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ACYLATING AND ARYLSULFONYLATING ABILITY OF O-DERIVATIVES OF ISATIN 3-OXIMES

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O-Acyl and O-arylsulfonyl derivatives of isatin 3-oximes have been synthesized and their interaction with alcohols and amines has been investigated. It was established that none of the esters of 1-substituted isatin 3-oximes reacted with the indicated nucleophiles. 1-Unsubstituted O-aryl and O-arylsulfonyl derivatives react with amines as acylating agents even at room temperature, but O-acetyl derivatives only on heating. Acylamides or arylsulfamides respectively are formed in this way. O-Acyl derivatives do not react with alcohols at room temperature. Only O-benzoyl derivatives form ethyl benzoate on heating in ethanol. A comparative analysis of mass spectrometric data on the processes of acylation and arylsulfonylation is given.

Keywords: O-acetates, O-benzoates, and O-arylsulfonates of 2,3-indoledione 3-oximes, acylation and arylsulfonation, mass spectrometry.

We recently reported [1] that, on heating O-acetyl derivatives of 1-unsubstituted isatin 3-oximes with alcohols in the presence of triethylamine, N-(2-cyanoaryl)carbamates are formed in good yield as a result of fission of the $C_{(2)}$-$C_{(3)}$ bond of the heterocycle. O-Aroyl- and O-arylsulfonyl-substituted isatin 3-oximes are more reactive than the corresponding O-acetates.

Investigation of the analogous reaction with aliphatic and aromatic amines showed that only heating of the latter with O-arylsulphonates of isatin 3-oxime leads to fission of the intercarbonyl bond and the corresponding N-(2-cyanoaryl)carbamates are obtained in high yield [2]. O-Acetyl derivatives did not display such reactivity, but 1-methyl-substituted derivatives generally did not react.

In this connection we decided to investigate in more detail the interaction of a series of O-acyl-substituted isatin 3-oximes, where the acyl fragment is aliphatic, aromatic, or arylsulfonic acid residue, with alcohols and amines under various conditions (Schemes 1 and 2).

On adding aniline to a solution of O-acetates **1a** or **1e** in acetonitrile at room temperature no reaction was observed during 15 min, according to TLC data. However boiling these solutions for 20 min led to the disappearance of even traces of the initial esters, and acetanilide and O-unsubstituted oximes **2a** and **2c** respectively were isolated in good yield from the reaction mixture. However the O-benzoate **1b** reacted completely with aniline even under mild conditions (20°C, 15 h) with the formation of oxime **2a** and benzanilide **3b**.

We have established that the oxime O-acetate **1a** did not react with ethanol either under mild (20°C, 15 h) or under more rigid conditions (boiling in alcohol for 30 min). Each time it was isolated in unchanged form from the reaction mixture. The O-benzoate **1e** also did not react with ethanol at room temperature, however

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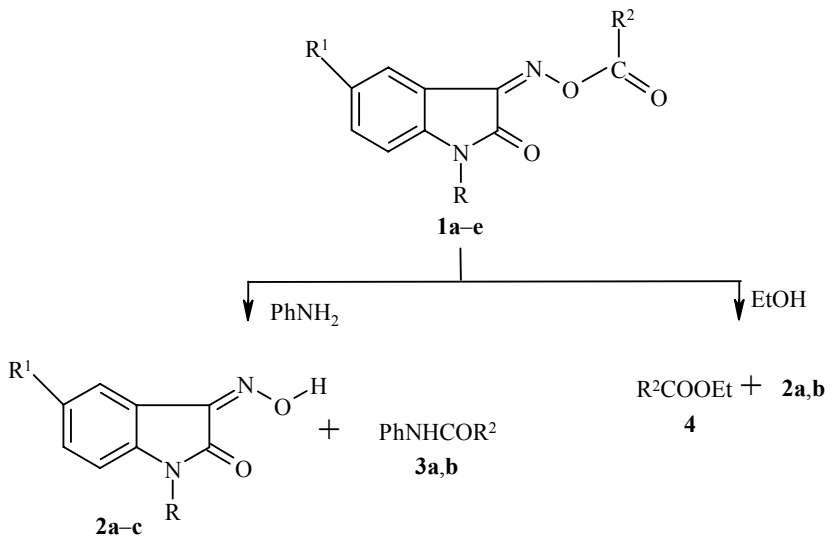
Scheme 1

