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Synthesis of some nitrogen mustrads (Quinazoline series)

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ABSTRACT

Several nitrogen mustards with quinazoline moiety have been synthesised by condensation of 4-chloroquinazoline and 4,6- dichloroquinazoline with ethanol amine, diethanolamine and N-bis (2-chloroethyl) amine hydrochloride respectively.

Key words: Nitrogen mustard, quinazoline, ethanolamine, diethanolamine.

INTRODUCTION

Quinazoline derivatives have been reported as pharmaceuticals which effect blood pressure produce local amaesthesia[1] and are active towards blood parasites[2]. Some derivatives have been found to be potential antimalarial similar to quinoline derivatives and are less toxic. [3-4] Moreover, nitrogen mustards have been found to be potential anticancerous. [5] A large number of a variety of substituted quinoline and acridine carrier derivatives, synthesised by Pick et al[6] and Creech et al[7] gave an idea that these compounds might permit the accumulation of the mustard moiety in specific tissues and pressumably also in the existing tumours of these tissues. These mustard derivatives, thus, might be deterimental to the idea of greater effectiveness, since any enhanced degree of activity displayed during the transport of drug to the affected area would tend to limit the localisation of effective compound. [8] So, we planned to synthesise a number of nitrogen mustards with quinazoline moiety.

MATERIAL AND METHODS

4-quinazoline (2,4-hydroxy-benzopyrimidine) was obtained by the reaction of anthranilic acid (1) with formamide[9]. Then it was treated with phosphorous oxychloride in order to replace OH group by C1 atom. Thus, 4-chloroquinazoline was obtained. Then it was subjected to react with ethanolamine and diethanolamine followed by treatment with thionyl chloride to form nitrogen mustards. Similarly, some nitrogen mustards were synthesised in the same way starting with 4,6-dichloroquinazolone.

Formation of (7) and (14) were also confirmed by second route using N[bis-(2-chloroethyl) amine] hydrochloride (prepared by reported method of F.G. Mann[10]).

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. All compounds gave satisfactory N-analysis**.**

N-Bis(2-chloroethylaminehydrochioride[10]

A mixture of thionyl chloride (65 ml.) in chloroform (65 ml.) and diethanolamine (25g) in chloroform was refluxed for half on hour. The product was isolated with ether and recrystallised from absolute alcohol and ether, m.p. 216-17°,found N, 7.85 (required N,7.85%).

4-Quinazolone or 4-hydroxy-quinazoline (2)

A mixture of anthranilic acid (13.1g, 0.1 mol) was heated with formamide(40g) in absolute alcohol at 120°-125° for four hours. Then it was cooled at room temperature. The mixture solidified. It was broken up and mixed with water and then filtered. The residue was crystallised fromethanol as wooly mass; m.p. 212-213°,found N,19.15 (required N, 19.17%); $\bar{\nu}_{max}$ .1460 $(-CH_2-CH_2-)$.1354 (C-N=), 3420-3210 (O-H); δ ($CDCl_3$), 5.5-5.7 (1H, N-H), 3.3-3.5 (4H, $-CH_2-CH_2-$) , 7.1-7.3 (4H, S, Ar-H), 8.5 (1H, m, pyrimidine-H).

4-Chloro-quinazoline (3)

4- Quinazolone,**2**, (7.15g ; 0.05 mol) was mixed with PCl_5 (15g, 0.07 mol) and 60 mL $POCl_3$ in an R.B. flask. The mixture was heated on an oil-bath at 118°-120° for 4 hours by which time all the solid had dissolved and then for a further period of one hour. The volatile materials were removed under reduced pressure. The viscous oily mass was added continously to ice-cold liquor ammonia. The precipitated materials was filtered and extracted with petroleum ether. The solid, thus obtained, was recrystallised from petroleum ether and benzene respectively, m.p. 97°-98° (yield 5.2g), found N, 17.01(required N, 17.02%).

4- [(2-Hydroxyethyl) amino]- quinazoline (4)

4- Chloro-quinazolone,**3**, (5g, 0.03 mol) was dissolved in 25 ml of warm absolute alcohol containing 2g (0.033 mol) of freshly distilled ethanolamine and 0.3 mol of concentrated hydrochloric acid (0.0036 mol) was then added. After standing for several hours, the mixture was made basic and solvents were removed by evaporation is vacuo. The solid was boiled with water, cooled and filtered. Then the white plates were melted and cooled. Anhydrous solid, thus obtained, was recrystallised with absolute alcohol, m.p 174-175°(yield 3.8g),found N, 22.26 (required N, 22.22%) ; $\bar{\nu}_{max}$, 3420-3210 $(O-H)$, 1460 $(-CH_2-CH_2-)$, 1354 (C-N=, tertiary N), 865 (isolated H); δ ($CDCl_3$), 3.6-3.7 (8H, m, $-CH_2-CH_2-$), 7.3-7.4 (4H, S, Ar-H) 8.4-8.5 (lH, m, pyrimidine H).

