SYNTHESIS OF SOME NEW 4(3H) QUINAZOLINONES AS POTENTIAL FUNGICIDES

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ABSTRACT

Several hydrochlorides of 2-β-N,N-diethylaminoethyl-3-(benzothiazol-2′-yl)-4(3H) quinazolinones have been synthesised. Their fungicidal activity has been screened on *Aspergillus niger* and *Draschlera australiansis* at two dilutions. The antifungal activity of some of them compared well with that of sodium pentachloro phenate, a known fungicide.

THE quinazolinone ring system is one of the most active heterocyclic systems in Medicinal Chemistry. 4(3H)quinazolinones have been successfully screened as antihypertensive[1], antifungal[2,3], herbicidal and bactericidal[4] agents. Virucidal activity has also been reported in some nitro substituted 4-quinazolinone derivatives[5]. Some piperizino quinazolinones as cardiovascular, hypotensive, nor adrenalin inhibiting, brady cardiac and trachy cardiac agents have recently been reported by Dubey *et al.*[6].

Keeping in view the wide spectrum activities of this system it was considered worthwhile to synthesise some hydrochlorides of 6,8-disubstituted-2-β-N,N-diethylaminoethyl-3-(benzothiazol-2′-yl)-4(3H) quinazolinones as potential antifungal agents. The compounds were prepared according to the scheme outlined.

Substituted-2-aminobenzothiazoles on refluxing with 3,5-disubstituted acetyl anthranilic acids and phosphorous trichloride in toluene for 4 hours gave 6,8-disubstituted-2-methyl-3-[(substituted) benzothiazol-2′-yl]-4 (3H) quinazolinones. This was refluxed with paraformaldehyde and diethylamine hydrochloride in absolute alcohol on a water bath for 9 hours to obtain the required product. The structure of the product was confirmed by elemental analysis and IR spectra.

EXPERIMENTAL

All melting points were recorded in open capillary in liquid bath and are uncorrected. IR spectra are recorded on Perkin Elmer 257 spectrophotometer and a Coleman analyser used for elemental analysis.

3,5-Dibromo anthranilic acid was prepared by a known method[7]. Acetyl derivatives of anthranilic acid and 3,5-dibromo anthranilic acid were prepared by the method of Vogel[8].

Substituted 2-aminobenzothiaole

Substituted 2-aminobenzothiazoles were prepared by the oxidation of asymmetrical aryl thiourea with liquid bromine in chloroform[9].

2-Methyl-3-[(substituted) benzothiazol-2′-yl]-4(3H) quinazolinones and 6,8-dibromo-2-methyl-3-[(substituted) benzothiazol-2′-yl]-4(3H) quinazolinones were prepared according to the method of Chaurasia *et al.*[10].

Hydrochloride of 2-β-N,N-diethylaminoethyl-3-(benzothiazol-2′-yl)-4(3H) quinazolinone

A mixture of 2-methyl-3-[benzothiazol-2′-yl)]-4(3H) quinazolinone (5 g) paraformaldehyde 0·57 g and diethylamine hydrochloride (1·4 g) was refluxed in

