Oxidation Products of 5-Isoxazolethiols and 5-Ethylthioisoxazoles: Sulfoxides, Sulfones, Sulfonic Acids, and Derivatives

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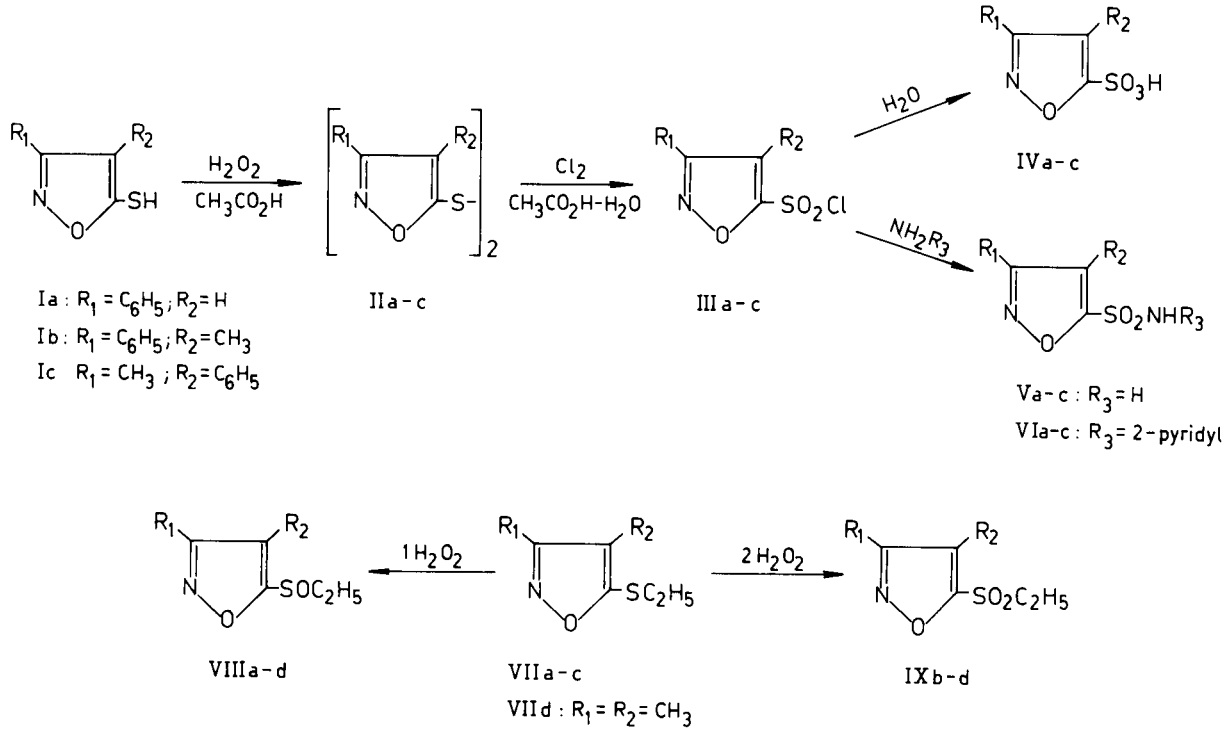
Recently (1) the preparation of a new class of isoxazole derivatives; namely, the 5-isoxazolethiols (Ia-c) obtained by action of potassium hydrosulfide on the corresponding 5-chloroisoxazoles was described. The synthesis of 5-ethylthioisoxazoles (VIIa-c) and bis(isoxazol-5-yl)disulfides (IIa-c) was also reported in the same paper.

In the present work, oxidation of compounds IIa-c with chlorine in aqueous acetic acid afforded 5-chlorosulfonylisoxazoles (IIIa-c) which could be easily hydrolysed by hot water to give the corresponding 5-isoxazolesulfonic acids (IVa-c). These compounds are very acidic, highly hygroscopic solids which were purified and characterized through their barium salts.

It is well known that isoxazole and 3-methylisoxazole can be sulfonated only at the 4-position by heating with 20% oleum and chlorosulfonic acid respectively (2-4). In the light of these results and bearing in mind that the conversions IIa-c → IIIa-c and IIIa-c → IVa-c can be carried out in good yields, it is clear that bis(isoxazol-5-yl)disulfides are very valuable intermediates for synthesizing both 5-isoxazolesulfonic acids with the free 4-position and those containing a phenyl group at 3- or 4-position.

