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N-NITROSAMINES AS REAGENTS FOR THE $\rangle C{=}S \rightarrow \rangle C{=}O$ TRANSFORMATION

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Abstract—N-nitrosopiperidine and N-nitroso-N-methylaniline react in acidic solution with thiocarbonyl compounds to give the corresponding carbonyl analogues. Secondary- and tertiary thioamides, xanthione, thio- and dithiobutyrolactone, thiocoumarin, certain thiourea derivatives, dithio-O,O-thiocarbonic, S,S-trithiocarbonic- and N,N disubstituted thiocarbamic esters are all converted into the corresponding O-analogues. Thiobenzamide and N-phenylthiourea yield 1,2,4-thiadiazoles. All the reactions are run with iodide (I^-) as NO^+-carrier. The kinetics of the reaction have been studied under pseudo-first order conditions, and the reaction rate is proportional to the Pearson's nucleophilicity parameter of ions. The $\rangle C{=}S \rightarrow \rangle C{=}O$ transformation is also found to take place in gastric juice.

Different methods for the transformation of thiocarbonyl compounds into their corresponding oxo-analogues are known: sodium nitrite in aqueous acid solution,[1] potassium t-butoxide,[2] sodium ethoxide,[2] sodium hydroxide with halogens under conditions of phase transfer catalysis,[2] DMSO/acids,[3,4] DMSO/I_2,[5] bis(*p*-methoxyphenyl) telluroxide,[6] benzeneselenic anhydride,[7] diaryl selenoxide,[8] and dimethyl selenoxide[9] have all been used for this transformation.

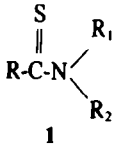
N-nitrosamines belong to a class of compounds whose biological activities have been widely investigated during the last few decades due to their mutagenic and carcinogenic nature.[10] However, less attention has been given to their chemical properties. Transnitrosation which is defined as the transfer of a nitroso group from one N-nitrosamine to another amine,[11] is a well known characteristic reaction of aromatic-[12-15] and aliphatic N-nitrosamines.[11,16] Transnitrosation is also catalyzed by species such as Cl , Br^-, I^- and SCN^- which fits the HSAB (hard and soft acids and bases) principle.[17-23] Nitrosation of amines is also catalyzed by the same species.[18,21] Sodium nitrite and N-nitroso-N-methylaniline in acidic solution have been used for nitrosation of thiourea.[17,24,25] In these reactions S-nitrosation occurs to give the intermediate $(NH_2)_2\overset{+}{C}\text{-S-NO}$ which decomposes to give CC' - dithiodiformamidinium ion: $(NH_2)_2\overset{+}{C}SSC(NH_2)_2\overset{+}{}$ and NO. These results can also be accounted for by the HSAB-principle: NO^+ belongs to the group of borderline acids with a tendency to be soft,[26] and, in accordance with Savilles rule stating that soft-soft (hard-hard) interaction is preferred,[27] NO^+ attacks the soft sulfur in the thiocarbonyl function[28] with formation of an S-nitroso compound.

As an extension of our work involving nitrosation of thiocarbonyl compounds in aqueous acid solution with formation of the corresponding O-analogues[1,29] this paper presents the $\rangle C{=}S \rightarrow \rangle C{=}O$ transformation for a series of thiocarbonyl compounds using either N-nitroso-N-methylaniline (NMA) or N-nitrosopiperidine (NP) as nitrosation reagents in aqueous acid solution with I^- as a NO^+-carrier. A new aspect of the Fischer-Hepp rearrangement is presented. The kinetics of the transformation have been studied with different nucleophilic ions and with cysteine as carriers of NO^+.

RESULTS AND DISCUSSION

(a) *Synthetic aspects.* It is found that the reaction of NMA or NP with thiocarbonyl compounds in acidic solution and potassium iodide yields the corresponding carbonyl compounds (Table 1).

Thioamides, **1b–e** are all transformed into the corresponding amides by this reaction.



