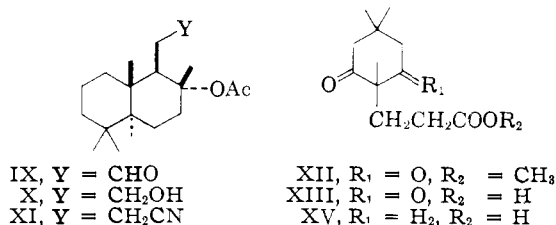
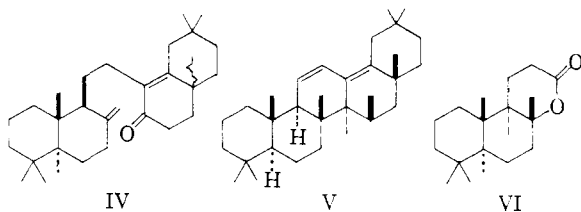
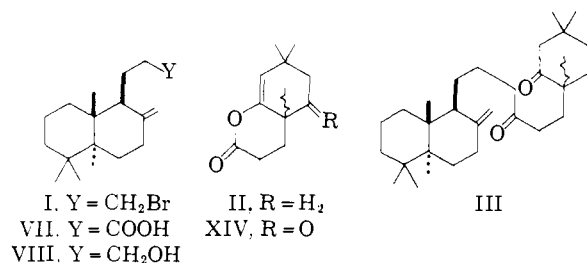


for 3 hours. Extensive chromatography afforded olean-11,12;13,18-diene (V),<sup>1</sup> m.p. 218°, mixture m.p. 218° with an authentic sample (of m.p. 219°),  $[\alpha]^{25}_D -65^\circ$  as compared to  $-66^\circ$  for authentic material<sup>2</sup> and ultraviolet and infrared spectra identical with those of pure olean-11,12;13,18-diene [ultraviolet:  $\lambda\lambda_{\max}^{\text{hexane}}$  242, 250, 259  $\mu$  ( $\epsilon$  26,670, 29,860, 19,710)]. The yield of V was poor (ca. 2%), somewhat less than that (ca. 10%) for the onoceradiene  $\rightarrow$  pentacyclosqualene conversion.<sup>3,4</sup> However, isolation of V was greatly facilitated by its characteristic and intense ultraviolet absorption.



The synthesis of the (+)-bromide (I) was accomplished by two different procedures. In the first (+)-ambreinolide<sup>5</sup> (VI) was converted by hydrolysis, methylation (CH<sub>2</sub>N<sub>2</sub>) dehydration (POCl<sub>3</sub>-C<sub>6</sub>H<sub>5</sub>N) and saponification to the olefinic acid VII, m.p. 113–115°,  $[\alpha]^{20}_D +52.1^\circ$  (C, 76.95; H, 10.94). Reduction of VII (LiAlH<sub>4</sub>) afforded the liquid alcohol VIII, b.p. 150° (0.4 mm.),  $[\alpha]^{20}_D +33.3^\circ$  (CHCl<sub>3</sub>),  $\nu_{\max}^{\text{CS}_2}$  890, 1645 cm.<sup>-1</sup> (C, 81.95; H, 12.14), which was transformed via the tosylate to the bromide I (LiBr-acetone). The acid VII was also prepared from the acetoxyaldehyde IX<sup>4</sup> via the corresponding alcohol (X) (NaBH<sub>4</sub>), brosylate and cyanide (XI), m.p. 84–86°,  $[\alpha]^{20}_D -10.1^\circ$  (C, 75.10; H, 10.02; N, 4.62). Treatment of the acetoxy nitrile XI with

quinoline at reflux and then basic hydrolysis gave the acid VII.

