THE SYNTHESIS OF 2-KETOCYCLOHEXYLSUCCINIC ACID AND RELATED SUBSTANCES

IV. STUDIES ON SOME CIS- AND TRANS-FUSED Y-LACTONES¹

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ABSTRACT

The *cis* and *trans* lactones of cyclohexanol-2-acetic acid and cyclohexanol-2- α -propionic acid have been subjected to alkaline hydrolysis to determine the relative ease of ring opening. In addition, a new synthesis by way of a Reformatsky reaction followed by dehydration and cyclization has been shown to yield the *cis* lactone. Finally, the first overtone band of the fundamental carbonyl stretching frequency has been identified.

INTRODUCTION

The reaction of sodiomalonic ester with cyclohexene oxide, followed by hydrolysis and decarboxylation, affords the *trans* lactone (Ia) (1). An isomeric *cis* lactone (Ib) is obtained by catalytic reduction of cyclohexanone-2-acetic acid (2).



This investigation has shown the latter compound to be identical with the lactone obtained by the acid-catalyzed cyclization of ethyl cyclohexene-1-acetate (IIIa). This substance was produced by a Reformatsky reaction between cyclohexanone and ethyl bromoacetate, followed by dehydration of the β -hydroxy ester with phosphorus pentoxide.

The *cis* and *trans* configurations shown for the lactones follow from (a) the known stereochemistry of the reaction of nucleophiles with epoxides (3); (b) the known stereochemistry of the catalytic reduction of substituted cyclohexanones (4); and (c) the greater ease with which (Ib) is formed from the corresponding hydroxy acid (2, cf. 5). Similar arguments apply to the lactones (IIa) (6) and (IIb), available by essentially the same reactions.

Further support for these configurational assignments is given by studies on the rates of ring opening by alkali. In both cases the isomer assigned the *trans* configuration hydrolyzed more rapidly, as shown in Fig. 1. This was to be expected in view of the less stable *trans* configuration. The greater stability of the methyl-substituted ring is in accordance with the many analogous cases in the literature (7).

All lactones showed peak absorption at about 2.8μ in the infrared region accessible to the Beckmann D.K. recording spectrophotometer. This is undoubtedly the first overtone (8) of the powerful carbonyl adsorption band observed for (Ia) and (Ib) at 5.62μ and 5.70μ respectively, by Brewster and Kucera (9). As in the case of the fundamental frequencies, a wavelength shift was observed for these 2.8μ bands indicating the more strained condition of the *trans* form. Rasmussen and Brattain (10) noticed absorption in this 2.8μ region by several lactones, but suggested that it might be due to traces of

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FIG. 1. Rates of hydrolysis of *cis-trans* γ -lactones by .0765 N NaOH at 20° C (Δ -Ia, \bigcirc -Ib, \blacktriangle -IIa, \bigcirc -IIb).

water. However, in a re-examination of the spectrum of γ -valerolactone in carbon tetrachloride, we find the peak at 2.8 μ to be unaffected by drying the solvent, while a less prominent band at 2.71 μ diminishes (but could not be eliminated altogether). The latter band is undoubtedly due to water, which in carbon tetrachloride alone causes absorption at 2.696 μ ; the shift to longer wavelength in the presence of lactones is evidence of hydrogen-bonding between the two molecules.

TABLE I

Some physical constants and derivatives of the lactones

	γ -Lactone of cyclohexanol- 2-acetic acid			γ -Lactone of cyclohexanol- 2- α -propionic acid		
		cis Ib			cis IIb	
	trans (Ia) Method (1)	Method (2)	Reformatsky method	trans (IIa) Method (6)	Reformatsky method	Method (2)
B.p. (per mm) D_{4}^{20}	131–132°/12 1.0859	129–130°/13 1.0921	128128.5°/10 1.0923	125–128°/10 1.0519	131-134°/11 1.0589	132–135°/13
Position of C==O over-	1.4752	1.4784	1.4773	1.4719	1.4756	1.4751
tone in millimicrons M.p. of hydroxy acid M.p. of hydrazide M.p. of N-benzylamide	$\begin{array}{c} 2802 \\ 105 - 106^{\circ} \\ 167 - 167 . 5^{\circ} \\ 141 - 142^{\circ*} \end{array}$	2808 	2808 140–141° 97–98°*	2812 110–111° 191–192°	2819 136–137° 	2819

*Brewster and Kucera (9).

