(neat) 3340, 1710 cm^{-1}; MS *m/e* 338 (M − H_2O), 320 (M − $2H_2O$).

Anal. Calcd for $C_{20}H_{36}O_5$: C, 67.38; H, 10.18. Found: C, 67.64; H, 9.94.

Acknowledgment. I wish to thank Mr. L. Brancone and his staff for microanalyses, and Messrs. W. Fulmor and G. Morton and Dr. R. T. Hargreaves and staff for spectral data. I would also like to thank Dr. M. J. Weiss for many helpful discussions.

Registry No.—1, 5239-43-0; (13*R*)-**2**, 60676-39-3; (13*S*)-**2**, 60676-40-6; **4**, 54556-60-4; (8α)-**5**, 60733-21-3; (8β)-**5**, 60676-41-7; (13*R*)-**6**, 60676-42-8; (13*S*)-**6**, 60676-43-9; **7**, 60676-44-0; 1-octanol, 111-87-5.

References and Notes

(1) For part 10 of this series see A. Wissner, *J. Org. Chem.*, submitted for publication.
(2) M. B. Floyd, R. E. Schaub, and M. J. Weiss, *Prostaglandins*, **10**, 289 (1975).
(3) G. Traverso and D. Pirillo, *Farmaco, Ed. Sci.*, **29**, 883 (1975).
(4) (a) A. E. Greene, G. R. Girard, and J. F. Kerwin, *Tetrahedron Lett.*, 937 (1975); (b) J. A. Noguez and L. A. Maldonado, *Synth. Commun.*, **6**, 39 (1976).
(5) K. F. Bernady and M. J. Weiss, *Tetrahedron Lett.*, 4083 (1972).
(6) For a discussion of the photoaddition of alcohols to α,β-unsaturated ketones see B. Fraser-Reid, D. R. Hicks, D. L. Walker, D. E. Iley, M. B. Yunker, S. Tamm, and R. C. Anderson, *Tetrahedron Lett.*, 297 (1975).
(7) M. B. Floyd, *Synth. Commun.*, **4**, 317 (1974).

Influence of a 9α-Fluorine on the Epoxidation of an 11β-Hydroxy-Δ⁴-3-keto Steroid with Basic Hydrogen Peroxide

Hsin-Lan Chang, Christopher M. Cimarusti,* Patrick A. Diassi, and Paul Grabowich

The Squibb Institute for Medical Research, P.O. Box 4000, Princeton, New Jersey 08540

Received May 18, 1976

Epoxidation of Δ⁴-3-keto steroids with hydrogen peroxide and base generally gives the β 4,5-epoxide as the major or exclusive product.[1] Various polar substituents including the 11β-hydroxyl group increase the proportion of α epoxide produced. We describe herein the effect of a 9α-fluorine on the epoxidation of an 11β-hydroxy steroid.

Reaction of enone **1a** with hydrogen peroxide and sodium hydroxide in methanol was complete in 4 h. From the resulting mixture of epoxides (ca. 2:1 ratio based on the intensity of the C-19 methyl signals in the NMR spectrum) the major isomer was isolated and characterized as the β epoxide **2a** by consideration of the molecular rotation difference (+4°) that attends the conversion of **1a** to **2a** (comparison values[2] for the cholestane and pregnan-20-one series are found in Table I).

Epoxidation of **1b** under identical conditions proved to be both slower and more stereoselective. After 4 days a 49% yield of a single epoxide and 25% of unreacted **1b** were obtained. The molecular rotation difference (−19.8°) suggested that this epoxide was the β isomer **2b.** Because of the uncertain influence of the 1,3-diaxial interaction (F-C-4) in **2b** on conformation and optical rotation, we decided to provide further evidence for the stereochemistry of **2b.**

