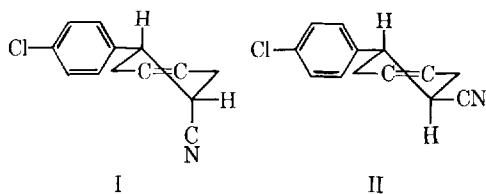


Characterization of Epoxides of *cis*- and *trans*-4-(*p*-Chlorophenyl)-5-cyanocyclohexene from NMR Spectra of Derivatives

By DAVID B. ROLL* and ALAIN C. HUITRIC

The epoxidation of *cis*-4-(*p*-chlorophenyl)-5-cyanocyclohexene with *m*-chloroperbenzoic acid in diethyl ether yielded *trans*-4-(*p*-chlorophenyl)-*trans*-5-cyano-1,2-epoxycyclohexane as the only product. Epoxidation of *trans*-4-(*p*-chlorophenyl)-5-cyanocyclohexene with *m*-chloroperbenzoic acid yielded *cis*-4-(*p*-chlorophenyl)-*trans*-5-cyano-1,2-epoxycyclohexane and *trans*-4-(*p*-chlorophenyl)-*cis*-5-cyano-1,2-epoxycyclohexane in ratio of about 7 to 3, respectively, when carried out in ether but in ratio of about 1 to 1 in 1,2-dichloroethane. The epoxides were characterized from the NMR spectra of the derived diols, mono-, and diacetates by taking advantage of the difference between the spatial 1,3-diaxial deshielding effects of hydroxyl and acetoxy groups.

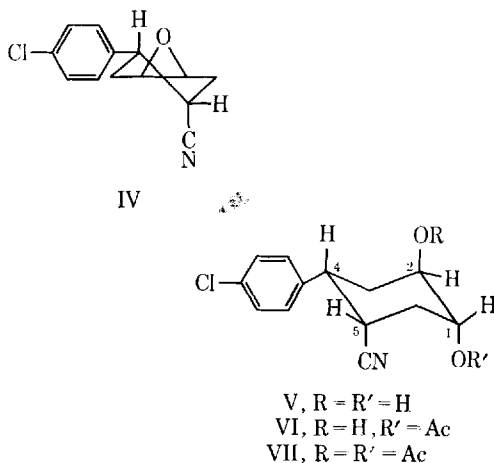
IN THE course of the synthesis of certain agents of possible medicinal interest it was necessary to characterize the epoxidation products of *cis*- and *trans*-4-(*p*-chlorophenyl)-5-cyanocyclohexene, compounds I and II, respectively. Compounds I and II were prepared by the Diels-Alder condensation of butadiene with *cis*- and *trans*-*p*-chloro- β -cyanostyrene (1), respectively. Epoxidation of I with *m*-chloroperbenzoic acid in diethyl ether yielded a single product, while epoxidation of II yielded two products in ratio of about 7 to 3 when carried out in ether but in ratio of 1 to 1 when carried out in 1,2-dichloroethane. The epoxidation of I was not carried out in 1,2-dichloroethane. Analysis was done by gas chromatography. These epoxides have been characterized from the nuclear magnetic resonance spectra of some of their derivatives by taking advantage of the long-range 1,3-diaxial deshielding effects of the hydroxyl and acetoxy functional groups.



CONFIGURATIONAL ASSIGNMENT OF EPOXIDE DERIVED FROM I

Assignment of configuration of the single epoxide obtained from I was not possible from its NMR spectrum. The epoxide was characterized as the isomer with the epoxy group *trans* to the cyano group, compound IV, from the NMR spectra of the diol (V), the monoacetate (VI), and the diacetate (VII) derived from it. It is interesting to note that of the

two possible epoxides only IV was obtained in detectable quantity. From consideration of steric factors it is not surprising that the rate of formation of IV should be faster than that of the isomer with the epoxy group *cis* to the cyano group.



The relevant portions of the spectra of V, VI, and VII, measured in pyridine, are given in Fig. 1, A, B, and C, respectively. Analysis of the spectra shows that in pyridine all three derivatives exist predominantly in the chair conformation with the aromatic ring in equatorial orientation.

