REATIONS OF 6-ARYLMETHYLENE-THIAZOLO[3,2-a]PYRIMIDINE-3,5,7(2H)-TRONES

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ABSTRACT. 5-Arylmethylene-2-carboxymethylthiobarbituric acids 2 are cyclised to 6-arylmethylene-thiazolo[3,2-a]pyrimidine-3,5,7-(2H)-triones 3. Structural assignments are based on IR and NMR spectra. 2,6-Diarylmethylene-thiazolo[3,2-a]pyrimidine-3,5,7-triones 4 were prepared by several methods. Compound 3 coupled with diazotized anilines to give 6-arylmethylene-thiazolo[3,2-a]pyrimidine-3,5,7-trione-2-arylhydrazones 5. The thiazolone ring of 3a is opened by amines to yield acetamide derivatives 6.

INTRODUCTION

A number of thiobarbituric acid derivatives have found applications in the determination of lipid peroxides (1-4), metals (5-10), aldehydes and amines (11-19), sorbic acid in food stuff (20), quinic acid (21), shikimic acid (22), cyanides (23), fats and oils (24-32), carbohydrates (33-38), in the detection and monitoring of cancer (39), and in the analysis of foods (40-45) and drugs (46-49). In continuation of our interest in the condensation reaction of thiazolo compounds with aldehydes and amines (50-53), we report here some new derivatives.

RESULTS AND DISCUSSION

Condensation of 2-thiobarbituric acid with aromatic aldehydes gives 5-aryl methylene-2-thiobarbituric acid 1 (54-56). Chloroacetic acid reacted with 2-thiobarbituric acid to give 2-carboxymethylthiobarbituric acid (57,58). Similarly chloroacetic acid reacts with 1 to give 5-arylmethylene-2-carboxymethylthiobarbituric acid 2. Cyclisation of 2 by acetic anhydride in acetic acid yields products which are formulated as 6-arylmethylene-thiazolo[3,2-a]pyrimidine-3,5,7(2H)-triones 3 or its geometrical isomeric stuctural form 3'.

The IR spectrum of 1a shows a broad band at 1725 cm⁻¹ (CO) and a broad band at 3200 cm⁻¹ (NH). The NMR spectrum of 1a shows the =CH proton (s, H) at δ 5.25 (1H), the NH protons as a singlet at 8.9, and the second proton appears at 8.15 and the aromatic protons as a multiplet in the 7.2-7.6 ppm regions.

The IR spectrum of 2a shows broad absorption band at 1690 cm⁻¹ (CO bands) and at 3100 cm⁻¹ (NH and OH).

The IR spectrum of 3a shows three absorption bands at 1685, 1700 and at 1730 cm⁻¹ (CO). The NMR spectrum showed the methylene group (s, 2H) at δ 3.2, the =CH group (s, 1H) at 5.6 and the aromatic protons as a multiplet in the 7.4-7.9 ppm region.

The methylene group of compounds 3 was found to condense with aromatic aldehydes to give 2,6-diarylmethylene-thiazolo[3,2-a]pyrimidine-3,5,7-triones 4 or its isomer 4'.
These arylmethylene derivatives were better prepared directly from arylmethylene-2-thiobarbituric acid by the action of chloroacetic acid, the aromatic aldehydes in the presence of acetic acid, acetic anhydride and sodium acetate. The arylmethylene-2-carboxymethylthiobarbituric acid 2 is also under these experimental conditions converted to the arylmethylene derivatives 4 and/or 4'.

The IR spectrum of 4a shows an absorption band at 1655 and a broad band at 1715 cm$^{-1}$ (CO). The NMR spectrum of 4a, shows the $\text{=CH}$ protons as (s, 1H) at $\delta$ 6.1 ppm, and the aromatic protons as a multiplet in the $\delta$ 7.4–7.8 ppm region.
The thiazolopyrimidine triones 3 coupled with diazotised anilines in sodium acetate buffered solution, to give 6-arylmethylene-thiazolo[3,2-a]pyrimidine-3,5,7-trione-2-arylhydrazones 5.

\[
\text{ArCH} = \text{C} = \text{C} = \text{C} = \text{N} = \text{N} \text{Ar'}
\]

5a, Ar = C₆H₅; Ar' = C₆H₅  
b, Ar = C₆H₄; Ar' = C₆H₄,CH₃-m  
c, Ar = C₆H₃; Ar' = C₆H₄,CH₃-p  
d, Ar = C₆H₄, OCH₃-p; Ar' = C₆H₅

That these compounds exist in the hydrazone rather than in the azo form is supported by spectral data.

The UV spectrum of 5a shows a maximum band at 380 nm. The azo compounds have a strong band at 270-280 nm. The monophenyl-hydrazones give a weak absorption band (or no band) in this region and a strong absorption band at a wavelength higher than 320 nm (59-61).

