

**129. Studies in Stereochemical Structure. Part XIII.\* Derivatives of the Hydratropic Acids and Hydratropic Alcohols.**

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(-)-Hydratropic acid has been obtained from the ( $\pm$ )-acid by use of (-)-ephedrine and reduced to (+)-2-phenylpropan-1-ol. The alcohol was converted into (+)-2-phenylpropyl (-)-mandelimidate which gave a (-)-mandelamidinium chloride of approximately 63% optical purity.

(+)-HYDRATROPIC ACID was isolated first by Raper<sup>1</sup> by using strychnine; Arcus and Kenyon<sup>2</sup> modified Raper's method and thereby also obtained a small portion of the (-)-acid. The use of quinine by Levene and Marker<sup>3</sup> and by Fredga<sup>4</sup> gave the (-)-form of the acid; the latter also obtained the (+)-form with strychnine. Roger<sup>5</sup> obtained both forms of mandelic acid in good yields with ephedrine and this led us to apply the same method to hydratropic acid. This alkaloid, however, gave only the pure (-)-form, the crude (+)-acid forming an uncrystallisable oil with only half the optical value of the pure (-)-form. The following Table shows the specific rotations obtained by various workers for the optically active hydratropic acids. Clearly, with the exception of the values quoted by Levene and Marker, there is good agreement between these figures.

Alkaloid used	$[\alpha]_{5893}$	$[\alpha]_{5461}$	Solvent	Temp.	Authors
Strychnine .....	+76.2°	—	CHCl <sub>3</sub>	20°	Raper <sup>1</sup>
Quinine .....	-74.1	—	Homog.	25	Levene and Marker <sup>3</sup>
Strychnine .....	+94.2	—	Homog.	16	Arcus and Kenyon <sup>2</sup>
" .....	—	+111.5°	Homog.	19.4	
" .....	+74.8	—	CHCl <sub>3</sub>	—	
" .....	—	+110.3	C <sub>6</sub> H <sub>6</sub>	—	
Quinine .....	-79.1	—	EtOH	25	Fredga <sup>4</sup>
" .....	-75.3	—	CHCl <sub>3</sub>	25	
Strychnine .....	+79.0	—	EtOH	25	
Ephedrine .....	—	-109.6	Homog.	19	This paper
" .....	—	-113.1	C <sub>6</sub> H <sub>6</sub>	19	

The optically active forms of 2-phenylpropan-1-ol were isolated first by Cohen, Marshall, and Woodman<sup>6</sup> by resolution of the ( $\pm$ )-alcohol; they record  $[\alpha]_{5893} +15.3^\circ$  (homogeneous). The value,  $[\alpha]_{5893} +3.3^\circ$  (homogeneous), for the product obtained by reduction of (+)-hydratropic acid with sodium and alcohol by Levene, Marker, and Rothen<sup>7</sup> may be due to the starting material's being partly racemised. Eliel and Freeman<sup>8</sup> obtained a similar value after reduction of the (-)-acid with lithium aluminium hydride but recognised that their starting material was four-fifths ( $\pm$ )-acid. From pure

\* Part XII, *J.*, 1959, 688.

<sup>1</sup> Raper, *J.*, 1923, 2557.

<sup>2</sup> Arcus and Kenyon, *J.*, 1939, 916.

<sup>3</sup> Levene and Marker, *J. Biol. Chem.*, 1933, **100**, 685.

<sup>4</sup> Fredga, *Arkiv Kemi*, 1954, **7**, 241.

<sup>5</sup> Roger, *J.*, 1935, 1544.

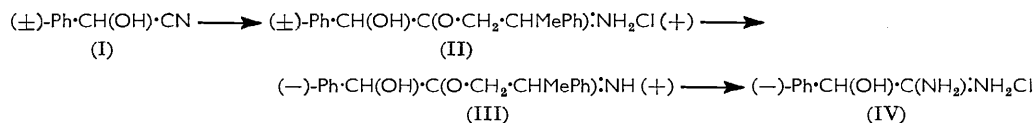
<sup>6</sup> Cohen, Marshall, and Woodman, *J.*, 1915, **107**, 887.

