Chemoselective Heterocyclizations of (4-Oxo-2-thioxothiazolidin-5-yl) *N*-Aryldithiocarbamates to Antifungal 1,3-Dithiolo-, 1,3-Oxathiolo, and Thiazolothiazoles

Lal Dhar S. Yadav,† Rajani K. Tripathi,‡ Rajesh Dwivedi,‡ and Harendra Singh*,‡

Department of Chemistry, University of Gorakhpur, Gorakhpur 273009, India, and Department of Chemistry, University of Allahabad, Allahabad 211002, India

(4-Oxo-2-thioxothiazolidin-5-yl) N-aryldithiocarbamates IVa–d undergo chemoselective heterocyclization with concentrated H_2SO_4, CH_3I, and NaOH to yield 1,3-dithiolo[4,5-*d*]thiazoles Va–d, 1,3-oxathiolo-[5,4-*d*]thiazoles VIa–d, and thiazolo[4,5-*d*]thiazoles VIIa–d, respectively. Compounds IVa–d—VIIa–d were tested in vitro for their antifungal action against *Helminthosporium oryzae* and *Cephalosporium saccharii* and found to be less active than mancozeb (M-45).

INTRODUCTION

In view of the antifungal activity associated with condensed ring systems incorporating a thiazole nucleus fused with imidazoles (Gupta et al., 1983; Ali and Saxena, 1981), 1,3,4-oxa(thia)diazoles (Yadav et al., 1989a; Dutta et al., 1986; Tokunaga et al., 1989; Singh et al., 1987), and 1,2,4-triazoles (Sahu and Nayak, 1990; Khalil et al., 1990), the synthesis of some new condensed 1,3-dithiolo[4,5-*d*]-thiazoles, 1,3-oxathiolo[5,4-*d*]thiazoles, and thiazolo[4,5-*d*]thiazoles has been undertaken in the present investigation as shown in Scheme I.

3-Aryl-5-bromorhodanines IIa,b were refluxed with ammonium *N*-aryldithiocarbamates IIIa,b for 2 h to furnish compounds IVa–d, which on cyclization with concentrated H_2SO_4, CH_3I, and NaOH afforded 6-aryl-2-(arylimino)-5,6-dihydro-2*H*-1,3-dithiolo[4,5-*d*]thiazole-5-thiones Va–d, 6-aryl-2-(arylimino)-5,6-dihydro-1,3-oxathiolo[5,4-*d*]thiazole-5-thiones VIa–d, and 3,4-diaryl-2,3,4,5-tetrahydro[4,5-*d*]thiazole-2,5-dithiones VIIa–d, respectively. It is interesting to note that compounds IVa–d—VIIa–d reported herein have been synthesized for the first time.

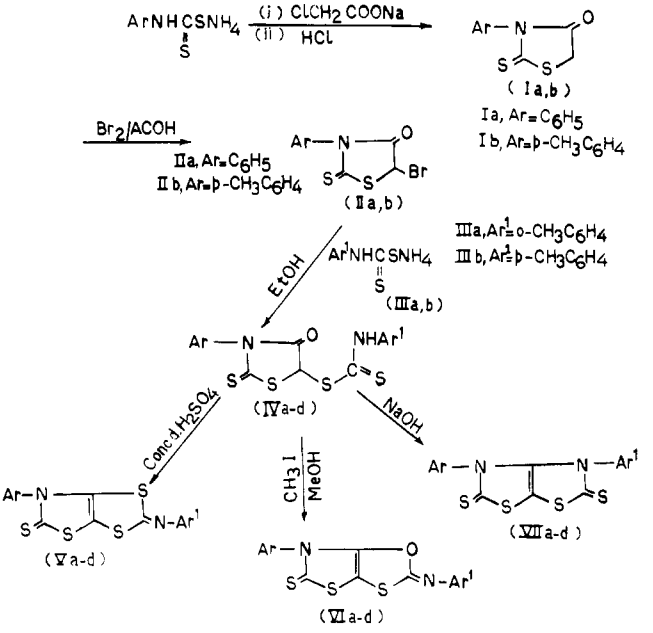
The starting materials, 3-arylrhodanines Ia,b, were prepared according to the method of Brown et al. (1956), and 3-aryl-5-bromorhodanines IIa,b were obtained by the bromination of the corresponding 3-arylrhodanines in glacial acetic acid (Gakhar et al., 1975). Structural assignments of the synthesized compounds were based on their elemental analyses and IR, ^1H NMR, and mass spectra (Tables I and II). Of the tested compounds IVa–d—VIIa–d, compounds VId, VIIc, and VIId displayed antifungal activity of the order of mancozeb (M-45) [a commercial fungicide; mixed manganous and zinc salt of *N,N'*-ethylenebis(dithiocarbamic acid)] at 1000 ppm concentration against *Helminthosporium oryzae* and *Cephalosporium saccharii*.

