Acknowledgment.—The authors are very thankful to Dr. R. H. Marchessault, American Viscose Corporation, Marcus Hook, Pa., for valuable help and advice. They are also grateful to the referee of this paper for his constructive criticism of the manuscript. C. P. J. G. wishes to express his thanks to the Celanese Corporation of America for two fellowships and to the Pulp and Paper Research Institute of Canada for two summer stipends.

MONTREAL, QUEBEC

[CONTRIBUTION FROM THE DIVISION OF STEROID METABOLISM AND BIOCHEMISTRY, SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH]

Synthesis of 2-Methoxyestrogens[1]

BY JACK FISHMAN

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The synthesis of 2-methoxyestrone, a new urinary metabolite of estradiol, and 2-methoxyestradiol, a possible metabolite, is described.

The isolation of 2-methoxyestrone, a new metabolite of estradiol, from human urine recently was reported from this Laboratory.[2] Since the amount of material isolated precluded degradation studies, the structure of the metabolite was determined by synthesis,[2,3] which resulted in a small quantity of product sufficient only for comparison purposes. In order to satisfy a need for substantial quantities of 2-methoxyestrone for isotopic dilution studies and other contemplated metabolic experiments, a more productive method of synthesis was necessary. In addition, the possibility that other 2-methoxy metabolites might be present in human urine added interest to an alternative synthesis that might yield new products of natural origin. A recently developed method of *o*-hydroxylation of phenols[4] appeared to provide the answer to these requirements. In general the scheme involves reaction of the phenol with 2-chloro-5-nitrobenzophenone, cyclization of the resultant diaryl ether to the xanthylium salt and oxidation of the latter with hydrogen peroxide to give the *o*-hydroxylated product. This could then be cleaved with piperidine to give the pyrocatechol. Methylation prior to cleavage would result in the corresponding guaiacol.

The initial attempt to use this sequence with estrone resulted in a crystalline compound, m.p. 204–207°, the ultraviolet spectrum of which was identical with 2-methoxyestrone. The infrared spectrum, however, showed that the 17-ketone was no longer present. The spectrum indicated that a ring D lactone had been formed by oxidation with the hydrogen peroxide in the acidic medium.[5] Under several conditions the 17-ketone group failed to survive the oxidation step and therefore attention was directed to the use of a compound lacking this group, from which, however, it could subsequently be generated. Estradiol appeared particularly suitable in that it would also lead to 2-methoxyestradiol which was of interest in itself. The etherification of estradiol-17β with 2-chloro-5-nitrobenzophenone proceeded smoothly in ethanolic potassium hydroxide solution. The nitrobenzophenone ether (Ib) was obtained in better than 90% yield, based on the reagent, and the excess unreacted estradiol was separated easily by alkali extraction. The only by-product, 2-ethoxy-5-nitrobenzophenone, was formed in very small amounts by alcoholysis of the 2-chloro-5-nitrobenzophenone, and could be separated readily from the desired product by chromatography. Since the 17-hydroxy group also failed to survive treatment with acidic hydrogen peroxide, Ib was acetylated to give the non-crystalline 17-acetate Ic. The latter was dissolved in a minimum of acetic acid and cyclized with cold concentrated sulfuric acid. The dark red solution of the xanthylium acid sulfate salt II was diluted with more acetic acid and oxidized with an excess of 30% hydrogen peroxide. The resultant precipitate, 2-hydroxy-17β-acetoxy-$\Delta^{1,3,5(10)}$-estratriene 3-(2-benzoyl-4-nitro)-phenyl ether (IIIa), showed carbonyl absorption at 1655 cm.$^{-1}$ in chloroform, interpreted as indicating bonding between the carbonyl and the phenolic groups. Methylation of the phenol with diazomethane gave the methyl ether IIIb, the carbonyl absorption of which was at 1672 cm.$^{-1}$ in chloroform. The choice of diazomethane as a methylating agent in preference to dimethyl sulfate in alkali was dictated by the desire to avoid the complicating possibility of a Smiles rearrangement.[4] Piperidine cleavage of IIIb proceeded smoothly to give 2-piperidino-5-nitrobenzophenone and 2-methoxy-3-hydroxy-17β-acetoxyestra-1,3,5-(10)-triene (IVa). Separation of the two compounds was achieved by chromatography on alumina. Hydrolysis of the acetate IVa with ethanolic potassium hydroxide gave the desired 2-methoxyestradiol-17β (IVb). The same compound (IVb) was obtained directly from IIIb by hot alkaline hydrolysis, the other product being 2-hydroxy-5-nitrobenzophenone. In this case separation was effected readily by extracting the nitrophenol with alkali, the 2-methoxyestradiol remaining in the organic phase.

