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Reactions of 2,3-Dioxopyrrolo[2,1-*a*]isoquinolinecarboxylic Acid Esters and Amides with Nitrogen-Centered Nucleophiles

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Abstract—Reactions of ethyl 2,3-dioxopyrrolo[2,1-*a*]isoquinoline-1-carboxylates with active nitrogen-centered nucleophiles (phenylhydrazine, hydroxylamine, and benzylamine) involve opening of the pyrrole ring with formation of 2-(3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-ylidene)-N'^1,N'^4-diphenyl-3-(2-phenylhydrazono)succinohydrazide, 5-(6,7-dimethoxy-3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-ylidene)-2,3,4,5-tetrahydro-1*H*-1,2-oxazine-3,4,6-trione, and ethyl 4-benzylamino-2-(3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-ylidene)-3,4-dioxobutanoate, respectively. Cyclic amides derived from 5,5-dimethyl-2,3-dioxo-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinoline-1-carboxylic acid react with benzylamine in a similar way. Reactions of the title compounds with weaker nucleophiles, such as semicarbazide and thiosemicarbazide, are not accompanied by opening of the pyrrole ring, and the products are the corresponding semicarbazones and thiosemicarbazones at the C^2=O carbonyl group.

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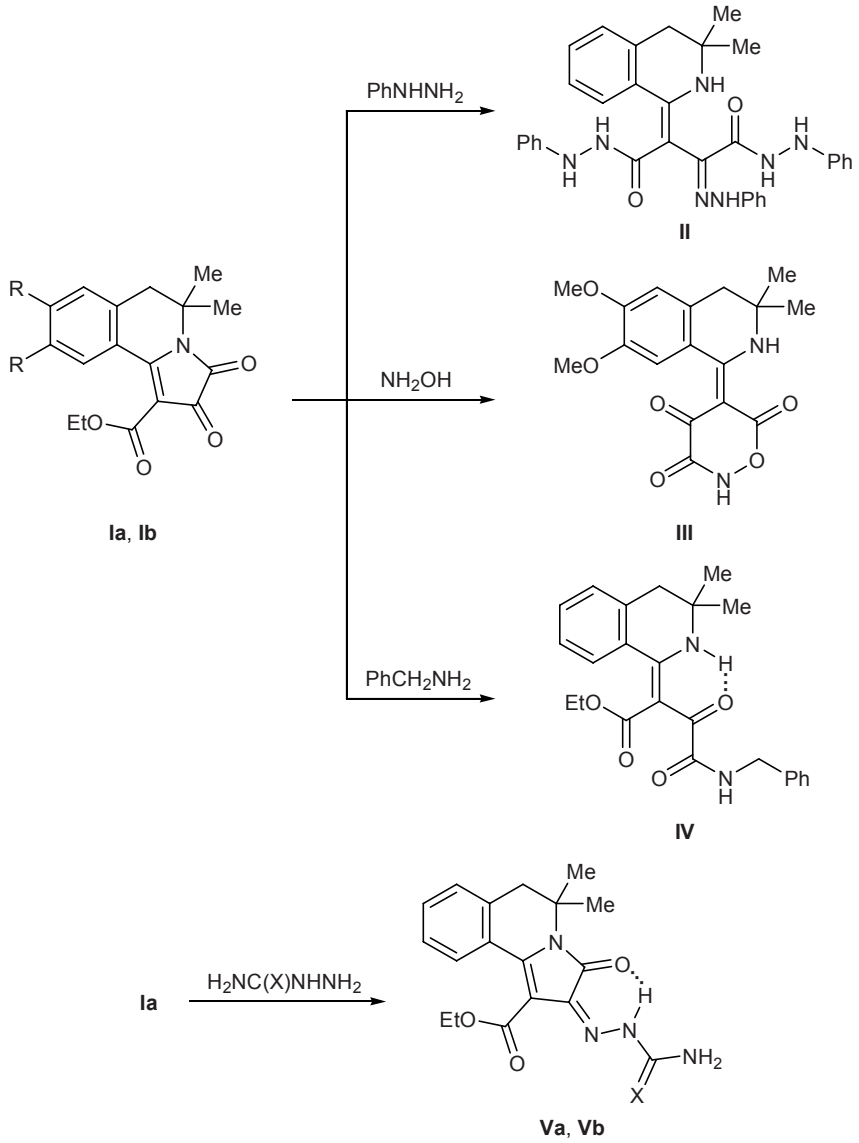
We previously studied reactions of 2,3-dioxopyrrolo[2,1-*a*]isoquinolines with various nitrogen-containing nucleophiles [1–5] and found that their reactivity depends on the substituent in the pyrrole ring. It might be presumed that introduction of a carbamoyl or alkoxycarbonyl group into the pyrrole ring should reduce the electron density on the pyrrole ring and thus affect the direction of reactions of such 2,3-dioxopyrrolo[2,1-*a*]isoquinolines with nucleophiles. Moreover, the ester moiety therein is also capable of reacting with N-nucleophiles. The goal of the present work was to study the structure of products formed in the reactions of 2,3-dioxopyrrolo[2,1-*a*]isoquinoline-1-carboxylic acid esters and amides with nitrogen-centered nucleophiles, depending on the substrate structure.

