Wool Wax. Part VI. The Synthesis and Stereochemistry of the Straight-chain α-Hydroxy-acids.*

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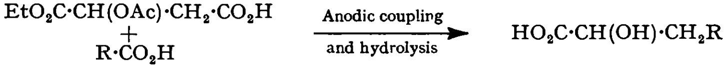
A series of optically active straight-chain α-hydroxy-acids of known configuration has been synthesised from an optically active half-ester of (−)-malic acid by anodic coupling with aliphatic acids. The naturally occurring α-hydroxy-acids of wool wax and the derived 1 : 2-diols, phrenosinic (cerebronic) acid, and the 2-hydroxypentadecanoic acid from ustilic acids are assigned the $\mathrm{D_S}$-configuration.

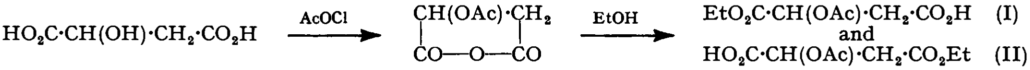
CONFIGURATIONAL correlation of optically active α-hydroxy-acids is unusually difficult, partly because higher homologues cannot be derived from lower ones by applying conventional methods of chain building to the carboxyl group, and partly because other chemical methods, which have been used for the correlation of the lower homologues (Levene *et al.*, *J. Biol. Chem.*, 1927, **71**, 465; 1928, **77**, 555), would be very laborious with higher homologues. For these reasons, only lactic acid, 2-hydroxybutanoic acid,† and 2-hydroxypentanoic acid have been directly correlated with glyceraldehyde, the stereochemical reference standard. However, Lemieux (*Canad. J. Chem.*, 1953, **31**, 396) has attempted a correlation of several naturally occurring higher α-hydroxy-acids by comparing the rotations of these acids and some of their derivatives with those of the corresponding lower homologues; but a formal chemical correlation has yet to be made. Our interest in the α-hydroxy-acids of wool wax (Horn, Hougen, and von Rudloff, *Chem. and Ind.*, 1953, 106, and Part V *) has led us to devise a simple synthetical method to accomplish this.

An optically active form of the monoethyl ester of acetylmalic acid has been used to obtain optically active 2-hydroxybutanoic, 2-hydroxyhexanoic, 2-hydroxyoctanoic, 2-hydroxydecanoic, and 2-hydroxyhexadecanoic acid by anodic coupling with the appropriate normal carboxylic acids in the following manner:



$$\begin{matrix}EtO_2C\cdot CH(OAc)\cdot CH_2\cdot CO_2H\\ +\\ R\cdot CO_2H\end{matrix} \xrightarrow[\text{and hydrolysis}]{\text{Anodic coupling}} HO_2C\cdot CH(OH)\cdot CH_2R$$

The required malic ester has been conveniently prepared by the reactions:



$$HO_2C\cdot CH(OH)\cdot CH_2\cdot CO_2H \xrightarrow{AcOCl} \begin{matrix}CH(OAc)\cdot CH_2\\ | \qquad\qquad | \\ CO\text{—}O\text{—}CO\end{matrix} \xrightarrow{EtOH} \begin{matrix}EtO_2C\cdot CH(OAc)\cdot CH_2\cdot CO_2H \quad (I)\\ \text{and}\\ HO_2C\cdot CH(OAc)\cdot CH_2\cdot CO_2Et \quad (II)\end{matrix}$$

Although the product is a mixture of two isomers (I) and (II), it is not necessary to isolate the required acid (I), because its isomer (II), which has an α-substituent, does not undergo

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* Part V, *J.*, 1954, 177.

† Geneva numbering, $CO_2H = 1$.

anodic coupling. The properties of the acids synthesised in this manner from the naturally occurring (—)-malic acid (lævorotatory in dilute aqueous solutions) are summarised in section A of the Table.

A comparison of the properties of the naturally occurring α-hydroxy-acids, summarised in section C of the Table, with those synthesised from (—)-malic acid, clearly shows that they belong to the enantiomorphous series, which would be obtained from (+)-malic acid. Thus the 2-hydroxyhexadecanoic acid obtained from (—)-malic acid on admixture in exactly equal proportions with the 2-hydroxyhexadecanoic acid from wool wax was identical with a (±)-mixture synthesised from (±)-malic acid.

