with diethylamine in benzene or heating the ester alone with diethylamine in a bomb at 100° both resulted in complete recovery of ester **28a**.
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(32) (a) E. L. Eliel, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 358; (b) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 230.
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(38) It is unlikely that the product is the conjugated amide **32b** which theoretically can arise from a rearrangement of **6b**, since **5** cannot be rearranged to its conjugated ester isomer[39] and 6-methyl-$\Delta^{8,9}$-ergoline-8-carboxylic acid rearranges quite easily to lysergic acid.[40] Furthermore, the uv spectrum of **32b** would be expected to show only low-intensity (ϵ less than 300) *o*-xylene-like absorption in the 255-nm region.
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(40) H. Kobel, E. Schreier, and J. Rutschmann, *Helv. Chim. Acta*, **47**, 1052 (1964).
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Carboxylation of γ-Butyrolactones with Methyl Methoxymagnesium Carbonate. A New Synthesis of *dl*-Protolichesterinic Acid

Jack Martin, Paul C. Watts, and Francis Johnson*

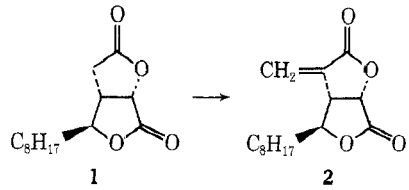
Dow Chemical U. S. A., Eastern Research Laboratory, Wayland, Massachusetts 01778

Received October 30, 1973

The carboxylation of γ-lactones at the α position is, in most cases, easily accomplished by means of Stiles' reagent (methyl methoxymagnesium carbonate). This combined with a simplified decarboxylative methylenation procedure, namely treatment of the α-carboxylactones with a mixture of formaldehyde and diethylamine, usually in a buffered acidic medium, affords a relatively simple method of synthesizing α-methylenelactones. These methods have been used in a new synthesis of *dl*-protolichesterinic acid. Free-radical addition of tetradecanal to dimethyl maleate led to methyl 3-methoxycarbonyl-4-oxoheptadecanoate, which was reduced by borohydride and cyclized to a 50:50 mixture of the methyl esters of *cis*- and *trans*-3-carboxy-4-*n*-tridecylbutyrolactones, **20b** (R = CH_3) and **20a** (R = CH_3), respectively. Carbonylation of the acid from the latter isomer afforded 2,3-dicarboxy-4-*n*-tridecylbutyrolactone, which when treated with formaldehyde and diethylamine at room temperature afforded *dl*-protolichesterinic acid. Acylative decarboxylation of tricarballylic acid by tetradecanoic anhydride gives the di-γ-lactone of 3-(1,1-dihydroxytetradecyl)glutaric acid. The action of alkaline borohydride on the latter leads to *trans*-3-carboxymethyl-4-*n*-tridecylbutyrolactone (**24**, R = H). The methyl ester of this acid is also obtained almost exclusively when **20a** (R = H) is subjected to an Arndt-Eistert homologation sequence. The cis acid **20b** (R = H) on homologation gives varying mixtures containing both **24** (R = CH_3) and its cis isomer. The latter results together with other evidence allow the tentative assignment of stereochemistry to the carboxylactones **20a** and **20b** (R = H), the former being trans and the latter cis.

In a pair of communications[1,2] in 1969 we reported briefly a new method for the preparation of α-methylenebutyrolactones. This paper describes that work in detail and reports its application to a new synthesis of protolichesterinic acid.

The origins of our research lay in our need to methylenate the bislactone **1** in order to obtain avenaciolide (**2**),

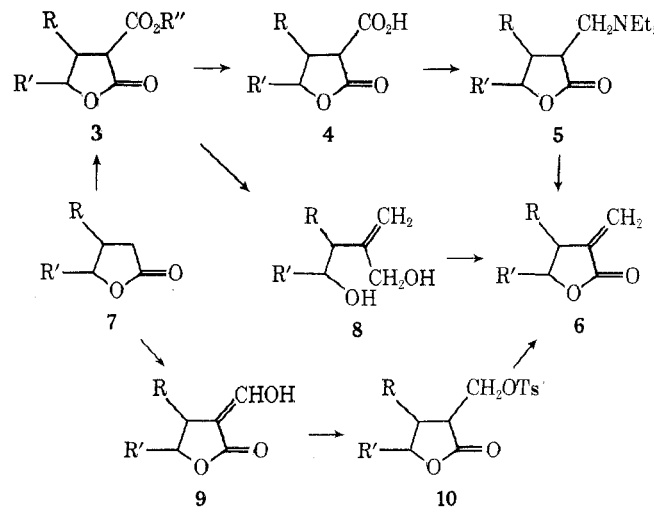


1 **2**

the object of an earlier synthetic program.[2] The methods available to us at that time left much to be desired. The early procedure due to van Tamelen and Bach[3a,b] demanded the construction of a butyrolactone such as **3**, already provided with an alkoxycarbonyl group at the α position. Subsequent steps involved hydrolysis and relactonization of **3** to give **4**, which when subjected to a Mannich reaction led to **5**. Quaterization of **5** followed by heating with base gave the desired **6** (Chart I).

Two quite different methods began with a butyrolactone of structure **7**. In the first, due to Marshall and Cohen,[4] the sodium salt of **3**, derived directly from the alkoxycarbonylation of **7**, was reduced mainly to **8** with lithium aluminum hydride. Manganese dioxide oxidation of

Chart I

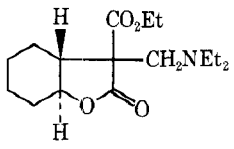


3 **4** **5** **6** **7** **8** **9** **10**

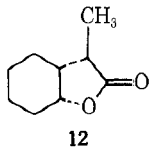
8 gave **6** directly. The second procedure, reported by Minato and Horibe,[5] involved formylation of **7** give **9**, which was reduced and tosylated, affording **10**. Refluxing pyridine converted **10** to **6**.

