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Bicyclo[2.2.2]octane-2,5-carbolactone

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Abstract

The title compound has been synthesized and compared with bicyclo[2.2.2]octane-2,6-carbolactone. Ambiguities in the literature concerning the preparation of the title compound have been resolved.

Introduction

During research[1,2] in which it was established that a number of stable lactones in the bicyclo[2.2.2]octane series have the γ-2,6-carbolactone (1) rather than the δ-2,5-carbolactone (2) structure, we were hampered by the lack of reliable data concerning the simple lactones (1a) and (2a) and we now report details of these compounds.

Boehme[3] reported that iodolactonization of the unsaturated acid (3a) gave γ-lactone (1b), m.p. 81–82°, i.r. 1785 cm^{-1}, after one day, and δ-lactone (2b), m.p. 74–75°, i.r. 1760 cm^{-1} after three days, thereby implying that lactone (2b) was thermodynamically more stable than (1b). Later workers[4,5] have failed to prepare compound (2b) and we have also been unsuccessful. From experimental work reported earlier[1,2] it is clear that δ-lactones in this series are less stable than γ-lactones, and this result is supported[2] by Molecular Mechanics calculations.

Boehme[3] also reported the simple lactone (1a), m.p. 207–208°, i.r. 1760 cm^{-1}. The same compound has been synthesized by others,[6–9] all of whom record m.p. 204–208°, i.r. 1760–1765 cm^{-1}. In all cases, the compound was obtained either by acid-catalysed lactonization of olefin (3) or by reduction of iodide (1b). Storm and Koshland[6] also reported a second product from the acid-catalysed lactonization, m.p. 229–230°,

[1] Carman, R. M., and Smith, S. S., *Aust. J. Chem.*, 1981, **34**, 1285.
[2] Alberts, V., Brecknell, D. J., Carman, R. M., and Smith, S. S., *Aust. J. Chem.*, 1981, **34**, 1719.
[3] Boehme, W. R., Schipper, E., Scharpf, W. G., and Nichols, J., *J. Am. Chem. Soc.*, 1958, **80**, 5488.
[4] Moriarty, R. M., and Adams, T., *J. Am. Chem. Soc.*, 1973, **95**, 4071.
[5] Mirrington, R. N., and Schmalzl, K. J., *J. Org. Chem.*, 1969, **34**, 2358.
[6] Storm, D. R., and Koshland, D. E., *J. Am. Chem. Soc.*, 1972, **94**, 5815.
[7] Lee, R. A., *Tetrahedron Lett.*, 1973, 3333.
[8] Wagner, A. F., Wittreich, P. E., Arison, B. H., and Sarett, L. H., *J. Org. Chem.*, 1971, **36**, 2609.
[9] Whitlock, H. W., *J. Am. Chem. Soc.*, 1962, **84**, 3412.

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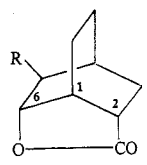
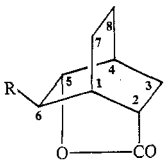
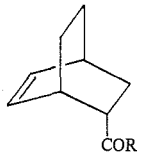
i.r. 1735 cm^{-1}, to which they assigned the δ-lactone structure (2a). Moriarty[10] challenged this assignment, claiming that the second product was actually a δ-lactone of the rearranged bicyclo[3.2.1] skeleton (4).



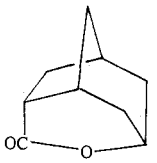
(1a) R = H
(1b) R = I
(1c) R = SPh



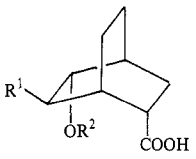
(2a) R = H
(2b) R = I



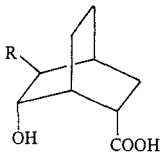
(3a) R = OH
(3b) R = NH(c-C_6H_{11})



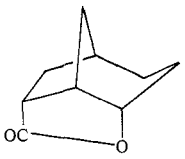
(4)



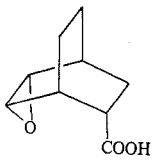
	R^1	R^2
(5a)	H	H
(5b)	SPh	H
(5c)	H	COMe



(6a) R = H
(6b) R = SPh



(7)



(8)

