SOME REACTIONS OF 2-CHLORO-3-(β-CHLOROETHYL)-4,6-DIHYDROXYPYRIDINE

Synthesis of Derivatives of 5-Azabenzofuran

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Khimiya Geterotsiklicheskikh Soedinenii, Vol. 4, No. 1, pp. 18–22, 1968

UDC 547.821.42.07

The chemical properties of 2-chloro-3-(β-chloroethyl)-4,6-dihydroxypyridine (I) have been studied. It has been shown that this compound, which is relatively stable in acids and in neutral and, particularly, in alkaline media, readily splits off hydrogen chloride under mild conditions and is converted into derivatives of 2,3-dihydro-5-azabenzofuran. The dehalogenation of I in an acid medium yielded 3-(β-chloroethyl)-4,6-dihydroxypyridine, which was converted into 4,6-dichloro-3-(β-chloroethyl)pyridine and into 6-chloro-4-methoxy-3-vinylpyridine.

In one of the preceding communications [1] it was shown that 2-chloro-3-(β-chloroethyl)-4,6-dihydroxypyridine (I), which is readily formed by the reaction of malonyl chloride with γ-chlorobutyronitrile [2], possesses a high capacity for splitting off a molecule of hydrogen chloride. The dehydrohalogenation of I takes place quantitatively when it is treated with 20% ethanolic ammonia, even at room temperature. A more profound study of the product formed in this reaction by the NMR* method has shown that it does not have the structure of 2-chloro-4,6-dihydroxy-3-vinylpyridine (II) but is the isomeric compound 4-chloro-6-oxo-2,3-dihydro-5-azabenzofuran (III). In the NMR* spectrum of this compound (Fig. 1) there are two triplets at 2.91 and 4.50 ppm with a spin-spin splitting of ~8 Hz due to the $-CH_2-CH_2-O$ grouping, and also the singlet of a proton in position 7 at 6.30 ppm. There is no system of signals characteristic for a vinyl group attached to a pyridine nucleus. The IR spectrum of this compound has the strong absorption band at 1678 cm^{-1} characteristic for a lactam carbonyl, which shows that III exists in the oxo form.

A further study of the properties of 2-chloro-3-(β-chloroethyl)-4,6-dihydropyridine (I) showed that the splitting off of hydrogen chloride from this compound with closure of the dihydrofuran ring takes place with exceptional ease. This process takes place even when the substance is stored at room temperature, while boiling I in an acetone solution converts it into III quantitatively. Hydrogen chloride is split off equally readily when I is heated in a capillary to determine its melting point. Consequently, the mp of 257° C reported previously in the literature for I is actually the corresponding constant of the dihydrofuran derivative III. In addition to this, the closure of the dihydrofuran ring is a reversible process, and when III is heated with concentrated hydrochloric acid, I is re-formed. As was to be expected, the splitting out of a molecule of HCl from I is facilitated in an alkaline medium. Thus, for example, in the alkylation of I with methyl iodide and ethyl iodide in the presence of potassium carbonate, 5-methyl-and 5-ethyl-4-chloro-6-oxo-2,3-dihydro-5-azabenzofurans (VIa and b) were obtained, respectively. The same compounds are formed by the alkylation of III. The dehalogenation of VIb in the presence of a palladium catalyst yielded 5-ethyl-6-oxo-2,3-dihydro-5-azabenzofuran (VIII). The position of the alkyl groups in VIa, VIb, and VIII on the nitrogen atom and not on the oxygen atom was confirmed by their IR spectra (1682, 1678, and 1776 cm^{-1}), and the position of the dihydrofuran ring by their NMR spectra (Fig. 1). In all cases, the reaction of I, III, VIa, and VIb with phosphorus oxychloride led to the same product, 2,4,6-trichloro-3-(β-chloroethyl)pyridine (VII) [1].

In the reactions of I with various reagents in an acid medium, no splitting off of hydrogen chloride with closure of the dihydrofuran ring takes place. Thus, for example, the acetylation of I with acetic anhydride enabled 4,6-diacetoxy-2-chloro-3-(β-chloroethyl)pyridine (IV) to be obtained. The position of the acetyl groups on the oxygen atoms and not on the nitrogen in this compound was confirmed by the IR spectrum (1783 cm^{-1}, $-OOCCH_3$).

