HETEROCYCLES, Vol.9, No.9, 1978

THIAZOLE N-OXIDES FROM 2-DIALKYLAMINO-1,3-OXATHIOLIUM CATION[1]

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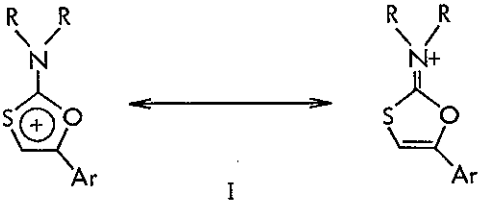
Reaction of hydroxylamine with 2-dialkylamino-5-phenyl-1,3-oxathiolium cation gave ω-(dialkylamino-oximinomercapto)acetophenone which was readily cyclized to afford 2-dialkylamino-4-phenylthiazole-3-oxide hydrochloride by ethanolic hydrochloric acid.

Based on studies on the chemistry of 2-dialkylamino-1,3-oxathiolium cation (I), we previously reported on the reactions of I with various nucleophiles giving a variety of heterocycles and related compounds.[1-7] The present communication deals with a novel and convenient synthesis of thiazole N-oxides from I by the reaction with hydroxylamine followed by acid treatment. We previously reported that heating of an aqueous solution of I hydrogensulfate (Ia) gave 2-oxo-3-phenyl-1,3-oxathiole (II) and allowing a DMF or CH_3CN solution of Ia with hydrogen sulfide to stand at room temperature gave 2-thioxo-5-phenyl-1,3-oxathiole (III) in quantitative yield.[7a,b] On the other hand, reactions of Ia with sodium hydroxide or sodium sulfide in aqueous solution afforded ring-opened derivatives (IV and V), respectively.[7a] These indicate that the pH of the solution of the reaction mixture affects the course of the



I

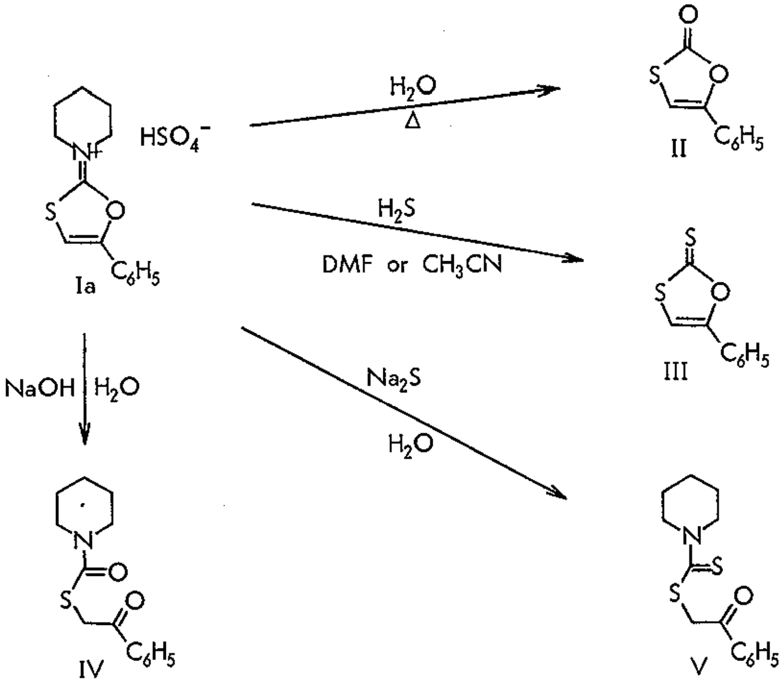


Chart 1

reaction of Ia giving substituted or ring-opened products.

Reaction of Ia with an excess of hydroxylamine in aqueous solution gave a complex mixture accompanied by decomposition and the products could not be isolated. But reaction of Ia with hydroxylamine hydrochloride in aqueous solution gave 2-oxo-5-phenyl-1,3-oxathiole (II) as the sole product.

In order to control the pH of the reaction mixture, six molar equivalents of hydroxylamine hydrochloride was neutralized with four molar equivalents of sodium hydroxide in aqueous solution and this solution was added to Ia under ice cooling. After 30 min extraction of this reaction mixture with ethyl acetate gave an oily product which showed a single spot on TLC. The structure of this compound was confirmed to be ω-(piperidino-oximinomercapto)acetophenone (VIa) on the basis of elemental analysis [$C_{14}H_{18}N_2O_2S$] and spectral data [ν_{max}^{Nuj} 1690 cm^{-1}(C=O); δ^{CDCl_3} 3.72 (2H, s, CH_2S)]. Treatment of VIa with ethanolic hydrochloric acid gave colorless crystals of mp 156-159°C (decomp) (VIIa). The yield of VIIa from Ia was 81%. Elemental analysis of VIIa gave a value which indicated one mole less of H_2O and one mole more of HCl than expected value. The possible structure of thiaoxazepine X was excluded on the basis of the spectral data and that of thiazole N-oxide hydrochloride (VIIa) was chosen as the NMR signal for the thiazole ring proton appeared at δ 6.78 and strong broad IR bands due to $N^+O\text{-}H$ at 2170 and $C=N^+$ at 1585 cm^{-1} (Table I). This

