Anal. Calcd. for $C_{26}H_{28}O_4$: C, 77.20; H, 6.98. Found: C, 77.21; H, 7.13.

Acknowledgments.—The author wishes to express his thanks to Dr. T. F. Gallagher for his advice and interest in this work and his assistance in the preparation of this manuscript. He wishes to thank Dr. G. Roberts and staff for the infrared spectra. The technical assistance of Jerome Boxer and Rosemarie Lehman is also gratefully acknowledged.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Optical Rotatory Dispersion Studies. XIV.[1] α-Haloketones (Part 2)[2,3]

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The optical rotatory dispersion of a variety of α-halogenated steroid ketones has been measured and the resulting curves have been compared with those of the parent ketones. A number of generalizations can be made, the most important of which are the following: (a) chlorine and bromine produce essentially the same effect while fluorine behaves in a distinctly different fashion; (b) equatorial chlorine or bromine do not create marked dispersion changes except for minor wave length shifts, generally toward the ultraviolet; (c) axial chlorine or bromine lead to bathochromic shifts which can be correlated closely with the known ultraviolet spectral changes of these chromophores; the amplitude of the dispersion curve is generally increased greatly; the sign of the Cotton effect of such axial α-haloketones can be predicted by the empirical "axial haloketone dispersion rule" described in ref. 2 thus offering a useful tool for relative and absolute configuration studies. The above generalizations appear only applicable to cyclohexanones, and rotatory dispersion results with a few α-halocyclopentanones are also recorded.

The broad scope of the rotatory dispersion method—insofar as it applies to carbonyl compounds—has been established in earlier papers of this series[4] and it is now necessary to examine the more subtle aspects as well as limitations of this physico-chemical tool. The connection between ultraviolet absorption and anomalous optical rotatory dispersion (*i.e.*, curves which exhibit peaks and troughs[5]) already has been covered in the past[4,6-8] and since the relation between ultraviolet absorption and conformation of α-haloketones has been studied[9] in detail, it was felt that an analysis of the rotatory dispersion curves of such α-haloketones would be very pertinent.

In contrast to the majority of earlier studied ketones[4] where the characteristic rotatory dispersion changes were due chiefly to conformational and stereochemical alterations, strong electronic effects can be expected to operate as well in α-haloketones and this will be demonstrated below in a comparative examination of the various halogen atoms (F, Cl, Br). In order to keep the stereochemical situation as simple as possible, the present investigation is limited to polycyclic α-haloketones where the conformation of any given α-haloketone can be expected to be more or less identical with that of the parent ketone[10] in contrast to the equilibrium mixtures of conformational isomers encountered in monocyclic α-haloketones,[11] whose rotatory dispersion will form the subject of a future paper.

The characteristic spectroscopic changes observed among α-bromo- and α-chlorocyclohexanones have been ascribed[12a] to a large extent to a field effect involving the C—Br and C=O dipoles, the electrostatic repulsion being greatest when the halogen atom is equatorially oriented and least when it is axial; as a consequence, the infrared carbonyl band[12a,b] of the α-haloketone remains essentially unchanged (by comparison to the halogen-free ketone) when the halogen atom is axial but is moved to lower wave length when it is equatorial. Conversely, a bathochromic shift of *ca.* 28 mμ is observed in the ultraviolet absorption maximum[9] of an axial α-bromocyclohexanone, while a slight hypsochromic change (5 mμ) is noted with the corresponding equatorial isomers. As far as possible, we have selected for our rotatory dispersion studies haloketones whose stereochemistry has already been established on spectroscopic[9,12a,b] and often also chemical grounds[13] and these have been analyzed with respect to wave length shifts[14] and inversion of

(1) Paper XIII, C. Djerassi, J. Osiecki and W. Herz, *J. Org. Chem.*, **22**, 1361 (1957).

(2) Part 1, C. Djerassi and W. Klyne, THIS JOURNAL, **79**, 1506 (1957).

(3) Supported by Grant No. CY-2919 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(4) For a review and leading references see C. Djerassi, *Bull. soc. chim. France*, 741 (1957).

(5) For nomenclature in rotatory dispersion work and reporting of experimental data see C. Djerassi and W. Klyne, *Proc. Chem. Soc.*, 55 (1957).

(6) T. M. Lowry, "Optical Rotatory Power," Longmans, Green and Co., London, 1935, chapter XXXI.

(7) C. Djerassi, E. W. Foltz and A. E. Lippman, THIS JOURNAL, **77**, 4350 (1955).

(8) C. Djerassi, R. Riniker and B. Riniker, *ibid.*, **78**, 6377 (1956).

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

(10) An exception in the triterpene series has recently been recorded by D. H. R. Barton, D. A. Lewis and J. F. McGhie, *ibid.*, 2907 (1957).

(11) J. Allinger and N. L. Allinger, *Tetrahedron*, **1**, in press (1957).

(12) (a) R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, THIS JOURNAL, **74**, 2828 (1952); R. N. Jones, *ibid.*, **75**, 4839 (1953); E. G. Cummins and J. E. Page, *J. Chem. Soc.* 3847 (1957); (b) E. J. Corey, THIS JOURNAL, **75**, 2301 (1953), and later papers.

(13) *Inter al.*, E. Seebeck and T. Reichstein, *Helv. Chim. Acta*, **26**, 536 (1943); T. F. Gallagher and W. P. Long, *J. Biol. Chem.*, **162**, 495, 521 (1946); J. J. Beereboom, C. Djerassi, D. Ginsburg and L. F. Fieser, THIS JOURNAL, **75**, 3500 (1953); E. J. Corey, *ibid.*, **75**, 4832 (1953); L. F. Fieser and W. Huang, *ibid.*, **75**, 4837 (1953); D. R. James and C. W. Shoppee, *J. Chem. Soc.*, 1064 (1956).

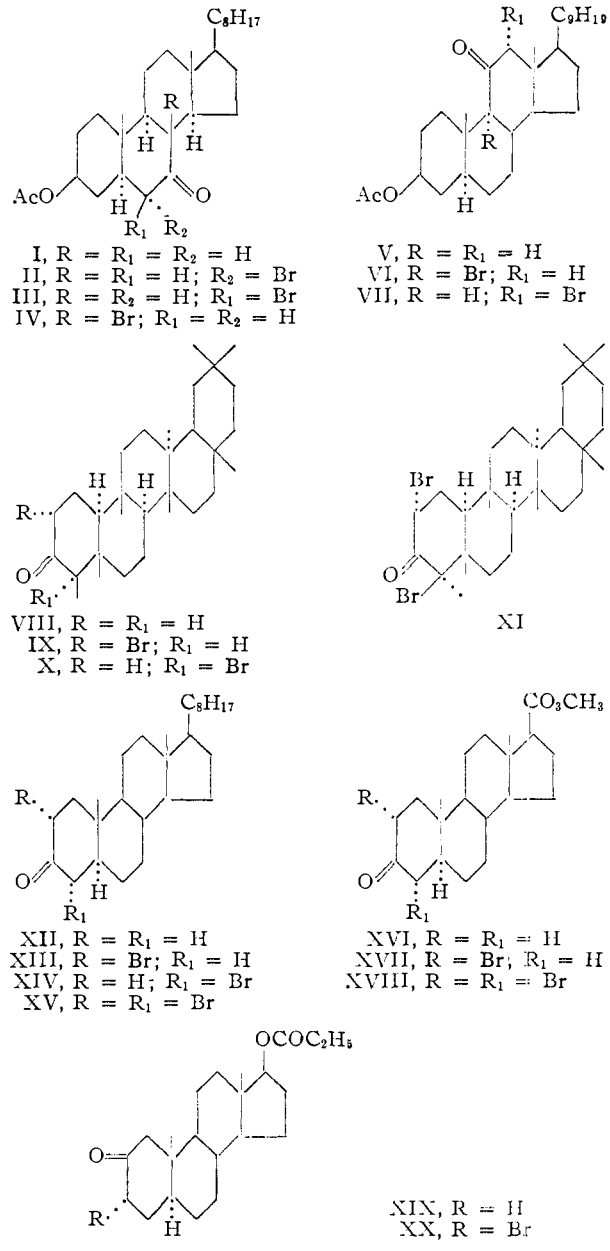
(14) We have selected as reference point the position of the peak in a positive, and of the trough in a negative single Cotton effect curve (see ref. 5) rather than the wave length corresponding to zero rotation or the mean between the peak and trough of any given single Cotton

the sign of the Cotton effect[5] as compared to the dispersion of the halogen-free ketone, Brief comments on amplitude[5] changes also will be made wherever warranted.

An instructive group, which already illustrates all of the changes observed among α-bromo ketones, is represented by 3β-acetoxycholestan-7-one (I) and its mono-bromo derivatives II, III and IV. The rotatory dispersion results are summarized in Fig. 1 and for reference purposes the curve[15] of the halogen-free 7-ketone (I) is again reproduced. It will be noted that this is characterized by a negative single Cotton effect curve of rather small amplitude with an initial trough at 310 mμ and that introduction of an equatorial bromine atom as in 6α-bromo-3β-acetoxycholestan-7-one (II) produces no major changes other than a hypsochromic shift of the trough to 300 mμ. On the other hand, profound alterations can be observed upon introduction of an axially oriented bromine atom and these depend upon the site of substitution, In contrast to the negative Cotton effect exhibited by the 7-ketone I and its 6α-bromo derivative II, the axial 6β-bromo isomer III[16] shows an inverted dispersion curve with a strong, positive Cotton effect and a peak at 335 mμ, representing a bathochromic shift of 25 mμ which is practically identical to that (26 mμ) reported for the ultraviolet absorption maxima.[9] Axial substitution on the other side of the carbonyl group as in 8β-bromo-3β-acetoxycholestan-7-one (IV) does not change the sign of the Cotton effect (as compared to the unsubstituted 3β-acetoxycholestan-7-one) but results in a tremendous increase in the amplitude and in precisely the same type of bathochromic shift recorded above for the other axial 6β-isomer (III).[17]

3β-Acetoxyergostan-11-one (V) and its two axially substituted bromination products VI and VII present exactly the same situation[18] as illustrated in Fig. 2. The parent 11-ketone V exhibits a weak positive Cotton effect curve with a peak at 322.5 mμ while its 9α-bromo derivative VI shows greatly increased amplitude and a peak at 347.5 mμ, again corresponding to the expected axial bromoketone shift of 25 mμ. The 12α-bromo isomer VII, on the other hand, is characterized by an inverted (negative) Cotton effect curve and the bathochromic shift (trough at 342,5 mμ) is of the same order of magnitude (20 mμ).

