and a dilute solution of sodium hydroxide. The organic layer was washed with water, dried, and evaporated. The residue was treated with dry ether, the material which crystallizes out was filtered off and dissolved in dry benzene, and the corresponding hydrochloride was precipitated with an alcoholic solution of hydrogen chloride (compounds XIII and XIV were first recrystallized from alcohol or benzene).

Method B. The residue was treated with hydrochloric acid (20 ml; 1 N) and extracted with chloroform (3 × 10 ml). The aqueous layer was treated with sodium carbonate, extracted with methylene chloride (3 × 15 ml), and the organic layer was washed with water, dried, and evaporated. The residue was dissolved in methyl ethyl ketone (XV, XVI) or in benzene (XVII), an alcoholic solution of hydrogen chloride was added, and the precipitated hydrochlorides of XII-XVII were recrystallized and dried in vacuum at 60-70°.

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*As in Russian original, no data given — Consultant's Bureau.

SYNTHESIS AND STUDY OF THE BIOLOGICAL ACTIVITY OF AMINOMETHYL DERIVATIVES OF 4-HYDROXYBENZOFURAN

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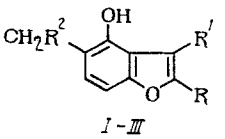
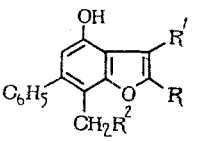
UDC 615.281.8:547.722

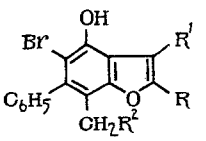
As there is considerable interest in the biological activity of various derivatives of benzofuran [1, 2], we synthesized some previously unknown aminomethyl derivatives of 4-hydroxybenzofuran and studied their antiviral and antimicrobial activity. We found that on reaction with bisdialkylaminomethanes, derivatives of 4-hydroxybenzofuran form Mannich bases, which can be isolated as salts (I-XII). Aminomethylation of 4-hydroxybenzofurans with no substituents on the benzene ring gave 5-aminomethyl derivatives (I-III), and aminomethylation of derivatives of 4-hydroxy-6-phenylbenzofuran with free 5 and 7 positions give 7-aminomethyl derivatives (IV-VIII, XII). When there is a bromine atom at the 5 or 7 position of the starting 4-hydroxybenzofuran, the aminomethyl substituent enters the free 7 or 5 position (IX-XI).



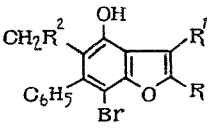
I-III



IV-VIII, XII



IX



X-XI

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0091-150X/77/1105-0661$07.50

TABLE 1. Aminomethyl Derivatives of 4-Hydroxybenzofurans (II-XII)

Compound	R	R^1	R^2	Yield, %	Melting point, deg	Found, %			Empirical formula	Calculated, %		
						C	H	Br or Cl		C	H	Br or Cl
II	$COOC_2H_5$	CH_3		80	183—4	57,1	6,3	9,9	$C_{17}H_{21}NO_5 \cdot HCl$	57,4	6,2	10,0
III	$COOC_2H_5$	CH_3	$N(CH_3)_2 \cdot HCl$	81	190 (decomp.)	57,6	6,5	12,0	$C_{15}H_{19}NO_4 \cdot HCl$	57,4	6,4	11,4
IV	C_6H_5	H		60	140(decomp.)	68,3	6,1	7,8	$C_{25}H_{23}NO_3 \cdot HCl \cdot H_2O$	68,3	6,0	8,1
V*	$COOC_2H_5$	CH_3	$(CH_3)_2 \cdot C_4H_6O_6 \cdot 2H_2O$	50	60(decomp.)	55,2	6,5	—	$C_{21}H_{23}NO_4 \cdot C_4H_6O_6 \cdot 2H_2O$	55,6	6,2	—
VI	$COOC_2H_5$	CH_3		67	169—71	64,0	6,1	7,9	$C_{23}H_{26}ClNO_5$	64,0	6,1	8,2
VII	C_6H_5	Br	$N(CH_3)_2 \cdot HCl$	75	130—2	60,0	4,6	25,0	$C_{23}H_{20}BrNO_2 \cdot HCl$	60,2	4,6	25,2
VIII	C_6H_5	Br		54	170—1	59,7	4,9	23,3	$C_{25}H_{22}BrNO_3 \cdot HCl$	59,9	4,6	23,0
IX	$COOC_2H_5$	CH_3		67	198—200	54,1	5,1	22,0	$C_{23}H_{24}BrNO_5 \cdot HCl$	54,0	4,9	22,6
X	C_6H_5	H	$N(CH_3)_2 \cdot HCl$	80	210 (разл.)	60,2	4,9	25,1	$C_{23}H_{20}BrNO_2 \cdot HCl$	60,2	4,6	25,2
XI	C_6H_5	H		30	170(decomp.)	59,7	4,7	22,9	$C_{25}H_{22}BrNO_3 \cdot HCl$	59,9	4,6	23,0
XII*	C_6H_5	NO_2	$N(CH_3)_2 \cdot C_4H_6O_6$	37	150(decomp.)	60,7	5,2	—	$C_{23}H_{20}N_2O_4 \cdot C_3H_6O_6$	60,2	4,9	—

