The Application of NMR in Determination of the Structure of Cyclanols. I. The Structures of Cyclohexane-1,3-diols

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The structure of the isomeric pairs of cyclohexane-1,3-diols and 5,5-dimethylcyclohexane-1,3-diols are established by means of the NMR spectra observed for solutions of each of the pure compounds. Origins and multiplicities of significant spectral lines are discussed in terms of molecular symmetry and conformational mobility. From the assigned *trans* conformations, the sum of the spin-spin coupling constants of the C-2 proton with the C-1 and C-3 protons is evaluated and shown to be a distinctive characteristic of the conformation. The sensitivity of the geminal dimethyl bands to changes in conformation is examined in some detail, and the range of applicability of this feature as a conformational criterion is discussed.

Several papers have dealt successfully with structural and conformational assignments in substituted six-membered rings using high-resolution NMR techniques.[2-6] For these problems other physical approaches usually successful in some structural and conformational assessments, such as determination of the dipole moment by dielectric measurements, or measurement and correlation of the vibrational bands, have often yielded only equivocal results. This has been found to be the case in determining the structure of substituted cyclohexane-1,3-diols and other cyclanols where the application of familiar structural criteria is often complicated by a lack of understanding of the limitations of these criteria.[7] It was felt that complications of this nature, often inherent in other approaches, may be eliminated by use of the high-resolution nuclear magnetic resonance method.

We are here immediately concerned with certain cyclohexanediols where it has been found impossible to apply some of the more acceptable diol structural criteria.[7] Thus, the respective structures of the isomeric pair of unsubstituted cyclohexane-1,3-diols (resorcitols) have been confirmed by the observation[7,8] that the *cis* isomer is proved by infrared measurement to possess a rather tight intramolecular hydrogen bond which is absent in the corresponding *trans* isomer. On the other hand, the 5,5-dimethylcyclohexane-1,3-diol isomeric pair[9-14] cannot be distinguished in this fashion since it has been reported[13,14] that neither of the pure isomers shows evidence of intramolecular hydrogen bonding. Other criteria which have been applied[14] such as the relative rates of chromic acid oxidation are dubious at best since they depend upon an assumed mechanism of chromic acid oxidation which is not at all well established.[15] Furthermore, the failure[14] to distinguish these isomers by means of the classical criterion of resolvability also suggests the need to develop a more generally applicable physical basis for structural determination in these cases.

Results and Discussion

The diols examined in this study are in the solid state at room temperature and were studied in pyridine solutions of different concentration. Marked changes were introduced into several of the chemical shift values by specific solvent effects, and these changes were, furthermore, found to be quite dependent on concentration. Consequently, their values serve primarily to identify bands rather than to suggest possible structural correlations with related alicyclic molecules studied under different conditions.

The spectra were obtained with a 60-Mc./sec. Varian spectrometer system using a thermally regulated twelve-inch electromagnet. Chemical shifts of all important signals were obtained by superposition of audio side bands even though field drift was almost negligible. Shift values are referenced from the internal standard, tetramethylsilane, and all chemical shifts whose magnetic field values fall below that of the reference standard are reported explicitly as negative quantities. The bands from the solvent and reference standard, which occur at

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(2) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958).

(3) L. W. Reeves and K. O. Stromme, *Can. J. Chem.*, **38**, 1241 (1960).

(4) S. Brownstein and R. Miller, *J. Org. Chem.*, **24**, 1886 (1959).

(5) E. I. Eliel, *Chem. Ind.* (London), 568 (1959).

(6) J. I. Musher, *Spectrochim. Acta*, **16**, 835 (1960).

(7) H. Kwart and G. C. Gatos, *J. Am. Chem. Soc.*, **80**, 881 (1958).

(8) L. P. Kuhn, *ibid.*, **74**, 2491 (1952).

(9) J. M. Sprague and H. Adkins, *ibid.*, **56**, 2669 (1934).

(10) T. Henskall, *J. Soc. Chem. Ind.*, **62**, 127 (1943).

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(12) A. S. Dreiding and J. A. Hartmann, *J. Am. Chem. Soc.*, **75**, 3723 (1953).

(13) Unpublished work of J. A. Ford, Jr., from the laboratories of the Department of Chemistry, The University of Delaware, Ph.D. thesis, June, 1957.

(14) H. Favre and J. C. Richer, *Can. J. Chem.*, **37**, 411 (1959).

