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Synthesis and Pharmacological Investigation of Derivatives of 9-Methyl-3,9-diazabicyclo-(3,3,1)-nonane

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3,9-Diazabicyclo-(3,3,1)-nonane (I) was first synthesized by Barnes and Fales[1] in 1953, but pharmacological investigations of compounds of this class have hardly been carried out. Only Barnes and Fales reported that 3-benzyl-9-methyl-3,9-diazabicyclo-(3,3,1)-nonane, when given to an anaesthetized cat, caused an immediate drop of the blood pressure. Nevertheless, pharmacological studies of derivatives of 3,9-diazabicyclo-(3,3,1)-nonane are undoubtedly of interest since this system has some structural similarity with a whole group of natural substances, in particular, with the alkaloids nicotine, anabasine, and others.

The chemistry of derivatives of 3,9-diazabicyclo-(3,3,1)-nonane has also not been studied to any extent. The present article describes the results of synthetic work in this series carried out by M. V. Rubtsov, E. C. Nikitskaya and V. S. Usovskaya, and of pharmacological researches carried out by M. D. Mashkovskiy and B. A. Medvedev.

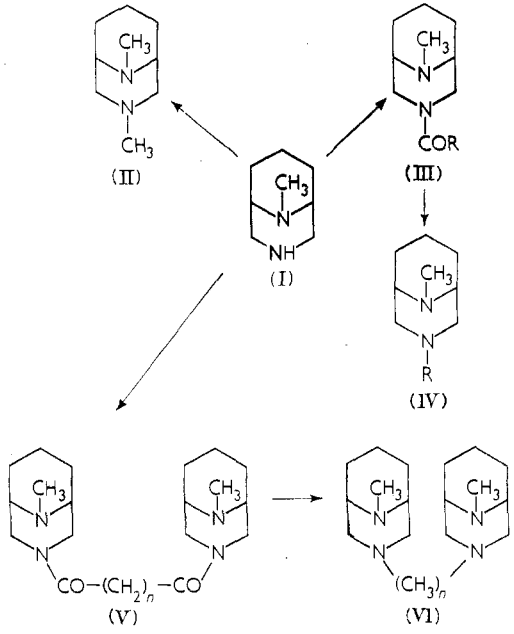
1. Chemistry

The 9-methyl-3,9-diazabicyclo-(3,3,1)-nonane used as starting material was synthesized by the method of Barnes and Fales,[1] with some modifications which simplified the synthesis and in the individual steps increased the yields.*

* For instance, *N*-methyldipipecolinic acid benzylimide was prepared by boiling the reaction mixture under simultaneous removal of the methanol as it was formed. This shortened the reaction time from 48 to 5 h, and simultaneously increased the yield. The reduction of the benzylimide with lithium aluminium hydride was carried out advantageously in ether–benzene medium. This cut the reaction time from 72 to 20 h.

Methylation of 9-methyl-3,9-diazabicyclo-(3,3,1)-nonane (I) with a mixture of formic acid and formaldehyde produced 3,9-dimethyl-3,9-diazabicyclo-(3,3,1)-nonane (II). This compound gives a quaternary salt with only one mole of methyl iodide, which points to the different basicities of the two nitrogen atoms.

By reaction of I with β-chloropropionyl chloride, α-bromopropionyl chloride, and chloroacetyl chloride, respectively, in alkaline aqueous medium or in anhydrous benzene, followed by treatment of the reaction product with dimethylamine, diethylamine,



piperidine and morpholine, the corresponding amides (III) of the substituted amino acids were obtained. These compounds contain three atoms of nitrogen and form only bis-quaternary salts with methyl iodide, since the nitrogen in position 3 is part of an amide group. However, when the amides were reduced with lithium aluminium hydride in ether or ether–benzene solution, the corresponding triamines were obtained which still gave only bis-quaternary salts with methyl iodide.

The formation of such bis-quaternary salts, in which one salt-forming nitrogen atom is in a side chain, and the other one in the 9-position of the bicyclic system, permits the conclusion that the above-mentioned 3,9-dimethyldiazabicyclo-(3,3,1)-nonane monomethiodide contains the methiodide group in position 9, and that therefore the nitrogen atom in this position is more basic than that in position 3.

