437. *The Preparation of Optically Active 2-α-Hydroxyalkylimidazolines.*

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Four optically active 2-α-hydroxyalkylimidazolines (II a, c, d, f) have been prepared by interaction of ethylenediamine with optically active α-hydroxy-amidinium chlorides in alcohol. Optical activity was maintained in all instances except in the case of (−)-4-methoxymandelamidinium chloride (Ie) where complete racemisation took place. The closely related (−)-2-α-hydroxybenzylimidazolinium chloride was prepared directly from ethyl (−)-mandelimidate hydrochloride without apparent racemisation.

ROGER, REID, NEILSON, and PETERS [1-4] prepared a series of optically active α-hydroxy-amidinium chlorides (Ia—f) by resolution of the (±)-compounds with the mandelic acids.[5] However, in no instance was it possible to isolate an optically active amidine base from its hydrochloride although in several instances (Ib and c) the (±)-bases were stable when pure.[1,2] In view of these results and in order to obtain amidine bases with optically active substituents, we synthesised imidazolines which contain the amidine group, modified only by the ring system.

As amidines [6,7] and, especially, imidates [8] have been used as intermediates in the formation of imidazolines by interaction with ethylenediamine, the syntheses were applied to the optically active α-hydroxy-amidinium chlorides (Ia, c—f). According to the

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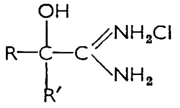
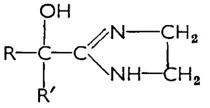
[1] Reid, Ph.D. Thesis, St. Andrews, 1949.
[2] Roger and Neilson, *J.*, 1959, 688.
[3] Roger and Neilson, *J.*, 1961, 3181.
[4] Neilson and Peters, *J.*, 1962, 1309.
[5] Roger, *J.*, 1935, 1544.
[6] Shriner and Neumann, *Chem. Rev.*, 1944, **35**, 351.
[7] Klarer and Urech, *Helv. Chim. Acta*, 1944, **27**, 1762.
[6] Roger and Neilson, *Chem. Rev.*, 1961, **61**, 179.

McKenzie rule for base-catalysed racemisation,[9,10] no racemisation would be expected, even in the strongly alkaline alcoholic solution of ethylenediamine, of the amidines (Ia, c, d, or f) or the imidazolines formed from them. Optically active imidazolines were in fact isolated from each of these precursors and only in the case of 2-1′-hydroxyethylimidazoline was there difficulty in preparing the product (owing to its very great solubility in aqueous media). However, (+)-4-methoxymandelamidinium chloride (Ie) has been shown to be very sensitive to base-catalysed racemisation even in aqueous solution,[4] and complete racemisation was noted during the formation of 2-(α-hydroxy-4-methoxybenzyl)imidazoline (IIe), owing to the base-catalytic effect either of the diamine or of the ammonia liberated during the reaction.

(I)





(II)

(a) R = Me, R′ = H
(b) R = Ph, R′ = H
(c) R = Ph, R′ = Me
(d) R = Ph, R′ = Et
(e) R = p-MeO·C_6H_4, R′ = H
(f) R = Ph·CHMe, R′ = H

The synthesis of 2-α-hydroxybenzylimidazoline (IIb) was carried out from amygdalin, which yielded in turn mandelonitrile[11] and ethyl (—)-mandelimidate hydrochloride.[1] The imidate salt was then treated with ethylenediamine in alcohol,[12] and ethanolic hydrogen chloride was added at intervals in an endeavour to neutralise the ammonia liberated during the reaction and hence prevent racemisation. [Roger and Reid[1] report racemisation of ethyl (—)-mandelimidate hydrochloride during the preparation of (—)-mandelamidinium chloride (Ib) when more than one mol. of ammonia was employed.]

Correlation of configuration of the imidazolines is possible in three cases only (IIa, b, c) as no report has been found for the configuration of α-hydroxy-α-phenyl- or α-hydroxy-β-phenyl-butyric acid or their simple derivatives. (+)-2-1′-Hydroxyethylimidazolinium chloride (IIa, as hydrochloride), prepared from (+)-lactamidinium chloride has the D-configuration (*R*) as the (+)-amidinium chloride has been related to D-(—)-lactic acid *via* D-(+)-2-1′-hydroxyethylbenzimidazole (*R*).[4,13] Ethyl (—)-mandelimidate hydrochloride, the precursor of (—)-mandelamidinium chloride (Ib) and of (—)-2-α-hydroxybenzylimidazolinium chloride (IIb, as hydrochloride) is known to be related to D-(—)-mandelic acid,[1] hence these compounds also belong to the D-series (*R*). Similarly, (+)-atrolactamidinium chloride can be hydrolysed to L-(+)-atrolactic acid[2,14] and hence (—)-2-(α-hydroxy-α-methylbenzyl)imidazoline (IIc) belongs to the L-series (*S*).