Another pair of axially brominated ketones is available in the friedelin series (Fig. 3), where friedelin (VIII)[4] and its 2α-bromo derivative IX exhibit negative Cotton effect curves while the other axial isomer, 4α-bromofriedelin (X) shows a positive Cotton effect. The bathochromic shift of the first trough, respectively peak, due to axial bromine amounts in each case to 20 mμ. An interesting example is presented by the dibromination product[19] of friedelin (see Experimental) where the rotatory dispersion curve affords strong evidence in favor of the 2α,4β-dibromo structure XI, Its Cotton effect is negative and the position of its trough (332.5 mμ *vs.* 315 mμ for friedelin) indicates only one axial



effect curve. The latter two criteria should correspond more or less to the position of the optically active absorption band, but in polycyclic molecules such as steroid ketones complicating factors arise at times as one proceeds into the ultraviolet (*e.g.*, 7-keto-5α-steroids (I) and 11-keto-5α-steroids (V)) and we have found that the results as expressed in this paper are equally meaningful and no exceptions need to be made.

(15) C. Djerassi, W. Closson and A. E. Lippman, THIS JOURNAL, **78**, 3163 (1956).

(16) Since submission of the manuscript a similar derivative in the 5β-series has become available through the courtesy of Prof. E. A. Doisy (see *J. Biol. Chem.*, **226**, 667 (1957)). In accordance with expectation (see ref. 2) methyl 3α-acetoxy-6β-bromo-7-ketocholanate exhibits a positive Cotton effect curve in methanol solution with a peak at 332.5 mμ ([α] +2383°) and a trough at 287 mμ ([α] −3025°).

(17) The pair of isomers (III and IV) possess dispersion curves which are in perfect agreement with each other (except for absolute amplitude values) as well as with the ultraviolet absorption maxima. In each case, the initial peak or trough occurs at 335 mμ, the corresponding trough or peak at 287.5 mμ and the point of zero rotation at 312.5 mμ (observed ultraviolet maximum at 313 mμ—ref. 9).

(18) This applies even to the amplitude changes.

(19) This dibromofriedelin appears to be different from the dibromofriedelin described by Corey and Ursprung (ref. 21) who isolated their product immediately after consumption of bromine.

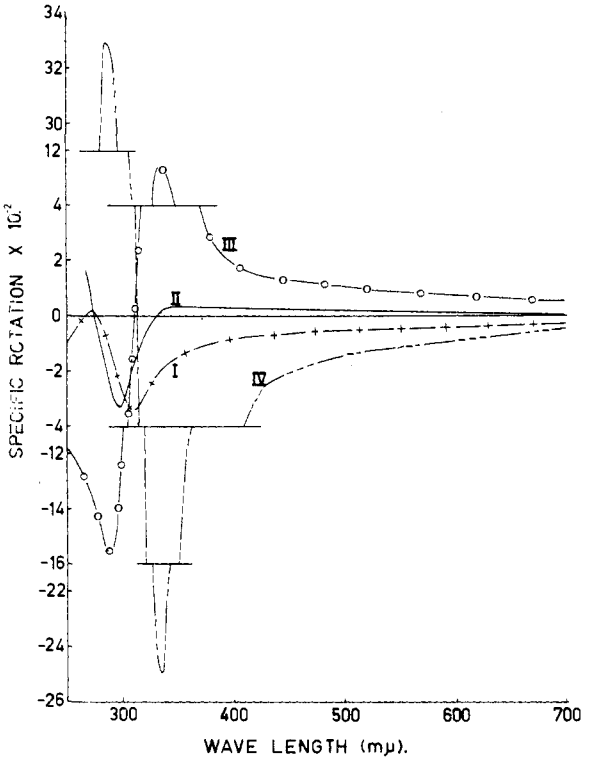


Fig. 1.—Rotatory dispersion curves of 3β-acetoxycholestan-7-one (I), 6α-bromo-3β-acetoxycholestan-7-one (II), 6β-bromo-3β-acetoxycholestan-7-one (III) and 8β-bromo-3β-acetoxycholestan-7-one (IV).

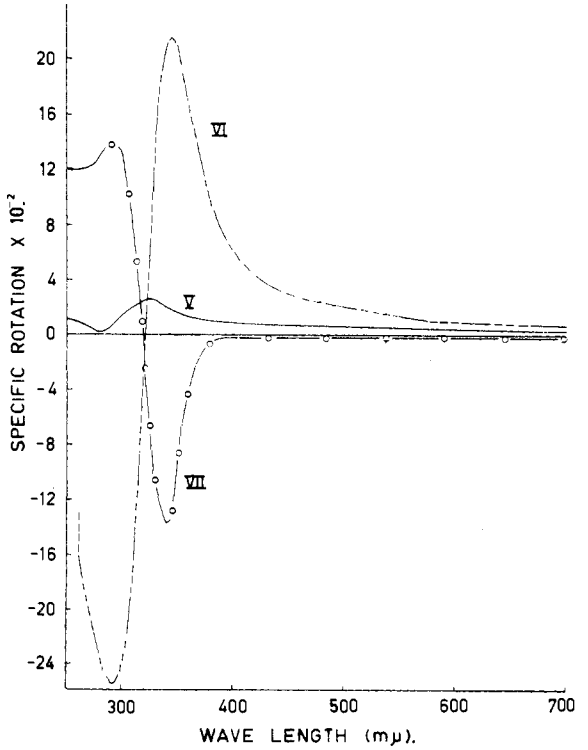


Fig. 2.—Rotatory dispersion curves of 3β-acetoxyergostan-11-one (V), 12α-bromo-3β-acetoxyergostan-11-one (VII) and 9α-bromo-3β-acetoxyergostan-11-one (VI).

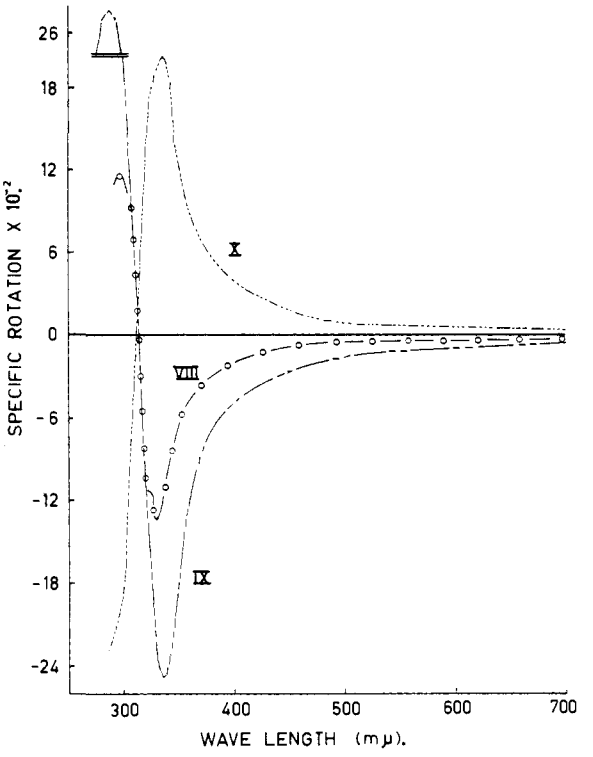


Fig. 3.—Rotatory dispersion curves of friedelin (VIII), 2α-bromofriedelin (IX) and 4α-bromofriedelin (X).

halogen atom[20] as does the ultraviolet absorption maximum. Since an axial 4α-bromine would have produced a positive Cotton effect (see X in Fig. 3), the above data are only consistent with a 2α,4β- (XI) or 2,2-dibromo structure, of which the former seems preferable in view of the experimental conditions employed in its synthesis.

The reason that the axial monobromination products[21] of friedelin (VIII) are the preferred ones is due to the absence of any competing 1,3-nonbonded interaction with an axial methyl group,[12b] In contrast, 3-keto-5α-steroids such as cholestan-3-one (XII)[15]—where such steric effects do operate—upon halogenation yield equatorially substituted derivatives, and in Fig. 4 there are collected the rotatory dispersion curves of cholestan-3-one (XII), its 2α- (XIII) and 4α- (XIV) monobromo derivatives and of 2α,4α-dibromocholestan-3-one (XV). These curves show that introduction of equatorial bromine on either side of the carbonyl group does not change the sign of the Cotton effect nor does it produce appreciable wave length changes (+3 mμ for XIII, −4.5 mμ for XIV, −2 mμ for XV) but only a diminution in amplitude, which reflects itself even at the sodium D line and is responsible for the changes observed in molecular rotation calculations.[22]

The rotatory dispersion results collected in Figs.

(20) If the product were the diequatorial 2β,4β-dibromofriedelin, then the initial trough should have been observed near 315 mμ, since the rotatory dispersion peaks or troughs in diequatorially substituted α,α'-dihaloketones are not appreciably displaced by comparison with the parent ketone.

(21) E. J. Corey and J. J. Ursprung, THIS JOURNAL, **78**, 5041 (1956).

