# Synthesis of 2-Hydroxy-2-phenylethylamino Derivatives as Potential α-Adrenergic Blocking Agents

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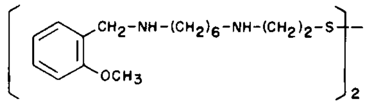
Received September 24, 1984

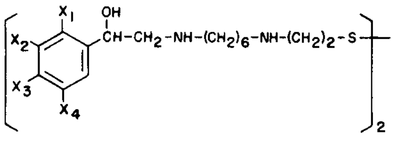
The synthesis of *N,N'*-bis[6-(2-hydroxy-2-phenylethylamino)hexyl] cystamines **4**, and *N*-(2-hydroxy-2-phenylethyl)-1,6-hexanediamines **6** are described. Compounds **4** were obtained by condensation of the requisite epoxide **2** with 3-(6-aminohexyl)-1,3-thiazolidine followed by dimerization with opening of the thiazolidine ring. A similar method was used for the preparation of compounds **6**. In order to prepare **4j** (*N,N'*-bis{6-[2-hydroxy-2-(3,4-dihydroxyphenyl)ethylamino]hexyl}cystamine), several procedures were tested; the method of choice involved the use of 3,4-dihydroxybenzaldehyde with both hydroxy groups protected as methoxymethyl ethers.

*J. Heterocyclic Chem.*, **22**, 745 (1985).

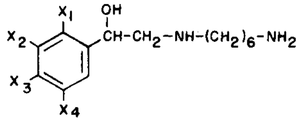
Melchiorre [1] has postulated a topographic model for the α-adrenoceptor based on the structural data obtained from a peculiar family of irreversible blocking molecules over such a receptor. This author has also proposed an hypothetical relationship between the catecholamine recognition site and the *o*-methoxybenzyl group present in the benextramine (BHC), which is, at the moment, the described product of the forementioned family with the highest α-adrenergic activity [2]. To confirm (or not confirm) that hypothesis, we have synthesized a series of molecules **4** for a posterior determination of their pharmacological activity; such molecules are tetramine disulfides with six methylene groups between the cystaminic and the benzylic nitrogen atoms, where the *o*-methoxybenzylamino residues present in BHC have been replaced by 2-hydroxy-2-phenylethylamino radicals, analogous to the catecholamines, diversely substituted in the benzene ring. We have also prepared the compounds **6**, structurally identical to the former molecules **4** except for the absence of the cystamine group, to test their action as an α-adrenergic reversible blocker.



BHC



4



6

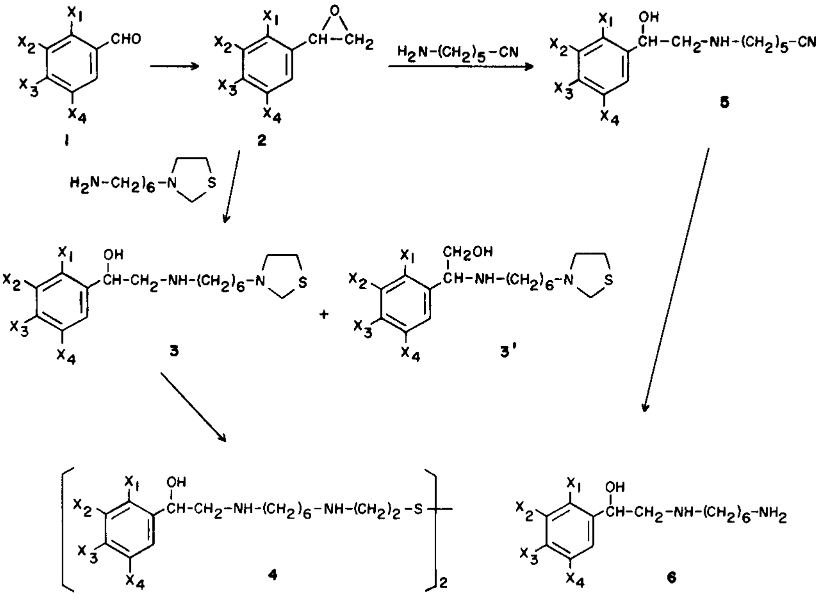
a, $X_1 = X_4 = H$, $X_2$, $X_3 = OCH_2O$
b, $X_2 = X_3 = X_4 = H$, $X_1 = OCH_3$
c, $X_1 = X_3 = X_4 = H$, $X_2 = OCH_3$
d, $X_1 = X_2 = X_4 = H$, $X_3 = OCH_3$
e, $X_1 = X_4 = H$, $X_2 = X_3 = OCH_3$
f, $X_1 = H$, $X_2 = X_3 = X_4 = OCH_3$
g, $X_1 = X_4 = H$, $X_2 = X_3 = OSi(CH_3)_3$
h, $X_1 = X_4 = H$, $X_2 = X_3 = OSi(CH_3)_2C(CH_3)_3$
i, $X_1 = X_4 = H$, $X_2 = X_3 = OCH_2OCH_3$
j, $X_1 = X_4 = H$, $X_2 = X_3 = OH$

