Tetracyclic Triterpene Synthesis. Part 2.[1] Deduction of Ring Fusion Configurations in *cis-* and *trans-*7-Methoxy-3a,9b-dimethyl-1,3,3a,4,5,9b-hexahydrobenz[e]inden-2-ones by Nuclear Magnetic Resonance Spectroscopy

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Detailed analyses of the ^1H and ^{13}C n.m.r. spectra of the *cis-* and *trans-*3a,9b-dimethyl derivatives of 7-methoxy-1,3,3a,4,5,9b-hexahydrobenz[e]inden-2-one enable a clear distinction to be made between the two ketones. The ^1H spectra show that the *cis-*ketone exhibits rapid inversion of the cyclohexene ring whereas the *trans-*ketone is conformationally rigid. The spectral parameters for these two compounds, and their 3a-CD_3 and 3a-CD_2H analogues, are discussed.

THE preceding paper[1] describes the stereospecific conversion of 6-methoxy-1-tetralone (1) by way of compound (9) into 7-methoxy-*trans-*3a,9b-dimethyl-1,3,3a,4,5,9b-hexahydrobenz[e]inden-2-one (10). The establishment of the *trans-*configuration in this compound was not immediately apparent from an n.m.r. spectroscopic study, and in order to aid the assignment of configuration the corresponding ketone of opposite configuration (12) was prepared. This paper describes how the configurations of the two ketones may be established with considerable certainty from the ^1H and ^{13}C n.m.r. spectral features of the ketones and their 3a-deuteriomethyl analogues. The conclusions based on the spectral evidence were subsequently confirmed by chemical evidence as described in the preceding paper.[1]

EXPERIMENTAL

Materials.—The *cis-* and *trans-*dimethylhexahydrobenzindenones were prepared as described in the preceding paper.[1] The dideuteriomethyl compound (11) was readily prepared by substituting dideuteriomethylene iodide for methylene iodide in the cyclopropanation of the unsaturated alcohol (9). The deuteriomethyl ketone (13) was prepared from the tetralone (1) by way of the compounds (2), (4), and (6).

The action of trideuteriomethylmagnesium iodide on the ketone (3) gave compound (7). If the acid-catalysed cyclisation step (5) ⟶ (12) which yields the *cis-*ketone is a concerted step then the corresponding reaction with (7) ought to lead, by way of the ion (8), to the deuteriated compound (14). In the event, when compound (7) was treated with formic acid it gave the undeuteriated compound (12). It follows that the cyclisation is not a concerted process.

Spectra.—100 MHz N.m.r. spectra were recorded with a JEOL MH-100 spectrometer operating under internal field-frequency lock conditions. When accurate comparisons were made with computed spectra, experimental line positions were measured with a frequency counter. Variable temperature measurements were carried out with the standard JES-VT-3 temperature controller. 220 MHz ^1H spectra and 22.63 MHz ^{13}C spectra were recorded at the P.C.M.U. Harwell with Varian HR-200 and Brüker
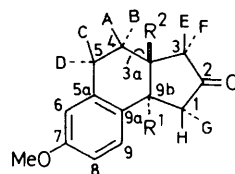
HX 90E spectrometers, respectively. Deuteriochloroform (>99.8%) was used as solvent for all the samples.
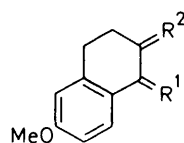
(1) $R^1 = O, R^2 = H_2$
(2) $R^1 = O, R^2 = H, CD_3$
(3) $R^1 = O, R^2 = Me, CH_2CCl:CH_2$
(4) $R^1 = O, R^2 = CD_3, CH_2CCl:CH_2$
(5) $R^1 = CH_2, R^2 = Me, CH_2CCl:CH_2$
(6) $R^1 = CH_2, R^2 = CD_3, CH_2CCl:CH_2$
(7) $R^1 = CD_2, R^2 = Me, CH_2CCl:CH_2$
(8) $R^1 = CHD_2, + charge; R^2 = Me, CH_2CCl:CH_2$
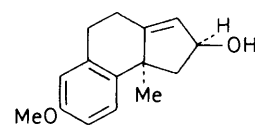
A—H are protons

(10) $R^1 = R^2 = Me$
(11) $R^1 = Me, R^2 = CHD_2$
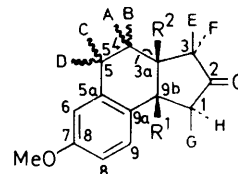
A—H are protons

