
**REACTIONS OF AROMATIC AMINES WITH 5-NITRO-3-FUROYL
AND 5-NITRO-2-FUROYL ISOTHIOCYANATES**

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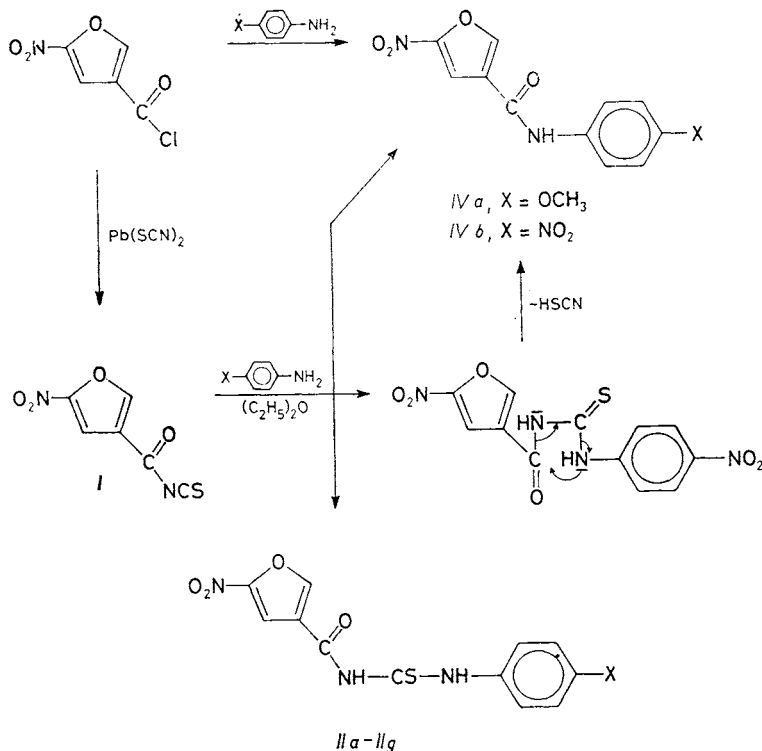
5-Nitro-3-furoyl isothiocyanate reacts with 4-X-anilines ($X = H, CH_3, OH, N(C_2H_5)_2, NHCOCH_3, Cl, Br$) to give the corresponding N-(5-nitro-3-furoyl)-N'-(4-X-phenyl)thioureas, in contrast to 4-methoxyaniline and 4-nitroaniline, which afford 5-nitro-3-furancarboxylic acid amides in a rather anomalous way. Formation of these amides is discussed and some properties of 2- and 3-substituted thioureas related to 5-nitrofurans are compared.

The known 5-substituted 2-furoylthiocarbonylides¹ and numerous further types of these compounds² are reported to exhibit an antibacterial activity. A high biological effect show also the well investigated 5-nitro-2-substituted furan derivatives³ some of which are utilized in practice⁴. So far, no much information is known on the biological activity and properties of 5-nitrofurans characteristic of one free α -position and variously substituted β -positions.

This paper presents the synthesis of N-(5-nitro-3-furoyl)-N'-arylthioureas prepared by reacting 5-nitro-3-furoyl isothiocyanate (*I*) with aromatic amines (Scheme 1). The starting isothiocyanate *I* was synthesized in 91% yield from 5-nitro-3-furoyl chloride and anhydrous lead thiocyanide in benzene. Substantially lower yields afforded the reaction with potassium, sodium or ammonium thiocyanides in acetone. It was found that treatment of isocyanate *I* with amines under conditions given in the experimental section afforded pure thioureas *II* when using 4-X-anilines with $X = H, CH_3, OH, N(C_2H_5)_2, NHCOCH_3, Cl$ and Br (Table I) only, where amines add to the NCS grouping. This reaction proceeds anomalously with 4-methoxyaniline and 4-nitroaniline, since no sulfur was found in the purified compound. Elemental analysis, spectral data and standards prepared by an alternative route show that the products are the corresponding amides of 5-nitro-3-furancarboxylic acid (*IVa, IVb*). The origination of these amides could be rationalized either by a direct substitution of the NCS group, or by an intramolecular degradation of the primarily formed thiourea.

