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Synthesis of Some Benzothiazole Derivatives with Potential Antibacterial Activity (Part III*)

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Abstract□The carbinols, hydrazide,Schiff's bases and acryloyl derivatives of 2-thiobenzethiazole were prepared. The acid and nitrile of 2-thiobenzothiazole were also obtained. The derivatives were tested for their antibacterial activities. Some derivatives showed the highest antifungal and antibacterial activity.

Key words□Benzothiazole, antibacterial effect.

Benzothiazole was long known to be effective as bacteriostatic, tuberculostatic fungistatic and molluscicidal agents[3-7]. The present work describes the synthesis of new 2-thiobenzothiazole derivatives with potential bacteriostatic activity.

Interaction of benzothiazole-2-thioformate prepared by interaction of the sodio-derivative of benzothiazole-2-thiole with ethyl chloroformate with Grignard reagents and hydrazine hydrate gave the corresponding thiocarbinols (**Ia-c**) and hydrazide (**II**) respectively. The hydrazide was previously prepared by another procedure[8].

The hydrazide derivative (**II**) with various aldehydes was converted to the corresponding hydrazones (**IIIa-e**).

Interaction of *p*-nitro and *p*-chlorophenylacryloyl chloride with the sodio-derivative of benzothiazole-2-thiol, gave the corresponding acryloyl derivatives (**IVa, b**).

Hydrolysis product of benzothiazole-2-thioformate, benzothiazole-2-thiocarboxylic acid (**V**) was converted to the amide and reaction of the amide with $POCl_3$ / DMF gave benzothiazole-2-thionitrile (**VI**).

The attempt to prepare 2-carboxy-6-nitrobenzothiazole (**VIII**) through the cycliazation of the thione acid (**VII**) with potassium ferrocyanide in alkaline medium was unsuccessful. The thione acid (**VII**) has been prepared *via* reaction of *p*-nitroaniline with diethyl oxalate to give *p*-nitrophenyl amidoethyl formate which on reacting with P_2S_5 yielded the monothione-ester and its hydrolysis gave the thione acid (**VII**).

The benzothiazole derivatives were tested for their antibacterial activites using 6 different bacteria.

In the thiocarbinol derivatives (**I**) of 2-benzothiazole the compounds of methyl group showed the highest antifungal activity against *Aspergillus niger, Candida albicans* and *Candida utilis,* but did not exert significant antibacterial activity. In the hydrazone derivatives (**III**) of some molecule, the presence of *p*-hydroxyl or *o*-dimethoxyl moiety in the condensed aryl aldehyde group showed the highest antifungal activity against *Candida albicans* and *Aerobacter aerogenes.* Also the *o*-dimethoxyl moiety showed the highest antibacterial activity against *Bacillus subtilis.*

In the aryloyl derivatives (**IV**) of 2-benzothiazole, introducation of a nitro group enhanced the antifungal effect against *Aspergillus niger* and *Aerobacter aerogenes,* while the presence of chloro group abolished the antibacterial activity and potentiated the antifungal activity against *Candida albican* and did not exert the high antifungal activity against *Aerobacter aerogenes.*

EXPERIMENTAL

IR (KBr) spectra were recorded on a Perkin Elmer 580. ^{1}HNMR spectra were recorded on a Jeol FX60 Q (DMSO-d6/TMS). Mass spectra were obtained on a varian MAT 311A.

Reaction of the benzothiazole-2-thioformate with Grignard Reagents

To 0.1 mole of an ethereal solution of the appropriate Grignard reagent, was added dropwise 0.1 mole of benzothiazole-2-thioformate in dry benzene. When the addition was complete, the solution was allowed to stand overnight. The Grignard complex was hydrolysed with a saturated solution of sodium sulphate. The benzene layer was separated, washed

*Part I and Part II were published[1,2]

with water, dried over anhydrous sodium sulphate and then evaporated under reduced pressure to give the corresponding thiocarbinol derivatives (**Ia-c**). IR spectrum showed a stretching frequency characteristic to OH at 3380 cm^{-1} (Table II). ^1H NMR : see Table V.

