3 hours (with stirring). The resulting mixture was neutralized with sodium hydroxide, and the solid removed by filtration. After washing thoroughly with water and ether and triturating with hot ethanol, X was obtained as a yellow solid (0.39 g., 50%), m.p. 330° dec. A sample, purified by sublimation, melted at 342° dec.

Anal. Calcd. for $C_{28}H_{15}ON$: C, 85.96; H, 4.71; N, 4.36. Found: C, 86.16; H, 4.74; N, 4.24.

A sample of this compound (0.25 g.) was heated with zinc dust (20 g.) to red heat in a combustion tube. The material, which distilled onto the walls of the tube, was resublimed at 160° (0.4 mm.), and recrystallized from ethanol, to give 5-phenylbenz[a]acridine, m.p. 146–146.5° (after drying at 100°). Admixture with VI (prepared above) gave no depression in the melting point.

DURHAM, NORTH CAROLINA

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, FACULTY OF SCIENCE, CAIRO UNIVERSITY]

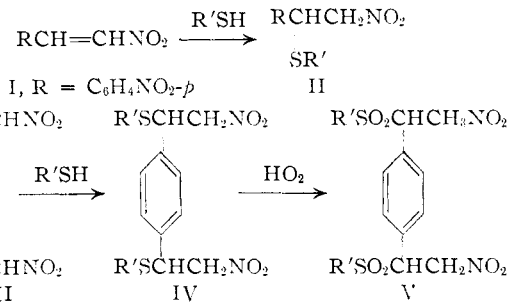
Reactions with Mercaptans. II.[1] Action of Aromatic Thiols on ω-Nitrostyrenes, 4-Styryl-5-oxazolones and 2-Phenyl-3,1-benzoxaz-4-one

BY AHMED MUSTAFA, ABDEL HAMID ELSAYED HARHASH AND MOHAMED KAMEL

RECEIVED SEPTEMBER 20, 1954

ω-Nitrostyrenes add aromatic thiols to give the β-nitrosulfides, which are oxidized readily to the β-nitrosulfones. The treatment of 4-styryl-5-oxazolones (VI and IX) with aromatic thiols resulted in opening of the hetero ring and addition to the double bond to yield VIII and X, respectively. Whereas, the hetero ring of benzo- and 3-benzoylbenzoxazol-2-one is stable toward aromatic thiols, that of 2-phenyl-3,1-benzoxaz-4-one (XI) is opened readily yielding the corresponding thioanthranilates (XII).

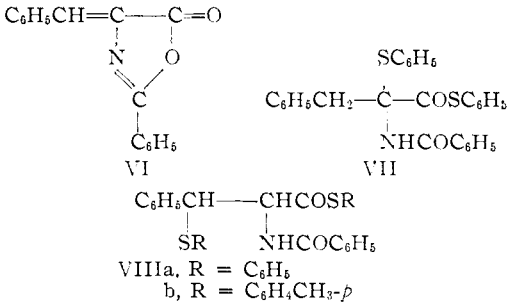
In conjunction with a study of the pharmacological action of sulfur-containing compounds against *Bilharziasis* snails,[2] the β-nitrosulfides (II and IV) were prepared by the addition of aromatic thiols to the ω-nitrostyrenes (I and III)[3] in the presence or absence of piperidine.[4]



The sulfides were oxidized to the corresponding sulfones (V) with hydrogen peroxide.[5] As the 1,4-addition of thiols to ω-nitrostyrene is established,[3] we have assigned structures II, IV and V, as indicated, to the β-nitrosulfides and sulfones prepared in this study, particularly since the reactions were not carried out under the influence of peroxides.[6]

The addition of mercaptans to the double bond of oxazolones of type VI, a reaction which has been extensively studied in connection with the synthesis of penicillamine, probably follows cleavage of the hetero ring.[7]

Ruhemann[8] has reported that thiophenol reacts with 2-phenyl-4-benzal-5-oxazolone (VI) to give the 2,1-addition product which he represented as VII. Under somewhat different conditions we have obtained the product described by Ruhemann. However, in view of the well-established mechanism for the addition of thiols to analogous α,β-unsaturated compounds (α,β-unsaturated ketones,[9] 1-cyano-1-cyclohexene[10] and alkylacrylonitriles[11]), this addition product of thiophenol and VI is probably VIIIa, β-phenylmercapto-β-phenyl-α-benzamidomonophenylthiopropionate, rather than VII.



