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Synthesis of N-[N^4-Aryl-N^1-Piperaziny Alkoxyl Phthalimides as Cardiovascular Agents

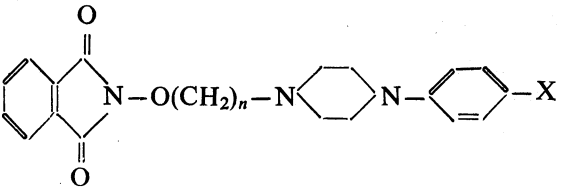
G. L. TALESARA* AND (LATE) K. S. SURESH

Department of Chemistry, College of Science, Sukhadia University Udaipur 313 001, India

Some phthalimido-oxy compounds of piperazine and related compounds have been prepared for the first time and screened for cardiovascular activity.

INTRODUCTION

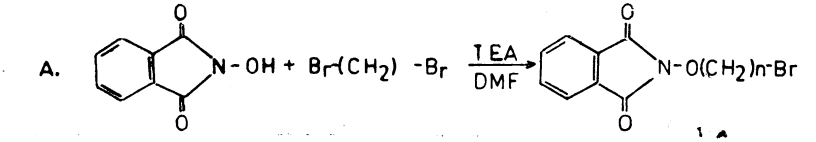
Many N-[N^1-alkyl aminoalkyl] phthalimides are reported[1] to exhibit various pharmacological properties. SomeN-[N-Aryl-N-piperazinylalkyl] phthalimides have been claimed[2] to be CNS depressents and cardiovascular agents. In view of many interesting pharmacological properties of several amino-oxy compounds[3–4], it was thought worthwhile to prepare some compounds having N-O-group. This idea prompted us to synthesize N-[N^4-Aryl—N^1—piperazinyl] phthalmides as cardiovascular agents and CNS depressents and many derivatives of following types (Ia-Ih) have been prepared.

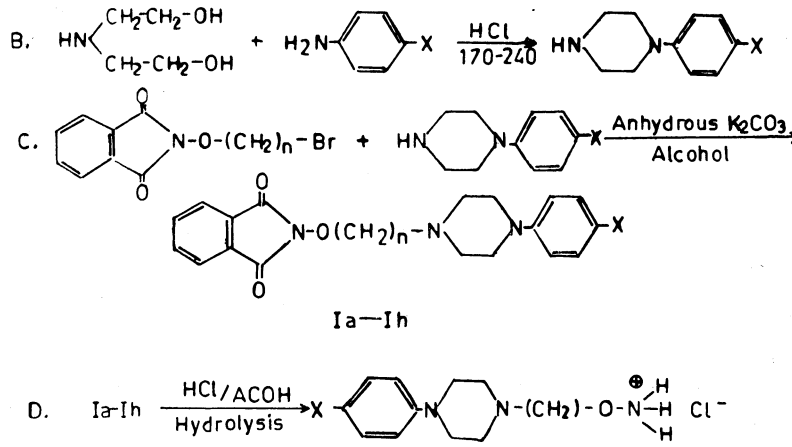


Ia=Ih

(1a) X = H, n = 2: (1b) X = H, n = 3; (1c) X = H, n = 4;
(1d) X = CH, n = 2, (1e) X = CH, n = 3; (1f) X = CH, n = 4;
(1g) X = CI, n = 2: (1h) X = CI, n = 4

the following reaction sequence were used to synthesise the above said compounds :





Phthalimido-oxyalkyl bromides were synthesised from N-hydroxy phthalimide and dibromoalkanes in presence of triethylamine as base and DMF as solvent (Method of Bauer and Suresh)[5]. Alkyl piperazines were prepared by following the method of pollard and Thomas[6] in which hydrochlorides of arylamines and diethanolamine are condensed at increasing temperature and water was removed. After neutralising the resulting cake, aryl piperazines were extracted with chloroform. N-aryl piperazines and phthalimido-oxy alkyl bromides were condensed together by refluxing in different solvents viz. dry alcohols. DMF etc. in presence of anhydrous K_2CO_3.

Alternatively the condensation was also carried out without base, by refluxing the reactants in absolute alcohol followed by neutralisation of filtrate by dilute alkali solution. The yield of the product, however, was poor, being 25 to 30% as compared to 65 to 80% in the first method (*vide supra*). The condensed products were crystallised by using various solvents and their structures were identified and confirmed by tests of different groups and physical methods *viz.* IR spectroscopy and elemental analysis for C, H and N.

