The Proton Magnetic Resonance Spectra of some Chlorinated Polycyclodiene Pesticide Metabolites. Rapid Assessment of Stereochemistry[1]

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The rapid and accurate determination of the relative stereochemistry of some postulated chlorinated polycyclodiene pesticide metabolites without excessive dependence on chemical methods is described. Proton assignments were made employing the new nuclear magnetic resonance (n.m.r.) shift reagent, $Eu(DPM)_3$, which effected the separation of superimposed signals in these systems. The assignments based on coupling constant information and requiring spin decoupling equipment are in good agreement with those obtained from the $Eu(DPM)_3$ studies. The data presented establishes the relative stereochemistry of these biologically important compounds and demonstrates the utility of one or both approaches in elucidating their overall structures.

On décrit une méthode rapide et précise de déterminer sans dépendre d'une façon excessive sur des méthodes chimiques la stéréochimie relative de quelques métabolites postulés de pesticides de polycyclodiènes chlorés. On a assigné les différents protons en utilisant, en r.m.n., le réactif $Eu(DPM)_3$ qui permet de séparer les signaux qui seraient par ailleurs superposés dans ce système. Les attributions faites en se basant sur des constantes de couplage ou nécessitant l'utilisation d'équipement pour le découplage des spins sont en bon accord avec celles découlant des études faites avec $Eu(DPM)_3$. Les données présentées permettent d'établir la stéréochimie relative de ces composés biologiquement importants et démontrent l'utilité de chacune des méthodes dans l'élucidation des structures.

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The chlorinated polycyclodiene pesticides have received considerable attention in the past few years since they are among the most stable and persistent insecticides that can contaminate our environment. Although these compounds have been studied extensively both chemically (1) as well as in living organisms (2–7), their mechanism(s) and mode(s) of action on a molecular level still remain, to a large extent, enigmatic. Metabolic studies of these pesticides have been complicated by difficulties in the unequivocal identification of the biotransformation products which in most cases also require proof of stereochemical structures since stereospecific as well as stereoselective transformations are possible. Detailed elucidation and elimination of metabolic possibilities are necessary in illuminating the possible differences in toxicity due to stereochemical factors (3). This paper describes the use of n.m.r. spectroscopy to more rapidly and accurately determine the stereochemical structures of some postulated chlorinated polycyclodiene pesticide metabolites by establishing patterns of identification in their spectra. The use of n.m.r. data in assigning the stereochemistry of analogous compounds without excessive dependence on chemical methods has been previously reported (8, 9).

A representative series of compounds were obtained for the most part by stereoselective syntheses as outlined in Scheme 1: *trans*-4,5-dihydroxy-4,5-dihydroaldrin (**1**), *cis-exo*-4,5-dihydroxy-4,5-dihydroaldrin (**2**), *exo*-4-hydroxy-4,5-dihydroaldrin (**3**), 4-oxo-4,5-dihydroaldrin (**4**), *endo*-4-hydroxy-4,5-dihydroaldrin (**5**), and *cis-exo*-4,5-dihydroxy-4,5-dihydroisodrin (**6**). All of these compounds, with the exception of **6**, have been implicated as metabolites or degradation products in diverse metabolism studies. However, in some cases the authenticity of standards used for obtaining comparison data with metabolites is not corroborated by a description of the synthetic methodology. Delta-keto endrin (**7**) was commercially available[4] and was examined primarily for any similarities its proton magnetic resonance (p.m.r.) spectra had with those of 4-oxo-4,5-dihydroaldrin (**4**).

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[4]The δ-keto endrin (7) used in this study was obtained from Shell Development Co., a Division of Shell Oil Co., Modesto, Calif.; however, it can also be obtained from thermal degradation of endrin (10).

The preparation of *cis*-diols (**2** and **6**) was accomplished via hydrolysis of their osmic acid esters (11) and gave somewhat higher yields than the previously reported method employing potassium permanganate as an oxidant. The *cis*-diols had identical properties to those obtained by the permanganate procedure [*cis*-dihydroaldrin diol (13); *cis*-dihydroisodrin diol (12)]. Both diols **2** and **6** formed their corresponding acetonides when treated with acetone in the presence of ferric chloride according to the literature method (12), and the facile formation of these acetonides confirms the *cis*-relationship of the two hydroxyl groups. The *trans*-diol (**1**) was prepared according to the literature synthesis (13); however, the yield was significantly increased by the addition of 1,4-dioxane to enhance homogeneity.

The *exo*-alcohol (**3**) was synthesized by hydroboration–oxidation of aldrin. Hydroboration–oxidation of the *endo-exo* octahydrodimethanonaphthalene system is known (14) to give the *exo*-alcohol. Oxidation of alcohol **3** with sodium dichromate in sulfuric acid gave 4-oxo-4,5-dihydroaldrin (**4**), a Lewis acid rearrangement product (15) of the parent pesticide dieldrin. The stereoselective reduction of ketone **4** with disiamylborane (16) afforded the *endo*-alcohol (**5**) which could be reconverted to ketone **4** by oxidation with chromic acid. Alcohols **3** and **5** have been previously characterized (17) as solid materials melting at 125 and 131°, respectively; however, in our hands these compounds, even though chromatographically pure, had no precise melting points. This anomaly has been previously observed (1) for other adducts of hexachlorocyclopentadiene.

The 100 MHz p.m.r. spectra of compounds **1**–**7** were analyzed with the aid of spin decoupling techniques and by addition of the n.m.r. shift reagent (18), *tris*(dipivalomethanato)europium [$Eu(DPM)_3$], which induces paramagnetic shifts in protons via association with lone-pair electron bearing functional groups. The magnitude of the shift is primarily dependent on the distance of each proton from the center of the europium atom (19). A variety of solvents, including chloroform-*d*, acetone-d_6, benzene-d_6, and acetonitrile-d_3, were employed in establishing indentification patterns. Comparison spectra reported in this paper for untreated and $Eu(DPM)_3$ treated samples were obtained in chloroform-*d*. Although the $Eu(DPM)_3$ was normally added to the chloroform solutions of the compounds in approximately one millimolar increments with spectra recorded with each addition, the data from the spectrum which gave the best separation of the protons involved was used for tabulative comparison with the normal spectrum. In almost all cases the p.m.r. data was obtained on 10 mg or less of sample.