The (+)-enol lactone II was prepared from 2,5,5-trimethylcyclohexane-1,3-dione<sup>6</sup> via the diketo-ester XII (methyl acrylate-potassium *t*-butoxide) and the acid XIII, m.p. 109–113° (C, 63.73; H, 7.98; neut. equiv., 218) (acid hydrolysis). The enol lactone XIV, m.p. 95–97° (C, 69.29; H, 7.88),  $\nu_{\max}^{\text{CS}_2}$  1765, 1720, 1675 cm.<sup>-1</sup>, obtained by the action of phosphorus pentachloride on XIII, was hydrogenated (platinum-acetic acid) to the keto acid XV, m.p. 68–70° (C, 68.00; H, 9.23 which was converted (PCl<sub>5</sub>) to II, m.p. 64–65° (C, 74.25; H, 9.40),  $\nu_{\max}^{\text{CS}_2}$  1755, 1673.

This work was supported in part by the National Science Foundation.

(6) E. G. Meek, J. H. Turnbull and W. Wilson, *J. Chem. Soc.*, 811 (1953).

(7) Department of Chemistry, Harvard University, Cambridge, Mass.

DEPARTMENT OF CHEMISTRY  
AND CHEMICAL ENGINEERING  
UNIVERSITY OF ILLINOIS  
URBANA, ILLINOIS

E. J. COREY<sup>7</sup>  
HANS-JÜRGEN HESS  
S. PROSKOW

RECEIVED AUGUST 17, 1959

#### THE REACTION OF PERCHLORYL FLUORIDE WITH ENOL ETHERS

Sir:

This communication describes the novel reaction between enol ethers and perchloryl fluoride to produce fluorinated ketones.<sup>1</sup> In the absence of acids, the fluorine atom of perchloryl fluoride appears to be electrophilic and reacts with the negative center established at the  $\alpha$ -carbon atom by the unshared electrons of the alkoxy group. For example, brief treatment of 1-ethoxycyclohexene in pyridine with FClO<sub>3</sub> at 0°, followed by dilution with water and acidification, gave 2-fluorocyclohexanone, b.p. 83–83.5° (20 mm.);  $n^{25}_D$  1.4432; found; C, 62.25; H, 7.81; F, 16.69; dinitrophenylhydrazone, m.p. 139–140°.

In the steroid series, the respective 3-ethoxy- $\Delta^2$ -compounds treated with FClO<sub>3</sub> in pyridine for two minutes at room temperature with subsequent hydrolysis produced I, II and III in yields of 75 to 90%. Acidic methanolysis of III gave IV. The same compounds are obtained from perchloryl fluoride and the corresponding steroid enamines, and IV is identical with fluorodihydrotestosterone obtained from the 2-hydroxymethylene steroid.<sup>2</sup> Fluorination at position 2 was established by conversion of I to the 2,4-dinitrophenylhydrazone of 1-cholesten-3-one,<sup>3</sup> whereas  $\alpha$ -orientation of fluorine in I is indicated by optical rotatory dispersion<sup>4</sup> and n.m.r. spectrum.<sup>5</sup>

(1) The analogous reaction of steroid "enamines" with FClO<sub>3</sub> was reported recently from this laboratory by R. B. Gabbard and E. V. Jensen, *J. Org. Chem.*, **23**, 1406 (1958).

(2) J. Edwards and H. J. Ringold, *THIS JOURNAL*, **81**, 5262 (1959). We are grateful to Dr. Ringold for sending us a sample of his material.

(3) J. J. Beereboom, C. Djerassi, D. Ginsburg and L. F. Fieser, *ibid.*, **75**, 3500 (1953).

(4) C. Djerassi, I. Fornaguera and O. Mancera, *ibid.*, **81**, 2383 (1959).

(5) E. J. Corey, private communication.

(1) J. Green, N. Mower, C. W. Picard and F. S. Spring, *J. Chem. Soc.*, 527 (1944).

(2) All rotations measured in chloroform; m.p.'s determined with a micro hot-stage.

(3) D. H. R. Barton and K. H. Overton, *J. Chem. Soc.*, 2639 (1955).

(4) E. J. Corey and R. R. Sauer, *THIS JOURNAL*, **81**, 1739 (1959).