Reaction of I with acyl chlorides of aliphatic dicarboxylic acids furnished the corresponding diamides (V) which were reduced with lithium aluminium hydride in ether–benzene medium to give α, ω-bis [3-(9-methyl-3,9-diazabicyclo-(3,3,1)]-nonano alkanes containing four tertiary nitrogen atoms. However, as expected, they formed only bis-quaternary salts.

Experimental

3,9-Dimethyl-3,9-diazabicyclo-(3,3,1)-nonane (II). A mixture of 9-methyl-3,9-diazabicyclo-(3,3,1)-nonane (0·73 g), 33·5 per cent formaldehyde solution (0·58 g), and formic acid (0·72 g) was heated in a boiling water bath for 15 h. At the end of the reaction, the mixture was made alkaline with an excess of 50 per cent potassium carbonate solution, extracted with ether, the ether extract was dried and the solvent evaporated. The residue distilled as a mobile colourless liquid, b.p. 69°/7 mm, yield, 0·54 g (67·5 per cent).

Anal. Calcd. for $C_9H_{18}N_2$: C, 70·13; H, 11·68; N, 18·18. Found: C, 70·07; H, 11·66; N, 18·45.

The *dihydrochloride* consists of colourless crystals, m.p. 275–276°.

Anal. Calcd. for $C_9H_{20}Cl_2N_2$: Cl, 31·27. Found: Cl, 30·95.

The *dimethiodide* formed colourless crystals, m.p. 291°.

Anal. Calcd. for $C_{11}H_{24}I_2N_2$: I, 42·90; N, 9·45. Found: I, 42·51; N, 9·25.

3-Dialkylamino-(or piperidino or morpholino)acyl-9-methyl-3,9-diazabicyclo-(3,3,1)-nonanes (III). For the preparation of these compounds, the following methods were employed.

(*A*) To a solution of 9-methyl-3,9-diazabicyclo-(3,3,1)-nonane dihydrochloride (5·48 g) in water (20 ml), cooled to 5°, was added dropwise with stirring a solution of sodium hydroxide (3·02 g) in water (4 ml) and β-chloropropionyl chloride (3·3 g). After stirring for another 30 min at the same temperature, cooling was

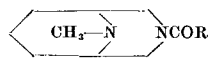
discontinued and the mixture was stirred until the temperature did not rise above 16°. The mixture was made alkaline with an excess of 50 per cent potassium carbonate solution, extracted with ether, the extract was dried over anhydrous sodium sulphate, and the ether was removed. The yield of colourless oily 3-(β-chloropropionyl)-9-methyl-3,9-diazabicyclo-(3,3,1)-nonane was 4·1 g (74 per cent). This chloroacyl derivative was refluxed with 3–5 moles of secondary amine in alcohol solution for 5 h, the solvent was removed, the residue treated with potassium carbonate, and the base extracted with ether. After drying over sodium sulphate, the ether was removed and the residue distilled in vacuum.

(*B*) A solution of chloroacetyl chloride (2·39 g) in dry benzene (10 ml) was added dropwise to an ice-cold solution of 9-methyl-3,9-diazabicyclo-(3,3,1)-nonane (2·97 g) in benzene (15 ml). After completion of the addition, the reaction mixture was stirred for another 1·5 h at 0° and 3 h at room temperature. It was then diluted with 35 ml of anhydrous ether and the precipitate was filtered off. The yield of 3-chloroacetyl-9-methyl-3,9-diazabicyclo-(3,3,1)-nonane hydrochloride was 4·63 g (86 per cent). This material was boiled with a solution of morpholine (6·36 g) in anhydrous ethanol (30 ml) for 5 h, the alcohol was evaporated, the residue treated with excess 50 per cent potassium carbonate solution, and extracted with ether. The ether was dried, evaporated, and the residue distilled in vacuum. The compounds thus obtained are described in Table I.

Succinyl bis {3-[9-methyl-3,9-diazabicyclo-(3,3,1)-nonane]} (V, $n = 2$). To a solution of 9-methyl-3,9-diazabicyclo-(3,3,1)-nonane dihydrochloride (10 g) in water (25 ml) was added with stirring a solution of sodium hydroxide (3·35 g) in water (10 ml) and the mixture was cooled to −5°. At this temperature, succinyl chloride (3·7 g) and a solution of sodium hydroxide (1·7 g) in water (5 ml) were added dropwise and simultaneously. Then 15 ml of a 50 per cent potassium carbonate solution was added, and the precipitated oil was extracted into chloroform. The extract was dried over anhydrous sodium sulphate, the chloroform was removed, and the residue distilled under reduced pressure. The yield of caramel-like pale-yellow material was 4 g (51 per cent), b.p. 254–255°/0·4 mm.

