893. *Tetronic Acids and Related Compounds. Part II.* The Synthesis of (±)-Carolinic Acid.*

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Use of ethoxymagnesiomalonic ester in place of sodiomalonic ester gives improved yields in Benary's method for the synthesis of tetronic acids. This modification is used in the condensation of ethyl β-oxoadipate and α-chloropropionyl chloride to give, after cyclisation and hydrolysis of the product, (±)-carolinic acid. Condensation of γ-bromobutyryl chloride with ethoxymagnesiomalonic ester gives diethyl tetrahydro-2-furylidenemalonate (III).

THE mould *Penicillium Charlesii* G. Smith, when grown on a nutrient medium containing glucose, produces among other products a number of tetronic acid derivatives,[1] the structures of which were established by degradation.[2] Of these products, only γ-methyltetronic acid (I; R = H) had hitherto been synthesised, and it seemed desirable to confirm the structure of a more typical member, *e.g.*, carolinic acid (I; R = $CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$), by synthesis.

Anschütz[3] and Benary[4] prepared ethoxycarbonyltetronic acids by condensing α-acetoxy- or α-halogeno-acyl halides with an excess of ethyl sodiomalonate and cyclisation of the product *in situ*. We have improved this approach by the use of ethyl ethoxymagnesiomalonate,[5] and have thus prepared α-ethoxycarbonyltetronic, α-ethoxycarbonyl-γ-phenyltetronic, and (±)-carolinic acid.

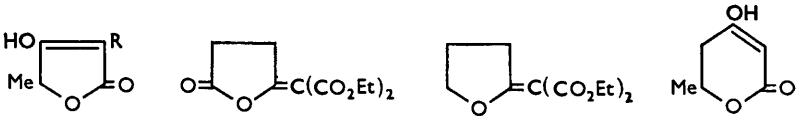
Equimolecular amounts of chloroacetyl chloride and ethyl ethoxymagnesiomalonate gave α-chloroacetylmalonic ester in good yield: this was cyclised when kept at room temperature or heated, giving α-ethoxycarbonyltetronic acid. In this cyclisation the yields are not good, although this route is a considerable improvement in ease and in yield on

* Part I, *J.*, 1956, 4103.

[1] Clutterbuck, Haworth, Raistrick, Smith, and Stacey, *Biochem. J.*, 1934, **28**, 94.
[2] Clutterbuck, Raistrick, and Reuter, *ibid.*, 1935, **29**, 300.
[3] Anschütz and Bertram, *Ber.*, 1903, **36**, 468; Anschütz and Böcker, *Annalen*, 1909, **368**, 53.
[4] Benary, *Ber.*, 1907, **40**, 1079; 1911, **44**, 1759.
[5] Lund, *Ber.*, 1934, **67**, 935.

Benary's. Reaction of acetylmandelyl chloride with ethyl ethoxymagnesiomalonate gave a 65% overall yield of γ-phenyltetronic acid, whereas with ethyl sodiomalonate the overall yield was 48%.

Reaction of the ethoxymagnesio-derivative of ethyl β-oxoadipate [6] in benzene with α-chloropropionyl chloride and subsequent hydrolysis gave crude ethyl 6-chloro-4-ethoxycarbonyl-3 : 5-dioxo-octanoate as an oil which cyclised to ethyl carolinate on standing for



(I) (II) (III) (VI)

some weeks or when heated at 120°/25 mm. Alkaline hydrolysis gave (±)-carolinic acid, m. p. 137·5° [cf. (+)-carolinic acid, m. p. 123°], identical with the natural acid in ultraviolet absorption and behaviour on paper chromatography and to ferric chloride. It formed a 2 : 4-dinitrophenylhydrazone, m. p. 228° [(+)-isomer, m. p. 228°].