In 1973, Lee[7] briefly reported a synthesis of δ-lactone (2a), m.p. 205–206°, i.r. 1750 cm^{-1}, from the hydroxy acid (5a). Lee's synthesis of compound (2a) was not entirely unambiguous, but the fact that hydroxy acid (5a) could be isolated adds weight to his assignment, since the isomeric γ-hydroxy acid (6a) cannot be isolated because it spontaneously lactonizes. Garratt[11] in 1977 noted a further synthesis of structure (2a), m.p. 205–206°, from hydroxy acid (5a). Garratt's identification was based upon Lee's evidence, although Garratt recorded i.r. 1760 cm^{-1}. Both these workers lactonized hydroxy acid (5a) under hot acidic catalysis; conditions which notoriously cause rearrangements in this series.[10,12] Neither Garratt[11] nor Lee[7] comment upon the coincidence in the melting points of lactones (1a) and (2a).

Riguera[13] recorded the ^{13}C n.m.r. spectra of several δ-lactones in the bicyclo-[2.2.2]octane series, and the shifts reported by Garratt[11] for structure (2a) are probably consistent with this data, although it is not entirely clear how Garratt has numbered his carbon skeleton (2a). However others[14] have recently used ^{13}C n.m.r. data to assign δ-lactone structures to compounds later shown[1,2,15] to be γ-lactones, and since the apparent coincidence in m.p. and i.r. carbonyl stretching frequency of (1a) and (2a) has not been examined, we have now reinvestigated structures (1a) and (2a).

[10] Moriarty, R. M., Chien, C. C., and Adams, T. B., *J. Org. Chem.*, 1979, **44**, 2210.
[11] Davalien, D., Garratt, P. J., and Riguera, R., *J. Org. Chem.*, 1977, **42**, 368.
[12] Roche, U. F., Roche, E. B., and Nagel, D. L., *J. Org. Chem.*, 1982, **47**, 1368.
[13] Riguera, R., *Tetrahedron*, 1978, **34**, 2039.
[14] Garratt, D. G., Ryan, M. D., and Beaulieu, P. L., *J. Org. Chem.*, 1980, **45**, 839.
[15] Carman, R. M., Smith, S. S., Kennard, C. H. L., Smith, G., White, A. H., and Skelton, B. W., *Aust. J. Chem.*, 1982, **35**, 457.

Discussion

The structural integrity of the bicyclo[2.2.2]octane system was critical to the synthesis of lactones (1a) and (2a), and, in view of the experience we have developed[1,2] with this system, we determined to synthesize the carbon skeleton first and then to position the functional groups.

Compound (1a), m.p. 205–206°, i.r. 1760–1765 cm^{-1} (Nujol), 1782 cm^{-1} (CCl_4), n.m.r. spectral data arleady recorded,[1] is readily obtained by acid treatment of the Diels–Alder adduct (3a). Prolonged acid treatment leads to lactones (4) and (7)[10] in the bicyclo[3.2.1]octane series but no lactone (2a) could be isolated from either (3a) or (1a) by acid catalysis (see below).

Compound (2a) was prepared by the route (3a) → (1b) → (8) → (5b) → (5a) → (2a). Iodolactonization of olefin (3a) gave lactone (1b) which, upon treatment with 2 equiv. of hydroxide, gave epoxide (8). Attempted hydride displacement of the epoxide group in (8) was unsuccessful due to interference by the acid group. Consequently the epoxide ring was opened with thiophenoxide ion, with interesting results. Treatment of compound (8) with thiophenol in the presence of 1 equiv. of alkali generated compounds (5b) and (6b) in approximately equal amounts. Compound (6b) spontaneously lactonized upon acidification to give lactone (1c). However epoxide (8) reacted with thiophenol in an excess of alkali to give only isomer (5b), presumably because the dianion formed from (5b) is more stable than the equivalent dianion from (6b). In support of this view, we find that lactone (1c) rearranges quantitatively into compound (5b) upon treatment with hydroxide ion.

Attempts to desulfurize compound (5b) in acetic acid led to a range of products, including γ-lactone (1a). That product (1a) resulted from an acid-catalysed isomerization was confirmed when compound (5b) in dilute hydrochloric acid was found to give a quantitative yield of the thio-γ-lactone (1c). This rearrangement further serves to illustrate the stability of the γ-lactones in this series. The reduction of sulfide (5b) to hydroxy acid (5a) was eventually accomplished by using Raney nickel in aqueous sodium carbonate.

