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The 1,3-diamino-propan-2-ol series. II. *N*-Cycloalkyl and azacyclo derivatives

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anti-arrhythmic / β-blocker / β-amino-alcohols / X-ray structure

Introduction

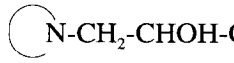
In a preceding article [1] we described the synthesis of compounds in the 1,3-diamino propan-2-ol series, with the general formula:

$$Ar–NH–CH_2–CHOH–CH_2–N–\Sigma\Sigma'$$

An anti-arrhythmic activity has been found for four of them. In this paper we describe two new series of compounds, *N*-cycloalkyl and azacyclo derivatives with a CH_2-CHOH-CH_2-N-$\Sigma\Sigma'$ side chain. The first series is described by general formula:

$$Al\text{-}NR\text{-}CH_2\text{-}CHOH\text{-}CH_2\text{-}N\text{-}\Sigma\Sigma'$$

where Al is a bulky aliphatic group and R = H, *i*-Pr or cyclohexyl. The second series is described by the general formula:



Or a tertiary nitrogen was included in a saturated cyclic framework; its basicity (high or medium) was dependent on the nature of the heterocycle, or a tertiary non-basic nitrogen was included in a polycyclic system. All compounds have been submitted to pharmacological screening.

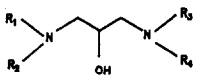
Chemistry

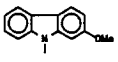
Compounds **1–17** shown in table I were synthesized according to schemes 1 and 2, each synthesis consisting of two steps.

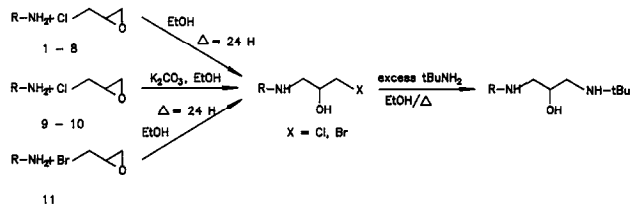
1) The first step constitutes the only difference between these two schemes and leads to the formation of an halohydrin (scheme 1) or an epoxide (scheme 2) according to the basicity and steric hindrance of the considered amine. Compounds **1–11** were prepared according to scheme 1. Compounds **1–8** derived from primary and secondary hindered amines were synthesized by refluxing epichlorohydrin and the required amine in absolute ethanol over 24 h. Compounds **9** and **10** proceeding from very basic amines were obtained in the same conditions with equimolecular equivalents of K_2CO_3. For compound **11** it was necessary to use the more reactive epibromohydrin in refluxing absolute ethanol. Compounds **12–17** were prepared from low basicity heterocyclic amines according to scheme 2. Appropriate amine and epibromohydrin were reacted under phase-transfer catalysis conditions in presence of aqueous sodium hydroxide (50%) at room temperature. Catalysts were selected according to the considered amine: aliquat 336 in equimolecular amounts for **12** and **13** [2], $Bu_4N^+HSO_4^-$ (catalytic amounts) in benzene for **14** and **15** [3] and the mixture TEBA/DMSO (1/9) for **16** and **17** [4]. Most intermediate compounds prepared in the first step were used without any purification. Synthesis of the chlorohydrins corresponding to **1** and **2** led to the formation of 3-azetidinols [5]. For intermediates **3** and **4**, syntheses were very complex and several compounds were isolated [1]. Therefore compounds **1–4** were obtained in poor yields.

2) The second step of schemes 1 and 2 was carried out using the same procedure: the previous intermediate and the required amine were refluxed in absolute ethanol during 24 h. Symmetrical compound **18** was

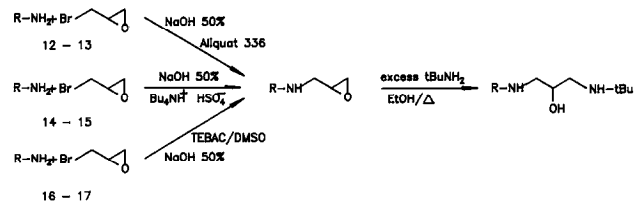
Table I. Synthesized compounds.



