C. To a solution of (IV) (R = CH_3) (2.86 g, 0.01 mole) in ethanol (50 ml) were added o-carboxyaniline (1.37 g, 0.01 mole) and triethylamine (2.02 g, 0.02 mole). The mixture was heated for 10 h and then treated by the method of [9]. The yield was 1.51 g (40%).

The three samples of (Ib) prepared by the different methods did not depress the melting point of their admixtures.

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 3-ARYLBENZOFURAN DERIVATIVES

A. N. Grinev, S. A. Zotova, I. N. Mikhailova, A. A. Stolyarchuk, G. I. Stepanyuk, V. V. Matsak, T. N. Sizova, and G. N. Pershin

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Continuing the search for compounds with biological activity we have synthesized and examined the pharmacological and antimicrobial properties of various functional derivatives of 3-arylbenzofuran.

2-Methylbenzofurans with an acetoxy group on the benzene ring are brominated exclusively at the methyl group by N-bromosuccinimide [1]. After bromination of 2-methyl-3-phenyl-5-acetoxybenzofuran [2] with bromine in refluxing carbon tetrachloride we were able to isolate not only 2-bromomethyl-3-phenyl-5-acetoxybenzofuran but also the dibromo derivative, 2-bromomethyl-3-phenyl-5-acetoxy-6-bromobenzofuran (I), in 37.8% yield.

Unlike the 5-acetoxy compound, 2-methyl-3-phenyl-6-acetoxybenzofuran (II), prepared by acylation of the 6-hydroxy compound [3], formed only 2-bromomethyl-3-phenyl-6-acetoxybenzofuran (III) in 66.8% yield on bromination with bromine in refluxing carbon tetrachloride.

Bromination of 2-methyl-3-phenyl-5-hydroxybenzofuran with bromine or N-bromosuccinimide gave only 2-methyl-3-phenyl-4,6-dibromo-5-hydroxybenzofuran (IV), characterized by the 5-acetoxy derivative (V) synthesized from it.

Condensation of 2-bromomethyl-3-phenyl-5-acetoxybenzofuran with potassium thiophenolate gave 2-phenylthiomethyl-3-phenyl-5-acetoxybenzofuran (VI). Hydrolysis of compound (VI) formed the 5-hydroxy derivative (VII).

Reaction of 2-bromomethyl-3-phenyl-5-chlorobenzofuran [4] with methyl thioglycollate also gave methyl [3-phenyl-5-chlorobenzofuran-2-ylmethyl)thio] acetate (VIII):

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical Chemistry Institute, Moscow. N. I. Pirogov Vinnitsa Medical Institute.

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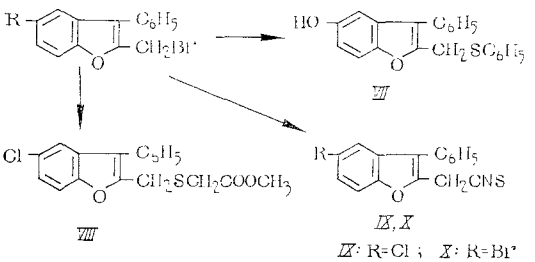
TABLE 1. Toxicity on Single (Intragastric) Administration and Antiarrhythmic Activity of Benzofuran Derivatives

Compound	Index of toxicity, mg/kg			Symptoms of poisoning	Antiarrhythmic activity*	
	DMT	LD_{50}	LD_{100}		a	b
XX	700	910	1100	Respiratory depression	2	6
XXI		1500		No symptoms apparent	1	7
XXVIII	700	842.5	1000	Respiratory depression	3	8
XXIX	700	870	1100	»	0	7
Novocainamide	—	—	—	—	4	6

*Number of tests (a) showing and (b) not showing antiarrhythmic effect.



We carried out the thiocyanation of 2-bromomethyl-3-phenylbenzofurans with a chlorine or bromine atom in position 5 [2] under mild conditions with potassium thiocyanate. 2-Thiocyanatomethyl-3-phenyl-5-chloro- (IX) and 2-thiocyanatomethyl-3-phenyl-5-bromobenzofuran (X) were formed in 20 and 61% yield respectively.

