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

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ABSTRACT. 5-Arylmethylene-2-carboxymethylthiobarbituric acids **2** are cyclised to 6-arylmethylenethiazolo[3,2-a]pyrimidine-3,5,7-(2H)-triones **3**. Structural assignments are based on IR and NMR spectra. 2,6-Diarylmethylenethiazolo [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 yeild 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

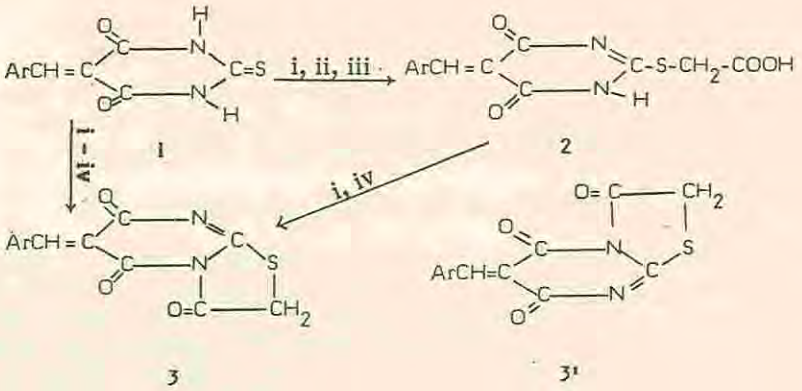
Condensation of 2-thiobarbituric acid with aromatic aldehydes gives 5-aryl methylene-2-thiobarbituric acid **1** (54-56). Chloroacetic acid reacted with 2-thiobarbituric acid to give 2-carboxymethylthiobarbituric acid (57,58). Similarly chloroacetic acid reacts with **1** to give 5-arylmethylene-2-carboxy-methylthiobarbituric 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 δ9.15 and the aromatic protons as a multiplet in the 7.2-7.8 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).

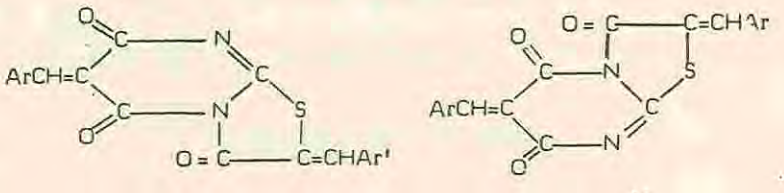
The IR spectrum of **3a** shows three absorption bands at 1665, 1700 and at 1730 cm^{-1} (CO). The NMR spectrum showed the methylene group (s, 2H) at δ 3.2, the =CH group (s, 1H) at 5.6 and the aromatic protons as a multiplet in the δ 7.4-7.9 ppm region.

The methylene group of compounds **3** was found to condense with aromatic aldehydes to give 2,6-diarylmethylenethiazolo[3,2-a]pyrimidine-3,5,7-triones **4** or its isomer **4'**.



1,2,3 a, Ar = C_6H_5
b, Ar = $C_6H_4.OCH_3$-p
c, Ar = $C_6H_4NO_2$-m
d, Ar = $C_6H_4NO_2$-p

i = acetic acid; ii = anhyd. sodium acetate;
iii = chloroacetic acid; iv = acetic anhydride

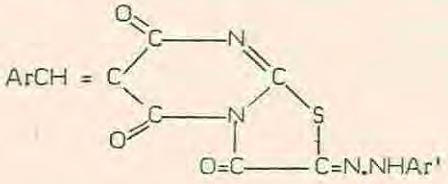


4 a, Ar = C_6H_5; Ar' = C_6H_5
b, Ar = C_6H_5; Ar' = $C_6H_4.OCH_3$-p
c, Ar = C_6H_5; Ar' = $C_6H_4.NO_2$-m
d, Ar = C_6H_5; Ar' = $C_6H_4.NO_2$-p
e, Ar = $C_6H_4.NO_2$-m; Ar' = C_6H_5
f, Ar = $C_6H_4.NO_2$-m; Ar' = $C_6H_4.NO_2$-p
g, Ar = $C_6H_4.NO_2$-p; Ar' = C_6H_5

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 =CH protons as (s, 1H) at δ 6.1 ppm, and the aromatic protons as a multiplet in the δ 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.**



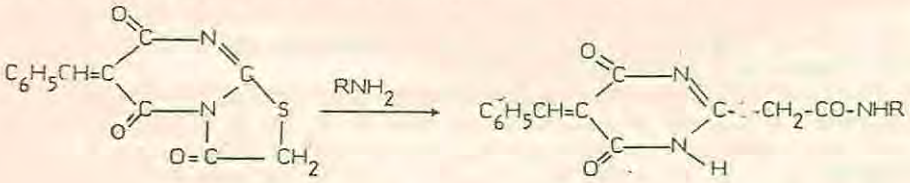
5

5 a, Ar = C_6H_5; Ar' = C_6H_5
b, Ar = C_6H_5; Ar' = $C_6H_4.CH_3$-m
c, Ar = C_6H_5; Ar' = $C_6H_4.CH_3$-p
d, Ar = $C_6H_4.OCH_3$-p; Ar' = C_6H_5

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.**



3a 6

6 a, R = NH_2
b, R = $NH.C_6H_5$
c, R = C_6H_5
d, R = $C_6H_4.OCH_3$-p
e, R = $C_6H_4.CH_3$-m
f, R = $C_6H_4.CH_3$-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-d_6) 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 exscess 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**.

