

## Preparation and fungicidal properties of (phenylthio)-acetoxyhydroxamic acids and related compounds

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1-Chloro-4,5-dimethoxy-2-nitrobenzene and 1-bromo-2,5-dimethoxy-4-nitrobenzene condensed readily with thioglycollic acid in alkaline medium to give the corresponding sulphides. (4,5-Dimethoxy-2-nitrophenylthio)- and (2,5-dimethoxy-4-nitrophenylthio)acetic acid, as well as the corresponding amides and hydroxamic acids, have been prepared and tested for their fungicidal properties against *Aspergillus niger* and *Rhizoctonia solani*. The (phenylthio)acetoxyhydroxamic acids were found to be more fungicidal than the corresponding carboxylic acids against the phytopathogenic fungus *Rhizoctonia solani*.

RECENTLY, phenoxyacetoxyhydroxamic acids have been reported to possess fungicidal activity. Eckstein & others (1956, 1959, 1960, 1963) have studied the influence of substituents in the aromatic ring of phenoxyacetoxyhydroxamic acids on fungicidal properties. It seemed, therefore, of interest to investigate the properties of (arylthio)acetoxyhydroxamic acids, as it is known that (arylthio)alkanecarboxylic acids are more fungicidal than the corresponding aryloxy derivatives (Crowdy & Wain, 1951; Fawcett, Spencer & Wain, 1955, 1957). In an attempt to prepare biologically active compounds from 1-chloro-4,5-dimethoxy-2-nitrobenzene, its condensation with thioglycollic acid has been investigated. The veratrole structure, a benzene ring carrying two adjacent methoxyl groups, is of interest since it is present in a number of physiologically active alkaloids including papaverine, gnoscopine and brucine.

(4,5-Dimethoxy-2-nitrophenylthio)acetic acid (Ia) and (2,5-dimethoxy-4-nitrophenylthio)acetic acid (IIa), as well as some of their derivatives, have been prepared. The carboxylic acids Ia and IIa, the hydroxamine acids Id and IId, and the amides Ic and IIc have been assessed for their fungistatic effect on *Aspergillus niger* and *Rhizoctonia solani*.

Thioglycollic acid condensed readily with 1-chloro-4,5-dimethoxy-2-nitrobenzene in alkaline medium to give Ia. For comparison, the other isomer (2,5-dimethoxy-4-nitrophenylthio)acetic acid (IIa), was similarly prepared from 1-bromo-2,5-dimethoxy-4-nitrobenzene. The methyl esters Ib and IIb were obtained from the corresponding acids by the action of ethereal diazomethane solution. These carboxylic acids and their methyl esters were easily oxidised with hydrogen peroxide in acetic acid to the corresponding sulphones. The methyl esters were converted into the corresponding hydroxamic acids by reaction with a freshly prepared alkaline hydroxylamine solution in methanol. The free hydroxamic acids were precipitated from the aqueous solution of their potassium salts by acidification. Hydroxamic acids corresponding to the sulphones of the methyl esters were unstable and could not easily be isolated.

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The acid chlorides of Ia and IIa were relatively stable crystalline compounds. They condensed readily with ammonia to give the corresponding amides.

## Experimental

(4,5-Dimethoxy-2-nitrophenylthio)acetic acid (Ia) and its sulphone (Ie). To a solution of 1-chloro-4,5-dimethoxy-2-nitrobenzene (4 g) in hot ethanol (30 ml) 80% thioglycollic acid (3 ml) was added, followed by the dropwise addition of N sodium hydroxide (52 ml) to the refluxing mixture over 3 hr, and then further heating for 1 hr. The ethanol was distilled off and the remaining deep-red solution filtered. Compound Ia was precipitated from the cooled filtrate by the addition of dilute hydrochloric acid and was obtained as yellow needles from ethanol, m.p. 217°, yield 95%. Found: C, 43.9; H, 4.1; N, 5.4.  $C_{10}H_{11}NO_6S$  requires C, 44.0; H, 4.0; N, 5.1%.

By oxidation of compound Ia, the sulphone Ie was obtained in 80% yield as colourless crystals from ethanol, m.p. 201°. Found: N, 4.4; S, 10.8.  $C_{10}H_{11}NO_8S$  requires N, 4.6; S, 10.5%.

