*Asian Journal of Chemistry* Vol. 12, No. 1 (2000), 14–18

# Synthesis of Some Amino-oxy, Biguanidino-oxy and Piperazinyl Derivatives of Propane *via* reaction between *n*-Hydroxyphthalimide and Epichlorohydrin

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2,3-Epoxypropoxyphthalimide (III) was prepared by condensation of epichlorohydrin (II) with *n*-hydroxyphthalimide (I) when refluxed for a short time in presence of sodium hydride but produced bis-phthalimidoxy-2-hydroxypropane (IV) when refluxed for a long time. Hydroxy group was replaced by chlorine and subsequent reaction with N-hydroxyphthalimide gave triphthalimidoxypropane (VI) derivative. Hydrolysis of 1,2,3-triphthalimidoxypropane in acidic media produced triamino-oxy trihydrohalide salt of propane (VII). Condensation of polyamino-oxy compound with various *para* substituted dicyandiamide gave corresponding biguanidino-oxy compounds (VIIIa–b).

## INTRODUCTION

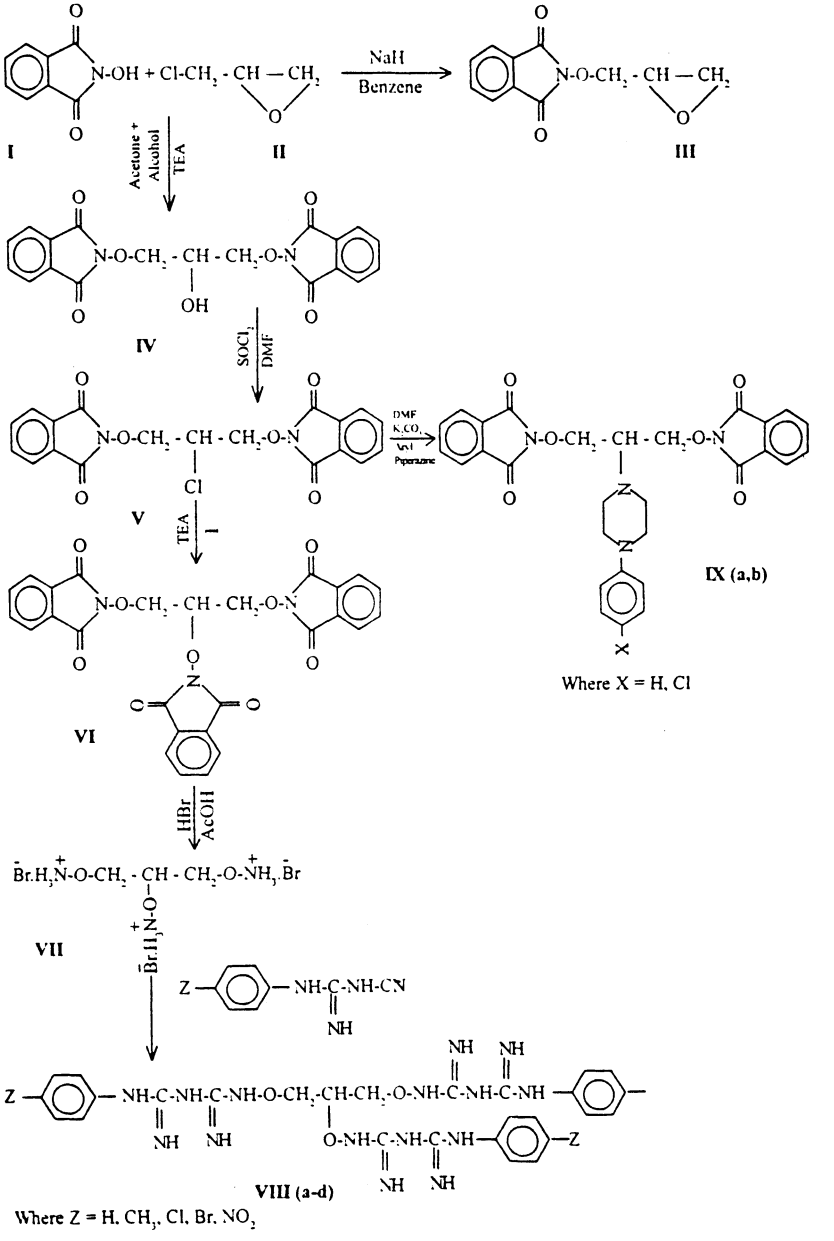
N-(ω-amino-oxyalkyl)phthalimide shows hypotensive[1–3], antihypertensive[4] and ganglion blocking[5] activities. Versatile pharmacophoric properties of amino-oxy[6, 7], phthalimidoxy[8, 9], biguanidino-oxy[10, 11] compounds are reported. Epoxy compounds are found to possess antihypertensive and CNS effects[12]. Reactions of N-hydroxyphthalimide with epichlorohydrin has been reported[13] not to occur but when the authors treated it in different conditions, variable products were obtained.

