Reactions of Aromatic Amines on 5-Arylidene-4-methylmercapto-hydantoin and 5-Arylazo-2-methylmercapto-hydantoin

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Aromatic Amines, 5-Arylidene-4-methylmercapto-hydantoin, 5-Arylazo-2-methylmercapto-hydantoin

Treatment of 5-arylidene-4-methylmercapto-hydantoin (1a, b) and 1-phenyl-4-thiohydantoin (3) with aromatic amines gave 5-arylidene-4-arylimino hydantoin (2a-h) and 4-arylimino-1-phenyl-hydantoin (4a-e) respectively. 2a and 4a were hydrolysed with concentrated hydrochloric acid and gave 5-benzylidene-hydantoin and 1-phenyl-hydantoin respectively. N²-phenylglycocyamidine (7) was found to condense with aromatic aldehydes yielding (6a-e). Compound 6a was also obtained from 5-benzylidene-2-methylmercapto-hydantoin (5) and aniline. Treatment of 5-arylidene-2-methylmercapto-hydantoin (8a-e) with aromatic amines gave the products 9a-h. The compound 9a was hydrolysed with a mixture of concentrated hydrochloric acid and acetic acid yielding (10).

Two series of monothiohydantoin derivatives are possible, with C=S replacing the C=O group in either the 2- or the 4-position of the heterocyclic ring. 4-Thiohydantoins are less well known, the parent substance was synthesised by Johnson and Chernoff3 and recently it was obtained by treating hydantoin with phosphorous pentasulphide in di-oxane5.

Investigating the action of primary aromatic amines on 5-arylidene-4-methylmercapto-hydantoin derivatives (1a, b) prepared in this laboratory4, neither an addition occured on the exocyclic double bond nor the heterocyclic ring opening was observed but condensation occured at position 4. On fusion of 1a, b with aromatic amines at 150-160 °C (bath temperature) the corresponding 4-arylimino-1-phenylhydantoin (4a-e) were obtained in good yield.

The coloured products 2a-h gave the correct analytical values. 2a was hydrolysed with a mixture of hot acetic-hydrochloric acid yielding 5-benzylidenehydantoin4.

When 3 was fused with each of aniline, o-chloroaniline and benzylamine at 150-160 °C (bath temperature) the corresponding 4-arylimino-1-phenylhydantoin (4a-e) were obtained in good yield.

The products 4a-e are all colourless compounds, gave the correct analytical values. 4a was hydrolysed with a mixture of concentrated hydrochloric acid-ethanol yielding 1-phenyl-hydantoin4.

Our interest was extended to the reactivity of the 2-thio atom of thiourea type present in 5-benzyl-
idene-2-thiohydantoin aiming to transfer it into the corresponding glycoxyamide derivative. This transformation was achieved by aminolysis of 5-benzylidene-2-methylmercapto-hydantoin (5) which when fused with aniline on oil bath at 150–160 °C, 5-benzylidene-2-phenylimino-4-imidazolidinono (6a) was obtained.

\[ \text{PhCH=CH-C=0} \rightarrow \text{RCH=CH-C=0} \]

\[ \text{N-Ph} \]

a) \( R = \text{C}_{6} \text{H}_{5} \)
b) \( R = \text{p-CH}_{3} \cdot \text{C}_{6} \text{H}_{4} \)
c) \( R = \text{o-Cl} \cdot \text{C}_{6} \text{H}_{4} \)
d) \( R = \text{H} \)
e) \( R = \text{R'} = \text{C}_{6} \text{H}_{5} \)
f) \( Ar = o-\text{CH}_{3} \cdot \text{C}_{6} \text{H}_{4}; R = \text{H}; R' = \text{C}_{6} \text{H}_{5} \)
g) \( Ar = o-\text{CH}_{3} \cdot \text{C}_{6} \text{H}_{4}; R = \text{H}; R' = o-\text{CH}_{3} \cdot \text{C}_{6} \text{H}_{4} \)
h) \( Ar = o-\text{CH}_{3} \cdot \text{C}_{6} \text{H}_{4}; R = \text{H}; R' = \text{m-CH}_{3} \cdot \text{C}_{6} \text{H}_{4} \)
i) \( Ar = o-\text{CH}_{3} \cdot \text{C}_{6} \text{H}_{4}; R = \text{H}; R' = \text{p-CH}_{3} \cdot \text{C}_{6} \text{H}_{4} \)
j) \( Ar = o-\text{CH}_{3} \cdot \text{C}_{6} \text{H}_{4}; R = \text{H}; R' = \text{C}_{6} \text{H}_{5} \)
k) \( Ar = p-\text{Cl} \cdot \text{C}_{6} \text{H}_{4}; R = \text{R'} = \text{C}_{6} \text{H}_{5} \)

