

The Use of Optically Active Half-esters of Methoxy-substituted Succinic Acids in the Stereospecific Synthesis of Long Chain Oxygenated Compounds

GÖRAN ODHAM,^a BENITE PETERSSON^a and EINAR STENHAGEN^b

^aLipid Chemistry Laboratory, University of Göteborg, Kråketorpsgatan 20, S-431 33 Mölndal, Sweden and

^bInstitute of Medical Biochemistry, University of Göteborg, S-400 33 Göteborg 33, Sweden

The isomeric half-esters of (*S*)-methoxysuccinic acid have been prepared in the search for suitable intermediates for the synthesis of the β -glycol group of phthiocerol. The half-esters have very similar properties and differ mainly in the mass spectra and IR-spectra. Chain-lengthening of (*S*)-methyl 2-methoxy-3-carboxypropanoate by mixed electrolysis with dodecanoic acid in dimethylformamide gave a 21 % yield of (*S*)-methyl 2-methoxytetradecanoate.

In the further search for routes for the stereospecific synthesis of phthiocerol and other optically active complex glycols we have investigated the possibilities of using the monoesters of methoxy succinic acids as suitable initial materials. These compounds were considered attractive as they are readily prepared from the commercially available D- and L-malic acids. The half-esters should be suitable for chain-lengthening by the use of the Kolbe reaction. There appears to be only one report in the literature concerning the synthesis of such a half-ester.¹ In this work the half-ester was prepared by boiling a solution of the anhydride of methylated L-malic acid in methanol. The optical rotation of the resulting product is reported as $[\alpha]_D^{20} - 57.64^\circ$ (c, 3.4874, acetone). No indication of the structure of this material is given.

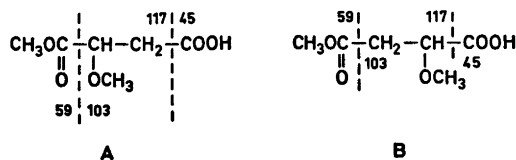
Present work. It is well known that introduction of electron attracting groups (e.g. $-\text{OCH}_3$) next to the carbonyl carbon of the ester group markedly increases its positive character and hence will increase the velocity of base-

catalyzed hydrolysis. Partial hydrolysis of dimethyl methoxysuccinate would thus predominantly result in the half-ester with the methoxyl substituent next to the free carboxyl group.

In contrast, formation of half-esters from unsymmetric anhydrides by reaction with hydroxyl compounds leads to predominance of ester on the more acidic carboxyl group. Accordingly, the material obtained by Purdie *et al.*¹ should have the structure (*S*)-methyl 2-methoxy-3-carboxypropanoate. We have repeated this work and obtained a product (A) with $[\alpha]_D^{22} - 55.9^\circ$ (c, 3.775, acetone), which is in good agreement with the value reported previously. An attempt by us to prepare the isomeric monoester (*S*)-methyl 3-methoxy-3-carboxypropanoate (B) *via* partial alkaline hydrolysis of the diester resulted in a compound with $[\alpha]_D^{24} - 45.8^\circ$ (c, 3.290, acetone).

The two monoesters (A and B) had practically identical gas chromatographic retention times on polar and non-polar stationary phases. This means unfortunately that it is at present impossible to state the isomeric purity of the two half-esters. The NMR spectra were also virtually identical whereas the infra-red spectra showed minor differences in the 1400 and 1050 cm^{-1} regions.

The mass spectra of the two esters show differences, however, which are consistent with the structures expected on theoretical grounds. None of the esters shows a peak due to the molecular ion ($M = 162$). The peaks of highest mass



number in both spectra are seen at $m/e = M - 18$ (loss of water). Significant peaks appear at the following mass numbers. Half ester A: 61(100), 103 (67), 61(27), 75(18), 132(16), 117(6), 114(5), 144(2); half ester B: 117(100), 59(64), 61(60), 103(60), 75(46), 71(30), 89(20), 99(20), 131(17), 144(5).

Attempts to lengthen the chain of the two half-esters by mixed anodic coupling with dodecanoic acid in dimethylformamide² gave a 21 % yield of (*S*)-methyl 2-methoxytetradecanoate when half-ester (A) was used. Practically no cross-coupling was observed for half-ester (B). Similar experiments with (*S*)-methyl 2-acetoxy-3-carboxypropanoate as optically active unit as used by Horn and Pretorius³ gave a yield of 14 % of the corresponding acetoxy-substituted compound.

We feel that optically active 2-methoxy-substituted esters prepared in the manner described are suitable as intermediates in the syntheses of more complex lipids containing methoxyl or hydroxyl groups. It has been shown previously⁴ that the methoxyl compounds may be demethylated to the corresponding hydroxyl compounds without loss of optical activity. The methoxyl group can be retained as protecting group during chain lengthening operations to give for example polymethoxy or, after demethylation, polyhydroxy compounds.

EXPERIMENTAL

L-Malic acid (Fluka AG, Buchs, Switzerland) was used as initial material.

(*S*)-Dimethyl 2-hydroxysuccinate (dimethyl malate) was prepared from 50.0 g (0.373 mol) of *L*-malic acid by refluxing overnight with 500 ml of methanol containing 1 % of dry hydrogen chloride. After removal of the excess of methanol the crude ester was distilled. Yield 42.2 g (70.0 %) of b.p. 134–136°, 11 mm.

