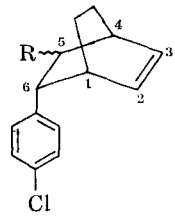
Proton Magnetic Resonance Spectra and Stereochemistry of Some 5,6-Disubstituted Bicyclo[2.2.2]oct-2-enes

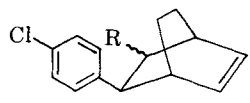
By DAVID B. ROLL* and ALAIN C. HUITRIC

The four adducts obtained from the Diels-Alder condensation between 1,3-cyclohexadiene and *cis*- and *trans*-*p*-chloro-β-cyanostyrene have been characterized from the NMR spectrum of the cyclohexane dicarboxylic acid obtained from chromic acid oxidation of the major *trans* adduct and from long-range shielding effects of the double bond of the bicyclo[2.2.2]octene system on *endo* and *exo* protons. The major adduct of the *trans* styrene has the cyano group *exo* to the double bond, whereas the major adduct of the *cis* styrene has both substituents *endo* to the double bond. Hydrogenation of the two *trans* adducts yielded one product, as did the hydrogenation of the two *cis* adducts, the NMR spectrum being consistent with the expected product in each case. Deuterium exchange on the cyano-bearing carbon was used for identification of the signals. The major *cis* and *trans* adducts and their hydrogenation products were converted to the corresponding amines by lithium aluminum hydride reduction. The NMR spectra of these amines are discussed. The usefulness of solvent effects in the separation of overlapping NMR signals is demonstrated by the downfield shift of the signal of the hydrogen attached to the cyano-bearing carbon in pyridine *versus* deuterochloroform in the six cyano-bicyclic compounds prepared.

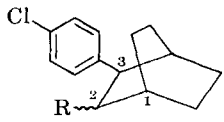
In the Diels-Alder reaction between *trans*-*p*-chloro-β-cyanostyrene and 1,3-cyclohexadiene, two isomers are expected.[1] These adducts, which result from *cis* addition, are *exo*-5-cyano-*endo* - 6 - (*p* - chlorophenyl) - bicyclo[2.2.2]oct-2-ene (I) and *endo*-5-cyano-*exo*-6-(*p*-chlorophenyl) - bicyclo[2.2.2]oct - 2 - ene (II). The reaction yielded two isomers which give correct elemental analyses for I and II. The major isomer was recovered in about sixfold excess over the minor isomer. This ratio is that of the recovered materials and does not necessarily represent the exact ratio in the reaction mixture. Proof was obtained from nuclear magnetic resonance (NMR) that the major isomer has structure I with the aromatic group *endo* to the double bond. This is in contrast to the results obtained from the reaction of *trans*-*p*-chloro-β-nitrostyrene with 1,3-cyclohexadiene, in which case the isomer with the aromatic group *exo* to the double bond was obtained in largest amount (1).



I, R = C≡N, *exo*
III, R = C≡N, *endo*
VII, R = CH_2NH_2, *exo*
VIII, R = CH_2NH_2, *endo*



II, R = C≡N, *endo*
IV, R = C≡N, *exo*



V, R = C≡N, *trans*
VI, R = C≡N, *cis*
IX, R = CH_2NH_2, *trans*
X, R = CH_2NH_2, *cis*

The hydrogenation products of I and II gave identical infrared spectra and melting points and showed no depression in melting point upon admixture. This compound gave the correct elemental analysis for *trans*-2-cyano-3-(*p*-chlorophenyl)-bicyclo[2.2.2]octane (V).

Similarly, the Diels-Alder reaction of *cis*-*p*-chloro-β-cyanostyrene and 1,3-cyclohexadiene yielded a major and a minor isomer which gave the correct analysis for the expected *endo*-5-cyano - *endo* - 6 - (*p* - chlorophenyl) - bicyclo-[2.2.2]-oct-2-ene (III) and *exo*-5-cyano-*exo*-6-(*p* - chlorophenyl) - bicyclo[2.2.2]oct - 2 - ene

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[1] Disregarding any reaction in which the cyano group could act as a dienophile.

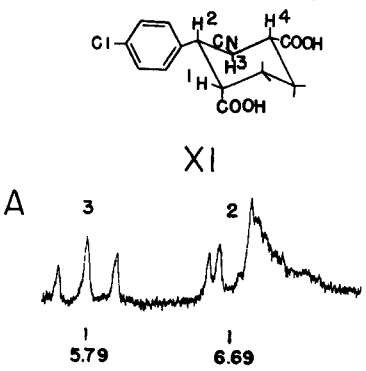


Fig. 1.—Portion of NMR spectrum of *cis*-2-(*p*-chlorophenyl)-*trans*-3-cyano-*cis*-1,4-cyclohexanedicarboxylic acid; 60 mc., about 1 *M* in deuterated acetone at 37°. The chemical shifts are expressed in τ units.

(IV). The two isomers were recovered in a ratio of about 7 to 1. Proof was obtained from NMR and from isomerization of I that the major isomer has structure III with both the aromatic and cyano groups *endo* to the double bond and that the minor isomer has structure IV. This result is consistent with the rule of maximum accumulation of unsaturation (2).

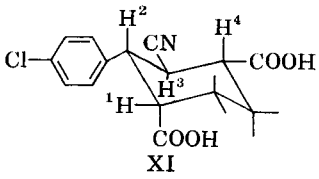
The hydrogenation products of III and IV gave identical infrared spectra and melting points and showed no depression in melting point upon admixture. This compound gave the correct elemental analysis for *cis*-2-cyano-3-(*p*-chlorophenyl)-bicyclo[2.2.2]octane (VI).

