[CONTRIBUTION OF THE COLLEGE OF PHARMACY OF THE UNIVERSITY OF WASHINGTON]

Proton Magnetic Resonance Spectra, Stereochemistry, and Synthesis of 2-(Chlorophenyl)cyclohexanols¹

ALAIN C. HUITRIC, WILLIAM G. CLARKE, JR., KAREN LEIGH, AND DONALD C. STAIFF

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The six isomeric cis- and trans-2-(chlorophenyl)cyclohexanols with the chlorine in ortho, metha, and para positions have been synthesized and their stereochemistry investigated by NMR. The NMR spectra of all isomers and their corresponding acetoxy derivatives are consistent with structures in which the cyclohexane ring is in a chair conformation with the aromatic ring in equatorial orientation. The signals of the 1- and 2-hydrogen atoms of the ortho isomers have larger paramagnetic shifts than those of the meta or para isomers which are almost identical for a given stereoisomer. This is explained in terms of long range shielding effects. The Nef reaction on 2-(o-chlorophenyl)nitrocyclohexane yielded a mixture of the ketone and the corresponding oxime. The production of the oxime was not observed with either the m- or p-chloro isomers.

The application of NMR in conformation analysis of substituted six-membered ring compounds is well established.² In compounds with fixed chair conformation there is stronger spin-spin coupling between axial hydrogens on neighboring carbon atoms than between neighboring hydrogens in other orientations. The method is especially useful in the assignment of configuration and conformation of 1,2-disubstituted six-membered ring compounds in which the signals of the 1- and 2-hydrogen atoms are isolated from those of the other ring hydrogens due to chemical shifts brought about by the substituents, as demonstrated with 2-o-tolylcyclohexanols and their acetoxy derivatives.³ The investigation is now extended to 2-(chlorophenyl)cyclohexanols.

The signals for the 1- and 2-hydrogens of the NMR spectra of the six isomers and their acetoxy derivatives are shown in Figure 1. The signals are readily differentiated by the large downfield shift of the 1-hydrogen upon acetylation. The signals of the 2-hydrogen of I and II are overlapped by the signals of the hydroxyl hydrogens and in part by those of other ring hydrogens. The broad unresolved multiplets of the 1- and 2-hydrogens for compounds I, II, and III and their acetates are consistent with the trans configuration and that chair conformation with the aromatic group equatorial, as with this geometry the 1- and 2-hydrogens are both axial and each is adjacent to two nonidentical axial hydrogens. The cis configuration, and the chair conformation with the aromatic group equatorial, are clearly established in each case for IV, V, VI, and their acetates by the singlet of the 1-hydrogen and the doublet of the 2-hydrogen. In this geometry the 1-hydrogen is equatorial and has little spin-spin coupling with adjacent hydrogens, while the 2-hydrogen is axial and adjacent to only one other axial hydrogen, giving rise to the doublet with $J_{2,3}$ of about 11.5 cycles per second.

The chemical shifts, listed in Table I, indicate that for any given stereoisomer the shielding of the 2-hydrogen is almost identical when the chlorine is meta or para, but that compared to these a significant paramagnetic shift occurs when the chlorine is in the *ortho* position. The same applies to the 1-hydrogen but the downfield shift is much smaller. Analogous differences are observed between the ortho and para isomers of trans-2-tolylcyclohexanol. This suggests that steric factors of the ortho substituents play a role in increasing the long range deshielding effect caused by the benzene ring current fields. Maximum deshielding by the benzene ring takes place in regions falling in the plane of the ring.^{4,5} Maximum deshielding of the 2-hydrogen will therefore occur when the phenyl ring is perpendicular to the plane of the cyclohexane ring. Approximately the same orientation of the phenyl group is necessary for maximum deshielding of the 1-hydrogen in the trans isomers. The 1-hydrogen is further from the aromatic ring but still well within its range of influence.⁴ Substituents in the ortho position will hinder rotation of the phenyl ring in such a way as to cause the rings to be oriented more closely perpendicular to each other. From these considerations the observed paramagnetic shifts, due to ortho substituents, of the 2-hydrogen in all stereoisomers and of the 1hydrogen of the trans isomers are as expected. The diamagnetic anisotropy of the ortho C-Cl

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Fig. 1. NMR spectra showing the signals of the 1- and 2-hydrogens of 2-(chlorophenyl)cyclohexanols and their acetoxy derivatives (60 mc.; about 1 molar in carbon tetra-chloride at 23° with tetramethylsilane as internal reference)

bond may also play a role since there is also a paramagnetic shift of the 1-hydrogen in the *cis* isomers of the ortho-chloro compounds, while little effect would be expected here on steric consideration alone.

