SYNTHESIS OF DERIVATIVES OF 1,2-DIAZABICYCLO[2,2,2]OCTANE. III*

E. E. Mikhlina, K. F. Turchin, N. A. Komarova, and M. V. Rubtsov

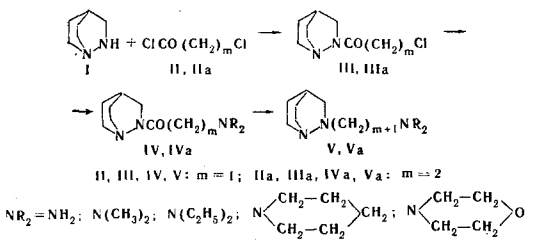
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 2, pp. 340–344, 1969

UDC 547.852.07:541.67

Synthesis of a number of 2-dialkylaminoalkyl-1,2-diazabicyclo[2,2,2]octanes has been carried out starting from 1,2-diazabicyclo[2,2,2]-octane and passing through its 2-chloroacyl and 2-dialkylaminoacyl derivatives. It has been shown by means of NMR spectra that the methiodide of 2-methyl-1,2-diazabicyclo[2,2,2]octane has the structure of 1,2-dimethyl-2-aza-1-azoniabicyclo[2,2,2]octane iodide.

In preceding papers, we have described a general method for obtaining 1,2-diazabicycloalkanes and the synthesis of several representatives of this class and their derivatives [1,2]. In order to broaden our studies of the bicyclic systems mentioned—in particular, the 1,2-diazabicyclo[2,2,2]octane system—we have carried out the synthesis of a number of 2-substituted derivatives of this class of compounds and have studied their chemical and biological properties.

2-Dialkylaminoalkyl-1,2-diazabicyclo[2,2,2]octanes (V) were obtained by the following scheme:

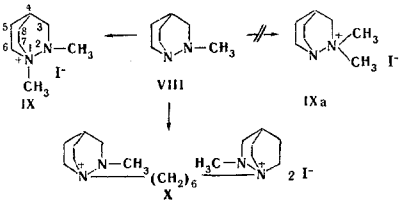


1,2-Diazabicyclo[2,2,2]octane (I) was subjected to the action of chloroacetyl and β-chloropropionyl chlorides (II) in benzene. The hydrochlorides of the 2-chloroacetyl- and 2-(β-chloropropionyl)-1,2-diazabicyclo-[2,2,2]octanes (III) so formed, without additional purification, were heated in ethanolic solution with diethylamine, piperidine, and morpholine in excess. The resulting 2-dialkylaminoalkyl-1,2-diazabicyclo[2,2,2]-octanes (IV) were then reduced with lithium aluminum hydride to the amines V. All stages of the synthesis took place mainly with fairly high yields (70–90%). A lower yield (39–42%) was obtained only in the case of the reactions of the hydrochloride of 2-(β-chloropropionyl)-1,2-diazabicyclo[2,2,2]octane (IIIa) with piperidine and morpholine. This is due to the fact that in the reaction of IIIa with these amines, in addition to the replacement of chlorine by the tertiary amino group, dehydrohalogenation took place with the formation of considerable amounts of acrylic acid derivatives.

2-(γ-Aminopropyl)-1,2-diazabicyclo[2,2,2]octane (Va; $NR_2 = NH_2$) was synthesized by the reduction of 2-(β-cyanoethyl)-1,2-diazabicyclo[2,2,2]octane [2] with lithium aluminum hydride; subsequent methylation led to compound Va, where $NR_2 = N(CH_3)_2$.

The synthesis of 2-(β-hydroxyethyl)-1,2-diazabicyclo[2,2,2]octane (VI) was carried out by two methods: a) by the reaction of I with ethylene oxide; under various experimental conditions, the reaction took place ambiguously, and from the total reaction products it was possible to isolate compound VI in only low yield; b) 2-cyanomethyl-1,2-diazabicyclo[2,2,2]octane [2] was subjected to hydrolysis and then to esterification; the 2-methoxycarbonyl-1,2-diazabicyclo[2,2,2]octane (VII) so obtained was reduced with lithium aluminum hydride to VI.

In addition to the substances mentioned, several mono- and ditertiary salts of 2-methyl-1,2-diazabicyclo[2,2,2]octane (VIII) were synthesized by the reaction of the latter with alkyl halides and with α,ω-dihalogenoalkanes. The reaction of compound VIII with methyl iodide led to a monotertiary salt which may have structure IX or IXa. To elucidate the structure of this methiodide, its PMR spectrum was recorded on a JNM-4H-100 spectrometer with a working frequency of 100 MHz using pyridine as the solvent and tetramethylsilane as internal standard.



