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SYNTHESIS AND BIOLOGICAL ACTIVITY OF DERIVATIVES OF 2-METHYL-5-METHOXYBENZOFURAN

A. N. Grinev, S. A. Zotova, and T. M. Gololobova

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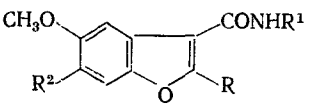
Continuing the search for biologically active benzofurans, we have synthesized amides, anilides, and other derivatives of 5-methoxybenzofuran-3-carboxylic acid.

From 2-methyl-5-methoxy- [1], 2-phenylthiomethyl-5-methoxy-6-bromo- [2], and 2-phenylthiomethyl-5-methoxybenzofuran-3-carboxylic acid (II), obtained by the methylation of the corresponding hydroxy derivative (I), were synthesized the acid chlorides, which without further purification were treated with ammonia, aniline, or γ-aminobutyric acid to give the amide of 2-methyl-5-methoxybenzofuran-3-carboxylic acid (IIIa), the amide and anilide of 2-phenylthiomethyl-5-methoxybenzofuran-3-carboxylic acid (IIIb and c), N-(2-methyl-5-methoxybenzofuroyl-3)- (IIId), and N-(2-phenylthiomethyl-5-methoxy-6-bromobenzofuroyl-3)-γ-aminobutyric acid (IIIe). Compound IIIc was oxidized with sodium iodide to the anilide of 2-phenylsulfinylmethyl-5-methoxybenzofuran-3-carboxylic acid (IIIf). Reaction with $SOCl_2$ led to the replacement of the phenylsulfinyl group of IIIf by chlorine to give the anilide of 2-chloromethyl-5-methoxybenzofuran-3-carboxylic acid (IIIg).



IIIa-g

a: R=Me, R^1=R^2=H; b: R=CH_2SPh, R^1=R^2=H; c: R=CH_2SPh, R^1=Ph, R^2=H;
d: R=Me, R^1=$(CH_2)_3COOH$, R^2=H; e: R=CH_2SPh, R^1=$(CH_2)_3COOH$, R_2=Br;
f: R=CH_2SOPh, R^1=Ph, R^2=H; g: R=CH_2Cl, R^1=Ph, R^2=H.

In addition, some reactions of 3-acyl-5-methoxybenzofuran derivatives were studied. It was found that on bromination of 2-methyl-3-acetyl-5-methoxybenzofuran [3] with an equimolar quantity of dibromodioxane, only 2-methyl-3-bromoacetyl-5-methoxybenzofuran (IV) was obtained; bromination of compound IV with dioxanedibromide gave 2-methyl-3-dibromoacetyl-5-methoxy-6-bromobenzofuran (V). Treatment of compound V with morpholine and hydrochloric acid gave (2-methyl-5-methoxy-6-bromobenzofuroyl-3)glyoxal (VI). The NMR spectrum of compound VI contained two singlets with δ 6.8 and 7.6 ppm, indicating the presence of a bromine atom at position 6 in both compound VI and the parent compound V.

Treatment of compound IV with morpholine and hydrogen chloride in ether gave the hydrochloride of 3-morpholinoacetyl, derivative (VII). Reaction of compound IV with sodium sulfide gave bis(2-methyl-5-methoxy-3-benzofuroylmethyl)sulfide (VIII).

It is interesting to note that bromination of 2-methyl-3-acetyl-5-methoxybenzofuran with N-bromosuccinimide gave 2-bromomethyl-3-acetyl-5-methoxybenzofuran (IX), not the bromoacetyl derivative of IV which was obtained on bromination with dioxanedibromide. Reaction of compound IX with morpholine gave 2-morpholinomethyl-3-acetyl-5-methoxybenzofuran (X), and treatment of IX with thiourea gave the thiourea salt (XI). With sodium sulfide, compound IX gave bis(2-methylene-3-acetyl-5-methoxybenzofuranyl)sulfide (XII).