To verify the above-mentioned possibilities, the isothiocyanate *I* was reacted with 4-methoxyaniline also at a lowered temperature ($-10^\circ C$) and the reaction course

was monitored by thin-layer chromatography on Silufol sheets. As found, even at such a temperature, where the reaction commences, exclusively the corresponding 4-methoxyphenylamide *IVa* was formed, thus evidencing a direct substitution of



SCHEME 1

isothiocyanate group by the amine. It is noteworthy that the isomeric 5-nitro-2-furoyl isothiocyanate does not yield the proper amide with 4-methoxyaniline, but N-(4-methoxyphenyl)-N'-(5-nitro-2-furoyl)thiourea of m.p. 173–177°C (ref.¹ 175–176°C). Melting point of this substance after crystallization from ethanol dropped to 148–150°C, but the mass and ¹H NMR spectra proved this compound to be pure thiourea. The change in m.p. might be due to polymorphism already reported with other nitrofuran derivatives⁵. Isothiocyanate *I* was treated with 4-nitroaniline at 0°C, because at a lower temperature the reaction did not proceed. The mixture was separated by chromatography over silica gel in benzene–ether 4 : 6 to give compound of m.p. 148–154°C, which is thermolabile both in crystalline form and in solution. Elemental analysis showed that the content of sulfur (7.01%) is approxi-

mately by 2.5% lower than required for thiourea, but its IR spectrum displayed a characteristic band of thiourea $\text{NH}-\text{C}=\text{S}$ at $1\,120\text{ cm}^{-1}$. Thin-layer chromatography on Silufol sheets showed that this compound in solution passed into the corresponding 4-nitrophenylamide *IVb* at about 5°C ; the latter can probably originate by an N,N-transacylation of the primarily formed thiourea (Scheme 1). A recrystallization of a sample afforded a product, which successively loses sulfur and its temperature rises up to that of the pure amide *IVb*. This decomposition route of thioureas was evidenced by the ^{15}N isotope when investigating thioureas synthesized from benzoyl isothiocyanate and aminoazoles⁶.

Some known^{1,7} and new N-(5-nitro-2-furoyl)-N'-arylthioureas *III* (Tables I, II) were synthesized (the analyses and spectral characteristics evidenced their thiourea

TABLE I
N-(5-Nitro-3-furoyl)-N'-(4-X-phenyl)thioureas *Ila*–*Ilg* and N-(5-nitro-2-furoyl)-N'-(4-X-phenyl)thioureas *IIIe*–*IIIg*

Compound X	Formula (M.w.)	M.p., °C Yield, %	Calculated/Found		λ_{max} , (log ϵ , nm	nm $\text{m}^2\text{ mol}^{-1}$)
			% N	% S		
<i>Ila</i> H	$\text{C}_{12}\text{H}_9\text{N}_3\text{O}_4\text{S}$ (291.3)	179–181 ^a (90)	14.43 14.41	10.98 10.35	242 (3.00)	298 (3.24)
<i>Ilb</i> CH_3	$\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_4\text{S}$ (305.3)	164.5–167 ^b (59)	13.77 13.26	10.05 9.95	236 (3.04)	294 (3.03)
<i>Ilc</i> OH	$\text{C}_{12}\text{H}_9\text{N}_3\text{O}_4\text{S}$ (291.3)	164–170 ^b (99)	14.42 14.43	10.99 10.51	245 (2.70)	292 (3.08)
<i>Ild</i> $\text{N}(\text{C}_2\text{H}_5)_2$	$\text{C}_{16}\text{H}_{18}\text{N}_4\text{O}_5\text{S}$ (362.4)	155–158 ^b (98)	15.46 15.45	8.85 8.88	236 (3.03)	272 (3.26)
<i>Ile</i> NHCOCH_3	$\text{C}_{14}\text{H}_{12}\text{N}_4\text{O}_5\text{S}$ (348.3)	165–171 ^b (96)	16.08 15.56	9.21 9.27	261 (3.14)	291 (3.12)
<i>Ilf</i> Cl	$\text{C}_{12}\text{H}_8\text{ClN}_3\text{O}_4\text{S}$ (325.7)	154–156 ^a (83)	12.90 12.23	9.85 9.49	239 (3.09)	291 (3.06)
<i>Ilg</i> Br	$\text{C}_{12}\text{H}_8\text{BrN}_3\text{O}_4\text{S}$ (370.2)	175.5–178 ^b (97)	11.35 11.22	8.66 8.52	254 (3.09)	289 (3.04)
<i>IIIg</i> NHCOCH_3	$\text{C}_{14}\text{H}_{12}\text{N}_4\text{O}_5\text{S}$ (348.3)	211–213 ^a (98)	16.66 16.31	9.52 9.30	265 (3.26)	—
<i>IIIe</i> Br	$\text{C}_{12}\text{H}_8\text{BrN}_3\text{O}_4\text{S}$ (370.2)	155–157 ^a (45)	11.35 11.34	8.64 8.71	239 (3.23)	303 (3.06)

