Conformational Equilibria of Eremophilanes, Naturally Occurring *cis*-Decalin Derivatives, Studied by N.M.R. and C.D. Spectroscopy [1]

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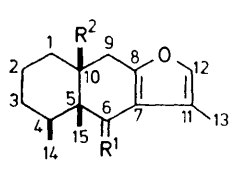
Variable-temperature ^1H and ^{13}C n.m.r. spectra of ligularol (1), 6-*epi*-ligularol (3), ligularone (4), isoligularone (5), and fukinone (6) have demonstrated that these compounds exist in solution as two conformational isomers in equilibrium, the so-called ' steroid-like ' and ' non-steroid-like ' conformers. The conformations of the major and minor isomers, frozen on the n.m.r. time scale at low temperatures, have been determined by ^1H n.m.r. spectral analyses. The ratios of the conformational isomers at equilibrium for the alcohols (1) and (3) are considerably affected by concentration and solvent, probably because of intermolecular hydrogen-bonding. The stable isomer adopts predominantly the ' non-steroid-like ' conformation for compound (4) and ligularol acetate (2), but the ' steroid-like ' conformation for compounds (5) and (6). Gibbs free-energy of activation has been determined for the conformational changes of compounds (1), (3), and (4) ($\Delta G_c^{\ddagger}$ *ca.* 46, 51, and 52 kJ mol^{-1}, respectively) from the signal-coalescence temperatures of the ^{13}C dynamic n.m.r. spectra in [$^2H_6$]acetone. All the ^{13}C n.m.r. signals have been assigned and the ^{13}C n.m.r. chemical-shifts of the two conformers are compared. Variable-temperature c.d. spectra are also examined for the ketones (4)—(6) and 10β-hydroxyligularone (7). Temperature-dependent Cotton effects showed the same conformational equilibria as obtained by n.m.r. spectroscopy, and 10β-hydroxyligularone is assumed to have mainly the ' steroid-like ' conformation.

During the past 20 years, more than 100 eremophilanes have been isolated mainly from Compositae.[2] Eremophilanes are naturally occurring *cis*-decalin derivatives. *cis*-Decalin can adopt two alternative chair–chair conformations, commonly termed ' steroid-like ' and ' non-steroid-like ' conformations (see Figure 1). However, sesquiterpenes of the eremophilane type are generally reported to adopt a single, preferred conformation. In the course of our studies of eremophilane chemistry, we have found that many eremophilanes exist in solution as two conformational isomers in equilibrium. The ^1H and ^{13}C n.m.r. spectra of many eremophilane derivatives of the *cis*-decalin type generally show a set of sharp signals on the n.m.r. time scale at normal probe temperatures, because of relatively low Gibbs energies of activation between the conformational isomers.



(1) R^1 =  , R^2 = H

(2) R^1 =  , R^2 = H

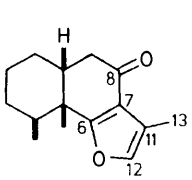
(3) R^1 =  , R^2 = H

(4) R^1 = O, R^2 = H

(7) R^1 = O, R^2 = OH

(8) R^1 =  , R^2 = OH

(9) R^1 = H_2, R^2 = H



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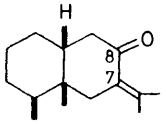

(6)

We report here ^1H and ^{13}C n.m.r. and/or c.d. spectroscopic evidence for the equilibria between conformational isomers of the eremophilane alcohols ligularol (1) and 6-*epi*-ligularol (3), the ketones, ligularone (4), isoligularone (5), and fukinone (6), and for the conformations of the major and the minor conformers of these compounds at equilibria. We also discuss the significant effects of intermolecular hydrogen-bonding upon the equilibria of these sesquiterpene alcohols.

Alcohols.—The ^1H n.m.r. (60 MHz) spectrum of ligularol (1) [3] in [$^2H_6$]acetone at 35 °C shows one set of relatively sharp signals. At lower temperatures all the signals are broader; a broad doublet due to 6α-H at δ 4.74 (*J ca.* 8 Hz), observed at 35 °C, finally splits into a pair of doublets at δ 4.97 (*J ca.* 8 Hz) and 4.34 (*J ca.* 8 Hz) in the ratio 2.3 : 1, at −90 °C [Figure 2, (a) and (b)]. On addition of small amounts of [$^2H_2$]O to the acetone solution of compound (1), the 6α-H signal appears as a singlet at δ 4.71 at 35 °C, and as a pair of singlets at −90 °C, *i.e.* a broad singlet at δ 4.95 ($W_{\frac{1}{2}}$ *ca.* 6 Hz, quasi-axial hydrogen) and a relatively sharp singlet at δ 4.36 ($W_{\frac{1}{2}}$ *ca.* 2 Hz, quasi-equatorial hydrogen) in the ratio 2.3 : 1 [see Figure 2, (c) and (d)]. The former, broad signal suggests the presence of a stronger long-range spin coupling of 6α-H of the ' non-steroid-like ' conformer (B) (R = OH, R′ = H), 6α-H and 9β-H of which are in a quasi-axial [4] relationship (Figure 1). The latter, sharper signal is assigned to 6α-H (A) of the ' steroid-like ' conformer (A) (R = OH, R′ = H). Thus, the predominant conformer of ligularol (1) is assigned the non-steroid-like conformation (B) (see Figure 1). The ^{13}C n.m.r. (15 MHz) spectrum of compound (1) in [$^2H_6$] acetone shows one set

