616. *The Resolution and Reactions of Tertiary Alcohols: Two Disubstituted Glycollic Acids and the Corresponding Disubstituted Glycols.*

By Alwyn G. Davies, F. M. Ebeid, and J. Kenyon.

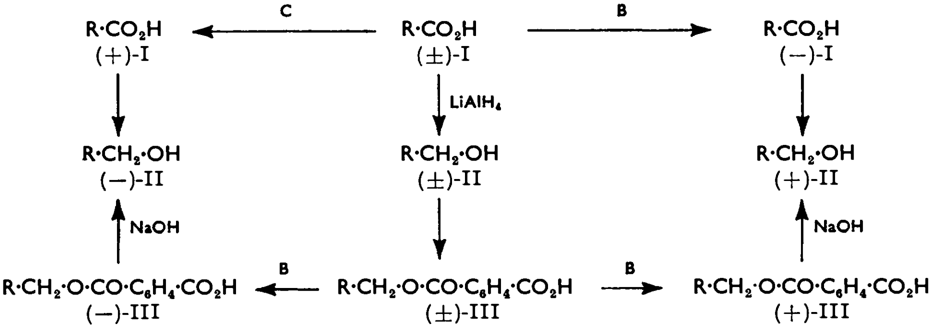
As model experiments for the optical resolution of other tertiary alcohols, the behaviour of two disubstituted glycollic acids, and the corresponding glycols, has been investigated. Each of these compounds contains a second functional group through which resolution can readily be effected. A previous report of failure to resolve 4-methoxybenzilic acid probably resulted from failure to observe its very small rotatory power.

At the time of other investigations of tertiary alcohols [1-4] it appeared that the resolution of tertiary alcohols might be especially difficult; [3] for example, the resolution of 2:4-dimethylhexan-4-ol [5] and 2-phenylbutan-2-ol [6, 3] approached completion only after fifteen crystallisations of the brucine salt of the hydrogen phthalate. We therefore attempted to resolve tertiary alcohols through a second functional group in the molecule to ascertain whether any difficulties could be associated with the characteristic structure of tertiary alcohols.

The disubstituted glycollic acids, and the corresponding glycols obtained on reduction, were chosen as affording the CO_2H and $CH_2{\cdot}OH$ groups respectively through which resolution might be effected.

The reactions investigated are illustrated for 4-methoxybenzilic acid (I). Reduction of the acid or its ethyl ester gave the primary-tertiary glycol (II), which with phthalic anhydride in the presence of pyridine gave the acid ester (III) at the primary alcohol group.

The benzilic acid (I) was readily resolved as its cinchonine and brucine salts, and the hydrogen phthalate (III) as its brucine salt. The active acids were reduced, and the active hydrogen phthalates were hydrolysed, giving the active glycols (+)- and (−)-II. The internal consistency of the rotatory powers in these cycles of operations, and the fact that both isomers of all three compounds have been obtained, place it beyond reasonable doubt that the three alcohols (I), (II), and (III) have been obtained optically pure.



(R = *p*-$MeO{\cdot}C_6H_4{\cdot}CPh(OH)$–. B = brucine. C = cinchonine.)

Christie, McKenzie, and Ritchie [7] reported their failure to resolve 4-methoxybenzilic acid (I), although crystalline alkaloidal salts were obtained, thus supporting the contention that the resolution of tertiary alcohols was difficult. The present work shows that in all probability their resolution was successful and that they did not realise this because the

---

[1] Hickman and Kenyon, *J.*, 1955, 2051.

[2] Davies, Kenyon, and Thaker, *J.*, 1956, 3394.

[3] Davies, Kenyon, and Salamé, *J.*, 1957, 3148.

[4] Davies, Kenyon, and Thaker, preceding paper.

[5] Doering and Zeiss, *J. Amer. Chem. Soc.*, 1948, **70**, 3966; 1950, **72**, 147.

[6] Zeiss, *ibid.*, 1951, **73**, 2391.

[7] Christie, McKenzie, and Ritchie, *J.*, 1935, 153.

optically pure acid in most solvents has intrinsically a very low rotatory power. The highest value of $[\alpha]_D$ which we obtained was 1·2°, in dioxan.

