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Synthesis of some nitrogen mustrads

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ABSTRACT

Nitrogen mustards with pyrimidine moiety have been synthesized by condensation of benzaldehyde mustard[7] with 4-hydroxy-2, 6-dimethyl pyrimidine, 4-chloro-2, 6-dimethyl pyrimidine. Also, N, N-bis(2-chloroethyl)amine hydrochloride, ethanolamine and diethanolamine have been condensed with 4-chloro-2, 6-dimethyl-pyrimidine respectively.

Key words: Nitrogen mustard, pyrimidine. Ethanolamine, diethanolamine.

INTRODUCTION

Nitrogen mustards have been found to be potential anticancerous[1], pyrimidine derivtives find an important role in life process[2]. Both simple and complex forms of pyrimidine are important as their chemotherapeutic potential has also given a considerable impetus to their study[3]. The early use of barbiturates (hydroxyl pyrimidine derivatives) as soporifices. Widely use of sulphadiazine in clinical practice and antithyroid activity of thiouracil highlight the important pharmacological activity of pyrimidines[10-11]. These pyrimidines have also close relation with the nucleic acids, enzymes and vitamins, e.g. thymine and cytosine and uracil and cytosine are pyrimidine base constituents of DNA and RNA respectively.

In addition to this, variety of alkaloids, also contain this pyrimidine ring system such as xanthine, hypoxanthine (occurring in tea and caffeine) and theophylise (in tea leaves.)

MATERIAL AND METHODS

All the chemical and reagents used were of AR or equivalent purity. Materials used for the synthesis of the reported compounds were ethanolamine, diethanolamine, aniline, ethylacetoacetate, and acetonitrile were procured from reputed companies.

Acetamidine hydrochloride

(1) was synthesized by Baumann's method[4],it was condensed with ethylacetoacetate to form 2, 6-dimethyl-4-hydroxypyrimidine (2) by the reported method of A. Pinner[5] with some modification.[6] It was condensed with benzaldehyde mustard [p-N, N-bis (2-chloroethyl) amino benzaldehyde] (5) [prepared by the procedure of Ross[7]]in 1:1 and 1:2 molar ratios to get 2-[4-N, N-bis(â-chloroethyl) amino] styrryl-4-hydroxy-methyl pyrimidine (4) and the distyrrl Nitrogen mustard derivative (6)Compound (2) was converted into 4-chloro-2, 6-dimethylpyrimidine (3) by Hilbert and john method.[8] In the same way (3) was converted into nitrogen mustard derivatives (7) and (8) on condensation with compound (5)respectively.

The compound (3) was also condensed with ethanolamine and diethanolamine to get (9) and (11) which were then treated with thionyl chloride to form (10) and (12) respectively.

Formation of (10) was also confirmed by the second route, condensing (3) with N,N-bis (2-chloroethyl) amine hydrochloride, prepared by the method of F.G.Mann,[8]

EXPERIMENTAL

All the melting points were determined in open capillaries and are uncorrected. The IR spectra

was taken on 157 spectrophotometer in KBr and pmr spectra on a varian A 60 D instrument using TMS as internal standard.

Acetamidine Hydrochloride (1)

A solution of thoroughly dry acetonitrile (100g. 2.44 moles) in absolute ethanol(113g) was prepared in a one – liter weighed suction flask surrounded by a freezing mixture of ice and salt. Dry HCI was passed into this solution. Until increase in weight of 90g (2-5)moles was obtained. This took about 5 hours. Then the flask was tightly stoppered. The side arm being attached to a $CaCl_2$-tube and was allowed to stand until the mixture had set a solid mass of crystals in 3 days.

