*Anal.* Calcd. for $C_{26}H_{32}O_3$: C, 79.55; H, 8.22. Found: C, 79.64; H, 8.07.

**3β-Hydroxyandrost-4-en-17-one** (1).—The benzoate **4** (725 mg.) was hydrolyzed overnight with 5% potassium hydroxide in aqueous methanol under a nitrogen atmosphere. The solution was diluted with water and the product was extracted into ethyl acetate, washed with sodium bicarbonate solution and with water, dried over sodium sulfate, and evaporated to an oil. Repeated crystallizations from hexane gave the analytical sample of 3β-hydroxyandrost-4-en-17-one (**1**, 198 mg., 37% yield based on 3β-benzoyloxyandrost-4-en-17-one) m.p. 133.5–134° undepressed on admixture with an authentic sample[21] (lit.[3] m.p. 128.5–130°); $[\alpha]_D$ +134°; $\lambda_{max}$ no selective absorption; $\nu_{max}$ 3450 (hydroxyl), 1744 (17-ketone), and 854 cm.$^{-1}$ (C=C—H); n.m.r. $\delta = 0.88$ (singlet), 1.08 (singlet), 1.55 (singlet), 4.1 (probably quintet), and 5.32 (doublet, 1H) p.p.m.

*Anal.* Calcd. for $C_{19}H_{28}O_2$; C, 79.12; H, 9.79. Found: C, 78.98, 78.54; H, 7.92, 9.53.

The pure allylic alcohol in ethanol solution slowly underwent oxidation to androst-4-ene-3,17-dione. However, it was stable in the crystalline state. Exposure to acid or passage through a gas–liquid chromatograph or alumina column partially dehydrated the compound to form a substance corresponding in mobility to androsta-3,5-dien-17-one.

3β-Hydroxyandrost-4-en-17-one (1) was precipitated by digitonin.[22]

**Androst-4-ene-3,17-dione.**—The allylic alcohol **1** (47 mg.) was dissolved in dioxane (twice distilled from sodium), and 2,3-dichloro-5,6-dicyanobenzoquinone (55 mg.) was added. After standing overnight the mixture was diluted with methylene chloride and applied to a column of activity III alumina (3 g.), and the steroids were eluted with methylene chloride (150 ml.). The product was shown by thin layer chromatography (cyclohexane–ethyl acetate, 3:1) to contain at least 95% androst-4-ene-3,17-dione, with only traces of a more mobile and of a less mobile compound. A single crystallization from acetone yielded androst-4-ene-3,17-dione: m.p. 170–172°, undepressed on admixture with an authentic sample of m.p. 169–172°; $\lambda_{max}$ 240 mμ (ε 17,300); the infrared spectrum was identical with that of authentic material.

**Androsta-3,5-dien-17-one.**—The allylic alcohol **1** (96 mg.), was refluxed under nitrogen with 5 *N* sulfuric acid (7 ml.) and 95% ethanol (20 ml.) for 45 min. Water was added and the reaction mixture was extracted with ethyl acetate, washed with water, and dried with sodium sulfate. The solvent was evaporated and the residue was shown to be homogeneous by gas chromatography and thin layer chromatography (ether–benzene, 2:1). Crystallization from methanol gave androsta-3,5-dien-17-one: m.p. 85–89° (lit.[23] m.p. 88–89°); $\lambda_{max}$ 243 mμ (ε 10,700), 235 (15,800), and 228 (14,000); $\nu_{max}$ 1743 cm.$^{-1}$ (17-ketone), no free hydroxyl band.

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[21] We thank Dr. Joseph S. Mihina of G. D. Searle and Co. for the sample of 3β-hydroxyandrost-4-en-17-one.

[22] L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 30.

[23] H. Burrows, J. W. Cook, E. Roe, and F. L. Warren, *Biochem. J.*, **31**, 950 (1937).

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# Conformational Analysis. XXXIX. The Conformations of Ring A in Bromo Derivatives of Cholestan-3-one and Related Compounds[1,2]

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*Received October 4, 1963*

The preferred conformations of ring A for a variety of 2- and 4-methylated and brominated steroids have been predicted by *a priori* calculations. In a number of cases the predictions have been checked by experimental measurements, mainly dipole moments and optical rotatory dispersion. The 5-halocholestan-3-ones were also studied.

The previous paper in this series discussed the various possible conformations of cyclohexanone rings and developed methods for the *a priori* calculation of such conformations as they occur in more complicated systems, including in particular methylated derivatives of cholestanone.[1] There are a number of cholestanone derivatives known with bromine at C-2 or C-4, or halogen at C-5, and the conformations of these compounds form the subject of the present paper. Because of the presence of two dipoles, the halo ketones present some complicating features not found in the methyl derivatives studied earlier, but they are experimentally more amenable to study by various physical methods. Most of the necessary numerical data required are available or deducible from earlier studies on cholestanones and/or α-halo ketones. The β-halo ketones require, in addition, the evaluation of the electrostatic interactions between dipoles. The present objectives are to illustrate how the *a priori* calculations for these systems can be carried out, and to make predictions for a variety of systems. In a number of cases these predictions have then been tested experimentally.

The starting point for the calculations was the parent molecule, cholestan-3-one. The conformational energy of the chair form, relative to an arbitrary zero based on cyclohexanone, can be taken as 1.8 kcal./mole, the energy of the C-19 methyl axial to ring A. The second conformation to be considered for cholestanone is the flat chair, in which C-3 has moved upward approximately into the plane of C-1, C-2, and C-4. The energy of this form was calculated to be 3.0 kcal./mole using the methods and numbers developed earlier (the interactions and their corresponding energies are given in Table I). This value is sufficiently close to that of the undeformed chair that it may be expected that the conformation of minimum energy will be between those of the chair and the flat chair, but much nearer the former, and the ordinary chair will therefore be used herein as the best approximation to the real chair.

