SYNTHESIS AND RADIOPROTECTANT ACTIVITY OF N,N'DIPIPERIDINOALKANE HYDROCHLORIDES

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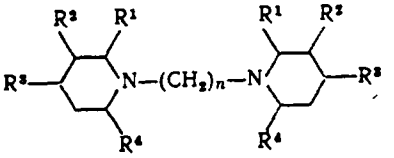
According to the literature, N,N'-dipiperidinoalkanes display diverse biological activity. 1,2-Dipiperidinoethane has received most attention, having been examined for bradycardiac, antihistamine, hypotensive, and synaptolytic effects [5, 12], neurotoxicity [9, 10], and antileukemic activity [8]. 1,6-Dipiperidinohexane, 1,5-di-(2,6-dimethylpiperidino)pentane, and 1,6-di-(2,6-dimethylpiperidyl)hexane have been examined as possible hypotensive agents [1, 11]. There have been no reports of the radioprotectant activity of these or similar compounds.

In a search for novel radioprotectants, and in order to study structure-activity relationships, we have now synthesized and determined the toxicity and radioprotectant activity of some N,N'-dipiperidinoalkane dihydrochlorides (I-XII).



I—XII

Compounds (I), (II), and (V) are obtained by condensing the appropriate α, w-dibromoalkanes with piperidine [4, 12], and (III), (IV), and (VI-XII) (Table 1) by reducing the appropriate dipyridinium salts with hydrogen in the presence of Adams' catalyst [6, 7]. In order to obtain the dihydrochlorides of the N,N'-dipiperidinoalkanes, the dichlorides of the dipyridinium salts were reduced, thus avoding isolation of the dipiperidinoalkane free bases. Since it was found impossible to obtain dipyridiniopropane dichlorides by condensation if 2,6- and 2,4-lutidines with dichloropropane, the corresponding dibromides were obtained, these being reduced to the dipiperidinoalkanes, which were then converted into their dihydrochlorides. The principal characteristics of the compounds obtained are given in Table 1. Compounds (VI-XII) have not been described in the literature.

EXPERIMENTAL CHEMICAL PART

Melting points were determined on a Boetius hot plate.

1,3-Di-(2-methylpiperidino)propane Dihydrochloride (VI). A mixture of 1.7 g of 1,3-dichloropropane and 4.2 g of α-picoline in 5 ml of ethanol was heated under reflux at the temperature of a glycerine bath (150-160°C) for 40 h, then excess base was removed on the water bath under reduced pressure. The solid was washed three times with dry ether, and dried in vacuo. The 1,3-di(2-methylpyridinio)propane dichloride thus obtained (4.7 g) was dissolved in 20 ml of glacial acetic acid, 0.2 g of PtO_2 added, and hydrogenation carried out at room temperature and atmospheric pressure until uptake of hydrogen ceased. The mixture was then heated to dissolve the hydrogenation which had partially separated, and the catalyst filtered off. The filtrate was evaporated under reduced pressure to dryness, and the residue crystallized from absolute ethanol to give colorless crystals.

1,4-Dipiperidinobutane dihydrochlroride (III) and 1,5-dipiperidinopentane dihydrochloride (IV) were obtained as for (VI), but the reduction was carried out in absolute ethanol. 1,3-Di-(3-methylpiperidino)propane dihydrochloride (VIII), 1,4-di-(2-methylpiperidino)butane dihydrochloride (IX), and 1,4-di-(3-methylpiperidino)butane dihydrochloride (X) were obtained

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TABLE 1. Melting Points, Yields, and Elemental Analyses of N,N' Dipiperidinoalkane Dihydrochlorides

