Synthesis of bis(2-Chloroethyl)amino-1,8-naphthyridines for Evaluation as Anticancer Agents

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Some 1,8-naphthyridine nitrogen mustards have been synthesized for studies of their antitumor potentialities. All the tested intermediate and target compounds are devoid of antitumor properties.

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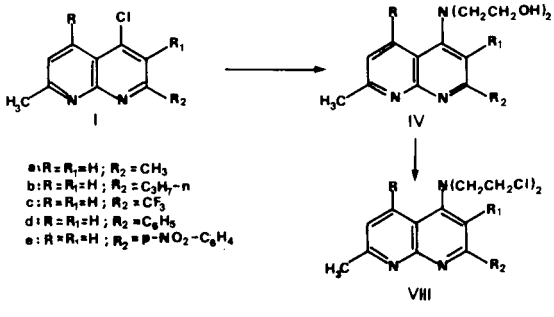
A considerable number of aromatic nitrogen mustards have been synthesized during the course of continuing research for antitumor agents. In these compounds, the bis(2-chloroethyl)amino group is attached to an aromatic or a heterocyclic nucleus (benzene, naphthalene, pyridine, pyrimidine, *etc.*) [1,2].

In continuing our studies directed toward the synthesis of products with potential biological interest, we now report the preparation of some compounds, related to aromatic alkylating agents particularly chlornaphazine, in which the cytotoxic side chain is attached to the 1,8-naphthyridine nucleus.

The ideal starting materials for the synthesis of compounds of this type were considered to be the chloronaphthyridines I, II and III.

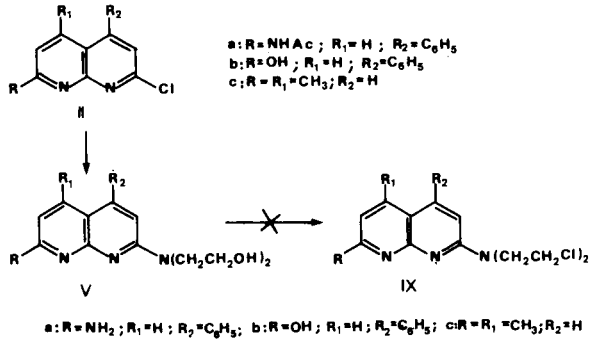
Treatment of Ia-c, Id [3], Ie-g [4], IIa,b [5], IIc [6], IId [7], IIIa [8] and IIIb [9] with diethanolamine at 120° for several hours generally gave the required bis(2-hydroxyethyl)amino derivatives IV (Table I), V and VI (Table II) respectively. Under these conditions acetamidonaphthyridine IIa afforded directly amino derivative Va in 55% yield.

Scheme I



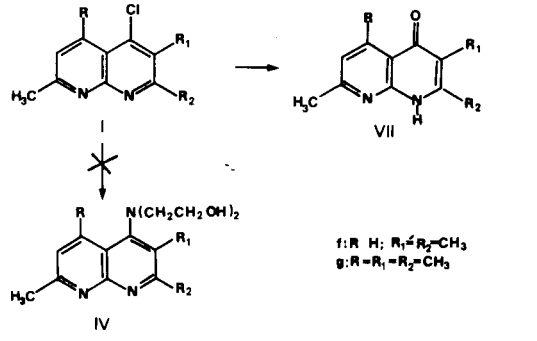
The chloronaphthyridines If and Ig [4], when treated with diethanolamine under various conditions (100-160° for several hours), gave in poor yields, 2,3,7-trimethyl- and 2,3,6,7-tetramethyl-1,8-naphthyridin-4-one VIIf,g [4] respectively, but not the corresponding diols IVf,g.

Scheme II



The bis(2-hydroxyethyl)amino derivatives IV, V and VI were then allowed to react with phosphoryl or thionyl chloride in order to obtain the corresponding mustards.

