PAPERS

Acid-Catalyzed Ring Opening of 2-Substituted Aziridines with Alcohols

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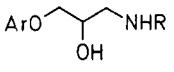
Study of nucleophilic ring opening of various functionalized aziridines (2-alkoxycarbonyl, 2-hydroxymethyl, 2-cyano- and 2-aminomethyl) by alcohols in presence of diethyl ether–boron trifluoride complex.

Amines with two functional groups on their carbon chain are particularly interesting compounds due to their biological and, more particularly, pharmacological activities. For example, 1-alkylamino-3-aryloxy-2-propanols **1**, 3-alkoxy-1,2-diaminopropanes **2**, and 1,3-dialkoxy-2-aminopropanes **3**, which possess some interesting pharmacological activities in cardiovascular research (inhibiting trans-membrane movement of calcium,[1,2] or glutamic acid **4** and its derivatives which constitute CNS neurotransmitters.



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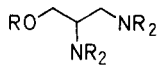

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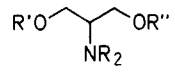

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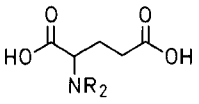

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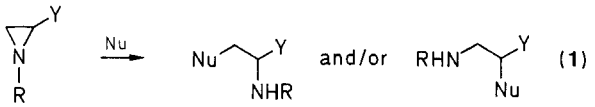
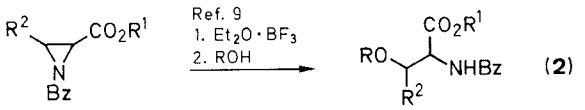
The nucleophilic opening of aziridines possessing functional groups on the carbon atoms can, in principle, give easy access to such structures (eq. 1).



(1)

Several recent publications on the opening of unsubstituted aziridines by nucleophiles such as amines,[3] alcohols,[4,5] and carbanions,[6–8] have led us to describe our own results obtained from opening of various 2-substituted aziridines, e.g., 2-alkoxycarbonyl-, 2-cyano-, 2-aminomethylaziridines.

Ring Opening of 1-Alkyl-2-alkoxycarbonylaziridines with Alcohols. Okawa et al. have shown that 1-benzoyl-2-alkoxycarbonylaziridines react with alcohols in presence of a catalytic amount of diethyl ether–boron trifluoride complex, producing α-acylamino-β-alkoxy esters **5** (eq. 2).[9]

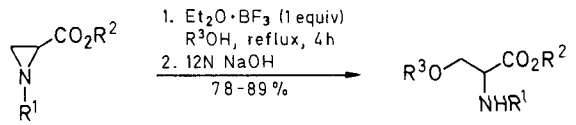


(2)

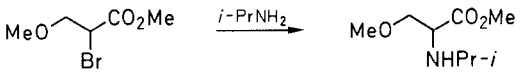
5

Our contribution has been to examine the behavior of *N*-unactived aziridines esters towards various alcohols (Table 1).

The action of methanol on 1-isopropyl-2-methoxycarbonylaziridine **(6)** has been chosen to illustrate this study (Scheme 1). When a solution of aziridine **6** in methanol was stirred in the presence of 5% diethyl ether–boron trifluoride complex for 24 hours at room temperature, no transformation was observed. After heating for 18 hours under reflux, followed by neutralization by sodium hydroxide solution, the formation of a ring-opened compound **7** was observed. Several tests were carried out in the presence of increasing amounts of Lewis acid, that showed that the amount of the transformation of aziridine increases with the concentration of diethyl ether–boron trifluoride complex. If one equivalent diethyl ether–boron trifluoride complex per mole of aziridine was used, the transformation was quantitative after a 4 hours reflux. The ^{1}H NMR and ^{13}C NMR spectra of the resulting product are analogous to those of the derivatives formed by the action of isopropylamine on methyl 1-bromo-2-methoxypropanoate **(8)**. From its microanalysis, the structure can be attributed to that of methyl 1-isopropylamino-2-methoxypropanoate.[7a]



