[CONTRIBUTION FROM THE COLLEGE OF PHARMACY OF THE UNIVERSITY OF CALIFORNIA]

Dipole Moments of Steroids. III

BY W. D. KUMLER

This is a continuation of study of the relation between dipole moments and structure of steroids. The first two papers dealt with the bile acids[1] and certain sex hormones.[2] In this paper fourteen additional steroids have been measured. Evidence has been obtained that the nucleus in the sex hormones is not completely flat with the ketone groups in the plane of the nucleus and additional proof has been acquired that the hydroxyl groups do not have freedom of rotation. A structure that fits the data is one in which the carbon atoms are staggered, and the A/B, B/C and C/D rings are all linked *trans*.

Results

The equations used in calculating the moments are:[3]

$$p_{2_0} = \frac{3\alpha v_1}{(\epsilon_1 + 2)^2} + (v_1 + \beta)\frac{\epsilon_1 - 1}{\epsilon_1 + 2}$$

$$P_{2_0} = p_{2_0} M_2$$

$$\mu = 0.0127\sqrt{(P_{2_0} - P_{E_{2_0}})T}$$

The p_{20} values were obtained by the method of Halverstadt and Kumler[3] using the graphical modification. $P_{E_{2_0}}$ values were calculated from the group refractions given by Smyth.[4] The

TABLE I

MEASUREMENTS IN DIOXANE AT 25°

w_2	ϵ_{12}	v_{12}
	Dihydrocholesterol	
0.003189	2.2145	0.97391
.004818	2.2161	.97405
.006647	2.2181	.97414
.008833	2.2203	.97425
	Cholesterol	
0.007841	2.2247	0.97477
.011436	2.2295	.97494
.015243	2.2353	.97515
.017761	2.2406	.97533
	Androstanediol-3α,17α	
0.002813	2.2226	0.97418
.005732	2.2300	.97398
.008625	2.2375	.97378
.011162	2.2437	.97367
	Androstanediol-3β,17α	
0.002009	2.2230	0.97414
.003978	2.2316	.97400
.005826	2.2370	.97391
.010706	2.2580	.97376
	Androstanedione-3,17	
0.002862	2.2268	0.97409
.005794	2.2432	.97391
.008742	2.2538	.97369
.011096	2.2635	.97355
	17-Methyl-Δ^5-androstenediol-3β,17α	
0.002900	2.2268	0.97407
.005913	2.2374	.97391
.008643	2.2474	.97371
.011253	2.2565	.97355
	17-Methyl-testosterone	
0.003029	2.2359	0.97407
.005802	2.2565	.97385
.008702	2.2771	.97362
.011052	2.2951	.97346
	3,17-Dimethyl-androstane-ol-17α	
0.002671	2.2211	0.97429
.004653	2.2253	.97425
.007304	2.2301	.97409
.011078	2.2380	.97394
	3,17-Dimethyl-androstadiene-ol-17α	
0.002912	2.2205	0.97423
.005875	2.2269	.97409
.008234	2.2306	.97405
.011540	2.2370	.97396
	3,17-Dimethyl-androstanediol-3,17α (Fr. A)	
0.002889	2.2216	0.97420
.004664	2.2269	.97411
.008611	2.2327	.97400
.010951	2.2380	.97394
	3,17-Dimethyl-androstanediol-3,17 (Fr. B)	
0.002931	2.2231	0.97429
.005030	2.2289	.97420
.007313	2.2337	.97396
.009319	2.2380	.97391
	Tigogenin	
0.002743	2.2125	0.97418
.004010	2.2152	.97409
.005240	2.2164	.97402
.005944	2.2183	.97400
	Gitogenin	
0.002099	2.2163	0.97407
.002924	2.2183	.97398
.003887	2.2199	.97391
.004962	2.2226	.97385
	Chlorogenin	
0.002714	2.2147	0.97398
.003684	2.2168	.97382
.004826	2.2195	.97369
.005774	2.2215	.97362

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[1] Kumler and Halverstadt, THIS JOURNAL, **64**, 1941 (1942).

