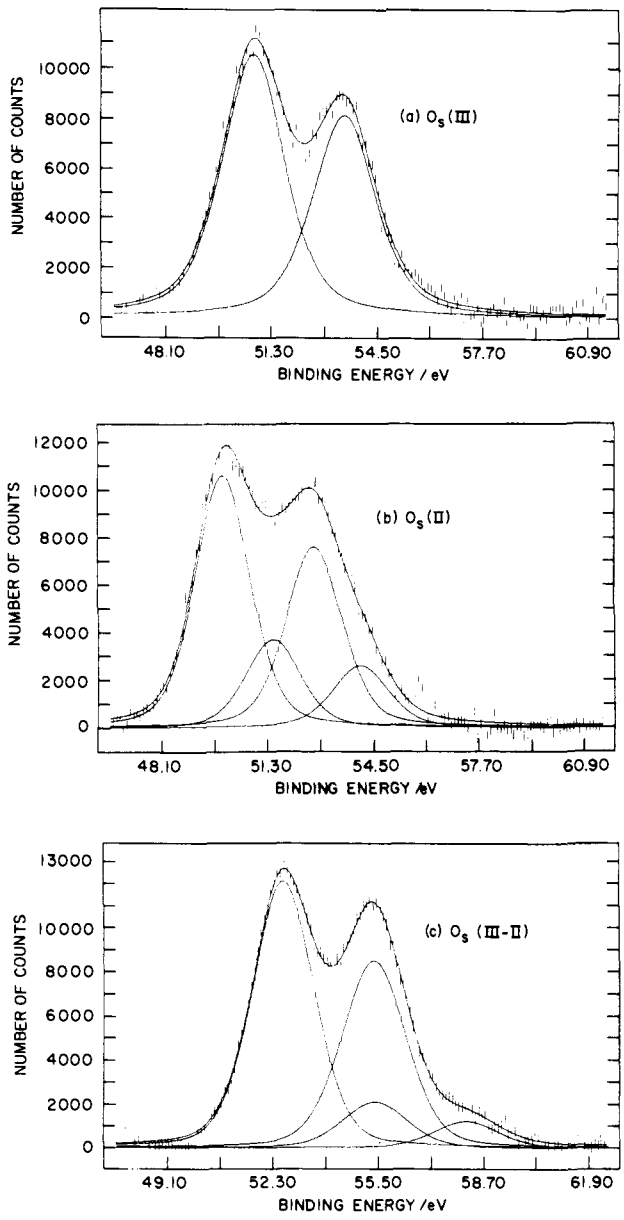


Figure 1. Os 4f spectrum of (a) $[Os(NH_3)_5Cl]Cl_2$, (b) $[Os(NH_3)_5N_2]Cl_2$, and (c) $[Os(NH_3)_4ClN_2Cl(NH_3)_4Os]Cl_3$.

Figure 1c except that the width is now reduced from ~2.3 to 1.8 eV owing to improvement in spectrometer resolution. This strongly suggests that the main peaks observed in the mixed-valence compound do not derive, as Hush proposed,[3] from two distinct final states which would show either two sets of spin orbit coupled peaks having comparable intensities or at least an envelope appearing as two broadened peaks. On the other hand, these results strongly support the view that $\{[Os(NH_3)_4Cl]_2N_2\}Cl_3$ is a true class III type of mixed-valence compound,[8] which could not be concluded on the basis of the results previously reported.[2] In that report it was stated also that a shoulder was observed at a binding energy 1.5 eV lower than that of the Os $4f_{7/2}$ peak for $[(NH_3)_4OsCl(pZ)]Cl_2$. Further there was said to be enhancement of the lower binding energy side of the Os $4f_{7/2}$ peak for $\{[Os(NH_3)_4Cl]_2N_2\}Cl_3$. These effects were attributed to surface reduction of Os(III) due to radiation damage. It is obvious from Figure 1 that such spectral features[2] are not observable in the mixed-valence compound in our experiment. It is difficult to assess the reasons for these discrepancies as the previous workers did not describe in detail the conditions under which their experiments were conducted, nor did they show figures of their results.

Our work does not contradict the work of Hush,[3] as it is apparent that there must be more than one final state possible for the $\{[Os(NH_3)_4Cl]_2N_2\}Cl_3$. However, it is apparent from the spectrum that the higher binding energy states are much less probable than the principal $4f_{7/2}$ final state. In addition, satellite structure was observed in the Os(II) compounds (Figure 1). It is conceivable that in some cases it may be possible for satellites to be probable enough, so that they are mistaken for peaks arising from the presence of more than one oxidation state in a compound.