Note. Compounds II-IV, VI-VIII, XI, and XII were recrystallized from alcohol, compound V, IX, and X from acetone.
*Tartrate.

The structures of the compounds synthesized were verified from PMR spectra of the free Mannich bases* (Ia-XIIa, respectively). In the PMR spectrum of compound Ia there is a doublet at δ = 7.12 and 7.6 ppm, related to protons in the 7 and 6 positions, respectively (I = 8.5 Hz), and a singlet at δ = 7.75 ppm, related to the 3H proton, which confirms the substitution of the hydrogen in the 5 position. The peaks in the spectrum of compound IIa are very close (δ = 6.82 and 6.99 ppm) and it is impossible to make a definite assignment thus determine the position of the substituent. However, comparing the spectrum of compound IIa with the spectrum of the starting 2-carbethoxy-3-methyl-4-hydroxybenzofuran, and noting the donor character of the morpholinomethyl group, it can be assumed that the peak at δ = 6.82 ppm is related to the 6H proton, and the peak at δ = 6.99 ppm to the 7H proton. To verify this assumption the IR spectrum of compound IIa was taken, both without any solvent, and as 0.01 and 0.02% solutions in carbon tetrachloride. No strong bands were found in the region 3600-3000 cm^{-1} either in the spectrum without solvent or those with solvent; this indicates that the hydroxyl group participates in intramolecular hydrogen bonding, and that there is no intermolecular hydrogen bonding [3]. The PMR spectra of compounds IVa, VIa, and VIIa contain singlets at δ = 6.87, 6.75, and 6.86 ppm, respectively, related to the 5H proton, which confirms the substitution of the hydrogen in the 7 position. The PMR spectrum of compound Xa has a singlet in the region δ = 6.7-6.9 ppm, confirming the substitution of the hydrogen in the 5 position.

EXPERIMENTAL

Pharmacology

Derivatives of benzofuran, I, III, VI-VIII, IX, and X were studied in contact experiments *in vitro* with influenza virus A/PR8 and with microvirus FPV using methods described earlier [4]. One compound, the hydrochloride of 2,6-diphenyl-3-bromo-4-hydroxy-7-dimethylaminomethylbenzofuran (VII), was found to possess a weak antiviral action. This compound at a dose of 50 μg is partially effective against influenza virus A/PR in mice (LD_{100}). The antimicrobial activity of the compounds was studied in *in vitro* experiments on ten types of bacteria, among them tuberculase microbacteria, and five types of pathogenic fungi using the method described in [5]. It was found that the hydrochloride of 2,6-diphenyl-4-hydroxy-5-dimethylaminomethyl-7-bromobenzofuran (X) displays medium tuberculostatic activity [minimum bacteriostatic concentration (MBC) = 8 μg/ml]. The hydrochlorides of 2,6-diphenyl-3-bromo-4-hydroxy-7-morpholinomethylbenzofuran (VIII) (MBC = 1000 μg/ml) and 2-carbethoxy-3-methyl-4-hydroxy-5-morpholinomethylbenzofuran (II) (MBC = 250 μg/ml) display weak tuberculostatic activity. The latter also displays weak fungistatic action [minimum fungistatic concentration (MFC = 250 μg/ml)].