The thiazolone ring of compound 3a has been found to be opened by amines and hydrazines to yield the corresponding anilides or hydrazides 6.

\[
\begin{align*}
\text{C}_6\text{H}_5\text{CH}=\text{C} & \quad \xrightarrow{\text{RNH}_2} \\
\text{O} & \quad \text{O} = \text{C} = \text{CH}_2 \quad \text{C} = \text{N} - \text{CH}_2 - \text{CO-NHR} \\
\text{3a} & \quad \text{6}
\end{align*}
\]

6a, R = NH₂  
b, R = NH,C₆H₅  
c, R = C₆H₅  
d, R = C₆H₄, OCH₃-p  
e, R = C₆H₄,CH₃-m  
f, R = C₆H₄,CH₃-p

**EXPERIMENTAL**

Melting points are not corrected. IR spectra were recorded on Beckman IR 20. The UV spectrum was recorded on Beckman DK 2A. NMR spectra were recorded (DMSO-d₆) on a Varian A60 A spectrophotometer.

6-Arylmethylene-2-thiobarbituric acid 1. A mixture of thiobarbituric acid (0.01 mole), an equimolecular amount of the appropriate aromatic aldehydes in 30 ml acetic acid was refluxed for 3 hr, cooled and poured into 500 ml water.
The residue washed with water and crystallised (see Table 1). 5-Arylmethylene-2-carboxymethyl-thiobarbituric acids 2. A mixture of 1 (0.01 mole), a slight excess of chloroacetic acid, about 2 gm of fused sodium acetate in 50 ml of acetic acid were refluxed for 3 hr and the solution was left overnight. The precipitate formed was collected and crystallised from the proper solvent (see Table 1). The compounds are soluble in sodium carbonate solution with effervescence and in sodium hydroxide solution.

6-Arylmethylene-thiazolo[3,2-a]pyrimidine-3,5,7(2H)-triones 3. (a) A mixture of 1 (0.01 mole), 1.5 gm of chloroacetic acid and 2 g of fused sodium acetate in 25 ml of acetic acid and 15 ml of acetic anhydride was refluxed for 2 hr and cooled. The precipitate formed after dilution (if necessary) was collected and crystallised from the proper solvent (see Table 1).

Table 1. 5-Arylmethylene-2-carboxymethyl thiobarbituric acid 2 and 6-arylmethylenethiazolo[3,2-a]pyrimidine-3,5,7(2H)-triones 3.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
<th>Solvent m.p. (°C)</th>
<th>Formula</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Carbon</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Calcd.</td>
</tr>
<tr>
<td>2a</td>
<td>82</td>
<td>A d</td>
<td>C_{13}H_{10}N_{2}O_{4}S</td>
<td>53.78</td>
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<td>2b</td>
<td>99</td>
<td>A d</td>
<td>C_{13}H_{12}N_{2}O_{4}S</td>
<td>53.39</td>
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<tr>
<td>2c</td>
<td>95</td>
<td>A d</td>
<td>C_{13}H_{12}N_{2}O_{4}S</td>
<td>53.97</td>
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<tr>
<td>2d</td>
<td>80</td>
<td>A d</td>
<td>C_{13}H_{12}N_{2}O_{4}S</td>
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</tr>
<tr>
<td>3a</td>
<td>85</td>
<td>A 285</td>
<td>C_{13}H_{12}N_{2}O_{4}S</td>
<td>53.35</td>
</tr>
<tr>
<td>3b</td>
<td>70</td>
<td>B 285</td>
<td>C_{13}H_{12}N_{2}O_{4}S</td>
<td>53.95</td>
</tr>
<tr>
<td>3c</td>
<td>65</td>
<td>C 285</td>
<td>C_{13}H_{12}N_{2}O_{4}S</td>
<td>53.95</td>
</tr>
<tr>
<td>3d</td>
<td>60</td>
<td>C 285</td>
<td>C_{13}H_{12}N_{2}O_{4}S</td>
<td>53.95</td>
</tr>
</tbody>
</table>

A = acetic acid
B = ethyl alcohol
d = decomposed

(b) 3 gm of compound 2, 30 ml of acetic anhydride and 12 ml of acetic acid were refluxed for 2 hr and worked as above.

2,6-Diarylmethylene-thiazolo[3,2-a]pyrimidine-3,5,7-triones 4. (a) General procedure: A mixture of 0.01 mole of 1a, c or d, 1.5 g of chloroacetic acid, 2 g of fused sodium acetate, an equimolecular amount of the appropriate aromatic aldehydes in 25 ml of acetic acid and 15 ml of acetic anhydride was refluxed gently for 2 hr and cooled. The precipitate formed (after dilution if necessary) was collected and crystallised from the proper solvent (see Table 2).

