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THE PREPARATION OF OPTICALLY ACTIVE CHLOROFLUOROACETIC ACID AND CHLOROFLUOROETHANOL

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Abstract—(±)-Chlorofluoroacetic acid (**1**) has been resolved into its enantiomers through the dehydroabietylamine salts; LAH reduction of methyl (−)-chlorofluoroacetate has given (−)-chlorofluoroethanol. An approximate estimation of the optical purity of (−)-**1** has been carried out by a GLPC method. Partial kinetic resolutions of (±)-**1** have been achieved through reactions with half-molar amounts of 5,6α-epoxy-5α-cholestan-3β-ol and 5,6β-epoxy-5β-cholestan-3β-ol.

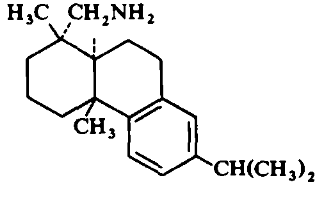
Optically active compounds such as polyhalomethanes, owing their chirality exclusively to simple atomic asymmetry, have never been obtained. Although these compounds would be of considerable theoretical interest, only few and contradictory reports are available even on the resolution of polyhaloacetic acids of the CHXY–COOH and CXYZ–COOH types. Read and McMath[1] isolated (−)-hydroxyhydrindamine (+)-chlorobromoacetate, but were not able to obtain the active free acid, a fact which they attributed to its easy racemization in aqueous solution. Backer and Mook,[2] who isolated the same acid with a low specific rotation, reported that it was optically quite stable. Chloroiodoacetic acid has been resolved,[3] but its enantiomers were obtained only as ammonium salts in aqueous solution. Swarts[4] attributed his abortive attempts at the resolution of bromochlorofluoroacetic acid to its great tendency to racemization and decarboxylation.

We began a study on optically active polyhaloacetic acids, as possible precursors for active polyhalomethanes and catalysts for asymmetric acid-catalyzed reactions, with an investigation of the resolution of chlorofluoroacetic acid (**1**) because it is readily available and chemically stable. The first attempts, made with brucine as the resolving agent, gave negative results, but the resolution of (±)-**1** could be carried out with dehydroabietylamine (**5**), a base that has lately been used with success in many optical resolutions. Six crystallizations of the diastereoisomeric salts obtained from (±)-**1** and (+)-**5**, followed by recovery of the acid, gave (+)-**1**, $[\alpha]_D^{27}$ +24·7° (neat). Five crystallizations of the more soluble salts obtained from the mother liquors led to (−)-**1**, $[\alpha]_D^{28}$ −29·9° (neat). These products were optically stable, their specific rotations remaining unchanged after distillation or standing for a long time, even in aqueous solutions in the presence of hydrochloric acid, or as the ammonium salt.

Compound (−)-**1** was converted into its methyl ester (−)-**3**, which was reduced with the stoichiometric amount of LAH to (−)-2-chloro-2-fluoroethanol, (−)-**4**.

No simple way was available for correlating the acid **1** or the alcohol **4** with chiral substances of known specific rotation. In order to establish their optical purity and

$CHFClX$
1: $X = COOH$
2: $X = COCl$
3: $X = COOCH_3$
4: $X = CH_2OH$



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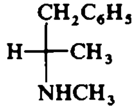
absolute configurations, the gas-chromatographic analysis of the diastereoisomers of a derivative with an optically active reagent[5] was undertaken. After several attempts on esters of **1** and **4** with various optically active alcohols and acids, which were unsatisfactory because of poor chromatographic separation, better results were achieved with the amides **7** derived from **1** and *S*-(+)-2-methylamino-1-phenylpropane [(+)-desoxyephedrine, **6**]. The compounds gave distinct peaks in the GLP



$$\begin{array}{c}\mathrm{CH_2C_6H_5}\\ \mathrm{H}-\!\!\!+\!\!\!-\mathrm{CH_3}\\ \mathrm{NHCH_3}\end{array}$$

