123. *The Resolution of Some Substituted Lactamidines and Atrolactamidines by means of the Mandelic Acids.*

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m- and *p*-Methylatrolactamidines were prepared from the corresponding methylacetophenones and were resolved by means of the mandelic acids. *o*-Methylacetophenone failed to give an amidine. α-Benzyl-lactamidine was also resolved by means of these acids but β-phenyllactamidine showed no separation of the diastereoisomeris.

Continuing the study of optically active amidines,[1,2] we turned attention to a series of methyl-substituted atrolactamidinium chlorides in order to obtain further amidines which are less susceptible to base-catalysed racemisation than are the substituted mandelamidines.[2] Although it was not possible to convert *o*-methylacetophenone into its cyanohydrin by the standard procedure,[1] both the (±)-*m*- and (±)-*p*-methylatrolactamidinium chlorides were readily available by the Pinner synthesis [3,4] after the cyanohydrins had been purified by distillation in the presence of iodine.[5]

$\mathrm{Me{\cdot}C_6H_4{\cdot}CMe(OH){\cdot}C(NH_2){:}NH_2Cl}$ (I); a, *p* b, *m*

$\mathrm{PhCH_2{\cdot}CR(OH){\cdot}C(NH_2){:}NH_2Cl}$ (II); a, R = Me b, R = H

(±)-*p*-Methylatrolactamidinium chloride (Ia) with sodium (−)-mandelate afforded optically pure (+)-amidinium (−)-mandelate after four crystallisations from water. When (+)-*p*-methylatrolactamidinium chloride, [α] +62·6° (in water),* obtained from the mandelate by the action of hydrogen chloride in alcohol, was hydrolysed with hot sodium hydroxide solution, (+)-*p*-methylatrolactic acid, [α] + 52·9° (in ethanol), was obtained. Christie, McKenzie, and Ritchie [6] quote [α] −51·2° (in ethanol) for acid obtained by direct resolution, but their method leads to very small yields of the acid and furthermore no claim is made that, even after ten crystallisations, optical purity has been reached. The (−)-amidinium chloride was obtained similarly using (+)-mandelic acid. Interaction of (±)- and (−)-amidinium chlorides with ethylenediamine in alcohol gave the corresponding (±)- and (−)-2-(α-hydroxy-α-*p*-tolylethyl)imidazolinium chlorides which proved to be extremely hygroscopic and had to be converted into the more manageable picrates.

The isomeric (±)-*m*-methylatrolactamidinium chloride (Ib) was also resolved by means of sodium (+)-mandelate which gave, after four crystallisations from water, optically pure (−)-amidinium (+)-mandelate which in turn afforded (−)-amidinium chloride, [α] −65·3° (in water). Unfortunately, although the resolution gives reasonable yields of one

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* [α] was measured at 5461 Å, unless otherwise stated.

[1] Roger and Neilson, *J.*, 1959, 688; 1961, 3181.

[2] Neilson and Peters, *J.*, (*a*) 1962, 1309; (*b*) 1963, 4455.

[3] Pinner, " Die Imidoänther und ihre Derivate," Oppenheim, Berlin, 1892.

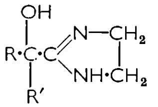
[4] Roger and Neilson, *Chem. Rev.*, 1961, **61**, 179.

[5] Hansley, U.S.P. 2,416,624 (*Chem. Abs.*, 1947, **41**, 3483).

[6] Christie, McKenzie, and Ritchie, *J.*, 1935, 153.

diastereoisomer, our initial yields of cyanohydrin were small and the final samples were too small to undertake further synthetic work.

