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

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The isomeric half-esters of (S)-methoxy succinic 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. 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 \([\alpha]_D^{25} = 57.64^\circ\) (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. –OCH₃) 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 \([\alpha]_D^{25} = 55.9^\circ\) (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 dimethylformamide gave
a 21% yield of (S)-methyl 2-methoxytetradeca
canoate when halfester (A) was used. Practically no cross-coupling was observed for
half-ester (B). Similar experiments with (S)-
methyl 2-acetoxy-3-carboxypropanoate as an
optically active unit as used by Horn and
Pretorius gave a yield of 14% of the corre-
sponding 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
methoxy or hydroxyl groups. It has been shown
previously that the methoxyl compounds may
be demethylated to the corresponding hydroxyl
compounds without loss of optical activity.
The methoxyl group can be retained as a
protecting group during chain shortening opera-
tions 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-hydroxy succinate (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-hydroxymethyl succinate. 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 80 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.
[x]_D$^{20}$/ -50.7° (acetone; l, 0.2; c, 3.24); [x]_D$^{20}$/
-42.2° (chloroform; l, 0.2; c, 1.60). Lardon and
Reichstein reported [x]_D$^{25}$/ -47.8° (c, 3.047
in acetone) and Fodor and Sóti reported [x]_D$^{25}$/
-50.09° (c, 3.27 in acetone).

(S)-2-Methoxy succinic acid. 17.3 g (0.0550
mol) of Ba(OH)$_2.8$H$_2$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 rotary
evaporator and the residue dried under vacuum
over P$_2$O$_5$. 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 (0.0383 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 chromato-
graphed on silicic acid (50 g) (Mallinkrodt,
100–200 mesh, activated at 110° overnight)
with ether:light petroleum (b.p. 40–60°) (35:65
by 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. [x]_D$^{24}$/ -55.9° (acetone; l, 0.2; c, 3.775).
Purdie et al. reported [x]_D$^{24}$/ -37.64° (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 meth-
anol 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 evacu-
ated to dryness. 2 ml of distilled water was
added to the residue and the solution ex-
tracted 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
above (A). Yield 0.52 g of half-ester (B), being a
colourless viscous oil. [x]_D$^{24}$/ -45.8° (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°C) 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°C) 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. α_D^20 = –0.22° (l, 0.2; c, 4.20, chloroform), [α]_D^20 = –26.4° and [M]_D^20 –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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REFERENCES


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