at the various positions. Inclusion of the paired interactions of the heteroatoms makes it possible to improve the accuracy of the calculation. The proton affinities of the aminoheterc cycles decreases progressively in the series of 4-NH, 2-NH, 4-O, and 2-O derivatives. During aza substitution the β positions are equivalent, while the α positions are nonequivalent, and substitution at the formal double bond has an effect approximately twice as large as substitution at a single bond.

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ELECTROPHILIC SUBSTITUTION REACTIONS OF 3-ACETYLAMINO-5-METHOXYBENZOFURAN

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The formylation, aminomethylation, azo coupling, and bromination reactions of 3-acetylamino-5-methoxybenzofuran have been investigated.

We have previously developed two methods for the preparation of 3-acetylaminobenzofurans with an unsubstituted 2 position; one of these methods is based on the Schmidt rearrangement of 3-(azidoacetyl)benzofurans [1], whereas the other is based on the decarboxylation of 3-acetylaminobenzofuran-2-carboxylic acids [2, 3]. The literature does not contain any reports concerning the chemical properties of these substances.

It was of interest to us to examine the effect of the acetylamino group on electrophilic substitution reactions and also, more importantly, to study the feasibility of using these compounds in Mannich and azo coupling reactions; benzofuran itself is known not to undergo these reactions. It was anticipated that the acetylamino group would activate the 2-position with respect to electrophilic reagents due to resonance participation of the unshared pair of electrons on the nitrogen atom. In the present paper we demonstrate that formylation, aminomethylation, bromination, and azo coupling reactions are directed exclusively to the 2-position of the heterocycle.

The Villsmeier reaction occurs at 20°C and results in the formation of 3-acetylamino-2-formylbenzofuran (II) in 50% yield. The position of the formyl group was established on the basis of formation of a pyrimidine ring upon treatment of the formylation product II with ammonium acetate; this resulted in the formation of 2-methyl-8-methoxybenzofuro[3,2 d]pyrimidine (III). The IR spectrum of compound II contains absorption bands due to the aldehyde (1710 cm^{-1}) and amide (1580 and 1650 cm^{-1}) groups; these bands are not present in the spectrum of compound III. The UV spectral characteristics of this compound and its comparison with the spectral data of other structurally analogous benzofuro[3,2-d]pyrimidines [4] confirmed the structure

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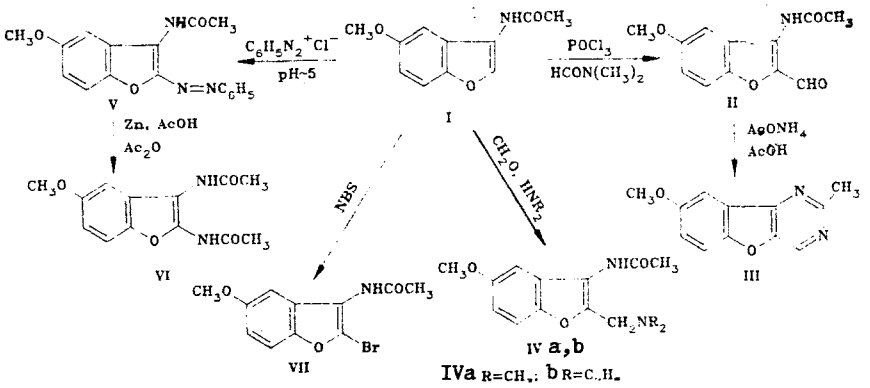

Aminomethylation proceeds without difficulty. The Mannich bases IVa and b could be prepared both under classical conditions, upon treatment of benzofuran I with a secondary amine and formaldehyde in acetic acid, as well as by refluxing it with bis(dimethylamino)methane in dioxane.

The effect of the 3-acetylamino group are also noticeable in reactions with weak electrophiles such as phenyldiazonium chloride, which gave 3-acetylamino-5-methoxy-2-phenylazobenzofuran (V) in 70% yield. The chemistry of benzofuran does not contain any other examples of azo coupling or aminomethylation reactions occurring in the 2-position. An acetyl heteroanalog of o-phenylenediamine, 2,3-di(acetylamino)-5-methoxybenzofuran (VI), was obtained via reductive acylation of compound V.

Bromination of compound I with N-bromosuccinimide led to the formation of 3-acetylamino-2-bromo-5-methoxybenzofuran (VII) in excellent yield. The positions of the substituents in compounds IV, V, and VII was established using PMR spectroscopy, which clearly showed the disappearance of the signal due to the proton in the 2-position (8.28 ppm) and the retention of the multiplet due to the three aromatic protons in the 6.8-7.2 ppm region.

In conclusion, the present studies have revealed that the presence of a 3-acetylamino group on benzofuran significantly increases the reactivity of the 2-position with respect to electrophilic reagents.

EXPERIMENTAL

IR spectra were recorded for KBr pellets or for chloroform solutions on a UR-10 spectrophotometer. UV spectra of alcohol solutions were obtained on a Unicam 8000 spectrophotometer PMR spectra were taken on JNM-4H-100 and C-60H spectrometers versus HMDS as internal standard

3-Acetylamino-5-methoxy-2-formylbenzofuran (II). A solution of 2 g (10 mmole) of 3-acetylamino-5-methoxybenzofuran (I) in 2 ml DMF was treated dropwise under ice cooling and with stirring with 1.6 g (10 mmole) of phosphorus oxychloride. Stirring was continued for 2 h at 20°C. The reaction mixture was poured into ice and the resulting crystals were filtered. Yield 1.1 g (50%), mp 192-193°C (from alcohol). IR spectrum: 1580, 1650 (amide I and II), 1710 (C=O), and 3290 cm^{-1} (N–H). Found: C 61.8; H 4.7; N 6.0%. $C_{12}H_{11}NO_4$. Calculated: C 61.8; H 4.7; H 6.0%.

