312. *The Resolution of Some Halogen-substituted Mandelamidines and a Study of the Optical Stability of their Mandelate Salts at Elevated Temperatures*

By D. G. Neilson and L. H. Roach

(±)-2-Chloro-, -2-bromo-, and -2,4-dichloro-mandelamidines have been resolved by means of the optically active mandelic acids which, however, failed to resolve the 3- and 4-chloromandelamidines. The lower-melting diastereoisomerides formed between mandelic acid and the corresponding 2- and 2,4-substituted mandelamidines were optically labile at the α-hydroxy-amidinium centre and could be converted into the higher-melting diastereoisomerides by heating to just below their melting points. Attempts have been made to assign configurations to the amidinium chlorides by considering the stability and inter-relationship of these diastereoisomerides.

Neilson and Peters [1] prepared a series of methoxy- and ethoxy-mandelamidines and resolved them by means of mandelic acid or its *O*-methyl derivative. (—)-*o*-Methoxy- and (—)-*o*-ethoxy-mandelamidinium (—)-mandelates, which have lower melting points and greater solubilities than their corresponding diastereoisomerides, were found to be optically labile at the α-hydroxy-amidinium centre. Thus, on heating at temperatures approaching their melting points, these compounds transformed into the higher-melting diastereoisomerides.[2] (—)-Mandelamidinium (—)-mandelate behaved somewhat similarly but the results were masked by marked decomposition at the elevated temperature required for this epimerisation.[2] Hence, although this phenomenon is not limited to mandelamidines having *ortho*-substituents, for example (—)-3,4-dimethoxymandelamidinium (—)-mandelate also epimerises at its melting point,[3] the ease of epimerisation and the yield of recovered material appear optimum when the ring carries an *ortho*-substituent. With this in view, we attempted the resolution of the following series of halogen-substituted mandelamidines which were prepared from the corresponding halogen-substituted benzaldehyde cyanohydrins by the Pinner method.[4,5]

(±)-2-Chloromandelamidine and (—)-mandelic acid in ethanol deposited the (+)-amidinium (—)-mandelate with constant [α] —2·4° (in methanol) (see Experimental section) after one recrystallisation. This, in turn, yielded the (+)-amidinium chloride, [α] +56·2° (in

---

[1] D. G. Neilson and D. A. V. Peters, *J.*, 1963, 4455.
[2] P. Bellingham, D. A. V. Peters, and D. G. Neilson, *J.*, 1964, 2118.
[3] D. G. Neilson, Symposium on Aspects of Molecular Dissymmetry, London, 1964; cf. *Proc. Chem. Soc.*, 1964, 135.
[4] A. Pinner, " Die Imidoäther und ihre Derivate," Oppenheim, Berlin, 1892.
[5] R. Roger and D. G. Neilson, *Chem. Rev.*, 1961, **61**, 179.

water). The original liquors, on concentration, deposited the diastereoisomeric mandelate which if heated rapidly exhibited two melting points, 133° and 163—164°, *i.e.*, close to the melting point of the (+)-amidinium (—)-mandelate. This double melting point was further investigated by heating a weighed sample of the (—)-amidinium (—)-mandelate just below its melting point for *ca.* 30 minutes. The recovered material (83% by total weight) was shown to be the (+)-amidinium (—)-mandelate, [α] —4·5° (in methanol) which agreed closely with material obtained by direct resolution, and hence epimerisation had taken place at the α-hydroxy-centre of the amidine. A further sample, which was heated in a silica tube over the same temperature range, gave analogous results showing that the inversion was not being catalysed by the alkaline nature of the glass. In another experiment, (±)-2-chloromandelamidinium (—)-mandelate was heated just below its melting point and, although the percentage recovery was poorer, the resultant material, which constituted more than 50% by weight of the starting material, was shown to be the (+)-amidinium (—)-mandelate, [α] —4·9° (in methanol).

3- and 4-Chloromandelamidines both readily formed salts with the mandelic acids but in neither case was separation of the diastereoisomers noted. Neilson and Peters [1] had similar difficulty on trying to resolve the 3-ethoxy- and 3-methoxy-mandelamidines whereas the 2-ethoxy- and 2-methoxy-isomers were readily resolved with the mandelic acids.