The dehalogenation of I in an alcoholic solution of hydrogen chloride in the presence of a palladium catalyst enabled us to obtain 3-(β-chloroethyl)-4,6-dihydroxypyridine (V), a compound more stable than I. The reaction of V with phosphorus oxychloride gave 4,6-dichloro-3-(β-chloroethyl)pyridine (IX). In this compound, the mobilities of the chlorine atoms proved to be very different. While when IX was treated with an ethanolic alkali under mild conditions at room temperature only dehydrohalogenation took place and both chlorine atoms in the pyridine ring remained, when IX was boiled with alcoholic alkali it was not 4,6-dichloro-3-vinylpyridine but 6-chloro-4-ethoxy-

*The NMR spectra were taken on an N-6013 instrument in the form of solutions in CCl_4 and $CHCl_3$ with TMS as internal standard. The IR spectra were taken on a UR-10 recording spectrophotometer in the form of mulls in paraffin oil, and the UV spectra on a SF-4 spectrophotometer in the form of a solution in ethanol.

We consider it our pleasant duty to express our thanks to Yu. N. Sheinker, E. M. Peresleni, P. V. Petrovskii, and Yu. I. Pomerantsev for assistance in the performance of the spectroscopic investigation.

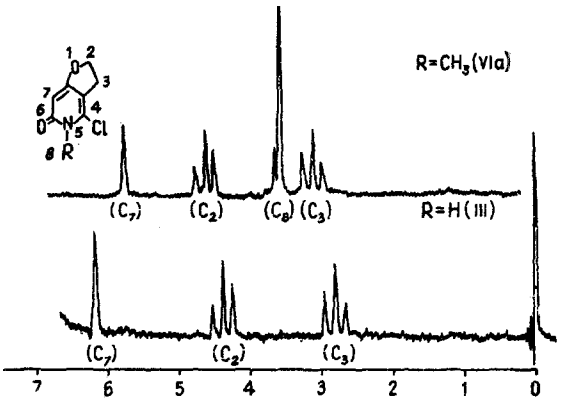


Fig. 1. NMR spectra of 4-chloro-6-oxo-2,3-dihydro-5-azabenzofuran (III) and 4-chloro-5-methyl-6-oxo-2,3-dihydro-5-azabenzofuran (VIa).

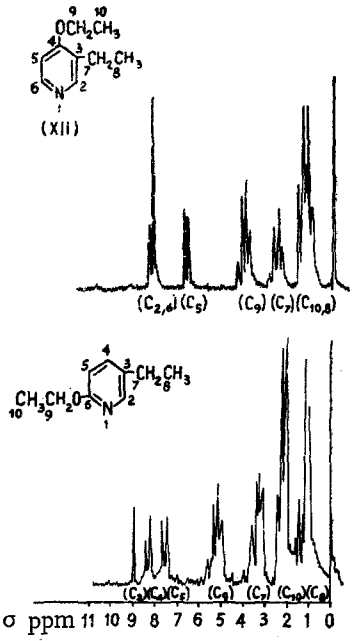
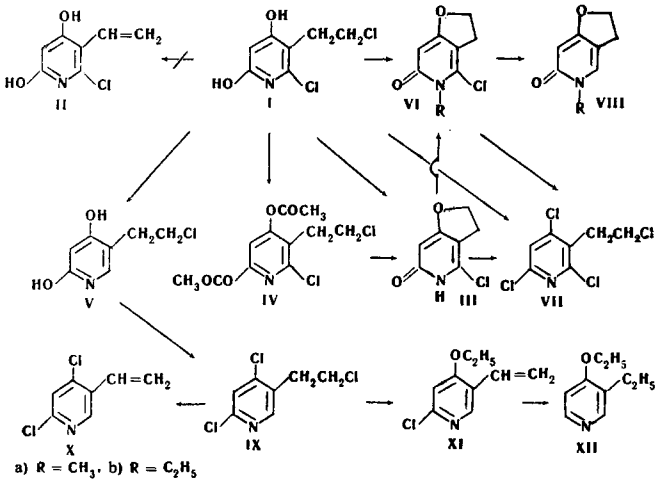


Fig. 2. NMR spectra of 4-ethoxy-3-ethylpyridine (XII) and 6-ethoxy-3-ethylpyridine (taken in a TsLA-55-35 instrument at 40 MHz).