Because the resolution of the above compounds was straightforward, a similar study was made of benzylmethylglycollic acid and the corresponding glycol, 2-methyl-3-phenylpropane-1 : 2-diol. Again this acid was resolved without difficulty as its brucine salt, and the glycol through the strychnine salt of its hydrogen 3-nitrophthalate. Hydrolysis of the ester and reduction of the glycollic acid gave specimens of the glycol of identical rotatory power, indicating that both resolutions were complete.

The optical resolution of the tertiary alcohols described in this paper therefore proceeds as readily as that of many secondary alcohols. Concurrently, other workers in these laboratories found that 3-methylpent-1-yn-3-ol,[1] 1-phenyl-1-2′-pyridylethanol,[2] 1-phenyl-1-2′-pyridylpropanol,[2] and 2-1′-naphthylbutan-2-ol[4] were also readily resolved.

Thus whereas the resolution of some tertiary alcohols is tedious,[3, 5, 6] and some of the compounds involved have very low rotatory powers,[3, 8] these drawbacks are also encountered in the series of secondary alcohols; no special difficulties appear to be associated with the characteristic structure of tertiary alcohols.

EXPERIMENTAL

4-*Methoxybenzilic Acid.*—The action of potassium bromate on 4-methoxybenzoin gave 4-methoxybenzilic acid (I), m. p. 148—149°, in 92·5% yield. Its *ethyl ester* (Fischer–Speier) has b. p. 170—172°/0·5 mm. (Found : C, 71·1; H, 6·2. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·3%).

1-p-*Methoxyphenyl*-1-*phenylethane*-1 : 2-*diol.*—Reduction of the above ethyl ester (30 g.) in ether (100 c.c.) with lithium aluminium hydride (2·5 g.) gave the corresponding *glycol* (II) (23·5 g., 91·7%) as needles (from light petroleum), m. p. 101—102°. Reduction of the acid in a like manner gave a 75% yield of the glycol (Found : C, 73·7; H, 6·6. $C_{15}H_{16}O_3$ requires C, 73·7; H, 6·6%).

The alcohol (50 g.), phthalic anhydride (35 g.), and pyridine (100 g.) were kept at 60—65° for 3 hr., mixed with an equal volume of acetone, acidified with dilute hydrochloric acid, and poured on crushed ice. When the precipitated paste was triturated with ice-cold very dilute acid it rapidly solidified. Crystallisation from benzene yielded the *hydrogen phthalate* (III) (74 g.), m. p. 141—142° (Found : C, 70·3; H, 5·2%; *M*, 392. $C_{23}H_{20}O_6$ requires C, 70·4; H, 5·1%; *M*, 392).

(+)-4-*Methoxybenzilic Acid.*—A solution of the (±)-acid (79 g.) and cinchonine (90 g.) in hot acetone (300 c.c.) after 2 hr. had deposited the cinchonine salt (100 g.) in compact cubes, m. p. 105—106°. The acid liberated from this salt showed no optical rotation in 5% solution in dioxan, ethanol, or pyridine, but the amount of salt which separated, and its great decrease in solubility in acetone, indicated that resolution was taking place. Accordingly the salt was recrystallised eight times from ethanol; it was then optically pure : cubes, m. p. 93—95°, unchanged by further recrystallisation. By decomposition with dilute hydrochloric acid it yielded (+)-4-methoxybenzilic acid (16 g.; m. p. 147·5—149°) which separated from benzene as needles, m. p. 148—149°, $[\alpha]_D^{19}$ +1·2°, $[\alpha]_{5461}^{19}$ +1·7° (*l* 2; *c* 5·76 in dioxan). These low rotatory powers were not raised when dioxan was replaced by ethanol or pyridine.

(−)-4-*Methoxybenzilic Acid.*—The cinchonine salt from the first mother-liquor yielded 4-methoxybenzilic acid (33 g.), m. p. 147—148°, $[\alpha]_{5461}$ $\not>$0·02° (in dioxan). A solution of this acid (1·8 g.) and brucine (2·75 g.) in acetone (6 c.c.) rapidly deposited the brucine salt, needles (3·4 g.), m. p. 195—198°. Decomposition of this salt with hydrochloric acid–acetone yielded (−)-4-methoxybenzilic acid (1·2 g.) which by recrystallisation from benzene was obtained optically pure, as the less soluble fraction, m. p. 147—148°, $[\alpha]_D^{18}$ −1·2°, $[\alpha]_{5461}^{18}$ −1·35° (*l* 2; *c* 2·52 in dioxan).