In preliminary experiments on the analogous synthesis of carolic acid (I; R = $CO{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}OH$), we condensed ethoxymagnesiomalonic ester with γ-bromobutyryl chloride in the hope that this would lead to the carolic acid side chain. However, instead of the expected product $CH_2Br{\cdot}[CH_2]_2{\cdot}CO{\cdot}CH(CO_2Et)_2$, a solid compound, $C_{11}H_{16}O_5$, was obtained. On acid hydrolysis this gave γ-butyrolactone. The compound gave no colour with ferric chloride solution and had an absorption maximum at 2470 Å (ε 13,800). Ruggli and Maeder [7] have shown that reaction of succinoyl chloride or succinic anhydride with sodiomalonic ester gives the $\Delta^{1:2}$-enol lactone (II), and we consider that our product is diethyl tetrahydro-2-furylidenemalonate (III) formed by cyclisation with loss of hydrogen bromide from the enolic form of the expected bromo-compound. In agreement with this suggestion, condensation of diethyl ethoxymagnesioethylmalonate with γ-bromobutyryl chloride gave the expected ester (IV) which did not cyclise, either to a furan derivative or to a seven-membered analogue of a tetronic acid. It was hydrolysed by dilute aqueous-ethanolic potassium hydroxide at room temperature, to yield ethylmalonic acid. These findings led us to prepare the chloro-ester (V) : this showed no tendency to cyclise, even when kept for two years. Cyclisation of the bromo-compound (IV) to a seven-membered ring analogue of a tetronic acid may be regarded as unlikely; but the cyclisation of the chloro-compound (V) should lead to the lower homologue of the six-membered ring analogue (VI) of tetronic acid which has been prepared [8] from 5-hydroxyhex-2-ynoic acid [9] and is known to show properties similar to those of tetronic acid, so it seems that the cyclisation which leads to a tetronic acid from an α-substituted γ-halogenoacetoacetic ester depends on activation of the halogen atom by an adjacent carbonyl group.

Experimental

α-Ethoxycarbonyltetronic Acid.—Dry ethanol (25 ml.) and carbon tetrachloride (0·5 ml.) were added to magnesium (5 g.). When the vigorous reaction had subsided, more ethanol (11 ml.) was added and the mixture heated under reflux for 1 hr. Next morning redistilled diethyl malonate (33·7 g.) was added and dissolution of the magnesium completed by heating the mixture on a water-bath for 1 hr. The resulting complex was dissolved in dry ether and the solution cooled in ice. Chloroacetyl chloride (25 g.) in dry ether (17 ml.) was added during 1 hr., the mixture heated under reflux for 30 min., then cooled to 0°, and the complex decomposed, first, with ice and then with dilute sulphuric acid. The ether layer was separated, dried (Na_2SO_4) and evaporated *in vacuo*, to leave a yellow oil (30 g.) (Found : Cl, 14·3%). Distillation of a sample gave diethyl malonate, b. p. 85°/10 mm., and then *diethyl chloroacetylmalonate*, b. p.

[6] Macdonald, *J.*, 1952, 4176; Eisner, Elvidge, and Linstead, *J.*, 1950, 2223; Riegel and Lilienfield, *J. Amer. Chem. Soc.*, 1945, **67**, 1274.
[7] Ruggli and Maeder, *Helv. Chim. Acta*, 1943, **26**, 1476, 1499; 1944, **27**, 436.
[8] Jones and Whiting, *J.*, 1949, 1419.
[9] Haynes and Jones, *J.*, 1946, 503.

130—133°/10 mm., n_D^{10} 1·4648 (Found : Cl, 15·0. $C_9H_{13}O_5Cl$ requires Cl, 15·0). Only small quantities of this compound could be obtained as decomposition occurred during the distillation with the formation of solid α-ethoxycarbonyltetronic acid.

The crude chloro-compound (25 g.) in xylene (30 ml.) was heated under reflux for 2 hr. Addition of light petroleum (b. p. 40—60°) precipitated α-ethoxycarbonyltetronic acid (7·5 g.), m. p. 125° (from ethyl acetate) (Benary [4] gives m. p. 124—125°).

