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A Reaction of Nitroxides with Ethyl Mercaptane: A Mild Method for the Conversion of Nitroxides into Their Corresponding Amines

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Summary. The mild reduction of the nitroxides **1 a–j** to the corresponding sterically hindered amines **2 a–j** by means of ethyl mercaptane is reported. The reaction mixtures of **1 a, b, g** were analyzed by glc/ms.

Keywords. Reduction of nitroxides; Ethylmercaptane; Hindered amines.

Die Reaktion von Nitroxiden mit Ethylmercaptan: Eine milde Methode für die Umsetzung von Nitroxiden zu den entsprechenden Aminen

Zusammenfassung. Es wird über die milde Reduktion der Nitroxide **1 a–j** zu den entsprechenden sterisch gehinderten Aminen **2 a–j** mittels Ethylmerkaptan berichtet. Die Reaktionsmischungen von **1 a, b, g** wurden mittels GLC/MS analysiert.

Introduction

The reduction of nitroxides leads usually to corresponding hydroxyloamines (for reviews see e.g. Refs. [1, 2]). However, some chemical procedures have been developed for the conversion of nitroxides into their corresponding hindered amines. This has been observed when hydrogen over Raney nickel (e. g. [3]), copper (II) perchlorate [4], triethyl phosphite [5], methyl iodide [6], triiron dodecacarbonyl [7], sulphur dioxide [8], thiiram [9], disodium sulphide [10], and hydrogen sulphide [11] have been used as co-reagents. A reaction of 2,2,6,6-tetramethyl-4-oxopiperidine-1-oxyl (**1 a**) with a series of thiophenols was investigated by Murayama [12]. The corresponding hindered amine 2,2,6,6-tetramethyl-4-oxopiperidine (triacetonamine, **2 a**) was one of the identified products (yield 38%) [12]. Also in Ref. [10], the reducing ability of thiophenoxides was remarked. These examples demonstrate that an interaction between both inorganic and organic sulfhydryl groups and nitroxides takes place, and the formation of a hindered amine is observed. The interaction between sulfhydryl groups and nitroxides in biological systems causing the decay of the esr nitroxyl signal is well recognized, and reported in a large number of papers (e.g. [13–16]. In this communication the reaction of the nitroxides **1 a–j** with ethyl mercaptane is described.

Table 1. Amines **2a–j** obtained by ethyl mercaptane reduction of the nitroxides **1a–j**

Amine **2**	*Z*	Purification method	Yield %	Physical data m.p., b.p. (°C), $n_D^{temp.}$ (Ref.)
a	CH_2COCH_2	Twice sublimation[b]	16	m.p. 57.5–60.5 (55–60[a])
b	$(CH_2)_3$[c]	Distillation[d]	45	b.p. 140–150 (151–152 [1])
c	$CH_2CH(OH)CH_2$	Twice crystallization (xylene)	19	m.p. 127–130 (128–131[a])
d	$CH_2CH(OCOPh)CH_2$	Twice crystallization (hexane)	13	m.p. 90–93 (94–95[a])
e	$CH_2CH(OCOC_4H_9)CH_2$	Twice distillation, twice column chromatography[e]	26	b.p. $_1$99–100[f]
f	$CH_2CH=CH$	Twice distillation	13	b.p. $_8$35–37 ($_{14}$41–43[a]) n_D^{15} 1.4536
g	$CH_2CHClCH_2$	Distillation	26	b.p. $_{10}$82–84 ($_{13}$82[a])
h	bis-(2,2,6,6-tetra-methyl-4-piperidinyl)-sebacate	Crystallization (hexane)	17	m.p. 80.5–82.5 (83–84[h])
i	$CH=C(CONH_2)$	Twice crystallization (benzene, charcoal)	34	m.p. 176–179 (178–179 [1, 31])
j	CH_2CO	Distillation, column chromatography[g]	10	b.p. 173–174 (169 [31]) $n_D^{22.3}$ 1.4443 (^{24}1.446 [31])

[a] For references see [18]

[b] Triacetonamine hydrate is obtained

[c] The reaction mixture was acidified with buffers *pH* 2–6, but no difference in the yield and the purity of the **2b** was observed

