# The Resolution of 1-Bromo-1-chloro-1-fluoroacetone and the Preparation of (+)- and (−)-Bromochlorofluoromethane

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1-Bromo-1-chloro-1-fluoroacetone has been resolved into its optical antipodes by means of its 'menthydrazide' derivative. The optically active ketones were converted into the active haloforms by use of 9N-potassium hydroxide solution.

A NUMBER of attempts have been made to obtain a pentatomic tetrahedral molecule in optically active form. Such an attempt necessarily involves the use of monovalent atoms and thus of hydrogen and the halogens. Swarts in 1896 attempted to resolve bromochlorofluoroacetic acid,[1] but was unable to obtain the active acid and was only able to infer resolution from the rotatory powers of the alkaloidal salts. In 1942 Berry and Sturtevant[2] failed to obtain conclusive results in their attempted resolution of bromochlorofluoromethane by means of its digitonide complex. An attempt at the resolution of the haloform by crystallisation of its tri-*o*-thymotide complex[3] in the presence of iso-octane, by one of the present authors,[4] gave evidence of success in that individual crystals could be recognised as (+)- or (−)- by means of Airy's Spirals in convergent monochromatic light between crossed Nicols, but it was not possible to recover the haloform in sufficient quantity for proof of resolution. In fact this method could be said to have failed for logistic rather than scientific reasons. The solubility of the various components and the volatility and the high density of the haloform made it almost impossible to assemble sufficient active molecules in one place at one time. In principle the resolution by this method could be proved by growing a large single crystal. In practice no crystals larger than 5 mm in length could be grown under ordinary laboratory conditions and these could only be obtained when the haloform was diluted with iso-octane.

1-Bromo-1-chloro-1-fluoroacetone[5] did not react to form an enamine derivative, so that it could not be

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resolved by a recently reported method.[6] Treatment with pyrrolidine caused elimination of bromine, and pyrrolidine perchlorate did not react. This behaviour is in contrast with that of acetone, which readily forms crystalline *N*-isopropylidenepyrrolidinium perchlorate when mixed with pyrrolidine perchlorate at room temperature.[7] Also 5-(α-phenylethyl)semioxamazide [8] and tartramic acid hydrazide,[9] both used as resolving agents for carbonyl compounds, did not react with the halogeno-ketone under all conditions tried.

Attempted formation of a 'bisulphite' compound with an amine hydrogen sulphite [10] gave an unstable pasty derivative. Crystallisation from benzene, in which the paste was sparingly soluble, gave a small yield of long crystalline, hygroscopic needles m.p. 138—141°, they contained no sulphur or nitrogen but all three halogens; this material was not further investigated.

The diastereoisomeric '(−)-menthydrazone' was formed smoothly by treatment of the halogeno-ketone with (−)-menthyl *N*-aminocarbamate, '(−)-menthydrazide' [11] (m.p. 96—98°; lit., 101·5—102°), in anhydrous benzene. The condensation product underwent solvolysis in polar solvents with the breaking of the $C-CX_3$ bond, ultimate loss of bromine, and the development of a red colouration in the solution. Recrystallisation of the product from the minimum quantity of hot ethanol, or more conveniently from light petroleum–ethanol (3 : 1) gave white fluffy needles, which contained no halogen; m.p. 130—131° $[\alpha]_D^{22}$ −50° (l 1 dm, *c* 1 in EtOH). Recrystallisation from warm ethanol with removal of the solvent under reduced pressure also resulted in some solvolysis. Crystallisation from ethanol in the cold, when conducted quickly under vacuum, did not lead to appreciable solvolysis, but no separation of the two diastereoisomers was achieved in this manner. Slow solvolysis of the derivative occurs in ethanol at room temperature.

Acetone, caused some loss of bromine when it was boiled with the menthydrazone. Crystallisation of the menthydrazone from carbon tetrachloride gave long needles which contained one molecule of solvent per hydrazone residue. Other solvents which readily yielded crystals of the hydrazone were light petroleum (b.p. 100—120°), cyclohexane, toluene, and ether. Unfortunately there was no change in the rotation on recrystallisation from any of these solvents.

Slow crystallisation of the (−)-menthydrazone from anhydrous benzene gave the less soluble (+)-derivative as rosettes. The more soluble (−)-form remained as a gel in the mother liquor. The (−)-form could be worked up into a white powder; it also separated as powdery spheres from acetone.

The hydrolytic scission of the menthydrazone was not straightforward. Acid hydrolysis in the presence of ethanol as reported by Woodward [11] could not be carried out because of the effect of ethanol on the rest of the molecule.

