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SYNTHESIS AND PRELIMINARY ALKYLATING ACTIVITIES OF CERTAIN NEW 1,4-DIHYDROPYRIDINES, PYRIDINIUM SALTS AND 2,7-DIAZABICYCLO [4.1.0] HEPT-3-ENES*

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ABSTRACT: *3-Substituted-1-{2-chloro- or [2-bis(2-chloroethyl)amino]}ethyl-1,4-dihydropyridines 3 and 6 were prepared by reduction of the corresponding pyridinium chlorides 2 and 5 with sodium dithionite in alkaline medium. The 1,3-dipolar cycloaddition of either phenylsulphonyl or p-tolylsulphonyl azides to the 1,4-dihydropyridines 3 afforded the corresponding 2,7-diazabicyclo[4.1.0]hept-3-enes 7. The alkylating activities of twelve new compounds (2b-d; 3b,c; 5a-c and 7a-d) were determined kinetically in comparison to chlorambucil as a reference drug. Compounds 5a-c showed higher activities than chlorambucil while 2c,d and 7a,b showed lower activities. The dihydropyridines (the CDS) 3b,c were inactive as alkylating agents as expected.*

INTRODUCTION

Alkylating agents have been widely explored and used in cancer research and treatment,e.g. Chlorambucil[1] and Melphalan[2]. Very few examples show activity against primary brain tumors,e.g.1-(2-chloroethyl)-1-nitrosourea[3,4]. The major problem associated with the treatment of tumors of CNS is the poor delivery of the drug to the tumor site. The use of the brain-specific dihydropyridine ⇆ pyridinium salt redox chemical delivery system (CDS)[5-8] provides an important flexible method for site-specific and sustained delivery of drugs to the brain. Bodor,who designed the system, applied it to deliver certain antineoplastic agents to the brain by administering their corresponding CDS[9-12].

Two main approaches were followed in the design of the title compounds to accomplish the objective of optimising their therapeutic index. The first approach was to increase organ specificity[3,7,8,10] which could be represented by compounds 2 and 5. These compounds being quaternary alkylating agents might be tested for skin neoplasms and advanced cases of psoriasis,since they are exp^Xxted to be localized and non or very poorly absorbed to cause any systemic toxicity. On the other hand,the corresponding 1,4-dihydropyridines 3 and 6 could be considered as CDS for delivery of the quaternaries specifically to the brain. Compounds 3 and 6 being lipid soluble might penetrate the deep sites,e.g. brain, testicles, ovaries...etc, where they are expected to be oxidized to the corresponding quaternaries 2 and 5 which would be "locked-in" there.

The second approach was to manipulate the electron density whether on the ethyleneamino nitrogen or on the ß-carbon atom to study the effect of this change on the alkylating activities of the test compounds. Quaternaries 2 and 5, their corresponding dihydros 3 and 6 and the diazabicyclo derivatives 7 are representatives of this approach. Some azabicyclo compounds were reported to possess antineoplastic activities[13].

