854. *The Preparation of Optically Active, Substituted Mandelamidinium Chlorides.*

By Douglas G. Neilson and David A. V. Peters.

Eight *Bz*-substituted (±)-mandelamidinium chlorides have been prepared by the Pinner method and attempts made to resolve them by means of (+)- and (−)-mandelic acid. 2-Methoxy-, 2-ethoxy-, and 3,4-dimethoxy-mandelamidinium chloride were readily resolved, the 4-ethoxy-derivative less easily, and the 3-methoxy- and the 3-ethoxy-compound only partially. 2,3-Dimethoxy- and 3-ethoxy-mandelamidine which could not be thus resolved were resolved by using (+)- and (−)-α-methoxy-α-phenylacetic acid which, however, gave no separation of the enantiomers of (±)-mandelamidine. Optically pure ethyl (+)- and (−)-α-methoxy-α-phenylacetimidate hydrochloride and the corresponding α-methoxy-α-phenylacetamidinium chlorides (II) were prepared from the α-methoxy-α-phenylacetic acids, whereas resolution of the (±)-amidinium chloride (II) by use of the mandelic acids gave only partially active material.

The mandelic acids have been used by Roger, Neilson, and Peters [1-4] to resolve a series of six (±)-α-hydroxyamidinium chlorides although no separation was noted for five other (aliphatic) members of the series.[4,5] In an attempt to find the effect of substituents on the mandelamidinium system, the compounds (Ia—h) have been prepared and studied.

(I) $Ar\cdot CH(OH)\cdot C(NH_2){:}NH_2Cl$ $Ar\cdot CH(OMe)\cdot C(NH_2){:}NH_2Cl$ (II)

Ar	Ar	Ar
a, o-$MeO\cdot C_6H_4$	d, m-$EtO\cdot C_6H_4$	g, $2,3$-$(MeO)_2C_6H_3$
b, o-$EtO\cdot C_6H_4$	e, p-$MeO\cdot C_6H_4$ *	h, $3,4$-$(MeO)_2C_6H_3$
c, m-$MeO\cdot C_6H_4$	f, p-$EtO\cdot C_6H_4$	i, Ph

* Ref. 4.

The cyanohydrins of methoxy- and ethoxy-benzaldehyde [6] were converted by the Pinner method [7,8] into the (±)-*Bz*-alkoxymandelamidinium chlorides (Ia—d, f—h). Interaction of the amidines with the (+)- and (—)-mandelic acid, or of their hydrochlorides with sodium (+)- and (—)-mandelate, gave reasonable separation of the diastereoisomers in all cases except those of the 2,3-dimethoxy-, 3-methoxy-, and 3-ethoxy-compounds. However, a stable hydrogen carbonate was obtained from 2,3-dimethoxymandelamidinium chloride, and this with the (+)- and (—)-α-methoxy-α-phenylacetic acid [6] gave diastereoisomerides separable by crystallisation. Because of the much greater ease of racemisation of α-methoxy-α-phenylacetic acids than of mandelic acids,[10,11] use of the former acids is limited to resolution of those amidines which readily yield the free base or the hydrogen carbonate. Thus, although a sodium α-methoxy-α-phenylacetate of $[\alpha]_{5461}$ −142·4° (in methanol) was obtained by treating the (—)-acid with sodium hydrogen carbonate and then removing the solvent at room temperature, this salt was readily racemised when heated in water (the normal way of preparing an organic acid salt from

---

[1] Roger and Neilson, *J.*, 1959, 688.
[2] Roger and Neilson, *J.*, 1961, 3181.
[3] Neilson, Ph.D. Thesis, University of St. Andrews, 1955.
[4] Neilson and Peters, *J.*, 1962, 1309.
[5] Neilson and Peters, unpublished work.
[6] Shoesmith and Connor, *J.*, 1927, 2230.
[7] Pinner, " Die Imidoäther und ihre Derivate," Oppenheim, Berlin, 1892.
[8] Roger and Neilson, *Chem. Rev.*, 1961, **61**, 179.
[9] Neilson and Peters, *J.*, 1962, 1519.
[10] Smith, *J.*, 1935, 194.
[11] McKenzie and Smith, *J.*, 1922, **121**, 1348.

an amidinium chloride). By contrast, sodium (+)- and (—)-mandelate are optically stable under similar conditions.