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a: R = –Ph; $R_1 = R_2 = -H$
b: R = –Ph; $R_1, R_2 = -(CH_2)_2-O-(CH_2)_2-$
c: R = –Ph; $R_1 = R_2 = -CH_3$
d: R = $-CH_2$–Ph; R_1 = –Ph; $R_2 = -H$
e: R = –H; $R_1 = R_2 = -CH_3$

Cyclic thiocarbonyl compounds such as N-methyl-2-thiopyrrolidone, **2**, xanthione, **3**, thio-butyrolactone, **4**, dithiobutyrolactone, **5**, thiocoumarin, **6**, are all transformed into the corresponding O-analogues in reasonable yields.

The thioureas, **7a–c**, the dithio, S,S-trithiocarbonic, O,O-thiocarbonic and N-ethyl-N-phenyl-O-ethyl-carbamic esters, **8–11** respectively give also the carbonyl compounds.

Thiobenzamide, **1a** and phenylthiourea, **7d** react in a quite different way: Thiobenzamide reacts with NMA and KI in acidic solution to give 3,5-diphenyl-1,2,4-thiadiazole, **12**[30] and phenylthiourea reacts with NP under the same conditions to give 5-imino-4-phenyl-3-phenyl

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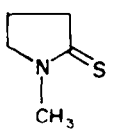

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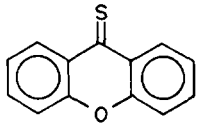

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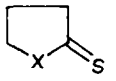
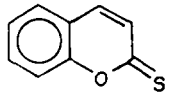


4: X=O
5: X=S



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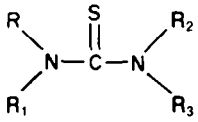

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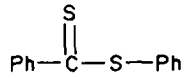

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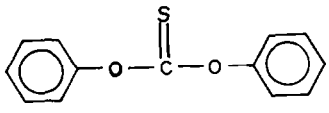
a: R=R₁=R₂=R₃=-CH₃
b: R=R₂=-H; R₁=R₃=-C₆H₁₁
c: R=R₁=R₂=-CH₃; R₃=-H
d: R=R₁=R₂=-H; R₃=-Ph



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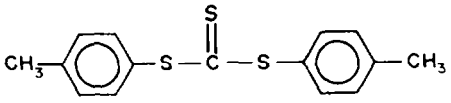

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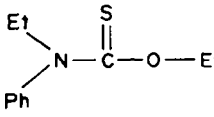

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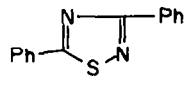

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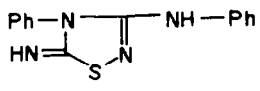

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amino-4,5-dihydro-1,2,4,-thiadiazoline, **13**[31] and traces of phenylurea (<5%).

All the reactions are run with equimolar amounts of the thiocarbonyl compounds and potassium iodide and 10% excess of NP or NMA. When no potassium iodide is present the reaction rate is very low. The reaction of thiocoumarin, **6** with NP in 4M HI gives only 5% (GLC) of coumarin after 24 hr.

Both NP and NMA are able to act as NO^+-donors, and two examples (Table 1) show only very small differences in yields, but longer reaction time is required when NP is used. This difference in the time can be related to their

Table 1. Experimental data for the $\rangle C{=}S \rightarrow \rangle C{=}O$ transformation

Compound	NP[a] (NMA[b])[c]	
	reac. time (hrs.)	yield (%)
1b	17 (3)	92 (89[d])
1c	50	94; (95[d])
1d	48	65[d]
1e	48	64[d]
2	22 (2½)	65 (72)
3	5	100
4	24	83
5	24	95
6	24	83
7a	48	85
7b	48	86[d]
7c	48	73d
8	44	64
9	43	78
10	55	73[d]
11	(16)	(57)

a: NP - N-nitrosopiperidine;

b: NMA - N-Nitroso-N-methylaniline;

c: The results for NMA are given in the brackets.

d: Based on GLC analyses, the others are isolated yields.

