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# Synthesis of 3-(4-Bromophenyl)-1-morpholino-2-phenylalkan-3-ol Hydrochlorides

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**Abstract**—Reactions of 1-(4-bromophenyl)-3-morpholino-2-phenylpropan-1-one with various Grignard compounds in diethyl ether gave a broad series of tertiary amino alcohols, 3-(4-bromophenyl)-1-morpholino-2-phenylalkan-3-ol hydrochlorides, that can be regarded as Trihexyphenidyl analogs.

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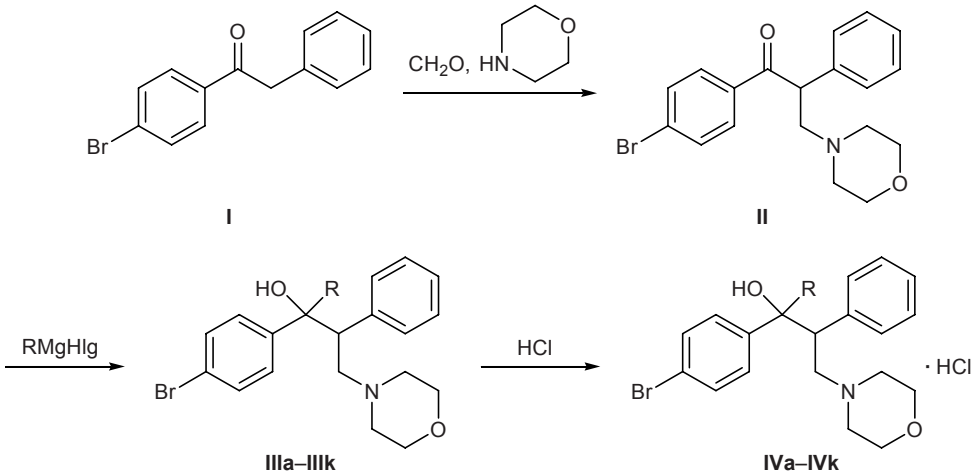
In continuation of our studies on the synthesis of amino ketones and the corresponding tertiary amino alcohols [1–4] we have prepared a series of new 3-(4-bromophenyl)-1-morpholino-2-phenylalkan-3-ol hydrochlorides and examined their antiphlogistic and cholinolytic action. As starting compound we used 1-(4-bromophenyl)-3-morpholino-2-phenylpropan-1-one (**II**) which was synthesized by the Mannich reaction of 1-(4-bromophenyl)-2-phenylethanone (**I**) with paraformaldehyde and morpholine in ethanol or dioxane. Ketone **II** reacted with Grignard compounds in anhydrous diethyl ether to produce 3-(4-bromophenyl)-1-morpholino-2-phenylalkan-3-ols **IIIa**–**IIIk** which were isolated as thick oily substances and converted into the corresponding hydrochlorides **IVa**–**IVk** (Scheme 1).

The structure of hydrochlorides **IVa**–**IVk** was confirmed by the $^1$H NMR and IR spectra. The IR spectra of initial compounds **I** and **II** contained carbonyl absorption band ν(C=O) at 1680 cm$^{-1}$, whereas amino alcohols **IVa**–**IVk** showed no absorption assignable to carbonyl groups, but absorption bands at 3400–3270 cm$^{-1}$ were present in their IR spectra due to stretching vibrations of the hydroxy group.

**Scheme 1.**




R = Me (**a**), Et (**b**), Pr (**c**), *i*-Pr (**d**), Bu (**e**), *i*-Bu (**f**), *iso*-$C_5H_{11}$ (**g**), $C_6H_{13}$ (**h**), $C_7H_{15}$ (**i**), Ph (**j**), *cyclo*-$C_6H_{11}$ (**k**).

The results of biological testing of the newly synthesized compounds will be reported elsewhere.

## EXPERIMENTAL

The IR spectra were recorded on a UR-20 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 instrument using tetramethylsilane as internal reference. The purity of the products was checked by TLC on Silufol UV-254 plates (butan-1-ol–ethanol–acetic acid–water, 8:2:1:3; development with iodine vapor.

1-(4-Bromophenyl)-2-phenylethanone (**I**) [2] and 1-(4-bromophenyl)-3-morpholino-2-phenylpropan-1-one (**II**) [3] were synthesized according to the procedures described previously.