(±)-3-Ethoxymandelamidine was ultimately resolved by using the α-methoxy-α-phenylacetic acids, whereas the 3-methoxy-compound which did not yield a free base could not be so resolved. As the resolution of (±)-mandelamidine with the mandelic acids gives very poor yields of optically pure material,[3] this amidine was treated with (+)-α-methoxy-α-phenylacetic acid but no separation of the diastereoisomers was noted. On completion of a resolution, the amidinium chlorides were regenerated in the usual way.[1,2,4]

(—)-Mandelamidinium chloride and its 4-methoxy-derivative have been shown to be readily racemised by alkali or heat.[4,12,13] 2-Ethoxymandelamidinium chloride is now also found to racemise when heated above its melting point (175—177°), then resolidifying and remelting at 206—208°, *i.e.*, near the melting point of the racemate (235—236°). (—)-2-Methoxymandelamidinium (—)-mandelate also exhibits the double melting points of 152—153° and 182—183°.

The ready racemisation of these substances in alkali prevented the determination of their configurations,[1,2,4] as sodium hydroxide solutions of varying concentrations gave only (±)-derivatives of the parent acids (the assignment of configurations is the subject of further study). This base-catalysed racemisation also prevented comparison of optical purities with previously reported derivatives. However, the mandelate or α-methoxy-α-phenylacetate of the 2-methoxy-, 2- and 3-ethoxy-, 2,3- and 3,4-dimethoxy-mandelamidines recrystallised to constant rotation (in most cases three concurrent values were obtained), and it is therefore tentatively suggested that their resolution is complete. The close agreement of the specific rotations of the (+)- and the (—)-forms of the amidinium chlorides adds weight to this argument (cf. Table 2). For the 3-methoxy- and the 4-ethoxy-compounds, less reliance can be given to the final values of the specific rotations of the amidinium chlorides as the mandelate salts gave erratic values on successive crystallisations and the quoted results are the best obtained.

The corresponding *O*-methylmandelic acids[9] were prepared as follows. (±)-α-Methoxy-α-phenylacetonitrile, obtained from the (±)-acid by dehydration of its amide by Smith's method,[10] was converted into the (±)-amidinium chloride in the usual way.[7,8] When the (+)- and (—)-amides were used, however, the temperature of dehydration was found to be critical. Smith[10] used a temperature of 110° and we have found that this is in fact an optimum temperature. Thermal decomposition of ethyl (+)- and (—)-α-methoxy-α-phenylacetimidate hydrochloride prepared from the optically pure (—)- and (+)-nitriles, yielded amides which were over 98% optically pure.

Treatment of the (+)- and (—)-imidate salts with equimolar quantities of ammonia in ethanol gave (+)- and (—)-α-methoxy-α-phenylacetamidinium chloride (II), $[\alpha]_{5461}$ +122·0° and —123·1° (in water), respectively. Unfortunately it was not possible to relate the optical purity of these amidines by decomposition back to the acid or amide owing to the ease of base-catalysed racemisation of α-methoxy-α-phenylacetic acids[10,11] (cf. above). However, Reid,[12,13] in similar work, reported that ethyl (—)-mandelimidate hydrochloride with equimolar quantities of ammonia yielded (—)-mandelamidinium chloride of high optical purity, whereas use of an excess of ammonia led to the (±)-amidinium chloride. It is suggested, therefore, that the alkoxy-amidines (II) are of high optical purity. In an attempt to confirm this, the (±)-amidinium chloride (II) was treated with sodium (+)-mandelate, to give a salt which had a constant rotation after six crystallisations from ethanol. This salt, however, gave only a partially active amidinium chloride, $[\alpha]_{5461}$ —48·1° (in water), which is to be compared with the value $[\alpha]_{5461}$ —123·1° for compound (II) obtained by direct synthesis.

As (—)-α-methoxy-α-phenylacetic acid has been formed from D-(—)-mandelic acid

---

[12] Reid, Ph.D. Thesis, University of St. Andrews, 1949.

