Syntheis of 2-Aryloxy- and 2-Arylalkoxy-1-(2-piperidyl)ethanols

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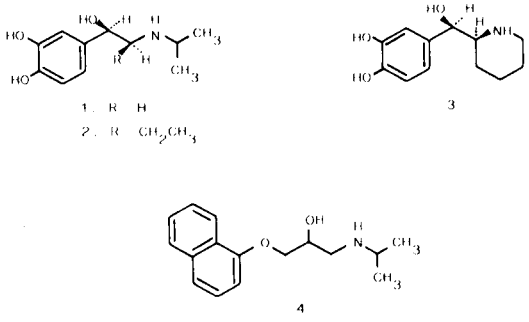
Received March 15, 1988

The preparation and separation of diastereomeric pairs of a series of 2-aryloxy- and 2-arylalkoxy-1-(2-piperidyl)ethanols is reported. The *erythro* aminoalcohols were converted into *threo* isomers by thionyl chloride treatment of their *N*-acetyl derivatives and alkaline hydrolysis.

J. Heterocyclic Chem., **26**, 693 (1989).

The arylethanolamine drugs as isoproterenol (**1**) or isoetharine (**2**) were the first structures showing β-adrenergic stimulant properties. These compounds can be modified by cyclization to the aryl(2-piperidyl)methanol structure without loss of β-adrenergic potency. Thus, rimiterol (**3**) is a selective β_2-agonist [1-3]. In the field of β-adrenergic blockers, the most active structures are the aryloxypropanolamines [4], as propanolol (**4**), whose side chain contains that of arylethanolamines **1** and **2**. Nevertheless, to our knowledge the aryloxypropanolamines have not been cyclized to the corresponding 2-aryloxy-1-(2-piperidyl)ethanols **5**.

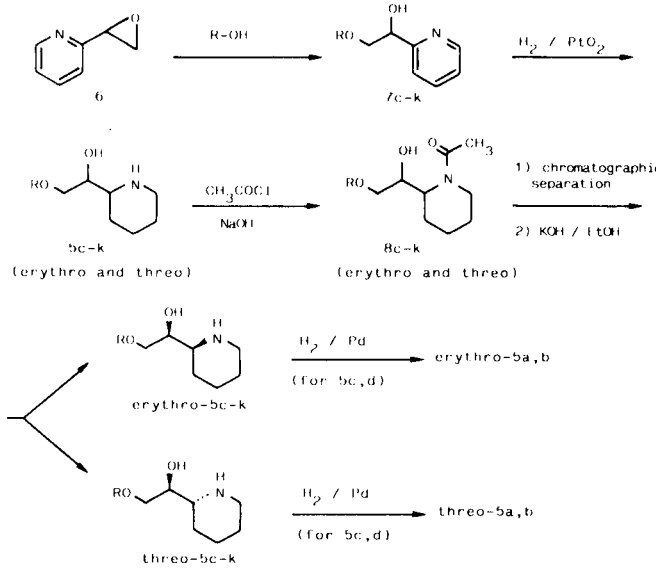
Scheme 1



In this paper we describe the synthesis of several piperidylethanols **5a-k** (Scheme 2) of known *erythro* and *threo* stereochemistry, from 2-oxiranylpyridine (**6**).

2-Vinylpyridine was epoxidated in 64% yield, as described by Hanzlick [5]. The aryl ethers **7c-i** were obtained by oxirane ring opening with the appropriate sodium phenoxide, either added as the salt to the reaction mixture or generated *in situ* by sodium hydride treatment. The expected 2-aryloxy-1-(2-pyridyl)ethanols **7c-i** were usually impurified with variable amounts (5-15%) of 2-acetylpyridine, arising from deprotonation of the α-position of **7c-i** and elimination of the corresponding phenoxide to give the enolic form of 2-acetylpyridine. The arylalkyl ethers **7j,k** were obtained by treatment of epoxide **6** with benzyl alcohol or 3-phenylpropanol respectively, in the presence of boron trifluoride ethyletherate. The observed regiospecificity in the oxirane ring opening can be attributed to the destabilizing effect of the *N*-complexed pyridinium substituent upon the benzylic carbonium ion, which prevents the usual benzylic opening of aryloxiranes in acidic media.

