γ-Lactones from Malonic Acid Derivatives (1)

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The acid catalyzed cyclization of isopropylidene malonate derivatives of ketones to form α -carboxy- γ -lactones has been shown to occur with boron trifluoride etherate or p-toluenesulfonic acid, as well as with concentrated sulfuric or polyphosphoric acids. A similar cyclization of a diethyl ylidenemalonate to a lactone ester, in relatively poor yield, has also been accomplished. Acid catalyzed cyclization of the ylidenemalononitrile derived from pinacolone to form an α -carbamoyl- γ -lactone has been shown to occur with rearrangement. However, that derived from 2,2-dimethylcyclohexanone cyclized to the secondary carbon of the ring without rearrangement. The isopropylidene malonate derivatives of several ring-substituted and bridged ketones have been converted to α -carboxy- γ -lactones without rearrangement.

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Ylidenemalonitriles have been shown to be useful precursors for the synthesis of substituted γ -lactones (3). Recently this synthesis was extended to provide a convenient route to α -methylene- γ -lactones (4). We have since shown that Meldrum's acid (isopropylidene malonate) can substitute for malononitrile in this scheme (5) thus shortening the synthetic scheme by one step, and leading to selected α -methylenelactones in improved yields.

It has been suggested (3b) that the acid catalyzed cyclization of ylidenemalononitriles that leads to γ -lactones proceeds by way of a carbenium ion intermediate. This proposal is based on the observation that lactonization will not take place when the γ -position bears only primary hydrogens, as in 2-cyano-3-methylcinnamonitrile. Additionally, the reaction proceeds more readily when the γ -hydrogen is tertiary as in 1a than when it is secondary as in 1b (Scheme 1) (3a).

We have already demonstrated that Meldrum's acid adducts, such as 3 (Scheme 1) are readily cyclized in concentrated sulfuric acid (5). Presumably this reaction also proceeds via an analogous carbenium ion mechanism, in-

volving initial protonation of one of the carbonyl groups of the cyclic acylal (e.g. 3) followed by bond isomerization to the carbenium ion (e.g. 4), and lactonization by attack of the second carbonyl, leaving a 1,3-dioxolanium species easily hydrolyzed to the lactone-acid (e.g. 5). The reaction conditions used to effect cyclization-stirring in concentrated sulfuric acid-are quite drastic and would limit the use of this synthesis to very simple molecules. However, the scope of permissible substrates has now been extended by our observation that less severe reaction conditions will also induce the desired lactone formation. Boron trifluroide etherate and p-toluenesulfonic acid have been used to effect cyclization of 3, leading to the formation of 5 in 72% yield in the first case, and 33% yield in the second, as compared to 68% for sulfuric acid (5b). It is apparent from this data that a Lewis acid is as effective as a proton acid in bringing about lactonization. This has significant and encouraging implications for the use of this annelation sequence in the synthesis of more complex molecules.

We had anticipated that the cyclic acylals would hydrolyze readily to give α-carboxylactones, but did not know whether or not the diethyl malonate adducts would hydrolyze and/or cyclize under these conditions. Therefore, the diethyl ylidenemalonate 6 was synthesized and treated with concentrated sulfuric acid. The lactone ester 7 was obtained cleanly, but in relatively low yield, compared to the yields of 2-substituted lactones by acid treatment of malonate 3 or malononitriles 1a or 1b (3a).

Further evidence for a carbenium-like intermediate is provided by the reactions described here for a derivative of 3,3-dimethylbutanone. Since lactonization to a primary γ -carbenium site should not be expected to take place, cyclization of 2-cyano-3,4,4-trimethyl-2-pentenonitrile (8) to a γ -lactone would require the migration of a γ -methyl group to the β -carbon. This would produce a tertiary carbenium ion at the γ -position which should lactonize readily to give a tetra substituted lactone. This was indeed the observed result. Treatment of 8 with polyphosphoric acid gave the tetramethylcarbamyllactone 9. Amide 9 was then hydrolyzed to the carboxylic acid 10 and converted

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to the α -methylenelactone 11 (Scheme 2).

