Synthesis of 6-, and 7-Nitro-1,2-di-oxo-4-thioindeno[2,3,d] Pyrimidines

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6-Nitro-1,2-di-oxo-4-thioindeno[2,3,d] Pyrimidines

Ethyl 5-nitroindan-1,3-dione-2-carboxylate (3; 5-NO₂) was prepared via esterification of 5-nitrophthalic acid and subsequent treatment of the resulting diester with ethyl acetate in sodium ethoxide solution. Attempted synthesis of 3; 4-NO₂ via a similar route was obscured by inability to effect diesterification of 1; 3-NO₂ by ethanol and hydrochloric acid. The diester 2; 3-NO₂ could be prepared by the action of ethanol on the anhydride 5. This ester could then be converted into 3; 4-NO₂ by treatment with ethyl acetate and sodium ethoxide.

Compounds 3 (4- and 5-NO₂) could be converted into the corresponding indeno[2,3-d]-pyrimidine derivatives (9a,b) by their reaction with thiourea. The behaviour of 9a,b toward the action of hydrazine hydrate, monochloroacetic acid and hydrogen peroxide is reported.

For a continuing investigation of the biological activity of indenopyrimidines, derivatives of 6 and 7 nitroindenothiouracil were required. The reaction of thiourea with ethyl 4-, or 5-nitroindan-1,3-dione-2-carboxylate seemed to be a logical route for synthesis of the required compounds. As a simple method for the synthesis of 4- and 5-nitroindandione-2-carboxylate the reaction scheme illustrated in Chart 1 was considered. Surprisingly, these reactions have not been reported for diethyl nitrophthalate, although analogous reactions have been utilised for synthesis of several 2-ethoxycarbonylindan-1,3-dione.

\[
\begin{align*}
\text{C}_2\text{H}_4\text{C}=\text{O} & \quad \text{C}_2\text{H}_4\text{C}=\text{O} \\
\text{H}_3\text{C}\text{O} & \quad \text{H}_3\text{C}\text{O} \\
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{H}_3\text{C}\text{O} & \quad \text{H}_3\text{C}\text{O} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

In our laboratory 4-nitrophthalic acid was readily converted into the corresponding diester (2; 4-NO₂).

Requests for reprints should be sent to Prof. Dr. M. T. ZIMAITY, Chemistry Department, Faculty of Science, Mansoura University, Mansoura, A. R. Egypt.

This was converted into the corresponding 3; 5-NO₂ by reaction with ethyl acetate under Dieckmann reaction conditions. However, attempted synthesis of 8 was obscured by inability to obtain the diester 7 via esterification of the corresponding 1. The monoester 4 was the only isolable product. Failier to esterify the carboxylic acid group adjacent to the nitro group of 1 might be rationalised for by the steric interference of the bulky nitro group in position 3 (cf. Chart 2). Trials to synthesis diethyl 3-nitrophthalate via the action of ethyl iodide on the silver salt of 1; 3-NO₂ as has been previously reported afforded very low yield of the required product. It seemed to us that a new procedure for the preparation of 7 is required. Successful synthesis of the diester of 1 could be achieved via esterification of its anhydride (5), with the latter, esterification would proceed via acyl carbonium ion mechanism (cf. Chart 2). When 7, so obtained was treated with ethyl acetate under conditions similar to that used to effect condensation of 2; 4-NO₂ with the same reagent, ethyl 4-nitroindan-1,2-dione-4-carboxylate (8) was formed.

Compound 8 reacted with thiourea using reaction conditions similar to those reported for its reaction with 1,3-indanedione to yield a product for which structures 9 or 10 seemed possible. Now, taking into account the production of 9a,b, the reaction of 8 with thiourea is considered to be a logical route for the synthesis of compounds 9a,b.

