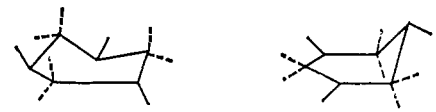
sponds to a conformational process in which chair form II goes to the equivalent form II′ with axial and equatorial protons interchanged in each methylene group. Possible reaction paths include: (a) ring inversion synchronous with inversion of all three nitrogens;[18] (b) ring inversion followed and/or preceded by fast inversion of one, two, or three nitrogens to give a net inversion of all three nitrogens; and (c) ring inversion synchronous with inversion of one or two nitrogens, followed or preceded by fast inversion of the other two or one nitrogens. Of these, the latter is preferred.

For the case of the cyclohexane ring inversion, Hendrickson has considered the nature of the transition state in detail.[15] The most probable transition state[19] is a cyclohexene-like[3a] form of C_2 symmetry which has four ring atoms coplanar. Another, less probable state is a "half-boat" form of C_s symmetry with five ring atoms coplanar and about 1.5 kcal/mole higher in energy than the C_2 form. In adapting these to HTMT, we note that ring strain and repulsive interactions can be reduced by having the nitrogen atom(s) in the main coplanar part of the ring assume the sp^2 configuration(s) shown in IV and V. Thus, IV and V are transition states not only for ring inversion but also for the



IV V

simultaneous inversion of one and two nitrogens, respectively.[20] Therefore, if ring inversion of HTMT is similar to that of cyclohexane, it is accompanied by inversion of only one or two of the nitrogens. And this process must be followed or preceded by the fast inversion of the other one or two nitrogens in order that the net conformational change agree with the nmr results.

Acknowledgment. We, particularly P. A. T., wish to thank Dr. Jiri Jonas for his help in many ways.

(18) This seems to have been suggested by Harris and Spragg in the case of morpholine and piperazine derivatives; see ref 3c.

(19) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Division, John Wiley and Sons, Inc., New York, N. Y., 1965.

(20) The energy of the transition state with all six ring atoms planar is probably too high for it to contribute appreciably to the exchange process; see, *e.g.*, ref 15.

7,12-Dihydropleiadenes. VI. Conformational Preferences of 7-Alkyl-7,12-dihydropleiadenes[1]

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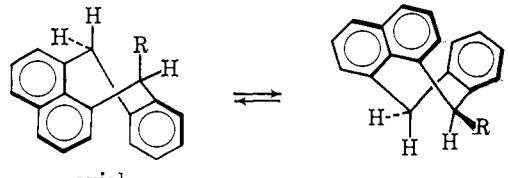
Contribution from the Department of Chemistry, State University of New York, Buffalo, New York 14214. *Received February 11, 1967*

Abstract: The conformational preferences of the alkyl groups in 7-methyl-, 7-ethyl-, and 7-isopropyl-7,12-dihydropleiadenes have been shown to vary widely, from mainly equatorial for methyl to overwhelmingly axial for isopropyl. These results are derived from conformational equilibrium measurements by nmr and equilibration studies involving *cis* and *trans* isomers of 7,12-dialkyl-7,12-dihydropleiadenes and 7-alkyl-12-methoxy-7,12-dihydropleiadenes. It is proposed that the steric effect of β as well as α atoms of the 7-alkyl group play a role in determining the relative stabilities of the two possible conformations.

A 7-substituted 7,12-dihydropleiadene has available to it two readily interconvertible[4] folded conformations in which the substituent can occupy either an axial or equatorial position.[5]



axial equatorial

We have already studied the conformational equilibria of several derivatives of 7,12-dihydropleiadenes[5] (DHP). It was found that phenyl, carbomethoxy, and chlorine substituents exist overwhelmingly ($\gtrsim$98%) in the axial conformation and methoxy and acetoxy groups have modest axial preferences also.[5] When we extended our studies to 7-alkyl DHP's, we were somewhat surprised to find that a 7-methyl group had a strong preference for the equatorial position and furthermore that substantially different results are obtained with 7-ethyl and 7-isopropyl groups[1] (increasing axial preference). In this paper we present several approaches used to establish preferred conformations of 7-alkyl DHP's. In addition to direct conformer population measurements on these compounds (by low-temperature nmr), equilibrations of diastereomers were also carried out, *e.g.*, *cis*- $\rightleftarrows$ *trans*-7,12-dimethyl DHP's. A possible rationale for experimental results is presented.

(1) A preliminary account of some of this research has appeared: P. T. Lansbury and A. J. Lacher, *J. Am. Chem. Soc.*, **88**, 3877 (1966).

(2) Alfred P. Sloan Foundation Fellow, 1963–1967.

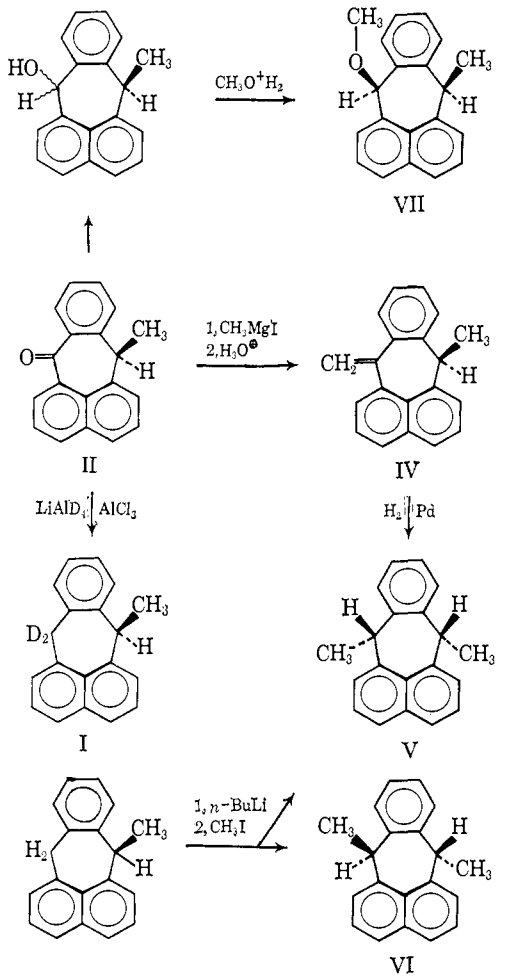
(3) Du Pont Predoctoral Teaching Fellow, 1966–1967.