Compound	Yield (%)	Solvent	m.p. (°C)	Formula	Analysis							
					Carbon		Hydrogen		Nitrogen		Sulphur	
					Calcd.	Found	Calcd.	Found	Clacd.	Found	Calcd.	Found
2a	62	A	d	$C_{13}H_{10}N_2O_4S$	53.78	53.9	3.47	3.2	9.65	9.5	11.04	11.2
2b	68	B	d	$C_{14}H_{12}N_2O_5S$	52.49	52.2	3.78	3.5	—	—	10.00	10.1
2c	55	A	d	$C_{13}H_9N_3O_6S$	—	—	—	—	9.84	9.6	9.86	10.0
2d	60	A	d	$C_{13}H_9N_3O_6S$	—	—	—	—	9.84	9.7	9.86	9.7
3a	65	A	265	$C_{13}H_8N_2O_3S$	57.35	57.1	2.96	3.1	10.29	10.0	11.77	11.9
3b	70	B	257	$C_{14}H_{10}N_2O_4S$	55.62	55.8	3.33	3.2	9.26	9.4	10.61	10.5
3c	61	C	294	$C_{13}H_7N_3O_5S$	—	—	—	—	—	—	10.10	10.2
3d	67	C	288	$C_{13}H_7N_3O_5S$	49.21	49.5	3.22	3.1	13.24	13.4	10.10	10.0

A = acetic acid
B = ethyl alcohol
C = nitrobenzene
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**.

Compound	Yield (%)	Solvent	m.p. (°C)	Formula	Analysis							
					Carbon		Hydrogen		Nitrogen		Sulphr	
					Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
4a	69	A	272	$C_{20}H_{12}N_2O_3S$	66.65	66.4	3.36	3.4	7.77	7.5	8.89	8.0
4b	72	B	265	$C_{20}H_{13}N_2O_4S$	63.65	63.7	3.47	3.6	7.42	7.2	8.49	8.7
4c	66	C	>300	$C_{20}H_{11}N_3O_5S$	59.26	59.3	2.73	2.4	10.36	10.5	7.97	7.7
4d	61	A	>300	$C_{20}H_{11}N_3O_5S$	—	—	—	—	10.36	10.1	—	—
4e	66	D	>300	$C_{20}H_{11}N_3O_5S$	59.26	59.0	2.73	2.5	10.36	10.2	7.91	7.7
4f	57	D	>300	$C_{20}H_{10}N_4O_7S$	53.33	53.1	2.24	1.9	—	—	—	—
4g	64	A	>300	$C_{20}H_{11}N_3O_5S$	59.26	59.1	2.73	2.4	10.36	10.3	7.91	7.7

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

(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.

(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-arylhydrazines **5.** 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-arylhydrazones 5.

Compound	Yield (%)	Solvent	m.p. (°C)	Formula	Analysis							
					Carbon		Hydrogen		Nitrogen		Sulphur	
					Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
5a	55	A	280	$C_{19}H_{12}N_4O_3S$	60.63	60.4	3.12	2.9	14.88	15.1	8.52	8.3
5b	61	A	271	$C_{20}H_{14}N_4O_3S$	61.53	61.3	3.62	3.8	14.35	14.1	8.21	8.1
5c	63	A	267	$C_{20}H_{14}N_4O_3S$	61.53	61.7	3.62	3.4	—	—	8.21	8.0
5d	56	B	273	$C_{20}H_{14}N_4O_3S$	—	—	—	—	13.78	13.6	7.89	8.1

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.

Compound	Yield (%)	Solvent	m.p. (°C)	Formula	Analysis							
					Carbon		Hydrogen		Nitrogen		Sulphur	
					Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
6a	48	A	242	$C_{13}H_{12}N_4O_3S$	51.31	51.1	3.97	4.1	18.41	18.2	—	—
6b	60	A	251	$C_{19}H_{16}N_4O_3S$	59.98	60.2	4.24	4.4	14.73	14.9	8.43	8.2
6c	63	B	273	$C_{19}H_{15}N_3O_3S$	62.45	62.2	4.14	3.9	11.50	11.7	8.77	8.9
6d	52	A	264	$C_{20}H_{17}N_3O_4S$	60.75	60.9	4.33	4.5	—	—	—	—
6e	55	C	255	$C_{20}H_{17}N_3O_3S$	—	—	—	—	11.07	10.8	8.45	8.3
6f	68	C	247	$C_{20}H_{17}N_3O_3S$	63.31	63.1	4.51	4.3	11.07	11.1	8.45	8.6

A = ethyl alcohol
B = acetic acid
C = dioxane

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