S. Ordzhonikidze All-Union Pharmaceutical Chemistry Research Institute, Moscow.
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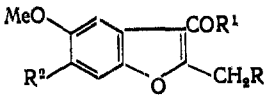
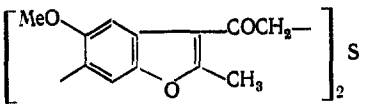


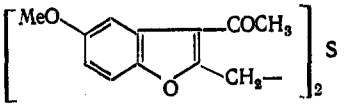
IV—VII, IX—XI

IV: R = R^2 = H, R^1 = CH_2Br; V: R = H, R^1 = $CHBr_2$, R^2 = Br; VI: R = H, R^1 = CHO, R^2 = Br; VII: R = H, R^1 = $CH_2N(CH_2)_2O(CH_2)_2$; IX: R = Br, R^1 = Me, R^2 = H;

X: R = $\overline{N(CH_2)_2O(CH_2)_2}$, R^1 = Me, R^2 = H; XI: R = $SC(=NH)NH_2HBr$, R^1 = Me, R^2 = H.



VIII



XII

A study of biological activity, carried out by L. M. Polukhin at the All-Union Scientific Research Institute of Pharmaceutical Chemistry Laboratory for Chemotherapy of Infectious Diseases (Director – Member-correspondent of the Academy of Medical Science of the USSR, G. N. Pershin), showed that only compounds IV and VII possess moderate antimicrobial activity in vitro tests, while compound IIIg showed weak activity against gram-positive bacteria.

EXPERIMENTAL

2-Phenylthiomethyl-3-carboxy-5-hydroxybenzofuran (I). A solution of 22.9 g (0.07 moles) or 2-phenylthiomethyl-3-carbethoxy-5-hydroxybenzofuran and 13.7 g (0.25 moles) of KOH in 140 ml of water was refluxed for 2 h; the reaction mixture ws cooled and acidified with HCl. The precipitated material was separated, washed with water, and recrystallized from MeOH to give 12.8 g (61%) of I with mp 219-221°C. Found, %: C 63.93; H 4.47; S 10.98. $C_{16}H_{12}SO_4$. Calculated, %: C 63.99; H 4.03; S 10.68.

2-Phenylthiomethyl-3-carboxy-5-methoxybenzofuran (II). To a vigorously stirred solution of 22.5 g (0.08 moles) of I and 6.4 g (0.16 moles) of NaOH in 70 ml of water was slowly added 7.9 ml (0.08 moles) of Me_2SO_4, and when methylation was complete, a further 7.9 ml of Me_2SO_4 and 11 ml of dioxane was added. The rection was refluxed for 0.5 h, 12 g of NaOH added, and refluxing continued until the reaction mixture was homogeneous. The resulting solution was cooled, and the acid separated by the addition of concentrated HCl. The precipitated material was chromatographed on potassium sulfate ($CHCl_3$), to give 6.1 g (24.3%) of II with mp 192-193°C (ethyl acetate). Found, %: C 65.20; H 4.60; S 10.17. $C_{17}H_{14}SO_4$. Calculated, %: C 64.95; H 4.49; S 10.20.

Acid Chlorides of 3-Carboxy-5-methoxybenzofuran Derivatives (General Method). The acid (0.1 mole) in a mixture of 50 ml of absolute dioxane and 0.4 mole of $SOCl_2$ was refluxed for 2 h, then allowed to stand overnight at ∿20°C. The solvent and excess $SOCl_2$ were evaporated off, and the acid chloride was used without further purification for the synthesis of the amides.

