Ring–ring interconversion: the rearrangement of 6-(4-chlorophenyl)-3-methyl-5-nitrosoimidazo[2,1-*b*][1,3]thiazole into 8-(4-chlorophenyl)-8-hydroxy-5-methyl-8*H*-[1,4]thiazino[3,4-*c*][1,2,4]oxadiazol-3-one. Elucidation of the reaction product through spectroscopic and X-ray crystal structure analysis

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The reactivity of 6-(4-chlorophenyl)-3-methyl-5-nitrosoimidazo[2,1-*b*][1,3]thiazole (a member of a class of mutagenic compounds) with hydrochloric acid in ethanol has been investigated and the nature of the reaction product unambiguously established on the basis of infrared, NMR and mass spectra and a crystal structure determination.

In the course of our studies on nitrogen compounds (nitroso and nitro derivatives) with mutagenic activity[1] and on ring–ring interconversions[2] we have recently examined[3] the reactivity of 6-(4-chlorophenyl)-3-methyl-5-nitrosoimidazo[2,1-*b*][1,3]thiazole **1** with hydrochloric acid. The study of the reactivity of compounds showing biological activity is useful in providing information concerning their biological transformations.[4] Several nitrosoimidazo[2,1-*b*][1,3]thiazoles have been shown to be mutagenic on both base-pair and frame shift substitution strains of *Salmonella typhimurium* and on yeast.[5]

In order to gain more insight into the above mentioned reaction of **1** and in view of its applicability to other 5-nitrosoimidazo[2,1-*b*][1,3]thiazoles, we carried out a complete IR, NMR (^{1}H and ^{13}C) and mass spectroscopic study. The proposed product structure is in complete agreement with that obtained from X-ray diffraction.

Experimental

^{1}H and ^{13}C NMR spectra were determined in [$^2H_6$]DMSO (dimethyl sulfoxide) with a Varian Gemini 300 Instrument in the Fourier transform mode at 21 ± 0.5 °C. Chemical shifts (δ) are reported in ppm high frequency from tetramethylsilane as the secondary reference. The mass spectra were recorded with a VG70 70E apparatus. The IR spectra were obtained on a Perkin-Elmer 1600 FTIR instrument. X-Ray diffraction data were measured on an Enraf-Nonius CAD-4 diffractometer.

Materials

Compound **1** was prepared according to a literature method.[1b]

8-(4-Chlorophenyl)-8-hydroxy-5-methyl-8*H*-[1,4]thiazino-[3,4-*c*][1,2,4]oxadiazol-3-one 2. Compound **1** (1 g, 3.6 mmol) was suspended in ethanol (30 cm^3) and treated at 80 °C under stirring with hydrochloric acid (2 mol dm^{-3}, 3 cm^3) until complete disappearance of the green colour (*ca.* 2.5 h). Removal of the solvent left a light pink solid (0.90 g, 90% yield) which was purified by recrystallization from ethanol (colourless crystals), mp 190 °C (decomp.) (Found: C, 48.6; H, 3.1; N, 9.3; S, 10.9. Calc. for $C_{12}H_9ClN_2O_3S$: C, 48.6; H, 3.1; N, 9.4; S, 10.8%; Found *m*/*z* 296.001 91, $C_{12}H_9ClN_2O_3S$ requires 296.002 24).

Crystal data

$C_{12}H_9ClN_2O_3S$, M = 296.7. Triclinic, a = 7.501(2), b = 7.770(2), c = 11.293(2) Å, α = 85.43(2), β = 72.84(2), γ = 82.26(3)° V = 622.6(3) Å^3 (by least-squares refinement on diffractometer angles for 25 automatically centred reflections, λ = 0.7107 Å), space group $P\bar{1}$ (No. 2), Z = 2, D_c = 1.583 g cm^{-3}, F(000) = 304. Crystal dimensions 0.38 × 0.42 × 0.29 mm, μ(Mo-Kα) = 4.79 cm^{-1}.

