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Novel Lactonization of γ-Cyclopropyl Carboxylic Acid *via* Acid-catalyzed Cleavage of Cyclopropane Ring

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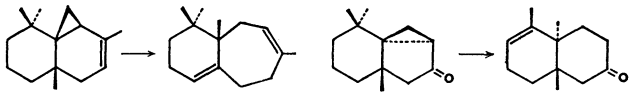
Synopsis. 4,6,10,10-Tetramethyltricyclo[4.4.0.0^{1,3}]-undec-4-ene-5-carboxylic acid has been converted to a tricyclic γ-butyrolactone by perchloric acid catalyzed isomerization. Acetalization of the ketocarboxylic acid afforded an acetal derivative of γ-butyrolactone.

The acid-catalyzed rearrangement of cyclopropylcarbonyl or cyclopropylcarbinyl systems have been extensively investigated. Most of these reactions have known to undergo acid-catalyzed cleavage of the cyclopropane ring and migration of the angular methyl group and/or one of a *gem*-dimethyl groups. For example, under acid conditions, *cis*-thujopsene (**1**) is converted by ring enlargement and angular methyl group migration into a diene (**2**).[1] The acid-catalyzed isomerization of 6,10,10-trimethyl-4-oxotricyclo-[4.4.0.0^{1,3}]decane (**3**) caused ring enlargement and *gem*-dimethyl group migration giving the product **4**.[2]

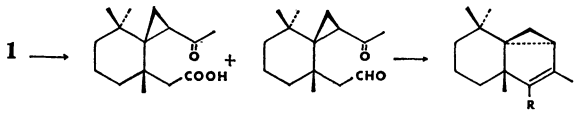


1 **2** **3** **4**

Marshall and Ellison[3] reported that cyclopropylmethanols were subjected to solvolysis in aqueous acid to give γ-butyrolactones fused with cycloheptene and cyclohexene rings. Interest in these reactions prompted the authors to investigate the acid-catalyzed isomerization of 4,6,10,10-tetramethyltricyclo[4.4.0.0^{1,3}]undec-4-ene-5-carboxylic acid (**8**) and its related compound (**5**). It was found that compounds **5** and **8** were converted into the γ-butylolactones (**9** and **11**) *via* cleavage of the cyclopropane ring, and that migration of the angular methyl or *gem*-dimethyl group of **5** and **8** did not occur.

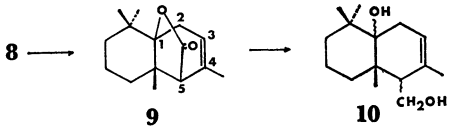
The starting materials (**5** and **8**) were synthesized from *cis*-thujopsene (**1**) as follows. Ozonolysis of *cis*-thujopsene (**1**) in acetic acid gave **6** (47.5%) and **5** (26.6%). The IR and NMR spectra of **6** were identical with those of the sensitized photo-oxidation products of *cis*-thujopsene (**1**).[4] Compound **5** was identical with the spectra of the ozonolysis products of *cis*-thujopsene (**1**) obtained in methanol and ethyl acetate by Norin.[5] One of the ozonolysis products (**6**) was converted into a carboxylic acid (**8**) *via* the aldehyde (**7**)[4,6] as reported by Ohloff *et al.*[6]

The reaction of tricyclic carboxylic acid (**8**) with 70% perchloric acid in benzene gave a γ-butyrolactone (**9**) in 65.5% yield. The structure of **9** was deduced from the spectral data together with the following evidence. The IR absorption of **9** at 1760 cm^{-1} shows the presence of γ-butyrolactone. The presence of a methyl group



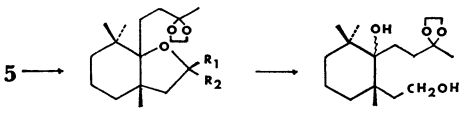
5 **6** **7**: R=CHO **8**: R=COOH

on the olefinic carbon, a C_5–H proton, and a vinyl proton are indicated by the NMR signals at δ 1.80, 2.35, and 5.45 ppm, respectively. Reduction of **9** with lithium aluminium hydride in ether gave an alcohol (**10**). The IR absorptions of **10** at 3260 and 3100 cm^{-1} show the presence of a hydroxyl group. The presence of a methyl group on the olefinic carbon, a vinyl proton, and a hydroxymethyl group are indicated by the NMR signals at δ 1.75, 5.41, and 2.78 ppm (d, J=3.0 Hz), respectively.