Lastly, the flexible form of ring A must be considered. Following earlier methods,[1] the various interaction energies as functions of θ were calculated (Table I). The sum of these energies yields a conformation of minimum energy of 4.4 kcal./mole for the flexible form at about θ = 35°, which will again show a wide and unsymmetrical pseudo-rotation, leaning somewhat toward higher values of θ. The flexible form will have a greater entropy than the rigid forms, and this will

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[1] Paper XXXVIII: N. L. Allinger, J. Allinger, and M. A. DaRooge, *J. Am. Chem. Soc.*, **86**, 4061 (1964).

[2] This investigation was supported by Public Health Service Research Grant A-5836 from the National Institute of Arthritis and Metabolic Diseases.

TABLE I

CALCULATED CONFORMATIONAL FREE ENERGIES OF CHOLESTANONE DERIVATIVES

| | Chair | Flat | Boat 0° | Boat 30° | Boat 60° |
|---|---|---|---|---|---|
| Compd. **1** | | | | | |
| C-19 Me/C-4 β-H | 0.9 | 0.2 | 0 | 0.2 | 0.9 |
| C-19 Me/C-2 β-H | 0.9 | 0.2 | 0 | 0 | 0 |
| C-4/C-5 torsion | 0 | 1.7 | 0.5 | 0.2 | 0 |
| C-1/C-2 torsion | 0 | 1.4 | 0 | 0 | 0 |
| Carbonyl torsion | 0 | −1.6 | ... | ... | ... |
| Angle def. | 0 | 1.3 | 0 | 0 | 0 |
| C-1/C-10 torsion | 0 | 0 | 0 | 0.5 | 1.0 |
| C-19 Me/C-3 | 0 | 0 | 3.0 | 0 | 0 |
| Ring | 0 | 0 | 6.3 | 2.9 | 2.1 |
| | 1.8 | 3.2 | 9.8 | 3.8 | 4.0 |
| Compd. **3** | | | | | |
| Parent **1** | 1.8 | 3.2 | 9.8 | 3.8 | 4.0 |
| Electrostatic | 1.0 | 0.5 | 0 | 0 | 0 |
| C-1/C-2 torsion | 0 | 0.3 | 0.7 | 0.4 | 0 |
| 2-α Br/4-α H | 0 | 0 | 0.2 | 0 | 0 |
| 2-α Br/5-α H | 0 | 0 | 0 | 0 | 0.6 |
| | 2.8 | 4.0 | 10.7 | 4.2 | 4.6 |
| Compd. **8** | | | | | |
| Parent **3** | 2.8 | 4.0 | 10.7 | 4.2 | 4.6 |
| 2-Me/19-Me | 3.7 | 0.9 | 0 | 0 | 0 |
| 2-Me/4-β H | 0.8 | 0.2 | 0 | 0 | 0 |
| 19-Me/2-β H | −0.9 | −0.2 | 0 | 0 | 0 |
| C-1/C-2 torsion | 0 | 0.3 | 0.5 | 0.3 | 0 |
| | 6.4 | 5.2 | 11.2 | 4.5 | 4.6 |

affect the conformational free energy. For a somewhat more flexible cyclohexanone,[3] the flexible form has a greater entropy than does the chair by 2.5 e.u.; so we will estimate the flexible form to have the greater entropy by 2 e.u. At room temperature, then, the chair has a more negative free energy than does the flexible form by 1.9 kcal./mole. This means that at room temperature cholestanone will have about 4% of the ring A flexible form in equilibrium with the chair.

The results of *a priori* calculations of the conformations of compounds **1**–**14** are summarized in Table II and were carried out by the same general method, and a sample calculation is included in Table I. Most of the necessary data are given in the previous paper.[1] Other pertinent facts are that electrostatic energy of an equatorial bromine exceeds that of the axial by the following amounts (kcal./mole) in various solvents[4]—heptane 1.4, benzene 1.0, dioxane 0.8, dimethyl sulfoxide 0.6; the flat chair is taken to have an electrostatic energy half-way between that of the boat and chair under the same conditions; and the rotational barrier of ethyl bromide is 3.6 kcal./mole[5] or 0.7 kcal. above the value used for ethane. The calculations are for benzene solution and are free energies, 2 e.u. being allowed for the flexible boat forms, except for compounds **7** and **12**, where there is not much flexibility, and only 1 e.u. is added.

In cases where the two major conformations have different resultant dipole moments, a shift of the equilibrium in the direction of the conformation of lower dipole moment will occur if the solvent is changed from benzene to something less polar, and in the other direction if it is made more polar.[4,6] In most cases (compounds **1**–**7**) the amount of ordinary chair form is predicted to be present to the extent of about 90% or more, and such a situation is at present usually indistinguishable experimentally from pure chair (see I) conformation (Table III). Such experimental evidence as was available in the literature for these cases was examined and was consistent with 90–100% chair form. We chose to investigate some of these cases experimentally for various reasons, which follow.

TABLE II

PREDICTED CONFORMATIONS FOR SUBSTITUTED CHOLESTANONES (I) IN BENZENE SOLVENT

| | Substituents[a] | | | | |
|---|---|---|---|---|---|
| | C-2 | | C-4 | | |
| Compd. | Axial | Equatorial | Axial | Equatorial | Predicted forms |
| **1** | | | | | 96% chair, 4% boat |
| **2** | | Me | | | 96% chair, 4% boat |
| **3** | | Br | | | 87% chair, 13% boat |
| **4** | Br | | | | 93% chair, 7% boat |
| **5** | | | Br | | 98% chair, 2% boat |
| **6** | Br | Br | | | 88% chair, 12% boat |
| **7** | Br | Me | | | 98% chair, 2% boat |
| **8** | Me | Br | | | 23% flat chair, 77% boat |
| **9** | | Br | Me | Me | 85% flat chair, 15% boat |
| **10** | Br | | Me | Me | 30% flat chair, 70% boat |
| **11** | Me | Br | Me | Me | 34% flat chair, 66% boat |
| **12** | Br | Me | Me | Me | 50% flat chair, 50% boat |
| **13** | Br | Br | Me | Me | 30% flat chair, 70% boat |
| **14** | | | Me | Me | 80% flat chair, 20% boat |

[a] If no substituent is listed, hydrogen is assumed.