Data collection and processing

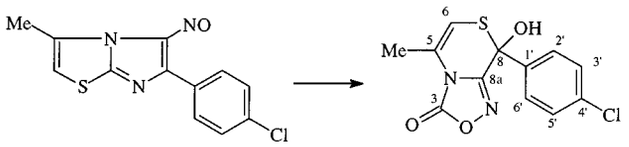
CAD-4 diffractometer, ω scan mode with scan width = 1.5°, scan speed 0.9–20° min^{-1}, graphite-monochromated Mo-Kα radiation; 3605 unique reflections measured ($2.5 \leqslant \theta \leqslant 30°$), 3184 with $F > 4\sigma(F)$. Absorption correction[6] (max., min. transmission factors = 1.00, 0.92). No crystal decay was observed.

Structure determination and refinement

Direct methods, NRCVAX.[7] The structure was solved with no reference to a structural model; the identity of the peaks which appeared on the *E*-map was assessed during the refinement, by monitoring of bond distances and thermal factors. All hydrogen atoms were obtained from difference syntheses. Full-matrix least-squares analysis (SHELXL93)[8] on F^2, with all heavier atoms refined as anisotropic and all hydrogens as isotropic. In the last cycles, zero weight was given to three reflections affected by extinction or experimental error. The weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.0519P)^2 + 0.20P]$ with $P = (F_o^2 + 2F_c^2)/3$ and $\sigma(F_o^2)$ from counting statistics gave good agreement analyses. Convergence was reached with a maximum shift-to-e.s.d. ratio 0.001. Final $R1$ = 0.0359 (on F, 3184 reflections), $wR2$ = 0.1009 (on F^2, 3602 reflections), with a goodness of fit S = 1.029. Scattering factors taken from SHELXL93. All geometry calculations were done using PARST93.[9] Standard deviations for bond lengths and bond angles not involving hydrogen atoms are in the ranges 0.0014–0.0023 Å and 0.07–0.16°, respectively. Atomic coordinates, thermal parameters, bond distances, bond angles and torsion angles have been deposited at the Cambridge Crystallographic Data Centre. For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 2*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 188/86. Tables of observed and calculated structure factors are available from the author (A. M.) on request.

Results

The green suspension of nitroso compound **1** in ethanol by the action of hydrochloric acid furnished a solid which on purification gave a single product. Elemental analysis and exact mass spectrum agree with the formula $C_{12}H_9ClN_2O_3S$ (Scheme 1).

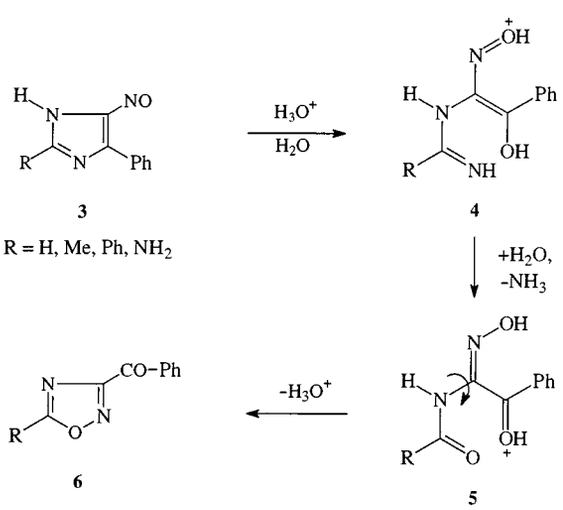


1 **2**

Scheme 1

To understand the product structure and the reason for its formation it is necessary to consider the behaviour of nitrosoimidazoles with hydrochloric acid.[10,11]

It is well known that some 4(5)-nitroso-5(4)-phenylimidazoles **3**, by the action of acids, undergo a ring-opening–ring-closing reaction furnishing 3-benzoyl-1,2,4-oxadiazoles **6** by elimination of ammonia (Scheme 2).



