SYNTHESIS OF DERIVATIVES OF 5-AZABENZOFURAN WITH FUNCTIONAL SUBSTITUTES IN POSITIONS 4 AND 7

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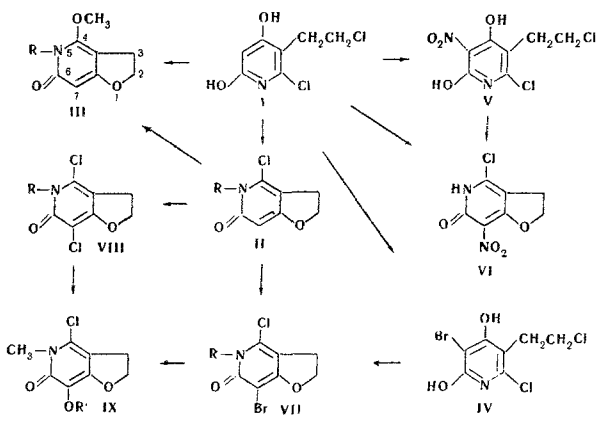
Methods for synthesizing derivatives of 5-azabenzofuran with functional substitutes in position 4 and 7 have been elaborated. The reactions of electrophilic substitution in position 7 have been studied.

An examination was made of the substitution of halogens in position 4 of derivatives of 5-azabenzofuran by the methoxy-group during the action of dimethyl sulfate in an aqueous alkali medium.

There are few syntheses of the derivatives of 5-azabenzofuran described in the literature [1–5], and almost all of these are concerned with the closure of the pyridine nucleus based on 2-(β-aminoethyl)furan according to the reaction of Bishler-Napiral'skii. By the above-mentioned method, it is not possible to obtain compounds with functional substitutes in position 4. In regard to the 7-substituted 5-azabenzofuran series, before the present communication only the lactone of 2, 4, 6-trioxy-5-carbethoxypyridyl-3-acetic acid [6] had been described.

By means of a previously elaborated general method of ring closure of the 3-(β-chloroethyl)-4-oxypyridines [7, 8], it was possible to obtain various derivatives of 5-azabenzofuran, including compounds containing functional substitutions in positions 4 and 7. Thus, for example, on ring closure of 2-chloro-3-(β-chlorethyl)-4, 6-dioxypyridine (I), the 4-chloro-derivative of 5-azabenzofuran, 4-chloro-6-oxo-2, 3-dihydro-5-azabenzofuran (IIa), was obtained, and when compounds I and IIa were treated with alkyl halides in the presense of potash, N-methyl- and N-ethylderivatives of compound II (IIb and IIc) [7] were obtained.

The interaction of compound I in aqueous alkali medium with dimethyl sulfate proceeded in a different manner in comparison with the alkyl halides. In addition to the cleavage of hydrogen



II, III, VII, VIII a R = H, b R = CH_3, c R = C_2H_5; IX a R' = H, b R' = CH_3, c R' = C_2H_5

chloride and the closure of the dihydrofuran ring, and also the alkylation of the α-oxypyridine group in this reaction, it was found unexpectedly that a methoxy group was introduced in place of the halogen into position 4 of the azabenzofuran nucleus. The final product of the transformations of compound I was found to be 4-methoxy-5-methyl-6-oxo-2, 3-dihydro-5-azabenzofuran (IIIb), the structure of which was confirmed by the PMR spectrum*. The presence of two triplets of CH_2 groups of the dihydrofuran nucleus at 3.08 and 4.66 ppm (J ~ 8Hz), a singlet signal of the proton at C_7 (σ, 5.34 ppm), and two singlets in three proton units each from N—CH_3 (3.42 ppm) and OCH_3 (3.89 ppm) groups was characteristic for the spectrum of compound IIIb. In the PMR spectrum of the corresponding 4-chloro-derivative (IIb) there are also two triplets of CH_2 groups (σ, 3.08 and 4.62 ppm, J ~ 8Hz), a proton singlet at C_7 (σ, 5.79 ppm) and only one signal of the CH_3 group at nitrogen (3.58 ppm).

The interaction between 4-chloro-5-ethyl-6-oxo-2, 3-dihydro-5-azabenzofuran (IIc) in aqueous alkali medium with dimethyl sulfate led to the formation of 4-methoxy-5-ethyl-6-oxo-2, 3-dihydro-5-azabenzofuran (IIIc) with a yield of 61.5%.

