ISSN 1070-4280, Russian Journal of Organic Chemistry, 2009, Vol. 45, No. 12, pp. 1853–1855. © Pleiades Publishing, Ltd., 2009.
Original Russian Text © G.A. Gevorgyan, A.P. Avakyan, N.K. Gasparyan, G.A. Panosyan, 2009, published in Zhurnal Organicheskoi Khimii, 2009, Vol. 45, No. 12, pp. 1854–1856.

SHORT COMMUNICATIONS

Mannich Synthesis of 3-Amino-1-aryl-2-(4-chlorophenyl)-propan-1-ones

G. A. Gevorgyan[a], A. P. Avakyan[a], N. K. Gasparyan[a], and G. A. Panosyan[b]

[a] *Scientific and Technological Center of Organic and Pharmaceutical Chemistry, National Academy of Sciences of Armenia Mndzhoyan Institute of Fine Organic Chemistry, pr. Azatutyan 26, Erevan, 375014 Armenia e-mail: gyulgev@gmail.com*

[b] *Molecular Structure Research Center, National Academy of Sciences of Armenia, Erevan, Armenia*

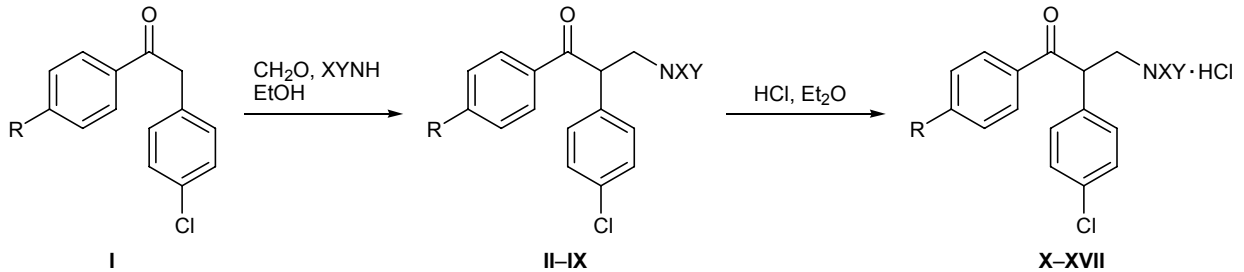
Received September 17, 2008

DOI: 10.1134/S1070428009120173

β-Amino ketones (Mannich bases) are potential biologically active compounds [1, 2]. In continuation of our previous studies [3–5] we have synthesized a new series of β-amino ketones, 3-amino-1-aryl-2-(4-chlorophenyl)propan-1-ones **II**–**IX** by aminomethylation of 4-substituted 4-chlorobenzyl phenyl ketones **I** with paraformaldehyde and various amines, in particular azepane, 4-(3-chlorophenyl)piperazine, 4-(2-fluorophenyl)piperazine, 4-ethylpiperazine, and 4-(2-furylcarbonyl)piperazine. The best yields were obtained by carrying out the reaction at pH 8–9. For example, the yields of compound **II** in the condensation of 4-chlorobenzyl 4-methoxyphenyl ketone with azepane (as hydrochloride) and paraformaldehyde in ethanol (or dioxane) were as follows: 67% at pH 8–9, 22% at pH 4, and 5% at pH 1. β-Amino ketones **II**–**IX** were converted into the corresponding hydrochlorides **X**–**XVII** with a view to examine their biological activity. Initial ketones **I** were prepared by Friedel–Crafts acylation of the corresponding substituted benzenes with 4-chlorophenylacetyl chloride.

Compounds **II**–**IX** were isolated as colorless crystalline substances which were insoluble in water. They showed in the IR spectra carbonyl absorption band in the region 1660–1680 cm^{-1}. Hydrochlorides **X**–**XVII** were water-soluble crystalline substances.

3-Amino-1-aryl-2-(4-chlorophenyl)propan-1-ones II–IX and their hydrochlorides X–XVII (*general procedure***).** A mixture of 0.1 mol of substituted phenyl 4-chlorobenzyl ketone **I**, 3.6 g (0.12 mol) of paraformaldehyde, and 0.12 mol of the corresponding amine in 80 ml of ethanol was heated for 8–10 h. The solvent was distilled off, the residue was dissolved in water, and the solution was acidified to pH 1–2 with 10% hydrochloric acid and extracted with diethyl ether or benzene to remove unreacted ketone. The aqueous phase was adjusted to pH 8–9 by adding 40% aqueous sodium hydroxide and extracted with diethyl ether or benzene (3 × 100 ml). The combined extracts were dried over anhydrous sodium sulfate, the solvent was distilled off, and the precipitate was filtered off and recrystallized from ethanol. Compounds **II**–**IX** thus