EXPERIMENTAL

REFORMATSKY REACTIONS AND SUBSEQUENT PROCEDURE

Ethyl 1-Cyclohexanolacetate

Cyclohexanone (49 g), zinc filings (33 g), and dry benzene (200 ml) were placed in a 1-l. three-necked flask equipped with a stirrer and condenser. The mixture was heated to boiling and the addition of ethyl bromoacetate (167 g) containing a trace of iodine was begun. At the first sign of reaction, heating was discontinued, the stirrer started, and the addition continued at such a rate that moderate refluxing was maintained. Following addition of the ester, refluxing was continued for a further half hour. No attempt should

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be made to dissolve the unreacted zinc by prolonged heating, as this decreases the yield and quality of the product. A little ice was added to the cooled solution and with the stirrer running, cold sulphuric acid (250 ml, 6 N) was added slowly. After half an hour the benzene layer was separated, washed with water and sodium carbonate solution, and dried over calcium chloride. The benzene was removed and the ethyl 1-cyclohexanolacetate (66.5 g, 72% yield) distilled *in vacuo* at 108–118° C (11 mm). Auwers and Ellinger (11) report 141° C (33 mm) and Charlesworth *et al.* (12) 143–146° C (37 mm).

Ethyl Cyclohexene-1-acetate (IIIa)

Ethyl 1-cyclohexanolacetate (50 g) was dissolved in dry benzene (150 ml), and phosphorus pentoxide (40 g) was added to the solution. It was refluxed on the water bath for 3 hours and allowed to cool. The benzene solution was decanted, the porous residue rinsed twice with benzene (25-ml portions), and the washings combined with the main solution. The benzene was removed and the unsaturated ester (30.5 g, 68%) was distilled at 93–95° C (10 mm). Wallach (13) reports 100° C (12 mm).

Lactone of cis-Cyclohexanol-2-acetic Acid (Ib)

Ethyl cyclohexene-1-acetate (10 g) and sulphuric acid (60 ml, 50% by volume) were heated on the water bath under reflux with stirring for 1 hour. By this time the oily layer had disappeared and the solution was yellow-orange in color. Only a small amount of polymeric material clinging to the walls of the flask was observed. The solution was allowed to cool, water (150 ml) was added, and the solution heated to boiling. It was cooled and extracted four times with ether (50-ml portions). The ethereal extract was washed with saturated salt solution, sodium carbonate solution, and thoroughly dried with anhydrous potassium carbonate. The ether was removed and distillation gave a colorless liquid (5.0 g, 60% yield) with a characteristic smell, which boiled at 129–130° C (13 mm); $n_{\rm p}^{20} = 1.4784$. It was neutral to litmus and solidified at -20° C into long white needles. The original ethyl cyclohexene-1-acetate does not solidify at -80° C. Found: C, 69.1; H, 8.72%. Calc. for the lactone C₈H₁₂O₂: C, 68.6; H, 8.57%.

When crude cyclohexene-1-acetic acid (m.p. $34-36^{\circ}$ C) prepared by the hydrolysis of the ester according to the directions of Wallach (13) was treated with 50% sulphuric acid according to the above directions, there was considerably more darkening than with the ester. Acidification of the sodium carbonate washings showed that very little unlactonized acid was left. Distillation gave the lactone in slightly smaller yield (43%), but with the same properties and constants as before. Found: C, 68.8; H, 8.97%. There was more dark viscous distillation residue than in the previous case.

When ethyl 1-cyclohexanolacetate was lactonized according to the above conditions there was considerably more dark polymeric material produced than in the previous cases. The lactone was isolable as before, but only in about 26% yield.

Ethyl α -(1-Cyclohexanol) Propionate

This ester was obtained in 76% yield in a Reformatsky reaction with ethyl α -bromopropionate. It distilled at 115–119° C (11 mm). Wallach reported 125–127° C (12 mm).

Ethyl Cyclohexene-1- α -propionate (IIIb)

This was obtained in 70% yield by dehydration of the previous ester. It boiled at $97-99^{\circ}$ C (11 mm) or $68-70^{\circ}$ C (1 mm).

Lactone of cis-Cyclohexanol-2-a-propionic Acid (IIb)

This was obtained in 66% yield by cyclization of the previous unsaturated ester with

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50% sulphuric acid. It boiled at 131–134° C (11 mm); $n_D^{20} = 1.4756$. It did not solidify at -20° C. Found: C, 69.5; H, 9.24%. Calc. for C₉H₁₄O₂: C, 70.0; H, 9.15%.

