SOME STEREOCHEMICAL FUNCTIONS OF THE CHOLESTERYL GROUP.

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for the Degree of Doctor of Philosophy

By

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ABSTRACT OF THE THESIS.

Two stereochemical functions of the cholesteryl group were investigated and are described in Sections "A" and "B".

In Section "A" cholesterol has been investigated as a potential resolving group. PART I of this Section deals with the preparation of (±)-hydratropic acid, (±)-hydratropoyl chloride and the synthesis and partial resolution of cholesteryl (±) hydratropate. A review of the various methods of making (±)-hydratropic acid is given. PART II deals with the resolution of (±)-hydratropic acid, the preparation of optically pure (+)- and (-)-hydratropyl alcohol, optically pure cholesteryl (+) hydratropate, cholesteryl (-) hydratropate and cholesteryl (±) hydratropate. The synthesis of optically pure (-)-hydratropyl alcohol from cholesteryl (+) hydratropate is described.

In Section "B" is described the use of cholesterol as an activating alcohol for asymmetric synthesis and its comparison with (-)-menthol. It deals with the preparation of (-)-menthyl benzoylformate and cholesteryl benzoylformate and their reduction by

(a) Lithium aluminium hydride,

(b) Aluminium amalgam, Sodium borohydride and Aluminium isopropoxide followed by Lithium aluminium hydride.

Cholesterol was found to exert an opposite activating influence to that of (-)-menthol on the course of asymmetric synthesis.

ACKNOWLEDGEMENT.

I wish to express my deep gratitude to Professor E. E. Turner, Bedford College, London, for supervising this research work and for his invaluable advice and criticism.

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GENERAL NOTES.

1. Analyses were carried out by Drs. Weiler and Strauss, Oxford.
2. Melting points are un-corrected.
3. All rotations were determined by using a 2 dcm. polarimeter tube unless otherwise stated.
4. For work in which temperature control was required, a water jacketted polarimeter tube was used. The desired temperature was obtained by changing the temperature of the water in a large bath which was connected to the polarimeter tube jacket through a circulating pump. The solution in the polarimeter tube was maintained at a constant temperature $\pm 0.1^{\circ}$.
5. The letters "G" and "D" stand for mercury green and Na yellow light, i.e. wave lengths 5461 and 5893 respectively.

I. INTRODUCTION.

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Numerous investigations have involved the use of (-)-menthol as a source of an optically active centre in a molecule with which various reactions can be carried out. The following are typical examples:-

(a) Resolution.

1. Wren and Wright (J.Chem.Soc., 1921, 119, 798) found that the mixture of esters derived from (±)-α-hydroxy-β-phenyl-propionic acid and (-)-menthol, when crystallised from light petroleum, yields the (-)-menthyl ester of (+)-acid in well defined crystals and on hydrolysis, this gives the (+)-acid.

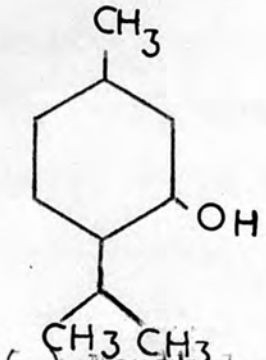
2. (-)-Menthoxyacetic acid has been used for the resolution of phenols, glycols and alcohols of high molecular weight. The resolution of glycols is usually difficult by other methods. (±)-Menthol and (±)-neomenthol were completely resolved by the successive use of (-)-menthoxy-acetic acid and (+)-menthoxyacetic acids. Also, (-)-menthoxyacetic acid has been used successfully by Wilson and Read (J. Chem. Soc., 1935, 1269) for resolving (±)-trans cyclohexane - 1,2-diol.

3. Marckwald and McKenzie (Ber., 1901, 34, 469) effected partial resolutions of (±)-mandelic acid and related acids with (-)-menthol. If an excess of the racemic acid is employed, the unesterified acid, at the end of the reaction, was found to be optically active.

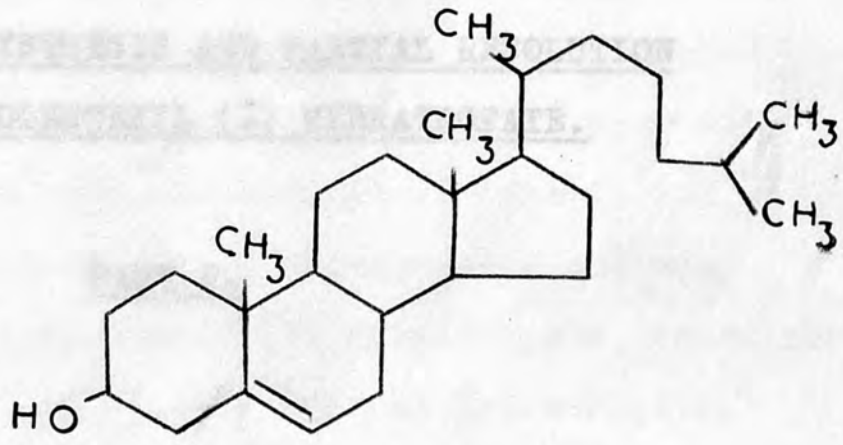
(b) Partial Asymmetric Synthesis.

1. An excess of the (-)-form of mandelic acid has been obtained by esterifying benzoylformic acid with menthol, acetylating the reduced ester and finally hydrolysing the product formed (McKenzie, J.Chem.Soc., 1904, 85, 1249; McKenzie and Humphries, J. Chem. Soc., 1909, 95, 1105). McKenzie and his colleagues also obtained similar results with Grignard reagents.

2. Reid and Turner (J.Chem.Soc., 1949, 3365; 1950, 3694) obtained a dextrorotatory β-hydroxy-β-phenylbutyric acid by using acetophenone, (-)-menthyl bromoacetate and zinc (Reformatsky reaction).



(-)-Menthol.



Cholesterol.

Cholesterol has not been used in the way that menthol has, and it appeared to be of some interest to investigate it, particularly as it is accessible in a reasonably pure condition and is known to form readily crystallisable derivatives.

SECTION A.

II. THE SYNTHESIS AND PARTIAL RESOLUTION OF CHOLESTERYL (±) HYDRATROPATE.

PART I.

II. The Synthesis and Partial Resolution of Cholesteryl (±) Hydratropate.

PART I.

PRESENT WORK.

Cholesteryl (±) hydratropate has been prepared and crystallised from various solvents in the hope that the cholesteryl (+) hydratropate and cholesteryl (-) hydratropate could be separated. The work involved the preparation of (±)-hydratropic acid and (±)-hydratropoyl chloride, the conversion of the latter into cholesteryl (±) hydratropate and the systematic crystallisation of the ester. It was thought at first that resolution was occurring, since crystallisation gave a very sparingly soluble ester and a very soluble ester. The former, however, accumulated in great preponderance and was later shown to be cholesteryl (±) hydratropate, containing a very small amount of cholesteryl (+) hydratropate. Confirmation of this followed from the fact that reduction of the very sparingly soluble ester with lithium aluminium hydride gave (-)-hydratropyl alcohol with $[\alpha]_D^{19.6}$ -1.0°(±0.02°), $[\alpha]_G^{19.6}$ -1.2°(±0.02°), (l = 1 dm, homogeneous). Optical purity 6%.

From the mother liquors, using various solvents, a small amount of cholesteryl (-) hydratropate was isolated.

It is concluded that although the (+)-ester is very sparingly soluble in most solvents, the (±)-ester is almost equally so and therefore, when it first separates, it may contain an amount of (+)-ester equal in quantity to that of the very soluble (-)-ester.

Under crystallisation conditions used the (-)-ester did not undergo partial inversion, nor could it be made to do so in hot pyridine solution in presence or not of pyridine hydrochloride.

EXPERIMENTAL.

Preparation of (±)-hydratropic acid.

Method 1.

Hydrolysis of hydratropnitrile.

The method of Campbell and Kenyon (J. Chem. Soc., 1946, 25) was used.

A suspension of sodamide (50g.; 1.28 moles) in dry ether was added during 2 hr. to a well stirred solution of redistilled benzyl cyanide (140.9g.; 1.2 moles) b.p. 102-103°/13mm., in dry ether (100 ml.), placed in 2litre three-necked flask, fitted with a Hershberg stirrer and a reflux condenser. It was then cooled in ice and dimethyl sulphate (170g.; 1.34 moles) added dropwise during 3hr. After stirring for a further 6hr. at room temperature, water was added and the ethereal layer separated, dried ($MgSO_4$) and distilled, 103.4g. (82.6%) of hydratropnitrile b.p. 100-103°/14mm. were obtained.

Hydratropnitrile (130.4g.; 0.99 mole) was added to a mixture of water (110 ml.), glacial acetic acid (140 ml.) and concentrated sulphuric acid (150 ml.). Boiling under reflux began spontaneously and was maintained under reflux by heating on a wire gauze for 3 hr. The mixture was cooled and the upper oily layer separated. It was washed with water and dissolved in 2N. sodium

hydroxide. The alkaline solution was extracted with ether and acidified. The resulting hydratropic acid was dried ($MgSO_4$) and distilled. It yielded 80.6g. (54%), b.p. 153-156°/23mm.

Method 2.

Oxidation of hydratropic aldehyde.

The method of Abbott, (Ph.D. Thesis, London, 1951), was used.

Redistilled commercial hydratropic aldehyde (200g.; 1.49 moles), b.p. 90°/17mm. was placed in a 2 l. three-necked flask. Acetone (400 ml.) and water (150 ml.) were added. The mixture was boiled under reflux and vigorously stirred. Finely ground and sieved (40 mesh sieve) potassium permanganate (150 g.) and hydrated magnesium sulphate (118g.) were added during 1hr. The reaction was moderated by cooling to 0°. After further stirring for 2 hr. at room temperature, the mixture was cooled and sulphur dioxide passed through it until the precipitated manganese dioxide just dissolved and the solution was clear. The pink solution was extracted with ether. The ether was distilled off and the residue mixed with excess of sodium bicarbonate (130g. in 1500 ml. water). The undissolved oil was removed by extraction with ether and the alkaline solution acidified with hydrochloric

acid. It was extracted with ether, dried (Na_2SO_4) and distilled. It yielded hydratropic acid (52.5g.; 23.4%) b.p. 150°/17mm. In the second experiment, the yield was 30%.

Method 3.

Action of carbon dioxide on a Grignard reagent.

Preparation of α-phenylethyl chloride.

The procedure of Norris, Watt, Thomas (J. Amer. Chem. Soc., 1916, 38, 1071) was modified to the following.

A mixture of redistilled secondary methylphenylcarbinol, b.p. 90°/15mm. (122g. ; 1 mole) and concentrated hydrochloric acid (1 litre; d 1.18) was shaken vigorously for 45 min. at room temperature. The oily layer was separated and twice shaken with concentrated hydrochloric acid (200 ml.) It was dried (Na_2SO_4) and distilled. α-phenylethyl chloride; b.p. 92-94°/34-35mm. was obtained in 92% yield.

Preparation of (±)-hydratropic acid.

1st preparation.

α-phenylethyl chloride (120.7g.; 0.85 mole) in dry ether (300 ml.) was added during 45 min. to a Grignard reagent prepared from magnesium (28g.; 1.1 atoms)

and α-phenylethyl chloride (8.4g. ; 0.059 mole) in dry ether (200 ml.), stirred mechanically. After the completion of the addition, refluxing was maintained by external heating for 15 min. The cooled solution was decanted slowly from the excess of magnesium on to solid carbon dioxide (345g.). The flask was rinsed with two 25 ml. portions of dry ether, which were added to the carbonation mixture. When the bulk of the solid carbon dioxide had evaporated, concentrated hydrochloric acid (50 ml.) and enough ice to keep the mixture cool were added with stirring. The oily layer was separated and the aqueous layer thrice extracted with ether. The combined extracts were treated with 25% sodium hydroxide solution. The alkaline extract was distilled on a water bath, until its volume was reduced to about 10%, allowed to cool and acidified with concentrated hydrochloric acid. The hydratropic acid was dried (Na_2SO_4) and distilled. Yield 65.2g. (47%), b.p. 152-153°/20mm.

Under different conditions, dimethyldiphenylethane m.p. 122-124° (lit. 126°) was obtained (cf. Salkind, Peschekerowa, Chem. Zentr., 1914, II, 1269 and Ott. Ber., 1928, 61, 2124).

Second preparation.

α-Phenylethyl chloride (70.2g. ; 0.5 mole) in a dropping funnel; 8g. were added to a mixture of magnesium turnings (18.5g. ; 0.75 atoms) and sodium-dried ether (200 ml.) contained in a 2 l. two-necked flask equipped with two double reflux condensers;one above the other, and a dropping funnel each being protected from moisture until completion of the reaction by calcium chloride tubes attached to the openings. A crystal of iodine was added and the mixture gently warmed to initiate the reaction. After the iodine colour disappeared, the remaining 62.2g. of α-phenylethyl chloride were added dropwise with intermittent shaking over a period of 45 min., so as to maintain gentle refluxing of the ether. After the completion of the addition, refluxing was maintained by external heating for 15 min. The mixture was cooled and the solution decanted slowly from the excess of magnesium on to pulverized solid carbon dioxide (500g.) . The flask was rinsed with two 25 ml. portions of dry ether, which were added to the carbonation mixture. The mass was well stirred and when the bulk of solid carbon dioxide had evaporated, concentrated hydrochloric acid (50 ml.) and enough ice to keep the mixture cool were added with stirring. The oily layer was separated and the aqueous layer thrice extracted with ether. The combined extracts were treated with 25% sodium hydroxide

solution. The ethereal layer was separated and the alkaline extract acidified with concentrated hydrochloric acid. No hydratropic acid was obtained, however, the ethereal layer on distillation gave dimethyldiphenyl—ethane. It had a m.p. 122-124° after two crystallisations from diethyl ether.

Because of this unexpected result diethyl ether and magnesium turnings were super dried and were used in the subsequent preparations.

Drying of the reagents.

Diethyl ether.

Anhydrous ether for the Grignard reaction, was prepared from the commercial variety by drying, first with anhydrous calcium chloride for three nights and finally with sodium wire, with which it was then stored.

Magnesium turnings.

Magnesium turnings were dried at 100° in an oven for 3 hours and then cooled in a vacuum desiccator over calcium chloride.

Third preparation.

This preparation was carried out in a similar manner and with the same quantities of the starting materials as in the second preparation. Only dimethyldiphenylethane was recovered on the distillation of the ethereal layer

and no hydratropic acid was isolated.

Fourth preparation.

The experiment was repeated according to the second preparation with half of the starting materials used there. As before dimethyldiphenylethane was obtained on the distillation of the ethereal layer and no hydratropic acid was isolated.

Fifth preparation.

This experiment was a repetition of the first preparation with the difference that the quantities of the starting materials used were half of those mentioned there, the use of a mechanical stirrer was avoided and the flask was shaken by hand. The product was worked up in the usual way. Again no hydratropic acid was obtained but the ethereal layer on distillation gave only dimethyldiphenyl-ethane.

The total yield of dimethyldiphenylethane from the above four preparations was 128.5 gms.

Sixth preparation.

The procedure was the same as for the first preparation, using α-phenylethyl chloride (45.5g.), dry ether (210 ml.) and magnesium turnings (11g.) It yielded hydratropic acid 28.6g. (59%), b.p. 153-155°/18mm., which when twice distilled gave 24.2g. of the hydratropic acid

b.p. 152-154°/20mm., n_D^{21} 1.5217.

Seventh preparation.

The procedure was the same as for the 1st preparation. α-Phenylethyl chloride (118.6g.), dry ether (575 ml.) and magnesium turnings (31g.) were used. It yielded hydratropic acid (73.5g. ; 58%), b.p. 155°/21mm; plus dimethyldiphenylethane, m.p. 124-125° after two crystallisations from methanol. The overall yield of hydratropic acid was 75% based on the recovered hydrocarbon. This hydratropic acid was redistilled when 68.5g. of the acid, b.p. 159°/25mm. n_D^{25} 1.5204 were obtained.

Preparation of (±)-hydratropoyl chloride.

(a) (±)-Hydratropic acid (method 1) (80.6g. ; 0.53 mole) was mixed with thionyl chloride (111g. ; 0.93 mole) b.p. 76-78°, in a 500 ml. flask. The mixture boiled spontaneously under reflux. It was occasionally shaken and left overnight and then heated on a water bath for 1 hr., when the evolution of hydrogen chloride and sulphur dioxide had ceased. Removal of excess of thionyl chloride by distillation followed by distillation and redistillation under reduced pressure gave hydratropoyl chloride (74g. ; 81.7%), b.p. 81-83°/10 mm. It had a bright pink colour.

Found: Cl, 21.0.
C_9H_9OCl requires Cl, 21.0%.

(b) (±)-Hydratropic acid (method 2) (33g.) gave colourless hydratropoyl chloride (31.5g.), b.p. 84-85°/11mm, (85%). It gave hydratropamide, needles from aqueous ethyl alcohol, m.p. 91-92°, (lit., 91-92°).

(c) Hydratropoyl chloride (63.2g.) prepared from (±)-hydratropic acid (method 3). (65.2g.), had a b.p. 81-82°/8mm., n_D^{20} 1.5209. It was obtained in 86% yield and was colourless. (Hydratropamide m.p. and mixed m.p. 91-92°).

Purification of cholesterol.

A solution of the commercial product (B.D.H., m.p. 145-149°) in methylated spirit was boiled in presence of charcoal. The hot suspension was filtered and allowed to cool. Pearly plates of cholesterol were filtered off. They were dried in the air, on a boiling water bath and finally in a vacuum desiccator over concentrated sulphuric acid. They then melted at 145°. After two re-crystallisations from methylated spirit the product melted at 147-148° and had

$[\alpha]_D^{22.4}$ -39.3° (± 0.4°), $[\alpha]_G^{23.2}$ -47.6°(±0.4°),

(c 2.4490 in $CHCl_3$) as compared with m.p. anhydrous 148.5° and $[\alpha]_D$ -39.5°, $[\alpha]_G$ -48° (in $CHCl_3$) recorded in the literature.

Preparation of Cholesteryl (±) hydratropate.

(d) Dried cholesterol (152g. ; 0.39 mole) was dissolved in dried pyridine (600 ml.) Hydratropoyl chloride (a) (72g. ; 0.42 mole) was gradually added with frequent shaking. A light yellow precipitate suddenly separated. The temperature rose to 45°. Was allowed to stand for 2hr. Heated on a boiling water bath for ½ hr. The mixture was kept overnight and then poured into cold 5% hydrochloric acid. The precipitate was washed with cold 5% hydrochloric acid and then with cold water. It was taken up in chloroform, extracted thrice with 5% hydrochloric acid, twice with 5% sodium bicarbonate and thrice with water. The chloroform was removed by evaporation. The residue crystallised from methylated spirit, yield 179 g. (88%).

