31. *Reduction of Cholesteryl Benzoylformate (Phenylglyoxylate).*

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Cholesteryl benzoylformate has been prepared. Its partial asymmetric reduction to cholesteryl mandelate and its reductive scission to phenylethylene glycol have been examined and compared with the corresponding processes with (−)-menthyl benzoylformate.

The reduction of (−)-menthyl benzoylformate (phenylglyoxylate) can take place in two stages to give (−)-menthyl mandelate or, with scission, phenylethylene glycol. We have made a number of observations, the results of which are tabulated below and compared, where possible, with those of previous workers. From them we conclude that all the reductions go in the lævorotatory sense. Sodium borohydride is the most stereoselective reducing agent used, but it was necessary to have boric acid present in order to prevent saponification of the esters by the alkali formed.

Reference	Reducing agent	Rotation of (−)-menthyl mandelate in EtOH		Rotation of HO·CHPh·CH_2·OH
McKenzie [1]	Al–Hg in Et_2O–H_2O	$[\alpha]_D^{18}$ −76·9°		
		$[\alpha]_D^{20}$ −77·6°		
McKenzie and Humphries [2]	,, ,,	$[\alpha]_D^{18\cdot5}$ −81·5°		
		$[\alpha]_D^{15}$ −80·3°		
Present work	,, ,,	$[\alpha]_D^{22\cdot6}$ −76·3°	LiAlH$_4$	$[\alpha]_D^{25}$ −4·4° ($CHCl_3$)
		$[\alpha]_{5461}^{22\cdot6}$ −90·8°	→	$[\alpha]_D^{20}$ −2·95° (EtOH)
Prelog *et al.*[3]	$LiAlH_4$	—		$[\alpha]_D^{21}$ −3·4° (EtOH)
Present work	,,	—		−5·2° ($CHCl_3$)
Present work	$NaBH_4$	$[\alpha]_D^{24\cdot8}$ −91·45°	LiAlH$_4$	
		$[\alpha]_{5461}^{24\cdot8}$ −110·1°	→	4 $[\alpha]_D^{22\cdot8}$ −18·4° ($CHCl_3$)

(−)-Menthyl (±)-mandelate has $[\alpha]_{5461}^{19\cdot6}$ −87·3° (EtOH).
(−)-Menthyl (−)-mandelate has $[\alpha]_{5461}^{19}$ −163·5° (EtOH) (Jamison and Turner [4]).

Cholesteryl benzoylformate has also been prepared, and has been examined with the results tabulated. All these reductions go in the dextrorotatory sense. Judged by the rotations of the phenylethylene glycols, aluminium amalgam is the most stereospecifically efficient in this case.

Reducing agent	Rotation of cholesteryl mandelate in $CHCl_3$		Rotation of HO·CHPh·CH_2·OH
Al–Hg	$[\alpha]_D^{22\cdot6}$ −16·87°	LiAlH$_4$ →	$[\alpha]_D^{21\cdot4}$ +2·66° ($CHCl_3$)
$NaBH_4$	$[\alpha]_D^{25}$ −18·69°	LiAlH$_4$ →	$[\alpha]_D^{25\cdot2}$ +1·79° (EtOH)
$Al(OPr^i)_3$	$[\alpha]_D^{21}$ −28·26°	LiAlH$_4$ →	$[\alpha]_D^{22}$ +1·09° ($CHCl_3$)
$LiAlH_4$	—		$[\alpha]_D^{21\cdot8}$ +1·14° (EtOH)

Cholesteryl benzoylformate melts first at 119—120° and solidifies to a more stable form, m. p. 128—129°, a blue-green fluorescence usually appearing between 119° and 129°. The two forms sometimes separate side-by-side from an ethanolic solution.

The sparing solubility of cholesteryl benzoylformate in ethanol prevented a study being made of the expected mutarotation based on hemiacetal formation.

Experimental

Reduction of (±)-Mandelic Acid by Lithium Aluminium Hydride.—(±)-Mandelic acid (10 g., 0·065 mole) in dry ether (200 c.c.) was added during 30 min. to lithium aluminium hydride (5 g.,

[1] McKenzie, *J.*, 1904, **85**, 1249.
[2] McKenzie and Humphries, *J.*, 1909, **95**, 1105.
[3] Prelog, Wilhelm, and Bright, *Helv. Chim. Acta*, 1954, **37**, 2217.
[4] Jamison and Turner, *J.*, 1942, 611.