EXPERIMENTAL PROCEDURES

3-Arylrhodanines (Ia,b). These were prepared according to the method of Brown et al. (1956). Thus, a solution of sodium chloroacetate (0.2 mol) [prepared by mixing cold solutions of chloroacetic acid (0.2 mol) and NaOH (0.2 mol) in water] was adjusted to pH 7.1–7.5 by adding solid sodium carbonate. The solution was stirred and cooled to 5–10 °C, and then an aqueous suspension of ammonium *N*-aryldithiocarbamate was added dropwise and the stirring continued. The flask was allowed to warm to 35–40 °C. Then a warm solution of concentrated HCl plus H_2O (66 mL + 26 mL) was added to it, and the mixture was heated to 85–90 °C for 15 min. The yellow oil, which formed, was extracted with hot water to remove amine hydrochloride. Upon cooling, the desired product was solidified, which was recrystallized from ethanol. Compounds Ia and Ib agreed well with their analytical data already reported in literature (Brown et al., 1956).

3-Aryl-5-bromorhodanines (IIa,b). Rhodanines Ia,b (0.035 mol) were treated with 1.8 mL of bromine (5.58 g, 0.035 mol) in glacial acetic acid (150 mL) at 40–45 °C (Gakhar et al., 1975). Then the reaction mixture was kept overnight at room temperature and diluted with ice–water. The products thus precipitated were filtered, washed with saturated Na_2CO_3 solution followed

Scheme I



IVa-d to VIIa-d: a, Ar=C_6H_5, Ar¹=o-$CH_3C_6H_4$; b, Ar=C_6H_5, Ar¹=p-$CH_3C_6H_4$; c, Ar=p-$CH_3C_6H_4$, Ar¹=o-$CH_3C_6H_4$; d, Ar=Ar¹=p-$CH_3C_6H_4$.

* Author to whom correspondence should be addressed.
† University of Allahabad.
‡ University of Gorakhpur.

0021-8561/92/1440-1700$03.00/0

Table I. Analytical Data of Compounds IVa–d—VIIa–d

compd	yield, %	mp, °C	molecular formula	found (calcd), % C	H	N
IVa	62	135	$C_{17}H_{14}N_2OS_4$	52.29 (52.31)	3.62 3.59	7.22 7.18)
IVb	60	139	$C_{17}H_{14}N_2OS_4$	52.36 (52.31)	3.48 3.59	7.06 7.18)
IVc	59	128	$C_{18}H_{16}N_2OS_4$	53.50 (53.47)	3.85 3.96	7.01 6.93)
IVd	65	141–142	$C_{18}H_{16}N_2OS_4$	53.33 (53.47)	4.10 3.96	6.86 6.93)
Va	76	148–149	$C_{17}H_{12}N_2S_4$	54.92 (54.84)	3.33 3.23	7.67 7.53)
Vb	80	151	$C_{17}H_{12}N_2S_4$	54.98 (54.84)	3.36 3.23	7.42 7.53)
Vc	83	154–155	$C_{18}H_{14}N_2S_4$	56.02 (55.96)	3.78 3.63	7.35 7.26)
Vd	88	167	$C_{18}H_{14}N_2S_4$	55.89 (55.96)	3.58 3.63	7.15 7.26)
VIa	75	173–174	$C_{17}H_{12}N_2OS_3$	57.26 (57.30)	3.39 3.37	7.75 7.87)
VIb	81	152–153	$C_{17}H_{12}N_2OS_3$	57.45 (57.30)	3.42 3.37	7.95 7.87)
VIc	79	166	$C_{18}H_{14}N_2OS_3$	58.56 (58.38)	3.86 3.78	7.62 7.57)
VId	86	172	$C_{18}H_{14}N_2OS_3$	58.59 (58.38)	3.82 3.78	7.65 7.57)
VIIa	70	185	$C_{17}H_{12}N_2S_4$	54.68 (54.84)	3.11 3.23	7.62 7.53)
VIIb	73	168	$C_{17}H_{12}N_2S_4$	54.76 (54.84)	3.18 3.23	7.50 7.53)
VIIc	78	189	$C_{18}H_{14}N_2S_4$	56.08 (55.96)	3.76 3.63	7.39 7.23)
VIId	72	164–165	$C_{18}H_{14}N_2S_4$	56.12 (55.96)	3.96 3.63	7.12 7.23)