The presence of satellites in the Os(II) compounds, $[Os(NH_3)_5N_2]Cl_2$ and the mixed-valence compounds, may be associated with the N_2 ligand. In general, satellites are not observed in second- and third-row transition metal core level spectra,[9] with the exception of CO complexes.[10] N_2 is isoelectronic with CO, and, in addition, the π back-bonding effect is very strong in Os(II) analogous to some metal carbonyls.[10] The ground- and excited-state levels arising from N_2 and Os(II) interaction may induce, during photoemission, monopole transitions which give rise to observable satellites.

Acknowledgments. We gratefully acknowledge Dr. J. D. Buhr and Dr. H. Taube for supplying us with the osmium compounds used in this study. We also thank Dr. M. L. Perlman and Dr. C. A. Creutz for their valuable comments. Acknowledgment is made by one of us (M.S.L.) to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. Research was performed at BNL under contract with the U.S. Department of Energy and supported by its Division of Basic Energy Sciences.

References and Notes

(1) Citrin, P. H. *J. Am. Chem. Soc.* **1973**, *95*, 6472.
(2) Battistoni, C; Furlani, C.; Mattogno, G.; Tom, G. *Inorg. Chim. Acta* **1977**, *21*, L25.
(3) Hush, N. S. *Chem. Phys.* **1975**, *10*, 361.
(4) Jørgenson, C. F. *Structure Bonding (Berlin)* **1975**, *24*, 1.
(5) Robin, M. B.; Day, P. *Adv. Inorg. Chem. Radiochem.* **1967**, *10*, 247.
(6) Magnuson, R. H.; Taube, H. *J. Am. Chem. Soc.* **1972**, *94*, 7213.
(7) Magnuson, R. H. Ph.D. Thesis, Stanford University, Stanford, Calif., 1975.
(8) Taube, H. *Proc. R. Aust. Chem. Inst.* **1975**, *42* (6), 139.
(9) Vernon, G. A.; Stucky, G.; Carlson, T. A. *Inorg. Chem.* **1976**, *15*, 278.
(10) Bancroft, G. M.; Boyd, B. D.; Creber, D. K. *Inorg. Chem.* **1978**, *17*, 1008.

M. S. Lazarus*
Department of Chemistry
H. H. Lehman College of the City University of New York
Bronx, New York 10468

T. K. Sham*
Department of Chemistry, Brookhaven National Laboratory
Upton, New York 11973

Received January 2, 1979

Synthesis of a 4a,5-Epoxy-5-deazaflavin Derivative

Sir:

Oxidized flavins undergo nucleophilic addition reactions with H_2O_2 to form flavin hydroperoxide derivatives which are also observed as intermediates during reaction of reduced flavin with O_2.[1] Compared with the corresponding flavin derivative, 5-deaza analogues I are more susceptible toward nucleophilic attack which typically occurs at position 5 to yield 1,5-dihydro adducts IIa.[2-4] In this communication we report the formation of a novel 4a,5-epoxy derivative (III) by reaction of 5-deazaisoalloxazine (I) with H_2O_2, *tert*-butyl hydroperoxide, or *m*-chloroperoxybenzoic acid. This epoxide is isoelectronic with the N-5 oxide formed by reaction of the isoalloxazine analogue

0002-7863/79/1501-7623$01.00/0

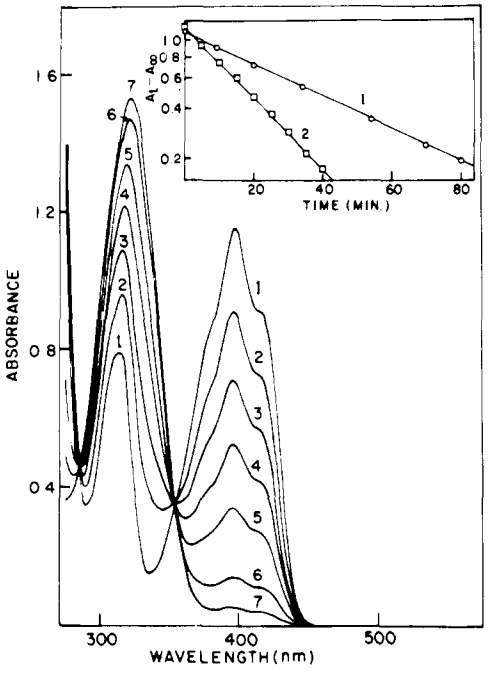
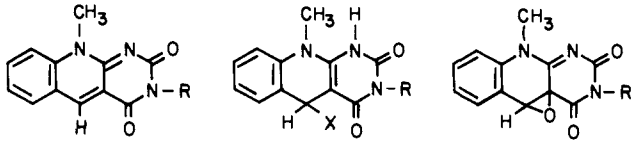