The compounds **4** have been prepared by a convergent synthesis (Scheme 1). Condensation of the requisite epoxide **2** with 3-(6-aminohexyl)-1,3-thiazolidine [3] to yield **3**, compounds with the 2-hydroxy-2-phenethylamino group, that by the oxidative opening of the thiazolidine ring affords **4**. A similar strategy has permitted us to obtain the analogues **6** by reaction between the corresponding epoxides and 6-aminohexanenitrile [4], which contains a primary amine and a cyano group, precursors respectively, of the secondary and primary amines of **6**.

The preparation of the epoxides **3** was carried out by two alternative procedures starting from a conveniently substituted benzaldehyde **1**. The first (method A) is an extension of Corey's method [5]. The reaction between benzaldehyde and dimethylsulfoniummethylide, generated from trimethylsulfonium iodide [6] with sodium hydride, gives the epoxides **3** in high yields but impurified by small amount of diols, originated by the ring opening, and by its dehydratation products. The second method (B) for the preparation of the epoxides is a phase-transfer procedure [7] with tetrabutylammonium bromide as transfer agent. The yields in both procedures are similar (see Table 3), however, the second method (B) is advantageous because of the purity of the products and the more simple handling and working-up, notwithstanding the reaction time is longer, up to 4 days.

3-(6-Aminohexyl)-1,3-thiazolidine has been prepared from 1,6-hexanodiamine by reaction with thiirane [3] and treatment of the resulting aminothiol with formaldehyde bisulfite. Once again the usefulness of 3-(6-aminohexyl)-1,3-thiazolidine as a precursor of tetramine disulfides is manifested because of its two clearly different amino groups. The thiazolidine ring simultaneously acts as a pro-

Scheme I



a, $X_1 = X_4 = H$, $X_2$, $X_3 = OCH_2O$
b, $X_2 = X_3 = X_4 = H$, $X_1 = OCH_3$
c, $X_1 = X_3 = X_4 = H$, $X_2 = OCH_3$
d, $X_1 = X_2 = X_4 = H$, $X_3 = OCH_3$
e, $X_1 = X_4 = H$, $X_2 = X_3 = OCH_3$
f, $X_1 = H$, $X_2 = X_3 = X_4 = OCH_3$
g, $X_1 = X_4 = H$, $X_2 = X_3 = OSi(CH_3)_3$
h, $X_1 = X_4 = H$, $X_2 = X_3 = OSi(CH_3)_2C(CH_3)_3$
i, $X_1 = X_4 = H$, $X_2 = X_3 = OCH_2OCH_3$
j, $X_1 = X_4 = H$, $X_2 = X_3 = OH$

Table 1

Conditions for Preparation of **4j**

| Starting compound | Reactive (solvent) | Reaction time Temperature | Reaction product | References |
|---|---|---|---|---|
| **4a** | HBr 45% | 2 hours (reflux) | Resin Material | [8] |
| **4a** | NaOH 5 M | 24 hours (reflux) | N.R. | [9] |
| **4e** | DIBAL (benzene) | 1.5 hours (reflux) | Starting material + **4j**<br>(15% total yield) | [10] |

tetive group of the secondary amine and the mercapto groups and it can be directly converted into the cystamine residue of the disulfides **4**, avoiding the deprotective step with the subsequent improvement in the goal yield.

