QUATERNARY SALTS OF ALKALOIDS

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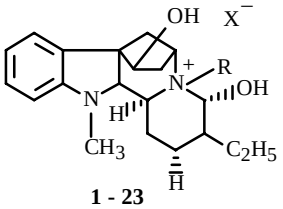
New biologically active quaternary salts of the alkaloids ajmaline, quinine, hyoscyamine, codeine, and strychnine were synthesized. So-called separable conformers were observed among the ajmaline derivatives.

Key words: alkaloids, ajmaline, hyoscyamine, quinine, codeine, strychnine, *N*-quaternary salts, separable conformers, antiarrhythmic activity.

We reported previously [1] on the preparation of several quaternary salts of the alkaloid ajmaline. The present article contains both information from the previous study [1] and new results on the preparation of biologically active derivatives of ajmaline and other alkaloids.

Quaternary salts of ajmaline were first prepared by Keck [2]. It was also found that conversion of ajmaline to certain quaternary salts increases significantly its antiarrhythmic activity. Thus, *N*(b)-propylajmaline bromide was 8-10 times more active than ajmaline and was proposed by us as a medicinal preparation called "propajmaline."

Compounds **1**-**36** (Table 1) were synthesized in one step by direct reaction of the appropriate alkaloid and alkyl halide. The reaction occurred selectively at the *N*(b)-atom for ajmaline.



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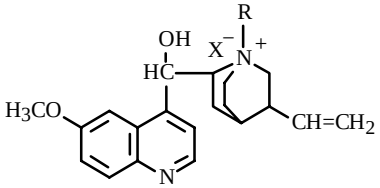

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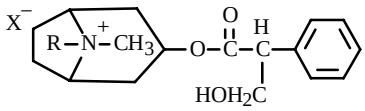

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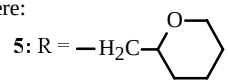
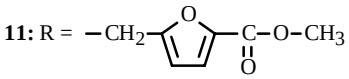
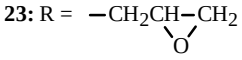
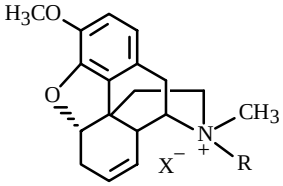
5: R = 

11: R = 

23: R = 



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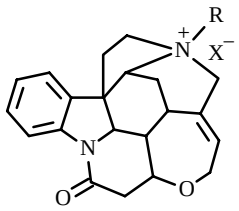

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Low-molecular-weight alkyl halides react with alkaloids at room temperature whereas bulky reagents require heating and in some instances for a rather long time. All quinine derivatives were prepared with heating.

We synthesized previously alkaloid cardenolides [3-10] that had cardiotonic and antiarrhythmic activity with relatively low toxicity. The synthesis was based on quaternary salts of the alkaloids. However, these syntheses were carried out in two steps. The first was preparation of the cardenolide halide derivatives; the second, reaction of the alkaloids with the cardenolide halides. The course of the reactions was monitored using paper chromatography and MEK:*m*-xylene (1:1)/formamide and *n*-butanol:toluene (1:2)/water.

During the investigations of *N*(b)-alkyl ajmaline derivatives, so-called separable conformers were observed. This is a rather rare observation in stereochemistry. This happens mainly in compounds with a long alkyl chain. The occurrence of separable conformers is due to hindered rotation around the N–C_1 bond of the alkyl chain.

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TABLE 1. Physicochemical Properties of **1**-**36**

