Although resonance Raman spectroscopy has been shown to be useful in the characterization of both enzymes and enzyme–substrate complexes, we believe that we have now been able to identify a metal–substrate bond in a protein–substrate complex. This result supports a protein–substrate structure with the carbonyl oxygen bound directly to the catalytic zinc in LADH as championed by Brändén and Eklund[9] and Dunn.[1-5] However, the evidence for the formation of the Zn–O bond and loss of the carbonyl moiety is much stronger.

Acknowledgment. Support of this work by NSF Grant PCM76-82222 and PHS Grant GM15547 is gratefully acknowledged.

(9) Brändén, C.-I.; Eklund, H. In "Molecular Interactions and Activity in Proteins"; *Ciba Found. Symp. Excerpta Med.* **1978**, *60*, 63-80.

Convenient Thermal Sources of β-Cyanoalkyl Radicals from α-Hydroxydiazenes

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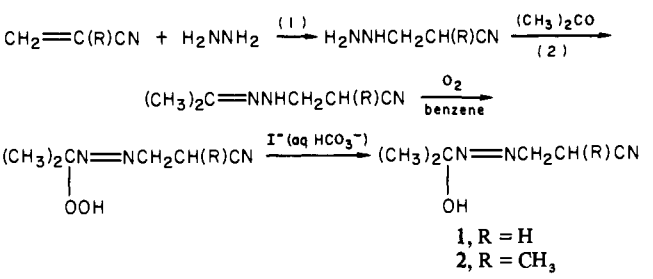
A general effect of the structural change $RCH_2H \rightarrow RCH_2X$, where X is a substitutent, is to lower the bond dissociation energy of the α C–H bonds.[1-3] A common consequence of this feature is that homolytic abstractions α to X, rather than β or further removed from X, are kinetically favored.[4,5] Well-known examples include the strong preference for radical substitution on ethylbenzene, ethanol, and propionitrile to form, respectively, 1-phenylethyl, 1-hydroxyethyl, and 1-cyanoethyl radicals instead of 2-phenylethyl, 2-hydroxyethyl, and 2-cyanoethyl radicals. Precursors for relatively inaccessible radicals of the latter types are therefore of considerable interest, especially if they afford those radicals uncontaminated by their normally favored isomers under mild conditions. We wish to report convenient thermal sources of 2-cyanoethyl and 2-cyanopropyl radicals and a preliminary synthetic application of one of those radicals.

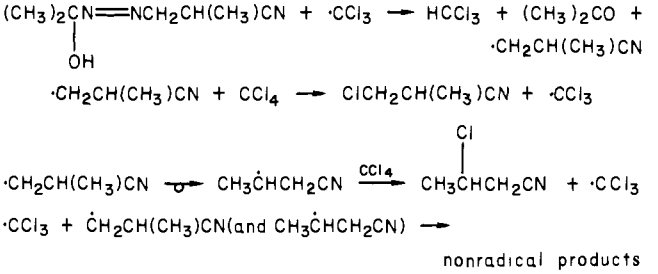
α-Hydroxydiazenes **1**, **2** (also known as azocarbinols) were synthesized by the route shown in Scheme I.[6] The alkylhydrazines from the first step (70–80% yield) were distilled (4 torr, pot temperature 130 °C) to remove products of overalkylation. Alkylhydrazones (ca. 80% yields) from the second step were distilled under the same conditions. Omission of these purification steps led to induction periods of hours or days for the subsequent autoxidation step.

Hydroperoxide intermediates were not isolated, except in small quantities for ^{1}H NMR spectra,[7] but were decomposed[8] directly after concentration of the solutions with a rotary evaporator (**Caution**: do not heat or remove all solvent). Azocarbinols **1** and **2** were identified from their thermolysis chemistry, infrared spectra (CN and OH), and ^{1}H NMR spectra. **1**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.45 (s, 6 H), 2.83 (t, 2 H, J = 6 Hz), 4.18 (t, 2 H, J = 6 Hz), 4.33 (s, 1 H). **2**: δ 1.43 (d, 3 H, J = 7 Hz), 1.48 (s, 6 H), 3.25 (m, 1 H), 4.00 (d, 2 H, J = 7 Hz), 4.28 (s, 1 H). A trace of acetone, from spontaneous decomposition of the azocarbinols, could be detected from the ^{1}H NMR spectra of freshly prepared **1** and **2**.