2,4-Dichloromandelamidinium chloride and sodium (+)-mandelate in water gave the (—)-amidinium (+)-mandelate which had constant [α] +10·2° (in methanol) on recrystallisation. The (+)-amidinium (+)-mandelate recovered from the original liquors had [α] +97·0° (in methanol) and exhibited two melting points, 110—114° and 135—145°. Amidinium chlorides from these mandelates had [α] —51·5° and +50·0° (in water), respectively. To test its optical stability, (—)-2,4-dichloromandelamidinium (—)-mandelate, [α] —72·0° (in methanol), was heated for about one hour over the range 124—135° but the sample showed marked decomposition and the final yield was low, moreover only partial transformation into the diastereoisomeride was noted.

(±)-2-Bromomandelamidinium chloride also resolved readily with sodium (—)-mandelate in aqueous methanol. The initial crop of needle crystals proved to be the (+)-amidinium (—)-mandelate which had constant [α] ~0·0° (in methanol) after one recrystallisation. The liquors, on concentration, deposited rhombic as well as needle crystals and the former were separated mechanically and purified. These rhombs were the (—)-amidinium (—)-mandelate, [α] —95·5° (in methanol), which melted at 127—128°, resolidified and then remelted at 165—167°. To test the optical stability of this substance, a sample [α] —86·0° (in methanol) was heated in a silica vessel, the temperature being raised from 120—135° over 30 minutes. The recovered material (82% by weight) was shown to be the (+)-amidinium (—)-mandelate [α] ~0·0° (in methanol), inversion being once again complete at the α-hydroxy-amidinium centre.

To date we have little idea of the mechanism of this inversion, but the large melting-point differences between the diastereoisomers (often 30—40°) could point to fundamental differences in crystal packing in the systems which readily undergo this inversion. It was with this in view that the above synthesis, resolution, and epimerisation of a system containing a heavy atom, *viz.* bromine, was undertaken and Dr. J. Iball of this department is now carrying out a crystallographic determination of structure on the (—)- and (+)-2-bromomandelamidinium (—)-mandelates to help elucidate this problem. As chemical means, *e.g.* hydrolysis, have failed to give the configuration of the substituted mandelamidinium chlorides, owing to the ease of base-catalysed racemisation,[1] the relationship of the two α-hydroxy-centres across the planar amidinium carboxylate system [6] is unknown in the foregoing cases. However, the epimerisation of (—)-mandelamidinium (—)-mandelate [2] shows that, when both centres are of the same configuration (namely D),[7] the

---

[6] O. Kennard and J. Walker, *J.*, 1963, 5513.

[7] S. Reid, Ph.D. Thesis, St. Andrews, 1949.

amidinium centre is optically labile and hence, if in this case we consider a *threo*-arrangement across the planar amidinium carboxylate ring system,[6] the molecule is labile whereas the *erythro*-arrangement is optically stable. Such arrangements are known to hold in other systems provided steric interactions only are present.[8] If this analogy of a stable *erythro*-configuration is applied to the 2-bromo- and 2-chloro-compounds, for which the (+)-amidinium (−)-mandelate is the more stable diastereoisomer, it would suggest that the (+)-2-bromo- and (+)-2-chloro-mandelamidinium chlorides have the L-configuration (*S*). Similarly, (+)-2-ethoxy- and (+)-2-methoxy-mandelamidinium chlorides,[1,2] the mandelates of which behave in an analogous fashion, would also have the L-configuration (*S*). This tentative assignment will require substantiation by chemical means should this prove possible later. However, support for these conclusions may be derived from the work of Ricci [9] who has recently attempted to rationalise the " quasi-racemate " method of Fredga [10] and to extend it to systems in which both (or neither) of the diastereoisomers form compounds. Ricci states that when " both diastereoisomers form compounds, the compound containing the components in opposite configurations has the higher melting point " due to " the higher compound-forming tendency or greater negative deviations for such configurations." Thus, all the (+)-amidinium systems mentioned above would have the opposite configuration to that of D-(−)-mandelic acid (*R*) and hence would belong to the L-series (*S*) in agreement with our earlier predictions. In addition, as Ricci [9] points out, Winther's rule—that, for different (±)-acids, one alkaloid will tend to precipitate as the salt formed from acids of related configuration—is generally true unless there is non-ideality within the system solvent + diastereoisomer. In the case of the 2-chloro-, 2-ethoxy-, and 2-methoxy-mandelamidinium systems, the same solvent, water, is employed in the resolutions and hence, since the (+)-amidinium (−)-mandelate is the less soluble and more stable diastereoisomer in each case, it is feasible that the (+)-amidinium systems are all related in configuration. As the 2-bromo-system is less soluble in water and required some methanol in the resolution solvent these latter remarks may not be strictly applicable to it. Whilst this last evidence may be more circumstantial, it nevertheless fits our general assignment of configuration for the 2-substituted mandelamidinium chlorides.