3 **4**

R = H, Me, Ph, NH_2

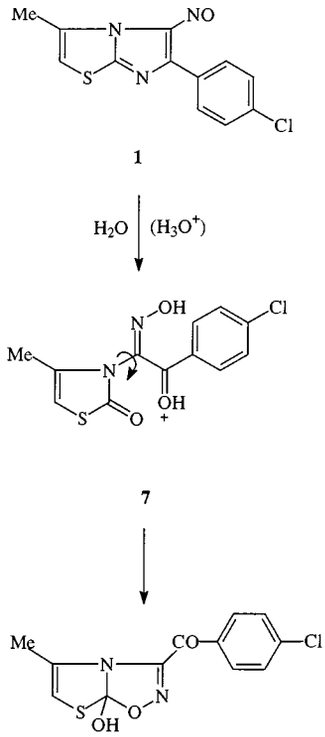
6 **5**

Scheme 2

The reaction can be regarded as an acid-catalysed nucleophilic attack of a water molecule to the conjugated system C4=C5–N=O of **3**, which causes the opening of the imidazole ring, followed by the hydrolytic elimination of ammonia. The cation intermediate **5** by rotation along the nitrogen–carbon bond collapses by a ring-closing reaction to the 1,2,4-oxadiazole **6**, losing a hydronium ion.

A similar pathway can be envisaged for the reaction of **1** with acids. The acid-catalysed opening of the imidazole ring would give the analogous cation intermediate **7** which by rotation about the nitrogen–carbon bond would furnish **8** as the reaction product (Scheme 3): analytical data appear to agree with this scheme (**8**: $C_{12}H_9ClN_2O_3S$).

To confirm this hypothesis a detailed analysis of the spectroscopic data has been carried out: ν_{max}(KBr)/cm^{-1}: 3284 (OH), 1750 (C=O; typical for C=O conjugated with oxygen or nitrogen), 1590 (aromatic C=C), 1345, 1230, 1180, 910, 895; *m/z* (%): 296 (M^+, 26), 263 ($M^+ - 32$, 8), 252 ($M^+ - CO_2$, 2), 219 ($M^+ - 32 - CO_2$, 2), 165 (4-ClC_6H_4COCN, 2), 157 ($M^+ - 4$-ClC_6H_4COCN, 36), 139 (4-ClC_6H_4CO, 100), 111 (4-ClC_6H_4, 40), 75 (C_6H_3, 16); δ_H([$^2H_6$]DMSO, 300 MHz, *J* values in Hz) 8.30 (1H, br s, exch. OH); 7.66 (2H, AA′ part of AA′BB′ system, H-Ar); 7.53 (2H, BB′ part of AA′BB′ system, H-Ar); 6.24 (1H, q, $J_{6,Me}$ 1.3, H-6); 2.42 (3H, d, $J_{Me,6}$ 1.3, Me); δ_C([$^2H_6$]DMSO, 75 MHz, * may be reversed) 155.55 (s, C-3*), 154.85 (s, C-8*a**), 135.87 (t, $J_{1',3'}$ $J_{1',5'}$ 7.7, C-1′), 133.94 (tt, $J_{4',2'}$



1

7

8

Scheme 3

$J_{4',6'}$ 10.8, $J_{4',3'}$ $J_{4',5'}$ 3.1, C-4′), 128.99 (dd, $J_{2',2'}$ 164.8, $J_{2',6'}$ 6.6, C-2′), 128.73 (qd, $J_{5,Me}$ 7.3, $J_{5,6}$ 5.2, C-5), 128.17 (dd, $J_{3',3'}$ 168.4, $J_{3',5'}$ 5.2, C-3′), 105.03 (dq, $J_{6,6}$ 183.4, $J_{6,Me}$ 6.4, C-6), 76.25 (dt, appears as quartet, $J_{8,OH}$ $J_{8.2'}$ $J_{8,6'}$ 3.7, C-8), 16.67 (qd, *J* 130.7, $J_{Me,6}$ 4.2, Me).

The IR spectrum of this compound exhibits bands at 3284 cm^{-1} (*ν* OH), 1750 cm^{-1} (*ν* C=O), 1590 cm^{-1} (*ν* aromatic C=C) and bands at 1350–1225, 1180–1140 and 920–883 cm^{-1} which are characteristic of 1,2,4-oxadiazole rings.[11] The base peak in the mass spectrum has *m/z* = 139 (4-$ClC_6H_4CO^+$) and the peak at *m/z* = 157 ($M^{\cdot+} - 139$) is also particularly abundant. In the spectrum the $M^{\cdot+}$ peak (*m/z* = 296) is also observable. The ^{1}H NMR spectrum of this compound shows interesting features that allow the identification of the nature of the protons. Thus, the ^{1}H NMR spectrum shows the presence of nine protons in a ratio of 1:(2+2):1:3 that can be assigned as follows: (*a*) one exchangeable proton at δ 8.30; (*b*) four aromatic protons corresponding to an AA′BB′ system at δ 7.66 and 7.53 which can be confidently attributed to the 4-chlorophenyl moiety; (*c*) one olefinic proton at δ 6.24; (*d*) three aliphatic protons at δ 2.42 corresponding to a methyl group. The protons sub *c* and *d* show a long range coupling indicating the presence of the structure **A**.