Spectrum A indicates the equatorial orientation for H-1, H-2, and H-5, and the axial orientation for H-4. The equatorial orientation is established for H-1 at τ 5.65 and H-2 at 5.46 from their narrow signals, half-height width of 6 to 7 c.p.s. The axial orientation is established for H-4 from the sextet at τ 6.23. The sextet indicates a coupling constant of about 13 c.p.s. between H-4 and axial H-3 with additional minor coupling of about 3.5 c.p.s. with equatorial H-3 and H-5. The signal of H-5 at τ 6.73 is partially overlapped with the signal of axial H-3, but the approximate width of the signal indicates that H-5 has the equatorial orientation. The signal centered at τ 7.05, which appears as a main triplet with separation of 13 c.p.s., plus additional minor splitting, is attributed to axial H-3. The main splitting of about 13 c.p.s. results from geminal

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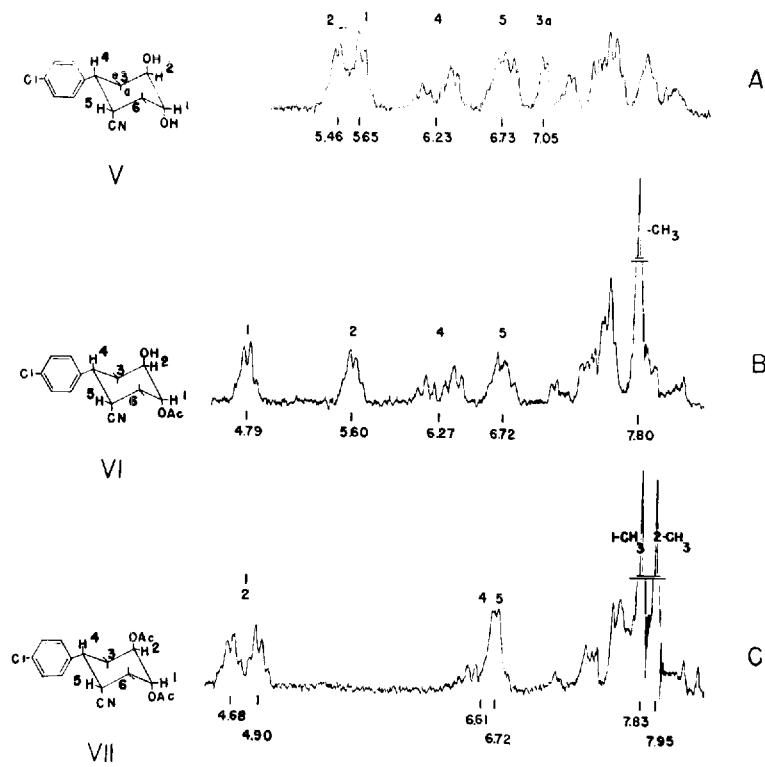


Fig. 1.—NMR spectra of *trans*-2-hydroxy-*cis*-4-(*p*-chlorophenyl)-*cis*-5-cyanocyclohexanol (A), the corresponding 1-acetate (B), and the corresponding 1,2-diacetate (C) at 60 mc. in pyridine at 37°; chemical shifts in τ units; TMS internal reference.

coupling with equatorial H-3 and vicinal coupling with axial H-4. The minor splitting results from coupling with equatorial H-2. The downfield shift of axial H-3 results from long-range deshielding by the axial hydroxyl and cyano groups on C-1 and C-5, respectively. Differentiation of the signals of H-1 and H-2 was done by spin-spin decoupling. Irradiation at τ 5.46 caused the sextet of axial H-3 at τ 7.05 to collapse into a sharp triplet with separations of 13 c.p.s., while irradiation at 5.65 caused no change in this signal.

The given chair conformation is established as the predominant structure of VI from spectrum B in a similar way. The narrow signals of half-height width of about 7 c.p.s. for H-1 at τ 4.79 and H-2 at τ 5.60 indicate the equatorial orientation of these two protons. The axial orientation is established for H-4 from its sextet at τ 6.27 with apparent coupling of 13 c.p.s. with axial H-3 and about 3.5 c.p.s. with equatorial H-3 and H-5. The half-height width of about 8 c.p.s. for the signal of H-5 at τ 6.72 indicates the equatorial orientation of H-5.