(22) C. Djerassi, *J. Org. Chem.*, **12**, 823 (1947).

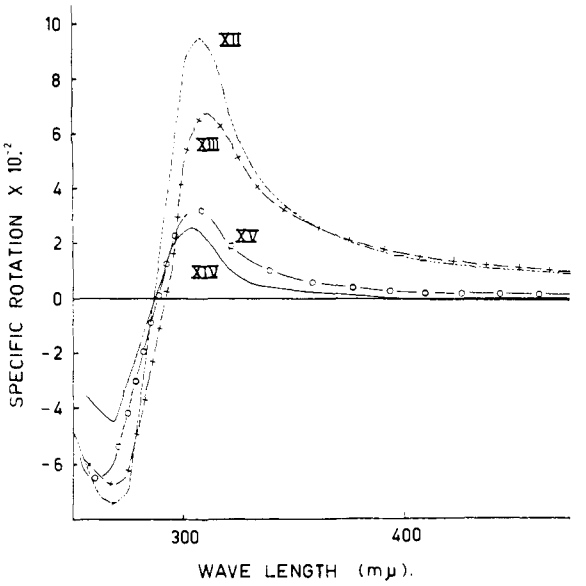


Fig. 4.—Rotatory dispersion curves of cholestan-3-one (XII), 2α-bromocholestan-3-one (XIII), 4α-bromocholestan-3-one (XIV) and 2α,4α-dibromocholestan-3-one (XV).

1–4 can now be summarized in the following fashion before proceeding with further documentation. Introduction of an equatorial bromine atom[23] at the α- and/or α′-positions of a ketosteroid (*e.g.*, XII *vs.* XIII and XIV) does not change the nature of the Cotton effect curve and the wave length shifts are negligible or tend toward the ultraviolet; the amplitude (in terms of *specific* rather than *molecular* rotation) of the curves usually is reduced. Substitution of axial bromine[23] at the α-position produces a dispersion curve whose Cotton effect is invariably opposite in sign to that of the corresponding axial α′-bromoketone (*e.g.*, III *vs.* IV). By comparison with the unsubstituted ketone, the amplitude of the dispersion curve is usually greatly enhanced and the position of the relevant peak or trough is moved towards the visible by 20–25 mμ. An empirical analysis of all the dispersion curves listed in this paper has led to the conclusion[2] that the sign of the Cotton effect of *axially substituted* α-bromo- and α-chloro-ketones forming part of a cyclohexanone ring in the chair conformation can be predicted. This is easily done[2] by constructing a model of the chair conformation of the appropriate cyclohexanone ring with the carbonyl group at the head of the chair and looking down the O=C axis. Halogen to the left of the observer will show a negative Cotton effect and to the right of the observer a positive one. As pointed out in our earlier paper[2] this provides a novel approach to the determination of absolute configuration[24] of certain α-haloketones without requiring a reference compound of known absolute configuration[25] and the use of this "axial haloketone dispersion rule" to examine the bromination of monocyclic ketones is now under way.

The multiplicity of ring A halogenated 3-keto-steroids offers many additional examples both with respect to supporting the above statements and extending them. In the experimental section are listed rotatory dispersion data for methyl 2α-bromo-3-keto-5α-etianate (XVII) and methyl 2α,4α-dibromo-3-keto-5α-etianate (XVIII) and their relation to the dispersion curve of the unsubstituted methyl 3-keto-5α-etianate (XVI)[26] is the same as discussed above for the analogous cholestan-3-one derivatives (XII, XIII, XV). In 2-keto-5α-steroids, the stable bromination product is the axial isomer[27] and the dispersion curves of such an example—androstan-17β-ol-2-one 17-propionate (XIX) and its 3α-bromo derivative (XX)—given in the Experimental section again support the above conclusions, the axial halogen producing a bathochromic shift and an increased amplitude of the positive Cotton effect, which is not changed in sign in this instance since the halogen is to the right of the observer according to the empirical rule described earlier.[2]

The availability in this Laboratory[28] of a series of ring A chlorinated cholestan-3-ones has provided the first opportunity to compare the effect of chlorine *vs.* bromine upon the rotatory dispersion curve.

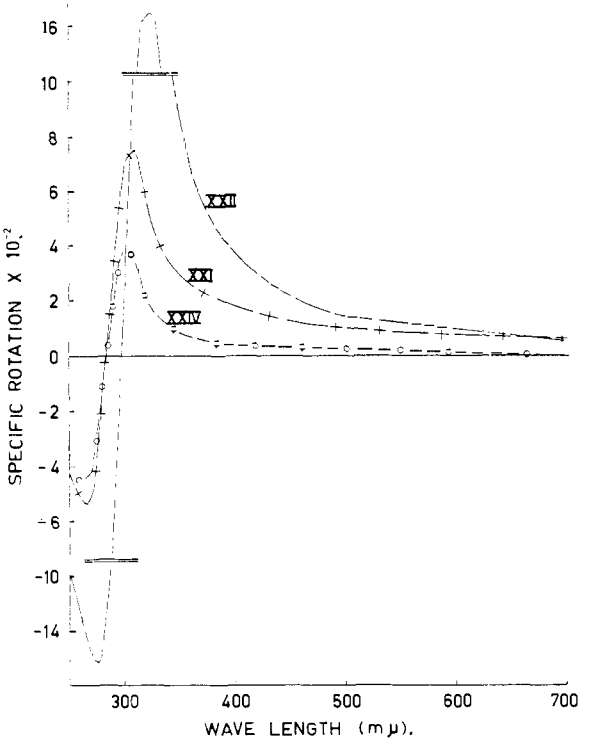


Fig. 5.—Rotatory dispersion curves of 2α-chlorocholestan-3-one (XXI), 2,2-dichlorocholestan-3-one (XXII) and 2α-chloro-4α-bromocholestan-3-one (XXIV).

(23) As will be shown below, this statement also applies to chlorine but not fluorine.

(24) Corey and Ursprung (ref. 21)—on the basis of molecular rotation difference calculations using $[\alpha]_D$ values of 5α- and 7α-bromo-3β-acetoxycholestan-6-one—have used this approach to assign absolute configurations to the bromofriedelins (IX, X).

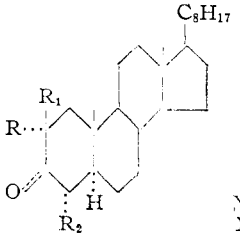
(25) This statement only refers to the *use* of this rotatory dispersion rule (ref. 2). The rule itself was of course established empirically by examining data of substances of known absolute configuration and thus differs fundamentally from the X-ray approach (see J. M. Bijvoet, *Endeavour*, **14**, 71 (1955)), which requires no reference substance at all.

(26) C. Djerassi and W. Closson, THIS JOURNAL, **78**, 3751 (1956).

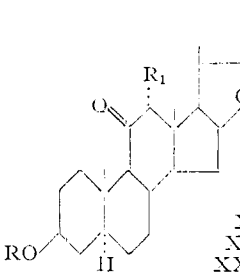
(27) See E. J. Corey, *ibid.*, **76**, 175 (1954).

(28) J. J. Beereboom and C. Djerassi, *J. Org. Chem.*, **19**, 1196 (1954).

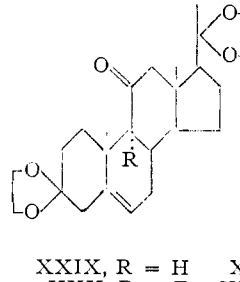
As far as the introduction of an equatorial chlorine atom in cholestan-3-one (XII) is concerned, the result is essentially the same as with bromine as demonstrated in Fig. 5. Thus the dispersion curves of 2α-chlorocholestan-3-one (XXI) and 2α-chloro-4α-bromocholestan-3-one (XXIV) do not differ to any marked extent (considering both wave lengths of peaks and troughs as well as amplitude) from those (Fig. 4) of the 2α-bromo (XIII) and 2α,4α-dibromo (XV) derivatives. 2,2-Dichlorocholestan-3-one (XXII) represents an interesting example since one of the chlorine atoms must be axially oriented and its dispersion curve (Fig. 5) shows increased amplitude as well as a bathochromic shift—both associated with axial halogens. Quantitatively, the bathochromic change (17 mμ) is nearly identical with that observed (XII → XXIII) in the rotatory dispersion curve of 2,2-dibromocholestan-3-one (XXIII) and this in turn is in substantial agreement with the ultraviolet absorption shifts[9] for these two compounds (XXII, XXIII).