[d] Glc analysis (OV-1, 70°C) was performed; the composition of the mixture before distillation: **1b** 22.4%, **2b** 77.6%, after distillation: **1b** 4.6%, **2b** 95.1%; in the artificial mixture (**1b** 13.2%, **2b** 86.8%) 86% of **2b** was calculated (area normalization)

[e] Elution with benzene, benzene/methanol 9/1, 3/1 methanol; elution was controlled with tlc (benzene/methanol 9/1)

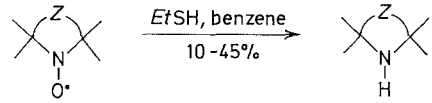
[f] The analytical data for **2e** (microanalysis): found C 69.47, H 12.37, N 5.42, calc. C 69.66, H 11.28, N 5.80; ms (*m*/e, int. %): 241 (0.9 *M*), 226 (9, *M*-CH_3), 140 (11), 124 (100, *M*-CH_3 – C_4H_9COOH), 58 (29); ir (film), ν (cm^{-1}): 1710 (C=O), 3300 (NH); ^{1}H-nmr ($CDCl_3$/*TMS*), δ, *J* (Hz): 0.92 [t, 3H, CH_3 (butyl C-4), *J* = 6.1], 1.15 [s, 6H, 2 × CH_3 (ring, ax)], 1.24 [s, 6H, 2 × CH_3 (ring, eq)], 1.53 [m, 4H, CH_2CH_2 (butyl C-3, C-2)], 1.91 [dd, 2H, $CH[H]_{eq}$ $CH[H]_{eq}$ (ring), *J* = 12.7, 4.2], 2.27 [t, 2H, $COCH_2$ (butyl C-1), *J* = 7.0], 5.19 [tt, 1H, CH (ring), *J* = 11.5, 4.2], the interpretation is in agreement with that of **2c** [32]; ^{13}C-nmr ($CDCl_3$/*TMS*), δ: 13.65 [q, CH_3 (butyl C-4)], 22.21 [t, CH_2 (butyl C-3)], 27.09 [t, CH_2 (butyl C-2)], 29.09 [q, CH_3 (ring)], 34.40 [t, CH_2 (butyl C-1)], 43.94 [t, CH_2 (ring)], 51.42 [s, $C(CH_3)_2$], 68.43 (d, CH), 173.16 (s, C=O)

[g] Elution with benzene/methanol 95/5

[h] Recrystallized (hexane) industrial sample of Ciba-Geigy – Tinuvin 770

Results and Discussion

Simple mixing of the nitroxides **1 a–j**, ethyl mercaptane and benzene leads to a colourless mixture of products. After purification, the isolation of the amines **2 a–j** is possible. The yields are not high, and the reaction mixture requires a thorough

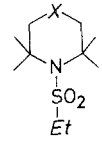


1 a-j **2 a-j**

purification, but the presented method is of practical synthetic importance due to valuable advantage: ethyl mercaptane is a reductor which under mild reaction conditions (neutral solvent-benzene, room temperature) does not affect other functional groups in a nitroxide molecule, but it converts [in contrary to the widely cited (e.g. [4]) opinion expressed in [2] (p. 229)] a nitroxide into the corresponding hindered amine, that means a farther reduction than into the corresponding hydroxylamine as usual reductors do.

The amines synthesized are summarized in Tables 1, 2.

In order to evaluate the other possible products of the reaction, the reactions mixtures after the reduction of **1 a, b, g** have been analyzed with the glc/ms technique. In the all three cases the presence of the eight substances has been discovered. The percentage of the identified (ms) compounds in the mixture is presented in Table 3.



3

The mass spectra of sulphonamides **3** are presented in Table 4. Similarities of the all three mass spectra and the characteristic fragmentations for the hindered piperidine ring [17, 18] – M, M-CH_3, M-CH_3-HCl (in the case of **3 g**) – strongly support the proposed structures for **3 a, b, g**. Murayama [12] examined the reaction of **1 a** with thiophenols. The presence of about 10% amide with a slightly different structure (sulfinyl group instead sulfonyl one – as in **3**) was identified in Ref. [12].