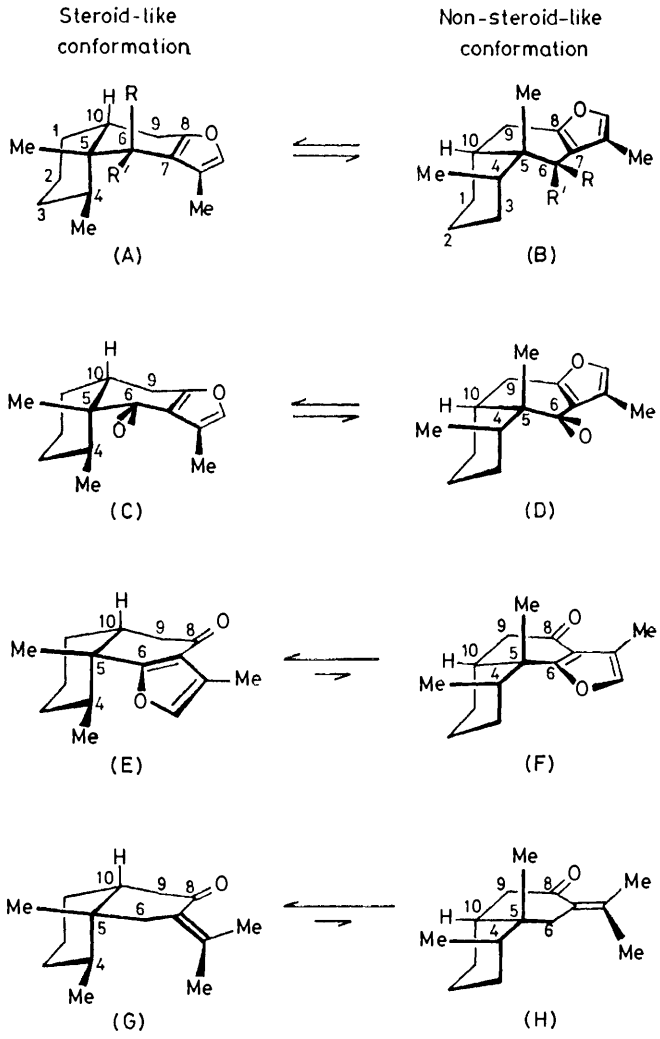

FIGURE 1 Conformations of eremophilane derivatives

of sharp signals at 35 °C. At lower temperatures, these signals are broader; at −90 °C two sets of sharp signals appear in the ratio 2.3 : 1, which also indicates the co-existence of the two conformers (see Figure 3 and Table 1). Gibbs free-energies of activation ($\Delta G_c^{\ddagger}$) at coalescence temperatures (T_c) were estimated from the ^{13}C dynamic n.m.r. spectra using the signals due to C-7, C-8, C-11, and C-13 (T_c 203, 213, 213, and 128 K, respectively) (see Experimental section). The average $\Delta G_c^{\ddagger}$ [(B)→(A)] and $\Delta G_c^{\ddagger}$ [(A)→(B)] values are 46.0 ± 1.5 and 44.7 ± 1.5 kJ mol^{-1}, respectively.

The ^1H n.m.r. (100 MHz) spectral features of ligularol acetate (2),[3] examined at various temperatures in carbon disulphide, are similar to those of ligularol (1). Below −60 °C, two sets of sharp signals occur in the ratio 2 : 1. At −70 °C, two singlets due to 6α-H (B) and 6α-H (A) occur at δ 6.21 ($W_{\frac{1}{2}}$ *ca.* 5 Hz) and 5.66 ($W_{\frac{1}{2}}$ *ca.* 2 Hz), respectively. A broadened signal at δ *ca.* 2.76, assigned to 9β-H (B), becomes a distinct doublet of doublets (J −17.0 and 6.5 Hz) on double irradiation of the broad singlet at δ 6.21, whereas a signal pattern at δ *ca.* 2.08 [9α-H (B)] shows no significant change. On the other hand, with irradiation at δ 2.76 [9β-H (B)], the broad singlet due to 6α-H (B) became a sharper singlet ($W_{\frac{1}{2}}$ *ca.* 3 Hz). The presence of the stronger long-range spin coupling between 6α-H (B) at δ 6.21 and 9β-H (B) at δ 2.76 indicates that these are quasi-axial.[4] The observed J(9β, 10β) (6.5 Hz) and J(9α, 10β) (<1 Hz) values of the predominant conformer agree well with those predicted from molecular models of compound (2) in the 'non-steroid-like' conformation. Hence the conclusion that

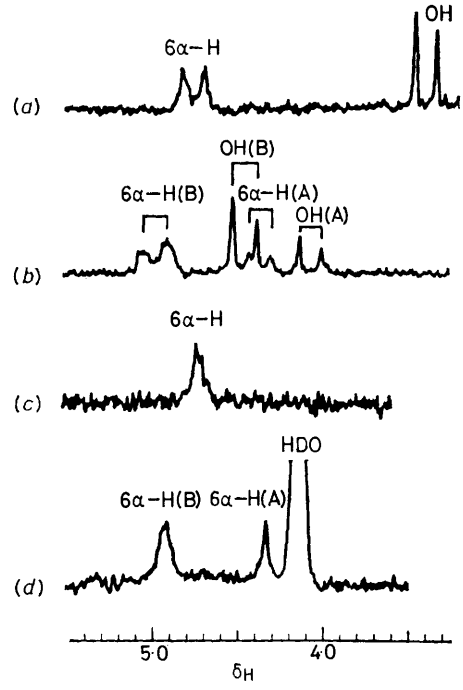

FIGURE 2 Variable-temperature ^1H n.m.r. spectra of ligularol (1) at 60 MHz (shown in part); (a) in [$^2H_6$]acetone at 35 °C and (b) at −90 °C; (c) in [$^2H_6$]acetone–[$^2H_2$]O at 35 °C and (d) at −90 °C

the predominant conformer of ligularol acetate (2) also adopts the 'non-steroid-like' conformation (B) (R = OAc, R′ = H) (Figure 1).

