The Acid-catalysed Lactonisation of the Norborn-5-en-2-ylacetic Acids

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The acid-catalysed lactonisation of the norborn-5-en-2-ylacetic acids affords a mixture of 2-*exo*-hydroxynorborn-7-*syn*-ylacetic acid δ-lactone and 2-*exo*-hydroxynorborn-3-*exo*-ylacetic acid γ-lactone. The latter appears to be the thermodynamically more stable lactone, and is the predominant product under extended reaction times. Product formation may be rationalised *via* a series of equilibrating norbornyl cations.

ALDER and STEIN [1] reported that the acid-catalysed lactonisation of norborn-5-en-2-*endo*-ylcarboxylic acid (1a) [1-4] afforded the γ-lactone (2a). Later it was shown by Beckmann and Geiger [3] that when either the *exo*- (3a) or *endo*- (1a) unsaturated acids were treated with 75% sulphuric acid a mixture of the γ-lactones (2a) and (4a) was initially produced, but when the reaction was prolonged the sole product was (2a) obtained in very high yield. Spectroscopic [4,5] and unambiguous synthetic [3,6] studies have rigorously established the structure (2a).

[1] K. Alder and G. Stein, *Annalen*, 1934, **514**, 197.
[2] J. D. Roberts, E. R. Trumbull Jun., W. Bennett, and R. Armstrong, *J. Amer. Chem. Soc.*, 1950, **72**, 3117
[3] S. Beckmann and H. Geiger, *Chem. Ber.*, 1961, **94**, 48.
[4] A. Factor and T. G. Traylor, *J. Org. Chem.*, 1968, **33**, 2607.
[5] (*a*) D. R. Storm and D. E. Koshland Jun., *J. Amer. Chem. Soc.*, 1972, **94**, 5805; (*b*) *ibid.*, p. 5815.
[6] G. W. Oxer and D. Wege, *Tetrahedron Letters*, 1969, 3513.

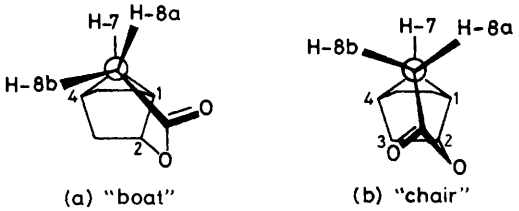


FIGURE 1

TABLE 1

Variation of product proportions with reaction time

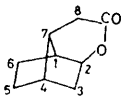
Starting acid	Reaction time (h)	Lactone % (5b)	(4b)
10 : 1 Mixture of (1b) and (3b)	1	54	36
10 : 1 Mixture of (1b) and (3b)	2	60	40
(1b)	2.5	70	30
10 : 1 Mixture of (1b) and (3b)	3	74	26
10 : 1 Mixture of (1b) and (3b)	4	93	7

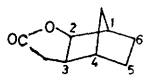
We now find, that in an extension of the above observations, norborn-5-en-2-ylacetic acids (1b) and (3b) on reaction with 50% sulphuric acid produce a mixture of the δ-lactone (4b) and the γ-lactone (5b). No δ-lactone (2b), corresponding to the γ-lactone (2a) derived from acid (1a), was found. [*cf.* Iodolactonisation of (1b) which leads to the δ-iodolactone analogue of (2b).[7]] Both lactones (4b) and (5b) were formed when either a 10 : 1 mixture of norborn-5-en-2-*endo*-ylacetic acid (1b) and its 2-*exo*-isomer (3b), or the pure *endo*-acid (1b) were employed. The relative amounts of (4b) and (5b) were dependent on the reaction time, with the proportion of the γ-lactone (5b) increasing with increase in reaction time suggesting that (5b) is the thermodynamically more stable product (see Table 1).