Experimental

Melting points are uncorrected; ms and glc/ms: LKB 9 000 A (EI, 70 eV); ir: Specord IR-75, Beckman IR-12; ^{1}H-nmr: Tesla BS 567 A (100 MHz); ^{13}C-nmr: Jeol FX 90 Q (22.5 MHz); glc: Chromatron GCHF 18.3 (FID); column chromatography: silica gel G, 70–230 mesh (Merck 7754); tlc: silica gel GF_{254} (Merck 5562, 5554), visualisation – uv 254 nm, iodine vapours, dipicrylamine.

Starting nitroxides **1 a–j** have been synthesized according to known procedures (sometimes with modifications): **1 a** [19–21], **1 b** [22], **1 d** (see also below), **g** [1, 23], **1 f, j** [1], **1 i** [1, 24].

1 c: oxidation of **2 c** (30% hydrogen peroxide, sodium tungstate, *EDTA*Na_2), stirring 20 h, extraction from acidified water solution [24, 25], yield 83%, m.p. 70–71°C (cyclohexane).

1 e: esterification of **1 c** (valeryl chloride, triethylamine, dry benzene) [26–28], yield 72%, b.p. $_3$160–168 °C, tlc (eluent, R_f): benzene/methanol 3/1, 0.71, benzene/ethyl acetate 1/1, 0.65, carbon

Table 2. Ms and ir spectra of the amines **2a–d, f–j**[a] obtained by ethyl mercaptane reduction of the nitroxides **1a–d, f–j**

Amine **2**	ms (*m*/e, int.%)	ir, ν (cm^{-1})
a	155 (11, *M*), 140 (100, *M*-CH_3), 112 (7), 98 (19), 84 (28), 83 (81), 58 (65), 55 (19), 42 (51)	3600, 3250, 3150, 2200, 1700, 1300[c]
b	141 (6, *M*), 126 (100, *M*-CH_3), 98 (4), 70 (27), 69 (15), 58 (29), 42 (22), 41 (20)	1370, 1240, 1130[d]
c	157 (3, *M*), 142 (100, *M*-CH_3), 124 (8), 107 (3), 86 (13), 85 (12), 58 (81), 42 (16), 41 (10)	3250, 3200, 1400, 1090[c]
d	261 (1, *M*), 246 (18, *M*-CH_3), 124 (100), 105 (15), 77 (11), 58 (17)	3500, 3350, 1750, 1650, 1320, 1160[c]
f	139 (3, *M*), 124 (100, *M*-CH_3), 107 (15), 82 (17), 67 (15), 58 (24), 42 (17), 41 (11)	1650, 1350, 1230, 1130[d]
g	175 (4, *M*), 160 (100, *M*-CH_3)[b], 140 (16), 124 (35), 107 (21), 58 (67), 55 (25), 42 (40), 41 (34)	3300, 3250, 1450, 1360, 1230[d]
h	480 (1, *M*), 465 (13, *M*-CH_3), 140 (12), 124 (100), 58 (16)	3400, 3300, 1700, 1150[c]
i	168 (0.4, *M*), 153 (51, *M*-CH_3), 110 (100), 95 (18)	3330, 3160, 1650, 1590[c]
j	141 (4, *M*), 126 (10, *M*-CH_3), 113 (38), 98 (15), 71 (7), 70 (7), 58 (100), 57 (18), 42 (37), 41 (14)	3450, 3330, 1730, 1350, 1180[d]

[a] For the full analytical data of **2e** see footnote [f] of Table 1

[b] In the ms spectrum of the independently synthesized **2g** the intensities of *m*/e 160 and *m*/e 58 were inverted: 160 (81, *M*-CH_3), 58 (100)

[c] KBr

[d] Film

Table 3. Percent[a] of identified substances (based on glc/ms) in the reaction mixtures after the reduction of **1a, b, g** with ethyl mercaptane