(5) For total synthesis see P. Dietrich and E. Lederer, *Helv. Chim. Acta*, **35**, 1148 (1952).

TABLE I  
 PHYSICAL CONSTANTS OF FLUORINATED STEROID KETONES

	Compound	M.p., °C.	[ $\alpha$ ] <sub>CHCl<sub>3</sub></sub> <sup>D</sup>	$\lambda_{C=O}^{KBr}$	Found:		
					Carbon, %	Hydrogen, %	Fluorine, %
I	2 $\alpha$ -Fluorocholestan-3-one <sup>1</sup>	173-174	+ 60°	5.78 $\mu$	80.20	11.19	4.71
II	2 $\alpha$ -Fluoroandrostane-3,17-dione	204-205	+133	5.78	74.28	8.86	5.99
III	2 $\alpha$ -Fluorodihydrotestosterone acetate	195-196	+ 59	5.80	71.93	8.84	5.38
IV	2 $\alpha$ -Fluorodihydrotestosterone	187-188	+ 62	5.79	73.91	9.33	6.10
V	6 $\beta$ -Fluoro-4-cholesten-3-one	103-104	+ 10	5.95	80.26	10.78	4.61
VI	6 $\alpha$ -Fluoro-4-cholesten-3-one <sup>7</sup>	117-118.5	+102	5.97	80.60	10.77	4.58
VII	6 $\alpha$ -Fluoroprogesterone <sup>7,9</sup>	144-145	+191	5.98	...	...	...
VIII	21,21-Difluoro-3 $\beta$ -hydroxy-5-pregnen-20-one	135-136	+ 54	5.81	71.29	3.48	10.73
IX	21,21,21-Trifluoro-3 $\beta$ -hydroxy-5-pregnen-20-one	179-181	+ 56	5.74	67.89	8.03	15.69
X	21,21-Difluoroprogesterone	147-147.5	+203	5.81	71.77	8.61	11.03
XI	21,21,21-Trifluoroprogesterone	159-160	+212	5.74	68.22	7.67	15.55

In contrast to enamines which yield 4,4-difluoro-3-keto- $\Delta^5$ -steroids,<sup>6</sup> enol ethers of  $\Delta^4$ -3-ketosteroids are fluorinated at position 6. Thus, 3-ethoxy-3,5-cholestadiene with perchloryl fluoride in pyridine three minutes at  $-20^\circ$  gave the 6 $\beta$ -fluoro derivative, V, isomerized by hydrogen chloride in chloroform-ethanol to the known<sup>7</sup> 6 $\alpha$ -isomer, VI. Similarly, 3-ethoxy-3,5-pregnadien-20-one gave a mixture<sup>8</sup> of 6 $\beta$ - and 6 $\alpha$ -fluoroprogesterones<sup>7,9</sup> isomerized by acid to yield VII, identical with authentic 6 $\alpha$ -fluoroprogesterone.<sup>10</sup>

Certain ketones already bearing  $\alpha$ -fluoro-substituents can be fluorinated further without intermediate conversion to enol ether derivatives. Thus VIII, prepared from perchloryl fluoride and sodio-21-ethoxyalyl-3 $\beta$ -hydroxy-5-pregnen-20-one in ethanol containing one extra equivalent of sodium ethoxide, as its acetate ester (m.p. 127.5-129°) was treated with FClO<sub>3</sub> for 90 minutes at room temperature in pyridine containing *t*-butyl alcohol and sodium *t*-butoxide to produce 21,21,21-trifluoro-3 $\beta$ -acetoxy-5-pregnen-20-one (m.p. 155-156°) saponified by methanolic potash to yield IX. Oxidation of VIII by Djerassi's procedure<sup>11</sup> gave X, whereas Oppenauer oxidation of IX furnished XI.