[2] Kumler and Fohlen, *ibid.*, **67**, 437 (1945).

[3] Halverstadt and Kumler, *ibid.*, **64**, 2988 (1942).

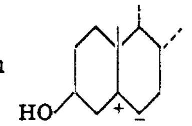
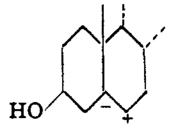
[4] Smyth, "Dielectric Constants and Molecular Structure," Chemical Catalog Co., New York, N. Y., 1931.

TABLE II

Compound	ϵ_1 extrap.	v_1 extrap.	α	β	$P_{2\infty}$	PE_{2}	μ
Dihydrocholesterol	2.2111	0.97364	1.050	0.0956	186.58	118.42	1.81
Cholesterol.	2.2134	.97435	1.422	− .0517	204.63	121.40	1.99
Androstanediol-3α,17α	2.2156	.97436	2.52	− .066	193.32	84.21	2.29
Androstanediol-3β,17α	2.2152	.97420	3.98	− .046	269.76	84.21	2.99
Androstanedione-3,17	2.2165	.97428	4.24	− .066	300.70	81.18	3.25
17-Methyl-Δ^5-androstenediol-3β,17α	2.2164	.97429	3.58	− .066	258.98	88.36	2.78
17-Methyl-testosterone	2.2130	.97430	7.40	− .0770	446.67	85.64	4.17
3,17-Dimethyl-androstane-ol-17α	2.2159	.97442	1.97	− .0434	180.45	91.93	2.06
3,17-Dimethyl-androstadiene-ol-17α	2.2152	.97428	1.90	− .0277	159.04	90.99	1.81
3,17-Dimethyl-androstanediol-3,17α (Fr. A)	2.2166	.97424	1.92	− .0271	188.74	93.45	2.14
3,17-Dimethyl-androstanediol-3,17α (Fr. B)	2.2148	.97453	2.43	− .0688	211.84	93.45	2.39
Tigogenin	2.2074	.97433	1.82	− .058	234.21	118.52	2.36
Gitogenin	2.2119	.97420	2.14	− .0734	264.60	120.04	2.64
Chlorogenin	2.2086	.97426	2.26	− .1142	268.18	120.04	2.67

data are given in Tables I and II and the structures of the compounds in Fig. 1.

Discussion

Moment of a Hydroxyl Attached to a Five- or Six-Membered Ring.—Dihydrochloesterol has a dipole moment of 1.81, which is equal to that of cyclohexanol, 1.82,[5] within the experimental error. Cholesterol which differs only in having a double bond in the Δ^5-position has a moment of 1.99, 0.18 unit higher. The double bond being located in an unsymmetrical position with respect to the rest of the molecule would give rise to a small moment. The most likely direction for this moment would be such as to augment the hydroxyl moment since the form  with the plus charge on the 5-carbon which has no hydrogen would be expected to predominate over the form  with the charges reversed. Another explanation, that the double bond in the Δ^5-position has a direct effect on the hydroxyl moment is given some support from the enhanced reactivity of the hydroxyl in some of these compounds but of the two explanations the first seems to be the most straight-forward.

The moment of 3,17-dimethyl-androstane-ol-17α, 2.06 is 0.25 unit higher than the moment of dihydrocholesterol. This could be due to the presence of a methyl group on the same carbon as the hydroxyl but this seems unlikely because the moment of 17-methyl-Δ^5-androstenediol-3β,17α is lower than the moment of Δ^5-androstenediol-3β,17α, and 17-methyl-testosterone has a lower moment than testosterone. The other explanation is that a hydroxyl group attached to a five-membered ring has a higher moment than one attached to a six-membered ring. The moment of cyclopentanol would be of interest in this connection but so far as I know it has not been measured. The latter explanation is given support, however, by the fact that cyclopentanone, 3.00[6] has a higher moment than cyclohexanone, 2.90.

