**245.*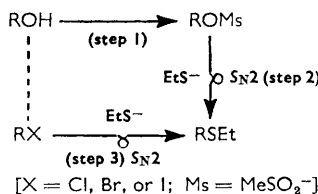* *Reaction Kinetics and the Walden Inversion. Part X.[1] A Method for Estimating the Optical Purity of Certain Secondary and Primary Alkyl Halides. Application to 1-Methylheptyl Chloride, Bromide, and Iodide.*

By H. M. R. HOFFMANN.

The rotations of optically pure 1-methylheptyl chloride, bromide, and iodide have been determined by a sequence of stereospecific reactions, and are shown to be in good agreement with the best values in the literature, obtained from the preparation of these halides from octan-2-ol. It is suggested that thiolate ions are excellent nucleophiles for carrying out stereospecific displacements at saturated carbon atoms which are susceptible to S_N2 reactions; experiments with different excesses of nucleophile are proposed as a criterion for complete inversion. The applicability of the method to other alkyl systems, and its limitations, are discussed.

IT has been stated that there is no satisfactory method for demonstrating the optical purity of alkyl halides with halogen at the asymmetric centre.[2] We now report a Walden cycle, involving a series of stereospecific reactions, which can be used to determine the maximum rotations of most secondary alkyl halides (Scheme 1).

$$ROH \xrightarrow{\text{(step I)}} ROMs$$

EtS⁻ ⟶ S_N2 (step 2)

$$RX \xrightarrow[\text{(step 3) } S_N2]{EtS^-} RSEt$$

[X = Cl, Br, or I; Ms = MeSO₂⁻]

Scheme 1.

The resolved or partly resolved alcohol, ROH, is converted in step 1, with complete preservation of optical purity, into the methanesulphonate. In step 2, this methanesulphonic ester is converted into a stable reference compound, which is independently prepared in step 3 from the alkyl halide. Steps 2 and 3 are again stereospecific, and can be carried out easily. We have found the nucleophilic displacement by thiolate ion to be most convenient, since it is one of the strongest nucleophiles towards saturated carbon

[1] Part IX, Hoffmann and Hughes, preceding paper.
[2] Skell, Allen, and Helmkamp, *J. Amer. Chem. Soc.*, 1960, **82**, 410.

which is available at present.* Therefore, the displacement of halide proceeds quickly and is of mechanism S_N2, ensuring stereospecificity, *i.e.*, 100% inversion in accord with the S_N2 rule.[3] Furthermore, side-reactions, *e.g.*, elimination, normally play a minor role and do not affect the optical purity of the reference compound.

Mechanism S_N2 in steps **2** and **3** need not be demonstrated kinetically. If the strong nucleophile is present in excess, complete inversion will normally be a foregone conclusion. However, it can be demonstrated unmistakably, by using different excesses of nucleophile for each step as a criterion, as already described for two reactions in Part IX [1] and now for 1-methylheptyl bromide (see below), where the nucleophile : substrate ratios were 4 : 1 and 10 : 1, and for 1-methylheptyl methanesulphonate, where they were 4·5 : 1 and 7·5 : 1. If the product is formed in identical optical purity in both experiments, 100% inversion is confirmed.

This method obviously depends on the condition that the alcohol is convertible into a substrate capable of undergoing an S_N2 displacement; this is normally fulfilled for secondary alcohols and for primary alcohols of the type $R \cdot CHD \cdot OH$ having an asymmetric centre. For reactive secondary systems such as 1-phenylethyl, where the methane-sulphonate or toluene-*p*-sulphonate are unstable, a less reactive leaving group has to be chosen, *e.g.*, sulphate, or else the correlation must be made through another route, as illustrated in Part IX.[1] An alternative, but slightly less satisfactory, Walden cycle is shown in Scheme 2, which was discussed earlier for 1-phenylethyl

ROH ⟶ ROEt

⋮
RX

Scheme 2.

chloride.[1] This cycle, as applied to 1-methylheptyl bromide,[4] was the first example of an estimation of an unknown rotation by way of kinetically controlled routes. Although Scheme 2 appears to be more straightforward than Scheme 1, there is the difficulty of converting the alkyl halide stereospecifically into the ethyl ether. This reaction requires much higher temperatures, where elimination, and, more seriously, solvolysis with racemisation might compete effectively.

