Lanthanoid-induced Shifts as a Configurational Tool for Some Bicyclo[3.1.0]hexane Derivatives

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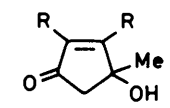
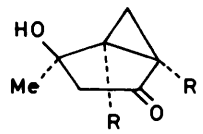
The ^{1}H n.m.r. spectra of 1,5-diacetyl-4-hydroxy-4-methylbicyclo[3.1.0]hexan-2-ones (**2**) and (**3**) and diethyl 4-hydroxy-4-methyl-2-oxobicyclo[3.1.0]hexane-1,5-dicarboxylate (**6**) were determined in the presence of the shift reagent Eu(fod)$_3$. The observed induced shifts provide evidence for the relative configuration of the asymmetric centres of these compounds.

Our research on activated ethylenic systems has included bicyclo[3.1.0]hexane derivatives.[1–3] We have reported that 2,3-diacetyl-4-hydroxy-4-methylcyclopent-2-enone (**1**) reacts with diazomethane to give a mixture of the stereoisomeric 1,5-diacetyl-4-hydroxy-4-methylbicyclo[3.1.0]hexan-2-ones (**2**) and (**3**) and the cyclopenta[*b*]oxetane (**4**), and that diethyl 3-hydroxy-3-methyl-5-oxocyclopent-1-ene-1,2-dicarboxylate (**5**) reacts with diazomethane to yield only one bicyclo[3.1.0]hexane derivative (**6**) and the cyclopenta[*b*]oxetane (**7**).

Since the stereochemical assignment of compounds (**2**), (**3**), and (**6**) remained uncertain, we have applied the lanthanoid shift-reagent technique to this problem.



(1) R = Ac
(5) R = CO_2Et



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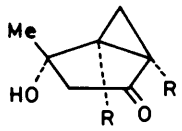

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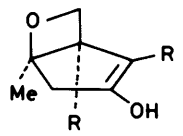
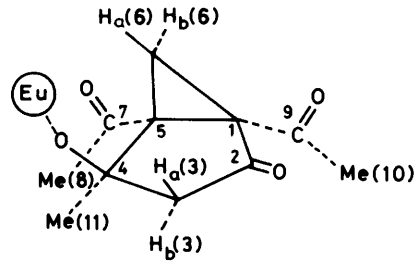
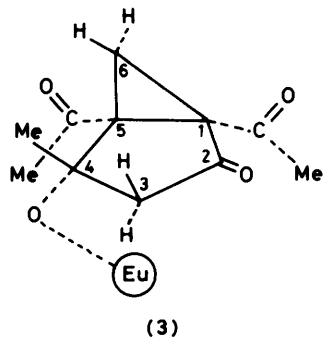


(4) R = Ac
(7) R = CO_2Et



(2)



(3)

Figure. Views of (**2**) and (**3**) showing the approximate position of europium

Results and Discussion

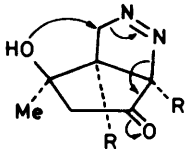
Examination of the induced shifts led us to exclude a chair conformation for compounds (**2**), (**3**), and (**6**). They are assumed to exist in a boat or a flattened boat conformation in view of literature data on bicyclo[3.1.0]-hexanes and -hexanones.[4–7]

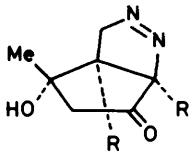
The slopes of the least-squares linear plots of the induced shifts *vs.* Eu(fod)$_3$-to-substrate concentration ratios (C_{Eu}/C_s) are referred to as binding shifts (ΔM).[8,9] The values of these shifts for compounds (**2**), (**3**), and (**6**) are reported in the Table together with relative correlation coefficients. Since ΔM_{OH} = 20 for all these compounds, we assume that the binding centre for the lanthanoid ion was the hydroxy group, in accord with literature data: OH is a far stronger co-ordinating centre than carbonyl or carboxy groups.[8,9] Moreover the lines obtained in the plots are good straight lines, which excludes the possibility of competition amongst functional groups in co-ordinating Eu(fod)$_3$.[8,9]

The rigidity of the three compounds results in nearly fixed distance relationships amongst the protons at positions 3 and 6 and the methyl protons at position 4, allowing the identification of the isomers on the sole basis of the direct proportionality between ΔM and the reciprocal of the Ln–proton distances,[8,9] *i.e.* as the distance increases, ΔM decreases ($\Delta M \propto r^{-1}$).

Analysis of the ΔM values of the isomers (**2**) and (**3**) enables the following conclusions to be drawn: (i) the ΔM values of the isomer of m.p. 100 °C are nearly twice those of the other; (ii) in both isomers the sequence of binding shifts is the same: ΔM (methylene) > ΔM (cyclopropane protons) > ΔM (methyls). For the isomer of m.p. 78 °C ΔM of one methylene proton is slightly smaller than that of one proton of the cyclopropane ring: however, this fact does not alter this discussion and the conclusion. (iii) For the isomer of m.p. 78 °C the ΔM values of the three methyl groups are nearly the same; for the other isomer only two methyl groups (4-Me and one acetyl group) show the same ΔM, the third one being notably different.

If we suppose that the OH group is *cis* to the cyclopropane ring, the only binding environment for the europium ion which fits the ΔM sequence is that depicted in the Figure. In this situation two methyl groups are nearer to the europium ion than the third: *i.e.* the 4-Me and the 5-acetyl Me (in the latter case an average distance must be considered). Consequently the corresponding ΔM values for these two are greater than the


(8)


(9)

third. Thus the compound showing this ΔM behaviour must be the isomer (2), and the other isomer (3). If the OH group is *trans* with respect to the cyclopropane protons, the europium position in the complex will be as depicted in the Figure, to satisfy the ΔM sequence. In this position the distances between Eu and the three methyl groups are nearly the same; moreover all the Eu–proton distances are greater and consequently ΔM values are lower, as is observed.

