BIOLOGICAL STUDIES OF SOME ORGANOBORON COMPLEXES ON PATHOGENIC MICROBES

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ABSTRACT

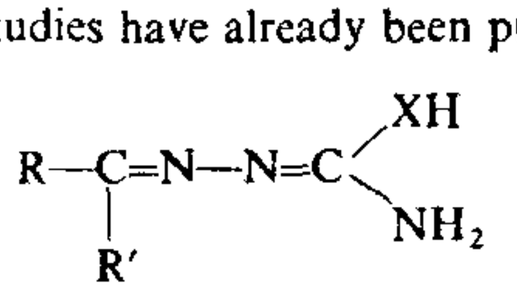
The bactericidal and fungicidal properties of some organoboron semicarbazones and thiosemicarbazones *in vitro* are described. These complexes have been synthesised by the reactions of mixed borate esters with the ligand moieties and found to be highly active against gram-positive bacteria and surprisingly against gram-negative bacteria and equally effective against fungi. The organoboron derivatives of thioboroles are more active than the oxaboroles and the difference in activity has been correlated with the structure. Further, the activity of these new derivatives has been compared with a few well-known antimicrobial drugs.

INTRODUCTION

THE first important fungicide was reported in 1882 and since then, a large number of such a class of compounds has been developed and studied. Probably, the most important fungicides of the last decade are the sulphur and nitrogen containing compounds like dithiocarbamates[1], Ziram[2], semicarbazones[3], thiosemicarbazones[4], and ferbam[5]. A variety of organoboron complexes have also been reported to possess fungicidal as well as bactericidal activities[6,7]. Our continuing interest in the synthesis of such potent fungicides and bacteriocides, has led us to synthesize a new class of organo boron complexes and study their activity *in vitro*.

MATERIALS AND METHODS

The agar disc diffusion technique is the method most commonly used in clinical laboratories for testing antimicrobial activity of various antibiotic agents and their compounds and the same was used in the present investigation. Seven-day old cultures of various micro-organisms representing gram-positive and gram-negative bacteria and fungi of various taxonomic groups were used as test organisms and the details of these studies are similar to those previously reported. The paper discs of standard size (0.5 mm in diameter) were prepared from Whatman no. 1 filter paper and soaked for 5 min in methanol solution (1000 ppm concentration) of the resulting complexes. These soaked paper discs were then placed in petri plates previously seeded with the individual test organisms. Two control sets were also maintained wherein the paper discs were soaked in the solution of the fungicides, whose activity was already known. The inhibition zone if formed was measured as the distance (cms) between the edge of the paper disc and the growth of the test organisms and the mean of the three replicates has been recorded in table 1. The ligand and mixed borate ester *i.e.* $C_6H_4O_2B(OPr^i)$, $C_2H_4S_2B(OPr^i)$ were prepared by the literature method. The ligands having the general structure as shown below were reacted with the esters in 1 : 1 and 2 : 1 molar ratios in refluxing benzene and the resulting complexes were dried in vacuo. These were analysed and characterised on the basis of IR, UV, NMR (^1H, ^{13}C, ^{11}B) and x-ray powder diffraction. The results of these studies have already been published[10].



where X = O or S,
R = C_6H_4OH, C_6H_4, C_2H_5, C_4H_9
R′ = H, CH_3, C_4H_9

RESULTS AND DISCUSSION

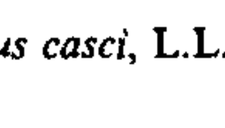
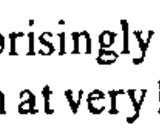
All the complexes were tested against gram-positive and gram-negative bacteria and various fungi; for comparison, similar studies were carried out with two known fungicides and the results are recorded in table 2. These studies indicate that the complexes are very much active against gram-positive bacteria and