Treatment of chlorosulfonyl derivatives IIIa-c with aqueous ammonium hydroxide and 2-aminopyridine gave 5-isoxazolesulfonamides (Va-c and VIa-c), respectively.

Scarpati and coworkers (5) previously reported oxidation of some 3-substituted-5-ethylthioisoxazoles to the corresponding sulfones by reaction with an excess of hydrogen peroxide in boiling acetic acid. Following this method, 5-ethylsulfonylisoxazoles (IXb-d) were prepared



from the thioethers VIIb-d; however, oxidation with hydrogen peroxide in the 1:1.5 molar ratio at a lower temperature gave the hitherto unknown 5-ethylsulfinylisoxazoles (VIIIa-d). 3,4-Dimethyl-5-ethylthioisoxazole (VIId) was prepared from 3,4-dimethyl-5-chloroisoxazole (X), obtained by chlorination of 3,4-dimethylisoxazolin-5-one. The structures of compounds VIIIa-d and IXb-d were assigned on the basis of analytical and spectroscopic evidence. In the infrared spectra of sulfoxides a strong band for the -SO- stretching vibration is present between 1055 and 1070 cm^{-1}, and the spectra of sulfones show two very strong bands in the regions of 1325-1334 and 1134-1145 cm^{-1}, which can be assigned to the $-SO_2-$ group symmetric and asymmetric stretching vibrations.

EXPERIMENTAL

All melting points are uncorrected. Unless otherwise stated, the infrared spectra were recorded for potassium bromide discs with a Perkin-Elmer 457 Spectrometer. The ultraviolet spectra were taken in methanol with a Cary 14 Spectrophotometer. Light petroleum refers to the fraction, b.p. 40-70°.

General Procedure for 5-Chlorosulfonylisoxazoles (IIIa-c).

A solution of bis(isoxazol-5-yl)disulfide (2 g.) in acetic acid containing enough water to furnish the required amount of oxygen was slowly saturated with chlorine gas at 20-25°. Air was bubbled to remove the excess of chlorine and the solution was diluted with cold water to give the chlorosulfonyl derivative as a white solid which was purified by several recrystallizations from light petroleum.

3-Phenyl-5-chlorosulfonylisoxazole (IIIa).

This compound was obtained in 87% yield (2.41 g.), m.p. 91-93°.

Anal. Calcd. for $C_9H_6ClNO_3S$: C, 44.4; H, 2.5; N, 5.7; Cl, 14.6; S, 13.1. Found: C, 44.3; H, 2.7; N, 5.8; Cl, 14.4; S, 13.0.

3-Phenyl-4-methyl-5-chlorosulfonylisoxazole (IIIb).

This compound was obtained in 93% yield (2.5 g.), m.p. 59-61°.

Anal. Calcd. for $C_{10}H_8ClNO_3S$: C, 46.6; H, 3.1; N, 5.4; Cl, 13.8; S, 12.4. Found: C, 46.7; H, 3.1; N, 5.5; Cl, 13.5; S, 12.5.

3-Methyl-4-phenyl-5-chlorosulfonylisoxazole (IIIc).

This compound was obtained in 92% yield (2.48 g.), m.p. 88-89°.

Anal. Calcd. for $C_{10}H_8ClNO_3S$: C, 46.6; H, 3.1; N, 5.4; Cl, 13.8; S, 12.4. Found: C, 46.8; H, 2.9; N, 5.6; Cl, 13.6; S, 12.5.

3-Phenyl-5-isoxazolesulfonic Acid (IVa).

Compound IIIa (1 g.) was refluxed in water (35 ml.) until the solid was completely dissolved (7 hours). Removal of the solvent left a hygroscopic white residue which was allowed to stand over potassium hydroxide *in vacuo* for several hours. The solid (0.9 g.) was dissolved in water and treated with a small excess of barium carbonate; the precipitate was filtered off and the solution evaporated to dryness to give the barium salt of IVa as white crystals soluble in water and methanol. A pure specimen, obtained by dissolving the salt in methanol and reprecipitating with chloroform, slowly decomposed by heating above 300°.