The isomerization of 2-cyano-3,4,4-trimethyl-2-pentenonitrile (8) during cyclization to the lactone-amide 9, and the convenient acid cyclization of Meldrum's acid adducts (e.g. 3-5) suggested the possibility that similar carbenium ion rearrangements might occur in this sequence, and lead to some interesting lactones, not readily available by other means. Unfortunately, we were unable to condense pinacolone with Meldrum's acid, under any condi-However, treatment of the methylnorboranane derivative 12 with sulfuric acid might yield a mixture of products due to a non-classical type of carbenium ion rearrangement. The product expected from such a rearrangement reaction would be the δ -lactone 13. In fact, treatment of 11 with sulfuric acid gave only one product (one peak on gc). The nmr spectrum of the isolated material showed no peaks between 4.5 and 5.0 ppm. This is the region in which a proton on the carbon adjacent to the ether oxygen of a lactone is expected (5b). Further, the infrared absorption of the lactone carbonyl was observed at 1765 cm⁻¹. This is consistent with a γ -lactone (predicted absorption at 1770 $\mbox{cm}^{-1})$ but not with a $\delta\textsubscript{-}$ lactone (predicted absorption at 1735 cm⁻¹) (6). On the basis of this data is is apparent that rearrangement did not take place and the product of the reaction was assigned structure 14.

It may be argued that the rearranged product 13 would not be observed even if the intermediate were a non-classical carbenium ion. If cyclization occurred by attack on the more stable carbenium site of such an intermediate, formation of the unrearranged product 14 would be preferred since it is the result of closure to a tertiary carbenium ion; compound 13 would have to result from attack on a secondary ion.

Derivatives of 2,2-dimethylcyclohexanone (15) should offer possibilities of carbenium ion rearrangements, by analogy with 8. In this case, acid treatment of an ylidene derivative would give a product or products reflecting the relative preference of the molecule for lactonization to a secondary carbon or rearrangement followed by lactonization to a tertiary carbon. Treatment of 15 with Meldrum's acid under the usual conditions (5,7) did not give the expected isopropylidene ester condensation product. However, the malonic acid adduct 16 could be isolated from the bicarbonate washes. Treatment of 16 with sulfuric acid gave a lactone acid product which was identified as 17 from its nmr spectrum. This spectrum showed three separate peaks for single protons at 2.86, 3.50 and 4.72 ppm. The spectrum also showed double peaks at 1.02 and 1.37 ppm for the two methyl groups, because it is a mixture of diasterioisomers. Such a spectrum is not consistent with structure 18. In this case, cyclization of the ylidenemalonate and of the ylidenemalononitrile gave analogous results, for treatment of 19 with polyphosphoric acid gave the amide 20 (Scheme 2). Therefore, no rearrangements were observed in the acid cyclization of 12, 16, or 19.

It is interesting to note the isolation of 16 from the condensation reaction of 15 and Meldrum's acid. This indicated the ease with which hydrolysis of the cyclic acylals may actually involve an initial hydrolysis step followed by cyclication of the acid.

EXPERIMENTAL

Melting points were obtained on a Mel-Temp capillary melting point apparatus and are uncorrected. Boiling points are also uncorrected. Infrared spectra were obtained on a Perkin Elmer model 137 Infracord and were run neat for liquids and as potassium bromide pellets for solids. Nmr spectra were obtained on a Varian Associates' Anaspect EM-360 spectrometer or an HA-100 instrument operating in the frequency sweep mode and using tetramethylsilane as internal reference. Magnesium sulfate was used as drying agent. Microanalysis was done through the courtesy of Midwest MicroLabs, Indianapolis, Indiana. Mass spectra were determined on a Varian MAT CH-7 spectrometer at 70 eV.

7-Methyl-2-oxo-cis-octahydrobenzofuran-3-carboxylic Acid (5).

