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SYNTHESIS OF NEW BENZOTHIAZOLE-2-ACRYLIC ACID DERIVATIVES

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Benthothiazole-2-acrylic acid IV reacted with thiourea to give the thiazole derivative V which reacted with different aldehydes to give compounds of the type VI.Also, compound IV reacted with some sulfa drugs and some amines to give amide derivatives of the type VII and IX, respectively. The prepared compounds showed potential antimicrobial activity.

Key words: Maleic anhydride, O-aminothiophenol, Benzothiazole-2-acrylic acid.

Introduction

A wide variety of benzothiazole-2-acrylic acid derivatives have been described for their chemotherapeutic importance [1-6]. Also,it is of interest to incorporate the thiazole moiety in the new prepared compounds since a wide range of thiazole compounds showed biological activity against schistosoma [7,8].

In the present work, benzothiazole-2-acrylic acid derivatives were prepared with various biologically active moieties hoping to synthesize more potent and less toxic drugs in the area of parasitic diseases.

Synthesis of the desired compounds was accomplished by the condensation of maleic anhydride I with o-aminothiophenol II in dry benzene, then cyclizing the product III with concentrated sulfuric acid to benzothiazole-2-acrylic acid IV, which was identical to that reported in the literature [9].

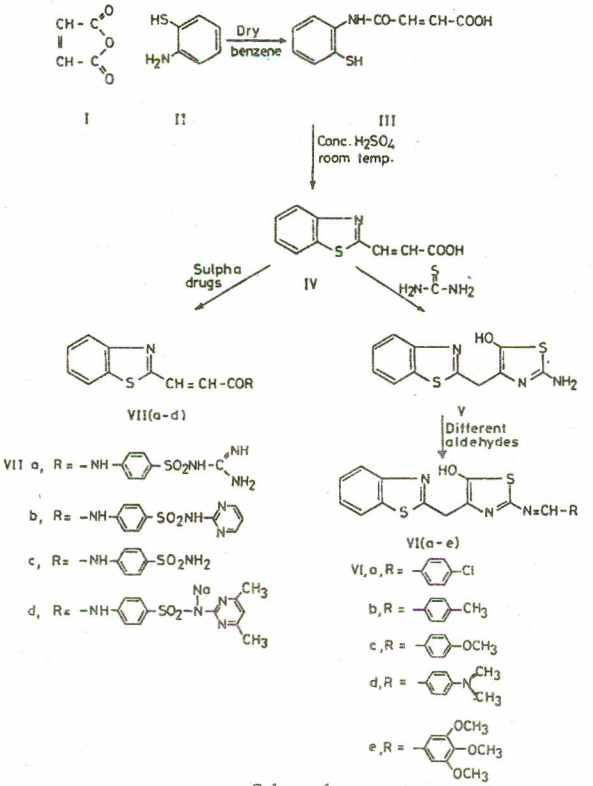
Benzothiazole-2-acrylic acid IV, reacted with thiourea in acidic medium to give 2-amino-4-(2-benzothiazolylmethyl)-5-thiazolol V (Scheme 1) [10,11]. Condensation of V with different aromatic aldehydes, namely, p-chlorobenzaldehyde, p-methylbenzaldehyde, p-anisaldehyde p-dimethylaminobenzaldehyde and/or 3,4,5-trimethoxybenzaldehyde gave the corresponding Schiffs bases derivatives VI (a-e), respectively (Scheme 1).

Due to the high biological activity of sulfa drugs [12], it was of importance to combine the sulfa drug moiety with the starting material IV hoping to obtain new compounds with high antimicrobial activity. Thus, the reaction of the acid IV with sulfa guanidine, sulfadiazine, sulfanilamide and/or sulfadimidine sodium salt afforded the compounds VII (a-d), respectively, (Scheme 1).

