A New Ring Transformation: Conversion of 6-*p*-Chlorophenyl-3-methyl-5-nitrosoimidazo[2,1-*b*]thiazole into 8-*p*-Chlorophenyl-8-hydroxy-5-methyl-3-oxo-1,2,4-oxadiazolo[3,4-*c*][1,4-]thiazine by the Action of Mineral Acids

Domenico Spinelli,[a] Angelo Mugnoli,[b] Aldo Andreani,[c] Mirella Rambaldi[c] and Sara Frascari[a]

[a] *Dipartimento di Chimica Organica 'A. Mangini', Via S. Donato 15, I-40127 Bologna, Italy*
[b] *Istituto di Chimica Fisica, Corso Europa 26, I-16132 Genova, Italy*
[c] *Dipartimento di Scienze Farmaceutiche, Via Belmeloro 6, I-40126 Bologna, Italy*

6-*p*-Chlorophenyl-3-methyl-5-nitrosoimidazo[2,1-*b*]thiazole **1** by treatment with dilute hydrochloric acid in dioxane at room temperature gave 8-*p*-chlorophenyl-8-hydroxy-5-methyl-3-oxo-1,2,4-oxadiazolo[3,4-*c*][1,4]thiazine **2**, containing a new condensed ring system the molecular structure of which was ascertained by physical methods (^{1}H and ^{13}C NMR, electron impact-mass and IR spectra, and XRD).

Reactivity studies of compounds showing biological activity are of great interest, as they can often provide information concerning their biological transformations.[1] On these grounds and continuing our research on the study of ring–ring interconversions,[2a] we have performed a study of the reactivity of imidazo[2,1-*b*]thiazole **1**,[3a] which is mutagenic on both base-pair and frame-shift substitution strains of *Salmonella typhimurium* and on yeast.[3b]

Compound **1** ($C_{12}H_8ClN_3OS$, green, 1 g) was suspended in dioxane (30 ml) and treated at room temperature under stirring with hydrochloric acid (2 mol dm^{-3}; 3 ml) for a few minutes. **1** gave **2**, which was sparingly soluble in the reaction mixture and gave colourless crystals from ethanol (decomp. 190 °C), the analytical results agree with the formula $C_{12}H_9ClN_2O_3S$ (Scheme 1). It did not contain either the starting imidazo[2,1-*b*]thiazole system nor one of the previous rings (imidazole or thiazole ring).

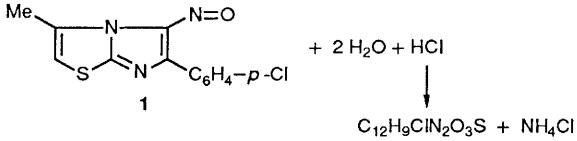
The structure of compound **2** has been assigned on the basis of ^{1}H and ^{13}C NMR, electron impact-mass and IR spectra,† and XRD.[4]

The new ring transformation can be understood bearing in mind the known reactivity of some 4-nitroso-5-phenylimidazoles **3**, which, by the action of acids, give a ring-opening–ring-closing reaction with the elimination of ammonia and furnish 3-benzoyl-1,2,4-oxadiazoles **4**[2b] (Scheme 2). In a similar way the formation of compound **5** ($C_{12}H_9ClN_2O_3S$) *via* intermediates **6** and **7** (see Scheme 3) could be expected and appeared to be confirmed by MS relative molecular mass determination as well as by ^{1}H NMR data and some MS fragments.

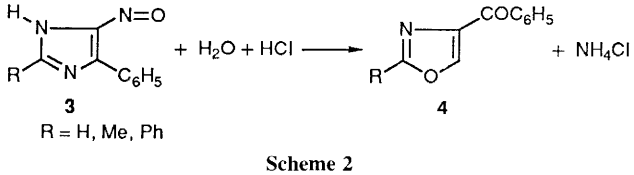
In contrast, ^{13}C NMR data excluded this structure for the obtained compound since no signal in the range of ketonic carbon atoms (δ *ca.* 195) was observed.[5] On the other hand, the occurrence of a signal at δ *ca.* 155 indicated the presence of a carbonyl carbon bound to oxygen (ester or lactone) and/or to nitrogen (amide or lactam),[5] as confirmed by MS fragmentation ($M^{+\cdot}$ −44, typical of esters or lactones).[5] Thus, a further ring-opening–ring-closing reaction involving the unstable intermediate **7** was assumed with the final formation of **2**: a new condensed ring system which therefore contains a thiazine ring fused to a 1,2,4-oxadiazole.[4]

A tentative pathway of the new observed ring transformation is reported in Scheme 3.

