Reactions with 4-Thiohydantoin. Preparation of 5-Arylidene-4-Thiohydantoin, their Reactions towards Grignard Reagents and the Alkylating Agents

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4-Thiohydantoin, Grignard reagents, 5-arylidene-4-thiohydantoin

4-Thiohydantoin and 1-phenyl-4-thiohydantoin reacted with aromatic aldehydes to give the corresponding 5-arylidene-4-thiohydantoin (1a–h). 1a was obtained also from 5-benzylidene hydantoin and phosphorous pentasulphide. Grignard reagents added to the lateral double bond of (1a–e) to give after hydrolysis the colorless products 3. Treatment of (1a, b) with alkylating agents gave the corresponding alkylmercapto derivatives (4a–h). Also (4a, e) were obtained by the action of ethereal diazomethane on (1a, b). By further methylation of (4e) with diazomethane, a cyclopropane derivative could be isolated.

It was first shown by WHEELER and HOFFMANN¹ that hydantoin reacts with aromatic aldehydes to give C-5 unsaturated hydantoin derivatives. The reaction was carried out in glacial acetic acid to which had been added fused sodium acetate and acetic anhydride, and was found to proceed smoothly with a number of aromatic aldehydes. It has been found that 2-thiohydantoins also undergo condensations with aromatic aldehydes, and that the condensation occurs easier than that with the corresponding hydantoins².

Recently, 4-thiohydantoin was prepared by refluxing hydantoin with phosphorous pentasulphide in dioxane³. Under controlled conditions, 4-thiohydantoin was found to react with aromatic aldehydes in glacial acetic acid and in presence of fused sodium acetate at 120 °C to give the corresponding arylidene derivatives (1a–h). While hydantoin and N-3 substituted hydantoins condensed readily

\[
\begin{align*}
\text{(1)} & \\
\text{a) } & R = \text{C}_6\text{H}_5 \\
\text{b) } & R = \text{p-CH}_3\text{O} \cdot \text{C}_6\text{H}_4 \\
\text{c) } & R = \text{p-CH}_3 \cdot \text{C}_6\text{H}_4
\end{align*}
\]

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d) \( R = \text{o-OH} \cdot \text{C}_6\text{H}_4 \)
e) \( R = \text{p-OH} \cdot \text{C}_6\text{H}_4 \)
f) \( R = \text{2,4-(OH)}_2\text{C}_6\text{H}_3 \)
g) \( R = \text{o-Cl} \cdot \text{C}_6\text{H}_4 \)
h) \( R = \text{p-CH}_3\text{O} \cdot \text{NC}_6\text{H}_4 \)

It was shown that 4-thiohydantoin reacted with aromatic aldehydes to give 5-arylidene-4-thiohydantoin derivatives. The reaction was carried out in glacial acetic acid to give the corresponding 5-arylidene-4-thiohydantoin (1a–h). 1a was obtained also from 5-benzylidene hydantoin and phosphorous pentasulphide. Grignard reagents added to the lateral double bond of (1a–e) to give after hydrolysis the colorless products 3. Treatment of (1a, b) with alkylating agents gave the corresponding alkylmercapto derivatives (4a–h). Also (4a, e) were obtained by the action of ethereal diazomethane on (1a, b). By further methylation of (4e) with diazomethane, a cyclopropane derivative could be isolated.

The arylidene-4-thiohydantoins (1a–h) are coloured compounds, they gave the correct analytical data and 1a was obtained in good yield when 5-benzylidene hydantoin was refluxed with phosphorous pentasulphide in boiling dioxane.

In extension of the work on the action of Grignard reagents on heterocyclic nitrogen compounds⁵,⁷, the action of these reagents on 5-benzylidene, 5-anisylidene and 5-(p-methyl benzylidene)-4-thiohydantoin now has been investigated. Thus, when the 5-arylidene-4-thiohydantoin derivatives were treated with Grignard reagents, followed by hydrolysis, the colourless products (3a–d) were obtained. The

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structure of the products was inferred from the fact they gave the correct analytical data. Also the finding that \( 3b \) was obtained by the action of phenylmagnesium bromide on \( 1 \) and by the action of p-tolylmagnesium iodide on \( 2 \).

