CHEMIJA. 2007. Vol. 18. No. 2. P. 29–32
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Synthesis and ammonolysis of 4-acyl and 4-arylsulfonylpiperazine-2,6-diones

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A series of 4-acylated derivatives of piperazine-2,6-dione were synthesized. Ammonolysis of the synthesized piperazine-2,6-diones with aqueous ammonia led to a ring-opening reaction and the formation of corresponding iminodiacetic acid diamides with a good yield. The optimal conditions of ammonolysis were analysed.

Key words: piperazine-2,6-dione, diamide, iminodiacetic acid, ammonolysis, ring-opening

INTRODUCTION

The first known derivative of piperazine-2,6-dione was synthesized in 1889 [1]. Now piperazine-2,6-diones are an important class of compounds, which display a variety of interesting properties [2–18]. Bis(dioxopiperazine)s, including (±)-1,2-bis (3,5-dioxopiperazin-1-yl)propane (ICRF·159, razoxane), (+)-1,2-bis(3,5-dioxopiperazinyl-1-yl)propane (ICRF-187, dexrazoxane) and meso-2,3-bis(3,5-dioxopiperazin-1-yl)butane (ICRF-193), have been studied for an anticancer activity and interactions with other anticancer drugs and radiation [12–15]. They were reported to be strong catalytic inhibitors of DNA topoisomerase II [16]. ICRF-193 is the most potent of the analogs studied [17] and ICRF-187 is likely to exert its action through a ring-opened hydrolysis product, a compound that has an EDTA-type structure and, likewise, strongly binds metal ions [18].

There are no specific and comprehensive investigations of the chemical and physical properties of piperazine-2,6-diones, and compounds of this type have been synthesized basically for practical purposes. The studies of the mentioned properties are very important for the choice of the appropriate method of synthesis and for biological activity of derivatives of this heterocycle. By analogy with widely known cyclic imides, piperazine-2,6-diones can participate in reactions with preservation and opening of a cycle (ring-opening). In this case, the aim of this study was the ring-opening reactions.

It is known that hydrolysis in acidic or basic media, alcoholysis and ammonolysis of widely known cyclic imides, such as succinimide, phtalimide and others, lead to the opening of a ring and the formation of corresponding acids, monoamides or diamides [19]. Hydroxylaminolysis of some cyclic imides, including piperazine-2,6-dione, was studied in [20], but triamide of nitrilotriacetic acid, the product of ammonolysis of 3,5-dioxo-1-piperazinoacetamide, was mentioned only in [21]. In general, there is no information concerning ammonolysis of 4-acylated derivatives of piperazine-2,6-dione. The reaction of ammonia with piperazine-2,6-diones is of great interest to understand some important chemical processes that take place in the biochemical reactions of these compounds.

The method of the synthesis of piperazine-2,6-dione, a key intermediate link in the synthesis of the derivatives of this cyclic imide, as well as the synthesis and biological research series of 4-acyl and 4-sulfonyl derivatives, were reported in our previous work [22–24]. On the basis of the previous work and in connection with the planned research on the biological activity of piperazine-2,6-diones and their ring-opening products, this study presents the results of the synthesis of some 4-acylated piperazine-2,6-diones and products of their ammonolysis.

RESULTS AND DISCUSSION

The starting piperazine-2,6-dione (1) was prepared according to our new method based on the condensation of iminodiacetic acid with ammonium formate at 150–170 °C in *N, N*-dimethylformamide [22]. New 4-acyl (2b) and 4-sulfonyl (3b), and resynthesized (2a, c–f, 3a, c–e) derivatives of piperazine-2,6-dione were synthesized by acylation of hydrochloride of 1 with corresponding acyl and sulfonyl chlorides following the manner described in [24]. The majority of the synthesized 4-acylated piperazine-2,6-diones are colorless substances, poorly soluble in water (except for 2e), but soluble in some organic solvents.

The action of ammonia on 4-acylated piperazine-2,6-diones was studied. Anhydrous and 30% aqueous ammonia were used. In dry methanol or acetone, saturated with ammonia, the reaction of ring-opening failed. Though the majority of 4-acylated piperazine-2,6-diones are poorly soluble in water, the opening of the ring and the formation of corresponding diamides of iminodiacetic acid occurred only in the aqueous ammonia. The application of organic solvents (methanol, acetone) and equimolar quantities of the 30% aqueous ammonia resulted in a worse yield, but excessive 30% aqueous ammonia produced a similar yield even without organic solvents. The best yield of diamides was obtained at a 10-fold excess of the 30% aqueous ammonia.