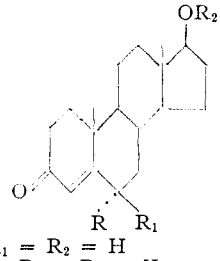
XXI, R = Cl; R_1 = R_2 = H
XXII, R = R_1 = Cl; R_2 = H
XXIII, R = R_1 = Br; R_2 = H
XXIV, R = Cl; R_1 = H; R_2 = Br



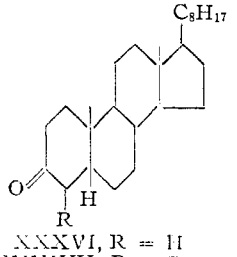
XXV, R = R_1 = R_2 = H
XXVI, R = Ac; R_1 = R_2 = Br
XXVII, R = Ac; R_1 = Cl; R_2 = H
XXVIII, R = Ac; R_1 = F; R_2 = H



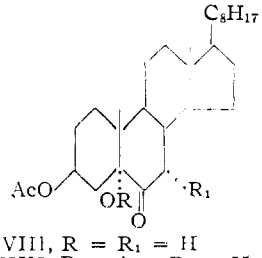
XXIX, R = H
XXX, R = F



XXXI, R = R_1 = R_2 = H
XXXII, R = F; R_1 = R_2 = H
XXXIII, R = R_2 = H; R_1 = F
XXXIV, R = H; R_1 = Cl; R_2 = Ac
XXXV, R = H; R_1 = Br; R_2 = Ac



XXXVI, R = H
XXXVII, R = Br



XXXVIII, R = R_1 = H
XXXIX, R = Ac; R_1 = H
XL, R = H; R_1 = Br
XLI, R = Ac; R_1 = Br

An even more instructive comparison of various axial halogen atoms is available in the sapogenin series and the pertinent curves are collected in Fig. 6. 11-Ketotigogenin (XXV) is characterized by a weak, positive single Cotton effect curve[29] associated[30] with 11-ketosteroids and introduction of an axial bromine[31] or chlorine atom at C-12 as in XXVI and XXVII results in the anticipated increased amplitude and bathochromic shift[32] as well as in an inversion of the sign of the Cotton effect. The latter observation is, of course, in full accord with the empirical rule recorded earlier.[2] In this series, the opportunity was also available to examine the effect of a fluorine atom and as can be seen from Fig. 6, 12α-fluoro-11-ketotigogenin acetate (XXVIII) exhibits the same wave length shifts as does the corresponding 12α-chloro analog XXVII, but the Cotton effect is of opposite sign. This grossly different behavior of axial fluorine—already anticipated in work with certain polycarbonyl compounds[33]—is further documented in Fig. 7 by comparing an 11-ketosteroid (11-ketoprogesterone 3,20-bis-cycloethylene ketal (XXIX)) with its 9α-fluoro derivative XXX. It will be noted that introduction of a 9α-fluorine atom causes an inversion of the sign of the Cotton effect in contrast to the action of a 9α-bromine substituent (Fig. 2, V *vs.* VI) where a positive single Cotton effect is maintained.

The remarkable difference in the rotatory dispersion of axial α-fluoroketones—manifesting itself by an inversion of the Cotton effect—as compared to axial α-chloro- and α-bromo-ketones can probably be ascribed to a large extent to the greatly enhanced electronegativity of fluorine over that of the other halogen atoms, although it is interesting to note that no major shifts in the dispersion peaks or troughs are associated with changes in the nature of the halogen atom. Nevertheless, steric factors may also play a role, particularly in a situation exemplified by 6-halo-Δ^4-3-ketones (XXXII–XXXV) and whose rotatory dispersion curves are collected in Fig. 8. While an equatorial (6α) grouping in 6-substituted-Δ^4-3-ketosteroids does not appear to affect the characteristic shape of the dispersion curve of a Δ^4-3-ketone, an axial (6β) substituent plays a definite role as has been demonstrated by examining pairs of C-6 epimeric hydroxy[8] and methyl[34] testosterones. At least in the latter case (6β-methyltestosterone[34]) this is probably due almost exclusively to steric interaction between the axial methyl groups at C-6 and C-10. Turning now to Fig. 8, it will be observed that the rotatory dis-

(29) C. Djerassi and R. Ehrlich, THIS JOURNAL, **78**, 440 (1956).

(30) E. W. Foltz, A. E. Lippman and C. Djerassi, *ibid.*, **77**, 4359 (1955).

(31) The presence of an additional bromine substituent in the spiroketal side chain as in XXVI has no effect on the dispersion curve as already has been demonstrated in ref. 29.

(32) The bathochromic shift in the position of the troughs of XXVI and XXVII as compared to the peak of the parent ketone XXV amounts to 20 mμ in the case of the 12α-bromide XXVI and 15 mμ for the 12α-chloro derivative XXVII. A somewhat smaller shift of axial chlorine compared to axial bromine already has been recorded earlier in an ultraviolet spectroscopic study of α-haloketones by R. C. Cookson and S. H. Dandegaonker (*J. Chem. Soc.*, 352 (1955)).

(33) Reference 8, p. 6384.

(34) These results will be described in a detailed paper now in preparation dealing with the rotatory dispersion effects of methyl groups in various polycyclic ketones.

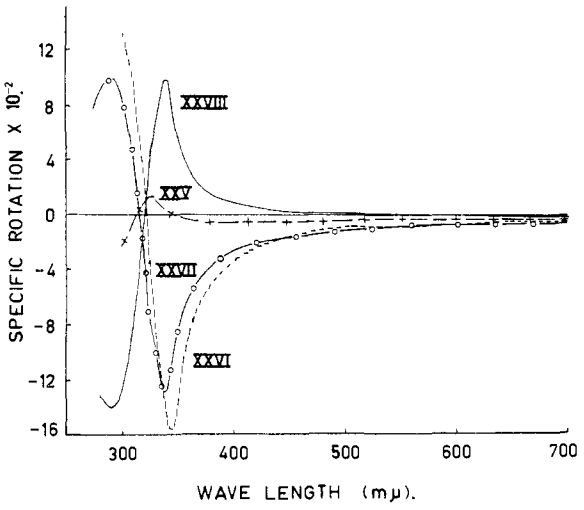


Fig. 6.—Rotatory dispersion curves of 11-ketotigogenin (XXV), 12α,23-dibromo-11-ketotigogenin acetate (XXVI), 12α-chloro-11-ketotigogenin acetate (XXVII) and 12α-fluoro-11-ketotigogenin acetate (XXVIII).

persion curve of the equatorial 6α-fluorotestosterone (XXXII) is virtually identical with that of testosterone (XXXI)[8] itself, while the axial epimer 6β-fluorotestosterone (XXXIII) exhibits an altered one. On the other hand, the axial 6β-chloro- (XXXIV) and 6β-bromo- (XXXV) testosterone acetates possess rotatory dispersion curves which resemble each other closely but are completely distinct from those of testosterone (XXXI)[8] or of 6β-fluorotestosterone (XXXIII). In summary, comparing the three 6β-halotestosterones (XXXIII–XXXV), it is clear that the electronic and/or steric factors responsible for this "axial dispersion effect" are of the same order of magnitude for chlorine and bromine but again completely different for fluorine.

The ring A halogenated ketones discussed so far (Figs. 4 and 5) all refer to A/B *trans* (allo) steroids. The single example of the A/B *cis* series available

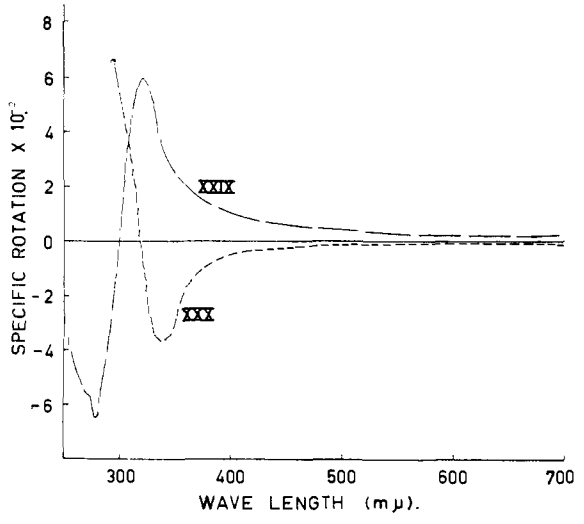


Fig. 7.—Rotatory dispersion curves of 11-ketoprogesterone 3,20-bis-cycloethylene ketal (XXIX) and 9α-fluoro-11-ketoprogesterone 3,20-bis-cycloethylene ketal (XXX).

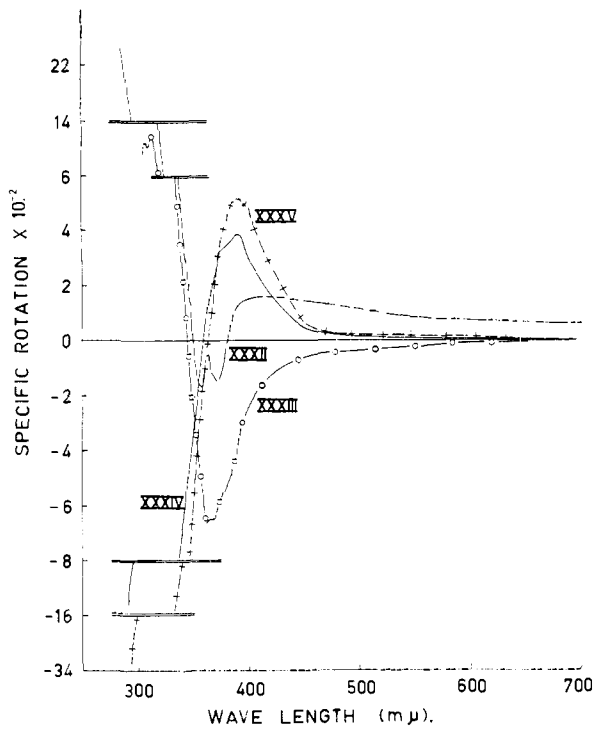


Fig. 8.—Rotatory dispersion curves of 6α-fluorotestosterone (XXXII), 6β-fluorotestosterone (XXXIII), 6β-chlorotestosterone acetate (XXXIV) and 6β-bromotestosterone acetate (XXXV).

to us—coprostanone (XXXVI) and 4β-bromocoprostanone (XXXVII)—suggests a similar behavior as in the *trans* series (*cf.* XII) in that equatorial bromine[35] produces no major alterations in the dispersion picture (Fig, 9),

The following data, dealing with ring B and ring C brominated keto steroids afford additional excellent evidence for the substantial coincidence between the reported ultraviolet spectral shifts[9,32] and those observed with dispersion peaks and troughs. Furthermore, additional examples are provided to support the "axial haloketone dispersion rule."[2]

Figure 10 depicts the rotatory dispersion curves of two 7α-bromo-3β-acetoxycholestan-6-ones which possess a 5α-hydroxy (XL) and 5α-acetoxy (XLI) substituent[36] together with the appropriate bromine-free ketones (XXXVIII and XXXIX). The expected[2] inversion of sign of the Cotton effect is observed in each case and the wave length shifts (see Experimental) are of the order of magnitude already recorded by Cookson and Dandegaonker[32] for their ultraviolet absorption maxima. One noticeable feature of these curves is that introduction of axial bromine did not result in the expected increased amplitude observed above for other axial haloketones (*e.g.*, Figs, 1 and 2) and this may be due to the presence of an axial grouping on the other

(35) The equatorial orientation of 4-bromo-3-keto-5β-steroids has been established by L. F. Fieser and R. Ettore, THIS JOURNAL, **75**, 1700 (1953); see also ref. 27.

