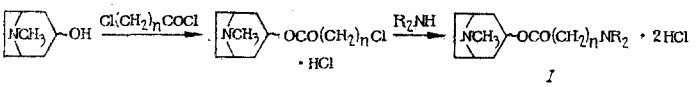
SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF ω-AMINOACYL ESTERS OF THE STEREOISOMERIC TROPAN-3-OLS

L. M. Kostochka, A. P. Rodionov, A. P. Skoldinov, and V. V. Zakusov

UDC 615.218.2:547.747].012.1

According to the literature esters of tropine show different pharmacological effects, depending upon the character of the esterifying acid. Thus, esters of tropic acid exhibit antihistaminic, antiserotonin, and stimulant activity [1, 2], esters of pyrrole-4-carboxylic acid are analgesics [3], esters of 5-aryl-furan-2-carboxylic acid are anesthetics [4], tropine esters of 3-indolylphenylacetic acid show spasmolytic activity [5], and esters of diarylacetic acids are anticholinergic substances [6]. Furthermore, many derivatives of tropane show stimulant activity on the central nervous system [7]. We therefore prepared a series of ω-aminoacyl esters (I) of the stereoisomeric α- and β-tropanols (tropane and pseudotropane) in order to study their stimulant activity. Synthesis of the esters was brought about by the general scheme:



I

Acylation of tropine or pseudotropine with the acyl chlorides of ω-chlorocarboxylic acids proceeded in toluene, and the resulting ester hydrochloride after filtration was used in the subsequent step without further purification. Aminolysis of the chloroester proceeded easily by heating the hydrochloride with three moles of secondary amine in toluene: The salt of the secondary amine precipitated and the weakly basic aminoester remained in solution. It is more convenient, however, to carry out the reaction of the hydrochloride with one mole of secondary amine in alcohol to give the dihydrochloride of the aminoester directly. The secondary amines studied were dimethyl amine, pyrrolidine, piperidine, morpholine, and N-methylpiperazine. Several of the hydrochlorides prepared were hydroscopic or contained water of crystallization.

The stimulant activity of these compounds was studied in experiments on rabbits. As a criterion of physiological activity, their influence on the phenomenon of impulse summation in the central nervous system was used. The dependence of a reflex motor reaction (tail flexion) on the number and amplitude of the stimuli applied to the skin of the back feet of the rabbits was determined. As shown in Table 1, all of the compounds studied to some degree relieve the summation at a dose of 0.5-1.0 and 3.0 mg/kg, and impede it at a dose of 5-20 mg/kg. Thus, they possess the property of stimulating one of the basic manifestations of nerve activity: the alleviation of impulse summation. As shown in special pharmacological analysis, the indicated compounds act by an adrenergic mechanism and therefore we used cocaine as a standard of comparison. All of these compounds are of comparatively low toxicity: Their LD_{50} (in white mice with intraperitoneal introduction) ranged between 270 and 1100 mg/kg.

EXPERIMENTAL

The purity of the compounds prepared was estimated by GLC on a Tsvet-1 chromatograph. Melting points were determined on a Boethius apparatus, and mass spectra were recorded on an MAT-112 mass spectrometer.

Tropinyl-β-Chloropropionate Hydrochloride (General Method). To a solution of 30 g of freshly-distilled tropine in 100 ml of toluene was added gradually with stirring a solution of 30 g of β-chloropropionyl chloride in 50 ml of toluene, and the mixture was stirred and boiled for 4 h. The precipitate which formed upon cooling was filtered off and washed with acetone on the filter, to give 46.6 g (83%, based on tropine) of hydrochloride, which was used in the following step without further purification. mp 193-194°C (from acetone–alcohol). Found, %: C 49.5; H 7.2; Cl 26.3. $C_{11}H_{18}ClN \cdot HCl$. Calculated, %: C 49.6; H 7.0; Cl 26.4.

Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 17, No. 5, pp. 558-561, May, 1983. Original article submitted November 5, 1982.