I **II–IX** **X–XVII**

II–**V**, **X**–**XIII**, XYN = azepan-1-yl; **VI**, **XIV**, XYN = 4-(3-chlorophenyl)piperazin-1-yl; **VII**, **XV**, XYN = 4-(2-fluorophenyl)piperazin-1-yl; **VIII**, **XVI**, XYN = 4-ethylpiperazin-1-yl; **IX**, **XVII**, XYN = 4-(furan-2-ylcarbonyl)piperazin-1-yl; **II**, **VI**, **VII**, **X**, **XIV**, **XV**, R =MeO; **III**, **VIII**, **IX**, **XI**, **XVI**, **XVII**, R = EtO; **IV**, **XII**, R = Me; **V**, **XIII**, R = *sec*-butyl.

obtained were dissolved in ether, and a solution of hydrogen chloride in diethyl ether was slowly added dropwise until pH 1. The precipitate was filtered off, washed with anhydrous diethyl ether, and recrystallized from anhydrous acetone. We thus isolated hydrochlorides **X**–**XVII**.

3-(Azepan-1-yl)-2-(4-chlorophenyl)-1-(4-methoxyphenyl)propan-1-one (II). *a*. A mixture of 24.6 g (0.1 mol) of 4-chlorobenzyl 4-methoxyphenyl ketone, 3.6 g (0.12 mol) of paraformaldehyde, and 11.9 g (0.12 mol) of hexamethyleneimine in 80 ml of ethanol was heated for 8 h. The mixture was then treated according to the general procedure described above. Yield 24.9 g (67%), mp 99–101°C, R_f 0.62. IR spectrum: ν 1664 cm^{-1} (C=O). Found, %: C 71.15; H 7.08; N 3.74. $C_{22}H_{26}ClNO_2$. Calculated, %: C 71.05; H 7.05; N 3.77.

b. A mixture of 24.6 g (0.1 mol) of 4-chlorobenzyl 4-methoxyphenyl ketone, 3.6 g (0.12 mol) of paraformaldehyde, and 16.3 g (0.12 mol) of hexamethyleneimine hydrochloride in 80 ml of ethanol was heated for 10 h. The solvent was distilled off, the residue was dissolved in water, and 10% hydrochloric acid was added to the solution until pH 1. The mixture was then treated acording to the general procedure. Yield 8.2 g (22%), mp 99–101°C, R_f 0.62.

c. Hydrochloric acid was added dropwise to a mixture of 24.6 g (0.1 mol) of 4-chlorobenzyl 4-methoxyphenyl ketone, 3.6 g (0.12 mol) of paraformaldehyde, and 16.3 g (0.12 mol) of hexamethyleneimine hydrochloride in 80 ml of dioxane until pH 1. The mixture was heated for 10 h, The solvent was distilled off, the residue was dissolved in water, and the product was isolated according to the general procedure. Yield 1.9 g (5%), mp 99–101°C, R_f 0.62.

3-(Azepan-1-yl)-2-(4-chlorophenyl)-1-(4-methoxyphenyl)propan-1-one hydrochloride (X). mp 158–159°C. ^{1}H NMR spectrum, δ, ppm: 1.62 m (2H), 1.78 m (4H), and 1.98 m (2H, $C_6H_{12}N$); 2.91–3.10 m and 3.26–3.34 m [2H each, $N(CH_2)$]; 3.22 m and 4.07 m (1H each, NCH_2); 3.84 s (3H, OCH_3); 6.05 d.d (1H, CH, J = 7.3, 3.6 Hz); 6.95 m and 8.03 m (2H each, $CH_3OC_6\mathbf{H}_4$); 7.28 m and 7.44 m (2H each, ClC_6H_4); 12.05 br.s (1H, HCl). Found, %: C 71.15; H 7.08; N 3.74. $C_{22}H_{26}ClNO_2 \cdot HCl$. Calculated, %: C 71.05; H 7.05; N 3.77.

3-(Azepan-1-yl)-2-(4-chlorophenyl)-1-(4-ethoxyphenyl)propan-1-one (III). Yield 70%, mp 105–107°C, R_f 0.63. IR spectrum: ν 1670 cm^{-1} (C=O). ^{1}H NMR spectrum, δ, ppm: 1.41 t (3H, CH_3, J = 6.9 Hz); 1.46 br and 1.57 br (4H each, $C_6H_{12}N$); 2.58–2.66 m [4H, $N(CH_2)_2$]; 2.72 d.d (1H, CH_2, J = 12.8, 5.4 Hz); 3.33 d.d (1H, CH_2, J = 12.8, 8.6 Hz); 4.08 q (2H, OCH_2, J = 6.9 Hz); 4.81 d.d (1H, CH, J = 8.6, J = 5.4 Hz); 6.87 m and 7.92 m (2H each, C_6H_4O); 7.22 m and 7.30 m (2H each, C_6H_4Cl). Found, %: C 71.68; H 7.35; N 3.71. $C_{23}H_{28}ClNO_2$. Calculated, %: C 71.58; H 7.31; N 3.63.

