SYNTHESIS AND ANTIVIRAL ACTIVITY OF 5-METHOXYBENZOFURANS

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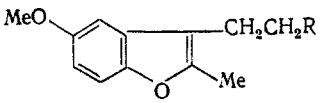
The search for antiviral drugs is currently being pursued with several classes of compounds. Many compounds with antiviral activity have been found in heterocycles, especially benzofurans [3].

We have previously reported the synthesis of some benzofuryl-3-propionic and -butyric acids [2]. We have now used these compounds to prepare the corresponding amides, amines, and other functional derivatives, the antiviral activity of which was of interest to examine.

Boiling (2-methyl-5-methoxy-3-benzofuryl)propionic acid in alcohol in the presence of KU-2-8 resin affords the ethyl ester (I). This reacts with hydrazine hydrate to give (2-methyl-5-methoxy-3-benzofuryl)propionic hydrazide (II). Reduction of (I) with $LiAlH_4$ affords high yields of 2-methyl-3-γ-hydroxypropyl-5-methoxybenzofuran (III).



I: R = COOEt; II: R = $CONHNH_2$;
III: R = CH_2OH; IV: R = $CONHCH_2CH_2OH$;
V: R = $CONEt_2$; VI: R = $CONH_2$;
VII: R = $CH_2NHCH_2CH_2OH$;
VIII: R = CH_2NEt_2; IX: R = CH_2NH_2;
X: R = piperidinomethyl; XI: R = NHCOOEt;
XII: R = phthalimido; XIII: R = NH_2;
XIV: R = CH_2COOEt; XV: R = $CH_2CONHNH_2$;
XVI: R = $CH_2CONHCH_2CH_2OH$.

(3-Benzofuryl)propionamides are of interest as potentially biologically active compounds, as well as being possible intermediates for the synthesis of aminoalkyl-5-hydroxybenzofurans. Three methods were used to obtain the amides. Aminolysis of the ethyl ester (I) with an excess of monoethanolamine gave (2-methyl-5-methoxy-3-benzofuryl)propionic β-hydroxyethylamide (IV). Prolonged boiling of (2-methyl-5-methoxy-3-benzofuryl)propionic acid with PCl_5 in chloroform in the presence of dimethylformamide (DMF) gave the acid chloride, which was treated without further purification with diethylamine to give (2-methyl-5-methoxy-3-benzofuryl)propionic diethylamide (V). Reaction of the acid chloride with ammonia failed to give the unsubstituted amide. (2-Methyl-5-methoxy-3-benzofuryl)propionamide (VI) was obtained by reducing the hydrazide (II) over Raney nickel.

Amides (IV-VI) were reduced with $LiAlH_4$ to the amines, 3-γ-hydroxyethylaminopropyl- (VII), 3-γ-diethylaminopropyl- (VIII), and 3-γ-aminopropyl- (IX) 2-methyl-5-methoxybenzofurans. 2-Methyl-3-γ-piperidinopropyl-5-methoxybenzofuran (X) was obtained by replacing the hydroxy-group in (III) by the piperidine residue in the presence of a skeletal nickel catalyst.

In addition to 3-aminopropyl derivatives of 5-hydroxybenzofuran, we have obtained some 3-aminoethyl derivatives. 2-Methyl-3-aminoethyl-5-methoxybenzofuran (XIII) has been obtained from the hydrazide (II) via 2-methyl-3-β-ethoxycarbonylaminoethyl-5-methoxybenzofuran (XI) and 2-methyl-3-(β-phthalimidoethyl)-5-methoxybenzofuran (XII).

Some of the above reactions were also carried out with (2-methyl-5-methoxy-3-benzofuryl)-butyric acid. Esterification of the acid gave the ethyl ester (XIV). This served as the starting material for the preparation of (2-methyl-5-methoxy-3-benzofuryl)butyrohydrazide (XV) and (2-methyl-5-methoxy-3-benzofuryl)-butyric β-hydroxyethylamide (XVI).