Subsequent to our initial reports, Behare and Miller[6] reported that α-methylene lactones could be synthesized by first treating lactones such as **3** (R, R′ = $-(CH_2)_4-$; R″ = Et) with formaldehyde and diethylamine to give **11**, followed by heating the methiodide of the latter in dimethylformamide. An entirely different approach has been taken

* Department of Pharmacology, State University of New York at Stony Brook, Stony Brook, N. Y. 11790.



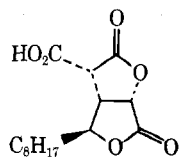
11



12

by Ourisson, *et al.*,[7] who α-brominated the anion of **12** with 1,2-dibromoethane and dehydrobrominated the product with diazabicyclononene. The trans isomer of **12**, however, gave only the product with endocyclic double bond.

On our part, an attempt to alkoxycarbonylate **1** led to extensive decomposition and we were discouraged from trying a formylation under what are similar conditions. We, therefore, looked for an alternate method. Realizing that the acidity of the α position in a γ-butyrolactone lies somewhat closer to that of a methylene group adjacent to a ketone rather than of a methylene adjacent to a simple ester group, we decided to subject **1** to the very mild Stiles' reagent,[8] methyl methoxymagnesium carbonate (MMC). This proved to be eminently successful and provided the desired acid **13** in excellent yield. Subsequent

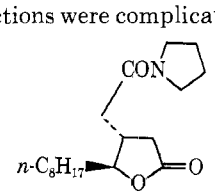


13

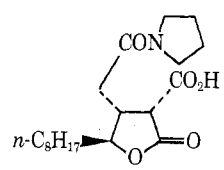
efforts to apply the conditions of van Tamelen and Bach[2] to **13** in an attempt to obtain **2** were unsuccessful, but by treating **13** with a mixture of diethylamine, formalin, sodium acetate, and acetic acid, avenaciolide (**2**) was obtained directly in good yield.

Thus a method became available which it appeared would permit us to go in two steps from **7** to **6** *via* the acid **4**.

Application of the Stiles' carboxylation method to a series of lactones **7** (R = H; R′ = Ph, n-C_4H_9, or n-C_6H_{13}) was then tried and in all cases proceeded to give **4** in yields of better than 95%. A somewhat reduced yield of **15** was obtained in the carboxylation[2,9] of **14** but none of the reactions were complicated.



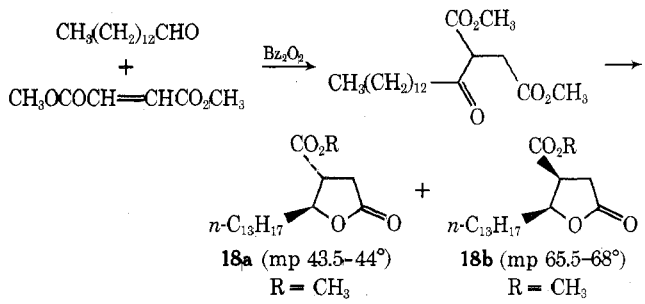
14



15

Decarboxylative methylenation of the 2-carboxylactones **4** (R = H; R′ = Ph) and **15** was easily accomplished by treatment with a mixture of formalin, diethylamine, sodium acetate, and acetic acid followed by a brief period of heating. In the case of the lactones **4** (R = H; R′ = n-C_4H_9 or n-C_6H_{13}) better results were obtained by treatment first with a formalin and diethylamine mixture and subsequently, after isolation of the crude product, with a solution of sodium acetate in acetic acid. Dalton and Elmes[10] in a recent variation of this methylenation procedure have claimed that the acetic acid and sodium acetate are not necessary. However, in our experience this seems to depend on the carboxylactone in question. In the synthesis of avenaciolide (**1**) we observed that, in the absence of sodium acetate–acetic acid, virtually the only product that we could obtain was the product of addition of diethylamine to the double bond. On the other hand, in the synthesis of protolichesterinic acid (**16**) described below, the final step was certainly best accomplished by

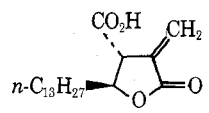
Chart II



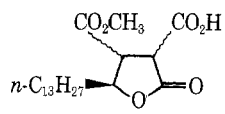
18a (mp 43.5–44°) R = CH_3 **18b** (mp 65.5–68°) R = CH_3

treatment with formalin and diethylamine alone at room temperature. In this case any heating of the mixture on a water bath, as recommended by the Australian workers, simply destroyed the desired product. It seems likely that except in strictly analogous cases the methylenation should be followed by nmr to achieve the best results.

We now attempted to use the α-methylenelactone synthesis in a new preparation of protolichesterinic acid (**16**).



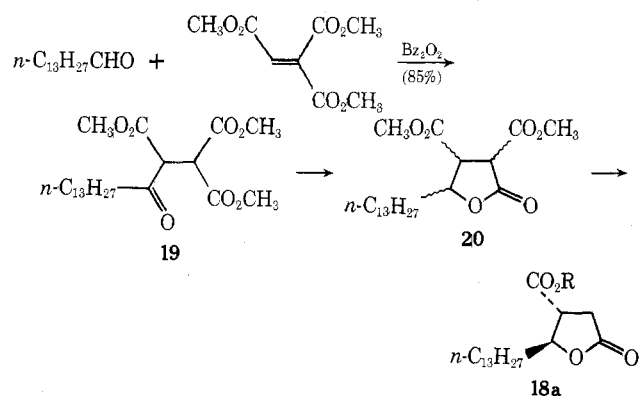
16



17

We initially thought that the carboxylation procedure might be mild enough to produce **17** from **18** (R = CH_3), although van Tamelen and Bach[3b] had obtained only ring-cleavage products when they had attempted carboethoxylation or formylation of **18**. The required lactones **18a** (R = CH_3) and **18b** (R = CH_3) were synthesized using a new procedure shown in Chart II. Free-radical addition[11] of n-tetradecanal to dimethyl maleate afforded methyl 3-methoxycarbonyl-4-oxoheptadecanoate in good yield. Reduction of the latter by means of potassium borohydride in aqueous methanol followed by treatment of the crude product with a trace of p-toluenesulfonic acid in boiling benzene led to a good yield of a mixture of **18a** (R = CH_3) and **18b** (R = CH_3). Direct crystallization cleanly allowed the isolation of one of the isomers, mp 65.5–68°, in moderate yield whose stereochemistry proved to be cis but which we did not know at the time. Extensive crystallization of the material in the mother liquor permitted the isolation of a crude sample of the second component, which required an extensive chromatography to give the pure material, mp 43.5–44°.

