Novel Rearrangement of 5-Arylazo-2-thiohydantoin Derivatives with Alkali and Aromatic Amines

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2-Thiohydantoin Derivatives, Alkali Amines, Aromatic Amines

5-Arylazo-2-thiohydantoin derivatives (2a,c) were cleaved and rearranged by aqueous sodium hydroxide to give the corresponding 1-aryl-1,2,4-triazole-5-imino-3-carboxylic acids (3a–c). 2a was decarboxylated to 1-phenyl-1,2,4-triazole-5-imine (5). Hydrolysis of 5-arylazo-1-phenyl-2-thiohydantoins (6a–e) behaved in different manner affording 1-aryl-4-phenyl-1,2,4-triazoline-5-thione-3-carboxylic acids (7a–e). Fusing (2a–e) with aromatic amines at high temperature gave the corresponding anilides (8a–h). Treatment of 5-arylidene-2-thiohydantoin derivatives (9a–e) with hydrazine hydrate gave colourless products of thioureido cinnamic acid hydrazide derivatives (10a–e), while refluxing 5-arylidene-2-methylmercaptohydantoin (11a–d) with hydrazine hydrate and/or benzophenone hydrazone gave the corresponding glycocynamidine derivatives (12a–g).

It was reported that in an alkaline solution 5-substituted-2-thiohydantoins (1) ionise as weak acids to give the corresponding anions [1, 2] and they are also hydrolysed slowly with ring fission to give the thioureido acids [3]. This last reaction was studied spectrophotometrically and in alkaline solution the spectra changed from those characterised of 2-thiohydantoins to those characteristic of the thioureido acids. When the solutions were made strongly acid, these changes were reversed [4].

Although the reaction of alkali with 5-substituted-2-thiohydantoins yielding substituted thioureido acids has been studied, no attention has been paid to the hydrolysis of the corresponding 5-hydrazo-2-thiohydantoin derivatives in which the electron withdrawing group i.e. the arylazo group attached to carbon-5.

Treatment of 5-arylazo-2-thiohydantoins (2a–e) with aqueous sodium hydroxide affected hetero-ring opening followed by recyclisation via loss of hydrogen sulphide with the formation of 1-aryl-1,2,4-triazole-5-imino-3-carboxylic acids (3a–e).

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hetero-ring fission occurred with the formation of 1-aryl-4-phenyl-1\(^2\)H-1,2,4-triazoline-5-thione-3-carboxylic acids (7a–e). In this reaction the presence of substituent at N-1 favoured the rearrangement which took place with the elimination of a molecule of ammonia faster than hydrogen sulphide as shown in the previous case.

\[
\begin{align*}
6a: & \text{Ar} = \text{C}_6\text{H}_5 \\
6b: & \text{Ar} = \text{o-CH}_3 \cdot \text{C}_6\text{H}_4 \\
6c: & \text{Ar} = \text{p-CH}_3 \cdot \text{C}_6\text{H}_4 \\
6d: & \text{Ar} = \text{p-CH}_3 \cdot \text{o-Cl} \cdot \text{C}_6\text{H}_4 \\
6e: & \text{Ar} = \text{o-Cl} \cdot \text{m-NO}_2 \cdot \text{C}_6\text{H}_4 \\
6f: & \text{Ar} = \text{p-CH}_3 \cdot \text{C}_6\text{H}_4 \\
6g: & \text{Ar} = \text{p-CH}_3 \cdot \text{o-Cl} \cdot \text{C}_6\text{H}_4 \\
6h: & \text{Ar} = \text{p-CH}_3 \cdot \text{o-Cl} \cdot \text{C}_6\text{H}_4
\end{align*}
\]

The obtained products 7a–e gave the correct analytical data. They are colourless and show acidic property.

In a previous publication [7] aromatic amines were found to react with 5-aryloxy-2-methylmercaptopyridine derivatives to give the corresponding glycoamydines without affecting the hetero-ring opening. Now by fusing 2a–c with aromatic amines i.e. aniline, o-toluidine and p-toluidine in an oil bath at 140–150 °C afforded the corresponding 1-aryl-1\(^2\)H-1,2,4-triazoline-5-thione-3-carboxylic acid (8a-h). While fusion of 6a–e, having a phenyl substituent at N-1, with the previous aromatic amines under the same experimental conditions afforded the starting materials unchanged. This proved that the phenyl group connected to the nitrogen at position-1 stabilized the hetero-ring of 2-thiohydantoin.

