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Reaction of 2-(Phenylamino)benzoic and 2-(Phenylamino)- and 2-Methyl-6-phenylpyridine-3-carboxylic Acid Hydrazides with Succininc Anhydride

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Abstract—Reactions of 2-(phenylamino)benzoic and 2-(phenylamino)- and 2-methyl-6-phenylpyridine-3-carboxylic acid hydrazides with succinic anhydride in organic solvents at room temperature gave the corresponding 4-(2-aroylhydrazinyl)-4-oxobutanoic acids. The reactions in boiling acetic acid afforded *N*-(2,5-dioxopyrrolidin-1-yl)benzamide or *N*-(2,5-dioxopyrrolidin-1-yl)pyridine-3-carboxamide.

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Derivatives of 2-(phenylamino)benzoic [1] and 2-(phenylamino)pyridine-3-carboxylic acid hydrazides [2] exhibit a broad spectrum of biological activity (anticonvulsant, anti-inflammatory, and bactericidal). They are also used in the synthesis of biologically active substituted 3-aminoquinazolin-4-ones [3, 4].

A conventional procedure for the preparation of acylhydrazides is based on the reaction of hydrazides with carboxylic acid anhydrides. As shown in [5, 6], 2-(phenylamino)benzohydrazide reacts with succinic anhydride to give either 4-oxo-4-{2-[2-(phenylamino)-benzoyl]hydrazinyl}butanoic acid or 2,3,4,10-tetrahydro-1*H*-pyridazino[3,2-*b*]quinazoline-2,10-dione, depending on the conditions.

We examined the reactions of succinic anhydride with 2-(phenylamino)benzohydrazide (**Ia**), 2-(phenylamino)pyridine-3-carbohydrazide (**Ib**), and (for comparison) 2-methyl-6-phenylpyridine-3-carbohydrazide (**Ic**) at different temperature conditions. We expected to obtain compounds like **A** under severe conditions, i.e., by heating hydrazides **Ia** and **Ib** with succinic anhydride in boiling glacial acetic acid.

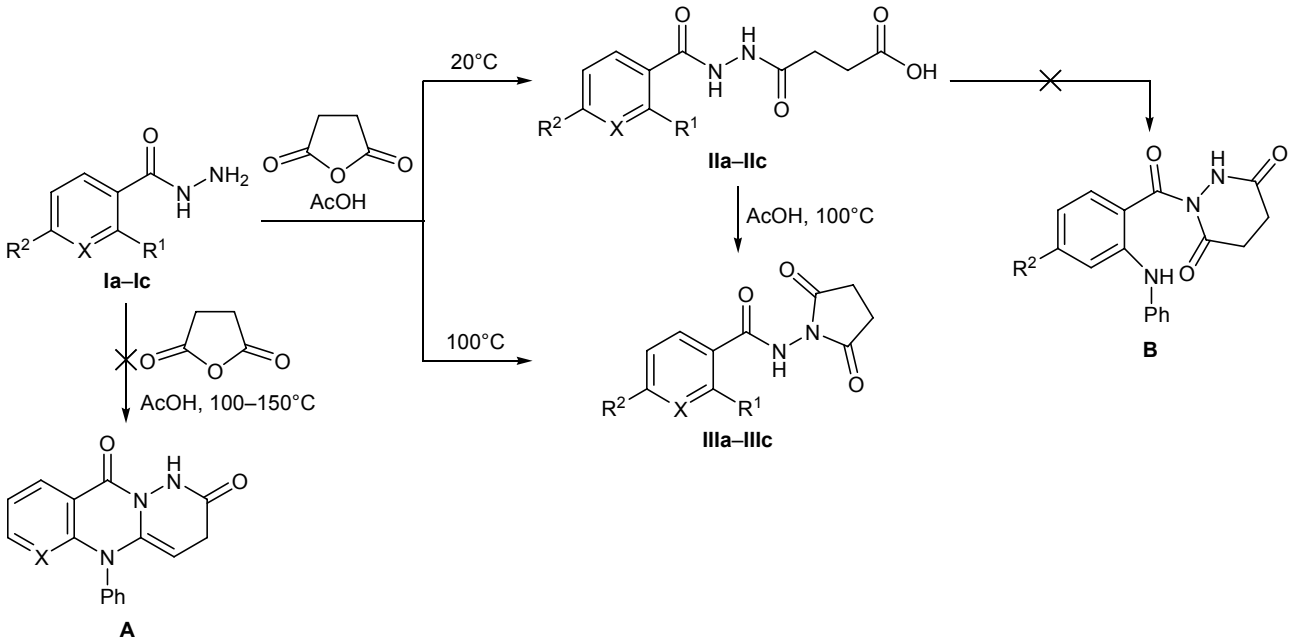
The reactions performed at room temperature in different solvents (glacial acetic acid, chloroform, benzene) gave the corresponding 4-(2-aroylhydrazinyl)-4-oxobutanoic acids **IIa**–**IIc** (Scheme 1). By heating the reactants in acetic acid at 100°C we obtained high-melting compounds **IIIa**–**IIIc** which were insoluble in aqueous sodium hydrogen carbonate. Compounds **IIIa**–**IIIc** were also formed when hydrazides **IIa**–**IIc** were heated in glacial acetic acid. Analogous results were obtained at 140°C.