Scheme I



Scheme II



In degassed CCl_4, in a sealed tube, **1** and **2** decompose slowly at room temperature. Decomposition is first order in azocarbinol with rate constant $k_{35}(\mathbf{2}) = 1.4 \times 10^{-5}$ s^{-1}. Major products from **1** are acetone (84%), chloroform, and 3-chloropropionitrile (84%). Similarly, **2** affords acetone (81%), chloroform (87%), 3-chloro-2-methylpropionitrile (~46%), and 3-chlorobutyronitrile (~46%). The latter is an expected product from rearrangement of the primary 2-cyano-1-propyl radical to the 1-methyl-2-cyanoethyl radical.[9,10]

Decompositions of **1** and **2** in degassed benzene are about 3-fold slower than those in CCl_4 and produce cyanoalkanes and acetone as major products. Inhibition of the decomposition of **2**, in benzene, by added free radicals diphenylpicrylhydrazyl (DPPH) or 2,2,6,6-tetramethylpiperidinyl-1-oxy (TMPO) indicates that a chain mechanism is involved. Thus, decomposition of **2** (0.271 M) at 35 °C, in the presence of DPPH (1.07×10^{-2} M), had an induction period of 110 min. Similarly, with **2** (0.361 M) and TMPO (3.97×10^{-2} M) at 80 °C, decomposition did not begin until 30 min had elapsed. Corresponding samples not containing added free radical started smoothly without detectable induction periods.

Heating a solution of **1** (0.282 g, 2.00 mmol) and azobenzene (1.46 g, 8.02 mmol) in benzene (5.0 mL) at 75 °C for 10 h

(1) Benson, S. W. "Thermochemical Kinetics", 2nd ed; Wiley: New York, 1976; p 309, for example.

(2) "Handbook of Chemistry and Physics", 59th ed; Weast, R. C., Ed.; CRC Press: Boca Raton, FL, 1978-1979; pp F-237-F-241.

(3) Notable exceptions are the fluoro and trifluoromethyl substituents which raise bond dissociation energies of α C–H bonds slightly or else leave them essentially unchanged.[2]

(4) Since there is no strong connection between thermodynamics and kinetics, there are many exceptions arising from dominance of polar and/or steric effects, over bond enthalpy effects, on the free energies of transition states.

(5) For a recent discussion of the effects of substituents on the kinetics of H abstraction from substituted toluenes, see: Fisher, T. H.; Meierhoefer, A. W. *J. Org. Chem.* **1978**, *43*, 224 and references cited there.

(6) Autoxidation of hydrazones has been extensively studied. See, for example: (a) Pausacker, K. H. *J. Chem. Soc.* **1950**, 3478. (b) Criegee, R.; Lohaus, G. *Chem. Ber.* **1951**, *84*, 219. (c) Belamy, A. J.; Guthrie, R. D. *J. Chem. Soc.* **1965**, 2788. (d) Taylor, W. F.; Weiss, H. A.; Wallace, T. J. *J. Org. Chem.* **1969**, *34*, 1759. (e) Schulz, M.; Missol, U. *Z. Chem.* **1974**, *14*, 265.

(7) ^{1}H NMR spectra (90 MHz, $CDCl_3$) of the hydroperoxides and their precursors: $(CH_3)_2C(OOH)N{=}NCH_2CH_2CN$—δ 1.47 (s, 6 H), 2.83 (t, 2 H, J = 6 Hz), 4.18 (t, 2 H, J = 6 Hz), 9.08 (s br, 1 H); $(CH_3)_2C(OOH)N{=}NCH_2CH(CH_3)CN$—δ 1.38 (d, 3 H, J = 7 Hz), 1.50 (s, 6 H), 3.25 (m, 1 H), 4.00 (d, 2 H, J = 7 Hz), 9.05 (s, 1 H); $(CH_3)_2C{=}NNHCH_2CH_2CN$—δ 1.88 (s, 3 H), 1.95 (s, 3 H), 2.65 (t, 2 H, J = 6 Hz), 3.43 (t, 2 H, J = 6 Hz), 4.75 (s br, 1 H); $(CH_3)_2C{=}NNHCH_2CH(CH_3)CN$—δ 1.30 (d, 3 H, J = 7 Hz), 1.75 (s, 3 H), 1.93 (s, 3 H), 3.05 (m, 1 H), 3.25 (d, 2 H, J = 7 Hz), 4.85 (s br, 1 H).

(8) Triphenylphosphine is an alternative reagent for converting hydroperoxides to alcohols under mild conditions.[6e]

(9) Intramolecular radical additions to the nitrile function are well-known[10] and homopropargyl radicals, which are close analogues of 2-cyanopropyl radicals, rearrange with ease: Ingold, K. U.; Warkentin, J. *Can. J. Chem.* **1980**, *58*, 348.