Scheme 2



a. R= 4-(OH)C_6H_4-
b. R= 3-(OH)C_6H_4-
c. R= 4-($C_6H_5CH_2O$)C_6H_4-
d. R= 3-($C_6H_5CH_2O$)C_6H_4-
e. R= C_6H_5-
f. R= 1-naphthoxy
g. R= 2-naphthoxy
h. R= 4-(CH_3)C_6H_4-
i. R= 3-(CH_3)C_6H_4-
j. R= $C_6H_5CH_2$-
k. R= $C_6H_5CH_2CH_2CH_2$-

Hydrogenation of **7c-k** (hydrochlorides) over Adams platinum catalyst gave mixtures of *erythro* and *threo* diastereomers of **5c-k**, in good yields. The major product in each case was the *erythro* isomer, as expected from the results described for the pyridine reduction in related pyridylmethanols [6,7]. Physical properties of *erythro*-**5c-k** and *threo*-**5c-k** were very similar and we were unable to separate them by crystallization or chromatography. In a previous work [8] we had found that *N*-acylation allowed the chromatographic separation of diastereomeric α-hydroxymethylpiperidines. So, the mixtures **5c-k** were acetylated with acetyl chloride in chloroform and aqueous sodium hydroxide to give *erythro*- and *threo*-**8c-k**. These

Table I

Experimental and Spectroscopic Data for Compounds **8c-k**

Compound	Yield %	Chromatographic eluent [a]	Formula	Analyses (%) Calcd./(Found) C	H	N	IR C=O (cm^{-1})	^{1}H NMR [b] CH_3	C^2H_e [c]	C^6H_a [d]	C^6H_e [e]	^{13}C NMR [b] CH_3	C^2 [f]	C^6 [g]
erythro-**8c**	57	A-H (90:10)	$C_{22}H_{27}NO_4$	71.52 (71.50)	7.36 (7.38)	3.79 (3.76)	1620	2.06 (2.06)	4.63 (3.99)	3.18 (2.48)	3.60 (4.60)	21.97 (21.43)	50.90 (55.11)	43.70 (37.85)
threo-**8c**	32	A-E (98:2)	$C_{22}H_{27}NO_4$	71.52 (71.48)	7.36 (7.40)	3.79 (3.77)	1620	2.15 (2.18)	4.84 (4.13)	3.33 (2.70)	3.67 (4.55)	21.93 (22.01)	51.42 (56.11)	43.28 (37.06)
erythro-**8d**	64	A-H (90:10)	$C_{22}H_{27}NO_4$	71.52 (71.56)	7.36 (7.60)	3.79 (3.60)	1600	2.08 (2.07)	4.65 (4.03)	3.20 (2.49)	3.62 (4.60)	21.98 (21.42)	50.97 (55.02)	43.68 (37.83)
threo-**8d**	18	A-E (98:2)	$C_{22}H_{27}NO_4$	71.52 (71.25)	7.36 (7.70)	3.79 (3.60)	1600	2.14 (2.18)	4.82 (4.12)	3.31 (2.68)	3.68 (4.58)	21.96 (22.07)	51.48 (56.01)	43.24 (37.06)
erythro-**8e**	35	H-A (60:40)	$C_{15}H_{21}NO_3$	68.42 (68.37)	8.04 (8.07)	5.31 (5.34)	1600	2.08 (2.08)	4.60 (4.36)	3.20 (2.47)	3.63 (4.58)	21.80 (21.96)	51.45 (56.41)	43.24 (37.23)
threo-**8e**	17	H-A (60:40)	$C_{15}H_{21}NO_3$	68.42 (68.35)	8.04 (8.09)	5.31 (5.29)	1600	2.13 (2.20)	4.88 (4.36)	3.33 (2.70)	3.70 (4.58)	21.93 (21.37)	50.99 (55.13)	43.70 (37.88)
erythro-**8f**	32	H-A (60:40)	$C_{19}H_{23}NO_3$	72.81 (72.84)	7.39 (7.37)	4.47 (4.51)	1580	2.10 (2.10)	4.68 (4.20)	3.30 (2.64)	3.66 (4.24)	21.92 (21.35)	51.42 (55.28)	43.73 (37.89)
threo-**8f**	24	A-H (70:30)	$C_{19}H_{23}NO_3$	72.81 (72.77)	7.39 (7.35)	4.47 (4.48)	1600	2.10 (2.13)	4.90 (4.52)	3.30 (2.72)	3.66 (4.60)	21.90 (21.90)	51.55 (56.72)	43.17 (37.10)
erythro-**8g**	34	H-A (70:30)	$C_{19}H_{23}NO_3$	72.81 (72.69)	7.39 (7.18)	4.47 (4.51)	1600	2.04 (2.04)	4.70 (4.36)	3.20 (2.52)	3.64 (4.22)	22.00 (21.43)	50.96 (55.25)	43.69 (37.88)
threo-**8g**	22	H-A (60:40)	$C_{19}H_{23}NO_3$	72.81 (72.60)	7.39 (7.31)	4.47 (4.52)	1660	2.04 (2.14)	4.90 (4.46)	3.32 (2.70)	3.68 (4.60)	21.92 (22.08)	51.51 (56.34)	43.24 (37.10)
erythro-**8h**	38	H-A (60:40)	$C_{16}H_{23}NO_3$	69.28 (69.43)	8.36 (8.13)	5.05 (5.10)	1600	2.04 (2.02)	4.62 (4.28)	3.21 (2.50)	3.60 (4.48)	21.49 (21.97)	50.93 (55.09)	43.89 (37.84)
threo-**8g**	26	A	$C_{16}H_{23}NO_3$	69.28 (69.34)	8.36 (8.41)	5.05 (5.08)	1650	1.92 (1.96)	4.32 (3.90)	2.98 (2.38)	3.32 (4.10)	21.50 (21.96)	51.44 (56.20)	43.26 (37.07)
erythro-**8i**	60	H-A (70:30)	$C_{16}H_{23}NO_3$	69.28 (69.34)	8.36 (8.52)	5.05 (5.07)	1630	2.21 (2.06)	4.60 (4.28)	3.22 (2.50)	3.62 (4.30)	21.75 (21.21)	50.78 (54.93)	43.49 (36.68)
threo-**8i**	31	H-A (50:50)	$C_{16}H_{23}NO_3$	69.28 (69.45)	8.36 (8.16)	5.05 (5.21)	1615	2.16 (2.18)	4.86 (4.38)	3.36 (2.70)	3.68 (4.60)	21.50 (21.61)	51.05 (56.09)	42.91 (36.91)
erythro-**8j**	33	A	$C_{16}H_{23}NO_3$	69.28 (69.14)	8.36 (8.12)	5.05 (5.03)	1660	2.04 (2.06)	4.12 (3.82)	3.10 (2.44)	3.28 (3.46)	21.92 (21.47)	50.58 (55.25)	43.59 (37.78)