CONFIGURATIONAL ASSIGNMENT OF ADDUCTS OF THE *trans*-STYRENE

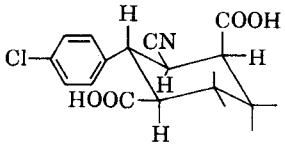
Spectrum A, Fig. 1, shows the pertinent portion of the NMR spectrum of the dicarboxylic acid obtained from the oxidation of the major adduct. The spectra of the two *trans*-isomers and of their reduction product are given in Fig. 2. Spectrum B is that of the isomer obtained in largest quantity, C is that of the minor isomer, and D is that of the hydrogenation product of I and II. Figure 3 shows the pertinent sections of the spectra of the two amines obtained from the compound which gives spectrum B. Spectrum E is that of the amine obtained from the lithium aluminum hydride reduction of the major adduct, and spectrum F is that of the hydrogenation product of this amine.

Proof of structures I and II for the isomers which give spectra B and C, respectively, was obtained from the NMR spectrum of the dicarboxylic acid synthesized by the oxidation of the adducts which gives spectrum B. Supporting evidence was also obtained from the shift in position of the NMR signals of H-5 and H-6 upon hydrogenation of the double bond of each adduct.

Proof from NMR Spectrum of Oxidation Product.—Oxidation of adduct I will give the dicarboxylic acid (XI) with the aromatic group *cis* to the carboxyl groups, while the oxidation of II will give structure XII with the aromatic group *trans* to the carboxyl groups. The oxidation product of the minor adduct was not obtained in sufficient quantity for NMR study. Figure 1 shows the relevant portion of the spectrum of the dicarboxylic acid synthesized by the oxidation of the major adduct. The signal of H-3 appears as a triplet at τ 5.79 with separations of 11.4 c.p.s. This triplet establishes that H-3 has an axial orientation and that it is adjacent to two axial protons (1), and indicates that J_{32} and J_{34} are approximately equal and close to 11.4 c.p.s. The signal of H-2 is partially overlapped by those of H-1 and H-4, but a quartet centered at τ 6.69 is clearly indicated from the spectrum and by the fact that the signal collapses to a doublet (J_{21} = 3.8 c.p.s.) centered at τ 6.69 when H-3 is replaced with deuterium. The area under the downfield portion of the quartet integrates to half a proton. The quartet establishes that H-2 has an axial orientation and is adjacent to one axial and one equatorial proton. Proof of the correct assignment of the signals of H-3 and H-2 in spectrum A was obtained from the spectrum of the corresponding acid deuterated at C-3. The deuterated acid was obtained from the oxidation of the major adduct which had previously been subjected to deuterium exchange on C-5. Proof of the position of deuterium exchange is given in the discussion of the spectra of the amines. On deuteration, the triplet at τ 5.79 almost vanished, thus establishing this signal as that of H-3, and the quartet of τ 6.69 collapsed into a doublet still centered at τ 6.69 as expected for H-2. Of the two dicarboxylic acids, only structure XI, in the conformation shown, can give the observed triplet for H-3 and quartet for H-2. The spectrum of XII would give a quartet for H-3 and a triplet for H-2. Thus, structure XI is established for the oxidation product of the major adduct and this in turn establishes structure I for the main adduct. It is also of interest that spectrum A is very similar to the NMR spectrum of the corresponding 3-nitro compound (1).



XI



XII

endo and exo Proton Signal Shifts on Hydrogenation.—The long-range shielding effects resulting from the magnetic anisotropy of the ethylene group have been recognized for some time (3). There is a region of shielding above and below the plane of the sp^2 hybridized carbon atoms and a region of deshielding extending within this plane. A molecular model of bicyclo[2.2.2]oct-2-ene indicates that

