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Optical Rotatory Dispersion Studies. LXXI.[1] Halogen Atoms and the Octant Rule. The Conformations of Some 5α-Halocholestan-3-ones[2]

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Until now only the rotatory contribution of halogen atoms adjacent to a carbonyl group has been studied and this has led to the previously enunciated α-haloketone rule. Introduction of halogen atoms (chlorine, bromine and iodine) β and/or γ to a keto group, as in 5- and/or 6-halogenated cholestan-3-ones, has led to unexpected rotatory dispersion results. In the case of the 5α-bromo- and 5α-chloro-3-ketones, as well as their 5α,6-dihalo analogs, this has been interpreted in terms of a conformational distortion from the chair toward a boat-like conformation, the driving force being ascribed to electrostatic repulsion. The negative contribution of 6β-halo-3-ketones is attributed to the location of the halogen atom in a negative octant. The distinct role of fluorine, as compared to the other halogens, is again pointed out.

Our earlier systematic study[4] of the effect of α-halogen substitution upon the rotatory dispersion behavior of cyclohexanones has led to the "axial haloketone rule,"[5] a generalization which has proved to be of considerable utility[6,7] in the solution of a variety of stereochemical problems, notably in the area of detection of subtle conformational changes. Subsequently, it was shown that the tenets of the axial haloketone rule[5] are incorporated in the octant rule,[8] which encompasses substituents other than halogen. By attributing quantitative values to certain substituents, the octant rule has been used with considerable success in the solution of several conformational problems[9] and it seemed to us very pertinent to attempt to accumulate such data for halogen substituents which are not adjacent to a carbonyl group. The main difficulty in such a projected study was assumed to lie in the relative instability of such substances, notably the β-halo ketones, and the requirement for optical activity. It is for this reason that we concentrated on halogenated steroidal ketones, as a number of crystalline β- and γ-substituted halo-ketones or halo-alcohols were known, while related ones could be prepared by similar procedures.

A suitable source of β-halo-ketones is available in the addition of hydrogen halides to the double bond of cholesterol (or cholesteryl acetate) followed by oxidation of the hydroxy group to give the 5α-halocholestan-3-ones, the rotatory dispersion curves of which can then be compared with that of cholestan-3-one (I). For the preparation of 5α-fluorocholestan-3-one (II), it was found essential to use cholesteryl acetate which was exposed to hydrogen fluoride affording 5α-fluorocholestan-3β-ol acetate. The fluorine atom in this compound proved very stable to lithium aluminum hydride reduction in ether and the free alcohol formed in that reaction was easily oxidized with chromium trioxide in acetic acid to give the relatively stable II.

The addition of hydrogen chloride to cholesterol followed by oxidation has been used to form 5α-chlorocholestan-3-one (III),[10] while a similar method with hydrogen bromide has been employed in the preparation of 5α-bromocholestan-3-one (IV)[11]; that the halogen atom had added at the 5-position as expected from Markownikoff's rule has already been shown[11] for the bromo-ketone IV by dehydrobromination to the unsaturated ketone, Δ⁴-cholesten-3-one. A similar proof for the fluoro-ketone II is described in the Experimental section. Mechanistic considerations[12] require further that the halogen atom will have the 5α-axial configuration and this is confirmed by the X-ray analysis of 3β,5α-dichlorocholestane[13] which is formed in a manner analogous to the above examples by the addition of hydrogen chloride to the double bond of cholesteryl chloride.[14]

The octant rule correctly predicts[8] that cholestan-3-one (I) itself should have a positive Cotton effect, since the significant substituents lie in a positive octant. Furthermore, since a 5α-substituent is also located in this same octant, the 5α-halocholestan-3-ones (II, III and IV) should, if the ring system retains the all-chair conformation, have positive Cotton effects of increased amplitude. In fact this proved not to be so, since in each case it was found (Table I, Fig. 1) that the halogen substituent made a progressively more negative contribution with increasing atomic weight of the halogen atom. Thus the positive molecular amplitude ($a = +46$)[15] of cholestan-3-one (I) was reduced to +30 by a 5α-fluorine (II), to +12 by a

(1) Paper LXX, B. Sjöberg, D. J. Cram, L. Wolf and C. Djerassi, *Acta Chem. Scand.*, in press.

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(3) Postdoctorate research fellow on leave from the C. S. I. R. O. Chemical Research Laboratories, Melbourne, Australia.

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

(5) C. Djerassi and W. Klyne, *ibid.*, **79**, 1506 (1957).

(6) C. Djerassi, "Optical Rotatory Dispersion: Applications to Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, Chapter 9.

(7) *Inter al.*, (a) C. Djerassi, N. Finch, R. C. Cookson and C. W. Bird, *J. Am. Chem. Soc.*, **82**, 5488 (1960); (b) D. T. Cropp, B. B. Dewhurst and J. S. E. Holker, *Chemistry & Industry*, 209 (1961).

(8) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 4013 (1961).

(9) (a) C. Djerassi, E. J. Warawa, J. M. Berddahl and E. J. Eisenbraun, *ibid.*, **83**, 3334 (1961); (b) C. Djerassi, E. Lund and A. A. Akhrem, *ibid.*, **84**, 1249 (1962); (c) C. Djerassi and W. Klyne, *J. Chem. Soc.*, in press, (1962); (d) C. Beard, C. Djerassi, T. Elliott and R. C. Tao, *J. Am. Chem. Soc.*, **84**, in press (1962).

(10) A. Butenandt, A. Schramm, A. Wolf and K. Kudszus, *Ber.*, **69**, 2779 (1936).

(11) J. Urushibara and S. Mori, *J. Chem. Soc. Japan*, **64**, 1285 (1943).

(12) G. H. Alt and D. H. R. Barton, *J. Chem. Soc.*, 4284 (1954).

(13) J. D. Bernal, D. Crowfoot and I. Fankuchen, *Philos. Trans. Roy. Soc. (London)*, **A239**, 135 (1940).

(14) J. Mauthner, *Monatsh.*, **27**, 305 (1906).

