Title: Application of the Decarboxy-nitrosustitution Reaction on Nitration of Furan Derivatives

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Citation: Bulletin of the Institute for Chemical Research, Kyoto University (1955), 33(2): 39-48

Issue Date: 1955-03-31

URL: http://hdl.handle.net/2433/75503

Type: Departmental Bulletin Paper

Textversion: publisher

Kyoto University
Application of the Decarboxy-nitrosustitution Reaction on Nitration of Furan Derivatives*

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Received January 13, 1955

The decarboxy-nitrosubstitution reaction is discussed as a general preparation of α-substituted furan derivatives. As a rule, this reaction is successful for derivatives with a nucleophilic substituent, but only poor results are obtained for those on the compounds with an electrophilic one. In the latter case, with increasing negativity of the substituent the more drastic condition is required.

INTRODUCTION

In general, the substitution reactions of furan derivatives, although relatively ready to occur, are often difficult to be controlled because of the sensitivity of the furan nucleus to the acid reagents. The sensitivity, or stability of the ring toward acidic cleavage varies over a wide range and is determined by the type of ring substituents and by the reaction conditions, such as concentration of acid and temperature. The relationship between the structure and reactivity of furan derivatives was studied by the author***. In this paper the application of the decarboxy-nitrosubstitution to various furan derivatives is reported.

The first example of the nitration of furan derivatives was reported by Klinkhardt:

\[ \text{HOOC} - \text{COOH} \rightarrow \text{O}_2\text{N} - \text{COOH} \]

This nitration is clearly a D-N reaction****. As reported before†, the nitration of furan-carboxylic acid is another D-N reaction. In Table 1, V is furan. From I to IV the furan derivatives with a nucleophilic substituent are represented and from VI to XI those with an electrophilic substituent. If we want to obtain a 5-nitro-2-R-substituted furan derivative, it is a common method that a proper starting material is nitrated according to the following two routes, either through i or ii:

* Part III, Studies on Nitration of Furan Derivatives; Part I and II, see Reference, (1).
**佐々木正
*** D-N reaction means decarboxy-nitrosubstitution reaction and is considered a displacement of carboxyl group by the nitro group.
Table 1. Preparation of 5-nitro-2-R-substituted furan.

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>R</th>
<th>Reaction type i</th>
<th>Product</th>
<th>Reaction type ii</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>NHCOCH₃</td>
<td>Dinitro Compds</td>
<td>←</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>OH</td>
<td></td>
<td>←</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>CH₃</td>
<td>Mononitro Compd</td>
<td>←</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Br</td>
<td></td>
<td>←</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>H</td>
<td></td>
<td>←</td>
<td></td>
</tr>
<tr>
<td>VI</td>
<td>CHO</td>
<td></td>
<td>←</td>
<td></td>
</tr>
<tr>
<td>VII</td>
<td>COCH₃</td>
<td></td>
<td>(Hardly occur)</td>
<td></td>
</tr>
<tr>
<td>VIII</td>
<td>CH₂OCOCH₃</td>
<td></td>
<td>←</td>
<td>(Drastic nitration)</td>
</tr>
<tr>
<td>IX</td>
<td>COCH₂COOC₂H₃</td>
<td></td>
<td>←</td>
<td>(Drastic nitration)</td>
</tr>
<tr>
<td>X</td>
<td>COOH</td>
<td></td>
<td>←</td>
<td></td>
</tr>
<tr>
<td>XI</td>
<td>NO₂</td>
<td>(Drastic nitration)</td>
<td>←</td>
<td></td>
</tr>
</tbody>
</table>

Here the reaction type i is the usual nitration, and the type ii is the so-called D-N reaction.

As reported before, the desulfoxy-nitrosubstitution reaction is more advantageous than the D-N reaction in its yield and its simple procedure, although it has the difficulty of sulfonation of furan derivatives. Therefore in the present study the D-N reaction was studied. Most of the nitration were carried out by using a mixture of fuming nitric acid (d. 1.46) and acetic anhydride.

EXPERIMENTAL

I. 2-(5-Nitro) acetylaminofuran

Acetylaminofuran was prepared by the decarboxylation of acetylaminofuran-carboxylic acid and therefore, the nitration of 2-acetylaminofuran-carboxylic acid was carried out, except for 2-acetylaminofuran.