9 **10**

The other ozonolysis product (**5**) was refluxed for 10 h with ethylene glycol and *p*-toluenesulfonic acid in benzene and the reaction mixture chromatographed to give compound **11**. The structure of **11** was deduced from the spectral data as well as the following evidence. The IR absorption of **11** at 1755 cm^{-1} shows the presence of an γ-butyrolactone ring. Reduction of **11** with lithium aluminium hydride in ether at room temperature gave the lactol (**12**). The lithium aluminium hydride reduction of **11** in ether at boiling point however for 2 h gave the diol (**13**).



11: R_1=R_2=O **13**

12: R_1=H, R_2=OH

Experimental

The melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. The NMR spectra were recorded on a JEOL PMX-60 spectrometer at 60 MHz, using Me_4Si as an internal standard. The IR spectra were determined on a Shimadzu IR-400 spectrometer. Elemental analyses were performed by a Hitachi 026 CHN analyzer. The analytical GLC was performed on a Shimadzu GC-4B apparatus with a 3 m stainless steel column packed with 3% SE-30, at 10 °C/min 150—250 °C.

Ozonolysis of cis-*Thujopsene (1).* A stream of ozone at 20—35 °C was passed through a stirred solution of **1** (20.4 g, 0.1 mol) in acetic acid (200 ml), until all the starting material had disappeared. The reaction mixture was subsequently treated with zinc dust (30 g) for 1 h at 60—70 °C to reduce the ozonide, filtered, and concentrated. The residue was dissolved in ether (500 ml) and the ether solution washed with 5% aqueous NaOH (50 ml×3), water, dried (Na_2SO_4), and evaporated to give an oily residue (16.2 g). The product was purified by column chromatography using silica gel. Elution with benzene gave **6** (11.2 g) as a colorless liquid. **6**; NMR ($CDCl_3$) δ 0.72 (s, 3, CH_3), 1.13 (s, 3, CH_3), 1.30 (s, 3, CH_3), 2.37 (s, 3, CH_3), 3.00 (dd, 1, J=10.0 and 3.5 Hz), and 9.68 (t, 1, J=3.0 Hz). The combined water layer was acidified with 10% HCl, and extracted with ether. The ether solution was washed with water, dried (Na_2SO_4), and evaporated to give a solid residue (7.9 g). A pure sample of **5** was obtained by recrystallization from hexane. **5**; mp 165—168 °C (lit,[6] mp 166—168 °C).

Cyclization of 6. To a stirred solution of **6** (10.5 g, 40 mmol) in ethanol (200 ml), maintained at 15 °C was added powdered KOH (50 mg, 10 mmol). The solution was stirred for 2 h at room temperature, and then the solvent evaporated under reduced pressure and the residue diluted with water and extracted with ether. The ether solution was washed with water, dried (Na_2SO_4), and evaporated to give an oily residue (9.8 g). The product was separated by column chromatography using silica gel. Elution with benzene gave colorless crystals (**7**) (5.2 g). A pure sample of **7** was obtained by recrystallization from hexane. **7**; mp 73.5—75 °C (lit,[6] mp 73—74 °C).

Oxidation of 7. Compound **7** (2.16 g, 10 mmol) was oxidized in acetone (25 ml) with Jones reagent (8 mole ratio, 2.8 ml) at room temperature for 1 h. The mixture was evaporated and ice-cooled water poured into the resulting residue, which was then extracted with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated to give crude crystals (1.98 g). Recrystallization from hexane gave pure **8**. **8**; mp 148—149 °C (lit,[6] mp 147—149 °C).

