# Synthesis and Alkylation of *cis*-3-α-Hydroxyisopropylindanone-2-carboxylic Acid Lactone (1)



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The Meldrum's acid adduct of isobutyrophenone was cyclized directly and in high yield to the title compound, which could then be alkylated at the 2-position with methyl iodide or ethyl 6-bromohexanoate. In the latter case, acid hydrolysis of the resultant ester gave the analogous acid, but alkaline hydrolysis resulted in ring opening of the indanone portion of the molecule.

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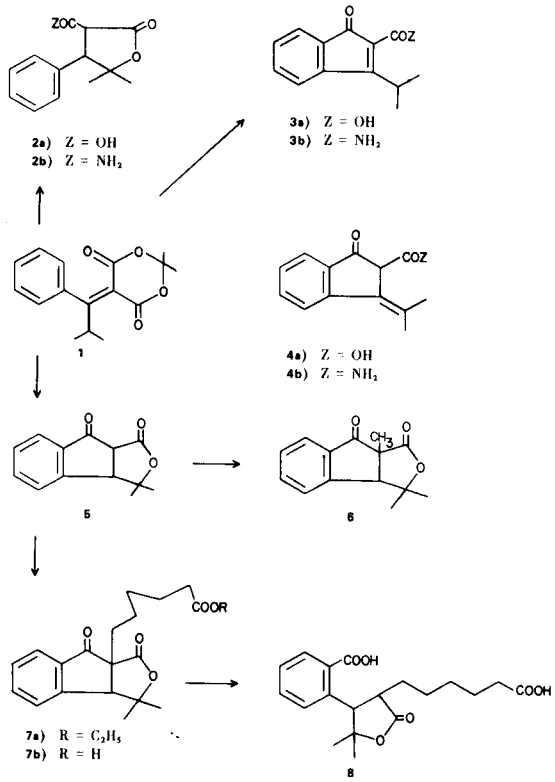
We have shown (3) that malononitrile, when condensed with aryl ketones, is a versatile reagent for the formation of either indanones and indenones or γ-lactones, depending on the acidic conditions employed. For example, the ylidene-malononitrile derived from isobutyrophenone gave a mixture of 3-isopropylindenone-2-carboxamide and 3-isoproylideneindanone-2-carboxamide (**3b** and **4b**, Scheme I) with **4b** the major product, in concentrated sulfuric acid (4). However, the same compound in polyphosphoric acid gave a high yield of the lactone-amide **2b** (Scheme I) (5). Possible mechanisms for these different results have been discussed (3,5).

Recently Meldrum's acid, isopropylidene malonate, has been shown to be a useful alternate reagent in the synthesis of lactones from the corresponding ketones (6), and some special examples of Meldrum's acid adducts, where rearrangements might occur during acid catalyzed cyclization, have been reported (7). These lactone cyclizations have all occurred cleanly in concentrated sulfuric acid. We wish to report now an interesting example of a double cyclization, where both ketone and lactone are formed in the same molecule. Thus the Meldrum's acid adduct **1** (Scheme I) is converted directly and in high yield to the indanone-lactone **5** by stirring in concentrated sulfuric acid. Compound **5** is undoubtedly *cis*-3-α-hydroxyisopropylindanone-2-carboxylic acid lactone, for steric reasons as well as the characteristic J value for the *cis* hydrogens at the 2 and 3 positions, and characteristic infra-red bands for a 5-5 fused ring system.

Refluxing **1** in trifluoroacetic acid led to the formation of the expected 3-isopropylindenone-2-carboxylic acid (**3a**) in reasonable yield, and work-up of the mother liquors from this reaction produced a small amount of the known lactone-acid **2a** (5). If the acid **3a** was stirred in concentrated sulfuric acid, the ketolactone **5** was also formed in good yield.

