REACTION OF ANTHRANILIC ACID AND METHOXY- AND NITRO-SUBSTITUTED ANTHRANILIC ACID WITH p-TOLUENESULFONYL CHLORIDE IN PYRIDINE

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The reaction of anthranilic acid and methoxy- and nitro-substituted anthranilic acid with p-toluenesulfonyl chloride in pyridine was investigated. Anthranilic acid and its methoxy-substituted derivatives react to give the corresponding 2-(2-tosylaminophenyl)-4H-3,1-benzoxazin-4-ones and N,N'-ditosyldianthranilides. At 20°C, 4-nitroanthranilic acid gives primarily 2-(2-amino-4-nitrophenyl)-7-nitro-4H-3,1-benzoxazin-4-one, while its tosyl derivative is obtained at 114°. The products of the reaction of 5-nitroanthranilic acid with p-toluenesulfonyl chloride are 2-nitro-11H-pyrido[2,1-b]quinazolin-11-one and 2-(2-amino-5-nitrophenyl)-6-nitro-4H-3,1-benzoxazin-4-one. The yield of benzoxazinone generally increases as the temperature is raised.

We have previously shown [1] that 2-(2-tosylaminophenyl)-4H-3,1-benzoxazin-4-one and N,N'-ditosyldianthranilide are formed in the reaction of p-toluenesulfonyl chloride with anthranilic acid in pyridine. Continuing our study of this reaction, we have investigated the effect of temperature, reactant concentrations, and the nature and position of the substituents on the yields and structures of the compounds obtained (Table 1).

It is apparent from the data in Table 1 that the 4- and 5-methoxy-substituted acids, like anthranilic acid, react to give the corresponding benzoxazinones and dianthranilides. However, in the case of 5-

TABLE 1. Yields of Products of the Reaction of Anthranilic Acid and Its Derivatives with p-Toluenesulfonyl Chloride in Pyridine*

Expt. No.	R	Temp., °C	Yield, %					
			Va	VI	VIII†	IVa	Vb	VII
1	H	−30	8	13	78	—	—	—
2	H	20	50	47	3	—	—	—
3	H	114	89	9	0	—	—	—
4‡	H	20	46	20	19	—	—	—
5	5-OCH_3	20	23	69	5	—	—	—
6	5-OCH_3	114	59	38	0	—	—	—
7	4-OCH_3	20	45	31	17	—	—	—
8	4-OCH_3	114	90	2	0	—	—	—
9	4-NO_2	20	—	—	—	7	90	—
10	4-NO_2	114	51	—	3	42	—	—
11	5-NO_2	20	—	—	—	—	26	72
12	5-NO_2	114	—	—	—	—	68	29

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* See the reaction scheme.

† N-Tosylanthranilic acid.

‡ The experiment was carried out with a tenfold increase in the amount of pyridine.

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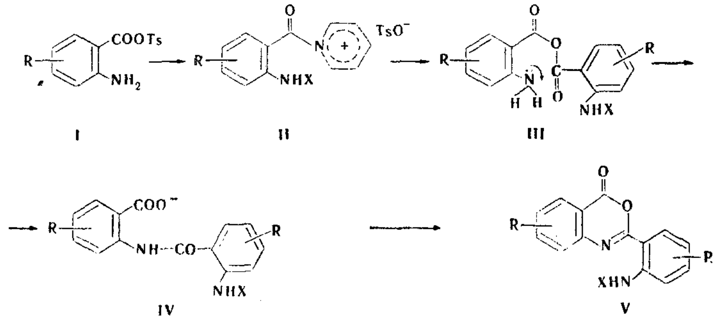
methoxyanthranilic acid the yield of benzoxazinone falls, while the yield of dianthranilide increases. Raising the reaction temperature leads to an increase in the yield of benzoxazinone in all cases.