The moment of 3,17-dimethyl-androstadiene-ol-17α is the same as that of dihydrocholesterol and 0.25 unit less than the saturated compound 3,17-dimethyl-androstane-ol-17α. This can be accounted for by the double bonds giving rise to a small moment which is opposed in direction to the moment of the hydroxyl group.

Restricted Rotation of the Hydroxyl Groups.—In the previous paper[2] it was found that the measured moments were outside the range of the calculated moments for free rotation with four out of eleven compounds.

TABLE III

CALCULATED MOMENTS FOR FREE ROTATION

Compound	Maximum, $\sigma = 0°$	Minimum, $\sigma = 180°$	Measured moments
Androstanediol-3α,17α	2.68	2.46	2.29
Androstanediol-3β,17α	2.68	2.46	2.99
17-Methyl-Δ^5-androstanediol-3β,17α	2.68	2.46	2.78
3,17-Dimethyl-androstanediol-3,17α (Fr. A)	2.68	2.46	2.14
3,17-Dimethyl-androstanediol-3,17α (Fr. B)	2.68	2.46	2.39
17-Methyl-testosterone	4.82	3.85	4.17

In Table III are listed the calculated and measured moments for six additional compounds that have two hydroxyl groups or a hydroxyl group and a ketone group as the only polar groups in the molecule. With five of the six compounds the measured moment is outside the range for free rotation by amounts greater than the experimental error.

In the previous work[2] we could conclude that the 3β and 17β positions were restricted. From

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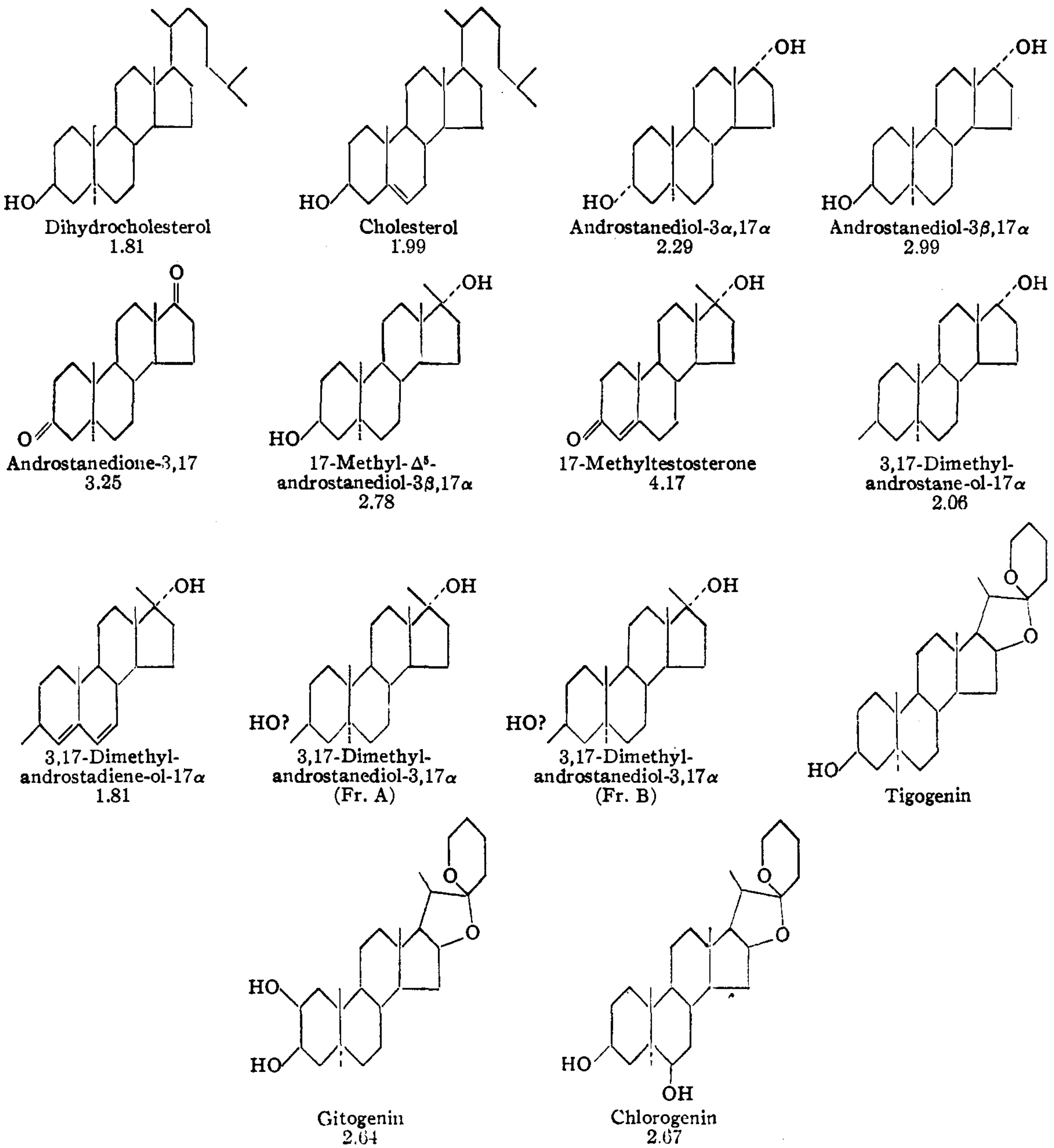
[5] Halverstadt and Kumler, THIS JOURNAL, **64**, 1982 (1942).