Since the best yields of **5** were obtained if the acid solutions were let stand overnight before quenching, the indanone-carboxylic acid **4a** is presumed to be the intermediate formed as the major product of cyclization of **1** in sulfuric acid. Such β,γ-unsaturated acids readily form

Scheme I




lactones in strong acid (8). The minor product **3a** would be isomerized to a mixture of **3a** and **4a**, as has been shown to occur in acidic solution (4) and thus the ultimate result is the formation of **5** in high yield. We have been unable to isolate any **4a** in these experiments.

Compound **5** has intrinsic interest as an indanone of potential intermediacy in the synthesis of certain benzo analogs of prostaglandin antagonists, as Witiak has proposed (9). We therefore investigated the alkylation of **5**. Reaction of **5** with methyl iodide gave an excellent yield of the expected 2-methyl-*cis*-3-α-hydroxyisopropylindanone-2-carboxylic acid lactone (6). Similar alkylation with ethyl 6-bromohexanoate gave a nearly quantitative yield of the ester **7a** as an oil which could be distilled

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with some decomposition. The crude ester could be hydrolyzed with 48% hydrobromic acid to the corresponding crystalline lactone-acid **7b**. Other acid conditions were less satisfactory, leading to mixtures. Alkaline hydrolysis caused fascile acid cleavage of the ketone to form the dicarboxylic acid **8**. Similar acid cleavage of an analogous structure has previously been reported (10).

The structures of the various lactones **2**, **5**, **6**, **7a**, **7b**, and **8** were supported by mass spectral fragmentation. Some of the compounds gave the appropriate mass ion, but in all cases the major peak, sometimes the 100% peak, was the mass ion minus 86, characteristic of the loss of carbon monoxide and an acetone fragment.

## EXPERIMENTAL

Melting points were obtained on a Mel-temp capillary melting point apparatus and are uncorrected. Infrared spectra were obtained either neat (liquids) or in potassium bromide pellets (solids) on a Perkin-Elmer Model 137 Infracord, calibrated with polystyrene. Proton magnetic resonance spectra were obtained on a Varian T-60 or a Varian Anaspect EM-360 spectrometer, using tetramethylsilane as an internal standard. Mass spectra were determined on a Varian MAT CH-7 spectrometer at 70 eV. Microanalyses were performed by Midwest Microlabs, Indianapolis, Indiana.

### Isopropylidene Phenylisopropylmethylidenemalonate (**1**).

Using the method of Lehnert (11), Meldrum's acid, prepared as described by Davidson and Bernhard (12), was condensed with isobutyrophenone as follows. A dry 3-neck flask was flushed with dry nitrogen, then 100 ml. of THF, freshly distilled from lithium aluminum hydride was added. A solution of 11 ml. (0.10 mole) of titanium tetrachloride (13) in 25 ml. of carbon tetrachloride was placed in the dropping funnel, and the THF in the flask cooled below 0° by a dry ice/methanol bath. Slow addition of the titanium tetrachloride solution was then begun, keeping the solution well below 0°. The dropping funnel was then rinsed with about 10 ml. of dry carbon tetrachloride, and 7.4 g. (0.05 mole) of isobutyrophenone was added to the flask with stirring, then 7.2 g. (0.05 mole) of Meldrum's acid dissolved in 16 ml. of pyridine and 35 ml. of dry THF was added drop-wise, keeping the well-stirred mixture at 0°. When the addition was complete, the mixture was allowed to warm slowly to room temperature with continuous stirring, then quenched by the addition of 50 ml. of ice water. After solids had dissolved, the water layer was separated, washed once with ether, and the combined organic layers washed well with brine and saturated sodium bicarbonate solutions, then dried (magnesium sulfate). Evaporation gave a crude crystalline mass which was recrystallized from aqueous acetonitrile to give 9.96 g. (72%) of white crystals of **1**, m.p. 139-140° [lit. (14) 138.5-139°]; ir: 5.65, 5.80 $\mu$; nmr (deuteriochloroform): $\delta$ 1.10 (d, J = 7 Hz, 6H), 1.81 (s, 6H), 4.00 (m, J = 7 Hz, 1H), 6.80-7.50 (m, 5H).