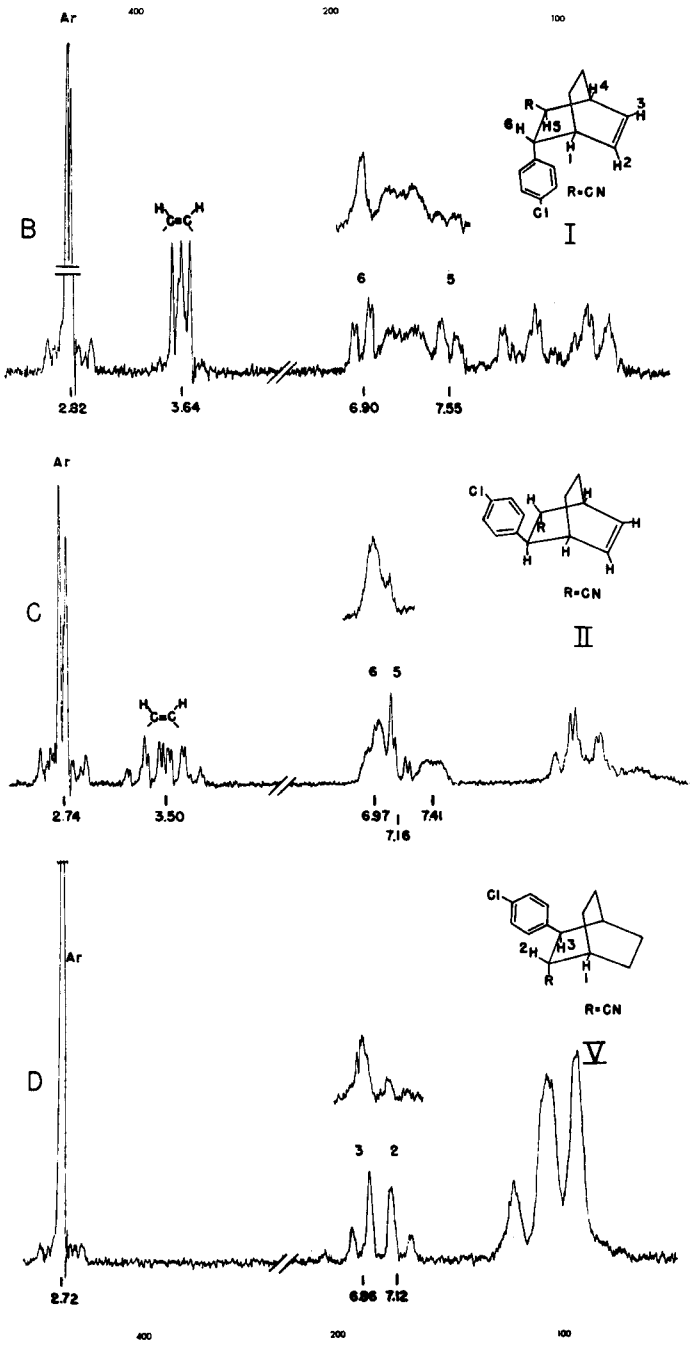


Fig. 2.—NMR spectra of *exo*-5-cyano-*endo*-6-(*p*-chlorophenyl)-bicyclo[2.2.2]oct-2-ene (B), *endo*-5-cyano-*exo*-6-(*p*-chlorophenyl)-bicyclo[2.2.2]oct-2-ene (C), *trans*-2-cyano-3-(*p*-chlorophenyl)-bicyclo[2.2.2]octane (D); portions of the spectra of the deuterated compounds are shown above the main spectra; 60 mc., about 1 *M* in deuterated chloroform at 37°; chemical shifts in τ units.

protons at positions 5 and 6 fall in a region of shielding when *endo* and in a region of slight deshielding when *exo* to the double bond. Hydrogenation of the double bond should therefore cause a downfield shift of the signals of the *endo* protons and an upfield shift of the signals of the *exo* protons. Tori and co-workers (4) report good agreement between calculated shifts and the average of observed shifts in a series of substituted bicyclo-[2.2.2]oct-2-enes. Their calculated shielding effects of the double bond are +0.18 p.p.m. for *endo* protons, and −0.08 for the *exo* protons. It should be noticed that although their average values are in good agreement with calculated values, their data show significant variations between members of the series. The method has also been used in configurational analysis of bicyclo[2.2.1]hept-2-enes (5, 6).

In compounds I and II (Fig. 2), the *endo* protons (H-5, τ 7.55 in I; H-6, τ 6.97 in II) experience the expected downfield shift upon hydrogenation, but the positions of the signals of the *exo* protons (H-6, τ 6.90 in I; H-5, τ 7.16 in II) are practically unchanged. The shifts of the *endo* protons differ

significantly in I and II: *endo* proton H-5 in I is shifted 26 c.p.s., while *endo* H-6 in II is shifted only 7 c.p.s. upon going to V. A difference of this magnitude would not be expected if the shift of the *endo* protons in going from I to V resulted entirely from the long-range shielding effect of the double bond. Other factors are obviously responsible for the observed difference, and the long-range shielding effects resulting from the magnetic anisotropy of the benzene ring certainly play an important role. The long-range effects of the benzene ring are exerted on both H-5 and H-6, but the effects on H-5 will be more sensitive to changes in orientation of the benzene ring, because the effect of H-5 can be changed from one of maximum shielding to one of maximum deshielding by 90° rotation of the aromatic ring. Differences in restriction to rotation of the benzene ring in going from I or II to V will affect the chemical shift of H-5 more than that of H-6. The greatest difference in restriction to rotation of the aromatic ring upon hydrogenation will occur in I where the benzene ring is *endo* to the double bond.

The assignment of the signals of H-5 and H-6 in I and II, and H-2 and H-3 in V was done by partial deuterium exchange of the hydrogen on the carbon substituted with the cyano group. The deuterium exchange was done by refluxing the substance in deuterated methanol in the presence of sodium methoxide. The deuterium exchange of the major adduct gave some isomerization and some amide formation in addition to simple deuterium exchange. The pertinent section of the spectrum of each deuterated compound is shown above the original curve in spectra B, C, and D. Deuterium exchange in I causes a large decrease in the intensity of the broad doublet with separation of 6.8 cycles at τ 7.55 and a collapse of the quartet (main separation of 6.8 cycles) at τ 6.90 into an unresolved singlet. This also establishes the coupling constant between H-5 and H-6 as J_{56} = 6.8 c.p.s. The minor splitting of 1.5 c.p.s. in the quartet at τ 6.90 probably results from coupling between H-6 and H-1. The fact that the signal of H-5 does not yield a similar quartet implies long-range coupling of H-5 with other ring proton(s) in addition to coupling with H-4. The signals of the bridgehead protons fall between the signals of H-5 and H-6. Similarly, deuterium exchange on II causes a disappearance of the quartet at τ 7.16 (J_{56} = 6.5 and minor coupling of 2.0 c.p.s.) and a collapse of the broad doublet of H-6 at τ 6.97 into an unresolved singlet. The signal of one of the bridgehead protons is overlapped by the signal of H-6 and that of the other bridgehead proton is centered at τ 7.41. Deuterium exchange on the hydrogenated compound V causes decrease in intensity of the original doublet of H-2 (J_{23} = 8.2 c.p.s.) at τ 7.12 and a collapse of the doublet of H-3 (J_{32} = 8.2 c.p.s.) at τ 6.86.