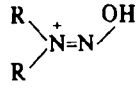
For the reaction of 1a and 7d with NMA and NP, see experimental section.

respective activation energies (E_A(NMA) 60kJ/mole; E_A(NP) 120 kJ/mole)[14], consistent with the faster reaction with NMA.

For the reaction of **1a** and **7d** with NMA and NP, see Experimental .

(b) *Mechanism and kinetics.* In attempts to use aliphatic N-nitrosamines for transnitrosation, no reaction takes place unless a suitable carrier is present. Transnitrosation takes place in 3M HCl (Cl^- acts as carrier/catalyst)[16,32] whereas no reaction takes place in 3M $HClO_4$,[33] since the perchlorate ion belongs to the class of very hard bases[34] (a very weak nucleophile). Aromatic N-nitrosamines can effect transfer by a direct uncatalyzed reaction[14,21] depending on the nature of the substrate.

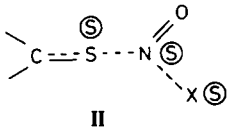
Different sites for the protonation are possible: in very strong acidic media O-protonation (I) has been observed in NMR studies,[35] which is in accordance



I

with the dipolar structure of N-nitrosamines, whereas in dilute acidic media UV-experiments show protonation at several sites.

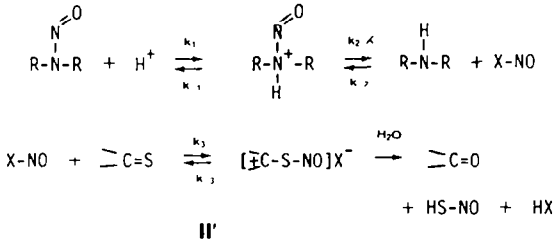
The mechanism chosen for the protonation of the N-nitrosamine and the reaction with the carrier of $NO^+(X^-)$ is similar to that proposed by Challis *et al.*[14] The nucleophilic attack of X^- – an S_N2 displacement reaction takes place with formation of the amine and nitrosyl-X, which in the rate determining step, attacks the sulfur of the thiocarbonyl compound. Soft X^- (I, SCN) are more reactive than less soft anions X^- (Cl, Br, CN) which is due to the formation of a soft–soft transition intermediate, **II**, giving an S-nitroso-intermediate (Scheme 1, II')



II

Subsequent hydrolysis produces the carbonyl compound, HS-NO and HX.

The proposed mechanism for the >C=S→ >C=O transformation is outlined in Scheme 1.



II'

Scheme 1

The kinetics of the >C=S→ >C=O transformation have been studied. N-thiobenzoyl-morpholine, **1b** and N-nitrosopiperidine, NP are chosen as model compounds. In deriving the kinetic expression for the transformation, the use of a steady state approximation is made; it is also assumed that $k_3 \gg k_{-3}$. The rate expression can be formulated as follows:

$$-\frac{d[\rangle C=S]}{dt} = \frac{k_1k_2k_3[H^+][NP]_0[\rangle C=S][X^-]}{k_{-1}k_2[P] + k_1k_{-2}[P][H^+] + k_1k_2[H^+][X^-]} \quad (1)$$

where [P] is the concentration of piperidine.

The kinetics are studied by observing the change in absorbance at 290 nm of the thiocarbonyl compound under pseudo-first order conditions. While the transformation occurs readily under acidic conditions (1.8 M HCl or 1.0 M $HClO_4$), no reaction takes place at pH = 7. The reaction has been studied with the use of several ions (Cl^-, Br^-, CN^- and SCN^-) as carriers.

The initial reaction rate of **1b** with NP at 22° in 1.0 M $HClO_4$ with thiocyanate ions as carrier depends on the concentration of NP (Fig. 1). Each individual run showed a first-order dependence upon the concentration of NP, and a probable first order dependence upon the concentration of thiocyanate is found by varying this concentration (Table 2).

From Table 2 is seen that the chloride ion exerts a small contribution to the reaction rate due to the low nucleophilicity parameter.

Table 3 gives the initial reaction rate of **1b** with Br^-, Cl^-, CN and cysteine as carrier/catalyst of NO^+ in 1.0 M perchloric acid.