Compound	n	R¹	R²	R³	R⁴	mp, °C	Yield,** %	Found, %			Empirical formula	Calculated, %		
								C	H	N		C	H	N
I	2	H	H	H	H	300—2	67.5	53.66	9.75	10.61	$C_{12}H_{26}Cl_2N_2$	53.53	9.73	10.40
II	3	H	H	H	H	262—4	74	55.14	10.13	10.00	$C_{13}H_{28}Cl_2N_2$	55.12	9.96	9.89
III	4	H	H	H	H	228—30	55	56.24	10.35	9.55	$C_{14}H_{30}Cl_2N_2$	56.56	10.17	9.42
IV	5	H	H	H	H	253—4	61.5	57.94	10.35	8.82	$C_{15}H_{32}Cl_2N_2$	57.87	10.36	9.00
V	6	H	H	H	H	260—2	75	59.18	10.30	8.55	$C_{16}H_{34}Cl_2N_2$	59.06	10.53	8.61
VI	3	Me	H	H	H	270—2	53	57.50	10.58	8.81	$C_{15}H_{32}Cl_2N_2$	57.87	10.36	9.00
VII	3	H	Me	H	H	262—4	80	57.58	10.32	9.16	$C_{15}H_{32}Cl_2N_2$	57.87	10.36	9.00
VIII	3	H	H	Me	H	255—8	83	57.88	10.49	8.78	$C_{15}H_{32}Cl_2N_2$	57.87	10.36	9.00
IX	4	Me	H	H	H	275—7	50	59.22	10.08	8.92	$C_{16}H_{34}Cl_2N_2$	59.06	10.53	8.61
X	4	H	CH_3	H	H	260—2	58	59.40	10.16	8.73	$C_{16}H_{34}Cl_2N_2$	59.06	10.53	8.61
XI	3	Me	H	H	Me	279—81	79	59.80	10.69	8.93	$C_{17}H_{36}Cl_2N_2$	60.18	10.69	8.26
XII	3	Me	H	Me	H	259—61	80	60.26	10.39	8.20	$C_{17}H_{36}Cl_2N_2$	60.18	10.69	8.26

*Solvents for crystallization: (I) and (II) 96% ethanol, (III-XI) absolute ethanol, (XII) glacial acetic acid.
**Yields calculated on the dihaloalkane starting material.

as for (VI). They were all colorless crystalline solids which were nonhygroscopic, melted without decomposition, and were readily soluble in water and alcohol but insoluble in ether, benzene, and chloroform.

1,3-Di-(2,6-dimethylpiperidino)propane Dihydrochloride (XI). A mixture of 1.93 g of 1,3-dibromopropane and 9.63 g of 2,6-lutidine in 25 ml of absolute ethanol was boiled on a glycerine bath under reflux at 150°C for 30 h. The mixture was then evaporated to dryness in vacuo on a boiling water bath. The residue was washed with dry ether and dried in vacuo. The 1,3-di-(2,6-dimethyl-pyridinio)propane dibromide thus obtained (4.9 g) was dissolved in 20 ml of glacial acetic acid and hydrogenated over 0.2 g of PtO_2 as described for (VI). The residue after removal of the acetic acid was dissolved in the minimum amount of water, saturated with solid KOH, and the free base which separated was extracted with ether. The ether extract was dried over $CaCl_2$, filtered, and converted into the dihydrochloride by adding a saturated solution of HCl in dry ether. The solid was filtered off and dried in a vacuum desiccator over P_2O_5, followed by crystallization from absolute ethanol. The colorless crystals were readily soluble in water.

1,3-Di-(2,4-dimethylpiperidino)propane dihydrochloride (XII) was obtained as for (XI). The colorless crystals (from glacial acetic acid) were readily soluble in water.

1,2-Dipiperidinoethane dihydrochloride (I), 1,3-dipiperidinopropane dihydrochloride (II), and 1,6-dipiperidinohexane dihydrochloride (V) were obtained as described in [4].

EXPERIMENTAL BIOLOGICAL PART

Toxicities and radioprotectant activity were assessed in 3-month old mice of strains BALB and CBA. The compounds were administered intraperitoneally or orally as the aqueous solutions of pH 6.0-7.0, in a volume of 0.2 ml per 20 g body weight.

