Isothiazoles IV: 4-Isothiazolin-3-one 1-Oxide and 1,1-Dioxides

S. N. Lewis, G. A. Miller, M. Hausman, and E. C. Szamborski

Research Division, Rohm and Haas Company, Spring House, Pennsylvania 19477

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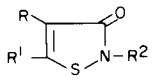
Representative 4-isothiazolin-3-one 1-oxides and 1,1-dioxides have been prepared by the reaction of *m*-chloroperbenzoic acid with the respective 4-isothiazolin-3-ones. Chromic acid, dinitrogen tetroxide, and nitric acid have also been successfully employed in the oxidation of several 3-hydroxyisothiazoles to their respective 1-oxides.

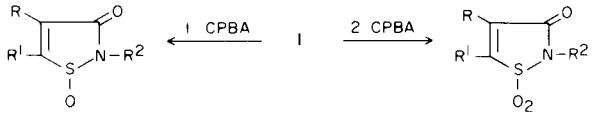
Recent advances (1,2) in the synthesis of the 4-isothiazolin-3-one ring system (I) have made this series readily available for investigation. We now report their chemical oxidation.



I

The reaction of I (Scheme I) with *m*-chloroperbenzoic acid (CPBA) gave either the 4-isothiazolin-3-one 1-oxide (II) or 1,1-dioxide (III) in good yield (Table I) depending upon the reaction stoichiometry. Other oxidants, including

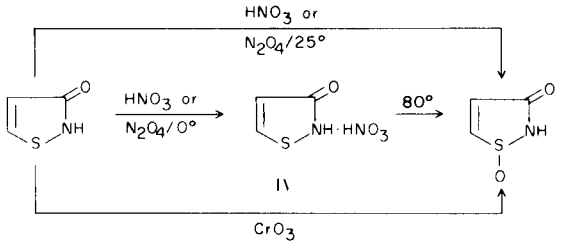
SCHEME I



II III

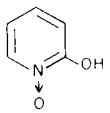
nitric acid, dinitrogen tetroxide, and chromic acid were especially effective in converting 3-hydroxyisothiazoles (I, R^2 = H) to their 1-oxides (Scheme II). The intermediacy of the nitrate salt IV in the nitric acid oxidation of I ($R = R^1 = R^2 = H$) was confirmed by its isolation and subsequent thermal decomposition to IIa. Surprisingly, at 0° dinitrogen tetroxide also gave the nitrate salt even with precautions to exclude moisture.

SCHEME II

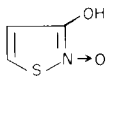


IV

The products II and III were identified by their elemental analyses and infrared and NMR spectra. Typical sulfoxide and sulfonyl absorptions were observed in the infrared (Nujol) at 1060-1190 cm^{-1} and at 1330 cm^{-1} and 1150-1190 cm^{-1}, respectively. Although Katritzky and Jones (3) have assigned the 1110 cm^{-1} region in pyridin-2-one 1-oxide (V) to an N-O stretching vibration, the analogous structure VI for the monoxide IIa was excluded by its ready oxidation to IIIa, which in turn displayed the typical strong sulfonyl absorptions at 1330 cm^{-1} and 1150 cm^{-1}.

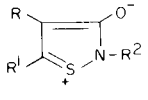


V



VI

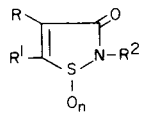
The NMR spectra of I, II, and III (Table II) revealed an interesting relationship of the 4- and 5-proton absorptions with increasing sulfur oxidation. The 4-proton absorption was shifted downfield (7-33 Hz) with sulfur oxidation in accord with an expected increase in electron withdrawal from the isothiazole ring. In contrast, the 5 proton absorption was shifted upfield by 31-38 Hz. This apparent anomaly can be rationalized by consideration of VII as a resonance contributor to the parent 4-isothiazolin-