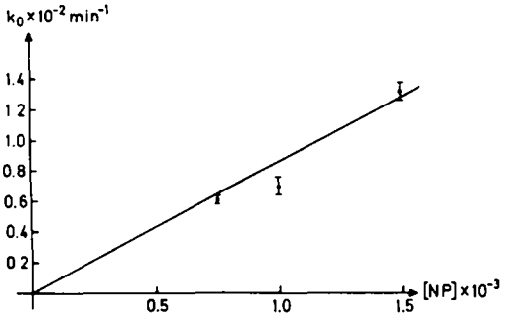


Fig. 1. Effect on the initial reaction rate of **NP** in 1 M $HClO_4$. t = 22°C, $[SCN^-] = 2.7 \times 10^{-3}$ M, [**1b**] = 2×10^{-5} M.

Comparing the data of Tables 2 and 3 with Pearson's nucleophilicity parameter *n* for a conventional S_N2 substitution at saturated carbon[20] the same order of effect of the ions ($Cl^- < Br^- < CN^- < SCN^-$) is observed. The same reactivity of nucleophiles is also found in the denitrosation of NMA.[17]

Ascorbic acid is known to inhibit nitrosation.[36,37] The effect of ascorbic acid on the >C=S→ >C=O transformation with thiocyanate as carrier is shown in Fig. 2, and it is seen that the transformation is inhibited extensively at small concentrations of ascorbic acid.

Table 2. Variation of k_0 with the concentration of thiocyanate in 1.8 M HCl and 1.0 M $HClO_4$

NaSCN M	HCl 1.8 M k_0, min^{-1}	$HClO_4$ 1.0 M k_0, min^{-1}
4.0×10^{-3}	1.45×10^{-2} (±3.6%)	1.43×10^{-2} (±2.1%)
3.0×10^{-3}	1.14×10^{-2} (±1.8%)	
2.0×10^{-3}	0.58×10^{-2} (±4.1%)	0.47×10^{-2} (±4.2%)
1.0×10^{-3}		0.18×10^{-2} (±22%)
0.4×10^{-3}	0.12×10^{-2} (±1.8%)	

Reaction conditions are as follows: t = 22°C, [**1b**] = 2×10^{-5} M, [NP] = 1.0×10^{-3} M.

Table 3. Variation of k_0 with different carrier/catalysts in 1.0 M $HClO_4$

Acid	carrier/catalyst	k_0, min^{-1}
1.0 M $HClO_4$	NaCl 4×10^{-3} M	1.6×10^{-3} (±5.2%)
1.0 M $HClO_4$	KBr 4×10^{-3} M	3.5×10^{-3} (±1.6%)
1.0 M $HClO_4$	KCN 4×10^{-3} M	4.8×10^{-3} (±6.3%)
1.0 M $HClO_4$	Cysteine 4×10^{-3} M	1×10^{-3}

Reaction conditions are as follows: t = 22°C, [**1b**] = 2×10^{-5} M, [NP] = 1.0×10^{-3} M.

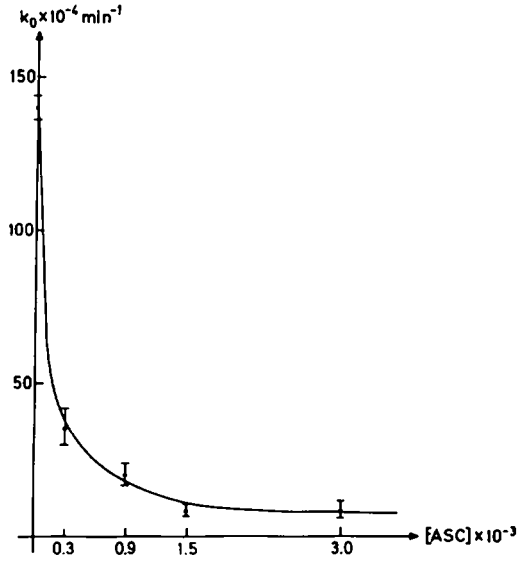
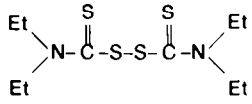


Fig. 2. The effect of the initial reaction rate of **1b** as a function of the concentration of ascorbic acid in 1 M $HClO_4$. t = 22°C, $[SCN^-] = 4 \times 10^{-3}$ M, [**1b**] ≃ 2×10^{-5} M, [NP] = 1×10^{-3} M.

