

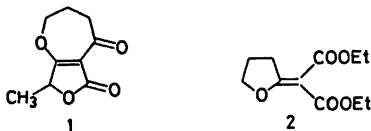
Naturally Occurring Lactones and Lactams. VI.* A Novel Synthetic Route to Carolic Acid

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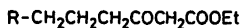
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In a reinvestigation of the total synthesis of carolic acid the problem of the side chain construction has been solved *via* the preparation of the hitherto unknown compound ethyl 6-chloro-3-oxohexanoate **4**. When condensed with 2-bromopropionyl bromide **4** gave an intermediate bromo ester which could be cyclized to the natural product with 2.5 N potassium hydroxide. Cyclization of **4** *per se* with sodium hydride afforded the tetrahydrofurylidene acetate **8**.

In an attempt to prepare the mold tetrone acid carolic acid **1** Haynes, Plimmer and Stanners² condensed 4-bromobutyryl chloride with ethoxymagnesiummalonic ester in order to obtain the carolic acid side chain, but instead a solid product, C₁₁H₁₈O₅, of m.p. 52.5–54.0 °C was isolated, to which they assigned the structure **2**.



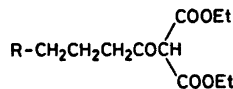
Later Sudo *et al.*³ in their synthesis of carolic acid circumvented the problem of a labile halogen atom by means of the benzyloxy ester **3**.



In connection with our studies on the synthesis of naturally occurring tetrone acids we

* Part V, see Ref. 1.

have investigated the possibility of preparing the chloro ester **4** as a useful building block since a chloro derivative might be less labile than the corresponding bromo derivative. At first the synthetic route of Haynes, Plimmer and Stanners was reexamined. In our hands, when 4-bromobutyryl bromide was condensed with diethyl ethoxymagnesiummalonate no solid product was obtained. Instead a 60 % yield of a viscous oil was isolated. Upon standing for months at room temp. or at –15 °C with agitation and scratching from time to time this oil showed no tendency to solidify. Since elemental analysis and spectroscopic data of this liquid product were in agreement with the structure and formula (C₁₁H₁₈O₅) of **2**, we were led, initially, to think that the original structure report might be erroneous. In any case it was obvious that the bromo compound **5** could not be prepared by this method. In contrast the chloro derivative **6** from 4-chlorobutyryl chloride and diethyl ethoxymagnesiummalonate was isolated without difficulty.



This established that the chloro diester was less prone to spontaneous cyclization than the bromo derivative. More vigorous conditions were demanded for this reaction and the transformation of **6** to the tetrahydrofurylidene malonate **2** was achieved with sodium hydride in refluxing

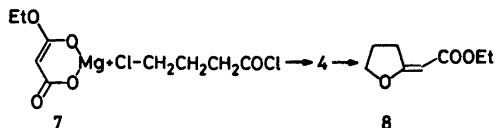
benzene to give only liquid material. On the other hand, when performed in abs. ethanol with potassium hydroxide acting as a base the cyclization led to a crystalline sample of m.p. 55–56 °C. When any of the aforementioned oily samples of **2** were seeded with solid **2** a rapid crystallization took place to solid products with m.p. 55–56 °C. The identity of our material with that previously prepared and assigned the structure **2** was thus fully established.

The decarboxylation of **6** would offer a convenient route to the key compound **4**. In an attempt to carry out this degradation **6** was refluxed in dilute acetic acid for 4 h, after which time a quantitative amount of carbon dioxide gas had been collected. Careful work-up afforded only traces of organic material indicating progressive destruction of **6** to watersoluble fragments.

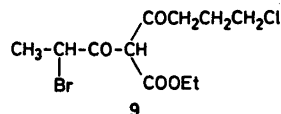
By analogy with the application of *t*-butyl ethyl malonate in the preparation of other β -keto esters, e.g. diethyl β -keto adipate,^{4,5} we condensed this mixed ester with 4-chlorobutyryl chloride and obtained an almost quantitative yield of a colourless oil which when pyrolyzed at 130 °C (0.2 mmHg) with *p*-TsOH as catalyst only sluggishly evolved gas. The prolonged subjection to heating (10 h) was damaging and distillation of the pyrolysis product afforded no **6**. Finally modification of earlier synthetic procedures for β -keto esters gave us **6** in hand.

