SYNTHESIS, ANTIAGGREGATIONAL AND HYPOTENSIVE ACTIVITY OF SOME ISOQUINOLINES

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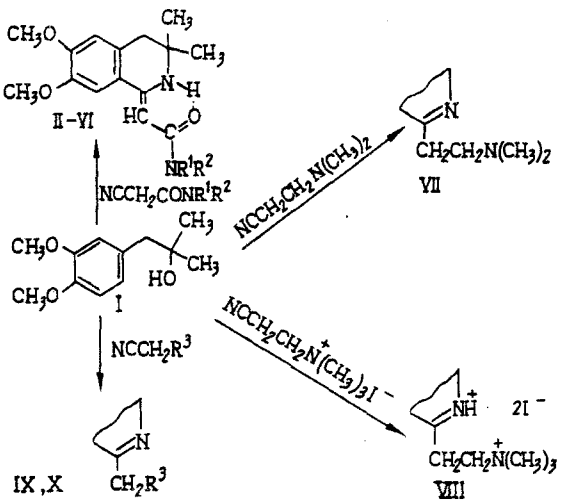
It has been reported [3, 4, 8] that compounds containing the isoquinoline ring show high antiaggregational activity with respect to thrombocytes, but the pharmacological activity of these compounds is low, being no greater than that of papaverine. It was therefore of interest to carry out a further search for novel isoquinolines in order to establish structure-activity relationships. Hypotensive activity is a classical feature of isoquinolines [7]. It would be particularly useful if antiaggregational and hypotensive activity, for example, were possessed by the same compound. The aim of the present investigation was to identify such compounds. With this in mind, some novel isoquinolines have been synthesized, in which the sub-



R^1=H (II, III, IV); R^2=C_6H_5 (II), n-$C_6H_4CH_3$ (III), p-$CO_2C_2H_5C_6H_4$ (IV); R^1+R^2= $-(CH_2)_5-$(V), $-(CH_2)_2O(CH_2)_2-$(VI); R^3=C_6H_5 (IX), 3,4-$(CH_3O)_2C_6H_3$ (X)

stituent in the 1-position is varied. Bearing in mind that naturally occurring isoquinoline alkaloids, which show activity of these types [4, 7, 8], bear methoxy groups in the 6- and 7-positions, the starting material used was 2-methyl-1-(3,4-dimethoxyphenyl)propan-2-ol (I). Depending on the structure of the nitrile component, the products of its cyclization with the carbinol (I) could either be the amides (II-VI), the amines (VII, VIII), or benzylisoquinolines (IX, X).

For the pharmacological tests, stable salts were used, namely the hydrochlorides of (II-VI), (IX) hydrides of (VII) and (VIII), and the salicylate of (X).

The structures of the compounds obtained were established by the PMR and IR spectra. The PMR spectra of the bases of amides (II-VI) (Table 1) showed singlets for the vinyl proton at 4.97-5.08 ppm, and for the proton of the ring NH group (9.37-9.78 ppm), which were shifted to low field on treatment with CF_3COOH. In the IR spectra of the bases of these compounds, obtained as 0.01 M solutions in chloroform, broadened bands for the associated C=O groups were

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TABLE 1. PMR Spectra of Bases (II-X)

Compound	C_3-2CH_3 (s)	C_4-CH_2 (s)	H—C_5 (s)	H—C_8 (s)	$2CH_3O$ (d)	NH ring (s)	CH_n-C_1 (n=1,2)	Ar (m)	Other signals
II	1,17	2,62	6,45	6,71	3,72	9,52	5,03 (s)	6,97—7,35	—
III	1,18	2,57	6,40	6,82	3,68	9,71	5,08 (s)	7,0—7,40	2,18, CH_3 (s)
IV	1,15	2,67	6,48	6,74	3,67	9,37	5,07 (s)	7,05—7,45	1,26 (t) and 4,18 (q), C_2H_5
V	1,16	2,63	6,46	6,78	3,73	9,66	5,02 (s)	—	1,78, $(CH_2)_3-C$ (br.m) 3,42, $(CH_2)_2N$ (br.t)
VI	1,14	2,54	6,40	6,90	3,62	9,78	4,97 (s)	—	3,72 (br.s), $4CH_2$
VII	1,10	2,60	6,38	6,82	3,76	—	2,22 (m)	—	2,57—2,78 (m), $CH_2N(CH_3)_2$
VIII	1,15	2,67	6,51	6,87	3,70	—	2,48 (m)	—	2,90—3,83 (m), $CH_2N^+(CH_3)_2$
IX	1,12	2,62	6,46	6,72	3,70	—	3,97 (s)	7,00—7,42	—
X	1,10	2,72	6,42	6,68	3,75	—	3,87 (s)	6,95—7,40	—

TABLE 2. Properties of Compounds (II-X)

