ACTA CHEMICA SCANDINAVICA 25 (1971) 625–630

The Reaction of 1-Substituted and 1,4-Disubstituted Thiosemicarbazides with Nitrous Acid. 3-Substituted *N*-[5-(1,2,3,4-oxatriazolio)]amides

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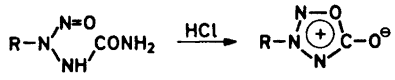
Some new derivatives of the meso-ionic ring system *N*-[5-(1,2,3,4-oxatriazolio)]amide have been prepared from both 1-substituted and 1,4-disubstituted thiosemicarbazides and nitrous acid. The products from the reaction of 4-substituted 1-arylthiosemicarbazides and nitrous acid have earlier been described as derivatives of a four-membered ring system. We now consider these compounds, mainly on the basis of chemical evidence, to be derivatives of *N*-[3-aryl-5-(1,2,3,4-oxatriazolio)]amides. Mass spectra of some of the substances have been interpreted on the basis of this structural assignment.

Recently, the meso-ionic *O*-[3-alkyl-5-(1,2,3,4-oxatriazolio)]oxides (I) have attracted some attention as potential hypotensive agents.[1] One of the synthetic procedures developed for these compounds consists of treating 1-nitroso-1-alkylsemicarbazide with hot hydrochloric acid.[2]



I

The corresponding reaction of thiosemicarbazides has been investigated. A solution of 1-propylthiosemicarbazide in ethanolic hydrochloric acid was treated with aqueous sodium nitrite. Even below 10°C elemental sulfur precipitated from the reaction mixture. The elemental composition of the product isolated from the supernatant corresponded to that calculated for the hydrochloride of *N*-[3-propyl-5-(1,2,3,4-oxatriazolio)]amide (IIa) (Scheme 1).

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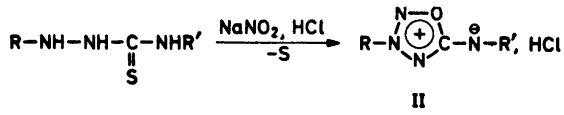


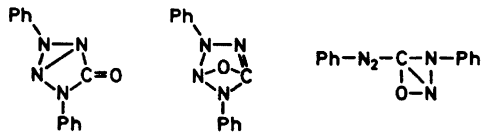
II

a: R=propyl, R'=H
b: R=cyclohexyl, R'=H
c: R=phenyl, R'=ethyl
d: R=phenyl, R'=*tert*-butyl
e: R=phenyl, R'=4-nitrophenyl

Scheme 1

Apparently, only one representative of the *N*-[3-alkyl-5-(1,2,3,4-oxatriazolio)]amides (IIb) has, as yet, been recorded in the literature.[3] This product, prepared from 1-(cyclohexylamino) guanidine, sodium nitrite, and hydrochloric acid, proved to be identical to a sample prepared from 1-cyclohexylthiosemicarbazide in the manner outlined above. The compounds IIc and IId were also successfully prepared from the corresponding thiosemicarbazides under similar conditions.

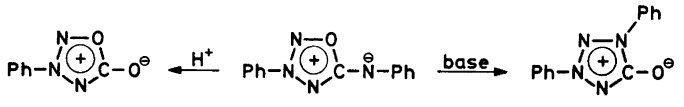
1-Arylsemicarbazides are known not to form meso-ionic derivatives analogous to (I) on treatment with nitrous acid but, instead, are oxidized to arylazoformamides.[4] We have found, however that 1-phenyl-4-(4-nitrophenyl) thiosemicarbazide reacted with nitrous acid with elimination of sulfur. An orange solid, the elemental composition of which is in accordance with its formulation as *N*-[3-phenyl-5-(1,2,3,4-oxatriazolio)]4-nitrophenylamide, was isolated from the reaction mixture (IIe as the base).