Dimethyl (*S*)-2-methoxysuccinate. To a mixture of 30.0 g (0.185 mol) of dimethyl malate and 105 g (0.740 mol) of methyl iodide was added during a period of 6 h 86 g (0.370 mol) of silver oxide (Fluka AG, Buchs, Switzerland). A spontaneous reaction occurred after initial

heating. A further portion (25 g) of methyl iodide was added when about 2/3 of the silver oxide had been used. The reaction mixture was finally heated for 2 h and, after cooling, triturated with ether. After filtration and removal of volatile material the product was distilled yielding 24.1 g (74.0 %) of the methoxy ester. B.p. 116°, 11 mm. Purity 98.5 % as indicated by GC with HI-EFF 4 B as stationary phase. $[\alpha]_{\text{D}}^{25} - 50.7^\circ$ (acetone; *l*, 0.2; *c*, 3.24); $[\alpha]_{\text{D}}^{25} - 42.2^\circ$ (chloroform; *l*, 0.2; *c*, 1.60). Lardon and Reichstein⁵ reported $[\alpha]_{\text{D}}^{16} - 47.8^\circ$ (*c*, 3.047 in acetone) and Fodor and Sóti⁶ $[\alpha]_{\text{D}}^{28} - 50.09^\circ$ (*c*, 3.27 in acetone).

(*S*)-2-Methoxysuccinic acid. 17.3 g (0.0550 mol) of $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ in 125 ml of distilled water was added to 8.7 g (0.0455 mol) of the above diester. The mixture was left for 1 h at room temperature and then for 2 h at 50°. After cooling the product was run through 70 g of Dowex 50 WX8 50/100 mesh ion exchange (H^+ form). Water was removed in a rotatory evaporator and the residue dried under vacuum over P_2O_5 . The acid had m.p. 78.8–80.2°. Yield 5.6 g (77.0 %).

(*S*)-Methyl 2-methoxy-3-carboxypropanoate (half-ester A). The free acid (5.5 g) was refluxed by heating in an oil bath at 60° for 4.5 h with 30 ml of acetyl chloride. The crude anhydride formed weighed 4.6 g after evaporation of volatile material. A mixture of 4.58 g (0.0353 mol) of the anhydride and 1.13 g (0.0353 mol) of methanol was heated at 50° for 4.5 h. 2.0 g of the reaction product which contained in addition to half-ester a small amount of diester (5 %) as indicated by GLC was chromatographed on silicic acid (50 g) (Mallinckrodt, 100–200 mesh, activated at 110° overnight) with ether:light petroleum (b.p. 40–60°) (35:65 v/v). After a small forerun (diester) 1.32 g of half-ester was eluted. It was a colorless viscous oil and had a purity of 98.5 % as indicated by GLC. $[\alpha]_{\text{D}}^{26} - 55.9^\circ$ (acetone; *l*, 0.2; *c*, 3.775). Purdie *et al.*¹ reported $[\alpha]_{\text{D}}^{20} - 57.64^\circ$ (*c*, 3.4874 in acetone).

(*S*)-Methyl 3-methoxy-3-carboxypropanoate (half-ester B). A solution of 5.68 mmol of potassium hydroxide dissolved in 5 ml of methanol was added drop-wise at +4° to 1.00 g (5.68 mmol) of the diester dissolved in 5 ml of methanol. The reaction mixture was stirred overnight at room temperature and then evaporated to dryness. 2 ml of distilled water was added to the residue and the solution extracted twice with light petroleum (b.p. 40–60°). The aqueous phase was acidified with diluted hydrochloric acid (pH 1), saturated with sodium chloride and extracted five times with ethyl acetate. The combined organic extracts were dried (MgSO_4) and evaporated to dryness. The crude half-ester was purified by chromatography on silicic acid as described for (A). Yield 0.82 g of half-ester (B), being a colourless viscous oil. $[\alpha]_{\text{D}}^{24} - 45.8^\circ$ (acetone, *l*, 0.2; *c*, 3.290).

Chain-lengthening of half-ester (A). A mixture of (A) (1.083 g, 6.70 mmol) and 2.68 g (13.40 mmol) of dodecanoic acid in 35 ml of dimethylformamide containing 203 mg (2.01 mmol) of triethylamine was electrolyzed at 0.4 A (100 V) between platinum electrodes for 6 h. The methoxyester obtained was worked up by addition of light petroleum (b.p. 40–60°) and water to the reaction product. The aqueous phase was extracted once more with light petroleum and the combined organic phases washed with sodium carbonate, (5 % solution in water) and with water until neutral. Yield after drying (MgSO_4) and evaporation of solvent 1.40 g. The product was chromatographed on 30 g of the silicic acid described with ether:light petroleum (b.p. 40–60°) mixtures. 458 mg of docosane was eluted with 1:99 (v/v) and 389 mg (21.4 %) of (S)-methyl 2-methoxytetradecanoate with 1:1 (v/v). GLC indicated satisfactory purity (98 %) and the mass spectrum was consistent with the structure assumed. $\alpha_D^{30} - 0.22^\circ$ (l, 0.2; c, 4.20, chloroform), $[\alpha]_D^{30} - 26.4^\circ$ and $[M]_D^{30} - 72$. A similar experiment using half-ester (B) was made. GLC of the reaction product indicated only 2 % of methoxyester.

Chain-lengthening of (S)-ethyl hydrogen 2-acetoxy succinate. A mixture of the acetoxy half-ester (4) 1.37 g (6.70 mmol) and 2.68 g (13.40 mmol) of dodecanoic acid was electrolyzed for 10 h in 40 ml of dimethylformamide containing 203 mg (2.09 mmol) of triethylamine (0.4 A, 120 V). The reaction product was worked up and purified as described. 303 mg (14 %) of (S)-ethyl 2-acetoxytetradecanoate was obtained.

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