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

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

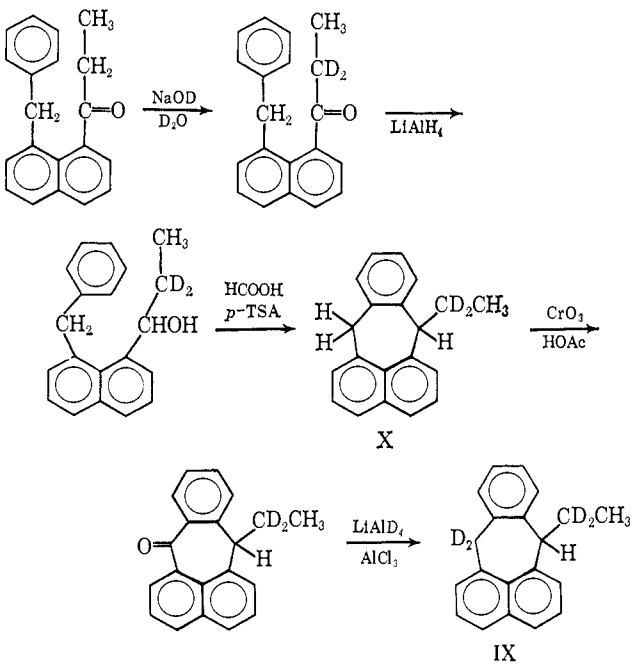
Results and Discussion

The 7-alkyl DHP's could be prepared in good yield by alkylation of α-metalated 7,12-dihydropleiadene with alkyl iodides or tosylates. However, in order to simplify their low-temperature nmr spectra and to remove interfering peaks, specifically deuterated compounds were synthesized. For example, 7-methyl DHP-12,12-d_2 (I) was prepared by lithium aluminum deuteride–aluminum chloride reduction of 12-methyl-7-(12H)-pleiadenone (II), so that the two coincidental C_{12}-methylene quartets appearing at low temperature did not prevent observation and integration of the two C_7-methine quartets.

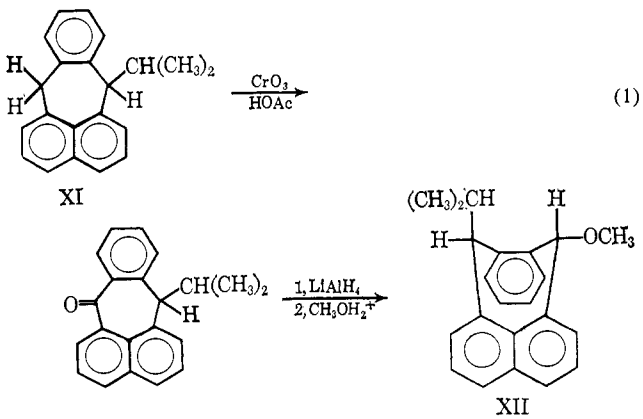


The above flow sheet also indicates how the *cis* and *trans* isomers of 7,12-dimethyl DHP were obtained. The *cis* isomer V was prepared by catalytic hydrogenation of the methylene derivative IV resulting from Grignard addition to II and dehydration; its diequatorial conformation was established by nmr chemical shift and long-range coupling data (see below) and the absence of nmr temperature effects characteristic of *trans*-7,12-disubstituted DHP's.[4] *trans*-7,12-Dimethyl DHP (VI) was obtained by fractional crystallization of the mixture of V and VI resulting from further alkylation of 7-methyl-7,12-dihydropleiadene. As expected,[4] the time-average methine quartet in VI separated into two quartets at $\sim -38°$, verifying the *trans* geometry. For further studies of 7-methyl conformer populations in DHP's, II was reduced to the alcohol and subsequently converted to the diastereomeric methyl ether mixture, from which the less soluble *cis* isomer VII was separated by fractional crystallization. This latter compound was desirable, since the conformational preference of the methoxy group was already known,[5] and a similar equilibrium distribution of methoxy groups might be observed in view of the pronounced equatorial preference of methyl.

In the low-temperature nmr spectrum of 7-ethyl DHP (VIII), the two C_{12}-methylene AB spectra were again virtually superimpossible, being separable only at 100 mHz, and they also interfered with the C_7-methine peaks. In addition, since it was desirable to observe the latter signals as singlets, as well as the methyl signals of the ethyl groups in each conformer, we wished to prepare 7-(ethyl-α,α-d_2)-DHP-12,12-d_2 (IX) and 7-(ethyl-α,α-d_2)-DHP (X), especially the former. The synthetic scheme is outlined below. The hydrogen–deuterium exchange of 8-benzyl-1-propionylnaphthalene was continued until the methyl signal appeared as a sharp singlet, signifying essentially complete replacement of the protons adjacent to the carbonyl group. The deuterium contents of IX and X were determined



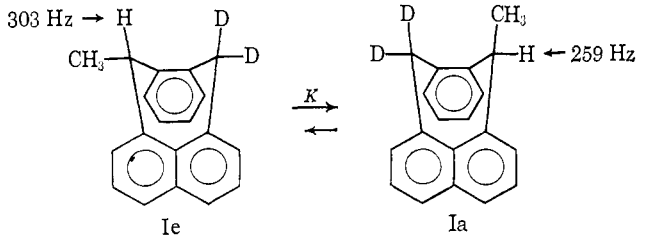
qualitatively by nmr spectral analysis and their structures were additionally confirmed by comparison with VIII obtained by monoalkylation of 7-lithio DHP with ethyl tosylate.



(1)

7-Isopropyl DHP (XI) was prepared by alkylation of 7-lithio DHP with isopropyl tosylate. Selective chromic acid oxidation of XI, followed by $LiAlH_4$ reduction to the alcohol and acid-catalyzed methanolysis, produced the expected *trans*-7-methoxy-12-isopropyl DHP (XII), whose stereochemistry is discussed in eq 1.

The preferred conformation of the C_7-methyl group in DHP was initially established as largely equatorial by "freezing out" the inversion of I (on the nmr time scale) and integration of the individual methine quartets ($J \cong 7$ Hz). The C_7-CH_3 peaks overlapped almost



Ie Ia

perfectly, and thus were useless for determining the conformational equilibrium constant. In the temperature range -20 to $-40°$, K_{eq}[6] ranged from 0.13 to 0.09, corresponding to $\Delta F = +1.0$ and $+1.1 \pm 0.1$ kcal/mole. Since integration of two quartets of significantly different areas can introduce substantial error in determining K, no efforts were made to calculate ΔH and ΔS for I. The assignment of the methine resonances is based on previous findings[5] that equatorial C_7 and C_{12} protons always resonate at higher field than their axial counterparts in a variety of DHP's.[5] This is specifically illustrated in Table I below, which gives chemical shift

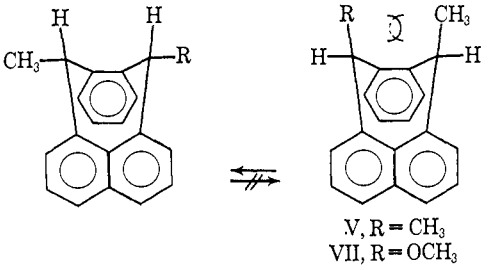
Table I. Chemical Shifts of Methine Protons in Some C_7- and C_{12}-Methyl DHP's

Compound	Temp, °C	Methine quartet(s)[a] Ax	Av	Eq
cis-7,12-Dimethyl DHP (V)	+40 to −40	325		
1,12-Dimethyl DHP	35	...	...	282
7-Methyl DHP-12,12-d_2 (I)	+40	...	294	...
	−50	303	...	259
trans-7,12-Dimethyl DHP (VI)	35	...	290	...
	−40	313	...	267
1,7,12-Trimethyl DHP	35	315	...	269
cis-7-Methoxy-12-methyl DHP (VII)	35	304	...	...

