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THE PROTON MAGNETIC RESONANCE SPECTRA AND PREFERRED CONFORMATIONS OF DERIVATIVES OF CIS-2-DECALONE

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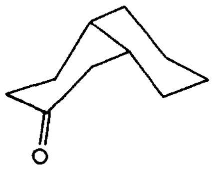
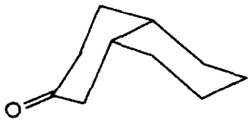
CONFORMATIONAL equilibria in derivatives of _cis_-2-decalone have provided a perplexing problem. There is a clear contradiction between predictions based on conformational analysis (1-4), supported, for 10-methyl-_cis_-2-decalone, by the differences in the stabilities of 3α,10β-dimethyl- and 3β,10β-dimethyl-_cis_-2-decalone (4), and the results of optical rotatory dispersion (ORD) and circular dichroism (CD) measurements, interpreted by the application of the Octant Rule (5), which are claimed to lead 'to the inescapable conclusion that the anticipated "nonsteroid" form A does not play an important role in the conformational equilibrium in 10-methyl-_cis_-2-decalone' (6).

The application of conformational analysis with the usual approximations to the two-chair conformations A and B of 10-methyl-_cis_-2-decalone suggests that A should be more stable than B by the magnitude , _c_ 0.4 kcal./mole, of the



A



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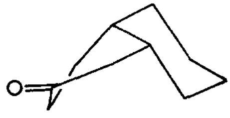

C

'3-alkylketone effect'[*] (the <u>difference</u> between a 'normal' skew interaction between two methylene, or methyl, groups and one between a methylene group and the π-electrons of a carbonyl group in a cyclohexanone). Djerassi and Stork (6) have suggested that the conformation C, which, like B, is consistent with the ORD and CD results but which, unlike B, does not have a large 1,3-diaxial interaction when a 7α-alkyl substituent is present, may be considerably more stable than A. This is because converting the ketone ring into a boat (with C-2 and C-10 at the prow and stern) greatly diminishes or eliminates repulsions totalling 2.7 kcal./mole,[†] while the 'well known unfavourable interactions associated with such a classical boat are in turn largely relieved by rotating the axis of the carbonyl group towards C-4 by about 20°: i.e. by making a twist with the points at C-1 and C-4,' as in conformation C. We are unable to accept the statement quoted because in C substituents on

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[*] Unfortunately this term has mistakenly been used for the skew interaction between a methylene group and the π-electrons of a carbonyl group (6), using Rickborn's value of 0.9 kcal./mole (7) which is considerably higher than other estimates but which almost coincides numerically with the earliest estimates of the 3-alkylketone effect (1).

[†] An estimate based on Rickborn's value (7) for the 3-alkylketone effect.

TABLE 1

Chemical Shifts (τ-Scale) and Coupling Constants (J, cps) for Protons in Derivatives of Cis-2-Decalone.

Derivative of Cis-2-Decalone[j]	Chemical Shifts τ_A	τ_B	τ_X	Coupling Constants $\lvert J_{AB}\rvert$	$\lvert J_{AX}\rvert$	$\lvert J_{BX}\rvert$
I	7.36[b]	7.83[a]	-[g]	14.3	5.1	4.3
	8.0[e]	8.6[f]		13.0		
II[k]	7.43[b]	7.69[g]		6.4		
	7.97[e]	8.36[f]		13.2		
III	7.20[b]	7.98[a]	-[g]	14.4	5.4	-[l]
V	7.19[b]	8.04[a]	-[g]	13.8	5.7	1.8
VII			5.08[d]			
	7.06[b]	7.67[a]	-[g]	14.4[n]	5.4[n]	
VIII	7.48[e]	8.07[f]	5.11[d]	13.0	13.3	6.7
	7.08[b]	7.67[a]	-[g]	14.5	5.1[m]	-[l]
IX			5.23[c]			
X			4.67[b]		4.7	
XI			4.70[b]		4.5	
XII	7.33[e]	7.92[f]	5.04[d]	13.1	13.0	7.1
			4.65[b]		4.9	
XIII	7.38[e]	7.94[f]	5.07[d]	13.2	13.0	6.8
			4.67[b]		4.4	
XIV[o]	7.18[f]	7.83[e]	5.20[c]	13.6	5.8	13.9
			5.06[a]		13.0	
-[p]	7.31[b]	7.9[a]	5.30[h]	13.0	6.0	13.2