α-Benzyl-lactamidinium chloride (IIa) was prepared from benzyl methyl ketone, but unfortunately this system showed a marked tendency to produce oils at every stage. (±)-Amidinium chloride with sodium (+)-mandelate, after treatment with various solvents, gave a solid which on further crystallisation from propan-2-ol furnished optically pure (+)-amidinium (+)-mandelate, [α] +86·6° (in methanol). The original liquors on being worked up gave more solid which, after recrystallisation from acetone–ethyl methyl ketone, proved to be (—)-amidinium (+)-mandelate, [α] +18·5° (in methanol). The diastereoisomeric mandelates yielded amidinium chlorides, [α] +52·3 and —50·9° (in methanol) respectively, in the usual way. (+)-Amidinium chloride, [α] +52·3°, was hydrolysed to (+)-α-benzyl-lactic acid, [α] +19·4° (in dioxan), in good agreement with the literature [7] value, [α] +20·0° (in dioxan). (±)- and (+)-2-(α-Benzyl-α-hydroxyethyl)imidazolines were prepared by the interaction of the respective amidinium chlorides and ethylenediamine. The (+)-imidazoline had [α] +44·6° (in methanol), and [α] +56·4° on protonation by the addition of a few drops of concentrated hydrochloric acid. In earlier work [8] we drew attention to the fact that " the α-hydroxy-imidazolines have an ' inverse ' system to that of the α-amino-acids, having a terminal, basic amidino-group within the ring system and a weakly acidic α-hydroxygroup " and that comparison with the work of Lutz and Jirgensons [9] on the effect of pH on the specific rotation of α-amino-acids might prove useful. Imidazolines (III) derived from lactic acid [10] (IIIa), mandelic acid [10] (IIIb), atrolactic acid [8] (IIIc) and α-hydroxy-α-phenylbutyric acid [8] (IIId) systems, have been shown to have a positive shift in specific rotation on protonation if the configuration at the α-hydroxy-centre is L. (The L-(+) configuration has just recently been assigned [11] to α-hydroxy-α-phenylbutyric acid and hence the (+)-amidinium chloride and (+)-imidazolinium chloride [8] can now also be assigned the L-configuration.) On this basis we *very tentatively* suggest that the (+)-imidazoline (III; R = Me–, R′ = Bz–), the (+)-amidinium chloride, and (+)-α-benzyl-lactic acid are of the L-configuration.


(III)

a, R = H-; R′ = Me-
b, R = H-; R′ = Ph-
c, R = Me-; R′ = Ph-
d, R = Et-; R′ = Ph-

Phenylacetaldehyde was similarly converted into β-phenyl-lactamidinium chloride (IIb), but this substance did not show any separation of the diastereoisomers on treatment with sodium (+)-mandelate. As (±)- and (+)-*o*-methoxymandelamidinium (+)-mandelates have been shown to be transformed into the more stable (—)-amidinium (+)-mandelate in about 85% yield on being heated at their respective melting points,[12] this technique was applied to (±)-β-phenyl-lactamidinium (+)-mandelate, but both diastereoisomers appeared to have about the same stability towards heat as no change in specific rotation was observed using this method.

EXPERIMENTAL

All specific rotations were measured in a 2-dm. tube at 5461 Å within the temperature range 18—20° unless otherwise stated.

Mandelic Acids.—These acids had [α] ±180° and were converted into their sodium salts as previously reported.[2a,13]

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[7] Davies, Ebeid, and Kenyon, *J.*, 1957, 3154.
[8] Neilson, Peters, and Roach, *J.*, 1962, 2272.
[9] Lutz and Jirgensons, *Ber.*, 1930, **63**, 448; 1931, **64**, 1221.
[10] Neilson, unpublished observation.
[11] Mitsui, Imaizumi, Senda, and Konno, *Chem. and Ind.*, 1964, 233.
[12] Bellingham, Peters, and Neilson, *J.*, 1964, 2118.
[13] Roger, *J.*, 1935, 1544.