A solution of dry ammonia gas was prepared in absolute alcohol and it was titrated against standard HCI using methyl oranges as indicator. In this way, ammonia solution with 9% ammonia by weight was obtained. The solid crystalline mass of acetimido enthyl chloride was broken up and transferred to a dry mortar in which it was ground to paste with 100ml. of absolute alcohol and returned to flask. Then it was stirred mechanically with an excess of alcoholic ammonia solution (500ml, of 9%) The crystals gradually dissolved & ammonium chloride separated. After stirring for three hours, ammonium chloride was filtered by suction and the filtrate was evaporated to a volume of about 200ml, when a considerable quantity of crystals separated. On cooling, the long colourless crystals of cetmidine hydrochloride separated. These were filtered by suction, washed with 60ml, of cold alcohol and dried in a desicator, over sulphuric, acid. Concentration of mother liquor gave a second crop. The total acetamidine hydrochloride. Weighted 186 g (80%yield) with m.p.164^o-60^0. It was some what deliquescent and so it was kept in a tightly stoppered bottle, N.29 61 (required 29.63).

4-Hydroxy-2, 6-dimethyl-pyrimidine (2)

Ethylacetoacetate (14.0g, 0.01 mol(2.4:0.1g atom) was added to cetamidine hydrochloride (5.22g, 0.09mol). The mixture was refluxed for 4 hours with stirfrring. After evaporation of the solvent, the residue was dissolved in 60ml. water and acidified with HCL, colourless crystals were collected. From the filtrate, another crop of crystals, was obtained which was combined with the above. It was recrystallised from benzene and ether respectively. Colourless plates (8g, yield 58%) were obtained with melting point 196^o-197^{o}C, N 22.60 (required 22.58%).

4-Chloro-2, 6-dimethyl-pyrimidine(3)

4-Hydroxy-2,6-dimethyl pyrimidine [2;1.24g, 0.01 mol] was added portionwise to a mixture of dimethylaniline (2ml.) and $POCl_3$(4ml.) The mixture was refluxed for an hour and the dark brown liquid was poured on ice (2.5g). The deep purple solution was filtered and extracted with ether (5 times with 10ml. each times). The combined dried extract gave crystals of 4-chloro-2, 6-dimethyl-pyrimidine, crystallized with ether-alcohol, mp. 221^{o}C (d); N,19.64(required 19.65%).

2-[4-N,N-Bis(β-chloroethylmino]styrryl-4-hydroxy-6-methyl pyrimidine (4)

4-hydroxy-2, 6-dimethl pyrimidine. [2;1.24g,0.01mol] and P-N, N-bis (2-chloroethl) amino benzaldehyde [2.46g, 0.01 mol] were taken in glacial acetic acid (50ml.)in an R.B., Flask. A little anhydrous zinc chloride was added to it. The mixture was refluxed for 4-hours with an arrangement to remove water formed during the reaction. The reaction mixture was then concentrated and left overnight. Colourless crystals were obtained in excellent. Yield, Recrystallised from ether,m.p. 86-87^o (yield, 60%N, 11.64(required 11.65). max, 3070-3120(O-H),1670(carbonyl due to tautomerism), 1610 (CH=CH), 1450(-CH_2-CH_2,1356 (C-N=), 872 (isolated H), 730 (C-Cl): δ(CD^2Cl_3).3.3-3.5 (8H,m,CH_2-CH_2x2), 7.2(4H,s,Ar-H), CH=CH,merged with aromatic protions; 8.4 (pyrimidine H,) 2.4(3H,s,CH_3),5.2(1H,m-NH).