In section B of the Table, the properties of (+)-2-hydroxybutanoic acid and (+)-2-hydroxypentanoic acid are compared with those of (+)-lactic acid, with which they have been correlated chemically by Levene and his co-workers (*loc. cit.*). The dextrorotatory 2-hydroxy-butanoic and -pentanoic acids, as shown, are reported by Levene to yield lævorotatory sodium salts. On the other hand, the lævorotatory 2-hydroxybutanoic acid obtained by us from (—)-malic acid was found to yield, unexpectedly, a lævorotatory sodium salt. However, Levene did not measure the rotations of the pure acids in water, as we have done; he liberated the acids from their barium salts with an excess of hydrochloric acid and measured the rotations of the resulting solution directly. When our acid was examined under these conditions, it was also dextrorotatory (see section A of the Table). When the solution was diluted with water and the rotation measured in a longer tube, it became lævorotatory (cf. Fredga, Tenow, and Billström, *Arkiv Kemi, Min., Geol.*, 1943, **16**, *A*, No. 21). Similar effects of concentration, pH, and salts on the sign of rotation are well known (Stubbs, *J.*, 1911, **99**, 2268). It is clear then, that the lævorotatory 2-hydroxybutanoic acid from (—)-malic acid is the same as Levene's acid, which he erroneously reported to be dextrorotatory. While this observation does not alter the configurational correlation of (—)-sodium lactate with (—)-sodium 2-hydroxybutanoate, it becomes necessary to recognise (+)-lactic acid to have the same configuration as (—)-2-hydroxybutanoic acid, provided that Levene's chemical correlation is valid; and it almost certainly is valid, since our correlation of (—)-2-hydroxybutanoic acid with (—)-malic acid, as will be seen later, offers confirmation of this step by another route. Also this observation does not affect Levene's rule (*J. Biol. Chem.*, 1927, **75**, 337) that α-hydroxy-

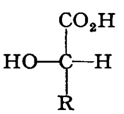
		$[\alpha]_D$ of acid				$[\alpha]_D$ of Na salt		$[\alpha]_D$ of Me ester	
R in (I)	M. p.	H_2O	Aq. HCl	EtOH	$CHCl_3$	H_2O	50% EtOH	Homog.	$CHCl_3$
Section A									
C_2H_5 ...	52·7—53·5°	−3·0°	+1·2°	−4·4°	+6·4°	−13·2°	—	—	—
C_4H_9 ...	61·0—61·6	−1·6	+1·3	−1·5	+5·6	−14·1	—	—	—
C_6H_{13} ...	70·2—70·6	+3	—	+1·5	+6·2	−10·3	−18°	+2·8°	+11°
C_8H_{17}	77·6—78·0	—	—	+1·6	+5·3	—	−15	+3·0	—
$C_{14}H_{29}$...	93·3—93·6	—	—	+1	+2·7	—	−15	—	—
Section B									
CH_3 ...	—	+2·67— +3·8 [a]	—	—	—	− 10·5 [b]	—	−8·22 [c] *	—
C_2H_5 ...	55·0—55·5	−2·5 [d]	+2·3 [e]	−3·8 [d]	+6·8 [d]	− 8·7 [f]	—	−3·83 [e] *	—
C_3H_7 ...	—	—	+1·4 [f]	—	—	− 2·7 [f]	−20·7 [g]	−5·1 [h] *	+16 [h]
Section C									
$C_{12}H_{25}$ [i]	88·2—88·5	—	—	—	−3·1	—	—	—	−3·6
$C_{14}H_{29}$ [i]	93·3—93·5	—	—	−1	−3·2 [j]	—	+16	—	−3·6
$C_{24}H_{49}$...	100·5—101 [k]	—	—	—	—	—	—	—	—
	102·3—102·6 [m]	—	—	—	−1·76	—	—	—	—
$C_{13}H_{27}$ [g]	89·5—90·0	—	—	−2·1	—	—	+ 4·2	—	—

* Et ester.

