VI is more prolonged but is accompanied by bradycardia. Compound III, while not affecting the MAP, causes a persistent decrease in the heart rhythm by a factor of three, and IV displays pronounced pressor activity without affecting the FHC.

In a study of the character of the MAP and FHC in the course of 5 h after the administration of the investigated substances into the stomach in a dose of 50 mg/kg into animals with no restriction on their behavior we did not observe any changes in the MAP and FHC for any of the compounds. The manifestation of biological activity in the case of intravenous administration and the absence of such activity in the case of oral administration provide a basis for the assumption that the substances undergo inactivation in the stomach.

Thus the results of our investigation make it possible for us to draw some conclusions relative to the interrelationship between the pharmacological activity of the compounds and their structures. In the series of epimeric pairs of alcohols II and III and their acetates IV and V the cardiotropic activity is strongly dependent on the spatial orientation of the substituents attached to the $C_{(4)}$ atom. Thus alcohol II, with an equatorial hydroxy groups, has a rapidly passing hypotensive property, while its epimer III does not have this sort of activity. The reverse pattern is observed with respect to the effect on the change in the FHC: equatorial alcohol II does not affect the FHC, whereas its epimer III causes bradycardia. In the case of acetates IV and V hypertensive activity vanishes on passing from an equatorial to an axial ester group. Replacement of the hydroxy group of equatorial dehydroquinolol II by an acetoxy group (to give IV) leads to a marked change in the effect on the MAP. Acetate IV has hypertensive activity, while benzoate VI has stronger hypotensive activity than alcohol II.

LITERATURE CITED

1. A. Eliel, N. Allinger, S. Angyal, and H. Morrison, Conformational Analysis [Russian translation], Moscow (1969).
2. K. D. Praliev, E. V. Fishchuk, V. B. Rozhnov, et al., Khim.-farm. Zh., No. 8 (1989).
3. E. R. Lax, K. Militzer, and A. Trauschel, Lab. Anim., 17, 50-54 (1983).
4. J. R. Weeks and J. A. Jones, Proc. Soc. Exp. Biol. (New York), 104, 646-648 (1960).

SYNTHESIS AND CARDIOTROPIC ACTIVITY OF NEW DERIVATIVES OF TWO STEREOISOMERS OF 1-[2-(3,4-DIMETHOXYPHENYL)ETHYL]-2-METHYL-4-ETHYNYL-4-HYDROXYL-trans-DECAHYDROQUINOLINE

K. D. Praliev, E. V. Fishchuk, L. S. Mal'chikova, and E. V. Oranovskaya

UDC 615.22:547.831].012.1

In continuation of our investigations [1, 2] on the synthesis, stereochemistry and pharmacology of stereoisomers of 1-[2-(3,4-dimethoxyphenyl)ethyl]-2-methyl-4-ethynyl-4-hydroxy-trans-decahydroquinoline and its derivatives, synthesis of tertiary alcohols III-XIV was carried out and their influence on the cardiovascular system was studied. Up to now these isomeric decahydroquinolines were not known. It could be expected that replacement of the ethynyl group at $C_{(4)}$ by other substituents will substantially affect the pharmacological properties of these compounds.

Selective hydrogenation of the triple bond of acetylenic alcohols (I, II) on a palladium catalyst deposited on $CaCO_3$ gave the corresponding 1-[2-(3,4-dimethoxyphenyl)ethyl]-2-methyl-4-vinyl-4-hydroxydecahydroquinolines III, IV, while on the exhaustive hydrogenation of these amino alcohols on a Raney nickel catalyst, 1-[2-(3,4-dimethoxyphenyl)ethyl]-2-methyl-4-ethyl-4-hydroxydecahydroquinolines V, VI were obtained. Hydration of the acetylenic alcohols I, II according to Kucher gave 1-[2-(3,4-dimethoxyphenyl)ethyl]-2-methyl-4-acetyl-4-hydroxy-trans-decahydroquinolines VII, VIII. The aminomethylation of the terminal acetylenic hydrogen of

Institute of Chemical Sciences, Academy of Sciences of the Kazakh SSR, Alma Ata. Institute of Experimental Cardiology, All-Union Cardiological Scientific Center, Academy of Medical Sciences Moscow.