threo-**8j**	20	A	$C_{16}H_{23}NO_3$	69.28 (69.35)	8.36 (8.37)	5.05 (5.12)	1660	2.04 (2.06)	4.56 (3.84)	3.06 (2.40)	3.10 (4.08)	21.16 (21.60)	51.92 (55.25)	43.23 (37.48)
erythro-**8k**	33	H-A (50:50)	$C_{18}H_{27}NO_3$	70.78 (70.42)	8.91 (8.82)	4.58 (4.63)	1660	2.18 (2.10)	4.52 (4.06)	3.18 (2.72)	3.30 (4.20)	20.00 (20.22)	50.97 (55.72)	44.17 (37.45)
threo-**8k**	23	H-A (50:50)	$C_{18}H_{27}NO_3$	70.78 (70.57)	8.91 (8.67)	4.58 (4.33)	1650	2.08 (2.12)	4.72 (4.12)	3.28 (2.42)	2.90 (4.06)	21.89 (21.89)	50.51 (55.80)	43.12 (37.46)

[a] All compounds were purified by chromatography prior elemental analysis, except for *erythro*-**8e-g**, which were crystallized from ether-ethanol (mp 98-100°, 43-45°, and 46-48° respectively). Chromatographic eluents are: A, ethyl acetate; E, ethanol; H, hexane. [b] Chemical shifts in values indicated in parentheses are those from rotamer B (see scheme 3). [c] Mean values: 4.66 ±0.20 (4.18 ±0.21). [d] Mean values: 3.23 ±0.10 (2.56 ±0.12). [e] Mean values: 3.52 ±0.23 (4.36 ±0.30). [f] Mean values: 51.18 ±0.37 (55.65 ±0.55). [g] Mean values: 43.46 ±0.31 (37.48 ±0.35).