Similarly, the treatment of VI with *p*-thiocresol caused opening of the hetero ring and addition to the double bond[12] to give VIIIb which was decomposed readily by alcoholic hydroxide[13] to give α-benzamidocinnamic acid and *p*-thiocresol. The acid was transformed readily to the oxazolone VI with acetic anhydride.

Terephthalylidene-bis-(2-phenyl-5-oxazolone) (IX) reacted with aromatic thiols in the presence of piperidine, in a manner similar to VI, to give the corresponding addition products X. The *p*-thiocresol addition product, on treatment with alcoholic potassium hydroxide, yielded *p*-thiocresol and an

(1) Part I: A. Mustafa, *J. Chem. Soc.*, 1370 (1951).

(2) M. O. Nolan, H. W. Bond and E. R. Mann, *Am. J. Trop. Med. and Hyg.*, **2** [4], 716 (1953).

(3) L. F. Cason and C. C. Wanser, THIS JOURNAL, **73**, 142 (1951); R. L. Heath and A. Lambert, *J. Chem. Soc.*, 1477 (1947).

(4) R. M. Ross, THIS JOURNAL, **71**, 3458 (1949).

(5) H. Gilman and N. J. Beaber, *ibid.*, **47**, 1450 (1925).

(6) S. O. Jones and E. E. Reid, *ibid.*, **60**, 2452 (1938); M. S. Kharasch, A. T. Read and F. R. Mayo, *Chemistry & Industry*, 752 (1938).

(7) H. T. Clarke, J. H. Johnson and R. Robinson, ed., "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 737.

(8) S. Ruhemann, *J. Chem. Soc.*, **87**, 468 (1905).

(9) T. Posner, *Ber.*, **35**, 809 (1902); B. H. Nicolet, THIS JOURNAL, **53**, 3066 (1931).

(10) R. M. Ross and F. W. Raths, *ibid.*, **73**, 129 (1951).

(11) R. M. Ross, H. L. Bushey and R. J. Rolih, *ibid.*, **73**, 540 (1951); R. M. Ross, *ibid.*, **71**, 3458 (1949).

(12) *Cf.* the action of hydrogen sulfide on 2-phenyl-4-isopropylidene-5-oxazolone in the presence of triethylamine; ref. 7.

(13) The instability of the S-C bond toward alkali has been demonstrated by B. H. Nicolet, THIS JOURNAL, **53**, 3066 (1931).

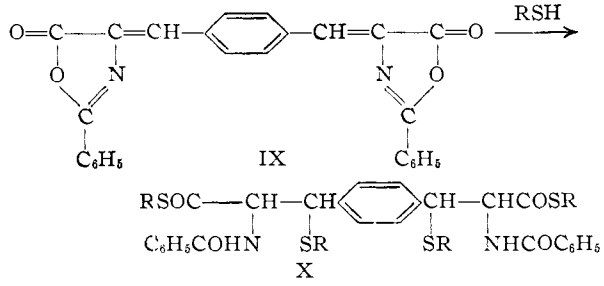
TABLE I

NITROSULFIDES II, IV AND NITROSULFONES V

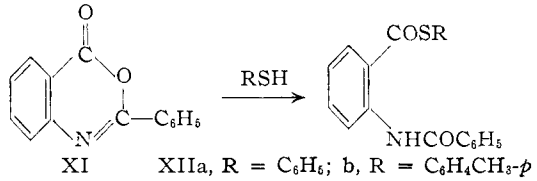
Compound	Thiol R′ =	M.p.,[a] °C.	Yield, %	Color[b] with H_2SO_4	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
II	C_6H_5[c]	121	82	Red	$C_{14}H_{12}N_2O_4S$	55.3	55.1	3.9	3.8	9.2	9.2	10.5	10.4
	$C_6H_4CH_3$-*o*	75	66	Red	$C_{15}H_{14}N_2O_4S$	56.6	56.5	4.4	4.4	8.8	8.6	10.1	9.9
	$C_6H_4CH_3$-*p*	72	85	Violet			56.3		4.2		8.7		10.0
	$CH_2C_6H_5$	73	71	Yell.-gr.			56.6		4.3		8.7		9.8
	$C_6H_4CH_3$-*p*[d,e]	70	74	Brown			56.4		4.1		8.8		9.8
IV	C_6H_5	167	78	Brown	$C_{22}H_{20}N_2O_4S_2$	60.0	59.8	4.5	4.4	6.4	6.1	14.5	14.2
	$C_6H_4CH_3$-*o*	121	65	Green	$C_{24}H_{24}N_2O_4S_2$	61.5	61.5	5.1	5.0	5.9	5.7	13.6	13.5
	$C_6H_4CH_3$-*m*	140	68	Brown			61.3		4.8		5.8		13.5
	$C_6H_4CH_3$-*p*	119–120	81	Green			61.5		5.0		5.9		13.5
	$CH_2C_6H_5$	89	72	Yell.-gr.			61.5		4.9		5.6		13.3
V	C_6H_5	238	91	.....	$C_{22}H_{20}N_2O_3S_2$	52.4	52.1	3.9	3.7	5.6	5.6	12.7	12.7
	$C_6H_4CH_3$-*o*	224	82	.....	$C_{24}H_{24}N_2O_3S_2$	54.1	53.8	4.5	4.3	5.3	5.3	12.0	11.7
	$C_6H_4CH_3$-*m*	226	84	.....			54.1		4.2		5.0		11.9
	$C_6H_4CH_3$-*p*	228	91	.....			53.7		4.5		5.1		12.0
	$CH_2C_6H_5$	204	86	.....			53.9		4.4		5.0		11.7