Acetylaminofuran-carboxylic acid (2.4 g.) was added portionwise to a stirred mixture of 20 cc. of acetic anhydride and 9 g. of fuming nitric acid at -7°. The resulting mixture, turning to red in color, was stirred for two and a half hours at the same temperature, poured on cracked ice and left standing overnight. The resulting light yellow solution was neutralized slightly to acid by an aq. sodium carbonate solution and then extracted with ether. The ether layer was washed with sodium carbonate solution until the washing layer became alkaline. From the ether layer 0.5 g. of light yellow crystals, m.p. 155°, decomp. 160°, was obtained after recrystallization from ethanol-water mixture.
Application of the Decarboxy-nitrosubstitution

Anal. Calcd.* for C₆H₆O₂N₂ : C, 42.35 ; H, 3.53 ; N, 16.47.
C₆H₆O₂N₂ : C, 33.49 ; H, 2.33 ; N, 19.53.
Found : C, 33.90 ; H, 3.05 ; N, 19.53.

Elementary analysis of the resulting product showed acetylamino-dinitrofuran and not 2-(5-nitro) acetylamino-furan. Concerning the position of two nitro groups in furan nucleus, there has been no direct evidence, but judging from the result of the nitration of 2-methyl-5-nitrofuran to 2-methyl-3,5-dinitrofuran, this dinitro compound is thought to be 2-acetylamino-3,5-dinitrofuran and initially produced 2-acetylamino-5-nitrofuran might be further nitrated to this dinitro compound.

II. 2-(5-Nitro)hydroxylfuran

The synthesis of 2-hydroxylfuran has been carried out by decarboxylation of 2-hydroxylfuran-carboxylic acid. But the author's reinvestigation on the preparation of this hydroxylfuran has been failed in spite of the numerous trials.

III. 2-(5-Nitro)methylfuran

Rinkes reported on both methods of nitration. The yield of nitromethylfuran by the usual method was about 20 % and the formation of the so-called nitration intermediate was observed. The yield by the D-N reaction was 33 % with a small amount of 5-methyl-4-nitrofuran carboxylic acid as a by-product.

IV. 2-(5-Nitro)bromofuran

Since bromofuran, the starting material for the type i nitration, was labil, the type i nitration is not suitable for preparing nitrobromofuran. On the contrary, 5-bromofuran-carboxylic acid was easily obtained by the bromination of furan-carboxylic acid. This bromination, however, did not give the constant yield, ranging irregularly from 40 to 60 % according to the literature. Since this reaction took place between solid acid and gaseous bromine, it was conceivable the yield to be influenced by the contact area between these two phases, the bromination method was modified in the present study and was found to give a constant 65 % yield.

Thirty grams of dry, fine powdered furan-carboxylic acid was scattered on thin layers of glass wool which were piled carefully in a 1 L-three-necked flask. The flask was equipped with a Dimroth cooler on the central mouth and a dropping funnel on one side mouth, the third being closed with a rubber stopper. The flask was immersed in a water bath up to its mouth. When the bath water was boiled violently a part of the acid sublimed, but the loss of this acid was minimised by the piled glass wool. 40.5g. of bromine was added dropwise from a dropping funnel at such a rate that the refluxed amount of bromine was small as possible. After the addition of bromine, boiling of the water bath was continued, till the evolution of hydrogen bromide gas ceased completely which took for about two or three
hours. Excess of bromine was removed from the flask under slight vacuum and 500 cc. of water mixed with a small amount of Norite was added, and the mixture was boiled and filtered while hot. This procedure was repeated thrice to result in a 65 % yield of bromofuran-carboxylic acid, mp. 183-4°, which was used for the following nitration.

Nitration of bromofuran-carboxylic acid was carried out under several conditions according to the procedure of Rinkes101. The results shown in Table 2 explain the following facts: (i) The maximum yield was obtained when nitration was controlled so as to prevent from remaining of the unreacted material, that is, when the addition of nitric acid was divided in two parts and one drop of sulfuric acid was added to the reaction mixture. In that case the mole ratio of bromofuran-carboxylic acid, fuming nitric acid and acetic anhydride was 1 : 7.6 : 15.3 (30 g. : 90 g. : 240 g.). (ii) In order to complete the D-N reaction, the reaction temperature need not to be so low as other nitration*, and the time of stirring after addition of the starting material was two or three hours. (iii) The best yield was 56 %, the highest even known.

* The reaction temperature was an important factor when furfurylacetate was nitrated as shown later in this paper.

