1244 *Hoffmann and Hughes:*

244. *Reaction Kinetics and the Walden Inversion. Part IX.[1] The Rotations of Optically Pure* 1-*Phenylethyl Chloride and Bromide.*

By H. M. R. HOFFMANN and (the late) E. D. HUGHES.

The rotations of optically pure 1-phenylethyl chloride and 1-phenylethyl bromide have been determined by a series of stereospecific reactions and are shown to be substantially greater than the best values obtained in the preparation of these halides from 1-phenylethanol. 1-Phenylethyl chloride and, for the first time, 1-phenylethyl bromide have been prepared with 87% optical purity.

THE 1-phenylethyl system is a classical example for the investigation of reaction mechanisms. Since 1-phenylethyl toluene-*p*-sulphonate is unstable,[2] optically active 1-phenylethyl chloride and 1-phenylethyl bromide, in particular, have been used as substrates and products in numerous stereochemical studies, and renewed use of them is made in the accompanying Parts XI and XII.

So far, the maximum rotations for both halides are still not known accurately. The values reported from the preparations have been increasing steadily ever since these compounds were first obtained in optically active form. Gerrard obtained rotations which so far have held the record, by adding phosphorus trihalides or oxyhalides to resolved 1-phenylethanol in the presence of a base. His best values are α_D^{20} 109° for 1-phenylethyl chloride [3] and α_D^{20} 131·4° for the bromide,[4] and these represent lower limits for the rotations of the pure enantiomers (all values of α in this Paper refer to neat liquids and *l* 1 dm.). An identical value for 1-phenylethyl chloride was obtained both by Burwell *et al.*[5] and by us. However, this remarkable reproducibility is no proof of stereospecificity, *i.e.*, 100% inversion, as has sometimes been assumed in the past, since all three preparations were carried out under the same conditions. In fact, we will show later that this value corresponds to only 87% optical purity.

Using the same method, we have prepared 1-phenylethyl bromide. As it was found that pure samples of this compound quickly racemised at room temperature (the first half-life being *ca.* 30 hr.*), preparations were carried out as swiftly as possible, and it was

---

* However, in a solvent, it was found to be much more stable. The unimolecular racemisation, by way of reversible ionisation, in acetonitrile at 59·8° had $k_1 \gtrsim 1·3 \times 10^{-5}$ sec.$^{-1}$.

[1] Part VIII, Harvey, Hoye, Hughes, and Ingold, *J.*, 1960, 800.
[2] Preliminary account, Hoffmann, *Chem. and Ind.*, 1963, 336.
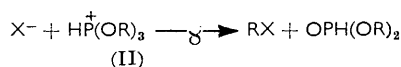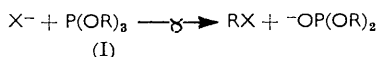[3] Gerrard, *J.*, 1945, 106. In one experiment, Me·CHPh·OH with α_D^{20} −25·6° gave Me·CHPh·Cl with α_D^{20} 63°.
[4] Gerrard, *J.*, 1946, 741.
[5] Burwell, Shields, and Hart, *J. Amer. Chem. Soc.*, 1954, **76**, 908.

particularly important to distil the product at low temperatures. After a number of attempts, we obtained 1-phenylethyl bromide with α_D^{20} 146·5°, which is a new lower limit for the maximum rotation. This value again, remarkably enough, corresponds to 87% optical purity (see below).

The path of this reaction (in the absence of base) is assumed [6] to involve the rate-determining bimolecular attack of halide ion on the highly reactive trialkyl phosphite (I) or its conjugate acid (II):

$$X^- + P(OR)_3 \xrightarrow{\hspace{0.3cm}\delta\hspace{0.3cm}} RX + {}^-OP(OR)_2$$
$$(I)$$

$$X^- + H\overset{+}{P}(OR)_3 \xrightarrow{\hspace{0.3cm}\delta\hspace{0.3cm}} RX + OPH(OR)_2$$
$$(II)$$

with alkyl–oxygen fission. However, in the presence of base, as is the case here, the reaction sequences will be more difficult to predict. Removal of hydrogen chloride certainly prevents the configuration-retaining reaction:

$$ROH + HCl \longrightarrow ROH_2{}^+Cl^- \xrightarrow{-H_2O} RCl$$

which otherwise would be an important side-reaction for the 1-phenylethyl system, a structure comparable in its reactivity (*via* the S_N1 mechanism) to the t-butyl system.

