REACTION OF BENZIMIDAZOLES WITH CHLOROSULFONIC ACID

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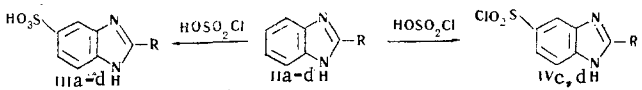
The reaction of benzimidazole and its 2-substituted derivatives with chlorosulfonic acid is examined. It is shown that only compounds containing electrophilic substituents in the 2-position yield sulfonic chlorides. Benzimidazole and its 2-methyl derivative give the sulfonic acids. Substitution occurs at the 5-position of the benzimidazole nucleus.

Previous attempts [1] to obtain benzimidazolesulfonyl chlorides by the reaction of benzimidazoles with chlorosulfonic acid (CSA) were unsuccessful. The authors isolated from the reaction mixture only unchanged benzimidazoles or the sulfonic acids, which could not be converted into the sulfonyl chlorides by treatment with PCl_5, or by other commonly used methods.

In a previous communication [2], we showed that the reaction of CSA with derivatives of 2-imino-1,3-dimethylbenzimidazoline (I) gave the sulfonyl chlorides only when the exocyclic N-atom bore substituents which reduced the basicity of the imidazoline ring. Since the chlorosulfonation reaction takes place in strongly acidic media, derivatives of I apparently exist therein as their chlorosulfate salts which, according to our results [3], possess the benzimidazolium salt structure. Therefore we expected the reaction of CSA with benzimidazoles (II) to occur by the same mechanism as above. In fact, reaction of benzimidazole and 2-methylbenzimidazole with CSA does not give the sulfonyl chlorides, but the sulfonic acids (III), which are, respectively, identical to the benzimidazole-5-sulfonic acid (IIIa) and 2-methylbenzimidazole-5-sulfonic acid (IIIb) obtained by sintering the sulfate salts of IIb [4]. Reaction of 2-phenyl- and 2-p-nitrophenylbenzimidazole with CSA yields the sulfonyl chlorides (IV), which are readily converted into sulfonamides and sulfonic acids. The sulfonamide obtained by ammonolysis of the sulfonyl chloride IVc is identical with 5-sulphamoyl-2-phenylbenzimidazole, prepared by reacting 3,4-diaminobenzenesulfonamide [5] with benzaldehyde. This indicates that chlorosulfonation occurs at the 5-position of the benzimidazole nucleus.



II–IV a R = H; b R = CH_3; c R = C_6H_5; d R = p-$NO_2C_6H_4$

The first stage of the chlorosulfonation reaction (i.e., formation of the sulfonic acid), therefore, occurs for all the compounds II. The sulfonic acid product apparently exists in the strongly acid reaction medium as the salt of chlorosulfonic acid or HCl (V). The fine structure of this salt, depending on the nature of R, apparently also determines whether the second stage of the chlorosulfonation reaction will occur, i.e., the nucleophilic attack of chlorosulfonic acid on the sulfonic acid group, with replacement of the OH by a chlorine atom. Attack on the sulfur atom is hindered if its positive charge is reduced by the imidazolium system. The presence of an electrophilic group in the 2-position, reducing the basicity of the system, apparently suppresses this influence, and conversion of the sulfonic acid into the sulfonyl chloride becomes possible. The higher the electrophilic nature of R, the more readily the sulfonyl chloride is formed, since the yield of IVc is 80%, and that of IVd is 90%.

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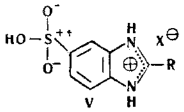

V

X=SO_3Cl or Cl

It appears that similar considerations must also hold in discussing the results of the chlorosulfonation of 2-iminobenzimidazolines [2].

EXPERIMENTAL

Benzimidazole-5-sulfonic Acid (IIIa). In a three-necked flask, fitted with a stirrer and a reflux air condenser with a calcium chloride tube, 4 ml (~ 0.06 mole) of freshly distilled CSA was placed and 1.18 g (0.01 mole) of benzimidazole was added in small portions with stirring during a period of 30 min. The reaction mixture was stirred for 30 min at 105-110° C and, after cooling, it was poured into 25 g of ice. Sodium carbonate was added cautiously until the pH of the solution was 1-2, then the resulting precipitate of inorganic salts was quickly separated off. On standing for several hr, the sulfonic acid slowly separated from the filtrate. The precipitate was filtered off, recrystallized from water, and dried at 110° C, giving 1.65 g (80%), mp 365° C, in agreement with the literature value [4]. A mixed mp with benzimidazole-5-sulfonic acid gave no depression. Their IR spectra were absolutely identical.

2-Methylbenzimidazole-5-sulfonic Acid (IIIb). This was obtained in a similar manner from IIb, but the reaction was completed at 50-60° C. Yield 92%, colorless needles, decomposing at about 380° C (according to [4], this compound has a high and indistinct mp). The IR spectra of the sulfonic acid product and 2-methylbenzimidazole-5-sulfonic acid were identical. Found, %: N 13.14. Calculated for $C_8H_8N_2O_3S$, %: N 13.20.