[a] Chemical shifts in Hz at 60 mHz, relative to internal tetramethylsilane.

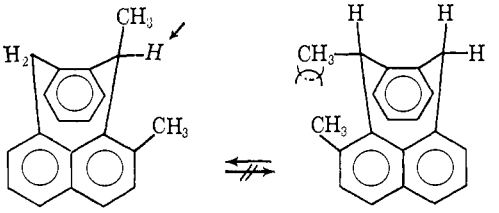
data for methine protons geminal to methyl groups in a number of methyl- and dimethyl-7,12-dihydropleiadenes. Among the compounds listed in Table I, *cis*-7,12-dimethyl DHP and *cis*-7-methoxy-12-methyl DHP (VII) both exist only in conformations where the pertinent methine protons are axial, and the substituents are equatorial, since 7,12-diaxially substituted DHP's would be too compressed to exist (except for the diol, where intramolecular hydrogen bonding stabilizes that conformation). As expected for axial methine protons in V, long-range spin coupling with the *ortho* and *para* aromatic hydrogens[5] causes peak broadening of the quartet lines (relative to the methyl signals), which

(6) All conformational equilibrium constants in this paper are [A]/[E].

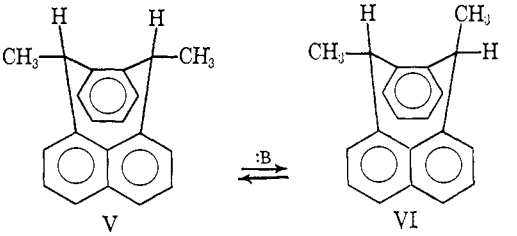


V, R = CH_3
VII, R = OCH_3

decreases upon simultaneous irradiation of the aromatic protons.[5] The resulting half-height widths ($W_{h/2}$) for the methine signals in V are then comparable to $W_{h/2}$ for the methyl signal, or an equatorial methine signal in a suitable example.[5] Again, based on steric compression arguments derived from examination of models, 1,12-dimethyl DHP exists in only one conformation (in all such cases a temperature-invariant nmr spectrum results), this time with an equatorial methine proton, whose chemical shift is seen to lie upfield from the axial ones mentioned.



On the basis of the equatorial preference of a methyl group, one would predict that *cis*-7,12-dimethyl DHP (V) would be more stable than the *trans* isomer VI since the main difference (other than entropy of mixing) between the two isomers is the configuration of one methyl group, assuming V to have only the diequatorial conformation. Equilibration of V and VI was achieved



V VI

from both directions with potassium *t*-butoxide in dimethyl sulfoxide at 25–40° for 5 hr or more. Integration of the methine quartets at 290 Hz (in VI) and 325 Hz (in V) revealed an equilibrium composition of 65 ± 2% V and 35 ± 2% VI, corresponding to $K \simeq 0.54$ and $\Delta F_{298} \simeq +0.4$ kcal/mole. This value differs somewhat from the conformational free energy difference in I ($\Delta F_{233} \simeq +1.0$ kcal/mole), largely because VI, being a *dl* pair whereas V is a *meso* compound, possesses an entropy of mixing, R ln 2, which lowers its free energy relative to V. Consideration of this gives $\Delta H_{298} = \Delta F + T\Delta S_{mix} \simeq +0.8$ kcal/mole for the *cis* ⇄ *trans* equilibration. Assuming $\Delta S \simeq 0$ in the conformational equilibration of I, $\Delta H \simeq +1.0$ kcal/mole in the monomethyl compound, in close agreement with the dimethyl equilibrium.[7]

(7) The slight differences in ΔH between Ia ⇄ Ie and V ⇄ VI may be due to experimental error and/or differences in ring geometry in 7,12-dihydropleiadenes containing two rather than one substituent. It is also conceivable that ΔS is *not* zero for the above equilibrations.

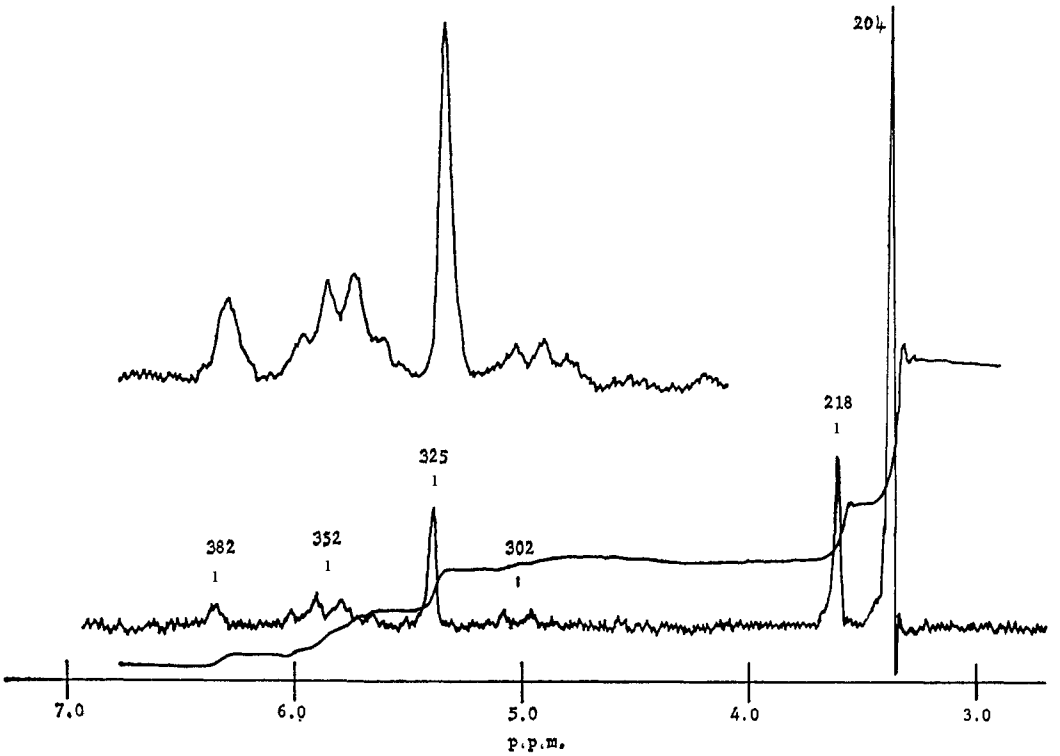
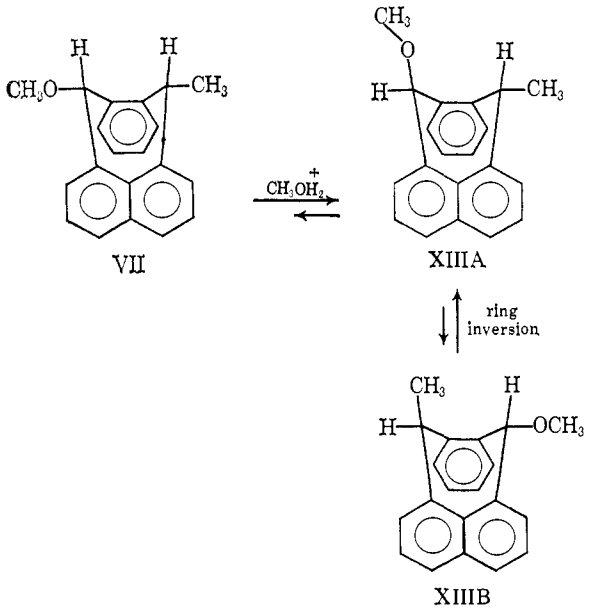
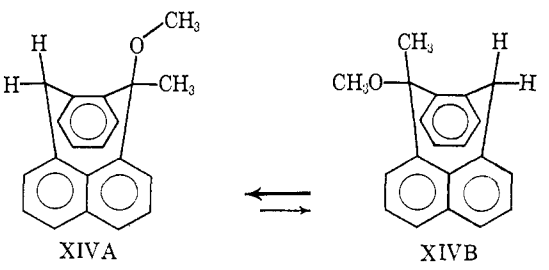