In fixed six-membered ring systems an equatorial hydrogen is known to absorb at lower frequencies than its axial counterpart.⁵ The lower τ value for

the 1-hydrogen of any cis isomer compared to the corresponding trans isomer in the present series is consistent with this, although the diamagnetic anisotropy of the benzene ring would be expected to have a greater deshielding effect on the 1hydrogen in the trans compounds where the 1hydrogen is axial. The higher τ value for the 2hydrogen of any trans-cyclohexanol compared to its cis isomer is attributed to the magnetic anisotropy of the C-O bond and the difference is as expected since the magnetic anisotropy of a carbon-oxygen single bond is similar to that of a carbon-carbon single bond (ref. 5, page 117). The effect of the magnetic anisotropy of the C-O bond will be to shield the 2-hydrogen in the trans isomers and deshield it in the cis isomers. In the acetates the magnetic anisotropy of the carbonyl bond can play an additional role.

trans-2-(p-Chlorophenyl)cyclohexanol (I) and trans-2-(m-chlorophenyl)cyclohexanol (IJ) were prepared from the corresponding chlorophenyllithium and cyclohexene oxide. o-Chlorophenyllithium is known to be unstable at temperatures above -50° while good yields can be obtained at $-90^{\circ.6}$ None of the desired product was obtained when cyclohexene oxide was added to o-chlorophenyllithium at -90° in ether, stirring the mixture at -90° to -80° for one hour and allowing the mixture to warm to room temperature. Triphenylene was isolated from the reaction mixture indicating that the formation of the benzyne intermediate from o-chlorophenyllithium occurs at lower temperature than the reaction of the latter with cyclohexene oxide. trans-2-(o-Chlorophenyl)cyclohexanol (III) was obtained by lithium aluminum hydride reduction of 2-(o-chlorophenyl)cyclohexanone. The reaction of the *p*-chlorophenylmagnesium bromide with cyclohexene oxide yielded the bromohydrin trans-2-bromocyclohexanol. cis-2-(p-Chlorophenyl)cyclohexanol (IV), cis-2-(m-chlorophenyl)cyclo-hexanol (V), and cis-2-(o-chlorophenyl)cyclohexanol (VI) were prepared by the reduction of the corresponding 2-(chlorophenyl)cyclohexanones with cyclopentylmagnesium bromide, a method previously used for the preparation of *cis*-2-o-tolylcvclohexanol.^{*} The 2-(chlorophenyl)cvclohexanones were obtained by the Nef reaction on the corresponding nitro compounds which in turn were obtained by the Diels-Alder condensation of the appropriate β -nitrostyrene with butadiene^{7,8} followed by catalytic hydrogenation of the double bond. The pseudonitrole side reaction products of the Nef reaction⁹ were greatly reduced by the addition of sodium bisulfite to the acidic solution

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TABLE I

^a Values from ref. 2. ^b The τ value is not known as the signal is overlapped with that of the methyl group but it is larger than 7.7 p.p.m.

before the addition of the conjugate base of the nitro compound. Yields of the ketones were almost doubled by this method.

In addition to the expected ketone, the Nef reaction on 2-(o-chlorophenyl)cyclohexanone gave a larger amount of the corresponding oxime (about 1.5 to 1). The overall yield was also increased by the addition of sodium bisulfite, but the ratio of oxime to ketone remained about the same. Some oxime was also formed by the Nef reaction on 2-o-tolylnitrocyclohexane.¹⁰ This suggests that, in addition to the usual acid-catalyzed hydrolytic reaction,¹¹ a reduction reaction is possible under the conditions of the Nef reaction and that steric factors of the ortho substituents in substituted 2-phenylnitrocyclohexanes play a role in either slowing down the hydrolytic reaction or speeding up the reduction reaction. Further investigation of ortho substituent effects is being pursued. The formation of cyclohexanone oxime from nitrocyclohexane under conditions somewhat analogous to those of the Nef reaction has been reported¹² and a partial mechanism going through an aci-nitrocyclohexane ester intermediate has been proposed.13