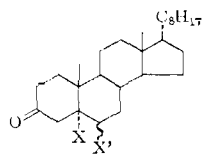
(15) Molecular amplitudes, a, are divided for the sake of convenience by 100: $a = ([\phi]_{\text{first extremun}} - [\phi]_{\text{second extremun}}) \times 10^{-2}$.

5α-chlorine (III) and to +6 by a 5α-bromine (IV) substituent.

In the case of fluorine, a negative contribution is to be expected since this atom lies below hydrogen in the atomic refractivity and specific rotativity[16] scales. Indeed, axial α-fluoroketones have been shown[4] to exhibit a rotational contribution, which is opposite to that of chlorine, bromine or iodine. However, with the 5α-chloro and 5α-bromo substituents (III, IV), it is apparent that some other effect is operating, since these atoms lie in a positive octant if the ring system remains in an all-chair form. We propose, therefore, that ring A is actually distorted toward a boat-like conformation[17] where two effects may operate. First, in the ideal case of a full-boat conformation, the ring A substituents including the 5α-halogens now lie in a negative octant and so make a negative contribution of a magnitude depending on their position in the specific rotativity scale.[16] The driving force for this conformational change can be expected to arise from the repulsive interaction through space of the relatively closely located partial negative charges on the carbonyl oxygen and the halogen atom, while the absence of a 3β-substituent removes the possibility of the destabilizing interaction which would otherwise occur between it and the angular methyl group. Secondly, although the relative orders of the inductive effects might suggest a greater repulsive interaction from chlorine than from bromine, and hence a greater contribution to the boat form with a larger negative contribution to the Cotton effect from a chlorine atom, the greater size of the electron cloud of the bromine atom would in fact bring its charge closer to the carbonyl oxygen than would be the case with chlorine. Consequently, the conversion to the boat form might be more complete with a bromine substituent than with a chlorine substituent and the negative contribution to the Cotton effect would be greater in the case of the former. In actual fact, either one or both of these factors may be operating and it is impossible to state at this time definitely which one is responsible for the quantitative differences observed (Fig. 1 and Table I) between III and IV. Furthermore, it is also possible that III and IV exist as a mixture of chair and boat-like conformers, the actual equilibrium being different in the chloro (III) as compared to bromo (IV) ketone.

TABLE I

OPTICAL ROTATORY DISPERSION PROPERTIES OF HALOGENATED CHOLESTAN-3-ONES



Substance			Molecular rotation × 10⁻² (dioxane) — Peak		Trough		
	X	X'	λ, mμ	[φ] × 10⁻²	λ, mμ	[φ] × 10⁻²	Amplitude
I	H	H	320	+28°	279	−18°	+46
II	F	H	318	+20	270	−10	+30
III	Cl	H	310	+12	274	± 0	+12
IV	Br	H	300	+ 5	270	− 1	+ 6
V	Cl	(β)Cl	270	− 3	309	−11	− 8
VI	Br	(β)Br	270	− 8	307	−41	−33
VII	Cl	(α)Cl	280	+ 1	317	− 3	− 4
VIII	Br	(β)Cl	277	− 6	312	−21	−15
IX	F	(α)F	312	+14	275	− 2	+16
X	F	(β)I	280[a]	−13	315	−21	−8 (incompl.)
XI	H	(β)Br	310	− 1	260	−11	+10

[a] This represents the lowest wave length measured, rather than the peak which could not be reached because of absorption associated with the iodine atom.

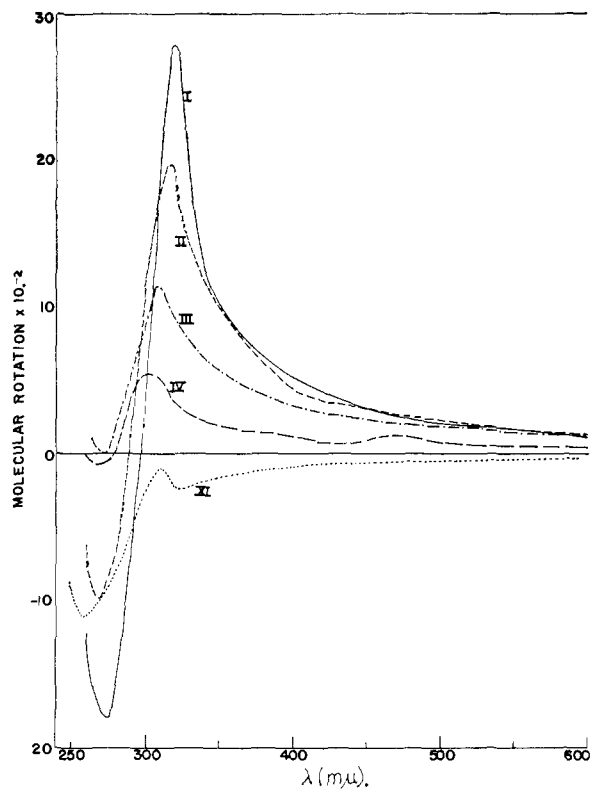


Fig. 1.—Optical rotatory dispersion curves (dioxane solution) of cholestan-3-one (I), 5α-fluorocholestan-3-one (II), 5α-chlorocholestan-3-one (III), 5α-bromocholestan-3-one (IV) and 6β-bromocholestan-3-one (XI).

The next class of substituted cholestan-3-ones to be examined possessed halogens at both the 5α- and 6-positions. The 5α,6β-dichloro-(V)[18] and 5α,6β-dibromo-(VI)[19] cholestan-3-ones are readily available by the addition of the corresponding halogens to cholesterol, followed by chromium trioxide oxidation in acetic acid solution, the configuration of the halogens having been shown beyond doubt.[20] Both dihalo-ketones V and VI showed negative Cotton effects (Table I, Fig. 2) with the dibromo ketone VI having an amplitude (−33) greater than that (−8) of the dichloro analog V. The additional negative contribution of the 6β-halogen in each of these examples can now be attributed to its presence in a negative octant, because of the above discussed distortion produced

(16) See footnote 11 in ref. 8.

(17) See preliminary note by C. S. Barnes and C. Djerassi, *Chemistry & Industry*, 177 (1962).

(18) D. H. R. Barton and E. Miller, *J. Am. Chem. Soc.*, **72**, 370 (1950).