(1) This investigation was supported in part by a grant from the American Cancer Society and a research grant (CY-3207) from the National Cancer Institute of the National Institutes of Health, United States Public Health Service.

(2) S. Kraychy and T. F. Gallagher, THIS JOURNAL, **79**, 754 (1957).

(3) S. Kraychy and T. F. Gallagher, *J. Biol. Chem.*, **229**, 519 (1957).

(4) J. D. Loudon and J. A. Scott, *J. Chem. Soc.*, 265 (1953).

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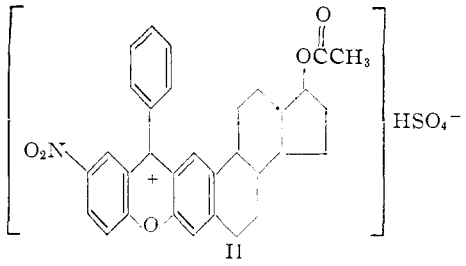
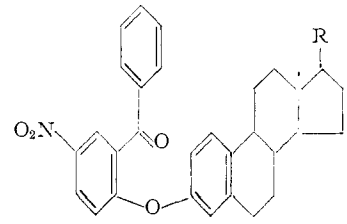
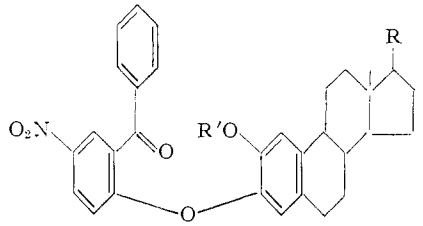


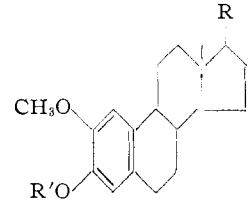
II



Ia, R = O
b, R = OH
c, R = CH_3COO



IIIa, R = CH_3COO, R′ = H
b, R = CH_3COO, R′ = CH
c, R = OH, R′ = CH_3
d, R = O, R′ = CH_2



IVa, R = CH_3COO, R′ = H
b, R = OH, R′ = H
c, R = OH, R′ = C_6H_5CO
d, R = CH_3COO, R′ = CH_3CO
e, R = O, R′ = H
f, R = O, R′ = C_6H_5CO

Attempts to oxidize 2-methoxyestradiol directly to 2-methoxyestrone, using various mild oxidation methods resulted in poor yields at best. A lengthier but more satisfactory method was therefore used. Hydrolysis of IIIb in acid removed the acetoxy group leaving the ether at 3 intact to give IIIc. Oxidation of the latter with chromic acid in acetone[6] gave the 17-keto compound IIId. Piperidine cleavage or hot alkaline hydrolysis of IIId provided 2-methoxyestrone, m.p. 187–188°, identical in all respects with the compound prepared by the previous method.[2] 2-Methoxyestrone could also be obtained from 2-methoxyestradiol by protecting the phenolic group as the benzoate, oxidation of the C-17 alcohol and subsequent hydrolysis. The first method, however, was preferred since selective benzoylation of the relatively alkali-insoluble 2-methoxyestradiol was difficult. The synthesis of 2-methoxyestrone resulted in over-all yields of better than 30%, and served to confirm further the structure assigned to the new metabolite.

The cyclization with sulfuric acid appeared to be exclusively with C-2 and no C-4 substituted products were isolated. Molecular models indicate that the formation of the xanthylium ion at C-4 would result in some steric interference between the unsubstituted benzene ring and the hydrogens at C-6. An even more likely explanation for the non-cyclization at C-4 is that the xanthylium ion at that position would be forced out of planarity and thus lose some of its stabilizing resonance forms.

It is hoped in the future to use this method to prepare other 2-methoxyestrogens as well as other possible ring A metabolites. These will be useful in the further elucidation of the metabolism of estradiol.

(6) A. Bowers, T. G. Halsall, E. R. H. Jones and in part A. J. Lemin, *J. Chem. Soc.*, 2555 (1953).