The n.m.r. spectrum of compound (5a) (Table 1) assisted in confirming the structure. In particular, the protons geminal to the hydroxyl and acid groups (H 2 and H 5), are coupled neither to each other nor to a common vicinal proton, thus ensuring that these two substituents must be 2,5 on the bicyclo skeleton.

In previous work,[7,11] the hydroxy acid (5a) was lactonized by use of *p*-toluenesulfonic acid with azeotropic removal of water. Because of fears that these acid conditions might lead to rearrangement, we sought milder conditions. However the use of dicyclohexylcarbodiimide in pyridine to dehydrate compound (5a) gave only the unsaturated amide (3b), while acetic anhydride in pyridine yielded only the acetate (5c). Lactonization was finally achieved with 2-chloro-1-methylpyridinium iodide[16] in the presence of triethylamine. We then confirmed that lactonization (5a) → (2a) could also be achieved by acid-catalysed dehydration.

The lactone (2a) had m.p. 205–206°, i.r. 1765 cm^{-1}, and showed a large m.p. depression upon admixture with lactone (1a). Hydrolysis of (2a) regenerated hydroxy acid (5a).

The ^1H n.m.r. coupling constants of lactone (2a) were obtained with the aid of shift reagent ($Eu(fod)_3$) and decoupling experiments and are recorded in Table 1.

[16] Livers, M., and Miller, J., *Aust. J. Chem.*, 1958, **11**, 297.

Also included in Table 1 are the relevant torsion angles calculated by the MM2 molecular mechanics program, together with calculated coupling constants obtained from these angles by use of the Karplus equations[17]

$$J = 8{\cdot}5\cos^2\phi - 0{\cdot}28 \qquad (0° < \phi < 90°)$$

$$J = 9{\cdot}5\cos^2\phi - 0{\cdot}28 \qquad (90° < \phi < 180°)$$

The agreement between observed and calculated coupling constants is good.

Table 1. ^{1}H n.m.r. coupling constants

Coupling constant	Compound (5a) J_{exp} (Hz)	Compound (2a) J_{exp} (Hz)	Compound (2a) Torsion angle[A] (deg)	Compound (2a) J_{calc}[B] (Hz)
$J_{1,2}$	2·8	6·4	32·4	5·8
$J_{1,6x}$	2·5	<1·0	82·5	0·1
$J_{1,6n}$	[C]	5·2	36·6	5·2
$J_{2,3x}$	11·0	5·2	41·7	4·5
$J_{2,3n}$	4·9	0·9	77·6	0·1
$J_{2,6x}$	1·5	0	—	—
$J_{3n,3x}$	14·2	12·4	(106·0)	—
$J_{3n,4}$	2·3	6·4	36·0	5·3
$J_{3x,4}$	[C]	<1·0	83·2	0·2
$J_{3x,5}$	1·5	0	—	—
$J_{4,5}$	1·5	6·6	33·4	5·6
$J_{5,6x}$	9·8	3·9	40·2	4·7
$J_{5,6n}$	1·5	1·0	78·9	0·1
$J_{6x,6n}$	15·4	13·3	(106·0)	—

[A] Calculated by MM2 molecular mechanics.
[B] Calculated by using the torsion angles listed and applying the Karplus equations listed in the text.
[C] Unavailable.

Garratt, Ryan and Beaulieu[14] have recently argued erroneously from other bicyclo[2.2.2]octane carbolactones that an *exo,endo* coupling (H 5x,H 6n) of *c.* 1 Hz indicates the δ-2,5-carbolactone (2a) while a H 6*exo*, H 5*endo* coupling of *c.* 4·8 Hz indicates the γ-2,6-carbolactone structure (1a). This argument has been refuted earlier.[2] We now find that the coupling H 5x,H 6n of lactone (2a) and the coupling H 6x,H 5n of lactone (1a) are both *c.* 1·0 Hz. The coupling $J_{2x,3n}$, which is symmetrically similar to the above couplings in compound (2a) ($J_{2x,3n}$ 0·9 Hz) and in (1a) ($J_{2x,3n}$ 1 Hz), also does not allow a differentiation between the two series. However it was again possible to show for lactone (2a) that the protons geminal to the lactone system (H 2 and H 5) do not couple each other nor a common third proton, and hence that they must be 2,5 to each other. This allows an ^{1}H n.m.r. differentiation between compounds (2a) and (1a) as the latter compound has both the protons geminal to the lactone system (H 2 and H 6) coupled to a common bridgehead proton (H 1).[1]