(19) A. Butenandt and J. Schmidt-Thomé, *Ber.*, **69**, 882 (1936).

(20) D. H. R. Barton and E. Miller, *J. Am. Chem. Soc.*, **72**, 1066 (1950).

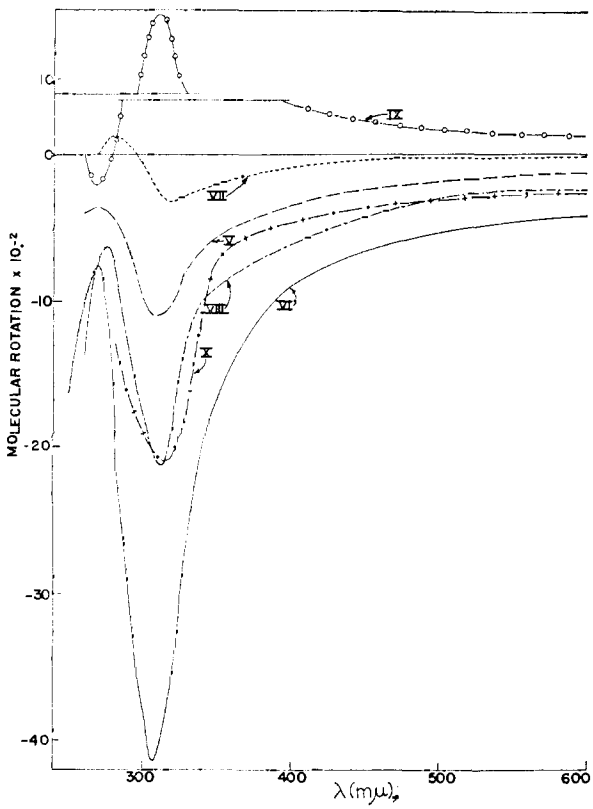


Fig. 2.—Optical rotatory dispersion curves (dioxane solution) of 5α,6β-dichlorocholestan-3-one (V), 5α,6β-dibromocholestan-3-one (VI), 5α,6α-dichlorocholestan-3-one (VII), 5α-bromo-6β-chlorocholestan-3-one (VIII), 5α,6α-difluorocholestan-3-one (IX) and 5α-fluoro-6β-iodocholestan-3-one (X).

in ring A by the 5α-halogen. Similarly 5α,6α-dichlorocholestan-3-one (VII), prepared by oxidation of the known[18] alcohol, has the 6α-chlorine atom in this same octant, and shows (Table I, Fig. 2) a negative Cotton effect.

On the basis of the arguments outlined above, it can be predicted that 5α-bromo-6β-chlorocholestan-3-one[21] (VIII) should have a greater negative amplitude than either 5α,6β-(V) or 5α,6α-(VII) dichlorocholestan-3-one for the same reason that 5α-bromocholestan-3-one (IV) has a more negative Cotton effect than 5α-chlorocholestan-3-one (III). Furthermore, the mixed dihalide VIII should have a less negative Cotton effect than 5α,6β-dibromocholestan-3-one (VI) because of the smaller rotatory contribution of the 6β-chloro-substituent in VIII, as compared to the 6β-bromo-substituent in VI. In agreement with these views, the amplitude of VIII (−15, Table I, Fig. 2) lies between that of VI (−33) and either V (−8) or VII (−4).

In view of the unusual position of fluorine in the rotativity scale,[16] it seemed of interest to examine some dihalo-ketones containing fluorine. Using lead tetrafluoride,[22] fluorine was added in a *cis* manner[22] to the double bond of cholesteryl acetate to give 5α,6α-difluorocholestan-3β-ol acetate which was converted to the corresponding ketone IX by standard methods. Elimination of the 5α-fluorine atom of IX gave the known 6α-fluoro-Δ⁴-cholesten-3-one.[23] The reduced amplitude (+16, Table I, Fig. 2) of the Cotton effect of 5α,6α-difluorocholestan-3-one (IX) in comparison with that (+30, Table I, Fig. 1) of 5α-fluorocholestan-3-one (II) can be accounted for by the negative contribution of the 6α-fluorine atom which occurs in a positive octant in an all-chair ring system.[24]

Addition of F–I to the double bond of cholesteryl acetate occurred in the manner described by Bowers, *et al.*,[25] for pregnenolone acetate to give 5α-fluoro-6β-iodo-cholestan-3β-ol acetate which was converted to the corresponding ketone X by the usual saponification and oxidation procedure. In contrast to the other 5α-fluoro ketones (II, IX), 5α-fluoro-6β-iodocholestan-3-one (X) had a strong negative Cotton effect (Fig. 2), the full amplitude of which could not be determined because the second extremum was obscured by the increasing absorption of the iodine atom. This strong negative contribution of the iodine substituent is attributed in an all-chair system[24] to the protrusion of the iodine atom[26] into a negative octant where it exerts a powerful effect in keeping with its position on the specific rotativity scale.[16] This argument was confirmed by examination of 6β-bromocholestan-3-one (XI)[27] which also showed that the 6β-bromine atom made a strong negative contribution (amplitude +10 *vs.* cholestan-3-one +46) although C-6 lies in a positive octant. Here again we consider that the bromine atom extends beyond into the negative octant.[26]

Recently Jacquesy and Levisalles[28] examined the rotatory dispersion curves of 5α-chloro-(III), 5α,6β-dichloro-(V), 5α,6β-dibromo-(VI) and 6β-bromo-(XI) cholestan-3-ones and commented on the negative contribution of the halogens in each example. No precise explanation was given for the negative rotatory contribution of the 5α-halogen in 5α-chlorocholestan-3-one (III), but it was tentatively suggested that the chlorine atom might protrude into a negative front octant. Examination of models shows clearly that this could not be so and the conformational change of ring A described above offers a more satisfactory explanation. Indeed, support for our proposal comes from a study of the rotatory dispersion of 5α-chlorocholestan-3-one (III) in methanol, dioxane and isoöctane solutions. If the conformational change suggested above is really due to electrostatic repulsion, then one would expect[29]

(21) J. B. Ziegler and A. C. Shabica, *J. Am. Chem. Soc.*, **74**, 4891 (1952).