On hydrogenation of I and II to V, there is an increase of 1.4 and 1.7 c.p.s., respectively, in the coupling constant between the protons on the substituted carbons. The increase is of the same order of magnitude as that found on hydrogenation of the corresponding nitro compounds (1). This increase has been explained as being due to a greater flexibility of the bicyclo[2.2.2]octane system allowing the dihedral angle between H-2 and H-3 to be larger than the dihedral angle of 120° between H-5 and H-6 in a nondistorted bicyclo[2.2.2]oct-2-ene ring system. Such an increase in dihedral angle above 120° would result in an increase in the coupling constant. The minor coupling of the signals H-6 in I and H-5 in II is not present in the signals of H-2 and H-3 in V. This complication of the spectrum has also been observed for the signal of H-3 in *trans*-2-nitro-3-(*p*-chlorophenyl)-bicyclo-[2.2.2]octane and is believed due to virtual long-range coupling of H-3 with other ring protons (1). Such an explanation seems valid in the present case, where both H-2 and H-3 are virtually coupled with other protons. Proof that the deuterium exchange had occurred on the carbon substituted with the cyano group was obtained from the spectrum of the amine resulting from lithium aluminum hydride reduction of deuterated V, where deuterated V was obtained either from deuterium exchange on V or by hydrogenation of deuterated I.

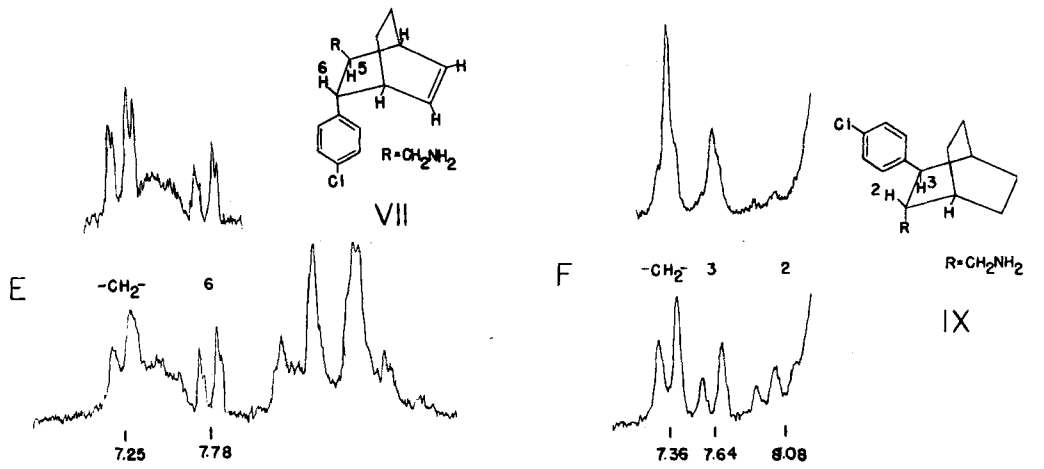


Fig. 3.—Portions of NMR spectra of *exo*-5-aminomethyl-*endo*-6-(*p*-chlorophenyl)-bicyclo[2.2.2]oct-2-ene (E) and the corresponding *N*-deuterated compound (upper curve), *trans*-2-aminomethyl-3-(*p*-chlorophenyl)-bicyclo[2.2.2]octane (F) and the corresponding C-2 deuterated compound (upper curve), 60 mc., about 1 *M* in deuterated chloroform at 37°; chemical shifts in τ units.

Spectrum E (Fig. 3) is that of amine VII measured in deuterated chloroform. The signal which appears as a doublet at τ 7.25 was found to move downfield upon forming the salt by addition of trifluoroacetic acid to the chloroform solution and was assigned to the methylene protons of the aminomethyl group. The doublet results from coupling with H-5, $J_{5(CH_2)}$ = 7.0 c.p.s. Exchange of the amino protons with deuterium caused each component of the doublet to split into a doublet with separation of about two cycles, indicating long-range coupling of the methylene protons with one of the ring protons. A portion of the resulting spectrum is shown above the original spectrum E. The signal at τ 7.78 is assigned to H-6. The major coupling is with H-5, J_{65} = 6.7, and there is evidence of minor coupling, probably with the bridgehead proton.

The broad band between the signals of H-6 and the methylene protons is due to the bridgehead protons and, as expected, is no longer present in the spectrum of the hydrogenation product, compound IX. Spectrum F (Fig. 3) is that of IX measured in chloroform. The doublet at τ 7.36 integrates for two protons and is assigned to the methylene protons, $J_{2(CH_2)}$ = 7.0 c.p.s. The sharpness of this doublet indicates rapid exchange of the amino protons and that the observed long-range coupling by a ring proton in VII has been reduced if not entirely eliminated in IX. The signal of H-3 appears as a doublet at τ 7.64, J_{32} = 7.5 c.p.s. Since $J_{2(CH_2)}$ and J_{23} are almost identical, the signal of H-2 should be a quartet with component intensity ratio of 1:3:3:1. Part of such a quartet can be seen centered at τ 8.08. This signal is greatly decreased in intensity in the spectrum of the corresponding amine prepared from I which had previously been subjected to deuterium exchange. The important section of this spectrum is shown above spectrum F (Fig. 3). A very important aspect of the spectrum of the deuterated amine is that the signal of the methylene protons at τ 7.36 and that of H-3 at τ 7.64 are now both singlets. This gives conclusive proof that deuterium exchange on I had occurred at C-5 and not at C-6. This proof definitely establishes the correct assignment of the signal of H-3 in the dicarboxylic acid (XI).

