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FORMYLATION OF 2-PHENYL- AND 3-PHENYL-5-HYDROXYBENZOFURAN DERIVATIVES

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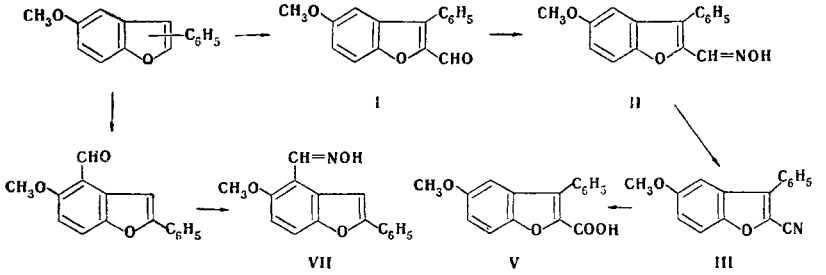
UDC 547.727.728:543.422.25

The Vilsmeier formylation of 2-phenyl- and 3-phenyl-5-hydroxybenzofuran derivatives was studied. It is shown that 2-phenyl-5-methoxybenzofuran is formylated in the 4 position, whereas 3-phenyl-5-methoxybenzofuran is formylated in the 2 position.

In a previous study of electrophilic substitution reactions it was noted that substituents enter primarily the benzene ring in the bromination and nitration of 2(3)-phenyl-5(6)-hydroxybenzofurans. The acetoxy derivatives of the same benzofurans are brominated and nitrated only in the free position of the furan ring [1]. Continuing our investigation of electrophilic substitution reactions in the benzofuran series, we studied the Vilsmeier formylation of 2-phenyl- and 3-phenyl-5-hydroxybenzofuran derivatives. It was found that in the reaction of phosphorus oxychloride and dimethylformamide (DMF) with 3-phenyl-5-methoxybenzofuran [2] the formyl group enters the 2 position of the molecule to give 2-formyl-3-phenyl-5-methoxybenzofuran (I) in 98% yield. Aldehyde I is converted to the corresponding oxime (II) on treatment with hydroxylamine hydrochloride. 2-Cayno-3-phenyl-5-methoxybenzofuran (III) was obtained by the action of acetic anhydride on II, and 2-formyl-3-phenyl-5-methoxybenzofuran O-acetyloxime (IV) was obtained as a side product. Alkaline hydrolysis of III gives 3-phenyl-5-methoxybenzofuran-2-carboxylic acid (V). The thiosemicarbazone (VI) was obtained for aldehyde I.



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The formylation of 2-phenyl-5-methoxybenzofuran [2] gives a mixture of substances, treatment of which with hydroxylamine and thiosemicarbazide hydrochlorides gave the oxime VII and thiosemicarbazone (VIII), respectively, of 2-phenyl-4-formyl-5-methoxybenzofuran.

2-Phenyl-5-acetoxybenzofuran [1] does not react with the Vilsmeier complex.

The structure of the compounds were established by PMR spectroscopy. The PMR spectrum of I contains a quartet ($J_1 = 8.8$ Hz, $J_2 = 2.5$ Hz) and a doublet ($J = 2.5$ Hz) at δ 7.03 and 7.20 ppm, respectively, which correspond to the 6-H and 4-H protons. The structure of these signals indicate that the formyl group enters the 2 position of the benzofuran ring. The 4-H signal is overlapped by the multiplet of the phenyl group. The presence in the spectrum of VII of two doublets with $J = 9.0$ Hz, which correspond to coupling of the ortho protons, proves that substitution takes place in the 4 position.

EXPERIMENTAL

The PMR spectra of deuteroacetone solutions of the compounds were recorded with a JEOL JNM-4H-100 spectrometer with tetramethylsilane as the internal standard.

2-Formyl-3-phenyl-5-methoxybenzofuran (I). A 3.75-g (0.0245 mole) sample of phosphorus oxychloride was added gradually at 20° to a mixture of 5 g (0.0233 mole) of 3-phenyl-5-methoxybenzofuran and 1.75 g (0.024 mole) of DMF, after which the temperature was raised to 100°, and the mixture was stirred at this temperature for 2 h. The complex was decomposed by heating the reaction mixture for 30 min with 50 ml of a saturated sodium acetate solution. The mixture was then cooled, and the precipitate was separated and recrystallized from benzene–petroleum ether to give I with mp 161-163° in 98% yield. Found: C 75.6; H 4.8%. $C_{16}H_{12}O_3$. Calculated: C 76.1; H 4.8%.

2-Formyl-3-phenyl-5-methoxybenzofuran Oxime (II). A solution of 1.26 g (5 mmole) of I in a mixture of 17 ml of ethanol and 33 ml of pyridine was refluxed for 2 h with 1.77 g (25 mmole) of hydroxylamine hydrochloride. The bulk of the solvent was removed by vacuum distillation, the residue was poured into water, and the precipitate was removed by filtration to give II, with mp 188-189° (from alcohol), in 96% yield. Found: %: C 72.0; H 4.9%. $C_{16}H_{13}NO_3$. Calculated: C 71.9; H 4.9%.

2-Cyano-3-phenyl-5-methoxybenzofuran (III). A solution of 5.34 g (0.02 mole) of II in 30 ml of acetic anhydride was refluxed for 1 h, after which it was poured into 200 ml of water. The resulting precipitate was removed by filtration, dried, dissolved in chloroform, and chromatographed with a column filled with KSK silica gel. The first fraction was collected, the solvent was evaporated, and the residue was crystallized to give 1.6 g (32%) of III with mp 137-138° (from alcohol). Found: C 77.0; H 4.4; N 5.6%. $C_{16}H_{11}NO_2$. Calculated: C 77.1; H 4.4; N 5.6%.

