Reaction of 4-Aryl-1,2,4-triazines with Hydrazine

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The action of hydrazine on 3,5-dioxo-4-aryl-2,3,4,5-tetrahydro-1,2,4-triazines gave 4-amino-3,5-dixo-2,3,4,5-tetrahydro-1,2,4-triazines. The intermediates of this reaction were isolated and shown to be α-ketoacidhydrazide 4-arylsemicarbazones and not the α-ketoanilidecarbohydrazones. The realtive rates of cyclization of the latter isomeric derivatives provide a support for a proposed intermediates which were not isolated in the reaction of 3-mercapto and 3-methylmercapto-4-aryl-5-oxo-4,5-dihydro-1,2,4-triazines with hydrazine.

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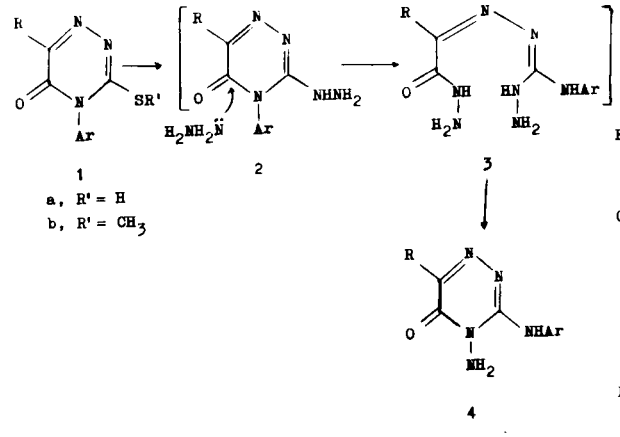
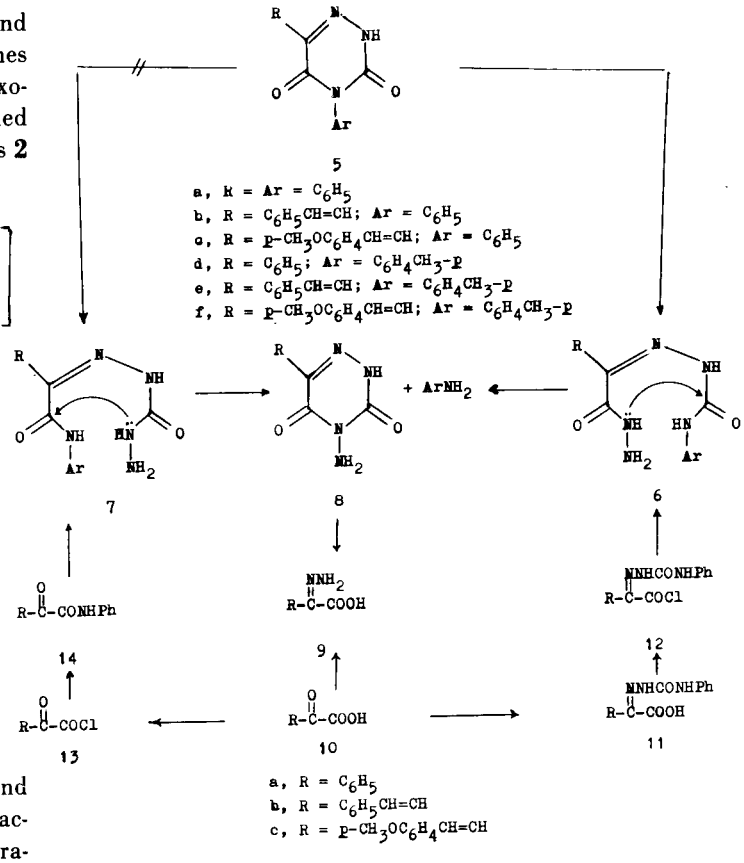
The action of hydrazine hydrate on 3-mercapto and 3-methylmercapto-4-aryl-5-oxo-4,5-dihydro-1,2,4-triazines (**1a,b**) was shown to give the 3-arylamino-4-amino-5-oxo--4,5-dihydro-1,2,4-triazines (**4**). The reaction was assumed to proceed as illustrated in Scheme 1 *via* intermediates **2** and **3** (1).