4- [(2-Chloroethyl) amino]- quinazoline hydrochloride (5)

4- (2 -Hydroxyethyl) aminoquinazoline,**4**, (1.89g, 0.01 mol) was suspended in chloroform (40 ml). Then thionyl chloride (3.0g) in chloroform (15 ml) was added to it dropwise. The mixture was refluxed for 1h on a water bath. The solvent was removed by fractional distillation under reduced pressure, pale yellow solid was obtained. It was washed with petroleum ether and recrystallised from the chloroform, m.p. 210-211°(yield 1.5g), found N,20.21(required N,20.24%); $\bar{\nu}_{max}$, 1466 $(-CH_2-CH_2-)$, 1320 (-N=; tertiary N-atom), 755 (C-Cl), 855 (isolated H); δ ($CDCl_3$), 3.4-3.6 (4H, $-CH_2-CH_2-$) , 7.2-7.4 (4H,S,Ar-H), 8.4-8.6 (1H, m, pyrimidine-H); 5.6 (1H,m,N-H).

4- [N-Bis (2 -hydroxyethyl) amino]-quinazoline (6)

4-Chloroquinazoline,**3**, (5g, 0.03 mol) was dissolved in 25 ml of warm absolute alcohol containing freshly distilled diethanolamine (3.5g, 0.033 mol) and conc. HCl (0.3 ml, 0.0036 mol) was then added. After standing for several hours, the mixture was made alkaline with sodium hydroxide solution. Solvents were removed by evaporation in vacuo. The solid was boiled with water, cooled and filtered. White plates, thus obtained, were melted and cooled.Anhydrous solid ,thus obtained , was recrystallised with absolute alcohol, m.p. 182-83°,yield 3.6g, found N,20.07(required N,20.10%); $\bar{\nu}_{max}$, 3420-3265 (O-H), 1450 $(-CH_2-CH_2-)$, 1320 (C-N=; tertiary N), 852 (isolated H) ; δ ($CDCl_3$), 3.6 (8H, m, $-CH_2-CH_2-$ 2), 7.2-7.4 (4H, S, Ar-H), 8.4-8.5 (1H, m, pyrimidine H).

4- [N-Bis (2-chloroethyl) amino]-quinazoline hydrochloride (7a) ,(First route)

Thionyl chloride (3.0g) was dissolved in chloroform (15ml.) and the mixture was added dropwise to a suspension of 4-[N-bis (2-hydroxyethyl) amino]- quinazoline,**6**, in chloroform(40ml). It was refluxed for an hour on a water bath. Solvents were removed by evaporation under reduced pressure. Brown coloured crude solid was obtained. It was washed with petroleum ether and recrystallised from chloroform in pale yellow crystal, m.p. 140-41°(yield2.6g),found N,17.04(required N,17.07%); $\bar{\nu}_{max}$, 1470 $(-CH_2-CH_2-)$, 1325 (C-N=, tertiary N), 770 (C-Cl); δ ($CDCl_3$), 3.5-3.7 (8H, m, $-CH_2-CH_2-$), 7.1-7.3 (4H, S, Ar-H) 8.4 (lH, m, pyrimidine H).

5 - chloro-anthranilic acid (8)

Anthranilic acid (20.0g, 0.15 mol) was added in small portions with shaking to a mixture of well-cooled sulphuryl chloride (26.4g, 0.19 mol) and ether (400 ml.) in a flask fitted with a reflux condenser and an addition tube. After the removal of ether and sulphuryl chloride at reduced pressure, the residue was treated with water. It was filtered and the solid was digested for 2h at 60° with HCl (400 ml, 8%) and again filtered. The filtrate was neutralised partially with NaOH solution (6 M) and finally with saturated sodium acetate solution. The precipitate was filtered, dissolved in hot ethanol (95%) and hot water added to it till cloudiness. Yellow crystals separated, m.p. 204-205°; found N,8.18 (required N,8.16%).