Reaction of the benzothiazole-2-thioformate with hydrazine hydrate

A mixture of benzothiazole-2-thioformate (0.01 mole) and hydrazine hydrate (0.05 mole) in ethanol (20 m*l*) was heated under reflux for 2 hours. The reaction mixture was left to cool, then diluted with water. The separated solid was collected, washed with water, and crystallised from ethanol-water mixture to give the hydrazine (**II**) (Table II). ^1H NMR : see Table V.

Table I. he antibacterial activity of benzothiazole derivatives

Compound	Inhibition zone					
	B. subtilis	*E. coli*	*A. niger*	*C. albicans*	*A. aerogenes*	*C. utilis*
Ia	+	–	+ + +	+ + +	+	+ + +
b	+ +	+	+ +	+ +	–	+
c	+	+	+ +	+ +	+ + +	+
II	+	+ +	+ + +	+	+ +	–
IIIa	+ +	+	+	+ +	+ +	+ +
b	+ +	+	+	+ + +	+ + +	+ +
c	+ +	+ +	+ +	+	+	+ + +
d	+	+	+ +	+	–	–
e	+ + +	+ +	+ +	+ + +	+ + +	+
IVa	+ +	+ +	+ + +	+ +	+ + +	–
VIIIb	–	+	+ +	+ + +	+ + +	–

\+ Slight activity
\+ + Medium activity
\+ + + High activity

Condensation of hydrazide with aldehydes

A solution of the hydrazide (**II**) (0.02 mole) and aldehyde (0.01 mole) in ethanol in the presence of few drops of glacial acetic acid, was heated under reflux for 4 hours. The reaction mixture was left to cool, then diluted with water. The separated solid was collected, washed with water, and crystallised from ethanol-water mixture to give the Schiff's bases (**IIIa-e**). Their IR spectra showed bands in the 1730 cm^{-1} region corresponding to C=O and C=N, respectively (Table III). ^1H NMR : see Table V.

Reaction of acrylic acid derivatives with sodo-derivatives of 2-thiobenzothiazole

A mixture of *p*-substituted phenyl acryloyl chloride (0.01 mole) the sodo-derivatives of 2-thiobenzothiazole (0.01 mole) in dry benzene was stirred for two hours. Addition of pet.-ether (40-60°), gave a crude product which when crystallised from benzene yielded the styryl compound of type **IV**. IR spectra showed bands in the region of 1710 cm^{-1} and 1580 cm^{-1} due to carbonyl and C=C (Table IV). ^1H NMR : see Table V.

Hydrolysis of benzothiazole-2-thioformate

A mixture of 11.9g of benzothiazole-2-thioformate and a solution of 4g of sodium hydroxide in 80 m*l* of water, was boiled in 5-10 minutes or until the ester disappeared, and the water. The diluted reaction mixture was added with vigorous stirring into 125 m*l* of conc. HCl. After cooling, the crude acid was filtered, washed with a little water, crystallised from water, or light petroleum (40-60°) : gave the product, **V**. IR spectra : 1700 (C=O), 3400 (OH). ^1H

Table II. M.P., Yield, M.S. and elemental analysis of Ia-c and II

Comp.	M.P. °C	Yield %	Formula (M.W.)	[M.S m/z] %	Analyses Calc./Found		
					C	H	N
Ia	115	35	$C_{10}H_{11}NOS_2$	235 (M^+, 42)	53.33	4.89	6.22
			(225.32)	224 (100), 209 (62)	53.67	4.30	6.58
Ib	130	48	$C_{12}H_{15}NOS_2$	253 (M^+, 54)	56.92	5.93	5.33
			(253.38)	252 (100), 236 (42)	57.27	5.37	5.93
Ic	170	20	$C_{20}H_{27}NOS_2$	361 (M^+, 39)	66.48	7.48	3.87
			(361.56)	360 (100), 344 (36)	66.04	7.89	3.72
II	175	60	$C_8H_7N_3OS_2$	225 (M^+, 49)	42.67	3.11	18.65
			(225.32)	224 (100), 209 (72)	43.06	3.58	18.42