6 **7**



8 **7a**

6	R^1	R^2	6	R^1	R^2
a	*i*-Pr	Me	c	*c*-C_6H_{11}	Me
b	CH_2Ph	Me	d	H	*i*-Pr

7	R^1	R^2	R^3	7	R^1	R^2	R^3
a	*i*-Pr	Me	Me	f	CH_2Ph	Me	Me
b	*i*-Pr	Me	*i*-Bu	g	*c*-C_6H_{11}	Me	Me
c	*i*-Pr	Me	$CH_2C{\equiv}CH$	h	*c*-C_6H_{11}	Me	*i*-Pr
d	*i*-Pr	Me	*i*-Pr	i	*c*-C_6H_{11}	Me	*t*-Bu
e	*i*-Pr	Me	*t*-Bu	j	H	*i*-Pr	Me

Scheme 1

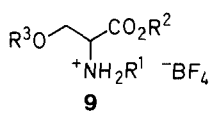
Table 1. Acid-Catalyzed Alcoholysis of Azirdines **6**.

Substrate	Alcohol	Product	Yield (%)[a]	Molecular Formula[b]	IR ($CDCl_3$)[c] ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)	^{13}C NMR ($CDCl_3$) δ
6a	MeOH	**7a**	88	$C_8H_{17}NO_3$ (175.2)	3300, 1740, 1150	1.00 and 1.08 (2d, 6H, J = 6), 2.12 (s, 1H), 2.81 (hept, 1H), 3.36 (s, 3H), 3.50 (m, 3H), 3.75 (s, 3H)	22.20, 23.65, 46.97, 51.53, 58.00, 59.20, 72.20, 174.53
6a	$(CH_3)_2CHCH_2OH$	**7b**	89	$C_{11}H_{23}NO_3$ (217.3)	3300, 1740, 1150	0.95, 1.00, 1.05 (3d, 12H, J = 6), 1.80 (hept, 1H), 2.00 (s, 1H), 2.80 (hept, 1H), 3.20 (d, 2H, J = 6), 3.58 (m, 3H), 3.75 (s, 3H)	19.23, 22.15, 23.65, 28.26, 46.97, 51.78, 58.99, 72.31, 78.28, 174.45
6a	$HC{\equiv}CCH_2OH$	**7c**	78	$C_{10}H_{17}NO_3$ (199.2)	3300, 1740, 1150	0.95, 1.00 (2d, 6H, J = 6), 1.80 (s, 1H), 2.38 (t, 1H, J = 2.2), 2.84 (hept, 1H), 3.30–3.80 (m, 3H), 3.65 (s, 3H), 4.10 (d, 2H, J = 2.2)	22.15, 23.58, 46.97, 52.04, 58.54, 58.73, 71.01, 74.91, 173.99
6a	*i*-PrOH	**7d**	87	$C_{10}H_{21}NO_3$ (203.2)	3300, 1740, 1150	1.07, 1.08 (2d, 12H, J = 6), 2.12 (s, 1H), 2.83 (hept, 2H), 3.30–3.80 (m, 3H), 3.72 (s, 3H)	21.83, 22.02, 23.52, 46.97, 51.84, 59.19, 69.39, 72.25
6a	*t*-BuOH	**7e**	79	$C_{11}H_{23}NO_3$ (217.3)	3300, 1740, 1150	0.95, 1.00 (2d, 6H, J = 6), 1.20 (s, 9H), 1.95 (s, 1H), 2.84 (hept, 1H), 3.30–3.50 (m, 3H), 3.72 (s, 3H)	22.16, 23.66, 27.36, 46.92, 51.73, 59.59, 63.65, 73.23, 174.80
6b	MeOH	**7f**	80	$C_{12}H_{17}NO_3$ (223.2)	3300, 1740, 1150	2.12 (s, 1H), 3.32 (s, 3H), 3.30–3.60 (m, 3H), 3.65 (s, 3H), 3.80 (s, 2H), 7.30 (s, 5H)	
6c	MeOH	**7g**	82	$C_{11}H_{21}NO_3$ (215.3)	3300, 1740, 1150	1.00 and 2.80 (m, 11H), 1.98 (s, 1H), 3.32 (s, 3H), 3.40–3.60 (m, 3H), 3.75 (s, 3H)	23.98, 24.24, 25.35, 32.10, 33.27, 50.95, 54.33, 57.51, 58.28, 73.43, 173.41
6c	*i*-PrOH	**7h**	80	$C_{13}H_{25}NO_3$ (243.3)	3300, 1740, 1150	1.00–2.60 (m, 11H), 1.16 (d, 6H, J = 6), 1.95 (s, 1H), 3.40–3.60 (m, 4H), 3.78 (s, 3H)	21.83, 22.02, 24.81, 25.01, 25.98, 26.31, 32.81, 34.04, 51.78, 55.22, 58.73, 69.58, 72.18, 174.71
6c	*t*-BuOH	**7i**	82	$C_{14}H_{27}NO_3$ (257.3)	3300, 1740, 1150	1.18 (s, 9H), 1.00–2.70 (m, 11H), 1.90 (s, 1H), 3.30–3.58 (m, 3H), 3.73 (s, 3H)	24.81, 25.07, 26.05, 27.35, 32.81, 34.04, 51.71, 55.16, 59.06, 63.60, 73.22, 174.83
6d	MeOH	**7j**	85	$C_7H_{15}NO_3$ (161.2)	3300, 1740, 1150	1.25 (d, 6H, J = 6), 2.42 (s, 1H), 3.38 (m, 3H), 3.62 (s, 3H), 5.10 (hept, 1H)	17.34, 54.70, 59.23, 64.25, 70.03, 168.78