The protons of compound (2a) move downfield during titration with Eu(fod)$_3$ at rates qualitatively expected for complexation at the lactone system (see Experimental). Both lactones (1a) and (2a) equilibrate in acid solution into a common

[17] Karplus, M., *J. Chem. Phys.*, 1959, **30**, 11.

lactone mixture. In 70% sulfuric acid this comprises (1a) : (2a) : (4) : (7) = 11 : trace : 33 : 56; while in 90% sulfuric acid the same mixture shows trace : trace : 46 : 54. These ratios in highly acidic medium do not closely reflect the relative ground state steric energies of the isolated lactones (0, 32·5, 10·0, 12·6 kJ/mol respectively; from MM2 calculations).

Experimental

The ^1H and ^{13}C n.m.r. spectra were recorded upon Jeol JNM-PS-100, Jeol FX-100 and (for compounds (1a), (2a) and (5a)) Bruker CXP-300 spectrometers for $CDCl_3$ solutions unless otherwise stated. Infrared spectra were recorded upon a Perkin–Elmer 397 spectrometer by using polystyrene marked bands (1943·5, 1601·0 cm^{-1}) and are for CCl_4 solutions unless otherwise stated. G.c.–m.s. data were obtained upon a Hewlett–Packard 5992B instrument.

Compound (3a)

Cyclohexadiene (20 g, 0·25 mol) and methyl acrylate (30 g, 0·35 mol) were refluxed (2 days) and then distilled (8 mmHg). The methyl esters of adduct (3a) and its *exo* isomer (95 : 5 by g.l.c.) were collected at 84°. ^1H n.m.r. δ 3·53, s, *endo* OMe; 3·60, s, *exo* OMe.

The esters (18 g, 0·11 mol) in toluene were treated (2 days reflux) with potassium hydroxide (20 g, 0·36 mol) in water (10 ml) with a catalytic amount of 18-crown-6-ether. Water was added, the two layers separated and the toluene washed with aqueous bicarbonate. The combined aqueous extracts were acidified (pH 2) and extracted with dichloromethane to yield, after normal workup, a yellow oil which crystallized upon standing to give bicyclo[2.2.2]oct-5-ene-*endo*-2-carboxylic acid (3a), m.p. 53–54° (from aqueous ethanol) (lit.[7] 54°). ^1H n.m.r. δ 1·09–1·99, m, 6H; 2·49–3·16, m, 3H; 6·03–6·56, m, 2H; 10·37, br s, 1H.

Iodo Lactone (1b)

Acid (3a) (11·6 g, 0·08 mol) in aqueous sodium bicarbonate (8·8%, 250 ml, 0·26 mol) was stirred (24 h) with iodine (20 g, 0·08 mol) in ethyl acetate (20 ml). The organic phase was washed with aqueous sodium thiosulfate and with aqueous sodium bicarbonate after which normal workup gave *exo*-5-iodobicyclo[2.2.2]octane-2,6-carbolactone (1b) (22·0 g), m.p. 80° (lit.[3] 81–82°). ^1H n.m.r. δ 1·60–2·48, m, 7H; 2·56–2·83, m, 2H; 4·66, m, H6; 5·29, d, J 6·3 Hz, H5.

Epoxy Acid (8)

Iodo lactone (1b) (22 g, 0·08 mol) in ethanol (280 ml) was refluxed (3 h) with aqueous sodium hydroxide (1·35 M, 120 ml). Hydrochloric acid (4 M, 40 ml) followed by water (790 ml) was added to the cooled solution. Extraction with ethyl acetate gave a yellow solid which upon chromatography (Kieselgel 60, elution with hexane/ether (1 : 1)) yielded *endo*-5,6-epoxybicyclo[2.2.2]octane-*endo*-2-carboxylic acid (8) (8·3 g, 63% yield), m.p. 146–147° (from acetone/hexane) (lit.[18] 148–149°). ^1H n.m.r. δ 1·50–1·67, m, 5H; 2·07–2·33, m, 3H; 2·73, m, 1H; 3·25, m, 2H; 10·02, br s, COOH. ^{13}C n.m.r. δ 21·68; 21·85; 26·38; 27·15; 29·92; 41·07; 52·13; 53·21; 180·77.