(e) Hydratropoyl chloride (b) 31g., when added to dry cholesterol (65g.) in pyridine gave by above procedure cholesteryl (±) hydratropate 79.2g. (91%).

(f) (i) Hydratropoyl chloride (c) 14.6 g., when added to a pyridine solution of cholesterol (25.3g.) gave cholesteryl (±) hydratropate 30.3 g. (88%).

(ii) In the second experiment hydratropoyl chloride (c) 28g., when added to cholesterol (55g.) in pyridine (160 ml.) gave cholesteryl (±) hydratropate 70 g., (95%).

Partial resolution of cholesteryl (±) hydratropate.

It is readily soluble in benzene, chloroform, ether, carbon tetrachloride and pyridine, sparingly soluble in cold ethyl alcohol, methylated spirit, acetic acid, ethyl acetate and light petroleum (b.p. 60-80°) but easily soluble in hot solvents. It is practically insoluble in water.

Cholesteryl (±) hydratropate (d).

By Crystallisation from (i) Light Petroleum (b.p. 60-80°), and (ii) Chloroform-Methanol.

Cholesteryl (±) hydratropate (d) 179.5g. were dissolved in boiling light petroleum (b.p. 60-80°; 1100 ml.) and the solution allowed to crystallise in a refrigerator overnight. The crop which separated was filtered, giving 55.4 g. of a cholesteryl hydratropate in white, glistening prisms. The concentration of the filtrate by evaporation

yielded a second crop (31.6g.) These two crops were combined and recrystallised as before from light petroleum (b.p. 60-80°). After three crystallisations, maximum activity was obtained from this solvent, when 48.9g. were obtained, which melted at 115-116° and had

$[\alpha]_D^{20.6}$ -19.3° (±0.4°),

$[\alpha]_G^{20.6}$ -22.9° (±0.4°),

(c 2.4950 in $CHCl_3$).

On crystallising from a mixture of chloroform-methanol at the temperature of the laboratory, the cholesteryl hydratropate in white pearly plates, amounted to 41.5 g., m.p. 116-117° and had

$[\alpha]_D^{24.8}$ -19.9° (±0.4°),

$[\alpha]_G^{24.8}$ -21.7° (±0.4°),

(c 2.3950 in $CHCl_3$).

For analysis it was dried in a drying pistol.
(Found: C, 83.4; H, 10.4 $C_{36}H_{54}O_2$ requires C, 83.3; H, 10.5%).

After three more crystallisations from chloroform-methanol the yield was 25g. and the m.p. of the product was the same whilst the specific rotation was

$[\alpha]_D^{23}$ -21.5° (±0.4°),

$[\alpha]_G^{23}$ -26.04° (±0.4°),

(c 2.4860 in $CHCl_3$).

(Found: C, 83.6; H, 10.4%).

There was no change in melting point or specific rotation on further recrystallisations from (a) chloroform-methanol and (b) light petroleum (b.p. 60-80°). This abnormal behaviour was also shown by the central crops. A total weight of 78g. (44%) of this cholesteryl hydratropate of the same specific rotation was obtained by systematic working up of the various mother liquors.

By Crystallisation from Benzene-Methanol.

The residual mother liquor on concentration by evaporation yielded a crude more soluble cholesteryl hydratropate (28g.), as a light yellow powder, m.p.78-83°,

$[\alpha]_D^{21.8}$ -36.5° (±0.4°),

$[\alpha]_G^{21.8}$ -43.6° (±0.4°),

(c 2.3640 in $CHCl_3$).

This crude ester was purified by heating its solution in benzene with charcoal, filtering and adding a little methanol and boiling off methanol to the point of slight turbidity. On cooling a cholesteryl hydratropate crystallised out in shiny needles. On several crystallisations from this mixture, the m.p. gradually rose, as also did the rotatory power. After five crystallisations the ester amounted to 2.2 g., m.p. 137-138°,

$[\alpha]_D^{21.8}$ -56.2° (±2°),

$[\alpha]_G^{21.8}$ -67.7° (±2°),

(c 0.5380 in $CHCl_3$).

(Found: C, 82.9; H, 10.35%).

Further recrystallisations did not increase the amount of rotation. In all 3.7 g. (2%) of the more soluble cholesteryl hydratropate of the same maximum activity was isolated by systematic working of the mother liquors.

Traces of cholesterol were isolated during the fractionation of this cholesteryl (±) hydratropate.

Cholesteryl (±) hydratropate (e)

Cholesteryl (±) hydratropate (e) 79.2g., were dissolved in boiling light petroleum (b.p. 60-80°) and the solution was allowed to crystallise in a refrigerator as above. Impure cholesteryl hydratropate 73 g. was obtained from the first eight crops. This was subsequently recrystallised three times from a mixture of chloroform-methanol to constant specific rotation. Yield, 13.8 g.; m.p. 116-117°, $[\alpha]_G^{24.4}$ -25.8° (±0.5°), (c 2.1030 in $CHCl_3$). Altogether 38.2 g. (48%) of the cholesteryl hydratropate with the same specific rotation was obtained. A small portion of this ester was crystallised from acetone. It crystallised in pearly plates, m.p. 116-117°,

$[\alpha]_D^{27.8}$ -20.6° (± 1°),

$[\alpha]_G^{28.4}$ -25.02°(± 1°),

(c 0.8890 in $CHCl_3$).

(Found: C, 83.6; H, 10.1%).

Subsequent experiments showed that the separation could be effected more readily by crystallisation from acetone.

The evaporation of the final mother liquor gave an impure cholesteryl hydratropate (7.7g.), contaminated with traces of cholesterol. This was repeatedly recrystallised from acetone, chloroform-methanol and benzene-methanol, whereby a cholesteryl hydratropate (0.9g.; 1%) was isolated with m.p. 137-138° and

$[\alpha]_D^{23.4}$ -57.3° (±0.4°),

$[\alpha]_G^{23.4}$ -68.4° (±0.4°),

(c 2.2700 in $CHCl_3$).

Cholesteryl (±) hydratropate (f (i)).

By Crystallisation from Chloroform-Methanol.

Partial resolution of cholesteryl (±) hydratropate (f (i)) 30g., was effected by fractional crystallisation from chloroform-methanol. By repeated crystallisation, an individual cholesteryl hydratropate was isolated in the pure condition (18.4g.; 61%); it melted at 116-117° and had $[\alpha]_G^{26.8}$ -26.1° (±0.6°), (c 1.9130 in $CHCl_3$). A small portion after crystallisation from acetone melted at 116-117° and had

$[\alpha]_D^{28.4}$ -21.7° (± 1°),

$[\alpha]_G^{28.4}$ -25.6° (± 1°),

(c 0.8980 in $CHCl_3$).

(Found: C, 83.35; H, 10.5%).

Evaporation of the mother liquor and repeated crystallisations from benzene-methanol gave a cholesteryl hydratropate 0.5g. (1.6%); m.p. 138-139° with $[\alpha]_D^{20.6}$ -57.2° (±1°), $[\alpha]_G^{20.6}$ -68.1° (±1°), (c 0.9530 in $CHCl_3$). (Found: C, 83.2 ; H, 9.8%).

Cholesteryl (±) hydratropate (f (ii)).

By Crystallisation from Acetone.

Cholesteryl (±) hydratropate (f (ii)) 70g., were dissolved in boiling acetone. Crystallisation began after the solution was allowed to cool at the ordinary temperature. The crop, which separated, weighed 50.3g., melted at 116.5-117.5° and had $[\alpha]_D^{22.6}$ - 22.1° (±1°), $[\alpha]_G^{22.8}$ -25.8° (±1°), (c 0.9260 in $CHCl_3$).
(Found: C, 83.9; H, 10.1%).

Further crystallisation from acetone produced no significant change in the melting point or in the specific rotation. By systematic working up of the mother liquors, a total weight of 60g. (86%) of a cholesteryl hydratropate, with the same specific rotation was obtained. The specific rotation was unchanged after crystallisation from chloroform-methanol.

The crude cholesteryl hydratropate obtained from the residual mother liquor by evaporation was purified by repeated crystallisations from benzene-methanol, whereby a cholesteryl hydratropate (2.2g. ; 3%) was isolated.

$[\alpha]_D^{24.4}$ -56.5° (± 2°),
$[\alpha]_G^{24.6}$ -69.1° (± 2°),
(c 0.5390 in $CHCl_3$).
(Found: C, 82.9; H, 9.9%).

Action of (a) Pyridine and (b) Pyridine hydrochloride and pyridine on a more soluble sample of cholesteryl hydratropate.

(a) Action of Pyridine.

Cholesteryl hydratropate (1g.; 0.001 mole), m.p. 138-139° with $[\alpha]_D^{21.6}$ -56.8° (±0.4°), $[\alpha]_G^{21.6}$ -68.1°(±0.4°), (c 2.7210 in $CHCl_3$), was boiled under reflux during one hour with anhydrous pyridine (6 ml.), after remaining during two days at the temperature of the laboratory, customary isolation gave 0.8g. of cholesteryl hydratropate, m.p. 137° with $[\alpha]_D^{21.2}$ -56.9°(±0.4°), $[\alpha]_G^{21.2}$ -68.02°(±0.4°), (c 2.4300 in $CHCl_3$).

(b) Action of Pyridine and Pyridine hydrochloride.

Cholesteryl hydratropate (0.8g.; 0.001 mole), m.p. 137°, with $[\alpha]_D^{21.2}$ -56.9°(±0.4°), $[\alpha]_G^{21.2}$ -68.02°(±0.4°), (c 2.4300 in $CHCl_3$), was boiled under reflux with pyridine (10 ml.) and pyridine hydrochloride (1g.) during one and a half hours. It was allowed to stand for two nights and the ester isolated in the usual manner. Yield 0.6g. It melted at 137-138° and had $[\alpha]_D^{15.8}$ -56.6°(±0.5°), $[\alpha]_G^{16}$ -67.6(±0.5°), (c 2.1320 in $CHCl_3$).

Reduction of a less soluble sample of cholesteryl hydratropate (f (i)) with Lithium Aluminium Hydride.

A solution of the cholesteryl hydratropate (f (i)) with $[\alpha]_D^{23}$ -21.5°(±0.4°), $[\alpha]_G^{23}$ -26.04°(±0.4°), (c 2.4860 in $CHCl_3$), (20g.; 0.038 mole) in dry ether (200 ml.) was added dropwise to a suspension of lithium aluminium hydride (2.5g.; 0.065 mole) in dry ether (100 ml.) with continued shaking. 20 min. after the completion of the addition, water was added to decompose excess hydride. The precipitated hydroxides were then dissolved by the addition of dil. sulphuric acid. Ether and aqueous phases were separated and the latter was extracted with ether three times. The ether layers were combined, washed with dil. potassium carbonate solution and then with water. After drying over anhydrous sodium sulphate and the removal of ether, the residue was distilled and redistilled to yield colourless oil 4.3 g. (82%) of (-)-hydratropyl alchol, of which 0.8 g. was collected at 97°/10mm., had n_D^{25} 1.5218, and 3.5 g. was collected at 100°/12mm., had n_D^{25} 1.5229, $d^{21.6}$=1.000, $[\alpha]_D^{21.2}$ -0.8° (±0.02°), $[\alpha]_G^{21.2}$ -0.9° (±0.02°), (l = 1 dm, homogeneous) whereas the optically pure (-)-hydratropyl alcohol (p.47) has $d^{21.6}$= 1.000 $[\alpha]_D^{24.2}$ -17.4° (±0.02°), $[\alpha]_G^{24.1}$ -21.2° (±0.02°), (l = 1 dm, homogeneous).

The recovered cholesterol 14.9 g. (100%) was crystallised from ethyl alcohol. It melted at 146-147° and

had $[\alpha]_D^{16.2}$ -39.3° (± 0.4°), $[\alpha]_G^{16.4}$ -47.0° (±0.4°), (c 2.2450 in $CHCl_3$). It gave an insoluble digitonide with digitonin in 90% alcohol.

Reduction of a second less soluble sample of cholesteryl hydratropate (f (ii)) with Lithium Aluminium Hydride.

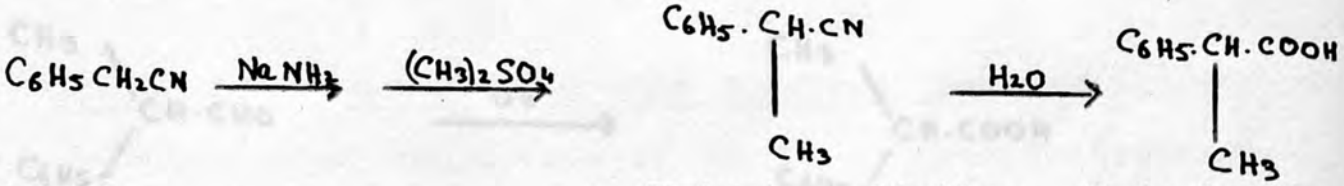
This reaction was carried out in the same manner as the reduction just described. From 10g. (0.019 mole) of cholesteryl hydratropate with $[\alpha]_D^{28.4}$ -21.7° (± 1°), $[\alpha]_G^{28.7}$ -25.6° (± 1°), (c 0.8980 in $CHCl_3$), and 1.2g. (0.03 mole) of lithium aluminium hydride, were obtained 1.7g. (65%) of (-)-hydratropyl alcohol, b.p. 90°/16mm, $d^{21.6} = 1.000$, $[\alpha]_D^{19.6}$ -1.0° (±0.02°), $[\alpha]_G^{19.6}$ -1.2° (± 0.02°), (l = 1dm, homogeneous). Optical purity 6%.

A review of the various methods of making (±)-hydratropic acid.

Of the six methods of synthesising (±)-hydratropic acid given in the literature, only first three were considered worth being examined in detail. The six methods are as follows:

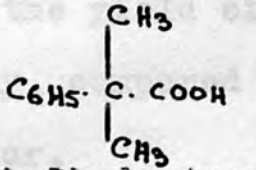
1. From benzyl cyanide.

This method is due to Campbell and Kenyon (J.Chem.Soc., 1946, 25). Starting with benzyl cyanide, addition of one equivalent of sodamide followed by a solution of the calculated amount of dimethyl sulphate in dry ether, yielded hydratropnitrile. The acid was obtained in 54% yield by the subsequent hydrolysis of hydratropnitrile.



Benzyl cyanide. Hydratropnitrile. Hydratropic acid.

A study of the recent literature (Mislow and Brenner, J. Amer. Chem. Soc., 1953, 75, 2318) has shown that the samples of the acid prepared by this method were always contaminated with α-methylhydratropic acid.

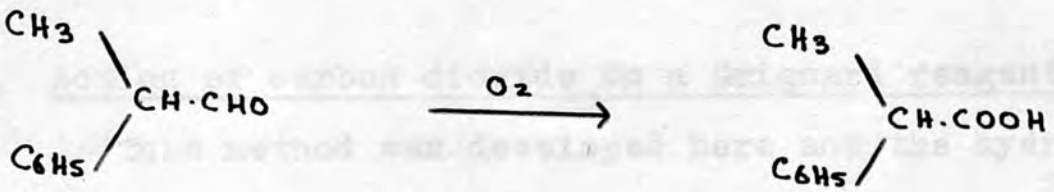


α-methylhydratropic acid.

It is almost impossible to separate benzyl cyanide and hydratropnitrile by fractional distillation, as their boiling points lie within two degrees of each other at 13 mm. pressure. The method of synthesis is lengthy, benzyl cyanide and dimethyl sulphate are highly poisonous and sodamide can be dangerous, when exposed to limited amounts of air. In addition to this, the samples of the hydratropoyl chloride prepared by us from the hydratropic acid obtained by this method always had a pink colour. The method therefore is not very promising.

2. Oxidation of hydratropic aldehyde.

Hydratropic acid in this method was prepared by the oxidation of hydratropic aldehyde by neutral potassium permanganate.



Hydratropic aldehyde. Hydratropic acid.

This method is due to D.C.Abbott (Ph.D. Thesis, London, 1951) and was communicated to us by courtesy of Dr. J. Kenyon, F.R.S. Hydratropic aldehyde is not easily accessible, and some commercial samples are far from pure.

In the two experiments, the yield of (±)-hydratropic acid was 23% and 30% respectively, compared with the 38% yield recorded by the above author.

The oxidation can also be carried out with (a) hydrogen peroxide in a weakly alkaline solution. The acid obtained is of a high degree of purity, but the method gives low yields (Zdanksy, Arkiv för Kemi., 1954, 7, No.63, 577), (b) oxidation with silver oxide in potassium hydroxide suspension is faster and gives better yields (Delepine and Bonnet, Compt. rend., 1909, 149, 39; Kay and Raper, J.Biochem. 1922, 16, 465). Eliel and Freeman (J.Amer.Chem.Soc., 1952, 74, 923) record a yield of 74% of (±)-hydratropic acid plus 8% of acetophenone by the oxidation of hydratropic aldehyde by a suspension of silver oxide in sodium hydroxide.

This method has one serious disadvantage: the non-availability and high cost of hydratropic aldehyde. When potassium permanganate is used as an oxidising agent, a second disadvantage is the low yield.

3. Action of carbon dioxide on a Grignard reagent.

This method was developed here and the hydratropic acid was obtained in 58% yield b.p. 159/25 mm., n_D^{25} 1.5204 plus 22.6% of dimethyldiphenylethane m.p. 124-125°. The overall yield of the acid was 75% based on the recovered hydrocarbon.