CONFIGURATIONAL ASSIGNMENT OF ADDUCTS OF THE *cis*-STYRENE

Chemical Proof.—A small amount of isomerization product was also recovered from the deuterium exchange reaction brought about by refluxing the major *trans* adduct in deuterated methanol in the presence of sodium methoxide. The isomerization product was found to have identical melting point as the major *cis* adduct, and there was no depression in melting point upon admixture. Furthermore, the NMR spectrum of the isomerization product differs with that of the major *cis* adduct only in having the signal of H-5 greatly reduced in intensity. Since the configuration of the major *trans* isomer has been established as structure I and since the deuterium exchange has been shown to occur only on C-5, the structure of the isomerization product of I is established as structure III. This in turn establishes structure III for the major adduct of *cis*-*p*-chloro-β-cyanostyrene.

Endo and Exo Proton Signal Shifts on Hydrogenation.—Hydrogenation of the minor adduct of *cis*-*p*-chloro-β-cyanostyrene to give compound VI causes a downfield shift of the signals of H-5 and H-6 of 12.0 and 7.5 c.p.s., respectively, when measured in deuterated chloroform at 60 mc. This is in good agreement with the calculated shift (10.8 c.p.s.) of Tori and co-workers (4) for *endo* protons and substantiates structure IV for the minor adduct. Hydrogenation of the major *cis* adduct to give compound VI causes an upfield shift of 1 c.p.s. for H-5 and 3.8 c.p.s. for H-6, when measured in deuterated chloroform at 60 mc. The calculated upfield shift of Tori and co-workers (4) for *exo* protons is 4.8 c.p.s. at 60 mc. Structure III is therefore further confirmed for the major adduct.

Spectrum G (Fig. 4) is that of the major *cis* adduct and spectrum H is that of the hydrogenation product of either the major or minor adduct. Spectra G and H were obtained in deuterated chloroform. The pertinent section of the spectrum of each compound obtained in pyridine is shown above the main spectrum. The chemical shifts were calculated by the AB analysis described by Jackman (7). The assignment of the signals of H-5 and H-6 in spectrum G, and of H-2 and H-3 in spectrum H, was done from the spectra of the corresponding compounds deuterated on the cyano-bearing carbon atom.

Excellent examples of solvent effects on chemical shifts are provided by the signals of H-5 and H-6 in spectrum G, and H-2 and H-3 in spectrum H, measured in deuterated chloroform and pyridine. The signals of the two adjacent protons which are overlapped in the chloroform spectra become individual signals amenable to first-order analysis when measured in pyridine. The coupling constant between the adjacent eclipsed protons measured in pyridine is J_{56} = 10.2 c.p.s. in III and J_{23} = 11.0 c.p.s. in VI. There is minor splitting of 2.3 c.p.s. of the signal of H-5 in III and 3.0 c.p.s. of the signal of H-2 in VI which presumably arises from coupling with the bridgehead proton. It is not immediately evident why similar coupling does not occur between H-6 in III or H-3 in VI and the respective adjacent bridgehead protons. Concerning the solvent effect on chemical shift, it is interesting to note that in each case it is the signal of the proton bonded to the cyano-bearing carbon that has experienced a significant downfield shift while the chemical shift of the signal of the proton on the carbon bearing the aromatic group is essentially the same in the two solvents. The same phenomenon was also observed in compounds I, II, IV, and V.

An interesting demonstration of the long-range shielding effects of the double bond is provided by the signals of the methylene protons on C-7 and C-8 of structure III in spectrum G. The doublet at τ 8.65 (J_{gem} = 10.0 c.p.s.) is attributed to the C-7 and C-8 protons *endo* to the double bond which are located in a region of positive shielding, and the doublet at τ 8.39 (J_{gem} = 10.0 c.p.s.) is attributed to the C-7 and C-8 protons *exo* to the double bond which are located in a region of slight deshielding. It is of special interest to note that the difference in chemical shift between these *endo* and *exo* protons is exactly identical to the calculated difference of 0.26 p.p.m. of Tori and co-workers (4).