[13] Roger and Neilson, *J.*, 1960, 627.

(*R*),[14] this acid, the (—)-amide, (+)-nitrile, ethyl (—)-α-methoxy-α-phenylacetimidate hydrochloride, and the (—)-amidinium chloride (II) all belong to the D-series (*R*).

EXPERIMENTAL

Specific rotations are for MeOH solutions in a 2-dm. tube, unless otherwise stated.

Optically Active Mandelic Acids.—The acids, $[\alpha]_{5461}$ ±185·0° (in acetone), were converted into their sodium salts as previously reported.[4,15]

Alkoxybenzaldehydes.—2- and 3-Methoxy-, 2-, 3-, and 4-ethoxy-, and 2,3- and 3,4-dimethoxy-benzaldehyde were obtained from the *o*-, *m*-, and *p*-hydroxybenzaldehydes, *o*-vanillin, and vanillin, respectively, by Shoesmith and Connor's method.[6]

(±)-*Amidinium Chlorides.*—The crude cyanohydrins prepared from the aldehydes through their sodium hydrogen sulphite complexes were converted into the methyl and ethyl imidate hydrochlorides by the Pinner method [2,7,8] (cf. Table 1). Reaction of these imidate salts with dry alcoholic ammonia gave the (±)-amidinium chlorides [2] (cf. Table 2).

TABLE 1.

Substituted mandelimidates, $C_6H_3RR'\cdot CH(OH)\cdot C(OR''){:}NH_2Cl$.

R	R′	R″	M. p.*	Yield (%) †
H	2-MeO	Et	Deliquescent	90
H	2-EtO	Et	112—113°	21
H	3-MeO	Et	88—89 ‡	80
H	3-EtO	Me	112—113	28
H	4-EtO	Me	99—100	28
2-MeO	3-MeO	Me	114—115	73
3-MeO	4-MeO	Me	102—103	71

* With decomp. † Based on the hydroxybenzaldehyde. ‡ Bristow (*J.*, 1957, 513) refers to this ester as a wax.

Resolution of (±)-*Amidinium Chlorides by Means of the Mandelic Acids.*—The calculated quantities of (±)-amidinium chloride and (+)- or (—)-sodium mandelate were dissolved in the minimum of hot water and the mixture was allowed to crystallise. The resultant salts were then recrystallised to constant rotation.

(+)- *and* (—)-2-*Methoxymandelamidinium* (+)-*Mandelate.*—The (±)-amidinium chloride (Ia) (32·8 g.) and (+)-sodium mandelate (26·2 g.) in water (250 ml.) gave (—)-2-*methoxymandelamidinium* (+)-*mandelate* (19·5 g.), $[\alpha]^{19}_{5461}$ —30·4° (*c* 0·55), m. p. 193—194° [after one recrystallisation from water (200 ml.)] (Found: C, 61·5; H, 6·0. $C_{17}H_{20}N_2O_5$ requires C, 61·5; H, 6·0%). The reaction liquors gave a second small crop of low rotation, followed, on concentration, by a third crop (16·7 g.) of almost pure (+)-amidinium (+)-mandelate, $[\alpha]^{19}_{5461}$ +120° (*c* 0·37).

(—)-2-*Methoxymandelamidinium* (—)-*mandelate*, prepared from the (—)-amidinium chloride and (—)-sodium mandelate, had $[\alpha]^{21}_{5461}$ —131·5° (*c* 0·49) and melted at 152—153°, resolidified, and remelted at 182—183° (Found: C, 61·6; H, 6·2%).

(+)- *and* (—)-2-*Ethoxymandelamidinium* (+)-*Mandelate.*—The (±)-amidinium chloride (Ib) (10 g.) and (+)-sodium mandelate (7·5 g.) in water (50 ml.) gave a salt (5·7 g.), $[\alpha]^{20}_{5461}$ —33·5° (*c* 1·01), which after one crystallisation from ethanol (75 ml.) gave (—)-2-*ethoxymandelamidinium* (+)-*mandelate* (4·6 g.), $[\alpha]^{19}_{5461}$ —34·6° (*c* 1·03), m. p. 170—171° (Found: C, 62·3; H, 6·3. $C_{18}H_{22}N_2O_5$ requires C, 62·4; H, 6·4%). After 24 hr., the reaction liquor gave a second crop (2·5 g.) which after one crystallisation from ethanol consisted of virtually optically pure (+)-2-*ethoxymandelamidinium* (+)-*mandelate*, $[\alpha]^{20}_{5461}$ +133·0° (*c* 1·03), m. p. 143—144° (Found: C, 62·6; H, 6·3%).