Because of its high reactivity, the bromine in the 2-bromomethyl-3-arylbenzofurans can also be substituted by other functional groups. Treatment of 2-bromomethyl-3-phenyl-5-acetoxy-6-bromobenzofuran (I) with diethylamine formed 2-diethylaminomethyl-3-phenyl-5-acetoxy-6-bromobenzofuran (XI), isolated as the hydrochloride.

On heating with methyl alcohol the bromine of the 2-bromomethyl group was substituted by the methoxy group. We prepared 3-phenyl- (XII), 3-(chlorophenyl)- (XIII), and 3-(p-methoxyphenyl)-2-methoxymethyl-5-chlorobenzofuran (XIV) in high yield. When refluxed in aqueous dioxane the 2-bromomethyl compounds formed the 2-hydroxymethyl derivatives of 3-phenyl-5-chloro- (XV), 3-phenyl-5-bromo- (XVI), 3-phenyl-5-methyl- (XVII), 3-(p-chlorophenyl)-5-chloro- (XVIII), and 3-(p-methoxyphenyl)-5-chlorobenzofuran (XIX).

We prepared the phenylcarbamates (XX) and (XXI) from compounds XV and XVI.

We attempted to acylate 2-hydroxy-3-phenyl-5-chlorobenzofuran (XV) at the hydroxyl group with chloroacetyl chloride. However, instead of the expected 2-chloroacetoxymethyl derivatives we isolated 2-chloromethyl-3-phenyl-5-chlorobenzofuran (XXII), i.e., substitution of the hydroxyl group by chlorine occurred.

We found that oxidation of the 2-hydroxymethyl compound (XV), (XVI), and (XVIII) with the pyridine–chromic anhydride complex formed the 2-formyl derivatives, namely 2-formyl-3-phenyl-5-chloro-(XXIII), 2-formyl-3-phenyl-5-bromo- (XXIV), and 2-formyl-3-(p-chlorophenyl)-5-chlorobenzofuran (XXV).

We characterized aldehydes (XXIII) and (XXIV) as the thiosemicarbazones (XXVI) and (XXVII) and isonicotinoylhydrazones (XXVIII) and (XXIX) (see scheme on following page).

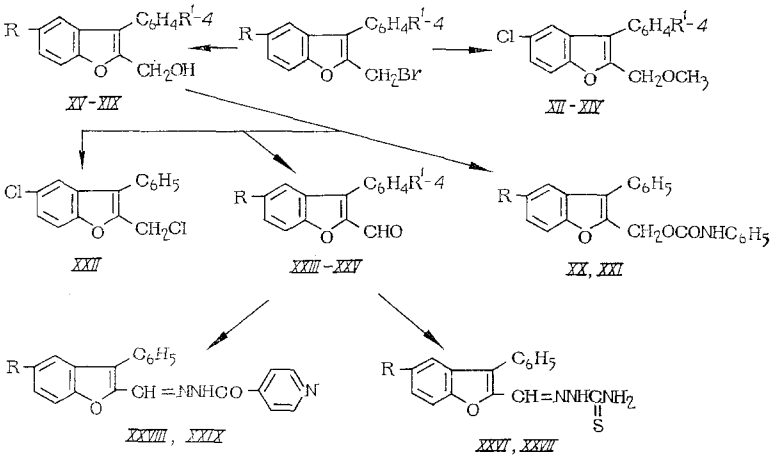
EXPERIMENTAL BIOLOGY

We evaluated the toxicity in white mice of both sexes weighing 18-28 g. Compounds were administered as suspensions in 2% starch slurry. Five animals received the compound at each dose level; LD_{50} was calculated after G. N. Pershin [5].

We assayed the antiarrhythmic activity in white rats against aconitine-induced disruption of the cardiac rhythm [6]. Aconitine was administered intravenously in a dose of 30 μg/kg. The test compounds were administered intragastrically in doses of 10% LD_{50} 30-40 min before aconitine. The novocainamide used for comparison was administered intravenously in a dose of 50 mg/kg to counteract the arrhythmia.