## RESULTS AND DISCUSSIONS

Reactions of N-hydroxyphthalimide (I) and epichlorohydrin (II) when carried out for only 2 h in presence of sodium hydride 2,3-epoxypropoxyphthalimide (III) was formed. The reaction when carried out for 24 h in presence of triethylamine in dimethylformamide, interestingly bis-phthalimidoxy-2-hydroxypropane (IV) was formed. The compound (IV) when treated with thionyl chloride, —OH group was replaced by —Cl; thus 1,3-bis-phthalimidoxychloropropane (V) was obtained. Condensation of (V) with one more molecule of (I) in dry benzene in presence of sodium hydride resulted in the formation of 1,2,3-triphthalimidoxypropane (VI). Hydrolysis of (VI) using HBr/AcOH separated phthalic acid and on evaporation of solvent under reduced pressure yielded triamino-oxy trihydrobromide salt (VII). Nucleophilic addition of (VII) on *para* substituted dicyandiamide derivative produced corresponding biguanidino-oxy compound of structure (VIIIa–d). Dicyandiamide derivatives required for this purpose were

prepared using the method of Curd and Rose[14] and condensed according to the method of Fuller and King[15]. Alternatively, bis-phthalimido-oxy chloro compound (V) was condensed with *para* substituted arylpiperazine to produce (IXa, b). It has been reported[8] that phthalimidoxy piperazinyl compounds are potent cardiovascular and CNS agents.

Following reaction sequences have been used



## EXPERIMENTAL

All the m.p.s are uncorrected and determined in open capillaries. Purity of compounds was checked by thin layer chromatography on silica gel in various nonaqueous media. The structure of compounds has been characterised by their microelemental and spectral studies.

### Synthesis of *n*-hydroxy phthalimide

Prepared by already reported method[16].

### Synthesis of 2,3-epoxypropoxyphthalimide(III) (Condensation of epichlorohydrin with N-hydroxyphthalimide)

16.3 g (0.1 mole) N-hydroxyphthalimide was taken in 100 mL dry benzene and then treated very slowly with sodium hydride while stirring (15 min). 9.2 g (0.1 mole) epichlorohydrin was added dropwise with constant stirring in 0.5 h at 10–15°C. Stirring was further continued for the next 45 min. The mixture was filtered and the solvent evaporated under reduced pressure. The solid obtained was crystallised using absolute alcohol, m.p. 123°C, yield 20%.

### Synthesis of 1,3-bis-phthalimidoxy-2-hydroxypropane (IV)

16.3 g (0.1 mole) N-hydroxyphthalimide in acetone and alcohol mixture (1 : 1) was stirred with epichlorohydrin 4.6 g (0.05 mole) in presence of triethylamine at 50–60°C for 30–35 h till the colour of reaction mixture changed to light yellow. It was filtered hot and the volume was reduced to one-fourth by distillation. Solid triethylammonium bromide was filtered and the residual syrupy liquid was treated with the appropriate mixture of benzene and acetone. The solid separated on standing for 0.5 h was crystallised from rectified spirit, m.p. 169–171°C, yield 48%.

### Synthesis of 2-chloro-1,3-bis-phthalimidoxypropane (V) and 1,2,3-triphthalimidoxypropane (VI)

7.4 g (0.02 mole) 1,3-bis-phthalimidoxy-2-hydroxypropane was dissolved in 40 mL dimethylformamide and redistilled thionyl chloride (0.01 mole) was added very slowly with constant stirring during 2 h. The mixture was refluxed for 40 min and filtered. Thionyl chloride was cautiously removed by distillation. To the above mixture equivalent amount of N-hydroxyphthalimide was added in small lots. Triethylamine was added and the mixture stirred for 48 h. Triethylammonium chloride separated was filtred and the resulting filterate was poured on crushed ice with constant stirring. A white solid, m.p. 182°C, crystallized from methanol, m.p. 184–185°C, yield 66%, was obtained.

### Preparation of 1,2,3-triamino-oxypropane trihydrobromide (VII)

Hydrolysis/dephthallylation of 1,2,3-triphthalimidoxy (5.2 g) was dissolved in glacial acetic acid and 48% hydrobromic acid was added. The suspension was boiled for 3–5 min. Phthalic acid separated was filtered and the solvent of filtrate was removed under reduced pressure. The solid obtained was crystallized from the mixture of chloroform and methanol, m.p. 265°C, yield 35%.