α-Ethoxycarbonyl-γ-phenyltetronic Acid.—Diethyl malonate (40 g.) in dry ether (100 ml.) was added during 30 min. to a suspension of magnesium ethoxide (from magnesium, 6·08 g.) in ether. The mixture was heated under reflux for 30 min. and set aside overnight. Excess of ethanol was then removed by azeotropic distillation with toluene, and the resulting green syrupy complex was dissolved in dry ether (150 ml.). *O*-Acetylmandelyl chloride [10] (53 g.) in dry ether (60 ml.) was added with stirring to the solution at such a rate that the solvent refluxed gently. When the addition was nearly complete an insoluble greenish-white complex separated. The mixture was set aside overnight, then heated on a water-bath for 30 min. The complex was decomposed by ice and then sulphuric acid (17 ml. of concentrated acid diluted with water to 40 ml.). The ether layer was separated and the aqueous layer extracted with ether. The ethereal solutions were combined, dried (Na_2SO_4), and evaporated *in vacuo*. The residual yellow oil (91 g.) was dissolved in aqueous 4N-sodium hydroxide (250 ml.) and set aside for 3 days. Addition of an excess of sulphuric acid precipitated α-ethoxycarbonyl-γ-phenyltetronic acid (42·5 g.) containing a little γ-phenyltetronic acid. Recrystallisation from ethyl acetate or ethanol gave the ethoxycarbonyl compound as prisms, m. p. 145° (Anschütz and Böcker [3] give m. p. 140°).

γ-Phenyltetronic Acid.—The above crude α-ethoxycarbonyl-γ-phenyltetronic acid (20 g.) was boiled under reflux with aqueous 2N-sodium hydroxide (100 ml.) for 45 min. Addition of concentrated hydrochloric acid precipitated a cream-coloured solid; recrystallisation of this from water gave γ-phenyltetronic acid (13·5 g.), m. p. 127° (Anschütz and Böcker [3] give m. p. 127·5—128·5°). Its 2 : 4-*dinitrophenylhydrazone* had m. p. 137° (from ethanol) (Found : C, 53·5; H, 3·8; N, 15·6. $C_{16}H_{12}O_6N_4$ requires C, 53·5; H, 3·4; N, 16·2%).

O-*Acetyl-γ-phenyltetronic Acid.*—(*a*) γ-Phenyltetronic acid (2 g.) was heated with *iso*propenyl acetate (10 ml.) and 3 drops of 10% methanolic 2 : 5-dichlorobenzenesulphonic acid on a water-bath for 30 min., then set aside overnight. Volatile material was evaporated *in vacuo*. The remaining dark brown oil slowly solidified. Extraction with boiling light petroleum (b. p. 40—60°) and recrystallisation from the same solvent gave O-*acetyl-γ-phenyltetronic acid* as needles, m. p. 79·5° (Found : C, 65·8; H, 4·6. $C_{12}H_{10}O_4$ requires C, 66·1; H, 4·6%).

(*b*) γ-Phenyltetronic acid (1·5 g.), treated with acetic anhydride (4 ml.) and a drop of concentrated sulphuric acid, gave *O*-acetyl-γ-phenyltetronic acid, m. p. and mixed m. p. 79°.

2-(4-*Acetonyl*-2 : 5-*dihydro*-2-*oxo*-5-*phenyl*-3-*furyl*)-2-(2 : 5-*dihydro*-4-*hydroxy*-2-*oxo*-5-*phenyl*-3-*furyl*)*propane* (cf. ref. 11).—A solution of γ-phenyltetronic acid (2 g.) in acetone (60 ml.) containing 2 drops of piperidine was refluxed during 2 hr. The excess of acetone was evaporated under reduced pressure. The residual gum solidified on treatment with ether. The solid was ground with a little ethyl acetate, and the colourless residue collected. Recrystallisation from ethanol gave the iso*propylidene compound* as prisms m. p. 177° (Found : C, 72·1; H, 5·7. $C_{26}H_{24}O_6$ requires C, 72·2; H, 5·6%). The substance gave a red colour with ferric chloride.