No	R_1	R_2	R_3	R_4	*Yield*
1	Cyclooctyl	H	H	*t*-Bu	10
2	Cyclododecyl	H	H	*t*-Bu	38
3	*i*-Pr	*i*-Pr	H	*t*-Bu	26
4	Cyclohexyl	Cyclohexyl	H	*t*-Bu	16
5			H	*t*-Bu	40
6			H	*t*-Bu	58
7			H	*t*-Bu	40
8					44
9			H	*t*-Bu	45
10			H	*t*-Bu	46
11			H	*t*-Bu	42
12			H	*t*-Bu	56
13			H	*t*-Bu	43
14			H	*t*-Bu	55
15			H	*t*-Bu	47
16			H	*t*-Bu	68
17			H	*t*-Bu	63



Scheme 1.

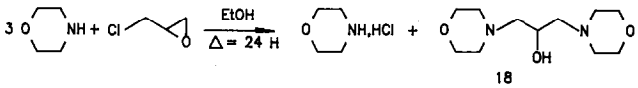


Scheme 2.

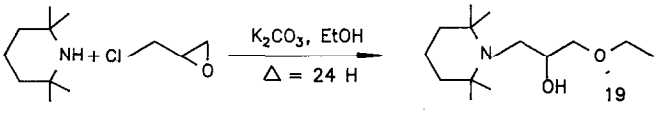
synthesized according to scheme 3. Epichlorohydrin and three molar equivalents of morpholine were refluxed in absolute ethanol during 1 day. Finally compound **19** was prepared according to scheme 4: 2,2,6,6-tetramethyl piperidine and a small excess of epichlorohydrin were refluxed with K_2CO_3 in absolute ethanol for 24 h.

Results

All compounds were tested for their anti-arrhythmic activity according to the protocol described in [1]. None of them showed any noticeable activity. The



Scheme 3.



Scheme 4.

compounds were then tested for their ß-adrenergic activity. Only compound **14** emerged from the preliminary tests and was selected for further pharmacological evaluation, *ie* ratio determination of cardiac to vascular ß-receptor blockade in the rat *in vivo* using propranolol as reference. Treatments with propranolol and **14** changed base line of heart rate (HR) and blood pressure (BP) but only changes in HR after propranolol administration seemed to be dose-dependent. Both changes in HR and BP did not influence the construction of dose– response curves, when changes in percent of the maximum were used as responses. Results obtained with both drugs are summarized in table II. From *in vivo* pA_2 the relative potency (RP) in inhibiting isoproterenol-induced tachycardia or vasodilatation for **14** was 25-fold less for propranolol. The slope values of the Schild plot regression, near unity for propranolol but not for **14** indicate a competitive inhibition on ß-receptors only for propranolol. The cardiac to vascular (C/V) ratios of 0.69 and 0.71 for propranolol and **14** respectively indicate non-selective blocking activity on cardiac ß-receptors or vascular ß-receptors under the present experimental conditions.

Discussion

None of the synthesized compounds described in this article present an anti-arrhythmic activity. In compounds **1–5** and **7–11** the absence of an aromatic ring leads to a second basic secondary or tertiary amine. In the *N*-aryl derivatives, the corresponding amino group has a low to medium basicity. This fact alone could explain the loss of the anti-arrhythmic activity. However, it does not explain the inactivity of compound **6** *vs* compound **2** reported in the previous article but in compound **6** we have a tertiary amine and consequently no possibility of hydrogen-bonding with the receptor. This hypothesis is accredited by the inactivity of the only tertiary amino *N*-aryl derivative investigated in [1]. The same explanation can be advanced for the inactive compounds **12–17**. Suitable crystals of compound **14** as a dihydrate have been obtained and investigated by X-ray diffraction. Figure 1 shows the superposition of the crystal conformation of D-propranolol [6] onto that of compound **14**, 2 H_2O. There is a very good fit between the two side-chains whereas the aromatic rings are almost perpendicular. In compound **14** the spatial orientation of the aromatic ring *vs* the side chain is imposed by the steric hindrance of the two *peri* hydrogens of the carbazole nucleus. In D-propranolol (only one *peri* hydrogen), the ether oxygen is oriented towards the *peri* hydrogen and the 'bulky' -CH_2- towards the 'free' space; for this reason the side chain can be in the same plane as the naphthyl ring. Obtaining a similar coplanar conformation for compound **14** is possible but energetically expensive.