[a] Jungfleisch and Godchot, *Compt. rend.*, 1905, **140**, 720. [b] Levene and Kuna, *J. Biol. Chem.*, 1941, **141**, 391. [c] Patterson and Lawson, *J.*, 1929, 2047. [d] Fredga, Tenow, and Billström, *Arkiv Kemi, Min., Geol.*, 1943, **16**, *A*, No. 21. [e] Levene and Haller, *J. Biol. Chem.*, 1927, **74**, 343. [f] Levene, Mori, and Mikeska, *ibid.*, 1927, **75**, 337. [g] Lemieux, *Canad. J. Chem.*, 1953, **31**, 396. [h] α_D for homogeneous value; *idem, ibid.*, 1951, **29**, 681. [i] Part V, *loc. cit.* [j] +3·6° in pyridine. [k] Klenk and Clarenz, *Z. physiol. Chem.*, 1939, **257**, 268. [l] *Idem, ibid.*, 1928, **174**, 221; $[\alpha]_D$ of acid +3·41° in pyridine. [m] Chibnall, Piper, and Williams, *Biochem. J.*, 1936, **30**, 100; $[\alpha]_D$ of acid +3·33° in pyridine.

acids with the configuration of L(+)-lactic acid show a shift in the rotation towards the left on passing from the free acids into their salts, and conversely; and, as is shown in the Table, this rule is now extended to the higher homologues, where the rotations of the free acids, measured in ethanol, are compared with those of their sodium salts in 50% ethanol.

The acids prepared by our method from (−)-malic acid have the configuration (III; R = alkyl) and, by analogy with the amino-acid convention, can be denoted as L$_S$ (Rosanoff, *J. Amer. Chem. Soc.*, 1906, **28**, 114; Wolfrom, Lemieux, Olin, and Weisblat, *ibid.*, 1949, **71**, 4057; cf. I.U.P.A.C. rules, *J.*, 1951, 3522).*


$HO{-}\overset{CO_2H}{\underset{R}{C}}{-}H$

(III)

In conformity with the above proposals, the straight-chain α-hydroxy-acids of wool wax; the 1 : 2-diols of wool wax, which may be obtained from them by reduction with lithium aluminium hydride (Part IV, *J.*, 1953, 3533); phrenosinic (cerebronic) acid of brain (the stereoisomer of 2-hydroxytetracosanoic acid dextrorotatory in pyridine, Chibnall *et al.*, *Biochem. J.*, 1936, **30**, 100); and the 2-hydroxypentadecanoic acid obtained from ustilic acids (Lemieux, *loc. cit.*) are assigned the D$_S$-configuration. Although the chemical correlations made here confirm the indirect correlations of Lemieux, this correlation is partly fortuitous because, in passing up the homologous series from D$_S$-(−)-lactic acid to the naturally occurring 2-D$_S$-(−)-hydroxyhecadecanoic acid, there are two changes of sign (cf. Table); the first occurs as one passes from lactic acid to 2-hydroxypropionic acid, and the second, predicted on theoretical grounds (Levene, *J. Biol. Chem.*, 1928, **79**, 475) and confirmed by us, between 2-hydroxyhexanoic acid and 2-hydroxyoctanoic acid.

Since this paper was submitted for publication, a paper by Serck-Hanssen, Ställberg-Stenhagen, and Stenhagen (*Arhiv Kemi*, 1953, **5**, 203) has come to our notice. In it the possibility of synthesising long-chain optically active hydroxy-acids from smaller optically active acids by the anodic coupling method is suggested. It seems appropriate to record that we have extended our synthesis to unsaturated hydroxy-acids and have prepared, for example, 2-D$_S$-hydroxy-*cis*-tetracos-15-enoic acid (2-hydroxynervonic acid) from (+)-malic acid and erucic acid.

