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SYNTHESIS OF SOME 5-BENZIMIDAZOLE SULPHONAMIDE DERIVATIVES WITH POTENTIAL ANTIMICROBIAL ACTIVITY

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ABSTRACT

Some new 2-methylbenzimidazole-5-sulphonylchoride derivatives and 2-methylbenzimidazole-5-N(p-carbohydrazidephenyl)sulphonamide derivatives were synthesized. Some of these compounds were found to posses antimicrobial activities towards different microorganisms.

INTRODUCTION

The chemical and pharmacological properties of benzimidazole derivatives have commanded the interest of organic and medicinal chemists[1-4]. Unfortunately, little is knwon about 2-methylbenzimidazole-5-sulphonic acid[5]. The need for additional information is further magnified by the many useful biological properites e.g. antibacterial (clemizole)[6,7], anthelmintic (cambendazole)[8,9], antitumour [pyrrolo(1,2-a) benzimidazole][10-12], cardiotonic (azobenzimidazole)[13], anxiolytic [pyrido(1,2-a)benzimidazole][14] and antiviral agents[15,16].

Furthermore, many substituted sulphonamide derivatives exhibit bactereostatic, hypoglycemic, diuretic and other pharmacological activities[17-20].

These findings have attracted our attention to preparation of a series of 2-methylbenzimidazole-5-sulphonylchloride derivatives to examine the antimicrobial activities

EXPERIMENTAL

Thin layer chromatography for analytical purposes were taken on silica gel G glass coated plates and developed with n-butanol-acetic acid-water (4:1:1) using ninhydrin or Dragendorff's reagent as spraying agent. Melting points were uncorrected using Stuart Scientific Melting Point Apparatus SMP2. Infrared spectra were taken in KBr discs using Schimadzu IR 404 spectrophotometer and ^{1}HNMR spectra were measured using a varian EM 360L Spectrophotometer.

A- Synthesis :

2-Methylbenzimidazole I was prepared according to previously reported procedures[21,22].

2-Methylbenzimidazole-5-sulphonic acid II was achieved according to published method[5].

2-Methylbenzimidazole-5-sulphonylchloride III :

This compound was obtained by adding 0.1 mole of 2-methylbenzimidazole to cold 0.2 mole chlorosulphonic acid at 0-5°C gradually. The reaction mixture was stirred at room temperature for 2h then heated at 60°C for 4h. The mixture was cooled to 5°C. The oily product was washed with cold dioxan several times and left in the refrigerator over night then filtered rapidly. The product was insoluble in 10% Na_2CO_3 solution; yield 80%, b.p. 96°C (76 mm Hg). IR spectrum (ν, cm^{-1}): 3350 (NH), 1370, 1180 (SO_2).

2-Methylbenzimidazole-5-sulphonamide derivatives IVa-e :

A solution of compound **III** (0.1 mole) in 10 ml absolute alcohol was added to cold appropriate solution of 0.1 mole of the amino acid (p-aminobenzoic acid, glycine, methionine, alanine and threonine) in 10 ml 1N NaOH solution. The temperature of the reaction mixture was maintained at 0°C until complete addition, then the mixture was heated at 60°C for 3h. The aqueous solution was cooled to 0°C and acidified with 1N HCl to pH 5.3. The crude product was collected and recrystallized from methonal-water mixture (Table 1).

IR spectrum of 2-methylbenzimidazole-5-(N-carboxymethyl)sulphonamide **(IVb)** (ν, cm^{-1}): 3360-2800 (COOH/NH), 1670 (C=O), 1370, 1170 (SO_2).