Scheme I

In an attempt to through more light upon the scope and mechanism of the above reaction, we now studied the action of hydrazine hydrate on 3,5-dioxo-4-aryl-2,3,4,5-tetrahydro-1,2,4-triazines (**5a-f**). In this case the hydrazinotriazines **2** could not be an intermediate (1) and thus the study will hopefully deal with the ring opening only.

Heating each of compounds **5a-f** in ethanolic solution with hydrazine hydrate under reflux for 3.5 hours afforded the corresponding 4-amino-3,5-dioxo-2,3,4,5-tetrahydro--1,2,4-triazines (**8a-c**) (2) together with aniline or *p*-toluidine (3). When compounds **5a,b** were reacted with hydrazine for one hour only the intermediate open ring compounds were isolated, which were assigned either structures **6a,b** or **7a,b** on the basis of the analytical data.



Scheme 2

Attempts to partially hydrolyse these intermediates led to either cyclization to the corresponding 4-aminotriazines (**8a,b**) (with 10% hydrochloric acid) or the destruction of both amide moieties yielding the corresponding ketoacid-hydrazones **9a,b** (with 10% sodium hydroxide). Compounds **9a,b** were identified by comparison with authentic samples prepared from the appropriate ketoacid and hydrazine (Scheme 2).

Whether the intermediates have structures **6** or **7** was established by independent synthesis of each of com-

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Table I

Products (a)	Mp °C	Yield %	Formula (Molecular Weight)	Analysis % Calcd./Found C	H	N
8a	196	93	$C_9H_8N_4O_2$	52.94	3.95	27.44
			(204.18)	53.20	4.10	27.80
8b	282-283	81	$C_{11}H_{10}N_4O_2$	57.38	4.37	24.33
			(230.22)	57.40	4.50	24.50
8c	248-249	78	$C_{12}H_{12}N_4O_3$	55.38	4.64	21.53
			(260.25)	55.60	4.50	21.20

(a) Compound **8a** was crystallized from ethanol, and **8b,c** from DMF; **8a**, ir (potassium bromide): 3300, 3200, 2900, 1990, 1710, 1650 and 1565 cm^{-1}; **8b**, ir (potassium bromide): 3300, 3200, 3020, 2910, 1990, 1710, 1640 and 1550 cm^{-1}; **8c**, ir (potassium bromide): 3360, 3270, 1725, 1660, 1640, 1610, 1565 and 1515 cm^{-1}.

Table 2

Products (a)	Mp °C	Yield %	Formula (Molecular Weight)	Analysis % Calcd./Found C	H	N	S
15a	277	53	$C_{18}H_{15}N_3SO$	67.26	4.70	13.07	9.97
			(321.38)	67.50	4.40	12.90	10.00
15b	263	56	$C_{18}H_{15}N_3SO_2$	64.07	4.48	12.45	9.50
			(337.38)	64.40	5.00	12.60	9.60
15c	281	56	$C_{19}H_{17}N_3SO_2$	64.93	4.87	11.95	9.12
			(351.41)	65.30	5.10	11.90	9.50
15d	170	59	$C_{19}H_{17}N_3SO$	68.03	5.11	12.52	9.56
			(335.41)	68.10	5.50	12.90	9.60
15e	203	73	$C_{19}H_{17}N_3SO_2$	64.93	4.87	11.95	9.12
			(351.41)	65.30	5.40	12.30	9.00
15f	184	65	$C_{20}H_{19}N_3SO_2$	65.73	5.24	11.50	8.74
			(365.43)	66.00	4.90	11.50	8.90
5c	228	91	$C_{18}H_{15}N_3O_3$	67.27	4.70	13.07	
			(321.32)	67.70	4.90	13.50	
5e	271	89	$C_{18}H_{15}N_3O_2$	70.80	4.95	13.76	
			(305.32)	71.20	4.90	14.00	
5f	229	89	$C_{19}H_{17}N_3O_3$	68.04	5.11	12.53	
			(335.35)	68.10	4.70	12.70	

