COMPETITIVE NUCLEOPHILIC SUBSTITUTION REACTIONS OF METHYLSULFONYL AND NITRO DERIVATIVES OF POLYCHLOROPYRIDINES

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2,6-Di(methylsulfonyl)-3,4,5-trichloropyridine (II) and 4-nitro-2,6-di(methylsulfonyl)-3,5-dichloropyridine (IX) were synthesized, and their reactions with nucleophilic reagents were studied. It was found that the methylsulfonyl groups are replaced on reaction with alkali and sodium alkoxides; on reaction with amines, the chlorine atoms are replaced in the case of II and the nitro group is replaced in the case of IX. The nitro and methylsulfonyl groups are simultaneously replaced in the reaction of excess sodium methoxide with IX.

According to the kinetic data, in nucleophilic substitution reactions in nitrogen heterocycles, methylsulfonyl groups are displayed considerably more rapidly than the chlorine atoms in the corresponding chloro derivatives [1, 2], and hetaryl methyl sulfones are therefore valuable intermediates for all sorts of chemical transformations.

Suszhitzky and co-workers [3] in a study of the reaction of 4-methylsulfonyltetrachloropyridine with nucleophilic reagents found that the reactions with nucleophiles of small size proceed exclusively with replacement of the methylsulfonyl group, whereas the chlorine atom in the 2 position is replaced by bulky nucleophiles.

Our preceding communication [4] was devoted to a study of the reaction of 2-methylsulfonyltetrachloropyridine N-oxide and 2,6-di(methylsulfonyl(trichloropyridine N-oxide with nucleophilic reagents. The methylsulfonyl groups rather than the chlorine atoms are replaced by the action of nucleophilic reagents on them.

It seemed of interest to study reactions with nucleophilic reagents of polychloropyridines containing methylsulfonyl groups in the 2 and 6 positions and to compare their reactivities with the corresponding N-oxides. For this, 2,6-di(methylthio)3,4,5-trichloropyridine (I) [4] was oxidized with hydrogen peroxide in trifluoroacetic acid to 2,6-di(methylsulfonyl)-3,4,5-trichloropyridine (II). The reactions of II with sodium hydroxide, potassium hydrosulfide, sodium ethoxide, and amines were investigated. It was found that in the case of sodium hydroxide, potassium hydrosulfide, and sodium ethoxide, depending on the ratios of the starting reagents and the temperature conditions, the reactions proceed with replacement of one of two sulfonyl groups. Thus 2-hydroxy-, 2-ethoxy-, and 2-mercapto-6-methylsulfonyl-3,4,5-trichloropyridines (IIIa-c), respectively, are formed by the action of 1% aqueous NaOH, 1 mole of sodium ethoxide, and potassium hydrosulfide. 2-Methylthio-6-methylsulfonyl-3,4,5-trichloropyridine (IV) was obtained by the action of dimethyl sulfate on IIIc. 2,6-Dihydroxy- and 2,6-diethoxy-3,4,5-trichloropyridines (Va, b), respectively, are formed in the reaction of II with 10% aqueous alkali or excess sodium ethoxide.

However, in the reaction of amines with II the chlorine atoms in the 3 or 4 position are replaced rather than the methylsulfonyl groups. Mixtures of two isomers are formed in the reaction of sulfone II with morpholine, methylamine, and hydrazine, respectively: 3-morpholino-2,6-di(methylsulfonyl)-4,5-dichloropyridine (VIa) and 4-morpholino-2,6-di(methyl-