Table II. Effects of propranolol and **14** on heart rate, blood pressure and C/V ratio.

Drug	*DL-propranolol*	***14***
Heart rate		
pA_2	7.03 (7.02–7.04)	5.67 (5.55–5.78)
Slope	0.86 (0.85–0.87)	0.42 (0.36–0.48)
RP	1	0.04
Blood pressure		
pA_2	7.19 (7.07–7.31)	5.82 (5.57–6.05)
Slope	0.95 (0.85–0.87)	0.51 (0.37–0.64)
RP	1	0.042
C/V ratio	0.69	0.71

RP: relative potency.

Experimental protocols

Pharmacology ß-blocking activity

Male Sprague–Dawley (Charles River) rats weighing 350–400 g were anaesthetized with pentobarbital sodium (60 mg/kg, ip). The trachea was intubated and animals were allowed to breathe spontaneously. The dorsal penis vein and the left carotid artery were cannulated for intravenous injection and blood pressure (BP) recording. Mean arterial blood pressure and heart rate (HR) were recorded using a Beckman RT511 device. BP and HR were maintained at 100–125 mmHg and 325–400 beats/min, respectively, by supplemental pentobarbital sodium as needed throughout the experiment. Rectal temperature was maintained at 37 ± 0.2°C by a heating device.

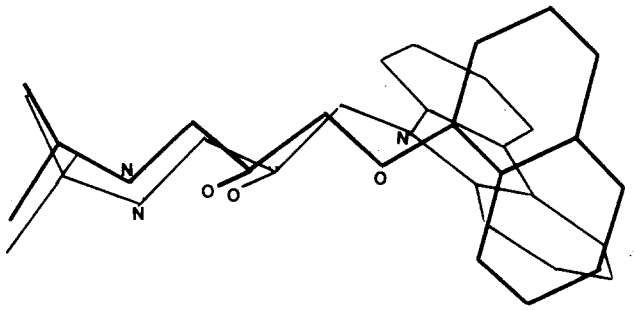


Fig 1. Superposition of X-ray structure of D-propanolol (bold line) with **14** dihydrate (thin line).

Table III. Synthesis, purification and physico-chemical data of prepared compounds.

Compound	*Method*	*Step 1*			*Step 2*		
		Chrom	*Mp (Slv)*	*Yield %*	*Chrom*	*Mp (Slv)*	*Yield (%)*
1	A	–		100	A(AcOEt)	–	10
2	A	–		100	A(AcOEt/ MeOH = 9/1	125 (dec)	38
3	A	–		100	S(MeOH)	77–79	26
4	A	–		100	S(MeOH)	74–75	16
5	A	–		100	A(Et_2O/ MeOH = 92/8)	50–51	40
6	A	–		82	–	100–101 (C_6H_6)	70
7	A	–		100	A(Et_2O/ $CHCl_3$ = 92/8)	205 (dec)	40
8	A	–		100	S($CHCl_3$)	208–210	44
9	B	–		60	A(Et_2O/ MeOH = 9/1)	230 (dec)	75
10	B	–		57	A(CH_2Cl_2/ MeOH = 99/1)	95–97 (C_6H_6)	81
11	C	A(C_6H_{12}/ Et_2O = 1/1)		85	–	112–113 (Et_2O)	50
12	D(60H)	–	187–189 (Et_2O)	60	–	135–136 (C_6H_{12})	94
13	D(20H)	S(C_6H_{14}/ Et_2O = 1/1)	94–95 (Et_2O)	52	–	110–111 (C_6H_6)	82
14	D(2H)	A(C_6H_{12}/ CH_2Cl_2 = 7/3)	100-101 (C_6H_6)	60	–	115–116 (C_6H_6)	91
15	E	–		100	–	96–97 (C_6H_6)	47
16	E	–		100	–	99–100	68
17	F	–		100	–	129–130 (C_6H_6)	63

A = alumina column; S = silicagel column.