3-(6-Aminohexyl)-1,3-thiazolidine condenses with the epoxides **2** in 2-propanol and the thiazolidine itself affords the suitable basic medium necessary to favor nucleophilic attack on the less substituted atom of the oxirane system. In all cases the corresponding compound **3** has been obtained in high yield. The study by nmr spectroscopy of the crude mixtures obtained always shows a signal at $\delta$ within the 3.3 and 3.6 ppm range, depending on cases, that corresponds to the $PhCHCH_2OH$ group of the compounds **3'** resulting from the attack of the amine on the other possible position in the oxirane ring. Such compounds **3'** represent a percentage of 5% on the average and it was not possible to isolate them by column chromatography as a definitive pure product. The compounds **3** were isolated by such a technique or by recrystallization of the oxalates prepared directly from the crude mixture. The nmr characteristic signals of **3** are a singlet between 3.83 and 3.93 ppm due to $NCH_2S$ group of the thiazolidine ring and a complex signal centerd between 4.46 and 4.65 ppm due to the benzylic protons.

The dimerization of **3** was carried out by reaction with a 0.1 *N* ethanolic iodine solution with a 2.5% potassium iodide, always with a high yield in the symmetric disulfides **4a-f** (see Table 4).

The compound *N*,*N'*-bis{6-[2-hydroxy-2-(3,4-dihydroxyphenyl)ethylamino]hexyl}cystamine (**4j**) is the most impor-