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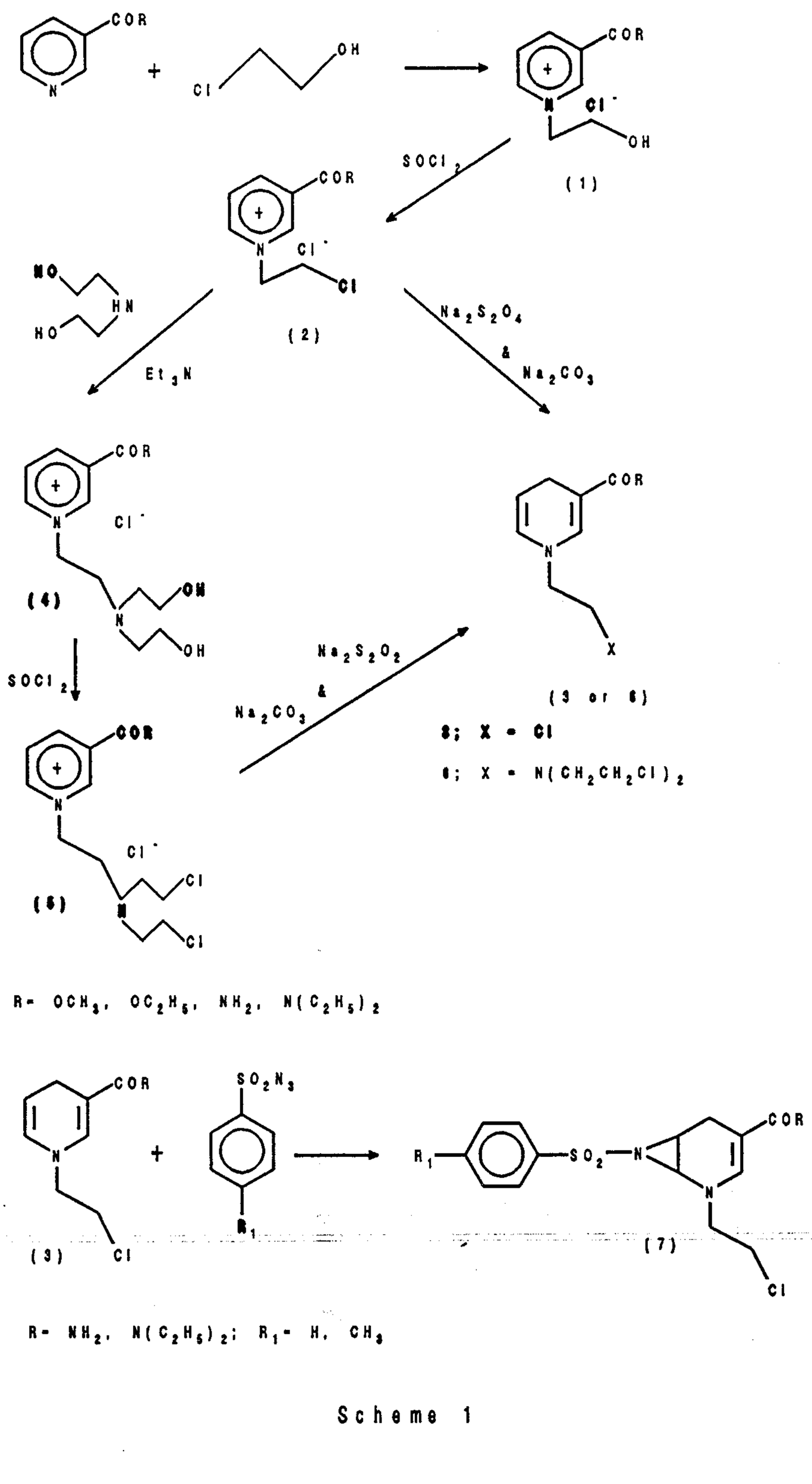

COR
OH
Cl
(1)
SOCl2
(2)
Et3N
Na2S2O4
&
Na2CO3
HO
HN
HO
(4)
SOCl2
(8; X = Cl
6; X = N(CH2CH2Cl)2
(3 or 6)
(5)
R= OCH3, OC2H5, NH2, N(C2H5)2
SO2N3
R1
(3)
(7)
R= NH2, N(C2H5)2; R1= H, CH3

Scheme 1

EXPERIMENTAL

A) Synthesis:

Melting points were determined in open glass capillaries and were uncorrected. UV spectra were recorded on Pye Unicam SP-1750 UV/VIS spectrophotometer. IR spectra (in KBr or Nujol) were recorded on a Pye Unicam SP-1000 IR spectrophotometer. ^{1}H-NMR spectra were recorded on a 90 MHz EM-390 spectrometer in DMSO or D_2O and TMS as internal standard. Chemical shift (δ) are given in ppm and coupling constants (J) are given in Hz. Elemental analyses for C,H and N were performed at the unit of microanalysis, Cairo University. Analytical TLC were performed on precoated TLC plates of silica gel 60 F-254 of layer thickness 0.25 mm (Merck) and using chromatography grade solvents.

