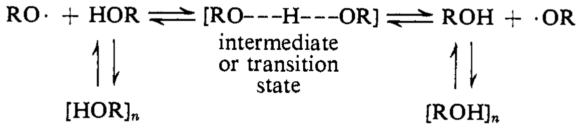


$$\begin{array}{ccccc} RO\cdot + HOR & \rightleftharpoons & [RO{-}{-}{-}H{-}{-}{-}OR] & \rightleftharpoons & ROH + \cdot OR \\ \uparrow\downarrow & & \text{intermediate or transition state} & & \uparrow\downarrow \\ [HOR]_n & & & & [ROH]_n \end{array}$$

We infer that iminoxy radicals form hydrogen bonds more reluctantly than nitroxides[20] (or peroxy radicals[21]) from the observations that the a_N value of **1** in isopentane is within 1% of its value in ethanol and that the visible spectra of **1** in cyclohexane and in ethanol are virtually identical. Substantial changes of these properties in nitroxides have been associated with the formation of hydrogen bonds.[22,23] Reluctance to form a hydrogen-bonded intermediate probably explains the high activation energy and low rate constant for the **1** + **1**-H reaction.

The large value of $K_{eq}^{25°}$ for the **1** + **2c**-H system cannot be accounted for on this basis. We believe that it is due mainly to severe intramolecular repulsive interactions (principally R_1–R_2 and R_2–O) in the oxime **1**-H that are lessened by a more relaxed geometry in **1**. Evidence supporting this suggestion will be presented later.

The present results appear to be relevant to the potential use of stable iminoxy radicals as spin labels[24,25] and in other studies of local molecular environment.[26–28]

Acknowledgment. We gratefully acknowledge receipt of a generous sample of di-*tert*-butylketimine from Dr. H. D. Hartzler (Du Pont).

---

(16) J. A. Howard and K. U. Ingold, *Can. J. Chem.*, 40, 1851 (1962), and subsequent papers in this series.

(17) L. R. Mahoney and M. A. DaRooge, *J. Amer. Chem. Soc.*, **92**, 4063 (1970).

(18) J. R. Thomas, *ibid.*, **86**, 4807 (1964).

(19) L. R. Mahoney and M. A. DaRooge, *ibid.*, **92**, 890 (1970); **94**, 7002 (1972).

(20) Iminoxy radicals ($a_N \sim$ 30 G) have greater s character in the radical orbital at N than do aliphatic nitroxides ($a_N \sim$ 14–19 G) and would therefore be expected to be less basic.

(21) See, *e.g.*, L. M. Andronov, G. E. Zaikov, and Z. K. Maizus, *Russ. J. Phys. Chem.*, 41, 590 (1967).

(22) R. Briere, H. Lemaire, and A. Rassat, *Bull. Soc. Chim. Fr.*, 3273 (1965).

(23) Y. Y. Lim and R. S. Drago, *J. Amer. Chem. Soc.*, **93**, 891 (1971).

(24) W. L. Hubbell and H. M. McConnell, *ibid.*, **93**, 314 (1971).

(25) J. F. Homer, R. W. Henkens, and D. B. Chesnut, *ibid.*, **93**, 6665 (1971).

(26) I. Morishima, K. Endo, and T. Yonezawa, *ibid.*, **93**, 2048 (1971).

(27) I. Morishima, T. Inubushi, K. Endo, T. Yonezawa, and K. Goto, *ibid.*, **94**, 4812 (1972).

(28) K. D. Kopple and T. J. Schamper, *ibid.*, **94**, 3644 (1972).

(29) NRCC Postdoctoral Fellow, 1971–1973.

G. David Mendenhall,[29] Keith U. Ingold*
Division of Chemistry, National Research Council of Canada
Ottawa, Canada

Received September 22, 1972

Synthesis of Corticosteroids from Marine Sources

Sir:

Corticosteroids are generally synthesized either from plant sapogenins (*e.g.*, diosgenin, hecogenin) or from bile acids. The recent reports[1] of the occurrence of 5α-pregn-9(11)-ene-3β,6α-diol-20-one (**1**) in starfish raised the intriguing question whether corticosteroids might become available from marine sources. Since it has been shown that 11β-hydroxyprogesterone (**2**) and 11-oxoprogesterone (**3**) can be converted to corticosterone[2] as well as to cortisone[2] and cortisol[3] and since **2** can be prepared conveniently from pregna-4,9(11)-diene-3,20-dione (**4**),[4,5] the latter compound is the key missing link in a potentially practical synthesis of corticosteroids from a marine source. We record herewith the completion of the missing steps.