An intimate mixture of equivalents of the (+)- and the (−)-form had m. p. 147·5—149°.

Reduction of (+)- *and* (−)-*Methoxybenzilic Acid.*—The (+)-acid (10 g.) in ethereal solution was reduced with lithium aluminium hydride (3·3 g.). The resulting (−)-glycol separated from ether–light petroleum as needles (7 g.), m. p. 101—102°, $[\alpha]_D^{18}$ −19·4°, $[\alpha]_{5461}$ −23·5° (*l* 2; *c* 4·255 in pyridine), $[\alpha]_D$ −12·3° (*l* 1; *c* 3·910 in dioxan), $[\alpha]_D^{18}$ −8·0° (*l* 1; 3·76 in $CHCl_3$).

---

[8] This paper.

The corresponding optically impure (−)-acid, $[\alpha]_D \not> 0{\cdot}02°$ (20 g.), obtained from the more soluble fractions of the brucine salt, was similarly reduced. The resulting (+)-glycol (13·65 g.), after three recrystallisations from ether–light petroleum, had m. p. 101—102°, $[\alpha]_D$ +18·7° (in pyridine).

(+)-2-*Hydroxy*-2-p-*methoxyphenylphenethyl Hydrogen Phthalate* (III).—Anhydrous brucine (80 g.) was dissolved in a warm solution of the (±)-hydrogen phthalate (80 g.) in acetone (160 c.c.); next day the crystalline brucine salt (88 g.) was removed and washed with acetone (30 c.c.). After two further crystallisations from acetone (100 c.c.; 120 c.c.) the brucine salt (50 g.) was optically pure, needles, m. p. 74—75°. On decomposition with dilute hydrochloric acid–acetone it yielded the (+)-hydrogen phthalate (24·5 g.), m. p. 135—136°, $[\alpha]_D^{19}$ +6·30° (in pyridine), which separated from benzene in needles, m. p. 136—137°, $[\alpha]_D^{19}$ +6·31°, $[\alpha]_{5461}^{19}$ +8·30° (*l* 2; *c* 5·145 in pyridine), $[\alpha]_D^{19}$ −2·83°, $[\alpha]_{5461}$ −3·10° (*l* 2; *c* 5·305 in AcOH).

(−)-2-*Hydroxy*-2-p-*methoxyphenylphenethyl Hydrogen Phthalate* [(−)-III].—The mother-liquor (100 c.c.) from which the less soluble brucine salt had been removed was acidified with dilute hydrochloric acid and then diluted with ice-water until precipitation was complete. This hydrogen phthalate (36 g.) had m. p. 124—126° and $[\alpha]_D$ −5·6° (in pyridine). It was dissolved in hot benzene (500 c.c.) and the solution allowed to cool. The less soluble racemic hydrogen phthalate separated (6·5 g.), m. p. 138—140°. The second crop (30 g.) consisted of optically pure (−)-hydrogen phthalate, needles, m. p. 136—137°, $[\alpha]_D^{19}$ −6·29°, $[\alpha]_{5461}$ −8·27° (*l* 2; *c* 4·530 in pyridine).

An intimate mixture of equivalents of the (+)- and the (−)-hydrogen phthalate had m. p. 141—142°.

(+)- and (−)-1-p-*Methoxyphenyl*-1-*phenylethane*-1 : 2-*diol*.—A solution of the (+)-hydrogen phthalate (4 g.) in 3N-sodium hydroxide (8 c.c.), after 15 min. on the steam-bath, liberated an oil which set to a crystalline mass (2·22 g.), m. p. 100—102°. This, by recrystallisation from ether–light petroleum, yielded the (+)-glycol as needles (2·1 g.), m. p. 101—102° unchanged by further recrystallisation, $[\alpha]_D^{17}$ +20·3°, $[\alpha]_{5461}^{17}$ +24·9° (*l* 2; *c* 4·315 in pyridine).

Similarly the (−)-hydrogen phthalate yielded the (−)-glycol, m. p. 101—102°, $[\alpha]_D^{17}$ −20·2°, $[\alpha]_{5461}^{17}$ −24·6° (*l* 2; *c* 2·615 in pyridine).

