nium salt was run, or when the reaction was quenched with hydrochloric acid immediately after starting.

Mass Spectrometry. An Atlas CH-4 instrument was used. Inlet temperatures ranged from ambient to 140°, and about 500–600 units of sample pressure were used. The same precautions as before[3,4] were taken to keep initial scale deflection and attenuator settings the same for all samples compared. The entire mass spectrum (up to *m/e* 100) was scanned for each sample as a precaution against impurities. Minor peaks (0.3–1.0% of the *m/e* 62 peak) were noted at 74 and 76 in some samples, but the *m/e* 78 peak (dimethyl sulfoxide) was always less than 0.1%. Masses 62 and 64 were then scanned successively 20 times.[18] At least 10, and almost always 15–20 scans were used in each calculation. The *m/e* 62/64 ratios use each peak twice: a given peak is compared both with the peak preceding and the peak following. This procedure minimizes the effect of the slow decrease in peak height resulting from sample depletion. Standard deviation of the mean for the ratios usually ran around 0.05–0.1%, and never above 0.15%.

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[18] Though the instrument is capable of simultaneous collection, the dual collector available for this work would have collected *m/e* 62 and 63 together, and *m/e* 63 contains both S^{32} and S^{34} species.

7,12-Dihydropleiadenes. VII. Application of Nuclear Overhauser Effects to Stereochemical Problems

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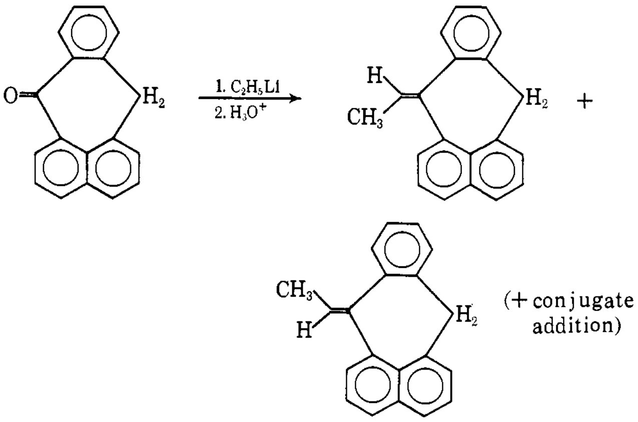
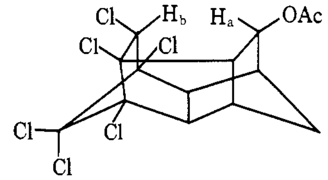
Abstract: Nuclear Overhauser Effects (NOE) between axial C_7 and C_{12} protons and between equatorial C_7 protons and adjacent aromatic methyl groups in 7,12-dihydropleiadenes have been observed, in accord with the proximity of such groups to each other. Several structural assignments which were otherwise tenuous could be conclusively made by using NOE's.

In some previous studies of 7,12-dihydropleiadene (DHP) chemistry,[3–5] we have determined the preferred conformations of various groups on the C_7 and C_{12} positions of the DHP molecule.[4,5] In addition, it was clearly established that axial protons on these positions always appeared at lower field in the nuclear magnetic resonance (nmr) spectrum in chloroform than their equatorial counterparts from nmr chemical shift studies of model compounds,[4,5] spin decoupling of axial benzylic protons from aromatic protons,[4] and relative kinetic acidities in conformationally fixed compounds.[3] These findings were insufficient, however, to allow unambiguous stereochemical assignments to be made for certain isomeric dihydropleiadenes. For example, the geometric isomers resulting from carbonyl addition of ethyllithium to 7-(12H)-pleiadenone and subsequent dehydration could not be readily distinguished by existing chemical and physical techniques.[6] We hoped that this problem, as well as several others (*vide infra*), could be efficiently solved by investigating intramolecular nuclear Overhauser effects (NOE). Anet[7a] and others[7b] have shown that this technique has great promise for identifying adjacent protons in molecules, such as in the example below.





These Overhauser effects are best observed in conformationally rigid molecules[7a] in which magnetic nuclei are proximal and show no scalar spin–spin coupling, but are coupled by a direct dipole–dipole interaction. As a result of this coupling, the populations of the nuclear energy levels are not independent of each other. In the case of two protons A and B coupled only by the above-mentioned dipole–dipole interaction, in a conformation such that $1/T_1^{A} = 1/T_1^{AB}$, any changes in the populations of the nuclear energy levels of proton

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[1] Hooker Chemical Corp.

