N,O-Heterocycles, 24[1]

Novel Approach to the Ring-Opening Reaction of Isoxazolidinium Salts to 1,3-Amino Alcohols

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Received June 25, 1987

Substituted isoxazolidinium salts 6–14 undergo ring-opening reaction when treated with lithium iodide to yield 1,3-amino alcohols 15–23 having multiple chiral centres. The overall process proceeds through a probable single-electron-transfer mechanism with the redox system being the N,O-heterocyclic cations and the iodide anion.

N,O-Heterocyclen, 24[1]. – Eine neue Untersuchung der Ringöffnung von Isoxazolidiniumsalzen zu 1,3-Aminoalkoholen

Die Umsetzung der substituierten Isoxazolidiniumsalze **6–14** mit Lithiumiodid führt zur Ringöffnung, aus der 1,3-Aminoalkohole **15–23** entstehen, die verschiedene chirale Atome enthalten. Vermutlich verläuft die Reaktion über einen Single-electron-transfer-Mechanismus, in dem das Redoxsystem aus dem N,O-heterocyclischen Kation und dem Iodid-Ion besteht.

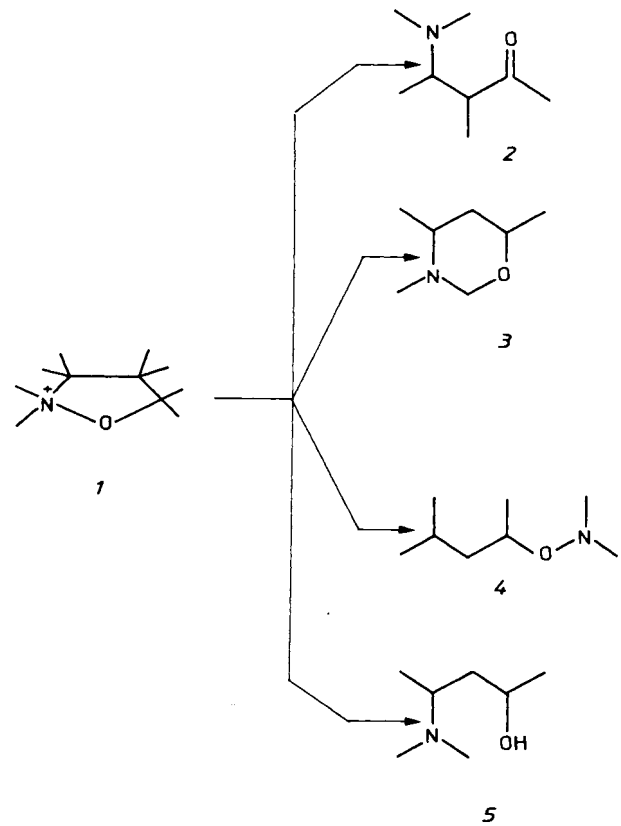
Isoxazolidines[2], 1,3-dipolar cycloadduct products of nitrones to olefines[3], are versatile intermediates in organic synthesis for simple[4–6] and complex molecules having biological interest[3,7–11]. This remarkably powerful approach to the formation of carbon-carbon and carbon-oxygen bonds involves the initial condensation of carbonyl compounds with *N*-substituted hydroxylamines to nitrones[3] or other alternative procedures[12–15], followed by the inter-[3–9] or intramolecular[10,11,15] 1,3-dipolar cycloaddition to double bonds.