The low-temperature ^1H (60 MHz) and ^{13}C (15 MHz) n.m.r. spectra of 6-*epi*-ligularol (3) [3] in [$^2H_6$]acetone show two sets of signals in the ratio 3.2 : 1 [see, for example, Figure 4(b)]. In the ^1H n.m.r. spectrum in [$^2H_6$]acetone–[$^2H_2$]O at −70 °C [Figure 4(d)], 6β-H signals of the two conformers occur at δ 4.20 ($W_{\frac{1}{2}}$ *ca.* 3 Hz) and 4.50 ($W_{\frac{1}{2}}$ *ca.* 6 Hz) in the ratio *ca.* 3 : 1, which indicates the predominance of the non-steroid-like conformer (B) (R = H, R′ = OH) (Figure 1). For both compounds (1) and (3) in acetone the concentration did not affect the isomer ratios. The average values for $\Delta G_c^{\ddagger}$ [(B)→(A)] and $\Delta G_c^{\ddagger}$[(A)→(B)] of 51.4 ± 1.5 and 49.3 ± 1.5 kJ mol^{-1}, respectively, were estimated using the signals of C-6, C-8, and C-13 (T_c 248, 230, and 233 K, respectively).

The ^{13}C and ^1H n.m.r. spectra of compounds (1) and (3) were also examined in less polar solvents. The ^{13}C n.m.r. spectrum of ligularol (1) at high concentration (200 mg cm^{-3}) in [$^2H_2$]dichloromethane at −60 °C shows that,

TABLE 1

^{13}C N.m.r. chemical-shifts, δ_C, of the eremophilane alcohols (1) and (3)

	Ligularol (1)						6-Epiligularol (3)					
Carbon no.	$CDCl_3$ 30 °C	CD_2Cl_2 34 °C	CD_2Cl_2 −60 °C [a]	δ(calc) [b]	$(CD_3)_2CO$ 34 °C	$(CD_3)_2CO$ −90 °C [c]	$CDCl_3$ 30 °C	CD_2Cl_2 30 °C	CD_2Cl_2 −80 °C [d]	δ(calc) [b]	$(CD_3)_2CO$ 34 °C	$(CD_3)_2CO$ −70 °C [e]
1	27.2	27.5	29.3 (25.1)	28.6 (26.7)	28.1	25.5 (29.3)	29.5	29.7	30.6	29.6 (28.6)	29.3	*h* (*h*)
2	20.4	20.8	20.3 (21.0)	22.2 (22.2)	21.2	21.3 (20.5)	21.3	21.6	22.0	22.2 (22.2)	22.0	22.6 (20.3)
3	29.7	30.0	29.9 (29.3)	31.3 (28.6)	30.2	29.3 (29.9)	31.7	32.0	31.6	31.3 (31.4)	32.3	*h* (*h*)
4	31.1	31.5	32.3 (29.9)	34.3 (33.0)	31.9	30.5 (32.5)	34.2	34.5	36.0	37.0 (32.4)	34.2	*h* (*h*)
5	40.7	41.0	40.4 (40.6)	39.5 (*ca.* 41)	41.5	41.3 (41.0)	40.5	40.8	40.1	*ca.* 39 (37.6)	41.3	40.3 (41.6)
6	68.0	68.1	67.2 (67.7)		67.4	67.0 (67.0)	75.2	75.4	73.6		75.1	72.6 (77.0)
7	118.6	119.0	118.9 (117.8)		119.8	119.0 (119.9) [f]	118.7	119.3	118.8		119.9	119.1 (119.5)
8	150.9	151.1	151.6 (150.2)		150.6	149.6 (151.3)	149.8	150.3	150.6		149.6	149.6 (148.3)
9	25.7	26.0	27.3 (23.9)		26.5	24.3 (27.7)	26.9	27.1	27.7		27.2	27.8 (24.4)
10	35.5	35.9	33.3 (37.7)	34.4 (38.4)	36.4	37.8 (33.8)	37.0	37.3	36.0	36.5 (40.2)	38.1	36.1 (40.3)
11	119.9	120.4	120.1 (121.1)		121.0	121.4 (120.2) [f]	119.7	120.4	120.6		120.8	120.6 (120.6)
12	137.9	138.2	137.3 (138.0)		138.3	138.5 (137.9)	137.8	138.2	137.8		138.0	137.3 (137.3)
13	8.4	8.6	8.1 (9.7)		8.7	9.8 (8.0)	8.5	8.6	8.5		8.8	8.5 (10.3)
14	15.3	15.4	16.2 (14.8)	16.5 (12.0)	15.5	15.0 (16.4) [g]	17.7	17.7	17.2	12.0 (19.4)	18.1	17.3 (19.6)
15	17.4	17.6	16.2 (19.2)	15.3 (15.3)	18.0	19.7 (16.6) [g]	23.0	23.2	25.4	21.1 (15.3)	22.8	25.5 (20.3)

[a] Values in parentheses are for the minor conformer (B) (ratio, 1.3 : 1). [b] Calculated values; see the text. [c] Values in parentheses are for the minor conformer (A) (ratio, 2.3 : 1). [d] The minor conformer was not detected. [e] Values in parentheses are for the minor conformer (A) (ratio, 3.2 : 1). [f,g] Assignments may be reversed. [h] Not assignable.