### 3-Isopropylindenone-2-carboxylic Acid (**3a**).

A solution of 1.0 g. (3.65 mmoles) of **1** in 15 ml. of trifluoroacetic acid was refluxed for 4 hours to give a dark red solution. A bright yellow-orange precipitate formed when the acid solution was poured over 50 g. of ice. It was collected and recrystallized from carbon tetrachloride to give 500 mg. (63%) of orange plates, m.p. 128-130°; ir: 5.76, 5.94 $\mu$; nmr (deuteriochloroform): $\delta$ 1.45 (d, J = 7 Hz, 6H), 4.45 (m, J = 7 Hz, 1H), 7.22-7.75 (m, 5H).

*Anal.* Calcd. for $C_{13}H_{12}O_3$: C, 72.22; H, 5,56. Found: C, 72.46; H, 5.39.

### 4-Phenyl-5,5-dimethyl-2-oxotetrahydrofuran-3-carboxylic Acid (**2a**).

The aqueous mother liquor from the above preparation was extracted with methylene dichloride, and the organic layer then washed several times with saturated sodium bicarbonate solution. The alkaline solutions were then treated with Norite, filtered, acidified and extracted again with methylene dichloride. After drying over magnesium sulfate, evaporation gave 197 mg. of pale yellow crystals. Several washings with carbon tetrachloride left colorless crystals, which after recrystallization from ethyl acetate gave 64 mg. (7.5%) of **2a** melting at 155-157° dec., identical in all respects to that previously reported (5).

### *cis*-3-α-Hydroxyisopropylindanone-2-carboxylic Acid Lactone (**5**).

A.

A solution of 1.9 g. (6.9 mmoles) of **1** in 20 ml. of concentrated sulfuric acid was stirred at room temperature for 2 hours. The red solution was poured over 190 g. of ice, and the solution, which contained some yellow-orange solid, was stirred over night. The off-white precipitate was collected and recrystallized from ethanol to give 1.21 g (81%) of white cubic crystals of **5**, m.p. 144-145°; ir: 5.68, 5.85, 6.23 $\mu$; nmr (hexadeuterioacetone): $\delta$ 1.25 (s, 3H), 1.73 (s, 3H), 4.15 (d, J = 8 Hz, 1H), 4.35 (d, J = 8 Hz, 1H), 7.45-8.05 (m, 4H).

*Anal.* Calcd. for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59; M.W. 216.0787. Found: C, 72.50; H, 5.40; $M^+$ 216.0776 (100% peak, 130).

Evaporation of the ethanol mother liquors gave a solid, which was stirred with bicarbonate solution. On acidification of this solution, 96 mg. (6%) of the lactone acid **2a** was recovered.

A solution of 170 mg. (0.8 mmole) of **3a** was stirred in 5 ml. of concentrated sulfuric acid for 2 hours. At the end of this time the blood red solution was poured over ice and the precipitate collected and recrystallized from ethanol to give 118 mg. (64%) of **5**, melting at 142-144°, and identical by ir spectrum to that prepared above.

### 2-Methyl-*cis*-α-hydroxyisopropylindanone-2-carboxylic Acid Lactone (**6**).

A solution of 660 mg. (3.0 mmoles) of **5** in 25 ml. of acetone was mixed with 420 mg. (3.0 mmoles) of potassium carbonate, 530 mg. (3.7 mmoles) of methyl iodide added, and the mixture refluxed for 24 hours. After standing 48 hours at room temperature, the mixture was filtered and the inorganic salts washed with acetone. On evaporation of the acetone solution a white solid, recrystallized from ethanol as chunky white crystals (610 mg., 87%) melting at 99-101° was obtained; ir: 5.68, 5.84, 6.23 $\mu$; nmr (hexadeuterioacetone): $\delta$ 1.10 (s, 3H), 1.60 (s, 3H), 1.75 (s, 3H), 3.98 (s, 1H), 7.30-7.90 (m, 4H).