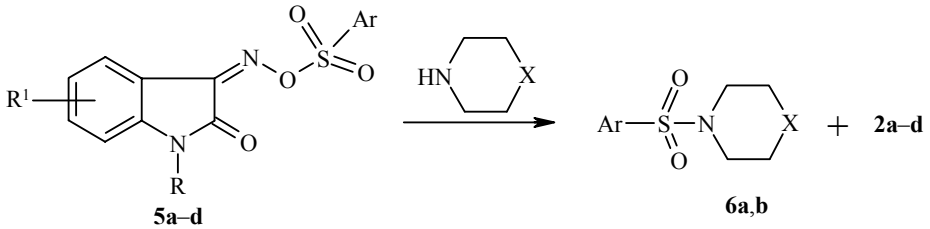


1 a, **b**, **e** R = H, **c**, **d** R = Me, **a-d** R^1 = H, **e** R^1 = Br; **a**, **c**, **e** R^2 = Me, **b**, **d** R^2 = Ph; **2 a**, **c** R = H, **b** R = Me, **a**, **b** R^1 = H, **c** R^1 = Br; **3 a** R^2 = Me, **b** R^2 = Ph; **4** R^2 = Ph

after boiling a solution in ethanol for 30 min the crystalline oxime **2c** was isolated from the reaction mixture in 62% yield, and the filtrate had the odor of ethyl benzoate. Crystals of benzamide (34% yield) were obtained by treating the filtrate with 25% ammonia solution. It must be stressed that oxime acetate **1c** and oxime benzoate **1d** did not react under any conditions with amines or with alcohols, and were isolated from the medium in unchanged form. Traces of oxime **2b** were successfully detected in the filtrate only by TLC.

Finally, the isatin 3-oxime O-arylsulfonates **5a,c,d** reacted smoothly with an excess of morpholine or piperidine in dioxane at room temperature with the formation in high yield of oximes **2a,c,d** and N-arylsulfonamides **6a,b**. The presence of substituents in the benzene ring had essentially no influence on the course of the indicated reactions.