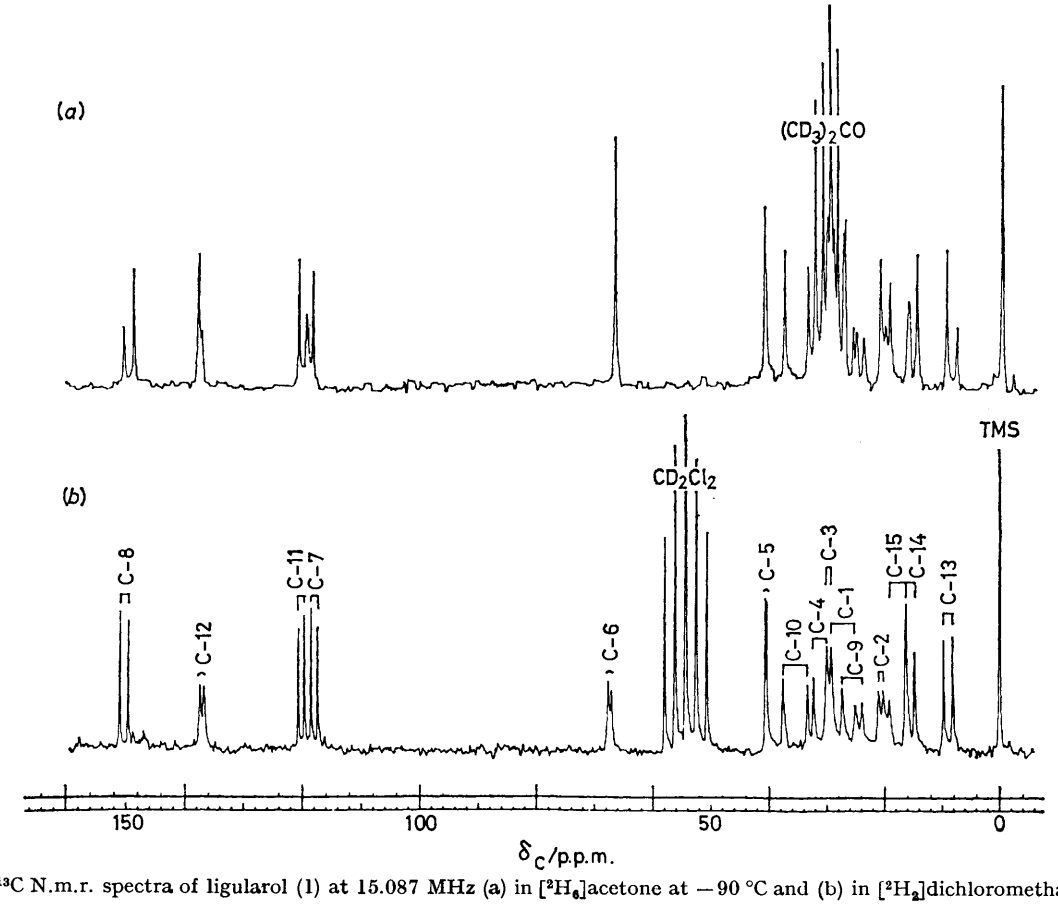

FIGURE 3 ^{13}C N.m.r. spectra of ligularol (1) at 15.087 MHz (a) in [$^2H_6$]acetone at −90 °C and (b) in [$^2H_2$]dichloromethane at −60 °C

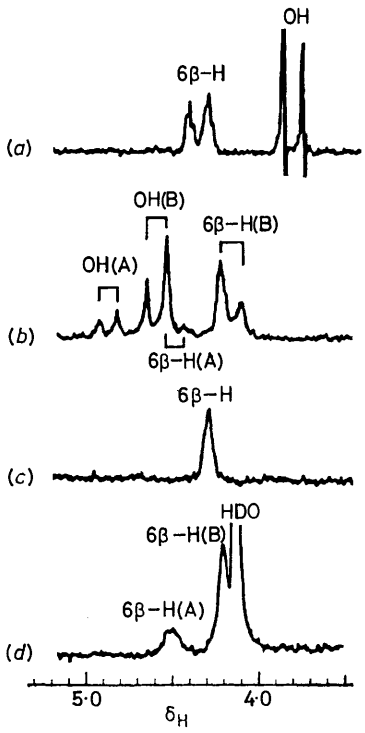

FIGURE 4 Variable-temperature ^1H n.m.r. spectra of 6-*epi*-ligularol (3) at 60 MHz (shown in part); (a) in [$^2H_6$]acetone at 35 °C and (b) at −70 °C; (c) in [$^2H_6$]acetone–[$^2H_2$]O at 35 °C and (d) at −70 °C

under these conditions, the conformer relationship is reversed, with the 'steroid-like' conformer (A) the major one in the ratio 1.3 : 1 (Figure 3). Dilution of the solution (100 mg cm^{-3}) increased the ratio of the 'non-steroid-like' conformer (B). The ^1H n.m.r. spectrum of ligularol (1) in carbon disulphide–[^2H]chloroform (2 : 1) (30 mg cm^{-3}) at −85 °C also shows that the 'non-steroid-like' conformer is more abundant in this case, in the ratio 1 : 1.3. On the other hand, the ^{13}C and ^1H n.m.r. spectra of 6-*epi*-ligularol (3) demonstrate that this molecule exists mostly as the 'non-steroid-like' conformer (B) in these solvents, because no signals assignable to the minor 'steroid-like' conformer (A) were detected below −60 °C.

