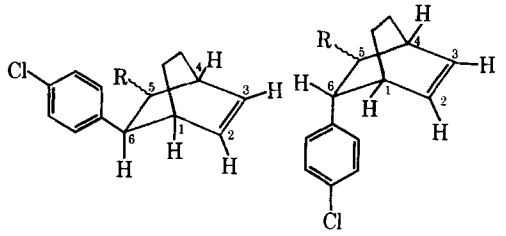
NMR Spin–Spin Decoupling Studies of Some 5,6-Disubstituted Bicyclo[2.2.2]oct-2-enes

Assignment of Vinylic Protons and Demonstration of Allylic Coupling

By DAVID B. ROLL*, BERNARD J. NIST, and ALAIN C. HUITRIC

Assignment of the NMR signals of the vinylic protons has been accomplished by spin–spin decoupling in endo-5-nitro-exo-6-(*p*-chlorophenyl)-bicyclo[2.2.2]oct-2-ene (I), endo-5-amino-exo-6-(*p*-chlorophenyl)-bicyclo[2.2.2]oct-2-ene hydrobromide (IV), endo-5-cyano-exo-6-(*p*-chlorophenyl)-bicyclo[2.2.2]oct-2-ene (V), endo-5-cyano-endo-6-(*p*-chlorophenyl)-bicyclo[2.2.2]oct-2-ene (VII), all of which show significant differences in the chemical shifts of the two vinylic protons. A long-range coupling of 1.5 c.p.s. is demonstrated between H-1 and H-3 and between H-4 and H-2 in these systems.

In two recent publications (1, 2) the authors have reported partial analyses of the NMR spectra of some 5,6-disubstituted bicyclo[2.2.2]-oct-2-enes. The analyses have now been expanded by spin–spin decoupling through frequency sweep double resonance technique.



I, R = NO_2, endo
III, R = NH_2, endo
IV, R = NH_3^+, endo[1]
V, R = CN, endo
VIII, R = CN, exo

II, R = NO_2, exo
VI, R = CN, exo
VIII, R = CN, endo

DISCUSSION

In the initial analysis of the spectra of compounds I and II (1) it was possible to assign the signals of H-1, H-4, H-5, and H-6, but unambigous differentiation of the signals of H-2 and H-3 was not possible, even though these signals are separated by about 23 c.p.s. in the spectrum of compound I measured in carbon tetrachloride at 60 Mc. In the isomeric compound II, in which the nitro group is exo and the aromatic group endo to the double bond, the difference in the chemical shift of the vinylic protons is much smaller (1). The differences in chemical shifts of H-2 and H-3 are attributed to the long-range shielding effects resulting from the magnetic anisotropy of the aromatic ring (3) and the nitro group (4).

Assignment of the signals of H-2 and H-3 in the spectrum of I has now been accomplished by spin–spin decoupling. Pertinent portions of the spectrum and decoupled spectra of I are given in Fig. 1.

Only that portion of the spectrum including the signals of H-1 through H-6 is given in each case. In spectrum F, prior to decoupling, the signals of the vinylic protons appear essentially as triplets centered at τ 3.46 and 3.85. Components of the triplet at τ 3.46 are further split by about 1.5 c.p.s., and those of the upper field triplet are broadened, indicating the presence of long-range coupling. Irradiation at the resonance of H-1, spectrum E, caused the triplet at τ 3.46 to collapse into a doublet, J_{23} = 8.5 c.p.s., while the triplet at τ 3.85 now appears as a quartet, J_{32} = 8.5 and J_{34} = 6.0 c.p.s. These results establish the signal at τ 3.46 as that of H-2. The sharpening of the signal at τ 3.85 into a well-defined quartet by irradiating at the signal of H-1 shows that H-3 is coupled slightly with the allylic H-1 in spectrum F.