Table III. M.P., yield, M.S. and elemental analysis of IIIa-e

Comp.	M.P. °C	Yield %	Formula (M.W.)	[M.S m/z] %	Analyses Calc./Found		
					C	H	N
IIIa	140	30	$C_{13}H_9N_3O_2S_2$	303 (M^+, 28)	51.49	2.97	13.85
			(303.35)	302 (100), 235 (42)	51.58	3.27	13.57
b	133	55	$C_{15}H_{11}N_3O_2S_2$	329 (M^+, 39)	54.71	3.34	12.76
			(329.43)	328 (100), 235 (57)	55.13	3.57	12.40
c	179	40	$C_{16}H_{13}N_3OS_2$	327 (M^+, 34)	58.72	3.98	12.83
			(327.42)	326 (100), 232 (52)	58.27	4.34	13.21
d	161	60	$C_{15}H_{10}N_4O_3S_2$	359 (M^+, 73)	50.28	2.79	15.63
			(359.39)	358 (100), 233 (70)	50.30	2.65	15.57
e	108	40	$C_{17}H_{15}N_3O_3S_2$	373 (M^+, 50)	54.69	4.02	11.72
			(373.44)	372 (100), 232 (56)	54.20	4.37	11.72

Table IV. M.P., yield, M.S. and elemental analysis of IVa,b and V-VII

Comp.	M.P. °C	Yield %	Formula (M.W.)	[M.S m/z] %	Analyses Calc./Found		
					C	H	N
IVa	216	60	$C_{16}H_{10}N_2O_3S_2$	342 (M^+, 37)	56.13	2.94	8.18
			(342.39)	341 (100), 219 (55)	56.40	2.56	8.16
IVb	164	45	$C_{16}H_{10}NOS_2Cl$	331 (M^+, 54)	58.00	3.03	4.22
			(331.83)	330 (100)	58.30	2.66	4.57
V	115	40	$C_8H_5NO_2S_2$	211 (M^+, 22)	45.54	2.37	6.63
			(211.25)	210 (100), 166 (75)	45.03	2.95	7.20
VI	154	70	$C_8H_4N_2S_2$	192 (M^+, 57)	50.00	2.08	14.58
			(192.25)	166 (100)	50.18	2.58	15.07
VII	170	45	$C_8H_6N_2O_4S$	226 (M^+, 26)	42.47	2.65	12.38
			(226.21)	177 (63)	41.78	2.43	12.57

NMR : see Table V.

Benzothiazole-2-thioamide

Freshly distilled thionyl chloride (3 m*l*) was added to a solution of benzothiazole-2-thioacid (**V**) (0.01 mole) in dry benzene (50 m*l*). The reaction mixture was boiled for two hr cooled, the excess thionyl chloride together with the solvent evaporated under reduced pressure and the remaining solid dissolved in dry benzene (20 m*l*) and treated with ammonia until the reaction become alkaline. Ammonium chloride was removed by filtration, and the filtrate evaporated under reduced pressure. The remaining solid collected, washed with a solution of sodium carbonate (5%), and recrystallized from ethanol to give benzothiazole-2-thioamine.

Benzothiazole-2-thionitrile

To a cooled solution of benzothiazole-2-thioamide (0.005 mole) in DMF (5 m*l*), 0.01 mole $POCl_3$ was added. After one hours, water was added, and the precipitated solid collected and crystallized from petroleum ether (60-80°), to give benzothiazole-2-thionitrile (**VI**) (70% yield), as colourless crystals of m.p. 154°C. Its IR spectra showed band in the 2280 cm^{-1} region due to the nitrile group. ^1H NMR : see Table V.