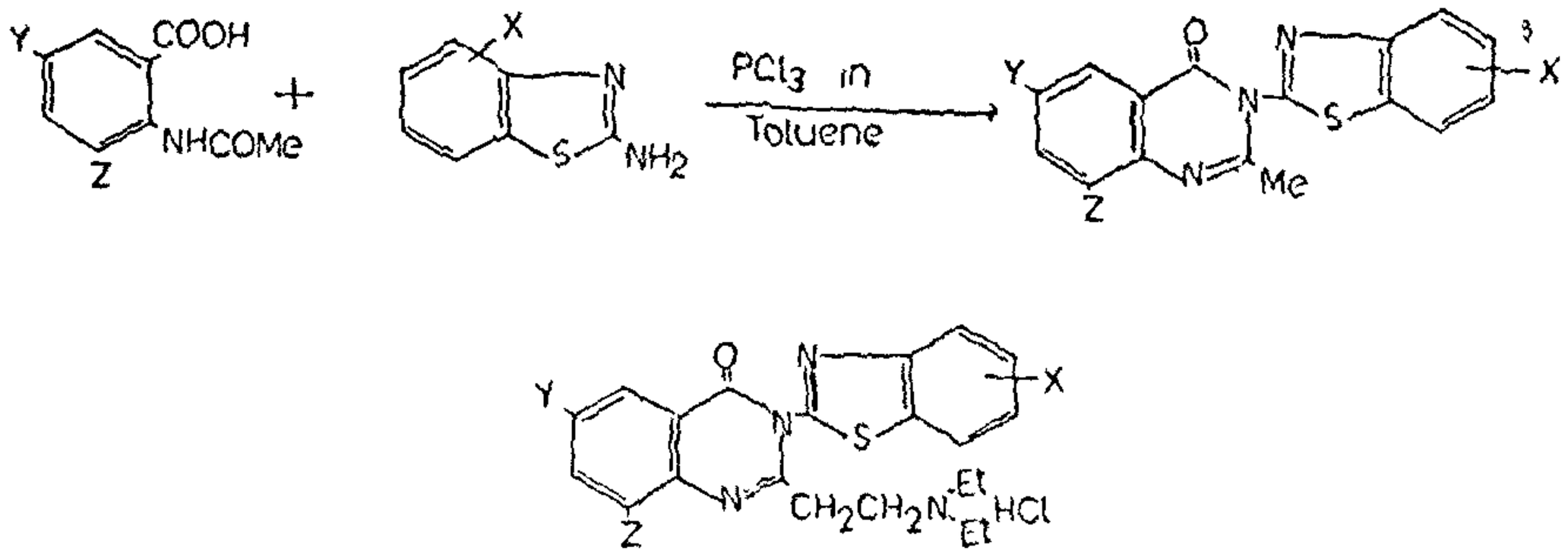

TABLE I

Hydrochlorides of 6,8-disubstituted-2-β-N-N-diethylaminoethyl-3-[(substituted)benzothiazol-2'-yl]-4(3H) quinazolinones

Substituents X	Substituents Y = Z	Yield %	M.P.	Fungicidal activity: % Inhibition of *Aspergillus niger* at dilutions 1:1,500	1:3,500	% Inhibition of *Draschlera australiensis* dilutions 1:1,500	1:3,500
H	H	47	110	67	28	60	61
5-Me	H	51	185	54	28	71	60
6-Me	H	61	210	100	59	100	87
4-Cl	H	46	108	38	28	50	36
5-Cl	H	59	208	71	72	100	61
6-Cl	H	64	196	100	59	60	61
6-EtO	H	66	80	100	66	100	39
6-Br	H	69	101	29	17	65	50
H	Br	43	135	81	71	81	76
4-Me	Br	52	191	82	78	81	80
5-Me	Br	63	180	75	81	100	84
6-Me	Br	47	208	100	75	100	72
4-Cl	Br	32	105	100	78	100	36
5-Cl	Br	67	145	52	49	64	55
6-Cl	Br	71	181	75	79	70	64
6-MeO	Br	69	80	58	52	55	54
6-EtO	Br	74	101	54	38	70	54
NaPCP				100	100	100	100

* Analytical data for nitrogen and sulphur agreed with the calculated values within the limits of experimental error.

ethanol on a water bath for 9 hours. The product obtained was washed with ether and filtered. Recrystallisation from ethanol gave hydrochlorides of 2β-N,N-diethylaminoethyl-3-(benzothiazol-2-yl)-4 (3H)quinazolinone: yield 41%, m.p. 110°. Anal. Calcd. for $C_{21}H_{23}ClN_4OS$, N, 13·51, S, 7·72. Found: N, 13·26, S, 7·5%.

IR (nujol): 1140 m, 1300 m, 1380 s, 1620 s, 1700 s cm^{-1}.

Following this procedure other hydrochlorides of 2-β-N,N-diethylaminoethyl-3-[(substituted) benzothiazol-2'-yl]-4(3H) quinazolinones were synthesised. Their melting points, yields and analytical data are listed in Table I.

PHARMACOLOGICAL SCREENING

The compounds synthesised were tested for fungicidal action on *Aspergillus niger* and *Draschlera australiensis* by the agar diffusion technique[11] at two dilutions and their activity compared with that of sodium pentachloro phenate (NaPCP), a well-known fungicide.

The percentage inhibition of growth was determined by comparison with growth in controls and the results are recorded in Table I. All solutions were prepared in absolute alcohol. The medium in controls and treated plates was potato dextrose agar culture medium and the incubation time 96 hours at 28 ± 1° C.

The results indicate that the activity of the compounds is of high order against both the pathogenic species tested. Replacement of hydrogen in benzothiazole nucleus with methyl, chloro and ethoxy groups when the quinazolinone ring is unsubstituted leads to considerable enhancement of fungicidal action in all cases except when the substituent is 5-methyl in case of *Aspergillus niger*. Introduction of bromo group in the benzothiazole nucleus also decreases the fungicidal action considerably in the case of *Aspergillus niger*. The decrease is less marked in case of *Draschlera australiensis*. Introduction of two bromine atoms at positions 6 and 8 in the quinazolinone nucleus does not have much effect on the fungicidal action in the case of *Aspergillus niger*. The effect is however considerably

enhanced in case of *Draschlera australiensis* at both dilutions.

