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^{13}C NMR CHEMICAL SHIFTS IN BICYCLO[2.2.2]OCTANES—III

HYDROXY ACIDS AND LACTONES

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Abstract—A number of hydroxybicyclo[2.2.2]octane carboxylic acids and the corresponding delta lactones have been prepared, and the ^{13}C NMR spectra show trends that, together with some deuteration experiments, provide a self consistent and unambiguous assignment of the resonance peaks. The effects produced by the substituents and the changes in chemical shifts brought about by the lactonization process are analysed.

The utility of ^{13}C NMR spectroscopy as a powerful tool for establishing the otherwise difficult to assign stereochemistry of bicyclo[2.2.2]octane derivative has recently been reported.[2] It was shown that the various substituent effects which were observed could be treated additively, thus allowing chemical shifts to be predicted in other differently substituted bicyclo[2.2.2]octanes. A special case in which additivity was not observed was in geminally disubstituted derivatives, and these have been reported elsewhere.[3]

As a continuation of a programme to establish ^{13}C NMR as a spectroscopic aid for structure elucidation in this type of compounds, and also to analyse the chemical shift-structure relationship, we wish to report the synthesis and ^{13}C NMR spectra of a number of hydroxybicyclo[2.2.2]octane carboxylic acids and the corresponding lactones.

RESULTS AND DISCUSSION

The ^{13}C chemical shifts of the hydroxy acids and the corresponding lactones are shown in Tables 1 and 2. The assignment of the resonance peaks is based on proton noise and off resonance decoupling, intensity data, selective deuteration and the application of general chemical shift theory. This latter procedure has been particularly fruitful when coupled with the information obtained by comparison of compounds within each series. In a similar way a comparison of the data shown in Table 1 with that of Table 2 permitted us to relate the effects produced upon lactonization with the change of structure involved. A brief comment on the assignments and on the effects observed upon lactonization follows.

Assignments

The C-2 signal in both series of compounds is very easily assigned on the basis of the off-resonance results and the small size of the peak. The shift remains practically the same in all the compounds, reflecting the negligible influence of the various C-5 substituents.

Similarly, the signal corresponding to the C-9 methyl groups is found at an almost constant chemical shift within each series, (about 26 ppm for the acids and 18 ppm for the lactones). There is, then, no difficulty in distinguishing between C-9 and C-10 in compounds **2** and **8**.

The C-10 and C-11 resonances in compounds **3** and **9** were identified by deuteration. In the rest of the compounds these carbons were assigned without difficulty, the shifts obtained being in perfect agreement with the ones which are characteristic of those functional groups.

The C-7 and C-8 shifts are all very close together and in the range 20–22 ppm. This fact and the lack of additivity of γ and δ effects which is characteristic of geminally disubstituted compounds make a rigorous assignment difficult.

The signal corresponding to C-5 can be readily identified on the basis of its expected shift and off-resonance experiments. The introduction of a second substituent at the C-5 position in these molecules causes that carbon to shift downfield, the shift ranging from 2.5 to 4.0 ppm (relative to **1**) in the acids, and from 6.0 to 8.0 ppm (relative to **7**) in the lactones. The C-5 chemical shift in compounds **4** and **10** serves to illustrate the known fact[4] that in those cases where conjugation by the substituent is not important, the alkene group behaves like an alkyl group.

The negative upfield shift observed for C-5 in **5** and **11** corresponds to the characteristic behaviour of propargyl alcohols in the C-13 NMR spectrum. The observed effect is well within the range of values reported for similar compounds.[5]

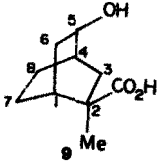
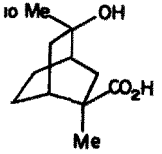
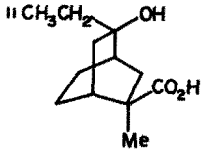
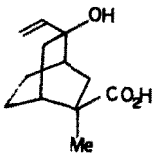
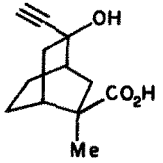
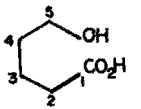
The resonance peaks corresponding to C-1 and C-4 can be readily identified by off-resonance experiments. The analysis of the downfield effects produced by the introduction of substituents on C-5 enabled us to distinguish between C-1 and C-4 since the effect on C-4 is much larger, the chemical shift of C-1 remaining practically unchanged.