Solutions of initial dioxopyrroloisoquinolines **Ia** and **Ib** are bright red. Opening of the pyrrole ring is accompanied by decoloration, so that the progress of reactions can be readily controlled. Compounds **Ia** and **Ib** reacted with phenylhydrazine, hydroxylamine, and benzylamine in different ways, depending on the nucleophile nature. The reaction of **Ia** with phenylhydrazine involved all three carbonyl groups of the substrate to give phenylhydrazono-substituted bis-hydrazide **II** (Scheme 1). The reaction of compound **Ib** with hydroxylamine occurred in a fairly unusual fashion, yielding 1,2-oxazinetrione derivative **III**. In the reaction of **Ia** with benzylamine amido ester **IV** was obtained. The reactions of ester **Ia** with ammonia and lower aliphatic amines (methylamine, ethylamine) were accompanied by decoloration of the reaction mixture, indicating opening of the pyrrole ring, i.e., normal reaction pathway. However, we failed to identify the oily products which did not form stable salts. According to the TLC data, no reaction occurred between ester **Ia** and aromatic amines in the absence of acid catalyst. No expected amides were isolated when compound **I** was heated with aromatic amines in boiling glacial acetic acid. The latter fact may be rationalized in terms of increased tendency of ester **Ia** to undergo decarbonylation [6], in contrast to its analogs having no electron-withdrawing ester group [4].

The pyrrole ring in amides **VIa**–**VIc** [7] is readily opened by the action of benzylamine to give the corresponding keto amides **VIIa**–**VIIc** (Scheme 2). In the reaction of **VIa**–**VIc** with thiosemicarbazide, the pyrrole ring remained intact, and the product was thiosemicarbazone **VIII**.

The obtained isoquinoline derivatives are crystalline substances. Their structure was confirmed by the IR, ^{1}H NMR, and mass spectra. Unlike initial ester **I** [7] and amide **IV**, the IR spectrum of dihydrazide **II**

Scheme 1.

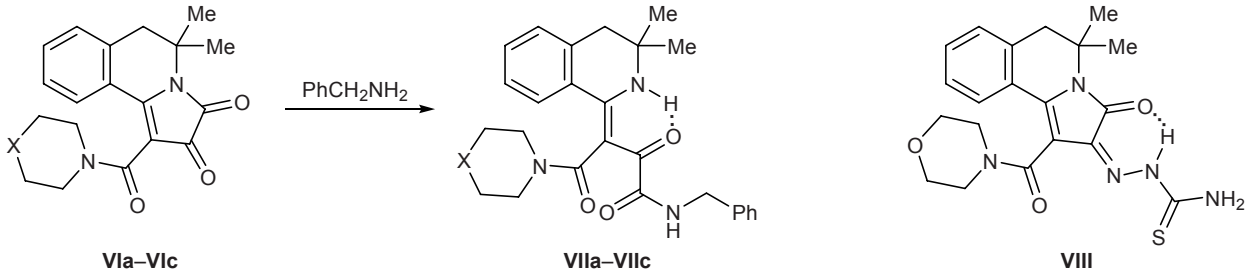


I, R = H (a), MeO (b); **V**, X = O (**a**), S (**b**).

lacked ester carbonyl absorption at 1730 cm^{-1}. Diamides **VIIa**–**VIIc** displayed in the IR spectra absorption bands belonging to stretching vibrations of the ketone carbonyl group involved in intramolecular hydrogen bond (1620 cm^{-1}), two amide carbonyl groups (1645–1650 and 1670 cm^{-1}), and NH group in the isoquinoline ring (3120–3150 cm^{-1}). The semicarbazide and thiosemicarbazide NH and NH_2 fragments in compounds **Va**, **Vb**, and **VIII** give rise to absorption bands in the region 3300–3410 cm^{-1}. The C=O group in the pyrrole ring is involved in H-chelate ring, and its stretching vibrations are characterized by a frequency of 1680–1690 cm^{-1}. Thus the above data are consistent with the presence or absence of pyrrole ring in molecules **II**–**V**, **VII**, and **VIII** and (what is especially important) with the presence of ethoxycarbonyl group in molecules **IV** and **V**.