(10) Beckwith, A. L. J.; Ingold, K. U. In "Rearrangements in Ground and Excited States"; de Mayo, P., Ed.; Academic Press: in press.

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afforded β-cyanoethyl-1,2-diphenylhydrazine, 78%, mp 122–123 °C, after recrystallization from benzene/pentane; MS m/z 237 (calcd for $C_{15}H_{15}N_3$, 237); ^1H NMR (60 MHz, $CDCl_3$) δ 2.73 (t, 2 H, J = 7 Hz), 3.83 (t, 2 H, J = 7 Hz), 5.67 (s br, 1 H), 6.7–7.4 (m, 10 H).

The products formed in CCl_4 are clearly indicative of free radical chemistry, and the faster rates in that solvent, relative to those for benzene, together with inhibition by persistent radicals in the latter medium strongly suggest radical chain chemistry in both solvents. Although the detailed mechanism(s) by which **1** and **2** decompose are still under investigation, we assume that radical chain induced decomposition, as suggested earlier for an analogue,[11] is involved. The gross features of that mechanism are illustrated in Scheme II for reaction of **2** in CCl_4.[12] Similar chain processes can account for their decomposition in benzene to cyanoalkanes and the hydro-β-cyanoalkylation of azobenzene with **1**.

Work on synthetic applications of **1** and **2** and on the reaction mechanisms (including the use of **2** as a source for "radical clock" experiments[10,13]) is in progress.

Acknowledgments are made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the Natural Sciences and Engineering Research Council of Canada for support of this work.

(11) (a) Yeung, D. W. K.; Warkentin, J. *Can. J. Chem.* **1976**, *54*, 1349. (b) *Ibid.* **1976**, *54*, 1345.

(12) The nature of the initiating step in these "self-starting" reactions is not known nor is the timing of the two C–N bond scissions known. At least one C–N bond must be breaking in concert with H abstraction ()C(OH)-N=N—R + R′· → R′H +)=O + ·N=NR) since abstraction of H to form an alkoxy radical intermediate is known to be too difficult (see ref 11). Fully concerted, induced decomposition is plausible also, for the two C–N bonds of a trans azo compound are correctly aligned for the concerted process.

(13) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317.

Stereocontrolled Synthesis of Steroidal Side Chains

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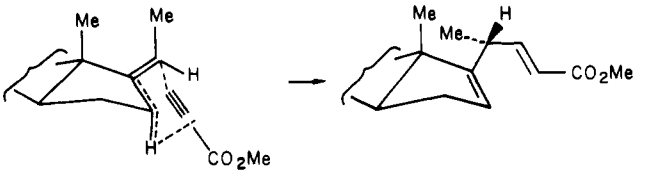
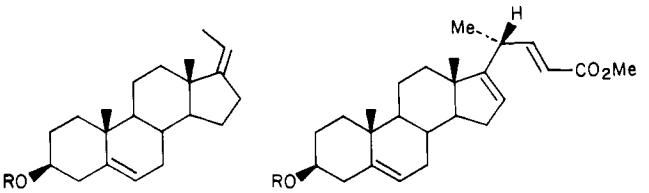
The introduction of the steroid side chain onto tetracyclic steroidal starting materials has been the subject of recent investigation by several research groups.[1,2] These efforts have been pursuing the introduction of functionalized side chains directed toward the synthesis of a variety of ecdysones,[3] vitamin D metabolites,[4] and unusual marine sterols.[5] We wish to report one of the most simple and efficient stereospecific syntheses of a steroidal side chain from $\Delta^{17(20)}$ steroid. This approach makes use of the known preference for attack on the α face of the C-17(20) double bond[6] and the highly ordered transition state

Scheme I



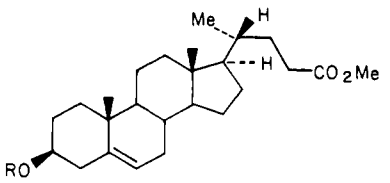
of the ene reaction to set the stereochemistry of the C-20 carbon in the natural configuration (see Scheme I).

Diene **1**[7] was allowed to react with 1.2 equiv of methyl propiolate and 2.0 equiv of diethylaluminum chloride[8] in benzene for 24 h at room temperature. The reaction mixture was treated with an aqueous sodium bicarbonate solution and then extracted with ether to afford triene **3**[9] (95%), mp 128–129 °C; $[\alpha]_D$ ($CHCl_3$) −24.0°; IR ($CHCl_3$) 1720, 1650, 1020, and 980 cm^{-1}; NMR ($CDCl_3$) δ 1.17 (d, 3, J = 6 Hz, 21-H), 5.40 (dd, 2), 5.80 (dd, 1, J = 1.5, 16 Hz), 6.90 (dd, 1, J = 8, 16 Hz).

