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SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF AMINOMETHYL DERIVATIVES OF 5- AND 6-HYDROXYBENZOFURAN

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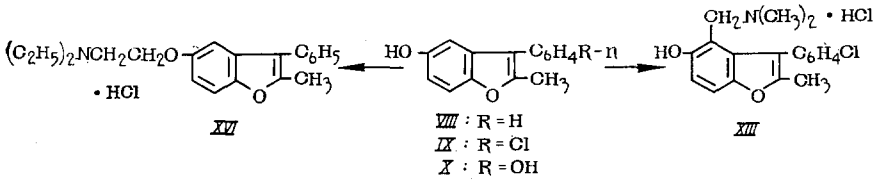
In view of the interest in benzofuran derivatives as cardiovascular drugs [1, 2] we have synthesized several derivatives of 2-methyl-3-aryl-5- and -6-hydroxybenzofuran and examined some of their pharmacological properties. We used the reaction of substituted α-aryloxypropiophenones (I-III) with polyphosphoric acid by the literature method [3] to prepare several hitherto unknown benzofuran derivatives — 2-methyl-3-(p-chlorophenyl)-5-methoxy- (IV), 2-methyl-3-(p-methoxyphenyl)-5-methoxy- (V), and 2-methyl-3-(p-chlorophenyl)-6-methoxybenzofuran (VI), together with 2-methyl-3-phenyl-5-methoxybenzofuran (VII), which we have described earlier [4].

We synthesized the 5- and 6-hydroxybenzofuran derivatives by demethylating compounds IV-VII with pyridine hydrochloride at 200°C. This gave 2-methyl-3-phenyl-5-hydroxy- (VIII), 2-methyl-3-(p-chlorophenyl)-5-hydroxy- (IX), 2-methyl-3-(p-chlorophenyl)-5-hydroxy- (X), 2-methyl-3-(p-chlorophenyl)-6-hydroxybenzofuran (XI), and 2-methyl-3-phenylbenzofuran (reported earlier [5]).

We examined aminomethylation of the 5- and 6-hydroxybenzofuran derivatives for the synthesis of analogs of the preparation phenykoberan [2]. We found that the 5-hydroxybenzofuran derivatives were aminomethylated at position 4 and the 6-hydroxybenzofurans at position 7; this was supported by the presence in the PMR spectra of the aminomethylbenzofurans of two doublets with J = 9.0 Hz, due to the coupling of the two o-protons.* In this way we synthesized 2-methyl-3-(p-chlorophenyl)-4-dimethylaminomethyl-5-hydroxy- (XIII), 2-methyl-3-phenyl-6-hydroxy-7-dimethylaminomethyl- (XIV), and 2-methyl-3-(p-chlorophenyl)-6-hydroxy-7-dimethylaminomethylbenzofuran (XV).

We also synthesized by the usual method the aminoalkyl ethers of the hydroxybenzofurans, 2-methyl-3-phenyl-5-diethylaminoethoxy- (XVI), 2-methyl-3-phenyl-6-diethylaminoethoxy- (XVII) and 2-methyl-3-(p-chlorophenyl)-6-diethylaminoethoxybenzofuran (XVIII), as the hydrochlorides.



*We have assigned the PMR spectra of 5- and 6-hydroxybenzofuran derivatives earlier [6].

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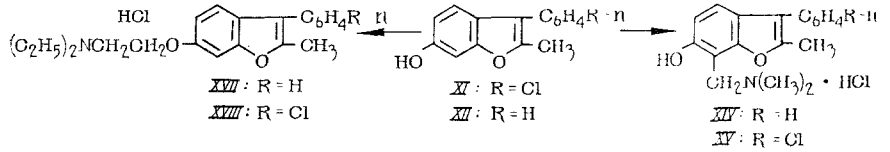

EXPERIMENTAL PHARMACOLOGY

We evaluated the toxicity in white mice of both sexes weighing 18-28 g. Water-soluble compounds were administered intraperitoneally, insoluble compounds as suspensions in 2% starch slurry. Five animals received each dose level. We calculated LD_{50} following G. N. Pershin [7].