An intimate mixture of equivalents of the (+)- and the (−)-glycol had m. p. 101—102°.

Benzyl Methyl Ketone Cyanohydrin.—40% Sulphuric acid (325 g.) was added dropwise to a cooled and stirred solution of potassium cyanide (130 g.) in water (300 c.c.) and benzyl methyl ketone (260 g.) in methanol (750 c.c.). Next day the liquid was decanted from the potassium sulphate into cold water (1 l.) and the *cyanohydrin* separated as an oil. It was extracted with ether, dried, and distilled (b. p. 108—110°/0·05 mm.; 220 g.) (Found: C, 74·5; H, 6·9; N, 8·6. $C_{10}H_{11}ON$ requires C, 74·5; H, 6·8; N, 8·7%).

α-*Hydroxy*-α-*methyl*-β-*phenylpropionic Acid*.—A stirred mixture of the cyanohydrin (210 g.) and hydrochloric acid (500 c.c.) was heated under reflux for 6 hr. After recrystallisation from benzene the glycollic acid was obtained as prismatic needles (145 g.), m. p. 97—99°. Gabriel and Michael[9] report m. p. 97—99°.

2-*Methyl*-3-*phenylpropane*-1 : 2-*diol*.—A solution of the glycollic acid (100 g.) in ether (1 l.) was added, as rapidly as the reaction allowed, to a solution of lithium aluminium hydride (25 g.) in ether (1 l.). The resultant *alcohol* separated from ether–*cyclo*hexane in needles (66 g.), m. p. 55—56°, unchanged by further crystallisation. It is soluble in water and in most organic solvents except *cyclo*hexane (Found: C, 72·9; H, 8·6. $C_{10}H_{14}O_2$ requires C, 72·3; H, 8·5%).

The hydrogen phthalate was an oil from which no crystalline alkaloidal salts could be obtained. The resolution was therefore carried out through the hydrogen 3-nitrophthalate as follows.

The alcohol (40 g.), 3-nitrophthalic anhydride (50 g.), and pyridine (65 g.) were kept at 50° for 0·5 hr., dissolved in acetone, and decomposed with dilute acid. The precipitated *hydrogen* 3-*nitrophthalate* was washed and crystallised twice from acetic acid (200 c.c.)–water (50 c.c.) mixture, separating as needles (70 g.), m. p. 171—173°, unchanged by further crystallisation (Found: C, 60·5; H, 4·7; N, 4·0%; *M*, 359. $C_{18}H_{17}O_7N$ requires C, 60·2; H, 4·7; N, 3·9%; *M*, 359).

(+)- *and* (−)-α-*Hydroxy*-α-*methyl*-β-*phenylpropionic Acid*.—Brucine (132 g.) was dissolved in a warm solution of the (±)-acid (60 g.) in acetone (270 c.c.); next day the crystalline salt (101 g.) was separated and washed with cold acetone. Because of its low solubility it was heated with acetone

---

[9] Gabriel and Michael, *Ber.*, 1879, **12**, 814.

(200 c.c.) under reflux for 15 min. After two repetitions of this extraction the m. p. and rotatory power of the brucine salt (cubic crystals, 86 g.) became constant at m. p. 186—188° and $[\alpha]_D^{18}$ $-7{\cdot}6°$ (l 1; c 6·090 in $CHCl_3$). The salt was decomposed by cold 3N-hydrochloric acid (350 c.c.) and ether (500 c.c.). The washed and dried ethereal extract yielded a crystalline residue (m. p. 116—118°) which after two recrystallisations from benzene (80 c.c.) formed needles, (24·2 g.), m. p. 118—119·5°, $[\alpha]_D$ $+17{\cdot}0°$, $[\alpha]_{5461}$ $+20{\cdot}1°$ (l 2; c 5·595 in dioxan).

The acetone filtrate (220 c.c.) from the first crop of brucine salt described above, was allowed to evaporate at room temperature for several days. The cubic crystals (m. p. 130—131°; 90 g.) which had separated were recrystallised twice from acetone (130 c.c.; 100 c.c.) with decantation each time from the insoluble compact brucine salt of the (+)-acid, of m. p. 185—186°, yielding the brucine salt of the (−)-acid as cubes, m. p. 134° (57 g.).