γ -Lactones (Other than by Reformatsky Method)

The preparation of the *cis* lactones by the Reformatsky method (D. L. Stachiw) is described above. These samples were compared with *cis* lactones prepared from the corresponding keto acids by the catalytic hydrogenation method of Newman and Van der Werf (2) and found to be identical in all respects (Table I).

The *trans* lactones (Ia and IIa) were prepared by the method of Coffey (1) and of McRae, Charlesworth, and Alexander (6) from cyclohexene oxide.

γ -Lactone of trans-Cyclohexanol-2-methylmalonic Acid

This product was isolated prior to the decarboxylation step in the cyclohexene oxide synthesis of the *trans* lactone (II*a*). After recrystallization from benzene-ligroin, white crystals were obtained melting at 151–152° C. Found: C, 60.98; H, 7.22%; neut. equiv., 198.0. Calc. for $C_{10}H_{14}O_4$: C, 60.6; H, 7.12%; neut. equiv., 198.2.

trans-Cyclohexanol-2-acetic Acid

Upon alkaline hydrolysis and acidification of the *trans* lactone (Ia) Newman and Van der Werf (2) obtained an acid of m.p. $105-106^{\circ}$ C. They claimed that their product was not identical with the 97-102° melting acid obtained by Coffey (1) by hydrogen chloride treatment of the potassium salt of (Ia) because the latter had a tendency to relactonize in solution. The two methods were repeated and, although several recrystallizations failed to raise the melting point of Coffey's product, a mixed melting point revealed little or no depression. It seems more reasonable, therefore, to view the instability of this low-melting acid as resulting merely from its impurity.

trans-Cyclohexanol-2- α -propionic Acid

The method previously outlined (2) was used to obtain an acid which, after recrystallization from water, melted at 110° C. Found: C, 63.0; H, 9.16%; neut. equiv., 173.5. Calc. for $C_9H_{16}O_3$: C, 62.8; H, 9.31%; neut. equiv., 172.2.

Hydrazide Derivatives

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The method described by Coffey (1) was used. A 10% solution of the lactone in alcohol was boiled with hydrazine (95%) for a few minutes. When the solution was cooled, the hydrazide separated.

The Reformatsky-produced lactone (III $a \rightarrow Ib$) and the Newman *cis* lactone (Ib) both gave a hydrazide which, when recrystallized from benzene–ligroin, melted at 140–141° C. Found: N, 16.12%. Calc. for C₈H₁₆O₂N₂: N, 16.26%. This derivative was far more soluble in polar and non-polar solvents than the corresponding *trans* hydrazide, which melted at 167.5°, as reported by Coffey (1).

The *trans* lactone of cyclohexanol-2- α -propionic acid (IIa) gave a derivative which, upon recrystallization from water, melted at 191–192° C. Found: N, 14.76%. Calc. for C₉H₁₈O₂N₂: N, 15.04%.

The Reformatsky-produced *cis* lactone (IIIb \rightarrow IIb) yielded a hydrazide which, after two recrystallizations from benzene-ligroin, melted at 136-137° C. Found: N, 15.15%. Calc. for C₉H₁₈O₂N₂: N, 15.04%.

N-Benzylamide Derivatives

The method used was that of Dermer and King (14). The Reformatsky-produced lactone (1 g) was refluxed with benzylamine (3 ml) in the presence of ammonium chloride

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(1 g). The amide, when recrystallized from benzene-ligroin, melted at 97-98° C. Brewster and Kucera (9) reported an identical melting point for the N-benzvlamide prepared from Newman's cis lactone.

Hydrolyses of γ -Lactones

The technique used was adapted from that described by Kendall, Osterberg, and MacKenzie (15) for the determination of the rate of ring opening of a γ -lactone. The lactone (1/200 mole) was dissolved in ethanol (25 ml) and introduced into a flask containing .0860 N sodium hydroxide (200 ml), stirred gently, and thermostated at 20° C. At periodic intervals, 20-ml portions were withdrawn and run into hydrochloric acid (20 ml, .0896 N). The excess acid was then titrated with standard alkali and the hydrolysis rate plotted (Fig. 1).

Infrared Spectra

A Beckmann D.K. recording spectrophotometer was used to investigate the small portion of the infrared region up to 2.85 μ . A pair of quartz cells were used whose 100% line did not deviate more than 3% on either side. The lactone samples were weighed directly into the cell and a measured amount of solvent carbon tetrachloride added.

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