Essentially all the recent applications of such N,O-heterocyclic intermediates to the total synthesis of natural products depend on the subsequent facility with which the chemical modification of the N–O bond in the five-membered ring can be performed under mild conditions producing open-chain derivatives. Many chemical methods rely on catalytic hydrogenation of the isoxazolidine nucleus, which is regioselectively cleaved at the N–O bond by hydrogenolysis[2,16–22] to unmask the 1,3-amino alcohol moiety. Thus, reductive scission of substituted isoxazolidines to acyclic derivatives takes place in the presence of 10% Pd/C with uptake of only one equivalent of hydrogen leading to variable yield of products[16–22]. Reductive procedures other than catalytic hydrogenation have also to be applied in some cases, owing to the obvious limitation imposed by schemes which include hydrogenation, i.e. double bonds present in the molecules are clearly not amenable. The reduction with zinc in acetic acid/water[2,23–25] has, therefore, also been used, while the oxidation with *m*-chloroperbenzoic acid[26a,b] has been exploited in order to achieve the chemical transformation of the initial N,O-heterocycles. Some peculiar isoxazolidine structures are ring-opened by $LiAlH_4$ treatment[27,28], by heating in methanol[29], in toluene with potassium *tert*-butoxide[28], in methanol with sodium methoxide[30], and by the reaction with dilute hydrogen fluoride[31].

Since there has been a continuing search of simple and different procedures for functional group transformation to the open ring products, the quaternary ammonium cations of isoxazolidinium structure **1** (Scheme 1) have also been used for the chemical conversion of the primary 1,3-dipolar cycloadducts.

The isoxazolidinium salts can undergo chemical modifications leading to opening of the five-membered ring as shown in Scheme 1 by basic reagents[2,6,9,28,32], by hydrogenolysis[16,33–35], by zinc dust in acetic acid[7,8,26b,36–40], and $LiAlH_4$ treatment[4,5,7,9,26b,41].

Scheme 1



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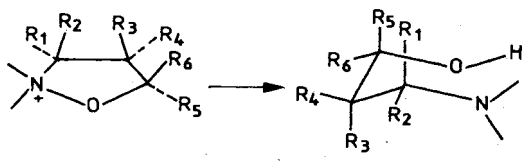
The development of a novel and convenient method for the transformation of the five-membered ring of the model N,O-heterocyclic compounds **1** to the corresponding 1,3-amino alcohols **5** has now been achieved by the use of alkaline iodides as reagents. The synthetic procedure here reported allows the stereoselective creation of open-chain molecules having multiple chiral moieties.

Results and Discussion

A 1:2 mixture of the reactants **6**–**14** and LiI in dioxane solution afforded, after 7–12 h refluxing, the 1,3-amino alcohols **15**–**23** (Table) in yields ranging from 53 to 85% according to the precursor isoxazolidinium salts, as shown in Scheme 2.

Scheme 2



6 - 14 15 - 23

Reaction of some isoxazolidinium salts **6**–**14** with LiI to form 1,3-amino alcohols (yields in %)

Compounds	R_1	R_2	R_3	R_4	R_5	R_6	Products	Yield
6	H	C_6H_5	H	H	H	C_6H_5	**15**	85
7	H	C_6H_5	H	H	C_6H_5	H	**16**	53
8	H	C_6H_5	H	H	CH_3	C_6H_5	**17**	76
9	H	p-$CH_3OC_6H_4$	H	$-(CH_2)_3-$		H	**18**	75
10	H	C_6H_5	H	$-(CH_2)_4-$		H	**19**	69
11	H	p-$CH_3OC_6H_4$	H	$-(CH_2)_4-$		H	**20**	63
12	H	p-ClC_6H_4	H	$-(CH_2)_4-$		H	**21**	68
13	H	p-$CH_3OC_6H_4$	H	$-(CH_2)_6-$		H	**22**	71
14	H	C_6H_5	H	$-(CH_2)_6-$		H	**23**	79

When the reaction is carried out with equivalent amounts of LiI, longer reaction times are required for the conversion of the heterocycles **6**–**14** to the acyclic products **15**–**23**. Analogous results have been obtained when Na^+ and K^+ are used as counter ions. The choice of LiI results in a more efficient reaction procedure for its solubility properties. Moreover, the isoxazolidinium iodides **6**–**14** do not react, under identical conditions, when the iodide ion is not added, as experimentally proved.