TABLE III

EXPERIMENTAL DATA FOR SUBSTITUTED CHOLESTANONES (I)[a]

| Compd. | Ultraviolet $\lambda_{max}$, mμ (ε) | Infrared, cm.$^{-1}$ | O.R.D., [A] | μ, D. |
|---|---|---|---|---|
| | | | +57.8 M | 3.10$^{b}$ |
| **1** | 287 (15) D | 1703 | +46.0 D | |
| | 280 (25) | 1719 H | +37.9 | |
| **2** | 280 (40) | | +63 E | 3.50 H |
| | 283 (35) D | 1702 | | 3.00 B |
| | | 1716 H | | 3.07 D |
| **3** | | | +41 E | 4.22 H |
| | 280 (51) | 1723 | +35 | 4.31 B |
| | 285 (30) D | 1735 H | | 4.41 D |
| **4** | | 1720 | | |
| **5** | 308 (133) | | −83.80 F | 3.51 |
| | 312 (116) D | 1704 | −92.9 | |
| **6** | 294 (135)$^{c}$ | 1732 C$^{d}$ | +186 D$^{e}$ | |
| **7** | 308 (115)$^{f}$ | 1712$^{f}$ | +281 D$^{f}$ | |
| **8** | | | −136 E | 3.24 H |
| | 310 (135) | 1708 | −178 H | 3.31 B |
| | 313 (129) D | 1717 H | | 3.34 D |
| **9** | 287 (30)$^{g}$ | 1724 C$^{g}$ | −22.7 M$^{g}$ | *h* |
| **10** | 285 (45)$^{g}$ | 1727 C$^{g}$ | +75 M$^{g}$ | |
| **13** | 318 (95) H$^{i}$ | 1709 L$^{i}$ | −(>22) D$^{i}$ | |

[a] Unless otherwise stated ultraviolet spectra are in 100% ethanol, infrared and n.m.r. spectra in chloroform, O.R.D. in cyclohexane or hexane, and dipole moments in benzene. The following symbols are used for solvents: H, hexane or cyclohexane; C, carbon disulfide; D, dioxane; E, 100% ethanol; M, methanol; L, methylene chloride; F, chloroform. Many of the values reported here have been determined earlier by others. For the sake of self-consistency we have employed our own values whenever possible. [b] Ref. 1. [c] Ref. 16. [d] Ref. 24. [e] Ref. 11. [f] Ref. 12. [g] Ref. 20b. [h] See text. [i] Ref. 23.

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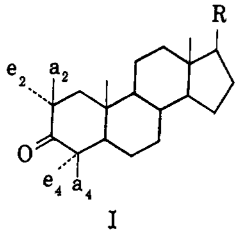
(3) N. L. Allinger and H. M. Blatter, *J. Am. Chem. Soc.*, **83**, 994 (1961).

(4) N. L. Allinger, J. Allinger, and N. A. LeBel, *ibid.*, **82**, 2926 (1960).

(5) D. R. Lide, Jr., *J. Chem. Phys.*, **30**, 37 (1959).

(6) J. Allinger and N. L. Allinger, *Tetrahedron*, **2**, 64 (1958).



I

Beginning with cholestanone itself, its conformation is assumed to be solvent independent, although many of its properties (infrared, ultraviolet, rotatory dispersion) do vary with solvent. Similarly, the conformation of 2$\alpha$-methylcholestanone (**2**) should be solvent independent. This was checked by measuring the dipole moment of this compound in heptane, benzene, and dioxane. The values obtained were 3.05, 3.00, and 3.07 D., respectively, with probable errors of about ±0.02 D. Hence the dipole moment of the compound appears to be almost independent of solvent, and there is no systematic change of the moment with solvent polarity. Next, the dipole moment of 2$\alpha$-bromocholestanone (**3**) was determined in the solvents mentioned previously, and gave values of 4.22, 4.31, and 4.41 D., respectively. The variation here is small but definite, and, when contrasted with 2-methylcholestanone and other conformationally homogeneous compounds[7] such as *cis*-2-fluoro-4-*t*-butylcyclohexanone and *trans*-2-bromo-4-*t*-butylcyclohexanone, this variation clearly indicates an equilibrium between two forms differing in polarity. From the energetics of the system, *a priori* calculations indicate that the amount of boat form expected is 9% in dioxane, 13% in benzene, and 20% in heptane.[1] From the dipole moment of cholestanone (3.10 D.)[1] and cyclohexyl bromide (2.24 D.),[4] assuming that the mutual induction in the equatorial conformer will reduce these values to 2.93 and 1.91 D.[8] and assuming idealized bond angles, the dipole moment calculated[9] utilizing Dreiding models for the ordinary equatorial (chair) conformation is 4.3 ± 0.2 D. For the boat forms, similar calculations gave 3.0 and 2.7 D. for $\theta = 0$ and 60°, respectively, and a value of 2.8 D. is perhaps a good approximation to the present case. We do not know the moments of the individual conformations sufficiently well (about ±0.2 D.) to calculate the per cent of them in the mixture with much accuracy. The observed moment shows clearly that we have a strong predominance of the chair form. We can try to decide if the variation of dipole moment with solvent is reasonable in the following way. If we accept a moment of 2.80 D. for the boat conformation, and accept the calculated value of 13% boat at equilibrium in benzene, from the observed moment (4.31 D.) we can calculate that the chair conformation must have a moment of 4.50 D. In heptane solution there should be 20% boat, in dioxane 9%; so the moments in these solvents calculated from the above numbers should be 4.20 and 4.36 D., respectively (found 4.22 and 4.41). The variation and, in fact, the numbers themselves are in quite reasonable agreement with experiment. The conclusions drawn from the dipole moments are consistent with the predictions, but are only qualitatively convincing as the amount of boat form is so small as to be right at the limit of detection. The ultraviolet spectrum of the compound shows a small augmentation in the extinction coefficient, and the rotatory dispersion curve shows a small amplitude shift with solvent in the predicted direction, but again the changes are too small to be definitive. The n.m.r. spectrum shows the C-2 proton as a quartet as expected for the chair form.