In a similar way, derivatives of glutaric and adipic acids were obtained. These compounds are shown in Table III.

Table I.

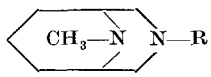


(III)

No.	R	b.p., °C (m.p., °C)	Pressure, mm	Yield, %	Elementary Composition	Analyses							
						Calcd.				Found			
						C	H	N	Halogen	C	H	N	Hal.
1	—$CH_2CH_2N(CH_3)_2$ [a]	133–135	0·3	68·9	$C_{13}H_{25}ON_3$	—	—	17·57	—	—	—	17·14	—
2	—$CH_2CH_2N(C_2H_5)_2$ [a]	148–150	0·25	72·0	$C_{12}H_{29}ON_3$	67·41	10·86	15·73		67·54	11·02	15·59	
		(231–232)			$C_{15}H_{29}ON_3 \cdot 2CH_3I$			7·62	I, 46·09			7·74	I, 45·83
3	—CH_2CH_2–N⟨ ⟩ [a]	170 (216–218)	0·25	65·9	$C_{16}H_{29}ON_3 \cdot 2HCl$	—	—	11·93	Cl, 20·17	—	—	11·61	19·79
4	—CH_2CH_2–N⟨ ⟩O [a]	170–172	0·3	66·0	$C_{15}H_{27}O_2N_3$	64·05	9·60	14·94		64·48	9·69	15·02	
		(238–240)			$C_{15}H_{27}O_2N_3 \cdot 2HCl$			11·86	Cl, 20·05			11·88	19·93
5	—CH_2–N⟨ ⟩O [b]	157–159	0·25	48·5	$C_{14}H_{25}O_2N_3$	62·92	9·36	15·73		63·11	9·66	15·80	
6	—CH(–CH_3)–N⟨ ⟩O [b]	163–165	0·3	42·7	$C_{15}H_{27}O_2N_3$	64·05	9·61	14·94		63·59	9·58	14·86	
		(265–267)			$C_{15}H_{27}O_2N_3 \cdot 2HCl$			11·86	Cl, 20·05			11·76	20·28

[a] Obtained by Method *A*. [b] Obtained by Method *B*.

Table II.



(IV)

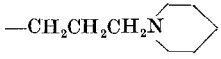
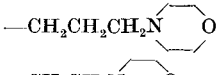
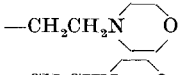
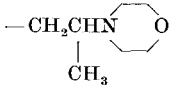
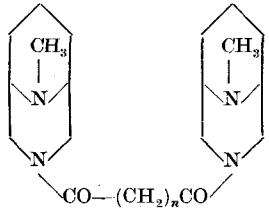
No.	R	Yield, %	b.p., °C	Pressure, mm	Analyses					
					Calcd.			Found		
					C	H	N	C	H	N
1	$-CH_2CH_2CH_2N(CH_3)_2$	75·0	94–96	0·35	69·33	12·00	—	69·10	12·02	—
2	$-CH_2CH_2CH_2N(C_2H_5)_2$	76·5	113–115	0·3	71·14	12·25	—	71·11	12·18	—
3		76·0	133–135	0·35	72·45	11·70	15·84	72·73	11·90	15·89
4		72·3	127–130	0·9	—	—	15·73	—	—	15·52
5		66·0	118–120	0·4	66·40	10·66	16·60	66·44	10·65	16·36
6		50·0	123–125	0·3	67·41	10·86	15·73	66·97	10·92	15·70

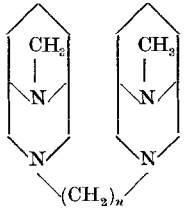
Table III.



(V)

No.	n	Yield, %	b.p., °C	Pressure mm	Analyses					
					Calcd.			Found		
					C	H	H	C	H	N
1	2	51·0	254–255	0·4	66·60	9·39	—	66·32	9·16	—
2	3	63·0	255	0·4	67·02	9·57	14·89	67·00	9·78	14·84
3	4	74·3	244	0·5	67·69	9·10	14·35	67·42	9·52	14·27

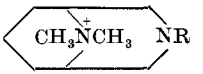
Table IV.

