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PROTON MAGNETIC RESONANCE AND STEREOCHEMISTRY OF SOME 5,6-DISUBSTITUTED BICYCLO[2.2.2]OCT-2-ENES AND THEIR OXIDATION PRODUCTS

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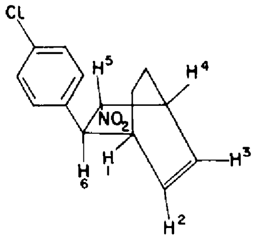
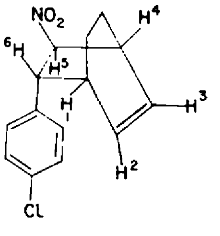
Abstract—The two adducts obtained from the Diels-Alder condensation between 1,3-cyclohexadiene and *trans-p*-chloro-β-nitrostyrene have been characterized from the PMR spectra of the respective cyclohexane dicarboxylic acids obtained from chromic acid oxidation of the adducts. The Diels-Alder condensation yielded a larger quantity of the isomer with the nitro group *endo* to the double bond. Hydrogenation of the double bond in the two adducts yielded one product, the PMR spectrum of which is consistent with the expected product. The PMR spectra of the adducts, their oxidation products and the hydrogenation product are reported and discussed.

Two *trans* isomers are possible from the *cis* addition[3] in the Diels–Alder reaction of *trans-p*-chloro-β-nitrostyrene and 1,3-cyclohexadiene. These are *endo*-5-nitro-*exo*-6-(*p*-chlorophenyl)-bicyclo[2.2.2]oct-2-ene (I) and *exo*-5-nitro-*endo*-6-(*p*-chlorophenyl)-bicyclo[2.2.2]oct-2-ene (II). On running the reaction two adducts were obtained which gave the correct elementary analysis for I and II. One isomer was obtained in much larger quantity. The PMR spectra of the dicarboxylic acids resulting from oxidation of the two isomers prove that the isomer recovered in the larger quantity has structure I, while the isomer obtained in lower yield has structure II. The predominance of the isomer with the nitro group *endo* is analogous to the results of Poos *et al.*[4] in the reaction of trans-β-nitrostyrene with cyclopentadiene.

The hydrogenation products of I and II gave identical IR spectra, had identical m.ps



I



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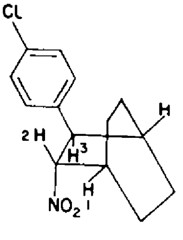

III

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[3] K. Alder and G. Stein, *Angew. Chem.* **50**, 510 (1937).

[4] G. I. Poos, J. Kleis, R. R. Wittekind and J. D. Rosenau, *J. Org. Chem.* **26**, 4898 (1961).

and showed no depression in m.p. upon admixture. The compound gave the correct elementary analysis for *trans*-2-nitro-3-(*p*-chlorophenyl)-bicyclo[2.2.2]octane (III).

The PMR spectra of several bicyclo[2.2.1]heptanes and heptenes have been reported and discussed,[5-7] but little PMR work has been reported on the bicyclo [2.2.2]oct-2-ene system. The PMR spectra of I, II and III are given in Fig. 1. The upper spectrum, A, is that of the isomer obtained in the larger quantity. Unequivocal proof of the correct assignment of structure I to the compound giving spectrum A, and of structure II to the compound giving spectrum B, is obtained from the PMR spectra of their respective oxidation products, spectra D and E, Fig. 2.

There is a much greater difference in the chemical shift of H-2 and H-3 in A than in B. These differences are caused, at least in part, by long-range shielding effects resulting from the magnetic anisotropy of the aromatic ring and the nitro group[8] but unambiguous assignment isn't possible. Spin-spin decoupling studies will be undertaken in order to make an unequivocal assignment of the signals of H-2 and H-3 in A. The results will be reported in a subsequent publication. Assignment of the remaining isolated signals can be made with a good degree of certainty. The quartets at τ 5·32 in A and 5·67 in B are assigned to H-5, and the quartet at τ 6·35 in B is assigned to H-6 from their splitting patterns and by comparison of their τ values with those of reference compounds.[9]