Similarly, the C-3 and C-6 resonances have been distinguished by considering compounds **1** and **7** as models and observing that upon introduction of a substituent at C-5 a much more intense downfield effect is produced on one carbon (C-6, +4 to +7 ppm) than on the other (C-3). In particular, the β effect acting on C-6 in compounds **5** and **11** is in perfect agreement with the value deduced from the norbornyl system.[5b,6]

Effects observed on lactonisation

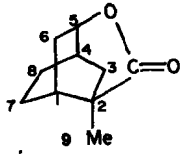
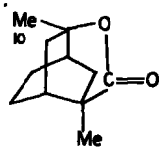
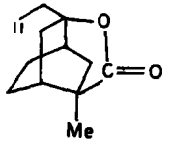
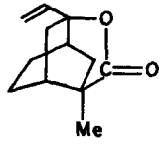
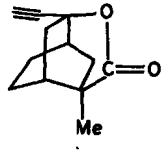
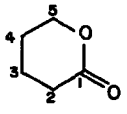
A comparison of the data shown in Tables 1 and 2 reveals that the formation of the lactone from the hydroxy acid produces changes in the C-13 chemical

Table 1. ^{13}C NMR chemical shifts of substituted hydroxybicyclo[2.2.2]octane carboxylic acids[a]

No.	Compound	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	C_{11}
1		33.43*	43.44	30.01	32.53*	68.29	35.80[b]	20.07	22.76	26.73		
2		35.05	42.52	32.61	37.72	70.80	42.52	20.19*	22.36*	26.26	28.83	
3		34.71*	42.95	32.61	34.96*	72.46	41.64	20.24**	21.84**	26.34	33.93[b]	7.29[b]
4		33.93	42.47	31.97	36.66	72.17	39.10	19.82*	21.13*	26.05	143.85	111.72
5		33.32	42.38	30.90	37.50	67.70	42.91	19.73*	21.84*	26.59	88.96	70.55
6[c]		—	34.8	21.9	33.1	62.7						

[a]The chemical shifts are in ppm downfield from internal Me_4Si; the asterisks indicate pairs of shifts which have been assigned for consistency of parameter values but which could be interchanged. [b]Identified by deuteration. [c]Predicted shifts obtained by adding the shift constants for the introduction of a $-CO_2H$ group to the chemical shifts of *n*-butanol. See ref. 8, pp. 140–148.

Table 2. ^{13}C NMR chemical shifts of substituted bicyclo[2.2.2]octane δ-lactones[a]

No.	Compound	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	C_{11}
7		30.69	43.00	35.39	27.01	76.67	34.95[b]	20.51*	21.59*	18.12		
8		31.68	42.86	36.04	34.11	83.37	40.73	20.81*	22.22*	17.91	22.71	
9		31.42	42.85	36.10	32.22	85.91	38.50	20.35*	20.84*	17.89	28.71[b]	7.24[b]
10		31.18	43.17	35.81	32.94	84.50	39.18	20.66*	21.68*	17.95	136.56	114.63
11		30.59	42.65	35.29	35.29	77.20	41.47	20.43*	21.46*	17.94	81.47	74.56
12[b]		—	29.9	19.1	22.3	69.3						

[a]See footnotes to Table 1. [b]See Ref. 9.

shifts of some of the carbon atoms which can be interpreted as the result of two different factors:

(a) Deformation of the carbon skeleton involved in the change from the flexible boat-twist structure of the hydroxyacids to the rigid twist conformation forced on the cyclohexane rings in the lactone.

(b) Modification of the charge distribution which acts mainly on those carbons most closely situated to the carboxyl and hydroxyl groups.

A large number of ^{13}C NMR spectra of delta lactones, mainly in the area of natural products, have been reported,[7] but as far as I am aware, no comparative study to include the corresponding hydroxy acids has been undertaken. The known changes[8] which occur to the spectra of alcohols and carboxylic acids upon esterification have been used to assist in assigning chemical shifts, as have those between valerolactone **12**[9] and the predicted spectrum of 5-hydroxy valeric acid **6** (see footnote c in Table 1).

By comparing the data shown in Tables 1 and 2, it is seen that the signals due to C-7 and C-8 remain practically unchanged on conversion of the hydroxyacid to the lactone. Carbons 7 and 8 are remote from the lactone group and presumably only small changes in steric compression occur at these positions on lactonisation. These observations appear to provide support for the suggestion that steric compression is not the major factor governing the γ and δ effects.[10] However, if we consider the existence of intramolecular hydrogen bonding in the hydroxy acids, we should consider a fixed hydrogen bonded twist form rather than a flexible conformation. The twisted conformation would be very similar to the structure of the lactone, and thus no significant difference might be expected for C_7 and C_8 on lactonisation.