**3-(4-Bromophenyl)-1-morpholino-2-phenylalkan-3-ol hydrochlorides IVa–IVk (*general procedure*).** A solution of 0.01 mol of 1-(4-bromophenyl)-3-morpholino-2-phenylpropan-1-one (**II**) in 30 ml of anhydrous diethyl ether was added dropwise to the Grignard compound prepared from 2.4 g (0.1 mol) of magnesium and 0.11 mol of the corresponding alkyl or aryl halide in 50 ml of anhydrous diethyl ether. The mixture was heated to 40–50°C and cooled to –5°C, and 10 ml of water was slowly added in a dropwise mode. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (2×20 ml). The extracts were combined with the organic phase and dried over sodium carbonate, the drying agent was filtered off, and 10 ml of a saturated solution of HCl in diethyl ether was added dropwise until pH 1 (universal indicator paper). The precipitate was filtered off and recrystallized from anhydrous acetone.

**3-(4-Bromophenyl)-1-morpholino-2-phenylbutan-3-ol hydrochloride (IVa).** Yield 77%, mp 238–240°C, $R_f$ 0.63. IR spectrum: ν 3310 cm$^{-1}$ (OH). $^1$H NMR spectrum, δ, ppm: 1.64 s (3H, $CH_3$); 2.70 br (1H), 2.92 br (1H), and 3.06 br (2H) ($NCH_2$); 3.38 br (1H) and 3.65–4.00 m (6H) ($OCH_2$, $CHCH_2$); 5.50 br (1H, OH); 6.98 m (2H) and 7.10–7.14 m (3H) ($C_6H_5$); 7.00–7.24 d (4H, $C_6H_4$, $J$ = 8.7 Hz); 11.67 br (1H, HCl). Found, %: C 56.13; H 5.70; Cl 8.24; N 3.19. $C_{20}H_{24}BrNO_2\cdot HCl$. Calculated, %: C 56.27; H 5.86; Cl 8.32; N 3.28.

**3-(4-Bromophenyl)-1-morpholino-2-phenylpentan-3-ol hydrochloride (IVb).** Yield 66%, mp 210–212°C, $R_f$ 0.62. IR spectrum: ν 3290 cm$^{-1}$ (OH). $^1$H NMR spectrum, δ, ppm: 0.68 t (3H, $CH_3$, $J$ = 7.2 Hz); 1.97 m (2H, C**H**$_2$CH$_3$); 2.63 m (1H) and 2.92–3.22 m (3H) ($NCH_2$); 3.41 m (1H) and 3.69 m (1H, $NCH_2$); 3.78–4.08 m (5H, $OCH_2$, CH); 5.20 br (1H, OH); 6.86–7.00 m (4H) and 7.11–7.28 m (5H) ($H_{arom}$); 11.91 br (1H, HCl). Found, %: C 57.18; H 6.10; Cl 8.03; N 3.16. $C_{21}H_{26}BrNO_2\cdot HCl$. Calculated, %: C 57.20; H 6.12; Cl 8.05; N 3.17.

**3-(4-Bromophenyl)-1-morpholino-2-phenylhexan-3-ol hydrochloride (IVc).** Yield 60%, mp 218–220°C, $R_f$ 0.63. IR spectrum: ν 3270 cm$^{-1}$ (OH). $^1$H NMR spectrum, δ, ppm: 0.84 m (3H, $CH_3$); 0.79–1.40 m (2H, $CH_2$); 1.79–1.95 m (2H, $CH_2$); 2.62 br (1H) and 2.83–3.17 m (3H) ($NCH_2$); 3.40 br (1H) and 3.60–4.10 br (6H, $OCH_2$, CH); 5.25 br (1H, OH); 6.92 d (2H, $C_6H_4$, $J$ = 8.7 Hz); 6.93 br (2H) and 7.14–7.18 m (3H) ($C_6H_5$); 7.26 d (2H, $C_6H_4$, $J$ = 8.7 Hz); 11.91 br (1H, HCl). Found, %: C 58.10; H 6.41; Cl 7.75; N 3.11. $C_{22}H_{28}BrNO_2\cdot HCl$. Calculated, %: C 58.08; H 6.38; Cl 7.81; N 3.08.