2-Phenylbenzimidazole-5-sulfonyl Chloride Hydrochloride (IVc · HCl) and 2-Phenylbenzimidazole-5-sulfonic Acid (IIIc). IIc was added to CSA, as in the first preparation, while cooling the flask in cold water. The reaction mixture was stirred for 30 min at 70-75° C, then it was cooled and poured into 20 g of ice. The precipitate was filtered off, washed with ice water, and dried in a desiccator over $CaCl_2$. The colorless, crystalline product was insoluble in the usual solvents. It was purified by washing on the filter with hot benzene and chloroform, to give 80% of product, mp 363° C (decomp). Found, %: N 8.75, 8.82. Calculated for $C_{13}H_9ClN_2O_2S \cdot HCl$, %: N 8.51.

From the filtrate, after separation of IVc · HCl, IIIc precipitated on standing. It was filtered off, recrystallized from water, and dried at 110° C to give 14% of colorless needles, mp 410° C (decomp). The compound was identical with the sulfonic acid obtained by boiling IVc or IVc · HCl with water. Found, %: C 57.13; H 3.82; N 10.28; S 11.35. Calculated for $C_{13}H_{10}N_2O_3S$, %: C 59.92; H 3.67; N 10.21; S 11.69.

2-Phenylbenzimidazole-5-sulfonyl Chloride (IVc). A 0.66-g (2 mmole) quantity of IVc · HCl ($R=C_6H_5$) was carefully triturated with 15 ml of cold 20% Na_2CO_3 solution. The residue was filtered off, washed with ice water, and dried in a desiccator over $CaCl_2$, giving 0.48 g (82%) of colorless needles (from benzene), mp 265° C (decomp). Found, %: N 9.52. Calculated for $C_{13}H_9ClN_2O_2S$, %: N 9.57.

2-p-Nitrophenylbenzimidazole-5-sulfonyl Chloride (IVd). The reaction with CSA, and the isolation of the product, were carried out as in the preparation of IVc · HCl. The yellow sulfonyl chloride precipitate was filtered off, washed with cold water, carefully pressed, and triturated with 20 ml of acetone. The residue was separated and dried in a vacuum desiccator over $CaCl_2$ to give 91% of a yellow crystalline product, insoluble in the usual solvents, and decomposing at about 300° C. Found, %: N 12.26. Calculated for $C_{13}H_8ClN_3O_4S$, %: N 12.45.

5-Sulfamoyl-2-phenylbenzimidazole (VI). A) To a solution of 0.46 g (2.5 mmole) of 3,4-diaminobenzenesulfonamide (VII) [5] in 5 ml of alcohol was added a solution of 0.25 g (2.5 mmole) of benzaldehyde in 1 ml of alcohol, and the mixture was boiled for 10 min. Nitrobenzene (1 ml) was then added, and the mixture was boiled for 5 min, thus removing the alcohol and the water formed during the reaction. To the cooled nitrobenzene solution was added a threefold volume of ethyl acetate, and a current of dry HCl was passed in. The hydrochloride precipitate was filtered off, washed with ethyl acetate, and dried. On treatment with concentrated ammonia, VI was obtained in 0.42 g (60%) yield, mp 275° C. Colorless needles (from methanol), mp 292° C. Found, %: C 57.05; H 4.21; N 15.35; S 11.40; Calculated for $C_{13}H_{11}N_3O_2S$, %: C 57.12; H 4.06; N 15.37; S 11.73.

B) Compound IVc and its hydrochloride were boiled with excess concentrated ammonia. On cooling, the mixture was diluted with an equal volume of water, and the sulfonamide precipitate was filtered off and recrystallized from methanol to give colorless needles, mp 292° C. The compound was identical with the sulfonamide obtained from VII.

5-Sulphamoyl-2-p-nitrophenylbenzimidazole. Obtained by treatment of IVd with ammonia as yellow prisms (from aqueous alcohol), mp 285° C. Found, %: C 48.74; H 3.30; N 17.87; S 9.71. Calculated for $C_{13}H_{10}N_4O_4S$, %: C 49.06; H 3.17; N 17.60; S 10.07.

2-p-Nitrophenylbenzimidazole-5-sulfonic Acid. A 0.68-g (2 mmole) quantity of IVd was boiled for 15-20 min with 30 ml of water. After cooling, the sulfonic acid precipitate was filtered off, recrystallized from water, and dried at 110° C to give 0.61 g (95%) of yellow needles, decomposing at about 390° C. Found, %: C 48.90; H 3.04; N 13.22; S 9.80. Calculated for $C_{13}H_9N_3O_5S$, %: C 48.90; H 2.84; N 13.16; S 10.04.

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