It is obvious that added halide ion will increase the yields.[5] On the other hand, the symmetrical Finkelstein racemisation:

$$X^- + (+)\text{-Me·CHPh·X} \rightleftharpoons (-)\text{-Me·CHPh·X} + X^-$$

is probably very slow below 0°, even in the case of 1-phenylethyl bromide, if a non-polar or a weakly polar solvent like pentane of dichloromethane is used.

In the preparation of the 1-phenylethyl halides, it was observed that the reaction solution turned slightly yellow during the initial stages when adding the phosphorus trihalide to the solution of alcohol and pyridine in pentane, although the temperature was kept well below −10°. We suspect that this is due to the formation of a little styrene, possibly by mechanism $E1$, which could explain a simultaneous racemisation by mechanism S_N1 (or reversible ionisation) [7] during the initial stages of the reaction when there is as yet insufficient halide ion present. In accord with this suggestion, the loss of optical activity for the preparation of the 1-methylheptyl halides is nil (or only very slight for the chloride), *i.e.*, the formation of these less-reactive alkyl halides proceeds almost exclusively by mechanism S_N2 (cf. Part X, following paper). It is predicted that careful experiments at lower temperature (about −20°) in a homogeneous medium (*e.g.*, dichloromethane as solvent), and with added halide ion (from a tetra-alkylammonium salt), will lead to a product of even higher optical purity.

The maximum rotation for both 1-phenylethyl halides has now been determined by a sequence of stereospecific reactions, namely, conversion of the halides into methyl 1-phenylethyl sulphide which was correlated with the rotation of 1-phenylethanethiol, as shown in Scheme 1.

RCl
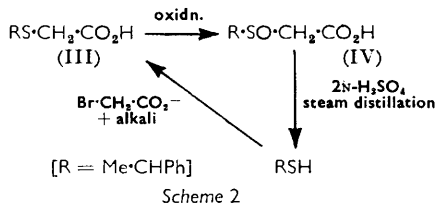
RSMe ⟵ RSH

[R = Me·CHPh]

RBr
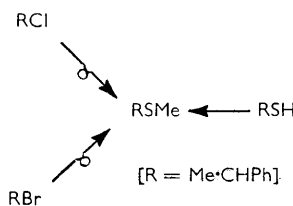
Scheme 1

---

[6] Cook, Coulson, Gerrard, and Hudson, *Chem. and Ind.*, 1962, 1506.
[7] Winstein, Clippinger, Fainberg, Heck, and Robinson, *J. Amer. Chem. Soc.*, 1956, **78**, 328.

The rotation of optically pure 1-phenylethanethiol follows from an interesting reaction sequence,[8] shown in Scheme 2.

$$RS \cdot CH_2 \cdot CO_2H \xrightarrow{\text{oxidn.}} R \cdot SO \cdot CH_2 \cdot CO_2H$$

(III)   (IV)

Br·CH₂·CO₂⁻ + alkali

2N-H₂SO₄ steam distillation

[R = Me·CHPh]   RSH

Scheme 2

Holmberg [8] fully resolved (phenylethylthio)acetic acid (III), and oxidised it to the sulphoxide (IV) in 2 experiments with (i) hydrogen peroxide, and (ii) potassium persulphate. Steam distillation with dilute acid gave (+)-1-phenylethanethiol with (i) α_D^{20} 108·0°, (ii) α_D^{20} 108·2°. It appears that this step is analogous to the decarboxylation of α-keto-acids, and proceeds by way of a cyclic transition state with the formation of an enol-like intermediate:

$$R \cdot SO \cdot CH_2 \cdot CO_2H \longrightarrow \cdots \longrightarrow R - S = CH_2 \quad [R = Me \cdot CHPh]$$
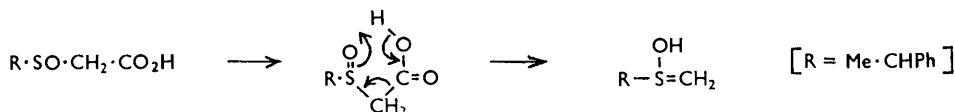
The S=CH₂ bond is probably so reactive that it breaks immediately; methylene is trapped to form the observed formaldehyde, and the thiol is obtained without any alteration of configuration at the asymmetric centre. Decarboxylations of this type seem to be very " clean "; *e.g.*, 2-methylpropane-2-thiol has been prepared in the same way.[9] Whether the formation of some sulphoxide, however, can be completely excluded, appears to be unknown.

The final step, *i.e.*, nucleophilic displacement of bromide by the 1-phenylethanethiolate ion, gave starting material (III) with unchanged rotation. Therefore, the maximum rotation of (+)-1-phenylethanethiol is α_D^{20} 108·1°.