In a similar way the narrow signals of half-height width of about 6 to 7 c.p.s. for H-1 and H-2 at τ 4.68 and 4.90, and H-5 at τ 6.72 in spectrum C establish the equatorial orientation of these three protons, and, therefore, also establish the given chair conformation of VII in pyridine. Signals of H-1 and H-2 cannot be differentiated with certainty. The signal of H-4 is partially overlapped by the signal of H-5, but its chemical shift is approximated as 6.61. The acetoxy methyl groups are magnetically non-equivalent. Assignment was made by comparison with spectrum B of VI. The downfield shift of the group on C-1 is attributed to the long-range deshielding effect of the axial cyano group.

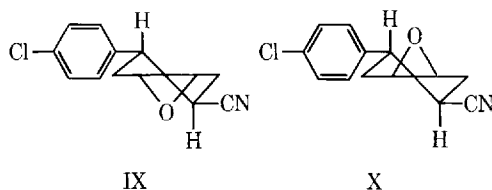
Having established the conformations of V, VI, and VII, the assignment of the configuration of the parent epoxide was possible from the chemical shifts of H-4 of the three derivatives by taking advantage of the spatial 1,3-diaxial deshielding effect of a hydroxyl group on ring hydrogens (2-4) and of the larger deshielding effect of a hydroxyl group compared to the corresponding acetoxy group (3, 4). The chemical shifts of H-4 of the diol V and the monoacetate VI are almost identical, τ 6.23 and 6.27, respectively; but the signal of H-4 appears at about τ 6.61 in the spectrum of the diacetate (VII), about 20 to 23 c.p.s. upfield from that of the monoacetate or diol. This establishes that axial H-4 is deshielded by an axial hydroxyl group on C-2 in the monoacetate (VI) as well as in the diol (V) and in turn establishes that the parent epoxide has the epoxy group *trans* to the cyano group (IV). The established structures of the derivatives indicate that the epoxide opening occurred *via* a transition state with the aromatic group essentially equatorial. A transition state with the aromatic group axial would yield a diol which would differ from structure V by having the *trans* diequatorial hydroxyl groups. The two possible isomeric epoxides would yield identical diaxial diols and diacetates but different monoacetates *via* the transition state with the aromatic group equatorial. If the product of epoxidation had been the *cis*-epoxide, the chemical shift of H-4 should have been almost identical in the mono- and diacetate but significantly different in the monoacetate compared to the diol.

Hydrogenation of I and II yielded *cis*-2-(*p*-chlorophenyl)-1-cyanocyclohexane (III) and *trans*-2-(*p*-chlorophenyl)-1-cyanocyclohexane (VIII), respectively. The NMR spectrum of III measured in

pyridine clearly establishes the *cis* configuration. The signal of H-2 appears as a broad multiplet of about 23 c.p.s. width at τ 7.33. The width of the signal indicates that H-2 has an axial orientation. The signal of H-1 gives a much narrower peak of half-height width of about 7 c.p.s. at τ 6.92, indicating that H-1 has the equatorial orientation. In the spectrum of the *trans* isomer there is overlapping of the broad signals of axial H-2 and H-1 when measured in carbon tetrachloride. The spectrum of VIII was not obtained in pyridine.

CONFIGURATIONAL ASSIGNMENT OF EPOXIDES DERIVED FROM II

The NMR spectra of the two epoxides (IX and X) obtained from II did not provide unequivocal characterization of the two isomers.



The major component of the epoxidation reaction of II in ether was converted to the diol, monoacetate, and diacetate derivatives, compounds XI, XII, and XIII, respectively, but the spectra of these three derivatives did not allow an unambiguous application of the method used for characterization of epoxide (IV) because of overlapping of signals of H-4 and H-5. In order to obtain reliable chemical shifts for H-4 the three corresponding derivatives deuterated at C-5 were prepared. The deuterium exchange on the cyano-bearing carbon was accomplished by refluxing II in methanol-*d* in the presence of sodium methoxide. Some isomerization occurred during the deuterium exchange process and pure deuterated II was obtained by recrystallization from absolute ethanol. Deuterated II was epoxidized in ether and the major component was converted to the diol, monoacetate, and diacetate derivatives, compounds XI*d*, XII*d*, and XIII*d*, respectively. The pertinent portions of the NMR spectra of the deuterated derivatives measured in pyridine are given in Fig. 2. The effect of deuteration on C-5 is demonstrated by the portions of the spectra of the corresponding nondeuterated compounds shown above the signal of H-4 in each spectrum. In the spectra of the nondeuterated compounds there is partial overlap of the signals of H-4 and H-5. Replacement of H-5 with deuterium also simplifies the signal of H-4 which is now coupled only with the two protons on C-3.

