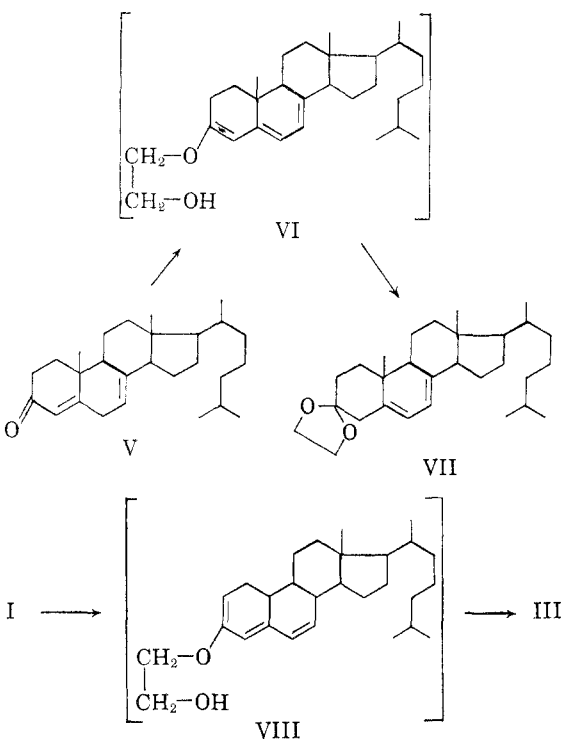
The same ketal derivatives were obtained by both the acid catalyzed reaction of the ketones with ethylene glycol and by the exchange dioxolanation method.[2]

The proposed mechanism of ketal formation[3] suggests that double bond isomerization in the course of cycloethylene ketal formation of a Δ^4-3-ketosteroid results from the formation of an intermediate $\Delta^{3,5}$-dienol ether species. Thus, $\Delta^{4,7}$-cholestadiene-3-one, V, forms $\Delta^{5,7}$-cholestadiene-3-one-3 cycloethylene ketal VII *via* the probable intermediate VI.



In the case of the $\Delta^{4,6}$-3-ketosteroids, the process may involve the intermediate $\Delta^{2,4,6}$-trienol ether VIII rather than the isomeric species VI. The intermediate trienols VI and VIII apparently are not capable of interconversion under the reaction conditions employed and examination of the mother liquors from the preparation of III by ultraviolet spectroscopy gave no indication of the isomeric cycloethylene ketal VII.

The structural assignments of the cycloethylene ketals were verified by reversion of each ketal to its parent $\Delta^{4,6}$-3-ketosteroid precursor upon acid hydrolysis and by the characteristic ultraviolet absorption of each derivative. The $\Delta^{4,6}$-cholestadiene-3-one-3-cycloethylene ketal III exhibited λ_{max} 236 mμ (ϵ = 18,700) and the corresponding $\Delta^{4,6,22}$-ergostatriene-3-one-3-cycloethylene ketal IV had λ_{max} 235 mμ (ϵ = 19,200) which is characteristic of the $\Delta^{4,6}$-diene system ascribed.[4] The isomeric $\Delta^{5,7}$-cholestadiene-3-one-3-cycloethylene ketal VI,[1c] absorbs at λ_{max} 271, 282, 293 mμ. The ergosterol analog exhibits similar absorption.[1c] Hydrolysis of the $\Delta^{5,7}$-3-keto-3-cycloethylene ketals yields the $\Delta^{4,7}$-3-ketosteroids.[1c]

EXPERIMENTAL

$\Delta^{4,6}$-Cholestadiene-3-one-3-cycloethylene ketal. A solution of 200 mg. (0.523 mmole) of $\Delta^{4,6}$-cholestadiene-3-one, 10 mg. of *p*-toluenesulfonic acid, 10 ml. of ethylene glycol, and 50 ml. of benzene was allowed to reflux for 5 hr. The water which separated was collected in a Dean-Stark phase separator. When the reflux period had ended, the solution was poured into 100 ml. of a 5% aqueous sodium carbonate solution and the mixture was extracted with two 100-ml. portions of ether. The ether extracts were washed with water, combined and dried over anhydrous sodium sulfate, and evaporated to dryness at reduced pressure. The residual pale yellow oil crystallized upon trituration with acetone and there was obtained 193 mg. of pale yellow needles, m.p. 112–114.5°. Two recrystallizations from acetone afforded 142 mg. (64%) of colorless needles, m.p., 116–117.5°, $[\alpha]_D^{25}$ + 57° ($CHCl_3$) λ_{max}^{CasOH} 236 mμ (ϵ = 18,700).

Anal. Calcd. for $C_{29}H_{46}O_2$: C, 81.63; H, 10.87. Found: C, 81.69; H, 11.04.