Experimental[7]

Estrone 3-(2-Benzoyl-4-nitro)-phenyl Ether (Ia).—To a solution of 0.210 g. of potassium hydroxide in 50 ml. of absolute ethanol, 1.71 g. of estrone (0.0063 mole) was added. To the warm ethanol solution 0.853 g. (0.0033 mole) of 2-chloro-5-nitrobenzophenone[8] was added, and the reddish solution was refluxed for 24 hours; during this time a precipitate of potassium chloride formed. After concentration to one-half volume, the cooled mixture was poured into 1 *N* sodium hydroxide solution and extracted with chloroform. Removal of the solvent yielded 1.365 g. (84%) of white solid, m.p. 238–241°. The analytical sample was crystallized from a large amount of methanol, m.p. 240–243°, $[\alpha]^{26}D$ +88°; λ_{max} 254 mμ (ε 18,000), 296 mμ (ε 12,000); λ_{min} 237 mμ (ε 14,000), 283 mμ (ε 11,600).

Anal. Calcd. for $C_{31}H_{29}O_5N$: C, 75.13; H, 5.90; N, 2.83. Found: C, 74.60; H, 5.91; N, 2.73.

On acidification of the aqueous alkali solution 0.7 g. of estrone was recovered.

Attempted Preparation of 2-Methoxyestrone from Ia.—One hundred milligrams of Ia was dissolved in 0.5 ml. of cold concentrated sulfuric acid to give a deep red solution. After 30 minutes 4 ml. of glacial acetic acid was added and oxidation was accomplished with an excess of 30% hydrogen peroxide (0.5 ml.). When the color had changed to pale amber (30 minutes) the solution was poured into ice-water, the dark brown precipitate was filtered off and washed with water. The product was methylated with excess diazomethane in ether. Long silky needles, m.p. 144–147°, were obtained from ethanol. The material was refluxed with piperidine for 1 hour, diluted with benzene and washed well with dilute sulfuric acid. The benzene solution was extracted with dilute sodium hydroxide solution which after acidification and extraction with chloroform yielded a few crystals, m.p. 204–207° from methanol, λ_{max} 286 mμ, λ_{min} 254 mμ. The infrared spectrum exhibited carbonyl absorption at 1720 $cm.^{-1}$ in chloroform rather than the normal 17-ketone absorption at 1736 $cm.^{-1}$ in chloroform. This, together with bands at 1121, 1100, 1060 and 962 $cm.^{-1}$, strongly indicated that the 17-ketone had been oxidized to the 13,17-seco-lactone. Modification, using an equimolar amount of hydrogen peroxide failed to give the desired 2-methoxyestrone and further work with Ia was abandoned.

17β-Hydroxy-$\Delta^{1,3,5(10)}$-estratriene 3-(2-Benzoyl-4-nitro)-phenyl Ether (Ib).—To a solution of 5 g. of estradiol 17β (0.0184 mole) and 0.586 g. (0.0105 mole) of potassium hydroxide in 100 ml. of ethanol, 2.4 g. (0.0092 mole) of 2-chloro-5-nitrobenzophenone was added. After refluxing for 48 hours the solution was concentrated to half the volume and poured into 200 ml. of 1 *N* sodium hydroxide solution. The white suspension was extracted 3 times with chloroform, and after drying over sodium sulfate and evaporation there was obtained a yellow viscous oil. The oil was dissolved in 50 ml. of 1:1 petroleum ether–benzene and chromatographed on 150 g. of alumina (Merck, acid-washed). Elution with 1:1 petroleum ether–benzene and crystallization from ethanol gave 90 mg. of 2-ethoxy-5-nitrobenzophenone, m.p. 114–116°.

(7) The estrone and estradiol used in this work were kindly supplied by Schering Corporation and Chas. Pfizer and Co. Rotations were determined in a 2-dcm. tube and chloroform was the solvent unless otherwise noted. Ultraviolet spectra were measured in ethanol using a Cary recording spectrophotometer and ethanol was the solvent unless otherwise noted. Melting points were determined on a micro hot-stage apparatus. Analyses were performed by Spang Microanalytical Laboratories.

(8) A. Fries, *Ann.*, **454**, 287 (1927).

Anal. Calcd. for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.47; H, 4.86; N, 5.15.

Elution with benzene gave 4.12 g. (90%) of an oil which on trituration with ether crystallized as prisms melting to a viscous oil at 95–100°. Further crystallizations from ether or benzene–petroleum ether gave a melting point of 97–105°, which could not be improved further. That the melting point range was a characteristic of the compound and not due to impurities was shown by oxidation of a small sample to give only Ia in excellent yield. The analytical sample melted at 97–105°, $[\alpha]^{26}D$ +40°; λ_{max} 254.5 mμ (ε 17,000), 296 mμ (ε 11,300); λ_{min} 237 mμ (ε 13,700), 284 mμ (ε 11,000).

