STUDIES ON INTRAMOLECULAR MANNICH REACTION OF (S)-2-(α-HYDROXYETHYL)BENZIMIDAZOLE. SYNTHESIS OF (1S)-4-ARYL- 4,5-DIHYDRO-1-METHYL-1H,3H-[1,3,5]OXADIAZEPINO[5,6-a]BENZIMIDAZOLES – A NEW CLASS OF HETEROCYCLIC COMPOUNDS

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Abstract – The intramolecular Mannich reaction of (S)-2-(α-hydroxyethyl)benzimidazole with primary aromatic amines IIa-g and formaldehyde has been shown to furnish a new class of heterocyclic compounds: (1S)-4-aryl-4, 5-dihydro-1-methyl-1H , 3H-[1, 3, 5]oxadiazepino [5, 6-a]benzimidazoles IIIa-g. The antibacterial activity of these compounds has also been evaluated.

INTRODUCTION

The discovery that 5, 6-dimethylbenzimidazole is an integral part of the chemical structure of vitamin B_{12}[1] has led to massive research effort directed towards synthesising new benzimidazole compounds for pharmacological screening. In fact several synthetic benzimidazoles were found useful therapeutic agents[2] to combat human and veterinary diseases.

The N-Mannich bases of benzimidazoles are reported to possess antibacterial, anthelmintic and anti-inflammatory properties.[3] In earlier reports preparation of N-Mannich bases was accomplished employing secondary amines, while polymeric products were obtained with primary aromatic amines. However, in a previous paper[4] we described the preparation of N-Mannich bases of 1, 2, 3-benzotriazoles in good yield, using primary aromatic amines. These compounds also exhibited varied degree of antibacterial activity. In the present studies, intramolecular Mannich condensation of (S)-2-(α-hydroxyethyl)benzimidazole I with primary aromatic amines IIa-g and formaldehyde resulting in the formation of a new class of heterocyclic compounds: (1S)-4-aryl-4,5-dihydro-1-methyl-1H,3H-[1, 3, 5]oxadiazepino [5, 6-a]benzimidazoles IIIa-g are described.

(S)-2-(α-Hydroxyethyl)benzimidazole I on reaction with 3-acetylaniline and formalin (37%) under Mannich conditions afforded IIIa. The ir spectrum of the condensation product IIIa showed intense absorptions at 1678 (C = O) and 1145 cm^{-1} (C-O-C) and absence of the characteristic absorptions due to -OH and -NH groups. Further, its 300 MHz ^{1}H-nmr spectrum (Table I) indicated the presence of two methylene groups as double doublets[5] centred at δ 5.44, J = 14.7Hz; δ 5.99, J = 14.7Hz and δ 5.09, J = 11.9Hz; δ 5.54, J = 11.9Hz. A doublet at δ1.84, J = 6.5Hz for C-CH_3 group and the methine proton appearing as quartet at δ 4.86, J = 6.5Hz suggested the presence

of -CHCH$_3$ moiety in IIIa. Its mass spectrum showed molecular ion at m/z 321 corresponding to the molecular formula $C_{19}H_{19}N_3O_2$. The ^{13}C-nmr (Table II) also accounted for 19 carbon atoms; the two methylene groups appeared at δ 59.99 (C-3) and δ 85.39 (C-5).