The i.r. spectra of the lactones (4b) and (5b) in chloroform solution exhibited lactone carbonyl frequencies at 1 729 and 1 767 cm^{-1} respectively, which are characteristic [8] of δ- and γ-lactone structures. The n.m.r. spectral parameters given in Table 2 are also consistent with the proposed structures (4b) and (5b). Assignments were made on the basis of chemical shifts, coupling constants, and extensive spin-decoupling experiments. Protons H-8a and H-8b exhibited a large mutual geminal coupling (19.5 Hz) together with vicinal couplings with H-7 of 6.7 and 0.5 Hz, respectively. These vicinal couplings facilitated identification of the H-7 signal and suggest that the δ-lactone ring tends towards a ' boat conformation ' (*cf.* ref. 7). The dihedral angles determining the magnitude of J(7,8a) and J(7,8b) are given in Figure 1(a). In the alternative ' chair conformation ' shown in Figure 1(b) the two dihedral angles are of comparable size, and if this had been the conformation of (4b) vicinal couplings of roughly equal values would have been expected. The ^{13}C spectral parameters for the δ-lactone (4b) and γ-lactone (5b) are given in Table 3 together with those reported by Storm and Koshland [5a]

TABLE 2

N.m.r. data for lactones (4b) and (5b)


(4b)

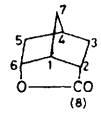

(5b)

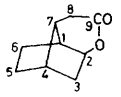
Proton	δ	Multiplicity	J	Hz	Proton	δ	Multiplicity	J	Hz
1	2.32	brm	2,3*n*	6.1	1	2.46	brd	1,6*x*	*ca.* 4
2	4.37	d of m	2,3*x*	2.5	2	4.46	d	2,3	6.5
3*n*	1.76	m	3*n*,3*x*	*ca.* 14	3	2.34	m	2.4	*ca.* 1
3*x*	1.87	brd of m	3*x*,4	3.5	4	2.08	brs	2,7*a*	*ca.* 1
4	2.30	brm	4,5*x*	3.5	5*n*	1.14	m	3,8*a*	11.1
5*n*	1.15	m	5*n*,5*x*	*ca.* 15	5*x*	1.57	m	3,8*b*	3.5
5*x*	1.54	m	5*x*,6*n*	6.5	6*n*	1.11	m	7*a*,7*b*	11.1
6*n*	1.19	m	5*x*,6*x*	10.5	6*x*	1.46	m	8*a*,8*b*	18.6
6*x*	1.73	m	7,8*a*	6.7	7*a*	1.52	m		
7	2.08	brd	7,8*b*	0.5	7*b*	1.23	m		
8*a*	2.73	d of d	8*a*,8*b*	19.5	8*a*	2.71	q		
8*b*	2.60	d of d			8*b*	2.15	q		

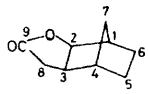
x = *exo*, *n* = *endo*, s = singlet, d = doublet, q = quartet, m = multiplet, br = broad.

TABLE 3

^{13}C N.m.r. data for lactones (2a), (4a), and (5b)


(2a)


(4b)


(5b)

(2a) δ	(4b) δ mult.	(5b) δ mult.
35.49	C-1 (41.7) d	C-1 42.0 d
37.63	C-2 80.9 d	C-2 86.4 d
38.92	C-3 37.8 t	C-3 41.0 d
39.23	C-4 (40.5) d	C-4 41.8 d
40.20	C-5 29.1 t	C-5 (28.0) t
47.55	C-6 22.2 t	C-6 (23.3) t
C-6 62.23	C-7 41.1 d	C-7 33.3 t
C-8 183.3	C-8 31.7 t	C-8 31.4 t
	C-9 176.9 s	C-9 178.1 s

For (4b) and (5b) spectra in $CDCl_3$ and δ values relative to $SiMe_4$. For (2a) literature values [5a] quoted relative to CS_2 are here given relative to $SiMe_4$ (value of CS_2 relative to $SiMe_4$ taken as 192.8 p.p.m.). Assignments in brackets may need to be reversed.

for the γ-lactone (2a), and are consistent with assigned structures.

