Oxidative Demethylation at C-4 of a Steroid *via* Nitroxide Photolysis

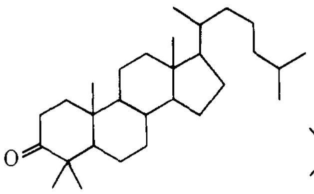
Sir:

In addition to studying the oxidative demethylation at C-4 during steroid biosynthesis,[1-3] we have been seeking a laboratory method of effecting selective oxidation at that geminal methyl grouping based on chemistry of the naturally occurring C-3 oxygen function. This goal has been realized by photolysis of the 4,4-dimethyloxazolidine-*N*-oxyl (doxyl) derivative (**4**) of 4,4-dimethylcholestanone (**1**), which affords substances **6** and **7** containing a functionalized C-4 β methyl.

Hydrogen atom abstraction by photoexcited nitroxides has been reported recently by Keana[4] and Ullman.[5] Keana[6] also was the first to prepare doxyl derivatives, a type of nitroxide which, when formed from **1**, provides the possibility of a six-membered transition state for hydrogen atom abstraction[7] from a C-4 methyl substituent.

Treatment of **1** with 2-amino-2-methyl-1-propanol containing *p*-toluenesulfonic acid at 165° for 5 days (much more vigorous conditions than required for unhindered ketones[6]) afforded 78% of a mixture of rather unstable oxazolidines **2**[8] and **3**. Oxidation of this mixture with *m*-chloroperbenzoic acid gave 53% of doxyl **4** and 18% of doxyl **5**, which were separable by repeated preparative tlc. Both **4** and **5** were reconverted to **1** quantitatively with nitrogen dioxide in ethanol.[9]

Stereochemical assignments to **4** and **5** were based initially on their esr spectra. Whereas **4** showed an esr triplet (a_N = 15.4 G) typical of doxyls,[6] **5** showed a triplet of doublets (a_N = 14.7 G, a_H = 3.5 G). The pronounced hyperfine coupling in the latter case can only reasonably be ascribed to long-range interaction between the spin density in the NO moiety and the 2β-H of **5**, which conform to the "W-rule."[10] Doxyl **4** has no hydrogen disposed so as to afford effective long-range coupling.[11]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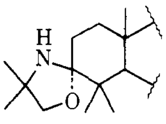

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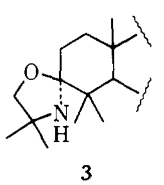

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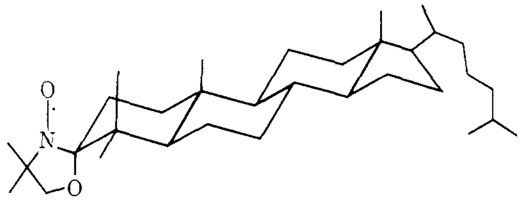

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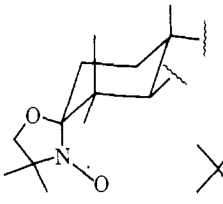

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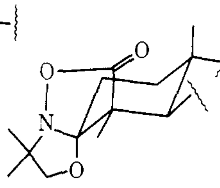

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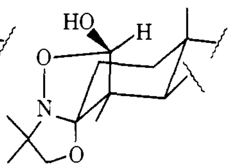

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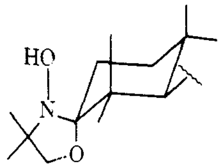

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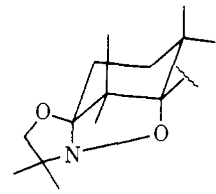