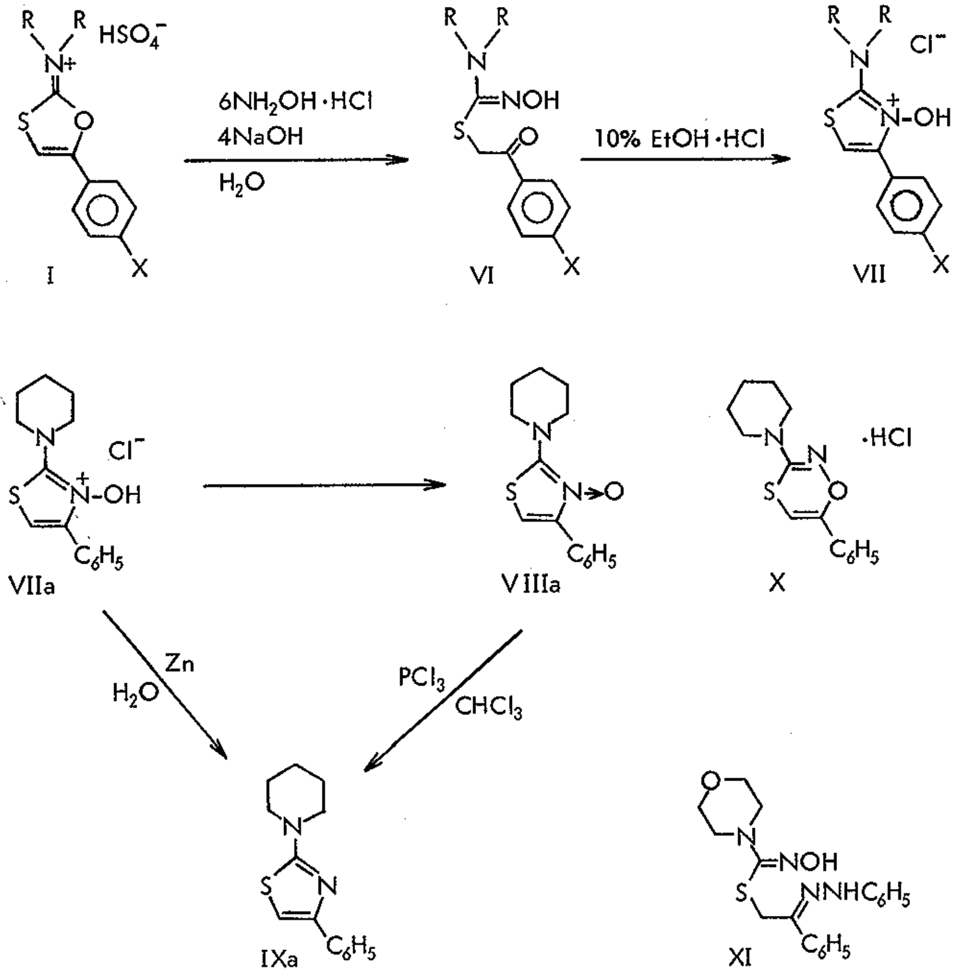


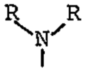
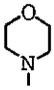
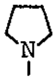
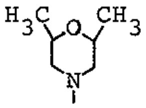
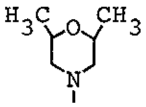
Chart 2

structure was confirmed by the following chemical conversion. Neutralization of this salt (VIIa) with aqueous sodium bicarbonate solution gave a free base (VIIIa), mp 94-95°C (decomp), in which the $N^{+}O$-H band disappeared and the C=N band appeared at 1500 cm^{-1} [δ^{CDCl_3} 6.75 (s, 1H, CH=)]. Deoxygenation of VIIIa was achieved by reaction with PCl_3 in chloroform or reaction of VIIa with zinc powder in water giving 4-phenyl-2-piperidinothiazole (IXa).[1]

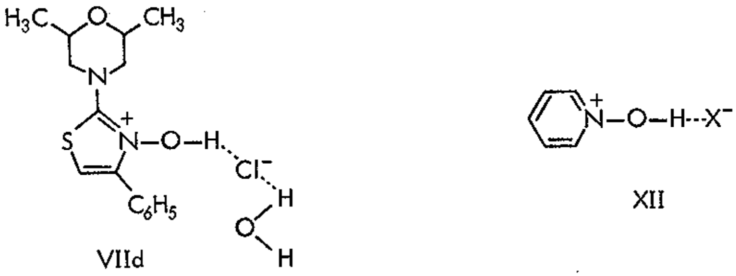
Since only a few examples of the synthesis of thiazole N-oxide by cyclization reaction are known,[8-10] our method is interesting as a novel one for obtaining thiazole N-oxides under mild conditions.

