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REACTIONS OF 2,3-DIOXOPYRROLO[2,1-*a*]-ISOQUINOLINES WITH ACTIVE N-NUCLEOPHILES

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It is shown that 2,3-dioxopyrrolo[2,1-a]isoquinolines react readily with aliphatic diamines and hydroxyamine with opening of the dioxopyrrole ring and formation of the corresponding bisenaminoketoamides and hydroxamic acids. Reaction with the thiosemicarbazide and hydrazides of aromatic acids proceeds without opening of the pyrrole ring at the ketone carbonyl. Derivatives of hexahydropyridazine are formed when compounds with carboxyethyl groups at position 1 react with hydrazine.

Keywords: aliphatic diamines, bisenaminoketoamides, hydrazides of aromatic acids, hydrazine, hydroxamic acids, hydroxylamine, 5,5-dialkyl-2,3-dioxopyrrolo[2,1-*a*]isoquinolines, perhydropyridazine, thiosemicarbazide.

It has been shown previously that 2,3-dioxopyrrolo[2,1-*a*]isoquinolines react with N-nucleophiles with opening of the pyrrole ring to give enaminohydrazides [1] and enaminoketoamides [2-4].

The objective of the present work was to investigate the dependence of the direction of the reaction on the structures of the N-nucleophiles. The most reactive compounds, such as aliphatic diamines, hydroxylamine, hydrazides of aromatic and heteroaromatic acids, and hydrazine, were chosen as the N-nucleophiles.

It was shown that the bisamides **2a,b** were formed on simply mixing compound **1a** with ethylenediamine or pentamethylenediamine in 2-propanol at 20°C. The hydroxamic acids **3a,b** were formed on heating solutions of **1a,b** in the same solvent for a short time with an excess of hydroxylamine. Analogously interaction of a derivative of benzo[*f*]isoquinoline with hydroxylamine gave compound **4**. When thiosemicarbazide or the hydrazides of benzoic, nicotinic, or isonicotinic acids were used as the nucleophile opening of the pyrrole ring did not occur and the imines **5a-d** were formed.

The dioxopyrroline **6** with a carbethoxy group at position 1 formed derivatives of perhydropyridazine **7** on opening of the pyrrole ring. The course of the reaction is readily controlled by the decoloration of the solution of the original substance, which is deep red with the exception of compounds **5a-d** which are orange, and for them reaction is monitored by TLC.

The fact that opening of the dioxopyrrole ring did not occur with thiosemicarbazide or the hydrazides (compounds **5a-d**) is explained by the lower reactivity of these nucleophiles in comparison with aliphatic amines, hydroxylamine, and hydrazine. It was shown previously that opening of the dioxopyrrole ring in compounds **1a,b** by N-nucleophiles was facilitated by acid catalysis (heating in glacial acetic acid) [4]. Investigation showed that on boiling (2 h) compound **1a** in acetic acid with the nucleophiles used to obtain compounds **5a-d**, ring opening did not occur and the same products were obtained as from simply boiling in alcohol (Table 1).