EXPERIMENTAL

Specific Rotations.—All specific rotations were measured in a 2 dm. tube at 5461 Å at 18—22°, unless otherwise recorded.

Optically Active Mandelic Acids.—These acids,[11] $[\alpha] \geqslant \pm 180°$ (in acetone) were resolved by the method of Roger, and converted into their sodium salts as previously described.[12]

Resolution of (±)-*2-Chloromandelamidinium Chloride*.—(*a*) The (±)-amidinium chloride [13] (3 g.), m. p. 170—171°, was boiled with sodium (−)-mandelate (2·4 g.) in water (50 ml.) and the solution set aside to cool slowly. The resultant solid (1·8 g.) was recrystallised from water (10 ml.) and had constant [α] −2·4° (*c* 0·48 in methanol). (+)-*2-Chloromandelamidinium* (−)-*mandelate* had m. p. 168—169° (Found: C, 57·2; H, 5·1. $C_{16}H_{17}ClN_2O_4$ requires C, 57·1; H, 5·1%). An ethanolic solution of the (+)-amidinium (−)-mandelate, [α] −2·4° (in methanol) was treated at 0° with dry hydrogen chloride and the solution evaporated to dryness *in vacuo*. The resultant solid was treated with hot benzene–acetone to remove mandelic acid and was then purified by dissolution in the minimum amount of alcohol and reprecipitation with ether. The yield was almost theoretical. (+)-*2-Chloromandelamidinium chloride* had m. p. 199—200°, [α] +56·3° (*c* 0·75 in water) (Found: C, 43·8; H, 4·3. $C_8H_{10}Cl_2N_2O$ requires C, 43·4; H, 4·5%).

(*b*) The (±)-amidinium chloride was dissolved in the minimum amount of water and cooled to 0°. 4N-Sodium hydroxide solution was added dropwise until just over the calculated quantity

---

[8] E. L. Eliel, " Stereochemistry of Carbon Compounds," McGraw-Hill, 1962, p. 137.
[9] J. E. Ricci, *Tetrahedron*, 1962, **18**, 605.
[10] A. Fredga, " The Svedberg " (Memorial Volume), Almqvist and Wiksells, Uppsala, 1944, p. 261.
[11] R. Roger, *J*., 1935, 1544.
[12] D. G. Neilson and D. A. V. Peters, *J*., 1962, 1309.
[13] F. E. King, T. J. King, and I. H. M. Muir, *J*., 1946, 5.

was present. The amidine base which precipitated on scratching the vessel was filtered, washed with a little cold water, and recrystallised from acetone–ethanol. 2-Chloromandelamidine (7 g.) and (−)-mandelic acid (5·8 g.) were heated in ethanol (70 ml.) and allowed to cool. The resultant solid (3 g.) was recrystallised from ethanol (80 ml.) and had constant [α] −2·4° (*c* 0·53 in methanol). This gave (+)-2-chloromandelamidinium chloride, m. p. 199—200° and [α] +56·2° (*c* 0·43 in water) by the method described above. The original liquors deposited a second crop, which was treated as above, and then they were allowed to evaporate to dryness. The resultant solid was taken up in acetone–ethanol–ether, and (−)-2-chloromandelamidinium (−)-mandelate, [α] −92·8° (*c* 0·91 in methanol) precipitated on standing. This had m. p.s 133° and 163—164° if rapidly heated. With a slow rate of heating there was contraction but no actual observed melt at the lower melting point, followed by melting at 163—165°. The (−)-amidinium (−)-mandelate, on treatment with alcoholic hydrogen chloride as described above, gave (−)-2-*chloromandelamidinium chloride*, m. p. 198—199°, [α] −54·1° (*c* 0·45 in water) (Found: C, 43·3; H, 4·8%).

Preparation and Attempted Resolution of 3- *and* 4-*Chloromandelamidinium Chlorides*.—These compounds were prepared by the method of Bristow;[14] (±)-3-chloromandelamidinium chloride had m. p. 141—142° (lit.,[14] 141°) and the 4-chloro-isomer had m. p. 253—254° (lit.,[14] 254°).

3-Chloromandelamidine was prepared (60% yield) from its hydrochloride as described for the 2-chloro-isomer, and combined with an equivalent weight of mandelic acid in hot ethanol. The resultant solid, on repeated crystallisation from ethanol, had m. p. 157—159° and constant [α] −53·5° (*c* 0·63 in methanol), and yielded the hydrochloride, [α] 0·0°, m. p. and mixed m. p. 142°, as described above.