Table 1 *Antibacterial activity of organoboron complexes*

Compound	Diameter of inhibition zone (mm)				
	Name of bacteria				
	B.S. 1	E.C 2	L.C. 3	L.L. 4	S.A. 5
$(\overline{O.C_6H_4O.B}.C_2H_5.C(CH_3)N:NCSNH_2)$	20	21	12	13	15
$(\overline{O.C_6H_4.O.B}.C_4H_9.C(C_4H_9):N.N.CSNH_2)$	12	15	10	12	13
$(\overline{O.C_6H_4.OB}.HOC_6H_4.C(CH_3):NNCSNH_2)$	18	14	25	21	20
$(\overline{O.C_6H_4.OB})_2.OC_6H_4.C(CH_3):NNCSNH_2)$	21	17	18	20	22
$(\overline{O.C_6H_4.OB}.C_6H_5.C(CH_3):NNCSNH_2)$	25	22	15	15	16
$(\overline{O.C_6H_4.OB}.C_6H_5.C(H):N.NCSNH_2)$	13	10	26	25	22
$(\overline{O.C_6H_4.OB}.C_4H_9.C(C_4H_9).N:N.C.O.NH_2)$	18	19	10	14	20
$(\overline{O.C_6H_4.O.B}.C_2H_5.C.(CH_3).N:N.C.O.NH_2)$	25	10	18	21	20
$C_2H_5.C.(CH_3):NNCSNH_2$	6	7	6	6	7
$C_4H_9.C.(C_4H_9):NNCSNH_2$	6	8	5	6	7
$(\overline{S.CH_2.CH_2SB})_2O.C_6H_4.C(H):NNCSNH_2)$	22	19	23	20	15
$(\overline{S.CH_2.CH_2.S.B})_2O.C_6H_4.C(CH_3):NNCSNH_2)$	26	24	21	19	18
$(\overline{S.CH_2.CH_2.S.B}.C_2H_5.C(CH_3)N:N.CSNH_2)$	27	22	21	19	21
$(\overline{S.CH_2.CH_2.SB}.C_4H_9.C(C_4H_9):NNCONH_2)$	17	10	13	14	14
$(\overline{O.C_6H_4OB}.C_2H_5.C(CH_3)N.N.C.ONH_2)$	16	15	12	14	22
$(O.C_6H_4OB.C_6H_5.C.(CH_3)N:N.C.ONH_2)$	15	14	20	21	10
$(\overline{SCH_2.CH_2S.B})_2O.C_6H_4.C(H)NNC.ONH_2)$	12	10	11	13	11

B.S., *B. subtilis*, E.C., *E. Coli*, L.C., *Lactobacillus casei*, L.L., *L. leishmenii*, S.A., *Staph aurius*.

surprisingly active against gram-negative bacteria too, even at very low concentrations. It is also clear from the table that the activity of the complexes is appreciably higher than that of the two well-known fungicides, reported to be quite active against phytopathogens[11]. Further, the compounds under study are active towards some of the test organisms against which the known antimicrobial agents are not at all active.

The activity of the present complexes against gram-negative bacteria is in marked contrast to the previously reported results about the boron semicarbazones and thiosemicarbazones, reported earlier[12]. It can thus be inferred that the introduction of  and  moieties in the boron complexes has resulted in producing this type of activity.

However, boron complexes of thiosemicarbazones have been found to be more active in all the test organisms as compared with the corresponding semicarbazone derivatives; the greater activity in the former case may be due to the presence of –N=C–S group. The presence of sulphur also accounts for the higher activity of complexes derived from 2-isopropoxy 1,3,2-dithioborole as compared with the complexes derived from 2-isopropoxy 1,3,2 dioxaboroles. Tweedy[13] has suggested that sulphur beats oxygen for the protons and electrons in fungus respiration and takes electron between cytochrome b and c of the electron transport system. In general, complexes of the ligands derived from aliphatic ketones are more active as compared with those obtained from aldehydes.

The antimicrobial activity of a drug can be ascribed to the formation of hydrogen bonds between nitrogen atom of the drug and some bioreceptors of bacteria and fungi, which in turn block the synthesis of proteins in them by inhibiting the movement of ribosome along mRNA. DNA synthesis is blocked secondarily.

It is rather difficult at this stage to emphatically give a structure activity relationship; it can be suggested that part of the activity may be due to the presence of metal chelates with bulky donor ligands moieties.