Amide of 2-Methyl-3-carboxy-5-methoxybenzofuran (IIIa). The acid chloride obtained from 25 g of 2-methyl-3-carboxy-5-methoxybenzofuran was dissolved in 600 ml of dry ether and NH_3 bubbled through the solution for 0.5 h. The precipitated material was separated and washed on the filter with water and with alcohol and finally with ether. A yield of 10.5 g (42.3%) of IIIa with mp 174-175°C (from benzene) was obtained. Found, %: C 64.70; H 5.30; N 6.79. $C_{11}H_{11}NO_3$. Calculated, %: C 64.40; H 5.40; N 6.86.

Amide of 2-phenylthiomethyl-3-carboxy-5-methoxybenzofuran (IIIb) was prepared in the same way as IIIa in 100% yield with mp 140°C (from ethanol). Found, %: C 65.25; H 4.87; S 10.65. $C_{17}H_{15}NO_3S$. Calculated, %: C 65.16; H 4.82; S 10.23.

Anilide of 2-Phenylthiomethyl-3-carboxy-5-methoxybenzofuran (IIIc). A solution of the acid chloride obtained from 3.7 g (0.0118 mole) of II, in 70 ml of dry ether was stirred at room temperature and 2.15 g (0.0236 mole) of aniline added. The following day, the precipitated material was separated, washed with water to remove excess aniline hydrochloride, and recrystallized from ethanol to give 3.14 g (68.3%), of IIIc with mp 149-150°C. Found, %: S 8.33. $C_{23}H_{19}NO_3S$. Calculated, %: S 8.23.

N-(2-Methyl-5-methoxybenzofuroyl-3)-γ-aminobutyric Acid (IIId). To the acid chloride obtained form 5.15 g (0.025 mole) of 2-methyl-3-carboxy-5-methoxybenzofuran, was added a solution of 2.6 g (0.025 mole) of γ-aminobutyric acid in 20 ml of 10% aqueous alkali. After

1 h the solution was filtered and the filtrate acidified with dilute HCl (d 1.18). The precipitated material was separated, washed many times with water to remove γ-aminobutyric acid, and chromatographed on potassium sulfate ($CHCl_3$); the second fraction yielded 3.4 g (46.7%) of IIId with mp 115-117°C. Found, %: C 61.96; H 5.73; N 4.90. $M^{+\cdot}$ 291. $C_{15}H_{17}NO_5$. Calculated, %: C 61.85; H 5.88; N 4.81. M 291.

N-(2-Phenylthiomethyl-5-methoxy-6-bromobenzofuroyl-3)-γ-aminobutyric acid (IIIe) was obtained in the same way as compound IIId in 45.3% yield with mp 120°C (ethyl acetate). Found, %: C 52.90; H 4.40; S 6.56. $M^{+\cdot}$ 477. $C_{21}H_{20}BrNO_5S$. Calculated, %: C 52.73; H 4.21; S 6.70. M 477.

Anilide of 2-Phenylsulfinylmethyl-3-carboxy-5-methoxybenzofuran (IIIf). A solution of 1 g (0.0026 mole) of IIIc in 75 ml of MeOH was refluxed for 1 h with 1.21 g (0.0056 mole) of $NaIO_4$ in 6 ml of water. The solvent was evaporated in vacuum and the residue washed with water and recrystallized from ethanol to give 0.7 g (83.8%) of IIIf with mp 150-151°C. Found %: C 67.95; H 4.70; S 7.80. $C_{23}H_{19}NO_4S$. Calculated, %: C 68.13; H 4.72; S 7.91.

Anilide of 2-Chloromethyl-3-carboxy-5-methoxybenzofuran (IIIg). A mixture of 0.68 g (0.00168 mole) of IIIf and 0.2 ml (0.0028 mole) of $SOCl_2$ in 4 ml of CH_2Cl_2 was refluxed for 2.5 h. The solvent and excess $SOCl_2$ were evaporated off and the residue chromatographed on potassium sulfate to give 0.3 g (56.7%) of IIIg with mp 163-164°C (ethanol). Found, %: C 64.46; H 4.83; Cl 10.90. $M^{+\cdot}$ 315. $C_{17}H_{14}ClNO_3$. Calculated, %: C 64.66; H 4.47; Cl 11.22. M 315.