(a) **15b**, ir (potassium bromide): 3180, 2970, 1710, 1605, 1575 and 1520 cm^{-1}; **15c**, ir (potassium bromide): 3200, 3120, 3030, 2980, 1715, 1610, 1575 and 1520 cm^{-1}; **15e**, ir (potassium bromide): 3000, 2950, 1710, 1640, 1610, 1555 and 1515 cm^{-1}; **15f**, ir (potassium bromide): 2950, 1700, 1630, 1610, 1580, 1550 and 1520 cm^{-1}; **5c**, ir (potassium bromide): 3120, 2960, 1725, 1695, 1610, 1580 and 1520 cm^{-1}; **5f**, ir (potassium bromide): 3130, 2920, 1725, 1675, 1635, 1610, 1580 and 1520 cm^{-1}.

pounds **6a,b** and **7a,b** by the reaction sequence illustrated in Scheme 2. Thus condensation of the ketoacids **10a,b** with 4-phenylsemicarbazide afforded the corresponding 4-phenylsemicarbazones **11a,b** which were converted to the acid chlorides **12a,b** by the action of thionyl chloride. Compounds **12a,b** reacted readily on cold with hydrazine hydrate to give the hydrazides **6a,b**, repectively. On the other hand synthesis of the isomeric compounds **7a,b** was accomplished by converting the ketoacids **10a,b** into the corresponding acid chlorides **13a,b** (4) (with thionyl chloride), which were reacted with aniline to give the ketoanilides **14a,b**, respectively. Compounds **14a,b** were condensed with carbohydrazide to the desired compounds **7a,b**, respectively.

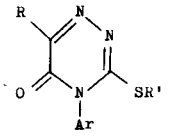
Only the authentic compounds **6a,b** and not **7a,b** were found identical in every respect with the intermediates obtained from the reaction of **5a,b** with hydrazine hydrate (Scheme 2).

Both series of the isomeric compounds **6a,b** and **7a,b** were found to undergo cyclization into the same 4-amino--3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazines **8a,b** together with aniline, when their alcoholic solution were heated under reflux. However, whereas compounds **7a,b** cyclized almost completely after 25 minutes, compounds **6a,b** needed more than two hours for complete cyclization [the reaction was monitored by tlc using solvent system ethanol/formic acid (99:1) on Selufol tlc plates uv 254]. The formation of the same 4-aminotriazines **8a,b** from both **6a,b** and **7a,b** could be explained by the attack of the more nucleophilic amide nitrogen (of hydrazide) on the other carboxyanilide group leading to the extrusion of aniline. It is worthwhile to mention that to the best of our knowledge,

the mode of cyclization of compounds **6** is unprecedented and constitutes a new route for the synthesis of this ring system [cyclization like that of **7** are the most common in which the semicarbazone N-4 is the one that is involved in the cyclization (5)] (6).

The previous findings show that the action of hydrazine hydrate on **5a-f** proceed by nucleophilic attack of hydrazine on C-5 leading to compounds **6a-f** which then cyclize to **8a-c**. This also supports the mechanism previously proposed for the action of hydrazine hydrate on **1a,b** and explains why the intermediate **3** could not be isolated as they are like the hydrazides **7a,b** rapidly undergo cyclisation.

The starting 3,5-dioxo-4-aryl-2,3,4,5-tetrahydro-1,2,4--triazines (**5c,e,f**) were obtained from the appropriate ketoacid **10** first by condensation with 4-phenyl(or *p*-tolyl)-thiosemicarbazide into the 3-mercapto-4-aryl-5-oxo-4,5-dihydro-1,2,4-triazines (**15a-c**) which were then methylated into the corresponding 3-mehtylmercapto derivatives **15d-f** followed by hydrolysis of the latters with ethanolic hydrochloric aicd into **5c,e,f**, respectively.



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a, R = $C_6H_5CH=CH$; Ar = $C_6H_4CH_3$-p; R'= H
b, R = p-$CH_3OC_6H_4CH=CH$; Ar = C_6H_5; R'= H
c, R = p-$CH_3OC_6H_4CH=CH$; Ar = $C_6H_4CH_3$-p; R'= H
d, R = $C_6H_5CH=CH$; Ar = $C_6H_4CH_3$-p; R'= CH_3
e, R = p-$CH_3OC_6H_4CH=CH$; Ar = C_6H_5; R'= CH_3
f, R = p-$CH_3OC_6H_4CH=CH$; Ar = $C_6H_4CH_3$-p; R'= CH_3

Scheme 3

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with a Unicam Sp 1200 infrared spectrophotometer. Elemental analyses were carried out by the Microanalytical Center, Cairo University.