[2] (a) Alfred P. Sloan Foundation Fellow, 1963–1967. (b) Du Pont Predoctoral Teaching Fellow, 1966–1967.

[3] P. T. Lansbury, J. F. Bieron, and M. Klein, *J. Am. Chem. Soc.*, **88**, 1477 (1966).

[4] P. T. Lansbury, J. F. Bieron, and A. J. Lacher, *ibid.*, **88**, 1482 (1966).

[5] P. T. Lansbury, A. J. Lacher, and F. D. Saeva, *ibid.*, **89**, 4361 (1967).

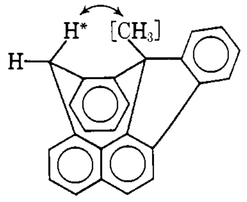
[6] E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, Chapter 12.

[7] (a) F. A. L. Anet and A. J. R. Bourn, *J. Am. Chem. Soc.*, **87**, 5250 (1965); (b) M. C. Woods, I. Miura, Y. Nakadaira, A. Terahara, M. Maruyama, and K. Nakanishi, *Tetrahedron Letters*, 321 (1967).

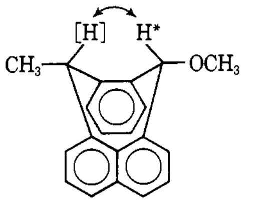
A will cause a redistribution in the populations of the corresponding levels of proton B.[7a,8] It can be seen that on applying an intense radiofrequency field (H_2) at the transition energy of proton A (saturation) an increment will be observed in the absorption of proton B. Since the geometry of the molecule has not been altered with or without H_2, the spin–spin relaxation (T_2) remains the same (no change in line width at half-height). Relaxation now takes place primarily by a double quantum transition.

Results and Discussion

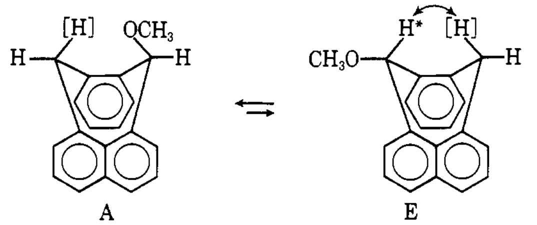
From examination of models, it appeared that axial protons in DHP's would show NOE's when an axial methyl or hydrogen across the ring was irradiated. Three distinctively different examples of known stereochemistry were first studied. In 12-methyl-1,12-(*o*-phenylene)-7,12-dihydropleiadene (I), conformational inversion is impossible[4] and the axial C_7-proton signal intensity (downfield doublet of AB spectrum) should be strongly enhanced when the methyl signal is irradiated.[9] This was indeed observed, there being a 27% increase in signal intensity, relative to the equatorial C_7-proton signal. *cis*-7-Methoxy-12-methyl-7,12-dihydropleiadene (II), on the other hand, can undergo ring inversion but exists only in the diequatorial conformation,[5] as shown below, a fact consistent with the observation of NOE's between the transannular axial methine protons. Finally, the third example chosen was 7-methoxy7,12-dihydropleiadene (III) which exists as a 2:1 mixture of axial and equatorial conformers at −20°.[4] In the low-temperature spectrum of III, irradiation of the axial C_{12} proton of the conformer with C_7-methoxy equatorial produced a NOE at the axial C_7 proton (27% intensity increase), whereas smilar irradiation of the axial C_{12} proton in the other conformer produced no effect, since the C_7 proton was now equatorial.