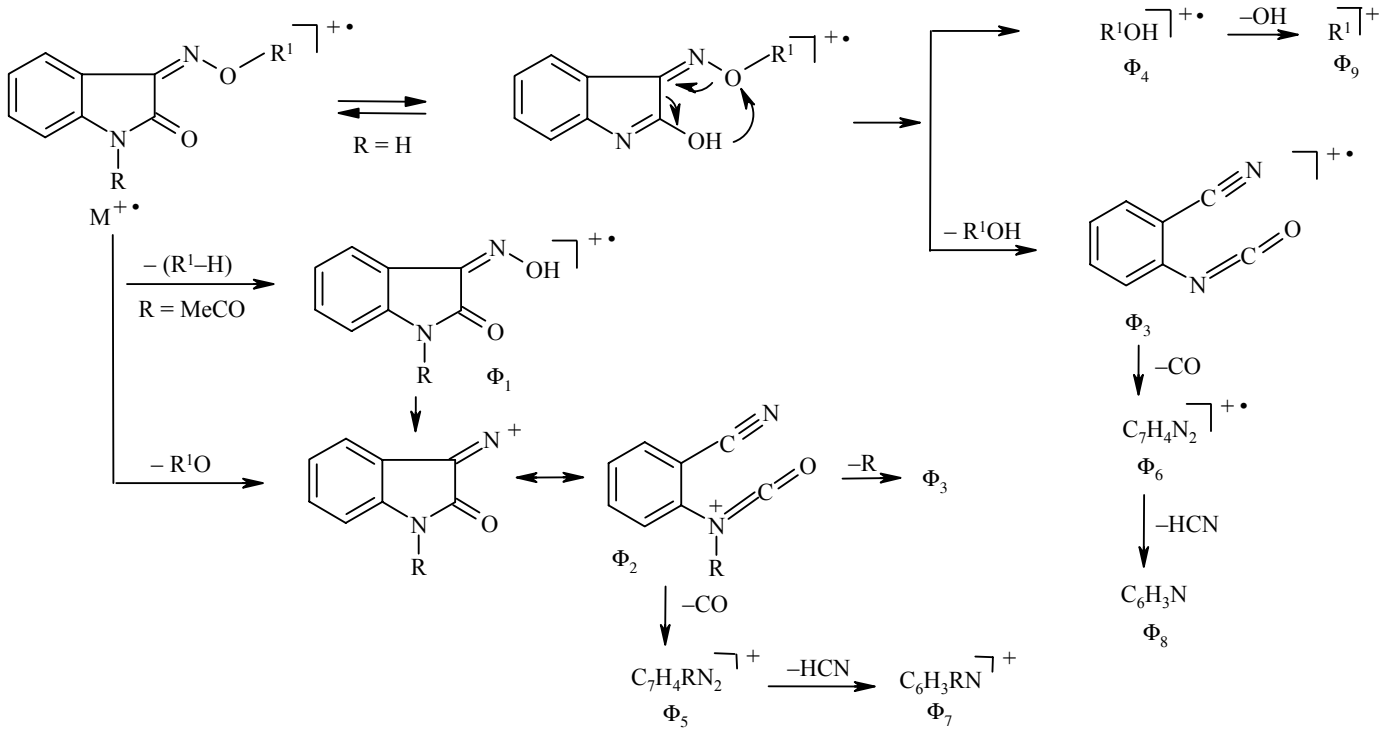
Scheme 2



5 a,**c**,**d** R = H, **b** R = Me, **a**,**b** R^1 = H, **c** R^1 = 5-Br, **d** R^1 = 5-Me, **a**, **c**, **d** Ar = $C_6H_4NO_2$-2, **b** Ar = C_6H_4Me-4; **2 a**, **c**, **d** R = H, **b** R = Me, **a**, **b** R^1 = H, **c** R^1 = 5-Br, **d** R^1 = 5-Me; **6 a** X = O, **b** X = CH_2, **a**, **b** Ar = $C_6H_4NO_2$-2

In the reaction of the 1-substituted derivative **5b**, 1-methyl-2,3-indoledione 3-oxime was detected only by chromatography, and a resinous substance was formed on heating on a water bath for 30 min. Such a clear difference in reactivity of the 3-oxime O-esters of isatin and 1-methylisatin is probably linked with the different lability of the $C_{(2)}$–$C_{(3)}$ bond of the heterocycle and also with the possibility in the case of the 1-unsubstituted compounds (and the impossibility for 1-substituted compounds) of tautomeric conversion into a 2-hydroxy form (Scheme 3).

Scheme 3



Such a form facilitates elimination of a molecule of acid (which is aided by base catalysis) with the formation of the reactive 2-cyanophenyl isocyanate molecule, interaction of which with nucleophiles, alcohols [1], amines [2], and hydrazines [3] , leads to the formation of urethanes, carbamides, and cyclization products of semicarbazides respectively.

In a less polar medium in the absence of base, attack of the nucleophile is directed to the electrophilic ester carbonyl-carbon (or sulfonyl-sulfur) atom with the formation of esters or amides and O-unsubstituted oximes.