[a-h] Protons: 1α[a],1β[b],3α[c],3β[d],4α[e],4β[f],2β[h](3-oxosteroid only).
[j] Substituents as in Table 2. [k] 7,7-Dimethyl-cis-2-decalone (and 1α,3,3,8,8,10β-d_6 derivative). [l] Small but obscured by overlappimg bands. [m] Some uncertainty caused by overlapping bands. [n] First order splittings. [o] 1β,3β-dibromo-5β,7β-dimethyl-cis-2-decalone. [p] 2α-bromo-5α-cholestan-3-one; reference 10.

three vicinal pairs of tetrahedral carbon atoms are about half-way between staggered and eclipsed arrangements, which results in a torsional strain of about $3x\frac{1}{2}x3 = 4.5$ kcal./mole, and the 3α- and 8α-hydrogen atoms are very close together (*c* 1.6A).* If it were confirmed that conformation C was more stable than A there would be a serious anomaly to be explained. We now report some preliminary results relevant to this problem from a detailed examination of the proton magnetic resonance (PMR) spectra of 2-decalones, all of which appear to be in chair conformations contrary to the ORD and CD evidence for some cis-2-decalones.

A striking feature of the PMR spectrum of the ketone I (Tables 1 and 2) is a low field quartet due to the 1β-proton, while the 1α-, 3α- and 3β-protons are at 0.3-0.5 ppm higher field; the 1α,3,3,8,-d_5 derivative shows the appropriate pair triplets. In the spectrum of the 3,3-d_2 derivative the quartet due to the 1α-proton, together with a pair of unresolved multiplets (^1H-^2H couplings) due to the 4α-proton, may also be observed. Similar multuplets attributable to 1α- and 1β-protons are found in the spectra of other ketones (II and V, as well as bromoketones discussed later) expected to exist largely in the conformation A, according to the predictions made from conformational analysis. The relatively low field positions of the 1β-protons may be attributed to the diagagnetic anisotropy of the C-8, C-9 bond provided the 1β-proton and the 8-methylene group are both axial to the ketone ring. This requirement is best

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* This distance increases only if the twisted boat changes back towards the classical boat.

TABLE 2

Chemical Shifts (τ-Scale) of Angular Methyl Groups in Cis-2-Decalones.

	Substituents in Cis-2-decalone	Preferred Conformation	Chemical Shift (τ) ($\pm$0.005)
I:	10β-Me[a]	–[b]	8.807
III:	6β-t-Bu,10β-Me	A	8.747
IV:	6α-t-Bu,10β-Me	B	8.968
V:	3α10β-Me$_2$	A	8.712
VI:	3β,10β-Me$_2$	B	8.970
VII:	10β-Me,3α-Br	A	8.673
VIII:	6β-t-Bu,10β-Me,3α-Br	A	8.677
IX:	10β-Me,3β-Br	B	8.838
X:	10β-Me,1α-Br	A	8.645
XI:	6β-t-Bu,10β-Me,1α-Br	A	8.647
XII:	10β-Me,1α,3α-Br$_2$	A	8.580
XIII:	6β-t-Bu,10β-Me,1α,3α-Br$_2$	A	8.587

[a] Including 3,3-d$_2$ and 1α,3,3,8,8-d$_5$ derivatives.

[b] A:B ≃ 2:1; reference 4.

satisfied by the conformation A, but C may be nearly as good in the ketones I-III and V (although <u>not</u> for the bromoketones discussed below). The difference between the chemical shifts of the 1β-protons in the ketone II and in III and V, however, is evidence for a normal diaxial relationship between the 10β-methyl group and the 1β-proton in III and V (8); such deshielding decreases rapidly with distance and would not be expected to be nearly as large in C as in A.

