32. *The Hydratropic Acids and the Related 2-Phenylpropanols.*

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Cholesteryl (+)- and (−)-hydratropate have been obtained from the optically pure hydratropic acids, which have been reduced to the pure 2-phenylpropanols.

As a method of obtaining optically pure (+)- and (−)-2-phenylpropan-1-ol, we selected the reductive scission of cholesteryl (−)- and (+)-hydratropate, thinking that the mixture of these esters formed by the condensation of cholesterol with (±)-hydratropoyl chloride should be resolvable by crystallisation. In fact, although highly crystalline material was obtained from "cholesteryl (±)-hydratropate," the only individual compound that could be isolated was, curiously, the more soluble cholesteryl (−)-hydratropate, and this only in very small yield. In spite of extensive crystallisations from different solvents, the bulk of the material obtained contained (+)- and (−)-esters in the proportion of about 53 : 47.

Pure cholesteryl (+)- and (−)-hydratropate have been prepared from the corresponding active acids, which were obtained by resolving the (±)-acid; strychnine leads to the (+)-acid (cf. Raper [1]), and quinine to the (−)-acid (cf. Levene, Mikeska, and Passoth [2]). The (+)-acid had m. p. 31·5—32°, $[\alpha]_D^{25}$ +76·3° ± 0·6°, $[\alpha]_{5461}^{25}$ +91·7° ± 0·6° (*c* 1·613 in $CHCl_3$); the (−)-acid had m. p. 31—32°, $[\alpha]_D^{25}$ −76·1° ± 0·6°, $[\alpha]_{5461}^{25}$ −91·5° ± 0·6° (*c* 1·599 in $CHCl_3$). The best previous figures are those of Fredga [3] who recorded for the (−)-acid, m. p. 30·2—30·9°, and for the (−)-acid, m. p. 30·3—31°, $[\alpha]_D^{25}$ −75·3° (*c* 1·587 in $CHCl_3$).

Conversion of the active acids into the acid chlorides, following by condensation with cholesterol in presence of pyridine, led to cholesteryl (+)-hydratropate, $[\alpha]_D^{20}$ +10·6° ± 0·4°, $[\alpha]_{5461}^{20}$ +13·3° ± 0·4° (*c* 2·3990 in $CHCl_3$), and cholesteryl (−)-hydratropate, $[\alpha]_D^{24}$ −58·2° ± 0·6°, $[\alpha]_{5461}^{24}$ −69·9° ± 0·6° (*c* 1·6170 in $CHCl_3$).

Racemic hydratropic acid has hitherto been prepared (*a*) from benzyl cyanide by methylation and subsequent hydrolysis (Campbell and Kenyon [4]) (Mislow and Brenner [5] showed that acid so prepared contains α-methylhydratropic acid), (*b*) from hydratropaldehyde by oxidation (Arcus and Kenyon [6]), and by other, less satisfactory, methods. The simplest synthesis appeared to be by the action of carbon dioxide on 1-phenylethylmagnesium halides, but Ott [7] obtained *meso*- and racemic 2,3-diphenylbutane as the sole products from magnesium, 1-phenylethyl chloride, and carbon dioxide. We find that, when 1-phenylethyl chloride is allowed to react with magnesium with occasional shaking, the entire product is *meso*-2,3-diphenylbutane, but that with a sufficiently dilute mixture and with good stirring a solution is obtained which after reaction with carbon dioxide gives hydratropic acid and the *meso*-form of the hydrocarbon in about 58% and 22% yield respectively. This is therefore the simplest method of making hydratropic acid.

Reduction of cholesteryl (+)-hydratropate or of (+)-hydratropic acid with lithium aluminium hydride in ether gave (−)-2-phenylpropan-1-ol, $[\alpha]_{5461}^{24}$ −21·2° ± 0·02° (*l* = 1; *d* 1·00). Similarly, (+)-2-phenylpropan-1-ol was obtained with $[\alpha]_{5461}^{23}$ +21·02° ± 0·02°.

[1] Raper, *J.*, 1923, **123**, 2557.
[2] Levene, Mikeska, and Passoth, *J. Biol. Chem.*, 1930, **88**, 27.
[3] Fredga, *Arkiv Kemi*, 1954, **7**, 241.
[4] Campbell and Kenyon, *J.*, 1946, 25.
[5] Mislow and Brenner, *J. Amer. Chem. Soc.*, 1953, **75**, 2318.
[6] Arcus and Kenyon, *J.*, 1939, 916.
[7] Ott, *Ber.*, 1928, **61**, 2124.