A. Cyclization of 3 with p-Toluenesulfonic Acid.

Three grams of 3 (5b) and 3.18 g. p-toluenesulfonic acid (1.3 equiv.) in 75 ml. benzene were refluxed gently for 2.75 hours. The reaction was poured into cold water, extracted into ether, dried and concentrated to a yellow liquid. This was taken up in a minimum of hot water, treated with Norite, and cooled overnight in a refrigerator, to give 0.83 g. (33%) of 5, m.p., $101-104^{\circ}$ (5b); ir (potassium bromide): ν max = 1790 (lactone), 1706 cm⁻¹ (acid); nmr (deuteriochloroform): δ 0.9-1.4 (m, 6H), 1.54 (s, 3H), 2.32 (m, 2H), 2.78 (d, 1H, J = 13 Hz), 3.69 (d, 1H, J =

13 Hz), 9.91 ppm (s, 1H).

Anal. Calcd. for C₁₀H₁₄O₄: C, 60.60; H, 7.07. Found: C, 60.38; H, 7.17.

B. Cyclization of 3 with Boron Trifluoride Etherate.

Three grams of 3 and 20 ml. freshly distilled boron trifluoride etherate were stirred for 2 hours at room temperature. The mixture was poured over ice and stirred overnight to break up complexes of the product with boron trifluoride. This was extracted into ether, dried and concentrated to a red-brown oil, which was recrystallized as above to yield 1.81 g. (72%) of 5.

Diethyl 2-Methylcyclohexylidenemalonate (6).

2-Methylcyclohexanone was condensed with diethyl malonate according to the method of Lehnert (7) and described below for the preparation of 12. Distillation of the product gave diethyl malonate (57.8% recovery) and 6 in 38.0% yield, b.p. 104-108°/0.7 mm; ir (thin film): 5.82 (C=O), 6.18 μ (C=C); nmr (deuteriochloroform): δ 1.24 (d, 3H, J = 7 Hz), 1.0-2.0 (m, 6H), 1.32 (t, 6H, J = 7.5 Hz), 2.83 (m, 2H), 3.02 (d, 1H, J = 7 Hz), 4.29 (q, 4H, J = 7.5 Hz); ms: M⁺ 230, (calcd. molecular weight for C₁₄H₂₂O₄, 230).

Ethyl 7-Methyl-2-oxo-cis-octahydrobenzofuran-3-carboxylate (7).

Ylidenemalonate **6** (4.1 g., 16.15 mmoles) was stirred with 41 ml. concentrated sulfuric acid for 2 hours at room temperature. The mixture was poured over ice, extracted into ether, dried and concentrated to give a quantitative yield of a brown liquid which solidified on standing. This was taken up in ethanol and treated with decolorizing charcoal. The solution was concentrated to about 15 ml., cooled in a dry ice alcohol bath and the precipitate was filtered and washed with cold ethanol. Recrystallization from hexane gave colorless prisms of **7** (1.27 g., 35%), m.p., 71-73°; ir (potassium bromide): 5.64 (C=O, lactone), 5.82 μ (C=O, ester); nmr (deuteriochloroform): δ 0.9-1.5 (m, 6H), 1.33 (t, 3H, J = 7 Hz), 1.51 (s, 3H), 2.24 (m, 2H), 2.78 (d of t, 1H, J₃,₃ = 13 Hz, J₃a,₄ = 4 Hz), 3.63 (d, 1H, J₃a,₃ = 13 Hz), 4.27 (q, 2H, J = 7 Hz). Anal. Calcd. for C₁₂H₁₈O₄: C, 63.70; H, 8.02. Found: C, 63.43; H, 8.00.

2-Cyano-3,4,4-trimethyl-2-pentenonitrile (8).

Pinacolone (10 g., 0.10 mole), malononitrile (7.93 g., 0.12 mole), ammonium acetate (3.0 g.) and glacial acetic acid (3 ml.) were refluxed in benzene with removal of water (8). After 18 hours the mixture was washed with water and distilled to give 8 in 71.4% yield, b.p. 129-131°/16 mm (Lit. b.p. 137-138°/120 torr (9)).

4,4,5,5-Tetramethyl-2-oxotetrahydrofuran-3-carboxamide (9).