The assignment of H-5 and H-6 was confirmed by partial deuterium exchange of H-5 in II. This deuterium exchange caused a decrease in intensity of the signal at τ 5·67 and a collapse of the quartet at τ 6·35 into an unresolved singlet. The singlet of the deuterated compound is shown above the quartet of H-6 at τ 6·35. The quartets for H-5 in A and B result from spin-spin coupling of H-5 with H-6 and H-4, producing coupling constants of $J_{56} = 5{\cdot}3$ c/s, $J_{45} = 2{\cdot}3$ in A and $J_{56} = 5{\cdot}6$, $J_{45} = 2{\cdot}6$ in B. The coupling constants were obtained directly from the spectra by simple first order treatment. All coupling constants are reported in cycles per second. The reproducibility of the measurements was ± 0·2 cycles. The quartet for H-6 in B results from coupling of H-6 with H-5 and H-1, $J_{56} = 5{\cdot}8$ and $J_{16} = 1{\cdot}8$. The fact that the quartet of H-6 in B collapses to a narrow signal upon replacement of H-5 with deuterium confirms the assignment of the large coupling constant as that between H-6 and H-5, rather than between H-6 and H-1. If J_{16} had the largest coupling value, replacement of H-5 with deuterium would cause the signal of H-6 to collapse into a doublet with a coupling constant of 5·8 cycles sec.$^{-1}$. Assuming that there is no great difference in bond angles in the bicyclo systems of I and II the deuterium exchange in II also confirms the assignment of coupling constants made from the signal of H-5 of I in spectrum A, where the largest coupling constant of 5·3 c/s is attributed to coupling between H-5 and H-6.

The signal at τ 6·59 in spectrum A integrates for two protons, labeled 4 and 6. Since these signals are approximately the same τ value, coupling constants between H-6 and H-1 could not be determined. The differentiation between the signals of H-4 and H-1 in A and B is based on the greater deshielding of H-4 by the nitro group due to

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[5] J. I. Musher, *Mol. Phys.* **6**, 93 (1963).

[6] F. A. L. Anet, *Canad. J. Chem.* **39**, 789 (1961).

[7] R. R. Frazer, *Canad. J. Chem.* **40**, 78 (1962).

[8] A. C. Huitric and W. F. Trager, *J. Org. Chem.* **27**, 1926 (1962).

[9] W. F. Trager, F. F. Vincenzi and A. C. Huitric, *J. Org. Chem.* **27**, 3006 (1962).