Table I: ^{1}H-Nmr data of IIIa-g

No.	Compound No. Mol. Formula	Aromatic protons of Benzimidazole		C_1-CH_3	C_1-H	$-C_5\langle^{H}_{H}$	$-C_5\langle^{H}_{H}$	Substituted Aryl group
		C_{10}-H δ, J(Hz)	3H δ, J(Hz)	δ, J(Hz)	δ, J(Hz)	δ, J(Hz)	δ, J(Hz)	δ, J(Hz)
1.	IIIa $C_{19}H_{19}N_3O_2$	7.69(m)	7.11-7.36(m)	1.84(d) J = 6.5	4.86(q) J = 6.5	5.44 (d, 1H) 5.99 (d, 1H) J_{gem} = 14.70	5.09 (d, 1H) 5.54 (d, 1H) J_{gem} = 11.8	2.25 (s, 3H, -COCH$_3$) 7.11-7.36 (m, 3H arom) 7.52 (m, 1H, H-2)
2.	IIIb $C_{20}H_{21}N_3O_2$	7.70(m)	7.05-7.16(m)	1.91(d) J = 6.5	5.00(q) J = 6.5	5.42 (d, 1H) 6.24 (d, 1H) J_{gem} = 14.50	5.15 (d, 1H) 5.39 (d, 1H) J_{gem} = 11.9	1.57 (t, 3H, J = 7.0, -OCH$_2$-CH$_3$); 4.17 (q, 2H, J = 7.0, -OCH$_2$-CH$_3$); 6.20 (ddd, 1H, J = 0.6, J = 1.5, J = 7.4, H-5); 6.80 (dd, 1H, J = 1.5, J = 8.2, H-6); 6.90 (ddd, 1H, J = 0.6, J = 1.6, J = 7.3, H-4); 7.18 (dd, 1H, J = 1.6, J = 7.9, H-3)
3.	IIIc $C_{17}H_{16}ClN_3O$	7.17(m)	7.16-7.25(m)	1.86(d) J = 6.5	4.85(q) J = 6.5	5.36 (d,1H) 5.74 (d,1H) J_{gem} = 14.70	5.01 (d,1H) 5.40 (d,1H) J_{gem} = 11.8	6.86 (dd, 2H, J = 2.3, J = 6.8, H-2, 6); 7.02 (dd, 2H, J = 3, J = 6.8, H-3, 5)
4.	IIId $C_{17}H_{16}BrN_3O$	7.73(m)	7.19-7.31(m)	1.88(d) J = 6.5	4.91(q) J = 6.5	5.53 (d,1H) 5.84 (d,1H) J_{gem} = 14.60	5.11 (d,1H) 5.46 (d,1H) J_{gem} = 11.6	6.85 (dd, 2H, J = 2.2, J = 9.0, H-2, 6); 7.19-7.30 (m, 2H, H-3 , 5)
5.	IIIe $C_{17}H_{16}IN_3O$	7.72(m)	7.19-7.32(m)	1.85(d) J = 6.5	4.99(q) J = 6.5	5.50 (d,1H) 5.80 (d,1H) J_{gem} = 14.60	5.09 (d,1H) 5.46 (d,1H) J_{gem} = 11.68	6.73 (dd, 2H, J = 2.1, J = 6.8, H-2, 6); 7.41 (dd, 2H, J = 2.1, J = 6.8, H-3, 5)
6.	IIIf $C_{21}H_{21}N_3O_2$	7.71(d) J = 7.2	7.11-7.33(m)	1.84(d) J = 6.5	4.86(q) J = 6.5	5.43 (d,1H) 5.78 (d, 1H) J_{gem} = 14.50	5.09 (d,1H) 5.39 (d,1H) J_{gem} = 11.8	2.93 (t, 4H, J = 4.6, CH$_2$-N-CH$_2$O); 3.74 (t, 4H, J = 4.5, CH$_2$-O-CH$_2$); 6.62 (d, 2H, J = 8.8, H-2, 6)
7.	IIIg* $C_{17}H_{18}N_4O_3S$	7.85(m)	7.21-7.36	1.96(d) J = 6.5	5.11(q) J = 6.5	5.75 (d,1H) 6.45 (d,1H) J_{gem} = 14.90	5.21 (d,1H) 5.71 (d,1H) J_{gem} = 12.10	7.35 (d, 2H, J = 8.9, H-2, 6); 7.90 (d, 2H, J = 8.9, H-3, 5); 4.98 (s, 2H, SO_2NH_2)

*Recorded in Pyridine-d_5

On the basis of above spectroscopic data, the condensation product IIIa was formulated as (1S)- 4-(3-acetyl-phenyl)-4,5-dihydro-1-methyl-1H,3H-[1,3,5]oxadiazepino[5,6-a]benzimidazole not reported previously. However, in a related study Ishiwata and Shiokawa[6] reported the formation of 1,3,4,5-tetrahydro-4-methyl [1,3,6]oxadiazepino[3,4-a]benzimidazole through intramolecular Mannich reaction of 2-alkylaminomethyl-benzimidazole.

It is conceivable that the condensation product IIIa was formed through a concerted reaction mechanism involving intramolecular Mannich condensation. The sequence of reactions is believed to proceed with the Mannich reaction