Table 1 : Physico-chemical and analytical data of compound (1-15)

Compounds No.	Molecular Formula	m.p. (°C)	yield (%)	Elemental analysis calculated		
				C	H	N
1.	$C_7H_7O_2N$	147°	82	61.02 (61.31)	5.03 (5.11)	10.13 (10.22)
2.	$C_8H_6O_2N$	212-213°	80	64.98 (65.75)	4.09 (4.11)	19.15 (19.18)
3.	$C_8H_5N_2Cl$	97-98°	65	58.21 (58.36)	3.01 (3.04)	17.01 (17.02)
4.	$C_{10}H_{11}N_3O$	174-175°	67	63.28 (63.49)	5.71 (5.82)	22.26 (22.22)
5.	$C_{10}H_{10}N_3Cl$	210-211°	76	57.58 (57.83)	4.72 (4.82)	20.21 (20.24)
6.	$C_{12}H_{15}N_3O_2$	182-183°	61	57.38 (57.42)	7.13 (7.18)	20.07 (20.10)
7a.	$C_{12}H_{13}N_3Cl_2$	140-141°	68	48.75 (48.78)	5.58 (5.69)	17.04 (17.07)
7b.	$C_{12}H_{13}N_3Cl_2$	139-140°	65	48.72 (48.78)	5.61 (5.69)	17.03 (17.07)
8.	$C_7H_6O_2NCl$	204-205°	72	48.95 (48.98)	3.45 (3.40)	8.18 (8.16)
9.	$C_8H_5OClN_2$	262-263°	68	53.21 (53.19)	2.73 (2.77)	15.53 (15.50)
10.	$C_8H_4Cl_2N_2$	154-155°	72	40.10 (40.17)	1.61 (1.67)	14.09 (14.07)
11.	$C_{10}H_{10}N_3ClO$	178-179°	77	53.51 (53.69)	4.42 (4.45)	18.24 (18.22)
12.	$C_{10}H_{10}N_3Cl_3$	148-149°	61	43.11 (43.17)	3.34 (3.36)	15.05 (15.02)
13.	$C_{12}H_{14}N_3O_2Cl$	190-191°	67	49.21 (49.28)	5.68 (5.75)	17.21 (17.25)
14a.	$C_{12}H_{13}Cl_4N_3$	160-161°	78	37.80 (37.85)	4.08 (4.10)	13.21 (13.25)
14b.	$C_{12}H_{13}C_{l4}N_3$	160-161°	73	37.77 (37.85)	4.05 (4.10)	13.19 (13.25)
15.	$C_4H_9Cl_3N$	216-217°	82	27.01 (27.04)	5.05 (5.07)	7.85 (7.88)

6 - Chloroquinazolone (9)

5-Chloro-anthranilic acid,8, (8.6g, 0.05 mol) and formamide (8.6g, 0.2 mol) were heated for one hour at 130-40°, for three hours at 160-65°. The light yellow brown crystals were filtered, washed with ethanol - benzene (1:1) and dried in vacuo. This was then recrystallised from 50% acetic acid, long plate like needles, m.p. 262-63°; found N,15.53 (required N,15.50%).

4, 6 - Dichloroquinazoline (10)

A mixture of 6-chloroquinazolone,**9**, (5.4g, 0.03 mol), PCl_5 (6.35g, 0.30 mol) and $POCl_3$ (36 ml.) was refluxed for 5 hours at 125-30°. After removal of $POCl_3$by distillation the solid was treated with chloroform (200 ml.), the last traces of solid being dissolved in 10 ml. of 3N-NaOH. The residue from the chloroform extract was recrystallised from benzene-petroleum ether. Feathery crystals obtained, m.p. 154-155°; found N,14.09 (found N, 14.07).

6 - Chloro-4-[(2-hydroxyethyl) amino] quinazoline (11)

4,6-Dichloroquinazoline,**10**, (5g, 0.025 mol) was dissolved in 25 ml warm absolute alcohol containing freshly distilled ethanolamine (2g, 0.033 mol) and conc. HCl (0.3 ml, 0.0036 mol) was then added. After standing for several hours, the mixture was made alkaline and solvents were removed by evaporation in vacuo. The residue was dissolved in hot 30% alcohol, treated with charcoal and then made basic with an excess of 50% KOH solution. The product separated out as the monohydrate[11] on cooling; by concentration of the mother liquor an additional amount was obtained. The combined fractions of crude material were recrystallised several times with small amount of dil. HCl. Then the solid was recrystallised from 30% alcohol, m.p., 178-79°; N, 18.24 (required 18.22%); $\bar{\nu}_{max}$, 3420-33 (O-H), 1450 $(-CH_2-CH_2-)$ 1320 (C-N = , tertiary N), 855 (isolated H), 770 (C-Cl); δ ($CDCl_3$) , 5.5 (1H, m, -NH), 7.2-7.4 (3H,S, Ar-H), 8.4-8.5 (1H,m, pyrimidine H).