Hydrolysis has proved a useful procedure for the replacement of sulphur by oxygen in some thiohydantoins and similar reaction paths are followed in the conversion of 2-thiohydantoins to hydantoins by refluxing with chloroacetic acid\(^{10}\) and by mercuric salts\(^{11}\).

**Action of diazomethane on \( 1a, b \) (S-methylation) and on \( 4e \) (cyclopropane formation):**

Treatment of \( 1a, b \) with an ethereal diazomethane solution resulted in the formation of \( 4a, e \) in quantitative yield [cf. the action of diazomethane on 5-arylidene-2-thiohydantoin]. Its oxygen analogues were reported to react with diazomethane to give the corresponding N-methyl derivatives\(^{12}\).

Formation of cyclopropane (6) has been observed upon treatment of 1,2-diphenyl-4-benzylidene-5-imidazolone (5) with ethereal diazomethane\(^{13-15}\).

We found that treatment of the yellow 5-anisylidene-4-methylmercapto hydantoin \( 4e \) with ethereal diazomethane solution yielded the colourless cyclopropane (7).

**Experimental**

**Preparation of 5-arylidene-4-thiohydantoins (1a–h):**

**General procedure**

A mixture of 4-thiohydantoin (0.96 g, 0.006 mole), fused sodium acetate (2 g) and a slight excess (0.0065 mole) of the appropriate aldehyde in 25 ml glacial acetic acid was gently heated at 120 °C for 2 hours. During the reaction the solution became dark brown. The reaction mixture was cooled poured over ice cold water, then the separated solid was filtered off, washed with water and recrystallised from ethyl alcohol (cf. Table I).

The 5-arylidene derivatives (1a–h), listed in Table I, are yellowish in colour soluble in sodium hydroxide (10%). They are insoluble in petroleum ether and sparingly soluble in hot benzene.
Table I. 5-Arylidene-4-thiohydantoin.

<table>
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<th>Compound</th>
<th>m.p. [°C]</th>
<th>Yield [%]</th>
<th>Colour of Formula</th>
<th>Carbon Analysis</th>
<th>Hydrogen Analysis</th>
<th>Nitrogen Analysis</th>
<th>Sulphur Analysis</th>
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<td>228</td>
<td>85</td>
<td>Brown</td>
<td>C_{9}H_{13}O_{4}N_{2}S</td>
<td>58.92 58.91</td>
<td>3.95 3.90</td>
<td>13.72 13.85</td>
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<tr>
<td>1b</td>
<td>266</td>
<td>82</td>
<td>Deep red</td>
<td>C_{10}H_{12}O_{5}N_{2}S</td>
<td>58.41 56.37</td>
<td>4.30 4.28</td>
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<tr>
<td>1c</td>
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<td>12.84 12.92</td>
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<tr>
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<td>225</td>
<td>85</td>
<td>Brown</td>
<td>C_{9}H_{13}O_{4}N_{2}S</td>
<td>54.55 54.61</td>
<td>3.66 3.70</td>
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<td>3.66 3.72</td>
<td>12.72 12.69</td>
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<tr>
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<td>343</td>
<td>75</td>
<td>Red</td>
<td>C_{9}H_{13}O_{4}N_{2}S</td>
<td>50.83 50.91</td>
<td>3.41 3.38</td>
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<td>70</td>
<td>Orange</td>
<td>C_{10}H_{12}O_{5}N_{2}SCl*</td>
<td>50.31 50.28</td>
<td>2.93 2.33</td>
<td>11.74 11.81</td>
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<td>1h</td>
<td>286</td>
<td>82</td>
<td>Red</td>
<td>C_{12}H_{13}O_{5}N_{2}S</td>
<td>58.29 58.33</td>
<td>5.30 5.27</td>
<td>17.00 16.88</td>
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</table>

* Cl: Calcd. 14.88, Found 15.00%.