<table>
<thead>
<tr>
<th>B.F.C. in Ac₂O</th>
<th>Nitr. HNO₃</th>
<th>Mix. Ac₂O</th>
<th>Reaction Temp.</th>
<th>Dropping Hour</th>
<th>Stirring Hour</th>
<th>Product (Yield %)</th>
<th>Recovered B.F.C.</th>
</tr>
</thead>
<tbody>
<tr>
<td>30g. in 150cc.</td>
<td>80g.</td>
<td>180cc.</td>
<td>-5°</td>
<td>2</td>
<td>4</td>
<td>8.5g. (28)</td>
<td>4g.</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>150</td>
<td></td>
<td></td>
<td></td>
<td>10.0 (33)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>150</td>
<td></td>
<td></td>
<td></td>
<td>11.0 (36)</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>150</td>
<td></td>
<td></td>
<td></td>
<td>10.0 (33)</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>120</td>
<td></td>
<td></td>
<td></td>
<td>12.5 (42)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td>15.0 (50)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>80</td>
<td></td>
<td></td>
<td></td>
<td>13.5 (45)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>150</td>
<td></td>
<td></td>
<td></td>
<td>10.0 (33)</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>150</td>
<td>15</td>
<td>1</td>
<td>3</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>60+30a</td>
<td>90</td>
<td>-5</td>
<td>2</td>
<td>4</td>
<td>11.0 (36)</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>60+30b</td>
<td>90</td>
<td></td>
<td></td>
<td></td>
<td>17.0 (50)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>150</td>
<td>150</td>
<td></td>
<td></td>
<td></td>
<td>9.0 (30)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>90</td>
<td>-11</td>
<td>2</td>
<td></td>
<td>8.5 (28)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>84</td>
<td>180</td>
<td>-7</td>
<td>1½</td>
<td>5</td>
<td>5.4 (18)</td>
<td>5.7</td>
</tr>
<tr>
<td>34</td>
<td>180</td>
<td>100</td>
<td>200</td>
<td>2</td>
<td>3</td>
<td>8.2 (28)</td>
<td>6</td>
</tr>
<tr>
<td>28</td>
<td>100</td>
<td>49</td>
<td>100</td>
<td>2</td>
<td>3½</td>
<td>8.3 (28)</td>
<td>5.4</td>
</tr>
<tr>
<td>a 60+30 means that the addition of fuming nitric acid was divided in two parts, 60g. and 30g., which were added separately.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| b In this case, the addition of nitric acid was divided in two parts and one drop of conc. sulfuric acid was added to the reaction mixture and the best yield, 56 %, was obtained.
Application of the Decarboxy-nitrosubstitution

V. 2-Nitronfuran

Nitration of furan by the reaction type i was reported by Marquis, and Freure and Johnson, but they did not describe the yield. As this nitration was thought to be the standard for other furan derivatives, it was studied quantitatively concerning the relationship between the nitration temperature and the yield.

A solution of 30 g. of furan in 60 g. of acetic anhydride was nitrated under stirring at -7° with the mixture of 150 g. of acetic anhydride and 100 g. of fuming nitric acid. The color of the reaction mixture turned from yellow to blue. Stirring was continued at the same temperature for one hour after the addition. Then it was poured on cracked ice and left standing overnight. A small amount of a yellow precipitate, 1 g., was filtered to give yellow crystals, mp. 210° (decomp.).

Anal. Calcd. for C₈H₈O₆N₂ : C, 42.40 ; H, 1.90 ; N, 12.05.
Found : C, 42.43 ; H, 2.10 ; N, 12.17.

By the above elementary analysis this compound was identified to be dinitrodifuryl, reported by Rinkes. The filtered yellow solution was extracted with ether and the ether layer was treated with an aq. Na₂CO₃ solution to result in an ether insoluble precipitate, 0.02 g. of a yellow powder, mp. 167-175° (decomp.), which was identified to be the same compound as that of decomp. p. 210° from the elementary analysis after further purification.

The ether layer was dried with anhydrous Na₂SO₄, and ether removed to give 10 g. of a red oil, which was treated with the same amount of pyridine to result in a dark red solution with some evolution of heat. It was left to cool at room temperature and was decomposed with HCl. The mixture was distilled with steam and the water distillate was extracted with ether, from which 6.5 g. of nitrofuran, mp. 28°, was obtained. During the storage in a bottle, some part of nitrofuran has changed into a high melting compound of unknown structure.