Ylidenemalononitrile **8** (5.4 g., 40 mmoles) was stirred with about 55 g. polyphosphoric acid at 100° according to the procedure of Campaigne and Ellis (3a). After 40 hours it was quenched with 350 ml. water, saturated with sodium chloride and extracted continuously with ether for 5 days. Concentration of the ether layer gave a 91% yield of **9** as a yellow oil which solidified on standing. Recrystallization from water gave 1.96 g. of the carboxamidolactone **9**, m.p. $125-127^{\circ}$; ir (potassium bromide): ν max = 3400 and 3150 (NH), 1750 (C=O, lactone), 1565 (C=O, amide) cm⁻¹; nmr (deuteriochloroform): δ 1.07 (s, 3H), 1.33 (s, 3H), 1.34 (s, 6H), 3.37 (s, 1H).

Anal. Calcd. for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.22; H, 7.93; N, 7.37.

4,4,5,5-Tetramethyl-2-oxotetrahydrofuran-3-carboxylic Acid (10).

The α -carbamyllactone 9 (7.54 g., 40.8 mmoles) was stirred

at room temperature with 120 ml. of 10% sodium hydroxide until the evolution of ammonia had ceased (5 days). The mixture was cooled to 0° , acidified with concentrated hydrochloric acid and the precipitate was filtered. Additional product was obtained from an ether extract of the sodium chloride saturated filtrate. Recrystallization of the combined solid products from ethyl acetate gave 4.42 g. (58.3%) of α -carboxylactone 10 as colorless prisms, m.p. 132-135° dec.; ir (potassium bromide): ν max (potassium bromide): ν max (potassium bromide): ν max (1780-1680 (broad, C=0) cm⁻¹; nmr(deuteriochloroform): δ 1.10 (s, 3H), 1.24 (s, 3H), 1.36 (s, 6H), 3.51 (s, 1H), 11.15 (s, 1H).

Anal. Calcd. for C₉H₁₄O₄: C, 58.05; H, 7.58. Found: C, 58.24; H, 7.45.

3,4,4-Trimethyl-2-methylenevalerolactone (11).

Lactone 10 (3.52 g., 18.9 mmoles) was treated with formaldehyde, diethylamine, acetic acid and sodium acetate according to the procedure of Grieco and Hiroi (10). After refluxing for 15 minutes, the mixture was poured over ice, extracted with ether, and the ether extracts washed with water, 5% bicarbonate, dried and concentrated to give 2.38 g. (81%) of a soft yellow glass. This material was dissolved in hexane, cooled to -78°, and the resulting colorless precipate was collected, m.p. 35-38°. This solid was extremely hydroscopic, but could be restored to its crystalline state by sublimation and maintained in fairly good condition for several weeks by storage over phosphoric oxide in a desicator, m.p. 37-38°; ir (potassium bromide): ν max = 1750 cm⁻¹; nmr (deuteriochloroform): δ 1.16 (s, 6H), 1.32 (s, 6H), 5.47 (s, 1H), 6.17 (s, 1H).

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.13; H, 9.09, m.w. 154.0995. Found: C, 70.01; H, 9.00; M⁺ 154.1002.

Isopropylidene 3-Methylnorborn-2-ylidenemalonate (12).

A solution of titanium tetrachloride (22 ml., 0.20 mole) in 50 ml. carbon tetrachloride was added dropwise under nitrogen to 300 ml. dry tetrahydrofuran stirring in a dry ice/alcohol bath. This gave a bright yellow precipitate after an exothermic reaction. The dropping rate was adjusted so the internal temperature remained below 0° throughout the addition; then the dry ice bath was replaced by an ice/salt water bath. A solution of 3-methyl-2-norbornanone (Aldrich Chemical Co.) (12.4 g., 0.10 mole) and Meldrum's acid (14.4 g., 0.10 mole) in 50 ml. tetrahydrofuran was added to the titanium tetrachloride/tetrahydrofuran mixture. Pyridine (32 ml., 0.40 mole) in 70 ml. tetrahydrofuran was added dropwise over 1 hour. The reaction was stirred overnight, then quenched with 100 ml. water and 100 ml. ether. The layers were separated, the aqueous layer extracted once with ether and the combined organic fractions washed well with 5% sodium bicarbonate and brine and dried (magnesium sulfate). Concentration gave a crude solid which was recrystallized from ethanol to give 14 g. (56%) of 12 m.p. $122-123^{\circ}$; ir (potassium bromide): ν max = 1740 and 1725 (C=O), 1608 cm⁻¹ (C=C); nmr (deuteriochloroform): δ 1.0-2.3 (6H), 1.23 (d, 3H, J = 7 Hz), 1.74 (s, 6H), 2.46 (broad, 1H), 3.33 (t, 1H, J = 6 Hz), 4.58 ppm (broad, 1H).