EXPERIMENTAL

*Ethyl Hydrogen 2-*L$_S$*-Acetoxysuccinates.*—Pure L$_S$-(−)-malic acid (naturally occurring form lævorotatory in dilute aqueous solutions) (25 g.) was obtained commercially or prepared by resolution with cinchonine (Dakin, *J. Biol. Chem.*, 1924, **59**, 9); the cinchonine (−)-malate formed was recrystallised at least 3 times; this is necessary if a purity of greater than 98% (−)-malic is required. The yield, based on the (±)-malic acid used, was *ca.* 10%. The acid was heated with acetyl chloride (75 c.c.) for 3 hr. The excess of chloride was removed at reduced pressure on a water-bath. To the residue was added dry ethanol (12 c.c.), and the mixture was heated for ½ hr. at 50°. Ethyl acetate (2 c.c.) was added and the crystal mass, which formed on cooling, was filtered off (23 g. or 60%). The *half-ester* crystallised from ethyl acetate in colourless needles, m. p. 50—51°, $[\alpha]^{22}_{D}$ −29·1° (*l*, 0·5; *c*, 10·5 in EtOH) (Found: C, 47·0; H, 6·0; Ac, 20·9%; equiv., 203. $C_8H_{12}O_6$ requires C, 47·1; H, 5·9; Ac, 21·1%; equiv., 204).

Ethyl Hydrogen DL*-2-Acetoxysuccinates.*—This mixture was prepared from (±)-malic acid as described above for the optically active forms. It crystallised from ethyl acetate in needles, m. p. 70·4—71·2° (Found: C, 47·3; H, 6·1; Ac, 21·2%; equiv., 203).

*2-*L$_S$*-Hydroxybutanoic Acid.*—Mixed ethyl hydrogen L$_S$-2-acetoxysuccinates (10 g.; the same amount was used in all subsequent electrolyses) were dissolved in methanol (80 c.c.) containing sodium (0·1 g.). Acetic acid (10 c.c.) was added and the mixture electrolysed in a cell containing a stainless-steel cooling-coil and two platinum-foil electrodes (25 × 35 cm.) reinforced with platinum wire (0·5 mm. diam.) and set 2 mm. apart. A current of about 1 amp. at about 50 v was passed until the mixture became neutral (10—15 hr.). The temperature in the vicinity of the plates was not allowed to exceed 35°. Sufficient water was added to make a 50% (v/v) alcoholic solution and the mixture was extracted with hexane. The hexane extract was washed with a dilute solution of potassium hydrogen carbonate and the hexane distilled off. The remaining *ethyl* L$_S$*-2-acetoxybutanoate* (5·1 g.) was distilled and the fraction of b. p. 92°/21 mm. retained (3·2 g.). It was refluxed for 30 min. with potassium hydroxide (3·2 g.) in water (40 c.c.).

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* The Cahn–Ingold sequence rule (*J.*, 1951, 621) and Klyne's proposals (*Chem. and Ind.*, 1951, 1022) both lead to the prefix L.

To the cooled solution sufficient N-hydrochloric acid was added to neutralise 95% of the potassium hydroxide used. The solution was continuously extracted with ether for 2 hr. The ethereal extract was dried (Na_2SO_4) and evaporated, to yield L_s-2-*hydroxybutanoic acid* (1·5 g.). Volatile impurities were removed by steam-distillation. The acid crystallised from carbon tetrachloride–hexane in needles, m. p. 52·7—53·5° (Found: C, 46·4; H, 7·8%; equiv., 105. $C_4H_8O_3$ requires C, 46·1; H, 7·7%; equiv., 104), $[\alpha]_D^{16}$ −3·0° (*l*, 1; *c*, 6·19 in H_2O), $[\alpha]_D^{16}$ +6·4° (*l*, 0·5; *c*, 11·03 in $CHCl_3$), $[\alpha]_D^{16}$ −4·4° (*l*, 0·5; *c*, 8·53 in EtOH). Fredga *et al.* (*loc. cit.*) record m. p. 55·0—55·5°, $[\alpha]_D^{25}$ −2·5° (*l*, 2; *c*, 2·24 in H_2O), $[\alpha]_D^{25}$ −3·8° (*l*, 2; *c*, 2·15 in EtOH), and $[\alpha]_D^{25}$ +6·8° (*l*, 2; *c*, 2·48 in $CHCl_3$).