Experimental

(±)-*Hydratropic Acid.*—Thoroughly dried ether (175 c.c.) and dried magnesium turnings (31 g.) were stirred together mechanically in a flask fitted with a protected reflux condenser. A mixture of 1-phenylethyl chloride (118·6 g.) and dry ether (400 c.c.) was added during 45 min. To complete the last stage of the reaction, the mixture was boiled for a further 30 min. The cooled solution was then decanted on to 350 g. of solid carbon dioxide in a 4-l. flask. The residual magnesium was twice extracted with dry ether, and the extract added to the carbon dioxide. When the latter had mostly disappeared, the mixture was acidified with concentrated hydrochloric acid, ice being added as required. The ethereal layer, together with three ethereal extracts of the aqueous layer, was extracted with 25% sodium hydroxide solution. The alkaline extract was evaporated to one-tenth of the bulk and then acidified with hydrochloric acid. The hydratropic acid was separated, dried (Na_2SO_4), and distilled. The yield was 73·5 g. (58%) and the b. p. 155°/21 mm. The ethereal layer gave *meso*-2,3-diphenylbutane (20 g.), m. p. 124—125° after two crystallisations from methanol (Paterno and Chieffi [8] gave m. p. 124—125°). Redistillation of the hydratropic acid gave 68·5 g., of b. p. 159°/25 mm., n_D^{25} 1·5204.

In our hands the synthesis of hydratropic acid from benzyl cyanide by the method of Campbell and Kenyon [4] gave a yield of about 45% but was less convenient than the above.

Optical Resolution of (±)-*Hydratropic Acid.*—Raper's method,[1] using strychnine (24 g.) in aqueous ethanol, gave strychnine (+)-hydratropate (21 g.) with $[\alpha]_D^{21}$ −30·8° ± 0·7°, $[\alpha]_{5461}^{22}$ −38·3° ± 0·7° (*c* 1·4090 in $CHCl_3$). From this, (+)-hydratropic acid was obtained with m. p. 31·5—32°, $[\alpha]_D^{25}$ +76·3° ± 0·6°, $[\alpha]_{5461}^{25}$ +91·7° ± 0·6° (*c* 1·613 in $CHCl_3$).

The combined mother-liquors from the strychnine salt were concentrated and acidified. The hydratropic acid obtained, after distillation, had $[\alpha]_{5461}^{20}$ −43·3° ± 3·0° (*c* 3·190 in $CHCl_3$). Of it, 31·6 g. were treated with 67 g. of anhydrous quinine in hot acetone solution. On cooling, quinine (−)-hydratropate separated and this, after systematic fractionation and crystallisation from acetone, gave a salt (33·4 g.), m. p. 176—177°, $[\alpha]_D^{22}$ −109·0° ± 0·6°, $[\alpha]_{5461}^{22}$ −132·0° ± 0·6° (*c* 1·7800 in $CHCl_3$). From this salt (−)-hydratropic acid was obtained, with m. p. 31—32°, $[\alpha]_D^{25}$ −76·1° ± 0·6°, $[\alpha]_{5461}^{25}$ −91·5° ± 0·6° (*c* 1·5990 in $CHCl_3$). After our work had been completed [see S. P. Bakshi (Chibber), Ph.D. Thesis, London, June, 1959], Roger and Neilson [9] recorded an incomplete resolution of (±)-hydratropic acid. Their (+)-acid failed to crystallise.

The hydratropoyl chlorides, obtained from the acid and thionyl chloride, had b. p. 81—83°/10 mm. The (+)-chloride, from the (+)-acid, had $[\alpha]_D^{22}$ +101·5° ± 0·4°, $[\alpha]_{5461}^{22}$ +124·2° ± 0·4° (*c* 2·4390 in C_6H_6), and $[\alpha]_D^{23}$ +87·8° ± 0·3°, $[\alpha]_{5461}^{23}$ +108·6° ± 0·3° (*c* 2·8460 in ether) {Booner, Zderic, and Castaetto [10] found $[\alpha]_D^{20}$ +50·5° (*c* 2·5, in ether)} (Found: Cl, 20·9. Calc. for C_9H_9ClO: Cl, 21·0%). The (−)-chloride from the (−)-acid had $[\alpha]_D^{21}$ −103·1° ± 0·4°, $[\alpha]_{5461}^{21}$ −126·5° ± 0·4° (*c* 2·3510 in C_6H_6) {Levene, Mikeska, and Passoth [2] recorded $[\alpha]_D^{24}$ −68·8° (*c* 21·496 in ether)} (Found: Cl, 21·6%).

Cholesteryl Hydratropates.—(*a*) A solution of cholesterol (55 g.), m. p. 147—148°, $[\alpha]_D^{22}$ −39·3° ± 0·4° (*c* 2·4490 in $CHCl_3$), in dry pyridine (160 c.c.) was treated with (±)-hydratropoyl chloride (28 g.) with frequent shaking. The suspension formed was kept at the room temperature for 2 hr., then heated at 100° for ½ hr. The cooled mixture was then poured into an excess of cold 5% hydrochloric acid with stirring. The precipitate was filtered off and washed first with 5% hydrochloric acid and later with cold water. It was taken up in chloroform and extracted thrice with 5% hydrochloric acid, twice with 5% sodium hydrogen carbonate solution, and thrice with water. The chloroform was removed and the residue crystallised from the minimum amount of alcohol (yield, 95%). On repeated crystallisation of this product from acetone, 86% was obtained as a mixture of cholesteryl hydratropates, which was almost unaffected by recrystallisation. One specimen had m. p. 116—117°, $[\alpha]_D^{23}$ −22·1° ± 1°, $[\alpha]_{5461}^{23}$ −25·8° ± 1° (*c* 0·9260 in $CHCl_3$) (Found: C, 83·9; H, 10·1. Calc. for $C_{36}H_{54}O_2$: C, 83·3; H, 10·5%). From the mother-liquors, by crystallisation from methanol–benzene, cholesteryl (−)-hydratropate was obtained, with m. p. 138—139°, $[\alpha]_D^{24}$ −56·5° ± 0·6°, $[\alpha]_{5461}^{24}$ −69·1° ± 0·6° (*c* 0·5390, in $CHCl_3$).