When the same nitration was carried out under the different temperatures, the yield of the produced nitrofuran varied, viz., the yield was 20 % at -15° (0.6 g. of dinitrodifuryl), 12 % at -7° (1.02 g.) and 5 % at -3° (2 g.). In other words, the production of dinitrodifuryl was inevitable, and the yield of dinitrodifuryl was larger and that of nitrofuran was smaller with the rise of nitration temperature. Therefore, it was necessary to keep the nitration temperature as low as possible in order to increase the yield.*

Nitration of furan-carboxylic acid to nitrofuran by the D-N reaction was carried out by Rinkes, where nitrofuran and nitrofuran-carboxylic acid were obtained.

---

* The mechanism of the formation of dinitrodifuryl in the course of nitration of furan is very interesting. Presumably nitration intermediate (A) of furan once produced is deacetylated simultaneously by two routes, i and ii, to nitrofuran (B) and dinitrodifuryl (C) as follows:

( 43 )
with low yields.\textsuperscript{23}

VI. 2-(5-Nitro)furfural

Nitrations of furfural diacetate and furfural were reported\textsuperscript{7} by Gilman\textsuperscript{3} and recently by Saikachi et al\textsuperscript{14}. The application of the D-N reaction was not suitable for the preparation of nitrofurfural because of the difficulty of the preparation of its starting material, 5-formyl-2-furfural.

VII. 2-(5-Nitro)acetylfuran

Rinkes\textsuperscript{15} reported on the nitration of acetylfuran and in this case nitroacetylfuran was obtained as a main product and nitrofuran as a by-product. This showed that the acetyl group can be displaced by nitro group like carboxyl or sulfonyl group. In this study D-N reaction was carried out in parallel with the reinvestigation of the nitration of acetylfuran.

Nitration of acetylfuran was carried out according to nearly the same procedure as that of Rinkes\textsuperscript{15} but the nitration temperature was \(-3^\circ\). The results of the experiments are given in Table 3. The maximum yield of nitrofuran-carboxylic acid was only 15%.

<table>
<thead>
<tr>
<th>A.F. in Ac(_2)O</th>
<th>Nitrating HNO(_3)</th>
<th>Mixture Ac(_2)O</th>
<th>Nitrating Temperature</th>
<th>N.F. (Yield)</th>
<th>N.A.F. (Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18g. 36cc. 90g. 144cc. -3(^\circ)</td>
<td>3.0g. (16%)</td>
<td>4.0g. (15%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 20 63 102</td>
<td>-3(^\circ)</td>
<td>4.0 (16)</td>
<td>3.0 (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 48 75</td>
<td>-2 (30)</td>
<td>3.0 (27)</td>
<td>2.0 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 32 51</td>
<td>-2 (30)</td>
<td>3.5 (30)</td>
<td>2.0 (13)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(a\) Products: N.F. is nitrofuran, mp. 28\(^\circ\), and N.A.F. is nitroacetylfuran, mp. 77-8\(^\circ\).

\(b\) In the course of procedure after nitration, Na\(_2\)CO\(_3\) was used instead of pyridine. For the purpose of separating nitrofuran and nitroacetylfuran, vacuum distillation was applied directly to the ether extract of the product. The same procedure was repeated in the following three experiments.

Nitration of acetylfuran-carboxylic acid was carried out under several conditions. The results in Table 4 show that the D-N reaction took place with diffi-

\[
\begin{align*}
\text{O} & \quad \text{N} \quad \text{NO}_2 \quad \text{(B)} \\
\text{NO}_2^+ \text{OCOCH}_3 & \quad \text{H} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \\
\text{O} & \quad \text{O} \quad \text{NO}_2 \quad \text{(C)}
\end{align*}
\]

Application of the Decarboxy-nitrosubstitution

Table 4. Nitration of acetylfuran-carboxylic acid (A. F. C.).

<table>
<thead>
<tr>
<th>A.F.C.</th>
<th>Nitration Mixture</th>
<th>Reaction Condition</th>
<th>Recovered A. F. C.</th>
<th>Product (Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2g. HNO(_3) (a), 4cc.</td>
<td>30(^\circ), 5 hrs.</td>
<td>1.7g.</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>60(^\circ), 3 hrs.</td>
<td>1.7</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>8cc.; H(_2)SO(_4) (b), 8cc.</td>
<td>15(^\circ), 1 day</td>
<td>2.0</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>30cc.; H(_2)SO(_4), 10cc.</td>
<td>60(^\circ), 3 hrs.</td>
<td>3.0</td>
<td>trace</td>
</tr>
<tr>
<td>4, 5</td>
<td>14cc.; Ac(_2)O, 50cc.</td>
<td>10-15(^\circ), 4 hrs.</td>
<td>2.0</td>
<td>0.05g. (2%)</td>
</tr>
<tr>
<td>5</td>
<td>HNO(_3), 4cc.; Ac(_2)O, 55cc.; H(_2)SO(_4), 5cc.</td>
<td>10(^\circ), 2 hrs.</td>
<td>2.0</td>
<td>0.15g. (5%)</td>
</tr>
</tbody>
</table>

\(a\) HNO\(_3\); d : 1.46, \(b\) H\(_2\)SO\(_4\); d : 1.840.