3-(Diethylcarbamoyl)-1-(2-hydroxyethyl) pyridinium chloride (1b):

To a solution of Nikethamide (8.9 g, 0.05 mol) in methanol (25 ml) was slowly added a solution of ethylene chlorohydrin (4.0 g, 0.05 mol) in methanol (10 ml). The reaction mixture was refluxed for 20-25 h,the solvent was removed under reduced pressure and the residue was triturated with three portions of dry ether (15 ml each). A granular hygroscopic product was obtained which was dried under reduced pressure over anhydrous sodium sulphate. The yield and physical data are given in Table I.
3-(Methoxycarbonyl)-1-(hydroxyethyl)pyridinium chloride 1c and 3-(ethoxycarbonyl)-1- (2-hyroxy-ethyl)pyridinium chloride 1d (Table I) were prepared as described above by using either methyl nicotinate or ethyl nicotinate. Compounds 1b-d were used immediately for the next reactions without further purification.

3-(Diethylcarbamoyl)-1-(2-chloroethyl) pyridinium chloride (2b):

To an ice cooled suspension of 1b (2.6 g, 0.01 mol) in chloroform (50 ml) was dropped, over 10 minutes, a solution of thionyl chloride (1 ml) in chloroform (10 ml) while stirring. The reaction mixture was then refluxed for 1 h and the solvent was removed under reduced pressure. The product was successively triturated with dry ether and absolute ethanol, filtered, dried with suction and crystallized. The yields and physical data are listed in Table II.
3-(Methoxycarbonyl)-1-(2-chloroethyl)pyridinium chloride 2c and 3-(ethoxycarbonyl)-1-(2-chloroethyl)pyridinium chloride 2d were synthesized following the same procedure of preparation of 2b using the corresponding quaternary alcohols 1c and 1d.

3-Carbamoyl-1-[2-bis(2-hydroxyethyl)amino] ethylpyridinium chloride 4a (Table I):

To a stirred solution of 2a (2.2 g,0.01 mol) in methanol (25 ml), triethylamine (1.4 ml) was added followed by dropping a solution of diethanolamine (1.05 g,0.01 mol) in methanol (10 ml) over 10 minutes. The reaction mixture was refluxed for 4 hs. The solvent was evaporated under reduced pressure and the viscous residue was triturated with dry ether. The granular precipitate obtained was filtered, washed with ether and crystallized from methanol.

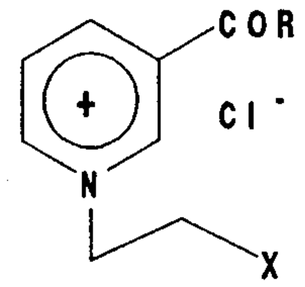
3-(Diethylcarbamoyl)-1-[2-bis(2-hydroxyethyl) amino]ethyl- pyridinium chloride 4b and 3-(ethoxycarbonyl)-1-[2-bis(2-hydroxyethyl) amino]ethylpyridinium chloride 4c (Table I):

were prepared following the same procedure for the preparation of 4a using 2b and 2d as the starting intermediates respectively.

3-Substituted-1-[2-bis(2-chloroethyl)amino] ethylpyridinium chlorides 5a-c (Table II):

To an ice cooled and stirred suspension of the appropriate alcohol 4a-c (0.01 mol) in chloroform (50 ml), a solution of thionyl chloride (2 ml) in chloroform (10 ml) was dropped over 10 minutes. The reaction mixture was thereafter refluxed for 1 h. The solvent was removed under reduced pressure and the product was crystallized from the proper solvent.

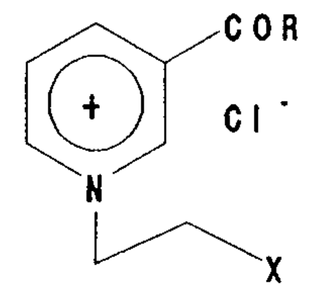
Table I: 3-Substituted-1-{2-hydroxy-or[2-bis(2-hydroxyethyl) amino]} ethylpyridinium chlorides I_{b-d} and 4_{a-c}.