TABLE 2. Antimicrobial Activity of the Benzofuran Derivatives

Compound	Staphylococcus	Streptococcus	Microsporum	Trichophyton	Achorion	Actinomyces	Candida
	minimum inhibitory concentration, μg/ml						
IX	inactive	inactive	inactive	inactive	250	250	500
X	62,5	62,5	»	»	inactive	inactive	inactive
XXII	inactive	inactive	»	»	500	500	500
XXIV	125	125	»	»	inactive	inactive	



XII : R′ = H; XIII : R′ = Cl; XIV : R′ = CH_3O; XV : R = Cl, R′ = H;
XVI : R = Br, R′ = H; XVII : R = CH_3, R′ = H; XVIII : R = R′ = Cl;
XIX : R = Cl; R′ = CH_3O; XX : R = Cl; XXI : R = Br;
XXIII : R = Cl, R′ = H; XXIV : R = Br, R′ = H; XXV : R = R′ = Cl;
XXVI : R = Cl; XXVII : R = Br; XXVIII : R = Cl; XXIX : R = Br.

The toxicity (LD_{50}) of compounds XX, XXVIII, and XXIX is 842.5-910 mg/kg. Compound XXI produced no symptoms of poisoning in a dose of 1500 mg/kg.

Administration of aconitine (0.03 mg/kg) to rats induced after 4-8 min prolonged (up to 1.5 h and more) disruption of the cardiac rhythm. The antiarrhythmic effect of compounds XX, XXI, and XXVIII was apparent only in some of the tests and was typified by the postponement of the onset of arrhythmia after administration of aconitine from 4-8 min to 10-11 min. The other test compounds displayed no antiarrhythmic activity (Table 1).

We assayed the antimicrobial activity of compounds IX, X, XIII, XIV, XVIII-XXIV, XXVIII, and XXIX in vitro by serial dilution in nutrient broth [7] toward nine species of Gram-negative and Gram-positive bacteria and five species of pathogenic fungi. We found that only compounds IX, X, XXII, and XXIV have any marked antimicrobial activity (Table 2).

The 2-thiocyanatomethyl-3-phenylbenzofuran with a 5-chloro substituent (IX) has fungistatic activity. Replacement of chlorine by bromine, compound X, results in the appearance of bacteriostatic activity. The same applies to compounds XXII and XXIV.

EXPERIMENTAL CHEMISTRY

The PMR spectra were recorded on a Jeol JNM-4H-100 (Japan) with tetramethylsilane as internal standard.

2-Bromomethyl-3-phenyl-5-acetoxy-6-bromobenzofuran (I). To a refluxing solution of 2-methyl-3-phenyl-5-acetoxybenzofuran (1.3 g, 0.005 mole) in carbon tetrachloride (10 ml) was added dropwise with vigorous stirring a solution of bromine (0.51 ml, 0.01 mole) in carbon tetrachloride (5 ml). The mixture was then stirred and heated for 3 h. The solvent was stripped off. The residue was chromatographed on a silica gel column; the reaction products were eluted with benzene. The yield of I was 0.8 g, (37.8%), mp 149-150°C (from isopropyl alcohol). PMR spectrum (DMSO), δ, ppm: 2.31s (CH_3), 4.82s (CH_2) 7.52s (7H), 8.08s (4H), 7.55 (C_6H_5).

Found, %: C 48.47; H 2.75; Br 37.30. $C_{17}H_{12}Br_2O_3$. Calculated, %: C 48.15; H 2.85; Br 37.69. The yield of 2-bromomethyl-3-phenyl-5-acetoxybenzofuran was 0.3 g (17.4%).

2-Methyl-3-phenyl-6-acetoxybenzofuran (II). A solution of 2-methyl-3-phenyl-6-hydroxybenzofuran (3 g) in acetic anhydride (18 ml) and triethylamine (0.1 ml) was refluxed for 1 h. The bulk of the acetic anhydride was stripped off under vacuum. Water was added to the residue and the precipitate was separated. The yield was 87%, mp 78-79°C (from methanol). Found, %: C 77.00; H 5.40. $C_{17}H_{14}O_3$. Calculated, %: C 76.68; H 5.30.