(—)-3-*Methoxymandelamidinium* (+)-*Mandelate.*—The (±)-amidinium chloride (Ic) (10 g.) and (+)-sodium mandelate (8·2 g.) in water (50 ml.) gave, after one recrystallisation from water, (±)-amidinium (+)-mandelate (4·0 g.), $[\alpha]^{19}_{5461}$ +44·6° (*c* 1·12). After four further crystallisations from 50% aqueous ethanol (30 ml. portions) the salt (0·5 g.) had $[\alpha]^{19}_{5461}$ +37·2° (*c* 0·54), m. p. 141—142°. Further crystallisation from water, ethanol, and aqueous ethanol did not alter these values. Similarly, (+)-3-*methoxymandelamidinium* (—)-*mandelate*, $[\alpha]^{19}_{5461}$ —34·6° (*c* 0·56), m. p. as above, was obtained by using (—)-sodium mandelate (Found: C,

---

[14] McKenzie, *J.*, 1899, **75**, 753.

[15] Roger, *J.*, 1935, 1544.

TABLE 2.

Bz-Substituted mandelamidinium chlorides, $Ar\cdot CH(OH)\cdot C(NH_2){:}NH_2Cl$.

Compound	Amidinium acetate or mandelate	$[\alpha]_{5461}$ (in MeOH)	Sign	Yield (%)	M. p.	$[\alpha]_{5461}^{18-20}$ in H_2O	
Ia	—	—	(±)	50	202—203°	—	
	(−)-A (+)-M	−30·4°	(−)	*	228—229	−106·5°	0·5
	(+)-A (+)-M	+120 §	(+)	*	228—229	+105·2	1·0
Ib	—	—	(±)	87	235—236	—	
	(−)-A (+)-M	−34·6	(−)	*	175—177 †	−107·5	0·97
	(+)-A (+)-M	+133·0	(+)	*	175—177 †	+108·5	0·98
Ic	—	—	(±)	87	187—189 ‡	—	
	(−)-A (+)-M	+37·2	(−)	*	186—187	−22·5	1·01
Id	—	—	(±)	90	237—238	—	
	(−)-A (−)-A	−105·5	(−)	*	234—235	−84·3	1·25
Ie [4]	(−)-A (−)-M	−119·0	(−)	*	215	−87·9	—
	(+)-A (+)-M	+119·0	(+)	*	215	+87·8	—
If	—	—	(±)	93	230 (d.)		
	(−)-A (+)-M	−6·7	(−)	*	253 (d.)	−75·8	0·5
	(+)-A (−)-M	~0·0	(+)	*	253 (d.)	+59·2	0·48
Ig	—	—	(±)	84	183—184		
	(+)-A (+)-A	+106·0°	(+)	*	178—179	+61·8	1·86
	(−)-A (−)-A	−106·0	(−)	*	178—179	−61·4	1·28
Ih	—	—	(±)	85	201—203	—	
	(+)-A (−)-M	+12·2	(+)	*	191—192	+93·2	1·03
	(−)-A (+)-M	−12·3	(−)	*	191—192	−92·5	1·01
Ii [13]	(±)-A (+)-A	+67·5	(±)	*	216—217	0·0	—