Figure 2 indicates diagramatically how both the *endo*-acid (1b) and the *exo*-acid (3b), *via* a series of hydride

[7] D. I. Davies and M. D. Dowle, *J.C.S. Perkin I*, 1976, 2267.
[8] L. J. Bellamy, ' The Infrared Spectra of Complex Molecules ', 2nd Edition, Methuen, London, 1958.

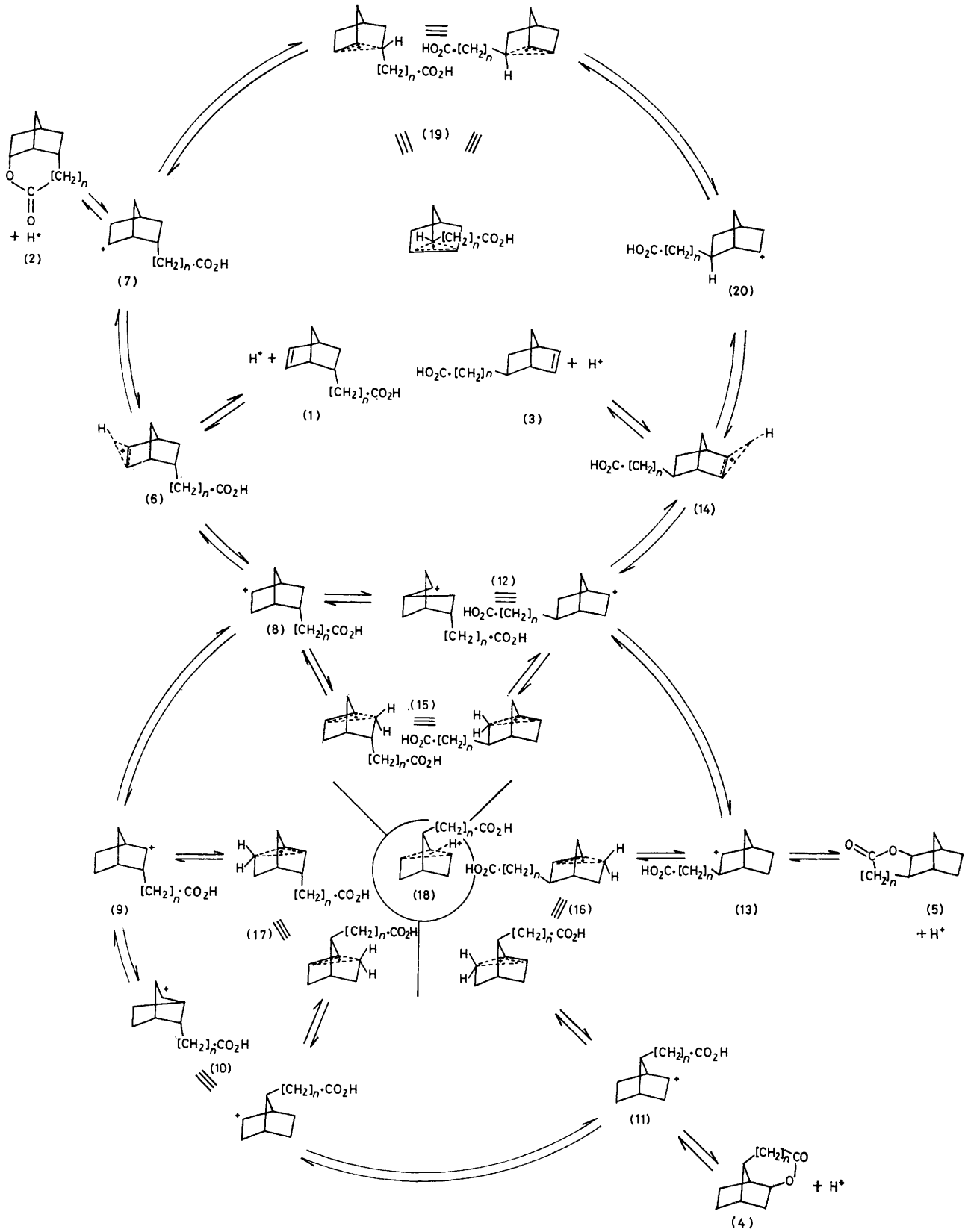


FIGURE 2 a; $n = 0$, b; $n = 1$

shifts and Wagner–Meerwein-type rearrangements, give rise to the same series of equilibrating norbornyl cations, and hence to products (4b) and (5b). Failure to observe the δ-lactone (2b) as a product suggests that the 'onium ion (6b) collapses preferentially to (8b) rather than (7b) since in (8b) the carbocation centre is more remote from the electron-withdrawing carboxy-group. A related

