SYNTHESIS AND BLOOD COAGULATION PROPERTIES OF DROTAVERINE DERIVATIVES

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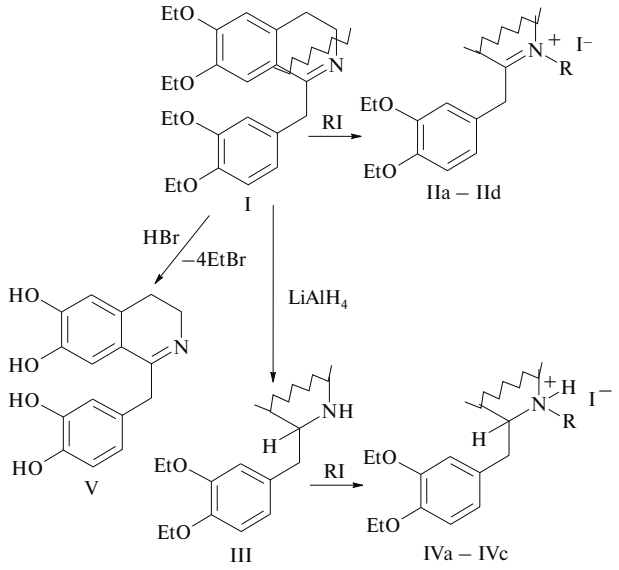
Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 41, No. 10, pp. 19 – 21, October, 2007.

Original article submitted November 15, 2005.

Quaternary ammonium salts have been obtained via the reaction of drotaverine base and its tetrahydroisoquinoline derivative with alkyl iodides. Boiling of drotaverine with HBr leads to the cleavage of ethoxy groups with the formation of hydroxy groups. It is established that all the synthesized compounds increase blood coagu1ation. For the most active compounds, the effect reaches 26%.

As is known, isoquinoline derivatives are capable of influencing blood coagulation [1 – %]. The results of previous investigations showed that important structural factors determining this activity are the presence of methoxy groups in positions 6 and 7 of the isoquinoline cycle and the presence of a benzyl residue in position 1 of this cycle. In this context, it was of interest to study the properties of derivatives of the drug drotaverine, which is based on 1-benzylisoquinoline and contains ethoxy groups in positions 6 and 7 of the isoquinoline cycle.

This investigation was aimed at establishing the structure – activity relationships in a series of drotaverine derivatives, using this benzylisoquinoline derivative as a matrix for modification. The effect of drotaverine derivatives on blood coagulation was studied using a model of direct action, since the properties of isoquinoiline derivatives in this respect have not been studied until now.



I; IIa — IId; III; IVa – IVc; V

A series of drotaverine (I) derivatives were obtained using well-known methods of chemical modification. The alkylation of drotaverine by iodine-containing alkyls led to the formation of quaternary salts (IIa – IId). The hydrogenation of base I with $LiAlH_4$ yielded compound III. The interaction of this compound with iodine-containing alkyls led to the formation of salts IVa – IVc. Finally, the reduction of ethoxy groups in drotaverine under the action of HBr [6] led to the formation of norlaudanosine V.

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TABLE 1. Yields and Physicochemical Characteristics of Compounds II – V

Compound	*R*	Yield, %	M.p., °C	Empirical formula
IIa	Me	70	178 – 180	$C_{25}H_{34}INO_4$
IIb	Et	72	170 – 172	$C_{26}H_{36}INO_4$
IIc	*i*-Pr	68	188 – 190	$C_{27}H_{38}INO_4$
IId	CH_2CO_2Me	67	213 – 215	$C_{27}H_{36}INO_6$
III · HCl	—	55	163 – 165	$C_{24}H_{33}NO_4 \cdot HCl$
IVa	Me	64	175 – 176	$C_{25}H_{36}INO_4$
IVb	Et	87	187 – 190	$C_{26}H_{38}INO_4$
IVc	*i*-Pr	62	210 – 212	$C_{27}H_{40}INO_4$
V · HCl	—	63	198 – 200	$C_{16}H_{15}NO_4 \cdot HCl$