(12) $R^1 = R^2 = Me$
(13) $R^1 = Me, R^2 = CD_3$
(14) $R^1 = CHD_2, R^2 = Me$

RESULTS AND DISCUSSION

The ^1H 100 MHz spectrum of the *cis-*ketone (12), prepared from (1) by way of (3) and (5), was examined first. The spectrum was essentially first order in appearance with the exception of the 4- and 5-H_2 region, which exhibited lines typical of an ABCD system simplified by virtue of certain chemical shifts and coupling constants being fortuitously equal (see later). The three aromatic proton signals were assigned on the basis of the relative magnitudes of *ortho-*, *meta-*, and *para-*coupling constants. The two signals in the methyl region could not be unequivocally assigned at this stage.

[1] Part 1, R. A. Packer and J. S. Whitehurst, preceding paper.

The 4- and 5-H_2 region showed an unexpected spectral pattern. The low-field portion was assigned to the protons (c and d) on C-5 on the basis of their proximity to the aromatic ring and their smaller lanthanoid-induced shifts (LIS) as compared with the C-4 protons (A and B). It was not possible to distinguish between

however, for this parameter to be exactly zero. In the present case it appears that $\Delta\delta(AB) \leqslant 0.01$. The 4,5-$H_2$ region spectrum was accurately analysed, using a modified version of the LAOCNR program,[2] on the basis of an ABCD system with the nuclei A and B both isochronous [3] and magnetically equivalent and with all

TABLE 1

220 MHz ^{1}H Spectral parameters for ketones (10) and (12)

Position	*trans*-Ketone (10)			*cis*-Ketone (12)		Ketone (10) − ketone (12)
	δ_i(p.p.m.)	i,j	J_{ij}/Hz	δ_i(p.p.m.)	J_{ij}/Hz	$\Delta\delta_i$(p.p.m.)
9	6.87	8,9	9.2	7.20	8.9	0.33
8	6.69	6,8	3.0	6.76	2.9	0.07
6	6.70	6,9	<0.4	6.60	<0.4	−0.10
7-OCH$_3$	3.74			3.80		0.06
4	1.81 (A)	A,B	−13.2	1.77	?	−0.04
	2.20 (B)	A,C	10.5	1.77	6.7	−0.43
5	2.97 (C)	A,D	0.8	2.79	6.7	−0.18
	3.01 (D)	B,C	9.0	2.90	6.7	−0.11
3	2.15 (E)	B,D	9.0	2.21	6.7	0.06
	2.43 (F)	C,D	−18.2	2.29	−17.8	−0.14
1	2.39 (G)	E,F	−18.0	2.49	−18.0	0.10
	2.71 (H)	G,H	−18.0	2.68	−18.0	−0.03
3a-CH$_3$	0.81	3a-CH$_3$,F	0.5	1.14		0.33
9b-CH$_3$	1.18	9b-CH$_3$,H	0.5	1.35		0.17

A and B nor between C and D in view of the small internal shift in the former case and the essentially zero shift difference in the latter. This shift difference, $\Delta\delta(AB)$,
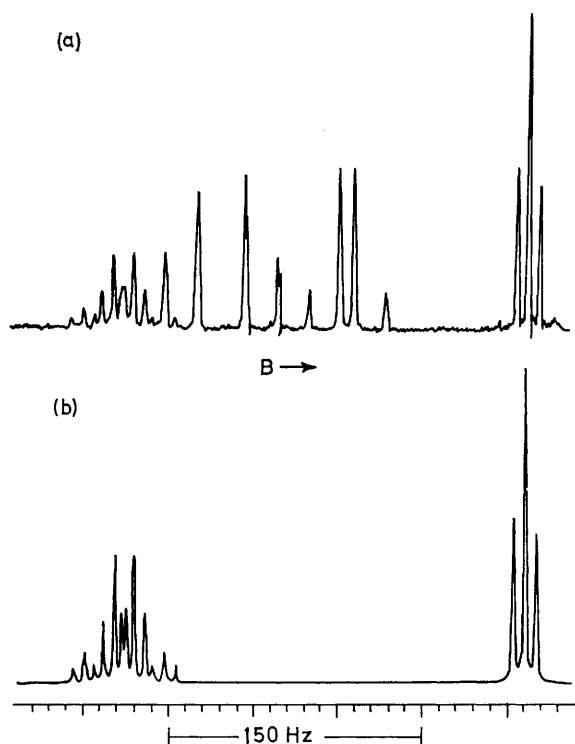

