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Synthesis of Pharmacologically Important 2-[ω-(4-Morpholinyl)Alkyloxy]-1H-Isoindole-1,3-(2H)-Diones

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Morpholine when stirred with 3-bromopropene and ω-bromo-alkyloxyphthalimide separately gave N-allyl morpholine **(XIV)** and α-phthalimidoxy-ω-(4-morpholinyl)alkane **(XII)** respectively. **XIV** on bromination and subsequent treatment with 2-hydroxy-1H-isoindole-1,3-(2H)-diones gave bis-1,2-phthalimidoxy-3-(N-morpholinyl) propane **(XVI)**. Some compounds were tested for antimicrobial activity.

INTRODUCTION

Morpholine possesses broad spectrum pharmacological properties[1–4] including analgesic[5, 10], antiarhythmic[6], antihistaminic[7], antitussive[8], tranquillizer[9], antibacterial[11] etc. Amino-oxy and related compounds are reported to possess[12–19] versatile pharmacological importance. Some novel morpholine compounds containing phthalimidoxy moeity have been prepared.

RESULTS AND DISCUSSION

Phthalimidoxyalkyl bromide (ω-bromo-N-alkoxy isoindole-1,3-dione), when refluxed with morpholine in presence of a base (sodium hydride, sodium ethoxide etc.) or in presence of active metal (sodium), results in the formation of ω-(N-morpholinylalkoxyphthalimide (3-morpholinyl-1-phthalimidoxyalkane). This reaction does not take place in presence of weak organic bases, *viz.*, triethylamine, pyridine, etc. The solvents used were dry benzene, toluene, xylene or dimethylformamide, etc. Yields in arene solvent are generally poor as compared to those in DMF. Aromatic hydrocarbon solvents are generally removed under reduced pressure and resultant concentrate is cooled to obtain crystalline solid. Reaction filtrate of DMF is slowly added to crushed ice with constant stirring; gelatinous precipitate is obtained. The solid is washed with 1 : 10 alcohol-water mixture.

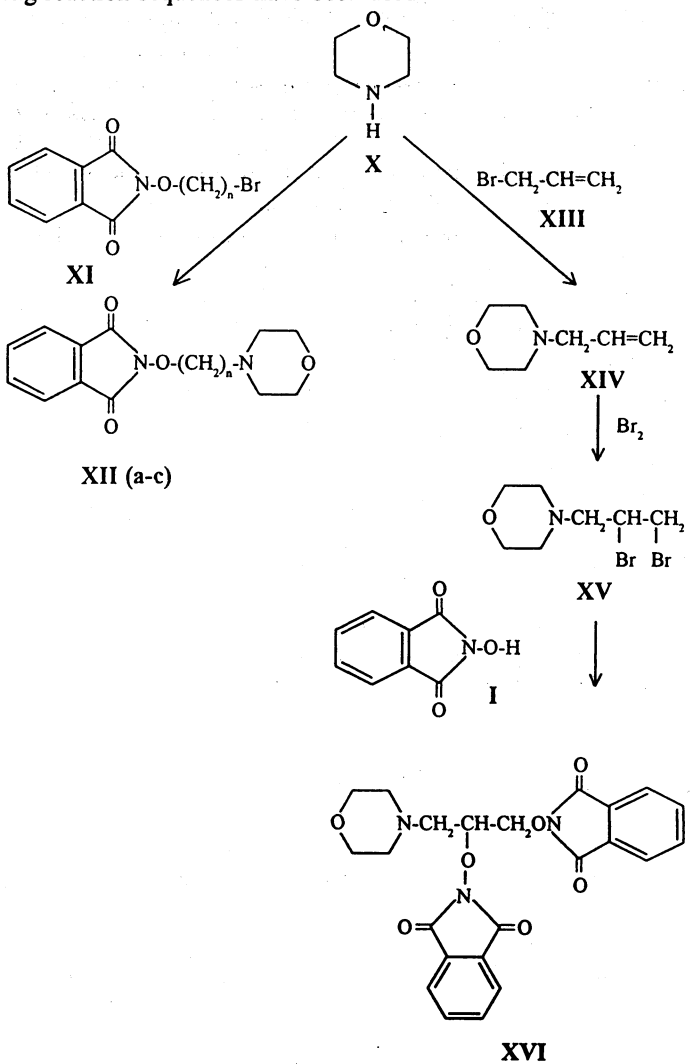
A similar procedure was followed to condense morpholine with allyl bromide. It is obvious and also observed that the reaction is relatively faster than in phthalimidoxyalkyl bromide. The solvent used was dry benzene. After the completion of the reaction, solvent was evaporated on a water bath along with unreacted allyl bromide and the residual mass was dissolved in chloroform. Calculated amount of bromine was added through a separating funnel very slowly while stirring on a magnetic stirrer. Stirring was continued till a colourless solution was obtained; chloroform was removed by distillation and the residue was transferred to minimum amount of DMF. Solution of N-hydroxy phthalimide in DMF was added to above solution and triethylamine (calculated) was added

to it. The reaction mixture was kept for 24–30 h at room temperature. Solid triethylammonium bromide was filtered and filtrate was poured on crushed ice while constant stirring. Solid (bis-2,3-phthalimidoxy-1-morpholinylpropane) obtained was filtered through a Buchner funnel and was recrystallised from alcohol.