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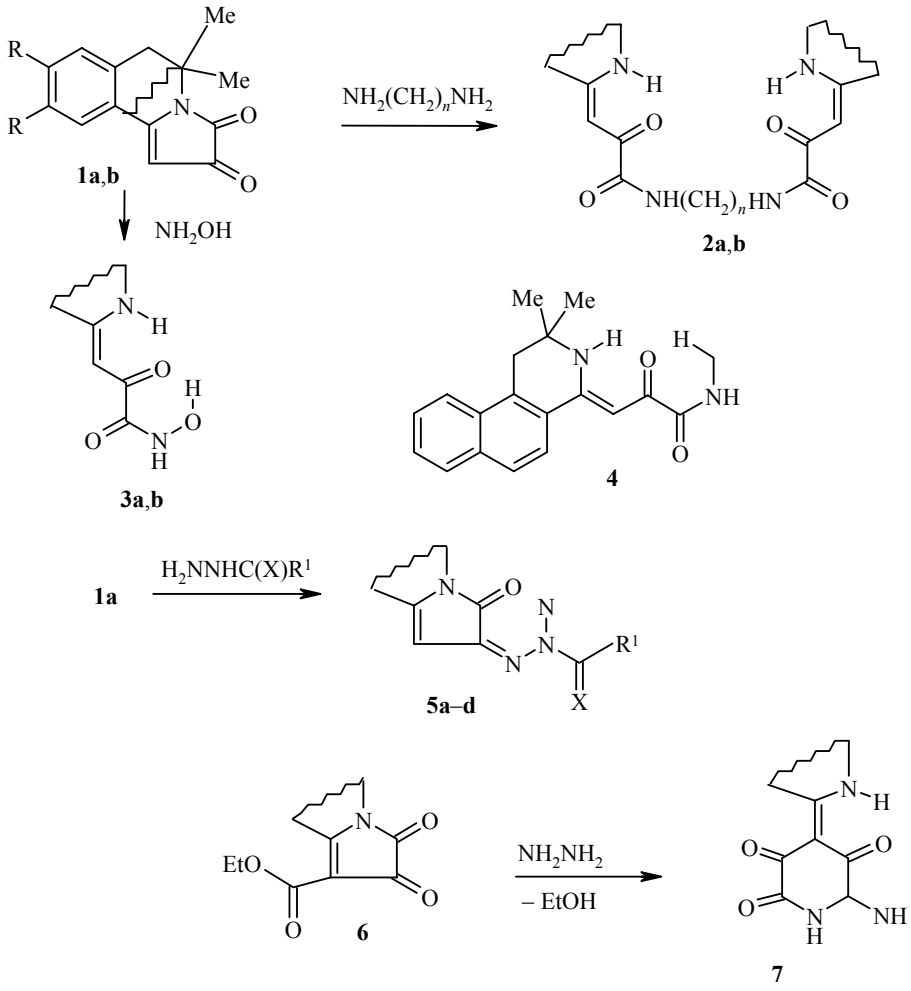

2 a *n* = 2, **b** *n* = 5; **3a** R = H, **b** R = MeO; **5 a** X = S, **b-d** X = O; **a** $R^1 = NH_2$, **b** R^1 = Ph, **c** R^1 = 2-pyridyl, **d** R^1 = 4-pyridyl

In the ^{1}H NMR spectra of amides **2a,b** (Table 2), in contrast to the spectra of the starting materials, singlets of the ring NH are present (11.65 and 11.60 ppm), the basic nature of which was confirmed by the shift to weak field on the addition of CF_3COOH, and also singlets of the amide NH (8.50 and 8.47 ppm) and the corresponding multiplets of the methylene group. The spectra of the hydroxamic acids **3a,b, 4** contain a singlet of the ring NH proton (11.35-11.50 ppm) and the hydroxamic NHOH unit (8.80-8.90 and 10.73-11.10 ppm). In the spectra of compounds **5a-d** the singlet of the ring NH proton is absent, but singlets for the proton of a NH group between two acceptor substituents are present (13.85-14.0 ppm). In the spectrum of compound **7**, in contrast to that of the starting material, the signal of the ethyl group is absent but the singlet for the NH proton of the isoquinoline ring is present (10.50 ppm). The protons of the NH groups of the hexahydropyridazine fragment appear as a singlet with an integrated intensity corresponding to two protons (4.75 ppm) which shifts to 10.0 ppm on addition of CF_3COOH.