[a] Melting points are uncorrected. [b] The color was developed after the solution had stood at room temperature for a few minutes. [c] Van der Lee, *Rec. trav. chim.*, **44**, 1809 (1924). [d] R = $C_6H_4NO_2$-*o*. [e] J. Thiele, *Ber.*, **32**, 1294 (1899).

acid which was converted to the original oxazolone with acetic anhydride.

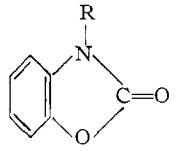


When 2-phenyl-3,1-benzoxaz-4-one (**XI**) was treated with thiophenol or *p*-thiocresol, the hetero ring was opened and the corresponding thioanthranilates (**XIIa,b**) were obtained. **XIIa** was hydrolyzed readily to N-benzoylanthranilic acid which was also prepared by the hydrolysis of N-benzoylphenylanthranilate, obtained by the action of phenol on **XI**.



XI XIIa, R = C_6H_5; b, R = $C_6H_4CH_3$-*p*

When benzoxazol-2-one (**XIIIa**) or 3-benzoylbenzoxazol-2-one (**XIIIb**) was treated with thiophenol, it was recovered almost unchanged. The oxazole ring seems to be more stable than the oxazone ring under these experimental conditions.



XIIIa, R = H
b, R = COC_6H_5

Experimental

β-Nitrosulfides.—Equimolecular quantities of the unsaturated nitro compound and the aromatic thiol were warmed on a water-bath for a half-hour after all of the solid had melted. The cooled reaction mixture was washed with cold light petroleum[14] and the resulting solid crystallized from ethyl alcohol to give the nitrosulfide.

The nitrosulfides (Table I) are colorless, easily soluble in benzene and choroform, but sparingly soluble in light petroleum and cold ethyl alcohol. They give an orange-red solution with hot aqueous sodium hydroxide (20%), but are insoluble in the cold reagent.

β-Nitrosulfones.—The nitrosulfide dissolved in glacial acetic acid was oxidized with hydrogen peroxide (30%). In the case of compounds of structure II, the mixture was kept overnight at room temperature; in the case of nitrosulfides of structure IV, the mixture was refluxed for a half-hour, a procedure which when applied to II, resulted in decomposition to give the original ω-nitrostyrene and thiol. The nitrosulfones derived from IV are listed in Table I. β-(Phenylsulfonyl)-β-(*p*-nitrophenyl)-α-nitroethane was obtained from II (R = $C_6H_4CH_3$-*p*); yield 60%, m.p. 185°.

Anal. Calcd. for $C_{15}H_{14}N_2O_6S$: C, 51.4; H, 4.0; N, 8.0; S, 9.1. Found: C, 51.2; H, 3.8; N, 7.9; S, 9.0.

In general, the nitrosulfones are sharply melting crystalline compounds easily soluble in hot glacial acetic acid and hot benzene, but difficultly soluble in light petroleum. They give an orange-red solution in hot aqueous sodium hydroxide, but are insoluble in the cold reagent; they show no color reaction with concentrated sulfuric acid.