The hypotheses expressed above are confirmed in our opinion by data of a comparative analysis of the mass spectra of the 1-methyl-substituted O-acetates **1a** and **1c**, O-benzoates **1b** and **1d**, and also the O-tosylate **5b** and the O-tosylate of 2,3-indole-2,3-dione 3-oxime (**5e**, R = H, Ar = C_6H_4Me-4). The synthesis and mass spectra of compounds **1a,c** and **5b,e** are given in [1], and the mass spectra of benzoates **1b,d** are given in Experimental.

It follows from the data of Table 1, that the stability (W_M) of the molecular ions of the 1-unsubstituted compounds is 1-2 orders of magnitude less than that of 1-methyl-substituted compounds, which is probably linked with the inability of the latter to tautomerize in the gas phase.

The primary decomposition of the molecular ions of O-acetates **1a,b** is linked first of all with loss of a molecule of ketene (Scheme 3) and with the formation of the odd-electron ion Φ_1, which then gives up a hydroxyl group (the sequence of these processes was confirmed by the corresponding metastable ions). In the case of the other unsubstituted O-esters the ion Φ_1 is formed directly from the molecular ion by fission of the N–O bond. The stability of this ion (fraction of the whole ion current) is significantly greater when R = Me. In all probability this ion is isomerized into 2-cyanophenyl isocyanate, since it then eliminates molecules of CO and HCN sequentially (ions Φ_5 and Φ_7).

The second breakdown path of the molecular ions of the 1-unsubstituted compounds is linked with cleavage of a molecule (or cation radical) of acid R^2OH by a McLafferty rearrangement (*ortho*-effect) with the formation of pseudomolecular ions of acid Φ_4 and 2-cyanophenyl isocyanate Φ_3. Such a process in fact models the reaction described by us previously of O-esters of isatin 3-monooximes with nucleophilic reagents [1-3]. Further decomposition of Φ_3 ions is linked with loss of molecules of CO and HCN.

Summarizing the dissociative ionization of these compounds we may note that the 1-unsubstituted compounds (**1a,b, 5e**) are characterized by low intensities for the molecular ion peaks and by intense peaks for the Φ_3, Φ_4, and Φ_6 ions.

The mass spectra of 1-substituted esters (**1c,d, 5b**) on the other hand are characterized by intense peaks for the molecular ions and the even-electron fragments Φ_2. However rearranged ions Φ_3 are completely absent from the mass spectra of these compounds. It may also be noted that the decrease in the stability of $M^{+\cdot}$ ions in

TABLE 1. Peak Intensities of Characteristic Ions in the Mass Spectra of Compounds **1a-d**, **5b,e** (ΣI, %)

Compound	W_M	Φ_1	Φ_2	Φ_3	Φ_4	Φ_5	Φ_6	Φ_7	Φ_8	Φ_9	$\Sigma_{\Phi 1\text{-}\Phi 9}$
1a	1.3	7.7	4.4	35.2	4.2	1.1	7.0	1.4	3.9	7.4	72.3
1c	9.8	5.2	16.9	—	—	6.3	0.7	2.2	1.3	8.6	41.2
1b	0.1	—	0.2	25.4	17.5	0.5	9.8	0.3	2.4	17.8	85.8*
1d	4.7	—	6.8	—	—	2.9	0.4	0.7	0.3	52.0	68.3*
5e	0.05	—	3.1	10.3	1.2	1.3	7.7	1.9	8.5	3.7	47.5*[2]
5b	5.9	—	15.5	—	—	2.8	0.5	2.5	1.9	8.6	71.9*[2]

* Including ions $C_6H_5^+$(77): **1b** [11.6]; **1d** [4.7].

*[2] Including ions $C_7H_7^+$(91): **2e** [9.8]; **2b** [34.4].

the series R^1 = MeCO > PhCO > Tos is not in agreement with their reactivity in the acylation of nucleophilic compounds (alcohols and amines), which may be used for mild selective acylation and arylsulfonation of polyfunctional organic compounds.