By comparison, thiolate ions usually react 100 to 1000 times faster than alkoxide ions in S_N2 reactions at saturated carbon; however in $E2$ reactions the rate for thiolate ion predominates by a factor of the order of 10 only, thus increasing the proportion of substitution.[5] This argument, of course, is only valid if the carbon atom attacked can undergo an S_N2 displacement. It breaks down for tertiary alkyl structures, and in alicyclic systems where an approach from the rear can be difficult, elimination might dominate even when thiolate ion is being used,[6] although this should not matter as long as some product of an S_N2 mechanism can be isolated, and mechanism S_N1 does not compete.

The example chosen for demonstration was the 1-methylheptyl system. The fully resolved parent alcohol [7] has α_D^{20} 8·15° (all values for α are observed rotations for the neat liquids and l 1 dm.). In two independent experiments (+)-octan-2-ol, of 94·1% optical purity, was converted into the methanesulphonate. Subsequently, both samples were converted into (−)-ethyl 1-methylheptyl sulphide, using a 4·5- and a 7·5-fold excess of sodium ethyl sulphide. The optical results for both experiments were identical. The isolated sulphide had α_D^{20} −13·5° and, therefore, optically pure sulphide has α_D^{20} −14·3°. Likewise, the (−)-1-methylheptyl halides were converted into this reference compound, and again a large excess of nucleophile was used, as shown in the Table, column 3.

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* Although metal alkyls are even stronger nucleophiles, they simultaneously behave as electrophiles, and this leads to side-reactions such as metal–halogen exchange: RNa + R*X ⟶ R*Na + RX, and entails racemisation. This is especially true if alkyl bromides or iodides are taken as the substrates (cf. Letsinger, *Angew. Chem.*, 1958, **70**, 151).
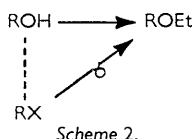
[3] Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953.
[4] Hughes, Ingold, and Masterman, *J.*, 1937, 1192.
[5] de la Mare and Vernon, *J.*, 1956, 41.
[6] Eliel and Haber, *J. Amer. Chem. Soc.*, 1959, **81**, 1249.
[7] Brauns, *Rec. Trav. chim.*, 1946, **65**, 803, and references therein.

Optical data for the conversions of 1-methylheptyl halides into ethyl
1-methylheptyl sulphide.

| | | | | Rotations for the halides | |
Halide	α_D^{20}	$\dfrac{[\text{EtSNa}]_0}{[\text{Halide}]_0}$	α_D for sulphide	Max. value from this work	Best lit. values
Chloride	$-29\cdot36°$	$3\cdot9 : 1$	$13\cdot0°$	$32\cdot4°$	$31\cdot3°$ [7,8]
Bromide	$-39\cdot6$	$10\cdot6 : 1$	$12\cdot78$	$44\cdot5$	$45\cdot0$ [7]
	$-37\cdot67$	$4\cdot1 : 1$	$12\cdot26$	$44\cdot1$	
Iodide	$-60\cdot2$	$8 : 1$	$13\cdot46$	$64\cdot2$	$63\cdot3$ [7]

Column 4 lists the rotations observed for the isolated ethyl 1-methylheptyl sulphide. In column 5, the rotations of the optically pure 1-methylheptyl halides are calculated, based upon α_D^{20} $14\cdot3°$ as the maximum rotation for ethyl 1-methylheptyl sulphide. For comparison, the best values obtained in the preparations of the halides from the alcohol are shown in column 6. The agreement with our values is within the experimental error, perhaps with the exception of 1-methylheptyl chloride, where the best value appears to be 2 or 3% lower than the theoretical maximum.

