Nuclear Magnetic Resonance Line Widths of Angular Methyl Groups in Decalins, Steroids, and N-Methylquinolizidinium Ions. Determination of Ring Fusion Stereochemistry

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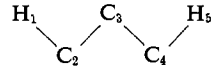
Abstract: Careful measurements of the n.m.r. line widths at half-height ($W_{h/2}$) of angular methyl groups in some 40 *cis*- and *trans*-decalins and -steroids indicate that an unequivocal assignment of the stereochemistry of the A,B-ring juncture in both types of compounds can be made. The peak width at half-height for the *trans*-fused isomer is always larger than that for the *cis*-fused isomer. This is true also for the heterocyclic *cis*- and *trans*-N-methylquinolizidinium ions. For carbocyclic compounds having undistorted chair–chair conformations of their six-membered rings, an *absolute* line width measurement serves to distinguish *cis*- from *trans*-fused compounds since all *cis*-fused compounds have smaller line widths than all *trans*-fused compounds. The effect of various substituents on $W_{h/2}$ and the splitting of the angular methyl peak is discussed.

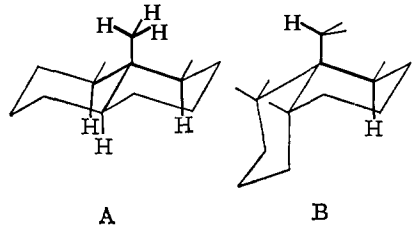
The determination of ring fusion stereochemistry in angularly methylated six-membered ring compounds is not an easy task by either chemical or physical methods. N.m.r. spectroscopy may, however, greatly aid in the solution of this problem, for the n.m.r. peak width at half-height ($W_{h/2}$) of the angular methyl group is strongly dependent on the ring fusion stereochemistry. Careful measurements of $W_{h/2}$ in some 40 *cis* and *trans* angularly methylated compounds indicate that $W_{h/2}$ for a *trans* compound is always greater than for the corresponding *cis* isomer. This generalization is found to hold for a wide variety of decalin and steroid derivatives. It is true even when the methyl group is bound to positively charged nitrogen in the heterocyclic *cis*- and *trans*-N-methylquinolizidinium ions.

The first indication that angular methyl groups were stereospecifically coupled to certain protons on the steroid nucleus came when Bhacca and Williams[2] showed by double resonance experiments that the C-18 doublet reported[3] for an 11-keto steroid was due to coupling with the 12α proton. They subsequently showed this to be true for the C-19 methyl in 2-keto steroids (in which coupling takes place to the 1α proton) as well as other 11-keto steroids,[4] in keeping with observations made by Shoppee, *et al.*[5] This stereospecific coupling of a tertiary methyl group with protons four bonds away has very recently been observed in geminal methyl groups in six-membered rings, a *cis–trans* pair of hydrindanones, and some decalin derivatives by Robinson[6] who has pointed out that line widths would be useful in determining the stereochemistry of ring fusion.

There are good theoretical reasons why the peak width of a *trans*-fused compound should be greater than that of the corresponding *cis* isomer. Valence bond calculations[7] seem to indicate that the long-range coupling constant (at least the "indirect, through-the-bond" contribution) for two protons separated by four saturated bonds is dependent on the dihedral angle between the coupling protons. The calculated results correlate a wide variety of long-range coupling constant data.[8] In particular, theory indicates that the largest long-range couplings should be found when the system adopts the extended zigzag (the coplanar "M" or "W") conformation which has been recognized for some time[9-11] as the most favorable conformation for long-range coupling.



For a freely rotating methyl group (which would correspond to rotation about the C-3–C-4 bond above) the value of +0.81 c.p.s. is obtained[7] for the *trans* ($\phi_1' = 180°$)[12] conformation. In a *trans*-fused six-membered ring compound three axial protons can adopt this conformation with respect to the methyl group (A). In *cis*-fused compounds (B) only one ring



A B

proton can be *trans* and coplanar to the methyl group. The other four protons in B that are located four bonds

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(2) D. H. Williams and N. S. Bhacca, *J. Am. Chem. Soc.*, **85**, 2861 (1963).

(3) H. Wehrli, M. S. Heller, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **44**, 2162 (1961).

(4) N. S. Bhacca, J. E. Gurst, and D. H. Williams, *J. Am. Chem. Soc.*, **87**, 302 (1965).

(5) C. W. Shoppee, F. P. Johnson, R. Lack, and S. Sternhell, *Tetrahedron Letters*, 2319 (1964).

(6) M. J. T. Robinson, *ibid.*, 1685 (1965).

(7) M. Barfield, *J. Chem. Phys.*, **41**, 3825 (1964).

(8) S. Sternhell, *Rev. Pure Appl. Chem.*, **14**, 15 (1964).

(9) J. Meinwald and A. Lewis, *J. Am. Chem. Soc.*, **83**, 2769 (1961).

(10) K. B. Wiberg, B. R. Lowry, and B. J. Nist, *ibid.*, **84**, 1594 (1962).

(11) A. Rassat, C. W. Jefford, J. M. Lehn, and B. Waegell, *Tetrahedron Letters*, 233 (1964).

(12) The dihedral angle ϕ_1' is defined as the angle between the plane described by H-1, C-2, and C-3, and the plane described by C-2, C-3, and C-4.

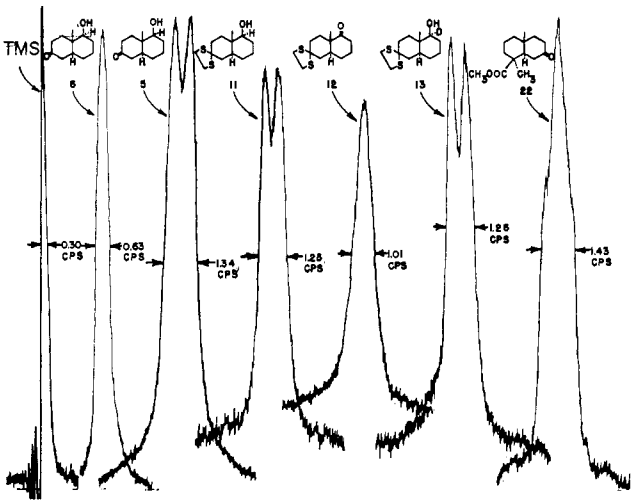


Figure 1. N.m.r. spectra of angular methyl peaks under high-resolution conditions. The same horizontal scale is employed for all peaks.

from the methyl protons are disposed at $\phi_1' = 60°$ to the angular methyl. This 60° dihedral angle would be expected to give a coupling only one-fourth as large, $J = +0.20$ c.p.s.[13] Thus one would predict, as has been found, that *trans*-fused compounds should have a greater $W_{h/2}$ than their *cis* isomers.