The spectrum of the protons of the bicyclic nucleus of the methiodide consists of groups of overlapping peaks with a center at δ 1.85 ppm and having a total intensity of five proton units (protons at C_4, C_5, and C_8), a broadened peak of two proton units with δ 2.98 ppm (protons at C_3), and two groups of signals of two proton units with centers at δ 3.85 and 4.35 ppm (protons at C_6 and C_7). The protons of the methyl groups give two distinct narrow peaks which enables structure IXa to be excluded, since in this case the CH_3 groups would be in equivalent positions with respect to the plane of symmetry of the molecule passing through the C_3, C_4, N_1; and N_2 atoms and, consequently, have identical chemical shifts. On the basis of the information given, it may be concluded that the spectrum of the methiodide of compound VIII corresponds to structure IX with nonequivalent methyl groups at N_2 ($N-CH_3$, δ 2.68 ppm) and at N_1 ($\overset{+}{N}-CH_3$, δ 3.29 ppm), the signal from the latter appearing in a weaker field because of the inductive effect of the positively charged nitrogen atom. A similar spectrum has been obtained for a solution of the methiodide of IX in D_2O, where the difference in the

*For part II, see [2].

R	Bp,° C (pressure mm) (mp,° C)	Empirical formula	Found, %			Calculated, %			Yield, %
			C	H	N	C	H	N	
$COCH_2Cl$	(162—164)	$C_8H_{13}ClN_2O \cdot HCl$	—	—	12.58	—	—	12.44	89.5
$COCH_2N(C_2H_5)_2$	110—111 (0.3)	$C_{12}H_{23}N_3O$	64.30	10.40	18.46	63.96	10.29	18.64	72.2
$COCH_2$ 	146—147 (0.5)	$C_{13}H_{23}N_3O$	65.54	9.79	17.72	65.82	9.75	17.70	74.4
$COCH_2$ 	174—175 (1)	$C_{12}H_{21}N_3O_2$	59.93	8.66	17.61	60.23	8.84	17.56	75.3
$CO(CH_2)_2N(C_2H_5)_2$	150—152 (2)	$C_{13}H_{25}N_3O$	64.85	10.40	17.78	65.30	10.52	17.55	48.8
$CO(CH_2)_2$ 	160—162 (0.8) (70—73)	$C_{14}H_{25}N_3O$	66.91	10.09	17.02	66.89	10.02	16.72	39.4
$CO(CH_2)_2$ 	180—182 (1)	$C_{13}H_{23}N_3O_2$	61.4	9.04	16.51	61.63	9.15	16.58	67.2
$(CH_2)_2N(C_2H_5)_2$	120—122 (7)	$C_{12}H_{25}N_3$	67.97	12.13	19.91	68.15	11.92	19.98	81.5
$(CH_2)_2$ 	105—106 (0.6) (224—226)[a]	$C_{13}H_{25}N_3$	70.00	11.58	19.01	69.95	11.28	18.81	73.5
$(CH_2)_2$ 	(228—231) 133—134 (3)[b]	$C_{12}H_{23}N_3O \cdot 2HCl$	48.58	8.72	14.15	48.32	8.45	14.12	79.5
$(CH_2)_3N(C_2H_5)_2$	125—126 (4)	$C_{13}H_{27}N_3$	—	—	18.34	—	—	18.64	85.0
$(CH_2)_3$ 	122—125 (1) (209—211)[c]	$C_{14}H_{27}N_3$	70.85	11.24	17.90	70.83	11.47	17.70	79.6
$(CH_2)_3$ 	125—126 (1) (219—221)[a]	$C_{13}H_{25}N_3O$	64.98	10.33	17.47	65.23	10.51	17.55	88.3
$(CH_2)_3NH_2$	132—135 (12)	$C_9H_{19}N_3$	63.79	11.35	24.42	63.86	11.36	24.82	79.2
$(CH_2)_3N(CH_3)_2$	119—121 (10) (215—217)[a]	$C_{11}H_{23}N_3$	66.72	11.40	20.48	66.98	11.75	21.31	81.6
CHO	(60—62) (201—203)[d]	$C_7H_{12}N_2O$	60.00	8.51	20.06	59.97	8.63	19.98	87.2
$CH_2COOC_2H_5$	100—101 (2)	$C_{10}H_{18}N_2O_2$	60.45	8.89	14.12	60.58	9.14	14.13	20.7
CH_2CH_2OH	112—114 (8)	$C_8H_{16}N_2O$	61.80	10.65	17.57	61.50	10.32	17.87	77.3[e]
$CH_2CH_2OCOCH_3$	129—131 (10)	$C_{10}H_{18}N_2O_2$	60.53	9.14	14.13	60.58	9.04	14.23	71.0