3-(Azepan-1-yl)-2-(4-chlorophenyl)-1-(4-ethoxyphenyl)propan-1-one hydrochloride (XI). mp 164–166°C. Found, %: Cl 8.34; N 3.35. $C_{23}H_{28}ClNO_2 \cdot HCl$. Calculated, %: Cl 8.41; N 3.32.

3-(Azepan-1-yl)-2-(4-chlorophenyl)-1-(4-methylphenyl)propan-1-one (IV). Yield 62%, mp 97–99°C, R_f 0.58. IR spectrum: ν 1672 cm^{-1} (C=O). Found, %: C 74.36; H 7.34; N 3.88. $C_{22}H_{26}ClNO$. Calculated, %: C 74.24; H 7.36; N 3.94.

3-(Azepan-1-yl)-2-(4-chlorophenyl)-1-(4-methylphenyl)propan-1-one hydrochloride (XII). mp 154–157°C. Found, %: Cl 9.14; N 3.51. $C_{22}H_{26}ClNO \cdot HCl$. Calculated, %: Cl 9.05; N 3.57.

3-(Azepan-1-yl)-1-(4-*sec*-butylphenyl)-2-(4-chlorophenyl)propan-1-one (V). Yield 56%, mp 103–104°C, R_f 0.61. IR spectrum: ν 1672 cm^{-1} (C=O). Found, %: C 75.51; H 8.17; N 3.44. $C_{25}H_{32}ClNO$. Calculated, %: C 75.45; H 8.10; N 3.52.

3-(Azepan-1-yl)-1-(4-*sec*-butylphenyl)-2-(4-chlorophenyl)propan-1-one hydrochloride (XIII). mp 140–142°C. Found, %: Cl 8.26; N 3.24. $C_{25}H_{32}ClNO \cdot HCl$. Calculated, %: Cl 8.18; N 3.22.

2-(4-Chlorophenyl)-3-[4-(3-chlorophenyl)piperazin-1-yl]-1-(4-methoxyphenyl)propan-1-one (VI). Yield 58%, mp 138–140°C, R_f 0.64. IR spectrum: ν 1670 cm^{-1} (C=O). ^{1}H NMR spectrum, δ, ppm: 2.61 d.d (1H, CH_2, J = 12.5, 5.3 Hz); 2.62 m [4H, $CH_2N(CH_2)_2$]; 3.08 t [4H, $C_6H_4N(C\mathbf{H}_2)_2$, J = 5.1 Hz]; 3.28 d.d (1H, CH_2, J = 12.5, 8.5 Hz); 3.84 s (3H, OCH_3); 4.96 d.d (1H, CH, J = 8.5, 5.3 Hz); 6.66–6.73 m (2H), 6.77 t (1H, J = 2.2 Hz), and 7.09 t (1H, J = 8.1 Hz) (C_6H_4Cl-3); 6.90 m and 7.97 m (2H each, $C_6\mathbf{H}_4OCH_3$); 7.23 m and 7.33 m (2H each, C_6H_4Cl-4). Found, %: C 66.61; H 5.52; N 6.04. $C_{26}H_{26}Cl_2N_2O_2$. Calculated, %: C 66.53; H 5.58; N 5.97.

2-(4-Chlorophenyl)-3-[4-(3-chlorophenyl)piperazin-1-yl]-1-(4-methoxyphenyl)propan-1-one hydrochloride (XIV). mp 177–179°C. Found, %: Cl 13.15; N 5.09. $C_{26}H_{26}Cl_2N_2O_2 \cdot HCl$. Calculated, %: Cl 13.10; N 5.17.

2-(4-Chlorophenyl)-3-[4-(2-fluorophenyl)piperazin-1-yl]-1-(4-methoxyphenyl)propan-1-one (VII).

Yield 55%, mp 79–82°C, R_f 0.63. IR spectrum: ν 1666 cm^{-1} (C=O). ^1H NMR spectrum, δ, ppm: 2.61 d.d (1H, CH_2, J = 12.5, 8.5 Hz); 2.59–2.69 m [4H, $CH_2N(CH_2)_2$]; 2.96 t [4H, $C_6H_4N(CH_2)_2$, J = 5.0 Hz]; 3.29 d.d (1H, CH_2, J = 12.5, 8.5 Hz); 3.84 s (3H, OCH_3); 4.94 d.d (1H, CH, J = 8.5, 5.3 Hz); 6.80–7.00 m (4H, C_6H_4F); 6.90 m and 7.97 m (2H each, $C_6H_4OCH_3$); 7.29 m and 7.33 m (2H each, C_6H_4Cl). Found, %: C 69.05; H 5.80; N 6.14. $C_{26}H_{26}ClFN_2O_2$. Calculated, %: C 68.94; H 5.79; N 6.18.