2-Methyl-8-methoxybenzofuro[3,2-d]pyrimidine (III). A mixture of 1 g (4.3 mmole) of benzofuran II, 0.33 g (4.3 mmole) ammonium acetate, and 10 ml glacial acetic acid was refluxed for 1 h. The mixture was cooled and the solvent was evaporated under vacuum. The residue was recrystallized from carbon tetrachloride. Yield 0.8 g (87%), mp 117-117.5°C (from CCl_4). IR spectrum: 1600, 1620 cm^{-1} (C=N). UV spectrum, λ_{max} (log ε): 216 (4.48), 247 (4.13), 293 (4.40), and 340 nm (3.81). Found: C 67.6; H 5.1; N 13.7%. $C_{12}H_{10}N_2O_2$. Calculated: C 67.8; H 4.7; N 13.1%.

3-Acetylamino-2-dimethylaminomethyl-5-methoxybenzofuran (IVa). A solution of 1.5 g (7.5 mmole) of compound I in 4 ml absolute dioxane was treated with 1.05 ml (7.5 mmole) of bis(dimethylamino)methane and the mixture was refluxed for 2.5 h. The mixture was cooled and the solvent was evaporated under vacuum. The residue was recrystallized from propanol and then from carbon tetrachloride. Yield 1 g (53%), mp 134-135°C (from CCl_4). PMR spectrum ($CDCl_3$), δ: 2.0 (s, $COCH_3$); 2.17 [s, $(CH_3)_2$]; 3.42 (s, CH_2); 3.7 (s, OCH_3); 6.9-7.3 (m, H_{arom}): 8.11 ppm (br. s, N–H). Found: C 64.1; H 7.2; N 10.8%. $C_{14}H_{18}N_2O_3$. Calculated: C 64.1; H 6.9; N 10.6%.

3-Acetylamino-2-diethylaminomethyl-5-methoxybenzofuran (IVb). A mixture of 0.38 ml (5.8 mmole) of 40% aqueous formaldehyde, 7 ml acetic acid, and 0.36 g (5 mmole) of diethylamine was treated with 1 g (5 mmole) of compound I and the mixture was heated until everything dissolved. The mixture was allowed to stand overnight at 20°C. Workup involved dilution with sodium hydroxide solution to a mildly basic state. The resulting precipitate was removed by filtration. Yield 0.7 g (50%), mp 134-135°C (from ethyl acetate). Found: C 65.9; H 7.7; N 10.1%. $C_{16}H_{22}N_2O_3$. Calculated: C 66.2; H 7.6; N 9.7%.

3-Acetylamino-5-methoxy-2-phenylazobenzofuran (V). A solution of phenyldiazonium chloride, prepared from 2.2 g (24 mmole) aniline, 5.5 ml conc. HCl, 5 ml H_2O, and 1.66 g (24 mmole) sodium nitrite, was treated with 9 g sodium acetate while maintaining the temperature below 0°C. A solution of 4.1 g (20 mmole) of benzofuran I in 100 ml alcohol was added dropwise with stirring with the temperature maintained between 0-5°C. Stirring was continued for 1 h after completion of the reaction, and then the mixture was diluted with water and the precipitate was filtered. Yield 4.3 g (70%), mp 180-181°C (from hexane). PMR spectrum ($CDCl_3$): 2.28 (s, $COCH_3$), 3.8 (s, OCH_3), 6.93-7.80 ppm (m, H_{arom}). Found: C 65.9; H 5.1; N 13.5%. $C_{17}H_{15}N_3O_3$. Calculated: C 66.0; H 4.9; N 13.6%.

2,3-Di(acetylamino)-5-methoxybenzofuran (VI). A mixture of 3.1 g (10 mmole) phenylazobenzofuran V, 3 ml acetic anhydride, and 50 ml glacial acetic acid was heated to 60°C and 3.3 g (50 mmole) of zinc powder was added in portions. The reaction mixture was refluxed for 3.5 h with stirring. The mixture was cooled, poured into water, and filtered. The solution was than treated stepwise with 10-15% aqueous ammonia to a basic reaction point, and filtered. The filtrate was extracted with chloroform, dried with sodium sulfate, and evaporated to dryness. Yield 0.5 g (20%), mp 204-206°C (dec., from alcohol). IR spectrum: 1610, 1680, 1715 (C=O), 3225 cm^{-1} (N–H). Found: C 59.5; H 5.3; N 10.7%. $C_{13}H_{14}N_2O_4$. Calculated: C 59.5; H 5.3; N 10.6%.

3-Acetylamino-2-bromo-5-methoxybenzofuran (VII). A mixture of 0.5 g (2.4 mmole) compound I and 0.43 g (2.4 mmole) of N-bromosuccinimide in 10 ml benzene was refluxed 2 h. The precipitate was filtered and washed carefully with hot water. The product was recrystallized from benzene. Yield 0.5 g (73%), mp 161-162°C (from benzene). PMR spectrum (DMSO-D_6): 2.17 (s, $COCH_3$), 3.8 s (OCH_3), 6.9-7.4 (m, H_{arom}), 8.95 ppm (br. s, NH). Found: C 46.7; H 3.6; N 4.8%. $C_{11}H_{10}BrNO_3$. Calculated: C 46.5; H 3.5; N 4.9%.

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