[a] Oil.
[b] Satisfactory microanalysis obtained: C ±0.40, H ±0.30, N ±0.30.
[c] Recorded on a Perkin-Elmer 157 Infra Red Spectrophotometer.

The reaction produced by various alcohols (Table 1) turns out to be regioselective and only gives the product which results from the attack of the nucleophile on the ring methylene (80–90% yield). The necessity of using an equivalent amount of Lewis acid implies the quantitative complexing of the heterocyclic ring. The following observation had led us to put forward a hypothesis on the nature of the intermediates that are formed.

After evaporation of the solvent, and before the addition of sodium hydroxide, crystals are often seen to appear in the oily fraction. Thus, in the case of the opening of **6a** by methanol the crystalline fraction represents approximately 50% of the total mixture: the crystals, which are only slightly soluble in water, are soluble in chloroform. The ^1H NMR spectra of the crystalline derivatives and their microanalyses correspond to the structure of ammonium tetrafluoroborates **9** (Table 2).



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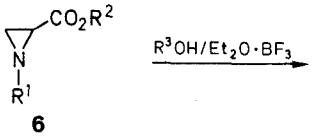
9	R^1	R^2	R^3	9	R^1	R^2	R^3
a	*i*-Pr	Me	Me	**g**	*c*-C_6H_{11}	Me	Me
d	*i*-Pr	Me	*i*-Pr	**h**	*c*-C_6H_{11}	Me	*i*-Pr
f	CH_2Ph	Me	Me	**i**	*c*-C_6H_{11}	Me	*t*-Bu

After treatment with aqueous sodium hydroxide solution, the derivatives **9** liberate the β-alkoxy α-amino esters **7**. The formation of tetrafluoroborate may be interpreted as shown in eq. 3.



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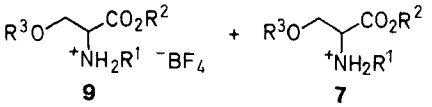


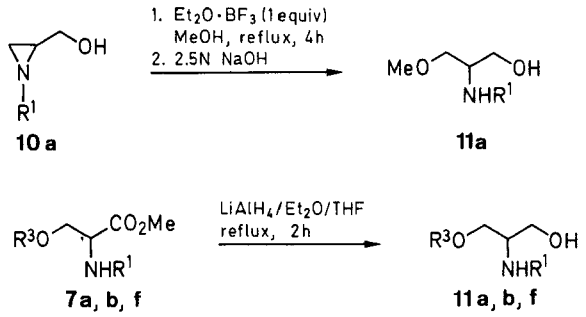
9 **7** (3)

Ring Opening of 2-(Hydroxymethyl)aziridine. The preceding procedure was applied to the opening of 1-isopropyl-2-(hydroxymethyl)aziridine (**10a**). Under the