Compound	Yield, %	Mp, °C	Empirical formula
II	79	203—205	$C_{21}H_{24}N_2O_3 \cdot HCl$
III	77	184—186	$C_{22}H_{26}N_2O_3 \cdot HCl$
IV	58	206—208	$C_{24}H_{28}N_2O_5 \cdot HCl$
V	60	184—185	$C_{20}H_{28}N_2O_3 \cdot HCl$
VI	87	165—166	$C_{19}H_{26}N_2O_4 \cdot HCl$
VII	76	200—202	$C_{17}H_{25}N_2O_2 \cdot 2HI$
VIII	52	195—197	$C_{18}H_{29}IN_2O_2 \cdot HI$
IX	82	211—212	$C_{20}H_{23}NO_2 \cdot HCl$
X	74	134—136	$C_{22}H_{27}NO_4 \cdot C_7H_8O_3$

TABLE 3. Pharmacological Activity of Compounds Prepared

Compound	Acute toxicity (LD_{50}, mg/kg)	Inhibition of thromobocyte aggregation, %	Reduction of AP, mm Hg	Hypotensive effect, min
II	90,0 (78,1—112,2)	31,3	—	—
III	90,3 (75,0—110,2)	16,7	—	—
IV	50,0 (46,7—53,5)	4,6	—	—
V	70,8 (60,1—83,2)	62,5	—	—
VI	141,0 (127,3—158,4)	67,0	—	—
VII	35,0 (32,1—38,1)	87,5	10	1—2
VIII	15,2 (12,2—18,6)	89,2	60	1—9
IX	15,0 (12,4—18,6)	74,6	40	0,25—0,5
X	20,0 (16,2—24,6)	70,0	60	0,25—0,5

Note. Range of variation given in brackets. A dash indicates no effect.

seen (1620-1630 cm^{-1}) and for the ring NH (3320-3240 cm^{-1}). Hence, the positions of the signals for the NH proton at low field in the PMR spectra, together with the nature of the IR spectra, indicate intramolecular association, which suggests that the enamines (II-VI) exist exclusively as the Z-isomers.

The IR spectra of (II-VI) also show absorption for the amide NH (3425-3430 cm^{-1}), while that of the ester (IV) also shows ester carbonyl absorption (1720 cm^{-1}).

Factors stabilizing the enamine structure in the bases (II-VI) are the acceptor properties of the amide group and intramolecular association. In the case of bases (VII-X), in which these factors are absent, the isoquinolines exist in the azomethine form. This is confirmed by the positions of the signals for the $CH_2:C_1$ protons (2.22-3.87 ppm), and the absence of NH signals in the PMR spectra, together with the presence of C=N absorption in the IR spectrum (at 1630 cm^{-1}).

EXPERIMENTAL (CHEMISTRY)

IR spectra were obtained on a UR-20 spectrometer (East Germany) in chloroform, and PMR spectra on an RYa-2310 (60 MHz) spectrometer in $CDCl_3$, internal standard HMDS (Table 1).

The starting carbinol (I) was obtained as in [3]. The yields and melting points of the salts obtained are shown in Table 2. The salts were all recrystallized from 2-propanol. The elemental analyses for C, H, N, and Cl were in agreement with the calculated values.

3,3-Dimethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolylidene-1-N-R^1,R^2-acetamides (II-VI). To 0.01 mole of the appropriate N-R^1,R^1χ-cyanoacetamide in 30 ml of benzene was added, at a temperature not exceeding 5°C, first 2 ml of glacial acetic acid, then 4 ml of conc. sulfuric acid and 2.10 g (0.01 mole) of the carbinol (I) in 20 ml of benzene. The mixture was stirred rapidly for 30 min at 60°C, cooled, poured into 200 ml of ice water, and the benzene layer separated. The aqueous phase was neutralized with ammonia solution, then the base separated as a solid which was filtered off, dried, dissolved in diethyl acetate, and converted into its hydrochloride by passing in gaseous HCl. The salts obtained were filtered off, dried, and recrystallized.

General Method of Preparation of 3,3-Dimethyl-6,7-dimethoxy-1-(2-dimethylaminoethyl)-3,4-dihydroisoquinoline (VII), Trimethyl-[2-(3,3-dimethyl-6,7-dimethoxy-3,4-dihydroisoquinolin-1-io)]ethylammonium Diiodide (VIII) and 1-(R^3-Methyl)-3,3-dimethyl-6,7-dimethoxy-3,4-dihydroisoquinolines (IX, X). To 0.01 mole of the appropriate nitrile [6] in 30 ml of benzene was added at a temperature not exceeding 5°C, first 2 ml of glacial acetic acid, then 4 ml of conc. sulfuric acid and 2.10 g (0.01 mole) of the carbinol (I) in 20 ml of benzene. The mixture was stirred rapidly for 40 min at 60°C, then cooled, poured into 200 ml of ice water, and the benzene layer separated. The aqueous phase was neutralized with ammonia solution, and the oil which separated was extracted with ether, dried over NaOH, and the solvent distilled off. The dihydriodide (VII) and the iodide hydriodide (VIII) were obtained by adding to the residue obtained 2.80 ml of 50% HI in 20 ml of ethanol. The base (IX) was dissolved in ether, and HCl passed through to obtain the hydrochloride. The salicylate (X) was obtained by adding 1.38 g (0.01 mole) of salicylic acid in 50 ml of ether to the base. The salts were filtered off, dried, and recrystallized.

