Research is continuing on the ground-state chemistry of the bicyclo[1.1.1]pentanol system, and a detailed investigation of the acid-catalyzed transformations of this bicyclic ring system will be reported at a later date.

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(16) Alfred P. Sloan Fellow, 1968–1970.

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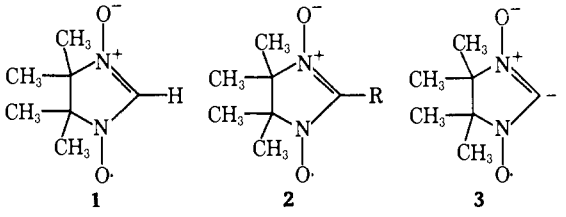
Studies of Stable Free Radicals. III. A 1,3-Dioxy-2-imidazolidone Zwitterion and Its Stable Nitronyl Nitroxide Radical Anion

Sir:

In a previous communication the highly stable nitronyl nitroxide free radical **1** was described.[1] Deuterium exchange at position 2 in **1** was found to occur by both a base-catalyzed and a pH-independent process. The most likely pH-independent exchange mechanism is electrophilic substitution with deuterium oxide as the electrophile. This suggested the possibility that the nitronyl nitroxide **1** may undergo chemically more interesting substitution reactions directly on the radical π system. We present here results of our studies of electrophilic and nucleophilic substitution of the nitronyl nitroxide radical.

When a carbon tetrachloride solution of the nitronyl nitroxide **1** containing a little pyridine was treated with iodine, there was isolated a deep purple radical, **2**,



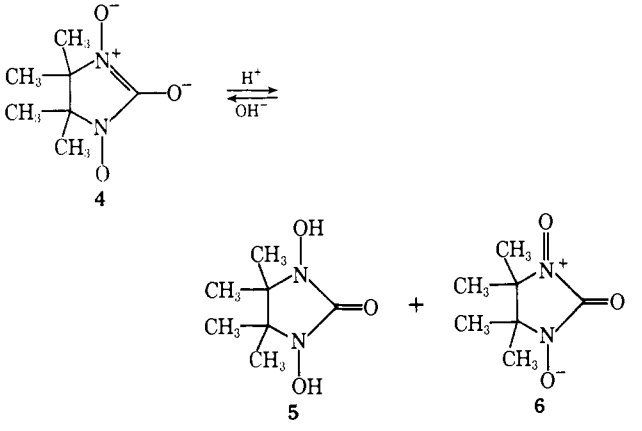
1 **2** **3**

R = I, which displayed a simple five-line esr pattern characteristic of the nitronyl nitroxide grouping [$a_N^{C_6H_6}$ = 7.3 G, *m/e* 283 (M); λ_{max}^{EtOH} 326 mμ (ϵ 14,000), 550 (1240), 585 (1060)].[2] Identical treatment of **1** with bromine led to the corresponding bromo radical **2**, R = Br [*m/e* 235 and 237 (M); λ_{max}^{EtOH} 320 mμ (ϵ 15,600), 540 (1240), 565 (1160)][2] which, unlike the iodo derivative, had an esr spectrum of five quartets resulting from weak coupling with bromine ($a_N^{C_6H_6}$ = 7.3 G, $a_{Br}^{C_6H_6}$ incompletely resolved; $a_N^{C_6H_{14}}$ = 7.15, $a_{Br}^{C_6H_{14}}$ = 1.4 G). Failure to observe coupling with iodine in **2**, R = I, despite the large iodine nuclear magnetic moment may be due to rapid quadrupole relaxation of the iodine nucleus. Hyperfine coupling with bromine and iodine is rare in organic free radicals and has not previously been observed in π radicals. However, coupling in several haloiminoxyl σ-type radicals has recently been reported.[3] The spectra of **2**, R = Br, like that of the iminoxyl radicals, display the pronounced viscosity dependence expected from the effect of nuclear-quadruople relaxation.[3b]

Alternative and more efficient preparations of **2**, R = Br and I, were possible by treatment of bicarbonate solutions of **1** with cyanogen bromide or iodide, respectively (>80% yields). Although **2**, R = Cl, was not formed using cyanogen chloride, direct chlorination of **1** gave 75% of this very hydrolytically unstable radical [*m/e* 191 and 193 (M); λ_{max}^{EtOH} 315 mμ (ϵ 19,300), 536 (1350), 562 (1340)].[2] This compound displayed the usual five-line esr pattern ($a_N^{C_6H_6}$ = 7.25 G) in which the unobserved coupling with chlorine may be of the same order of magnitude as unresolved coupling with the α-methyl protons (~0.2 G).[1]