The synthetic scheme described afforded also side products of α,β-enonic and isoxazolidinic structure with yields depending on the precursor isoxazolidinium salts, which have been isolated and characterized after the conventional workup followed by short-column chromatography under slight pressure[42]. The structures of all the isolated products have been assigned on the basis of their analytical and spectral properties (see Experimental). The regiochemistry of the substituted isoxazolidine precursors and of the isoxazolidinium salts derived is based on ^{1}H-NMR resonance signals[43,41] and on NOE experiments[44]. The relative configurational assignment to the enantiomeric 1,3-amino alcohols **15**–**23** has been attributed by correlation of their NMR chemical shifts and $J_{1,2}$ coupling constants with those of similar corresponding derivatives of known configuration[45,46] and by NOE experiments[44].

The novel ring-opening of isoxazolidinium salts has been performed on the 1,3-dipolar cycloaddition adducts between nitrones and alkenes followed by the chemical activation of the N–O bond of the five-membered heterocyclic molecules by methoiodide formation. This process is a simple procedure which can evolve through a complex redox reaction with the formation of iodine, experimentally ascertained, from the iodide oxidation. The competitive reaction channels show that the most facile process is that leading to substituted 1,3-amino alcohols probably by a single-electron-transfer mechanism[47,48].

This work was supported by *Consiglio Nazionale delle Ricerche* (CNR) and *Ministero della Pubblica Istruzione* (MPI, project of national interest-40%) grants.

Experimental

The isoxazolidinic substrates were prepared, as isomeric mixtures, from *N*-methyl,α-phenylnitrone and the appropriate olefines[2]. Pure epimers were obtained with 70–90% isolated yields, based on the composition of the crude mixture, by flash chromatography[42] (diethyl ether/petrolether 40–70). – Melting points: Kofler hot-stage apparatus, uncorrected. – IR spectra: Perkin Elmer 377. – ^{1}H-NMR spectra: Varian XL-100 (100 MHz) or Brucker WM 300 (300 MHz), tetramethylsilane as internal standard, $CDCl_3$ as solvent. Axial and equatorial hydrogen atoms in compounds **15**–**23** (Scheme 2) are indicated as H_a and H_e, respectively. – EI mass spectra: Varian MAT CH-5 DF spectrometer equipped with a Varian spectro-system SS-100 computer. – FAB spectra: Glycerol solutions, VG ZAB 2F mass spectrometer equipped with a MSCAN stearable gun operated with xenon gas at 9.5 keV at 1000 resolution. – Merck silica gel 60 H without gypsum was used for preparative short column chromatography and Merck silica gel precoated plates for analytical thin layer chromatography. – Elemental analyses: Perkin Elmer 240 elemental analyser.

Preparation of Substituted Isoxazolidinium Salts **6**–**14**: The solution of the purified isoxazolidine epimer (10 mmol) in iodomethane (1 ml) was stirred at room temperature for ca. 12 h. The iodomethane was removed and the residue washed with ether (2 × 10 ml) to give 80–99% yields of the expected isoxazolidinium salts **6**–**14** as solids.

(3RS, 5SR)-2,2-Dimethyl-3,5-diphenylisoxazolidinium Iodide (**6**): 99% yield; m.p. 115–117°C. – IR (1% KBr disc): ν = 3080–2800 cm^{-1}, 1600, 1450, 1240, 1010, 765, 705. – ^{1}H NMR (100 MHz): δ = 3.10–3.44 (2H, m, 4-H_2), 3.16 (3H, s, NMe), 4.02 (3H, s, NMe) 6.46 (1H, m, 5-H), 6.76 (3H, m, 3-H), 7.36–7.96 (10H, m, Ar). – FAB: *m/z* = 254 [(M – I)$^+$].

$C_{17}H_{20}INO$ (381.2) Calcd. C 53.55 H 5.28 N 3.67
Found C 53.60 H 5.24 N 3.72

(3RS, 5RS)-2,2-Dimethyl-3,5-diphenylisoxazolidinium Iodide (**7**): 99% yield; m.p. 135–137°C. – IR (1% KBr disc): ν = 3080–2800 cm^{-1}, 1450, 1000, 930, 760, 700. – ^{1}H NMR (100 MHz): δ = 2.82–2.95 (1H, m, 4-H), 3.43 (3H, s, NMe), 3.80 (3H, s, NMe), 4.15

(1H, m, 4-H), 6.10 (1H, dd, 5-H), 6.30 (1H, dd, 3-H), 7.28–8.15 (10H, m, Ar). – FAB: m/z = 254 [(M – I)$^+$].

