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Synthesis and Antimicrobial Activity of Some Mannich Bases of Benzimidazolyl Substituted 1H-Isoindole-1,3(2H) Diones

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The synthesis of some Mannich bases from benzimidazole substituted 1H-isoindole-1,3(2H) diones have been reported. The compounds were evaluated for their antibacterial and antifungal activity. The screening results have shown greater inhibition against fungi than against bacterial strains.

Key Words: Synthesis, Antimicrobial Activity, Mannich bases.

INTRODUCTION

Benzimidazoles belonging to the fused heterocyclic system prepared from amino acids are associated with diverse pharmacological activities such as antibacterial[1], insecticidal[2], fungicidal[3], antimicrobial[4], as vitronectin receptors, antagonists[5], anthelmintic[6–8], antiinflammatory[9] etc. Thiabendazole reported to possess anthehnintic property has been the first of a series of benzimidazole derivatives.

Phthalimide derivatives are also reported to possess a broad spectrum of biological activities[10–12]. This prompted us to synthesize some Mannich bases incorporated with these bioactive nuclei.

EXPERIMENTAL

The melting points were taken in open capillaries and thus uncorrected IR was recorded on Shimadzu spectrophotometer. NMR was taken in DX × 300 with DMSO and $CDCl_3$ as the solvents.

2-Glycyl-1H-isoindole-1,3(2H)-dione (IIIb): 0.5 g of glyciue and 1.0 g of phthalic anhydride were taken in a test-tube and immersed in a previously heated oil bath (180–185°C). The mixture was stirred occasionally during the first 10 min and any phthalic anhydride which sublimed was pushed down into the reaction mixture till there was complete fusion. The mixture was kept undisturbed for 5 min when the liquid mass solidified. The solid obtained was then recrystallized from 10% ethanol (m.p. 140°C; yield 95%).

2-Alanyl-1H-isoindole-1,3(2H)-dione (IIIb): This was prepared in a similar way using alanine as the amino acid (m.p. 170°C; yield 95%).

2-Methyl (benzimidazolyl)-1H-isoindole-1,3(2H)-dione (IVa): 0.1 mol of **IIIa** and 0.1 mol of *o*-phenylene diamine were refluxed in 30 mL of 4 N HCl for 2 h. The solution on cooling gave a precipitate which was filtered, dried and recrystallised from ethanol. m.f. $C_{16}H_{11}O_2N_3$; m.p. above 210°C; yield 75%. Calculated (%): C, 69.31; H, 3.97; N, 15.16. Found (%): C, 69.41; H, 3.94; N, 15.15. IR (KBr, cm^{-1}): 1610 ν(C=N), 1770, 1710 ν(>C=O, phthalamido); 2896 ν(CH stretching vibrations).

2-Ethyl (benzimidazoyl) 1H-isoindole-1,3(2H)-dione (IVb): This was synthesized in a similar manner using 0.1 gmol of 2-alanyl-1H-isoindole-1,3(2H)-

dione **(IVb)** and condensing with *o*-phenylene diamine. m.f. $C_{17}H_{13}O_2N_3$; m.p. above 210°C; yield 75%. % Calculated (%): C, 70.10; H, 4.46; N, 14.43. Found (%): C, 70.06; H, 4.50; N, 14.42. IR (KBr, cm^{-1}): 1610 ν(C=N), 1770, 1715 ν(C=O, phthalamido), 2972 ν(—CH stretching vibrations of alkyl group).