(15) For a more extensive discussion of this see H. Kwart and P. F. Francis, *J. Am. Chem. Soc.*, **81**, 2116 (1959).

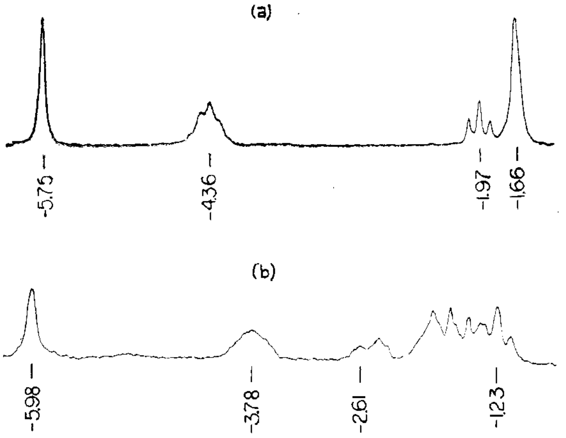


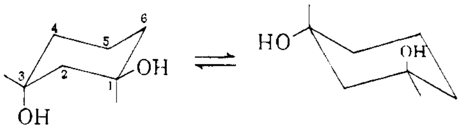
Fig. 1.—NMR spectra of isomeric 1,3-cyclohexanediols at 60 Mc./sec., taken at 30°. Chemical shifts are in p.p.m. referenced from tetramethylsilane as internal standard. In spectrum (a) which corresponds to isomer I, the bands at −1.66 and −1.97 p.p.m. have been recorded at reduced amplification. Spectrometer system resolution was better than 7 parts in 10^9 as demonstrated by the line separations in the pyridine spectrum. Spectrum (b) corresponds to isomer II.

the low[16] and high[17] field extremities of the spectra, respectively, are deleted from the figures.

In comparing the spectra of the unsubstituted diols (Fig. 1) we note immediately the considerable differences in complexity of the spectra of the stereoisomers (designated here as I and II; see accompanying table). In both of these spectra the single line absorptions at low magnetic field (−5.75 and −5.98 p.p.m.) are due to the hydroxyl protons. Attempts to utilize the different chemical shifts of these protons for conformational assignments usually founder, because the chemical shift values of hydroxyl protons are normally more sensitive to variations in hydrogen-bonding than to variations in molecular geometry, and the latter shifts are frequently masked by the former. In the systems studied here, the pyridine undoubtedly participates as donor solvent coordinating the solute hydroxyl protons, and so structural and conformational correlations of these absorptions are difficult to make.

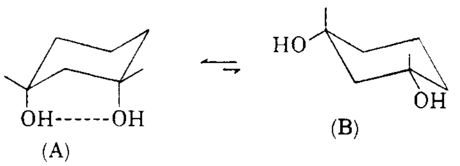
The absorption in the region of −4 p.p.m. in the spectra of both I and II are assigned to the ring protons on C-1 and C-3. This assignment is reasonable in view of the anticipated deshielding of protons attached to carbon atoms linked to oxygen. However, it is interesting to note that the chemical shift difference (0.58 p.p.m.) between isomers I and II in this region of the spectrum considerably exceeds the chemical shift difference of the hydroxyl protons (0.23 p.p.m.). This illustrates, as noted above, the much greater NMR sensitivity of ring protons as compared with hydroxyl protons to changes in molecular geometry.

The structural assignment of the hydroxyl groups in the spectra of both I and II can be quite clearly ascertained from the pattern of the ring proton absorptions in the vicinity of −1.75 p.p.m. The *trans* isomer of the cyclohexane-1,3-diol can exist as two chair structures in which the respective hydroxyl groups may assume either the axial or equatorial orientations, as depicted in the equilibrium:



The low barrier between these energetically identical conformers[18] can be expected to permit a thermal inversion frequency which, even at room temperatures, considerably exceeds that frequency corresponding to the typically small chemical shift difference between axial and equatorial ring protons (about 50 rads./sec. for 14 kilogauss magnetic fields). A consequence of this time-averaging of the environment of the axial and equatorial hydrogens on the corresponding carbon atoms throughout the ring is a marked simplification of the nuclear resonance spectrum (compared to the spectrum of a typically rigid cyclic molecule).[19]

In the *cis* relationship, however, the C-1 and C-3 hydroxyl groups may both be axial or both equatorial, and the corresponding chair structures are by no means equal in energy:



Here, the barrier to interconversion cannot be as

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(16) G. Slomp, *J. Am. Chem. Soc.*, **82**, 999 (1960).