<sup>7</sup> Levene, Marker, and Rothen, *J. Biol. Chem.*, 1933, **100**, 589.

<sup>8</sup> Eliel and Freeman, *J. Amer. Chem. Soc.*, 1952, **74**, 923.

(-)-hydratropic acid and lithium aluminium hydride we have obtained an alcohol,  $[\alpha]_{5893}^{25} +16.7^\circ$ ,  $[\alpha]_{5461}^{25} +20.54^\circ$  (homogeneous), a value above that reported by Cohen, Marshall, and Woodman.<sup>6</sup> Eliel and Freeman,<sup>8</sup> however, have calculated that Cohen, Marshall, and Woodman's figure is approximately 15% too low. There is little reason to think that any racemisation has occurred during the reduction as "lithium aluminium hydride does not normally affect the configuration of an asymmetric centre carrying a reducible group."<sup>9</sup> Baker and Jenkins<sup>10</sup> make a similar claim in the reduction of (+)-2,4-diphenylbutanoic acid to (+)-2,4-diphenylbutan-1-ol, and this is of interest as (+)-2,4-diphenylbutanoic acid and (-)-hydratropic acid both have easily racemisable systems according to McKenzie's racemisation rule<sup>11-13</sup>. Noyce and Denney<sup>14</sup> oxidised (-)-2-methylbutan-1-ol to (+)-2-methylbutanoic acid which they then reduced with lithium aluminium hydride to give the starting alcohol with undiminished rotation.

The treatment of ( $\pm$ )-mandelonitrile<sup>15</sup> (I) with ( $\pm$ )- and (+)-2-phenylpropan-1-ol in anhydrous ether-hydrogen chloride gave the corresponding 2-phenylpropyl ( $\pm$ )-mandelimidate hydrochlorides (II). These salts were decomposed to the imidates by alkali. The crude (+)-2-phenylpropyl ( $\pm$ )-mandelimidate was roughly separated into diastereoisomers on crystallisation from petroleum. One diastereoisomer (III) had  $[\alpha]_{5461}^{18} -84.3^\circ$ , whilst another crop apparently exhibited no rotatory power at that wavelength.



The first of these was converted into (-)-mandelamidinium chloride (IV) by addition of the calculated amount of alcoholic ammonia; a large excess of ammonia must be avoided since this can cause racemisation.<sup>16</sup> The (-)-amidinium chloride had  $[\alpha]_{5461}^{18} -56^\circ$  as compared with Reid's<sup>16</sup> value of  $[\alpha]_{5461}^{16} -88.9^\circ$ . Optical activity has been maintained throughout this series of reactions, therefore, to the extent of about 63%, but the small amount of material available precluded further investigation.

## EXPERIMENTAL

All specific rotations are measured in a 2-dm. tube unless otherwise stated.

( $\pm$ )-*Hydratropic Acid*.—Commercial ( $\pm$ )-hydratropaldehyde (53.6 g.) in rectified spirits (160 ml.) was mixed with hydroxylamine hydrochloride (33.6 g.) in warm water (40 ml.). Sodium hydroxide solution (24 g. in 32 ml. of water) was then added slowly. After 3 hr., crushed ice (200 g.) and a small quantity of solid carbon dioxide were added, and the mixture was then kept overnight. The dried ether extract ( $\text{Na}_2\text{SO}_4$ ) yielded the aldoxime (45 g.), b. p.  $133^\circ/11$  mm.; this was dehydrated for  $\frac{1}{2}$  hr. with refluxing freshly distilled acetic anhydride (80 g.), and the mixture then treated with concentrated sodium hydrogen carbonate solution. The ether extract gave ( $\pm$ )-hydratroponitrile (30 g.), b. p.  $106^\circ/12$  mm., and *acetophenone oxime acetate*, m. p.  $56^\circ$  (Found: N, 8.0.  $\text{C}_{10}\text{H}_{11}\text{O}_2\text{N}$  requires N, 7.9%). The nitrile was hydrolysed by boiling concentrated sodium hydroxide for 18 hr. The acidified solution on extraction with ether yielded ( $\pm$ )-hydratropic acid (28 g.), b. p.  $148^\circ/12$  mm.