The C-2 resonance also remains practically unaltered, in contradistinction to the upfield shift (*ca.* 4.5 ppm) observed for C-2 of **6** when it is lactonised to **12**. This difference in behaviour can be reconciled by the observation that the small upfield shift experienced by the α carbon of a carboxylic acid when it is converted to an ester is reduced almost to zero if the carbon under consideration is completely substituted.[8]

The large downfield shift (+5 to +13 ppm) observed at C-5 on lactonisation is also observed on lactonisation of **6** to **12** (+6.5 ppm). These shifts are of the same sign as, but larger than, the α effect produced when an alcohol is acetylated,[8] and can be explained by the greater electron-withdrawing power of the lactone group in combination with the structural changes due to lactonisation. The observed shifts correlate well with the different nature of the substituents at C-5 (alkyl and alkenyl as opposed to alkynl) and accord with their electron-releasing or electron-withdrawing properties.[4,11]

By comparing the C-9 and C-10 resonances of the hydroxy acids and the corresponding lactones we realize that they are associated with a large upfield shift (about 8 and 6.5 ppm respectively) which cannot be wholly justified by invoking the beta effects observed on esterification.[8] Furthermore, the rigidity of the lactone ring eliminates the slightest possibility of a steric effect between C-10 and the carbonyl group of the lactone. Part of this large shift may be due to the fact that on lactonisation groups C-9 and C-10 suffer the greatest change of all in their steric environment.

The analysis of the C-1, C-4 and C-6 signals indicates that a small upfield shift (smaller for C-6) is produced on passing from the acids to the lactones, while in C-3 a downfield effect (ranging from +3.5 to +5 ppm) is produced. This different behaviour can be explained on the basis of the relative position of both carbons with respect to the carbonyl and oxygen groups of the lactone function, and by the fact that C-3 and C-6 are in the acids in a γ position to the –OH and $-CO_2H$ groups respectively, the gamma effect of the –OH being the stronger.[2] Therefore it is to be expected that on lactonisation the disappearance of the γ interaction would affect preferentially the C-3 peak, moving it to the downfield region of the spectra.

Preparation of compounds

The compounds were prepared from the readily available[2] 5 - oxo - 2 - *exo* - methylbicyclo[2.2.2]octane 2 - *endo* - carboxylic acid (**13**, R = H) or its methyl ester (**13**, R = Me). Treatment of (**13**, R = Me) with methylmagnesium iodide gave the lactone **8**, from which the acid **2** could be obtained by hydrolysis. Ethynylation of (**13**, R = H) gave **5** as the sole isomer, from which **4** and **3** were prepared by catalytic hydrogenation. The lactones were prepared from the corresponding hydroxyacids except for **10**, which was more readily prepared by catalytic hydrogenation of the acetylenic lactone **9**.

The following sequences of reactions were used (**13**, R = H) → **5** → **4** → **3**; (**13**, R = Me) → **8** → **2**.

Compounds **1** and **7** were reported previously.[2]

EXPERIMENTAL

^1H NMR spectra ($CDCl_3$) were recorded on either a Varian T-60 or HA-100 spectrometer using Me_4Si as internal standard and are reported in δ units. ^{13}C NMR spectra ($CDCl_3$) were recorded on a Varian CFT-20 spectrometer with Me_4Si as internal standard and are reported in parts per million. IR ($CHCl_3$) spectra were recorded on a Unicam SP-200 spectrometer. Mass spectra were taken on either an AEI-MS 9 or MS-12 spectrometer at 70 eV. The gas–liquid chromatography analysis were performed on either Apiezon L or Carbowax-20M columns.

2 - exo - *Methyl* - 5 - exo - *ethynyl* - 5 - endo - *hydroxybicyclo*[2.2.2]*octane* - 2 - endo - *carboxylic acid* **5**

A solution of the ketoacid **13** (R = H, 6.13 g, 33.8 mmol) in dry DMF (35 ml) was slowly added by syringe to a stirred suspension of sodium hydride (1.49 g, 33.8 mmol, 57% in mineral oil) in dry DMF (50 ml) under N_2. The mixture was then stirred until evolution of H_2 ceased. The fine suspension was removed with a syringe and introduced into a stirred suspension of lithium acetylide ethylene diamine complex (5 g, 55 mmol) in dry DMF (180 ml). The mixture was then heated to 75°C with stirring and maintained at this temp. for 4 hr. The mixture was then poured onto ice-cold water (1.5 l.), aqueous HCl (10%) was added until the solution was acidic, and the solution was extracted with Et_2O (3 × 300 ml). The ethereal extracts were shaken with aqueous $NaHCO_3$ solution (2 × 100 ml), the aqueous phase reacidified and then extracted with Et_2O (200 ml). The ethereal solution was dried (Na_2SO_4), and removal of the solvent gave **5**, 5.5 g, 78%; m.p. 159–160°C (benzene–petrol); IR, 3350 (≡CH), 3000–3700, 1700 cm^{-1}; ^1H NMR, 6.8 (m, 2H, OH and CO_2H), 2.4 (s, 1H, ≡CH), 1.3 (s, 3H, Me); MS, *m/e* 208 (M^+), 190, 163, 162 (100%), 141; high resolution *m/e* 208.1100 ($C_{12}H_{16}O_3$ requires: 208.1099).

