Studies on Nitration of Furan Derivatives. Part I. On the Nitration of Furan-carboxylic Acid[*]

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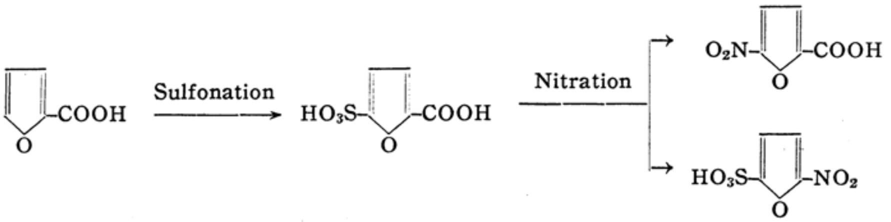
Many types of α-nitrofuran derivatives have been synthesized by Saikachi and the present author to find any chemotherapeutically interesting compound.[1] In every case, the nitration of furan derivatives appears to be the most important. The object of the present studies is to find out the relationship between the structure of furan derivatives and the possibility of their nitration. In this paper the nitration of furan-carboxylic acid is reported.

As to the preparation of nitrofuran-carboxylic acid, there have been several methods,[2] but only a few of them are thought to be applicable for practical use. Hill and his collaborators[3,4] succeeded in carrying out the preparation of nitrofuran-carboxylic acid, in which furan-carboxylic acid was at first sulfonated with fuming sulfuric acid, then nitrated with fuming nitric acid. Their results showed that the product of sulfonation was stable against an acidic reagent and when it was treated with fuming nitric acid, it was converted to nitrofuran-carboxylic acid and nitrofuran-sulfonic acid by nitrosubstitution after decarboxylation or desulfonation as follows:



As, unfortunately, their reports lacked details on the experiments, the present study was carried out. In Part I, the nitration of furan-carboxylic acid was carried out in accordance with the procedure of Hill and White[4] and the relation of the yield of the product to the temperature and the time of reaction was studied. In Part II, the yield of the nitration of sulfofuran-carboxylic acid, obtained by the sulfonation of furan-carboxylic acid, in accordance with the procedure of Hill ane Palmer[3], was investigated. In Part III, the nitration of sulfofuran-carboxylic acid by the mixture of fuming nitric acid and acetic anhydride was studied.

Experimental

I. Nitration of Furan-carboxylic Acid

30 g. of furan-carboxylic acid was sulfonated with 90 g. of fuming sulfonic acid (d=1.951), with stirring below 20°C according to the known method[5]. After allowing it to stand at room temperature for one day, the resulting black viscous mixture was nitrated with 75 g. of fuming nitric acid (d=1.46), by dropping it to the solution at 0°, and then warming it gradually to the definite temperature as shown in Table I, and kept for three hours. The further treatment was the same as the procedure of Hill and White[4]. When the reaction mixture was above 40°, considerable bubbling started and the viscosity of the mixture diminished, the color turning to a light yellow. Above 50° the evolution of nitrogen oxide was observed. As shown in Table I, the lower the temperature of the reaction, the larger the yield of nitrofuran-carboxylic acid. The increasing yield of dinitrofuran with the rising of the temperature of the reaction is probably due to the conversion of nitrofuran-carboxylic acid into dinitrofuran and the conversion is presumably promoted by a catalytic action of the present sulfuric acid. Furthermore, in this reaction the production of nitrofuran-sulfonic acid can hardly be seen. This fact clearly shows that nitrofuran-sulfonic acid is more easily convertible to dinitrofuran than nitrofuran-carboxylic acid is. The effect

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[1] T. Takahashi, H. Saikachi and T. Sasaki, *J. Pharm. Soc. Japan*, **68**, 42 (1948); **69**, 284 (1949).

[2] Four methods are given in Beilstein's Org. Chem., **18**, 287 (Hauptband).

[3] H. B. Hill and Palmer, *Am. Chem. J.*, **10**, 380 (1888).

[4] H. B. Hill and R. White, Ibid., **27**, 196 (1905).

[5] H. Schwanert, *Ann.*, **116**, 269 (1860); H. Hodgson and H. R. Davies, *J. Chem. Soc.*, 806 (1939).

with the time of the reaction at 7° after the addition of fuming nitric acid on the yield is given in Table II. The products in the above experiments were identified by their m.p. which were in good accordance with the description of Hill and White[4].

TABLE I

No.	Reaction Temp.	N.F.C.*	Yield	D.F.*	Yield	N.F.S.*	Yield
1	0 °C	13.5 g.	32%**	1.2 g.	3%	Trace	
2	10	12.0	30	1.5	3.5	—	
3	20	7.0	17	2.0	5	—	
4	30	4.0	10	3.5	8	—	
5	40	4.0	10	3.0	7	—	
6	50	1.0	2.5	4.0	10	—	
7	60	—		3.0	7	—	

* N.F.C.: nitrofuran-carboxylic acid, m.p. 184°.
N.F.S.: nitrofuran-sulfonic acid potassium salt.
D.F.: dinitrofuran, m.p. 101°.