*Anal.* Calcd. for $C_{14}H_{14}O_3$: C, 73.04; H, 6.09; M.W. 230. Found: C, 73.16; H, 6.24; $M^+$ 230 (70% peak, 144).

### 2-(5'-Carbethoxypentyl)*cis*-3-α-hydroxyisopropylindanone-2-carboxylic Acid Lactone (**7a**).

A 65% oil dispersion containing 697 mg. (29 mmoles) of sodium hydride was washed under a nitrogen atmosphere with hexane in a 3-neck flask, then a stirring bar was introduced and a solution of 6.26 g. (29 mmoles) of **5** in 80 ml. of DMF was

added. After stirring for a few minutes, evolution of hydrogen became vigorous, and a greyish slurry was formed. When hydrogen evolution ceased, 6.85 g. (31 mmoles) of ethyl 6-bromohexanoate, dissolved in a little DMF, was added in 2 portions. The reaction mixture was stirred at room temperature for 6 hours, then refluxed for 12 additional hours, by which time the solution had become clear. The DMF was then removed by distillation at reduced pressure, leaving a thick brown sludge. The flask was washed out with ether, the ether solution washed twice with water and dried over magnesium sulfate. Evaporation left 10.2 g. (98%) of oily crude **7a**. A small quantity of this oil was distilled in a Hickman still at 180-185°/0.09 mm as a pale yellow viscous oil; ir: 5.65, 5.78, 5.85, 6.22 μ; nmr (carbon tetrachloride): δ 0.90-2.40 (m, 19H), 3.90 (s, 1H), 4.00 (q, 2H), 7.00-7.90 (m, 4H).

*Anal.* Calcd. for $C_{21}H_{26}O_5$: C, 70.37; H, 7,31; M.W. 358. Found: C, 70.42; H, 7.19; $M^+ - C_4H_6O_2$, 272.

2-(5′-Carboxypentyl)*cis*-3-α-hydroxyisopropylindanone-2-carboxylic Acid Lactone (**7b**).

A solution of 3.0 g. (8.4 mmoles) of crude **7a** in 20 ml. of 48% hydrobromic acid was gently refluxed for 3 hours, then filtered through a sintered glass funnel and let stand overnight. The long needles which formed were collected and recrystallized once from water to give 2.49 g. (90%) of **7b**, melting at 139-140°; ir: 3.10, 5.70 (broad), 5.88, 6.23 μ; nmr (DMSO-$d_6$): δ 0.90-2.30 (m, 16H), 4.10 (s, 1H), 7.20-7.88 (m, 4H).

*Anal.* Calcd. for $C_{19}H_{22}O_5$: C, 69.09; H, 6.67; M.W. 330. Found: C, 69.04; H, 6.51; $M^+ - C_4H_6O_2$, 244.

2-(5′-Carboxypentyl)-3-*o*-carboxyphenyl-4-methyl-γ-valerolactone (**8**).

A sample of crude **7a** (1.8 g., 5.0 mmoles) in 25 ml. of 5% sodium hydroxide was refluxed for 30 minutes, cooled, and filtered through a Norite pad. Acidification of the clear solution gave a white precipitate, which was recrystallized from water to give 1.22 g. (70%) of **8**, melting at 146-148°; ir: 3.10-3.30 (broad) 5.70, 5.90 μ; nmr (hexadeuterioacetone): δ 0.90-2.30 (m, 16H), 3.25 (q, 1H), 4.38 (d, J = 11 Hz, 1H), 7.15-7.93 (m, 4H), 8.35 (s, 2H).

*Anal.* Calcd. for $C_{19}H_{24}O_6$: C, 65.52; H, 6.90; M.W. 348. Found: C, 65.30; H, 6.85; $M^+$ 348 (70% peak, 262).

## REFERENCE AND NOTES

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(2) Taken in part from the thesis of M. Frierson, submitted in partial fulfillment of the requirements for the M.S. degree at Indiana University, August, 1977.

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