It has long been known (Grignard, Ann. chim. phys., 1901, [24], [7], 433) that the condensation of Grignard reagents with carbon dioxide leads to the formation of the corresponding acids. A more recent technique involves pouring the

solution onto excess crushed solid carbon dioxide. The superiority of the procedure rests not only on temperature but also on concentration control. Of course, it is necessary to decompose the addition compounds with mineral acids to isolate the organic acid. This process is not so simple as it may seem; difficulties are encountered, such as in addition to the formation of the RMgX compound in the reaction between RX compound and magnesium in dry ether, the following side reactions occur:

$$2\ RX + Mg \longrightarrow R\text{———}R + MgX_2 \qquad (i)$$

Under certain conditions Grignard reagent may react with the unaltered RX compound to give R———R compound and magnesium halide.

$$RMgX + RX \longrightarrow R\text{———}R + MgX_2 \qquad (ii)$$

According to Fuson (J. Amer. Chem. Soc., 1926, 48, 830, 2681, 2937) under certain conditions the coupling reaction is best interpreted as follows:

$$2\ RX + 2R'MgX \longrightarrow R\text{———}R + R'\text{—}R' + 2\ MgX_2 \qquad (iii)$$

Salkind, Peschekerowa (Chem. Zentr. 1914, II, 1269) obtained (±)-hydratropic acid in 15% yield besides the dimethyldiphenylethane by the action of carbon dioxide gas on magnesium α-bromoethylbenzene at 0°, whereas Ott (Ber., 1928, 61, 2124) got only meso and racemic dimethyldiphenylethane on the "Grignardation" of α-phenylethyl chloride in the usual way. Similar results with related compounds are mentioned

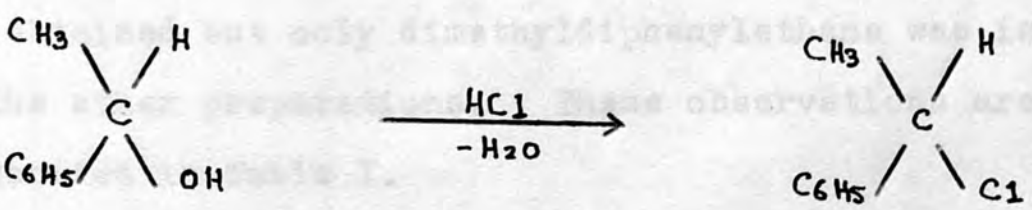
by von Braun, Grabowski and Kirschbaum (Ber., 1913, 46, 1266), Liepin (Chem. Abstracts, 1931, 25, 3328) and Zdansky (Arkiv für Kemi, 1954, 7, No. 63, 577). Zdansky even made use of a "Cyclic Reactor" while attempting to prepare 2:4- and 3:4-dichlorohydratropic acid by this method from dichloro-α-phenylethyl chloride and bromide. The "Cyclic Reactor" has been described by Rowlands, Greenlee and Boord (Abstracts of Papers, American Chemical Society Meeting, Philadelphia, Penna., April 9-13, 1950, p.8L) and also by Gaertner (J. Amer. Chem. Soc., 1951, 73, 3934). This coupling reaction has also been observed by several investigators with other compounds. It is thought by some to involve free radicals (Kharasch, Mayo and Goldberg, J. Amer. Chem. Soc., 1938, 60, 2004), Waters (Chemistry of Free Radicals, Oxford, 1946, p.211-14).

Lucas and Pressman (Principles and Practice in Organic Chemistry, J. Wiley: Chapman and Hall, 1949, p.197) state: "The coupling reaction may be minimized by: (a) violent agitation, (b) high dilution of the Grignard reagent, (c) excess of magnesium, and (d) use of alkyl chlorides rather than iodides or bromides, especially in the case of secondary and tertiary alkyl halides....." while Gilman and Zoellner (J. Amer. Chem. Soc., 1931, 53, 1945) state that "not only does the chloride give higher yields of RMgX compound, but it gives higher yields with an astonishing abuse or lack of care in addition. Furthermore, RMgCl

compounds enjoy other advantages over RMgBr and RMgI compounds: (i) they frequently undergo more ready reaction with another compound; (ii) they generally give higher yields of products with a given reactant, and on the basis of an equal content of RMgX compound; and (iii) there is probably a general lesser opportunity for side reactions because the binary system ($MgCl_2$ + Mg) is less active than the corresponding systems with magnesium bromide and magnesium iodide." Therefore the choice of α-phenylethyl chloride instead of the bromide or the iodide, as the starting material for the synthesis of hydratropic acid by this method, seemed well indicated.

Preparation of α-phenylethyl chloride.

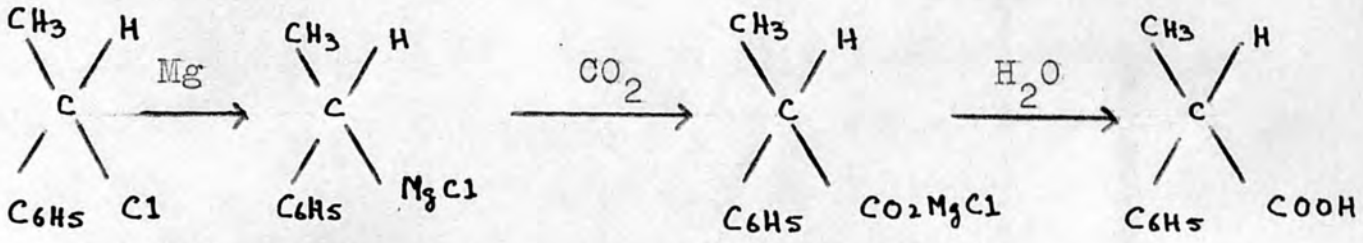
This we obtained in 92% yield, b.p.92-94°/34-35mm., by the repeated (three times) action of fresh concentrated hydrochloric acid on methylphenylcarbinol. This procedure was a modification of the method of Norris, Watt, Thomas (J. Amer. Chem. Soc., 1916, 38, 1071), who record a yield of 75% for it.



Methylphenylcarbinol. α-phenylethyl chloride.

Preparation of (±)-hydratropic acid.

This was obtained by the action of solid carbon dioxide on α-phenylethylmagnesium chloride.



Seven experiments were performed with slight variations. In the 1st and 2nd, sodium dried ether was used, while in the rest, ether and magnesium were super dried. Only in the 1st, 5th, 6th and 7th preparations α-phenylethylmagnesium chloride and α-phenylethyl chloride were diluted with dry ether, while the initial optimal concentration of the chloride was the same in all cases. The reaction mixture was mechanically stirred in the 1st, 6th and 7th preparations, while in the others the flask was intermittently shaken. Hydratropic acid was obtained in the 1st, 6th and 7th preparations. No hydratropic acid was obtained but only dimethyldiphenylethane was isolated in the other preparations. These observations are summarised in Table I.

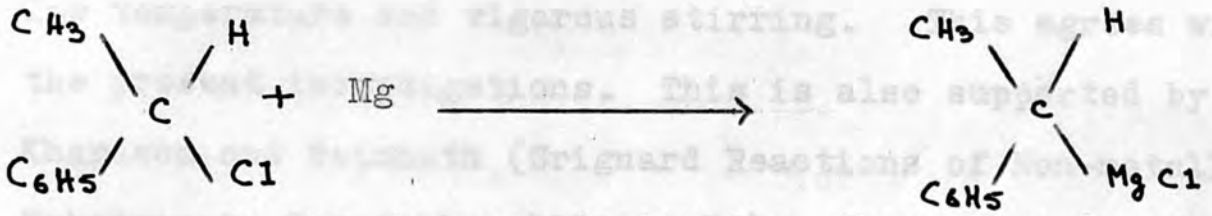
TABLE I.

Expt.	Reactants: Moles of α-phenylethyl chloride.	Moles of ether.	Mg. g. atom.	Initial concentration of the chloride g/100ml.	Dil. of the Grignard Reagent. ether ml.	Dil. of the halide. g/100ml.	Products: Dimethyldiphenylethane recov., g.	Hydratropic acid. g.
* 1.	1	6	1.1	4.2	100ml.	40.2	-	65.2g., 47%
¥ 2.	0.5	1.89	0.77	4.0	-	-	-	-
¥ 3.	0.5	1.89	0.77	4.0	-	-		-
¥ 4.	0.25	.945	0.387	4.0	-	-		-
¥ 5.	0.25	2.0	0.387	6.0	35	22.3	128.5g.	-
* 6.	0.32	2.0	0.458	10.5	70	54.5	-	28.6g., 59%
* 7.	0.84	5.47	1.29	4.2	100	40.07	20g., 22.6%	73.5g., 58%

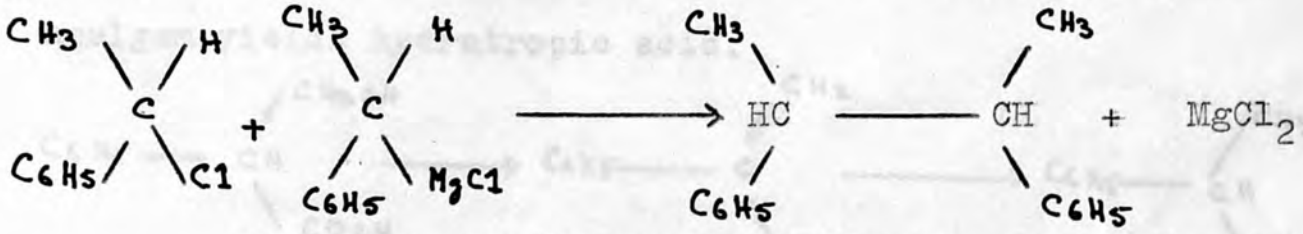
* Reaction mixture stirred mechanically.

¥ Flask intermittently shaken and the use of a mechanical stirrer avoided.

It is clear from these seven preparations that under ordinary conditions (absence of a mechanical stirrer) it is practically impossible to prepare hydratropic acid because of an extreme tendency for coupling, which results in a 100% yield of the dimethyldiphenylethane. Discussion of this abnormal reaction is largely a restatement of the experimental facts. The following seems to be most satisfactory. With stirring uniform concentration is ensured and addition reaction takes place very rapidly.



In the absence of stirring, there is a decrease in the rate of this addition. Under such conditions, the Grignard reagent may react with unaltered α-phenylethyl chloride to give dimethyldiphenylethane and magnesium halide.

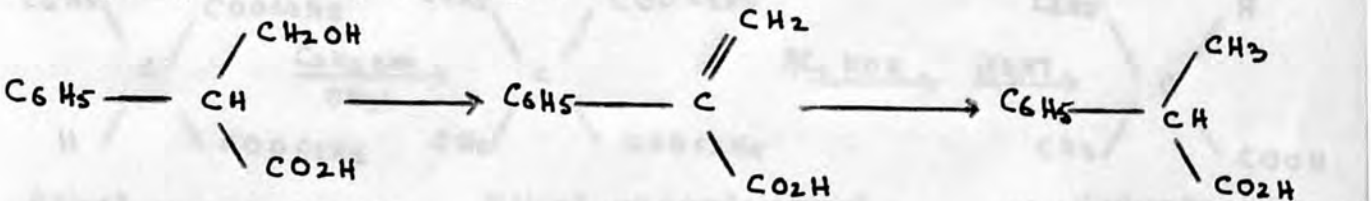


Or other reactions ordinarily too slow to be observed and which are less subject to hindrance become predominant. Gilman and Meyers (J. Amer. Chem. Soc., 1923, 45, 159) found in the preparation of ethyl magnesium iodide that by completely avoiding the use of a stirrer, the reaction was slow to start,

did not proceed vigorously when once started and gave a very low yield of reagent. In this connection the observations of Gilman and Parker (J. Amer. Chem. Soc., 1924, 46, 2816) are also of special interest. They have studied the optimum conditions for the preparation of n-valeric acid from n-butylmagnesium bromide and carbon dioxide, and found that the yield of the acid suffered a very decided drop (about 40%), when the rate of stirring was lowered from 845 to 200 revolutions per minute. According to them, factors influencing the yield are a low temperature and vigorous stirring. This agrees with the present investigations. This is also supported by Kharasch and Reinmuth (Grignard Reactions of Non-metallic Substances, Constable, 1954, p.19).

4. From tropic acid.

Tropic acid when heated with barium hydroxide, gives atropic acid; the latter when reduced with sodium amalgam yields hydratropic acid.

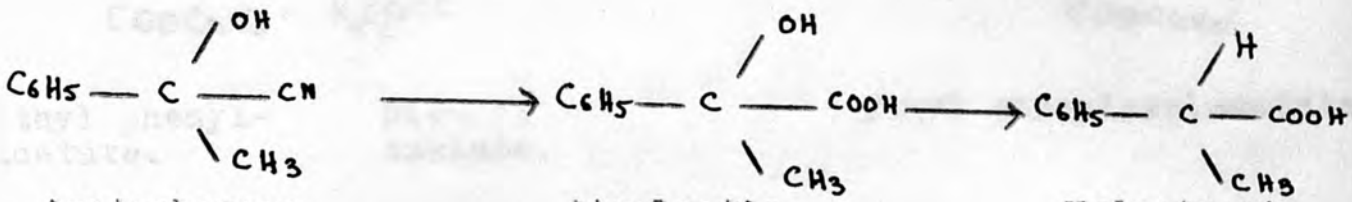


Tropic acid. Atropic acid. Hydratropic acid.

It was adopted by Kraut (Annalen, 1868, 148, 242), Fittig and Wurster (Annalen, 1879, 195, 145), Kay and Raper (J. Biochem., 1922, 16, 465) and Raper (J. Chem. Soc., 1923, 2557). The method is quick and convenient for use on a small scale but is costly.

5. From acetophenone cyanohydrin.

By the action of hydriodic acid and red phosphorus on acetophenone cyanohydrin Janssen (Annalen, 1889, 250, 125) obtained hydratropic acid in 13-14% yield



Acetophenone cyanohydrin. Atrolactic acid. Hydratropic acid.

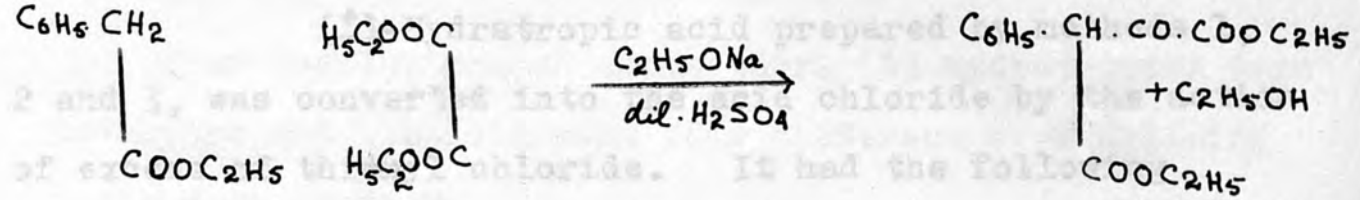
6. By the malonic ester synthesis.

Bernstein and Whitmore (J. Amer. Chem. Soc., 1939, 61, 1324) state without recording any experimental details that it was obtained in 78% yield by malonic ester synthesis, involving ethyl phenylmalonate and methyl iodide, whereas Whitmore (Organic Chemistry, Second Edition, (Van Nostrand), 1951, p.702) states that the yield by this method is not good.

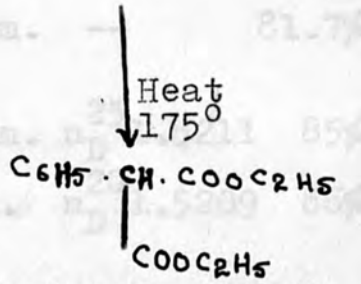
Ethyl phenylmalonate. Ethyl phenylmethyl-malonate. Hydratropic acid.

This method requires the preparation of ethyl phenylmalonate which is obtained by condensing pure ethyl phenylacetate and diethyl oxalate and decomposing the ethyl

phenyloxalacetate by heat.



Ethyl phenyl-acetate. Diethyl oxalate. Ethyl phenyloxalacetate.



Ethyl phenylmalonate.

Levene and Marker (J. Biol. Chem., 1933, 100, 685) also obtained the inactive hydratropic acid by this method, though no experimental details are recorded by them in their paper. Because of the lack of experimental details, the controversial statements about the yield of hydratropic acid and the number of stages involved in the synthesis, this method was not considered.

Thus method No.3 was found definitely superior on account of:

(i) the lower cost of the starting materials,

(ii) the fewer stages involved in the synthesis, and

(iii) the higher yield of (±)-hydratropic acid.

A note on (±)-hydratropoyl chloride.

(±)-Hydratropic acid prepared by methods 1, 2 and 3, was converted into the acid chloride by the action of excess of thionyl chloride. It had the following physical constants:-

Hydratropic acid Method	Hydratropoyl chloride	Colour	B.P.	R.I.	Yield.
1.	(a)	Pink	81-83/10mm.	--	81.7%
2.	(b)	Colour-less	84-85/11mm.	n_D^{25} 1.5211	85%
3.	(c)	-do-	81-82/8mm.	n_D^{20} 1.5209	86%

It is difficult to explain the pink colour under (a).

A review of the partial resolution of cholesteryl (±) hydratropate.

Four resolutions of cholesteryl (±) hydratropate were attempted and the following four different crystallising media were used:

(i) Light petroleum (b.p. 60-80°),

(ii) Chloroform-methanol,

(iii) Acetone, and

(iv) Benzene-methanol.

(i), (ii) and (iii) favour the separation of the less soluble form which has been shown to be a partial racemate containing a slight preponderance of cholesteryl (+) hydratropate. It remains unchanged in melting point and rotatory power after repeated crystallisations.

Residues recovered from the mother liquors when fractionally crystallised from (iv) yielded 1-3% of the more soluble form, in the form of shiny needles. This has been found to be cholesteryl (-) hydratropate (Part II).

Traces of cholesterol were isolated during the fractionation of cholesteryl (±) hydratropate (d) and (e). It was found that they could be avoided by reducing the volume of pyridine during the preparation of cholesteryl (±) hydratropate from 20 moles to 14 moles for 1 mole of cholesterol.

The results of the four partial resolutions are summarised in Table II.

TABLE II.

YIELDS, PHYSICAL PROPERTIES AND ANALYSES OF THE ISOMERS.

Cholesteryl (±) hydratropate	M.P., °C.	Yield	$[\alpha]_D$	$[\alpha]_G$	c, in $CHCl_3$	Cryd. medium	Molecular formula	Analyses			
								Carbon		Hydrogen	
								Calcd.	Found	Calcd.	Found
(d) Less Soluble Form	115-116°		-19.3±0.4°	-22.9°±0.4°	2.4950	P.E.60-80°	$C_{36}H_{54}O_2$	83.3	83.4	10.5	10.4
	116-117.5°	44%	-21.5±0.4°	-26.04°±0.4°	2.4860	$CH_3OH+CHCl_3$	$C_{36}H_{54}O_2$	83.3	83.6	10.5	10.4
More Soluble Form	137-138°	2%	-56.2° ±2°	-67.7°±2°	0.5380	$CH_3OH+C_6H_6$	-do-	83.3	82.9	10.5	10.35
(e) Less Soluble Form	116-117°	48%	-20.6°±1°	-25.02±1°	0.8890	Acetone	-do-	83.3	83.6	10.5	10.1
More Soluble Form	137-138°	1%	-57.3±0.4°	-68.4°±0.4°	2.2700	$CH_3OH+C_6H_6$	-do-	—	By mixed m.p. —		
(f.i) Less Soluble Form	116-117°	61%	-21.7°±1°	-25.6° ±1°	0.8980	Acetone	-do-	83.3	83.35	10.5	10.5
More Soluble Form	138-139°	1.6%	-57.2°±1°	-68.1° ±1°	0.9530	$CH_3OH+C_6H_6$	-do-	83.3	83.2	10.5	9.8
(f.ii) Less Soluble Form	116.5-117.5°	86%	-22.1° ±1°	-25.8° ±1°	0.9260	Acetone	-do-	83.3	83.9	10.5	10.1
More Soluble Form	138-139°	3%	-56.5° ±2°	-69.1° ±2°	0.5390	$CH_3OH+C_6H_6$	-do-	83.3	82.9	10.5	9.9

III. The Synthesis and Partial Resolution of Cholesteryl (±) Hydratropate.

PART II.

