SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF 2-ARYL-3-ETHOXY-CARBONYL-5-HYDROXYBENZOFURANS

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An intensive search for pharmaceuticals of the benzofuran series led to the development of the cardiovascular drug fenicarberan (2-phenyl-3-ethoxycarbonyl-4-dimethylaminomethyl-5-hydroxybenzofuran hydrochloride) [3]. There have also been reports in the literature that a considerable number of 2-aryl-5-hydroxybenzofurans display antifungal [13], antibacterial [11], β-adrenoblocking [10], anticonvulsant and psychotropic activity [2, 7]. For this reason, it was of interest to synthesize analogs of fenicarberan containing various substituents in the phenyl substituent, namely one or more methoxy groups, chlorine, bromine, or iodine atoms.

Reaction of anisic acid [13], veratric acid, 3,5-dibromo- [14], 3,5-diiodo- [20], 3,5-dichloro-4-methoxybenzoic acid [17], or 3,4,5-trimethoxybenzoic acid [15] with an excess of thionyl chloride gave the acid chlorides, which were treated without further purification with acetoacetic easter. There were obtained the known 4-methoxy [19] and 3,4,5-trimethoxybenzoylacetic ester [16], together with the novel 3,4-dimethoxy- (I), 3,5-dibromo-4-methoxy- (II), 3,5-dichloro-4-methoxy- (III), and 3,5-diiodo-4-methoxybenzoylacetic esters (IV).

Condensation of the substituted benzoylacetic esters with p-benzoquinone as described in [3] afforded 3-ethoxycarbonyl-5-hydroxybenzofurans, bearing in the 2-position the substituents 4'-methoxy- (V), 3',4'-dimethoxy- (VI), 3',4',5'-trimethoxy- (VII), 3',5'-dibromo-4'-methoxy- (VIII), 3',5'-dichloro-4'-methoxy- (IX), and 3',5'-diiodo-4'-methoxyphenyl (X). As by-products in the condensation of (I-IV) with p-benzoquinone, there were isolated 2-16% of the diethyl 2,6-diarylbenzo[1,2-b:4,5-b]difuran-3,7-dicarboxylates (XI-XIV).

Heating (V-X) in DMF with formamide and $Me_2NH \cdot HCl$ gave the 4-dimethylaminomethyl derivatives. In the case of (VII), it was shown that the Mannich reaction when carried out with an equimolar amount of bisdimethylaminomethane in dioxane also gave the monoaminomethyl derivative (XVI). The use of an excess of bisdimethylaminomethane and increasing the reaction time resulted in the formation of the 4,6-bisdimethylaminomethyl derivatives (XXI-XXII). An exception was 2-(4'-methoxyphenyl)-3-ethoxycarbonyl-4-dimethylaminomethyl-5-hydroxybenzofuran (XX). Under the conditions for the synthesis of the disubstituted product (XXIII), we obtained high yields of the monosubstituted compound (XX) only. 2-(4-Methoxyphenyl)-3-ethoxycarbonyl-4,6-bis(dimethylaminomethyl)-5-hydroxybenzofuran (XXIII) was only obtained when the aminomethylation of (XX) with bisdimethylaminomethane was carried out in acetic acid.

TABLE 1. Properties of Esters (I-IV)

Compound	Yield %	mp, °C	Found, %			Empirical formula	Calculated, %		
			C	H	Hal		C	H	Hal
II	63,8	79—81	37,92	3,18	42,05	$C_{12}H_{12}Br_2O_4$	37,48	3,05	41,91
III	56,6	79—80	49,76	4,20	24,05	$C_{12}H_{12}Cl_2O_4$	49,51	4,15	24,36
IV	70	87—90	30,90	2,46	55,08	$C_{12}H_{12}I_2O_4$	30,40	2,55	53,54

Note. Compound (I) (an oil) was obtained in 57% yield, R_f 0.38 (chloroform).

