Reactions of Amino Acids on 2-Methylmercaptocarbonyldantoins Derivatives. 
Synthesis of Imidazoimidazoline and Imidazoquinazoline Derivatives


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Amino Acids, 2-Methylmercaptocarbonyldantoins, Imidazoimidazolines, Imidazoquinazolines

Treatment of 5-arylidene-2-methylmercaptocarbonyldantoins (1a–d) and 5-aryazo-2-methylmercaptocarbonyldantoins (3a, b) with glycine in acetic acid gave 5-arylidene-N\textsuperscript{2}-carboxymethylglycocymidines (2a–d) and 5-aryazo-N\textsuperscript{2}-carboxymethylglycocymidines (4a, b) respectively. 2a, b, d were cyclised with acetic anhydride to give imidazoimidazoline derivatives (5a–c). 2-Methylmercapto-3-phenylhydantoin (7) reacted with anthranilic acid to give 9 which previously prepared by the action of aniline on ethyl 2-methylthio-4-oxo-3,4-dihydro-3-quinazolinylacetate (8). Aryldienones 1a–e, 10a–e and arylazo derivatives 3a, b reacted with anthranilic acid to give imidazoquinazoline derivatives 11a–l and 12a, b, respectively.

Johnson et al. [1] reported that 5-benzal-2-alkylmercaptocarbonyldantoins reacted with methylene to give 5-benzal-N\textsuperscript{2}-methylglycocymidine. In our previous publication [2], aromatic amines were found to react with 5-arylidene- and/or 5-aryazo-2-methylmercaptocarbonyldantoins derivatives to give the corresponding N\textsuperscript{2}-arylglycocymidines without affecting the hetero ring opening.

Investigating the action of glycine on 5-arylidene-2-methylmercaptocarbonyldantoins (1a–d) [3], the hetero ring proved to be stable and condensation occurred with the formation of 5-arylidene-N\textsuperscript{2}-carboxymethylglycocymidines (2a–d).

The products 2a–d and 4a, b are soluble in aqueous sodium hydroxide and sodium carbonate solutions. The IR spectrum of 2a shows absorption bands characteristic for carboxylic group.

Cyclisation of the products 2a, b, d was affected by refluxing with acetic anhydride to give 3-aryliden-2,3,5,6-tetrahydro-1H-imidazo[1,2-a]imidazole-2,5-dione (5a–c).

Similarly, 5-aryazo-2-methylmercaptocarbonyldantoins (3a, b) [4] gave 5-aryazo-N\textsuperscript{2}-carboxymethylglycocymidines (4a, b).

The products 5a–c are insoluble in sodium carbonate solution. Also, the absence of absorption characteristic for carboxylic group in IR spectrum of compound 5a is taken as an evidence of cyclic structure proposed for these compound. Although two isomeric structures are possible for the cyclisation products (cf. structures 5 and 6), the structure 5 was considered most likely based on analogy to the well established behaviour of 5-arylidene-2-carbethoxymethylmercaptocarbonyldantoins on cyclisation under similar conditions [5].

It was reported that anthranilic acid condensed with 3-aryl-2-thiohydantoins at position 4 and 5 to give 2-thiono-3-aryl-4,5-(4'-hydroxy)-2,3'-quinolinimidazolidine [6, 7]. We found that 2-methylmercapto-3-phenylhydantoin (7) (prepared from 3-phenyl-2-thiohydantoin [8] (as in Lempert and Breuer methylation [9]) reacted with anthranilic acid to give 5-arylidene-2-methylmercaptocarbonyldantoins (1a–d) and 5-aryazo-2-methylmercaptocarbonyldantoins (3a, b) with glycine in acetic acid gave 5-arylidene-N\textsuperscript{2}-carboxymethylglycocymidines (2a–d) and 5-aryazo-N\textsuperscript{2}-carboxymethylglycocymidines (4a, b) respectively. 2a, b, d were cyclised with acetic anhydride to give imidazoimidazoline derivatives (5a–c). 2-Methylmercapto-3-phenylhydantoin (7) reacted with anthranilic acid to give 9 which previously prepared by the action of aniline on ethyl 2-methylthio-4-oxo-3,4-dihydro-3-quinazolinylacetate (8). Aryldienones 1a–e, 10a–e and arylazo derivatives 3a, b reacted with anthranilic acid to give imidazoquinazoline derivatives 11a–l and 12a, b, respectively.