Table II

Physical and Spectroscopic Data for Compounds **5c-k**

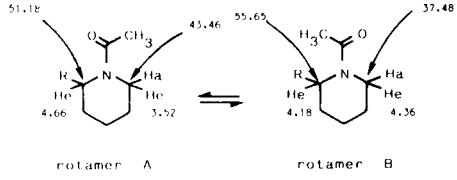
Compound	Yield %	Purification method [a]	mp °C (crystallization solvent) [b]	Formula	Analyses (%) Calcd./(Found) C	H	N	Cl	^{13}C NMR C^2	C^3	C^4	C^5	C^6	C-OH	OCH_2
erythro-**5a**	62.5	A	182-183 (B-E)	$C_{13}H_{20}ClNO_3$	57.03 (56.82)	7.36 (7.20)	5.12 (5.10)	12.95 (13.00)	58.50	21.88	21.59	21.59	44.90	67.72	68.58
threo-**5a**	90.0	B		$C_{13}H_{20}ClNO_3$	57.03 (57.20)	7.36 (7.25)	5.12 (5.12)	12.95 (12.72)	59.05	25.36	22.03	22.20	45.11	70.11	69.83
erythro-**5b**	89.0	A	170-172 (B-E)	$C_{13}H_{20}ClNO_3$	57.03 (57.00)	7.36 (7.40)	5.12 (5.08)	12.95 (12.85)	58.54	21.67	21.33	21.71	44.93	67.53	67.62
threo-**5b**	80.0	B		$C_{13}H_{20}ClNO_3$	57.03 (57.32)	7.36 (7.58)	5.12 (4.98)	12.95 (12.66)	59.41	25.84	22.24	22.53	45.34	70.25	69.46
erythro-**5c**	86.5	A	182-184 (B-E)	$C_{20}H_{26}ClNO_3$	66.01 (66.20)	7.20 (7.10)	3.85 (3.73)	9.74 (9.85)	58.65	25.44	23.28	25.44	46.41	41.71	69.63
threo-**5c**	80.0	A	168-170 (B-E)	$C_{20}H_{26}ClNO_3$	66.01 (66.15)	7.20 (7.30)	3.85 (4.05)	9.74 (9.75)	58.40	28.40	24.02	25.67	46.22	72.55	70.07
erythro-**5d**	85.0	B		$C_{20}H_{25}NO_3$	73.36 (73.26)	7.69 (7.82)	4.28 (4.10)		58.78	26.59	24.55	27.25	47.05	72.57	69.36
threo-**5d**	85.0	B		$C_{20}H_{25}NO_3$	73.36 (73.30)	7.69 (7.75)	4.28 (4.32)		58.21	28.95	24.30	26.24	46.39	72.81	70.02
erythro-**5e**	96.0	A	114-117 (E)	$C_{13}H_{19}NO_2$	70.96 (70.37)	8.65 (8.83)	6.32 (6.26)		58.83	27.27	24.56	26.59	47.06	72.61	69.22
threo-**5e**	91.0	A	114-117 (E)	$C_{13}H_{19}NO_2$	70.96 (70.56)	8.65 (8.84)	6.32 (6.24)		58.29	28.92	24.28	26.23	46.39	72.88	69.90

erythro-**5f**	75.0	A	102-104 (H-A)	$C_{17}H_{21}NO_2$	75.25 (75.58)	7.80 (8.02)	5.16 (5.37)	58.95	26.17	24.50	26.62	47.04	72.43	69.53
threo-**5f**	77.0	A	124-129 (E-A)	$C_{17}H_{21}NO_2$	75.25 (75.42)	7.80 (7.93)	5.16 (5.08)	58.26	28.95	24.30	26.16	46.47	72.90	70.27
erythro-**5g**	86.0	A	139-141 (A)	$C_{17}H_{21}NO_2$	75.25 (75.28)	7.80 (7.69)	5.16 (5.11)	58.90	26.95	24.40	26.37	46.95	72.28	69.35
threo-**5g**	90.0	A	82-85 (A)	$C_{17}H_{21}NO_2$	75.25 (73.30)	7.80 (7.75)	5.16 (4.32)	58.30	29.03	24.34	26.31	46.43	72.91	70.08
erythro-**5h**	80.0	A	112-115 (H-A)	$C_{14}H_{21}NO_2$	71.45 (71.42)	8.99 (8.96)	5.95 (5.86)	58.78	26.38	24.21	25.96	46.72	71.83	68.90
threo-**5h**	66.0	A	86.88 (A-E)	$C_{14}H_{21}NO_2$	71.45 (71.40)	8.99 (8.94)	5.95 (6.01)	58.28	28.62	24.16	25.86	46.27	72.56	69.82
erythro-**5i**	80.0	B		$C_{14}H_{21}NO_2$	71.45 (71.51)	8.99 (9.05)	5.59 (5.90)	58.51	26.43	24.19	26.17	46.59	71.84	69.29
threo-**5i**	93.0	B		$C_{14}H_{21}NO_2$	71.45 (71.37)	8.99 (9.04)	5.95 (5.87)	58.06	28.07	23.96	25.46	46.02	72.50	69.74
erythro-**5j**	93.0	A	69-71 (H-A)	$C_{14}H_{21}NO_2$	71.45 (71.21)	8.99 (8.97)	5.95 (5.92)	58.89	27.18	24.53	26.51	46.89	72.79	71.58
threo-**5j**	89.0	A	80-82 (H-A)	$C_{14}H_{21}NO_2$	71.45 (71.23)	8.99 (8.86)	5.95 (5.98)	58.91	28.76	24.57	26.57	46.95	72.91	71.56
erythro-**5k**	87.0	A	98-100 (H-A)	$C_{16}H_{25}NO_2$	72.96 (72.92)	9.57 (9.52)	5.32 (5.28)	58.93	27.48	24.61	26.65	47.59	71.93	72.91
threo-**5k**	80.0	B		$C_{16}H_{25}NO_2$	72.96 (72.95)	9.57 (9.53)	5.32 (5.31)	58.60	28.75	24.32	26.14	46.36	72.71	70.71