A study of the effects of varied concentrations of $Eu(DPM)_3$ on the p.m.r. spectra of some of the parent chlorinated polycyclodiene pesticides has been made (20). The objective of our study was to obtain, for the most part, qualitative information which would permit a rapid and at the same time accurate stereochemical description of these types of compounds. In elaborating the p.m.r. data of these representative compounds, three comparative analyses were made, *i.e.*, dihydroxy compounds (**1**, **2**, and **6**), monohydroxy compounds (**3** and **5**), and ketonic compounds (**4** and **7**).

The chemical shifts obtained for the dihydroxy compounds and derivatives with and without the presence of $Eu(DPM)_3$ are given in Table 1. Examination of the data shown for compound **1** reveals the non-equivalency of all protons except the methylene bridge protons (12a, 12s).[5] The most reasonable explanation for this result would be the presence of both an *endo*- and *exo*-hydroxyl group in the molecule at positions C-4 and C-5 destroying the plane of symmetry present in the parent compound. The *trans*-1,2-relationship[6] of the hydroxyls at C-4 and C-5 is supported by the observed coupling constants of $J_{3,4} = 4.5$, $J_{5,6} < 0.5$, and $J_{4,5} = 1.5$ Hz which conform well to the measured dihedral angles of about 35, 80, and 120°, respectively.[7] The presence of the "W effect"[8] coupling ($J_{5n,12a} = 2.0$ Hz) of the C-5 *endo*-proton with the C-12 *anti*-proton and the absence of such a coupling with the C-4 proton, as deduced from decoupling experiments on various combinations of protons, confirm

[5]The p.m.r. spectrum of **1** in acetonitrile-d_3 also demonstrated the non-equivalency of the C-12 protons (H_{12a} τ 8.66, H_{12s} τ 8.41; where *a* and *s* refer to *anti* and *syn* configurations relative to the C-4, C-5 positions).

[6]It was necessary to confirm the 1,2-relationship of these groups since rearrangement equilibria (21) of the bridged norbornyl cation formed during the synthesis of **1** could have led to other isomers.

[7]A study of the variation of coupling constants with dihedral angle in the p.m.r. spectra of the camphane-2,3-diols has been made (22).

[8]Meinwald's "W-letter rule" (23).

TABLE 1. Chemical shifts (τ in $CDCl_3$) for dihydroxy compounds and derivatives

H	**1** (< 0.1 *M*)	**1** + 0.2 *M* Eu(DPM)$_3$	**2**	Acetonide of **2**	Acetonide of **2** + excess Eu(DPM)$_3$	**6** (< 0.1 *M*)	**6** + 0.06 *M* Eu(DPM)$_3$	Acetonide of **6**
2	6.67	1.87	7.47	7.55	7.53	6.82	5.74	6.79
7	7.38	3.42						
3	7.51	*ca.* 3.36	7.66	7.56	6.35	7.47	5.00	7.37
6	7.71	0.94						
4	6.13	−6.32	6.31	6.02	4.77	5.93	2.22	5.65
5	6.64	−5.62						
12a	8.52	4.83	8.66	8.72	8.46	8.61	7.02	8.71
12s	8.52	1.20	8.35	8.40	7.28	7.84	4.11	7.88
OH	7.56	—	8.73	—	—	7.18	—	—
CH_3	—	—	—	8.56	7.30	—	—	8.58
CH_3	—	—	—	8.72	7.79	—	—	8.74

the *trans*-stereochemistry of the hydroxyl groups. Eu(DPM)$_3$ treatment of the *trans*-diol (**1**) is complicated by the presence of two different associable oxygen atoms which produce a cumulative and unequal deshielding of the various protons since they are not equidistant from the two europium complexes. However, the C-2 and C-7 protons which are distant (4 bonds away) from both hydroxyl groups show comparatively larger deshielding of the C-2 proton by the C-4 *endo*-hydroxyl than that observed for the C-7 proton ($J_{2,7}$ = 8.0 Hz). On the other hand, H_{12s} experiences larger deshielding than H_{12a} by the *exo*-hydroxyl group at C-5 (see Fig. 1) thus corroborating the H_2, H_7, H_4, H_5, H_{12s}, and H_{12a} signal assignments as well as the *trans*-stereochemistry of the diol. Likewise, the two bridgehead protons experience unequal deshielding; H_6 is shifted downfield 6.77 p.p.m. while H_3 is shifted 4.15 p.p.m. downfield. This confirms the H_3 and H_6 signal assignments since Dreiding models show that the bridgehead protons are spatially closer to the *exo*-hydroxyl oxygen (2.6 Å), and hence to the europium complex, than to the *endo*-hydroxyl oxygen (2.9 Å). The extremely large deshielding observed for the H_4 and H_5 signals would be expected since contact as well as pseudocontact interactions of these protons with the complex are possible.

Since the *cis*-relationship of the hydroxyl groups in diols **2** and **6** has been established on chemical grounds *via* acetonide formation, it was only necessary to verify that the expected *exo*-addition to the double bond had occurred. Although *endo*-attack is unlikely chemically,[9] it is a reasonable possibility in studying the metabolism of these compounds. The occurrence of the equivalent pairs of protons H_2–H_7, H_3–H_6, and H_4–H_5 is consistent with the presence of a plane of symmetry generated by two *cis*-oriented hydroxyl groups at positions C-4 and C-5. The *exo*-stereochemistry of these hydroxyl groups is in agreement with the small difference ($\Delta\delta$ 0.09) in the value of the chemical shift obtained for the C-2–C-7 protons of **2** with the value of the C-7 proton proximal to an *exo*-hydroxyl group in **1**. The "W effect" coupling (J = 2.0 Hz) of H_{12a} with $H_{4,5}$ is also present since $H_{4,5}$ collapses to an apparent singlet on irradiation of 12a, thereby confirming the absence of appreciable coupling (J < 0.5 Hz) for $H_{3,4}$ and $H_{5,6}$. The *cis*-diol (**2**) was not amenable to n.m.r. analysis in the presence of Eu(DPM)$_3$ due to its insolubility in suitable solvents. The more soluble acetonide derivative of **2** might be expected to associate with the europium complex *via* association with the ether type oxygens of the dimethylmethylenedioxy ring system. However, a large excess (saturated solution) of Eu(DPM)$_3$ was required to produce significant deshielding of protons in this compound. Since this has been shown (19) to be an equilibrium association, the weaker association of this acetonide can be attributed to the poorer Lewis base character of the ether type oxygens

[9]An *endo*-epoxide has been isolated as an epoxidation product of norbornene which was attributed to *endo*-attack on the system (24).

