STRUCTURE AND REACTIONS OF 6-OXO-1,2,4-TRIAZINES

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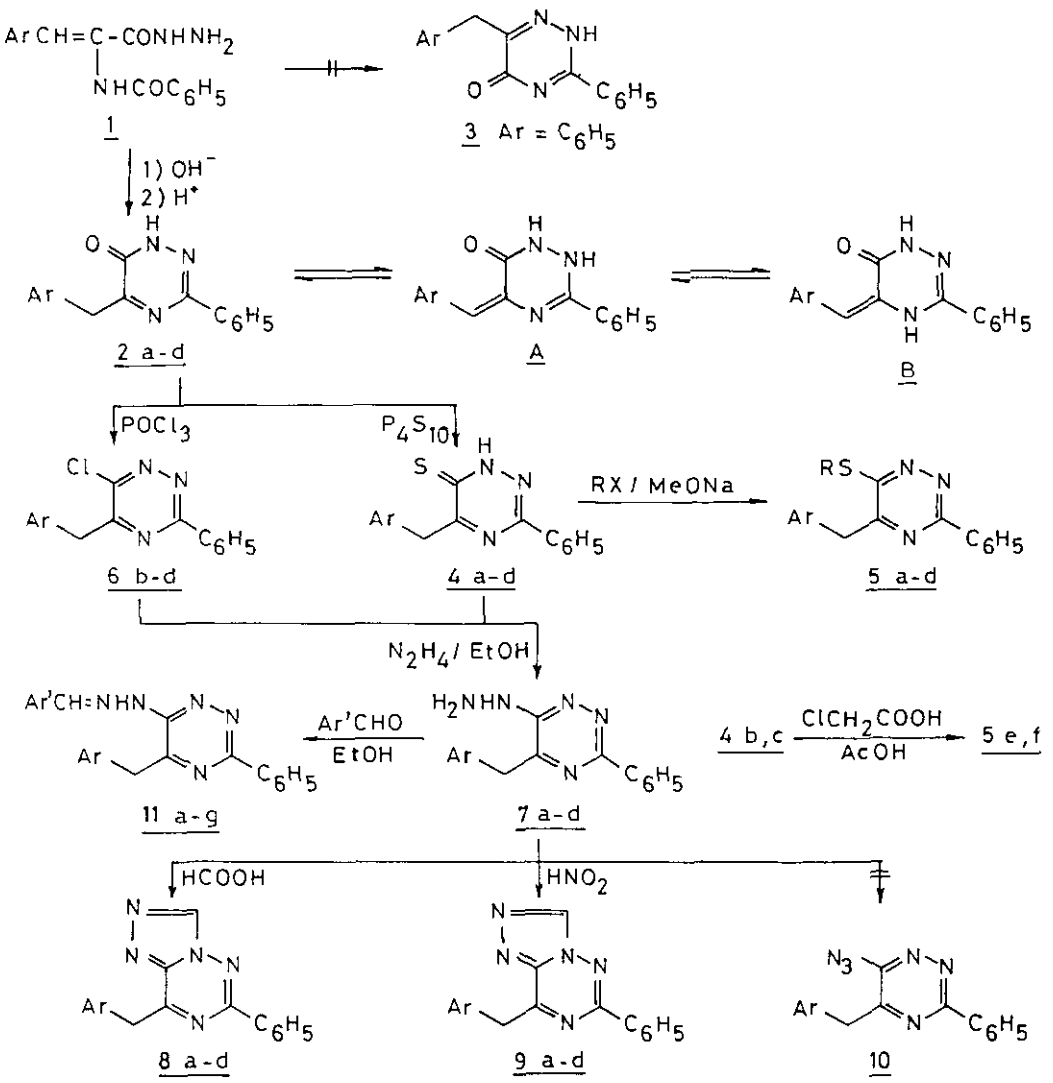
Abstract - The structure of 6-oxo-1,2,4-triazine derivatives obtained by cyclization of α-acylaminoacryloylhydrazides is now confirmed spectroscopically and through their chemical transformation to the corresponding 6-thioxo and 6-chloro derivatives and reactions.