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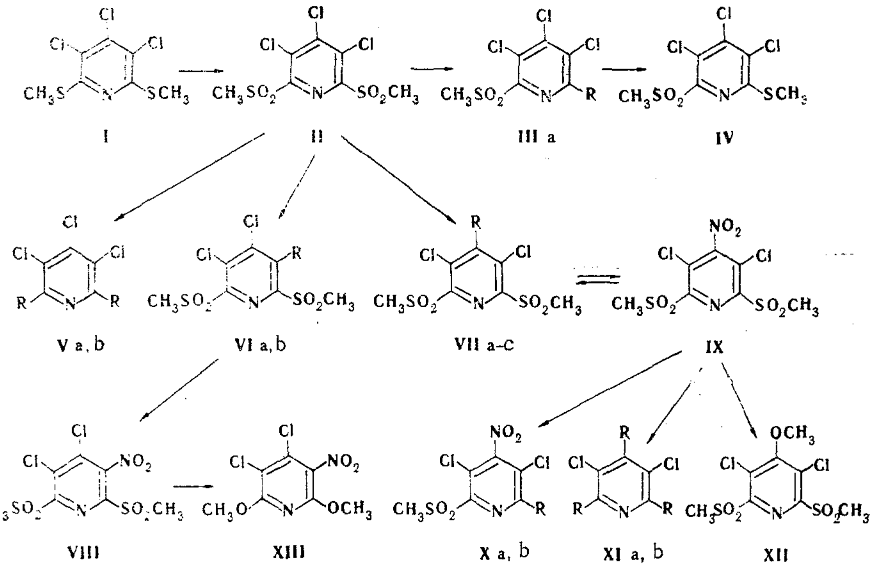
sulfonyl)-3,5-dichloropyridine (VIIa); 3-methylamino-2,6-di(methylsulfonyl)4,5-dichloropyridine (VIb) and 4-methylamino-2,6-di(methylsulfonyl)-3,5-dichloropyridine (VIIb). In the reaction of II with hydrazine we were able to isolate only 4-hydrazino-2,6-di(methylsulfonyl)-3,5-dichloropyridine (VIIc) from the reaction mixture.

The direction of substitution of the chlorine atoms by amino groups in sulfone II was proved by oxidation of isomeric amines VIb and VIIb with hydrogen peroxide in trifluoroacetic acid to the corresponding 3-nitro and 4-nitro derivatives (VIII, IX), which themselves were interesting subjects for a study of competitive nucleophilic substitution reactions. Even with excess morpholine, methylamine, and hydrazine at room teperature and heating, IX reacts exclusively with substitution of the nitro group and formation of VIIa-c. However, heating sulfone IX with excess sodium hydroxide gives exclusively 2-hydroxy-4-nitro-6-methylsulfonyl-3,5-dichloropyridine (Xa). The reaction of IX with excess sodium alkoxide leads to substitution of the nitro and sulfonyl groups. 2,4,6-Trimethoxy-3,5-dichloropyridine (XIa) is formed on reaction with sodium methoxide, whereas 2,4,6-triethoxy-3,5-dichloropyridine (XIb) is formed on reaction with sodium ethoxide. The preparation of XIa in [5] proves the location of the nitro group in IX and, consequently, the structure of VIIa-c obtained from sulfone IIa and amines.

In order to ascertain the sequence of substitution of the nitro and methylsulfonyl groups on reaction of sulfone IX with sodium alkoxides, we studied its reaction with 1 mole of sodium methoxide. Considering that the reaction of IX with excess alkali leads to substitution exclusively of the sulfonyl group, one might have assumed that the reaction with sodium methoxide also initially would proceed with successive splitting out of a sulfonyl group and a nitro group.



III, V, Xa R=OH; VI, VIIa R= morpholino XIa R=CH_3O; III, V, XIb R=C_2H_5O; VI, VIIb R=CH_3NH; Xb R=CH_3O; IIIc R=SH; VIIc R=NH_2—NH

However, we found that the reaction with 1 mole of sodium methoxide leads to two products: 4-methoxy-2,6-di(methylsulfonyl)-3,5-dichloropyridine (XII) (70%) and 2-methoxy-4-nitro-6-methylsulfonyl-3,5-dichloropyridine (Xb) (30%). The ratio of the reaction products indicates that the nitro group is more reactive than the sulfonyl group in the reaction of IX with alkoxides.

In contrast to isomeric IX, the reaction of sulfone VIII with excess sodium methoxide at room temperature gives 3-nitro-2,6-dimethoxy-4,5-dichloropyridine (XIII).

EXPERIMENTAL METHOD

2,6-Di(methylsulfonyl)3,4,5-trichloropyridine (II). A 27.4-g (0.1 mole) sample of sulfide I was dissolved in 250 ml of trifluoroacetic acid, 50 ml (0.44 mole) of 30% aqueous hydrogen peroxide was added, and the mixture was refluxed for 15 min. It was then diluted with water and worked up to give 33 g (98%) of a product with mp 257-258° (from dioxane). Found: Cl 31.4; S 18.8%. $C_7H_6Cl_3NO_4S_2$. Calculated: Cl 31.5; S 18.9%.