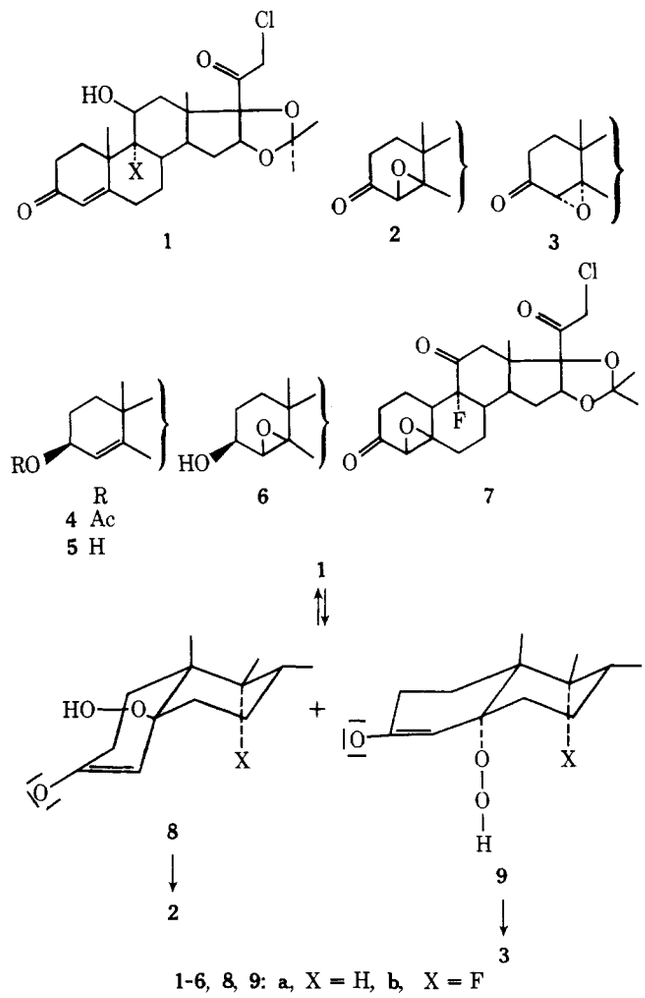
Epoxidation of allylic alcohols with peracid, which occurs on the side cis to the hydroxyl group,[3] provides the basis for the preparation of epoxy ketones of known stereochemistry provided that the requisite allylic alcohol is available.[4] Reduction of **1b** with sodium borohydride gave a single allylic alcohol **5b** after purification via its acetate **4b.** β stereochemistry is assigned to **5b** based on comparison of the molecular rotation differences in Table I with those for **4b** (−298.5°) and **5b** (−230°).[5] The NMR spectrum of **5b** is also consistent with this conclusion as the vinylic hydrogen lacks the characteristic (6–10 Hz) coupling expected for the α epimer which contains a pseudoequatorial 3β hydrogen.[6]

Table I. Molecular Rotation Differences

	Δ[M]D cholestane[a]	Δ[M]D pregnan-20-one[a]
4α,5α-Epoxid-3-one	−510.8	−546.1
4β,5β-Epoxid-3-one	+174	+108
3β-OH-Δ⁴-Ene	−152.9	−199.6
3β-OAc-Δ⁴-Ene	−299.9	−291.4
3α-OH-Δ⁴-Ene	+106.1	
3α-OAc-Δ⁴-Ene	+418.1	

[a] Based on conversion of the Δ⁴-3-one to the functionality indicated. Values of optical rotation from ref 2 were used to calculate these molecular rotation differences.

Epoxidation of **5b** with *m*-chloroperbenzoic acid followed by Jones oxidation of the crude product gave a single epoxy triketone (**7b**) via epoxy alcohol **6b** in 70% yield. Oxidation of



2b with Jones reagent gave the same epoxide **7b.** This sequence establishes the stereochemistry of **2b** as β and validates the use of molecular rotation differences in spite of the diaxial interaction present in **2b.**

The effect of the 9α-fluorine in **1b** on both the rate and stereochemistry of epoxidation is attributable to the steric and field effects present in transition states leading from intermediates **8** and **9** to epoxides **2** and **3,** respectively. Henbest[1] has suggested that (when X = H) more strain is released in the transition state leading from **8a** to **2a** than in that from **9a** to

3a. The presence of a larger fluorine atom in **8b** and **9b** should increase this difference. Similarly, relief of the electrostatic repulsion between the pseudoaxial enolate anion at C-4 and the axial fluorine atom in **8b** should be more important than relief of the corresponding interaction in **9b.** Both steric and electrostatic effects therefore favor the formation of the observed β-epoxide **2a.**

Experimental Section

Optical rotations were determined in chloroform at ambient temperature on a Perkin-Elmer 141 polarimeter. NMR spectra were determined in deuteriochloroform on Varian A-60 or XL-100 spectrometers. Preparative thin layer chromatography was performed with Merck silica gel plates (PF-254, 20 × 20 × 0.2 cm).

