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Synthesis and Separation of Diastereoisomeric 1-Aryl-3-piperidino(morpholino)-2-phenylpropan-1-ols and Their Hydrochlorides

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Abstract—1-Aryl-3-piperidino(morpholino)-2-phenylpropan-1-ols were synthesized by reduction of the corresponding 1-aryl-3-piperidino(morpholino)-2-phenylpropan-1-ones with lithium tetrahydridoaluminate, and the products were separated into *erythro* and *threo* isomers by fractional crystallization. Their relative configuration and diastereoisomeric purity was determined by ^{1}H NMR spectroscopy.

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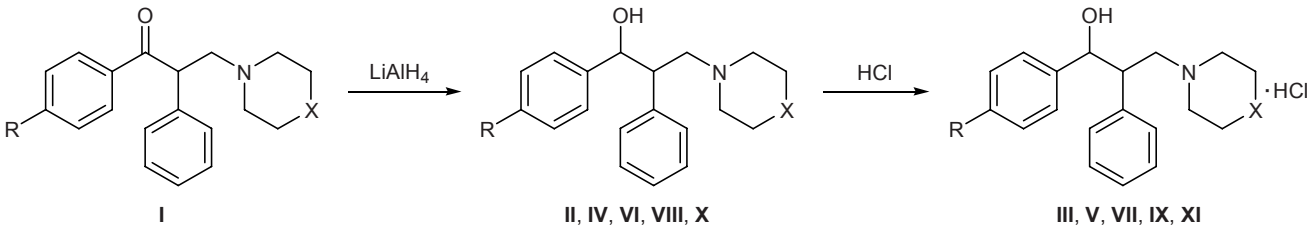
Amino alcohols of the arylaliphatic series exhibit a broad spectrum of pharmacological activity [1, 2]. Among these, compounds possessing one or more asymmetric centers attract specific interest. With a view to obtain new potential biologically active compounds, we synthesized 1-aryl-3-piperidino(morpholino)-2-phenylpropan-1-ols **II**, **IV**, **VI**, and **VIII**, and **X** by reduction of 1-aryl-3-piperidino(morpholino)-2-phenylpropan-1-ones **I** with lithium tetrahydridoaluminate in anhydrous diethyl ether (Scheme 1). The yields of amino alcohols **II**, **IV**, **VI**, **VIII**, and **X** were nearly quantitative (89–96%). Compounds **II**, **IV**, **VI**, **VIII**, and **X** were converted into the corresponding hydrochlorides **III**, **V**, **VII**, **IX**, and **XI**.

Molecules **II**–**XI** possess two chiral centers, so that these compounds may exist as *threo* and *erythro* diastereoisomers. Insofar as configuration of molecules is an important factor responsible for their biological activity, isolation of chiral compounds as pure diastereoisomers is a significant problem. Therefore, we tried to separate the obtained aminopropanols into individual diastereoisomers. As followed from the TLC and ^{1}H NMR data, reduction products **II**, **IV**, **VI**, **VIII**, **X** were mixtures of two isomers, the *erythro* isomer considerably prevailing (*erythro/threo* ratio ~80:20). Diastereoisomers of amino alcohols **II**, **IV**, **VI**, and **VIII** were separated by fractional crystallization from petroleum ether according to the procedure described in [3]. The authors showed that *erythro* isomers of some 3-aminopropan-1-ols having two asymmetric centers are generally less soluble; therefore, they separate from solution first. Analogous pattern was observed for compounds **II**, **IV**, **VI**, and **VIII**. Insofar as the corresponding *erythro* isomers prevailed, by fractional crys-

Scheme 1.



I **II**, **IV**, **VI**, **VIII**, **X** **III**, **V**, **VII**, **IX**, **XI**

II–**VII**, X = CH_2; **VIII**–**XI**, X= O; **II**, **III**, R = MeO; **IV**, **V**, R = EtO; **VI**, **VII**, R = PrO; **VIII**, **IX**, R = H; **X**, **XI**, R = MeO.

tallization we succeeded in isolating free bases **IIa**, **IVa**, **VIa**, and **VIIIa** containing 92 to 95% of the *eryhtro* isomer; from propoxy derivative **VIa** we obtained pure (100%) *erythro* isomer **VIb** and the corresponding hydrochloride **VII**.