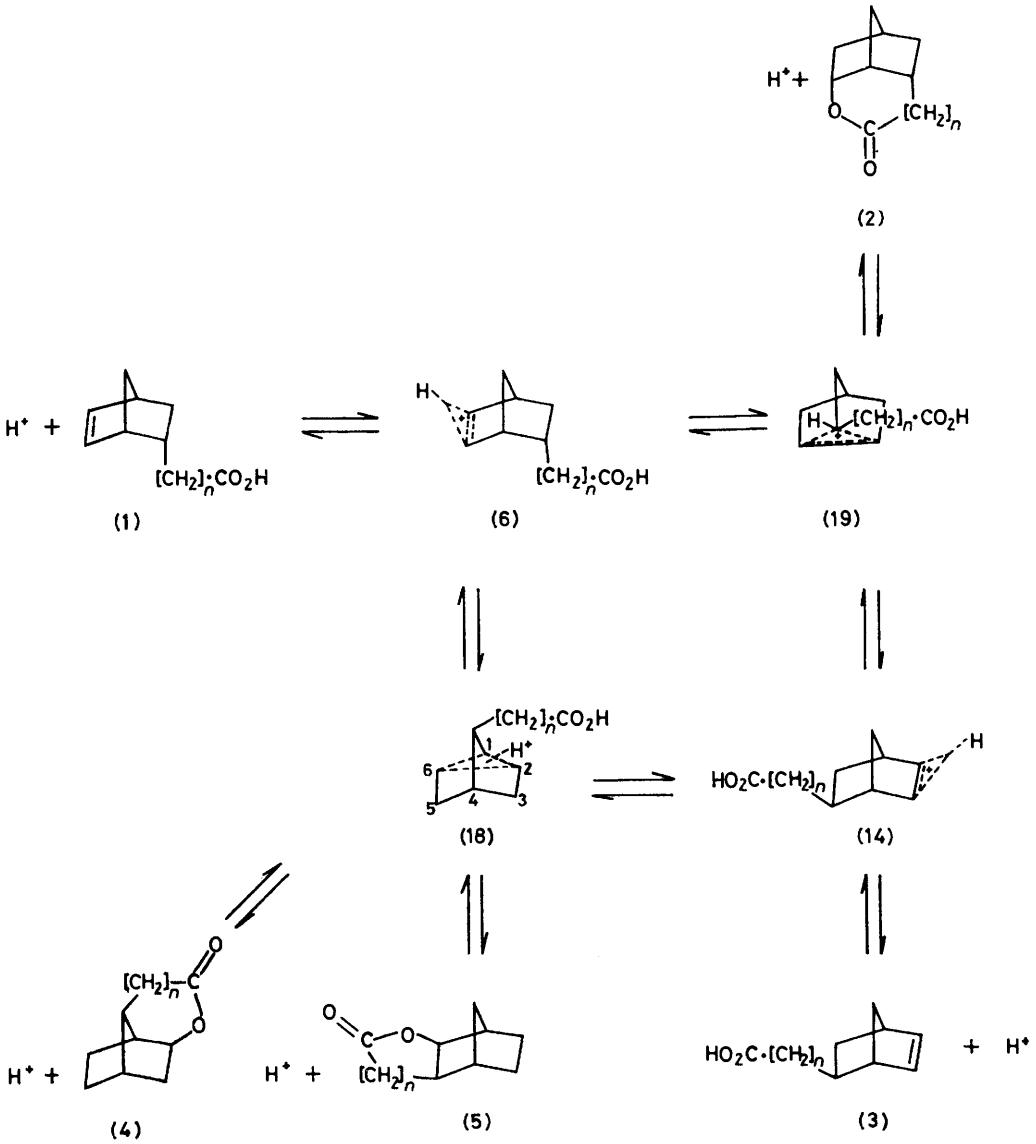


FIGURE 3 a; $n = 0$, b; $n = 1$

represented by the composite non-classical ion (18b). Similarly the non-classical ion (19b) is an alternative to classical ions (7b) and (20b). Hydride shifts in (19b) which would give the other two related non-classical ions are less likely than the hydride shifts between (15b), (16b), and (17b) because of the electron-withdrawing carboxy-group, which in (19b) is attached *via* a methylene group to the carbon atom from which a hydride shift must take place to give the related non-classical ions.

but less complete scheme than Figure 2, which involves comparable classical ions (bridged species were considered equally valid), was proposed by Berson and Grubb [9] to account for the formation of products from 3-*endo*-deuterio-3-*exo*-methylnorborn-5-en-2-*endo*-ylcarboxylic acid.

Instead of the classical ions (8b)—(13b) it may also be appropriate to consider the non-classical ions (15b)—(17b) as intermediates. They differ from each other in the site of corner protonation and may, therefore, be

On the basis of non-classical ions being the species of lowest energies, the reaction scheme of Figure 2 reduces to Figure 3. Both the lactones (4b) and (5b), on protonation, lead to (18b) and this readily explains how (4b) may be converted into (5b) and why the proportion

[9] J. A. Berson and P. W. Grubb, *J. Amer. Chem. Soc.*, 1965, **87**, 4016.

of (5b), which must be the thermodynamically more stable product, can increase with increase in reaction time (see Table 1).

