Rearrangement of 3-Arylhydantoins into 3-Aminoglycocyamidines

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The action of hydrazine hydrate on 5-arylidene-3-aryl-2-methylmercaptohydantoins led to ring opening and rearrangement into 5-arylidene-3-amino-N^2-aryl-glycocyamidines (**9a-f**). The structure of the products **9a-f** was established and the mechanism of their formation was discussed.

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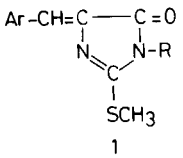
The action of hydrazine on several derivatives of 2-thiohydantoins (1-5) and their 2-alkylmercapto derivatives (5,6) has been reported. Thus 5-arylidene-2-methylmercaptohydantoins **1a,c** and the 3-methyl derivatives **1d** have been shown to give the 2-hydrazone derivatives **2a,c,d** respectively (5,6).



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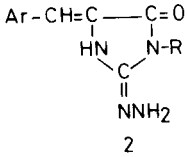

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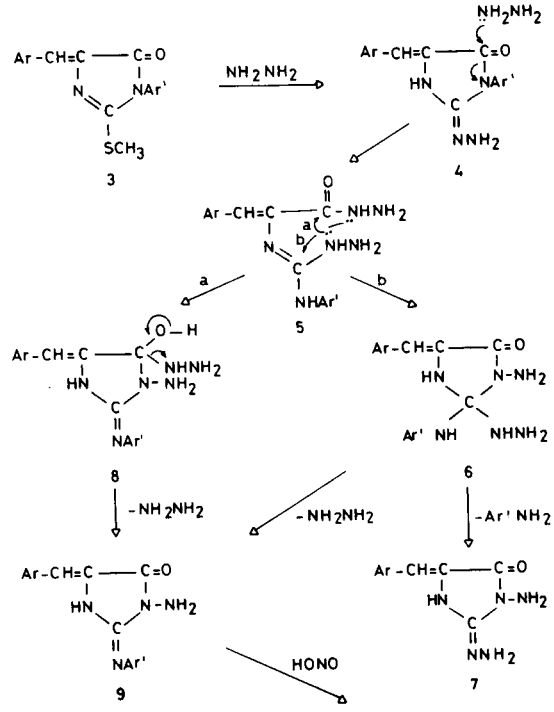
a, R = H; Ar = C_6H_5
b, R = H; Ar = $C_6H_4CH_3$-p
c, R = H; Ar = $C_6H_4OCH_3$-p
d, R = CH_3; Ar = C_6H_5

Our interest has now been extended to study the behavior of 5-arylidene-3-aryl-2-methylmercaptohydantoins (**3a-f**) toward hydrazine. Instead of obtaining the expected 2-hydrazone-3-aryl derivatives **4a-f**, the products from this reaction were established to be 5-arylidene-3-amino-N^2-arylglycocyamidines (**9a-f**). This reaction offers an avenue to these biologically interesting new aminoglycocyamidines. Assignment of structures **9a-f** is based on the fact that they underwent ready deamination (7,8) by the action of nitrous acid into the corresponding 5-arylidene-N^2-arylglycocyamidines (**10a-f**). The structure of the latter compounds was established by independent synthesis by the action of aniline and/or *p*-toluidine on the appropriate 5-arylidene-2-methylmercapto hydantoins (**1a-c**).

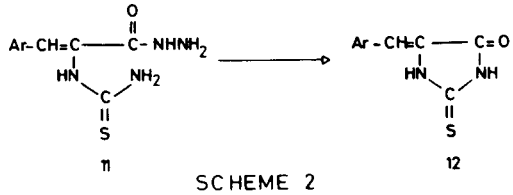
Scheme 1 illustrates the possible mechanism for this novel rearrangement in this class of compounds. The formation of the hydrazones **4a-f** is probably the first step followed by nucleophilic attack of a second hydrazine molecule on C-4 to give intermediate **5**. Apparently, the increased electrophilicity of this carbon atom is due to the presence of the 3-aryl substituent (7) (in cases where there are no such 3-aryl substituents, no such rearrangements has been reported (5, 6)). Intermediate **5** may undergo ring closure according to two possible pathways a and b. However, pathway b can be excluded since it can lead to 2-hydrazone derivatives **7** (by extrusion of $Ar'NH_2$) as well as compounds **9** (by estrusion of NH_2NH_2).



a, Ar = Ar' = C_6H_5
b, Ar = C_6H_5; Ar' = $C_6H_4CH_3$-p
c, Ar = $C_6H_4CH_3$-p; Ar' = C_6H_5
d, Ar = Ar' = $C_6H_4CH_3$-p
e, Ar = $C_6H_4OCH_3$-p; Ar' = C_6H_5
f, Ar = $C_6H_4OCH_3$-p; Ar' = $C_6H_4CH_3$-p

SCHEME 1

A further support in favor of pathway a is the fact that the thioureido cinnamic acid hydrazide derivatives **11** undergo cyclization into **12** similar to pathway a and not similar to pathway b (4,5) (Scheme 2).