Figure 1. Reaction of 10-methyl-5-deazaisoalloxazine (9.0×10^{-5} M) with hydrogen peroxide at 25 °C: curve 1, initial spectrum in acetonitrile containing 7.0×10^{-2} M triethylamine; curves 2–7 were recorded 8, 19, 33, 53, 95, and 150 min, respectively, after addition of 7.1×10^{-2} M H_2O_2. The inset shows the first-order plot for the reaction in acetonitrile (line 1) and in 0.01 M sodium carbonate buffer pH 9.0 (line 2).



I a, R = H; b, R = CH_3 — II a, X = CN, SO_3^-, OH; b, X = OOH — III a, R = H; b, R = CH_3

of I with RCO_3H.[5] A species with spectral properties similar to those of III has been observed during the reaction of several 5-deazaflavoenzymes with H_2O_2.[6] A 5-hydroperoxy structure (IIb) was previously proposed by Chan and Bruice for the product formed from I and H_2O_2.[4]

The reaction of I with H_2O_2 in various organic solvents requires a basic catalyst and is accompanied by a bathochromic shift (4–7 nm)[7] of the absorption band near 320 nm and a bleaching of the band near 390 nm (Figure 1). The absorption maximum of the product in water (λ_{max} ~330 nm)[8] appears at longer wavelengths than those of 1,5-dihydro adducts IIa (λ_{max} <310 nm).[2-4] The product does not revert to I upon neutralization of the base required for its formation nor upon removal of free H_2O_2. This indicates that the reaction with H_2O_2 is not an equilibrium reaction, in agreement with previous studies,[4] but different from the reversible reactions observed for 1,5-dihydro adducts IIa.[2-4]

The reaction of I with $(CH_3)_3COOH$ also requires a basic catalyst and exhibits a spectral course similar to the reaction with H_2O_2. Higher concentrations of the less reactive $(CH_3)_3COOH$ are required in order to observe comparable reaction rates.[9] The observed reaction is not due to a H_2O_2 contaminant as evidenced by control studies involving preincubation with catalase. Thin layer chromatography[10] showed that identical products are formed with H_2O_2 and $(CH_3)_3COOH$. This indicated that IIb could not be the product but might be an intermediate in the formation of a 4a,5-epoxide (III) (Scheme I).

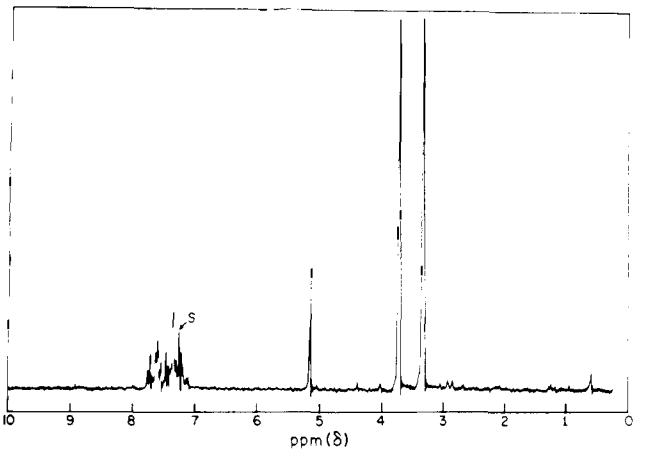
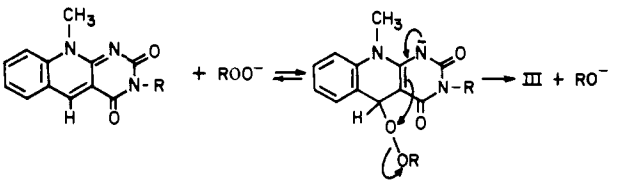


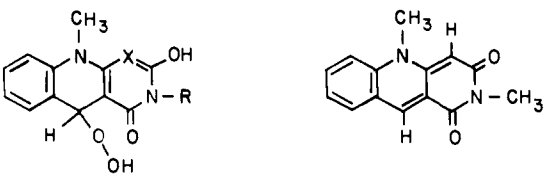
Figure 2. NMR spectrum of 4a,5-epoxy-3,10-dimethyl-5-deazaisoalloxazine (IIIb) in $CDCl_3$ obtained with a Varian EM-360L (60 MHz) spectrophotometer. Peak s is due to the solvent.