EXPERIMENTAL

trans-2-(p-Chlorophenyl)cyclohexanol (I). Cyclohexene oxide (30.5 g., 0.31 mole) was added with stirring over a period of 5 min. to a solution of 0.8 mole of p-chlorophenyllithium¹⁴ in 400 ml. of anhydrous ether maintained at 0°. Spontaneous refluxing started after removal of the ice bath. The mixture was heated to refluxing for 90 min. after the initial refluxing had subsided. The excess lithium was removed by filtration through glass wool; the mixture hydrolyzed by pouring into an ice water mixture, acidified with 10% hydrochloric acid, and extracted with ether. The ether

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solution was neutralized by washing with sodium bicarbonate solution and dried with anhydrous sodium sulfate. Removal of the ether and recrystallization from hexane gave 25 g. of product, m.p. 83-84.5°. This yield can be undoubtedly increased by more careful recovery of recrystallization product. By very careful determination on a Kofler micro hot stage the substance is seen to melt at 83°, followed by resolidification and remelting at 84.5°.

Anal. Calcd. for $\bar{C}_{12}H_{15}ClO: C, 68.40; H, 7.18; Cl, 16.83.$ Found: C, 68.12; H, 7.13; Cl, 16.76.

Acetate of I b.p. 100° at 0.25 mm., calcd. for $C_{14}H_{17}ClO_2$: C, 66.53; H, 6.78. Found: C, 66.36; H, 6.71.

trans-2-(m-Chlorophenyl)cyclohexanol (II). This compound was obtained by the procedure described for I, using 0.2 mole of m-chlorophenyllithium.¹⁵ The crude liquid product was distilled under reduced pressure. The fraction with b.p. 116-118° at 0.7 mm. solidified. Recrystallization from hexane gave 16 g. of crystalline material m.p. 47-47.5°.

Anal. Calcd. for $C_{12}H_{15}ClO$: C, 68.40; H, 7.18; Cl, 16.83. Found: C, 68.54; H, 7.18; Cl, 16.79.

Acetate of II. B.p. 100° at 0.28 mm.

Anal. Caled. for $C_{14}H_{17}ClO_2$: C, 66.53; H, 6.78. Found: C, 66.65: H, 6.97.

 α -Naphthylurethan of II. M.p. 146–146.5°.

Anal. Calcd. for C₂₃H₂₂ClNO₂: C, 72.72; H, 5.84; N, 3.69. Found: C, 72.46; H, 5.78; N, 3.59.

trans-2-(o-Chlorophenyl)cyclohexanol (III). Lithium aluminum hydride reduction, in ether, of 6 g. of 2-(o-chlorophenyl)cyclohexanone yielded 5.3 g. of solid material and a small amount of oily substance. Recrystallization from hexane yielded 4.75 g. (78.5%) of colorless crystalline material, m.p. 58-59°. This was shown by NMR to be the *trans* isomer.

Anal. Calcd. for C₁₂H₁₆ClO: C, 68.40; H, 7.18. Found: C, 68.19, H, 7.08.

Acetate of III. B.p. 102° at 0.5 mm.

Anal. Calcd. for C₁₄H₁₇ClO₂: C, 66.53; H, 6.78. Found: C, 66.48; H, 6.77.

cis-2-(p-Chlorophenyl)cyclohexanol (IV). The cis isomer was obtained by the reduction of 2-(p-chlorophenyl)cyclohexanone⁸ with cyclopentylmagnesium bromide, a method previously reported for cis-2-o-tolylcyclohexanol.³ A solution of 5 g. (0.024 mole) of 2-(p-chlorophenyl)cyclohexanone in 30 ml. of anhydrous ether was added with stirring to a solution of 0.05 mole of cyclopentylmagnesium bromide in 50 ml. of anhydrous ether and the mixture was refluxed for 90 min. Work-up of the reaction mixture in the usual manner⁸ gave 5.4 g. of liquid material. The infrared spectrum indicated contamination with a carbonyl containing compound. The material was treated with Girard's "T"

(15) H. Gilman and S. M. Spatz, J. Am. Chem. Soc., 66, 621 (1944).

reagent and 0.2 g. of original ketone (characterized by mixed melting point) was recovered. The nonketonic material, 4.6 g., solidified. Chromatography of 1 g. of the solid material on 30 g. of neutral alumina¹⁶ gave two main fractions. The largest fraction, about 60%, m.p. 55~55.5° is shown by NMR to be the *cis* isomer.