**3-(4-Bromophenyl)-4-methyl-1-morpholino-2-phenylpentan-3-ol hydrochloride (IVd).** Yield 49%, mp 215–217°C, $R_f$ 0.61. IR spectrum: ν 3400 cm$^{-1}$ (OH). $^1$H NMR spectrum, δ, ppm: 0.58 d (3H, $CH_3$, $J$ = 6.6 Hz); 1.26 d (3H, $CH_3$, $J$ = 6.6 Hz); 2.01 sept (1H, CH, $J$ = 6.6 Hz); 2.49 m (1H) and 2.91–3.10 m (3H) ($NCH_2$); 3.42 m (1H), 3.46 (1H), and 3.77–4.03 m (2H) ($OCH_2$); 3.67 d (1H, $J$ = 12.5 Hz) and 3.99 m (1H) ($NCH_2$); 4.20 d.d (1H, CH, $J$ = 7.4, 1.8 Hz); 4.87 br (1H, OH); 6.85–7.32 m (9H, $H_{arom}$); 12.00 br (1H, HCl). Found, %: C 58.11; H 6.40; Cl 7.78; N 3.10. $C_{22}H_{28}BrNO_2\cdot HCl$. Calculated, %: C 58.08; H 6.38; Cl 7.81; N 3.08.

**3-(4-Bromophenyl)-1-morpholino-2-phenylheptan-3-ol hydrochloride (IVe).** Yield 52%, mp 215–217°C, $R_f$ 0.64. IR spectrum: ν 3380 cm$^{-1}$ (OH). $^1$H NMR spectrum, δ, ppm: 0.74 m (1H) and 1.24 m (1H, $CH_2$); 0.82 t (3H, $CH_3$, $J$ = 7.2 Hz); 1.32 m (2H, $CH_2$); 1.90 m (2H, $CH_2$); 2.63 m (1H) and 2.99–3.17 m (3H) ($NCH_2$); 3.41 m (1H) and 3.69 m (1H) ($NCH_2$); 3.74–4.07 m (5H, $OCH_2$, CH); 5.27 br (1H, OH); 6.91 m (2H) and 7.26 m (2H) ($C_6H_4$); 6.91 m (2H) and 7.16 m (3H) ($C_6H_5$), 11.95 br (1H, HCl). Found, %: C 58.92; H 6.62; Cl 7.55; N 2.99. $C_{23}H_{30}BrNO_2\cdot HCl$. Calculated, %: C 58.91; H 6.61; Cl 7.57; N 2.98.

**3-(4-Bromophenyl)-5-methyl-1-morpholino-2-phenylhexan-3-ol hydrochloride (IVf).** Yield 41%, mp 214–216°C, $R_f$ 0.63. IR spectrum: ν 3290 cm$^{-1}$ (OH). Found, %: C 58.90; H 6.60; Cl 7.56; N 2.97. $C_{23}H_{30}BrNO_2\cdot HCl$. Calculated, %: C 58.91; H 6.61; Cl 7.57; N 2.98.

**3-(4-Bromophenyl)-6-methyl-1-morpholino-2-phenylheptan-3-ol hydrochloride (IVg).** Yield 70%, mp 202–204°C, $R_f$ 0.63. IR spectrum: ν 3280 $cm^{-1}$ (OH). $^1H$ NMR spectrum, δ, ppm: 0.64 m (1H) and 1.29 m (1H) ($CH_2$); 0.78 d (3H, $CH_3$, $J$ = 6.6 Hz); 0.85 d (3H, $CH_3$, $J$ = 6.6 Hz); 1.45 m (1H, CH, $J$ = 6.6 Hz); 1.91 m (2H, $CH_2$); 2.63 m (1H) and 2.97–3.16 m (3H) ($NCH_2$); 3.41 m (1H) and 3.70 m (1H) ($NCH_2$); 3.74–4.07 m (5H, $OCH_2$, CH); 5.25 br (1H, OH); 6.89 m (2H) and 7.26 m (2H) ($C_6H_4$); 6.90 m (2H) and 7.16 m (3H) ($C_6H_5$); 11.90 br (1H, HCl). Found, %: C 59.67; H 6.82; Cl 7.36; N 2.91. $C_{24}H_{32}BrNO_2 \cdot HCl$. Calculated, %: C 59.68; H 6.83; Cl 7.35; N 2.90.