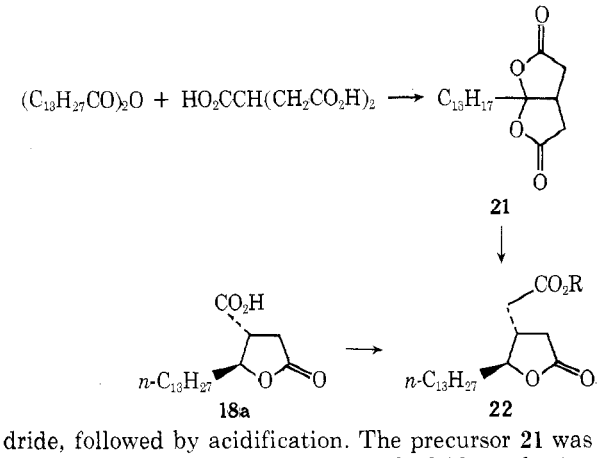
Attempts to isomerize either of these materials by means of a variety of basic catalysts either left them untouched or produced complex mixtures. Fortunately we were able to effect a reasonable stereochemical proof in an unexpected way. In attempting to approach the synthesis of **17** by an alternate method we carried out a Raney nickel catalyzed hydrogenation of **19**, the product of the free-radical addition of tetradecanal to trimethyl ethenetricar-

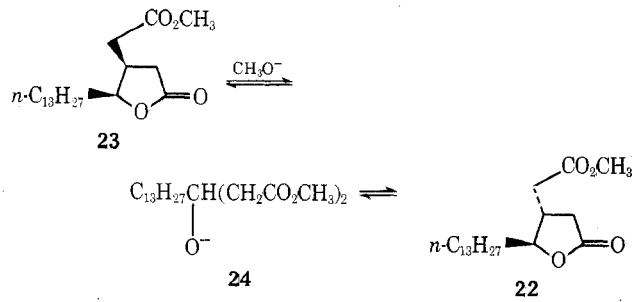


19 20 18a

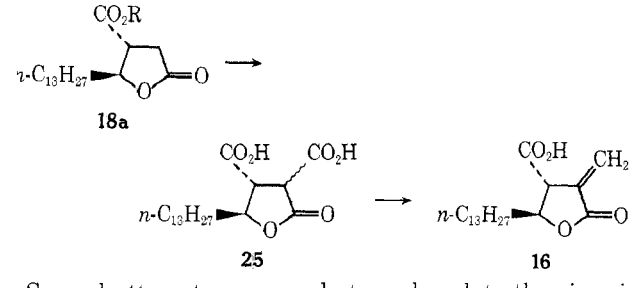
boxylate. This gave a rather complex mixture, obviously containing some **20** in view of its spectral characteristics, but which could not be purified easily. Direct hot acid catalyzed hydrolysis of the mixture led only to a 50:50 mixture of the acids **18a** (R = H) and **18b** (R = H). However, it was found that if the crude mixture containing **20** were allowed to equilibrate in the presence of sodium methoxide in methanol, prior to hydrolysis and decarboxylation, the acid **18a** (R = H), mp 100–102°, could be isolated pure after one crystallization of the crude product, although in poor yield. Methylation of this acid with diazomethane led to **18a** (R = CH_3), proving its correspondence with the lower melting ester. Acid-catalyzed hydrolysis of **18b** (R = CH_3) gave a new acid[12] **18b** (R = H), mp 115–116.5°, reconverted easily by diazomethane exclusively to the starting ester **18b** (R = CH_3).

The successful equilibration of **20** but not of **18a** (R = CH_3) or **18b** is in keeping with van Tamelen's observation[3a] that in this series a substituent at the 2 position of the lactone seems to inhibit base-catalyzed fragmentation of the ring. It also strongly suggested to us that the lower melting acid and ester had trans geometry while the higher melting isomeric compounds belonged to the cis series. Tentative evidence for the correctness of this viewpoint was obtained by carrying out a correlation of the suspected trans acid with its next higher homolog **22** (R = H). The latter was obtained as virtually the only product when **21** was treated with highly alkaline sodium borohydride, followed by acidification. The precursor **21** was easily synthesized from tridecanoic anhydride and tricarballylic acid according to previously described work[2,9,13], and the stereochemistry of **22** is assigned on the basis of work with lower homologs.[9] In any case Arndt–Eistert reaction in methanol of the diazo ketone derived from the chloride of the lower melting acid led to the methyl ester **22** (R = CH_3). Surprisingly, the same series of reactions when applied to the higher melting acid proved capricious and also produced varying quantities of **22** (R = CH_3) together with up to 50% of a compound with a higher R_f. Although we did not completely characterize the second component, its assignment as the cis isomer (**23**) seems justified, since its molecular weight and fragmentation pattern as determined mass spectrometrically (from a sample obtained pure by glc) were those expected. The exact intermediate in this second homologation sequence that suffers isomerization more or less is open to speculation, but we believe that the change occurs during the final step, when the diazo ketone is heated with the basic silver benzoate–triethylamine complex in methanol. Here on account of Pitzer strain a base such as CH_3O^- which must be present in small concentration) might easily produce intermediate **24**, which could then be expected on stereochemical grounds to favor **22** in a recyclization process.