III. The Synthesis and Partial Resolution of Cholesteryl (±) Hydratropate.

PART II.

PRESENT WORK.

(±)-Hydratropic acid has been resolved by known methods, using alkaloids, and optically pure cholesteryl (+) hydratropate and cholesteryl (-) hydratropate synthesised.

The following physical properties were observed:-

Cholesteryl (+) hydratropate M.P. 104.5°-106°,
$[\alpha]_D^{26}$ + 10.7°(±0.4°),
$[\alpha]_G^{26}$ + 13.8°(±0.4°),
(c 2.3010 in $CHCl_3$).

Cholesteryl (-) hydratropate M.P. 139.5° $[\alpha]_D^{24.4}$ -58.15°(±0.6°),
$[\alpha]_G^{24.4}$ -69.90°(±0.6°),
(c 1.6170 in $CHCl_3$).

Cholesteryl (±) hydratropate M.P. 116-117°
$[\alpha]_D^{25.4}$ -23.4°(±0.3°),
$[\alpha]_G^{25.4}$ -28.2°(±0.3°),
(c 3.2080 in $CHCl_3$).

Reduction of (+)-hydratropic acid with lithium aluminium hydride gave (-)-hydratropyl alcohol with $[\alpha]_D^{24.2}$ -17.4° (± 0.02°), $[\alpha]_G^{24.1}$ -21.2° (±0.02°), (l=1dm, homogeneous, $d^{21.6°}$=1.00).

From the (-)-hydratropic acid, (+)-hydratropyl alcohol

with $[\alpha]_D^{23.1}$ +17.2° (±0.02°), $[\alpha]_G^{23.2}$ + 21.02° (±0.02°),

21.6°

(l = 1dm, homogeneous, d = 1.00) was obtained.

The Resolution of (±)-Hydratropic Acid.

The Resolution of (±)-Hydratropic Acid.

HISTORICAL.

(±)-Hydratropic acid was first prepared 90 years ago by Kraut (Annalen, 1868, 148, 242), who described it as "Nicht krystallisierbar". Later, it was investigated more thoroughly by Fittig and Wurster (Annalen, 1879, 195, 145), who purified it through the calcium salt and found that it did not solidify even at -20°. In 1889, Janssen (Annalen, 1889, 250, 125) obtained it in 13-14% yield by the action of hydriodic acid and red phosphorus on acetophenone cyanohydrin. Raper, (J. Chem. Soc., 1923, 123, 2557) 34 years later, succeeded in resolving it with the help of strychnine. He only isolated the (+)-hydratropic acid which failed to crystallise. However, in 1930, Levene, Mikeska and Passoth (J. Biol. Chem., 1930, 88, 27) isolated the (-)-hydratropic acid with $[\alpha]_D^{25}$ -59.1° (homogeneous) by the fractional crystallisation of its quinine salt. Three years later, Levene and Marker (J. Biol. Chem., 1933, 100, 685) repeated the fractional crystallisation of its quinine salt and gave $[\alpha]_D^{25}$ -76.0° (benzene), as the maximum value of (-)-hydratropic acid.

During recent years it has been the subject of considerable investigation. Among recent workers who have studied optically active hydratropic acid in some way,

mention must be made of Ott and Kramer (Ber., 1935, 68, 1655), Arcus and Kenyon (J. Chem. Soc., 1939, 916), Bernstein and Whitmore (J. Amer. Chem. Soc., 1939, 61, 1324) Mislow and Heffler (J.Amer. Chem. Soc., 1952, 74, 3668) Bonner (J. Amer. Chem. Soc., 1952, 74, 1034), Elhafez and Cram (J. Amer. Chem. Soc., 1952, 74, 5846), Fredga (Arkiv för Kemi., 1954, 7 No 27, 241) and Greene (J. Amer. Chem. Soc., 1955, 77, 4869). The optical activity data of these authors are compared in Table III. Their data, in most cases, refer to different solvents, concentrations and temperatures. In some cases temperature is not indicated.

TABLE III.

OPTICALLY ACTIVE HYDROTRAPIC ACID.

Studied by.	m.p.	Absolute ethanol.	Benzene.	Homogeneous..	Chloroform.	‖ % of active acid.
1. Raper (J. Chem. Soc., 1923, 123, 2557).		$[\alpha]_D^{20}$ +81.1° (c 3.108)			$[\alpha]_D^{20}$ +76.2° (c 2.834)	97
2. Levene, Mikeska and Passoth (J. Biol. Chem., 1930, 88, 27.)		$[\alpha]_D^{25}$ -54.2° (c 21.332 in 75% ethanol).		$[\alpha]_D^{25}$ -59.1°		64
3. Levene and Marker (J. Biol. Chem., 1933, 100, 685,).			$[\alpha]_D^{25}$ -76.0° (c 15.14)	$[\alpha]_D^{25}$ -74.1°		80.5
4. Ott and Kramer (Ber. 1935, 68, 1655).				† $[\alpha]_D^{20}$ +89.7°		‡ 97.5
5. Arcus and Kenyon (J. Chem. Soc., 1939, 916).	(+)-,29°		*$[\alpha]_D$ +92.5° (c 3.4825)		*$[\alpha]_D$ +74.8° *$[\alpha]_G$ +90.9° (c 3.060)	‡ 98
6. Bernstein and Whitmore (J. Amer. Chem. Soc., 1939, 61, 1324).				† $[\alpha]_D^{25.5}$ +86.1°		93.5
7. Booner (ibid., 1952, 74, 1034).		$[\alpha]_D^{25}$ -58.0° (c 1.881 in 75% ethanol).				69
8. Mislow and Heffler (ibid., 1952, 74, 3668).			$[\alpha]_D^{26}$ +90.8° (c 3.48)			‡ 96
9. Elhafez and Cram (ibid., 1952, 74, 5846).			$[\alpha]_D^{21}$ +95.5° (c 3.5)	$[\alpha]_D^{21}$ +98.8°		‡ 107.4
10. Fredga (Arkiv for Kemi, 1954, 7 No. 27 241).	(+)- 30.2- 30.9°	$[\alpha]_D^{25}$ +79.0° (c 1.674)			$[\alpha]_D^{20}$ -76.7° $[\alpha]_D^{25}$ -75.3° (c 1.587)	99
	(-)- 30.3-31°	$[\alpha]_D^{20}$ +81.0° (c 1.674)				
11. Greene (J. Amer. Chem. Soc., 1955, 77, 4869).				$[\alpha]_D^{25.5}$ +98.72° (1.1dm,neat)		107.3
12. Found.	(+)-, 31.5-32° (-)- 31-32°				$[\alpha]_D^{20}$ +78.4° $[\alpha]_G^{20}$ +93.7° $[\alpha]_D^{25}$ +76.3° $[\alpha]_G^{25}$ +91.7° (c 1.6130)	$[\alpha]_D^{20}$ -77.5° $[\alpha]_G^{20}$ -93.6° (c 1.5770) $[\alpha]_D^{25}$ -76.1° $[\alpha]_G$ -91.5° (c 1.5990).
					(p.46)	(p.47,53)

* Temperature is not reported.

† They do not indicate whether the rotation reported was for the homogeneous acid or a solution of it.

‡ Calculated on the basis of t = 25.

‖ Calculated on the basis of the maximum rotation of the acid obtained by us.

EXPERIMENTAL.

"A".

Purification of quinine.

The commercial product (B.D.H.) 80g. was dissolved in chloroform (750 ml.) and shaken with anhydrous sodium sulphate. The solution was allowed to stand for 1½ hours. It was filtered and the chloroform was removed by evaporation on a boiling water bath and then in a vacuum desiccator. The alkaloid had m.p. 170-172°, $[\alpha]_D^{20.2}$ -118.8° (±0.6°), $[\alpha]_G^{20.2}$ -145.1° (±0.6°), (C 1.7400 in $CHCl_3$). Lit. m.p. 174° (anhydrous), $[\alpha]_D^{17}$ -117° ($CHCl_3$).

Resolution of (±)-hydratropic acid.

Preparation of strychnine (±) hydratropate.

The procedure adopted here is due to Raper (J. Chem. Soc., 1923, 123, 2557).

(±)-Hydratropic acid obtained by the Grignard method (24g.; 0.16 mole) and strychnine (54g.; 0.16 mole) were dissolved in hot aqueous ethanol (250 ml.). The solution was filtered and allowed to crystallise in a refrigerator overnight. It crystallised in glassy rhombs. The crystals were filtered off, dried in air and then in a vacuum desiccator over concentrated sulphuric acid; 30.4g.

were obtained. After five recrystallisations, optical purity was reached when 4.3g. of strychnine (+)hydratropate were obtained. The product had no sharp m.p., and had $[\alpha]_D^{21}$ -30.8° (±0.7°), $[\alpha]_G^{21.8}$ -38.3° (±0.7°), (c 1.4090 in $CHCl_3$). Intermediate crops were repeatedly recrystallised and even 4-5 times boiled with charcoal. The total yield of the less soluble optically pure strychnine salt was 21g. The experiment was repeated with (±)-hydratropic acid (40g.; 0.26 mole) and strychnine (90g.; 0.26 mole) dissolved in hot 75% aqueous ethanol (400 ml.). Altogether 78.7g. of the less soluble strychnine salt (optically pure or nearly so) were obtained from the two preparations.

Preparation of (+)-hydratropic acid.

A solution of strychnine (+) hydratropate (63g.) in chloroform, was extracted twice with dilute hydrochloric acid. The oily layer was separated and the aqueous layer twice extracted with chloroform. The combined extracts were twice washed with water and dried (Na_2SO_4). The removal of chloroform gave 10.4g. of (+)-hydratropic acid with $[\alpha]_D^{19.6}$ +72.0°(±0.3°), $[\alpha]_G^{20.2}$ +85.7° (±0.3°), (c 3.3330 in $CHCl_3$). It was dissolved in petroleum ether (b.p. 40-60°), boiled with charcoal. The solution was filtered and allowed to crystallise at 0°. It crystallised in glassy prisms. Fractional crystallisation from petroleum

ether (b.p. 40-60°) at 0° yielded 7.9g. of (+)-hydratropic acid, m.p. 31.5-32°, $[\alpha]_D^{20}$ +78.4° (±0.6°), $[\alpha]_G^{20}$ +93.7°(±0.6°), $[\alpha]_D^{25}$ + 76.3° (±0.6°), $[\alpha]_G^{25}$ +91.7° (±0.6°), (c 1.6130 in $CHCl_3$). 0.2180g. acid; 14.25 ml. 0.1028-N. NaOH.

$C_9H_{10}O_2$ Equiv. wt. calculated. 150, Found: 148.9.

Preparation of quinine (±) hydratropate.

The combined mother liquors from the first crystallisations with strychnine were concentrated. The acid was liberated; 31.6g. were obtained with

$[\alpha]_D^{23.6}$ -34.5° (±3.0°), $[\alpha]_G^{23}$ -43.3° (±3.0°),

(c 3.190 in $CHCl_3$).

It was dissolved in hot acetone (1600 ml.) and anhydrous quinine (67g.; 0.2 mole) with decolourising charcoal was added. It was boiled and the hot solution was filtered and allowed to stand at room temperature, after the method of Levene, Mikesha and Passoth (J. Biol. Chem., 1930, 88, 27). Quinine (-) hydratropate (29g.) separated in transparent stout rods. Systematic fractionation of the quinine salt from the mother liquors yielded in all 33.4g. of quinine (-) hydratropate, containing salt of the same activity. It had m.p. 176-177°,

$[\alpha]_D^{22.2}$ -109.0° (±0.6°),

$[\alpha]_G^{22.4}$ -132.0° (±0.6°),

(c 1.7800 in $CHCl_3$).

Preparation of (-)-hydratropic acid.

A solution of the optically pure quinine (-)-hydratropate (32g.) in chloroform was twice shaken with dilute hydrochloric acid. The lower layer was separated and the aqueous layer twice extracted with chloroform. The chloroform layers were then combined, washed twice with water and dried (Na_2SO_4). The chloroform was removed and the (-)-hydratropic acid fractionally crystallised from petroleum ether (b.p. 40-60°) as described under (+)-hydratropic acid. The yield of optically pure (-)-hydratropic acid was 6.5 g. It had m.p. 31-32°,

$[\alpha]_D^{20}$ -76.7° (±0.6°), $[\alpha]_D^{25}$ -76.1° (±0.6°),

$[\alpha]_G^{20}$ -93.3° (±0.6°), $[\alpha]_G^{25}$ -91.5° (±0.6°),

(c 1.4050 in $CHCl_3$). (c 1.5990 in $CHCl_3$).

0.2806g. acid : 18.38 ml 0.1028-N.NaOH.

$C_9H_{10}O_2$ Equiv. wt. calculated. 150. Found 148.6.

Preparation of (-)-hydratropyl alcohol.

To a solution of lithium aluminium hydride (2g. ; 0.052 mole) in dry ether (100 ml.) was added a solution of optically pure (+)-hydratropic acid (5.8g.; 0.0386 mole) in dry ether (100 ml.) during 20 min. at a rate so as to produce gentle refluxing. The experimental details were the same as those outlined previously (p.22). The residue was distilled and redistilled when 4.7 g. (92%)

of (-)-hydratropyl alcohol were obtained of which

1.4 g., was collected at 96°/10mm. had $n_D^{25.5}$ 1.5231, $d^{21.6°}$ = 1.000

$[\alpha]_D^{24.2}$ -17.4° (±0.02°),

$[\alpha]_G^{24.1}$ -21.2° (±0.02°),

(l=1dm, homogeneous) .

3.3g., was collected at 99-100°/11mm. had $n_D^{25.5}$ 1.5232, $d^{23.5°}$ = 0.9984

$[\alpha]_D^{26.1}$ -16.9° (±0.02°),

$[\alpha]_G^{26.4}$ -20.7° (±0.02°),

(l = 1dm, homogeneous)

Cohen, Marshall, Woodman (J.Chem. Soc., 1915, 107, 887) record $[\alpha]_D^{20}$ -15.16° as the rotation of (-)-hydratropyl alcohol.

Preparation of (+)-hydratropyl alcohol.

Optically pure (-)-hydratropic acid (5.6g.; 0.0373 mole) in dry ether (100 ml.) was added during 25 min. to lithium aluminium hydride (2g.; 0.052 mole) in dry ether (100 ml.) with continued shaking. The product was worked up in the manner employed before. There was obtained 4.7g. (92.6%) of colourless (+)-hydratropyl alcohol of which

1.1g. collected at 108°/12mm., had n_D^{25} 1.5232, $d^{21.6°}$=1.000

and 3.6g., collected at 100-1°/11 mm., had $^{n}D^{25}$ 1.5238,

$[\alpha]_D^{23.1}$ + 17.23° (±0.02°),

$[\alpha]_G^{23.2}$ + 21.02° (±0.02°),

(l=1dm, homogeneous).

as compared with $[\alpha]_D^{20}$ +15.25° recorded by Cohen, Marshal, Woodman (J.Chem.Soc., 1915, 107, 887). Eliel and Freeman (J. Amer. Chem. Soc., 1952, 74, 923) give the following physical constants for the (+)-hydratropyl alcohol:

b.p. 105-106°/11 mm., $^{n}D^{25}$ 1.5230,

$[\alpha]_D^{25.5}$ +3.18° (±0.01°) (α = +6.37° ±0.02°, l = 2 dm, homogeneous). The optical purity calculated by them on the basis of literature data is 20.6%.

The results obtained under "A" (p. 44) are summarised in Table IV.

TABLE IV.

(±) Hydratropic acid.

↓ Strychnine.

Strychnine salt of hydratropic acid.

$[\alpha]_D^{21}$ -30.8°(±0.7°),

$[\alpha]_G^{21.8}$ -38.3°(±0.7°),

(c 1.4090 in $CHCl_3$).

↓ H^+.

(+)-Hydratropic acid.
m.p.31.5-32°

$[\alpha]_D^{25}$ +76.3°(±0.6°)

$[\alpha]_G^{25}$ +91.7°(±0.6°),

(c 1.6130 in $CHCl_3$).

↓ $LiAlH_4$

(-)-Hydratropyl alcohol.

$[\alpha]_D^{24.2}$ -17.4°(±0.02°),

$[\alpha]_G^{24.1}$ -21.2°(±0.02°),

(l = ldm, homogeneous).

+ Filtrates.

↓ 1. H^+.

↓ 2. Quinine.

Quinine salt of hydratropic acid.

$[\alpha]_D^{22.2}$ -109.0°(±0.6°),

$[\alpha]_G^{22.4}$ -132.0°(±0.6°),

(c 1.7800 in $CHCl_3$).

↓ H^+.

(-)-Hydratropic acid.
m.p. 31-32°

$[\alpha]_D^{25}$ -76.1°(±0.6°),

$[\alpha]_G^{25}$ -91.5°(±0.6°),

(c 1.5990 in $CHCl_3$).

↓ $LiAlH_4$

(+)-Hydratropyl alcohol.

$[\alpha]_D^{23.1}$ +17.23°(±0.02°),

$[\alpha]_G^{23.2}$ +21.02°(±0.02°),

(l = ldm, homogeneous).

"B".

Preparation of (+)-hydratropoyl chloride.