Catalytic hydrogenation of **5** in hexane–THF (4:1) at atmospheric pressure and temperature over Lindlar catalyst gave **4** in quantitative yield; m.p. 135–136°C (benzene); IR, 3500, 1720 cm^{-1}; ^1H NMR, 7.3 (m, 2H, OH and CO_2H), 5.0–6.4 (m, 3H, vinyl H), 1.3 (s, 3H, Me); MS, *m/e* 210 (M^+), 192, 164, 123, 95 (100%), 83, 70; high resolution *m/e* 210.1248 ($C_{12}H_{18}O_3$ requires: 210.1256).

Catalytic hydrogenation of **5** or **4** in hexane–THF (4:1) using PtO_2 gave **3** in quantitative yield; m.p. 130–131°C (benzene); IR, 3500, 1710 cm^{-1}; ^1H NMR, 7.4 (s, 2H, OH and CO_2H), 1.3 (s, 3H,

Me), 0.9 (t, 3H, Me); MS, *m/e* 212 (M^+), 194, 183, 166, 137, 123, 95, 94, 93, 85 (100%); high resolution *m/e* 212.1403 ($C_{12}H_{20}O_3$ requires: 212.1412).

Lactonisation of **5** *and* **3**

A soln of the hydroxyacid (150 mg) and a trace of *p*-toluenesulphonic acid in benzene (5 ml) was heated to reflux for 30 min. The soln was then cooled, washed with aq. $NaHCO_3$ soln (10%) until the washings were neutral, and the solvent was then dried (Na_2SO_4). Evaporation of the solvent gave the corresponding lactone in 85–90% yield.

11; m.p. 154–155°C (benzene); IR, 3350 (≡CH), 1760 cm^{-1}; ^{1}H NMR, 2.6 (s, 1H, ≡CH), 1.2 (s, 3H, Me); MS, *m/e* 190.0992 ($C_{12}H_{14}O_2$ requires: 190.0097). **9**; m.p. 50°C (petrol); IR, 1760 cm^{-1}; ^{1}H NMR, 1.2 (s, 3H, Me), 1.0 (t, 3H, Me); MS, *m/e* 194 (M^+), 192, 166, 150, 137, 123, 109, 107, 94; high resolution *m/e* 194.1298 ($C_{12}H_{18}O_2$ requires: 194.1307).

Catalytic hydrogenation of **11** in hexane–THF (4:1) using Lindlar catalyst gave **10** in 90% yield; m.p. 55–57°C, IR, 1760 cm^{-1}; ^{1}H NMR, 5.0–6.4 (m, 3H, vinylic H), 1.2 (s, 3H, Me); MS, *m/e* 192 (M^+), 164, 95, 94 (100%), 80, 79, 77, 55; high resolution *m/e* 192.1155 ($C_{12}H_{16}O_2$ requires: 192.1150).

2 - exo - 5 - exo - *Dimethyl* - 5 - endo - *hydroxybicyclo*-[2.2.2]*octane* 2 - endo - *carboxylic acid lactone* **8**

The keto ester **13** (R = Me, 400 mg, 2 mmol) in dry Et_2O (2.5 ml) was added at 0°C to methylmagnesium iodide (2 mmol) in Et_2O (15 ml). The mixture was treated with water (15 ml), the ethereal extracts dried (Na_2SO_4) and the solvent removed by evaporation. Preparative TLC on Kieselgel, eluting with EtOAc–C_6H_6 1:3 gave **8**, 240 mg, 60% yield; m.p. 118–119°C (benzene–petrol); IR, 1760 cm^{-1}; ^{1}H NMR, 1.3 (s, 3H, Me), 1.2 (s, 3H, Me), 1.6–2.8 (m, 10H); MS, *m/e* 180 (M^+), 152, 138, 136, 123, 109, 107, 94, 93, 91, 80, 79, 77; high resolution *m/e* 180.1154 ($C_{11}H_{16}O_2$ requires: 180.1150).

Hydrolysis of **8** with boiling 10% NaOH (5 ml) for 3 hr, followed by addition of 10% HCl (20 ml), extraction ($CHCl_3$ 20 ml), drying and concentration gave **2** in 90% yield; m.p. 138–139°C ($CHCl_3$); IR, 3700–3000, 1700 cm^{-1}; ^{1}H NMR, 7.2 (m, 2H, OH and CO_2H), 1.6–2.8 (m, 10H), 1.3 (s, 3H, Me), 1.2 (s, 3H, Me); MS, high resolution *m/e* 198.1259 ($C_{11}H_{18}O_3$ requires: 198.1256).

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