(±)-*Carolinic Acid.*—Ethyl β-oxoadipate [6] (16 g.) was added to a solution of magnesium ethoxide (from 1·75 g. of magnesium) in dry benzene (50 ml.) : when the vigorous reaction had subsided the solution was evaporated under reduced pressure to remove ethanol, leaving a green syrupy residue. (±)-α-Chloropropionyl chloride (9·5 g.) in dry benzene (25 ml.) was added slowly to a solution of the syrup in dry benzene; no immediate reaction was observed but a green viscous complex separated when the solution was warmed. The mixture was refluxed for 2 hr., left overnight, cooled to 0°, and treated with ice-water and then dilute sulphuric acid. The benzene layer was separated and the aqueous layer extracted several times with ether. The combined ether extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue, crude ethyl 6-chloro-4-ethoxycarbonyl-3 : 5-dioxo-octanoate, was a pale yellow oil which gave an orange-red colour with ferric chloride. When this compound was kept for some weeks or heated at 120°/25 mm. for 3 hr., its chlorine content dropped to zero, showing that cyclisation had taken place. The crude cyclised product (10 g.) was set aside in 2% aqueous sodium hydroxide (200 ml.) for 48 hr. at room temperature. The solution

[10] Thayer, *Org. Synth.*, Coll. Vol. I, 1st edn., p. 12.
[11] Wolff and Schlimpff, *Annalen*, 1901, **315**, 151.

was extracted with ether to remove unhydrolysed material and then acidified to pH 3 with dilute hydrochloric acid. Extraction with ether gave a small amount of β-oxoadipic acid (0·1 g.). The aqueous residue was then continuously extracted with ether during 24 hr. Evaporation of the dried (Na_2SO_4) extract gave crude (±)-carolinic acid, m. p. 116°, which recrystallised from ethyl acetate as prisms, m. p. 137·5° [Found: C, 50·45; H, 4·75%; equiv., 113. Calc. for $C_9H_{10}O_6$: C, 50·45; H, 4·7%; equiv. (dibasic), 107]. Both the synthetic and the natural acid gave orange colours, stable to concentrated hydrochloric acid, with ferric chloride. They showed identical R_F's on paper chromatography with use of the solvent systems: ethanol–ammonia (*d* 0·880)–water (20 : 1 : 4 v/v), R_F 0·49; butanol–acetic acid–water (4 : 1 : 5 v/v), R_F 0·50; propanol–ammonia (*d* 0·880)–water (2 : 1 : 1 v/v), R_F 0·60.

The 2 : 4-*dinitrophenylhydrazone*, prepared in the usual way and recrystallised from nitrobenzene–toluene, had m. p. 228—229° (decomp.) (Found: C, 46·7; H, 3·75; N, 13·9. $C_{15}H_{14}O_9N_4$ requires C, 45·7; H, 3·6; N, 14·2%). Clutterbuck, Raistrick, and Reuter[2] give m. p. 228° (decomp.) for (+)-carolinic acid 2 : 4-dinitrophenylhydrazone.

