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Search for New Fungicides. Part-I. Synthesis and Mercuration of Some New 2-Thio-Δ^4-thiazolines and Their Possible Use as Fungicides and Bactericides

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A series of new 2-thio-3-*p*-ethoxyphenyl-4,5-disubstituted-Δ^4-thiazolines (I) have been synthesised by condensing ammonium *p*-ethoxyphenyldithiocarbamate with a number of ketones in the presence of bromine in an alcoholic medium. The thiazolines have been mercurated with one equivalent of mercuric acetate in acetic acid medium. All the compounds have been assayed against the fungus *Pyricularia oryzae* (Cav) and the bacteria *E. coli* and *S. aureus*.

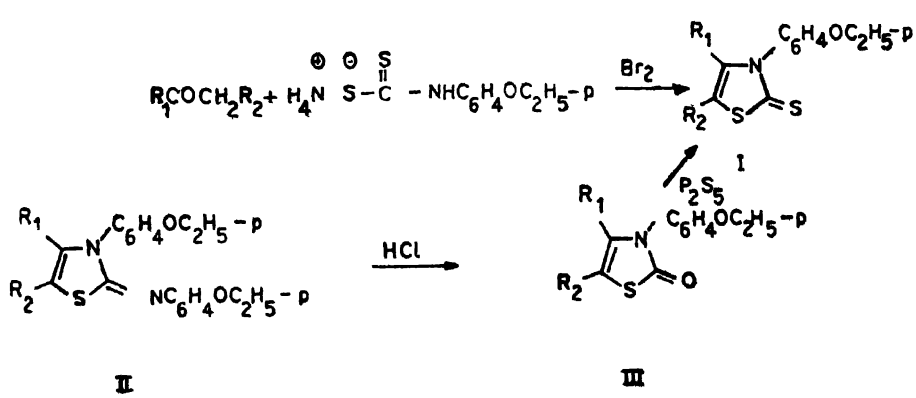
RECENT use of 2-thio-thiazolines as antifungal[1] agents prompted us to synthesise new 2-thio-thiazolines with the hope of finding out potent fungicides. The present paper deals with the synthesis of twelve 2-thio-3-*p*-ethoxyphenyl-Δ^4-thiazolines (**I**) by condensing different ketones with ammonium *p*-ethoxyphenyldithiocarbamate in the presence of bromine in an alcoholic medium. The structure **I** has been confirmed through its unequivocal synthesis. 2-*p*-Ethoxyphenylimino-3-*p*-ethoxyphenyl-4-phenyl thiazoline (**II** ; $R_1=C_6H_5$, $R_2=H$) prepared by the condensation of sym-di-*p*-ethoxyphenylthiourea and acetophenone in the presence of bromine, on acid hydrolysis gives 2-oxo-3-*p*-ethoxyphenyl-4-phenyl-Δ^4-thiazoline (**III** ; $R_1=C_6H_5$, $R_2=H$) which on treatment with P_2S_5 in dry benzene gives **I** ($R_1=C_6H_5$, $R_2=H$).

When compound **I** is treated with mercuric acetate, it gives the monoacetoxy mercuric compound in which the acetoxy mercuric group enters into the *ortho*-position of the aryl nucleus attached to the N_3-position of the thiazoline moiety as the *para*-position is already occupied and never goes to the C_4-aryl nucleus[2,3].

Experimental

Ammonium p-*ethoxyphenyldithiocarbamate* : To a mixture of *p*-phenetidine (52 ml) and carbon disulphide (20 ml) in rectified spirit (40 ml) kept in ice bath, concentrated ammonia (41 ml) was added slowly. The mixture was stirred vigorously with a mechanical stirrer till a clear solution was obtained. The temperature was not allowed to rise above 30°. The dithiocarbamate was precipitated out, filtered and washed with ether and air dried (70%), m.p. 148° (Found : S, 27.74. $C_9H_{14}N_2S_2O$ requires S, 27.82%).