2-Methyl-(1H-aminomethyl-morpholino-benzimidazolyl)-1H-isoindole-1,3 (2H)-dione (Va): 0.1 mol of **IVa** was dissolved in 0.2 mL of 35% formaldehyde mixed in ethanol. To this was added 0.2 mol of morpholine gradually with stirring and then stirred further for 1 h at room temperature. The mixture was left overnight. The solid which separated out was filtered, dried and recrystallized from ethanol. m.p. 190–192°C; yield 63%; m.f. $C_{21}H_{20}O_3N_4$; Calculated (%): C, 67.02; H, 5.31; N, 14.89; Found (%): C, 66.96; H, 5.32; N, 14.86. IR (KBr, cm^{-1}): 1615 ν(C=N), 1775, 1715 ν(>C=O, phthalamido), 2978 ν(—CH stretching vibrations). NMR: CH_2, 2H, δ 4.60 (s), N—CH_2—N, 2H, δ 4.92 (s), CH_2—N—CH_2, 4H, δ 2.56(t), CH_2—H—CH_2, 4H, δ 3.52 (t), ArH, 8H, δ 7.26–7.87 (m).

2-Ethyl-(1H-aminomethyl-morpholino-benzimidazolyl)-1H-isoindole-1,3 (2H)-dione (Vh): This was synthesized in a similar way as for **Va. IVb** was treated with formaldehyde and morpholine in ethanol. m.p. 175–176°C; yield 62%; m.f. $C_{22}H_{22}O_3N_4$; Calculated (%): C, 67.69; H, 5.64; N, 14.35; Found (%): C, 67.62; H, 5.60; N, 14.32. IR (KBr, cm^{-1}): 1610 ν(C=N), 1770, 1710 ν(>C=O, phthalamido), 2972 ν(—CH stretching vibrations). NMR (DMSO): —CH—CH_3, 3H, δ 1.58 (d), CH—CH_3, 1H, δ 2.19 (q), N—CH_2, —N, 2H, δ 4.88 (s), CH_2—N—CH_2, 4H, δ 2.61 (t), CH_2—H—CH_2, 4H, 3.5 (t), ArH, 8H, δ 7.33–7.85 (m).

2-Methyl-(1H-aminomethyl-nitroanilino-benzimidazolyl)-1H-isoindole-1,3 (2H)-dione (Vg): 0.1 mol of IVa was dissolved in 0.2 mL of 35% formaldehyde mixed in ethanol. To this was added 0.2 mol of *p*-nitroaniline and the mixture was refluxed for 4–5 h on a water bath. The solution was left overnight in a freezer. The solid obtained was filtered, dried and recrystallised from ethanol.

m.f. $C_{23}H_{17}O_4N_5$; m.p. 155–157°C; yield 58%; % Calcd. C, 64.63; H, 3.98; N, 16.39; % Found C, 67.52; H, 3.86; N, 16.41.

Spectral Interpretation (Vg): IR (KBr, cm^{-1}): 1610 ν(C=N); 1770, 1710 ν(>C=O, phthalamido); 2972 ν(CH stretching); 1487 ν(NO_2 group); NMR ($CdCl_3$): CH_2—NH, 2H, δ 4.78(s), CH_2—NH, 1H, δ 3.78 (t), ArH, 12H, δ 7.21–7.65 (m).

Other Mannich bases were synthesized in a similar manner. The physical data are given in Table-1.

Antibacterial: The titled compounds were screened for their antibacterial activity using different strains, *i.e.*, *E. coli*, *S. aureus*, *Pr. vulgaris*, *Pseudomonas* sp. and *Klebsiella* using Kirbey-Bauer disc-diffusion method[13-14] at a concentration of 250 μg/disc with DMF as the solvent. After 24 h of incubation at 37°C the zones of inhibition were measured in mm with standard drugs Ampicillin (30–33 mm) and Streptomycin (200–25 mm). These values are given in Table-2.

Antifungal: The synthesized compounds were screened for their antifungal activity against *Candida albicans, Penicillin* and *Aspergillus niger* at a concentration of 50 μg/mL with incubation for 72 h at 37°C. Standard drugs used were Griseofulvin and Gentamycin. Similar procedure as for antibacterial drugs was followed. The activity data are given in Table-3.