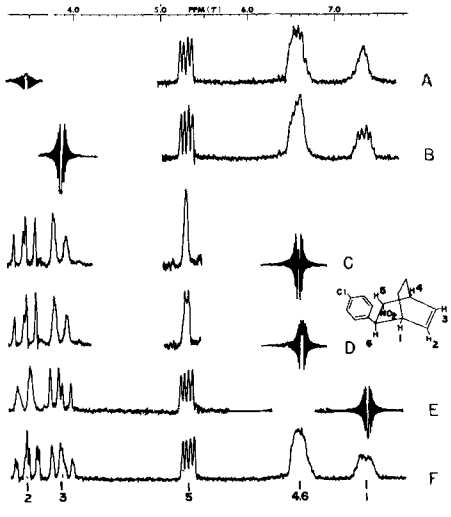


Fig. 1.—Portions of NMR spectrum and decoupled spectra of endo-5-nitro-exo-6-(*p*-chlorophenyl)-bicyclo[2.2.2]oct-2-ene; 60 Mc., about 1 *M* in carbon tetrachloride with TMS internal reference.

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[1] As the hydrobromide salt.

Irradiation at the position of overlapping signals of H-4 and H-6 (spectra C and D) caused the triplet at τ 3.85 to collapse into a doublet, $J_{23} = J_{32} =$ 8.5 c.p.s., and simultaneously produced a sharp quartet, $J_{23} = 8.5$ and $J_{21} = 6.5$ c.p.s., for the signal of H-2. This confirms the assignment of H-2 and H-3 and also shows an allylic coupling of 1.5 c.p.s. between H-2 and H-4 in spectrum F. The sharp singlet of H-5 in spectrum C shows that H-5 is simultaneously decoupled from H-4 and H-6, while in spectrum D H-4 is not completely decoupled from H-5.

Additional evidence for long-range allylic coupling between H-1 and H-3 is found in spectrum B. Irradiation at the position of the signal of H-3 produced a much better resolved signal for H-1. Irradiation at H-3 also caused a narrowing of the combined signals of H-4 and H-6 as expected due to decoupling of H-3 from H-4. Spectrum A shows the expected narrowing of the signal of H-1 by irradiation at the signal of H-2.

Compound III was obtained by the reduction of I with iron in acetic acid by the method of Kornblum and co-workers (5). The spectrum of the free amine (not shown) was measured in tetrachloroethylene with TMS as internal reference. The vinylic protons give two triplets, centered at τ 3.57 and 3.89, which are quite analogous in shape to those of the corresponding nitro compound I. The spectrum has a signal at τ 7.10 which integrates to 1 proton, a signal at τ 7.60 which integrates to 2 protons, and a signal at 7.83 which accounts for 1 proton. Signals of the remaining hydrogens, including the amino protons, are overlapping at higher field. The spectrum of the hydrobromide salt of III, determined in D_2O with sodium 3-(trimethylsilyl)-1-propane sulfonate as internal reference, has the following pattern: the vinylic protons give 2 triplets centered at τ 3.03 and 3.39; there are unresolved singlets each integrating to 1 proton, at τ 5.82, 6.66, 6.90, and 7.25. The signals of the remaining ring protons are overlapped over a broad region at higher field and the exchangeable protons gave a signal at τ 4.89. The signal at τ 5.82 has experienced the largest downfield shift upon protonation and is assigned to H-5. Decoupling studies of the spectrum of this amine salt in D_2O made it possible to assign the signals of H-1 through H-6. Irradiation of the signal at τ 6.66 caused the signal of H-5 at τ 5.82 to appear as a poorly resolved doublet with separation of about 4.5 c.p.s., and caused the signal of the vinylic proton at τ 3.39 to collapse to a doublet with separation of about 7.5 c.p.s. These results show that the signal at τ 6.66 is due to H-4 and that the signal at τ 3.39 is that of the vinylic H-3. Irradiation at τ 7.25 caused the triplet at τ 3.03 to collapse to a doublet with separation of about 7.5 c.p.s. and a narrowing of the signal at τ 6.90. Irradiation at τ 6.90 caused a narrowing of the signal at τ 5.82 but did not cause any change in the signal of the vinylic protons. These results show that the signal at τ 7.25, 3.03, and 6.90 are due to H-1, H-2, and H-6, respectively.

