MEDICINAL PLANTS

ANTIARRHYTHMIC ACTIVITY OF DITERPENOID ALKALOIDS OF THE NAPELLINE TYPE AND THEIR ACYLATED DERIVATIVES

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Diterpenoid alkaloids possess a broad spectrum of pharmacological properties [1 – 3]. The pronounced antiarrhythmic activity of some compounds belonging to this class and, in particular, the successful practical application of allapinine [4] and aclezine [5] preparations justify the further search for antiarrhythmic drugs among various structural types of diterpenoid alkaloids and their synthetic analogs.

Below we present the results of investigation of the antiarrhythmic activity of some alkaloids with the structural skeleton of napelline (I), which were isolated from the plants of *Aconitum karakolicum Rapaics*. In addition, we studied a series of acylated derivatives of napelline and songorine containing an acyl residue at C-1. These compounds were synthesized by selective hydrolysis based on the difference in the rates of hydrolysis of ester groups occurring in various positions of the skeleton [6].

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TABLE 1. Physicochemical Properties of the Synthesized Compounds

Compound	Empirical formula	M.p., °C	M^+	Ref.
I	$C_{22}H_{33}NO_3$	162 – 164	359	[9]
II	$C_{24}H_{35}NO_4$	205 – 206	401	[7]
III	$C_{22}H_{33}NO_3$	118 – 121	359	[10]
IV	$C_{22}H_{33}NO_4$	197 – 199	375	[11]
V	$C_{22}H_{31}NO_3$	201 – 203	357	[9]
VI	$C_{22}H_{33}NO_3$	202 – 204	359	[12]
VII	$C_{28}H_{39}NO_6$	Amorphous	485	
VIII	$C_{24}H_{35}NO_4$	167 – 169	401	
IX	$C_{43}H_{45}NO_6$	170 – 172	671	
X	$C_{29}H_{37}NO_4$	112 – 114	463	
XI	$C_{26}H_{35}NO_5$	180 – 182	441	
XII	$C_{36}H_{33}NO_5$	Amorphous	565	
XIII	$C_{23}H_{35}NO_4$	101 – 103	399	
XIV	$C_{29}H_{35}NO_4$	Amorphous	461	

EXPERIMENTAL CHEMICAL PART

The group of substances studied in this work included alkaloids napelline (I), 12-O-acetylnapelline (II), 12-epinapelline (III), napelline N-oxide (IV), songorine (V), dihydrosongorine (VI), and acylated derivatives of napelline and songorine: 1-O-acetylnapelline (VIII), 1,15-O-tribenzoylnapelline (IX), 1-O-benzoylnapelline (X), 1,15-O-diacetylsongorine (XI), 1-O-acetylsongorine (XIII), and 1-O-benzoylsongorine (XIV). Some physicochemical properties of the synthesized compounds are listed in Table 1.

Compounds VII and XI were synthesized as described in [7] and [8], respectively.

1-O-Acetylnapelline (VIII). A mixture of 1.0 g (20 mmole) of 1,12,15-O-triacetylnapelline (VII) with 40 ml of a 5% KOH solution in methanol was boiled with reflux for 35 min. Upon cooling, methanol was evaporated and the residue dissolved in 50 ml water and extracted with chloroform. The extract was dried over sodium sulfate, after which chloroform was distilled off. The residue was treated with acetone to isolate the target compound VIII (yield, 67%).

An analogous procedure was used for the synthesis of 1-O-acetylsongorine (XIII) from diacetylsongorine (XI).

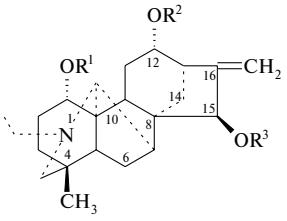
1,12,15-O-Tribenzoylnapelline (IX). To a solution of 2.4 mg (6.7 mmole) napelline in 80 ml piperidine was added dropwise 5.6 g (40.2 mmole) of benzoyl chloride, after which the reaction mixture was allowed to stand at room temperature for 40 h. Then piperidine and excess benzoyl chloride were distilled off and the residue was dissolved in 2% sulfuric acid. The acid solution was triply washed with benzene, alkalized on cooling with sodium carbonate, and exhaustively extracted with chloroform. The extract was dried over sodium sulfate, after which chloroform was distilled off. The residue was treated with methanol to isolate the target compound IX (yield, 89%).

An analogous procedure was used for the synthesis of dibenzoylsongorine (XII) from songorine (V).

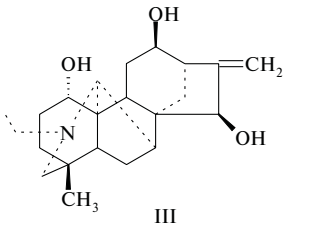
1-O-Benzoylnapelline (X). A mixture of 2.1 g (3.1 mmole) of 1,12,15-O-tribenzoylnapelline (IX) with

70 ml of a 5% KOH solution in methanol was boiled with reflux for 45 min. Upon cooling, methanol was evaporated and the residue dissolved in 100 ml water and extracted with chloroform. The extract was dried over sodium sulfate, after which chloroform was distilled off. The residue was treated with methanol to crystallize the target compound X (yield, 72%).