3-vinylpyridine (XI) that was formed. Thus, the chlorine atom in position 6 of IX proved to be more stable to the attack of nucleophilic agents. The structure of compound XI was shown unambiguously by its reduction in the presence of a palladium catalyst to 4-ethoxy-3-ethylpyridine (XII). The XII formed in this way proved to be identical with the 4-ethoxy-3-ethylpyridine [3] obtained by independent synthesis from β-collidine via 3-ethylisonicotinic acid and 4-bromo-3-ethylpyridine. The 6-ethoxy-3-ethylpyridine [3] isomeric with it differed from XII in its physicochemical constants and also in its IR and NMR spectra (Fig. 2).



EXPERIMENTAL

4-Chloro-6-oxo-2, 3-dihydro-5-azabenzofuran (III).

a) Five milliliters of 20% ethanolic ammonia solution was added to 0.5 g (0.0025 mole) of 2-chloro-3-(β-chloroethyl)-4, 6-dihydroxypyridine (I), and the reaction mixture was kept at room temperature for 7 hr and was then evaporated in vacuum. The residue was washed with 4 ml of distilled water and recrystallized from ethanol. This gave 0.3 g (75%) of III in the form of colorless crystals, mp 255° C (decomp). The substance is sparingly soluble in cold water and the usual organic solvents and soluble in water and ethanol on heating.

IR spectrum: 1678 cm^{-1} (CON). Found, %: C 48.94; H 3.54; Cl 20.86; N 8.47. Calculated for $C_7H_6ClNO_2$, %: C 48.98; H 3.50; Cl 20.70; N 8.10.

On Volhard titration in an aqueous solution after the separation of the III, 0.085 g of Cl' was found (theoretically 0.085 g).

b) One gram (0.005 mole) of 2-chloro-3-(β-chloroethyl)-4, 6-dihydroxypyridine (I) was boiled with acetone for 10 minutes three times, using 5 ml of acetone each time. After cooling, the acetonic solutions were decanted from the residue and combined. The residue (0.7 g) was identified with III by a mixed melting point. In the acetonic solution, Volhard titration found 0.17 g of Cl^- (theoretically 0.17 g).

4, 6-Diacetoxy-2-chloro-3-(β-chloroethyl)Pyridine (IV). One gram (0.005 mole) of 2-chloro-3-(β-chloroethyl)-4, 6-dihydroxypyridine (I) was boiled with 10 ml of acetic anhydride for 3 hr. The reaction mixture was evaporated in vacuum. The residue was dissolved in benzene, and the benzene solution was washed with saturated sodium carbonate solution (3 × 5 ml) and dried with magnesium sulfate. The benzene was driven off in vacuum to give 1 g (71.5%) of IV. Colorless oily substance, readily soluble in the usual organic solvents, sparingly soluble in water, bp 178° C (4 mm), n_D^{20} 1.5270. IR spectrum: 1783 cm^{-1} (—OOCCH$_3$). Found, %: C 45.44; H 3.86; Cl 24.76; N 5.10. Calculated for $C_{11}H_{11}Cl_2NO_4$, %: C 45.20; H 3.77; Cl 24.32; N 4.7.

4-Chloro-5-methyl-6-oxo-2, 3-dihydro-5-azabenzofuran (VIa). To a solution of 1 g (0.005 mole) of 2-chloro-3-β-chloroethyl-4, 6-dihydroxypyridine (I) in 10 ml of anhydrous ethanol were added 2 g (0.015 mole) of freshly calcined potassium carbonate and then, in drops, 1 g (0.007 mole) of methyl iodide in 5 ml of anhydrous ethanol. The reaction mixture was boiled with stirring for 7 hr and the ethanol was distilled off in vacuum. The residue was treated with 10 ml of water and extracted with chloroform. The chloroform extract was dried with potassium carbonate and evaporated to give 0.6 g (68%) of VIa. Colorless crystals, mp 185° C (from petroleum ether). The substance is readily soluble in chloroform, less readily in ethanol, benzene, and acetone, and sparingly soluble in ether and water. IR spectrum: 1682 cm^{-1} (—CO—N). UV spectrum: 216 nm (log ε 4.22); 296 nm (log ε 3.72). Found, %: C 51.49; H 4.26; Cl 19.37; N 7.81. Calculated for $C_8H_8ClNO_2$, %: C 51.75; H 4.31; Cl 19.14; N 7.55.