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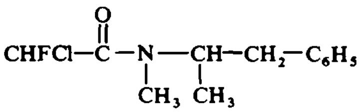

$$\mathrm{CHFCl{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}\underset{CH_3}{N}{-}\underset{CH_3}{CH}{-}CH_2{-}C_6H_5}$$

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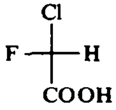
chromatogram, and could also be separated by TLC. The acid **1**, $[\alpha]_D^{28}$ −29·9°, was converted into the corresponding chloride (**2**) with PCl$_5$; no racemization took place, as shown by reconversion of the chloride into the acid. Reaction of the acid chloride with excess of (+)-**6** gave a mixture of the diastereoisomers of **7** in a ratio of 86:14, as shown by GLPC analysis. The optical purity of the starting acid could be determined if the auxiliary chiral reagent used was optically pure, or if the reaction took place without any asymmetric induction. Unfortunately, none of these assumptions proved to be true. The (+)-**6** was obtained by resolution of the racemic compound with (+)-tartaric acid and had the maximum specific rotation reported for the compound prepared by this method[6] ($[\alpha]_D^{25}$ +14·7° for the hydrochloride). However there is considerable uncertainty about the specific rotation of this amine,[7] values of up to 21·6° having been reported for the hydrochloride of the compound prepared from ephedrine. While the latter value[7c] is probably too high, because of an inconsistency in the specific rotation of the corresponding methiodide,[7e] the most reliable value is probably the one given by Emde ($[\alpha]_D$ +18°).[7b] This would indicate that the (+)-**6** used in this work was only of about 82% optical purity. Therefore, if there were no asymmetric induction in the reaction of **6** with **2**, the acid **1**, $[\alpha]_D^{28}$ −29·0°, would be of about 88% optical purity. However a quite sizable asymmetric kinetic effect is present in the reaction, as shown by the fact that reaction of (±)-**2** with (±)-**6** gives a mixture of the two diastereoisomeric (±)-**7** in a ratio of 3:2. The larger peak in the GLP chromatogram, which has the higher retention time, corresponds to the (+)-acid (+)-amide and (−)-acid (−)-amide, as can be established by comparison with the chromatogram obtained from the reaction product of (−)-**2** with (+)-**6**. This asymmetric induction prevents a precise determination of the optical purity of **1**. The error should not be too large, as shown by the fact that reaction of (±)-**2** with an excess of the same (+)-**6** gave the diastereoisomeric amides in a ratio of 52:48. As the data for the determination of the optical purity were obtained from **1** containing a large excess of the (−) enantiomer and **6** having a large excess of the (+) one, the ratio of the peaks should be corrected by decreasing the area corresponding to the amides formed from **2** and **6** of the same sign, and increasing the area of the other peak. Although the uncertainty in the maximum specific rotation of (+)-**6** does not allow a precise calculation which would be very difficult to carry out, one can admit that 88% is a minimum value for the optical purity of **1** with $[\alpha]_D^{28}$ $-29{\cdot}9°$, the actual value being probably somewhat above 90%.

If the usual hypothesis about the relation between chirality and polarizabilities of substituents holds, (+)-**1** should have the (*R*) configuration (**8**), provided the order of polarizabilities is the usually accepted one: F < H < COOH < Cl.[8] Since there is some uncertainty about the relative orders of F and H in this series, a direct proof of the configuration would be very interesting in order to clear up the latter point. Here again the problem could not be solved by chemical correlation with a compound of known chirality. A preliminary attempt was therefore made to apply a method recently proposed by Červinka and Hub[7d] for the determination of the configurations of several alkylphenylacetic acids, based on the incomplete reaction of the (±)-acid with (+)-**6**, in the presence of dicyclohexylcarbodiimide, followed by measurement of the rotation of the recovered acid. The attempt failed because it was not possible to convert **1** into the amide **7** under the conditions given by Červinka. However, considerations based on the asymmetric induction effects in the reactions of **2** with **6**, provided a hint even if a rather frail one. It has been seen that in this reaction an asymmetric kinetic effect favors the reaction of each enantiomer with the partner of the same sign. Therefore the (−)-acid (−)-amide is formed preferentially with respect to its diastereoisomers. If one assumes that the transition states in this reaction (**9**) are similar and have the same steric requirements as the ones in Červinka's reaction (**10**), and that the working hypothesis made to explain the asymmetric induction, i.e. that only the different sizes of the groups attached to the chiral centers cause the preferential formation of diastereoisomer A, is correct, the (−)-acid should have the (*S*) configuration, in accordance with the assignment made on the basis of the polarizabilities. This conclusion must however be taken as very tentative, because no experimental proof is available to confirm the similarities in the mechanisms of the two reactions, which are conducted under rather different conditions.