Methylacetophenone Cyanohydrins.—The *o*- and *m*-methylacetophenones were prepared by the method of Pearson and Cole [14] from the corresponding tolunitriles giving the *o*-isomer, b. p. 92—94°/12 mm. (reported,[14] b. p. 67°/3 mm.), and the *m*-isomer, b. p. 91—93°/9 mm. (reported [15] b. p. 109°/12 mm.). The *para*-isomer is available commercially. In a typical preparation, ketone (134 g.) in ether (100 ml.) was stirred at 0° with sodium cyanide (123 g.) in water (150 ml.) whilst concentrated hydrochloric acid (210 ml.) was added during 2 hr. Stirring was then continued for a further 2 hr. at 0° and the solution was then extracted with ether. The dried extract ($MgSO_4$) was distilled in the presence of iodine (1 g.) as stabiliser.[5] No cyanohydrin was obtained from the *ortho*-isomer, and ketone, b. p. 91—93°/13 mm. was recovered. *m*-Methylatrolactonitrile had b. p. 150—152°/10 mm. (28% yield) and *p*-methylatrolactonitrile had b. p. 156°/22 mm., m. p. 60—61° (25% yield).

(±)-*Methylatrolactimidate Hydrochlorides.*—*p*-Methylatrolactonitrile (39 g.) was dissolved in anhydrous ethanol (16 ml.) and ether (30 ml.), then anhydrous hydrogen chloride was passed in at 0°. After 24 hr. at 0°, *ethyl* p-*methylatrolactimidate* hydrochloride, m. p. 112° (decomp.), was precipitated on the addition of anhydrous ether (Found: Cl, 14·9. $C_{12}H_{18}ClNO_2$ requires Cl, 14·6%).

Ethyl (±)-p-*methylatrolactimidate* (1·4 g.), m. p. 81—82°, was prepared from its hydrochloride (2 g.) by treatment with excess of sodium hydroxide solution (4N), followed by extraction with ether and recrystallisation of the resultant base from petrol (b. p. 60—80°) (Found: C, 69·5; H, 8·1. $C_{12}H_{17}NO_2$ requires C, 69·5; H, 8·3%).

Ethyl (±)-*m*-methylatrolactimidate hydrochloride prepared similarly in 40% yield had m. p. 62° (decomp.).

(±)-*Methylatrolactamidinium Chlorides.*—The imidates (0·1 mole) were shaken with anhydrous alcoholic ammonia (8·5 g./100 ml.) solution for 6—10 hr. at room temperature, and the solvent was then evaporated *in vacuo*. The resultant oils were taken up in the minimum of hot ethanol, dry hydrogen chloride passed in, and the amidinium chlorides precipitated with anhydrous ether. After crystallisation from hydrochloric acid solution (5N) (±)-p-*methylatrolactamidinium chloride* had m. p. 146—147° (Found: Cl, 16·7. $C_{10}H_{15}ClN_2O$ requires Cl, 16·6%); (±)-m-*methylatrolactamidinium chloride* had m. p. 199° (Found: C, 55·7; H, 7·1. $C_{10}H_{15}ClN_2O$ requires C, 56·0; H, 7·0%). Attempts to prepare (±)-*p*-methylatrolactamidine by treatment of the hydrochloride with sodium hydroxide solution (4N) yielded no crystalline product.

Resolution via *the Mandelic Acids.*—(±)-p-*Methylatrolactamidinium chloride.* (±)-Amidinium chloride (10 g.) and sodium (−)-mandelate (8·1 g.) were heated in water (70 ml.); the volume of water was quite critical, smaller amounts yielding only oils. After 3 days the solid was removed and crystallised 4 times from water to give (+)-p-*methylatrolactamidinium* (−)-*mandelate* (A) (3 g.), [α] −6·0° (*c* 0·54 in methanol), which softened at 164° and melted at 167—169° (Found: C, 65·3; H, 6·9. $C_{18}H_{22}N_2O_4$ requires C, 65·5; H, 6·7%). Similarly sodium (+)-mandelate afforded (−)-amidinium (+)-mandelate (B), [α] +6·9° (*c* 1·15 in methanol), after 4 crystallisations from water. (±)-*Amidinium* (±)-*mandelate* prepared as above had m. p. 159—160° (Found: C, 65·5; H, 6·7%).

