A ^{13}C and ^{1}H Nuclear Magnetic Resonance Study of Some Diastereoisomeric Homoeburnane Derivatives

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Several 14-hydroxy-*E*-homoeburnane diastereoisomers have been synthesized and studied by ^{1}H and ^{13}C n.m.r. spectroscopy. The relative configurations and predominating conformations have been established. It has been shown that previous assignments of C-17 and C-20 signals of *trans-D/E*-ring-fused Vinca alkaloids must be reversed.

Buzas *et al.*[1] obtained the 14-hydroxy-*E*-homoeburnane epimers (**1**)—(**4**) either by the reaction of acrylaldehyde with a suitable indolo[2,3-*a*]quinolizinium perchlorate followed by reduction, or by treatment of the appropriate lactams with lithium aluminium hydride. A similar route has been followed in the chiral synthesis of Vinca alkaloids.[2] Compounds (**3**) and (**4**) have also been synthesized by researchers at Roussel-Uclaf, but the configuration of C-14 has not been established.[3] Compounds (**1**)—(**4**) are to be used as intermediates in producing further derivatives in order to study pharmacological structure–activity relationships. Thus, a thorough stereochemical investigation of these compounds has become of particular importance.

On reproducing Buzas' experiments, *i.e.* reducing the appropriate pentacyclic iminium salt with sodium borohydride, the *trans-D/E*-ring-fused derivative (**1**) was obtained under kinetic control as the main product. Under basic conditions (**1**) was transformed into the more stable epimer (**2**). In synthesizing the *cis-D/E*-ring-fused 14-OH epimers we used the more readily available optically active (+)-14-oxo-*E*-homoeburnane (**5**) as starting material instead of the racemic compounds.[4] Reduction of (**5**) with lithium aluminium hydride gave a 100:1 mixture of epimeric alcohols (**3**) and (**4**).

In contrast to the vincanol derivatives having a six-membered ring *E*, in compounds (**1**)—(**4**) two possible stable conformations of the seven-membered ring must be taken into account, a chair and a twist boat (Scheme) making stereochemical investigation more difficult. A boat conformation involves severe strain and steric interaction, and can thus be discounted as being the predominant conformation. Although compounds (**1**) and (**2**) were racemates, we show in the structural formulae only enantiomers containing the 3-H in the α-position. The assignments of the relative configurations at C-14 in compounds (**1**)—(**4**) were based by Buzas *et al.*[1] on the fact that the chemical shift of 14-H in the pairs of epimers (**1**) and (**2**), and (**3**) and (**4**), differs by about 0.3 p.p.m. On the basis of the well known relationship $\delta H_{ax} < \delta H_{eq}$ it was concluded that in (**1**) and (**3**) the 14-OH group is α and axial, whereas in (**2**) and (**4**) it is β and equatorial. However, in view of the conformational possibilities shown in the Scheme, and also the multiplicity of the 14-H signals, their interpretation appears unacceptable.

The characteristic ^{1}H and ^{13}C n.m.r. data of compounds (**1**)—(**7**) are collected in Tables 1 and 2. The 14-H signals show small splittings in the spectra of both (**1**) and (**2**); this indicates that the predominant conformation of ring *E* in epimer (**1**) is a twist boat, whereas in epimer (**2**) it is a chair. The OH group becomes quasi-axial in both compounds, thus avoiding steric compression with 12-H. Since the unambiguous identifications of epimers (**1**) and (**2**) is not possible on the basis of the multiplicities and chemical shifts of the 14-H signals, we determined the characteristic lanthanoid-induced shift (l.i.s.) values, which were derived from a linear extrapolation to a lanthanoid–substrate molar ratio of 1:1 using $Eu(fod)_3$ as shift reagent. If we assume a normal 30 pm length for the Eu–O bond, and that the Eu atom is in the energetically preferential antiperiplanar position with respect to N-1, application of the MacConnell equation[5] shows that the 3-H resonance will be shifted more in the case of (**2**) than that of (**1**). In order to minimize the effects of possible measurement errors, the Δδ(3-H) values were divided by the appropriate Δδ(12-H) values. The latter are expected to be identical for the two compounds, since the steric surroundings of the Eu atom and the 12-H are essentially the same. The quotients 0.58 and 1.70 thus obtained show that the main product corresponds to structure (**1**), and the secondary product to structure (**2**).