Table 2. ^1H NMR Data of Tetrafluoroborates **9** Isolated

Product	^1H NMR ($CDCl_3$/TMS), δ, J (Hz)
9a	1.42 (d, 6H, J = 6), 3.42 (s, OCH_3), 3.45 (hept, 1H), 3.80 (m, 2H, CH_2O), 3.82 (s, 3H, CO_2Me), 4.23 (dd, 1H, J = 4, 6), 6.50 (br s, 2H, NH_2)
9d	1.04 and 1.06 (2d, 6H, J = 6), 1.43 (d, 6H, J = 6), 3.50 (hept, 2H), 3.80 (m, 2H, CH_2O), 3.90 (s, 3H, CO_2Me), 4.23 (dd, 1H, J = 4, 6), 6.40 (br s, 2H, NH_2)
9f	3.30 (s, 3H, OCH_3), 3.80 (m, 2H, CH_2O), 3.90 (s, 3H, CO_2Me), 4.19 (dd, 1H, J = 4, 6), 4.42 (s, 2H, CH_2Ph), 6.40 (br s, 2H, NH_2), 7.50 (s, 5H, Ph)
9g	1.0–2.4 (m, 11H, C_6H_{11}), 3.42 (s, 3H, OCH_3), 3.80 (m, 2H, CH_2O), 3.90 (s, 3H, CO_2Me), 4.25 (dd, 1H, J = 4, 6), 6.20 (br s, 2H, NH_2)
9h	1.0–2.5 (m, 11H, C_6H_{11}), 1.22 (d, 6H, J = 6), 3.50 (hept, 1H), 3.80 (m, 2H, CH_2O), 3.90 (s, 3H, OCH_3)
9i	1.0–2.4 (m, 11H, C_6H_{11}), 1.22 (s, 9H, $(CH_3)_3$), 3.80 (m, 2H, CH_2O), 3.90 (s, 3H, CO_2Me), 4.30 (dd, 1H, J = 4, 6), 6.05 (br s, 2H, NH_2)

experimental conditions mentioned, no etherification was observed. The 2-isopropylamino-3-methoxypropanol **11a** formed in this way can also be obtained by reducing ester **7a** with lithium aluminum hydride (Scheme 2).

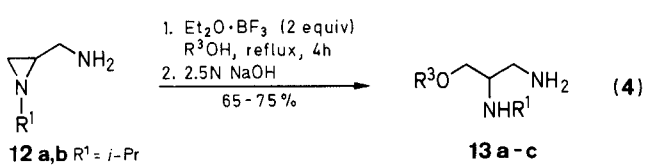


10a **11a** **7a, b, f** **11a, b, f**

7, 10, 11	a	b	f
R^1	*i*-Pr	*i*-Pr	CH_2Ph
R^3	Me	*i*-Bu	Me

Scheme 2

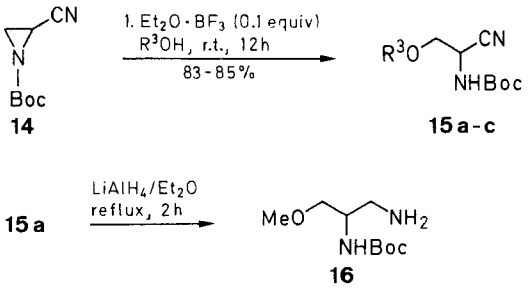
Ring Opening of 2-Aminomethylaziridine. 2-Aminomethyl-1-isopropylaziridine **12a** and 2-aminomethylaziridine **12b** have been opened in a similar way. The reaction, however, requires the use of two equivalents of Lewis acid in order to complex the two amino groups (eq. 4).



12 a,b R^1 = *i*-Pr **c** R^1 = H **13a-c** (4)

13	R^1	R^3
a	*i*-Pr	Me
b	*i*-Pr	*i*-Bu
c	H	Me

Ring Opening of 1-(tert-Butoxycarbonyl)-2-cyanoaziridine by Alcohols. The presence of an electrophilic group (Boc) on nitrogen considerably increases the reactivity of the aziridine. The reaction carried out in the presence of a catalytic amount of diethyl ether–boron trifluoride complex is regioselective (Scheme 3, Table 3).



14 **15a-c** **15a** **16**

15	a	b	c
R^3	Me	*i*-Pr	*t*-Bu

Scheme 3

The reduction of nitrile **15a** by $LiAlH_4$ gives diamine **16**.

This work shows that nucleophilic ring opening of various 2-substituted aziridines activated or non-activated on nitrogen, by alcohols can be carried out in presence of diethyl ether–boron trifluoride complex.