2-(4-Chlorophenyl)-3-[4-(2-fluorophenyl)piperazin-1-yl]-1-(4-methoxyphenyl)propan-1-one hydrochloride (XV). mp 177–178°C. Found, %: Cl 13.58; N 5.37. $C_{26}H_{26}ClFN_2O_2 \cdot HCl$. Calculated, %: Cl 13.51; N 5.33.

2-(4-Chlorophenyl)-1-(4-ethoxyphenyl)-3-(4-ethylpiperazin-1-yl)propan-1-one (VIII). Yield 59%, mp 120–122°C, R_f 0.62. IR spectrum: ν 1672 cm^{-1} (C=O). ^1H NMR spectrum, δ, ppm: 0.99 t (3H, CH_3CH_2N, J = 7.2 Hz); 1.41 t (3H, CH_3CH_2O, J = 7.0 Hz); 2.26 q (2H, CH_3CH_2N, J = 7.2 Hz); 2.27 m and 2.45 m (4H each, $C_4H_8N_2$); 2.52 d.d (1H, CH_2, J = 12.5, 5.1 Hz); 3.21 d.d (1H, CH_2, J = 12.5, 8.5 Hz); 4.08 q (2H, CH_3CH_2O, J = 7.0 Hz); 4.85 d.d (1H, CH, J = 8.5, 5.1 Hz); 6.86 m and 7.92 m (2H each, C_6H_4OEt); 7.21 m and 7.29 m (2H each, C_6H_4Cl). Found, %: C 68.98; H 7.27; N 7.03. $C_{23}H_{29}ClN_2O_2$. Calculated, %: C 68.90; H 7.29; N 6.99.

2-(4-Chlorophenyl)-1-(4-ethoxyphenyl)-3-(4-ethylpiperazin-1-yl)propan-1-one hydrochloride (XVI). mp 182–184°C. Found, %: Cl 15.07; N 5.86. $C_{23}H_{29}ClN_2O_2 \cdot HCl$. Calculated, %: Cl 14.99; N 5.91.

2-(4-Chlorophenyl)-1-(4-ethoxyphenyl)-3-[4-(furan-2-ylcarbonyl)piperazin-1-yl]propan-1-one (IX). Yield 63%, mp 124–126°C, R_f 0.59. IR spectrum: ν 1662 cm^{-1} (C=O). Found, %: C 66.97; H 5.74; N 5.93. $C_{26}H_{27}ClN_2O_2$. Calculated, %: C 66.88; H 5.83; N 6.00.

2-(4-Chlorophenyl)-1-(4-ethoxyphenyl)-3-[4-(furan-2-ylcarbonyl)piperazin-1-yl]propan-1-one hydrochloride (XVII). mp 138–141°C. Found, %: Cl 13.25; N 5.26. $C_{26}H_{27}ClN_2O_2 \cdot HCl$. Calculated, %: Cl 13.16; N 5.1.

The IR spectra were measured on Specord 75IR and Nexus FT-IR spectrometers. The ^1H NMR spectra were recorded on a Varian Mercury-300 instrument using DMSO-d_6 as solvent. Thin-layer chromatography was performed on Silufol UV-254 plates using butan-1-ol–ethanol–acetic acid–water (8:2:1:3) as eluent; development with iodine vapor.

REFERENCES

1. Tramontini, M. and Angiolini, L., *Tetrahedron*, 1990, vol. 46, p. 1791.
2. Gevorgyan, G.A., Agababyan, A.G., and Mndzhoyan, O.L., *Usp. Khim*., 1984, vol. 53, p. 971.
3. Gevorgyan, G.A., Agababyan, A.G., Gabrielyan, S.A., Avakyan, A.P., Isakhanyan, A.U., Gasparyan, N.K., Galstyan, D.A., Mndzhoyan, O.L., Apoyan, N.A., and Durgaryan, L.K., *Vzaimosvyaz' khimicheskaya struktura–biologicheskaya aktivnost'* (Chemical Structure–Biological Activity Relationship), Erevan: Apaga, 1998, p. 187.
4. Gevorgyan, G.A., Gasparyan, N.K., Tumajyan, H.E., Hamazaspyan, G.S., and Panosyan, G.A., *Electronic J. Nat. Sci. Natl, Acad. Sci., Resp. Arm*., 2006, vol. 1, p. 30.
5. Agababyan, A.G., Isakhanyan, A.U., Papoyan, O.A., Tumadzhyan, A.E., Balasanyan, A.S., and Gevorgyan, G.A., *Khim.-Farm. Zh*., 2005, vol. 39, no. 7, p. 26.