The chemical shifts of the angular methyl groups

(Table 2) are sensitive to the relationship between the methyl and carbonyl groups (9-11).* A 10β-methyl group in A should be markedly deshielded compared with those in B and C: since a 3β-substituent can be accommodated in equatorial positions in B or in C, while only A allows an equatorial 3α-substituent (and similarly for 1-substituents), the chemical shifts of the angular methyl groups may be used to determine the configuration and conformation of 3(or 1)-substituted derivatives of 10-methyl-cis-2-decalone (I). Independently, when the 3- and 4-protons,,or the 1- and 9-protons, give analysable AX or ABX spectra (12), as in the bromo- and deutero-ketones, coupling constants may also be used.

Bromination of the ketones I and III in acetic acid under conditions which allow epimerisation at C-1 and C-3 gave the derivatives listed in Table 1. The three monobromo derivatives of I were not obtained pure but silica gel chromatography concentrated each isomer sufficiently to allow unambiguous identification of the low-field proton multiplets and of the 10β-methyl group absorptions. In the 1- and 3-bromoketones VII, IX and X and in the dimethyl ketones V and VI the α-stereoisomer, with the low field methyl absorption, predominates in each epimeric pair (the 1β-stereoisomer of X was not detected with certainty). The 3α-substituted ketones V, VII and VIII all show relatively low field quartets due to the 1β-protons. The bromoketones VIII and XI-XIII are the predominant stereoisomers in the various bromination mixtures and have low field methyl

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* Differences due to the cis or trans fusion of the rings and to the shielding or deshielding effects of substituents must, of course, be allowed for.

resonances expected for conformation A. The coupling constants for the 3- and 4-protons in these ketones are very similar to the analogous coupling constants for 2α-bromo-3-oxo-5α-steroids (12) (an example is given in Table 1) and in 3α-bromo-10β-methyl-trans-2-decalones (13,14) for which there appears to be no doubt that all-chair conformations predominate. The chemical shifts, however, are unusual insofar as the 4α(axial)-protons are deshielded relative to the 4β(equatorial)-protons. The 1β-protons in the 1α-bromoketones X-XIII show the coupling constants ($J_{1,9}$) and low field shifts (already noted for the ketones I-III, VII and VIII) which are consistent only with an α-configuration for the equatorial 1-bromine substituents in conformation A. If C were the preferred conformation of the ring system then the bromine atoms would be expected to be β-oriented and $J_{1,9}$ would be ~0 cps (corresponding to 1α-9β dihedral angle close to 90°). The three ketones (IV, VI and IX) expected to exist in conformation B all have methyl resonances at about 0.2 ppm higher field than the analogous ketones (III, V and VII) with the preferred conformation A. The ketone XIV is an example of a bromoketone in conformation B.

Finally, some preliminary measurements of the temperature dependence of the chemical shifts of the protons of the 10-methyl groups have been made. The band for the methyl group in I moves to lower field as the temperature is lowered from $+30^{\circ}$ to -50°, as would be expected if conformation A has the lowest enthalpy (4). In contrast, the chemical shift of the 10β-methyl group in the ketone III (in dimethylsulphoxide) does not change significantly over the temperature range +30° to +120°; since the deshielding of the 10β-methyl group by the carbonyl group will be much less in IIIC than in IIIA (9,10) (IIIB may be neglected because it would have the t-butyl group axial) we conclude that IIIC is not present to a significant extent even at higher temperatures.

All the evidence from PMR spectra is consistent with the predominance of two-chair-conformations in derivatives of *cis*-2-decalones, the relative stabilities of A and B being dependent on the configurations of the substituents. This evidence, however, does not exclude small unsymmetrical distortions of the chair rings. Because ORD and CD are very sensitive to such distortions it is unwise to base firm conclusions on r sults from these methods alone.

The spectra were measured on a Varian A60 spectrometer, using dilute solutions (10% w/v in most instances) in chloroform and side-band calibrations, in the Robert Robinson Laboratories, University of Liverpool.

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