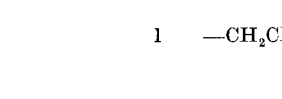
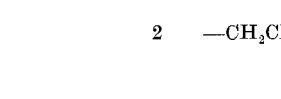
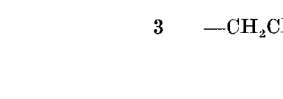
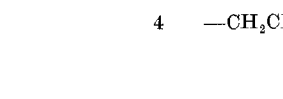
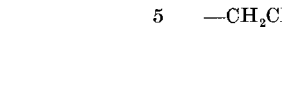
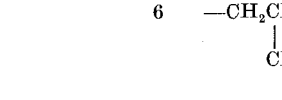
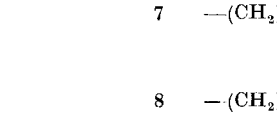
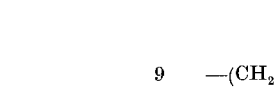


(VI)

No.	n	Yield, %	b.p., °C	Pressure, mm	Analyses					
					Calcd.			Found		
					C	H	N	C	H	N
1	4	77·0	178–180	0·3	—	—	16·76	—	—	16·42
2	5	80·0	206–207	0·5	72·41	11·49	16·09	72·20	11·54	15·58
3	6	75·4	175–177	0·2	72·92	11·60	15·46	72·24	11·31	15·44

Table V.



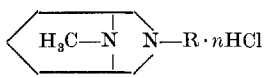
No.	R	Anion	m.p., °C	Analyses			
				Calcd.		Found	
				N	I	N	I
1		2I⁻	255–257	8·25	49·90	8·14	49·84
2		2I⁻	244–245	7·82	47·29	7·68	46·83
3		2I⁻	258–260	7·65	46·26	7·45	45·87
4		2I⁻	244–245	7·62	46·09	7·65	45·90
5		2I⁻	235–237	7·82	47·30	7·70	47·28
6		2I⁻	212–214	7·62	46·09	7·59	46·09
7		2I⁻	261–263	9·06	41·10	8·87	40·69
8		2I⁻	240–242	8·86	40·19	9·03	39·68
9		2I⁻	244–244·5	8·66	39·31	8·41	39·55

3-Dialkylamino (or piperidino or morpholino)-alkyl-9-methyl-3,9-diazabicyclo-(3,3,1)-nonanes, and α, ω-bis[9-methyl-3,9-diazabicyclo-(3,3,1)-nonano-3]alkanes (IV and VI). These compounds were usually obtained by the reduction of the corresponding amides (III) and diamides (V) with lithium aluminium hydride in ether or ether–benzene solution. They are listed in Tables II and IV. For pharmacological studies they were converted to the quaternary salts represented in Table V.

II. Pharmacology

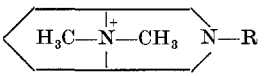
Twenty of the compounds synthesized were subjected to pharmacological study. Their formulae are listed in Table VI.

Table VI. Comparative activity and toxicity of derivatives of 3,9-diazabicyclo-(3,3,1)-nonane



No.	R	*n*	Effect on superior cervical ganglion	Effect on vagal ganglia	Effect on neuro-muscular trans-mission	LD_{50}, mg/kg mouse, i.v.
1131	—H	2	—	—	—	37·9
1325	$—CH_3$	2	1/20	1/20	1/2	30·7
1305	$—CH_2—C_6H_5$	2	1/20	1/20	0	20·7
1235	$—COCH_2CH_2N$	2	0	1/100	0	204·4
1328	$—CH_2CH_2CH_2N$	3	1/4	1	1/10	41·4
1326	$—COCH_2CH_2N(C_2H_5)_2$	2	1/1000	1/50	1/30	158·0
1332	$—CH_2CH_2CH_2N(C_2H_5)_2$	3	1/20	1	1/10	28·7
1556	$—CH_2CH_2CH_2N(CH_3)_2$	3	1/20	1/10	1/30	99·7