(22) A. Bowers, P. G. Holton, E. Denot, M. C. Loza and R. Urquiza, *ibid.*, **84**, in press (1962); A. Bowers, E. Denot and R. Urquiza, *Tetrahedron Letters*, No. **20**, 34 (1960).

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

(24) As noted above, we assume a chair conformation for II in contrast to the deformation of ring A in III and IV, with fluorine making an opposite-sign rotatory contribution as compared to the other substituents.

(25) A. Bowers, E. Denot and R. Becerra, *J. Am. Chem. Soc.*, **82**, 4007 (1960).

(26) L. Pauling ("The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1945, 2nd edit., p. 167) quotes 2.10 Å. and 1.91 Å. as the length of the C–I and C–Br bonds as compared to 1.54 Å. for a C–C bond.

(27) C. W. Shoppee and R. Lack, *J. Chem. Soc.*, 4864 (1960).

(28) J. C. Jacquesy and L. Levisalles, *Chemistry & Industry*, 1310 (1961).

(29) J. Allinger and N. L. Allinger, *Tetrahedron*, **2**, 64 (1958); see

an increased proportion (and hence a more negative Cotton effect) of the boat-like conformer in a nonpolar medium (isoöctane and dioxane) as compared to a polar solvent (methanol). This is actually what is found, III showing $a + 6$ in isooctane, $a + 12$ in dioxane (see Table I) and a nearly 100% increase to $a + 22$ in methanol.

In all of the examples having a 6β-halogen (V, VI, XI) the negative contribution of the halogens was attributed by the French authors[28] to the 6β-halogen projecting into a negative octant beyond the positive octant containing C-6. As we have shown, this is reasonable for 6β-bromocholestan-3-one (XI), but such an explanation is precluded for the dihalides because of the negative Cotton effect curve (Fig. 2) of 5α,6α-dichlorocholestan-3-one (VII). In the chair conformation assumed by Jacquesy and Levisalles,[28] the 6α-chloro atom could be situated only in a positive octant making the amplitude of the 5α,6α-dichloride VII more strongly positive than that of 5α-chlorocholestan-3-one (III). That this is not so (Table I) is strong evidence in favor of our explanation of a conformational distortion toward a boat form.

The present results illustrate again the power of the optical rotatory dispersion method for the detection of small and frequently unexpected conformational alterations. At the same time, they illustrate also the relative complexity which can arise when halogen substituents are present, thus calling for caution in the interpretation of optical rotatory dispersion curves of polyhalogenated ketones as well as for consideration of the quantitative differences in the rotatory contributions of the various halogen atoms which can make themselves felt over appreciable distances.

Experimental[30]

5α-Fluorocholestan-3β-ol Acetate.—Cholesteryl acetate (3.0 g.) in methylene chloride (50 ml.) was added to a stirred solution of anhydrous hydrogen fluoride (20 g.) in methylene chloride (50 ml.) in a Dry Ice–acetone-bath. After standing for 20 min. the solution was poured onto ice and sodium carbonate and the product isolated by extraction with methylene chloride. Chromatography of the product in hexane solution over silica gel gave in the first eluted fractions unchanged cholesteryl acetate (1.1 g.). Subsequent fractions (1.3 g.) yielded, on crystallization from methanol, **5α-fluorocholestan-3β-ol acetate** (1.1 g.), m.p. 115–116°, $[\alpha]_D$ +20° (*c* 1.2); $\lambda_{max}^{CS_2}$ 5.89, 8.18, 9.79, 12.25 μ.

Anal. Calcd. for $C_{29}H_{49}O_2F$: C, 77.62; H, 11.01; F, 4.23. Found: C, 77.42; H, 11.31; F, 4.30.

5α-Fluorocholestan-3β-ol.—To a stirred solution of 5α-fluorocholestan-3β-ol acetate (100 mg.) in ether (100 ml.) at room temperature was added lithium aluminum hydride (50 mg.) in ether (50 ml.). After standing for 15 min. the solution was poured onto ice and ammonium chloride and the product (100 mg.) recovered by ether extraction. Crystallization of part of the product from methanol gave **5α-fluorocholestan-3β-ol**, m.p. 133–134°, $[\alpha]_D$ +22° (*c* 0.89); $\lambda_{max}^{CHCl_3}$ 2.90, 3.0, 9.73 μ.

Anal. Calcd. for $C_{27}H_{47}OF$: C, 79.76; H, 11.63. Found: C, 79.62; H, 11.84.

The same product, as shown by comparison of infrared spectra, was obtained when the ethereal solution of lithium aluminum hydride and the acetate were heated under reflux for 5 hours.

5α-Fluorocholestan-3-one (II).—A solution of chromium trioxide (100 mg.) in water (1 ml.) and acetic acid (20 ml.) was added to 5α-fluorocholestan-3β-ol (200 mg.) and the mixture stirred at room temperature. Thirty minutes after solution was complete (45 min.), water was added dropwise to produce a crystalline product (100 mg., m.p. 149°), recovered by filtration. Crystallization from methylene chloride–methanol gave 5α-fluorocholestan-3-one (II), m.p. 150–151°, decomposing at 155°; λ_{inf}^{diox} 275 mμ, ε 100; $\lambda_{max}^{CHCl_3}$ 5.85 μ; R.D. (Fig. 1) in dioxane (*c* 0.147): $[\phi]_{600}$ +143°, $[\phi]_{589}$ +154°, $[\phi]_{318}$ +1988°, $[\phi]_{270}$ −990°, $[\phi]_{260}$ −606°.

Anal. Calcd. for $C_{27}H_{45}OF$: C, 80.13; H, 11.21; F, 4.69. Found: C, 80.05; H, 11.31; F, 4.60.

5α-Fluorocholestan-3-one (40 mg.) was treated for 2 hr. in a refluxing solution of potassium acetate (200 mg.) in methanol (15 ml.). Addition of water to the cooled solution gave crystals of Δ^4-cholesten-3-one, m.p. 79–80°; λ_{max}^{EtOH} 241 mμ, ε 13,000; λ_{max}^{Nujol} 6.13, 6.25 μ.