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acid to give 1-phenyl-imidazo[2,1-b]quinazoline-
2,5(1H,3H)-dione (9) in quantitative yield which proved to be identical with that previously prepared from ethyl 2-methylthio-4-oxo-3,4-dihydro-3-quinazolinylacetate (8) with aniline and aniline hydrochloride [10].

To condense the aromatic aldehydes Trials were done with methylene group in 9. By fusing anthranilic acid with 5-arylidene-2-methyl-mercaptohydantoin (la-c) and/or 5-arylidene-3-phenyl-2-methylmercaptohydantoins [11] 10a-e at 150 °C the products 11a-f were formed, which were also obtained by boiling the reactants in glacial acetic acid.

The infrared spectrum of 11d was characterised by the presence of the absorption bands at 1710 cm⁻¹ and 1742 cm⁻¹ due to the presence of the two carbonyl groups, whereas the absence of the -NH absorption band in the compound 11d was in favour of the cyclic structure proposed for the products 11a-f.

On the other hand, the coloured arylazo derivatives 3a, b when treated with anthranilic acid in presence of acetic acid afforded the products 12a, b.

Experimental

All melting points are uncorrected. IR spectra were recorded on a Pye Unicam SP-1000 spectrophotometer. Analytical data were performed in the analytical data.

Preparation of 5-arylidene-2-carboxymethylglyco-
cyamidine derivatives (2a-d)

A mixture of 0.0041 mole of each of 5-arylidene-2-methylmercaptohydantoin (1a-d) [3] and 0.0042 mole of glycine was heated in 20 ml glacial acetic acid. During the reaction the odour of methane thiol could easily be detected, and after about ½ h, white precipitate was separated. When the reaction was completed, it was left to cool at room temperature. The product was filtered, washed with water and crystallised from diluted dimethyl formamide as 2a-d.

2a-d are all colourless. They gave no colour with concentrated sulphuric acid. They were soluble in sodium hydroxide and sodium carbonate solutions.

2a: m.p. 260 °C; yield 70%.
Analysis: C₁₂H₁₁O₂N₃
Calcd C 58.78 H 4.49 N 17.14,
Found C 58.8 H 4.5 N 17.1.

2b: m.p. 263 °C; yield 65%.
Analysis: C₁₃H₁₃O₂N₃
Calcd C 56.73 H 4.73 N 15.27,
Found C 56.8 H 4.7 N 15.3.

2c: m.p. 250 °C; yield 75%.
Analysis: C₁₃H₁₀O₂N₃Cl
Calcd C 51.61 H 3.58 N 15.05 Cl 12.72,
Found C 51.5 H 3.6 N 15.1 Cl 12.7.

2d: m.p. 269 °C; yield 70%.
Analysis: C₁₃H₁₀O₂N₃Cl
Calcd C 51.61 H 3.58 N 15.05 Cl 12.72,
Found C 51.5 H 3.6 N 15.1 Cl 12.7.
Preparation of 5-p-tolylazo-2-methylmercaptopyridine (3b)

To 5-p-tolylazo-2-thiohydantoin [4] (0.06 mole) dissolved in a mixture of aqueous sodium hydroxide (8%, 33 ml) and ethyl alcohol (33 ml), was added the methyl iodide (0.066 mole). The deep red colour dissolved in a mixture of aqueous sodium hydroxide (8%, 33 ml) and ethyl alcohol (33 ml), was added the methyl iodide (0.066 mole). The deep red colour of the reaction mixture gradually changed to orange, followed by precipitation of the product. The reaction mixture was left overnight at room temperature. The solid, obtained, was collected by filtration and recrystallised from dilute ethyl alcohol as 3b, m.p. 169 °C; yield 75%.