Toxicities were determined by the reaction of mice to administration of the compounds, and deaths over a period of seven days. The data were subjected to probit analysis.

Antiirradiation activity was assessed by survival to 30 days. The mice were irradiated with the minimum absolute lethal dose of gamma-rays from ^{137}Cs in the "Igur" apparatus (dose 209 mCi/kg, dose rate 0.5 mA/kg. The compounds were administered in amounts equal to $^1/_2$ the LD_{16}, from 15 to 180 min prior to irradiation. In some cases, other doses were also used.

The test results are given in Table 2.

The toxicities of the compounds depended on the number of carbon atoms in the aliphatic chain and the substituents in the heterocycle.

Unsubstituted N,N'-dipiperidinoalkanes with form three to five carbon atoms in the aliphatic chain displayed high antiirradiation activity which was maintained over an extended period; compounds (III) and (IV), in a dose of half the LD_{16} 30 to 120 min prior to irradiation, protected up to 90% of the mice, the effect still being pronounced after 3 h (in the

TABLE 2. Radioprotectant Activity of N,N'-Dipiperidinoalkanes

Compound	Toxic dose, mg/kg		Mode of administration	Dose given, mg/kg	Time of administration before irradiation, min	Survival, %
	LD_{16}	LD_{50}				
I	282	305	i/p	134,6	15	15
					30	44
			p/o	269	45	5
II	470	728	i/p	235	30	70
				283	30	63
					60	35
					120	5
			p/o	567	30	5
					60	15
					120	10
III	515	597	i/p	178,4	15	75
					30	50
				208	15	89
					30	35
					60	45
			p/o	297	30	0
					60	5
IV	295	394	i/p	93,4	15	25
					30	50
				218	15	69, 60
					30	90, 85
					60	70, 90
					120	60
			p/o	467	45	25, 90
					90	45
V	123	130	i/p	65	15	0
					30	0
VI	228	250,4	i/p	125,3	15	20
					30	21
					60	15
			p/o	313,4	30	0
					60	0
VII	295	309	i/p	156,7	30	35
					60	5
				172,3	15	0
					30	10
			p/o	313,4	30	0
					60	5
VIII	223	255,4	i/p	112,8	15	15
					30	10, 20
					60	5
			p/o	225	30	0
IX	296	306,5	i/p	148,7	15	45
					30	0
			p/o	323,4	30	0
					60	0
X	327	344	i/p	161,7	15	0, 0
					20	0, 0
					30	0, 0
			p/o	323,4	30	0
					60	0
XI	225,5	309	i/p	112,7	15	20
					30	0
			p/o	239	30	17
XII	225	269,5	i/p	119,5	15	0
					30	5
			p/o	239	30	0

Note. i/p = intraperitoneal, p/o = peroral; 20-40 mice used for each time interval; deaths in the controls were 98-100%.

case of (IV), 50%). The protectant indices of these compounds were 5.8 and 6.3 respectively, values which are substantially higher than those for the well-known radioprotectant β-mercaptoethylamine [3]. Replacement of hydrogen in the piperidine ring by one or two methyl groups, irrespective of position, either reduced or totally eliminated the radioprotectant effect.

In order to determine the mechanism of the radioprotectant effect, the effects of the active compounds (II, III, IV) on the oxygen requirement of the body were studied (the method used has been described previously [2]). In doses of half the LD_{16}, these compounds reduced the oxygen requirement within 15 min of administration, the effect of (III) being greatest (by a factor of five over 30-120 min) and most prolonged (even after 6 h the oxygen requirement was half of its initial value).

Hence, highly active N,N'-dipiperidinoalkane dihydrochlorides have been identified amongst those tested, with prolonged antiradiation activity and a broad range of therapeutic effect. It is assumed that the mode of action of these compounds involves changes in bodily redox processes.

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