0·13 mole) in dry ether (150 c.c.). Then the mixture was boiled under reflux for 2 hr., cooled, and treated with water and then with dilute sulphuric acid. The aqueous layer was extracted with ether, and the extracts were dried (K_2CO_3) and evaporated, giving phenylethylene glycol, m. p. 62—65° (7 g., 77%).

Reduction of (−)-Mandelic Acid by Lithium Aluminium Hydride.—(−)-Mandelic acid, m. p. 132—134°, $[\alpha]_D^{23\cdot6}$ −154·3° ± 0·6°, $[\alpha]_{5461}^{23\cdot6}$ −184·7° ± 0·6° (*c* 1·6430 in H_2O) (8·83 g., 0·05 mole), with lithium aluminium hydride (5 g., 0·13 mole) gave phenylethylene glycol (6·9 g., 87%). After being sublimed under reduced pressure this had m. p. 66—67°, $[\alpha]_D^{24}$ −39·9° ± 0·3°, $[\alpha]_{5461}^{24}$ −47·7° ± 0·3° (*l* 1, *c* 6·562 in EtOH), and $[\alpha]_D^{23}$ −63·8° ± 0·2°, $[\alpha]_{5461}^{23}$ −75·8° ± 0·2°, (*l* 1, *c* 9·522 in $CHCl_3$). Prelog and his co-workers [3] give $[\alpha]_D^{20}$ +40·6° (*l* 2, *c* 3·23, in EtOH) for phenylethylene glycol obtained from (+)-mandelic acid with $[\alpha]_D^{18}$ +157·5° (*l* 2, *c* 3·50, in H_2O).

Reduction of (−)-Menthyl Benzoylformate.—(a) *By lithium aluminium hydride.* A solution of (−)-menthyl benzoylformate (10 g., 0·06 mole) in dry ether (200 c.c.) was added in small portions during 30 min. to a suspension of lithium aluminium hydride (3·3 g., 0·08 mole) in dry ether (200 c.c.). Then the mixture was boiled under reflux for 30 min., cooled in ice, and worked up normally. The menthol obtained weighed 4·9 g. (90%). 4·2 g. (89%) of phenylethylene glycol were obtained, with m. p. 62—66°, $[\alpha]_D^{21}$ −3·4° ± 0·1°, $[\alpha]_{5461}^{21}$ −3·9° ± 0·1° (*c* 9·15 in EtOH), and $[\alpha]_D^{20}$ −5·2° ± 0·1°, $[\alpha]_{5461}^{20}$ −5·9° ± 0·1° (*c* 10·88 in $CHCl_3$). The optical purity was 8%. Prelog and his co-workers [3] gave m. p. 62—63°, $[\alpha]_D$ −2·95° (*l* 2, *c* 10·6 in EtOH).

(b) *By aluminium amalgam.* The (−)-ester (5 g., 0·017 mole) in moist ether (150 c.c.) was added to aluminium amalgam (~5 g.). After the reaction had subsided, the whole was shaken for 5 hr., then filtered, and the residue was washed with ether. The solution was dried (Na_2SO_4) and evaporated, giving (−)-menthyl mandelate (4·2 g., 80%), m. p. 84—86°, $[\alpha]_D^{22\cdot6}$ −76·3° ± 0·5°, $[\alpha]_{5461}^{22\cdot6}$ −90·8° ± 0·5° (*c* 1·8480 in EtOH).

To a solution of lithium aluminium hydride (1·5 g., 0·03 mole) in dry ether (75 c.c.) was added in small portions a solution of the foregoing (−)-menthyl mandelate (2 g., 0·006 mole) in dry ether (100 c.c.) at room temperature during 15 min. The products were isolated in the usual way, and yielded phenylethylene glycol (0·82 g., 89%), m. p. 64—66°, $[\alpha]_D^{23}$ −4·4° ± 0·25°, $[\alpha]_{5461}^{23}$ −5·2° ± 0·25° (*l* 1, *c* 8·340, in $CHCl_3$) (Found: C, 69·8; H, 7·3. Calc. for $C_8H_{10}O_2$: C, 69·5; H, 7·3%). The optical purity was 7%.