Table VI—*continued*



No.	R	Anion	Effect on superior cervical ganglion	Effect on vagal ganglia	Effect on neuro-muscular trans-mission	LD_{50}, mg/kg mouse, i.v.
1166	$-CH_3$	I^-	1/4	1	2	15·0
1130	$-CH_2-C_6H_5$	I^-	1/10	1	1	4·3
1327	$-COCH_2CH_2(CH_3)\overset{+}{N}$	$2I^-$	1/20	1/10	1/5	27·2
1237	$-CH_2CH_2CH_2(CH_3)\overset{+}{N}$	$2I^-$	1/4	1	1/5	2·4
1236	$-COCH_2CH_2(CH_3)^+N(C_2H_5)_2$	$2I^-$	1/100	1/50	1/10	42·8
1238	$-CH_2CH_2CH_2(CH_3)^+N(C_2H_5)_2$	$2I^-$	1/10	2	1/5	2·4
1539	$-CH_2CH_2CH_2(CH_3)^+N(CH_3)_2$	$2I^-$	1/2	2	1/5	6·9
1537	$-CH_2CH_2(CH_3)\overset{+}{N}$O	$2I^-$	1/2	1	1/5	5·7
1538	$-CH_2CH_2CH_2(CH_3)\overset{+}{N}$O	$2I^-$	1	1	1/5	6·4
1301	$-(CH_2)_6-N$ $H_3C-\overset{+}{N}-CH_3$	$2I^-$	1/40	1/5	7	0·964
1300	$-(CH_2)_5-N$ $H_3C-\overset{+}{N}-CH_3$	$2I^-$	1/40	1/5	20	0·759
1478	$-(CH_2)_4-N$ $H_3C-\overset{+}{N}-CH_3$	$2I^-$	1/10	1/5	100	1·074
	Hexamethonium		1	1	—	—
	Diplacine		—	—	1	—

Methods

The majority of the experiments was carried out on cats under urethan anaesthesia. Kymographic recordings of the carotid blood pressure and respiration were obtained in the usual manner. The effect of the compounds on the superior cervical ganglion was determined by the change of tone of the nictitating membrane;

preganglionic stimulation of the cervical sympathetic chain was effected by square-wave stimuli delivered from an electronic stimulator at 4–5/sec and 0·5 msec duration. The action on cardiac vagal ganglia was determined by change of the depressive reaction following electrical stimulation of the distal end of the vagus, separated and cut in the neck. The effect on neuromuscular transmission was judged by the size of the contractions of the gastrocnemius stimulated through the sciatic nerve with square-wave stimuli at 0·2/sec and 0·2 msec duration. The effect on intestinal ganglia was studied on isolated strips of rabbit intestine. Toxicity was tested in white mice; the drugs were injected into a tail vein.

Results

9-Methyl-3,9-diazabicyclo-(3,3,1)-nonane dihydrochloride (Table VI, No. 1131) showed a pronounced nicotine-like action on the autonomic nervous system. Administered intravenously to

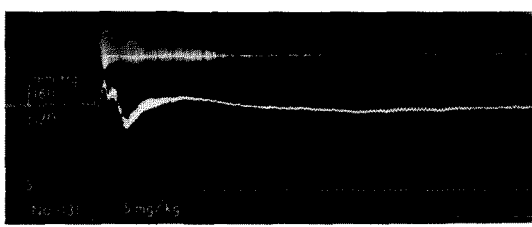


Fig. 1. Cat, 2·2 kg. Curves, from top: respiration, blood pressure, nictitating membrane. Time mark, 5 sec. Administration of 9-methyl-3,9-diazabicyclo-(3,3,1)-nonane dihydrochloride (Table VI, No. 1131), 5 mg/kg i.v.

anaesthetized cats, it caused, at a dose of 0·5 mg/kg, a rise in arterial pressure, respiratory stimulation and contraction of the nictitating membrane (Fig. 1). These reactions persisted for doses of 1–10 mg/kg, while a further increase or repeated frequent injections at short intervals caused a drop in the blood pressure and a decrease of respiratory rate, and produced less pronounced

contraction of the nictitating membrane. In a dose of 20 mg/kg the compound caused respiratory arrest and death of the animals.

In bilaterally adrenalectomized cats, the pressor activity and contraction of the nictitating membrane were decreased considerably or were entirely absent (Fig. 2). Previous administration of the ganglionic blocking agent, pentamine (Azamethonium bromide) in doses of 2 mg/kg also decreased pressor, ganglionic