Figure 1. Partial nmr spectrum of equilibrium mixture of *cis*- and *trans*-7-methoxy-12-methyl-7,12-dihydropleiadene at room temperature in chloroform-*d*. Inset shows methine protons at enhanced spectrum amplitude.

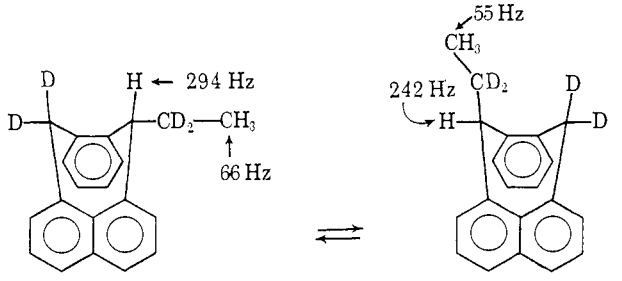
In view of the well-established equatorial preference for methyl and the previously noted 2:1 axial preference of methoxyl,[5] we became interested in the equilibration of 7-methoxy-12-methyl DHP, where conformational equilibration involving diastereomeric forms in the *trans* isomer XIII, as well as epimerization, required attention. The situation is depicted below (longer arrows inferring the predicted predominance of XIIIA, with methoxy and methyl *both* in their preferred conformations). The above equilibration was effected by refluxing VII in acidified methanol for a day, then pouring over ice water containing sodium bicarbonate, and working up. The equilibrium mixture was directly examined by nmr producing the spectrum shown in Figure 1. The methoxy peak at 204 Hz is the time-average signal of XIII whereas that at 218 Hz is due to diequatorial VII, the ratios from integration being 73% XIII and 27% VII. Similar peak ratios were obtained by integrating the C_7-methine singlets at 325 Hz in XIII (time average but mainly equatorial) and 382 Hz in VII (axial H), which were in good agreement with the corresponding chemical shifts in the two conformers of 7-methoxy DHP[5] (318 and 377 Hz, respectively). With both methyl and methoxyl in unfavorable positions, XIIIB is not expected to be present in significant amounts when the conformational inversion of XIII is frozen out. In fact, K_{eq} for [XIIIA]/[XIIIB] can be estimated as *ca.* 25 at $-40°$, using conformational energies for 7-methyl and 7-methoxy[5] groups; thus attempts to detect some XIIIB were rendered ambiguous by experimental uncertainty. It is quite clear from the above data that XIIIa is the major species present in the equilibration of VII and XIII, as was expected from the results in 7-methyl and 7-methoxy DHP's. A final confirmatory piece of evidence comes from 7-methoxy-7-methyl DHP (XIV), whose C_{12}-methylene protons appear in the room-temperature nmr spectrum as an AB quartet centered at 287 Hz with $\Delta\nu_{AB}$ = 105 Hz at room tem-





perature, much like the axial-methoxy conformer of 7-methoxy DHP[5] (AB quartet centered at 286 Hz with $\Delta\nu_{AB}$ = 114 Hz). If XIVB were present in substantial amount, the axial C_{12}-proton doublet should be shifted upfield up to *ca.* 45 Hz, since equatorial 7-methoxy DHP shows its low-temperature AB quartet centered at 265 Hz with $\Delta\nu_{AB} \sim 67$ Hz.[5] The low-temperature nmr spectrum (−40°) showed no observable changes, indicating the overwhelming preponderance of XIVA from *ca.* 35° down to −40°.

The most reliable data on conformer populations in 7-ethyl DHP was obtained with the tetradeuterated analog IX, in which case the low-temperature nmr spectra showed the C_7 methine signals of both conformers (assigned as above in the 7-CH_3 analogs) as well separated singlets easily integrated without interference from the missing C_{12} protons. Integration of the methyl singlets in IX and X was also possible but more difficult due to the smaller chemical shift difference separating them. Over the temperature range 252–