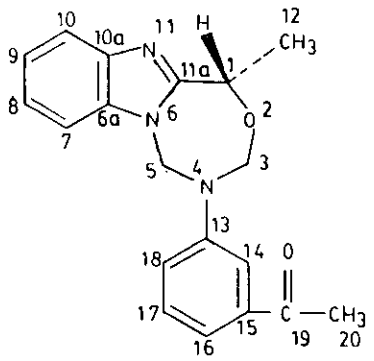
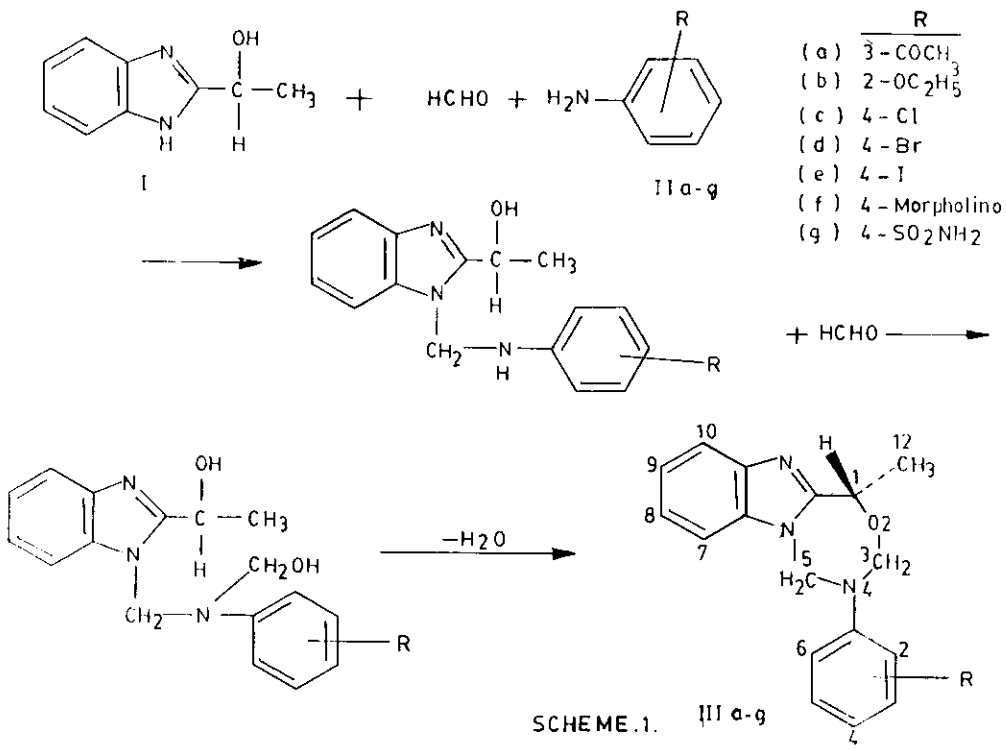


Table II: ^{13}C-Nmr chemical shift assignments of III-a

No.	Carbon No.	δ	No.	Carbon No.	δ
1.	C-1	73.05	11.	C-12	18.25
2.	C-3	59.99	12.	C-13	137.94
3.	C-5	85.39	13.	C-14	122.00
4.	C-6a	141.58	14.	C-15	134.82
5.	C-7	116.70	15.	C-16	123.33
6.	C-8	121.94	16.	C-17	129.54
7.	C-9	120.11	17.	C-18	122.06
8.	C-10	108.50	18.	C-19	197.70
9.	C-10a	145.58	19.	C-20	26.34
10.	C-11a	156.62			

-NH of benzimidazole. The resulting N-Mannich base then condenses with another molecule of formaldehyde forming the aminomethanol followed by intramolecular condensation with elimination of water forming IIIa (Scheme I).



SCHEME.1. IIIa-g

Similarly intramolecular Mannich condensation of (S) 2-(α-hydroxyethyl)benzimidazole with other primary aromatic amines IIb-g and formalin afforded condensation products IIIb-g.

Compounds IIIa-g were also tested for antibacterial activity against *Streptococcus faecalis*, *Staphylococcus aureus*,

Bacillus subtilis (Gram positive); *Escherichia coli, Pseudomonas sp., Salmonella typhi* and *Salmonella para B* (Gram negative). The results indicated IIIg to have maximum activity against both types of organisms followed by IIIb, IIIa and IIIf in order of activity. IIIe was active against Gram negative bacteria only, while IIIc and IIId did not show any significant activity.

EXPERIMENTAL

Melting points were taken on a Büchi 510 melting point apparatus and are uncorrected. The ir spectra were measured in KBr on a JASCO A-302 spectrophotometer. The ^{1}H and ^{13}C-nmr spectra were recorded in $CDCl_3$ on Brucker AM-300 ASPECT 3000 spectrometer using TMS as internal reference. Mass spectra were taken on Finningen MAT 112-S and MAT 312 spectrometer connected to PDP 11/34 and MAT 188 computer. The uv spectra were measured on a JASCO Model 7800 UV/VIS spectrophotometer in methanol, unless otherwise stated. The optical rotations were measured on polartronic-D-polarimeter.