The IR spectra of the ketoamides **2a,b** and the ketohydroxamic acids **3a,b, 4** contain broad bands in the 3000-3070 region (ring NH) and in the ketone carbonyl region (1615-1620 cm^{-1}) which correspond to the H-chelate form. The secondary amide group appears in the spectra of compounds **2a,b** as bands at 1670-1675 (C=O) and 3270-3280 cm^{-1} (NH). In the spectra of the hydroxamic acids **3a,b, 4** the NH–O group absorbs in the 3230-3270 cm^{-1} region. In the spectra of compounds **5a-d** the NH group appears as a band at

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
2a	$C_{30}H_{34}N_4O_4$	69.9 / 70.1	6.6 / 6.7	11.0 / 10.9	280 (dec.)	77
2b	$C_{33}H_{40}N_4O_4$	71.1 / 71.2	7.1 / 7.2	10.2 / 10.1	164-166	58
3a	$C_{14}H_{16}N_2O_3$	64.5 / 64.6	6.1 / 6.2	15.9 / 16.1	177-178	63
3b	$C_{16}H_{20}N_2O_5$	59.8 / 60.0	6.2 / 6.3	8.9 / 8.8	190-192	57
4	$C_{18}H_{18}N_2O_3$	70.9 / 71.1	5.8 / 6.0	9.0 / 9.1	260 (dec.)	74
5a*	$C_{15}H_{16}N_4OS$	59.8 / 60.0	5.3 / 5.4	18.8 / 18.7	182-183	62
5b	$C_{21}H_{19}N_3O_2$	72.8 / 73.0	5.3 / 5.5	12.1 / 12.2	224-226	60
5c	$C_{20}H_{18}N_4O_2$	69.1 / 69.3	5.1 / 5.2	16.3 / 16.2	233-235	61
5d	$C_{20}H_{18}N_4O_2$	69.1 / 69.3	5.0 / 5.2	16.1 / 16.2	226-228	59
7	$C_{15}H_{15}N_3O_3$	63.0 / 63.2	5.2 / 5.3	14.8 / 14.7	189-191	76

* Found, %: S 10.6; calculated, %: S 10.7.

TABLE 2. ^{1}H NMR Spectra of the Compounds Synthesized.

Compound	Chemical shifts, δ, ppm.						
	3(2)-$(CH_3)_2$, s	4(1)-CH_2, s	1(4)-HC=, s	Aromatic protons	NH cycle, s	Other NH protons, s, and OH, s	Other protons
2a	1.30	2.95	6.52	7.35-7.83 (4H, m)	11.65	8.50	3.33 (4H, m, $2CH_2$–N)
2b	1.28	2.95	6.51	7.65-7.85 (4H, m)	11.60	8.47	3.15 (4H, m, $2CH_2$–N); 2.93 (6H, m, $C(CH_2)_3C$)
3a	1.23	2.90	6.30	7.10-7.65 (4H, m)	11.40	8.80 and 10.90	—
3b	1.25	2.87	6.25	6.80 (s, H-5), 7.13 (s, H-8)	11.50	8.90 and 10.73	3.75 (2s, $2CH_3O$)
4	1.30	3.30	6.80	7.43-8.20 (6H, m)	12.35	8.90 and 11.10	—
5a	1.45	2.90	6.20	7.10-7.85 (4H, m)	—	8.50 (2H) and 11.00	—
5b	1.50	2.85	6.20	7.00-7.90 (9H, m)	—	13.85	—
5c	1.50	2.85	6.20	7.00-9.00 (8H, m)	—	14.00	—
5d	1.50	2.85	6.15	7.00-8.65 (8H, m)	—	14.00	—
7	1.25	2.90	—	7.10-8.10 (4H, m)	10.50	4.75	—

3100-3120, and the lactam carbonyl as a band at 1690-1700 cm^{-1}. The $NHNH_2$ group of the thiosemicarbazide unit absorbs at 3300 cm^{-1}. The IR spectrum of compound **7** contains absorption bands at 3050 (ring NH) and 3180 cm^{-1} (NH of hexahydropyridazine).

