

The Synthesis of Novel Annelated 2-Oxopiperazines by the Interaction Methyl (3-Oxopiperazin-2-Ylidene) Acetate with an *N*-Arylmaleimides

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Abstract: It is studied that the interaction of methyl (3-oxopiperazin-2-ylidene) acetate with an *N*-arylmaleimides. It is established that methyl (3-oxo-piperazine-2-ylidene) acetate is reacted with *N*-arylmaleimides in boiling methanol in the presence of catalytic amounts of acetic acid as the *C*-*N*-dinucleophile to form not previously described methyl-1, 6-dioxo-8-[(arylamino)carbonyl]-1, 3, 4, 6, 7, 8-hexahydro-2H-pyrido [1, 2-a] pyrazine-9-carboxylates. An excess of acid (in a mixture of methanol and acetic acid in the ratio 1:1) occurs 1, 3-dipolar cycloaddition of the *N*-arylmaleimides toward tautomeric form methyl (3-oxo-piperazine-2-ylidene) acetate - methyl (3-oxo-3, 4, 5, 6-tetrahydropyrazine-2-yl) acetate with the formation of new heterocyclic system-methyl-2-aryl-1, 3, 8-trioxodecahydro-1H-pyrrolo [3', 4':4, 5] pyrrolo [1, 2-a] pyrazine-9-carboxylates.

Key words: 2-oxopiperazine, methyl (3-oxo-piperazine-2-ylidene) acetate, *N*-arylmaleimide, pyrrolo[3', 4':4, 5] pyrrolo[1, 2-a] pyrazine, pyrido [1, 2-a] pyrazine.

1. Introduction

The 2-oxopiperazine fragment is an important pharmacophore which is found in a large number of biologically active molecules. Oxopiperazines are amongst the most important scaffolds in today's drug discovery industries. Due to the high number of positive hits encountered in biological screens with this heterocycle and its congeners, the substituted oxopiperazine is widely recognized as a "privileged scaffold" in medicinal chemistry [1]. Fragment of 2-oxopiperazine is a composite element natural substances of various structural complexity and biological activity [2-5]. It should be noted that in the structure many alkaloids (e.g., agelastatine A, marcfortine B, Phakellin group) 2-oxopiperazine moiety condensed to various cycles [3-5]. To date it was developed many effective methods for synthesis of highly substituted, including chiral

2-oxopiperazines [6-9], while only a small number of them affords 2-oxopiperazin annelated by the bond C(3)-N(4) [7-9]. In this connection, it is of interest that the synthesis of a novel polyheterocyclic structures containing 2-oxopiperazine moiety were annelated by the C(3)-N(4) bond to different cycles. The purpose of this paper is to provide novel annelated heterocycles among 2-oxopiperazine.

2. Experiment

2.1. Characterization

Control over the individuality of the reagents and the obtained compounds, as well as the progress of the reaction was monitored by TLC on Silufol UV-254. As eluent was used chloroform; the manifestation of chromatograms was in UV light and iodine vapor. ¹H NMR spectra were recorded on the instrument Bruker AC-300 (300 MHz); internal standard-TMS, solvents-dimethylsulfoxide, deuterium. Mass-spectra were removed on the device LKB 9000 with the input of the substance directly in the ionizing source, the

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energy of ionizing electrons 70 EV. All solvents and chemicals used in this work were analytical grade and used without purification.

2.2. General Method for the Synthesis of Methyl-2-Aryl - 1, 3, 8 - Trioxodecahydro-1H-Pyrrolo [3', 4':4, 5] Pyrrolo [1, 2-a] Pyrazine-9-Carboxylates 3a, b

A mixture of 0.85 g (0.5 mmol) of 2-oxopiperazine 1 and 0.51 mmol of the corresponding *N*-arylmaleimide in a mixture of 5 mL of methanol and 5 mL of acetic acid are refluxed for 10 h (control-TLC). The precipitate formed is filtered off after cooling, washed with ethanol. For removal of impurities recyclization products recrystallized twice from dimethylformamide. Received compounds 3a, b:

Methyl-2-(4-methylphenyl)-1, 3, 8-trioxodecahydro-1*H*-pyrrolo [3', 4':4, 5] pyrrolo [1, 2-a] pyrazine-9-carboxylate 3a. Yield 65%, mp 180-181 °C. MS (EI, 70 ev) *m/z*, %: 357 (8, M +); 343 (25); 326 (6); 236 (63); 218 (100); 191 (24). ¹H NMR (300 MHz, $\mathcal{I}MSO$ -*d*₆) δ : 2.42 (3H, s, CH₃); 2.53-2.59 (1H, m, CH); 2.90-2.98 (1H, m, CH); 3.22-3.26 (2H, m, CH₂NH); 3.40-3.44 (1H, m, CH); 3.46-3.50 (1H, m, <u>CH₂NH)</u>; 3.62 (3H, s, CH₃O); 3.72-3.74 (1H, m, <u>CH₂NH)</u>; 4.46 (1H, d, J=6.8, CH); 7.08 (2H, d, J=8.6; H-3,5 Ar); 7.19 (2H, d, J=8.6, H-2,6 Ar); 8.62 (1H, d, J=2.1, NH). Analysis: calc. for C₁₈H₁₉N₃O₅: C 60.50, H 5.36, N 11.76. Found. C 60.44, H 5.33, N 11.60.

Methyl-2-(4-ethoxyphenyl)-1, 3, 8-trioxodecahydro-1*H*-pyrrolo [3', 4':4, 5] pyrrolo [1, 2-a] pyrazine-9-carboxylate 3b. Yield 48%, mp 165-166 °C. MS (EI, 70 ev) m/z, %: 387 (8, M+); 373 (21); 356 (5); 236 (67); 218 (100); 191 (25). ¹H NMR (300 MHz, μ MSO- d_6) δ : 1.39 (3H, t, J = 7.1, CH₂<u>CH₃</u>); 2.62-2.68 (1H, m, CH); 2.82-2.88 (1H, m, CH); 3.21-3.25 (2H, m, CH₂NH); 3.51-3.56 (1H, m, CH); 3.57-3.62 (1H, m, <u>CH₂</u>NH); 3.66 (3H, s, CH₃O); 3.71-3.73 (1H, m, <u>CH₂</u>NH); 4.10-4.14 (2H, m, CH₂O); 4.37 (1H, d, J = 7.3, CH); 7.01 (2H, d, J = 8.7; H-3,5 Ar); 7.09 (2H, d, J = 8.7, H-2,6 Ar); 8.39 (1H, d, J = 2.7, NH). Analysis: calc. for C₁₉H₂₁N₃O₆: C 58.91, H 5.46, N 10.85. Found. C 58.82, H 5.39, N 10.90.

2.3. General Method for the Synthesis of Methyl-1,6-Dioxo-8-[(Arylamino) Carbonyl] - 1, 3, 4, 6, 7, 8 -Hexahydro-2H-Pyrido[1, 2-a]Pyrazine-9-Carboxylates 4a-e

A mixture of 0.85 g (0.5 mmol) of 2-oxopiperazine 1 and 0.51 mmol of the corresponding *N*-arylmaleimide in 15 ml of methanol with the addition of 2-3 drops of acetic acid is refluxed for 14 hours (control-TLC). The precipitate formed is filtered off after cooling, washed with ethanol. For removal of impurities addition products recrystallized twice from dimethylformamide. Received compounds 4a-e:

Methyl-1, 6-dioxo-8-[(phenylamino) carbonyl]-1, 3, 6. 8-hexahydro-2H-pyrido 4. 7. [1, 2-a] pyrazine-9-carboxylate 4a. Yield 52%, mp 155-156°C. MS (EI, 70 ev) m/z, %: 343 (51, M+); 311 (100); 284 (23); 192 (42); 163 (41). ¹H NMR (300 MHz, ДМSO-*d*₆) δ: 2.42 (2H, d, J=15.8, CH₂CO); 3.26-3.30 (2H, m, CH₂N); 3.46-3.50 (1H, m, CH₂NH); 3.62 (3H, s, CH₃O); 3.72-3.74 (1H, m, CH₂NH); 5.14 (1H, br s, CH); 7.05 (2H, t, J=7.8; H-3,5 Ar); 7.12 (2H, d, J=7.8, H-2,6 Ar); 7.18 (2H, t, J=7.8; H-3,5 Ar); 8.74 (1H, d, J=2.3, NH); 9.48 (1H, s, NH-Ar). Analysis: calc. for C17H17N3O5: C 59.47, H 4.99, N 12.24. Found. C 59.54, H 4.92, N 12.30.