Few methods have been reported for the synthesis of 6-oxo-1,2,4-triazines.[1-5] In one of these methods a simple approach was described depending on the cyclization of α-acylaminoacryloylhydrazides **1** under basic conditions.[1,2] However, the proposed structure of the obtained 6-oxo-1,2,4-triazine derivatives **2** was questionable and the isomeric 5-oxo-1,2,4-triazine derivatives **3** were claimed as possible rearrangement products.[6] This conflict about the structure of compounds **2**, which are, now, needed for further synthetic studies prompted us to reinvestigate and establish their structure.

Independent synthesis of compound **3** as a representative example is, now, readily achieved by cyclocondensation of phenylpyruvic acid[7] with benzamidrazone[8,9] by heating under reflux in ethanol. The product obtained unambiguously by this method is found to possess physical characteristics which are completely different from those described by Nalepa et al.[1,2] for compound **2a** and its derivatives. Thus, whereas compound **2a** is yellow, compound **3** is colourless and the two compounds have quite different melting points. Furthermore, whereas compound **2a** exists in the two tautomeric forms A and B, compound **3** exists exclusively in one form as shown from its ^{1}H-nmr spectrum. Thus, the ^{1}H-nmr spectrum (DMSO-d_6) of **3** shows signals at 3.90 (s, 2H, CH_2), 7.25-8.00 (m, 10H, aromatic H's) and 14.00 (br, 1H, NH) ppm. Compound **2a** was reported to have both methylene and methine protons at 4.12 and 6.28 ppm for both tautomers A and B.[2] In addition, the ir spectrum (KBr) of compound **2a** showed a carbonyl band at 1660 cm^{-1} while that of compound **3** showed a broad carbonyl band at 1640-1580 cm^{-1}.

The structures of the 6-oxo-1,2,4-triazines is further investigated by studying some of their chemical transforamtions. Thus, thiation of compounds **2a-d** with phosphorus pentasulfide in refluxing pyridine or xylene gave the corresponding 6-thioxo-1,2,4-triazines **4a-d**. Alkylation of the latter with the appropriate alkylating agent in the presence of equivalent molar of sodium methoxide at ambient temperature overnight afforded exclusively 6-alkylthio-1,2,4-triazines **5a-d**. The ^{1}H-nmr spectrum ($CDCl_3$) of compound **5b** as a typical example shows signals at δ 1.45 (t, J = 7 Hz, 3H, CH_3CH_2), 3.30 (q, J = 7 Hz,



	Ar
2a, 4a, , 7a, 8a, 9a	C_6H_5
2b, 4b, 6b, 7b, 8b, 9b	$C_6H_4OCH_3$-o
2c, 4c, 6c, 7c, 8c, 9c	$C_6H_4OCH_3$-p
2d, 4d, 6d, 7d, 8d, 9d	C_6H_4Cl-p

	R	Ar
5 a	CH_3	C_6H_5
b	C_2H_5	$C_6H_4OCH_3$-p
c	$CH_2C_6H_5$	$C_6H_4OCH_3$-p
d	$CH_2C_6H_5$	$C_6H_4OCH_3$-o
e	CH_2COOH	$C_6H_4OCH_3$-o
f	CH_2COOH	$C_6H_4OCH_3$-p

	Ar	Ar'
11 a	$C_6H_4OCH_3$-p	C_6H_4Cl-p
b	$C_6H_4OCH_3$-p	C_6H_5
c	$C_6H_4OCH_3$-o	$C_6H_3OCH_3$-p
d	$C_6H_4OCH_3$-o	C_6H_4Cl-p
e	$C_6H_4OCH_3$-o	C_6H_5
f	C_6H_5	$C_6H_4OCH_3$-p
g	C_6H_4Cl-p	$C_6H_4OCH_3$-p

2H, $CH_3\underline{CH}_2$), 3.75 (s, 3H, OCH_3), 4.10 (s, 2H, CH_2) and 6.80-8.50 (m, 9H, aromatic H's) ppm. On the other hand, the 6-carboxymethylthio derivatives **5e,f** were obtained by heating under reflux an equimolar mixture of compounds **4b,c** and chloroacetic acid in 70 % acetic acid.