The solvent was evaporated from the second fraction, and the residue was crystallized to give 3.4 g (57%) of 2-formyl-3-phenyl-5-methoxybenzofuran O-acetyloxime (IV) with mp 139-141° (from alcohol). Found: C 70.0; H 4.9; N 4.6%. $C_{18}H_{15}NO_4$. Calculated: C 69.9; H 4.9; N 4.5%.

3-Phenyl-5-methoxybenzofuran-2-carboxylic Acid (V). A solution of 1.68 g (6.75 mmole) of III in 25 ml of alcohol was refluxed for 8 h with 1.3 g (23.2 mmole) of potassium hydroxide in 1.6 ml of water, after which it was poured into 100 ml of water. The resulting precipitate of unchanged nitrile III was extracted with ether. The aqueous layer was acidified with hydrochloric acid, and the precipitate was removed by filtration to give 1.4 g (77.5%) of a product with mp 202-204° (from methanol). Found: C 71.5; H 4.5%. $C_{16}H_{12}O_4$. Calculated: C 71.6; H 4.5%.

2-Formyl-3-phenyl-5-methoxybenzofuran Thiosemicarbazone (VI). A solution of 1.26 g (5 mmole) of I in 15 ml of absolute alcohol was refluxed for 2 h with 0.64 g (5 mmole) of thiosemicarbazide hydrochloride in 3 ml of water. The precipitate was removed by filtration to give 1.1 g (68%) of the thiosemicarbazone with mp 222-223° (from acetic acid). Found: C 62.6; H 4.6; S 9.9%. $C_{17}H_{15}N_3SO_2$. Calculated: C 62.7; H 4.7; S 9.9%.

2-Phenyl-4-formyl-5-methoxybenzofuran Oxime (VII). A mixture of products, from which the aldehyde was isolated in the form of the oxime, was obtained from 5 g (0.0224 mole) of 2-phenyl-5-methoxybenzofuran under the conditions of the synthesis of I. The yield of VII, with mp 177-178° (from methanol), was 4.5 g (75%). Found: C 71.5; H 4.9; N 5.2%. $C_{16}H_{13}NO_3$. Calculated: C 71.9; H 4.9; N 5.2%.

2-Phenyl-4-formyl-5-methoxybenzofuran Thiosemicarbazone (VIII). A mixture of products, from which the aldehyde was isolated in the form of the thiosemicarbazone, was obtained from 5 g (0.0224 mole) of 2-phenyl-5-methoxybenzofuran under the conditions of the synthesis of I. The yield of VIII, with mp 206-207°

(dec., from acetic acid), was 4.5 g (61.5%). Found: C 63.2; H 4.6; N 12.7; S 9.9%. $C_{17}H_{15}N_3SO_2$. Calculated: C 62.8; H 4.6; N 12.9; S 9.9%.

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BASICITIES AND TRANSFORMATIONS OF PYRYLIUM AND PYRIDINIUM SALTS CONTAINING p-AMINOPHENYL SUBSTITUENTS

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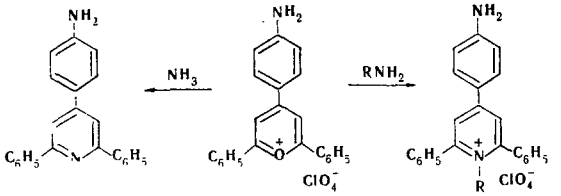
UDC 547.813'821.3'828:542.951.7

On the basis of the measured basicity constants of pyrylium and pyridinium salts containing p-aminophenyl substituents it is shown that the positive charge in the pyrylium cation is considerably higher than in the pyridinium cation. The σ constants of the pyrylium and pyridinium substituents, which show that the magnitude of the electronic effect of the pyrylium ring is considerably higher than that of the pyrydinium ring, were calculated. The reaction of the indicated pyrylium salts with some electrophilic and nucleophilic reagents was examined.

Pyrylium salts containing a p-aminophenyl group are interesting subjects for investigation because of the presence of two reactive centers (the amino group and the carbon atom in the α position of the pyrylium ring). The literature does not contain data on p-aminophenylpyrydinium perchlorates. We obtained 2,6-diphenyl-4-(p-aminophenyl)pyridine (II) and its N-substituted perchlorates (IV and V) from 2,6-diphenyl-4-(p-aminophenyl)pyrylium perchlorate (I) [1]:



II I III–V

III R = H; IV R = CH_3; V R = C_6H_5

The basicity constants in absolute acetonitrile were measured for these compounds and for 2,6-diphenyl-4-(p-aminophenyl)pyridinium (III) and 4-(p-aminophenyl)flavylium (VI) [2] perchlorates and 2,4,6-triphenylpyridine (VII) (see Table 1). It is apparent from a comparison of the pK_a values of VII and II that the amino group, as an electron-donor substituent, raises the basicity of 2,4,6-triphenylpyridine by 1.34 pK_a units; as one should have expected, the N-methyl substituent in pyridinium salt IV is a weak electron donor, and the N-phenyl residue in salt V displays weak acceptor properties.

These data also show that the positive charge in pyrylium cation I is considerably higher than in the corresponding pyridinium ion III, since the basicity of the NH_2 group in salt I is reduced by two orders of magnitude. If one of the two phenyl substituents is condensed with the pyrylium ring (salt VI), it partially compensates the charge of the latter, and this raises the basicity of the amino group by a whole order of magnitude.

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1025-1028, August, 1976. Original article submitted April 28, 1975; revision submitted January 19, 1976.