[a]Dinitrochloride [b]Base [c]Dimethiodide [d]Methiodide [e]Obtained in the ester VII.

chemical shifts of the $\overset{+}{N}-CH_3$ and $N-CH_3$ groups amounted to 0.33 ppm.

The data on the structure of compound IX obtained by studying the PMR spectrum give grounds for assuming that the diquaternary salt formed by the reaction VIII with 1,6-diiodohexane has the structure of hexamethylene-di(2-methyl-2-aza-1-azoniabicyclo[2,2,2]octane iodide) (X).

In a study of the biological properties of compounds V and X, it was found that the amines V exhibit a weak pharmacological activity, while the diquaternary salt X was found to have curaremimetic and weak ganglion-blocking properties. The biological properties were studied in the pharmacology division of VNIKhFI [Ordzhonikidze All-Union Chemical and Pharmaceutical Scientific Research Institute] by senior scientific workers K. A. Zaitseva and B. A. Medvedev under the direction of Corresponding Member of the Academy of Medical Sciences of the USSR Prof. M. D. Mashkovskii.

EXPERIMENTAL

Hydrochloride of 2-chloroacetyl-1,2-diazabicyclo[2,2,2]octane (III). A solution of 2.47 g (0.0218 mole) of chloroacetyl chloride in 12 ml of absolute benzene was added over 40 min with stirring and ice water cooling to a solution of 2.45 g (0.0128 mole) of 1,2-diazabicyclo[2,2,2]octane (I) in 12 ml of absolute benzene. The reaction mixture was stirred for another 1 hr 30 min with cooling and for 3 hr at room temperature. The precipitate formed was filtered off with suction, washed with benzene, and dried. The yields, constants, and analytical results for this compound and for the other 2-substituted 1,2-diazabicyclo[2,2,2]octanes are given in the table.

By this method, the hydrochloride of 2-(β-chloropropionyl)-1,2-diazabicyclo[2,2,2]octane was obtained in the form of colorless extremely hygroscopic crystals with a yield of 80.2%.

2-Diethylaminoacetyl-1,2-diazabicyclo[2,2,2]octane. A solution of 3.7 g (0.0164 mole) of III and 5.4 g (0.074 mole) of diethylamine in 30 ml of absolute ethanol was boiled for 5 hr. The reaction mixture was evaporated in vacuum, the residue was dissolved in 10 ml of water, 15 ml of 50% potassium carbonate solution was added, and the mixture was extracted with benzene.

The other 2-aminoacyl derivatives of 1,2-diazabicyclo[2,2,2]-octane (IV, IVa) were obtained similarly.

2-(β-Diethylaminoethyl)-1,2-diazabicyclo[2,2,2]octane. With stirring, a solution of 2.38 g (0.0106 mole) of 2-diethylaminoacetyl-1,2-diazabicyclo[2,2,2]octane in 50 ml of absolute benzene was added to a suspension of 0.8 g (0.21 mole) of lithium aluminum hydride in 50 ml of absolute ether. The reaction mixture was boiled for 18 hr, cooled, and treated with 2 ml of water. The inorganic salts were filtered off with suction and carefully washed with benzene. The combined solutions were evaporated, and the residue was distilled in vacuum. All the 2-dialkylaminoalkyl-1,2-diazabicyclo[2,2,2]octanes (V, Va) were synthesized similarly.

Reduction of 2-(β-cyanoethyl)-1,2-diazabicyclo[2,2,2]octane [2] with lithium aluminum hydride gave 2-(γ-aminopropy)-1,2-diazabicyclo[2,2,2]octane.

2-(γ-Dimethylaminopropyl)-1,2-diazabicyclo[2,2,2]octane. A mixture of 2.85 g (0.017 mole) of 2-(γ-aminopropyl)-1,2-diazabicyclo[2,2,2]octane, 3.5 g (0.043 mole) of 37% formaldehyde solution, 4.7 g (0.102 mole) of formic acid, and 3 ml of water was heated at 100° C for 15 hr. The reaction mixture was evaporated in vacuum, and the residue was treated with 50% potassium carbonate solution and extract with ether.