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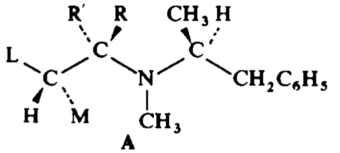
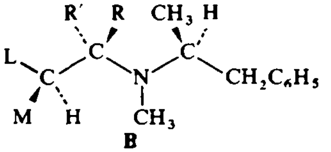


A



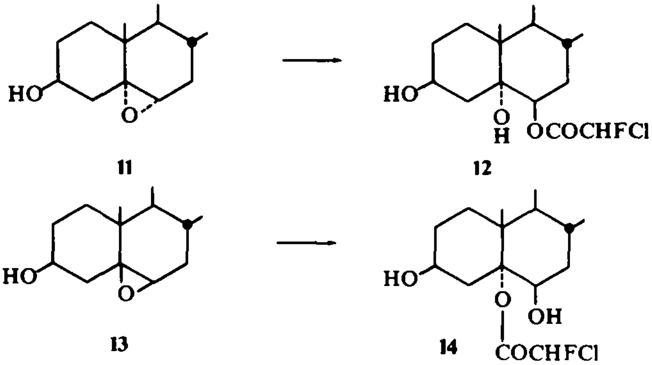
B

9: R, R' = OH or Cl

10: R, R' = OH or $-O-C(=NC_6H_{11})NHC_6H_{11}$

Furthermore doubt has been expressed on an explanation of the asymmetric induction based only on group sizes,[9] and most schemes proposed to explain kinetic effects of this type usually hold well only for homologous series, while replacement of a Ph group with a Cl atom and of an alkyl group with a F atom can hardly be regarded as a minor change. It will therefore be tried to clear up the configurational problem through a reliable X-ray technique.

Since chlorofluoroacetic acid is a reasonably strong acid, its enantiomers could be of some use as catalysts for asymmetric kinetic transformations involving acids as reactants or catalysts. In a preliminary investigation on reactions of this type, and in connection with our work on epoxides, it was interesting to establish if some asymmetric induction could be observed in the reaction of **1** with epoxides. (±)-**1** was therefore reacted with half molar amounts of 5,6α-epoxy-5α-cholestan-3β-ol (**11**) and 5,6β-epoxy-5β-cholestan-3β-ol (**13**). After isolation of the excess unreacted acid it was found that it had $[\alpha]_D^{30}$ +1·50° (ca. 4·5% optical yield) in the case of the reaction with **11**, and −0·13° (0·4% optical yield) in the second case. Both reactions very probably take place with diaxial ring opening[10] to give respectively the 5α-hydroxy-6β-acyloxy- (**12**) and the 5α-acyloxy-6β-hydroxy compound (**14**). The large difference in the optical yields can in part be accounted for by the presence of the 10β-Me group, making the β side more shielded than the α one; anyway the degree of asymmetric induction in the reaction with **11** is unexpectedly high for a reaction of this type and indicates definite steric requirements in the transition state. An extension of work in this field appears worth while, as it could give some useful information about the geometry of the transition states in epoxide ring openings, on which very little is known at present.



EXPERIMENTAL

M.ps were determined on a Kofler apparatus and were not corrected. Rotatory powers were taken on a Perkin–Elmer, Mod. 141, photoelectric polarimeter. A dual column Carlo Erba Fractovap G.V. with flame ionization detectors was used for the GLPC analyses.