Determination of the Specific Rotation in the Manner described by Levene and Haller (J. Biol. Chem., 1927, **74**, 346).—L_s-2-Hydroxybutanoic acid (233 mg.), barium hydroxide (175 mg.), and concentrated hydrochloric acid (0·25 c.c.) were dissolved in water (up to 2 c.c.): the solution had $[\alpha]_D^{16}$ +1·2° (*l*, 0·5; *c*, 11·7). Levene and Haller (*loc. cit.*) record $[\alpha]_D^{22}$ +2·3°. The solution was diluted with water (up to 9 c.c.) and the rotation again measured ($[\alpha]_D^{16}$ −1·5°).

Sodium L_s-2-*Hydroxybutanoate*.—A solution of the acid in water was exactly neutralised with sodium hydroxide; the rotation measured directly was $[\alpha]_D^{20}$ −13·2° (*l*, 1; *c*, 4·17). Levene *et al.* (*J. Biol. Chem.*, 1927, **75**, 337) record $[M]_D$ −9·6°, *i.e.*, $[\alpha]_D$ −8·7° in water (the temperature and concentration are not given).

L_s-2-*Hydroxyhexanoic Acid*.—This *acid* was prepared from pure butanoic acid (18 c.c.) as described for L_s-2-hydroxybutanoic acid. The product on distillation yielded ethyl L_s-2-*acetoxyhexanoate* (5·5 g.), b. p. 120—124°/27—28 mm. The acid was recovered and purified as before. It crystallised from *iso*propyl ether–hexane (1 : 5) in needles, m. p. 61·0—61·6°, $[\alpha]_D^{18}$ +5·6° (*l*, 1; *c*, 6·84 in $CHCl_3$), $[\alpha]_D^{18}$ −1·5° (*l*, 1; *c*, 6·76 in EtOH), $[\alpha]_D^{18}$ −1·6° (*l*, 1; *c*, 4·40 in H_2O) (Found: C, 54·7; H, 9·2%; equiv., 134. $C_6H_{12}O_3$ requires C, 54·5; H, 9·2%; equiv., 132). To the pure acid (200 mg.) was added concentrated hydrochloric acid (0·2 c.c.) in water (up to 2 c.c.): $[\alpha]_D^{18}$ +1·3°. The solution was diluted with water (up to 9 c.c.) and the rotation measured: $[\alpha]_D^{18}$ −1·5°.

Sodium L_s-2-hydroxyhexanoate, prepared in solution, had $[\alpha]_D^{18}$ −14·1° (*l*, 2; *c*, 3·55 in H_2O).

L_s-2-*Hydroxyoctanoic Acid*.—This *acid*, prepared as described above from hexanoic acid [9·6 g., purified by fractional distillation and crystallisation (cf. Coulson and Jones, *J. Soc. Chem. Ind.*, 1946, **65**, 169), had f. p. −4·6°, n_D^{20} 1·4162. Ralston ("Fatty Acids and Their Derivatives," John Wiley and Sons, New York, 1948, p. 20) records f. p. −3·9°, n_D^{20} 1·41635]. It crystallised from *iso*propyl ether in needles, m. p. 70·2—70·6° (2·8 g.) (*l*, 0·5; *c*, 9·05 in $CHCl_3$), $[\alpha]_D^{19}$ +1·5° (*l*, 0·5; *c*, 6·80 in EtOH), $[\alpha]_D^{19}$ +3° (*l*, 0·5; *c*, 4·27 in H_2O containing 10—15% of MeOH) (Found: C, 60·0; H, 10·2%; equiv., 160. $C_8H_{16}O_3$ requires C, 60·0; H, 10·1%; equiv., 160). $[\alpha]_D^{19}$ +6·2°.

Sodium L_s-2-hydroxyoctanoate, prepared in aqueous solution by titration with 0·185N-sodium hydroxide, had $[\alpha]_D^{19}$ −10·3° (*l*, 0·5; *c*, 10·10 in H_2O), $[\alpha]_D^{19}$ −18° (*l*, 0·5; *c*, 5·05 in 50% aq. EtOH).