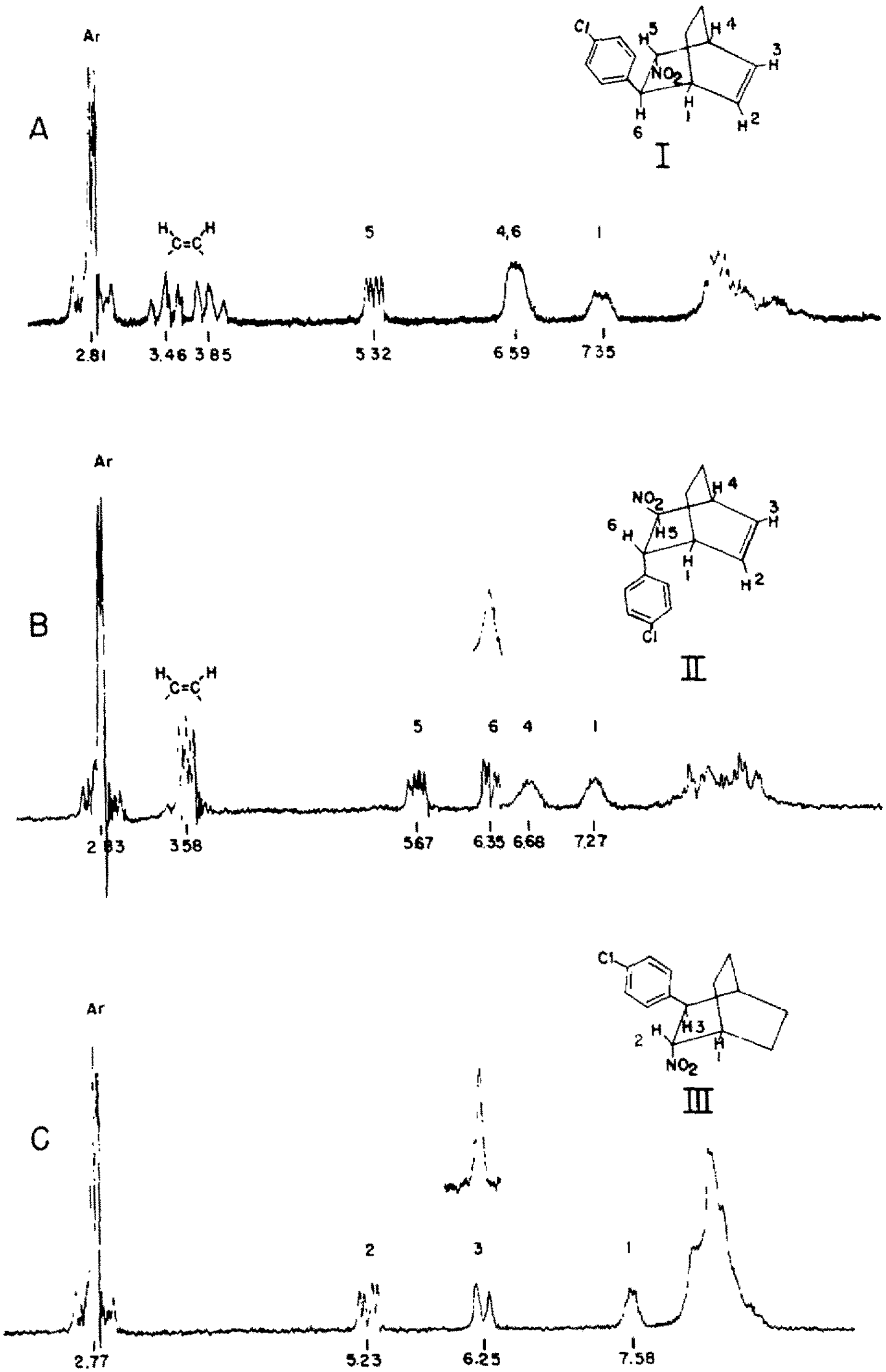

Fig. 1. PMR spectra of *endo*-5-nitro-*exo*-6-(*p*-chlorophenyl)-bicyclo[2.2.2]-oct-2-ene (A), *exo*-5-nitro-*endo*-6-(*p*-chlorophenyl)-bicyclo[2.2.2]oct-2-ene (B) and *trans*-2-nitro-3-(*p*-chlorophenyl)-bicyclo[2.2.2]octane (C); 60 Mc, about 1 M in carbon tetrachloride at 23°. The chemical shifts, expressed in *tau* units, are referred to tetramethylsilane used as internal reference.

inductive effect through bonding orbitals and spatial long-range effects. This assignment will be checked by spin-spin decoupling studies and the results will be reported in a subsequent publication.

Table 1. Coupling Constant in Compounds I, II and III (c/s)

Compounds	J_{56}	J_{45}	J_{16}
I	5·3	2·3	—
II	5·7[a]	2·6	1·8
III[b]	6·9[c](J_{23})	2·4(J_{12})	—

[a] This is an average value obtained from the signals of H-5 and H-6.
[b] The numbering is different in the reduced compound (III).
[c] Average value from signals of H-2 and H-3.