For compound (6) (i) the ΔM values for the 3-protons and the 4-methyl group are close to the corresponding values for isomer (2); (ii) ΔM of 6-H_b is smaller than in (2) but still nearer to the value for (2) than to that for (3); (iii) ΔM of 6-H_a is midway between those for (2) and (3). Thus for the proton(s) that can be compared, the ΔM sequence of (6) gives an overall picture closer to (2) than to (3).

Notwithstanding the absence of the stereoisomer of (6), the shift data point to a configuration at C-4 the same as that in compound (2).

Reaction Mechanism

The orientation rules for diazoalkane cycloadditions to electron-deficient multiple bonds require formation of the dihydropyrazoles (8) and (9) from the interaction of diazomethane and the alkenes (1) and (5).

Although there are many studies on the regioselectivity of these cycloadditions, few deal with the stereochemical orientation.[10] Our results show that the presence of an asymmetric carbon at position 4 of the cyclopentenones (1) and (5) has an important effect on the approach of the diazomethane.

The cyclopentapyrazole (8) gives rise to the bicyclo[3.1.0]-hexane (2) or the cyclopenta[*b*]oxetane (4). The formation of the latter may be explained by nucleophilic attack by the neighbouring OH group on the methylene of the dihydropyrazole. The overall yields of (2) and (4) account for 71.2%; compound (3), derived from the dihydropyrazole (9), accounts for 3.1%. Thus diazomethane shows a marked preference for approach to the cyclopentenone from the less hindered side, *i.e.* the OH face. Although the steric factor seems to play a dominant role, one cannot in principle disregard the possibility of a co-ordinating action between the OH group and the diazomethane molecule.[11]

In the case of the cyclopentenone (5) we obtained the bicyclo[3.1.0]hexane (6) and the cyclopenta[*b*]oxetane (7) in 86% overall yield. Examination by ^{1}H n.m.r. of all the different fractions of the reaction mixture separated by column chromatography showed no trace of the other stereoisomer. Thus the nature of the substituents at positions 2 and 3 must also have some influence on the stereochemistry of the cycloadducts. It follows that the structural assignment for compound (6) based on a stereoselective effect due to the presence of an asymmetric centre is in complete accord with that inferred from the n.m.r. shift study.

Experimental

The synthesis of compounds (2), (3), and (6) is reported in refs. 2 and 3; 60 MHz ^{1}H n.m.r. spectra were obtained with a Hitachi-Perkin-Elmer spectrometer operating in the Fourier transform mode, with Me_4Si as internal reference at 35 °C. Compounds (2), (3), and (6) were dissolved in dry $CDCl_3$ (99.8% deuteriated; Merck), to give 0.3M-solutions; Eu(fod)$_3$ (C. Erba) was sublimed at 15 °C and 0.05 mmHg, dried *in vacuo* (P_2O_5) for 24 h, and then added to each solution in successive steps (a few mg at time).

Compound (2): δ($CDCl_3$) 1.51 (s, 3 H, 11-Me), 1.92 (br d, 1 H, 6-H_b), 2.31 (s, 3 H, 10-Me), 2.44 (d, 1 H, 6-H_a), 2.46 (s, 3 H, 8-Me), 2.50 (AB, 2 H, 3-H_2), and 2.92 (br s, 1 H, OH).

Compound (3): δ($CDCl_3$) 1.50 (s, 3 H, 11-Me), 1.70 (d, 1 H, 6-H_b), 2.17 (s, 3 H, 8 or 10-Me), 2.30 (AB, 2 H, 3-H_2), 2.47 (s, 3 H, 10 or 8-Me), 2.60 (br d, 1 H, 6-H_a), and 4.98 (br s, 1 H, OH).

Compound (6): δ($CDCl_3$) 1.26 (t, 3 H, *Me*CH_2), 1.29 (t, 3 H, *Me*CH_2), 1.64 (s, 3 H, 11-Me), 1.99 (d, 1 H, 6-H_b), 2.20 (d, 1 H, 3-H_b), 2.22 (br d, 1 H, 6-H_a), 2.61 (br d, 1 H, 3-H_a), 2.74 (vbr s, 1 H, OH), 4.21 (q, 2 H, CH_2), and 4.23 (q, 2 H, CH_2).

Table. Experimental binding shifts (ΔM) of compounds (2), (3), and (6)[a]

(2)		(3)		(6)[b]	
Proton(s)	ΔM	Proton(s)	ΔM	Proton(s)	ΔM
H_a(3)	8.09	H_b(3)	4.71	H_a(3)	7.80
H_b(3)	7.01	H_a(3)	3.63	H_b(3)	6.82
H_a(6)	6.71	H_a(6)	3.69	Me(11)	6.31
H_b(6)	6.30	H_b(6)	3.12	H_a(6)	5.34
Me(11)	6.10	Me(11)	2.84	H_b(6)	5.13
Me(8)	6.03	Me(8)[c]	2.95	Me(8)	2.17
Me(10)	4.71	Me(10)[c]	2.70	Me(10)	1.43

[a] Correlation coefficients of the least-squares linear plots (9 points) are 0.997, 0.996, and 0.991 or better for compounds (2), (3), and (6), respectively. For numbering of structures see Figure. [b] It was impossible to follow unambiguously the two methylene signals of the ethoxycarbonyl groups, so we do not report them. [c] These assignments may be interchanged.

Acknowledgements

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