Compounds 6a was also obtained by treating N-phenyl-glycoxyamide (7) with benzaldehyde in glacial acetic acid and in the presence of sodium acetate; similarly anisaldehyde and o-chlorobenzaldehyde condensed with 7 to give 6b, c respectively.

Compounds 9a–k are yellow in colour and gave the correct analytical values. In favour of the proposed structure for the products; 9a was also obtained by heating 2-ethylmercapto-5-phenylazo-hydantoin with aniline on a water bath and was hydrolysed with a mixture of concentrated hydrochloric acid and acetic acid to give 5-phenylazo-hydantoin 10.

![Structural formula for 6a](image)

**Experimental**

Melting points are uncorrected.

**Action of aromatic amines on:**

(a) 5-Arylidene-4-methylmercapto-hydantoin (1a, b)

**General procedure:** A mixture of 0.004 mole of 5-arylidene-4-methylmercapto-hydantoin namely 1a, b and 0.0045 mole of the appropriate primary aromatic amine was mixed well and heated in an oilbath at 150–160 °C. During the reaction the odour of methane thiol could easily be detected and the heating was continued for two hours. When the reaction was completed and no odour of the methane thiol could be detected, it was left to cool at room temperature, washed with petroleum ether (60–80 °C) and the residual solid obtained was crystallised from the proper solvent (cf. Table I).

The 5-arylidene-4-arylimino-hydantoin (2a–h) listed in Table I are all coloured. They gave brown colour with concentrated sulphuric acid.

(b) 5-Benzylidene-4-thio-hydantoin

A mixture of 1 g of 5-benzylidene-4-thiohydantoin and 0.5 ml of aniline was mixed well then heated in an oil bath at 150–160 °C till the odour of the evolved hydrogen sulphide could not be detected. After the reaction was completed, it was left to cool at room temperature, washed with petroleum ether (60–80 °C) and the residual solid obtained was crystallised from acetic acid as yellow crystals m.p. 267 °C. It was proved to be 2a by melting point and mixed melting point determinations.
Table I. 5-Arylidene-4-arylimino-hydantoin.

<table>
<thead>
<tr>
<th>Compound</th>
<th>m.p. [°C]</th>
<th>Yield [%]</th>
<th>Solvent of crystn.</th>
<th>Formula</th>
<th>Carbon Analysis [%]</th>
<th>Nitrogen Analysis [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Caled. Found</td>
<td>Caled. Found</td>
</tr>
<tr>
<td>2a</td>
<td>267</td>
<td>80</td>
<td>Acetic acid</td>
<td>C₁₅H₁₉ON₃</td>
<td>73.00 72.88</td>
<td>4.94 5.00</td>
</tr>
<tr>
<td>2b</td>
<td>162</td>
<td>75</td>
<td>Ethanol</td>
<td>C₁₅H₁₉ON₃Cl</td>
<td>64.54 64.48</td>
<td>4.03 4.13</td>
</tr>
<tr>
<td>2c</td>
<td>354</td>
<td>70</td>
<td>Acetic acid</td>
<td>C₁₅H₁₉ON₃</td>
<td>73.65 73.70</td>
<td>5.41 5.38</td>
</tr>
<tr>
<td>2d</td>
<td>194</td>
<td>70</td>
<td>Benzene-benzine</td>
<td>C₁₅H₁₉ON₃</td>
<td>73.65 73.61</td>
<td>5.41 5.39</td>
</tr>
<tr>
<td>2e</td>
<td>190</td>
<td>82</td>
<td>aq. DMF (70%)</td>
<td>C₁₅H₁₉ON₃Cl</td>
<td>69.62 69.57</td>
<td>5.12 5.23</td>
</tr>
<tr>
<td>2f</td>
<td>184</td>
<td>78</td>
<td>Ethanol (80%)</td>
<td>C₁₅H₁₉ON₃</td>
<td>62.29 62.31</td>
<td>4.27 4.22</td>
</tr>
<tr>
<td>2g</td>
<td>178</td>
<td>73</td>
<td>Ethanol (80%)</td>
<td>C₁₆H₁₅ON₃</td>
<td>70.36 70.42</td>
<td>5.54 5.60</td>
</tr>
<tr>
<td>2h</td>
<td>192</td>
<td>70</td>
<td>Ethanol (80%)</td>
<td>C₁₆H₁₅ON₃</td>
<td>70.30 70.49</td>
<td>5.54 5.59</td>
</tr>
</tbody>
</table>