Determination of dose–response (DR) curves for HR and BP were obtained following administration of DL-isoproterenol. Isoproterenol was injected every 45 s in a volume of 0.5 ml/kg. The venous cannula was flushed with 0.05 ml of 0.9% NaCl solution after each injection. Doses of isoproterenol were cumulatively increased from 3.10 mg/kg until the maximal responses for HR and BP were obtained. Changes of HR and BP expressed as percent of the maximum changes were used as the responses. When HR and BP had recovered their basal values, propanolol or **14** were administered intravenously in a volume of 1 ml/kg. Dose–response curves were performed again after 20 min. The procedures were completed within 5–7 min. Three doses were used for each ß-blocker, but only one dose was tested for the same rat. Five rats were used per dose.

In vivo pA_2 values for HR and BP responses were calculated by Schild plots as described for the *in vitro* method. The pA_2 means negative log of the molar dose per kg of an antagonist which produces the agonist dose ratio of two. The slope of the regression line (Schild plot) may be the unity for a competitive antagonist. Dose ratios were determined at 50% of the maximal responses on a pair of DR curves for each rat. Potency ratio of **14** to propanolol was obtained as the antilog of differences in pA_2 values *in vivo*. Ratio of cardiac to vascular ß-receptor blockade (index of cardioselectivity) was calculated using the equation: C/V ratio = antilog[pA_2 (HR) – pA_2 (BP].

Drugs

The following drugs and doses were used: DL-propanolol hydrochloride (Sigma; 1.10, 3.10, 1.10 m/kg), 14 (3.10, 1.10 m/kg). Tween 80, 5% in 0.9% NaCl solution was used as vehicle.

*X-Ray structure determination of compound **14***

Monoclinic symmetry was obtained with: a = 14.943(3) Å; b = 5.908(8) Å; c = 21.465(4) Å; ß = 95.00(2) Å; V = 1887.9 Å^3; space group P_21/n, Z = 4; d_x = 1.17; and final R = 0.051.

Chemistry

Melting points were taken on a Kofler apparatus and are uncorrected. Elemental analyses were carried out by the Service Central d'Analyses du CNRS (F-69390 Vernaison). ^{1}H-NMR spectra were recorded at 60 MHz on a Perkin–Elmer Hitachi R 24B instrument in $CDCl_3$ solutions using TMS as internal standard.

*Synthesis of compounds **1–17***

All the products were synthesized in two steps according to the schemes 1 and 2: the chlorohydrins or epoxides were prepared

according to *Procedures A–F* as detailed below (step No 1). The 3-amino 2-propanol amines were obtained following the general method described below (step No 2). All compounds were transformed into their hydrochloride salts except **6** which was transformed into a hemimaleate salt. Hydrochloride salt: gaseous hydrogen chloride was bubbled through a solution of 3-amino 2-propanol amine in anhydrous ether or methanol. The collected precipitate was recrystallized in an *i*-Pr_2O/MeOH mixture, filtered, washed with *i*-Pr_2O and dried *in vacuo*. Hemimaleate salt: a saturated solution of maleic acid in tetrahydrofuran (1 g for 5 ml) was poured into a solution of **6** in a minimum amount of the same solvent. The precipitate was collected, washed with THF and dried *in vacuo*.

Detailed procedure for step No 1
*Method A (for compounds **1–8**).* In a round-bottomed flask fitted to a reflux condenser connected to a calcium chloride column, a mixture of amine (0.05 mol) and epichlorohydrin (4.5 ml; 0.065 mol) was refluxed in absolute ethanol (50 ml) for 24 h. The solution was concentrated under reduced pressure. The resulting oil was used in the next step without further purification, except in the case of **6**.

*Method B (for compounds **9** and **10**).* This method is identical to *Method A* but it is necessary to add powdered K_2CO_3 (7.5 g; 0.05 mol) to the mixture.

*Method C (for compound **11**).* In a round-bottomed flask fitted to a reflux condenser connected to a calcium chloride column, an absolute ethanol solution of amine (5.4 g; 0.0344 mol) and epibromohydrin (4.5 ml; 0.0475 mol) was heated at reflux for 4 days. The resulting mixture was then concentrated under reduced pressure to give a yellow oil (9.87 g) which was chromatographed on an alumina column.

*Method D (for compounds **12, 13** and **14**).* In a flask fitted to a calcium chloride column, a mixture of amine (0.015 mol), epibromohydrin (3 ml; 0.035 mol), aliquat 336 (8.5 g) and a 50% aqueous sodium hydroxide solution (15 ml) was vigorously stirred at room temperature. The mixture was poured into water (200 ml) and extracted with CH_2Cl_2 (3 x 75 ml). The organic layer was dried over sodium sulfate and concentrated *in vacuo*.