FIGURE 1   220 MHz ^{1}H Spectrum of the 4- and 5-H_2 of the *cis*-ketone (12);   (a) experimental, (b) simulated

was not distinguished from zero even in the 220 MHz spectrum (Figure 1, Table 1). There is no reason,

four vicinal coupling constants equal (Figure 1). No other basis of analysis would explain the observed spectrum. Such an analysis is incompatible with a rigid ring structure and a rapid ring inversion process appeared to be operating. A Dreiding model of the *cis*-ketone (12) revealed that a rapid ring inversion process was indeed likely. In contrast, the model of the *trans*-ketone (10) suggests considerable strain in the cyclohexene ring which cannot be relieved by any conformational inter-conversion. This observation was of decisive importance in distinguishing between the ketones (10) and (12). Experimental evidence for the presence of a rapid ring inversion process in the compound presumed to be the *cis*-isomer (12) was sought from the low temperature (*ca.* −80 °C) spectrum of the compound in CS_2 as solvent. At this temperature appreciable broadening of all the methylene proton lines was observed ($\Delta v_{\frac{1}{2}}$ *ca.* 6 Hz) but no coalescence phenomena were seen. Cooling to *ca.* −100 °C would presumably have revealed a further slowing of the inversion process but experimental difficulties were encountered on cooling the n.m.r. probe below −80 °C. Evidence supporting the view that the inversion barrier is too low to be easily detected by ^{1}H n.m.r. methods was found in some studies on 9,10-dihydrophenanthrene,[4] where inversion was rapid even at −90 °C. Rapid ring inversion would explain why the coupling $J_{AD} = J_{BC}$ and $J_{AC} = J_{BD}$, since the observed couplings would be averaged over the dihedral angles, $\theta = 60°-0°-60°$ and $\theta = 180°-120°-60°$ respectively; but this does not explain why $J_{AC} = J_{AD}$ and $J_{BC} = J_{BD}$. However, the experimental equality of the chemical shifts δ_A and δ_B (even at 220 MHz) remains surprising. The methylene protons at C-1 and C-3

[2] S. Castellano and A. A. Bothner-By, *J. Chem. Phys.*, 1964, **41**, 3863.

[3] M. van Gorkom and G. E. Hall, *Quart. Rev.*, 1968, **22**, 14.

[4] P. W. Rabideau, R. G. Harvey, and J. B. Stothers, *Chem. Comm.*, 1969, 1005.

exhibited AB quartets and the signals were assigned on the assumption that the C-1 methylene absorbed at lower applied field as a result of deshielding by the aromatic ring. Assignment of the individual proton signals in the C-1 and C-3 methylene groups was made by analogy with the other isomer, where long-range couplings between the methyl protons and *one* of each pair of C-1 and C-3 methylene protons enabled an unambiguous assignment to be made (see later). The 3a-CD$_3$ derivative (13) was subsequently prepared to confirm further the above assignment and (particularly) to enable a distinction to be made between the two methyl signals at δ 1.14 and 1.35. The deuteriated derivative exhibited a single signal at δ 1.35 and thus it was possible to conclude that the 3a-Me group absorbs at higher field than the 9b-Me group.

In an attempt to confirm the *cis*-configuration of the CH$_3$ groups a nuclear Overhauser effect (n.O.e.) experiment [5] was performed. Despite careful control of the experimental decoupling conditions no conclusive results were obtained on irradiating at the frequency of either CH$_3$ group and observing the other CH$_3$ signal. It thus appears that the protons are affected by a variety of relaxation mechanisms (*i.e.* the dipolar mechanism cannot be the dominant one) which are tending to minimise the n.O.e. factor between the two CH$_3$ groups.

The ^{13}C chemical shift data of the *cis*-compound (12) are given in Table 2. The assignments of the low-field bands were fairly straightforward. The small chemical shift difference between the quaternary C-5a and C-9a makes definitive assignment difficult but, on the basis of the high-field substituent shifts [6] of a MeO group on *ortho*- and *para*-carbon atoms, the higher field signal is