EXPERIMENTAL

(+)-Octan-2-ol, resolved by conventional methods, was kindly supplied by Dr. A. G. Davies and had α_D^{20} $7\cdot67°$, corresponding to $94\cdot1\%$ optical purity. The 1-methylheptyl halides were prepared by published methods [7,8] and checked for purity by infrared spectroscopy.

1-*Methylheptyl Methanesulphonate.*[9]—Octan-2-ol, α_D^{20} $7\cdot67°$ ($5\cdot24$ g.), was mixed with methanesulphonyl chloride ($4\cdot69$ g.), and pyridine ($8\cdot8$ g.) was added, with cooling to $0°$, during 15 min. The reaction mixture was kept for $2\cdot5$ hr. between 0 and $5°$ and then poured on to 10% hydrochloric acid cooled below $0°$. The product was extracted with light petroleum, and the organic layer was washed and dried ($MgSO_4$). The solvent was removed, leaving 1-methyl-heptyl methanesulphonate ($6\cdot8$ g.). The unpurified ester was used for the subsequent conversion into ethyl 1-methylheptyl sulphide, since on distillation it appeared to give some decomposition.

(−)-*Ethyl 1-Methylheptyl Sulphide from* (+)-1-*Methylheptyl Methanesulphonate.*—A solution of the crude methanesulphonate ($6\cdot33$ g.) in $1\cdot36\text{M}$-sodium ethyl sulphide in ethanol (100 ml.) was kept at $60°$ for 80 min., giving a thick precipitate of sodium methanesulphonate. The mixture was cooled and poured into light petroleum (100 ml.). The organic layer was washed three times with water and dried, yielding (−)-ethyl 1-methylheptyl sulphide, b. p. 66—$67°/4$ mm., α_D^{20} $-13\cdot5°$. A similar experiment with a $7\cdot5$-fold excess of nucleophile over substrate (as compared to a $4\cdot5$-fold excess in the above experiment) gave a product with an identical rotation.

(+)-*Ethyl 1-Methylheptyl Sulphide from the* 1-*Methylheptyl Halides.*—(−)-1-Methylheptyl chloride, α_D^{24} $-29\cdot36°$ ($2\cdot25$ g.) in a $1\cdot18\text{M}$-solution (50 ml.) of sodium ethyl sulphide in ethanol was kept for 6 hr. at $60°$ and (+)-ethyl 1-methylheptyl sulphide, α_D^{24} $13\cdot0°$, was isolated by the above method.

(−)-1-Methylheptyl bromide, α_D^{20} $-39\cdot6°$ ($1\cdot99$ g.), in a $1\cdot09\text{M}$-solution (100 ml.) of sodium ethyl sulphide in ethanol, gave, after 1 hr. at $60°$, (+)-ethyl 1-methylheptyl sulphide, α_D^{20} $12\cdot78°$. In a second experiment, (−)-1-methylheptyl bromide, α_D^{24} $-37\cdot67°$ ($2\cdot76$ g.), in a $1\cdot18\text{M}$-solution (50 ml.) of sodium ethyl sulphide in ethanol, gave (+)-ethyl 1-methylheptyl sulphide, α_D^{24} $12\cdot26°$.

(−)-1-Methylheptyl iodide, α_D^{21} $-60\cdot2°$ ($3\cdot52$ g.), in a $1\cdot18\text{M}$-solution (100 ml.) of sodium ethyl sulphide in ethanol, gave (+)-ethyl 1-methylheptyl sulphide, α_D^{22} $13\cdot46°$.

   [8] Cook, Coulson, Gerrard, and Hudson, *Chem. and Ind.*, 1962, 1506; Gerrard, *J.*, 1946, 744; Berlak and Gerrard, *J.*, 1949, 2311.
   [9] Williams and Mosher, *J. Amer. Chem. Soc.*, 1954, **76**, 2984.