I

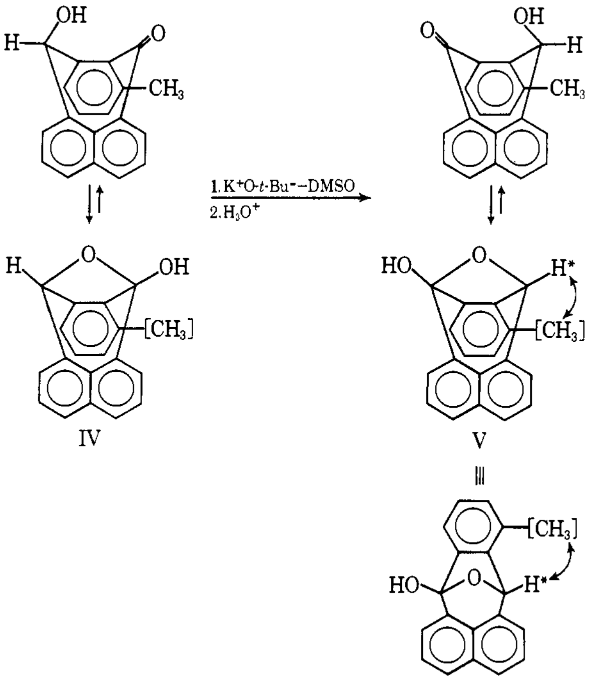


II



III

The foregoing results with I–III establish transannular NOE's between C_7- and C_{12}-axial groupings. Models show also that NOE's between equatorial C_7 protons and adjacent aryl methyl groups can be anticipated. A useful example for exploring this situation was verification of reactant and product structures in the base-induced rearrangement[10] of 7-hydroxy-11-methyl-12-(7H)-pleiadenone (IV) to 12-hydroxy-11-methyl-7-(12H)-pleiadenone (V). Ketol IV was obtained by selective borohydride reduction of 8-methyl-7,12-pleiadione (VI), by analogy with the 1-methyl- and 1-chloro-7,12-pleiadiones,[10] and rearranged to isomeric V. Since IV and V were both available only in small amounts and were themselves each ketol–hemiketal mixtures in solution,[10] unambiguous characterization of IV and V as formulated, rather than *vice versa*, seemed quite a formidable task. However, the C_{12}-methine proton (starred) in V-hemiketal (as well as in the one conformer of V-ketol shown) is close enough to the C_{11}-methyl group to undergo an increase in signal intensity when the latter is irradiated, whereas no change in the C_7-methine intensity of IV-hemiketal[11] would occur if the methyl signal were saturated. Dimethyl-d_6 sulfoxide solutions of tautomeric mixtures of IV and V were observed by the frequency sweep method, and the methyl signals in each were irradiated; a NOE (17% intensity enhancement) was observed with V only, thus verifying the structural assignments.



In the case of the two geometric isomers of 7-ethylidene-7,12-dihydropleiadene, we were able to obtain only one stereoisomer (VI) in pure form,[12] after varied attempts at acid-catalyzed and photochemical isomerization of olefin mixtures. The relevant chemical shift data for VI, the minor isomer VII, together with the related 7-methylene-7,12-dihydropleiadene (VIII) and 7-isopropylidene-7,12-dihydropleiadene (IX), are listed below (in hertz at 60 MHz) with the structures. The methyl and methine signals at lower field have been arbitrarily assigned as *syn* to the naphthalene ring, so

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(8) For discussions of nuclear Overhauser effects, see ref 7a and (a) J. D. Baldeschweiler and E. W. Randall, *Chem. Rev.*, **63**, 81 (1963). (b) M. Bersohn and J. C. Baird, "An Introduction to Electron Paramagnetic Resonance," W. A. Benjamin, Inc., New York, N. Y., 1966, Chapter 10.

(9) In this paper, we will indicate nuclear Overhauser effects in structural formulas by enclosing the group undergoing saturation in brackets [ ] and the group showing signal enhancement by an asterisk, with a double-headed arrow connecting the two. When only a bracket appears, the NOE was *not* observed.

(10) P. T. Lansbury and F. D. Saeva, *J. Am. Chem. Soc.*, **89**, 1890 (1967).

(11) Both IV and V exist predominantly in the cyclic hemiketal form, rather than the tautomeric ketol, K = [hemiketal]/[ketol] $\simeq$ 3 at *ca.* 35° for both.

(12) M. Klein, unpublished observations in these laboratories.