SCHEME 2

Finally, the 3-amino products **9a,b,d,f** were condensed with benzaldehyde to give the corresponding 3-benzalamino derivatives **13a-d**, respectively.

Table 1

5-Arylidene-3-aryl-2-methylmercaptohydantoins (**3b-f**)

Products	Mp °C	Yeild %	Formula (Mol. Wt.)	Analysis % Calcd./Found C	H	N	S
3b	149	92	$C_{18}H_{16}N_2OS$	70.09	5.23	9.08	10.39
			(308.39)	70.02	5.10	8.90	10.50
3c	169	90	$C_{18}H_{16}N_2OS$	70.09	5.23	9.08	10.39
			(308.39)	70.30	5.40	8.80	10.20
3d	165	93	$C_{19}H_{18}N_2OS$	70.79	5.62	8.69	9.94
			(322.31)	70.50	5.40	8.80	9.80
3e	189	90	$C_{18}H_{16}N_2O_2S$	66.64	4.97	8.63	9.88
			(324.39)	66.40	5.10	8.70	9.90
3f	158	92	$C_{19}H_{18}N_2O_2S$	67.44	5.36	8.28	9.47
			(338.31)	67.20	5.50	8.40	9.30

Table 2

5-Arylidene-3-amino-N^2-arylglycocyamidines (**9a-f**)

Products	Mp (a)°C	Yield %	Formula (Mol. Wt.)	Analysis % Calcd./Found C	H	N
9a	201	35	$C_{16}H_{14}N_4O$	69.05	5.07	20.13
			(278.30)	68.90	5.20	19.90
9b	222	38	$C_{17}H_{16}N_4O$	69.84	5.52	19.17
			(292.33)	70.00	5.40	19.30
9c	239	42	$C_{17}H_{16}N_4O$	69.84	5.52	19.17
			(292.33)	69.90	5.30	19.20
9d	244	32	$C_{18}H_{18}N_4O$	70.56	5.92	18.29
			(306.36)	70.60	6.10	18.40
9e	219	30	$C_{17}H_{16}N_4O_2$	66.22	5.23	18.17
			(308.33)	66.10	5.10	17.90
9f	214	34	$C_{18}H_{18}N_4O_2$	67.06	5.63	17.38
			(322.36)	66.90	5.70	17.20

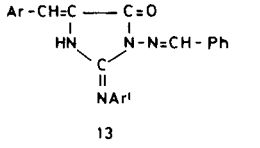
(a) Compound **9b**, ir (potassium bromide): 3320, 3290, 1690 cm^{-1}; **9c**, ir (potassium bromide): 3380, 3350, 1730 cm^{-1}; **9d**, ir (potassium bromide): 3330, 3295, 1715 cm^{-1}; **9e**, ir (potassium bromide): 3395, 3350, 1710 cm^{-1}; **9f**, ir (potassium bromide): 3325, 3260, 1700 cm^{-1}.

Table 3

5-Arylidene-N^2-arylglycocyamidines (**10a-f**)

Products	Mp °C	Yield %	Formula (Mol. Wt.)	Analysis % Calcd./Found C	H	N
10a	299	90, 95	$C_{16}H_{13}N_3O$	72.98	4.98	15.96
			(263.29)	73.10	4.80	16.20
10b	290	85, 92	$C_{17}H_{15}N_3O$	73.63	5.45	15.15
			(277.31)	73.50	5.40	15.30
10c	>305	85, 90	$C_{17}H_{15}N_3O$	73.63	5.45	15.15
			(277.31)	73.40	5.60	14.90
10d	>305	78, 93	$C_{18}H_{17}N_3O$	74.20	5.88	14.42
			(291.34)	74.20	5.70	14.50
10e	279	80, 88	$C_{17}H_{15}N_3O_2$	69.61	5.15	14.33
			(293.31)	69.90	5.20	14.50
10f	292	75, 80	$C_{18}H_{17}N_3O_2$	70.34	5.58	13.67
			(307.34)	70.50	5.70	13.50

(a) These yields correspond to the starting materials **9a-f** and **1a-c**, respectively.



