SYNTHESIS, ANTIARRHYTHMIC AND ANTICOAGULANT ACTIVITY OF 1-METHYLISOQUINOLINES AND ISOQUINOLINECARBOXYLIC ACIDS

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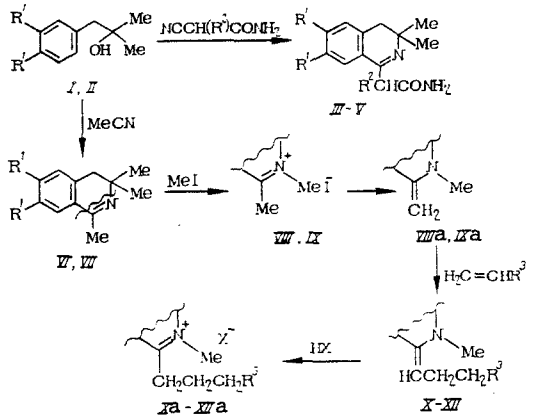
Isoquinoline alkaloids and their synthetic analogs are known to possess antiarrhythmic properties [1, 14], and to influence the process of blood clotting [6-8, 13]. The relationships between the structures of these compounds and their antiarrhythmic or anticoagulant properties has hitherto received no attention. We are also unaware of any isoquinoline derivatives which display both these types of activity simultaneously. Such a combination would be very advantageous, since the joint occurrence of arrhythmia and thrombosis seriously exacerbates cardiovascular conditions.



$R^1 = H$ (I, III—VI, VIII, VIIIa, X, Xa, XI, XIa), OMe (II, VII, IX, IXa, XII, XIIa);
R^2=Pr-*i* (I—III), Am=*i* (IV), CH_2Ph (V); R^3=COOEt (X, Xa), CN (XI, XIa, XII, XIIa);
$X^- = BF_4^-$ (Xa), I^- (XIa, XIIa).

In a search for compounds with high antiarrhythmic and anticoagulant activity, we have used the Ritter reaction [12] to synthesize from the carbinols (I) and (II) the 3, 3-dimethyl-3,4-dihydroisoquinolines (III-XII), which bear in the 1-position a methyl group or carboxylic acid derivative (esters, amides, and nitriles).

Amides (III-V), which exist in the azomethine form, are analogous to the previously-reported esters [2]. Reaction of the carbinols (I) and (II) with acetonitrile has afforded the azomethines (VI) and (VII), which readily undergo iodomethylation to give the iodides (VIII) and (IX). Treatment of (VIII) and (IX) with alkaline solutions converts them into the bases (VIIIa) and (IXa), which are tertiary enamines. These enamines are such reactive nucleophiles that they react even at 20°C in the absence of a catalyst with ethyl acrylate, to give the ester (X), and with acrylonitrile to give (XI) and (XII).

The pharmacological tests were carried out with stable salts, namely the hydrochlorides of the amides (III)-(V), and the iodides of (VI), (VII), (VIIIa), (IXa), (XI), and (XII) (the ester (X) was exceptional, only the fluoroborate being stable).

The structures of the products and attribution of the azomethine or enamine forms were assigned from the PMR and IR spectra. The PMR spectra of (III-XII) (in $CDCl_3$) are shown in Table 1. In the spectra of the amides (III-V), the α-CH group of the acetamide fragment appears as a signal with a multiplicity of n + 1, where n is the number of protons at the adjacent carbon atom, affording unambiguous proof of the azomethine structure. The structures

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TABLE 1. PMR Spectra of Bases (III-V), (VII), (VIIIa), (IXa), and (X-XII), δ, ppm

Compound	C_3-CH_3 (s)	C_1-CH_2 (s)	Ar (m) or H-(C_5) and H-(C_3)	$2CH_3O$ (d)	CH_3N (s)	CH_n-C_1 ($n=1-3$)	Other signals
III	1,20	2,60	6,84—7,43	—	—	3,85, 1H (d)	1,20, $(CH_3)_3CH$ (m); 6,72, NH_2 (s)
IV	1,20	2,60	6,78—7,52	—	—	3,75, 1H (t)	1,20, $(CH_3)_2CH(CH_2)_2$ (m); 6,55, NH_2 (s)
V	1,20	2,55	6,82—7,40	—	—	4,10, 1H (t)	3,22, CH_2 benzyl (d) 6,28, NH_2 (s)
VII	1,07	2,48	6,50 (s) and 6,83 (s)	3,76	—	2,17, 3H (s)	—
VIIIa	1,00	2,54	6,90—7,37	—	2,57	3,64, 1H (s) and 4,47, 1H (s) and	—
IXa	1,07	2,58	6,34 (s) and 7,00 (s)	3,67	2,53	3,56, 1H (s) and 4,41, 1H (s)	—
X	1,00	2,60	6,73—7,47	—	2,40	5,54, 1H (t)	2,50—2,60, $CH_2CH_2CO_2$ (m); 1,10 (t) and 3,94 (q), CH_3CH_2O
XI	1,03	2,52	6,86—7,43	—	2,30	5,43, 1H (t)	2,50—2,60, CH_2CH_2CN (m)
XII	1,05	2,52	6,38 (s) and 6,87 (s)	3,76	2,26	5,45, 1H (t)	2,50—2,60, CH_2CH_2CN (m)