In addition to the 3-aminoalkyl derivatives, we have obtained some 2-aminoalkyl-5-methoxybenzofurans. The key intermediate in the preparation of these compounds was 2-bromo-

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methyl-3-ethoxycarbonyl-5-methoxy-6-bromobenzofuran [1], which was converted on treatment with potassium phthalimide into 2-phthalimidomethyl-3-ethoxycarbonyl-5-methoxy-6-bromobenzofuran (XVII), then hydrolyzed with alkali to the acid. The latter was treated without further purification with hydrazine hydrate to give 2-aminomethyl-3-carboxy-5-methoxy-6-bromobenzofuran in admixture with phthalazine (XVIII). From the analytical data, the components of this mixture were present in a ratio of 1:1, irrespective of the number of times it was crystallized. It is likely that these components formed a complex.

Treatment of 2-bromomethyl-3-ethoxycarbonyl-5-methoxy-6-bromobenzofuran with potassium thiocyanate afforded 2-thiocyanatomethyl-3-ethoxycarbonyl-5-methoxy-6-bromobenzofuran (XIX), and treatment with N-methylanisidine gave 2-(N-methyl-N-3'-methoxyphenyl)aminomethyl-3-ethoxycarbonyl-5-methoxy-6-bromobenzofuran (XX). The ester (XX) was hydrolyzed to the acid (XXI). Reaction of (XXI) with $(CF_3)_2CO$ resulted in the formation of 2-(N-methyl-N-3'-methoxy-6'-trifluoroacetylphenyl)aminomethyl-3-carboxy-5-methoxy-6-bromobenzofuran (XXII).

The antiviral activity of the compounds was examined against influenza virus A/FPV(H_7N_7), Weybridge strain, and Venezuelan equine encephalomyelitis virus (VEM) in primarily trypsinized cultures of chick embryo fibroblasts (CEF).

A monolayer of CEF cells was infected with 10-100 doses (CDT_{50}) of virus, and when it had been absorbed (incubation for 1 h at 37°C), the test compound was added. The compounds were taken in concentrations of 1/4 and 1/8 of the MTC, as found in examining the cytotoxic effects of the compounds. Viral inhibitory activity was assessed by the inhibition of the cytopathic effects (ICE) of the virus on the cells, and the reduction in the infective titer of the virus (as lg CDT_{50}) as compared with the controls.

It was found that in concentrations of 20 μg/ml the test compounds had no cytopathic effects on the CEF cell culture. In concentrations of 5.0 and 2.5 μg/ml, compounds (VI), (IX), and (XI) had pronounced inhibitory activity on the replication of VEM virus, preventing cytopathic effects of the virus on the cells and reducing its infective titer by 2.0 and 1.5 lg CDT_{50} respectively. Compound (II) was less active. In the same concentrations, it reduced the infective titer by 0.75-1.0 lg CTD_{50}. Compound (VII) was inactive.

No viral inhibitory effects on the replication of the influenza virus in CEF cell culture were found.

These 5-methoxybenzofurans therefore include compounds active against the VEM virus (an RNA virus of the arbovirus family), but they were devoid of activity against the replication of another RNA virus, the influenza virus (an orthomyxovirus).

EXPERIMENTAL (CHEMISTRY)

Ethyl (2-Methyl-5-methoxy-3-benzofuryl)propionate (I). A solution of 1 g (4.2 mmole) of (2-methyl-5-methoxy-3-benzofuryl)propionic acid in 15 ml of ethanol was boiled for 10 h with 0.2 g of KU-2-8 resin. The resin was then filtered off, and washed on the filter with alcohol. The alcohol was removed, and the oily residue chromatographed on a silica column (chloroform), the first fraction being collected. Yield 0.8 g (71%). Found: $M^{+\cdot}$ 262. $C_{15}H_{18}O_4$. Calculated: M 262.

