SYNTHESIS AND BIOLOGICAL ACTIVITY OF AMINOMETHYL AND OTHER DERIVATIVES OF 5-HYDROXYBENZOFURAN

A. N. Grinev, S. A. Zotova,
T. M. Gololobova, A. A. Stolyarchuk,
B. G. Storozhuk, T. V. Taratuta,
and V. A. Stolyarchuk

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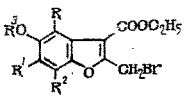
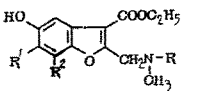
The intensive search for drugs among derivatives of benzofuran has led to the introduction of cordaron, amplivix, fenkaberan, and other cardivascular drugs [1-3], and this stimulated our interest in the synthesis and study of the biological activity of aminomethyl and other derivatives of 5-hydroxybenzofuran. For this purpose, we have studied the bromination with N-bromosuccinimide of the methyl group in 2-methyl-3-ethoxycarbonyl-4-chloro-5-acetoxybenzofuran (I), 2-methyl-3-ethoxycarbonyl-5-hydroxy-6,7-dichlorobenzofuran (II), and 2-methyl-3-ethoxycarbonyl-5-methoxy-6-bromobenzofuran (III), all obtained in the present investigation, and we have synthesized a series of 2-bromoethyl derivatives (IV-VI).



IV: $R = Cl$, $R_1 = R_2 = H$, $R_3 = CH_3CO$; V: $R = H$, $R_1 = R_2 = Cl$, $R_3 = CH_3CO$;
VI: $R = R_2 = H$, $R_1 = Br$, $R_3 = CH_3$; VII: $R = R_1 = R_2 = H$, $R_3 = CH_3CO$;
VIII: $R = R_2 = H$, $R_1 = Br$, $R_3 = CH_3CO$.

In addition to (IV-VI), also used for the preparation of aminomethyl derivatives were the previously prepared 2-bromomethyl compounds, 2-bromomethyl-3-ethoxycarbonyl-5-acetoxybenzofuran (VII) and 2-bromomethyl-3-ethoxycarbonyl-5-acetoxy-6-bromobenzofuran (VIII) [4]. When 2-bromomethyl-3-ethoxycarbonyl-3-ethoxycarbonyl-5-acetoxybenzofuran was brominated with bromine in carbon tetrachloride, 2-dibromomethyl-3-ethoxycarbonyl-5-acetoxybenzofuran (IX) was obtained, which on successive treatment with morpholine and hydrochloric acid was converted into 2-formyl-3-ethoxycarbonyl-5-hydroxybenzofuran (X).

The aminomethyl derivatives were obtained by reacting the bromomethyl compounds with amines. Reaction of (VI) with aniline gave N-phenyl-NN-bis-(2-methylene-3-ethoxycarbonyl-5-methoxy-6-bromobenzofuranyl)amine (XI). Condensation of the 2-bromomethyl compounds (V), (VII), and (VIII) with secondary amines (dimethylamine or aniline) followed by hydrolysis of the acetoxy-group gave 2-dimethylaminomethyl-3-ethoxycarbonyl-5-hydroxybenzofuran (XII), 2-N-methyl-N-phenylaminomethyl-3-ethoxycarbonyl-5-hydroxybenzofuran (XIII), 6-bromo- (XIV), and 6,7-dichloro-2-N-methyl-N-phenylaminomethyl-3-ethoxycarbonyl-5-hydroxybenzofuran (XV).



XII: $R = CH_3$, $R_1 = R_2 = H$; XIII: $R = C_6H_5$, $R_1 = R_2 = H$;
XIV: $R = C_6H_5$, $R_1 = Br$, $R_2 = H$; XV: $R = C_6H_5$, $R_1 = R_2 = Cl$.

Aminomethylation of (XII-XV) with bisdimethylaminomethane afforded the 4-dimethylaminomethyl derivatives (XVI-XX).

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. N. I. Pirogov Vinnitsa Institute of Medicine. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 16, No.12, pp. 1470-1474, December, 1982. Original article submitted January 22, 1982.