( $\pm$ )-2-*Phenylpropan-1-ol*.—( $\pm$ )-Hydratropaldehyde was reduced with aluminium isopropoxide to give ( $\pm$ )-2-phenylpropan-1-ol, b. p.  $116\text{--}117^\circ/18$  mm., in 73% yield.

<sup>9</sup> Battersby, *Ann. Reports*, 1956, **53**, 160.

<sup>10</sup> Baker and Jenkins, *J. Amer. Chem. Soc.*, 1949, **71**, 3969.

<sup>11</sup> McKenzie and Wren, *J.*, 1919, **115**, 602.

<sup>12</sup> McKenzie and Smith, *J.*, 1922, **121**, 1348.

<sup>13</sup> *Idem*, *Ber.*, 1925, **58**, 894.

<sup>14</sup> Noyce and Denney, *J. Amer. Chem. Soc.*, 1950, **72**, 5743.

<sup>15</sup> *Org. Synth.*, Coll. Vol. I, p. 329.

<sup>16</sup> Reid, Ph.D. Thesis, St. Andrews, 1949.

*Resolution of (±)-Hydratropic Acid with (-)-Ephedrine.*—(-)-Ephedrine (40 g.) and (±)-hydratropic acid (32 g.) were dissolved in warm aqueous alcohol (160 ml.; water : alcohol = 3 : 1 v/v). The salt which crystallised overnight at 0° was crystallised five times from 75% aqueous alcohol (120 ml.). The final crop was decomposed with 5*N*-sulphuric acid to give (-)-hydratropic acid (6 g.), b. p. 147°/11 mm., m. p. 29°,  $\alpha_{5461}^{19}$  - 60·30° (homogeneous, *l* 0·5),  $[\alpha]_{5461}^{19}$  - 113·1° (*c* 3·58 in benzene).

Decomposition of the mother liquors yielded a (+)-hydratropic acid,  $\alpha_{5401}^{19}$  + 28·0° (homogeneous, *l* 0·5), which did not crystallise.

*Reduction of (-)-Hydratropic Acid.*—(-)-Hydratropic acid (15 g.),  $[\alpha]_{5461}$  - 113·1° (in benzene), in ether was added to an excess of lithium aluminium hydride (6 g.) in ether; stirring was continued for 4 hr. and the mixture then refluxed for ½ hr. The complex was worked up in the usual way, and the ether extract shaken with sodium hydrogen carbonate solution. (+)-2-Phenylpropan-1-ol (11 g.) had b. p. 115°/17 mm.,  $\alpha_{5893}^{25}$  + 8·4° (homogeneous, *l* 0·5),  $[\alpha]_{5893}^{25}$  + 16·7°,  $[\alpha]_{5461}^{25}$  + 20·54° (homogeneous, *l* 0·5, *d* 1·0049).

(±)-2-Phenylpropyl (±)-Mandelimide Hydrochloride.—(±)-2-Phenylpropan-1-ol (6·8 g.) and (±)-mandelonitrile (6·7 g.) were treated in anhydrous ether with dry hydrogen chloride (0·05 mole) at 0°. After 24 hr. in an ice-chest, the mixture had deposited crystals of (±)-2-phenylpropyl (±)-mandelimidate hydrochloride (3·5 g.), m. p. 128—129° (decomp.).