Scheme I



Similar alkaline epoxidation reactions with ROOH have been observed with compounds containing a carbon double bond conjugated to an unsaturated electron-withdrawing group.[11] Epoxidation of carbon double bonds with organic peroxy acids is a general reaction observed with a much broader spectrum of unsaturated compounds.[12] Reaction of I with *m*-chloroperoxybenzoic acid in $CHCl_3$ occurs at room temperature, does not require a basic catalyst, and is quantitative in the presence of a slight excess (1.3-fold) of purified[13] peroxy acid. The isolated product exhibited spectral (visible,[8a] NMR) and chromatographic[10] properties identical with those observed for the product formed with alkaline peroxide.[14]

Compared with the NMR spectrum of Ib, the major difference in the NMR spectrum observed for the product (Figure 2) is the position of the peak attributable to the hydrogen at C-5 (δ 8.9 ppm for Ib in $CDCl_3$) which is shifted upfield and appears as a singlet at δ 5.2 ppm, indicating that substitution has occurred at this position. Peaks expected for the exchangeable protons in IIb were not detected (δ 0–20 ppm). The spectrum observed in anhydrous $CDCl_3$ was not affected by addition of D_2O. Unlike previous studies,[4] which yielded otherwise similar NMR data, the absence of these peaks cannot be attributed to exchange with H_2O. The infrared spectrum of the product (KBr pellet) did not show evidence for an -OH group. The results exclude IIb and also tautomers of IIb (e.g., IV). The latter were proposed as alternative



IV X = N, CH — V

structures by Chan and Bruice[4b] since an apparently analogous product, formed by reaction of alkaline H_2O_2 with V, contained a single nonexchangeable proton at C-1. The mass spectrum obtained for the product formed from Ib (M^+ 241

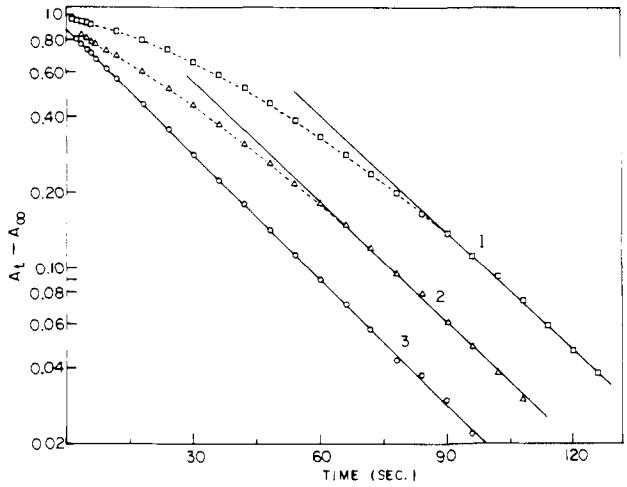
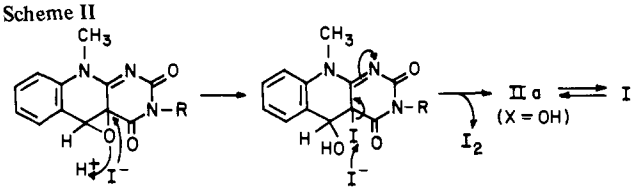


Figure 3. First-order plots for the reaction of 10-methyl-5-deazaisoalloxazine (8.0×10^{-5} M) with 7.1×10^{-2} M H_2O_2 in 1.0 M sodium carbonate buffer pH 9.0 at 25 °C. Lines 1-3 were obtained for reactions initiated after prior incubation of H_2O_2 with the buffer for 0, 30 and 120 s, respectively.