Compound	R	X	Formula	mp, °C	$[\alpha]_D$ in MeOH
			N(b)-Alkylated ajmaline		
1	$CH_3(CH_2)_{10}$-	Br	$C_{31}H_{49}N_2O_2Br$	222-224	+111±2°
2	$CH_3(CH_2)_{13}$-	Br	$C_{34}H_{55}N_2O_2Br$	Amorf.	+92±2°
3	$CH_3(CH_2)_6$-	J	$C_{27}H_{41}N_2O_2J$	212-215	+123±2°
4	N≡C-CH_2-CH_2-	Br	$C_{23}H_{30}N_3O_2Br$	257-260	+148±2°
5	see the formula	Br	$C_{26}H_{37}N_2O_3Br$	266-268	+98±2°
6	$CH_3(CH_2)_8$-	Br	$C_{29}H_{45}N_2O_2Br$	230-233	+105±2°
7	$CH_3(CH_2)_7$-	J	$C_{28}H_{43}N_2O_2J$	215-218	+85.5±2°
8	$CH_3(CH_2)_5$-	Br	$C_{26}H_{39}N_2O_2Br$	264-267	+123±2°
9	$(CH_3)_2C$=CH-CH_2-CH_2-	J	$C_{26}H_{37}N_2O_2J$	235-238	+99±2°
10	Br-CH_2-$(CH_2)_2$-	Br	$C_{23}H_{32}N_2O_2Br_2$	360	+121±2°
11	see the formula	Br	$C_{27}H_{33}N_2O_5Br$	172-175	+103±3°
12	Br-CH_2-$(CH_2)_3$-	Br	$C_{24}H_{34}N_2O_2Br_2$	261-263	+110±3°
13	Bz	Br	$C_{27}H_{33}N_2O_2Br$	187-189	+100±2°
14	$CH_3(CH_2)_9$-	Br	$C_{30}H_{47}N_2O_2Br$	215-217	+89±2°
15	CH_3CH_2-	Br	$C_{22}H_{31}N_2O_2Br$	272-275	+115±2°
16	$CH_3(CH_2)_2$-	Br	$C_{23}H_{33}N_2O_2Br$	311-314	+112±3°
17	$CH_3(CH_2)_3$-	Br	$C_{24}H_{35}N_2O_2Br$	283-286	+124±2°
18	CH_2=CH-CH_2-	Br	$C_{23}H_{31}N_2O_2Br$	268-272	+117±2°
19	$CH_3(CH_2)_3$-	J	$C_{24}H_{35}N_2O_2J$		+99.5±2°
20	CH_3-	J	$C_{21}H_{29}N_2O_2J$		+119.2±2°
21	Br$(CH_2)_2$-	Br	$C_{22}H_{30}N_2O_2Br_2$	238-240/257-260	+118±2°
22	CH_3CH_2-	J	$C_{22}H_{31}N_2O_2J$	247-249/265-268	+113.6±3°
23	see the formula	Br	$C_{23}H_{31}N_2O_3Br$	200-203	+97.7±2°
			N(b)-Alkylated quinine		
24	CH_3-	J	$C_{21}H_{27}N_2O_2J$	182-185/215-220	-128.8±2°
25	CH_3-CH_2-	Br	$C_{25}H_{29}N_2O_2Br$	155-158	-113.6±3°
26	Br-CH_2-$(CH_2)_3$-	Br	$C_{24}H_{32}N_2O_2Br_2$	193-196/215-217	-69.8±2°
27	CH_3-$(CH_2)_3$-	J	$C_{24}H_{33}N_2O_2J$	144-147	-55.7±3°
			N-Alkylated hyoscyamine		
28	CH_3-	J	$C_{18}H_{26}NO_3J$	128-130/151-153	-12.7±2°
29	Br-CH_2-$(CH_2)_3$-	Br	$C_{21}H_{31}NO_3Br_2$	248-252/285-290	-8.7±2°
30	CH_3-$(CH_2)_3$-	Br	$C_{21}H_{32}NO_3Br$	105-109	-9.4±2°
31	CH_3-CH_2-	Br	$C_{19}H_{28}NO_3Br$	204-206/210-211	-10.2±2°
32	CH_3-$(CH_2)_3$-	J	$C_{24}H_{32}NO_3J$	128-130/151-153	-12.7±2°
			N-Alkylated codeine		
33	CH_3-	J	$C_{19}H_{24}NO_3J$	254-256	-63.3±4°
34	CH_3-CH_2-	Br	$C_{29}H_{26}NO_3Br$	172-175	-127±4°
			N-Alkylated strychnine		
35	CH_3-	J	$C_{21}H_{24}N_2O_2J$	304-307	0
36	CH_3-CH_2-	Br	$C_{22}H_{26}N_2O_2Br$	312-314	0

Thus, compounds with a C_5-C_{14} and higher alkyl chain form two separable conformers (Figs. 1 and 2) for **6** with a C_9 alkyl chain. Paper chromatography showed two compounds of similar polarity that gave clearly distinct spots.

Computer modeling of the stereochemistry showed that only two conformations can be constructed with retention of the bond angles and the minimum free energy. In one of these the hydrocarbon chain is directed toward the methyl on the N(α)-atom; in the other, toward the ethyl group.

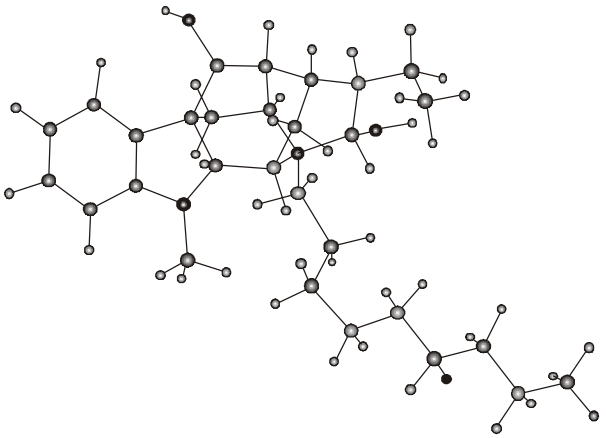

Fig. 1. Conformer 1 of **6**.