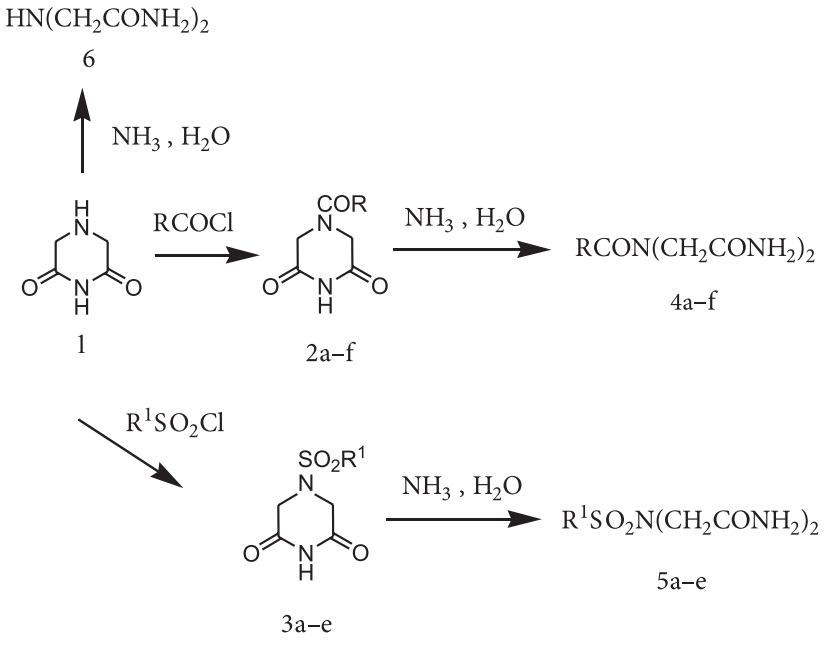
The course of ammonolysis was controlled by thin-layer chromatography (TLC).

It was established that the ammonolysis of 4-acyl and 4-sulfonyl derivatives of piperazine-2,6-dione in aqueous ammonia is an applicable and practical method for the synthesis of *N*-acylated iminodiacetic acid diamides with good to excellent yields (79–97 %).

The synthetic pathways used for the preparation of 4-acylated piperazine-2,6-diones (2a–f, 3a–e) and their products of ammonolysis, corresponding iminodiacetic acid diamides (4a–f, 5a–e), are presented in Scheme.

IR, ^{1}H NMR spectral and elemental analysis data confirmed the structures of the synthesized compounds.

Scheme



R = $CH_3(CH_2)_n$, n = 6 (2a, 4a), 10 (2b, 4b), 12 (2c, 4c), 14 (2d, 4d), 4-$CH_3C_6H_4$ (2e, 4e), 9-fluorenylmethyl (2f, 4f).
R^1 = C_6H_5 (3a, 5a), 2-$NO_2C_6H_4$ (3b, 5b), 3-$NO_2C_6H_4$ (3c, 5c), $NO_2C_6H_4$ (3d, 5d), 2-fluorenyl (3e, 5e).

EXPERIMENTAL

Melting points were determined in open capillaries and were uncorrected. IR spectra were recorded on a Specord 75 instrument (Germany) in KBr pellets, ^{1}H NMR spectra were measured with a Hitachi R-22 spectrometer (90 MHz, Japan) using HMDS as internal references (δ = 0.05 ppm to TMS) in DMSO-d_6 solution. Chemical shifts δ are reported in ppm, coupling constants (*J*) are given in Hz. The course of reaction and purity of compounds were controlled by TLC (silufol UV-254 (aluminium sheets coated with silica gel)). TLC analyses were performed visually under UV light (254 nm), and spots were revealed with a solution prepared from $CoCl_2 \cdot 6H_2O$ (1.83 g), K_2CrO_7 (2 g) and glacial acetic acid (10 ml) in water (100ml) (blue spots for imides and diamides). The compounds were purified by silica gel column chromatography (eluent–chloroform: acetone (3:1, 5:1)).

4-Acyl derivatives of piperazine-2,6-dione (2 a–f) were obtained by acylation of piperazine-2,6-dione (1) hydrochloride with corresponding acylchlorides according to the procedure described earlier [24].