Susceptibility of the nitronyl nitroxide ring to nucleophilic attack was demonstrated by heating the halides with sodium cyanide in dimethylformamide. Thus **2**, R = Br, gave a 38% yield of the blue nitrile **2**, R = CN [$a_N^{C_6H_6}$ = 6.94 G; ν_{max}^{KBr} 2240 cm^{-1} (CN); *m/e* 182 (M)],[2] which displayed the usual five-line esr spectrum with no observable coupling with the nitrile nitrogen.[4] Unexpectedly, attempts to prepare the nitrile in methanol as solvent led quantitatively to the imino ester **2**, R = C(=NH)OCH$_3$ [$a_N^{C_6H_6}$ = 7.17 G (five lines);[4] $\nu_{max}^{CHCl_3}$ 1635 (C=N), 3260 cm^{-1} (NH); *m/e* 214 (M)].[2] This product was also formed when the nitrile **2**, R = CN, was treated with methanolic sodium carbonate. Hence the normal base-catalyzed equilibrium of nitriles with imino esters[5] is strongly shifted toward the imino ester because of the strong electron-withdrawing effect of the nitronyl nitroxide grouping.[1]

Nucleophilic displacement on the halo radicals was also possible with hydroxide ion. On warming **2**, R = I, with aqueous sodium hydroxide the solution became intensely blue. Extraction with chloroform yielded small amounts of the starting iodide and **1**, which is presumably formed by nucleophilic displacement on iodine with expulsion of the relatively stable anion **3**.[1] The major product was a water-soluble blue radical anion, **4** [$\lambda_{max}^{H_2O}$ 251 mμ (ϵ 4200), 650 (5000)], which displayed the largest nitronyl nitroxide nitrogen coupling yet observed ($a_N^{H_2O}$ = 8.75, $a_H^{H_2O}$ = 0.21 G). Although no attempt to isolate this compound has been made, in alkaline solutions it was extraordinarily stable toward heat, light, and oxygen. On

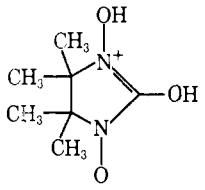


4 **5** **6**

(1) D. G. B. Boocock, R. Darcy, and E. F. Ullman, *J. Am. Chem. Soc.*, **90**, 5945 (1968).
(2) Satisfactory elemental analyses were obtained.
(3) (a) W. M. Fox and W. A. Waters, *J. Chem. Soc.*, 4628 (1965); (b) B. C. Gilbert and R. O. C. Norman, *ibid.*, *C*, 981 (1967); 123 (1968).
(4) Lack of coupling with the side-chain nitrogen is consistent with MO calculations suggesting that the free electron is in an antisymmetric orbital with a node at C_2.
(5) F. C. Schaeffer and G. A. Peters, *J. Org. Chem.*, **26**, 412 (1961).

acidification the expected hydroxy nitronyl nitroxide **2**, R = OH, was not formed, and a quantitatively reversible disproportionation occurred to give the dihydroxyurea **5** [ν_{max}^{KBr} 1680 (C=O), 3200 cm^{-1} (OH); τ 8.95 (12 H), 1.97 (2 H) (DMSO); *m/e* 174 (M)][2] and the stable diamagnetic orange zwitterion **6** [ν_{max}^{KBr} 1765 cm^{-1} (C=O); λ_{max}^{EtOH} 310 mμ (ϵ 3600), 424 (7800); τ 8.46 ($CDCl_3$); *m/e* 172 (M)].[2] In alkaline solution air oxidation of **5** gave back the radical anion **4**, and on oxidation of **5** with lead dioxide the zwitterion **6** was formed. Quantitative reduction of **6** to the anion **4** could be achieved with alkaline hydrogen peroxide, and reduction to **5** was effected by neutral sodium thiosulfate.

The action of base on **2**, R = Cl or Br, likewise yields the anion **4**, but much smoother substitution of the halo radicals could be achieved with acid. Thus **2**, R = Br, was converted to the zwitterion **6** in 76% yield with 2 *N* hydrochloric acid at 25° for 30 min. Apparently nucleophilic attack by water on the halo nitronyl nitroxide is accelerated by protonation of a nitrone oxygen, and the resulting product **7** becomes air oxidized to give **6**.