Compound **4**, the 2$\beta$-bromocholestanone, is known from literature[10] data to have its halogen largely in the axial position. This compound proved to be very difficult to prepare and was rather unstable. We were able to confirm the reported position of the carbonyl absorption in the infrared,[10] but further studies were carried out on 4$\beta$-bromocholestanone (**5**),[10] which is more easily handled, and for which essentially the same conformational situation is predicted. The observed moment was somewhat larger than that of an ordinary axial halo ketone, 3.51 D. *vs.* 3.20 D. for *trans*-2-bromo-4-*t*-butylcyclohexanone,[4] but, as the repulsion between the bromine and the 19-methyl would be expected to bend the C–Br bond more toward the C=O plane, the observed increase in moment is not evidence for the boat form. The other available measurements are also consistent with most of the molecules in the ordinary chair form (Table III).

The information available for **6** is uninformative except for its Cotton effect curve.[11] The reported amplitude (+186) is very much larger than that of cholestanone and shows the compound must be very largely in the chair form since the amplitude of the curve would be small or negative for flat or boat forms.

Compounds **7** and **8** form an interesting pair, and earlier studies[12] have shown conclusively that **7** is largely in the chair form while **8** is largely boat. The present calculations proceed in the following way (see Table I). The repulsion between *syn*-diaxial methyls is 3.7 kcal./mole,[13] while that between similarly oriented methyl and bromine is only 2.5 kcal./mole.[14] In addition there is an electrostatic energy of 1 kcal./mole[8] that tends to keep the bromine axial, and thus favors the chair for **7** and the boat for **8**. The repulsion between the 2$\beta$-methyl and the 4$\beta$-hydrogen is 0.8 kcal./mole,[3,15] while the corresponding energy for the bromine compound is only 0.2 kcal./mole. All of these energies together favor the boat form in **8** by 3.8 kcal./mole more than in **7**. The experimental evidence for the conformation of **7** is quite consistent with largely the chair form.[12] Compound **8**, on the other hand, yielded the more interesting prediction of a more stable boat form, for which there is qualitatively convincing experimental evidence.[12] More significantly, the theory indicated a mixture, containing an appreciable amount (23%) of

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[7] (a) N. L. Allinger and H. M. Blatter, *J. Org. Chem.*, **27**, 1523 (1962); (b) L. Chow, unpublished.

[8] N. L. Allinger, J. Allinger, L. A. Freiberg, R. Czaja, and N. A. LeBel, *J. Am. Chem. Soc.*, **82**, 5876 (1960).

[9] N. L. Allinger, M. A. DaRooge, M. A. Miller, and B. Waegell, *J. Org. Chem.*, **28**, 780 (1963).

[10] I. Malunowicz, J. Fajkos, and F. Sorm, *Collection Czech. Chem. Commun.*, **25**, 1359 (1960).

[11] C. Djerassi, J. Osiecki, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **80**, 1216 (1958).

[12] (a) C. Djerassi, N. Finch, R. C. Cookson, and C. W. Bird, *ibid.*, **82**, 5488 (1960); (b) C. Djerassi, N. Finch, and R. Mauli, *ibid.*, **81**, 4997 (1959).

[13] N. L. Allinger and M. A. Miller, *ibid.*, **83**, 2145 (1961).

[14] L. Chow and G. Wang, unpublished.

[15] B. Rickborn, *J. Am. Chem. Soc.*, **84**, 2414 (1962).

the minor component. This, then, was a case susceptible to a definitive experimental test. The infrared and ultraviolet spectra, the rotatory dispersion curve, and the dipole moment of the compound were all determined in various solvents. Since the conformation with the axial halogen has a much higher extinction coefficient in the ultraviolet,[16] this method shows only that considerable axial halogen is present. The infrared spectrum shows a shift of the carbonyl frequency of +1 cm.$^{-1}$ in cyclohexane and +7 cm.$^{-1}$ in chloroform, which is consistent with a substantial per cent of equatorial halogen in chloroform, and very little in cyclohexane.[6,17] Somewhat more convincing is the variation of the amplitude of the rotatory dispersion curve with solvent.[18] The amplitude is $-178$ in cyclohexane, and shifts to $-136$ in alcohol. The change in amplitude is over twice that of cholestanone itself (see below), and it is consistent with a quite high percentage of boat in heptane, and somewhat less in alcohol.

It would be difficult to attach numbers to the conformational compositions detected by the spectroscopic methods for various reasons, and we have not attempted to do so. The dipole moment is a more quantitative measurement. Using the observed moments of 2-methylcholestanone (3.00 D.) and of 1-bromo-1-methylcyclohexane (2.26 D.), the type of calculation described for 2$\alpha$-bromocholestanone led to calculated values for the moments of the boat and chair forms of 2.8 and 4.5 D., respectively. The observed moments were 3.24, 3.31, and 3.34 in heptane, benzene, and dioxane, indicating that the boat conformation predominated to the extent of 75 ± 12% in benzene, and there was the small anticipated solvent shift, as predicted by the theory.

As confirmation of the above conclusions, 2$\alpha$-bromo-2$\beta$-methylandrostane-3,7-dione (**7a**) was also studied. For this compound the moments calculated for the chair, 0° boat, and 60° boat were 4.7, 2.9, and 2.3 D., respectively. The 35° boat is estimated to have a calculated moment of about 2.6 D. Assuming the equilibrium can be calculated on the basis of only the chair and 35° boat, the observed moment (3.63 D.) indicates that the latter predominates to the extent of 58 ± 12% in satisfactory agreement with the values from the cholestane derivatives and from theory.[19]

Predictions were made for **9** and **10**, again for which qualitative data exist in the literature.[20] In both cases the flat chair is predicted to be better than the ordinary chair, as with 4,4-dimethylcholestanone (**14**) itself.[21] The flat chair is at an energy minimum, while the ordinary chair is merely on the slope of the energy curve, an extreme reached occasionally by the vibration of the flat chair. The flat chair should predominate over the boat in **9**, and the reverse is predicted for **10**. The evidence available is qualitatively in agreement with the predictions.