(+)-2-Phenylpropyl (±)-Mandelimidate Hydrochloride.—This was prepared, as for the racemic compound, from the (+)-alcohol,  $\alpha_{5893}$  + 8·4° (homogeneous, *l* 0·5); but the anhydrous ether was added 1 hr. after absorption of hydrogen chloride. After 24 hr. at 0°, the crude imidate was filtered off, taken up in cold, dry ethanol, and reprecipitated with anhydrous ether. The last traces of diluent were removed by a porous plate. (+)-2-Phenylpropyl (±)-mandelimidate hydrochloride had m. p. 115—116° (without evolution of gas),  $[\alpha]_{5461}^{18}$  - 15·1° (*c* 1·01 in ethanol) (Found: Cl, 11·9. C<sub>17</sub>H<sub>20</sub>O<sub>2</sub>NCl requires Cl, 11·6%).

(+)-2-Phenylpropyl (-)-Mandelimidate.—(+)-2-Phenylpropyl (±)-mandelimidate hydrochloride (8 g.),  $[\alpha]_{5461}^{20}$  - 14·8° (in ethanol), prepared from (+)-alcohol,  $\alpha_{8893}$  + 8·08° (homogeneous, *l* 0·5), was shaken with sodium hydroxide solution (40 ml.; 4*N*) and immediately extracted with ether, which, when dried, was removed under reduced pressure at 20°. The crude imidate base (5 g.) was recrystallised from petroleum (b. p. 60—80°) containing a trace of alcohol.

There resulted two crops (*A* and *B*) of crystals and an unidentified red oil. Crop *A*, consisting of (+)-2-phenylpropyl (±)-mandelimidate, softened at 82°, melted at 88—89°, and had  $[\alpha]_{5461}^{18}$  - 13·9° (*c* 0·98 in ether). One further crystallisation of crop *A* from the same solvent yielded a (+)-2-phenylpropyl (-)-mandelimidate (0·15 g.), m. p. 108—109°,  $[\alpha]_{5461}^{18}$  - 84·3° (*c* 0·55 in ether) (crop *C*). Crop *B* had  $[\alpha]_{5461}^{18}$  0·0° (*c* 0·57 in ether), and m. p. similar to that of crop *A*.

The hydrochlorides of crops *B* and *C* were re-formed. Crop *B* yielded a hydrochloride,  $[\alpha]_{5461}^{18}$  - 13·7° (*c* 0·874 in ethanol), having a small but definite difference in rotatory power from (+)-2-phenylpropyl (±)-mandelimidate hydrochloride. Crop *C* gave (+)-2-phenylpropyl (-)-mandelimidate hydrochloride (0·15 g.), m. p. 121—122°,  $[\alpha]_{5461}^{19}$  - 92·3° (*c* 0·47 in ethanol).

(-)-Mandelamidinium Chloride.—(+)-2-Phenylpropyl (-)-mandelimidate hydrochloride ( $[\alpha]_{5461}$  - 92·3°; 0·1 g. in 20 ml. of ethanol) was treated with dry alcoholic ammonia (0·4 ml.; 1·5*N*) and shaken for 4 hr. The solvent was removed under reduced pressure, and the amidinium chloride taken up in alcohol and reprecipitated with ether. (-)-Mandelamidinium chloride,  $[\alpha]_{5461}^{18}$  - 56·0° (*c* 0·155 in water), softened at 165°, resolidified and melted again at 217°. A mixture with pure (-)-mandelamidinium chloride had the same m. p. Roger and Reid,<sup>16</sup> who prepared (-)-mandelamidinium chloride (Found: N, 14·9. C<sub>8</sub>H<sub>11</sub>ON<sub>2</sub>Cl requires N, 15·0%) from amygdalin, recorded  $[\alpha]_{5461}^{16}$  - 88·9° (in water), m. p. 166—167°, resolidifying at about 185° and finally remelting at 214°—the m. p. of (±)-mandelamidinium chloride. Our amidinium chloride had an optical purity of about 63%.