(2,5-Dimethoxy-4-nitrophenylthio)acetic acid (IIa) and the sulphone (IIe). 1-Bromo-2,5-dimethoxy-4-nitrobenzene (4 g) was allowed to react with thioglycollic acid in presence of sodium hydroxide as above. Compound IIa was obtained as yellow crystals from benzene, m.p. 167°, yield quantitative. Found: C, 44.3; H, 3.9; N, 4.9.  $C_{10}H_{11}NO_6S$  requires C, 44.0; H, 4.0; N, 5.1%.

The oxidation of compound IIa gave the sulphone IIe, m.p. 188° (from ethanol). Found: C, 39.9; H, 3.7.  $C_{10}H_{11}NO_8S$  requires C, 39.3; H, 3.6%.

*Preparation of the methyl esters of compounds Ia and IIa and the sulphone If.* The appropriate acid (1 g) was treated with an ethereal diazomethane solution (prepared from 2 g of nitrosomethylurea) and the mixture was left at room temperature for 12 hr. After evaporating off the ether the residue was crystallised from ethanol, yield quantitative.

Compound Ib formed orange crystals, m.p. 163°. Found: C, 45.9; H, 4.6.  $C_{11}H_{13}NO_6S$  requires C, 46.0; H, 4.5%.

The sulphone If, obtained by oxidation of the methyl ester Ib with hydrogen peroxide, was identical with that obtained by esterification of the sulphonyl acetic acid Ie with diazomethane; it had a m.p. of 163° from dilute ethanol. Found: C, 41.2; H, 4.4.  $C_{11}H_{13}NO_8S$  requires C, 41.4; H, 4.1%.

Compound IIb formed orange crystals, m.p. 117°. Found: C, 46.1; H, 4.7.  $C_{11}H_{13}NO_6S$  requires C, 46.0; H, 4.5%.

*Preparation of the hydroxamic acids Id and IId.* A methanolic solution of alkaline hydroxylamine (prepared from 0.005 mole of hydroxylamine hydrochloride and 0.01 mole potassium hydroxide) was added to the methyl ester Ib or IIb (0.5 g) and the reaction mixture left at room temperature for 1 hr with occasional shaking. The methanol was then removed and water (10 ml) added. Acidification of the deep-red solution

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with dilute sulphuric acid gave the corresponding hydroxamic acid Id or IId (orange crystals from ethanol) in a yield of 75–80%. Compound Id melted at 180°. Found: C, 41.4; H, 4.3; N, 10.1; S, 10.7.  $C_{10}H_{12}N_2O_6S$  requires C, 41.7; H, 4.2; N, 9.7; S, 11.1%. Compound IId melted at 162°. Found: N, 9.5; S, 11.4.  $C_{10}H_{12}N_2O_6S$  requires N, 9.7; S, 11.1%. Compounds Id and IId were readily soluble in dilute sodium hydroxide solution and gave an intense violet colour with ethanolic ferric chloride solution.

*Preparation of the acid amides Ic and IIC.* The carboxylic acids Ia and IIa were converted into their acid chlorides by heating with an excess of thionyl chloride in carbon disulphide for 1 hr. The solution was filtered and the filtrate cooled, whereupon the acid chloride crystallised out. The acid chloride (1 g) was shaken vigorously with concentrated ammonia solution (5 ml) for 10 min, whereupon the amides separated at once. They were obtained in quantitative yields and were crystallised from ethanol. Compound Ic formed yellow crystals, m.p. 222°. Found: C, 43.9; H, 4.5; N, 10.0.  $C_{10}H_{12}N_2O_5S$  requires C, 44.1; H, 4.4; N, 10.3%. Compound IIC gave yellow crystals, m.p. 186°. Found: C, 44.2; H, 4.4; N, 10.2.  $C_{10}H_{12}N_2O_5S$  requires C, 44.1; H, 4.4; N, 10.3%.

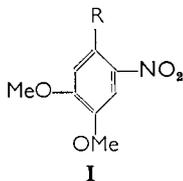
## BIOLOGICAL RESULTS

The biological tests on the fungicidal activity were made on *Aspergillus niger* and the phytopathogenic mould *Rhizoctonia solani*. The effects were assessed with concentrations of the compounds of  $10^{-4}$  and  $10^{-5}$  M using the Dox liquid medium. Because of their slight solubility in water the compounds were dissolved in aqueous ethanol (final ethanol concentrations were 1 and 0.1% for the  $10^{-4}$  and  $10^{-5}$  M solutions respectively). The same ethanol concentrations were added to the nutrient media of the controls. Flasks were inoculated with a spore suspension of *Aspergillus niger* or with discs of *Rhizoctonia solani* and incubated at 25° for five days. At the end of the incubation period, the mycelial mats produced were filtered, washed, dried at 100° and weighed. Replicate samples were used for each treatment.