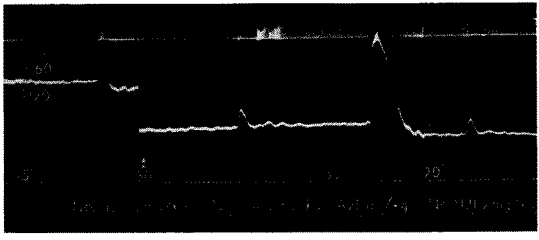


Fig. 2. Cat, 2·3 kg. Atropine, 0·5 mg/kg. Curves, from top: respiration, blood pressure, nictitating membrane. Time mark, 15 sec. Stop of kymograph in minutes. Administration of 9-methyl-3,9-diazabicyclo-(3,3,1)-nonane dihydrochloride (Table VI, No. 1131), 2 mg/kg, and adrenaline (A), 25 mg/kg i.v. (↑) Adrenalectomy.

as well as respiratory effects of compound No. 1131 (Fig. 3). Respiratory stimulation also disappeared when the carotid sinuses were infiltrated with an 0·25 per cent solution of procaine hydrochloride.

In the isolated rabbit ileum, compound No. 1131 at a concentration of 2×10^{-5} caused an increase of muscle tone. This was abolished by a concentration of 2×10^{-5} of pentamine. In higher concentrations of $1–3 \times 10^{-4}$, this compound exhibited initial stimulation but after 10–15 sec reduced the tone and amplitude of intestinal contractions almost to their disappearance; apparently, more concentrated solutions depressed intestinal ganglia. Indeed, previous administration of compound No. 1131 in a concentration of 3×10^{-4} reduced the intestinal contractions caused by nicotine,

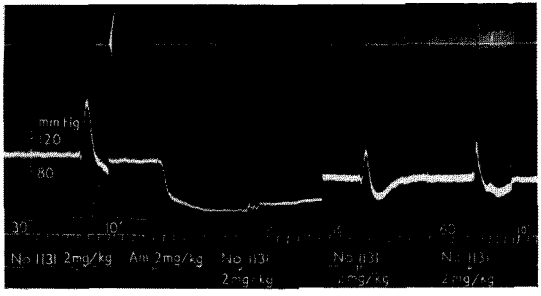


Fig. 3. Cat, 2·6 kg. Atropine, 0·5 mg/kg. Curves, from top: respiration, blood pressure, nictitating membrane. Time mark, 30 sec. Stop of kymograph in minutes. Administration of 9-methyl-3,9-diazabicyclo-(3,3,1)-nonane dihydrochloride (Table VI, No. 1131) and Azamethonium (AM), 2 mg/kg i.v.

but did not materially affect contractions caused by acetylcholine (Fig. 4). The increase of contraction due to compound No. 1131 was not prevented by pretreatment with atropine. Such an

Fig. 4. Isolated rabbit duodenum. Time mark, 15 sec. *N:* introduction of nicotine, 3×10^{-7}. *ACh:* introduction of acetylcholine, 1×10^{-7}. No. 1131: introduction of 9-methyl-3,9-diazabicyclo-(3,3,1)-nonane dihydrochloride, 3×10^{-4}.

atropine-resistant action of nicotine on the isolated rabbit intestine had been reported by Euler[2] and by Ellis and Rasmussen.[3]

The introduction of alkyl, aminoalkyl and aminoacyl groups into position 3 of the ring system changes the pharmacological characteristics of the substances. The tertiary amines studied show a more or less pronounced blocking action on autonomic ganglia or on the neuromuscular synapse. Table VI shows the comparative activity of the substances in different observations. Ganglionic blocking activity was compared with that of hexamethonium (= 1), curaremimetic acitivity with that of diplacine [1,3-bis(β-platineciniumethoxy)-benzene dichloride].* Comparison was made at approximately equi-effective doses. Among the

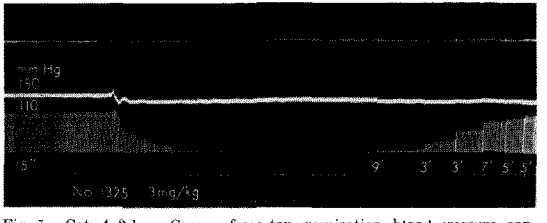


Fig. 5. Cat, 4·2 kg. Curves, from top: respiration, blood pressure, contraction of gastrocnemius. Time mark, 15 sec. Stop of kymograph in minutes. 3,9-Dimethyl-3,9-diazabicyclo-(3,3,1)-nonane dihydrochloride (No. 1325), 3 mg/kg i.v.

tertiary amines, 3-(γ-piperidinopropyl)-9-methyl-3,9-diazabicyclo-(3,3,1)-nonane trihydrochloride (No. 1328), and 3-(β-diethylaminopropyl)-9-methyl-3,9-diazabicyclo-(3,3,1)-nonane trihydrochloride (No. 1332) proved to be the most active ganglionic blocking substances. Their activity on the cardiac ganglia of the vagus is similar to that of hexamethonium, but their activity on the superior cervical ganglion is below that of the standard.

