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LETTERS TO THE EDITOR

Synthesis of Functionally Substituted Glutarimides

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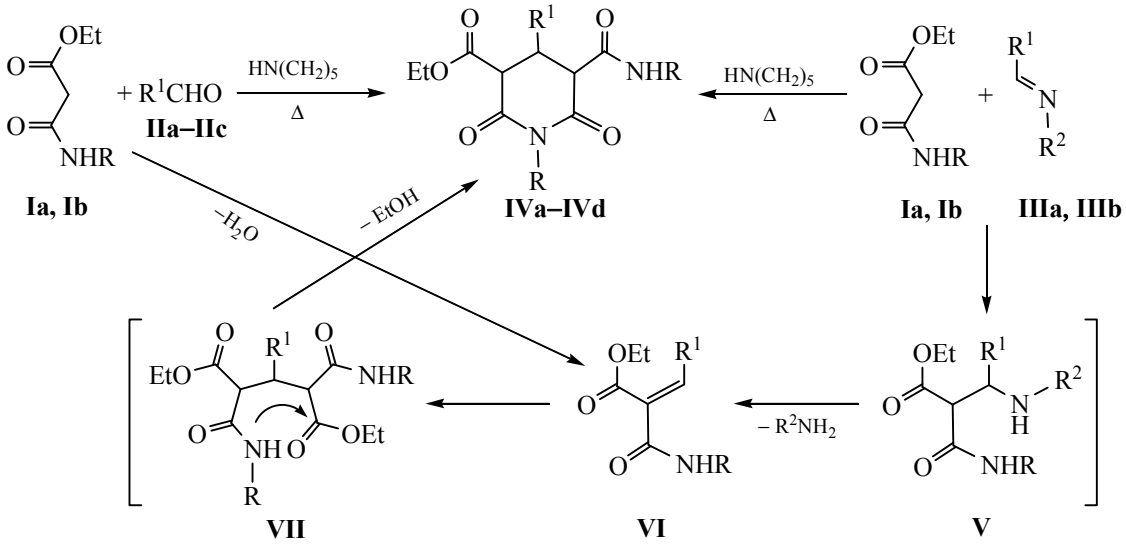
It is known, that many compounds containing amide or imide group exhibit versatile biological activity. Therefore the development of new methods for synthesis of compounds containing these pharmacophore groups is of particular interest. We have recently shown that the interaction of secondary arylamides of acetoacetic acid with Schiff bases resulted in 8-aryl-*N*,6-diaryl-3-hydroxy-1,3-dimethyl-5-oxo-2-oxa-6-azabicyclo[2.2.2]octane-7-carboxamide [1].

The reaction of ethyl 3-arylamino-3-oxopropionate **I** with aromatic aldehydes **II** or imines **III** in the presence of piperidine in refluxing ethanol results in ethyl 1,4-diaryl-2,6-dioxo-5-arylcarbamoylpiperidine-3-carboxylates **IV** (glutarimide derivatives), containing both amide and imide groups. It should be noted that in the case of aldehydes yields of the product is higher (57–84%) compared with the corresponding imines (23–26%). The structure of the products obtained was confirmed by the ^{1}H and ^{13}C NMR spectroscopy.

In both cases the interaction, probably, proceeds through the intermediate formation of α,β-unsaturated compound **V**, which adds the second molecule of amidoester **I** followed by intramolecular cyclization of the resulting adduct **VII**.



R = *o*-tolyl (**Ia**, **IVa**, **IVb**, **IVc**); 2,4-$(CH_3)_2C_6H_3$ (**Ib**, **IVd**); R^1 = Ph (**IIa**, **IIIa**, **IIIb**, **IVa**, **IVd**), 4-Cl-C_6H_4 (**IIb**, **IVb**), 4-NO_2-C_6H_4 (**IIc**, **IVc**); R^2 = CH_2Ph (**IIIa**), CH_2CH_2OH (**IIIb**).

It should be noted that similar investigations are not known in the literature, except for one patent, where the reaction of methyl 3-methyl-amino-3-oxopropionate with dimethyl 2-(4-fluoro)-benzylidenemalonate is described, leading to dimethyl 4-(4-fluoro)-phenyl-1-methyl-2,6-dioxopiperidine-3,5-dicarboxylate [2].

General procedure for the synthesis of the substituted glutarimides (IVa–IVd). A mixture of amide **I** and aldehyde **II** or imine **III** (2:1) was refluxed in the presence of an equimolar amount of piperidine in anhydrous ethanol for several hours. The formed crystals were filtered off, washed with anhydrous diethyl ether, and recrystallized from anhydrous ethanol.

Ethyl 2,6-dioxo-4-phenyl-1-*o*-tolyl-5-*o*-tolylcarbamoylpiperidine-3-carboxylate (IVa) was obtained from a mixture of 1.25 g (5.6 mmol) of amide **Ia** and 0.3 g (2.8 mmol) of aldehyde **IIa** in 15 ml of anhydrous ethanol. Reaction time 15 h. Yield 0.98 g (73%), mp 230°C. IR spectrum, ν, cm^{-1}: 1660 (CON), 1680 (O=CNC=O), 1725 (COO), 3370 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.03 t (3H, C<u>H</u>$_3$CH$_2$, ^2J 7.1), 1.81 s (3H, CH$_3$Ar), 2.18 s (3H, CH$_3$Ar), 3.99 q (2H, C<u>H</u>$_2$CH$_3$, ^2J 7.1), 4.05–4.22 m (1H, 4-CH), 4.40 d (1H, CH, ^2J 12.5), 4.55 d (1H, CH, ^2J 13.1), 6.97–7.06 m (4H, Ph), 7.11–7.15 m (1H, Ph), 7.24–7.46 m (8H, Ph), 9.40 s (1H, NH).