Examination of the literature[6–10] suggested that selective oxidation of the diequatorial diol system in **1** would not be feasible. The availability[1] of the fully oxidized triketone **5** suggested that selectivity at C-3 might be achieved at this stage.[8,11–13] *p*-Toluenesulfonic acid catalyzed reaction of the trione **5** with methanol at reflux for 1 hr furnished the oily 3,3-dimethoxy-5α-pregn-9(11)-ene-6,20-dione (**7**) [M^+ 374 (87%), *m/e* 342 ($M^+ - CH_3OH$), 257 (ring D cleavage + CH_3OH) 143, and a base peak at 101[14] ($MeOC(={}^{+}OMe)CH{=}CH_2$); nmr (60 MHz, $CDCl_3$) C-18 CH_3, 0.60 (s, 3 H), C-19 CH_3, 0.91 (s, 3 H), C-21 CH_3, 2.15 (s, 3 H), 3-OCH_3 3.13, 3.23 (s, 3 H each), and an olefinic proton 5.60 (c, 1 H)]. The work of Wheeler and Mateos[15] suggested that the 6-oxo group should be reduced 60 times faster than the 20-oxo functionality. Indeed, in 2-propanol solvent at room temperature, nmr studies[16] indicated that C-20 is not reduced during a 2–3-hr period by a 3–6 molar excess of sodium borohydride and the predominant product is 3,3-dimethoxy-6β-hydroxy-5α-pregn-9(11)-en-20-one (**8**). Hydrolysis (*p*-TsOH–acetone) of crude **8** furnished crystalline **10** [mp 223–226° (needles from benzene); ir ($CHCl_3$) 3500 (OH), 1700 cm^{-1} (>C=O); nmr ($CDCl_3$, 60 MHz) C-18 CH_3, 0.63 (s, 3 H), C-19 CH_3, 1.35 (s, 3 H), C-21 CH_3, 2.13 (s, 3 H), 6β-carbinol methine, 3.90 (c, 1 H, $^1/_2$ peak-height width, 8 Hz), and an olefinic proton, 5.42 (c, 1 H); mass spectrum M^+ 330, *m/e* 312 ($M^+ - H_2O$), 269 (312 − C_2H_3O), 255 (312 − C_3H_5O), 242 (ring A cleavage from 312), 227 (ring D cleavage + H_2O), and 85 [$CH_3CO(CH_2)_3$], all spectral properties consistent with the structure]. Dehydration of a mixture of **8** and **9** ($POCl_3$–Py), cleavage of the ketal, and migration of the double bond ($\Delta^5 \rightarrow \Delta^4$) furnished $\Delta^{9(11)}$-progesterone (**11**) [30–35% overall yield based on triketone **5**, mp 115–118°, mmp 115–120°; gc, ir, nmr, and mass

---

(1) (a) Y. M. Sheikh, B. M. Tursch, and C. Djerassi, *J. Amer. Chem. Soc.*, **94**, 3278 (1972); similar observations were reported shortly thereafter by (b) S. Ikegami, Y. Kamiya, and S. Tamura, *Tetrahedron Lett.*, 1601 (1972); (c) Y. Shimizu, *J. Amer. Chem. Soc.*, 94, 4051 (1972).

(2) J. A. Hogg and A. H. Nathan, U. S. Patent 2,683,724 (1954).

(3) J. A. Hogg, P. F. Beal, A. H. Nathan, F. H. Lincoln, W. P. Schneider, B. J. Magerlein, A. R. Hanze, and R. W. Jackson, *J. Amer. Chem. Soc.*, 77, 4436 (1955).

(4) D. H. R. Barton, N. K. Basu, R. H. Hesse, F. S. Morehouse, and M. M. Pechet, *ibid.*, **88**, 3016 (1966).

(5) J. Fried and E. F. Sabo, *ibid.*, **79**, 1130 (1957).

(6) G. Grimmer, *Ann. Chim.*, **636**, 42 (1960).

(7) J. Kawanami, *Bull. Chem. Soc. Jap.*, 34, 671 (1961).

(8) J. Fried and J. A. Edwards, Ed., "Organic Reactions in Steroid Chemistry," Van Nostrand Reinhold, New York, N. Y., 1972.