Fluorination of Cholesterol.—Following the method of Bowers, *et al.*,[22] cholesterol (10 g.) in methylene chloride (200 ml.) at −50° was added to a stirred solution of anhydrous hydrogen fluoride (25 g.) and lead tetraacetate (40 g.) in methylene chloride (150 ml.) in a Dry Ice–acetone-bath. After stirring for 1 hr., the product was isolated by pouring onto ice and sodium carbonate and extracting with methylene chloride. Prior experiments had shown that under similar reaction conditions cholesteryl acetate was recovered largely unchanged, but that the acetates rather than the hydroxy-product could be purified by chromatography. The reaction product was therefore acetylated (acetic anhydride–pyridine overnight at room temperature) and the acetates chromatographed on silica gel. Using hexane–ethyl acetate (19:1) for elution there were obtained 20 fractions (50 ml.), the first of which proved to be mainly cholesteryl acetate (2.5 g.). Rechromatography of the remainder of the fractions gave **5α,6α-difluorocholestan-3β-ol acetate** (600 mg.), crystallizing from methylene chloride–methanol to show m.p. 120–121°, $[\alpha]_D$ +25° (*c* 0.71); $\lambda_{max}^{CHCl_3}$ 5.84, 8.23, 9.25 μ.

Anal. Calcd. for $C_{29}H_{48}O_2F_2$: C, 74.63; H, 10.33; F, 8.14. Found: C, 74.61; H, 10.19; F, 8.41.

A small quantity (20 mg.) of an unidentified **fluoro compound** crystallizing from methylene chloride–methanol (m.p. 170–172°) was also obtained from the mother liquors of the first two fractions. Found: C, 75.29; H, 9.63; F, 8.7.

Elution of the original chromatogram with hexane–ethyl acetate (9:1) gave 20 fractions consisting of brown oils. During slow evaporation of methanol solutions of these there was obtained white crystals which after charcoaling and crystallizing from methanol gave a **difluoro alcohol** (100 mg.), m.p. 120–121°, $[\alpha]_D$ +8° (*c* 0.91); λ_{max}^{Nujol} 5.85, 8.23, 9.61, 9.82 μ.

Anal. Calcd. for $C_{27}H_{46}OF_2$: C, 76.36; H, 10.87; F, 8.94. Found: C, 76.73; H, 10.97; F, 8.93.

This by-product is not the 5β,6β-difluoro isomer, since oxidation yielded a base-stable difluoro ketone, m.p. 143–144°.

Anal. Calcd. for $C_{27}H_{44}OF_2$: C, 76.71; H, 10.44; F, 8.99. Found: C, 76.54; H, 10.22; F, 9.23.

5α,6α-Difluorocholestan-3β-ol.—A solution of lithium aluminum hydride (100 mg.) in ether (75 ml.) was added to a stirred solution of 5α,6α-difluorocholestan-3β-ol acetate (200 mg.) in ether (75 ml.) at room temperature. After standing 1.5 hr. the product was isolated by pouring onto ice and ammonium chloride followed by ether extraction. Crystallization from methanol gave **5α,6α-difluorocholestan-3β-ol** (90 mg.) m.p. 144–145°, $[\alpha]_D$ +20° (*c* 0.93); $\lambda_{max}^{CHCl_3}$ 2.85, 9.15 μ.

Anal. Calcd. for $C_{27}H_{46}OF_2$: C, 76.36; H, 10.87; F, 8.94. Found: C, 76.24; H, 10.75; F, 9.37.

5α,6α-Difluorocholestan-3-one (IX).—A solution of chromium trioxide (50 mg.) in water (1 ml.) and acetic acid (15

C. Djerassi, L. E. Geller and E. J. Eisenbraun, *J. Org. Chem.*, **25**, 1 (1960), where the effect of solvent polarity upon the rotatory dispersion of α-haloketones is described.

(30) Melting points were measured in open soft glass capillaries and are uncorrected. All optical rotations at the D line were measured in chloroform solution. Where the stability of the compounds would permit, their purity, and the course of reactions, was followed by thin-layer chromatography, using silica gel as the stationary phase, and appropriate mixtures of hexane and ethyl acetate as the mobile phase. Elementary analyses were made by Mr. E. Meier and Mr. J. Consulo, Stanford University Microanalytical Laboratory.

ml.) was added to 5α,6α-difluorocholestan-3β-ol (50 mg.), and the mixture stirred 1 hr. at room temperature. Addition of water gave crystals which on recrystallization from methanol gave 20 mg. of **5α,6α-difluorocholestan-3-one (IX)**, m.p. 173–174°; λ_{max}^{diox} 282 mμ, ε 30; $\lambda_{max}^{CHCl_3}$ 5.85 μ; R.D. (Fig. 2) in dioxane (*c* 0.104): $[\phi]_{600}$ +110°, $[\phi]_{589}$ +110°, $[\phi]_{312}$ +1447°, $[\phi]_{275}$ −165°, $[\phi]_{263}$ 0°.

Anal. Calcd. for $C_{27}H_{44}OF_2$: C, 76.71; H, 10.44; F, 8.99. Found: C, 76.77; H, 10.25; F, 9.35.

Treatment of 5α,6α-difluorocholestan-3-one (IX) (20 mg.) in refluxing methanol (15 ml.) with potassium acetate (100 mg.) for 3 hr. gave, on the addition of water, 6α-fluoro-Δ⁴-cholesten-3-one,[23] m.p. 118°, $[\alpha]_D$ +70° (*c* 0.51); λ_{max}^{EtOH} 237 mμ, ε 16,000. Direct comparison by Dr. A. Bowers (infrared spectrum and mixture m.p.) with an authentic sample[23] showed the two to be identical.

5α-Fluoro-6β-iodocholestan-3β-ol Acetate.—Following the method of Bowers, *et al.*,[25] a solution of cholesteryl acetate (10 g.) and N-iodosuccinimide (6.5 g.) in methylene chloride (100 ml.) was added to a stirred solution of anhydrous hydrogen fluoride (45 g.) in tetrahydrofuran (41 g.) in a Dry Ice–acetone-bath. After stirring at the temperature of the bath for 2 hr. the solution was let stand for 16 hr. in the refrigerator and worked up by pouring onto ice and potassium carbonate followed by extraction with methylene chloride. The methylene chloride solution was shaken with mercury to remove some free iodine, dried over magnesium sulfate, filtered through a short column of silica gel and evaporated to dryness. Crystallization from hexane–ether gave **5α-fluoro-6β-iodocholestan-3β-ol acetate** (5 g.), m.p. 138–139°, $[\alpha]_D$ −20° (*c* 1.2); λ_{max}^{EtOH} 263 mμ, ε 475; λ_{max}^{Nujol} 5.78, 8.15, 9.72 μ.

