137. *Studies in Stereochemical Structure. Part XII.* The Resolution of (±)-Atrolactamidinium Chloride.*

By R. Roger and D. G. Neilson.

(±)-Atrolactamidinium chloride has been prepared from acetophenone cyanohydrin *via* ethyl (±)-atrolactimidate hydrochloride. (±)-Atrolactamidine was resolved by separation of the diastereoisomeric salts with optical active mandelic acid. (−)-Atrolactic acid, isolated from (−)-atrolactamidinium chloride, was of at least 90% optical purity.

The amidines have been studied extensively;[1] few optically active amidines, however, have been described, although Cohen and Marshall[2] prepared and unsuccessfully attempted to resolve *N*-(−)-bornyl-*N*′-(+)-bornylbenzamidine with (+)-camphorsulphonic acid. The amidinium ion (I) so formed, however, is now known to be a *meso*-form[1] and hence cannot be resolved. Cohen and Marshall[2] also prepared substituted benzamidines [II; R = (−)-menthyl, R′ = Me, Et, and Ph] but in these the optically-active centres were constituents of the functional amidine groups.

(I) $[C_{10}H_{17}\cdot NH{=}{=}CPh{=}{=}NH\cdot C_{10}H_{17}]^+$ $R'\cdot NH\cdot CPh{:}NR$ (II)

In an attempt to prepare amidines with a permanent centre of asymmetry external to, and separate from the amidine system, Roger and Reid[3] synthesised (−)-mandelamidinium chloride from amygdalin. They also resolved (±)-mandelamidine by means of (+)-camphorsulphonic acid and (+)-bromocamphorsulphonic acid. The following resolution, with optically active mandelic acid,[4] was undertaken to obtain other optically-active amidines.

Acetophenone cyanohydrin,[5] which could be distilled *in vacuo* in the presence of iodine as stabiliser,[6] was converted by the action of ethanol and anhydrous hydrogen chloride[7] into ethyl (±)-atrolactimidate hydrochloride (III). This was treated with alcoholic ammonia[7] to give (±)-atrolactamidinium chloride (IV), from which the base was obtained by use of aqueous alkali.

(±)-Atrolactamidinium chloride and sodium (+)-mandelate in water yielded (−)-atrolactamidine (+)-mandelate (V) of about 90% optical purity. (−)-Atrolactamidine (+)-mandelate and its stereoisomer were synthesised also by direct reaction of (±)-atrolactamidine and (+)- and (−)-mandelic acid, respectively.

Treatment of an ethereal suspension of (−)-atrolactamidine (+)-mandelate with dry hydrogen chloride yielded (−)-atrolactamidinium chloride (VI) which then was heated with aqueous sodium hydroxide. According to McKenzie's racemisation rule[8-10] (cf. also Rothe[11]), no racemisation of the atrolactic system is possible with alkali, and on acidification of the solution, (−)-atrolactic acid (VII) was isolated.

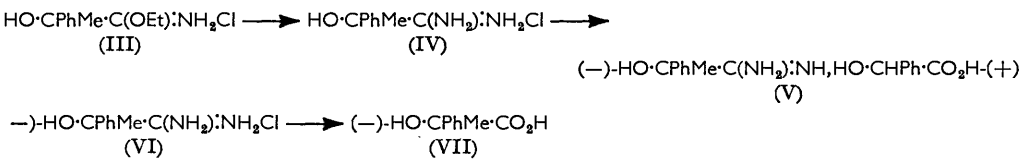
Whilst (±)-atrolactamidine was readily prepared from its hydrochloride and was quite stable, all attempts to prepare the (+)- and (−)-bases from the corresponding optically active hydrochlorides failed.

The rotatory powers of the optically-active atrolactamidinium chlorides at three

* Part XI, *J.*, 1954, 3453.