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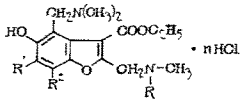

XVI: R = C_6H_5, $R_1 = R_2 = H$, $n = 2$; XVII: R = C_6H_5, R_1 = Br, $R_2 = H$, $n = 0$;
XVIII: R = C_6H_5, $R_1 = R_2 = Cl$, $n = 0$; XIX: R = C_6H_5, $R_1 = R_2 = Cl$, $n = 2$;
XX: R = CH_3, $R_1 = R_2 = H$, $n = 2$.

The high reactivity of the bromine atom of the 2-bromomethyl-3-ethoxycarbonylbenzofurans enables it to be replaced by other functional groups. Thus, condensation of (VII) and (IV) with diethyl acetamidomalonate in the presence of sodium ethoxide gave 2-($\beta\beta$-diethoxycarbonyl-β-acetamido)ethyl-3-ethoxycarbonyl-5-hydroxybenzofuran (XXI) and 2-($\beta\beta$-diethoxycarbonyl-β-acetamido)ethyl-3-ethoxycarbonyl-4-chloro-5-acetoxybenzofuran (XXII). Heating (VI) with water gave 2-hydroxymethyl-3-ethoxycarbonyl-5-methoxy-6-bromobenzofuran (XXIII). Condensation of the 2-bromomethyl compound (VI) with potassium thiophenoxide gave 2-phenyl-thiomethyl-3-ethoxycarbonyl-5-methoxy-6-bromobenzofuran, basic hydrolysis of which yielded the corresponding acid (XXIV).

Compounds (X, XVI, XVII, XIX, XX, and XXIII) were examined for a variety of chemotherapeutic and pharmacological effects. High pharmacological activity was only shown by (XVI), (XIX), and (XX).

EXPERIMENTAL PHARMACOLOGICAL SECTION

Toxicities were determined using 140 mice, by the intraperitoneal route, and the LD_{50} values were calculated by the method of G. N. Pershin.

Antiarrhythmic activity was examined in rats, using an aconitine model for disturbances of rhythm [5], anticonvulsive activity in the maximum electroshock method in mice [6], anticataleptic activity in rats in which the akineto-rigid syndrome had been induced by administration of haloperidol (1 mg/kg) or trifluoperazine (1.5 mg/kg). Effects on the smooth musculature were studied on isolated segments of rabbit small intestine by the method of Magnus, and effects on the cerebral blood flow rate were studied in narcotized cats by measuring the amount of blood leaving the jugular vein in unit time [7].

The LD_{50} in mice of (XVI) is 50 kg/kg, of (XIX) 425 mg/kg, and of (XX), 151 mg/kg. These compounds had a depressive effect, causing tremor and convulsions.

Administration of aconitine to rats in a dose of 0.03 mg/kg intravenously over a period of 4-8 min caused prolonged (1.5 h or more) disturbance of the cardiac rhythm. In doses of 10% of the LD_{50}, (XIX) and (XX) showed antiarrhythmic effects, briefly (for 2-4 min) restoring the disturbed rhythm in 7 out of 10 rats and 6 out of 10 rats respectively.

Compound (XIX) showed antiarrhythmic activity in a dose of 50% of the LD_{50}.

An anticataleptic activity was observed in the test compounds.

A brief stimulatory effect on the cerebral blood flow rate (for 3-7 min) was induced by (XIX) and (XX). Intravenous administration of these compounds in doses of 10% of the LD_{50} increased the cerebral blood flow, (XX) by 5-13%, and (XIX) by 5-24%.

All the compounds had a hypotonic effect on isolated segments of rabbit small intestine, (XVI) and (XX), like papaverine, in concentrations of $1 \cdot 10^{-6}$ g/ml, and (XIX) in a concentration of $5 \cdot 10^{-6}$ g/ml.

Thus, (XVI), (XIX), and (XX) possess valuable pharmacological properties in that they have antiarrhythmic and antispasmodic effects, relax the smooth musculature, and increase the cerebral blood flow. The test compounds do not, however, show any advantages over the known drugs having similar effects.