2-Bromomethyl-3-phenyl-6-acetoxybenzofuran (III) was prepared in the same way as compound (I). Yield 66.8%, mp 96-98°C (from isopropyl alcohol). Foumd, %: Br 23.76. $C_{17}H_{13}BrO_3$. Calculated, %: Br 23.15.

2-Methyl-3-phenyl-4,6-dibromo-5-hydroxybenzofuran (IV). To a suspension of 2-methyl-3-phenyl-5-hydroxybenzofuran (3.3 g, 0.015 mole) in carbon tetrachloride (40 ml) was added dropwise with stirring at 22°C a solution of bromine (2.4 ml, 0.015 mole) in carbon tetrachloride (10 ml). The mixture was then stirred for 1.5 h. The solvent was stripped off under vacuum and the residue was recrystallized from methanol. The yield was 2.7 g (60%), mp 102-103°C. Found, %: C 46.67; H 2.69. $C_{15}H_{11}Br_2O_2$. Calculated, %: C 47.10; H 2.64.

2-Methyl-3-phenyl-4,6-dibromo-5-acetoxybenzofuran (V) was prepared in the same way as compound II. The yield was 33%, mp 99-100°C (from isopropyl alcohol). PMR spectrum (DMSO), δ, ppm: 2.29 and 2.35s (CH_3), 7.64d (7H), 7.34 (C_6H_5). Found, %: C 48.11; H 3.23; Br 38.02. $C_{17}H_{12}Br_2O_3$. Calculated, %: C 48.14; H 2.85; Br 37.70.

2-Phenylthiomethyl-3-phenyl-5-acetoxybenzofuran (VI). To 2-bromomethyl-3-phenyl-5-acetoxybenzofuran, prepared from 2-methyl-3-phenyl-5-acetoxybenzofuran (0.005 mole), was added a solution of potassium hydroxide (0.28 g, 0.005 mole) and thiophenol (0.51 ml, 0.005 mole) in absolute alcohol (7 ml). The reaction mixture was allowed to stand at room temperature for 3 h and then poured into water. The precipitate was recrystallized from alcohol. The yield was 0.9 g (48%), mp 92-93°C. Found, %: C 73.46; H 4.81; S 8.41. $C_{23}H_{18}O_3S$. Calculated, %: C 73.86; H 4.85; S 8.57.

2-Phenylthiomethyl-3-phenyl-5-hydroxybenzofuran (VII). A solution of VI (0.6 g, 0.0016 mole) in ethanol (60 ml) was refluxed for 1 h with potassium hydroxide (0.09 g, 0.0016 mole). The bulk of the alcohol was stripped off. The residue was poured into water and acidified with hydrochloric acid. The precipitate was separated. The yield was 0.52 g (97%), mp 112-113°C (from carbon tetrachloride). Found, %: S 9.09. $C_{21}H_{16}SO_2$. Calculated, %: S 9.64.

Methyl [(3-Phenyl-5-chlorobenzofuran-2-ylmethyl)thio]acetate (VIII). A solution of 2-bromomethyl-3-phenyl-5-chlorobenzofuran (9.63 g, 0.03 mole) in ether (170 ml) was stirred with the sodium salt of methyl thioglycollate (3.84 g, 0.03 mole) at 22°C for 6 h. The precipitate was filtered off, ether was stripped off, and the residue was distilled. The yield was 7.4 g (71.5%), bp 238-240°C (1 mm). Found, %: C 62.40; H 4.42; Cl 10.13; S 9.72. $C_{18}H_{15}ClSO_3$. Calculated, %: C 62.33; H 4.36; Cl 10.22; S 9.24.

2-Thiocyanatomethyl-3-phenyl-5-chlorobenzofuran (IX). A refluxing solution of 2-bromomethyl-3-phenyl-5-chlorobenzofuran (1.6 g, 0.005 mole) in glacial acetic acid (10 ml) was treated with potassium thiocyanate (0.8 g, 0.0085 mole) and kept overnight at 22°C. The reaction mixture was diluted with water and the precipitate was recrystallized from methanol. The yield was 0.3 g (20%), mp 69-71°C. Found, %: C 64.12; H 3.28; Cl 11.89; S 10.65. $C_{16}H_{10}ClNOS$. Calculated, %: C 64.10; H 3.36; Cl 11.83; S 10.70.