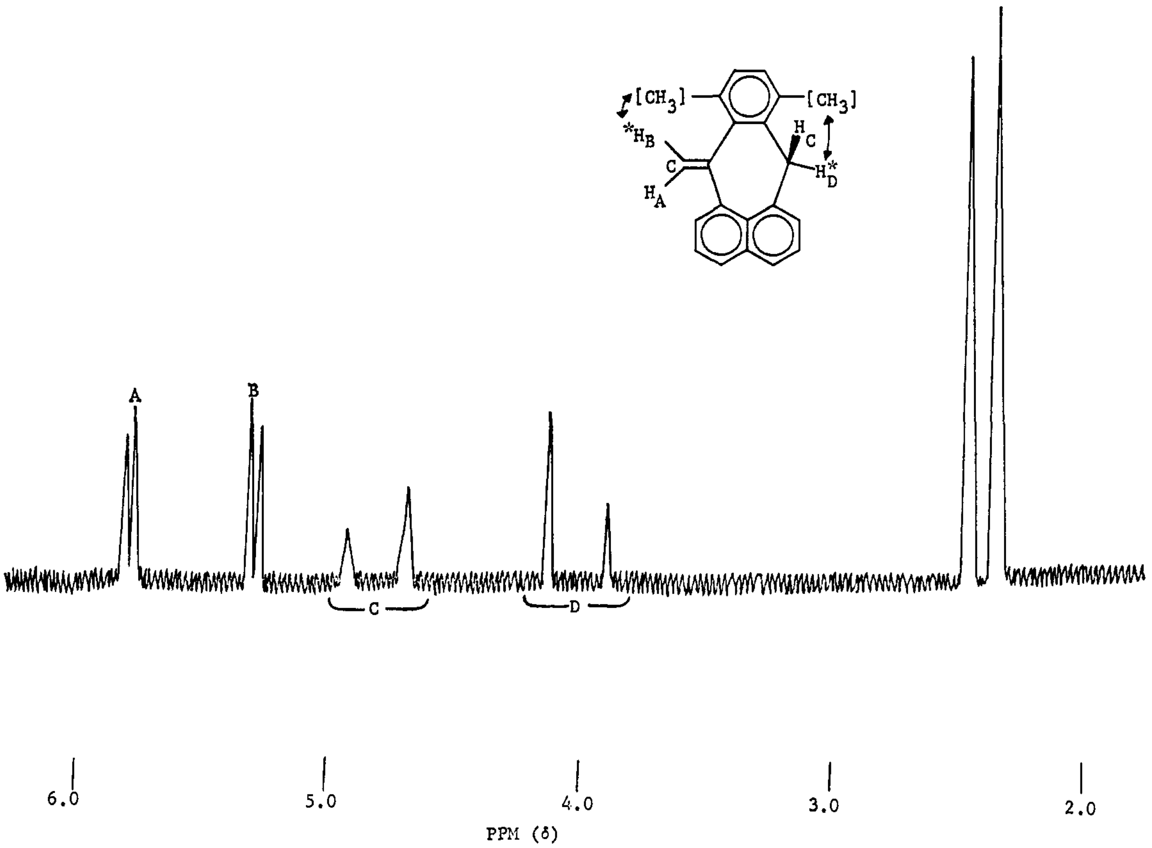
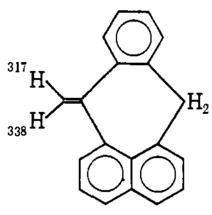
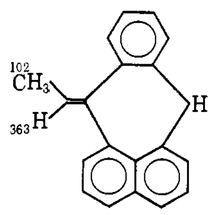


Figure 1. Partial 60-MHz nmr spectrum of 7-methylene-8,11-dimethyl-7,12-dihydropleiadene (X).

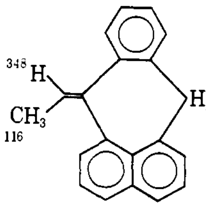
that the high field signals would now be *syn*-phenyl, but it should be noted that all *these assignments, while internally consistent, could be exactly the reverse.* This ambiguity was removed when double resonance experiments were carried out with 7-methylene-8,11-dimethyl-7,12-dihydropleiadene (X), which we prepared by methyllithium addition to 8,11-dimethyl-7-(12*H*)-pleiadenone and subsequent dehydration. The 60-MHz nmr spectrum of X (Figure 1) shows two methyl signals at 140 and 146 Hz, an AB quartet ($J_{AB} \cong 14$ Hz) centered at 263 Hz ($\Delta\nu_{AB} = 45$ Hz) originating from the C_{12}-methylene group, and two doublets ($J \cong 2$ Hz) attributable to the vinylidene protons at 317 and 347 Hz. The latter chemical shifts correspond closely with those of the vinyl protons in VIII. Furthermore, models suggest that the vinyl proton *syn* to the adjacent methyl group at C_8 is sufficiently close, so that irradiation of the latter should produce a NOE on the former. We were gratified to find that irradiation of the low-field methyl signal in X produced a signal intensity increase (20%) in the *upfield* vinyl proton (317 Hz), which must, therefore, lie closer to C_8-methyl than the low-field proton. In addition, irradiation of the high-field C_{11}-methyl group produced a NOE at the adjacent equatorial C_{12} proton, as was the case in V. This result confirms all of the previously arbitrary nmr methyl and methine chemical shift assignments in the series VI–IX and the stereochemistry of the ethylidene derivatives VI and VII is now clarified.[13]