(c) *By sodium borohydride.* A solution of sodium borohydride (2·4 g., 0·06 mole) in water (40 c.c.) was added during 20 min. to a cooled (0°) and stirred mixture of (−)-menthyl benzoylformate (4 g., 0·013 mole), ethyl alcohol (200 c.c.), water (40 c.c.), and boric acid (8 g.). After being stirred for another 20 min. the mixture was diluted with water and acidified with dilute sulphuric acid. (−)-Menthyl mandelate was filtered off, washed with water, dissolved in chloroform, and dried (Na_2SO_4). After the removal of chloroform there was obtained (−)-menthyl mandelate (2·3 g., 57·5%), m. p. 82—84°, $[\alpha]_D^{24\cdot8}$ −91·45° ± 0·8°, $[\alpha]_{5461}^{24\cdot8}$ −110·1° ± 0·8° (*c* 1·1700 in EtOH) (Found: C, 74·6; H, 8·8. Calc. for $C_{18}H_{26}O_3$: C, 74·4; H, 9·0%).

Reduction of this crude (−)-menthyl mandelate (2 g., 0·006 mole) in dry ether (100 c.c.) with lithium aluminium hydride (1·5 g., 0·03 mole) in dry ether (75 c.c.) gave phenylethylene glycol (0·82 g., 89%), m. p. 58—62°, $[\alpha]_D^{22\cdot8}$ −18·44° ± 0·24°, $[\alpha]_{5461}^{22\cdot8}$ −21·5° ± 0·24° (*l* 1, *c* 9·1340 in $CHCl_3$) (optical purity 29%) (Found: C, 69·5; H, 7·5%).

(d) *By aluminium isopropoxide.* A mixture of (−)-menthyl benzoylformate (4 g.), aluminium isopropoxide (10 g.), and isopropyl alcohol (120 c.c.) was boiled under reflux for 1 hr. After removal of the acetone formed and the solvent, the residue was treated with ice-cold dilute sulphuric acid. Ether-extraction of the product, followed by the usual procedure, gave (−)-menthyl mandelate (2·8 g., 70%) as a colourless liquid. After 3 weeks it had changed to a wax. The smell of menthol was perceptible. It had $[\alpha]_D^{22\cdot4}$ −39·7° ± 0·4°, $[\alpha]_{5461}^{22\cdot4}$ −47·2° ± 0·4° (*c* 2·2470 in $CHCl_3$). In view of the contamination of this (−)-menthyl mandelate with menthol, no attempt was made to analyse or to reduce it with lithium aluminium hydride.

Preparation of Cholesteryl Benzoylformate.—Benzoylformyl chloride (20·8 g., 0·12 mole) in benzene (160 c.c.) was added in small portions to a solution of cholesterol (40 g., 0·1 mole) in benzene (240 c.c.) and pyridine (160 c.c.) during 30 min. at room temperature. The mixture was left overnight, then extracted twice with water, twice with dilute hydrochloric acid, twice with 5% sodium hydrogen carbonate solution, and twice with water. Evaporation of the benzene gave crude *cholesteryl benzoylformate* which, crystallised twice from acetone, formed rectangular plates (46 g., 86%), m. p. 119—120°, remelting point 128—129° (at the melting

range it showed blue-green fluorescence), $[\alpha]_D^{26\cdot6}$ $-15\cdot01° \pm 0\cdot8°$, $[\alpha]_{5461}^{26\cdot6}$ $-16\cdot7° \pm 0\cdot8°$ (*c* 1·1790 in $CHCl_3$) (Found: C, 81·0; H, 8·55. $C_{35}H_{50}O_3$ requires C, 81·0; H, 9·7%).

Reduction of Cholesteryl Benzoylformate.—(a) *With lithium aluminium hydride.* A solution of cholesteryl benzoylformate (10 g., 0·019 mole) in dry ether (250 c.c.) was added during 30 min. to a suspension of lithium aluminium hydride (3·3 g., 0·08 mole) in dry ether (180 c.c.). The mixture was worked up in the usual way. The residue was washed with water. The cholesterol (7·2 g., 97%) had m. p. 143—145°.

Evaporation of the filtrate yielded phenylethylene glycol. After sublimation under reduced pressure it (1·35 g.) had m. p. 63—67°, $[\alpha]_D^{21\cdot8}$ $+1\cdot14° \pm 0\cdot16°$, $[\alpha]_{5461}^{21\cdot8}$ $+1\cdot37° \pm 0\cdot15°$ (*c* 6·1240 in EtOH) (optical purity 2·7%) (Found: C, 70·0; H, 7·6%).