Results and Discussion

All of the peak widths measured in this work lie in the range 0.25–1.50 c.p.s. which puts these measurements right at the limit of the resolution of an n.m.r. spectrometer. We sought to ascertain at the outset the reproducibility and reliability of these measurements in terms of spectrometer resolution, and differing samples, sample tubes, spectrometer probes, and operators. In Table I are listed the line widths with their average deviations for five pairs of *cis*- and *trans*-decalin isomers. As detailed in the Experimental Section each $W_{h/2}$ is the average of from four to twelve measurements which were made by two different operators on freshly prepared (but not degassed) samples at various times during the last year. Thus the average deviations in $W_{h/2}$ reflect variations in resolution caused by different batches of solvent, different sample tubes, operators, two different probes, and the normal day-to-day changes in instrument operating characteristics.

Each time a line width was measured the $W_{h/2}$ of the tetramethylsilane (TMS) reference was measured. The average TMS $W_{h/2}$ for the measurements reported in Table I is 0.37 ± 0.04 c.p.s. Measurements on four of the decalins employed here have been reported in which the TMS $W_{h/2}$ varied from 0.40 to 1.0 c.p.s.[6] Because of wide variations in the resolution of his spectrometer, Robinson employed the useful expedient of reporting the difference between the line widths for a methyl group and for TMS ($\Delta W_{h/2}$) which was found to be constant for a given methyl peak.[6] It is gratifying that the values of $\Delta W_{h/2}$ obtained independently in two different laboratories are the same within experimental error for the first four compounds in Table I.

(13) It should be borne in mind that a number of assumptions have been made in the theoretical calculations[7] which result in these coupling constants. They are quoted here merely to indicate the approximate size of a long-range coupling constant expected for a given conformation.

10-Methyldecalins. In Figure 1 are shown typical methyl group spectra for some of the decalins and a typical TMS line for comparison. The angular methyl peak for **6** has the shape typical of all those peaks referred to as "singlets" while **5** is a typical "doublet." The difference in the line width at half-height, $W_{h/2}$, is immediately obvious for this pair of isomers.

With the approximate limits of error of these measurements in mind, an examination of the data in Table I reveals that in a given *pair* of isomers the one having the *trans*-ring juncture *always* has the greater line width, confirming the prediction one would make on the basis of theory[7] and the observations of Robinson.[6] Thus it is easy to distinguish *between* isomers if both are available. Often, however, only one of the two possible isomers is obtainable and a more useful criterion to apply would be the absolute value of $W_{h/2}$ or $\Delta W_{h/2}$. It will be noted in Table I that the average $\Delta W_{h/2}$ for the five *trans*-decalin isomers is 0.80 ± 0.20 c.p.s.,[14] and that the average $\Delta W_{h/2}$ for the five *cis*-decalin isomers is 0.25 ± 0.11 c.p.s. It is possible to distinguish between the *cis*- and *trans*-decalins reported in Table I by an *absolute* measurement of $W_{h/2}$ since all of the $W_{h/2}$ for *cis*-decalins are smaller than all the $W_{h/2}$ for the *trans*-decalins. An absolute line-width measurement can be applied to ascertain *cis* or *trans* configuration in all of the compounds reported in this paper which are in undistorted, chair–chair conformations. Further data are necessary before one can definitely assert that an absolute line-width measurement can be used for determination of ring fusion stereochemistry; however, our data indicate that a knowledgeable guess can be made on this basis.

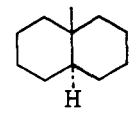
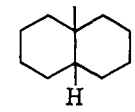
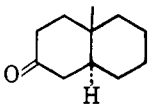
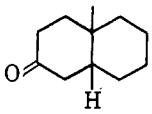
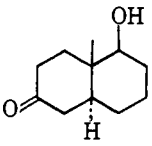
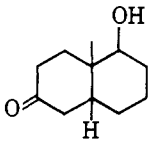
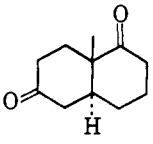
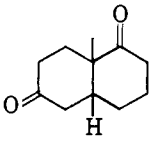
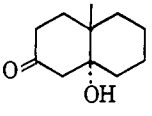
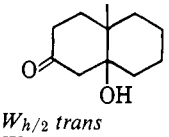
We have seen above that in a *trans*-fused decalin more protons can have the extended zigzag relationship to the methyl group than in *cis*-decalins; however, there is not a good correlation between the number of protons in the coplanar zigzag conformation and the line width. When only one proton is in this position, $\Delta W_{h/2}$ is 0.25 ± 0.11 c.p.s. (the *cis*-decalins) but compounds **7** and **9** with two protons so situated have $\Delta W_{h/2}$ of 0.53 and 1.01 c.p.s. while compounds **1, 3,** and **5** with three protons so placed have $\Delta W_{h/2}$ of 0.52, 1.01, and 0.91 c.p.s. In short the differing pattern of substitution in the *trans*-decalins has a greater effect on line widths than the number of protons in the extended zigzag conformation.

Complete elucidation of all the effects that cause variations in line width would necessitate much experimentation. In compounds **1–4** there are, for instance, five protons that are within four bonds of the three methyl protons. When one considers the variety of effects (*e.g.*, conformational mobility of the ring system, free or hindered rotation of the angular methyl group, and substituent effects in this eight-spin system), it is not surprising that inexplicable differences in $W_{h/2}$ occur.

Angular Methyl Doublets. One aspect of the spectra of these and similar compounds that has occupied our attention, as well as that of many other investigators[2,4–6] is the doublet character of certain of the methyl peaks. Without exception all methyl peak doublets reported for steroids have involved 11-keto or 2-keto

(14) $\Delta W_{h/2}$ for the 12 *trans*-decalin derivatives in Table II is 0.96 ± 0.09 c.p.s.; all 17 *trans*-decalins have $\Delta W_{h/2} = 0.91 \pm 0.13$ c.p.s.