As the first step in Scheme 1, (+)-1-phenylethanethiol was methylated, which led to the rotation for optically pure methyl 1-phenylethyl sulphide. This reaction proceeded smoothly under very mild conditions when diazomethane in ether was used at room temperature, the sulphide being formed in quantitative yield. Similar methylations without electrophilic catalysts have been reported in a few isolated cases,[10] but they concerned the more acidic thiophenols. This methylation does not affect the asymmetric centre, and two experiments gave consistent results; thus the derived rotation of optically pure methyl 1-phenylethyl sulphide is α_D^{20} (max) 196°.* The final and crucial steps were the conversions of the two halides into methyl 1-phenylethyl sulphide (Scheme 1). These are reactions which proceed at the asymmetric centre and therefore could conceivably result in some racemisation. A kinetic investigation [1] of the reaction:

$$MeSNa + Me \cdot CHPh \cdot Cl \xrightarrow{\text{C}} Me \cdot CHPh \cdot SMe + NaCl$$
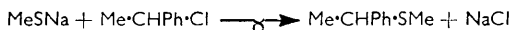
in ethanol at 35° gave clear-cut second-order kinetics, with an average value for k_2 of $1 \cdot 54 \times 10^{-3}$ l. mole⁻¹ sec.⁻¹, indicating the S_N2 mechanism. In the stereochemical investigation (expt. 1, Table 1), Harvey *et al.*[1] obtained a correlation which was in agreement with our control experiment (no. 2, Table 1) carried out at a higher temperature, although the reaction times and concentrations were substantially different. This establishes that

---

* The correlation given by Siegel and Graefe, *J. Amer. Chem. Soc.*, 1953, **75**, 4521, is inaccurate, as is a previous correlation (ref. 1).

[8] Holmberg, *Arkiv Kemi, Min., Geol.*, 1939, **13**, *A*, 8.

[9] Hellström and Lauritzon, *Ber.*, 1936, **69**, 2003.

[10] Schöberl and Wagner in Houben-Weyl, " Methoden der Organischen Chemie," Vol. IX, Thieme, Stuttgart, 1955, p. 116.
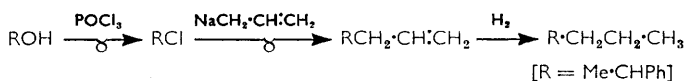
TABLE 1.

The reaction of sodium methyl sulphide with optically active 1-phenylethyl chloride in ethanol.

Expt.	Initial concns. (moles l.$^{-1}$)		$\dfrac{[MeSNa]_0}{[Me \cdot CHPh \cdot Cl]_0}$	Reaction conditions	Optical rotations ($\alpha_D{}^{20}$)	
	$[MeSNa]_0$	$[Me \cdot CHPh \cdot Cl]_0$			$Me \cdot CHPh \cdot Cl$	$Me \cdot CHPh \cdot SMe$
1	0·25	0·15	1·7 : 1	48 hr. at 35°	56·60°	−88·54°
2	0·90	0·37	2·4 : 1	20 min. at 45°	21·13°	−33·0°

both reactions proceed with 100% inversion, under the conditions cited; if side-reactions had occurred in the first experiment, then the second experiment, with the higher nucleophile : substrate ratio and much shorter reaction time, should have given a product of higher optical purity; this was not the case. Therefore, the rotation of optically pure 1-phenylethyl chloride, in contrast to an earlier suggestion,[1] is $\alpha_D{}^{20} = 56 \cdot 60 \times 196/88 \cdot 54 = 125°$.

An upper limit to the rotation of optically pure 1-phenylethyl chloride can be calculated from a number of sources, as was pointed out some time ago.[5] Using a 45-fold and a 20-fold excess, respectively, of nucleophile over substrate, optically active 1-phenylethyl chloride was converted into the methyl and the ethyl ether.[11] Independently, these ethers were obtained by refluxing optically active 1-phenylethanol with methyl iodide or ethyl iodide in the presence of freshly precipitated silver oxide.[12] One would not expect any racemisation during the course of these last two reactions.[13] We have confirmed this by methylating the alcohol with diazomethane in the presence of boron trifluoride, which gave the same correlation as did Mislow's preparation. The upper limits calculated for 1-phenylethyl chloride are $\alpha_D{}^{20}$ 133°, from methyl 1-phenylethyl ether, and $\alpha_D{}^{20}$ 129°, from the ethyl ether. As the ethyl ether was prepared in a medium less ionising, and with a lyate ion more nucleophilic than for the preparation of the methyl ether, we should expect the ethyl figure to be smaller and hence the closer upper limit.

