6- And 7-Aryl-1,2,4-triazolo[4,3-*b*]-1,2,4-triazines. Synthesis and Characterization (1)

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Received May 8, 1979

Synthetic methods for the preparation of 6-aryl-1,2,4-triazolo[4,3-*b*]-1,2,4-triazines (**1**) and the 7-aryl isomers (**2**) are described. Compounds **1** were prepared from aryl glyoxaldoximes **76** *via* 6-aryl-1,2,4-triazin-3(2*H*)ones (**75**). A simple procedure for the preparation of the 7-aryl isomers was effected using arylglyoxals **11** and the triazoles (**4**, **12a** and **12b**). However, complete regioselectivity was not realized in all cases, especially when the triazoles were substituted at the C-5 position. A regiospecific synthesis of the 7-aryl isomers **2** was developed *via* the 3-methylthio-5-aryl-1,2,4-triazines (**61**). The structure of the parent 6-phenyl derivative **5** was confirmed by x-ray crystallography.

J. Heterocyclic Chem., **16**, 1393 (1979).

As part of a program to prepare novel aryl-substituted bicyclic heterocycles, we became interested in the synthesis of 6- and 7-aryl-1,2,4-triazolo[4,3-*b*]-1,2,4-triazines, **1** and **2**, respectively.

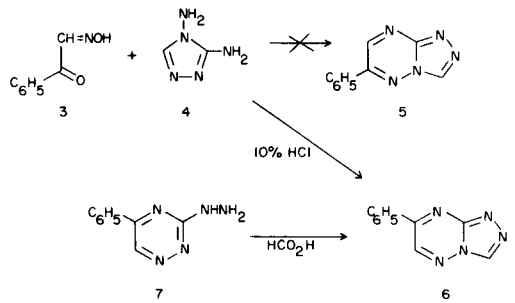
Structures

1 2

While no 6-aryl derivatives **1** have been reported, the parent compounds in the 7-aryl series **2** (Ar = C_6H_5; R = H, CH_3) have been described (2).

Our initial attention was directed toward structure **1**, and we envisioned the approach shown in Scheme I (3).

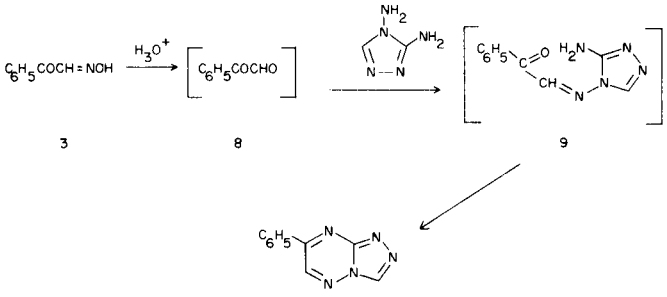
Scheme I



3 4 5 7 6

Surprisingly, oxime **3** did not react with triazole **4** under mild acid treatment (3). However, prolonged heating with acid did afford a single crystalline product. Subsequent examination revealed that the product was not the desired 6-phenyl isomer **5**, but the 7-phenyl isomer **6**. An alternate synthesis of **6** from 3-hydrazino-5-phenyl-1,2,4-triazine (**7**) (2,4) confirmed the structural assignment. It is believed (Figure 1) that the triazole **4** is not sufficiently reactive to condense on the ketone carbonyl of oxime **3**. Instead, **3**

Figure 1

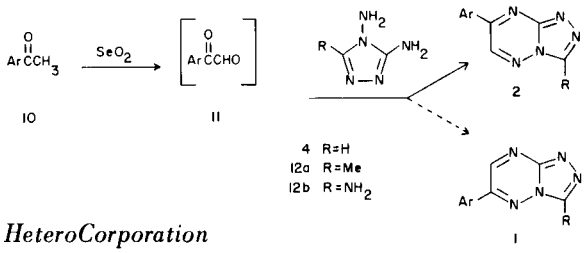


3 8 9 6

is first hydrolyzed to phenylglyoxal (**8**) which then condenses with the 4-amino group of triazole **4** to give intermediate **9**, which cyclizes to **6**.

