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Synthesis of Some Nitrogen Mustards (Mannich Bases)

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ABSTRACT

Several Mannich base half nitrogen mustards have been synthesised by the condensation of 3-substituted phthalimides and 4-substituted phthalimides with (2-chloroethyl) amine in ethanol- formalin.

Key words: Substituted phthalimides, Ethanolamine, Half nitrogen mustard, Mannich base.

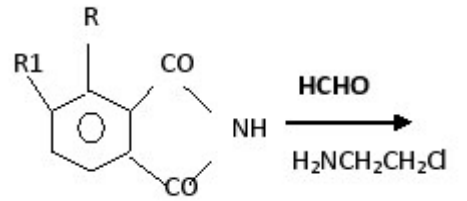
INTRODUCTION

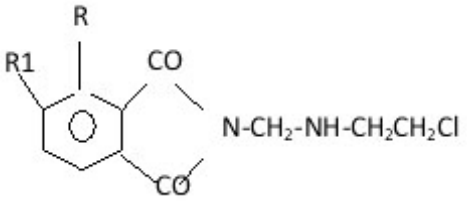
Mannich base nitrogen mustards have been found to be antineoplastic agents.[1,3] These compounds find applications in a variety of ways including their use as polymers, resins, surface active agents, detergents, additives and antioxidants. They have been found to be antipsychotic, anticonvulsant, centrally acting muscle relaxant, antimalarial and with antiviral properties.[2] In addition, nitrogen mustards obtained from cyclohexanone and acetophenone displayed antitumour efficacy against Walker 256 tumour in rats[2]. In 1961, George R. Pettit and Joseph A Settepani [4] reported the synthesis of nitrogen mustards derived from cyclohexanone and variety of acetophenone employing a Mannich reaction. A number of amides and nitrogen heterocycles containing a labile N-H bond have been condensed with formaldehyde and a primary or secondary amine[6-10]. Considering the reactivity of this labile N-H bond, the Mannich base nitrogen mustards have been synthesised from phthalimide, saccharin, isatin, and isatin semicarbazone.[4]

MATERIAL AND METHODS

We have synthesised a number of Mannich base half nitrogen mustards (IIa, b,c,d,e,f) derived from condensation of substituted phthalimides (Ia,b,c,d,e,f) with 2-chloroethylamine in ethanol- formalin (37%) solution.

Substituted phthalimides were synthesized from 3- nitrophthalic acid and 4- nitro-phthalic acid, respectively. These were heated with ammonium carbonate to produce corresponding nitrophthalimides (Ia, Id) which were converted into amino- phthalimides (Ib, Ie) by reduction with stannous chloride and conc, HCl. Further chlorophthalimides (Ic, If) were prepared by diazotising aminophthalimides followed by treatment

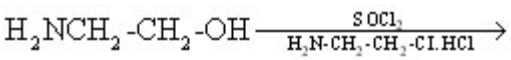




I a. R = NO_2, R_1 = H
b. R = NH_2, R_1 = H
c. R = Cl, R_1 = H
d. R = H, R_1 = NO_2
e. R = H, R_1 = NH_2
f. R = H, R_1 = Cl

II a. R = NO_2, R_1 = H
b. R = NH_2, R_1 = H
c. R = Cl, R_1 = H
d. R = H, R_1 = NO_2
e. R = H, R_1 = NH_2
f. R = H, R_1 = Cl

with curprous chloride applying Sandmeyer's reaction. (2-chloroethyl) amine hydrochloride (IV) was obtained by chlorinating ethanolamine (III) with thionyl choride following the method reported by F.G.Mann[5].



Mannich reactions were carried out in a neutral solvent composed of ethanol and formalin. Occasionally condensation was essentially complete within a few minutes at ice-bath temperature but often the reaction periods were one or more hours at room temperature.

EXPERIMENTAL

All the melting points were determined in open capillaries and are uncorrected. The i.r. spectra was taken in KBr disc on 157 spectrometer and pmr spectra on a Varian A 60 D instrument using $CDCl_3$ as internal standard. All compounds gave satisfactory N- analysis.

2-Chloroethylamine Hydrochloride

A mixture of thionyl chioride (65ml) in chloroform (65ml) and ethanolamine (25g) in chloroform was refluxed for half an hour, The product was isolated with ether and recrystallised from absolute alcohol and ether, white crystals obtained, m.p 143-146°C.

3- Nitro-Phthalimide (Ia) & 4- Nitrophthalimide (Id)

21.2g(O.1 mole) nitrophthalic acid and 12 g (0.125 mole) ammonium carbonate were heated at 220-230°C with occasional stirring for an hour. The solid mass was crystallised from water. Nitrophthalimides were obtained in cream coloured square plates, m.p. 216-217°C for 3-nitrophthalimide and 196-197°C for 4-nitrophthalimide.

3- Aminophthalimide (Ib) & 4- Aminophthalimide (Ie)

20 g (about 0.1 mole) nitrophthalimide was stirred into a solution of 84 g stannous chloride (0.11 mole) in 450ml HCl and 150 ml water. The product was collected at 0°C and washed with hot water. Yellow needles were obtained, m.p. 294-295°C for 4- amino- phthalimide and 264°C (d) for 3- amino-phthalimide.

3-Chlorophthalimide (Ic) and 4- chloro phthalimide(If)

10g aminophthalimide (1 mole) was added to a mixture of 100 ml HCl and 100 ml water, diazotised at 0^0-3^0C and added rapidly to freshly precipitate cuprous chloride. After three hours stirring, the reaction mixture was warmed on water bath. Solid separated which was recrystallised with acetic acid, m.p. 209^0-210^0C for 4- chlorphthalimide and 235^0c for 3-chlorophthalimide.