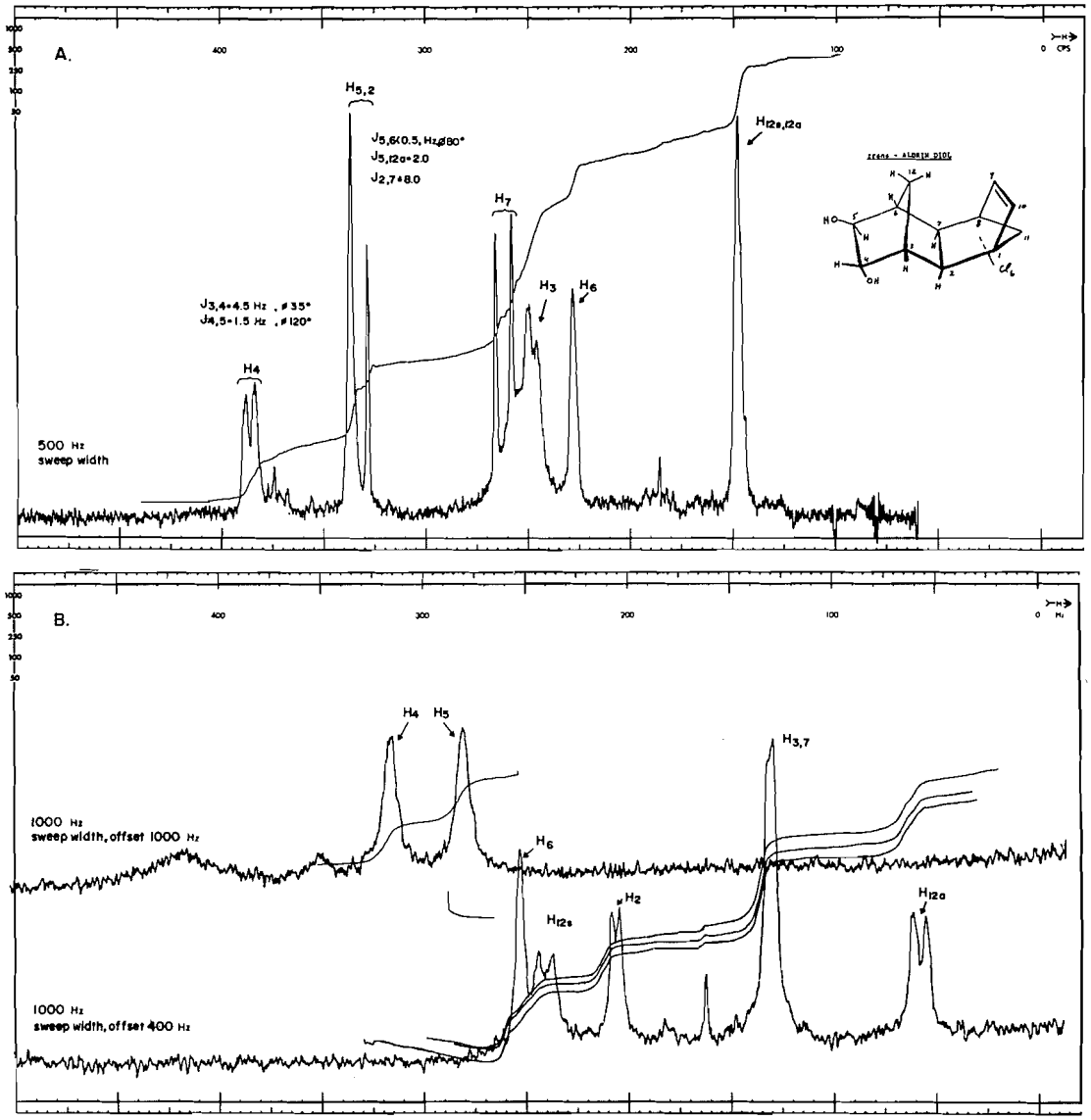

FIG. 1. (*A*) *trans*-Aldrin diol (< 0.1 *M*) without $Eu(DPM)_3$ and (*B*) with 0.2 *M* $Eu(DPM)_3$ in $CDCl_3$ at 100 MHz; 1000 Hz sweep width; sweep offset (*a*) 400 Hz, (*b*) 100 Hz.

as well as the steric requirements of the *gem* dimethyl groups. Nevertheless, the comparatively large deshielding of the H_{12s} signal ($\Delta\delta$ H_{12s} = 1.12 p.p.m.; $\Delta\delta$ H_{12a} = 0.26 p.p.m.) was noted and confirmed the *cis-exo*-stereochemistry of diol **2**.