[1] See Shriner and Neumann, *Chem. Reviews*, 1944, **35**, 351.
[2] Cohen and Marshall, *J.*, 1910, **97**, 328.
[3] Roger and Reid, Ph.D. Thesis, University of St. Andrews, 1949.
[4] Roger, *J.*, 1935, 1544.
[5] Eliel and Freeman, *Org. Synth.*, 1953, **33**, 7.
[6] Hansley, U.S.P. 2,416,624 (*Chem. Abs.*, 1947, **41**, 3483).
[7] Pinner, " Die Imidoäther und ihre Derivate," Berlin, 1892.
[8] McKenzie and Wren, *J.*, 1919, **115**, 602.
[9] McKenzie and Smith, *J.*, 1922, **121**, 1348.
[10] *Idem*, *Ber.*, 1925, **58**, 894.
[11] Rothe, *Ber.*, 1914, **47**, 843.

wavelengths in the visible spectrum gave approximately straight line Lowry–Dickson plots but the determinations were not sufficient to warrant discussion; this aspect is being studied further.



Experimental

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

Optically-active Mandelic Acids.—These were prepared by resolution of (±)-mandelic acid by Roger's method.[4]

Acetophenone Cyanohydrin.—As in the literature,[5] acetophenone (120 g.) in ether (90 ml.) was added to a solution of freshly ground sodium cyanide (123 g.) in water (150 ml.). The mixture was stirred well, and maintained at 5° during the addition of concentrated hydrochloric acid (210 ml.). The addition required two hours and stirring was continued for a further two hours at room temperature. The ether layer was separated and the aqueous layer again extracted with ether. The crude product could be distilled in the presence of iodine [6] (1 g.) yielding acetophenone cyanohydrin (48 g. from 120 g. of acetophenone), b. p. 147—149°/18 mm., as a pale yellow oil.

Ethyl (±)-Atrolactimidate Hydrochloride.—Moisture was excluded during this experiment. Acetophenone cyanohydrin (48 g.) and anhydrous ethanol (16 g.) were treated at 0° with dry hydrogen chloride (13·2 g.). After 48 hours in the ice-chest the mixture was treated with anhydrous ether, furnishing *ethyl (±)-atrolactimidate hydrochloride* (60 g.), m. p. 101—102° (decomp.) (Found: Cl^-, 15·3. $C_{11}H_{16}O_2NCl$ requires Cl^-, 15·5%).

Ethyl (±)-Atrolactimidate.—The imidate hydrochloride (5 g.) was treated with 4N-sodium hydroxide (12 ml.). The dried ethereal extract afforded *ethyl (±)-atrolactimidate* (2 g.), m. p. 56—57° [from petroleum (b. p. 60—80°)] (Found: N, 7·05. $C_{11}H_{15}O_2N$ requires N, 7·2%).

(±)-Atrolactamidinium Chloride.—An anhydrous solution of ammonia (8·5 g.) in ethanol (100 ml.) was shaken with ethyl (±)-atrolactimidate hydrochloride (23 g.) for 12 hr., and the solvent then evaporated at room temperature. The resultant solid on crystallisation from dilute hydrochloric acid gave *(±)-atrolactamidine hydrochloride* (17 g.), m. p. 174—175° after softening at 171° (Found: C, 53·6; H, 6·3; N, 14·7. $C_9H_{13}ON_2Cl$ requires C, 53·9; H, 6·5; N, 14·0%).

(±)-Atrolactamidine.—(±)-Atrolactamidinium chloride (6 g.) was shaken with 10N-sodium hydroxide (15 ml.) at 0° until a clear solution resulted. Addition of water, dropwise, afforded a flocculent precipitate which was washed with water and recrystallised from acetone. (±)-Atrolactamidine (3·7 g.) had m. p. 77—78° (decomp.). Samples of a picrate prepared (*a*) from the amidine base and (*b*) from the hydrochloride, both had m. p. 188—189°.

(±)-Atrolactamidine (±)-Mandelate.—(±)-Atrolactamidinium chloride (2·5 g.) was heated with sodium (±)-mandelate (2·2 g.) in water until a clear solution resulted. The crystals which separated on cooling were twice recrystallised from water to give *(±)-atrolactamidine (±)-mandelate* (1 g.) which softened at 152° and had m. p. 155—156° (Found: C, 64·3; H, 6·4; N, 8·2. $C_{17}H_{20}O_4N_2$ requires C, 64·6; H, 6·3; N, 8·8%).