Anal. Calcd. for $C_{29}H_{48}O_2FI$: C, 60.69; H, 8.42; F, 3.31; I, 22.08. Found: C, 60.25; H, 8.37; F, 3.40; I, 22.32.

5α-Fluoro-6β-iodocholestan-3β-ol.—A solution of lithium aluminum hydride (500 mg.) in ether (50 ml.) was added to a stirred solution of 5α-fluoro-6β-iodocholestan-3β-ol (1.1 g.) in ether (200 ml.) at room temperature. After 30 min. the solution was poured onto ice and ammonium chloride and the product recovered by ether extraction. Crystallization of the product from methanol–water gave solvated crystals of 5α-fluoro-6β-iodocholestan-3β-ol (300 mg.), m.p. after drying 117°, $[\alpha]_D$ −25° (*c* 0.72); λ_{max}^{Nujol} 3.07, 9.48, 9.65 μ; λ_{max}^{EtOH} 261 mμ, ε 245.

Anal. Calcd. for $C_{27}H_{46}OFI$: C, 60.90; H, 8.70; F, 3.67; I, 23.83. Found: C, 61.17; H, 8.54; F, 3.20; I, 23.92.

5α-Fluoro-6β-iodocholestan-3-one (X).—A solution of chromium trioxide (300 mg.) in water (2 ml.) and acetic acid (50 ml.) was added to 5α-fluoro-6β-iodocholestan-3β-ol (400 mg.) and stirred at room temperature for 45 min. Dropwise addition of water gave **5α-fluoro-6β-iodocholestan-3-one (X)** (260 mg.), which was crystallized from ethyl acetate–methanol showing m.p. 90–91°; $\lambda_{max}^{CHCl_3}$ 260 mμ, ε 300; $\lambda_{max}^{CHCl_3}$ 5.85 μ; R.D. (Fig. 2) in dioxane (*c* 0.122): $[\phi]_{600}$ −212°, $[\phi]_{589}$ −212°, $[\phi]_{315}$ (trough) −2088°, $[\phi]_{280}$ −1272°.

Anal. Calcd. for $C_{27}H_{44}OFI$: C, 61.12; H, 8.36; F, 3.59; I, 23.92. Found: C, 61.10; H, 8.25; F, 3.80; I, 24.20.

5α-Chlorocholestan-3-one (III).—A solution of chromium trioxide (200 mg.) in water (2 ml.) and acetic acid (50 ml.) was added to 5α-chlorocholestan-3β-ol (m.p. 164°), and stirred at room temperature for 1 hr. Addition of water gave the relatively stable 5α-chlorocholestan-3-one (III),[10,31] m.p. 150° dec. Crystallization from acetone gave a lower melting form, m.p. 135°, which could be converted to the higher melting form by seeding; λ_{max}^{EtOH} 284 mμ, ε 24; $\lambda_{max}^{CS_2}$ 5.85, 8.24 μ; R.D. (Fig. 1) in dioxane (*c* 0.064): $[\phi]_{600}$ +130°, $[\phi]_{589}$ +130°, $[\phi]_{316}$ (infl.) +1078°, $[\phi]_{310}$ +1158°, $[\phi]_{303}$ (infl.) +947°, $[\phi]_{274}$ ±0°, $[\phi]_{265}$ +105°: R.D. in methanol (*c* 0.098): $[\phi]_{650}$ +112°, $[\phi]_{589}$ +112°, $[\phi]_{300}$ +1953, $[\phi]_{250}$ −257°, $[\phi]_{237}$ ± 0°: R.D. in isooctane (*c* 0.10): $[\phi]_{589}$ +130°, $[\phi]_{309}$ +943°, $[\phi]_{275}$ +320°, $[\phi]_{250}$ +572°.

(31) Butenandt, *et al.*,[10] report m.p. 102° for a solvated form, and 135° for an unsolvated form of this compound, but without giving details of its formation or other physical constants.

Anal. Calcd. for $C_{27}H_{45}OCl$: C, 77.03; H, 10.77; Cl, 8.42. Found: C, 77.03; H, 10.43; Cl, 8.77.

5α,6β-Dichlorocholestan-3-one (V).—Prepared by the method of Barton and Miller,[18] this compound had m.p. 98–100°, λ_{infl}^{diox} 285 mμ, ε 25; $\lambda_{max}^{CHCl_3}$ 5.85, 10.35, 11.37 μ; $[\alpha]_D$ −27° (*c* 0.87); R.D. (Fig. 2) in dioxane (*c* 0.064): $[\phi]_{650}$ −93°, $[\phi]_{589}$ −122°, $[\phi]_{309}$ −1101°, $[\phi]_{270}$ −350°, $[\phi]_{260}$ −386°.

5α,6α-Dichlorocholestan-3β-ol.[18,32] (a).—A solution of lithium aluminum hydride (200 mg.) in ether (50 ml.) was added to a stirred solution of 5α,6α-dichlorocholestan-3β-ol benzoate[18] (400 mg.) in ether (150 ml.) in an ice-bath. After stirring for 15 min. the ethereal solution was poured onto ice and ammonium chloride and the product recovered by ether extraction. Chromatography over silica gel using hexane–ethyl acetate (9:1) as eluting solvent gave 5α,6α-dichlorocholestan-3β-ol (90 mg.), m.p. 173–175°.