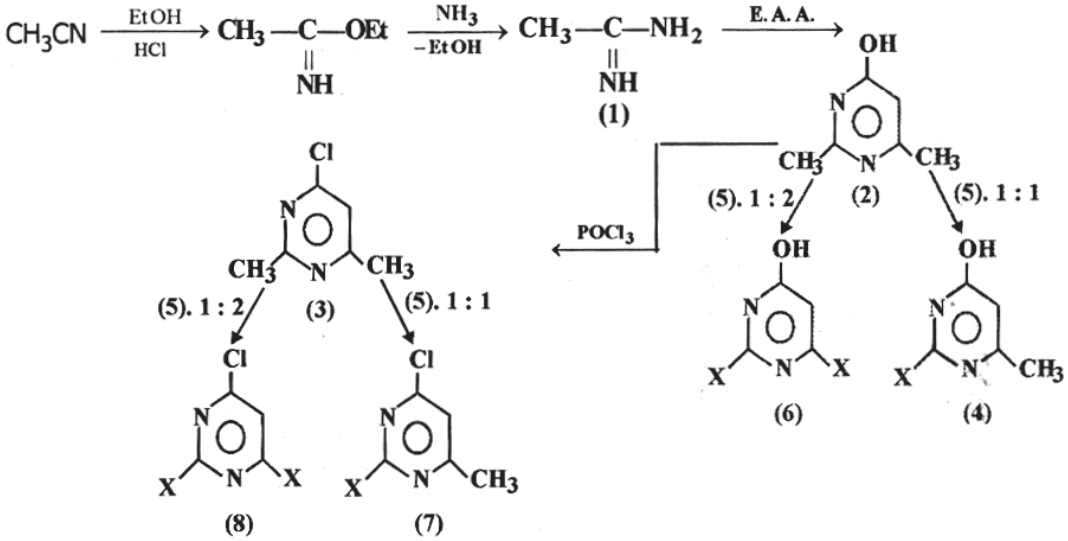
4-Hydroxy-2,6-Di[4-N,N-bis(β-chloroethyl) amino] styrryl pyrimidine (6)

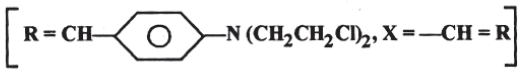
The same method as in preparation of (4) was adopted using 1:2 molar ratio of the compound (2) and (5). Colourless plates were obtained which were recrystallised with alcohol – either, needle shaped yellow crystals, m-p, 89-90^o, yield(72%), N.6.66(required 6.65), max, 3120(O-H), 1700 (carbonl group due to tautomerism), 1610 (CH=CH), 1430 (-CH_2- CH_2),1310 (C-N=, tertiary N-atom), 844(isolated H), 830 (2adjacent H-atoms), 750(C-Cl); δ($CDCl_3$), 3.4-3.6(16H,s,CH_2- CH_2-x4), 7.1-7.4

(8H,s,Ar-H), protons of CH=CH merged with the aromatic protons, 5.2(1H,m,N-H)due to tautomerism), 8.5(1H,m,pyrimidine H).

4-Hydroxy-26-Di[4-N,N-bis (β-chloroethy) amino] styrryl pyrimidine (6)

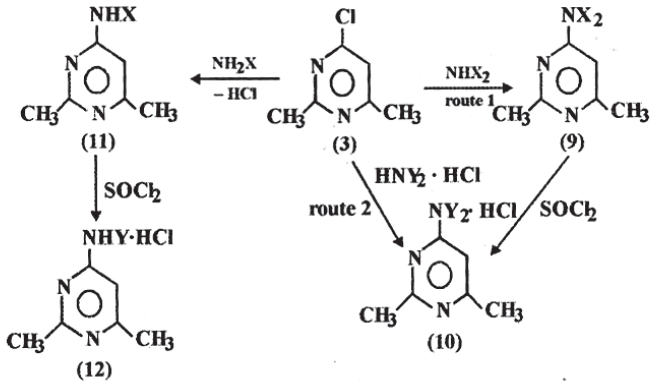
The same method as in preparation of (4) was adopted using 1:2 molar ratio of the compound (2) and (5). Colourless plates were obtained which very recrystallised with alcohol-either needle shaped yellow crystals, m-p, 89-90°, yield (72%):, N.6.66 (required 6.65), max, 3120 (O-H), 1700 (carbonyl group due to tautomerism), 1610 (CH), 1430 (-CH_2-CH_2) 1310 (C-N=, tertiary N-atom), 844 (isolated





(Scheme A)

The compound (3) was also condensed with ethanolamine and diethanolamine to get (9) and (11) which were then treated with thionyl chloride to form (10) and (12) respectively.



X = –CH_2CH_2OH; Y = –CH_2CH_2Cl

(Scheme B)

Scheme

H), 830 (2 adjacent H-atoms), 750 (C-Cl): δ ($CDCl_3$), 3.4-3.6 (16H,s, CH_2-CH_2-x4), 7.1-7.4(8H,s,Ar-H), protons of CH=CH merged with the aromatic protons, 5.2 (1H,m,N-H) due to tautomerism), 8.5 (1H,m,pyrimidine H).