In view of the marked change in optical rotatory power of certain of the imidazolines (IIc and d) in neutral and in acid solution, and because of the difficulty in obtaining reasonably large samples of 2-1′-hydroxyethylimidazoline (which like most lactic acid derivatives has but a small specific rotation), a separate study of these compounds by spectropolarimeter is now under way in conjunction with another laboratory. It is of interest that the α-hydroxyimidazolines 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-hydroxy-group. Comparison of this work with that of Lutz and Jirgensons[15] on the effect of pH on the α-amino-acids may thus prove relevant.

Imidazoline	$[\alpha]_{5461}$ in EtOH	EtOH–HCl
IIc	−110·2°	+24·6°
IId	−105·6	+27·1

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[9] McKenzie and Wren, *J.*, 1919, **115**, 602.
[10] McKenzie and Smith, *J.*, 1922, **121**, 1348; *Ber.*, 1925, **58**, 894.
[11] Smith, *Ber.*, 1931, **64**, 427.
[12] Bristow, *J.*, 1957, 513.
[13] Dimler and Link, *J. Biol. Chem.*, 1942, **143**, 557.
[14] Mislow and Heffler, *J. Amer. Chem. Soc.*, 1952, **74**, 3668.
[15] Lutz and Jirgensons, *Ber.*, 1930, **63**, 448; 1931, **64**, 1221.

EXPERIMENTAL

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

(+)-2-1′-*Hydroxyethylimidazolinium Chloride* (IIa).—Prepared from (+)-lactamidinium chloride (1 g.), $[\alpha]_{5461}$ +16·8° (in water) {lit.,[4] $[\alpha]_{5461}$ +16·8° (in water)}, by the method used by Klarer and Urech [7] for the (±)-compound, (+)-2-1′-*hydroxyethylimidazolinium chloride* (0·5 g.) had $[\alpha]_{5461}^{22}$ +10·3° (*c* 0·51 in water), softened at 200°, and melted at 202—203° (Found: C, 40·4; H, 7·9; N, 19·2. $C_5H_{11}ClN_2O$ requires C, 39·9; H, 7·3; N, 18·6%). The (+)-imidazolinium chloride (0·5 g.) was dissolved in water (0·2 ml.) and treated with concentrated potassium carbonate solution. The precipitate, formed on cooling, recrystallised from ethyl acetate (charcoal), giving the imidazoline (0·15 g.), m. p. 92—94°, which decomposed within about 21 days. The hydrochloride re-formed from the freshly prepared imidazoline had m. p. 201—202° and gave no depression with authentic material.

Ethyl (−)-*Mandelimidate Hydrochloride.*—Optically active mandelonitrile was prepared from amygdalin by Smith's method [11] and obtained by evaporation of the benzene solution *in vacuo*. It was then converted by the Pinner method [8,16] into ethyl (−)-mandelimidate hydrochloride (59%, based on amygdalin), $[\alpha]_{5461}^{20}$ −169·0° (*c* 0·53 in ethanol), m. p. 106—108° (decomp.; softens at 103°) {Roger and Reid [1] give m. p. 106—108° (decomp.), $[\alpha]_{5461}^{18}$ −171° (in ethanol)} (Found: N, 6·5. Calc. for $C_{10}H_{14}ClNO_2$: N, 6·5%).