Anal. Calcd. for $C_{31}H_{31}O_5N$: C, 74.83; H, 6.28; N, 2.82. Found: C, 74.75; H, 6.19; N, 2.57.

Elution of the column with ether afforded some unreacted estradiol which together with that recovered from the alkaline solution amounted to 1.43 g.

17β-Acetoxy-$\Delta^{1,3,5(10)}$-estratriene 3-(2-Benzoyl-4-nitro)-phenyl Ether (Ic).—Acetylation of Ib with acetic anhydride and pyridine yielded the 17-acetate as a viscous oil which resisted crystallization. The infrared spectrum in chloroform showed the presence of the acetate band at 1723 cm.$^{-1}$ and there was no evidence of hydroxyl absorption at 3600 cm.$^{-1}$.

2-Hydroxy-17β-acetoxy-$\Delta^{1,3,5(10)}$-estratriene 3-(2-Benzoyl-4-nitro)-phenyl Ether (IIIa).—To a solution of 7.5 g. of the acetate Ic in 4 ml. of glacial acetic acid, 10 ml. of cold concentrated sulfuric acid was added slowly with cooling and shaking. The dark red solution was stored at room temperature for 30 minutes. It was then diluted with 40 ml. of glacial acetic acid, and 10 ml. of a 1:1 mixture of acetic acid and 30% hydrogen peroxide was added dropwise with shaking. After 10 minutes the color of the solution lightened and a tan precipitate began to appear. The mixture was allowed to stand 20 minutes more, poured into ice-water and the precipitate was filtered off. After washing well with 5% sodium bicarbonate solution and water, the precipitate was dried and crystallized from methanol to give 4.6 g., m.p. 167–170°. A second crop of 1.6 g., m.p. 166–170°, was obtained on concentration of the mother liquors, yield 80%. The infrared spectrum in chloroform showed bands at 1723 cm.$^{-1}$ (acetate) and 1652–1657 cm.$^{-1}$ (strongly bonded conjugated ketone). The analytical sample melted at 170–172°, $[\alpha]^{28.5}D$ +21.0°; λ_{max} 255 mμ (ε 17,250), 289 mμ (ε 14,620); λ_{min} 238 mμ (ε 13,100), 276 mμ (ε 13,500).

Anal. Calcd. for $C_{33}H_{33}O_7N$: C, 71.33; H, 5.99. Found: C, 70.86; H, 5.84.

2-Methoxy-17β-acetoxy-$\Delta^{1,3,5(10)}$-estratriene 3-(2-Benzoyl-4-nitro)-phenyl Ether (IIIb).—A solution of 2.2 g. of IIIa in 50 ml. of ethanol was stored for 24 hours at 5° with an excess of diazomethane in ether. Evaporation of the ether and excess diazomethane and cooling the remaining ethanol solution gave 2 g. (89%) of product as white feathery crystals, m.p. 166–167°. The infrared carbonyl absorption bands in chloroform were at 1726 cm.$^{-1}$ (acetate) and 1672 cm.$^{-1}$ (unbonded conjugated ketone) and no hydroxyl band was present. The analytical sample melted at 169–171°, $[\alpha]^{26}D$ +36°; λ_{max} 254 mμ (ε 15,960), 287 mμ (ε 13,350); λ_{min} 239 mμ (ε 12,790), 275 mμ (ε 12,470).

Anal. Calcd. for $C_{34}H_{35}O_7N$: C, 71.69; H, 6.19. Found: C, 71.84; H, 6.45.

2-Methoxy-3-hydroxy-17β-acetoxyestra-1,3,5(10)-triene (IVa).—A sample of IIIb (432 mg.) was refluxed for 1 hour in 20 ml. of piperidine. The dark solution was diluted with 100 ml. of benzene and washed with dilute sulfuric acid until the washings were acidic. Extraction with 1 *N* sodium hydroxide solution failed to remove any material from the organic phase. Evaporation of the benzene gave 446 mg. of dark red oil which was dissolved in a small amount of petroleum ether–benzene 1:1 and chromatographed on 16 g. of acid-washed alumina. Elution with 1:1 petroleum ether–benzene gave 2-piperidino-5-nitrobenzophenone[9] as a yellow oil which crystallized on standing. Further elution with the same solvent mixture resulted in 180 mg. (70%) of crystalline material. Recrystallization from benzene–petroleum ether gave plates changing to needles, m.p. 192–195°. The analytical sample melted at 194–196°, $[\alpha]^{26}D$ +125°.

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.34; H, 8.26.

