SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF ESTERS OF 3-METHYL-9-β-HYDROXYETHYL-3, 9-DIAZABICYCLO-(3,3,1)-NONANE

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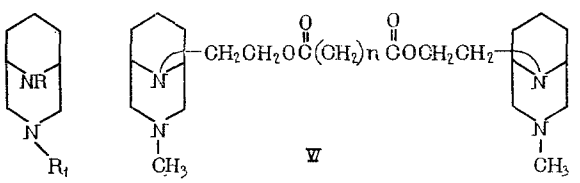
Considering our study of derivatives of 3-9-diazabicyclo-(3,3,1)-nonane [1], we synthesized 9-substituted derivatives of this bicyclic structure, namely, esters of 3-methyl-9-β-hydroxyethyl-3,9-diazabicyclo-(3,3,1)-nonane with certain dibasic aliphatic acids.

The initial compound in the synthesis was 9-benzyl-3,9-diazabicyclo-(3,3,1)-nonane (I), produced by the method described in the literature [2].

When I was heated with the ethyl ester of monochloroacetic acid in benzene in the presence of diethylamine, we obtained 3-benzyl-9-(carbethoxymethyl-3,9-diazabicyclo-(3,3,1)-nonane (II), reduction of which with lithium aluminum hydride yields 3-benzyl-9-β-hydroxyethyl-3,9-diazabicyclo-(3,3,1)-nonane (III). Debenzylation with palladium in acid medium yielded 9-β-hydroxyethyl-3,9-diazabicyclo-(3,3,1)-nonane (IV), which was methylated at the nitrogen in the 3-position with a mixture of formic acid and formalin. The 3-methyl-9-β-hydroxyethyl-3,9-diazabicyclo-(3,3,1)-nonane (V) thus obtained gave the corresponding esters (VI) upon interaction with dichlorides of dibasic aliphatic acids.



V

I R=H; $R_1=CH_2C_6H_5$, II R=$CH_2COOC_2H_5$, $R_1=CH_2C_6H_5$

III R=CH_2CH_2OH; $R_1=CH_2C_6H_5$ IV R=CH_2CH_2OH; R_1=H

V R=CH_2CH_2OH; $R_1=CH_3$

The esters obtained, when redistilled under vacuum (0.2-0.3 mm) decomposed entirely. For a biological study, the esters were converted by the usual means to tetrahydrochlorides, which crystallize with four moles of water.

The compounds obtained were studied according to their influence upon a number of functions and systems of the organism. The toxicity and general action, influence on the arterial pressure and respiration, adreno- and cholinoreactive structures, antispasmodic action, spasmolytic, antiarrythmic, and antihistamine activities were investigated. The experiments were conducted on various laboratory animals (cats, white mice) and isolated organs (isolated rabbit intestine).

Our experiments indicate that the preparations studied are rather inactive with respect to all the investigated indices. We should mention only a certain central n-cholinolytic action exerted by all the compounds, manifested in the case of intravenous injection in a dose of 50 mg/kg. The most active in this respect proved to be the tetrahydrochloride of the diester of adipic acid and 3-methyl-9-β-hydroxyethyl-3,9-diazabicyclo-(3,3,1)-nonane, which in a dose of 50 mg/kg entirely protected all the experimental mice from the effects of a lethal dose of nicotine; the remaining compounds investigated, in a dose of 50 mg/kg, protected part of the animals from death.

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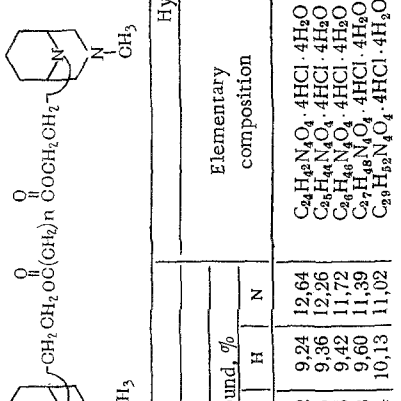
TABLE 1. Esters of 3-Methyl-9-β-hydroxyethyl-3,9-diazabicyclo-(3,3,1)-nonane (VI)



n	Yield (in %)	Base: Elementary composition	Base: Analysis Calculated, % C	H	N	Base: Analysis Found, % C	H	N	Hydrochloride: Elementary composition	Hydrochloride: Melting point (in degrees)	Hydrochloride: Analysis Calc., % Cl	N	Hydrochloride: Analysis Found, % Cl	N
2	41	$C_{24}H_{42}N_4O_4$	63,96	9,39	12,43	63,82	9,24	12,64	$C_{24}H_{42}N_4O_4 \cdot 4HCl \cdot 4H_2O$	97—100 (dec.)	21,21	8,38	21,65	8,59
3	71	$C_{25}H_{44}N_4O_4$	64,62	9,54	12,05	64,86	9,36	12,26	$C_{25}H_{44}N_4O_4 \cdot 4HCl \cdot 4H_2O$	182—184 (dec.)	20,77	8,20	20,68	8,58
4	77	$C_{26}H_{46}N_4O_4$	65,23	9,68	11,70	64,85	9,42	11,72	$C_{26}H_{46}N_4O_4 \cdot 4HCl \cdot 4H_2O$	77—80 (dec.)	20,35	8,04	20,14	8,18
5	76	$C_{27}H_{48}N_4O_4$	65,81	9,82	11,37	65,53	9,60	11,39	$C_{27}H_{48}N_4O_4 \cdot 4HCl \cdot 4H_2O$	50—53 (dec.)	19,95	7,88	19,54	7,52
7	81	$C_{29}H_{52}N_4O_4$	66,88	10,06	10,76	66,64	10,13	11,02	$C_{29}H_{52}N_4O_4 \cdot 4HCl \cdot 4H_2O$	67—70 (dec.)	19,20	7,58	19,31	7,41

LD_{50} of the preparations for white mice in the case of intravenous injection lies in the range 240-114 mg/kg; moreover, with increasing number of methyl groups in the chain, the toxicity increases.