TABLE 2

[13]C Spectral data for ketones (10) and (12)

trans-Ketone (10)		*cis*-Ketone (12)		Ketone(12) − ketone(10)
δ$_i$(p.p.m.)	*i*	δ$_i$(p.p.m.)	*i*	Δδ$_i$(p.p.m.)
23.5	3a-CH$_3$	23.1	3a-CH$_3$	− 0.4
25.3	9b-CH$_3$	25.3	9b-CH$_3$	0.0
28.0⎱ 28.9⎰	4,5	26.5	4	
		30.7	5	
40.8⎱ 45.2⎰	3a,9b	40.4⎱ 43.9⎰	3a,9b	
48.0⎱ 50.3⎰	1,3	50.4⎱ 53.7⎰	1,3	
55.2	7-OCH$_3$	55.1	7-OCH$_3$	− 0.1
111.1	8	113.2	8	2.1
114.6	6	113.2	6	− 1.4
125.4	9	129.3	9	3.9
136.6⎱ 136.7⎰	5a,9a	134.9⎱ 135.6⎰	5a,9a	
157.9	7	157.6	7	− 0.3
218.0	2	217.5	2	− 0.5

ascribed to C-9a. An unusual feature of the aromatic carbon absorption is the exact equality of the C-6 and C-8 shifts. No explanation is apparent and the effect is not present in the other isomer (10). In the saturated

carbon region distinction between the pairs C-1 and -3 and C-3 and -9b is not conclusive, but the proximity of C-1 and C-9b to the aromatic ring suggests that these nuclei provide the low field members of the two pairs of signals. A similar argument leads to the assignment of C-4 and C-5 signals. Assignment of the methyl signals at δ 23.1 and 25.3 was made by analogy with the *trans*-isomer, where the higher field signal (δ 23.5) was the one modified on deuteriation of the 3a-CH$_3$ group.

The 100 MHz ^{1}H spectrum of the *trans*-ketone (10) proved rather intractable, and detailed analysis was based on the 220 MHz spectrum. The aromatic region of the 220 MHz spectrum is depicted in Figure 2(a).
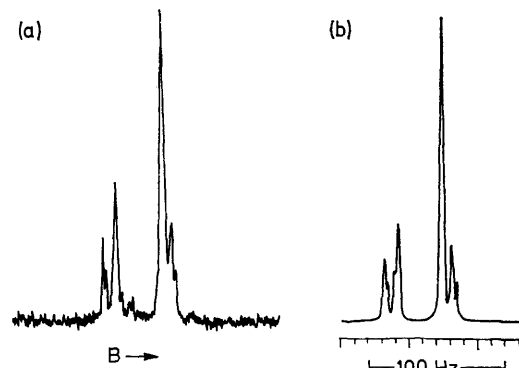

FIGURE 2   220 MHz [1]H Spectrum of the aromatic protons of the *trans*-ketone (10); (a) experimental, (b) simulated

Unlike the *cis*-ketone the aromatic region of this isomer constitutes a strongly coupled ABC system. Iterative analysis using a modified LAOCNR program [2] yielded the spectrum [Figure 2(b)] corresponding to the parameters listed in Table 1. The chemical shifts v_A and v_C, assigned to H-8 and H-6, respectively, are very similar, and are the main cause of the second-order nature of the spectrum. These shift values reflect the usual upfield shifts [7] of protons *ortho* to a methoxy-substituent. The methylene region of the ^{1}H spectrum [Figure 3(a)] posed considerable analytical problems. It basically comprises two overlapping AB quartet patterns and a four-spin ABCD system, one portion of which overlaps with one of the AB quartets. Assignments of the AB systems to the pairs of protons on C-1 and C-3 and the ABCD system to the protons on C-4 and C-5 are straightforward, but individual proton assignments are less obvious. However, the presence of long-range couplings involving the CH$_3$ groups and *one* of the C-1 and C-3 proton pairs enabled a complete assignment to be made with some confidence. In order to utilize this coupling evidence it was necessary to assign unambiguously the two methyl signals (δ 0.81 and 1.18). This required the preparation and n.m.r. study of a deuteriomethyl analogue of the ketone (10).

[5] J. H. Noggle and R. E. Schirmer, ' The Nuclear Overhauser Effect.' Academic Press, New York, 1971.

[6] G. C. Levy and G. L. Nelson, ' Carbon-13 Nuclear Magnetic Resonance for Organic Chemists,' Wiley–Interscience, New York, 1972, p. 81.

[7] H. Spiesecke and W. G. Schneider, *J. Chem. Phys.*, 1961, **35**, 731.