VII

TABLE I

1-Oxo and 1,1-Dioxo-4-isothiazolin-3-ones

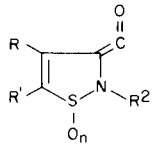


Compound	R	R^1	R^2	n	Yield, %	M.p. °C	Empirical Formula	Elemental Analysis Calcd. C	H	N	S	Found C	H	N	S
IIa	H	H	H	1	60 (a)	95-96	$C_3H_3NO_2S$	30.77	2.56	11.97	27.35	30.54	2.32	11.80	27.10
a	H	H	H	1	60 (b)	93-95	$C_3H_3NO_2S$	30.77	2.56	11.97	27.35	30.78	2.63	11.21	27.38
a	H	H	H	1	35 (c)	92-94	$C_3H_3NO_2S$	30.77	2.56	11.97	27.35	30.98	2.80	11.94	27.42
b	Br	CH_3	H	1	46 (a)	136-138	$C_4H_4BrNO_2S$	22.86	1.90	6.67	15.24	23.05	2.01	6.55	14.96
b	Br	CH_3	H	1	100 (b)	138-140	$C_4H_4BrNO_2S$	22.86	1.90	6.67	15.24	23.15	2.17	6.65	15.10
b	Br	CH_3	H	1	56 (d)	136-138	$C_4H_4BrNO_2S$	22.86	1.90	6.67	15.24	22.98	2.03	6.24	15.18
c	H	H	C_8H_{17}-*t*	1	100 (a)	75-76	$C_{11}H_{19}NO_2S$	57.64	8.30	6.11	13.97	57.75	8.48	6.18	13.75
d	CH_3	H	$C_6H_3Cl_2$(3,4)	1	89 (a)	108-111	$C_{10}H_7Cl_2NO_2S$		2.54	5.07	11.59		2.56	5.15	11.80
e	H	H	$CONHCH_3$	1	80 (a)	160-163	$C_5H_6N_2O_3S$	34.48	3.45	16.09	18.39	34.52	3.48	16.00	18.35
f	H	H	$CONHC_2H_5$	1	70 (a)	102-103	$C_6H_8N_2O_3S$	38.30	4.26	14.89	17.02	38.29	4.40	14.77	16.93
g	H	H	$CONHCH_2CO_2C_2H_5$	1	61 (a)	88-91	$C_8H_{10}N_2O_5S$	39.02	4.07	11.38	13.01	39.70	4.15	11.35	12.87
h	H	CH_3	$CONHC_6H_5$	1	67 (a)	170-173	$C_{11}H_{10}N_2O_3S$	52.80	4.00	11.20	12.80	52.98	4.27	11.41	12.47
i	H	H	$CONHC_6H_4Cl$(3)	1	87 (a)	148-151	$C_{10}H_7ClN_2O_3S$	44.36	2.59	10.35	11.83	44.26	2.80	10.34	12.08
j	H	H	$CONHC_6H_3Cl_2$(2,5)	1	72 (a)	153-154	$C_{10}H_6Cl_2N_2O_3S$	39.34	1.97	9.18	10.49	39.49	2.04	9.24	10.82
k	H	H	$CONHC_6H_3Cl_2$(3,4)	1	81 (a)	189-192	$C_{10}H_6Cl_2N_2O_3S$	39.34	1.97	9.18	10.49	39.49	1.93	9.24	10.20
l	H	CH_3	$CONHC_6H_3Cl_2$(3,4)	1	72 (a)	172-175	$C_{11}H_8Cl_2N_2O_3S$	41.38	2.51	8.78	10.03	41.66	2.60	8.90	9.83
m	Cl	Cl	H	1	50 (b)	146-148	$C_3HCl_2NO_2S$	19.35	0.54	7.53	17.20	19.47	0.60	7.55	17.31
IIIa	H	H	H	2	50 (a)	118-120 dec.	$C_3H_3NO_3S$	27.07	2.26	10.53	24.06	27.23	2.61	10.36	23.98
b	H	CH_3	H	2	20 (a)	105-110	$C_4H_5NO_3S$	32.65	3.40	9.52	21.77	32.83	3.47	9.21	21.45
c	H	H	C_8H_7-*t*	2	82 (a)	63-65	$C_{11}H_{19}NO_3S$	53.88	7.76	5.71	13.06	53.77	7.79	5.73	12.82
d	CH_3	H	$C_6H_3Cl_2$(3,4)	2	51 (a)	167-170	$C_{10}H_7Cl_2NO_3S$	41.10	2.40	4.79	10.96	41.11	2.55	4.82	10.90
e	H	H	$CONHC_2H_5$	2	44 (a)	125-128 dec.	$C_6H_8N_2O_4S$	35.29	3.92	13.72	15.69	35.33	4.26	13.59	15.50

(a) CPBA was used as oxidant. (b) Dinitrogen tetroxide was used as oxidant. (c) Nitric acid was used as oxidant. (d) Chromic acid was used as oxidant.