Reaction of Aromatic Thiols with Oxazolones, 2-Phenyl-3,1-benzoxaz-4-one and Benzoxazol-2-one. A. 2-Phenyl-4-benzal-5-oxazolone (VI).—(1) A Schlenk[15] tube containing 1 g. of VI[16] and 1 ml. of freshly distilled thiophenol was sealed in a dry carbon dioxide atmosphere, wrapped in dark cloth and immersed in a boiling water-bath for 2 hours. The reaction mixture, after cooling, was washed several times with cold light petroleum (*ca.* 40 ml.) and the oily residue dissolved in petroleum ether. The colorless crystals, that separated on cooling, were recrystallized from benzene and identified as VIIIa (m.p. and mixed m.p.).

(2) A mixture of 0.5 g. of VI and 0.5 g. of *p*-thiocresol was warmed on the water-bath until all of the solid had melted; 5 drops of piperidine was then added. After the slight exothermic reaction had subsided, the mixture was heated for half an hour. The reaction mixture was allowed to cool, washed with light petroleum (*ca.* 25 ml.) and the resulting solid crystallized from benzene as colorless crystals of β-(*p*-tolylmercapto)-β-phenyl-α-benzamido-mono-(*p*-tolylthio)-propionate (VIIIb); yield 0.32 g., m.p. 159°. VIIIb is easily soluble in benzene, but sparingly soluble in cold ethyl alcohol; it gives a red color with concentrated sulfuric acid and is insoluble in aqueous sodium hydroxide.

(14) Light petroleum is the fraction boiling at 50–70° and petroleum ether that boiling at 60–80°.

(15) W. Schlenk and A. Thal, *Ber.*, **46**, 2840 (1913).

(16) E. Erlenmeyer, *Ann.*, **275**, 3 (1893).

TABLE II

OXAZOLONE ADDITION PRODUCTS (VIII, X); ADDITION PRODUCTS (XII) OF 2-PHENYL-3,1-BENZOXAZ-4-ONE

Compound	Thil. R =	M.p.,[a] °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
VIIIa	C_6H_5	156	42	$C_{28}H_{23}NO_2S_2$	71.6	71.5	4.9	4.7	2.9	2.8	13.6	13.5
	$C_6H_4CH_3$-*p*	159	37	$C_{30}H_{27}NO_2S_2$	72.4	72.1	5.4	5.3	2.8	2.7	12.9	12.7
X	C_6H_5	234	88	$C_{60}H_{40}N_2O_4S_4$	69.8	69.6	4.6	4.5	3.3	3.1	14.9	14.7
	$C_6H_4CH_3$-*o*	229	71	$C_{54}H_{48}N_2O_4S_4$	70.7	70.6	5.2	5.2	3.1	3.0	14.0	13.9
	$C_6H_4CH_3$-*m*	181	69			70.7		5.0		2.9		13.7
	$C_6H_4CH_3$-*p*	232	86			70.4		5.0		2.8		14.0
XII	C_6H_5	169–170	33	$C_{20}H_{15}NO_2S$	72.1	71.9	4.5	4.4	4.2	4.1	9.6	9.4
	$C_6H_4CH_3$-*p*	124–125	15	$C_{21}H_{17}NO_2S$	72.6	72.5	4.9	4.7	4.0	3.8	9.2	9.0
	C_6H_5[b]	160–161	33	$C_{20}H_{15}NO_3$	75.7	75.5	4.7	4.5	4.4	4.4		

[a] Melting points are uncorrected. [b] Prepared from XI and phenol.

B. **Terephthalylidene-bis-(2-phenyl-5-oxazolone)** (IX)[17] **and 2-Phenyl-3,1-benzoxaz-4-one** (XI).[18]—The reactions between IX or XI and the thiols were carried out by substantially the procedure described under A(2).[19] N-Benzoylphenylanthranilate was prepared from XI and phenol.

The corresponding reaction products X and XII which were obtained as colorless crystals are listed in Table II. The derivatives of IX are easily soluble in benzene and alcohol, difficultly soluble in light petroleum, and insoluble in cold aqueous sodium hydroxide (10%); they give an orange color with concentrated sulfuric acid on standing. The derivatives of XI, N-benzoylmonophenyl- and N-benzoylmono-*p*-tolyl thioanthranilates (XIIa, b), are soluble in chloroform and benzene, but sparingly soluble in light petroleum; they give a yellow color with concentrated sulfuric acid.