Anal. Calcd. for $C_{12}H_{16}ClO$: C, 68.40; H, 7.18. Found: C, 68.21, H, 7.14.

Acetate of IV. M.p. 99-100°.

Anal. Caled. for C₁₄H₁₇ClO₂: C, 66.53; H, 6.78. Found: C, 66.65; H, 6.97.

The second fraction from chromatography, m.p. $83-84^\circ$, was identical with I (mixed melting point and infrared spectra).

cis-2-(m-Chlorophenyl)cyclohexanol (V). This compound was obtained by the reduction of 10 g. of 2-(m-chlorophenyl)cyclohexanone with cyclopentylmagnesium bromide in the same manner as IV. The resulting liquid material was distilled giving 9 g. of viscous, colorless liquid, b.p. 106-108° at 0.25 mm. Chromatography on alumina of 1 g. of the material gave a small amount of unchanged ketone; a fraction of solid, m.p. 47-47.5°, identical with II, and about 60% of a liquid shown by NMR to be the cis-2-(m-chlorophenyl)cyclohexanol. The pure cis isomer was obtained by separation of the α -naphthylurethans by fractional crystallization and subsequent reduction of the α -naphthylurethan of the cis isomer with lithium aluminum hydride in the presence of aluminum chloride in tetrahydrofuran.³ The separated α -naphthylurethans were characterized by comparison with the α -naphthylurethan of pure II. The product was distilled under reduced pressure, b.p. 108° at 0.3 mm. (a colorless liquid).

Anal. for V. Caled. for $C_{12}H_{15}ClO$: C, 68.40; H, 7.18. Found: C, 68.71; H, 7.39.

α-Naphthylurethan of V. M.p. 142-143°.

Anal. Caled. for $C_{22}H_{22}ClNO_2$: C, 72.72; H, 5.84; N, 3.69. Found: C, 72.41; H, 5.92; N, 3.46.

Acetate of V. B.p. 108° at 0.4 mm.

Anal. Calcd. for C₁₄H₁₇ClO₂: C, 66.53; H, 6.78. Found: C, 66.65; H, 7.11.

cis-2-(o-Chlorophenyl)cyclohexanol (VI) was prepared by the reduction of 2-(o-chlorophenyl)cyclohexanone with cyclopentylmagnesium bromide and isolated in the same manner as described for V. The yield of the *cis* isomer, determined by chromatography on alumina, was approximately 60%. The α -naphthylurethans of the *trans* and *cis* isomers were differentiated by comparison with the α naphthylurethan of pure III, which has a m.p. of 131-132°. The product was distilled under reduced pressure, b.p. 93° at 0.3 mm. (a colorless liquid).

Anal. Caled. for C₁₂H₁₅ClO: C, 68.40; H, 7.18. Found: C, 68.74; H, 7.21.

α-Naphthylurethan of VI. M.p., 206-207°.

Anal. Caled. for $C_{23}H_{22}ClNO_2$: C, 72.72; H, 5.84; N, 3.69. Found: C, 72.42; H, 5.90; N, 3.64.

4-Nitro-5-(chlorophenyl)cyclohexenes. These compounds were prepared by the method of Wildman and Wildman⁷ by heating 20 g. of the appropriate β -nitrostyrene with about 20 ml. of condensed butadiene, 30 ml. of toluene, and trace amount of hydroquinone in a Pyrex bomb at 110° for 6 or 7 days. The yield of the purified products, recrystallized from isopropyl alcohol, was about 70%.

| Isomers | M.P. | Calcd. | Found |
|------------------------|--------|-----------|------------------|
| <i>m</i> -Chlorophenyl | 66–67° | Cl, 14.92 | $14.76 \\ 14.78$ |
| <i>o</i> -Chlorophenyl | 80–81° | Cl, 14.92 | |

2-(Chlorophenyl)nitrocyclohexanes. These compounds were obtained in quantitative yield by low pressure (about

(16) T. Reichstein and C. W. Shoppee, Far. Soc. Disc., 7, 305 (1949).