$C_{17}H_{20}INO$ (381.2) Calcd. C 53.55 H 5.28 N 3.67
Found C 53.57 H 5.21 N 3.59

(3RS, 5SR)-2,2,5-Trimethyl-3,5-diphenylisoxazolidinium Iodide (**8**): 99% yield, m.p. 185–187°C. – IR (1% KBr disc): ν = 3080–2800 cm^{-1}, 1430, 1090, 1030, 890, 760, 700. – ^{1}H NMR (100 MHz): δ = 2.05 (3H, s, 5-Me), 3.24–3.48 (1H, m, 4-H), 3.54 (3H, s, NMe), 3.80 (3H, s, NMe), 4.44 (1H, m, 4-H), 5.02 (1H, dd, 3-H), 7.08–8.24 (10H, m, Ar). – FAB: m/z = 268 [(M – I)$^+$].

$C_{18}H_{22}INO$ (395.3) Calcd. C 54.69 H 5.61 N 3.54
Found C 54.67 H 5.57 N 3.57

(3RS, 3aSR, 6aSR)-3,3a,4,5,6,6a-Hexahydro-3-(4-methoxyphenyl)cyclopent[d]isoxazolium Iodide (**9**): 88% yield; m.p. 158–162°C. – IR (1% KBr disc): ν = 3060–2800 cm^{-1}, 1060, 850, 760, 700. – ^{1}H NMR (100 MHz): δ = 1.62–2.40 [6H, m, $-(CH_2)_3-$], 3.40 (3H, s, NMe), 3.67 (3H, s, NMe), 3.87 (3H, s, OMe), 4.06–4.42 (1H, m, 3a-H), 5.16 (1H, d, 3-H), 5.60 (1H, m, 6a-H), 7.00–7.14 (2H, m, Ar), 8.00–8.18 (2H, m, Ar). – FAB: m/z = 248 [(M – I)$^+$].

$C_{15}H_{22}INO_2$ (375.2) Calcd. C 48.01 H 5.91 N 3.73
Found C 47.96 H 5.96 N 3.66

(3RS, 3aSR, 7aSR)-Octahydro-2,2-dimethyl-3-phenyl-1,2-benzisoxazolium Iodide (**10**): 90% yield; m.p. 153–155°C. – IR (1% KBr disc): ν = 3040 cm^{-1}, 1450, 740, 700. – ^{1}H NMR (100 MHz): δ = 1.12–2.40 [8H, m, $-(CH_2)_4-$], 3.22 (3H, s, NMe), 3.88 (3H, s, NMe), 3.76–4.22 (1H, m, 3a-H), 5.10 (1H, m, 7a-H), 6.10 (1H, d, 3-H), 7.52–7.74 (3H, m, Ar), 8.04–8.20 (2H, m, Ar). – FAB: m/z = 232 [(M – I)$^+$].

$C_{15}H_{22}INO$ (359.2) Calcd. C 50.15 H 6.17 N 3.89
Found C 50.19 H 6.14 N 3.83

(3RS, 3aSR, 7aSR)-Octahydro-3-(4-methoxyphenyl)-2,2-dimethyl-1,2-benzisoxazolium Iodide (**11**): 81% yield; m.p. 96–98°C. – IR (1% KBr disc): ν = 3400–2830 cm^{-1}, 1600, 1500, 1250, 1020, 835, 760. – ^{1}H NMR (100 MHz): δ = 1.18–2.28 [8H, m, $-(CH_2)_4$], 3.18 (3H, s, NMe), 3.84 (3H, s, NMe), 3.80–4.00 (1H, m, 3a-H), 4.92 (1H, m, 7a-H), 5.96 (1H, d, 3-H, 7.00–7.16 (2H, m, Ar), 7.92–8.06 (2H, m, Ar). – FAB: m/z = 262 [(M – I)$^+$].