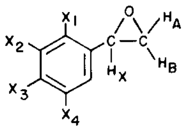
Table 2

| Compound | Mp °C (solvent) [a] | Yield [b] | Formula | Analyses Carbon % | | Hydrogen % | | Nitrogen % | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Calcd. | Found | Calcd. | Found | Calcd. | Found |
| **3a** | 93-95<br>M-E | 49 | $C_{18}H_{28}N_2O_3S.2(C_2H_2O_4)$<br>532.54 | 49.61 | 50.01 | 6.05 | 5.94 | 5.25 | 5.17 |
| **3b** | 75-80<br>M-E | 81 | $C_{18}H_{30}N_2O_2S.2(C_2H_2O_4)$<br>518.56 | 50.95 | 50.77 | 6.61 | 6.66 | 5.40 | 5.75 |
| **3c** | 50-52<br>M-E | 62 | $C_{18}H_{30}N_2O_2S.2(C_2H_2O_4).C_4H_{10}O$<br>592.68 | 52.68 | 52.36 | 7.48 | 7.18 | 4.72 | 4.50 |
| **3d** | 134-136<br>M-E | 64 | $C_{18}H_{30}N_2O_2S.2(C_2H_2O_4)$<br>518.56 | 50.95 | 50.65 | 6.60 | 6.75 | 5.40 | 5.73 |
| **3e** | 162-165<br>M-E | 66 | $C_{19}H_{32}N_2O_3S.2(C_2H_2O_4).CH_3OH$<br>580.62 | 49.64 | 49.68 | 6.94 | 6.69 | 4.82 | 4.95 |
| **3f** | 100-102<br>M-E | 77 | $C_{20}H_{34}N_2O_4S.2(C_2H_2O_4)$<br>578.61 | 49.81 | 49.70 | 6.61 | 6.65 | 4.84 | 4.53 |
| **3i** | 68-70<br>M-E | 75 | $C_{21}H_{36}N_2O_5S.2(C_2H_2O_4)$<br>608.64 | 49.33 | 49.00 | 6.62 | 6.45 | 4.60 | 4.75 |
| **4a** | 155-160<br>M | 75 | $C_{34}H_{52}N_4O_6S_2.3(C_2H_2O_4).2H_2O$<br>985.11 | 48.77 | 49.09 | 6.54 | 6.26 | 5.68 | 5.64 |
| **4b** | 133-136<br>M | 88 | $C_{34}H_{58}N_4O_4S_2.4(C_2H_2O_4).2H_2O$<br>1047.20 | 48.17 | 47.96 | 6.70 | 6.69 | 5.35 | 5.32 |
| **4c** | 135-138<br>M | 77 | $C_{34}H_{58}N_4O_4S_2.3(C_2H_2O_4).H_2O$<br>939.08 | 51.16 | 51.06 | 7.08 | 6.80 | 5.96 | 5.63 |
| **4d** | 135-137<br>M | 54 | $C_{34}H_{58}N_4O_4S_2.4(C_2H_2O_4)$<br>1011.17 | 49.89 | 50.10 | 6.58 | 6.95 | 5.54 | 5.75 |
| **4e** | 200-203<br>M | 88 | $C_{36}H_{62}N_4O_6S_2.4(C_2H_2O_4)$<br>1071.15 | 49.33 | 48.98 | 6.58 | 6.64 | 5.23 | 5.40 |
| **4f** | 200-202<br>M-W | 89 | $C_{38}H_{66}N_4O_8S_2.4(C_2H_2O_4).H_2O$<br>1148.21 | 48.00 | 47.68 | 6.65 | 6.60 | 4.80 | 4.43 |
| **4i** | 152-155<br>M-W | 56 | $C_{40}H_{70}N_4O_{10}S_2.4(C_2H_2O_4)$<br>1091.26 | 52.82 | 52.78 | 7.20 | 7.10 | 5.13 | 5.12 |
| **6a** | 117-120<br>M | 85 | $C_{15}H_{24}N_2O_3.2(C_2H_2O_4)$<br>460.41 | 49.56 | 49.49 | 6.13 | 6.21 | 6.08 | 5.81 |
| **6b** | 125-128<br>F | 91 | $C_{15}H_{26}N_2O_2.2(C_2H_2O_4)$<br>446.42 | 51.11 | 51.04 | 6.77 | 7.05 | 6.27 | 6.58 |

[a] M = Methanol, F. = Ethanol, M-W = Methanol-Water, M-E = Methanol-Ether. [b] Yield of pure isolated product.

Table 3

2-Phenyloxiranes



| Compound No. | Systematic name | $X_1$ | $X_2$ | $X_3$ | $X_4$ | Yield [a] A | B | H-NMR [b] Chemical Shifts $H_a$ | $H_b$ | $H_x$ |
|---|---|---|---|---|---|---|---|---|---|---|
| **2a** | 2-(3,4-methylenedioxyphenyl)oxirane | H | O-CH₂-O | | H | 80 | 81 | 2,50 | 2,90 | 3,56 |
| **2b** | 2-(*o*-methoxyphenyl)oxirane | $OCH_3$ | H | H | H | 83 | — | 2,43 | 2,90 | 4,00 |
| **2c** | 2-(*m*-methoxyphenyl)oxirane | H | $OCH_3$ | H | H | 71 | 93 | 2,50 | 2,83 | 3,56 |
| **2d** | 2-(*p*-methoxyphenyl)oxirane | H | H | $OCH_3$ | H | 51 | 64 | 2,46 | 2.80 | 3,56 |
| **2e** | 2-(3,4-dimethoxyphenyl)oxirane | H | $OCH_3$ | $OCH_3$ | H | 76 | 74 | 2,46 | 2,80 | 3.46 |
| **2f** | 2-(3,4,5-trimethoxyphenyl)oxirane | H | $OCH_3$ | $OCH_3$ | $OCH_3$ | 72 | 95 | 2,46 | 2,85 | 3,56 |
| **2i** | 2-[3,4-bis(methoxymethoxy)phenyl]oxirane | H | $OCH_2OCH_3$ | $OCH_2OCH_3$ | H | — | 99 | 2,53 | 2,89 | 3,55 |

[a] Yield of pure isolated product. [b] Spectrum in carbon tetrachloride. All the signals are doublet of doublets with $J_{AB}$ = 6 Hz, $J_{AX}$ = 2 Hz and $J_{BX}$ = 4 Hz.

tant from a pharmacological standpoint because it has the real catecholamine structure at both ends of the straight chain, however, it cannot be directly prepared in the same way as their analogues because the two hydroxyl groups in the benzene ring must be protected to avoid undesireable side-reactions in the preparation of the epoxide **2j** and in the dimerization of **3j**.