EXPERIMENTAL CHEMICAL SECTION

2-Methyl-3-ethoxycarbonyl-4-chloro-5-acetoxybenzofuran (I). A solution of 15 g of 2-methyl-3-ethoxycarbonyl-4-chloro-5-hydroxybenzofuran [8] in 60 ml of acetic anhydride and 0.5 ml of triethylamine was boiled for 3 h, poured into water, and the solid filtered off. Yield, 15.1 g (86.3%), mp 65-67°C (from methanol). Found, %: C 56.80; H 4.45; Cl 11.58. $C_{14}H_{13}ClO_5$. Calculated, %: C 56.57; H 4.42; Cl 11.95.

2-Methyl-3-ethoxycarbonyl-5-acetoxy-6,7-dichlorobenzofuran (II) was obtained similarly. Yield, 88.1%, mp 158-159°C (from methanol). Found, %: C 50.55; H 3.60. $C_{14}H_{12}Cl_2O_5$. Calculated, %: C 50.78; H 3.65.

2-Methyl-3-ethoxycarbonyl-5-methoxy-6-bromobenzofuran (III). To a solution of 50 g (0.162 mole) of 2-methyl-3-ethoxycarbonyl-5-hydroxy-6-bromobenzofuran [9] in 400 ml of acetone and 100 ml of 6.5% caustic alkali was added dropwise with stirring at room temperature 15.9 ml (0.162 mole) of dimethyl sulfate. On the following day, the reaction mixture was diluted with water, and the solid separated and recrystallized from ethanol. Yield, 39.3 g (77.6%), mp 129-130°C. Found, %: C 49.75; H 4.20. $C_{13}H_{13}BrO_4$. Calculated, %: C 49.85; H 4.18.

2-Bromomethyl-3-ethoxycarbonyl-4-chloro-5-acetoxybenzofuran (IV). A solution of 15.1 g (0.051 mole) of (I) in 150 ml of carbon tetrachloride was boiled for 5 h with 9.1 g (0.051 mole) of N-bromosuccinimide with irradiation and in the presence of benzoyl peroxide. The precipitate of succinimide was filtered off, and the carbon tetrachloride distilled off in vacuo. The residue was recrystallized from ethanol. Yield, 14 g (73%), mp 97-98°C. Found, %: C 44.43; H 3.11; Br 21.12; Cl 9.49. $C_{14}H_{12}BrClO_5$. Calculated, %: C 44.77; H 3.22; Br 21.28; Cl 9.44.

2-Bromomethyl-3-ethoxycarbonyl-5-acetoxy-6,7-dichlorobenzofuran (V) was obtained similarly to (IV). Yield 84.5%, mp 163-165°C (from methanol). Found, %: C 40.7; H 2.65. $C_{14}H_{11}BrCl_2O_5$. Calculated, %: C 41.00; H 2.70.

2-Bromomethyl-3-ethoxycarbonyl-5-methoxy-6-bromobenzofuran (VI) was obtained by brominating (III) with bromine in boiling carbon tetrachloride. Yield 84%, mp 133-134°C (from ethanol). Found, %: C 40.46; H 3.08; Br 41.24. $C_{13}H_{12}Br_2O_4$. Calculated, %: C 39.82; H 3.08; Br 40.77.

2-Dibromomethyl-3-ethoxycarbonyl-5-acetoxybenzofuran (IX). To a solution of 34 g (0.1 mole) of 2-bromomethyl-3-ethoxycarbonyl-5-acetoxybenzofuran in 100 ml of carbon tetrachloride was added dropwise at the boil under UV irradiation a solution of 5.2 ml (0.1 mole) of bromine in 10 ml of carbon tetrachloride over 4 h. The solvent was removed, and the residue recrystallized from alcohol to give a yield of 72.4%, mp 127-128°C. Found, %: C 40.53; H 3.00; Br 37.73. $C_{14}H_{12}Br_2O_5$. Calculated, %: C 40.03; H 2.88; Br 38.04.