[8] Paterno and Chieffi, *Gazzetta*, 1909, **39**, II, 426.
[9] Roger and Neilson, *J.*, 1960, 627.
[10] Booner, Zderic, and Castaetto, *J. Amer. Chem. Soc.*, 1952, **74**, 5086.

Crystallisation of the cholesteryl (±)-hydratropate from light petroleum (b. p. 60—80°), or from mixtures of methanol with benzene or chloroform, gave two products, one sparingly soluble, m. p. 116—117°, $[\alpha]_D$ −20·5° to −22·0° in $CHCl_3$ (Found, for example: C, 83·3; H, 9·5%), and another, readily soluble in most solvents, m. p. 137—138°, $[\alpha]_D$ −56° to −57° (Found, for example: C, 82·9; H, 9·9%).

(*b*) Cholesterol was condensed with (+)-hydratropoyl chloride in pyridine, and the product worked up as in (*a*). The *cholesteryl* (+)-*hydratropate* crystallised from acetone or chloroform–methanol in pearly plates, m. p. 105—106°, $[\alpha]_D^{20}$ +10·6° ± 0·4°, $[\alpha]_{5461}^{20}$ +13·3° ± 0·4° (*c* 3990 in $CHCl_3$) (Found: C, 83·9; H, 10·1%).

(*c*) Cholesterol and (−)-hydratropoyl chloride in pyridine similarly led to cholesteryl (−)-hydratropate, which crystallised from acetone in long pearly needles, m. p. 139·5°, $[\alpha]_D^{24}$ −58·2° ± 0·6°, $[\alpha]_{5461}^{24}$ −69·9° ± 0·6° (*c* 1·6170 in $CHCl_3$) (Found: C, 83·2; H, 9·8%).

Reduction of (+)- *and* (−)-*Hydratropic Acid.*—A solution of the acid in dry ether was added gradually to lithium aluminium hydride (1·5 mol.) in dry ether, with shaking. The mixture was allowed to boil under reflux for ½ hr. and then worked up normally. From pure (+)-hydratropic acid (−)-2-phenylpropan-1-ol was obtained, with b. p. 96°/10 mm., $d^{21.1}$ 1·000, $[\alpha]_D^{24}$ −17·4° ± 0·02°, $[\alpha]_{5461}^{24}$ −21·2° ± 0·2° (l = 1). Cohen, Marshall, and Woodman [11] recorded $[\alpha]_D^{20}$ −15·16°.

From pure (−)-hydratropic acid (+)-2-phenylpropan-1-ol was obtained with b. p. 100—101°/11 mm., $d^{21.6}$ 1·000 n_D^{25} 1·5238, $[\alpha]_D^{23}$ +17·23° ± 0·02°, $[\alpha]_{5461}^{23}$ +21·02° ± 0·02° (l = 1). Cohen *et al.*[11] recorded $[\alpha]_D^{20}$ +15·25°. Eliel and Freeman [12] gave b. p. 105—106°/11 mm., n_D^{25} 1·5230, $[\alpha]_D^{25}$ +3·18° ± 0·01°, for their product, which they calculated was 20·6% pure. Roger and Neilson,[9] by reducing (−)-hydratropic acid, obtained (+)-2-phenylpropan-1-ol with $[\alpha]_{5461}^{25}$ +20·54° (homogeneous).

Reductive Scission of Cholesteryl (+)-*Hydratropate.*—A solution of cholesteryl (+)-hydratropate in 15 parts of ether was added gradually to a suspension of 2 mols. of lithium aluminium hydride in 40 parts of ether, stirred under reflux. After a further ½ hr., water and then dilute sulphuric acid were added. The aqueous layer was thrice extracted with ether, and the combined ethereal extracts were washed with dilute potassium carbonate solution and then with water. After drying (Na_2SO_4), the ethereal solution was evaporated and the residue was distilled. The (−)-2-phenylpropan-1-ol (80% yield) had $[\alpha]_D^{21}$ −17·2° ± 0·02°, $[\alpha]_{5461}^{21}$ −21·1° ± 0·02° (l = 1). Cholesterol was isolated in almost theoretical yield.

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[*Received, July 7th,* 1960.]

[11] Cohen, Marshall, and Woodman, *J.*, 1915, **107**, 887.
[12] Eliel and Freeman, *J. Amer. Chem. Soc.*, 1952, **74**, 923.