III IV V

A study of the reaction of 1,4-diphenylthiosemicarbazide with nitrous acid was published as early as in 1896 by Busch and Becker.[5] The product was named "1,4-diphenylisotetrazolon" and formulated as a bicyclic compound (III). A detailed investigation of this compound, together with description of some analogous derivatives, appeared in 1929.[6] In the latter paper, the "isotetrazolon" structure (III) was rejected, partly because a base catalysed isomerization was observed, the product of which was thought to be an "endoxytetrazol" (IV). The primary product was now described as "1-phenylazo-2-phenyl-1,3-endoxy-hydrazomethylen" (V). The structure of the isomerization product has since been revised [7a] and the compound is now accepted to be the meso-ionic *O*-(1,3-diphenyl-5-tetrazolio)oxide (VII).[7b]

We have examined the primary compound and formulate it, on the basis of reasons given below, as *N*-[3-phenyl-5-(1,2,3,4-oxatriazolio)]phenylamide (VI). If this assignment is is correct, the above mentioned isomerization must proceed as follows:

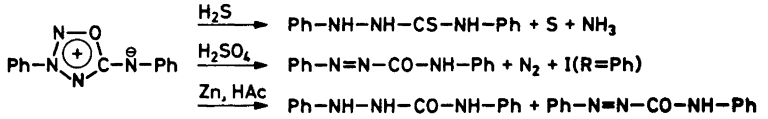


VI VII

This isomerization is formally analogous to the recorded base catalyzed conversion of 5-arylamino-1,2,3,4-thiatriazoles to 1-aryltetrazole-5-thiones.[8] The latter reaction fails to yield tetrazoles when the substituent is alkylamino; the same limitation was found for the reaction VI→VII.

On treatment with boiling mineral acid, VI, which is a red solid, is hydrolysed. Among the hydrolysis products, Busch and Schmidt found a colourless compound, m.p. 85°C. As the compound was isolated in low yield and regarded as a by-product, no attempt was made to elucidate the structure.[6] We have now repeated the preparation of this compound and compared it with a sample of authentic *O*-[3-phenyl-5-(1,2,3,4-oxatriazolio)]oxide.[9] The compounds are identical (superimposable IR spectra and identical m.p.) and the reaction may thus be formulated VI $\xrightarrow{\text{acid}}$ I (R = phenyl).

Hydrolysis and reduction products identified by Busch and Schmidt[6] are compatible with the structure VI. The structure of the products provide



independent evidence that no rearrangement has occurred prior to, or during, the cyclization step (Scheme 1). It can then be concluded that VI contains the 1,4-diphenylsemicarbazide chain and that VI is a derivative of the 1,2,3,4-oxatriazolio ring system. These facts leave little doubt that VI is *N*-[3-phenyl-5-(1,2,3,4-oxatriazolio)]phenylamide.

Although very little at present can be said about the mechanism of the cyclization of 1-nitroso-1,4-disubstituted thiosemicarbazides, a few possibilities can be ruled out. Phenylazothioformic acid *tert*-butylamide is not an intermediate in the preparation of IId, since we have shown that the amide is unaffected by nitrous acid under the experimental conditions used in the preparation of IId. Also, phenylazoformanilide cannot be an intermediate in the preparation of VI, since it does not react with nitrous acid.[5]

Further evidence for the assigned structures (IIa, b, c, d, and VI) was obtained by comparison of the UV absorption spectra. The main absorption of the oxatriazolioamides occurred between 269 and 283 mμ. Consistent with this, the main absorption of *O*-[3-phenyl-5-(1,2,3,4-oxatriazolio)]oxide (I)

(R = phenyl) occurred at 269 mμ. Although the spectra cannot probably, at present, be interpreted in detail, their characteristics are compatible with the aromatic character associated with the oxatriazolio system and support the view that all the substances share a common chromophore (the oxatriazolio ring system).

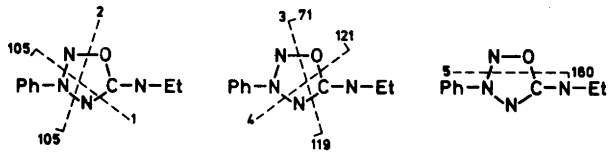
The mass spectra of the six oxatriazolioamide hydrochlorides support the proposed structures. The mass spectrum of *N*-[3-phenyl-5-(1,2,3,4-oxatriazolio)]ethylamide hydrochloride (Fig. 1) is representative for these compounds.