Anal. Calcd. for $C_{18}H_{12}N_2O_8S_2Ba$: C, 36.9; H, 2.1; N, 4.8; S, 10.9. Found: C, 36.9; H, 2.2; N, 4.7; S, 10.6.

3-Phenyl-4-methyl-5-isoxazolesulfonic Acid (IVb).

Compound IVb (0.7 g.) was prepared by refluxing IIIb (1 g.) in water for 13 hours. The corresponding barium salt was obtained as described above and purified by crystallization from water; it slowly decomposed by heating above 300°.

Anal. Calcd. for $C_{20}H_{16}N_2O_8S_2Ba$: C, 39.2; H, 2.6; N, 4.6; S, 10.4. Found: C, 39.0; H, 2.6; N, 4.5; S, 10.2.

3-Methyl-4-phenyl-5-isoxazolesulfonic Acid (IVc).

Refluxing of IIIc (0.75 g.) in water for 7 hours yielded almost a quantitative yield of the sulfonic acid IVc as a very hygroscopic white solid which was converted into the corresponding barium salt as above. An analytical sample, prepared by dissolving the salt in acetone and reprecipitating with ethyl ether, darkened by heating above 290° and melted with decomposition at about 300°.

Anal. Calcd. for $C_{20}H_{16}N_2O_8S_2Ba \cdot 2H_2O$: C, 37.0; H, 3.1; N, 4.3; S, 9.9. Found: C, 37.0; H, 2.8; N, 4.2; S, 10.1.

General Procedure for 5-Isoxazolesulfonamides (Va-c).

A mixture of 5-chlorosulfonylisoxazole (1 g.) and aqueous ammonium hydroxide (32%, 20 ml.) was refluxed for 5-10 minutes. Evaporation of the solvent under reduced pressure left a solid residue which was washed with water and dried.

3-Phenyl-5-isoxazolesulfonamide (Va).

This compound (0.75 g., 82%) was purified by several recrystallizations from aqueous ethanol, m.p. 158°.

Anal. Calcd. for $C_9H_8N_2O_3S$: C, 48.2; H, 3.6; N, 12.5; S, 14.3. Found: C, 48.0; H, 3.5; N, 12.4; S, 14.6.

3-Phenyl-4-methyl-5-isoxazolesulfonamide (Vb).

This compound (0.85 g., 92%) was crystallized from carbon tetrachloride to give white crystals, m.p. 157-158°.

Anal. Calcd. for $C_{10}H_{10}N_2O_3S$: C, 50.4; H, 4.2; N, 11.8; S, 13.4. Found: C, 50.4; H, 4.2; N, 11.6; S, 13.7.

3-Methyl-4-phenyl-5-isoxazolesulfonamide (Vc).

This compound (0.85 g., 92%) melted at 111-112° after several recrystallizations from aqueous ethanol.

Anal. Calcd. for $C_{10}H_{10}N_2O_3S$: C, 50.4; H, 4.2; N, 11.8; S, 13.4. Found: C, 50.5; H, 4.4; N, 11.7; S, 13.2.

General Procedure for *N*-(2-pyridyl)-5-isoxazolesulfonamides (VIa-c).

2-Aminopyridine (0.006 mole) in dry pyridine (10 ml.) was added dropwise to a solution of 5-chlorosulfonylisoxazole (0.004 moles) in the same solvent (10 ml.) and the mixture heated at 60-70° for 10-30 minutes. After removal of the solvent under reduced pressure the solid residue was washed with water and dried.

3-Phenyl-*N*-(2-pyridyl)-5-isoxazolesulfonamide (VIa).

This compound obtained in 71% yield was purified by recrystallization from ethanol, m.p. 200-202° dec.

Anal. Calcd. for $C_{14}H_{11}N_3O_3S$: C, 55.8; H, 3.7; N, 13.9; S, 10.6. Found: C, 55.8; H, 3.8; N, 13.8; S, 10.7.

3-Phenyl-4-methyl-*N*-(2-pyridyl)-5-isoxazolesulfonamide (VIb).

This compound was obtained in 65% yield and was recrystallized from ethanol giving white flakes, m.p. 215-216° dec.

Anal. Calcd. for $C_{15}H_{13}N_3O_3S$: C, 57.1; H, 4.1; N, 13.3; S, 10.2. Found: C, 57.4; H, 4.2; N, 13.4; S, 10.3.