Action of Hydrazine Hydrate on 3,5-Dioxo-4-aryl-2,3,4,5-tetrahydro-1,2,4--triazines (**5a-f**).

To each of compounds **5a-f** (1.0 g) in ethanol (15 ml) was added hydrazine hydrate (1 ml, 80%). The reaction mixture was heated under reflux for 3.5 hours, and left to cool. The preciptate was collected and recrystallized from ethanol into **8a** (from **5a,d**), or from DMF into **8b** (from **5b,e**) and **8c** (from **5c,f**) (*cf.*, Table 1).

The filtrate from the above reactions was diazotized and coupled with β-naphthol to the corresponding azo-dye and also reacted with benzoyl chloride to yield the benzoyl derivatives of aniline or *p*-toluidine.

α-Ketoacidhydrazide-4-arylsemicarbazones (**6a,b**) by the Action of Hydrazine Hydrate on **5a,b**.

To each of compounds **5a,b** (0.001 mole) in ethanol (15 ml) was added hydrazine hydrate (1 ml, 80%). The reaction mixture was heated under reflux for 1 hour, cooled and the precipitate was collected and recrystallized from ethanol into yellow crystals of **6a,b**, respectively.

Compound **6a**.

This compound had mp 161°, yield 70%; ir (potassium bromide): 3400, 2860, 1690, 1675, 1660 and 1550 cm^{-1}.

Anal. Calcd. for $C_{15}H_{15}N_5O_2$: C, 60.59; H, 5.08; N, 23.55. Found: C, 60.30; H, 4.80; N, 23.60.

Compound **6b**.

This compound had mp 196°, yield 76%; ir (potassium bromide): 3350, 3040, 3000, 1725, 1680, 1655, 1600, 1555 cm^{-1}.

Anal. Calcd. for $C_{17}H_{17}N_5O_2$: C, 63.14; H, 5.30; N, 21.66. Found: C, 63.20; H, 5.50, N, 22.00.

Action of Hydrochloric Acid on Compounds **6** and **7**.

Each of compounds **6a,b** and **7a,b** (0.001 mole) in 10% ethanolic hydrochloric acid solution (15 ml) was heated under reflux for 1 hour, and left to cool. The precipitate was collected and recrystallized into yellow needles of **8a** (from ethanol) and pale yellow crystals of **8b** (from DMF), respectively (mp and ir).

Action of Sodium Hydroxide on Compounds **6** and **7**.

Each of compounds **6a,b** and **7a,b** in aqueous sodium hydroxide (5 ml, 10%) was heated under reflux for 0.5 hour, left to cool and then acidified with hydrochloric acid (1*N*). The precipitate was collected and crystallized from ethanol into yellowish white crystals of **9a**, yield 70%, mp 119°, and **9b**, yield 64%, mp 99°, respectively. Compounds **9a,b** are identical in every respect with the same compounds prepared independently from each of the α-ketoacids **10a,b** and hydrazine hydrate.

α-Ketoacid-4-phenylsemicarbazones (**11a,b**).

Compounds **11a,b** were prepared by adding 4-phenylsemicarbazide (0.001 mole) to each of compounds **10a,b** (0.001 mole) in water (10 ml). The reaction mixture was heated for 5 minutes, then kept at room temperture for 24 hours. The precipitate was filtered and crystallized from dilute ethanol (50%) into **11a**, yield 71%, mp 180°, and **11b**, yield, 78%, mp 190° respectively.

α-Ketoacid Chloride 4-Phenylsemicarbazones (**12a,b**).

A mixture of each of compounds **11a,b** (0.001 mole) and thionyl chloride was heated under reflux over a steam bath for 3 minutes. After cooling petroleum ether (10 ml, 60-80) was added, the precipitate was collected and crystallized from benzene into yellow crystals of **12a**, mp 112°, yield 48% and **12b**, mp 208°, yield 70% respectively.

Action of Hydrazine Hydrate on **12a,b**.

To each of compounds **12a,b** (0.001 mole) was added with stirring and cooling hydrazine hydrate (0.001 mole, 99%). The reaction mixture was left for 5 minutes at room temperature, then diluted with water. The precipitate was collected and recrystallized from ethanol into yellow crystals of **6a,b** respectively (mixed mp and ir).