We assayed the antiarrhythmic activity in white rats using aconitine-induced disruption of the cardiac rhythm [8]. Aconitine was administered intravenously in a dose of 30 μg/kg. The test compounds in doses of 10% LD_{50} were administered intravenously (water-soluble compounds) immediately after the appearance of arrhythmia and by gastric gavage (water-insoluble compounds) 30-40 min before the administration of aconitine. This revealed the arrhythmia-reducing and preventing activity. The novocainamide used for comparison was administered intravenously in a dose of 50 mg/kg to reduce the arrhythmia.

We assayed the local anesthetic activity in the terminal mode in rabbits (each preparation on eight eyes) by Renier's method and in the infiltration mode in guinea pigs by Bülbring and Wajda's method (each preparation in 12 areas, observation over 1 h). We compared the results with the effects of dicaine (terminal anesthesia) and novocain (infiltration anesthesia), used in the same concentrations [9]. We employed Veits's method to assay the stimulant activity [10]. The tests revealed compounds XIII and XV as the most interesting. Compound XIII had LD_{50} 865 mg/kg on gastric administration (causing general depression). Compound XV had LD_{50} 242.5 mg/kg on intraperitoneal administration (poisoning was accompanied by convulsions).

When administered to rats in a dose of 0.03 mg/kg aconitine caused after 4-8 min prolonged disruption of the cardiac rhythm (1.5 h and longer). Compound XV and novocainamide reduced arrhythmia in some of the tests (nine out of 13 for compound XV and four out of 10 for novocainamide). However, their effect lasted for the first 2-6 min after administration, after which arrhythmia reappeared. Compound XIII also prevented arrhythmia in some of the tests (four out of 14) and was characterized by delay in the onset of arrhythmia until the tenth or eleventh minute after administration of aconitine.

The local anesthetic activity of compound XV in the terminal mode was lower than that of dicaine. The preparation was superior to novocain in infiltration anesthesia.

The water-soluble compounds had a hypotonic effect on the tonus of isolated sections of rabbit small intestine. The minimum effective concentration of compound XV was $1 \cdot 10^{-6}$ g/ml.

Thus, some of the test compounds were pharmacologically active, exhibiting antiarrhythmic and local anesthetic effects and reducing the tonus of smooth muscle. However, they had no advantages over known pharmaceuticals with the same effect.

EXPERIMENTAL CHEMISTRY

α-(p-Methoxyphenoxy)ethyl p-Methoxyphenyl Ketone (I). To a solution of hydroquinone monomethyl ether (0.12 mole) in acetone (120 ml) with stirring were added potassium carbonate (0.13 mole) and then α-bromoethyl p-methoxyphenyl ketone (0.122 mole). The reaction mixture was heated with stirring for 5 h and then filtered. The acetone was stripped off. The residue was distilled. The yield was 46.5%, bp 236°C (1 mm). Found, %: C 71.37; H 6.47; $C_{17}H_{18}O_4$. Calculated, %: C 71.39; H 6.34.

α-(p-Methoxyphenoxy)ethyl p-Chlorophenyl Ketone (II). This compound was prepared like compound I and was used subsequently without isolation.

α-(m-Methoxyphenoxy)ethyl p-Chlorophenyl Ketone (III). This was prepared like compound I in 92% yield, mp 105-106°C (from methanol). Found, %: C 66.09; H 5.26; Cl 12.50. $C_{16}H_{15}ClO_3$. Calculated, %: C 66.10; H 5.20; Cl 12.19.