*Method E (for compounds **15** and **16**).* In a flask connected to a calcium chloride column, a mixture of nitrogen compound (4.5 g; 0.04 mol), epibromohydrin (5 ml; 0.058 mol), a 50% solution of sodium hydroxide (25 ml) and tetrabutylammonium hydrogensulfate (0.7 g) was vigorously stirred in benzene (40 ml) at room temperature during 24 h. The resulting dark mixture was poured into water (100 ml) and then extracted with ether (3 x 50 ml). The combined ethereal layers were dried over sodium sulfate and concentrated *in vacuo* to give an oil which crystallized spontaneously.

*Method F (for compound **17**).* A mixture of amine (4.9 g; 0.024 mol), epibromohydrin (6 ml; 0.007 mol), a 50% solution of sodium hydroxide (20 ml), benzyl triethylammonium chloride (2 g) and DMSO (10 ml) was stirred at room temperature for 48 h in a flask connected to a calcium chloride column. The resulting solution was then poured into water (100 ml) and extracted with $CHCl_3$ (3 x 50 ml). The organic layers were combined, carefully washed with water to remove residual DMSO, dried over sodium sulfate and then concentrated under reduced pressure. The oily residue was triturated in benzene to yield crystals.

General procedure for step No 2 (for all products)
In a round-bottomed flask fitted to a reflux condenser connected to a calcium chloride column, a mixture of epoxide or chlorohydrin detailed above (0.1 mol) and a large excess of freshly distillated *tert*-butylamine (0.3 mol) was refluxed in absolute ethanol (150 ml) during 24 h. After concentration under vacuum, the oily residue was dissolved in $CHCl_3$ (150 ml). The resulting solution was washed with water (3 x 50 ml), dried over sodium sulfate and then concentrated under reduced pressure. The residue was in most of the cases purified by column chromatography.

*Synthesis of **18**.* In a round-bottomed flask fitted to a reflux condenser connected to a calcium chloride column, morpholin (3 g; 0.034 mol) and epichlorohydrin (0.9 ml; 0.0115 mol) were refluxed in absolute ethanol (25 ml) during 24 h. After concentration *in vacuo* and elimination of morpholin hydrochloride which crystallized in the mixture, the resulting oil (2.5 g) was chromatographed on a silica gel column (60 g), with a $CHCl_3$/MeOH: 97/3 mixture to yield **18** as an oil (1.65 g; 42%). After formation of salt according to general procedure, **18** was obtained crystallised as a dichlorohydrate in the mixture *i*-PrOH/MeOH: mp: 244°C.

*Synthesis of **19**.* A mixture of tetramethyl-2,2,6,6 piperidine (12.7 ml; 0.075 mol) and epichlorohydrin (7.5 ml; 0.096 mol), anhydrous potassium carbonate (11.5 g; 0.083 mol) and absolute ethanol (80 ml) was refluxed for 24 h in a round-bottomed flask fitted with a reflux condenser connected to a calcium chloride column. The resulting solution was concentrated under reduced pressure to give an oil (14.4 g) which was chromatographed on an alumina column (240 g). The first elution (C_6H_{12}/Et_2O: 98/2) gave the epoxide corresponding to **9**, then the second elution (C_6H_{12}/EtO: 9/1) led to **19** as a yellow oil (1.8 g; 20%). **19** was obtained in crystallised form as a monochlorohydrate: mp: 143–145°C (AcOEt).

References

1 Laguerre M, Boyer C, Carpy A, Leger JM, Panconi E, Vaugien B, Cognic F (1992) *Eur J Med Chem* 27, 000–000
2 Bocchi V, Casnati G, Dossena A, Villani F (1976) *Synthesis*, 414–416
3 Barco A, Bebetti S, Pollini GP (1976) *Synthesis* 124–125
4 Heaney H, Ley SV (1973) *J Chem Soc Perkin Trans* 1, 499–500
5 Laguerre M, Boyer C, Leger JM, Carpy A (1989) *Can J Chem* 67, 1514–1522
6 Gadret M, Goursolle M, Leger JM, Colleter JC (1975) *Acta Crystallogr Sect B* 31, 1938–1942