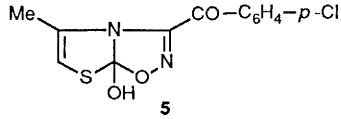
Some brief comments on the reactivity of **1** and then on the different behaviour of **1** and **3** seem to be necessary. Concerning the first point, the ring-opening reaction appears to be strictly related to the presence of the 5-nitroso group on the imidazole ring.[2b] In fact, the same ring-opening reaction did not occur in 6-*p*-chlorophenyl-3-methylimidazo[2,1-*b*]thiazole **9**, which did not rearrange or hydrolyse by the action of acids in comparable experimental conditions. Concerning

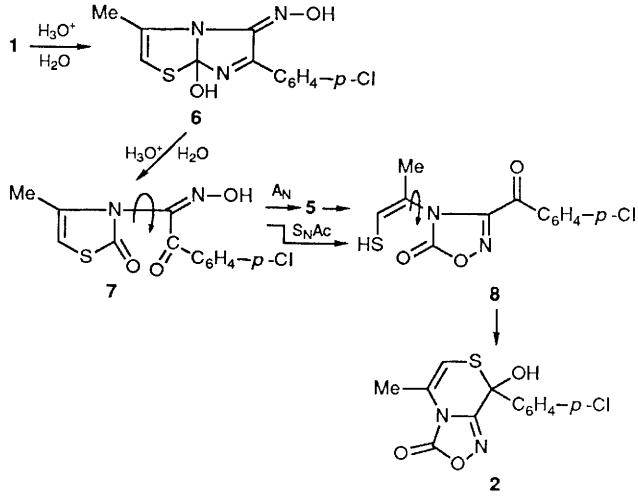


Scheme 1

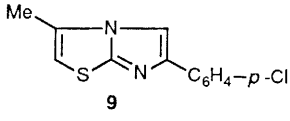


Scheme 2





Scheme 3



† ^{1}H and ^{13}C NMR spectra in $(CD_3)_2SO$ solutions were recorded on a Varian Gemini 300 with $SiMe_4$ and $(CD_3)_2SO$ (δ 39.5 ppm), respectively as internal standard. The IR spectrum was recorded in Nujol on a Perkin-Elmer 298. EI-MS were recorded on a VG 70 70E mass spectrometer. Satisfactory elemental analyses (C, H, N and S) and exact mass spectra were obtained for the new compound **2**. *Selected spectroscopic data*: δ 2.41 (3 H, s), 6.23 (1 H, s), 8.32 (1 H, s, exchangeable proton); ν_{CO} 1741 cm^{-1}.

the second point, the ring-opening–ring-closing reaction of **3** gave **4**, which contains the aromatic 1,2,4-oxadiazole (as formed heterocyclic ring). Accordingly, **1** would have given **5**, containing the non-aromatic 1,2,4-oxadiazole ring, through a nucleophilic addition (A_N) to the carbonyl carbon of the thiazolone intermediate **7**. Perhaps **5** is only an unstable intermediate which collapses to **8** or alternatively **7** gives directly **8** by an acylic nucleophilic substitution (S_NAc) at the same atom with the cleavage of the feeble carbonyl–sulfur bond.[6] The thiol group of **8** in turn gives 2 by addition to the ketonic carbonyl carbon[7] and formation of a six-membered cyclic hemithioacetal.

The authors are grateful to one of the referees for his suggestion on the role of **5**.

We thank the CNR and MURST for financial support.

Received, 30th March 1992; Com. 2/01670B

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4 An X-ray crystal structure determination confirmed the structure of the obtained product as **2** (unpublished work).

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6 In agreement with the low resonance energy of the –CO–S– group, the thiolo esters show a marked tendency to act as acylating agents *via* S_NAc reactions. This reactivity is well supported in chemical (on the reactivity of thiolo esters, see M. J. Janssen, *The Chemistry of Carboxylic Acids and Esters*, ed. S. Patai, Interscience, New York, 1969, pp. 724 and following) and biological (see the role of acetyl coenzyme A in biological acylation) systems.

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