2-Hydroxy-6-methylsulfonyl-3,4,5-trichloropyridine (IIIa). A mixture of 0.34 g (1 mmole) of sulfone II in 20 ml (5 mmole) of 1% aqueous sodium hydroxide was refluxed for 30 min, after which it was cooled, acidified with hydrochloric acid, and worked up to give 0.25 g (90%) of a product with mp 166-167° (from water). Found: Cl 38.6; S 11.8%. $C_6H_4Cl_3NO_3S$. Calculated: Cl 38.5; S 11.6%.

2-Ethoxy-6-methylsulfonyl-3,4,5-trichloropyridine (IIIb). A 0.34-g (1 mmole) sample of sulfone II was dissolved in 150 ml of tetrahydrofuran (THF), the solution was cooled to −10°, and a solution of sodium ethoxide prepared from 0.03 g (0.0013 g-atom) of sodium in 100 ml of absolute ethanol was added dropwise with stirring. The mixture was stirred at −10° for 45 min, after which it was acidified with hydrochloric acid and the solvent was vacuum evaporated to give 0.26 g (86%) of a product with mp 112-113° (from heptane). Found: Cl 34.7; S 10.7%. $C_8H_8Cl_3NO_3S$. Calculated: Cl 34.9; S 10.5%.

2-Mercapto-6-methylsulfonyl-3,4,5-trichloropyridine (IIIc). A solution of 1.1 g (0.02 mole) of potassium hydroxide in 100 ml of ethanol was saturated with hydrogen sulfide at 20° for 30 min, after which 0.7 g (2 mmole) of sulfone II was added, and the mixture was stirred and saturated with hydrogen sulfide at 20° for 6 h. The precipitated sodium salt of IIIc was removed by filtration and dissolved in water. The solution was acidified with hydrochloric acid, and the product was extracted with diethyl ether to give 0.4 g (65%) of a product with mp 129-131° (from diethyl ether and heptane). Found: Cl 36.8; S 21.7%. $C_6H_4Cl_3NO_2S_2$. Calculated: Cl 36.5; S 21.9%.

2-Methylthio-6-methylsulfonyl-3,4,5-trichloropyridine (IV). A 0.3-g (1 mmole) sample of IIIc was dissolved in 50 ml of 1% aqueous sodium hydroxide, and 5 ml of dimethyl sulfate was added dropwise slowly at 20°. The mixture was then stirred at room temperature for 3 h and worked up to give 0.3 g (97%) of a product with mp 175-177° (from aqueous alcohol). Found: Cl 35.1; S 20.6%. $C_7H_6Cl_3NO_2S_2$. Calculated: Cl 34.8; S 20.9%.

2,6-Dihydroxy-3,4,5-trichloropyridine (Va). A mixture of 0.34 g (1 mmole) of sulfone II and 10 ml of 20% aqueous sodium hydroxide was refluxed for 15 min, after which it was acidified with hydrochloric acid, and the precipitated product was removed by filtration to give 0.2 g (93%) of a product with mp 190-191° (from alcohol—heptane). Found Cl 49.6; N 6.6%. $C_5H_2Cl_3NO_2$. Calculated: Cl 49.7; N 6.5%.

2,6-Diethoxy-3,4,5-trichloropyridine (Vb). A) A mixture of 50 ml of ethanol, 0.34 g (1 mmole) of sulfone II, and 0.1 g (2 mmole) of sodium hydroxide was refluxed for 30 min, after which the alcohol was removed by vacuum distillation, and the residue was treated with water to give 0.14 g (52%) of product with mp 102-103° (from aqueous methanol). Found: Cl 39.6; N 5.2%. $C_9H_{10}Cl_3NO_3$. Calculated: Cl 39.4; N 5.2%.

B) A 0.34-g (1 mmole) sample of sulfone II was added in small portions at 20° to a solution of sodium ethoxide prepared from 0.046 g (0.002 g-atom) of sodium in 250 ml of absolute ethanol, after which the mixture was stirred at room temperature for 3 h. The alcohol was then removed by vacuum distillation, and the residue was treated with water to give 0.23 g (85%) of product.