The formation of the acetonide of diol **6** which is derived from isodrin (*endo–endo* skeleton) not only establishes the *cis*-relationship of the hydroxyl groups but also supports the *exo*-configuration of these groups since such a derivative of the *endo*-isomer of **6**, if it could be formed at all, would have severe steric interactions. The equivalency of protons is also characteristic of this diol as well, with marked differences in chemical shifts for the H_{12s}, $H_{2,7}$, and $H_{4,5}$ signals due to significant differences in the magnetic anisotropy of these protons in the *endo–endo* skeleton. As in diol **2**, the "W effect" coupling (J = 1.8 Hz) of H_{12a} and $H_{4,5}$ and

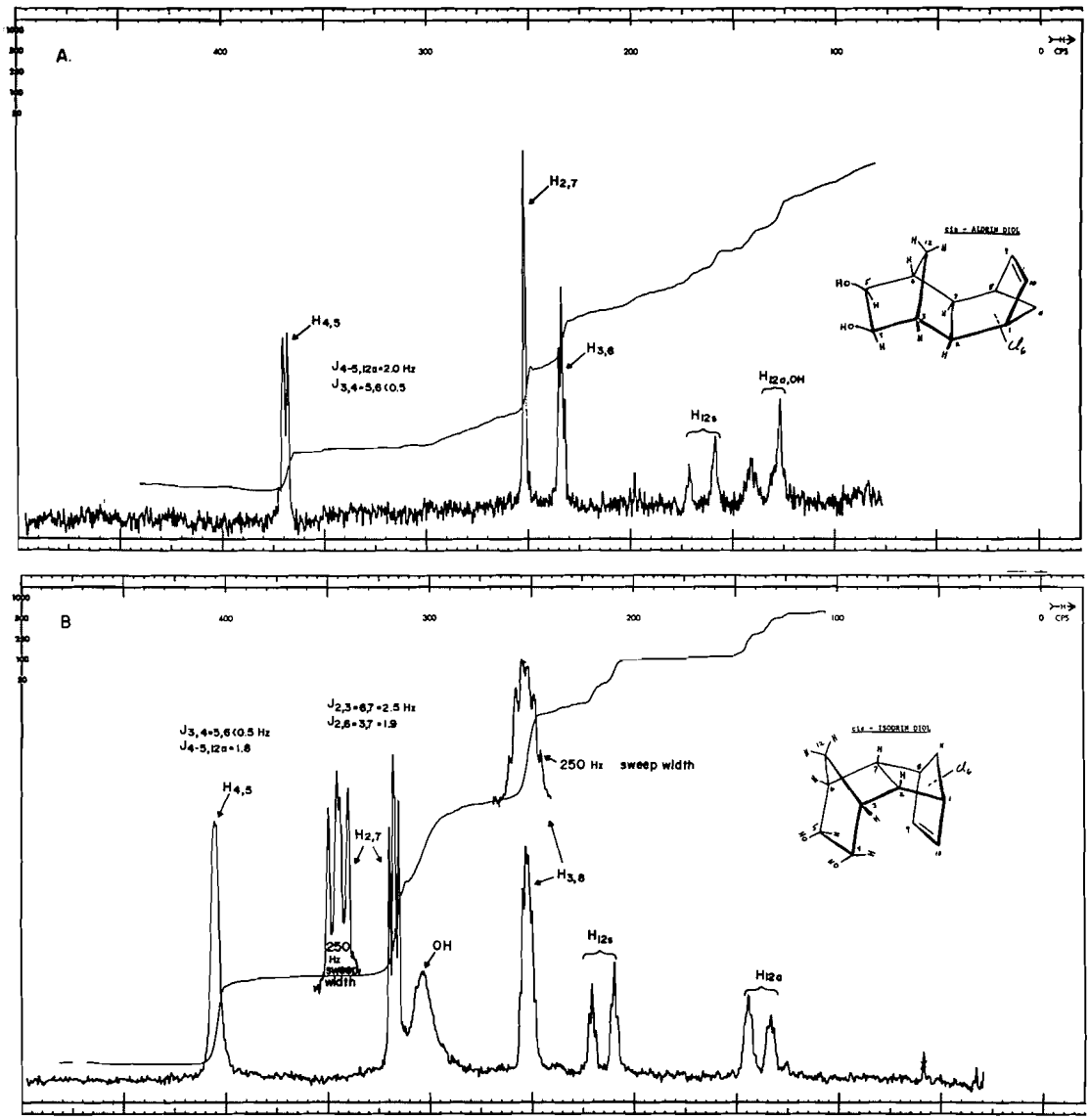

FIG. 2. (*A*) *cis*-Aldrin diol and (*B*) *cis*-isodrin diol in $CDCl_3$ at 100 MHz.

small couplings ($J < 0.5$ Hz) of $H_{3,4}$ and $H_{5,6}$ are characteristic. The most salient difference in the p.m.r. spectrum of diol **6** is the expected pair of doublets for $H_{2,7}$ due to vicinal coupling ($J_{2,3} = J_{6,7} = 2.5$ Hz) with the adjacent bridgehead proton and long-range coupling ($J_{2,6} = J_{3,7} = 1.9$ Hz) with the distant bridgehead proton (Fig. 2) *via* a somewhat distorted "W" (26). As previously reported (25), the presence of these couplings is characteristic of compounds possessing the *endo–endo* skeleton since the $H_{2,7}$ signal in symmetrical compounds possessing the *endo–exo* skeleton appears uniformly as a singlet. In unsymmetrical compounds of the *endo–exo* type such as **1**, **3**, and **5**, the $H_{2,7}$ signals occur as an easily recognizable pair of doublets ($J = 7.5$–8.0 Hz). Addition of $Eu(DPM)_3$ to the chloroform solution of diol **6** produced the larger deshielding of H_{12s} ($\Delta\delta\ H_{12s} = 3.73$ p.p.m.; $\Delta\delta\ H_{12a} = 1.49$ p.p.m.) and completes delineation of the *cis-exo* stereochemistry of the hydroxyl groups.

In light of the information acquired from the dihydroxy compounds, the spectra of the less

