

396. *Asymmetric Transformations of Optically-active Mandelamidine Derivatives at Elevated Temperatures.*

By P. BELLINGHAM, D. A. V. PETERS, and D. G. NEILSON.

At temperatures closely approaching that of their melting points, the more soluble (in aqueous solution) of the diastereoisomers formed between mandelamidine, *o*-methoxy- or *o*-ethoxy-mandelamidine and the optically-active mandelic acids have been found to be optically labile; the α -hydroxy-amidinium centres undergo virtually complete inversion in the case of the *o*-methoxy and *o*-ethoxy-compounds.

MANY molecules, optically stable at ordinary temperatures, may become optically labile at higher temperatures,¹ *e.g.*, Roger and Reid² showed that at 160—170° the optically-active mandelamidinium chlorides were optically labile and underwent thermal racemisation. Thus, heating (–)-mandelamidinium chloride at temperatures below 160° for up to 2 hours in a quartz vessel produced little change in specific rotation, whereas heating at 170° for a matter of minutes gave complete racemisation. We³ have since reported that (+)- and (–)-*o*-ethoxymandelamidinium chlorides similarly racemise on melting, then resolidify and remelt close to the melting point of the (\pm)-form. We also noted that (–)-*o*-methoxymandelamidinium (–)-mandelate exhibited a double melting point. In this case, any change of the α -hydroxy-amidinium centre would be taking place under the influence of the second centre situated on the (–)-mandelic acid, always provided this second centre was optically stable at these elevated temperatures. Thus there would be a strong possibility that the final product would not be the (\pm)-amidinium (–)-mandelate but might be biased in favour of one or other diastereoisomer.

Accordingly, (–)-*o*-methoxymandelamidinium (–)-mandelate,³ $[\alpha] -134.6^\circ$ (in methanol) * was kept at 155—160° for 7 minutes in a Pyrex tube. Some decomposition

* $[\alpha]$ was measured at 5461 Å, unless otherwise recorded.

¹ Turner and Harris, *Quart. Rev.*, 1948, **1**, 299.

² Reid, Ph.D. Thesis, St. Andrews, 1949.

³ Neilson and Peters, *J.*, 1963, 4455.

took place but the bulk sample did not appear to melt. Purification of the residue gave authentic (+)-*o*-methoxymandelamidinium (–)-mandelate, $[\alpha] +30.4^\circ$ (in methanol), and which with methanolic hydrogen chloride furnished (+)-*o*-methoxymandelamidinium chloride, $[\alpha] +103.2^\circ$ (in water) [lit.,³ $[\alpha] +105.2^\circ$ (in water)]. Thus the (–)-amidinium (–)-mandelate is unstable optically at 155–160° and is transformed completely into the diastereoisomer, apart from some little loss due to decomposition.

On the other hand, under similar conditions (–)-methoxymandelamidinium (+)-mandelate, $[\alpha] -30.8^\circ$ (in methanol), was recovered virtually unchanged in specific rotation. Hence, it would appear that the diastereoisomer which had the greater solubility in aqueous media was optically labile at elevated temperatures.

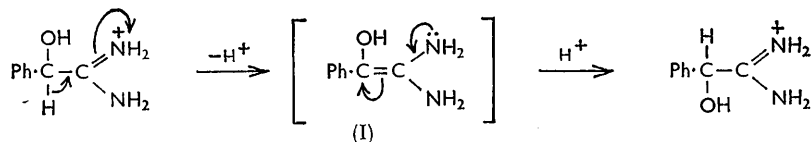
It was next decided to examine the effect of heat on (±)-*o*-methoxymandelamidinium (+)-mandelate but it proved difficult to prepare a pure sample of this compound, in view of the easy resolution of the amidine with the mandelic acids.³ However, a specimen, $[\alpha] +40.1^\circ$ (in methanol) [specific rotation calculated on the basis of the best values obtained for the diastereoisomers would give $[\alpha] +59.0^\circ$, approximately, for the (±)-amidinium (+)-mandelate] was heated at 160° for 7 minutes, then purified. (–)-*o*-Methoxymandelamidinium (+)-mandelate, $[\alpha] -30.4^\circ$ (in methanol), resulted in 85% yield, and which gave optically pure (–)-amidinium chloride and (+)-mandelic acid on treatment with methanolic hydrogen chloride.

Similarly, (+)-*o*-ethoxymandelamidinium (+)-mandelate, $[\alpha] +133.0^\circ$ (in methanol), underwent inversion at the amidinium centre when heated at 142° for 10 minutes. Some decomposition again took place, but the residual sample proved to be (–)-amidinium (+)-mandelate, $[\alpha] -32.6^\circ$ (in methanol) [lit.,³ $[\alpha] -33.5^\circ$ (in methanol)], from which there was obtained (–)-*o*-ethoxymandelamidinium chloride, $[\alpha] -99.6^\circ$ (in water).