The ^1H NMR spectra of compounds **II** and **VIIa**–**VIIIc** contained two singlets from two nonequivalent methyl groups in position *3* of the isoquinoline ring. Correspondingly, each proton in the methylene group in position *4* gave a singlet. Taking into account nonequivalence of the methyl and methylene protons, as well as anomalously low melting point of hydrazide **II** (78–80°C), it was reasonable to presume that it exists as a mixture of stereoisomers. In the ^1H NMR spectra of the other products, both methyl groups on C^3 and methylene protons on C^4 are magnetically equivalent.

Scheme 2.



VIa–VIc **VIIa–VIIc** **VIII**

VI, **VII**, X = O (**a**), CH_2 (**b**), $(CH_2)_2$ (**c**).

Presumably, magnetic anisotropy of molecules **VIIa**–**VIIc** increases due to conformational mobility of the cyclic amine residue. The spectra of the products formed as a result of opening of the pyrrole ring contained singlets from the NH groups, which were displaced downfield upon addition of trifluoroacetic acid. In addition, signals from the corresponding substituents were present in the ^{1}H NMR spectra.

Semicarbazone **Va** and thiosemicarbazones **Vb** and **VIII** showed in the mass spectra peaks from the molecular ions with *m*/*z* values (I_{rel}, %) of 356 (80), 372 (100), and 413 (100), respectively. Fragmentation of the molecular ion of **Va** involves elimination of the semicarbazone fragment $[M - NNHCONH_2]^+$ [*m*/*z* 285 (48%)] and subsequent loss of the ethoxycarbonyl group [*m*/*z* 212 (I_{rel} 56%)]. The mass spectrum of thiosemicarbazone **Vb** contained peak from the $[M - NNHC(S)NH_2]^+$ ion with *m*/*z* 253 (I_{rel} 12%).

Thus reactions of ester **Ia** with benzylamine, semicarbazide, and thiosemicarbazide occur with conservation of the ester fragment, i.e., they are regioselective. The isolated isoquinoline derivatives can be used as intermediate products in further syntheses.

EXPERIMENTAL

The IR spectra were recorded on a Specord-80 spectrometer from samples dispersed in mineral oil. The ^{1}H NMR spectra were measured on a Bruker 300 instrument (300 MHz) from solutions in DMSO-d_6 (compounds **II**–**IV**) or $CDCl_3$ (the other compounds) using hexamethyldisiloxane as internal reference (δ 0.05 ppm). The NH signals in the spectra of **IV** and **Va**–**Vc** were often overlapped by the aromatic multiplet or exchanged with water present in the solvent (DMSO-d_6). The mass spectra (electron impact, 70 eV) were obtained on a MAT-311 spectrometer. The purity of the isolated compounds was checked by thin-layer chromatography on Silufol UV-254 plates using acetone–isopropyl alcohol–chloroform (1:3:6) as eluent; development with iodine vapor.

Compound **IV** was recrystallized from petroleum ether, compound **Va** was recrystallized from benzene, and the others, from acetonitrile. The procedures for the synthesis of initial esters **Ia** and **Ib** and amides **VIa**–**VIc** were reported in [7, 8].

2-(3,3-Dimethyl-1,2,3,4-tetrahydroisoquinolin-1-ylidene)-*N′*^{1},*N′*^{4}-diphenyl-3-phenylhydrazonosuccinohydrazide (II). Phenylhydrazine, 3.2 ml (0.033 mol), was added at 20°C to a suspension of 2.27 g (0.01 mol) of compound **Ia** in 10 ml of benzene. The mixture turned colorless within 2 min. It was diluted with 100 ml of hexane, and the precipitate was filtered off, dried, and recrystallized. Yield 4.5 g (80%), yellow crystals, mp 78–80°C. IR spectrum, ν, cm^{-1}: 1620, 1640, 1670 (C=O); 3050, 3180 (NH). ^{1}H NMR spectrum, δ, ppm: 1.22 s (3H, CH_3), 1.43 s (3H, CH_3), 3.21 s (1H, 4-H), 3.32 s (1H, 4-H), 6.62–7.83 m (19H, H_{arom}), 10.47 s (2-H), 4.22 s (1H, NHCO), 4.27 s (1H, NHCO). Found, %: C 70.67; H 17.64; N 6.03. $C_{33}H_{35}N_7O_2$. Calculated, %: C 70.82; H 17.52; N 5.94.