3-Methyl-4-phenyl-*N*-(2-pyridyl)-5-isoxazolesulfonamide (VIc).

This compound was obtained in 66% yield and was recrystallized from methanol to yield white needles, m.p. 192-193° dec.

Anal. Calcd. for $C_{15}H_{13}N_3O_3S$: C, 57.1; H, 4.1; N, 13.3; S, 10.2. Found: C, 57.3; H, 3.9; N, 13.5; S, 9.9.

3,4-Dimethyl-5-chloroisoxazole (X).

Following the method described by Adembri and Tedeschi (6), 3,4-dimethylisoxazolin-5-one (7) (5 g.) was allowed to react with phosphorus oxychloride (25 g.) and triethylamine (6.2 ml.) to yield the chloro derivative X (3.97 g., 69%) as a colorless liquid which was purified by distillation under reduced pressure, b.p. 70° at 30 mm. Hg; uv λ max (log ε) 223 (3.75) nm.

Anal. Calcd. for C_5H_6ClNO: C, 45.6; H, 4.6; N, 10.6; Cl, 27.0. Found: C, 45.3; H, 4.8; N, 10.3; Cl, 26.7.

3,4-Dimethyl-5-ethylthioisoxazole (VIId).

3,4-Dimethyl-5-chloroisoxazole (16 g.) and sodium ethyl mercaptide (15 g.) were refluxed in anhydrous ethanol (200 ml.) for 22 hours. Removal of the solvent left a residue which was extracted with anhydrous ethyl ether; the ethereal solution was washed with water, dried and evaporated to dryness giving an oily product (16.7 g., 87%), b.p. 52-55° at 0.1 mm. Hg. After a further distillation a colorless liquid was obtained, b.p. 40° at 0.05 mm. Hg; uv λ max (log ε) 224 (3.65), 263 (3.70), and 285 (sh) (3.20) nm.

Anal. Calcd. for $C_7H_{11}NOS$: C, 53.5; H, 7.1; N, 8.9; S, 20.4. Found: C, 53.7; H, 7.3; N, 8.7; S, 20.1.

3-Phenyl-5-ethylsulfinylisoxazole (VIIIa).

A mixture of VIIa (1 g.) and hydrogen peroxide (35.5% w/v; 0.69 ml.) in glacial acetic acid (2 ml.) was heated at 60-65° for 2 hours. The solution was cooled and diluted with water to give an oily product which solidified as white crystals by standing overnight in the refrigerator (0.95 g., 88%), m.p. 71-73° after several recrystallizations from light petroleum; ir ν (SO) 1065 cm^{-1}; uv λ max (log ε) 212 (sh) (4.25) and 247 (4.11) nm.

Anal. Calcd. for $C_{11}H_{11}NO_2S$: C, 59.7; H, 5.0; N, 6.3; S, 14.5. Found: C, 59.6; H, 5.2; N, 6.4; S, 14.4.

3-Phenyl-4-methyl-5-ethylsulfinylisoxazole (VIIIb).

Compound VIIb (1 g.) was allowed to react with hydrogen peroxide (35.5% w/v; 0.65 ml.) in glacial acetic acid (4 ml.) at 60-65° for 4 hours. Operating as above, VIIIb (0.8 g., 75%) was obtained, m.p. 81° after several recrystallizations from light petroleum; ir ν (SO) 1055 cm^{-1}; uv λ max (log ε) 211 (sh) (4.24) and 247 (3.99) nm.

Anal. Calcd. for $C_{12}H_{13}NO_2S$: C, 61.3; H, 5.5; N, 6.0; S, 13.6. Found: C, 61.0; H, 5.4; N, 6.0; S, 13.5.

3-Methyl-4-phenyl-5-ethylsulfinylisoxazole (VIIIc).

The reaction conditions described for VIIIb were followed; VIIc (1 g.) gave an oily residue which was washed with light petroleum and left overnight in the refrigerator to yield VIIIc (0.5 g., 47%) as white crystals, m.p. 50-52° after several recrystallizations from pentane; ir ν (SO) 1058 cm^{-1}; uv λ max (log ε) 253 (3.82) nm.

Anal. Calcd. for $C_{12}H_{13}NO_2S$: C, 61.3; H, 5.5; N, 6.0; S, 13.6. Found: C, 61.2; H, 5.7; N, 6.1; S, 13.8.