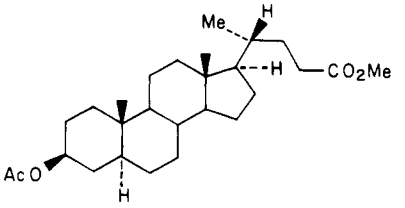


1, R = Ac
2, R = H

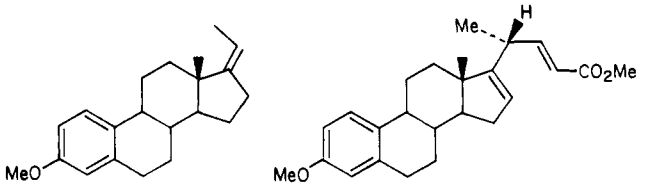
3, R = Ac
4, R = H



5, R = Ac
6, R = H



7



8 **9**

In order to prove the structure of triene **3**, especially the natural configuration at C-20, the reaction product was selectively hydrogenated with palladium on calcium carbonate in ethyl acetate to **5** (98%), mp 162–163 °C (lit.[10] 159–161 °C). The spectral data from this compound were identical with those previously reported.[10] Also the melting point of a mixture of **5** and authentic

† NIH Postdoctoral Fellow, 1979–1981.

(1) For a review on steroid side chain homologation, see: Piatak, D. M.; Wicha, J. *Chem. Rev.* **1978**, *78*, 199.

(2) (a) Trost, B. M.; Matsumura, Y. *J. Org. Chem.* **1977**, *42*, 2036. (b) Trost, B. M.; Verhoeven, T. K. *J. Am. Chem. Soc.* **1978**, *100*, 3435. (c) Trost, B. M.; Bernstein, P. R.; Funfschilling, P. C. *Ibid.* **1979**, *101*, 4378. (d) Grieco, P. A.; Tukigawa, T.; Moore, D. R. *Ibid.* **1979**, *101*, 4380. (e) Schow, S. R.; McMorris, T. C. *J. Org. Chem.* **1979**, *44*, 3760. (f) Koreeda, M.; Tanaka, Y.; Schwartz, A. *Ibid.* **1980**, *45*, 1172. (g) Tanabe, M.; Hayashi, K. *J. Am. Chem. Soc.* **1980**, *102*, 862. (h) Midland, M.; Kwon, Y., private communication.

(3) (a) Nakanishi, K. *Pure Appl. Chem.* **1971**, *25*, 167. (b) Hikino, H.; Hikino, Y. *Fortschr. Chem. Org. Naturst.* **1970**, *28*, 256.

(4) (a) DeLuca, H. F.; Schnoes, H. K. *Annu. Rev. Biochem.* **1976**, *45*, 631. (b) Georghiou, P. E. *Chem. Soc. Rev.* **1977**, *6*, 85.

(5) (a) Nes, W. R.; McKean, M. L. "Biochemistry of Steroids and Other Isoprenoids"; University Park Press: Baltimore, MD, 1977. (b) Minale, L.; Sodano, G. In "Marine Natural Products Chemistry"; Faulkner, D. J., Fenical, W. H., Eds.; Plenum Press: New York, 1977, p 87.

(6) (a) Krubiner, A. M.; Oliveto, E. P. *J. Org. Chem.* **1966**, *31*, 24. (b) Krubiner, A. M.; Gottfried, N.; Oliveto, E. P. *Ibid.* **1968**, *33*, 1715.

(7) Drefahl, G.; Ponsold, K.; Schick, H. *Chem. Ber.* **1965**, *98*, 604.

(8) The use of mild Lewis acids to catalyze ene reactions has been previously reported: Snider, B. B.; Rodini, D. J.; Conn, R. S. E.; Sealfon, S. *J. Am. Chem. Soc.* **1979**, *101*, 5283.

(9) Spectroscopic data and elemental composition in full accord with the assigned structure have been obtained. The C NMR spectra of **3**, **4**, **5**, **7**, and **9** showed the expected number of signals. Of particular importance is the presence of only one absorption for the C-18 methyl group, the values being δ 16.17, 16.42, 11.88, 12.17, and 16.55, respectively.

(10) Vanderah, D. J.; Djerassi, C. *J. Org. Chem.* **1978**, *43*, 1442.

0002-7863/81/1503-237$01.00/0