Action of phosphorus pentasulphide on 5-benzylidene hydantoin

9.4 g of 5-benzylidene hydantoin were mixed well with 4.5 g phosphorus pentasulphide then covered with 90 ml of dry dioxane (dried over potassium hydroxide then over metallic sodium). The reaction mixture was refluxed for 40 min at 115-120 °C (bath temperature). During the reaction the dioxane aquires deep red colour. After the reaction was completed the dioxane solution is filtered and then concentrated to half its volume and then it was left to cool. The yellow crystals, that separated, was collected by filtration and it was proved to be 1a by melting point and mixed melting point determination (yield 7 g).

Action of phosphorus pentasulphide on 1-phenyl hydantoin

8.8 g of 1-phenyl hydantoin were mixed well with 4.5 g phosphorus pentasulphide then covered with 90 ml of dry dioxane. The reaction mixture was refluxed for 40 min at 115-120 °C (bath temperature). Then the reaction was completed, the dioxane solution is filtered and then concentrated to half its volume and then it was left to cool. The yellow crystals, that separated, was collected by filtration and it was proved to be 1a by melting point and mixed melting point determination (yield 7 g).

Condensation of 1-phenyl-4-thiohydantoin with benzaldehyde

A mixture of 1-phenyl-4-thiohydantoin (0.96 g, 0.005 mole), fused sodium acetate (2 g) and a slight excess of benzaldehyde (0.583 g, 0.0055 mole) in 25 ml of glacial acetic acid was refluxed for 12 hours. During the reaction the solution became dark brown and the reaction mixture was left aside over night at room temperature, poured over water. The product, separated, was filtered off, and recrystallised from xylene as yellow crystals m.p. 185 °C; yield (20%). The product gives brown colour with concentrated sulphuric acid.

Analysis: C_{14}H_{13}O_{4}N_{2}S

Calcd C 68.57 H 4.28 N 10.00 S 11.43,

Found C 68.60 H 4.30 N 10.06 S 11.39.

Action of phenylmagnesium bromide on 1a, b

To an ethereal solution of phenylmagnesium bromide (prepared from 0.9 g of magnesium and 9 g of bromobenzene in 50 ml of dry ether) was added the appropriate arylidene-4-thiohydantoin dissolved in 50 ml dry benzene. The reaction mixture was refluxed on a steam bath for 2 hours then it was left to cool at room temperature. It was decomposed by 200 ml of cooled saturated aqueous ammonium chloride solution and extracted with ether. The ethereal layer was dried over anhydrous sodium sulphate and evaporated. The solid residue, so obtained, was washed with petroleum ether (b.p. 40-60 °C) and was recrystallised from ethanol as colourless crystals. 1a gave 3a, m.p. 228 °C; yield 75%.

Analysis: C_{14}H_{13}O_{4}N_{2}S

Calcd C 68.08 H 4.96 N 9.92 S 11.34,

Found C 68.00 H 4.90 N 10.00 S 11.29.

1b gave 3c, m.p. 146 °C, yield 69%.

Analysis: C_{14}H_{14}O_{4}N_{2}S

Calcd C 65.38 H 5.13 N 8.97 S 10.25,

Found C 65.41 H 5.09 N 8.91 S 10.31.

Action of p-tolylmagnesium iodide on 1a, b

To an ethereal solution of p-tolylmagnesium iodide (prepared from 0.8 g of magnesium and 7.5 g of p-iodotoluene in 40 ml of dry ether) was added the appropriate arylidene-4-thiohydantoin followed by 50 ml of dry benzene. The reaction mixture was worked up as above and the residual substance was crystallised from ethyl alcohol as colourless crystals. 1a gave 3b, m.p. 145 °C; yield 70%.
Analysis: C_{17}H_{16}ON_{2}S
Calcd C 68.91 H 5.40 N 9.45 S 10.81,
Found C 68.89 H 5.38 N 9.49 S 10.78.

