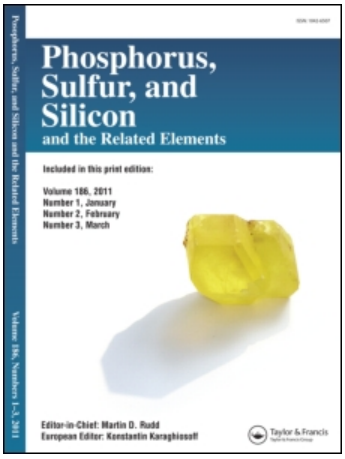

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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF IMIDAZOBENZOTHIADIAZOLE DERIVATIVES

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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF IMIDAZOBENZOTHIADIAZOLE DERIVATIVES

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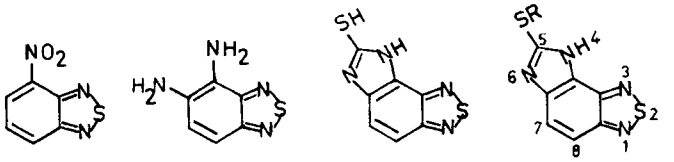
4,5-Diamino(2,1,3)benzothiadiazole (**II**) Was treated with carbondisulphide in alkaline medium to furnish 5-mercapto-4**H**-imidazo(4,5-e)(2,1,3)benzothiadiazole (**III**). Treatment of **III** with alkyl/aralkyl halides in DMF gave the corresponding thioethers (**IV**). Compounds were characterised by their elemental, IR, PMR and mass spectral analyses. A few selected compounds were screened for their antimicrobial activity.



I II III IV

Benzothiadiazoles have been broadly applied in the areas of pharmaceutical, agricultural, industrial and polymer chemistry. Several of them are reported to be excellent insecticide synergists together with carbaryl.[1] A few derivatives have got sedative and hypnotic actions comparable to benzodiazepines.[2] A good number of imidazobenzothiadiazoles have been patented as insecticides, herbicides[3] and fungicides.[4] Many imidazobenzothiadiazoles have been used for making cyanine dyes.[5] 2-Mercapto benzimidazoles and their derivatives have been reported to possess a wide range of physiological and industrial applications. However, synthesis of 5-substituted mercapto-4**H**-imidazo(4,5-e)(2,1,3)-benzothiadiazoles does not seem to have been reported so far. The present investigation is therefore undertaken to build the mercaptoimidazole system on 2,1,3-benzothiadiazole and to study their antimicrobial activity.

5-Mercapto-4**H**-imidazo(4,5-e)(12,1,3)benzothiadiazole (**III**) has been prepared by the cyclisation of 4,5-diamino-2,1,3-benzothiadiazole (**II**) with carbondisulfide in presence of alcoholic potassium hydroxide. The diamine (**II**) has been synthesised by the amination of 4-nitro-2,1,3-benzothiadiazole (**I**) with hydroxylaminehydrochloride in methanolic potassium hydroxide followed by subsequent reduction with sodium hydrosulfite.

The structure of **III** has been confirmed by its elemental, IR, PMR and mass spectral data. The IR absorption band between 3500–3000 cm^{-1} has been assigned to the intermolecularly hydrogen bonded N—H stretching vibrations. The weak but sharp band at 2650 cm^{-1} reveals the presence of —SH group.[6] The strong bands at 1610, 1580, 1500 and 1390 cm^{-1} are due to aromatic ring

stretchings. The other IR bands are at 1100 cm^{-1} (C—S), 2800 cm^{-1} (N—H), 1350–1300 cm^{-1} (C=S) regions.

The H^1NMR spectrum offered further confirmation for the structure of **III**. The —SH and —NH protons are embedded under a broad singlet around δ8.7–9.5 ppm. The aromatic protons at 7 and 8 positions appeared as a singlet at δ7.6 ppm.

In the mass spectrum of **III**, the molecular ion peak appeared as a base peak at m/z 208. M + 2 peak indicates the presence of a sulphur atom in the molecular ion. The fragmentation starts with the ejection of the sulphur atom from the molecular ion to give the ion peak at m/z 176, followed by the successive loss of HCN and CN to record at m/z 149 and 123 respectively.

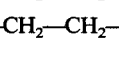
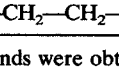
The reaction of 5-mercapto-4**H**-imidazo(4,5-e)(2,1,3)-benzothiadiazole (**III**) with various alkyl and aralkyl halides in methanol containing dimethyl formamide under anhydrous conditions afforded a series of the respective 5-substituted mercapto-4**H**-imidazo(4,5-e)(2,1,3)benzothiadiazoles (**IV**). The structures of the compounds have been characterized by their elemental and spectral analyses.

Most of IR absorptions for alkyl/aralkyl derivatives are similar to those of **III**, except for the additional bands around 2810 and 1430 cm^{-1} (—S—CH_2—), 1340 cm^{-1} (—S—CH_3) and 1680 cm^{-1} (C=O) etc.

The H^1NMR signals are observed in the same regions as specified for compound **III**. The mass spectra of alkyl/aralkyl derivatives also indicate the same type of fragmentation. The important fragments in the mass spectrum of **IVf** are recorded at m/z values of 298, 265, 221, 207, 189, 149, 117 etc.

