SYNTHESIS AND CHOLERETIC ACTIVITY OF 2-BENZYLTETRAHYDROISOQUINOLINE DERIVATIVES

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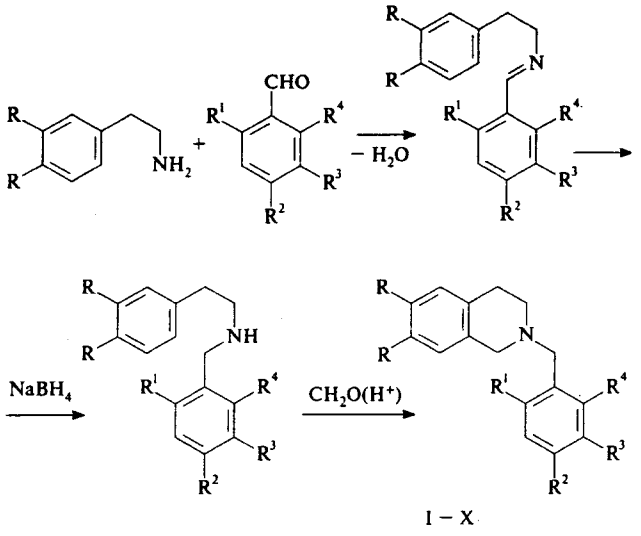
Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 31, No. 9, pp. 30 – 32, September, 1997.

Original article submitted September 25, 1995.

Some of the N-benzyltetrahydroisoquinoline derivatives synthesized in our previous works [1, 2] exhibit a pronounced choleretic activity. However, we failed to find any data on the effect of these compounds on the process of bile secretion and the antitoxic function of liver in the available literature.

In this connection it was of interest to continue our investigations on the synthesis of N-benzyltetrahydroisoquinolines and study their choleretic activity. The new derivatives (I – X) were synthesized using homoveratrylamine or homopiperonylamine and substituted benzaldehydes [3] obtained by halogenation or nitrogenation of the corresponding benzaldehydes [4, 5].



I – X

The proposed structures were confirmed by data of elemental analyses, mass spectrometry, and ^1H NMR spectroscopy. The characteristics of the synthesized compounds are listed in Table 1.

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EXPERIMENTAL CHEMICAL PART

The ^1H NMR spectra were measured on a Tesla BS-567A (100 MHz) instrument using $CDCl_3$ as a solvent and HMDS as the internal standard. The mass spectra were obtained on an MX-1310 spectrometer with an electron ionization energy of 70 eV. The data of elemental analyses agree with the results of calculations according to the empirical formulas.

2-Benzyltetrahydroisoquinolines (I – X). To a solution of 0.02 mole of substituted phenylethylamine (homoveratrylamine or homopiperonylamine) in 100 ml of benzene was added 0.02 mole of the corresponding benzaldehyde and the mixture was boiled for 1 – 2 h with distillation of the azeotropic water. Then benzene was distilled off and the resulting imine dissolved in methanol (200 – 300 ml) and reduced by sodium borohydride (0.15 mole) for 3 h at 0 – 5°C. The solvent was evaporated and the reaction products dissolved in water and extracted with chloroform. The extract was washed with water and dried over Na_2SO_4. The technical-purity amine obtained upon distillation of the solvent was dissolved in acetone and acidified to pH 3 – 4 with concentrated hydrochloric acid. The precipitate was filtered and recrystallized from acetone. The resulting mixture of amine hydrochloride (0.02 mole), methanol (50 – 100 ml), and formalin (20 ml, 30%) was acidified to pH 2 with concentrated HCl (3 drops) and boiled with reflux for 2 – 4 h. The solution was partly evaporated, the residue alkalized to pH 9 – 10 with concentrated NH_4OH, and the reaction product extracted with chloroform. The extract was dried over Na_2SO_4 and the solvent was evaporated. The target amine (I – X) was dissolved in acetone and acidified to pH 3 – 4 with concentrated HCl to obtain the corresponding 2-benzyltetrahydroisoquinoline hydrochloride. The product was crystallized from an ethanol – acetone (1 : 5) mixture.