Burwell and his co-workers[5] converted 1-phenylethanol, in three steps, into 2-phenylpentane:

$$ROH \xrightarrow[\text{?}]{POCl_3} RCl \xrightarrow[\text{?}]{NaCH_2 \cdot CH \dot{:} CH_2} RCH_2 \cdot CH \dot{:} CH_2 \xrightarrow{H_2} R \cdot CH_2CH_2 \cdot CH_3$$

$$[R = Me \cdot CHPh]$$

Scheme 3

In the second step, 4-phenylpent-1-ene was prepared by reaction of 1-phenylethyl chloride with allylsodium in octane at about −30°. Hydrogenation gave 2-phenylpentane (which had been resolved independently) with a lower optical purity than the alcohol used as the starting material. Since the optical purity of 1-phenylethyl chloride must lie between that of the starting material, 1-phenylethanol, and the product, 2-phenylpentane, an upper limit to the rotation of optically pure 1-phenylethyl chloride could be calculated, and was $\alpha_D{}^{20}$ 125·4°. It is now clear that the loss in optical purity during the course of Scheme 3 occurred exclusively in step 1, *i.e.*, in the conversion of 1-phenylethanol into the chloride, for the upper limit calculated is identical with the rotation of optically pure 1-phenylethyl chloride. The fact that the second step has proceeded with complete inversion of configuration is not self-evident; when alkyl bromides or iodides are chosen as the substrates, metal alkyls often cause complete racemisation (Part X, footnote p. 1250).

The maximum rotation of 1-phenylethyl bromide was determined in two analogous experiments, *i.e.*, by converting 1-phenylethyl bromide into methyl 1-phenylethyl sulphide (cf. Table 2). The optical result for both experiments is again the same, irrespective of a 2-fold or a 4-fold excess of sodium methyl sulphide; this is consistent with the high nucleophilic reactivity of the methanethiolate ion. The bimolecular rate constant (k_2) for the reaction in ethanol at 25° was *ca.* $4 \cdot 2 \times 10^{-2}$ l. mole^{-1} sec.$^{-1}$, corresponding to a first half-life for 1-phenylethyl bromide of 47 sec. in expt. 1, and 27 sec. in expt. 2. This

[11] Hughes, Ingold, and Scott, *J.*, 1937, 1201.
[12] Mislow, *J. Amer. Chem. Soc.*, 1951, **73**, 4043.
[13] However, see Streitwieser and Wolfe, *J. Amer. Chem. Soc.*, 1959, **81**, 4912.

TABLE 2.

The reaction of sodium methyl sulphide with optically active 1-phenylethyl bromide in ethanol.

Expt.	Initial concns. (moles l.$^{-1}$)		$\dfrac{[\text{MeSNa}]_0}{[\text{Me·CHPh·Br}]_0}$	Reaction conditions	Optical rotations (α_D^{20})	
	$[\text{MeSNa}]_0$	$[\text{Me·CHPh·Br}]_0$			Me·CHPh·Br	Me·CHPh·SMe
1	0·396	0·171	2·3 : 1	10 min. at 25°	88·9°	−102·2°
2	0·642	0·157	4·1 : 1	10 min. at 25°	88·9°	−102·3°

proves convincingly that both reactions proceeded with 100% inversion, as expected from the S_N2 rule.

Based upon the maximum rotation of methyl 1-phenylethyl sulphide, α_D^{20} 196°, the rotation of optically pure 1-phenylethyl bromide can now be calculated as α_D^{20} 170°. Previously, only a lower limit, α_D^{20} 131·4°, was known.[4]

EXPERIMENTAL

The purity of all compounds was checked by infrared spectroscopy.

(−)-*1-Phenylethyl Chloride.*[3,5]—(+)-1-Phenylethanol, α_D^{20} 25·6° (22 g.), was added to AnalaR pyridine (42·6 g.) in dry pentane (100 ml.). Phosphorus oxychloride (27·6 g.) in dry pentane (30 ml.) was added dropwise at −20°. The reaction mixture was kept at 0° overnight, and then washed successively with cold water, sodium hydrogen carbonate solution, and twice with water, and finally dried (MgSO$_4$). The product (5·3 g.) had b. p. 29°/0·5 mm., α_D^{20} −63·2° (corrected for optically pure alcohol,[14] α_D^{20} −109·0°).