Phenylthio Acid (5b)

(A) The epoxy acid (8) (90 mg, 0·54 mmol) was refluxed (24 h) with thiophenol (120 mg, 1·09 mmol) and sodium hydroxide (300 mg, 7·5 mmol) in water (20 ml). Acidification (pH 2) and extraction with ethyl acetate gave endo-*5-hydroxy*-exo-*6-phenylthiobicyclo[2.2.2]octane*-endo-*2-carboxylic acid* (5b) (110 mg, 74% yield), m.p. 170–171° (Found: C, 64·5; H, 6·6. $C_{15}H_{18}O_3S$ requires C, 64·7; H, 6·6%). I.r. (hexachlorobutadiene) 3392, 1700 cm^{-1}. ^1H n.m.r. δ [$(CD_3)_2CO$] 1·44–2·44, m, 8H; 2·52–2·80, m, H2; 3·44–3·64, m, H5 and H6; 4·40–4·88, br s, OH + COOH; 7·08–7·48, m, 5H. ^{13}C n.m.r. δ [$(CD_3)_2CO$] 20·74, t, C7; 22·17, t, C8; 23·34, t, C3; 33·84, 34·40, two d, C1 and C4; 41·86, d, C2; 51·54, d, C6; 75·15, d, C5; 126·25, d, C4′; 129·52, d, 4C, C2′, C3′, C5′, C6′; 137·63, s, C1′; 176·59, s, carboxyl.

[18] Moriarty, R. M., and Adams, T. B., *Tetrahedron*, 1979, **35**, 2225.

When this reaction was carried out with only 2 equiv. of sodium hydroxide, the acidic product was compound (5b) as above while the neutral product was compound (1c) (see below).

(B) The lactone (1c) (0·33 g) was refluxed (4 h) with sodium hydroxide (15 g) in water (100 ml). Acidification (pH 2) followed by extraction with ethyl acetate yielded compound (5b) (0·33 g) with m.p. as well as ^{1}H and ^{13}C n.m.r. spectra identical with those reported above.

Lactone (1c)

The phenylthio acid (5b) (980 mg) was stirred (12 h, 25°) in hydrochloric acid (1 M). Extraction into ether yielded exo-*5-phenylthiobicyclo[2.2.2]octane-2,6-carbolactone* (1c) (980 mg), m.p. 118·5–120° (from hexane) (Found: C, 68·9; H, 6·3; S, 12·3. $C_{15}H_{16}O_2S$ requires C, 69·2; H, 6·2; S, 12·3%). I.r. 2943, 1788 cm^{-1}. ^{1}H n.m.r. δ 1·48–2·16, m, 7H; 2·36–2·52, m, H1 and H2; 3·44, br m, H5; 4·34, br d, $J_{5,6}$ 6 Hz, H6; 7·12–7·44, m, 5H. | ^{13}C n.m.r. δ 15·06, t, C7; 20·48, t, C8; 28·28, d, C4; 28·93, t, C3; 34·60, d, C1; 36·51, d, C2; 48·85, d, C5; 82·02, d, C6; 126·66, d, C4′; 129·26, d, 2C; 129·67, d, 2C; 134·09, s, C1′; 180·16, s, lactone carbonyl.