When (–)-mandelamidinium (–)-mandelate, $[\alpha] -114.0^\circ$ (in methanol) [lit.,² $[\alpha] -122.0^\circ$ (in methanol)], was heated at 155° for 10 minutes, some decomposition took place but the recovered material was virtually unchanged in specific rotation. However, when the temperature was elevated to 165°, despite marked decomposition, there was obtained (+)-mandelamidinium (–)-mandelate, $[\alpha] -23.1^\circ$ (in methanol), as against $[\alpha] \sim 0.0^\circ$ (in methanol) for the optically pure compound (cf. Experimental section). The large loss due to decomposition makes this system less reliable, but again inversion of configuration has taken place on the amidinium moiety.

Despite the fact that we have carried out the resolution of several alkoxy-³ and chloro-mandelamidines⁴ we have found no evidence for second-order asymmetric transformations^{1,5} taking place at the lower temperatures employed for resolution, *e.g.*, we have never obtained more than 50% of one diastereoisomer and hence we conclude that these are true resolutions.

A possible mechanism for the reaction would involve the removal of a proton from the α -hydroxy-amidinium centre giving the somewhat unstable intermediate (I) which could then be re-protonated under the influence of the optically stable centre situated on the mandelic acid to give the more stable diastereoisomer.



As no special precautions were taken with the glass-ware it is feasible that either the mandelate ion, or traces of alkali in the glass or even traces of basic decomposition products could act as proton acceptors and catalyse the inversion. The very high degree of optical inversion may well be accounted for by the close packing of the molecules in the solid phase

⁴ Neilson and Roach, unpublished observations.

⁵ Harris, "Progress in Stereochemistry," Vol. 2, Butterworths, 1958, p. 157.

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which appears to be maintained during the reaction resulting in a greater influence of the stable centre on the labile one than would be possible in solution.

Furthermore, this interconversion of diastereoisomers would add weight to our belief that the *o*-ethoxy- and *o*-methoxy-mandelamidinium chlorides were completely resolved by means of the mandelic acids,³ in that the samples obtained by direct resolution and by this method agree in specific rotation within reasonable experimental error.

EXPERIMENTAL

Optically-active Mandelic Acids.—These acids, $[\alpha] \pm 180^\circ$ (in acetone) were converted into their sodium salts as previously reported.^{6,7}

Specific Rotations.—All specific rotations were measured in a 2-dm. tube with methanol as solvent for all amidinium mandelates and water in the case of all amidinium chlorides.

(-)-*o*-Methoxymandelamidinium (-)-Mandelate.—This salt³ (1 g.), $[\alpha] -134.6^\circ$ (quoted,³ $[\alpha] -131.5^\circ$) was heated for 7 min. at 155–160° in a Pyrex tube immersed in an oil-bath. Slight melting with partial decomposition took place, and the residual brown solid was purified by treatment with alcohol-ether. The resultant salt (0.7 g.), $[\alpha] +30.4^\circ$ (*c* 1.08), did not depress the m. p. of authentic (+)-*o*-methoxymandelamidinium (-)-mandelate (lit.,³ m. p. 193–194°, $[\alpha] -30.4^\circ$ for the (-)-(+)-isomer). Treatment of this salt with methanolic hydrogen chloride and isolation of the resultant hydrochloride by means of ether gave (+)-*o*-methoxymandelamidinium chloride (0.3 g.), $[\alpha] +103.8^\circ$ (*c* 1.07), which did not depress the m. p. of an authentic sample (quoted³ $[\alpha] +105.2^\circ$).

(-)-*o*-Methoxymandelamidinium (+)-Mandelate.—This salt³ (1 g.), $[\alpha] -30.8^\circ$ (*c* 0.58), was treated as above. The resultant solid (0.8 g.), which did not depress the m. p. of starting material, had $[\alpha] -31.2^\circ$ (*c* 1.12) and gave (-)-amidinium chloride (0.4 g.), $[\alpha] -105.0^\circ$ (*c* 1.2), in the usual way.

(±)-*o*-Methoxymandelamidinium (+)-Mandelate.—The (±)-amidinium chloride (15 g.) was stirred with sodium hydroxide solution (2.8 g. in 24 ml.) giving (±)-*o*-methoxymandelamidinium (7.8 g.) which was filtered off, washed with a little water, and dried *in vacuo*. The (±)-amidine (5.0 g.) and (+)-mandelic acid (4.1 g.) were dissolved in methanol (25 ml.) and after several hours were treated with an excess of anhydrous ether. There resulted salt (7.2 g.), $[\alpha] +40.1^\circ$ (*c* 1.53), which with methanolic hydrogen chloride gave amidinium chloride, $[\alpha] -15.3^\circ$ (*c* 1.17).