The compounds thus inhibit fungal growth to a considerable extent. Some of them compare well with the fungicidal activity of sodium pentachloro phenate as is evident from Table I.

ACKNOWLEDGEMENTS

Sincere thanks are due to the CSIR for the award of fellowships to SKS and SK. Thanks are also due to the authorities of D.A.V. (P.G.) College, Dehra Dun, for providing necessary facilities.

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Fe(II), Co(II), Ni(II) AND Cu(II) PERCHLORATE COMPLEXES WITH AMINOPYRINE

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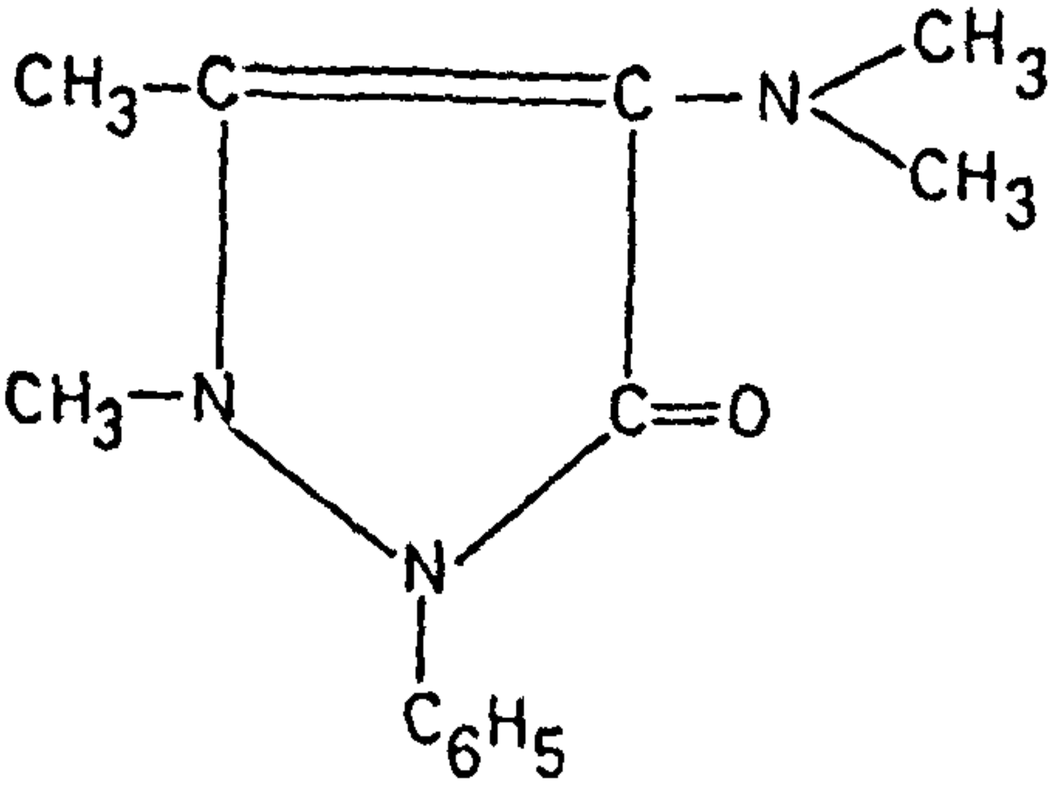
ABSTRACT

Aminopyrine complexes with metal(II) perchlorate of the types $[M(AMP)_4 2H_2O](ClO_4)_2$, $[M(AMP)_2](ClO_4)_2$ and $[M(AMP)_2 H_2O](ClO_4)_2$, where M = Fe(II), Co(II), Ni(II) and Cu(II), AMP = aminopyrine, were prepared and characterised by analysis, molar conductance, magnetic measurements, electronic and infrared spectral studies.

INTRODUCTION

AMINOPYRINE (2,3-dimethyl, 4-dimethylamino-1-phenyl-3-pyrazolin-5-one) acts as a bidentate ligand and belongs to the pyrazole group. It has antipyretic and analgesic properties[1]. Metal complexes with aminopyrine[2] (Structure I) and antipyrine[3] have been reported. In view of our interest in the metal complexes of drugs, we report here the metal(II) perchlorate complexes of aminopyrine.



Aminopyrine
(Structure I)

EXPERIMENTAL

Freshly prepared metal(II) perchlorate solutions in dilute ethanol and aminopyrine (E. Merck grade) were reacted in 1:2 (M:Drug) molar ratios. The complexes, which were precipitated or crystallised, were washed with, dilute ethanol and dried in a desiccator. Metal part, drug and anion in the complexes were

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