Anal. Calcd. for C₁₄H₁₈O₄: C, 67.18; H, 7.25. Found: C, 67.35; H, 7.18.

cis-3-Methyl-3-hydroxy-2-norbornylmalonic Acid Lactone (14).

Ylidenemalonate 12(12.5 g., 0.05 mole) was stirred for 2 hours at room temperature with ten times its weight of concentrated sulfuric acid. The reaction was poured over ice, stirred for 10 minutes then saturated with sodium chloride, extracted into ether, dried and concentrated. This crude material was recrystallized twice from ethyl acetate to yield 6.8 g. (65%) of 14 as colorless crystals, m.p. $137\cdot139^{\circ}$ dec.; ir (potassium bromide): ν max = 1765 (lactone), 1730 cm⁻¹ (acid); nmr (deuteriochloroform): δ

1.13-1.90 with superiomposed singlets at 1.53 (9H), 2.03-2.77 (m, 3H), 3.26 (d, 1H, J = 3 Hz), 10.79 ppm (s, 1H).

Anal. Calcd. for C₁₁H₁₄O₄: C, 62.85; H, 6.71. Found: C, 62.92; H, 6.64.

2,2-Dimethylcyclohexanone (15).

Compound 15 was prepared in 39.2% yield from 2-methylcyclohexanone according to the procedure of Boatman, Harris and Hauser (11). Sodium methoxide was prepared by dissolving sodium metal in an excess of anhydrous methanol, removing the excess alcohol under reduced pressure, and heating the solid at 100° for 2.5 hours under vacuum. To a cooled solution of this sodium methoxide (27 g., 0.5 mole) in anhydrous ether was added a solution of 2-methylcyclohexanone (61.5 g., 0.55 mole) and ethyl formate (40.7 g., 0.55 mole). After 15 minutes the ice bath was removed and the reaction was stirred at room temperature overnight. The resulting slurry was filtered and washed with ether under a nitrogen cone to protect from atmospheric moisture. The solid sodio-2-formyl-6-methylcyclohexanone was dried, powdered and dried again in a vacuum oven at 70°, giving 63.96 g. (79%) of the salt.

Ammonia (about 700 ml.) was distilled into a dry I liter flask under nitrogen and equipped with an ALL GLASS mechanical stirrer. A few flakes of potassium metal were added until the blue color persisted. A small amount of ferric nitrate catalyst was added, and then 7.0 g. (0.18 g. atom) of potassium metal were added and stirring continued until the blue color was discharged. Sodio-2-formyl-6-methylcyclohexanone (24.9 g., 0.154 mole) was added through a powder funnel and the reaction was stirred for $90\,$ minutes. Methyl iodide (29.8 g., 0.21 mole) in $50\,$ ml. dry ether was added dropwise over 25 minutes. After 2 hours the dry ice condenser was replaced by a water condenser and the flask was warmed to drive off the ammonia while 400 ml. ether added. After the ether had refluxed for 5 minutes, ice and water were added to bring the total volume to about 800 ml. The layers were separated and the ether extracted twice with 100 ml. cold water. The combined aqueous protions were warmed briefly to drive off the remaining ether and then cautiously treated with 6.4 g. sodium hydroxide. This was refluxed for 11 hours, cooled and extracted three times with 200 ml. ether. The combined ether portions were washed with 1N hydrochloric acid and brine and dried (magnesium sulfate). Distillation gave 9.65 g. (49.7%) of 15 collected between 110° and 140° (12); nmr (deuteriochloroform): δ 1.11 (s, 6H), 1.73 (m, 6H), 2.38 (m, 2H); ms: molecular weight calcd. for C₈H₁₄O: 126.1045. Found: M⁺ 126.1042.

2,2-Dimethylcyclohexylidenemalonic Acid (16).