Returning now to protolichesterinic acid, we observed, in keeping with the results of van Tamelen,[3a] that the ester **18a** (R = CH_3) simply underwent fragmentation when treated with Stiles' reagent. However, it was with some gratification that we found, true to our expectations,[14] that the corresponding carboxylic acid **18a** (R = H) underwent carboxylation smoothly (if somewhat slowly) and afforded a very soluble dicarboxylic acid **25** in good yield. This seems to be a single isomer, since methylation with diazomethane gave a beautifully crystalline diester in high yield. The dicarboxylic acid now when treated at room temperature with a mixture of formalin and diethylamine rapidly evolved carbon dioxide and afforded *dl*-protolichesterinic acid (**16**) as a highly crystalline white solid, mp 92–93.5°, identical in all respects with an authentic sample and with which, when admixed, it showed no depression in melting point.



Several attempts were made to carboxylate the cis acid **18b** (R = H) with the intention of synthesizing the cis isomer of **16**, but no discreet product could be isolated. Spectroscopic evidence from the reaction mixture, however, suggested that the lactonic ring was being opened, rather than carboxylation taking place, a result that would be in accord with the strain that exists in the molecule.

Finally it should be noted that recently Drieding, *et al.*,[15] have synthesized *dl*-protolichesterinic acid in 12% yield by a Reformatsky reaction between 2-bromomethylmaleic anhydride and tetradecanal, thus introducing yet another method for the synthesis of α-methylenebutyrolactones. Similar work has also been reported by Oehler, *et al.*[16]

Experimental Section

Melting points are not corrected. Nmr spectra were recorded in deuteriochloroform on a Varian A56-60 and are not calibrated. Infrared spectra were recorded on a Perkin-Elmer 337 spectrometer. Silica gel used for tlc was Brinkmann PF-254.

2-Carboxy-4-phenylbutyrolactone. 4-Phenylbutyrolactone (5.0 g) was added to MMC (45 ml) and the mixture was heated at 140° for 6 hr while a stream of dry nitrogen was passed through the flask. After cooling, the contents of the flask were *carefully* added to cold 6 *N* HCl (100 ml) and ether (100 ml). The mixture was stirred and after the vigorous gas evolution had subsided the ether layer was separated and the aqueous layer was again extracted with ether (100 ml). The combined ether extracts then were washed four times with water, dried over anhydrous magnesium sulfate, and evaporated to small bulk at <40°. The residual yellow oil (5.49 g) by tlc showed virtually no starting material to be present. The nmr spectrum indicated that two isomers were present, one in dominant amount. The latter could be obtained

pure by crystallization of the product from ether–petroleum ether (bp 30–60°) as a white solid (2.2 g): mp 103–104° (lit.[3a,10] mp 149.3–150°); nmr 2.0–3.2 (CH_2, m), 3.7–4.2 (COCHCO, m), 5.4–5.9 (PHCHO, m), 7.4 (Ph, s), and 10.2 ppm (CO_2H, s); ir (film) 1770 (lactonic CO) and 1735 cm^{-1} (CO_2H).

Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 64.11; H, 4.91.

2-Carboxy-4-(1′-hexyl)butyrolactone. γ-Decanoic lactone (2.0 g) was carboxylated using MMC solution (20 ml) according to the above procedure. The product was worked up in the usual way, the crude material (2.77 g) was dissolved in ether, and the acidic component was extracted with sodium bicarbonate solution. Acidification of the extract and reisolation of the product using ether led to a pale yellow oil (2.47 g, 98%) whose tlc (1:1 benzene–ether) showed the absence of a spot for starting material but the presence of two merging spots for the two expected isomers of the product. Crystallization of a sample of this material from ether–petroleum ether (bp 30–60°) afforded one isomer pure (1.1 g): mp 60.5–61.5°; nmr 4.50 (m, 1, >CHO), 3.80 (m, 1, COCHCO), and 11.00 ppm (s, 1, CO_2H); ir (film) 1770, 1735 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66, H, 8.47. Found: C, 61.56; H, 8.73.

2-Carboxy-4-(1′-butyl)butyrolactone. γ-Octanoic lactone (2.0 g) was treated with MMC (20 ml) as described above for γ-decanoic lactone and the product was isolated in the same way. This afforded 2.56 g (98%) of a pale yellow, viscous oil which failed to crystallize. It displayed almost identical behavior with that of 2-carboxy-6-hexylbutyrolactone, again appearing to be a mixture of the two expected isomers; absorption bands in the nmr spectrum were also extremely similar to the higher homolog, ir (film) 3700–2500, 1775, and 1735 cm^{-1}.

Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.95; H, 7.61.

2-Methylene-4-phenylbutyrolactone. 2-Carboxy-4-phenylbutyrolactone (1.50 g) was added with stirring to 7.28 ml of a stock solution prepared from glacial acetic acid (40 ml), formalin (29.2 ml), diethylamine (10 ml), and sodium acetate (1.1 g). The mixture, after 5 min at room temperature, was heated on the steam bath for 10 min, then diluted with water and extracted with ether. The ether extract was washed with saturated sodium bicarbonate solution, 1.0 *N* HCl solution, and then water and dried over anhydrous magnesium sulfate. The ether was removed at reduced pressure and yielded a clear, colorless, mobile oil (0.76 g) which rapidly crystallized. One recrystallization from ether afforded the pure material (0.71 g), mp 52.5–53.5° (lit.[6,16] mp 46 and 49–54°), ir (film) 1760, 1660, and 935 cm^{-1}.

Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.84; H, 5.84.

2-Methylene-4-(1′-hexyl)butyrolactone. 2-Carboxy-4-(1′-hexyl)butyrolactone (0.469 g) was treated with a mixture of formalin (0.75 ml) and diethylamine (0.25 ml), and after mixing the solution was allowed to stand at room temperature until no more CO_2 was evolved (45 min). The mixture was then poured into saturated sodium chloride solution and ether. The ether layer was separated, washed with water, and then evaporated to small bulk at <40°. The residual oil (0.452 g) was then warmed for 20 min on the steam bath with a solution of sodium acetate (0.1 g) in acetic acid (1.0 ml). The solution was treated subsequently with a mixture of ether and sodium bicarbonate solution and the ether layer was separated and washed consecutively with 1 *N* hydrochloric acid, water, and sodium bicarbonate solution, then dried over magnesium sulfate. Removal of the solvent at room temperature afforded 0.27 g (68%) of the desired product, whose tlc (9:1 benzene–ether) showed essentially only one component to be present, nmr 5.5 (C=CH_2, t, $J \cong 3$ Hz), 6.3 (C=CH_2, t, $J \cong 3$ Hz), ir 1760 (lactone), 1660, and 935 cm^{-1} (C=CH_2). The mass spectrum of the material showed a small molecular ion peak at *m/e* 182 (calcd for $C_{11}H_{18}O_2$, 182.25). At low voltages, in addition to this peak, fragments were present at *m/e* 140 and 97 corresponding to M − C_3H_6 and M − C_6H_{13}. The material became resinous on long standing.