The spectra of compounds V, VI, and VII have been published previously (2). The spectra of V and VII show a greater difference in chemical shifts of the vinylic protons than the spectrum of VI. The assignment of the signals of the vinylic protons was not done in the original publication. This has now been done by double resonance for compounds V and VII. A large solvent effect on chemical shift in going from deuterochloroform to pyridine was observed for H-5 of VII, causing the overlapped signals of H-5 and H-6 in chloroform to appear as discrete peaks in pyridine (2), but the pattern of the vinylic protons was almost identical in the two solvents.

Pertinent portions of the spectrum and decoupled spectra of VII measured in pyridine are given in Fig. 2. Spectrum C shows the signals of H-1 through H-6 without decoupling. The assignment of H-5 at τ 6.64 and H-6 at τ 6.82 was accomplished by deuteration at C-5 (2). The vinylic protons give partially overlapped sextets (doublets of triplets with minor splitting of 1.5 c.p.s.) centered at τ 3.48 and 3.67. The signals of the bridgehead protons appear at τ 7.14 and 7.39. Spectrum B shows the effects of irradiating at τ 7.14. The signal of H-5 has collapsed to a doublet, $J_{56} = 10$ c.p.s., showing that the signal at τ 7.14 is due to H-4 and that H-4 is now decoupled from H-5. In addition, the signal at τ 3.67 has collapsed to a broad doublet with separation of about 8.5 c.p.s., and the minor splitting of 1.5 c.p.s., due to allylic long-range coupling has disappeared in the signal at τ 3.48. This permits assignment of the signal at τ 3.67 to H-3 and that at τ 3.48 to H-2. These assignments are confirmed by irradiation of the signal of the other bridgehead proton (H-1) at τ 7.39, spectrum A, which causes no change in the signal of H-5 but causes the signal at τ 3.48 to collapse to a broad doublet with separation of about 8.5 c.p.s. and causes the signal at τ 3.67 to become a triplet with separation of 8.5 c.p.s., $J_{12} \simeq J_{23} = 8.5$ c.p.s.

The decoupled spectra of V are not shown. The original spectrum measured in deuterochloroform without decoupling (2) shows two sextets (essentially triplets with minor splitting of 1.5 c.p.s.) for the vinylic protons centered at τ 3.42 and 3.68; a sharp quartet for H-5 at τ 7.16; a signal accounting for two hydrogens at τ 6.97 which shows the poorly re-

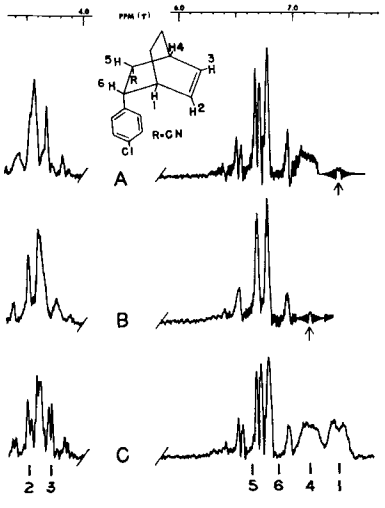


Fig. 2.—Portions of the NMR spectrum and decoupled spectra of endo-5-cyano-endo-6-(*p*-chlorophenyl)-bicyclo[2.2.2]oct-2-ene; 60 Mc. about 1 *M* in pyridine with TMS as internal reference.

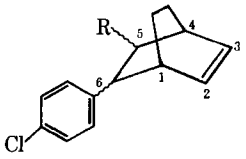
solved quartet of H-6 overlapped by the signal of one of the bridgehead protons; and the signal of the other bridgehead proton at τ 7.41. Decoupling was done in deuterochloroform. Irradiation at τ 7.41 did not cause any change in the quartet of H-5 but caused the poorly resolved signal of H-6 to appear as a sharper doublet and also caused the sextet at τ 3.42 to collapse to a doublet with separation of 8.5 c.p.s., with simultaneous change of the sextet at τ 3.68 to a quartet of coupling constants of 8.5 and 6.0 c.p.s. These changes in the pattern of the vinylic protons are analogous to those shown in spectrum E of Fig. 1, compound I. The results allow the assignment of the signal of H-1 at τ 7.41; H-2 at 3.42; H-3 at 3.68; and $J_{23} = J_{32} =$ 8.5 and $J_{21} = J_{34} =$ 6.0 c.p.s. The long-range allylic coupling of 1.5 c.p.s. is again demonstrated. These assignments are confirmed by irradiation in the vicinity of τ 6.97 where the other bridgehead proton (H-4) overlaps with the signal of H-6. This caused a collapse of the signal at τ 3.68 to a doublet with separation of 8.5 c.p.s. and a simultaneous change of the signal at τ 3.42 to a quartet, $J_{23} = 8.5$ and $J_{21} = 6.0$ c.p.s., changes similar to those seen in spectra C and D of Fig. 1.