The three spectra show that in pyridine all three derivatives exist predominantly in the chair conformation with the aromatic ring in equatorial orientation. The spectra also establish that the epoxide from which they were derived has the epoxy group *trans* to the cyano group, structure IX.

Spectrum D establishes the equatorial orientation of H-1 and H-2 in XI*d* from their overlapping signals at τ 5.65 which give a narrow peak of half-height width of about 6 to 7 c.p.s. The axial orientation of H-4 is established from the quartet at

τ 6.42. The quartet gives apparent coupling constants of 12.0 c.p.s. between H-4 and axial H-3 and about 3.5 to 4 c.p.s. between H-4 and equatorial H-3. The spectrum is consistent with the conformation shown in Fig. 2.

The given conformation of XIII*d* is established in the same fashion from the narrow signals (half-height width of 6 to 7 c.p.s.) of H-1, at τ 5.74 and H-2 at τ 4.73 which establish the equatorial orientation of H-1 and H-2, and from the quartet of H-4 at τ 6.74 ($J_{43a} \approx 12$ c.p.s. and $J_{43e} \approx 4$ c.p.s.) which established the axial orientation of H-4.

In the spectrum of the diacetate (XIII*d*), spectrum F, the signals of H-1 and H-2 are overlapping to give a narrow signal at τ 4.87. The half-height width of the combined signals is about 7 c.p.s. indicating that H-1 and H-2 have the equatorial orientation. Any significant contribution of the other chair conformation with H-1 and H-2 axial would give wider signals for H-1 and H-2. In this spectrum the signal of H-4 appears as a symmetrical triplet with separation of 8.2 c.p.s. instead of the expected quartet. The important thing to note is that the width of the signal of 16.4 c.p.s. is about identical to the width of the signals of H-4 in spectra D and E. A deceptively simple spectrum, giving a triplet instead of the expected quartet, will occur for the signal of H-4 if averaging of coupling constants J_{43a} and J_{43e} results due to strong coupling effects (5-7). Averaging of coupling constants due to strong coupling effects will become operative when the difference between the chemical shifts of the axial and equatorial protons on C-3 approaches, or become smaller than, the geminal coupling constant between the two protons on C-3. In the limit where the chemical shifts of axial and equatorial H-3 are equal the signal of H-4 will yield a symmetrical triplet with separations equal to $(J_{43a} + J_{43e})/2$ (7). Complications due to strong coupling effects do not cause any change in the width of the signal. Inspection of the upper field portion of spectrum F and comparison with spectra D and E indicates that similar chemical shifts of the two protons on C-3 probably prevails in XIII*d*. In compounds XI*d* and XII*d* the deshielding effect of the C-1 axial OH will cause a downfield shift of the signal of axial H-3 of more than 50 c.p.s. when measured in pyridine at 60 mc. (2). The signal of axial H-3 will, therefore, be downfield from that of equatorial H-3 in XI*d* and XII*d*. This is also indicated to be the case from the up-field portions of spectra D and E. Since the 1,3-diaxial deshielding effect of the acetoxy group is about 20 cycles less than that of the OH group, nearly identical chemical shifts of axial and equatorial H-3 is not unexpected and provides a logical explanation for the observed triplet of H-4. The width of the signal definitely establishes the axial orientation of H-4.

Having established the conformations of XI*d*, XII*d*, and XIII*d*, the configuration of the parent epoxide was possible from the chemical shifts of H-4 in the three derivatives. The chemical shift of H-4 is almost the same in the mono- and diacetate but it is from 19 to 24 cycles to lower field in the diol. This establishes that the acetoxy group is *cis* to axial H-4 in the monoacetate and in turn establishes the configuration of its parent epoxide as the isomer with the epoxy group *trans* to the cyano group, structure IX. The two epoxides obtained from peracid