(−)-Atrolactamidine (+)-Mandelate.—Method A. (±)-Atrolactamidinium chloride (6·7 g.) and sodium (+)-mandelate (5·8 g.), $[\alpha]_{5461}$ +123° (in water), were heated in water (37 ml.). Crystals which separated when the solution cooled were recrystallised twice from water (in each case the crystallisations were allowed to proceed undisturbed otherwise crystals of low optical purity were obtained). There resulted large rhombic crystals of (−)-atrolactamidine (+)-mandelate (2 g.) which softened at 162° and had m. p. 165° (decomp.), $[\alpha]^{18}_{5461}$ +12·1° (*c* 0·91 in methanol).

Method B. Ethereal (+)-mandelic acid (1·5 g.), $[\alpha]_{5461}$ +186° (in acetone), was mixed with (±)-atrolactamidine (1·6 g.) dissolved in alcohol, the amidine salt being precipitated. *(−)-Atrolactamidine (+)-mandelate* (0·7 g.), with m. p. as above, had $[\alpha]_{5461}$ + 15·6° (*c* 0·86

in methanol) after two recrystallisations from water (Found: C, 64·8; H, 6·0. $C_{17}H_{20}O_4N_2$ requires C, 64·6; H, 6·3%).

(+)-*Atrolactamidine* (−)-*Mandelate.*—This salt was prepared as in method B, but with (−)-mandelic acid, $[\alpha]_{5461}$ −188° (in acetone). After being twice recrystallised from water, (+)-*atrolactamidine* (−)-*mandelate* softened at 162°, melted at 165° (decomp.), and had $[\alpha]^{16}_{5416}$ −13·5° (*c* 0·86 in methanol) (Found: C, 65·2; H, 6·6; N, 9·3%).

(−)-*Atrolactamidinium Chloride.*—(−)-Atrolactamidine (+)-mandelate, $[\alpha]_{5461}$ +12·4° (in methanol), was set aside with an anhydrous ether solution of hydrogen chloride for 24 hr. The amidinium chloride was filtered off, dissolved in warm ethanol, cooled, and reprecipitated with ether. (−)-*Atrolactamidinium chloride*, m. p. 200—201° (decomp.) after softening at 197°, had $[\alpha]^{15}_{5461}$ −55·6° (*c* 0·54 in water) (Found: C, 54·1; H, 6·4; N, 13·2. $C_9H_{13}N_2OCl$ requires C, 53·9; H, 6·5; N, 14·0%).

(+)-*Atrolactamidinium Chloride.*—Similarly, (+)-atrolactamidine (−)-mandelate, $[\alpha]_{5461}$ −13·5° (in methanol), yielded (+)-*atrolactamidinium chloride*, which softened at 197°, melted at 201° (decomp.), and had $[\alpha]^{15}_{5461}$ +54·8° (*c* 0·58 in water). The yield was almost theoretical.

Optical Rotations $[\alpha]^{15}_{\lambda}$ *(in Water) of the Optically-active Hydrochlorides.*—

λ (Å)	6234	5780	5461
(−)-Atrolactamidinium chloride (*c* 0·54)	−42·9°	−51·9°	−55·6°
(+)-Atrolactamidinium chloride (*c* 0·58)	+43·7°	+49·7°	+54·8°

(−)-*Atrolactic Acid.*—(−)-Atrolactamidinium chloride (0·5 g.), $[\alpha]_{5461}$ −54·7° (in water), was heated in 4N-sodium hydroxide until evolution of ammonia ceased. The acidified solution, on extraction with ether, yielded (−)-atrolactic acid (0·2 g.) which was crystallised from benzene (charcoal), and did not depress the m. p. of authentic acid. It had $[\alpha]_D^{22}$ −48·3° (*c* 0·55 in water); McKenzie and Clough [12] record $[\alpha]_D^{14}$ −53·8° (in water).

(+)- *and* (−)-*Atrolactamidines.*—Treatment of (+)- and (−)-atrolactamidinium chloride at 0° with alkali solutions of varying strengths did not give crystalline products.

One of us (D. G. N.) is indebted to the University of St. Andrews for a Post Graduate Scholarship.

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

[*Received, August 21st,* 1958.]

[12] McKenzie and Clough, *J.*, 1910, **97**, 1016.