TABLE II

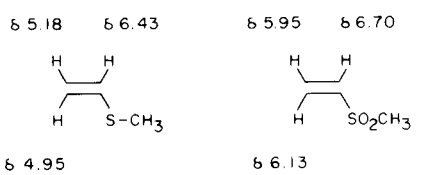
Nuclear Magnetic Resonance Data



Compound	R^2	R	R^1	n	Chemical Shifts (a,b) δ R^2	R	R^1	Coupling Constant $J_{4,5}$ Hz	4H Δ Hz	5H Δ Hz
	H (c)	H	H	0	4.30(s)	6.90(d)	9.03(d)	4.0		
IIa	H (c)	H	H	1	4.26(s)	7.21(d)	8.41(d)	6.0	+19	-37
IIIa	H (c)	H	H	2	5.58(s)	7.22(d)	8.50(d)	7.0	+1	+5
	H	H	CH_3	0	12.20(s)	6.20(m)	2.42(m)			
IIIb	H	H	CH_3	2	8.05(s)	6.32(m)	2.35(d)		+7	
	C_8H_{17}-*t*	H	H	0	2.12(s)	6.05(d)	7.82(d)	6.5		
					1.65(s)					
					0.92(s)					
IIc	C_8H_{17}-*t*	H	H	1	1.96(d)	6.50(d)	7.31(d)	7.01(d)	+27	-31
					1.68(d)					
					0.94(s)					
IIIc	C_8H_{17}-*t*	H	H	2	2.03(s)	6.55(d)	7.30(d)	8.0	+3	-1
					1.73(s)					
					0.97(s)					
	$C_6H_3Cl_2$-3,4	CH_3	H	0	7.71(s)	2.05(s)	7.71(s) (d)			
					7.40(s)					
IId	$C_6H_3Cl_2$-3,4	CH_3	H	1	7.12(m)	2.12(m)	6.96(m) (d)			
IIId	$C_6H_3Cl_2$-3,4	CH_3	H	2	7.50(m)	2.15(d)	7.13(m) (d)			
					7.31(m)					
					7.13(m)					
	$CONHC_2H_5$	H	H	0	3.47(m)	6.27(d)	7.91(d)	6.5		
					1.33(t)					
IIIe	$CONHC_2H_5$	H	H	2	3.44(m)	6.63(d)	7.37(d)	6.5	+22	-32
					1.23(t)					
	$CONHCH_3$	H	H	0	2.98(d)	6.20(d)	8.12(d)	6.5		
IIe	$CONHCH_3$	H	H	1	2.90(d)	6.58(d)	7.49(d)	7.0	+23	-38
	$CONHC_6H_3Cl_2$-2,5	H	H	0	8.37(d)	6.31(d)	8.28(d)	6.5		
					7.21(s)					
IIj	$CONHC_6H_3Cl_2$-2,5	H	H	1	8.38(d)	6.86(d)	7.73(d)	6.5	+33	-33
					7.21(s)					
	$CONHC_6H_5$	H	CH_3	0	7.30(m)	6.10(m)	2.47(d)			
IIh	$CONHC_6H_5$	H	CH_3	1	7.38(m)	6.42(m)	2.39(d)		+19	

(a) Deuteriochloroform solutions with tetramethylsilane internal standard. (b) Multiplicity in brackets: s = singlet; d = doublet; t = triplet; m = multiplet. (c) Deuteriodimethylsulfoxide solution. (d) Overlap with aromatic protons.

3-one system (I). Presumably the consequent electron deficiency at sulfur encouraged by this delocalization becomes less favorable with oxidation, resulting in an overall upfield shift of the 5-proton absorption of II and III with respect to I. This effect apparently is large enough to overcome the downfield shift suggested by simple comparison of I, II, and III to the model system VIII (5) which, without benefit of extended delocalization, displays only the evidence of increased inductive deshielding by the sulfonyl group.



VIII

Infrared data also support the contribution of VII to the 4-isothiazolin-3-one system (I), indicating a progressive

shift to higher frequency of the carbonyl absorption for I (1610-1650 cm^{-1}) to 1670-1730 cm^{-1} and 1690-1740 cm^{-1} for II and III, respectively.

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian T-60 Spectrometer. Elemental analyses were performed by the analytical department of the Research Division of Rohm and Haas Company. The 4-isothiazolin-3-ones (I) were prepared according to previously reported procedures (1,2,4). The *m*-chloroperbenzoic acid was from FMC Corporation and was 81% active oxygen by iodide-thiosulfate titration.

4-Isothiazolin-3-one 1-Oxide (IIa). The following procedure illustrates the use of CPBA.