TABLE 2. ^{1}H NMR Spectra of Drotaverine and Its Derivatives

Compound	$C\underline{H}_3CH_2O$, (4 tripl.)	$CH_3C\underline{H}_2O$, (4 quadr.)	CH_2 (benzyl)	3-CH_2 (m)	4-CH_2 (m)	Ar (m, 5H)	NH^+ (s)	Other protons
IIa	1.3 – 1.5	4.0 – 4.2	2.7 s	2.9 – 3.0	2.6	6.1 – 6.8	—	3.2 s, N^+CH_3
IIb	1.3 – 1.5	3.8 – 4.1	2.7 s	2.8 – 3.1	2.6	6.2 – 6.8	—	1.4 (t $N^+CH_2C\underline{H}_3$); 3.1 (q, $N^+C\underline{H}_2CH_3$)
IIc	1.3 – 1.5	3.9 – 4.0	2.8 s	2.8 – 3.1	2.6	6.2 – 6.9	—	1.5 (d, $(C\underline{H}_3)_2CH$); 3.6 (sept $(CH)_2C\underline{H}$)
IId	1.3 – 1.5	3.8 – 4.0	2.9 s	2.8 – 3.0	2.7	6.3 – 6.9	—	4.1 s CH_2CO; 4.0 s, CH_3O
III · HCl	1.3 – 1.6	3.8 – 4.1	2.1 d	3.0 – 3.2	2.7	6.2 – 7.1	10.3	4.6 (t, CH–N^+)
IVa	1.2 – 1.5	3.6 – 4.1	2.8 d	3.0 – 3.2	2.8	6.1 – 7.1	11.3	3.3 (s, N^+CH_3); 4.6 (t, CH–N^+)
IVb	1.2 – 1.5	3.7 – 4.1	2.8 d	2.8 – 3.3	2.9	6.2 – 7.1	11.2	1.3 (t $N^+CH_2C\underline{H}_3$); 3.4 (q, $N^+C\underline{H}_2CH_3$); 4.7 (t, CH-N^+)
IV c	1.3 – 1.6	3.6 – 4.0	2.8 d	2.9 – 3.3	2.7	6.2 – 7.1	11.0	1.5 (d, $(C\underline{H}_3)_2CH$); 3.6 (sept $(CH_3)_2C\underline{H}$); 4.7 (t, CH-N^+)
V · HCl	—	—	2.4 d	2.7 – 3.3	3.1	6.1 – 7.4	12.1	5.6 – 6.0 (4OH)

Table 1 presents data on the yields and physicochemical properties of compounds with various radicals R. For pharmacological characterization, compounds II and V were obtained in the form of hydrochlorides, while the other compounds were studied as iodides.

The proposed structures of drotaverine derivatives was confirmed by the data of ^{1}H NMR spectroscopy (Table 2). The spectra of iodine-containing alkyls exhibit signals from protons of the N-alkyl groups at $\delta = 3.1 – 3.6$ ppm; in the spectrum of compound IId, the corresponding singlet appears at 4.1 ppm. The spectrum of ester IId displays a singlet due to methoxy group protons (4.0 pp). The spectrum of 1,2,3,4-tetrahysroisoquinoline III, in contrast to that of the initial compound I, contains a triplet due to CH group in position 1 (4.6 ppm) and a doublet due to benzyl CH_2 group (2.1 ppm). The corresponding triplet from CH groups (observed at 4.6 – 4.7 ppm) is characteristic of tetrahydroisoquinolines IVa – IVc. Methylene groups of the benzyl fragments of these iodides are manifested by doublets in the region of 2.8 ppm.

The IR spectrum of compound III displays a characteristic absorption band due to the NH group of the isoquinoline cycle (3400 cm^{-1}), the spectrum of ester IId exhibits a band due to the carbonyl groups (1700 cm^{-1}), and the spectrum of phenol V contains an absorption band due to hydroxy groups (330 cm^{-1}).

TABLE 3. Effect of Drotaverine Derivatives II— V (1 mg/ml) on Blood Coagulation

Compound	*R*	Coagulation time, sec		*P*
		Control	Test	
IIa	Me	59.5 ± 2.67	44.6 ± 3.57	< 0.01
IIb	Et	68.9 ± 2.47	61.9 ± 1.85	< 0.05
IIc	*i*-Pr	55.1 ± 2.67	53.4 ± 3.01	> 0.05
IId	CH_2CO_2Me	44.8 ± 1.27	39.7 ± 1.45	< 0.02
III · HCl	—	55.0 ± 4.11	50.2 ± 3.36	> 0.05
IVa	Me	64.5 ± 1.56	58.0 ± 2.88	> 0.05
IVb	Et	68.9 ± 2.47	61.9 ± 1.85	> 0.05
IVc	*i*-Pr	51.3 ± 2.77	41.1 ± 1.62	< 0.01
V · HCl	—	57.5 ± 1.92	42.2 ± 2.29	< 0.001
Heparin	—	29.9 ± 0.48	36.6 ± 1.82	< 0.01
Drotaverine*	—	55.7 ± 2.46	48.8 ± 2.59	> 0.05
Papaverine*	—	40.9 ± 3.12	47.8 ± 3.17	< 0.05

* Hydrochlorides.

