# SYNTHESIS AND CARDIOTROPIC ACTIVITY OF STEREOISOMERIC 1-[2-(3,4-DIMETHOXYPHENYL)ETHYL]-2-METHYL-4-ETHYNYL-4-ACYLOXY-trans-DECAHYDROQUINOLINES

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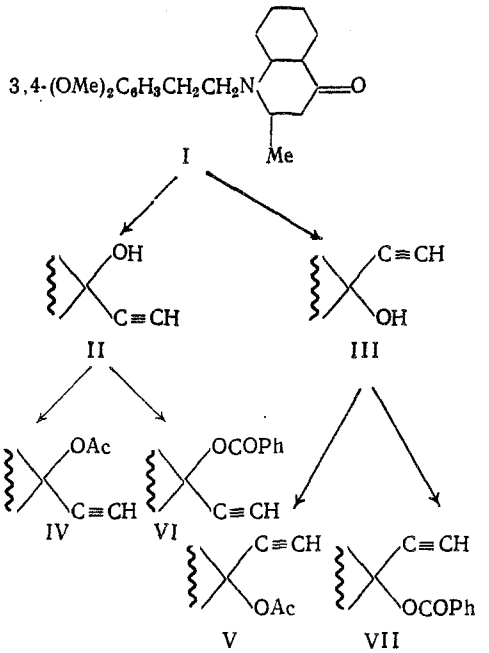
We have previously [2] described the synthesis of the trans isomer (I) of 1-[2-(3,4-dimethoxyphenyl)ethyl]-2-methyl-4-ketodecahydroquinoline and the two acetylenic alcohol isomers (II and III) corresponding to it. It was shown that II has pronounced spasmolytic activity. In order to study their new cardiotropic properties and the effect of the nature of the ester group on the pharmacological activity in the present paper we have developed a method for obtaining the acetate and benzoate esters on the basis of the individual isomers II and III and have studied their cardiovascular action.




Acetates IV and V were obtained in high yields by the reaction of the corresponding acetylenic alcohol isomer II or III with a mixture of AcCl and $(EtCO)_2O$. The synthesis of benzoates IV and VII was accomplished by two methods. In method A benzoates VI and VII were obtained by heating acetylenic alcohols II or III with excess PhCOCl at 190°C for 10 min. However, because of the high temperature, pronounced resinification of the reaction medium occurs, and this leads to a decrease in the yield of the reaction product. In method B, in order to increase the yield we carried out benzoylation by a different method — by heating the corresponding acetylenic alcohol with PhCOCl in refluxing pyridine; in this case the reaction time was increased to 1 h, and the yield increased significantly (Table 1). It is apparent from Table 1 that benzoate VI·HCl, synthesized on the basis of acetylenic alcohol II with an equatorial hydroxy group, is obtained in both cases in much higher yield than the epimeric benzoate VII·HCl with an axial benzoyloxy group. These data, in accordance with the fundamental positions of conformational analysis [1], serve as an additional confirmation of the correctness of the configurations of acetylenic alcohols II and III that we previously presented in [2].

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TABLE 1. Characteristics of the Synthesized Compounds

| Compound | Reaction time | Yield, % | mp, °C | $R_f$ | Empirical formulas |
|---|---|---|---|---|---|
| IV | — | — | 138—9 | 0,81 | $C_{22}H_{33}NO_4$ |
| IV·HCl | 4 h | 92,2 | 213—4 | — | $C_{24}H_{33}NO_4 \cdot HCl$ |
| V | — | — | 112—3 | 0,9 | $C_{24}H_{33}NO_4$ |
| V·HCl | 1 h | 96,0 | 222—3 | — | $C_{24}H_{33}NO_4 \cdot HCl$ |
| VI | — | — | 133—4 | 0,49 | $C_{29}H_{35}NO_4$ |
| VI·HCl | 10 min*<br>1 h** | 27,8*<br>67,8* | 218—9 | — | $C_{29}H_{35}NO_4 \cdot HCl$ |
| VII·HCl | 10 min*<br>40 min** | 15*<br>30,1** | 212—3 | 0,85 | $C_{29}H_{35}NO_4 \cdot HCl$ |

Note. The yields of benzoates and the reaction times that are designated by asterisks have the following meaning: one asterisk indicates preparation by method A, while two asterisks indicate preparation by method B.

TABLE 2. Changes in the Mean Arterial Pressure (MAP) and the Frequency of the Heart Contractions (FHC) (in percent of the starting values; M ± m) under the Influence of I after Intravenous Administration in a Dose of 5 mg/kg (n = 6)

| Time after administration, min | MAP | FHC |
|---|---|---|
| 0 | 100 | 100 |
| 10 | 95±4 | 105±7 |
| 30 | 85±3 | 104±6 |
| 60 | 86±7 | 113±9 |
| 90 | 92±12 | 111±8 |

The strong absorption band at 3300 $cm^{-1}$ that is characteristic for the terminal hydrogen atom of the ethynyl group is retained in the IR spectra of esters IV-VII, and intense absorption bands at 1720-1740 $cm^{-1}$, which we assigned to the stretching vibrations of an ester carbonyl group, appear. In addition, absorption bands of a hydroxy group are absent in the IR spectra of these compounds.

