622. Studies in Stereochemical Structure. Part XIV.[1] The Resolution of α-Hydroxy-amidinium Chlorides by the Use of Mandelic Acids.

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(±)-α-Hydroxy-α- and -β-phenylbutyramidinium chlorides have been synthesised and have been resolved by use of mandelic acids. The specific rotation of (+)-α-hydroxy-α-phenylbutyric acid prepared from the (+)-α-hydroxy-α-phenylbutyramidinium chloride showed the latter to be almost optically pure. In the case of the β-phenylamidinium chloride, although resolution was established, the extent could not be determined owing to lack of reference data.

The readily accessible, optically active mandelic acids [2] are useful agents for the resolution of various types of (±)-bases. They have the advantages of sharp melting points (133°) and high specific rotations, $[\alpha]_{5461}$ ±190° (in acetone). In addition, they are soluble in the

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[1] Part XIII, *J.*, 1960, 627.

[2] Roger, *J.*, 1935, 1544.

more usual organic solvents and their sodium or ammonium salts[3] are readily available for the resolution of (±)-base hydrochlorides or sulphates. Typical examples of their use are the preparation of (—)-ephedrine[4,5] and related compounds of the ephedrine series,[6] amines,[7,8,9] amino-glycols,[10,11] $R\cdot CH(OH)\cdot CH(NH_2)\cdot CH_2\cdot OH$ ($R = p\text{-}NO_2\cdot C_6H_4$ and $p\text{-}Me\cdot SO_2\cdot C_6H_4$), and s-butylmercury compounds.[12] We have also used them to prepare (—)-mandelamidinium chloride[1,13] and the (+)- and (—)-atrolactamidinium chloride.[14]

We have now prepared (±)-α-hydroxy-α- and -β-phenylbutyramidinium chloride and resolved them in a similar way. Pure propiophenone cyanohydrin, obtained by distillation *in vacuo* in the presence of iodine[15] as stabiliser, was converted by the Pinner synthesis[16,17] into ethyl (±)-α-hydroxy-α-phenylbutyrimidate hydrochloride (I) which on treatment with alcoholic ammonia yielded (±)-α-hydroxy-α-phenylbutyramidinium chloride (II). This furnished a (±)-mandelate on treatment with aqueous sodium (±)-mandelate.

The (±)-amidinium chloride and sodium (—)-mandelate in water deposited (+)-α-hydroxy-α-phenyl-butyramidinium (—)-mandelate which was optically pure after three crystallisations and with hydrogen chloride gave (+)-α-hydroxy-α-phenylbutyramidinium chloride, $[\alpha]_{5461}$ +48·9° (in water). The mother-liquors from the (+)-base (—)-acid salt, when treated with hydrochloric acid and freed from mandelic acid, deposited (—)-α-hydroxy-α-phenyl-butyramidinium chloride, having $[\alpha]_{5461}$ —48·9° (in water), but with a melting point below that of its enantiomorph. Crystallisation did not improve its melting point substantially, but purification through its (+)-mandelate gave a chloride that agreed in melting point and rotatory power with its enantiomorph.

$$\text{(I)}\quad (\pm)\text{-}HO\cdot CPhEt\cdot C(OEt){:}NH_2Cl \longrightarrow (\pm)\text{-}HO\cdot CPhEt\cdot C(NH_2){:}NH_2Cl\quad \text{(II)}$$

With hot aqueous sodium hydroxide, (+)-α-hydroxy-α-phenylbutyramidinium chloride, $[\alpha]_{5461}$ +47·8° (in water; *i.e.*, 97% of the previous value), gave (+)-α-hydroxy-α-phenylbutyric acid, $[\alpha]_{5461}$ +37·0° (in water). This value represents 97% of the specific rotation, $[\alpha]_{5461}$ —38·1° (in water), found by McKenzie and Ritchie,[18] and hence the resolution is regarded as almost complete. Moreover, as this hydrolysis occurs in a position remote from the asymmetric centre, the (+)-amidinium chloride and (+)-α-hydroxy-α-phenylbutyric acid will be related in absolute configuration.

Attempts to form the (±)-, (+)-, and (—)-α-hydroxy-α-phenylbutyramidines from their respective hydrochlorides by the action of sodium hydroxide solutions of varying strengths failed. Somewhat similar difficulties were encountered by Reid[19] who obtained (±)-mandelamidine but not (+)- or (—)-mandelamidine and by Roger and Neilson[14] who failed to isolate (+)- and (—)-atrolactamidine.