EXPERIMENTAL BIOLOGICAL PART

The effects of the synthesized compounds on the excretory function of liver were studied on male rats weighing 180 – 220 g, narcotized with sodium pentobarbital

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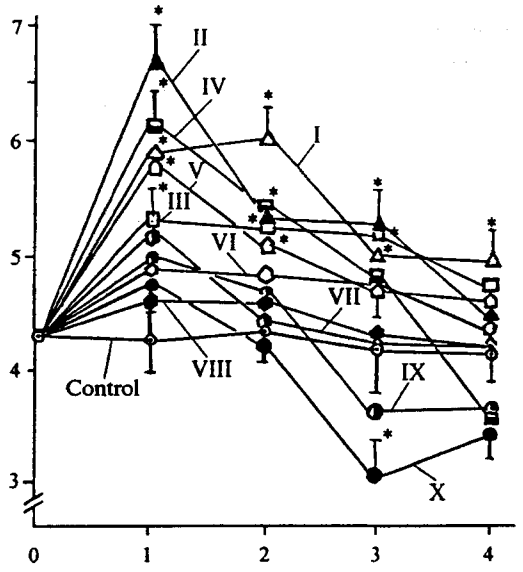

Fig. 1. Effect of compounds I – X on the bile secretion intensity. Abscissa: observation time, h; ordinate: secretion intensity, mg / (100 g min); * $p < 0.05$ against control.

(50 mg / kg, i.p.). After opening the abdominal cavity, the common bile duct was cannulated and the bile was collected in 1-h intervals during a 4-h period. The bile was analyzed for the content of cholates (bile acids), cholesterol, and bilirubin [6 – 8]. As is known, many of the cholagogic agents improve the antitoxic function of the liver. In this connection, we have studied a group of white mice weighing 20 – 22 g with toxemia induced by heliotrine injections (300 mg / kg, s.c.). The synthesized compounds were assessed by their effect (upon preliminary administration during 6 days at a dose of 5 mg / kg) on the detoxication of hexenal, as evaluated by the duration of stay in a lying position (on flank) after the hexenal injection (70 mg / kg).

The spasmolytic activity of the test compounds upon preliminary administration at various concentrations (1×10^{-7} to 1×10^{-5} g / ml) was studied on rats using a sample of isolated ileum stimulated by barium chloride [9].

The experimental data were processed using the Student's criterion [10].

The results of experiments showed that compounds I – V produce a reliable choleretic effect during 1 – 3 h (see Fig. 1); the effect of compounds I and II lasted for 4 h (Table 2). Most of the compounds tested induced an increase in the content of cholates (except for VI and X), cholesterol (except VIII – X), and bilirubin (except II – IV, VII, and X) in the gall (Table 2).

The duration of hexenal-induced sleep in animals intoxicated with heliotrine was 78.2 ± 17.9 min against 47.3 ± 4.6 min in the control group. The hexenal sleep response of mice in the group that received compounds I – VI before the

