247. *The Use of Mandelic Acids in the Resolution of α-Hydroxy-amidinium Chlorides.*

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(±)-Lactamidinium chloride has been resolved by means of she optically active mandelic acids. Optically active 2-1′-hydroxyethylbenzimidazoles prepared from the amidinium chlorides pointed to the latter compounds' having an optical purity of approximately 95%. No resolution was obtained for α-hydroxyvaleramidinium chloride with these reagents, but (±)-4-methoxymandelamidinium chloride was readily resolved and then considered to be optically pure.

Roger and Neilson [1,2] have resolved a series of (±)-α-hydroxy-amidinium chlorides (I; R = H, Me, or Et, R′ = Ph) and (II) by using (+)- and (−)-mandelic acid.[3] In an attempt to prepare other optically active amidines in which the α-hydroxy-group was secondary we studied the compounds (I; R = H, R′ = Me, Pr^n, and *p*-MeO·C$_6$H$_4$).

(I) RR′C(OH)·C(:NH$_2$Cl)·NH$_2$ Ph·CHMe·CH(OH)·C(:NH$_2$Cl)·NH$_2$ (II)

(±)-Lactamidinium chloride (I; R = H, R′ = Me) was prepared by the Pinner method [4] from the cyanohydrin. With an equimolar amount of sodium (+)-mandelate in water it gave a salt which after three further crystallisations from water had $[\alpha]_{5461}^{19}$ +61° (in methanol) and with ethanolic hydrogen chloride yielded (−)-lactamidinium chloride, $[\alpha]_{5461}^{18}$ −16·5° (in water). (+)-Lactamidinium chloride, similarly prepared by the use of sodium (−)-mandelate had $[\alpha]_{5461}^{22}$ +16·8° (in water).

The configuration and optical purity of the compounds (I; R = Me or Et, R′ = Ph) have been determined by hydrolysis to the parent acid.[1] However, in addition to having low melting points, the lactic acids have low and temperature-sensitive specific rotations and hence are of little use in the characterisation of the amidines. On the other hand, Moore, Dimler, and Link [5,6] have described the optically active 2-1′-hydroxyethylbenzimidazoles, $[\alpha]_D$ ±33·4° (in ethanol; *c* 4·0). Accordingly, (+)-lactamidinium chloride, $[\alpha]_{5461}$ +16·6°, was converted into lactic acid by the action of hot sodium hydroxide solution and then by the action of *o*-phenylenediamine into (+)-2-1′-hydroxyethylbenzimidazole which had $[\alpha]_D^{20}$ +32·0° (*c* 0·48 in ethanol). Direct interaction of (−)-lactamidinium chloride, $[\alpha]_{5461}$ −15·3°, with the diamine gave a (−)-benzimidazole, $[\alpha]_D$ −28·8° (*c* 0·28 in ethanol). The exact procedure of Moore, Dimler, and Link [5] for purification of the benzimidazole by means of its silver complex was not followed as α-hydroxy-amidines themselves act as ligands.[7] Calculations from the foregoing figures point to the lactamidinium chlorides' having $[\alpha]_{5461}$ ± 17·5° (±0·2°) (in water) as their maximum specific rotations. However, the specific rotations of the benzimidazoles fall with decreasing concentration [5] but there are no data for the low concentrations used by us, so the purity of our lactamidinium chlorides may be better than represented by calculation. In addition, as the (+)-benzimidazole belongs to the D-series, being derived from (−)-lactic acid,[5,6] (+)-lactamidinium chloride also has the D-configuration.

(±)-α-Hydroxyvaleramidinium chloride, synthesised by the Pinner method from butyraldehyde cyanohydrin, formed salts with the (+)- and (−)-mandelic acid but no separation of the diastereoisomers was observed in water, methanol, ethanol, propan-1-ol, butan-1-ol, benzene–methanol, or dioxan.

[1] Roger and Neilson, *J.*, 1959, 688; 1961, 3181.
[2] Roger and Neilson, *J.*, 1960, 627; Neilson, Ph.D. Thesis, St. Andrews, 1955.
[3] Roger, *J.*, 1935, 1544.
[4] Pinner, "Die Imidoäther und ihre Derivate," Oppenheim, Berlin, 1892; Roger and Neilson, *Chem. Rev.*, 1961, **61**, 179.
[5] Moore, Dimler, and Link, *Ind. Eng. Chem., Analyt.*, 1941, **13**, 160.
[6] Dimler and Link, *J. Biol. Chem.*, 1942, **143**, 557.
[7] Gould, Jameson, and Neilson, *Proc. Chem. Soc.*, 1960, 314; Gould and Jameson, *J.*, 1962, 296.