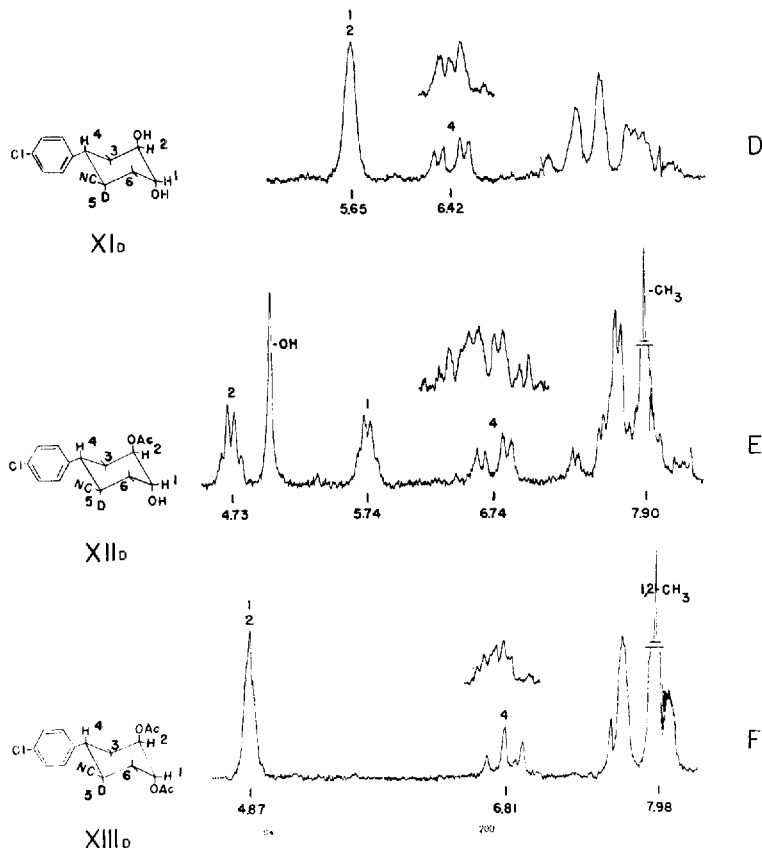


Fig. 2.—NMR spectra of *trans*-2-hydroxy-*cis*-4-(*p*-chlorophenyl)-*trans*-5-cyanocyclohexanol-5-*d* (D), the corresponding 2-acetate (E), and 1,2-diacetate (F); portions of the spectra of the corresponding non-deuterated compounds are shown above signals of H-4; all at 60 mc. in pyridine at 37°; chemical shifts in τ units; TMS internal reference.

oxidation of II yield the same diol (XI) on acid catalyzed hydrolysis. The major product of the epoxidation reaction in ether is, therefore, characterized as structure IX and the minor product has structure X.

cis-2-(*p*-Chlorophenyl)-1-aminomethylcyclohexane (XIV) and the *trans* isomer (XV) were prepared by lithium aluminum hydride reduction of the corresponding cyano compounds (III and VIII). The NMR spectra of these compounds were not very informative. The hydrobromide salts of the two amines elicited strong CNS excitation in mice when injected i.p., but there was little observable difference in potency between the two isomers.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage. The NMR spectra were determined with a Varian A-60 spectrometer. Spectra were taken in pyridine, unless otherwise indicated in a concentration of about 150 mg./0.5 ml. with tetramethylsilane as internal reference.

***cis*-4-(*p*-Chlorophenyl)-5-cyanocyclohexene (I).**—In a typical synthesis 20 Gm. (0.122 mole) of *cis*-*p*-chloro- β -cyanostyrene (1), about 80 ml. of condensed butadiene, 20 ml. of toluene, and a trace of hydroquinone were heated with shaking under a nitrogen atmosphere in a stainless steel bomb for 16 days at a temperature of 138°. Analysis of the reaction mixture by gas chromatography on a 10-ft. column of 20% silicon QF-1 on acid-washed Chromosorb W at 185° showed a ratio of unchanged styrene

to product I of about 2 to 1. The dark crude material was passed on a column of 0.05–0.2 mm. silica gel using benzene as solvent, resulting in the removal of much colored material. After removal of the benzene the residue was washed repeatedly with hot isopropyl alcohol. This treatment resulted in the extraction of the product and unreacted styrene from a considerable amount of rubbery polymeric material which was left behind. The isopropyl alcohol was removed and product I was separated from the unchanged styrene by numerous recrystallizations from hexane. Because of the distinctive crystal structure of I the purification could be speeded up by preliminary mechanical separation of crystals. The separation was also accomplished by column chromatography on 0.05–0.2 mm. silica gel using petroleum ether–benzene mixtures as solvent. Final recrystallization was from isopropyl alcohol–benzene mixture, m.p. 48–49°.

