SYNTHESIS AND HYPOTENSIVE ACTIVITY OF NEW AMINO DERIVATIVES OF TERPENOIDS AND THEIR STRUCTURAL ANALOGS

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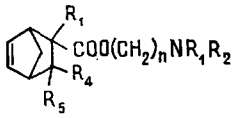
Thirty-five new salts of amino ester derivatives of terpenoids have been synthesized and their influence on the level of arterial pressure has been investigated.

A broad investigation of the biological activities of derivatives of terpenoids and their structural analogs has revealed among them a large number of compounds acting on the cardiovascular system. Thus, of norborane systems exhibiting an action on the cardiovascular system extensive studies have been made of norbornylalkylamines [1-3], the stereoisomers of 2-amino-3-phenylnorbornane [4], and derivatives of bicyclo[2.2.1]heptane in which a nitrogen atom is a component part of a spirocyclic system [5].

Particular interest is presented by amino esters containing a norbornane fragment in view of their considerable hypotensive action. Thus, amino esters of general formula (I) are known as substances considerably lowering the blood pressure. Their quaternary salts are ganglion-blockers.



I

II [sic]

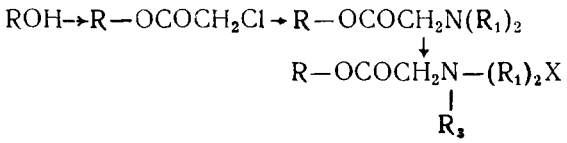
a. $X = R_2N-(CH_2)_n-OOC$

b. $X = (R_1)_2N-(CH_2)_m-OCC(CH_2)_n-N(CH_2)R_2$ [sic]

Quaternary salts of amino esters of formula (II) have been synthesized and subjected to broad biological trials. Among them the methiodide of (IIa) with n = 2 in which R_2N is morpholine is a commercial preparation lowering the blood pressure.

These facts induced us to investigate the action on the systemic arterial pressure of new salts of amino ester derivatives of terpenoids and their structural analogs that we had synthesized.

The synthesis of the compounds was effected by the scheme:



where X = I or Cl; R_3 = H or CH_3: $N(R)_2$ = $N(CH_3)_2$, $N(C_2H_5)_2$, $N(C_4H_9)_2$, morpholine, or piperidine; and ROH = 2-hydroxymethylbicyclo[2.2.1]hept-5-ene (A), 2-hydroxethylbicyclo[2.2.2]oct-5-ene (B), isoborneol (C), fenchol (D), borneol (E),; camphanol (G), or menthol (F). The methiodides and hydrochlorides of the compounds synthesized are readily soluble in water and ethanol and are therefore convenient for biotesting.

The characteristics of the compounds obtained are given in Table 1. The structures of the substances were established with the aid of their IR, mass and ^{13}C NMR spectra and were confirmed by elementary analysis.

According to ^{13}C NMR, in the norbornane, bicyclo[2.2.2]octane, borneol and fenchone derivatives the substituent at C_2 was present in the endo position, and in the isoborneol derivatives in the exo position. The menthol derivatives were individual isomers with the

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TABLE 1. Characteristics of the Compounds Synthesized and Their Action on the Level of Arterial Pressure