EXPERIMENTAL

The mass spectra of compounds were obtained on a Varian MAT-212 mass spectrometer with direct insertion of samples into the ion source. The energy of the ionizing electrons was 70 eV. Monitoring of the progress of reactions and the purity of the compounds obtained was effected by TLC on Silufol UV 254 plates in the systems: a) chloroform–acetone, 9:1, b) acetone–chloroform, 4:1, c) benzene–dioxane, 2:1, d) ethyl acetate–carbon tetrachloride, 1:1. Spots were detected with iodine vapor.

2,3-Indoledione 3-Oxime O-Acetate (1a) was obtained by the procedure of [1]; mp 130°C (chloroform). Mass spectrum, *m/z* (*I*, %): 204 (3) $[M]^+$, 162 (20), 144 (100), 116 (20), 91 (3), 90 (4), 89 (11), 65 (4), 63 (5), 62 (65), 60 (12).

2,3-Indoledione 3-Oxime O-Benzoate (1b). A solution of NaOH (2.4 g, 60 mmol) in water (20 ml) was added dropwise to a mixture of compound **2a** (8.1 g, 0.05 mol), benzoic anhydride (12.43 g, 55 mmol), and dilute (2:1) aqueous acetone (90 ml) with stirring and cooling to -5°C. The mixture was stirred for some time, diluted with water (100 ml), the solid filtered off, and dried. After recrystallization from chloroform, compound **1b** (11.3 g, 85%) was obtained; mp 135°C, R_f 0.17 (a). Found, %: N 10.36. $C_{15}H_{10}N_2O_3$. Calculated, %: N 10.52. Mass spectrum, *m/z* (*I*, %): 266 (0.4) $[M]^{+\cdot}$, 145 (11), 144 (100), 122 (68), 116 (20), 105 (4), 89 (10), 77 (45), 51 (18), 50 (10).

1-Methyl-2,3-indoledione 3-Oxime O-Acetate (1c) was obtained by the procedure of [1]; mp 154°C (chloroform), R_f 0.38 (a). Mass spectrum, *m/z* (*I*, %): 218 (19) $[M]^+$, 176 (100) $[M\text{-}CH_2CO]^+$, 159 (25) $[M\text{-}CH_3CO_2]^+$, 144 (3), 131 (6), 117 (3), 104 (3), 102 (3), 90 (4), 76 (4), 43 (47) $[CH_3CO]^+$.

1-Methyl-2,3-indoledione 3-Oxime O-Benzoate (1d) was obtained analogously to compound **1b** from 1-methyl-2,3-indoledione 3-oxime (**2b**) (1.76 g, 10 mmol), benzoic anhydride (2.44 g, 11 mmol), aqueous acetone (1:2) (70 ml), and NaOH (0.48 g, 12 mmol) in water (5 ml). Yield 2.4 g (86%); mp 178°C (chloroform), R_f 0.54 (a). Mass spectrum, *m/z* (*I*, %): 280 (8) $[M]^+$, 160 (6), 132 (3), 131 (6), 105 (100), 104 (3), 78 (2), 77 (9), 76 (2), 51 (5), 50 (2).

5-Bromo-2,3-indoledione 3-Oxime O-Acetate (1e) was obtained analogously to the previous experiment from 5-bromo-2,3-indoledione 3-oxime (**2c**) (2.41 g, 10 mmol), acetic anhydride (1.12 g, 11 mmol), acetone (30 ml), and NaOH (0.48 g, 12 mmol) in water (5 ml). Yield 2.7 g (95%); mp 146-147°C (DMF–chloroform, 1:3), R_f 0.28 (b). Found, %: Br 28.16; N 9.72. $C_{10}H_7BrN_2O_3$. Calculated, %: Br 28.27; N 9.89.