Scheme II



(base peak)) showed prominent peaks at *m/e* 257, 241, and 200 (base peak). The peak at 257 is attributed to the molecular ion formed from IIIb. The product formed from V exhibited peaks (*m/e* 256, 240, 199 (base peak))[4b] at positions suggesting an epoxide structure identical with IIIb except for the substitution of N at position 1 by CH.[15]

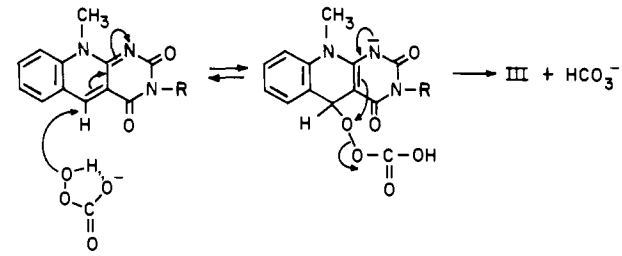
No reaction was observed with III and thioxane,[16] although formation of I was reported under these conditions.[4] Results[17] obtained for the reaction of III with iodide are similar to previous studies:[4]

$$\text{compound III} + 3I^- \rightarrow \text{compound I} + I_3^- \qquad (1)$$

A different mechanism is proposed for iodide oxidation which involves reduction of an epoxide rather than a hydroperoxide derivative (Scheme II). The final equilibrium step in this mechanism lies completely to the right under the conditions of eq 1, as previously described (K_D = 6.7 M).[4] While addition reactions are commonly observed with epoxides and iodide, a similar oxidation reaction has been observed with epoxide derivatives substituted with unsaturated electron-withdrawing groups,[18] the same structural feature required for alkaline epoxidation of carbon double bonds.

An unusual effect of carbonate buffer has been observed on the reaction of I with H_2O_2. The rate of formation of III, which is unstable in aqueous alkaline solution,[19a] can be monitored at 390 nm, a wavelength where neither III nor its decomposition products absorb. Linear first-order plots are observed for the reaction in 0.01 M sodium carbonate pH 9.0 (Figure 1). The observed rate at 7.1×10^{-2} M H_2O_2 ($k_{obsd} = 8.0 \times 10^{-4}$ s^{-1}) is comparable with the rate of decomposition,[19b] and only small amounts of III are detected. The rate of decomposition is not appreciably altered in 1.0 M carbonate, but the rate of formation is greatly accelerated (complete within ~2 min) and a >90% yield of III is detected before the slower decomposition reaction occurs. First-order plots for this reaction exhibit a distinct lag phase which can be eliminated by prior incubation of H_2O_2 with the buffer (Figure 3). The rate observed after the lag is identical with the rate obtained from the linear plots

Scheme III



(k_{obsd} = 0.036 s^{-1}). A relatively slow formation of peroxycarbonic acid (eq 2), analogous to reactions[20] observed for CO_2

$$CO_2 + H_2O_2 \underset{}{\overset{\text{slow}}{\rightleftharpoons}} \underset{\text{HOCOOH}}{\overset{\text{O}}{\overset{\|}{\text{C}}}} \overset{\text{fast}}{\rightleftharpoons} \underset{{}^-\text{OCOOH}}{\overset{\text{O}}{\overset{\|}{\text{C}}}} \qquad (2)$$

$$\updownarrow \text{slow}$$

$$CO_2 + HOO^-$$

with H_2O and OH^-, could account for the observed lag (Scheme III). A tentative mechanism involving nucleophilic attack by $^-OC(=O)OOH$ is proposed since this is likely to be the major species present in solution at pH 9.0.[21] Epoxide formation is facilitated as compared with that in the uncatalyzed reaction since HCO_3^- replaces OH^- as the leaving group. Further studies to evaluate this mechanism and to determine whether the catalytic effect of carbonate is observed for other epoxidation reactions are in progress.

Acknowledgment. This work was supported by a grant from the National Institutes of Health (GM 22662).

