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SYNTHESIS AND REACTIONS OF SOME BENZOFURAN β- AND γ-KETOACIDS

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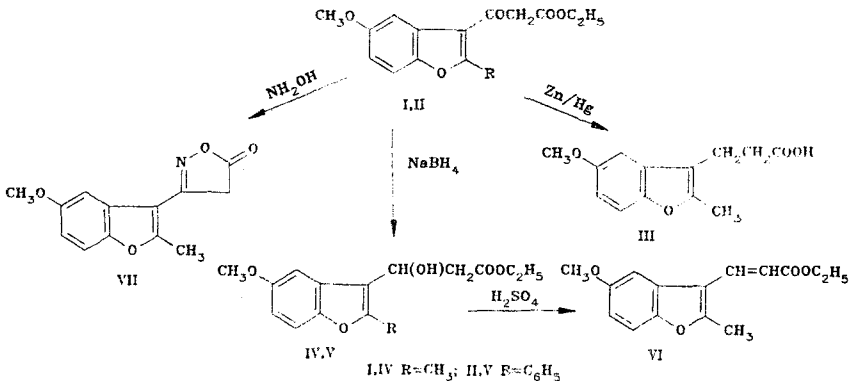
Derivatives of 5-hydroxybenzofuroyl-3-acetic and propionic acids were synthesized, and some of the reactions were studied.

Esters of β-ketoacids are widely known as intermediates in the synthesis of a variety of aliphatic-aromatic, and, especially, heterocyclic compounds. However, their heterocyclic analogs — ethyl esters of benzofuroyl acids — have not been synthesized. Moreover, they are important compounds in the synthesis of benzofuran derivatives; for example, in the present work they are converted to benzofuroylpropionic, benzofuroylacrylic, and benzofuroylbutyric acid derivatives, compounds which have been used in a number of chemical and biological studies.

We obtained the ethyl esters of α-(2-methyl-5-methoxybenzofuroyl-3)-acetic acid (I) and α-(2-phenyl-5-methoxybenzofuroyl-3)-acetic acid (II) by the benzoylacetic ester synthesis [1] from the acid chlorides of 2-methyl- and 2-phenyl-5-methoxybenzofuran-3-carboxylic acids. The reduction of the ketoacid esters I and II was studied. The reduction of I with zinc amalgam gave β-(2-methyl-5-methoxybenzofuroyl-3)propionic acid (III), and the reduction of I and II with sodium borohydride gave the ethyl esters of β-(2-methyl- (IV) and β-(2-phenyl-5-methoxybenzofuroyl-3)-β-hydroxypropionic acids (V). The latter on dehydration in acetic acid in the presence of a catalytic amount of concentrated sulfuric acid gave the ethyl ester of β-(2-phenyl-5-methoxybenzofuryl-3)acrylic acid (VI). Compound I with hydroxylamine gave 3-(2'-methyl-5'-methoxybenzofuryl-3')isoxazolin-Δ^2-5-one (VII).



The reaction of the sodium derivatives of the esters of the β-ketoacids I and II of bromoacetic ester gave the ethyl esters of β-carbethoxy-β-(2-methyl- (VIII) and β-carbethoxy-β-(2-phenyl-5-methoxybenzofuroyl-3)propionic acid (IX)) respectively. Heating compounds VIII and IX with hydrochloric acid in alcohol gave the ethyl esters of β-(2-methyl- (X) and β-(2-phenyl-5-methoxybenzofuroyl-3) propionic acid (XI)), and treatment of compound VIII with sulfuric acid in acetic acid gave β-(2-methyl-5-methoxybenzofuroyl-3)propionic acid (XII). From compound X was obtained the oxime XIII and the thiosemicarbazone XIV. Treatment of the ester X with zinc amalgam in hydrochloric acid gave γ-(2-methyl-5-methoxybenzofuryl-3)