(17) G. V. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

(18) The energetic invariance of the inversion conformers is easily seen with the aid of "ball-and-stick" type molecular models.

(19) The chemical shift of the C-2 protons, however, may be further removed from those of the C-4, C-5, and C-6 protons because C-2 is bonded to carbon atoms both of which are linked to hydroxyl groups. This change in chemical shift of the C-2 protons compared with the C-4, C-5, and C-6 protons follows from considerations of long-range shielding. At all times either one of the two C-2 protons will maintain the same spatial relationship to an adjacent C—O bond. For example, at any instant an axial C-2 proton will make a specific angle and be a specific distance away from the electrical center of gravity of the C_1—O bond. At the next instant when the other C-2 proton assumes an axial position, it will make the same angle and be the same distance away from the electrical center of gravity of the C_3—O bond. Such a geometric relationship cannot be obtained for the C-4, C-5, and C-6 protons. The long-range shielding effect of the C—O bonds on the time-averaged shift of the C-2 protons will therefore be different from the shielding effect of the same bonds on the time-averaged shift of the protons on C-4, C-5, and C-6.[20,21] Furthermore, the chemical-shifted band systems of the C-1 and C-3 protons on the one hand, and the C-2 protons on the other hand, may both be expected to show some fine structure due to the vicinal spin-spin coupling constants. However, lines may coalesce, broaden, or sharpen depending on the specific values of the frequency separations, line widths, conformational energy barrier, and temperature involved, so that the multiplicity of these bands cannot readily be predicted.

(20) A. A. Bothner-By and C. Naar-Colin, *Ann. N. Y. Acad. Sci.*, **70**, 833 (1958).

(21) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, 1959, pp. 176 ff.

low as in the *trans* isomer, where the conformers have higher symmetry. Furthermore, internal hydrogen bonding may contribute to a greater population of the diaxial conformation as judged from infrared measurements ($\Delta\nu = 75$ cm.$^{-1}$).[7,8] The chemical shifts of the axial and equatorial protons on each of the ring carbons will not be degenerate under these circumstances and a complex pattern is to be expected from the several chemical shifts and spin coupling constants of the geminal and vicinal protons of the seven sets of non-equivalent ring protons. An unknown population of the diequatorial species may further diffuse the spectrum.

Therefore, one can utilize this distinctive difference in NMR spectral complexity as a criterion for establishing without further analysis the respective isomeric structures. On this basis, I, which gives a relatively simple spectrum, can correlate with the structure of the *trans* isomer, while II is assigned to the *cis* isomer. Thus, in the spectrum of I, the C-4, C-5, and C-6 protons absorb at -1.66 p.p.m., the C-2 protons give a slightly broadened triplet centered at -1.97 p.p.m., and the C-1 and C-3 protons absorb at -4.36 p.p.m. In the spectrum of II the axial and equatorial protons show a complex pattern extending from -2.61 to -1.23 p.p.m., which is not analyzable by inspection.

The observation in the *trans* isomer of what appears to be a simple triplet pattern at -1.97 p.p.m., corresponding to a splitting of the C-2 protons by the C-1 and C-3 ring protons, may occasion some surprise at first glance. Since this band can be considered as the A_2 part of an approximate A_2X_2 model,[21] we might have expected the fine structure to reflect more complexity due to the existence of unequal vicinal coupling constants. Such inequality has been observed in the analyzed spectra of many ring compounds.[2] However, Abraham and Bernstein,[22] and Grant and Gutowsky[23] have recently calculated the condition for which the fine structure pattern may appear the same for unequal and equal vicinal coupling constants in experimentally obtained A_2X_2 and A_2B_2 spectra. According to Abraham and Bernstein, this condition obtains when the line-width of a component of the observed triplet is greater than the ratio obtained by dividing the square of the difference between the two vicinal coupling constants by twice the difference of the remaining two coupling constants. We can ascertain the applicability of Abraham and Bernstein's thesis in our case even though it is not possible to determine directly all the relevant coupling constants from the limited spectral data. We take the value $\pm J_{AA} = 12$ c.p.s. as the coupling constant between the C-2 protons given by the theoretical treatment of geminal coupling constants,[24] using a value of 109° for the HCH angle.[25] We arbitrarily select $\pm J_{A'X} = 8$ c.p.s. as the value for the *trans* coupling constant, which is in the short range observed for such coupling constants in other ring compounds.[2] For the *cis* coupling constant, we take 3 c.p.s. as a reasonable value,[2] and the separation of the triplet lines, 5.6. c.p.s., as the limiting value. We take $J_{XX'} = 0$ as the value of the coupling constant between the C-1 and C-3 ring protons (reasonable in view of the four-bond separation between these protons). The actual line-width of the central component of the triplet measured directly from the spectrum is 2.2 c.p.s., and we find that the above ratio is equal to or less than approximately 1 c.p.s. Thus, the condition cited by Abraham and Bernstein obtains here, and the failure to observe a more complex pattern at -1.97 p.p.m. need not be interpreted in this case as a necessary indication of equal vicinal coupling.