To a solution of 10.1 g. (0.10 mole) of 3-hydroxyisothiazole (Ia) in 100 ml. of methylene chloride was added dropwise at 0-10° a solution of 21.3 g. (0.10 mole) of *m*-chloroperbenzoic acid in 200 ml. of methylene chloride. After completion of the addition, the reaction slurry was stirred 0.5 hour, then evaporated to dryness. The solid residue was triturated with ether, and the insoluble solid was collected by filtration. Obtained in this way was 7.1 g. (60%) of IIa, m.p. 95-96° from hot benzene and not depressed when mixed with IIa prepared by dinitrogen tetroxide or nitric acid oxidation.

4-Isothiazolin-3-one 1-Oxide (IIa). The following procedure illustrates the use of dinitrogen tetroxide.

To a solution of 20.2 g. (0.20 mole) of 3-hydroxyisothiazole (Ia) in 150 ml. of ether at 0-5° was added a solution of 18.4 g. (0.20 mole) of dinitrogen tetroxide (N_2O_4) in 25 ml. of hexane over a period of 5 minutes. The reaction slurry which formed was stirred for 10 minutes, then filtered to give 21 g. (64%) of white solid 3-hydroxyisothiazole nitrate salt, m.p. 87° (vigorous dec.).

Anal. Calcd. for $C_3H_4N_2O_4S$: C, 21.98; H, 2.44; N, 17.07; S, 19.52. Found: C, 21.96; H, 2.54; N, 16.73; S, 19.20.

This nitrate salt when crystallized from hot benzene gave off brown fumes, presumably nitrogen dioxide, and the benzene solution yielded when cooled 14 g. (60%) of IIa, m.p. 93-95°.

4-Isothiazolin-3-one 1-Oxide (IIa). The following procedure illustrates the use of nitric acid.

A solution of 5 g. (0.05 mole) of 3-hydroxyisothiazole in 30 ml. of water was added to 50 g. of concentrated (70%) nitric acid at 0°. The precipitate was filtered off and dried to give 6.2 g. (76%) of 3-hydroxyisothiazole nitrate salt, m.p. 89° (vigorous dec.).

Anal. Found: C, 22.13; H, 2.58; N, 16.78; S, 19.65.

Two g. of this salt when crystallized from hot benzene gave evolution of a brown gas and yielded 0.5 g. (35%) of IIa, m.p. 92-94°, identical to IIa prepared by CPBA and dinitrogen tetroxide oxidations.

4,5-Dichloro-4-isothiazolin-3-one 1-Oxide (IIm).

A solution of 5 g. (0.029 mole) of 4,5-dichloro-3-hydroxyisothiazole (I) in 200 ml. of ether was treated at 10° with 2.7 g. (0.029 mole) of dinitrogen tetroxide in 20 ml. of hexane over a period of 10 minutes. The reaction was then evaporated to a solid residue which was crystallized from benzene to give 2.75 g. (50%) of IImm, m.p. 146-148°.

4-Bromo-5-methyl-4-isothiazolin-3-one 1-Oxide (IIb). The following procedure illustrates the use of chromic acid.

A solution of 19.4 g. (0.1 mole) of 4-bromo-5-methyl-3-hydroxyisothiazole (4) in 750 ml. of acetone (purified by distillation from solid potassium permanganate) was treated dropwise at 25°, under a continuous stream of nitrogen, with 50 ml. (0.20 mole) of Jones' reagent (6) over a period of 1.5 hours. After stirring for 18 hours at 25°, the reaction was concentrated to a green, oily solid residue. Ether extraction of this residue yielded, after drying and evaporation of the ether 11.8 g. (56%) of IIb, m.p. 136-138° from chloroform.

2-*t*-Octyl-4-isothiazolin-3-one 1-Oxide (IIc).

To an acetone solution (200 ml.) of 8.5 g. (0.04 mole) of 2-*t*-octyl-4-isothiazolin-3-one (1) at 5° was added a solution of 8.5 g. (0.04 mole) of *m*-chloroperbenzoic acid in 30 ml. of acetone over 20 minutes. After stirring overnight the acetone solution was evaporated to a gummy solid residue, which was extracted with cold chloroform, and filtered to remove *m*-chlorobenzoic acid. The chloroform filtrate was then evaporated to yield 9.2 g. (100%) of IIc, m.p. 75-76° (ligroin (90-120°)).

2-(3,4-Dichlorophenyl)-4-methyl-4-isothiazolin-3-one 1-Oxide (IId).