(+)-Hydratropic acid (10g.; 0.06 mole) with
$[\alpha]_D^{20}$ +77.3° (±0.6°),
$[\alpha]_G^{20}$ +92.5° (±0.6°),
(c 1.5850 in $CHCl_3$).

was mixed with redistilled thionyl chloride (35 ml.). The experimental details were the same as described for the preparation of (±)-hydratropoyl chloride. In view of the observation of Levene and his co-workers (J. Biol. Chem., 1930, 88, 27) that (-)-hydratropoyl chloride underwent partial racemization on distillation, no attempt was made to purify or analyze the present product. There was obtained (+)-hydratropoyl chloride 9.9g. (88%) as a clear amber oil, n_D^{25} 1.5204, $[\alpha]_D^{21.8}$ +101.5° (±0.4°),
$[\alpha]_G^{21.8}$ +124.2° (±0.4°),
(c 2.4390 in benzene) and
$[\alpha]_D^{23.1}$ +87.8° (±0.3°),
$[\alpha]_G^{23.1}$ +108.6°(±0.3°),
(c 2.8460 in ether),

compared with $[\alpha]_D^{20}$ +50.5° (c 2.5, ether) and corresponding to 86% optical purity recorded by Booner, Zderic and Castaetto (J. Amer. Chem. Soc., 1952, 74, 5086). 0.4958g. (+)-hydratropoyl chloride required 29.25 c.c. 0.1 N $AgNO_3$ (titration), (Found: Cl, 20.94. C_9H_9OCl requires Cl, 21.0%).

Preparation of optically pure cholesteryl (+) hydratropate.

After dissolving by gentle warming dried cholesterol (10g. ; 0.025 mole) in anhydrous pyridine (36 ml.), the foregoing (+)-hydratropoyl chloride (4.8g. ; 0.028 mole) was added and the product worked up in the manner described for the preparation of cholesteryl (±) hydratropate. The ester was fractionally crystallised from chloroform-methanol. It furnished 5.3g. (39.5%) of cholesteryl (+) hydratropate m.p. 105-106°, with

$[\alpha]_D^{20.4}$ +10.6° (±0.4°),
$[\alpha]_G^{20.4}$ +13.3° (±0.4°),
(c 2.3990 in $CHCl_3$).

A small portion of it was crystallised from acetone. It crystallised in pearly plates, melted at 104.5-106° and had

$[\alpha]_D^{26}$ +10.7° (±0.4°),
$[\alpha]_G^{26}$ +13.8° (±0.4°),
(c 2.3010 in $CHCl_3$).

(Found: C, 83.9; H, 10.1. $C_{36}H_{54}O_2$ requires C, 83.3; H, 10.5%)

Lithium Aluminium Hydride reduction of optically pure cholesteryl (+) hydratropate.

The reduction of this optically pure ester (9.6g.; 0.018 mole) was carried out with lithium aluminium hydride in ether solution. The experimental details were the same

as those outlined previously. There was obtained 2g. (80%) of (-)-hydratropyl alcohol, b.p. 82°/10mm., $n_D^{25.5}$ 1.5222 $d^{21.6} = 1.000$,

$[\alpha]_D^{21}$ -17.2° (±0.02°),

$[\alpha]_G^{21}$ -21.1° (±0.02°),

(l = 1 dm, homogeneous).

The rotations for $[\alpha]_D$ and $[\alpha]_G$ are thus in close agreement with the values

$[\alpha]_D^{24.2}$ -17.4° (±0.02°),

$[\alpha]_G^{24.1}$ -21.2° (±0.02°),

(l = 1 dm, homogeneous),

found for the optically pure (-)-hydratropyl alcohol.

Preparation of (-)-hydratropoyl chloride.

(-)-Hydratropic acid (9.8g.; 0.06 mole) with

$[\alpha]_D^{20}$ -77.5° (±0.6°),

$[\alpha]_G^{20}$ -93.6° (±0.6°),

(c 1.5770 in $CHCl_3$).

was mixed with redistilled thionyl chloride (35 ml.). The experimental details were the same as described for the preparation of (+)-hydratropoyl chloride. It gave (-)-hydratropoyl chloride (11g.; 98%), $n_D^{25.5}$ 1.5203, $[\alpha]_D^{21.4}$ -103.1°(±0.4°), $[\alpha]_G^{21.4}$ -126.5° (±0.4°), (c 2.3510 in benzene), whereas Levene, Mikeska and Passoth (J.Biol.Chem., 1930, 88, 27) give

$[\alpha]_D^{25}$ -68.8°, (c 21.496 ether) for it. It was obtained as a clear amber oil.

0.6824g. of (-)-hydratropoyl chloride required 41.5 c.c. 0.1N $AgNO_3$ (titration). (Found: Cl, 21.6. C_9H_9OCl requires Cl, 21.0%).

Preparation of optically pure cholesteryl (-) hydratropate.

The foregoing (-)-hydratropoyl chloride (9.9g.; 0.052 mole) was added to the solution of cholesterol (20g.; 0.051 mole) in anhydrous pyridine (75 ml.). The experimental details were the same as those outlined for cholesteryl (±) hydratropate. The ester was fractionally crystallised from acetone. It gave cholesteryl (-) hydratropate (16.3g.; 61%) in small pearly needles, m.p. 139.5°, with $[\alpha]_D^{24.4}$ -58.15° ($\pm 0.6^\circ$), $[\alpha]_G^{24.4}$ -69.88° ($\pm 0.6^\circ$), (c 1.6170 in $CHCl_3$).
(Found: C,83.5; H, 10.6. $C_{36}H_{54}O_2$ requires C, 83.3; H, 10.5%).
It also crystallised in long pearly needles from benzene-methanol, had a m.p. 139-140°, with $[\alpha]_D^{25.8}$ -57.9° ($\pm 0.5^\circ$), $[\alpha]_G^{25.8}$ -69.2° ($\pm 0.5^\circ$), (c 1.9930 in $CHCl_3$). When mixed with the resolved ester (Part I) there was no depression of the melting point. This cholesteryl (-) hydratropate

was thus identical with that obtained from the resolution of cholesteryl (±) hydratropate.

Preparation of cholesteryl (±) hydratropate.

A mixture of 0.3208g. of cholesteryl (+) hydratropate having $[\alpha]_D^{26}$ +10.7° (± 0.4°),
$[\alpha]_G^{26}$ +13.8° (± 0.4°),
(c 2.3010 in $CHCl_3$).
with an equal weight of cholesteryl (-) hydratropate having
$[\alpha]_D^{24.4}$ -58.15° (±0.6°),
$[\alpha]_G^{24.4}$ -69.9° (±0.6°),
(c 1.6170 in $CHCl_3$).
was made up to 20 c.c. with chloroform, and the rotation determined. It had
$[\alpha]_D^{25.4}$ -23.4° (±0.3°),
$[\alpha]_G^{25.4}$ -28.2° (±0.3°),
(c 3.2080 in $CHCl_3$).
(These values are practically identical with $[\alpha]_D$ -23.72° and $[\alpha]_G$ -28.0° calculated from the rotations of the diastereoisomerides).
The solvent was then removed; after drying, the resulting cholesteryl (±) hydratropate melted at 116-117°.

The results obtained under "B" (p.51) are summarised in Table V.

TABLE V.

(±)-Hydratropic acid.

Strychnine.

Strychnine salt of hydratropic acid.

H^+

(+)-Hydratropic acid

$[\alpha]_D^{20}$ +77.3°(± 0.6°),

$[\alpha]_G^{20}$ +92.55°(±0.6°),

(c 1.5850 in $CHCl_3$).

$SOCl_2$

(+)-Hydratropoyl chloride.

$[\alpha]_D^{21.8}$ +101.5°(±0.4°),

$[\alpha]_G^{21.8}$ +124.2°(±0.4°),

(c 2.4390 in benzene).

Cholesterol.

Cholesteryl (+) hydratropate.

$[\alpha]_D^{26}$ +10.7°(±0.4°),

$[\alpha]_G^{26}$ +13.8°(±0.4°),

(c 2.3010 in $CHCl_3$)

$LiAlH_4$.

(-)-Hydratropyl alcohol

$[\alpha]_D^{21}$ -17.2°(±0.02°),

$[\alpha]_G^{21}$ -21.1°(±0.02°),

(l = 1 dm, homogeneous).

Filtrates.
1. H^+
2. Quinine

Quinine salt of hydratropic acid

H^+.

(-)-Hydratropic acid

$[\alpha]_D^{20}$ -77.5° (±0.6°),

$[\alpha]_G^{20}$ -93.6° (±0.6°),

(c 1.5770 in $CHCl_3$).

$SOCl_2$

(-)-Hydratropoyl chloride.

$[\alpha]_D^{21.4}$ -103.1°(±0.4°)

$[\alpha]_G^{21.4}$ -126.5°(±0.4°),

(c 2.3510 in benzene).

Cholesterol.

Cholesteryl (-) hydratropate.

$[\alpha]_D^{24.4}$ -58.15°(±0.6°),

$[\alpha]_G^{24.4}$ -69.9°(±0.6°),

(c 1.6170 in $CHCl_3$).

0.3208 g.

0.3208 g.

Cholesteryl (±) hydratropate.

$[\alpha]_D^{25.4}$ -23.4° (± 0.3°),

$[\alpha]_G^{25.4}$ -28.2° (± 0.3°),

(c 3.2080 in $CHCl_3$).

Examination under a microscope between crossed nicols of the partial racemate and cholesteryl (+) hydratropate.

On examination of the partial racemate and cholesteryl (+) hydratropate under a microscope between crossed nicols, like other cholesteryl esters, a brilliant display of colours is observed among which blue, yellow and various shades of brown are most prominent. Unlike cholesteryl benzoate, it does not show the liquid crystalline (an isotropic) state.

Conclusions.

I. In PART I the separation of cholesteryl (±) hydratropate to the less soluble form (86%) and the more soluble form (1-3%) has been described. The more soluble form was shown to be stable to pyridine and to pyridine plus pyridine hydrochloride and therefore there was no transformation of the more soluble to the less soluble form during synthesis.

II. In PART II, optically pure (+)-hydratropyl alcohol and (-)-hydratropyl alcohol were prepared. The rotation comparison of (-)-hydratropyl alcohol obtained from the less soluble form with the optically pure (-)-hydratropyl alcohol indicated that it was a partial racemate with a slight preponderance of cholesteryl (+) hydratropate. This was confirmed by the synthesis of optically pure cholesteryl (+) hydratropate and its reduction to optically pure (-)-hydratropyl alcohol. The more soluble form isolated was found to be identical with the synthetic specimen of optically pure cholesteryl (-) hydratropate.

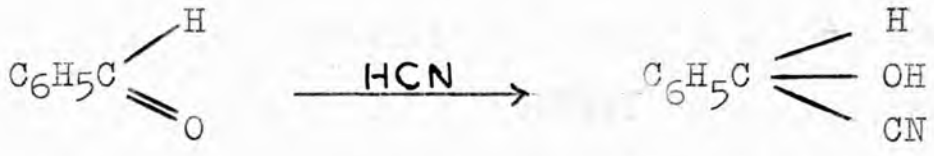
SECTION B.

IV. ASYMMETRIC SYNTHESIS.

IV. ASYMMETRIC SYNTHESIS.

INTRODUCTION.

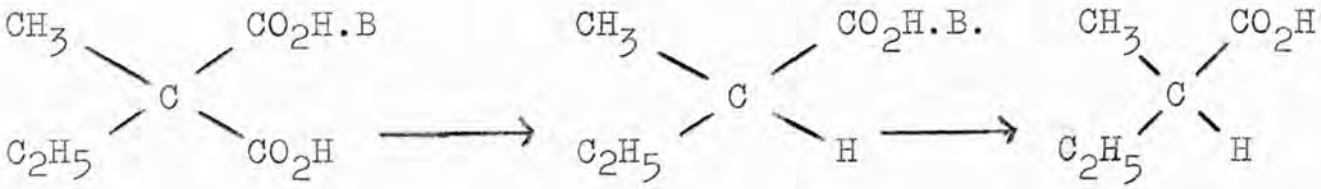
When a symmetrical compound is converted by ordinary chemical reaction into one of the asymmetric type, the new product is not optically active but is of the racemic variety, e.g.



(±)-Mandelonitrile.

If, however, asymmetric compounds are prepared in the presence of another optically active compound, the latter being finally removed, the synthetic product may exhibit optical activity. Cases of this kind have been observed in the laboratory. In nature the occurrence is common.

The first partial asymmetric synthesis was carried out by Marckwald (Ber., 1904, 37, 349, 1368) who prepared slightly (-)-rotatory α -methylbutyric acid by decarboxylation of a mono-brucine salt of methylethyl-malonic acid.



(-)-rotation

B = Brucine.

He defined "Asymmetric synthesis" as those processes which produce optically active compounds from symmetrically constituted molecules by the intermediate use of optically active reagents, but without the use of any of the methods of resolution. This type of asymmetric synthesis is now known as "Partial asymmetric synthesis." Among the optically active compounds of known constitution which have been used, mention may be made of (-)-menthol, (-)-borneol, optically active amyl alcohol and sec-octyl alcohol, etc., etc.

A special case of asymmetric synthesis is absolute asymmetric synthesis. This is the preparation of an optically active compound without the intermediate use of optically active reagents. A simple case can be cited. Kuhn and Knopf (Naturwiss, 1930, 18, 183; Z. physik Chem., 1930, 7(B), 292), irradiated (±)- α -azidopropionic dimethylamide,

$$CH_3 - \underset{\displaystyle N_3}{\overset{\displaystyle |}{CH}} - CON(CH_3)_2$$

with dextro-circularly polarised light and obtained a

product that was slightly dextrorotatory. When the amide was irradiated with laevo-circularly polarised light, the product was slightly laevo-rotatory.

Asymmetric synthesis was studied very extensively during the earlier part of this century, particularly by McKenzie and his colleagues (for a bibliography see Ritchie, Adv. in Enzymology, 1947, 7, 65).

McKenzie (J. Chem. Soc., 1904, 85, 1249), McKenzie and Humphries (J. Chem. Soc., 1909, 95, 1105) obtained slightly laevoratory mandelic acid by reducing (-)-menthyl benzoylformate with aluminium amalgam, acetylating the reduced ester and hydrolysing the resulting product.

$$C_6H_5.CO.CO.O.C_{10}H_{19} \xrightarrow{2H} C_6H_5CHOH.CO.O.C_{10}H_{19}$$

(-)-menthyl benzoylformate.

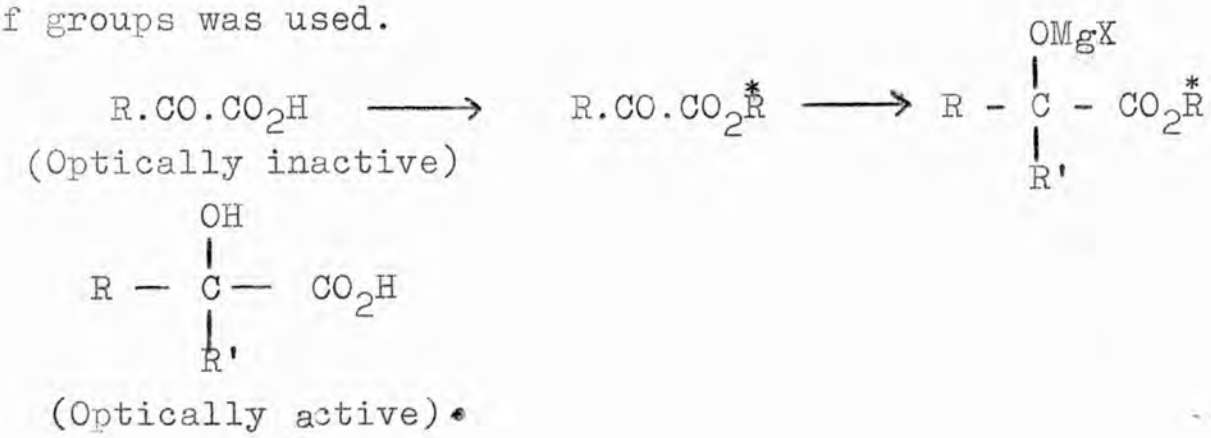
$$\xrightarrow{Ac_2O} \xrightarrow{H_2O} C_6H_5\ CHOH.COOH.$$

(-)-Mandelic acid.

In a similar manner, the pyruvates of (-)-menthol, (-)-borneol and (-)-amyl alcohol yielded optically active lactic acids by reduction and hydrolysis.

McKenzie and his colleagues obtained similar results with Grignard reagents. They investigated some thirty examples of the following type in which a variety

of groups was used.



Some of the groups were:

R = C_6H_5- ; (p) CH_3-O-C_6H_4 - ; CH_3- ; $C_{10}H_7$- ;

(Opt. act.) $\overset{*}{R}$ = (-)-menthyl ; (-)-bornyl ; (-)- and (+)-sec-octyl ;

R^i = CH_3- ; C_2H_5- ; n-C_3H_7- ; iso-C_3H_7- ; C_4H_9-; C_6H_5-.

In each case, partial asymmetric synthesis was effected and the resulting hydroxy acids contained an excess of one of the optical isomers.

In the above type of partial asymmetric synthesis, where the unsaturated group is separated from the optically active centre, the product is not optically pure. Tiffeneau, Levy and Ditz (Compt. rend., 1931, 192, 955; Bull. soc. chim., 1935, 5, 1848, 1855) suggested that as the number of atoms introduced between the optically active centre and the carbonyl group is increased, so will the extent of partial asymmetric synthesis decrease. in this way, the low degree of partial asymmetric

synthesis in the McKenzie type reaction was attributed to the separation of the two groups by the -CO-O- group. Support for this idea arises from the observation of Roger (J. Chem. Soc., 1937, 1048; 1939, 108) that only one of the two possible diastereoisomerides is formed on the addition of a Grignard reagent to benzoin.

Ph - CH(OH) - CO- Ph
(-)

Benzoin.

Ph - CH(OH) - C(CH_3)OH - Ph.
(-) (+)

(+)Methylhydrobenzoin.

In this case the dissymmetric group and the carbonyl group are adjacent.

McKenzie and Muller (J. Chem. Soc., 1909, 95, 544) thought it might be possible to correlate the degree of asymmetric synthesis with the magnitude of the optical rotatory power of the alcohol ($\overset{*}{R}OH$), but this was not confirmed by Ritchie (Asymmetric Synthesis and Asymmetric Induction, Oxford Univ. Press, 1933, p.110) who commented as follows:

> "The degree of asymmetric synthesis in this type of reaction depends not only upon the rotatory power of the directing system but also upon the conditions obtaining during the Grignard reaction; on repeating such a synthesis several times, the activity of the product has been found to vary markedly."