The dependence of coupling constants between vicinal protons upon the dihedral angle between the C—H bonds involved is well-established. Coupling constants are greatest for dihedral angles of 0° and 180° and least for 90°.[10] If molecules I and II were perfectly rigid, the dihedral angle between H-5 and H-6 would be 120°, while the dihedral angle between H-5 and H-4 and between H-6 and H-1 would be 60°. According to the theoretical treatment of Karplus,[10] such rigid structures would lead to similar coupling constants of about 2·0 c/s for J_{45}, J_{56}, and J_{16}. If this were the case the signals of H-5 and H-6 in spectra A and B should be triplets. However, deviations from the Karplus calculated values are common. For example, in substituted cyclohexanes,[11] the observed axial-axial coupling constants are generally larger than the theoretical value of Karplus. Substituent effects on coupling constants are also well-recognized,[11] but the observed differences between J_{45} or J_{16} and J_{56} in structures I and II are considerably larger than expected and would require some reasonable explanation. A possible explanation might be found if one assumes that the bicyclo [2.2.2]oct-2-ene system is not completely rigid and that, in carbon tetrachloride solution at least, the carbon and hydrogen atoms of the ring system are not in the completely eclipsed form. A slight staggering of bonds in the direction that would cause an increase in the dihedral angle between H-5 and H-6 would, at the same time, increase the dihedral angle between H-5 and H-4 as well as between H-6 and H-1. It should be noted that the suggested staggering of bonds is in the direction that would relieve any strain resulting from steric repulsion of either the *p*-chlorophenyl or the nitro group. An increase of the dihedral angle between H-5 and H-6, above the normal 120° angle, will cause an increase in J_{56}. An increase in the dihedral angle between H-5 and H-4 and between H-6 and H-1, above the normal angle of 60°, will cause a decrease in J_{45} and J_{16}.

Spectrum C, (Fig. 1), is that of compound III. The signals were assigned to the various protons in a manner similar to that for A and B. The signal of H-2 gives a well-defined quartet with $J_{23} = 7·0$, and $J_{12} = 2·4$. The signal of H-3 yields a doublet $J_{23} = 6·8$ instead of the expected quartet. The assignment of the signals for H-2 and H-3 was confirmed by partial deuterium replacement of H-2. The relevant portion of the spectrum of the deuterated compound is shown above the signal of H-3 at τ 6·25. There was a decrease in intensity of the signal at τ 5·23 upon partial

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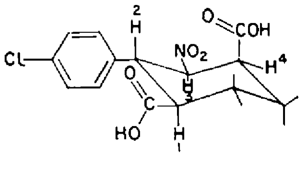
[10] M. Karplus, *J. Chem. Phys.* **30**, 11 (1959).

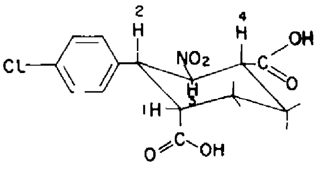
[11] A. C. Huitric, J. B. Carr, W. F. Trager and B. J. Nist, *Tetrahedron* **19**, 2145 (1963).

deuteration which establishes the signal of H-2. The collapse of the doublet at τ 6·25 into a singlet establishes the signal of H-3 and also confirms the assignment of coupling constants. Since the doublet of H-3 degenerates into a singlet when H-2 is replaced by deuterium, the doublet must result from coupling of H-3 with H-2 and not with H-4. This also confirms the assignment of the coupling constant for the quartet of H-2. It should be noted that although not shown on the spectrum, the signal of H-1 was sharpened considerably in the deuterated compound. This is as expected since the first order quartet of H-2 shows that H-1 and H-2 are coupled, $J_{12} = 2{\cdot}4$. Yet to be explained, however, is the fact that the signal of H-3 does not give a first order quartet analogous to that of H-2. The most logical explanation is that the spectrum of H-3 is complicated due to virtual long-range coupling of H-3 with protons on C-5 and C-8. Such complications are expected if the difference in chemical shift between H-4 and the protons on C-5 and C-8 is less than twice the coupling constant between H-4 and the protons on C-5 and C-8. The fact that the signal of H-4 is overlapped by the signals of other ring methylene protons indicates that this situation very likely exists. Since the signal of H-1 appears at much lower field than the signals of protons on C-6 and C-7, complications from virtual coupling of H-2 and protons on C-6 and C-7 are not expected. This explains the first order quartet for the signal of H-2. The fact that the coupling constant between H-2 and H-3 in C is larger than J_{56} in A and B can be explained by the greater flexibility of the bicyclo[2.2.2]octane system, thus allowing a larger increase in the dihedral angle between the C—H bonds for H-2 and H-3.