(−)2-α-*Hydroxybenzylimidazolinium Chloride* (IIb).—This was prepared by an adaptation of Bristow's method [12] for the (±)-compound. Ethyl (−)-mandelimidate hydrochloride (3 g.) was treated at 0° with ethylenediamine (0·9 g.) in ethanol (15 ml.). Traces of ethanolic hydrogen chloride were added from time to time in an effort to reduce the ammonia concentration. After 1 hr. the product was filtered off, washed with ether, and heated in ethanolic hydrogen chloride, attempts being made to keep the solution just acid. The crude product (2 g.) was finally precipitated with ether, filtered, dissolved in water, and treated with dilute ammonia. 2-α-*Hydroxybenzylimidazoline*, after crystallisation from ethyl alcohol–acetone, had m. p. 142—146° (hot stage) (Found: C, 67·6; H, 7·2; N, 15·8. $C_{10}H_{12}N_2O$ requires C, 68·2; H, 6·8; N, 15·9%). (−)-2-α-*Hydroxybenzylimidazolinium chloride*, formed by interaction of the base and ethanolic hydrogen chloride, had $[\alpha]_{5461}^{19}$ −81·8° (*c* 0·54 in water), became yellow above 200°, and contracted and melted to a dark oil at 212—213° (Found: C, 56·6; H, 6·3. $C_{10}H_{13}ClN_2O$ requires C, 56·5; H, 6·1%).

2-(α-*Hydroxy*-α- *or* -β-*phenyl-alkyl*)*imidazolines* (IIc, d, e, f).—The amidinium chlorides (1 g.) were heated with ethylenediamine (0·5 g.) in alcohol (5 ml.) for 1 hr. Sodium hydroxide or ammonia solution was then added to the alcohol solution with cooling and the resulting *imidazoline* filtered off and recrystallised from ethyl acetate (charcoal) (see Table).

(−)-2-(α-*Hydroxy*-α-*methylbenzyl*)*imidazoline* (IIc), prepared from (+)-atrolactamidinium chloride, $[\alpha]_{5461}$ +55·2° (in water) {lit.,[2] $[\alpha]_{5461}$ +54·8°; (in water)}, had $[\alpha]_{5461}^{25}$ −110·2° (*c* 1·0 in ethanol) and after addition of three drops of concentrated hydrochloric acid had $[\alpha]_{5461}^{25}$ +24·6°.

Imidazoline	M. p.*	Yield (%)	Found (%)			Required (%)		
			C	H	N	C	H	N
(±)-(IIc)	157—158°	56	69·1	7·1	15·6	69·5	7·4	14·8
(−)-(IIc)	143—144	50	70·1	7·4	14·6	,,	,,	,,
(±)-(IId)	129—130	55	70·9	8·0	13·5	70·6	7·8	13·7
(−)-(IId)	150—151	52	70·3	8·0	13·9	,,	,,	,,
(±)-(IIf)	179—181	60	71·1	7·9	13·5	,,	,,	,,
(−)-(IIf)	175—177	60	70·4	7·8	13·6	,,	,,	,,
(±)-(IIe)	148—150	45	64·2	7·4	13·6	64·1	6·8	13·6

* All samples contract about 2° below the m. p.

(−)-2-(α-*Hydroxy*-α-*ethylbenzyl*)*imidazoline* (IId), prepared from (+)-α-hydroxy-α-phenylbutyramidinium chloride, $[\alpha]_{5461}$ +50·3° (in water {lit.,[3] $[\alpha]_{5461}$ +48·9° (in water)}, had $[\alpha]_{5461}^{19}$ −105·6° (*c* 0·8 in ethanol), and after addition of three drops of concentrated hydrochloric acid had $[\alpha]_{5461}^{19}$ +27·1°.

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[16] Pinner, " Die Imidoäther und ihre Derivate," Oppenheim, Berlin, 1892.

(−)-2-(α-*Hydroxy*-β-*methylphenethyl*)*imidazoline* (IIf), prepared from (−)-α-hydroxy-β-phenylbutyramidinium chloride, $[\alpha]_{5461}$ −39·2° (in water) {lit.,[3] $[\alpha]_{5461}$ −43·6° (in water)}, had $[\alpha]_{5461}^{20}$ −34·0° (*c* 0·80 in ethanol).

Attempted Preparation of Optically Active 2-(α-*Hydroxy*-4-*methoxybenzyl*)*imidazoline* (IIe).—(−)-4-Methoxymandelamidinium chloride (1 g.), $[\alpha]_{5461}$ −87·9° (in water) {lit.,[4] $[\alpha]_{5461}$ −87·9° (in water)}, and ethylenediamine (0·3 g.) in ethanol (5 ml.) were refluxed together for 40 min. Ethanolic hydrogen chloride was added from time to time in an endeavour to neutralise ammonia as it was formed. The product, worked up as described above, had m. p. 146—149°, $[\alpha]_{5461}$ 0·0° (in ethanol), and was identical with the (±)-imidazoline prepared from the (±)-amidinium chloride (Ie).

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