It has been reported⁶ that methylene chloride may serve well as medium of reaction for Grignard compounds if these are prepared first in ether, but this possibility does not seem to have been considered very much since. The condensation of ethyl hydrogen malonate with acid chlorides or anhydrides and subsequent hydrolysis and decarboxylation is an existing route to β -keto esters. The magnesium complex **7** has been prepared previously by treatment of the mono ester with magnesium ethoxide or isopropylmagnesium bromide in tetrahydrofuran.^{7,8} We prepared **7** as a soluble complex in methylene chloride from ethyl hydrogen malonate and two equivalents of ethylmagnesium bromide in the same solvent. Addition of 4-chlorobutyryl chloride, hydrolysis with concentrated hydrochloric acid and work-up by distillation provided analytically pure **4** in good yield. In analogy with **6** cyclization of **4** by treatment with sodium hydride in benzene gave

the tetrahydrofurylidene acetate **8**. The indicated geometry of this compound rests upon the identity of **8** with a compound whose structure has been unambiguously assigned from shift reagent studies.⁹



Recently we have demonstrated the cyclization of γ -bromo- β -keto esters by means of 2.5 N potassium hydroxide to tetrone acids.¹ Among other tetrone acids the naturally occurring carolinic acid was obtained. Following this route 2-bromopropionyl bromide was condensed with **4** in methylene chloride with ethylmagnesium bromide acting as base. The condensation product **9**



was not purified by any means since TLC revealed only trace amounts of impurities. Treatment of **9** with 2.5 N potassium hydroxide for 24 h simultaneously induced cyclization and replacement of the side chain chlorine atom by hydroxide, just as NMR and TLC data clearly indicated the presence of carolic acid in the resulting oily product, but the isolation of pure material was not straightforward. Preparative layer chromatography on silica gel with abs. ethanol as eluent separated two bands of almost equal intensity but reextraction was unsuccessful. Finally, when the oil was left standing with a mixture of ether/light petrol for two days crystals were produced. This material was identical in all respects with carolic acid.

EXPERIMENTAL

All m.p.'s are uncorrected. ¹H NMR spectra were recorded on a JEOL C-60 HL spectrometer with TMS as internal standard. The chemical shifts are expressed in δ -values (ppm downfield from TMS). Coupling constants are expressed in Hz. UV spectra were recorded on a Beckman

ACTA III spectrophotometer. Microanalysis was performed at the microanalytical department of the University of Copenhagen. The progression of the reactions was monitored conveniently on TLC with ether as eluent.

4-Bromobutyryl bromide.¹⁰ Butyrolactone (86 g, 1 mol) and phosphorus tribromide (67 ml) were mixed at room temp. and heated at 140 °C for 2 h. The temp. was raised to 180 °C and all volatile material distilled off; b.p. 65–110 °C (13 mmHg). Redistillation afforded 89 g (39 %) of the title compound; b.p. 90–93 °C (13 mmHg) [lit.¹⁰ b.p. 90–91 °C (13 mmHg)]; n_D^{20} : 1.5300; NMR (CCl_4): 2.21 (2 H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 3.21 (2 H, t, $J=6.5$, $\text{CH}_2\text{CH}_2\text{CO}$), 3.44 (2 H, t, $J=6$, BrCH_2CH_2).

4-Chlorobutyryl chloride. Prepared in 80 % yield by the method of Reppe *et al.*;¹¹ b.p. 67–69 °C (13 mmHg); n_D^{19} : 1.4600.

Diethyl 4-chlorobutyrylmalonate (6). To a solution of diethyl ethoxymagnesiummalonate from Mg (25 g, 1 mol) abs. ethanol (105 ml) and diethyl malonate (160 g, 1 mol) in dry ether (300 ml) was added 4-chlorobutyryl chloride (141 g, 1 mol) in ether (100 ml) as rapidly as possible with ice cooling. After complete addition the mixture was refluxed briefly giving a greenish viscous complex. The reaction mixture was chilled with ice and poured into ice-cooled 4 N HCl (500 ml). After vigorous shaking the ether layer was separated, washed with sat. NaHCO_3 aq., then water, dried and the solvent stripped off to give 265 g of a slightly coloured oil. Distillation afforded the title compound (234 g, 88 %), b.p. 145–147 °C (0.5 mmHg); n_D^{21} : 1.4670; NMR (CDCl_3): 1.31 (6 H, t, $J=7$), 1.85–2.40 (2 H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.50–3.08 (2 H, m, $\text{CH}_2\text{CH}_2\text{CO}$), 3.61 (2 H, t, $J=6$, ClCH_2CH_2), 4.31 (4 H, q, $J=7$), 4.51 (1 H, s, COCHCO). (Found: C 50.15; H 6.56; Cl 13.05. Calc. for $\text{C}_{11}\text{H}_{17}\text{ClO}_5$: C 49.91; H 6.48; Cl 13.39).