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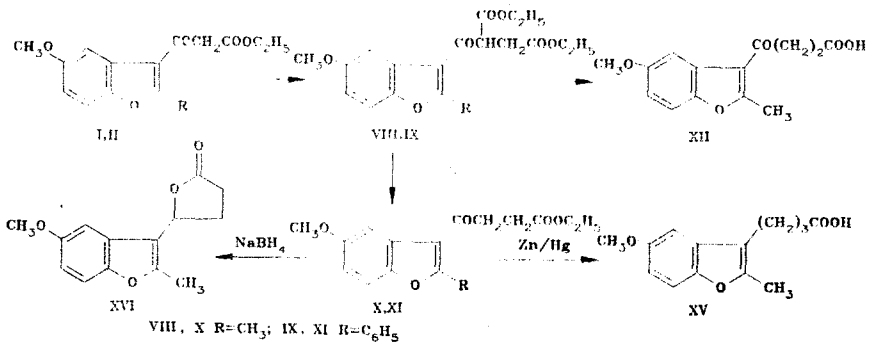
butyric acid (XV). The lactone of γ-(2-methyl-5-methoxybenzofuryl-3)-γ-hydroxybutyric acid (XVI) was formed by the reduction of compound X with sodium borohydride.



VIII, X R=CH_3; IX, XI R=C_6H_5

In the infrared spectrum of compound XVI, no absorption was observed in the region in which the hydroxyl group absorbs, but an absorption band at 1765 cm^{-1} indicated the presence of the lactone structure.

EXPERIMENTAL

Ethyl Ester of α-(2-Methyl-5-methoxybenzofuroyl-3)acetic Acid (I). A mixture of 5 ml of water, 2.93 g (22.5 mmoles) of acetoacetic ester, and 2 ml of toluene was stirred and the temperature kept below 7°C; to this was added dropwise a 33% solution of sodium hydroxide until the solution reached pH 11 (1.2 ml). Mixing and cooling were continued, and a solution of the acid chloride of 2-methyl-3-carboxy-5-methoxybenzofuran, obtained from 3.1 g (15 mmoles) of acid, in 5 ml of toluene was slowly added and at the same time the addition of the 33% sodium hydroxide solution (3.45 ml) was continued. The rate of addition of the reagents was regulated so that the temperature did not exceed 7°C at pH 10.5-11.5. The reaction mixture was then mixed for 1.5 at room temperature and for 1 h at 27-33°C, 0.81 g (15 mmoles) of ammonium chloride was added, and the reaction mixture was left overnight. The layers were separated and the aqueous layer washed with toluene. The combined toluene fractions were washed with saturated salt solution, dried with magnesium sulfate, the solvent evaporated, and the residue chromatographed on a KSK column (chloroform). The first fraction was collected. Yield, 3.0 g (72.2%), mp 51-52°C. Found: C 65.2; H 5.8%; $M^{+\cdot}$ 276. $C_{15}H_{16}O_5$. Calculated: C 65.2; H 5.8%; M 276.

Ethyl ester of α-(2-phenyl-5-methoxybenzofuroyl-3)acetic Acid (II) was prepared in the same way as compound I; yield 80.2%. Found: C 71.0; H 5.4%; $M^{+\cdot}$ 338. $C_{20}H_{18}O_5$. Calculated 71.0; H 5.4%; M 338.

β-(2-Methyl-5-methoxybenzofuryl-3)propionic Acid (III). To zinc amalgam, obtained from 7 g of zinc dust and 0.7 g of mercuric chloride, was added 30 ml of acetic acid and 13 ml of concentrated hydrochloric acid, followed by a solution of 2.76 g (10 mmoles) of compound I in 35 ml of acetic acid. The reaction mixture was left to stand at room temperature for 2 days. The reduction was completed by heating for 1 h with 10 ml of concentrated hydrochloric acid. The solution was decanted from the zinc amalgam, poured into water, and the oil which separated extracted with chloroform. The chloroform layer was separated and chromatographed on a KSK column (chloroform). A yield of 1.36 g (58.2%) of III with mp 209-211°C (from methanol) was obtained. Found: C 66.6; H 5.7%; $M^{+\cdot}$ 234. $C_{13}H_{14}O_4$. Calculated: C 66.6; H 6.0%; M 234.

Ethyl Ester of β-(2-Methyl-5-methoxybenzofuryl-3)-β-hydroxypropionic Acid (IV). A solution of 0.37g (10 mmoles) of sodium borohydride in 4 ml of water was slowly added (30 minutes) to a stirred solution of 2.76 g (10 mmoles) of compound I in 10 ml of dioxane at 40-50°C. The reaction mixture was then refluxed for 2.5 h, cooled, and neutralized with 3 ml of 2N sulfuric acid. The oily product was extracted with chloroform. The chloroform layer was separated and chromatographed on a KSK column (chloroform). The first fraction was collected and yielded 0.9g of compound IV. Found: $M^{+\cdot}$ 278. Calculated: M 278. Compound IV was used for subsequent reactions without further purification.