Compounds **9**[22] and **10** show Cotton effect curves of amplitude $-22.7$ and $+75$, compared to the parent value of $-11$. The bromine in **9** should make a negative contribution, whether the compound is in the flat chair or boat form, and this is what is observed. In **10** the bromine should make a positive contribution in either the boat of chair form, again as observed. It is noted that the O.R.D. extrema occur at a much longer wave length in **9** than in **10**. In the boat form of **9** the bromine is truly axial, and the effect is pronounced even though the amount of boat is rather small. In **10**, the flat chair has the bromine quasi-axial, and the observed effect is much smaller. Compound **10** is of historical interest since it was the first known case of a molecule actually preferring to exist in a boat form.[20a]

Predictions have been made for **11** and **12**, although the compounds do not yet appear to be known. Compound **13** has been studied in some detail by earlier workers.[23,24] The infrared and ultraviolet spectra are not informative, but the compound is known to exhibit a negative Cotton effect. The ordinary chair would exhibit a positive Cotton effect, while that of the flat chair should be near zero, and for the boat it should be strongly negative, and the observations are thus in agreement with the predictions.

These calculations can also be used to predict the positions of the equilibria between epimers. Thus **4** should be converted to **3**, **8** to **7**, and **10** to **9**. The available numbers would apply to dilute solutions in pure benzene, and such experimental data as are available refer to various other reaction conditions, but appear to be qualitatively correct in each case.[12,20a]

It is noteworthy that conformational equilibria appear to exist with substantial amounts of more than a single form in quite a number of cases. The existence of an equilibrium, if not recognized, may render certain kinds of conformational conclusions questionable. The significance of coupling constants in the n.m.r. spectra might be especially misleading in such cases, and we regard **10** as a probable example of such a case. It has been concluded[25] that ring A in 2$\beta$-bromolanost-3-one has a conformation intermediate between the classical boats with $\theta = 60°$ and 0°, but nearer the latter. The calculations suggest it is quite close to 30°, but slightly nearer the former. The presence of a substantial amount of the flat chair, as calculated, could easily lead to the observed coupling constants.

As part of a study of the effects of halogen substituents on optical rotatory dispersion behavior in $\beta$-halo ketones, Barnes and Djerassi[26] recently examined the rotatory dispersion curves of 5$\alpha$-halocholestan-3-ones. It was observed that the halogen substituents progressively reduced the molecular amplitude with increasing atomic weight. This diminution is to be

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(16) R. C. Cookson, *J. Chem. Soc.*, 282 (1954).

(17) (a) R. N. Jones, D. A. Ramsay, F. Herling, and K. Dobriner, *J. Am. Chem. Soc.*, **74**, 2828 (1952); (b) E. J. Corey, *ibid.*, **75**, 2301 (1953).

(18) (a) N. L. Allinger, J. Allinger, L. E. Geller, and C. Djerassi, *J. Org. Chem.*, **25**, 6 (1960); (b) C. Djerassi, L. E. Geller, and E. J. Eisenbraun, *ibid.*, **25**, 1 (1960).

(19) Subsequent to the preparation of this manuscript, Professor Djerassi informed us that this compound shows a circular dichroism curve which becomes more strongly negative with decreasing temperature, consistent with the above conclusions.

(20) (a) D. H. R. Barton, D. A. Lewis, and J. F. McGhie, *J. Chem. Soc.*, 2907 (1957); (b) G. R. Chaudhry, T. G. Halsall, and E. R. H. Jones, *ibid.*, 2725 (1961).

(21) N. L. Allinger and M. A. DaRooge, *J. Am. Chem. Soc.*, **84**, 4561 (1962).

(22) In ref. 20b in the discussion part of the paper this amplitude is referred to as having the value +20, but the data given in the Experimental corresponds to an amplitude of $-22.7$, and we assume this later value is the correct one.

(23) H. P. Sigg and C. Tamm, *Helv. Chim. Acta*, **43**, 1402 (1960).

(24) E. G. Cummins and J. E. Page, *J. Chem. Soc.*, 3847 (1957).

(25) R. J. Abraham and J. S. E. Holker, *ibid.*, 806 (1963).

(26) C. S. Barnes and C. Djerassi, *J. Am. Chem. Soc.*, **84**, 1962 (1962).

expected in the case of fluorine, since this element lies below hydrogen in the atomic refractivity and specific rotativity scales. Chlorine and bromine, however, should have caused a shift the reverse of that observed, provided that the A ring of such compounds is in the chair conformation. To explain the observed results, Barnes and Djerassi have proposed that ring A in $5\alpha$-chloro- and $5\alpha$-bromocholestan-3-ones is "distorted toward a boat-like conformation."[26] The driving force for the distortion was considered to arise from electrostatic and steric repulsions between the carbonyl and the halogen.

As auxiliary evidence for the existence of a nonchair form, Barnes and Djerassi reported a change in amplitude of the rotatory dispersion curve of $5\alpha$-chlorocholestan-3-one with solvent, an effect which could be attributed to an equilibrium of conformers of differing polarity.[6,18] While nonchair conformers of ring A in these compounds might explain the observed rotatory dispersion curves, the evidence was not completely conclusive; moreover, the proposed driving force (an axial halogen, known to have a small conformational energy,[27] and the interaction of two rather distant dipoles) did not appear to be sufficient to bring about such a conformational change. Since the calculation described above appeared to give good results with $\alpha$-bromocholestanones, they were extended to the $\beta$-halo compounds.

The effect on the conformational energies that would result from replacing the $5\alpha$-hydrogen by the different halogens was first considered. The halogen suffers a repulsion from the C-1 $\alpha$-hydrogen and from C-3, both of which could be relieved if the molecule were in a boat form with $\theta$ between about 15 and 45°. From a van der Waals calculation[28] by the Hill method[29] these energies each amount to about 0.2 kcal./mole for chlorine, and these values are consistent with its known small conformational energy. The corresponding calculated energies are negligible for fluorine, and about 0.4 kcal./mole for bromine. The latter can be reduced in bromocyclohexane itself by bending the bromine away from the ring,[30] but here the halogen is sufficiently surrounded by various atoms that such a relief of strain in the chair form does not appear possible; so the calculated energies were used.