Scheme III



Scheme IV

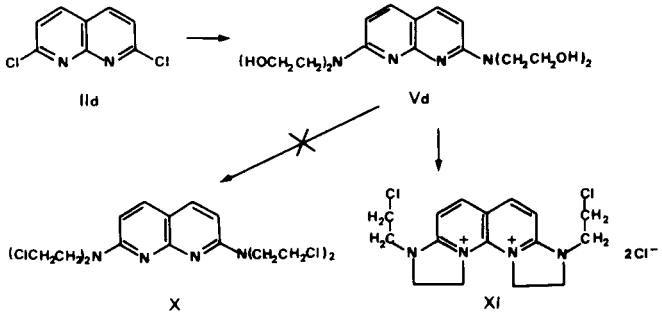
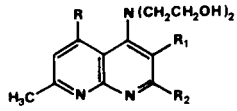
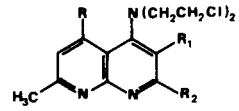


Table I



IV

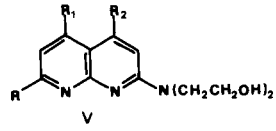


VIII

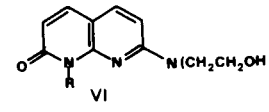
Compound No.	Yield %	Mp °C	Empirical formula	Elemental Analyses Calcd. % C	H	N	Found % C	H	N
IVa	63	150-155 dec [a]	$C_{14}H_{19}N_3O_2$	64.34	7.33	16.08	64.65	7.45	16.31
IVb	39	130-132 [a]	$C_{16}H_{23}N_3O_2$	66.41	8.01	14.52	66.73	8.07	14.48
IVc	52	174-176 [b]	$C_{14}H_{16}F_3N_3O_2$	53.33	5.11	13.33	53.46	5.32	13.20
IVd	79	177-178 [c]	$C_{19}H_{21}N_3O_2$	70.56	6.55	13.00	70.31	6.54	12.69
IVe	68	>320 [d]	$C_{19}H_{20}N_4O_4$	61.94	5.47	15.21	61.70	5.40	15.15
VIIIa	70	132-134 [e]	$C_{14}H_{17}Cl_2N_3$	56.38	5.74	14.09	56.68	5.75	13.88
VIIIb	71	87-89 [f]	$C_{16}H_{21}Cl_2N_3$	58.90	6.49	12.88	59.05	6.44	12.75
VIIIc	22	148-150 [g]	$C_{14}H_{14}Cl_2F_3N_3$	47.74	4.00	11.93	47.97	4.27	11.62
VIIId	73	144-145 [e]	$C_{19}H_{19}Cl_2N_3$	63.34	5.31	11.66	63.34	5.47	11.76
VIIIe	23	193-195 [e]	$C_{19}H_{18}Cl_2N_4O_2$	56.30	4.47	13.82	55.99	4.57	13.49

Recrystallization solvent: [a] THF, [b] water, [c] chloroform, [d] ethanol, [e] benzene, [f] petroleum ether 60-80°, [g] petroleum ether 100-140°.

Table II



V



VI

Compound No.	Yield %	Mp °C	Empirical formula	Elemental Analyses Calcd. % C	H	N	Found % C	H	N
Va	55	193-195 [a]	$C_{18}H_{20}N_4O_2$	66.65	6.22	17.27	66.30	6.10	17.05
Vb	88	204-206 [a]	$C_{18}H_{19}N_3O_3$	66.44	5.89	12.92	66.76	5.61	12.99
Vc	73	112-114 [b]	$C_{14}H_{19}N_3O_2$	64.34	7.33	16.08	64.65	7.39	15.73
Vd	81	175-177 [a]	$C_{16}H_{24}N_4O_4 \cdot H_2O$	54.22	7.40	15.81	54.48	7.14	15.68
VIa	51	190-192 [c]	$C_{12}H_{15}N_3O_3$	57.82	6.07	16.86	57.96	6.06	17.03
VIb	81	132-134 [d]	$C_{13}H_{17}N_3O_3$	59.30	6.51	15.96	59.25	6.58	15.78

Recrystallization solvent: [a] water, [b] benzene, [c] ethanol, [d] dioxane.