by water, and recrystallized from ethanol. IIa,b agreed well with their analytical data already reported in literature (Gakhar et al., 1975).

Ammonium *N*-Aryldithiocarbamates (IIIa,b). Following the standard procedure (Vogel, 1956) the amine (0.2 mol) was treated with ammonia solution (30 mL, sp gr 0.88) in an ice bath. To this was added CS_2 (0.25 mol) dropwise with continuous stirring. The mixture was stirred at room temperature for 2 h and kept overnight. The desired dithiocarbamate thus precipitated was filtered, washed with cold ethanol/ether (40 mL, v/v), and, after suction drying, used in the subsequent reaction.

(4-Oxo-2-thioxothiazolidin-5-yl) *N*-Aryldithiocarbamates (IVa–d). A mixture of IIa,b (0.05 mol), ammonium *N*-aryldithiocarbamates IIIa,b (0.05 mol), and anhydrous sodium acetate (0.05 mol) was refluxed in 250–300 mL of ethanol for 2 h. Then the solution was concentrated, cooled, and poured into water. The products thus precipitated were recrystallized from ethanol.

6-Aryl-2-(arylimino)-5,6-dihydro-2*H*-1,3-dithiolo[4,5-*d*]thiazole-5-thiones (Va–d). This was prepared by cyclodehydration of IVa–d (Maffii et al., 1958). Thus, compounds IVa–d (0.01 mol) were treated with concentrated H_2SO_4 (10 mL) dropwise and left for 30 min. Then crushed ice was added to it. Upon neutralization with NH_4OH the desired products precipitated, which were recrystallized from ethanol.

6-Aryl-2-(arylimino)-5,6-dihydro-2*H*-1,3-oxathiolo[5,4-*d*]thiazole-5-thiones (VIa–d). An equimolar mixture of IVa–d and CH_3I was refluxed for 6 h in 100 mL of methanol, and excess solvent was distilled under reduced pressure. The residues were treated with a 5% aqueous solution of NaOH, and the products thus obtained were washed with water and recrystallized from ethanol to furnish VIa–d.

3,4-Diaryl-2,3,4,5-tetrahydrothiazolo[4,5-*d*]thiazole-2,5-dithiones (VIIa–d). Solutions of IVa–d (0.01 mol) in aqueous NaOH (4%, 33 mL) and ethanol (20 mL) were refluxed for 2 h, cooled, and poured into water and brought to pH 5–6 with 5 N HCl. The precipitates thus obtained were filtered and recrystallized from ethanol.

Analytical data of all the synthesized compounds are recorded in Table I, and spectral data are given in Table II.

Antifungal Screening. The antifungal activity of the compounds IVa–d—VIIa–d was evaluated against two fungi, viz. *H. oryzae* and *C. saccharii*, by usual agar plate technique