Table I. Line Widths at Half-Height for Angular Methyl Groups (15% w./v. in $CDCl_3$)

		Angular methyl $W_{h/2}$, c.p.s.	TMS $W_{h/2}$, c.p.s.	$\Delta W_{h/2}$,[a] c.p.s.	Coplanar protons[b]	Methyl peak multiplicity[c]
1		0.90 ± 0.08	0.38 ± 0.05	0.52 ± 0.13 (0.65 ± 0.05)	3	s
2		0.39 ± 0.10	0.33 ± 0.09	0.06 ± 0.19 (0.15 ± 0.05)	1	s
3		1.36 ± 0.27	0.35 ± 0.08	1.01 ± 0.35 (1.05 ± 0.05)	3	s
4		0.84 ± 0.01	0.43 ± 0.02	0.41 ± 0.03 (0.35 ± 0.05)[d] (0.40 ± 0.05)[d]	1	s
5		1.34 ± 0.12	0.43 ± 0.04	0.91 ± 0.16	3	d (0.51 ± 0.01)
6		0.63 ± 0.04	0.27 ± 0.01	0.36 ± 0.05	1	s
7		0.90 ± 0.08	0.37 ± 0.01	0.53 ± 0.09	2	d (0.41 ± 0.01)
8		0.64 ± 0.04	0.41 ± 0.07	0.23 ± 0.11	1	s
9		1.40 ± 0.05	0.39 ± 0.07	1.01 ± 0.12	2	s
10		0.51 ± 0.03	0.34 ± 0.07	0.17 ± 0.10	1	s
Av. $W_{h/2}$ *trans*		1.18 ± 0.22	Av. 0.37 ± 0.04	Av. $\Delta W_{h/2}$ *trans* 0.80 ± 0.20		
Av. $W_{h/2}$ *cis*		0.60 ± 0.12		Av. $\Delta W_{h/2}$ *cis* 0.25 ± 0.11		

[a] $\Delta W_{h/2}$ = angular methyl $W_{h/2}$ − TMS $W_{h/2}$. Values in parentheses are taken from Table I of ref. 6. [b] The number of ring protons that can adopt the coplanar zigzag conformation with angular methyl protons. [c] Single peak (s) or doublet (d). The spacing in c.p.s. of the doublet peaks is given in parentheses. [d] Robinson[6] reports the smaller value in his Table I and the larger value in Table III.

steroids in which it has been shown by specific deuterium labeling,[4] deuterium exchange of all protons adjacent to the carbonyl group,[4,5] and double resonance experiments[2,4] that most of the splitting of the C-19 methyl peak is due to stereospecific coupling to the 1α proton in 2-keto steroids and most of the splitting of the C-18 methyl is due to the 12α proton in 11-keto steroids. However, some steroids with carbonyls at C-2 and/or C-11 do not show split methyl peaks.[4] Similar splitting of the methyl peak into a doublet has been observed in the analogous 9-methyl-*cis*-2-decalone and two of its derivatives as well as 1,3-dibenzylidene-10β-methyl-*cis*-2-decalone.[6,15] Robinson[6] postulates that

(15) This part of Robinson's communication[6] is difficult to read because the conformational drawing labeled "D" should be labeled "E" and *vice versa*.

Table II. Line Widths at Half-Height for Angular Methyl Protons

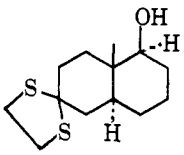
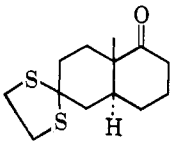
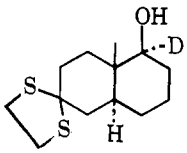
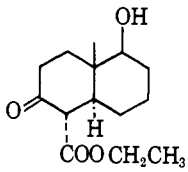
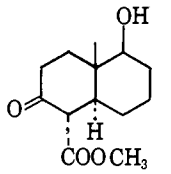
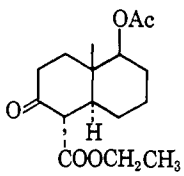
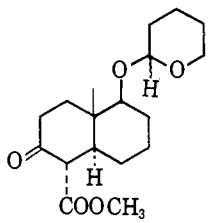
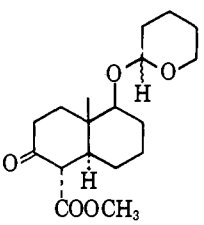
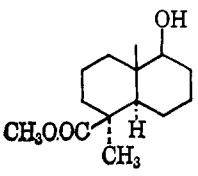
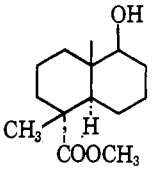
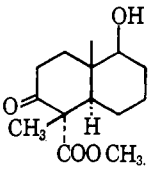
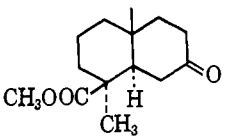
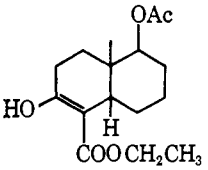
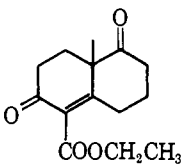
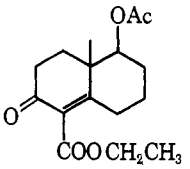
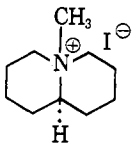
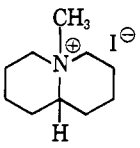
		Angular methyl $W_{h/2}$, c.p.s.	TMS $W_{h/2}$, c.p.s.	$\Delta W_{h/2}$,[a] c.p.s.	Angular methyl peak multiplicity and splitting[b]	Chemical shift[c]	Solvent	Other methyl groups $W_{h/2}$, c.p.s.	Other methyl groups Chem. shift[c]
11		1.27	0.42	0.85	d (0.57)	50.5	$CDCl_3$		
12		1.01	0.38	0.63	s				
13		1.25	0.34	0.91	d (0.64)	50.5	$CDCl_3$		
14		1.40	0.41	0.99	d (0.57)	62.5	CS_2		
15		1.27	0.30	0.97	d (0.60)	60.0	CS_2	Ester 0.41	217.5
16		1.45	0.40	1.05	d (0.52)	65.2	CS_2		
17		1.32	0.33	0.99	d (0.59)	61.5	CS_2	Ester 0.45	
18		1.41	0.41	1.00	d (0.45)	63.3	CS_2	Ester 0.53	217.6
19		1.51	0.52	0.99	d (0.55)	35.0	CS_2	C-1 0.94 Ester 0.57	65.5 212.2