(c) *Fischer–Hepp rearrangement.* Equimolar amounts of N-thiobenzoyl-morpholine, **1b**, NMA and potassium iodide in 4M HCl yield N-benzoyl-morpholine (89%), N-methylaniline (79%) and *p*-nitroso-N-methyl-aniline (13%). The formation of the C-isomer which is normally formed in the Fischer–Hepp rearrangement can be accounted for by an intermolecular rearrangement.

The question of the inter- or intra-molecularity of the Fischer–Hepp rearrangement has been discussed during recent years and different opinions have been presented.[38,39] It is conceivable that the rearrangement under our conditions is intermolecular. Two nitrosation reagents: X–NO and HS–NO are present in the solution as suggested in Scheme 2. Further HS–NO may act as a C-nitrosation reagent (NO^+ is softer with HS^- than with X) or may decompose to elemental S and nitrogen-oxide (Scheme 2).

(d) *Carcinogenic aspects.* Thio-compounds are important constituents of drugs.[40] Tetraethyl-thiuram-disulfide (Antabus, Disulfiram), **14** is known to react with $NaNO_2$ in dilute acetic acid to give N-nitrosodiethyl-amin,[41] which is known to be very carcinogenic.[10]



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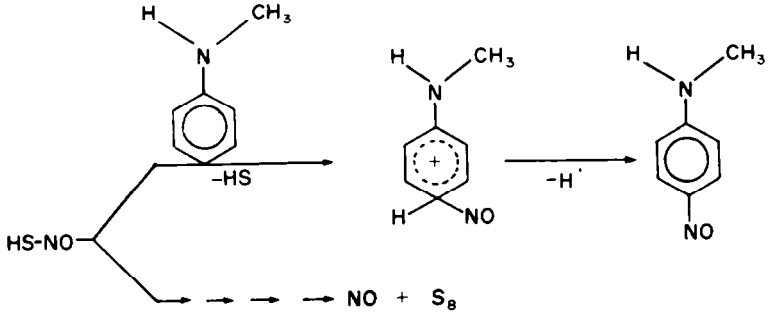
We have found that N-thiobenzoyl-morpholine is transformed into the corresponding O-analogue in small yield both with and without NP present in human gastric juice at 37°. The human gastric juice (pH = 1.8) is stimulated from a person with duodenal ulcers.

Chloride and thiocyanate ions and cystein are all present in the human organism. The chloride ions present in the gastric juice can accelerate the $\rangle C{=}S \rightarrow \rangle C{=}O$ transformation and by that reason also the destruction of the N-nitrosamines. Thiocyanates are of utmost importance due to the high concentration in saliva and urine of smokers (the concentration of thiocyanate is 203–212 μg/ml in saliva and 39–47 μg/ml in urine for heavy smokers whereas for non-smokers the concentrations are 47–52 μg/ml and 14–17 μg/ml).[42] The denitrosation of N-nitrosamines is then probably favoured in smokers, but the nitrosyl-thiocyanate formed can act as nitrosation reagent of amines and thiocarbonyl compounds. Sulfur compounds (particularly -SH) are involved in the metabolism of the cell division.[43] Cysteine is found to have activity as NO^+ -carrier in the $\rangle C{=}S \rightarrow \rangle C{=}O$ transformation (Table 3), and by this way the cell division can be disturbed.

EXPERIMENTAL

^{1}H NMR spectra were recorded at 60 MHz on a Varian EM 360 spectrometer. TMS was used as internal standards. IR spectra were recorded on a Bechman IR-18 spectrometer. Mass spectra were recorded at a Micromass 7070 F spectrometer operating at



Scheme 2

70 eV using direct inlet. The kinetic measurements were carried out at 22° on a recording UV-Visible spectrophotometer (Varian-Cary 219). Gastric juice was obtained from a patient with duodenal ulcers. Pentagastrin was used to stimulate the production of gastric juice. The gastric juice was used 72 hr after collection and stored at −30°.