2-Methylene-4-(1′-butyl)butyrolactone. When 2-carboxy-4-(1-butyl)butyrolactone (0.53 g) was subjected to exactly the same conditions as described above for the 4-*n*-hexyl homolog, a 62.4% yield of 2-methylene-4-(1′-butyl)butyrolactone was obtained. This showed only one spot on tlc (4:1 benzene–ether). The mass spectrum showed a molecular ion peak at *m/e* 154 (calcd for $C_9H_{14}O_2$, 154.20) and at low voltages this was the only peak evident in the spectrum apart from a peak at *m/e* 97 (M − C_4H_9). Its infrared spectrum (film) showed significant bands at 1760, 1660, and 935 cm^{-1} and was all but identical with that of the *n*-hexyl analog described above. The material polymerized on standing.

2-Methylene-3-[(1′-pyrrolydinylcarbonyl)methyl]-4-(1-octyl)butyrolactone [2-Hydroxy-1′-(1-pyrrolidinylcarbonyl)methyl]-decylmalonic acid γ-lactone[2,9] (**15**, 0.77 g) was treated with the stock solution (2 ml) as described above for the preparation of 2-methylene-4-phenylbutyrolactone. After isolation of the product in the usual way there was obtained 0.29 g (48%) of a viscous, colorless oil which showed only one spot on tlc and whose nmr spectrum showed the presence of two coupled doublets at 5.60 and 6.25 ppm (J = 3.0 Hz) typical for a methylene group at the α position of a butyrolactone. The mass spectrum showed a parent ion peak at *m/e* 321 (mol wt 321.25) and at low voltages this was the only peak of significance above *m/e* 278, the latter corresponding to M − C_3H_7; ir (film) 1760, 1640, and 955 cm^{-1}.

Anal. Calcd for $C_{19}H_{31}NO_3$: C, 70.99; H, 9.72; N, 4.36. Found: C, 71.11; H, 9.84; N, 4.21.

Methyl 3-Methoxycarbonyl-4-oxoheptadecanoate. Redistilled tetradecylaldehyde (40.0 g) and dimethyl maleate (18.0 g) were mixed and heated to about 84° under a nitrogen atmosphere. Benzoyl peroxide (62.5 mg) was added in one portion and stirring and heating were continued. A short time later the temperature rose to ~86°, remained there for 3.5 hr, then fell to 84°. A second addition of benzoyl peroxide (62.5 mg) was then added and again the temperature rose to 86°. Heating was then continued for an additional 16 hr. The mixture was then distilled and the fraction (30.3 g, 68%) that boiled at 175–185° (0.05 mm) was collected using a steam-jacketed condenser. The product, mp 39–43°, crystallized in the receiver. A sample recrystallized for analysis had mp 44–45°; nmr 2.61 (-$CH_2CO_2CH_3$, d, J = 3.5 Hz) coupled to the signal at 4.0 (-$COCHCO_2CH_3$, t, J = 3.5 Hz), and 2.88 ppm (RCH_2CH_2CO–, d of d, J = 3.5 and 1.1 Hz), the latter probably being due to hindered rotation about the C-4 and C-5 methylene groups; ir (Nujol) 1725 and 1745 cm^{-1}. It gave only a faint violet color with ferric chloride solution.

Anal. Calcd for $C_{20}H_{36}O_5$: C, 67.38; H, 10.18. Found: C, 67.67; H, 10.14.

Timethyl 1,1,2-Ethenetricarboxylate. Trimethyl 1,1,2-ethanetricarboxylate (87.3 g, 0.43 mol) and selenium dioxide (34.3 g, 0.435 mol) were added to acetic acid and the mixture was heated at reflux with stirring for 7 hr. The solution was cooled and filtered through Celite to remove selenium, and the acetic acid was removed *in vacuo*. The residue was taken up in ethyl acetate (500 ml) and the solution was washed successively with brine (100 ml) and sodium bicarbonate solution (2 × 50 ml) and then dried over anhydrous magnesium sulfate. Removal of the solvent left an oil which was distilled. The fraction (60 g) which distilled at 88–98° (0.2 mm) was crystallized from ether–hexane to give the pure product (46.0 g, yield 53%), mp 37–39°, nmr 7.0 (vinylic H, s) and ~4 ppm (CO_2CH_3, 3 s).

Anal. Calcd for $C_8H_{10}O_6$: C, 47.53; H, 4.99. Found: C, 47.75; H, 5.12.

Methyl 2,3-Bis(methoxycarbonyl)-4-oxoheptadecanoate. Freshly distilled tetradecanal (46.64 g, 0.22 mol) and trimethyl 1,1,2-ethenetricarboxylate (46.0 g, 0.227 mol) were mixed and heated together to 81°. To the homogeneous melt there was added benzoyl peroxide (50 mg) and an immediate exotherm was observed, the temperature rising to 85°. After 1 hr a second addition of benzoyl peroxide (50 mg) was made and 30 min later a third. Heating was then continued for 17 hr at 80–90°. At this point nmr analysis of a sample indicated complete reaction, and the mixture was diluted with methanol (500 ml). When crystallization appeared complete the white precipitate was removed by filtration, washed with methanol, and air dried: yield 79.1 g (85%); mp 80–82°; nmr 3.67 (CO_2CH_3, 3 s), 4.22 (q, J = 12 Hz), and 2.68 ppm (RCH_2CH_2CO, m).