TABLE 2. Chemical shifts (τ in $CDCl_3$) for monohydroxy compounds

H	3 (exo)	3 + excess Eu(DPM)$_3$	5 (*endo*)	5 + excess Eu(DPM)$_3$
2	7.44	6.56	6.46	4.76
7	7.56	6.70	7.20	6.58
3	7.60	5.73	*ca.* 7.5	6.76
6	7.70	6.12	*ca.* 7.6	7.28
4	6.24	2.56	5.77	4.20
5*n*	8.38	6.89	7.93	7.36
5x	*ca.* 8.5	6.37	9.12	7.83
12*a*	8.56	7.51	8.51	8.15
12s		5.93	8.82	8.64
OH	8.00	5.46	7.80	—

discernible monohydroxy compounds **3** and **5** were obtained. The proton chemical shifts of these alcohols are given in Table 2. The most diagnostic observations in rapidly differentiating between *exo*-alcohol **3** and *endo*-alcohol **5** are the appreciable deshieldings of H_2 in the *endo*-alcohol and H_{12s} in the *exo*-alcohol which are markedly increased by the addition of Eu(DPM)$_3$ and the ostensible doublet-character of the H_4 signal in **3** as compared to the octet multiplicity produced by the same proton in **5** (see Fig. 3). The multiplicity differences can be ascribed to large couplings ($J_{4,5x}$ = 10.0 Hz, $J_{4,5n}$ = 3.5 Hz, and $J_{4,3}$ = 5.0 Hz) of H_{4x} in the *endo*-alcohol and comparatively smaller couplings ($J_{4,5x}$ = 1.5 Hz, $J_{4,5n}$ = 6.0 Hz, and $J_{4,3} < 0.5$ Hz) of H_{4n} in the *exo*-alcohol. These couplings are also in good agreement with coupling constants calculated on the basis of dihedral angles. Comparison of $J_{4,5x}$ of **3** and $J_{4,5n}$ of **5** shows the effect of the angle of the hydroxyl substituent to the coupling path and reflects greater distortion of bond angles in the *endo*-alcohol. Greater shielding of H_{5x} by the pseudoaxial hydroxyl substituent in the *endo*-alcohol was also notable. This shielding effect would be consistent with earlier observations (27) on the effect of an axial alkyl substituent on the adjacent equatorial proton in cyclohexane compounds. Although the "W effect" coupling of H_{4n} with H_{12a} was not resolvable in the *exo*-alcohol **3**, the relatively large deshielding of H_{12s} on treatment with Eu(DPM)$_3$ is also in accord with the *exo*-configuration of the hydroxyl group.

The $H_{3,6}$ signals for both alcohols appeared for the most part as broad singlets except for H_3 in the *endo*-alcohol which had doublet character due to its relatively large coupling with H_4 previously described. Decoupling experiments of both alcohols involving H_4 permitted resolution of the H_5 ($J_{5x,5n}$ *exo* and *endo* cpds. = 13 Hz) and H_{12} ($J_{12a,12s}^{exo}$ = 12.5 Hz, $J_{12a,12s}^{endo}$ = 13 Hz) couplings as well as chemical shift assignments of these protons. Addition of Eu(DPM)$_3$ to these alcohols further facilitated the assignment of chemical shifts. The position and configuration of the hydroxyl group in compounds **3** and **5** are consistent both with the p.m.r. spectral data and the methods of preparation.

The p.m.r. spectral characteristics of 4-oxo-4,5-dihydroaldrin (**4**) were investigated as a reference compound for comparing the effects of the carbonyl group on the proton environments of the *endo-exo* skeletal system. *Delta*-keto endrin (**7**) provided less relevant data as a ketonic compound of the *endo–endo* type skeleton. (See Table 3.) The expected non-equivalency of protons at H_2 and H_7 ($J_{2,7}$ = 7.5 Hz) and of H_3 and H_6 in **4** was present but was not as perceptible as in the hydroxy compounds. Double decouplings of $H_{5x,5n}$, $H_{3,6}$, and of $H_{12a,12s}$ provided the most interpretative data for assigning chemical shifts; however, the smaller coupling constants of these protons remained undecipherable. Eu(DPM)$_3$ studies confirmed the assignments and were helpful in revealing the multiplicities of some protons; in particular the characteristic four pairs of doublets produced by the C-5 methylene protons from the large geminal coupling of $H_{5n,5x}$ ($J_{5x,5n}$ = 18.0 Hz) and the smaller vicinal couplings of the $H_{5,6}$ ($J_{5n,6}$ = 5.0 Hz, $J_{5x,6}$ = 4.5 Hz) signals (see Fig. 4). Table 4 summarizes the decoupling experiments employed in establishing the major coupling constants of all compounds discussed thus far. Other decoupling experiments were helpful in some cases to confirm our signal assignments.

The assignments given for δ-keto endrin (**7**) are to some degree tenuous since neither decoupling experiments nor Eu(DPM)$_3$ treatment produced adequate changes in its spectra. The H_2, H_4, and H_6 signals were differentiated primarily on the basis of the expected larger deshielding of H_2 by the proximal C-1 chlorine and the presence of the large vicinal coupling ($J_{2,6}$ = 7.0 Hz) suspected of H_2 and H_6 which conforms well to the dihedral angle of 25° as measured from a Dreiding model. The vicinal coupling of $H_{6,7}$ and $H_{4,8}$ ($J_{6,7} = J_{4,8}$ = 2.0 Hz) and the long-range coupling of $H_{4,7}$ and $H_{6,8}$ ($J_{4,7} = J_{6,8}$ = 1.3 Hz) characteristic of compounds possessing