First, we thought it would be possible to obtain **4j** from the previously synthesized disulfides **4a** and **4e** by breaking the C-O bonds of the methylenedioxy or methoxy groups respectively. Several procedures were tested (see Table 1) but no satisfactory results were obtained. Only the treatment of **4e** with diisobuthylaluminium hydride (DIBAL) yields a crude material, 15% from the starting material, where **4j** was detected by nmr spectroscopy (see Table 1).

We also attempted the preparation of **4j** from 3,4-dihydroxybenzaldehyde with the hydroxy groups protected as silyl ethers; 3,4-bis(trimethylsilyloxy)benzaldehyde **1g** [11] and 3,4-bis(*t*-butyldimethylsilyloxy)benzaldehyde **1h** [12] were tested. The epoxides **2g** and **2h** prepared from **1g** and **1h** respectively, make it impossible to go on with the synthesis because of the very low formation yield and the hydrolysis of the protecting groups, which probably happened during the work-up.

Finally, the most adequate protecting group was the methoxymethyl derivative prepared in the usual way [13] by reaction of 3,4-dihydroxybenzaldehyde and methoxymethyl chloride.

Compound **1i** thus synthesized was converted into the epoxide **2i** under phase-transfer conditions (method B) in good yield (see Table 2) without alteration of the protecting groups. This compound reacted with 3-(6-aminohexyl)-1,3-thiazolidine affording **3i** that was dimerized to **4i** by a previously described procedure. The protecting groups were removed by treatment with a methanol-methylene chloride solution of hydrochloric acid and *N,N'*-bis-{6-[2-hydroxy-2-(3,4-dihydroxyphenyl)ethylamino]hexyl}cystamine (**4j**) was isolated in high yield and purity.

The epoxides **2a** and **2b** were condensed with 6-aminohexanonitrile [4] yielding **5a** and **5b** that were characterized from their spectroscopic data (Table 5). The reduction of the cyano groups of **5a** and **5b** was performed with lithium aluminium hydride in dioxane afforing **6a** and **6b** respectively.

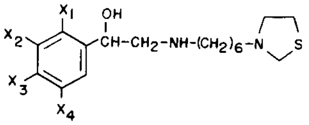
## EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Perkin-Elmer R-14B Spectrometer (60 MHz, tetramethylsilane at $\delta$ 0.0 (ppm) as internal standard). Chemical shifts are reported as $\delta$ values and are in parts per million (ppm). Infrared spectra were determined on a Perkin-Elmer 1430 Spectrophotometer. Elemental analyses were performed by Instituto de Química Bioorgánica, Barcelona.

### Oxiranes 2. Method A.

Anhydrous dimethyl sulfoxide (70 ml) was added to sodium hydride (4.2 g, 0.1 mole) and the mixture was stirred at 70° for 45 minutes under nitrogen atmosphere, after which time the solution was cooled to room temperature and anhydrous tetrahydrofurane (70 ml) was added. Then the mixture was stirred in an ice bath (0-5°) and trimethylsulfonium iodide (20 g, 0.1 mole) was slowly added (5 minutes) under nitrogen stream and after 1 minute a solution of aldehyde **1** (25 mmoles) in anhydrous tetrahydrofurane (15 ml) was added. The mixture was stirred 15 minutes at 0-5° and 90 minutes at room temperature. Water (250 ml) was added and the resulting solution was extracted with ether (4 × 80 ml). The organic layer was washed with water (5 × 30 ml) and dried with anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the resulting oily residue was the oxirane **2**.