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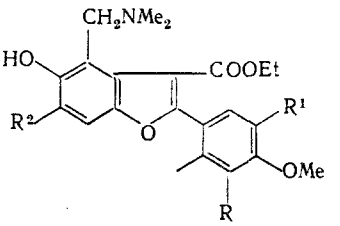
TABLE 2. Properties of 2-Aryl-3-ethoxycarbonyl-5-hydroxybenzofurans (V-X) and Benzodifurans (XI-XIV)

Compound	Yield, %	mp, °C	Found, %			Empirical formula	Calculated, %		
			C	H	Hal		C	H	Hal
V	81	174—6*	67,53	5,23		$C_{18}H_{16}O_5$	69,22	5,16	
VI**	18					$C_{19}H_{18}O_6$			
VII	30,5	165—6	64,56	5,43		$C_{20}H_{20}O_7$	64,51	5,41	
VIII	54	202—3	45,97	3,31	34,09	$C_{18}H_{14}Br_2O_5$	45,98	3,00	34,00
IX	54,4	180—1	56,52	3,75	18,69	$C_{18}H_{14}Cl_2O_5$	56,71	3,70	18,60
X	28	181—2	38,52	2,59		$C_{18}H_{14}I_2O_5$	38,32	2,50	
XI	3,2	249—50	66,52	5,17		$C_{32}H_{30}O_{10}$	66,89	5,26	
XII	3,8	251—3	43,49	2,72	38,18	$C_{30}H_{22}Br_4O_8$	43,40	2,67	38,51
XIII	16	240—2	55,33	3,87	21,64	$C_{30}H_{22}Cl_4O_8$	55,24	3,40	21,74
XIV	2,75	265—6	36,20	2,13		$C_{30}H_{22}I_4O_8$	35,39	2,18	

*Literature value [18], mp 172-173°C.
**Oil, M^+. 342.



XV—XXIII

R=H (XV); R = R¹=OMe (XVI, XXI), Br (XVII), Cl (XVIII), I (XIX, XXII), H (XX, XXIII); R¹=OMe (XV); R² = H (XV—XX), CH_2NMe_2 (XXI—XXIII)

The compounds obtained were examined for various types of pharmacological activity, under the direction of A. N. Grinev.

EXPERIMENTAL (CHEMISTRY)

General Method of Preparation of Substituted Benzoyl Chlorides. The substituted p-methoxybenzoic acid (1 mmole) was boiled for 3 h with 3 moles of thionyl chloride. On the following day, excess thionyl chloride was distilled off, and the residue used without further purification in the subsequent reactions.

General Method of Preparation of Substituted Benzoylacetic Esters (I-IV). (Table 1). To a mixture of 200 ml of water, 120 ml of toluene, and 137.5 ml (1.06 mole) of acetoacetic ester was added dropwise with stirring at 3-7°C 33% NaOH until the pH reached 11. There was then added, dropwise with continued stirring and cooling, 0.59 mole of the acid chloride in 50 ml, at such a rate that the temperature of the mixture did not rise above 7°C at pH 10.0-11.0. At the same time, dropwise addition of 33% NaOH (1.4 mole) was continued. The mixture was stirred for 1.5 h at ambient temperature and 1 h at 27-33°C, and treated with 32 g (0.59 mole) of ammonium chloride. On the following day, after adding 25 g of sodium chloride and stirring for 30 min the toluene layer was separaed, washed with saturated aqueous sodium chloride, dried over magnesium sulfate, and the toluene distilled off. The residue was recrystallized from alcohol. Compound (I) was purified on a silica gel column (chloroform).

General Method of Preparation of 2-Aryl-3-ethoxycarbonyl-5-hydroxybenzofurans (V-X). (Table 2). To a mixture of 1.03 mole of the benzoylacetic ester, 14.9 g (1.09 mole) of anhydrous zinc chloride, and 0.4 ml of glacial acetic acid was added slowly and regularly over 10 h with stirring at 78-83°C a solution of 5.57 g (51.5 mole) of p-benzoquinone in 30 ml of d chloromethane, the dichloromethane being simultaneously distilled from the mixture. When the addition of the quinone was complete, the mixture was kept at the same temperature for 1.5-2 h, cooled to ambient temperature, and chromatographed on a column of silica gel (chloroform).