Diethyl tetrahydro-2-furylidene malonate (2) (a) From diethyl 4-bromobutyrylmalonate. Diethyl ethoxymagnesiummalonate was prepared from Mg (7.5 g), abs. ethanol (7.5 ml), and CCl_4 (0.5 ml) in ether (100 ml). Excess abs. ethanol was removed by azeotropic distillation with benzene (100 ml). The salt was redissolved in ether (80 ml) and 4-bromobutyryl bromide (69.0 g, 0.3 mol) in ether (50 ml) added as rapidly as possible with ice cooling. The resulting green complex was very viscous. Careful hydrolysis with 4 N HCl (300 ml) at 0 °C gave 61.0 g of crude oily product. Distillation afforded 43.0 g (60 %) of analytically pure 2 as a colourless liquid; b.p. 127–129 °C (0.1 mmHg); [lit.² b.p. 129 °C (0.1 mmHg)]; n_D^{21} : 1.4891; NMR (CDCl_3): 1.26 (3 H, t, $J=7.5$), 1.30 (3 H, t, $J=7.5$), 1.75–2.33 (2 H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 3.14 (2 H, t, $J=7.5$, $\text{CH}_2\text{CH}_2\text{CO}$), 4.16 (2 H, q, $J=7.5$), 4.19 (2 H, q, $J=7.5$), 4.34 (2 H, t, $J=7.5$, OCH_2CH_2). (Found: C 58.10; H 7.11. Calc. for $\text{C}_{11}\text{H}_{18}\text{O}_5$: C 57.88; H 7.07).

(b) From diethyl 4-chlorobutyrylmalonate and NaH in benzene. NaH (5.0 g of a 55–60 %

dispersion in oil, 0.11 mol) was washed thoroughly with dry benzene (3×25 ml) and suspended in benzene (60 ml). A solution of 6 (26.5 g, 0.1 mol) in benzene (40 ml) was added at room temp. under vigorous evolution of H_2 . The reaction was exothermic and a final temp. of 60 °C was reached. When the gas evolution ceased the mixture was refluxed for 2 h, after which time all NaH had been consumed. After cooling at 0 °C 4 N HCl (100 ml) was added, the benzene layer separated, washed with sat. NaHCO_3 aq. (100 ml) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the remaining oil distilled to yield 18.3 g (80 %) of 2 as a colourless liquid; n_D^{20} : 1.4880; b.p. 139–141 °C (0.15 mmHg); NMR data as above. (Found: C 58.00; H 7.06).

(c) From diethyl 4-chlorobutyrylmalonate 6 and potassium hydroxide in abs. ethanol. To a solution of 5 (52.9 g, 0.2 mol) in abs. ethanol (100 ml) was added a solution of potassium hydroxide (13.0 g of 86 % pellets) in abs. ethanol (150 ml) at room temp. During the addition of potassium hydroxide a white precipitate was formed. After stirring for 15 h, the mixture was chilled to 0 °C and the precipitated potassium chloride (12.0 g) was filtered off and washed with ether. The filtrate was concentrated to 100 ml *in vacuo*, water (300 ml) was added and organic material extracted with ether (3×50 ml). The pooled ether extracts were dried (Na_2SO_4) and evaporated *in vacuo* to leave 42.0 g of an oil which rapidly solidified to a material with m.p. 54–55 °C. Recrystallization from light petroleum (boiling range 50–70 °C) afforded 39.9 g (83 %) of pure 2 as a solid m.p. 55–57 °C; NMR (CCl_4): 1.25 (6 H, t, $J=7.5$), 1.81–2.38 (2 H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 3.10 (2 H, t, $J=7.5$, $\text{CH}_2\text{CH}_2\text{CO}$), 4.09 (2 H, q, $J=7.5$), 4.11 (2 H, q, $J=7.5$), 4.32 (2 H, t, $J=7.5$, OCH_2CH_2). (Found: C 57.70; H 7.00).