The spectrum of exo-5-cyano-exo-6-(*p*-chlorophenyl)-bicyclo[2.2.2]oct-2-ene (VIII) was determined in deuterochloroform and in pyridine. The spectra are not shown. In deuterochloroform the signals of H-5 and H-6 overlap to give a single peak at τ 7.02. The signals of the bridgehead protons are centered at about τ 7.11 and 7.40. The signals of the vinylic protons at τ 3.50 and 3.76 have a pattern of complex triplets analogous to those of H-2 and H-3 in spectrum F of Fig. 1. In the spectrum measured in pyridine the signals of the vinylic protons appear at τ 3.62 and 3.89 and there is no significant change in the pattern of the complex triplets. The signals of the bridgehead protons are centered at about τ 7.27 and 7.51. The most significant difference in the spectra from the two solvents is a separation of the signals of H-5 and H-6 in pyridine which appear at τ 6.88 and 7.08 and give a pattern analogous to that of H-5 and H-6 of VII in pyridine, spectrum C, Fig. 2. The signal of one of these two hydrogens is shifted downfield, while the other one experiences very little change in pyridine compared to deuterochloroform. This effect has been observed in other isomers of VIII (2) where the assignment of H-5 and H-6 had been done through deuteration and in each case it was the signal of the hydrogen on the cyano-bearing carbon which experienced the downfield shift. Decoupling was done on VIII in pyridine by irradiation of the positions of the signals of the bridgehead protons. Irradiation at τ 7.51 caused the vinylic signal at τ 3.62 to collapse to a doublet and did not bring any change in the signal at 6.88, while irradiation at τ 7.27 caused a collapse of the signal of the vinylic proton at τ 3.89 to a doublet and caused the quartet at 6.88 to appear as a doublet with separation of 10.5 c.p.s. This shows that the bridgehead proton giving the signal at 7.51 is located between the vinylic proton responsible for the signal at τ 3.62 and the proton responsible for the signal at τ 7.08 while the bridgehead proton giving the signal at τ 7.27 is located between the other vinylic proton, τ 3.89, and the proton giving the signal at τ 6.88. If, as observed in other isomers (2), it is H-5 which experiences the deshielding effect in pyridine then the following chemical shifts would hold: H-1, 7.51; H-2, 3.62; H-3, 3.89; H-4, 7.27; H-5, 6.88; H-6, 7.08.

A summary of chemical shifts is given in Table I.

In all bicyclo[2.2.2]oct-2-enes with a nitro or cyano group at C-5 and a *p*-chlorophenyl group at C-6 in which the signals of the vinylic protons could be differentiated by spin–spin decoupling the signal of H-2 was found to be further downfield. Since the spatial orientation of the functional groups varies in these compounds and since the long-range shielding effects due to the magnetic anisotropy of the aromatic and nitro groups are affected by con-

TABLE I.—SUMMARY OF CHEMICAL SHIFTS IN τ UNITS



		Solvent	Vinylic H-2	Vinylic H-3	Bridgehead H-1	Bridgehead H-4	H-5	H-6
I,	Ar exo R = NO_2, endo	CCl_4	3.46	3.85	7.35	~6.59	5.32	~6.59
II,	Ar endo R = NO_2, exo	CCl_4	[a]	[a]	7.27	6.68	5.67	6.35
IV,	Ar exo R = NH_3^+ endo	D_2O[b]	3.03	3.39	7.25	6.66	5.82	6.90
V,	Ar exo R = CN, endo	$CDCl_3$	3.42	3.68	7.41	~6.97	7.16	~6.97
VI,	Ar endo R = CN, exo	$CDCl_3$	[c]	[b]	[d]	[d]	7.55	6.90
VII,	Ar endo R = CN, endo	Pyridine	3.48	3.67	7.39	7.14	6.64	6.82
VIII,	Ar exo R = CN, exo	$CDCl_3$ Pyridine	[e]	[e]	[e]	[e]	[e]	[e]