The amidinium (+)-mandelate (0.6 g.), $[\alpha] +40.1^\circ$, was heated at 160° for 7 min. and worked up as before. There resulted (-)-amidinium (+)-mandelate (0.52 g.), $[\alpha] -30.4^\circ$ (*c* 1.28), which after being kept with methanolic hydrogen chloride and then treated with anhydrous ether, gave (-)-*o*-methoxymandelamidinium chloride, $[\alpha] -106.5^\circ$ (*c* 1.0), and (+)-mandelic acid, $[\alpha] +180.0^\circ$ (*c* 1.05 in acetone). Both these substances exhibited no depression of m. p. with known samples.

(+)-*o*-Ethoxymandelamidinium (+)-Mandelate.—(+)-Amidinium (+)-mandelate (0.25 g.), $[\alpha] +133.0^\circ$ (*c* 1.03) (lit.,³ $[\alpha] +133.0^\circ$), was heated for 10 min. at 140–142°. After partial melting there resulted a yellow solid, which was purified as before, giving (-)-*o*-ethoxymandelamidinium (+)-mandelate (0.18 g.), $[\alpha] -32.6^\circ$ (*c* 0.89) (quoted³ $[\alpha] -33.5^\circ$). Decomposition with hydrogen chloride gave (-)-*o*-ethoxymandelamidinium chloride $[\alpha] -99.6^\circ$ (*c* 0.36) (lit.,³ $[\alpha] -107.5^\circ$), and which gave no depression of m. p. with an authentic specimen.

Resolution of (±)-Mandelamidinium Chloride. Sodium (+)-mandelate (8.7 g.) and (±)-amidinium chloride (9.3 g.) were heated in water (75 ml.). Cooling gave amidinium (+)-mandelate (6.5 g.), crop A $[\alpha] +51.4^\circ$ (*c* 0.63), which in turn gave (-)-amidinium chloride $[\alpha] -6.2^\circ$ with methanolic hydrogen chloride. Crop A was then recrystallised successively from 50% aqueous acetone (25, 25, 10, 15, 10 ml. portions) giving (-)-mandelamidinium (+)-mandelate (0.1 g.), $[\alpha] \sim 0.0^\circ$ (*c* 0.36), m. p. 171–172° (decomp.). A larger sample of this rotation obtained from various sources was decomposed in the usual way to give (-)-mandelamidinium chloride, $[\alpha] -90.0^\circ$ (*c* 0.34), which melted at 166–167°, resolidified above 170°, and remelted 210–212° (decomp.). Authentic material obtained from amygdalin^{8,9} gave no depression in m. p. (Reid^{2,9} records $[\alpha] -88.9^\circ$, m. p. as above for the amidinium chloride).

⁶ Roger, *J.*, 1935, 1544.

⁷ Neilson and Peters, *J.*, 1962, 1309.

⁸ Neilson and Peters, *J.*, 1962, 2272.

⁹ Roger and Neilson, *J.*, 1960, 627.

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(-)-Mandelamidinium (-)-Mandelate.—Ethyl (-)-mandelimidate hydrochloride was prepared by the method of Roger and Reid,^{2,8} and converted into (-)-mandelamidinium chloride by interaction with an equimolar solution of anhydrous ammonia in ethanol⁹ (excess of ammonia caused racemisation²). The (-)-amidinium chloride (0.93 g.), $[\alpha] -90^\circ$, and sodium (-)-mandelate (0.87 g.), $[\alpha] -116^\circ$ (in water), were heated in water (7 ml.), and the crystals which formed were recrystallised once from water and finally treated with alcohol-ether. (-)-Mandelamidinium (-)-mandelate (0.65 g.) had $[\alpha] -114.0^\circ$ (*c* 0.31), m. p. 171–172° (Roger and Reid² record $[\alpha] -122.0^\circ$).

The (-)-amidinium (-)-mandelate (0.65 g.) was heated at 154–158° for 10 min. The material recovered proved to be unchanged (-)-amidinium (-)-mandelate, $[\alpha] -116.1^\circ$ (*c* 1.2 g.). A further sample (0.38 g.) was heated at 163–165° for 7 min.; marked decomposition was observed, only 0.15 g. of material being recovered. This had $[\alpha] -23.1$ (*c* 0.4) and on treatment with methanolic hydrogen chloride afforded (+)-mandelamidinium chloride, $[\alpha] +28.1^\circ$ (*c* 0.25), *i.e.*, about 30% of optical purity.

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CHEMISTRY DEPARTMENT, QUEEN'S COLLEGE,
UNIVERSITY OF ST. ANDREWS, DUNDEE.

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