Methyl-8-{[(4-methylphenyl) amino] carbonyl}-1, 6-dioxo-1, 3, 4, 6, 7, 8-hexahydro-2*H*-pyrido [1, 2-a] pyrazine-9-carboxylate 4b. Yield 52%, mp 152-153°C. MS (EI, 70 ev) *m/z*, %: 357 (48, M+); 325 (100); 298 (23); 192 (44); 163 (40). ¹H NMR (300 MHz, μ SO-*d*₆) δ : 2.12 (3H, s, CH₃); 2.26 (2H, d, J=15.2, CH₂CO); 3.34-3.39 (2H, m, CH₂N); 3.43-3.48 (1H, m, <u>CH₂NH)</u>; 3.70 (3H, s, CH₃O); 3.73-3.75 (1H, m, <u>CH₂NH)</u>; 5.28 (1H, br s, CH); 7.09 (2H, d, J=8.4; H-3,5 Ar); 7.28 (2H, d, J=8.4, H-2,6 Ar); 8.63 (1H, d, J=2.7, NH); 9.52 (1H, s, NH-Ar). Analysis: calc. for C₁₈H₁₉N₃O₅: C 60.50, H 5.36, N 11.76. Found. C 60.59, H 5.42, N 11.62.

Methyl-8-({[4-(ethyloxy) phenyl] amino} carbonyl)-1, 6-dioxo-1, 3. 4. 6. 7, 8-hexahydro-2H-pyrido [1, 2-a] pyrazine-9-carboxylate 4c. Yield 42%, mp 170-171 °C. MS (EI, 70 ev) *m/z*, %: 387 (58, M+); 355 (100); 328 (25); 192 (49); 163 (29). ¹H NMR (300 MHz. $\square MSO-d_6$) δ : 1.40 (3H, t, J = 7.3, CH₂CH₃); 2.20 (2H, d, J = 15.8, CH₂CO); 3.32-3.36 (2H, m, CH₂N); 3.51-3.58 (1H, m, <u>CH2NH</u>); 3.71 (3H, s, CH3O); 3.76-3.80 (1H, m, <u>CH₂NH</u>); 4.02-4.08 (2H, m, CH₂O); 5.26 (1H, br s, CH); 6.98 (2H, d, J = 8.2; H-3,5 Ar); 7.14 (2H, d, J = 8.2, H-2,6 Ar); 8.60 (1H, d, J = 2.1, NH); 9.54 (1H, s, NH-Ar). Analysis: calc. for C₁₉H₂₁N₃O₆: C 58.91, H 5.46, N 10.85. Found. C 58.80, H 5.52, N 10.75.

Methyl-8-{[(4-chlorophenyl) amino] carbonyl}-1, 6-dioxo-1, 3, 4, 6, 7, 8-hexahydro-2*H*-pyrido [1, 2-a] pyrazine-9-carboxylate 4d. Yield 45%, mp 163-164 °C. MS (EI, 70 ev) m/z, %: 377 (52, M +); 345 (100); 318 (21); 192 (37); 163 (25). ¹H NMR (300 MHz, μ MSO- d_6) δ : 2.65 (2H, d, J = 16.1, CH₂CO); 3.31-3.36 (2H, m, CH₂N); 3.39-3.43 (1H, m, <u>CH₂NH);</u> 3.66-3.70 (1H, m, <u>CH₂NH);</u> 3.72 (3H, s, CH₃O); 5.31 (1H, br s, CH); 7.38 (2H, d, J = 8.7; H-3,5 Ar); 7.52 (2H, d, J = 8.7, H-2,6 Ar); 8.78 (1H, d, J = 3.6, NH); 9.58 (1H, s, NH-Ar). Analysis: calc. for C₁₇H₁₆ClN₃O₅: C 54.05, H 4.27, N 11.11. Found. C 54.00, H 4.38, N 11.22.

