614. *The Resolution and Reactions of Tertiary Alcohols: 2-Phenylbutan-2-ol and 3-Methylhexan-3-ol.*

By Alwyn G. Davies, J. Kenyon, and L. W. F. Salamé.

The resolution of 2-phenylbutan-2-ol by Zeiss's method has been repeated; some simplifications of procedure are suggested.

Preliminary experiments show that the resolution of 3-methylhexan-3-ol takes place slowly by the same method.

Although some scores of secondary alcohols have been resolved into their optical isomers, usually by the crystallisation of alkaloidal salts of their hydrogen phthalates,[1] it is only recently that this method has been applied successfully to tertiary alcohols.[2] In 1948 the resolution of 2 : 4-dimethylhexan-4-ol was announced,[3] followed shortly by that of 2-phenylbutan-2-ol.[4] Since then, similar resolutions of 3-methylpent-1-yn-3-ol [5] and of 1-phenyl-1-2′-pyridylethanol [6] have been described, and 1-phenyl-1-2′-pyridylpropanol [6] has been resolved as its salt with (+)-tartaric acid.*

As a preliminary to further work on optically active tertiary alcohols, we re-investigated the resolution of 2-phenylbutan-2-ol. Zeiss's work [4] has, in general, been confirmed, but with the following significant modifications.

The reaction of tertiary alcohols with phthalic anhydride is usually carried out through their potassium salts, as the alcohols are unreactive towards the anhydride in the presence of pyridine.[9,4] It is now shown that the esters can be prepared more conveniently and in equally good yield by treating the alcohol with phthalic anhydride in the presence of the stronger base, triethylamine. By this procedure, the hydrogen phthalates of 2-phenylbutan-2-ol, *tert.*-butyl alcohol, 3-methylhexan-3-ol, and 2-methyl-1-phenylbutan-2-ol have been prepared.

Fractional crystallisation of the brucine salt of the hydrogen phthalate yielded as the less soluble fractions the salt of the (+)-hydrogen phthalate, whereas Zeiss obtained the salt of the (−)-acid ester. The brucine salt is solvated with one molecule of acetone per molecule of salt, and it seems possible that the temperature at which crystallisation is

---

* γ-Hydroxy-γ-phenylvaleric acid,[7] 4-hydroxy-4-methylhexanoic acid ($CO_2H = 1$), and a number of disubstituted glycollic acids, which may be regarded as tertiary alcohols, have also been resolved.[8]

[1] Pickard and Kenyon, *J.*, 1907, **91**, 2058 *et seq.*; Ingersoll, *Organic Reactions*, 1944, **2**, 376.

[2] See, *e.g.*, Wilson, *Trans. Faraday Soc.*, 1941, **37**, 706; Lowry, " Optical Rotatory Power," Longmans, Green & Co., London, 1935, p. 262.

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

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

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

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

[7] Reid and Turner, *J.*, 1951, 3219.

[8] Kenyon and Symons, *J.*, 1953, 3580; Christie, McKenzie, and Ritchie, *J.*, 1935, 153; McKenzie and Clough, *J.*, 1910, **97**, 1016.

[9] Fuller and Kenyon, *J.*, 1924, **125**, 2304; Balfe, Kenyon, and Thain, *J.*, 1951, 386.

induced from the acetone solution may favour the separation of one or other of the diastereomeric salts.[10]

Separation of the salts was slow and erratic and eventually it proved more convenient to liberate a small amount of hydrogen phthalate from each crop of salt and on the basis of their rotatory powers decide which crops could be mixed for further fractionation. By following this procedure, both diastereoisomeric salts have been obtained optically pure. Both the (+)- and the (—)-form of the hydrogen phthalate are oils, but a mixture of equal weights of these combine to re-form the crystalline, more stable, racemate.

The optically pure (—)-alcohol has been obtained by the action of sodium ethoxide directly on the brucine salt of the (+)-hydrogen phthalate, and the structural identity of the (—)- and the (±)-alcohol has been confirmed by preparation from each of identical specimens of, dimorphic, 1-methyl-1-phenylpropyl *p*-tolyl sulphone.

The optically active hydrogen phthalates undergo hydrolysis with ethanolic potassium hydroxide to yield optically active alcohols without loss of rotatory power, as is shown by their reconversion into hydrogen phthalates possessing their original rotatory powers. Thus the use, for this purpose,[4] of lithium aluminium hydride or Grignard reagents appears unnecessary.