Chlorofluoroacetic acid (**1**), b.p. 165°/760 mm, n_D^{21} 1·4143 (lit.[11] b.p. 162°, n_D^{25} 1·4085) was prepared by hydrolysis of the corresponding ethyl ester,[11] obtained from chlorotrifluoroethylene (Matheson Co.) by the method of Englund.[12]

Resolution of **1**. Dehydroabietylamine (**5**) was obtained from commercial Amine 750 (Hercules Powder Co., Inc.) through repeated crystallizations from toluene of its acetate[13] to a m.p. 144–146°, $[\alpha]_D^{25}$ +31° (*c*, 5, MeOH) (lit.,[13] m.p. 141–143·5°, $[\alpha]_D^{25}$ +30·2°); the free base had m.p. 41·5–43° (lit.,[13] m.p. 44–45°).

A soln of **5** (70 g, 0·246 mole) in EtOAc (400 ml) was added to a soln of (±)-**1** (27·5 g, 0·246 mole) in the same solvent (100 ml). After 4 hr at room temp the salt (75 g) was collected, washed with EtOAc (150 ml) and recrystallized from 600 ml EtOAc to give 51 g, m.p. 145–148°, $[\alpha]_{\mathrm{D}}^{25}$ +29·4° (*c*, 0·65, $CHCl_3$); after 4 more crystallizations from EtOAc, m.p. and specific rotation remained constant: m.p. 150·5–151·5°, $[\alpha]_{\mathrm{D}}^{24}$ +36·3° (*c*, 0·595, $CHCl_3$). (Found: C, 66·28; H, 8·50; N, 3·42; F, 4·77; Cl, 9·28. $C_{22}H_{33}ClFNO_2$ requires: C, 66·40; H, 8·36; N, 3·52; F, 4·77; Cl, 8·91%). A soln of this salt (12 g) in water was made alkaline with 5% ammonia, **5** was eliminated by extracting 4 times with 100-ml portions ether, the aqueous layer was acidified with HCl and extracted again with 5 100-ml portions ether; the dried ($MgSO_4$) ether extracts were evaporated and the residue was distilled to give 2·2 g of (+)-**1**, b.p. 65–67°/10 mm, n_{D}^{23} 1·4140, d_4^{25} 1·532, $[\alpha]_{\mathrm{D}}^{27}$ +24·7° (neat). The specific rotation did not change after a second distillation. Table 1 gives the specific rotations in several different solvents.

The combined mother liquors from the initial precipitation and from the first crystallization were evaporated to dryness and the residue was crystallized twice from 200 ml $CHCl_3$ to give 15·2 g of a salt, m.p. 146–147°, $[\alpha]_{\mathrm{D}}^{25}$ +21·4° (*c*, 0·50, $CHCl_3$). Three more crystallizations led to constant m.p. and specific rotation: 7·2 g, m.p. 148·5–149°, $[\alpha]_{\mathrm{D}}^{25}$ +16·9° (*c*, 0·476, $CHCl_3$). (Found: N, 3·62. $C_{22}H_{33}ClFNO_2$ requires: N, 3·52%). The acid (−)-**1** was isolated as described above: 1·25 g, b.p. 65–67°/10 mm, n_{D}^{22} 1·4144, $[\alpha]_{\mathrm{D}}^{28}$ −29·9° (neat).

TABLE 1

Solvent	*c*	$[\alpha]_{589}$	$[\alpha]_{578}$	$[\alpha]_{546}$	$[\alpha]_{436}$	$[\alpha]_{365}$
neat		+24·7°	+24·8°	+28·8°	+57·4°	+103·5°
benzene	3·18	+46·5°	+46·5°	+52·7°	+94·3°	+157·4°
ethyl ether	3·48	+24·7°	+25·0°	+27·2°	+52·8°	+91·6°
water	2·03	+16·4°	—	—	—	—
0·46N HCl aq	5·15	+24·2°	+24·2°	+28·4°	+55·0°	+102·1°
ammonium salt in water	2·34	+6·3	+6·3°	+7·8°	+17·8°	+39·4°