Table 4



$^1$H-NMR [a] Chemical Shifts

| Compound No. | $(CH_2)_4$ | $CH_2NHCH_2$<br>$CH_2NH(CH_2)_2S$ | $NCH_2S$ | CHOH | X | ArH |
|---|---|---|---|---|---|---|
| **3a** | 1.33 | 2.03-3.33 | 3.86 | 4.50 | 5.80 | 6.23-6.93 |
| **3b** | 1.33 | 2.00-3.10 | 3.90 | 5.00 | 3.70 | 6.56-7.60 |
| **3c** | 1.33 | 2.10-2.93 | 3.90 | 4.56 | 3.70 | 6.50-7.33 |
| **3d** | 1.33 | 2.00-3.10 | 3.86 | 4.50 | 3.66 | 6.56-7.06 |
| **3e** | 1.30 | 2.10-3.10 | 3.83 | 4.50 | 3.73 | 6.45-6.93 |
| **3f** | 1.36 | 2.06-2.90 | 3.93 | 4.46 | 3.75<br>3.70 | 6.46 |
| **3i** | 1.35 | 2.07-3.16 | 3.93 | 4.40 | 3.43<br>5.09 | 6.46-7.50 |

[a] Spectrum in deuteriochloroform.

### Method B.

In a round-bottom flask was placed aldehyde **1** (25 mmoles), methylene chloride (100 ml), sodium hydroxide (100 ml, 50%), tetrabuthylammonium bromide (0.11 g, 3.8 mmoles) and trimethylsulphonium iodide (10 g, 50 mmoles). The mixture was stirred at 50° for 4 days. After cooling, water (100 ml) was added, the organic layer was removed and the aqueous solution was extracted with methylene chloride (3 × 30 ml). The combined organic layers were dried over anhydrous magnesium sulfate and the solvent removed. The compounds **2** were obtained in high yield.

### General Process for Preparation of 3-(2-Hydroxy-2-phenylethylaminohexyl)-1,3-thiazolidines (**3**).

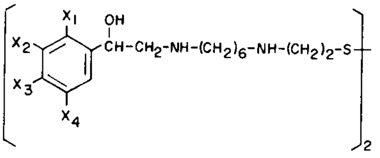
A solution of 3-(6-aminohexyl)-1,3-thiazolidine [3] (20 mmoles) and the oxirane **2** (20 mmoles) in 2-propanol (60 ml) was stirred for 22 hours at reflux temperature under a nitrogen atmosphere. The solvent was removed at reduced pressure, the residue was dissolved in methylene chloride (100 ml) and extracted with 2*N* hydrochloric acid (4 × 25 ml). The aqueous layer was basified with 5 *N* sodium hydroxide (40 ml) and extracted with methylene chloride (4 × 25 ml). The organic solution was dried with anhydrous magnesium sulfate and the solvent removed under reduced pressure. The compounds **3** were obtained as oils and then purified by successive crystallization of the dioxalate derivative.

The previous process permits us to obtain the following compounds: 3-{6-[2-Hydroxy-2-(3,4-methylenedioxyphenyl)ethylamino]hexyl}-1,3-thiazolidine (**3a**); 3-{6-[2-hydroxy-2-(*o*-methoxyphenyl)ethylamino]hexyl}-1,3-thiazolidine (**3b**); 3-{6-[2-hydroxy-2-(*m*-methoxyphenyl)ethylamino]-hexyl}-1,3-thiazolidine (**3c**); 3-{6-[2-hydroxy-2-(*p*-methoxyphenyl)ethylamino]hexyl}-1,3-thiazolidene (**3d**); 3-{6-[2-hydroxy-2-(3,4-dimethoxyphenyl)-ethylamino]hexyl}-1,3-thiazolidine (**3e**); 3-{6-[2-hydroxy-(3,4,5-trimethoxyphenyl)ethylamino]hexyl}-1,3-thiazolidine (**3f**); 3-{6-{2-hydroxy-2-[3,4-bis(methoxymethoxy)phenyl]ethylamino}hexyl}-1,3-thiazolidine (**3i**).