No peak corresponding to the ionized hydrochloride was observed, hence HCl is probably eliminated in the inlet system. Five fragmentation processes involve the meso-ionic ring (Table 1):

Table 1. Abundance of ring fragments from the six oxatriazolioamides relative to the base peak.

Fragmentation No.		1, 2	3	3	4	5	6
R	R′	RN_2^+	$RN_3^{+\cdot}$	$R'NCO^{+\cdot}$	RN_2O^+	M − NO	$M - N_2O$
Ph	Ph	36.0	0	4.4[a]	0	0.4	0.8
Ph	*p*-$O_2NC_6H_4$	32.2	0	1.0	0	0.8	0
Ph	Et	25.0	1.7	4.8	1.8	9.5	1.2
Ph	Bu^t	49.0	1.0	0.	3.9	14.3	0.8
Pr	H	0	0	37.8	0	6.2	0
Cyclo-hexyl	H	0	1.5	44.7	0	0.9	0

[a] High-resolution mass measurements revealed the composition of the *m/e* 119 to be C_7H_4NO.



Among these fragmentation modes, either 1 or 2 give the most abundant peak, *m/e* 105, corresponding to PhN_2^+. The fragmentation mode 3 gives rise to peaks, *m/e* 119 and *m/e* 71, which are due to $PhN_3^{+\cdot}$ and $EtNCO^{+\cdot}$, respectively. By loss of a hydrogen atom, $PhN_3^{+\cdot}$ may be stabilized with formation of the ion at *m/e* 118, which may have the structure of benzotriazole. The fourth fragmentation gives the ion PhN_2O^+ (*m/e* 121), and the last ring cleavage, 5, the prominent peak *m/e* 160, corresponding to loss of NO.

A sixth fragmentation mode is observed, resulting in the loss of N_2O. This elimination requires a skeletal rearrangement with a migration of the 3-substituent to the 4-position. This process is only observed when a phenyl group is attached at the 3-position. Loss of a hydrogen atom forms the ion at *m/e* 189, and an α-cleavage in the ethyl group results in *m/e* 175. Finally, in IIc, a peak was observed at *m/e* 93, which is believed to be $PhNH_2^{+\cdot}$;

this assignment is supported by a metastable peak at *m/e* 46.8, indicating the loss of HCN from $PhN_2^{+\cdot}$.[10]

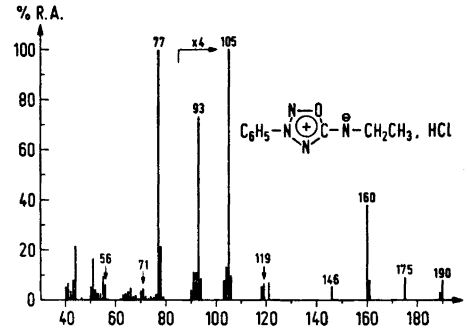


Fig. 1. The mass spectrum of *N*-[3-phenyl-5-(1,2,3,4-oxatriazolio)]-ethylamide hydrochloride.

EXPERIMENTAL

Melting points were determined on a Reichert melting point microscope and are uncorrected. The infrared spectra were recorded, using a Perkin-Elmer model 157 Infracord Ultraviolet spectra were recorded on a Unicam *SP* 800 Ultraviolet spectrophotometer. The mass spectra were obtained, using a double focusing mass spectrometer, type AEI-MS 902, operating at 70 eV. The ion source temperature was 200°C, and the ionizing current was 100 μA. The samples were introduced into the instrument through the direct insertion probe.

