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

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The intensive search for drugs among derivatives of benzofuran has led to the introduction of cordaron, amplivix, fenkaberan, and other cardiovascular 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, R1 = R2 = H, R3 = CH3CO; V: R = H, R1 = R2 = Cl, R3 = CH3CO;
VI: R = R1 = H, R2 = Br, R3 = CH3; VII: R1 = R2 = H, R3 = CH3;
VIII: R = R1 = R2 = H, R3 = CH3CO.

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-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 = CH3, R1 = R2 = H; XIII: R = C6H5, R1 = R2 = H;
XIV: R = C6H5, R1 = Br, R2 = H; XV: R = C6H5, R1 = R2 = Cl.

Aminomethylation of (XII-XV) with bisdimethylaminomethane afforded the 4-dimethylaminomethyl derivatives (XVI-XX).
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-(β-diethoxycarbonyl-β-acetamido)ethyl-3-ethoxycarbonyl-5-hydroxybenzofuran (XXI) and 2-(β-diethoxycarbonyl-β-acetamido)ethyl-3-ethoxycarbonyl-4-chloro-5-acetoxybenzofuran (XXII). Heating (VI) with water gave 2-hydroxymethyl-3-ethoxycarbonyl-5-methoxy-6-bromo-benzofuran (XXIV), 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 LD50 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], anticitaleptic 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 LD50 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 LD50, (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 LD50.

An anticitaleptic 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 LD50 increased the cerebral blood flow, (XX) by 5-13%, and (XX) 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 1·10⁻⁶ g/ml, and (XIX) in a concentration of 5·10⁻⁶ 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 4.46; Cl 11.58. C14H13ClO5. Calculated, %: C 56.57; H 4.42; Cl 11.95.