(+)-*1-Phenylethyl Bromide.*—Gerrard's procedure[4] was slightly modified. (−)-1-Phenylethanol, α_D^{20} −26·8° (39 g.), and pyridine (54 g.) were dissolved in ether (200 ml.). Phosphorus tribromide (95 g.) in ether (300 ml.) was added during 45 min. at −30°. The solution, after standing for 6 hr. in the dark at 0°, was decomposed with ice–water and then washed successively with ice–water, 85% phosphoric acid, ice–water, sodium hydrogen carbonate solution, and twice again with ice–water. It was dried (MgSO$_4$), yielding (+)-1-phenylethyl bromide (7·8 g., middle fraction), b. p. 33°/0·2 mm., α_D^{20} 88·9° (corrected for optically pure alcohol, α_D^{20} 146·5°). The compound was stable at −80°.

(+)-*Methyl 1-Phenylethyl Sulphide from* (+)-*1-Phenylethanethiol.*—(+)-1-Phenylethanethiol, α_D^{20} 20·7° (1·62 g.) (cf. Part XI), was treated with a 3-fold excess of diazomethane in ether. After 3 hr. at room temperature, evolution of nitrogen had ceased and the smell of the thiol had disappeared. After a further 12 hr., the ether and the excess of diazomethane were pumped off, leaving (+)-methyl 1-phenylethyl sulphide, b. p. 58—59°/1 mm., α_D^{20} 37·6°, in almost quantitative yield. A second experiment gave methyl 1-phenylethyl sulphide, α_D^{20} 64·4°, from 1-phenylethanethiol, α_D^{20} 35·7°.

(+)-*Methyl 1-Phenylethyl Ether from* (+)-*1-Phenylethanol.*[15]—(+)-1-Phenylethanol, α_D^{20} 25·6° (3·42 g.) was mixed with freshly distilled boron trifluoride etherate (0·86 g.), and diazomethane in ether was added with stirring to the mixture, cooled in ice, until the yellow colour persisted. The solution was washed with water, dried, and distilled, giving (+)-methyl 1-phenylethyl ether, b. p. 27°/0·6 mm., α_D^{20} 69·2°.

(−)-*Methyl 1-Phenylethyl Sulphide from* (+)-*1-Phenylethyl Chloride.*—(+)-1-Phenylethyl chloride, α_D^{20} 21·13° (2·60 g.), in a 0·90M-solution (50 ml.) of sodium methyl sulphide in ethanol, was kept at 45° for 20 min. The reaction mixture was run into an aqueous solution (60 ml.) of sodium chloride, then acidified, and twice extracted with pentane. The combined pentane solutions were washed with water, and dried, and the solvent was evaporated. Distillation of the residue in a small-scale unit gave (−)-methyl 1-phenylethyl sulphide, b. p. 58—59°/1 mm., α_D^{20} −33·0°.*

(−)-*Methyl 1-Phenylethyl Sulphide from* (+)-*1-Phenylethyl Bromide.—Kinetic investigation.* 1-Phenylethyl bromide (0·5640 g.) was made up to 50 ml. with 0·0792M-sodium methyl sulphide in ethanol at 25°. Timed samples (5·23 ml.) were run into 50 ml. of ice-cold water and titrated

---

* The literature correlation (Siegel and Graefe, *J. Amer. Chem. Soc.*, 1953, **75**, 4521), methyl 1-phenyl-ethylsulphide (α_D^{25} 40·24°) from 1-phenylethyl chloride (α_D^{27} −24·3°) is inaccurate because the product is optically purer than the starting material.

[14] Downer and Kenyon, *J.*, 1939, 1156, found α_D^{17} (max.) 44·2°.
[15] Cf. Müller and Rundell, *Z. Naturforsch.*, 1959, **14**b, 209.

immediately with standard acid, using a mixed indicator (Bromocresol Green–Methyl Red, 3 : 1). The reaction was very fast; the " zero-time " sample, taken after *ca.* 6 min., corresponded to 85% reaction. The average bimolecular rate constant, k_2, as determined graphically from the first four points, was *ca.* $4 \cdot 2 \times 10^{-2}$ l. mole^{-1} sec.$^{-1}$.

Stereochemical investigation. (+)-1-Phenylethyl bromide, α_D^{20} 88·9° (3·17 g.), in 0·396M-sodium methyl sulphide in ethanol (100 ml.) was kept for 10 min. at room temperature, and (−)-methyl 1-phenylethyl sulphide, α_D^{20} −102·2°, was isolated by the above method. In a control experiment, (+)-1-phenylethyl bromide, α_D^{20} 88·9° (2·03 g.), in 0·642M-sodium methyl sulphide in ethanol (70 ml.) gave the sulphide, α_D^{20} −102·3°. It was shown independently that optically active methyl 1-phenylethyl sulphide was stable under the conditions of isolation.

WILLIAM RAMSAY ·AND RALPH FORSTER LABORATORIES,
    UNIVERSITY COLLEGE, GOWER ST., LONDON W.C.1.