(b) *With aluminium amalgam.* A solution of cholesteryl benzoylformate (5 g.) in moist ether (150 c.c.) was shaken with aluminium amalgam (~5 g.) for 5 hr., then filtered and dried (Na_2SO_4). The *cholesteryl mandelate* (4 g., 78%) obtained after the removal of ether had m. p. 148—153°, $[\alpha]_D^{22\cdot6}$ $-16\cdot87° \pm 0\cdot5°$, $[\alpha]_{5461}^{22\cdot6}$ $-21\cdot6° \pm 0\cdot5°$ (*c* 1·8820 in $CHCl_3$) (Found: C, 81·0; H, 10·15. $C_{35}H_{52}O_3$ requires C, 80·7; H, 10·1%).

To a solution of lithium aluminium hydride (1·5 g., 0·03 mole) in dry ether (75 c.c.) was added in small portions a solution of the cholesteryl mandelate (2 g., 0·003 mole) in dry ether (100 c.c.) during 25 min. The products, isolated in the usual way, afforded phenylethylene glycol (0·29 g., 54·7%), m. p. 58—64°, $[\alpha]_D^{21\cdot4}$ $+2\cdot66° \pm 0\cdot8°$, $[\alpha]_{5461}^{21\cdot8}$ $+3\cdot35° \pm 0\cdot8°$ (*l* 1, *c* 2·472 in $CHCl_3$) (optical purity 4%) (Found: C, 69·8; H, 7·65%).

(c) *With sodium borohydride.* Sodium borohydride (1·2 g., 0·03 mole) was added in small portions to a mixture of cholesteryl benzoylformate (2 g., 0·003 mole), dioxan (250 c.c.), water (16 c.c.), and boric acid (4 g.). The pH of the mixture, after the reaction was completed, was 7. The dioxan was removed by distillation. The mixture was diluted with water, acidified with dilute sulphuric acid, and extracted with ether four times. The combined ethereal extracts were dried (Na_2SO_4). Removal of ether gave cholesteryl mandelate (1·95 g., 93%), m. p. 147—150°, $[\alpha]_D^{25\cdot4}$ $-18\cdot69° \pm 0\cdot7°$, $[\alpha]_{5461}^{25\cdot4}$ $-20\cdot77° \pm 0\cdot7°$ (*c* 1·3240 in $CHCl_3$) (Found: C, 80·2; H, 10·1%).

Reduction of this ester (1·4 g., 0·002 mole) in dry ether (75 c.c.) with lithium aluminium hydride (1 g., 0·026 mole) in ether (50 c.c.) gave phenylethylene glycol (0·17 g., 46%), m. p. 64—66°, $[\alpha]_D^{24\cdot2}$ $+1\cdot85° \pm 1°$, $[\alpha]_{5461}^{24\cdot2}$ $+3\cdot08° \pm 1°$ (*l* 1, *c* 1·7220 in $CHCl_3$), and $[\alpha]_D^{25\cdot2}$ $+1\cdot79° \pm 1\cdot8°$, $[\alpha]_{5461}^{25\cdot2}$ $+3\cdot76° \pm 1\cdot8°$ (*l* 1, *c* 1·118 in EtOH) (optical purity 2·8%) (Found: C, 68·45; H, 7·0%).

(d) *With aluminium isopropoxide.* Cholesteryl benzoylformate (3 g.) was boiled with aluminium isopropoxide (7·5 g.) and isopropyl alcohol (180 c.c.) for 3½ hr. After removal of the acetone formed and the solvent, the residue was treated with ice-cold dilute sulphuric acid. Ether-extraction followed by the usual procedure gave cholesteryl mandelate (3 g., 92%), m. p. 125—131°, $[\alpha]_D^{21}$ $-28\cdot26° \pm 0\cdot3°$, $[\alpha]_{5461}^{21}$ $-33\cdot8° \pm 0\cdot3°$ (*c* 2·9140 in $CHCl_3$) (Found: C, 81·2; H, 11·15%).

This (2 g.) in dry ether (100 c.c.) was reduced with lithium aluminium hydride (1·15 g.) in ether (100 c.c.), giving phenylethylene glycol (0·17 g., 32%), m. p. 62—64°, $[\alpha]_D^{22}$ $+1\cdot09° \pm 1°$, $[\alpha]_{5461}^{21}$ $+1\cdot27° \pm 1°$ (*l* 1, *c* 1·738, in $CHCl_3$) (optical purity 1·5%) (Found: C, 68·8; H, 7·4%).

Dimorphism of Cholesteryl Benzoylformate.—Cholesteryl benzoylformate crystallised from ethanol in two forms that were separated by hand-picking. One formed leaflets, m. p. 119—120°. The stable form, rectangular plates melted at 128—129°. A blue-green fluorescence appeared between melting and re-solidification.

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