Table II. Spectral Data of Compounds IVa–d—VIIa–d

compd	IR (KBr), cm^{-1} νC=O* νC=N	νC=S (exocyclic)	^{1}H NMR ($CDCl_3$) δ	MS/M$^+$ *m/z*
IVa	1710*	1110	9.44 (1 H, br s, N*H*) 7.10–8.08 (9 H, m, Ar *H*) 5.48 (1 H, s, SC*H*) 2.34 (3 H, s, *o*-CH_3)	390
IVb	1705*	1110	9.40 (1 H, br s, N*H*) 7.00–8.10 (9 H, m, Ar *H*) 5.50 (1 H, s, SC*H*) 2.26 (3 H, s, *p*-CH_3)	390
IVc	1710*	1100	9.46 (1 H, br s, N*H*) 7.16–8.10 (8 H, m, Ar *H*) 5.46 (1 H, s, SC*H*) 2.36 (3 H, s, *o*-CH_3) 2.20 (3 H, s, *p*-CH_3)	404
IVd	1695*	1105	9.52 (1 H, br s, N*H*) 7.18–8.16 (8 H, m, Ar *H*) 5.42 (1 H, s, SC*H*) 2.28 (6 H, s, 2 × *p*-CH_3)	404
Va	1670	1095	7.00–8.10 (9 H, m, Ar *H*) 2.32 (3 H, s, *o*-CH_3)	372
Vb	1680	1105	7.02–8.14 (9 H, m, Ar *H*) 2.20 (3 H, s, *p*-CH_3)	372
Vc	1675	1100	7.08–8.00 (8 H, m, Ar *H*) 2.34 (3 H, s, *o*-CH_3) 2.22 (3 H, s, *p*-CH_3)	386
Vd	1680	1100	7.10–8.20 (8 H, m, Ar *H*) 2.26 (6 H, s, 2 × *p*-CH_3)	386
VIa	1680	1105	6.98–8.00 (9 H, m, Ar *H*) 2.30 (3 H, s, *o*-CH_3)	358
VIb	1675	1100	6.96–8.02 (9 H, m, Ar *H*) 2.24 (3 H, s, *p*-CH_3)	358
VIc	1685	1105	7.12–8.16 (8 H, m, Ar *H*) 2.38 (3 H, s, *o*-CH_3) 2.20 (3 H, s, *p*-CH_3)	370
VId	1680	1105	7.18–8.22 (8 H, m, Ar *H*) 2.26 (6 H, s, 2 × *p*-CH_3)	370
VIIa		1090	6.98–8.02 (9 H, m, Ar *H*) 2.34 (3 H, s, *o*-CH_3)	372
VIIb		1095	7.10–8.12 (9 H, m, Ar *H*) 2.26 (3 H, s, *p*-CH_3)	372
VIIc		1100	7.16–8.12 (8 H, m, Ar *H*) 2.38 (3 H, s, *o*-CH_3) 2.20 (3 H, s, *p*-CH_3)	386
VIId		1095	7.20–8.22 (8 H, m, Ar *H*) 2.28 (6 H, s, 2 × *p*-CH_3)	386

(Horsfall, 1945) at 1000, 100, and 10 ppm concentrations exactly in the same way as described earlier (Yadav et al., 1988). The compounds were applied as suspensions in an acetone–water (20:80 v/v) mixture. Three replicate Petri plates per concentration of test compound and six replicate controls were used. The plates were incubated at 28 °C (±1 °C) for 96 h. The percent inhibition of mycelial growth was calculated by

$$\% \text{ inhibition} = [(C - T) \times 100]/C$$

where C is the average diameter of a fungal colony in millimeters in the control plates and T is the average diameter of a fungal colony in millimeters in the treated plates.

Mancozeb (M-45), a commercial fungicide, was also tested under similar conditions for comparison. The antifungal screening results of synthesized compounds are summarized in Table III.

RESULTS AND DISCUSSION

Chemoselectivity in the intramolecular cyclizations of IVa–d—VIIa–d may be rationalized by the "hard and soft acids and bases, *HSAB*, principle". In the case of cyclization of IVa–d with concentrated H_2SO_4, the protonation of carbonyl oxygen leads to the corresponding Va–d via intramolecular nucleophilic attack by thionic S of the dithiocarbamate moiety (Maffii et al., 1958). Methyl iodide, a soft Lewis acid, methylated the thionic S of the dithiocarbamate function of IV followed by cyclization to

Table III. Antifungal Screening Results of Compounds IVa–d—VIIa–d

compd	av % inhibition after 96 h against *H. oryzae* 1000 ppm	*H. oryzae* 100 ppm	*H. oryzae* 10 ppm	*C. saccharii* 1000 ppm	*C. saccharii* 100 ppm	*C. saccharii* 10 ppm
IVa	49	27	10	46	25	10
IVb	50	29	12	49	30	16
IVc	57	32	20	55	36	20
IVd	61	39	24	60	40	30
Va	70	51	39	75	48	38
Vb	75	52	40	74	51	42
Vc	78	56	42	78	56	43
Vd	79	59	46	81	57	46
VIa	73	53	40	73	53	41
VIb	80	55	45	82	55	44
VIc	86	58	48	85	58	47
VId	92	68	51	91	60	50
VIIa	83	61	48	80	55	41
VIIb	85	63	50	84	61	49
VIIc	91	68	50	94	68	51
VIId	95	71	53	97	71	54
mancozeb (M-45)[a]	100	85	71	100	83	70

[a] Commercial fungicide.