The isomeric (±)-α-hydroxy-β-phenylbutyramidinium chloride with sodium (±)-mandelate gave a monohydrated (±)-amidinium (±)-mandelate that became anhydrous *in vacuo* at 100°: in one instance, under apparently identical conditions, a non-hydrated

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[3] McKenzie and Walker, *J.*, 1928, 646.
[4] Manske and Johnson, *J. Amer. Chem. Soc.*, 1929, **51**, 1906.
[5] Skita, Keil, and Meiner, *Ber.*, 1933, **66**, 974.
[6] Jarowski and Hartung, *J. Org. Chem.*, 1943, **8**, 564.
[7] Ingersoll and DeWitt, *J. Amer. Chem. Soc.*, 1951, **73**, 3360.
[8] Brode and Raasch, *J. Amer. Chem. Soc.*, 1942, **64**, 1449.
[9] Roger, unpublished work.
[10] Crooks, jun., Rebstock, Controulis, and Bartz, U.S.P., 2,483,884.
[11] Rebstock and Bambas, *J. Amer. Chem. Soc.*, 1955, **77**, 186.
[12] Jensen, Whipple, Wedegaetner, and Landgrebe, *J. Amer. Chem. Soc.*, 1959, **81**, 1262.
[13] Neilson, Ph.D. Thesis, St. Andrews, 1955.
[14] Roger and Neilson, *J.*, 1959, 688.
[15] Hansley, U.S.P. 2,416,624.
[16] Roger and Neilson, *Chem. Rev.*, 1961, **61**, 179.
[17] Pinner, " Die Imidoäther und ihre Derivate," Oppenheim, Berlin, 1892.
[18] McKenzie and Ritchie, *Ber.*, 1937, **70**, 23.
[19] Reid, Ph.D. Thesis, St. Andrews, 1949.

form of the (±)-mandelate was obtained, despite the reaction's taking place in water. Whilst hydration of amidinium salts is not very usual, Ashley and his co-workers [20] report several cases.

Use of sodium (—)-mandelate produced, after four crystallisations, (—)-α-hydroxy-β-phenylbutyramidinium (—)-mandelate hemihydrate which yielded a lævorotatory chloride on treatment with hydrogen chloride. Decomposition of the mother-liquors from the (—) (—)-salt with hydrochloric acid yielded inactive chloride, showing that the separation of the diastereoisomers took place mainly during the subsequent recrystallisations, and hence the final yields were small. The diastereoisomeric (+)-α-hydroxy-β-phenylbutyramidinium (+)-mandelate hemihydrate was obtained in a similar way by using sodium (+)-mandelate. Decomposition of the (—)-amidinium chloride with hot alkali furnished a (—)-α-hydroxy-β-phenylbutyric acid, but we have found no recorded rotations for this acid or its diastereoisomers and therefore cannot estimate the extent of resolution. Moreover, paucity of the final amidinium mandelate samples precluded the determination of optical purity by crystallisation to constant rotatory power.

EXPERIMENTAL

Specific rotations were measured in a 2-dm. tube unless otherwise stated.

Optically Active Mandelic Acids.—These acids [2] and the calculated quantity of sodium hydrogen carbonate solution were evaporated and the residues of sodium salts were recrystallised from aqueous ethanol.

Propiophenone Cyanohydrin.—Propiophenone (134 g.) in ether (100 ml.) was added to a solution of sodium cyanide (123 g.) in water (150 ml.). The mixture was stirred at 5° during addition of concentrated hydrochloric acid (210 ml.). The addition required 2 hr. and the mixture was then stirred for a further hr. at 5°, then extracted with ether. The extract, after drying (Na_2SO_4), afforded propiophenone cyanohydrin (54 g.), b. p. 148—150°/16 mm. in the presence of iodine (0·5 g.) as stabiliser.[15]

Hydratropaldehyde Cyanohydrin.[21]—Freshly distilled hydratropaldehyde (36 g.) was stirred with a solution of sodium cyanide (12·5 g.) in water (50 ml.) and ice (100 g.). Saturated sodium hydrogen sulphite solution (72 ml.) was run slowly into the stirred mixture. Stirring was continued for ½ hr., then the solution was extracted with ether. The ether was removed from the dried extract (Na_2SO_4), and the cyanohydrin again dried (Na_2SO_4) and then converted directly into the imidate hydrochloride.