(2-Methyl-5-methoxy-3-benzofuryl)propionohydrazide (II). A solution of 4.8 g (18 mmole) of (I) in 45 ml of ethanol was boiled for 25 h with 7 ml (0.14 mole) of hydrazine hydrate. The alcohol and excess hydrazine hydrate were distilled off, and the residue crystallized from aqueous methanol to give 4.0 g (90.5%) of product, mp 213-214°C. $C_{13}H_{16}N_2O_3$.

2-Methyl-3-γ-hydroxypropyl-5-methoxybenzofuran (III). To a suspension of 1.96 g (51.7 mmole) of $LiAlH_4$ in 75 ml of dry ether was added portionwise with stirring 4 g (15.2 mmole) of (I). The mixture was boiled for 3 h, cooled, and decomposed with 25 ml of alcohol followed by 30 ml of water. The solid was filtered off, and the ether layer separated and chromatographed on a column of silica (ether), the first fraction being collected, to give 3.2 g (95.5%) of (III) as an oil. Found, $M^{+\cdot}$ 220. $C_{13}H_{16}O_3$. Calculated, M 220.

(2-Methyl-5-methoxy-3-benzofuryl)pripionic β-Hydroxyethylamide (IV). A mixture of 1.52 g (5.8 mmole) of (I) and 3.5 ml (58 mmole) of monoethanolamine was heated at 170°C for 2 h. The mixture was then cooled, diluted with water, and the oil which separated extracted with chloroform. The solvent was distilled off, and the residue recrystallized from chloroform–light petroleum to give 1.3 g (80.8%) of (IV), mp 70°C. Found: $M^{+\cdot}$ 277. $C_{15}H_{19}NO_4$. Calculated: M 277.

(2-Methyl-5-methoxy-3-benzofuryl)propionic Diethylamide (V). To a solution of 1.5 g (6.4 mmole) of (2-methyl-5-methoxy-3-benzofuryl)propionic acid in 30 ml of chloroform in the presence of a catalytic amount of DMF was added at ambient temperature with stirring over 0.3 h 1.47 g (7 mmole) of PCl_5. Stirring was continued for 2 h at ambient temperature and 14 h at the boiling point of the solvent. Removal of the solvent left a dark-colored oil. The crude acid chloride was dissolved without further purification in 35 ml of benzene, treated with 1.33 ml (12.8 mmole) of diethylamine, and the mixture boiled for 5 h. The solid diethylamine hydrochloride was filtered off and washed with benzene. The solvent was removed, and the oily residue chromatographed on a column of silica(chloroform), the second fraction being collected, to give 1.4 g (75.6%) of product. Found: $M^{+\cdot}$ 289. $C_{17}H_{23}NO_3$. Calculated: M 289.

(2-Methyl-5-methoxy-3-benzofuryl)propionamide (VI). A mixture of 1 g (4 mmole) of (II) and 3 g of Raney nickel in 15 ml of absolute ethanol was boiled for 2 h. The nickel was filtered off and washed with ethanol, and the solvent removed. The residue was recrystallized from aqueous methanol to give 0.64 g (76%) of product, mp 127-128°C. $C_{13}H_{15}NO_3$.

2-Methyl-3-γ-Hydroxyethylaminopropyl-5-methoxybenzofuran (VII). To a suspension of 0.65 g of $LiAlH_4$ in 15 ml of dry ether was added with stirring at ambient temperature over 30 min a suspension of 1.38 g of (IV) in 20 ml of dry ether. The mixture was boiled for 3 h, cooled, and excess $LiAlH_4$ decomposed first with alcohol, then with water. The combined ether extracts were dried over $MgSO_4$, the ether removed, and the residue chromatographed on a column of silica (ether) to give 0.8 g (61%) of (VII) as an oil. Found: $M^{+\cdot}$ 263. $C_{15}H_{21}NO_3$. Calculated: M 263.

2-Methyl-3-γ-diethylaminopropyl-5-methoxybenzofuran (VIII) was obtained as for (VII). The oil was chromatographed on a column of alumina (ether), the first fraction being collected. Yield 83.5%. Found: $M^{+\cdot}$ 275. $C_{17}H_{25}NO_2$. Calculated: M 275.