2-Methyl-3-bromoacetyl-5-methoxybenzofuran (IV). To a solution of 1.31 g (0.0064 mole) of 2-methyl-3-acetyl-5-methoxybenzofuran in 5 ml of dioxane at ∿20°C was added dropwise a solution of 1.02 g (0.0064 mole) of bromine in 8 ml of dioxane. The reaction mixture was stirred for 3 h at the same temperature and then diluted with water. The precipitated material was separated, washed with water, and recrystallized from alcohol to give 1.2 g (66.2%) of IV with mp 83-85°C. Found, %: C 50.55; H 3.78. $M^{+\cdot}$ 282. $C_{12}H_{11}BrO_3$. Calculated, %: C 50.91; H 3.92. M 282.

2-Methyl-3-dibromoacetyl-5-methoxy-6-bromobenzofuran (V) was obtained in the same way as compound IV from 7.7 g (0.0272 mole) of IV and 8.7 g (0.0544 mole) of bromine. The viscous oil obtained was used without purification for further reaction.

(2-Methyl-5-methoxy-6-bromobenzofuranyl-3)glyoxal (VI). To a solution of 0.0272 mole of V in 40 ml of benzene was added 8.7 ml (0.1 mole) of morpholine. The rection mixture was allowed to stand at ∿20°C for 2 days, the precipitated morpholine hydrobromide separated, and the benzene driven off. The residue was treated with ice and 6 ml of dilute HCl (d 1.18) and allowed to stand overnight. The precipitated material was filtered off to give 2.48 g (30.9%) of VI with mp 231°C (ethyl acetate). Found, %: C 48.80; H 3.08; Br 26.81. $M^{+\cdot}$ 296. $C_{12}H_9BrO_4$. Calculated, %: C 48.51; H 3.05; Br 26.90. M 296.

Hydrochloride of 2-methyl-3-morpholinoacetyl-5-methoxybenzofuran (VII) was obtained from 5.4 g (0.0191 mole) of IV and 3 ml (0.0382 mole) of morpholine in benzene at ∿20°C in 81.2% yield (5.2 g) with mp 210-211°C (from a mixture of acetone, MeOH, and ether). Found, %: C 57.52; H 6.34; Cl 11.07. $C_{16}H_{19}NO \cdot HCl \cdot 0.5H_2O$. Calculated, %: C 57.40; H 6.32; Cl 10.59.

Bis(2-methyl-5-methoxy-3-benzofuroylmethyl)sulfide (VIII). To a refluxing solution of 3.6 g (0.0127 mole) of IVc in 13 ml of ethanol was added dropwise with mixing a solution of 1.53 g (0.0064 mole) of $Na_2S \cdot 9H_2O$ in 4 ml of water. Refluxing was continued for 1 h, and the precipitate separated and washed on the filter with ethanol to give 2.7 g (93%) of VIII with mp 138-140°C (acetone). Found, %: C 65.55; H 5.10; S 7.42. $M^{+\cdot}$ 438. $C_{24}H_{22}O_6S$. Calculated, %: C 65.74; H 5.06; S 7.31. M 438.

2-Bromomethyl-3-acetyl-5-methoxybenzofuran (IX). A solution of 2.04 g (0.01 mole) of 2-methyl-3-acetyl-5-methoxybenzofuran in 20 ml of CCl_4 was refluxed for 5 h with 1.78 g (0.01 mole) of N-bromosuccinimide under illumination. The residual succinimide was filtered off and the CCl_4 removed in vacuum. The residue was recrystallized from ethanol to give 1.9 g (67.2%) of IX with mp 91°C. Found, %: C 51.00; H 4.07; Br 28.46. $M^{+\cdot}$ 282. $C_{12}H_{11}BrO_3$. Calculated, %: C 50.91; H 3.92; Br 28.23. M 282.