These facts suggest that intermolecular hydrogen-bonding between the solute molecules significantly affects the equilibrium ratio between the two conformers, although the contribution of dipole–dipole interactions to the equilibrium should not be neglected. In less polar solvents {[$^2H_2$]dichloromethane and carbon disulphide–[^2H]chloroform (2 : 1)}, a quasi-axial hydroxy-group of the preferred 'steroid-like' conformation (A) may form an intermolecular hydrogen-bond with another solute molecule of compound (1), also in conformation (A) more easily than with a quasi-equatorial hydroxy-group in the minor 'non-steroid-like' conformer (B). However, in acetone, ligularol (1) should be preferably hydrogen-bonded with the smaller acetone molecule in conformation (B). On the other hand, the 'non-steroid-like' conformer (B) of 6-*epi*-ligularol (3) seemed stable in [$^2H_2$]dichloromethane and carbon disulphide–[^2H]chloroform, and was not influenced by the concentration. In acetone, the strong hydrogen-bond of compound (3) with an acetone molecule may decrease the Gibbs free-energy difference ($|\Delta G°|$ values) between the two conformers (A) and (B) solvated with acetone molecules. The average values for $\Delta G_c^{\ddagger}$ [(A)→(B)] and $\Delta G_c^{\ddagger}$ [(B)→(A)] of 53.1 ± 1.5 and 52.7 ± 1.5 kJ mol^{-1}, respectively, were determined for ligularol (1) using the C-7, C-8, C-11, and C-13 signals (T_c 248, 248, 243, and 252 K, respectively) in the ^{13}C dynamic n.m.r. spectra (see Figure 3). The observed differences in $\Delta G_c^{\ddagger}$ values for the conformational change of ligularol (1) between [$^2H_6$]acetone and [$^2H_2$]dichloromethane may originate from the solvation of acetone.

The ^{13}C n.m.r. signals of compounds (1) and (3) in [^2H]chloroform at room temperature were first assigned using ^1H single-frequency off-resonance decoupling (SFORD) techniques and chemical-shift comparisons with other furanosesquiterpenes.[5] Shifts induced by a lanthanide shift-reagent (L.I.S.), observed for 6-*epi*-ligularol (3) using Yb(fod)$_3$ (fod = 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionate) and shown in Figure 5, were useful for the signal assignments, which

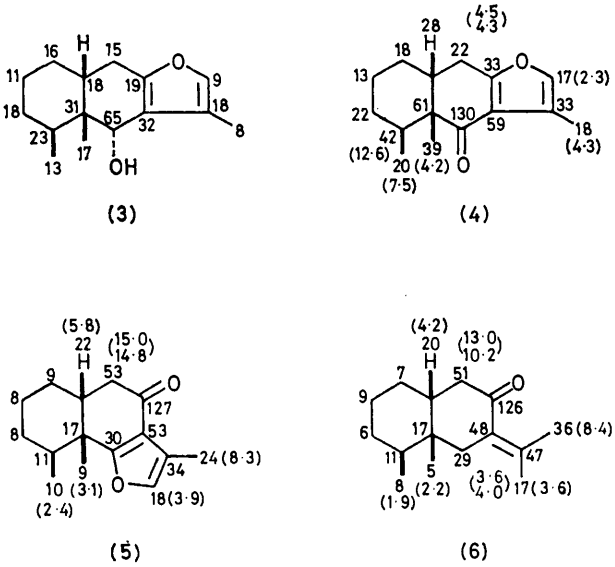

FIGURE 5 Lanthanide-induced shift (L.I.S.) values obtained from initial slopes of shift curves of ^{13}C and ^1H (in parentheses) n.m.r. signals of 6-*epi*-gularol (3), ligularone (4), isoligularone (5), and fukinone (6) in p.p.m. Sample concentrations were 0.87, 1.32 (0.30), 1.25 (0.30), and 1.25 (0.31) mmol cm^{-3} for compounds (3), (4), (5), and (6), respectively. Lanthanide shift-reagents used were Yb(fod)$_3$ for ^{13}C and [$^2H_{27}$]Eu(fod)$_3$ for ^1H n.m.r.

are listed in Table 1. On the basis of these assignments, those for other solvents and temperatures were determined. Signal pairs which arose from the same carbon atoms of the two conformers were distinguished on the basis of variable-temperature spectral patterns (see Table 1).

In order to examine the stereochemical relationships between ^{13}C n.m.r. chemical-shifts and the two conformers and also to obtain further support for the signal assign-

ments, the ^{13}C n.m.r. chemical-shifts of the A-rings of the two conformers of compounds (1) and (3) were calculated by the method of Beierbeck *et al.*[6] (the furan ring was regarded as a double bond). The calculation results are also shown in Table 1 [see δ(calc)]. As can be seen, the δ(calc) values agree excellently with the assignments of the ^{13}C n.m.r. signals and fairly well with the observed values, except for the methyl groups. Evidently, the structural differences are reflected in the δ_C values.