4-Chloro-5-ethyl-6-oxo-2, 3-dihydro-5-azabenzofuran (VIb). To a solution of 3 g (0.015 mole) of I in 20 ml of anhydrous ethanol were added 6 g (0.045 mole) of freshly calcined potassium carbonate and then, in drops, 6 g (0.04 mole) of ethyl iodide in 10 ml of anhydrous ethanol. The reaction mixture was boiled for 12 hr and evaporated to dryness. The residue was treated with 20 ml of water and the IVb was extracted with benzene. The benzene extract was dried with potassium carbonate and evaporated in vacuum. The residue was distilled at 145°–146° C (2 mm). Yield 1.5 g (53%). The distillate crystallized. Colorless crystals, mp 90°–91° C (from petroleum ether). The substance is soluble in benzene, chloroform, ethanol, and acetone, and sparingly soluble in water, ether, and petroleum ether. IR spectrum: 1678 cm^{-1} (—CO—N). Found, %: C 53.77; H 4.87; Cl 17.77; N 7.40. Calculated for $C_9H_{10}ClNO_2$, %: C 54.13; H 5.01; Cl 17.79; N 7.02.

5-Ethyl-6-oxo-2, 3-dihydro-5-azabenzofuran (VIII). A solution of 2 g (0.01 mole) of VIb in 50 ml of ethanol was hydrogenated in the presence of a palladium catalyst (from 2 g of palladium chloride) at room temperature and a pressure of 20–30 cm of water. The catalyst was filtered off, the filtrate was evaporated to dryness, and the residue (1.8 g) was treated with a saturated ethanolic solution of picric acid. The picrate of VIII that deposited was filtered off and washed with ethanol. Yield 1.2 g (40.5%). Light yellow crystals, mp 169°–170° C (from ethanol). The substance is sparingly soluble in ether, ethanol, acetone, and water, and readily soluble in hot ethanol. IR spectrum: 1676 cm^{-1} (—CO—N). Found, %: C 45.65; H 3.81; N 14.01. Calculated for $C_9H_{11}NO_2 \cdot C_6H_3O_7$, %: C 45.68; H 3.55; N 14.21.

The base was isolated from the picrate by chromatography on a column of alumina with elution by acetone. From 0.4 g of the picrate of VIII, 0.2 g (100%) of the base was obtained. Colorless crystals, mp 129°–130° C (from acetone). The substance is readily soluble in alcohols and sparingly soluble in ether, benzene, acetone, chloroform, and water. Found, %: C 65.37; H 6.89; N 8.63. Calculated for $C_9H_{11}NO_2$, %: C 65.45; H 6.67; N 8.48.

2, 4, 6-Trichloro-3-(β-chloroethyl)pyridine (VII). A mixture of 1 g (0.006 mole) of 4-chloro-5-methyl-6-oxo-2, 3-dihydro-5-azabenzofuran (VIa) and 5 ml (0.05 mole) of phosphorus oxychloride was boiled under reflux for 5 hr. The reaction mixture was poured onto ice and the VII was extracted with benzene. The yield was 0.9 g (68%). Colorless crystals, mp 55° C (from petroleum ether). The substance gave a depression of the melting point in admixture with a sample of VII obtained from 2-chloro-3-(β-chloroethyl)-4, 6-dihydroxypyridine (I) [1].

Similarly, 0.85 g (0.004 mole) of 4-chloro-5-ethyl-6-oxo-2, 3-dihydro-5-azabenzofuran (VIb) and 5 ml (0.02 mole) of phosphorus oxychloride gave VII with a yield of 0.75 g (61%).