$\Delta^{4,6,22}$-Ergostatriene-3-one-3-cycloethylene ketal. A solution of 800 mg. (2.01 moles) of $\Delta^{4,6,22}$-ergostatriene-3-one, 40 mg. of *p*-toluenesulfonic acid, 30 ml. of ethylene glycol, and 100 ml. of benzene was allowed to reflux for 6 hr. The water which separated was collected in a Dean-Stark separator. Upon completion of the reflux period, the cooled mixture was poured into 300 ml. of a 5% aqueous sodium carbonate solution. The benzene layer was separated and the aqueous phase was extracted with 100 ml. of ether. The combined benzene and ether extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness at reduced pressure. The yellow residual oil crystallized upon trituration with acetone. The crude crystalline product was twice recrystallized from acetone and afforded 672 mg. (77%) of colorless leaflets, m.p. 129–130°, $[\alpha]_D^{25}$ ± 0.0° ($CHCL_3$), λ_{max}^{CasOH} 235 mμ (ϵ = 19,200).

Anal. Calcd. for $C_{30}H_{46}O_2$: C, 82.13; H, 10.57. Found: C, 82.30; H, 10.41.

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Conformational Analysis. XV. The Dipole Moment of 2-Fluorocholestanone[1,2]

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Since various biologically active steroids have been found to have their activity increased by the

(1) Paper XIV, A. M. Wilson and N. L. Allinger, *J. Am. Chem. Soc.*, **83**, 0000 (1961).

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substitution of fluorine for hydrogen,[3] a number of compounds have recently been prepared containing a fluorine atom on a carbon adjacent to a carbonyl group.[3-5] This paper is concerned with the determination of the conformation of the fluorine atom in such compounds.

2-Bromo- and 2-chlorocyclohexanone derivatives have been studied in great detail with regards to conformation (or in rigid systems, configuration).[6] It has been shown that the conformation of the halogen (bromine or chlorine) can be determined in a variety of ways, namely by dipole moment,[7] infrared spectra,[8] ultraviolet spectra,[9] rotatory dispersion measurements,[10] nuclear magnetic resonance spectra,[11] or polarographic reduction potential.[1] The method of choice depends on the system involved.

The 2-fluorocyclohexanones are rather less well studied with regard to conformation. From the small amount of available data it would seem that the carbonyl shifts in the infrared will be of limited use.[3,12] Equatorial fluorine causes the carbonyl stretching frequency to be raised by about 30 cm.$^{-1}$, while for the axial fluorine the shift is about 20 cm.$^{-1}$. Very few ultraviolet data are available[12,13] for conformationally pure compounds. Many of the steroidal systems described[3,4] are of the 2-fluoro-3-keto-Δ^4 type and only the wave length of the $\pi \rightarrow \pi^*$ transition has usually been reported. Rotatory dispersion measurements appear to be of limited use for fluoro ketones,[13] and the NMR and polarographic methods have not been extensively used as of yet.

The measurement of the dipole moment appears to offer an unambiguous way for determining the conformation of a 2-fluorocyclohexanone, within certain well defined limitations, and was the method used in this work. Since 2-fluorocholestanone is more or less the "parent" steroid example of the system in question, it was the compound studied. Earlier workers[5] have assumed the fluorine was α (equatorial) in this compound, based on the shift of the carbonyl stretching frequency, and by analogy to the conclusions drawn by Kende[14] regarding 2-fluorocyclohexanone.

While the qualitative conclusion of Kende that the equatorial conformer is more stable has been confirmed,[12] the difference in stability between the conformers is much less than Kende has indicated. The carbonyl band in 2-fluorocholestanone is shifted[5] by 26 cm.$^{-1}$, and the configuration previously assigned to the compound was not therefore regarded as unequivocal.

The angle between the dipoles of a 2-halocyclohexanone was calculated earlier[15] using the model of Corey and Sneen[16] for both the axial and equatorial conformations. Ideal geometry was assumed. This assumption is an approximation which will be satisfactory if the difference in the calculated moments for the epimers is sufficiently large, which is the case here.

The dipole moment of 3-cholestanone was measured and found to have the value 3.01 D in benzene solution. This value is very close to that of cyclohexanone (3.08 D).[17] Because of the relatively high polarizability of the carbonyl oxygen (0.84×10^{-24} cm.^{3}),[18] the moment induced in the C=O group by the neighboring equatorial C—F dipole must be taken into account. The value 3.01 D is consequently used for the C=O dipole when the fluorine is axial, and 2.84 D is used when it is equatorial. The latter value is arrived at by assuming the moment induced in the carbonyl by the C—F dipole has the same magnitude as that induced by the C—Br dipole, which must be very nearly true. The value in the case of the C—Br dipole is known experimentally.[19]

Since the polarizability of the fluorine (0.38×10^{-24} cm.^{3})[18] is the same as that of a hydrogen (0.42×10^{-24} cm.^{3}),[18] the same value for the C—F bond moment,[20] 1.90 D, is used throughout the calculations.

From these bond moments and the known angles between the dipoles (109°51′ axial and 51°54′

(2a) Predoctoral U. S. Public Health Service Fellow, General Division of Medical Sciences, 1960–62.

