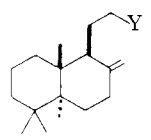
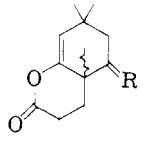
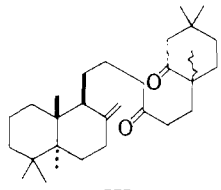
for 3 hours. Extensive chromatography afforded olean-11,12;13,18-diene (V),[1] m.p. 218°, mixture m.p. 218° with an authentic sample (of m.p. 219°), $[\alpha]^{25}D$ −65° as compared to −66° for authentic material[2] and ultraviolet and infrared spectra identical with those of pure olean-11,12; 13,18-diene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



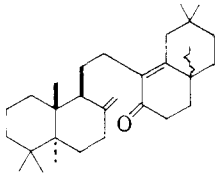
I, Y = CH_2Br
VII, Y = COOH
VIII, Y = CH_2OH



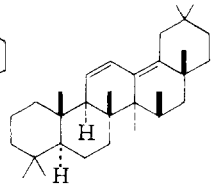
II, R = H_2
XIV, R = O



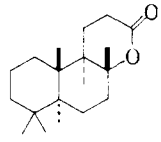
III



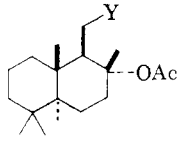
IV



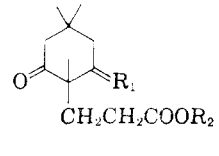
V



VI



IX, Y = CHO
X, Y = CH_2OH
XI, Y = CH_2CN



XII, R_1 = O, R_2 = CH_3
XIII, R_1 = O, R_2 = H
XV, R_1 = H_2, R_2 = H

The synthesis of the (+)-bromide (I) was accomplished by two different procedures. In the first (+)-ambreinolide[5] (VI) was converted by hydrolysis, methylation (CH_2N_2) dehydration ($POCl_3$–C_5H_5N) and saponification to the olefinic acid VII, m.p. 113–115°, $[\alpha]^{20}D$ +52.1° (C, 76.95; H, 10.94). Reduction of VII ($LiAlH_4$) afforded the liquid alcohol VIII, b.p. 150° (0.4 mm.), $[\alpha]^{20}D$ +33.3° ($CHCl_3$), $\nu_{max}^{CS_2}$ 890, 1645 cm.$^{-1}$ (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[4] via the corresponding alcohol (X) ($NaBH_4$), brosylate and cyanide (XI), m.p. 84–86°, $[\alpha]^{20}D$ − 10.1° (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[6] via the diketoester 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), $\nu_{max}^{CS_2}$ 1765, 1720, 1675 cm.$^{-1}$, 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_5) to II, m.p. 64–65° (C, 74.25; H, 9.40), $\nu_{max}^{CS_2}$ 1755, 1673.

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

(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. Sauers, THIS JOURNAL, **81**, 1739 (1959).

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

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

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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.[1] In the absence of acids, the fluorine atom of perchloryl fluoride appears to be electrophilic and reacts with the negative center established at the α-carbon atom by the unshared electrons of the alkoxy group. For example, brief treatment of 1-ethoxycyclohexene in pyridine with $FClO_3$ 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-Δ^2-compounds treated with $FClO_3$ 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.[2] Fluorination at position 2 was established by conversion of I to the 2,4-dinitrophenylhydrazone of 1-cholesten-3-one,[3] whereas α-orientation of fluorine in I is indicated by optical rotatory dispersion[4] and n.m.r. spectrum.[5]

(1) The analogous reaction of steroid "enamines" with $FClO_3$ 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.

TABLE I

PHYSICAL CONSTANTS OF FLUORINATED STEROID KETONES

	Compound	M.p., °C.	$[\alpha]^{CHCl_3}D$	$\lambda^{KBr}_{C=O}$	Found: Carbon, %	Hydrogen, %	Fluorine, %
I	2α-Fluorocholestan-3-one[1]	173–174	+ 60°	5.78μ	80.20	11.19	4.71
II	2α-Fluoroandrostane-3,17-dione	204–205	+133	5.78	74.28	8.86	5.99
III	2α-Fluorodihydrotestosterone acetate	195–196	+ 59	5.80	71.93	8.84	5.38
IV	2α-Fluorodihydrotestosterone	187–188	+ 62	5.79	73.91	9.33	6.10
V	6β-Fluoro-4-cholesten-3-one	103–104	+ 10	5.95	80.26	10.78	4.61
VI	6α-Fluoro-4-cholesten-3-one[7]	117–118.5	+102	5.97	80.60	10.77	4.58
VII	6α-Fluoroprogesterone[7,9]	144–145	+191	5.98	...	...	...
VIII	21,21-Difluoro-3β-hydroxy-5-pregnen-20-one	135–136	+ 54	5.81	71.29	3.48	10.73
IX	21,21,21-Trifluoro-3β-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-Δ^5-steroids,[6] enol ethers of Δ^4-3-ketosteroids are fluorinated at position 6. Thus, 3-ethoxy-3,5-cholestadiene with perchloryl fluoride in pyridine three minutes at −20° gave the 6β-fluoro derivative, V, isomerized by hydrogen chloride in chloroform–ethanol to the known[7] 6α-isomer, VI. Similarly, 3-ethoxy-3,5-pregnadien-20-one gave a mixture[8] of 6β- and 6α-fluoroprogesterones[7,9] isomerized by acid to yield VII, identical with authentic 6α-fluoroprogesterone.[10]

Certain ketones already bearing α-fluoro-substituents can be fluorinated further without intermediate conversion to enol ether derivatives. Thus VIII, prepared from perchloryl fluoride and sodio-21-ethoxyalyl-3β-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 $FClO_3$ for 90 minutes at room temperature in pyridine containing *t*-butyl alcohol and sodium *t*-butoxide to produce 21,21,21-trifluoro-3β-acetoxy-5-pregnen-20-one (m.p. 155–156°) saponified by methanolic potash to yield IX. Oxidation of VIII by Djerassi's procedure[11] gave X, whereas Oppenauer oxidation of IX furnished XI.

In contrast to the enhanced biological activity of 21-fluoroprogesterone,[12] X and XI are progestationally inactive at 0.25 mg.[13] Preliminary tests of II at 0.2 mg. and III at 0.1 mg. in castrate male rats[13] 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.[14] Thus 2α-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.[15]

(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.

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

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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

$$Br + R_1H = HBr + R_1 \qquad (1)$$

of their intrinsic interest and because Kistiakowsky and Van Artsdalen[1] 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

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

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.[2] Absolute values of the Arrhenius parameters have been obtained by relating the rate constant for ethane to that for methyl bromide[1]

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

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-

(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**, 778 (1951).

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