2-Thiocyanatomethyl-3-phenyl-5-bromobenzofuran (X) was prepared in the same way as compound IX. The yield was 61%, mp 88.5-89°C (from methanol). Found, %: C 56.13; H 2.90; Br 23.50; S 9.19. $C_{16}H_{10}BrNOS$. Calculated, %: C 55.82; H 2.93; Br 23.21; S 9.31.

2-Diethylaminomethyl-3-phenyl-5-acetoxy-6-bromobenzofuran Hydrochloride (XI). To a solution of I (0.01 mole) in benzene (30 ml) was added diethylamine (0.02 mole). The reaction mixture was left at room temperature for 12 h. The precipitated diethylamine hydrobromide was filtered off and the benzene was stripped off. The residue was dissolved in ether and treated with ethereal hydrogen chloride. The yield was 57.5%, mp 214-215°C (from methanol–acetone–ether). Found, %: C 55.32; H 5.14; Br 17.42; Cl 7.71. $C_{21}H_{22}BrNO_3 \cdot HCl$. Calculated, %: C 55.71; H 5.12; Br 17.65; Cl 7.84.

2-Methoxymethyl-3-phenyl-5-chlorobenzofuran (XII). A solution of 2-bromomethyl-3-phenyl-5-chlorobenzofuran (1 g, 0.0031 mole) in methanol (5 ml) was refluxed for 3 h. After cooling the precipitate was separated. The yield was 0.7 g (84%), mp 96-97°C (from methanol). PMR spectrum (DMSO + d-acetone), δ, ppm:

3.35s (OCH_3), 4.55s (CH_2), 7.35d (6H), 7.45-7.68 (4H, 7H, C_6H_5). Found, %: C 70.37; H 4.72; Cl 13.07. $C_{16}H_{13}ClO_2$. Calculated, %: C 70.46; H 4.80; Cl 13.00.

The same method as for compound XII was used to prepare: a) 2-methoxymethyl-3-(p-chlorophenyl)-5-chlorobenzofuran (XIII), yield 65.2%, mp 123-124°C (from methanol). Found, %: C 62.63; H 4.03; Cl 22.79. $C_{16}H_{12}Cl_2O_2$. Calculated, %: C 62.60; H 3.93; Cl 23.09. b) 2-methoxymethyl-3-(p-methoxymethyl)-5-chlorobenzofuran (XIV), yield 96%, mp 81-83°C (from isopropyl alcohol). Found, %: C 67.30; H 4.90; Cl 12.08. $C_{17}H_{15}ClO_3$. Calculated, %: C 67.61; H 5.00; Cl 11.74.

2-Hydroxymethyl-3-phenyl-5-chlorobenzofuran (XV). 2-Bromomethyl-3-phenyl-5-chlorobenzofuran (1 g, 0.0031 mole) was refluxed for 3 h in a mixture of dioxane (7 ml) and water (5 ml). The reaction mixture was diluted with water and the precipitate was recrystallized from aqueous acetic acid. The yield was 0.7 g (87%), mp 140-141°C. PMR spectrum ($CDCl_3$), δ, ppm: 4.73s (CH_2), 7.19-7.44 (C_6H_5), 10.14s (OH). Found, %: C 69.24; H 4.38; Cl 13.76. $C_{15}H_{11}ClO_2$. Calculated, %: C 69.64; H 4.28; Cl 13.71.