(b).—To a stirred solution of cholesteryl tetrahydropyranyl ether[33] (1 g.) in chloroform (150 ml.), dried azeotropically, was added phenyl iodosodichloride[34] (600 mg.). The solution was heated to reflux for 1 min., then concentrated to 20 ml. under reduced pressure. Methanol (300 ml.) and *p*-toluenesulfonic acid (50 mg.) were added and the solution was refluxed for 50 min. in order to hydrolyze the acetal grouping. Dropwise addition of water gave crystals (750 mg.) which were recovered by filtration and chromatographed on silica gel. Elution with hexane–ethyl acetate (19:1) gave 5α,6β-dichlorocholestan-3β-ol (390 mg.) crystallizing from acetone to show, after drying, m.p. 141–142°. Elution with hexane–ethyl acetate (9:1) gave 5α,6α-dichlorocholestan-3β-ol (310 mg.), m.p. 167–169°, after recrystallization from acetone–hexane.

5α,6α-Dichlorocholestan-3-one (VII).[35]—A solution of chromium trioxide (50 mg.) in water (1 ml.) and acetic acid (20 ml.) was added to 5α,6α-dichlorocholestan-3β-ol (80 mg.) and stirred at room temperature for 1 hr. Water was added dropwise and the resulting gel recovered by filtration. **5α,6α-Dichlorocholestan-3-one (VII)** (20 mg.) was crystallized by dissolving in methanol at room temperature and cooling to −20°. It had m.p. 123° dec.; λ_{infl}^{diox} 280 mμ, ε 20; $\lambda_{max}^{CHCl_3}$ 5.87 μ; R.D. (Fig. 2) in dioxane (*c* 0.08): $[\phi]_{650}$ −34°, $[\phi]_{589}$ −9°, $[\phi]_{317}$ −302°, $[\phi]_{280}$ +113°, $[\phi]_{260}$ 0°.

Anal. Calcd. for $C_{27}H_{44}OCl_2$: C, 71.18; H, 9.74; Cl, 15.57. Found: C, 70.98; H, 9.60; Cl, 15.35.

5α-Bromocholestan-3β-ol.[36]—A solution of lithium aluminum hydride (50 mg.) in ether (50 ml.) was added to a stirred solution of 5α-bromocholestan-3β-ol acetate[27] at room temperature. After 15 min., the solution was poured onto ice and ammonium chloride and the product recovered by ether extraction. Crystallization from light petroleum or, more wastefully, from acetone gave 5α-bromocholestan-3β-ol, m.p. 135–136° dec., $[\alpha]_D$ −2° (*c* 1.1); $\lambda_{max}^{CHCl_3}$ 2.85, 3.00, 9.78 μ.

Anal. Calcd. for $C_{27}H_{47}OBr$: C, 69.35; H, 10.13; Br, 17.09. Found: C, 69.24; H, 9.93; Br, 16.98.

5α-Bromocholestan-3-one (IV).[11]—A solution of chromium trioxide (300 mg.) in water (2 ml.) and acetic acid [(75 ml.) was added to 5α-bromocholestan-3β-ol and the mixture stirred at room temperature for 1 hr. Dropwise addition of water gave the crystalline ketone which was recrystallized by dissolving in the minimum quantity of ice-cold ether and cooling to −20°. 5α-Bromocholestan-3-one was highly unstable and decomposed rapidly and spontaneously in solution to give Δ⁴-cholesten-3-one, which was the sole product obtained when the solution from the oxidation reaction was worked up by ether extraction. 5α-Bromocholestan-3-one[11] had m.p. 109–111° dec.; λ_{infl}^{diox} 280 mμ,

(32) Barton and Miller[18] prepared this compound, m.p. 171–172°, by hydrolysis of the corresponding benzoate in refluxing ethanolic sulfuric acid for 20 hr. In our hands this reaction went only partly to completion and alternative methods of preparation were sought.

(33) W. G. Dauben and H. C. Bradlow, *J. Am. Chem. Soc.*, **74**, 559 (1952).

(34) B. S. Garvey, L. F. Halley and C. F. H. Allen, *ibid.*, **59**, 1827 (1937).

(35) Prepared as an uncharacterized intermediate by Barton and Miller (ref. 18).

(36) As prepared by Y. Urushibara and S. Mori (ref. 11) by direct addition of hydrogen bromide to cholesterol, this compound had m.p. 120–121°. We found this reaction difficult to control due to competitive displacement of the hydroxyl function by bromine.

ϵ 30; $\lambda_{max}^{CHCl_3}$ 5.80 μ; R.D. (Fig. 1) in dioxane (c 0.107 on freshly prepared material): $[\phi]_{650}$ ±0°, $[\phi]_{589}$ +26°, $[\phi]_{465}$ +130°, $[\phi]_{425}$ +56°, $[\phi]_{300}$ +521°, $[\phi]_{270}$ −88°, $[\phi]_{260}$ ±0°.

6β-Bromo-5α-cholestan-3-one (XI).[27]—A sample of this compound kindly provided by Professor Shoppee had m.p. 180° after crystallization from acetone. Shoppee and Lack[27] report m.p. 155° for this compound. In a personal communication, Professor Shoppee suggested that these different m.p.'s arise from different polymorphic forms. In agreement, it was found that infrared spectra of the two forms were identical. 6β-Bromo-5α-cholestan-3-one had $\lambda_{max}^{CHCl_3}$ 282 mμ, ϵ 25; R.D. (Fig. 1) in dioxane (c 0.125): $[\phi]_{650}$ ±0°, $[\phi]_{589}$ −27°, $[\phi]_{323}$ −237°, $[\phi]_{310}$ −100°, $[\phi]_{260}$ 1113°, $[\phi]_{250}$ −987°; R.D. in methanol (c 0.100): $[\phi]_{650}$ −149°, $[\phi]_{589}$ −140°, $[\phi]_{300}$ −37°, $[\phi]_{265}$ −465°.

5α,6β-Dibromocholestan-3-one (VI).[19]—After crystallizing from cold ether this compound had m.p. 82–84° dec.; λ_{max}^{diox} 280 mμ, ϵ 150; $\lambda_{max}^{CHCl_3}$ 5.90 μ; R.D. (Fig. 2) in dioxane (c 0.096): $[\phi]_{650}$ −424°, $[\phi]_{589}$ −424°, $[\phi]_{307}$ −4134°, $[\phi]_{270}$ −794°, $[\phi]_{250}$ −1642°; R.D. in isooctane (c 0.079): $[\phi]_{650}$ −256°, $[\phi]_{589}$ −248°, $[\phi]_{310}$ −3569°, $[\phi]_{265}$ −65°, $[\phi]_{250}$ −968°.