2-Formyl-1,2-diazabicyclo[2,2,2]octane. A mixture of 6.75 g (0.066 mole) of acetic anhydride and 2.8 g (0.06 mole) of formic acid was heated at 60° C for 2 hr. With cooling, the resulting solution was treated with 5 g (0.0445 mole) of I in 20 ml of ether. The mixture was left at room temperature for 40 hr and then evaporated in vacuum, and the residue was made alkaline with 50% potassium carbonate solution and extracted with ether.

2-Ethoxycarbonylmethyl-1,2-diazabicyclo[2,2,2]octane (VII). With cooling, 7 g (0.0463 mole) of 2-cyanomethyl-1,2-diazabicyclo[2,2,2]octane [2] was added to 80 ml of a 28% ethanolic solution of hydrogen chloride. The reaction mixture was left at room temperature for 20 hr and was then boiled for 4 hr, after which it was evaporated in vacuum. The residue was dissolved in 25 ml of water, and the solution was treated with 25 ml of 50% potassium carbonate solution and extracted with ether. The ethereal solution was dried with potassium carbonate and evaporated, and the residue was distilled.

2-(β-Hydroxyethyl)-1,2-diazabicyclo[2,2,2]octane (VI). A. A solution of 1.85 g (0.0095 mole) of VII in 50 ml of ether and 50 ml of benzene was reduced with 1.05 g (0.286 mole) of lithium aluminum hydride at the boil for 3 hr. The reaction mixture was treated in the usual way. The VI obtained was distilled in vacuum. B. With cooling, a solution of 3 g (0.068 mole) of ethylene oxide in 6 ml of ethanol was added to a solution of 5 g (0.0445 mole) of I in 20 ml of ethanol. The reaction mixture was left at room temperature for 4 days and was then evaporated in vacuum and the residue distilled. A fraction with bp 110–115° C (10 mm) (0.7 g) was collected. Found, %: C 61.57; H 10.90; N 17.48. Calculated for $C_8H_{16}N_2O$, %: C 61.50; H 10.32; N 17.87.

2-(β-Acetoxyethyl)-1,2-diazabicyclo[2,2,2]octane. A mixture of 1 g (0.0064 mole) of VI and 3 ml of acetic anhydride was heated in the water bath for 2 hr. The reaction mixture was evaporated in vacuum, and the residue was treated with 50% potassium carbonate solution and extracted with ether.

1,2-Dimethyl-2-aza-1-azoniabicyclo[2,2,2]octane iodide (IX). A solution of 1.15 g (0.0091 mole) of 2-methyl-1,2-diazabicyclo[2,2,2]octane (VIII) and 2 g (0.0141 mole) of methyl iodide in 20 ml of acetone was left at room temperature for 20 hr. The precipitate that deposited was filtered off with suction and recrystallized from a mixture of acetone and ethanol, giving 1.7 g (69.5%) of the methiodide IX. Colorless crystals, readily soluble in water and ethanol, insoluble in acetone and ether. Mp 225–227° C. Found, %: I 47.33; N 10.10. Calculated for $C_8H_{17}IN_2$, %: I 47.33; N 10.44.

Hexamethylenedi(2-methyl-2-aza-1-azoniabicyclo[2,2,2]octane iodide) (X). A solution of 1.1 g (0.0087 mole) of VIII and 1.35 g (0.004 mole) of diiodohexane in 10 ml of acetonitrile was boiled for 15 hr. The mixture was evaporated in vacuum, and the residue was triturated with ethanol, giving 1.87 g (80%) of the diiodide in the form of colorless crystals readily soluble in water, moderately soluble in ethanol, and insoluble in acetone and ether; mp 156–159° C (from ethanol). Found, %: I 43.34; N 9.73. Calculated for $C_{20}H_{40}I_2N_4$, %: I 43.05; N 9.49.

REFERENCES

1. E. E. Mikhlina, N. A. Komarova, and M. V. Rubtsov, KhGS [Chemistry of Heterocyclic Compounds], 2, 91, 1966.

2. E. E. Mikhlina, N. A. Komarova, and M. V. Rubtsov, KhGS [Chemistry of Heterocyclic Compounds], 2, 259, 1966.

24 November 1966

Ordzhonikidze All-Union Chemical and Pharmaceutical Scientific-Research Institute, Moscow