of bases (VIIIa) and (IXa) were proved by the presence of singlet for the CH_3N group (2.57 and 2.53 ppm), and two singlets for the protons of the $CH_2{=}C_1$ group. Calculation according to [5] gave δ values for these protons of 4.43 and 3.99 ppm, in agreement with the experimental data shown in Table 1. The structure of the bases (X-XII) was confirmed by the triplet for the vinyl proton $HC{=}C_1$ and the singlet for the CH_3N group. On adding CF_3COOH to solutions of these compounds their PMR spectra changed, losing the enamine structure and adopting structures similar to those of the iodides (VIII) and (IX), the fluoroborate (Xa), and iodides (XIa) and (XIIa).

EXPERIMENTAL (CHEMISTRY)

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

The synthesis of the starting carbinols (I) and (II) has been described [10]. The yields and melting points of the salts are given in Table 2. The elemental analyses corresponded to the calculated values.

α-(3,3-Dimethyl-3,4-dihydroisoquinol-1-yl)-R^2acetamides (III-V). To 0.01 mole of the α-R^2-cyanoacetamide in 30 ml of benzene was added with stirring 4 ml of conc. sulfuric acid, at a temperature no higher than 5°C, followed by 1.50 g (0.01 mole) of dimethyl benzyl carbinol in 20 ml of benzene. The mixture was boiled with vigorous stirring for 1 h, cooled, poured into 200 ml of ice water, and the benzene layer separated. The aqueous phase was neutralized with aqueous ammonia, whereupon the base separated as a solid, which was filtered off, dried, dissolved in ethyl acetate, and gaseous hydrogen chloride passed through the solution to give the hydrochloride. The salt was filtered off, dried, and recrystallized from ethanol. IR spectra of bases (III-V), ν_{max}, cm^{-1}: 3395 and 3485 (NH_2, ν_s and ν_{as}), 1680 (CO) and 1625 (C=N).

1,3,3-Trimethyl-3,4-dihydroisoquinoline (VI). To 7.25 g (0.015 mole) of 85% acetonitrile in 30 ml of benzene was added 4 ml of conc. sulfuric acid at a temperature not exceeding 5°C, followed by 1.50 g (0.01 mole) of dimethyl benzyl carbinol in 20 ml of benzene. The mixture was boiled for 2.5 h with vigorous stirring, cooled, poured into 200 ml of ice water, and the benzene layer separated. The aqueous phase was neutralized with aqueous ammonia, and the oil which separated was extracted with pentane, dried over NaOH, and the solvent removed to give 65% (1.13 g) of material which was identical in its constants and spectra to that synthesized previously by a different route [11]. The hydroiodide of (VI) was obtained by adding 1.40 ml of 50% HI in 20 ml of ethanol, followed by recrystallization from the same solvent.

1,3,3-Trimethyl-6,7-dimethoxy-3,4-dihydroisoquinoline (VII). To 7.25 g (0.015 mole) of 85% acetonitrile in 30 ml of benzene was added at a temperature not exceeding 5°C first and

TABLE 2. Properties of Salts of (III-V), (VII-IX), and (Xa-XIIa)

Compound	Yield, %	mp, °C	Empirical formula
III·HCl	82	209—10	$C_{16}H_{23}ClN_2O$
IV·HCl	80	185—6	$C_{18}H_{27}ClN_2O$
V·HCl	92	195—6	$C_{20}H_{23}ClN_2O$
VIIHV	95	205—6	$C_{14}H_{20}INO_2$
VIII	97	217—9	$C_{13}H_{18}IN$
IX	90	198—9	$C_{15}H_{22}INO_2$
X[a]	67	92—3	$C_{18}H_{26}BF_4NO_2$
XI[a]	81	218—20	$C_{16}H_{21}IN_2$
XII[a]	72	193—5	$C_{18}H_{25}IN_2O_2$

2 ml of glacial acetic acid, then 4 ml of conc. sulfuric acid and 2.10 g (0.01 mole) of 2-methyl-1-(3,4-dimethoxyphenyl)propan-2-ol in 20 ml of benzene. The mixture was stirred vigorously at 60°C for 40 min, cooled, poured into 200 ml of ice water, and the benzene layer separated. The aqueous phase was neutralized with aqueous ammonia, and the oil which separated was extracted with ether, dried over NaOH, and the solvent removed. The hydroiodide was obtained and recrystallized as for the salt of (VI). IR spectrum of the base, ν_{max}, cm^{-1}: 1620 (C=N).