TABLE-1
PHYSICAL DATA

Cmpd. No.	R	R′	m.p. (°C)	Colour	Yield (%)	m.f.	% N Calcd. (Found)
IIIa	H	—	140	Colourless	95	$C_{10}H_7O_4N$	6.82 (6.76)
IIIb	CH_3	—	170	Colourless	95	$C_{11}H_9O_4N$	6.39 (6.43)
IVa	H	—	> 210	Greyish	75	$C_{16}H_{11}O_2N_3$	15.16 (15.15)
IVb	CH_3	—	> 210	Greyish	75	$C_{17}H_{13}O_2N_3$	14.43 (14.42)
Va	H	Morpholino	190–192	White	63	$C_{21}H_{20}O_3N_4$	14.89 (14.86)
Vb	H	Pyrrolo	> 210	Black	64	$C_{21}H_{16}O_2N_4$	15.73 (15.83)
Vc	H	Diphenylamino	155	Greenish	66	$C_{29}H_{22}O_2N_4$	12.01 (11.96)
Vd	H	Piperidino	171	Creamish	52	$C_{22}H_{22}O_2N_4$	14.97 (15.03)
Ve	H	*p*-Amino benzoic acid	> 220	Pale yellow	49	$C_{24}H_{18}O_4N_4$	13.11 (13.17)
Vf	H	N-Ethyl anilino	94	Brownish	51	$C_{25}H_{24}O_2N_5$	16.43 (16.39)
Vg	H	*p*-Nitroanilino	155–157	Yellow	58	$C_{23}H_{17}O_4N_5$	16.39 (16.41)
Vh	CH_3	Morpholino	175–176	White	62	$C_{22}H_{22}O_3N_4$	14.35 (14.32)
Vi	CH_3	Pyrrolo	> 210	Black	60	$C_{22}H_{18}O_2N_4$	15.13 (15.09)
Vj	CH_3	Diphenylamino	195–196	Greenish	68	$C_{30}H_{24}O_2N_4$	11.66 (11.65)
Vk	CH_3	Piperidino	180–182	Creamish	48	$C_{23}H_{24}O_2N_4$	14.43 (14.39)
Vl	CH_3	*p*-Amino benzoic acid	> 220	Pale yellow	45	$C_{25}H_{20}O_4N_4$	12.72 (12.71)
Vm	CH_3	N-Ethyl anilino	96–98	Brown	52	$C_{26}H_{26}O_2N_5$	15.90 (15.88)
Vn	CH_3	*p*-Nitroanilino	133–135	Yellow	58	$C_{24}H_{19}O_4N_5$	15.87 (15.76)