1b gave 3d, m.p. 134 °C; yield 65%.

Analysis: C_{12}H_{9}ON_{2}S
Calcd C 66.21 H 5.58 N 8.63 S 9.77,

The Grignard products 3a-d are all colourless, soluble in aqueous sodium hydroxide (10%) and give red colour with concentrated sulphuric acid.

Action of phenylmagnesium bromide on p-methyl benzylidene-4-thiohydantoin (1c)

To an ethereal solution of phenylmagnesium bromide (prepared in a similar manner as above), was added 1.5 g of 1c in 50 ml of dry benzene. The reaction mixture was worked up and the solid so obtained was washed with light petroleum ether (b.p. 40–60 °C) and recrystallised from ethanol as colourless crystals, m.p. 146 °C. It was proved to be 3b by melting point and mixed melting point determinations.

Attempted action of phenylmagnesium bromide on 4-thiohydantoin

To an ethereal solution of phenylmagnesium bromide (prepared in a similar manner as above), was added 1.5 g of 4-thiohydantoin in 50 ml of dry benzene. The Grignard reaction was worked up and the starting material was recovered almost unchanged (melting point and mixed melting point determinations).

Action of alkyl halides on 5-arylidene-4-thiohydantoin (1a, b)

To each of 1a, b (0.06 mole) in 120 ml of sodium hydroxide (2%) and ethanol (90 ml) was added the appropriate alkyl halide (0.066 mole). The reaction mixture was stirred for 15 min till it became turbid followed by the separation of the product. The reaction mixture was left aside overnight at room temperature. The product was filtered off, washed with water and recrystallised from alcohol (cf. Table II).

The 4-alkylmercapto derivatives 4a–h, listed in Table II, are yellow in colour, insoluble in sodium hydroxide (10%) and give orange colour with concentrated sulphuric acid.

Action of concentrated hydrochloric acid on 4a

A mixture of 1 g of 4a in 40 ml alcohol and 8 ml of concentrated hydrochloric acid was refluxed till the odour of the evolved methyl thiol could not be detected. The reaction mixture was allowed to cool, poured over water and the solid, so obtained, was collected by filtration and was crystallised from alcohol, m.p. 220 °C, and identified as 5-arylidene hydantoin by melting point and mixed melting point determination.

Action of ethereal diazomethane on 1a, b

An ethereal diazomethane solution (from 4 g of nitrosomethylurea) was added to 1 g of each of 1a, b suspended in 30 ml of ether, and in the presence of two drops of methanol. The reaction mixture was kept overnight in the ice chest and then treated with a fresh amount of an ethereal diazomethane solution (from 4 g nitrosomethylurea). After three days, the reaction mixture was evaporated and the solid, so obtained, was crystallised from ethanol as yellow crystals. The product was identified as 5-arylidene-4-methylmercapto hydantoin by melting point and mixed melting point determinations.

1a gives 4a m.p. 233 °C; yield 88%.
1b gives 4e m.p. 240 °C; yield 85%.

Action of ethereal diazomethane on 5-anisylidene-4-methyl-mercapto hydantoin (1e)

An ethereal diazomethane solution (prepared in a similar manner as described above) was added to 1.0 g of 1e dissolved in 30 ml of dry ether. After the reaction was completed a colourless crystals were separated, collected by filtration and recrystallised from a mixture of dimethylformamide and water (1:1) as 7 m.p. 220 °C; yield (0.6 g).

Analysis: C_{13}H_{14}ON_{2}S
Calcd C 59.54 H 5.34 N 10.68 S 12.21,
Found C 59.60 H 5.29 N 10.71 S 12.19.

<table>
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<tr>
<th>Compound</th>
<th>m.p. [°C]</th>
<th>Yield [%]</th>
<th>Formula</th>
<th>Carbon</th>
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<tr>
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