TABLE I

Physical data of 5-substituted mercaptoimidazobenzothiadiazoles

Compound[a]	R	M.P.[b] °C	Mol. formula	N%[c] Found	N%[c] Calc.	S% Found	S% Calc.
IVa	—CH_3	263–265	$C_8H_6N_4S_2$	25.25	25.22	28.85	28.83
b	—C_2H_5	255	$C_9H_8N_4S_2$	23.75	23.72	27.15	27.12
c	—CH_2—CH_2—CH_3	240	$C_{10}H_{10}N_4S_2$	22.42	22.40	25.63	25.60
d	—CH_2—CH_2—CH_2—CH_3	272	$C_{11}H_{12}N_4S_2$	21.25	21.21	24.26	24.24
e	—CH_2—CH_2=CH_2	247	$C_{10}H_8N_4S_2$	22.60	22.58	25.83	25.81
f	—CH_2—Ph	201	$C_{14}H_{10}N_4S_2$	18.81	18.79	21.50	21.48
g	—CH_2—CO—ph	191	$C_{15}H_{10}N_4OS_2$	17.20	17.17	19.65	19.62
h	—CH_2—CO—C_6H_4—Cl(P)	180	$C_{15}H_9N_4OS_2Cl$	15.51	15.53	17.73	17.75
i	—CH_2—CO—C_6H_4—Br(P)	186	$C_{15}H_9N_4OS_2Br$	13.85	13.83	15.84	15.81
j	—CH_2—CH_2—$N(CH_3)_2$	165	$C_{11}H_{13}N_5S_2$	25.12	25.08	22.97	22.94
k	—CH_2—CH_2— 	231	$C_{13}H_{11}N_5OS_2$	21.83	21.81	20.0	19.94
l	—CH_2—CH_2— 	220	$C_{14}H_{17}N_5S_2$	21.99	21.94	20.10	20.06

[a] Compounds were obtained in 50–60% yields.

[b] Compounds **IVg** to **IVj** were recrystallised from aqueous dioxan and the rest were recrystallised from alcohol.

[c] Satisfactory analysis for C and H were also obtained.

TABLE II

Antibacterial activity

Compound	Conc. μg/ml	% of inhibition in mm. *B.s.* (+)	*S.a.* (+)	*E.c.* (−)	*P.v.* (−)
IVb	400	—	—	—	—
	600	—	—	—	—
e	400	—	0.4	—	—
	600	—	—	0.1	—
g	400	—	—	0.4	—
	600	—	0.2	0.9	—
j	400	—	0.4	—	—
	600	—	0.7	0.1	—
l	400	—	—	—	—
	600	—	—	—	—

BIOLOGICAL EVALUATION

Antibacterial activity

A few selected compounds of the type **IV** were screened for their antibacterial activity by Vincent and Vincent[7] filter paper disc diffusion plate method. The gram positive and gram negative bacteria employed for the tests were *Bacillus subtilus, Staphylococcus aureus* and *Proteus vulgaris, Escherichia coli* respectively. All the compounds tested were ineffective against *P. vulgaris* (−), but feebly active against *E. coli* (−). They show little action against *B. subtilus* (+), but moderately active against *S. aureus* (+). The results were provided in Table III.

TABLE III

Antifungal activity

Compound	Conc. μg/ml	% of germination inhibition *D.s.*	*F.s.*
IVb	360	9.37	17.98
	600	28.71	30.18
	840	100.00	100.00
e	360	—	—
	600	—	—
	840	—	17.44
g	360	100.00	100.00
	600	100.00	100.00
	840	100.00	100.00
j	360	—	—
	600	—	19.76
	840	38.37	100.00
l	360	—	17.24
	600	—	61.20
	840	76.02	100.00

Antifungal activity

A five selected compounds of the type **IV** were tested for their antifungal activity by glass-slide humid chamber technique.[8] The fungi employed were *Dreschlera speciferum* and *Fusarium solani.* Compound **IVg** was highly toxic and showed 100% inhibition of spore germination of both fungi at 360 μg/ml. The same toxicity was found with **IVb**, against the same fungi but at 840 μg/ml. Compounds **IVj, l** showed 100% inhibition of *F. solani* at 840 μg/ml. **IVl** also registered more than 70% inhibition of spore germination of *D. speciferum* at 840 μg/ml. Compound **IVe** was virtually inactive against *D. speciferum* at all doses of investigation. Thus **IVg** and **IVb** may be exploited as future fungicides. The results of activity were given in Table III.

EXPERIMENTAL

The IR spectra were recorded on Perkin-Elmer model 137 in KBr discs. H^1NMR spectra were recorded on a Varian A 90-D instrument with TMS as internal reference and mass spectra on a JMS-D 300 mass spectrometer at 70 eV. Melting points were uncorrected. 4,5-Diamino(2,1,3)benzothiadiazole was prepared according to literature.[9] The physical and analytical data were shown in Table I.

5-Mercapto-4H-imidazo(4,5-e)(2,1,3)benzothiadiazole (**III**). A mixture of 4,5-diamino(2,1,3)benzothiadiazole, **II**, (0.01 mol), carbondisulphide (30 ml), potassium hydroxide (0.02 mol), methanol (40 ml) and water (10 ml) was refluxed for 30 hrs. and the excess carbondisulphide was recovered. The reaction mixture was cooled and acidified with acetic acid. The precipitate thus obtained was filtered, washed with cold water and dried. It was recrystallised from alcohol. Yield: 2.25 g (65%). m.p. 278°C.

5-Substitutedmercapto-4H-imidazo(4,5-e)(2,1,3)benzothiadiazoles (**IVa–l**). Compound **III** (0.01 mol) was dissolved in dry methanol (20 ml) containing anhydrous dimethyl formamide (20 ml) and the appropriate alkyl/aralkyl halide (0.01 mol) was added. The mixture was refluxed for 3 hrs., cooled and poured over crushed ice with stirring. The solid obtained was filtered, washed with cold water and dried. It was recrystallised from alcohol/aqueous dioxan.

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