$C_{16}H_{24}INO_2$ (389.3) Calcd. C 49.37 H 6.21 N 3.60
Found C 49.39 H 6.24 N 3.55

(3RS, 3aSR, 7aSR)-3-(4-Chlorophenyl)-2,2-dimethyl-1,2-benzisoxazolium Iodide (**12**): 95% yield; m.p. 117–120°C. – IR (1% KBr disc): ν = 3030–2800 cm^{-1}, 1600, 1490, 940, 870, 850. – ^{1}H NMR (100 MHz): δ = 1.18–2.32 [8H, m, $-(CH_2)_4-$], 3.20 (3H, s, NMe), 3.89 (3H, s, NMe), 3.92–4.16 (1H, m, 3a-H), 5.06 (1H, m, 7a-H), 6.12 (1H, d, 3-H), 7.50–7.64 (2H, m, Ar), 7.64–7.78 (2H, m, Ar). – FAB: m/z = 268 [(M – I)$^+$][49].

$C_{15}H_{21}ClINO$ (393.7) Calcd. C 45.76 H 5.37 N 3.56
Found C 45.79 H 5.35 N 3.52

(3RS, 3aSR, 9aSR)-Decahydro-3-(4-methoxyphenyl)-2,2-dimethylcyclooct[d]isoxazolium Iodide (**13**): 84% yield; m.p. 176–178°C. – IR (1% KBr disc): ν = 3030–2720 cm^{-1}, 1600, 1510, 1250, 1170, 850, 775. – ^{1}H NMR (100 MHz): δ = 1.06–2.49 [12H, m, $-(CH_2)_6-$], 3.40 (3H, s, NMe), 3.66 (3H, s, NMe), 3.80–4.00 (1H, m, 3a-H), 3.90 (3H, s, OMe), 4.94–5.52 (2H, m, 3,9a-H), 7.00–7.18 (2H, m, Ar), 7.90–8.10 (2H, m, Ar). – FAB: m/z = 290 [(M – I)$^+$].

$C_{18}H_{28}INO_2$ (417.3) Calcd. C 51.80 H 6.76 N 3.36
Found C 51.81 H 6.73 N 3.32

(3RS, 3aSR, 9aSR)-Decahydro-2,2-dimethyl-3-phenylcyclooct[d]isoxazolium Iodide (**14**): 95% yield; m.p. 120–122°C. – IR (1% KBr disc): ν = 3060–2800 cm^{-1}, 1465, 1455, 735, 700. – ^{1}H NMR (100 MHz): δ = 1.10–2.38 [12H, m, $-(CH_2)_6-$], 3.40 (3H, s, NMe), 3.68 (3H, s, NMe), 3.85–3.98 (1H, m, 3a-H), 5.22 (1H, t, 9a-H), 5.46 (1H, d, 3-H), 7.48–7.60 (3H, m, Ar), 7.97–8.04 (2H, m, Ar). – FAB: m/z = 260 [(M – I)$^+$].

$C_{17}H_{26}INO$ (387.3) Calcd. C 52.72 H 6.77 N 3.62
Found C 52.70 H 6.78 N 3.65

General Procedure for the Synthesis of Substituted Amino Alcohols **15–23**: Lithium iodide (20 mmol) was slowly added to a stirred solution of isoxazolidinium iodide **6–14** (10 mmol) in 35 ml of dioxane. The mixture was then refluxed with stirring for 7–12 h, except for **10**, which was refluxed for 4 h. 10 ml of 10% sodium sulfite solution was added and after 5 min stirring the solution was extracted with chloroform (3 × 10 ml). The solvent was evaporated in vacuo and the residue was purified by flash chromatography [methanol/chloroform (3:97/v:v)] to give the amino alcohols **15–23** as solid or oil. Similar treatment was performed on 10 mmol of compound **10**, without the addition of lithium iodide, with recovering of unreacted starting material. Isoxazolidinium salt **10** (10 mmol) was also refluxed for 8 h with an equimolar amount of lithium iodide (10 mol) in dioxane. After the usual workup, the amino alcohol **19** was recovered with 54% yield.