5α-Bromo-6β-chlorocholestan-3-one (VIII).[21]—After crystallizing from ether–methanol, this substance had m.p. 70° dec.; λ_{max}^{diox} 285 mμ, ϵ 50; $\lambda_{max}^{CHCl_3}$ 5.85 mμ; R.D. (Fig. 2) in dioxane (c 0.103): $[\phi]_{600}$ −255°, $[\phi]_{589}$ −255°, $[\phi]_{312}$ −2120°, $[\phi]_{277}$ −630°, $[\phi]_{260}$ −1360°.

Cholestan-3-one (I): m.p. 129°; λ_{max}^{diox} 287 mμ, ϵ 25; R.D. (Fig. 1) in dioxane (c 0.108): $[\phi]_{600}$ +170°, $[\phi]_{589}$ +170°, $[\phi]_{317}$ +2749°, $[\phi]_{275}$ −1972°, $[\phi]_{260}$ −1318°.

[CONTRIBUTION FROM NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, URBANA, ILL.]

Effect of Solvent on the Steric Stability of Lithium Reagents[1]

BY DAVID Y. CURTIN AND WILLIAM J. KOEHL, JR.[2]

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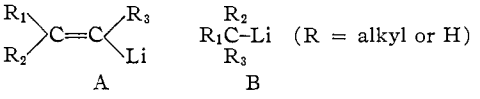
It has been found that solutions of *cis*-α-stilbenyllithium (*cis*-I) and of *cis*- and *trans*-2-*p*-chlorophenyl-1,2-diphenylvinyllithium (*cis*- and *trans*-V) in hydrocarbon solvents have very much greater stereochemical stability than in diethyl ether. Tetrahydrofuran is still much more effective than ether in promoting the isomerization of *cis*- to *trans*-I. It has been found further that optically active *sec*-butyllithium in the absence of ether can be prepared and carbonated with at least 83% retention of configuration. Again the isomerization (racemization in this case) is greatly accelerated even by small amounts of added diethyl ether. It has been found that *t*-butyllithium can be conveniently prepared from lithium metal containing only 0.2% sodium if the surface is coated with copper powder before reaction.

It has been demonstrated previously[4] that the vinyllithium group can be formed and caused to react with a high degree of retention of steric configuration. The steric stability of a lithium compound with the structure A or B furthermore is known to be highly dependent on the nature of the

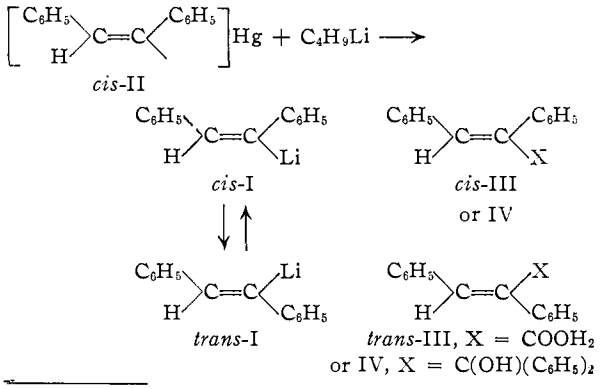


R groups.[4–9] The present paper is concerned with another aspect of the loss of configuration of such compounds, the effect of solvent.

Both the formation and reactions of lithium reagents have for many years been known to proceed much more slowly in hydrocarbon solvents than in solvents such as diethyl ether.[10]

The system chosen initially for study was the equilibration of *cis*- and *trans*-stilbenyllithium (*cis*- and *trans*-I).[11,12] These two isomers had been prepared by a lithium–bromine exchange from the corresponding bromides in benzene–ether at temperatures of −35° and below and react with no observable loss of configuration.[11] On the other hand, at higher temperatures or with sufficiently prolonged reaction times there was isomerization of the *cis* isomer to the *trans*, the equilibrium lying far toward the *trans* isomer.[12] The one-sided equilibrium, presumably due to the large unfavorable steric interaction of the two phenyl groups in the *cis* isomer[13] made the study of this equilibration particularly attractive.

The *cis*-α-stilbenyllithium (*cis*-I) was prepared from bis-*cis*-α-stilbenylmercury[12] (*cis*-II) by a lithium–mercury exchange in the appropriate solvent. This method, rather than the more conventional ones involving lithium metal or a lithium–halogen exchange with butyllithium, was chosen because of the slowness of such reactions in hydrocarbon solvents. The lithium reagent thus formed was then converted to the carboxylic acid(s) *cis*-



(1) Taken from the Ph.D. Thesis of W. J. Koehl, Jr., submitted to the University of Illinois, 1960. The work was presented at the 138th Meeting of the American Chemical Society, New York, N. Y., September, 1960; Abstracts, p. 52P. A part of the work has been published in preliminary form.[3]

(2) National Science Foundation Fellow, 1958–1960.

(3) D. Y. Curtin and W. J. Koehl, Jr., *Chemistry & Industry*, 262 (1960).

(4) See D. Y. Curtin and J. W. Crump, *J. Am. Chem. Soc.*, **80**, 1922 (1958), and references therein cited.

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(8) H. M. Walborsky, unpublished results, quoted in the Communication to the Editor by H. M. Walborsky and A. E. Young, *J. Am. Chem. Soc.*, **83**, 2595 (1961).

(9) D. Y. Curtin and J. W. Hausser, *ibid.*, **83**, 3474 (1961).

(10) See K. Ziegler and H. Colonius, *Ann.*, **479**, 135 (1930), for example.

(11) D. Y. Curtin and E. E. Harris, *J. Am. Chem. Soc.*, **73**, 4519 (1951).

(12) A. N. Nesmeyanov, A. E. Borisov and N. A. Vol'kenau, *Izvest. Akad. Nauk (S.S.S.R.) Otdel. Khim. Nauk*, 992 (1954).

(13) See D. Y. Curtin, H. Gruen, Y. G. Hendrickson and H. E. Knipmeyer, *J. Am. Chem. Soc.*, **84**, 4838 (1962), for a discussion of the phenyl–phenyl interaction in other systems.