[a] A = crystallization, B = column chromatography. [b] (A) ethyl acetate, (B) ethanol, (E) ether, (H) hexane.

diastereomeric amides were easily separated by column chromatography and identified by ^1H and ^{13}C nmr spectroscopy (Table I). The existence of two rotameric forms for each *N*-acetyl derivative precluded the direct determination of stereochemistry in compounds **8c-k**, because of the duplication of the most significative signals. However, the different intensities and chemical shifts of the ^{13}C nmr signals, as well as the use of two-dimensional ^1H-^{13}C heterocorrelation spectra, allowed us to determinate that the major rotamers around the CO-N bond were in all cases those having the C=O group and the axial [9] side chain in a syn disposition (rotamer A, Scheme 3).

Scheme 3

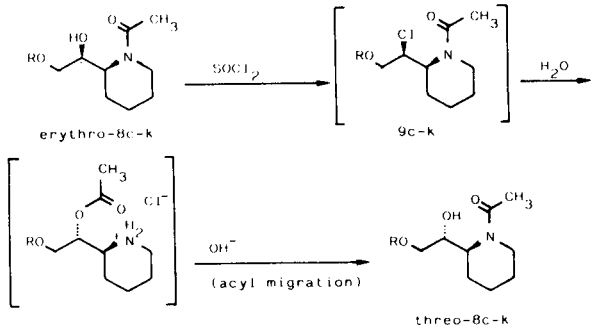


The mean chemical shifts for the equatorial protons and the carbon atoms in positions 2 and 6 of the piperidine ring are indicated in Table 1 and in Scheme 3. The carbonyl group causes an anisotropic deshielding of proton C^2H_e in rotamer **A** ($\Delta\delta$ = 0.48 ± 0.15 ppm) and of proton C^6H_e in rotamer **B** ($\Delta\delta$ = 0.84 ± 0.21 ppm). On the contrary, the effect of the carbonyl group upon the adjacent α carbon atom of the piperidine ring is a steric shielding, more intense than the compressive shielding exterted by the methyl group. Thus, the mean chemical shifts of C^2 and C^6 are 4.49 ±0.49 ppm lower and 5.99 ±0.34 ppm higher, respectively, in rotamer **A** than in rotamer **B**.

The assignment of acetamides **8c-k** as *erythro* or *threo* was carried out indirectly, after individual alkaline hydrolysis to the corresponding isomerically pure piperidylethanols **5c-k**. The stereochemistry of these aminoalcohols was determined principally on the basis of their C*H*OH-C*H*N coupling constant in ^1H nmr, which were expected [10] to be in the range of 2-5 Hz for the *erythro* isomers and of 5-8 Hz for the *threo* ones. These coupling constants could not be directly measured in the spectra of **5c-k**, due to the complexity of the -OCH_2-CHOH-C^2HN-C^3H_2- coupling system. In consequence, two-dimensional sensitive phase homocorrelation nmr experiments were carried out [11] with representative compounds *erythro*- and *threo*-**5c,d**, and the resulting coupling constants, as well as those of *erythro*- and *threo*-**5e**, were optimized by means of the LAOCOON-3 program [12]. Thus, *erythro*-**5c-e** showed $J_{CHO\text{-}CHN}$ values of 3.3, 3.8 and 4.0 Hz, respectively, whereas the corresponding coupling in *threo*-**5c-e** isomers were 6.3, 6.8, and 7.0 Hz. The stereochemistry of the remaining compounds **5a,b,f-k** [13] was determined through comparison of their ^1H nmr spectra with those of the unequivocally assigned **5c-e**, as well as by the ^{13}C nmr steric shielding ($\Delta\delta$ = 2.38 ±0.85 ppm, Table II) consistently observed for the C^3 carbon of the piperidine ring in the *erythro* diastereomers.