Imidate Hydrochlorides.—These were prepared by the Pinner method,[16,17] interaction of equimolar quantities of the cyanohydrin, ethanol, and hydrogen chloride under anhydrous conditions. After 24 hr. at 0° the reactants were treated with anhydrous ether. The imidate salts crystallised almost immediately.

Ethyl (±)-α-hydroxy-α-phenylbutyrimidate hydrochloride (45%) had m. p. 98—99° (decomp.). The hydrochloride (4·8 g.) with 4N-sodium hydroxide (12 ml.) yielded the *imidate* (3·4 g.), m. p. 71—72° [from light petroleum (b. p. 60—80°)] (Found: C, 69·9; H, 8·3; N, 6·9. $C_{12}H_{17}NO_2$ requires C, 69·6; H, 8·2; N, 6·8%).

Ethyl (±)-α-hydroxy-β-phenylbutyrimidate hydrochloride (60%) had m. p. 108—109°.

Amidinium Chlorides.—The imidate hydrochlorides (0·1 mole) were shaken with anhydrous solutions of ammonia (8·5 g.) in ethanol (100 ml.) for 8 hr. and the alcohol then evaporated at room temperature. The resultant amidinium chlorides were recrystallised from dilute hydrochloric acid [samples for analysis were prepared by decomposition of the (±)-mandelate salts with hydrogen chloride].

(±)-α-*Hydroxy*-α-*phenylbutyramidinium chloride* (72%) had m. p. 133—134° (decomp.) (Found: C, 55·5; H, 7·1; N, 13·2. $C_{10}H_{15}ClN_2O$ requires C, 55·9; H, 7·0; N, 13·05%).

(±)-α-*Hydroxy*-β-*phenylbutyramidinium chloride* (80%) contracted at 250° and melted at 259—260° (decomp.) after darkening (Found: C, 56·25; H, 7·0; N, 13·1%).

(±)-*Amidinium* (±)-*Mandelates.*—Equimolar quantities of sodium (±)-mandelate and

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[20] Ashley, Barber, Ewins, Newbery, and Self, *J.*, 1942, 103.

[21] Biquard, *Compt. rend.*, 1932, **194**, 983.

amidinium chloride were heated together in water until a clear solution resulted. The crystals which separated on cooling were twice recrystallised from water (charcoal). (±)-*α-Hydroxy-α-phenylbutyramidinium* (±)-*mandelate* (52%) softened at 171° and melted at 173—174° (decomp.) (Found: C, 65·4; H, 6·4; N, 8·55. $C_{18}H_{22}N_2O_4$ requires C, 65·5; H, 6·7; N, 8·5%).

(±)-*α-Hydroxy-β-phenylbutyramidinium* (±)-*mandelate monohydrate* (53%), after drying *in vacuo* below 50°, contracted at 76° and melted at 82—83° (Found: C, 62·0; H, 6·9; N, 8·4. $C_{18}H_{22}N_2O_4,H_2O$ requires C, 62·1; H, 6·9; N, 8·05%). In one instance a similar preparation resulted in an anhydrous *salt* which softened at 160° and melted at 165—166° (decomp.) (Found: C, 65·3; H, 6·5; N, 8·4%). A mixed m. p. with the hydrate was at 154—155°. The monohydrate, on drying *in vacuo* at 100° to constant weight (5 hr.) lost 17·9 parts by weight per mole.

Optically Active Amidinium Mandelates.—(a) *α-Hydroxy-α-phenylbutyramidinium salts.* (±) α-Hydroxy-α-phenylbutyramidinium chloride (5·4 g.) and sodium (−)-mandelate (4·4 g.), $[\alpha]_{5461}$ −120° (in water), were heated in water (50 ml.). The solid which was deposited on cooling was recrystallised three times from water, giving rhombic crystals of (+)-*α-hydroxy-α-phenylbutyramidinium* (−)-*mandelate* (1·2 g.), which softened at 172° and had m. p. 175—176° (decomp), $[\alpha]^{17}_{5461}$ −9·9° (*c* 0·96 in methanol) (Found: C, 66·15; H, 6·7; N, 8·3%).

(−)-*α-Hydroxy-α-phenylbutyramidinium* (+)-*mandelate*, prepared as above from sodium (+)-mandelate, $[\alpha]_{5461}$ +120° (in water), softened at 172°, and had m. p. 175—176° (decomp.), $[\alpha]^{17}_{5461}$ +9·3° (*c* 0·78 in methanol) (Found: C, 65·2; H, 6·4; N, 8·55%).