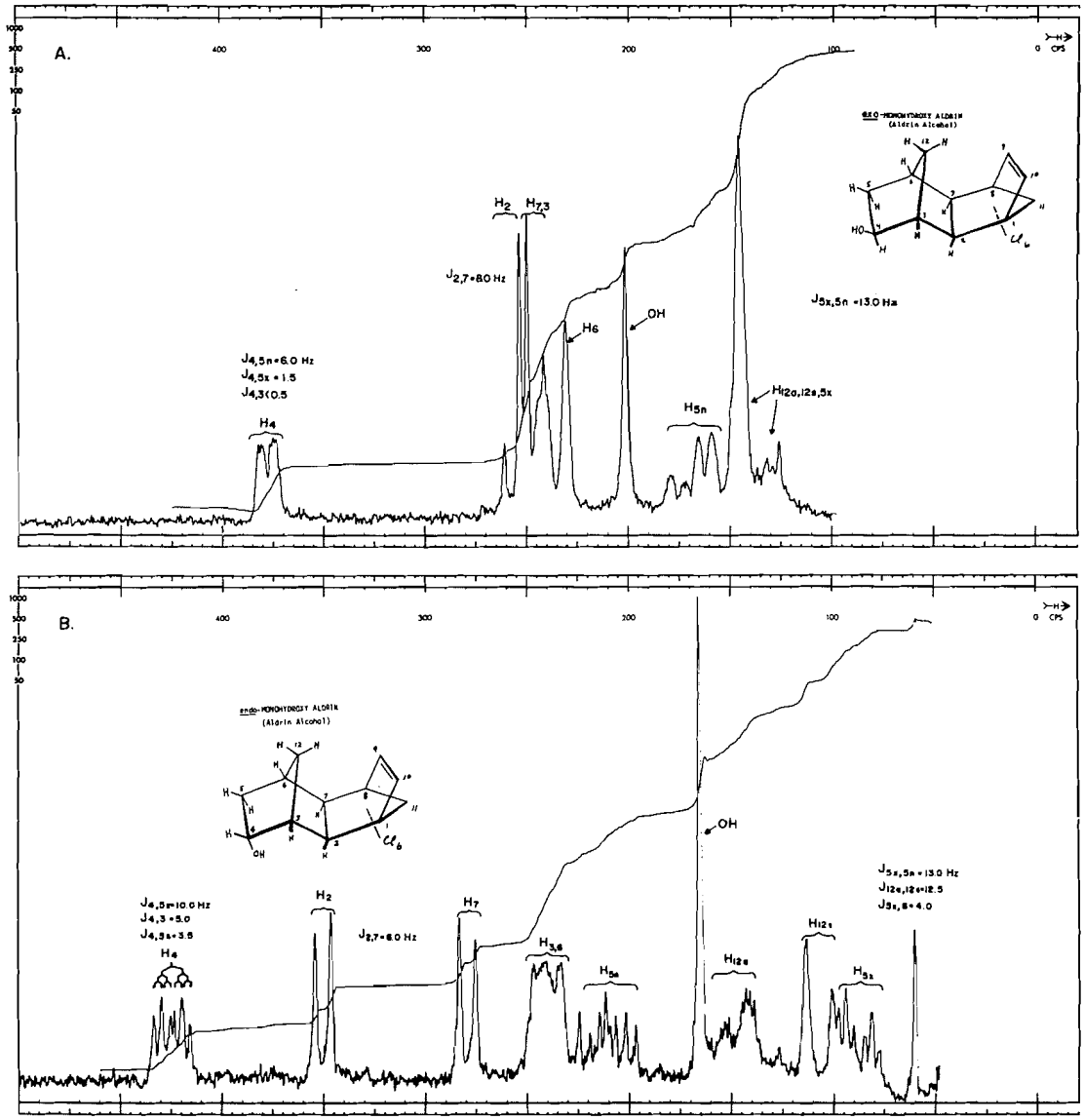

FIG. 3. (*A*) *exo*-Monohydroxy aldrin and (*B*) *endo*-monohydroxy aldrin in $CDCl_3$ at 100 MHz.

the *endo–endo* skeleton were also resolvable. These couplings are smaller in magnitude than those observed (25) for unbridged *endo–endo* systems due to the distortion of bond angles which is a manifestation of the half-cage system. Addition of $Eu(DPM)_3$ to **7** did not provide more substantial data for confirming our signal assignments since sufficient deshielding of protons to resolve all the signals was still not achieved.

In general, addition of $Eu(DPM)_3$ to the keto compounds produced paramagnetic shifts of smaller magnitude than those observed for the hydroxy containing compounds. This finding is consistent with earlier observations (18) and with the stronger associating properties which might be expected for the hydroxyl group on electronic grounds.

The results presented demonstrate that, in rigid systems such as these, a great deal of structural information can be obtained from their p.m.r. spectra. Such information will permit

TABLE 3. Chemical shifts (τ in $CDCl_3$) for keto compounds

H	4 (< 0.1 *M*)	4 + 0.14 *M* Eu(DPM)$_3$	H	7 (< 0.1 *M*)	7 + 0.06 *M* Eu(DPM)$_3$
2	7.04	6.18	2	6.67	6.40
3	7.22	5.38	3	—	—
4	—	—	4	7.11	6.98
5x	8.08	6.47	5a	8.31	8.24
5*n*	7.71	6.07	5s	8.18	8.13
6	*ca.* 7.2	6.60	6	6.91	6.67
7	7.14	6.42	7	6.66	*ca.* 6.6
9	—	—	8	6.66	*ca.* 6.6
12a	*ca.* 8.1	7.46	12	4.98	4.81
12s	8.51				

rapid assessment of the stereochemistry as well as other structural characteristics of these systems whether they be of theoretical or metabolic interest. In addition, the deshielding effects of Eu(DPM)$_3$ were shown to be useful as a confirmatory technique of signal assignments without the requirement of spin decoupling equipment and as a selective shift reagent enabling superimposed signals in these systems to be separated from one another.

Experimental

Melting points were taken on a Fisher–John melting point apparatus and are uncorrected. The n.m.r. studies were made with a Varian HA-100 spectrometer with spin decoupling accessories using tetramethylsilane (TMS) as an internal reference. The Eu(DPM)$_3$ used in these studies was obtained from Alfa Inorganics, Beverly, Massachusetts, and the chloroform-*d* employed in obtaining spectra of Eu(DPM)$_3$ treated samples was stored over anhydrous sodium carbonate. The i.r. spectra were obtained with a Perkin–Elmer Model 337 spectrophotometer, and the low resolution mass spectra were obtained with a Perkin–Elmer Model 270 gas chromatograph-mass spectrometer. The preparative thin layer chromatography (t.l.c.) was done on Uniplate, Silica Gel GF plates 250 microns in thickness. The bands were detected with u.v. light.

Preparation of Dihydroxy Compounds

The *trans*-diol **1** was prepared by a modification of Korte and Arent (13) procedure. To a solution of 243 mg (0.61 mmol) of dieldrin (from Shell Development Co.) in 25 ml of 1,4-dioxane was added 22 ml of water and 3.5 ml of concentrated H_2SO_4. The resulting solution was refluxed for 72 h in oil bath. After cooling, the reaction mixture was diluted with an equal volume of H_2O extracted with two 50-ml portions of ethyl acetate. The combined extracts were washed with sodium carbonate, water and then dried over anhydrous sodium sulfate. Evaporations of these extracts gave a residue which was redissolved and streaked on t.l.c. plates. Elution of the plates with benzene – ethyl acetate (3 to 1) followed by removal of the largest band as detected by u.v. light gave 117 mg (49%) of solid material. Recrystallization from hexane afforded crystalline material melting at 132–134°. Spectral properties were characteristic of *trans*-4,5-dihydroxy-4,5-dihydroaldrin (2).