**3-(4-Bromophenyl)-1-morpholino-2-phenylnonan-3-ol hydrochloride (IVh).** Yield 69%, mp 211–213°C, $R_f$ 0.62. IR spectrum: ν 3390 $cm^{-1}$ (OH). $^1H$ NMR spectrum, δ, ppm: 0.75 m (1H) and 1.37 m (1H) ($CH_2$); 0.84 t (3H, $CH_3$, $J$ = 6.9 Hz); 1.13–1.28 m (6H, $CH_2$); 1.80–1.97 m (2H, $CH_2$); 2.63 m (1H), 3.00 m (2H), and 3.41 m (1H, $NCH_2$); 3.11 d.d (1H, $J$ = 3.7, 8.0 Hz) and 3.80 d.d (1H, $J$ = 13.7, 2.9 Hz) ($NCH_2$); 3.64–4.08 m (5H, $OCH_2$, CH); 5.25 br (1H, OH); 6.90 m (2H) and 7.26 m (2H) ($C_6H_4$); 6.91 m (2H) and 7.17 m (3H) ($C_6H_5$); 11.94 br (1H, HCl). Found, %: C 60.41; H 7.03; Cl 7.16; N 2.80. $C_{25}H_{34}BrNO_2 \cdot HCl$. Calculated, %: C 60.42; H 7.04; Cl 7.15; N 2.81.

**3-(4-Bromophenyl)-1-morpholino-2-phenyldecan-3-ol hydrochloride (IVi).** Yield 72%, mp 205–207°C, $R_f$ 0.63. IR spectrum: ν 3380–3250 $cm^{-1}$ (OH). $^1H$ NMR spectrum, δ, ppm: 0.75 m (1H) and 1.37 m (1H) ($CH_2$); 0.85 t (3H, $CH_3$, $J$ = 6.9 Hz); 1.13–1.29 m (8H, $CH_2$); 1.79–1.96 m (2H, $CH_2$); 2.62 m (1H), 2.99 m (2H), and 3.39 m (1H) ($NCH_2$); 3.10 m (1H) and 3.68 m (1H) ($NCH_2$); 3.62–4.07 m (5H, $CH_2$, CH); 5.25 br (1H, OH); 6.90 m (2H) and 7.26 m (2H) ($C_6H_4$); 6.91 m (2H) and 7.16 m (3H) ($C_6H_5$); 11.95 br (1H, HCl). Found, %: C 61.13; H 7.32; Cl 6.70; N 2.75. $C_{26}H_{36}BrNO_2 \cdot HCl$. Calculated, %: C 61.12; H 7.30; Cl 6.98; N 2.74.

**3-(4-Bromophenyl)-1-morpholino-2,3-diphenylpropan-3-ol hydrochloride (IVj).** Yield 73%, mp 220–222°C, $R_f$ 0.60. IR spectrum: ν 3330 $cm^{-1}$ (COH). $^1H$ NMR spectrum, δ, ppm: 2.55 br (1H) and 2.96 br (3H) ($NCH_2$); 3.32 br.d (1H, $J$ = 13.5 Hz) and 4.08 br (1H) ($NCH_2$); 3.51–3.96 br.m (4H, $OCH_2$); 4.92 br (1H, CH); 5.95 br (1H, OH); 7.01–7.15 m (7H), 7.24–7.3 t (1H), 7.33 m (2H), 7.40 t (2H, $J$ = 7.7 Hz), and 7.97 br.d (2H, $J$ = 7.8 Hz) ($H_{arom}$); 2.90 br (1H, HCl). Found, %: C 61.40; H 5.51; Cl 7.27; N 2.85. $C_{25}H_{26}BrNO_2 \cdot HCl$. Calculated, %: C 61.41; H 5.52; Cl 7.26; N 2.86.

**3-(4-Bromophenyl)-3-cyclohexyl-1-morpholino-2-phenylpropan-3-ol hydrochloride (IVk).** Yield 59%, mp 198–200°C, $R_f$ 0.62. IR spectrum: ν 3380 $cm^{-1}$ (OH). $^1H$ NMR spectrum, δ, ppm: 0.91–1.64 m (10H) and 1.92 m (1H) ($C_6H_{11}$); 2.36 m (1H) and 2.79–3.09 m (3H) ($NCH_2$); 3.40 br (2H, $NCH_2$); 3.80 m (4H, $OCH_2$); 4.09 m (1H, CH); 5.01 br (1H, OH); 6.91 m (4H), 7.20 m (3H), and 7.27 m (2H) ($H_{arom}$); 11.86 br (1H, HCl). Found, %: C 60.66; H 6.65; Cl 7.22; N 2.81. $C_{25}H_{32}BrNO_2 \cdot HCl$. Calculated, %: C 60.67; H 6.67; Cl 7.18; N 2.83.

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