4-chloro-6methyl-2-[4-N,N-bis (β-chloroethyl) amino] styrryl-pryimidine(7)

The same method as for preparation of (4) was adopted yellow solid was obtained recrystallised with ether, m-p85-86°;N 11.221 (required 11.33), max 1460 (-CH_2—CH_2), 1310 (-C-N=tertiary N) 855 (isolated H,) (2 adjacent H,) 710 (C-Cl), δ ($CDCl_3$), 3.3 – 3.5[8H, m, CH_2-CH_2x2], 7.2-7.3 ormation of (10^3) was also confirmed by the second route, condesing (3) with N, N-bis (2-chloroethyl) amine hydrochloride, prepared by the method of F.G. Mann.[8](4H,s,Ar-H), proton of CH=CH merged with aromatic protons, 8.4 (1H,m,pyrimidine-H), 2.4 (3H,m,CH_3).

4-chloro-2, 6 –di-[4-N,N-bis (β-chloroethyl) amino] styrryl-pryimidine(8)

The same method as for preparation of (4) was adopted using 1:2 molar ratio of the compounds (3) and (5). Yellow solid, recrystallised with ether, m-p. 72-73°N.9.38(required 9.35) max 1460 (-CH_2-CH_2), 1305 (-C-N=tertiary N) 850 (isolated H,)830 (2 adjacent H,) 710 (C-Cl), δ ($CDCl_3$), 3.3 – 3.6[16H, s, CH_2-CH_2x4], 7.1-7.3 (8H,s,Ar-H), protons of CH=CH merged with aromatic protons, 8.4 (1H, m, pryrimidine H).

2-6Dimethyl-4-[N,N-bis (β-hydroxyethyl) amino] pryimidine (9)

4-chloro-2, 6-dimethyl pryrimidine [3,1.41g,0.10 mol] and reshly distilled diethanolamine (2.10g, 0.02 mol) were taken in n-butanol, Sodium cabonate was added to it and the mixture was refluxed at 140°Con an oil bath for 16 hours The solution was filtered hot and the solvent

Table 1: Physico-chemical and analytical data of compound (1-11)

Compounds No.	Molecular Formula	m.p. (°C)	% yield	Elemental analysis Calculated C	H	N
1.	$C_2H_6N_2$.HCl	164°-160°	80	25.3 (25.4)	7.3 (7.4)	29.61 (29.63)
2.	$C_6H_8N_2$.O	196°-197°	58	58.10 (58.60)	6.46 (6.45)	22.60 (22.58)
3.	$C_6H_7N_2$.Cl	221°	58	50.51 (50.52)	4.90 (4.91)	19.64 (19.65)
4.	$C_{17}H_{19}N_3$.Cl_2O	86-87°	60	57.95 (57.93)	5.38 (5.40)	11.91 (11.93)
5.	$C_{28}H_{30}N_4$.Cl_4O	89-90°	72	57.95 (57.93)	5.19 (5.17)	9.66 (9.65)
6.	$C_{17}H_{18}N_3$.Cl_3	85-86°	65	55.04 (55.06)	4.84 (4.86)	11.31 (11.33)
7.	$C_{28}H_{29}N_4$.Cl_5	72-73°	68	56.21 (56.19)	4.86 (4.85)	9.38 (9.35)
8.	$C_{10}H_{17}N_3$.O_2	85°at 20 mm (b.p.)	70	56.85 (56.87)	8.04 (8.06)	19.88 (19.90)
9.	$C_{10}H_{15}N_3$.Cl_2	125-126°	62	48.38 (48.39)	6.04 (6.05)	16.91 (16.94)
10.	$C_8H_{13}N_3$.O	70-71°at 20mm (b.p.)	59	57.46 (57.48)	7.77 (7.78)	26.11 (26.15)
11.	$C_8H_{12}N_3$.Cl.HCl	115-116°	73	43.22 (43.24)	5.39 (5.40)	18.89 (18.91)

was removed by distillation under reduced pressure, b.p.85°20mm. Yield 1.5g: N,19.88 (required 19.90): max, 3400-3200(O-H), 2930(C-H), 1450 (-CH_2—CH_2), 1380 CH_3), 1315 (C-N) =, tertiary N-atom) 865 (isolated H,)ä($CDCl_3$) 2.7-2.9 (6H,m,CH_3x2), 8.4 (1H, m, pyrimidine proton), 3.4-3.5(8H,s, CH_2-CH_2x2),