This second salt, on decomposition as described above, yielded a crystalline acid, m. p. 115—117°, which in two recrystallisations from benzene (60 c.c.) gave optically pure (−)-acid (12·6 g.), needles, m. p. 118—119·5°, $[\alpha]_D$ $-16{\cdot}9°$, $[\alpha]_{5461}$ $-20{\cdot}0°$ (l 2; c 4·645 in dioxan).

An intimate mixture of equivalents of the (+)- and the (−)-acid had m. p. 97—99°.

Reduction of the (+)-*Acid*.—The (+)-acid (24 g.) was reduced with lithium aluminium hydride (10 g.) as described for the (±)-acid. The *alcohol* was fractionally crystallised from ether–*cyclo*hexane but all fractions formed prismatic rods and had rotatory powers approxinating to $[\alpha]_D$ $+23{\cdot}9°$, $[\alpha]_{5790}$ $+25{\cdot}7°$, $[\alpha]_{5461}$ $+28{\cdot}9°$ (l 2; c 2·430 in H_2O) (Found: C, 72·4; H, 8·2. $C_{10}H_{14}O_2$ requires C, 72·3; H, 8·5%).

An intimate mixture of equivalents of this (+)-alcohol and the (−)-alcohol, obtained by hydrolysis of its (−)-hydrogen nitrophthalate, had m. p. 55—56°.

(+)- *and* (−)-2-*Hydroxy*-2-*methyl*-3-*phenylpropyl Hydrogen* 3-*Nitrophthalate*.—A mixture of the (±)-acid ester (72 g.) and strychnine (68 g.) was dissolved in warm acetone (200 c.c.). The strychnine salt began to separate within an hour and was filtered off next day (73 g.; m. p. 194—196°). After recrystallisation from methanol it was dissolved in chloroform and decomposed by dilute ammonia. The resultant (+)-acid ester, m. p. 202—204°, separated from glacial acetic acid in needles, m. p. 203—204°, $[\alpha]_D^{19}$ $+12{\cdot}5°$, $[\alpha]_{5461}$ $+15{\cdot}0°$ (l 2; c 5·830 in pyridine).

The acetone filtrate from the original strychnine salt was decomposed with ammonia, yielding strychnine (31 g.) and the (−)-acid ester (32 g.). The latter separated after three crystallisations from glacial acetic acid in needles, m. p. 203—204°, $[\alpha]_D$ $-12{\cdot}5$, $[\alpha]_{5461}$ $-14{\cdot}7°$ (l 2; c 6·125 in pyridine), $[\alpha]_D$ $-4{\cdot}1°$, $[\alpha]_{5461}$ $-4{\cdot}7°$ (l 2; c 5·945 in dioxan).

A solution of equal weights of the (+)- and the (−)-acid ester in dioxan was allowed to evaporate to dryness. The crystalline residue had m. p. 171—173°, identical with that of the original (±)-ester.

(+)-*and* (−)-2-*Methyl*-3-*phenylpropane*-1 : 2-*diol*.—A solution of the hydrogen 3-nitrophthalate (3 g.; $[\alpha]_D^{20}$ $-12{\cdot}48°$ in pyridine) in 10% aqueous sodium hydroxide (10 c.c.) was heated on the steam-bath for 0·5 hr., cooled, and extracted with ether. The dried and concentrated extract, after dilution with *cyclo*hexane, deposited the (−)-alcohol (0·9 g.) as rods, m. p. 67—68°, $[\alpha]_D$ $-23{\cdot}3°$, $[\alpha]_{5790}$ $-26{\cdot}2°$, $[\alpha]_{5461}$ $-28{\cdot}7°$ (l 2; c 3·053 in H_2O).

The (+)-alcohol was obtained similarly from the corresponding (+)-ester, as prismatic rods, m. p. 67—68°, $[\alpha]_D$ $+23{\cdot}8°$, $[\alpha]_{5790}$ $+27{\cdot}8°$, $[\alpha]_{5461}$ $+29{\cdot}4°$ (l 2; c 3·140 in H_2O). A mixture of equal weights of the (+)- and the (−)-alcohol had m. p. 55—57°.

CHEMISTRY DEPARTMENT, BATTERSEA POLYTECHNIC,
LONDON, S.W.11.

[*Received, February* 26*th*, 1957.]