[6] Donle and Volkert, *Z. physik. Chem.*, **B8**, 60 (1930).



Dihydrocholesterol
1.81

Cholesterol
1.99

Androstanediol-3α,17α
2.29

Androstanediol-3β,17α
2.99

Androstanedione-3,17
3.25

17-Methyl-Δ^5-androstanediol-3β,17α
2.78

17-Methyltestosterone
4.17

3,17-Dimethyl-androstane-ol-17α
2.06

3,17-Dimethyl-androstadiene-ol-17α
1.81

3,17-Dimethyl-androstanediol-3,17α
(Fr. A)

3,17-Dimethyl-androstanediol-3,17α
(Fr. B)

Tigogenin

Gitogenin
2.64

Chlorogenin
2.67

Fig. 1.

the above there is evidence that either the 3α or 17α position is restricted because the measured moment of androstanediol-3α,17α falls outside the calculated range for free rotation. The fact that the measured moments of both 3,17-dimethyl-androstanediol-3,17α (Fr. A) and 3,17-dimethyl-androstanediol-3,17α (Fr. B) fall outside the range for free rotation also indicates that the 3α or 17α positions are restricted when a methyl group is on the 3 and 17 positions, for one of these compounds has the hydroxyl groups in the 3α,17α positions.

From the Fisher–Hershfeld models it appears that the 3β position is the least confined and if this hydroxyl is restricted as the previous work[2] has indicated it is probable that the hydroxyl groups in the other positions are restricted as well.

Angle between Ketone Groups: Shape of the Nucleus.—In androstanedione-3,17 we have a compound in which complications resulting from rotation or oscillation of a dipole about a single bond do not enter. Taking the moment of the 3-ketone from that of cyclohexanone[5] and that of the 17-ketone from cyclopentanone[6] we calculate the angle the ketone groups must make with each other to give the observed moment. This angle is found to be 113°.