3,4-Dimethyl-5-ethylsulfinylisoxazole (VIIId).

A solution of VIId (2 g.) and hydrogen peroxide (35.5% w/v; 1.83 ml.) in glacial acetic acid (5 ml.) was stirred at room temperature for 16 hours. The reaction mixture was made slightly alkaline with a saturated solution of sodium carbonate and extracted with ethyl ether. By evaporation of the ethereal extracts an oil (1.3 g.) was obtained which was washed with light petroleum and distilled under reduced pressure to give a colorless liquid, b.p. 68-69° at 0.06 mm. Hg; ir ν (SO) 1070 cm^{-1}; uv λ max (log ε) 215 (sh) (3.75) and 227 (3.8) nm.

Anal. Calcd. for $C_7H_{11}NO_2S$: C, 48.5; H, 6.4; N, 8.1; S, 18.5. Found: C, 48.7; H, 6.5; N, 7.9; S, 18.2.

3-Phenyl-4-methyl-5-ethylsulfonylisoxazole (IXb).

Compound VIIb (0.9 g.) and hydrogen peroxide (35.5% w/v; 1.16 ml.) were refluxed in glacial acetic acid (4 ml.) for 2 hours. The solution was cooled and diluted with water to give IXb (0.65 g., 63%) as white crystals, m.p. 69-70° from heptane; ir ν (SO_2) 1325 and 1134 cm^{-1}; uv λ max (log ε) 212 (4.23) and 242 (3.92) nm.

Anal. Calcd. for $C_{12}H_{13}NO_3S$: C, 57.4; H, 5.2; N, 5.6; S, 12.7. Found: C, 57.3; H, 5.2; N, 5.7; S, 13.0.

3-Methyl-4-phenyl-5-ethylsulfonylisoxazole (IXc).

A mixture of VIIc (1 g.) and hydrogen peroxide (35.5% w/v; 1.29 ml.) in glacial acetic acid (4 ml.) was refluxed for 1 hour. Operating as above, IXc (0.9 g., 79%) was obtained as a white solid, m.p. 88-89° from light petroleum; ir ν (SO_2) 1327 and 1138 cm^{-1}; uv λ max (log ε) 246 (3.72) nm.

Anal. Calcd. for $C_{12}H_{13}NO_3S$: C, 57.4; H, 5.2; N, 5.6; S, 12.7. Found: C, 57.4; H, 5.2; N, 5.4; S, 12.9.

3,4-Dimethyl-5-ethylsulfonylisoxazole (IXd).

A solution of VIId (2 g.) and hydrogen peroxide (35.5% w/v; 3.66 ml.) in glacial acetic acid (6 ml.) was refluxed for 2 hours. After cooling, the reaction mixture was made slightly alkaline with a saturated solution of sodium carbonate and extracted with ethyl ether. The ethereal extracts were dried and evaporated to dryness yielding a liquid residue (2 g., 83%) which solidified after standing for several days. Attempts to distill the crude product, even under reduced pressure, led to extensive decomposition; recrystallization from pentane gave white needles, m.p. 40-43°; ir ν (SO_2) 1334 and 1145 cm^{-1}; uv λ max (log ε) 204 (3.86) and 220 (sh) (3.81) nm.

Anal. Calcd. for $C_7H_{11}NO_3S$: C, 44.4; H, 5.8; N, 7.4; S, 16.9. Found: C, 44.3; H, 5.9; N, 7.2; S, 17.0.

REFERENCES

(1) G. Adembri and R. Nesi, *J. Heterocyclic Chem.*, **4**, 54 (1967).

(2) N. K. Kochetkov and E. D. Khomutova, *Zhur. Obshch. Khim.*, **29**, 535 (1959).

(3) A. Quilico and R. Justoni, *Gazz. Chim. Ital.*, **70**, 1 (1940).

(4) A. Quilico and R. Justoni, *ibid.*, **70**, 11 (1940).

(5) R. Scarpati, C. Santacroce, and D. Sica, *ibid.*, **93**, 1706 (1963).

(6) G. Adembri and P. Tedeschi, *Boll. Fac. Sci. Chim. Ind. Bologna*, **23**, 203 (1965).

(7) F. De Sarlo, *Tetrahedron*, **23**, 831 (1967).