\[
\begin{align*}
2a-c & \xrightarrow{R\text{NH}_2} \xrightarrow{140-150\degree C} \xrightarrow{\text{CONHR}}
\end{align*}
\]

The structure of these products (8a–h) was inferred from the analytical data and the formation of the appropriate acid, when 8a was hydrolysed with 70% alcoholic potassium hydroxide afforded 1-phenyl-1\(^2\)H-1,2,4-triazoline-5-thione-3-carboxylic acid [8]. Also 8a was alkylated with benzyl chloride in alkylne medium and the corresponding 1-phenyl-5-benzylmercapto-1\(^2\)H-1,2,4-triazole-3-carboxylic anilide was separated, which on refluxing with hydrochloric acid solution till the odour of the benzylthiol could not be detected, 1-phenyl-1\(^2\)H-1,2,4-triazoline-5-one-3-carboxylic anilide was separated which was proved by an authentic sample [8].

When the yellow 5-arylidene-2-thiohydantoin derivatives (9a–e) were treated with hydrazine hydrate in absolute ethyl alcohol at room temperature, colourless products of thioureido cinnamic acid hydrazide derivatives (10a–e) were obtained. When (10a–e) was heated with glacial acetic acid, cyclization occurred with the formation of the parent substances.

\[
\begin{align*}
9a: & \text{Ar} = \text{C}_6\text{H}_5 \\
9b: & \text{Ar} = \text{p-CH}_3 \cdot \text{C}_6\text{H}_4 \\
9c: & \text{Ar} = \text{o-Cl} \cdot \text{C}_6\text{H}_4 \\
9d: & \text{Ar} = \text{o-Cl} \cdot \text{C}_6\text{H}_4
\end{align*}
\]

Previously we studied the reactivity of the thione group present in 5-arylidene-2-thiohydantoin aiming to transfer it into the corresponding glycoamydine derivatives. This transformation was achieved by heating 5-benzylidene-2-methylmercaptopyridyldantoin with aniline [7].

When 5-arylidene-2-methylmercapto hydantoin derivatives (11a–d) was refluxed with hydrazine hydrate and/or benzophenone hydrazone in boiling acetic acid till the odour of methanethiol could not be detected, the corresponding glycoamydine derivatives (12a–g) were obtained.

\[
\begin{align*}
11a: & \text{Ar} = \text{C}_6\text{H}_5 \\
11b: & \text{Ar} = \text{o-Cl} \cdot \text{C}_6\text{H}_4 \\
11c: & \text{Ar} = \text{m-NO}_2 \cdot \text{C}_6\text{H}_4 \\
11d: & \text{Ar} = \text{p-CH}_3 \cdot \text{C}_6\text{H}_4 \\
12a: & \text{Ar} = \text{C}_6\text{H}_5 \\
12b: & \text{Ar} = \text{o-Cl} \cdot \text{C}_6\text{H}_4 \\
12c: & \text{Ar} = \text{m-NO}_2 \cdot \text{C}_6\text{H}_4 \\
12d: & \text{Ar} = \text{p-CH}_3 \cdot \text{C}_6\text{H}_4 \\
12e: & \text{Ar} = \text{C}_6\text{H}_5 \\
12f: & \text{Ar} = \text{o-Cl} \cdot \text{C}_6\text{H}_4 \\
12g: & \text{Ar} = \text{m-NO}_2 \cdot \text{C}_6\text{H}_4 \\
\end{align*}
\]
Experimental

Action of aqueous sodium hydroxide on 5-arylazo-2-thiohydantoin derivatives (2a-c)

1 g of each of 2a-c was added to 25 ml of sodium hydroxide (2%) and the reaction mixture was refluxed for 1 h. It was cooled and acidified with cold sulphuric acid till complete precipitation. The products were collected and crystallised from ethyl alcohol as colourless substances (3a-c). The acids (3a-c) are soluble in aqueous sodium hydroxide and gave effervescence with sodium bicarbonate solution.

3a: m.p. 204 °C; yield 85%.
Analysis: C₁₀H₁₀O₂N₄
Calcd C 55.04 H 4.58 N 25.68,
Found C 55.1 H 4.5 N 25.7.

3b: m.p. 199 °C; yield 78%.
Analysis: C₁₀H₁₀O₂N₄
Calcd C 55.04 H 4.58 N 25.68,
Found C 55.1 H 4.6 N 25.7.