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a, Ar = Ar' = C_6H_5

b, Ar = C_6H_5; Ar' = $C_6H_4CH_3$-p

c, Ar = Ar' = $C_6H_4CH_3$-p

d, Ar = $C_6H_4OCH_3$-p; Ar' = $C_6H_4CH_3$-p

Table 4

5-Arylidene-3-benzalamino-N^2-arylglycocyamidines (**13a-d**)

Products	Mp °C	Yield %	Formula (Mol. Wt.)	Analysis % Calcd./Found C	H	N
13a	196	95	$C_{23}H_{18}N_4O$	75.39	4.95	15.29
			(366.41)	75.40	5.10	15.10
13b	200	98	$C_{24}H_{20}N_4O$	75.77	5.30	14.73
			(380.43)	75.60	5.40	14.90
13c	244	92	$C_{25}H_{22}N_4O$	76.12	5.62	14.20
			(394.46)	75.90	5.50	14.30
13d	256	95	$C_{25}H_{22}N_4O_2$	73.15	5.40	13.65
			(410.46)	73.30	5.60	13.60

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 centre, Cairo University.

5-Arylidene-2-methylmercaptohydantoins (**1a-c**).

5-*p*-Methylbenzylidene-2-methylmercaptohydantoin (**1b**) was prepared by the action of excess methyl iodide on 5-*p*-methyl-benzylidene-2-thiohydrantoin (9) in aqueous solution containing one equivalent of potassium hydroxide, following the same procedure described previously for the synthesis of compounds **1a,c** (5,10). Compound 1b was crystallized from ethanol into straw yellow crystals, mp 218° (yield *ca.*, 92%).

Anal. Calcd. for $C_{12}H_{12}N_2OS$: C, 62.04; H, 5.21; N, 12.06; S, 13.80. Found: C, 61.90; H, 5.30; N, 12.10; S, 13.60.

5-Arylidene-3-aryl-2-methylmercaptohydantoins (**3a-f**).

2-Methylmercaptohydantoins **3b-f** listed in Table 1 were prepared by the action of methyl iodide on methanolic solution of 5-arylidene-3-aryl-2-thiohydantoins (11-14) containing one equivalent of sodium methoxide following the same procedure described previously for the synthesis of compound **3a** (11). Compounds **3b-f** (Table 1) were crystallized from ethanol into straw yellow crystals.

5-Arylidene-3-amino-N^2-arylglycocyamidines (**9a-f**).

To a suspension of each of compounds **3a-f** (1 g) in methanol (20 ml) was added hydrazine hydrate (1ml, 90%). The reaction mixture was heated under reflux for 1 hour (during which time all the starting material went into solution). The precipitate formed after cooling was collected and recrystallized from ethanol as yellow crystals of **9a-f** (Table 2).

5-Arylidene-N^2-aryglycocyamidines (**10a-f**).

(a) By the Action of Nitrons Acid on **9a-f**.

To each of compounds **9a-f** (0.2 g) in 2*N* hydrochloric acid (10 ml) was added aqueous sodium nitrite (5 ml, 5%) at 10 ° dropwise with stirring over 15 minutes. The mixture was then allowed to stand 2 hours at room temperature and the precipitate was collected and recrystallized from DMF into pale yellow crystals of **10a-f** (Table 3).

(b) By the Action of Aniline and/or *p*-Toluidine on **1a-c**.

An equimolecular amount of aniline and/or *p*-toluidine and the appropriate 5-arylidene-2-methylmercaptohydantoins (**1a-c**) was heated in an oil bath at 150-160° for 1 hour. The solid obtained after cooling was washed with ethanol and recrystallized from DMF into pale yellow crystals of **10a-f** which were identical with the compounds obtained in procedure (a) (mixed mp and ir spectra).

5-Arylidene-3-benzalamino-N^2-arylglycocyamidines (**13a-d**).

A solution of each of compounds **9a,b,d,f** (4 mmoles) and benzaldehyde (5 mmoles) in DMF (2 ml) was heated under reflux for 1 hour. The precipitate obtained after dilution with water was recrystallized from DMF/ethanol into yellow crystals of **13a-d** (Table 4).

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