Compd.	X	R	Yield (%)	mp* (°C)	Molecular formula	Microanalyses calcd./found			IR (cm^{-1})
						%C	%H	%N	
I_b	OH	$N(C_2H_5)_2$	45	98-100	$C_{12}H_{19}ClN_2O_2$	55.70 55.50	7.35 7.20	10.87 10.60	3400-3200(OH),1665(C=O)
I_C	OH	OCH_3	29	105-107	$C_9H_{12}ClNO_3$	49.65 49.06	5.51 5.61	6.43 6.90	3350-3220(OH),1720(C=O)
I_d	OH	OC_2H_5	32	115-118	$C_{10}H_{14}ClNO_3$	51.83 51.60	6.04 6.20	6.04 5.60	3350-3220(OH),1730(C=O)
4_a	$N(ch_2CH_2OH)_2$	NH_2	63	160-162	$C_{12}H_{20}ClN_3O_3$	49.74 50.00	6.90 7.00	14.50 13.90	3500-3200(NH_2,OH),1680(C=O)
4_b	$N(ch_2CH_2OH)_2$	$N(C_2H_5)_2$	44	172-174	$C_{16}H_{28}ClN_3O_3$	55.57 55.60	8.10 8.00		3400-3200(OH),1665(C=O)
4_c	$N(ch_2CH_2OH)_2$	OC_2H_5	70	180-181	$C_{14}H_{23}ClN_2O_4$	52.74 52.90	7.22 7.00	8.79 8.90	3400-3200(OH),1730(C=O)

* Compounds $4^{a,}{}_b$ were recrystallized from mathanol, while compound 4_c from ethanol.

Table II: 3-substituted-1-{2-chloro- or [2-bis(2-chloroethyl) amino]} ethylpyridinium chlorides 2_{b-d} and 5_{a-c}



Compd.	X	R	Yield (%)	mp. (°C)	Molecular formula	Microanalyses calcd./found			λ_{max}	IR	^{1}H-NMR δ (ppm)				
						%C	%H	%N	(nm)	(cm^{-1})	C_2-H	C_6-H;C_4-H	C_5-H	$^+NCH_2$; CH_2Cl	R
2_b	Cl	$N(C_2H_5)_2$	40	229-230	$C_{12}H_{18}Cl_2N_2O$	51.98 52.00	6.49 6.50	10.10 9.70	266	1665(C=O)	----	----	----	----	----
2_c	Cl	OCH_3	35	202-203	$C_9H_{11}Cl_2NO_2$	45.76 45.90	4.66 4.90	5.32 5.60	263	1720(C=O)	----	----	----	----	----
2_d	Cl	OC_2H_5	35	195-197	$C_{10}H_{13}Cl_2NO_2$	48.00 47.80	5.20 5.30	5.60 5.90	263	1730(C=O)	9.76 (s,1H)	9.41(d,1H, $J_{6,5}$=6Hz); 9.08(d,1H, $J_{4,5}$=8Hz)	8.38(dd, 1H,$J_{5,6}$= 6Hz,$J_{5,4}$= 8Hz)	5.45(bs, 2H);3.33 (bs,2H, CH_2Cl)	4.46(q,2H, J=8Hz,OCH_2), 1.4(t,3H, J=8Hz,CH_3)
5_a	$N(CH_2CH_2Cl)_2$	NH_2	70	222-223	$C_{12}H_{18}Cl_3N_3O$	44.10 44.50	5.51 5.20	12.86 12.37	262	3500-3300 (NH_2),1680 (C=O)	9.06 (s,1H)	8.86-8.60 (m,2H, $J_{6,5}$=6Hz, $J_{4,5}$=9Hz) (C_6-H&C_4-H)	8.1-7.86 (m,1H, $J_{5,6}$=6Hz, $J_{4,5}$=9Hz)	4.66-4.33 (m,10H; NCH_2,CH_2N, $2CH_2Cl$ and H_2O),4.03-3.63(m,4H, $N(CH_2)_2$	$CONH_2$ exchanged
5_b	$N(CH_2CH_2Cl)_2$	$N(C_2H_5)_2$	50	120-122	$C_{16}H_{26}Cl_3N_3O$	50.19 50.20	6.79 7.00		266	1665(C=O)	----	----	----	----	----
5_c	$N(CH_2CH_2Cl)_2$	OC_2H_5	82	188-189	$C_{14}H_{21}Cl_3N_2O_2$	47.25 47.80	5.90 5.80	7.87 8.00	265	1730(C=O)	----	----	----	----	----

* Compounds $2_{b,d}$ were recrystallized from mixture of ethanol and acetone (1:1), 2_c from methanol and 5_{a-c} from ethanol.