21-Chloro-4β,5-epoxy-11β-hydroxy-2′,2′-dimethyl-5β-pregnano[16α,17-*d*][1,3]dioxolane-3,20-dione (2a). A solution of 3 g (0.00662 mol) of **1a** ([α]D +153°, *c* 0.56) in 300 ml of methanol was stirred with 7.2 ml (0.07 mol) of 30% hydrogen peroxide and 4.8 ml (0.0192 mol) of 4 N sodium hydroxide solution. After 4 h no **1a** could be detected by TLC and the solution was diluted with water and extracted with chloroform to give 2.0 g of a mixture of epoxides **2a** and **3a** in the ratio of ca. 2:1. Preparative TLC using chloroform–ethyl acetate (3:1) as the developing solvent gave a pure sample of the major isomer **2a** (higher R_f material), mp 265–267 °C from methanol, [α]D +154° (*c* 0.45). A similar sample had mp 262–264 °C and [α]D +145.5° (*c* 0.26); NMR 1.34 ppm (s, C-19 CH_3).

Anal. Calcd for $C_{24}H_{33}ClO_6$: C, 63.64; H, 7.34; Cl, 7.83. Found: C, 63.90; H, 7.09; Cl, 7.89.

21-Chloro-4β,5-epoxy-9-fluoro-11β-hydroxy-2′,2′-dimethyl-5β-pregnano[16α,17-*d*][1,3]dioxolane-3,20-dione (2b). A solution of 30 g of **1b** ([α]D +156°, *c* 0.73) in 3 l. of methanol was stirred with 72 ml of 30% hydrogen peroxide and 48 ml of 4 N sodium hydroxide solution for 4 days and poured into 36 l. of water, and the resulting solid filtered. This was combined with three identical batches and chromatographed on silica gel to give a total of 60.11 g of **2b** and 30.4 g of recovered **1b.** A similar sample of **2b** had mp 254–256 °C from ethanol–water; [α]D +146.5° (*c* 0.24); NMR 1.40 ppm (s, C-19 CH_3).

Anal. Calcd for $C_{24}H_{32}ClFO_6$: C, 61.21; H, 6.85; Cl, 7.53; F, 4.03. Found: C, 61.48; H, 6.75; Cl, 7.30; F, 3.91.

Similar experiments worked up by extraction gave no TLC or NMR evidence for the presence of a second epoxide or any other nonacidic compound.

3β-(Acetyloxy)-21-chloro-9-fluoro-11β-hydroxy-2′,2′-dimethylpregn-4-eno[16α,17-*d*][1,3]dioxolan-20-one (4b). A solution of 1.83 g (0.004 mol) of **1b** in 200 ml of methanol was stirred for 1 h at room temperature with 2.2 equiv of sodium borohydride. After the usual workup the product was acetylated with 10 ml of pyridine and 5 ml of acetic anhydride overnight. The reaction mixture was poured into ice–water, stirred for 1 h, and filtered to give 2.1 g of solid. Purification by preparative TLC with chloroform as the developing solvent gave 738 mg (37%) of **4b,** mp 218–220 °C dec from methanol, [α]D +80.0° (*c* 1.6).

Anal. Calcd for $C_{26}H_{36}ClFO_6$: C, 62.58; H, 7.27; Cl, 7.11. Found: C, 62.64; H, 7.01; Cl, 6.91.

21-Chloro-9-fluoro-3β,11β-dihydroxy-2′,2′-dimethylpregn-4-eno[16α,17-*d*][1,3]dioxolan-20-one (5b). A solution of 500 mg of **4b** in 80 ml of methanol and 20 ml of tetrahydrofuran was stirred for 1 h under nitrogen with 10 ml of 10% potassium carbonate solution, and then diluted with water and extracted with chloroform to give 455 mg of crude product. Preparative TLC twice with chloroform as the developing solvent followed by crystallization from benzene–hexane gave **5b:** mp 182–184 °C dec; [α]D +101° (*c* 0.746); NMR 5.41 ppm (broad s, width at half-height = 5 Hz, C-4 H).

Anal. Calcd for $C_{24}H_{34}ClFO_5$: C, 63.10; H, 7.50; Cl, 7.76; F, 4.16. Found: C, 63.40; H, 7.49; Cl, 7.62; F, 4.08.