The formation of 4-methoxy-derivatives of azabenzofuran in the above-mentioned reaction is apparently associated with the substitution of the corresponding halogen atoms in compound I (or the product of its ring formation, IIa) under the action of alkali, and also in compound IIc by hydroxylation with subsequent methylation by dimethyl sulfate. Further experiments indicated that boiling of compound I in an aqueous-alkaline solution before addition of dimethyl sulfate, which assists saponification, increases the yield of the methoxy compound IIIb.

In order to introduce different functional groups into position 7 of the 5-azabenzofuran molecule, a study was made of the reaction of electrophilic substitution both for 2-chloro-3-(β-chloroethyl)-4, 6-dioxypyridine (I) and also for the corresponding 5-azabenzofuran compounds IIa–c). The interaction of compound I with bromine in acetic acid and also ni-

*The PMR spectrum was recorded in a JNM-4H-100(100 MHz) apparatus. The internal standard was TMS, and solvents were $CDCl_3$ and CF_3COOH. The IR spectrum was determined in a UR-10 recording spectrophotometer in the form of a paste in vaseline. UV spectra were recorded in an SF-4 spectrophotometer. The solvent was ethylaalcohol.

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tration with 33% nitric acid at room temperature in accordance with the stability of compound I in acid medium established previously [7] proceeded without closure of the dihydrofuran ring. The yields of 5-bromo- (IV) and 5-nitropyridine (V) derivatives were 71.5 and 48% respectively. It was found unexpectedly that, during the nitration of compound I by fuming nitric acid for 1 hr at 0° C, the process was accompanied by dehydrohalogenation with the formation of 4-chloro-6-oxo-7-nitro-2,3-dihydro-5-azabenzofuran (VI). Compound VI was also obtained with a yield of 87.5% during ring formation of the substituted 3-(β-chloroethyl)-4-oxy-5-nitropyridine (V) in alkaline medium. Ring formation of the 5-bromo-derivative (IV) proceeded in an analogous manner with a yield of 89%.

Unexpected results were obtained on prolonged boiling (8 hours) of 4-chloro-5-methyl-6-oxo-2,3-dihydro-5-azabenzofuran (IIb) with thionyl chloride. In this case chlorination of the pyridine nucleus was observed and 4,7-dichloro-5-methyl-6-oxo-2,3-dihydro-5-azabenzofuran (VIIIb) was isolated from the products of the reaction with a yield of 40%. One should note that the process of chlorination in the above-mentioned reaction is not associated with an impurity of sulfuryl chloride in the thionyl chloride, as purification of the original compounds guaranteed the absence of such an impurity, and heating of compound IIb with sulphuryl chloride under the same condition did not lead to the formation of compound VIIIb.

The above-mentioned reaction between compound IIb and thionyl chloride is of great preparative interest. Further experiments showed that the interaction of compound IIb with chlorine proceeds in a complex manner and chlorination in position 7 is accompanied by processes in which more profound changes in the molecule occur. Thus, for example, when compound IIb is treated with an equimolecular quantity of chlorine, 60% of the original compound IIb was reformed and a mixture of products of chlorination and oxidation which was very difficult to separate was obtained. The maximum yield of the 7-chloro-derivative of compound VIIIb (43%) was achieved when 50% excess chlorine was used. Further increase in the quantity of chlorine sharply decreased the yield because of the formation of a mixture of more oxides and chlorinated products. It was of interest to note that the process of bromination of compound IIb proceeds in a more simple manner, and the corresponding 7-bromo-derivative (VIIb) was obtained with a yield of 89%. A study of the chemical properties of the 4,7-dihalogen-derivatives VII and VIII showed that the halogen atoms in position 7 of these compounds are readily replaced by the alkoxy group on heating with alcoholic solutions of sodium hydroxide. Thus, for example, the interaction of compound VIIIb with a methanolic solution of alkali led to the formation of 4-chloro-5-methyl-6-oxo-7-methoxy-2,3-dihydro-5-azabenzofuran (IXb) with a yield of 60%, and the reaction between compound VIIIb and an alkali solution in ethyl alcohol led to formation of 4-chloro-5-methyl-6-oxo-7-ethoxy-2,3-dihydro-5-azabenzofuran (IX) with a yield of 48%. The formation of a single compound, IXb, from 4,7-dichloro- (VIIIb) and 4-chloro-7-bromoderivatives (VIIb) on heating with a methanolic solution of sodium hydroxide convincingly indicated that the alkoxyl group was situated at position 7. On treatment with 16% hydrochloric acid and heating to 100° C, the 7-alkoxy-derivatives (IXb and c) were readily saponified to 4-chloro-5-methyl-6-oxo-7-hydroxy-2,3-dihydro-5-azabenzofuran.