2-Formyl-3-ethoxycarbonyl-5-hydroxybenzofuran (X). To a solution of 17.4 g (0.041 mole) of (VII) in 45 ml of benzene was added 13 ml (0.165 mole) of morpholine, and the mixture was kept at room temperature overnight. The solvent was removed, ice added to the residue, and acidified with hydrochloric acid. On the following day, the solid was isolated. Yield, 4.1 g (42.2%), mp 172-174°C (from benzene). Found, %: C 61.59; H 4.63. $C_{12}H_{10}O_3$. Calculated, %: C 61.54; H 4.30.

N-Phenyl-NN-bis-(2-methylene-3-ethoxycarbonyl-5-methoxy-6-bromobenzofuranyl)amine (XI). To a solution of 3.92 g (0.01 mole) of (VI) in 40 ml of benzene was added 1.8 ml (0.02 mole) of aniline. The reaction mixture was kept for one week at room temperature, the precipitated aniline hydrobromine filtered off, and the benzene evaporated. Recrystallization from acetone gave 1 g (14%), mp 173-175°C. $M^{+\cdot}$ 7.13. Found, %: C 54.24; H 4.23. $C_{32}H_{29}Br_2NO_8$. Calculated, %: C 53.72; H 4.08.

2-Dimethylaminomethyl-3-ethoxycarbonyl-5-hydroxybenzofuran hydrochloride (XII) was obtained from 6.82 g (0.02 mole) of (VII) and 3.6 g (0.08 mole) of dimethylamine in benzene at room temperature. Yield, 4.7 g (78.4%), mp 200-201°C (from acetone–methanol). Found, %: Cl 11.43. $C_{14}H_{18}ClNO_4$. Calculated, %: Cl 11.83.

2-N-Methyl-N-phenylaminomethyl-3-ethoxycarbonyl-5-hydroxybenzofuran (XIII). To a solution of 6.82 g (0.02 mole) of 2-bromomethyl-3-ethoxycarbonyl-5-hydroxybenzofuran in 70 ml of benzene was added 4.3 ml (0.08 mole) of N-methylaniline. The reaction mixture was kept for 2 h at room temperature, then heated at the boil for 18 h. The precipitated N-methylaniline hydrobromide was filtered off, and the benzene distilled off. The residue was dissolved in 35 ml of isopropanol, 4 ml of concentrated hydrochloric acid added, and the mixture boiled for 17 h. The solvent was distilled off, the residue neutralized with aqueous ammonia, and the solid filtered off. Yield 4.8 g (74%), mp 143-145°C (from benzene). Found, %: C 70.11; H 6.00; N 4.14. $C_{19}H_{19}NO_4$. Calculated, %: C 70.14; H 5.89; N 4.30.

2-N-Methyl-N-phenylaminomethyl-3-ethoxycarbonyl-5-hydroxy-6-bromobenzofuran (XIV) was obtained as for (XIII). Yield, 74.1%, mp 151-152°C (from alcohol). Found, %: C 56.16; H 4.61; Br 19.98. $C_{19}H_{18}BrNO_4$. Calculated, %: C 56.45; H 4.49; Br 19.97.

2-N-Methyl-N-phenylaminomethyl-3-ethoxycarbonyl-5-hydroxy-6,7-dichlorobenzofuran (XV) was obtained as for (XIII). Yield, 50.7%, mp 165-167°C (from aqueous methanol). Found, %: C 58.04; H 4.50. $C_{19}H_{17}Cl_2NO_4$. Calculated, %: C 57.88; H 4.35.

2-N-Methyl-N-phenylaminomethyl-3-ethoxycarbonyl-4-dimethylaminomethyl-5-hydroxybenzofuran (XVI). A mixture of 4.6 g (0.0141 mole) of (XII) and 5 ml of bisdimethylaminomethane in 45 ml of dioxane was boiled for 3 h. The solvent and excess amine were removed in vacuo and the residue dissolved in ether and neutralized with ethereal hydrogen chloride to give 5.1 g (79%) of (XVI), mp 181-183°C (decomp., from acetone–ethanol). Found, %: C 58.21; H 6.50; Cl 15.01. $C_{22}H_{28}Cl_2N_2O_4$. Calculated, %: C 58.02; H 6.20; Cl 15.57.