McKenzie and Wood (J. Chem. Soc., 1939, 1536) have suggested that the formation of the active hydroxy

acid may be due to R - CO - $CO_2\overset{*}{R}$ to be an unequal mixture of diastereoisomerids I and II,

$$\underset{(-)}{R} - CO - CO_2\overset{*}{\underset{(-)}{R}} \qquad \underset{(+)}{R} - CO - CO_2\overset{*}{\underset{(-)}{R}}$$

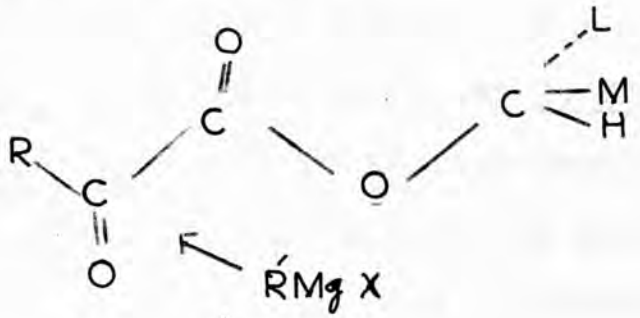
I. II.

$\overset{*}{R}$ = (-)-menthyl.

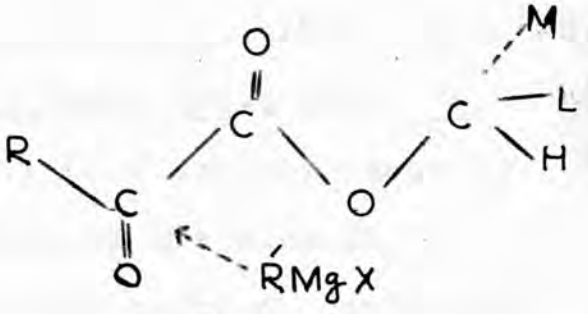
in which the -CO- group existed as a labile centre of asymmetry. The mutarotation which occurs in alcoholic solvents being connected with the attainment of equilibrium between the two forms. Jamison and Turner (J.Chem.Soc., 1941, 538) have, however, concluded that the mutarotation is due to solvation or hemiacetal formation. Glazer and Turner (J.Chem.Soc., 1949, S 169) have demonstrated that mutarotation of (-)-menthyl benzoylformate in ethanol was due to hemiacetal formation. Since no mutarotation phenomena are observed in non-hydroxylic solvents, there is no reason to suppose that the ketonic group in the ester assumes an asymmetric configuration.

Evidence that the conformation of acyclic molecules determines the stereochemical course of reactions in which a new asymmetry centre is created adjacent to an old, is presented by Prelog (Helv. Chim. Acta., 1953, 36, 308) who examines the new asymmetry compound after the removal of the original activating centre. Prelog has chosen the much studied reaction of Grignard reagents with

α-Keto-esters of optically active alcohols and has advanced a hypothesis which satisfactorily explains the results of his own and earlier work. The two - CO - groups in the α-keto esters are assumed to take up the trans-position so that R - $\overset{*}{C}$O - CO-O - C$\begin{matrix} L \\ - M \\ S \end{matrix}$ will lie essentially in a plane. Grignard reagent RMgX would attack $\overset{*}{C}$ preferentially from the side on which the smallest substituent S lies. This requires a consideration of the possible conformations of the group CSML. In the case where S = H and L $\rangle$ M the determining factor is the reaction of the Grignard reagent with that conformation where S (H) is in the plane of the ester grouping and M and L in front and behind respectively. The preferential attack will be as shown in A and B.

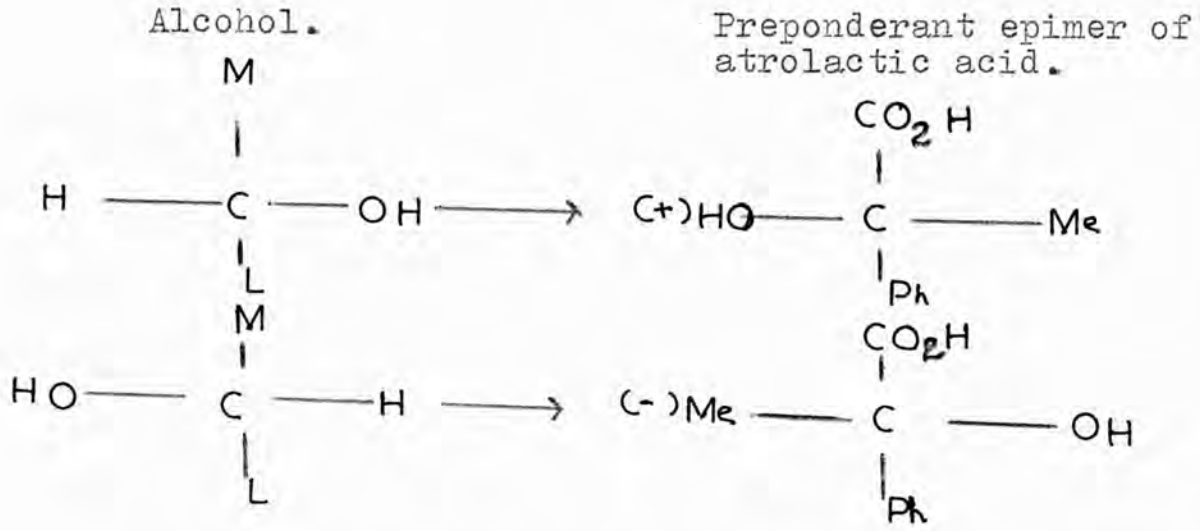


A.



B.

The results may be summarised as follows: the alcohols as phenylglyoxylic esters (R = Ph) are treated with methyl magnesium iodide (R´ = Me) giving esters of atrolactic acids which are then hydrolysed.



Prelog and his co-workers (Helv. Chim. Acta., 1954, 37, 221) described the reduction of α-keto acid esters of optically active alcohols with lithium aluminium hydride. This method eliminates the need for hydrolysis of the intermediate atrolactic acid ester in the former method, but the optical rotation of the product is smaller.

Cram and Elhafez (J. Amer. Chem. Soc., 1952, 74, 5828; etc., for references see J. Amer. Chem. Soc., 1954, 76, 5740) considered similar reactions in which the reacting carbonyl group is directly adjacent to the asymmetric carbon atom. Instead of removing the original centre of asymmetry, as was effected in the above cases, the relative proportions of the diastereoisomers formed were estimated from a study of their infra-red spectra. A rule was proposed to correlate and predict the stereochemical direction of asymmetric synthesis:

"In non-catalytic reactions of the following type, that diastereo-isomer will predominate which would be formed by the approach of the entering group (R') from the least hindered side of the double bond when the rotational conformation of the C-C bond is such that the double bond is flanked by the two least bulky groups (M and S) attached to the adjacent asymmetric centre ($\overset{*}{C}$)."

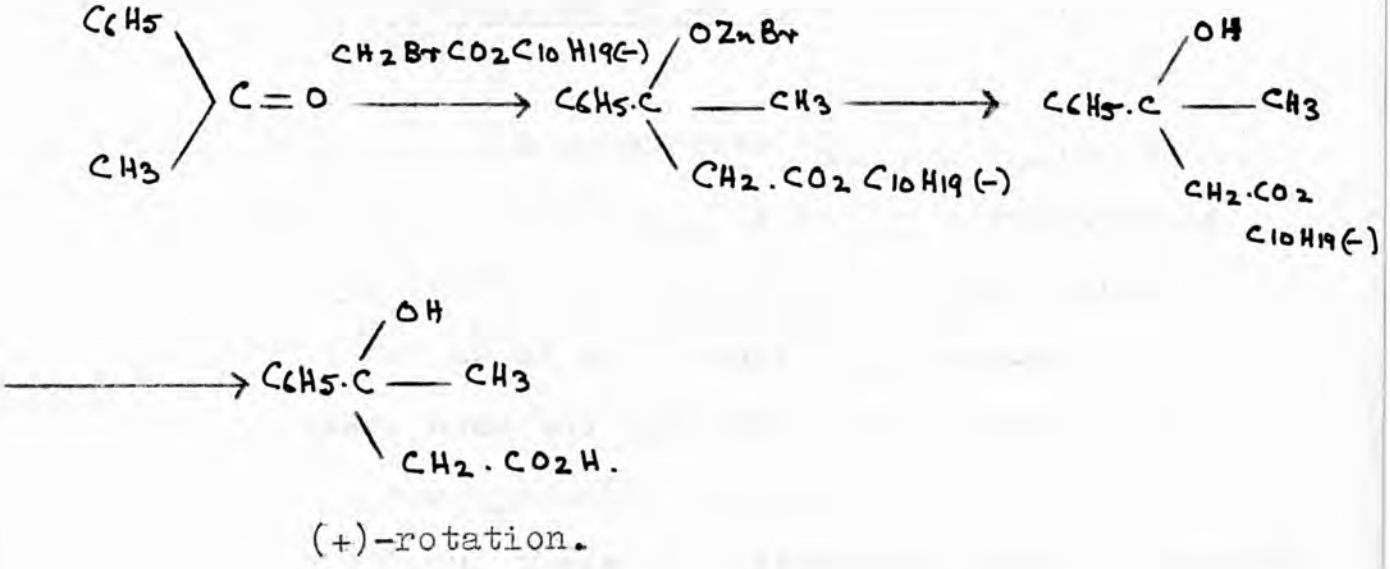
(Relative sizes, L $\rangle$ M $\rangle$ S).

One difficulty which may arise in applying the rules of Prelog and of Cram and Elhafez lies in deciding the order of effective bulk of the three groups (L, M and S) attached to the asymmetric carbon atom. Both rules of asymmetric synthesis will be of great value in correlation problems, particularly that of Prelog, since his method can be applied in principle to almost any carbinol.

Some more examples of partial asymmetric synthesis.

(a) Partial asymmetric synthesis involving an additional reaction between an optically active Grignard reagent and a ketone not containing an asymmetric centre.

Reid and Turner (J. Chem. Soc., 1949, 3365; 1950, 3694) obtained slightly dextrorotatory β-hydroxy-β-phenylbutyric acid by using acetophenone, (-)-menthyl bromoacetate and zinc (Reformatsky reaction).



(+)-rotation.

This was the first published example of a partial asymmetric synthesis, excluding asymmetric reduction, involving an organo-metallic compound in which the fixed centre of asymmetry is not in the molecule containing the carbonyl group.

(b) Partial asymmetric synthesis involving Meerwein Ponndorf reduction.

Jackman, Mills and Shannon (J. Amer. Chem. Soc., 1950, 72, 4814) reduced tert.-butyl n-hexyl ketone with aluminium (+)-1:2:2-trimethylpropoxide at 200°, and obtained a slightly laevorotatory alcohol.

$$(CH_3)_3C.CO.C_6H_{13} \xrightarrow{[(CH_3)_3C.CH(CH_3)O]_3\ Al} (CH_3)3C.CHOH.C_6H_{13}\ .$$

(-)-rotation.

(c) Asymmetric reduction by an optically active reducing agent.

1. Vavon and his co-workers (Compt. rend., 1946, 222, 959; 1947, 224, 1435) have reported the unique action of isobornyl magnesium chloride on a series of six phenyl alkyl ketones to give in each case the reduced phenylalkylcarbinol which was optically active. The optical activity of these products ranged from 19 to 72% of that reported for the pure dextro isomers.
2. Mosher and Combe (J. Amer. Chem. Soc., 1950, 72, 3994) obtained slightly dextrorotatory methyl-t-butyl carbinol by the reduction of methyl-t-butyl ketone by means of (+)-2-methylbutylmagnesium chloride.

$$(CH_3)_3C.CO.CH_3 \xrightarrow{(+)\text{-}CH_3.CH_2.CH(CH_3)CH_2MgCl} (CH_3)_3C.CHOH.CH_3\ .$$

(+) rotation.

(d) Partial asymmetric synthesis involving the presence of an optically active agent which is not combined with either of the reacting molecules.

1. Bothner - By (J. Amer. Chem. Soc., 1951, 73, 846), has reduced butanone with lithium aluminium hydride in the presence of (+)-camphor and thereby obtained (+)-isoborneol (from the camphor) and a small amount of a dextrorotatory s-butyl alcohol.

$$CH_3COC_2H_5 \xrightarrow[(+)\text{-camphor.}]{LiAlH_4.} CH_3\text{-}CHOH\text{-}C_2H_5.$$
(+)-rotation.

2. Cohen and Wright (J. Org. Chem., 1953, 18, 432) obtained slightly dextrorotatory 2-hydroxy-2-phenyl butanoic acid by the addition of ethyl chloride Grignard reagent to ethyl benzoylformate in a mixture of benzene and (+)-2,3-dimethoxybutane.

$$C_6H_5.CO.CO_2C_2H_5 \xrightarrow{C_2H_5MgBr} C_6H_5-\underset{\displaystyle COOC_2H_5}{\overset{\displaystyle OH}{\overset{|}{\underset{|}{C}}}}-C_2H_5$$

(+)-2,3-dimethoxybutane

$$\xrightarrow{H_2O} C_6H_5-\underset{\displaystyle COOH}{\overset{\displaystyle OH}{\overset{|}{\underset{|}{C}}}}-C_2H_5$$

(+)-rotation.

Present Work.

Benzoylformic acid, (-)-menthyl benzoylformate and benzoylformyl chloride have been prepared by known methods. Cholesteryl benzoylformate, which had not been prepared previously, was obtained by combining benzoylformyl chloride in benzene with cholesterol dissolved in benzene and pyridine. It had a m.p. 119-120°, remelting point 128-129° with

$[\alpha]_D^{26.6}$ -15.01° (± 0.8°),

$[\alpha]_G^{26.6}$ -16.7° (±0.8°),

(c 1.1790 in $CHCl_3$).

Optically pure (-)-phenylethylene glycol has been prepared and its partial asymmetric synthesis from (-)-menthyl benzoylformate and cholesteryl benzoylformate by reducing them with

(a) Lithium aluminium hydride,

(b) Aluminium amalgam, Sodium borohydride and Aluminium isopropoxide followed by Lithium aluminium hydride

has been investigated.

EXPERIMENTAL.

Preparation of benzoylformic acid.

Method 1.

Oxidation of acetophenone.

The method of McKenzie (J.Chem.Soc., 1904, 85, 1249) modified by Professor Turner (private communication) was used.

A hot (70°) solution of potassium permanganate (32g.) and sodium hydroxide (8.5g.) in 200 ml. of water was added slowly to a well stirred mixture of acetophenone (12g.) in 200 ml. of water. The manganese dioxide was filtered off immediately and washed with water. This operation was repeated four times. The filtrate and washings were combined and evaporated to 200 ml. and then acidified with concentrated hydrochloric acid. The benzoic acid (17.4g.) which separated was filtered off and the filtrate was made alkaline with 30% aqueous caustic soda. The unchanged part of acetophenone was extracted twice with ether and the aqueous solution was then acidified with concentrated hydrochloric acid and extracted five times with ether. The entire experiment was repeated up to this

stage. The combined ether extracts were dried over anhydrous sodium sulphate, and the solvent was removed. The residue was ground with carbon disulphide to dissolve the benzoic acid. The crude benzoylformic acid 73.7g. was crystallised from benzene and dried in vacuo over phosphorus pentoxide. Yield 52.3g. (35%). After standing it developed light yellow colour on the exposed surface.

Method 2.

Oxidation of (±)-mandelic acid.

(Organic Syntheses, Coll. Vol.I, 1941, 241).

To a well stirred solution of mandelic acid (187.5g.; 1.25 mole) in 250 ml. of water was added a cold solution of sodium hydroxide (55g.) in 250 ml. of water and crushed ice (1000g.). After a few minutes finely powdered potassium permanganate (137.5g.) was added in small portions over a period of one and a half hours. It was further stirred for one and a half hours, the temperature being maintained at -2° to -4°. The excess of potassium permanganate was reduced with about 100 ml. of ethanol. The stirrer was stopped and the manganese dioxide allowed to coagulate for one hour. The manganese dioxide was filtered off and washed with water. The filtrate and washings were combined and evaporated to 1000 ml., then acidified with 50 ml.

concentrated sulphuric acid previously diluted with an equal volume of water. The benzoic acid which separated weighed 19g. The filtrate was made alkaline with sodium hydroxide, cooled and acidified with concentrated sulphuric acid. The yellow oil of benzoylformic acid was separated and the solution extracted five times with ether. The oily layer was combined with the ethereal layers, dried (Na_2SO_4) and the solvent removed. The solid mass was ground with carbon disulphide to dissolve the benzoic acid. Crude benzoylformic acid 106.6g. was crystallised twice from benzene and dried in vacuo over phosphorus pentoxide. Yield 42g. (23%). It also developed a light yellow colour on the surface on exposure.

Preparation of (-)-menthyl benzoylformate.

The method of McKenzie (J. Chem. Soc., 1904, 85, 1249) was used.

The benzoylformic acid (30g.) was heated on a water bath with three times its weight of (-)-menthol in the presence of dry hydrogen chloride for eight hours. The ethereal solution of the product was washed twice with water and twice with 10% sodium bicarbonate solution. The ether was distilled off and the residue distilled in steam to remove unattacked menthol. The solid was crystallised from ethyl alcohol. It yielded 43g. (74%) of (-)-menthyl

benzoylformate m.p. 72.5-73.5°,

$[\alpha]_D^{25.4}$ -44.9° (± 0.4°),

(c 2.6270 in ethanol),

and

$[\alpha]_D^{25.4}$ -51.1° (±0.5°),

$[\alpha]_G^{25.4}$ -61.3° (±0.5°),

(c 1.8270 in $CHCl_3$).

McKenzie gives m.p. 73-74°, $[\alpha]_D^{20}$ -44.4° (c 4.7832 in ethanol) for it.

Preparation of aluminium amalgam.

Aluminium foils were treated with a 2% solution of mercuric chloride for two seconds and then washed quickly with water (thrice), methyl alcohol (twice) and ether (twice). The amalgamated aluminium was covered with moist ether and used at once.

Preparation of aluminium isopropoxide.

27g. of aluminium foil, 300 ml. of anhydrous isopropyl alcohol (dried over K_2CO_3) and 0.5g. of mercuric chloride were placed in a litre flask, provided with a reflux condenser. The flask was gently warmed on a water bath. When the liquid was boiling, 2 ml. of carbon tetrachloride were added and the gentle refluxing maintained for six hours. The product was purified by distillation. Yield 115g. (56%), b.p. 130-142/7mm. It solidified on cooling.

Lithium Aluminium Hydride reduction of (±)-mandelic acid.