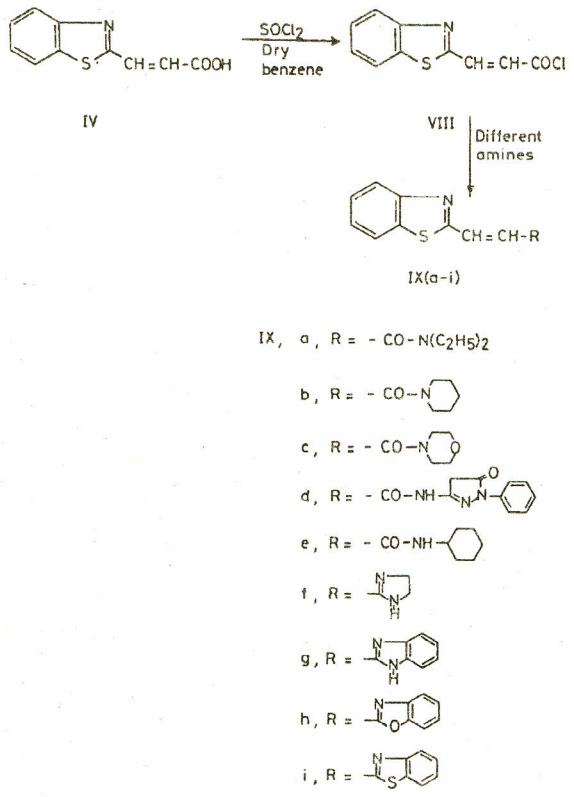
Finally, treatment of the acid IV, with thionyl chloride in dry benzene, afforded the acid chloride VIII [13, 14], which was condensed with different amines, namely, diethylamine, piperidine, morpholine, 3-amino-1-phenyl-5-pyrazolone, cyclohexylamine, ethylene diamine, o-phenylene diamine, o-aminophenol and/or o-aminothiophenol to give the respective derivatives IX (a-i) (Scheme 2).

Biological activity. The antibacterial and antifungal activity of compounds V, VIa, VIb, VIc, VId and VIe were tested for two strains of gram-positive, two strains of gram-negative bacteria, yeast and fungi. Table 1 illustrates the preliminary test of the prepared compounds while Table 2 illustrates the minimal inhibitory concentration (MIC) of the highly sensitive compounds.

From the data obtained in Tables 1&2, it is clear that compounds V, VIb and VId possess high activity against



Scheme 1.



Scheme 2.

gram-positive bacteria. Compounds VIa and VIe possesses moderate activity against gram-positive bacteria. Compound VIc possesses slight activity towards gram-positive bacteria.

Further, compound VIa possesses high activity towards gram-negative bacteria. Compounds V, VIb, VIc and VId possess moderate activity against gram-negative bacteria. Compound VIe posseses slight activity against gram-negative bacteria.

On the other hand, compound VIa possesses high activity against each of yeast and fungi. Compounds V, VIb, VIc, VId and VIe possess slight activity against yeast and fungi.

TABLE 1. THE PRELIMINARY SCREENING OF BIOLOGICAL ACTIVITY OF THE PREPARED COMPOUNDS.

Comp. No.	Micro-organism 1	2	3	4	5	6
V	++	+++	++	+	+	+
VIa	++	++	+	++	+++	++
VIb	+++	+++	+	+	+	+
VIc	+	++	++	++	-	-
VId	+++	+++	++	+	+	+
VIe	++	++	+	+	+	+

Micro-organisms: 1. *Bacillus subtilis*, 2. *Staphylococcus aureus*, 3. *Escherichia coli*, 4. *Pseudomonas aeruginosa*, 5. *Candida albicans*, 6. *Aspergillus niger*.

Experimental

All melting points were uncorrected and were obtained on a Boetuis melting point microscope. The IR spectra were recorded on Carl-Zeiss spectrophotometer model UR10 using KBr. The ^{1}H-NMR spectra were determined on Varian EM 360 spectrometer 60 MHz, using tetramethylsilane as an internal standard.

Reaction of o-aminothiophenol with maleic anhydride. 0.01 mole of maleic anhydride I was dissolved in 25 ml of dry benzene and 0.01 mole of o-aminothiophenol II was added to it portionwise with stirring and reflux for 5 hrs. The separated product was filtered off and crystallized from the proper solvent to give compound III. The physical and analytical data are listed in Table 3.