By comparing the PMR spectra of certain of the synthesized derivatives of 2,3-dihydro-5-azabenzofuran (IIb, IIIb, VIIa, VIIIb, IXa) and analogous 3-(β-chloroethyl)pyridines (V, VI) and also 2,4,6-trichloro-3-(β-chloroethyl)pyridine (X) [7], it is possible to note the differences in nature of triplets of CH_2—CH_2 groups for both classes of compounds. These differences indicated that for pyridine derivatives and for compounds of the 2,3-dihydro-5-azabenzofuran series the cleavage in the triplet consists of 6Hz and 8Hz*, respectively. In addition, in the transition from the pyridine derivatives V, VI, X to the dihydroazabenzofurans IIa, IIb, IIIb, VIIa, VIIIb, and IXa the difference between chemical displacements of protons of both CH_2 groups ($\Delta\delta$ protons at C_2 and C_3) increases from 0.5 to 1.51–1.64 ppm.

The observed features of the triplet signals are characteristic and may be used for grouping compounds on the basis of PMR spectra into the 3-(β-chloroethyl)pyridine series or the 2,3-dihydro-5-azabenzofuran series.

EXPERIMENTAL

4-Methoxy-5-ethyl-6-oxo-2,3-dihydro-5-azabenzofuran (IIIc). A 0.5 g (2.5 mM) quantity of compound IIc was dissolved in 10 ml of a 20% aqueous solution of sodium hydroxide (50 mM), and 1.5 ml (10 mM) dimethyl sulfate was added with mixing at room temperature. The reaction mixture was heated for 30 min in a water bath. Compound IIIc was extracted with benzene. Yield, 0.3 g (61.5%). Colorless, crystals, mp 94° (from benzene). Soluble in chloroform, alcohol and acetone. Less soluble in benzene, slightly soluble in ether and water. IR spectrum: 1674 cm^{-1} (CO—N). Found, %: C 61.23; H 6.54; N 6.96. Calculated for $C_{10}H_{13}NO_3$, %: C 61.53; H 6.67; N 7.18.

4-Methoxy-5-methyl-6-oxo-2,3-dihydro-5-benzofuran (IIIb). A 1.5 g (7.0 mM) quantity of compound I was boiled with 10 ml of 40% aqueous solution of sodium hydroxide (0.1 mole) for 2 hr. The solution was cooled to 50° C, and at this temperature 4 ml (24 mM) of dimethyl sulfate was added with mixing. The mixture was heated in a

*One should note that for the derivatives of 2,3-hydro-5-azabenzofuran studied cleavage of the lines in the triplets do not correspond to the constants of spin-spin interaction, as the systems examined relate to type AA'XX'. In this regard the values J presented for the above-mentioned compounds in the article represent only the characteristics of the signals.

water bath for 2 hr. After the solution was cooled, compound IIIb was extracted with chloroform. Yield was 0.3 g (23%). Colorless crystals, mp 162° C (from acetone). Soluble in alcohol, benzene, and chloroform. Slightly soluble in ether, acetone, and water. Found, %: C 59.68; H 6.33; N 7.60. Calculated for $C_8H_{11}NO_3$, %: C 59.67; H 6.08; N 7.73.

2-Chloro-3-(β-chloroethyl)-4, 6-dioxy-5-bromopyridine (IV). A 1.5 g (10 mm) quantity of bromine in 5 ml glacial acetic acid was added to a solution of 1 g (5 mM) of compound I in 50 ml glacial acetic acid cooled to 50° C. After standing overnight the reaction mixture was evaporated under vacuum. The residue was washed with ether. Yield, 1 g (71.5%).

Colorless crystals, mp 218–219° C (decomposed from benzene). Readily soluble in chloroform, less soluble in alcohol, benzene, and acetone, and slightly soluble in ether and water. PMR spectra: two triplets σ 3.20 and 3.71 ppm (J ~ 6Hz) (—CH_2CH_2Cl). Found, %: C 29.30; H 2.34; Br 27.99; Cl 25.05; N 4.78. Calculated for $C_7H_6BrCl_2NO_2$, %: C 29.27; H 2.09; Br 27.84; Cl 24.74; N 4.88.