A possibly important interaction in the halogen compound is the electrostatic repulsion between the dipoles. This type of electrostatic repulsion has been studied previously.[6,31] An error in the original equations has recently been pointed out,[32] and the corrected equations were used in the present work. The effective dielectric constants required for solution of the equations were obtained utilizing the known equilibrium constants for the 2-halocyclohexanones[8] allowing for the steric energy and adjusting the electrostatic energy to fit experiment. In fact the effective dielectric constants for heptane and benzene turned out to be close to the bulk values, and dioxane was somewhat more polar, the numerical values being 1.86, 2.48, and 3.83, respectively. As a rather good approximation one should be able to calculate the electrostatic interactions of the $5\alpha$-halo 3-ketones using the same methods and these effective dielectric constants. The resulting electrostatic energies for the different halogen derivatives of the flexible form in different solvents vary only slowly with $\theta$. The energy minimum of the flexible form will therefore still be near $\theta = 40°$. If the electrostatic and steric energies for the halogen interactions are now added to the conformational energies for the cholestanone framework, the total conformational energy of each form is obtained for each different halogen, and these data are summarized in Table IV.

The predictions made from Table IV are that, while cholestanone itself contains only a few per cent of molecules in which ring A is in the flexible form ($\theta$ near 35°), (a) substitution of an $\alpha$-halogen at C-5 will increase the amount of flexible form in the equilibrium, and the increase will be greater for chlorine than for fluorine, and still greater for bromine; and (b) the position of equilibrium with the halogenated derivatives will be solvent dependent, the fraction in the flexible form increasing as the effective dielectric constant of the solvent decreases. The shift should be larger in the order bromine > chlorine > fluorine.

We have now replaced our intuitive guesses by numerical predictions for these systems and note that the behavior of the Cotton effect curves reported previously are qualitatively what would be anticipated from these predictions. We wished next to try to obtain additional (hopefully quantitative) experimental evidence to test the predictions, and the resultants of the two dipoles, both for the fluoro and chloro steroids, were calculated as previously described.[9] The dipole moment of $5\alpha$-fluorocholestan-3-one in benzene and of $5\alpha$-chlorocholestan-3-one both in benzene and in heptane were measured, and the calculated and observed moments are as shown in Table V.

It is somewhat unfortunate that the equilibrium is as one sided as it is in those systems, since it cannot be measured with sufficient accuracy to provide a stringent test of the calculations. The change in dipole moment with solvent shows there is some nonchair form present, and the magnitude of the moments themselves shows the amount is small.

TABLE IV

TOTAL CALCULATED CONFORMATIONAL ENERGIES OF $5\alpha$-HALOCHOLESTAN-3-ONES IN BENZENE SOLUTION[a]

| | $\Delta F°$, kcal./mole | | | |
|---|---|---|---|---|
| | 5-$\alpha$ H | 5-$\alpha$ F | 5-$\alpha$ Cl | 5-$\alpha$ Br |
| Chair (c) | 1.8 | 2.7 | 3.3 | 3.8 |
| Flexible (f)[b] | 3.7 | 4.4 | 4.8 | 4.9 |
| $c \rightleftharpoons f$ | +1.9 | +1.7 | +1.5 | +1.1 |

[a] $\Delta F°$ for cholestanone is solvent independent, and for the others is about 0.1 kcal./mole less in heptane and 0.1 kcal./mole greater in dioxane. [b] $\theta = 40°$.

TABLE V

CALCULATED AND EXPERIMENTAL DIPOLE MOMENTS OF $5\alpha$-HALOCHOLESTANONES

| | Calcd. | | | Obsd. | |
|---|---|---|---|---|---|
| Halogen | Chair | $\theta = 0°$ | $\theta = 60°$ | Benzene | Heptane |
| Fluorine | 4.21 | 1.56 | 3.25 | 4.02 | . . . |
| Chlorine | 4.44 | 1.41 | 3.38 | 4.25 | 4.15 |

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(28) N. L. Allinger and W. Szkrybalo, *J. Org. Chem.*, **27**, 4601 (1962).

(29) T. L. Hill, *J. Chem. Phys.*, **16**, 399 (1948).

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(32) J. Lehn and G. Ourisson, *Bull. soc. chim. France*, 1113 (1963).

TABLE VI

O.R.D. MOLECULAR AMPLITUDES

| Solvent | Cholestanone | 5α-Fluoro-cholestanone | 5α-Chloro-cholestanone |
|---|---|---|---|
| Cyclohexane | 37.9 | 24.8 | 6.2[a] |
| Dioxane | 46.0 | 29.8 | 11.6 |
| Methanol | 57.8 | 41.0 | 22.1 |

[a] Measured in isooctane.[26]

TABLE VII

| Compd. | M.p., °C. | Ref. |
|---|---|---|
| 2α-Methylcholestan-3-one | 119.5–120 | *a* |
| 2α-Bromo-2β-methylcholestan-3-one | 136.5–137 | *b* |
| 2α-Bromocholestan-3-one | 166–167.5 | *c* |
| 2β-Bromocholestan-3-one | 122.5–124 | *d* |
| 4β-Bromocholestan-3-one | 100–100.5 | *d* |
| 4,4-Dimethylcholestan-3-one | 99–101 | *e* |

[a] Ref. 12. [b] Y. Mazur and F. Sondheimer, *J. Am. Chem. Soc.*, **80**, 5220 (1958). [c] L. F. Fieser and X. A. Dominguez, *ibid.*, **75**, 1704 (1953). [d] Ref. 10. [e] R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *J. Am. Chem. Soc.*, **76**, 2852 (1954).