Ketones.—The ^1H n.m.r. spectra of ligularone (4) in carbon disulphide and in [$^2H_6$]acetone were examined at various temperatures. The ^1H n.m.r. spectrum of compound (4) in carbon disulphide at −65 °C shows two sets of sharp signals due to two conformers present in the ratio *ca.* 4 : 1. The signals of 9α- and 9β-H of the major conformer of ligularone (4) appear at δ 2.45 [J — 17.5 and <1 Hz] and 3.10 [J — 17.5 and 6.0 Hz], respectively. These coupling patterns show that the major conformer of ligularone (4) adopts the ' non-steroid-like ' conformation (D). In [$^2H_6$]acetone, the major conformer also prefers the ' non-steroid-like ' conformation (D) in the ratio 2.1 : 1 at −65 °C. The ^{13}C n.m.r. spectrum of ligularone (4) in [$^2H_6$]acetone at −65 °C shows two sets of signals in the ratio 2.1 : 1. The average $\Delta G_c^{\ddagger}$[(D)→(C)] and $\Delta G_c^{\ddagger}$[(C) →(D)] values of 52.3 ± 1.5 and 51.0 ± 1.5 kJ mol^{-1}, respectively, were estimated using the C-7, C-8, C-10, and C-14 signals (T_c 233, 238, 251, and 248 K, respectively).

In a similar manner, the variable-temperature ^1H n.m.r. spectra of isoligularone (5), which was prepared by thermal isomerization of ligularone (4),[7] were investigated in carbon disulphide–[^2H]chloroform (2 : 1) and [$^2H_6$]-acetone. Only the signals due to the major conformer occur below −70 °C, although the lines broaden at lower temperatures. The observed J(9α, 10β) (15 Hz) and J(9β, 10β) (4 Hz) [δ(9α-H) 2.95, δ(9β-H) 2.17] values and Dreiding models indicate that the dominant conformer of compound (5) is the ' steroid-like ' (E); the J values at room temperature are 13.5 and 4 Hz [δ(9α-H) 2.83, δ(9β-H) 2.20], respectively. In the ^{13}C n.m.r. spectrum of isoligularone (5) in [$^2H_6$]acetone–[^2H]chloroform (2 : 1) at −130 °C, only one set of signals, due to the dominant ' steroid-like ' conformation (E), occur, as in the case of the ^1H n.m.r. spectrum. Thus the population of the minor conformer (F) of compound (5) at −130 °C should be less than *ca.* 5%.

The ^{13}C n.m.r. spectrum of fukinone (6) [8] in [$^2H_6$]acetone at −130 °C shows two sets of signals in the ratio *ca.* 10 : 1. However, the ^1H n.m.r. spectra in carbon disulphide below −70 °C merely shows one set of signals due to the predominant conformer which is assigned the ' steroid-like ' conformation (G) from the J values [J(9α, 10β) 13.5 and J(9β,10β) 4.5 Hz] [δ(9α-H) 2.78, δ(9β-H) 2.18]; the J values at room temperature are *ca.* 11 and 6 Hz [δ(9α-H) 2.54, δ(9β-H) 2.23], respectively.

The procedures used to assign the ^{13}C n.m.r. signals for

TABLE 2

^{13}C N.m.r. chemical-shifts, δ_C, of the eremophilane ketones (4)—(6)

	Ligularone (4)				Isoligularone (5)			Fukinone (6)			
						$CDCl_3$–$(CD_3)_2CO$					
Carbon	$CDCl_3$	$(CD_3)_2CO$			$CDCl_3$	(1 : 2)		$CDCl_3$	$(CD_3)_2CO$		
no.	30 °C	45 °C	−65 °C [a]	δ(calc) [b]	30 °C	38 °C	−130 °C [c]	30 °C	30 °C	−130 °C [d]	δ(calc) [b]
1	28.6	28.9	*f*	26.7	26.1 [g]	26.4 [g]	25.6 [g]	27.3 [g]	27.8 [g]	26.7 [g]	28.6
			(*f*)	(28.6)						(*f*)	(26.7)
2	20.2	20.7	20.2 [g]	22.2	20.4 [g]	20.7 [g]	20.5 [g]	21.6 [g]	21.3 [g]	21.0 [g]	22.2
			(20.8) [g]	(22.2)						(*f*)	(22.2)
3	29.9	30.4	*f*	28.6	30.0 [g]	30.4 [g]	30.0 [g]	30.2	30.7	30.6	31.3
			(*f*)	(31.3)						(*f*)	(28.6)
4	31.1	31.7	31.4	32.2	34.8	35.2	34.6	32.5	32.8	30.8	34.3
			(*f*)	(37.6)						(*f*)	(38.8)
5	49.7	50.1	49.8	*ca.* 51	39.7	40.0	40.0	36.7	37.3	37.5	*ca.* 40
			(49.8)	(50.0)						(38.4) [g]	(*ca.* 42)
6	199.8	198.7	199.4		174.4	174.8	174.5	40.7	41.0	41.6	
			(199.4)							(36.5) [g]	
7	117.9	118.2	117.5		118.5	119.1	118.0	139.9	138.9	137.6	
			(118.1)							(140.1)	
8	164.2	164.6	164.6		195.7	194.9	195.7	205.4	204.0	205.3	
			(165.6)							(*f*)	
9	26.8	27.0	*f*		41.3	41.4	40.7	44.0	44.3	44.0	42.1
			(24.9)							(46.2)	(*ca.* 43)
10	39.0	39.7	37.7	*ca.* 43	42.1	42.4	42.4	41.4	42.0	43.1	42.1
			(41.0)	(40.8)						(49.0)	(*ca.* 43)
11	119.8	120.1	119.6		119.1	120.3	118.0	131.2	131.8	131.8	
			(119.6)							(132.3)	
12	139.2	140.1	140.5		139.1	140.0	139.7	22.6	22.3	22.5	
			(140.5)							(*f*)	
13	9.1	9.1	9.7		9.1	9.0	9.5	21.6	21.7	21.0	
			(9.7)							(25.1)	
14	15.0	15.2	14.0	12.0	16.6 [e]	16.8 [e]	15.4 [e]	16.0	16.3	16.8	16.5
			(17.3)	(16.5)						(15.3)	(12.0)
15	19.2	19.1	23.4 [g]	21.7	17.0 [e]	17.0 [e]	17.6 [e]	20.5	20.9	20.7	21.1
			(14.0) [g]	(11.8)						(*f*)	(21.1)