Heating each of compounds **4a-d** in ethanol with a slight excess of hydrazine hydrate (80 %) gave the corresponding 6-hydrazino-1,2,4-triazines **7a-d**. Compounds **7b-d** were alternatively synthesized by the action of hydrazine hydrate on the appropriate 6-chloro-1,2,4-triazines **6b-d**. Compounds **6b-d** were obtained via the action of excess phosphorus oxychloride on **2b-d**.

The bicyclic triazolo[3,4-*f*][1,2,4]triazines **8a-d** were synthesized by heating each of compounds **7a-d** with formic acid. The tetrazolo[5,1-*f*][1,2,4]triazines **9a-d** were obtained by stirring a suspension of each of **7a-d** in hydrochloric acid while adding a cold solution of sodium nitrite. The tautomeric 6-azido-1,2,4-triazines **10** were excluded as evidenced by the absence of the characteristic azide band at 2300-2000 cm^{-1} in the ir spectra of **9a-d**.

Finally, condensation of compounds **7a-d** with aromatic aldehydes afforded the corresponding hydrazones **11a-g**.

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra (KBr) were recorded on a Unicam SP 1200 Spectrophotometer. ^1H Nmr spectra in deuterated chloroform and DMSO were recorded on a Varian EM 390 90 MHz Spectrometer using tetramethylsilane as an internal reference. Compounds prepared by different procedures were confirmed by mixed melting points and infrared spectra. Elemental analyses were carried out at the Microanalytical Centre at the University of Cairo, Giza, Egypt.

6-Benzyl-3-phenyl-1,2,4-triazin-5(2H)-one 3.

Phenylpyruvic acid (1.64 g, 10 mmol) was added to an ethanolic solution of benzamidrazone[8,9] (1.35 g, 10 mmol in 15 ml of ethanol) and the reaction mixture was heated under reflux for 2 h. After cooling, the product was collected and crystallized from dimethylformamide to give colorless crystals of **3**, mp 256°C, yield 1.97 g, 75 %. Anal. Calcd for $C_{16}H_{13}N_3O$: C, 72.98; H, 4.97; N, 15.96. Found: C, 73.10; H, 4.80; N, 15.90. ^1H-NMR δ (DMSO-d_6): 3.90 (s, 2H, CH_2), 7.25-8.00 (m, 10H), 14.00 (br s, 1H, NH) ppm; ν (KBr) 1640-1580 cm^{-1} (C=O).

5-Benzyl(or substituted benzyl)-3-phenyl-1,2,4-triazine-6(1H)-thiones 4a-d. General Method.

A mixture of each of compounds **2a-d** (5 mmol) and phosphorus pentasulphide (5 mmol) was heated under reflux in pyridine (15 ml) for 6 h or in xylene (20 ml) for 2 h. After cooling, the mixture was diluted with water and the precipitate was collected and recrystallized from the proper solvent to give the corresponding **4** (Table). The precipitate separated after cooling the xylene mixture was separated, washed with benzene and recrystallized from the proper solvent to give the corresponding 1,2,4-triazine-6-thiones **4** (Table).

Compound **4a** had δ ($CDCl_3$) 4.45 (s, 2H, CH_2), 7.15-7.45, 8.00-8.15 (m, 10H), 12.35 (br s, 1H); ν (KBr) 3150, 3040, 2900 (br), 1550, 1370, 1280 cm^{-1}.

6-Alkylmercapto-5-benzyl(or substituted benzyl)-3-phenyl-1,2,4-triazines 5a-d. General Method

To a solution of each of compounds **4a-d** (10mmol) in sodium methoxide (prepared from 0.23 g, 10 mmol of sodium and 50 ml of absolute methanol) was added the appropriate alkyl halide or benzyl chloride (10 mmol) while stirring at ambient temperature for 1 h. The mixture was then left at room temperature overnight. The precipitate was collected and recrystallized from ethanol to yield the corresponding 6-alkylthio-1,2,4-triazine derivatives **5a-d** (Table).