A popular conception of the steroid nucleus is that the six-membered rings are flat due to oscillations between the chair and boat-forms of the cyclohexane rings and the cyclopentane ring is flat. If this is the case then the ketone groups should be in the plane of the rings. A calculation has been made to find the angle between the ketone groups for a flat nucleus with the ketone groups in the plane of the nucleus. This angle is found to be 138°, which is 25° larger than the angle calculated from the observed moment of the compound. It is apparent that the molecule does not have this configuration.

The concept of a flat steroid nucleus has been based in part on a fairly general but what we believe to be an erroneous concept in regard to cyclohexane. In many organic text-books are to be found statements essentially like the following: "However, no isomeric forms of cyclohexane or its derivatives have been isolated with certainty up to the present time. It seems probable that there is an equilibrium between the two forms of such molecules and that the two structures vibrate from one to the other so rapidly that the net average result is a planar molecule."[7]

Two lines of evidence in the literature rule out this concept in regard to cyclohexane. Pitzer[8] and co-workers have found that there is an energy hump of about 3000 calories in ethane and other hydrocarbons when the hydrogen atoms on adjacent carbon atoms are opposed as compared with the staggered position. Now in the boat form of cyclohexane there are two opposed CH_2 pairs at the ends of the boat which would cause the boat form to be unstable with respect to the chair form, in which all the CH_2 pairs are staggered, by about 6000 calories. In addition there is an indication of considerable steric hindrance between two hydrogen atoms across the top of the boat which would add, say, another 1000–4000 calories. Thus the boat form would have from 7000–10,000 calories more energy than the chair form. The percentage of the compound in the boat form in equilibrium with the chair form at 25° is then $10^{-3} - 5 \times 10^{-6}\%$. It is apparent that if the compound is an equilibrium mixture between the boat and chair forms, the compound is 99.999% in the chair form and the boat form is present in such small amounts that the over-all shape of the molecule is not going to be appreciably altered by its presence.

Aston and co-workers[9] have found the symmetry number of cyclohexane to be six which likewise means that the molecule must be in the chair form. The boat form would have a symmetry number of two and the flat molecule a symmetry number of twelve. Thus both lines of evidence show that cyclohexane exists as the chair form with each carbon staggered with respect to its neighbor.

When several cyclohexane rings are present in a condensed nucleus such as the steroid nucleus the same factors that keep the carbon atoms staggered in cyclohexane itself would cause the carbon atoms in the six-membered rings of the condensed nucleus to be staggered as well.

In the case of cyclopentane the molecule would be expected to be flat on the basis of the Bayer strain theory since the angle in a pentagon, 108°, is less than the tetrahedral angle of 109°28′ and any puckering of the ring would introduce additional strain. However, a flat molecule would have five opposed CH_2 pairs which would give rise to considerable instability due to repulsions of the hydrogen atoms. Of these two opposing effects apparently the latter is the stronger because two lines of evidence[9,10] indicate that cyclopentane is not flat.

When cyclopentane is linked *trans* to a chair form of a cyclohexane ring considerable strain would be involved unless one or more of the CH_2 pairs in cyclopentane were staggered. The predominant chemical evidence is that the C and D rings in steroids are linked *trans* so if that is the union actually present there evidently is not too much strain in such a linkage.

The chemical evidence also indicates that the A/B and B/C rings in the six hormones are also linked *trans*. We will now assume that all the rings are linked *trans*, each cyclohexane ring is in the chair form with the carbon atoms staggered and at least one of the carbon atoms in the cyclopentane ring is out of the plane of the rest of the D ring. In such a model the nucleus is essentially flat except for the thickening resulting from the staggering of the carbon atoms. A plane can be passed through this molecule and half the carbon atoms in the A, B and C rings are above it and half of them below the plane. The carbon–oxygen double bond in the 3-ketone group as a consequence of the staggered carbon atoms in the A ring makes an angle of 35° with the plane through the nucleus. The direction of the 17-ketone carbon–oxygen double bond with respect to this plane depends on whether there are one or two atoms out of the plane of the D ring. If just one is out then that atom and one of its neighbors would be involved in the link with the C ring and the ketone would be approximately in this plane. On the other hand if two atoms were out of the plane then the carbon–oxygen bond of the ketone group could be at an angle to this plane.