By converting compounds **IIa**, **IVa**, and **VIIIa** into hydrochlorides **III**, **V**, and **IX** we were also able to isolate *erythro* isomers with a higher diastereoisomeric purity (up to 100%). Compound **X** was first converted into hydrochloride, and pure *erythro* isomer **XI** was then isolated.

threo Isomers **IIb**, **IIIa**, **IVb**, **Vb**, **VIc**, and **VIIIb** were isolated from the filtrates after separation of the corresponding *erythro* isomer. Among the *threo* isomers, only 1-(4-methoxyphenyl)-3-piperidino-2-phenylpropan-1-ol (**IIIa**) was isolated with a relatively high diastereoisomeric purity (80%, see table).

Diastereoisomeric purity of individual isomers, as well as the purity of diastereoisomer mixtures **II**, **IV**, **VI**, **VIII**, and **X**, was determined on the basis of the ^{1}H NMR spectra. The *erythro* and *threo* configurations were assigned taking into account that the C^1**H**OH proton in *erythro* isomers of known amino alcohols resonates in a weaker field as compared to the corresponding *threo* isomer and that the coupling constant $^3J_{1,2}$ for the former is lower [3]. Thus the ^{1}H NMR data allowed us to unambiguously determine configuration of diastereoisomeric amino propanols and their hydrochlorides **II**–**XI**.

EXPERIMENTAL

The IR spectra were recorded on a Specord 75IR spectrometer from samples dispersed in mineral oil. The ^{1}H NMR spectra were measured from solutions in DMSO-d_6 on a Varian Mercury-300 spectrometer using tetramethylsilane as internal reference. The purity of the products was checked by TLC on Silufol UV-254 plates using butan-1-ol–ethanol–acetic acid–water (8 : 2 : 1 : 3) as eluent; spots were detected by treatment with iodine vapor. The melting points were determined on a Boetius melting point apparatus.

1-Aryl-3-piperidino(morpholino)-2-phenylpropan-1-ols II, IV, VI, VIII, and X and the corresponding hydrochlorides III, V, VII, IX, and XI (*general procedure***).** A solution of 0.02 mol of β-amino ketone **I** [4] in 100 ml of anhydrous diethyl ether was slowly added dropwise under stirring to a suspension of 0.8 g (0.02 mol) of $LiAlH_4$ in 50 ml of anhydrous diethyl ether. The mixture was heated for 1 h under reflux and cooled with ice, and 20–30 ml of water was added dropwise. The organic layer was separated, and the aqueous phase was extracted with diethyl ether (2×30 ml). The extracts were combined with the organic phase, washed with water, dried over anhydrous sodium carbonate, and evaporated. The residue was ~90% of diastereoisomer mixture. Compounds **II**, **IV**, **VI**, **VIII**, and **X** were then converted into hydrochlorides **III**, **V**, **VII**, **IX**, and **XI**.

Diastereoisomeric purity and ^{1}H NMR data for diastereoisomer mixtures **IIb**, **IIIa**, **IVb**, **Vb**, **VIc**, and **VIIIb** with maximal concentration of the *threo* isomer

Comp no.	Configuration	Fraction, %	δ(OCH), ppm	$^3J_{1,2}$, Hz
IIb	*erythro*	45	4.86 d	4.1
	threo	55	4.75 d	8.7
IIIa	*erythro*	20	5.21 d	3.4
	threo	80	4.57 d	9.2
IVb	*erythro*	65	4.85 d	4.1
	threo	35	4.75 d	8.7
Vb	*erythro*	50	5.06 d	3.5
	threo	50	4.64 d	8.4
VIc	*erythro*	57	4.85 d	4.2
	threo	43	4.75 d	8.7
VIIIb	*erythro*	50	5.03 d	4.2
	threo	50	4.88 d	7.8

Separation of diastereoisomers. 3-Piperidino-1-(4-propoxyphenyl)-2-phenylpropan-1-ol (**VI**), 2 g (5.7 mmol, a mixture of *erythro* and *threo* isomers at a ratio of 82 : 18 according to the ^{1}H NMR data), in 30–40 ml of petroleum ether (bp 60–80°C) was heated under reflux until complete dissolution. After cooling to 35°C, compound **VIa** with an *erhytro*-to-*threo* isomer ratio of 92 : 8 (R_f 0.78, 0.66) separated from the solution and was filtered off. Products separated from the filtrate subsequently were repeatedly filtered off, and the isomer ratios were determined by ^{1}H NMR spectroscopy. Each new separated fraction contained a larger portion of the *threo* isomer. As a result we isolated a compound containing 43% of the *threo* isomer (**VIc**, see table). Pure (100%) *erythro* isomer **VIb** was isolated by repeated recrystallization of **VIa** from petroleum ether. Compound **VIb** was converted into hydrochloride **VII**.