3,9-Dimethyl-3,9-diazabicyclo-(3,3,1)-nonane dihydrochloride (No. 1325) pronouncedly blocks neuromuscular conduction (Fig. 5). 3-Benzyl-9-methyl-3,9-diazabicyclo-(3,3,1)-nonane dihydrochloride (No. 1305) weakly blocks the superior cervical ganglion

* A curare-like drug with a concurrent type of action used in the U.S.S.R.

and the vagal ganglia, but stimulates the carotid sinuses and thereby continually stimulates respiration. Intravenous administration of pentamine (2 mg/kg) and also infiltration of the carotid sinuses with procaine hydrochloride abolish the respiratory stimulating activity of compound No. 1305 (Fig. 6).

The 3-acyl derivatives were the least active compounds for ganglionic blocking and curareform activity (see Table VI).

The mono- and bis-quaternary salts of 9-methyl-3,9-diazabicyclo-(3,3,1)-nonane differ only little from the respective tertiary amines, since the majority of both the tertiary amines and quaternary salts here investigated possess pronounced

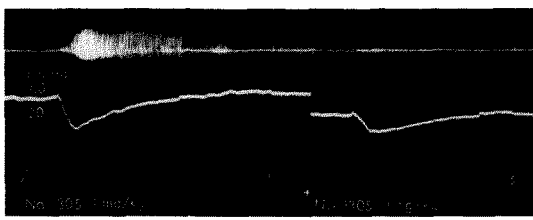


Fig. 6. Cat, 3·1 kg. Curves, from top: respiration, blood pressure. Time mark, 15 sec. Stop of kymograph in minutes. Administration of 3-benzyl-9-methyl-3,9-diazabicyclo-(3,3,1)-nonane dihydrochloride, 1 mg/kg i.v. (+): Infiltration of carotid sinuses by 0·25 per cent procaine. HCl.

autonomic blocking activity. Ordinarily, quaternization increases the blocking action of a substance. The dimethiodide of 3-(γ-dimethylaminopropyl)-9-methyl-3,9-diazabicyclo-(3,3,1)-nonane (No. 1539) is only half as active as hexamethonium on the superior cervical ganglion, and surpasses hexamethonium in its vagal cardiac ganglionic blocking activity. With this substance (No. 1539) and also with 3-(γ-piperidinopropyl)-9-methyl-3,9-diazabicyclo-(3,3,1)-nonane (No. 1237), a pronounced hypotensive effect was noted, similar to that of hexamethonium. Quaternization also increases curareform activity. For instance, 3,9-dimethyl-3,9-diazabicyclo-(3,3,1)-nonane methiodide (No. 1166) is

caused head drop, while the dose for decamethonium was 0·35 mg/kg.

Concerning the mode of action of DNB, it was found that intravenous administration of 0·1 mg/kg of proserine (Neostigmine methyl sulphate) or of 15 μg/kg of succinylcholine to cats increased