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consideration that the enolate anion of 8 is the species that condenses with thiourea, it seems most likely that the condensation product with ethyl acetate would be 9 rather than 10 since the enolate anion in which the negative charge is localised at the oxygen atom at C-3 would be much more predominating than the other form in which the negative charge is localised at C-1. However, evidence for such theoretical analysis seemed mandatory. Confirmatory evidence for structure 9 was obtained via inspection of the IR spectrum of the condensation product of thiourea and 8 which revealed a CO absorption at 1695 cm⁻¹. This absorption is shifted by 40 cm⁻¹ than the CO absorption of 5-nitro isomer indicating that the indene ring CO has been involved in conjugation with the nitro group as required by structure 9. If this product is 10, it could be anticipated that the indene ring CO absorption would be approximately equal to that of the 5-nitro isomer.

Compound 3: 5-NO₂ also condensed with thiourea to afford the nitroindenouracil derivative (11). Structure 11 was prefered over possible isomeric 12 based on theoretical considerations similar to that discussed for formation of 9 from 8. However, no experimental evidence could be, by now, obtained to establish this structure assignment.

Compounds 9 and 11 reacted with monochloroacetic acid to afford the corresponding uracil derivatives (8a, b). This is similar to the reported conversion of thioxo heterocycles into the corresponding oxo analogues by the same reagent.

Compounds 9 and 11 also reacted with hydrazine hydrate to afford the corresponding hydrazones (14a, b).

When 9 and 11 were treated with hydrogen peroxide in alkaline media, H₂S was eliminated from the molecule and the indano pyrimidone derivatives (14a, b) were obtained.

Experimental

All melting points are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer Model 337 spectrometer.

Ethyl 5-nitroindan-1,3-dione-2-carboxylate

To a solution of 2: 4-NO₂ (0.2 mol) in benzene (40 ml) was added 3.7 g of sodium metal and the reaction mixture was heated to boiling. To the refluxing solution a solution of ethyl acetate (8.8ml) in ethanol (20 ml) was added gradually over a period of two hours. After complete addition of ethyl acetate the reaction mixture was refluxed for 12 hours, left to cool, treated with 300 ml of dry ether and left overnight at room temperature. The solid product, so formed was collected by filtration, dissolved in ice cold water treated with concentrated sulphuric acid and extracted with ether. Evaporation of the ether layer afforded 3: 5-NO₂ as orange powder. Recrystallization from ethanol afforded analytically pure sample.

Compound 3: 5-NO₂; brownish semi solid; yield 60%.

C₁₂H₁₉O₄N
Found C 54.70  H 3.3  N 5.00,
Calcd C 54.75  H 3.42  N 5.32.
**Diethyl 3-nitrophthalate (5)**

Hydrogen chloride gas was published through a solution of 5 (0.2 mol) in ethanol (100 ml) for six hours at room temperature then refluxed for two hours. The solvent was then removed by vacuo. The remaining product was triturated with ethanol and the resulting solid product was collected by filtration and crystallised from ethanol.

Compound 5 formed pale yellow crystals: m.p. 48 °C; not depressed when admixed with authentic specimen.

**Ethyl 4-nitroindan-1,3-dione-2-carboxylate (8)**

The experimental procedure described above for the synthesis of 3: 5-NO₂ was adopted. Compound 8 was formed in 50% yield.

Compound 8, formed yellow crystals from ethanol; m.p. 135 °C.

**1,2,3,4-Tetrahydro-6-nitro-1,2-oxo-4-thioindene [2,3-d] pyrimidine (9)**

To a sodium ethoxide solution (prepared from 2.3 g of sodium metal and 200 ml of ethanol) was added a mixture of 19.9 g of 8 and 9.9 g of thiourea. The mixture was refluxed for ten hours. The solvent was removed by vacuo. The remaining product was then dissolved in water and then acidified with dilute hydrochloric acid. The solid product, so obtained was collected by filtration and crystallised from ethanol.

Compound 9 formed pale yellow crystals: m.p. 370 °C; yield 43%.