VI with the elimination of methanethiol, which could be easily detected. The reaction of IV with NaOH furnishes N,S-ambident anion, the terminal nitrogen of which attacks the carbonyl carbon to yield the corresponding VII (Postovskii and Vereshchagina, 1957).

From the antifungal screening data (Table III) it is obvious that most of the compounds had significant activity at higher concentration (1000 ppm) against both test fungi, but their activity considerably decreases on dilution (100 and 10 ppm). Of the tested compounds IVa–d—VIIa–d the most active compounds, VId, VIIc, and VIId, showed 91–97% growth inhibition of the test fungi compared with 100% inhibition by mancozeb (M-45) at 1000 ppm and inhibited more than 50% growth even at 10 ppm concentration. In general, compounds Va–d—VIIa–d were invariably more potent than their parent IVa–d. However, thiazolothiazoles VIIa–d were more active than dithiolothiazoles Va–d and oxathiolothiazoles VIa–d.

The greater antifungal activity of the compounds Va–d—VIIa–d than their parent IVa–d might be attributed to the more planar and compact structures of the former (Va–d—VIIa–d) than the latter (IVa–d). This presumption is supported by the earlier observations that compact size and planarity of a molecule often enhance its pesticidal properties (Rothwell and Wain, 1964; Singh et al., 1985; Yadav et al., 1989b). It was noted that introduction of a methyl group into the phenyl nucleus augments the antifungal action appreciably. Presumably, this is due to the lipophilic property of the methyl group, which favors the permeation of the compounds through lipoid barriers in the fungal cell membrane.

ACKNOWLEDGMENT

We are thankful to Prof. S. Giri, Head, Chemistry Department, Gorakhpur University, Gorakhpur, for providing necessary laboratory facilities and to RSIC Lucknow for recording the spectra and elemental analyses. R.K.T. sincerely thanks UGC, New Delhi, for the award of a Junior Research Fellowship.

LITERATURE CITED

Ali, A.; Saxena, R. K. Synthetic and Fungicidal Studies on Some 2-Arylidene-5-phenyl-4*H*-imidazo[2,1-b]thiazol-3(2*H*)-ones and Their Dibromo Products. *J. Indian Chem. Soc.* **1981**, *58*, 1117–18.

Brown, F. C.; Bradsher, C. K.; Morgan, E. C.; Tetenbaum, M.; Wilder, P., Jr. Some 3-Substituted Rhodanines. *J. Am. Chem. Soc.* **1956**, *78*, 384–88.

Dutta, M. M.; Goswami, B. N.; Kataky J. C. S. Studies on Biologically Active Heterocycles. Part I. Synthesis and Antifungal Activity of Some New Aroyl Hydrazones and 2,5-Substituted-1,3,4-oxadiazoles. *J. Heterocycl. Chem.* **1986**, *23* (3), 793–95.

Gakhar, H. K.; Chander, S. H.; Khurana, H. C. Pyrimido-ThiazoloThiadiazines. *J. Indian Chem. Soc.* **1975**, *52*, 155–57.

Gupta, G. D.; Jain, K. K.; Gupta, R. P.; Pujari, H. K. Heterocyclic Systems Containing Bridgehead Nitrogen Atom. Part XLVI. Reaction of 4,5-Disubstituted-2-mercaptoimidazoles with α-Halogenoketones and 1,2-Dibromoethane. *Indian J. Chem.* **1983**, *22B*, 268–69.

Horsfall, J. G. Quantitative Bioassay of Fungicides in the Laboratory. *Bot. Rev.* **1945**, *11*, 357–97.

Khalil, Z. H.; Abdel, H.; Ali, A.; Abdo Ahmed, A. New Pyrimidine Derivatives. Synthesis and Application of Thiazolo-[3,2-a]- and Triazolo[4,3-a]pyrimidine as Bactericides, Fungicides and Bioregulators. *Phosphorus Sulfur Silicon Relat. Elem.* **1989**, *45* (1–2), 81–93; *Chem. Abstr.* **1990**, *112*, 178857d.