TABLE 4. Coupling constants (J) obtained from specified decoupling experiments for compounds **1**–**6**

Compound	Irradiated at	J (Hz)
1	2	$J_{2,7} = 8.0$
	3	$J_{3,4} = 4.5$
	4,6	$J_{5n,12a} = 2.0$
	5,12a	$J_{5,6} < 0.5$
	6,12a	$J_{4,5} = 1.5$
2	3,6	$J_{4,5-12a} = 2.0$
	12a	$J_{3,4=5,6} < 0.5$
3	3,12a	$J_{4,5x} = 1.5$
	5x	$J_{5x,5n} = 13$
	5x,12a	$J_{4n,5n} = 6.0$
	12a*	$J_{12a,12s} = 12.5$
	12a,12s*	$J_{4,3} < 0.5$
4	6	$J_{5x,5n} = 18$
		$J_{5n,6} = 5.0$
		$J_{5x,6} = 4.5$
	7*	$J_{2,7} = 7.5$
	12a	$J_{12a,12s} = 12.5$
5	3,5*n*	$J_{4,5x} = 10.0$
	3,5x	$J_{4,5n} = 3.5$
	4	$J_{5x,6} = 4.0$
	4,6	$J_{5x,5n} = 13$
	5*n*,5x	$J_{4,3} = 5.0$
	12a	$J_{12a,12s} = 13$
6	3,6	$J_{4,5-12a} = 1.8$
		$J_{2,3=6,7} = 2.5$
		$J_{2,6=3,7} = 1.9$
	12a	$J_{3,4=5,6} < 0.5$

*Decoupling experiments were done on a sample of compound to which Eu(DPM)$_3$ had been added to separate superimposed signals.

The *cis*-diols **2** and **6** were prepared according to the following general procedure: To solution of 719 mg (2.1 mmol) of the olefinic compound (aldrin or isodrin) in 10 ml of absolute ether and 1 ml of pyridine was added 500 mg (1.97 mmol) of osmium tetroxide in 50 ml of absolute ether, resulting in the immediate formation of a creamy brown precipitate. The reaction mixture was stirred magnetically for 1 h and allowed to stand overnight unexposed to any light. The light brown precipitate was removed by filtration and dissolved in 50 ml of methylene chloride. The hydrolysis of the olefin–OsO_4–

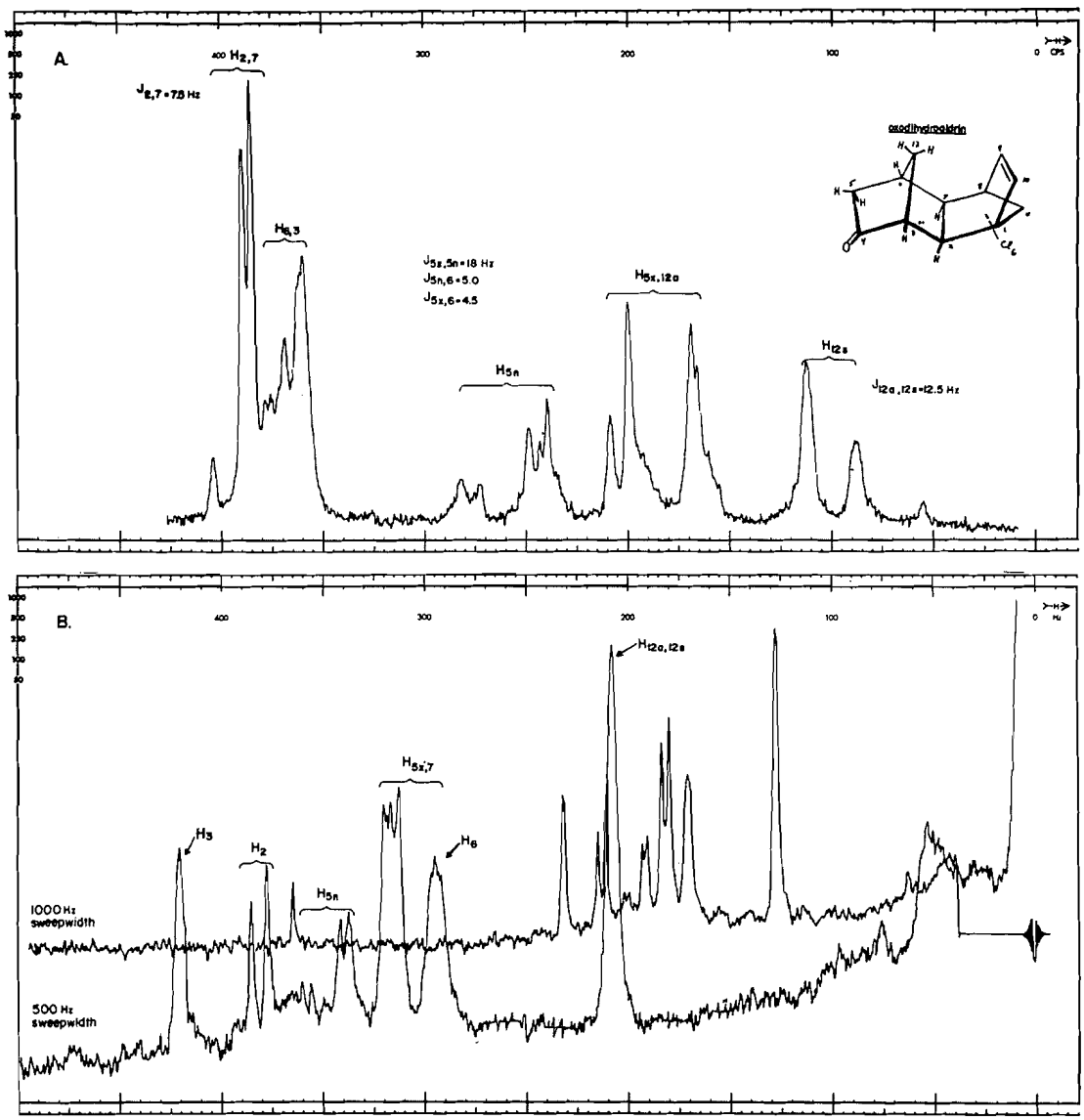

FIG. 4. (*A*) Oxodihydroaldrin (<0.1 *M*) in $CDCl_3$ at 100 MHz; sweep width 250 Hz and (*B*) with 0.14 *M* $Eu(DPM)_3$; sweep width 500 Hz.