Like compound XV the following were prepared: a) 2-hydroxymethyl-3-phenyl-5-bromobenzofuran (XVI), yield 97%, mp 132-134°C (from aqueous acetic acid). Found, %: Br 26.59. $C_{15}H_{11}BrO_2$. Calculated, %: Br 26.36 b) 2-hydroxymethyl-3-phenyl-5-methylbenzofuran (XVII), yield 42%, mp 100-102°C. Found, %: C 80.87; H 5.64. $C_{16}H_{14}O_2$. Calculated, %: C 80.65; H 5.92; c) 2-hydroxymethyl-3-(p-chlorophenyl)-5-chlorobenzofuran (XVIII), yield 69.5%, mp 124-125°C (from methanol–DMF). Found, %: C 61.60; H 3.43; Cl 24.30. $C_{15}H_{10}Cl_2O_2$. Calculated, %: C 61.46; H 3.44; Cl 24.19; d) 2-hydroxymethyl-3-(p-methoxyphenyl)-5-chlorobenzofuran (XIX), yield 79.8%, mp 121-123°C (from acetic acid). Found, %: C 66.93; H 4.34; Cl 12.51. $C_{16}H_{13}ClO_3$. Calculated, %: C 66.56; H 4.53; Cl 12.28.

2-Hydroxymethyl-3-phenyl-5-chlorobenzofuran Phenylcarbamate (XX). Compound XV (2.59 g, 0.01 mole) and phenyl isocyanate (1.08 ml, 0.01 mole) in benzene (30 ml) were kept at 22°C for 2 days. The solvent was stripped off and the residue was recrystallized from methanol. The yield was 3.1 g (82.3%), mp 161-162°C. Found, %: C 69.94; H 4.00; Cl 9.25. $C_{22}H_{16}ClNO_3$. Calculated, %: C 69.94; H 4.27; Cl 9.38.

2-Hydroxymethyl-3-phenyl-5-bromobenzofuran Phenylcarbamate (XXI) was prepared in the same way as compound XX. The yield was 69%, mp 233-235°C (from methanol). Found, %: C 62.63; H 3.75; Br 18.52. $C_{22}H_{16}BrNO_3$. Calculated, %: C 62.57; H 3.82; Br 18.92.

2-Chloromethyl-3-phenyl-5-chlorobenzofuran (XXII). Compound XV (3 g, 0.0116 mole) and chloroacetyl chloride (4 ml, 0.053 mole) in dioxane (6 ml) were refluxed for 6 h in the presence of a catalytic amount of p-toluenesulfonic acid. The solvent was stripped off. The residue was chromatographed on a silica gel column; the reaction products were eluted with carbon tetrachloride. The eluate was evaporated. The yield of XXII was 2.55 g (79.4%), mp 121-122°C (from ethyl acetate). Found, %: C 65.10; H 3.70; Cl 25.12. $C_{15}H_{10}Cl_2O$. Calculated, %: C 65.01; H 3.64; Cl 25.58.

2-Formyl-3-phenyl-5-chlorobenzofuran (XXIII). To a mixture of chromic anhydride (0.78 g) and pyridine (8 ml) was added compound XV (1 g, 0.004 mole). The mixture was shaken and kept at 22°C overnight. Next day the reaction mixture was diluted with 19% hydrochloric acid and extracted with chloroform. The chloroform was stripped off. The residue was chromatographed on a silica gel column; the reaction products were eluted with chloroform. The yield was 0.35 g (35.4%), mp 133-135°C (from aqueous acetic acid). IR spectrum: $\nu_{C=O}$ 1680 cm^{-1}. Found, %: C 70.41; H 3.62; Cl 13.79. $C_{15}H_9ClO_2$. Calculated, %: C 70.19; H 3.53; Cl 13.81.

The same method as for compound XXIII was used to prepare: a) 2-formyl-3-phenyl-5-bromobenzofuran (XXIV), yield 56.3%, mp 135-137°C (from aqueous acetic acid). Found, %: C 59.82; H 3.01; Br 26.80. $C_{15}H_9BrO_2$. Calculated, %: C 59.82; H 3.01; Br 26.54; b) 2-formyl-3-(p-chlorophenyl)-5-chlorobenzofuran (XXV), yield 44.6%, mp 201-203°C (from isopropyl alcohol–DMF). Found, %: C 61.66; H 2.83; Cl 24.56. $C_{15}H_8Cl_2O_2$. Calculated, %: C 61.91; H 2.77; Cl 24.36.