2-N-Methyl-N-phenylaminomethyl-3-ethoxycarbonyl-4-dimethylaminomethyl-5-hydroxy-6-bromobenzofuran (XVII) was obtained as for (XVI). Yield, 29.2%, mp 138-139°C (from methanol). Found, %: C 57.00; H 5.50; N 6.21. $C_{22}H_{25}BrN_2O_3$. Calculated, %: C 57.27; H 5.46; N 6.07.

2-N-Methyl-N-phenylaminomethyl-3-ethoxycarbonyl-4-dimethylaminomethyl-5-hydroxy-6,7-dichlorobenzofuran (XVIII) was obtained in the same way as (XVI). Yield 72%, mp 126-127°C (from ethanol). Found, %: C 58.60; H 5.32. $C_{22}H_{24}Cl_2N_2O_4$. Calculated, %: C 58.54; H 5.36.

The hydrochloride of XVIII (XIX) was obtained in the same way as (XVI). Yield 91%, mp 185°C (decomp., from acetone–methanol–ether). Found, %: C 50.56; H 5.19; Cl 27.16. $C_{22}H_{26}Cl_4N_2O_4$. Calculated, %: C 50.40; H 5.00; Cl 27.05.

2,4-Bis(dimethylaminomethyl)-3-ethoxycarbonyl-5-hydroxybenzofuran dihydrochloride monohydrate (XX) was obtained in the same way as (XVI). Yield 66%, mp 223-224°C (decomp., from acetone–methanol–ether). Found, %: C 49.55; H 6.84; N 6.73. $C_{17}H_{28}Cl_2N_2O_5$. Calculated, %: C 49.50; H 6.88; N 6.83.

2-(ββ-Bisethoxycarbonyl-β-acetamido)ethyl-3-ethoxycarbonyl-5-hydroxybenzofuran (XXI). To a solution of sodium ethoxide, obtained from 0.23 g (0.01 mole) of sodium, in 30 ml of absolute alcohol was added 2.2 g (0.01 mole) of diethyl acetamidomalonate, followed after stirring for 10 min by a solution of 3.41 g (0.01 mole) of 2-bromomethyl-3-ethoxycarbonyl-5-acetoxybenzofuran in 50 ml of absolute alcohol. The reaction mixture was boiled for 2 h, the alcohol distilled off, and the residue chromatographed on a column with KSK chloroform. Yield, 1.3 g (30%), $M^{+\cdot}$ 435.

2-(ββ-Bisethoxycarbonyl-β-acetamido)ethyl-3-ethoxycarbonyl-4-chloro-5-acetoxybenzofuran (XXII) was obtained in the same way as (XXI), but at room temperature. Yield, 2.9 g (78.3%), $M^{+\cdot}$ 511.

2-Hydroxymethyl-3-ethoxycarbonyl-5-methoxy-6-bromobenzofuran (XXIII). A solution of 5.88 g (0.015 mole) of (VI) in a mixture of 20 ml of dioxane and 10 ml of water was boiled for 24 h, cooled, poured into water, and the solid separated and chromatographed on a column with KSK chloroform, the second fraction being collected. Yield, 1.7 g (34.4%), mp 130-131°C (from aqueous alcohol). Found, %: C 46.92; H 3.90; H 3.90; Br 24.33. $C_{13}H_{13}BrO_5$. Calculated, %: C 47.44; H 3.98; Br 24.28

2-Phenylthiomethyl-3-carboxy-5-methoxy-6-bromobenzofuran (XXIV). To a solution of 1.12 g (0.02 mole) of potassium hydroxide in 50 ml of absolute alcohol was added with stirring 2.04 ml (0.02 mole) of thiophenol, followed by a solution of 7.84 g (0.02 mole) of (VI) in 30 ml of absolute alcohol. After 3 h, a solution of 20 g (0.5 mole) of sodium hydroxide in 250 ml of alcohol was added, and the mixture boiled for 1 h. The alcohol was then distilled off, the residue dissolved in water, and neutralized with hydrochloric acid to give 5.2 g (66.5%) of (XXVI), mp 227-228°C (from ethyl acetate). Found, %: C 51.61; H 3.65. $C_{17}H_{13}BrO_4S$. Calculated, %: C 51.92; H 3.33.

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