pyridine adduct was accomplished by shaking the methylene chloride solution with 65 ml of water containing KOH (11.6 mmol) and mannitol (34.9 mmol) for 2 h or until the brown methylene chloride layer becomes relatively colorless while the aqueous phase acquires a deep reddish brown color. The methylene chloride layer is removed, washed with an equal volume of water, and dried over anhydrous sodium sulfate. Evaporation of this layer left a brown residue from which the *cis*-diol could be obtained by dissolving in hot benzene, decolorizing the resulting solution with charcoal, filtering and cooling the filtrate. Successive recrystallizations afforded 60–75% yields of pure material. The *cis-exo*-4,5-dihydroxy-4,5-dihydroaldrin (**2**) melted at 218–219 °C (m.p. 217 °C (13)) and *cis-exo*-4,5-dihydroxy-4,5-dihydroisodrin (**6**) melted at 201–203 °C (m.p. 199–201 °C (12)). The acetonides of these materials, which were prepared according to the method of Soloway *et al.* (12) in refluxing acetone in the presence of ferric chloride hexahydrate, melted at 151–153 °C (from **2**) and 136–138 °C (from **6**), and had the expected spectral properties for the dimethylmethylenedioxy ring system.

Preparation of Monohydroxy and Keto Compounds

To a solution of 145 mg (3.8 mmol) of sodium borohydride and 1.62 ml of boron trifluoride etherate in 10 ml

of tetrahydrofuran (THF) was added dropwise a 10 ml solution of 2.88 g (7.9 mmol) of aldrin. The resulting solution was stored for 70 h at room temperature and then 1.4 ml of 3 *N* NaOH solution was added followed by 1.4 ml of 30% hydrogen peroxide. The mixture was stirred at room temperature for 3 h and then diluted with 50-ml portions of ether. The combined extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated under vacuum. The residue was transferred to preparative t.l.c. plates which were eluted with a mixture of chloroform – ethyl acetate (9 to 1). Two major bands were detected with u.v.-light. The material in the band nearest the solvent front was cochromatographical with aldrin. The material in the band nearest the origin was removed and repeatedly chromatographed until pure. Solid material (1.19 g, 39%) obtained from crystallization of the latter purified material from *n*-hexane had no precise melting point but had the expected mass spectral properties ($C_{12}H_{10}O^{35}Cl_{4.5}{}^{37}Cl_{1.5}$, *m/e* 383, 347, 329, 311, and 301) of the *exo*-alcohol (**3**).

A solution of 1.15 g (3.0 mmol) of (**3**) in 10 ml of ether was added dropwise to 10 ml of water containing 880 mg (3.0 mmol) of sodium dichromate and 0.66 ml of 96% H_2SO_4 over a 15-min period while maintaining the temperature below 20 °C. The solution was stirred for 3 h and allowed to reach room temperature followed by stirring for an additional 22 h. The ether layer was separated and the aqueous phase extracted with three 25-ml portions of ether. The combined ether extracts, including the initial ether phase, were washed twice with 50-ml portions of saturated sodium bicarbonate solution, water, and then dried over anhydrous sodium sulfate. A white solid was obtained on evaporation of the extracts to dryness under vacuum and recrystallization from hot *n*-hexane afforded 1.03 g (90% yield) of 4-oxo-4,5-dihydroaldrin (**4**). The material melting at 136–137 °C was chromatographically pure and had the expected spectral properties (i.r., (KBr), C=O, 5.72 μ; MS, $C_{12}H_8O^{35}Cl_{4.5}{}^{37}Cl_{1.5}$, *m/e* 381, 339).

Anal. Calcd. for $C_{12}H_8OCl_6$: C, 37.82; H, 2.10; O, 4.20; Cl, 55.89. Found: C, 37.93; H, 2.26; O, 5.05; Cl, 55.32.

The *endo*-alcohol (**5**) was prepared from (**4**) by the following procedure. Ketone **4** (130 mg, 0.34 mmol) was dissolved in 10 ml of 1 *M* disiamylborane in THF and stirred at room temperature for 20 h. The excess disiamylborane was destroyed by the cautious addition of 0.5 ml of water followed by stirring for 4 h. The reaction was then diluted further with 20 ml of water and extracted with two 15-ml portions of ethyl acetate. The combined dried extracts were taken to dryness and the residue was dissolved in 1 ml of 1,4-dioxane to which was added 0.1 ml of concentrated HCl. (The organoborane had resisted earlier attempts at hydrolysis *in situ* with acetic acid.) The resulting solution was heated at 85 °C for 0.5 h. The reaction solution was diluted to 5 ml with water and extracted with two 4-ml portions of ether. The combined ethers were washed with water, dried, and evaporated to dryness under vacuum. The residue was transferred to preparative t.l.c. plates and developed with a mixture of chloroform – ethyl acetate (9 to 1). Two major bands were detectable with u.v.-light. The band nearest the solvent front was identified as starting ketone **4**. The material in the band nearest the origin was repeatedly chromatographed until pure and crystallized from *n*-hexane. The pure solid (40 mg, 30%) had no precise melting point, but appeared to melt over a long range. This material had the expected mass spectral properties ($C_{12}H_{10}O^{35}Cl_{4.5}{}^{37}Cl_{1.5}$, *m/e* 383, 347, 329, 301) of the *endo*-alcohol (**5**) and was reconverted, in part, to ketone **4** using the dichromate oxidation procedure. The oxidation product had identical gas-chromatographic retention time and superimposable mass spectrum to an authentic sample of **4**.

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