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SYNTHESIS OF SOME N^1,N^4-BIS (N^5, $N^{5'}$-ALKOXYARYLBIGUANIDINO) PIPERAZINE

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ABSTRACT

ω-Bromoalkoxyphthalimides (**1a-c**) were condensed with anhydrous piperazine in presence of anhydrous potassium carbonate to give N^1,N^4-bisalkoxyphthalimido piperazine (**2a-c**). Gabriel's hydrolysis in acidic media (HBr/Acetic acid) led to formation of corresponding amino-oxy salt (**3a-c**). These (**3a-c**) on condensation with substituted phenyl dicyanadimide (**4a-c**) yield N^1,N^4-bis (N^5,$N^{5'}$- alkoxyarylbiguanido) piperazine (**5a-l**).

Key words : ω-Bromoalkoxyphthalimides, phenyl dicyanadimide, anhydrous piperazine, amino-oxy.

INTRODUCTION

Piperazine compounds have been known to posses antihistaminic[1], antineoplastic[2], antidepressent[3], anticholinergic[4], antiematic[5], antispasmodic[6] and many other activities. N-(N'-alkylaminoalkyl) phthalimides are reported to exhibit various pharmacological properties[7]. Some N-(N-aryl-N-piperazino alkyl) phthalimides have been claimed as CNS depressants and cardio-vascular agents[8]. Many alkoxyphthalimido derivatives reported to possess potent anticonvulsant[9-11], anticancer[12], antiepileptic[13] etc. activities.

In the present communication, N^1,N^4-bis (alkoxyamino piperazine) have been prepared from corresponding phthalimide and condensed with aryldicyanadiamides to give corresponding biguanides.

EXPERIMENTAL

Uncorrected melting points were measured in open capillaries. IR, ^{1}H NMR and FAB MASS were recorded on Perkin-Elmer RXI 4000-4500 cm^{-1}, Brucker DRX -300 (300 MHz FT NMR), Jeol SX-102 (FAB) spectrophotometer, respectively. Purity of compounds was checked on silica gel-G TLC plates of 2 mm thickness using benzene and ethyl acetate as solvent. The visualization was carried out in an iodine chamber. ω-Bromoalkoxyphthalimides (**1a-c**) have been prepared by reported method[14]. Solvents were dried and purified by standard procedures.

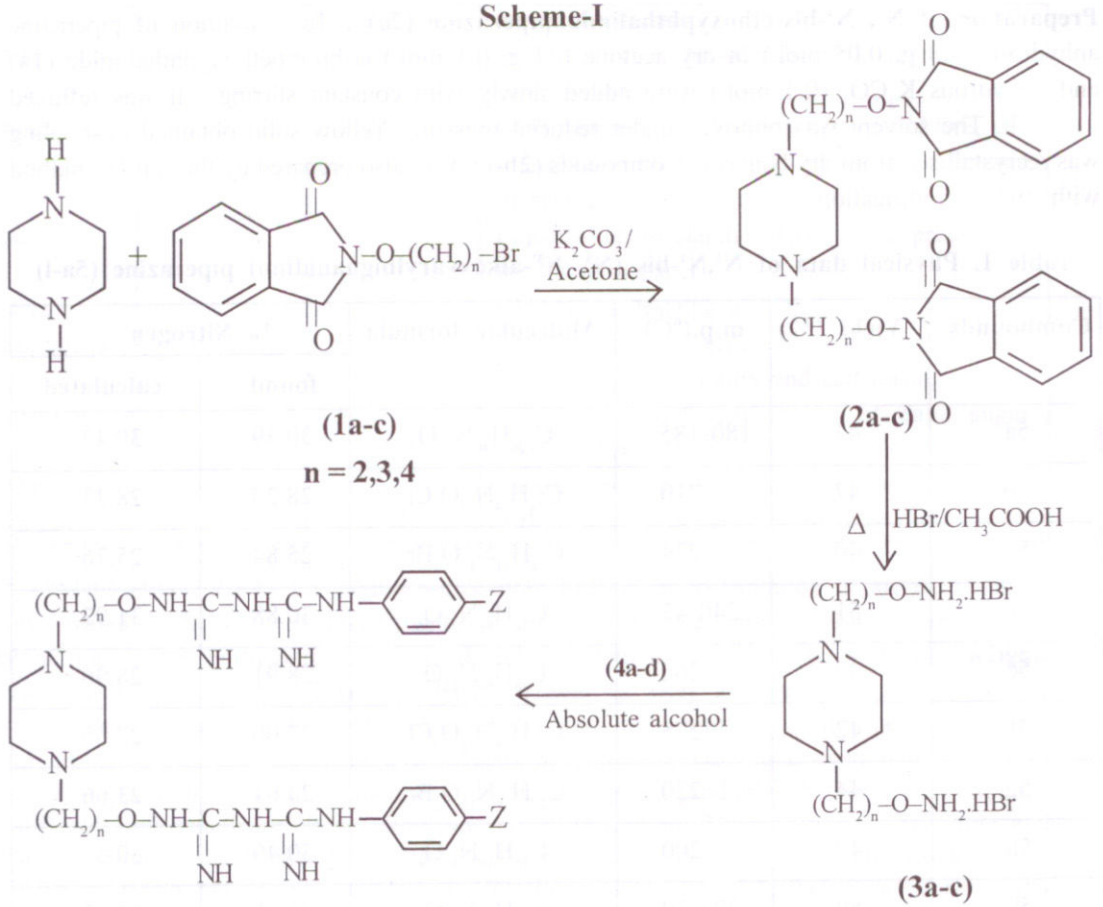
Preparation of N^1, N^4-bis-ethoxyphthalimidopiperazine (*2a*) : To a solution of piperazine anhydrous (4.3 g, 0.05 mol.) in dry acetone (27 g, 0.1 mol.) ω-bromoethoxyphthalimide (**1a**) and anhydrous K_2CO_3 (0.1 mol.) were added slowly with constant stirring. It was refluxed for 12 h. The solvent was removed under reduced pressure. Yellow solid obtained on cooling was recrystallised from dry benzene. Compounds (**2b-c**) were also prepared by the similar method with minor modification.