(1RS, 3SR)-3-(Dimethylamino)-1,3-diphenyl-1-propanol (**15**) was purified by flash chromatography to give 85% of a colourless oil. – IR (neat): ν = 3500–3100 cm^{-1}, 3080–2760, 1445, 1060, 1020, 755, 700. – ^{1}H NMR (300 MHz): δ = 1.74–1.85 (1H, m, 2-H$_e$), 2.23 (6H, s, NMe_2), 2.32–2.46 (1H, m, 2-H$_a$), 4.4 (1H, dd, J = 3 and 13 Hz, 2-H$_a$), 5.1 (1H, dd, J = 3 and 13 Hz, 1-H$_a$), 7.14–7.48 (10H, m, Ar). – MS: m/z (%) = 255 ($M^{+\cdot}$, <2), 135 (11), 134 (100), 105 (11), 104 (12), 91 (9), 77 (16). – FAB: m/z = 256 [(M + H)$^+$].

$C_{17}H_{21}NO$ (255.4) Calcd. C 79.96 H 8.29 N 5.48
Found C 79.99 H 8.33 N 5.44

(1RS, 3RS)-3-(Dimethylamino)-1,3-diphenyl-1-propanol (**16**) was purified by flash chromatography to give an oil in 53% yield. – IR (neat): ν = 3500–3100 cm^{-1}, 3080–2770, 1445, 1065, 760, 700. – ^{1}H NMR (300 MHz): δ = 1.88–1.98 (1H, m, 2-H$_e$), 2.17 (6H, s, NMe_2), 2.67–2.79 (1H, m, 2-H$_a$), 3.60 (1H, dd, 3-H$_a$), 5.09 (1H, t, J = 3 and 5 Hz, 1-H$_e$), 6.18 (1H, broad, OH), 7.08–7.41 (10H, m, Ar). – MS: m/z (%) = 255 ($M^{+\cdot}$, <2), 135 (9), 134 (100), 105 (7), 104 (5), 91 (5), 77 (11). – FAB: m/z = 256 [(M + H)$^+$].

$C_{17}H_{21}NO$ (255.4) Calcd. C 79.96 H 8.29 N 5.48
Found C 79.91 H 8.30 N 5.43

(2RS, 4SR)-4-(Dimethylamino)-2,4-diphenyl-2-butanol (**17**) was purified by flash chromatography to give 76% of a colourless solid with m.p. 78–80°C. – IR (1% KBr disc): ν = 3500–3100 cm^{-1}, 3080–2730, 1440, 1210, 1065, 765, 700. – ^{1}H NMR (300 MHz): δ = 1.55 (3H, s, 1-H$_3$), 1.98 (1H, dd, 3-H$_e$), 2.18 (6H, s, NMe_2), 2.63 (1H, dd, J = 3 and 14 Hz, 3-H$_a$), 3.66 (1H, dd, 4-H$_a$), 6.98–7.50 (10H, m, Ar). – MS: m/z (%) = 269 ($M^{+\cdot}$, <2), 135 (8), 134 (100), 91 (5), 77 (5). – FAB: m/z = 270 [(M + H)$^+$].

$C_{18}H_{23}NO$ (269.4) Calcd. C 80.25 H 8.61 N 5.20
Found C 80.24 H 8.58 N 5.15

(1RS, 2RS, 1'SR)-2-[(Dimethylamino)(4-methoxyphenyl)methyl]-cyclopentanol (**18**) was purified by flash chromatography to give 75% of a colourless solid with m.p. 69–70°C. – IR (1% KBr disc): ν = 3400 cm^{-1}, 3020–2740, 1500, 1245, 1030, 850, 800. – ^{1}H NMR (300 MHz): δ = 1.06–2.04 [6H, m, $-(CH_2)_3-$], 2.14 (6H, s, NMe_2), 2.34–2.68 (1H, m, 2-H$_a$), 3.67 (1H, d, J = 12 Hz, 1'-H$_a$), 3.82 (3H, s, OMe), 4.34–4.58 (1H, m, 1-H$_e$), 6.82–7.34 (4H, m,

Ar). – MS: *m/z* (%) = 249 ($M^{+\cdot}$, <1), 165 (11), 164 (100), 121 (15). – FAB: *m/z* = 250 [(M + H)$^+$].