(36) A detailed discussion of the rotatory dispersion effects produced by α-hydroxy and α-acetoxy substituents in ketosteroids will be published in *Helv. Chim. Acta* together with dispersion data on cardiac aglycones.

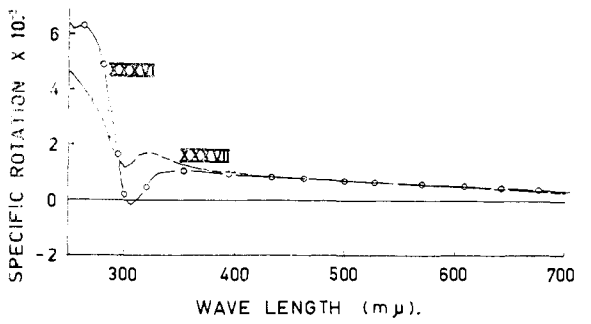
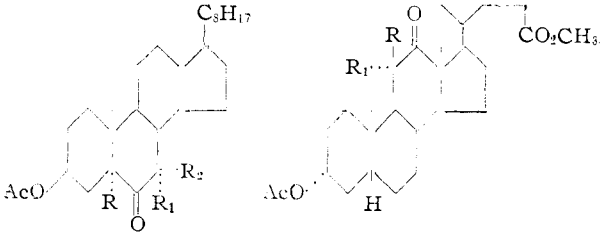


Fig. 9—Rotatory dispersion curves of coprostan-3-one (XXXVI) and 4β-bromocoprostan-3-one (XXXVII).

side of the carbonyl group (see also XLIII in Fig. 11).

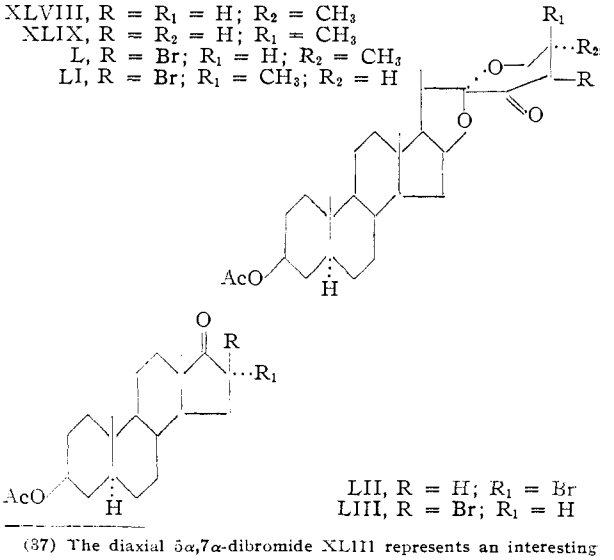
Cookson[9,32] has noted that the bathochromic ultraviolet, spectral shift due to axial bromine is additive in α,α′-dibrominated ketones as in 5α,7α-dibromo-3β-acetoxycholestan-6-one (XLIII). That this applies also to the rotatory dispersion is demonstrated in Fig. 11 which contains the dispersion curves of 3β-acetoxycholestan-6-one (XLII)[15] and



XLII, R = R_1 = R_2 = H
XLIII, R = R_1 = Br; R_2 = H
XLIV, R = R_2 = Br; R_1 = H

XLV, R = R_1 = H
XLVI, R = H; R_1 = Br
XLVII, R = Br; R_1 = H

XLVIII, R = R_1 = H; R_2 = CH_3
XLIX, R = R_2 = H; R_1 = CH_3
L, R = Br; R_1 = H; R_2 = CH_3
LI, R = Br; R_1 = CH_3; R_2 = H



LII, R = H; R_1 = Br
LIII, R = Br; R_1 = H

(37) The diaxial 5α,7α-dibromide XLIII represents an interesting case since the 5α-monobromide would be expected (ref. 2) to show a negative and the 7α-monobromide a positive Cotton effect. The isomer with the axial halogen atom at the ring juncture (see Figs. 1 and 2) shows dispersion curves with greater amplitude and, in accordance with this generalization, the 5α-substituent plays the dominant role in the 5α,7α-dibromide and imposes its negative Cotton effect over the positive component due to the 7α-halogen atom. The reduced amplitude of the resulting diaxial 5α,7α-dibromide curve as compared to the axial-equatorial 5α,7β-dibromide (the 7β-bromine atom not offering an opposing Cotton effect) further supports this interpretation.

of its 5α,7α-(XLIII) and 5α,7β-(XLIV) dibromides. All three curves are characterized by a single negative Cotton effect[37] and the bathochromic shifts of the trough due to one axial (XLII *vs.* XLIV, 24 mμ) and two axial (XLII *vs.* XLIII, 56 mμ) bromine atoms are virtually duplicated by the recorded[9] ultraviolet spectral changes of 25 and 60 mμ.

An instructive example for the preferred use of rotatory dispersion curves over conventional $[\alpha]_D$ measurements is afforded by the epimeric methyl 11-bromo-3β-acetoxy-12-ketocholanates (XLVI and XLVII). Their specific rotations at the sodium D

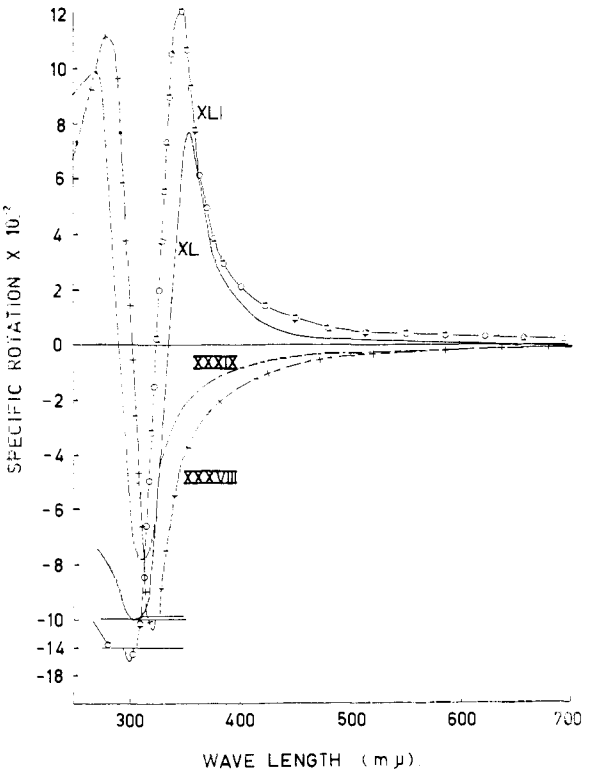


Fig. 10—Rotatory dispersion curves of cholestane-3β,5α-diol-6-one 3-acetate (XXXVIII), cholestane-3β,5α-diol-6-one 3,5-diacetate (XXXIX), 7α-bromocholestane-3α-,5α diol-6-one 3-acetate (XL) and 7α-bromocholestane-3β,5α-diol-6-one 3,5-diacetate (XLI).

line are essentially identical, but as demonstrated in Fig. 12 as rotation measurements are continued into the ultraviolet region the dispersion curves differ greatly. In accordance with the "axial haloketone dispersion rule,"[2] the axial 11β-bromo isomer XLVII exhibits a negative Cotton effect curve (in contrast to the positive one of the parent ketone XLV[26]), moved toward the visible and with greatly increased amplitude, while the equatorial 11α-bromo-12-ketone XLVI possesses a dispersion curve which is not greatly changed with respect to the unsubstituted 12-ketone XLV except for a small hypsochromic shift. In this particular pair of epimers the rotatory dispersion curves are probably more useful than the infrared spectra since the latter[12a] show some overlapping of bands due to the presence of three absorbing carbonyl systems.

It appeared of interest to determine whether the

much-debated configuration at C-22 of steroidal sapogenins could be attacked by rotatory dispersion measurements. Callow and Massy-Beresford[38] have described the preparation and bromination of 23-ketotigogenin acetate (XLVIII) and 23-ketoneotigogenin acetate (XLIX) and if the resulting bromoketones possessed the axial orientation, then the rotatory dispersion results would have been of considerable stereochemical utility. However, ultraviolet spectral measurements suggested[38] that the bromine atom in both substances L and LI was equatorial and this is now supported by the rotatory dispersion curves of these four ketones listed in the Experimental section.

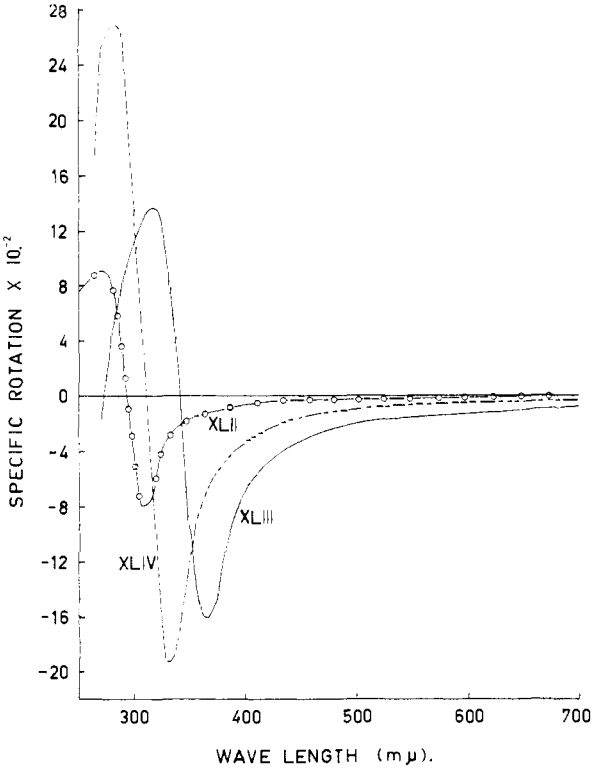


Fig. 11.—Rotatory dispersion curves of 3β-acetoxycholestan-6-one (XLII), 5α,7α-dibromo-3β-acetoxycholestan-6-one (XLIII) and 5α,7β-dibromo-3β-acetoxycholestan-6-one (XLIV).