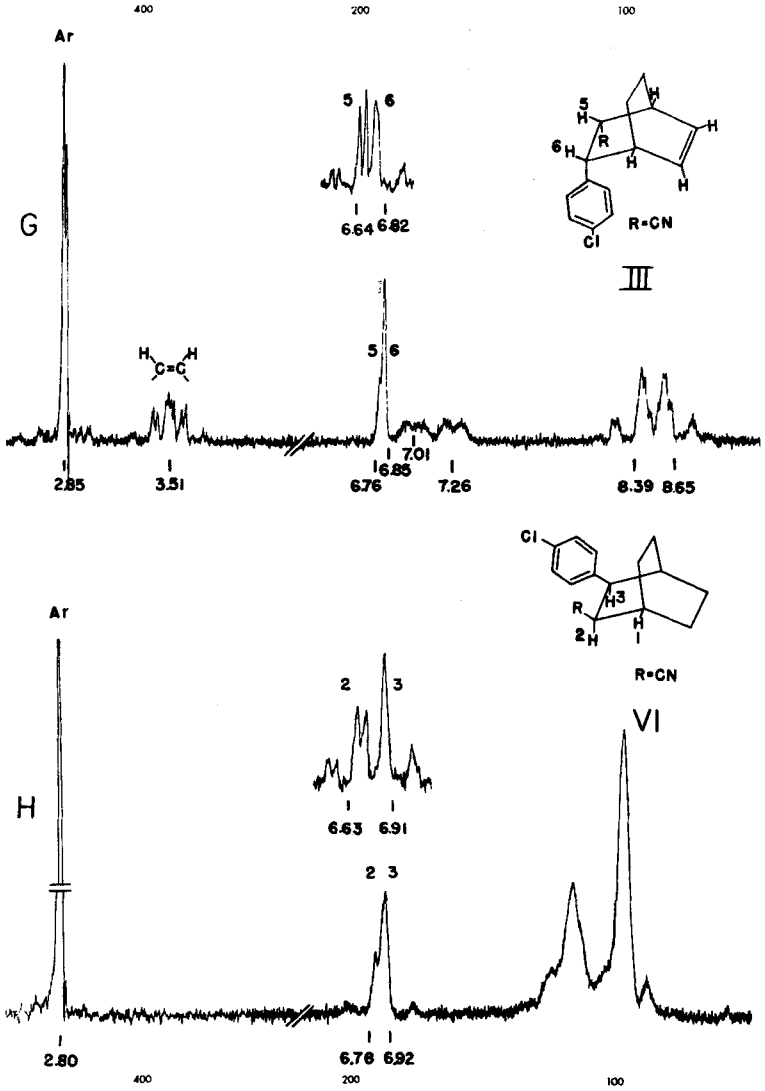


Fig. 4.—NMR spectra of *endo*-5-cyano-*endo*-6-(*p*-chlorophenyl)-bicyclo-[2.2.2]oct-2-ene (G) and *cis*-2-cyano-3-(*p*-chlorophenyl) - bicyclo[2.2.2] - octane (H) in deuterated chloroform at 60 mc. and 37°. The signals of H-5 and H-6 of III and H-2 and H-3 of VI measured in pyridine are shown above the main spectra. Chemical shifts are expressed in τ units.

TABLE I.—SHIFTS IN POSITION OF SIGNALS OF *endo* AND *exo* PROTONS UPON HYDROGENATION OF SOME BICYCLO[2.2.2]OCTENES TO BICYCLO[2.2.2]OCTANES[a]

Octene	→	Octane	Shifts ($\nu_{octane}-\nu_{octene}$), c.p.s. at 60 mc. *endo*-H H-5	*endo*-H H-6	*exo*-H H-5	*exo*-H H-6
I	⟶	V	+26.0	...	...	+2.5
II		V	...	+7.0	+2.5	...
III		VI	...	...	−1.0	−3.8
IV		VI	+12.0	+7.5	...	...
VII		IX	...	...	...	+8.5
VIII		X	...	...	...	−1.4

[a] Spectra determined in deuterated chloroform.

The spectrum of the minor *cis* adduct is not shown. This spectrum, obtained in deuterated chloroform, gives a singlet at τ 2.76 for the aromatic protons; a multiplet centered at τ 3.63 for the vinylic protons; a pair of overlapped doublets (analogous to those of spectrum G) for H-5 and H-6 of τ 6.98 and 7.04, respectively, and $J_{56} \simeq$ 10.5 from AB analysis; broad peaks at about τ 7.11 and τ 7.38 for the bridgehead protons; and an upfield broad complex of unresolved signals spread over a range of about 80 cycles for the hydrogens on C-7 and C-8.

The NMR spectra of *endo*-5-aminomethyl-*endo*-6-(*p*-chlorophenyl)-bicyclo[2.2.2]oct-2-ene (VIII) and *cis*-2-aminomethyl-3-(*p*-chlorophenyl)-bicyclo[2.2.2]octane (X) were determined in deuterated chloroform but are not shown. The most interesting aspect of the spectrum of VIII is the upfield portion which gives a pair of doublets for the C-7 and C-8 methylene protons analogous to

what is observed in the spectrum of III (Fig. 4). The upfield doublet at τ 8.64 (J_{gem} = 10.0 c.p.s.) is attributed to the C-7 and C-8 protons *endo* to the double bond, and the other doublet at τ 8.34 (J_{gem} = 10.0 c.p.s.) is attributed to the C-7 and C-8 protons *exo* to the double bond. There is considerable overlapping of signals in the spectrum of X, but the signal of H-3 appears as a doublet at τ 6.85 with separation of 9.7 c.p.s.

The shifts in positions of the signals of *endo* and *exo* protons upon hydrogenation of the double bond in six bicyclo[2.2.2]octenes are listed in Table I. The calculated shifts of Tori and co-workers (4) at 60 mc. are +10.8 c.p.s. for *endo* and −4.8 c.p.s. for *exo* protons. The observed shifts for the *endo* protons are in the expected direction and are generally of larger magnitude than those of the *exo* protons, in agreement with predictions from the long-range shielding effects of the double bond. But the data in Table I show variations, such as H-5 of I and H-6 of VII, which cannot be explained by the shielding effects of the double bond and indicate the presence of additional factors affecting chemical shifts. Long-range shielding effects resulting from the magnetic anisotropy of the aromatic ring have been discussed for compound I. In the amines the long-range effect of the amino group could be an additional factor.

The observed variations serve to emphasize the caution that must be exercised in reaching conclusions based on chemical shifts in compounds which have functional groups possessing magnetic anisotropy. This is especially true in systems where the functional group can assume different conformations and where a small change in structure (or even in solvent) may cause a change in the population of the preferred conformation.

Several differences are observed in the signals of the vinylic protons. The analysis of these signals will be undertaken by decoupling through double resonance technique, and the results reported in a subsequent publication.