From a comparison of the predominant conformations of (**1**) and (**2**), the driving force for the epimerization (**1**) → (**2**) can be attributed to the fact that in compound (**2**) ring *E* possesses the more preferred chair conformation. Furthermore there is no steric repulsion between 14-OH and C-20. ^{13}C N.m.r. measurements provide further evidence for the deduced stereostructures. In the interpretation of the ^{13}C spectra we have used the assignments for Vinca alkaloids originally given by Danielli *et al.*,[6] and slightly modified by Kalaus *et al.*[7] However, these data lead to contradictions concerning the C-17 and C-20 signals in our compounds. Therefore we studied 14-*epi*- (**6**) and 14-*epi*, 3-*epi*-vincanol (**7**). In the epimer (**6**), C-17 exists in a γ-gauche arrangement with C-14 and C-2, but these interactions are not found in the epimer (**7**). Therefore we expect the C-17 signal to appear at significantly higher field in the case of the epimer (**6**). Moreover, in compound (**7**) C-20 enters into a γ-gauche interaction with C-14 and C-2; thus a characteristic decrease in the chemical shift of C-20 is expected. Consequently, it seems that in the ^{13}C assignments for (**7**) based on the literature data,[6] the assignments [δ(C-17) = 21.1, δ(C-20) = 32.1] should be reversed. In order to prove this point, we performed ^{13}C shift reagent measurements with $Eu(fod)_3$, and also obtained the noise-modulated off-resonance spectrum of (**7**).[8] The characteristic l.i.s. values are shown in Table 2. In the light of the stereostructure of (**7**), of the induced shifts of C-6, C-17, C-18, and C-20, the effect on C-20 is expected to be the largest and that on C-17 the smallest, irrespective of whether the Eu atom is attached to N-4 or to oxygen. As the obtained l.i.s.

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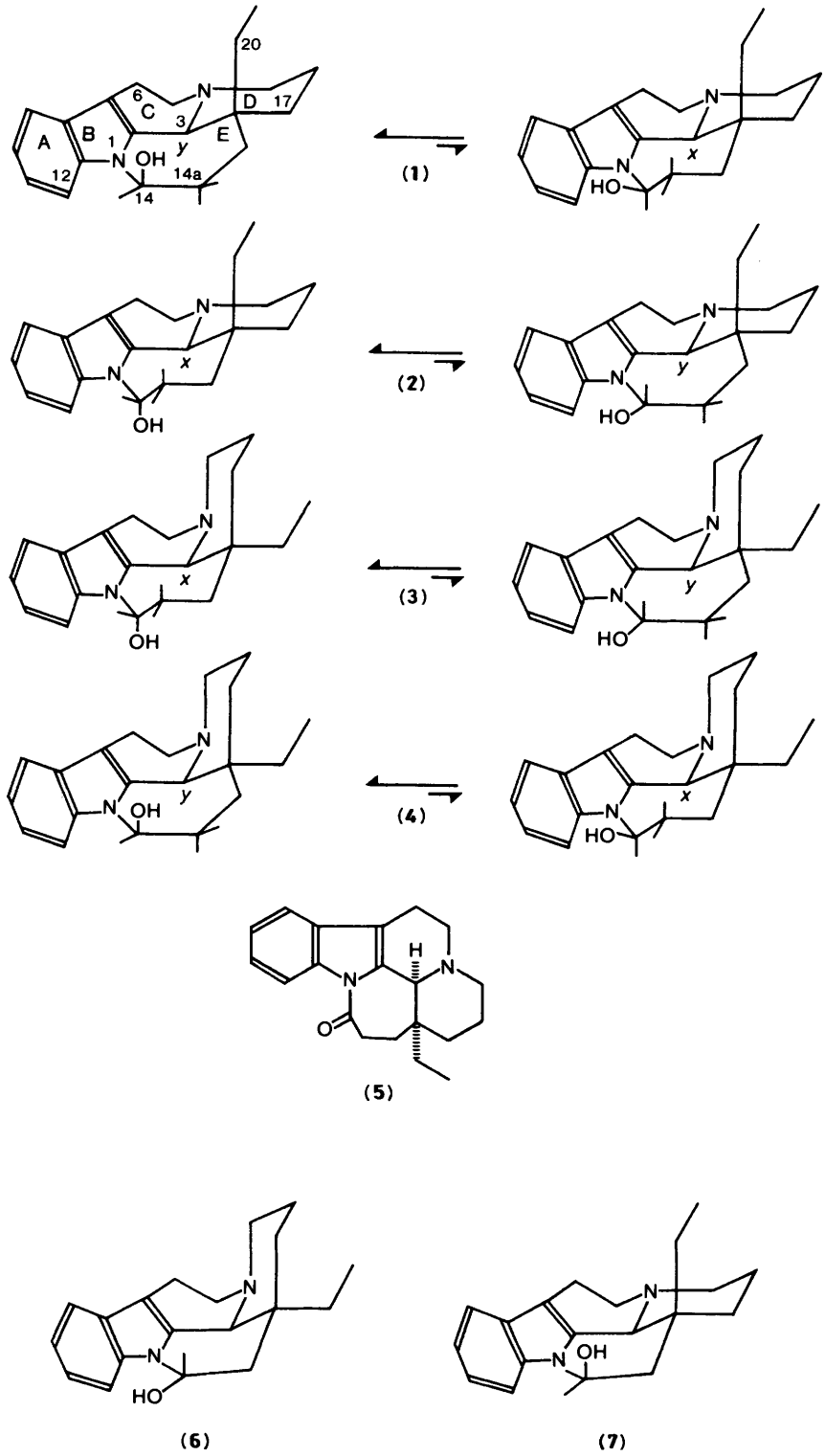