3-Substituted-1-{2-chloro or [2-bis(2-chloroethyl)amino]ethyl-1,4-dihydropyridines 3b-d and 6a (Table III):

To a solution of the appropriate quaternary compound 2b-d or 5a (0.01 mol) in degassed water (100 ml), sodium carbonate (6.5 g.0.06 mol) was added. The mixture was stirred in ice bath and sodium dithionite (7.1 g,0.04 mol) was added portion-wise over 10 minutes. The reaction mixture was stirred for further 2h under nitrogen. The bright yellowish mixture was extracted with three portions (25 ml each) of methylene chloride. The extract was washed with water,dried with anhydrous sodium sulfate and distilled under reduced pressure at 25° . The yellowish product obtained was dried over P_2O_5 in a vacuum desiccator and chromatographed on silica gel plates,eluted with degassed chloroform-methanol (9:1) mixture and visualized by UV where a single spot shows up for each compound. These dihydro compounds were kept dry,under nitrogen and in the freezer.

4-Substituted-2-(2-chloroethyl)7-phenyl-(or p-tolyl) sulfonyl-2,7-diazabicyclo[4.1.0] hept-3-enes 7a-d (Table IV)

To an ice cold stirred solution of the appropriate freshly prepared 1,4-dihydropyridine 3a or 3b (0.01 mol) in methylene chloride (100 ml), a solution of either phenylsulphonyl or p-tolylsulphonyl azide (0.01 mol) in methylene chloride (50 ml) was added and the mixture was kept stirring for 4 h. The solvent was evaporated on rotavapor and the yellowish solid product obtained was crystallized from ethyl acetate. Compounds 7c,d were directly chromatographed on silica gel plates,eluted with ethyl acetate and visualized by UV, where a single spot shows up for each compound.

B- Alkylating Kinetics: Evaluation of alkylating activities

Apparatus and reagents:

The Intensity of the purple colors produced in the test were measured on a Shimadzu UV 120-02 spectrophotometer. Methyl ethyl ketone (M&B) and acetone AR (Merck) were used as solvents. 4-(4-nitrobenzyl)pyridine (Aldrich) was freshly recrystallized from cyclohexane and used as 5% solution in methyl ethyl ketone. Triethylamine (Aldrich) was used as 17% solution in acetone. Chlorambucil was obtained by extraction from Leukeran [R] tablets (Wellcome) by acetone and was used as the reference drug.

Method:

To a solution of the appropriate alkylating agent (10 mg in 5 ml of methyl ethyl ketone), were added 4-(4-nitrobenzyl)pyridine reagent (5 ml) and water (1 ml). The mixture was then heated to either 55° or 79° in a water bath. From the reaction mixture 1.5 ml were pipetted at different time intervals (5,10,15,20,25 and 30 min), cooled for 1 minute in an ice bath and triethylamine reagent (1.5 ml) was then added and mixed. The intensity of the purple color formed was measured within 2 minutes at the appropriate wavelength against the reagent as blank. The results are shown in Table V.

RESULTS AND DISCUSSION

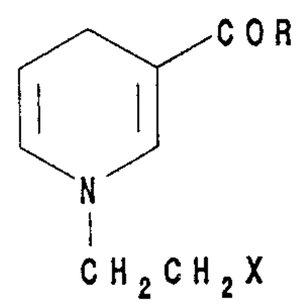
A- Chemistry:

3-Substituted-1-{2-chloro or [2-bis (2-chloroethyl)amino]}ethyl-1,4-dihydropyridines 3 and 6 were prepared as outlined in scheme 1 via reduction of the corresponding quaternary pyridinium chlorides 2 and 5 with sodium dithionite in alkaline medium in analogy to reported procedures[14,15].

4-Substituted-2-(2-chloroethyl)-7-phenyl-(or p-tolyl)sulfonyl-2,7-diazabicyclo[4.1.0]hept-3-enes (7) were synthesized via the conventional regioselective 1,3-dipolar cycloaddition reaction of phenyl-(or p-tolyl)sulfonyl azide to the 1,4-dihydropyridines 3 in methylene chloride at 25°C[16].