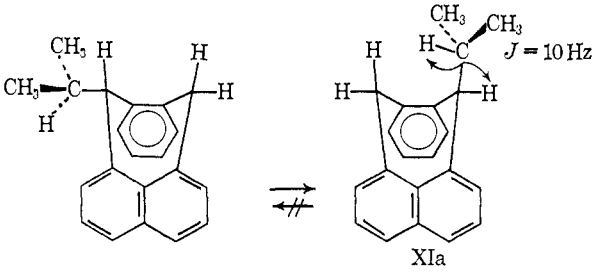


IXe IXa

Compd.	$K_{253°}$	$K_{233°}$
X	1.1	0.7
IX	1.3	1.0

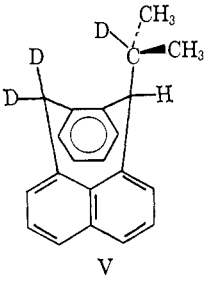
227°K, K_{eq} ranged from 1.3 to 0.8, corresponding to $\Delta F°$ going from *ca.* −0.14 to +0.07 kcal/mole. A plot of ln K *vs.* $1/T$ gave $\Delta H° \simeq 1.9$ kcal/mole and $\Delta S° \simeq +8$ eu. Again, due to experimental errors in integration, we do not wish to interpret the calculated entropy change (probable error ±4 eu) other than to note the apparent greater rotational freedom of an *axial* ethyl group. The conformational equilibrium of IX shows a slightly greater axial-ethyl preference than in X (see above) where the axial-ethyl group encounters a hydrogen atom across the ring rather than the less bulky deuterium. If this difference is real, then a small equilibrium deuterium isotope effect is indicated. A similar steric equilibrium isotope effect was noted by Jensen,[8] who found unequal amounts of the two nonplanar conformations of 7-deuteriocycloheptatriene at very low temperatures. The main conclusion from studying IX and X is that the conformational preference of C_7-ethyl groups in DHP's is substantially different from the corresponding methyl groups.

A further pronounced increase in axial preference was noted in passing to 7-isopropyl DHP (XI), which showed a temperature-independent nmr spectrum (+40 to −45°), in which the C_{12} AB spectrum showed doublets ($J \simeq 16$ Hz) at 310 Hz (axial C_{12}-H) and 229 Hz (equatorial C_{12}-H) and the C_7-methine doublet at 214 Hz[9] with $J \simeq 10$ Hz. The latter vicinal coupling constant indicates that the C_7-H and isopropyl α-C–H dihedral angle is *ca.* 150° (as predicted from models) in the exclusively *axial* isopropyl conformer present.[10,11] It is quite clear from above arguments that the C_7-proton signal corresponds to an equatorial proton. In order



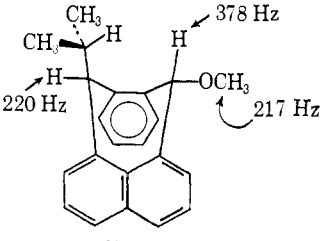
XIa

to check further for any of the other conformer, the nmr spectrum of the trideuterated analog XV was examined at room temperature and at −50°. The C_7-methine proton now appeared as a singlet at 220 Hz,

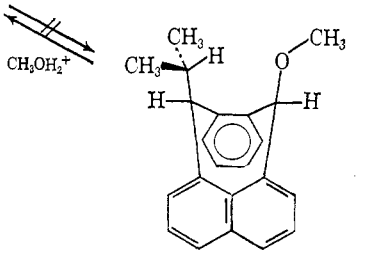


V

with no other methine peak visible. Furthermore, the isopropyl group gave rise to two singlets at 50 and 54 Hz, indicative of the conformation shown for XV, in which the methyl groups are in substantially different magnetic environments.[12] A final proof of the pronounced axial preference of the isopropyl group comes from the nmr spectrum of 7-isopropyl-12-methoxy DHP (XII), which was prepared from the alcohol by thermo-



XII



(8) F. R. Jensen and L. A. Smith, *J. Am. Chem. Soc.*, **86**, 956 (1964).
(9) Erroneously reported as 209 Hz in ref 1.
(10) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 50.
(11) Even at 100 mHz, using the more sensitive HA-100 spectrometer, no evidence for the second conformer could be found in the low-temperature spectrum of XI.
(12) That "intrinsic asymmetry" is not the major cause of this chemical shift difference is indicated by the behavior of the isopropyl methyl signal of XI in nitrobenzene: two overlapping doublets ($J \cong 7$ Hz) are observed at room temperature whereas a single doublet remains at 190°, where conformer populations are more equal.

dynamically controlled methanolysis (see below). Although methoxy groups have a modest axial preference,[5] as discussed above in the 7-methyl-12-methoxy DHP *cis–trans* equilibrations, an axial-isopropyl group should force the methoxy group to be entirely equatorial under equilibrating conditions, in order to avoid severe axial:axial compression. As expected, the single methoxy signal in XII appeared at 217 Hz, a value consistent with equatorial C_7-methoxy groups,[5] and the remaining C_7- and C_{12}-proton signals were also at expected positions (see above). Thus, assuming $K \geq 20$ for XI, the conformational energy for the isopropyl group ($\Delta F^\circ \simeq -1.5$ kcal/mole) is at least 2.5 kcal/mole different from the methyl group in dihydropleiadenes. In contrast, methyl, ethyl, and isopropyl groups on cyclohexane rings all exhibit very similar conformational preferences.[13]

It is now appropriate to speculate on the differences in steric effects of methyl, ethyl, and isopropyl groups located on the 7 position of a dihydropleiadene as compared with a position on a cyclohexane ring. In the latter compounds, only the atom of the substituent next to the cyclohexane ring is of major importance in determining the conformational energy provided the group may be rotated so as to place other atoms away from the ring.[13] Thus, not only do methyl, ethyl, and isopropyl groups have similar conformational energies, but also the groups OH, OAc, OCH_3, OC_2H_5, and OTs (O next to ring) and SH, SCH_3, and SC_6H_5 (S next to ring).[13] However in the 7-alkyl-7,12-dihydropleiadenes, the second atom(s) of the groups appears to be of great importance. Although the methyl group in I prefers the equatorial position, the *β-methyl groups* of the isopropyl group in XI (as well as in the ethyl group of IX) can be seen to be sterically compressed by the adjacent ring protons from both sides when the isopropyl group is equatorial whereas no such compression (H–H > 2.4 A) is evident in the axial conformer, based on examination of models. For the same reason, the ethyl group showed a greater axial preference than methyl. Although other factors may be involved, or even of greater significance in determining the preferred positions of these alkyl groups on the 7,12-dihydropleiadene ring, it is quite clear that conformational energies of substituents on cyclohexanes can be misleading when predicting similar stereochemical preferences in any dissimilar ring system. For example, it is already well known that the "buttressing" effects of groups on the barrier to racemization of optically active biphenyls[14] (a steric bulk effect) do not parallel their apparent steric bulks when occupying an axial position on a cyclohexane ring. In this work, we are mainly stressing the unexpectedly large difference of groups often considered[13–16] to have similar steric bulk.