An equally detailed study of the rotatory dispersion of α-halo-cyclopentanones was not possible because an insufficient number of examples were available. Recent infrared[12b,39] and ultraviolet[9] spectral investigations already have shown that no noticeable wave length shifts are to be anticipated between two epimeric α-halocyclopentanones. This is also borne out by the rotatory dispersion measurements given in the Experimental portion of this paper, although as a definite test case it would be attractive to measure the rotatory dispersion curves of a pair of isomeric α-bromoketones (as yet unavailable) such as a 15α-bromo-16-keto- and a 17α-bromo-16-ketosteroid, in order to determine

(38) R. K. Callow and P. N. Massy-Beresford, *Chemistry & Industry*, 1146 (1956); *J. Chem. Soc.*, 4482 (1957).

(39) F. V. Brutcher, T. Roberts, S. J. Barr and N. Pearson, THIS JOURNAL, **78**, 1507 (1956).

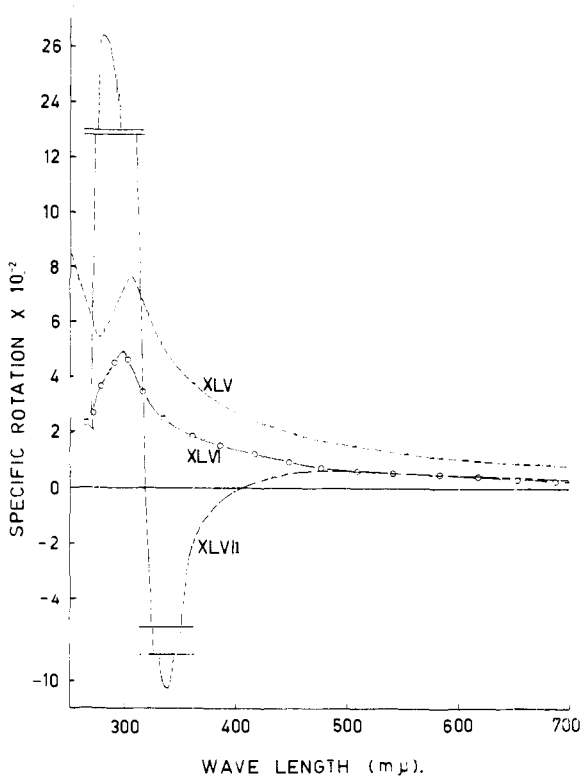


Fig. 12.—Rotatory dispersion curves of methyl 3β-acetoxy-12-ketocholanate (XLV), methyl 11α-bromo-3α-acetoxy-12-ketocholanate (XLVI) and methyl 11β-bromo-3α-acetoxy-12-ketocholanate (XLVII).

whether the Cotton effect in each case remains negative as has been found to be characteristic[15,40] for steroidal 16-ketones.

A pair of steroidal α-bromocyclopentanones is represented by the epimeric 16α-bromo-(LII) and 16β-bromo-(LIII) isoandrosterone acetates. Except for some amplitude differences, their dispersion curves (including positions of peaks and troughs) are identical and this also applied to their ultraviolet absorption maxima (LII, 315 mμ; LIII, 314 mμ). We also have determined the rotatory dispersion of a series of halogenated camphor derivatives, since the earlier measurements[41] by the photographic method did not go far enough into the ultraviolet region. The relevant ultraviolet[9] and infrared[39] spectral data for these compounds have been reported already and the rotatory dispersion data are practically self-explanatory. All of the halo-camphors studied had a positive Cotton effect, as does (+)-camphor itself,[42] the wave length shifts of the dispersion peaks being of essentially the same order of magnitude as found[9] for the corresponding ultraviolet absorption maxima. Thus the peaks of 3α- and 3β-chlorocamphor[43] occur at practically the same wave length while that of 3,3-dichlorocamphor is moved to longer wave length by

(40) C. Djerassi, R. Riniker and B. Riniker, *ibid.*, **78**, 6362 (1956).

(41) J. O. Cutter, H. Burgess and T. M. Lowry, *J. Chem. Soc.*, 1260 (1925).

(42) T. M. Lowry and H. K. Gore, *Proc. Roy. Soc. (London)*, **A135**, 13 (1932).

(43) The numbering system employed by Cookson (ref. 9) is used here.

about 10 mμ. 3α-Bromocamphor and 3,3-dibromocamphor behave similarly except that in accordance with expectation[9] the peaks are found somewhat closer to the visible side of the spectrum.

Experimental[44]

6α-Bromo-3β-acetoxycholestan-7-one (II) (E. J. Corey), R.D. (Fig. 1) in methanol (*c* 0.019): $[\alpha]_{700}$ −5°, $[\alpha]_{589}$ +20°, $[\alpha]_{355}$ +50° (sh.), $[\alpha]_{300}$ −335°, $[\alpha]_{265}$ +180°, $[\alpha]_{260}$ +175°.

6β-Bromo-3β-acetoxycholestan-7-one (III) (E. J. Corey), R.D. (Fig. 1) in methanol (*c* 0.010): $[\alpha]_{700}$ +40°, $[\alpha]_{589}$ +90°, $[\alpha]_{335}$ +1130°, $[\alpha]_{287.5}$ −1560°, $[\alpha]_{245}$ −1110°.

8β-Bromo-3β-acetoxycholestan-7-one (IV) (E. R. H. Jones), R.D. (Fig. 1) in methanol (*c* 0.071): $[\alpha]_{700}$ −55°, $[\alpha]_{589}$ −97°, $[\alpha]_{335}$ −2495°, $[\alpha]_{287.5}$ +3288°, $[\alpha]_{270}$ +1908°.

3β-Acetoxyergostan-11-one (V) (H. B. Henbest), R.D. (Fig. 2) in methanol (*c* 0.090): $[\alpha]_{700}$ +15°, $[\alpha]_{589}$ +32°, $[\alpha]_{322.5}$ +283°, $[\alpha]_{282.5}$ +28°, $[\alpha]_{255}$ +127° (infl.), $[\alpha]_{250}$ +229°.

9α-Bromo-3β-acetoxyergostan-11-one (VI) (H. B. Henbest), R.D. (Fig. 2) in methanol (*c* 0.104): $[\alpha]_{700}$ +79°, $[\alpha]_{589}$ +112°, $[\alpha]_{347.5}$ +2160°, $[\alpha]_{297.5}$ −2560°, $[\alpha]_{265}$ −1310°.

12α-Bromo-3β-acetoxyergostan-11-one (VII) (H. B. Henbest), R.D. (Fig. 2) in methanol (*c* 0.10): $[\alpha]_{700}$ +13°, $[\alpha]_{589}$ +7°, $[\alpha]_{342.5}$ −1361°, $[\alpha]_{292.5}$ +1411°, $[\alpha]_{270}$ +1221°.

2α-Bromofriedelin (IX),[45] R.D. (Fig. 3) in dioxane (*c* 0.104): $[\alpha]_{700}$ −46°, $[\alpha]_{589}$ −95°, $[\alpha]_{335}$ −2496°, $[\alpha]_{285}$ +2712°, $[\alpha]_{275}$ +2394°; λ_{max}^{dox} 313 mμ (as compared to 285.5 mμ for friedelin).

4α-Bromofriedelin (X),[45] R.D. (Fig. 3) in dioxane (*c* 0.070): $[\alpha]_{700}$ +30°, $[\alpha]_{589}$ +81°, $[\alpha]_{335}$ +2056°, $[\alpha]_{290}$ −2134°, $[\alpha]_{285}$ −2126°.

2α,4β-Dibromofriedelin (XI),[46] R.D. in dioxane (*c* 0.09): $[\alpha]_{700}$ −60°, $[\alpha]_{589}$ −107°, $[\alpha]_{332.5}$ −2799°, $[\alpha]_{290}$ +3853°, $[\alpha]_{280}$ +3756°; λ_{max}^{dox} 310.5 mμ.

2α-Bromocholestan-3-one (XIII), R.D. (Fig. 4) in methanol (*c* 0.098): $[\alpha]_{700}$ +42°, $[\alpha]_{589}$ +52°, $[\alpha]_{310}$ +684°, $[\alpha]_{270}$ −664°, $[\alpha]_{255}$ −578°.

4α-Bromocholestan-3-one (XIV) (B. A. Hems), R.D. (Fig. 4) in methanol (*c* 0.065): $[\alpha]_{700}$ −21°, $[\alpha]_{589}$ +8°, $[\alpha]_{302.5}$ +265°, $[\alpha]_{267.5}$ −456°, $[\alpha]_{255}$ −351°.

2α,4α-Dibromocholestan-3-one (XV), R.D. (Fig. 4) in methanol (*c* 0.090): $[\alpha]_{700}$ +2°, $[\alpha]_{589}$ +10°, $[\alpha]_{305}$ +328°, $[\alpha]_{260}$ −647°, $[\alpha]_{252.5}$ −581°.