Presumably, heating of hydrazides **Ia**–**Ic** with succinic anhydride in acetic acid initially gives acylhydrazides **IIa**–**IIc** whose cyclization can take two paths with closure of pyrrolidine (**IIIa**–**IIIc**) or pyridazine ring (**B**). According to [6, 7], cyclodehydration of *N*′-acyl succinic acid hydrazides yields succinimide derivatives. We believe that the cyclization of hydrazides **IIa**–**IIc** also leads to the formation of succinimides **IIIa**–**IIIc**. To confirm this assumption we calculated the total energies of compound **IIIa** and its pyridazine analog **B**, which turned out to be –2733553.92 and –2733496.89 kJ/mol, respectively. It is seen that structure **IIIa** is more stable; therefore, its formation should be preferred.

No products like **A** were detected, presumably because of lower nucleophilicity of the arylamino group in **IIa** and **IIb** as compared to amino group in anthranilic acid derivatives; in addition, steric factor cannot be ruled out.

The structure of the newly synthesized compounds was confirmed by their ^{1}H NMR and mass spectra. All compounds characteristically underwent McLafferty rearrangement [8] under electron impact, which is

Scheme 1.



R^1 = PhNH, R^2 = H, X = CH (**a**); R^1 = PhNH, R^2 = H, X = N (**b**); R^1 = Me, R^2 = Ph, X = N (**c**).

typical of anthranilic and 2-methylbenzoic acid derivatives. The mass spectrum of **IIa** contained no molecular ion peak, but that belonging to **IIIa** was observed. Presumably, in the course of mass spectrometric analysis compound **IIa** is readily converted into **IIIa** via elimination of water.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Tesla BS-567A spectrometer at 100 MHz from 5% solutions in DMSO-d_6 using hexamethyldisiloxane as internal reference. Quantum-chemical calculations were performed at the RHF/6-31-G(*d*) level of theory with full geometry optimization using Gaussian 03W [9]. The mass spectra were obtained on an Agilent Technologies 6890N/5975B GC–MS system (HP-5ms column, 30 m×0.25 mm, film thickness 0.25 μm; carrier gas helium; electron impact, 70 eV). The elemental compositions were determined on a LECO CHNS-932 analyzer (USA).

4-Oxo-4-{2-[2-(phenylamino)benzoyl]hydrazinyl}-butanoic acid (IIa). A solution of 0.5 g (5 mmol) of succininc anhydride in 10 ml of chloroform was added to a solution of 1.14 g (5 mmol) of 2-(phenylamino)-benzohydrazide (**Ia**) in 10 ml of chloroform, and the mixture was kept for 2 h at 20°C. The precipitate was filtered off and recrystallized from aqueous ethanol. Yield 1.05 g (68%), mp 154–155°C. ^{1}H NMR spectrum, δ, ppm: 2.44 m (4H, CH_2CH_2), 7.16 m (9H, H_{arom}), 9.21 s (1H, $C_6H_5N\mathbf{H}$), 9.81 s, 10.19 s (2H, NHNH), 11.80 br.s (1H, OH). Mass spectrum, *m*/*z* (I_{rel}, %): 309.10 (37.9) $[M - H_2O]^+$, 195 (100), 167 (38.5), 139 (5.0), 115 (2.4), 77.0 (4.4), 51 (2.3). Found, %: C 59.32; H 5.57; N 12.10. $C_{17}H_{17}N_3O_4$. Calculated, %: C 59.18; H 5.54; N 12.07. *M* 327.32.

Compounds **IIb** and **IIc** were synthesized in a similar way.

4-Oxo-4-{2-[2-(phenylamino)pyridin-3-ylcarbonyl]hydrazinyl}butanoic acid (IIb) was obtained from 1.14 g (5 mmol) of 2-(phenylamino)pyridine-3-carbohydrazide (**Ib**) and 0.5 g (5 mmol) of succinic anhydride in anhydrous benzene. Yield 0.95 g (61%), mp 145–147°C. ^{1}H NMR spectrum, δ, ppm: 2.44 m (4H, CH_2CH_2), 7.49 m (8H, H_{arom}), 9.92 s and 10.30 s (2H, NHNH), 10.50 br.s (1H, N**H**Ph). Found, %: C 58.75; H 4.95; N 16.93. $C_{16}H_{17}N_4O_4$. Calculated, %: C 58.53; H 4.88; N 17.07.