20 p.s.i.) catalytic hydrogenation of the corresponding cyclohexenes using 10% palladium-on-carbon as catalyst and ethyl acetate as solvent. One equivalent of hydrogen was taken up within 15 to 20 min. and the uptake of hydrogen would then come to a stop. There was no evidence of any reduction of the nitro group when the hydrogenation was carried out for 90 min. We have direct experimental evidence from NMR that the 2-arylnitrocyclohexanes obtained through the above sequence of reactions involving a Diels-Alder condensation are the *trans* isomers as expected. This will be described in a later publication.

| Isomers | M.P. | Calcd. | Found |
|--------------------------------------|-----------------|-------------------------------------|-----------------------|
| <i>m</i> -Chlorophenyl | 74–75° | C, 60.13 H, 5.89 N, 5.84 | 60.02 5.79 5.70 |
| o-Chlorophenyl | 81 -8 2° | C, 60.13 H, 5.89 N 5.84 | 60.25 5.76 5.69 |
| <i>p</i> -Chlorophenyl ¹⁷ | 51-51.5° | C, 60.13 H, 5.89 N, 5.84 | |

Nef reaction of 2-(chlorophenyl)nitrocyclohexanes. The Nef reaction on 4-nitro-5-arylcyclohexenes¹⁸ resulted in poor yields of the ketones and always produced a considerable amount of blue or green material. Such colored products during the Nef reaction are usually attributed to nitrosation side reactions.⁹ The colored side reaction products can be greatly reduced and the yield of the ketone almost doubled by the addition of sodium bisulfite.

A basic solution prepared by reacting 2.54 g. (0.112 g.atom) of sodium in 65 ml. of 95% ethanol was added to a solution of 13.3 g. (0.056 mole) of 2-(p-chlorophenyl)nitrocyclohexane in 230 ml. of 95% ethanol through which oxygen-free nitrogen had been bubbled for 20 min. A slow stream of nitrogen was bubbled through the mixture for one hour. The mixture was then added with stirring over a period of 1 hr. to a mixture of 330 ml. of water, 235 ml. of ethanol, 110 ml. of concd. hydrochloric acid, and 5.8 g. of sodium bisulfite, cooled to 0°. Stirring was continued at 0° for 1 hr. and at room temperature for 4 hr. One liter of water was added, the mixture extracted with ether, and the ether solution neutralized with sodium bicarbonate solution and dried with calcium sulfate. Removal of the ether gave a solid material which was recrystallized from isopropyl alcohol, giving 8.5 g. (73%) of the known ketone⁸ and a small amount of green oily residue. The Nef reaction on 5 g. of 2-(p-chlorophenyl)nitrocyclohexane under identical conditions without sodium bisulfite gave 34% of the ketone and much more of the green oily residue, which gradually turned to brown resinous material. Running the reaction under the same conditions but in the presence of urea yielded about 35% of ketone and gave no appreciable decrease of the green side reaction product.

2-(m-Chlorophenyl) cyclohexanone. The Nef reaction of 18 g. of 2-(m-chlorophenyl)nitrocyclohexane, using the above conditions with addition of sodium bisulfite, gave a liquid material which upon distillation gave 14.2 g. of viscous material, b.p. 109-110° at 0.2 mm. Crystallization could not be induced so 1 g. of the substance was converted to the oxime and the recrystallized oxime was hydrolyzed by refluxing in 20% sulfuric acid for 3 hr. A solid ketone, m.p. 39-40° was obtained. Seeding of the remaining 13.2 g. of liquid ketone caused it to solidify upon cooling. Recrystallization from hexane gave 10.5 g. of crystalline material, m.p. 39.5-40°.

Anal. Caled. for C₁₂H₁₃ClO: C, 69.06; H, 6.28; Cl, 16.99. Found: C, 69.12; H, 6.19; Cl, 16.75.

(17) Obtained by hydrogenation of 4-nitro-5-(*p*-chlorophenyl)cyclohexene previously reported in ref. 8. 2-(o-Chlorophenyl)cyclohexanone. Reaction of 25 g. of 2-(o-chlorophenyl)nitrocyclohexane under the conditions described for the para isomer, without the sodium bisulfite, gave a white precipitate in the acid mixture. Filtration and recrystallization from ethanol gave 6 g. of crystalline material (A) m.p. 215-216°. Work-up of the remaining reaction mixture in the usual way gave 4 g. of the desired ketone (B) m.p. 70-71°. A was shown to be the oxime of 2-(o-chlorophenyl)cyclohexanone. A and B gave identical 2,4-dinitrophenylhydrazones, m.p. 171.5-172.5° (no depression of mixed melting point). Hydrolysis of A by refluxing in 20% sulfuric acid yielded B. The oxime prepared from B is identical to A. Anal. of ketone. Calcd. for $C_{12}H_{13}ClO$: C, 69.06; H, 6.28; Cl, 16.99. Found: C, 68.83; H, 6.45; Cl, 16.87.