Crystallized from: ^a ethanol; ^b methanol.

nature) to compare properties of 2- and 3-furan substituted thioureas. The structure of new compounds was backed by elemental and spectral analyses (Tables I, II). The IR spectra exhibited absorption bands $\tilde{\nu}(\text{NH})$ at 3 175–3 380 cm^{-1} , $\tilde{\nu}(\text{CO})$ at almost 1 670 cm^{-1} , $\tilde{\nu}(\text{NO}_2)_{\text{as}}$ at 1 540–1 530 cm^{-1} , and $\tilde{\nu}(\text{NO}_2)_{\text{s}}$ at 1 360–1 340 cm^{-1} . Bands indicative of $\text{NHC}=\text{S}$, furan $\tilde{\nu}(\text{C}-\text{O}-\text{C})$ and $\gamma(\text{CH})$ appeared

TABLE II
 ^1H NMR spectra of N-(5-nitro-3-furoyl)-N'-arylthioureas *II* and N-(5-nitro-2-furoyl)-N'-arylthioureas *III* (δ , ppm; *J*, Hz)

Compound X	H-2 ^a	H-4 ^b	H-2' ^c	H-3' ^c	<i>J</i> (2', 3') ^c
<i>IIa</i> H	8.77 d	8.11 d	7.25 —	7.87 m	—
<i>IIb</i> CH ₃	8.45 d	7.95 d	7.15 m	7.64 m	8.5
<i>IIc</i> OH	8.74 d	8.03 d	6.87 m	7.50 m	8.6
<i>IId</i> N(C ₂ H ₅) ₂	8.72 d	8.08 d	6.73 m	7.53 m	9.1
<i>IIe</i> NHCOCH ₃	8.74 d	8.08 d	7.68 ^d	7.68 ^d	—
<i>IIf</i> Cl	8.76 d	8.10 d	7.44 m	7.78 m	8.9
<i>IIg</i> Br	8.76 d	8.09 d	7.59 m	7.74 m	9.1
<i>IIIa</i> H	7.68 d	7.80 d	7.25 —	7.87 m	—
<i>IIIb</i> CH ₃	7.68 d	7.81 d	7.23 m	7.64 m	8.6
<i>IIIc</i> OCH ₃	7.69 d	7.82 d	7.97 m	7.75 m	9.0
<i>III d</i> NHCOCH ₃	7.69 d	7.82 d	7.69 ^d	7.69 ^d	—
<i>IIIe</i> Br	7.69 d	7.83 d	7.59 m	7.77 m	8.6

^a H-3 for compounds *IIIa*–*IIIe*; ^b for *IIa*–*IIg* *J*(1,4) = 1.1 Hz, for *IIIa*–*IIIe* *J*(3,4) = 3.9 Hz; ^c apostrophized numerals refer to *o*- and *m*-carbons of the benzene ring; ^d bs (4 H).

at 1120–1140, 1005–1080 and 850–870 cm^{-1} , respectively. The UV spectra (Table I) of all thioureas displayed two complex bands involving electronic transitions localized in the 5-nitrofuranyl and benzene moieties of the molecule; for 3,5-disubstituted derivatives *IIa–IIg* and for 2,5-disubstituted derivatives *III* the absorptions are at 236–261 nm, 272–298 nm and at 239–265 nm, 303–305 nm, respectively. Although the differences are not great, still the absorption bands for all 3-substituted derivatives are hypsochromically shifted up to 15 nm due to a weak delocalization of π -electrons in these compounds.