Although the above synthetic route is adequate for the preparation of *erythro*-**5a-k**, the *threo* isomers were obtained in poor yields, due to the stereoselectivity of the pyridine reduction step. In the aryl(2-piperidyl)methanol series, it has been described [14-18] that *erythro* diastereomers can be converted to their *threo* counterparts by inversion of the CHOH center. We have extended this isomerization procedure to our 2-aryloxy-1-(2-piperidyl)ethanols **5**. Thus, *N*-acetyl derivatives *erythro*-**8c-k** were treated with excess thionyl chloride and the intermediate chlorides **9c-k** were hydrolyzed with aqueous ammonium hydroxide to give acetamides *threo*-**8c-k** in 90-95% yield (Scheme 4).

Scheme 4



These *threo* acetamides were identical to that obtained by the route depicted in Scheme 2. The inverse isomerization, from *threo*-**8** to *erythro*-**8**, can be also carried out through the above procedure, but yields were somewhat lower (70-75%).

EXPERIMENTAL

Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. The nmr spectra were measured at 200 MHz and 60 MHz (^1H) or 50.3 MHz (^{13}C) with a FT Varian XL-200 spectrometer, using TMS as an internal standard (δ = 0). Multiplicity of the ^{13}C nmr signals was determined by means of the DEPT program [19]. The two-dimensional ^1H-^{13}C heterocorrelation spectra were made with HETCOR program [20]. Tlc was performed on silica gel 60 Merck HF_{254} (5-25 μm) and the spots were located with uv light or iodoplatinate reagent. Column chromatography was conducted on silica gel Merck 60 (63-200 μm) and flash chromatography [21] was performed on silica gel Scharlau 60 (40-60 μm). All microdistillations were made on a Büchi GKR-50 Kugelrohr apparatus. Solutions in organic solvents were dried over anhydrous sodium sulfate and evaporations were made *in vacuo* (rotating evaporator). Elemental analysis were performed by Instituto de Química Bioorgánica, C.S.I.C., Barcelona.

2-Aryloxy-1-(2-pyridyl)ethanols **7c-i**.

Method A.

A solution of 4 mmoles of the appropriate phenol in 3 ml of dimethylformamide was added under nitrogen to a suspension of 4 mmoles of sodium hydride in 24 ml of dimethylformamide. The suspension was heated at 60-70° (80-90° for compounds **7c** and **7d**) and 4 mmoles of 2-oxiranylpyridine (**6**) [5] were added. The resulting mixture was stirred at the indicated temperature for 7 hours (2 hours for compounds **7c** and **7d**), cooled, and poured over ice-water. The solution was extracted with ether and the ethereal layers were washed with diluted hydrochloric aicd. The aqueous layers were made alkaline with sodium hydroxide solution and extracted with ether. Purification and identification of the resulting pyridylethanols was performed as indicated below.

Method B.

A solution of 1 mmole of epoxide **6** in 5 ml of anhydrous dioxane was added to a solution of 2 mmoles of the appropriate sodium phenoxide or naphthoxide in 12 ml of anhydrous dioxane. The mixture was stirred at the reflux temperature, under nitrogen, for 1.5 hours. After evaporation of the solvent, the residue was taken up with water and extracted with toluene. The final work-up was identical to that described in Method A.

2-(4-Benzyloxyphenoxy)-1-(2-pyridyl)ethanol (**7c**).

This compound was obtained in a yield of 57% purified by crystallization (ether-hexane), mp 91-92°; ^{1}H nmr (deuteriochloroform): 60 MHz, 4.0 (d, J = 6 Hz, 2H, OCH_2), 4.7 (s, 2H, benzyl-CH_2), 4.9 (t, J = 6 Hz, 1H, C*H*OH), 6.6 (s, 4H, C_6H_4), 7.1 (s, 5H, C_6H_5), 8.3 (m, 1H, pyridine-α).

Anal. Calcd. for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.74; H, 5.96; N, 4.35.

2-(3-Benzyloxyphenoxy)-1-(2-pyridyl)ethanol (**7d**).