(b) *α-Hydroxy-β-phenylbutyramidinium salts.* (±)-α-Hydroxy-β-phenylbutyramidinium chloride (10·7 g.) and sodium (−)-mandelate, $[\alpha]_{5461}$ −121° (in water), in water (125 ml.) gave rhombic crystals that were recrystallised thrice from water, giving (−)-*α-hydroxy-β-phenylbutyramidinium* (−)-*mandelate hemihydrate* (1·5 g.) as needles which softened at 115°, became yellow at 160°, and melted at 174—175° (decomp.), and had $[\alpha]^{18}_{5461}$ −102·3° (*c* 0·98 in methanol) (Found: C, 63·5; H, 6·8; N, 8·25. $C_{18}H_{22}N_2O_4,\frac{1}{2}H_2O$ requires C, 63·7; H, 6·8; N, 8·3%).

(+)-*α-Hydroxy-β-phenylbutyramidinium* (+)-*mandelate hemihydrate* was prepared similarly from sodium (+)-mandelate, $[\alpha]_{5461}$ +120° (in water), and had m. p. 174—175° (decomp.), after softening at 115° and becoming yellow at 160°, $[\alpha]^{17}_{5461}$ +105·8° (*c* 0·58 in methanol) (Found: C, 63·3; H, 6·7; N, 8·15%). Solid which was deposited after the original reaction liquors had been decomposed with hydrochloric acid and the liberated mandelic acid removed with ether proved to be (±)-α-hydroxy-β-phenylbutyramidinium chloride.

Optically Active Amidinium Chlorides.—A cooled solution of the optically active amidinium mandelate in alcohol was treated with dry hydrogen chloride and set aside for 24 hr. The alcohol was then evaporated *in vacuo* and the resultant solid treated several times with hot benzene–acetone to remove mandelic acid. The residue was then washed with ether, dissolved in warm alcohol, cooled, and reprecipitated with ether. The yields were almost theoretical.

(+)-*α-Hydroxy-α-phenylbutyramidinium chloride*, prepared from (+ −)-salt of $[\alpha]_{5461}$ −9·9°, melted at 201—202° (decomp.) and had $[\alpha]^{19}_{5461}$ +48·9° (*c* 0·44 in water) (Found: C, 55·9; H, 6·9; N, 13·2. $C_{10}H_{15}ClN_2O$ requires C, 55·9; H, 7·0; N, 13·05%).

(1) (−)-*α-Hydroxy-α-phenylbutyramidinium chloride*, prepared from (− +)-salt of $[\alpha]_{5461}$ +9·3°, had m. p. 201—202° (decomp.) and $[\alpha]^{17}_{5461}$ −49° (*c* 0·68 in water) (Found: C, 55·7; H, 7·0; N, 13·2%).

The mother-liquors from the (+)-salt were heated with hydrochloric acid and the mandelic acid liberated was removed with ether. After 2 days the solution deposited (−)-α-hydroxy-α-phenylbutyramidinium chloride, $[\alpha]^{17}_{5461}$ −48·9°, m. p. 179—180°.

(−)-*α-Hydroxy-β-phenylbutyramidinium chloride*, from (− −)-salt of $[\alpha]_{5461}$ −102·3°, softened at 197°, melted at 210—212°, and decomposed above 215° and had $[\alpha]^{13}_{5461}$ −43·6° (*c* 0·86 in water) (Found: C, 55·7; H, 6·75; N, 13·0%).

(+)-*α-Hydroxy-α-phenylbutyric Acid.*—(+)-α-Hydroxy-α-phenylbutyramidinium chloride (0·4 g.), $[\alpha]^{30}_{5461}$ +47·8° (in water), was heated in 4N-sodium hydroxide (5 ml.) until evolution of ammonia ceased. The acidified solution, on extraction with ether, evaporation of this extract, and crystallisation of the resultant solid from benzene (charcoal), yielded (+)-α-hydroxy-α-phenylbutyric acid (0·1 g.), $[\alpha]^{22}_{5461}$ +37° (*c* 0·27 in water). A mixed m. p. with authentic (+)-acid was satisfactory.

(−)-*α-Hydroxy-β-phenylbutyric Acid.*—(−)-α-Hydroxy-β-phenylbutyramidinium chloride (0·3 g.), $[\alpha]_{5461}$ −43·6° (in water), treated as above, gave (−)-α-hydroxy-β-phenylbutyric acid which softened at 123°, melted at 130—131°, and had $[\alpha]^{18}_{5461}$ −24·0° (*c* 0·19 in water). The smallness of the sample precluded analysis.

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