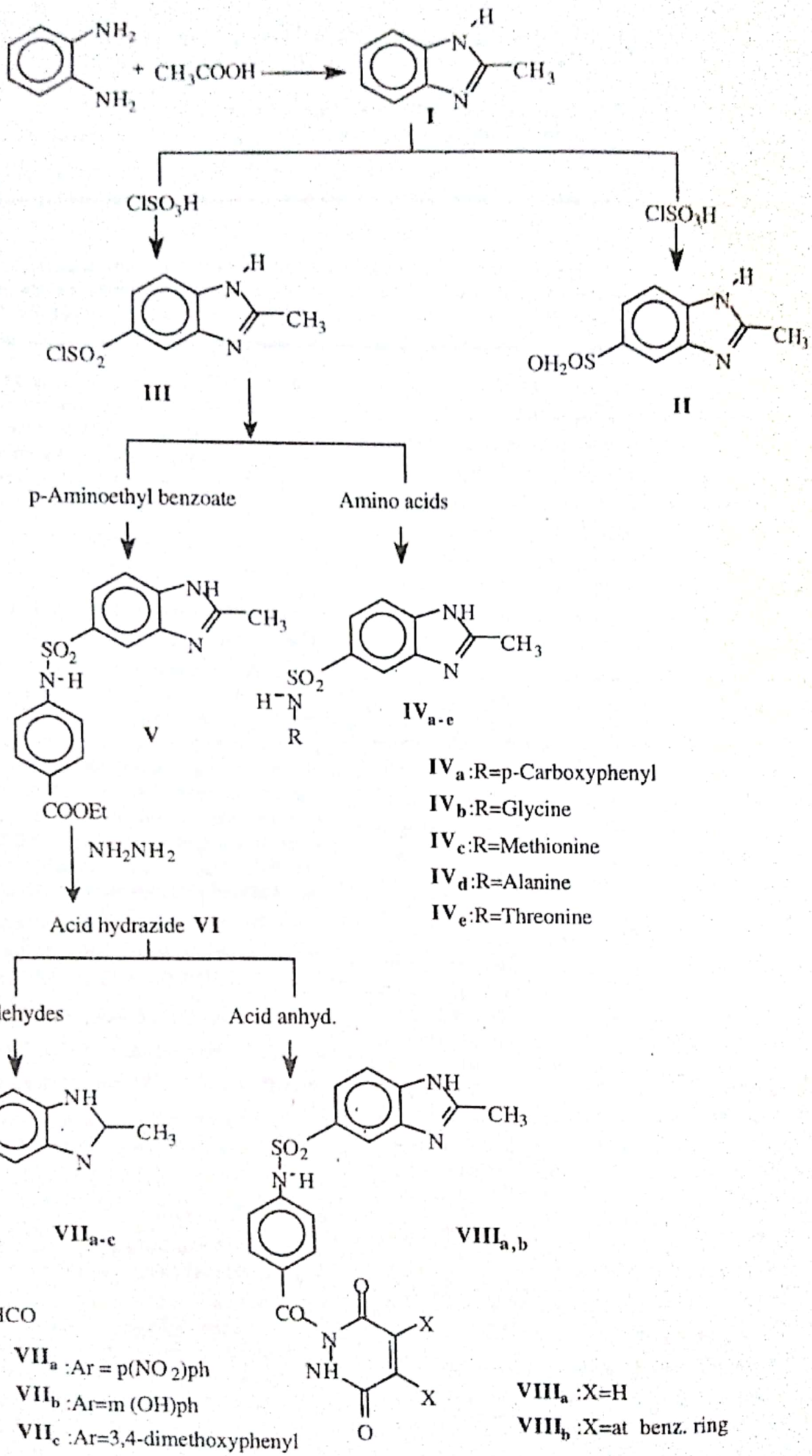
^{1}HNMR spectrum of compound **IV b** (δ, pyridine-d_5): 2.1 (s,3H,-CH_3), 3.3 (s,2H,.CH_2), 5.3 (s, $NHSO_2$), 7-5-8 (m,ArH), 8.2 (s,1H, NH benzimidazole).

^{1}HNMR spectrum of 2-methylbenzimidazole-5-N-(p-carboxyphenyl)sulphonamide **IVa** (δ, pyridine-d_5): 2.2 (s,3H, CH_3), 5.6 (s,br., NHO_2), 7-8.2 (m., ArH), 8.4 (s, 1H, NH).

Unequivocal synthesis of 2-methylbenzimidazole-5-N-(p-carbethoxyphenyl) sulphonamide (V) :

A solution of 0.1 mole of the compound II in dichloroethane (10 ml) was added dropwise to cold solution of p-aminoethylbenzoate (0.1 mole) in dichloroethane (10 ml) while stirring. The temperature of the reaction mixture was maintained at 5°C until complete addition and then it was refluxed on water

Scheme 1


+ CH3COOH
I
ClSO3H
ClSO3H
III
II
p-Aminoethyl benzoate
Amino acids
V
IVa-e
IVa :R=p-Carboxyphenyl
IVb :R=Glycine
IVc :R=Methionine
IVd :R=Alanine
IVe :R=Threonine
NH2NH2
Acid hydrazide VI
Aldehydes
Acid anhyd.
VIIa-e
VIIIa,b
VIIa :Ar = p(NO2)ph
VIIb :Ar=m (OH)ph
VIIc :Ar=3,4-dimethoxyphenyl
VIIIa :X=H
VIIIb :X=at benz. ring

bath for 7hr. After cooling the product was filtered and recrystallized from methanol (Table 1). IR spectrum (ν, cm^{-1}): 3300 (NH), 1720, 1680 (COOEt), 1370, 1160 (SO_2). ^{1}HNMR (δ, DMSO-d_6): 1, (t,3H, CH_3 ester) 2.8 (s,3H, CH_3), 4.2 (q,2H,J = 3 cps, CH_2 ester) 6.3 (s,1H, $NHSO_2$), 7-8 (m,ArH), 8.3 (s, 1H, NH).