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TABLE I

DIPOLE MOMENT DATA

N_2	d_{12}	ϵ_{12}
	Cholestan-3-one	
0.00000000	0.873735	2.2729
0.00069839	0.874023	2.2831
0.00137615	0.874371	2.2929
0.00298159	0.875150	2.3141
0.00429121	0.875814	2.3312
α 13.531	ϵ_1 2.2736	d_1 0.87371
β 0.488	$P_{2\infty}$ 315.7	M_R 118.73
(Pe + Pa) 130.60	μ 3.01 D	
	2-Fluorocholestan-3-one	
0.00000000	0.873579	2.2743
0.00038680	0.873977	2.2858
0.00080923	0.874248	2.2974
0.00096282	0.874377	2.3012
0.00111752	0.874433	2.3057
α 27.913	ϵ_1 2.2746	d_1 0.87361
β 0.776	$P_{2\infty}$ 524.2	M_R 118.51
(Pe + Pa) 130.36	μ 4.39 D.	

equatorial),[15] the moment for 2α-fluorocholestanone was calculated to be 4.28 D, while that of 2β-fluorocholestanone was calculated to be 2.95 D.

The dipole moment of the only known 2-fluorocholestanone was measured in benzene solution, and the value found was 4.39 D. The configuration at C-2 is therefore unequivocally established as α and the earlier configurational assignment is confirmed.

EXPERIMENTAL

Cholestanone, m.p. 130–130.5°, was prepared from cholesterol in the usual way. The 2-fluorocholestanone, m.p. 173.0–173.5° was used as received after drying under vacuum for a few hours.

Dipole moment apparatus. The Dipolemeter DM01 manufactured by Wissenshaftlich-Technische Werkstatten obtainable through the Kahl Scientific Instrument Corporation, El Cajon, Calif., was used for the measurements reported herein. The apparatus utilizes the heterodyne beat method and operates at 1,800 kilocycles. It is internally thermostated and of good stability. The cell used was of metal with a gold plated interior and had an effective capacity of about 35$\mu\mu$F with a volume of 40 ml. It was thermostated at 25° ±0.01°.

The dipole moments were measured in benzene solution. The moments were calculated by essentially the method of Halverstadt and Kumler[21] utilizing an IBM 650 computer programmed as described earlier.[22] Since the cholestanone derivatives are of such high molecular weight the usual neglect of the atomic polarization may introduce some error[23] in the present case. Unfortunately there is no very good, simple method for determining the atomic polarization. What has been done in the present case is to set it equal to 10% of the molar refractivity, for both cholestanone and the fluoro derivative. The effect of taking the atomic polarization into account is to lower the experimental moment of cholestanone from 3.10 to 3.01 D, and the moment of the fluoro compound is similarly lowered from 4.46 to 4.39 D. These changes are not of great significance since the experimental error is about 0.03 D, but the values which take atomic polarization into account have been used throughout the paper. The data are summarized in Table I.

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(20) This is an average of values reported for a number of aliphatic fluorides by M. T. Rogers and J. D. Roberts, *J. Am. Chem. Soc.*, **68**, 843 (1946) and by M. T. Rogers, *J. Am. Chem. Soc.*, **69**, 457 (1947).

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17α,20α-Dihydroxy-4-pregnene-3-one

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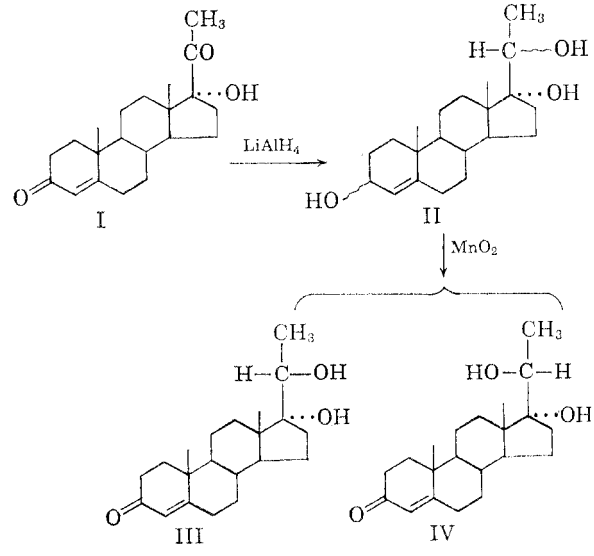
Presumptive evidence for the presence of 17α,-20α-dihydroxy-4-pregnene-3-one in biological material was presented by Sandor and Lanthier,[1] but no physical constants were given and only chromatographic behavior of the compound was included. A search of the literature revealed that this compound was not previously synthesized and we wish to report its synthesis. 17α-Hydroxyprogesterone (I) was reduced with lithium aluminum



hydride. The resulting mixture of epimeric 3ξ,-17α,20ξ-glycols (II) was oxidized with manganese dioxide[2] at room temperature to give a mixture

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