Conformational Isomers and Ring Inversion of Neolinderalactone, a Ten-membered-ring Furanosesquiterpene

By Kazuo Tori,* Isao Horibe, Kaoru Kuriyama, and Ken'ichi Takeda

(*Shionogi Research Laboratory, Shionogi & Co., Ltd., Fukushima-ku, Osaka, Japan*)

Summary The ^1H n.m.r. and c.d. spectra of two conformational isomers of neolinderalactone (I) at various temperatures have been examined to determine their conformations, their Gibbs' free energy difference, and the potential barrier to inversion of the ten-membered ring.

In the course of conformational studies of ten-membered carbocyclic rings in furanosesquiterpenes isolated from natural sources,[1–3] we have found that the ^1H n.m.r. spectra of neolinderalactone (I)[4] in various solvents show two conformational isomers existing in a ratio of about 8 : 2 at room temperature, as reported for isabelin.[5] We report here the unambiguous determination of these two conformations of the ten-membered ring, the enthalpy difference between the isomers, and the potential barrier to ring inversion, by the use of ^1H n.m.r. and c.d. spectroscopy.

The 100 MHz ^1H n.m.r. spectra of (I) at various temperatures showed that two sets of signals, one set corresponding to each conformer, gradually collapse to one set of signals at about 55—85° in [^2H]chloroform and in [$^2H_6$]benzene. The low-temperature spectra in both solvents were therefore examined to determine each conformation (see Table 1). As the temperature becomes lower, the population of the major conformer increases; the ratio is 79 : 21 at 30° and

TABLE 1

Chemical shifts (τ *value*) *and N.O.E. values* (*increases in integrated intensities,* %)[a] *for the conformers* (A) *and* (B) *of neolinderalactone in* $CDCl_3$ *at* —40° *and in* C_6D_6 *at* 8° (*in parentheses*)[b]

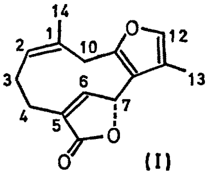
		Signal							
Conformer		2-H	6-H	7-H	10α-H	10β-H	12-H	13-H	14-H
A	τ	4·83 br t	3·11 d	4·21 q	6·93 d	7·20 br d	2·90 q	7·92 d	8·42 br s
(major)	τ	(5·22)	(3·85)	(4·69)	(7·05)	(7·48)	(3·24)	(8·30)	(8·55)
	N.O.E.	15 (22) [14-H]	12 (11) [7-H]	10 (15) [6-H]			27 (28) [13-H]		
B	τ	4·83 br t	2·64 br s	4·21	6·42 d	7·08 br d	2·88 br s	7·91 d	8·54 br s
(minor)	τ	(4·98)	(3·43)	(4·69)	(6·71)	(7·25)	(3·17)	(8·26)	(8·59)
	N.O.E.		6 (13) [7-H] (7) [10α-H]	(12) [6-H]					

[a] Saturated signals are shown in square brackets.

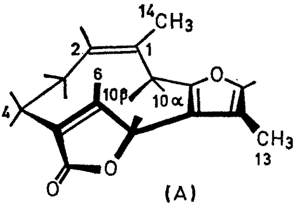
[b] The experimental procedures are similar to those previously described.[1] Accuracies are about $\pm\ \tau$ 0·01 for chemical shifts and about $\pm 2\%$ for N.O.E.'s.

81 : 19 at —40° in [^{2}H]chloroform. The signal assignments of the spectra were made by double- and triple-resonance experiments.

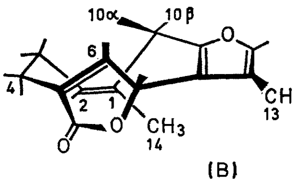
Examination of molecular models suggests two conformations (A) and (B) for (I). The major and minor isomers were unambiguously concluded to adopt the conformations (A) and (B), respectively, from the following facts. (a) An intramolecular nuclear Overhauser effect (N.O.E.)[6] was observed on the 6-H(B) signal, when the 10α-H(B) signal was saturated on double irradiation, whereas no N.O.E.'s were observed for the 6-H(A) and the 6-H(B) signals on saturation of the 10α-H(A) signal.[7] (b) A large difference in the chemical shift between 6-H(A) and 6-H(B) results from the difference in anisotropic shielding effects of their C-1 : C-2 double bond;[8] similarly, the higher-field position of the 1-Me(B) signal as compared with that of the 1-Me(A) signal can be accounted for by anisotropy of the αβ-unsaturated ketone.[9] (c) Benzene-induced shifts[10,11] are large for the 2-H(A) and 1-Me(A) signals, whereas they are fairly small for the 2-H(B) and 1-Me(B) signals, though still upfield, as would be expected from their conformations.



(I)



(A)



(B)

The potential barrier to inversion of the ten-membered ring was obtained by comparing the variable-temperature spectra of the 6-H signal in [$^2H_6$]benzene (see the Figure) and of the 1-Me signal in [^{2}H]chloroform with the theoretical signal-shapes[12] calculated on the following assumptions; (a) $T_2(A) = T_2(B)$, (b) the 8 : 2 ratio of the fractional population of the isomers is constant over the temperature range examined (55—85°), and (c) the differences in the relevant signal-shapes between the isomers due to several weak spin-couplings are negligibly small. This approximate method gave linear relationships between log $(1/\pi\tau_B\Delta\nu)$ and $1/T$ (when $p_A = 0{\cdot}8$) for the two relevant signals; τ, $\Delta\nu$, and p are mean life-time, chemical-shift difference, and fractional population, respectively. Thus, the barrier to the inversion, ΔE, was determined as about 10 kcal/mole.