C. **Benzoxaz-** (XIIIa) **and N-Benzoylbenzoxaz-2-one** (XIIIb).—XIIIa[20] or XIIIb,[21] heated with thiophenol and piperidine, was recovered almost unchanged.

(17) P. Ruggli and O. Schetty, *Helv. Chim. Acta*, **23**, 721 (1940).

(18) G. Heller and G. Fiesselmann, *Ann.*, **324**, 118 (1902).

(19) XI and thiophenol were heated for 3 hours over a steam-bath without piperidine; the same reaction product in almost quantitative yield was obtained in the presence of piperidine with a heating period of a half-hour. The reaction of XI and *p*-thiocresol was carried out in the presence of piperidine.

(20) H. Lindemann and W. Schultheis, *Ann.*, **451**, 253 (1927).

(21) E. von Meyer, *J. prakt. Chem.*, **92**, 257 (1915).

Hydrolysis of Addition Products (VIIIb, X and XII).—A solution of 1 g. of VIIIb in 30 ml. of alcoholic potassium hydroxide (10%) was refluxed for a half-hour (water-bath). After cooling, the reaction mixture was poured onto crushed ice and acidified with dilute hydrochloric acid. The resulting solid was collected, washed with water and treated with carbonate solution. After recrystallization from light petroleum, the insoluble fraction gave colorless crystals, yield *ca.* 0.13 g., m.p. 43°, which were identified as *p*-thiocresol (m.p. and mixed m.p. and formation of a yellow lead salt). The carbonate solution, on acidification, gave colorless crystals which upon recrystallization from alcohol melted at 225°; they were identified as α-benzamidocinnamic acid (m.p. and mixed m.p.[22]). The acid, on boiling with acetic anhydride, was converted readily to the original oxazolone (VI) (m.p. and mixed m.p.).

X (R = $C_6H_4CH_3$-*p*) yielded *p*-thiocresol and an acid which could not be crystallized, but which was converted to the original oxazolone IX by acetic anhydride (m.p. and mixed m.p.). XIIa yielded colorless crystals which were identified as N-benzoylanthranilic acid (m.p. and mixed m.p.),[23] yield 89%, m.p. 180–181°. N-Benzoylanthranilate, prepared from XI and phenol, was hydrolyzed to the acid.

(22) E. Erlenmeyer, *Ber.*, **33**, 2036 (1900).

(23) von A. Brüchner, *Ann.*, **113**, 205 (1890).

GIZA, CAIRO, EGYPT

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Studies in the 10-Ethylphenothiazine System: Reductive Halogenation and N-Ethylation

BY HENRY GILMAN AND JOHN EISCH

RECEIVED FEBRUARY 21, 1955

The action of hydrohalic acids on 10-ethylphenothiazine-5-oxide was studied. With hydrochloric acid 3-chloro-10-ethylphenothiazine was obtained in improved yield. Hydrobromic acid gave a compound which was shown to be 3-bromo-10-ethylphenothiazine; hydriodic acid produced 10-ethylphenothiazine and a salt of 10-ethylphenothiazine-5-oxide and hydriodic acid. That the mechanism of this reaction involves reduction of the sulfoxide group and electrophilic attack of free halogen was shown by the isolation of *p*-bromophenol from the interaction of hydrobromic acid and 10-ethylphenothiazine-5-oxide in the presence of phenol. The N-ethylation of phenothiazine-5-oxide was accomplished in low yield and phenothiazine-5-dioxide underwent no discernible ethylation.

The action of hydrochloric acid on various phenothiazine sulfoxides to yield chlorophenothiazines has been termed reductive chlorination. Page and Smiles[1] first observed this reaction with phenothiazine-5-oxide and hydrochloric acid. The product was found to be an isomorphic mixture of mono- and dichlorophenothiazines. A chloro-3-nitrophenothiazine also was reported from the action of hydrochloric acid on 3-nitrophenothiazine-5-oxide.[2] The analogous reaction with 10-methylphenothiazine-5-oxide led to a monochloro-10-methylphenothiazine in excellent yield.[1] Recently, this latter compound was shown to be the 3-chloro derivative.[3] Workers in these laboratories have applied successfully the reaction to 10-

(1) H. J. Page and S. Smiles, *J. Chem. Soc.*, **97**, 1112 (1910).

(2) F. Kehrmann and O. Nossekno, *Ber.*, **46**, 2809 (1913).

(3) A. C. Schmalz and A. Burger, THIS JOURNAL, **76**, 5455 (1954).