### Preparation of 1,2,3-tri-[5-(*p*-substituted)biguadinio-oxy] propane (VIIIa–d)

*Para*-substituted dicyandiamide (0.02 mole) and triamino-oxypropane hydrobromide (0.02 mole, 7.6 g) were mixed and ethanol (15 mL) was added. The mixture was refluxed for 14–18 h. The filtrate was diluted with water. Dilute $NaHCO_3$ solution was added dropwise. The precipitate obtained was filtered (m.p. 187–200°C). It was crystallized from methanol, m.p. 190–200°C, yield 55–75%.

### Preparation of 1,3-bis-phthalimidoxypropane-2-(*p*-substituted) arylpiperazine (IXa, b)

2-Chloro-1,3-bis-phthalimidoxypropane in dimethylformamide (0.01 mole) was added to arylpiperazine (0.01 mole) dissolved in alcohol. Anhydrous potassium carbonate (0.01 mole) was added. The mixture was refluxed for 20–25 h. It was filtered hot. A white solid was obtained on cooling. Crystals from ethanol and benzene mixture were obtained, m.p. 242–246°C, yield 45–56%.

PHYSICAL DATA OF COMPOUNDS SYNTHESISED

| Compound number | m.f. | m.w. | Solvent of crystallisation | m.p. (°C) | Yield (%) |
|---|---|---|---|---|---|
| III | $C_{11}H_9O_4N$ | 219 | Absolute alcohol | 123 | 20 |
| IV | $C_{19}H_{14}O_7N_2$ | 382 | Rectified spirit | 169–171 | 48 |
| VI | $C_{27}H_{17}O_9N_3$ | 527 | Methanol | 182 | 66 |
| VII | $C_3H_{14}O_3N_3Br_3$ | 380 | Chloroform + methanol | 265 | 35 |
| VIIIa | $C_{28}H_{35}O_3N_{15}$ | 629 | Methanol | 190 | 70 |
| VIIIb | $C_{27}H_{32}O_3N_{15}Cl$ | 649.5 | Methanol | 192 | 75 |
| VIIIc | $C_{27}H_{32}O_3N_{15}Br$ | 694 | Methanol | 200 | 60 |
| VIIId | $C_{27}H_{32}O_5N_{16}$ | 660 | Methanol | 180 | 55 |
| IXa | $C_{29}H_{26}O_6N_4$ | 526 | Ethanol + benzene | 242 | 56 |
| IXb | $C_{29}H_{25}O_6N_4Cl$ | 560.5 | Ethanol + benzene | 246 | 45 |

## ACKNOWLEDGEMENTS

The authors are thankful to the Head, Department of Chemistry, College of Science, Sukhadia University, Udaipur, for providing necessary departmental facilities; to the Director, CDRI, Lucknow for spectral and elemental analysis, and to the UGC for providing minor research project to ML Sukhadia University, Udaipur.

## RERERENCES

1. T. Nakajima, Y. Nakamoto and S. Suga, *Bull Chem. Soc. (Japan)*, **48**, 960 (1976).
2. M. Inoue, T. Sugita and K.T. Ichikawa, *Bull Chem. Soc. (Japan)*, **49**, 1063 (1976).
3. ———, *Bull Chem. Soc. (Japan)*, **51**, 174 (1978).
4. R.E. Parket and N.S. Issacs, *Chem. Review*, **59**, 768 (1959).
5. W.T. Sommerville and P.E. Spoerri, *J. Am. Chem. Soc.*, **72**, 2185 (1950).
6. P. Mamalis, *Xenobiotica*, **1**, 569 (1971).

7. G.L. Talesara and K.S. Suresh, *Asian J. Chem.*, **9**, 635 (1997).
8. ———, *Asian J. Chem.*, **3**, 428 (1991).
9. S. Rajora, D. Khatri and G.L. Talesara, *Asian J. Chem.*, **11**, 59 (1999).
10. P. Mamalis, J. Green and D. McHale, *J. Chem. Soc.*, 225 (1960).
11. G.L. Talesara and K.S. Suresh, *J. Ind. Council Chem.*, **15**, 19 (1998).
12. B.M. Khadilkar and S.D. Samant, *Indian. J. Chem.*, **32B**, 1137 (1993); **63B**, 529 (1986).
13. V.B. Ranadive and S.D. Samant, *Indian. J. Chem.*, 104 (1995).
14. Curd and Rose, *Indian. J. Chem.*, 729 (1946).
15. A.T. Fuller and H. Fing, *Indian. J. Chem.*, 963 (1947).
16. W.R. Orndorf and D.S. Pratt, *Am. Chem. J.*, **47**, 89 (1912).

(*Received*: 9 June 1999; *Accepted*: 16 September 1999) AJC-1843

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