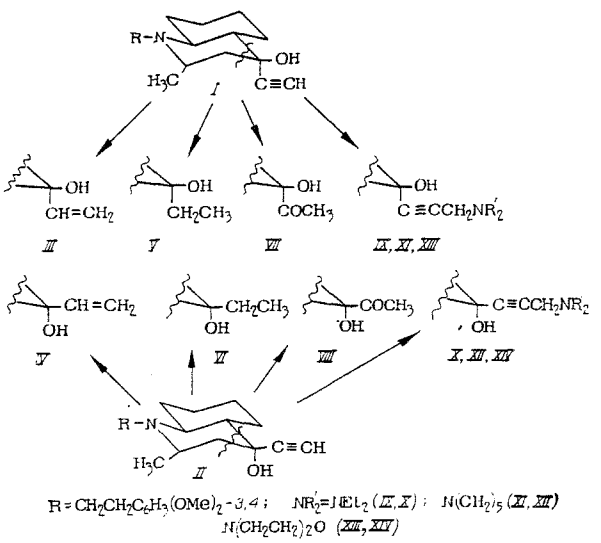
Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 23, No. 8, pp. 939-941, August, 1989. Original article submitted November 18, 1988.

0091-150X/89/2308-0656$12.50

TABLE 1. Characteristics of Synthesized Tertiary Alcohols III-XIV

Compound	Time of reaction, h	Yield, %	mp, °C	Crystallization (solvent)	R_f	Empirical formula
III	2,5	96,1	998—9	Ether	0,10	$C_{22}H_{33}NO_3$
III·HCl	—	—	147—8	Ethanol + ether	—	$C_{22}H_{33}NO_3 \cdot HCl$
IV	1,5	88,2	86—7	Petroleum ether	0,14	$C_{22}H_{33}NO_3$
IV·HCl	—	—	163—4	Ethanol + ether	—	$C_{22}H_{33}NO_3 \cdot HCl$
V	1,5	96,3	65—6	Ether	0,15	$C_{22}H_{35}NO_3$
V·HCl	—	—	141—2	Ethanol	—	$C_{22}H_{35}NO_3 \cdot HCl$
VI	0,5	93,1	91—2	Ether	0,57	$C_{22}H_{35}NO_3$
VI·HCl	—	—	165—6	Ethanol	—	$C_{22}H_{35}NO_3 \cdot HCl$
VII	3,5	58,9	100—1	Ether	0,12	$C_{22}H_{33}NO_3$
VII·HCl	—	—	187—8	Ethanol	—	$C_{22}H_{33}NO_3 \cdot HCl$
VIII	1	61,8	99—100	Benzene + ether	0,55	$C_{22}H_{33}NO_3$
VIII·HCl	—	—	177—8	Ethanol	—	$C_{22}H_{33}NO_3 \cdot HCl$
IX	2,5	81,0	198—9	Petroleum ether	0,13	$C_{27}H_{42}N_2O_3$
IX·HCl	—	—	236—7	Ethanol	—	$C_{27}H_{42}N_2O_3 \cdot 2HCl$
X	2	73,2	141—2	Petroleum ether	0,44	$C_{27}H_{42}N_2O_3$
X·HCl	—	—	237—8	Ethanol	—	$C_{27}H_{42}N_2O_3 \cdot 2HCl$
XI	1	75,2	101—2	Ether	0,20	$C_{28}H_{42}N_2O_3$
XI·HCl	—	—	186—7	Isopropanol	—	$C_{28}H_{42}N_2O_3 \cdot 2HCl$
XII	1	68,6	162—3	Ether	0,43	$C_{28}H_{42}N_2O_3$
XII·HCl	—	—	197—8	Ethanol	—	$C_{28}H_{42}N_2O_3 \cdot 2HCl$
XIII·HCl	5	75,7	168—9	Benzene + isopropanol	0,18	$C_{27}H_{40}N_2O_4 \cdot 2HCl$
XIV·HCl	3	71,4	171—2	Isopropanol	0,36	$C_{27}H_{49}N_2O_4 \cdot 2HCl$