6 - Chloro-4- [(2 -chloroethyl) amino] - quinazoline hydrochloride (12)

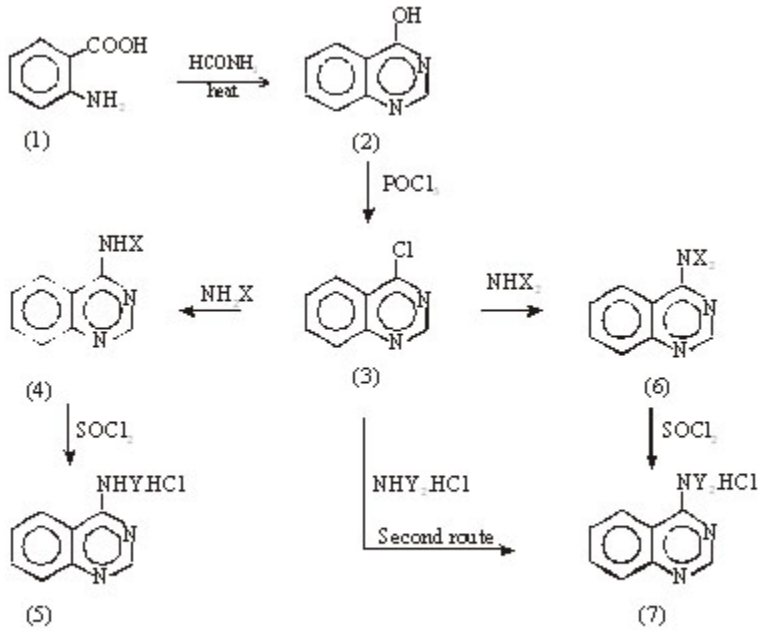
Thionyl chloride (3.0g) was dissolved in chloroform (15 ml.) and the solution was added dropwise to a suspension of (**11**) in chloroform (40 ml.). It was refluxed on water-bath for one hour and cooled. The solvent was removed by fractional distillation under reduced pressure. Pale yellow solid was obtained. It was washed with petroleum ether and recrystallized from the chloroform,m.p.148-49°,found N , 15.05(required N , 15.02%) ; $\bar{\nu}_{max}$, 1466 $(-CH_2-CH_2-)$1360 (C-N=; tertiary N), 710 (C-Cl) ; δ ($CDCl_3$) 3.6-3.7 (8H, m, $-CH_2-CH_2-$) , 7.1-7.2 (3H, S, Ar-H), 8.4-8.5 (1H,m, pyrimidine H).

6 - Chloro-4- [N,N-bis(2-hydroxyethyl amino] - quinazoline (13)

4,6-Dichloroquinazoline,**10**, (5g, 0.025 mole) was dissolved in 25 ml. warm absolute alcohol containing freshly distilled diethanolamine(35g, 0.033 mol) and concentrated hydrochloric acid (0.3 ml, 0.0036 mol) was then added. After standing for several hours, the mixture was made basic with sodium hydroxide solution. Solvents were removed by evaporation under reduced pressure. The residue was dissolved in hot 30% alchohol, treated with charcoal and then made basic with an excessof 50% KOH solution. The product separated out as the monohydrate on cooling; by concentration of the mother liquor an additional amount was obtained The combined fractions of crude material were recrystallised several times with small amount of dil. HCl. Then the solid mass was recrystallised from 30% alcohol; m.p. 190-191° , found N, 17.21 (required N,17.25%); $\bar{\nu}_{max}$, 1448 $(-CH_2-CH_2-)$, 1325 (C-N = , tertiary N), 850 (isolated H), 765 (C-Cl); δ ($CDCl_3$), 5.4-5.5 (8H, m, $-CH_2-CH_2-$), 7.1-7.2 (3H, S, Ar-H), 8.5-8.6 (1H, m, pyrimidine H).

