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# THE STRUCTURE OF LACTONES OBTAINED FROM 3-METHYLENEBICYCLO[2.2.1]HEPT-5-ENE-2-*ENDO*-CARBOXYLIC ACID

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**Abstract**—Treatment of 3-methylenebicyclo[2.2.1]hept-5-ene-2-endocarboxylic acid with electrophilic reagents gives lactones of 5-hydroxy-2-methyltricyclo[2.2.1.$0^{2,6}$]heptane-3-carboxylic acid.

THE preparation of lactones from 3-methylenebicyclo[2.2.1]hept-5-ene-2-carboxylic acid (I) has been described by Jones *et al.*[1] They ascribed structures II (X = H or Br) although they were unable to detect the anticipated characteristic IR absorption bands for $C{=}CH_2$ around 1650 cm$^{-1}$ (C=C stretching) or around 890 cm$^{-1}$ (C—H out of plane deformation), finding instead several bands between 900–1000 cm$^{-1}$. They suggested these anomalies could be due to the strained environment of the 3-methylene group, which gave the anticipated bands in the acid (I). They also reported isolation of formaldehyde dimedone after ozonolysis of either lactone.

Our interest in endocyclic ketolactones[2] led us to repeat the ozonolysis of the lactone (II, X = H) in the hope of isolating the 3-oxolactone. However, the original lactone was recovered in high yield after attempted ozonolysis, and it also survived treatment with potassium permanganate/periodate. These properties, and the reported IR spectrum are more consistent with formulation as the nortricyclene lactone (III, R = $CH_3$), which would be expected to show more numerous bands between 900–1000 cm$^{-1}$ because of ring vibrations. Reexamination of the IR spectrum in carbon disulphide showed also a weak band at 3070 cm$^{-1}$ (typical of nortricyclene) and a doublet at 1800 and 1785 cm$^{-1}$ (CO). The known[3,4] lactone (III, R = H) was found to have a very similar spectrum including a doublet at 1800, 1780 cm$^{-1}$.

NMR spectra (Table 1) support this conclusion. The acid (I) shows two protons at 5·00 τ which are absent in the acid (IV, R = Me, $R^1$ = H) and can be assigned to the *exo*-methylene group. These protons are also absent in the lactone (III, R = Me) which in addition shows three protons at 8·67 τ. If cyclization is carried out in deuterium oxide/deuterosulphuric acid the resultant lactone shows only two protons at 8·67 τ. This Me group appears as a singlet and is more deshielded than that seen as a doublet ($J$ = 7 c/s) at 8·92 τ in the bicycloheptane lactone (V, R = Me, $R^1$ = H). The remainder of the spectrum of III (R = Me) resembles that of the nortricyclene lactone (III, R = H). The spectrum of lactone III (R = $CH_2Br$) can be interpreted similarly. The two protons centred at 6·30 τ appear as a sharply defined quartet of the AB type, $J$ = 11 c/s, typical of geminal coupling due to the highly assymetrical environment.

These conclusions were confirmed by an independent synthesis of lactone III (R = $CH_2Br$). The known[7] nortricyclene lactone III, R = COCl) was reduced to the

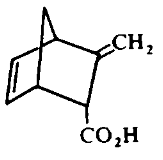
TABLE 1

| Compound | Reference | Chemical shift (τ) | Number of protons | Assigned to proton |
|---|---|---|---|---|
| III, R = H | Alder *et al.*[3, 4] | 5·26 | 1 | 5 |
| | | 7·42, 7·55 | 2 | 2, 4 |
| | | 8·0 to 8·4 | 5 | |
| III, R = Me | Jones *et al.*[1] | 5·25 | 1 | 5 |
| | | 7·46 | 2 | 2, 4 |
| | | 8·20 | 2 | |
| | | 8·3 to 8·6 | 2 | |
| | | 8·67 | 3 | $CH_3$ |
| III, R = $CH_2Br$ | Jones *et al.*[1] | 5·15 | 1 | 5 |
| | | 6·30 | 2 | $CH_2Br$ |
| | | 7·10, 7·30 | 2 | 2,4 |
| | | 8·00, 8·13 | 4 | |
| IV, R = Me<br>$R^1$ = H | Alder *et al.*[5] | 3·8 | 2 | 5,6 |
| | | 6·85 | 1 | |
| | | 7·4 to 7·7 | 2 | |
| | | 8·1 to 8·6 | 3 | |
| | | 8·80 | 3 | $CH_3$ |
| V, R = Me<br>$R^1$ = H | Beckmann *et al.*[6] | 5·32 | 1 | 6 |
| | | 6·90 | 1 | 2 |
| | | 7·8 to 8·7 | 7 | |
| | | 8·92 | 3 | $CH_3$ |
| I | Jones *et al.*[1] | 3·89 | 2 | 5,6 |
| | | 5·00 | 2 | $=CH_2$ |
| | | 6·0–7·0 | 3 | |
| | | 7·5 | 2 | |

hydroxylactone (III, R = $CH_2OH$). This was converted to a bromolactone (III, R = $CH_2Br$) identical in m.p., mixed m.p., IR and NMR spectra with the lactone obtained by bromination of acid I. Moreover, the same hydroxylactone (III, R = $CH_2OH$) was obtained by treatment of acid I with performic acid.