Ethyl 6-chloro-3-oxohexanoate (4). A solution of ethylmagnesium bromide was prepared from Mg flakes (12.5 g) and ethyl bromide (60 g) in ether (200 ml). The ether was evaporated *in vacuo* and replaced by methylene chloride (100 ml). Freshly distilled ethyl hydrogen malonate (13.2 g, 0.1 mol) was dissolved in methylene chloride (75 ml) and cooled to 0 °C. To this solution a freshly prepared solution of ethylmagnesium bromide in methylene chloride was added with instantaneous evolution of gas. During the addition the reaction mixture became very viscous and efficient mechanical stirring was imperative. Extra methylene chloride (25 ml) was added and when the calculated amount of gas (~ 2.4 l) had been collected the addition of ethylmagnesium bromide was stopped. The clear, moderately viscous complex was stirred for further 5 min, when a solution of 4-chlorobutyryl chloride (14.3 g, 0.1 mol) in methylene chloride (50 ml) was added dropwise, still at 0 °C. The mixture was left for 10 h at ambient temp. and then chilled at 0 °C. Concentrated HCl (100 ml) was added dropwise

with vigorous stirring. The organic layer was separated, shaken thoroughly with sat. NaHCO_3 aq. (100 ml) and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* left 19.3 g of oily product. The oil was distilled twice affording 10.9 g (56 %) of analytically pure **4**; b.p. 80–85 °C (0.15 mmHg); n_D^{20} : 1.4575; NMR (CCl_4): 1.28 (3 H, t, $J=7.5$), 1.75–2.36 (2 H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.70 (2 H, t, $J=6$, $\text{CH}_2\text{CH}_2\text{CO}$), 3.35 (2 H, s, COCH_2CO), 3.54 (2 H, t, $J=6$, ClCH_2CH_2), 4.13 (2 H, q, $J=7.5$). (Found: C 49.70; H 6.93; Cl 18.25. Calc. for $\text{C}_8\text{H}_{13}\text{ClO}_3$: C 49.88; H 6.80; Cl 18.40).

Ethyl α -(tetrahydro-2-furylidene)acetate (**8**). Sodium hydride (4.0 g of a 55–60 % dispersion in mineral oil, ~ 9.1 mmol) was liberated from dispersing agent by repeated washing with dry benzene (3×15 ml) and suspended in benzene (50 ml). A solution of **4** (16.0 g, 8.3 mmol) in benzene (25 ml) was added dropwise at 0 °C with evolution of H_2 . When the addition was finished the mixture was refluxed for 2 h, after which time a white slurry had been formed. After cooling at 0 °C 4 N HCl (40 ml) was added and the organic layer was separated, washed with sat. NaHCO_3 aq. and dried. Evaporation of the solvent *in vacuo* left 13.7 g of slightly coloured oil. Distillation yielded 7.3 g (56 %) of **8** as a colourless liquid; b.p. 62 °C (0.15 mmHg); n_D^{20} : 1.4868; [lit.⁹ b.p. 50 °C (0.05 mmHg)]; the NMR spectrum was identical in all respects with that recently published.⁹

(\pm)-*Carolic acid* (**1**). A solution of **4** (9.65 g, 0.05 mol) in methylene chloride (50 ml) chilled to 0 °C was treated with a solution of ethylmagnesium bromide in methylene chloride, prepared as described above, until the calculated amount of gas (~ 1.2 l) had been collected. The resulting clear solution of magnesium complex was then added dropwise at 0 °C to a solution of freshly distilled 2-bromopropionyl bromide (11.1 g, 0.051 mol) in methylene chloride (50 ml). No immediate colour reaction was observed, but on standing at room temp. for 12 h the reaction mixture turned wine red. After this time 4 N HCl (100 ml) was added at 0 °C to hydrolyse the magnesium complex and possibly unreacted acid chloride. The organic layer was separated, washed with sat. NaHCO_3 aq. and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* left 16.0 g of brown oil. TLC (silica gel, elution with ether) revealed the presence of one major component ($R_F=0.61$) and traces of 2 other components. The crude product (8.0 g) was dissolved in ether (25 ml) at 0 °C and 2.5 N potassium hydroxide (25 ml) was added with vigorous stirring in 30 min. The stirring was continued for 12 h and the ether layer containing 0.6 g of unidentified material discarded. The water phase was acidified with 4 N HCl and extracted with chloroform (3×25 ml). The combined chloroform extracts were dried (Na_2SO_4) and the solvent distilled off *in vacuo* to give 5.0 g of viscous brown oil. TLC (silica gel, elution with abs. ethanol) revealed two

spots $R_F=0.70$ and $R_F=0.82$ of equal intensity. A mixture of ether/light petroleum 1:1 (50 ml) was added and the whole left at room temp. for two days. Impurities went into solution and beautiful rosettes of crystals appeared. The solvent was decanted and the crystals collected had m.p. 111–112 °C [lit.⁹ m.p. 113 °C]; UV 227 nm ($\log \epsilon$ 3.47) and 272 nm ($\log \epsilon$ 4.11). The NMR spectrum was completely in accord with that published.¹²

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