References and Notes

(1) (a) Kemal, C.; Bruice, T. C. *Proc. Natl. Acad. Sci. U.S.A.* **1976**, *73*, 995-999. (b) Mager, H. I. X. *Tetrahedron* **1977**, *33*, 981-989. (c) van Schagen, W. J. H.; Grande, H. J.; Müller, F. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 179-180. (d) Entsch, B.; Ballou, D. P.; Massey, V. *J. Biol. Chem.* **1976**, *251*, 2550-2563. (e) Hastings, J. W.; Tu, S.-C.; Becvar, J. E.; Presswood, R. B. *Photochem. Photobiol.* **1979**, *29*, 383-387.
(2) Jorns, M. S.; Hersh, L. B. *J. Biol. Chem.* **1976**, *251*, 4872-4881.
(3) Brüstlein, M.; Bruice, T. C. *J. Am. Chem. Soc.*, **1972**, *94*, 6548-6549.
(4) (a) Chan, R. L.; Bruice, T. C. *J. Am. Chem. Soc.* **1977**, *99*, 6721-6730. (b) Chan, R. L.; Bruice, T. C. *Ibid.* **1978**, 100, 7375-7382.
(5) (a) Gladys, M.; Knappe, W. *Z. Naturforsch. B* **1974**, *29*, 549-551. (b) Yoneda, F.; Sakuma, Y.; Ichiba, M.; Shinomura, K. *J. Am. Chem. Soc.* **1976**, *98*, 830-835.
(6) These studies will be reported separately.
(7) This differs from the hypsochromic shifts observed during reactions with nucleophiles which form 1,5-dihydro adducts.[2]
(8) (a) IIIa, λ_{max} 329 nm (ϵ 16 000 at pH 7.5); IIIb, λ_{max} 331 (ϵ 15 500 at pH 7.5). Previous studies[2,8b] suggest that the unknown isoalloxazine analogue of III (a 4a,5-oxaziridine) would exhibit a similar spectrum but the absorption maximum would be shifted to longer wavelengths (~380 nm). Conversion of an initial 4a-hydroperoxyflavin intermediate into an oxaziridine has been postulated for enzymic hydroxylation reactions.[8c] It may be significant that the second intermediate detected during hydroxylation by *p*-hydroxybenzoate hydroxylase does absorb near 380 nm. (b) Spencer, R.; Fisher, J.; Walsh, C. *Biochemistry* **1976**, *15*, 1043-1053. (c) See Rastetter, W. H.; Gadek, T. R.; Tane, J. P.; Frost, J. W. *J. Am. Chem. Soc.* **1979**, *101*, 2228-2231, and references therein.
(9) At 4.7 M $(CH_3)_3COOH$ and 0.34 M $(CH_3CH_2)_3N$ in acetonitrile at 25 °C; $t_{1/2}$ = 30 min with Ia (0.94 μM).
(10) Chromatograms (silica gel F-254) were developed using the following solvent systems: chloroform-ethanol (4:1), benzene-methanol (65:35), 2-butanol-ethanol-water (7:2:1). In all systems parent compounds were separated from the corresponding nonfluorescent products. The first two systems separated products IIIa and IIIb which differ by a single methyl group. Acidic and basic solvent systems were avoided owing to the instability of III.
(11) (a) Bunton, C. A.; Minkoff, G. J. *J. Chem. Soc.*, **1949**, 665-670. (b) Yang, N. C.; Finnegan, R. A. *J. Am. Chem. Soc.* **1958**, *80*, 5845-5848. (c) Payne, G. B. *J. Org. Chem.* **1960**, *25*, 275-276. (d) Payne, G. B. *ibid.* **1959** *24*, 2048-2049.
(12) Swern, D. In "Organic Peroxides", Swern, D., Ed.; Wiley-Interscience: New York, 1971; Vol. 2, pp 355-533.
(13) Schwartz, N. N.; Blumbergs, J. H. *J. Org. Chem.* **1964**, *29*, 1976-1979.
(14) (a) Compound Ib (3.05 mmol) was added to 5 mL of a $CHCl_3$ solution containing 3.77 mmol of *m*-chloroperoxybenzoic acid and the resulting suspension stirred at room temperature. After 150 min, the absorption spectrum obtained for a diluted aliquot indicated that 98% conversion into IIIb had occurred. The solvent was then evaporated and the residue recrystallized from DMF-ether. (b) Compound Ib (1.23 mmol) was dissolved in a solution containing acetonitrile (7 mL), triethylamine (0.7 mL), and H_2O_2 (0.7 mL, 30%). After 15 min at room temperature, the reaction was com-

plete and the product began to crystallize out of solution. The crystals were collected after cooling to −20 °C and washed with water, ethanol, and ether (59% yield, mp 219–220 °C). (In addition to other criteria, the identity of the products prepared by these methods was verified by mixture melting point determinations.) Anal. Calcd for $C_{13}H_{11}N_3O_3$: C, 60.70; H, 4.31; N, 16.33. Found: C, 60.71; H, 4.37; N, 16.33.

(15) In aquoeus alkaline solution this product was converted into 3,10-dimethyl-1-hydroxy-1,5-dideazaisoalloxazine (VI).[4b] Cleavage of the epoxide ring via Michael addition of OH^- at C-1 would yield a 1,5-dihydroxy-1,5-dihydro intermediate. Formation of VI and the associated lag phase could be accounted for by dehydration of this intermediate initiated by ionization at C-1 (pK = 6.8 for 1,5-dihydro-1,5-dideazaisoalloxazine[4b]).