Maffii, G.; Testa, E.; Ettorre, R. Synthesis and Pharmacology of Some Substituted 1,3,4-Thiadiazoles. *Farmaco. Ed. Sci.* 1958, *13*, 187–217; *Chem. Abstr.* **1959**, *53*, 2211c.

Postovskii, I. Ya.; Vereshchagina, N. N. Heterocyclic Compounds Prepared from Hydrazides I. 1,3,4-Triazole-5-thiones. *Zh. Obshch. Khim.* **1956**, 2583–88; *Chem. Abstr.* **1957**, *51*, 5055b.

Rothwell, K.; Wein, R. L. Plant Growth Regulating Substance XVII. S-Esters of Dithiocarbamates Derived from Amino Acids. *Ann. Appl. Biol.* **1963**, *51*, 161–67; *Chem. Abstr.* **1964**, *60*, 1041c.

Sahu, M.; Nayak, A. Studies on Thiazolidinones Part XX. Synthesis of Thiazolo[2,3-c]-s-triazol-5(6H)-ones and Their Arylidene Derivatives. *J. Indian Chem. Soc.* **1990**, *67* (3), 226–28.

Singh, H.; Yadav, L. D. S.; Chaudhary, J. P. "Synthesis of Some Fungitoxic 1,3,4-Oxadiazolo[3,2-a]-1,3,4-dithia/thiadiazines Involving Oxidative N-N and N-S Bond Formation. *Acta Chim. Hung.* **1985**, *118*, 11–15.

Singh, H.; Misra, A. R.; Yadav, L. D. S. Synthesis and Fungitoxicity of New 1,3,4-Oxadiazolo[3,2-a]-s-triazine-5,7-diones and Their Thione Analogues. *Indian J. Chem.* **1987**, *26B*, 1000–02.

Tokunaga, Y.; Ito, S.; Kojima, Y.; Maeno, S.; Sawai, N.; Sasao, Y. Preparation of 2-Phenylsulfinyl-5H-1,3,4-thiadiazolo-[3,2-a]pyrimidin-5-one Derivatives as Agricultural and Horticultural Fungicides. *Jpn. Kokai Tokkyo Koho* JP 0183,084 8983,084, 1989; *Chem. Abstr.* **1989**, *111*, 194785p.

Vogel, A. I. *A Text Book of Practical Organic Chemistry Including Qualitative Organic Analysis*, 3rd ed.; Longmans: London, 1956; p 643.

Yadav, L. D. S.; Misra, A. R.; Singh, H. Ring Transformation of Michael Adducts of 4-Benzylidene-5-oxazolones and 3-Mercapto-s-triazoles to 2,3-Dihydro-4H-s-triazolo[3,4-b][1,3]-thiazin-4-ones with Some Antifungal Activity. *J. Agric. Food. Chem.* **1988**, *36*, 633–36.

Yadav, L. D. S.; Shukla, K. N.; Singh, H. (4+2) Cycloaddition of conjugated Azomethines to Aryl Isothiocyanates and Fungitoxicity of the Resulting 6,7-Dihydro-1,3,4-thiadiazolo-[3,2-a]-s-triazine-5(H)-thiones. *Indian J. Chem.* **1989a**, *28B*, 78–80.

Yadav, L. D. S.; Misra, A. R.; Singh, H. Synthesis of New 7H-1,3,4-thiadiazolo[3,2-a][1,3,5]triazine-7-thiones as Potential Fungicides. *Pestic. Sci.* **1989b**, *25*, 219–225.

Received for review July 3, 1991. Revised manuscript received January 2, 1992. Accepted June 2, 1992.

Registry No. Ia, 1457-46-1; Ib, 3919-81-1; IIa, 56921-38-1; IIb, 56921-39-2; IIIa, 52908-85-7; IIIb, 13036-91-4; IVa, 142979-65-5; IVb, 142979-66-6; IVc, 142979-67-7; IVd, 142979-68-8; Va, 142979-69-9; Vb, 142979-70-2; Vc, 142979-71-3; Vd, 142979-72-4; VIa, 142979-73-5; VIb, 142979-74-6; VIc, 142979-75-7; VId, 142979-76-8; VIIa, 142979-77-9; VIIb, 143006-14-8; VIIc, 143006-15-9; VIId, 143006-16-0; ammonium *N*-phenyldithiocarbamate, 1074-52-8; sodium chloroacetate, 3926-62-3.