According to the procedure of Lehnert (7), titanium tetrachloride (4.5 ml., 40 mmoles) in 6 ml. carbon tetrachloride was added to 80 ml. dry THF in a dry ice/alcohol bath. A solution of Meldrum's acid (2.88 g., 20 mmoles) and 15 (2.52 g., 20 mmoles) in THF was added. The dry ice/alcohol bath was replaced by a salt/ice water bath and 6.3 ml. (80 mmoles) pyridine in 20 ml. THF were added dropwise over 0.5 hour. The reaction was stirred overnight at room temperature, quenched with 40 ml. water and extracted into ether. The organic portions were washed well with 5% sodium bicarbonate, and the bicarbonate washes acidified, extracted into ether, dried and concentrated to an oil which was triturated with benzene, filtered and washed to give 1.0 g. (23.6%) of 16 as colorless prisms, m.p. 149° dec.; ir (potassium bromide): 5.95 μ (broad, C=O); nmr (deuteriochloroform): δ 0.98 (s, 6H), 1.54 (m, 6H), 2.03 (m, 2H), 11.79 (2H).

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.26; H, 7.60. Found: C, 62.06; H, 7.50.

4,4-Dimethyl-2-oxo-cis-octahydrobenzofuran-3-carboxylic Acid (17).

Three hundred milligrams (1.41 mmoles) of **16** and 3 ml. concentrated sulfuric acid were stirred for 2 hours at room temperature. The mixture was then poured over ice, extracted into ether, dried and concentrated. Recrystallization from benzene/hexane gave 195 mg. (65%) of **17**, m.p. 132-134° dec.; ir (potassium bromide): 5.68 (C=0, lactone), 5.88 μ (C=0, acid); nmr (deuteriochloroform): δ 0.8-2.2 with superimposed doublets at 1.02 and 1.37 (12H), 2.86 (d of d, 1H, J_{3a,3} = 7 Hz, J_{3a,7} = 12 Hz), 3.50 (d, 1H, J = 7 Hz), 4.72 (1H, J = 12 Hz), 8.03 (s, 1H).

Anal. Calcd. for C₁₁H₁₆O₄: C, 62.25; H, 7.60. Found: C, 62.46; H. 7.42.

2,2-Dimethylcyclohexylidenemalononitrile (19).

Ketone **15** (1.89 g., 15 mmoles) and excess malononitrile were refluxed with removal of water in benzene with a few milligrams of ammonium acetate and 15 drops of acetic acid. After 15 hours the mixture was washed with water, dried and concentrated. Several recrystallizations from hexane gave colorless needles of **19** (1.98 g., 76%), m.p. $58-60^{\circ}$; ir (potassium bromide): 4.50 (C=N), 6.37 μ (C=C); nmr (deuteriochloroform): δ 1.41 (s, 6H), 1.66 (m, 6H), 2.73 (m, 2H).

Anal. Calcd. for $C_{11}H_{14}N_2$: C, 75.82; H, 8.09; N, 16.08. Found: C, 75.69; H, 8.06; N, 16.28.

4,4-Dimethyl-2-oxo-cis-octahydrobenzofuran-3-carboxamide (20).

A mixture of **19** (0.62 g., 3.56 mmoles) and 6 g. polyphosphoric acid were stirred at 95-100° for 9 hours. The reaction was quenched with ice and water, saturated with sodium chloride, extracted into ether, dried and concentrated to 90 mg. of colorless solid. The aqueous portion was extracted continuously with ether for 15 hours and gave 600 mg. oil (combined crude yield: 95%) which solidified on standing. Trituration with benzene gave a colorless powder; recrystallization from ethyl acetate gave 490 mg. (65%) of needles of **20**, m.p. 162-163°; ir (potassium bromide): 2.88 (N-H), 5.70 (C=O, lactone), 5.82 μ (C=O, amide); nmr (deuteriochloroform): δ 0.94 (s, 3H), 1.01 (s, 3H), 1.2-2.2 (m, 5H), 2.93 (m, 1H), 3.57 (d, 1H, J = 11 Hz), 4.67 (m, 1H).

Anal. Calcd. for $C_{11}H_{17}NO_3$: C, 62.56; H, 8.06; N, 6.63; m.w. 211.1209. Found: C, 62.36; H, 7.99; N, 6.49; M^+ 211.1212.

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