This compound was obtained in a yield of 68% purified by column chromatography (hexane-ethyl acetate 1:1); ^{1}H nmr (deuteriochloroform): 60 MHz, 4.0 (d, J = 6 Hz, 2H, OCH_2), 4.8 (s, 2H, benzyl CH_2), 4.9 (t, J = 6 Hz, 1H, C*H*OH), 6.1-7.6 (m, 8H aromatic), 7.1 (s, 5H, C_6H_5), 8.2 (m, 1H, pyridine-α).

Anal. Calcd. for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.80; H, 6.03; N, 4.10.

2-(Phenoxy)-1-(2-pyridyl)ethanol (**7e**).

This compound was obtained in a yield of 58% purified by crystallization of the hydrochloride (ethanol-ether), mp 134-136°; ^{1}H nmr (deuteriochloroform): 60 MHz, 4.2 (m, 2H, OCH_2), 4.9 (t, 1H, C*H*OH), 6.4-7.5 (m, 8H, aromatic), 8.3 (m, 1H, pyridine-α).

Anal. Calcd. for $C_{13}H_{14}ClNO_2$: C, 62.03; H, 5.61; N, 5.56; Cl, 14.08. Found: C, 61.75; H, 5.60; N, 5.54; Cl, 14.07.

2-(1-Naphthoxy)-1-(2-pyridyl)ethanol (**7f**).

This compound was obtained in a yield of 50% purified by crystallization (ether-ethyl acetate), mp 102-104°; ^{1}H nmr (deuteriochloroform): 60 MHz, 4.2-4.4 (m, 2H, OCH_2), 5.2 (t, 1H, C*H*OH), 6.8 (dd, 1H, C_2H naphthyl), 8.5 (m, 1H, pyridine-α).

Anal. Calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.69; N, 5.56. Found: C, 77.02; H, 5.63; N, 5.25.

2-(2-Naphthoxy)-1-(2-pyridyl)ethanol (**7g**).

This compound was obtained in a yield of 38% purified by crystallization of the hydrochloride (ethyl acetate-ether), mp 165-167°; ^{1}H nmr (deuteriochloroform): 60 MHz, 4.1 (d, 2H, OCH_2), 5.0 (t, 1H, C*H*OH), 6.4-7.5 (m, 7H, aromatic), 8.2 (m, 1H, pyridine-α).

Anal. Calcd. for $C_{17}H_{16}ClNO_2$: C, 67.66; H, 5.34; N, 4.64; Cl, 11.75. Found: C, 67.40; H, 5.31; N, 4.52; Cl, 11.81.

2-(4-Methylphenoxy)-1-(2-pyridyl)ethanol (**7h**).

This compound was obtained in a yield of 60% purified by column chromatography (hexane-ethyl acetate 3:7); ^{1}H nmr (deuteriochloroform): 60 MHz, 3.3 (s, 3H, CH_3), 4.1 (d, 2H, OCH_2), 4.8 (m, 1H, C*H*OH), 6.4-7.5 (m, 7H, aromatic), 8.2 (m, 1H, pyridine-α).

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.43; H, 6.59; N, 6.11. Found: C, 73.38; H, 6.54; N, 6.06.

2-(3-Methylphenoxy)-1-(2-pyridyl)ethanol (**7i**).

This compound was obtained in a yield of 53%, purified by column chromatography (hexane-ethyl acetate 4:6); ^{1}H nmr (deuteriochloroform): 60 MHz, 2.1 (s, 3H, CH_3), 4.1 (d, 2H, OCH_2), 4.9 (t, 1H, C*H*OH), 6.5-7.5 (m, 7H, aromatic), 8.4 (m, 1H, pyridine-α).

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.43; H, 6.59; N, 6.11. Found: C, 73.42; H, 6.62; N, 6.16.

2-Arylalkoxy-1-(2-pyridyl)ethanols **5j** and **5k**.

Two mmoles of boron trifluoride etherate were added, under a nitrogen atmosphere, to a solution of 2 mmoles of benzyl alcohol or 3-phenylpropanol in 5 ml of dichloromethane. To this mixture was added a solution of 1 mmole of oxiranylpyridine **6** in 1 ml of dichloromethane and the resulting solution was stirred under reflux for 2 hours. After cooling, the reaction mixture was poured into water and the final work-up described in method A was followed.

2-Benzyloxy-1-(2-pyridyl)ethanol (**7j**).

This compound was obtained in a yield of 91%, purified by crystallization (ether-ethyl acetate), mp 123-126°; ^{1}H nmr (deuteriochloroform): 60 MHz, 3.6 (m, 2H, OCH_2), 4.5 (s, 2H, benzyl-CH_2), 4.8 (t, 1H, C*H*OH), 7.3-7.6 (m, 8H, aromatic), 8.3 (m, 1H, pyridine-α).