2-Chloro-3-(β-chloroethyl)-4, 6-dioxy-5-nitropyrindine (V). A 3 g (15 mM) quantity of compound I was added with mixing to 15 ml of 33% nitric acid at room temperature. The mixture was stirred for 1 hr, left overnight, neutralized to pH 7 with potash and left for 3 hr in the refrigerator. The precipitateon was removed by filtration. Yield, 1.7 g (48%); colorless crystals. On determination of the mp a change in the 160–165° C interval was found (cleavage of hydrogen chloride), after which the compound melted at 242–243° C (decomposition). Readily soluble in chloroform, and slightly soluble in benzene, alcohol, acetone, and water. PMR spectrum: two triplets σ 3.16 and 3.70 ppm (J ~ 6Hz) (—CH_2CH_2Cl). Found, %: C 33.02; H 2.33; Cl 27.84; N 11.02. Calculated for $C_7H_6Cl_2N_2O_4$, %: C 33.20; H 2.37; Cl 28.06; N 11.07.

4-Chloro-6-oxo-7-nitro-2, 3-dihydro-5-azabenzofuran (VI). a) A 0.5 g (3 mM) quantity of compound I was dissolved in 5 ml fuming nitric acid (d 1.51) at 0° C. The mixture was maintained for one hour at this temperature, poured onto 5 g ice, and neutralized with ammonia to pH 7. The resulting precipitate was removed by filtration. Yield, 0.15 g (29%). Yellow crystals, mp 242–243° C (decomposition, from alcohol). Soluble in alcohol and water on heating, insoluble in ether and benzene, and slightly soluble in chloroform and acetone. Found, %: C 38.60; H 2.67; Cl 16.07; N 13.01. Calculated for $C_7H_5ClN_2O_4$, %: C 38.80; H 2.31; Cl 16.40; N 12.93. b) A 1 ml volume of a 25% aqueous solution of ammonia was added to 0.1 g (0.4 mm) of compound V. The reaction mass was carefully ground, filtered, and washed with water. Yield was 0.07 g (87.5%), mp 242–243° C (decomposition). Found, %: Cl 16.01. Calculated for $C_7H_5ClN_2O_4$, %: Cl 16.40.

4-Chloro-6-oxo-7-bromo-2, 3-dihydro-5-azabenzofuran (VIIa). a) A 0.8 g (5 mM) quantity of bromine in 2 ml glacial acetic acid was added dropwise with stirring to a solution of 0.5 g (3 mm) of compound IIa in 30 ml glacial acetic acid at room temperature. After standing overnight the reaction mass was evaporated under vacuum. The residue was washed with ether. A 0.5 g (63.5%) quantity was obtained. Colorless crystals, mp 242° C (decomposition, form alcohol). Soluble in water and alcohol on heating, slightly soluble in ether and benzene, chloroform and acetone. PMR spectrum: two triplets σ 3.33 and 4.97 ppm (J ~ 8Hz) (—CH_2CH_2—group of the dihydrofuran nucleus). Found, %: C 33.76; H 2.08; Br 32.05; Cl 14.20; N 5.81. Calculated for $C_7H_5BrClNO_2$, %: C 33.53; H 2.00; Br 31.94; Cl 14.17; N 5.59.

b) A 0.1 g (0.4 mM) quantity of compound IV was carefully ground with 1 ml of a 25% aqueous solution of ammonia. The residue was removed by filtration and washed with water. Yield, 0.08 g (89%); mp 242° C (decomposition). Found, %: Br 31.75; Cl 13.98. Calculated for $C_7H_5BrClNO_2$, %: Br 31.94; Cl 14.17.

4-Chloro-5-methyl-6-oxo-7-bromo-2, 3-dihydro-5-azabenzofuran (VIIb). A 0.53 ml (10 mM) quantity of bromine in 5 ml chloroform was added with mixing to a solution of 0.5 g (2.1 mM) of compound IIb in 10 ml chloroform at room temperature. The precipitate of the perbromide of VIIb was removed by filtration. Yield, 1 g (89%). Bright-yellow crystals, mp 158° C (decomposition). Slightly soluble in organic solvents and in water. Found, %: C 22.73; H 1.57; Br 56.05; Cl 8.08; N 3.66%. $C_8H_7BrClNO_2 \cdot Br_2$. Calculated: C 22.60; H 1.65; Br 56.50; Cl 8.40; N 3.30. On storage, heating, or recrystallization from alcohol and acetone, the compound loses a molecule of bromine and is converted into VIIb with a mp of 218–219° C (from alcohol). Found, %: C 36.57; H 2.65; Br 30.32; Cl 13.45; N 5.55. Calculated for $C_8H_7BrClNO_2$, %: C 36.36; H 2.64; Br 30.20; Cl 13.40; N 5.30.