2-Methylbenzimidazole-5-N9Pcarbohydrazidephenyl)sulphonamide VI :

A mixture of compound V (0.1 mole) and hydrazine hydrate 80% (20 ml) was heated at 80°C for 9h, then cooled. The product was poured into water then extracted by dichloroethane. The solvent was dried over anhydrous Na_2SO_4 and evaporated. An oil product was obtained in yield 84%, b.p 116°C (76 mm Hg). IR spectrum (ν, cm^{-1}): broad band 3370-3120 (br.$NHNH_2$), 1670 (C=O), 1370, 1170 (SO_2).

2-Methylbenzimidazole-5-N(p-substitutedbenzyliden e carbohydrazidephenyl)sulphonamide (VIIa-c) :

A mixture of 0.1 mole of compound VI and 0.1 mole of the required aldehyde (p-nitrobenzaldehyde, m-hydroxybenzaldehyde or 3,4-dimethoxybenzaldehyde) in 30 ml dichloroethane was heated at 80°C for 6 h then cooled and filtered. The prduct was recrystallized from ethanol. (Table 1).

IR spectrum of compound VIIa (ν, cm^{-1}): 3340, 3150 (NH, $NHSO_2$), 1680 (C=O), 1630 (C=N), 1380, 1170 (SO_2). ^{1}HNMR spectrum (σ, DMSO-d_6): 2.6 (s, 3H, CH_3), 6.8 (s, 1H, $NHSO_2$), 7.5-8.5 (m, ArH), 8.7 (s, 1H, N = CH), 9.6 (s, 1H, NHCO).

2-Methylbenzimidazole-5-N-(p-(3,6-dioxo-2H-pyridazin-l-yl)carbophenyl)sulphonamide (VIII a-b):

A 0.1 mole of the compound VI was dissolved in 25 ml dichloroethane and 0.1 mole of acid anhydride (maleic or phthalic anhydride) was added while stirring. The mixture was heated at 80°C for 7h. The solvent was evaporated under vacuum. The product washed with 10% Na_2CO_3 solution, then, recrystallized from water. (Table 1).

IR spectrum of compound VIIIb (ν, cm^{-1}): 3350 (NH) 1720, 1680 (C=O), 1370, 1180 (SO_2). ^{1}HNMR (δ, DMSO-d_6): 2.6 (s,3H, CH_3), 6.3 (s,1H, SONH), 7.5-8.5 (m, ArH), 9.5 (s, 1H, CONH).

B- Biological Screening :

The prepared compounds were tested against bacteria (*S. aureus* and *E. coli)* and fungi *(A. niger)* by agar plate diffusion method[23-25]. The compounds to be tested were dissolved in 10% aq KOH. Sterile discs of Whatman filter paper containing 15µl of the above solution were placed over the surface of nutrient agar containing standardized inoculum from the tested microorganisms.

The plate were incubated at 37°C for 24h for bacteria and at 25°C for 48h for fungi.

The inhibition zones appearing after incubation were measured. A disc impregnated with 5µl of aq. KOH is used as a control. The other disc impreganated with 15µl of thiabendazole solution in aq. KOH is used as standard for each microorganism. The results are summarized in Table 2.

A main finding is that some of the prepared compounds especially compound II showed a powerfull antifungal activity and compounds IVb, IVc, IVe, VIIa and VIIc showed sigificant antifungal and antibacterial activities.