α-Ketoacid Chlorides (**13a,b**).

Compound **13a** was prepared after the procedure described by Acree (4).

Compound **13b** was prepared from benzylidene pyruvic acid **10b** (0.001 mole) in benezene (7 ml) by heating under reflux with thionyl chloride (0.001 mole) for 10 minutes. Upon cooling and dilution with petroleum ether the precipitate obtained was collected and recrystallized from benzene into yellow needles of **13b**, mp 55°, yield 73%.

α-Ketoanilides (**14a,b**).

Each of compounds **13a,b** (0.001 mole) was treated with aniline (0.002 mole) and the reaction mixture was heated over steam bath for 5 minutes, cooled and washed with ethanol. The solid obtained was then recrystallized from ethanol into yellow needles of **14a**, mp 140°, yield 58%, and **14b**, mp 166°, yield 76%, respectively.

Compound 14a.

Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.21. Found: C, 75.00; H, 4.80; N, 6.20.

Compound **14b**.

Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.30; H, 5.40; N, 5.80.

Action of Carbohydrazide on Compounds **14a,b**.

Each of compounds **14a,b** (0.001 mole) in ethanol (10 ml) was heated (1-2 minutes) with carbohydrazide (0.001 mole) in water (10 ml) and then left to cool at room temperature. The precipitate was collected and crystallized from ethanol into yellow crystals of **7a**, mp 186°, yield 60%, and **7b**, mp 256°, yield 58%, respectively.

Compound **7a**.

Anal. Calcd. for $C_{15}H_{15}N_5O_2$: C, 60.59; H, 5.08; N, 23.55. Found: C, 60.60; H, 5.30; N, 23.70.

Compound **7b**.

This compound showed ir (potassium bromide): 3350, 2980, 1720, 1705, 1660, 1610 and 1570 cm^{-1}.

Anal. Calcd. for $C_{17}H_{17}N_5O_2$: C, 63.14; H, 5.30; N, 21.66. Found: C, 63.40; H, 5.40; N, 21.20.

3-Thioxo-4-aryl-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazines (**15a-c**).

A solution of the appropriate arylidenepyruvic acid **10a-c** (0.01 mole) and 4-arylthiosemicarbazide (0.01 mole) in ethanol (200 ml, 80%) was heated under reflux for 8 hours. The precipitate was collected and crystallized from acetic acid as yellow needles of **15a-c** (Table 2).

3-Methylthio-4-aryl-5-oxo-4,5-dihydro-1,2,4-triazines (**15d-f**).

To a cold solution of each of **15a-c** (0.01 mole) in sodium methoxide (prepared from 0.23 g sodium in 25 ml of anhydrous methanol) was added methyl iodide (0.01 mole). The reaction mixture was shaken for 15 minutes and left overnight at room temperature. The precipitate was collected and recrystallized from butanol into crystals of **15d-f** (Table 2).

3,5-Dioxo-4-aryl-2,3,4,5-tetrahydro-1,2,4-triazines (**5c,e,f**).

A solution of each of compounds **15d-f** (0.01 mole) in ethanol (15 ml) and hydrochloric acid (3 ml, 10*N*) was heated under reflux for 1 hour and then cooled. The precipitate obtained was collected and crystallized from acetic acid as yellow crystals of **5c,e,f**, respectively (Table 2).

REFERENCES AND NOTES

(1) Y. A. Ibrahim, M. M. Eid and S. A. L. Abdel-Hady, *J. Heterocyclic Chem.*, **17**, 1733 (1980).

(2) Compounds **8a-c** have been independently synthesized from the appropriate α-ketoacid and carbohydrazide, Ph. D. thesis by M. A. Badawy, Cairo University (1980).

(3) Aniline and *p*-toluidine were identified as benzoyl derivatives and by diazotization and coupling with β-naphthol (*cf.*, Experimental).

(4) S. F. Acree, *Am. Chem. J.*, **50**, 393 (1913).

(5) H. Neunhoeffer and P. F. Wiley, "Chemistry of 1,2,3-Triazine and 1,2,4-Triazines, Tetrazines and Pentazines", John Wiley and Sons, Inc., New York, N. Y., 1978.

(6) The synthesis of differently substituted 1,2,4-triazines by this mode of cyclization is under further exploration in our laboratory.