Lactonization of 8. A mixture of **8** (1.16 g, 5 mmol) and perchloric acid (70%, 0.5 ml) in benzene was refluxed for 5 min. The reaction mixture was washed with water, dried (Na_2SO_4), and evaporated to give an oily residue (1.1 g). The product was separated by column chromatography using silica gel. Elution with benzene gave colorless crystals **9** (0.81 g). A pure sample of **9** was obtained by recrystallization from hexane. **9**; mp 122—125 °C; IR (KBr) ν 1760 cm^{-1} (γ-butyrolactone); NMR ($CDCl_3$) δ 1.03 (s, 6, $2CH_3$), 1.10 (s, 3, CH_3), 1.80 (d, 3, CH_3, J=3.0 Hz), 2.35 (s, 1, C_5–H), 2.48 (m, 2, C_2–H), and 5.45 (m, 1). Found: C, 76.97; H, 9.35%. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46%.

Reduction of 9. A mixture of **9** (117 mg, 0.5 mmol) and $LiAlH_4$ (46 mg, 1.2 mmol) in ether was refluxed for 3 h. To the stirred reaction mixture was added water (2 ml), and extracted with ether. The ether solution was washed with water, dried (Na_2SO_4) and evaporated to give a solid residue (116.5 mg). A pure sample of **10** was obtained by recrystallization from hexane. **10**; mp 140—141 °C; IR (KBr) ν 3250 and 3100 cm^{-1}; NMR ($CDCl_3$) δ 0.95 (s, 3, CH_3), 1.13 (s, 6, $2CH_3$), 1.75 (broad s, 3, CH_3), 2.78 (d, 2, $-CH_2OH$, J= 3.0 Hz), and 5.41 (m, 1).

Lactonization of 5. A benzene solution of **5** (2.52 g, 10 mmol), ethylene glycol (740 mg, 12 mmol), and *p*-TsOH (19 mg, 0.1 mmol) was refluxed for 10 h. The reaction mixture was washed with water, dried (Na_2SO_4), and evaporated to give an oily residue (3.17 g). The product was separated by column chromatography using silica gel. Elution with benzene gave colorless crystals (**11**) (1.58 g). A pure sample of **11** was obtained by recrystallization from hexane. **11**; mp 65—67 °C; IR (KBr) ν 1755 cm^{-1} (γ-butyrolactone); NMR ($CDCl_3$) δ 1.10 (s, 6, $2CH_3$), 1.25 (s, 3, CH_3), 1.32 (s, 3, CH_3), and 3.95 (s, 4, $-CH_2CH_2-$). Found: C, 69.02; H, 9.56%. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52%.

Reduction of 11 at Room Temperature. To a stirred solution of **11** (296 mg, 1 mmol) in ether (3 ml), maintained at 10 °C, $LiAlH_4$ (45.6 mg, 1.2 mmol) was added and the solution stirred for 2 h at room temperature. Water (1 ml) was added to the stirred solution, and the aqueous solution extracted with ether. The ether solution was washed with water, dried (Na_2SO_4), and evaporated to give an oily residue (294.2 mg). **12**; IR (neat) ν 3400 cm^{-1} (–OH); NMR ($CDCl_3$) δ 0.98 (s, 6, $2CH_3$), 1.10 (s, 3, CH_3), 1.33 (s, 3, CH_3), 3.97 (s, 4, $-CH_2CH_2-$), and 5.33 (m, 1).

Reduction of 11 at Boiling Point. A mixture of **11** (296 mg, 1 mmol) and $LiAlH_4$ (91 mg, 2.4 mmol) in ether (3 ml) was refluxed for 2 h. Water (2 ml) was added to the stirred solution and the aqueous solution extracted with ether. The ether solution was washed with water, dried (Na_2SO_4) and evaporated to give an oily residue (116.5 mg). **13**; IR (neat) ν 3395 cm^{-1} (–OH); NMR ($CDCl_3$) δ 0.95 (s, 3, CH_3), 1.07 (s, 6, $2CH_3$), 1.32 (s, 3, CH_3), 2.90 (broad s, 2, –OH), 3.68 (t, 2, $-CH_2OH$, J=6.0 Hz), and 3.97 (s, 4, $-CH_2CH_2-$).

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