Diastereoisomers of amino alcohols **II**, **IV**, and **VIII** were separated in a similar way. The maximal concentration of the *threo* isomer in **IIb**, **IVb**, and **VIIIb** was 55, 35, and 50%, respectively. Hydrochlorides **III**, **V**, **VII**, **IX**, **XI** were separated by repeated recrystallization from ethanol or acetone. From the filtrate obtained after recrystallization of hydrochloride **III** we isolated *threo* isomer **IIIa** with a diastereoisomeric purity of 80% (see table).

1-(4-Methoxyphenyl)-2-phenyl-3-piperidinopropan-1-ol (II, *erythro*/*threo* ratio 80:20**).** Yield 90%, mp 101–102°C, R_f 0.74/0.65. IR spectrum: ν 3160 cm^{-1} (O–H). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.40–1.70 m (6H, CH_2); 2.36 m (1.6H), 2.53 m (1.6H), and 2.74 t (0.4H) (NCH_2); 2.39 d.d (2H, *J* = 12.5, 5.2), 2.80 d.d (0.8H, *J* = 12.5, 9.5), and 3.08 d.d (0.2H, *J* = 11.9, 11.0) (NCH_2); 2.96 m (0.2H) and 3.24 d.d.d (0.8H, *J* = 9.5, 5.2, 4.2) (CH); 3.73 s (2.4H) and 3.76 s (0.6H) (OCH_3); 4.76 d (0.2H, *J* = 8.6) and 4.85 d (0.8H, *J* = 4.2) (OCH); 5.76 br (1H, OH); 6.56 m (0.4H) and 6.64 m (1.6H, *m*-H), 6.76 m (1.6H), and 6.86 m (0.4H, *o*-H) (C_6H_4); 6.90 m (2H, *o*-H) and 7.02–7.17 m (3H) (C_6H_5). Found, %: N 4.16. $C_{21}H_{27}NO_2$. Calculated, %: N 4.30.

Compound **IIa** (*erythro*/*threo* = 94:6). mp 105–106°C, R_f 0.74/0.65.

1-(4-Methoxyphenyl)-2-phenyl-3-piperidinopropan-1-ol hydrochloride (III, *erythro*/*threo* ratio 100:0**).** mp 218–221°C. IR spectrum: ν 3226 cm^{-1} (O–H). ^1H NMR spectrum, δ, ppm (*J*, Hz): 5.21 d (1H, OCH, *J* = 3.5). Found, %: Cl 9.73; N 3.81. $C_{21}H_{27}NO_2\cdot$ HCl. Calculated, %: Cl 9.80; N 3.87.

1-(4-Ethoxyphenyl)-2-phenyl-3-piperidinopropan-1-ol (IV, *erythro*/*threo* ratio 86:14**).** Yield 92%, mp 99–101°C, R_f 0.75/0.66. IR spectrum: ν 3200 cm^{-1} (O–H). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.38 t (3H, CH_3, *J* = 7.0); 1.45 m (2H), 1.56–1.64 m (4H), 2.54 m (2H), and 2.35 m (2H) (CH_2); 2.38 d.d (1H, *J* = 12.5, 5.0) and 2.80 d.d (1H, *J* = 12.5, 9.8) (NCH_2); 3.25 d.d.d (1H, 2-H, *J* = 9.8, 5.0, 4.2); 3.96 q (2H, OCH_2, *J* = 7.0); 4.75 d (0.2H, *J* = 8.8) and 4.84 d (0.8H, *J* = 4.2) (OCH); 5.74 br (1H, OH); 6.61 d (2H, *J* = 8.7) and 6.74 d (2H, *J* = 8.7) (C_6H_4); 6.89 d.d (2H, *J* = 7.7, 1.8) and 7.03–7.15 m (3H) (C_6H_5). Found, %: N 4.03. $C_{22}H_{29}NO_2$. Calculated, %: N 4.13.

Compound **IVa** (*erythro*/*threo* = 92:8). mp 103–104°C.

1-(4-Ethoxyphenyl)-2-phenyl-3-piperidinopropan-1-ol hydrochloride (V, *erythro*/*threo* ratio 96:4**).** mp 194–197°C. IR spectrum: ν 3285 cm^{-1} (O–H). ^1H NMR spectrum, δ, ppm (*J*, Hz): 5.21 d (0.8H, *J* = 3.2) and 4.56 d (0.2H, *J* = 9.2) (OCH). Found, %: Cl 9.36; N 3.82. $C_{22}H_{29}NO_2\cdot$HCl. Calculated, %: Cl 9.43; N 3.73.