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 deuterochloroform, unless otherwise noted, in a concentration of about 1 *M*, with tetramethylsilane as internal reference.

cis- and trans-p-Chloro-β-cyanostyrene.—These compounds were prepared from *p*-chlorobenzaldehyde and cyanoacetic acid by the method described by Ghosez (8) for the synthesis of *cis*- and *trans*-β-cyanostyrene. Gas chromatography analysis of the crude reaction mixture showed the presence of some unchanged aldehyde plus two main products in the ratio of 61.5 to 38.5. The major component (subsequently shown to be the *trans* product) was isolated and purified by crystallization from ethanol, m.p. 87–89°. The remaining mixture was distilled under reduced pressure with a Todd precise fractionation assembly, using a 90-cm. column packed with glass helices. The first fraction was mostly unchanged aldehyde. The second fraction, b.p. 132–134° at 1.5 mm., solidified and was recrystallized from hexane, m.p. 66.5–67.5°. This material was subsequently shown to be the *cis* product. A certain amount of resinous residue remained in the distillation flask. The *cis* and *trans* isomers were characterized by their NMR spectra. The major product gives a doublet with coupling constant of 17.0 c.p.s. for each vinylic proton (τ 2.64 and τ 4.14), and the minor product gives doublets at τ 2.96 and τ 4.57 with coupling constant of 12.6 c.p.s. The larger coupling constant establishes the *trans* structure for the major product.

Anal.—Calcd. for C_9H_6ClN: C, 66.07; H, 3.70; N, 8.56. Found: (*trans*) C, 66.55; H, 3.99; N, 8.21. (*cis*) C, 66.21; H, 3.62; N, 8.35.

exo - 5 - Cyano - endo - 6 - (p - chlorophenyl)-bicyclo[2.2.2]oct-2-ene (I) and endo-5-Cyano-exo-6-(p-chlorophenyl)-bicyclo[2.2.2]oct-2-ene (II).—In a typical synthesis 12.0 Gm. (0.073 mole) of *trans*-*p*-chloro-β-cyanostyrene, 21.4 Gm. (0.267 mole) of 1,3-cyclohexadiene, 22 ml. of toluene, and a trace of hydroquinone were heated with shaking under a nitrogen atmosphere in a stainless steel bomb for 10 days at 130°.

The dark brown reaction mixture was treated with activated charcoal in isopropyl alcohol. The solvent was removed, and the residue was chromatographed in several fractions on 0.05–0.2 mm. silica gel using mixtures of purified benzene and petroleum ether for elution. The over-all yield was approximately 40% of theoretical, and compound I was obtained in about sixfold excess over compound II. Purity of the various fractions from elution chromatography was followed by gas chromatography on a 10-ft. column of 20% silicon QF-1 on acid-washed Chromosorb W at 230°. The analytical sample of the major adduct, compound I, was recrystallized from isopropyl alcohol, m.p. 74–75°. The minor adduct (II) was crystallized from a mixture of isopropyl alcohol and methanol, m.p. 99–100°.

Anal.—Calcd. for $C_{15}H_{14}ClN$: C, 73.92; H, 5.79; N, 5.75. Found: (I) C, 73.85; H, 5.84; N, 5.91. (II) C, 74.01; H, 5.90; N, 5.60.

endo - 5 - Cyano - endo - 6 - (p - chlorophenyl)-bicyclo[2.2.2]oct-2-ene (III) and exo-5-Cyano-exo-6-(p-chlorophenyl)-bicyclo[2.2.2]oct-2-ene (IV).—These compounds were prepared by heating 10.7 Gm. (0.066 mole) of *cis*-*p*-chloro-β-cyanostyrene, 20.8 Gm. (0.26 mole) of 1,3-cyclohexadiene, 30 ml. of toluene, and a trace of hydroquinone at approximately 120° for 10 days in a stainless steel bomb, under a nitrogen atmosphere, with shaking. The reaction mixture was treated in a similar manner as that of I and II above. The yield of recovered purified adducts was 37%. The analytical sample of III recrystallized from benzene melted at 156.5–158° and IV recrystallized from a solution of ligroin and benzene melted at 117–118.5°. The ratio of recovered III to IV was about 7:1. The purity of the isomers was determined by gas chromatography similar to I and II above.

Anal.—Calcd. for $C_{15}H_{14}ClN$: C, 73.92; H, 5.79; N, 5.75. Found: (III) C, 73.97; H, 5.87; N, 5.69. (IV) C, 74.12; H, 5.90; N, 5.74.

trans - 2 - Cyano - 3 - (p - chlorophenyl) - bicyclo-[2.2.2]octane (V).—This compound was obtained by low-pressure catalytic hydrogenation of I or II using 10% Pd on carbon in absolute ethanol. Recrystallization from this solvent gave the pure product, m.p. 77.5–78.5°. The yield was quantitative.

Anal.—Calcd. for $C_{15}H_{16}ClN$: C, 73.31; H, 6.56; N, 5.70. Found: C, 73.47; H, 6.58; N, 5.65.

cis - 2 - Cyano - 3 - (p - chlorophenyl) - bicyclo-[2.2.2]octane (VI).—This compound was prepared by low-pressure catalytic hydrogenation of III or IV using 10% Pd on carbon in ethyl acetate. The product was recrystallized from a mixture of isopropyl alcohol and ligroin, m.p. 60.5–61.5°. The yield was quantitative.