The hydrochloride of 2-carbethoxy-3-methyl-4-hydroxy-5-dimethylaminomethylbenzofuran (III) also has a weak fungistatic action (MBC = 500 μg/ml). The remaining compounds in concentrations of 1000 μg/ml did not show any antimicrobial activity in tests *in vitro*.

Chemistry

The PMR spectra were taken on an INM-4H-60 (60 MHz) instrument, the internal standard was tetramethylsilane, in deuteroacetone. The IR spectra were taken in carbon tetrachloride and as thin layers on a UR = 10 apparatus.

The yields and constants of the synthesized compounds (II-XII) are given in Table 1.

Hydrochloride of 2-Phenyl-4-hydroxy-5-morpholinomethylbenzofuran (I). To a solution of 2-carbethoxy-3-methyl-4-hydroxybenzofuran (2.2 g, 0.01 mole) in dry dioxane (60 ml) was added bismorpholinomethane (2.7 g, 0.015 mole) and the reaction mixture was refluxed for 9 h. The solution was then poured into water (200 ml), the precipitate extracted with ether, and the ether extract dried over magnesium sulfate. The hydrochloride was obtained from the dry ether extract in the usual manner. Yield of compound I, 2.55 g (81%), mp 201-203°C (from acetone). PMR spectrum of Ia, δ ppm: singlet 4.43 ($Ar-CH_2-N$), 7.75 (3H), doublet 7.12 (7H), 7.60 (6H), multiplet 3.33 (CH_2); 3.96 (OCH_2), 7.42-7.91 (C_6H_5). Found, %: C 65.8; H 5.8; Cl 10.2. $C_{19}H_{20}ClNO_3$. Calculated, %: C 66.0; H 5.8; Cl 10.2.

Compounds I-XI were prepared using the same conditions, and compound XII by refluxing the reaction solution for 22 h.

*The Mannich bases were viscous liquids.

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SYNTHESIS OF PIPERIDINES AND DECAHYDROQUINOLINES, AND THEIR ANALGESIC AND PSYCHOTROPIC PROPERTIES.

V. N-γ-PHENYLPROPARGYL-SUBSTITUTED MONO- AND BICYCLIC 4-PIPERIDONES AND THEIR NEUROTROPIC ACTIVITY

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UDC 615.21:[547.822.3+547.831].012.1

The 1-phenylpropargyl derivative of 4-phenyl-4-piperidyl propionate, in contrast to its isomeric analog pethidine [1], possesses high analgesic activity. We have synthesized the phenylpropargyl derivatives of several ketones of the piperidine (VIII-XI) and decahydroquinoline (XII-XIV) series, with the aim of obtaining new analgesics, and to investigate their activity with respect to the structures of the parent heterocyclic systems.

We prepared these compounds as shown in the scheme below, by the aminomethylation of phenylacetylene using paraform and the secondary aminoketones (I-VII) [2-7] under the conditions of the Mannich reaction. It was found that the formation of representatives of both groups of tertiary aminoketones was largely complete within 20-30 min, as was readily shown by thin-layer chromatography.

The IR spectra of the compounds (Table 1) exhibited bands at 1707-1725 cm^{-1}, indicating the presence of carbonyl groups, while bands corresponding to the secondary amino group were absent.

Since the tertiary aminoketones (VIII-XIV) were the sole reaction products, their spatial structure must correspond with that of the initial ketones (I-VII), and it must be assumed that, in the case of the piperidine systems (I-IV), which are capable of existing in two interconvertible cis-trans forms [4-8, 10], aminomethylation of only one of these takes place, i.e., the energetically stable trans form bearing ring substituents in the equatorial position. In accordance with the principles of conformational analysis [11], the spatial orientation of the bulky phenylpropargyl group must be preferentially equatorial.

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 0091-150X/77/1105-0664$07.50