Experimental Section[17]

7-Methyl-12-(7H)-pleiadenone (II). In a typical experiment[18] 1.193 g (10.6 mmoles) of potassium *t*-butoxide was dissolved in 25 ml of dimethyl sulfoxide and 2.43 g (10.0 mmoles) of 7-(12H)-pleiadenone[4] added, producing an immediate purple coloration. After 10 min of stirring, 2.28 g (16 mmoles) of methyl iodide was slowly added (by syringe through a rubber serum cap into a nitrogen-flushed flask in ice bath), and the reaction mixture stirred at room temperature for 30 min prior to hydrolysis with ice water. The product was extracted into ether, washed with water, dried over sodium sulfate, and concentrated to a pale yellow solid. Recrystallization from ethanol–benzene gave 1.578 g (61%) of II, mp 159–160°; concentration of the filtrate gave further impure II. The carbonyl stretching band in II appeared at 1650 cm^{-1}.

Anal. Calcd for $C_{19}H_{14}O$: C, 88.3; H, 5.5. Found: C, 88.5; H, 5.3.

7-Methyl-7,12-dihydropleiadene-12,12-d_2 (I). A mixture of 320 mg (2.4 mmoles) of aluminum chloride, 87 mg (2.3 mmoles) of lithium aluminum deuteride (Alfa Inorganics), and 453 mg (1.76 mmoles) of 7-methyl-12-(7H)-pleiadenone (II) in 60 ml of ether was stirred under nitrogen for 5 hr, then hydrolyzed with ice water and 10% hydrochloric acid. The ethereal solution of product was washed with water, dried over magnesium sulfate, and evaporated to give a pale yellow oil that crystallized on standing. Recrystallization from ethanol gave 301 mg (64%) of I, mp 104–106° (lit.[18] for 7-methyl DHP: 104–105°) whose nmr spectrum verified the introduction of two deuterium atoms at C_{12}.

***cis*-7-Methyl-12-methoxy-7,12-dihydropleiadene** (VIII). A mixture of 0.456 g (12 mmoles) of lithium aluminum hydride and 1.769 g (6.85 mmoles) of II in 100 ml of 1:1 (v/v) ether–tetrahydrofuran was stirred for 14 hr at room temperature, then hydrolyzed with dilute sodium hydroxide solution. The inorganic salts were removed by filtration and washed with ether. The ether filtrates were combined, washed with water, dried over sodium sulfate, and evaporated to provide the crude alcohol as a solid which was recrystallized from ethanol–water, mp 182–184°, yield 1.2 g.

Anal. Calcd for $C_{19}H_{16}O$: C, 87.7; H, 6.2. Found: C, 87.5; H, 6.3.

A solution of 0.681 g of the above alcohol in 40 ml of methanol, containing a drop of concentrated hydrochloric acid, was refluxed for 12 hr, then reduced in volume and cooled to yield crystals. Several recrystallizations from methanol gave 0.25 g of VII, mp 144–145°, while work-up of the filtrates gave *cis–trans* mixtures having mp 130–145°.

Anal. Calcd for $C_{20}H_{18}O$: C, 87.6; H, 6.6. Found: C, 87.5; H, 6.8.

Infrared and nmr spectra confirmed the structure and stereochemistry of VII (see Discussion).

***cis*-7,12-Dimethyl-7,12-dihydropleiadene** (V).[18] To a solution of 1.66 g (6.44 mmoles) of 7-methyl-12-(7H)-pleiadenone (II) in tetrahedrofuran was added 22 ml of 0.65 *N* methyllithium in ether (14.5 mmoles). After 2 hr under nitrogen, the purple solution was hydrolyzed and worked up as usual. The oily alcohol (based on infrared, which also showed carbonyl due to II and/or conjugate addition product) was heated in formic acid for 2 hr on a steam bath, then poured into ice water, extracted with ether, washed with sodium bicarbonate solution, and dried over sodium sulfate. Concentration of the ether solution afforded a red oil which was chromatographed over alumina with petroleum ether (bp 30–60°) as eluent to give 0.50 g of 7-methyl-12-(7H)-methylenepleiadene, whose structure was verified by infrared and nmr, mp 89–91° (methanol–water).

Anal. Calcd for $C_{20}H_{16}$: C, 93.7; H, 6.3. Found: C, 93.7; H, 6.2.

The ketonic product(s), which was not further investigated, resulted from column elution with 1:1 benzene–petroleum ether.

Catalytic hydrogenation of the methylene compound in a Parr apparatus, using 5% palladium on charcoal and ethanol solvent, resulted in smooth uptake of 1 mole of hydrogen whereupon the solution was filtered and concentrated to provide a virtually quantitative yield of *cis*-7,12-dimethyl-7,12-dihydropleiadene (V),

(13) E. L. Eliel, *Angew. Chem. Intern. Ed. Engl.*, **4**, 765 (1965), and references cited therein.

(14) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 156–165.

(15) N. L. Allinger and L. A. Freiberg, *J. Org. Chem.*, **31**, 894 (1966).

(16) V. Gold, *Progr. Stereochem.*, **3**, 172, 191 (1962).

(17) Melting points were measured in a "Mel-temp" capillary tube apparatus and are uncorrected. Infrared spectra were obtained on a Beckmann IR-5A spectrometer, using Nujol mulls or neat films between sodium chloride plates, unless otherwise noted. Nuclear magnetic resonance spectra were obtained on a Varian A-60 spectrometer equipped with a variable-temperature probe and a Model A-6040 temperature controller (calibrated with methanol or ethylene glycol), using chloroform-*d* as solvent, except where noted, and tetramethylsilane as internal standard. Column chromatography was performed using Merck neutral alumina.

(18) J. F. Bieron, Ph.D. Dissertation, State University of New York, Buffalo, N. Y., 1965.

mp 168–169° (methanol–acetone), whose confirmatory nmr spectrum is mentioned in the Discussion.

Anal. Calcd for $C_{20}H_{18}$: C, 93.0; H, 7.0. Found: C, 92.8; H, 7.0.

***trans*-7,12-Dimethyl-7,12-dihydropleiadene (VI).** A dark purple color appeared when 1.272 g (11.35 mmoles) of potassium *t*-butoxide was added to a solution of 1.508 g (6.2 mmoles) of 7-methyl-7,12-dihydropleiadene in 50 ml of dimethyl sulfoxide. The solution was stirred under nitrogen for 30 min and then treated with 2.28 g (16.1 mmoles) of methyl iodide (*via* syringe), which produced instant decoloration. After an additional 0.5 hr, the mixture was hydrolyzed with ice water and worked up conventionally. Chromatography of the crude product on alumina led to rapid elution [with petroleum ether (bp 30–60°)] of a *cis–trans* mixture of V and VI, mp 120–150° (methanol–water), whose nmr spectrum showed characteristic methine resonances for both V and VI (see Discussion).

Anal. Calcd for $C_{18}H_{20}$: C, 93.0; H, 7.0. Found: C, 93.0; H, 7.0.