(16) The rate constant observed for the reaction of thioxane (Aldrich, vacuum distilled) with H_2O_2 ($k = 6.7 \times 10^{-5}\ M^{-1}\ s^{-1}$ in methanol at 25 °C) is similar to the value previously reported under the same conditions. Dankleff, M. A. P.; Curci, R.; Edwards, J. O.; Pyun, H. Y. *J. Am. Chem. Soc.* **1968**, *90*, 3209–3218.

(17) Values of 8.7×10^{-2} and $9.6 \times 10^{-2}\ M^{-1}\ s^{-1}$ were obtained for rate constants with IIIa and IIIb, respectively, in methanol at 25 °C. The same results were obtained with samples of IIIb prepared by different methods.[14]

(18) (a) Charpentier-Morize, M.; Laszlo, P.; Mayer, M. *Bull. Soc. Chim. Fr.* **1966**, 2264–2269. (b) Dullaghan, M. E.; Nord, F. F. *Mikrochim. Acta* **1953**, 17–21.

(19) (a) This instability, which is expected for an epoxide derivative, has previously been described.[4] (b) Rates of decomposition were determined in separate experiments under comparable conditions by monitoring the decrease in absorption at 330 nm observed immediately after preparing solutions of III in carbonate buffer.

(20) Cotton, F. A.; Wilkinson, G. "Advanced Inorganic Chemistry"; Interscience Publishers: New York, 1967; pp 308–310.

(21) Organic peroxy acids are generally weaker acids than the corresponding carboxylic acid, suggesting a similar relationship for the two ionizable protons in peroxycarbonic acid: Curci, R.; Edwards, J. O. In "Organic Peroxides", Swern, D., Ed.; Wiley-Interscience: New York, 1970; Vol. 1, pp 205–207.

Donald Vargo, Marilyn S. Jorns*

Department of Chemistry, The Ohio State University
Columbus, Ohio 43210

Received June 25, 1979

Total Synthesis of *dl*-Helenalin

Sir:

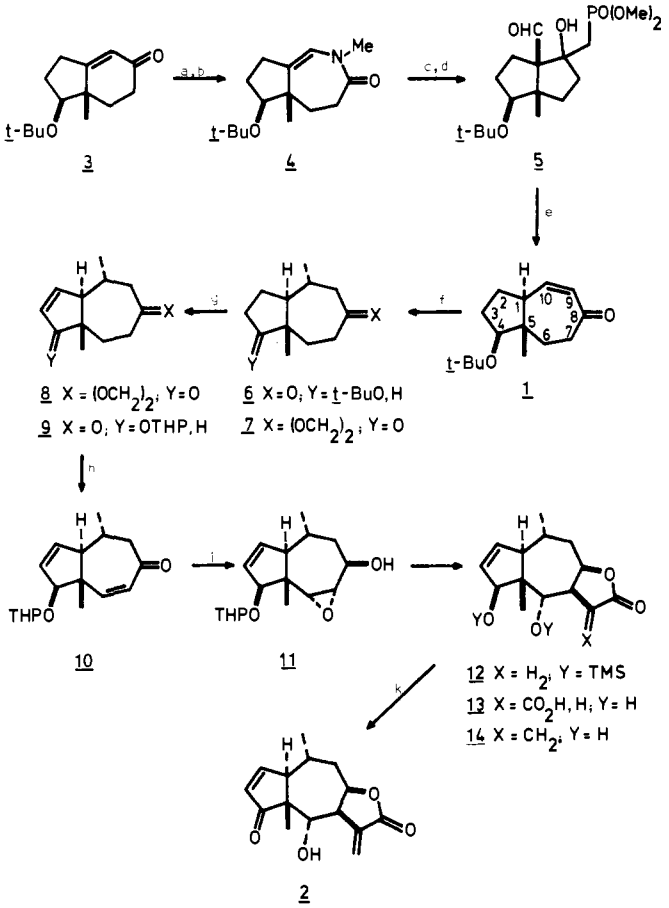
The group of sesquiterpenes called pseudoguaianolides has attracted considerable chemical attention not only because of their structurally challenging and esthetically pleasing nature, but also because of their cytotoxic properties.[1] Representatives of this class of natural products which have succumbed to total synthesis are the molecules helenalin,[2] confertin,[3] and damsin.[4] Our interest in these sesquiterpenes was stimulated by the desire to construct them from a common intermediate since they all possess a central seven-membered ring which holds the major elements of functionality and stereochemistry. Thus, we formulated the perhydroazulenone **1** containing an oxygen residue at C_8, an olefinic element between C_9 and C_{10}, and an angular methyl group at C_5. Acting in concert, these various aspects of **1** should permit stereoselective introduction of a methyl group at C_{10}, connection of the carbonaceous portion of a lactone residue at C_7, and oxygenation at C_6. Further, the oxygen atom borne at C_4 should allow functionalization at C_2 and C_3, when required. Herein, are described the preparation of **1** and its stereoselective conversion into helenalin (**2**). In the accompanying manuscript we report the synthesis of confertin and damsin from this same substance.