3-Morpholino-2,6-di(methylsulfonyl)-4,5-dichloropyridine (VIa) and 4-Morpholino-2,6-di(methylsulfonyl)-3,5-dichloropyridine (VIIa). A 3.4-g (0.01 mole) sample of sulfone II was dissolved in 500 ml of absolute dioxane, 10 ml of morpholine was added, and the mixture was stirred at 20° for 2 h. The solvent was then removed by vacuum distillation, and the residue was treated with a small amount of water to give a mixture of two isomeric products (VIa and VIIa), which were separated by fractional crystallization utilizing the different solubilities of the products in benzene and ethanol. Product VIa was considerably more soluble in benzene than isomer VIa. The yield of VIa, with mp 195-196° (dec., from ethanol), was 2 g (51%). Found: Cl 18.2; N 7.3%. $C_{11}H_{14}Cl_2N_2O_5S_2$. Calculated: Cl 18.2; N 7.2%. The yield of VIIa, with mp 257-258° (from benzene), was 1 g (26%). Found: Cl 18.3; S 16.3%. $C_{11}H_{14}Cl_2N_2O_5S_2$. Calculated: Cl 18.2; S 16.4%.

4-Morpholino-2,6-di(methylsulfonyl)-3,5-dichloropyridine (VIIa). A 0.35-g (1 mmole) sample of nitro compound IX was dissolved in 250 ml of absolute dioxane, 1 ml of morpholine was added, and the mixture was maintained at 20° for 24 h. The solvent was removed by vacuum distillation, and the residue was treated with water to give 0.25 g (64%) of a product with mp 257-258°

3-Methylamino-2,6-di(methylsulfonyl)4,5-dichloropyridine (VIb) and 4-Methylamino-2,6-di(methylsulfonyl)3,5-dichloropyridine (VIIb). A 3.4-g (0.01 mole) sample of sulfone II was dissolved in 300 ml of absolute THF, and dry gaseous methylamine was bubbled through the solution at 0° for 2 h. The precipitated methylamine hydrochloride was removed by filtration, the solution was vacuum evaporated to dryness, and the residue was treated with a small amount of water. Workup gave a mixture of two isomeric products (VIb and VIIb), which were separated utilizing their different solubilities in benzene. The yield of VIb, with mp 160-162° (from ethanol), was 0.9 g (27%). Found: Cl 21.1; N 8.6%. $C_8H_{10}Cl_2N_2O_4S_2$. Calculated: Cl 21.3; N 8.4%. The yield of VIIb, with mp 191-192° (from benzene), was 2.3 g (69%). Found: Cl 21.1; S 19.3%. $C_8H_{10}Cl_2N_2O_4S_2$. Calculated: Cl 21.3; S 19.2%.

4-Methylamino-2,6-di(methylsulfonyl)-3,5-dichloropyridine (VIIb). A 0.35-g (1 mmole) sample of nitro compound IX was dissolved in 150 ml of absolute THF, and dry gaseous methylamine was bubbled through the solution at 0° for 1 h. The solvent was removed by vacuum distillation, and the residue was treated with water to give 0.22 g (66%) of a product with mp 191-192°.

4-Hydrazino-2,6-di(methylsulfonyl)-3,5-dichloropyridine (VIIc). A) A 3.4-g (0.01 mole) sample of sulfone II was dissolved in 300 ml of THF, 10 ml of 90% hydrazine hydrate was added, and the mixture was stirred at 10° for 1 h. The solvent was removed by vacuum distillation, and the residue was treated with water to give 2.4 g (72%) of a product with mp 212-213° (dec., from ethanol). Found: Cl 21.2; S 19.5%. $C_7H_9Cl_2N_3O_4S_2$. Calculated: Cl 21.3; S 19.2%.

B) A 0.35-g (1 mmole) sample of nitro compound IX was dissolved in 150 ml of dioxane, 1 ml of 90% hydrazine hydrate was added, and the mixture was stirred at 20° for 1 h. The solvent was removed by vacuum distillation, and the residue was treated with water to give 0.27 g (81%) of a product with mp 213-214° (dec., from ethanol).

3-Nitro-2,6-di(methylsulfonyl)-4,5-dichloropyridine (VIII). A mixture of 3.3 g (0.01 mole) of amine VIb in 50 ml of trifluoroacetic acid and 25 ml of 30% hydrogen peroxide was refluxed for 1 h, after which the solution was cooled and diluted with half its volume of water. The precipitated product was removed by filtration to give 1.8 g (52%) of a product with mp 222-224° (dec., from methanol). Found: C 23.9; H 1.7; S 18.4%. $C_7H_6Cl_2N_2O_6S_2$. Calculated: C 24.1; H 1.7; S 18.3%.