The structures of the quaternaries 2b-d and 5a-c (Table II) were confirmed by their elemental microanalysis data and their UV,IR and ^{1}H-NMR data. Compounds 1a (X=OH,R=NH_2) and 2a (X=Cl,R=NH_2) are known and their constants are in agreement with the reported[14,17]. In the NMR spectrum of 2d the group $N^+CH_2CH_2Cl$ does not show the usual A_2X_2 two triplet system or A_2B_2 multiplet but

Table III: 3-substituted-1-{2-cholro- or [2-bis(2-chloroethyl) amino]} ethyl -1,4-dihydropyridines 3_{b-d} and 6_a.



Compd.	R	X	Yield (%)	mp (°C)	λ max (nm)
3_b	$N(C_2H_5)_2$	Cl	40	liquid	348
3_c	OCH_3	Cl	45	85-86	366
3_d	OC_2H_5	Cl	51	38-40	360
6_a	NH_2	$N(CH_2CH_2Cl)_2$	*	liquid	354

* The yield was not determined.

rather two separate singlets, which reflects a very weak coupling between these two sets of methylene protons even though they have quite different chemical shifts (Table II), (c.f.Melphalan in DMSO-d_6 and in DCl.D_2O[18]).

Structures of the 1,4-dihydropyridines 3b-d and 6a (Table III) were established by their UV spectra which show absorption maxima at 348-366 nm characteristic for the 1,4-dihydropyridine derivatives in addition to their oxidation, whether with alcoholic silver nitrate or hydrogen peroxide to give their corresponding quaternary compounds 2b-d and 5a respectively[8,15,19-21]. Compound 3a (X=Cl,R=NH_2) is known and its physical data comply with that reported[14].

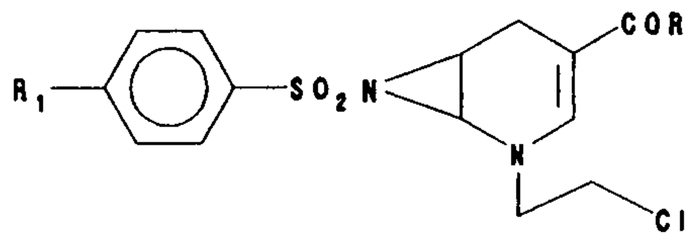
Structures of the diazabicyclo compounds 7a-d (Table IV) were ascertained by IR and ^{1}H-NMR spectra in addition to elemental microanalyses. ^{1}H-NMR spectra of 7a,b (Table IV) showed the absence of the A_2X_2 two triplets system of the chloroethyl group,which suggests the aziridinium chloride structure for compound 7. This was proved chemically by testing the presence of chloride ions by silver nitrate test in aqueous methanol solution.

Alkylating Kinetics:

To investigate the alkylating activities of the prepared compounds,the modified method of Koenigs et al.[22] reported by Epstein et al.[23] was used.

In the present investigation the authors tested first the hypothesis of equality of apparent molar absorptivities of two of the final compounds 2c,d and chlorambucil. They showed completely different apparent molar absorptivities e.g. 41727, 36111, 70204 respectively and their colored products showed absorption maxima at 560,550 and 560 nm respectively. Hence the authors tried to develop a quantitative general method which depends on temperature (55°C or 79°C) in ethyl methyl ketone, with large excess of the substrate to prevent interferences from traces of water or other nucleophilic reagents and in the same time assure the conditions of pseudo first order kinetics. Constant volumes were withdrawn from the reaction mixture at certain time intervals, cooled, alkalinized with triethylamine and diluted to constant volume with acetone. The color produced was measured at its specific wavelength of maximum absorption (Table V).