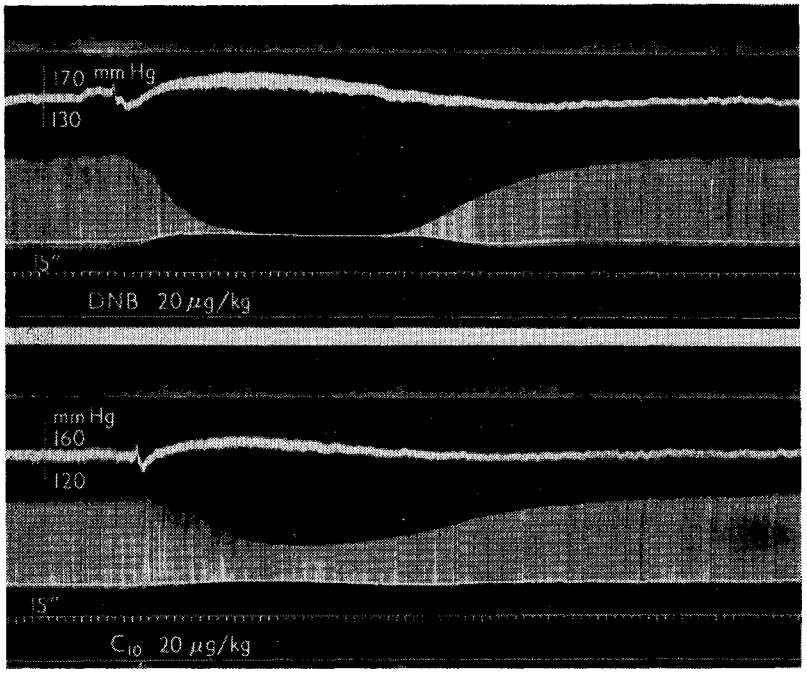


Fig. 7. Cat, 3·2 kg. (*a*) Curves, from top: respiration, blood pressure, contraction of gastrocnemius. Time mark, 15 sec. Administration of DNB, 20 μg/kg i.v. (*b*) Designations of curves as under (*a*). Decamethonium, 20 μg/kg i.v., shows less pronounced effect on neuromuscular transmission than DNB.

the neuromuscular block brought about by DNB, while 0·2–0·4 mg/kg of diplacine speeded up resumption of neuromuscular conductivity. That means that under these conditions, DNB acts like a depolarizing agent. However, in experiments with frog rectus abdominis muscle DNB acts like a competitive agent, since muscular contraction caused by acetylcholine (1×10^{-6}) decreased or was prevented by a DNB concentration of 1×10^{-6}

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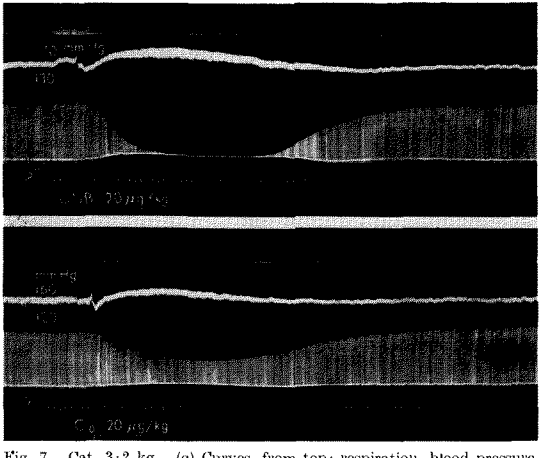

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to 1×10^{-4}. Besides, contraction of the rectus abdominis did not develop on treatment with DNB.

In its effect on autonomic ganglia, DNB does not differ substantially from decamethonium. It shows a threshold of blocking activity at doses of 0·5–1 mg/kg. In parenteral doses of 10–20 μg/kg which caused a temporary curareform effect, DNB did not change arterial blood pressure substantially. At doses of 50–60 μg/kg, respiratory arrest occurred with blood pressure changes characteristic for asphyxia. Artificial respiration prevented the death of the animals. When artificial respiration was used, DNB proved to be of low toxicity; the animals did not die from doses of 100–200 mg/kg.

Intravenous administration of DNB to white mice caused a toxicity picture typical of curareform compounds: immobility, irregular breathing, cyanosis and respiratory arrest leading to asphyxiation within a few minutes. The LD_{50} computed by the method of Kerber is 1074 μg/kg for white mice.

Summary. Derivatives of 3,9-diazabicyclo-(3,3,1)-nonane, containing a methyl group in position 9, and different substituents (alkyl, aminoalkyl and aminoacyl) in position 3, have been synthesized. Quaternary salt formation occurs only in position 9, pointing to a higher basicity of this nitrogen atom.

Starting with 9-methyl-3,9-diazabicyclo-(3,3,1)-nonane, bis[9-methyl-3,9-diazabicyclo-(3,3,1)-nonane-3]-alkanes and their bis-quaternary salts were prepared. The derivatives which have been tested pharmacologically showed a pronounced effect on the autonomic nervous system. 9-Methyl-3,9-diazabicyclo-(3,3,1)-nonane dihydrochloride possessed nicotine-like activity. The tertiary amines studied were blocking agents with a preferred action on autonomic ganglia. Compounds containing aminoacyl groups in position 3 of the ring system have little activity. Symmetrical bis-quaternary ammonium salts of 9-methyl-3,9-diazabicyclo-(3,3,1)-nonane were especially active in blocking neuromuscular transmission, 1,4-bis[9-methyl-3,9-diazabicyclo-(3,3,1)-nonane-3]-butane dimethiodide possessing the highest activity.

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