Table II (*Continued*)

		Angular methyl $W_{h/2}$, c.p.s.	TMS $W_{h/2}$, c.p.s.	$\Delta W_{h/2}$,[a] c.p.s.	Angular methyl peak multiplicity and splitting[b]	Chemical shift[c]	Solvent	—Other methyl groups— $W_{h/2}$, c.p.s.	Chem. shift[c]
20		1.39	0.52	0.87	d (0.48)	49.1	CS_2	C-1 0.80 Ester 0.56	64.8 211.4
21		1.46	0.37	1.11	d (0.67)	63.3	CS_2	C-1 0.54 Ester 0.48	78.3 218.9
22		1.43	0.30	1.13	s	53.3	CS_2	C-1 0.70 Ester 0.40	65.6 214.7
23		1.29	0.30	0.99	s	50.5	CS_2	OAc 0.33	123.7
24		0.71	0.35	0.36	s	89.5	CS_2		
25		0.89	0.33	0.56	s		CS_2	OAc 0.36	
26		1.53				*Ca.* 171	D_2O		
27		0.96				*Ca.* 183	D_2O		

[a] $\Delta W_{h/2}$ = angular methyl $W_{h/2}$ − TMS $W_{h/2}$. [b] s = singlet; d = doublet. The separation of the peaks, in c.p.s., for the doublet is given in parentheses. [c] Chemical shift in c.p.s. downfield from TMS at 60 Mc.

"the relatively large (0.59–0.94 c.p.s.) splittings may be caused by the trigonal carbon atom C-2 or C-3 modifying the axial 1α- or 4α-carbon–hydrogen orbital by a hyperconjugative type of effect."

In the present work we have observed and investigated splitting of the methyl peak in decalin derivatives in which the third carbon atom away from the carbon bearing the methyl group is *not* trigonal. In fact the splittings in decalin derivatives **11** and **13** having no trigonal carbon atoms are comparable to those reported by Robinson[6] for compounds having carbonyl groups.

In Table I it will be noted that two compounds, **5**

Table III. Line Widths at Half-Height for Angular Methyl Protons in Steroids

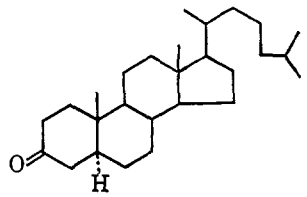
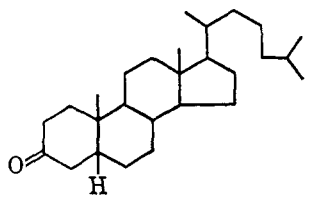
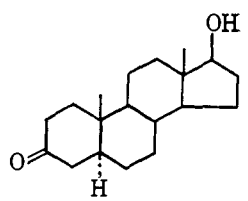
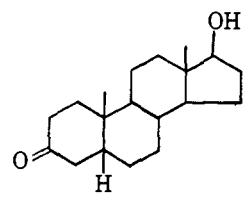
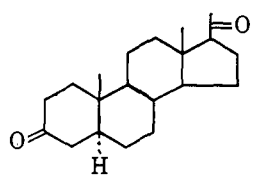
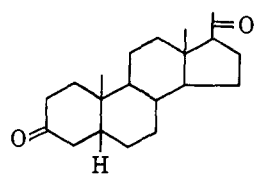
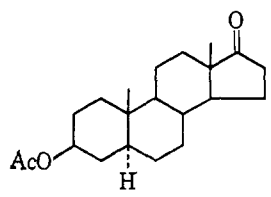
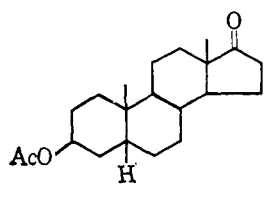
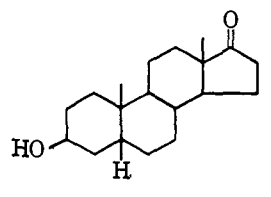
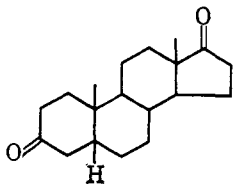
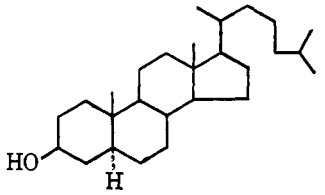
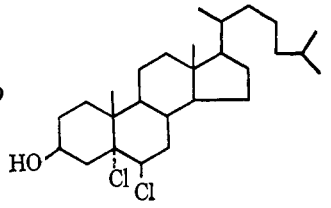
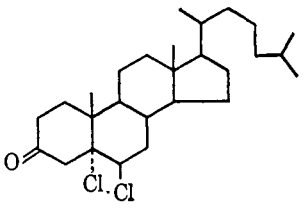
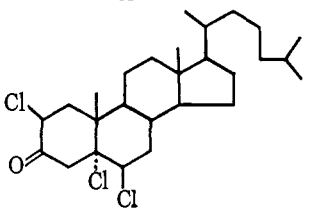
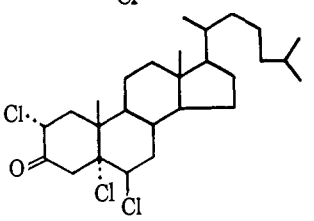
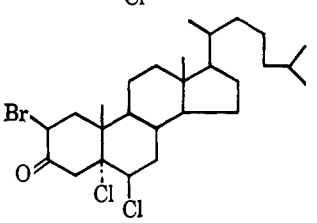
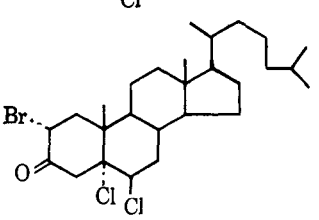
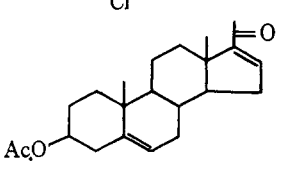
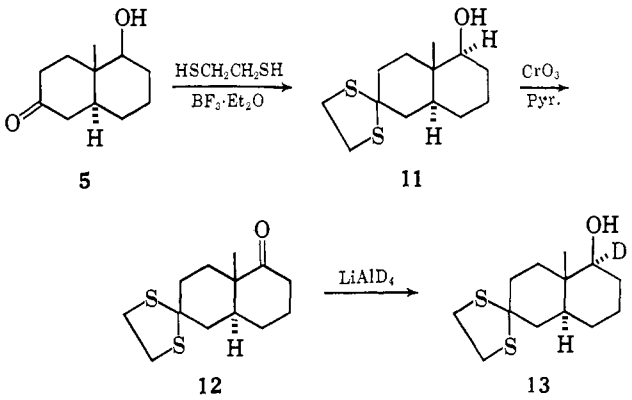
		$W_{h/2}$, c.p.s.			$\Delta W_{h/2}$, c.p.s.		
		C-19	C-18	TMS	C-19	C-18	Solvent
28		1.25	1.06	0.43	0.82	0.63	CS_2
29		0.72	0.91	0.45	0.27	0.46	$CDCl_3$
30		1.25	1.05	0.38	0.87	0.67	CS_2
31		0.93	1.07	0.40	0.53	0.67	CS_2
32		1.30 d (0.46)	1.10	0.42	0.88	0.68	$CDCl_3$
33		0.78	1.09	0.42	0.36	0.67	$CDCl_3$
34		1.13 d (0.37)	0.87	0.33	0.80	0.54	CS_2
35		0.63	0.64	0.24	0.39	0.40	$CDCl_3$
36		0.64	0.80	0.34	0.30	0.46	$CDCl_2$