Table IV: 4-substituted-2-(2-chloroethyl)-7-phenyl-(or tolyl-) sulphonyl-2,7-dizabicyclo[4.1.0] hept-3-enes 7_{a-d}



Compd.	R	R_1	Yield (%)	mp. (°C)	Molecular formula	Microanalyses calcd./found			IR (cm^{-1})	^{1}H-NMR data (ppm)			
						%C	%H	%N		Aromatic protons	$CONH_2$,C_5-H	NCH_2CH_2Cl; C_1-H,C_6-H	C_5-H
7_a	NH_2	H	30	124-126	$C_{14}H_{16}ClN_3O_3S$	49.19 49.55	4.68 5.00	12.29 12.46	3400-3200 (NH_2),1680 (c=O),1665-1650(C_3=C_4), 1370(SO_2 asym.),1165 (SO_2 sym.)	7.90-7.53 (m,5H)	7.25-6.80 hump super-imposed with singlet at (7.16,3H). After addition of D_2O, the hump disappeared and sharp singlet (1H) appeared at 7.16	3.93-3.76 (m,4H); 3.20-3.03 (m,2H)	2.40-2.30 (m,2H)
7_b	NH_2	CH_3	35	117-119	$C_{15}H_{18}ClN_3O_3S$	50.63 50.72	5.06 5.33	11.81 11.73	3400-3200 (NH_2),1680 (C=O),1665-1650(C_3=C_4), 1370(SO_2 asym.),1165 (SO_2 sym.)	7.70-7.30 (dd,4H)	7.25-6.80 hump super-imposed with singlet at (7.16,3H). After addition of D_2O, the hump disappeared and sharp singlet (1H) appeared at 7.16	3.90-3.73 (m,4H); 3.16-3.00 (m,2H)	2.40-2.20 (m,5H; p-CH_3,C_5-H)
7_c	$N(C_2H_5)_2$	H	25	liquid	$C_{18}H_{24}ClN_3O_3S$	54.33 54.60	6.03 5.60		1670(C=O), 1665-1650 (C_3=C_4),1365 (SO_2 asym.), 1160(SO_2 sym)	----	----	----	----
7_d	$N(C_2H_5)_2$	CH_3	30	liquid	$C_{19}H_{26}ClN_3O_3S$	55.40 55.82	6.31 6.31	10.20 10.00	1670(C=O), 1665-1650 (C_3=C_4),1365 (SO_2 asym.), 1160(SO_2 sym)	----	----	----	----

* Compounds $7_{a,b}$ were recrystallized from ethyl acetone. the kinetics of interaction between alkylating agent and the 4-(4-nitrobenzyl)pyridine at constant

The apparent pseudo first order rate constant K_{app} was determined from the regression line obtained by least square method between ln of absorbances against time in minutes.

$$\ln A = a + b\,t$$

The slope of the line (b) represents the K_{app} in min^{-1}. Chlorambucil was used as reference drug to compare its activity under the same conditions with the activities of the test compounds. Table V shows the results obtained with twelve selected compounds.

As shown from the table, the 2-chloroethyl-pyridinium compounds 2c,d and the diazabicyclo compounds 7a,b showed activities which are slightly lower than that of chlorambucil. On the other hand, reaction of bis-(2-chloroethyl) aminoethylpyridinium derivatives 5a-c with the reagent at 79°C was too fast to be monitored. The reaction was completed within few minutes and the product then starts to decompose. Accordingly these compounds, 5a-c, were tested at lower temperature, 55°C which indicated much higher activities than chlorambucil. These compounds could be considered as good highly reactive alkylating agents. Compounds 2b and 7c,d were inactive even at 79°C.

Representatives of the dihydro compounds (3b,c) were tested for their alkylating activities and were found inactive even at 79°C. The observed inactivity of 3b,c contradicts with the data reported by Friedman for the closely similar dihydrocompounds [14].

Table V: Alkylating activities of the test compounds 2,3,5 & 7 in comparison to chlorambucil.

Test compd.	R	R_1	λ_{max} (nm)	Reaction temp. (°C)	Regression data			
					K_{app} $min^{-1}.10^2$	t½(min)	r	n
2_a	$N(C_2H_5)_2$	-	560	79	faint color	--	--	
2_c	OCH_3	-	560	79	4.08 ± 0.09	16.96	0.973	5
2_d	OC_2H_5	-	550	79	4.52 ± 0.11	15.31	0.983	6
3_b	$N(C_2H_5)_2$	-	-	79	no color	--	--	
3_c	OCH_3	-	-	79	no color	--	--	
5_a	NH_2	-	560	55	4.21 ± 0.15	16.42	0.962	6
5_b	$N(C_2H_5)_2$	-	562	55	6.52 ± 0.15	10.62	0.950	6
5_c	OC_2H_5	-	550	55	4.02 ± 0.21	17.02	0.943	5
7_a	NH_2	H	550	79	3.13 ± 0.22	22.14	0.991	6
7_b	NH_2	CH_3	556	79	3.68 ± 0.10	18.81	0.970	6
7_c	$N(C_2H_5)_2$	H	-	79	no color	--	--	
7_d	$N(C_2H_5)_2$	CH_3	-	79	no color	--		
Chlorambucil			-	55	no color	--		
Chlorambucil			560	79	7.74 ± 0.23	8.94	0.998	6