0091-150X/83/1705-0345$07.50

TABLE 1. Stereoisomeric Tropane-3-ol ω-Aminoacyl Ester Hydrochlorides and Their Pharmacological Activity

Configurations	n	NR_2	mp, deg C	Yield, %	Found, %				Empirical formula	Calculated, %				Impulse summation		LD_{50}, mg/kg; intraperitoneal
					C	H	N	Cl		C	H	N	Cl	alleviation, mg/kg	impedance, mg/kg	
α	1	N-morpholinyl	264—8	58,6	49,33	7,71	8,22	20,67	$C_{14}H_{26}N_2O_3 \cdot 2HCl$	49,2	7,6	8,2	20,6	0,5	5	1100 (973,4—1243)
α	2	Dimethylamino	210—212	62,8[a]	47,2	8,47	8,50	21,4	$C_{13}H_{26}N_2O_3 \cdot 2HCl \cdot H_2O$	47,1	8,4	8,4	21,4	0,5	20	660 (471,4—924)
α	2	Diethylamino	200—203	57,8[b]	52,68	8,86	8,22	20,9	$C_{15}H_{30}O_2N_2 \cdot 2HCl$	52,7	8,7	8,2	20,8	3	20	600 (521,6—690)
α	2	N-pyrrolidinyl	239—40	57,1[c]	52,68	8,37	8,2	20,69	$C_{15}H_{28}N_2O_2 \cdot 2HCl$	53,0	8,25	8,2	20,9	1—3	20	580 (487,3—690,7)
α	2	N-piperidinyl	263—4	66,6[d]	53,8	8,5	7,7	20,0	$C_{16}H_{30}N_2O_2 \cdot 2HCl$	54,3	8,4	7,9	20,1	2	20	470 (493,2—502,9)
α	2	N-piperazinyl	231—233	51,2[e]	45,17	8,18	10,11	24,83	$C_{16}H_{34}N_3O_3 \cdot 3HCl \cdot H_2O$	45,2	8,0	9,9	25,0	0,5	10	480 (400—576)
α	2	N-morpholinyl	239—40	61,1[f]	50,56	7,9	7,9	19,83	$C_{15}H_{27}N_2O_3 \cdot 2HCl$	50,7	7,8	7,9	20,0	1	10	1000
α	4	N-morpholinyl	198—200	64,9	51,06	8,51	6,79	17,86	$C_{17}H_{34}O_4N_2 \cdot 2HCl \cdot H_2O$	50,8	8,4	6,9	17,7	1	20	270 (225—324,0)
β	1	N-morpholinyl	254	61,2	49,28	7,6	8,15	20,52	$C_{14}H_{26}O_3N_2 \cdot 2HCl$	49,2	7,6	8,2	20,6	1	10	540 (348,3—837)
β	2	Dimethylamino	218—9	52,2[a]	50,33	8,44	8,82	21,96	$C_{13}H_{26}N_2O_2 \cdot 2HCl$	49,84	8,3	8,6	22,6	—	20	620 (448,2—787,4)
β	2	Diethylamino	237—9	63,1	52,7	8,7	8,24	20,94	$C_{15}H_{30}N_2O_2 \cdot 2HCl$	52,7	8,7	8,2	20,8	1	20	560 (459—683,2)
β	2	N-piperidinyl	205—208	61,2	53,09	8,73	7,98	21,08	$C_{15}H_{28}N_2O_2 \cdot 2HCl \cdot 0,5H_2O$	53,0	8,25	8,2	20,9	1	10	580 (483,3—696,6)
β	2	N-piperazinyl	255—7	56,6[g]	43,29	8,66	7,95	20,02	$C_{16}H_{30}N_2O_2 \cdot 2HCl$	54,2	8,4	7,9	20,1	0,5	20	700 (593—826)
β	2	N-piperazinyl	259—60	55	46,22	8,05	10,16	25,4	$C_{16}H_{33}N_3O_2 \cdot 3HCl \cdot {}^1/_2H_2O$	46,5	7,9	10,1	25,5	0,5	5	380 (283,5—509,2)
β	2	N-morpholinyl	248—9	68,5	50,46	7,99	7,71	20,21	$C_{15}H_{27}N_2O_3 \cdot 2HCl$	50,7	7,8	7,9	20,9	0,1	0,5	1100
β	4	N-morpholinyl	155—7	45,2	53,0	8,3	6,9	18,48	$C_{17}H_{32}O_3N_2 \cdot 2HCl$	53,2	8,3	7,3	18,5	1	20	850
Cocaine (ethanol)			—	—	—	—	—	—	—	—	—	—	—	0,5—1	2,5—5	80

[a] By addition of a 20% solution of dimethylamine in toluene.

[b] Base: bp 123-125 deg C (2 mm), n_D^{20} 1.4810. Found, %: C 67,11; H 10,36; N 10,55. M+ 268. $C_{15}H_{28}O_2N_2$. Calculated, %: C 67,16; H 10,44; N 10,44.

[c] Base: bp 141-142 deg C (2 mm), n_D^{20} 1.4970. Found, %: N 10,66. M+ 266. $C_{15}H_{26}N_2O_2$. Calculated, %: N 10,52.

[d] Base: bp 145-147 deg C (2 mm), n_D^{20} 1.5000. Found, %: C 68,51; H 10,00; N 10,01. $C_{16}H_{28}N_2O_2$. Calculated, %: C 68,57; H 10,00; N 10,00.