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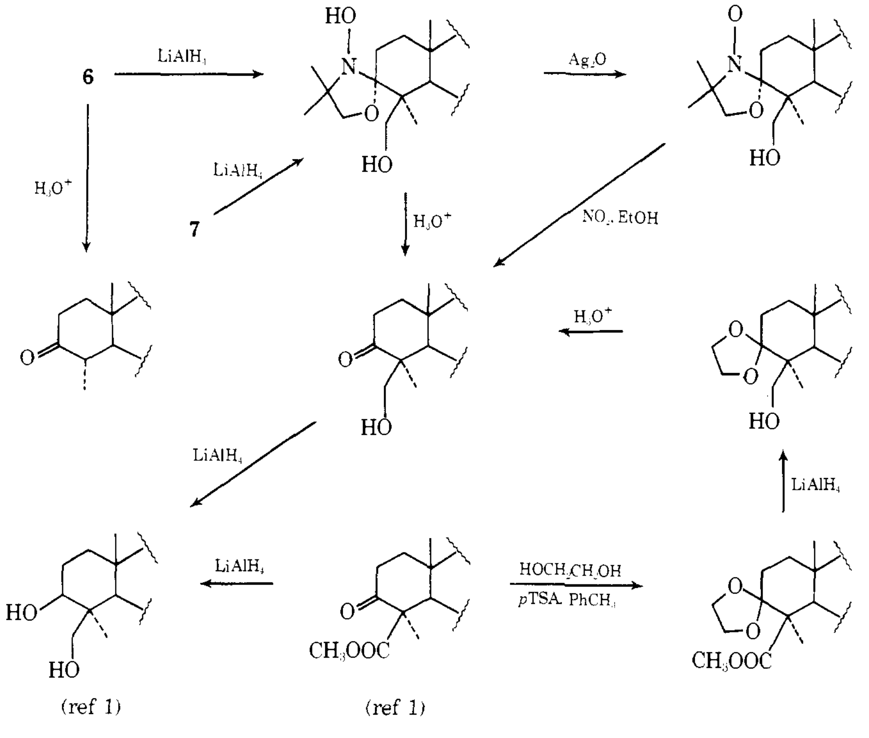
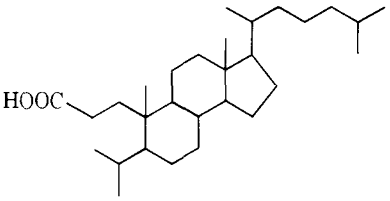
Photolysis of the major isomer **4** was first performed under conditions intended to promote fruitful trapping of the primary radical which would be generated by abstraction of a C-4 methyl hydrogen atom. Attempted photolysis in the presence of nitric oxide led to discovery of the reconversion of doxyls to their parent ketones by nitrogen dioxide.[9] Irradiation (450-W Hanovia lamp, Pyrex filter, 72 hr) of a 10% aqueous *tert*-butyl alcohol solution of **4** with oxygen bubbled through it[5] afforded *ca.* 35% of **8** containing a

Scheme I



small amount of **9**. These same substances, which were identified by an alternate synthesis,[12] were also obtained by identical photolysis of **1**. Irradiation in the same manner for 12 hr of a solution of **4** in $BrCCl_3$ afforded 63% of **10**. This substance, again identified by synthesis,[13] was obtained in 32% yield by irradiation of **1** in $BrCCl_3$. These results suggest that facile oxidative cleavage[9] of the doxyl moiety was occurring and precluding the desired reaction.



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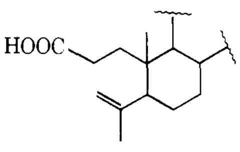

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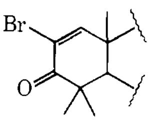

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When **4** was simply photolyzed in the same manner in benzene solution under nitrogen, the following, more interesting, mixture of products was obtained:[14] 4% **4**, 34% hydroxylamine **11** (ir (film) 3500 cm^{-1}, readily oxidized to **4** by air or Ag_2O), 21% of oxazolidine **2**,[15] 10% of as yet unidentified material,[16] and **6** and **7**, in 17 and 8% yield, respectively.

The substance assigned structure **6** had mp 149-50°: M^+ (*m/e*) 513.4182 (calcd 513.4181); ir (KBr) 1765 cm^{-1};[17] nmr (PhH-d_6) δ 1.35 ppm (s, 3, $>C(CH_3)C{=}O$). Upon treatment with $HCl\text{-}H_2O\text{-}CH_3OH$ at reflux for 10 hr it afforded 4α-methylcholestan-3-one, thus proving beyond reasonable doubt that functionalization at a C-4 methyl group had occurred and in a manner conducive to oxidative demethylation in the laboratory. Proof that it was the 4β-methyl group which had been oxidized was obtained from the conversions shown in Scheme I, which led to previously prepared compounds of known stereochemistry.[1]

The substance assigned structure **7** had mp 201-202°: M^+ (*m/e*) 515.4335 (calcd 515.4338); ir (KBr) 3180 cm^{-1}; nmr ($CDCl_3$) δ 5.20 ppm (s, 1, $\text{-}CH(OH)OR$). Its structure was also confirmed by the chemistry displayed in Scheme I. The configuration of the hemiacetal hydroxyl group was assigned on the basis of examination of molecular models, which show severe nonbonded interaction between the angular methyl and that hydroxyl group when it has the opposite configuration.

No products involving C-4α methyl functionalization were found, despite the fact that the nitroxide oxygen can "reach" the hydrogens of both the 4α and 4β methyl groups in **4** if ring A has a chair conformation. Very likely the absence of such products is related to a conformational distortion of ring A which decreases the 1,3-diaxial methyl interaction in **4** but also moves the nitroxide moiety away from the 4α methyl.