EXPERIMENTAL (PHARMACOLOGY)

The pharmacological effects of the compounds were assessed in terms of their acute toxicities, antiaggregational and hypotensive activity.

Acute toxicities were determined in mice of both sexes weighing 16-20 g by the intraperitoneal route [1].

Antiaggregational activity was determined using Born's photometric method [5], and expressed as the percentage reduction in optical density. Thrombocyte aggregation was induced by ADP in dose of 0.05 mg/ml of dog plasma. All compounds were tested at equal concentrations, namely 0.2 mg/ml of plasma.

Hypotensive activity was determined in cats weighing 2.5-3.5 kg under hexenal narcosis. The test compounds were administered into the femoral vein in a volume of 3 ml over 2 min. AP was measured in the carotid artery by the method given in [2]. All the compounds were tested in the same dose (5 mg/kg).

The tests showed that the acute toxicities (Table 3) of the amides (II-VI) were 50-90 mg/kg, except for (VI) (141 mg/kg). The amines (VII), (VIII), and the 1-benzylisoquinolines (IX) and (X) were more toxic, their LD_{50} values being 15-35 mg/kg. All the compounds showed antiaggregational activity. Of the amides, the most active were the piperidide (V) and the morpholide (VI). The amines and benzylisoquinolines (VII-X) were more active than the amides, the most active being the quaternary ammonium salt (VIII) (Table 3). None of the five amides showed hypotensive activity. The hypotensive activity of the amines (VII) and (VIII) was greater than that of the benzylisoquinolines (IX) and (X).

Comparing these findings with those reported previously [3, 8], it appears that the presence of methoxy-groups in the 6- and 7-positions of the isoquinoline ring, and of the amino-groups and benzyl radical, lead to the appearance of high antiaggregational activity. Hypotensive activity was shown by compounds containing an amino-group, and also by compounds with structures similar to that of papaverine. Compounds (VII-X) show high antiaggregational activity in conjunction with good hypotensive activity. The combination of these two types of activity is highly beneficial, since the development of vascular thrombosis in hypertension substantially increases the severity of cardiovascular conditions.

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SYNTHESIS AND CURARE-LIKE ACTIVITY OF TRIS(β-DIALKYLBENZYL-AMMONIO)ETHYL ESTERS OF CYANURIC AND ISOCYANURIC ACIDS

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It was shown earlier that tris(β-diethylbenzylammonio)ethyl esters of cyanuric acid have curaremimetic activity [7]. However, in view of the capacity of esters of cyanuric acid to isomerize to esters of isocyanuric acid [8] the structure of the described compounds seems unproven.

The purpose of this investigation is to study the conditions of the preparation of the corresponding esters of both cyanuric and isocyanuric acid in pure form. It was proposed to study their myorelaxant activity and to compare it with the activity of tubocurarine chloride.

It is clear from the reaction scheme that tris(dialkylbenzylammonio)ethyl esters of cyanuric (III) and isocyanuric (IV) acids are obtained by a single process from cyanuric chloride, dialkylaminoethanol, and benzyl halide. The formation of compounds III or IV as a result of the reaction is determined by the probability of the occurrence of thermal isomerization of I to II.

We determined the kinetic characteristics of the isomerization with the PMR method. Various full alkyl esters of cyanuric acid, both unsubstituted and with substituents, were involved in the isomerization. In all cases, at one and the same temperature and in one and the same solvent, regardless of the concentration of the cyanurate, stability of the semiconversion period was found, which is evidence of the fact that the process obeys a first-order equation. The relative rate of the isomerization is illustrated by the data of Table 1. The obtained results indicate that tris(β-dialkylamino)ethyl esters of cyanuric acid are much easier isomerized than unsubstituted esters. Therefore, under the reaction conditions proposed in [7], occurrence of isomerization is quite probable.

If one is to prepare tris(β-dialkylbenzylammonio)ethyl esters of cyanuric acid it is necessary, in order to avoid isomerization, to use mild reaction conditions (room temperature, carrying out the reaction in a solvent). On the other hand, corresponding esters of isocyanuric acid are prepared under much more rigorous conditions. Taking into consideration that increasing the temperature promotes isomerization, the reaction is carried out at 80-120°C.

Determination of the structure of the reaction products is reliably performed with data of IR and PMR spectroscopy. For example, in the IR spectra of cyanurates the absorption in

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