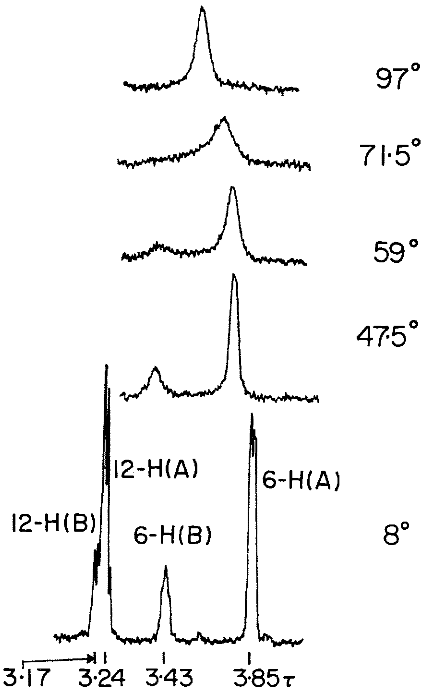


FIGURE. *The variable-temperature* ^{1}H *n.m.r. spectra of* 6-H *of neolinderalactone* (I) *in* C_6D_6 *at* 100 *MHz.*

The variable-temperature c.d. spectra of (I) were measured to obtain further insight into the conformational equilibrium (see Table 2). Examination of the temperature-dependency of the positive parts of the c.d. curve at 260 and 222 nm shows the Gibbs' free energy difference, ΔG, between (A) and (B) to be 0·6 ± 0·2 kcal/mole, assuming that the entropy difference is zero.[13]

TABLE 2

C.d. data on neolinderalactone at various temperatures in ethanol

	Observed rotational strength, R_o ($\times 10^{40}$ c.g.s.)				Calculated values		
	60°	25°	0°	−68°	R_a ($\times 10^{40}$ c.g.s.)	R_b	ΔG (kcal/mole)
222 nm	57·9	59·7	62·3	65·5	80	2	0·6 ± 0·2
260 nm	5·25	5·58	5·85	6·27	8·15	−1·85	0·6 ± 0·2

Provided that the octant rule[14] is applicable to the 260 nm Cotton effects for both conformers (A) and (B), it is suggested that (A) should exhibit a strong positive effect (because of the positive contribution of the furan ring), while (B) should give a weak negative Cotton effect (because of the more negative contribution of the C-1 : C-2 double bond as compared with the positive contribution of the furan ring). It follows that the conformer (A) is more stable than (B) in view of the experimental results. This conclusion is compatible with that from the n.m.r. spectra. Therefore, the octant rule can apparently be applied to a 260 nm Cotton effect due to the $n \rightarrow \pi^*$ transition of an $\alpha\beta$-unsaturated γ-lactone, when the carbonyl group is directly perturbed by another π-system.

(*Received, May 27th,* 1970; *Com.* 807.)

---

[1] K. Tori, M. Ohtsuru, I. Horibe, and K. Takeda, *Chem. Comm.*, 1968, 948.
[2] H. Hikino, C. Konno, T. Takemoto, K. Tori, M. Ohtsuru, and I. Horibe, *Chem. Comm.*, 1969, 662.
[3] K. Tori, M. Ohtsuru, I. Horibe, and K. Takeda, 6th International Symposium on the Chemistry of Natural Products (Steroids and Terpenes), Mexico City, April, 1969, Abstract p. 33.
[4] K. Takeda, I. Horibe, M. Teraoka, and H. Minato, *J. Chem. Soc.* (*C*), 1969, 2786.
[5] H. Yoshioka, T. J. Mabry, and H. E. Miller, *Chem. Comm.*, 1968, 1679; H. Yoshioka and T. J. Mabry, *Tetrahedron*, 1969, **25**, 4767.
[6] F. A. L. Anet and A. J. R. Bourn, *J. Amer. Chem. Soc.*, 1965, **87**, 5250.
[7] J. K. Saunders and R. A. Bell, *Canad. J. Chem.*, 1970, **48**, 512.
[8] J. W. ApSimon, W. G. Craig, P. V. Demarco, D. W. Mathieson, L. Saunders, and W. B. Whalley, *Tetrahedron*, 1967, **23**, 2357, and references therein.
[9] J. W. ApSimon, P. V. Demarco, D. W. Mathieson, W. G. Craig, A. Karim, L. Saunders, and W. B. Whalley, *Tetrahedron*, 1970, **26**, 119, and references therein.
[10] P. Laszlo, *Progr. NMR Spectroscopy*, 1968, **3**, 231.
[11] J. D. Connolly and R. McCrindle, *Chem. and Ind.*, 1965, 379, 2066.
[12] T. Nakagawa, *Ann. Report Shionogi Res. Lab.*, 1963, **13**, 60.
[13] A. Moscowitz, K. Wellman, and C. Djerassi, *J. Amer. Chem. Soc.*, 1963, **85**, 3515.
[14] W. Moffit, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, 1961, **83**, 4013.