The amidinium mandelate in ethanol was treated with hydrogen chloride and after several hours the solvent was removed *in vacuo*, the residue treated with hot benzene–acetone to remove mandelic acid, and the amidinium chloride recrystallised in almost theoretical yield from ethanol–ether. In this way (A) afforded (+)-p-*methylatrolactamidinium chloride*, [α] +62·1° (*c* 1·21 in water), which softened at 163° and melted at 164—165° (Found: C, 55·8; H, 6·9. $C_{10}H_{15}ClN_2O$ requires C, 56·0; H, 7·0%). Similarly (B) gave (−)-p-*methylatrolactamidinium chloride*, [α] −58·6° (*c* 0·92 in water), which softened at 163° and melted at 165° (Found: C, 56·0; H, 7·3%).

(±)-m-*Methylatrolactamidinium chloride.* (±)-Amidinium chloride (5·1 g.) and sodium (+)-mandelate (4·1 g.) were heated in water (30 ml.). After 5 days at 0°, solid deposited and this had constant rotation after 3 crystallisations from water. (−)-m-*Methylatrolactamidinium* (+)-*mandelate* (1·7 g.), [α] +7·2° (*c* 0·92 in methanol), had m. p. 166—167° (Found: C, 65·4; H, 6·7%), and on decomposition with ethanolic hydrogen chloride as above gave (−)-m-*methylatrolactamidinium chloride*, [α] −65·3° (*c* 0·8 in water), with m. p. 128—129° (Found: C, 55·7; H, 6·9%).

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[14] Pearson and Cole, *J. Org. Chem.*, 1955, **20**, 488.
[15] Auwers and Kolligs, *Ber.*, 1922, **55**, 41.

Methylatrolactic Acids.—The amidinium chloride was heated in a slight excess of sodium hydroxide solution (4N) until evolution of ammonia ceased. The acid, obtained by acidification, was extracted with ether, dried, and recrystallised from benzene—petrol (60—80°).

(*a*) (+)-*p*-Methylatrolactamidinium chloride, [α] +62·1°, afforded (+)-*p*-methylatrolactic acid, [α] +52·9° (*c* 0·7 in ethanol), m. p. 140—141° [lit.,[6] [α] −51·2° (in ethanol) and m. p. 140—142°]. The (±)-acid had m. p. 102—103° (lit.,[6] 102—104°).

(*b*) Similarly (−)-*m*-methylatrolactamidinium chloride, [α] −65·3°, furnished (−)-m-*methylatrolactic acid*, [α] −31·5° (in ethanol), m. p. 128—129° (Found: C, 66·5; H, 6·9. $C_{10}H_{12}O_3$ requires C, 66·7; H, 6·7%).

(±)- *and* (−)-2-(1-*Hydroxy*-1-p-*tolylethyl*)*imidazolinium Picrates.*—(±)-*p*-Methylatrolactamidinium chloride (1·2 g.) was heated with ethylenediamine (0·8 g.) in dry ethanol (10 ml.) for 3 hr. The solvent was removed *in vacuo* and the resultant oil treated at 0° with sodium hydroxide solution (5N). The crude imidazoline was crystallised from ethyl acetate yielding (±)-2-(1-*hydroxy*-1-*p*-*tolylethyl*)*imidazoline monohydrate* (0·8 g.) (Found: C, 65·0; H, 8·0. $C_{12}H_{16}N_2O,H_2O$ requires C, 65·1; H, 7·7%), m. p. 145—147° (decomp.). The hydrochloride was too hygroscopic to be handled.

(−)-*p*-Methylatrolactamidinium chloride, [α] −58·6° (in water), similarly yielded a crude imidazoline which failed to crystallise from common solvents. As the hydrochloride proved too hygroscopic to handle, the base was converted into the picrate and crystallised from aqueous methanol. (−)-2-(1-*Hydroxy*-1-*p*-*tolylethyl*)*imidazolinium picrate,* [α] −22·5° (*c* 0·71 in methanol), had m. p. 235° (decomp.) after softening at 230° (Found: C, 50·3; H, 4·7. $C_{18}H_{18}N_5O_8$ requires C, 50·0; H, 4·4%).