Compound **5b** had δ ($CDCl_3$) 1.45 (t, J = 7Hz, 3H, $C\underline{H}_3CH_2$), 3.30 (q, J = 7Hz, 2H, $CH_3C\underline{H}_2$), 3.75 (s, 3H, OCH_3), 4.10 (s, 2H, CH_2), 6.80-8.50 (m, 9H); ν (KBr) 2960, 2940, 1610, 1590, 1515, 1495, 1380, 1250, 1040 cm^{-1}.

6-Carboxymethylthio-5-substituted benzyl-3-phenyl-1,2,4-triazines 5e,f.

Chloroacetic acid (0.95 g, 10 mmol) was added to each of compounds **4b,c** (10 mmol) in acetic acid (50 ml, 70 %) and the reaction mixture was heated under reflux for 4 h. After cooling the product was collected and recrystallized from ethanol to give the corresponding 6-carboxymethylthio-1,2,4-triazines **5e,f** (Table).

Compound **5f** had δ (DMSO) 3.65 (s, 3H, OCH_3), 4.10 and 4.15 (each s, SCH_2COOH and $ArC\underline{H}_2$), 6.80-8.20 (m, 9H), 12.20 (br s, 1H, COOH).

Compound **5e** had ν(KBr) 2920, 1710, 1495, 1380, 1250, 750, 700 cm^{-1}.

5-Substituted benzyl-3-phenyl-6-chloro-1,2,4-triazines 6b-d. General Method

Phosphorus oxychloride (3 ml, 30 mmol) was added to each of compounds **2b-d** (3.4 mmol) and the reaction mixture was heated on a boiling water bath for 0.5 h. The excess phosphorus oxychloride was removed under reduced pressure and the residue was poured over crushed ice. The precipitate was collected, washed with water and recrystallized from absolute ethanol to give the corresponding 6-chloro-1,2,4-triazines **6b-d** (Table).

Compound **6c** had δ ($CDCl_3$) 3.70 (s, 3H, OCH_3), 4.10 (s, 2H, $ArC\underline{H}_2$), 6.70-8.40 (m, 9H); ν (KBr) 3000, 2960, 2940, 1610, 1590, 1510, 1490, 1380, 1250, 1040 cm^{-1}.

5-Benzyl (or substituted benzyl)-3-phenyl-6-hydrazino-1,2,4-triazines 7a-d.

(i) From compounds **4a-d.** A mixture of each of compounds **4a-d** (1.8 mmol) and hydrazine hydrate (1 ml, 50 mmol) in ethanol (5 ml) was heated under reflux for 4 h. After cooling the precipitate was collected and recrystallized from ethanol to give **7a-d**, respectively (Table).

(ii) From compounds **6b-d.** The same previous method was followed using compounds **6b-d** instead of the corresponding **4** to give the corresponding **7** (Table).

Compound **7a** had δ ($CDCl_3$) 4.10 (s, 2H, CH_2), 7.20-7.50, 8.30-8.40 (m, 10H), 5.00-5.80 (br, 3H, $N\underline{H}N\underline{H}_2$).

Compound **7b** had ν (KBr) 3340, 3280, 1630 cm^{-1}.

8-Benzyl(or substituted benzyl)-6-phenyltriazolo-[3,4-f][1,2,4]triazines 8a-d. General Method

A mixture of each of compounds **7a-d** (1 mmol) and formic acid (2 ml, 98-100 %) was heated under reflux for 3 h. After cooling and dilution with water, the precipitate was collected and recrystallized from ethanol to give the corresponding triazolotriazines **8** (Table).

Compound **8a** had δ ($CDCl_3$) 4.10 (s, 2H, CH_2), 7.20-7.60, 8.10-8.30 (m, 10H), 9.00 (s, 1H, triazole CH); ν (KBr) 3120, 1590, 1560, 1520, 1495, 1470, 1450, 1270, 960 cm^{-1}

8-Benzyl(or substituted benzyl)-6-phenyltetrazolo[5,1-f][1,2,4]triazines 9a-d. General Method.