Fractional recrystallization of such a *cis–trans* mixture from 95% ethanol gave a first crop rich in V, but subsequent crops rich in VI ultimately gave pure VI, mp 81–84° (from ethanol), whose nmr spectrum verified the structure and stereochemistry.

Anal. Found: C, 92.7; H, 7.0.

7-(Ethyl-α,α-d_2)-7,12-dihydropleiadene (X). 1-Benzyl-8-naphthoyl chloride was prepared by heating 8.52 g (31 mmoles) of 1-benzyl-8-naphthoic acid[4] with excess thionyl chloride on a steam bath for 3 hr, then removing unreacted thionyl chloride *in vacuo*. The residue was dissolved in 50 ml of ether in a three-necked flask equipped with condenser, nitrogen inlet, and dropping funnel. A solution of diethylcadmium (prepared by adding 25 mmoles of cadmium chloride to a Grignard solution made from 46 mmoles of ethyl bromide and 0.058 g-atom of magnesium in 100 ml of ether at 0°) was then added dropwise with stirring during 2 hr. Hydrolysis with dilute sulfuric acid and work-up in the usual manner gave a brown oily residue that was chromatographed over alumina. Elution with 2:1 petroleum ether (bp 30–60°):benzene provided 2.96 g (33%) of 1-benzyl-8-propionylnaphthalene as a colorless oil, $\lambda_{C=O}$ 5.95 μ, whose nmr spectrum showed a two-proton singlet at 4.2 ppm (benzylic), a methyl triplet ($J \cong 7.5$ Hz) at 1.04 ppm, and a methylene quartet ($J \cong 7.5$ Hz) at 2.45 ppm in addition to the complex aromatic absorption. Subsequent chromatography fractions provided small quantities of 8-phenylacenaphthen-7-one, mp 118–119° (lit.[19] mp 115–116.5°), as white crystals (from ethanol), which increased in yield when the inverse addition of cadmium reagent was not used.

The methylene protons adjacent to the carbonyl group of 1-benzyl-8-propionylnaphthalene were replaced by deuterium by stirring 1.4 g of ketone in 10 ml of deuterium oxide and 10 ml of dioxane containing some sodium deuteroxide for 3 days under nitrogen. The product, isolated by ether extraction and work-up, showed the methyl signal as a clean *singlet* at 1.04 ppm, indicating deuteration of the adjacent methylene group.

Lithium aluminum hydride reduction of the deuterated ketone in ether was carried out in a typical manner, providing quantitative conversion to a pale yellow oily carbinol, showing O–H absorption at 2.75 μ and no carbonyl absorption (CS_2 solution).

The above carbinol was dissolved in 30 ml of 97% formic acid containing a small amount of *p*-toluenesulfonic acid and heated on the steam bath for 5 hr. The cooled solution was diluted with water and extracted with ether. After the ether extract was washed with water and 10% sodium carbonate and dried over magnesium sulfate, it was evaporated and the residue chromatographed over alumina. The product X eluted with 2:1 petroleum ether (bp 30–60°):ether, was obtained as a colorless oil, whose nmr spectrum is given in the Discussion. The yield of X from deuterated ketone was 52%.

Anal. Calcd for $C_{20}H_{16}D_2$: C, 92.3; H, 7.7. Found: C, 92.8; H, 7.2.

7-(Ethyl-α,α-d_2)-7,12-dihydropleiadene-12,12-d_2 (IX). A solution of 20 ml of 90% acetic acid, 175 mg (1.75 mmoles) of chromium trioxide, and 2.96 mg (1.14 mmoles) of X were refluxed for 1.5 hr and then poured into ice water and the product extracted into ether, washed with 10% sodium carbonate, and dried over magnesium sulfate. Evaporation of solvent and alumina chromatography afforded 213 mg (65%) of 7-(ethyl-α,α-d_2)-12-(7H)-pleiadenone (eluted with 1:1 petroleum ether (bp 30–60°):benzene), showing a carbonyl band at 6.10 μ and having mp 150–151° (from ethanol).

Anal. Calcd for $C_{20}H_{14}D_2O$: C, 87.6; H, 6.6. Found: C, 8.77; H, 5.9.

The above ketone (93 mg, 0.34 mmole) was reduced in ether by 61 mg (0.46 mmole) of aluminum chloride and 18 mg (0.44 mmole) of lithium aluminum deuteride. Hydrolysis and work-up in the usual fashion (above) gave the tetradeuterated hydrocarbon IX in nearly quantitative yield. The structure was confirmed by nmr (see Discussion).

7-Isopropyl-7,12-dihydropleiadene (XI). The dark red lithium salt of 7,12-dihydropleiadene[4] (2.72 g, 12 mmoles) was formed in ether by addition of 6.0 ml of 2.5 *N* (15 mmoles, slight excess) *n*-butyllithium in hexane. Upon cooling to −40° (Dry Ice–acetone bath) 3.85 g (18 mmoles) of isopropyl *p*-toluenesulfonate in 15 ml of ether was gradually added by means of a syringe (1 hr). After the solution was stirred at room temperature for 4 hr, hydrolysis and work-up were carried out as usual. The mixture of XI and unreacted 7,12-dihydropleiadene was treated with a hot methanol solution of 2,4,7-trinitrofluorenone (TNF) whereupon the orange complex of TNF with *starting material only* crystallized out. Filtration and concentration of the filtrate produced an oily residue which was chromatographed on alumina to give XI as a colorless oil (0.58 g, 18%). The nmr spectrum is discussed in the text.

Anal. Calcd for $C_{21}H_{20}$: C, 92.6; H, 7.4. Found: C, 92.6; H, 7.5.

Higher yields of XI (50–60%) were ultimately obtained; some *trans*-7,12-diisopropyl DHP could be isolated in some runs also.

7-Isopropyl-12-methoxy-7,12-dihydropleiadene (XII). 12-Isopropyl-7-(12H)-pleiadenone (0.370 g, 1.3 mmoles) was obtained from the chromium trioxide oxidation of XI using the same procedure as with X. The ketone showed carbonyl absorption at 1645 cm^{-1} and strong bands at 1300 and 758 cm^{-1} and had mp 188–190°.

Anal. Calcd for $C_{21}H_{18}O$: C, 88.1; H, 6.3. Found: C, 88.5; H, 6.5.