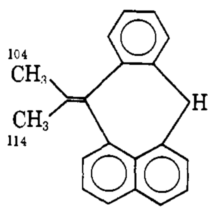
VIII



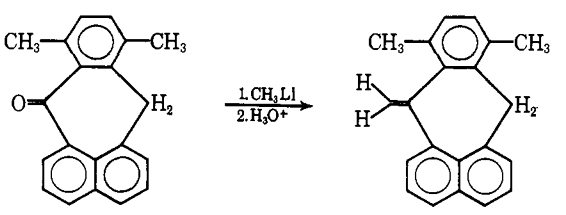
VI



VII



IX



X

In Table I, we have summarized the above NOE studies, showing which protons were irradiated, those which underwent signal enhancement, and the magnitude of the effect.

Our results show that intramolecular nuclear Overhauser effects are useful not only to distinguish between

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(13) The free-energy barriers to conformational inversion of VI–X are presently being determined and will be reported in a future publication.

Table I. Nuclear Overhauser Effects in 7,12-Dihydropleiadenes

Compd	Group irradiated (δ, ppm)	H obsd (δ)	A_0[a]	A[b]	Intensity[c] increase	Ref peak (δ)
I	C_{12}-CH_3 (2.06)	Ax. C_7 (5.65)	19	24	26%	Eq C_7H (4.04)
II	C_{12}-H (4.96)	C_7-H (6.36)	27	32	19	C_7-OCH_3 (3.62)
III[d] conformer E: axial	C_{12}-H (4.95)	Ax. C_7-H (6.22)	37	47	27	Eq C_7-H (5.21)
conformer A: axial	C_{12}-H (5.58)	Eq C_7-H (5.21)	45	45	0	Ax. C_7-H (6.22)
V	C_{11}-CH_3 (2.30)	C_{12}-H (6.34) (in hemiketal)	40	47	17	C_{12}-H in (6.18 ketol
X	C_8-CH_3 (2.43)	C_7-vinylidene H (5.27)	25	30	20	C_7-vinylidene H (5.77)
	C_{11}-CH_3 (2.32)	Eq C_{12}-H (4.02)	19	22	16	Ax. C_{12}-H (4.80)

[a] Integrated area before irradiation ($H_2 = 0$). [b] Integrated area after irradiation ($H_2 = 40$ mv). [c] $100 \times (A - A_0)/A_0$; estimated accuracy is ±3%. [d] At −45°.

stereoisomers, but between individual detectable conformers of a single compound as well.

Experimental Section[14]

Materials. The following compounds used in this study were reported previously: 12-methyl-1,12-(*o*-phenylene)-7,12-dihydropleiadene (I),[15] *cis*-7-methoxy-12-methyl-7,12-dihydropleiadene (II),[5] 7-methoxy-7,12-dihydropleiadene (III),[4] 7-methylene-7,12-dihydropleiadene (VIII),[3] and 7-isopropylidene-7,12-dihydropleiadene (IX).[3]

8-Methyl-12-hydroxy-7-(12H)-pleiadenone (IV). 11-Methyl-7-(12H)-pleiadenone[3] (0.31 mmole) and 0.46 mmole of chromium trioxide were refluxed for 20 hr in 90% aqueous acetic acid (100 cc) and poured onto 200 g of ice. After melting, the crude product was collected by suction filtration and recrystallized from ethanol to give 0.513 g (61% yield) of 8-methyl-7,12-pleiadione, mp 208–209°. The infrared spectrum of 8-methyl-7,12-pleiadione showed bands at 1660, 1305, 1032, 1000, 830, and 770 cm^{-1}.

Anal. Calcd for $C_{19}H_{12}O_2$: C, 83.79; H, 4.45. Found: C, 83.32; H, 4.47.