Anal of oxime. Calcd. for $C_{12}H_{14}ClNO: C, 64.43; H, 6.31; Cl, 15.85; N, 6.26. Found: C, 64.78; H, 6.64; Cl, 15.81; N, 6.64.$

About the same ratio of oxime and ketone was obtained when sodium bisulfite was used, but the over-all yield was increased. Ten grams of the nitro compound yielded 3.4 g. of purified oxime and 2.1 g. of purified ketone when sodium bisulfite was used.

SEATTLE 5, WASH.

[CONTRIBUTION FROM THE DEPARTMENTS OF PHARMACEUTICAL CHEMISTRY OF THE UNIVERSITY OF KANSAS AND THE UNIVERSITY OF WISCONSIN]

Stereoaspects of the Prins Reaction of Anethole¹

PHILIP S. PORTOGHESE AND EDWARD E. SMISSMAN

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The stereochemistry of 1-anisyl-2-methyl-1,3-diacetoxypropane diasteromers (Ia, Ib) which arise from the condensation of formaldehyde with anethole has been assigned by the use of conformational principles and intramolecular hydrogen bonding studies. The formation of the above compounds and 4-anisyl-5-methyl-1,3-dioxane (III) are rationalized as proceeding through a classical carbonium ion intermediate.

The mineral acid-catalyzed condensation of formaldehyde with olefins, commonly known as the Prins reaction,² is useful in the preparation of 1,3glycols and their derivatives.³ An investigation of the stereochemistry of the Prins reaction employing cyclohexene,^{4,5} demonstrated the condensation to proceed entirely with *trans* addition. Moreover, a recent study⁶ on the conformational analysis of the Prins reaction illustrated the *trans* product to arise only by diaxial addition. It was of interest, therefore, to investigate further the Prins reaction in order to determine if this condensation is stereospecific in all cases.



When anethole was refluxed with paraformaldehyde in glacial acetic acid for five hours, a mixture of 25.6 mole percent 4-anisyl-5-methyl-1,3dioxane (III)^{2,7} and 56.6 mole percent of two

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- (7) E. A. Drukker and M. G. J. Beets, *Rec. trav. Chem.*, **70**, 29 (1951).

diastereomers of 1-anisyl-2-methyl-1,3-diacetoxypropane (Ia and Ib) was obtained. The facility of the condensation in the absence of mineral acid catalyst is due to the activating influence of the anisyl group, as under similar conditions an unactivated olefin yielded no product.⁸ If the reaction is conducted in the presence of a trace of sulfuric acid catalyst, a considerable quantity of polymeric material is formed in addition to I and III. Separation of diastereomer Ia and Ib was accomplished by fractional crystallization from benzenepetroleum ether (b.p. 63-70°). Diacetate Ia crystallized in the form of prisms, m.p. 70-71°, and Ib as sheaths, m.p. 64-65°. Infrared analysis of the diacetate mixture indicated the composition to be 25% Ia and 75% Ib. Saponification of Ia and Ib affords the corresponding glycols, IIa, m.p. 62-63°, and IIb, m.p. 87-89°, which can be reconverted to the diacetates by treatment with acetic anhydride in the presence of anhydrous sodium acetate. It was observed that diol IIb was converted to a mixture of diastereomeric diacetates (Ia and Ib) when refluxed in glacial acetic acid. Significantly, the product contained an odor characteristic of anethole. When subjected to identical conditions, the m-dioxane, III, was partially transformed to the diacetates Ia and Ib and formaldehyde. A quantitative determination in both of the above instances revealed the presence of 25% Ia and 75% Ib. The presence of anethole in the transformation of IIb to the diacetate mixture is probably due to the escape of a small amount of formaldehyde during the cleavage process, thus

⁽⁸⁾ D. T. Witiak, Ph.D. thesis, 1961, University of Wisconsin.