The menthydrazone was dissolved in the minimum quantity of carbon tetrachloride and refluxed with 50% (w/v) sulphuric acid solution for 3—5 h; the carbon tetrachloride layer then contained small quantities of the ketone (detected by n.m.r.), the isolation of which in the pure state was not possible because it was contaminated with free menthol and polymeric products. A similar difficulty was encountered in the resolution of α-ionone by this method,[12] but in the latter case a successful hydrolysis was achieved by the use of phthalic anhydride. This alternative method failed to regenerate any of the halogeno-ketone; the worked up product was a pungent-smelling viscous liquid which could not be identified. Other unsuccessful attempts to regenerate the ketone included: (a) use of hydrogen chloride gas, concentrated hydrochloric acid, and perchloric acid solution; (b) equilibration with a reactive carbonyl compound, *e.g.* pyruvic acid,[13] formaldehyde,[14] or acetylacetone; [15] and (c) use of oxalic acid.[16]

The ketone was finally regenerated by refluxing a solution of the menthydrazone in ether with a large excess of 73% (w/v) sulphuric acid solution, ensuring that there was maximum surface interaction between the two phases by vigorous stirring.

The resulting (+)- and (−)-bromochlorofluoroacetones had specific rotations of +0·39° and −0·34°, respectively. The chemical purity of the optically active halogeno-ketones was confirmed by g.l.c. and n.m.r. and i.r. spectroscopy. Their b.p.s refractive indices, and g.l.c. and n.m.r. properties agreed with the characteristics of the racemic ketone.[16] Their rotatory powers remained constant during 2 months at room temperature.

The (+)-halogeno-ketone showed positive c.d. in cyclohexane, ether, or methanol, with maxima at 284, 280, and 284 nm, respectively. There is a decrease in in the magnitude of the ellipticity in going from non-polar to polar solvents in this group (Table).

*Preparation of Optically Active Haloform.*—Preliminary experiments established the conditions necessary for obtaining optically active haloform from the corresponding active ketone as follows.

When dilute aqueous sodium hydroxide was added slowly to the racemic halogeno-ketone (this being kept

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in excess) it was found that the haloform reaction occurred to a minor extent, but the major reaction was probably base-catalysed polymerisation [17] of the halogeno-ketone, and other side reactions were probably involved. Some crystalline by-product was also obtained in this way. If, on the other hand, the reaction was conducted in the presence of a large excess of dilute alkali (by adding the halogeno-ketone dropwise to the dilute base) then the yield of the haloform was improved but side reactions were still appreciable. Slow addition of the optically active halogeno-ketone to 9N-potassium hydroxide gave the optically active haloform in 54% yield. It was essential to remove the haloform under reduced pressure as it was formed so that it did not remain in the alkaline medium. Its great volatility is useful in this respect. For rotation measurements a small quantity of a higher boiling solvent (cyclohexane) was added, because the volatility makes it difficult to handle the neat substance in a polarimeter tube.

Cleavage of the (+)- and (−)-halogeno-ketones gave the corresponding haloforms, $[\alpha]_D^{19}$ +0·20° and −0·13°, respectively (in cyclohexane).[18] The b.p. and g.l.c. and n.m.r. properties of the optically active haloforms agreed with those of the pure racemic haloform prepared by the method of Hine.[19]

U.v. absorption and c.d. of (+)-1-bromo-1-chloro-1-fluoroacetone

| | U.v. absorption | | Molecular ellipticity | |
|---|---|---|---|---|
| Solvent | $\varepsilon_{max.}$ | $\lambda_{max.}$/nm | $\theta$ | $\lambda_{max.}$/nm |
| Cyclohexane | 95 | 298 | +169° | 284 |
| Ether | 111 | 293 | +118 | 280 |
| Methanol | 77 | 291 | +26 | 284 |

EXPERIMENTAL

*Resolution of* 1-*Bromo*-1-*chloro*-1-*fluoroacetone*.—To a solution of (−)-menthyl *N*-aminocarbamate (107·0 g, 0·5 mol), $[\alpha]_D^{25}$ −79° (*c* 2, *l* 2 dm) in abs. EtOH) in anhydrous benzene (900 ml) was added slowly with stirring (±)-1-bromo-1-chloro-1-fluoroacetone (94·7 g, 0·5 mol). The mixture was set aside at room temperature for 12 h, after which a white solid mass was filtered off (160·5 g), $[\alpha]_D^{22}$ −50·0° (*l* 2 dm, *c* 1 in $Me_2CO$), m.p. 180—185° (decomp.). The filtrate, which contained a gelatinous mass, was evaporated to dryness at room temperature. All subsequent mother liquors were treated similarly; the solid residues were kept for later use.

The original crop of solid was dissolved in a slight excess of hot anhydrous benzene (1·2 l). The hot solution deposited crystals on slow cooling (the flask was lagged with asbestos). Filtration gave material (100 g), $[\alpha]_D^{22}$ −48° (*l* 2 dm, *c* 1 in MeCO), m.p. 192—195° (decomp.). Recrystallisation of this material gave crystals (80·5 g), $[\alpha]_D^{22}$ −47° (*l* 2 dm, *c* 1 in $Me_2CO$), m.p. 201—203° (decomp.). Seven successive crystallisations gave pure (+)-1-bromo-1-chloro-1-fluoroacetone (−)-menthydrazone (58 g.) as fine silky needles, m.p. 214—215°, $[\alpha]_D^{22}$ −45·3° (*l* 2 dm, *c* 1), $[\alpha]_D^{22}$ −45·6° (*l* 2 dm, *c* 1·5) in acetone.