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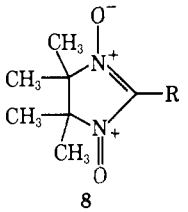

8

Interestingly, in strong acids the zwitterion **6** is an exceptionally good oxidizing agent. Thus, for example, in 10% trifluoroacetic acid in methylene chloride this compound oxidized several hydrocarbons, including 9,10-diphenylanthracene, perylene, and tetraphenylethylene, to their respective radical cations. The active oxidant is presumably the cation **8**, R = OH, since the related cation **8**, R = C_6H_5, has also been found to have very strong oxidizing properties.[6] Since no nitronyl nitroxide esr signals are observed in these acidic solutions, **8** must be reduced to a species such as **7** which can disproportionate to a protonated dihydroxyurea **5** and the zwitterion **6**.

Further studies on the chemistry of the 1,3-dioxy-2-imidazolidone zwitterion **6** are in progress.

(6) J. H. Osiecki and E. F. Ullman, *J. Am. Chem. Soc.*, **90**, 1078 (1968).

(7) Synvar Postdoctoral Fellow, 1967–1969.

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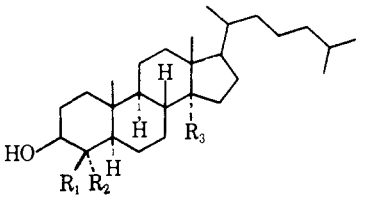
Biological Demethylation of 4,4-Dimethyl Sterols. Initial Removal of the 4α-Methyl Group

Sir:

One of the unresolved aspects of sterol biosynthesis[1] is the sequence of oxidative removal of the 4α- and 4β-methyl groups *en route* from lanosterol[2] to cholesterol. We herein report evidence that, contrary to earlier conclusions,[3] the equatorial 4α-methyl group is the site of initial attack in the demethylation process at C-4.

A preliminary study showed that 4,4-dimethylcholestanol (**1**)[4] was metabolized by rat liver homogenates to cholestanol (**2**) with 10–20% of the efficiency with which dihydrolanosterol (**3**)[5] was converted to cholesterol. The demethylation of each labeled substance was inhibited by a 20-fold concentration of the other in the unlabeled form, that of **1** to the extent of 86% and that of **3** to the extent of 38%. These results are to be expected if the 4,4-dimethyl Δ^8-sterol derived from lanosterol competes with 4,4-dimethylcholestanol for the same enzyme system. On the other hand, 4,4,14α-trimethylcholestanol (**4**)[6] was not measurably metabolized in this enzyme system. This finding implicates the Δ^8-olefinic linkage of lanosterol in the removal of the 14α-methyl group[7] and shows that this latter group inhibits enzymic attack on the 4,4-dimethyl substituents.



1, $R_1 = R_2 = CH_3$, R_3 = H
2, $R_1 = R_2 = R_3$ = H
4, $R_1 = R_2 = R_3 = CH_3$
10, $R_1 = R_3$ = H; $R_2 = CH_2OH$
11, $R_1 = CH_3$, $R_2 = CH_2OH$, R_3 = H
12, $R_1 = CH_2OH$, $R_2 = CH_3$, R_3 = H
13, $R_1 = R_3$ = H, $R_2 = CH_3$

The finding that **1** was metabolized to **2** permitted the use of readily synthesized and labeled substrate analogs in the cholestane series for more detailed studies of the demethylation process. The required model compounds were synthesized from 4α-carbomethoxycholestan-3-one (**5**),[8] which was conveniently prepared by reductive carbomethoxylation[9,10] of Δ^4-cholesten-3-one. Methylation of **5** (NaH, *t*-BuOH, and CH_3I in $H_3COCH_2CH_2OCH_3$) afforded 56% 4β-methyl-4α-carbomethoxycholestan-3-one (**6**), mp 100–101°,[11] and 19% 4α-methyl-4β-carbomethoxycholestan-3-one (**7**), mp 117–118°. That the expected[10,12] preponderance of β methylation had indeed been obtained was substantiated by the nmr spectra of **6** and **7**, in which the angular methyl group on C-10 of **7** appeared at a higher field (δ 0.97) than that of **6** (δ 1.06) owing to transannular shielding by the 4β-carbomethoxyl group.[10] Confirmation of these crucial stereochemical assignments was achieved by Clem-

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(2) J. A. Olson, M. G. Lindberg, and K. Bloch, *J. Biol. Chem.*, **226**, 94 (1957).

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(10) T. A. Spencer, T. D. Weaver, R. M. Villarica, R. J. Friary, J. Posler, and M. A. Schwartz, *J. Org. Chem.*, **33**, 712 (1968).

(11) Correct elemental analyses and ir and nmr spectral properties were obtained for all new compounds.

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