Figures 2 and 3 may also be used to explain the results of Beckmann and Geiger [3] relating to the formation of products (4a) and (2a) from the *endo*-acid (1a). Using the simplified scheme of Figure 3 cyclisation of the carboxy-group in (18a) onto C-2 gives the γ-lactone (4a) or onto C-1 the β-lactone (5a). Kinetically, formation of the β-lactone (5a) is favoured, but its ring strain will cause it to be thermodynamically less stable so that it was not observed as a product. The γ-lactone (2a) results from intramolecular cyclisation of the non-classical ion (19a). Since (2a) is the sole product when the reaction time is prolonged (4a) must be convertible to (2a) as is readily explicable from Figures 2 and 3. Although (18a) should be favoured on stability grounds over (19a) because the electron-withdrawing carboxy-group in (18a) is more remote from the site of positive charge than in (19a), the juxtaposition of the carboxy-group and a positive charge is more conveniently set up for product formation from (19a). In the case of (18b) and (19b) product formation from (18b) is favoured, particularly when cyclisation onto C-1 is involved.

EXPERIMENTAL

The 220 MHz n.m.r. spectral measurements were carried out by the P.C.M.U. at Harwell; the ^{13}C measurements were made using a Bruker HFX 90 spectrometer operating at 22.6282 MHz in the Fourier transform mode. A 10 : 1 mixture of norborn-5-en-2-*endo*-ylacetic acid (1b) and its 2-*exo*-isomer (3b) was prepared by the method of Alder and Windemuth.[10]