TABLE-2
ANTIBACTERIAL ACTIVITY OF SOME MANNICH BASES OF BENZIMIDAZOLYL SUBSTITUTED 1H-ISOINDOLE-1,3(2H)-DIONES

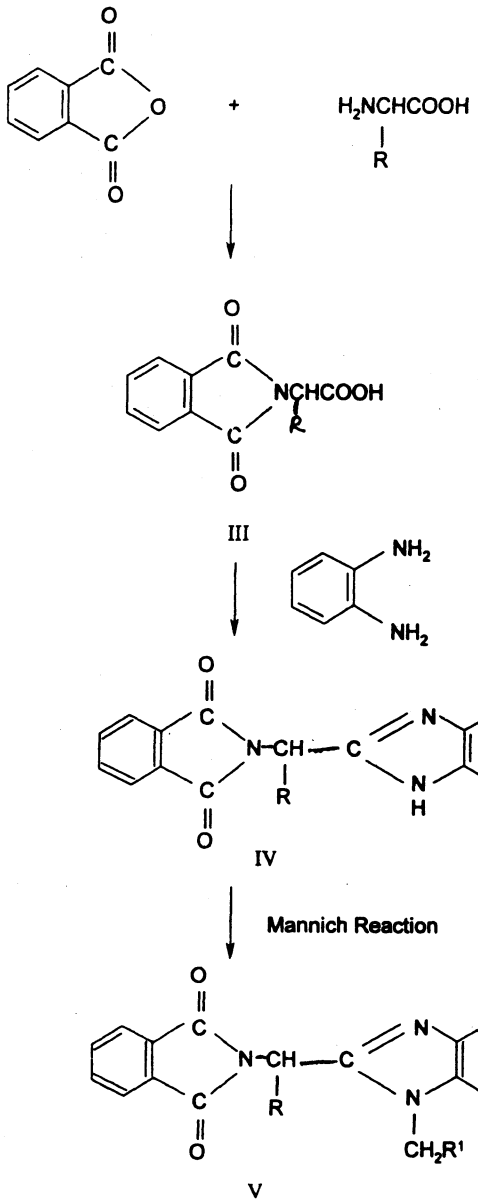
Cmpd. No.	*E. coli*	*S. aureus*	*P. vulgaris*	*Pseudomonas*	*Klebsiella*
Va	±	±	±	±	±
Vb	–	–	–	–	–
Vc	±	±	±	±	±
Vd	±	±	±	±	±
Ve	–	–	–	–	–
Vf	–	–	–	–	–
Vg	±	±	±	±	±
Vh	±	±	±	±	±
Vi	–	–	–	–	–
Vj	±	±	±	±	±
Vk	±	±	±	±	±
Vl	–	–	–	–	–
Vm	–	–	–	–	–
Vn	±	±	±	±	±

Concentration: 250 µg/disc. – = < 8 mm. ± =8–12 mm (Maximum zone of inhibition).
Standard drugs: Ampicillin Streptomycin (> 20 mm). Incubation: 24 h., 37°C.

TABLE-3
ANTIFUNGAL ACTIVITY OF SOME MANNICH BASES OF BENZIMIDAZOLYL SUBSTITUTED 1H-ISOINDOLE-1,3(2H)-DIONES

Cmpd. No.	*Candida albicans*	*Penicillin sp.*	*Aspergillus niger*
Va	±	–	–
Vb	–	++	++
Vc	±	–	–
Vd	–	++	–
Ve	–	–	–
Vf	–	–	–
Vg	+	+	++
Vh	±	–	–
Vi	–	–	–
Vj	+	–	+
Vk	–	–	–
Vl	–	–	–
Vm	–	–	–
Vn	+	–	++

Concentration: 50 µg/mL; ++ = Strongly active (no fungal colony);
+ = Moderately active (one colony); ± = Active (two colony); – = Inactive (heavy colony)
Standard drugs: Griseofulvin, Gentamycin (no fungal colony); Incubation: 72 h, 37°C.



Scheme

R = H, CH_3; R′ = Morpholino, pyrrolo, diphenylamino, piperidino, *p*-amino benzoic acid, N-ethyl amino, *p*-nitroanilino.

RESULTS AND DISCUSSION

The biological screening data show that compounds **(Va)**, **(Vc)**, **(Vd)**, **(Vg)**, **(Vh)**, **(Vj)**, **(Vk)** and **(Vn)** were found to be moderately active against all the strains of bacteria with zone of inhibition between 8 and 12 mm. Rest of the compounds were ineffective.

Regarding the antifungal activity, compounds **(Va)** and **(Vh)** were found to be active while **(Vc)**, **(Vg)**, **(Vj)** and **(Vn)** were moderately active against *Candida albicans*. However, maximum inhibition in compounds **(Vb)** and **(Vc)** was found against the *Penicillin* strains while **(Vg)** was moderately active. With *Aspergillus niger* as the fungi, three compounds **(Vb)**, **(Vg)** and **(Vn)** showed stronger inhibition as compared to **(Vj)**. The overall fungal activity shows **(Vb)** was the most active against two fungal strains, *i.e.*, *Penicillin* species and *Aspergillus niger*. While compounds **(Vg)** and **(Vn)** were highly active against one strain, *i.e., Aspergillus niger.*

Presence of Pyrrole nuclei and a nitro substituent in the aryl ring might be responsible for such behaviour.

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