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The 1,3-diamino-propan-2-ol series. I. *N*-Aryl derivatives

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Introduction

Most compounds with an aryloxypropanolamine (AOPA) structure (A) are efficient β-adrenergic blockers and anti-arrhythmic drugs.

$$Ar\text{-}O\text{-}CH_2\text{-}CHOH\text{-}C_2\text{-}NH\Sigma \ (\Sigma = i\text{-}Pr \text{ or } t\text{-}Bu) \quad (A)$$

The aromatic moiety including the oxymethylene group, the hydroxyl group and the substituted ionizable nitrogen are the recognized features responsible for the activity of this class of compounds. Experimental and theoretical results on several β-blockers have shown that the molecules prefer *trans*-extended conformations in which the aromatic ring, the oxymethylene group and the $CHOH\text{-}CH_2\text{-}NH\text{-}\Sigma$ side chain are almost coplanar [1, 2]. Consequently AOPAs with a bulky unsaturated *ortho* substituent preventing the conjugation of the ether oxygen with the aryl ring (and then the planarity), are apparently devoid of β-blocking activity. However, some of them still exhibit a noticeable anti-arrhythmic activity [3, 4]. *N*-aryl alkylenediamines (B) have been reported as anti-arrhythmics [5, 6]. The absence of an hydroxyl group in the side chain may be alone responsible for the unobserved β-blocking activity.

$$Ar\text{-}NR\text{-}(CH\ )\text{-}NR'R'' \quad (B)$$

R = H, Me R', R'' = H, Me, Et ...

Very few compounds of the general formula (C) (AOPAs in which the ether oxygen has been replaced by an -NH- group) have been investigated in the past [7, 8]. Some are local anaesthetic agents.

$$Ar\text{-}NR\text{-}CH\text{-}CHOH\text{-}CH\ \text{-}NR'R'' \quad (C)$$

R = H, Me R', R'' = H, Me, *t*-Bu

Here 18 compounds in the 1,3-diamino propan-2-ol series have been prepared and tested.

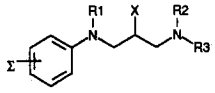
Chemistry

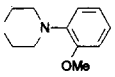
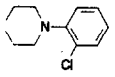
All synthesized compounds are shown in table I. Except for compounds **16–18** all were prepared according to scheme 1. Intermediate chlorohydrins prepared by refluxing epichlorohydrin with the required amine were used as obtained uithout any purification. Compounds **1–9**, **14–15** were obtained by refluxing the previous chlorohydrin with the appropriate amine in absolute ethanol. Owing to the volatility of the amine (Me_2NH and ammonia) used for preparing compounds **11–13**, it was necessary to utilise a stainless steel autoclave at 100°C. Compound **10** was prepared from **2** *via* the methiodide and subsequent neutralization with dilute sodium hydroxide. Symmetrical compounds **16–17** were obtained according to scheme 2. Two molar equivalents of *ortho*-cumidine were reacted with epichlorohydrin for **16** (absolute ethanol, 5 days in the presence of K_2CO_3) or with 1,3-dibromo propane for **17** (DMSO, 3 days at room temperature). Finally, compound **1** was prepared according to scheme 3. *Ortho*-cumidine was refluxed with 3-chloro propanol in absolute ethanol in presence of K_2CO_3; the resulting amino-alcohol was chlorinated with $SOCl_2$ in pyridine at room temperature and this halo-compound was condensed with *t*-$BuNH_2$ in refluxing absolute ethanol.

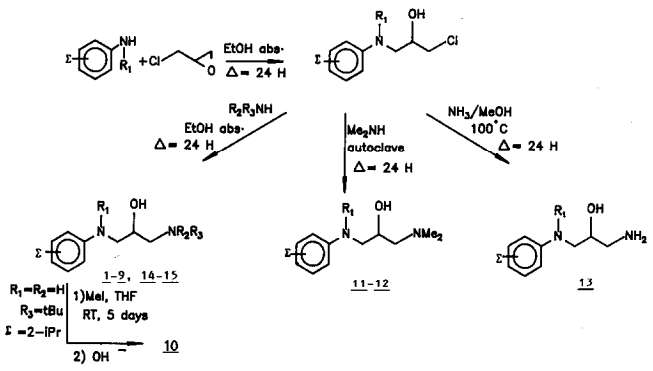
Results

The synthesized compounds were submitted to pharmacological screening. Only the anti-arrhythmic

Table I. Data of synthesized products.



