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Synthesis and properties of some new 4-succinamoyl piperazine-2,6-dione derivatives

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A new series of piperazine-2,6 dione derivatives containing N-substituted succinamic acid residue was synthesized and tested for the analgesic activity. 4-[N-(4-methylphenyl)succinamoyl]-piperazine-2,6-dione showed the best analgesic activity.

Key words: piperazine-2,6-dione, succinamic acid, synthesis, acylation, analgesic effect

INTRODUCTION

The interest in derivatives of piperazine-2,6-dione has significantly increased because of their practical usage. Bis(piperazine-2,6-dione)s (razoxane, ICRF·159 and their analogues) have been studied for the anticancerous activity, an interaction with other anticancerous drugs and sensitivity to radiation [1, 2]. Mono(piperazine-2,6-dione)s were found to be very active agents in various areas including pharmaceutical [3–6], agrochemical [7–9] and industrial [10, 11].

It is known that some of the derivatives of N-substituted succinamic acid [12] and piperazine-2,6-dione [3, 13, 14] exhibit the analgesic effect. Our previous studies have shown the biological activity of newly synthesized derivatives of 4-acetylated piperazine-2,6-diones [15, 16]. The purpose of this study was to synthesize new derivatives of piperazine-2,6-dione containing succinamic acid and various heterocyclic fragments, and to define the correlation between their chemical structure and analgesic activity.

RESULTS AND DISCUSSION

The starting compound, piperazine-2,6-dione hydrochloride (3), was a key intermediate not only for the synthesis of 4-succinamoyl piperazine-2,6-dione derivatives (7a–h), but also for the synthesis of 4-(3,5dioxopiperazin-1-yl)-4-oxobutanoic acid (5) and was prepared according to our new method [17]. The starting N-substituted succinamic acids, N-(4-methylphenyl)-(4a), N-(4-methoxyphenyl)- (4b), N-(4-ethoxyphenyl)- (4c), N-(3-nitrophenyl)- (4d), N-(4-sulfamoylphenyl) (4e), N-(2,3-dimethyl-1-phenyl-3-pyrazolon-5-yl)- (4f), 4-(N-4,6-dimethylpyrimidin-2-yl-sulfamoylphenyl)- (4g), N-(thiazol-2-yl) (4h) and a newly synthesized 4-(3,5-dioxopiperazin-1-yl)-4-oxobutanoic acid (5), were obtained by a direct acylation of corresponding amines with succinic anhydride according to the modified method [18, 19], and had a yield from good to excellent (75–90%).

The 4-succinamoylpiperazine-2,6-diones (7a–h) were obtained by an acylation of piperazine-2,6-dione hydrochloride (3) with corresponding N-substituted succinamic acids (4a–h) in the presence of N,N^1–dicyclohexylcarbodiimide (DCC). The solubility of the reaction products (7a–h) was similar to the solubility of N,N^1-dicyclohexylurea, therefore, the problems of the purification and separation of the products (7a–h) could be the reason of a small yield (39–52%) (method A).

Our attempts to prepare the corresponding succinamic acid chlorides were unsuccessful – a tail of succinamic acid was cyclized to the fragment of pyrrolidine-2,5-dione as described in [20].

We have used an alternative procedure to synthesize compounds 7a–h with a higher yield. The treatment of piperazine-2,6-dione hydrochloride (3) with succinic anhydride gave a compound 5. Then the acid chloride of compound 5 was obtained. After the acylation of amines (6a–h) with the acid chloride of compound 5, we obtained the derivatives of 4-succinamoyl piperazine-2,6-dione (7a–h) (method B) with a good yield (63–77%). The pathways of the synthesis of 4-succinamoylpiperazine-2,6-dione derivatives are summarized in Scheme.