The X_2 part of the spectrum at -4.36 p.p.m. is slightly more complex because of coupling with the C-4 and C-6 protons. Unsatisfactory resolution due to exchange broadening makes it impossible to analyze in detail this band.

The above demonstration that the vicinal coupling constants may not be equal, enables us to discount the 5.6 c.p.s. separation between the triplet lines as the value of the *cis* or the *trans* coupling constants. Furthermore, it is clear from the data observed by Lemieux *et al.*[2] for the analogous couplings in pyranose rings, that 5.6 c.p.s. is too large a value for the *cis* coupling constant and too small a value for the *trans*. Abraham and Bernstein have shown[22] that the separation of the triplet components is, in fact, equal to one half the sum of both these constants. Thus, while the spectral data do not permit an evaluation of either one of these couplings, we can conclusively estimate the value of their sum, $|J_{AX} + J_{A'X}| = |J_{AX'} + J_{AX}| = 11.2$ c.p.s. It will be shown below that this sum is useful for structural assessments.

The basis for assigning the respective structures of the 5,5-dimethylcyclohexane-1,3-diols (III and IV) from their NMR spectra (Fig. 2) is similar in principle to that applied to the simpler diols. In fact, the plausibility of the above assignments in the cases of the unsubstituted diols may now be verified since differences of the corresponding spectra that occur by substitution of angular methyl groups for geminal ring protons should be readily accounted for.

As in the case of the unsubstituted diols, we see that the inverted chair forms of the *trans* configuration are energetically identical. While the barrier to interconversion will probably be higher in this case due to the bulk and steric effects of the methyl groups, time-averaging of the magnetic environ-

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[22] R. J. Abraham and H. J. Bernstein, *Can. J. Chem.*, **39**, 216 (1961).

[23] D. M. Grant and H. S. Gutowsky, *J. Chem. Phys.*, **34**, 699 (1961).

[24] H. S. Gutowsky, Martin Karplus, and D. M. Grant, *J. Chem. Phys.*, **31**, 1278 (1959).

[25] "Tables of Interatomic Distances," Chem. Soc. Special Publication, No. 11, Chemical Society, London, 1958.

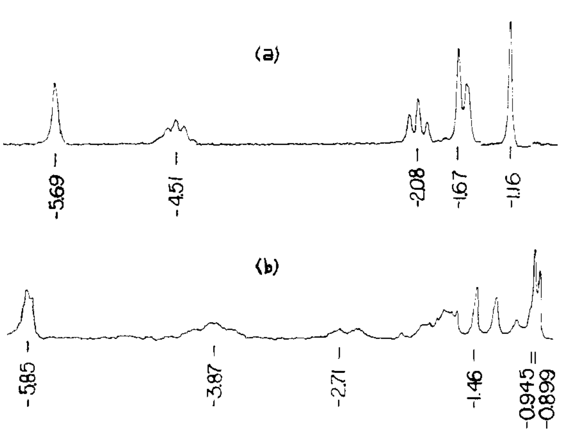

Fig. 2.—NMR spectra of isomeric 5,5-dimethyl-1,3-cyclohexanediols at 60 Mc./sec., taken at 30°. In spectrum (a) which corresponds to isomer III, the signal at −1.16 p.p.m. was recorded at reduced amplification. In spectrum (b) which corresponds to isomer IV, the signals at −0.899 and −0.945 p.p.m. have been recorded at reduced amplification. Spectrometer system resolution same as in Fig. 1.

ments may again be expected to simplify the spectrum and abet the structural assignment. We find that the spectrum of III, indeed, is very similar to I, which has already been assigned to the *trans* isomer of cyclohexane-1,3-diol. The chief distinction is the very strong and sharp signal at −1.16 p.p.m., which can immediately be ascribed to the degenerate chemical shift of the six methyl protons.