Independent synthesis of lactone III (R = Me) was also investigated. The most obvious route, analogous to the preparation of III (R=H), would be via the acid IV (R = Cl, $R^1$ = Me). However β-chlorocrotonic acid did not react with cyclopentadiene even at 150°, nor was the acid chloride more reactive. α-chlorocrotonic acid will react[3] though the yield is poor in contrast with the ease of reaction of α-chloroisocrotonic acid. ββ-dimethylacrylic acid gives [8, 9] a poor yield of adduct even at 180°. ββ-dichloroacrylic acid was also found unreactive. A combination of steric and electronic effects at the β-carbon appears to be critical. The known[10] lactone (VI) was then considered as an intermediate. Treatment with weak base gave mixtures from which the desired lactone III (R = Me), which could be formed by decarboxylative debromination, could not be isolated.

The direct formation of nortricyclene derivatives from the acid (I) by electrophilic addition to a homoconjugated diene is unusual as this ring system is normally formed by elimination. The possibility of a similar reaction occurring in the diene acid[11] (VII) was investigated but the anticipated lactone (III, R = H) could not be isolated from the mixture obtained on acid treatment.



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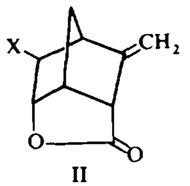

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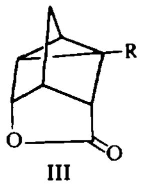

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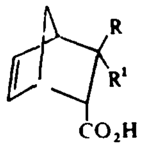

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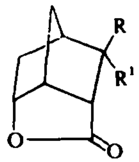

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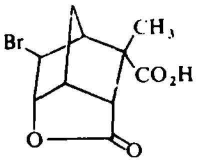
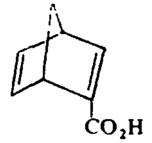


VI



VII

## EXPERIMENTAL

NMR spectra were measured at 60 mc on a Perkin–Elmer Model 10. IR spectra were determined using a Perkin–Elmer Model 257. M.ps are uncorrected. Elemental analyses were carried out by Dr. G. Crouch, School of Pharmacy, London University.

*5-Hydroxy-2-methyltricyclo*[2.2.1.0$^{2,6}$]*heptane-3-carboxylic acid γ-lactone* (III, R=Me)

3-Methylenebicyclo[2.2.1]hept-5-ene-2-*endo*carboxylic acid[1] (5 g) was shaken with 50% $H_2SO_4$ (200 ml) for 3 hr. The reaction mixture was then poured into water (800 ml) and extracted 4 times with $CHCl_3$. The combined extract (800 ml) was washed with 8% $NaHCO_3$ (100 ml), dried ($Na_2SO_4$) and concentrated to give a residue which, crystallized from petroleum (b.p. 40–60°), gave the lactone (1·71 g, 34%), m.p. 50–52·5°, lit.[1] m.p. 49·5–50·5°. NMR and IR spectra described in text (Found C, 71·80; H, 6·91. Calc. for $C_9H_{10}O_2$: C, 71·99; H, 6·67%).

*5-Hydroxy-2-bromomethyltricyclo*[2.2.1.0$^{2,6}$]*-heptane-3-carboxylic acid, γ-lactone* (III, R = $CH_2Br$)

(i) 3-Methylenebicyclo[2.2.1]hept-5-ene-2-*endo*carboxylic acid (1 g) was dissolved in 8% $NaHCO_3$aq (25 ml), stirred, cooled in ice-bath and $Br_2$ (1·05 g) in $CCl_4$ (15 ml) added over 15 min. The aqueous layer was then separated and extracted with $CCl_4$ (15 ml) which was added to the organic layer. The combined extract (30 ml) was dried ($Na_2SO_4$) and concentrated to leave a residue which solidified on cooling. Recrystallization from petroleum (b.p. 40–60°) gave the pure compound (0·54 g, 35%), m.p. 77–78°, lit.[1] m.p. 77–78°, $\nu_{max}(CS_2)$ 3060 (w) 1800 (s) 1785 (shoulder) $cm^{-1}$, NMR spectrum described in text.

(ii) Dry pyridine (2 ml) was added to $PBr_3$ (0·97 g) in dry benzene (20 ml). The mixture was stirred for 15 min at 18° and then cooled to − 5°, stirred, and 5-hydroxy-2-hydroxymethyltricyclo[2.2.1.0$^{2,6}$]heptane-3-carboxylic acid, γ-lactone (1·66 g) in dry benzene (40 ml) and dry diglyme (2 ml) added over 1 hr, keeping the temp of the reaction mixture between 0 and 5°. Stirring was continued at room temp for 48 hr. The reaction mixture was then poured into water (100 ml). The aqueous layer was separated and extracted with benzene (40 ml), which was added to the organic layer. The combined extract was dried ($Na_2SO_4$) and concentrated. The residue was dissolved in ether (80 ml), washed 5 times with 8% $NaHCO_3$ aq (60 ml) once with brine (60 ml), dried ($Na_2SO_4$) and concentrated to give a colourless liquid (2·60 g). This was chromatographed on silica gel (100 g) with benzene-acetone (80:20) and crystallized from petroleum (b.p. 40–60) to give the bromomethylnortricyclene lactone (0·62 g, 27%), m.p. 75–77° undepressed by mixture with the lactone obtained as described[1] and having identical IR and NMR spectra.