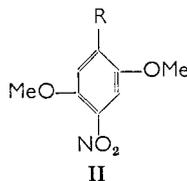
TABLE 1. DRY WEIGHTS OF FUNGAL MATS OF *Rhizoctonia solani* PRODUCED ON DOX MEDIUM AND INHIBITION (%) EFFECTED BY THE CARBOXYLIC ACIDS Ia AND IIa, THEIR AMIDES AND HYDROXAMIC ACIDS AT  $10^{-4}$  M CONCENTRATIONS

Substance	Compound	Dry weight* of the mycelium (mg)	% inhibition
Control	—	286	—
(4,5-Dimethoxy-2-nitrophenylthio)acetic acid	Ia	265	—
(2,5-Dimethoxy-4-nitrophenylthio)acetic acid	IIa	225	21
(4,5-Dimethoxy-2-nitrophenylthio)acetamide	Ic	70	75.5
(2,5-Dimethoxy-4-nitrophenylthio)acetamide	IIC	313	—
(4,5-Dimethoxy-2-nitrophenylthio)acetohydroxamic acid	Id	62	78.3
(2,5-Dimethoxy-4-nitrophenylthio)acetohydroxamic acid	IId	78	72.7

\* The dry weight is the mean of three replicates.



- Ia, R = S·CH<sub>2</sub>·CO<sub>2</sub>H  
 b, R = S·CH<sub>2</sub>·CO·O·Me  
 c, R = S·CH<sub>2</sub>·CO·NH<sub>2</sub>  
 d, R = S·CH<sub>2</sub>·C(:N·OH)·OH  
 e, R = SO<sub>2</sub>·CH<sub>2</sub>·CO<sub>2</sub>H  
 f, R = SO<sub>2</sub>·CH<sub>2</sub>·CO·O·Me



- IIa, R = S·CH<sub>2</sub>·CO<sub>2</sub>H  
 b, R = S·CH<sub>2</sub>·CO·O·Me  
 c, R = S·CH<sub>2</sub>·CO·NH<sub>2</sub>  
 d, R = S·CH<sub>2</sub>·C(:N·OH)·OH  
 e, R = SO<sub>2</sub>·CH<sub>2</sub>·CO<sub>2</sub>H

Statistical analysis of the results obtained showed that none of the chemicals tested possessed any fungicidal activity against *Aspergillus niger* at the above-mentioned concentrations. At a concentration of 10<sup>-4</sup> M compounds Ic, Id and IId effected significant inhibition in the growth of *Rhizoctonia solani* (cf. Table 1). The other compounds showed less activity but none of the compounds had an effect at concentration of 10<sup>-5</sup> M.

These results show that the hydroxamic acids Id and IId are more fungicidal to *Rhizoctonia solani* than the corresponding carboxylic acids Ia and IIa. The amide Ic, which contains an *o*-nitro-group, shows fungicidal properties comparable to those of the hydroxamic acids, while the *p*-nitro-amide IIc does not show such properties.

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## References

- Crowdy, S. H. & Wain, R. L. (1951). *Ann. appl. Biol.*, **38**, 318-333.  
 Eckstein, Z. & Czerwinska-Fejgin, E. (1959). *Przemysl Chem.*, **38**, 213-216; *Chem. Abstr.*, (1960), **54**, 11362  
 Eckstein, Z. & Kowalik, R. (1960). *Przemysl Chem.*, **39**, 756-759; *Chem. Abstr.* (1961), **55**, 15807.  
 Eckstein, Z. & Potocki, J. (1963). *Bull. Acad. Polon. Sci., Ser. Sci. Chim.*, **11**, 117-120. *Chem. Abstr.*, (1963), **59**, 7408.  
 Eckstein Z. & Urbánski, T. (1956). *Bull. Acad. Polon. Sci. Cl. III*, **4**, 627-630.  
 Fawcett, C. H., Spencer, D. M. & Wain R. L. (1955). *Ann. appl. Biol.*, **43**, 553-568.  
 Fawcett, C. H., Spencer, D. M. & Wain R. L. (1957). *Ibid.*, **45**, 158-176.