alcohols I and II was carried out with paraform and various secondary amines in the presence of catalytic amounts of freshly prepared CuCl in an absolute dioxane medium. Diethylamine, morpholine and piperidine were used as the secondary amines. In all the above transformations, the rate of reaction is markedly dependent on the steric disposition of the ethynyl group of the epimeric alcohols: the reactions proceed more rapidly with acetylenic alcohol II, in which the ethynyl group is positioned equatorially (Table 1). The structure of the synthesized compounds was confirmed by the elemental analysis and IR spectroscopy data. In the IR spectra of all the compounds obtained there are absorption bands of the stretching vibrations of the hydroxyl group (3550-3610 cm^{-1}), while the characteristic absorption band of the terminal acetylenic hydrogen atom (3320-3325 cm^{-1}) is absent. In the IR spectra of ketols VII, VIII there are ν_{CO} absorption bands of the acetyl group at 1710-1715 cm^{-1}.



EXPERIMENTAL (CHEMICAL)

The course of the reaction and the purity of the synthesized compounds was monitored by TLC on alkaline Al_2O_3 grade III of activity with development of the spots by iodine vapors, using ether as eluent. The IR spectra were recorded on a "Zeiss" UR-20 spectrometer (GDR) for bases in KBr tablets and for hydrochlorides in KBr tablets and in a CCl_4 solution. The physicochemical characteristics of the compounds are listed in Table 1. The results of the elemental analyses of the compounds correspond to the calculated values.

TABLE 2. Change in MAP and FHC (in % of initial data; M ± m) after Intravenous Administration of Decahydroquinoline Derivatives in a Dose of 5 mg/kg to Narcotized Animals (n = 6)

Compound	Change in MAP		Change in FHC	
	after 30 min	after 70 min	after 30 min	after 70 min
III·HCl	0	0	0	0
IV·HCl	−10±3	0	+15±5	+20±2
V·HCl	0	0	0	0
VI·HCl	After 10-20 min stoppage occurs in the respiration			
VII·HCl	−9±3	−33±4	+56±15	+34±8
VIII·HCl	0	0	0	0
IX·HCl	0	0	0	0
XIII·HCl	0	0	0	0

Note. The signs + and − before the index designate an increase or decrease in MAP or FHC.

1-[2-(3,4-Dimethoxyphenyl)ethyl]-2-methyl-4-vinyl-4-hydroxy-decahydroquinolines (III) and (IV) are obtained by hydrogenation under normal conditions of 2 g (5.6 mmoles) of the corresponding amino alcohol in anhydrous alcohol (100 ml) in the presence of 0.2 g of 0.5% Pd catalyst deposited on $CaCO_3$. After absorption of the theoretically required amount of H_2, the hydrogenation is discontinued, the solvent is evaporated off, and the residue is crystallized. The hydrochlorides of amino alcohols III·HCl and IV·HCl are obtained in quantitative yields by testing an alcoholic solution of bases III and IV with an ethereal solution of HCl.

1-[2-(3,4-Dimethoxyphenyl)ethyl]-2-methyl-4-ethyl-4-hydroxy-decahydroquinolines (V) and (VI) are obtained by hydrogenation under normal conditions of 2 g (5.6 mmoles) of the corresponding amino alcohol in 100 ml of anhydrous ethanol in the presence of 0.2 g of 5% Pd catalyst deposited on $CaCO_3$. After the absorption of the theoretically required amount of H_2, the hydrogenation is discontinued, the catalyst is filtered off, the solvent is evaporated, and the residue is crystallized. The hydrochlorides V·HCl and VI·HCl are obtained by the above described method.

1-[2-(3,4-Dimethoxyphenyl)-ethyl]-2-methyl-4-acetyl-4-hydroxy-decahydroquinolines (VII) and (VIII). A mixture of 2 g (5.6 mmoles) of the corresponding amino alcohol, 2 g of $HgSO_4$ and 2 ml of concentrated H_2SO_4 in 50 ml of water is heated on a boiling water bath. At the end of the reaction the solution is treated with zinc powder, made alkaline and extracted with benzene. The benzene extracts are combined, benzene is evaporated and the residue is crystallized. The hydrochlorides VII·HCl and VIII·HCl are obtained by the usual method.