EXPERIMENTAL CHEMICAL PART

The IR spectra were recorded on a Specord M-80 spectrophotometer (Germany) using samples prepared as nujol mulls. The ^{1}H NMR spectra were measured on a Tesla BS-567A spectrometer (Czech Republic) operating at a working frequency of 100 MHz, using $CDCl_3$ as the solvent and HMDS as the internal standard. The course of reactions was monitored by TLC on the plates eluted in eluted in an acetone – chloroform (1 : 9) solvent mixture and developed by exposure to bromine vapor. All the salts listed in Table 1 were recrystallized from 2-propanol. The data of elemental analyses (for C, H, N, Al, and Br) coincide with the results of analytical calculations.

N-Alkyl-1-(3′,4′-diethoxybenzyl)-6,7-diethoxy-3,4-dihydroisoquinolinium iodides (IIa – IId). To a solution of 3.97 g (10 mmole) of drotaverine base I in 30 ml of 2-prtopanol was added dropwise 15 mmole of the corresponding alkyl iodide and the reaction mixture was boiled for 2 h and cooled. The precipitate was separated by filtration, dried, and recrystallized.

1-(3′,4′-Diethoxybenzyl)-6,7-diethoxy-1,2,3,4-tetrahydroisoquinoline (III). To a solution of 3.99 g (0.01 mole) of drotaverine base I in 250 ml of anhydrous ether was gradu-

ally (in several fractions) added 0.38 g (10 mmole) of lithium alumohydride and this suspension was boiled with stirring for 2 h and cooled to 20°C. The complex compound was decomposed by adding first 2 ml of water and then 2 ml of a 25% aqueous ammonia solution. The precipitate of $Al(OH)_3$ was separated by filtration and washed with ether (3 × 50 ml). The combined ether solution was dried over NaOH and evaporated to dryness. The resulting base III is sufficiently pure (TLC data) and can be converted into hydrochloride by dissolving in ethyl acetate and bubbling anhydrous HCl through this solution. The precipitated hydrochloride is separated by filtration, dried, and recrystallized.

N-Alkyl-1-(3′,4′-diethoxybenzyl)-6,7-diethoxy-1,2,3,4-tetrahydroisoquinolinium iodides (IVa – IVc) were obtained using procedures analogous to those described above for compounds II.

1-(3′,4′-Diethoxybenzyl)-6,7-dihydroxy-3,4-dihydroisoquinoline (V). A mixture of 4.33 g (10 mmole) of drotaverine hydrochloride with 120 ml of 48% hydrobromic acid was boiled (with TLC monitoring of the reaction) and cooled to 20°C. The precipitate of compound V was separated by filtration, thoroughly washed on the filter with an aqueous Na_2CO_3 solution and water, dried, and dissolved in 150 ml of ethyl acetate. The resulting base can be converted into hydrochloride by bubbling anhydrous HCl through this solution. The precipitated hydrochloride is separated by filtration, dried, and recrystallized.

EXPERIMENTAL PHARMACOLOGICAL PART

The effect of drotaverine derivatives in a concentration of 1 mg/ml on blood coagulation was studied using a Minilab 701 coagulometer. The experiments were performed with citrate-containing (3.8%) blood of dogs (9 : 1) and referenced to a solution of heparin (1 U/ml), papaverine hydrochloride (1 mg/ml), and drotaverine hydrochloride (1 mg/ml). Each compound was studied in seven independent tests. The experimental results were statistically processed in terms of Student′s *t*-criterion and the comparative data were considered reliable for $p < 0.05$.

As can be seen from the data presented in Table 3, drotaverine base (I) and its derivatives accelerate the coagulation of blood (in contrast to papaverine hydrochloride). The most pronounced procoagulant action was observed for the methylated derivative IIa, N-isopropyl hydrogenated drotaverine derivative IVc, and phenol V. These results are indicative of good prospects in the search for new effective hemostatics in the series of drotaverine derivatives.

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