2-Methyl-3-(p-chlorophenyl)-5-methoxybenzofuran (IV). Polyphosphoric acid, prepared from phosphorus pentoxide (294 g) and o-phosphoric acid (140 ml), was heated to 60°C and compound II (0.115 mole) was added in a single batch with stirring. The reaction mixture was stirred at 60°C for 3.5 h. It was then cooled and poured into water. The precipitate was purified by distillation. The yield was 78%, bp 205°C (1 mm). Found, %: C 70.64; H 4.76; Cl 13.12. $C_{16}H_{13}ClO_2$. Calculated, %: C 70.46; H 4.80; Cl 13.00.

2-Methyl-3-(p-methoxyphenyl)-5-methoxybenzofuran (V). This was prepared like compound IV in 69% yield, bp 195°C (1 mm). Found, %: C 75.90; H 6.09. $C_{17}H_{16}O_3$. Calculated, %: C 76.19, H 6.01.

2-Methyl-3-(p-chlorophenyl)-6-methoxybenzofuran (VI). This compound was prepared like compound IV in 61% yield, mp 94-95°C (from methanol). Found, %: C 70.18; H 4.80, Cl 12.99. $C_{16}H_{13}ClO_2$. Calculated, %: C 70.46, H 4.80, Cl 13.00.

2-Methyl-3-phenyl-5-hydroxybenzofuran (VIII). A mixture of 2-methyl-3-phenyl-5-methoxybenzofuran (3 g, 0.0126 mole) and pyridine hydrochloride (8 g, 0.07 mole) was stirred at 190-200°C for 1 h in a stream of argon and then cooled and poured into water. The precipitate was filtered off. The yield was 2 g (71%), mp 135-136°C (from methanol). Found, %: C 80.67; H 5.46. $C_{15}H_{12}O_2$. Calculated, %: C 80.34, H 5.39.

2-Methyl-3-(p-chlorophenyl)-5-hydroxybenzofuran (IX). This was prepared like compound VIII in 79% yield, mp 72-73°C, bp 215°C (5 mm). Found, %: C 69.58; H 4.29; Cl 13.43. $C_{15}H_{11}ClO_2$. Calculated, %: C 69.64, H 4.28, Cl 13.70.

2-Methyl-3-(p-hydroxyphenyl)-5-hydroxybenzofuran (X). This compound was prepared like compound VIII in 94% yield, mp 189-190°C (from aqueous isopropanol). Found, %: C 74.98, H 5.17. $C_{15}H_{12}O_3$. Calculated, %: C 75.06, H 5.04.

2-Methyl-3-(p-chlorophenyl)-6-hydroxybenzofuran (XI). This was prepared like compound VIII in 96% yield, mp 115-116°C (from chloroform). Found, %: C 69.55, H 4.25. $C_{15}H_{11}ClO_2$. Calculated, %: C 69.64, H 4.29.

2-Methyl-3-(p-chlorophenyl)-4-dimethylaminomethyl-5-hydroxybenzofuran (XIII). Compound (IX) (2.5 g, 0.01 mole) and bis(dimethylamino)methane (2.75 ml, 0.02 mole) in dioxane (40 ml) were refluxed for 3 h. The solvent and excess amine were stripped off under vacuum. The residue was recrystallized from methanol. The yield was 1.7 g (54%), mp 145-146°C. Found, %: C 68.56, H 6.11, Cl 11.16, N 4.34. $C_{18}H_{18}ClNO_2$. Calculated, %: C 68.46, H 5.74, Cl 11.23, N 4.43.

2-Methyl-3-phenyl-6-hydroxy-7=dimethylaminomethylbenzofuran (XIV). This was prepared like compound XIII in 66% yield, mp 123-124°C (from methanol). Found, %: C 77.41, H 6.89. $C_{18}H_{19}NO_2$. Calculated, %: C 76.84, H 6.81.