5-(6,7-Dimethoxy-3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-ylidene)perhydro-1,2-oxazine-3,4,6-trione (III). Compound **Ib**, 2.27 g (0.01 mol), was dispersed in 10 ml of alcohol, and 2 ml of an aqueous solution of 0.83 g (0.012 mol) of hydroxylamine hydrochloride and 0.4 g (0.01 mol) of sodium hydroxide was added. The mixture instantaneously turned colorless. It was diluted with 100 ml of water, and the precipitate was filtered off, dried, and recrystallized. Yield 2.7 g (77%), colorless crystals, mp 270°C (decomp.). IR spectrum, ν, cm^{-1}: 1620, 1630, 1650 (C=O); 3100, 3300 (NH). ^{1}H NMR spectrum, δ, ppm: 1.48 s (6H, CH_3), 2.83 s (2H, 4-H), 6.92 s (1H, 5-H), 7.64 s (1H, 8-H), 8.93 s (2-H), 8.62 s

(1H, NHO), 3.72 s (3H, CH_3O), 3.83 s (3H, CH_3O). Found, %: C 58.82; H 5.10; N 8.91. $C_{17}H_{18}N_2O_6$. Calculated, %: C 58.93; H 5.22; N 8.83.

Ethyl 4-benzylamino-2-(3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-ylidene)-3,4-dioxobutanoate (IV) was synthesized as described above for compound **II**. Yield 3.1 g (76%), yellow crystals, mp 96–97°C. IR spectrum, ν, cm^{-1}: 1620, 1670, 1720 (C=O); 3100, 3290 (NH). ^1H NMR spectrum, δ, ppm: 1.61 s (6H, CH_3), 3.08 s (2H, 4-H), 1.22 t (3H, C**H**$_3$CH$_2$, J = 6.5 Hz), 4.12 q (2H, CH_2O, J = 6.5 Hz), 7.08–7.43 m (9H, H_{arom}), 10.48 s (2-H), 4.22 s (1H, NHCO), 4.42 d (2H, CH_2NH, J = 4.6 Hz). Found, %: C 70.73; H 6.57; N 7.03. $C_{24}H_{26}N_2O_4$. Calculated, %: C 70.91; H 6.45; N 6.89.

Ethyl 5,5-dimethyl-3-oxo-2-semicarbazono-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinoline-1-carboxylate (Va). A solution of 2.27 g (0.01 mol) of compound **Ia** in 70 ml of isopropyl alcohol was heated to the boiling point, and a solution of 1.12 g (0.01 mol) of semicarbazide hydrochloride and 0.4 g (0.01 mol) of sodium hydroxide in 5 ml of water was added. The mixture was heated for 1.5 h under reflux (TLC), cooled to 20°C, and diluted with 150 ml of water, and the precipitate was filtered off, dried, and recrystallized. Yield 3.0 g (85%), light orange crystals, mp 175–176°C. IR spectrum, ν, cm^{-1}: 1680, 1690, 1725 (C=O); 3150, 3410 (NH). ^1H NMR spectrum, δ, ppm: 1.52 s (6H, CH_3), 2.93 s (2H, 4-H), 1.28 t (3H, C**H**$_3$CH$_2$, J = 6.7 Hz), 4.18 q (2H, CH_2O, J = 6.5 Hz), 7.12–7.93 m (4H, H_{arom}), 6.72 s (2H, NH_2), 12.0 s (NH). Found, %: C 60.78; H 5.48; N 15.84. $C_{18}H_{20}N_4O_4$. Calculated, %: C 60.66; H 5.65; N 15.72.

Ethyl 5,5-dimethyl-3-oxo-2-thiosemicarbazono-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinoline-1-carboxylate (Vb). A solution of 2.27 g (0.01 mol) of compound **Ia** in 70 ml of isopropyl alcohol was heated to the boiling point, 0.91 g (0.01 mol) of thiosemicarbazide was added, and the subsequent procedure was the same as described above for the synthesis of pyrroloisoquinoline **Va**. Yield 3.1 g (84%), orange crystals, mp 204–205°C. IR spectrum, ν, cm^{-1}: 1690, 1720 (C=O); 3120, 3300 (NH). ^1H NMR spectrum, δ, ppm: 1.30 s (6H, CH_3), 2.95 s (2H, 4-H), 1.31 t (3H, C**H**$_3$CH$_2$, J = 6.6 Hz), 4.27 q (2H, CH_2O, J = 6.5 Hz), 7.14–7.85 m (4H, H_{arom}), 6.43 s (2H, NH_2), 12.92 s (NH). Found, %: C 57.95; H 5.53; N 15.15; S 8.47. $C_{18}H_{20}N_4O_3S$. Calculated, %: C 58.04; H 5.41; N 15.04; S 8.59.