The rotatory dispersion curve of 5α-fluorocholestan-3-one was measured in two solvents of differing polarity, cyclohexane and methanol, and compared with the curve measured in dioxane as published.[26]

A 50% increase in amplitude over the range from cyclohexane to methanol was observed (Table VI). In the past such a change in the amplitude of a rotatory dispersion curve has always indicated a conformational equilibrium.[18] Since the change in this case was not very large, the rotatory dispersion curve for cholestanone itself was determined as a function of solvent, and it showed a similar variation. The change is in the opposite direction to that expected from ketal formation, and is unquestionably real.[33] Such a change is theoretically reasonable, since an asymmetric ketone will solvate asymmetrically, and the solvent therefore enters into the various octants and should have an effect. Alternatively, a preferential solvation of the carbonyl of one conformation may yield a shift in the conformational equilibrium, even for cholestanone. It is surprising that no such effect has been previously observed. The shift found with the 5α-fluoro compound is similar to that found with cholestanone and suggests a conformational parallelism in the two molecules. The change in the amplitude of the cotton effect curve of the 5α-chloro derivative with solvent previously reported[26] is again similar, and this suggests that the solvent is exerting a very similar effect in each case. With the chloro compound the striking feature is not the change in amplitude with solvent, but rather the fact that the amplitude is so small. The matter does not seem worth further speculation at this time.

## Experimental

Most of the compounds used in the present work were obtained by standard procedures and had the properties reported in Table VII.

**2α-Bromo-2β-methylandrostane-3,17-dione.**—2α-Bromo-2β-methylandrostan-17-ol-3-one[34] was oxidized with chromium trioxide in acetic acid by the method used for the preparation of 2β-bromocholestan-3-one.

TABLE VIII

DIPOLE MOMENT DATA, 25°

| Cholestan-3-one | MR | Solvent[a] | $\alpha$ | $\epsilon_1$ | $d_1$ | $\beta$ | $P_{2\infty}$ | $\mu$, D. |
|---|---|---|---|---|---|---|---|---|
| 2α-Methyl- | 123.38 | B | 12.530 | 2.2756 | 0.87350 | 0.432 | 307.5 | 3.00 ± 0.03 |
| 2α-Methyl- | 123.38 | D | 13.570 | 2.2229 | 1.02799 | 0.302 | 315.8 | 3.07 ± 0.02 |
| 2α-Methyl- | 123.38 | H | 7.628 | 1.9137 | 0.67925 | 0.870 | 314.0 | 3.05 ± 0.02 |
| 2α-Methyl- | 123.38 | H | 7.587 | 1.9133 | 0.67955 | 0.892 | 311.6 | 3.03 + 0.02 |
| 2α-Bromo- | 126.45 | B | 26.257 | 2.2715 | 0.87322 | 1.284 | 505.7 | 4.31 ± 0.03 |
| 2α-Bromo- | 126.45 | D | 27.714 | 2.2062 | 1.02794 | 0.382 | 523.5 | 4.41 ± 0.03 |
| 2α-Bromo- | 126.45 | H | 13.764 | 1.9142 | 0.67923 | 1.329 | 490.3 | 4.22 ± 0.02 |
| 4β-Bromo- | 126.45 | B | 17.717 | 2.2727 | 0.87312 | 1.368 | 377.5 | 3.50 ± 0.02 |
| 2α-Bromo-2β-methyl- | 131.10 | B | 15.346 | 2.2767 | 0.87355 | 1.124 | 354.6 | 3.31 ± 0.07 |
| 2α-Bromo-2β-methyl- | 131.10 | D | 16.187 | 2.2257 | 1.02763 | 0.388 | 359.1 | 3.34 ± 0.03 |
| 2α-Bromo-2β-methyl- | 131.10 | H | 8.644 | 1.9137 | 0.67954 | 1.364 | 345.3 | 3.24 ± 0.02 |
| 2α-Bromo-2β-methylandrostane-3,17-dione | 93.88 | B | 17.753 | 2.2750 | 0.87354 | 0.906 | 363.1 | 3.63 ± 0.03 |
| 5α-Fluoro- | 118.50 | B | 22.684 | 2.2740 | 0.87304 | 0.722 | 449.4 | 4.02 ± 0.02 |
| 5α-Chloro- | 123.56 | B | 25.342 | 2.2731 | 0.87313 | 0.780 | 492.4 | 4.25 ± 0.01 |
| 5α-Chloro- | 123.56 | H | 13.353 | 1.9147 | 0.67925 | 1.070 | 476.2 | 4.15 ± 0.01 |

[a] B = benzene, H = heptane, D = dioxane.

**5α-Fluorocholestan-3-one** prepared from cholesteryl acetate by the published procedure had m.p. 148.5–149° (lit.[26] m.p. 150–151°) after crystallization from methylene chloride–methanol; O.R.D. ($c$ 0.039, methanol) $[\theta]_{400}$ +280°, $[\theta]_{305}$ +2880°, $[\theta]_{283}$ ±0°, $[\theta]_{270}$ −1222°; O.R.D. ($c$ 0.038, cyclohexane) $[\theta]_{400}$ +90°, $[\theta]_{319}$ +1060°, $[\theta]_{297}$ ± 0°, $[\theta]_{273}$ −1420°.

**5α-Chlorocholestan-3-one** was prepared according to Barnes and Djerassi,[26] m.p. 99–100° (lit.[26,35] m.p. 102°, 135°, 150°) from acetone.

**Cholestan-3-one** was crystallized twice from acetone and had m.p. 131–131.5°; O.R.D. ($c$ 0.037, methanol) $[\theta]_{400}$ +443°, $[\theta]_{308}$ +3280°, $[\theta]_{288}$ ±0°, $[\theta]_{270}$ −2500°; O.R.D. ($c$ 0.038, cyclohexane) $[\theta]_{400}$ +525°, $[\theta]_{320}$ +2606°, $[\theta]_{298}$ ±0°, $[\theta]_{280}$ −1182°.

**Dipole moments** of the various ketones were run at 25° in benzene solution using the dipole moment apparatus described previously.[36] The moments were calculated by essentially the method of Halverstadt and Kumler,[37] utilizing an IBM 7070 computer programmed as described earlier.[38] The molar re-

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(33) This change has been confirmed by C. Djerassi at our suggestion.

(34) R. Mauli, H. J. Ringold, and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 5494 (1960).