Table 1. Physical data of N^1,N^4-bis (N^5, $N^{5'}$-alkoxyarylbiguanidino) piperazine (5a-l)

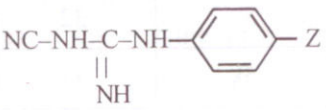
Compounds	Yield (%)	m.p.(^{0}C)	Molecular formula	% Nitrogen	
				found	calculated
5a	43	180-185	$C_{26}H_{40}N_{12}O_2$	30.39	30.43
5b	47	210	$C_{24}H_{34}N_{12}O_2Cl_2$	28.29	28.33
5c	40	234	$C_{24}H_{34}N_{12}O_2Br_2$	25.84	25.76
5d	51	240-43	$C_{24}H_{34}N_{14}O_6$	30.88	31.92
5e	37	260	$C_{28}H_{44}N_{12}O_2$	28.91	28.96
5f	42	275	$C_{26}H_{38}N_{12}O_2Cl_2$	27.00	27.05
5g	44	220	$C_{26}H_{38}N_{12}O_2Br_2$	23.61	23.66
5h	49	200	$C_{26}H_{38}N_{14}O_6$	30.49	30.52
5i	50	225-30	$C_{30}H_{48}N_{12}O_2$	27.58	27.63
5j	32	197	$C_{28}H_{42}N_{12}O_2Cl_2$	25.54	25.88
5k	35	285	$C_{28}H_{42}N_{12}O_2Br_2$	22.70	22.76
5l	40	270	$C_{28}H_{42}N_{14}O_6$	29.20	29.25

2a (45%); m.p. 210^0 (found N, 12.00 calcd. for $C_{24}H_{24}N_4O_6$; N,12.06%); ν_{max} 3100 (Aromatic C-H), 2866 (CH_2), 1745 (C=O), 1680 (CO-N-CO), 1120 (C-O), 640 (N-O) cm^{-1}; δ 7.2 (m, 8H, Ar-H), 3.4 (t, 4H, O-CH_2), 2.8 (t, 4H, N-CH_2), 2.2 (s, 8H, CH_2 protons of piperazine); m/z 464 [$M^{+\cdot}$], 274, 190, 176, 162, 146,132, 104, 84, 76; **2b** (43%); m.p. 225^0 (found : N,11.32. calcd. for $C_{26}H_{28}N_4O_6$; N,11.38%); m/z 492 [$M^{+\cdot}$], 288, 204, 162, 146,132, 104, 84, 76; **2c** (45%); m.p. 245^0(Found : N, 10.80. calcd. for $C_{28}H_{32}N_4O_6$; N,10.93%); m/z 512 [$M^{+\cdot}$], 302, 218, 162, 146, 132, 104, 84, 76.

Scheme-I



5	n	Z
a	2	$-CH_3$
b	2	-Cl
c	2	-Br
d	2	$-NO_2$
e	3	$-CH_3$
f	3	-Cl
g	3	-Br
h	3	$-NO_2$
i	4	$-CH_3$
j	4	-Cl
k	4	-Br
l	4	$-NO_2$

Where 

(4a-d)

4	Z
a	$-CH_3$
b	-Cl
c	-Br
d	$-NO_2$

Preparation of N^1, N^4-bis-alkoxyaminopiperazine salt (*3a*) : Compound **2a** (9.28 g, 0.1 mol.) was boiled with a mixture of glacial acetic acid (25.0 mL.) and 48% hydrobromic acid (30.0 mL.). Phthalic acid separated on cooling, was filtered. The solvent was removed under reduced pressure. Residue obtained was corresponding amino-oxy compound (**3a**), which was recrystallised from a mixture of methanol and chloroform. (**3b-c**) were also prepared by the similar method. **3a** (40%); m.p. 240°; **3b** (42%); m.p. 255° ; **3d** (47%) ; m.p. 270°.