Because of axial-equatorial orientation effects in a more rigid conformation, two distinct signals of equal intensity would be expected from the geminal dimethyl groups, each signal corresponding to three rapidly rotating methyl protons. The presence of only one sharp signal in the room temperature spectrum of III is sufficient indication that rapid inversion is here taking place. It is interesting to note, however, that the absorption of the C-4 and C-6 ring protons centered at −1.63 p.p.m. shows greater multiplicity than the corresponding absorption at −1.66 p.p.m. in the spectrum of I. We might have expected the reverse to be the case in view of the elimination of the spin coupling effects of the ring protons at the C-5 position in the spectrum of III. However, as noted earlier, the multiplicity of bands in the spectra of equilibrating conformers cannot be readily predicted.[19] It can be deduced from these spectral observations, nevertheless, that the inversion rate of III is less than that of I at room temperature, which is reasonable in view of the geminal substitution by bulky methyl groups at the C-5 position of III. This is further supported by spectral observation of a solution of III from room temperature to +195°. At this temperature considerable reduction of the multiplicity at −1.63 p.p.m. was noted, so that this band became very similar in shape to the −1.66 p.p.m. band in the room temperature spectrum of I. The relative sharpness of the methyl peak was still maintained at these higher temperatures, indicating that the change in band shape at −1.63 p.p.m. was not an artifact.

We note the triplet pattern of the C-2 protons at −2.08 p.p.m. in the spectrum of III, corresponding to the similar pattern at −1.97 p.p.m. in I. The 5.4 c.p.s. separation of the multiplet components, corresponding to one half the sum of the vicinal coupling constants, is close to the value of 5.6 c.p.s. observed in I. The −4.51 p.p.m. band due to the C-1 and C-3 ring protons shows better resolution of the fine structure components than the corresponding band at −4.36 p.p.m. in I. This may again be the result of slower ring inversion of III as compared with I.

The spectrum of IV shows considerable complexity and from this point of view is comparable to the spectrum of the *cis*-cyclohexane-1,3-diol (II). In addition, two intense signals, which no doubt arise from the methyl protons, are found at −0.945 and −0.899 p.p.m. This contrasts with isomer III, where only a single very intense signal attributable to the methyl protons was noted. We interpret this to mean that the signals from the axial and equatorial methyl protons are not being rapidly averaged in IV and that the conformational residence time at room temperature (as calculated from the chemical shift difference of the methyl signals) must be greater than approximately one-tenth second.[26] Therefore, from considerations of spectral complexity and the existence of two methyl signals, we assign the *cis* configuration to the isomer (IV).

Musher has recently analyzed in some detail the spectra of the stereoisomers of 2,2,5,5-tetramethylcyclohexyl-1,3-diacetate[27] (substituent positions renumbered as in our diagrams). These molecules are closely related to those discussed in this work and afford an opportunity for intercomparison of results. The chief differences in structure to be considered when compared to compounds (I–IV) are the substitution of *gem*-dimethyl at the C-2 (as well as the C-5) position, and acetylation of the hydroxyl groups. The additional *gem*-dimethyl group increases the molecular symmetry and also removes from the NMR spectrum the coupling effects of two ring protons. This contributes substantially to the possibility of detailed interpretation of the *cis* spectrum as well as the *trans*. The former shows substantially less "hash" than the spectrum of *cis*-5,5-dimethylcyclohexane-1,3-diol.

It is interesting to note that the sum of the vicinal coupling constants reported for *trans*-tetramethylcyclohexyl diacetate (11.6 c.p.s.) deviates by only

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(26) The calculation assumes that one of the intense methyl signals represents the accidentally degenerate (not time-averaged) chemical shifts of, say, the axial methyl protons, and the other the partially degenerate chemical shifts of the equatorial methyl protons in the two slowly interconverting configurational isomers. While we consider this the most probable interpretation of the spectrum in view of the unequal peak heights of the signals and the very narrow frequency range of methyl groups, it is not the only interpretation possible.

(27) J. I. Musher, *J. Chem. Phys.*, **34**, 594 (1961).

fractions of a c.p.s. from our findings of 11.2 c.p.s. for the unsubstituted and 10.8 c.p.s. for the substituted *trans*-cyclohexane diols. The value of this sum may, therefore, be regarded as a useful numerical index of configuration for this type of compound, since the characteristic value obtainable for the analogous *cis* isomer from the data reported by Musher is about 50% greater (16.6 c.p.s.).