VIII. 2-(5-Nitro)furfurylacetate

Furfurylalcohol is a comparatively labil compound and the nitration of this compound should be carried out after replacing its hydroxyl group with chlorine, acetoxyl or methoxyl radical as reported by Gilman\(^{10}\). In order to improve the yield, nitration of furfurylacetate was carried out by changing the reaction temperature and the results are given in Table 5, which shows that the nitration table and required a long reaction time probably on account of the acetyl radical, an electrophilic one.

Table 5. Nitration of furfurylacetate (F.Ac.).

<table>
<thead>
<tr>
<th>F.Ac. in Ac(_2)O</th>
<th>Nitration HNO(_3) Mixture Ac(_2)O</th>
<th>Reaction Temp.</th>
<th>Product (Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7g. 10cc. 8.7g. 30cc.</td>
<td>-5(^\circ)</td>
<td>2.5g. (27%)</td>
<td></td>
</tr>
<tr>
<td>&quot; &quot; &quot; &quot;</td>
<td>-10</td>
<td>3.0 (32)</td>
<td></td>
</tr>
<tr>
<td>&quot; &quot; &quot; &quot;</td>
<td>-15</td>
<td>3.0 (32)</td>
<td></td>
</tr>
<tr>
<td>&quot; &quot; &quot; &quot;</td>
<td>-20</td>
<td>4.0 (43)</td>
<td></td>
</tr>
<tr>
<td>&quot; &quot; &quot; &quot;</td>
<td>-25</td>
<td>5.0 (54)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>5.5 (60)</td>
<td></td>
</tr>
<tr>
<td>&quot; &quot;</td>
<td>&quot;</td>
<td>3.0 (32)</td>
<td></td>
</tr>
</tbody>
</table>

\(a\) Nitrofurfurylacetate, mp. 40-44\(^\circ\).

v One drop of conc. sulfuric acid was added, and the best yield, 60%, was obtained.

temperature was an important factor, the lower the temperature, the better the yield, and the yield was improved somewhat by the addition of a small amount of conc. sulfuric acid.

IX. 2-(5-Nitro)furoylacetate

Ethyl furoylacetate\(^{17}\) was nitrated as follows: A solution of 5 g. of ethyl furoylacetate, bp. \(\approx\) 170\(^\circ\), in 10 cc. of acetic anhydride was nitrated with a mixture of 9 g. of fuming nitric acid and 20 cc. of acetic anhydride at -7\(^\circ\). It took about an hour to drop the ester solution into the nitration mixture. The reaction mix-
ture changed its color into dark green. Stirring was continued for 2.5 hours at
the same temperature and then the mixture was poured on cracked ice to result
in an oily substance, which was extracted with ether and the ether layer was
washed with an aq. Na₂CO₃ solution until the latter became slightly alkaline. The
ether layer was further washed with a small amount of water and dried with
anhydrous Na₂SO₄. After removing ether, 2 g. of a red oil was obtained which
was mixed with 2 cc. of pyridine under cooling and then neutralized with dil.
HCl. The resulting solution was extracted with ether. After removing ether,
1.4 g. of light yellow crystals, mp. 91-3°, was obtained, yield 44.5%.

Anal. Calcd. for C₉H₉O₆N : C, 47.54 ; H, 3.96.
 Found : C, 47.71 ; H, 4.30.