The extremely facile synthesis of the parent 7-phenyl derivative **6** *via* the triazole-glyoxal condensation route led us to explore the preparation of other 7-aryl derivatives (Scheme II). Oxidation of aryl methyl ketones **10** with

Scheme II
(Method A)

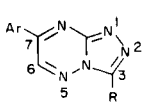


10 11 4 R=H 12a R=Me 12b R=NH_2 2 1

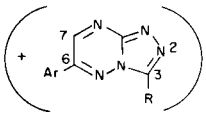
0022-152X/79/071393-11$02.25

Table I

7-Aryl-1,2,4-triazolo[4,3-*b*]1,2,4-triazines (**2**)



2



1

Compound No.	Ar	R	Formula	Method of Preparation	%1	Yield (a) (%)	M.p. °C	Pertinent Pmr Signals (b)			Analysis Calcd.	Found
6	C_6H_5	H	$C_{10}H_7N_5$	A	0	56	257-259.5 (c)	C-6H	9.56	C	60.90	60.85
										H	3.58	3.75
				B	0	33	258-260			N	35.52	35.33
13	C_6H_5	Me	$C_{11}H_9N_5$	A	0	57	227-233	C-3Me	3.00	C	62.55	62.18
								C-6H	9.56	H	4.30	4.00
										N	33.16	32.98
14	C_6H_5	NH_2	$C_{10}H_8N_6$	A	0	52	304-307	C-6H	9.10	C	56.59	56.41
										H	3.86	3.88
										N	39.61	39.52
15	*p*-Br-C_6H_4	H	$C_{10}H_6BrN_5$	A	0	70	>310	C-6H	9.57	C	43.50	43.28
										H	2.19	1.93
										N	25.37	25.13
16	*p*-Br-C_6H_4	Me	$C_{11}H_8BrN_5$	A	4	45	255-258	C-3Me (**2**)	2.99	C	45.52	45.41
								C-3Me (**1**)	3.11	H	2.78	2.72
								C-6H	9.51	N	24.15	24.31
								C-7H	9.59			
17	*p*-Cl-C_6H_4	H	$C_{10}H_6ClN_5$	A	5	51	280 dec	C-6H	9.54	C	51.85	52.15
								C-7H	9.65	H	2.61	2.70
										N	30.23	30.03
										Cl	15.30	15.39
18	*p*-Cl-C_6H_4	H	$C_{10}H_6ClN_5$	B	0	98	>300	C-6H	9.52			
19	*p*-Cl-C_6H_4	Me	$C_{11}H_8ClN_5$	A	0	18	240 dec	C-3Me	3.00	C	53.78	53.60
								C-6H	9.52	H	3.28	3.40
										N	28.51	27.21
										Cl	14.43	14.64
20	*p*-Cl-C_6H_4	NH_2	$C_{10}H_7ClN_6$	A	17	31	>300	C-6H	9.12	C	48.69	48.52
								C-7H	9.30	H	2.86	2.80
										N	34.08	33.90
										Cl	14.37	14.37
21	*p*-Cl-C_6H_4	NH_2	$C_{10}H_7ClN_6$	B	0	87	>300	C-6H	9.16			
22	*p*-Ph-C_6H_4	H	$C_{16}H_{11}N_5$	A	8	33	>300	C-6H	9.52	C	70.31	70.23
								C-7H	9.64	H	4.06	4.10
										N	25.63	25.55
23	*p*-Ph-C_6H_4	Me	$C_{17}H_{13}N_5$	A	0	21	267-282	C-3Me	2.97	C	71.06	70.68
										H	4.56	4.58
										N	24.38	24.43
24	*p*-Ph-C_6H_4	NH_2	$C_{16}H_{12}N_6$	A	0	20	>300	C-6H	9.16	C	66.65	66.54
										H	4.20	4.25
										N	29.15	28.95
25	2-Thienyl	H	$C_9H_5N_5S$	A	0	47	290-295	C-6H	9.16	C	47.28	46.84
										H	2.48	2.56
				B	0	63	294.5-296.5	C-6H	9.11	N	34.46	34.63
										S	15.78	15.54
26	2-Thienyl	Me	$C_9H_7N_5S$	A	18	32	215 dec	C-3Me (**2**)	2.92	C	49.76	49.56
								C-3Me (**1**)	3.04	H	3.25	3.30
								C-6H	9.28	N	32.24	32.60
								C-7H	9.48	S	14.76	14.69
27	2-Thienyl	Me	$C_9H_7N_5S$	B	0	90	232-236	C-3Me	2.93			
								C-6H	9.31			
28	2-Naphthyl	H	$C_{14}H_9N_5$	A	0	27	290-294	C-6H	9.66	C	68.00	68.38
										H	3.67	3.57
										N	28.33	27.94
29	2-Naphthyl	Me	$C_{15}H_{11}N_5$	B	0	88	270.5-276.5	C-3Me	2.98	C	68.95	68.71
								C-6H	9.63	H	4.24	4.42
										N	26.81	26.92
30	2-Naphthyl	NH_2	$C_{14}H_{10}N_6$	A	20	34	>300	C-6H	9.26	C	64.11	64.37
								C-7H	9.46	H	3.84	3.98
										N	32.05	31.74
31	*p*-CN-C_6H_4	H	$C_{11}H_6N_6$	A	0	42	>300	C-6H	9.60	C	59.46	59.06
										H	2.72	2.69
										N	37.82	37.36
32	*p*-CN-C_6H_4	Me	$C_{12}H_8N_6$	A	40	47	224-261	C-6H	9.60	C	61.01	60.63
								C-7H	9.64	H	3.41	3.30
										N	35.38	35.52