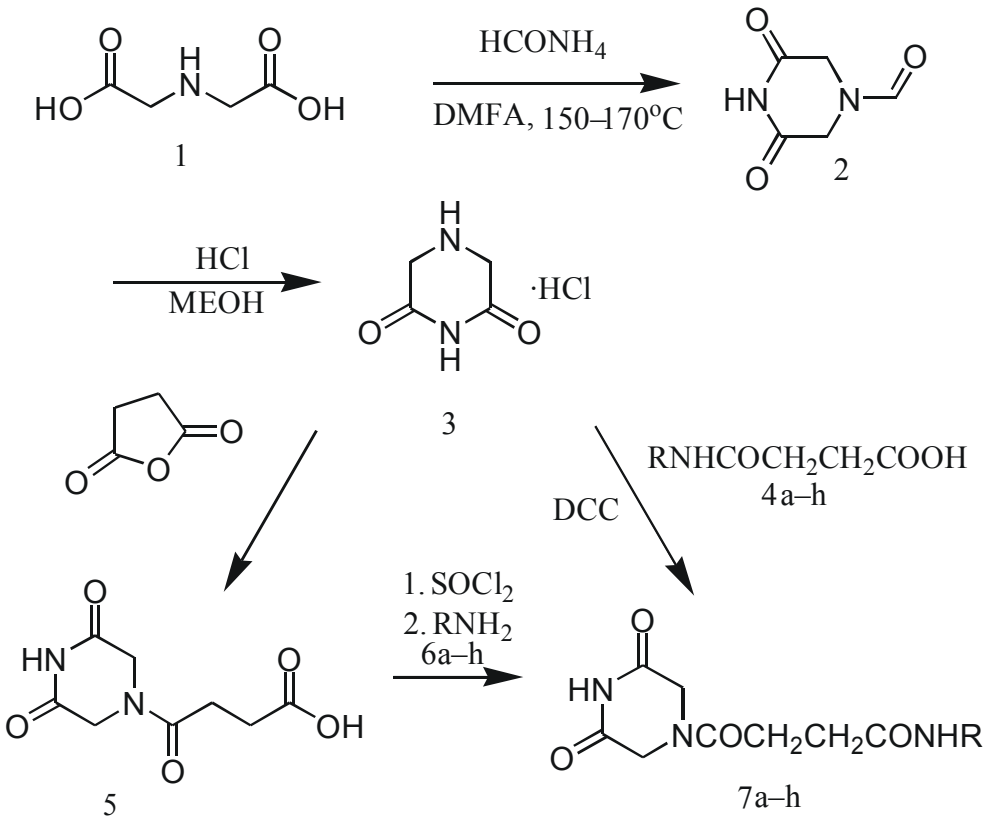
The structures of the synthesized compounds were confirmed by IR, ^{1}H NMR spectroscopy and elemental analysis. The purity was certified by TLC.

Preliminar screening of the analgesic activity of the compounds showed that 4-[N-(4-methylphenyl)succinamoyl]piperazine-2,6-dione (7a) had a potent analgesic effect.

EXPERIMENTAL

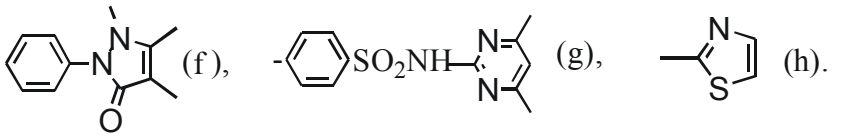
Melting points were determined by the open capillaries and were uncorrected. IR spectra were recorded on a Specord 75 instrument (Germany) in KBr pellets, ^{1}H

Scheme



1 2 3 5 7a–h

R = 4–$CH_3C_6H_4$ (a), 4–$CH_3OC_6H_4$ (b), 4–$C_2H_5OC_6H_4$ (c), 3–$NO_2C_6H_4$ (d), 4–$NH_2SO_2C_6H_4$ (e),



(f), (g), (h).

NMR spectra were measured on a Hitachi R-22 spectrometer (90 MHz, Japan) using HMDS as an internal standard (δ = 0.05 ppm to TMS) in DMSO-d_6 solution. Chemical δ shifts were reported in ppm, coupling constants (*J*) were given in Hz. The progress of the reaction and purity of compounds was controlled by TLC (silufol-UV-254 (aluminium sheets coated with silica gel). TLC analysis was performed 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 (100 ml) (blue spots for amides and imides). The compounds were purified by silica gel column chromatography (eluent : chloroform : acetone (1:1, 3:1) and chloroform : ethanol (7:1)).

4-(3,5-dioxopiperazine-1-yl)-4-oxobutanoic acid (5) was obtained by a direct acylation of piperazine-2,6-dione hydrochloride (3) with succinic anhydride according to the modified method [18, 19]. The yield was 89.6% and m. p. was 173–175 °C (from ethanol). IR (cm^{-1}): 3067 asoc, 3200, 3324 (NH), 1707, 1654 (C = O). ^{1}H NMR (DMSO-d_6, δ, ppm), 2.61 (4H, m, $COCH_2CH_2CO$), 4.32 (4H, br. s, $COCH_2N$), 11.33 (1H, br. s, CONHCO). During the elemental analysis of the data, it was found (%): C, 44.68; H, 4.55; N, 13.35; formula $C_8H_{10}N_2O_5$ requires: C, 44.86; H, 4.71; N, 13.08.