Anal. Calcd for $C_{22}H_{38}O_7$: C, 63.74; H, 9.24. Found: C, 63.72; H, 9.18.

***cis*- and *trans*-3-Methoxycarbonyl-4-*n*-tridecylbutyrolactone (18a and 18b, R = CH_3).** Methyl 3-methoxycarbonyl-4-oxoheptadecanoate (30.2 g) was dissolved in methanol (100 ml) and the solution was cooled in an ice bath. Potassium borohydride (5.4 g) dissolved in water (50 ml) and methanol (50 ml) was then added dropwise with stirring over 30 min. The mixture was allowed to warm to room temperature, stirred overnight, and then acidified carefully with 1 *N* hydrochloric acid. Isolation of the organic material by ether extraction led to an oil (26.9 g) which was added to benzene containing a trace of *p*-toluenesulfonic acid and then boiled for 12 hr. Again an oil was produced (23.81 g, 86%) which by tlc (10:1 benzene–ether) showed the material to consist principally of two components which ran very close together. Direct

crystallization of the product from methanol yielded the desired cis ester (8.1 g), mp 65.5–68°, corresponding to the compound with the lower R_f. A sample recrystallized for analysis had mp 65–66.5°; ir (neat) 1770 (γ-lactone) and 1730 cm^{-1} (ester); nmr pair of doublets at 2.79 (J = 8.5 Hz) and 2.88 (J = 5.5 Hz) indicative of the α hydrogens of the lactone ring, and multiplets centered at approximately 3.5 and 4.5 ppm representing the β- and γ-hydrogen atoms, respectively, 3.8 ppm (CH_3, s).

Anal. Calcd for $C_{19}H_{34}O_4$: C, 69.90; H, 10.50. Found: C, 69.97; H, 10.52.

Extensive crystallization of the material in the mother liquors using the triangulation method led to a still impure fraction (2.29 g) of the lactonic ester with the higher R_f. Further purification was effected by chromatography over silica gel using benzene containing 1% ether as the eluent. Ninety fractions (35 ml each) were collected and those (63–82) containing only the faster running component (detected by tlc) were combined. This afforded 0.975 g of the trans lactonic ester, which was recrystallized from methanol to give plates: mp 43.5–44°; nmr 2.88 (multiplets corresponding to the three hydrogens adjacent to ester carbonyl) and 4.60 ppm (>CHOCO); ir ($CHCl_3$) 1775 (γ-lactone) and 1735 cm^{-1} (ester).

Anal. Calcd for $C_{19}H_{34}O_4$: C, 69.90; H, 10.50. Found: C, 69.84; H, 10.49.

***cis*-3-Carboxy-4-*n*-tridecylbutyrolactone (18b, R = H).** Methyl *cis*-3-methoxycarbonyl-4-*n*-tridecylbutyrolactone (1.2 g) was dissolved in dioxane (35 ml), and 6 N hydrochloric acid (20 ml) was then added. The mixture was refluxed for 5 hr, cooled, and diluted with ether and water. The organic layer was removed and extracted with sodium bicarbonate solution and the extract was then reacidified with 6 N hydrochloric acid. Extraction with ether in the usual way then led to a crystalline white powder (1.0 g), mp 114–116°. A sample recrystallized for analysis from benzene formed nacreous plates, mp 115–116.5°. Its nmr spectrum was very similar to that of the starting ester except for the presence of the OCH_3 band, while its infrared spectrum showed carbonyl absorption at 1775 and 1720 cm^{-1}.

Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32. Found: C, 69.06; H, 10.32.

***trans*-3-Carboxy-4-*n*-tridecylbutyrolactone (18a, R = H).** Methyl 2,3-bis(methoxycarbonyl)-4-oxoheptadecanoate (**21**, 20 g), ethanol (200 ml), and Raney nickel (W4, 50 g) were placed in a stainless steel high-pressure bomb and hydrogenated at 1300 psi and 150° for 36 hr. When the product was worked up, tlc (10% Et_2O in benzene) showed starting material still to be present and the hydrogenation was repeated using 2 g of catalyst for an additional period of 42 hr. Isolation of the product afforded a thick oil, which was dissolved in methanol (200 ml) containing dissolved sodium (0.2 g). The solution was set aside for 6 days to allow equilibration to occur. The mixture was then diluted with water (50 ml) containing potassium hydroxide (10 g) and stirred for 15 hr at room temperature. The methanol was removed *in vacuo* at <40° and the residual liquid was then diluted to 250 ml with water, cooled in ice, neutralized with 2 N hydrochloric acid, and then heated briefly to effect decarboxylation. Isolation of the product by ethyl acetate (3 × 100 ml) extraction afforded a thick oil (9.5 g) which partially crystallized on standing. Crystallization of the material from methanol then afforded the desired lactonic acid **18a** (R = H) as plates (1.6 g), mp 100–102°. A sample prepared for analysis had mp 101–102.5°.

Since decarboxylation did not seem complete, the remaining material, after removal of the methanol, was dissolved in a mixture of 5 N hydrochloric acid and dioxane (100 ml) and the solution was refluxed again for 3 hr. Acidification of the cooled liquid and isolation of the organic material by ethyl acetate extraction (2 × 50 ml) led to a waxy solid, which afforded additional lactonic acid (1.5 g), mp 99–102°, when crystallized from methanol: total yield 20%; nmr 2.96 (H adjacent to carboxylic carbonyl, m), 4.67 (>CHO, m), and 11.23 ppm (CO_2H, s); ir ($CHCl_3$) 1775 and 1715 cm^{-1}.

Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32. Found: C, 69.14; H, 10.25.

A sample of the acid was esterified using diazomethane and afforded the methyl ester, mp 40–42°, undepressed in melting point when mixed with a sample prepared recording to the previous method. The infrared spectra of the two samples were also identical.