[e] Base: bp 158-160 deg C (2 mm), n_D^{20} 1.5020. Found, %: N 14,60. M+ 295. $C_{16}H_{29}N_3O_2$. Calculated, %: N 14,60.

[f] Base: bp 166-167 deg C (2 mm), n_D^{20} 1.4970. Found, %: C 63,70; H 9,33; N 9,84. M+ 282. $C_{15}H_{26}N_2O_3$. Calculated, %: C 63,82; H 9,2; N 9,92.

[g] Base: bp 148-150 deg C (2 mm), n_D^{20} 1.5010. Found, %: C 68,59; H 10,05; N 10,16. M+ 280. $C_{16}H_{28}N_2O_2$. Calculated, %: C 68,57; H 10,00; N 10,00.

Tropinyl β-(N-Morpholyl)propionate Hydrochloride (General Method). To a solution of 30 g of tropinyl β-chloropropionate hydrochloride in 150 ml of alcohol was added dropwise 9.76 g of morpholine, the mixture was heated under reflux for 8 h, and the alcohol was distilled. The residue was recrystallized from a mixture of acetone–alcohol (1:9) to give 31.4 g of dihydrochloride, mp 239-240°C.

The free base was isolated for characterization by vacuum distillation. The constants and analytical results are given in Table 1.

LITERATURE CITED

1. M. D. Mashkovskii and T. Ya. Shvarts, Farmakol. Toksikol., No. 1, 3-7 (1979).
2. R. Barloy, Introduction to Chemical Pharmacology [in Russian], Moscow (1959).
3. J. A. Waters, J. Med. Chem., 20, 1094-1096 (1977).
4. T. I. Vozyakova, N. I. Koretskaya, and M. D. Mashkovskii, Inventor's Certificate No. 508057 (USSR), Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki, No. 23, 197 (1977).
5. N. N. Suvorov and M. D. Mashkovskii, Khim. Geterotsikl. Soedin., No. 1, 73-75 (1975).
6. E. R. Atkinson and D. D. Merithie, J. Med. Chem., 20, 1612-1617 (1977).
7. V. V. Zakusov, L. M. Kostochka, and A. P. Skoldinov, Byull. Eksp. Biol., No. 10, 435-438 (1978).

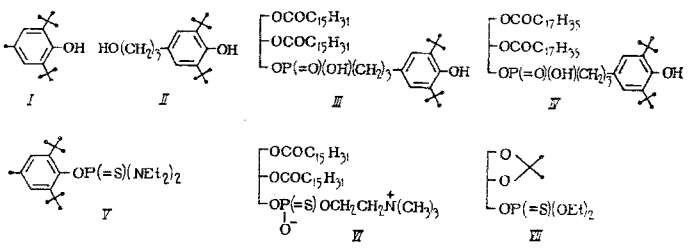
ANTIOXIDANT PROPERTIES OF THIOPHOSPHOLIPIDS AND IONOL PHOSPHOLIPIDS

T. V. Sotnichenko, I. A. Vasilenko, R. P. Evstigneeva, D. A. Predvoditelev, and É. E. Nifant'ev

UDC 547.953:547.568.5

The potential use of free radical oxidation inhibitors (ionol, α-tocopherol, etc.) in medicine has been reported [1]. Because of their chemical structure, these inhibitors have no affinity for the lipid component of biological membranes, i.e., for those substances which primarily are subject to free radical oxidation, a process which is responsible for the development on pathological symptoms [2, 3]. With this in mind, work was begun on the synthesis of phospholipid membrane directed inhibitors [4-7]. These compounds contain sterically hindered phenol or thiophosphoryl groups, which we consider responsible for the inhibition process.

Our article reports data on the evaluation of the antioxidant activity of some new bioantioxidants. In order to eliminate peroxide oxidation of the lipid antioxidants themselves, the latter (I-VII) were synthesized starting from saturated fatty acids. In the peroxide oxidation of phospholipids containing polyunsaturated fatty acids, accumulation of the first products of oxidation — hydroperoxides — is accompanied by the formation of conjugated double bonds which absorb in the UV at 233 nm. The relative intensities of the absorption bands I_{233} nm/I_{215} nm are known as the oxidation index [8], which is widely used in the field of lipid oxidation.



M. V. Lomonosov Moscow Institute of Fine Chemical Technology, V. I. Lenin Moscow Pedagogical Institute.

Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 17, No. 5, pp. 561-562, May, 1983. Original article submitted December 23, 1982.

0091-150X/83/1705-0347$07.50