Anal.—Calcd. for $C_{13}H_{12}ClN$: C, 71.72; H, 5.56. Found: C, 71.47; H, 5.70.

***trans*-4-(*p*-Chlorophenyl)-5-cyanocyclohexene (II).**—Compound II was prepared by the same method as I, except that the reaction time was 9 days, the temperature 130°, and the preliminary chromatography was not used in the purification procedure. There was some unchanged styrene present. The product was obtained in 44% yield by recrystallization from hexane. The final crystallization was from a mixture of isopropyl alcohol and benzene, m.p. 132.5–134°.

Anal.—Calcd. for $C_{13}H_{12}ClN$: C, 71.72; H, 5.56; N, 6.44. Found: C, 72.28; H, 5.43; N, 6.45.

cis- and trans-2-(p-Chlorophenyl)-1-cyanocyclohexane (III and VIII).—These compounds were obtained by low pressure catalytic hydrogenation of I and II, respectively, using 10% Pd on carbon in absolute ethanol. The yields were quantitative. An analytical sample of III recrystallized from hexane melted at 103.5–104.5°, whereas VIII recrystallized from the same solvent melted at 107–108°.

Anal.—Calcd. for $C_{13}H_{14}ClN$: C, 71.07; H, 6.42; N, 6.38. Found: (III) C, 71.29; H, 6.41; N, 6.65. (VIII) C, 71.04; H, 6.47; N, 6.20.

trans-4-(p-Chlorophenyl)-trans-5-cyano-1,2-epoxycyclohexane (IV), cis-4-(p-Chlorophenyl)-trans-5-cyano-1,2-epoxycyclohexane (IX), and trans-4-(p-Chlorophenyl)-cis-5-cyano-1,2-epoxycyclohexane (X).—In a typical synthesis, 3.27 Gm. (0.015 mole) of alkene and 7.68 Gm. of 85% *m*-chloroperbenzoic acid (0.38 mole) were dissolved in about 100 ml. of diethyl ether and allowed to stand at room temperature in the dark for 4 days. The reaction mixture was then washed twice with cold 10% sodium hydroxide. The ether solution was washed with water until the washings no longer were basic to litmus and dried with Drierite. The yield of crude product IV was 89%, which when crystallized from benzene-hexane mixture, melted at 109–110.5°. The yield of the mixture of epoxides (IX and X) from epoxidation of II was 86%. These were in a ratio of approximately 7 to 3 as determined by gas chromatography on a 10-ft. column of 20% silicon QF-1 on acid-washed Chromosorb W at 235°. When II was epoxidized in a similar manner as above, but with 1,2-dichloroethane as the solvent, the ratio of the two epoxides was about 1 to 1. Column chromatography of the mixture of epoxides on 0.05–0.2 mm. silica gel using mixtures of purified benzene and petroleum ether, followed by mixtures of benzene and diethyl ether resulted in the separation of substantial quantities of pure IX and only small quantities of X, still somewhat contaminated with IX, as well as a number of fractions with varying ratios of IX and X. Small amounts of pure X could be obtained by crystallizing fractions rich in X from absolute ethanol. The analytical samples of IX and X, when recrystallized from a mixture of benzene-hexane, melted at 128.5–129° and 148–150°, respectively.

Anal.—Calcd. for $C_{13}H_{12}ClNO$: C, 66.81; H, 5.18. Found: (IV) C, 67.12; H, 5.47. (IX) C, 66.94; H, 5.13. (X) C, 66.93; H, 5.21.