(±)-α-*Benzyl-lactamidinium Chloride.*—Benzyl methyl ketone bisulphite complex (208 g.) was stirred with potassium cyanide (65 g.) in water (200 ml.) for 2 hr. at 0°. The cyanohydrin was then extracted with ether and dried ($MgSO_4$), and the ether removed. The crude cyanohydrin (100 g.) was dissolved in dry ethanol (40 g.) and anhydrous hydrogen chloride (27 g.) passed in at 0°. The imidate hydrochloride failed to crystallise and so excess of hydrogen halide was removed *in vacuo* over solid sodium hydroxide. The resultant oil was treated with excess of alcoholic ammonia and ammonium chloride filtered off. Removal of the alcohol *in vacuo* followed by treatment of the crude amidine with dry ether gave α-*benzyl-lactamidinium chloride,* m. p. 166—167° (Found: C, 56·2; H, 7·2. $C_{10}H_{15}ClN_2O$ requires C, 56·0; H, 7·0%).

Resolution of (±)-α-*Benzyl-lactamidinium Chloride.*—(±)-Amidinium chloride (10 g.) and sodium (+)-mandelate (8 g.) were heated in water. Only an oil separated and the water was then evaporated off. The oily residue was taken up in ethanol and sodium chloride removed by filtration. Addition of ether to the oil produced, after 2 days at 0°, a solid (14 g.), m. p. 149—150°, [α] +50·6° (*c* 0·9 in methanol). The solid was recrystallised from propan-2-ol giving solid (A) (6 g.), [α] +80·0° (*c* 0·9 in methanol), m. p. 160—161°, as well as liquors (B). Crop (A) after 2 crystallisations from propan-2-ol gave (+)-α-*benzyl-lactamidinium* (+)-*mandelate* (2·6 g.), m. p. 170—171°, constant [α] +86·6° (*c* 1·1 in methanol) (Found: C, 65·8; H, 6·6. $C_{18}H_{22}N_2O_4$ requires C, 65·5; H, 6·7%). On partial evaporation, liquors (B) gave crop (D) (3·2 g.), which was worked up as above, and liquors (C). Fraction (C) was evaporated *in vacuo* to an oil which yielded solid (E) (2·7 g.), [α] +27·7° (*c* 0·62 in methanol), on treatment with ether. Crop (E) was recrystallised from acetone–ethyl methyl ketone to yield (−)-α-benzyl-lactamidinium (+)-mandelate, m. p. 165°, [α] +18·5° (*c* 0·72 in methanol).

The amidinium chlorides were re-formed as described above. Thus (+)-amidinium (+)-mandelate, [α] +86·6°, gave (+)-α-*benzyllactamidinium chloride,* [α] +52·3° (*c* 1·01 in methanol), m. p. 218—219° (decomp.) (Found: C, 55·8; H, 6·9. $C_{10}H_{15}ClN_2O$ requires C, 56·0; H, 7·0%). Similarly (−)-amidinium (+)-mandelate, [α] +18·5°, gave (−)-*amidinium chloride,* m. p. 212—213°, [α] −50·9° (*c* 1·2 in methanol) (Found: C, 55·6; H, 7·0%).

(±)- *and* (+)-α-*Benzyl-lactic Acids.*—By the method described above, (±)-α-benzyl-lactamidinium chloride (1 g.) gave (±)-α-benzyl-lactic acid (0·7 g.), m. p. 95—96° (lit.,[7] m. p. 95—97°). Similarly (+)-amidinium chloride (1 g.), [α] +52·3°, gave (+)-α-benzyl-lactic acid (0·5 g.), m. p. 119—120°, [α] +19·4° (*c* 0·61 in dioxan), [lit.,[7] m. p. 118—119° and [α] +20·0° (in dioxan)].