EXPERIMENTAL SECTION

3-Benzyl-9-carbethoxymethyl-3,9-diazabicyclo-(3,3,1)-nonane (II). A 15 g portion (0.069 mole) of I was dissolved in 100 ml of dry benzene, 7.04 g (0.069 mole) triethylamine and 8.53 g (0.069 mole) of the ethyl ester of monochloroacetic acid were added, and the reaction mixture was heated at boiling with mixing for 30 h. At the end of the reaction, the triethylamine hydrochloride precipitate was filtered off, washed with dry benzene, the combined benzene extract evaporated under vacuum, the residue treated with an excess of a 50% solution of potash, and extracted with ether. After drying and distillation of the solvent, we obtained 14.84 g (71%) of a substance in the form of a colorless oily liquid with bp 158-160°/0.35 mm, n_D^{21} 1.5310. Found, %: C 71.78; H 8.59; N 9.24. $C_{18}H_{26}N_2O_2$. Calculated, %: C 71.48; H 8.66; N 9.26.

3-Benzyl-9-β-hydroxyethyl-3,9-diazabicyclo-(3,3,1)-nonane (III). A 14.4 g portion (0.048 mole) of II was reduced with 2.7 g (0.072 mole) lithium aluminum hydride in ether solution for 2 h. Yield 10.06 g (81.1%) of a colorless oily liquid with bp 155-156°(0.4 mm), n_D^{21} 1.5490. Found, %: C 74.20; H 9.20; N 10.57. $C_{16}H_{24}N_2O$. Calculated, %: C 73.80; H 9.21; N 10.74.

9-β-Hydroxyethyl-3,9-diazabicyclo-(3,3,1)-nonane (IV). A 5.9 g portion (0.023 mole) of III was hydrogenated in alcohol (200 ml) in the presence of palladium chloride (0.5 g) under the conditions described earlier [3]. Yield 5 g (90.8%) of the dihydrochloride of 9-β-hydroxyethyl-3,9-diazabicyclo-(3,3,1)-nonane in the form of a fine-crystalline substance with mp 269-271° (dec. from alcohol). Found, %: Cl 29.12; N 11.66. $C_9H_{18}N_2O \cdot 2HCl$. Calculated, %: Cl 29.16; N 11.52.

The base—a colorless oily liquid with bp 120-122°/2 mm—was isolated from the dihydrochloride in the usual way. The substance crystallized upon standing, mp 41-43°. Found, %: C 63.25; H 10.90; N 16.62. $C_9H_{18}N_2O$. Calculated, %: C 63.48; H 10.65; N 16.45.

3-Methyl-9-β-hydroxyethyl-3,9-diazabicyclo-(3,3,1)-nonane (V). A 5.35 g portion (0.031 mole) of IV was methylated under the conditions described earlier [3] with a mixture of formic acid and formalin. Yield 4 g (70%) of a colorless free-flowing liquid with bp 98-100°/2 mm. Found, %: C 64.83; H 10.80; N 14.96. $C_{10}H_{20}N_2O$. Calculated, %: C 65.17; H 10.93; N 15.20.

The hydrochloride—white crystalline substance with mp 219-21°. Found, %: Cl 27.31; N 11.13. $C_{10}H_{20}N_2O \cdot 2HCl$. Calculated, %: Cl 27.57; N 10.88.

Methiodide—a white crystalline substance with mp 230-232° (dec.). Found, %: N 8.71; I 38.73. $C_{10}H_{20}N_2O \cdot CH_3I$. Calculated, %: N 8.58; I 38.90.

Esters of 3-Methyl-9-β-hydroxyethyl-3,9-diazabicyclo-(3,3,1)-nonane (VI). Esters of compound V with dibasic aliphatic acids were produced by boiling 2 moles of V in benzene with 1 mole of the dihydrochloride of the corresponding acid in the presence of 2 moles of triethylamine for 6 h. At the end of the reaction, the triethylamine hydrochloride formed was filtered off, the precipitate washed with dry benzene, the benzene mother liquors evaporated under vacuum, the residue treated with an excess of a 50% solution of potash and extracted with ether. After drying of the extract and the distillation of the solvent, the substances were analyzed without redistillation (since in the case of redistillation even at 0.1-0.2 mm they decompose) and were converted in the usual way to the hydrochlorides. The constants, yields, and analyses of the compounds obtained were cited in Table 1.

LITERATURE CITED

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3. E. S. Nikitskaya, V. S. Usovskaya, and M. V. Rubtsov, Zh. Obshch. Khim., 30, 3306 (1960).