Methyl 2α-bromo-3-keto-5α-etianate (XVII), R.D. in methanol (*c* 0.095): $[\alpha]_{700}$ +57°, $[\alpha]_{589}$ +95°, $[\alpha]_{312.5}$ +1030°, $[\alpha]_{272.5}$ −246°, $[\alpha]_{250}$ +323°.

Methyl 2α,4α-dibromo-3-keto-5α-etianate (XVIII), R.D. in methanol (*c* 0.10): $[\alpha]_{700}$ +25°, $[\alpha]_{589}$ +36°, $[\alpha]_{307.5}$ +483°, $[\alpha]_{267.5}$ −208°, $[\alpha]_{260}$ −3°.

Androstan-2-one-17β-ol propionate (XIX) (R. R. Engle), R.D. in dioxane (*c* 0.126): $[\alpha]_{700}$ −2°, $[\alpha]_{589}$ 0°, $[\alpha]_{320}$ +1140°, $[\alpha]_{280}$ −1100°, $[\alpha]_{275}$ −1070°.

3α-Bromoandrostan-2-one-17β-ol propionate (XX) (R. R. Engle), R.D. in methanol[47] (*c* 0.11): $[\alpha]_{700}$ +120°, $[\alpha]_{589}$ +152°, $[\alpha]_{335}$ +3050°, $[\alpha]_{290}$ −3320°, $[\alpha]_{260}$ −2100°.

2α-Chlorocholestan-3-one (XXI), R.D. (Fig. 5) in methanol (*c* 0.092): $[\alpha]_{700}$ +61°, $[\alpha]_{589}$ +74°, $[\alpha]_{310}$ +745°, $[\alpha]_{265}$ −535°, $[\alpha]_{250}$ −425°.

2,2-Dichlorocholestan-3-one (XXII), R.D. (Fig. 5) in methanol (*c* 0.040): $[\alpha]_{700}$ +47°, $[\alpha]_{589}$ +109°, $[\alpha]_{325}$ +1656°, $[\alpha]_{275}$ −1545°, $[\alpha]_{245}$ −815°.

2,2-Dibromocholestan-3-one (XXIII), R.D. in dioxane[47] (*c* 0.124): $[\alpha]_{700}$ +64°, $[\alpha]_{589}$ +119°, $[\alpha]_{330}$ +1830°, $[\alpha]_{290}$ −1590°, $[\alpha]_{285}$ −1496°.

2α-Chloro-4α-bromocholestan-3-one (XXIV), R.D. (Fig. 5) in methanol (*c* 0.096): $[\alpha]_{700}$ −9°, $[\alpha]_{589}$ +19°, $[\alpha]_{300}$ +364°, $[\alpha]_{260}$ −457°, $[\alpha]_{255}$ −435°.

12α-Chloro-11-ketotigogenin acetate (XXVII) (J. Fried), R.D. (Fig. 6) in dioxane (*c* 0.048): $[\alpha]_{700}$ −48°, $[\alpha]_{589}$ −61°, $[\alpha]_{340}$ −1296°, $[\alpha]_{290}$ +988°, $[\alpha]_{275}$ +756°; λ_{max}^{dox} 311 mμ.

12α-Fluoro-11-ketotigogenin acetate (XXVIII) (J. Fried), R.D. (Fig. 6) in dioxane (*c* 0.068): $[\alpha]_{700}$ −12°, $[\alpha]_{589}$ +6°, $[\alpha]_{340}$ +982°, $[\alpha]_{290}$ −1400°, $[\alpha]_{280}$ −1319°; λ_{max}^{dox} 311 mμ.

11-Ketoprogesterone 3,20-bis-cycloethylene ketal (XXIX) (J. Fried, G. H. Thomas), R.D. (Fig. 7) in methanol (*c* 0.110): $[\alpha]_{700}$ +23°, $[\alpha]_{589}$ +25°, $[\alpha]_{321.5}$ +596°, $[\alpha]_{280}$ −651°, $[\alpha]_{255}$ −357°.

9α-Fluoro-11-ketoprogesterone 3,20-bis-cycloethylene ketal (XXX) (J. Fried, G. H. Thomas), R.D. (Fig. 7) in methanol (*c* 0.133): $[\alpha]_{700}$ −13°, $[\alpha]_{589}$ −8°, $[\alpha]_{340}$ −368°, $[\alpha]_{292.5}$ +658°, $[\alpha]_{289}$ +642°.

6α-Fluorotestosterone (XXXII) (A. Bowers), R.D. (Fig. 8) in dioxane (*c* 0.12): $[\alpha]_{700}$ +61°, $[\alpha]_{589}$ +81°, $[\alpha]_{410}$ +164° (sh.), $[\alpha]_{355}$ −156°, $[\alpha]_{285}$ +2260°.

6β-Fluorotestosterone (XXXIII) (A. Bowers), R.D. (Fig. 8) in dioxane (*c* 0.10): $[\alpha]_{700}$ +4°, $[\alpha]_{589}$ −8°, $[\alpha]_{362.5}$ −654°, $[\alpha]_{312.5}$ +1353°, $[\alpha]_{290}$ +965°.

6β-Chlorotestosterone acetate (XXXIV) (A. Bowers), R.D. (Fig. 8) in dioxane (*c* 0.139): $[\alpha]_{700}$ +1°, $[\alpha]_{589}$ +5°, $[\alpha]_{390}$ +383°, $[\alpha]_{287.5}$ −2079°.

6β-Bromotestosterone acetate (XXXV) (A. Bowers), R.D. (Fig. 8) in dioxane (*c* 0.137): $[\alpha]_{700}$ −6°, $[\alpha]_{589}$ −3°, $[\alpha]_{397.5}$ +498°, $[\alpha]_{395}$ +470°, $[\alpha]_{390}$ +513°, $[\alpha]_{295}$ −3370°.

4β-Bromocoprostan-3-one (XXXVII), R.D. (Fig. 9) in methanol (*c* 0.095): $[\alpha]_{700}$ +36°, $[\alpha]_{589}$ +48°, $[\alpha]_{460}$ +88° (sh.), $[\alpha]_{425}$ +86°, $[\alpha]_{375}$ +129°, $[\alpha]_{370-350}$ +116° to +135° (broad sh.), $[\alpha]_{325}$ +171°, $[\alpha]_{300}$ +123°, $[\alpha]_{252.5}$ +472°.

Cholestane-3β,5α-diol-6-one 3-acetate (XXXVIII) (R. C. Cookson), R.D. (Fig. 10) in methanol (*c* 0.067): $[\alpha]_{700}$ −19°, $[\alpha]_{589}$ −30°, $[\alpha]_{322.5}$ −1275°, $[\alpha]_{282.5}$ +1115°, $[\alpha]_{240}$ +569°.

Cholestane-3β,5α-diol-6-one 3,5-diacetate (XXXIX) (R. C. Cookson), R.D. (Fig. 10) in methanol (*c* 0.065): $[\alpha]_{700}$ −28°, $[\alpha]_{589}$ −17°, $[\alpha]_{310}$ −780°, $[\alpha]_{275}$ +982°, $[\alpha]_{245}$ +874°.

7α-Bromocholestane-3β,5α-diol-6-one 3-acetate (XL) (R. C. Cookson), R.D. (Fig. 10) in methanol (*c* 0.089): $[\alpha]_{700}$ −8°, $[\alpha]_{589}$ +2°, $[\alpha]_{355}$ +777°, $[\alpha]_{305}$ −994°, $[\alpha]_{270}$ −733°.

7α-Bromocholestane-3β,5α-diol-6-one 3,5-diacetate (XLI) (R. C. Cookson), R.D. (Fig. 10) in methanol (*c* 0.041): $[\alpha]_{700}$ +12°, $[\alpha]_{589}$ +22°, $[\alpha]_{495}$ +59° (infl.), $[\alpha]_{347.5}$ +1260°, $[\alpha]_{300}$ −1698°, $[\alpha]_{260}$ −1012°.

5α,7α-Dibromo-3β-acetoxycholestan-6-one (XLIII) (R. C. Cookson), R.D. (Fig. 11) in methanol (*c* 0.066): $[\alpha]_{700}$ −72°, $[\alpha]_{589}$ −127°, $[\alpha]_{362.5}$ −1622°, $[\alpha]_{315}$ +1351°, $[\alpha]_{270}$ −185°.

5α,7β-Dibromo-3β-acetoxycholestan-6-one (XLIV) (R. C. Cookson), R.D. (Fig. 11) in methanol (*c* 0.068): $[\alpha]_{700}$ −21°, $[\alpha]_{589}$ −50°, $[\alpha]_{330}$ −1936°, $[\alpha]_{280}$ +2740°, $[\alpha]_{260}$ +1761°.

Methyl 11α-bromo-3α-acetoxy-12-ketocholanate (XLVI) (T. F. Gallagher), R.D. (Fig. 12) in methanol (*c* 0.094): $[\alpha]_{700}$ +27°, $[\alpha]_{589}$ +47°, $[\alpha]_{295}$ +498°, $[\alpha]_{270}$ +212°, $[\alpha]_{265}$ +232°.

Methyl 11β-bromo-3α-acetoxy-12-ketocholanate (XLVII) (T. F. Gallagher, T. Reichstein), R.D. (Fig. 12) in methanol (*c* 0.086): $[\alpha]_{700}$ +34°, $[\alpha]_{589}$ +50°, $[\alpha]_{450-500}$ +57° (sh.), $[\alpha]_{337.5}$ −1020°, $[\alpha]_{280}$ +2640°, $[\alpha]_{270}$ +2550°.

23-Ketotigogenin acetate (XLVIII) (R. K. Callow), R.D. in dioxane (*c* 0.10): $[\alpha]_{700}$ −50°, $[\alpha]_{589}$ −62°, $[\alpha]_{420-460}$ −89° (sh.), $[\alpha]_{410}$ −79°, $[\alpha]_{400}$ −83°, $[\alpha]_{330}$ +358°, $[\alpha]_{280}$ −1130°.