From the ^1H spectrum of the 3a-CD_2H analogue (11) the bands at δ 0.81 and 1.18 in the spectrum of (10) were assigned unambiguously to 3a-CH_3 and 9b-CH_3, respectively. Both these signals exhibited long-range couplings (^4J ca. 0.5 Hz) to the nuclei which provide the lower field halves of the AB quartets. This was confirmed both by
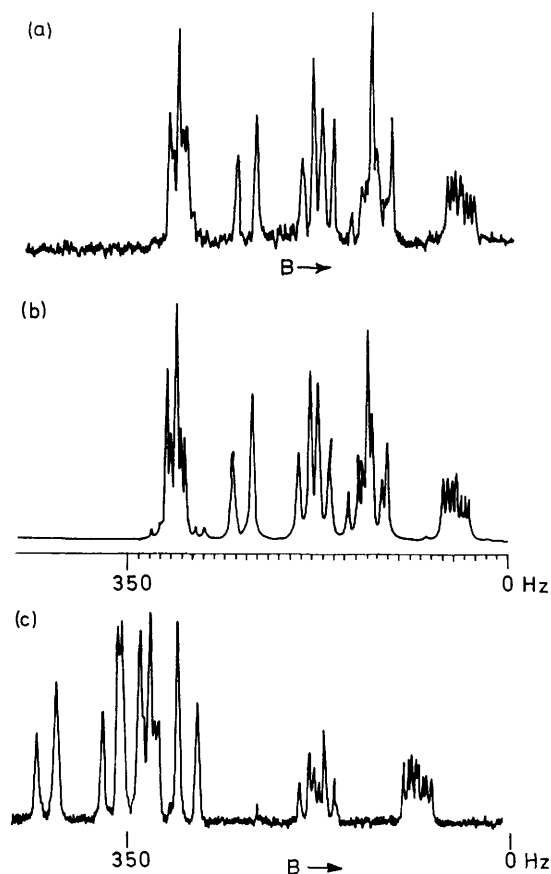

FIGURE 3   220 MHz ^1H Spectra of the methylene protons of the trans-ketone (10); (a) experimental without $Eu(fod)_3$, (b) simulated, (c) experimental with 10 mg $Eu(fod)$, showing the multiplet nature of the B methylene absorption

decoupling experiments and by study of the 3a-CD_2H derivative (11). Previous data [8] indicate that four-bond trans-H,CH_3 coupling constants averaged over the equilibrium conformations of the methyl group are appreciably larger (^4J ca. 0.6 Hz) than gauche-H,CH_3 coupling constants (^4J ca. -0.2 Hz). The low-field members of the AB quartets are accordingly assigned to the protons (F and H) trans to the CH_3 groups. Both AB systems experienced large and equal lanthanoid-induced shifts, the system centred at lower applied being assigned to the protons on C-1 by virtue of the proximity of the aromatic ring. The ABCD system arising from the protons on C-4 and C-5 was analysed in the following way. The low field (CD) region was

assigned with certainty to the hydrogens on C-5 as they will be deshielded by the aromatic ring and also since they exhibit a smaller lanthanoid-induced shift as compared with the AB pair. The addition of 10 mg of $Eu(fod)_3$, revealed the multiplet pattern of nucleus B as that of a perturbed doublet of triplets [Figure 3(c)]. This enabled an accurate iterative analysis of this four-spin system to be performed from a trial set of parameters based mainly on a first-order treatment of the AB regions. After three iterations an acceptable fit (r.m.s. error 0.323 Hz) of computed and experimental spectra was obtained [Figure 3(a) and (b)]. The strongly coupled nature of the CD region [$\Delta\delta(CD)$ 0.04] caused a number of the final iterated parameters (Table 1) to deviate appreciably from the first-order values. The values of the four vicinal coupling constants are of interest in that they provide insight into the conformation of the cyclohexene ring. First, the set of values is compatible only with a fixed ring conformation in distinct contrast to the cis-ketone (12). This is also borne out by the absence of any line broadening in the spectrum at low temperatures which would have indicated the slowing of a rapid ring inversion process. Furthermore, a molecular model of this trans-isomer suggests the presence of considerable strain in this six-membered ring with no possibility of interconversion between equal energy conformations. The values of the four vicinal coupling constants suggest, by reference to the Karplus equation,[9] that the saturated CH_2CH_2 fragment has adopted an approximately eclipsed conformation with dihedral angles of 20, 20, 100, and 140° for the two pairs of protons. Considering the upfield pair (AB) H_B exhibits long-range coupling (^4J ca. 0.5 Hz) with the 3a-CH_3 group. On the basis of sizeable long-range trans-H,CH_3 couplings, H_B was assigned as the proton trans to 3a-CH_3, and H_A as cis to 3a-CH_3. Since J_{AD} is small (0.8 Hz) H_A and H_D must be related by a dihedral angle of ca. 100°. It follows that the dihedral angle relating H_A and H_C must be ca. 20°. The hydrogen pair C and D may now be assigned such that C is cis to 3a-CH_3 and D trans to this group. An additional point in this portion of the spectrum is the appreciably smaller geminal coupling constant for the AB methylene pair as compared to the other geminal couplings in both this compound and the cis-isomer (12). This is a further indication of distortion in this six-membered ring particularly in the vicinity of C-4. A decrease in $^2J_{gem}$ indicates a decrease in the C-CH_2-C valence angle,[10] assuming that other factors contributing to the measured J_{gem} values are either weak or relatively constant for the two isomers (10) and (12). A decrease in the 3a,4,5-angle is most likely to occur by slight extensions of the 3a,4- and 4,5-bonds, particularly the former. Such an effect would necessarily be accompanied by a slight increase in the 4,5,5a-angle, with a consequent increase in magnitude of $J_{CD}(gem)$ as compared with geminal couplings of methylene protons in unstrained rings