A

These findings could be in agreement with the proposed structure **8**, but it must be rejected on the basis of the ^{13}C NMR spectra, since no signal in the range of conjugated ketonic carbon atoms (200 > δ > 180) was observed. The fully proton decoupled spectrum showed ten resonances for the twelve carbons in the molecule, owing to the symmetry of the 4-chlorophenyl moiety. The DEPT spectra distinguished one CH_3, three CH and six quaternary carbon resonances. The methine resonances were easily attributed to the four aromatic CH and to the olefinic CH, on the basis of chemical shifts and fine splitting patterns in the gated decoupled spectrum. Three

Table 1 Selected bond distances (Å) and angles (°) for **2**, with their e.s.d. values. Atoms are numbered according to Fig. 1

Bond	Distance/Å	Angle	(°)
O(1)–N(2)	1.432(2)	O(1)–N(2)–C(2)	104.4(1)
N(2)–C(2)	1.284(2)	N(2)–C(2)–C(3)	124.9(1)
C(2)–C(3)	1.500(2)	C(2)–C(3)–S	106.5(1)
C(3)–S	1.841(2)	C(3)–S–C(5)	99.1(1)
S–C(5)	1.748(2)	S–C(5)–C(6)	125.6(1)
C(5)–C(6)	1.330(2)	C(5)–C(6)–N(7)	117.9(1)
C(6)–N(7)	1.426(2)	C(6)–N(7)–C(8)	127.9(1)
N(7)–C(8)	1.382(2)	N(7)–C(8)–O(1)	106.3(1)
C(8)–O(1)	1.348(2)	C(8)–O(1)–N(2)	109.8(1)
C(2)–N(7)	1.378(2)	N(2)–C(2)–N(7)	113.2(1)
C(3)–O(2)	1.400(2)	C(3)–C(2)–N(7)	121.9(1)
C(8)–O(3)	1.208(2)	C(6)–N(7)–C(2)	125.4(1)
		C(8)–N(7)–C(2)	106.3(1)
		N(7)–C(8)–O(3)	129.6(1)
		O(1)–C(8)–O(3)	124.1(1)
		S–C(3)–O(2)	111.7(1)

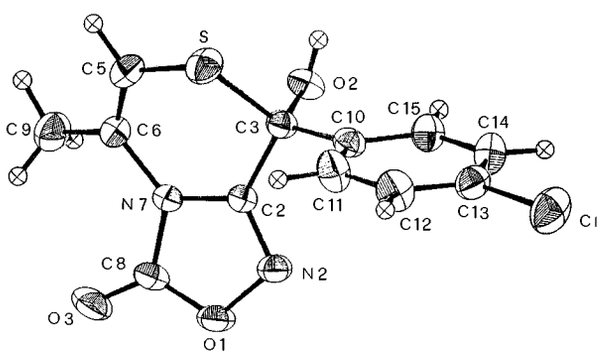


Fig. 1 ORTEP view of the structure of **2** in the crystal and numbering of atoms. Thermal ellipsoids are drawn at the 50% probability level; hydrogen atoms, treated as isotropic, are on an arbitrary scale.