$C_{15}H_{23}NO_2$ (249.3) Calcd. C 72.25 H 9.29 N 5.62
Found C 72.28 H 9.28 N 5.57

(1RS, 2RS, 1'SR)-2-[(Dimethylamino)phenylmethyl]cyclohexanol (**19**) was purified by flash chromatography to give 69% of a colourless solid with m.p. 112–113°C. – IR (1% KBr disc): ν = 3500 cm^{-1}, 3050–2730, 1440, 1005, 980, 750, 700. – ^{1}H NMR (300 MHz): δ = 1.22 [4H, m, $-(CH_2)_2-$], 1.78 [4H, m, $-(CH_2)_2-$], 2.18 (6H, s, NMe_2), 2.36–2.64 (1H, m, 2-H_a), 3.96 (1H, d, *J* = 12 Hz, 1'-H_a), 3.94–4.13 (1H, m, 1-H_e), 7.10–7.50 (5H, m, Ar). – MS: *m/z* (%) = 233 ($M^{+\cdot}$, <1), 135 (9), 134 (100), 91 (9). – FAB: *m/z* = 234 [(M + H)$^+$].

$C_{15}H_{23}NO$ (233.4) Calcd. C 77.20 H 9.93 N 6.00
Found C 77.16 H 9.88 N 5.96

(1RS, 2RS, 1'SR)-2-[(Dimethylamino)(4-methoxyphenyl)methyl]-cyclohexanol (**20**) was purified by flash chromatography to give 63% of a colourless solid with m.p. 93–95°C. – IR (1% KBr disc): ν = 3380 cm^{-1}, 3040–2720, 1500, 1250, 1040, 840. – ^{1}H NMR (300 MHz): δ = 1.22 [4H, m, $-(CH_2)_2-$], 1.78 (4H, m, $-(CH_2)_2-$], 2.2 (6H, s, NMe_2), 2.32–2.54 (1H, m, 2-H_a), 3.84 (3H, s, OMe), 3.95 (1H, d, *J* = 13 Hz, 1'-H_a), 3.98–4.16 (1H, m, 1-H_e), 4.96 (1H, broad, OH), 6.84–7.40 (4H, m, Ar). – MS: *m/z* (%) = 263 ($M^{+\cdot}$, <1), 165 (12), 164 (100), 121 (12). – FAB: *m/z* = 264 [(M + H)$^+$].

$C_{16}H_{25}NO_2$ (263.4) Calcd. C 72.96 H 9.57 N 5.32
Found C 72.95 H 9.54 N 5.29

(1RS, 2RS, 1'SR)-2-[(4-Chlorophenyl)(dimethylamino)methyl]-cyclohexanol (**21**) was purified by flash chromatography to give 68% of a colourless solid with m.p. 108–110°C. – IR (1% KBr disc): ν = 3230 cm^{-1}, 3030–2740, 1480, 1010, 845, 825, 790. – ^{1}H NMR (300 MHz): δ = 1.21 [4H, m, $-(CH_2)_2-$], 1.77 [4H, m, $-(CH_2)_2-$], 2.04 (6H, s, NMe_2), 2.27–2.55 (1H, m, 2-H_a), 3.93 (1H, d, *J* = 14 Hz, 1'-H_a), 3.94–4.14 (1H, m, 1-H_e), 5.36 (1H, broad, OH), 7.04–7.48 (4H, m, Ar). – MS: *m/z* (%)[49] = 269 ($M^{+\cdot}$, <1), 171 (5), 170 (32), 169 (11), 168 (100), 125 (6). – FAB[49]: *m/z* = 270 [(M + H)$^+$].