Compounds IVa-e were converted into the desired bis-(2-chloroethyl)aminonaphthyridines VIII (Table I). In contrast, the diols Va-c gave, instead of the corresponding compounds IX, only unidentified products.

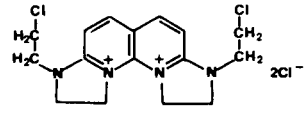
When the hydroxy derivatives Vd and VI were treated with thionyl or phosphoryl chloride, instead of the expected compounds X and XII, the quaternary salts XI and XIII were isolated.

These results are in accord with the behaviour observed with quinoline derivatives [10,11].

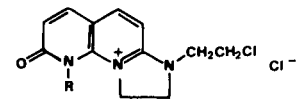
Attempts to obtain bis(2-chloroethyl)aminonaphthyridines by reaction of compounds I, II and III with bis(2-chloroethyl)amine hydrochloride in presence of triethylamine failed.

Table III

^{1}H NMR Spectral Data of XI and XIII
(δ values; observed chemical shifts, temperature 25°)



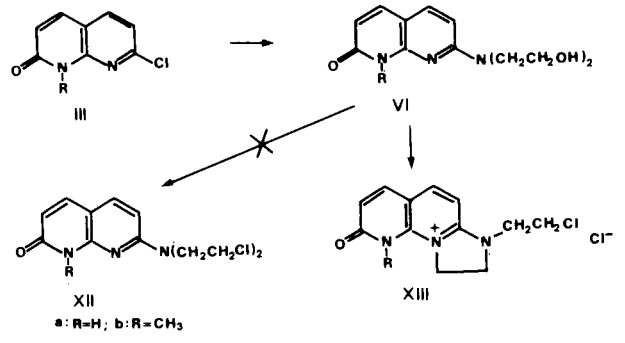
XI



XIII

Compound No.	$^+NCH_2$	CH_2N	NCH_2CH_2Cl
XI	5.25 (4H)	4.26 (4H)	4.12 (8H)
XIIIa	4.71 (2H)	4.27 (2H)	4.02 (4H)
XIIIb	5.27 (2H)	4.10 (2H)	3.87 (4H)

Scheme V



The assigned structures were fully confirmed by elemental analyses, ir and nmr spectral data.

The nmr spectra of IV, V and VIII show a sharp multiplet in the range δ 3.65-3.80 (8H, 16H) due to the side chain. By contrast the nmr spectra of the quaternary salts XI and XIII exhibit three characteristic signals, which appeared as two triplets and as sharp multiplet due to ^{+}N-CH_2-CH_2-N and to the side chain respectively (Table III).

The antitumor activity of the intermediate IV, V and VI, the target compounds VIII and the derivatives XI and XIII was measured in lymphocytic leukemia P-388.

All the tested compounds are devoid of antitumor properties [12].

EXPERIMENTAL

All compounds were routinely checked for their structure by ir and ^1H nmr spectroscopy. Melting points were determined on a Köfler hot-stage and are uncorrected. The ir spectra were measured with a Perkin-Elmer Infracord Model 137. The ^1H nmr spectra of compounds IV, V (DMSO-d_6) and VIII (deuteriochloroform) were determined on a Jeol C-60 HL spectrometer; the ^1H nmr spectra of compounds XI and XIII (DMSO-d_6) were determined on Varian CFT-20 spectrometer working in FT mode at 80 MHz. TMS was used as internal standard.

General Procedure for the Preparation of Substituted bis(2-Hydroxyethyl)amino-1,8-naphthyridines IV, V, VI.

A mixture of 5.0 mmoles of I, II and III, and 12.0 mmoles of bis(2-hydroxyethyl)amine was heated at 120° for 20 hours, then cooled, and diluted with water. The products were separated by one of the following methods and then purified by crystallization (Table I and II).