Diethyl Tetrahydro-2-furylidenemalonate (III).—γ-Bromobutyryl chloride[12] (135 g.) in dry ether (100 ml.) was added with stirring during 5 hr. to a solution of diethyl methoxymagnesiomalonate [from magnesium (24 g.) and diethyl malonate (160 g.)] in dry ether (300 ml.). A viscous yellow complex separated. The mixture was set aside for 48 hr., then hydrolysed at 0° with dilute sulphuric acid. The ether layer was separated, washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. Distillation of the residual oil (176 g.) gave a forerun of diethyl malonate, b. p. *ca.* 45°/0·1 mm., and then a fraction (110 g.), b. p. 129°/0·1 mm., which solidified. After recrystallisation from light petroleum (b. p. 40—60°) the product, *diethyl tetrahydro-2-furylidenemalonate*, had m. p. 52·5—54° (Found: C, 58·0; H, 6·9; Br, 0. $C_{11}H_{16}O_5$ requires C, 57·9; H, 7·1%). It was readily soluble in organic solvents and insoluble in water; it gave no colour with ferric chloride in aqueous ethanol and reduced aqueous potassium permanganate. Light absorption in EtOH: $\lambda_{max.}$ 2470 Å (ε 14,000).

The ester (5 g.) was refluxed for 1 hr. with 2N-sulphuric acid (50 ml.). The solution was then saturated with ammonium sulphate and extracted with ether. Isolation by the usual procedure gave γ-butyrolactone (1 g.), identified as the derived phenylhydrazide, m. p. and mixed m. p. 93—94° (Seib[13] gives m. p. 93·7—94°).

Diethyl 7-Bromo-4-oxoheptane-3 : 3-dicarboxylate.—γ-Bromobutyryl chloride (186 g.) in dry ether (75 ml.) was added dropwise with stirring during 2½ hr. to a solution of diethyl ethoxymagnesioethylmalonate [from magnesium (24 g.) and diethyl ethylmalonate (188 g.)] in dry ether (500 ml.). Stirring was continued for a further 4 hr. and the mixture then set aside for 36 hr. Hydrolysis with dilute sulphuric acid gave a light brown liquid (290 g.) which on distillation gave diethyl ethylmalonate and then the *diester* (173 g.), b. p. 119°/0·02 mm., $n_D^{17\cdot5}$ 1·4694 (Found: C, 47·4; H, 6·6. $C_{13}H_{21}O_5Br$ requires C, 46·2; H, 6·3%). Light absorption in EtOH: $\lambda_{max.}$ 2470 Å (ε 1500). The compound gave no colour with ferric chloride.

The bromo-compound (11 g.) was set aside for 2 days in 1 : 1 aqueous-ethanolic 5% potassium hydroxide (150 ml.) and then acidified with 2N-sulphuric acid (150 ml.). Isolation by the usual procedure gave ethylmalonic acid (3 g.), m. p. 110—112° (lit.,[14] m. p. 111°) (di-*p*-nitrobenzyl ester, m. p. 72—73°; lit.,[15] m. p. 75·2°).

Diethyl 4-Chloro-2-oxobutane-1 : 1-dicarboxylate.—β-Chloropropionyl chloride (64 g.) in dry ether (75 ml.) was added dropwise with stirring during 2 hr. to a solution of methoxymagnesiomalonic ester [from magnesium (12 g.) and diethyl malonate (80 g.)] in ether (200 ml.). A yellow-brown viscous complex separated. The mixture was set aside for 1 hr. Hydrolysis with dilute sulphuric acid gave the *diester* (85 g.), b. p. 106—109°/0·3 mm., $n_D^{21\cdot5}$ 1·4672 (Found: C, 47·6; H, 6·1; Cl, 14·7. $C_{10}H_{15}O_5Cl$ requires C, 47·9; H, 6·0; Cl, 14·2%). Light absorption in EtOH: $\lambda_{max.}$ 2600 Å (ε 9300).

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[12] McElvain and Carney, *J. Amer. Chem. Soc.*, 1946, **68**, 2599; Henry, *Bull. Soc. chim. France*, 1886, **46**, 65.
[13] Seib, *Ber.*, 1927, **60**, 1399.
[14] Markownikoff, *Annalen*, 1876, **182**, 332.
[15] Lyman and Reid, *J. Amer. Chem. Soc.*, 1917, **39**, 705.