Scheme.

values show, the signal at δ 32.1 can be assigned to C-17, and that at δ 21.1 to C-20.

In noise-modulated off-resonance spectra, both quaternary carbon atoms and methylene carbon atoms bearing isochronous protons give sharp singlet signals, the latter with 25% intensity.[8] In compound (7), although the C-20 protons are diastereotopic, they show very little shift difference, whereas that between the ring protons at C-17 is considerably larger, since their positions are axial and equatorial. From comparison of the broad-band proton-decoupled ^{13}C spectrum of (7) and the noise-modulated off-resonance spectrum, it becomes obvious that the 21.1 p.p.m. signal has to be assigned to C-20. Accordingly, the assignments of the appropriate Vinca and eburnane alkaloids (among them the 14-*epi*-, 3-*epi*-vincamine[6])

Table 1. Characteristic ^{1}H n.m.r. data and Δδ (l.i.s.) values ($CDCl_3$)

	(1)	(2)	(3)	(4)	(5)	(6)	(7)
3-H	3.34(s)	3.36(s)	4.01(s)	4.05(s)	4.45(s)	3.48(s)	3.10(s)
14-H	5.86(dd)	6.04(dd)	6.20(dd)	5.84(t)		5.40(dd)	5.81(t)
J/Hz	4.6[a]	4.4[a]	6.0[a]	5.4[a]		9.5, 4.9	5.1
Δδ(3-H)/Δδ(12-H)	0.58	1.70	1.40	0.65			

[a] J(14-H, 14a-H_{ax}) + J(14-H, 14a-H_{eq}).

Table 2. ^{13}C Chemical shifts and Δδ (l.i.s.) values ($CDCl_3$)

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(7)Δδ
C-2	134.8	135.1	134.7	134.2	129.8	132.7	132.3	
C-3	67.9	70.4	64.0	62.2	62.4	58.5	67.2	2.6
C-5	53.8	53.5	51.6	52.4	51.3	50.6	53.5	1.7
C-6	22.1[a]	22.1[a]	17.4	17.7	16.6	16.9	20.5	2.0
C-7	112.9	112.6	111.3	110.6	116.5	105.2	105.6	
C-8	127.3	126.9	128.1	128.3	129.0	128.7	128.6	
C-9	117.9	117.9	118.0	117.9	117.6[a]	118.1	118.3	
C-10	119.9	119.4	119.8	120.3	123.8	120.9	119.8	
C-11	121.8	121.2	121.6	122.1	125.1	121.6	120.8	
C-12	110.3	108.5	109.3	110.9	117.4	112.3	110.6	
C-13	136.8	138.0	136.5	137.9	136.2	136.8	135.4	
C-14	78.9	75.7	76.5	79.7	172.5	76.5	75.3	
C-14a	37.6	35.4	30.7	32.9	31.9[a]			
C-15	29.1	29.1	29.4	30.2	31.3[a]	43.1	39.6	4.4
C-16	38.4	38.8	38.8	38.9	38.2	36.7	35.2	2.9
C-17	30.1	31.0	26.3	29.0[a]	27.7	24.7	32.1	1.3
C-18	22.4[a]	22.0[a]	20.9	21.7	19.6	20.3	21.2	1.6
C-19	56.8	56.7	44.5	45.7	46.3	44.3	56.0	1.4
C-20	24.3	19.2	28.3	28.5[a]	30.6	28.5	21.1	2.8
C-21	6.9	6.8	7.5	7.7	7.4	7.5	7.4	

[a] Tentative assignment.

need modification as stated above. The data listed in Table 2 are modified to take this into account.

In view of the intramolecular distances between C-14a and C-3 and the protons attached to them in (**1**) and (**2**), on the basis of Grant's formula,[9] C-3 is expected to be more shielded in (**1**), which is in good agreement with the data obtained. The chemical shift of C-14a, however, is greater by 2.5 p.p.m. in (**1**) than in (**2**); this is due to the strong γ-gauche steric effect between C-14a and C-20 in compound (**2**).