2-Methyl-3-γ-aminopropyl-5-methoxybenzofuran Hydrochloride (IX) was obtained as for (VII). The ether was removed to a small volume, and the residue neutralized with ethereal HCl, to give 45.5% of (IX), mp 221-222°C (from acetone–methanol–ether). $C_{13}H_{18}NO_2 \cdot HCl$.

2-Methyl-3-piperidinopropyl-5-methoxybenzofuran Hydrochloride (X). A solution of 2.7 g (12 mmole) of (III) and 2.42 ml (24 mmole) of piperidine in 25 ml of xylene was boiled in the presence of skeletal nickel catalyst with a Dean and Stark apparatus for 8 h. The nickel was filtered off, washed on the filter with xylene, and the solvent removed. The residue was chromatographed on a column of silica (ether), the second fraction being collected. This was neutralized with ethereal HCl to give 0.88 g (22.7%) of (X), mp 181-183°C (from acetone–ether). $C_{18}H_{24}NO_2HCl$.

2-Methyl-3-β-ethoxycarbonylaminoethyl-5-methoxybenzofuran (XI). To a solution of 3.55 g (14.3 mmole) of (II) in 16 ml of acetic acid, 42 ml of water, and 23 ml of benzene was added over 0.5 h with stirring at 2-3°C a solution of 1.07 g (15.5 mmole) of $NaNO_2$ in 12 ml of water. Stirring was continued for a further 0.3 h, then the benzene layer was separated, washed with saturated $NaHCO_3$ solution, dried over $CaCl_2$, and most of the solvent distilled off. The residue was treated with 100 ml of absolute ethanol, and boiled until traces of azide were no longer visible on the chromatogram (1.5 h). The solvent was removed, and the residue chromatographed on a column of silica (ether), the second fraction being collected. Yield of (XI) 2.8 g (71.8%). The oil crystallized on standing, mp 64-66°C.

2-Methyl-3(β-phthalimidoethyl)-5-methoxybenzofuran (XII). A mixture of 0.48 g (1.73 mmole) of (XI) and 0.43 g (2.88 mmole) of phthalic anhydride was heated at 230-235°C for 3 h, cooled, unreacted phthalic anhydride decomposed by titration with $NaHCO_3$, the phthalimido-derivative extracted with chloroform, and the extract chromatographed on a column of silica (chloroform), the third fraction being collected. Yield of (XII) 0.25 g (43%), mp 97-100°C. Found: $M^{+\cdot}$ 335. $C_{20}H_{17}NO_4$. Calculated: M 335.

2-Methyl-3-aminoethyl-5-methoxybenzofuran Hydrochloride (XIII). A mixture of 0.25 g of (XII) and 0.1 ml of hydrazine hydrate in 5 ml of ethanol was boiled for 3 h, filtered, and the mother liquors evaporated and neutralized with ethereal HCl. Recrystallization from ethanol–ether gave 0.1 g (56%) of (XIII), mp 220-222°C. Found: $M^{+\cdot}$ 205. Calculated: M 205.

Ethyl (2-methyl-5-methoxy-3-benzofuryl)butyrate (XIV) was obtained as for (I), yield 89%. Found: $M^{+\cdot}$ 286. $C_{16}H_{20}O_4$. Calculated: M 276.

(2-Methyl-5-methoxy-3-benzofuryl)butyrohydrazide (XV) was obtained as for (III), yield 81.5%, mp 111-113°C (from benzene–heptane). $C_{14}H_{16}N_2O_3$.

(2-Methyl-5-methoxy-3-benzofuryl)butyric β-Hydroxyethylamide (XVI) was obtained as for (IV), yield 65.7%. mp 104-105°C (from propan-2-ol–light petroleum). $C_{16}H_{21}NO_4$.