The ^1H NMR data of synthesized compounds are listed in Table II. The signals of protons H-2 and H-4 of 5-nitro-3-substituted derivatives *IIa–IIg* appeared at δ 8.45–8.77 and 7.95–8.11, respectively. The chemical shifts of protons H-3 and H-4 of derivatives *IIIa–IIIe* occurred at δ 7.68–7.69 and 7.80–7.83, respectively.

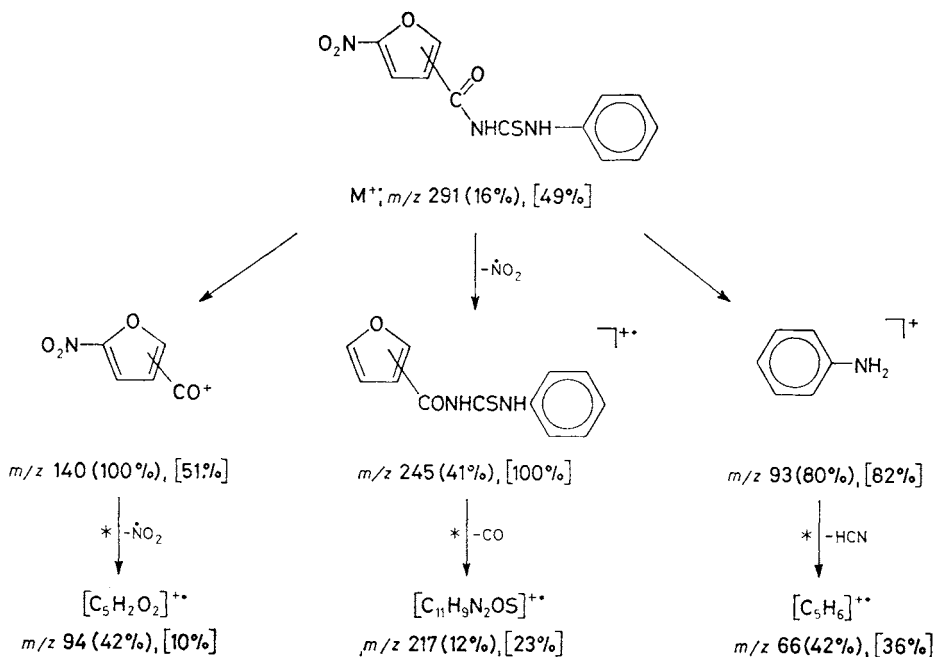
The fragmentation pattern of molecular radical ions of *II* and *III* is similar, nevertheless relative intensities of fragment ions being formed are considerably different (Table III, Scheme 2). Scheme 2 shows the relative abundances (in paren-

TABLE III
Mass spectral data of some compounds synthesized

Compound	m/z (relative abundances ^a)
<i>IIa</i>	291, $\text{M}^{+\cdot}$ (16), 140 (100), 93 (80), 135 (51), 77 (48), 94 (42), 245 (41), 66 (40), 99 (30), 65 (25), 51 (23)
<i>IIb</i>	305, $\text{M}^{+\cdot}$ (23), 140 (100), 106 (99), 107 (72), 149 (53), 91 (46), 259 (43), 94 (37), 77 (26), 99 (24)
<i>IIf</i>	325, $\text{M}^{+\cdot}$ (91), 251 (100), 55 (46), 192 (42), 111 (40), 138 (36), 253 (36), 327 (34), 75 (28), 324 (23)
<i>IIIa</i>	291, $\text{M}^{+\cdot}$ (51), 245 (100), 93 (84), 77 (77), 135 (68), 140 (54), 119 (51), 71 (38), 66 (38), 127 (33)
<i>IIIb</i>	305, $\text{M}^{+\cdot}$ (42), 259 (100), 106 (76), 149 (49), 107 (48), 91 (48), 140 (46), 133 (30), 71 (24), 77 (23)
<i>IIIc</i>	321, $\text{M}^{+\cdot}$ (42), 165 (100), 140 (65), 108 (61), 275 (55), 150 (48), 123 (36), 122 (29), 80 (18), 81 (16)
<i>IIId</i>	348, $\text{M}^{+\cdot}$ (10), 108 (100), 140 (97), 150 (72), 107 (52), 80 (33), 66 (27), 198 (10), 59 (10), 192 (8), 301 (3)
<i>IIIe</i>	369/371, $\text{M}^{+\cdot}/\text{M}^{+\cdot} + 2$ (27/27), 140 (100), 45 (85), 325 (72), 323 (68), 171 (67), 173 (64), 215 (52), 213 (50), 65 (46), 92 (43)