RESULTS AND DISCUSSION

In the present study, compound **I** 2-methylbenezimidazole was synthesized according to reported methods[21,22]. This compound **I** was allowed to react with five equivalent chlorosulphonic acid at 110°C to yield 2-methylbenzimidazole-5-sulphonic acid **II.**

On the other hand, 2-methylbenzimidazole **I** was reacted with two equivalent of chlorosulphonic acid at room temperature then at 60°C to give 2-methylbenzimidazole-5-sulphonylcholoride **III.**

Compound **III** was then reacted with various amino acids mainly, p-aminobenzoic acid, glycine, methionine, alanine and threonine to afford the corresponding sulphonamide **(IVa-e).**

Compound **IVa** was reacted with ethanol and few drops of conc. sulfuric acid to yield 2-methylbenzimidazole-5-N(p-carbethozphenyl) sulphonamide **V.** Also, the compound **V** was obtained via reaction of 2-methylbenzimidazole-5-sulphonylchlororide II with p-aminoethylbenzoate.

Furthermore, through the reaction of compound **V** with hydrazine hydrate, the acid hydrazide VI was obtained. Compound **VI** was then allowed to react with some aldehydes mainly P-nitrobenzaldehyde, m-hydroxybenzaldehyde or 3,4-dimethoxybenzaldehyde to afford the corresponding Schiff's bases **VIIa-c.**

In addition, compound **VI** was reacted with acid anhydride (maleic anhydride or phthalic anhydride) to give the corresponding pyridazinone derivatives **VIII a,b.**

The sequence of reactions adopted for the synthesis of the compounds is illustrated in Scheme 1.

The elemental analyses and physical properties of the prepared compounds are listed in Table 1.

The antimicrobial activity of the prepared compounds was examined using agar diffusion method[23-25]. The results (Table 2) showed that

Table 1: Melting points, Yield and Elemental Analyses of the Prepared Compounds.

Comp. No.	m.p.C°	yield %	Mol. Formula	Analyses % (Calcd / found)		
				C	H	N
IVa	159	75	$C_{15}H_{13}SN_3O_4$	54.4 54.0	3.9 4.3	12.7 12.2
IVb	305	65	$C_{10}H_{11}SN_3O_4$	44.6 45.0	4.1 4.5	15.0 15.2
IVc	260	60	$C_{13}H_{17}S_2N_3O_4$	45.5 45.9	4.9 5.3	12.2 11.8
IVd	320	75	$C_{11}H_{13}SN_3O_4$	46.6 46.1	4.6 4.2	14.8 15.3
IVe	300	63	$C_{12}H_{15}SN_3O_5$	46.0 46.5	4.8 5.2	13.4 13.0
V	380	76	$C_{17}H_{17}SN_3O_4$	56.8 57.3	4.7 4.2	11.7 12.0
VI	116	84	$C_{15}H_{15}SN_5O_4$	49.9 50.3	4.2 4.5	19.4 19.0
VIIa	290	80	$C_{22}H_{18}SN_6O_5$	50.3 55.2	4.5 3.8	19.0 17.6
VIIb	180	74	$C_{22}H_{19}SN_5O_4$	54.8 58.8	4.2 4.2	18.0 15.6
VIIc	150	70	$C_{24}H_{23}SN_5O_5$	59.2 58.4	3.9 4.7	16.0 14.2
VIIIa	320	60	$C_{19}H_{15}SN_5O_5$	58.0 53.6	4.3 3.5	14.5 16.5
VIIIb	250	68	$C_{23}H_{17}SN_5O_5$	53.2 58.1 58.5	4.0 3.6 3.3	16.0 14.6 14.3

Table 2: Antimicrobial Activity of Tested Compounds.

Comp. No	Inhibition Zones (cm)		
	A.niger	E.coli	S.aureus
II	6	-	-
IVb	2.8	5	5
IVc	2.4	4.5	4
IVe	2.2	5	5
VIIa	4	-	4.5
VIIc	3.4	5	4.5
Thiabendazole	7	5	5
Aq.KOH	-	-	-

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compound **II** possess a strong antifungal activity against *A. niger*. Also, the compounds **IVb, IVc, IVe, VIIa** and VIIc showed a significant activity against the tested organisms *(S. aureus* and *E. coli)*.

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تشييد بعض مشتقات ٥-بنزايميدازول سلفوناميد ودراسه نشاطها المضاد للميكروبات

نبويه شرف الدين

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تم تشييد بعض مشتقات المركب ٢-ميثيل بنزايميدازول -٥- سلفوناميد ومشتقات المركب ٢-ميثيل بنزيميدازول -٥- كربوهيدازيد فينيل سلفوناميد.

وقد تم أيضا دراسة تأثير هذه المركبات الشميده ضد بعض الميكروبات. وقد أظهرت الدراسه التأثير الإيجابي لبعض هذه المركبات ضد أنواع من البكتريا والفطريات.