4-Chloromandelamidinium chloride (15 g.) was treated in hot water with sodium (−)-mandelate (12 g.). The product (18 g.) on repeated recrystallisation from aqueous ethanol (1 : 1) had constant [α] −53·8° (*c* 0·48 in methanol) and m. p. 174°. Aqueous acetone gave analogous results. The amidinium chloride reformed in the usual way, had [α] 0·0° (*c* 0·41 in water) and m. p. and mixed m. p. 253°.

Preparation and Resolution of 2,4-*Dichloromandelamidinium Chloride*.—The crude cyanohydrin (70 g.), needles, m. p. 113—114°, prepared from 2,4-dichlorobenzaldehyde (100 g.) by way of the bisulphite complex, was converted by the Pinner method[4,5] into ethyl 2,4-dichloromandelimidate hydrochloride, m. p. 120—124°. Reaction of this imidate salt with alcoholic ammonia solution (anhydrous) gave (±)-2,4-*dichloromandelamidinium chloride*, m. p. 203—204° (60% yield based on cyanohydrin) (Found: C, 38·1; H, 3·6. $C_8H_9Cl_3N_2O$ requires C, 37·6; H, 3·5%).

The (±)-amidinium chloride (10 g.) and sodium (+)-mandelate (6·2 g.) were heated together in water (120 ml.). Solid (10·5 g.) which precipitated on cooling was recrystallised from aqueous ethanol (1 : 1). After two crystallisations this had constant [α] +10·2° (*c* 0·54 in methanol) and m. p. 152—154°. (−)-2,4-*Dichloromandelamidinium chloride*, reformed from this mandelate in the manner described above, had [α] −51·5° (*c* 0·47 in water) and m. p. 198—200° (Found: C, 38·1; H, 3·6. $C_8H_9Cl_3N_2O$ requires C, 37·6; H, 3·5%). The original aqueous solution was allowed to evaporate to dryness and was then treated with cold ethanol and the solution filtered to remove sodium chloride. This solution furnished (+)-2,4-dichloromandelamidinium (+)-mandelate on treatment with ether and this, on further crystallisation from ethanol–ether (charcoal), had [α] +97·0° (*c* 0·49 in methanol), m. p. 110—114° and 135—145°. The (+)-*amidinium chloride*, formed from it in the usual way, had [α] +50·0° (*c* 0·1 in water) and m. p. 198—200° (Found: C, 37·8: H, 3·9%).

Preparation and Resolution of (±)-2-*Bromomandelamidinium Chloride*.—2-Bromobenzaldehyde (40 g.) was converted into its bisulphite complex and then into its cyanohydrin. This cyanohydrin in a small volume of anhydrous ether was converted by the Pinner[4,5] method into ethyl 2-bromomandelimidate hydrochloride (33 g.) and then by the action of anhydrous alcoholic ammonia into (±)-2-bromomandelamidinium chloride (25 g.), m. p. 185—186°.

This chloride (13 g.) and sodium (−)-mandelate (8·7 g.) were heated together in water (150 ml.) containing about 10% methanol. Solid which deposited on cooling was twice recrystallised from aqueous methanol (50 ml.; 1 : 1) to give (+)-2-*bromomandelamidinium* (−)-*mandelate* (4 g.) as needles, m. p. 174—175°, constant [α] +1·9° (*c* 1·55 in methanol) (Found: C, 50·6; H, 4·6. $C_{16}H_{17}BrN_2O_4$ requires C, 50·4; H, 4·4%). When decomposed with ethanolic

---

[14] N. W. Bristow, *J.*, 1957, 513.

hydrogen chloride and worked up in the usual way, this gave (+)-2-*bromomandelamidinium chloride*, [α] +41·6° (*c* 0·91 in water), m. p. 205—206° (Found: C, 36·0; H, 3·9; N, 10·5. $C_8H_9BrClN_2O$ requires C, 36·2; H, 3·8; N, 10·5%). The original aqueous solution eventually deposited two types of crystals, needles and rhombs. These were separated by hand and the rhombs purified by dissolving in alcohol and reprecipitating with ether. (−)-2-*Bromomandelamidinium* (−)-*mandelate*, so obtained, had [α] −95·5° (*c* 0·9 in methanol); it softened at 125°, melted at 127—128°, resolidified, and remelted at 165—167° with some decomposition taking place between the two melting points (Found: C, 50·2; H, 4·5%). A further crop of the (−)-amidinium (−)-mandelate (2 g.) was obtained from the first recrystallisation liquors and was worked up as before. This had [α] −86·0° (*c* 0·9 in methanol) and gave (−)-2-*bromomandelamidinium chloride*, [α] −38·6° (*c* 0·33 in water), m. p. 205—206°, on treatment with ethanolic hydrogen chloride in the usual way (Found: C, 36·5; H, 4·0%).