### General Process for Preparation of *N*,*N'*-bis[6-(2-Hydroxy-2-phenylethylamino)hexyl]cystamines **4**.

To a stirred solution of thiazolidine **3** (20 mmoles) in ethanol (200 ml) a solution of 0.1 *N* iodine-2.5% potassium iodide (200 ml) was added slowly and then 2*N* hydrochloric acid (5 ml). The mixture was stirred at room temperature for 12 hours. The solvent was removed at reduced pressure and the residue was dissolved in 2.5 *N* sodium hydroxide (150 ml). The alkaline solution was extracted with methylene chloride (3 × 75 ml), the organic layer dried with anhydrous magnesium sulfate and the solvent removed. The disulfides **4** were obtained in high yield, and purified by crystallization of its tetraoxalate derivatives. This process permits us to obtain the following compounds: *N*,*N'*-bis{6-[2-Hydroxy-2-(3,4-methylenedioxyphenyl)ethylamino]hexyl}cystamine (**4a**); *N*,*N'*-bis{6-[2-hydroxy-2-(*o*-methoxyphenyl)ethylamino]hexyl}cystamine (**4b**); *N*,*N'*-bis{6-[2-hydroxy-2-(*m*-methoxyphenyl)ethylamino]hexyl}cystamine (**4c**); *N*,*N'*-bis{6-[2-hydroxy-2-(*p*-methoxyphenyl)ethylamino]hexyl}cystamine (**4d**); *N*,*N'*-bis-{6-[2-hydroxy-2-(3,4-dimethoxyphenyl)ethylamino]hexyl}cystamine (**4e**); *N*,*N'*-bis{6-[2-hydroxy-2-(3,4,5-trimethoxyphenyl)ethylamino]hexyl}cystamine (**4f**); *N*,*N'*-bis{6-[2-hydroxy-2-(3,4-bis(methoxymethoxy)phenyl)ethylamino]hexyl}cystamine (**4i**).

Table 5



$^1$H-NMR [a] Chemical Shifts

| Compound No. | $(CH_2)_4$ | $CH_2NHCH_2$ $CH_2NH(CH_2)_2S$ | CHOH | X | Ar-H |
|---|---|---|---|---|---|
| **4a** | 1.33 | 2.10-3.33 | 4.56 | 5.80 | 6.50-7.00 |
| **4b** | 1.37 | 2.10-3.06 | 4.90 | 3.76 | 6.53-7.66 |
| **4c** | 1.33 | 2.20-3.26 | 4.56 | 3.70 | 6.50-7.26 |
| **4d** | 1.26 | 2.10-3.13 | 4.46 | 3.56 | 6.53<br>7.00 |
| **4e** | 1.43 | 2.13-3.20 | 4.50 | 3.83 | 6.36-6.90 |
| **4f** | 1.43 | 2.13-3.20 | 4.66 | 3.76<br>3.83 | 6.46 |
| **4i** | 1.34 | 2.17-3.05 | 4.10 | 3.43<br>5.08 | 6.51-7.59 |

[a] Spectrum in deuteriochloroform.

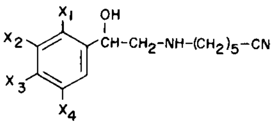
### *N*,*N'*-bis{6-[2-Hydroxy-2-(3,4-dihydroxyphenyl)ethylamino]hexyl}cystamine (**4j**).

Through a solution of **4i** (1.77 g, 2.13 mmoles) in dry methanol (40 ml) and methylene chloride (35 ml) a current of dry hydrogen chloride was passed until the solution *p*H was acidic. The solution was stirred for 20 hours at room temperature, the solvent was removed at reduced pressure and a yellow solid (1.1 g, 60%) was obtained and identified as the tetrahydrochloride of *N*,*N'*-bis{6-[2-hydroxy-2-(3,4-dihydroxyphenyl)ethylamino]hexyl}cystamine (**4j**) mp 107-110° (methanol-ether); $^1$H-nmr (DMSO-d$_6$): 1.40 (sa, $(CH_2)_4$, 16 H) 3,13 (sa, 20 H, $CH_2NHCH_2$, $CH_2NHCH_2CH_2S$), 4,33 (m, 2H CHOH), 6.38-7.35 (m, 6H, ArH).