$C_{15}H_{22}ClNO$ (267.8) Calcd. C 67.27 H 8.28 N 5.23
Found C 67.26 H 8.23 N 5.27

(1RS, 2RS, 1'SR)-2-[(Dimethylamino)(4-methoxyphenyl)methyl]-cyclooctanol (**22**) was purified by flash chromatography to give 71% of a viscous oil. – IR (neat): ν = 3390 cm^{-1}, 3060–2740, 1500, 1250, 1030, 835. – ^{1}H NMR (300 MHz): δ = 1.02–2.05 [12H, m, $-(CH_2)_6-$], 2.16 (6H, s, NMe_2), 2.36–2.48 (1H, m, 2-H_a), 3.65 (1H, d, *J* = 12 Hz, 1'-H_a), 3.82 (3H, s, OMe), 4.15–4.24 (1H, m, 1-H_e), 4.80 (1H, broad, OH), 6.88–7.16 (4H, m, Ar). – MS: *m/z* (%) = 291 ($M^{+\cdot}$, <1), 165 (15), 164 (100), 121 (14). – FAB: *m/z* = 292 [(M + H)$^+$].

$C_{18}H_{29}NO_2$ (291.4) Calcd. C 74.18 H 10.03 N 4.81
Found C 74.15 H 10.08 N 4.79

(1RS, 2RS, 1'SR)-2-[(Dimethylamino)phenylmethyl]cyclooctanol (**23**) was purified by flash chromatography to give 79% of a colourless solid with m.p. 109–111°C. – IR (1% KBr disc): ν = 3420 cm^{-1}, 3080–2740, 1490, 1260, 1040, 790, 755, 705. – ^{1}H NMR (300 MHz): δ = 1.02–2.03 [12H, m, $-(CH_2)_6-$], 2.12 (6H, s, NMe_2), 2.40–2.53 (1H, m, 2-H_a), 3.62 (1H, d, *J* = 13 Hz, 1'-H_a), 4.14–4.25 (1H, m, 1-H_e), 7.12–7.49 (5H, m, Ar). – MS: *m/z* (%) = 261 ($M^{+\cdot}$, <1), 135 (13), 134 (100), 91 (9). – FAB: *m/z* = 262 [(M + H)$^+$].

$C_{17}H_{27}NO$ (261.4) Calcd. C 78.11 H 10.41 N 5.36
Found C 78.80 H 10.40 N 5.34

Conversion of Isoxazolidinium Salt **10** *into Amino Alcohol* **19** *with NaI and KI:* The above described procedure was also applied to compound **10**, chosen as model system, using different reagents, i.e., sodium iodide and potassium iodide. The amino alcohol **19** was recovered with yields similar to those previously reported, but after prolonging the reaction time from 4 to 7 h.

CAS Registry Numbers

6: 110317-65-2 / **6** (dequaternized form): 110317-58-3 / **7**: 110317-66-3 / **7** (dequaternized form): 110317-59-4 / **8**: 110317-67-4 / **8** (dequaternized form): 110317-60-7 / **9**: 110317-68-5 / **9** (dequaternized form): 110317-61-8 / **10**: 110352-51-7 / **10** (dequaternized form): 61218-39-1 / **11**: 110317-69-6 / **11** (dequaternized form): 110317-62-9 / **12**: 110317-70-9 / **12** (dequaternized form): 110317-63-0 / **13**: 110317-71-0 / **13** (dequaternized form): 110317-64-1 / **14**: 110317-72-1 / **14** (dequaternized form): 33813-05-7 / **15**: 52937-57-2 / **16**: 110352-52-8 / **17**: 54713-29-0 / **18**: 110317-73-2 / **19**: 58641-40-0 / **20**: 110317-74-3 / **21**: 110352-53-9 / **22**: 110317-75-4 / **23**: 110317-76-5

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