2-6Dimethyl-4-[N,N-bis (β-chloroethyl) amino] pryimidine hydrochloride (10)

(A) 2-6Dimethyl-4-[bis (â- hydrochloride**)** amino] pryimidine [9,2.11g0.01 mol] was added to 15ml. of chloroform. Then thionll choride (4.76g, 0.02mol) in 25 ml. chloroform was added to this mixture. The whole liquid was refluxed on water bath for two hours. Then it was cooled. An yellow solid separated, recrystallised from alcohol-ether mixture, mp. 125-26°; N16.91(required max, 3250(N-H), 2932(C-H), 1460 (-CH_2—CH_2), 1364 (-CH_3), 1315 (C-N) =, tertiary N) 710 (C-Cl); δ($CDCl_3$) 3.6-3.7 (8H,s, CH_2-CH_2x2) 2.5-2.7 (6H,s,CH_3-x2) 8.4 (1H, m, pyrimidine H),

(B) 4-chloro2-6Dimethyl pryimidine [3,1.41g, 0.01mol] was dissolved in 252ml of warm absolute aocohol. Then N,N-bis (â-chloroethyl**)** amine hydrochloride[9] [1.05g. 0.01mol] was added two it.A few piece of fused sodium acetate was also added and the mixture was refluxed for 5 hours, then it was cooled and left overnight, yellow crystals separated which was recrystallised from alcohol-ether m.p. 125-126°; N16.91 (required 16.94) max, 3205(N-H), 1455(C-H), 1310(C-N=), 708(C-Cl); δ($CDCl_3$) 3.5-3.6 (8H,s, CH_2-CH_2x2) (6H,s,CH_3-x2)8.4-8.5(1H,m,pyrimidineH),

2,6-Dimethyl-4(â-hydroxyethyl) amino] pryimidine(11)

4-chloro-2, 6-dimethyl pryrimidine [1.41g,0.10 mol] and reshly distilled ethanolamine (1..83g, 0.003mol) were taken in n-butanol, and the mixture was refluxed for 24 hours on oil bath at 140°. Then it was filtered hot. The solvent was removed under reduced pressure and the residual liquid was distilled at 70-71° (20mm pressure) N, 26.11(required 26.15),ì max, 3440-3200 (O-H), 1480 (-CH_2—CH_2) 1360 (-CH_3)1310 (C-H), 1310 (C-N= tertiary N) ä($CDCl_3$) 2.7-2.8 (6H,s, CH_3x2)5.8-6.2 (1H,S,N-H),3.5-3.6(4H,M,-CH_2-CH_2)8.4(1H,m,prrimidineH).

2-6Dimethyl-4-[(â-chloroethyl) amino] pryimidine hydrochloride (12)

2-6Dimethyl-4-(â- hydrochloride**)** amino] pryimidine [1.67g0.01 mol] was added to 15ml. of chloroform. Then thionl choride (4.76g, 0.02mol) in 25 ml. chloroform was added to this mixture. The whole liquid was refluxed on water bath for two hours. Then it was cooled. An yellow solid separated, recrystallised from alcohol-ethanol-ether mp. 115-16°; N18.8 (required 18.91); max, 3310(N-H), 2832(C-H), 1460 (-CH_2—CH_2), 1364 (-CH_3), 1315 (C-N) =, tertiary N) 710 (C-Cl);ä($CDCl_3$) 2.7-2.8 (6H,s, CH_3x2)8.6(1H, m-pyrimidine H),3.6-3.8 (8H,m,CH_2- CH_2 x2).

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