No	*Σ*	R_1	*X*	R_2	R_3	*Yield (%)*	*mp (°C)*
1	Benzo-2,3	H	OH	*t*-Bu	H	60	92–93
2	2-*i*-Pr		OH	*t*-Bu	H	70	86 143–11 (HCl)
3	2-*i*-Pr 6-Me	H	OH	*t*-Bu	H	70	158 (HCl)
4	4-Me	H	OH	*t*-Bu	H	60	82 143–144 (HCl)
5	H	Me	OH	*t*-Bu	H	60	78
6	2-F	H	OH	*t*-Bu	E	55	94–95 148 (HCl)
7	3-F	H	OH	*t*-Bu	H	60	72–74
8	4-F	H	OH	*t*-Bu	H	54	96–97
9	2,6-Cl_2	H	OH	*t*-Bu	H	45	176 (HCl)
10	2-*i*-Pr	H	OH	*t*-Bu	Me	60	173 (HCl)
11	2-*i*-Pr	H	OH	Me	Me	47	Oil
12	2-*i*-Pr 6-Me	H	OH	Me	Me	42	Oil
13	2-*i*-Pr	H	OH	H	H	40	204 (HCl)
14	2-*i*-Pr	H	OH			40	Oil
15	2-*i*-Pr	H	OH			38	106
16	2-*i*-Pr	H	OH	(2-*i*-Pr)-Ph	H	50	172 (HCl)
17	2-*i*-Pr	H	H	(2-*i*-Pr)-Ph	H	35	154 (HCl)
18	2-*i*-Pr	H	H	*t*-Bu	H	10	178 (HCl)

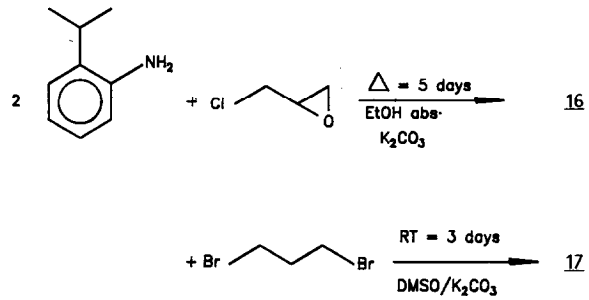


Scheme 1.

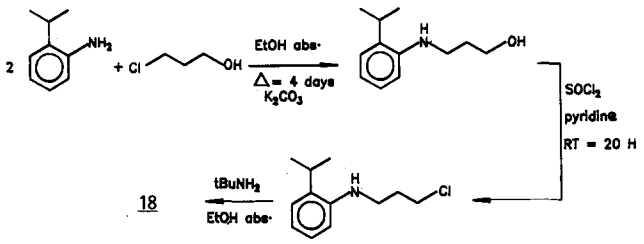
activity in mice deserved attention and four effective compounds were tested for their local anaesthetic activity in guinea-pigs.

Evaluation of anti-arrhythmic activity in mice

Compound **9** was effective after intraperitoneal administration (25 mg/kg): 100% of mice by group were protected. Compounds **2** and **3** were borderline at the same dose level since only 66% of mice by group were protected. Compound **2** still showed a significant activity at 10 mg/kg ip. The weak anti-arrhythmic activity of compound **12** may be related to a weak calcium antagonist activity observed *in vitro*. Other compounds did not present any anti-arrhythmic effect using these experimental conditions. Under the same



Scheme 2.



Scheme 3.

conditions, all mice were protected by the reference compound lidocaine at a dose level of 50 mg/kg (table II).

Evaluation of local anaesthetic activity in guinea-pigs

Only compounds found effective in the first test were screened for their local anaesthetic activity. Results are summarized in table III. Compounds **3** and **9** were effective at a concentration of 5%. Only compound **3** showed a good activity at a concentration of 0.5%. Nevertheless, for compound **9** this effect disappeared 60 min after topical administration. Compounds **2** and **12** did not present any activity. For compound **2**, this discrepancy could be due to a different mechanism of action related to its stabilizing membrane effect. Lidocaine at the concentration of 5% did not induce a blink response during the 60-min period after topical administration. None of the tested compounds showed any β-adrenergic activity. Regarding the activity of compound **2** and its good tolerance (LD_{50} in mice: *po* 750 < LD < 1000, iv = 56.6 mg/kg) this drug has been selected for further investigations in the field of anti-arrhythmic activity (data to be published elsewhere).