Ethyl Ester of β-(2-Phenyl-5-methoxybenzofuryl-3)-β-hydroxypropionic Acid (V). A solution of 0.42 g (11 mmoles) of sodium borohydride in 4 ml of water was slowly added (25

min) to a stirred solution of 3.7 g (11 mmoles) of compound II in 10 ml of dioxane at 40-50°C. The reaction mixture was refluxed for 2 h, cooled, and neutralized with 3 ml of 2N sulfuric acid. The oily product was extracted with chloroform. The chloroform layer was separated and chromatographed on a KSK column (chloroform) to give 0.64 g of compound V. Found: $M^{+\cdot}$ 340. Calculated: M 340. Compound V was used for subsequent reactions without further purification.

Ethyl Ester of β-(2-phenyl-5-methoxybenzofuryl-3)acrylic acid (VI). A solution of 0.64 g (1.88 mmoles) of compound IV in 5 ml of acetic acid containing 2 drops of concentrated sulfuric acid was refluxed for 1 h. The reaction mixture was cooled, water was added, and the precipitated material filtered off and chromatographed on a KSK column (chloroform). Yield, 0.35 g (58%), mp 150-152°C (from a mixture of chloroform and petroleum ether). Found: C 74.2; H 5.2%; $M^{+\cdot}$ 322. $C_{20}H_{18}O_4$. Calculated: C 74.5; H 5.6%; M 322.

3-(2'-Methyl-5'-methoxybenzofuryl-3')isoxazoline-Δ^2-one-5(VII). A solution of 2.76 g (10 mmoles) of compound I in 30 ml of 80% alcohol was refluxed for 3 h with 2.1 g (30 mmoles) of hydroxylamine hydrochloride and 4.1 g (30 mmoles) of sodium acetate. The reaction mixture was cooled, and diluted with 3 volumes of water. The resulting precipitate was separated, washed with water, dried, and recrystallized from ethyl acetate to give 1.7 g (69.2%), mp 196-197°C (decomp.). Found: C 63.9; H 4.5; N 5.7%; $M^{+\cdot}$ 245. $C_{13}H_{11}NO_4$. Calculated: 63.7, H 4.5; N 5.7%; M 245.

Ethyl Ester of β-carbethoxy-β-(2-methyl-5-methoxybenzofuroyl-3)propionic acid (VIII). To a solution of sodium ethoxide, obtained from 0.23 g of sodium and 10 ml of ethyl alcohol, was added 2.76 g (10 mmoles) of compound I, followed by 1.67 g (10 mmoles) of ethyl bromoacetate. The reaction mixture was allowed to stand at room temperature for 1 h, and then refluxed for 1 h. The sodium bromide was filtered off, the solvent evaporated, and the residual oil dissolved in chloroform and chromatographed on a KSK column (chloroform). A yield of 3.3 g of compound VIII was obtained. Found: $M^{+\cdot}$ 362. Calculated: M 362. Compound VIII was used for subsequent reactions without further purification.

Ethyl Ester of β-Carbethoxy-β-(2-methyl-5-methoxybenzofuroyl-3)propionic Acid (IX). For this reaction, 2.5 g (7.4 mmoles) of compound II and 1.24 g (7.4 mmoles) of ethyl bromoacetate were used. The synthesis was carried out under the same conditions as those used for the preparation of compound VIII, and yielded 3.2 g of compound IX. Found: M^+ 424. Calculated: M 424. Compound IX was used for subsequent reactions without further purification.

Ethyl Ester of β-(2-Methyl-5-methoxybenzofuroyl-3)propionic Acid (X). A solution of 3 g (8.3 mmoles) of compound VIII in 10 ml of ethyl alcohol was refluxed for 17 h with 7 ml of 12% hydrochloric acid. The precipitated material was filtered off and recrystallized from methanol to give 1.1 g (45.6%), mp 79-80°C. Found: C 66.6; H 6.2%; $M^{+\cdot}$ 290. $C_{16}H_{18}O_5$. Calculated: C 66.2; H 6.2%; M 290.

Ethyl Ester of β-(2-Phenyl-5-methoxybenzofuroyl-3)propionic acid (XI). Using the same conditions used for the synthesis of compound X, 3.2 g (7.5 mmoles) of compound IX gave 1.9 g of compound XI. Found: M^+ 352. Calculated: M 352. Compound XI was used for subsequent reactions without further purification.