REFERENCES

1- J.L.Everett, J.J.Roberts and W.C.J.Ross, J. Chem. Soc., 2286 (1953).
2- F.Bergel and J.A.Stock, J. Chem. Soc., 2409 (1954).
3- V.A.Levin and C.B.Wilson, Cancer Treat. Rep., 60, 719 (1976).
4- D.I.Ahmann, ibid, 60, 747 (1976).
5- N.Bodor N. and H.H.Farag, J. Med. Chem., 26, 528 (1983).
6- N.Bodor and H.H.Farag, J. Pharm. Sci., 73, 385 (1984).
7- A.A.Sinkula and S.H.Yalkowsky, J. Pharm. Sci., 64, 181 (1975).
8- N.Bodor and A.M.Abdel-Alim A.M., J. Pharm. Sci., 74.241 (1985).
9- N.Bodor N.and M.E.Brewster, Eur. J. Med. Chem., 18, 235 (1983).
10- K.S.Raghavan, E.Shek, and N.Bodor, Anticancer Drug Design, 2, 25 (1987).
11- N.Bodor, N.Vankatraghavan, D.Winwood,

K.Estes and M.E.Brewester, Int. J. Pharm., 53, 193-208 (1989).
12- K.Raghavan, T.Loftsson and N.Bodor, Pharm. Res., 9, 743-749 (1992).
13- R.W.Brockman, S.C.Shaddix, M.Williams and R.F.Struck, Cancer treat. Rep., 60, 1307 (1976).
14- O.M.Friedman, K.Pollak and E.Khedouri, J. Med. Chem., 6, 462 (1963).
15- G.Blankenhorn and E.G.Moore, J. Am. Chem. Soc., 102, 1092 (1980).
16- H.H.Farag, A.M.Abdel-Alim, H.Y.Hassan, H.A.Hemaiat-Alla, R.A.Abdel-Aal and A.M.Badr, Bull. Pharm. Sci. Assiut Univ., 9, 105 (1986).
17- H.G.Windmueller , C.J.Ackerman , H.Bakerman and O.Mickelson, J. Biol. Chem., 234, 889 (1959).
18- L.V.Feyns, "Analytical Profiles of Drug Substances", K. Florey ed., Academic Press, Inc., London (1984), 13, p.276.
19- D.J.Norris and R.Stewart, Can. J. Chem., 55, 1687 (1977)
20- U.Eisner and J.Kuthan, Chem. Rev., 72, 1-42 (1972).
21- A.C.Lovesey, J. Med. Chem., 13, 693 (1970).
22- E.Koenigs, K.Kohler and K.Blindow, Ber. 58B, 933 (1925).
23- J.Epstein, R.W.Rosenthal and R.J.Ess, Anal. Chem., 27, 1435 (1955).

تخليق بعض مشتقات ١،٤-ثنائى الهيدروبيريدين وأملاح البيريدينيم و٢،٧-ثنائى ازابيسكلو هيبت-٣-اين والفحص المبدئى للفاعلية الالكيلية لهذه المركبات

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يتناول البحث تخليق بعض مركبات أملاح البيريدينيم و٢،٧ ثنائى ازابيسيكلو (*4.1.0*) هيبت-٣-اين والتى صممت على أساس توقع فاعلية استعمالها فى التوصيل التفاضلى لأملاح البيريدنيم المكافىء الى المخ بتركيزات كبيرة. وتم عمل الفحص المبدئى للفاعلية البيولوجية والتى اثبتت صحة التصميم وتم مناقشة اسباب الفاعلية من عدمها لبعض هذه المركبات.

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