Methyl (−)-chlorofluoroacetate (**3**). A soln of (−)-**1** (5·03 g, $[\alpha]_{\mathrm{D}}^{26}$ −7·02°, neat) in ether (50 ml) was treated with a slight excess of diazomethane in ether. After 3 hr the solvent was eliminated and the residue distilled to give **3** (3·5 g), b.p. 70°/200 mm, n_{D}^{24} 1·3927, d_4^{25} 1·323, $[\alpha]_{\mathrm{D}}^{25}$ −6·76, $[\alpha]_{546}^{25}$ −7·88°, $[\alpha]_{436}^{25}$ −15·63°, $[\alpha]_{365}^{25}$ −28·94° (neat) (lit.[11] (±)-**3**, b.p. 116°, n_{D}^{25} 1·3903).

(−)-2-*Chloro-2-fluoroethanol* (**4**). A soln of **3** (3·5 g, 0·0276 mole, $[\alpha]_{\mathrm{D}}^{25}$ −6·76°) in 50 ml anhyd ether was treated dropwise during 40 min with a 0·052M LAH (300 ml) in ether,[14] refluxed for 90 min, treated with a few drops water, then with 2N H_2SO_4 (50 ml). The ether layer was separated and the aqueous repeatedly extracted with ether, the combined ether solns dried ($MgSO_4$), evaporated and the residue distilled to give two fractions: I, b.p. 75–80°/165 mm (0·64 g), n_{D}^{25} 1·4015, $[\alpha]_{\mathrm{D}}^{25}$ −5·72° (neat, 1 dm); II, b.p. 80–82°/165 mm (1·02 g), n_{D}^{25} 1·4037, $[\alpha]_{\mathrm{D}}^{25}$ −6·16°, $[\alpha]_{546}^{25}$ −7·00°, $[\alpha]_{436}^{25}$ −12·02°, $[\alpha]_{365}^{25}$ −18·97° (neat, 1 dm). The IR spectrum of fraction II was identical with that of (±)-**4**, b.p. 117–119°/760 mm, n_{D}^{26} 1·4036 (lit.,[15] b.p. 54°/60 mm, n_{D}^{20} 1·4080), prepared by similar reduction of ethyl (±)-chlorofluoroacetate; it was also characterized as the 3,5-dinitrobenzoate, m.p. 63·5–65° (from ether). (Found: N, 9·55; F, 6·51; Cl, 11·88. $C_9H_6ClFN_2O_6$ requires: N, 9·57; F, 6·49; Cl, 12·12%).

(−)-*Chlorofluoroacetyl chloride* (**2**). (−)-**1** (1·4 g, $[\alpha]_{\mathrm{D}}^{28}$ −29·9°) was added dropwise to PCl_5 (2·85 g) under exclusion of moisture and with external cooling, in order to keep the temp at 20°. The mixture was shaken for 90 min at room temp, then distilled while cooling the condenser and the collector at −25°: (−)-**2** (0·5 g), b.p. 33–35°/200 mm (lit.,[11] (±)-**2**, b.p. 69–70°/760 mm). A sample of this compound was hydrolysed with water; the soln had $[\alpha]_{\mathrm{D}}^{25}$ −29·30° (*c*, 5·28); a similar aqueous soln prepared from the starting acid ($[\alpha]_{\mathrm{D}}^{28}$ −29·9°, neat), in the presence of an equivalent amount of HCl had $[\alpha]_{\mathrm{D}}^{25}$ −29·35°, showing that no racemization takes place in passing from (−)-**1** to (−)-**2**.

Determination of the optical purity of (−)-**1**

Resolution of **6**. Compound **6** (30 g, 0·2 mole) and (+)-tartaric acid (30 g, 0·2 mole) in MeOH (100 ml) gave 43 g of a salt, which was crystallized 4 times from MeOH to give 10 g of (−)-**6** (+)-tartrate, m.p. 161–163°, $[\alpha]_{\mathrm{D}}^{25}$ +16·30° (*c*, 1·30, MeOH) (lit.,[6] m.p. 165–166°); the base obtained from this salt (4·2 g) had

