Asian Journal of Chemistry Vol. 11, No. 4 (1999), 1438–1444

Synthesis of Bis-1,2-Aryl-Biguanidino-Oxy, 3-Biguanidino Propane as Potential Antimalarials

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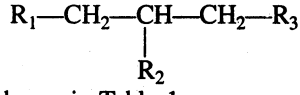
Various phthalimido-phthalimido-oxy, amino-amino-oxy, biguanidino-biguanidino-oxy and related derivatives of alkanes have been synthesized. For this purpose N-(allyl) phthalimide has been prepared and brominated to produce 2,3-dibromophthalimidopropane. This when condensed with N-hydroxy phthalimide, phthalimido, bis-phthalimido-oxypropane was resulted. Hydrolysis of above compound in HBr/AcOH acid produced 3-amino 1,2-bis-amino-oxypropane tri-hydrobromide. This compound on condensation with substituted aryldicyandiamide gave various biguanidino-biguanidino-oxy derivative.

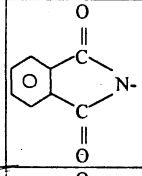
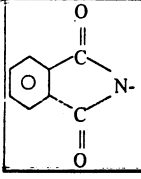
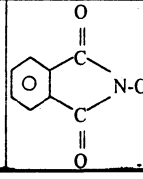
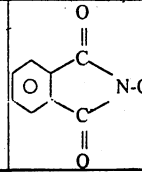
INTRODUCTION

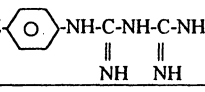
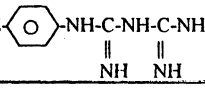
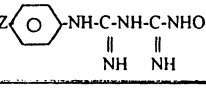
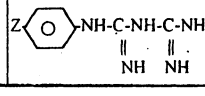
Certain compounds containing both amino, amino-oxy group have been shown to possess diverse pharmacological activities, such as inhibitors of ornithine decarboxylase[1], inhibit several mammalian polyamine biosynthetic enzymes *in vitro*, including ornithine decarboxylase[2], β-blocking adrenergic activity[3] and biguanidino-oxy compounds[4, 5] have been found to show certain pharmacological properties such as CNS depressant, cardio-vascular agents[6], antibacterial, antifungal, antimalarial[7]and other activities[8, 9]. In the light of versatile pharmacological activities it was thought worthwhile to synthesize some compound having amino and amino-oxy group. Following type of compounds have been synthesized.



where R_1, R_2 and R_3 are shown in Table-1.

TABLE-1

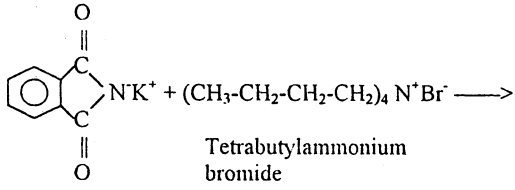
Comp. No.	R_1	R_2	R_3
IV		-Br	-Br
VI			

VII	$NH_3^+ Br^-$	-Br	-Br
VIII	$NH_3^+ Br^-$	$ONH_3^+ Br^-$	$ONH_3^+ Br^-$
IX abcd		-Br	-Br
X abcd			

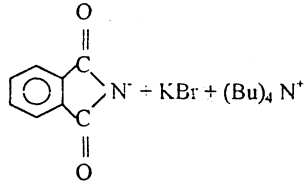
where IXa and Xa, Z = CH_3, IXb and Xb, Z = Br, I
Xc and Xc, Z = NO_2, IXd and Xd, Z = Cl

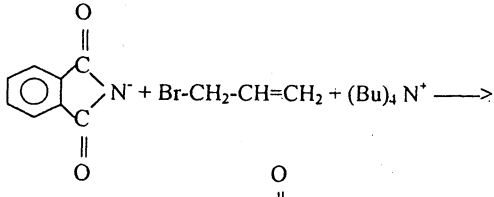
RESULTS AND DISCUSSION

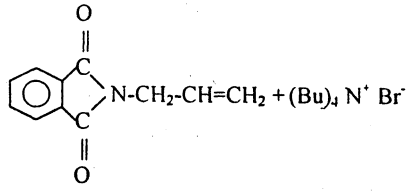
The starting material, N-(allyl) phthalimide for the synthesis of derivatives of the type (IV–X) has been prepared by condensation of potassium phthalimide and allyl bromide in presence of tetrabutyl ammonium chloride as phase transfer catalyst.