Ideally, photolysis of the isomeric doxyl **5** would have yielded the stereoisomer of **6** with the 4α methyl group functionalized, thus permitting selective functionalization of either methyl group and providing a simulation of the enzymic demethylation sequence, in which the 4α methyl group is initially oxidized.[1-3] However, irradiation of **5** has to date yielded only a substance (39%), mp 78-82°, M^+ (*m/e*) 499.4384 (calcd 499.4389), tentatively assigned structure **12**, resulting from abstraction of the tertiary hydrogen from the 5α position.

Efforts are being made to improve the efficiency of the novel remote functionalization reaction leading to **6** and **7** by attempting to provide an alternate to **4** as the (apparent) source of incorporated oxygen and by studying the photochemical process involved.

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References and Notes

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(5) L. Call and E. F. Ullman, *Tetrahedron Lett.*, 961 (1973).

(6) J. F. W. Keana, S. B. Keana, and D. Beetham, *J. Amer. Chem. Soc.*, **89**, 3055 (1967).

(7) Photolysis of the nitrite ester of a 3β-hydroxy-4,4-dimethyl steroid does not afford this possibility and did not lead to methyl group functionalization: G. R. Pettit, R. E. Kadunce, P. Sunder-Plassmann, and J. Occolowitz, *Can. J. Chem.*, **43**, 2872 (1965).

(8) All new compounds reported were characterized by ir and nmr or esr spectroscopy and by combustion analysis and/or high resolution mass spectroscopy.

(9) J. A. Nelson, S. Chou, and T. A. Spencer, *Chem. Commun.*, 1580 (1971); S. Chou, J. A. Nelson, and T. A. Spencer, *J. Org. Chem.*, **39**, 2356 (1974).

(10) A long-range hyperfine coupling of the same magnitude observed by A. Rassat and P. Rey (*Chem. Commun.*, 1161 (1971)) in 1,3,3-trimethyl-2-azabicyclo[2.2.2]octane-1-oxyl led to this "W-rule" explanation; *cf.*, A. Rassat and P. Rey, *Tetrahedron*, **28**, 741 (1972); **29**, 1599 (1973); Y. Ellinger, A. Rassat, R. Subra, and G. Berthier, *J. Amer. Chem. Soc.*, **95**, 2372 (1973). See P. Michon and A. Rassat, *J. Org. Chem.*, **39**, 2121 (1974), for a recent study of the stereochemistry of closely related doxyls.

(11) The conclusion that **5** but not **4** has a "W" is based on examination of Dreiding models using either planar or pyramidal nitrogen and with the steroid ring A in a normal or moderately distorted chair conformation.

(12) Baeyer-Villiger oxidation of **1** followed by treatment with H_2SO_4-HOAc according to J. S. E. Holker, W. R. Jones, and P. J. Ramm (*J. Chem. Soc. C*, 357 (1969)) produces **9**, which was reduced with H_2-Pd-C to **8**.

(13) Treatment of **1** sequentially with Br_2-HOAc, $CaCO_3$-DMA, and Br_2-CH_2Cl_2 afforded **10**.

(14) Exactly the same mixture of products is obtained whether the benzene is carefully degassed or not. Preliminary experiments using a Corning CS-3-73 filter (cutoff *ca.* 400 nm) suggest that the photochemistry is caused by excitation of the weak, long wavelength absorption of **4** ($\lambda_{max}^{Et_2O}$ 460 nm, ϵ = 6). The time required for completion of the photolysis of **4** can be reduced to 12 hr if the lamp is placed as close as possible to the reaction vessel and both are wrapped in Al foil. Under such conditions the reaction mixture refluxes, but this has no effect on the product distribution.

(15) Reference 5 provides a mechanistic scheme applicable to the formation of **2**.

(16) This material has the greatest tlc mobility of any of the products, has ir (film) 3500 cm^{-1}, and gives an unknown nitroxide on standing in air. Presumably therefore, it contains hydroxylamine other than **11**.

(17) H. A. Whaley, *J. Amer. Chem. Soc.*, **93**, 3767 (1971), reports an *O*-acylhydroxylamine with $\nu_{C=O}$ (Nujol) 1760 cm^{-1}.

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Synthesis of 1,4-Diketones by the Reaction of Silyl Enol Ether with Ag_2O. A Regiospecific Formation of Silver(I) Enolate Intermediates

Sir:

Synthetic utility of silyl enol ethers (**1**),[1] from which lithium enolates are regiospecifically produced using methyllithium, has been demonstrated in annelation reactions.[2] Herein, we wish to report the synthesis of 1,4-diketones by the reaction of silyl enol ethers with Ag_2O in dimethyl sulf-