Hydrolysis of Benzothiazole-2-thionitrile

Benzothiazole-2-thionitrile (**VI**) (15 g) was heated under reflux for 45-60 minutes in a mixture containing 10 m*l* water, 10 m*l* acitic acid and 10 m*l* conc. H_2SO_4. The reaction mixture was then diluted with 2-3 volumes of water and the drude acid collected by filtration, washed several times with small volumes of hot water, then the acid solidified on

Table V. Spectral properties of I-VI

No.	^{1}H NMR [δ in DMSO-d6]
Ia	1.32 (S,6H,2CH_3), 7.28 (S,4H,C_6H_4), 9.79 (S,1H,OH).
Ib	0.97 (E,J = 7 HZ,6H,CH_2CH_3), 2.17 (q,J = 7 HZ,4H, CH_2CH_3), 7.27 (S,4H, C_6H_4), 9.80 (S,1H,OH).
Ic	7.32 (S,4H,C_6H_4), 8.95 (S,22H,2C_6H_{11}), 9.83 (S,1H,OH).
II	7.25 (S,4H,C_6H_4), 7.53 (S,2H,NH_2), 8.75 (S,1H,NH).
IIIa	0.9 (S,1H,CH),1.53 (S,3H,C_4H_3O), 7.32 (S,4H,C_6H_4), 8.80 (S,1H,NH).
IIIb	0.87 (S,1H,CH), 7.25 (S,8H,2C_6H_4), 8.98 (S,1H,NH), 9.73 (S,1H,OH).
IIIc	0.95 (S,1H,CH), 2.34 (S,3H,CH_3), 7.18 (S,8H,2C_6H_4), 8.83 (S,1H,NH).
IIId	0.93 (S,1H,CH), 7.28 (S,8H,2C_6H_4), 8.78 (S,1H,NH).
IIIe	0.95 (S,1H,CH), 3.72 (S,6H,2OCH_3), 7.31 (S,7H,C_6H_3), 8.82 (S,1H,NH).
IVa	0.91 (S,2H,CH = CH), 7.29 (S,8H,2C_6H_4).
IVb	0.93 (S,2H,CH = CH), 7.35 (S,8H,2C_6H_4).
V	7.23 (S,4H,C_6H_4), 10.2 (S,1H,COOH).
VI	7.26 (S,4H,C_6H_4)

cooling. The solid was dissolved in a saturated solution of sodium carbonate, filtered, and precipitated from the clear filtrate by the addition of dil. H_2SO_4, recrystallized from hot water, or light petroleum (40-60°).

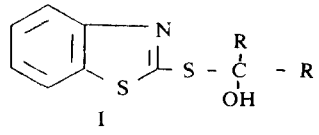
Action of P_2S_5 on p-nitrophenylamidoethyl formate

A mixture of *p*-nitrophenylamidoethyl formate (0.1 mole) prepared from the reaction of *p*-nitroaniline eith diethyloxalate and P_2S_5 (0.02 mole) in xylene, were heated under reflux for two hours. The cooled reaction mixture was filtered and the obtained solid washed several times with pet. ether (40-60°C) then recrystallized from benzene to give the thione ester (40%) as brownish crystals, m.p. 144°C.

Analysis for : $C_{10}H_{10}N_2O_4S$ (254.29)
Calc. : C, 47.24% H, 3.93% N, 11.52%
Found : C, 48.03% H, 4.25% N, 11.36%
[M.S. *m/z*] % : 254 (M^+,25), 253 (100), 209 (72)

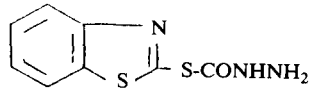
Hydrolysis of the thione ester

A mixture of the thione ester (0.01 mole) and sodium hydroxide solution (5%, 80 m*l*) was heated to boiling for 5-10 minutes or until the compleate