The introduction of an electron-acceptor substituent into the anthranilic acid molecule results in the formation of different reaction products. In the case of 4-nitroanthranilic acid, primarily 2-(2-amino-4-nitrophenyl)-7-nitro-4H-3,1-benzoxazin-4-one (Vb) is formed at room temperature, while the corresponding Va and 4-nitro-N-(2-tosylamino-4-nitrobenzoyl)anthranilic acid (IVa) are formed in refluxing pyridine.

Tosylated substances are not formed at all in the reaction of p-toluenesulfonyl chloride with 5-nitroanthranilic acid. The reaction products are the corresponding Vb, the yield of which increases as the temperature rises, and 2-nitro-11H-pyrido[2,1-b]quinazolin-11-one (VII).

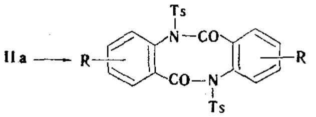


a X = Ts; b X = H

p-Toluenesulfonyl chloride reacts very readily with pyridine to give tosylpyridinium chloride [2]. This salt reacts with ionized (under the influence of pyridine) anthranilic acid primarily at the carboxyl group to give mixed anhydride I. Evidence in favor of this is the formation of only benzoylaniline during the reaction of a mixture of benzoic acid and aniline with p-toluensulfonyl chloride in pyridine in a ratio of 1 : 1 : 2. This experimental fact can be explained only as a result of the reaction of the initially formed mixed anhydride of benzoic acid and p-toluene sulfonic acid with aniline. It is known that this sort of mixed anhydride gives only benzoyl derivatives with nucleophilic reagents [3].

Pyridine, as a nucleophilic agent, reacts with mixed anhydride I or its tosylated derivative to give salts IIa and IIb. Salt IIa acylates the anthranilic acid anion at the carboxyl group to give mixed anhydride IIIa. In pyridine this reaction is reversible in pyridine. Under favorable conditions, however, intramolecular acylation similar to that which occurs for the anhydride of N-phenylanthranilic acid [4] can occur. In this case acid IVa is formed. The occurence of the reaction through a step involving the formation of IVa is confirmed by the fact that IVa is formed in addition to Va and N-tosylanthranilic acid in the reaction of insufficient p-toluenesulfonyl chloride with anthranilic acid. Compound IVa is readily converted to Va under the influence of tosylpyridinium chloride in pyridine. In fact, Va is formed in quantitative yield in the reaction of N-tosylanthranilylanthranilic acid with p-toluenesulfonyl chloride (1 : 1) in pyridine at room temperature. Since the conversion of IVa to Va proceeds readily, the sharp increase in the yield of Va as the temperature rises is explained by the high probability of the conversion of IIIa to IVa.

Another final product of the reaction of anthranilic acid with p-toluenesulfonyl chloride is N,N'-ditosyldianthranilide (VI), the formation of which is associated with the conversion of salt IIa. The following experimental facts are evidence for this: the yield of VI decreases appreciably when the amount of pyridine is increased by tenfold, and the yield of N-tosylanthranilic acid increases simultaneously; N-tosylanthranilic acid is converted quantitatively to VI in pyridine under the influence of p-toluenesulfonyl chloride.



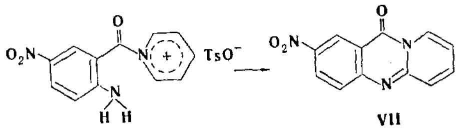
VI

Mixed anhydride IIIb, which gives Vb as a result of a chain of transformations similar to the transformations of IIa, is formed in the reaction of salt IIb with the anion of anthranilic acid.

The predominant occurrence of the reactions via one or another direction depends on the nature and position of the substituent in the anthranilic acid. The increased basicity of the amino group in 5-methoxyanthranilic acid increases the probability of the formation of salt IIa and the conversion of IIa to VI.