*2-Thio-3-*p*-ethoxyphenyl-4-phenyl-Δ^4-thiazoline* (**I** ; $R_1=C_6H_5$, $R_2=H$) : To acetophenone (2.4 g) in absolute alcohol (15 ml), bromine (4 g) dissolved in absolute alcohol (45 ml) was gradually added. Ammonium *p*-ethoxyphenyldithiocarbamate (5 g) was then added and refluxed for 18 h on a steam bath. Excess of alcohol was distilled off and residue was subjected to steam distillation to remove any excess of haloketone. The product was then treated with concentrated ammonia and the free base, thus obtained, was crystallised from ethanol to yield the product (70%), m.p. 140° (Found : S, 20.32.



II III

TABLE 1

Sl. no.	R_1	R_2	Thiazolines (I)* M.p. °C	Dilution for 50% germination of fungus	Inhibitory growth of bacteria in ppm *E. coli*	*S. aureus*	Mercuric derivatives of I** M.p. °C	Dilution for 50% germination of fungus	Inhibitory growth of bacteria in ppm *E. coli*	*S. aureus*
1.	C_6H_5	H	140	11.2	250	500	210	5	50	100
2.	CH_3	H	162	11.0	500	500	218	6	100	100
3.	p-HO-C_6H_4	H	185	9.0	500	500	228	3	50	50
4.	p-Cl-C_6H_4	H	148	7.0	100	250	>250	3	25	50
5.	p-H_3C-C_6H_4	H	120	11.3	500	250	>250	4	100	100
6.	p-O_2N-C_6H_4	H	210	10.0	250	250	>250	3	50	50
7.	p-H_3CO-C_6H_4	H	144	11.0	500	500	>250	5	100	100
8.	C_6H_5-CH_2-CH_2	H	201	10.2	250	250	>250	4	50	50
9.	CH_3	C_2H_5	125	10.8	500	500	195	5	100	100
10.	CH_3	CH_3	136	10.8	500	250	190	5	100	100
11.	α-$C_{10}H_7$	H	233	7.2	250	250	>250	5	50	100
12.	β-$C_{10}H_7$	H	165	8.0	250	250	245	3	50	100

* Elemental analysis (S) were within ±0.5% of the theoretical value.
** Elemental analysis (Hg) were within ±0.5% of the theoretical value.

$C_{17}H_{15}NS_2O$ requires S, 20.44%) ; IR : ν_{max}(KBr) 1489 (NCS), 1120 (CS) cm^{-1}.

2-Thio-3-o-acetoxymercuric-p-ethoxyphenyl-4-phenyl-Δ^4-thiazoline : I (R_1=C_6H_5, R_2=H ; 1.2 g) dissolved in minimum quantity of acetic acid-ethanol (1 : 1, v/v) was added to a solution of mercuric acetate (1.0 g) dissolved in minimum volume of water-ethanol with constant stirring. The resulting solution was kept overnight at room temperature. The solid, thus obtained, was washed with hot water followed by ethanol and very dilute acetic acid to yield the product (65%), m.p. 210° (Found : Hg, 34.85. $C_{19}H_{17}NSO_3Hg$ requires Hg, 35.04%).

Antifungal activity : For fungicidal assay the method of Montgomery and Moore[4] taking *Pyricularia oryzae* (Cav), the causative organism of rice blast as the test fungus was used. The fungicidal assay (based on dilution necessary for 50% germination) is given in the Table 1. The spores were allowed to be kept in contact with fungicide at different concentrations for 24 h and percentage of germination was studied in that dilution. From the result of the fungicidal tests, it is found that although sulphur itself has fungicidal activity, introduction of sulphur at C_2-position does not contribute towards fungitoxicity. The presence of chlorine and naphthyl group in I increases the activity. Introduction of acetoxymercuric group markedly enhances the fungicidal activity.

Antibacterial activity : For bactericidal test, Rideal-Walker serial drop dilution method[5] taking gram-positive *S. aureus* and gram-negative *E. coli* as test bacteria was used. From the result of bactericidal test it is found that they show higher activity against *E. coli* than against *S. aureus*. Complete inhibition of bacterial growth occurs between 250-500 ppm. The mercurated derivatives are found to be more active, complete inhibition of bacterial growth occurs between 50-100 ppm.

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