The effects of inversion barriers of the different configurations on the chemical shift of the methyl groups in the diacetates are also very analogous to the effects observed in the diols. Though the details have been omitted from the text, it is clear from the reproduced spectra that the four differing environments of the methyl groups are averaged by inversion in the *trans* isomer only. Rapid inversion in the *trans* isomer can be expected to average the chemical shift to two lines (even in the case of rapid inversion, it can be seen that there are two distinct environments for the four methyl groups in this molecule), which is exactly what the spectrum shows. On the other hand, the spectrum of the *cis* isomer includes three methyl signals, one of which appears from the intensity and line width to result from two overlapping lines. The absence of rapid inversion thereby indicated confirms the validity of the use of this feature in our work to assign the conformation of *cis*-dimethylcyclohexane diol.

TABLE OF STRUCTURAL ASSIGNMENTS

	Isomer designation	Structural assignment confirmed	Melting point	Reference to preparation method
Resorcitols	I	*trans*	116.0–116.5°	28
	II	*cis*	86–87°	28
5,5-Dimethylresorcitols	III	*trans*	108–109°	14
	IV	*cis*	146–147°	14

Experimental

The procedures followed in the preparation and purification of all the diols used were the same as those described in the references given in the accompanying table. Their physical constants, including m.p. and infrared spectral data where available, agreed well with those recorded in the literature in all cases.

Conclusion

On the basis of the arguments presented above, the structural assignments we have listed in the accompanying table seem to accord best with the observed NMR spectra of the individual isomers.

(28) M. F. Clark and L. N. Owen, *J. Chem. Soc.*, 2105 (1950).

Synthesis of Spiroundecatrienones from 2,6-Di-*t*-butylquinone Methide and Butadienes

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Spiro[5.5]undeca-1,4,8,-trien-3-ones (IIIa,b,c) were obtained as Diels-Alder adducts from the reactions of 2,6-di-*t*-butylquinone methide (II) with butadiene, isoprene, and chloroprene. The structure assigned to the butadiene product was unequivocally proved primarily by alternate synthesis of its hydrogenation product, 2,4-di-*t*-butylspiro[5.5]undeca-3-one (IV). The key step in the synthetic scheme was the conversion of 2,6-di-*t*-butyl-4-(5-tosyloxypentyl)phenol (Vb) to 2,4-di-*t*-butylspiro[5.5]undeca-1,4-dien-3-one (VI) in almost quantitative yield by Ar_1-5 participation reaction.

Although several highly substituted homologs of *p*-quinone methide are well authenticated compounds[1] only one, 10-methyleneanthrone[2] has been reported which contains its methide double bond terminally. With fewer substituents on the ring, the terminal quinone methides become much less stable, and attempts to isolate the simpler ones such as the 2,6-dimethyl[3] or 2,6-di-*t*-butyl compounds[4] have led only to dimeric products. Most recently, Filar and Winstein[5] have published spectroscopic evidence for the existence of both 2,6-dimethylquinone methide and 2,6-di-*t*-butylquinone methide in dilute hydrocarbon solution, although once again the quinone methides could not be isolated. 2,6-Di-*t*-butyl-4-methylene-2,5-cyclohexadienone[5] (II) was reported to be formed by treatment of 3,5-di-*t*-butyl-4-hydroxybenzyl bromide with triethylamine or by oxidation of 2,6-di-*t*-butyl-4-methylphenol with lead dioxide.

Complementing the work of Filar and Winstein, we have found that it is possible to trap the reactive intermediate, 2,6-di-*t*-butylquinone methide (II), as a Diels-Alder adduct with butadienes. Thus, spiro[5.5]undeca-1,4,8-trien-3-ones (IIIa,b,c) were

[1] C. D. Cook and B. E. Norcross, *J. Am. Chem. Soc.*, **78**, 3797 (1956); *ibid.*, **81**, 1176 (1959).

[2] E. Clar, *Ber.*, **69**, 1686 (1936).

[3] K. Fries and E. Brandes, *Ann.*, **542**, 48 (1939); H. Von Euler, E. Alder, J. O. Cedwell, and O. Törngren, *Arkiv-Kem. Mineral Geol.*, **15A**, No. 11 (1942).

[4] T. Fujisaki, *J. Chem. Soc. Japan*, **77**, 730 (1956).

[5] L. J. Filar and S. Winstein, *Tetrahedron Letters*, **25**, 9 (1960).