The nitro group in 4-nitroanthranilic acid is conjugated with the carboxyl group. This increases the probability of the formation of I and, particularly, IIb. The nitro group, which has a strong negative inductive effect, lowers the basicity of the nitrogen of the amino group and, consequently, hinders the formation of IIa. For these reasons, the reaction of 4-nitroanthranilic acid with p-toluenesulfonyl chloride should proceed primarily through salt IIb. In fact, the yield of the corresponding Vb at room temperature is 90%. The corresponding Va and IVa are formed at 114° in 51 and 42% yields, respectively. Thus, 4-nitroanthranilic acid reacts differently as a function of the temperature.

The nitro group in 5-nitroanthranilic acid is conjugated with the amino group, and this markedly hinders the formation of IIa and shifts the reaction to favor the formation of IIb. The occurrence of the reaction precisely through salt IIb is confirmed by the very fact of the formation of 2-nitro-11H-pyrido[2,1-b]quinazolin-11-one (VII), and the high yield of VII attests to the ease of formation of salt IIb. Compound Vb is formed in addition to VII. The yield of Vb increases at 114°, while the yield of VII decreases. This once again confirms that Vb is formed through IIb.



VII

It is apparent from the reaction scheme presented above that, if the reaction proceeds through a step involving the formation of salt IIb, untosylated amine Vb is obtained. In principle, the possibility of the conversion of Vb to Va under the influence of p-toluenesulfonyl chloride is not excluded. However, attempts to tosylate nitro-substituted amines Vb under the conditions of the formation of this amine do not give positive results. It follows from this fact and from the fact that Vb is absent in those cases when Va and VI are formed that the formation of different reaction products is explained by the existence of two reaction paths.

EXPERIMENTAL

General Method for Carrying Out the Reaction of Anthranilic Acids with p-Toluenesulfonyl Chloride. A solution of 0.04 mole of p-toluenesulfonyl chloride in 10 ml of pyridine was added with stirring to a solution of 0.02 mole of anthranilic acid in 10 ml of absolute pyridine. The mixture was stirred for another hour and was then carefully made alkaline at room temperature with aqueous sodium bicarbonate solution. The precipitate (A) was removed by filtration. Acidification of the filtrate with concentrated HCl precipitated B.

In experiments 1-8, 10 (see Table 1) precipitate A was treated with 80 ml of 2 N NaOH in the course of 1-2 min on a boiling-water bath (until the yellow-green luminescence vanished). In this case, benzoxazinone V hydrolyzed to N-tosylanthranilylanthranilic acid, while dianthranilide VI remained unchanged. It was removed by filtration to give N,N'-ditosyldianthranilide, N,N'-ditosyl-4,4'-dimethoxydianthranilide [mp 259.5° (from acetic acid). Found: C 59.5; H 4.5; N 4.3%. $C_{30}H_{26}N_2O_8S_2$. Calculated: C 59.4; H 4.3; N 4.6%] and N,N'-ditosyl-5,5'-dimethoxydianthranilide [mp 239° (from acetic acid). Found: C 59.5; H 4.4; N 4.5%. $C_{30}H_{26}N_2O_8S_2$. Calculated: C 59.4; H 4.3; N 4.6%]. The yield of benzoxazinone Va was judged from the amount of N-(N-tosylanthranilyl)anthranilic acid, N-(N-tosyl-4-methoxyanthranilyl)-4-methoxyanthranilic acid [mp 247.5° (from acetic acid). Found: C 58.3; H 4.7; N 5.9%. $C_{23}H_{22}N_2O_7S$. Calculated: C 58.7; H 4.7; N 5.9%], N-(N-tosyl-5-methoxyanthranilyl)-5-methoxyanthranilic acid [mp 209° (from acetic acid). Found: C 58.6; H 4.7; N 5.9%. $C_{23}H_{22}N_2O_7S$. Calculated: C 58.7; H 4.7; N 5.9%] or N-(N-tosyl-4-nitroanthranilyl)-4-nitroanthranilic acid [mp 197.5° (from acetic acid). Found: C 50.2; H 3.2; N 11.2%. $C_{21}H_{16}N_4O_9S$. Calculated: C 50.4; H 3.2; N 11.2%].