TABLE 1. Physicochemical Characteristics of compounds I – X

Compound	RR	R^1	R^2	R^3	R^4	Yield, %	M.p., °C (for hydrochlorides)	Empirical formula	M^+	Chemical shift (δ, ppm; J, Hz)							
										H-1 (s, 2H)	H-3, H-4 (m, 4H)	H-5 (s, 1H)	H-8 (s, 1H)	H-α (s, 2H)	Arom.	OCH_2O (s, 2H)	OMe (s, 3H)
I	$(OMe)_2$	Cl	OCH_2O		H	72	204	$C_{19}H_{20}ClNO_4$	363 / 361	3.50	2.73	6.38	6.48	3.58	6.70 (s, 1H), 6.93 (s, 1H)	5.66	3.76 3.77
II	$(OMe)_2$	H	OMe	Br	H	78	203	$C_{19}H_{22}BrNO_3$	393 / 391	3.55	2.64	6.37	6.48	3.40	6.68 (s, 1H), 6.78 (s, 1H), 7.20 (s, 1H)		3.72 3.73 3.76
III	$(OMe)_2$	OH	H	H	H	62	137*	$C_{18}H_{21}NO_3$	299	3.54	2.72	6.38	6.50	3.72	7.02 (m, 5H)		3.70 3.72
IV	$(OMe)_2$	Br	OMe	OMe	H	73	210	$C_{20}H_{24}BrNO_4$	423 / 421	3.52	2.71	6.41	6.51	3.62	6.88 (s, 1H), 7.02 (s, 1H)		3.74 3.76 (s, 6H), 3.78
V	$(OMe)_2$	NO_2	OCH_2O		H	64	187	$C_{19}H_{20}N_2O_6$	372	3.50	2.66	6.42	6.51	3.82	7.22, 7.35	5.99	3.73 3.75
VI	OCH_2O	OH	H	H	H	55	155*	$C_{17}H_{17}NO_3$	283	3.55	2.70	6.40	6.51	3.71	7.02 (m, 5H)	6.02	
VII	$(OCH_3)_2$	H	OMe	OH	Br	51	150	$C_{19}H_{22}BrNO_4$	409 / 407	3.54	2.74	6.41	6.50	3.59	6.85 (d, J 8.5)		3.85 (s, 9H)
VIII	OCH_2O	Br	OCH_2O		H	61	201 (decomp.)	$C_{19}H_{20}BrNO_4$	407 / 405	3.55	2.70	6.40	6.51	3.00	6.87 (s, 1H), 7.00 (s, 1H)	5.98 6.00	
IX	$(OMe)_2$	NO_2	OMe	OMe	H	66	193	$C_{20}H_{24}N_2O_6$	388	3.58	2.68	6.42	6.52	3.84	7.32 (s, 1H), 7.50 (s, 1H)		3.74 3.76 3.84
X	OCH_2O	OMe	H	Br	H	75	198 (decomp.)	$C_{18}H_{18}BrNO_3$	377 / 375	3.52	2.76	6.40	6.49	3.58	6.66 (d, J 8.5), 7.25 (dd, J 8.5, J 2), 7.50 (d, J 2)	5.80	3.72

* Melting point of the base.

heliotrine injection ranged from 89.4 ± 25.4 min to 102.0 ± 26.5 min. Thus, results in the test groups do not differ significantly from the toxemia control level. Therefore, the substances tested do not affect the activity of microsomal enzymes in liver cells to a noticeable extent.

Study of the spasmolytic effect of the synthesized substances showed that compounds I – V suppress the barium chloride spasms in isolated intestine beginning with a concentration of 1×10^{-7} g/ml, and a considerable inhibiting effect was observed at a concentration of 1×10^{-5} g/ml. The MIC_{50} values were as follows (g/ml): 4.0×10^{-6} (IV); 4.5×10^{-6} (I); 6.0×10^{-6} (II); 8.2×10^{-6} (V). Note that the spasmolytic effect and the choleretic activity (secretion intensity, see Fig. 1) exhibit a direct correlation.

Thus, most of the compounds in the series of substances studied exhibit a choleretic action. A considerable role in the mechanism of this action belongs, besides a spasmolytic effect, to stimulation of the cholate-forming processes in liver cells.

TABLE 2. Effect of Compounds I – X on the Bile Secretion and Composition in Rats

Compound	Total amount of bile (4-h experiment), mg/100 g	Contents of components (4-h experiment), mg/100 g		
		cholates	cholesterol	bilirubin
I	1335.2 ± 77.3*	14.051 ± 3.568	0.284 ± 0.067	0.658 ± 0.093*
II	1322.4 ± 114.4*	23.429 ± 3.696*	0.353 ± 0.056*	0.330 ± 0.062
III	1252.8 ± 179.7	21.246 ± 2.801*	0.323 ± 0.018*	0.412 ± 0.055
IV	1224.0 ± 116.0	12.481 ± 2.886	0.282 ± 0.110	0.325 ± 0.034
V	1222.2 ± 57.4	14.720 ± 2.251*	0.314 ± 0.038	0.510 ± 0.052*
VI	1154.4 ± 90.1	6.131 ± 1.955	0.228 ± 0.051	0.427 ± 0.010
VII	1096.2 ± 130.2	–	–	0.370 ± 0.078
VIII	1077.6 ± 93.1	11.153 ± 1.248	0.203 ± 0.008	0.444 ± 0.073
IX	1015.2 ± 98.2	13.989 ± 3.263	0.217 ± 0.031	0.580 ± 0.028*
X	879.0 ± 78.1	6.695 ± 2.574	0.128 ± 0.071	0.254 ± 0.028
Control	1038.6 ± 76.7	8.429 ± 0.635	0.205 ± 0.050	0.357 ± 0.058

* $p < 0.05$.

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