Methyl L_s-2-*Hydroxyoctanoate*.—This ester was prepared from the acid with methanol and sulphuric acid; it was a colourless liquid, n_D^{18} 1·4342, d_4^{16} 0·9686, b. p. 118°/22 mm., $[\alpha]_D^{16}$ +2·80° (*l*, 0·5; homog.) and $[\alpha]_D^{16}$ +11° (*l*, 0·5; *c*, 10·03 in $CHCl_3$).

L_s-2-*Hydroxydecanoic Acid*.—This *acid* (2·5 g.) was prepared from pure octanoic acid [6·4 g.; prepared as before by fractional distillation and crystallisation (cf. Coulson and Jones, *loc. cit.*), f. p. 16·1°, $n_D^{25\cdot2}$ 1·4256. Ralston (*op. cit.*, p. 23) records f. p. 16·3°, n_D^{20} 1·4285]. It crystallised from *iso*propyl ether in fine needles, m. p. 77·6—78·0°, $[\alpha]_D^{24}$ +5·3° (*l*, 0·5; *c*, 8·6 in $CHCl_3$), $[\alpha]_D^{24}$ +1·6° (*l*, 0·5; *c*, 7·3 in EtOH) (Found: C, 63·9; H, 10·7%; equiv., 189. $C_{10}H_{20}O_3$ requires C, 63·8; H, 10·7%; equiv., 188).

Sodium L_s-2-hydroxydecanoate, obtained in aqueous solution by titration with 0·185N-sodium hydroxide and diluted with ethanol to make a 50% mixture, had $[\alpha]_D^{24}$ −15° (*l*, 1; *c*, 1·48 in 50% aq. EtOH).

Methyl L_s-2-hydroxydecanoate, prepared in the usual way, was a colourless liquid, n_D^{25} 1·4371, b. p. 152—155°/22 mm., $[\alpha]_D^{22}$ +3·0° (*l*, 0·5; homog.).

DL-2-*Hydroxyhexadecanoic Acid*.—This *acid*, prepared in the usual manner from *n*-tetradecanoic acid [9·5 g.; prepared by fractionation of its methyl ester at 1 mm. in a spinning-band fractionation column, followed by crystallisation of the best distillates, m. p. 54·3—54·8°. Ralston (*op. cit.*, p. 32) records 54·5°]. The electrolysis product yielded the crude acid (2·3 g.), m. p. 80·5—82·8°. Twice recrystallised from methanol, it had m. p. 85·8—86·6° (Found: C, 70·7; H, 11·7%; equiv., 272. Calc. for $C_{16}H_{32}O_3$: C, 70·5; H, 11·8%; equiv., 272). A mixed m. p. with DL-2-hydroxyhexadecanoic acid (m. p. 86·0—86·5°; Part V) was 85·8—86·5°.

L_s-2-*Hydroxyhexadecanoic Acid*.—This *acid* was prepared as described for the DL-compound. Crystallised from methanol, and hexane, it had m. p. 93·3—93·6°, $[\alpha]_D^{26}$ +2·7° (*l*, 1; *c*, 1·98 in $CHCl_3$), $[\alpha]_D^{26}$ +1° (*l*, 0·5; *c*, 2·24 in EtOH) (Found: C, 70·3; H, 11·7%; equiv., 275. $C_{16}H_{32}O_3$ requires C, 70·5; H, 11·8%; equiv., 272). On admixture with an equal amount of D_s-2-hydroxyhexadecanoic acid (Part V) (m. p. 93·3—93·6°), the m. p. was 86·0—86·7°. The m. p. of this mixture on admixture with DL-2-hydroxyhexadecanoic acid was 86·0—86·6°.

A solution of sodium L_s-2-hydroxyhexadecanoate in 50% aqueous ethanol had $[\alpha]_D^{26}$ −15° (*l*, 1; *c*, 9·30).

D_s-2-*Hydroxyhexadecanoic Acid*.—The rotation of the acid described in Part V, measured in ethanol, was $[\alpha]_D^{22}$ +1° (*l*, 0·5; *c*, 7·3). Its sodium salt had $[\alpha]_D^{22}$ +16° (*l*, 1; *c*, 1·49 in 50% aq. EtOH).

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