General Method of Aminomethylation. A mixture of 4.2 mmoles of the corresponding initial acetylenic alcohol, 4.2 mmoles of a secondary amine, 6.3 mmoles of paraform, and a catalytic amount of a freshly prepared CuCl in 50 ml of anhydrous dioxane is heated on a water bath at 70-80°C. At the end of the reaction, the catalyst is filtered off, the filtrate is treated with water and repeatedly extracted with ether. The combined ethereal extracts are dried over $MgSO_4$. The ether is evaporated to yield the corresponding 1-[2-(3,4-dimethoxyphenyl-ethyl]-2-methyl-4-(3-aminopropyn-1-yl)-4-hydroxydecahydroquinolines IX-XII. The hydrochlorides IX·HCl-XIV·HCl are obtained by the usual method.

EXPERIMENTAL (PHARMACOLOGICAL)

The experimental study of compounds III·HCl-IX·HCl was carried out on narcotized and nonnarcotized rats of the Wistar line, weighing 250 g each (6 rats for each compound). In experiments on urethane-narcotized animals (40 mg/kg), the action of the above enumerated compounds was evaluated from the change in the mean arterial pressure (MAP) and the frequency of heart contractions (FHC) after a single administration into the jugular vein of 0.2 ml of the compound preliminarily dissolved in 10% alcohol. The dose of the compounds was 5 mg/kg. The MAP was recorded in carotid artery electromanometrically, the FHC was recorded by a cardiotachometer activated by a pulsed pressure wave. The recording of the MAP and FHC was carried out before introducing the compound, and for 90 min after its introduction. The recordings of MAP and FHC from animals to which 0.2 ml of 10% ethanol was introduced intravenously instead of the compounds tested, served as control. Compounds IV·HCl and VII·HCl were administered to nonnarcotized animals in the form of an aqueous suspension intragastrically (dose 50 mg/kg),

through a tube, using a modified Lax's method [3]. The MAP was recorded in these animals before administration, and for 5 h after administration in the abdominal aorta through a siliconated polyethylene catheter, implanted into the aorta one day before the experiment [4]. To evaluate the effect of the compounds studied, the MAP and FHC was calculated in percent of the initial values, designated as 100. The results were statistically treated by the Fischer–Student's method. The differences at a 95% significance level ($P \leq 0.5$) were considered as reliable.

Studies on the influence of the hydrochlorides of compounds III-IX and XIII on the MAP and FHC in narcotized rats during intravenous administration at doses of 5 mg/kg showed no effect in the case of III·HCl, V·HCl, VIII·HCl, IX·HCl, and XIII·HCl. The hydrochloride of ethyl alcohol VI causes a stoppage of respiration in the animals 10-20 min after the administration (n = 3). The action of IV·HCl and XII·HCl is of the same nature. The two compounds exhibit hypotensive activity, accompanied by pronounced (in particular in the case of VII·HCl) tachycardia (Table 2).

Intragastrical administration of IV·HCl and VII·HCl does not cause any changes in the MAP and FHC for 5 h in awakened rats.

Thus, in the series of the 4-ethynyldecahydroquinolol I derivatives having an axial ethynyl group, only the hydration product influences the MAP and FHC, and among the derivatives of its epimeric alcohol II, the ketol has no such activity, while the partially or completely hydrogenated 4-vinyl- and 4-ethyl derivatives have a biological action.

The above results indicate that compounds with pronounced action on the cardiovascular system should be sought among the 4-ketodecahydroquinoline derivatives.

LITERATURE CITED

1. E. V. Fishchuk, K. D. Praliev, A. S. Mal'chikova, et al., Khim.-farm. Zh., No. 8, 1989.
2. K. D. Praliev, E. V. Fishchuk, V. B. Rozhnov, et al., Khim.-farm. Zh., No. 8, 1989.
3. E. R. Lax, K. Militzer, and A. Trauschel, Lab. Anim., 17, 50-54 (1983).
4. J. R. Weeks and J. A. Jones, Proc. Soc. Exp. Biol. (N. Y.), 104, 646-648 (1960).