In contrast to the enhanced biological activity of 21-fluoroprogesterone,<sup>12</sup> X and XI are progestationally inactive at 0.25 mg.<sup>13</sup> Preliminary tests of II at 0.2 mg. and III at 0.1 mg. in castrate male rats<sup>13</sup> indicate that fluorination has abolished androgenic activity, although III is strongly anabolic in young female rats and markedly inhibits rat mammary cancer induced by feeding methylcholanthrene.<sup>14</sup> Thus 2 $\alpha$ -fluorination may well accomplish our long-standing objective of

eliminating primary hormonal activity by a molecular change so subtle that secondary actions including antitumor effects are retained.<sup>15</sup>

(15) T. C. Myers, R. J. Pratt, R. L. Morgan, J. O'Donnell and E. V. Jensen, *THIS JOURNAL*, **77**, 5655 (1955).

THE BEN MAY LABORATORY  
FOR CANCER RESEARCH  
UNIVERSITY OF CHICAGO  
CHICAGO 37, ILLINOIS

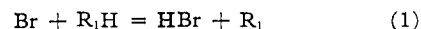
SUSUMU NAKANISHI  
KEN-ICHI MORITA  
ELWOOD V. JENSEN

RECEIVED JULY 29, 1959

#### THE REACTIONS OF BROMINE ATOMS AND THE STRENGTHS OF C-H BONDS

Sir:

Reactions of type (1) are important both because



of their intrinsic interest and because Kistiakowsky and Van Artsdalen<sup>1</sup> have shown how the strength of C-H bonds in alkanes can be deduced from measurements of the activation energies,  $E_1$ . The strengths are given by

$$D(\text{C-H}) = D(\text{H-Br}) + E_1 - E_{-1}$$

We have determined relative values of  $E_1$  for a number of hydrocarbons by a competitive method previously employed to study the reactions of fluorine and chlorine atoms.<sup>2</sup> Absolute values of the Arrhenius parameters have been obtained by relating the rate constant for ethane to that for methyl bromide<sup>1</sup>

$$\log k/\text{mole}^{-1} \text{ cm.}^3 \text{ sec.}^{-1} = 13.73 - (16050/2.3RT)$$

A mixture of two reactants together with bromine was irradiated in a Pyrex reaction vessel. The concentration of the less reactive compounds was usually about four times that of the more reactive. The products were analyzed by gas chromatography after the excess bromine had been removed. The relative rates of formation of the alkyl bromides, from which the relative rate con-

(6) R. L. Morgan and E. V. Jensen, to be published.

(7) A. Bowers and H. J. Ringold, *Tetrahedron*, **3**, 14 (1958).

(8) Characterized by papergram analysis carried out by Mr. L. M. Reineke, The Upjohn Co.

(9) J. A. Hogg, *et al.*, *Chem. and Ind.*, 1002 (1958).

(10) Kindly supplied by Dr. J. C. Babcock.

(11) C. Djerassi, R. R. Engle and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(12) P. Tannhauser, R. J. Pratt and E. V. Jensen, *THIS JOURNAL*, **78**, 2658 (1956); Ch. R. Engel and R. L. Noble, *Endocrinology*, **61**, 318 (1957).

(13) Subcutaneous assay by F. L. Schmidt, S. C. Lyster and W. E. Dulin, The Upjohn Co.

(14) Subcutaneous assay by Dr. C. Huggins, University of Chicago.

(1) G. B. Kistiakowsky and E. R. Van Artsdalen, *J. Chem. Phys.*, **12**, 469 (1944); H. C. Anderson and E. R. Van Artsdalen, *ibid.*, p. 479; B. H. Eckstein, H. A. Scheraga and E. R. Van Artsdalen, *ibid.*, **22**, 28 (1954); E. I. Hormats and E. R. Van Artsdalen, *ibid.*, **19**, 775 (1951).

(2) J. H. Knox and R. L. Nelson, *Trans. Faraday Soc.*, **55**, 937 (1959); G. C. Fettes and A. F. Trotman-Dickenson, to be published.