Reduction of the *cis-D/E*-ring-fused lactam (**5**) gave epimers (**3**) and (**4**), in which the seven-membered rings may also be considered to exist in two possible conformations. From the small splittings of the 14-H signals (Table 1) it follows that the 14-OH groups are again in the quasi-axial position in both (**3**) and (**4**).

The main product (**3**) is energetically more stable, and cannot be transformed into (**4**) with the aid of alkaline catalysts, whereas according to the literature[3] compound (**4**) can be epimerized into (**3**). From a comparison of the predominant conformations of (**3**) and (**4**), in compliance with the behaviour found for the *trans-D/E*-ring-fused analogues, ring *E* of (**3**) is expected to exist mainly in the chair conformation.

The ^{1}H shift reagent measurements with $Eu(fod)_3$ also confirmed the indicated configurations of C-14. The Δδ(3-H)/Δδ(12-H) value of 1.40 in the case of compound (**3**) correlates well with that found in compound (**2**). The value of 0.65 in the case of (**4**), similar to that of isomer (**1**), indicates a *trans* arrangement of OH and 3-H.

In comparing (**3**) with compound (**1**), it is seen that the greater shieldings observed for the signals of C-14a and C-17 in compound (**3**) are a consequence of the chair conformation of ring *E*, and are also due to the *cis-D/E*-ring fusion.

The stereostructure assigned to (**4**) is also supported by the fact that, for the same reasons as we have discussed in the case of compounds (**1**) and (**2**), a significant upfield shift of the signal of C-3 is also found in comparison with isomer (**3**). Position 14a is less shielded in (**4**) than in (**3**), and this, as already mentioned in discussing the comparison of (**1**) and (**2**), is due to the different conformations of rings *E*. Therefore the distance between C-14a and C-17 in epimer (**4**) is greater.

Experimental

The ^{1}H and ^{13}C n.m.r. spectra were recorded in the Fourier transform mode (16 K data points), at 99.6 and 25.0 MHz, with internal deuterium lock at ambient temperature, using a JEOL FX-100 spectrometer. The chemical shifts were determined on the δ scale, with tetramethylsilane as internal standard. The $^{13}C\{^1H\}$ off-resonance noise-decoupled spectrum was recorded with the centre frequency of the decoupler field 50 p.p.m. upfield from Me_4Si.

I.r. spectra were recorded with a Spectromom 2000 spectrometer. Mass spectra were taken with a JEOL-01 SG-2 instrument (70 eV; ion source temp. 150 °C, direct insertion).

(3S,14S,16S)-14α-*Hydroxy*-E-*homoeburnane* (**3**) *and* (3S,14R,16S)-14β-*Hydroxy*-E-*homoeburnane* (**4**).—Reduction of the (+)-lactam (**5**) was carried out according to the literature method.[3] The isomers were separated by preparative t.l.c. [silica gel; CH_2Cl_2–MeOH (20:2); R_F (**4**) > (**3**); elution with CH_2Cl_2–MeOH (8:2)] to yield the α-isomer (**3**) (56%), m.p. 134 °C (from light petroleum); $[\alpha]_{546}^{25}$ +78° (*c* 1.00 in $CHCl_3$); $\nu_{max.}$ 3 420 cm^{-1} (OH); *m/z* 311 (36.5%), 310 (M^+, 100; $C_{20}H_{26}N_2O$), 309 (87.5), 292 (53.6), 291 (31.7), 281 (41.5), and 267 (66.8); and the β-isomer (**4**) (0.58%), m.p. 149 °C (from light petroleum); $\nu_{max.}$

3 300 cm^{-1} (OH); *m/z* 311 (18.7%), 310 (M^+, 88.3; $C_{20}H_{26}N_2O$), 309 (62.8), 292 (53.9), 291 (33.1), 281 (22.9), 268 (21.2), and 267 (100).

14β-*Hydroxy*-3-epi-E-*homoeburnane* (**2**).—To a solution of the α-isomer (**1**) (0.20 g, 0.64 mmol) in methylene dichloride (5 ml) and methanol (2.5 ml), KOBu^t (80 mg, 0.71 mmol) was added, and the mixture was kept at room temperature for 2 h. The excess of base was decomposed with acetic acid, and the solution was evaporated to dryness. The residue was dissolved in water (5 ml), basified with NH_4OH to pH 9, and extracted with methylene dichloride (3 × 4 ml). The organic layer was dried, filtered, and evaporated to yield the β-isomer (**2**) (0.19 g, 95%), m.p. 168 °C (from EtOH); $\nu_{max.}$ 3 250 (OH), 2 790, and 2 720 cm^{-1} (Bohlmann bands); *m/z* 310 (M^+, 100; $C_{20}H_{26}N_2O$), 309 (52.9), 281 (30.4), 292 (13.0), 263 (19.2), and 237 (24.2).

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