Pharmacological Screening

All the compounds prepared were tested for cardiovascular activity, gross observations for spontaneous motor activity (SMA). Respiratory rate, ataxia and reflux action were studied at C. D. R. I. Lucknow. It was observed that:

(1) SMA is higher in higher doses for each compound and is highest in Ia, (2) Respiratory rate and reflux action for all the compounds were

similar, (3) Ataxia was observed in only two compounds Ia and Ic, and that is also at particular dose (464 mg/kg.) (4) Only two compounds showed positive hypotension effect *viz.*, Ia and Ic, other compounds.

In screening for cardiovascular activity response to blood pressure, heart rate and effect on other types of blood pressures were observed. Following tentative conclusions may be drawn on the basis of observations: (1) It is seen that with compounds Ia, Ic, Id, If, and Ig the blood pressure lowers progressively with increase of dose. (2) Blood pressure response was transient in all cases. (3) Other activities were found to be scattered and irregular.

IR Spectra

Peaks at 2670 cm^{-1} with shoulders at 2910 cm^{-1} and 2600 cm^{-1} typical for phthalimido group. Weak band at 3070 cm^{-1} is C-H str. of aromatic ring, peak at 1740 cm^{-1} is due to carbonyl group. Bands near 1600: 1570, 1480–1420 cm^{-1} show six membered heterocyclic rings indicates presence of piperazine ring. Aliphatic C–H stretch is clearly merged in the broad peak in region 2965–2850 cm^{-1} supported by the corresponding bending C–H modes in 1495–1485 cm^{-1} region. Absorptions of C-C multiple bond stretching of aromatic system are obvious from the shoulders at 1600, 1580, 1510, and 1430 cm^{-1}.

EXPERIMENTAL

All the melting points are uncorrected; purity of the compounds was tested by TLC and other usual methods.

Preparation of aryl piperazines

Vide method of pollard *et al.*[6] with certain modifications.

Preparation of phthalimido-oxy alkyl bromides

Method of Bauer and Suresh[5] has been used.

Preparation of N-(N^4-Aryl-N^1-Piperazinylalkoxy) Phthalimides

(Ia–Ih) ω-Phthalimido-oxy alkyl bromides (0.01 mol) and aryl piperazine (0.01 mol) were dissolved in absolute alcohol 15 ml and anhydrous potassium carbonate (0.01 mol) was added. The mixture was refluxed for 24 hr. It was filtered hot. White solid was separated on cooling. The product was recrystallised. Different solvents were used for refluxing and time for reflux is shown in Table.

Hydrolysis on N-(N^4-phenyl-N^1-Piperazinylethoxy Phthalimide (Ia)

Compound was boiled in a mixture of 12 N HCl (10 ml) and glacial

acetic acid (10 ml) for five minutes. Solution was allowed to cool and the phthalic acid formed was filtered. The filtrate was evaporated under reduced pressure to get hydrochloride of coresponding amino-oxy compound. Solid residue was washed with dry ether and recrystallised from methanol (m. pt. 312-314°C with decomposition. Yield 75%.) Physical and analytical data for the compounds are presented in Table 1.

TABLE 1

ANALYTICAL AND PHYSICAL DATA OF SYNTHESIZED COMPOUNDS (Ia—Ih)

Compound No.	Molecular formula	Mol. wt.	Reflux time (ws)	Solvent of reflux	Solvent of cryst.	M. Pt °C	Yield %
Ia	$C_{20}H_{21}O_3N_3$	351	24	Alcohol	Ethanol Benzene	131	75
Ib	$C_{21}H_{23}O_3N_3$	365	10	Alcohol	Ethanol Benzene	183	80
Ic	$C_{22}H_{25}O_3N_3$	379	36	Methanol	Methanol Benzene	154	50
Id	$C_{21}H_{23}O_3N_3$	365	14	Methanol	Methanol Ethanol	218	76
Ie	$C_{22}H_{25}O_3N_3$	379	7	Ethanol	Isopropanol	194	85
If	$C_{23}H_{27}O_3N_3$	393	10	Ethanol	Benzene	204	70
Ig	$C_{20}H_{20}O_3N_3Cl$	385.5	½	D.M.F.	Ab-alcohol	143	82
Ih	$C_{22}H_{24}O_3N_3Cl$	413.5	18	Alcohol Benzene	Alcohol	213	65

*All the compounds gave satisfactory elemental analysis.

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