TABLE 3. Properties of Aminomethyl Derivatives (XV-XXIII)

Compound	Method of preparation	Reaction time, h	Yield, %	mp, °C	Found, %			Emperical formula	Calculated, %		
					C	H	Hal		C	H	Hal
XV	A	4	34,5	180—1 (with dec.)	59,68	6,08	3,50	$C_{22}H_{25}NO_6 \cdot HCl$	60,62	6,01	3,24
XVI	A	4	56	185—6 (with dec.)	58,98	6,22	3,07	$C_{23}H_{27}NO_7 \cdot HCl$	59,29	6,06	3,00
XVII	A	4	53,3	209—10 (with dec.)	44,57	3,98	2,38	$C_{21}H_{21}Br_2NO_5 \cdot HCl$	44,75	3,93	2,48
XVIII	A	4	62,6	201—2 (with dec.)	53,22	4,64	2,86	$C_{21}H_{21}Cl_2NO_5 \cdot HCl$	53,13	4,67	2,95
XIX	A	4	60	190—1 (with dec.)	38,42	3,32	1,97	$C_{21}H_{21}I_2NO_5 \cdot HCl$	38,35	3,37	2,13
XX	B	3	81,5	190—2	61,96	6,01		$C_{21}H_{23}NO_5 \cdot HCl$	62,14	5,96	
XXI	B	23	70,5	196—7 (with dec.)	55,46	6,62	4,82	$C_{26}H_{34}N_2O_7 \cdot 2HCl$	55,81	6,49	5,01
XXII	B	3,5	15,1	210 (with dec.)	37,96	4,78	3,80	$C_{24}H_{28}I_2N_2O_5 \cdot 2HCl$	38,37	4,03	3,73
XXIII	C	2	36,6	216—7	57,92	6,52	5,51	$C_{24}H_{30}N_2O_5 \cdot 2HCl$	57,72	6,46	5,61

TABLE 4. Toxicities in Mice and Spasmolytic Activity of Benzofurans

Compund	Toxicities, mg/kg			Symptoms of intoxication	Hypotonic concentration, mg/ml
	LD_{16}	LD_{50}	LD_{84}		
XV	86,0	118,75±4,8	142,0	Convulsions	$1 \cdot 10^{-6}$
XVI	120,0	162,5±8,42	206,0	»	$5 \cdot 10^{-6}$
XVII	42,0	210,0±10,89	348,0	Depression	$5 \cdot 10^{-6}$
XVIII	128,0	187,5±9,89	247,0	Tremor	$5 \cdot 10^{-6}$
XX	54,0	68,75±2,36	71,0	Convulsions	$1 \cdot 10^{-6}$
XXI	316,0	353,48±6,79	386,0	Depression	$5 \cdot 10^{-7}$
XXII	324,0	425,0±14,39	481,0	»	$1 \cdot 10^{-6}$
XXIII	113,0	137,5±5,74	163,0	Tremor	$5 \cdot 10^{-6}$

Note. Compounds (XI) and (XIII) on intragastric administration in doses of 1000-1500 mg/kg caused depression, but not the death of the mice.

TABLE 5. Effects on the Coronary Circulatory Throughput and Myocardial Oxygen Requirement

Compound	Dose, mg/kg	Change in coronary circulatory throughput, % (M ± m)	Change in oxygen requirement, % (M ± m)	Duration of effect, min
XV	5	+96,6±12,5	+96,6±12,5	4±0
XVI	3	−21,3±6,7	−21,3±7,6	4,6±0,4
XVII	5	+53,0±9,6	+62±15,5	10,0±0
XVIII	4	+32,3±26,8	+35,0±31,3	30±8,3
XX	2	−18,3±0,8	−16,3±1,2	4,3±0,4
XXII	20	+27±2,0	+18±5	3,0±0
XXIII	4	+33,0±12,5	+76±5	26±6,6
Fenicarberan*	3	+54,6±17,1	+33±16,1	37,8±15,8
Cordaron*	5	+52,5±12,5	+21,8±5,1	42,8±12,8

*Mean values.