Tetrabutylammonium bromide







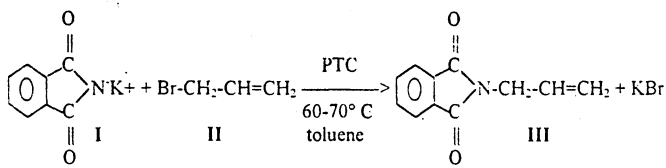
Here in presence of phase transfer catalyst[10–13] phthalimide becomes a more effective nucleophile. Reaction goes more smooth and product is easily separable. Role of phase transfer catalyst is to cause homogeneity between ionic and covalent phases.

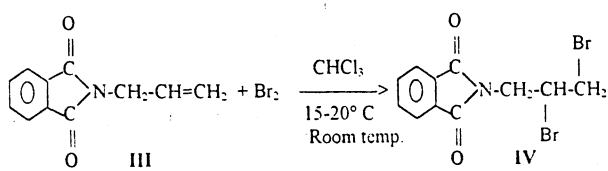
The ethylenic double bond was converted to dibromo derivative by usual electrophillic addition. Substitution of phthalimido-oxy group took a longer time and produced bis-phthalimido-oxyphthalimide derivatives (V and VI). Here it may be noted that primary bromine of dibromo compound is replaced with greater ease than secondary; thus the reaction mixture taken out prior to completion is composed of two components: one having bromine on C_2 with incomplete reaction giving mono compound and the other with complete reaction producing bis-phthalimido-oxyphthalimide derivative. Formation of monobromo derivative can be explained on the basis of steric hindrance at C_2·S

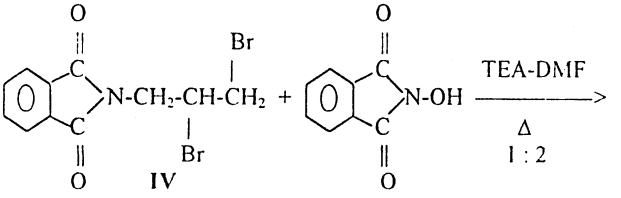
IR Spectra

IR spectra of IV and VI compounds show peak at 1780–1708 cm^{-1} which is due to ν(C=O) stretching. Out-of-plane bending of aromatic C=C—H appears at 713–700 cm^{-1}. Peak at 1241 cm^{-1} in the spectrum of (IV) is due to CH_2—Br group. Peak in the region 1406–1396 cm^{-1} is due to ν(C—O) stretching. Strong broad absorption between 3024–2997 cm^{-1} in the spectra of amino-oxy is due to asymmetric and symmetric stretching in NH_3^+ group. Peak at 1243 cm^{-1} in the spectra of VI is due to CH_2Br group. In the spectra of biguanidino-oxy compounds peak at 1648–1612 cm^{-1}, 1454–1419 cm^{-1} is due to ν(C=N) stretching of guanidino-oxy group. ν(N—O) symmetrical stretching appears at 1388–1253 cm^{-1}. Peak at 1360–1294 cm^{-1} is due to ν(C—N) stretching of (C—NH—C) group..

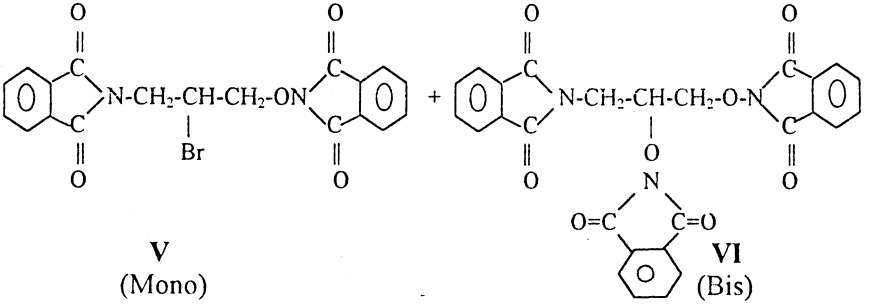
The following reaction sequences were used to synthesize the above said compounds.