Formation of benzothiazole-2-acrylic acid IV. Compound III (2 gm) was added portionwise to conc. sulfuric acid (20 gm) with stirring at room temperature and then left to stand for 5 hrs, then poured onto ice, the solid obtained was filtered off and washed with water several times. The crude was crystallized from ethanol. The physical and analytical data are identical to that reported in the literature [9]. IR spectra (cm^{-1}) showed bands at 2560 (OH,acid) and at 1705 (C=O, acid) ^{1}H-NMR spectrum (p.p.m.) showed signals at δ7.1 (m, 4H, aromatic); δ7.7-8.2 (dd, 2H, CH=CH) and at δ9.2 (s,1H,-COOH).

Formation of 2-amino-4-(2-benzothiazolylmethyl)-5-thiazolol V. 0.01 mole of the acid IV in 15 ml ethanol and 0.01 mole thiourea was treated with 10 drops glacial acetic acid. This mixture was refluxed for 6 hrs. The solid so formed after evaporation of the solvent under reduced pressure and cooling, was crytallized from the proper solvent. The physical and analytical data are listed in Table 3.

General method for preparation of compounds VI (a-e). A mixture of 0.01 mole of compound V and 0.01 mole of the appropriate aldehydes in absolute ethanol (20 ml) was refluxed for 5 hrs, then the solvent was evaporated under reduced pressure. The solid product was collected and crystallized from the proper solvent to give the title compounds.

TABLE 2. THE MINIMAL INHIBITORY CONCENTRATION OF THE ACTIVE COMPOUNDS.

Comp. No.	MIC (μg/ml) 1	2	3	4	5	6
V	100	100	100	100	-	>100
VIb	100	100	-	-	-	-
VId	100	>100	>100	75	75	75

Micro-organisms: 1. *Bacillus subtilis*, 2. *Staphylococcus aureus*, 3. *Escherichia coli*, 4. *Pseudomonas aeruginosa*, 5. *Candida albicans*, 6. *Aspergillus niger*.

TABLE 3. PHYSICAL AND ANALYTICAL DATA OF THE PREPARED COMPOUNDS.

Comp. No.	M.P.[C°] solvent for crystallization	yield [%]	Molecular formula (mol. mass)	Analysis calcd/found C%	H%	N%
III	185-187 (E)	56	$C_{10}H_9NO_3S$ (223.24)	53.80 54.21	4.06 4.44	6.28 6.58
V	188-190 (E)	33	$C_{11}H_9N_3OS_2$ (263.33)	50.17 50.55	3.44 3.89	15.96 16.37
VIa	174-176 (E)	48	$C_{18}H_{12}N_3ClOS_2$ (385.89)	56.02 56.37	3.13 3.60	10.89 11.11
VIb	204-206 (E)	65	$C_{19}H_{15}N_3OS_2$ (365.46)	62.44 62.90	4.14 4.60	11.50 11.23
VIc	154-156 (E)	48	$C_{19}H_{15}N_3O_2S_2$ (381.46)	59.82 60.30	3.96 4.40	11.02 10.94
VId	162-164 (E)	47	$C_{20}H_{18}N_4OS_2$ (394.50)	60.89 60.32	4.60 4.72	14.20 14.67
VIe	125-127 (E)	46	$C_{21}H_{19}N_3O_4S_2$ (441.51)	57.12 57.46	4.34 4.73	9.59 9.80
VIIa	238-240 (DMF/E)	48	$C_{17}H_{15}N_5O_3S_2$ (401.46)	50.86 50.81	3.77 4.28	17.45 17.62
VIIb	228-230 (THF/P)	56	$C_{20}H_{15}N_5O_3S_2$ (437.49)	54.90 54.73	3.46 3.74	16.01 15.79
VIIc	233-235 (DMF/P)	86	$C_{16}H_{13}N_3O_3S_2$ (359.41)	53.47 53.71	3.64 4.17	11.69 11.92
VIId	194-196 (DMF/E)	52.5	$C_{22}H_{18}N_5NaO_3S_2$ (487.53)	54.20 54.59	3.72 4.23	14.37 14.67
IXa	219-221 (DMF)	69	$C_{14}H_{16}N_2OS$ (260.35)	64.58 64.77	6.20 6.08	10.76 10.26
IXb	119-121 (M)	53	$C_{15}H_{16}N_2OS$ (272.36)	66.14 66.59	5.92 5.70	10.29 10.46
IXc	> 320 (THF/P)	45	$C_{14}H_{14}N_2O_2S$ (274.33)	61.29 61.75	5.14 4.81	10.21 10.06
IXd	> 320 (DMF/E)	62	$C_{19}H_{14}N_4O_2S$ (362.39)	62.97 63.02	3.89 3.70	15.46 14.98
IXe	d-315 (DMSO/H_2O)	65	$C_{16}H_{18}N_2OS$ (286.38)	67.13 67.80	6.29 5.83	9.79 10.15
IXf	> 330 (DMF/H_2O)	45	$C_{12}H_{11}N_3S$ (229.29)	62.85 63.15	4.84 5.15	18.33 18.01
IXg	> 330 (DMF/H_2O)	68	$C_{16}H_{11}N_3S$ (277.33)	69.29 68.88	4.00 4.25	15.15 15.43
IXh	>320 (DMF/H_2O)	44	$C_{16}H_{10}N_2OS$ (278.32)	69.04 69.55	3.62 3.25	10.07 9.80
IXi	d-300 (DMF/H_2O)	49	$C_{16}H_{10}N_2S_2$ (294.39)	65.27 65.59	3.42 3.82	9.52 9.09