We commenced our preparation of **1** starting from the readily available enone **3**,[5] converting this material into the lactam **4** (mp 39–42 °C) using technology recently described by Barton and co-workers.[6] On reaction with lithio dimethyl methylphosphonate in THF at −78 °C,[7] lactam **4** was transformed into the pentalene-derived aldehyde **5** (mp 49–51 °C)[8] which in turn gave the desired enone **1** as the only reaction product (oil, 50% overall yield from **3**) on treatment with slightly less than 1 equiv of potassium *tert*-butoxide in *tert*-butyl alcohol[9] (Scheme I).

Elaboration of **1** into helenalin was initiated by conversion of the enone into its C_{10} α-methyl analogue **6** (mp 66.5–68 °C, 87%) using methylmagnesium bromide in the presence of cuprous iodide-dimethyl sulfide.[10] Ketone **6** was then transformed into the ketal ketone **7** (mp 33–36 °C, 97% overall)[11] by sequential treatment with HCl-methanol (*tert*-butyl ether cleavage) followed by reaction with ethylene glycol (ketal formation) and finally oxidation with pyridinium chlorochromate buffered with sodium acetate.[12] The cyclopentanone residue of **7** was then converted into its cyclopentenone analogue **8** (mp 75–77 °C, 92% overall) by alkylation with diphenyl disulfide (NaH, DME), oxidation with *m*-chloroperbenzoic acid and sulfoxide elimination (110 °C, 30 h).[13] Lastly, **8** was transformed into the cycloheptanone **9** (oil, 84% overall) by diisobutylaluminum hydride reduction, ketal hydrolysis, and alcohol protection with dihydropyran.

In order to initiate the final stages of the synthesis, we intended to convert **9** into the cycloheptenone **10**, the latter substance serving as a vehicle for introduction of the lactone and hydroxyl residues. In our planning of this synthesis, we had examined molecular models of **9** and had tentatively concluded that proton abstraction from **9** might occur predominately at C_7—a result highly desirable to formulation of **10**.[14] We were pleased to find that **9** gave what appeared to be a single en-

Scheme I[a]



[a] (a) MeNHOH·HCl, C_5H_5N, 40 °C. (b) TsCl, C_5H_5N, 22 °C. (c) $LiCH_2PO(OCH_3)_2$, THF, −78 °C. (d) NaOAc, HOAc, H_2O, Et_2O, 0 °C. (e) *t*-BuOH, *t*-BuOK, 22 °C. (f) MeMgBr, CuI, DMS, Et_2O, 0 °C; HCl, MeOH, 0 °C; *p*-TSA, C_6H_6, $HOCH_2CH_2OH$, 90 °C; PCC, NaOAc, CH_2Cl_2, 22 °C. (g) NaH, Ph_2S_2, DME, 45 °C; *m*-CPBA, CH_2Cl_2, 0 °C; toluene, $P(OMe)_3$, 110 °C; diisobutylaluminum hydride, toluene, −40 °C; MeOH, HCl, 0 °C; DNP, *p*-TSA, CH_2Cl_2, 0 °C. (h) LiHMDS, TMSCl, THF, −78 °C; $Pd(OAc)_2$, CH_3CN, 22 °C. (i) MeOH, NaOH, H_2O_2, H_2O, 40 °C; triisobutylaluminum, toluene, 0 °C. (j) $LiCH_2CO_2Li$, HMPA, THF, 50 °C; 6 N HCl; TMSCL, Et_3N, THF, 22 °C; MMC, 140 °C; 30% CH_2O, Et_2NH. (k) MnO_2, $CHCl_3$, 45 °C.

0002-7863/79/1501-7626$01.00/0