(±)-Mandelic acid (10g.; 0.065 mole) in dry ether (200 ml.) was added during 30 mins. to lithium aluminium hydride (5g.; 0.13 mole) in dry ether (150 ml.). After the addition was complete, the mixture was boiled under reflux for two hours and then cooled in ice. The excess lithium aluminium hydride was destroyed by adding water. The precipitated hydroxides were dissolved by the addition of dilute sulphuric acid. The layers were separated and the aqueous layer was saturated with sodium chloride and extracted four times with ether. The ether layers

were combined and dried over anhydrous potassium carbonate. Evaporation of the ethereal layer gave 7g. (77%) of phenylethylene glycol m.p. 62-65°.

Lithium Aluminium Hydride reduction of (-)-mandelic acid.

(-)-Mandelic acid m.p. 132-134° with $[\alpha]_D^{23.6}$ -154.3°(±0.6°), $[\alpha]_G^{23.6}$ -184.7° (±0.6°), (c 1.6430 in H_2O), (8.83g. ; 0.05 mole) with lithium aluminium hydride (5g.; 0.13 mole) gave 6.9g. (87%) of phenylethylene glycol. It was sublimed under reduced pressure m.p. 66-67°,

$[\alpha]_D^{24}$ -39.9° (±0.3°),
$[\alpha]_G^{24}$ -47.7° (±0.3°),
(l = 1 , c 6.562 in ethanol).

and

$[\alpha]_D^{23}$ -63.8° (±0.2°),
$[\alpha]_G^{23}$ -75.8° (±0.2°),
(l = 1 , c 9.522 in $CHCl_3$).

Prelog and his co-workers (Helv. Chim. Acta., 1954, 37, 221) give $[\alpha]_D^{20}$ +40.6° (l = 2 , c 3.23 in ethanol) for phenylethylene glycol obtained from (+)-mandelic acid with $[\alpha]_D^{18}$ +157.5° (l = 2 , c 3.50 in H_2O).

Lithium Aluminium Hydride reduction of (-)-menthyl benzoylformate.

A solution of (-)-menthyl benzoylformate (10g.; 0.06 mole) in 200 ml. of dry ether was added in small portions over a period of 30 mins. to a suspension of lithium aluminium hydride (3.3g.; 0.08 mole) in dry ether (200 ml.). After the addition was complete, the mixture was boiled under reflux for 30 mins. and then cooled in ice. The excess of lithium aluminium hydride was destroyed by adding water. The precipitated hydroxides were dissolved by the addition of dilute sulphuric acid. The layers were separated and the aqueous layer was saturated with sodium chloride and extracted four times with ether. The ether layers were combined and dried over sodium sulphate. After the removal of ether, the residue was digested with hot water, cooled and filtered. The methol obtained weighed 4.9g. (90%). Evaporation of the filtrate gave 4.2g. (89%) of phenylethylene glycol, m.p. 62-66°, with

$[\alpha]_D^{21}$ -3.4° (±0.1°),
$[\alpha]_G^{21}$ -3.9° (±0.1°),
(c 9.1500 in ethanol),

and

$[\alpha]_D^{20}$ -5.2° (±0.1°),
$[\alpha]_G^{20}$ -5.9° (±0.1°),
(c 10.8810 in $CHCl_3$).

Optical purity: 8%.

Prelog and his co-workers (loc.cit.) give m.p. 62-63°, $[\alpha]_D$ -2.95° (l = 2 dm, c 10.6 in ethanol).

1. Reduction of (-)-menthyl benzoylformate.

(a) Reducing Agent Aluminium Amalgam.

A solution of 5g. (0.017 mole) of (-)-menthyl benzoylformate in 150 ml. moist ether was added to about 5g. of aluminium amalgam. After the reaction had subsided it was mechanically shaken for 5 hours. The ethereal solution was filtered and the residue washed with ether. It was dried (Na_2SO_4) and the ether removed by distillation. There was obtained 4.2g. (80.4%) of (-)-menthyl mandelate, m.p. 84-86°,

$[\alpha]_D^{22.6}$ -76.3° (±0.5°),
$[\alpha]_G^{22.6}$ -90.8° (±0.5°),
(c 1.8480 in ethanol).

McKenzie (J. Chem. Soc., 1904, 85, 1249) gives m.p. 85-86°, $[\alpha]_D^{18}$ -76.9° (c 6.174 in ethanol) and $[\alpha]_D^{20}$ -77.6° (c 2.558 in ethanol), while McKenzie and Humphries (J.Chem.Soc., 1909, 95, 1105) give $[\alpha]_D^{18.5}$ -81.5° (c 2.952 in ethanol) and $[\alpha]_D^{15}$ -80.2° (c 3.223 in ethanol) for the resulting mandelate.

Jamison and Turner (J.Chem.Soc., 1942, 611) give for the optically pure (-)-menthyl (±)-mandelate m.p. 85-86°, $[\alpha]_G^{19.7}$ -87.3°, (c 1.2485 in ethanol) and for the optically pure (-)-menthyl (-)-mandelate m.p. 81-82°, $[\alpha]_G^{19}$ -163.5° (c 2.3072 in ethanol).

Reduction of (-)-menthyl mandelate (l) with Lithium Aluminium Hydride.

To a solution of lithium aluminium hydride (1.5g.; 0.03 mole) in 75 ml. dry ether was added in small portions a solution of 2g. (0.006 mole) of the foregoing (-)-menthyl mandelate (l) in 100 ml. dry ether at room temperature over a period of 15 mins. The products were isolated in the usual way. It yielded 0.82g. (89%) of phenylethylene glycol, m.p. 64-66°,

$[\alpha]_D^{23}$ -4.4° (±0.25°),

$[\alpha]_G^{23}$ -5.2° (±0.25°),

(l = 1 , c 8.340 in $CHCl_3$)

Optical purity 7%.

(Found: C, 69.80; H, 7.26. $C_8H_{10}O_2$ requires C,69.54; H,7.29%).

2. Reduction of (-)-menthyl benzoylformate.

(b) Reducing Agent Sodium Borohydride.

A solution of sodium borohydride (2.4g.; 0.06 mole) in water (40 ml.) was added during 20 mins. to a cooled (0°) and mechanically stirred mixture of (-)-menthyl benzoylformate (4g.; 0.013 mole), ethyl alcohol (200 ml.), water (40 ml.) and boric acid (8g.). After stirring for another 20 mins., the mixture was diluted with water and acidified with dilute sulphuric acid. (-)-Menthyl mandelate was filtered off, washed with water. It was dissolved in chloroform and dried (Na_2SO_4). After the removal of chloroform on a boiling water bath, there was obtained 2.3g. (57.5%) of (-)-menthyl mandelate, m.p. $82-84^{\circ}$,

$[\alpha]_D^{24.8}$ -91.45° ($\pm 0.8^{\circ}$),

$[\alpha]_G^{24.8}$ -110.1° ($\pm 0.8^{\circ}$),

(c 1.1700 in ethanol).

(Found: C, 74.58; H, 8.80. $C_{18}H_{26}O_3$ requires C, 74.44; H, 9.02%).

Reduction of (-)-menthyl mandelate (2) with Lithium Aluminium Hydride.

Reduction of uncrystallised (-)-menthyl mandelate (2) (2g.; 0.006 mole) in dry ether (100 ml.) was carried out with lithium aluminium hydride (1.5g.; 0.03 mole) in dry ether (75 ml.). The reaction mixture was worked up as soon as the reduction was complete. There was obtained 0.82g. (89%) of phenylethylene glycol, m.p. 58-62°,

$[\alpha]_D^{22.8}$ -18.44° (±0.24°),

$[\alpha]_G^{22.8}$ -21.5° (±0.24°),

(l = 1 , c 8.1340 in $CHCl_3$).

Optical purity 29%.

(Found: C, 69.54; H, 7.53. $C_8H_{10}O_2$ requires C, 69.54; H, 7.29%).

3. Reduction of (-)-menthyl benzoylformate.

(c) Reducing Agent Aluminium Isopropoxide.

4g. of (-)-menthyl benzoylformate, 10g. of aluminium isopropoxide and 120 ml. of isopropyl alcohol were boiled under reflux for 1 hour. After distilling off the acetone formed and the solvent, the residue was hydrolysed with ice-cold dilute sulphuric acid. Ether extraction of the product followed by the usual procedure gave 2.8g. (70%) of (-)-menthyl mandelate as a colourless liquid. After standing for three weeks it changed to a waxy solid. The smell of menthol was perceptible. It had

$[\alpha]_D^{22.4}$ -39.7° ($\pm 0.4^\circ$),

$[\alpha]_G^{22.4}$ -47.2° ($\pm 0.4^\circ$),

(c 2.2470 in $CHCl_3$).

In view of the contamination of this (-)-menthyl mandelate with menthol, no attempt was made to analyse or reduce the present product with lithium aluminium hydride.

Preparation of oxalyl chloride.

The method of Staudinger (Ber., 1908, 41, 3563) was used.

Finely powdered anhydrous oxalic acid (180g.) was mixed very thoroughly with phosphorus pentachloride (800g.) and allowed to stand first at 0°, and then for three days at room temperature. It was decanted from the unreacted phosphorus pentachloride. Distillation and redistillation yielded 94g. (37%) of oxalyl chloride, b.p. 63-64°.

Staudinger records a yield of 45-51%.

Preparation of benzoylformyl chloride.

The method of Kharasch and Brown (J. Amer. Chem. Soc., 1942, 64, 329) was used.

Benzoylformic acid 21.4g. (0.14 mole), and oxalyl chloride, 73g. (0.57 mole) were boiled under reflux for six hours. Removal of excess of oxalyl chloride by distillation followed by distillation under reduced pressure gave benzoylformyl chloride (17.3g.; 72%) b.p. 87-88/11-12mm. It had a light yellow colour with a pungent odour. Kharasch and Brown give b.p. 91/9.5mm., while Acree (Amer. Chem. J., 1913, 50, 389) gives b.p. 125/9mm.

Preparation of cholesteryl benzoylformate.

Benzoylformyl chloride (20.8g. ; 0.12 mole) in benzene (160 ml.) was added in small portions to a solution of cholesterol (40g.; 0.1 mole) dissolved in benzene (240 ml.) and pyridine (160 ml.) during 30 mins. at room temperature. It was left over-night and extracted twice with water, twice with dilute hydrochloric acid, twice with 5% sodium bicarbonate and twice with water. Evaporation of benzene gave crude cholesteryl benzoylformate, which was crystallised twice from acetone: rectangular plates. Yield, 46g. (86%); m.p., 119-120°; remelting point, 128-129°. It showed blue-green fluorescence and had

$[\alpha]_D^{26.6}$ -15.01° (±0.8°),
$[\alpha]_G^{26.6}$ -16.7° (±0.8°),
(c 1.1790 in $CHCl_3$).

(Found: C, 80.96; H, 9.55. $C_{35}H_{50}O_3$ requires C, 81.02; H, 9.7%).

Examination under a microscope between crossed nicols of cholesteryl benzoylformate.

On examination of cholesteryl benzoylformate under a microscope between crossed nicols, like other cholesteryl esters, a brilliant display of colours is observed among which green, blue, yellow and various shades of brown are most prominent.

Reduction of cholesteryl benzoylformate with Lithium Aluminium Hydride.

A solution of cholesteryl benzoylformate (10g.,; 0.019 mole) in dry ether (250 ml.) was added during 30 mins. to a suspension of lithium aluminium hydride (3.3g. ; 0.08 mole) in dry ether (180 ml.) The reaction mixture was worked up in the usual way. The residue was digested with water three times and filtered. Cholesterol obtained weighed 7.2g. (97.3%), m.p. 143-145°, $[\alpha]_D^{20.6}$ -38.4° (±0.4°), $[\alpha]_G^{20.6}$ -46.5° (±0.4°), (c 2.5380 in $CHCl_3$).

Evaporation of the filtrate yielded 2g. (77%) of phenylethylene glycol m.p. 55-62°. It had a pink colour. It was sublimed under reduced pressure, yield 1.35g., m.p. 63-67°,

$[\alpha]_D^{21.8}$ +1.14° (±0.16°),
$[\alpha]_G^{21.8}$ +1.37° (±0.15°),
(c 6.1240 in ethanol).

Optical purity 2.7%

It crystallised from petroleum ether (b.p. 100-120°) in needles, m.p. 67-68°.

(Found: C, 69.99; H, 7.60. $C_8H_{10}O_2$ requires C, 69.54; H, 7.29%).

1. Reduction of cholesteryl benzoylformate.

(a) Reducing Agent Aluminium Amalgam.

A solution of 5g. of cholesteryl benzoylformate in 150 ml. of moist ether was added to about 5g. of aluminium amalgam and shaken mechanically for 5 hrs. The ethereal solution was filtered. It was dried (Na_2SO_4). The cholesteryl mandelate obtained after the removal of ether weighed 4g. (78.4%), m.p. 148-153°,

$[\alpha]_D^{22.6}$ -16.87° (±0.5°),

$[\alpha]_G^{22.6}$ -21.6° (±0.5°),

(c 1.8820 in $CHCl_3$).

(Found: C, 81.04; H, 10.15. $C_{35}H_{52}O_3$ requires C, 80.71, H, 10.06%).

Reduction of cholesteryl mandelate (l) with Lithium Aluminium Hydride.

To a solution of lithium aluminium hydride (1.5g. 0.03 mole) in 75 ml. dry ether was added in small portions a solution of 2g. (0.003 mole) of the cholesteryl mandelate (l) in 100 ml. dry ether over a period of 25 mins. The products were isolated in the usual way. Yield of phenylethylene glycol 0.29g. (54.7%), m.p. 58-64°,

$[\alpha]_D^{21.4}$ +2.66° (±0.8°), $[\alpha]_G^{21.8}$ +3.35°(±0.8°), (l = 1, c 2.472 in $CHCl_3$).

Optical purity 4%. (Found: C, 69.80; H, 7.65. $C_8H_{10}O_2$ requires C, 69.54; H, 7.29%).

2. Reduction of cholesteryl benzoylformate.

(b) Reducing Agent Sodium Borohydride.

Sodium borohydride (1.2g. ; 0.03 mole) was added in small portions to a mixture of cholesteryl benzoylformate (2g.; 0.003 mole), dioxan (250 ml.), water (16 ml.) and boric acid (4g.). The pH of the mixture, after the reaction was completed, was 7. The dioxan was removed on a boiling water bath by distillation. The reaction mixture was diluted with water, acidified with dilute sulphuric acid and extracted with ether four times. The combined ethereal extract was dried (Na_2SO_4). Removal of ether gave 1.95g. (93%) of cholesteryl mandelate, m.p. 147-150°,

$[\alpha]_D^{25.4}$ -18.69° (±0.7°),
$[\alpha]_G^{25.4}$ -20.77° (±0.7°),
(c 1.3240 in $CHCl_3$).

(Found: C, 80.16; H, 10.13. $C_{35}H_{52}O_3$ requires C, 80.71; H, 10.06%).

Crystallisation from ethanol gave pure material, m.p. 154-155°,

$[\alpha]_D^{24.8}$ -18.6° (± 1°),
$[\alpha]_G^{24.8}$ -22.16° (± 1°),
(c 0.9590 in $CHCl_3$).

(Found: C, 80.66; H, 10.06. $C_{35}H_{52}O_3$ requires C, 80.71; H, 10.06%).

Reduction of cholesteryl mandelate (2) with Lithium Aluminium Hydride.

Reduction of crude cholesteryl mandelate (2) (1.4g.; 0.002 mole) in dry ether (75ml.) was carried out with lithium aluminium hydride (1g.; 0.026 mole) in dry ether (50 ml.). The experimental details were the same as those outlined previously. There was obtained 0.17g. (46%) of phenylethylene glycol m.p. 64-66°,

$[\alpha]_D^{24.2}$ +1.85° (±1°),

$[\alpha]_G^{24.2}$ +3.08° (±1°),

(l = 1 , c 1.7220 in $CHCl_3$),

and

$[\alpha]_D^{25.2}$ +1.79° (±1.8°),

$[\alpha]_G^{25.2}$ +3.76° (±1.8°),

(l = 1 , c 1.118 in ethanol).

Optical purity 2.8%.

(Found: C, 68.45; H, 7.03. $C_8H_{10}O_2$ requires C, 69.54, H, 7.29%).

3. Reduction of cholesteryl benzoylformate.

(c) Reducing Agent Aluminium Isopropoxide.

3g. of cholesteryl benzoylformate, 7.5g. of aluminium isopropoxide and 180 ml. of isopropyl alcohol were boiled under reflux for 3½ hours. After distilling off the acetone formed and the solvent, the residue was hydrolysed with ice-cold dilute sulphuric acid. Ether extraction of the product followed by the usual procedure gave 3g. (97%) of cholesteryl mandelate, m.p. 125-131°,

$[\alpha]_D^{21}$ -28.26° (±0.3°),

$[\alpha]_G^{21}$ -33.8° (±0.3°),

(c 2.9140 in $CHCl_3$).

(Found: C, 81.20; H, 11.15. $C_{35}H_{52}O_3$ requires C, 80.71; H, 10.06%).

Reduction of cholesteryl mandelate (3) with Lithium Aluminium Hydride.

Reduction of crude cholesteryl mandelate (3) (2g.) in dry ether (100 ml.) was carried out with lithium aluminium hydride (1.5g.) in dry ether (100 ml.). The products were isolated in the usual manner. There was obtained 0.17g. (32%) of phenylethylene glycol, m.p. 62-64°, $[\alpha]_D^{22}$ +1.09°(±1°), $[\alpha]_G^{22}$ +1.27° (± 1°), (l = 1 , c 1.738 in $CHCl_3$).
Optical purity 1.5%.

(Found: C, 68.8; H, 7.38. $C_8H_{10}O_2$ requires C, 69.54; H, 7.29%).