A) The precipitated diols IVc-e, Vb,d were collected and washed with water. B) The mixture was extracted with chloroform. The combined extracts were washed with water, dried over magnesium sulfate and evaporated *in vacuo* to obtain IVa,b, Va,c. C) The mixture was extracted with chloroform continuously for 24 hours. The organic solution was evaporated to dryness *in vacuo* to give VIa,b.

General Procedure for the Preparation of Substituted-4-bis(2-Chloroethyl)amino-1,8-naphthyridines VIII.

The compounds IV (0.5 g) were added to ice cooled phosphoryl chloride (10 ml) and the mixture was heated at 80° for 12 hours. The cooled solution was slowly poured into a stirred mixture of concentrated ammonium hydroxide (100 ml), chloroform (100 ml) and ice. Stirring was continued for 5-10 minutes and the organic layer was then separated, washed with water, dried over magnesium sulfate and evaporated to dryness *in vacuo* to obtain the bis(2-chloroethyl)amino-1,8-naphthyridines VIII (Table I).

3,8-Di(2-chloroethyl)-2,3,9,10-tetrahydro-1*H*,8*H*-imidazo[1,2-*a*]imidazo-[2,1-*h*][1,8]naphthyridin-11,12-diium Dichloride XI.

Compound Vd (2.0 g) was added to ice cooled phosphoryl chloride (15 ml). The mixture was heated at 80° for 15 hours, concentrated *in vacuo* to a small volume and then absolute ethanol was added. The solution was diluted with diethyl ether until no more solid was precipitated. The solution was decanted and the residue dissolved in hot absolute ethanol. After standing overnight at 0° compound XI crystallized, 1.55 g (63%), mp 240-242°.

Anal. Calcd. for $C_{16}H_{20}Cl_4N_4 \cdot H_2O$: C, 44.88; H, 5.18; N, 13.08; Cl, 33.12. Found: C, 45.20; H, 5.27; N, 13.01; Cl, 32.80.

3-(2-Chloroethyl)-2,3,8,9-tetrahydro-8-oxo-1*H*-imidazo[1,2-*a*][1,8]naphthyridin-10-ium Chloride XIIIa.

A solution of 0.30 g of 7-[bis(2-hydroxyethyl)amino]-1,8-naphthyridin-2-one VIa was refluxed with thionyl chloride for 5 minutes. The separated solid was collected by filtration and crystallized from DMF to give 0.25 g (71%) of XIIIa, mp 275-277° dec.

Anal. Calcd. for $C_{12}H_{13}Cl_2N_3O$: C, 50.36; H, 4.58; N, 14.68; Cl, 24.78. Found: C, 50.39; H, 4.53; N, 14.34; Cl, 24.50.

3-(2-Chloroethyl)-9-methyl-2,3,8,9-tetrahydro-8-oxo-1*H*-imidazo[1,2-*a*]-[1,8]naphthyridin-10-ium Chloride XIIIb.

To 10 ml of thionyl chloride was added with cooling 2.0 g of 7-[bis(2-hydroxyethyl)amino]-1-methyl-1,8-naphthyridin-2-one (VIb). The solution was kept at room temperature for 4 days and excess of thionyl chloride removed *in vacuo*. The residue was decomposed with a small amount of absolute ethanol and the solvent was evaporated to dryness *in vacuo*. The residue was then crystallized from DMF to give 1.56 g (68%) of XIIIb, mp 205-210° dec.

Anal. Calcd. for $C_{13}H_{15}Cl_2N_3O \cdot H_2O$: C, 49.07; H, 5.38; N, 13.21; Cl, 22.28. Found: C, 49.17; H, 5.24; N, 13.02; Cl, 22.02.

Acknowledgement.

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[12] The pharmacological screening was carried out in the Institute for Pharmacological Research "Mario Negri", Milan.