The procedure, among other things, gives access to 3-alkoxy-1,2-diaminopropane and to 3-alkoxy-2-amino-1-propanols, which are of interest in the synthesis of pharmacological active substances in cardiovascular research.[1,2,11]

All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer model 157 spectrophotometer. ^1H and ^{13}C NMR spectra were taken on a JEOL FX60 (60 MHz) or on a Bruker MSL 300 (300 MHz) with TMS as internal standard.

Diethyl ether–boron trifluoride complex (48%) was purchased from Fluka and used in the supplied form. Alcohols used for the ring-opening were dried according ref 12. Aziridines were prepared according by known methods: 1-isopropyl-2-methoxycarbonylaziridine **(6a)**;[13] 1-benzyl-2-methoxycarbonylaziridine **(6b)**;[13] 1-cyclohexyl-2-methoxycarbonylaziridine **(6c)**;[13] 2-isopropyloxycarbonylaziridine **(6d)**;[14] 1-isopropyl-2-(hydroxymethyl)aziridine **(10)** by reduction of 1-isopropyl-2-methoxycarbonylaziridine **(6a)** with $LiAlH_4$;[15] 2-aminomethyl-1-isopropylaziridine **(12a)**, by reduction of 1-isopropyl-2-cyanoaziridine with $LiAlH_4$;[15] 2-aminomethylaziridine **(12b)** by reduction of 2-cyanoaziridine with $LiAlH_4$.[15]

Methyl 2-Isopropylamino-3-methoxypropanoate (7a); Typical Procedure for the Reaction of Aziridines 6 with Alcohols:

A solution of $Et_2O \cdot BF_3$ (12.5 mL, 0.1 mol) was added to a stirred solution of MeOH (250 mL) under cooling in an ice bath at 0°C Aziridine **6a** (14.3 g, 0.1 mol) was then added dropwise and stirring was continued at the same temperature; the mixture was then refluxed for 4 h; the solvent was removed and the residual syrup was neutralized to pH 7 with 12N NaOH solution. The organic layer was extracted with $CHCl_3$ (3 × 200 mL) and the extracts were dried ($MgSO_4$); the solvent was removed and the crude product was purified by silica gel column chromatography with hexane/EtOAc as eluent (80:20); yield: 15.4 g (88%); oil (Table 1). When *t*-BuOH was used as the alcohol, the temperature of addition was 10°C.

Table 3. β-Alkoxy-α-aminonitriles **15** Prepared

Product	Yield (%)[a]	Molecular Formula	IR ($CDCl_3$) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)	^{13}C NMR ($CDCl_3$) δ
15a	83	$C_9H_{16}N_2O_3$ (200.2)	3300 (NH), 2250 (CN), 1690 (NCOO)	1.45 (s, 9H, *t*-Bu), 3.48 (s, 3H, OCH_3), 3.59 (dd, 2H, J = 1.7, 2, 8, CH_2O), 4.70 (dd, J = 2, 8, 1H, CHCN), 5.42 (br s, 1H, NH)	28.10, 43.30, 63.62, 72.40, 81.20, 117.9, 154.20
15b	85	$C_{11}H_{20}N_2O_3$ (228.3)	3300 (NH), 2250 (CN), 1690 (NCO_2), 1150 (CO)	1.15 (d, 6H, J = 6), 1.40 (s, 9H, *t*-Bu), 3.50 (hept, 1H), 3.59 (dd, J = 1.7, 2, 8, 2H, CH_2), 4.60 (dd, 1H, J = 2, 8, CHCN), 5.30 (br s, 1H, NH)	21.70, 28.10, 43.10, 67.30, 72.90, 81.20, 117.70, 154.30
15c	84	$C_{12}H_{22}N_2O_3$ (242.3)	3300 (NH), 2250 (CN), 1690 (NCO_2), 1150 (CO)	1.16 (s, 9H, *t*-Bu), 1.41 (s, 9H, *t*-Bu), 3.53 (2dd, 2H, J = 1.7, 2, 8, CH_2), 4.60 (dd, 1H, J = 2, 8, CHCN), 5.30 (br s, 1H, NH)	27.30, 28.20, 43.50, 61.70, 74.40, 81.20, 117.90, 154.30

[a] Very hygroscopic oils.

