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The synthesis of $2-(\beta$ -aminoethyl)-5-methoxybenzofuran was accomplished by two different methods.

Since $3-(\beta$ -aminoethyl)-5-methoxybenzofuran displays interesting pharmacological properties [1-3], it seemed of interest to synthesize its isomer $-2-(\beta$ -aminoethyl)-5-methoxybenzofuran. 5-Methoxybenzo-furan-3-carboxylic acid (II), which was obtained from $3-(\omega$ -bromoacetyl)-5-methoxybenzofuran through a step involving 1-(5-methoxy-3-benzofuracyl)pyridinium bromide (I) [4] via the following scheme, was used as the starting compound:



The IR spectrum of II at $2800-3135 \text{ cm}^{-1}$ contains a number of bands of low intensity that belong to the vibrations of the aromatic C-H bonds and a band at 1680 cm^{-1} , which is due to vibrations of a carbonyl group conjugated with the benzofuran ring. The UV spectrum of II contains three absorption maxima at 228, 252, and 298 nm. Similar absorption bands were also observed in the spectrum of 2-methyl-3-ethoxy-carbonyl-5-methoxybenzofuran [5].

Decarboxylation of acid II gave 5-methoxybenzofuran (III), and Vilsmeier formylation of III gave 2formyl-5-methoxybenzofuran (IV). $2-(\beta$ -Nitrovinyl)-5-methoxybenzofuran (V), which was obtained by the action of nitromethane on IV, was reduced with lithium aluminum hydride to $2-(\beta$ -aminoethyl)-5-methoxybenzofuran (VI).



In connection with the fact that the signals of the aromatic protons in the PMR spectrum of IV did not make it possible to unambiguously interpret the position of the aldehyde group, for definitive elucidation of the structure of VI, we synthesized $2-(\beta$ -aminoethyl)-5-methoxybenzofuran from the known 5-methoxybenzofuran-2-carboxylic acid via the scheme

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The identical character of samples of VI obtained by the two different paths is confirmed by the absence of a depression of the melting point of a mixture of the samples and by thin-layer chromatography.

EXPERIMENTAL

The PMR spectrum of a chloroform solution was recorded with a JNM-4H-100 spectrometer with an operating frequency of 100 MHz and with hexamethyldisiloxane as the internal standard. The IR spectra of mineral oil suspensions were recorded with a UR-10 spectrophotometer. The UV spectra of alcohol solutions were recorded with a Unicam SP-800 spectrophotometer. The thin-layer chromatography was carried out on Silufol (UV-254) with separation in chloroform saturated with ammonia.

<u>1-(5-Methoxy-3-benzofuracyl)pyridinium Bromide (I)</u>. A 0.6-g (7.4 mmole) sample of dry pyridine was added to an ice-cooled solution of 2 g (7.4 mmole) of 3-(ω -bromoacetyl)-5-methoxybenzofuran [6] in 10 ml of dry ether, and the solution was allowed to stand at room temperature for 2 days. The resulting precipitate was removed by filtration and washed with dry ether to give 1.9 g (74%) of I with mp 215-216° (from absolute alcohol). Found: C 54.8; H 4.2%. C₁₆H₁₄BrNO₃. Calculated: C 55.1; H 4.0%.

<u>5-Methoxybenzofuran-3-carboxylic Acid (II)</u>. A 2-ml sample of 10 N sodium hydroxide was added to a solution of 1 g (2.9 g mmole) of I in 50 ml of 80% alcohol, and the mixture was allowed to stand at room temperature for 24 h. It was then cooled and treated with 3.5 ml of 12 N hydrochloric acid, and the resulting precipitate was removed by filtration and washed with water until the washings were neutral to give 0.5 g (91%) of II with mp 186-187° (from acetic acid). Found: C 62.4; H 4.5%. $C_{10}H_8O_4$. Calculated: C 62.5; H 4.2%. IR spectrum: 1680 cm⁻¹ (C = O). UV spectrum, λ_{max} , nm (log ε): 228 (3.73), 252 (3.73), 296 (3.60).

<u>5-Methoxybenzofuran (III)</u>. A mixture of 1 g (5.2 mmole) of II and 0.1 g of copper powder in 10 ml of quinoline was refluxed for 30 min, cooled, and treated with 100 ml of ether. The copper was removed by filtration, and the ether solution was washed with 2 N hydrochloric acid and water. The ether extract was dried with calcium chloride, and the solvent was removed by distillation to give 0.6 g (78%) of III with mp $32-33^{\circ}$ (mp 32° [7]).

2-Formyl-5-methoxybenzofuran (IV). A 13-g (84 mmole) sample of phosphorus oxychloride was added to an ice-cooled mixture of 11.2 g (79 mmole) of III and 15 g (200 mmole) of anhydrous dimethylformamide (DMF) in small portions in the course of 30 min, after which the mixture was refluxed on a water bath for 5 h. Another 5 g (69 mmole) of DMF and 4 g (26 mmole) of phosphorus oxychloride were added to the cooled mixture, and it was again refluxed for 5 h. The mixture was then cooled and neutralized with aqueous sodium bicarbonate solution, and the product was extracted with ether. The extract was washed with sodium carbonate solution and water, and dried with sodium sulfate. The ether was removed by distillation, and the residue was vacuum-distilled to give 5 g (38%) of IV with bp 152-153° (3.5 mm) and mp 64° (from petroleum ether). Found: C 68.3; H 4.6%. $C_{10}H_8O_3$. Calculated: C 68.2; H 4.6%. IR spectrum (KBr): 1685 cm⁻¹ (C = O). UV spectrum, λ_{max} , nm (log ε): 220 (4.11), 293 (4.30), 337 shoulder (3.76). PMR spectrum (CCl₄), δ , ppm: 3.78 (s), 6.94-7.41 (m), 9.77 (s).