** The maximum yield ever reported.

TABLE II

No.	Reaction Time	N.F.C	Yield	D.F.	Yield	N.F.S.	Yield
8	1 hour*	8.5 g.	20%	0.5 g.	1.2%	Trace	
9	1 day*	11.5	28	1.0	2.5	—	
10	3 days**	10.0	24	1.8	4.0	—	
11	7 days**	9.0	22	2.5	6.0	—	

* After nitric acid was added to a strirred solution at 7°, stirring was continued for one hour at 7°.

** After stirring of the mixture was continued for one hour at 7°, the mixture was left to stand at room temperature of 20° for 1, 3 and 7 days, respectively.

II. Indirect Nitration of Furan-carboxylic Acid*

Nitration was carried on the sulfofuran-carboxylic acid which was obtained from furan-calboxylic acid, after sulfonation similar to that in part I. Sulfofuran-carboxylic acid was obtained in the form of the barium salt by Hill and Palmer[3] and no physical constants of the free acid have been reported. The present author obtained free sulfofuran-carboxylic acid from its salt as follows: the calcium salt which was obtained by the same procedure as the barium salt, was treated with the calculated amount of sulfuric acid and the resulting calcium sulfate was filtered off. After the filtrate was condensed on a boiling water bath till its color changed to black, it was left to stand in a desiccator of conc. sulfuric acid for several days to yield a colorless amorphous solid of sulfofuran-carboxylic acid, which was used for nitration. The yield of the acid was 85% of the theoretical amount, calculated from the starting furan-carboxylic acid.

20 g. of sulfofuran-carboxylic acid was portionwise added to a stirred 60 g. of fuming nitric acid (d=1.46), at several reaction temperatures and the mixture was stirred for a while or left to stand at room temperature as shown in Table III. The following procedure and identification of the products were the same as those described by Hill and Palmer[3]. The results are shown in Table III, which indicates that at lower temperature the yield of nitrofuran-sulfonic acid is comparable to that of nitrofuran-carboxylic acid and the production of dinitrofuran can hardly be seen, but with the rising of the temperature, both yields, of nitrofuran-sulfonic acid and -carboxylic acid, decreased.

III. Nitration of Sulfofuran-carboxylic Acid

11 g. of sulfofuran-carboxylic acid was portionwise added at −5° to the nitrating mixture which was previously prepared by mixing 28 g of fuming nitric acid (d=1.46), with 60 g. of acetic anhydride at −10°. After the addition of sulfofuran-carboxylic acid, stirring was continued for three hours and then the reaction mixture was poured on ice and neutralized with potassium carbonate. Following the procedure of Hill and Palmer[3], there were obtained nitrofuran-carboxylic acid as a main product and dinitrofuran as a by-product and the production of nitrofuran-sulfonic acid could not be seen. The results given in Table IV show that desulfonation takes place more easily to some extent than decarboxylation.

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* Indirect nitration means that nitrofuran-carboxylic acid was obtained by the nitration of isolated sulfofuran-carboxylic acid, prepared by sulfonation of furan-carboxylic acid.

TABLE III

No.	Reaction Condition	N.F.C.	Yield	D.F.	N.F.S.	Yield
12	Addition at 10°, stirring at 10° for 5 hrs.	3.5 g.	22%	—	5.0 g.	20%
13	Addition at 10°, stirring at 30° for 5 hrs.	5.0	31	Trace	5.5	22
14	Addition at 10°, stirring at 45° for 5 hrs.	4.0	25	Trace	5.0	20
15	Addition at 10°, standing at 20°* for 3 days	5.0	31	—	4.5	18.5
16	Addition at 23°, stirring at 23° for 6 hrs.	4.0	25	—	4.5	18.5
17	Addition at 23°, standing at 20°* for 3 days	4.0	25	—	5.0	20
18	Addition at 60°, stirring at 60° for 6 hrs	2.0	13	1.0 g. (6%)	1.0	4
19	Addition at −3°, stirring at −3° for 2 hrs	3.5	22	—	4.5	18.5

* Room temperature of 20°.

TABLE IV

No.	Reaction Temp.	N.F.C.	Yield	D.F.	Yield	N.F.S.
20	− 5°C	2.5 g.	16%	0.3 g.	2%	—
21*	− 5	2.8	17	0.5	3	—
22	−10	2.5	16	0.15	1	—

* One drop of conc. sulfuric acid was added to the reaction mixture.

Summary

From the preparative point of view, the nitration of furan-carboxylic acid after sulfonation was studied with the following results:

(1) In order to obtain nitrofuran-carboxylic acid, the nitration of furan-carboxylic acid after sulfonation was carried out without separating the sulfonation product at several temperatures and the yield at 0° was about 32%, the highest ever known.

(2) In order to obtain nitrofuran-sulfonic acid, indirect nitration of sulfofurancarboxylic acid should be carried out at a low temperature, such as below 10°; the yield of which amounts to 20–22%. However, in this case, nitrofuran-carboxylic acid is produced simultaneously as a by-product.

(3) When the nitration of sulfofuran-carboxylic acid was carried out by using acetic anhydride and fuming nitric acid, nitrofuran-carboxylic acid and dinitrofuran were obtained, but not nitrofuran-sulfonic acid. This showed that desulfo-nitrosubstitution took place more easily than decarboxy-nitrosubstitution.

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