1,2,3,3-Tetramethyl-6,7-$(R^1)_2$-3,4-dihydroisoquinolinium Iodides (VIII, IX). The base (VI or VII) (0.01 mole) was mixed with 0.80 ml (0.013 mole) of MeI (in the case of (VII), 30 ml of acetone was added). The mixture was closely covered, and kept for 4 h at 20°C. The solid which separated was filtered off, and recrystallized from 2-propanol to give the iodides (VIII) and (IX). To obtain the bases (VIIIa) and (IXa), the appropriate methiodide was treated with 20% NaOH solution, extracted with ether, the ether extracts dried over NaOH, and the ether removed to give bases (VIIIa) and (IXa), ν_{max}, cm^{-1}: 1650 (C=C).

2,3,3-Trimethyl-1-(3-ethoxycarbonylpropyl)-3,4-dihydroisoquinolinium Fluoroborate (Xa). 1.87 g (0.01 mole) of the enamine (VIIIa) was mixed with 1.41 ml (0.013 mole) of ethyl acrylate at 20°C. After 10 h, addition of 2.2 ml of 40% HBF_4 in 20 ml of ethanol gave the fluoroborate (Xa), which was recrystallized from 2-propanol and converted into the free base (X) as described for (VIII) and (IX). IR spectrum of the base, ν_{max}, cm^{-1}: 1735 (CO), 1650 (C=C).

2,3,3-Trimethyl-6,7-$(R^1)_2$-1-(3-cyanopropyl)-3,4-dihydroisoquinolium Iodides (XIa) and (XIIa). 0.01 mole of the enamine (VIIIa) or (IXa) (in 20 ml of acetone) was mixed with 0.74 ml (0.011 mole) of acrylonitrile, and the mixture kept for 10 h at 20°C. The iodides (XIa) and (XIIa) were obtained and recrystallized as for the salt (VI), and the free bases (XI) and (XII) as described for bases (VIIIa) and (IXa). IR spectra of bases (XI) and (XII), ν_{max}, cm^{-1}: 2210 (C≡N), 1670 (C=C).

EXPERIMENTAL (PHARMACOLOGY)

The biological activity of the compounds was assessed by determination of the acute toxicities and the antiarrhythmic and antiaggregational activity in respect of thrombocytes.

Acute toxicities were measured in white mice of both sexes weighing 16-20 g by the intravenous route [3].

Antiarrhythmic activity was determined in model arrhythmias induced by intravenous administration of calcium chloride to white mice in a dose of 280 mg/kg [4].

Antiaggregational activity was examined using Born's photometric method [9] with dog plasma thrombocytes, and calculated as a percentage reduction in optical density. Aggregation of the thrombocytes was induced by ACP in a dose of 0.05 mg/ml of plasma. All the compounds were tested at the same dose, 0.2 mg/ml of plasma.

Results and Discussion. Measurements of acute toxicity showed (Table 3) that the toxicity in most cases was 20-25 mg/kg, only in the amide (III) was it 117 mg/kg, and in amide (V), 14.5 mg/kg. All the compounds showed antiaggregational activity, inhibiting aggregation by 10-20%, the most active compound in this test being (III). Antiarrhythmic activity was shown by three compounds only (III, IV, and V), the ED_{50} values of which were

TABLE 3. Acute Toxicities, Antiaggregational and Antiarrhythmic Activity of the Compounds Prepared

Compound	Acute toxicity (LD_{50}, mg/kg)	Inhibition of thrombocyte aggregation, %	Antiarrhythmic activity	
			ED_{50}, mg/kg	LD_{50}. ED_{50}
III·HCl	117,0(103,5—132,2)	27,5	6,8(5,6—8,2)	17,2
IV·HCl	26,0(22,8—29,6)	22,1	1,3(1,0—1,6)	20,8
V·HCl	14,5(13,5—15,5)	0,4	1,7(1,3—2,1)	8,8
VI·HI	25,0(21,7—28,7)	10,8	—	—
VII·HI	50,0(40,3—62,0)	23,3	—	—
VIII	28,1(24,6—32,0)	17,5	—	—
IX	25,0(21,5—29,0)	12,9	—	—
X[a]	20,0(16,1—24,8)	19,2	—	—
XI[a]	25,0(21,5—29,0)	11,7	—	—
XII[a]	25,2(21,7—29,1)	22,1	—	—

6.8, 1.25, and 1.65 mg/kg respectively, the antiarrhythmic indices (LD_{50}/ED_{50}) being 17.2, 20.8, and 8.8 (Table 3).

Comparison of the structures of the compounds with their antiarrhythmic activity showed that the isoquinoline ring is active in conjunction with the acetamide group when it is sterically hindered by alkyl or benzyl radicals. Comparing the antiaggregational activity with the data reported in [13], it may be assumed that this type of activity results from the presence of the isoquinoline ring. Amides (III) and (IV) display high antiaggregational activity and good antiarrhythmic activity. The conjunction of these two types of activity is most promising, since increased aggregational activity of the thrombocytes is often the reason for cardiac vascular thrombosis and the subsequent development of cardiac arrhythmias.

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