Table III (*Continued*)

		$W_{h/2}$, c.p.s.			$\Delta W_{h/2}$, c.p.s.		
		C-19	C-18	TMS	C-19	C-18	Solvent
37		0.80	0.95	0.37	0.43	0.58	$CDCl_3$
38		1.22	1.28	0.41	0.81	0.87	CS_2
39		1.40	1.17	0.48	0.92	0.69	CS_2
40		1.23	1.09	0.54	0.69	0.55	CS_2
41		1.68 d (0.50)	0.98	0.43	1.25	0.55	CS_2
42		1.39	1.07	0.45	0.94	0.62	CS_2
43		1.63 d (0.50)	1.04	0.54	1.09	0.50	CS_2
44		1.27	1.07	0.47	0.80	0.60	CS_2
45		1.30	0.90	0.42	0.88	0.48	$CDCl_3$

and **7**, exhibit split methyl peaks. Although compounds **1**, **3**, and **9** have somewhat broad peaks, there was no trace of splitting observed in these compounds. We prepared the thioketal derivative (**11**) of compound **5**, oxidized the thioketal alcohol **11** to the ketone **12**, and reduced this with lithium aluminum deuteride to the deuterio alcohol **13**. In Figure 1 are presented the angular methyl peaks of these four compounds. It



will be noted that the broad doublet for compound **5** becomes narrower and better resolved in the thioketal **11**, then paradoxically the ketone **12** has just one peak (whereas the diketone **7** displays a doublet). Finally, reduction to deuterio alcohol **13** causes reappearance of an angular methyl doublet; the effect of adding deuterium has not been to collapse the doublet observed in **11**, but instead to make it somewhat sharper. The only firm conclusion we can reach from these experiments is that the principal doublet splitting is *not* due to coupling with the proton at C-5 (the hydroxyl-bearing carbon atom). It is probably due to coupling with an axial (α) proton on C-4 and/or on C-9. It is apparent from this series of experiments that it would be difficult to predict, *a priori*, just what type of substitution will cause a methyl peak to be split.

In Table II are presented the line widths for a number of other decalin derivatives. It will be noted that all of those compounds (**13–21**) having a hydroxyl, an acetate, or tetrahydropyranyl ether group at C-5 and in the normal chair–chair conformation exhibit split methyl peaks. The presence or absence of other substituents on the ring system seems to have little effect on this splitting.

The presence of a carbonyl group at C-2 may have some influence on the angular methyl splitting in the decalins. This is seen by comparing **21** which has a broad ($\Delta W_{h/2}$ = 1.11 c.p.s.), well-resolved methyl peak (splitting 0.67 c.p.s.) with **20** which lacks the carbonyl group at C-2. The latter compound has a much narrower methyl peak ($\Delta W_{h/2}$ = 0.87 c.p.s.) and a smaller, poorly resolved splitting (0.48 c.p.s.). This may be a manifestation of the virtual coupling phenomenon discussed by Robinson.[6]

Removal of the C-5 oxygen function (**22**) also removes the doublet splitting of the methyl peak (see Figure 1), yet the peak width is still quite large ($W_{h/2}$ 1.43 c.p.s.). The spectrometer resolution was exceptionally good (TMS $W_{h/2}$ 0.30 c.p.s.) when the spectrum of **22** was determined. It will be noted in Figure 1 that this peak exhibits unmistakable traces of triplet character.

Introduction of a 1,9 double bond (**24** and **25**) with attendant loss of the C-9 proton and distortion of the ring geometry causes the methyl peak to become a narrow singlet. When a 1,2 double bond (**23**) is present the angular methyl peak appears as a broad singlet.

N-Methylquinolizidinium Ions. The *cis* and *trans* isomers of the heterocyclic angularly methylated quinolizidinium ions (**26** and **27**) in deuterium oxide have $W_{h/2}$ = 0.96 and 1.53 c.p.s., respectively; the *trans*-fused compound again has the larger line width. These values are slightly larger than the typical peak widths of the corresponding hydrocarbons, but it is evident that long-range coupling can take place through nitrogen just as it does through carbon; again it would appear that the line width of the angular methyl group, even though bound to positively charged nitrogen, is governed by the number of protons which can adopt the coplanar zigzag conformation ($\phi_1' = \phi_3' = 180°$) relative to the protons of the methyl group. In these compounds the N^{14} quadrupole moment and the fact that the compounds were run in water as a solvent may be complicating factors. However, if these line-width observations have any generality, it should be possible to extend this concept to the determination of ring fusion stereochemistry in all N-methylated heterocyclics of this type.