**C₆H₄O₅N₃**

<table>
<thead>
<tr>
<th>Found</th>
<th>C 54.50 H 3.2 N 38.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caled</td>
<td>C 54.75 H 3.42 N 38.40</td>
</tr>
</tbody>
</table>

**1,2,3,4-Tetrahydro-7-nitro-1,2-dioxo-4-thioindeno [2,3-d] pyrimidine (11)**

Compound 11 was synthesised from 3: 5-NO₂ and thiourea using the experimental procedure described above for the synthesis of 9.

Compound 11 formed brown crystals: m.p. 115 °C; yield 51%.

**C₆H₉O₅N₃**

<table>
<thead>
<tr>
<th>Found</th>
<th>C 48.00 H 2.00 N 23.00 S 11.30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caled</td>
<td>C 48.00 H 1.82 N 23.27 S 11.64</td>
</tr>
</tbody>
</table>

**Reaction of 9 and 11 with**

**a) Monochloroacetic acid:** A suspension of each of 9 and 11 (1.0 g) in water (100 ml) was treated with monochloroacetic acid (1.5 g). The reaction mixture was refluxed for two hours, reduced to 25 ml by evaporation in vacuo and then left to stand at room temperature. The solid product formed on standing was corrected by filtration and purified by dissolution in 10% sodium hydroxide solution filtration from insoluble impurities and reprecipitation by addition of hydrochloric acid.

Compound 13a, brown powder; m.p. 205 °C; yield 43%.

**C₆H₅O₅N₃**

<table>
<thead>
<tr>
<th>Found</th>
<th>C 50.60 H 1.80 N 15.90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caled</td>
<td>C 50.97 H 1.93 N 16.22</td>
</tr>
</tbody>
</table>

Compound 13b formed brown powder; m.p. 370 °C; yield 43%.

**C₆H₅O₅N₃**

<table>
<thead>
<tr>
<th>Found</th>
<th>C 49.60 H 1.80 N 15.80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caled</td>
<td>C 50.97 H 1.93 N 16.22</td>
</tr>
</tbody>
</table>

b) **Hydrazine hydrate:** To a solution of each of 9 and 11 (1.0 g) in ethanol (50 ml) was added hydrazine hydrate (1.2 ml; 99%). The reaction mixture was refluxed and then left to cool. The solid product, so obtained was collected by filtration and crystallised from ethanol.

Compound 14a: yellow crystals, m.p. 270 °C; yield 57%.

**C₆H₅O₅N₃**

<table>
<thead>
<tr>
<th>Found</th>
<th>C 49.00 H 2.70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caled</td>
<td>C 48.35 H 2.56</td>
</tr>
</tbody>
</table>

Compound 14b: yellow crystals, m.p. 140 °C; yield 51%.

**C₆H₅O₅N₃**

<table>
<thead>
<tr>
<th>Found</th>
<th>C 49.00 H 2.70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caled</td>
<td>C 48.35 H 2.56</td>
</tr>
</tbody>
</table>

c) **Hydrogen peroxide:** A solution each of 9 and 11 (1.0 g) in sodium hydroxide (20 ml; 5%) was added gradually with stirring to 1 ml of H₂O₂ (30%). The reaction mixture was left to stand for two hours and the solid, formed was collected by filtration and crystallised from ethanol.

Compound 15a, m.p. 229 °C; yield 56%.

**C₆H₅O₅N₃**

<table>
<thead>
<tr>
<th>Found</th>
<th>C 54.00 H 2.00 N 17.00</th>
</tr>
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<tbody>
<tr>
<td>Caled</td>
<td>C 54.32 H 2.06 N 17.28</td>
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</table>

Compound 15b, m.p. 320 °C; yield 42%.

**C₆H₅O₅N₃**

<table>
<thead>
<tr>
<th>Found</th>
<th>C 54.20 H 2.10 N 16.80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caled</td>
<td>C 54.32 H 2.06 N 17.28</td>
</tr>
</tbody>
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