In the mass spectra* of the amides **2a,b** the most intense (100%) peak was 200, which corresponds to the loss of an amide group, for compound **2b** a molecular ion peak was observed at 557 (16%). The molecular ion 300 (100%) was the base peak in the mass spectrum of the thiosemicarbazone **5a**. Molecular ion peaks were observed in the mass spectra of compounds **5b-d**, at 345 (**5b**) and 346 (**5c,d**) all with 100% relative intensities.

The hydroxamic acids **3a,b,4** gave positive qualitative complex formation tests for the hydroxamic group [5]: brownish-red with $FeCl_3$ and dark-green with $CuSO_4$.

EXPERIMENTAL

^{1}H NMR spectra of compounds **2** and **5** were recorded with a Bruker DRX 500 (500 MHz) machine, all the rest with a Tesla BS 567 (100 MHz) machine in DMSO-d_6 with HMDS (δ 0.05 ppm) as internal standard. IR spectra of chloroform solutions (0.01 mol/l) or of nujol mulls (**5a**, **7**) were recorded with a Specord-80 spectrometer. Mass spectra were recorded with a MAT-311 instrument (70 eV, EI).

Purity of the substances obtained was monitored by TLC on Silufol UV-254 plates using the system acetone–ethanol–chloroform (1:3:6) with detection by iodine vapor.

Compound **5a** was recrystallized from benzene, compounds **3a, 4, 5b** from acetonitrile, and the rest from isopropanol.

Syntheses of the starting materials are described in [6] (**1a,b**) and [7] (**6**).

N,N'-Polymethylen-*bis*-3[3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-iden]-2-oxopropanamides 2a,b. The corresponding diamine (5 mmol) was added with stirring to a solution of **1a** (2.27 g, 10 mmol) in 2-propanol (10 ml) at 20°C. The red colored solution was decolorized in about 10 min. The mixture was diluted with water (100 ml), the precipitate was filtered off, dried and recrystallized.

N-Hydroxyamides of 3-[3,3-(R')$_2$-1,2,3,4-Tetrahydroisoquinolin-1-iden]-2-oxopropanoic Acids 3a,b and the N-Hydroxyamide of 3-(2,2-Dimethyl-1,2,3,4-tetrahydrobenzo[*f*]isoquinolin-4-iden)-2-oxopropanoic Acid (4). An aqueous solution (5 ml) of hydroxylamine hydrochloride (1.04 g, 15 mmol) and NaOH (0.52 g, 13 mmol) was added to a boiling solution of compounds **1a, b**, or 2,5-dimethyl-2,3,5,6-tetrahydronaphto[1,2-*g*]indolizin-2,3-dione [8] (10 mmol) in 2-propanol (15 ml). The red solution was instantly decolorized. The mixture was cooled to 20°C, diluted with water (150 ml), the precipitate was filtered off, dried and recrystallized.

5,5-Dimethyl-3-oxo-2-thiosemicarbazono-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinoline (5a), and the 5,5-Dimethyl-3-oxo-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinoliniden-2-hydrazides of Benzoic (5b), Nicotinic (5c), and Isonicotinic (5d) Acids. The corresponding N-nucleophile (10 mmol) was added to a boiling solution of compound **1a** (2.27 g, 10 mmol) in 2-propanol (70 ml, 250 ml for compound **5a**) and the mixture was boiled for 2 to 2.5 h (monitored by TLC), cooled to 20°C, and added to water (150 ml). The precipitate was filtered off, dried and recrystallized.

4-(3,3-Dimethyl-1,2,3,4-tetrahydroisoquinolin-1-iden)hexahydropyridazin-3,5,6-trione (7). Hydrazine hydrate (2 ml 70%, 15 mmol) was added to a mixture of ester **6** (3.0 g, 10 mmol) in 2-propanol (15 ml). The solution was instantly decolorized. The mixture was diluted with water (10 ml), the precipitate was filtered, dried, and recrystallized.

* Here and subsequently *m/z* values are given for ion peaks.

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