8-Methyl-7,12-pleiadione (0.144 g, 0.6 mmole) was dissolved in 50 cc of a 2:1 methanol–tetrahydrofuran solvent mixture along with 25 mmoles of sodium hydroxide. After stirring for 15 min, 6 mmoles of sodium borohydride was added. After stirring for 30 min at room temperature, the reaction mixture was diluted with water and extracted with ether. The combined organic layer was washed with saturated salt solution, dried over anhydrous magnesium sulfate, and flash evaporated. The white crystalline product was recrystallized from benzene, giving 87 mg (0.31 mmole; 51% yield) of IV, mp 255–257°. The infrared spectrum of the ketol showed bands at 3470, 1645, 1009, 839, and 778 cm^{-1}.

Anal. Calcd for $C_{19}H_{14}O_2$: C, 83.18; H, 5.15. Found: C, 83.08; H, 5.08.

11-Methyl-12-hydroxy-7-(12H)-pleiadenone (V). 8-Methyl-12-hydroxy-7-(12H)-pleiadenone (76 mg, 0.28 mmole), obtained from the previous selective reduction of 8-methyl-7,12-pleiadenone with sodium borohydride, was dissolved in 10 cc of anhydrous dimethyl sulfoxide and treated with potassium *t*-butoxide (0.28 mmole) at 60° for 30 min. The reaction mixture was poured onto 50 g of ice and extracted with ether, and the ether layer was washed with water and dried over magnesium sulfate. Filtration and flash evaporation of the ether solution provided, after recrystallization from benzene, 70 mg (92% yield) of 11-methyl-12-hydroxy-7-(12H)-pleiadenone, mp 197–199°. In the infrared spectrum of the product, obtained as the hemiketal, pertinent absorption bands appeared at 3350, 1037, 975, 826, and 775 cm^{-1}.

Anal. Calcd for $C_{19}H_{14}O_2$: C, 83.18; H, 5.15. Found: C, 83.10; H, 5.21.

7-Methylene-8,11-dimethyl-7,12-dihydropleiadene (X). One mmole of methyllithium was added to 8,11-dimethyl-7-(12H)-pleiadenone[3] (1.0 mmole), under a nitrogen atmosphere, in 20 cc of anhydrous diethyl ether. The reaction mixture was stirred for 10 min before being hydrolyzed with a saturated ammonium chloride solution. The usual work-up procedure of extraction, drying, and flash evaporation provided 0.270 g of a colorless oil which showed the presence of O–H stretching in its infrared spectrum at 3300 cm^{-1} and no absorption in the carbonyl region. Without further purification, the crude alcohol was refluxed in formic acid (10 cc) for 5 min and poured onto 50 g of ice. The crude methylene compound was isolated by the usual extraction procedure and work-up, then purified by column chromatography on 25 g of alumina. The desired product was eluted with petroleum ether (30–60°) and then recrystallized from methanol, giving 0.25 mmole (25% yield) of 7-methylene-8,11-dimethyl-7,12-dihydropleiadene, mp 117–118°.

Anal. Calcd for $C_{20}H_{18}$: C, 92.97; H, 7.03. Found: C, 92.84; H, 6.86.

Procedure for Studying Nuclear Overhauser Effects. All spectra were recorded using an HA-100 spectrometer in the frequency sweep mode. The sweep width used was dependent on the difference in chemical shift between the group irradiated and the group observed. All spectra were recorded using nitrogen-sparged solutions (chloroform-*d* was solvent in all cases except IV and V, where dimethyl-d_6 sulfoxide was employed) and tetramethylsilane as an internal field frequency lock. The irradiating audio oscillator was a Hewlett-Packard 200 ABR with an impedance matching transformer. Power requirements were ascertained by slowly increasing the output in 10-mv increments (approximately 1 mgauss) until a signal increase was noted. Each peak of interest was integrated at least five times with no power and optimum power. Corrections were made for Bloch–Siegert shifts experimentally.

Acknowledgment. Partial support of this research by the National Science Foundation is gratefully acknowledged.

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(14) Melting points are obtained on a Mel-Temp capillary tube apparatus and are uncorrected. Infrared spectra were measured on a Beckman IR-5A spectrometer, using Nujol mulls for solids. A Varian A-60 nmr spectrometer was used for structure elucidation, whereas NOE studies were done on a HA-100 instrument. Elemental analyses were by Dr. A. Bernhardt, Mulheim, Germany.

(15) J. B. Bieber, Ph.D. Dissertation, State University of New York at Buffalo, Buffalo, N. Y., 1966.