Methyl-8- $\{[(2,$ 4-dichlorophenyl) amino] carbonyl}-1, 6-dioxo-1, 3. 4. 6, 7, 8-hexahydro-2H-pyrido [1, 2-a] pyrazine-9-carboxylate 4e. Yield 47%, mp 200-202°C. MS (EI, 70 ev) m/z, %: 412 (8, M +); 380 (100); 353 (17); 192 (46); 163 (29). ¹H NMR (300 MHz, \square MSO- d_6) δ : 2.63 (2H, d, J = 16.1, CH₂CO); 3.30-3.34 (2H, m, CH₂N); 3.40-3.45 (1H, m, CH₂NH); 3.66-3.71 (1H, m, CH₂NH); 3.74 (3H, s, CH₃O); 5.34 (1H, br s, CH); 7.32 (1H, s, H-3 Ar); 7.36 (1H, d, J = 8.7; H-5 Ar); 7.48 (1H, d, J = 8.7, H-6 Ar); 8.78 (1H, d, J = 3.6, NH); 9.58 (1H, s, NH-Ar). Analysis: calc. for C₁₇H₁₅Cl₂N₃O₅: C 49.53, H 3.67, N 10.19. Found. C 49.65, H 3.60, N 10.29.

3. Results and Discussion

3.1. Synthesis and Characterization

We have studied the interaction of methyl (3-oxo-piperazine-2-ylidene) acetate 1 (prepared by ethylenediamine reacting with dimethvl acetylenedicarboxylate [10]) with N-arylmaleimides 2. It is known that N-arylmaleimides are dipolarophiles [11], at the same time, under the action of nucleophiles occurs recyclization maleimide fragment [12]. It was reported earlier [10] that methvl (3-oxopiperazin-2-ylidene) acetate 1 in an acidic medium can be converted to the tautomeric form methyl (3-oxo-3, 4, 5, 6-tetrahydropyrazine-2-yl) acetate 1' (Fig. 1). We hypothesized that in the reactions of simultaneous involving nitrogen atoms N (4) and the side chain depending on the condition, the this heterocycle may act as the C-N-dinucleophile, being in the form of the enamine 1, and as the 1, 3-dipole- when transition to form imine 1'.

In this work, we have found that when the reaction of the starting compounds by refluxing in a mixture of methanol and acetic acid (in the ratio 1:1) arylmaleimides 2 attached to the imine 1' as a dipole to form a new heterocyclic system -methyl-2-aryl-1, 3, 8-trioxodecahydro-1H-pyrrolo [3', 4':4, 5] pyrrolo [1, 2-a] pyrazine-9-carboxylates 3a, b (Fig. 1). With a deficiency of acid (the use of catalytic amounts) starting compound is reacted with an arylmaleimide 2 mainly as enamine 1, wherein the maleimide recyclization occurs leading to not previously methyl-1, 6-dioxo-8-[(arylamino) described carbonyl]-1, 3, 4, 6, 7, 8-hexahydro-2H-pyrido [1,2-a] pyrazine-9-carboxylates 4a-e (Fig. 1).

At carrying out the reaction under different conditions (refluxing the reactants in toluene without catalyst, in the presence of acidic catalysts, in butanol-1-and stirring at room temperature in acetic acid) is formed inseparable mixture of products 3 and 4. The structure of the obtained for the first time chemical compounds 3 and 4 is uniquely proved by ¹H

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 $\label{eq:action} \begin{array}{l} 4 \mbox{ Ar }= C_{6} H_{5} \ (a), \ 4-C H_{3} - C_{6} H_{4} \ (b), \ 4-C_{2} H_{5} O - C_{6} H_{4} \ (c); \ 4-C I - C_{6} H_{4} \ (d), \ 2, \ 4-di C I - C_{6} H_{4} \ (e) \end{array}$

NMR spectroscopy and mass spectrometry.

4. Conclusions

It established is that methyl (3-oxo-piperazine-2-ylidene) acetate is reacted with *N*-arylmaleimides in boiling methanol in the presence of catalytic amounts of acetic acid as the C-N-dinucleophile. An excess of acid occurs 1,3-dipolar cycloaddition of the N-arylmaleimides toward tautomeric form methyl (3-oxo-piperazine-2-ylidene) acetate-methyl (3-oxo-3,4,5,6-tetrahydropyrazine-2-yl) acetate.

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