Norborn-5-en-2-endo-*ylacetic Acid* (1b).—(*Cf.* the procedure of Berson and Ben-Efraim [11] for the preparation of norborn-5-en-2-*endo*-ylcarboxylic acid.) AnalaR zinc powder (22.5 g, 0.34 g-atom) was added portionwise over 10 min to a vigorously stirred solution of 6-*endo*-hydroxy-5-*exo*-iodonorborn-2-*endo*-ylacetic acid δ-lactone (50.0 g, 0.18 mol) [7] in AnalaR glacial acetic acid (750 ml) at 15 °C. The reaction temperature rose to 19 °C, but fell back to 15 °C during 20 min. The mixture was stirred at 15 °C for 4 h and then at room temperature for 20 h before being filtered through Celite. The filtrate was diluted with water (5 l) and extracted with ether (3 × 1 l). The combined extracts were dried ($MgSO_4$), filtered, and evaporated. The pale yellow liquid residue was fractionally distilled to afford the endo-*acid* (1b) as a clear colourless liquid (22.6 g), b.p. 71—74 °C at 0.03 mmHg, n_D^{20} 1.4899, $\nu_{max.}(CCl_4)$ 3 400—2 300 (br,m, OH) and 1 712 cm^{-1} (s, C=O); $\delta(CDCl_3)$ 12.10 (s, CO_2H), 6.15 (q, C*H*=CH, *J* 5 and 3 Hz), 5.91 (q, CH=C*H*, *J* 5 and 2 Hz), 3.0—1.0 (overlapping resonances for 8H), and 0.58 (m, H-3-*endo*) (Found: C, 71.1; H, 7.15. $C_9H_{12}O_2$ requires C, 71.0; H, 7.95%).

Acid-catalysed Lactonisation of Norborn-5-en-2-ylacetic Acids (1b) *and* (3b).—Reactions were carried out using either a 10 : 1 mixture of the *endo*-acetic acid (1b) and its *exo*-isomer (3b) or the pure *endo*-acid (1b). In both cases the reaction procedure was the same and is typified by the example set out below.

The *endo*-acid (1b) (2.5 g, 0.016 mol) was added to sulphuric acid (50%, 34 ml) and the mixture was shaken at room temperature for 2.5 h. The resultant deep brown homogeneous solution was poured onto a mixture of ice (20 g) and water (20 ml), which was continuously extracted for 5 h using ethyl acetate (100 ml). The extract was evaporated to yield a mobile brown oil which contained acetic acid. This oil was dissolved in dichloromethane and washed with 10% aqueous sodium hydrogen carbonate (2 × 50 ml). The combined organic solutions were dried ($MgSO_4$), filtered, and evaporated to give a viscous yellow oil (2.013 g) containing two major products as judged by t.l.c.; these were separated by column chromatography using silica gel (Hopkin and Williams M.F.C.) (200 g) and dichloromethane as eluant. The first product (0.34 g) was further purified by preparative t.l.c. (silica plates 60 × 20 × 0.1 cm; dichloromethane as eluant) and distilled to give 2-exo-*hydroxynorborn*-7-syn-*ylacetic acid δ-lactone* (4b) (0.25 g) as a clear colourless oil, b.p., 80 °C at 0.05 mmHg, $\nu_{max.}$ ($CHCl_3$) 1 729 cm^{-1}, (C=O); n.m.r. data given in Tables 2 and 3 (Found: C, 71.1; H, 8.0. $C_9H_{12}O_2$ requires C, 71.0; H, 7.95%). The second product (1.51 g) was also obtained as an oil and was similarly purified to afford 2-exo-*hydroxynorborn*-3-exo-*ylacetic acid γ-lactone* (5b) (0.58 g) as a clear colourless oil, b.p. 51—52 °C at 0.03 mmHg, $\nu_{max.}(CHCl_3)$ 1 767 cm^{-1} (C=O); n.m.r. data are given in Tables 2 and 3 (Found: C, 70.85; H, 7.95. $C_9H_{12}O_2$ requires C, 71.0; H, 7.95%).

Product proportions for all reactions, estimated by n.m.r. and i.r., are given in Table 1.

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[10] K. Alder and E. Windemuth, *Chem. Ber.*, 1938, **71B**, 1939.
[11] J. A. Berson and D. A. Ben-Efraim, *J. Amer. Chem. Soc.*, 1959, **81**, 4083.