***N*-Benzyl-3-(3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-ylidene)-4-morpholino-2,4-dioxobutanamide (VIIa)** was synthesized as described above for amide **IV**. Yield 3.7 g (82%), yellow crystals, mp 185–186°C. IR spectrum, ν, cm^{-1}: 1620, 1645, 1670 (C=O); 3150, 3400 (NH). ^1H NMR spectrum, δ, ppm: 1.05 s (3H, CH_3), 1.51 s (3H, CH_3), 2.73 s (1H, 4-H), 2.91 s (1H, 4-H), 7.22–7.83 m (4H, H_{arom}), 12.64 s (2-H), 4.52 d (2H, C**H**$_2$NH, J = 4.6 Hz), 3.03–3.62 m (8H, NCH_2CH_2O, ^3J = 4.6 Hz). Found, %: C 69.83; H 6.37; N 9.45. $C_{26}H_{29}N_3O_4$. Calculated, %: C 69.71; H 6.53; N 9.38.

***N*-Benzyl-3-(3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-ylidene)-4-piperidino-2,4-dioxobutanamide (VIIb)** was synthesized as described above for amide **IV**. Yield 3.5 g (78%), yellow crystals, mp 158–160°C. IR spectrum, ν, cm^{-1}: 1620, 1650, 1670 (C=O); 3120, 3380 (NH). ^1H NMR spectrum, δ, ppm: 1.07 s (3H, CH_3), 1.52 s (3H, CH_3), 2.72 s (1H, 4-H), 2.93 s (1H, 4-H), 7.13–7.92 m (9H, H_{arom}), 12.71 s (2-H), 4.53 d (2H, C**H**$_2$NH, J = 4.6 Hz), 1.42–2.03 m (6H, CH_2, ^3J = 6.0 Hz), 3.03–3.81 m (4H, CH_2N, ^3J = 5.5 Hz). Found, %: C 72.64; H 6.87; N 9.32. $C_{27}H_{31}N_3O_3$. Calculated, %: C 72.78; H 7.01; N 9.43.

4-(Azepan-1-yl)-*N*-benzyl-3-(3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-ylidene)-2,4-dioxobutanamide (VIIc) was synthesized as described above for amide **IV**. Yield 3.5 g (75%), yellow crystals, mp 155–156°C. IR spectrum, ν, cm^{-1}: 1620, 1650, 1670 (C=O); 3150, 3400 (NH). ^1H NMR spectrum, δ, ppm: 1.03 s (3H, CH_3), 1.31 s (3H, CH_3), 2.70 s (1H, 4-H), 2.92 s (1H, 4-H), 7.12–8.13 m (9H, H_{arom}), 12.68 s (2-H), 4.47 d (2H, C**H**$_2$NH, J = 4.6 Hz), 1.43–2.03 m (8H, CH_2, ^3J = 6.2 Hz), 3.02–3.83 m (4H, CH_2N, ^3J = 5.5 Hz). Found, %: C 73.08; H 7.32; N 9.23. $C_{28}H_{33}N_3O_3$. Calculated, %: C 73.17; H 7.23; N 9.14.

5,5-Dimethyl-1-(morpholinocarbonyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2,3-dione 2-thiosemicarbazone (VIII) was synthesized as described above for compound **Vb** (reaction time 4 h, TLC). Yield 2.9 g (70%), orange crystals, mp 140–142°C. IR spectrum, ν, cm^{-1}: 1670, 1680 (C=O); 3120, 3410 (NH). ^1H NMR spectrum, δ, ppm: 1.42 s (6H, CH_3), 2.92 s (2H, 4-H), 7.23–7.95 m (4H, H_{arom}), 6.72 s (2H, NH_2), 12.03 s (NH), 3.02–3.63 m (8H, NCH_2CH_2O, ^3J = 6.5 Hz). Found, %: C 57.96; H 5.43; N 17.02; S 7.69. $C_{20}H_{23}N_5O_3S$. Calculated, %: C 58.09; H 5.60; N 16.94; S 7.75.

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