Preliminary experiments were also carried out on the resolution of 3-methylhexan-3-ol. Twelve recrystallisations of the brucine salt of the hydrogen phthalate from ethyl acetate raised the melting point of the salt from 154—155° (crop A) to 160—161° (crop L) but did not change the rotatory power of the salt, and the activity of the hydrogen phthalate recovered from crop L was negligibly small. The alcohol recovered from the hydrogen phthalate from various crops of brucine salt, however (Table 2), showed a progressive change in optical rotatory power. This is the behaviour to be expected from the steady separation of two diastereoisomeric salts by fractional crystallisation.

EXPERIMENTAL

2-Phenylbutan-2-ol was a good commercial sample, b. p. 100—102°/14 mm., n_D^{25} 1·517.

1-*Methyl*-1-*phenylpropyl Hydrogen Phthalate.*—A mixture of the alcohol (60 g.), phthalic anhydride (59·2 g.) and dry triethylamine (45 g.) was mechanically stirred at about 90° for 8 hr. The oily product was shaken with ether (250 c.c.) and iced N-hydrochloric acid (400 c.c.). The separated ethereal layer was washed with cold dilute acid and with water, and then extracted three times with dilute sodium carbonate solution. The combined extracts were washed with ether, cooled to 0°, and acidified to Congo-red with N-hydrochloric acid. The precipitated oil rapidly solidified; it was washed with water and dried *in vacuo*. Yields from 3 experiments were 64, 61, and 75 g., and the m. p. 107—108° (decomp.). The hydrogen phthalate separates from ether as rhombs, m. p. 111·5—113° (decomp.) (Found: *M*, 300. Calc. for $C_{18}H_{18}O_4$: *M*, 298).

By a similar method, *tert.*-butyl hydrogen phthalate was obtained in 75% yield, m. p. and mixed m. p. 79—80°, and 1-ethyl-1-methylbutyl and 1-benzyl-1-methylpropyl hydrogen phthalate as amber oils in 78% and 65% yield, respectively.

(+)-1-*Methyl*-1-*phenylpropyl Hydrogen Phthalate.*—The progress of the resolution was followed by determining the rotatory power (in ethanol solution, *c ca.* 5) of the hydrogen phthalate which was liberated from the brucine salt by Zeiss's method, modified by omitting the addition of ethanol.

A solution of the (±)-hydrogen phthalate (97 g.) and brucine (128 g.) in acetone (290 c.c.), deposited successive crystalline crops of the brucine salt A (200 g.), A^{I} (10·8 g.; hydrogen phthalate, $[\alpha]_D$ $-33°$), A^{II} (9·2 g.; hydrogen phthalate, $[\alpha]_D$ $-24°$), and A^{III} (3·8 g.; hydrogen phthalate, $[\alpha]_D$ $+3°$). Recrystallisation of crop A gave crop B. Concentration of the filtrate from B yielded subsidiary crops B^{I} (16·6 g.; hydrogen phthalate, $[\alpha]_D$ $-23·6°$), B^{II} (10 g.), and B^{III} (1 g.; hydrogen phthalate, $[\alpha]_D$ $+11°$).

Crop B was recrystallised five times, giving crop G (44 g.; hydrogen phthalate, $[\alpha]_D$ $+41°$). An additional nine recrystallisations yielded crop P (10 g.), m. p. 120—122°, which gave a hydrogen phthalate as an oil, $[\alpha]_D^{17}$ $+50·0°$ not raised by further recrystallisation of the salt.

---

[10] Cf. Houssa and Kenyon, *J.*, 1930, 2260.

The values for $[\alpha]_D$ of the (+)-hydrogen phthalate (*c* 5·320 in EtOH) vary linearly with temperature from 51·9° at 12·5° to 47·5° at 23°.

(−)-1-*Methyl*-1-*phenylpropyl Hydrogen Phthalate.*—Various specimens of the more soluble brucine salt from the filtrates (from which hydrogen phthalates of $[\alpha]_D$ varying from −13° to −33° had been obtained) were combined (total, 129 g.) and dissolved in acetone (650 c.c.). After 8 recrystallisations a brucine salt was obtained (10·3 g.) as rhombs, m. p. 131—132° (decomp.), which yielded an oily hydrogen phthalate, $[\alpha]_D^{18}$ −49·7° not raised by further recrystallisation of the brucine salt.