E = Ethanol , M =Methanol, DMF = Dimethyl formamide, P=Pet ether, THF = Tetrahydrofuran , DMSO=Dimethylsulfoxide

The physical and analytical data are listed in Table 3. IR (cm^{-1}) of VIc:3360 (-OH); 1640 (-N=CH-) and at 1470 ($-OCH_3$). IR (cm^{-1}) of VIe: 3340 (-OH); 1660 (-N=CH-) and at 1500, 1460, 1430 ($3-OCH_3$).

Condensation of the acid IV with sulfa drugs; formation of VII(a-d). 0.01 mole of the appropriate sulfa drugs and 0.01 mole of the acid IV were fused at 230-250 °C for 3 hrs. The reaction mixture was triturated with hot ethnol and the product was isolated by filtration and recystallized from the proper solvent to give VII (a-d) respectively. The physical and analytical data are listed in Table (3).

The IR spectra (cm^{-1}) of all compounds are in correspondence with their structures and that of VIIc showed bands at 3300 (-NH); 1665 (-CO-N-) and at 1380, 1150 ($-SO_2-N-$).

The ^{1}H-NMR spectrum (p.p.m.) of VIId in DMSO showed signals at 2.5-2.8 (s, 6H, 2-CH3); 7.0-7.3 (m, 8H, aromatic); 7.7-8.2 (dd,2H, -CH=CH-) and at 10.7 (s,1H,NH)

Condensation of acid chloride VIII with different amines; formation of IX (a-i). 0.01 mole of the appropriate amine was added portionwise to 0.01 mole of benzothiazole-2-acrylic acid chloride VIII in 30 ml dry benzene with stirring at 0-5°C, then 5 ml conc. sulfuric acid were add at the same condition for one hour, then the reaction mixture was refluxed for 3 hrs. After this time the reaction mixture was cooled, then poured onto ice water, the solid so obtined, was filtered off, washed with water several times and recrystallized from the proper solvent. The physical and analytical data are listed in Table 3. The IR spectra (cm^{-1}) of IXb: 3300 (-NH) and 1670 (-C=O).

The IR of IXd:3300 (-NH) and 1700, 1670 (2-C=O).

Biological activity test. The preliminary screening test was performed according to the cup-plate method [15]. The minimal inhibitory concentration (MIC) of the highly sensitive compounds was tested using the serial tube dilution technique [16]. The results obtained are summarized in Tables 1 and 2.

The sensitivity of micro-organisms to the tested compounds is identified in the following manner:

+++=Highly sensitive (inhibition zone 12-15mm).
++=Moderately sensitive (inhibition zone 9-12 mm).
+=Slightly sensitive (inhibition zone 6-9 mm).
-=Not sensitive.

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