Hydroxy Acid (5a)

The phenylthio acid (5b) (150 mg) was added to Raney nickel (1·5 g) in aqueous sodium carbonate (5%, 80 ml) and stirred (12 h). The solution was filtered and the nickel washed with aqueous carbonate. The combined solution was acidified (pH 2) and extracted with chloroform to yield *endo*-5-hydroxybicyclo[2.2.2]octane-*endo*-2-carboxylic acid (5a) (110 mg), m.p. 144–145° (from chloroform/hexane) (lit.[11] 143–144°) (Found: C, 63·3; H, 8·3. Calc. for $C_9H_{14}O_3$: C, 63·5; H, 8·3%). I.r. (Nujol) 3380, 1702 cm^{-1}. ^{1}H n.m.r. δ 1·47–1·59, m, 5H; 1·62, ddd, H3x (*exo*), 1·78, br s, H4; 1·94, dddd, H6x; 2·07, br s, H1; 2·32, ddd, H3n (*endo*); 2·65, dddd, H2; 3·87, ddddd, H5, with couplings as listed in Table 1 and with H5 showing a further (*c.* 1·2 Hz) long-range coupling (to one of the C8 protons?). Double irradiation confirmed the assigned couplings. ^{13}C n.m.r. δ 21·00, t, C3; 22·64, t, C8; 24·98, t, C7; 28·43, d, C1; 30·89, d, C4; 33·35, t, C6; 41·36, d, C2; 68·62, d, C5; 181·55, s, carboxyl.

The γ-Lactone (1a)

(A) The phenylthio γ-lactone (1c) (250 mg) in ethanol (50 ml) was stirred (12 h) with Raney nickel (3 g). The nickel was filtered off and washed with ethanol to yield bicyclo[2.2.2]octane-2,6-carbolactone (1a), m.p. 204–205° (from hexane) (lit.[6] 204·5–205°). I.r. 1782, 1184, 1148, 1087, 1040, 980 cm^{-1}. The ^{1}H and ^{13}C n.m.r. spectra were identical with those from an authentic sample and agreed with literature[1] values.

(B) Following the literature[3] procedure, the olefinic acid (3a) (100 mg) was refluxed (1 h) with aqueous sulfuric acid (30% v/v, 50 ml). The product was poured onto ice, extracted into chloroform, and washed with aqueous bicarbonate to yield a 5 : 1 mixture of lactones (1a) and (4) which were separated by h.p.l.c. (Merck Lobar column with chloroform/hexane (1 : 1)). The major product was identical with compound (1a) above.

The δ-Lactone (2a)

Hydroxy acid (5a) (0·30 g) and triethylamine (1·43 g) in dry dichloromethane (90 ml) were refluxed (*c.* 12 h) with 2-chloro-1-methylpyridinium iodide[16] (0·70 g). The dichloromethane was evaporated and the residue extracted with pentane. The pentane-soluble fraction was separated by preparative t.l.c. (silica, developing with chloroform) to yield two major products:

(A) Bicyclo[2.2.2]octane-2,5-carbolactone (2a), m.p. 204–205° (from hexane/chloroform) (lit.[7] 205–206°), mixed m.p. with the γ-lactone (1a), 180–187° (Found: C, 70·6; H, 7·9. Calc. for $C_9H_{12}O_2$: C, 71·0; H, 8·0%). I.r. 1765, 1205, 1050, 1030, 1020, 972 cm^{-1}. ^{1}H n.m.r. δ 1·52–1·80, m, 6H; 1·83–1·91, m, H3x and H6x; 2·12, m, H1; 2·29, m, H4; 2·77, ddd, H2; 4·74, ddd, H5. Addition of Eu(fod)$_3$ caused resonances to move downfield in the order H2 > H3n > H6n > H5 > H1 > H3x > H4 > H6x > H7 and H8. Decoupling irradiation at judiously chosen concentrations of Eu(fod)$_3$ provided the coupling constants listed in Table 1, and confirmed that H2 and H5 were not coupled to a common bridgehead proton. ^{13}C n.m.r. δ 21·46, 21·77, two t, C7 and C8; 23·50, d, C1; 26·17, d, C4; 27·89, t, C3; 35·07, t, C6; 40·60, d, C2; 78·33, d, C5; 177·51, s, lactone; consistent with that reported[11] provided the earlier workers' structure

is renumbered and apart from the fact that the lactone carbonyl is now observed. M.s. *m/z* 152 (M, 15%), 124 (37), 110 (26), 108 (27), 95 (20), 80 (82), 79 (62), 66 (100).

(B) 1-Methylpyridin-2(1*H*)-one; identical (g.c.–m.s.) with authentic material.

The lactone (2a) was also produced by azeotropic removal of water from a *p*-toluenesulfonic acid catalysed solution of (5a) in toluene following the literature[7] method.