2-Formyl-3-phenyl-5-chlorobenzofuran Thiosemicarbazone (XXVI). A suspension of compound XXIII (1 g, 0.004 mole) and thiosemicarbazide hydrochloride (0.51 g, 0.004 mole) in ethanol (10 ml) and dioxane (10 ml) was heated until boiling and then left overnight. The precipitate was separated and recrystallized from dioxane–methanol. The yield was 1 g (78%), mp 300°C. Found, %: C 58.69; H 3.65, N 2.75, S 9.60. $C_{16}H_{12}ClN_3OS$. Calculated, %: C 58.27; H 3.67; N 12.74; S 9.72.

2-Formyl-3-phenyl-5-bromobenzofuran Thiosemicarbazone (XXVII) was prepared in the same way as compound XXVI. The yield was 18.7%, mp 267-269°C. Found, %: C 51.09; H 3.37; N 10.93. $C_{15}H_{12}BrN_3OS$. Calculated, %: C 51.35; H 3.23; N 11.23.

2-Formyl-3-phenyl-5-chlorobenzofuran Isonicotinoylhydrazone (XXIII). A solution of compound XXIII (4.5 g, 0.0175 mole) and isonicotinic acid hydrazide (2.4 g, 0.0175 mole) in a mixture of ethanol (20 ml) and dioxane (10 ml) was refluxed for 3.5 h. After cooling the precipitate was filtered off. The yield was 3.7 g (54%), mp 150°C (from methanol). Found, %: C 64.21; H 4.09; Cl 9.00; N 10.67. $C_{21}H_{14}ClN_3O_2$. Calculated, %: C 64.04; H 4.09; Cl 9.00; N 10.67.

2-Formyl-3-phenyl-5-bromobenzofuran Nicotinoylhydrazone (XXIX) was prepared in the same way as compound XXVIII. The yield was 69%, mp 233-235°C. Found, %: C 57.93; H 3.64; Br 18.34; N 9.51. $C_{21}H_{14} \cdot BrN_3O_2 \cdot H_2O$. Calculated, %: C 57.55; H 3.68; Br 18.23; N 9.59.

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SYNTHESIS AND PHARMACOLOGICAL STUDY OF CONDENSED HETEROCYCLIC DERIVATIVES OF QUINUCLIDINE

V. A. Bondarenko, N. A. Komarova, N. I. Andreeva, T. Ya. Filipenko, K. F. Turchin, E. E. Mikhlina, M. D. Mashkovskii, Yu. N. Sheinker, and L. N. Yakhontov

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Earlier work has shown that 2-methylene-3-oxoquinuclidine (I), which is a bicyclic α, β-unsaturated ketone, readily adds nucleophiles – malonate esters, water, alcohols, amines, and phenols [1-6] – forming 2-substituted 3-oxoquinuclidines. We have attempted to move from the unsaturated ketone (I) to condensed heterocyclic derivatives of quinuclidine and to study their biological properties by examining the reactions of I with some bifunctional nucleophiles, notably o-phenylenediamine and its C-methyl derivatives.

o-Phenylenediamines react with I at both functional groups to form 11,11a-dihydro-10H-quinuclidino[2,3-c]-1,5-benzodiazepine (II) and its 7,8-dimethyl derivative (III). We carried out the reaction at room temperature in protic (alcohols) and aprotic (dioxane) solvents. The yield of compound II was substantially lower in the latter.

We examined the properties of the synthetic polycyclic derivatives of quinuclidine. Compound II is unstable toward acidic reagents; ethereal or alcoholic hydrogen chloride cleaves II to form 2-[(2-aminophenyl)·amino]methyl-3-oxoquinuclidine dihydrochloride (IV), which regenerates the tetracyclic compound II on treatment with aqueous sodium bicarbonate. Compound II is stable toward weaker acids forming a tartrate with tartaric acid, and is also stable when heated with water. (see scheme on following page).

Sodium borohydride reduction of II and III generates the 4a,5,11,11a-tetrahydro-10H-quinuclidino[2,3-c]-1,5-benzodiazepines (V) and (VI). The benzodiazepine compound (V) forms the 10-acetyl (VII) or 5,10-diacetyl (VIII) derivative, depending on the reaction conditions. Conversely heating with two equivalents of benzoyl

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