Anal.—Calcd. for $C_{15}H_{16}ClN$: C, 73.31; H, 6.56; N, 5.70. Found: C, 73.48; H, 6.71; N, 5.88.

exo - 5 - Aminomethyl - endo - 6 - (p - chlorophenyl) - bicyclo[2.2.2]oct-2-ene (VII) Hydrobromide.—A solution of compound I in anhydrous ether was added dropwise with stirring to an excess of $LiAlH_4$ in ether. Stirring was continued at room temperature for 1 hr. after the addition was completed. The excess $LiAlH_4$ was destroyed by careful addition of ice water. Aqueous 5% NaOH was then added to increase the water layer; the mixture was extracted with ether and the ether solution dried with Drierite. Removal of the solvent gave a quantitative yield of the crude amine. The hydrobromide salt was prepared by bubbling HBr in a solution of the amine in ligroin. Recrystallization from a mixture of isopropyl alcohol and ligroin yielded the purified salt in 88% yield, m.p. 252–256°.

Anal.—Calcd. for $C_{15}H_{19}BrClN$: C, 54.81; H, 5.83; N, 4.26. Found: C, 54.58; H, 6.26; N, 4.43.

endo - 5 - Aminomethyl - endo - 6 - (p - chlorophenyl)-bicyclo[2.2.2]oct-2-ene (VIII) Hydrobromide.—Compound III was dissolved in about 20 ml. of 50:50 dioxane–ether mixture and added slowly to a slurry of excess $LiAlH_4$ in the same solvent. The reaction mixture was allowed to stir at room temperature for 1 hr. after the addition was complete, and the reaction mixture worked up as for VII. The yield of the crude amine was quantitative. Some evidence of isomerization to VII was noticed from the NMR spectrum of the crude amine. The hydrobromide salt was prepared by bubbling HBr into a solution of the amine in a mixture of toluene and petroleum ether. The salt was purified by recrystallization from a mixture of methanol and acetone, m.p. 264–266°. The yield of the purified salt was 42%.

Anal.—Calcd. for $C_{15}H_{19}BrClN$: C, 54.81; H, 5.83; N, 4.26. Found: C, 54.82; H, 5.85; N, 4.20.

trans - 2 - Aminomethyl - 3 - (p - chlorophenyl)-bicyclo[2.2.2]octane (IX) Hydrobromide.—The hydrobromide salt of IX was prepared by catalytic hydrogenation of the hydrobromide salt of VII using 10% Pd on carbon in ethanol. The salt was recrystallized from a mixture of isopropyl alcohol and ligroin; yield 77%, m.p. 266–269°. The compound was also obtained by $LiAlH_4$ reduction of V, as described for VII, followed by salt formation.

Anal.—Calcd. for $C_{15}H_{21}BrClN$: C, 54.48, H, 6.40, N, 4.24. Found: C, 54.48; H, 6.46; N, 4.06.

cis - 2 - Aminomethyl - 3 - (p - chlorophenyl)-bicyclo[2.2.2]octane (X) Hydrobromide.—The free amine was prepared by $LiAlH_4$ reduction of VI in a manner analogous to the synthesis of VIII, except that ether was used exclusively as the solvent. The salt was prepared by bubbling HBr through a solution of the amine in hexane and purified by recrystallization from a solution of methanol and acetone to obtain the analytical sample, m.p. 273–276°.

Anal.—Calcd. for $C_{15}H_{21}BrClN$: C, 54.48; H, 6.40; N, 4.24. Found: C, 54.04; H, 6.19; N, 4.39.

cis - 2 - (p - Chlorophenyl) - trans - 3 - cyano-cis-1,4-cyclohexanedicarboxylic Acid (XI) and C-3 Deuterated XI.—One gram (4.1×10^{-3} mole) of compound I was dissolved in 10 ml. of glacial acetic acid, and 1.2 Gm. (1.2×10^{-2} mole) of solid CrO_3 was added in portions with stirring at room temperature, and stirring continued for 5 hr. after the addition was complete. About 100 ml. of water was added and the resulting mixture extracted with ether, dried with Drierite, and the solvent removed nearly to dryness. Benzene was then added, resulting in the precipitation of 320 mg. (25%) of product which, on recrystallization from a solution of acetone and benzene, yielded the analytical sample, m.p. 202–205°. The C-3 deuterated acid was prepared in a similar manner by oxidation of I deuterated at C-5.

Anal.—Calcd. for $C_{15}H_{14}ClNO_4$: C, 58.55; H, 4.59; N, 4.55. Found: C, 58.85; H, 4.72; N, 4.41.

Deuteration on C-5 of I, II, and III.—A mixture of sodium methoxide and I in a 3:1 molar ratio was refluxed for 24 hr. in deuterated methanol. The reaction mixture was extracted with anhydrous ether and dried over Drierite. On removal of the solvent, the residue was chromatographed on 0.05–0.20 mm. silica gel. A yield of about 50% C-5 deuterated I was obtained. In addition, a small amount (about 5%) of C-5 deuterated III was obtained as well as a 24% yield of a compound tentatively identified as an amide. Compound II was treated under similar conditions as I, except that the reaction mixture was not chromatographed on silica gel since there was no indication from gas chromatography of any product other than C-5 deuterated II.

Deuteration on C-2 of V, VI, and IX.—A mixture of sodium methoxide and V in a 3:1 molar ratio was refluxed for 24 hr. in deuterated methanol. The reaction mixture was extracted with anhydrous ether and dried over Drierite. A yield of 80% of the deuterated product was obtained with only trace amounts of other unidentified products. Compound VI deuterated on C-2 was prepared quantitatively by hydrogenation of C-5 deuterated III in the same manner as VI was obtained from III. Compound IX deuterated at C-2 was obtained by $LiAlH_4$ reduction of C-2 deuterated V which in turn had been obtained from hydrogenation of compound I deuterated at C-5.

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