Identified (ms) substance	Starting nitroxide radical		
	1a	**1b**	**1g**
Diethyl disulphide	9.6	21.2	18.6
Amine **2a, b, g**	71.2	44.7	54.4
Sulphonamide **3a, b, g** (see Table 4)	9.9	16.3	18.1
Starting nitroxide **1b, g**	–	3.6	3.3
Hydroxylamine corresponding to the nitroxide	1.0	–	–
Other substances	8.3	14.2	5.6

[a] Area normalization

Table 4. Mass spectra of the sulphonamides **3a, b, g**

3	*X*	ms (*m*/e, int.%)
a	C=O	247 (1, *M*), 232 (23, *M*-*-CH_3), 83 (100)
b	CH_2	233 (1, *M*), 218 (26, *M*-CH_3), 109 (100)
g	CHCl	267 (1, *M*), 252 (37, *M*-CH_3), 216 (100, *M*-CH_3-HCl)

tetrachloride/methanol 3/1, 0.67; ms (*m*/e, int. %): 265 (34, *M*), 241 (55, *M*-*-CH_3), 140 (100, *M*-CH_3-C_4H_9COO); ir (KBr), ν (cm^{-1}): 1735 (C=O).

1d, h: oxidation of **2d** or **2h**, respectively (30% hydrogen peroxide, sodium tungstate, *EDTA*Na_2, methanol, acetonitrile) [29], stirring several days, extraction from acidified water solution. **1d**: yield 54%, m.p. 104–106°C (methanol) [1, 23]; **1h**: column chromatography, elution with benzene/methanol 95/5, yield 10%, m.p. 98.5–100.5°C (hexane) [1, 30], tlc (eluent, R_f): benzene/methanol 9/1, 0.54, benzene/methanol 3:1, 0.65; ms (*m*/e, int %): 510 (13, *M*), 495 (4, *M*-CH_3), 480 (2), 356 (19), 155 (15), 140 (46), 124 (100), 109 (46); ir (KBr), ν (cm^{-1}): 1710 (C=O).

Independently Obtained Samples of the Hindered Amines

The samples of the hindered amines **2a–d, f–j** have been independentely synthesized according to known procedures: **2a, c, d, f** – references cited in [18], **2b** [1], **2i** [1, 31], **2j** [31]; **2g**: (by-product in the **2f** synthesis) yield 11%, b.p. $_{10}$82–84°C; **2h**: industrial sample from Ciba-Geigy-Tinuvin 770, m.p. 83–84°C (hexane). The physical and ms, ir data of the independentely synthesized hindered amines have been used for the identification of the amines **2a–d, f–j** isolated after the title reaction.

Reduction of the Nitroxides with Ethyl Mercaptane, General Procedure

The radical (**1a, c, d, f** – about 10 mmol, **1g, h, i, j** – about 2 mmol, **1e** – 19.5 mmol, **1b** – 56.4 mmol), excess of ethyl mercaptane (about 5 ml/1 g of the nitroxide) and benzene (**1f**-hexane, **1i**-methanol) (about 2.5 ml/1 ml of ethyl mercaptane) are mixed. After the reaction has been completed (solution becomes colourless), the mixture is extracted with 1 mol/1 hydrochloric acid. The acidic layer is carefully basified with potassium carbonate and extracted with dichloromethane. The organic layer is dried with magnesium sulphate, filtered off and evaporated. The crude amine is purified (distillation, crystallization, sublimation or chromatography). The methods of the purification, yields and physical data for the obtained amines are presented in Table 1. Mass and infrared spectra are presented in Table 2. The isolated amines **2a–d, f–j** are identified by comparison of their physical and spectral (ms, ir) data with those of the authentic, independentely synthesized samples and with the literature data.

Glc/ms Analysis

0.5 mmol of the nitroxide (**1a, b, g**) is dissolved in 1 ml of benzene, and 1 ml of ethyl mercaptane is added. After 24 h the excess of ethyl mercaptane is evaportated and benzene + methanol is added (0.5 ml + 0.5 ml). The reaction mixture is analyzed by glc/ms (2 m glass column, 3% OV-101 on Chromosorb G, program: 130°C, 8 min, 130°C to 200°C, 10°C/min, sample size: 1–2 μl). The results are presented in Tables 3 and 4.

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