*Anal.* Calcd. for $C_{32}H_{54}N_4S_2O_6.4HCl.C_4H_{10}O$ (874.88): C, 49.41; H, 7.83; N, 6.40. Found: C, 49.80; H, 7.45; N, 6.12.

### General Process for Preparation of *N*-(2-Hydroxy-2-phenylethyl)-1,6-hexanediamines (**6**).

Table 6

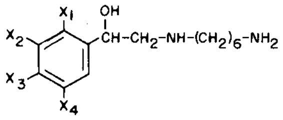


| Compound No. | Yield [a] | IR [b] (cm$^{-1}$) | $^1$H-NMR [c] Chemical Shifts $(CH_2)_3$ | $CH_2CN$ | $(CH_2)_2NH$ | CHOH | X | ArH |
|---|---|---|---|---|---|---|---|---|
| **5a** | 54 | 3300 2220 | 1.50 | 2.26 | 2.66 | 4.66 | 5.83 | 6.50-6.86 |
| **5b** | 77 | 3290 2220 | 1.46 | 2.26 | 2.46-3.00 | 4.96 | 3.80 | 6.60-7.56 |

[a] Yield of pure isolated product. [b] Spectrum in sodium chloride. [c] Spectrum in deuteriochloroform.

The corresponding epoxides **1a** or **1b** (20 mmoles) and 6-aminohexanonitrile (20 mmoles) in 2-propanol (60 ml) were placed in a round bottom flask under a nitrogen atmosphere and stirred at reflux temperature for 22 hours. After this time, 2-propanol was removed under reduced pressure. The residue was dissolved in methylene chloride (100 ml) and extracted with 2 *N* hydrochloric acid (3 × 40 ml). The aqueous layer was basified with 5*N* sodium hydroxide (50 ml) and extracted with methylene chloride (3 × 40 ml). The organic layer was dried with anhydrous magnesium sulfate and evaporated under reduced pressure to give the condensation product **5**. This process permits us to obtain the following compounds: 6-[2-hydroxy-2-(3,4-methylenedioxyphenyl)ethylamino]hexanonitrile (**5a**) and 6-[2-hydroxy-2-(*m*-methoxyphenyl)ethylamino]hexanonitrile (**5b**).

Table 7



$^1$H-NMR [a] Chemical Shifts

| Compound No. | $(CH_2)_4$ | $CH_2$-N | CHOH | X | ArH |
|---|---|---|---|---|---|
| **6a** | 1.40 | 2.16-3.10 | 4.60 | 5.83 | 6.50-6.86 |
| **6b** | 1.50 | 2.66-3.05 | 4.90 | 3.73 | 6.50-7.50 |

[a] Spectrum in deuteriochloroform.

A suspension of lithium aluminium hydride (13 mmoles) and the condensation product **5** (10 mmoles) in anhydrous dioxane (50 ml) was heated for 1 hour under a nitrogen atmosphere and then stirred at atmosphere temperature for one more hour.

After this time dioxane (0.5 ml) and water (0.5 ml) was slowly added and then 2 *N* sodium hydroxide (1.5 ml) and finally water (4 ml). The suspension was stirred for 15 minutes, filtered and the residue washed with chloroform (50 ml). All the organic layers were dried over anhydrous magnesium sulfate and the solvent was evaporated to give the compounds **6**. This process permits us to obtain the following compounds: *N*-[2-Hydroxy-2-(3,4-methylenedioxyphenyl)ethyl]-1,6-hexanediamine (**6a**) and *N*-[2-hydroxy-2-(*m*-methoxyphenyl)ethyl]-1,6-hexanediamine (**6b**).

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