To obtain unequivocal proof of the stereochemistry of the compounds giving spectra A and B, advantage was taken of the fact that PMR is known to be a very powerful tool in configurational and conformational analysis of six-membered ring compounds (e.g. Refers 9, 11–15). The oxidation of I and II results in the synthesis of two isomeric acids, IV and V respectively, the structures of which are shown below. The only difference between IV and V is in the orientation of the carboxyl groups and protons at the 1 and 4 positions. Since in both isomers a chair conformation is possible in which the *p*-chlorophenyl, the nitro, and one of the carboxyl groups are equatorial, the cyclohexane ring will likely be in this preferred chair conformation.



IV



V

Structures IV and V could readily be differentiated from their PMR spectra. The signal of H-3 of structures IV should be a quartet with coupling constants of $J_{23} \simeq 11$

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[12] A. C. Huitric, W. S. Stavropoulos and B. J. Nist, *J. Org. Chem.* **28**, 1539 (1963).

[13] J. A. Pople, W. G. Schneider and H. J. Bernstein, *High-Resolution Nuclear Magnetic Resonance* p.387 McGraw-Hill, New York, (1959).

[14] A. C. Huitric and J. B. Carr, *J. Org. Chem.* **26**, 2648 (1961).

[15] R. M. Lemieux, R. K. Kullnig, H. J. Bernstein and W. G. Schneider, *J. Amer. Chem. Soc.* **80**, 6098 (1958).

and $J_{34} \simeq 3$–4 since H-3 is axial and is adjacent to one axial and one equatorial proton (Jaa $\simeq$ 11; Jae $\simeq$ 3–4). On the other hand, the signal of H-3 of structure V should be a triplet, $J_{23} = J_{34} \simeq 11$, since H-3 is axial and adjacent to two axial protons. Similarly, the signal of H-2 of IV should be a triplet, $J_{12} = J_{23} \simeq 11$, since it is axial and adjacent to two other axial protons. In V, H-2 should give a quartet since it is axial and adjacent to one axial and one equatorial proton. In structure IV, the signal of H-1 should be broader than that of H-4 because the axial H-1 in IV is coupled with two axial and one equatorial protons, while H-4 has an equatorial orientation and Jae = Jee $\simeq$ 3–4 c/s. For the same reasons, the signal of H-4 should be broader than that of H-1 in structure V.

Spectrum D is that of the dicarboxylic acid obtained from the oxidation of the Diels–Alder adduct which gives spectrum A, and spectrum E is that of the dicarboxylic acid obtained from the oxidation of the adduct which gives spectrum B. Structure IV is established by the quartet of H-3 (τ 4·72, $J_{23} = 11{\cdot}8$, $J_{34} = 5{\cdot}1$) and the triplet of H-2 (τ 5·89, $J_{12} = J_{23} = 11{\cdot}3$) in spectrum D. Structure V is established by the triplet of H-3 (τ 3·90, $J_{23} = J_{34} = 11{\cdot}1$) and the quartet of H-2 (τ 6·42, $J_{23} = 11{\cdot}8$, $J_{12} = 4{\cdot}3$) in spectrum E. In spectrum D, the narrower signal of the equatorial H-4 (τ 6·28), and the broader signal of the axial H-1 (τ 7·17) are consistent with structure IV. In spectrum E there is an overlap of the signals of H-1 and H-4. Thus the PMR spectra of the dicarboxylic acids establish the structures of the bicyclo[2.2.2]oct-2-enes I and II.

The coupling constants between H-2 and H-3, in IV and V, are slightly larger when measured from the quartets than from the triplets. Direct measurement from the spectra is expected to yield the most reliable values from the quartets. The middle component of each triplet is composed of two halves of doublets which will be exactly superimposable only if J_{23} and J_{12} are equal in IV and J_{23} and J_{34} are equal in V. Measurements from the triplets will yield lower than true values for J_{23} if the actual values of J_{12} in IV and J_{34} in V are smaller than J_{23} in each structure. The differences observed are not significant but it is of interest to note that the quartets yield identical J_{23} values in the two structures.