A check can be obtained on this from the angle of 113° between the ketone groups in androstanedione-3,17 and the angle between the ketone groups of 138° when they are in the plane of the nucleus. It is extremely unlikely that the observed angle of 113° in the actual compound is acquired by altering the direction of the ketone

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(7) Gilman, "Organic Chemistry," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 321.

(8) Kemp and Pitzer, THIS JOURNAL, **59**, 276 (1937); Pitzer and Gwinn, *ibid.*, **63**, 3313 (1941); Pitzer, *Science*, **101**, 672 (1945).

(9) Aston, Schumann, Fink and Doty, THIS JOURNAL, **63**, 2029 (1941); Aston, Fink, Schumann, *ibid.*, **65**, 341 (1943).

(10) Rosenbaum and Jacobson, *ibid.*, **63**, 2841 (1941).

groups in the plane of the nucleus. This would involve an alteration of bond distances and angles that demand forces so large as to make such a situation virtually impossible. On the other hand the angle of 113° could be achieved in a quite reasonable way by tilting the ketone groups up from the plane of the nucleus. We have already seen that the 3-ketone group is tilted at an angle of 35° to the plane of the nucleus if we assume a chair form for the cyclohexane rings. One can tell whether the 17-ketone group is tilted or not by calculating the angle one ketone group would have to be tilted up with respect to the other to make the angle between the groups be the observed value of 113°. The amount of tilt required is found to be 55°. It therefore appears that the 17-ketone group is tilted up from the plane of the nucleus at an angle of $55° - 35° = 20°$. This suggests that two of the atoms in the D ring may be out of the plane of the ring.

Effect of a Double Bond on the Shape of the Nucleus.—A calculation of the angle between the ketone groups in Δ^4-androstenedion-3,17 from its observed moment of 3.32[2] gives a value of 125°. In making this calculation a value of 3.96[2] was used for the moment of the 3-ketone group conjugated with a double bond. The double bond thus increases the angle between the ketone groups by $125° - 113° = 12°$. The presence of the double bond flattens the A-ring and it also causes the distance between the 4 and 5-carbon atoms to be less. Both effects would increase the angle between the ketone groups. In the previous paper[2] by comparing the moments of β-androsterone, 2.95, and Δ^4-androstenol-3β-one-17, 2.46, it was concluded a double bond in the Δ^5-position likewise appreciably altered the shape of the nucleus.

Recently Carlisle and Crowfoot[11] completed a detailed analysis of the structure of cholesteryl iodide from X-ray measurements and their findings are in accord with the structure for the steroid nucleus which fits the dipole moment data. Thus they find the carbon atoms staggered except the ones attached to the double bond which causes the 4, 5, 6 and 10 carbon atoms to be almost in one plane. They also find the A, B, C and D rings to be essentially in one plane except for the thickening of the molecule resulting from the staggering of the carbon atoms.

Dimethyl-androstanediol Isomers.—Some indication is given by the dipole moment data in regard to which dimethyl-androstanediol (Fr. A) or (Fr. B) is the 3α-hydroxy compound and which is the 3β-compound. 17-Methyltestosterone, 4.17 has a moment 0.15 unit less than testosterone, 4.32. Likewise 17-methyl-Δ^5-androstendiol-3β,-17α, 2.78, has a moment 0.11 unit less than Δ^5-androstenediol-3β,17α, 2.89. If this lowering of the moment can be assumed to take place when methyl groups are substituted in the androstanediols then the (Fr. A) compound is the 3α-hydroxy compound and (Fr. B) the 3β-hydroxy compound, for then both dimethyl compounds have lower moments than the corresponding parent compounds. On the other hand this would no longer be true if (Fr. A) were the 3β-hydroxyl compound and (Fr. B) the 3α-compound.