$[\alpha]_D^{24}$ $-2{\cdot}21°$ (neat). Evaporation of the combined mother liquors from the initial mixture and from the first recrystallization, followed by two crystallizations from 2-propanol gave 20 g of (+)-**6** (+)-tartrate, m.p. 116–117°, $[\alpha]_D^{25}$ $+14{\cdot}4°$ (*c*, 1·30, MeOH) (lit.,[6] m.p. 118–119°); no change in m.p. and $[\alpha]_D$ occurred after a further crystallization from 2-propanol. The latter salt (18 g) gave (+)-**6** (8 g), $[\alpha]_D^{24}$ $+2{\cdot}48°$ (neat); hydrochloride: $[\alpha]_D^{25}$ $+14{\cdot}7°$ (*c*, 1·57, H_2O) (lit.,[6] $[\alpha]_D$ $+14{\cdot}8°$).

Reactions between **2** *and* **6**. A soln of (±)-**2** (0·246 g, 1·88 mmole) in benzene (5 ml) was treated with (±)-**6** (0·576 g, 3,85 mmole) in benzene (7 ml). After 1 day at room temp the precipitated hydrochloride was filtered off and the soln was washed with 2N HCl and satd Na_2CO_3aq, dried ($MgSO_4$) and evaporated. The oily residue (0·360 g) was analysed by GLPC (2-m glass column, 3 mm inner diam; 1% neopentylglycol succinate on silanized 60/80 mesh Chromosorb W; 40 ml/min N_2; column temp 150°). Two peaks were observed with retention times 28·5 min (A) and 30·5 min (B) in a ratio of 2/3.

When the reaction was repeated with (±)- **2** and (+)-**6**, $[\alpha]_D^{24}$ $+2{\cdot}48°$, in a molar ratio of 1 to 3, and the mixture was left at room temp for 36 hr, the product presented the same peaks in the GLP chromatogram, but the ratio of the areas of A and B was now 48/52; TLC of the mixture (silica gel, elution with benzene containing 1·5% MeOH, revelation by UV fluorescence) also showed two well separated spots of about equal intensity.

The reaction was then repeated under the same conditions with the (−)-**2** obtained from the (−)-**1**, $[\alpha]_D^{28}$ $-29{\cdot}9°$ and (+)-**6**, $[\alpha]_D^{24}$ $+2{\cdot}48°$. The GLP chromatogram now showed the two peaks A and B in a ratio of 86/14. Also TLC showed that one of the two diastereoisomeric amides was present in large excess. If (+)-**6** contains 9% of (−)-**6**, and if no asymmetric kinetic effect were operative, the amount of (+)-**1** (*x*) present in the starting (−)-**1** would be obtained by the equation:

$$0{\cdot}09\,x + 0{\cdot}91\,(100\text{-}x) = 86$$

Therefore $x = 6\%$. The minimum optical purity of (−)-**1** $[\alpha]_D^{28}$ $-29{\cdot}9°$, would therefore be about 88%.

Kinetic resolution of (±)-**1**

(a) 5,6α-Epoxy-5α-cholestan-3β-ol[16] (**11**, 3·65 g, 9 mmole) in benzene was added dropwise to (±)-**1**- (2·0 g, 18 mmole) in benzene (25 ml), cooled at 6°. The soln was left at room temp overnight, then extracted with four 20-ml portions of water. The aqueous extract was extracted again with four 40-ml portions of ether, the extract dried ($MgSO_4$), evaporated and distilled to give (+)-**1**, b.p 67°/10 mm, $[\alpha]_D^{30}$ $+1{\cdot}50°$, $[\alpha]_{546}^{30}$ $+1{\cdot}76°$, $[\alpha]_{436}^{30}$ $+3{\cdot}49°$, $[\alpha]_{365}^{30}$ $+6{\cdot}26°$.

(b) When the same reaction was repeated with **13**,[17] the isolated acid had $[\alpha]_D^{30}$ $-0{\cdot}13°$, $[\alpha]_{546}^{30}$ $-0{\cdot}15°$, $[\alpha]_{436}^{30}$ $-0{\cdot}30°$, $[\alpha]_{365}^{30}$ $-0{\cdot}55°$.

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