The hard solids obtained by evaporation of the original filtrate and the mother liquors from the first and second recrystallisations [containing the main bulk of the (−)-1-bromo-1-chloro-1-fluoroacetone (−)-menthydrazone] were combined and dissolved in a large volume of anhydrous benzene (30 g in 800 ml); the warm solution was then innoculated with a crystal of pure (+)-halogeno-ketone (−)-menthydrazone. The small amount of crystalline solid which separated after a few hours was filtered off; $[\alpha]_D^{22}$ −48·1° (*l* 2 dm, *c* 1 in $Me_2CO$), m.p. 190—193°. The mother liquor was evaporated to dryness; the solid obtained had $[\alpha]_D^{22}$ −53° (*l* 2 dm, *c* 1 in $Me_2CO$). This process was repeated once more; the solid obtained by evaporation of the liquor was then subjected to a four-stage fractional crystallisation from benzene. The final product, washed with a small quantity of cold acetone and thoroughly dried, gave fairly pure (−)-1-bromo-1-chloro-1-fluoroacetone (−)-menthydrazone, $[\alpha]_D^{22}$ −55·5° (*l* 2 dm, *c* 1 in $Me_2CO$), m.p. 195—196° (decomp.).

*Hydrolysis of the Menthydrazones*.—Pure (+)-halogeno-ketone (−)-menthydrazone (5·0 g) dissolved in ether (400 ml) was refluxed on a water bath with vigorous stirring in contact with 73% w/v sulphuric acid (300 ml) for 48—50 h. The mixture was then cooled, the aqueous layer was extracted with ether (3 × 100 ml), and the extracts were combined with the ether layer. The ether phase was washed with water until the aqueous layer was no longer acid; it was then dried with the minimum quantity of magnesium sulphate. The ether was removed on a water bath and the residue was distilled *in vacuo* to give 1-bromo-1-chloro-1-fluoroacetone (1·1 g, 45%), b.p. 43—45° at 60 mmHg, $n_D^{25}$ 1·4404, $d_4^{21}$ 1·7026, n.m.r. (neat; $Me_4Si$ reference): δ 2·51 p.p.m., $\alpha_D^{21}$ +0·66° (homogeneous; *l* 1 dm). $[\alpha]_D^{21}$ +0·39°. In the same way the (−)-halogeno-ketone was obtained by scission of the (−)-halogeno-ketone (- )-menthydrazone; it had $\alpha_D^{21}$ −0·59° (*l* 1 dm; homogeneous) $[\alpha]_D^{21}$ −0·34°, $n_D^{25}$ 1·4404.

(+) *and* (−)-*Bromochlorofluoromethane*.—A round-bottomed flask with a side inlet was equipped for distillation (semi-micro scale). The receiver consisted of an elongated tube fitting into a 16 cm long, solid carbon dioxide-cooled, test-tube receiver. 9N-Potassium hydroxide (26 ml) was placed in the flask and the pressure in the apparatus was reduced. Ice-cold water was circulated round the condenser, and the active ketone, $[\alpha]_D^{21}$ 0·39° (1·0 g) was added (1 drop every 3 s) with stirring. When the addition was nearly complete the flask was warmed slightly (water at 60°) and left under reduced pressure for a further 4 min. Bromochlorofluoromethane (0·38 g, 54%) was collected. This process was repeated twice more, and the products were combined and distilled; b.p. 36·0—36·5°, δ (neat; $Me_4Si$ ref.) 7·64 p.p.m. (d, $J_{HF}$ 52 Hz), $[\alpha]_D^{19}$ +0·20° (*l* 1 dm, *c* 125 in cyclohexane, $\alpha_D^{19}$ +0·25°).

Similarly the (−)-halogeno-ketone, $[\alpha]_D^{21}$ −0·34° gave the (−)-haloform, $[\alpha]_D^{19}$ −0·13° (*l* 1, *c* 124 in cyclohexane, $\alpha_D^{19}$ −0·16°).

The chemical purity of the optically active haloforms was confirmed by g.l.c. and n.m.r. spectroscopy. The b.p.s and the g.l.c. behaviour and n.m.r. spectra of the optically active haloforms were identical with those of the racemic forms prepared (*a*) from the racemic halogeno-ketone and (*b*) by the method of Hine.[17] The refractive index of the racemic haloform was measured at three temperatures: $n_D^2$ 1·428, $n_D^{13}$ 1·4200, $n_D^{25}$ 1·4141.

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