Preparation of (S)-2-(α-hydroxyethyl)benzimidazole (I)

(-)-(S)-2-(α-Hydroxyethyl)benzimidazole was prepared by the condensation of o-phenylenediamine and (S)-lactic acid in presence of HCl according to the procedure reported by Phillips.[7]

General procedure for preparation of (IIIa-g)

2-(α-Hydroxyethyl)benzimidazole I (0.01 mol) was dissolved in boiling methanol (20 ml). Formalin (2 ml, 37%), substituted aromatic amines IIa-g (0.01 mol) and acetic acid (0.5 ml) were added to it with good stirring. After the addition was over, refluxing continued for another 2 h and then left overnight at room temperature. The solvent was removed in vacuo and the resulting residue on crystallization from appropriate solvent gave IIIa-g.

(1S)-4-(3-Acetylphenyl)-4, 5-dihydro-1-methyl-1H, 3H-[1, 3, 5]oxadiazepino [5, 6-a]benzimidazole (IIIa)

Prisms from methanol (32%), mp 163-164° $[\alpha]_D^{32}$ + 78° (c = 3.86, chloroform). Uv: 400 (log ε 2.82), 322 (log ε 3.16), 277 (log ε 3.50) and 232 nm (log ε 4.15). Ir: 1678 (C=O), 1600, 1580 (aromatic), 1540 (C-N) and 1145 (C-O-C) cm^{-1}. ^{1}H-Nmr (Table I) and ^{13}C-nmr (Table II). Mass: m/z (rel. int.); 321 (M^+, 28), 291 (6), 276 (26), 230 (5), 195 (1), 174 (18), 158 (8), 144 (100), 133 (31), 118 (20), 104 (12), 91 (8), 77 (22) and 65 (7). Anal. Calcd for $C_{19}H_{19}N_3O_2$: C, 71.02; H, 5.90; N, 13.08. Found: C, 71.10; H, 5.96; N, 13.07.

(S)-4-(2-Ethoxyphenyl)-4, 5-dihydro-1-methyl-1H , 3H-[1, 3, 5]oxadiazepino [5, 6-a]benzimidazole (IIIb)

Needles from ethyl acetate-petroleum ether (57%), mp 183-184° $[\alpha]_D^{32}$ + 11.7° (c = 1.07, chloroform). Uv: 399 (log ε 2.96), 278 (log ε 3.92) and 241 nm (log ε 4.12). Ir: 1619, 1580, (aromatic), 1595 (C-N), 1142 (C-O-C) cm^{-1}. ^{1}H-Nmr (Table I). Mass: m/z (rel. int.); 323 (M^+, 56), 293 (16), 278 (56), 264 (2), 248 (1.5), 174 (4), 149 (60), 144 (23), 134

(16), 120 (100), 117 (16), 93 (17), 83 (22), 77 (16) and 65 (23). Anal. Calcd for $C_{19}H_{21}N_3O_2$: C, 70.58; H, 6.50; N, 13.00. Found: C, 70.61; H, 6.55; N, 12.97.

(S)-4-(4-Chlorophenyl)-4, 5-dihydro-1-methyl-1H, 3H-[1, 3, 5]oxadiazepino [5, 6-a]benzimidazole (IIIc)

Prisms from ethyl acetate-petroleum ether (60%), mp 170-171° $[\alpha]_D^{32}$ + 186.5° (c = 1.59, chloroform). Uv: 399 (log ε 3.25), 277 (log ε 3.89) and 249 nm (log ε 4.34). Ir: 1620, 1580 (aromatic), 1560 (C-N) and 1150 (C-O-C) cm^{-1}. ^{1}H-Nmr (Table I). Mass: m/z (rel.int.); 313 (M^+, 50), 285 (10), 283 (24), 279 (21), 268 (59), 175 (8), 174 (13), 159 (11), 148 (20), 144 (100), 139 (71), 138 (39), 131 (14), 118 (28), 111 (18), 108 (8), 99 (9), 83 (10), 77 (9), 75 (40) and 64 (7). Anal. Calcd for $C_{17}H_{16}ClN_3O$: C, 65.08; H, 5.10; N, 13.39. Found: C, 64.97; H, 5.21; N, 13.42.