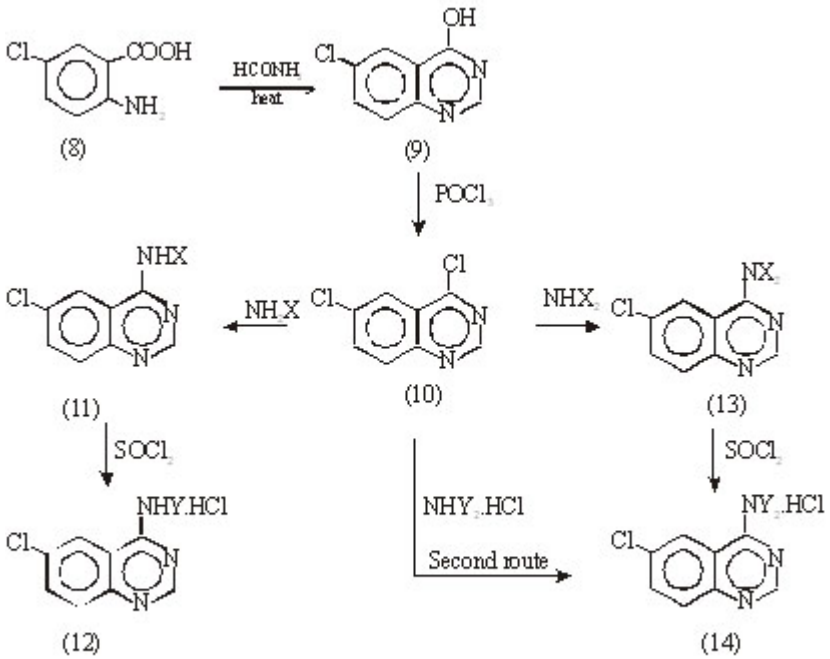
6 - Chloro-4- [(2 -chloroethylamino] - quinazoline hydrochloride (14a)

Thionyl chloride (3.0g) was dissolved in chloroform (15 ml.) and the solution was added dropwise to a suspension of compound (**13**) in chloroform (40 ml.). It was refluxed on water-bath for an hour and cooled. The solvent was removed by fractional distillation under reduced pressure. Pale yellow solid was obtained. It was washed with petroleum ether and recrystallised from the chloroform, m.p., 160-161°,found N, 13.21 (13.25%); $\bar{\nu}_{max}$, 1462 $(-CH_2-CH_2-)$, 1231 (C-N= , tertiary N), 852 (isolated H-atom), 754 (C-Cl) ; δ ($CDCl_3$) , 5.4-5.6 (8H, m, $-CH_2-CH_2-$), 7.2-7.3 (3H, S, Ar-H), 8.4 (lH, m, pyrimidine H) .



[Where, X = CH_2CH_2OH, Y = CH_2CH_2Cl]

Scheme 1



[Where, X = CH_2CH_2OH, Y = CH_2CH_2Cl]

Scheme 2

4-[N-Bis (2-chloroethyl) amlno] - quinazoline hydrochloride (7b) (Second route)

4-Chloroquinazoline,**3**, (31.66g, 0.01 mole) was dissolved in 25 ml. warmed absolute alcohol. N-Bis (2-chloroethyl) amine hydrochloride, 15 ,(1.05g; 0.01 mole) was added to it. Some pieces of fused sodium acetate was also added and the mixture was refluxed for 5 hours. Then it was cooled in the refrigerator and left overnight. Yellow crystals separated which was recrystallised from alcohol-ether, m.p., 139-40°; found N, 17.03 (required N, 17.07%); $\bar{\nu}_{max}$, 1465 $(-CH_2-CH_2-)$, 1321 (C-N = , tertiary N-atom) , 855 (isolated H-atom), 750 (C-Cl); δ ($CDCl_3$), 3.6-3.7 (8H, m, $-CH_2-CH_2-$), 7.2-7.3 (4H, S, Ar-H), 8.5-8.6 (lH, m, pyrimidine H).

6-Chloro-4-[N-bis(2-chloroethyl) amlno] - quinazoline (14b)
(Second route)

4, 6-Dichloroquinazoline,10, (2g, 0.01 mole) was dissolved in 25 ml. warmed absolute alcohol. N-bis (2-chloroethyl) amine hydrochloride (1.05g, 0.01 mole) was added to it. Some pieces of fused sodium acetate was also added and the mixture was refluxed for 6 hours.Then it was cooled in the refrigerator and left overnight. Yellow crystals separated which was recrystallised with alcohol-ether, m.p. 160-61°,found N, 13.19 (required N, 13.25%) $\bar{\nu}_{max}$, 1465 $(-CH_2-CH_2-)$ 1320 (C-N = , tertiary N) , 750 (C-Cl); δ ($CDCl_3$), 3.5-3.6 (8H, m, $-CH_2-CH_2-$), 7.2-7.3 (3H, S, Ar-H), 8.5-8.6 (lH, m, pyrimidine H).

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