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.43; H, 6.59; N, 6.11. Found: C, 73.52; H, 6.59; N, 6.04.

2-(3-Phenylpropoxy)-1-(2-pyridyl)ethanol (**7k**).

This compound was obtained in a yield of 51% purified by distillation (bp 200-220°, 0.5 mm Hg); ^{1}H nmr (deuteriochloroform): 60 MHz, 1.3 (m, 2H, CH_2), 2.4 (m, 2H, phenyl-CH_2), 2.5 (m, 2H, CH_2OCH_2), 4.7 (t, 1H, C*H*OH), 6.8-7.3 (m, 8H, aromatic), 8.2 (m, 1H, pyridine-α).

Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.53; H, 7.48; N, 5.42.

Catalytic Hydrogenation of Pyridine Hydrochlorides **7c-k**.HCl.

A suspension of 15 mmoles of the hydrochloride **7c-k** and a 5% (w/w) of platinum dioxide in 150 ml of absolute methanol was shaken under hydrogen atmosphere at room temperature until the theoretical volume of hydrogen was absorbed. The catalyst was filtered off and the clear solution was evaporated to dryness. The residue was dissolved in water, made alkaline with sodium hydroxide solution and extracted with ether. Evaporation of the dried extracts afforded a mixture of aminoalcohols *erythro-* and *threo*-**5c-k**.

2-Aryloxy- and 2-Arylalkoxy-1-hydroxyethyl-*N*-acetylpiperidines **8c-k**.

A solution of 7 mmoles of the diasteromeric mixtures **5c-k** in

70 ml of chloroform was mixed with 25 ml of a 2 *N* aqueous solution of sodium hydroxide. To the resulting mixture, 12.5 mmoles of acetyl chlorie were added with external cooling (ice bath). The mixture was stirred at room temperature for 1 hour, was diluted with 100 ml of water and extracted with chloroform. Evaporation of the dried extracts afforded a mixture of the *erythro* and *threo* diastereomers of acetamides **8c-k**, which were separated by column chromatography, with ethyl acetate and hexane as eluents. Individual yields, eluent mixtures, elemental analysis, and significative spectroscopic data for compounds **8c-k** are collected in Table I.

threo-Acetamidoalcohols **8c-k** from the *erythro* Isomers.

A solution of 2 mmoles of the appropriate *erythro*-**8c-k** in 5 ml of freshly distilled thionyl chloride was stirred at reflux temperature for 7 minutes. The solvent was evaporated at reduced pressure, the residue was dissolved in water and made alkaline with 10% ammonium hydroxide solution. After extraction with dichloromethane and evaporation, a 90-95% yield of the corresponding *threo*-**8c-k** was obtained. These *threo* isomers were chromatographically pure and identical to samples prepared by the above acetylation method.

erythro- And *threo*-2-(Aryloxy)- and 2-(Arylalkoxy)-1-(2-piperidyl)-ethanols, *erythro*- and *threo*-**5a-k**.

A solution of 15 mmoles of potassium hydroxide in 5 ml of water was added to a solution of 1 mmole of acetamidoalcohols *erythro*- or *threo*-**8c-k** in 15 ml of ethanol. The mixture was stirred under nitrogen at the reflux temperature for 3 hours diluted with 30 ml of water and the ethanol was evaporated *in vacuo*. The aqueous solution was extracted with dichloromethane and the organic phases were extracted with 2 *N* hydrochloric acid. The acidic phase was made alkaline with 5 *N* sodium hydroxide and extracted with dichloromethane. After drying and evaporation, the resulting aminoalcohol *erythro*- or *threo*-**5c-k** was purified as indicated in Table II.

For the synthesis of compounds **5a,b**, a solution of 3.4 mmoles of the appropriate aminoalcohol *erythro*- or *threo*-**5c,d** in 55 ml of methanol was hydrogenated over 5% palladium on charcoal, at atmospheric pressure and room temperature. After absorption of the expected volume of hydrogen, the catalyst was filtered off and the solvent was evaporated. The obtained aminoalcohol hydrochloride was purified by crystallization (*erythro* isomers) or direct column chromatography (*threo* isomers, isolated as oils).

Physical data, yields, elemental analysis, and significative ^{13}C nmr signals of aminoalcohols *erythro*- and *threo*-**5a-k** are collected in Table II.

Acknowledgements.

We are grateful to the Comisión Asesora de Investigación Científica y Técnica for financial support.

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