We used this method to prepare various thiazole N-oxides. The results are summarized in Table I. The intermediate VIb [mp 101-103°C (decomp); ν_{max}^{Nuj} 1690 cm^{-1} (C=O);

Table I. Physicochemical Properties of Thiazole N-Oxide Hydrochlorides (VII)

		X	mp (°C) (decomp)	Yield (% from I)	ν_{max}^{KBr} cm^{-1} N^+O–H	C=N$^+$	δ^{D_2O} (CH=)
VIIa		H	156-159	81	2170	1585	6.78
VIIb		H	182-185	65	2300	1560	7.13
VIIc		H	184-186	87	2280	1595	6.85
VIId*		Cl	155-157	76	2680	1600	7.28
VIIe		H	183	77	2210	1590	7.20

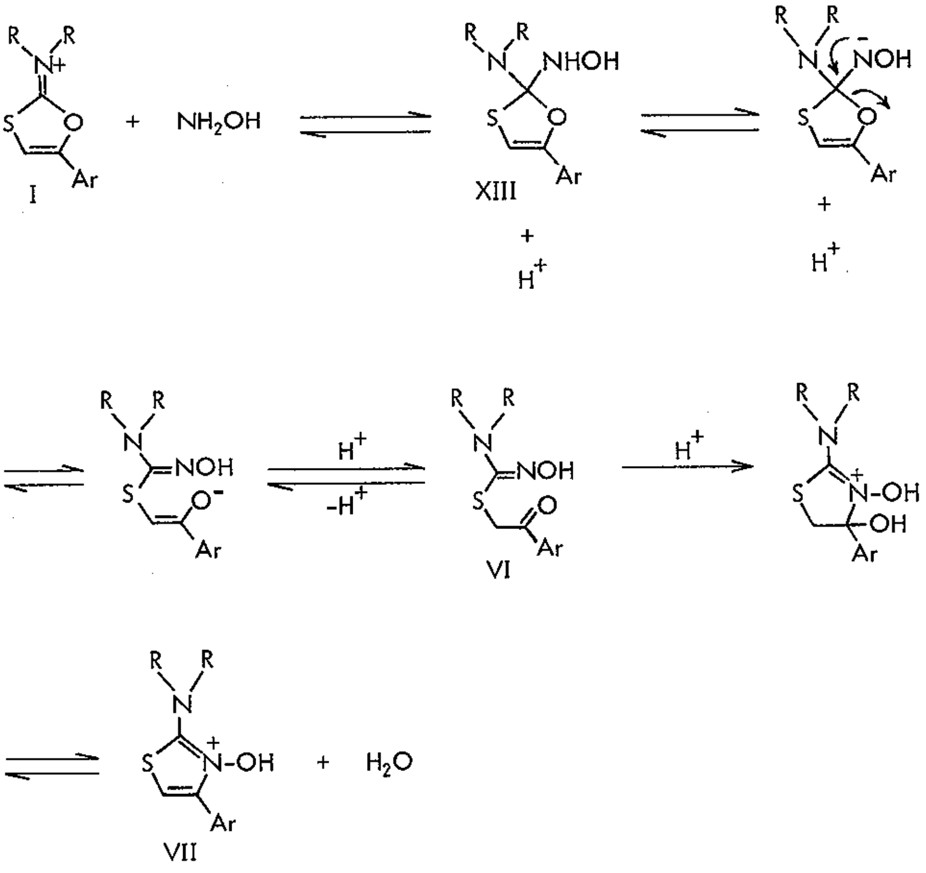
* Contains one mole of crystal H_2O.



VIId

XII

Chart 3



I

XIII

VI

VII

Chart 4

δ^{CDCl_3} 3.70 (s, 2H, SCH_2)] was converted into phenylhydrazone XI [mp 119-121°C, δ^{CDCl_3} 4.18 (s, 2H, SCH_2), 8.83 (br, 1H, NH)].

The N^+O-H band in VIId shifted to higher frequencies. This strong shift can be explained in terms of the strong interaction of crystal water with chlorine atom which reduces the ability of the chloride anion as a proton acceptor. As a result, N^+O-H bonding becomes strong and shifts to higher frequencies.[11] A proposed route from I to thiazole N-oxide (VII), which involves the neutral tetrahedral intermediate (XIII) formation[12,13] and the subsequent ring-opening to VI, then recyclization by acid is outlined in Chart 4.

Acknowledgement. The authors are grateful to Dr. Y. Matsui of this laboratory for his helpful discussions on the IR spectra.

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Received, 24th May, 1978