3-(β-Chloroethyl)-4, 6-dihydroxypyridine (V). Fifteen grams (0.072 mole) of 2-chloro-3-(β-chloroethyl)-4, 6-dihydroxypyridine was hydrogenated in 250 ml of methanol in the presence of a palladium catalyst (from 5 g of palladium chloride) at room temperature and a pressure of 20–30 cm of water. The catalyst was filtered off and the filtrate was evaporated in vacuum. The yield of V was 12.37 g (99%). Colorless crystals, mp 154°–155° C (from

water). The substance is readily soluble in alcohols, sparingly soluble in benzene, acetone, and water, and insoluble in ether, ethyl acetate, chloroform, and petroleum ether. Found, %: C 48.72; H 4.78; Cl 20.29; N 8.19. Calculated for $C_7H_8ClNO_2$, %: C 48.41; H 4.61; Cl 20.46; N 8.07.

4,6-Dichloro-3-(β-chloroethyl)pyridine (IX). A mixture of 2.37 g (0.0137 mole) of V and 20 ml (0.218 mole) of phosphorus oxychloride was heated in a sealed tube at 180° C for 5 hr. The excess of phosphorus oxychloride was distilled off in vacuum. The residue was made alkaline with a saturated solution of sodium carbonate and was extracted with benzene. The benzene extract was dried with potassium carbonate and evaporated in vacuum. The residue was distilled. A fraction boiling at 123°–125° C (1.5 mm) was collected. The yield of IX was 1.85 g (64.5%). Colorless oily substance, readily soluble in the usual organic solvents, insoluble in water, n_D^{20} 1.5647. Found, %: C 39.80; H 2.77; Cl 50.48; N 6.84. Calculated for $C_7H_6Cl_3N$, %: C 39.90; H 2.85; Cl 50.59; N 6.65.

4,6-Dichloro-3-vinylpyridine (X). A solution of 0.5 g (0.0024 mole) of IX and 0.14 g (0.0035 mole) of sodium hydroxide in 12 ml of anhydrous ethanol was left at room temperature for 24 hr. The precipitate of sodium chloride that deposited was filtered off. The filtrate was evaporated in vacuum and the residue was distilled. A fraction with bp 88°–91° C (2 mm) was collected. The substance was recrystallized with strong cooling. The yield of X was 0.38 g (82.5%); colorless crystals, mp 15.5° C. The substance is readily soluble in the usual organic solvents and insoluble in water. Found, %: C 47.98; H 2.87; Cl 40.78; N 8.30. Calculated for $C_7H_5Cl_2N$, %: C 48.28; H 2.87; Cl 40.80; N 8.05.

6-Chloro-4-ethoxy-3-vinylpyridine (XI). A solution of 2.63 g (0.0125 mole) of IX and 0.96 g (0.025 mole) of sodium hydroxide in 25 ml of anhydrous ethanol was boiled for 6 hr. The ethanol was distilled off, the residue was treated with 20 ml of water, and the XI was extracted with benzene. The benzene extract was dried with potassium carbonate and evaporated in vacuum. The residue was distilled at 125°–126° C (5 mm). The yield of XI was 1.25 g (66.3%). Colorless crystals, mp 70.5°–71.5° C (from petroleum ether). The substance is readily soluble in acetone, chloroform, benzene, and ethyl acetate, sparingly soluble in ether, petroleum ether, and alcohols, and insoluble in water. Found, %: C 59.05; H 5.55; Cl 19.63; N 7.98. Calculated for $C_9H_{10}ClNO$, %: C 58.86; H 5.45; Cl 19.35; N 7.62.

4-Ethoxy-3-ethylpyridine (XII). In the presence of a palladium catalyst (from 1 g of palladium chloride), 1.16 g (0.0063 mole) of XI in 50 ml of ethanol was reduced at room temperature and a pressure of 20–30 cm of water. This gave 1.04 g (83.3%) of 4-ethoxy-3-ethylpyridine hydrochloride with mp 141°–141.5° C (from ethyl acetate). The substance gave no depression of the melting point in admixture with a sample of the hydrochloride of XII prepared from β-collidine by a method described previously [3]. The IR spectra of the two samples were identical. A mixture with a sample of the hydrochloride of 6-ethoxy-3-ethylpyridine prepared by the previous method [3] gave a depression of the melting point. The IR and NMR spectra of the substances were different. Found, %: C 57.20; H 7.49; Cl 18.98; N 7.45. Calculated for $C_9H_{13}NO \cdot HCl$, %: C 57.60; H 7.47; Cl 18.93; N 7.47.

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22 March 1966

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