Table II. Anti-arrhythmic activity. Percentage of mice per group which did not display cardiac arrhythmia 30 min after ip administration of the tested compound.

	Dose (mg/kg ip)			
Compound	*100*	*50*	*25*	*10*
1	–[a]	–	–	0
2	100[b]	66[b]	66[b]	33
3	–	100	66	0
4	–	–	0	–
5	–	33	–	–
6	0	–	–	–
7	0	–	–	–
8	0	–	–	–
9	–	100[b]	100[b]	0
11	0	–	–	–
12	66	33	–	–
13	33	–	–	–
15	0	–	–	–
16	0	–	–	–
17	–	0	–	–
Lidocaine	–	100[b]	–	–

[a]Not tested. [b]Considered as effective.

Experimental protocols

Pharmacology

Anti-arrhythmic activity

Male Swiss mice (nine per group) were intraperitonealy injected with the tested compounds. Thirty min later, they were submitted to a deep chloroform anaethesia which prolongs the refractory period and depresses myocardial excitability [9]. A compound is assessed as anti-arrythmic if more than 66% of mice per group do not display cardiac arrythmia and heart rate > 200 beats/min (EKG). Tested compounds were prepared as aqueous solutions. Small amounts of DMSO were used to increase the solubility. At the concentration used, DMSO did not produce any arrhythmic or anti-arrhythmic effect.

Local anaesthetic activity

Surface anaesthesia was assessed on male Duncan–Hartley guinea pig according to the method of Régnier [10]. 0.1 ml of the tested solution was instilled on the cornea. After 30 s, the excess was allowed to trickle. The anesthesia was checked by means of a nylon thread applied five times to the cornea 5, 15, 30 and 60 min after topical administration of the tested compound. Activity was judged as positive in presence of a blink response in less than three of the five stimuli.

Chemistry

Melting points were taken on a Kofler apparatus and were uncorrected. Elemental analyses were carried out by the Service Central d'Analyses du CNRS (69390 Vernaison).

Table III. Local anesthetic activity. Number of blink responses at different concentrations of the tested compounds. Local anesthetic activity was assessed at different times after administration.

Compound	*Concentration (g/100 ml)*											
	5				*0.5*				*0.05*			
	Min after administration				*Min after administration*				*Min after administration*			
	5	*15*	*30*	*60*	*5*	*15*	*30*	*30*	*5*	*15*	*30*	*60*
2	5	5	5	5								
3	0	0	0	0	2	0	0	5	5	5	5	5
9	0	0	1	3	5	5	5	5				
12	5	5	5	5								
Lidocaine	0	0	0	0								

^{1}H-NMR spectra were recorded at 60 MHz on a Perkin–Elmer Hitachi R 24B instrument in different solutions listed 1, 2 or 3 using TMS as internal standard (1 = $CDCl_3$; 2 = CCl_4; 3 = $(CH_3)_2$ CO–d_6).

General procedure for synthesis of chlorohydrins
In a round-bottomed flask fitted with a reflux condenser connected to a calcium chloride column, a mixture of amine (0.1 mol) and epichlorohydrin (0.11 mol) was refluxed in absolute ethanol (100 ml) for 24 h (for the synthesis of chlorohydrin corresponding to **9**, the reflux time was 48 h because the corresponding amine showed a low basicity). The solvent was removed under reduced pressure. The resulting product, in most cases as an oil, was used in the next step without further purification.