 $2-(\beta-\text{Nitrovinyl})-5-\text{methoxybenzofuran (V)}$. A mixture of 2.8 g (16 mmole) of IV, 24 ml of nitromethane, and 1.2 g of ammonium acetate was heated on a boiling-water bath for 30 min, after which the solvent was removed by distillation until the volume was one-third of the original volume. The residue was cooled, and the precipitated crystals were removed by filtration, washed with 50% alcohol, and dried to give 1.9 g (55%) of V with mp 174-176° (from cyclohexane-absolute alcohol). Found: C 60.1; H 4.1; N 6.1%. C₁₁H₈NO₄. Calculated: C 60.3; H 4.1; N 6.4%.

<u>2-Diazoacetyl-5-methoxybenzofuran (VII)</u>. A suspension of 1 g (5.2 mmole) of 5-methoxybenzofuran-2-carboxylic acid [7] and 0.9 ml of thionyl chloride in 10 ml of anhydrous dioxane was heated at $50-60^{\circ}$ for 1.5 h and then refluxed for 2 h. The solvent and excess thionyl chloride were removed by vacuum distillation, dry ether was added to the residue, and the mixture was filtered. The filtrate was added dropwise to an ice-cooled ether solution of 0.6 g (0.01 mole) of diazomethane, and the reaction mixture was allowed to stand overnight. The ether was removed by distillation to give 1.45 g (quantitative yield) of VII with mp $103-104^{\circ}$ (from cyclohexane). Found: C 61.0; H 3.8%. C₁₁H₈N₂O₃. Calculated: C 61.1; H 3.7%.

<u>5-Methoxy-2-benzofurylacetamide (VII)</u>. A solution of 0.6 g (2.8 mmole) of VII in 10 ml of dioxane was added dropwise to a heated (to 65°) solution of 0.88 g (5 mmole) of silver nitrate in 8 ml of concentrated ammonium hydroxide, and the mixture was heated on a boiling-water bath for 1 h. The hot solution was filtered away from the sludge, and the filtrate was diluted with water and allowed to stand in a refrigerator overnight. The precipitate was removed by filtration and dried to give 0.24 g (42%) of VIII with mp 148-150° (from benzene). Found: C 64.4; H 5.4; N 6.6%. $C_{11}H_{11}NO_3$. Calculated: C 64.4; H 5.4; N 6.8%.

<u>2-(β -Aminoethyl)-5-methoxybenzofuran (VI)</u> Hydrochloride. A. A suspension of 1.3 g (6 mmole) of V in 30 ml of dry ether was added in small portions to 2.5 g (66 mmole) of lithium aluminum hydride in 60 ml of dry ether, and the mixture was refluxed for 6 h. The excess lithium aluminum hydride was decomposed by adding water to the cooled mixture, the mixture was filtered, and the filtrate was dried with sodium sulfate. Two thirds of the solvent was removed by distillation, and a solution of dry hydrogen chloride in ether was added to the residue to give 0.9 g (67%) of the hydrochloride of VI with mp 237-238° (from absolute alcohol) and R_f 0.46. Found: C 58.2; H 6.1; N 6.2%. $C_{11}H_{13}NO_2 \cdot HCI$. Calculated: C 58.0; H 6.2; N 6.1%.

B. A suspension of 0.9 g (4.4 mmole) of VIII in 10 ml of dry ether was added dropwise to 0.6 g (0.016 mole) of lithium aluminum hydride in 10 ml of dry ether, after which the mixture was refluxed for 3 h. The usual workup gave 0.25 g (25%) of the hydrochloride of VI with mp 238° and R_f 0.46. No melting-point depression was observed for a mixture of this product with a sample of VI obtained via the first method.

LITERATURE CITED

- 1. F. A. Trofimov, T. I. Mukhanova, A. N. Grinev, and K. S. Shadurskii, Khim.-Farmats. Zh., 11, 9 (1968).
- 2. T. Yu. Il'yuchenok, L. M. Frigidova, A. A. Maksimenko, and F. A. Trofimov, Farmakol. i Toksikol., <u>5</u>, 576 (1970).
- 3. F. A. Trofimov, T. I. Mukhanova, N. G. Tsyshkova, A. N. Grinev, and K. S. Shadurskii, Khim.-Farmats. Zh., 9, 14 (1967).
- 4. F. A. Trofimov, T. I. Mukhanova, A. N. Grinev, and V. I. Shvedov, USSR Author's Certificate No. 242,913 (1969); Byul. Izobr., No. 16, (1969).
- 5. C. A. Qiza and R. L. Hinman, J. Org. Chem., 29, 1457 (1964).
- 6. F. A. Trofimov, T. I. Mukhanova, A. N. Grinev, and V. I. Shvedov, Zh. Organ. Khim., 3, 2185 (1967).
- 7. S. Tanaka, J. Am. Chem. Soc., 73, 872 (1951).