[a] Values in parentheses are those for the minor conformer (C) (ratio, 2 : 1). [b] Calculated values; see the text. [c] Existed only as the major conformer (E). [d] Values in parentheses are those for the minor conformer (H) (ratio, 10 : 1). [e] Assignments may be reversed. [f] Not assignable. [g] Assignments were revised from those in ref. 1*c*.

compounds (4) and (5) are similar to those used for compounds (1) and (3). The L.I.S. values for the ^{13}C n.m.r. signals, as well as those for the ^{1}H n.m.r. signals (for comparison), are shown in Figure 5 and the assignments are listed in Table 2.

The ^{13}C n.m.r. chemical-shifts in the A-rings of compounds (4) and (6) were also calculated as for the alcohols; [6] the results are also listed in Table 2. In these cases, the δ(calc.) values agree excellently with the signal assignments and fairly well with the observed δ_C values.

The variable-temperature c.d. spectra of the ketones (4)—(6) and 10β-hydroxyligularone (7) [2a] were measured in diethyl ether–2-methylbutane–ethanol (5 : 5 : 2) to examine the conformational equilibria between the two isomers of each ketone.

The c.d. curves of fukinone (6) show the negative $n\rightarrow\pi^*$ and positive $\pi\rightarrow\pi^*$ Cotton effects listed in Table 3. low solubility of compound (7). Since the spectra exhibit a simple AB-type quartet for the 9α- and 9β-H signals and signals due to 1-H—4-H are difficult to analyse, the conformation of the major isomers could not be determined by the n.m.r. method. The c.d. spectra of compound (7) shows a negative $n\rightarrow\pi^*$ Cotton effect with an increase of the $|[\theta]_{max.}|$ value when the temperature decreases (Table 3). On the assumption that the B-ring of this molecule similarly adopts the sofa or deformed sofa conformation, we conclude that the major conformer of (7) is the ' steroid-like ' (C). Apparently, the non-bonded 1,3-interaction between the 4β-methyl- and the 10β-hydroxy-groups in the ' non-steroid-like ' conformation (D) decreases the population of this isomer.

An *X*-ray crystallographic analysis of 8,12-epoxyeremophila-7,11-diene-6β,10β-diol [2a] (β-tetradymodiol) [13] (8) has shown that this molecule adopts the ' steroid-like '

TABLE 3

Variable-temperature c.d. spectral data [a]

	(4)		(5)		(6)		(7)	
	$[\theta]_{max.}$		$[\theta]_{max.}$		$[\theta]_{max.}$		$[\theta]_{max.}$	
T/°C	$n\rightarrow\pi^*$ (λ 327 nm)	$\pi\rightarrow\pi^*$ (λ 287 nm)	$n\rightarrow\pi^*$ (λ 311 nm)	$\pi\rightarrow\pi^*$ (λ 267 nm)	$n\rightarrow\pi^*$ (λ 325 nm)	$\pi\rightarrow\pi^*$ (λ 243 nm)	$n\rightarrow\pi^*$ (λ 326 nm)	$\pi\rightarrow\pi^*$ (λ264 nm)
+24	+610	−630 (dioxan)	+7 810	−2 440	−1 240	+11 300	−910	+5 100
−68	+1 650		+14 200	−3 160	−1 740	+16 900	−1 700	
−190	+2 650		+23 600	−5 280	−1 520	+23 800	−2 960	

[a] In diethyl ether–2-methylbutane–ethanol (5 : 5 : 2).

The major conformer of compound (6) was predicted to be the ' steroid-like ' (G) from the cisoid-enone rule.[9,10] The positive $\pi\rightarrow\pi^*$ Cotton effect increases with lower temperatures; this indicates that the population of the major conformer (G) at the conformational equilibrium increases as the temperature decreases. The $|\Delta G^\circ|$ value is estimated to be *ca.* 3.8 kJ mol^{-1} from the temperature variation in the positive Cotton effects, on the assumption that compound (6) existed only as the two conformers (G) and (H). This value agrees approximately with the result obtained from n.m.r. spectroscopy ($|\Delta G^\circ|$ 5.4 kJ mol^{-1} estimated from the signal intensity ratios of the major to the minor conformers).

On the other hand, the application of the Snatzke rule [9,11] to compounds (4) and (5) required consideration of the conformation of the B-ring. Examination of the molecular models showed three possible conformations of the aryl ketone moiety, *i.e.* half-chair, sofa, and deformed sofa. The sign of the $n\rightarrow\pi^*$ Cotton effect for a wide variety of aryl ketones for which the absolute configurations were established has revealed that the preferred conformations were those of the sofa and deformed sofa.[12] The c.d. curves obtained from compounds (4) and (5) indicate the ' non-steroid-like ' conformation (D) for compound (4) and the ' steroid-like ' conformation (E) for compound (5) as the preferred ones.