2,3-Indoledione 3-Oxime O-(2-Nitrobenzene)sulfonate (5a) was obtained analogously from compound **2a** (1.62 g, 10 mmol), 2-nitrobenzenesulfonyl chloride (2.44 g, 11 mmol), acetone (30 ml), and NaOH (0.48 g, 12 mmol) in water (5 ml). Yield 2.3 g (66%); mp 197-198°C (DMF–chloroform, 1:2), R_f 0.65 (c). Found, %: N 12.02; S 9.09. $C_{14}H_9N_3O_6S$. Calculated, %: N 12.10; S 9.22.

1-Methyl-2,3-indoledione 3-Oxime O-Tosylate (5b) was obtained by the procedure of [1]; mp 177-178°C (ethyl acetate). Mass spectrum, *m/z* (*I*, %): 330 (19) $[M]^+$, 159 (45) $[M\text{-}TosO]^+$, 155 (25) $[Tos]^+$, 144 (11) $[M\text{-}TosO\text{-}CH_3]^+$, 133 (20) $[M\text{-}TosO\text{-}CN]^+$, 131 (15) $[M\text{-}TosO\text{-}CO]^+$, 103 (5), 102 (8), 91 (100), 76 (5), 65 (19).

5-Bromo-2,3-indoledione 3-Oxime O-(2-Nitrobenzene)sulfonate (5c) was obtained analogously from 5-bromo-2,3-indoledione 3-oxime (**2c**) (2.41 g, 10 mmol), 2-nitrobenzenesulfonyl chloride (2.44 g, 11 mmol), acetone (20 ml), and NaOH (0.48 g, 12 mmol) in water (5 ml). Yield 3.44 g, 81%); mp >250°C (DMF–chloroform, 1:1). Found, %: N 9.69; S 7.62. $C_{14}H_8BrN_3O_6S$. Calculated, %: N 9.85; S 7.51.

5-Methyl-2,3-indoledione 3-Oxime O-(2-Nitrobenzene)sulfonate (5d) was obtained analogously to benzoate **1b** from 5-methyl-2,3-indoledione 3-oxime (**2d**) (1.76 g, 10 mmol), 2-nitrobenzenesulfonyl chloride (2.44 g, 11 mmol), acetone (20 ml), and NaOH (0.48 g, 12 mmol) in water (5 ml). Yield 2.54 g (70%); mp 199°C (DMF–chloroform, 1:3). Found, %: N 11.52; S 8.74. $C_{15}H_{11}N_3O_6S$. Calculated, %: N 11.63; S 8.86.

2,3-Indoledione 3-Oxime O-Tosylate (5e) was obtained by the procedure of [1]; mp 210-211°C (chloroform). Mass spectrum, *m/z* (*I*, %): 316 [missing M]$^+$, 145 (18) [M-TosO]$^+$, 144 (100) [M-TosOH]$^+$, 118 (14) [M-TosOH-CN]$^+$, 116 (40) [M-TosOH-CO]$^+$, 102 (2) $[C_6H_4CN]^+$, 91 (8) $[C_7H_7]^+$, 89 (23), 76 (7), 64 (15) $[SO_2]^+$, 62 (18).

Interaction of 2,3-Indoledione 3-Oxime O-Acetate (1a) with Aniline. A mixture of compound **1a** (2.04 g, 10 mmol), aniline (1.86 g, 20 mmol), and acetonitrile (15 ml) was boiled for 20 min and cooled to room temperature. The solid, consisting of 2,3-indoledione 3-oxime (**2a**), was filtered off. Yield 1.1 g (68%); mp 234-235°C (ethanol) (mp 234-236°C [4]). The filtrate was diluted with water (80 ml), the precipitated solid was filtered off, washed with water, dried, then recrystallized from benzene (with addition of activated carbon). Acetanilide **3a** (0.98 g, 72%) was obtained having mp 114°C, which corresponds to [5], R_f 0.25 (d).

Analogously from O-acetate **1c** only traces were obtained of the corresponding oxime **2b**, R_f 0.2 (b) and the initial **1c**.