Compound	Found (%) ¶			Formula	Required (%)		
	C	H	Cl		C	H	Cl
Ia	— , 49·3, 50·0	—, 6·4, 6·1	16·5, — , —	$C_9H_{13}ClN_2O_2$	49·7	6·0	16·4
Ib	— , 51·9, 51·8	—, 6·2, 6·4	15·3, — , —	$C_{10}H_{15}ClN_2O_2$	52·1	6·5	15·4
Ic	— , 49·5	—, 6·2	—	$C_9H_{13}ClN_2O_2$	49·7	6·0	—
Id	52·2, 52·3	6·7, 6·6	—	$C_{10}H_{15}ClN_2O_2$	52·1	6·5	—
If	— , — , 52·3	—, —, 6·6	15·6, — , —	,,	52·1	6·5	15·4
Ig	— , 48·2, —	—, 6·2, —	14·2, — , —	$C_{10}H_{15}ClN_2O_3$	48·7	6·1	14·4
Ih	— , 48·9, 48·9	—, 6·0, 6·0	14·3, — , —	,,	,,	,,	,,

A M = Amidinium mandelate. A A = Amidinium α-methoxy-α-phenylacetate.

* Almost theoretical; other yields are based on the imidate ⟶ amidine change. † Double m. p. 175—177°, 206—208°. ‡ King, King, and Muir (*J.*, 1946, 5) give m. p. 190°. § May contain sodium chloride as pure (−)-A (−)-M has $[\alpha]_{5461}$ −131·0°. ¶ Values are given for preparations in the same order as in the first part of the Table.

61·4; H, 6·0. $C_{17}H_{20}N_2O_5$ requires C, 61·5; H, 6·1%). This compound does not, therefore, appear to be completely resolved.

(±)-3-*Ethoxymandelamidinium* (−)-*Mandelate*.—Potassium hydroxide solution (4·2 g. in 30 ml.) was added dropwise to a stirred slurry of powdered (±)-amidinium chloride (Id) (20 g.) in water (50 ml.), and the mixture was filtered after 10 min. and the resultant amidine was washed with cold water (25 ml.) and dried *in vacuo*. This amidine (16 g.) and (−)-mandelic acid (13·2 g.) were dissolved in 50% aqueous ethanol (100 ml.). The precipitate then formed was (±)-3-*ethoxymandelamidinium* (−)-*mandelate* (8·5 g.), $[\alpha]_{5461}^{20}$ −46·1° (*c* 0·96), m. p. 118—119° (Found: C, 62·3; H, 6·4%). After four further crystallisations from methanol (100 ml. portions) the salt had $[\alpha]_{5461}^{21}$ −48·0° (*c* 1·02).

(+)- *and* (−)-4-*Ethoxymandelamidinium* (+)- *and* (−)-*Mandelate*.—The (±)-amidinium chloride (If) was converted into (±)-4-ethoxymandelamidine (90%) as described for the 3-ethoxy-derivative. The (±)-amidine (17 g.) and (+)-mandelic acid (13·3 g.) in ethanol (70 ml.) furnished a salt which after recrystallisation from water (50 ml.) had $[\alpha]_{5461}^{21}$ +61·5° (*c* 1·12). After two further crystallisations from water, the salt had $[\alpha]_{5461}^{20}$ +59·2° (*c* 1·33) and m. p. 144—145°. These values correspond closely to the (±)-amidinium (+)-mandelate. The reaction mixture deposited a second crop (0·6 g.), composed of a (−)-4-*ethoxymandelamidinium* (+)-*mandelate*, $[\alpha]_{5461}^{20}$ −6·7° (*c* 0·99) (Found: C, 63·2; H, 6·7%). The value of the specific rotation did not alter on further crystallisation. A sample of (+)-amidinium (−)-mandelate obtained similarly from (−)-mandelic acid had $[\alpha]_{5461}^{19}$ ~0·0° (*c* 0·74).

(+)-3,4-*Dimethoxymandelamidinium* (−)-*Mandelate*.—The (±)-amidinium chloride (Ih)

(10 g.) and (−)-sodium mandelate (7·05 g.) in water (50 ml.) gave a salt (4·3 g.), $[\alpha]_{5461}^{20}$ +10·2° (*c* 1·04), after one recrystallisation from ethanol (50 ml.). After one further crystallisation from the same solvent, (+)-3,4-*dimethoxymandelamidinium* (−)-*mandelate* (3·8 g.) had $[\alpha]_{5461}^{17}$ +12·2° (*c* 1·08) and m. p. 174—175° (Found: C, 60·1; H, 6·2. $C_{18}H_{22}N_2O_6$ requires C, 59·7; H, 6·1%). (−)-Amidinium (+)-mandelate, prepared similarly from (+)-mandelic acid, had $[\alpha]_{5461}^{19}$ −12·3° (*c* 1·09) and m. p. as above.