Variable-temperature ^{1}H n.m.r. spectra of 10β-hydroxyligularone (7) in carbon disulphide–[^{2}H]chloroform (3 : 1) at 60 MHz shows no significant changes down to −60 °C for a highly diluted solution, because of the conformation (A) in the crystal state.[13] This is in good agreement with the present results.

An attempt to find which conformer is preferred for the 8,12-epoxyeremophila-7,11-diene (9) [14] using variable-temperature ^{13}C n.m.r. spectroscopy (15 MHz) down to −100 °C was not successful, because the Gibbs energy of activation is much smaller for compound (9); some signals broaden, but only below −90 °C.

Thus, this study (*a*) revealed the presence of conformational equilibria in solution for various types of eremophilane derivatives, (*b*) assigned the conformations of isomers in equilibrium together with their population for each compound studied, and (*c*) showed that the conformational equilibria or ΔG° values are strongly dependent upon the structure differences, *e.g.* hydroxy-substitutions, the positions of a double bond and a ketone group, *etc.*, and the solution conditions. Although the simple conformational analyses which were attempted do not explain the predominance of these conformers, the results obtained should enable the equilibrium conditions of eremophilane derivatives and other *cis*-decalin derivatives to be inferred.

EXPERIMENTAL

The ^{1}H n.m.r. spectra were measured using JEOL PS-100 (100 MHz), Hitachi R-20 (60 MHz), and/or JEOL FX-60 (60 MHz in the FT mode) spectrometers with Me_4Si as the internal reference. Accuracies of δ_H and *J* values are ±0.02 p.p.m. and ±0.5 Hz, respectively. The ^{13}C n.m.r. spectra were recorded on a Varian NV-14 FT n.m.r. spectrometer at

TABLE 4

^{1}H and ^{13}C N.m.r. spectral data of the eremophilane derivatives (1)—(6) and (9)

	^{1}H N.m.r. (δ_H) [a]						^{13}C N.m.r. (δ_C) of (9) [b]			
	(1)	(3)	(4)	(5)	(6)	(9)		$CDCl_3$	CD_2Cl_2	$(CD_3)_2CO$
6-H	4.69 (br,s)	4.31 (br,s)			2.05 (m) 2.70 (m)		C-1	29.7	30.0	30.2
							C-2	20.9	21.3	21.5
9-H			2.85 (m)	2.20 (m) 2.85 (m)	2.30 (m)		C-3	29.7	30.0	30.2
							C-4	36.2	36.4	36.8
10β-H				2.25 (m)	1.75 (m)		C-5	35.9	36.2	36.4
							C-6	28.9	29.3	29.5
12-H	7.05 (m)	7.08 (m)	7.07 (m)	7.08 (m)	1.96 (s)	7.10 (m)	C-7	115.4	115.8	116.0
							C-8	148.8	149.1	149.1
13-H	2.03 (d)	2.06 (d)	2.20 (d)	2.20 (d)	1.80 (s)	1.90 (d)	C-9	26.9	27.2	27.3
							C-10	36.6	36.9	37.2
14-H	0.88 (d)	1.04 (d)	0.88 (d)	0.98 (d)	0.86 (d)	0.96 (d)	C-11	119.9	120.3	120.3
							C-12	137.0	137.3	137.8
15-H	1.00 (s)	0.88 (s)	1.12 (s)	1.31 (s)	0.97 (s)	0.90 (s)	C-13	8.1	8.2	8.1
							C-14	15.2	15.3	15.4
							C-15	23.9	24.1	24.2

[a] At 38 °C in $CDCl_3$. [b] At 30 °C. Slow inversion was not observed down to −100 °C.

15.087 MHz using Me_4Si as the internal reference. Fourier-transform (FT) measurement conditions were as follows: spectral width 3 923 Hz, pulse flipping angle 16° (pulse width, 10 μs), acquisition time 0.6 s, number of data points 4 820, number of FT 8 192, number of transients *ca.* 12—20 K.

The ^{1}H n.m.r. spectral data for ligularol (1) (8,12-epoxyeremophila-7,11-dien-6β-ol), ligularol acetate (2) (6β-acetoxy-8,12-epoxyeremophila-7,11-diene), 6-*epi*-ligularol (3) 8,12-epoxyeremophila-7,11-dien-6α-ol), ligularone (4) (8,12-epoxyeremophila-7,11-dien-6-one), isoligularone (5) (6,12-epoxyeremophila-6,11-dien-8-one), fukinone (6) (eremophil-7-en-8-one), and 8,12-epoxyeremophila-7,11-diene (9) and the ^{13}C n.m.r. data for compound (9) are listed in Table 4.

Gibbs free-energies of activation at coalescence temperatures for 'steroid-like' ⇌ 'non-steroid-like' inversion, $\Delta G_c^{\ddagger}$, were calculated from the standard equations [15] using singlet-to-doublet splitting patterns (unequal intensities) of complete ^{1}H-decoupled ^{13}C dynamic n.m.r. spectra. The $\Delta G_c^{\ddagger}$ values, estimated using several ^{13}C signals which gave both clear T_c values (±3 K) and distinct chemical-shift differences ($\Delta\nu$, ±1.7 Hz), were almost equal within the estimated error range, ±1.5 kJ mol^{-1}. Thus, an average value of $\Delta G_c^{\ddagger}$ for each compound is given in the text.

The c.d. spectra were taken with a JASCO ORD/CD-5 spectrometer.

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