23-Ketoneotigogenin acetate (XLIX) (R. K. Callow), R.D. in dioxane (*c* 0.096): $[\alpha]_{700}$ −60°, $[\alpha]_{589}$ −71°, $[\alpha]_{450}$ −88°, $[\alpha]_{330}$ +588°, $[\alpha]_{280}$ −1491°.

24-Bromo-23-ketotigogenin acetate (L) (R. K. Callow), R.D. in dioxane (*c* 0.085): $[\alpha]_{700}$ −39°, $[\alpha]_{589}$ −50°, $[\alpha]_{410}$ −89°, $[\alpha]_{330}$ +147°, $[\alpha]_{290}$ −917°.

24-Bromo-23-ketotigogenin acetate (LI) (R. K. Callow), R.D. in dioxane (*c* 0.104): $[\alpha]_{700}$ −76°, $[\alpha]_{589}$ −95°, $[\alpha]_{410-420}$ −156° (broad peak), $[\alpha]_{357.5}$ −54°, $[\alpha]_{280}$ −1139°.

16α-Bromoisoandrosterone acetate (LII) (F. Sorm), R.D. in methanol (*c* 0.107): $[\alpha]_{700}$ +35°, $[\alpha]_{589}$ +56°, $[\alpha]_{341.5}$ +1290°, $[\alpha]_{294}$ −1536°, $[\alpha]_{260}$ −673°; λ_{max}^{EtOH} 315 mμ, log ε 1.99.

16β-Bromoisoandrosterone acetate (LIII) (F. Sorm),

(44) For experimental procedure, limits of error and nomenclature, see refs. 5, 7, 8. We are greatly indebted to the investigators listed in the Experimental section for donating samples. Where no source is given, the substance was available in the authors' laboratory. The measurements were carried out at room temperature (23–27°) without jacketed tubes, but the temperature variation for any given dispersion curve did not exceed 1°.

(45) Prepared by Dr. M. Cais in this Laboratory according to ref. 21.

(46) Synthesized by Dr. M. Cais by monobromination of 2-bromofriedelin in acetic acid and letting stand for 20 hr. The resulting precipitate and a second crop of equal purity obtained by partial dilution with water were recrystallized from ethanol–chloroform; m.p. 231–233°, $[\alpha]_D$ −123° ($CHCl_3$). *Anal.* Calcd. for $C_{30}H_{48}Br_2O$: C, 61.64; H, 8.27; Br, 27.34; O, 2.75. Found: C, 61.44; H, 8.43; Br, 27.43; O, 2.93.

(47) A correction of 8 mμ has to be applied in comparing rotatory dispersion curves run in methanol and dioxane (ref. 8).

R.D. in methanol (*c* 0.086): $[\alpha]_{700}$ +74°, $[\alpha]_{589}$ +112°, $[\alpha]_{341.5}$ +2097°, $[\alpha]_{294}$ −2733°, $[\alpha]_{260}$ −1762°; λ_{max}^{EtOH} 314 mμ, log ε 2.03.

(+)-**Camphor** (Eastman Kodak Co.), R.D. in methanol (*c* 0.10): $[\alpha]_{700}$ +5°, $[\alpha]_{589}$ +23°, $[\alpha]_{312.5}$ +2009°, $[\alpha]_{265}$ −3305°, $[\alpha]_{255}$ −2590°.

3α-Chlorocamphor[43] (F. V. Brutcher), R.D. in methanol (*c* 0.095): $[\alpha]_{700}$ +68°, $[\alpha]_{589}$ +95°, $[\alpha]_{331}$ +1798, $[\alpha]_{292.5}$ −1437°, $[\alpha]_{250}$ +603°,

3β-Chlorocamphor[43] (F. V, Brutcher), R.D. in methanol (*c* 0.097): $[\alpha]_{700}$ +22°, $[\alpha]_{589}$ +35°, $[\alpha]_{330}$ +1810°, $[\alpha]_{285}$ −2170°, $[\alpha]_{250}$ −1093°,

3,3-Dichlorocamphor (F, V. Brutcher) R.D. in methanol (*c* 0.101): $[\alpha]_{700}$ +21°, $[\alpha]_{589}$ +43°, $[\alpha]_{339}$ +1951°, $[\alpha]_{292.5}$ −2609°, $[\alpha]_{260}$ −1945°,

3α-Bromocamphor[43] (F, V. Brutcher), R.D. in methanol (*c* 0.107): $[\alpha]_{700}$ +84°, $[\alpha]_{589}$ +131°, $[\alpha]_{335}$ +1970°, $[\alpha]_{290}$ −1472°, $[\alpha]_{260}$ −177°.

3,3-Dibromocamphor (F. V, Brutcher), R.D. in methanol (*c* 0.10): $[\alpha]_{700}$ +23°, $[\alpha]_{589}$ +39°, $[\alpha]_{345}$ +1455°, $[\alpha]_{297.5}$ −2200°, $[\alpha]_{270}$ −1730°.

DETROIT, MICHIGAN

[CONTRIBUTION FROM THE MCARDLE MEMORIAL LABORATORY, THE MEDICAL SCHOOL, UNIVERSITY OF WISCONSIN]

The Synthesis of the Mono- and Dihydroxy Derivatives of 1,2,5,6-Dibenzanthracene Excreted by the Rabbit and of Other Hydroxylated Dibenzanthracene Derivatives[1]

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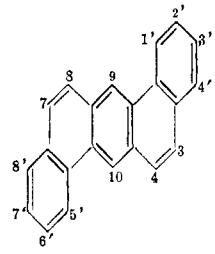
Two metabolites of 1,2,5,6-dibenzanthracene excreted by rabbits after administration of this polycyclic hydrocarbon have been characterized by synthesis as 2'-hydroxy- and 2',6'-dihydroxy-1,2,5,6-dibenzanthracene. In addition, derivatives of 4,8-dihydroxy- and 4,7-dihydroxy-1,2,5,6-dibenzanthracene have been prepared, and a new synthesis of 3,7-dihydroxy-1,2,5,6-dibenzanthracene is described. All the monohydroxy isomers of 1,2,5,6-dibenzanthracene are now known as the result of the synthesis of four new monohydroxy derivatives of this hydrocarbon.

In 1937, Levi and Boyland[2] reported the isolation of a dihydroxy-dibenzanthracene derivative from the urine of rabbits maintained on a diet containing 0.16% of 1,2,5,6-dibenzanthracene. The same compound was obtained by Dobriner, Rhoads and Lavin[3] from the urine and feces of rabbits injected subcutaneously or intramuscularly with dibenzanthracene, A different metabolite, isolated by Dobriner, *et al.*,[3] from the urine and feces of mice or rats injected with dibenzanthracene, was identified by synthesis as 4',8'-dihydroxy-1,2,5,6-dibenzanthracene by Cason and Fieser.[4] Cook and Schoental,[5] in a re-investigation of the metabolism of dibenzanthracene in rabbits, isolated a second phenolic metabolite from the feces, which they believed was a monohydroxy derivative of the hydrocarbon. Since studies concerning hydrocarbon carcinogenesis utilizing 1,2,5,6-dibenzanthracene are being carried out actively in this Laboratory,[6-8] we undertook the characterization of the two rabbit metabolites, not only for the purpose of determining the positions in the dibenzanthracene molecule hydroxylated by rabbits, a species relatively resistant to hydrocarbon carcinogenesis, but also in the interest of learning more about the chemistry of dibenzanthracene and of relieving the chemical literature of the embarrassment of two rather simple uncharacterized compounds. In the work reported here both rabbit metabolites were again isolated to provide samples for comparison with synthetic products,[9] and the metabolites were characterized by synthesis as 2'-hydroxy- and 2',6'-dihydroxy-1,2,5,6-dibenzanthracene. In addition, a number of other hydroxylated dibenzanthracene derivatives were prepared, and all of the monohydroxy-dibenzanthracene isomers are now known.



Initially we focused our attention on the dihydroxy metabolite, because more information concerning its structure was available. Levi and Boyland[2] had converted this compound to the corresponding dihydroxy-dibenz-9,10-anthraquinone, thereby eliminating the 9- and 10-positions as sites for the hydroxyl groups. They also concluded from the stability of the metabolite to air oxidation that the hydroxyl groups were not *ortho* or *para* to each other. In the present work 9,10-dihydroxy- and 3,4-dihydroxy-1,2,5,6-dibenzanthracene, prepared by reduction of the corresponding dibenzanthraquinones, were too unstable to be isolated as such and were therefore converted to the 9,10-dimethyl ether and the 3,4-diacetate X, respectively, A comparison of these two synthetic products with the corresponding derivatives of the dihydroxy metabolite demonstrated their non-

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(2) A. A. Levi and E. Boyland, *Chemistry & Industry*, **15**, 446 (1937).

(3) K. Dobriner, C. P. Rhoads and G. I. Lavin, *Proc. Soc. Exptl. Biol. Med.*, **41**, 67 (1939).

(4) J. Cason and L. F. Fieser, THIS JOURNAL, **62**, 2681 (1940).

(5) J. W. Cook and R. Schoental, *J. Chem. Soc.*, 9 (1952).

(6) C. Heidelberger, H. I. Hadler and G. Wolf, THIS JOURNAL, **75**, 1303 (1953).

(7) C. Heidelberger and M. Moldenhauer, *Cancer Research*, **16**, 442 (1956).

(8) P. M. Bhargava and C. Heidelberger, THIS JOURNAL, **78**, 3671 (1956).

(9) We thank Professor Eric Boyland for a sample of the dihydroxy rabbit metabolite, part of which we converted to the diacetoxy-dibenz-9,10-anthraquinone.