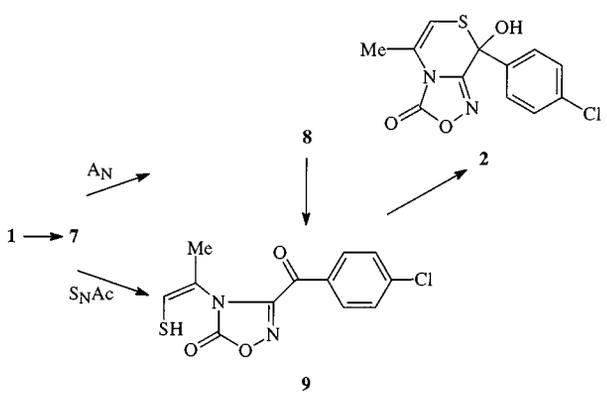
of the quaternary resonances were attributed in a similar manner (δ 135.87, 133.94 and 128.73 are C-1′, C-4′ and C-5 respectively) so there remain only three signals. The resonance at δ 76.25 is in the typical range of quaternary sp^3 carbons bearing an oxygen atom, and the fine splitting (a doublet of triplets appearing as a pseudo quartet) shows a coupling with the *ortho* protons of aromatic ring besides a coupling with the olefinic proton (COLOC spectrum) α to the sulfur atom; thus it was attributed to C-8 because a ring containing a nitrogen and a sulfur atom must be present. The chemical shifts of the last two carbons (δ 155.55 and 154.85) are very close and are in the range of esters (or lactones) as well as amides (or lactams) or imides and can be attributed to C-3 and C-8a. All these considerations allow us to hypothesize the presence of one 1,2,4-oxidiazol-5-one ring in the framework, so giving the final structure **2**. Strong confirmation of the presence of this ring is provided by the occurrence of a peak in the mass spectrum at *m*/*z* 252 corresponding to the expected loss of carbon dioxide.

The above NMR correlation is in full agreement with the crystal structure of **2**, as determined by X-ray diffraction (see Fig. 1). To our knowledge, this is the first crystal structure determination of a 1,4-thiazine ring condensed with a 1,2,4-oxadiazole system. Bond distances are in general good agreement with average values[12] taken from the Cambridge Structural Database;[13] even bond angles are in the normal range. Selected bond distances and bond angles are reported in Table 1. In the crystal (see Fig. 1 for the numbering scheme of atoms) a hydrogen bond O(2)–H(2)···O(3) connects the molecules in chains parallel to the *y* axis: O(2)–H(2) 0.79(2), O(2)···O(3) 2.797(2), H(2)···O(3) 2.01(2) Å, O(2)–H(2)···O(3) 171(2)°, O(3) in x, $-1 + y$, z. With the exception of a rather short Cl···Cl intermolecular distance (3.321 Å) there are no further contacts shorter by more than 0.10 Å with respect to the sum of the van der Waals radii involved. The oxadiazole moiety is planar within 0.004 Å, whereas the thiazine ring is in a distorted half-chair conformation, with a displacement asymmetry parameter ΔC_2(S–C3) = 0.031.[14]

Starting from the experimental results, the conformation of the isolated molecule was investigated by semi-empirical molecular-orbital calculations within the NDDO approach (method AM1,[15] program MOPAC[16]) with full optimization. The torsion angle for the phenyl ring, S–C(3)–C(10)–C(11), decreases from 46.3° (experimental value) to 37.6°, the oxadiazole ring remains substantially planar and the thiazine confirms its distorted half-chair conformation with a displacement asymmetry parameter ΔC_2(S–C3) = 0.038.

Discussion

The complete mechanism of the **1** ⟶ **2** rearrangement seems to be in accordance with Scheme 4: it requires however further comment. In the **3** ⟶ **6** ring–ring interconversion, a relevant role is probably played by the fact that the final product contains the aromatic 1,2,4-oxadiazole as the newly formed heterocyclic ring. In contrast, the ring–ring interconversion involving **1**, if the course of the reaction were the same, would furnish **8** where the newly formed ring, *i.e.* the 1,2,4-oxadiazole ring, would not be aromatic and this certainly would be an important factor. Moreover, it is probable that the intermediate thiazolone **7** does not give **8** by a nucleophilic addition (A_N) but **9** by an acylic nucleophilic substitution (S_NAc) at the same carbon atom with the cleavage of the feeble carbonyl–sulfur bond.[17] By rotation about the nitrogen–carbon bond the thiol group of **9** can in turn add to the ketonic carbonyl carbon[18] (formation of a six-membered cyclic hemithioacetal) giving **2**.



Scheme 4

This study also shows that the 6-(4-chlorophenyl)-3-methyl-5-nitrosoimidazo[2,1-*b*][1,3]thiazole **1** as 4(5)-nitroso-5(4)-phenylimidazoles **3**, can be converted into an 1,2,4-oxadiazole derivative, in this instance giving an unexpected derivative of a new fused ring system: the 1,2,4-oxadiazolo[3,4-*c*][1,4]thiazine. It has been possible to establish the structure of the reaction product **2** on the basis of ^{1}H and ^{13}C NMR spectroscopy as well as of X-ray analysis, while mass spectrometry has been able to give non-definitive information on its structure.