Also it will be observed that in the parent compounds the one with both hydroxyl groups α has the lower moment. For this to hold with the methyl derivative the (Fr. A) compound must be the 3α-hydroxyl compound. Thus one arrives at the same conclusion by either line of approach.

Sapogenins.—Three sapogenins have been measured. The compound with one hydroxyl group, tigogenin, 2.36, has a moment 0.55 unit higher than the moment of dihydrocholesterol. The two ether linkages thus contribute about 0.5 unit to the moment of the compound. The other sapogenins with two hydroxyl groups each, gitogenin, 2.64, and chlorogenin, 2.67, have the same moments within the experimental error. The structures that have been assigned to these compounds have the hydroxyl groups on the 2,3 and the 3,6-carbon atoms. The fact that the compounds have the same moment is not proof that the assignment of the positions of the hydroxyl groups is incorrect because the predominant evidence is that the hydroxyl groups in steroids do not have freedom of rotation so they could be oriented in such a way that both compounds have the same moment although the groups are on different carbon atoms. It is a rather marked coincidence that the two compounds should have both the same melting point and the same dipole moment and yet have different structures.

Experimental

Materials.—The following compounds were obtained from Dr. C. R. Scholz of Ciba Pharmaceutical Products Inc.

Compound	M. p., °C.
Androstanediol-3α,17α	220–222
Androstanediol-3β,17α	166.4–167.2
Androstanedione-3,17	132.0–132.6
17-Methyl-Δ^5-androstenediol-3β,17α	198–201
17-Methyl-testosterone	161.5–163
3,17-Dimethyl-androstane-ol-17α	180–181
3,17-Dimethyl-androstadiene-ol-17α	147–150
3,17-Dimethyl-androstanediol-3,17α (Fr. A)	205–208
3,17-Dimethyl-androstanediol-3,17α (Fr. B)	222–225

The following sapogenins were obtained from Professor C. R. Noller of Stanford University.

Compound	M. p., °C.
Tigogenin	198–203
Gitogenin	268–271
Chlorogenin	267–271

Cholesterol.—Cholesterol from the Eastman Kodak Company was brominated[12] and the prod-

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[11] Crowfoot, "Vitamines and Hormones," Vol. II, Academic Press, Inc., New York, N. Y., 1944, p. 409.

[12] Schoenheimer, *Z. physik. Chem.*, **192**, 77 (1930).

uct washed with alcohol. The cholesterol dibromide was then debrominated with sodium iodide[13] and the cholesterol recrystallized from alcohol, m. p. 146.7–147.5°.

Dihydrocholesterol.—This compound was prepared from cholesterol by the method given in "Organic Syntheses."[14] It had a melting point of 142.0–142.6°.

Dioxane.—Dioxane was purified as before.[1]

Acknowledgment.—We are grateful to Dr. C. R. Scholz of Ciba Pharmaceutical Products Inc. for supplying nine steroids and to Professor C. R. Noller of Stanford University for the three sapogenins used in this study.

Summary

The dipole moments of fourteen steroids were found to be as follows: dihydrocholesterol, 1.81; cholesterol, 1.99; androstanediol-3α,17α, 2.29; androstanediol-3β,17α, 2.99; androstanedione-3,17, 3.25; 17-methyl-Δ^5-androstenediol-3β,17α, 2.78; 17-methyl-testosterone, 4.17; 3,17-dimethyl-androstane-ol-17α, 2.06; 3,17-dimethyl-androstadiene-ol-17α, 1.81; 3,17-dimethyl-androstanediol-3,17α (Fr. A), 2.14; 3,17-dimethyl-androstanediol-3,17α (Fr. B), 2.39; tigogenin, 2.36; gitogenin, 2.64; chlorogenin, 2.67.