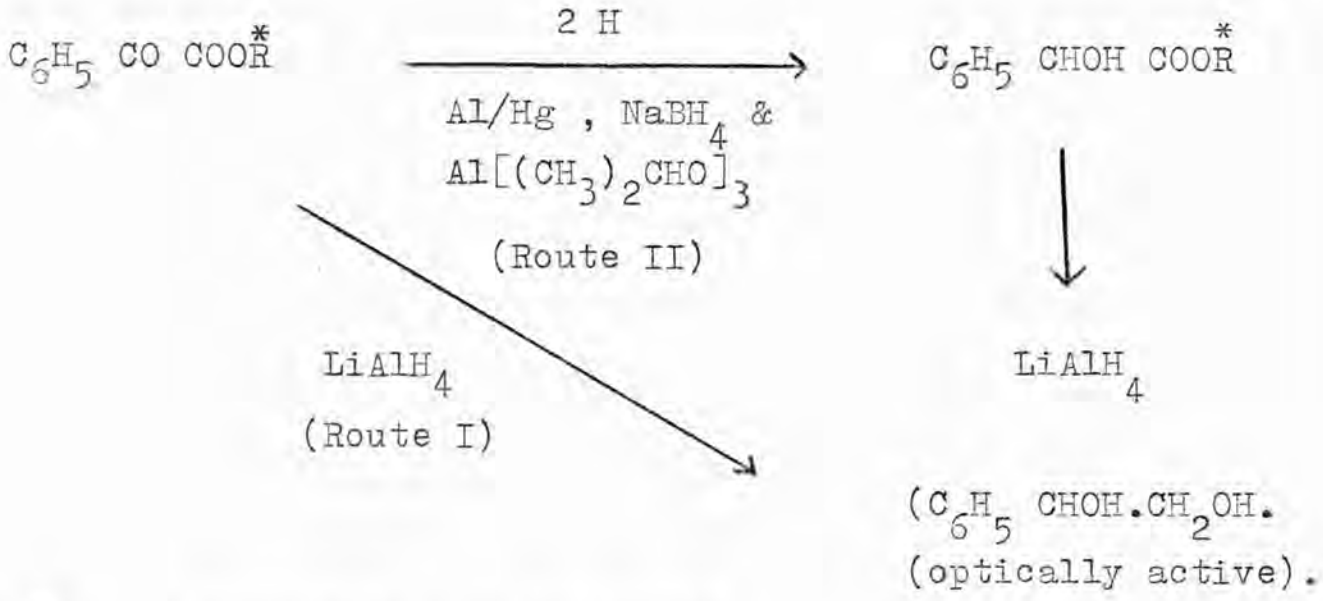
A note on the dimorphism of cholesteryl benzoylformate.

Cholesteryl benzoylformate was observed crystallising in two modifications from ethanol. The two forms were separated by picking with a spatula. One in narrow leaflets melted at 119.5-120.5° and the stable form crystallising in rectangular plates melted at 127-128°. The blue-green fluorescence shown after the crystals melted and solidified disappeared on remelting between 70-75°. Sometimes it reappeared when the substance underwent solidification.

A review of the partial asymmetric synthesis of phenylethylene glycol from (-)-menthyl benzoylformate and cholesteryl benzoylformate.

The partial asymmetric synthesis of phenylethylene glycol was carried out by reducing (-)-menthyl benzoylformate and cholesteryl benzoylformate. Both esters contain the -CO- and -COO- groups that can be reduced. Lithium aluminium hydride is a convenient reagent for the simultaneous reduction of -CO- and -COO- groups. Aluminium amalgam. Sodium borohydride and Aluminium isopropoxide show greater selectivity in action than Lithium aluminium hydride. They only reduce the -CO- group and the -COO- group is retained. Reduction with them results in the appearance of an additional a-symmetric centre. Two diastereoisomers are therefore possible (-)-menthyl (+)-mandelate and (-)-menthyl (-)-mandelate from (-)-menthyl benzoylformate and cholesteryl (+)-mandelate and cholesteryl (-)-mandelate from cholesteryl benzoylformate. On further reduction with Lithium aluminium hydride partially active phenylethylene glycol is obtained.

The two different routes are shown as follows:



($\overset{*}{R}$ = (-)-menthyl ; cholesteryl).

$LiAlH_4$ worked smoothly and readily gave pure phenylethylene glycol but with $NaBH_4$ reactions at room temperature were unsuccessful in the case of (-)-menthyl benzoylformate and satisfactory results were obtained only by using a vigorously stirred and an ice cold aqueous ethanol solution in the presence of boric acid. For the cholesteryl benzoylformate, reaction with $NaBH_4$ proceeded smoothly in aqueous dioxan in the presence of boric acid. Reduction with Al/Hg in both cases proceeded satisfactorily in moist ether. No satisfactory partially racemic mandelic esters of either (-)-menthol or cholesterol were obtained by the aluminium isopropoxide technique.

The partial asymmetric synthesis of phenylethylene

glycol

(i) from (-)-menthyl benzoylformate is shown in Table VI. It had a (-)-tive sign of rotation, and

(ii) from cholesteryl benzoylformate is shown in Table VII. It had a (+)-tive sign of rotation.

Cholesterol was thus found to exert an opposite activating influence to that of (-)-menthol in the partial asymmetric synthesis of phenylethylene glycol.

TABLE VI.

(-)-Menthyl benzoylformate, m.p. 72.5-73.5°,
$[\alpha]_D^{25.4}$ -51.1° (±0.5°),
$[\alpha]_G^{25.4}$ -61.3° (±0.5°),
(c 1.8270 in $CHCl_3$)

← $NaBH_4$ → (-)-Menthyl mandelate.
m.p. 82-84°,
$[\alpha]_D^{24.8}$ -91.45° (±0.8°),
$[\alpha]_G^{24.8}$ -110.1° (±0.8°),
(c 1.1700 in ethanol).

$LiAlH_4$ ↓

Phenylethylene glycol.
Yield (89%), m.p.62-66°,
$[\alpha]_D^{21}$ -3.4° (±0.1°),
$[\alpha]_G^{21}$ -3.9° (±0.1°),
(c 9.1500 in ethanol).&
$[\alpha]_D^{20}$ -5.2° (±0.1°),
$[\alpha]_G^{20}$ -5.9° (±0.1°),
(c 10.881 in $CHCl_3$).
Optical purity 8%.

Al/Hg ↓ (-)-Menthyl mandelate.
m.p. 84-86°,
$[\alpha]_D^{22.6}$ -76.3°(±0.5°),
$[\alpha]_G^{22.6}$ -90.8°(±0.5°),
(c 1.8480 in ethanol).

$LiAlH_4$ ↓

Phenylethylene glycol.
Yield (89%), m.p. 64-66°,
$[\alpha]_D^{23}$ -4.4° (±0.25°),
$[\alpha]_G^{23}$ -5.2° (±0.25°),
(l=1, c 8.340 in $CHCl_3$).
Optical purity 7%.

$Al[(CH_3)_2CHO]_3$ ↓ (-)-Menthyl mandelate
Waxy solid, smell of menthol perceptible.
$[\alpha]_D^{22.4}$ -39.7°(±0.4°),
$[\alpha]_G^{22.4}$ -47.2°(±0.4°),
(c 2.2470 in $CHCl_3$).

$LiAlH_4$ ↓

Phenylethylene glycol.
Yield (89%), m.p. 58-62°,
$[\alpha]_D^{22.8}$ -18.44° (±0.24°),
$[\alpha]_G^{22.8}$ -21.5° (±0.24°),
(l=1, C 8.1340 in $CHCl_3$).
Optical purity 29%.

TABLE VII.

Cholesteryl benzoylformate.

m.p. 119-120°, remelting point 128-129°,
$[\alpha]_D^{26.6}$ -15.01° (±0.8°),
$[\alpha]_G^{26.6}$ -16.7° (±0.8°),
(c 1.790 in $CHCl_3$).

$NaBH_4$

Cholesteryl mandelate.

m.p. 147-150°,
$[\alpha]_D^{25.4}$ -18.69° (±0.7°),
$[\alpha]_G^{25.4}$ -20.77° (±0.7°),
(c 1.3240 in $CHCl_3$).

$LiAlH_4$

Phenylethylene glycol.

Yield (77%).
m.p. 67-68° (cryd.)
$[\alpha]_D^{21.8}$ +1.1° (±0.16°),
$[\alpha]_G^{21.8}$ +1.3° (±0.15°),
(c 6.1240 in ethanol).
Optical purity 2.7%.

$LiAlH_4$

Phenylethylene glycol.

Yield (46%), m.p. 64-66°.
$[\alpha]_D^{24.2}$ +1.85° (±1°),
$[\alpha]_G^{24.2}$ +3.08° (±1°),
(l=1, c 1.7220 in $CHCl_3$).
Optical purity 2.8%.

Al/Hg

Cholesteryl mandelate.

m.p. 148-153°,
$[\alpha]_D^{22.6}$ -16.87 (±0.5°),
$[\alpha]_G^{22.6}$ -21.6° (±0.5°),
(c 1.8820 in $CHCl_3$),

$LiAlH_4$

Phenylethylene glycol.

Yield (55%), m.p. 58-64°.
$[\alpha]_D^{21.4}$ +2.66° (±0.8°),
$[\alpha]_G^{21.8}$ +3.35° (±0.8°),
(l=1, c 2.472 in $CHCl_3$).
Optical purity 4%.

$Al[(CH_3)_2CHO]_3$

Cholesteryl mandelate

m.p. 125-131°,
$[\alpha]_D^{21}$ -28.26° (±0.3°),
$[\alpha]_G^{21}$ -33.8° (±0.3°),
(c 2.9140 in $CHCl_3$).

$LiAlH_4$.

Phenylethylene glycol.

Yield (32%).
m.p. 62-64°,
$[\alpha]_D^{22}$ +1.09° (±1°),
$[\alpha]_G^{22}$ +1.27° (±1°),
(l=1, c 1.738 in $CHCl_3$).

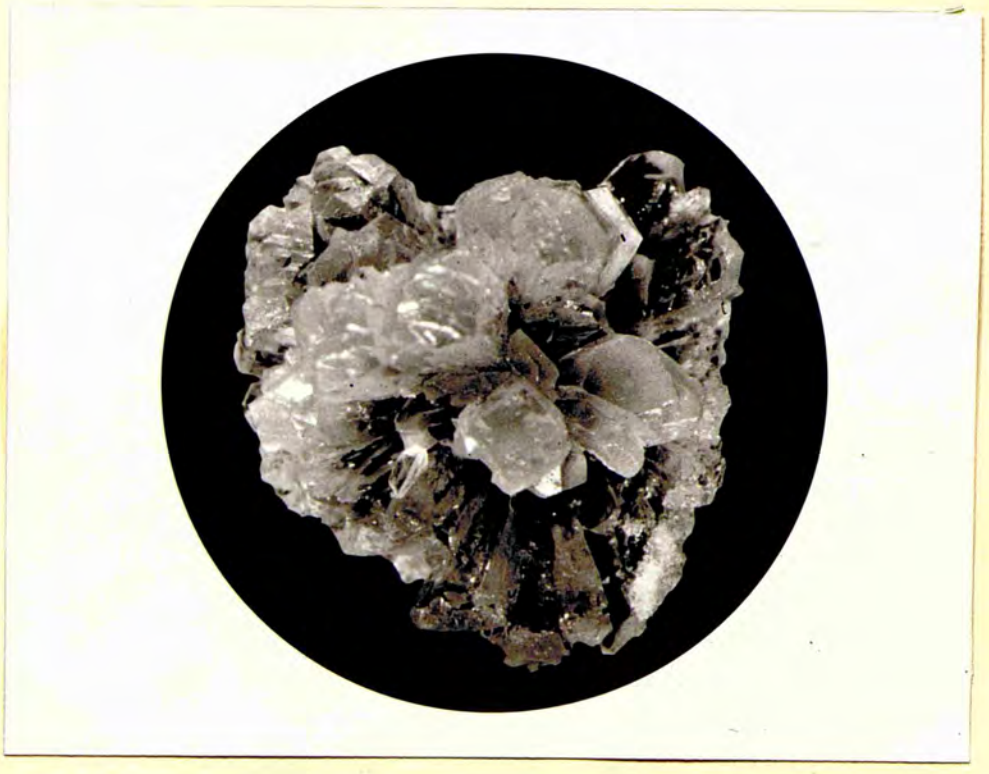
Optical purity 1.5%.

PHOTOGRAPHS.

STRYCHNINE (+) HYDRATROPATE.

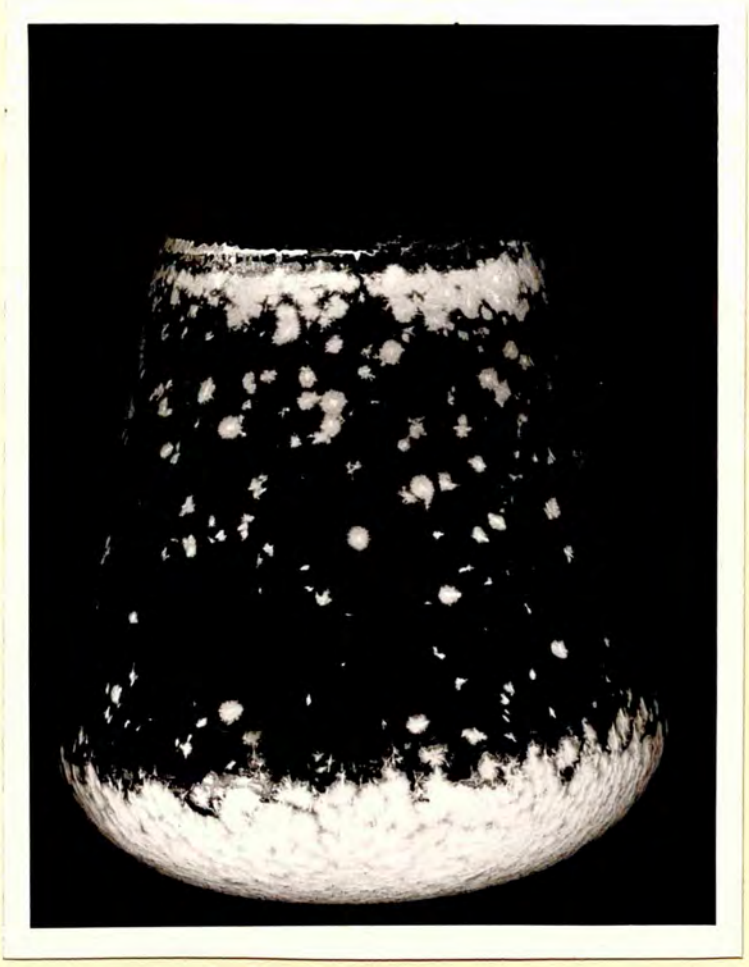
STRYCHNINE (+) HYDRATROPATE.

(+) HYDRATROPIC ACID.



(+) HYDRATROPIC ACID.

(+) HYDRATROPIC ACID.

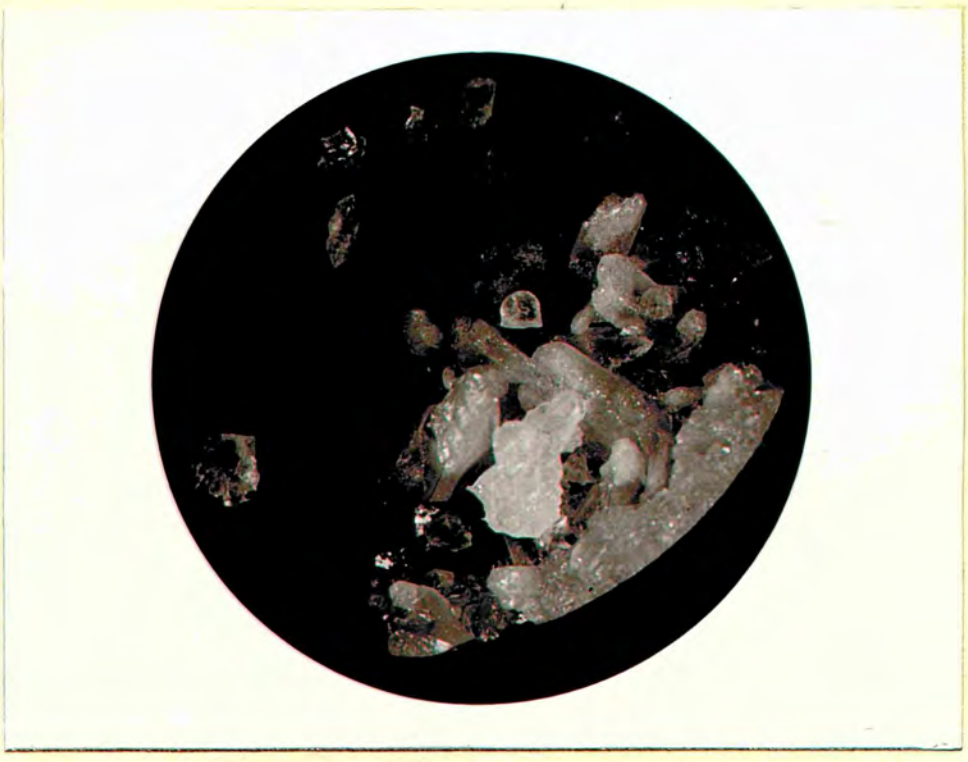


QUININE (±) HYDRATROPATE.
(PARTIAL RACEMATE)

QUININE (-) HYDRATROPATE.

QUININE (-) HYDRATROPATE.

(-) HYDRATROPIC ACID.



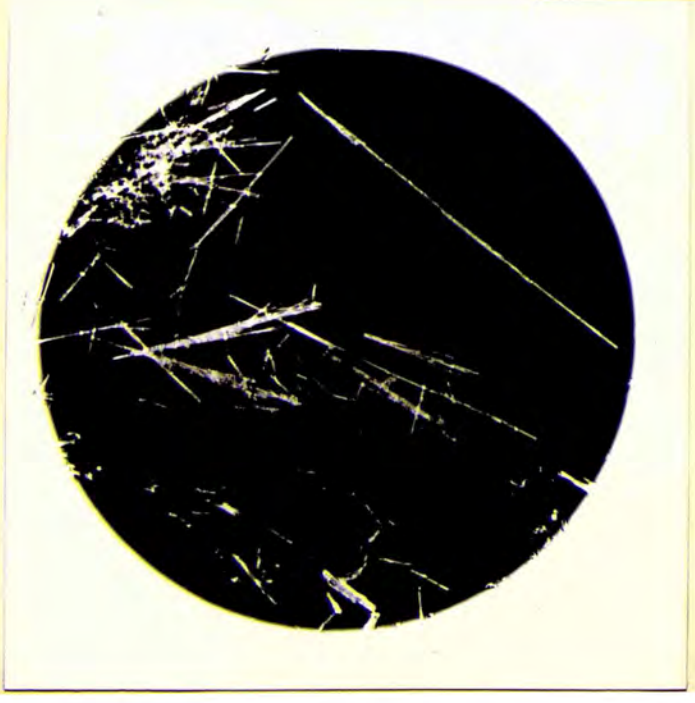
(-) HYDRATROPIC ACID.

CHOLESTERYL

(±) HYDRATROPATE.
(PARTIAL RACEMATE.)

CHOLESTERYL

(+) HYDRATROPATE.



CHOLESTERYL

(-) HYDRATROPATE.