3-(1,1-Dihydroxytetradecyl)glutaric Acid Di-γ-lactone. Tricarballylic acid (2.1 g) was added in three portions over 3 hr to tetradecanoic anhydride containing a trace of calcium chloride, maintained at 185°. After 8 hr no more CO_2 was evolved and the reaction mixture was cooled to room temperature. Hexane (~25 ml) was added and the mixture was stirred at 0° until crystallization was complete. The solid was removed by filtration, washed with hexane, and dissolved in ether. The ether solution was washed quickly with sodium bicarbonate solution, dried ($MgSO_4$), and decolorized with charcoal. Concentration of this solution afforded white crystals (4.5 g) of the desired product, mp 95–97°, ir (Nujol) 1785 and 1810 cm^{-1}.

Anal. Calcd for $C_{19}H_{32}O_4$: C, 70.33; H, 9.94. Found: C, 70.41; H, 9.93.

***trans*-3-Carboxymethyl-4-tridecylbutyrolactone (22, R = H) and Its Methyl Ester (22, R = CH_3).** The bislactone **21** (1.3 g) was dissolved in 1.0 N potassium hydroxide solution (12 ml) by warming on a steam bath. Sodium borohydride (0.38 g) was then added in small portions over 10 min, and heating was continued for 4 hr. The solution was cooled to room temperature, acidified with 6.0 N hydrochloric acid (10 ml), and then extracted with ether. Isolation of the product in the usual way led to 1.26 g of a white solid, mp 65–72°. Recrystallization of this material from methanol afforded the desired product (0.8 g): mp 78–80°; ir ($CHCl_3$) 1710 (CO_2H) and 1770 cm^{-1} (γ-lactone); nmr ~2.55 ($-CH_2CO_2$, 2 multiplets superimposed), 4.13 (>CHO, m), and 14.75 ppm (CO_2H, s).

Anal. Calcd for $C_{19}H_{34}O_4$: C, 69.90; H, 10.50. Found: C, 70.08; H, 10.38.

A sample of the acid was treated with ethereal diazomethane and the neutral product was isolated in the usual way. Two crystallizations from petroleum ether (bp 20–60°) afforded the pure methyl ester, mp 42–43°, ir ($CHCl_3$) 1735 and 1770 cm^{-1}.

Anal. Calcd for $C_{20}H_{36}O_4$: C, 70.54; H, 10.66. Found: C, 70.18; H, 10.82.

Homologation of *trans*- and *cis*-3-Carboxy-4-*n*-tridecylbutyrolactone. The acid lactone **18a** (R = H) (377 mg) together with about 0.5 ml of benzene was treated dropwise with thionyl chloride (0.65 ml). A microdrop of dimethylformamide was added and the mixture was heated on a steam bath for 3 hr. The solvent and excess reagent were removed under reduced pressure, leaving a yellow liquid which quickly crystallized. Without further purification the material was dissolved in dry ether (5 ml) and added dropwise to a cold, stirred solution of excess diazomethane in ether. The solution was allowed to warm to room temperature and then left for 15 hr. Traces of polymethylene were removed by filtration and the solvent was removed under reduced pressure at <40°. The resulting diazo ketone (450 mg), an off-white powder, was dissolved in methanol (25 ml) and to this solution was added slowly a solution of ~0.5 g of silver benzoate in triethylamine (5 ml). The mixture rapidly became dark brown in color and a little N_2 was evolved. It was then refluxed for 15 hr to complete gas evolution, and allowed to stand overnight. Ether and water were added to the mixture and the ether extract (~400 ml) was washed with 6 N hydrochloric acid, saturated sodium bicarbonate solution, and water, then finally dried ($MgSO_4$). Removal of the ether left an oil which crystallized when scratched. A glc (QF-1, 250°) of this material revealed the presence of two components in the ratio ~90:10, both having substantially longer retention times than those of either of the methyl esters of the starting trans acid or its cis isomer. Admixture of a small quantity of the trans homolog **22** (R = CH_3) prepared *via* the Fittig reaction augmented the larger and faster moving of the two peaks. Crystallization of the product from petroleum ether (bp 30–60°) then afforded pure **22** (R = CH_3), mp 42.5–43.5° (207 mg), whose spectral characteristics did not differ from those of the authentic specimen. On admixture no depression in melting point was observed.

When *cis*-3-carboxy-4-*n*-tridecylbutyrolactone (**18b**, R = H) was subjected to the exact same homologation procedure, a mixture of the same products was obtained as judged by glc and spectral methods. The ratio of the products varied, however, depending on the run, being 50:50 on one occasion and 80:20 in favor of the trans isomer on another. Attempts to obtain substantial quantities of the slower running component (cis isomer) in a pure state were unsuccessful. However, a few micrograms were isolated by glc and submitted to low-resolution mass spectrometric analysis. This revealed a small molecular ion peak at m/e 340 and a substantial peak at M − 183 indicative of the loss of the $C_{13}H_{27}$ side chain.

Carboxylation of *trans*-3-Carboxy-4-*n*-tridecylbutyrolactone. The acid (716 mg) was mixed with methyl methoxymagnesium carbonate solution (30 ml) and heated at 130–135° for 60 hr under a slow stream of dry, oxygen-free nitrogen. The mixture when cool was poured into ether (100 ml), then acidified with 6 N hydrochloric acid. The ether extract was separated and extracted with

saturated sodium bicarbonate solution. The latter in turn was acidified in the cold with hydrochloric acid and the desired compound was isolated by ether extraction. Removal of the ether afforded a tan-colored, crystalline material (761 mg, 92.5%), mp 80–85°, whose tlc (1:1 ether–benzene, containing a trace of formic acid) showed only one spot. Because the diacid **25** was very soluble in all of the common solvents, a specimen was purified by preparative tlc, mp 84–86°, ir (neat melt) 1785, 1735, 1220, 1165, and 970 cm^{-1}.

Anal. Calcd for $C_{19}H_{32}O_6$: C, 64.02; H, 9.05. Found: C, 64.39; H, 9.23.