Table 2. 2,6-Diarylmethylenethiazolo[3,2-a]pyrimidine-3,5,7-triones 4.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
<th>Solvent m.p. (°C)</th>
<th>Formula</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Carbon</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Calcd.</td>
</tr>
<tr>
<td>4a</td>
<td>69</td>
<td>A 272</td>
<td>C_{20}H_{13}N_{2}O_{4}S</td>
<td>66.68</td>
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<td>4b</td>
<td>72</td>
<td>B 265</td>
<td>C_{20}H_{13}N_{2}O_{4}S</td>
<td>66.65</td>
</tr>
<tr>
<td>4c</td>
<td>66</td>
<td>C 265</td>
<td>C_{20}H_{13}N_{2}O_{4}S</td>
<td>59.26</td>
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<tr>
<td>4d</td>
<td>61</td>
<td>A &gt;300</td>
<td>C_{20}H_{13}N_{2}O_{4}S</td>
<td>59.26</td>
</tr>
<tr>
<td>4e</td>
<td>66</td>
<td>D &gt;300</td>
<td>C_{20}H_{13}N_{2}O_{4}S</td>
<td>59.26</td>
</tr>
<tr>
<td>4f</td>
<td>57</td>
<td>D &gt;300</td>
<td>C_{20}H_{13}N_{2}O_{4}S</td>
<td>59.26</td>
</tr>
<tr>
<td>4g</td>
<td>64</td>
<td>A &gt;300</td>
<td>C_{20}H_{13}N_{2}O_{4}S</td>
<td>59.26</td>
</tr>
</tbody>
</table>

A = acetic acid
B = ethyl alcohol
C = dilute acetic acid
D = nitrobenzene

d = decomposed

(b) 0.01 mole of 2a or c and 0.01 mole of the aldehyde were refluxed in 15 ml of acetic anhydride and 8 ml of acetic acid for 1 hr and worked as above.
Reactions of thiazolopyrimidine triones

(c) 0.01 mole of 3a or b and 0.01 mole of the aldehyde were refluxed in 15 ml of acetic anhydride and 8 ml of acetic acid for 1 hr, and worked as above.

6-Arylmethylene-thiazolo[3,2-a]pyrimidine-3,5,7-trione-2-aryldiazines

Compound 3 (0.005 mole) was dissolved in 15 ml of ethanol containing 3 g of sodium acetate and cooled. The cold solution was treated dropwise with a cold solution of the diazonium salt (from 0.005 mole of the appropriate aniline in the usual way) and left for 1 hr in the ice bath. The precipitate formed was collected and crystallised from the proper solvent (see Table 3).

Table 3. 6-Arylmethylenethiazolo[3,2-a]pyrimidine-3,5,7-trione-2-aryldiazones 5.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
<th>Solvent m.p. (°C)</th>
<th>Formula</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>55</td>
<td>A</td>
<td>280</td>
<td>C_{19}H_{12}N_{4}O_{8}S</td>
</tr>
<tr>
<td>5b</td>
<td>61</td>
<td>A</td>
<td>271</td>
<td>C_{20}H_{14}N_{4}O_{8}S</td>
</tr>
<tr>
<td>5c</td>
<td>63</td>
<td>A</td>
<td>267</td>
<td>C_{20}H_{14}N_{4}O_{8}S</td>
</tr>
<tr>
<td>5d</td>
<td>56</td>
<td>B</td>
<td>273</td>
<td>C_{20}H_{14}N_{4}O_{8}S</td>
</tr>
</tbody>
</table>

A = ethyl alcohol
B = acetic acid

Action of amine and hydrazines on 3a. 0.01 mole of 3a and 0.012 mole of the hydrazines or the amines were refluxed in 15 ml of ethanol for 3 hr. The product 6 that separated on cooling or on dilution with water was collected and crystallised from the proper solvent (see Table 4).

Table 4. Acetanilide derivatives 6.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
<th>Solvent m.p. (°C)</th>
<th>Formula</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>48</td>
<td>A</td>
<td>242</td>
<td>C_{13}H_{12}N_{4}O_{8}S</td>
</tr>
<tr>
<td>6b</td>
<td>60</td>
<td>A</td>
<td>251</td>
<td>C_{19}H_{16}N_{4}O_{8}S</td>
</tr>
<tr>
<td>6c</td>
<td>63</td>
<td>B</td>
<td>273</td>
<td>C_{19}H_{15}N_{3}O_{8}S</td>
</tr>
<tr>
<td>6d</td>
<td>52</td>
<td>A</td>
<td>284</td>
<td>C_{20}H_{17}N_{3}O_{8}S</td>
</tr>
<tr>
<td>6e</td>
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<td>C</td>
<td>255</td>
<td>C_{20}H_{17}N_{3}O_{8}S</td>
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<tr>
<td>6f</td>
<td>68</td>
<td>C</td>
<td>247</td>
<td>C_{20}H_{17}N_{3}O_{8}S</td>
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</table>

A = ethyl alcohol
B = acetic acid
C = dioxane

ACKNOWLEDGEMENT

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REFERENCES

41. S. Navarro, A. Ortiz and F. Costa, Anales Bromatol 17, 269 (1965) (Span); C.A. 64, 2657h (1966).