Steroids. The observations and generalizations we have made for the decalins are applicable to the C-19 methyl groups of steroids as well. $W_{h/2}$ of the C-19 methyl peak in an A,B *trans*-fused steroid is always greater than $W_{h/2}$ for the corresponding *cis* isomer in the four pairs of compounds **28–35** cited in Table III. The average $\Delta W_{h/2}$ for the four *trans* compounds is 0.84 ± 0.03 c.p.s., and the average $\Delta W_{h/2}$ for the *cis* isomers is 0.36 ± 0.07 c.p.s. These values are within the ranges found for the *cis*- and *trans*-decalins discussed above. Here, as in the decalins, an *absolute* line-width measurement can be used to distinguish between a *cis* or *trans* A,B ring junction, at least insofar as can be concluded from the 17 A,B chair–chair steroids studied in this work.

The series of compounds **38–44** provides a good illustration of the effect of various substituents on the line width. The alcohol **38**, the dichloro alcohol **39**, the ketone **28**, and the dichloro ketone **40** have roughly comparable line widths. The introduction of a C-2 equatorial chlorine atom (**42**) or an equatorial bromine atom (**44**) does not noticeably change the line width (the average $\Delta W_{h/2}$ for these six compounds is 0.83 ± 0.07 c.p.s.). When the halogen at C-2 is axial, however, there is a marked increase in $\Delta W_{h/2}$ to 1.25 c.p.s. for the axial chloro isomer (**41**) and 1.09 c.p.s. for the axial bromo isomer (**43**). We have shown[16] that the A ring in **41** and **43** is not significantly distorted from the normal chair conformation even though there are two severe 1,3-diaxial interactions between the angular methyl group and the halogens at C-2 and C-6. The dramatic increase in $\Delta W_{h/2}$ for these two compounds (and splitting of the angular methyl peak of **41** into a doublet with a 0.5-c.p.s. separation) may be due to virtual coupling of the type mentioned above. The possibility also exists that in these two compounds there is some steric hindrance to free rotation of the angular methyl group which might lead to a particularly strong coupling of methyl and ring protons. However, enigmatically, models indicate that in the

(16) K. L. Williamson and T. Howell, unpublished work.

more favorable rotamers the angular methyl protons are not in the coplanar zigzag conformation with respect to the axial 1, 5, and 9 protons.

In **45** we note, as in the decalins, a decrease in $\Delta W_{h/2}$ upon introduction of a heteroannular double bond.

The values of $\Delta W_{h/2}$ for the C-18 methyl peak are also reported in Table III. Without C–D *cis*-fused steroids for comparison, no conclusions about the application of our generalizations to hydrindanes can be made.

Experimental Section

A Varian A-60 spectrometer was employed for all measurements. To ensure the best resolution possible the spectrometer was tuned by the standard procedure on the homogeneity test sample of water, then tuned up further on acetaldehyde (usually just a refinement of the Y-gradient control). It was found necessary to tune the spectrometer on each sample by adjustment of the Y-gradient control while observing the TMS line. The samples (10–15% w./v.) were dissolved in deuteriochloroform (Merck Ltd.) or carbon disulfide (Mallinckrodt AR) containing 2% tetramethylsilane as an internal reference and were not degassed. All spectra were run at a 0.1-c.p.s. sweep time employing a 50-cycle sweep width, a filter band width of 4, and radiofrequency power level of 0.04 (at which level no saturation was observed). For a given sample the line widths were the same, within experimental error, in both deuteriochloroform and carbon disulfide.

The values in Table I are averages, with attendant average deviations, of from four to twelve measurements. These measurements were made at various times by two different operators using freshly prepared solutions and consequently different batches of solvent and sample tubes, although the samples were always from the same lot. The line widths in all cases were measured to the nearest 0.01 cm. (0.01 c.p.s.) with a Bausch and Lomb 7-power measuring magnifier. The average deviations are a good measure of the reproducibility of these measurements.

The values in Table II are averages of from two to four measurements made in many, but not all, cases by two different operators.

The values in Table III were obtained from one to four measurements and are all the work of one spectroscopist. The variations in $\Delta W_{h/2}$ for similar steroids are more a reflection of inability to define a base line for the methyl peaks than poor spectrometer resolution. In the steroids, the methyl peaks usually are superimposed on the broad methylene envelope whereas the decalins usually have a flat base line where the methyl peak occurs. The angular methyl peaks were identified unambiguously by calculating the chemical shifts using the additivity data of Zurcher.[17]

trans-**9-Methyldecalin (1)** and *cis*-**9-methyldecalin (2)** were kindly supplied by Professor W. G. Dauben. *trans*-**10-Methyl-2-decalone (3)**, *cis*-**10-methyl-2-decalone (4)**, *trans*-**9-hydroxy-10-methyl-2-decalone (9)**, and *cis*-**9-hydroxy-10-methyl-2-decalone (10)** were kindly supplied by Professor J. A. Marshall. *trans*-**5β-Hydroxy-10β-methyl-2-decalone (5)** and *trans*-**10-methyldecalin-2,5-dione (7)** were prepared by the method of Birch, Pride, and Smith.[18] *cis*-**5β-Hydroxy-10β-methyl-2-decalone (6)** was prepared by the method of Boyce and Whitehurst.[19] *cis*-**10-Methyldecalin-2,5-dione (8)** was prepared by the method of Swaminathan and Newman.[20]

trans-**5β-Hydroxy-10β-methyl-2-decalone Thioketal (11).** To 0.54 g. (0.0032 mole) of the ketol **5**, m.p. 70–72°, in 7 ml. of warm (50°) glacial acetic acid were added 0.36 ml. (0.003 mole) of ethanedithiol (Eastman) and 0.4 ml. of boron trifluoride etherate (Eastman practical grade). After the solution cooled to room temperature a total of 15 ml. of water was added very slowly to the solution. The felt-like needles were collected, washed with water, dried, and crystallized from *ca.* 7 ml. of hexane to give 0.56 g. (72% yield) of white needles, m.p. 103–105°. A sample for analysis had m.p. 104–105°. *Anal.* Calcd. for $C_{13}H_{22}OS_2$: C, 60.45; H, 8.52. Found: C, 60.51; H, 8.61.