4-Methoxybenzaldehyde similarly gave 4-methoxymandelamidinium chloride. The (+)-amidinium (+)-mandelate which was obtained and separated when recrystallised four times from ethanol had constant $[\alpha]_{5461}$ +119·0° (in methanol). This salt yielded (+)-4-methoxymandelamidinium chloride, $[\alpha]_{5461}$ +87·8° (in water). Similarly (−)-amidinium (−)-mandelate, $[\alpha]_{5461}$ −119·0° (in methanol), gave the (−)-amidinium chloride, $[\alpha]_{5461}$ −87·9° (in water). As McKenzie and Pirie [8] have described the optically active 4-methoxymandelic acids and amides, (+)-4-methoxymandelamidinium chloride was hydrolysed with alkali but complete racemisation took place. McKenzie and Pirie [8] reported similar racemisation of the (−)-amide. On the other hand, Roger and Reid [9] were able to isolate (+)-mandelamide and (+)-mandelic acid, both of high optical purity, after reaction of (+)-mandelamidinium chloride with 4N-sodium hydroxide for 48 hr. Assignment of configuration cannot, therefore, be made. The amidines are believed to be optically pure, as the mandelates had reached constant activity but this cannot be checked by reference to the acids.

(+)- and (−)-4-Methoxymandelamidinium chloride, like (+)- and (−)-mandelamidinium chloride,[2] have double melting points; it is suggested that racemisation takes place at the lower melting point, as solid recovered at this temperature (~218°) was found after purification to be the (±)-salt and have only the higher melting point.

Experimental

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

Optically Active Mandelic Acids.—The acids,[3] $[\alpha]_{5461} > \pm 185°$ (in acetone), were neutralised with the calculated quantity of sodium hydrogen carbonate solution, the solutions were evaporated, and the salts recrystallised from aqueous alcohol.

(±)-*Amidinium Chlorides.*—Commercial crude lactonitrile was converted by way of ethyl (±)-lactimidate hydrochloride, m. p. 76° (decomp.) (lit.,[10] 79°), into (±)-lactamidinium chloride, m. p. 161—164° (lit.,[11] 162—166°).

n-Butyraldehyde (144 g.) was converted through the bisulphite complex into its cyanohydrin (82·1 g.), b. p. 128—130°/19 mm. in the presence of iodine as stabiliser,[12] and this with methanol and hydrogen chloride furnished methyl (±)-α-hydroxyvalerimidate hydrochloride (74·5 g.). Reaction with alcoholic ammonia then formed (±)-α-*hydroxyvaleramidinium chloride* (43 g.), m. p. 147—148° (Found: Cl, 23·3. $C_5H_{13}ClN_2O$ requires Cl, 23·25%).

Crude *p*-anisaldehyde cyanohydrin gave similarly methyl (±)-4-methoxymandelimidate hydrochloride (71%), m. p. 104—105° (decomp.), and the ethyl derivative (56%), m. p. 120—121° (decomp.), and these with alcoholic ammonia gave the (±)-amidinium chloride (51%), m. p. 233—234° (decomp.).

Resolution of (±)-*Lactamidinium Chloride.*—(±)-Lactamidinium chloride (12·4 g.) and sodium (+)-mandelate (17·4 g.) were heated in water (50 ml.), filtered hot, and set aside. The resultant solid recrystallised from water (15, 10, and 10 ml. portions), giving (−)-*lactamidinium* (+)-*mandelate* (3 g.), $[\alpha]_{5461}^{20}$ +61·0° (*c* 0·91 in methanol), which softened at 168°, became yellow and melted at 171—173° (Found: C, 54·9; H, 7·2; N, 11·3. $C_{11}H_{16}N_2O_4$ requires C, 55·0; H, 6·7; N, 11·7%).

Reaction as above with sodium (−)-mandelate gave (+)-*lactamidinium* (−)-*mandelate*, $[\alpha]_{5461}^{20}$ −61·4° (*c* 1·56 in methanol), which softened at 168°, became yellow and melted at 170—172° (Found: C, 55·1; H, 6·6; N, 11·6%).

(±)-Lactamidinium (±)-mandelate had m. p. 165—166° (Found: C, 55·2; H, 6·8; N, 11·9%).

(+)- and (−)-Mandelate were treated separately with ethanolic hydrogen chloride. After 48 hr., the solutions were evaporated *in vacuo* and the residues treated with hot benzene–acetone to remove mandelic acid. The residues were dissolved in alcohol and reprecipitated

[8] McKenzie and Pirie, *Ber.*, 1936, **69**, 861.
[9] Reid, Ph.D. Thesis, St. Andrews, 1949.
[10] Houben and Pfankuch, *Ber.*, 1926, **59**, 2397.
[11] Fanta and Hedman, *J. Amer. Chem. Soc.*, 1956, **78**, 1434.
[12] Hansley, U.S.P. 2,416,624.

with ether, giving (−)-, $[\alpha]_{5461}^{18}$ −16·5° (*c* 0·95 in water), m. p. 148—149° (decomp.) (Found: C, 29·3; H, 7·1; N, 22·7. $C_3H_9ClN_2O$ requires C, 28·9; H, 7·2; N, 22·5%), and (+)-*lactamidinium chloride*, m. p. 148—150° (decomp.), $[\alpha]_{5461}^{22}$ +16·8° (*c* 1·5 in water) (Found: C, 29·2; H, 7·6; N, 23·2%).