Compound	R_1	R_2	R_3	X	T mp, °C	Empirical formula	Dose, mg/kg	Mean fall in the AP, % of initial	Duration of the hypotensive effect, min
1	2	3	4	5	6	7	8	9	10
I	A	$C_5H_{10}N$	CH_3	I	140—141	$C_{16}H_{26}O_2NI$	10	—14∓2	60
II	"	$C_5H_{10}N$	H	Cl	150—152	$C_{15}H_{24}O_2ClN$	10	—13∓6,2	60
							20	—22,9∓8,3	60
III	"	C_4H_8NO	CH_3	I	155—156	$C_{15}H_{24}O_3NI$	20	—7∓2	60
IV	"	C_4H_8NO	H	Cl	170—171	$C_{14}H_{22}O_3ClN$	20	—14∓8	60
V	"	$C_4H_{10}N$	H	Cl	198—199	$C_{14}H_{24}O_2ClN$	10	—24∓7.3	60
							20	—30∓6,4	60
VI	"	$C_8H_{18}N$	CH_3	I	127—129	$C_{19}H_{34}O_2NI$	10	—27∓10	60
							20	—34∓7.3	60
VII	"	$C_8H_{18}N$	H	Cl	199—201	$C_{18}H_{32}O_2NCl$	10	—22,9∓8,3	60
							20	—25∓9.4	60
VIII	B	C_2H_6N	CH_3	I	203—204	$C_{15}H_{26}O_2NI$	10	—9∓2,2	60
IX	"	$C_8H_{18}N$	CH_3	I	167—168	$C_{21}H_{38}O_2NI$	10	—14∓2	60
							20	26∓3.8	>60
X	"	$C_4H_{10}N$	CH_3	I	144—145	$C_{18}H_{30}O_2NI$	10	—7,8∓2	>60
							20	—14∓8	>60
XI	"	$C_5H_{10}N$	CH_3	I	125—126	$C_{17}H_{30}O_2NI$	20	—5∓4	60
XII	"	C_4H_8ON	CH_3	I	157—158	$C_{17}H_{28}O_3NI$	20	—42,6∓10,1	60
XIII	"	C_4H_8NO	H	Cl	186—188	$C_{16}H_{26}O_2ClN$	20	—14∓8	60
XIV	C	$C_5H_{10}N$	H	Cl	210—212	$C_{17}H_{30}O_2ClN$	5	—26,6∓8	60
							10	—35,8∓9,4	<60
XV	"	$C_5H_{10}N$	CH_3	I	182—183	$C_{18}H_{32}O_2NI$	10	—16,3∓7,3	60
							25	—26,9∓2,5	60
XVI	"	C_4H_8NO	CH_3	I	198—199	$C_{17}H_{30}O_3NI$	10	—20∓2,4	60
							25	—46∓3,3	60
XVII	"	$C_4H_{10}N$	CH_3	I	177—179	$C_{17}H_{32}O_2NI$	10	—17∓2,4	60
XVIII	"	C_2H_6N	CH_3	I	201—202	$C_{15}H_{28}O_2NI$	5	—65∓2.4	>60
							10	—45∓3,3	>60
							25	—22∓7,6	
XIX	"	C_2H_6N	H	Cl	194—195	$C_{14}H_{24}O_2ClN$	10	—18∓2,6	60
							25	—50∓3.2	>60
XX	D	$C_5H_{10}N$	H	Cl	210—211	$C_{17}H_{30}O_2ClN$	5	—18∓2,1	>60
							10	—26∓4,2	>60
							25	—30∓2,9	<60
XXI	"	$C_5H_{10}N$	CH_3	I	218—220	$C_{18}H_{32}O_2NI$	10	—18∓3,2	>60
							25	—40∓7,6	>60
XXII	"	$C_4H_{10}N$	CH_3	I	170—171	$C_{17}H_{32}O_2NI$	5	—20∓2,4	60
							10	—4,6∓3,3	60
XXIII	"	$C_8H_{18}N$	CH_3	I	156—157	$C_{21}H_{40}O_2NI$	10	—6,5∓2,6	>60
							25	—45∓3,3	>60
XXIV	"	$C_5H_{10}N$	CH_3	I	172—174	$C_{18}H_{32}O_2NI$	10	—18∓2,9	60
							25	Death of the animals	
XXV	E	$C_4H_{10}N$	H	Cl	202—203	$C_{16}H_{30}O_2ClN$	10	—24∓4,2	60
							20	—20∓3	60
XXVI	"	$C_4H_{10}N$	CH_3	I	198—199	$C_{17}H_{32}O_2NI$	10	—10∓5	60
							20	—8∓3	60
XXVII	G	C_4H_8N	H	Cl	190—191	$C_{16}H_{28}O_3ClN$	10	—12∓5,0	60
							20	—16+2,9	60
XXVIII	"	C_4H_8NO	CH_3	I	215—216	$C_{18}H_{32}O_3NI$	10	—20∓4	60
							20	—24∓7,3	60
XXIX	F	C_4H_8NO	H	Cl	187—188	$C_{16}H_{30}O_3ClN$	10	—23∓6,2	60
							20	—62,9∓8,3	60
XXX	"	C_4H_8NO	CH_3	I	189—190	$C_{17}H_{32}O_3NI$	10	—22,3∓2,8	60
							20	—24,3∓6,1	60
XXXI	"	$C_5H_{10}N$	H	Cl	190—191	$C_{17}H_{32}O_2ClN$	10	—26∓3,2	60
							20	—29∓4	60
XXXII	A	$C_5H_{10}N$	CH_3	I	208—209	$C_{18}H_{34}O_2NI$	10	—16∓6,1	<60
							20	—27,9∓2,9	60
XXXIII	"	$C_4H_{10}N$	CH_3	I	165—166	$C_{17}H_{34}O_2NI$	5	—7	60
							10	—16∓3,4	60
XXXIV	"	$C_8H_{18}N$	CH_3	I	148—150	$C_{21}H_{42}O_2NI$	10	—24,7∓6,7	60
							5	—29∓9,2	60
XXXV	"	$C_8H_{18}N$	H	Cl	226—228	$C_{20}H_{40}O_2NCl$	5	—42∓12,7	60
							10	—40,9∓7,2	60

triequatorial position of the substituents. The camphanol derivatives were the 2-exo-6-exo isomers. The influence of the compounds synthesized on the arterial pressure was recorded in the common carotid artery in the usual way. The compounds were administered intravenously, distilled water being used as the solvent.

As can be seen from the results presented in Table 1, among the amino ester salts the most active were isoborneol piperidino- and diethylaminoacetates ((XV) and (XVIII), respectively). The endo isomers of these compounds ((XXIV) and (VI)) exhibited a similar, although somewhat less pronounced, action on the vascular system. Trials of the analogous derivatives of fenchol, isocamphanol, norborn-5-ene, and bicyclo[2.2.2]oct-5-ene did not reveal among them any substances appreciably affecting the arterial pressure. The results of the investigations are given in Table 1.

EXPERIMENTAL

IR and ^{13}C NMR spectra were taken on instruments and under conditions similar to those described previously [7]. The aminoacetates of the above-mentioned alcohols were synthesized by the procedure of [8].

The hydrochlorides of the aminoacetates were obtained by the passage of hydrogen chloride through an ethereal solution of the corresponding amine. They were recrystallized from solution in ether—ethanol.

The methiodides were obtained by heating equimolar amounts of the amines and methyl iodide in ethanol at 50-60°C for 1-2 h, followed by recrystallization from ethereal-ethanolic solution.

The methanol and fenchol derivatives were optically active, $[\alpha]_D^{20}$ (ethanol): (XXXI) −51.184° (c 1.02); (XXXII) −37.96° (c 1.001); (XXXIII) −44.0° (c 1.09); (XXXIV) −34.8° (c 1.06); (XXXV) −30.1° (c 1.6); (XX) +62.12° (c 0.999); (XXI) +64.82° (c 1.012); (XXII) +71.84° (c 0.998); (XXXIII) +84.12° (c 1.005).

SUMMARY

Thirty-five new salts of amino esters of terpenoids have been synthesized and their influence on the level of arterial pressure has been determined.

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