General procedure of the synthesis of 4-(N-substituted succinamoyl) piperazine-2,6-diones (7a–h). Method A: a mixture of 10 mmol of piperazine-2,6-dione hydrochloride (3) and 10mmol of a corresponding succinamic acid (4a–h) was blended in 15 ml of pyridine at 60 °C for 1 h. The mixture was cooled in an ice-bath, and 12mmol of N,N^I-dicyclohexylcarbodiimide (DCC) were added. The reaction mixture was left for 12 h in a refrigerator. At the end of the reaction, the precipitate of N,N^I-dicyclohexylurea was filtered and the pyridine was removed in vacuum**.** The residue was purified by washing with 1N hydrochloric acid and cold water. The precipitate was filtered and dried. The obtained crude material was chromatografied on a column using silicagel (40–100 μm) and a mixture

of eluent (chloroform : acetone, (1:1), (3:1), chloroform : ethanol (7:1)). After the evaporation of the solvent, the residue was recrystallized.

Method B: 10 mmol of 4-(3,5-dioxopiperazine-1-yl)-4-oxobutanoic acid (5) was stirred in 10 ml of thionyl chloride at 0 °C for 1 h. Then the mixture was refluxed for 0,5 h, and the excess of thionyl chloride was evaporated in vacuum. Acid chloride was obtained and used in the further synthesis without any additional purification in the same way. The solution of the obtained acid chloride in chloroform (10ml) was added dropwise into the mixture of the corresponding amine (9 mmol) and pyridine (1 ml) (in 15 ml of chloroform), cooled in the ice bath. Then the reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated in vacuum. The residue was purified as described in method A.

4-[N-(4-methylphenyl)succinamoyl]piperazine-2,6-dione (7a): yield 38.8% (method A), 62.4% (method B), m. p. 190–191.5 °C (from etilacetate). IR (cm^{-1}): 3324, 3200, 3067 (NH), 1707, 1654 (C = O). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.22 (3H, s, CH_3), 2.62 (4H, m, $COCH_2CH_2CO$), 4.29 (4H, br. s, $COCH_2N$), 7.05 (2H, d, J = 8.0, CH-arom), 7.43 (2H, d, J = 8.0, CH-arom), 9.78 (1H, br. s, NHCO), 11.31 (1H, br. s, CONHCO). During the elemental analysis of the data, it was found (%): C, 60.47; H, 5.45; N, 14.85; formula $C_{15}H_{17}N_3O_4$ requires: C, 59.40; H, 5.65; N, 13.85.

4-[N-(4-methoxyphenyl)succinamoyl]piperazine-2,6-dione (7b): yield 44.5% (method A), 67.5% (method B), m. p. 211–212 °C (from acetone/water). IR(cm^{-1}): 3460, 3323 (NH), 1700, (C = O). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.58 (4H, m, $COCH_2CH_2CO$), 3.65 (3H, s, OCH_3), 4.27 (4H, br. s, $COCH_2N$), 6.84 (2H, d, J = 9.0, CH-arom), 7.48 (2H, d, J = 8.0, CH-arom), 9.74 (1H, br. s, NHCO), 11.30 (1H, br. s, CONHCO). During the elemental analysis of the data, it was found (%): C, 56.19; H, 5.34; N, 13.40; formula $C_{15}H_{17}N_3O_5$: requires: C, 56.42; H, 5.37; N, 13.16.

4-[N-(4-ethoxyphenyl)succinamoyl]piperazine-2,6-dione (7c): yield 48.0% (method A), 72.2% (method B), m. p. 182.5–184.5 °C (from methanol/water). IR (cm^{-1}): 3380, 3210, 3110 (NH), 1710, 1687, 1640 (C = O). ^{1}H NMR (DMSO-d_6, δ, ppm): 1.28 (3H, t, J = 7.0, CH_3), 2.58 (4H, m, $COCH_2CH_2CO$), 3.94 (2H, k, J = 8.0, OCH_2), 4.31 (4H, br. s, $COCH_2N$), 6.77 (2H, d, J = 9.0, CH-arom), 7.44 (2H, d, J = 9.0, CH-arom), 9.73 (1H, br. s, NHCO), 11.31 (1H, br. s, CONHCO). During the elemental analysis of the data, it was found (%): C, 57.50; H, 5.88; N, 12.50; formula $C_{16}H_{19}N_3O_5$ requires: C, 57.65; H, 5.75; N, 12.61.

4-[N-(3-nitrophenyl)succinamoyl]piperazine-2,6-dione (7d): yield 43.6% (method A), 68.7% (method B), m. p. 164–165 °C (from ethanol/water). IR (cm^{-1}): 3474, 3287, 3107, 3090 (NH), 1706, 1658 (C = O), 1530, 1353 (NO_2). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.63 (4H, m, $COCH_2CH_2CO$), 4.29 (4H, br. s, $COCH_2N$), 7.05 (2H, d, J = 8.0, CH-arom), 7.43 (2H, d, J = 8.0, CH-arom), 9.78 (1H, br. s, NHCO, 11.31 (1H, br. s, CONHCO). During the elemental analysis of the data, it was found (%): C, 50.47; H, 4.45; N, 16.85; formula $C_{14}H_{14}N_4O_6$ requires: C, 50.30; H, 4.22; N, 16.76.