2-Methoxyestradiol-17β (IVb). A. From IVa.—Hydrolysis of the acetate IVa with 5% ethanolic potassium hydroxide in an atmosphere of nitrogen gave 2-methoxyestradiol which crystallized from a small amount of benzene, m.p. 184–186°.

B. From IIIb.—A solution of 1.43 g. of IIIb in 50 ml. of 6% ethanolic potassium hydroxide was refluxed for 2 hours in an atmosphere of nitrogen. The solution was diluted with water and extracted with benzene to give 700 mg. of yellow crystalline material (92%) which was recrystallized from chloroform as blades. These dried to an opalescent white solid, m.p. 184–186°. For analysis a sample was recrystallized from a small quantity of acetone, m.p. 188–190°, $[\alpha]^{21}D$ +100°, λ_{max} 286 mμ (ε 3640), λ_{min} 253 mμ (ε 335). The yield of 2-methoxyestradiol from estradiol was 59%.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.17; H, 8.87.

The diacetate IVd was prepared in the usual manner with pyridine and acetic anhydride. Crystallization from methanol gave needles, m.p. 165–166°, $[\alpha]^{26.5}D$ +53°.

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.23; H, 7.62.

The 3-monobenzoate IVc was prepared by partial solution of 2-methoxyestradiol in 1 *N* sodium hydroxide and shaking with an excess of benzoyl chloride. The product was filtered off, crystallized from methanol as prisms, m.p. 194–198°. Further crystallization gave the analytical sample, m.p. 195–198°, $[\alpha]^{28}D$ +72°.

Anal. Calcd. for $C_{26}H_{30}O_4$: C, 76.82; H, 7.44. Found: C, 77.09; H, 7.71.

2-Methoxy-17β-hydroxy-$\Delta^{1,3,5(10)}$-estratriene 3-(2-Benzoyl-4-nitro)-phenyl Ether (IIIc).—A solution of 203 mg. of IIIb in 40 ml. of ethanol containing 8 ml. of concentrated sulfuric acid was refluxed for 24 hours. The solution was diluted with water, extracted with ether, washed with sodium bicarbonate and evaporated to give 180 mg. of solid. Crystallization from methanol gave 164 mg. (85%), m.p. 123–125°. The analytical sample melted at 125–126°, $[\alpha]^{28}D$ +61°.

Anal. Calcd. for $C_{32}H_{33}O_6N$: C, 72.84; H, 6.30. Found: C, 73.24; H, 6.55.

The same product also was obtained by alkaline hydrolysis of IIIb at room temperature but in considerably lower yield.

2-Methoxyestrone 3-(2-Benzoyl-4-nitro)-phenyl Ether (IIId).—To a solution of 290 mg. of IIIc in 40 ml. of acetone, an 8 *N* solution of chromic oxide in sulfuric acid was added dropwise until the orange-brown color persisted. The solution was allowed to stand for 15 minutes at room temperature, poured into water and extracted with chloroform. Removal of the solvent gave 231 mg. (80%) of a solid which crystallized from methanol as needles, m.p. 203–205°. The analytical sample melted 204–205°, $[\alpha]^{28}D$ +89°.

Anal. Calcd. for $C_{32}H_{31}O_6N$: C, 73.12; H, 5.95. Found: C, 73.34; H, 5.77.

2-Methoxyestrone (IVe).—A solution of 240 mg. of IIId in 20 ml. of piperidine was refluxed for 1 hour. After cooling, 100 ml. of benzene was added, and the solution was washed well with dilute sulfuric acid. On drying and removing the benzene a yellow oil was obtained which was subjected to a 99-transfer countercurrent distribution between 70% aqueous methanol and carbon tetrachloride. Tubes 14–32 were combined to give 128 mg. of material which was filtered through a short alumina column and crystallized from dilute methanol to give 108 mg. (80%) of blades, m.p. 188–191°. The product was identical in all respects with that prepared by the other route; the yield from estradiol was 32%.

The 3-monobenzoate IVf was prepared both by Schotten–Baumann benzoylation of IVe and by chromic acid oxidation of 2-methoxyestradiol-3-benzoate (IVc). The products obtained by either method were identical. The analytical sample crystallized from methanol as broad needles, m.p. 225–228°.

(9) J. D. Loudon, J. R. Robertson, J. N. Watson and S. E. Aiton *J. Chem. Soc.*, 55 (1950).

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

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NEW YORK 21, N. Y.

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

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

BY CARL DJERASSI, JEANNE OSIECKI, ROSEMARIE RINIKER AND BERNHARD RINIKER

RECEIVED OCTOBER 14, 1957

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

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(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).

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

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(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.

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(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