(2-Chloroethyl) amino – methylene- substituted phthalimides (IIa, b,c,d,e,f)

0.7g (0.006mole) (2-chloroethyl) amino hydrochloride was added to a cold solution of NaoH (0.3g) in water (3ml). The resulting (2-chlorethyl) amine was extracted with ether. The combined ether extract was washed with ice-water and dried over fused $MgSO_4$. It was then concentrated in vacuo at ice-bath temperature.

0.006 moles of substituted phthalimides (Ia-f) was then added to cold ice-bath solution of

the oily residue in 4ml of 3:1 ethanol-formalin (37%). After warming to 35^0-40^0C for several minutes for complete dissolution of phthalimide the solution was maintained at room temperature for one to four hours. Then the reaction mixture was cooled which led to white solid, recrystallised from ethanol-ether.

2- Chloroethylamino-methylene-3-nitrophthalimide

Yellow solid, m.p 128-129°C found N 14.83 (required 14.18), υmax 1782 (m) and 1721 (vs) for C=O group, 1448 (C-H bending), 1545 (vs) and 1365 (-NO_2 group), 730 (C-Cl stretching); δ($CDCl_3$) , 3.5-3.7 (4H,m,- CH_2 -CH_2 -), 7.1-7.3 (3H,s, Ar-H).

2-chloroethylamino-methylene-3aminophtholimide(IIb)

Pale yellow solid m.p. 84-85°c, found N 16.53 (required 16.57), υmax 1760 m for 1700 vs (for C=O group), 1450 m for C-H bending, 3390 (N-H stretching), 750 (C-Cl stretching) δ($CDCl_3$), 3.6-3.7 (4H,m, – CH_2 – CH_2-) , 7.3-7.4 (3H,s,Ar-H), 5.21 (2H,br,- NH_2)

2-Chloroethylamino- methylne- 3 chlorophthalimide (IIC)

Colourless Solid, m.p. 178-179°C, found N 10.28 required 10.26); υmax, 1780 s and 1720 vs (For C=O group, 1442 m (for C-H bending), 750 s (for C-Cl stretching); δ($CDCl_3$), 3.4-3.6 (4H,m,- CH_2,- CH_2-) 7.2-7.4 (4H, s, Ar-H),

2- Choroethylamino- methylene- 4 nitrophthalimide (IId)

Yellow solid, m.p. 134-135°C, found N 14.76 required 14.81); υmax, 1780 s and 1710 vs (for C=O group), 1530 vs (for -NO_2 group), 1455m (for C-H bending), 720 s (for C-Cl stretching); δ

Table 1: Physico-chemical and analytical data of compounds (Ia-f) and (IIa-f)

Compounds No	Molecular formula	M.P. (^{0}C)	Colour	Elemental analysis calculated C	H	N
Ia.	$C_8H_4O_4N_2$	216-217°	Cream	50.11 (50.00)	2.07 (2.08)	15.35 (15.38)
Ib.	$C_8H_6N_2O_2$	263-264°(d)	Yellow	59.35 (59.26)	3.05 (3.07)	17.34 (17.28)
Ic.	$C_8H_4O_2ClN$	235-236°	Colourless	52.74 (52.89)	2.22 (2.20)	7.70 (7.71)
Id.	$C_8H_4O_4N_2$	196-197°	Cream	59.96 (60.00)	2.48 (2.50)	14.62 (14.57)
Ie.	$C_8H_6N_2O_2$	294-295°	Yellow	59.36 (59.89)	2.23 (2.20)	7.72 (7.71)
If.	$C_8H_4O_2ClN$	209-210°	Colourless	52.94 (52.89)	2.23 (2.20)	7.72 (7.71)
IIa.	$C_{11}H_{10}O_4N_3Cl$	128-129°	Yellow	38.18 (38.15)	3.60 (3.53)	14.83 (14.81)
IIb.	$C_{11}H_{12}O_2N_3Cl$	84-85°	Pale Yellow	52.17 (52.07)	4.78 (4.73)	16.53 (16.57)
IIc.	$C_{11}H_{10}Cl_2O_2N_2$	178-179°	Colourless	48.41 (48.35)	3.68 (3.66)	10.28 (10.26)
IId.	$C_{11}H_{10}O_4N_3Cl$	134-135°	Yellow	38.19 (38.15)	3.62 (3.53)	14.76 (14.81)
IIe.	$C_{11}H_{12}O_2N_3Cl$	130-131°	Pale Yellow	52.21 (52.07)	4.76 (4.73)	16.59 (16.57)
IIf.	$C_{11}H_{10}C_{l2}O_2N_2$	128-129°	Colourless	48.42 (48.35)	3.64 (3.66)	10.24 (10.26)

($CDCl_3$), 3.4-3.5 (4H,m,-CH_2-CH_2-), 7.2-7.4 (3H,s, Ar-H).

2-ChloroethylaminO – methylene -4- amino phthalimide (IIe)

Pale yellow solid, m.p- 130-131°C; found N 14.76 (required 14.81); υmax, 1710 vs (for C=O group) 3390 br and m (for N-H stretching), 1440 m (for C-H bending), 741 s (for C-Cl stretching). δ($CDCl_3$), 3.5-3.7 (4H,-CH_2- CH_2) 7.1-7.3 (3H,Sr, Ar-H), 5.25 (2H, br,-NH_2).

2- Chloroethyl amino – methylene- 4-chlorophthalimide

Colourless solid, m.p. 128-129°C; found N 10.24 required 10.26); υmax, 1785 s and 1710 vs (for C= O group) 1430 s (for C-H bending), 740 s for C-Cl stretching; δ($CDCl_3$), 3.3-3.5 (4H, m,-CH_2-CH_2-) 7.4-7.5 (3H, s Ar- H).

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