In Investigation of Quinoline Derivatives

III. Dinitro Derivatives of 1,2,3,4-Tetrahydroquinoline

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Some dinitro derivatives of 1,2,3,4-tetrahydroquinoline and its N-acyl analogs were synthesized. The structures of the dinitro isomers obtained were confirmed by NMR, UV, and IR spectroscopic data.

Several dinitro isomers of the 1,2,3,4-tetrahydroquinoline (THQ) series were synthesized to obtain potential physiologically active THQ derivatives. In the present study, the previously obtained [2] 6-nitro-(I) and 7-nitro-THQ (II) and their N-acyl analogs were nitrated in order to synthesize the dinitro isomers.

Except for 6,8-dinitro-THQ (III) [3-5], dinitro derivatives of the tetrahydroquinoline series are unknown in the literature. The methods described in the literature for the synthesis of this compound reduce to nitration of various N-substituted THQ in an aprotic solvent with fuming nitric acid. We obtained this same isomer in 50% yield by nitration of N-formyl-THQ with a nitrating mixture containing a twofold amount of nitric acid (sp. gr. 1.45).

The nitration of I with a nitrating mixture consisting of HNO₃ (sp. gr. 1.35) and 95% sulfuric acid gives only one dinitro isomer. Considering the orientation rules (the presence of a nitro group and a quaternary nitrogen atom and methylene group of the piperidine ring), one can expect the production of three reaction products:

\[ \text{III} \quad \text{IV} \quad \text{V} \]

The compound that we obtained is not the 6,8-isomer; it differs from an authentic sample of the 6,8-dinitro derivative [3] with respect to Rf value, melting point, and UV and NMR spectra. The negative Janovsky reaction [6, 7], which consists in the appearance of intense coloration on treatment of a compound containing meta-oriented nitro groups with acetone and alkali, attests to the ortho orientation of the nitro groups in the molecule. The choice in favor of the 6,7-dinitro isomer (IV) was made on the basis of an analysis of the NMR spectra of IV and its N-formyl derivative, which are characterized by a small splitting of the broadened singlet in the region of absorption of benzene protons with the following chemical shifts: -8.00 ppm (in trifluoroacetic acid) for N-formyl-6,7-dinitro-THQ (VI); -7.57 ppm (in trifluoroacetic acid) and 7.89 ppm (in dimethyl sulfoxide) for 6,7-dinitro-THQ (IV).

The nitration of II with a nitrating mixture containing nitric acid (sp. gr. 1.45) gives 5,7-dinitro-THQ (VII), which can be isolated in 5-10% yield only when the reaction is carried out at 0° and the reaction mass is worked up directly after mixing of the reagents. The process is accompanied by pronounced resinification. This sort of resinification was also noted in the indoline series [8] (indoline is a THQ analog).

*See [1] for communication II.


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TABLE 1. Results of Nitration of 7-Nitro-N-acyl-THQ

<table>
<thead>
<tr>
<th>Acyl</th>
<th>Ratio of dinitro isomers of THQ</th>
<th>5,7-</th>
<th>7,8-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formyl</td>
<td></td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Acetyl</td>
<td></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Chloroacetyl</td>
<td>Base</td>
<td>Traces in the mother liquor</td>
<td>1</td>
</tr>
<tr>
<td>Trifluoroacetyl</td>
<td>Base</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Benzoyl</td>
<td>Base</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

*All of the compounds were purified by recrystallization from ethanol.

The nitration of N-formyl- (VIII), N-acetyl- (IX), N-chloroacetyl- (X), N-trifluoroacetyl- (XI), and N-benzoyl-7-nitro-THQ (XII) was studied. Compounds VIII and IX were obtained by refluxing II with HCOOH and acetic anhydride, while X, XI, and XII were obtained by refluxing with the appropriate acid chlorides. The yields were 85-90%.

The nitration of VIII-XII was carried out with a nitrating mixture consisting of HNO₃ (sp. gr. 1.35) and concentrated H₂SO₄ at -10 to 0 °C. In this case, nitration of 7-nitro-N-benzoyl-THQ with subsequent removal of the benzoyl protecting group gives only one compound, which is identical to the 5,7-dinitro-THQ (VII) obtained above with respect to Rf value and UV and NMR spectra. In all the remaining cases (Table 1), the formation of a second dinitro derivative was also observed. Starting from the orientation rules, one might have expected the formation of 6,7- (IV) or 7,8-dinitro-THQ (XII). The derivative obtained proved to be the 7,8-dinitro isomer, since it differed from the previously synthesized 6,7-dinitro-THQ. When the conditions for nitration of 7-nitro-N-acetyl-THQ (IX) were changed, we still were unable to obtain the 6,7-dinitro isomer. The absence of 7,8-dinitro-THQ (XII) in the case of the nitration of 7-nitro-N-benzoyl-THQ (XII) is probably associated with steric hindrance, since the benzoyl group is sterically bulky and hinders the entry of a second nitro group into the 8 position. However, a comparison of the yields of these isomers in the nitration of IX and XI, which contain acetyl and trifluoroacetyl groups, which are close in volume but differ with respect to electronic effects, indicates that it is necessary to take into account not only steric but also electronic effects.

Chromatographic monitoring of the trend of these reactions demonstrated that basically 100% conversion of the N-acyl derivatives of 7-nitro-THQ occurs after 6 h and is not accompanied by deacylation. We were unable to separate the 5,7- and 7,8-dinitro isomers as their acyl derivatives because of their close solubilities and Rf values. A mixture of these dinitro derivatives was subjected to acid hydrolysis and was then separated preparatively in a thin layer on plates.

All of the dinitro derivatives of THQ obtained and their acyl analogs are brightly colored needles that have sharp melting points, are quite soluble in alcohol, acetone, and ether, and insoluble in petroleum ether.

The positions of the nitro groups in all of the synthesized dinitro isomers were confirmed by means of the NMR spectra recorded in dimethyl sulfoxide (DMSO) solution. Two singlets with chemical shifts of 7.60 and 8.26 ppm are observed in the spectrum of 6,8-dinitro isomer (III). The spectrum of isomeric 5,7-dinitro-THQ (VII) contains two singlets with chemical shifts of 6.73 and 7.70 ppm, while the spectrum of...