Methyl 2-Isopropylamino-3-methoxypropanoate (7a); Prepared from Methyl 2-Bromo-3-methoxypropanoate (8) and Isopropylamine:

i-$PrNH_2$ (6 g, 0.1 mol) was added to a stirred solution of **8** (10 g, 0.05 mol) [prepared by Michael addition of methyl 2-bromoacrylate with sodium methoxide] in MeCN (100 mL) under cooling in an ice bath, and stirring was continued at 0 °C for 24 h; the precipitate was filtered, the organic layer was washed with water (3 × 200 mL), dried ($MgSO_4$). The solvent was evaporated and the resulting oil was purified by silica gel chromatography with hexane/EtOAc as eluent (80:20); yield: 7 g (80%); spectroscopic and analytical data were the same as for **6a** described in Table 1.

Methyl 2-Isopropylamino-3-methoxypropanoate Tetrafluoroborate Salt (9a); Typical Procedure:

A solution of $Et_2O \cdot BF_3$ (12.5 mL, 0.1 mol) was added to a stirred solution of MeOH (250 mL) cooled to 0 °C in an ice bath. Aziridine **6a** (14.3 g, 0.1 mol) was then added dropwise and stirring was continued at the same temperature (0 °C or 10 °C); the mixture was then refluxed for 4 h, the solvent was removed and the resulting oil was recrystallized from heptane: yield: 13.14 g (50%); mp 96–97 °C

$C_8H_{18}NBF_4O_3$	calc.	C 36.53	H 6.90	N 5.32	B 4.10	F 28.90
(263.0)	found	36.01	6.91	5.25	3.85	28.07

^1H NMR data: see Table 2

Methyl 2-Isopropylamino-3-methoxypropanoate **(9d)**, *Methyl 2-Benzylamino-3-methoxypropanoate* **(9f)** *and Methyl 2-Cyclohexylamino-3-methoxypropanoates* **(9g)** *Tetrafluoroborate Salts*, were identified by their ^1H NMR spectra only.

Methyl 2-Cyclohexylamino-3-isopropyloxypropanoate Tetrafluoroborate Salt **(9h)**: yield: 16.54 g (50%); mp 104–106 °C (heptane).

$C_{13}H_{26}NBF_4O_3$	calc.	C 47.14	H 7.91	N 4.23	B 3.26	F 22.95
(331.1)	found	47.15	7.94	4.30	3.06	23.60

^1H NMR data: see Table 2

Methyl 3-tert-Butoxy-2-cyclohexylaminopropanoate Tetrafluoroborate Salt **(9i)**: as Typical Procedure for **9a**, exception *t*-BuOH is cooled to 10 °C instead of 0 °C; yield: 17.24 g (50%); mp 100–101 °C (heptane)

$C_{14}H_{28}NBF_4O_3$	calc.	C 48.71	H 8.17	N 4.05	B 3.13	F 22.03
(345.2)	found	48.86	7.95	4.09	3.11	22.11

^1H NMR data: see Table 2

2-Isopropylamino-3-methoxy-1-propanol (11a):

A solution of $Et_2O \cdot BF_3$ (6.15 mL, 0.05 mol) was added to a stirred solution of MeOH (200 mL) under cooling at 0 °C during 2 h. Aziridine **10a** was then added dropwise, and the mixture was refluxed for 4 h; the solvent was removed and the residual oil was neutralized with solution of NaOH (30 mL, 2.5 N). The organic layer was extracted with Et_2O (250 mL) and dried ($MgSO_4$), the solvent was removed and the crude product was purified by silica gel chromatography with hexane/EtOAc (30:70) as eluent; yield: 6.5 g (88%); mp 38.5–39 °C

$C_7H_{17}NO_2$	calc	C 57.10	H 11.64	N 9.51
(147.2)	found	57.15	11.43	9.30

IR ($CDCl_3$) ν = 3500 (OH), 3200 (NH), 1150 cm^{-1} (CO).

^1H NMR ($CDCl_3$/TMS): δ = 1.08 (d, 6H, J = 6 Hz), 2.80 (br s, NH), 2.84 (hept, 1H), 2.90 (m, 1H, CHN), 3.35 (s, OH), 3.50 (d, 2H, J = 7 Hz, CH_2OR), 3.55 (s, 3H, OCH_3), 3.60 (d, 2H, J = 7 Hz, CH_2OH).