β-(2-Methyl-5-methoxybenzofuroyl-3)propionic Acid (XII). A solution of 2.08 g (5.75 mmoles) of compound VIII in 10 ml of glacial acetic acid containing a catalytic quantity of concentrated sulfuric acid was refluxed for 8.5 h. The reaction mixture was cooled, diluted with water, and the precipitated material recrystallized from ethyl acetate to give 0.35 g (31%) of XII with mp 167-168°C. Found: C 64.1%; H 5.5%; M^+ 262. $C_{14}H_{15}O_5$. Calculated: C 64.1; H 5.4%; M 262.

Oxime of Ethyl β-(2-Methyl-5-methoxybenzofuroyl-3)propionate (XIII). A solution of 0.87 g (3 mmoles) of compound X in 10 ml of 80% alcohol was refluxed for 3.5 h with 0.7 g (10 mmoles) of hydroxylamine hydrochloride and 1.4 g (10 mmoles) of sodium acetate. The reaction mixture was diluted with water, and the oil which separated was extracted with chloroform and chromatographed on a KSK column (chloroform). The second fraction was collected and yielded 0.56 g of compound XIII. Found: M^+ 305. Calculated: M 305.

Thiosemicarbazone of Ethyl β-(2-methyl-5-methoxybenzofuroyl-3)propionate (XIV). A solution of 0.87 g (3 mmoles) of compound X in 10 ml of 80% of alcohol was refluxed for 3 h with 0.39 g (3 mmoles) of thiosemicarbazide hydrochloride. The reaction mixture was diluted with water, and the oil which separated was extracted with chloroform and

chromatographed on a KSK column (chloroform). The second fraction was collected and yielded 0.63 g (57.7%). Found: C 56.2; H 5.7%; $M^{+\cdot}$ 363. $C_{17}H_{21}N_3O_4S$. Calculated: C 56.2; H 5.8%; M 363.

γ-(2-Methyl-5-methoxybenzofuryl-3)butyric acid (XV) was prepared in the same way as compound III; yield 67%, mp 79-81°C. Found: C 67.8; H 6.5%; $M^{+\cdot}$ 248. $C_{14}H_{16}O_4$. Calculated: C 67.7; H 6.5%; M 248.

Lactone of γ-(2-methyl-5-methoxybenzofuryl-3)-γ-hydroxybutyric acid (XVI) was obtained from compound X, using the same conditions as for the preparation of compound IV, in 50.4% yield, mp 116-117°C (from methanol). Found: C 62.2; H 5.5%; $M^{+\cdot}$ 246. $C_{14}H_{14}O_4$. Calculated: C 68.3; H 5.7%; M 246.

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DIPOLAR ADDITION OF DIAZOMETHANE TO 5-METHYLENE-1,3-DIOXOLAN-4-ONE

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The reactions of 1-pyrazoline-3-spiro-4'-(1',3'-dioxolan-5'-one) were studied; this compound is the product of the 1,3-dipolar addition of diazomethane to 5-methylene-1,3-dioxolan-4-one. Depending on the conditions, thermolysis of the spiro compounds proceeds either with destruction of the pyrazoline ring, or with cleavage of the dioxolane ring, followed by rearrangement to give 1(2)-hydroxymethyl-3(5)-pyrazolecarboxylic acid.

The formation of a cyclic compound by the 1,3-dipolar addition of a diazoalkane addend to a vinylidene compound, in which one carbon atom is substituted with two groups with opposing mesomeric effects, proceeds readily [1, 2].

Of interest is the dipolar addition to 5-methylene-1,3-dioxolan-4-one (I) which we reported earlier [3]; in this compound, the gem-substituents at the carbon–carbon double bond are component parts of a heterocyclic ring, and exert identical I- and opposite M-effects.

The reaction of diazomethane with compound I proceeds smoothly even at room temperature. The first product of cyclization is 1-pyrazoline-3-spiro-4'-(1', 3'-dioxolan-5'-one) (II); the structure of this compound, which is obtained in high yield, was confirmed by elemental analysis and infrared spectroscopic data. It is known that in the formation of 3,3-disubstituted pyrazolines, the N=N bond is usually retained [1, 2, 4]. The infrared spectrum of the spirane II shows absorption due to stretching vibrations at 1565 cm^{-1} (N=N) [5] and at 1810 cm^{-1} (C=C) [6], while no absorption is seen in the region 3270-3305 cm^{-1} (NH) [5].

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