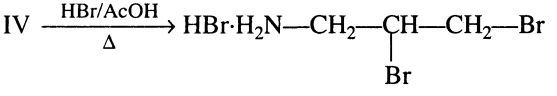


IV

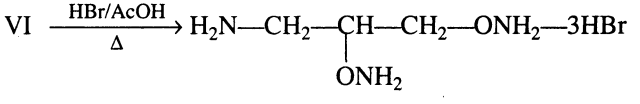


V
(Mono)

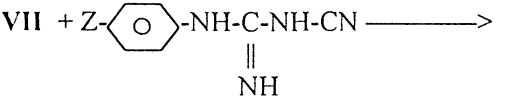
VI
(Bis)

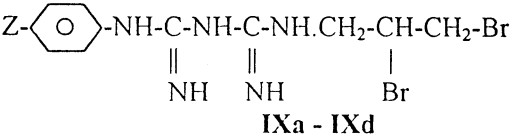


VII



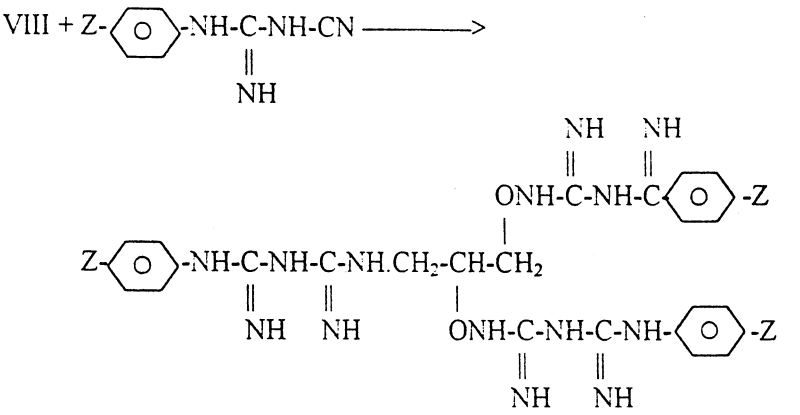
VIII





IXa - IXd

(Here Z may be —CH_3, —Cl, —Br or —NO_2)



Xa -Xd

(Here Z may be $-CH_3$, -Cl, -Br, or $-NO_2$)

EXPERIMENTAL

The structures of these compounds were established on the basis of elemental analysis, chemical properties and spectral analysis. Completion of the reaction and purity of the resultant compounds were checked by TLC. Melting points were taken in open capillaries and are uncorrected. IR spectra in KBr were recorded on a FT-IR spectrophotometer.

Preparation of N-allyl phthalimide

Potassium phthalimide 1.85 g (0.01 mol.) is suspended in dry toluene (50 mL) and allyl bromide 1.21 g (0.01 mol.) was added followed by tetrabutyl ammonium bromide (PTC) 0.322 g (0.001 mol.). It was refluxed with stirring for 10 to 12 h at 60–70°C. The solution was filtered and the filtrate added to 500 g crushed ice. White crystalline solid separated out was filtered, washed and dried. It was recrystallised from alcohol; yield: 79.5% (m.p. 46°C).

Preparation of N-(2,3-dibromo propyl) phthalimide

N-allyl phthalimide 1.87 g (0.01 mole) was dissolved in 30 mL chloroform and 10% solution of bromine in chloroform was added dropwise with constant stirring for 2 h till the colour of bromine decolourises. On cooling (1–5°C) the product appeared as white solid. It was recrystallised from chloroform (m.p. 90°C); yield 97%.