(S)-4-(4-Bromophenyl)-4, 5-dihydro-1-methyl-1H, 3H-[1, 3, 5]oxadiazepino [5, 6-a]benzimidazole (IIId)

Needles from ethyl acetate (68%), mp 174-175° $[\alpha]_D^{32}$ + 128° (c = 2.0, chloroform). Uv: 399 (log ε 3.64), 277 (log ε 4.10) and 249 nm (log ε 4.48). Ir: 1610, 1598 (aromatic), 1560 (C-N) and 1158 (C-O-C) cm^{-1}. ^{1}H-Nmr (Table I). Mass: m/z (rel. int.); 358 (M^+, 24), 328 (22), 327 (22), 314 (26), 233 (1), 184 (28), 174 (10), 164 (8), 156 (12), 145 (36), 144 (100), 131 (12), 118 (20), 104 (5), 93 (7), 83 (25), 77 (16) and 63 (6). Anal. Calcd for $C_{17}H_{16}BrN_3O$: C, 56.98; H, 4.47; N, 11.73. Found: C, 57.06; H, 4.51; N, 11.69.

(S)-4-(4-Iodophenyl)-4, 5-dihydro-1-methyl-1H, 3H-[1, 3, 5]oxadiazepino [5, 6-a]benzimidazole (IIIe)

Needles from ethyl acetate-petroleum ether (69%), mp 229-230° $[\alpha]_D^{32}$ + 181.8° (c = 0.064, chloroform). Uv: 399 (log ε 3.45), 272 (log ε 3.89) and 252 nm (log ε 4.33). Ir: 1619, 1582 (aromatic), 1560 (C-N) and 1150 (C-O-C) cm^{-1}. ^{1}H-Nmr (Table I). Mass: m/z (rel. int.); 405 (M^+, 42), 375 (17), 360 (34), 321 (3), 276 (4), 231 (60), 204 (6), 183 (7), 174 (12), 157 (8), 144 (100), 130 (12), 118 (24), 104 (12), 84 (21), 77 (42) and 63 (12). Anal. Calcd for $C_{17}H_{16}IN_3O$: C , 50.37; H, 3.95; N, 10.37. Found: C, 50.34; H, 4.03; N, 10.34.

(S)-4-(4-N-Morpholinophenyl)-4, 5-dihydro-1-methyl-1H, 3H-[1, 3, 5] oxadiazepino [5, 6-a]benzimidazole (IIIf)

Prisms from ethyl acetate-petroleum ether (49%), mp 222-223° $[\alpha]_D^{32}$ + 150.12° (c = 1.65, chloroform). Uv: 400 (log ε 3.14), 300 (log ε 3.51) and 256 nm (log ε 4.35). Ir: 1620, 1580 (aromatic), 1560 (C-N) and 1150 (C-O-C) cm^{-1}. ^{1}H-Nmr (Table I). Mass: m/z (rel. int.): 364 (M^+, 36), 336 (8), 319 (4), 230 (3), 190 (100), 167 (4), 144 (7), 131 (44), 118 (8), 164 (6), 83 (39), 78 (10) and 65 (6). Anal. Calcd for $C_{21}H_{24}N_4O_2$: C, 69.23; H, 6.59; N, 15.38. Found: C, 69.16; H, 6.62; N, 15.43.

(S)-4-(4-Sulfamidophenyl)-4, 5-dihydro-1-methyl-1H, 3H-[1, 3, 5]oxadiazepino [5, 6-a]benzimidazole (IIIg)

On usual work up a gummy solid was obtained which was dissolved in 5% NaOH, acidified with 5N-HCl and the precipitated solid was filtered, washed with water and dried. The resulting amorphous powder (50%) mp 234-235°

$[\alpha]_D^{32}$ + 114° (c = 0.88, pyridine). Uv (in DMF): 399 (log ε 3.14), 272 (log ε 4.57) and 265 nm (log ε 4.30). Ir: 3160 ($-NH_2$), 1600, 1585 (aromatic), 1510 (C-N), 1140 ($-SO_2NH_2$) and 1158 (C-O-C) cm^{-1}. ^1H-Nmr (Table I). Mass: m/z (rel. int.); 358 (M^+, 1), 313 (1), 262 (2), 239 (2), 185 (4), 162 (21), 148 (18), 118 (100), 91 (42) and 64 (6). Anal. Calcd for $C_{17}H_{18}N_4O_3S$: C, 56.98; H, 5.06; N, 15.63. Found: C, 57.01; H, 5.14; N, 15.59.

ACKNOWLEDGEMENT

The authors are indebted to H.E.J. Research Institute of Chemistry, University of Karachi for running the Mass and NMR spectra. The valuable technical assistance rendered by Mr. Umar Farooq is also gratefully acknowledged.

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Received, 18th October, 1989