4, 7-Dichloro-5-methyl-6-oxo-2, 3-dihydro-5-azabenzofuran (VIIIb). a) A 3 g (16 mM) quantity of compound IIb was boiled for 8 hr with 10 ml (55 mM) of purified thionyl chloride. On cooling the crystals were removed by filtration. The substance was washed with ether. Yield, 1.4 g (40%); mp 243–244° C (from benzene). Readily soluble in chloroform, and slightly soluble in other organic solvents and in water. IR spectrum: 1677 cm^{-1} (CON). UV spectrum: λ_{max}, nm ($\log\varepsilon$): 218 (4.42), 302 (3.86). PMR spectrum: two triplets σ 3.49 and 5.10 ppm (J ~ 8Hz) (—CH_2CH_2—group of the dihydrofuran ring). Found, %: C 43.83; H 3.12; Cl 32.18; N 6.58. Calculated for $C_8H_7Cl_2NO_2$, %: C 43.64; H 3.18; Cl 32.27; N 6.36.

b) Chlorine (4.5 mM), obtained from 0.25 g potassium permanganate and 2 ml hydrochloric acid, was passed into a solution of 0.5 g (3.2 mM) of IIb in 10 ml chloroform for 20 min. The reaction mixture was left for 30 min at room temperature, after which it was evaporated under vacuum. The residue was crystallized from alcohol. Yield, 0.25 g (43%); mp of a mixture sample with a sample obtained by method (a), 243–244° C.

4-Chloro-5-methyl-6-oxo-7-methoxy-2, 3-dihydro-5-azabenzofuran (IXb). a) A 0.5 g (2.3 mM) quantity of compound VIIIb, 0.3 g (7 mM) sodium hydroxide, and 20 ml methanol were boiled for 6 hours. The precipitate which formed on cooling the solution was removed by filtration and washed with water and alcohol. Yield, of IXb, 0.3 g (60.1%). Colorless crystals, mp 222° C (from alcohol). Readily soluble in chloroform, less soluble in alcohol, acetone and benzene, and slightly soluble in ether and water. Found, %: C 50.03; H 4.49; Cl 16.09; N 6.55. Calculated for $C_9H_{10}ClNO_3$, %: C 50.10; H 4.67; Cl 16.47; N 6.49.

b) A solution of 0.5 g (1.9 mM) of compound VIIb in 0.3 g (7 mM) sodium hydroxide in 10 ml methanol was boiled for 6 hr and subsequently treated as in the previous experiment. A 0.27 g (67%) quantity of compound IXb with a mp of 222° C was obtained. The substance does not produce a depression on melting the mixture sample with a sample of compound IXb obtained from compound VIIIb.

4-Chloro-5-methyl-6-oxo-7-ethoxy-2, 3-dihydro-5-azabenzofuran (IXc). A 1 g (4.5 mM) quantity of compound VIIIb and 0.6 g (15 mM) sodium hydroxide was boiled for 6 hr in 40 ml anhydrous ethyl alcohol, evaporated to dryness under vacuum, and compound IXc was extracted from the residue with hot benzene. Yield, 0.5 g (48%). Colorless crystals, mp 191° C (from alcohol). Readily soluble in chloroform, hot benzene and boiling alcohol, and slightly soluble in ether and water. IR spectrum: 1675 cm^{-1} (CON). Found, %: C 52.19; H 5.09; Cl 15.12; N 5.93. Calculated for $C_{10}H_{12}ClNO_3$, %: C 52.29; H 5.23; Cl 15.47; N 6.10.

4-Chloro-5-methyl-6-oxo-7-hydroxy-2, 3-dihydro-5-azabenzofuran (IXa). A 0.2 g (1 mM) quantity of compound IXb was heated for 1 hour in a water bath with 1 ml of 16% hydrochloric acid. The precipitate which formed on cooling was removed by filtration. Yield, 0.12 g (54%); colorless crystals, mp 198–199° C (from alcohol). Slightly soluble in ether, benzene, acetone, and water, and more soluble in chloroform. PMR spectrum: two triplets σ 3.41 and 4.92 ppm (J ~ 8Hz) (—CH_2CH_2—group of the dihydrofuran ring). Found, %: C 47.87; H 4.25; Cl 17.24; N 6.92. Calculated for $C_8H_8ClNO_3$, %: C 47.64; H 3.92; Cl 17.62; N 6.97.

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