Compound **2c** (1.2 g, 50%) was obtained analogously from **1e** (2.83 g, 10 mmol); mp 249-250°C (mp 250-251°C [6]). Acetanilide **3a** (0.92 g, 47%) of mp 114°C was also obtained.

Interaction of 2,3-Indoledione 3-Oxime O-Benzoate (1b) with Aniline. A mixture of aniline (3 ml, excess) and compound **1b** (2.66 g, 10 mmol) was stirred for several minutes and left at room temperature for 15 h. Acetone (10 ml) was added, the mixture stirred, the solid was filtered off, washed with acetone (5 ml), and recrystallized from ethanol. 2,3-Indoledione 3-oxime (**2a**) (1 g, 62%) was obtained; mp 233-234°C (mp 234-236°C [4]). The acetone filtrate was diluted with water (70 ml), acidified with dilute HCl to a weakly acid reaction, the solid was filtered off, and washed with water. After recrystallization from aqueous acetone (1:1) with activated carbon, benzanilide **3b** (1.2 g, 60.9%) was obtained of mp 162°C, which corresponds with the data of [5], R_f 0.25 (ethyl acetate–carbon tetrachloride, 1:1).

On carrying out the reaction in acetic acid (15 ml) the same result was obtained.

Interaction of 2,3-Indoledione 3-Oxime O-Benzoate (1b) with Ethanol. A mixture of compound **1b** (2.66 g, 10 mmol) and ethanol (15 ml) was heated on a water bath until complete solution and the heating continued for 30 min. The mixture was cooled, water (10 ml) added, the mixture stirred, the solid was filtered off, and washed with water (10 ml). After recrystallization compound **2a** (1.1 g, 68%) was obtained having mp 233-234°C (ethanol). A 25% aqueous ammonia solution (25 ml) was added to the filtrate with an odor of ethyl benzoate (**4**), the mixture was stopped, and shaked for 10-12 h. The solid was filtered off and washed with water. After recrystallization from water, benzamide (0.4 g) was obtained having mp 128-129°C (mp 129°C [5]).

Analogously from compound **1d** only traces of oxime **2b** were obtained in addition to the initial **1d**.

2-Nitrobenzenesulfomorpholide (6a). Analogously to the previous experiment compound **5a** (3.47 g, 10 mmol), dioxane (10 ml), and morpholine (1.7 g, 20 mmol) were stored for 15 h at room temperature. After separating oxime **2a** (60% yield); mp 234°C (234-236°C [4]), and diluting with water, the solid was filtered off, and recrystallized from ethanol with activated carbon to give compound **6a** (1.11 g, 40%) of mp 181°C. R_f 0.28 (ethyl acetate–carbon tetrachloride, 1:1). Found, %: N 10.34; S 11.68. $C_{10}H_{12}N_2O_5S$. Calculated, %: N 10.29; S 11.76.

Compound **6a** (37%) of mp 180-181°C, and compound **2d** (64%) of mp 202-204°C (ethanol) (mp 203-206°C [4]), were obtained analogously from compound **5d**.

2-Nitrobenzenesulfopiperidide (6b). Piperidide **6b** (1.4 g, 52%) of mp 95°C (ethanol) was obtained analogously to the previous experiment from compound **5a** (3.47 g, 10 mmol), dioxane (10 ml), and piperidine (1.7 g, 20 mmol) after separating oxime **2a** (40% yield). Found, %: N 10.24; S 11.93. $C_{11}H_{14}N_2O_4S$. Calculated, %: N 10.37; S 11.85.

Compound **6b** (1.5 g, 55%) of mp 95°C, and compound **2c** (1.51 g, 62%) of mp 249-251°C (mp 250-251°C [6]), were obtained analogously from **5c** (3.81 g, 10 mmol).

On carrying out the analogous reaction from compound **2b** (3.3 g, 10 mmol) no actual substances were successfully isolated from the resulting resinous mixture. Only traces of oxime **2b** were detected chromatographically (a) with the aid of a reference spot.

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