2-Phthalimidomethyl-3-ethoxycarbonyl-5-methoxy-6-bromobenzofuran (XVII). A solution of 3.92 g (0.01 mole) of 2-bromomethyl-3-ethoxycarbonyl-5-methoxy-6-bromobenzofuran and 1.85 g (0.01 mole) of potassium phthalimide in 30 ml of DMF was stirred at 50-60°C for 6 h. On the following day, the reaction mixture was diluted with water, and the solid which separated was filtered off, washed with water, dried, and recrystallized from DMF to give 2.03 g (44.3%) of product, mp 221-222°C. Found: $M^{+\cdot}$ 457. $C_{21}H_{16}BrNO_6$. Calculated: M 457.

Mixture of 2-Aminomethyl-3-carboxy-5-methoxy-6-bromobenzofuran Hydrochloride and Phthalazine (XVIII). A mixture of 1.8 g (3.93 mmole) of (XVII) and 0.53 g (13.3 mmole) of NaOH in 10 ml of ethanol was boiled for 2 h. The solvent was removed, and the residue dissolved in water and neutralized with HCl. The solid was filtered off and dried to give 1.65 g of the acid, which was boiled without further purification with 0.24 ml of hydrazine hydrate in 20 ml of ethanol for 7 h. The mixture was cooled, neutralized with HCl, and the solid filtered off. The yield calculated on the crude acid was 80.2%, mp 256-257°C (decomp., from alcohol–ether). Found: $M^{+\cdot}$ 299 + 162. $C_{11}H_{10}BrNO_4 \times HCl \times C_8H_6N_2O_2$. Calculated: M 299 + 162.

2-Thicyanatomethyl-3-ethoxycarbonyl-5-methoxy-6-bromobenzofuran (XIX). To a solution of 7.84 g (20 mmole) of 2-bromomethyl-3-ethoxycarbonyl-5-methoxy-6-bromobenzofuran in 20 ml of glacial acetic acid was added at room temperature 3.3 g (34 mmole) of potassium thiocyanate. On the following day, the mixture was diluted with water, and the solid which separated filtered off to give 7.1 g (96.2%) of product, mp 159-161°C (from alcohol). $C_{14}H_{12}BrNSO_4$.

2-(N-Methyl-N-3-methoxyphenyl)aminomethyl-3-ethoxycarbonyl-5-methoxy-6-bromobenzofuran (XX). A mixture of 3.92 g (0.01 mole) of 2-bromoethyl-3-ethoxycarbonyl-5-methoxy-6-bromobenzofuran and 2.74 g (0.02 mole) of N-methylanisidine in 50 ml of benzene was boiled for 22 h. The mixture was then cooled, the solid filtered off, the benzene removed, and the residual orange oil chromatographed on a column of silica (ether), the first fraction being collected. Yield of (XX) 2.36 g (52.68%), mp 73-74°C (from alcohol). Found: $M^{+\cdot}$ 447. $C_{21}H_{22}BrNO_5$. Calculated: M 447.

2-(N-Methyl-N-3'-methoxyphenyl)aminomethyl-3-carboxy-5-methoxy-6-bromobenzofuran (XXI). A mixture of 2.36 g (5.3 mmole) of (XX) and 0.8 g (20 mmole) of NaOH in 30 ml of alcohol was boiled for 2 h. The mixture was then diluted with water, and neutralized with HCl. The solid was filtered off to give 1.46 g (65.5%) of product, mp > 200°C. Found: $M^{+\cdot}$ 419. $C_{19}H_{18}BrNO_5$. Calculated: M 419.

2-(N-Methyl-N-3'-methoxy-6'-trifluoroacetylphenyl)aminomethyl-3-carboxy-5-methoxy-6-bromobenzofuran (XXII). A solution of 1.45 g of (III) in 100 ml of dry benzene was treated at ambient temperature with 1 ml of $(CF_3CO)_2CO$. After two days, the solvent was removed, and the residue chromatographed on a column of silica (ether), the first fraction being collected. There was obtained 0.84 g (47.2%) of (XXII), mp 245°C (decomp., from methanol). Found: $M^{+\cdot}$ 515. $C_{21}H_{17}BrF_3NO_6$. Calculated: M 515.

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