The above ketone, dissolved in tetrahydrofuran, was added dropwise to a solution of 0.042 g (1.0 mmole) of lithium aluminum hydride dissolved in 15 ml of anhydrous THF. The reaction mixture was then refluxed for 30 min before being hydrolyzed with 10% aqueous hydrochloric acid. A colorless oil (0.320 g, 1.1 mmoles) was obtained after the usual work-up procedure and flash evaporization. An infrared spectrum of the crude alcohol showed bands at 3420, 1063, and 765 cm^{-1}. The crude 7-isopropyl-12-hydroxy-7,12-dihydropleiadene was then dissolved in 25 ml of anhydrous methanol and a catalytic amount of sulfuric acid added. The mixture was refluxed for 5 min, poured onto ice, and extracted with ether. The combined organic layers were washed with sodium bicarbonate, dried over anhydrous magnesium sulfate, and flash evaporated to give 0.295 g (92%) of an oil which crystallized on standing, mp 112–114° (from methanol). The infrared spectrum of XII showed strong bands at 1120, 1090, and 773 cm^{-1}.

Anal. Calcd for $C_{22}H_{22}O$: C, 87.5; H, 7.3. Found: C, 87.5; H, 7.8.

Equilibrations of V and VI. Samples (50–100 mg) of V and VI (taken separately) were dissolved in 5 ml of dimethyl sulfoxide in a 10-ml ampoule, and a small amount of potassium *t*-butoxide was added. The ampoules were quickly sealed and placed in oil baths of the desired temperature or kept at room temperature for several hours or longer. The ampoules were then cooled and broken under ice water. After a conventional work-up, the oily mixtures of V and VI were dissolved in chloroform-*d* and analyzed by nmr spectroscopy, using integrated areas of the methine signals of V at 325 Hz and VI at 290 Hz (see Discussion).

Equilibration of *cis*-7-Methyl-12-methoxy-7,12-dihydropleiadene (VII). Compound VII (150 mg) in 15 ml of methanol containing two drops of concentrated hydrochloric acid was refluxed (~65°) for 24 hr, then worked up by quenching in ice water, extraction into ether, bicarbonate washing, drying over magnesium sulfate, and concentration. The resultant oil was taken up in a minimum amount of chloroform-*d* and the isomer mixture identified by nmr and peak areas integrated (see Discussion).

Determination of Conformational Equilibria by Variable-Temperature Nmr Spectroscopy. Low-temperature measurements[1,4,5]

(19) W. A. Bonner and C. J. Collins, *J. Am. Chem. Soc.*, 75, 2308 (1953).

were calibrated by using methanol, and integration of peak areas due to individual conformers in I, IX, X, and VII was carried out at least four times at each temperature. Equilibrium constants reported are average values of four to six determinations.

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Analysis of the Nuclear Magnetic Resonance Spectra of 2-Substituted 1,3-Oxathiolanes. Determination of the Conformation of the Oxathiolane Ring System and the Conformational Free Energy Values for the 2-Alkyl Substituents

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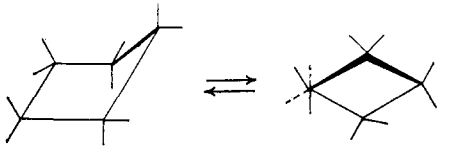
Abstract: The hydrogen magnetic resonance spectra of a number of 2-mono- and 2,2-disubstituted 1,3-oxathiolanes were analyzed by computer techniques to determine the chemical shifts and coupling constants of the C_4 and C_5 hydrogens. The nmr data were employed to predict the conformation of the oxathiolane ring system, to calculate the long-range shielding effects of alkyl and aryl groups in the 2 position, and to calculate the conformational free energy values for substituents in the 2 position. It is concluded that the conformation of the oxathiolane ring system most compatible with the nmr data is a slightly distorted envelope conformation with the oxygen atom at the "flap" position. Pseudo-rotation does not appear to be present in this ring system. The following $-\Delta G$ values (kcal/mole) were calculated for substituents in the 2 position: methyl, 1.13; ethyl, 1.16; isopropyl, 2.01; and phenyl, 1.87. It is also concluded that axial and pseudo-axial ring hydrogens in five-membered ring systems appear at higher field, except in cases involving long-range shielding effects, and that the chemical shifts of ring hydrogens are a better indicator of conformation than are just coupling constants. A review of the few examples of conformational analysis of heterocyclic five-membered ring systems is made with suggested alternatives for the conformations of the hydroxyprolines.

The study of the conformation of substituted five-membered rings is an area in which relatively little research has been devoted compared to the vast amount of work expended on cyclohexyl systems.[2]

The five-membered ring has been described as existing in a puckered conformation,[3] the puckering moving freely about the ring (pseudo-rotation). Two puckered forms may be written for cyclopentane, the C_s[3] or envelope[4] form **1a** and C_2[3] or half-chair[4] form **1b**, the interconversion apparently involving no substantial change in potential energy.[5] In monosubstituted



1a **1b**

cyclopentanes, the envelope form would appear to be favored in which the substituent is in the pseudo-equatorial position of the "flap" carbon. This would tend to relieve eclipsing between the substituent and the hydrogens on the adjacent carbon atoms. Calculation indicates this conformation to be more stable by 0.9 kcal/mole[6] whereas a value of 0.75 kcal/mole is suggested by entropy measurements.[7]

The determination of the conformation of substituted cyclopentanes by the general methods used in dealing with cyclohexyl systems (infrared, nmr, and chemical methods) is hindered by the numerous possible conformations available with relatively low energy barriers to interconversion. Further difficulties arise in the analysis of the spectral and chemical data in terms of the conformation of the ring, the orientation of the substituent, and the various ring hydrogens, and, in the use of nmr techniques, the dihedral angular relationships between vicinal pairs of closely similar hydrogens in the rapidly interconverting systems.

These problems partially disappear in the rigid polycyclic molecules and in more highly substituted systems. Brutcher and Leopold[8] have assigned conformations of the D ring in a number of steroids by X-ray techniques. In more highly substituted systems the number

(1) (a) National Science Foundation Predoctoral Fellow, 1963–1965, Lubrizol Fellow, 1965–1966; (b) McKenna Fellow, 1964–1966.

(2) (a) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962; (b) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965.

(3) J. E. Kilpatrick, K. S. Pitzer, and R. Spitzer, *J. Am. Chem. Soc.*, **69**, 2483 (1947).

(4) F. V. Brutchner, Jr., T. Roberts, S. J. Barr, and N. Pearson, *ibid.*, **81**, 4915 (1959).

(5) Reference 2a, p 249.

(6) K. S. Pitzer and W. E. Donath, *J. Am. Chem. Soc.*, **81**, 3213 (1959); *cf.* J. P. McCullough, R. E. Pennington, J. C. Smith, I. A. Hossenlopp, and G. Waddington, *ibid.*, **81**, 5880 (1959).

(7) J. E. Kilpatrick, H. G. Werner, C. W. Beckett, K. S. Pitzer, and F. D. Rossini, *J. Res. Natl. Bur. Std.*, **39**, 523 (1947).

(8) F. V. Brutcher and E. J. Leopold, *J. Am. Chem. Soc.*, **88**, 3156 (1966).