$C_{10}H_{23}NO_2$	calc	C 63.45	H 12.24	N 7.40
(189.3)	found	63.28	11.96	7.22

IR ($CDCl_3$): ν = 3500 (OH), 3200 (NH), 1150 cm^{-1} (CO).

^1H NMR ($CDCl_3$/TMS): δ = 0.90 (d, 6H, J = 6 Hz), 1.10 (d, 6H, J = 6 Hz), 1.80 (hept, 1H), 2.80 (hept, 1H), 2.90 (m, 1H, CHN), 3.16 (d, 2H, J = 7 Hz), 3.45 (d, 2H, J = 7 Hz, CH_2OR), 3.50 (d, 2H, J = 7 Hz, CH_2OH), 3.70 (s, 1H, OH), 3.80 (br s, 1H, NH).

^{13}C NMR ($CDCl_3$): δ = 1929, 23.19, 28.39, 55.61, 62.11, 71.34, 78.29.

IR ($CDCl_3$) = 3500 (OH), 3200 (NH), 1150 cm^{-1} (CO).

^1H NMR ($CDCl_3$/TMS) δ = 2.64 (sl, 1H, NH), 2.88 (m, 1H, CHN), 3.20 (s, 1H, OH), 3.22 (s, 3H, OCH_3), 3.45 (d, 2H, J = 7 Hz, CH_2OR), 3.60 (d, 2H, J = 7 Hz, CH_2OH), 3.85 (d, 2H, CH_2Ph), 7.35 (s, 5H, Ph)

^{13}C NMR ($CDCl_3$): δ = 51.26, 52.12, 57.56, 61.46, 73.22, 128.

2-Isopropylamino-3-methoxy-1-propanol (11a) from $LiAlH_4$ Reduction of Methyl 2-Isopropylamino-3-methoxypropanoate (7a); Typical Procedure:

To a solution of $LiAlH_4$ (4.55 g, 0.12 mol) suspended, in Et_2O at reflux, was added a solution of **7a** (17.5 g, 0.1 mol) in a mixture of THF/Et_2O (200 mL, 1:1); the mixture was stirred and then refluxed for 2 h. Excess $LiAlH_4$ was destroyed with MeOH (30 mL); the metal salts were removed by filtration; the organic layer was dried ($MgSO_4$). The solvent was evaporated and the oily product was purified by silica gel chromatography with hexane/EtOAc as eluent (40:60); yield: 11.32 g (77%); mp 38–39 °C. The solid was identified as **11a** identical to that described as above.

2-Isopropylamino-3-isobutoxy-1-propanol **(11b)**: from $LiAlH_4$ reduction of methyl 2-isopropylamino-3-isobutoxypropanoate **(7b)**; yield: 15.12 g (80%).

$C_{10}H_{23}NO_2$	calc	C 63.45	H 12.24	N 7.40
(189.3)	found	63.28	11.96	7.22

IR ($CDCl_3$): ν = 3500 (OH), 3200 (NH), 1150 cm^{-1} (CO).

^1H NMR ($CDCl_3$/TMS): δ = 0.90 (d, 6H, J = 6 Hz), 1.10 (6H, J = 6 Hz), 1.80 (hept, 1H), 2.80 (hept, 1H), 2.90 (m, 1H, CHN), 3.16 (d, 2H, J = 7 Hz), 3.45 (d, 2H, J = 7 Hz, CH_2OR), 3.50 (d, 2H, J = 7 Hz, CH_2OH), 3.70 (s, 1H, OH), 3.80 (br s, 1H, NH).

^{13}C NMR ($CDCl_3$): δ = 19.29, 23.19, 28.39, 55.61, 62.11, 71.34, 78.29.

2-Benzylamino-3-methoxy-1-propanol **(11f)**: from $LiAlH_4$ reduction of methyl 2-benzylamino-3-methoxypropanoate **(7f)**; yield: 19.74 g (84%).

IR ($CDCl_3$): ν = 3500 (OH), 3200 (NH), 1150 cm^{-1} (CO).

^1H NMR ($CDCl_3$/TMS) δ = 2.64 (s, 1H, NH), 2.88 (m, 1H, CHN),

3.20 (s, 1H, OH), 3.22 (s, 3H, OCH_3), 3.45 (d, 2H, $J = 7$ Hz, CH_2OR), 3.60 (d, 2H, $J = 7$ Hz, CH_2OH), 3.85 (d, 2H, CH_2Ph), 7.35 (s, 5H, Ph).