Analysis: C₁₁H₁₂ON₄S
Calcd C 53.23 H 4.84 N 22.58 S 12.90
Found C 53.3 H 4.9 N 22.4 S 13.0.

Preparation of 5-arylazo-N₂-carboxymethylglyco-cyanidine derivatives (4a, b)

A mixture of 0.004 mole of each of 5-arylazo-2-methylmercaptopyridine (3a, b) [4] and 0.0041 mole of glycine was heated in 20 ml glacial acetic acid. During the reaction the odour of methane thiol could easily be detected. When the reaction was completed, it was left to cool at room temperature, and the separated substance was filtered, washed with water and crystallised from the proper solvents as yellow crystals of 4a, b. They are soluble in sodium hydroxide and sodium carbonate solutions. They gave orange colour with concentrated sulphuric acid.

4a was crystallised from dilute dimethyl formamide, m.p. 277 °C; yield 80%.
Analysis: C₁₁H₁₁O₃N₅
Calcd C 55.07 H 4.2 N 25.4 Cl 13.58
Found C 55.1 H 4.3 N 25.1 Cl 13.6.

4b was crystallised from acetic acid, m.p. 268 °C; yield 75%.
Analysis: C₁₂H₁₂O₄N₅
Calcd C 52.36 H 4.73 N 25.45
Found C 52.4 H 4.8 N 25.4.

Cyclisation of the products 2a, b, d

A suspension of each of 2a, b, d (1 g) in acetic anhydride (10 ml) was heated till all the solid substance dissolved. The reaction mixture was refluxed for 4 h. It was cooled, poured into ice cold water and the separated product was collected by filtration and recrystallised from acetic acid, as colourless crystals of 5a–e.

The solid product was insoluble in sodium hydroxide and sodium carbonate solutions and gave no colour with concentrated sulphuric acid.

5a: m.p. 247 °C; yield 70%.
Analysis: C₁₂H₉O₃N₅
Calcd C 63.44 H 3.96 N 18.5
Found C 63.5 H 4.0 N 18.5.

5b: m.p. 229 °C; yield 65%.
Analysis: C₁₄H₁₂O₅N₅
Calcd C 60.70 H 4.28 N 16.34
Found C 60.8 H 4.3 N 16.4.

5c: m.p. 229 °C; yield 68%.
Analysis: C₁₃H₁₁O₄N₅Cl
Calcd C 55.07 H 3.06 N 16.06 Cl 13.58
Found C 55.1 H 3.1 N 16.0 Cl 13.6.

Preparation of the bicyclic 1-phenylimidazo-[2,1-b]quinazoline-2,5(1H,3H) dione (9)

1-Phenyl-imidazo[2,1-b]quinazoline-2,5(1H,3H) dione (9) was prepared from 5.8 g of 3-phenyl-2-thiohydantoin [8] dissolved in sodium hydroxide solution (16 ml, 12%) followed by the addition of 3.5 ml of methyl iodide in methanol (90 ml). The reaction mixture was stirred for one hour and left aside at room temperature overnight. The solution (contain compound 7) was evaporated to half its volume, diluted with 20 ml ethyl alcohol and 3.7 g of anthranilic acid was added to the dark purple solution. The reaction was refluxed for 1.5 h on water bath, till the complete precipitation of the colourless product. It was collected by filtration and recrystallised from dimethyl formamide as 9 m.p. 298 °C. It is proved to be identical with an authentic sample [10].

Action of anthranilic acid on 5-arylidene-2-methylmercaptopyridine derivatives (1a–e)

Method A: A mixture of 0.004 mole of each of 1a–e and 0.0041 mole of anthranilic acid was heated in a bath at 150–160 °C. During the reaction the odour of methane thiol could easily be detected and heating was continued for approximately 2 h. When the reaction was completed, it was left to cool at room temperature. It was washed with alcohol and the residual solid obtained, was crystallised from acetic acid as yellow crystals of 11a–e (cf. Table 1).

The solid product was insoluble in sodium hydroxide and sodium carbonate solutions and gave yellow colour when treated with concentrated sulphuric acid.