2-Phenyl-3-piperidino-1-(4-propoxyphenyl)propan-1-ol (VI, *erythro*/*threo* ratio 82:18**).** Yield 89%, mp 75–77°C, R_f 0.74/0.66. IR spectrum: ν 3200 cm^{-1} (O–H). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.04 t (2.4H, *J* = 7.4) and 1.02 t (0.6H, *J* = 7.4) (CH_3); 1.41–1.68 m (6H, CH_2); 1.70–1.83 m (2H, OCH_2); 2.31–2.58 m (3.2H) and 2.69–2.85 m (0.8H, NCH_2); 2.39 d.d (0.8H, *J* = 12.5, 5.0), 2.81 d.d (0.8H, *J* = 12.5, 9.6), and 2.93–3.12 m (0.4H) (NCH_2); 3.25 d.d.d (0.8H, 2-H, *J* = 9.6, 5.0, 4.2); 3.80 t (0.4H, *J* = 6.5) and 3.85 t (1.6H, *J* = 6.5) (OCH_2); 4.76 d (0.2H, *J* = 8.7) and 4.85 d (0.8H, *J* = 4.2) (OCH); 5.96 br (1H, OH); 6.55 m (0.4H) and 6.63 m (1.6H) (*m*-H, C_6H_4); 6.76 m (1.6H) and 6.85 m (0.4H) (*o*-H, C_6H_4); 6.91 m (2H, *o*-H) and 7.05–7.16 m (3H, *m*-H, *p*-H) (C_6H_5). Found, %: N 3.85. $C_{23}H_{31}NO_2$. Calculated, %: N 3.96.

Compound **VIa** (*erythro*/*threo* = 100:0). mp 81–83°C, R_f 0.66.

2-Phenyl-3-piperidino-1-(4-propoxyphenyl)-propan-1-ol hydrochloride (VII, *erythro*/*threo* ratio 100:0**).** mp 213–215°C. IR spectrum: ν 3280 cm^{-1} (O–H). ^1H NMR spectrum, δ, ppm (*J*, Hz): 5.20 d (1H, OCH, *J* = 3.3). Found, %: Cl 9.71; N 3.67. $C_{23}H_{31}NO_2\cdot$ HCl. Calculated, %: Cl 9.09; N 3.59.

3-Morpholino-1,2-diphenylpropan-1-ol (VIII, *erythro*/*threo* ratio 80:20**).** Yield 94%, mp 71–73°C, R_f 0.73/0.65. IR spectrum: ν 3180–3170 cm^{-1} (O–H). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.35–2.49 m (4H, NCH_2); 2.64 m (0.8H) and 3.03–3.13 m (1.2H (C**H**Ph, NCH_2); 2.86 d.d (1H, NCH_2, *J* = 12.5, 8.5); 3.57 t (3.2H, *J* = 4.7) and 3.63 t (0.8H, *J* = 4.7) (OCH_2); 4.81 d (0.2H, *J* = 7.7) and 4.95 d (0.8H, *J* = 4.2) (OCH); 5.22 br (1H, OH); 6.90–7.01 m (4H) and 7.03–7.15 m (6H) (C_6H_5). Found, %: N 4.65. $C_{19}H_{23}NO_2$. Calculated, %: N 4.71.

Compound **VIIIa** (*erythro*/*threo* = 95:5), mp 75–77°C.

3-Morpholino-1,2-diphenylpropan-1-ol hydrochloride (IX, *erythro*/*threo* ratio 97:3**).** mp 233–235°C. IR spectrum: ν 3291 cm^{-1} (O–H). ^1H NMR spectrum, δ, ppm (*J*, Hz): 5.31 d (0.8H, *J* = 3.2) and 4.46 d (0.2H, *J* = 8.8) (OCH). Found, %: Cl 10.68; N 4.32. $C_{19}H_{23}NO_2\cdot$HCl. Calculated, %: Cl 10.62; N 4.19.

1-(4-Methoxyphenyl)-3-morpholino-2-phenylpropan-1-ol (X). Yield 91%, mp 73–74°C, R_f 0.71/0.64. IR spectrum: ν 3170 cm^{-1} (O–H). Found, %: N 4.45. $C_{20}H_{25}NO_3$. Calculated, %: N 4.28.

1-(4-Methoxyphenyl)-3-morpholino-2-phenylpropan-1-ol hydrochloride (XI, *erythro*/*threo* ratio 100 : 0**).** mp 222–224°C. IR spectrum: ν 3283 cm^{-1} (O–H). ^1H NMR spectrum, δ, ppm (*J*, Hz): 5.29 d (1H, OCH, *J* = 3.1). Found, %: Cl 9.63; N 3.78. $C_{20}H_{25}NO_3 \cdot HCl$. Calculated, %: Cl 9.75: N 3.85.

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