4-Dodecanoylpiperazine-2,6-dione (2b): yield 94%, m. p. 113–114.5 °C (from acetone–water). IR (cm^{-1}): 3020, 3100 (NH), 1705, 1725 (C = O). ^{1}H NMR (DMSO-d_6, δ, ppm): 0.85 (3H, t, *J* = 5.0 Hz, CH_3), 1.25 (18H, br. s, CH_2), 2.34 (2H, t, *J* = 8.0 Hz, CH_2CO), 4.21 (4H, s, $COCH_2N$), 11.29 (1H, br. s, NH). Elemental analysis data: found, %: C, 65.13; H, 9.81; N, 9.26; formula $C_{16}H_{28}N_2O_3$: requires: C, 64.83; H, 9.52; N, 9.45.

4-Sulfonyl derivatives of piperazine-2,6-dione (3 a–e) were obtained by the acylation of piperazine-2,6-dione (1) hydrochloride with corresponding sulfonyl chlorides according to the procedure described earlier [24].

4-(2-Nitrophenylsulfonyl)piperazine-2,6-dione (3b): yield 72%, m. p. 161–162.5 °C (from acetone–water). IR (cm^{-1}): 3108, 3230 (NH), 1710, 1740 (C = O), 1533, 1373 (NO_2), 1350, 1163 (SO_2). ^{1}H NMR (DMSO-d_6, δ, ppm): 4.20 (4H, s, $COCH_2N$), 7.70–8.30 (4H, m, C_6H_4), 10.38 (1H, br. s, NH). Elemental analysis data: found, %: C, 40.22; H, 3.03; N, 14.11; S, 10.06; formula $C_{10}H_9N_3O_6S$: requires: C, 40.14; H, 3.03; N, 14.04; S, 10.71.

General method for the preparation of N-acyl- and N-arylsulfonyliminodiacetic acid diamides (4 a–f, 5 a–e).

A mixture of 10 mmol of the corresponding 4-acylated piperazine-2,6-dione in 10 ml of 30% aqueous ammonia was kept at 20 °C for 12 h (or boiled for 1 h). The precipitate was filtered, washed with cold methanol and recrystallized.

***N*-Octanoyliminodiacetic acid diamide (4a):** yield 92%, m. p. 167–168 °C (from ethanol–water). IR (cm^{-1}): 3353, 3180 (NH), 1670, 1640 (C = O), 1608 (amid II). ^{1}H NMR (DMSO-d_6, δ, ppm): 0.82 (3H, t, *J* = 6.0 Hz, CH_3), 1.31 (8H, br. s, CH_2), 1.42 (2H, t, *J* = 6.0 Hz, CH_3CH_2), 2.14 (2H, t, *J* = 6.0 Hz, CH_2CO), 3.77 (2H, s, $COCH_2N$), 3.93 (2H, s, $COCH_2N$), 6.98, 7.20, 7.67, 8.01 (4H, br. s, NH_2). Elemental analysis data: found, %: C, 56.23; H, 9.21; N, 15.96; formula $C_{12}H_{23}N_3O_3$: requires: C, 56.01; H, 9.01; N, 16.33.

***N*-Dodecanoyliminodiacetic acid diamide (4b):** yield 81%, m. p. 172–173 °C (from ethanol–water). IR (cm^{-1}): 3344, 3167 (NH), 1670, (C = O), 1600, 1634 (amid II). ^{1}H NMR (DMSO-d_6, δ, ppm): 0.81 (3H, t, *J* = 6.0 Hz, CH_3), 1.20 (18H, br. s, CH_2), 2.16 (2H, m, CH_2CO), 3.82 (2H, s, $COCH_2N$), 3.96 (2H, s, $COCH_2N$), 7.01, 7.19, 7.64, 8.12 (4H, br. s, NH_2). Elemental analysis data: found, %: C, 61.13; H, 9.74; N, 13.30; formula $C_{16}H_{31}N_3O_3$: requires: C, 61.31; H, 9.97; N, 13.41.

***N*-Tetradecanoyliminodiacetic acid diamide (4c):** yield 83%, m. p. 167–169 °C (from ethanol–water). IR (cm^{-1}): 3387, 3300, 3134 (NH), 1688, 1670 (C = O), 1643 (amid II); ^{1}H NMR (DMSO-d_6, δ, ppm): 0.83 (3H, t, *J* = 5.0 Hz, CH_3), 1.23 (22H, br. s, CH_2), 2.18 (2H, t, *J* = 6.0 Hz, CH_2CO), 3.83 (2H, s, $COCH_2N$), 3.95 (2H, s, $COCH_2N$), 7.02, 7.22, 7.67, 8.14 (4H, br. s, NH_2). Elemental analysis data: found, %: C, 63.43; H, 10.54; N, 12.10; formula $C_{18}H_{35}N_3O_3$: requires: C, 63.31; H, 10.33; N, 12.30.