Method B: A suspension of 0.004 mole of each of 5-arylidene-2-methylmercaptopyridine hydantoins (1a–e) and 0.0041 mole of anthranilic acid was heated in 20 ml glacial acetic acid. During the reaction the odour of methane thiol could easily be detected and the solution became dark brown. When the reaction was completed, it was left to cool at room temperature. The yellow crystalline substance was separated. The products were recrystallised from acetic acid and proved to be 11a–e and identical with those obtained from Method (A) by melting point and mixed melting point determinations.
Table I. 3-Arylidene imidazo[2,1-b]quinazoline-2,5(1H, 3H)dione (11a–f).

<table>
<thead>
<tr>
<th>Compound</th>
<th>m.p. [°C]</th>
<th>Yield [%]</th>
<th>Formula</th>
<th>Analysis [%]</th>
<th>Hydrogen Caled</th>
<th>Found</th>
<th>Nitrogen Caled</th>
<th>Found</th>
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<tbody>
<tr>
<td>11a</td>
<td>263</td>
<td>80</td>
<td>C_{17}H_{11}O_{2}N_{3}</td>
<td>70.59 70.6</td>
<td>3.81 3.8</td>
<td>14.53 14.6</td>
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<td></td>
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<tr>
<td>11b</td>
<td>295</td>
<td>82</td>
<td>C_{18}H_{13}O_{3}N_{3}</td>
<td>67.71 67.7</td>
<td>4.1 4.2</td>
<td>13.17 13.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11c</td>
<td>277</td>
<td>79</td>
<td>C_{17}H_{15}O_{2}N_{3}Cl*</td>
<td>63.06 63.1</td>
<td>3.09 3.1</td>
<td>12.98 13.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11d</td>
<td>273</td>
<td>85</td>
<td>C_{23}H_{15}O_{3}N_{3}</td>
<td>75.62 75.7</td>
<td>4.11 4.1</td>
<td>11.51 11.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11e</td>
<td>245</td>
<td>86</td>
<td>C_{24}H_{17}O_{3}N_{3}</td>
<td>72.91 72.9</td>
<td>4.30 4.3</td>
<td>10.63 10.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11f</td>
<td>219</td>
<td>90</td>
<td>C_{23}H_{14}O_{2}N_{3}Cl*</td>
<td>69.09 69.1</td>
<td>3.50 3.5</td>
<td>10.51 10.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Cl: Caled 10.97; Found 11.0; ** Cl: Caled 8.89; Found 8.89%.

Action of anthranilic acid on 5-arylidene-3-phenyl-2-methylmercaptanhydantoin (10a–c)

A suspension of each of 10a–c (0.004 mole) and anthranilic acid (0.0041 mole) was heated in 20 ml glacial acetic acid. The reaction mixture was worked up as above. The products were filtered, recrystallised from acetic acid as yellow crystals of 11d–f (cf. Table I).

11d–f are insoluble in sodium hydroxide and sodium carbonate solutions. They give yellow colour when treated with concentrated sulphuric acid.

Action of anthranilic acid on 5-arylazo-2-methylmercaptanhydantoin derivatives (3a, b)

A suspension of 0.004 mole of each of 3a, b and 0.0041 mole of anthranilic acid was heated in 20 ml glacial acetic acid. When the reaction was completed and no odour of methane thiol could be detected, it was left to cool at room temperature. The separated crystalline substance was filtered. The product was crystallised from the proper solvent as yellow crystals of 12a, b. They are insoluble in sodium hydroxide and sodium carbonate solutions. They gave orange colour when treated with concentrated sulphuric acid.

12a was crystallised from dilute dimethyl formamide, m.p. 289 °C; yield 75%.

Analysis: C_{16}H_{11}O_{2}N_{5}
Caled C 62.95  H 3.61  N 22.95
Found  C 63.0   H 3.6   N 22.9.

12b was crystallised from acetic acid, m.p. 242 °C; yield 70%.

Analysis: C_{17}H_{13}O_{2}N_{5}
Caled  C 63.85  H 4.08  N 21.94
Found  C 63.9   H 4.1   N 21.9.