trans-**10-Methyldecalin-2,5-dione-2-thioketal (12)** was prepared by Sarett oxidation[21] of the thioketal alcohol **11.**

To 14 ml. of magnetically stirred, chilled (ice bath) pyridine (Merck, reagent grade) was added 0.4 g. of chromium trioxide in small portions over a 30-min. period. To the cool slurry was added 0.40 g. (0.0115 mole) of the thioketal alcohol **11**, m.p. 103–105°, in 8 ml. of pyridine. The resulting black-brown slurry was stirred for 30 min., then allowed to stand overnight at room temperature. The reaction mixture then was poured into 60 ml. of water, and the product was extracted with three 30-ml. portions of ether. The ether extracts were combined, washed with 10% hydrochloric acid and water until neutral, and then dried over anhydrous sodium sulfate. Removal of the ether under reduced pressure gave a white, crystalline residue that was recrystallized from 1:1 dichloromethane–methanol to give 0.27 g. (68% yield) of needles, m.p. 122–123°. *Anal.* Calcd. for $C_{13}H_{20}OS_2$: C, 60.93; H, 7.80. Found: C, 60.89; H, 7.95.

trans-**5α-*d*-5β-Hydroxy-10β-methyl-2-decalone Thioketal (13).** To 0.19 g. (0.00074 mole) of the thioketal ketone **12**, m.p. 122–123°, and 0.10 g. of 99% lithium aluminum deuteride in a flame-dried, nitrogen-flushed, 50-ml., three-necked flask fitted with condenser and drying tube, dropping funnel, and nitrogen inlet was added 30 ml. of anhydrous ether while stirring the mixture with a magnetic stirring bar and cooling in an ice bath. The reaction mixture was refluxed for 2 hr., then 0.2 ml. of water was added carefully, followed by 0.15 ml. of a 10% solution of sodium hydroxide. The solution was stirred for 1 hr., and the gray precipitate was removed by filtration and washed with ether. The ether was evaporated and the residue was taken up in hot hexane to give on cooling 90 mg. (46%) of felt-like needles, m.p. 102–103°. On admixture with **11** the melting point was 102–104°. The absence of a peak at 98 c.p.s. in the n.m.r. spectrum assigned to the C-1 proton was taken as evidence that the compound was indeed deuterated. This was confirmed by the presence of a peak on the infrared spectrum at 2115 cm.$^{-1}$ for the axial C–D stretching vibration.[22]

10β-Methyl-1α-carboethoxy-5β-hydroxy-*trans*-decalone-2 (14), 10β-methyl-1α-carbomethoxy-5β-hydroxy-*trans*-decalone-2 (15), 10β-methyl-1α-carboethoxy-5β-acetoxy-*trans*-decalone-2 (16), 1α,10β-dimethyl-1β-carbomethoxy-5β-hydroxy-*trans*-decalin (19), and **1β,-10β-dimethyl-1α-carbomethoxy-5β-hydroxy-*trans*-decalin (20)** were prepared by the method of Spencer, *et al.*[23] **1α-Carbomethoxy-5β-tetrahydropyranyloxy-10β-methyl-*trans*-decalone-2 (17**; epimer A, m.p. 117–118.5°) and **(18**; epimer B, m.p. 130–131.5°) were prepared by the method of Spencer and Villarica.[24] **1β,10β-Dimethyl-1α-carbomethoxy-5β-hydroxy-*trans*-decalone-2 (21)** was prepared by the method of Spencer and Schmiegel.[25] **1α,10β-Dimethyl-1β-carbomethoxy-*trans*-decalone-7 (22)** was prepared by the method of Spencer, Schwartz, and Sharpless.[26] **10β-Methyl-1-carboethoxy-5β-acetoxy-*cis*-decalone-2 (23)** was prepared by the method of Spencer, *et al.*[23] **1-Carboethoxy-10-methyl-$\Delta^{1,9}$-octalin-2,5-dione (24)** and **1-carboethoxy-5β-acetoxy-10-methyl-$\Delta^{1,9}$-octalone-2 (25)** were prepared by the method of Spencer, Weaver, and Greco.[27]

trans-**N-Methylquinolizidinium iodide (26)** and *cis*-**N-methylquinolizidinium iodide (27)** were kindly supplied by Professor A. R. Katritzky.

Cholestan-3-one (28), coprostan-3-one (29), 5α-pregnane-3,20-dione (32), 5β-pregnane-3,20-dione (33), 5β-androstane-3,17-dione (37), and **5,16-pregnadien-3β-ol-20-one acetate (45)** were purchased from Chemed, Inc., Odenton, Md., and were used without further purification.

17β-Hydroxy-5α-androstan-3-one (30), 17β-hydroxy-5β-androstan-3-one (31), 3β-hydroxy-5β-androstan-17-one (34), 3β-hydroxy-5β-androstan-17-one acetate (35), and **3β-hydroxy-5β-androstan-17-one (36)** were kindly furnished by Dr. D. K. Phillips of the Sterling-Winthrop Research Institute.

5α-Cholestan-3β-ol (38) was purchased from Southeastern Biochemicals. **5α,6β-Dichlorocholestan-3β-ol (39)** and **5α,6β-dichlorocholestan-3-one (40)** were prepared according to the procedure of Barton and Miller.[28] **2β,5α,6β-Trichlorocholestan-3-one (41), 2α,-5α,6β-trichlorocholestan-3-one (42), 2β-bromo-5α,6β-dichlorocholes-**