Preparation of 1,2-bis-phthalimido-oxy 3-phthalimido propane

N-(2,3-dibromopropyl) phthalimide (0.2 mole) and N-hydroxy phthalimide (0.4 mole) were dissolved in DMF (150 mL) and were refluxed with constant stirring in presence of triethylamine (0.4 mole) for 20 h. Cold solution was filtered and the filtrate was added to 1000 g crushed ice. The brown solid was filtered dried (m.p. 168°C) and recrystallised from alcohol; yield 50% (m.p. 170°C).

Preparation of 3-amino-1,2-bis amino-oxypropane trihydrohalide Hydrolysis of Phthalimido-oxy phthalimido derivative

Compound (0.02 mole) was boiled in a mixture of 47% HBr (30 mL) and glacial acetic acid (20 mL) for 25 min. On cooling, the phthalic acid obtained was filtered. The solvents on evaporation in vacucm yielded a solid. This was washed with chloroform and recrystallised from acetone (m.p. 257°C, yield 62%).

Preparation of 3-biguanidino 1,2-bis-(biguanidino-oxy) propane

Aryl dicyandiamide (0.01 mole) amino, amino-oxy compounds (VII, VIII) were refluxed in absolute alcohol on a water bath for 15–22 h. The mixture was filtered hot, diluted with water and a very dilute solution of $NaHCO_3$ was added dropwise. The separated product was recrystallised from different solvents.

Solvents of crystallisation and physical data of compounds are presented in Tables 2–4.

TABLE-2
PHYSICAL DATA OF PHTHALIMIDO AND PHTHALIMIDOXY-PHTHALIMIDE COMPOUNDS

Compound No.	m.f.	m.w.	Solvent cryst.	m.p. (°C)	Yield (%)
III	$C_{11}H_9NO_2$	187	Ethanol	46	79.5
IV	$C_{11}H_9NO_2Br_2$	347	Chloroform	90	97
VI	$C_{27}H_{17}N_3O_8$	511	Ethanol	170	52

TABLE-3
PHYSICAL DATA OF AMINO AND AMINO-AMINO-OXY COMPOUNDS

Compound No.	m.f.	m.w.	Solvent cryst.	m.p. (°C)	Yield (%)
VII	$C_3H_8NBr_3$	298	Chloroform	236	65
VIII	$C_3H_{14}N_3O_2Br_3$	364	Chloroform/ Acetone	261	58

TABLE-4
PHYSICAL DATA OF BIGUANIDES AND BIGUANIDO AND BIGUANDINO-OXY COMPOUNDS

Compounds No.	m.f.	m.f.	Mol. fraction	Reflux time (h)	Solvent for crystalisation	m.p. (°C)	Yield (%)
IXa	$C_{12}H_{17}N_5Br_2$	391	1 : 1	17	Methanol	87	65
IXb	$C_{11}H_{14}N_5Br_2Cl$	411.5	1 : 1	13	Methanol	105	55
IXc	$C_{11}H_{15}N_5Br_3$	456	1 : 1	15	Methanol	112	61
IXd	$C_{11}H_{14}N_6O_2Br_2$	422	1 : 1	12	Benzene	105	63
Xa	$C_{30}H_{41}N_{15}O_2$	643	1 : 3	17	Methanol	188	58
Xb	$C_{27}H_{32}N_{15}O_2Cl_3$	704.5	1 : 3	25	Methanol	194	70
Xc	$C_{27}H_{32}N_{15}O_2Br_3$	838	1 : 3	19	Methanol	205	58
Xd	$C_{27}H_{32}N_{18}O_8$	736	1 : 3	13	Methanol	177	63

Percentage composition has been confirmed by elemental analysis.

ACKNOWLEDGEMENTS

The authors are thankful to the Head, Department of Chemistry, College of Science, Sukhadia University, Udaipur, for providing necessary departmental facilities and to the Director, CDRI, Lucknow for spectral and elemental analyses.

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(*Received*: 8 May 1999; *Accepted*: 28 July 1999) AJC–1811