Optical Stability at Elevated Temperatures.—(*a*) 2-*Chloromandelamidinium system.* (−)-2-Chloromandelamidinium (−)-mandelate (1 g.), [α] −92·8° (in methanol) was heated in a Pyrex tube in an oil-bath, the temperature being allowed to rise from room temperature with the sample in the bath. Heating over the range 120—128° occupied 13 min. and that over 128—133°, 15 min. The resultant yellow-brown sample was then taken up in the minimum of ethanol and reprecipitated with ether, care being taken to allow complete precipitation. The resultant solid (0·83 g.), [α] −4·5° (*c* 1·65 in methanol) contracted slightly at 130°, melted at 168—169°, and gave no depression of m. p. with an authentic sample of the (+)-amidinium (−)-mandelate. (+)-2-Chloromandelamidinium chloride formed from it in the usual way had [α] +51·0° (*c* 0·51 in water) and m. p. 199—200°.

(−)-2-Chloromandelamidinium (−)-mandelate (0·35 g.), [α] −92·8° (in methanol) was heated in a silica tube for 20 min. at 128—132°. The resultant sample (0·29 g.) was purified as above and had [α] −5·2° (*c* 1·34 in methanol) and yielded the (+)-amidinium chloride, [α] +50·0° (*c* 0·55 in water), m. p. 200—201° on treatment with ethanolic hydrogen chloride. No depression of melting point was observed with authentic samples of these compounds.

(±)-2-Chloromandelamidine (0·7 g.) and (−)-mandelic acid (0·55 g.), [α] −180° (in acetone) were dissolved in ethanol and warmed. Ether was added to the cooled solution giving solid (0·9 g.), [α] −48·5° (*c* 0·9 in methanol), m. p. 164° after slight contraction at 125°. The specific rotation of (±)-2-chloromandelamidinium (−)-mandelate, calculated on the best values obtained for the two diastereoisomers, would be −47·6° (in methanol). The (±)-amidinium (−)-mandelate (0·65 g.), [α] −48·5° was heated for 5 min. at 120° and then at 155° for a further 5 min. The recovered sample (0·42 g.), after purification in the usual way, had [α] −4·9° (*c* 0·91 in methanol), in good agreement with the value quoted for the other epimerisations.

(*b*) 2,4-*Dichloromandelamidinium system.* (−)-2,4-Dichloromandelamidinium (−)-mandelate (1 g.), m. p. 114—115°, [α] −72·0° (*c* in methanol), was heated at 110° for 10 min. and then at 114° for a similar time. The sample was markedly yellow-brown and was purified in the usual way. The resultant solid (0·8 g.) was heated for 10 min. at 124°. Again marked decomposition took place, and the sample was purified as above. The resultant solid (0·6 g.) which did not agree in melting point with the (+)-amidinium (−)-mandelate was heated at 124—135° for 45 min. The final sample (0·4 g.), after purification, had m. p. 132—142°, and yielded in the usual way with ethanolic hydrogen chloride, (+)-2,4-dichloromandelamidinium chloride, m. p. 201—202°, [α] +37·4° (*c* 1·0 in water), *i.e.*, *ca.* 74% of optical purity.

(*c*) 2-*Bromomandelamidinium system.* (−)-2-Bromomandelamidinium (−)-mandelate (1 g.), [α] −86·0° (in methanol) was heated in a silica tube for 10 min. at 120—122° and then the temperature was raised to 135° during 20 min. After purification as previously described, the resultant sample (0·82 g.) had m. p. 173—174°, [α] ~0·0° (*c* 2·2 in methanol) and gave no depression of melting point with authentic (+)-2-bromomandelamidinium (−)-mandelate. (+)-2-Bromomandelamidinium chloride formed from it in the usual way had [α] +39·5° (*c* 0·43 in water) and m. p. 204° after contraction at 201°.

One of us (L. H. R.) is indebted to the D.S.I.R. for a Research Grant which made part of this work possible.

Department of Chemistry, Queen's College,
University of St. Andrews, Dundee.

[*Received, August 5th*, 1964.]