(17) R. F. Zurcher, *Helv. Chim. Acta*, **46**, 2054 (1963).
(18) A. J. Birch, E. Pride, and H. Smith, *J. Chem. Soc.*, 4688 (1958).
(19) C. B. C. Boyce and J. S. Whitehurst, *ibid.*, 2680 (1960).
(20) S. Swaminathan and M. S. Newman, *Tetrahedron*, **2**, 88 (1958).
(21) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 423 (1953).
(22) *Cf.* M. Larnaudie, *Compt. Rend.*, **235**, 154 (1952).
(23) T. A. Spencer, T. D. Weaver, M. A. Schwartz, W. J. Greco, Jr., and J. L. Smith, *Chem. Ind.* (London), 577 (1964).
(24) T. A. Spencer and R. M. Villarica, unpublished work.
(25) T. A. Spencer and W. W. Schmiegel, unpublished work.
(26) T. A. Spencer, M. A. Schwartz, and K. B. Sharpless, *J. Org. Chem.*, **29**, 782 (1964).
(27) T. A. Spencer, T. D. Weaver, and W. G. Greco, Jr., *ibid.*, **30**, 3333 (1965).
(28) D. H. R. Barton and E. Miller, *J. Am. Chem. Soc.*, 72, 370 (1950).

tan-3-one (43), and 2α-bromo-5α,6β-dichlorocholestan-3-one (44) were prepared by the procedure of Jacquesy and Levisalles.[29]

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(29) J. C. Jacquesy and J. Levisalles, *Bull. Soc. Chim. France*, 1899 (1962).

A Conformational Analysis of the Favorskii Rearrangement[1]

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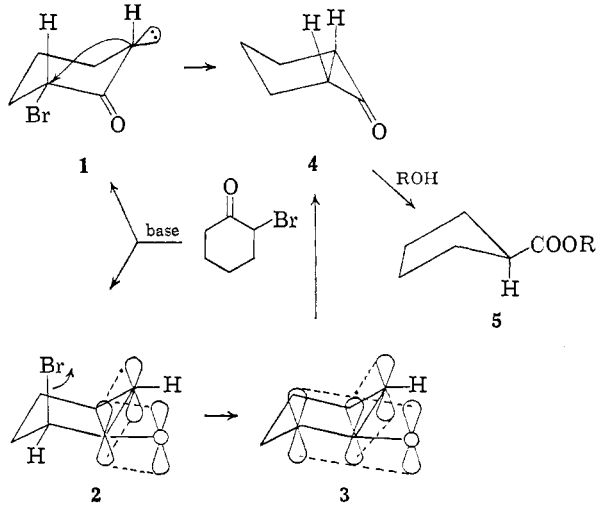
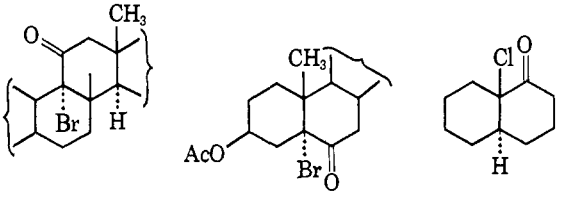
Abstract: In an attempt to elucidate the steric requirements of the Favorskii rearrangement, 3-a-bromo-*trans*-2-decalone (**11a**), 3-e-bromo-*trans*-2-decalone (**11e**), and 2-e-bromo-9-methyl-*trans*-3-decalone (**12**) were subjected to Favorskii rearrangement conditions in both polar and nonpolar solvents. The axial compound, **11a**, gave no rearrangement product in either solvent, whereas the equatorial compounds, **11e** and **12**, rearranged on treatment with sodium ethoxide in polar and nonpolar solvents. Evidence disputing the necessity of proposing a "zwitterion mechanism" in polar solvents is given.

The Favorskii rearrangement, the skeletal rearrangement of α-halogenated ketones in the presence of nucleophilic agents, has been reviewed by Kende.[2] Previous evidence suggested that the reaction proceeded through a "cyclopropanone intermediate," [3] which formed directly without involvement of an intermediate dipolar ion.[4] Recent studies have implied that the nature of the intermediate is solvent dependent with a cyclopropanone intermediate being facilitated by nonpolar solvents and a "zwitterion intermediate" by polar solvents.[5-7] The cyclopropanone intermediate could result from abstraction of the α′ hydrogen of an α-halo ketone, followed by an intramolecular backside displacement with inversion of configuration at the α-carbon atom. Such a displacement would require an equatorial halogen in the case of cyclic systems, as shown for α-bromocyclohexanone (**1**). The zwitterion intermediate would result from base abstraction of the α′ hydrogen followed by ionization of the halogen at the α-carbon atom. The ionization would be favored by an axial halogen as shown in **2**. When 3α,20β-dibenzoyloxy-9α-bromo-5β-pregnan-11-one (partial structure **6**),[8] 5α-bromocholestan-3β-ol-6-one acetate (partial structure **7**),[9] and 9-chloro-*trans*-1-decalone (**8**)[7] were treated with base in polar solvents, no Favorskii rearrangement products were found. The strain of the bicyclic system **4** was given as the reason for the absence of rearrangement.[7] Although no example of a rearrangement can be found with systems possessing a fixed axial halogen, the zwitterion intermediate, but not the cyclopropanone intermediate, can account for the loss of stereospecificity found when piperitone oxide (**9**) and 1-chloro-*cis*-1-acetyl-2-methylcyclohexanone (**10**) undergo rearrangement in polar media.[5,6] Several examples of successful Favorskii rearrangements have been reported in conformationally rigid systems which possess an equatorial halogen.[10-12]





(1) Taken in part from the dissertation presented by Odd Kristiansen, June 1962, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.
(2) A. S. Kende, *Org. Reactions*, **11**, 261 (1960).
(3) R. B. Loftfield, *J. Am. Chem. Soc.*, **73**, 4707 (1951).
(4) G. Stork and I. Borowitz, *ibid.*, **82**, 4307 (1960).
(5) H. O. House and W. F. Gilmore, *ibid.*, **83**, 3972 (1961).
(6) H. O. House and W. F. Gilmore, *ibid.*, **83**, 3980 (1961).
(7) H. O. House and H. W. Thompson, *J. Org. Chem.*, **28**, 164 (1963).
(8) J. S. G. Cox, *J. Chem. Soc.*, 4508 (1960).
(9) A. T. Rowland, *J. Org. Chem.*, **27**, 1135 (1962).
(10) D. E. Evans, A. C. DePaulet, C. W. Shoppee, and F. Winternitz, *J. Chem. Soc.*, 1451 (1957).
(11) N. Pappas and H. R. Nace, *J. Am. Chem. Soc.*, **81**, 4556 (1959).
(12) B. B. Smith and H. R. Nace, *ibid.*, **76**, 6119 (1954).