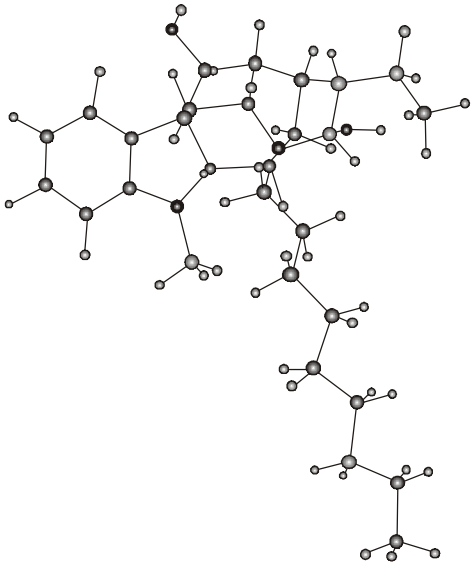

Fig. 2. Conformer 2 of **6**.

The biological activity has been determined for individual ajmaline derivatives (**1**, **15**, **16**). Compared with ajmaline, the antiarrhythmic activity of **15** and **16** was 7-10 times greater whereas that for **1** with a long hydrocarbon chain was about the same as for ajmaline.

EXPERIMENTAL

The course of reactions and purity of products were monitored using TLC on Silufol UV-254 plates with $CHCl_3$:CH_3OH:H_2O (85:15:0.7) eluent. Ajmaline and its derivatives were developed on chromatograms by spraying with conc. HNO_3 to form strongly colored red spots. Chromatograms were thoroughly dried beforehand to remove formamide in a drying chamber at 105-110°C. Quinine, hyoscyamine, codeine, strychnine, and their derivatives were developed on chromatograms by irradiation with unfiltered UV light. Elemental analyses were performed on a Model 1106 automated C-H-N-S analyzer and agreed for all compounds with those calculated.

***N*(b)-Nonylajmaline Bromide (6).** A solution of ajmaline (1.7 g) in CH_3CN:$CHCl_3$ (1.5:1, 25 mL) was treated with nonylbromide (2.4 g), refluxed for 8 h, concentrated to a volume of ~7 mL, and left overnight at room temperature. The resulting crystals were separated on a Buchner funnel and washed with CH_3CN (4 mL) and hexane (20 mL).

The crystals were recrystallized by dissolving in boiling CH_3CN (40 mL). The hot solution was filtered, concentrated to a volume of ~5 mL, and left for 5 h at room temperature. The crystals were separated and washed with CH_3CN (3 mL) to afford **6** (1.2 g), $C_{29}H_{45}N_2O_2Br$.

***N*(b)-Methylquinine Iodide (24).** Quinine (2 g) was dissolved in $CHCl_3$ (10 mL) and treated with methyliodide (3 mL). The solution was sealed in a glass ampul and held in a thermostat at -40°C for 17 h. The resulting crystals were separated on a Buchner funnel and washed with $CHCl_3$ (5 mL) and hexane (2 mL) to afford crystals (2.4 g) of the crude product.

The crystals were recrystallized by dissolving in CH_3OH (30 mL) with heating. The solution was concentrated to a volume of ~5 mL, treated with CH_3CN (15 mL), and evaporated to a volume of ~7 mL. The resulting golden yellow crystals were separated and washed with CH_3CN (5 mL) to afford **24** (1.7 g), $C_{21}H_{27}N_2O_2I$.

***N*-Bromobutylhyoscyamine Bromide (29).** Hyoscyamine (1.5 g) was dissolved with heating in CH_3CN (15 mL) and treated with 1,4-dibromobutane (3.7 mL). The solution was held at room temperature for 3 d. The product precipitated upon addition of hexane (45 mL). The resulting thick solid was triturated four times with hexane until it turned into a powder. The solvent was decanted. The amorphous powder was dried in vacuo.

The crude product was recrystallized by dissolving in CH_3CN (50 mL) with heating. The solution was concentrated to a volume of ~7 mL and left overnight. The resulting crystals were washed with CH_3CN (5 mL) to afford **29** (1.3 g), $C_{21}H_{31}NO_3Br_2$.

The remaining quaternary salts of the alkaloids were synthesized analogously.

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