X. 2-(5-Nitro)furan-carboxylic acid

Nitration of furan-carboxylic acid was already discussed before (V)¹² and
that of furan-dicarboxylic acid has been reported by Klinkhardt¹³ who used, as a
nitrating reagent, the warm mixture of nitric acid and conc. sulfuric acid. This
nitration did not take place by using the mixture of fuming nitric acid and acetic
anhydride at -5°. It was interesting, that the so-called nitration intermediate of
ethyl furoate could be isolated according to the method of methyl furoate¹¹. It
was a colorless plate crystal, mp. 48-50°, decomposed at 70-72°, after recrystalliza-
tion from absolute alcohol, and was stable in the air. This compound was readi-
ly convertible to ethyl nitrofuroate, mp. 99-101°³ by treating with pyridine. From
this result the structure of this nitration intermediate was supposed to be

\[
\begin{align*}
\text{NO}_2 & \quad \text{COOC}_2\text{H}_5 \\
\text{H} & \quad \text{O} \\
\text{OCOCH}_3 & \\
\text{C}_3\text{H}_7\text{O}_2\text{N}.
\end{align*}
\]

Anal. Calcd. for C₉H₉O₂N : C, 44.08 ; H, 4.49 ; N, 5.71.
 Found : C, 42.89 ; H, 4.50 ; N, 5.73.

XI. 2,5-Dinitrofuran

Nitrofuran as well as nitrofuran-carboxylic acid could not be nitrated by the
mixture of fuming nitric acid and acetic anhydride. Nitration of nitrofuran was
carried out by warming with nitric acid³, and that of nitrofuran-carboxylic acid
was also carried out by warming with the mixture of nitric acid and sulfuric
acid¹⁸.

DISCUSSION

From the experimental results it was deduced that the D-N reaction was a
good method for the nitration of furan derivatives bearing nucleophilic radicals,
such as NHCOCH₃, CH₃ and Br. However, when acetylamino-furan-carboxylic acid
was nitrated, the intermediate compound nitroacetylamino-furan might be assumed to be further nitrated to a dinitro compound. Generally, the compounds from I to IV in Table 1 the introduction of the electrophilic carboxyl group causes presumably to strengthen the stability against acid reagent and consequently their nitration becomes possible, though the furan derivatives without carboxyl group are labil against acid reagents. Furthermore, the decarboxylation due to the nucleophilic groups is more favorable than that due to the electrophilic ones. These conclusions might be consistent with the electronic consideration of furan compounds. This D-N reaction would proceed through the formation of unstable nitration intermediate. Unstability of the intermediate due to the two electrophilic groups, nitro and carboxyl, on the same carbon atom and might cause decarboxylation instantly as follows:

\[
\begin{align*}
\text{R-COOH} & \xrightarrow{\text{N}} \text{R-NO\textsubscript{2}CO\textsubscript{2}H} \\
\text{instantly} & \rightarrow \text{R-\text{NO\textsubscript{2}}+\text{CO\textsubscript{2}}+\text{AcOH}}
\end{align*}
\]

The D-N reaction took place generally by treating a mixture of fuming nitric acid and acetic anhydride at low temperature with the furan compounds \(\alpha\)-substituted with nucleophilic groups but with those of electrophilic substituents it proceeded either slowly or with difficulty and whereby it was necessary to heat the reaction mixture under the use of fuming nitric acid or the mixture with conc. sulfuric acid as in the case of nitration on furan-dicarboxylic acid or nitrofuran-carboxylic

* Furan has two electron lone pairs at oxygen atom as shown in (I). When a \(\alpha\)-hydrogen of furan nucleus is substituted by a nucleophilic group such as methyl in (II), electron-donating power of oxygen atom becomes stronger and consequently furan nucleus is easily destroyed by acid reagents. However, the electron density of another \(\alpha\)-carbon atom becomes more negative and it favors nitration, cationoid substitution.

When an \(\alpha\)-position of furan nucleus is substituted by an electrophilic group such as nitro in (III), the above relation reverses.

\[
\begin{align*}
\text{(I)} & \quad \text{(II)} & \quad \text{(III)}
\end{align*}
\]

** The stability of the nitration intermediate will depend on the structure of the adduct and only such an intermediate product which is stable and able to be isolated in a crystalline state is reported up to this time. This is the reason why the nitration intermediate of furan-carboxylic ester (methyl and ethyl) and furfural diacetate can be isolated.

Cf : (11)

acid. For the compounds VI-XI, the usual nitration provides a good method for the nitration. In these cases, however, with increase in negativity of the substituent, the nitration became more difficult to proceed and drastic condition should be applied as in the case of the nitration of nitrofuran.

ACKNOWLEDGMENT

The author is much indebted to Prof. H. Saikachi of Kyushu University for giving him many helpful advices and encouragement in the course of this study. Acknowledgment should also be given to Miss H. Iwata and Mr. K. Imaeda, who helped him in the elementary analysis.

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