*Lactonization of* 3-*methylenebicyclo*[2.2.1]*hept*-5-*ene*-2-endo*carboxylic acid with deuterosulphuric acid*

The unsaturated acid (0·45 g) was added to deuterosulphuric acid (5 g) in D2O (5 ml) and shaken vigorously for 3 hr. The mixture was then poured into water (100 ml) and extracted 5 times with ether. The combined extract (200 ml) was washed twice with 8% $NaHCO_3$ aq (40 ml), dried ($Na_2SO_4$) and concentrated to give a residue which crystallized from petroleum (b.p. 40–60°) to give the lactone (0·152 g, 34%) m.p. 52–54°, $\nu_{max}$ ($CS_2$) 3070 cm$^{-1}$ (w) 1795, 1785 cm$^{-1}$, NMR spectrum described in text.

*Attempted oxidative cleavage of supposed* 3-*methylene*-6-endo*hydroxybicyclo*[2.2.1]*heptane*-2-endo-*carboxylic acid γ-lactone* (II, R = H)

(i) The lactone[1] (150 mg) was dissolved in glacial AcOH (30 ml) and $O_3$ (1 ml/min) was passed through for 2 hr. The reaction mixture was then poured into water (70 ml), cautiously just neutralized with solid $NaHCO_3$ and extracted 4 times with EtOAc. The extract (200 ml) was dried ($Na_2SO_4$), concentrated and the residue crystallized from petroleum (b.p. 40–60°) to give a white crystalline solid (130 mg, 87%) m.p. 49–50° undepressed by mixture with original sample.

(ii) The lactone (150 mg) was shaken with $KMnO_4$ (25 mg), $K_2CO_3$ (1·0 g), $KIO_4$ (0·7 g), and water (10 ml) for 24 hr. The reaction mixture was then cooled (ice-bath), acidified with conc HCl and extracted 3 times with ether. The extract (60 ml) was dried ($Na_2SO_4$) concentrated and crystallized from petroleum (b.p. 40–60°) to give a solid (104 mg, 72%), m.p. 46–51° undepressed by mixture with the original material.

5-*Hydroxy*-2-*hydroxymethyltricyclo*[2.2.1.$0^{2,6}$]*heptane*-3-*carboxylic acid, γ-lactone* (III, R = $CH_2OH$)

(i) To a stirred and cooled (ice-bath) soln of 2-chlorocarbonyl-5-hydroxytricyclo[2.2.1.$0^{2,6}$]heptane-3-carboxylic acid γ-lactone[7] (10 g) in dry diglyme (100 ml), was added over 15 min $NaBH_4$ (2 g) in dry diglyme (100 ml). Water (10 ml) was then added, followed dil $H_2SO_4$ (about 30 ml) until the reaction mixture was just acid to litmus. Water (300 ml) was added and the soln concentrated and then continuously extracted with ether. The extract was dried ($Na_2SO_4$) and concentrated to give a colourless liquid (8·83 g). This, crystallized from a mixture of ether–petroleum (b.p. 40–60°), and dried *in vacuo* over $P_2O_5$ gave the lactone (3·5 g, 40·5%) m.p. 130–136°. This compound was very hygroscopic making it hard to purify and also difficult to obtain a satisfactory elemental analysis, $\nu_{max}$ ($CHCl_3$) 3250 (broad) 1775 (s) cm$^{-1}$, NMR τ 5·57, 6·13 (q, $J = 11$), 6·73, 7·1, 7·3, 8·23. (Found C: 58·39; H, 5·99. $C_9H_{10}O_3$. $H_2O$ requires: C, 58·69; H, 6·57%).

(ii) To a stirred cooled (−10°) suspension of 3-methylenebicyclo[2.2.1]hept-5-ene-2-endocarboxylic acid[1] (5 g) in 90% formic acid (15 ml) was added during 3 min, 30% $H_2O_2$ (12 ml). Stirring was continued for 10 min at −10° and for 5 min at 18°, when all the solid dissolved. The stirred cooled soln was cautiously made just alkaline to litmus with 8% $NaHCO_3$ aq and then continuously extracted with ether for 24 hr. The extract was dried ($Na_2SO_4$) and concentrated to give a yellow residue (2·43 g). This was chromatographed on silica gel (80 g) with graded amounts of dioxan in benzene. Fractions 1 to 20 gave non-lactonic products. Fractions 20 to 25 (total 0·90 g) on crystallization from ether gave the hydroxylmethylnortricyclene lactone (0·36 g, 6·5%) m.p. 130–134° undepressed by material obtained from borohydride reduction of the acid chloride, and with identical IR and NMR spectra.

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