Five of the six compounds in the group which have a hydroxyl and one other polar group in the molecule have moments outside the values calculated for free rotation, indicating that either the 3α or the 17α positions are hindered in addition to the 3β and 17β positions which were found to be hindered in the previous work.

The angle between the ketone groups in androstane-dione-3,17 was found to be 113°. This angle is inconsistent with a flat nucleus with the ketone groups in the plane of the ring. It is consistent with a structure in which the carbon atoms are staggered, *i. e.*, the cyclohexane rings are in the chair form, the A/B, B/C and C/D rings are linked *trans*, the 3-ketone group is at an angle of 35° to a plane which can be placed through all the rings, and the 17-ketone is at an angle of 20° to this plane.

The angle between the ketone groups in Δ^4-androstenedione-3,17 is 125°. The double bond thus appreciably changes the shape of the nucleus.

The fact that 3,17-dimethyl-androstane-ol-17α has a moment about 0.2 unit higher than that of dihydrocholesterol suggests that a hydroxyl group attached to a five-membered ring has a higher moment than one attached to a six-membered ring.

Some evidence is obtained in regard to the structure of the two 3,17-dimethyl-androstanediol-3,17α isomers.

Gitogenin and chlorogenin have the same dipole moment within the experimental error.

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[13] Schoenheimer, *J. Biol. Chem.*, **110**, 461 (1935).

[14] "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 191.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AT THE OHIO STATE UNIVERSITY]

Directed Chlorination of Aliphatic Fluorides

BY ALBERT L. HENNE, JAMES B. HINKAMP AND WILFORD J. ZIMMERSCHIED

Preceding papers[1,2,3,4] have shown that a CF_3 group and, to a smaller extent, a CF_2 group, direct chlorination away from the hydrogen atoms linked to a carbon alpha to the fluorinated group.

Fluoroform, CHF_3, is very slowly chlorinated to CF_3Cl but the operation can be carried out in quartz when brilliant illumination is provided.[5] Methyl fluoroform, CF_3CH_3, offers a marked lag to chlorination in sunlight, but when the chlorination starts it proceeds directly to completion and yields CF_3CCl_3 uncontaminated by either CF_3CHCl_2 or CF_3CH_2Cl; when chlorination is tried on the latter it proceeds without delay and makes CF_3CCl_3 at once.[6] Trifluoropropane, $CF_3CH_2CH_3$ goes very easily and stepwise to $CF_3CH_2CCl_3$, then after much lag, but in one step, directly to $CF_3CCl_2CCl_3$.[2] These observations illustrate the fact that alpha hydrogens are protected against chlorination, though only as long as the carbon atom that bears them does not carry a halogen atom also.

More examples of the directing effect are now listed, and advantage has been taken of this property to synthesize with ease some specific compounds. The experimental operations, such as hydrogen fluoride addition, halogen exchange, substitution of hydrogen by chlorine, were performed in the manner reported in our previous papers.

Ethylidene fluoride, CHF_2CH_3, was synthesized by quantitative addition of hydrogen fluoride to vinyl fluoride, and subjected to the action of gaseous chlorine in sunlight. This chlorination yielded 70% of CF_2ClCH_3, 6% of CF_2ClCH_2Cl, but no CHF_2CH_2Cl whatever; the reaction products were actually isolated in pure state. To account for the experimental results, the following working hypothesis is proposed: (1) The CF_2 cluster is electronegative, hence the lone hydrogen

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[1] Henne and Renoll, THIS JOURNAL, **59**, 2434 (1937).

[2] Henne and Whaley, *ibid.*, **64**, 1157 (1942).

[3] Henne and Hinkamp, *ibid.*, **67**, 1195 (1945).

[4] Henne and Hinkamp, *ibid.*, **67**, 1197 (1945).

[5] Henne, *ibid.*, **59**, 1200 (1937).

[6] Henne and Renoll, *ibid.*, **58**, 887 (1936).