General Method of Preparation of Aminomethyl 2-Aryl-3-ethoxycarbonyl-5-hydroxybenzofuran Hydrochlorides (XV-XXIII). (Table 3). A. A solution of 10 mmole of the benzofuran, 10 mmole of formalin, and 10 mmole of dimethylamine hydrochloride in 14 ml of DMF was heated at 100°C for 4 h. The solvent was removed, and the residue treated with acetone. On the following day, the solid was isolated and recrystallized from a mixture of acetone, methanol, and ether.

B. A solution of 11.5 mmole of the benzofuran and 6 ml (45 mmole) of bisdimethylaminomethane in 65 ml of dioxane was boiled for 3.5-23 h. The solvent was removed, and the residue neutralized with ethereal hydrogen chloride. The solid was filtered off, and recrystallized from a mixture of acetone, methanol, and ether.

C. A solution of 70 mmole of 2-(4-methoxyphenyl)-3-ethoxycarbonyl-4-dimethylaminomethyl-5-hydroxybenzofuran (XX) and 9.5 ml (70 mmole) of bisdimethylaminomethane in 23 ml of glacial acetic acid was heated at 80°C for 2 h. The mixture was then diluted with water, and neutralized with aqueous ammonia. The oil which separated was extracted with ether, and chromatographed on a column of alumina (ether). The ether was removed, and the residue neutralized with ethereal hydrogen chloride. The solid was filtered off, and recrystallized from a mixture of acetone, methanol, and ether.

EXPERIMENTAL (PHARMACOLOGY)

We here report results on spasmolytic activity, effects on coronary circulation and myocardial oxygen requirement, and analgesic and anticonvulsant activity.

The toxicities of water-soluble compounds by the intraperitoneal route, and of water-insoluble compounds by the intragastric route, were measured in 260 white rats by the method of Behrens [1], spasmolytic activity on isolated segments of the small intestine of the

rabbit by the Mangus method [7], effect on coronary circulation and myocardial oxygen requirement in 41 cats of both sexes weighing 2.4-3.8 kg by standard methods [5, 9]. The compounds were given intravenously in doses of 2-5% of the LD_{50}. Analgesic activity was determined in 196 mice using the hot plate and contraction methods [4], and anticonvulsant activity by the maximum electroshock method in 112 mice [6]. The compounds were administered into the stomach in doses of 30% of the LD_{50} (compounds (XI) and (XIII) in doses of 300 mg/kg).

The toxicities and hypotonic activity (threshold concentrations) of the test compounds are shown in Table 4.

The hypotonic effects of the test compounds are inferior to those of fencarberan, the threshold concentration of which causing weakening of isolated segements of rabbit intestine is $1 \cdot 10^{-7}$.

The test compounds also had a less pronounced effect on coronary circulation than fenicarberan, both in degree and duration of effectiveness (Table 5).

Fenicarberan and cordaron, in addition to increasing the coronary throughput, also increased the myocardial oxygen requirement, but this was less pronounced than the increase in coronary circulation, suggesting that these drugs create a small reserve of oxygen in the myocardium.

On chemical pain stimulation, (XX) had an analgesic effect, decreasing the number of spasms in mice to 15.5 ± 4.23, the control values being 33.8 ± 3.93, and (XV) resulted in 18.1 ± 4.53 spasms as compared to 34.3 ± 4.24 in the controls.

These benzofurans had no effect on thermal pain stimulation, nor did they have any anticonvulsant activity.

These benzofurans thus display biological activity, having a hypotonic effect on the intestinal smooth muscle, and some of them stimulate coronary circulation, but they offer no advantages over known drugs with this type of activity.

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