3c: m.p. 216 °C; yield 80%.
Analysis: C₁₀H₁₀O₂N₄
Calcd C 55.04 H 4.58 N 25.68,
Found C 55.1 H 4.5 N 25.7.

Action of aqueous sodium hydroxide on 5-phenyl-2-methylmercaptohydantoin (4)

A mixture of 4 and 25 ml of sodium hydroxide (2%) was refluxed for 1 h. The reaction mixture was completed as above and the solid so obtained was crystallised from ethyl alcohol as colourless crystals, m.p. 204 °C. It was proved to be 3a by melting point and mixed melting point determinations.

Decarboxylation of 1-phenyl-1,2,4-triazoline-5-imino-3-carboxylic acid (3a)

The acid 3a (1.0 g) was heated at 140–150 °C in an oil bath under reduced pressure (water pump) till the evolution of gas stopped. It was cooled and the residual solid was extracted with benzene and left to evaporate slowly at room temperature. The obtained solid was crystallised from ethyl alcohol as colourless crystals, m.p. 157 °C. It was proved to be 1-phenyl-1,2,4-triazoline-5-imino (5) [6] by melting point and mixed melting point determinations.

Picrate of 1-phenyl-5-imino-1,2,4-triazoline (5)

To a mixture of 0.2 g of 5 in 10 ml of acetone, a concentrated solution of picric acid was added drop wisely. The reaction mixture was left at room temperature till complete precipitation. The separated yellow crystals were collected by filtration and crystallised from ethyl alcohol (m.p. 175 °C) and it was identical with an authentic sample [6] by melting point and mixed melting point determinations.

Action of aqueous sodium hydroxide on 5-arylazo-1-phenyl-2-thiohydantoin (6a-c)

1 g of each of 6a-c was refluxed in 25 ml of sodium hydroxide (2%) for 1 h, the reaction mixture was cooled and worked up as above. The products were crystallised from ethyl alcohol as colourless crystals of 7a-c.

The acids 7a-c are soluble in aqueous sodium hydroxide and gave effervescence with sodium bicarbonate solution.

7a: m.p. 132 °C; yield 82%.
Analysis: C₁₅H₁₁O₂N₅S
Calcd C 61.73 H 4.18 N 13.50 S 10.28,
Found C 61.7 H 4.2 N 13.5 S 10.2.

7b: m.p. 117 °C; yield 79%.
Analysis: C₁₅H₁₁O₂N₅S
Calcd C 61.73 H 4.18 N 13.50 S 10.28,
Found C 61.8 H 4.2 N 13.6 S 10.3.

7c: m.p. 155 °C; yield 77%.
Analysis: C₁₅H₁₁O₂N₅S
Calcd C 61.73 H 4.18 N 13.50 S 10.28,
Found C 61.7 H 4.2 N 13.5 S 10.2.

Action of aromatic amines on 5-arylazo-2-thiohydantoin (2a-c)

A mixture of each of 2a-c (1.0 g) and the appropriate amine (2 ml) was heated at 140–150 °C in an oil bath for 4 h. It was cooled and triturated with dilute ethanol. The obtained solid was crystallised from hot ethanol as colourless crystals of the corresponding anilides (8a-h) (cf. Table I).

The products are insoluble in dilute sodium hydroxide solution and gave reddish brown colour when treated with concentrated sulphuric acid.

Alkaline hydrolysis of 1-phenyl-1,2,4-triazoline-5-thione-3-carboxyanilide (8a)

A mixture of 8a (1.0 g) in 30 ml of ethanolic potassium hydroxide (70%), was refluxed for 1 h on a water bath. It was cooled, diluted with water, acidified with cold hydrochloric acid, and extracted with chloroform. The extract layer was dried over anhydrous sodium sulphate, filtered and evaporated. The residual solid was crystallised from ethyl alcohol as colourless crystals m.p. 181 °C, it was proved to be 1-phenyl-1,2,4-triazoline-5-thione-3-carboxylic acid (8) by melting point and mixed melting point determinations.

Benzylation of 1-phenyl-1,2,4-triazoline-5-thione-3-carboxyanilide (8a)

To a solution of 0.5 g of 8a dissolved in a mixture of 15 ml aqueous sodium hydroxide (2%) and 15 ml of ethyl alcohol, was added 2 ml of benzyl chloride drop wisely. The reaction mixture was shaken for 1 h and was left aside overnight at room tem-
The obtained solid was collected by filtration and recrystallised from ethyl alcohol as colourless crystals m. p. 143 °C (yield 88%).