[8] M. Barfield and B. Chakrabarti, Chem. Rev., 1969, 69, 757.

[9] M. Karplus, J. Chem. Phys., 1959, 30, 11; J. Amer. Chem. Soc., 1963, 85, 2870.

[10] R. C. Cookson, J. J. Fraenkel, J. Hudec, and T. A. Crabb, Tetrahedron, Suppl. 1966, 7, 355.

(*e.g.* the *cis*-isomer). The data, *viz.* $J_{CD}(cis) = -17.8$ Hz and $J_{CD}(trans) = -18.2$ Hz, support such an interpretation. Details of the ^{13}C spectrum of the *trans*-ketone (10) are given in Table 2. The majority of the assignments are based on the arguments used for the *cis*-ketone. In the aromatic region this isomer, in contrast to the *cis*-isomer, exhibited the expected three carbon signals. Distinction between C-6 and C-8 was made on the basis of n.O.e. factors, the more intense band being assigned to C-8, which will be appreciably relaxed by the adjacent C-9 proton. As with the *cis*-ketone, distinction between the pairs C-1 and -3 and C-3a and -9b was not conclusive. The assignment of CH_3 carbon signals was based on the observation that the 3a-CD_2H analogue (11) displayed a $1:2:3:2:1$ quintet (J_{CD} 19.1 Hz) at δ 22.9 implying that the highest field signal (δ 23.5) in the *trans*-isomer spectrum be assigned to C-3a.

Tables 1 and 2 also show the changes in ^1H and ^{13}C shifts on going from the *trans*- to the *cis*-ketone. The aromatic ^1H and ^{13}C shifts show analogous trends. The very appreciable downfield shift of the 9-position ^{13}C and ^1H nuclei on going from the *trans*- to the *cis*-isomer is very indicative of strain in the aromatic ring of the *trans*-isomer. It is noteworthy that the ^1H methyl shifts are apparently more sensitive than the ^{13}C methyl shifts to the stereochemical relationship of the methyl groups. The lower field shifts for the *cis*-isomer are surprising, as mutual shielding of the methyl groups in this isomer would have been expected to cause higher field shifts than in the *trans*-isomer. It is also surprising that no nuclear Overhauser enhancements were detected for the CH_3 ^1H signals in the *cis*-ketone where the configuration of the groups would seem highly favourable to positive n.O.e.s. A further point of note is that the CH_3 ^{13}C signals do not appear to be particularly sensitive to the configuration of the ring fusion. In contrast to this, Gough, Guthrie, and Stothers [11] found that the ^{13}C shielding of the C-19 protons in 5α- and 5β-steroids (*i.e. single* bridgehead methyl groups) varied by 11—12 p.p.m. For example, the shift difference for 5α- and 5β-androstanes is 12.0 p.p.m., with the latter steroid appearing at lower applied field. The authors concluded that the C-19 methyl carbon shift can therefore be a reliable indicator of the stereochemistry of the AB ring junction. Our present findings suggest that this observation cannot be extended to fused alicyclic structures containing two bridgehead methyl groups.

[11] J. L. Gough, J. P. Guthrie, and J. B. Stothers, *J.C.S. Chem. Comm.*, 1972, 979.