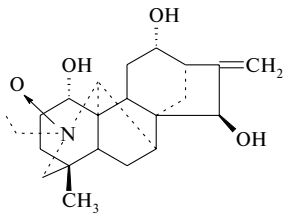
An analogous procedure was used for the synthesis of 1-O-benzoylsongorine (XIV) from dibenzoylsongorine (XII).



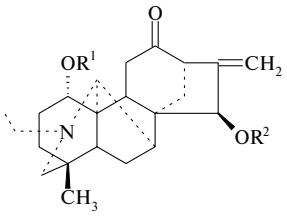
I: $R^1 = R^2 = R^3 = H$;
II: $R^1 = R^3 = H$, $R^2 = Ac$;
VII: $R^1 = R^2 = R^3 = Ac$;
VIII: $R^1 = Ac$, $R^2 = R^3 = H$;
IX: $R^1 = R^2 = R^3 = Bz$;
X: $R^1 = Bz$, $R^2 = R^3 = H$.



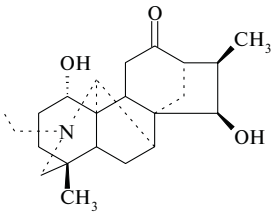
III



IV



V: $R^1 = R^2 = H$;
XI: $R^1 = R^2 = Ac$;
XII: $R^2 = R^2 = Bz$;
XIII: $R^1 = Ac$, $R^2 = H$;
XIV: $R^1 = Bz$, $R^2 = H$.



VI

EXPERIMENTAL PHARMACOLOGICAL PART

The acute toxicity was determined by intravenous injections in a group of 340 white mice weighing 18 – 22 g. The antiarrhythmic activity was studied on an aconitine-induced arrhythmia model in a group of rats weighing 200 – 250 g. The animals were narcotized by ethaminal sodium (40 mg/kg, i.p.), aconitine was intraperitoneally injected in a dose of 12 μg/kg, and EEG were measured in a second standard lead. The synthesized compounds were intravenously injected in increasing (3 – 4 steps) doses 3 – 5 min before aconitine injections. The effect of each dose was studied in a group of 5 – 6 animals.

The LD_{50} and ED_{50} were calculated by the Litchfield – Wilcoxon method. The therapeutic breadth was evaluated by the antiarrhythmic index (AAI) calculated as the ratio of lethal and effective doses (LD_{50}/ED_{50}).

TABLE 2. Antiarrhythmic Activity of the Synthesized Compounds on the Aconitine-Induced Arrhythmia Model in Rats

Compound	LD_{50}, mg/kg	ED_{50}, mg/kg	AAI = ED_{50}/LD_{50}
I	88.0	10.0	8.8
II	101.0	15.0	6.7
III	82.0	80.0	10.0
IV	725.0	28.0	25.8
V	142.0	7.3	19.0
VI	120.0	12.0	10.0
VIII	100.0	15.0	6.7
IX	175.0	20.0	8.8
X	30.0	0.24	133.3
XI	131.0	18.0	7.3
XIII	150.0	15.0	10.0
XIV	41.0	0.38	107.9
Novocainamide	110.0	40.0	2.75
Quinidine	66.9	20.0	3.3
Lidocaine	39.0	10.0	3.9

It was established that most of the studied compounds produce a more or less pronounced antiarrhythmic effect (Table 2). The maximum activity was observed for 1-O-benzoylnapelline (X), the effect of which markedly exceeded that of the initial napelline and the reference class I antiarrhythmic drugs novocainamide, quinidine, and lidocaine.

REFERENCES

1. F. N. Dzhakhangirov, *Abstracts of Papers. The All-Union congress of Pharmacists "Physiologically Active Substances in Medicine"* [in Russian], Yerevan (1983), p. 103.
2. Ì. N. Berai and J. M. Jacyno, in: *Alkaloids: Chemical and Biological Perspectives*, S. W. Pelletier (ed.), Wiley, New York (1984), Vol., 1 Ch. 4., p. 153.
3. F. N. Dzhakhangirov, *Abstracts of Papers. Int. Conf. "Medicinal Raw Materials and Phytopreparations for Medicine and Agriculture*," Karaganda (1999), p. 130.
4. F. N. Dzhakhangirov, F. Sokolov, and A. N. Verkhratskii, *Allapinine: A New Antiarrhythmic Preparation* [in Russian], Fan, Tashkent (1993).
5. Sh. Sh. Sagdullaev, A. Z. Sadikov, F. N. Dzhakhangirov, and T. T. Shakirov, *Khim. Prir. Soedin. (Spec. Issue)*, 134 – 137 (1999).
6. M. N. Sultankhodzhaev and M. S. Yunusov, *Khim. Prir. Soedin.*, No. 3, 381 – 383 (1975).
7. M. N. Sultankhodzhaev, M. S. Yunusov, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, No. 4, 479 – 482 (1978).
8. S. Yu. Yunusov, *Izv. Akad. Nauk UzSSR*, **3**, 31 (1947).
9. M. N. Sultankhodzhaev, M. S. Yunusov, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, No. 2, 199 – 205 (1973).
10. M. N. Sultankhodzhaev and M. S. Yunusov, *Khim. Prir. Soedin.*, No. 3, 386 – 388 (1987).
11. M. N. Sultankhodzhaev, L. V. Beshitaishvili, M. S. Yunusov, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, No. 6, 826 – 829 (1979).
12. M. N. Sultankhodzhaev and M. S. Yunusov, *Khim. Prir. Soedin.*, No. 6, 917 – 918 (1987).