* Cl: Calcd. 11.93; Found 12.01%; b Cl: Calcd. 10.84; Found 11.01%.

Acid hydrolysis of 2a: A suspension of 2a (0.5 g) in a mixture of concentrated hydrochloric acid (3 ml) and acetic acid (10 ml) was refluxed for 4 hours. The reaction mixture was cooled, poured into ice cold water and the separated product was collected by filtration and recrystallised from ethanol as colourless crystals m.p. 220 °C, it was identified as 5-benzylidene-hydantoin by melting point and mixed melting point determinations.

Action of aromatic amines on 1-phenyl-4-thiohydantoin (3) General procedure: A mixture of 0.006 mole of 1-phenyl-4-thiohydantoin and 0.007 mole of each of amine namely aniline, o-chloroaniline and benzylamine was mixed well and heated in an oil bath at 150-160 °C till the odour of the evolved hydrogen sulphide could not be detected. The reaction mixture was worked up as above. 4-Arylimino-1-phenyl-hydantoin derivatives (4a-e) are colourless compounds and they gave no colour when treated with concentrated sulphuric acid.

4a was crystallised from acetic acid, m.p. 291 °C; yield 75%.

Analysis: C₁₅H₁₉ON₃
Calcd C 71.71 H 5.18 N 16.73,
Found C 71.65 H 5.22 N 16.70.

4b was crystallised from ethanol, m.p. 215 °C; yield 65%.

Analysis: C₁₅H₁₉ON₃Cl
Calcd C 71.65 H 5.22 N 16.70,
Found C 71.65 H 5.22 N 16.70.

4c was crystallised from ethanol, m.p. 241 °C; yield 70%.

Analysis: C₁₆H₁₅ON₃
Calcd C 72.45 H 5.66 N 15.85,
Found C 72.42 H 5.70 N 15.82.

Action of concentrated hydrochloric acid on 4-phenylimino-1-phenyl-hydantoin 4a
A suspension of 4a (0.8 g) in a mixture of concentrated hydrochloric acid (4 ml) and ethyl alcohol (20 ml) was refluxed on a steam bath for 4 hours. The reaction mixture was cooled, poured over ice cold water and the product (0.4 g) crystallised from ethanol as colourless crystals m.p. 192 °C. It was identified as 1-phenyl-hydantoin by melting point and mixed melting point determinations.

Action of aniline on 5-benzylidene-2-methylmercaptohydantoin (5)
A mixture of 0.005 mole of 5 and 0.0055 mole of aniline was mixed well and then heated on an oil-bath at 150-160 °C till the odour of methane thiol could not be detected. The reaction mixture was worked up as above and then crystallised from dimethylformamide as pale yellow crystals of 6a, m.p. 299 °C, yield 80%.

Analysis: C₁₆H₁₅ON₃
Calcd C 73.00 H 4.94 N 15.97,
Found C 72.89 H 5.01 N 16.09.

Condensation of N₂-phenylglycocyamidine (7) with aromatic aldehydes
A mixture of 7 (1.05 g, 0.006 mole), fused sodium acetate (2 g) and a slight excess of benzaldehyde (0.0065 mole) in 25 ml glacial acetic acid was heated for 2 hours. The reaction mixture was cooled, poured over ice cold water. The solid, so obtained, was filtered off, washed with water and crystallised from dimethylformamide, m.p. 299 °C yield 65%. It was identified as 6a by melting and mixed melting point determination.