21-Chloro-4β,5-epoxy-9-fluoro-2′,2′-dimethyl-5β-pregnano[16α,17-*d*][1,3]dioxolane-3,11,20-trione (7). A solution of 200 mg (0.0044 mol) of **4b** in 10 ml of dichloromethane was stirred for 1 h with 100 mg (0.005 mol) of 85% *m*-chloroperbenzoic acid. After the usual workup a solution of the product in 25 ml of acetone was stirred with excess Jones reagent for 1.5 h. The usual workup gave a crude product that crystallized from methanol to give 139 mg (70%) of **7,** mp 202–204 °C.

Anal. Calcd for $C_{24}H_{30}ClFO_6$: C, 61.47; H, 6.45; Cl, 7.56; F, 4.05. Found: C, 61.53; H, 6.26; Cl, 7.51; F, 4.09.

Oxidation of 240 mg of **2b** as above gave 145 mg (60%) of **7,** mp and mmp with material from above 202–204 °C.

Acknowledgment. The authors are indebted to Mr. J. Alicino and associates for elemental analyses, and to Dr. A. I. Cohen and associates for NMR spectra.

Registry No.—1a, 630-44-4; **1b,** 3093-35-4; **2a,** 56896-66-3; **2b,** 56896-63-0; **4b,** 60646-27-7; **5b,** 60646-28-8; **7,** 60646-29-9.

References and Notes

(1) H. B. Henbest and W. R. Jackson, *J. Chem. Soc. C,* 2459 (1967).
(2) J. Jacques, H. Kagan, and G. Ourisson, "Optical Rotary Power, Ia Steroids", Pergamon Press, Elmsford, N.Y., 1965.
(3) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.,* 1958 (1957).
(4) For the application of a similar sequence to establish epoxide stereochemistry in a bicyclic case see B. M. Trost and T. N. Salzmann, *J. Chem. Soc., Chem. Commun.,* 571 (1975).
(5) F. Sondheimer and Y. Klibansky, *Tetrahedron,* **5,** 15 (1959).
(6) D. J. Collins and J. J. Hobbs, *Tetrahedron Lett.,* 197 (1963).

The Association Constants of Organic Complexes of Iodine. A Competitive Equilibrium Study[1]

P. D. Clark and K. E. Kolb*

Department of Chemistry, Bradley University, Peoria, Illinois 61625

Received June 1, 1976

Since Benesi and Hildebrand first studied the benzene–iodine complex,[2] many other organic complexes of iodine have been investigated in carbon tetrachloride. Andrews and Keefer have studied complexes of organic halides,[3] polymethylbenzenes,[4] and alkylbenzenes,[5] Tamres, Virzi, and Searles studied iodine complexes of alkylbenzenes.[6] Fluorobenzenes and fluorotoluenes were studied by Tamres,[7] and the iodine complex of benzonitrile was studied by Klaboe.[8] The complexes of polynuclear aromatics have been investigated by Bhattachara and Basu,[9] Peters and Person,[10] Blake, Winston, and Patterson,[11] and de Maine and Peone.[12] The association constants for all these complexes were found using ultraviolet spectroscopy and usually a modification of the Benesi–Hildebrand equation, such as the Scott equation.[13]

In this investigation the association constants were measured by a different technique. In the iodine–alkene addition reaction the position of the equilibrium is dependent on the nature of the solvent system.[14] A very convenient reaction to study is to determine the effects of a donor in the position of equilibrium in the cyclohexene–iodine addition reaction. A solution of 0.064 M cyclohexene and 0.032 M iodine in carbon tetrachloride reacts to 61.6% completion at 25.0 °C. A donor compound was added to the carbon tetrachloride solvent, generally to make a 1.0 M solution of the donor. The difference in the cyclohexene–iodine reaction in pure carbon tetrachloride and in the carbon tetrachloride–donor solvent system was used to determine the association constant of the complex formed. Assuming that only a 1:1 complex is formed, the association constant for the donor–iodine complex can be determined using eq 1.[15]

$$K_{sd} = \frac{X_1\,(S - d + X_1/K_a\,(b - X_1))}{K_a(b - X_1)d - X_1} \qquad (1)$$

K_a = equilibrium constant for I_2 addition to cyclohexene no donor in solvent)

X_1 = concentration of I_2 reacted = concentration of alkene reacted = concentration of diiodoalkane formed

S = initial concentration of donor

a = initial concentration of iodine

b = initial concentration of cyclohexene