(±)-2,3-*Dimethoxymandelamidinium Chloride.*—This compound crystallised unchanged from solutions containing (+)- or (−)-sodium mandelate. It quickly decomposed in the presence of sodium hydroxide. The (±)-amidinium chloride (20 g.) was stirred with a solution of sodium hydrogen carbonate (10 g.) in water (150 ml.) for 20 min. at 50° and the resultant solid was filtered off, washed with water, and air-dried. The (±)-amidinium hydrogen carbonate, when treated with the mandelic acids, formed the amidinium mandelates but these proved extremely difficult to crystallise and the use of the mandelic acids in this series was not pursued further.

(+)- *and* (−)-2,3-*Dimethoxymandelamidinium* (+)- *and* (−)-α-*Methoxy-α-phenylacetate.*—The preceding (±)-amidinium hydrogen carbonate (10 g.) and (+)-α-methoxy-α-phenylacetic acid [9] (6·6 g.), $[\alpha]_{5461}^{20}$ +172·6° (in ethanol), were dissolved in water (25 ml.), and the solid which was formed on cooling was recrystallised from ethanol (25 ml.). (+)-2,3-*Dimethoxymandelamidinium* (+)-α-*methoxy-α-phenylacetate* (3·3 g.) had $[\alpha]_{5461}^{18}$ +106·0° (*c* 1·02) and m. p. 155—156°, and the (−)-base (−)-acid salt obtained similarly from the (−)-acid, $[\alpha]_{5461}$ −176·0° (in ethanol), had $[\alpha]_{5461}^{19}$ −106·0° (*c* 1·11) (methanol) and m. p. as above (Found: C, 60·8; H, 6·2. $C_{19}H_{24}N_2O_6$ requires C, 60·7; H, 6·4%).

(−)-3-*Ethoxymandelamidinium* (−)-α-*Methoxy-α-phenylacetate.*—The amidine base (8·5 g.), prepared as above, and (−)-α-methoxy-α-phenylacetic acid (7·3 g.) were dissolved in methanol (25 ml.) and filtered hot. The resultant solid (6 g.) was recrystallised three times from methanol (30, 20, 20 ml.), yielding finally (−)-3-*ethoxymandelamidinium* (−)-α-*methoxy-α-phenylacetate* (1·9 g.), $[\alpha]_{5461}^{19}$ −105·5° (*c* 0·86), m. p. 165—166° (Found: C, 62·6; H, 6·8. $C_{19}H_{24}N_2O_5$ requires C, 63·4; H, 6·7%).

Attempted Resolution of (±)-*Mandelamidinium Chloride.*—(±)Mandelamidinium chloride [12] (Ii) (28 g.) was finely powdered and treated with 2N-sodium hydroxide (150 ml.). The precipitate (15 g.) was filtered off within 3 min., washed with a little water, and dried *in vacuo*. The resultant amidine base (15 g.) was treated with (+)-α-methoxy-α-phenylacetic acid, $[\alpha]_{5461}$ +170·5° (in ethanol), in boiling ethanol (100 ml.) and filtered hot. After two recrystallisations from ethanol (50, 100 ml.) the (±)-base (+)-acid salt (4·7 g.) had $[\alpha]_{5461}$ +67·5° (*c* 0·993). This value remained unchanged after crystallisation from methanol (50 ml.) and the 50% aqueous ethanol (100 ml.). Amidinium chloride recovered from the (+)-acid salt was identical with (±)-mandelamidinium chloride, showing that resolution was not taking place.

General Procedure for the Formation of (+)- *and* (−)-*Amidinium Chlorides.*—The optically active amidinium acetates or mandelates were dissolved in ethanol, or were finely powdered and suspended in ether, and were then treated with an excess of dry hydrogen chloride. After being kept overnight, the solutions were evaporated to small volume, and the amidinium chlorides precipitated with ether and crystallised from ethanol or ethanol–ether. The results are summarised in Table 2.