Hydrolysis of above compound does not yield any identifiable product.

In IR-spectra, CH_2 is represented by 2910–2850 cm^{-1} and C—H bending band present at 1040–980 cm^{-1}. CO—N—CO gives an IR stretch at 1720–1170 cm^{-1}. Intense band at 1750–1650 cm^{-1} is for C=O group. O—N band frequency is situated at 1310–1240 cm^{-1} due to asymmetric stretching, C—O, a weak band at 1190–1150 cm^{-1}. Free secondary (N—H) stretching absorbs at 3445–3400 cm^{-1}.

Peaks at 1360–1290 cm^{-1} are due to (C—N) stretching of C—NH—C. 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 TLC on silica gel. All these synthesized compounds have been-characterised by microelemental and spectral studies.

Synthesis of N-hydroxy phthalimide: By reported method[20].

Phthalimidoxyethyl bromide: Prepared by reported method[21].

2-Morpholinyl ethoxyphthalimide (XIIa): Morpholine and (0.01 mol, 2.7 g) phthalimidoxyethyl bromide were suspended in solvent (dry benzene, toluene, xylene or DMF). The mixture was stirred on a magnetic stirrer for 1/2 h and then (0.01 mol, 24 g) sodium hydride was added continuously; stirring was continued for 12 h with gentle heating. After cooling, it was filtered. Two different processess were used further when solvents were arenes; the filtrate was concentrated by evaporation under reduced pressure and cooled. Crystals were obtained (m.p. 117°C, yield 21%). In case of DMF as a solvent, the filtrate was slowly added to 250 g of crushed ice. Gelatinous precipitate so obtained was shaken with 1 : 10 alcohol/water mixture to get white solid. It was recrystallised from alcohol. Similar procedure was used for propyl and butyl compounds with minor changes in stirring time, solvent of crystallisation, etc.

TABLE-1
PHYSICAL DATA AND ELEMENTAL ANALYSIS OF COMPOUND SYNTHESIS

S.No.	Compd. No.	m.f.	m.w.	m.p. (°C)	Yield (%)	Nitrogen (%)	
						Obs.	Calc.
1.	**XIIa**	$C_{14}H_{16}N_2O_4$	276	170	65	10.10	10.14
2.	**XIIb**	$C_{15}H_{18}N_2O_4$	290	185	58	9.23	9.65
3.	**XIIc**	$C_{16}H_{20}N_2O_4$	304	224	62	9.15	9.21
4.	**XVI**	$C_{23}H_{21}N_3O_7$	451	283	45	9.25	9.31

Solvent of crystallisation is ethanol.

Preparation of N-2-propenyl morpholine (XIV): Equivalent moles of allylbromide (0.01 mol, 1.6 mL) and morpholine (8.4 mL, 0.1 mol) were stirred on a magnetic stirrer while heating in presence of sodium hydride and dry benzene as a media. The stirring was continued for 8 h. Allyl bromide and benzene were removed by downward distillation. 30 mL chloroform was added to dissolve the contents. The compound was not isolated and used for next step.

Preparation of 1,2-dibromo-3-morpholinylpropane (XV) (Bromination of N-allylmorpholine): To the above solution (vide supra) (0.1 mol, 8.9 mL) of bromine is added dropwise while stirring on a powerful magnetic stirrer. The solution is stirred for 1–2 h after complete addition of bromine. Chloroform is distilled off and to the syrupy residual liquid, DMF 40 mL is added.

Synthesis of 1,2-bis-phthalimidoxy-3-morpholinylpropane (XVI): DMF solution of dibromomorpholinyl propane **(XV)** obtained from above process was added to a solution of 0.2 mole of solution of N- hydroxyphthalimide in DMF slowly and with constant stirring in 1 h duration. The solution was kept for 30 h after addition of 25 mL triethylamine (0.2 mol) and occasional shaking. After

24 h, triethylammonium bromide (needle shaped crystals) were filtered on a buchner funnel, washed with two small lots of DMF and pressed to squeeze out the filtrate. Filtrate was poured on 700 g of crushed ice while stirring with a glass rod. Solid was filtered and recrystallised from alcohol (m.p. 110–112°C, yield 75%).

Antibacterial activity: Some of the compounds were screened for antibacterial activity on three gram positive and five gram negative strains using two controls. Out of seven compounds screened, 3 gave moderate activity (zone size 15–24), 2 showed good activity (25–35) whereas 2 showed no inibition against gram positive strains. All the compounds were inactive against gram negative organisms used.

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