Preparation of N^1,N^4-bis (N^5, $N^{5'}$- alkoxyarylbiguanidino) piperazine (*5a*) : p-Tolyl dicyanadiamide (**4a**, 0.02 mol.) and compound (**3a**, 0.1 mol.) were dissolved in ethanol (15.0 mL.). The reaction mixture was refluxed for 14 h. A very dilute solution of $NaHCO_3$ was added dropwise, till the appearance of turbidity. It was kept overnight at room temperature. Separated solid was filtered and recrystallised from methanol. Similar method was applied for preparation of compound (**5b-l**).

5a ν_{max} 3440 (N-H), 2950 (CH_2), 1652 (C=N), 1600-1400 (C=C),1180 (C-O), 750 (C-H),680 (N-O) cm^{-1}; δ 7.1 (m, 8H, Ar-H), 4.2 (m,10H, N-H), 3.4 (t, 4H, O-CH_2), 2.4 (t, 4H, N-CH_2), 2.2 (s, 8H, CH_2 protons of piperazine), 1.8 (s, 6H, CH_3); m/z 552 [M^{+}], 234, 220, 206, 190, 175, 148, 133, 106, 91, 74.

5b ν_{max} 3430 (N-H), 2862 (CH_2), 1650 (C=N), 1580-1450 (C=C), 1188 (C-O), 1020 (C-N), 750-700 (C-Cl), 670 (N-O) cm^{-1}; δ 7.3 (m, 8H, Ar-H), 4.4 (s, 10H, N-H), 3.3 (t, 4H, O-CH_2), 2.5 (t, 4H, N-CH_2) 2.2 (s, 8H, CH_2 protons of piperazine); m/z 557 [M^{+}], 254, 226, 217, 195, 168, 153, 126, 109, 74.

5c ν_{max} 3400 (N-H), 3050 (Ar-H), 2900 (CH_2),1680 (C=N), 1600-1400 (C=C), 1160 (C-O), 1080 (C-N), 840-800 (Ar-H para substituted), 600 (C-Br) cm^{-1}; δ 7.2 (m, 8H, Ar-H), 4.3 (s, 10H, N-H), 3.4 (t, 4H, O-CH_2), 2.4 (t, 4H, N-CH_2), 2.2 (s, 8H, CH_2 protons of piperazine); m/z 557 [M^{+}], 299, 271, 255, 240, 213, 171, 156, 74.

5d ν_{max} 3430 (N-H), 3010 (Ar-H), 2830 (CH_2), 1670 (C=N), 1580-1400 (C=C), 1530-1360 (C-NO_2), 1170 (C-O), 1088 (C-N), 670 (N-O) cm^{-1}; δ 7.1 (m, 8H, Ar-H), 4.1 (s, 10H, N-H), 3.4 (t, 4H, O-CH_2), 2.3 (t, 4H; N-CH_2), 2.1 (s, 8H, CH_2 protons of piperazine); m/z 600 [M^{+}], 237, 225, 221, 206, 179, 152, 74.

RESULTS AND DISCUSSION

ω-Bromoalkoxyphthalimides (**1a-c**) and piperazine anhydrous were condensed by two methods. In the first method, DMF was used as a solvent and NaH as a base. It was stirred overnight at room temperature. In the alternative route, reactants were refluxed in dry acetone in presence of anhydrous K_2CO_3. The hot solution was filtered and solvent was removed under reduced pressure. In the first method, the reaction time was 2h less as compared to second method but the physical state and yield of product were better in the second method. N^1,N^4-bis

alkoxyphthalimido piperazine (**2a-c**) were hydrolysed by boiling with a mixture of acetic acid and HBr. On cooling, crystals of phthalic acid separated, were filtered and the solvents was removed under reduced pressure, It gave N^1,N^4-bis alkoxyamino piperazine (**3a-c**) in poor yield. These were converted into N^1,N^4- bis (N^5, $N^{5'}$- alkoxyarylbiguanidino) piperazine (**5a-l**) by the nucleophilic addition reaction of aryl dicyanadiamide (**4a-d**) with (**3a-c**). Structure of compounds were finally confirmed by their spectral studies. IR spectra of compounds (**5a-l**) show a sharp absorption peak at 3400 cm^{-1} (N-H str.) and PMR shows singlet of N-H proton at 4.1.

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