Regeneration of the (±)-*Hydrogen Phthalate.*—Ethanol solutions of equivalent amounts of the liquid (+)- and (−)-hydrogen phthalate were mixed, giving an optically inactive solution which was evaporated to dryness at room temperature. The oily residue was dissolved in ether and seeded with the racemic hydrogen phthalate, and the solution allowed to evaporate, giving the crystalline (±)-hydrogen phthalate (68%), m. p. and mixed m. p. 113—115° (decomp.)

(−)-2-*Phenylbutan*-2-*ol.*—The sensitivity of the optically active hydrogen phthalate to dilute mineral acid prompted the direct recovery of the alcohol from the brucine salt of the hydrogen phthalate as follows. Solutions of sodium (2·8 g.) and of the brucine salt of the (+)-hydrogen phthalate (21·0 g.), each in ethanol (60 c.c.), were mixed and heated under reflux for 0·5 hr. During this period a white solid separated, which slowly became orange. The bulk of the ethanol was removed under reduced pressure at <65°. The semisolid residue was mixed with iced water (130 c.c.), the oily suspension was immediately extracted with ether (3 × 50 c.c.), and the extracts were washed and dried; these yielded the (−)-alcohol (3·6 g.), b. p. 112—114°/23 mm., n_D^{20} 1·5180, n_D^{25} 1·5156, d_D^{20} 0·982. Values for the rotatory power of the homogeneous liquid are tabulated. Zeiss[4] reports $[\alpha]_D^{22}$ +17·45° for the (+)-alcohol.

TABLE 1. *Optical rotatory power of* (—)-2-*phenylbutan*-2-*ol* (*l* 0·5).

λ	5893	5791	5461	4358
α^{22}	− 9·03°	− 9·40°	−10·8°	−19·4°
$[\alpha]^{22}$	−18·4°	−19·0°	−22·0°	−39·5°

The alcohol was recovered with undiminished rotatory power after being heated under reflux for 3 hr. with 0·1N-sodium hydroxide.

1-*Methyl*-1-*phenylpropyl* p-*Tolyl Sulphone.*—Both the (−)- and the (±)-alcohol with sodium toluene-*p*-sulphinate gave (±)-1-methyl-1-phenylpropyl *p*-tolyl sulphone, m. p. 63—64°, undepressed on admixture with a specimen described previously.[11] This sulphone has now been obtained also as a dimorphic *modification*, m. p. 80—82° (Found: C, 70·2; H, 6·85; S, 11·5. $C_{17}H_{20}O_2S$ requires C, 70·8; H, 7·0; S, 11·1%). The two forms are interconvertible by recrystallisation from methanol, and on melting both resolidify to the material of m. p. 80°.

Partial Resolution of 2-*Methylhexan*-3-*ol.*—A solution of brucine (53·6 g.) and 1-ethyl-1-methylbutyl hydrogen phthalate (35·9 g.) in boiling ethyl acetate (300 c.c.) was seeded with a crystal of the brucine salt from a previous fractionation. The salt obtained, crop A, m. p. 154—155°, was recrystallised eleven times by the same procedure giving crop L (5·4 g.), m. p. 160—161°. This final fraction had the same rotatory power as the brucine salt from crop B^{I}, $[\alpha]_D^{91}$ −7·8° (in EtOH), and gave a hydrogen phthalate of negligible rotatory power, $[\alpha]_D^{19}$ +0·03° (*l* 2; *c* 5·20 in EtOH).

Various fractions of the hydrogen phthalate were hydrolysed with sodium ethoxide in ethanol giving 3-methylhexan-3-ol. Typical properties were (alcohol from crops A^{I} and B^{I} combined), b. p. 58—59°/25 mm., n_D^{20} 1·4224 (Found: C, 72·4; H, 13·6. Calc. for $C_7H_{16}O$: C, 72·4; H, 13·9%). The rotatory powers of the alcohol are tabulated.

TABLE 2. *Rotatory powers of samples of* 3-*methylhexan*-3-*ol* (*l* 0·5) *recovered from successive crops of the brucine salt.*

Brucine salt, crop	A^{I}	B^{I}	C^{I}	E^{I}, F^{I}, G^{I} combined	H^{I}, I^{I}, J^{I}, K^{I}, L^{I}, L combined
Alcohol, α_D	+0·10°	+0·07°	+0·02°	−0·03°	−0·19°
Temp.	18°	22°	18°	22°	23°

Thanks are expressed to the Central Research Fund Committee of the University of London for Grants in respect of this and the following paper.

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

[*Received, February* 28*th*, 1957.]

---

[11] Davies, Foster, and Nery, *J.*, 1954, 2204.