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References

1 (*a*) P. Hrelia, F. Vigagni, F. Maffei, C. Fimognari, L. Lamartina, D. Spinelli, P. Juric, M. C. Guerra and G. Cantelli Forti, *Mutagenesis*, 1995, **10**, 171; P. Hrelia, F. Vigagni, M. Morotti, G. Cantelli Forti, C. L. Barbieri, D. Spinelli and L. Lamartina, *Chem.-Biol.*

Interactions, 1993, **86**, 229; (*b*) A. Andreani, M. Rambaldi, F. Andreani, P. Hrelia and G. Cantelli Forti, *Arch. Pharm. Chemi. Sci. Ed.*, 1987, **15**, 41.
2 M. Ruccia, N. Vivona and D. Spinelli, *Adv. Heterocycl. Chem.*, 1981, **29**, 141; V. Frenna, G. Macaluso, N. Vivona, D. Spinelli, G. Consiglio and E. Mezzina, *Tetrahedron*, 1994, **50**, 7315.
3 D. Spinelli, A. Mugnoli, A. Andreani, M. Rambaldi and S. Frascari, *J. Chem. Soc.*, *Chem. Commun.*, 1992, 1394.
4 *Drug Metabolism in Man*, ed. J. W. Gorrod and A. H. Beckett, Taylor and Francis, London, 1978.
5 P. Hrelia, L. Murelli, M. Paolini, E. Sapigni and G. Cantelli Forti, *Mutagenesis*, 1987, **2**, 425 and references cited therein.
6 A. C. T. North, D. C. Phillips and F. S. Mathews, *Acta Crystallogr.*, *Sect. A*, 1968, **24**, 351.
7 E. J. Gabe, Y. Le Page, J.-P. Charland, F. L. Lee and P. S. White, *J. Appl. Crystallogr.*, 1989, **22**, 384.
8 G. M. Sheldrick, SHELXL93, Program for Refinement of Crystal Structures, University of Göttingen, 1993.
9 M. Nardelli, PARST, *Comput. Chem.*, 1983, **7**, 95.
10 D. Spinelli, Thesis, University of Bari, 1955; S. Cusmano and M. Ruccia, *Gazz. Chim. Ital.*, 1955, **85**, 1686; S. Cusmano and M. Ruccia, *Gazz. Chim. Ital.*, 1958, **88**, 463.
11 B. Cavalleri, P. Bellani and G. Lancini, *J. Heterocycl. Chem.*, 1973, **10**, 357.
12 F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen and R. Taylor, *J. Chem. Soc.*, *Perkin Trans. 2*, 1987, S1.
13 F. H. Allen and O. Kennard, *Chemical Design Automation News*, 1993, **8**, 1, 31.
14 M. Nardelli, *Acta Crystallogr.*, *Sect. C*, 1983, **39**, 1141; W. L. Duax, C. M. Weeks and D. C. Rohrer, *Top. Stereochem.*, 1976, **9**, 271.
15 M. J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902.
16 J. J. P. Stewart, MOPAC, *QCPE Bull.*, 1983, **3**, 43.
17 The low resonance energy of the −CO−S− group means it can act as an acylating agent *via* S_NAc reactions. Several aspects of this reactivity are well supported in chemical (see M. J. Janssen, *The Chemistry of Carboxylic Acids and Esters*, ed. S. Patai, Interscience, New York, 1969, p. 724 and following) and biological (see the role of acetyl coenzyme A in biological acylation) systems.
18 L. Fournier, A. Natat, G. Lamaty and J. P. Roque, *Recl. Trav. Chim. Pays-Bas*, 1972, **91**, 1015; M. E. Peach, in *The Chemistry of the Thiol Group*, ed. S. Patai, Wiley, New York, 1974, p. 765 and following; T. H. Lowry and K. Schneller Richardson, *Mechanism and Theory in Organic Chemistry*, Harper and Row, 3rd edn., 1987, pp. 701–702 and references cited therein.

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