EXPERIMENTAL

5-*Nitro*-6-(p-*chlorophenyl*)-*bicyclo*[2.2.2]*oct*-2-*enes* (I *and* II). These compounds were prepared by heating 20 g (0·11 moles) *trans-p*-chloro-β-nitrostyrene[16] and 17·7 g (0·22 moles) 1,3-cyclohexadiene, 33 ml toluene and a trace of hydroquinone in a pyrex bomb under a N_2 atm at 110° for 8 days. The yield of recovered purified products was 53%. The two isomers were separated by fractional crystallization, initially from isopropyl alcohol until most of I (m.p. 94–95·5°) was obtained and then from hexane to obtain II (m.p. 55–56·5°). The amount of II obtained was only 2·6% of the total recovered product, but this does not necessarily represent the true ratio of the two isomers. Found: (I) C, 63·83; H, 5·33; N, 5·56. Found: (II) C, 63·45; H, 5·56; N, 5·29. Calc. for $C_{14}H_{14}O_2NCl$: C, 63·76; H, 5·35; N, 5·31%.

trans-2-*Nitro*-3-(p-*chlorophenyl*)-*bicyclo*[2.2.2]*octane* (III). This compound was obtained by low-pressure catalytic hydrogenation of I or II using 10% Pd—C in ethanol. The yield was quantitative. Found: C, 63·32; H, 6·15; N, 5·32. Calc. for $C_{14}H_{16}O_2NCl$: C, 63·28; H, 6·07; N, 5·27%.

trans-2-(p-*Chlorophenyl*)-cis-3-*nitro*-cis-1,4-*cyclohexane dicarboxylic acid* (IV). One g ($3{\cdot}8 \times 10^{-3}$ moles) I was dissolved in 25 ml glacial acetic acid and 1·1 g ($1{\cdot}1 \times 10^{-2}$ moles) solid CrO_3 was added in portions at room temp with stirring, and stirring continued for 2 hr after the addition was complete. Water (250 ml) was added and the mixture was extracted with ether, dried

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[16] A. C. Huitric and W. D. Kumler, *J. Amer. Chem. Soc.* **78**, 614 (1956).