Ethyl 2,6-dioxo-4-(4-chlorophenyl)-1-*o*-tolyl-5-*o*-tolylcarbamoylpiperidine-3-carboxylate (IVb) was obtained from a mixture of 0.88 g (4 mmol) of amide **Ia** and 0.28 g (2 mmol) of aldehyde **IIb** or a mixture of 0.68 g (3 mmol) of amide **Ia** and 0.35 g (1.5 mmol) of imine **IIIa** in 10 ml of anhydrous ethanol. Reaction time 8 or 15 h. Yield 0.87 g (84%) or 0.2 g (26%), mp 260°C. IR spectrum, ν, cm^{-1}: 1660 (CON), 1675 (O=CNC=O), 1720 (COO), 3360 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.08 t (3H, C<u>H</u>$_3$CH$_2$, ^2J 7.1), 1.84 s (3H, CH$_3$Ar), 2.17 s (3H, CH$_3$Ar), 3.98–4.08 m (2H, C<u>H</u>$_2$CH$_3$), 4.07–4.22 m (1H, 4-CH), 4.39 d (1H, CH, ^2J 12.3), 4.58 d (1H, CH, ^2J 13.1), 6.97–7.14 m (5H, Ph), 7.24–7.47 m (7H, Ph), 9.43 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 13.5 (CH$_3$, OEt), 16.8, 17.0 (CH$_3$), 40.6 (C^4), 54.7, 55.1 (C^3, C^5), 60.3 (CH$_2$); 125.1, 125.2, 125.3, 125.9, 128.0, 128.3, 129.1, 129.4, 129.6, 130.0 (CH, Ar); 132.0, 132.6, 133.9, 135.1, 135.3, 136.2 (C^{ipso}, Ar); 164.4, 166.4, 167.4, 168.2 (C=O).

Ethyl 2,6-dioxo-4-(4-nitrophenyl)-1-*o*-tolyl-5-*o*-tolylcarbamoylpiperidine-3-carboxylate (IVc) was obtained from a mixture of 0.45 g (2 mmol) of amide **Ia** and 0.15 g (1 mmol) of aldehyde **IIb** in 10 ml of anhydrous ethanol. Reaction time 6 h. Yield 0.3 g (57%), mp 270°C. IR spectrum, ν, cm^{-1}: 1670 (CON), 1680 (O=CNC=O), 1725 (COO), 3380 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.09 t (3H, C<u>H</u>$_3$CH$_2$, ^2J 7.5), 1.84 s (3H, CH$_3$Ar), 2.18 s (3H, CH$_3$Ar), 3.95–4.08 m (2H, C<u>H</u>$_2$CH$_3$), 4.21–4.40 m (1H, 4-CH), 4.51 d (1H, CH, ^2J 12.5), 4.75 d (1H, CH, ^2J 13.0), 6.95–7.16 m (5H, *o*-tolyl), 7.26–7.34 m (3H, *o*-tolyl), 7.68–7.73 m (2H, 4-NO$_2$-C$_6$H$_4$), 8.20–8.26 m (2H, 4-NO$_2$-C$_6$H$_4$), 9.53 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 13.6 (CH$_3$, OEt), 16.7, 17.0 (CH$_3$), 41.3 (C^4), 54.3, 55.0 (C^3, C^5), 61.1 (CH$_2$); 123.8, 125.7, 125.8, 126.8, 126.8, 128.5, 128.8, 129.5, 130.1, 130.6 (CH, Ar); 132.6, 133.9, 135.1, 135.2, 145.1, 147.2 (C^{ipso}, Ar); 164.7, 166.9, 167.8, 168.4 (4C=O).

Ethyl 2,6-dioxo-4-phenyl-1-(2,4-dimethylphenyl)-5-(2,4-dimethylphenyl)carbamoylpiperidine-3-carboxylate (IVd) was obtained from a mixture of 1.12 g (4.8 mmol) of amide **Ib** and 0.25 g (2.3 mmol) of aldehyde **IIa** or a mixture of 1.18 g (5 mmol) of amide **Ib** and 0.38 g (2.5 mmol) of imine **IIIb** in 15 ml of anhydrous ethanol. Reaction time 11 or 10 h. Yield of 0.9 g (73%) or 0.3 g (23%), mp 236–237°C. IR spectrum, ν, cm^{-1}: 1660 (CON), 1675 (O=CNC=O), 1725 (COO), 3350 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.03 t (3H, C<u>H</u>$_3$CH$_2$, ^2J 7.1), 1.74 s (3H, CH$_3$Ar), 2.13 s (3H, CH$_3$Ar), 2.23 s (3H, CH$_3$Ar), 2.38 s (3H, CH$_3$Ar), 3.99 q (2H, C<u>H</u>$_2$CH$_3$, ^2J 7.1), 4.04–4.19 m (1H, 4-CH), 4.34 d (1H, CH, ^2J 12.5), 4.49 d (1H, CH, ^2J 13.0), 6.78–6.89 m (3H, Ph), 7.22–7.44 m (3H, Ph), 7.22– 7.44 m (5H, Ph), 9.27 s (1H, NH).

The ^{1}H NMR and ^{13}C spectra were obtained on a Varian Mercury-300VX spectrometer (75.46 and 300.05 MHz, respectively) at 300 K in a DMSO-d_6–CCl_4 mixture (1:3), internal reference TMS. The IR spectra were recorded on a Specord 75 IR instrument in mineral oil (thin layer). The melting points were determined on a Boetius heating block.

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