General procedure for synthesis of 3-arylamino 2-propanol amines
Except for compounds **10**, **11**, **12**, **13**, **16**, **17** and **18** whose syntheses are detailed below, all products were prepared following this general method. In a round-bottomed flask fitted with a reflux condenser connected to a calcium chloride column, a mixture of chlorohydrin as above (0.1 mol) and an excess of the required amine (a large excess for *tert*-butylamine, dimethylamine and *N*-methyl *tert*-butylamine, 0.25 mol for substituted piperazines) were refluxed in absolute ethanol (100 ml). The resulting solution was concentrated under vacuum and dissolved in ether (150 ml). The ethereal layer was washed with water (3 x 100 ml) to remove the hydrochloride salt of excess amine, dried over sodium sulfate and then concentrated under reduced pressure. The oily residue was mainly purified by column chromatography or recrystallization. All compounds were transformed into their hydrochloride salt: gaseous hydrogen chloride was bubbled through a solution of 3-arylamino 2-propanol amine in anhydrous ether or methanol. Hydrochloride salt was filtered, washed with ether and dried under vacuum.

*Synthesis of **10**.* The preparation of **10** was derived from **2**: iodomethane (0.5 ml) was added to a solution of **2** as free base (2.05 g) in tetrahydrofuran (15 ml). The solution was vigorously stirred for 5 days at room temperature. The resulting mixture was concentrated under vacuum and the residue was rendered basic (pH ≈ 10) with 0.5 N sodium hydroxide. The mixture was extracted with ether (3 x 50 ml) . The organic layer was washed with water, dried over sodium sulfate and concentrated under vacuum to yield 1.9 g of a yellow oil which was chromatographed on an alumina column with $CHCl_3$ to give **10** as an oil (1.2 g; 60%).

*Synthesis of **11** and **12**.* A mixture of appropriate chlorohydrins and anhydrous dimethylamine was heated at 100°C in an autoclave and then treated according to the general procedure.

*Synthesis of **13**.* The corresponding chlorohydrin was dissolved in saturated methanolic ammonia. The mixture was then heated at 100°C in an autoclave and treated according to the general method.

*Synthesis of **16**.* In a 250-ml round-bottomed flask fitted with a reflux condenser connected to a calcium chloride column, *o*-cumidine (5.4 g; 0.04 mol), epichlorohydrin (1.85 g; 0.02 mol) and potassium carbonate (4 g; 0.03 mol) were refluxed in absolute ethanol (100 ml) for 5 days. The mixture was then concentrated under reduced pressure to leave 6.7 g of an oil which was chromatographed on a silica gel column. Elution with a mixture of heptane/ether: 9/1 gave **16** as an oil (3.2 g; 50%).

*Synthesis of **17**.* In a 250-ml round-bottomed flask, a mixture of *o*-cumidine (2.70 g; 0.02 mol), 1,3-dibromopropane (4.04 g; 0.02 mol) and potassium carbonate (4.14 g; 0.03 mol) was stirred in DMSO (80 ml) at room temperature for 3 days. The resulting solution was poured into water (150 ml) and extracted with chloroform (3 x 50 ml). The organic layer was carefully washed with water to remove DMSO, dried over sodium sulfate and then concentrated under reduced pressure. The oily residue (3.2 g) was chromatographed on a silica gel column (cyclohexane/ether: 8/2) to leave **17** (1.02 g; 33%).

*Synthesis of **18**.* A mixture of *o*-cumidine (6.75 g; 0.05 mol), 3-chloro 1-propanol (5 g; 0,05 mol), potassium carbonate (13.8 g; 0.1 mol) and absolute ethanol (80 ml) was refluxed during 4 days in a 250-ml round-bottomed flask fitted with a reflux condenser connected to a calcium chloride column. The mixture was then filtered to remove the residual salts and concentrated under vacuum. The oily residue was chromatographed on an alumina column (hexane/ether: 3/1) to yield 2.5 g of (1-(*o*-cumidinyl)propanol)chlorhydrate. This salt was refluxed in pyridine (100 ml) for 20 h. The slurry was coevaporated several times with a mixture of ethanol/toluene: 3/1. The oily residue was dissolved in choroform (100 ml), washed with water (3 x 60 ml) and concentrated under reduced pressure to give the amino-alcohol as an oil (2.2 g). This last product was dissolved in pyridine (50 ml) and was treated with thionyl chloride for 20 h at room temperature. After concentration under vacuum, a black oil was obtained which was chromatographed on a silica gel column (hexane/dichloromethane: 1/1) to yield 0.7 g of *N*-((3-chloro)propyl)*o*-cumidine. This product was treated with tertiobutylamine according to the general procedure.

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