A cold solution of sodium nitrite (0.5 g, 7.2 mmol in 5 ml water) was added dropwise to a cold (0-5°C) suspension of each of compounds **7a-d** (7.2 mmol) in concentrated hydrochloric acid (2 ml) while stirring. Stirring was continued for further 1 h and the mixture was left at room temperature overnight. The precipitate was collected, washed with water and recrystallized from ethanol to give the corresponding tetrazolotriazines **9** (Table).

Compound **9a** had ν (KBr) 1600, 1550, 1500, 1460, 1430, 1320,1300, 1280, 1250, 1170, 1100, 1060, 1040 1000, 940, 840, 700, 620 cm^{-1}.

5-Benzyl(or substituted benzyl)-3-phenyltriazin-6-ylhydrazones 11a-g. General Method.

A mixture of each of compounds **7a-d** (1 mmol) and the appropriate aromatic aldehyde (1 mmol) in ethanol (10 ml) was heated under reflux for 0.5 h. After cooling, the precipitate was collected and recrystallized from the proper solvent to give the corresponding hydrazones **11** (Table).

Compound **11f** had δ ($CDCl_3$) 3.80 (s, 3H, OCH_3), 4.20 (s, 2H, CH_2), 6.80-8.00 (m, 14H), 8.30 (s, 1H, N=CH).

Compound **11e** had $\bar{\nu}$ (KBr) 3200 (br), 1610, 1580, 1510, 1490, 1410, 1245, 1140, 750, 690 cm^{-1}.

Table

Compd*	Solvent of cryst.	mp °C	Yield** %	Mol. formula	Analysis % Calcd / Found C	H	N	S	Cl
4a	AcOH	190	94 (i)	$C_{16}H_{13}N_3S$	68.79	4.65	15.40	11.47	-
			96 (ii)		68.60	4.70	15.60	11.70	-
4b	EtOH	250	95 (i)	$C_{17}H_{15}N_3SO$	66.00	4.88	13.58	10.36	-
			95 (ii)		66.20	5.00	13.70	10.20	-
4c	DMF	205	96 (i)	$C_{17}H_{15}N_3SO$	66.00	4.88	13.58	10.36	-
			94 (ii)		65.80	4.70	13.40	10.30	-
4d	DMF	248	71 (ii)	$C_{16}H_{12}N_3SCl$	61.24	3.85	13.39	10.21	-
					61.40	3.90	13.30	10.00	-
5a	EtOH	87	80	$C_{17}H_{13}N_3S$	70.08	4.49	14.42	11.00	-
					69.90	4.20	14.50	10.90	-

Table Contd.