2,3-Bis(methoxycarbonyl)-4-*n*-tridecylbutyrolactone. The dicarboxylic acid (124 mg) was treated with a solution of diazomethane in ether until a faint yellow color persisted. The solvent was removed under reduced pressure and the residue was recrystallized from methanol. This afforded the pure diester: mp 43–45°; ir (film) 1635 (CO_2CH_3) and 1675 cm^{-1} (γ-lactone); nmr 3.63 (CO_2CH_3, s), 3.87 (CO_2CH_3, s), and 4.47 ppm (CHO–, m). Both signals due to the hydrogens α to the ester functions lie partially under the methoxy hydrogen peaks and could not be accurately identified.

Anal. Calcd for $C_{19}H_{34}O_6$: C, 65.59; H, 9.44. Found: C, 65.57; H, 9.48.

***dl*-Protolichesterinic Acid (16).** The dicarboxylic acid (504 mg) was treated at room temperature with a solution prepared from 0.6 ml of formalin and 0.2 ml of diethylamine. As the solid dissolved a substantial amount of gas evolution occurred. Stirring was continued for 3.5 hr and ether, followed by saturated sodium chloride solution containing a few drops of hydrochloric acid, was added to the reaction mixture. The ether extract was washed with salt solution and then dried ($MgSO_4$). Removal of the ether under reduced pressure then led to an oil which rapidly crystallized. The crude solid (192 mg, ~40% yield) had mp 65–83° and after one crystallization from acetic acid had mp 90–92° (160 mg). Further crystallization from the same solvent provided the analytically pure *dl*-protolichesterinic acid: mp 92–93.5°; ir ($CHCl_3$) 1715 (CO_2H), 1760 (γ-lactone), 1665, and 960 cm^{-1} (=CH_2); nmr 3.64 ($CHCO_2H$, m), 4.80 (CHO, m), 6.0 (=CH, d, J = 3.0 Hz), 6.43 (=CH, d, J = 2.8 Hz), and 15.3 ppm (CO_2H, s). Both spectra were identical with that of an authentic specimen. When the latter was mixed with our material no depression in melting point was observed, mmp 92–93°.

Anal. Calcd for $C_{19}H_{32}O_4$: C, 70.33; H, 9.94. Found: C, 70.18; H, 9.91.

Acknowledgment. We should like to thank Professor E. E. van Tamelen, who kindly provided an authentic sample of *dl*-protolichesterinic acid, and Mr. P. R. Briggs, who carried out the mass spectral analyses.

Registry No.—**4** (R = H; R′ = Ph), 6005-95-4; **4** (R = H; R′ = 1-hexyl), 26613-70-7; **4** (R = H; R′ = *n*-butyl), 26449-01-4; **6** (R = H; R′ = Ph), 26613-71-8; **6** (R = H; R′ = 1-hexyl), 26798-41-4; **6** (R = H; R′ = *n*-butyl), 26449-03-6; **6** [R = (1′-pyrrolidinylcarbonyl)methyl, R′ = 1-octyl], 51175-39-4; **7** (R = H; R′ = Ph), 1008-76-0; **15**, 39949-70-7; **16**, 51260-32-3; **18a** (R = H), 51175-40-7; **18a** (R = Me), 51175-41-8; **18b** (R = H), 51175-42-9; **18b** (R = Me), 51202-16-5; **19**, 51175-43-0; **21**, 51175-44-1; **22** (R = H), 51175-45-2; **22** (R = Me), 51202-17-6; **25**, 51175-46-3; γ-decanoic lactone, 706-14-9; γ-octanoic lactone, 104-50-7; methyl 3-methoxycarbonyl-4-oxoheptadecanoate, 51175-47-4; tetradecylaldehyde, 124-25-4; dimethyl maleate, 624-48-6; trimethyl 1,1,2-ethenetricarbonyl-4-oxoheptadecanoate, 51175-47-4; tetradecylaldehyde, 40967-67-7; tricarballylic acid, 99-14-9; 2,3-bis(methoxycarbonyl)-4-*n*-tridecylbutyrolactone, 51202-18-7.

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A Metal-Catalyzed Reaction of 8-Quinolyl Sulfate and Its Application to the Preparation of Biochemically Related Sulfate Esters

Kinzo Nagasawa* and Hisae Yoshidome

School of Pharmaceutical Sciences, Kitasato University, 9-1 Shirokane 5-chome, Minato-ku, Tokyo 108, Japan

Received June 26, 1973

The effect of Cu(II) and 8-hydroxyquinoline–Cu(II) complex on the hydrolysis and alcoholysis of 8-quinolyl sulfate in polar solvents was examined. The hydrolysis rate of 8-quinolyl sulfate in dimethylformamide containing water (1%, v/v) at 20° gave good pseudo-first-order plots (k_{obsd} 6.5 × 10^{-3} hr^{-1}), while it was markedly enhanced by the addition of Cu(II) (0.5 molar equiv) or 8-hydroxyquinoline–Cu(II) complex (0.1 molar equiv), although no satisfactory pseudo-first-order plots were obtained in these cases. Both Cu(II) and its 8-hydroxyquinoline complex also accelerated the alcoholysis of 8-quinolyl sulfate in dimethylformamide or pyridine containing ethanol (10%, v/v each). The effect of 8-hydroxyquinoline–Cu(II) complex was more than that of Cu(II) in both the hydrolysis and alcoholysis of 8-quinolyl sulfate. The factors (water content, solvent, metal ion) which affect this metal-catalyzed reaction were examined and a possible mechanism for this reaction was discussed. This metal-catalyzed reaction of 8-quinolyl sulfate was applied successfully for the preparation of D-galactose 6-sulfate, adenosine 5′-sulfate, and dextran sulfate.

Recently, the reactions of 8-quinolyl derivatives of amino acids[1] and phenylphosphoric acid[2] and their application to the synthesis of peptides and phosphate esters have been reported. In 1967, Hay and Edmonds[3] reported a kinetic study of the hydrolysis of 8-quinolyl sulfate catalyzed by cupric ions in aqueous media, and, in 1971, Murakami and Sunamoto[4] reported the solvolysis of 8-quinolyl dihydrogen phosphate in the presence of some bivalent