***N*-Hexadecanoyliminodiacetic acid diamide (4d):** yield 82%, m. p. 164–165 °C (from ethanol–water). IR (cm^{-1}): 3390, 3300, 3126 (NH), 1692, 1670 (C = O), 1640 (amid II); ^{1}H NMR (DMSO-d_6, δ, ppm): 0.83 (3H, t, *J* = 6.0 Hz, CH_3), 1.23 (26H, br. s, CH_2), 2.06 (2H, t, *J* = 6.0 Hz, CH_2CO), 3.82 (2H, s, $COCH_2N$), 3.95 (2H, s, $COCH_2N$), 6.98, 7.17, 7.63, 8.08 (4H, br. s, NH_2). Elemental analysis data: found, %: C, 65.21; H, 10.54; N, 11.54; formula $C_{20}H_{39}N_3O_3$: requires: C, 65.00; H, 10.64; N, 11.37.

***N*-(4-Methylphenyl)iminodiacetic acid diamide (4e):** yield 85%, m. p. 243–244 °C (dec.) (from methanol). IR (cm^{-1}): 3434, 3340, 3294, 3176 (NH), 1658, (C = O), 1620, 1600 (amid II); ^{1}H NMR (DMSO-d_6, δ, ppm): 1.94 (3H, s, CH_3), 3.77 (2H, br. s, $COCH_2N$), 3.87 (2H, br. s, $COCH_2N$), 7.06 (2H, br. s, NH_2), 7.16 (4H, s, C_6H_4), 7.79 (2H, br. s, NH_2). Elemental analysis data: found, %: C, 57.61; H, 6.24; N, 16.68; formula $C_{12}H_{15}N_3O_3$: requires: C, 57.82; H, 6.07; N, 16.86.

***N*-(9-Fluorenylacetyl)iminodiacetic acid diamide (4f):** yield 79%, m. p. 234–237 °C (from methanol). IR (cm^{-1}): 3380, 3270, 3176 (NH), 1687, 1673 (C = O), 1624, 1613 (amid II); ^{1}H NMR (DMSO-d_6, δ, ppm): 4.02 (7H, br. s, $COCH_2N$**,** $CHCH_2CO$), 7.03–8.21 (12H, m, NH_2, H- aromat). Elemental analysis data: found, %: C, 67.51; H, 5.48; N, 12.32; formula $C_{19}H_{19}N_3O_3$: requires: C, 67.64; H, 5.68; N, 12.46.

***N*-Phenylsulfonyliminodiacetic acid diamide (5a):** yield 89%, m. p. 185–187 °C (from methanol). IR (cm^{-1}): 3400, 3286, 3183 (NH), 1697, 1644 (C = O), 1614 (amid II), 1323, 1146 (SO_2); ^{1}H NMR (DMSO-d_6, δ, ppm): 3.83 (4H, s, $COCH_2N$), 7.19 (2H, br. s, NH_2), 7.49–8.01 (7H, m, C_6H_4, NH_2). Elemental analysis data: found, %: C, 44.41; H, 4.64; N, 15.57; S, 11.44; formula $C_{10}H_{13}N_3O_4S$: requires: C, 44.27; H, 4.83; N, 15.49; S, 11.82.

***N*-(2-Nitrophenylsulfonyl)iminodiacetic acid diamide (5b):** yield 83%, m. p. 233–234 °C (from methanol). IR (cm^{-1}): 3423, 3267, 3090 (NH), 1677, 1667(C = O), 1647, 1637 (amid II), 1533, 1366 (NO_2), 1353, 1153 (SO_2). ^{1}H NMR (DMSO-d_6, δ, ppm): 3.83 (4H, s, $COCH_2N$), 7.19 (2H, br. s, NH_2), 7.49–8.01 (6H, m, C_6H_4, NH_2). Elemental analysis data: found, %: C, 37.69; H, 3.64; N, 17.57; S, 10.44; formula $C_{10}H_{12}N_4O_6S$: requires: C, 37.97; H, 3.82; N, 17.71; S, 10.14.