(+)-Lactamidinium chloride (1·3 g.), $[\alpha]_{5461}^{21}$ +16·6° (in water), was heated with sodium hydroxide solution for 4 hr. The solution was acidified, and extracted with ether and the extract dried (Na_2SO_4). The crude acid from this extract was heated under reflux with *o*-phenylenediamine (0·3 g.) in 5N-hydrochloric acid (4 ml.) for 1 hr. Ammonia was added to the cooled solution, and the precipitated benzimidazole was washed with water and ether and recrystallised from water. (+)-2-1′-Hydroxyethylbenzimidazole (0·12 g.) softened at 173°, melted at 174—176°, and had $[\alpha]_D^{20}$ +32·0° (*c* 0·48 in ethanol) {lit.,[6] m. p. 175—177°, $[\alpha]_D$ ±33·4° (*c* 4·0 in ethanol)}.

(−)-Lactamidinium chloride (0·7 g.), $[\alpha]_{5461}^{18}$ −15·3° (in water), and *o*-phenylenediamine (0·5 g.) were boiled in ethanol for 8 hr. The alcohol was then removed *in vacuo*, the residue dissolved in dilute hydrochloric acid, and the benzimidazole precipitated with ammonia. The benzimidazole (0·1 g.), after crystallisation from water (charcoal), had m. p. 174—176°, $[\alpha]_D^{19}$ −28·8° (*c* 0·28 in ethanol; *l* 4).

Attempted Resolution of (±)-α-*Hydroxyvaleramidinium Chloride.*—The (±)-amidinium chloride (20 g.) was treated with sodium (+)-mandelate (23 g.) in water (50 ml.). The resultant (+)-mandelate (11·3 g.) was recrystallised six times from ethanol and had $[\alpha]_{5461}^{18}$ +65·5° (*c* 0·51 in methanol), virtually the same as that of earlier crops. The amidinium chloride, re-formed in the usual way, had m. p. 147—148°, $[\alpha]_{5461}$ 0·0° (in water). Disodium (+)-tartrate and sodium hydrogen (+)-tartrate did not yield crystalline salts with the (±)-amidinium chloride.

Resolution of (±)-4-*Methoxymandelamidinium Chloride.*—The (±)-amidinium chloride (50 g.) and sodium (+)-mandelate (40 g.) were heated in boiling water (200 ml.). After 12 hr. at room temperature, the resultant solid (33·5 g.) was collected, washed with water, and recrystallised from ethanol (4 × 150 ml.). $[\alpha]_{5461}^{21}$ of the amidinium (+)-mandelate rose from +72·7° to +119·0° (*c* 0·28 in methanol; *l* 1) and was not raised on further crystallisation from ethanol (150 ml.). (+)-4-*Methoxymandelamidinium* (+)-*mandelate* (13·5 g.) melted at 164—165° (Found: C, 61·3; H, 5·9. $C_{17}H_{20}N_2O_5$ requires C, 61·5; H, 6·0%).

(−)-4-Methoxymandelamidinium (−)-mandelate, prepared as above but using sodium (−)-mandelate, had $[\alpha]_{5461}^{21}$ −119·0° (*c* 0·42 in methanol), m. p. 163—164°.

The mandelates were treated with methanolic hydrogen chloride for 18 hr. and the products worked up as above, giving (+)-, m. p. 215°, resolidifies, and remelts 233—234°, $[\alpha]_{5461}^{22}$ +87·8° (*c* 0·56 in water) (Found: C, 49·4; H, 6·2; N, 12·7. $C_9H_{13}ClN_2O_2$ requires C, 49·7; H, 6·0; N, 12·9%), and (−)-4-*methoxymandelamidinium chloride*, $[\alpha]_{5461}^{22}$ −87·9° (*c* 0·44 in water), m. p. 213°, resolidifies, remelts 232—233° (decomp.) (Found: C, 49·95; H, 5·8; N, 12·6%).

(+)-4-Methoxymandelamidinium chloride was heated at 213—218° until melting was complete and then allowed to solidify. After purification from alcohol–ether the product was the (±)-amidinium chloride, m. p. and mixed m. p. 233—234°.

The (+)-amidinium chloride (1 mol.) was left in 5N-sodium hydroxide (2·2 mol.) overnight. The resultant solid, after crystallisation from alcohol, gave no m. p. depression with authentic (±)-4-methoxymandelamide and had $[\alpha]_{5461}$ 0·0° (in water).

(±)-4-*Methoxymandelamidinium* (±)-*mandelate* had m. p. 165—166° (Found: N, 8·5. $C_{17}H_{20}N_2O_5$ requires N, 8·4%).

We thank the Department of Scientific and Industrial Research for a Grant (to D. A. V. P.) and Queen's College, Dundee, for an Edward A. Deeds Research Fellowship in Chemistry (to D. G. N.).

DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ST. ANDREWS,
QUEEN'S COLLEGE, DUNDEE. [*Received, November 24th*, 1961.]