In general all the complexes studied were more

Table 2 *Antifungal activity of organoboron complexes*

Compound	Diameter of inhibition zone (m m)						
	Name of fungi						
	H G.	C.A.	H S.	At.So	A.R.	C.G.	At Br
$(\overline{O\ C_6H_4.O\ B}\ C_2H_5\ C(CH_3)N:NCSNH_2)$	10	—	—	—	14	13	12
$(\overline{O\ C_6H_4.O\ B}.C_4H_9.C(C_4H_9)\ N:NCSNH_2)$	15	—	14	16	—	12	17
$(\overline{O.C_6H_4O\ B}.HO.C_6H_4.C(CH_3):N:N.CSNH_2)$	22	16	—	14	12	—	—
$(\overline{O\ C_6H_4.O\ B})_2O\ C_6H_4.C(CH_3)N.N.CSNH_2)$	14	13	15	12	18	—	20
$(\overline{O.C_6H_4O.B}\ C_6H_5.C(CH_3).N:NCSNH_2)$	12	14	16	—	10	12	15
$(\overline{OC_6H_4.O.B}.C_6H_5.C(H)N\ N.CSNH_2)$	10	12	—	13	11	15	10
$(\overline{O.C_6H_4.O.B}\ C_4H_9\ C.(C_4H_9).N:N.C.ONH_2)$	11	10	—	15	—	11	9
$(\overline{O.C_6H_4.O.B}\ C_2H_5.C.(CH_3)N:N.CO.NH_2)$	13	12	—	—	10	9	8
$C_2H_5.C.(CH_3).N:N.CSNH_2$	6	6	5	5	6	7	7
$C_4H_9.C.(C_4H_9):N.N.CSNH_2$	7	5	7	7	6	7	7
$(\overline{S\ CH_2.CH_2.S.B}_2O.C_6H_4.C(H).N:N.CSNH_2)$	28	22	11	13	—	—	11
$(\overline{S.CH_2.CH_2\ S\ B}_2O.C_6H_4.C(CH_3).NNCSNH_2)$	30	18	14	10	—	10	12
$(\overline{S.CH_2.CH_2.S.B}\ C_2H_5.C.(CH_3)N:NCSNH_2)$	20	16	—	—	10	15	13
$(\overline{S\ CH_2.CH_2S.B}.C_4H_9.C(C_4H_9)N:NC.ONH_2)$	18	—	16	14	11	13	—
$(\overline{OC_6H_4.O\ B}.C_2H_5.C.(CH_3).N:N.CO.NH_2)$	15	9	18	—	—	11	—
$(\overline{OC_6H_4.O.B}\ C_6H_5.C(CH_3)N:N.CO.NH_2)$	13	14	6	10	—	—	16
$(\overline{SCH_2.CH_2.S.B})_2O.C_6H_4.C(H)NN.CONH_2)$	21	—	10	9	—	8	—
PCNB fungicide	10	—	15	8	—	—	14
Bavistin fungicide	12	—	32	30	30	25	28

Where H.G. = *H. griminium*, C.A = *Candida albicans*, H.S. = *Helminthosparium satium*, At.So. = *Alternaria solani*, A.R. = *Ascochyta rabiei*, C.G. = *Colletotrichum gleosporidis*, At Br. = *Alternaria brassicae*.

active as compared with the parent ligands and this is in accordance with the observations of Cifferi and Baldaccei[14], who state that chelation increases the activity of an organic ligand. Further, the higher activity of the present complexes may also be explained on the basis of their higher solubility and fineness of the particles.

Thus, the above studies clearly indicate that the new organoboron complexes now reported are highly active towards all the microbes examined in the present investigations.

9 August 1982; Revised 16 January 1984

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NEWS

RICE STRAW INTO ALCOHOL

A technology for converting rice straw into alcohol has been developed by the Biochemical Engineering Research Centre (BERC) at the Indian Institute of Technology (IIT), New Delhi.

Besides alcohol, the BERC process yields byproducts, such as improved and easily digestible fodder for animals, carbon dioxide gas which can be made into dry ice for storing vegetables, and pure lignin—a basic raw material for making a host of aromatic chemicals, presently made from coal and imported petroleum.

Prof. T. K. Ghose, head of BERC, says that the 70 million tonnes of rice straw available in India annually can be turned into liquid fuel and a chemical feedstock while creating a viable agroindustry utilizing agricultural wastes.

Following the success of the process in the laboratory, BERC, in collaboration with the Unique Biochemical Engineering Company in Bombay, has prepared a detailed project report for setting up a pilot plant that will produce daily 500 litres of alcohol, 965 kg of mixed fodder, 370 kg of carbon dioxide gas and 235 kg of lignin.

Besides rice straw, the pilot facility can process cane bagasse and wheat straw and will be non-polluting unlike the present alcohol industry based on molasses. The only effluent will be the combustion products of coal used in boilers which will be dispersed through a 35-metre stack. (*The Patriot*, 8 *September* 1983).

TV KNOW-HOW TO INDONESIA

Samsung Electronic Company, an affiliate of the Samsung Group, has signed a contract with Telesonic Company of Indonesia to export a plant manufacturing colour and black and white TV sets. The company will begin delivery of the plant facilities worth $15,000 by March, 1984. The plant in Indonesia is envisaged to produce 100,000 B/W sets and 60,000 colour sets annually. When the plant is constructed Samsung will be able to export $15 million worth of parts and components for TV sets annually to the Southeast Asia. Samsung also plans to send six Korean technicians immediately to provide technical guidance to Telesonic Company. According to official sources, the demand of colour TV sets in Indonesia is expected to be 300,000 sets worth $120 million and B/W to one million sets worth $150 million this year. (*Korean News, Jan.–Feb. 1984, p. 23*)