(±)-α-*Methoxy-α-phenylacetamidinium Chloride.*—(±)-α-Methoxy-α-phenylacetic acid [9] (50 g.) was heated under reflux with methanol (120 ml.) and concentrated sulphuric acid (10 g.) for 5 hr. The ester was worked up in the usual manner and then shaken with aqueous ammonia (*d* 0·88) and ethanol for 4 hr. After a further 12 hr. the crystalline amide was filtered off, and recrystallised from light petroleum (b. p. 60—80°)–chloroform. (±)-α-Methoxy-α-phenylacetamide (35 g.), m. p. 112—113° (lit.,[16] 111—112°), was dehydrated with phosphorus pentoxide (47 g.) in toluene (150 ml.) by Smith's method [10] and furnished the (±)-nitrile (15 g.), b. p. 159—160°/25 mm. The nitrile was converted by the Pinner reaction [7,8] into the methyl, m. p. 90—91° (82%), and the ethyl imidate hydrochloride, m. p. 85—86° (68%). The (±)-amidinium chloride (II) was prepared by the action of anhydrous alcoholic ammonia on the methyl imidate hydrochloride (95% yield) or on the ethyl compound (87% yield). It had m. p. 215—216° (Found: Cl, 17·6. $C_9H_{13}ClN_2O$ requires Cl, 17·8%).

(+)- *and* (−)-α-*Methoxy-α-phenylacetonitrile.*—(+)-α-Methoxy-α-phenylacetic acid [9] (60 g.), $[\alpha]_{5461}^{20}$ +177·0° (*c* 0·57 in EtOH), treated as above, gave the (+)-amide (39 g.), $[\alpha]_{5461}^{19}$ +125°, $[\alpha]_D^{19}$ +106·0° (*c* 0·49 in acetone), and similarly (−)-acid (57 g.), $[\alpha]_{5461}^{19}$ −177·5° (*c* 0·49 in EtOH)

[16] McKenzie, Martin, and Rule, *J.*, 1914, **105**, 1583.

TABLE 3.

Temp. of bath	Nitrile, $[\alpha]_{5461}$ in acetone	Yield (%)	Initial amide, $[\alpha]_{5461}$ in acetone
90—95°	+63·4° (*c* 3·8)	28	−125·0° (*c* 1·18)
110°	+63·6° (*c* 4·22)	49	−125·7 (*c* 0·53)
115°	−60·2° (*c* 1·80)	52	+121·0 (*c* 1·41)
120—125°	−19·0° (*c* 3·12)	43	+120·0 (*c* 1·06)

gave (−)-amide (38 g.), $[\alpha]_{5461}^{18}$ −125·7° (*c* 0·53 in acetone). The amides had m. p. 107—108°. McKenzie and Smith [11] give $[\alpha]_D^{19}$ −105·0° (*c* 4·0 in acetone) and m. p. 108—109° for the (−)-amide. The (+)-amide (25 g.), treated with phosphorus pentoxide (34 g.) in toluene (100 ml.) by Smith's method,[10] gave (−)-α-methoxy-α-phenylacetonitrile (11·5 g.), b. p. 142—145°/17 mm., $[\alpha]_{5461}^{19}$ −62·4° (*c* 1·01 in acetone). Similarly the (−)-amide yielded (+)-nitrile, b. p. 145—149°/20 mm., $[\alpha]_{5461}^{19}$ +63·6° (*c* 4·22 in acetone), α_D^{21} +30·32°, α_{5461}^{21} +35·83° (homogeneous, *l* ½). Smith [10] gives $[\alpha]_{5461}^{20}$ −63·5° (*c* 4·94 in acetone) for the (−)-nitrile. Table 3 illustrates the effect of temperature on the yield and optical purity of the nitrile throughout the dehydration reaction, showing that the temperature used by Smith [10] was optimum.