Compd*	Solvent of Cryst	mp °C	Yield** %	Mol. formula	Analysis % Calcd / Found C	H	N	S	Cl
5b	EtOH	107	68	$C_{19}H_{19}N_3SO$	67.63	5.67	12.45	9.50	-
					67.80	5.50	12.40	9.30	-
5c	EtOH	90	39	$C_{24}H_{21}N_3SO$	72.15	5.29	10.51	8.02	-
					71.90	5.10	10.70	8.30	-
5d	EtOH	125	53	$C_{24}H_{21}N_3SO$	72.15	5.29	10.51	8.02	-
					72.30	5.30	10.40	8.00	-
5e	EtOH	132	95	$C_{19}H_{17}N_3SO_3$	62.11	4.65	11.43	8.72	-
					61.90	4.50	11.30	8.90	-
5f	EtOH	130	95	$C_{19}H_{17}N_3SO_3$	62.11	4.65	11.43	8.72	-
					62.00	4.70	11.50	8.70	-
6b	EtOH	90	74	$C_{17}H_{14}N_3OCl$	65.49	4.52	13.47	-	11.37
					65.60	4.50	13.70	-	11.40
6c	EtOH	128	98	$C_{17}H_{14}N_3ClO$	65.49	4.52	13.47	-	11.37
					65.30	4.70	13.40	-	11.20
6d	EtOH	122	98	$C_{16}H_{11}N_3Cl_2$	60.87	3.50	13.28	-	22.42
					61.00	3.60	13.00	-	22.10
7a	EtOH	142-144	71 (iii)	$C_{16}H_{15}N_5$	69.30	5.44	25.25	-	-
					69.30	5.50	24.90	-	-
7b	EtOH	130	81 (iii)	$C_{17}H_{17}N_5O$	66.43	5.57	22.78	-	-
			83 (iv)		66.20	5.60	22.60	-	-
7c	EtOH	156	92 (iii)	$C_{17}H_{17}N_5O$	66.43	5.57	22.78	-	-
			90 (iv)		66.60	5.50	23.00	-	-
7d	EtOH	194	97 (iii)	$C_{16}H_{14}N_5Cl$	61.64	4.52	22.46	-	11.37
			81 (iv)		61.50	4.20	22.30	-	11.30
8a	EtOH	171	87	$C_{17}H_{13}N_5$	71.06	4.55	24.37	-	-
					71.20	4.30	24.20	-	-
8b	EtOH	107	66	$C_{18}H_{15}N_5O$	68.13	4.75	22.06	-	-
					67.90	4.50	21.90	-	-
8c	EtOH	203	50	$C_{18}H_{15}N_5O$	68.13	4.75	22.06	-	-
					68.30	4.90	22.04	-	-
8d	EtOH	182	75	$C_{17}H_{12}N_5Cl$	63.45	3.75	21.76	-	11.01
					63.20	4.00	21.40	-	11.40
9a	EtOH	204 (decomp.)	96	$C_{16}H_{12}N_6$	66.65	4.19	29.15	-	-
					66.40	4.00	28.80	-	-
9b	EtOH	138 (decomp.)	80	$C_{17}H_{14}N_6O$	64.14	4.42	26.40	-	-
					64.00	4.40	26.60	-	-
9c	EtOH	145 (decomp.)	84	$C_{17}H_{14}N_6O$	64.14	4.42	26.40	-	-
					64.40	4.70	26.10	-	-

Table Contd.

Compd*	Solvent of cryst	mp °C	Yield** %	Mol. formula	Analysis % Calcd / Found C	H	N	S	Cl
9d	EtOH	188 (decomp.)	90	$C_{16}H_{11}N_5Cl$	59.54 59.20	3.43 3.10	26.03 26.00	- -	10.98 11.20
11a	DMF	212	72	$C_{24}H_{20}N_5OCl$	67.05 66.90	4.68 4.80	16.29 16.30	- -	8.24 8.30
11b	BuOH	208	95	$C_{24}H_{21}N_5O$	72.89 73.00	5.34 5.30	17.71 17.40	- -	- -
11c	EtOH	176	79	$C_{25}H_{23}N_5O_2$	70.57 70.50	5.44 5.20	16.46 16.30	- -	- -
11d	BuOH	222-224	73	$C_{24}H_{20}N_5OCl$	67.05 66.90	4.68 4.60	16.29 16.60	- -	8.24 8.46
11e	EtOH	200-205	80	$C_{24}H_{21}N_5O$	72.89 72.60	5.34 5.70	17.71 17.50	- -	- -
11f	DMF	219	83	$C_{24}H_{21}N_5O$	72.89 73.20	5.34 5.10	17.71 17.40	- -	- -
11g	AcOH	228	92	$C_{24}H_{28}N_5OCl$	65.82 66.00	6.43 6.40	15.90 16.20	- -	8.09 8.00

* The identity of compounds synthesized by different procedures was confirmed by mp, mixed mp and ir (KBr) spectra.

** (i) and (ii) are yields corresponding to compounds synthesized by the action of P_4S_{10} on compounds **4a-d** in pyridine and xylene respectively.
(iii) and (iv) are yields obtained by the action of hydrazine hydrate on compounds **4a-d** and **6b-d** respectively.

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