Similarly, when 7 was treated with anisaldehyde under the above conditions, 6b was obtained and was crystallised from acetic acid, m.p. 279 °C yield 70%.

Analysis: C₁₇H₁₅O₂N₃
Calcd C 69.62 H 5.12 N 14.33,
Found C 69.55 H 5.09 N 14.41.
Also, when 7 was treated with o-chlorobenzaldehyde, 6a was obtained and was crystallised from nitrobenzene, m.p. 281 °C, yield 72%.

Analysis: $C_{16}H_{12}O_3Cl$

Caled C 64.54 H 4.03 N 14.12 Cl 11.93,
Found C 64.60 H 4.12 N 14.01 Cl 12.00.

Action of primary aromatic amines on 5-arylazo-2-methylmercapto-hydantoin (8a-e)

A mixture of 0.005 mole of each of 8a-e and 0.0055 mole of the appropriate primary aromatic amine was mixed well and heated on a water-bath till the odour of methane thiol could not be detected. The separated product was crystallised from acetic acid as yellow crystals of 9a-k (cf. Table II). They are soluble in aqueous sodium hydroxide (10%).

Action of aniline on 2-ethylmercapto-5-phenylazo-hydantoin

A mixture of 1 g 2-ethylmercapto-5-phenylazo-hydantoin and 0.5 g of aniline was heated on a water-bath till the odour of ethane thiol could not be detected. The reaction was worked up as above, and the product obtained was crystallised from acetic acid, m.p. 270 °C. It was identified as 9a by melting point and mixed melting point determination.

Acid hydrolysis of 9a

A suspension of 9a (0.5 g) in a mixture of acetic acid (70 ml) and concentrated hydrochloric acid (30 ml) was refluxed till complete dissolution and the heating was continued for 4 hours. It was left to cool and the obtained solid was crystallised from dilute ethyl alcohol as yellow crystals of 5-phenylazo-hydantoin (2 g), m.p. 250 °C; it did not depress when admixed with an authentic sample.

Table II. 5-Arylazo-2-arylimino-4-imidazolidinone.

<table>
<thead>
<tr>
<th>Compound</th>
<th>m.p.</th>
<th>Yield</th>
<th>Formula</th>
<th>Carbon</th>
<th>Hydrogen</th>
<th>Nitrogen</th>
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<tr>
<td></td>
<td>[°C]</td>
<td>[%]</td>
<td></td>
<td>Caled.</td>
<td>Found</td>
<td>Caled.</td>
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<tr>
<td>9a</td>
<td>260</td>
<td>92</td>
<td>$C_{15}H_{11}ON_2$</td>
<td>64.55</td>
<td>64.50</td>
<td>4.65</td>
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<tr>
<td>9b</td>
<td>236</td>
<td>85</td>
<td>$C_{15}H_{10}O_2$</td>
<td>65.53</td>
<td>65.50</td>
<td>4.52</td>
</tr>
<tr>
<td>9c</td>
<td>260</td>
<td>89</td>
<td>$C_{15}H_{10}O_2$</td>
<td>65.53</td>
<td>65.49</td>
<td>4.52</td>
</tr>
<tr>
<td>9d</td>
<td>265</td>
<td>88</td>
<td>$C_{15}H_{10}O_2$</td>
<td>65.53</td>
<td>65.55</td>
<td>4.52</td>
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<tr>
<td>9e</td>
<td>275</td>
<td>91</td>
<td>$C_{15}H_{10}O_2$</td>
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<td>71.02</td>
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<td>65.50</td>
<td>4.52</td>
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<td>66.44</td>
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<td>5.56</td>
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<td>9h</td>
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<td>$C_{15}H_{10}O_2$</td>
<td>66.44</td>
<td>66.50</td>
<td>5.56</td>
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<tr>
<td>9i</td>
<td>250</td>
<td>89</td>
<td>$C_{15}H_{10}O_2$</td>
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<td>66.49</td>
<td>5.56</td>
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<tr>
<td>9j</td>
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<td>$C_{15}H_{10}O_2$</td>
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<td>71.51</td>
<td>5.15</td>
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<td>90</td>
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<td>64.69</td>
<td>64.73</td>
<td>4.11</td>
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7 P. SchweppeL, Chem. Ber. 10, 2048 [1877].