[a] The signals were not differentiated. The partially overlapped signals are centered at τ 3.58. See *Reference 1* for spectrum. [b] Sodium 3-(trimethylsilyl)-1-propane sulfonate was used as internal reference. [c] The signals are partially overlapped at τ 3.64 and were not differentiated. See *Reference 2* for spectrum. [d] Signals of the bridgehead protons, centered at about τ 7.17 and 7.31 are partially overlapped. See *Reference 2* for spectrum. [e] See text for discussion.

formational changes, it is dangerous to make any generalization regarding relative shielding effects of these functional groups on the vinylic protons in these systems. This could best be accomplished on mono-substituted compounds.

EXPERIMENTAL

The NMR spectra were determined with a Varian A-60 and/or HR-60 spectrometer. Decoupling was achieved by frequency sweep, double resonance procedure with a Varian DA-60IL spectrometer.

Compounds I and II have been reported in a previous paper (1) as were compounds V–VIII (2).

endo - 5 - Amino - exo - 6 - (p - chlorophenyl)-bicyclo[2.2.2]oct-2-ene Hydrobromide.—The amine was obtained in 48% yield by the reduction of the corresponding nitro compound I with iron in acetic acid by the method of Kornblum and co-workers (5) and as previously described for analogous compounds (6). The hydrobromide salt was formed by bubbling HBr gas into a ligroin solution of the amine. The salt was recrystallized from a mixture of benzene and ethanol, m.p. 247–250° (Kofler micro hot stage).

Anal.—Calcd. for $C_{14}H_{17}BrClN$: C, 53.44; H, 5.45. Found: C, 53.03; H, 5.38.

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Synthesis of Tropine-Labeled Atropine I

Micro Methods for the Synthesis of Tropine and for Its Esterification with Tropic Acid

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Yields for each step in the esterification of tropine and tropic acid have been determined with micro and semimicro quantities of reactants. In a similar way, the Robinson condensation has been studied. Data are compared with the findings of other investigators. In the esterification of micro quantities of tropine and tropic acid, 70–75 per cent of theoretical atropine yields are obtained routinely. Based on any intermediate in the Robinson condensation, micro quantities of reactants routinely produce 67–72 per cent of theoretical tropine yields. Predicted yields of 47–54 per cent atropine from Robinson intermediates were confirmed by synthesis of atropine from each of the Robinson reactants. The procedures are designed for the synthesis of labeled tropine and tropine-labeled atropine from labeled arabinose.

THE ESTABLISHMENT of metabolic pathways in tropine metabolism awaits the development of synthetic methods for selectively labeling the tropine ring. The fate of this heterocycle, free or as a structural component of atropine and related compounds, is essentially unknown because suitably ring-labeled compounds are not available in amounts adequate for animal studies.

Tritium-labeled atropine (1) and randomly-^{14}C-labeled atropine (2) are of limited usefulness because the labeling is not specific. Biosynthetic atropines (3, 4) are suitably labeled, and could be used to determine the metabolic fate of the tropine moiety, but complexities of preparation have limited their availability and prevented their use in animal studies. Fodor *et al.* (5) and Werner *et al.* (6) prepared *N*-methyl-^{14}C-tropine, then esterified it with unlabeled tropic acid to obtain tropine-labeled atropine. Subsequent metabolic studies (7), although not extensive, clearly indicate the need to label tropine and atropine in other positions. During studies of atropine toxicity, this need became very apparent to the authors.

The extreme toxicity of atropine and related compounds is an added complication, because low doses must be used for *in vivo* studies, and minor metabolites are correspondingly difficult to detect. Compounds of reasonably high specific

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