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fractivities were obtained from tables,[39] and atomic polarization was neglected.[1] The data are summarized in Table VIII.

**Acknowledgment.**—The authors are indebted to Mr. J. Maul and to Dr. L. Tushaus for some of the rotatory dispersion measurements and to Mr. C. L. Neumann for some of the dipole moment measurements. The authors are also indebted to Dr. M. Emerson for the n.m.r. spectra and helpful discussion regarding them. Experimental approaches to problems similar to some of these reported in this paper have been independently carried out by Drs. A. K. Bose, M. S. Manhas, and E. R. Malinowski, Stevens Institute of Technology; Dr. J. Lehn and Professor G. Ourisson, Universite de Strasbourg; and by Drs. R. J. Abraham and J. S. E. Holker, University of Liverpool. The authors are indebted to them for information regarding their work prior to publication.

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# Fluorocarbon Peroxides. Synthesis and Characterization of *cis*- and *trans*-Perfluoro-3,5-dimethyl-1,2-dioxolane

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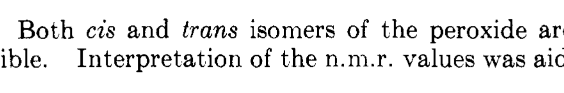
*Received December 28, 1964*

The reaction of fluorine with the copper(II) or the nickel(II) chelate of hexafluoroacetylacetone under mild conditions gives the fluorocarbon cyclic peroxide, perfluoro-3,5-dimethyl-1,2-dioxolane, as a mixture of the *cis* and *trans* isomers. The characterization of the peroxide is described.

With the exception of perfluorodimethyl peroxide,[1] fluorine-containing dialkyl peroxides have received little attention. This paper reports the synthesis and characterization of a member of a new class of organic fluorine-containing compounds, the cyclic fluorocarbon alkyl peroxides.

The reaction of elemental fluorine with the copper(II) or the nickel(II) chelate of hexafluoroacetylacetone gives a volatile, oxidizing liquid readily isolated by vapor phase chromatography. The elemental composition and molecular weight of the product are consistent with the formula $C_5F_{10}O_2$. Quantitative determination of the oxidizing power toward potassium iodide indicates the presence of one oxidizing group capable of undergoing a two-electron change. The infrared spectrum has no strong absorption bands in the region 2.5–7.3 $\mu$, suggesting the absence of any carbon–carbon unsaturation, carbonyl groups, or epoxide functions. Complex absorption peaks are observed in the $F^{19}$ n.m.r. spectrum of this material in the region 75–135 $\phi^*$, but there are no other absorption peaks. The proton n.m.r. spectrum of a 69% solution of this substance shows no absorption, indicating that the hydrogen in the starting material has been replaced by fluorine. The only structure consistent with these results is the cyclic structure, perfluoro-3,5-dimethyl-1,2-dioxolane.[2]



$$(CF_3\overset{\overset{O}{\|}}{C}CH{=}\overset{\overset{O^-}{|}}{C}CF_3)_2M \xrightarrow{F_2} CF_3\overset{\overset{O}{|}}{C}FCF_2\overset{\overset{O}{|}}{C}FCF_3 \qquad (1)$$
$$M = Cu(II), Ni(II)$$

Both *cis* and *trans* isomers of the peroxide are possible. Interpretation of the n.m.r. values was aided by the fact that both isomers were observed in varying ratios in different samples, although the isomer ratio of freshly prepared samples is reproducibly somewhat greater than two, with the *cis* isomer present in greater amount. Assignment of the peak positions can be made with certainty (see Table I), because the *cis* isomer in several samples decomposed, leaving only the *trans* isomer and the decomposition products. The area ratios are consistent with the assignments. In the *cis* isomer the fluorines of the $CF_2$ group are magnetically nonequivalent. The presence of an AB pattern in the n.m.r. spectrum for the *cis* isomer is consistent with this nonequivalence. The *trans* isomer does not exhibit an AB pattern under the conditions used to obtain the spectrum.

The chemical properties of perfluoro-3,5-dimethyl-1,2-dioxolane provide further support for the structure assignment. A freshly prepared sample (a mixture of the isomers) was stored in the gas phase in a clean, well-dried borosilicate glass bulb at room temperature in the absence of air. Decomposition was noticeable after 1 day. After 3 days over half of the *cis* isomer had decomposed, while the *trans* isomer remained. After 10 days all of the *cis* isomer had decomposed, but the *trans* isomer was still present in the mixture after 12 weeks. After several months the *trans* isomer was also observed to have decomposed. The major product found was trifluoroacetyl fluoride, while lesser amounts of trifluoroacetic acid, difluoromethyl trifluoroacetate,[3] silicon tetrafluoride, and small amounts of an unidentified material were also observed. Formation of the acid fluoride is explained by cleavage of the molecule at one or both of the positions indicated by the broken lines in eq. 2. The acid itself might have been formed by reaction of the acid fluoride with adventitious moisture at the surface of the glass, and this reaction would also explain the

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[1] F. Swarts, *Bull. soc. chim. Belges*, **42**, 102 (1933); R. S. Porter and G. H. Cady, *J. Am. Chem. Soc.*, **79**, 5628 (1957); R. T. Holzmann and M. S. Cohen, *Inorg. Chem.*, **1**, 972 (1962); R. A. Darby and E. K. Ellingboe, U.S. Patent 3,069,404 (1962).

[2] For recent publications regarding substituted hydrocarbon cyclic peroxides, see N. A. Milas, O. L. Mageli, A. Golubović, R. W. Arndt, and J. C. J. Ho, *J. Am. Chem. Soc.*, **85**, 222 (1963); A. Rieche and C. Bischoff, *Chem. Ber.*, **96**, 2607 (1963); G. B. Payne, *J. Org. Chem.*, **26**, 4793 (1961), and references cited therein.

[3] The preparation of $CF_3CO_2CF_2H$ has been reported by N. N. Yarovenko, M. A. Raksha, V. N. Shemanina, and A. S. Vasilyeva [*J. Gen. Chem. USSR*, **27**, 2305 (1957)].