In experiment 9 precipitate A contained only 2-(2-amino-4-nitrophenyl)-7-nitro-4H-3,1-benzoxazin-4-one (Vb) with mp 298° (from dioxane). Found: C 51 4; H 2.4; N 17.4%. $C_{14}H_8N_4O_6$. Calculated: C 51.2; H 2.5; N 17 1%. The N-tosyl derivative of Va had mp 251.5° (from pyridine). Found: C 52.2; H 3 0; N 11.3%. $C_{21}H_{14}N_4O_8S$. Calculated: C 52.3; H 2.9; N 11.6%.

In experiments 11 and 12 precipitate A was treated with hot dichloroethane. The insoluble portion was 2-(2-amino-5-nitrophenyl)-6-nitro-4H-3,1-benzoxazin-4-one with mp 290° (from acetic acid). Found: C 51.2; H 2.8; N 17.1%. $C_{14}H_8N_4O_6$. Calculated: C 51.2; H 2.5; N 17.1%. The dichloroethane extract was vacuum-evaporated, and the residue was dissolved in 20 ml of pyridine. The pyridine solution was introduced into a column filled with aluminum oxide and eluted with acetone. The residue after evaporation of the acetone was crystallized from acetic anhydride to give 2-nitro-11H-pyrido[2,1-b]quinazolin-11-one (VII) with mp 265.5°. Found: C 60.2; H 2.8; N 17.2%. $C_{12}H_7N_3O_3$. Calculated: C 59.8; H 2.9; N 17.4%.

Precipitate B was a mixture of the corresponding N-tosyl- and N-tosylanthranilylanthranilic acids. N-Tosylanthranilic acid was converted to the acid chloride on refluxing with 10 ml of thionyl chloride for 30 min, while N-tosylanthranilylanthranilic acid was converted to the corresponding benzoxazinone (Va). The excess thionyl chloride was removed by vacuum distillation, and the residue was treated with saturated sodium bicarbonate solution. The yield of N-tosylanthranilylanthranilic acid was judged from the amount of insoluble precipitate (benzoxazinone Va).

This method was used to obtain 2-(2-tosylamino-4-methoxyphenyl)-7-methoxy-4H-3,1-benzoxazin-4-one [mp 257.5° (from acetic acid). Found: C 61.0; H 4.4; N 6.2%. $C_{23}H_{20}N_2O_6S$. Calculated: C 61.0; H 4.5; N 6.2%], 2-(2-tosylamino-5-methoxyphenyl)-6-methoxy-4H-3,1-benzoxazin-4-one [mp 216° (from acetic acid). Found: C 61.1; H 4.5; N 6.2%] and 2-(2-tosylamino-5-nitrophenyl)-6-nitro-4H-3,1-benzoxazin-4-one (see above for the characteristics). Acidification of the sodium carbonate filtrate yielded N-tosylanthranilic, N-tosyl-5-methoxyanthranilic [mp 186° (from 50% acetic acid). Found: C 56.0; H 4.9; N 4.5%. $C_{15}H_{15}NO_5S$. Calculated: C 56.1; H 4.7; N 4.4%], N-tosyl-4-methoxyanthranilic [mp 224° (from 50% alcohol). Found: C 56.0; H 4.7; N 4.4%. $C_{15}H_{15}NO_5S$. Calculated: C 56.1; H 4.7; N 4.4%] or N-tosyl-4-nitroanthranilic acid [mp 226.5° (from dioxane). Found: C 50.1; H 3.4; N 8.4%. $C_{14}H_{12}N_2O_6S$. Calculated: C 50.0; H 3.6; N 8.3%].

In the case of 4-nitroanthranilic acid (reaction at room temperature), a portion of the acid remained unchanged, and in order to remove it the precipitate that formed on pouring the reaction mass into water was first treated with concentrated HCl.

Because of the limited solubility of 4- and 5-nitroanthranilic acids at room temperature, 50 ml of pyridine was used to dissolve them.

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