N-[3-Propyl-5-(1,2,3,4-oxatriazolio)]amide, hydrochloride. 1-Propylthiosemicarbazide (2.66 g), dissolved in ethanol (50 ml), and conc, hydrochloric acid (5 ml) were kept below 10°C. A solution of sodium nitrite (1.4 g) in water (2 ml) was added dropwise over a period of about 2 min, until the starch-iodide test for nitrous acid was positive. The reaction mixture slowly deposited elemental sulfur and sodium chloride. After completion of the reaction (30 min at ice-bath temperature), the undissolved material was removed by filtration, and the filtrate was evaporated to dryness *in vacuo*. After three recrystallizations from acetonitrile, the residue yielded 0.8 g (24 %) colourless crystals, m.p. 125 – 127°C (decomp.). (Found: C 29.18; H 5.47; Cl 21.52; N 33.90. Calc. for $C_4H_9ClN_4O$: C 29.19; H 5.51; Cl 21.54; N 34.04.) λ_{max} (in ethanol) 269 mμ (log ε 3.52).

*N-[3-Cyclohexyl-5-(1,2,3,4-oxatriazolio)]*amide, hydrochloride was prepared in a similar manner. The yield was 59 % after recrystallization from acetonitrile. M.p. 160°C (decomp.). (Found: C 40.92; H 6.40; Cl 17.56; N 27.73. Calc. for $C_7H_{13}ClN_4O$: C 41.06; H 6.41; Cl 17.33; N 27.38.) λ_{max} (in ethanol) 269 mμ (log ε 3.55). The IR spectrum was superimposable upon that of an authentic sample prepared according to the directions given by Finnegan and Henry.[3] The melting point (162 – 163°C, decomp.) was considerably higher than that reported by these authors (130 – 134°C, decomp.). Mixture m.p. 160 – 161°C (decomp.).

N-[3-Phenyl-5-(1,2,3,4-oxatriazolio)]ethylamide, hydrochloride was prepared in a similar manner, except that the reaction mixture was filtered into sodium hydroxide. The base was extracted with ether. The dried ethereal solution was then treated with hydrogen chloride and evaporated, leaving a yellow oil. Five recrystallizations from acetonitrile left a colourless solid. The yield was 18 %. (Found: C 47.41; H 4.96; Cl 15.74; N 24.80. Calc. for $C_9H_{11}ClN_4O$: C 47.69; H 4.89; Cl 15.64; N 24.72.) λ_{max} (in ethanol) 282 mμ (log ε 4.00). This substance was obtained by Busch and Schmidt,[6] but neither experimental conditions nor analytical data were given.

N-[3-Phenyl-5-(1,2,3,4-oxatriazolio)]tert-butylamide, hydrochloride. This compound was synthetized in a manner analogous to that used for the ethyl isomer. Yield 47 %. (Found: C 51.60; H 5.84; Cl 13.91; N 22.02. Calc. for $C_{11}H_{15}ClN_4O$: C 51.87; H 5.94; Cl 13.92; N 21.99.) λ_{max} (in ethanol) 283 mμ (log ε 3.97).

N-[3-Phenyl-5-(1,2,3,4-oxatriazolio)]4-nitrophenylamide. Substituting 1-phenyl-4-(4-nitrophenyl)thiosemicarbazide for 1,4-diphenylthiosemicarbazide, in the nitrosation procedure developed by Busch and Schmidt,[6] gave rise to an orange solid. Recrystallization from methanol afforded the analytical pure substance (78 %), m.p. 181 – 183°C. (Found: C 55.40; H 3.20; N 24.85. Calc. for $C_{13}H_9N_5O_3$: C 55.13; H 3.20; N 24.72.)

An attempt was made to make phenylazothioformic acid *tert*-butylamide react with nitrous acid; a solution of the azo compound [11] (2.5 mmol) in ethanol (10 ml) and hydrochloric acid (5 mmol) was stirred in an ice-bath, the temperature being kept below 10°C. One drop of an aqueous solution of sodium nitrite (1 ml, 2.5 mmol) was added. A persisting positive starch-iodide test for nitrous acid was evidence that no reaction had occurred.

Acknowledgements. The authors wish to thank Professor K. A. Jensen for helpful discussions during this study. We are also greatly indebted to Dr. G. Schroll for valuable suggestions concerning the mass spectrometric part of this investigation.

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Received June 18, 1970.