The starting compounds are easily prepared according to known methods or are commercially available. AnalR $HClO_4$, KI, NaCl, KCN, KBr, and cysteine were used without further purification.

The >C=S→ >C=O transformation.

General procedure. The thiocarbonyl compound (10 mmole) and NP or NMA (12 mmole) are mixed in 20 ml HCl (4 M) and 10 ml CH_2Cl_2. 10 mmole of KI is added under vigorous stirring. Reaction temp is 22° and times are given in Table 1. After neutralisation to pH 7, the phases are separated, the water phase is extracted with CH_2Cl_2 and the combined organic layers are washed with H_2O, dried ($MgSO_4$) and filtered. GLC analysis (with the carbonyl- and thiocarbonyl compounds as internal standards) or evaporation of the solvent on silica gel followed by column chromatography (eluent CH_2Cl_2 for the **1b–6**, **8–11** and 2% MeOH/98% CH_2Cl_2 for **7a–c**) yields the carbonyl compounds which are checked by MS, ^{1}H NMR, IR, and Mp.[1]

Reaction of thiobenzamide, **1a** *with NMA*

5 mmole of **1a**, 6 mmole NMA, and 5 mmole of KI are mixed in 5 ml CH_2Cl_2 and 20 ml 4M HCl under vigorous stirring and reacted for 2-1/2 hr. Neutralisation of the mixture to pH 7, extraction with CH_2Cl_2 and evaporation of the solvent on silica gel and column chromatography (CH_2Cl_2) yields, **12** in 84%[30], 89° (90).[30]

Reaction of phenylthiourea, **7d** *with NP.*

10 mmoles **7d**, 12 mmoles NP and 10 moles KI are mixed in 20 ml CH_2Cl_2 and 40 ml 4 M HCl under vigorous stirring at room temp and reacted for 50 hr. The mixture was neutralised to pH 7, extracted with CH_2Cl_2, dried ($MgSO_4$) and the solvent evaporated on silica gel. Column chromatography yielded **13** in 84% yield together with traces of phenylurea. **13**: m.p. 178 (180)[31], MS: 268, M^+.

Kinetic experiments. The decrease of absorbance at 290 nm of **1b** was recorded as a function of time. A typical run is shown in Table 4.

The Fischer–Hepp rearrangement

5 mmoles of **1b** and 5 mmoles NMA were mixed in 20 ml 4 M HCl and 5 mmoles KI was added under vigorous stirring at room temp. After 3 hr the soln was neutralized to pH 7, separated and the water phase extracted with CH_2Cl_2 and the combined organic layers washed with H_2O, filtered and dried ($MgSO_4$). Evaporation of the soln on silica gel followed by column chromatography (20% ether/80% CH_2Cl_2) yield N-benzoyl-morpholine in 89%, N-methylaniline in 79% and *p*-nitroso-N-methylaniline in 13%. N-benzoyl-morpholine: m.p. 72 (74–75)[44]. N-methylaniline: MS, ^{1}H NMR. (δ, $CDCl_3$): 2.72 (3H, s)-CH_3; 3,3-3,7 (1H, m)-NH-; 6.4–7.4 (5H, m)-Ph. *p*-nitroso-N-methylaniline: m.p. 110–112° (114°)[45].

Table 4. Decrease in absorbance of **1b**, initial [**1b**] 2×10^{-5} M, $[HClO_4] = 1.0$ M, $[NP] = 1.0 \times 10^{-3}$ M, $[SCN^-] = 4 \times 10^{-3}$ M

t/min	0	5	10	15	20
Abs.	0.199	0.186	0.174	0.162	0.152
k_o/min^{-1}	0.0138	0.0143	0.0151	0.139	0.0138

t/min	30	60	∞
Abs.	0.136	0.081	0.003
k_o/min^{-1}	0.0144		

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