Hydrolysis of the δ-Lactone (2a)

The lactone (2a) in aqueous sodium hydroxide (2 h, reflux) gave, upon acidification (pH 2) and extraction into chloroform, the hydroxy acid (5a) (100%) identical with that reported above.

Equilibrium Studies

The lactone (1a) or (2a) in sulfuric acid (35%, 70% or 90% v/v) was examined at intervals by pouring into water and extracting into dichloromethane. The product distribution was determined by g.c. (20-m OV101 capillary column, 100°). Both lactones equilibrated to the same mixtures listed in the Discussion.

The products were separated (h.p.l.c. on Merck Lobar columns, eluting with chloroform/hexane 4 : 1). No δ-lactone (2a) was recovered, but lactones (1a), (4) and (7) were isolated.

Bicyclo[3.2.1]octane-6,3-carbolactone (4) had m.p. 239–241° (lit.[4] 239–241°). I.r. 1750 cm^{-1}. ^1H n.m.r. δ 1·56–2·08, m, 8H; 2·48, br s, 1H; 2·75, br s, 1H; 3·06, m, H6; 4·63, br s, H3. ^{13}C n.m.r. δ 33·36, t, C7; 35·18, 35·85, two d, C1 and C5; 36·83, 38·87, two t, C2 and C4; 40·82, t, C8; 43·47, d, C6; 76·06, d, C3; 176·80, s, lactone.

Bicyclo[3.2.1]octane-6,4-carbolactone (7) had m.p. 169–172° (lit.[10] 173–176°). I.r. 1770 cm^{-1}. ^1H n.m.r. δ 1·26–2·32, m, 9H; 2·89, ddd, J 11·6, 7·9, 1·7 Hz, 1H; 3·03, m, H6; 4·89, br d, J 9 Hz, H4. ^{13}C n.m.r. δ 23·22, 24·87, two t, C2 and C3; 30·45, t, C7; 31·65, d, C1; 39·87, d, C5; 40·84, t, C8; 41·77, d, C6; 81·02, d, C4; 181·05, s, lactone.

Amide (3b)

Hydroxy acid (5a) (160 mg) and dicyclohexylcarbodiimide (1·8 g) in dry pyridine (20 ml) were stirred overnight at 25°. The pyridine was removed under vacuum and the residue chromatographed (silica, chloroform/hexane 4 : 1) to yield dicyclohexylcarbodiimide, dicyclohexylurea, and N-*cyclohexylbicyclo[2.2.2]oct-5-ene*-endo-*2-carboxamide* (3b), m.p. 159–161° (from acetone/hexane) (Found: C, 77·1; H, 10·3. $C_{15}H_{23}NO$ requires C, 77·2; H, 9·9%). I.r. 1670 cm^{-1}. ^1H n.m.r. δ 0·88–2·68, m, 19H; 3·48, m, 1H; 4·98, br s, 1H; 5·76–6·12, m, 2H. ^{13}C n.m.r. δ 24·02; 24·78; 25·59; 26·21; 29·69; 31·91; 33·08; 33·29; 44·76; 47·83; 131·52; 135·41; 174·98.

Authentic compound (3b) identical with the material above was synthesized from acid (3a) with thionyl chloride followed by cyclohexylamine.

Acetate (5c)

Hydroxy acid (5a) with acetic anhydride in pyridine (15 h, room temperature) gave the *acetate* (5c), m.p. 141–143° (from hexane/acetone after distillation at 156°/9 mm). The compound depressed the m.p. of acid (5a) and was homogeneous by ^1H and ^{13}C n.m.r. (Found: C, 61·8; H, 7·7. $C_{11}H_{16}O_4$ requires C, 62·3; H, 7·6%). ^1H n.m.r. δ 1·16–2·20, m, 10H; 1·96, s, acetoxy Me; 2·44, m, 1H; 4·52, m, H5. ^{13}C n.m.r. δ 21·38, q, acetate Me; 21·94, 22·49, 24·92, three t, C3, C7, C8; 27·41, d, C1; 28·67, d, C4; 30·42, t, C6; 40·92, d, C2; 71·84, d, C5; 171·06, s, acetate carboxyl; 180·92, s, acid carboxyl.

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