To a slurry of 5.2 g. (0.02 mole) of 2-(3,4-dichlorophenyl)-4-methyl-4-isothiazolin-3-one (1) in 200 ml. of acetone at 0-5° was added over 30 minutes 4.3 g. (0.02 mole) of *m*-chloroperbenzoic acid in 20 ml. of acetone. After stirring for 30 minutes a solution formed. The reaction was stirred overnight; then the acetone was removed to leave a solid residue. This material was slurried in 200 ml. of ether and filtered to give 4.9 g. (89%) of IId as the solid precipitate, m.p. 108-111° from ligroin (90-120°).

2-(*N*-Ethylcarbamoyl)-4-isothiazolin-3-one 1-Oxide (IIf). The following procedure illustrates the general method used to prepare 2-carbamoyl-4-isothiazolin-3-one 1-oxides.

A solution of 2-(*N*-ethylcarbamoyl)-4-isothiazolin-3-one (2) (6.0 g., 0.035 mole) in 250 ml. of acetone was treated in 20 minutes at 0-5° with 7.6 g. (0.036 mole) of *m*-chloroperbenzoic acid in 20 ml. of acetone. After stirring overnight the reaction was evaporated to a white solid residue. Extraction of this material with ether gave 4.6 g. (70%) of IIf as an insoluble solid, m.p. 102-103°.

4-Isothiazolin-3-one 1,1-Dioxide (IIIa).

A solution of 10.1 g. (0.10 mole) of 3-hydroxyisothiazole (I) in 200 ml. of methylene dichloride was treated in portions with 46.8 g. (0.22 mole) of *m*-chloroperbenzoic acid. A slurry formed after a few minutes and was stirred at 25° for several days. The solid precipitate obtained by filtration was thoroughly extracted with chloroform to leave 6.65 g. (50%) of IIIa as an insoluble white solid, m.p. 118-120° dec.

4-Isothiazolin-3-one 1,1-Dioxide (IIIa).

A solution of 2.85 g. (0.024 mole) of IIa in 100 ml. of methylene dichloride was treated in portions at 25° with 5.1 g. (0.024 mole) of *m*-chloroperbenzoic acid. A slurry formed and was stirred for two days at room temperature. The mixture was evaporated to dryness, and the residue was slurried with two successive portions of benzene. Obtained in this way was 1.7 g. (53%) of IIIa as an insoluble solid, m.p. 113-118°, identical to IIIa obtained by CPBA oxidation of 3-hydroxyisothiazole.

Anal. Calcd. for $C_3H_3NO_3S$: C, 27.06; H, 2.26; N, 10.53; S, 24.06. Found: C, 27.48; H, 2.30; N, 10.54; S, 24.02.

2-*t*-Octyl-4-isothiazolin-3-one 1,1-Dioxide (IIIc).

A solution of 10.65 g. (0.05 mole) of 2-*t*-octyl-4-isothiazolin-3-one (1) in 100 ml. of methylene dichloride was treated at 20° in portions with 23.4 g. (0.11 mole) of *m*-chloroperbenzoic acid. A slurry formed and was stirred at 25° for two days. The solid was removed by filtration, and the filtrate was then evaporated to an oil residue. This material was taken up in hexane, washed with aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and evaporated to give 10 g. (82%) of IIIc, m.p. 57-62°. Crystallization from pentane gave m.p. 63-65°.

2-(3,4-Dichlorophenyl)-4-methyl-4-isothiazolin-3-one 1,1-Dioxide (IIId).

A solution of 4.5 g. (17.3 mmoles) of 2-(3,4-dichlorophenyl)-4-methyl-4-isothiazolin-3-one (1) in 100 ml. of methylene dichloride at 25° was treated in portions with 8.1 g. (38.1 mmoles) of *m*-chloroperbenzoic acid. A slurry formed and was stirred at 25° for several days. The slurry was then filtered, and the filtrate was evaporated to leave a solid residue. Thorough extraction of this material with ether yielded 2.6 g. (51%) of IIId as an insoluble solid, m.p. 167-170°.

2-(*N*-Ethylcarbamoyl)-4-isothiazolin-3-one 1,1-Dioxide (IIIe).

A solution of 5.16 g. (0.03 mole) of 2-(*N*-ethylcarbamoyl)-4-isothiazolin-3-one (2) in 100 ml. of methylene dichloride was treated at 25° in portions with 14.0 g. (0.066 mole) of *m*-chloroperbenzoic acid. A slurry formed and was stirred for several days. The mixture was then filtered, and the filtrate was evaporated to a solid residue. This material was washed thoroughly with benzene to give 2.7 g. (44%) of IIIe as an insoluble solid, m.p. 125-128° dec.

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