(+)- *and* (−)-*Ethyl α-Methoxy-α-phenylacetimidate Hydrochloride.*—The anhydrous (−)-nitrile, $[\alpha]_{5461}$ −62·4° (in acetone) (11 g.), ethanol (3·5 g.), and hydrogen chloride (2·7 g.) gave ethyl (+)-imidate hydrochloride (12·5 g.) which was contaminated with ammonium chloride. Similarly, the (+)-nitrile, $[\alpha]_{5461}$ +63·6° (in acetone), gave (−)-ethyl α-methoxy-α-phenylacetimidate hydrochloride (8·0 g.), $[\alpha]_{5461}^{19}$ −166·8° (*c* 1·20 in EtOH), after purification by dissolution in chloroform and reprecipitation with ether. The (+)-nitrile similarly formed the (−)-methyl imidate hydrochloride (72%), $[\alpha]_{5461}^{19}$ −122·5° (*c* 1·53 in methanol), and m. p. 71—72°.

Test of Optical Purity of the Imidate Salts.—Samples (1 g.) of the ethyl imidate salts were heated just above the m. p. for 10 min. in a porcelain crucible, then dissolved in chloroform (10 ml.). The solutions were filtered, and the amides were precipitated by light petroleum (b. p. 60—80°) filtered off, and dried in the air. M. p.s of authentic (+)- and (−)-amides were not depressed by these samples. The results were:

Ethyl imidate hydrochloride, $[\alpha]_{5461}$ in EtOH	Amide from imidate, $[\alpha]_{5461}$ in acetone	Amide from acid, $[\alpha]_{5461}$ in acetone
−166·8°	−124·2° (*c* 1·2)	−125·7° (*c* 0·53)
—	+123·8° (*c* 1·44)	+125·0° (*c* 0·49)

(+)- *and* (−)-*α-Methoxy-α-phenylacetamidinium Chloride.*—The (−)-ethyl imidate hydrochloride (above) (12·5 g.) was shaken with ethanolic ammonia (0·93 g. in 75 ml.) and worked up as for the (±)-compound. (−)-*α-Methoxy-α-phenylacetamidinium chloride* (7·0 g.) had $[\alpha]_{5461}^{21}$ −123·1° (*c* 1·06 in H_2O) and m. p. 219—220° (Found: C, 53·9; H, 6·4; N, 13·7. $C_9H_{13}ClN_2O$ requires C, 53·9; H, 6·5; N, 14·0%). Similarly, the (+)-amidinium chloride had m. p. 216—217°, $[\alpha]_{5461}^{19}$ +122·0° (*c* 0·85 in H_2O).

Attempted Resolution of (±)-*α-Methoxy-α-phenylacetamidinium Chloride.*—The (±)-amidinium chloride (II) (10 g.) and (−)-sodium mandelate (8 g.) were dissolved in hot water (100 ml.). The resultant salt, after recrystallisation from water (80 ml.), had $[\alpha]_{5461}^{20}$ −60·6° (*c* 0·49) and m. p. 166—169°. After recrystallisations from ethanol (3 × 50 ml.) the (−)-amidinium (−)-mandelate (4·0 g.) had $[\alpha]_{5461}^{20}$ −84·0° (*c* 0·53). After further crystallisations from ethanol (2 × 40 ml.) the salt had $[\alpha]_{5461}^{19}$ −86·7° (*c* 1·06) and m. p. 174—175°. This value did not alter on further recrystallisation from methanol, ethanol, aqueous ethanol, or water. (−)-Methoxy-α-phenylacetamidinium chloride, generated from this salt by the usual method, had $[\alpha]_{5461}^{20}$ −48·1° (*c* 0·99 in H_2O) and m. p. 215—216°; the chloride prepared from the optically active acid had $[\alpha]_{5461}$ −123·1° (*c* 0·16 in H_2O).

Racemisation of Optically Active Amidinium Chlorides in Sodium Hydroxide Solutions.—In a typical experiment, (−)-2-ethoxymandelamidinium chloride (1 g.), $[\alpha]_{5461}$ −103·3° (in H_2O), was treated with sodium hydroxide solution (0·52 g. in 5 ml.). No solid product was isolated and after 2 hr. the solution had zero specific rotation.

One of us (D. A. V. P.) is indebted to the Department of Scientific and Industrial Research for a Research Grant which made this work possible.

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

[*Received, February 6th,* **1963**.]