4-[N-(4-sulfamoylphenyl)succinamoyl]piperazine-2,6-dione (7e): yield 51.8% (method A), 65.8% (method B), m. p. 216–218 °C (from water/DMFA). IR (cm^{-1}): 3318, 3240, 3127 (NH), 1730, 1700, 1647 (C = O). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.61 (4H, m, $COCH_2CH_2CO$), 4.27 (4H, s, $COCH_2N$), 7.12 (2H, br. s, NH_2), 7.67 (4H, s, CH-arom), 10.20 (1H, br. s, NHCO), 11.29 (1H, br. s, CONHCO). During the elemental analysis of the data, it was found (%): C, 50.27; H, 4.65; N, 16.85; formula $C_{14}H_{16}N_4O_6$ requires: C, 50.00; H, 4.80; N, 16.66.

4-[N-(2,3-dimethyl-1-phenyl-3-pyrazolon-5-yl)succinamoyl]piperazine-2,6-dione (7f): yield 44.0% (method A), 74.1% (method B), m. p. 209–210 °C (from ethanol/water). IR (cm^{-1}): 3324, 3270, 3067 (NH), 1725, 1654, 1625 (C = O). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.05 (3H, s, CH_3-C), 2.41 (4H, m, $COCH_2CH_2CO$), 2.66 (3H, s, CH_3-N), 4.30 (4H, br.s, $COCH_2N$), 7.38 (5H, m, CH-arom), 9.02 (1H, br. s, NHCO), 11.29 (1H, br. s, CONHCO). During the elemental analysis of the data, it was found (%): C, 57.22; H, 5.45; N, 17.29; formula $C_{19}H_{21}N_5O_5$ requires: C, 57.14; H, 5.30; N, 17.53.

4-(N-[4-(N-4,6-dimethylpyrimidin-2yl)sulfamoylphenylsuccinamoyl)-piperazine-2,6-dione (7g): yield 44.0% (method A), 76.5% (method B), m. p. > 250 °C (dec.) (from water/DMFA). IR (cm^{-1}): 3225, 3167, (NH), 1707, 1684, 1645 (C = O). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.22 (6H, s, 2 CH_3), 2.62 (4H, m, $COCH_2CH_2CO$), 4.32 (4H, br. s, $COCH_2N$), 6.75 (1H, s, CH-heter), 7.68–8.09 (5H, m, CH-arom, $NHSO_2$), 10.32 (1H, br. s, NHCO), 11.28 (1H, br. s, CONHCO). During the elemental analysis of the data, it was found (%): C, 50.47; H, 4.85; N, 17.85; formula $C_{20}H_{22}N_6O_6S$ requires: C, 50.63; H, 4.67; N, 17.71.

4-[N-(thiazol-2-yl)succinamoylpiperazine-2,6-dione (7h): yield 48.3% (method A), 73.5% (method B), m. p. 159–161 °C (from etilacetate/water). IR (cm^{-1}): 3285, 3238, 3128 (NH), 1681, 1650 (C = O). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.72 (4H, m, $COCH_2CH_2CO$), 4.27 (4H, br. s, $COCH_2N$), 6.79 (1H, d, J = 4.0, CHS), 7.18 (1H, d, J = 4.0, CHN), 10.68 (1H, br. s, NHCO), 11.29 (1H, br. s, CONHCO). During the elemental analysis of the data, it was found (%): C, 44.42 H, 4.35; N, 18.65; formula $C_{11}H_{12}N_4O_4S$ requires: C, 44.59; H, 4.08; N, 18.91.

CONCLUSIONS

1. A new series of 4-succinamoyl piperazine-2,6-diones was obtained: by acylation of piperazine-2,6-dione hydrochloride with appropriate N-substituted succinamic acid in the presence of N,N^I-dicyclohexylcarbodiimide (DCC) (method A) or by acylation of appropriate amines with 4-(3,5-dioxopiperazine-1-yl)-4-oxobutanoic acid chloride (method B).

2. A preliminary screening of the compounds for the analgesic activity revealed that 4-[N-(4-methylphenyl)succinamoyl]-piperazine-2,6-dione has the best analgesic effect.

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KAI KURIŲ NAUJŲ 4-SUKCINAMOILINIŲ PIPERAZIN-2,6-DIONO DARINIŲ SINTEZĖ IR SAVYBĖS

S a n t r a u k a

Susintetinta keletas naujų piperazin-2,6-diono darinių, turinčių N-pavaduotos sukcinaminorūgšties liekaną, ir ištirtas jų analgetinis aktyvumas. 4-[N-(4-metilfenil)succinamoil]piperazin-2,6-dionas rodė žymų analgetinį aktyvumą.