4-[2-(2-Methyl-6-phenylpyridin-3-ylcarbonyl)-hydrazinyl]-4-oxobutanoic acid (IIc) was obtained from 1.15 g (5 mmol) of 2-methyl-6-phenylpyridine-3-carbohydrazide (**Ic**) and 0.5 g (5 mmol) of succinic anhydride. Yield 1.15 g (71%), mp 207–208°C. ^{1}H NMR spectrum, δ, ppm: 2.39 m (4H, CH_2CH_2), 2.63 s (3H, CH_3), 7.80 m (7H, H_{arom}), 9.88 s and 10.1 s (2H, NHNH). Found, %: C 62.41; H 5.23; N 12.70. $C_{17}H_{17}N_3O_4$. Calculated, %: C 62.50; H 5.17; N 12.72.

***N*-(2,5-Dioxopyrrolidin-1-yl)-2-(phenylamino)-benzamide (IIIa).** *a*. A mixture of 0.4 g (4 mmol) of succinic anhydride and 1.0 g (4.4 mmol) of hydrazide **Ia** in 10 ml of glacial acetic acid was heated for 4–6 h at 100°C. The mixture was cooled and diluted with water, and the precipitate was filtered off and recrystallized from dioxane. Yield 1.0 g (80%), mp 178–180°C. ^{1}H NMR spectrum, δ, ppm: 2.82 m (4H, CH_2CH_2), 7.24 m (9H, H_{arom}), 9.22 s (1H, $C_6H_5N\mathbf{H}$), 10.94 s (1H, CONH). Mass spectrum, *m*/*z* (I_{rel}, %): 309.20 (36.88) $[M]^+$, 195 (100), 167 (38.5), 139 (5.0), 115 (2.4), 77 (4.4), 51 (2.3). Found, %: C 66.15; H 4.93; N 13.73. $C_{17}H_{15}N_3O_3$. Calculated, %: C 66.02; H 4.85; N 13.59. *M* 309.31.

b. A solution of 0.5 g (1.52 mmol) of **IIa** in 10 ml of glacial acetic acid was heated for 4–6 h at 100°C. The mixture was cooled and diluted with water, and the precipitate was filtered off and recrystallized from dioxane. Yield 0.25 g (53%), mp 178–180°C. The product showed no depression of the melting point on mixing with a sample prepared as described in *a*.

Compounds **IIIb** and **IIIc** were synthesized in a similar way (method *a*).

***N*-(2,5-Dioxopyrrolidin-1-yl)-2-(phenylamino)-pyridine-3-carboxamide (IIIb)** was obtained from 1.14 g (5 mmol) of **Ib** and 0.5 g (5 mmol) of succinic anhydride. Yield 0.4 g (37%), mp 210–211°C. ^{1}H NMR spectrum, δ, ppm: 2.86 m (4H, CH_2CH_2), 7.56 m (8H, H_{arom}), 10.15 s (1H, $C_6H_5N\mathbf{H}$), 11.18 s (1H, CONH). Mass spectrum, *m*/*z* (I_{rel}, %): 310.10 (55.3) $[M]^+$, 197 (100), 168 (71.7), 140 (7.8), 99 (8.2), 77 (17.9), 51 (6.6). Found, %: C 61.31; H 4.57; N 17.62. $C_{16}H_{14}N_4O_3$. Calculated, %: C 61.65; H 4.49; N 17.73. *M* 310.29.

***N*-(2,5-Dioxopyrrolidin-1-yl)-2-methyl-6-phenyl-pyridine-3-carboxamide (IIIc)** was obtained from 0.5 g (2.17 mmol) of **Ic** and 0.2 g (2 mmol) of succinic anhydride. Yield 0.20 g (29%), mp 192°C. ^{1}H NMR spectrum, δ, ppm: 2.65 s (3H, CH_3), 2.83 m (4H, CH_2CH_2), 7.7 m (7H, H_{arom}), 10.90 s (1H, CONH). Mass spectrum, *m*/*z* (I_{rel}, %): 309.10 (4.0) $[M]^+$, 196 (100), 168 (15.9), 141 (12.5), 115 (5.9), 77 (3.0), 51 (1.3). Found, %: C 62.33; H 5.22; N 12.75. $C_{17}H_{15}N_3O_3$. Calculated, %: C 62.27; H 5.01; N 12.73. *M* 309.31.

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