^a The table lists relative abundances of both $\text{M}^{+\cdot}$ and 9–10 most intense peaks.

theses) of 3,5-disubstituted *IIa* and in brackets those of the 2,5-disubstituted isomer *IIIa*.



SCHEME 2

EXPERIMENTAL

The melting points were determined on a Kofler micro hot-stage, the 1H NMR spectra of hexa-deuterioacetone solutions were measured with a Tesla BS 487 C apparatus operating at 80 MHz, tetramethylsilane being the internal reference. The IR, UV and mass spectra were recorded with UR 20 (Zeiss, Jena; 1 mg of substance per 300 mg of KBr), Specord UV VIS (Zeiss, Jena; $5 \cdot 10^{-5}$ mol l^{-1} dioxane solutions) and MS 902 S (AEI-Kratos; 70 eV electron energy, 120–140°C ion source temperature), respectively.

5-Nitro-3-furoyl Isothiocyanate (*I*)

Dry lead thiocyanide (11.3 g, 35 mmol) and 5-nitro-3-furoyl chloride (6.1 g, 35 mmol) in benzene were refluxed with stirring for 3 h under exclusion of air moisture. The inorganic products were filtered off, washed with benzene, the solvent was distilled off under diminished pressure and the residue was distilled. B.p. 143°C/2 kPa, yield 6.3 g (91%). The product was crystallized from ether-hexane, m.p. 39–40°C. For $C_6H_2N_2O_4S$ (198.2) calculated: 14.14% N, 16.16% S; found: 13.98% N, 15.47% S. IR spectrum, cm^{-1} : 1930 $\tilde{\nu}(NCS)$, 1700 $\tilde{\nu}(CO)$, 1540 $\tilde{\nu}(NO_2)_{as}$, 1360 $\tilde{\nu}(NO_2)_s$, 1060 $\tilde{\nu}(C-O-C)$, 850 $\gamma(C-H)$. 1H NMR spectrum: 7.82 d, 1 H (H-4); 8.73 d, 1 H (H-2).

N-(5-Nitro-3-furoyl)-N'-(4-X-phenyl)thioureas *IIa—IIg*

A mixture of 5-nitro-3-furoyl isothiocyanate (1.98 g, 10 mmol) in ether (25 ml) was added to the ethereal solution of the respective amine (10 mmol, 30–50 ml) at 5–10°C during 15 min. The mixture was stirred for 3 h and then left to stand at room temperature for 24 h. The separated yellow precipitate was filtered off and the product was crystallized from alcohol.

4-Methoxyphenylamide (*IVa*) and 4-Nitrophenylamide (*IVb*)
of 5-Nitro-3-furancarboxylic Acid

The particular amine (8 mmol) in a suitable solvent (10 ml) was successively added to a stirred dioxane solution (10 ml) of 5-nitro-3-furoyl chloride (0.7 g, 4 mmol) at 10–15°C. The mixture was poured into water after 15 min, acidified with dilute hydrochloric acid, the product was filtered off and crystallized from ethanol.

Amide IVa: m.p. 184–185°C, yield 75%. For $C_{13}H_{10}N_2O_5$ (262.2) calculated: 10.69% N; found: 10.79% N; M^{+} 262.

Amide IVb: m.p. 236–237°C, yield 50%. For $C_{11}H_7N_3O_6$ (277.2) calculated: 15.16% N; found 15.26% N; M^{+} 277.

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