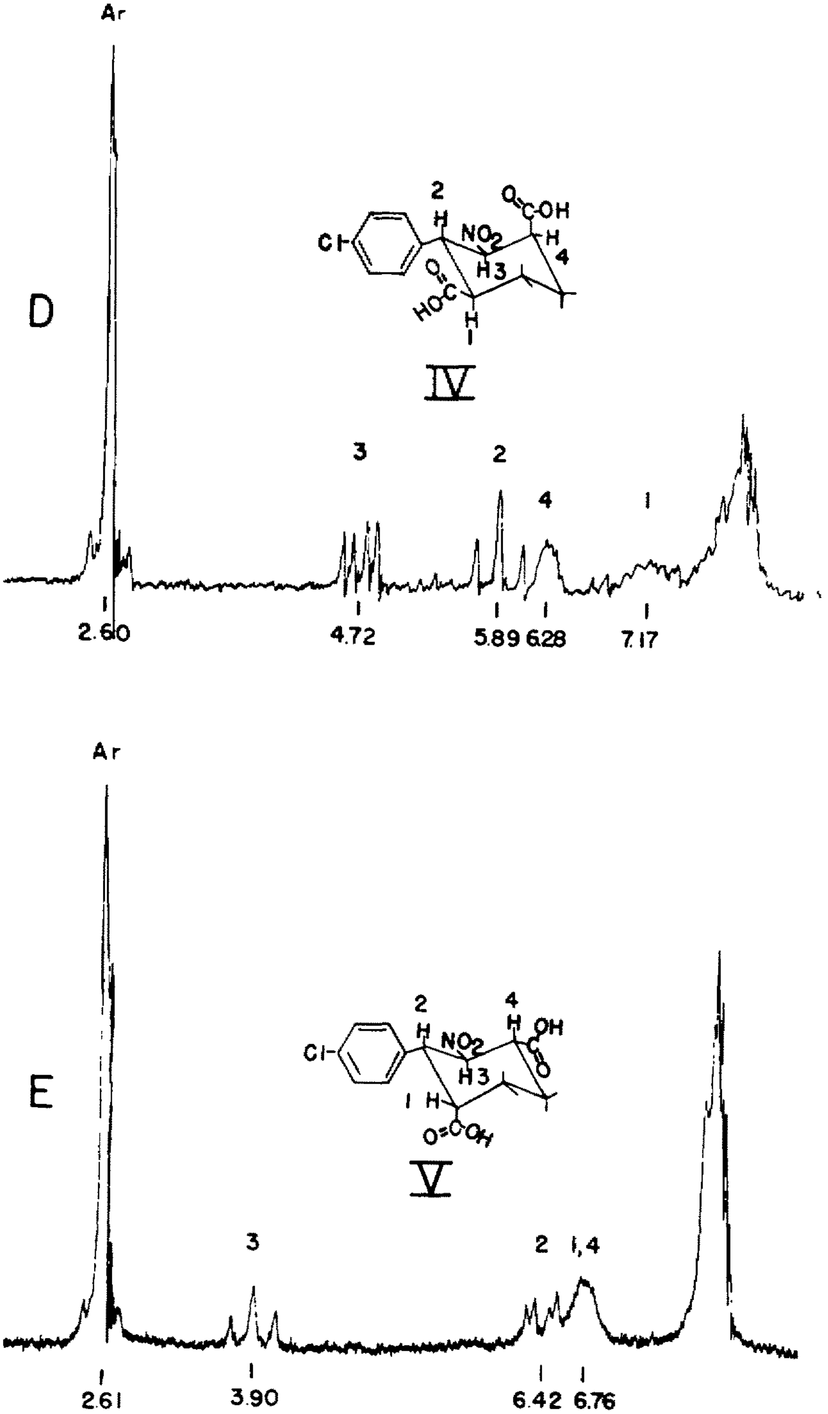

FIG. 2. PMR spectra of *trans*-2-(*p*-chlorophenyl)-*cis*-3-nitro-*cis*-1,4-cyclohexane dicarboxylic acid (D) and *cis*-2-(*p*-chlorophenyl)-*trans*-3-nitro-*cis*-1,4-cyclohexane dicarboxylic acid (E); 60 Mc, about 1 M in deuterated acetone at 23°. The chemical shifts, expressed in *tau* units, are referred to tetramethylsilane used as internal reference.

($CaSO_4$) and the solvent removed nearly to dryness. Benzene was then added, resulting in the precipitation of 450 mg (36%) of the diacid, m.p. 209·5–211° with dec. Found: C, 51·53; H, 4·49; N, 4·22. Calc. for $C_{14}H_{14}O_6NCl$: C, 51·31; H, 4·31; N, 4·27%.

cis-2-(p-*Chlorophenyl*)-trans-3-*nitro*-cis-1,4-*cyclohexane dicarboxylic acid* (V). Compound II, 180 mg ($6·8 \times 10^{-4}$ moles), was dissolved in 8 ml glacial acetic acid and 220 mg ($2·2 \times 10^{-3}$ moles) solid CrO_3 was added. The reaction was run as above, yielding 53 mg (24%) diacid, m.p. 222–230° with dec. A sharper m.p. could not be obtained. Found: C, 51·43; H, 4·34; N, 4·17. Calc. for $C_{14}H_{14}O_6NCl$: C, 51·31; H, 4·31; N, 4·27%.

Deuteration on C-2 *of* III. The octane (300 mg) and 90 mg anhydrous K_2CO_3 were dissolved in a solution of 16 ml dry, purified dioxane and 7·5 ml D_2O. This solution was allowed to equilibrate for several days and the solvent was removed by freeze-dry technique. The remaining solid material was dissolved in 9 ml D_2O and 16 ml dioxane and again allowed to equilibrate. Then more D_2O was added, forcing III out of solution where it was extracted with anhydrous ether, dried, and the solvent removed, yielding the deuterated product.

Deuteration on C-5 of II. The octene (125 mg) and 5 mg anhydrous K_2CO_3 were dissolved in 3 ml anhydrous dioxane and 1·3 ml D_2O and allowed to equilibrate for 1 week. The solvent was distilled at red. press. and the product dried by evacuation at 2 mm at 75° for 5 hr.

All m.ps were determined with a Kofler micro hot stage.

The NMR spectra were determined with a Varian HR-60 spectrometer.