2-Methyl-3-(p-chlorophenyl)-6-hydroxy-7-dimethylaminomethylbenzofuran (XV). This was prepared like compound XIII in 73% yield, mp 142-143°C (from methanol). Found, %: C 68.75, H 5.76, Cl 11.09. $C_{18}H_{18}ClNO_2$. Calculated, %: C 68.46, H 5.75, Cl 11.22. The hydrochloride of compound XV was prepared by neutralizing an acetone solution of the base with ethereal hydrogen chloride. The yield was quantitative, mp 235°C (from acetone—methanol—ether). Found, %: C 61.40, H 5.60, Cl 20.21. $C_{18}H_{18}ClNO_2 \cdot HCl$. Calculated, %: C 61.37, H 5.44, Cl 20.13.

2-Methyl-3-phenyl-5-diethylaminoethoxybenzofuran Hydrochloride (XVI). Compound VIII (2.32 g, 0.0103 mole) was refluxed for 3 h on a water bath with the sodium alcoholate prepared from sodium (0.27 g) and diethylaminoethyl chloride (1.6 g, 0.0117 mole) in absolute alcohol (25 ml). The precipitated sodium chloride was removed and the alcohol was stripped off under vacuum. The residue was dissolved in absolute ether and neutralized with ethereal hydrogen chloride. The crystals of the hydrochloride were separated. The yield was 2 g (54%), mp 149-150°C (from acetone). Found, %: C 70.24, H 7.31, Cl' 9.83. $C_{21}H_{24}NO_2 \cdot HCl$. Calculated, %: C 70.28, H 7.02, Cl' 9.88.

2-Methyl-3-phenyl-6-diethylaminoethoxybenzofuran Hydrochloride (XVII). This compound was prepared like compound XVI in 44.2% yield, mp 177-178°C (from acetone—methanol). Found, %: C 70.32, H 7.62, Cl' 9.45. $C_{21}H_{25}NO_2 \cdot HCl$. Calculated, %: C 70.08, H 7.28, Cl' 9.85.

2-Methyl-3-(p-chlorophenyl)-6-diethylaminoethoxybenzofuran Hydrochloride (XVIII). This was prepared like compound XVI in 80% yield, mp 142-144°C (from acetone—ether). Found, %: C 63.39, H 6.33, Cl 17.94. $C_{21}H_{24}ClNO_2 \cdot HCl$. Calculated, %: C 66.50, H 6.40, Cl 18.02.

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SYNTHESIS AND HYPOGLYCEMIC ACTIVITY OF N-ALKYL-N'-(2-AMINO-1,3,4-THIADIAZOL-5-YLSULFONYL)- AND N-ALKYL-N'-(5-SULFAMOYL-1,3,4-THIADIAZOL-2-YL)-OXAMIDES

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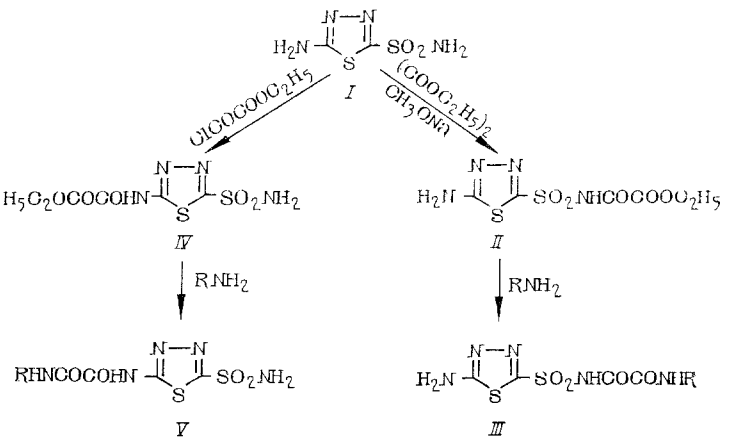
N-Substituted N'-arylsulfonyloxamides display marked sugar-reducing activity and are relatively nontoxic [1-3].

We thought it relevant to structure—activity studies to examine the biological activity of N-alkyl-N'-(2-amino-1,3,4-thiadiazol-5-ylsulfonyl)- and N-alkyl-N'-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)oxamides, in which the sulfonyl group is attached to a heterocycle.

We synthesized these groups of compounds by the reactions



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