2-Morpholinomethyl-3-acetyl-5-methoxybenzofuran hydrochloride (X) was prepared from 0.85 g (0.003 mole) of IX and 0.47 ml (0.006 mole) of morpholine in benzene at ∿20°C; 0.8 g (82%) of X was obtained with mp 216-217°C (from a mixture of acetone, MeOH, and ether).

Found, %: C 59.06; H 6.21; Cl 10.81. $C_{16}H_{19}NO_4 \cdot HCl$. Calculated, %: C 58.99; H 6.19; Cl 10.88.

2-S-Methylthiuronyl-3-acetyl-5-methoxybenzofuran (XI) Hydrobromide (XI). A solution of 0.75 g (0.00265 mole) of IV in 15 ml of ethanol was refluxed for 8.5 h with 0.22 g (0.00265 mole) of thiourea. The solvent was removed in vacuum, $CHCl_3$ added to the residue, and the precipitated material separated to give 0.33 g (34.7%) of XI, mp 141-143°C (with decomposition; recrystallized from ethanol). Found, %: S 8.96. $C_{13}H_{14}N_2O_3 \cdot HBr$. Calculated %: S 8.92.

Bis(2-methylene-3-acetyl-5-methoxybenzofuranyl)sulfide (XII) was prepared in the same way as compound III from 2.7 g (0.00954 mole) of IX in 67% yield (1.4 g), mp 94°C. Found: $M^{+\cdot}$ 438. $C_{24}H_{22}O_6S$. Calculated, M 438.

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COMPLEXES OF ISONICOTINOYLHYDRAZINE AND N-ACETYL-N'-ISONICOTINOYL-HYDRAZINE WITH TRANSITION METALS

N. M. Krymova, V. E. Ivanov, and N. A. Ostankevich

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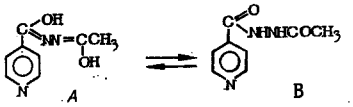
The formation of complexes with transition-metal ions plays a determining role in the mechanism of action of isonicotinoylhydrazine (hydrazide of isonicotinic acid, HN) on mycobacterium tuberculosis [1]. It is also known that in humans, part of the isonicotinoylhydrazine is acetylated to form N-acetyl-N'-isonicotinoylhydrazide (AC) [2].

Complexes of HN with transition metals have been described in some detail, although there are some inconsistencies in these reports [4, 5, 7, 8, 10], while complexes of AC have been obtained for only a small number of metals, all of which are coordinated to the hydroxyazine form of the compound [11]. Obviously, AC can be coordinated not only in the hydrazine form (A), but also in the amide form (B).



The present work seeks to investigate the synthesis of copper, cobalt, and nickel complexes of these two isonicotinoyl compounds, to compare the coordination ability of the ligands, and to determine the antituberculosis activity of the ligands and their complexes.

It is possible to displace the equilibrium of AC to the left, for example, by making the solution alkaline. Thus, when an aqueous alkaline solution of AC and solutions of the chlorides of copper, cobalt, and nickel were mixed, the compounds $(AC-2H) \cdot Cu$ (I), $(AC-2H) \cdot Co \cdot 2H_2O$ (II), and $(AC-2H) \cdot Ni \cdot 2H_2O$ (III), in which the ligand is coordinated in the hydroxyazine form, were precipitated. These compounds contain no chloride ions; from the infrared data, shown in Table 1, it can be seen that in place of bands corresponding to the stretching vibrations of the C=O group (1695, 1625 cm^{-1}) and NH group (3280 and 3200 cm^{-1}), there are bands at 1170, 1540, 1615, and 1620 cm^{-1}, which can be assigned to the stretching vibrations of the (C–O–), (NCO–), and coordinated C=N groups [11]. A broad band at 3400 cm^{-1} in the spectra of compounds II and III is due to the stretching vibrations of the uncoordinated

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