^{13}C NMR ($CDCl_3$): $\delta = 51.26$, 52.12, 57.56, 61.46, 73.22, 128.

2-Isopropylamino-3-methoxy-1-propylamine (13a); Typical Procedure:

A solution of $Et_2O \cdot BF_3$ (25 mL, 0.2 mol) was added to a solution of MeOH (100 mL) under cooling in an ice bath at 0 °C, the stirring was continued for 2 h. Aziridine **12a** (11.4 g, 0.1 mol) was then added dropwise and the mixture was refluxed for 4 h; the mixture was then treated with NaOH (10 g, 0.25 mol) and a vigorous stirring was continued for 2 h; the solvent was evaporated under reduced pressure, the residual oil was purified by silica gel, chromatography with MeOH/EtOAc as eluent (20:80); yield: 10.36 g (71%).

IR ($CDCl_3$) = 3300 (NH), 1150 cm^{-1} (CO).

^1H NMR ($CDCl_3$/TMS): $\delta = 1.08$ (d, 6H, $J = 6$ Hz), 1.32 (br s, 3H, NH and NH_2), 2.70 (d, 2H, $J = 7$ Hz, CH_2N), 2.80 (hept, 1H), 3.20 (m, 3H, CH_2O and CHN), 3.40 (s, 3H, OCH_3).

^{13}C NMR ($CDCl_3$): $\delta = 21.76$, 23.45, 43.40, 45.63, 56.00, 56.99, 73.81.

3-Isobutoxy-2-isopropylamino-1-propylamine **(13b)**: from **12a** and *i*-BuOH: yield: 14.28 g (76%) (hygroscopic oil).

^1H NMR ($CDCl_3$/TMS) $\delta = 1.12$ (d, 6H, $J = 6$ Hz), 1.82 (hept, 1H), 2.15 (br s, 3H, NH and NH_2), 2.80 (d, 2H, $J = 7$ Hz, CH_2N), 2.90 (hept, 1H), 3.22 (d, 2H, $J = 7$ Hz, CH_2O), 3.24 (m, 3H, CH_2O and CHN).

3-Methoxy-1,3-propanediamine **(13c)**: from **12b** and MeOH: yield: 6.5 g (65%) (hygroscopic oil).

^1H NMR ($CDCl_3$/TMS) $\delta = 1.90$ (br s, 3H, NH and NH_2), 2.78 (d, 2H, $J = 7$ Hz, CH_2N), 3.35 (s, 3H, CH_2O and CHN), 3.38 (s, 3H, OCH_3).

2-*tert*-Butoxycarbonylamino-3-methoxypropionitrile (15a); Typical Procedure:

A solution of $Et_2O \cdot BF_3$ (1.5 mL, 0.012 mol) was added to a stirred solution of MeOH (150 mL). Aziridine **14a** (16.8 g, 0.1 mol) was added dropwise at r.t., stirring was continued for 12 h; the solvent was evaporated and the residual oil was dissolved in $CHCl_3$ (200 mL). The organic layer was washed with H_2O (3 × 100 mL), dried ($MgSO_4$) and the solvent was then evaporated. The crude product was purified by silica gel column chromatography with hexane/EtOAc as eluent (75:25); yield: 16.60 g (83%) (oil).

^1H and ^{13}C NMR data are listed in Table 3.

2-*tert*-Butoxycarbonyl-3-methoxy-1-propylamine (16):

A solution of **15a** (4 g, 0.02 mol) in Et_2O (25 mL) was added over 2 h to $LiAlH_4$ (2 g, 0.05 mol) suspended in Et_2O (100 mL) at reflux. The mixture was stirred at reflux for 2 h. Excess $LiAlH_4$ was destroyed with MeOH (10 mL). The metal salts were removed by filtration, the organic layer was dried ($MgSO_4$), the solvent was removed to give an oily product; yield: 3.2 g (78%).

IR ($CDCl_3$) ν = 3500–3200 (NH), 1690 (NCO_2), 1150 cm^{-1}(CO).

^1H NMR ($CDCl_3$/TMS) $\delta = 1.45$ (s, 9H), 2.42 (s, 2H), 2.80 (d, 2H), 3.38 (s, 3H), 3.45 (m, 3H), 5.68 (br s, 1H).

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