trans-2-Hydroxy-cis-4-(p-chlorophenyl)-cis-5-cyanocyclohexyl Acetate (VI) and trans-2-Acetoxy-cis-4-(p-chlorophenyl)-trans-5-cyanocyclohexanol (XII).—In the synthesis of VI, 1 Gm. (0.0043 mole) of IV was dissolved in 6 ml. of glacial acetic acid and refluxed for 14 hr. The solution was added to 100 ml. of cold water, extracted 3 times with ether, the ether washed with 5% NaOH, and dried over Drierite. After drying, the residue was recrystallized from benzene-hexane mixture yielding 645 mg. (51%) of VI which melted at 149–151°. The rest of the material did not crystallize and was shown by comparison of NMR spectra to be a mixture of the monoacetate (VI) and the diacetate (VII). In the synthesis of XII, to avoid the possible formation of diacetate (XIII), 0.75 Gm. (0.0032 mole) of IX was dissolved in 5 ml. of glacial acetic acid containing 10% w/v of potassium acetate and allowed to stand

at room temperature for 24 hr. The reaction mixture was worked up in the same manner as the synthesis of VI above. Crystallization from benzene-hexane mixture yielded 685 mg. (73%) of XI, m.p. 148.5–150°.

Anal.—Calcd. for $C_{15}H_{16}ClNO_3$: C, 61.33; H, 5.49. Found: (VI) C, 61.08; H, 5.65. (XII) C, 61.19; H, 5.77.

trans-2-Hydroxy-cis-4-(p-chlorophenyl)-cis-5-cyanocyclohexanol (V) and trans-2-Hydroxy-cis-4-(p-chlorophenyl)-trans-5-cyanocyclohexanol (XI).—In the synthesis of V, 300 mg. (0.0013 mole) of IV was dissolved in 3 ml. of purified dioxane and 1.5 ml. of distilled water and a drop of concentrated sulfuric acid added. In the case of XI the same procedure was followed except either epoxide IX or a mixture of epoxides IX and X was used, since the glycol (XI) is the product of the hydrolysis of either IX or X. The reaction mixture was allowed to stand at room temperature for 24 hr., suspended in 20 ml. of water, extracted with ether, the ether dried with Drierite, and the solvent removed. The yields of unpurified crystalline product from typical syntheses of V and XI were 232 mg. (71%) and 245 mg. (75%), respectively. Recrystallization of both from benzene-acetone mixture yielded pure V, m.p. 189–190.5°, and pure XI, m.p. 175.5–177°.

Anal.—Calcd. for $C_{13}H_{14}ClNO_2$: C, 62.03; H, 5.61; N, 5.56. Found: (V) C, 62.26; H, 5.76. (XI) C, 61.71; H, 5.62; N, 5.31.

trans-2-Acetoxy-cis-4-(p-chlorophenyl)-cis-5-cyanocyclohexyl Acetate (VII) and trans-2-Acetoxy-cis-4-(p-chlorophenyl)-trans-5-cyanocyclohexyl Acetate (XIII).—The monoacetate VI or XII was placed in 2 ml. each of pyridine and acetic anhydride and allowed to stand at room temperature for 24 hr. The reaction mixture was dissolved in ether and extracted with cold 5% HCl and the ether layer dried over Drierite. In the case of VII, after removal of solvent, the yield of crude product was quantitative. Recrystallization from benzene-hexane mixture yielded pure VII, m.p. 127–128.5°. In the case of XIII, recrystallization from benzene gave a crystalline material melting at 58–61°. The NMR spectrum of this material indicated the presence of a considerable amount of benzene. Heating under vacuum at 80° resulted in removal of the benzene. On solidification, XIII melted over a wide range, 82–106°. The analysis was correct and the NMR spectrum consistent with the expected product.

Anal.—Calcd. for $C_{17}H_{18}ClNO_4$: C, 61.08; H, 5.40. Found: (VII) C, 61.35; H, 5.48. (XIII) C, 61.26; H, 5.16.

cis-2-(p-Chlorophenyl)-1-aminomethylcyclohexane Hydrobromide (XIV) and trans-2-(p-Chlorophenyl)-1-aminomethylcyclohexane Hydrobromide (XV).—A slurry of compound III in ether was added to an excess of $LiAlH_4$ in ether at a rate that maintained a gentle refluxing. The reaction mixture was allowed to stir at room temperature for 1 hr. after the addition was completed. The excess $LiAlH_4$ was destroyed by dropwise addition of ice water. Aqueous 5% NaOH was then added to increase the water layer, the mixture extracted with ether, and the ether solution dried with Drierite. Removal of the solvent gave a quantitative yield of the crude amine, the infrared spectrum of which

showed no $\text{--C}\equiv\text{N}$ absorption. The crude amine was dissolved in *n*-hexane and HBr gas bubbled into the solution. The yield of the salt was quantitative. Recrystallization from absolute ethanol yielded pure XIV, m.p. 290–292°.