(±)- *and* (+)-2-(1-*Benzyl*-1-*hydroxyethyl*)*imidazolines.*—The (±)- and (+)-amidinium chlorides (1 g.), [α] +53·0°, were treated with ethylenediamine (0·5 g.) under reflux in ethanol for 6 hr. The solvent was partly removed *in vacuo* and sodium hydroxide solution (5N) added to give crude imidazoline. (±)-2-(1-*Benzyl*-1-*hydroxyethyl*)*imidazoline* after recrystallisation from ethyl acetate–ethanol was obtained as plates (0·6 g.), m. p. 171—172° (Found: C, 70·3; H, 7·6; N, 13·7. $C_{12}H_{16}N_2O$ requires C, 70·6; H, 7·9; N, 13·7%). Similarly the (+)-imidazoline after recrystallisation from benzene–cyclohexane had m. p. 144—145°, [α] +44·6° (*c* 0·8 in methanol), which became [α] +56·4° on addition of four drops of concentrated hydrochloric acid to the solution (Found: C, 70·4; H, 8·0; N, 13·9%).

(±)-β-*Phenyl-lactamidinium Chloride.*—Phenylacetaldehyde cyanohydrin was prepared by the methods of Ruggli and Hegedus [16] and of Levy [17] giving comparable yields (~35%). The cyanohydrin (25 g.) was dissolved in dry methanol (30 ml.) and ether (20 ml.) and anhydrous hydrogen chloride (6 g.) passed in at 0°. The product did not crystallise after 24 hr at 0°, so the solvent was removed and the resultant oil treated with anhydrous ether. *Methyl* β-*phenyl-lactimidatehydrochloride* (17 g.), had m. p. 95—96° (decomp.) (Found: Cl, 17·8. $C_9H_{14}ClNO_2$ requires Cl 17·4%); the ethyl imidate salt, prepared similarly, had m. p. 104—105° (decomp.). Methyl imidate salt (17 g.) was shaken for 6 hr. with anhydrous alcoholic ammonia (17 g. in 200 ml.). Some alcohol was then removed *in vacuo* and the crude amidinium chloride precipitated with ether. β-*Phenyl-lactamidinium chloride*, after recrystallisation from alcohol, had m. p. 165—166° (decomp.) (Found: C, 53·4; H, 6·7. $C_9H_{13}ClN_2O$ requires C, 53·8; H, 6·5%); or after recrystallisation from water, the *monohydrate* had m. p. 156—157° (decomp.) (Found: C 50·0; H, 7·0. $C_9H_{13}ClN_2O{\cdot}H_2O$ requires C, 49·5; H, 6·9%). The hydrate lost the equivalent of 17·8 g./mole at 100° *in vacuo.*

Attempted Resolution of β-*Phenyl-lactamidinium Chloride.*—(±)-Amidinium chloride (10·0 g.) and sodium (+)-mandelate (8·7 g.) were heated in water (70 ml.). Solid (11·2 g.), m. p. 156—157°, [α] +54·6° (*c* 0·91 in methanol), separated when the mixture was cooled. After 8 crystallisations from water the product had [α] +50·2° (*c* 0·79 in methanol), m. p. 158—159°. Repeated recrystallisation from ethanol, aqueous ethanol, acetone, and ethanol–ethyl acetate caused no significant change in rotation. The amidinium chloride, re-formed as above, had m. p. 165—166°, [α] 0·0 (in water).

The Effect of Heat on (±)-β-*Phenyl-lactamidinium* (+)-*Mandelate.*—(±)-β-Phenyl-lactamidinium (+)-mandelate (1 g.), [α] +49·3° (in methanol), was heated at 149° for 10 min. The solid was then taken up in ethanol and precipitated with ether giving almost unchanged material (0·8 g.), [α] +49·9° (*c* 1·2 in methanol). A sample (0·7 g.) was reheated for 20 min. at 149° and the resultant solid purified as before; it then had [α] +49·9° (*c* 0·87 in methanol). Amidinium chloride formed from these samples had [α] 0·0°.

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[16] Ruggli and Hegedus, *Helv. Chim. Acta*, 1942, **25**, 1285.

[17] Levy, *Bull. Soc. chim. France*, 1923, **33**, 1661.