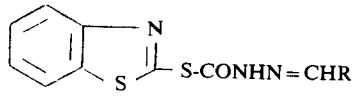


I

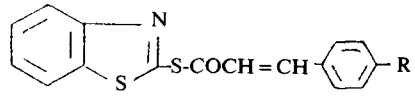
Ia R = CH_3; **Ib** R = C_2H_5; **Ic** R = C_6H_{11}-C



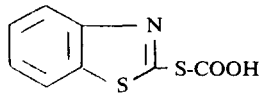
II



III	R
a	C_4H_3O-
b	HO-C_6H_4-p
c	CH_3-C_6H_4-p
d	NO_2-C_6H_4-p
e	3,4 $(CH_3O)_2C_6H_3$-



IVa R = NO_2; **IVb** R = Cl



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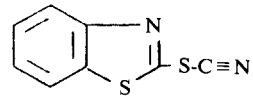
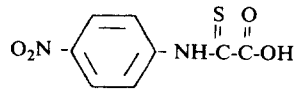
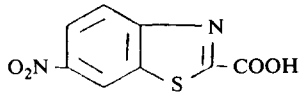


VI



VII



VIII

dissolution of the ester. Dilution with an equal volume of water was followed by acidification of the cold reaction mixture with dil. HCl. The obtained product was washed with water, dried, then recrystallized from light petroleum (40-60°), to give the acid (**VII**). Its IR spectrum showed bands in the region 1300 cm^{-1}, 3300 cm^{-1} corresponding to

C = S and OH groups, respectively.

Antibacterial activity

The bacteria were suspended in an agar culture media containing : 10 g/*l* glucose, 6 g/*l* peptone, 3 g/*l* yeast extract and 20 g/*l* agar (pH = 7). The organism-agar suspension were distributed in petri dishes (15 mm diameter) and allowed to solidify before the addition of the solution of the compounds in the glass ring. The concentration of each compound was 0.01 g/100 m*l*. The dishes were incubated at 37° for 24 hr and the inhibition zones were estimated (Table I).

LITERATURE CITED

1. Moharram, H.H., Abdel Fattah, A.M. and Manhey, F.M.: Synthesis of some Benzothiazole Derivatives of Expected Biological Activity. part I. *Egypt J. Chem.* **26,** 261 (1983).
2. Moharram, H.H., El-Bayouki, Kh.A. and Mansour S.A.: Synthesis of some Benzothiazole Derivatives of Expected Biological Activity. part II. *Egypt J. Chem.* **27,** 241 (1984).
3. Allen, R.E.R.S., Shelton and Vancampen, M.Q.: Antifungal Agents. Some 3-Imino-5-Alkylmercapto-1,2,4-dithiazole salts. *J. Amer. Chem. Soc.* **76,** 1158 (1954).
4. Mahapatra G.N.: Synthesis of Isomeric bromothiazolaylmines and the use of their Mercurated Derivatives as Fangicides and Bacteriosides. *J. Amer. Chem. Soc.* **79,** 988 (1957).
5. Kornfeld, E.C., Jones, R.G. and Parhe, T.V.: The structure and chemistry of Actidione, an Antibiotic from *Streptomyces grisens. J. Amer. Chem. Soc.* **71,** 150 (1949).
6. Christison, I.B., Conant, N.E. and Bradsher, T.H.: Therapy of fungus Diseases. Little, Brown and Co., Bostch. Mass, p.268, 1955.
7. Conant, N.F. and Rosebury. T.: Bacterial and Mycotic Infections of Man. 2nd ed. Lippincott, Philadelphia p.634, 1952.
8. Singh, S.P, Misra, R.S., Parmer and Stanly J. Brumleve: Synthesis of 2-(4-arylthiosemicarbazidocarbonylthio) benzothiazoles and their monoamies oxidase inhibitory and anticonvulsant properties. *J. Pharm. Sci.* **64,** 1245 (1975).