***N*-(3-Nitrophenylsulfonyl)iminodiacetic acid diamide (5c):** yield 95%, m. p. 252–254 °C (from methanol). IR (cm^{-1}): 3427, 3341, 3080 (NH), 1677, 1650 (C = O), 1634 (amid II), 1526, 1317 (NO_2), 1350, 1160 (SO_2). ^{1}H NMR (DMSO-d_6, δ, ppm): 3.98 (4H, s, $COCH_2N$), 7.23 (2H, br. s, NH_2), 7.71–8.60 (6H, m, C_6H_4, NH_2). Elemental analysis data: found, %: C, 37.78; H, 3.74; N, 17.60; S, 10.54; formula $C_{10}H_{12}N_4O_6S$: requires: C, 37.97; H, 3.82; N, 17.71; S, 10.14.

***N*-(4-Nitrophenylsulfonyl)iminodiacetic acid diamide (5d):** yield 86%, m. p. 240–242 °C (from methanol). IR (cm^{-1}): 3423, 3318, 3147 (NH), 1677, 1658 (C = O), 1647, 1642 (amid II), 1533, 1322 (NO_2), 1347, 1149 (SO_2). ^{1}H NMR (DMSO-d_6, δ, ppm): 3.82 (4H, s, $COCH_2N$), 7.09 (2H, br. s, NH_2), 7.16 (4H, s, C_6H_4), 7.74 (2H, br. s, NH_2). Elemental analysis data: found, %: C, 37.69; H, 3.64; N, 17.57; S, 10.44; formula $C_{10}H_{12}N_4O_6S$: requires: C, 37.97; H, 3.82; N, 17.71; S, 10.14.

***N*-(2-Fluorenylsulfonyl)iminodiacetic acid diamide (5e):** yield 97%, m. p. 258–259 °C (from acetone–water). IR (cm^{-1}): 3400, 3280, 3153 (NH), 1657, 1630 (C = O), 1600 (amid II), 1352, 1140 (SO_2). ^{1}H NMR (DMSO-d_6, δ, ppm): 3.88 (4H, s, $COCH_2N$), 4.09 (2H, s, CH_2- fluoren), 7.23–8.20 (11H, m, H-arom, NH_2). Elemental analysis data: found, %: C, 56.54; H, 4.94; N, 11.89; S, 8.34; formula $C_{17}H_{17}N_3O_4S$: requires: C, 56.81; H, 4.77; N, 11.69; S, 8.92.

Iminodiacetic acid diamide (6) was obtained by treating piperazine-2,6-dione(1) with equimolar quantity of the 30% aqueous ammonia in methanol at room temperature for 1 h: yield 84%, m. p. 147–149 °C (from methanol). IR (cm^{-1}): 3370, 3165 (NH), 1700 (C = O), 1650 (amide II). ^{1}HNMR (DMSO-d_6 , δ, ppm): 3.54 (1H, br. s, NH) d_6, δ, ppm), 3.77 (2H, s, $COCH_2N$), 3.93 (2H, s, $COCH_2N$), 6.98, 7.20, 7.67, 8.01 (4H, br. s, NH_2). The literature [25] reports that 6 was obtained from the ester of iminodiacetic acid and ammonia (m. p. 143 °C).

CONCLUSIONS

1. The ammonolysis of 4-acyl and 4-sulfonyl derivatives of piperazine-2,6-dione was studied in this work.

2. The ring-opening of 4-acylated piperazine-2,6-diones by the action of ammonia takes place only in the presence of water.

3. The ammonolysis of 4-acyl and 4-sulfonyl derivatives of piperazine-2,6-dione in aqueous ammonia is an applicable and practical method for the synthesis of *N*-acylated iminodiacetic acid diamides with good to excelent yields (79–97%).

Received 20 March 2007
Accepted 30 March 2007

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4-ACIL IR 4-ARILSULFONILPIPERAZIN-2,6-DIONŲ SINTEZĖ IR AMONOLIZĖ

S a n t r a u k a

Susintetinti 4-acilintų piperazin-2,6-diono dariniai. Dėl gautų piperazin-2,6-dionų amonolizės, veikiant vandeniniu amoniako tirpalu, įvyko ciklo atidarymo reakcija ir susidarė atitinkami geros išeigos iminodiacto rūgšties diamidai. Buvo ištirtos optimalios amonolizės sąlygos.