4-Nitro-2,6-di(methylsulfonyl)-3,5-dichloropyridine (IX). A mixture of 3.3 g (0.01 mole) of amine VIIb in 50 ml of trifluoroacetic acid and 25 ml of 30% hydrogen peroxide was maintained at 20° for 12 h, after which it was refluxed for 30 min and diluted with half its volume of water. Workup gave 2.5 g (72%) of a product with mp 287-288° (dec., from water). Found: Cl 20.5; S 18.1%. $C_7H_6Cl_2N_2O_6S_2$. Calculated: Cl 20.2; S 18.3%.

2-Hydroxy-4-nitro-6-methylsulfonyl-3,5-dichloropyridine (Xa). A mixture of 0.35 g (1 mmole) of nitro compound IX in 50 ml (0.012 mmole) of 1% aqueous NaOH was heated at 65° for 10 min, after which the solution was partially vacuum evaporated and acidified with hydrochloric acid to give 0.21 g (75%) of a product with mp 162-164° (dec., from alcohol and heptane). Found: Cl 24.3; N 9.6%. $C_6H_4Cl_2N_2O_5S$. Calculated: Cl 24.7; N 9.7%.

2-Methoxy-4-nitro-6-methylsulfonyl-3,5-dichloropyridine (Xb) and 4-Methoxy-2,6-di(methylsulfonyl)-3,5-dichloropyridine (XII). A solution of sodium methoxide prepared from 0.023 g (0.001 g-atom) of sodium in 10 ml of absolute methanol was added to a solution of 0.35 g (1 mmole) of nitro compound IX in 50 ml of absolute DMF, after which the mixture was heated at 80° for 30 min. The solvent was removed by vacuum distillation, and the residue was dissolved in dioxane. The solution was filtered away from the insoluble salts, and the filtrate was vacuum evaporated to give a mixture of two products (Xb and XII), which were separated by fractional crystallization utilizing their different solubilities in heptane. The yield of Xb, with mp 111-112° (from heptane), was 0.09 g (30%). Found: S 11.0; N 9.6%. $C_7H_6Cl_2N_2O_5S$. Calculated: S 10.6; N 9.3%. The yield of XII, with mp 250-252° (dec., from dioxane—heptane), was 0.23 g (69%). Found: N 4.2; S 18.9%. $C_8H_9Cl_2NO_5S_2$. Calculated: N 4.2; S 19.2%.

2,4,6-Trimethoxy-3,5-dichloropyridine (XIa). A mixture of 0.35 g (1 mmole) of nitro compound IX dissolved in 200 ml of absolute methanol and a solution of sodium methoxide prepared from 0.14 g (0.006 g-atom) of sodium in 100 ml of absolute methanol was refluxed for 1 h, after which the solvent was removed by vacuum distillation, and the residue was treated with water to give 2.3 g (96%) of a product with mp 92-93° (from aqueous methanol). Found: Cl 29.6; N 6.0%. $C_8H_9Cl_2NO_3$. Calculated: Cl 29.8; N 5.9%. According to [5], XIa has mp 93-94°.

2,4,6-Triethoxy-3,5-dichloropyridine (XIb). This compound, with mp 35-36° (from aqueous ethanol), was similarly obtained in 89% yield. Found: Cl 25.4; N 5.3%. $C_{11}H_{15}Cl_2NO_3$. Calculated: Cl 25.4; N 5.0%.

3-Nitro-2,6-dimethoxy-4,5-dichloropyridine (XIII). A 0.35-g (1 mmole) sample of nitro compound VIII was added to a solution of sodium methoxide prepared from 0.14 g (0.006 g-atom) of sodium in 25 ml of absolute methanol, after which the mixture was stirred at 20° for 2 h. The methanol was removed by vacuum distillation, and the residue was treated with water to give 0.23 g (91%) of a product with mp 75-76° (from aqueous methanol). Found: Cl 27.6; N 10.7%. $C_7H_6Cl_2N_2O_4$. Calculated: Cl 28.1; N 11.1%.

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