(9) I. T. Harrison and S. Harrison, "Compendium of Organic Synthetic Methods," Wiley-Interscience, New York, N. Y., 1971.

(10) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959.

(11) M. M. Janot, X. Lusinchi, and R. Goutarel, *Bull. Soc. Chim. Fr.*, 2109 (1961).

(12) J. H. Fried, A. N. Nutile, and G. E. Arth, *J. Amer. Chem. Soc.*, **82**, 5704 (1960).

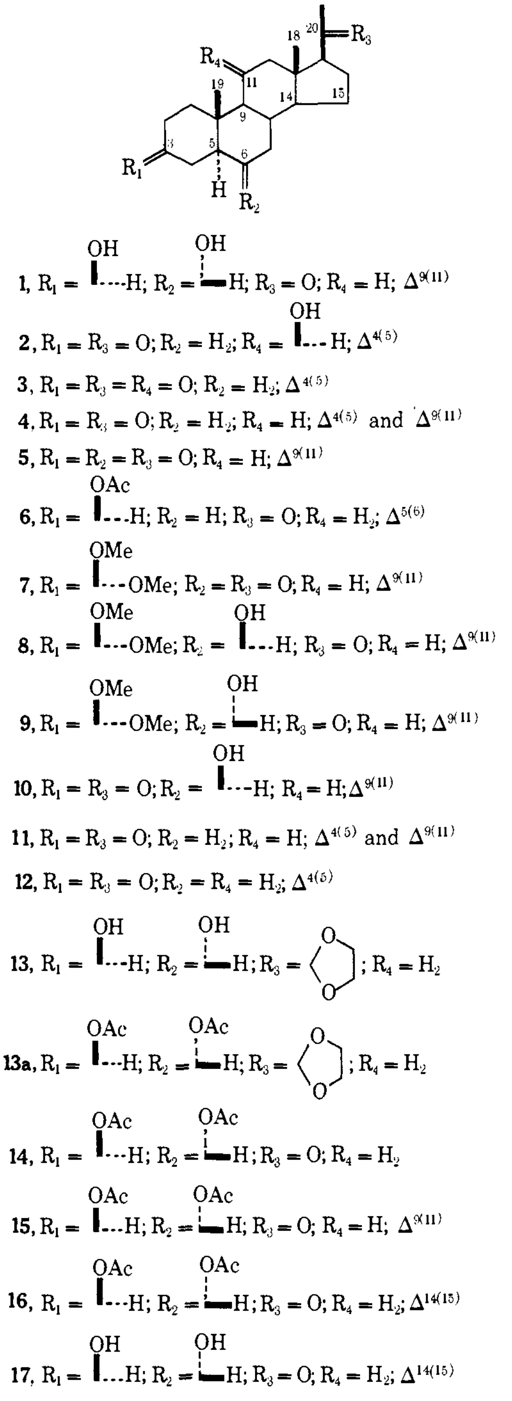
(13) R. Gardi and C. Pedrali, *Steroids*, **2**, 387 (1963).

(14) For a recent study on fragmentation of dimethyl ketals of methylcyclohexanones, see P. E. Manni, R. D. Cooper, and C. L. Hardesty, *Org. Mass Spectrom.*, **6**, 946 (1972).

(15) J. L. Mateos, *J. Org. Chem.*, 24, 2034 (1959); O. H. Wheeler and J. L. Mateos, *Can. J. Chem.*, **36**, 1049 (1958).

(16) R. F. Zürcher, *Helv. Chim. Acta*, 46, 2054 (1963).

spectra identical with an authentic sample[17,18]. Progesterone (**12**) was obtained in 40% overall yield by a similar reaction sequence from 5α-pregnane-3,6,20-trione.