**Analysis:** C_{16}H_{14}ON_{4}S 61.93 62.0 4.51 4.5 18.06 18.1 10.32 10.3

**Acid hydrolysis of 1-phenyl-5-benzylmercapt-1H-1,2,4-triazole-3-carboxyanilide**

The obtained benzyl derivative (0.5 g) was refluxed in a mixture of ethyl alcohol (20 ml) and concentrated hydrochloric acid (5 ml) on a water bath. The reaction mixture was heated for 4 h till the odour of the evolved thiol could not be detected. It was cooled and the precipitated product was filtered off and recrystallised from ethyl alcohol as colourless crystals m. p. 145 °C; yield 90%.

**Analysis:** C_{17}H_{16}ON_{4}S 62.96 63.0 4.93 4.9 17.28 17.2 9.87 9.9

**Formation of a-thioureido cinnamic acid hydrazide derivatives (10a-e)**

To a suspension of each of the yellow substances 9a-e (35 ml mole) in 50 ml of ethyl alcohol was added 8 ml of hydrazine hydrate. The reaction mixture was stirred at room temperature for five hours. During the reaction the yellow substances disappeared gradually and colourless product began to deposit. After complete precipitation the products were collected by filtration. The products were dissolved in ether, filtered and left to evaporate slowly at room temperature precipitating the colourless thioureido hydrazide (10a-e).

**Action of hydrazine hydrate on 11a-d**

A mixture of each of 11a-d (0.1 mole) and slight excess (0.11 mole) of hydrazine hydrate in 20 ml glacial acetic acid was refluxed for 4 h till the odour of methane thiol could not be detected. It was left to cool, and the separated product was washed with ethyl alcohol and crystallised from the proper solvent as coloured compounds of 5-arylidene-2-thiodyantoin derivatives (12a-d) (cf. Table II).

**Action of benzophenonehydrazone on 11a-e**

A mixture of each of 11a-e (0.1 mole) and (0.11 mole) of benzophenonehydrazone was dissolved in 25 ml glacial acetic acid. The reaction mixture was refluxed for 4 h till the odour of methane thiol could not be detected. It was left to cool. The obtained products were washed with ethyl alcohol, and crystallised from ethyl alcohol as coloured crystals of the crossed azine 12e-g (cf. Table II).
Table II. 5-Arylidene-2-hydrazohydantoin derivatives (12a-g).

| Compound | m.p. [°C] | Yield [%] | Solvent | Formula | Carbon Caled | Carbon Found | Hydrogen Caled | Hydrogen Found | Nitrogen Caled | Nitrogen Found |
|----------|-----------|-----------|---------|---------|--------------|--------------|---------------|----------------|---------------|----------------|----------------|
| 12a      | 246       | 70        | Ethanol | C_{10}H_{10}O_{4}N_{4} | 59.40        | 59.4         | 4.95          | 5.0            | 27.72         | 27.8           |
| 12b      | 300       | 70        | aq. DMF (70%) | C_{10}H_{10}O_{4}N_{4}Cl^a | 50.73        | 50.7         | 3.80          | 3.8            | 23.67         | 23.7           |
| 12c      | 180       | 65        | Ethanol | C_{10}H_{10}O_{4}N_{4} | 58.58        | 58.6         | 3.64          | 3.7            | 28.34         | 28.4           |
| 12d      | 290       | 68        | Acetic acid | C_{11}H_{12}O_{4}N_{4} | 56.89        | 56.9         | 5.17          | 5.2            | 24.13         | 24.2           |
| 12e      | 170       | 80        | Ethanol | C_{23}H_{18}O_{4}N_{4} | 75.40        | 75.4         | 4.91          | 5.0            | 15.30         | 15.3           |
| 12f      | 215       | 75        | Ethanol | C_{23}H_{18}O_{4}N_{4}Cl^b | 68.91        | 68.9         | 4.24          | 4.3            | 13.98         | 14.0           |
| 12g      | 255       | 78        | Ethanol | C_{23}H_{17}O_{3}N_{5} | 67.15        | 67.2         | 4.13          | 4.2            | 17.03         | 17.0           |

^a Cl: Caled. 15.01; Found 15.1%; ^b Cl: Caled. 8.86; Found 8.9%.