In the synthesis of XV tetrahydrofuran was used as solvent. Due to low solubility, compound VIII was added as a slurry to an excess of LiAlH_4 in tetrahydrofuran. The rest of the reaction and work-up was the same as in the synthesis of XIV above. The yield was quantitative for both the free amine and the salt. Pure XV melted at 237–239° when crystallized from absolute ethanol–benzene mixture.

Anal.—Calcd. for $\text{C}_{18}\text{H}_{19}\text{BrClN}$: C, 51.25; H, 6.29; N, 4.60. Found: (XIV) C, 51.46; H, 6.31; N, 4.44. (XV) C, 51.49; H, 6.24; N, 4.45.

Deuteration on C-5 of II, IX–XIII.—Deuterium exchange on C-5 of II was carried out by refluxing 1.5 Gm. of II in 15 ml. of CH_3OD in the presence of 1 Gm. of sodium methoxide. After cooling, 10 ml. of

deuterium oxide was added; the resulting suspension was extracted with anhydrous ether and the ether solution dried with Drierite. After removal of the ether, the NMR spectrum of the product indicated that a considerable amount of isomerization of II to I had occurred during the exchange. Deuterated II was obtained by recrystallization from ethanol. Compound II deuterated at C-5 was submitted to the same sequence of reactions as II in order to obtain compounds IX–XIII deuterated at C-5.

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Hypoiodite Oxidation of 3α -Bromo and 3α -Chloro- 2β -hydroxy- 5α -androstan-17-one

By R. E. COUNSELL and G. W. ADELSTEIN

Hypoiodite oxidation of 3α -bromo and 3α -chloro- 2β -hydroxy- 5α -androstan-17-one gave the expected $2\beta,19$ -oxide along with lesser amounts of 16-iodinated, 19-hydroxylated, and 19-acetoxy products. The product composition as well as the yield of each product was found to vary considerably even when the reaction was performed under presumably identical conditions. The structures were assigned on the basis of chemical and spectroscopic evidence. The NMR and other spectroscopic properties of the epimeric 16α - and 16β -iodinated derivatives of 3α -bromo- $2\beta,19$ -oxido- 5α -androstan-17-one are discussed.

INTEREST in 19-substituted steroids as potential anabolic agents led to the investigation of the hypoiodite oxidation of 2β -hydroxyandrostanes as a means of introducing functional groups at the C-19 position (1). During the course of these studies it was noted that a number of minor by-products were formed in addition to the expected oxidation product. This report involves a study of this reaction and structural elucidation of the by-products.

DISCUSSION

The conversion of 2β -hydroxysteroids to 19-functionalized products has been accomplished by: (a) oxidation with lead tetraacetate alone (2, 3) or in the presence of iodine (hypoiodite) (4) and (b) photolysis of nitrite esters (3, 5). In each case,

an alkoxy radical (A) is generated which can interact with the proximal angular methyl group. In the hypoiodite reaction, a furan (B) or an iodofuran (C) can form depending on the mechanism of ring closure. (Scheme I).¹ Although compounds of type C have not been isolated, the characterization of the corresponding hydroxy and acetoxy derivatives among the reaction products has suggested the intermediacy of such an iodinated precursor.

In these studies, hypoiodite oxidation of 3α -bromo- 2β -hydroxy- 5α -androstan-17-one (I) in refluxing carbon tetrachloride afforded a 36% yield of 3α -bromo- $2\beta,19$ -oxido- 5α -androstan-17-one (III) after chromatography.² In addition to this expected product, three other crystalline products were isolated. Two of these products preceded the major product on chromatography and were characterized as the 16β - and 16α -iodinated derivatives (IV and V). These epimers were obtained in 1.4 and 1.2% yield, respectively. The third product, obtained in 10% yield, followed the major product on chromatography and was identified as the hemiacetal (VI).

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¹ The mechanisms involved in the hypoiodite reaction have been excellently reviewed by Heuser, K., and Kalvoda, J., *Angew. Chem. Intern. Ed.*, **3**, 525 (1964).

² This product has been isolated in yields as high as 53% under presumably the same conditions (1).