The recently published procedure for remote group functionalization[19] suggested a simple synthesis of the starfish sterol **1** as a final step in its structure proof. The 20-ethylene ketal[20] of pregnenolone acetate (**6**) was treated with diborane in THF followed by alkaline hydrogen peroxide oxidation to give, in 60% yield, **13** [m/e 363 ($M^+ - CH_3$); mp 205–207° (needles from aqueous methanol); $[\alpha]^{22}D$ ($CHCl_3$) +29.5°; λ_{max} (KBr) 3400 cm^{-1}; nmr (60 MHz, $CDCl_3$) C-18 CH_3, 0.76 (s, 3 H), C-19 CH_3, 0.82 (s, 3 H), C-21 CH_3, 1.26 (s, 3 H), carbinol methines, 3.13–4.00 (c, 2 H) shifted to 4.40–5.0 in the diacetate **13a**, cyclic ethylene ketal methylene, 3.90 (c, 4 H)], which on acetylation furnished the diacetate **13a** [mp 165–167° (needles from aqueous methanol); $[\alpha]^{21}D$ ($CHCl_3$) +31.01°; λ_{max} (KBr) 1717–1735 cm^{-1}]. Treatment of **13a** with iodobenzene dichloride yielded a crude product containing the 9α-chloro derivative which was directly dehydrochlorinated with silver perchlorate in acetone. Preparative thin layer chromatography of the resulting mixture (50% yield) on 20% $AgNO_3$ impregnated silica gel led to three products. In order of elution these were 5α-pregnane-3β,6α-diol-20-one diacetate (**14**) (30%, identical with a sample prepared from its ketal **13a**); 5α-pregn-9(11)-ene-3β,6α-diol-20-one diacetate (**15**) [37%, identical (gc, ir, nmr, and mass spectra) with natural[1] starfish genin diacetate]; and **16** [33%, M^+ 416 (100%); nmr (60 MHz, $CDCl_3$) C-18 CH_3, 0.85 (s, 3 H), C-19 CH_3, 0.90 (s, 3 H), C-21 CH_3, 2.13 (s, 3 H), two acetates, 2.03 (s, 6 H), two acetate methines, 4.40–5.0 (c, 2 H), and an olefinic proton, 5.13 (c, 1 H)]. Hydrolysis of **15** provided **1** [identical in all respects with the natural[1] starfish genin, $[\alpha]^{21}D$ ($CHCl_3$) +98.7°[1c]] which on subsequent oxidation gave the known triketone **5**. Saponification of the Δ^{14} isomer **16** led to **17** [mp 198–200° (needles from aqueous ethanol); M^+ 332 (100%); nmr (100 MHz, $CDCl_3$) C-18 CH_3, 0.85 (s, 3 H), C-19 CH_3, 0.87 (s, 3 H), C-21 CH_3, 2.16 (s, 3 H), 17α-H, 2.90 (c, 1 H), two carbinol methines, 3.40–3.80 (c, 2 H), and an olefinic proton, 5.19 (c, 1 H)]. The mass spectrum of **17** displayed important peaks at m/e 317 ($M^+ - CH_3$), 314 ($M^+ - H_2O$), 299 (314 − CH_3), 289 ($M^+ - C_2H_3O$), 281 (299 − H_2O), 271 (314 − C_2H_3O), 253 (271 − H_2O), 95 (C_7H_{11}), and 43 (C_2H_3O). The nmr chemical shifts for the C-18 methyl group and the absence of ring D cleavage[21] in its mass spectrum firmly established the position of the double bond.

Acknowledgment. Financial assistance from the National Institutes of Health (Grants No. GM-06840 and AM-12758) is gratefully acknowledged.

---

(17) C. W. Shoppee and T. Reichstein, *Helv. Chim. Acta*, **24**, 351 (1941).

(18) L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, and A. D. Cross, *J. Org. Chem.*, **29**, 2187 (1964).

(19) R. Breslow, J. A. Dale, P. Kalicky, S. Y. Liu, and W. N. Washburn, *J. Amer. Chem. Soc.*, **94**, 3276 (1972).

(20) W. J. Adams, D. K. Patel, V. Petrow, I. A. Stuart-Webb, and B. Sturgeon, *J. Chem. Soc.*, 4490 (1956).

(21) L. Tökes, G. Jones, and C. Djerassi, *J. Amer. Chem. Soc.*, **90**, 5465 (1968); C. Djerassi, *Pure Appl. Chem.*, **21**, 205 (1970).

(22) Visiting Postdoctoral Scholar from the University of West Florida, Pensacola, Fla. 32504.

Jerome E. Gurst,[22] Younus M. Sheikh, Carl Djerassi*
Department of Chemistry, Stanford University
Stanford, California 94305

Received October 26, 1972

On Steric Attraction

Sir:

In certain exothermic association reactions there may be an electronic factor favoring formation of the sterically more hindered product. Consider the progress of a model reaction—the recombination of an ethyl cation with an ethyl anion. One likely approach, **1**, is sterically unhindered, leading to an anti conformation of butane. Another possible approach, **2**, leads to the higher energy eclipsed conformation.