## EXPERIMENTAL (CHEMICAL)

The monitoring of the course of the reactions and the individuality and the determination of the synthesized compounds were accomplished by chromatography in a loose thin layer of activity III aluminum oxide with development of the spots with iodine vapors; diethyl ether served as the eluent. The IR spectra of KCl pellets of the hydrochlorides and KBr pellets and solutions of the bases in $CCl_4$ were recorded with a UR-20 spectrometer (East Germany). The results of elementary analysis were in agreement with the calculated values.

General Method for Obtaining 1-[2-(3,4-Dimethoxyphenyl)ethyl]-2-methyl-4-ethynyl-4-acetoxydecahydroquinolines IV and V (see Table 1). A mixture of 2 g (5.6 mmole) of II, 5.7 g (56 mmole) of $Ac_2O$, and 3.88 g (5.6 mmole) of AcCl was heated on a boiling-water bath. At the end of the reaction the mixture was cooled, and dry ether was added to it. The precipitated hydrochloride (IV·HCl) was removed by filtration and recrystallized from absolute ethanol.

A 0.5-g sample of IV·HCl was treated with a saturated solution of potassium carbonate until the mixture was alkaline, the base was extracted with diethyl ether, and the extract was dried with $MgSO_4$. The ether was removed, and the residue was recrystallized from petroleum ether–diethyl ether to give base IV in quantitative yield.

General Method for Obtaining 1-[2-(3,4-Dimethoxyphenyl)ethyl]-2-methyl-4-ethynyl-4-benzoyloxydecahydroquinolines VI and VII (see Table 1). A) A mixture of 2 g (5.1 mmole) of II·HCl and 2.6 g (16.8 mmole) of PhCOCl was heated at 7-10°C per minute until the vigorous evolution of HCl began (180-190°C), after which it was maintained at this temperature until HCl evolution ceased. The mixture was then cooled, and dry ether was added. The precipitated

TABLE 3. Changes in the MAP and FHC (in percent of the starting values; M ± m) after the Intravenous Administration of II-VI in a Dose of 5 mg/kg (n = 6)

| Compound | Change in the MAP | | Change in the FHC | |
|---|---|---|---|---|
| | after 30 min | after 70 min | after 30 min | after 70 min |
| II | −15±7 | 0 | 0 | 0 |
| II | 0 | 0 | −33±3 | −37±4 |
| IV | +13±8 | +32±12 | 0 | 0 |
| V | 0 | 0 | 0 | 0 |
| VI | −37±12 | −18±4 | −13±9 | −30±8 |

Note: The plus and minus signs in front of the indexes denote, respectively, an increase and a decrease in the MAP or FHC.

VI·HCl was washed with ether, removed by filtration, and recrystallized from acetone until the melting point was constant. Hydrochloride VI·HCl was converted in almost quantitative yield to base VI via the method described above. Benzoate VII in the form of the base could not be isolated, since partial saponification of the ester group with recovery of the starting acetylenic alcohol occurred even in the case of treatment of VII·HCl under mild conditions (in the cold, ammonium hydroxide).

B) A mixture of 2 g (5.6 mmole) of II, 3 ml (20 mmole) of PhCOCl, and 5 ml of pyridine was heated at 130-140°C. At the end of the reaction the reaction mixture was cooled and treated with dry diethyl ether, and the precipitated VI·HCl was removed by filtration and recrystallized from acetone. Base VI was obtained by the usual method.

## EXPERIMENTAL (PHARMACOLOGICAL)

The experimental investigation of decahydroquinoline derivatives I-VI was carried out on rats of the Wistar strain with a mass of 250 g (six rats in each group). The animals were narcotized with Nembutal (40 mg/kg). In the experiments on the narcotized animals the action of the investigated 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 substance in a dose of 5 mg/kg. Compound I was first dissolved in a 10% solution of dimethyl sulfoxide, while II-VI were dissolved in 10% ethanol. The MAP was recorded in the carotid artery electromanometrically, while the FHS was recorded with a cardiotachometer started up by a pulse wave. Recording of the curves was carried out prior to administration of the substances and for 1.5 h after administration. Recordings of the MAP and FHC of animals into which the corresponding solvent in an equal (0.2 ml) volume had been introduced in place of the test compounds served as the control.

Into a group of non-narcotized animals II-V were administered in the form of an aqueous suspension [1 ml (dose 50 mg/kg)] into the stomach by means of a probe using a modification of the Lax method [3]. Prior to and after administration of the substances (in the course of 5 h) the MAP was recorded in the celiac aorta electromanometrically through a polyethylene catheter implanted into the aorta 24 h prior to the experiments [4].

The MAP and FHC were calculated in percent of the starting values, which were taken as 100. The results were treated statistically by means of the Fisher—Student method. The differences at a significance level of 95% were considered to be reliable ($P \leq 0.05$).

An experimental study of I showed (Table 2) that in a dose of 5 mg/kg 30 min after intravenous administration it causes a reliable decrease in the MAP of 15 ± 4% as compared with the starting value. The changes in the FHC were unreliable.

Tests of II-VI showed (Table 3) that the intravenous administration of V does not change the MAP and FHC, while II-IV and VI display biological activity.

It is apparent from Table 3 that the effect of the investigated substances on the MAP and FHC is ambiguous. Compounds II and VI have hypotensive action; the hypotension caused by

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.

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# 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


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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


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