Table I continued

Compound No.	Ar	R	Formula	Method of Preparation	%1	Yield (a) (%)	M.p. °C	Pertinent Pmr Signals (b)			Analysis Calcd.	Found
33	*p*-CN-C_6H_4	NH_2	$C_{11}H_7N_7$	A	0	24	>305	C-6H	9.15	C	55.69	55.32
										H	2.97	3.03
										N	41.34	41.79
34	*p*-t-Bu-C_6H_4	H	$C_{14}H_{17}N_5$	A	0	30	302.5-305	C-6H	9.52	C	66.38	66.73
										H	5.97	5.93
35	*p*-t-BuC$_6H_4$	Me	$C_{15}H_{17}N_5$	A	0	25	239.5-245	C-3Me	2.97	C	67.39	67.25
								C-6H	9.50	H	6.41	6.39
										N	26.20	26.03
36	*p*-t-Bu-C_6H_4	NH_2	$C_{14}H_{16}N_6$	A	0	30	>305	C-6H	9.19	C	62.67	63.03
										H	6.01	6.25
										N	31.32	31.33
37	*p*-MeO-C_6H_4	H	$C_{11}H_9N_5O$	A	0	8	282.5-284.5	C-6H	9.44	C	58.14	58.28
										H	3.99	4.05
										H	30.82	31.06
38	*p*-MeO-C_6H_4	NH_2	$C_{11}H_{10}N_6O$	A	0	12	>305	C-6H	9.14	C	54.54	54.62
										H	4.16	4.18
										N	34.69	34.68
39	m-CH_3-C_6H_4	H	$C_{11}H_8F_3N_5$	A	0	32	288-290	C-6H	9.62	C	49.82	49.82
										H	2.28	2.23
										N	26.41	26.66
										F	21.49	21.60
40	*m*-CF_3-C_6H_4	Me	$C_{12}H_8F_3N_5$	A	40	10	209-212.5	C-6H	9.58	C	51.62	52.02
								C-7H	9.63	H	2.89	2.79
								C-3Me (2)	3.02	N	25.08	25.42
								C-3Me (1)	3.12	F	20.41	20.63
41	*m*-CF_3-C_6H_4	Me	$C_{12}H_8F_3N_5$	B	0	87	230-233	C-3Me	3.02	C	51.62	51.29
								C-6H	9.61	H	2.89	2.94
										N	25.08	25.02
										F	20.41	20.96
42	*m*-CF_3-C_6H_4	NH_2	$C_{11}H_7F_3N_6$	A	0	34	>310	C-6H	9.20	C	47.15	47.17
										H	2.71	2.52
										N	29.99	29.86
										F	20.34	20.18
43	3,4-$(MeO)_2$-C_6H_3	H	$C_{13}H_{11}N_5O_2 \cdot \frac{1}{2}H_2O$	A	0	33	261 dec	C-6H	9.46	C	55.12	55.44
										H	4.34	4.26
										N	26.78	26.47
44	3,4-$(MeO)_2$-C_6H_3	NH_2	$C_{13}H_{13}N_6O_2 \cdot \frac{1}{2}H_2O$	A	20	46	292-297	C-6H	9.15	C	51.24	51.44
								C-7H	9.33	H	4.65	4.65
										N	29.88	29.87
45	*p*-F-C_6H_4	NH_2	$C_{10}H_7FN_6$	A	50	71	300 dec	C-6H	9.16	C	52.18	52.28
								C-7H	9.30	H	3.06	3.13
										N	36.51	36.28
										F	8.25	7.99
46	3,4,5-$(MeO)_3$-C_6H_2	H	$C_{14}H_{13}N_5O_3$	A	0	40	189-193 dec	C-6H	9.56	C	54.35	54.20
										H	4.56	4.25
										N	24.38	23.99
47	2,4-Cl_2-C_6H_3	H	$C_{10}H_5Cl_2N_5$	A	0	32	230-232	C-6H	9.57	C	45.14	45.03
										H	1.89	1.74
										N	26.80	26.32
										Cl	26.65	26.80
48	2,4-Cl-C_6H_3	NH_2	$C_{10}H_6Cl_2$	A	70	60	278-283	C-6H	9.03	C	42.73	42.35
								C-7H	9.14	H	2.15	2.14
										N	29.90	29.55
										Cl	25.22	25.23
49	5-Indanyl	NH_2	$C_{13}H_{12}N_6$	A	0	40	>300	C-6H	9.14	C	61.89	61.67
										H	4.79	4.91
										N	33.32	32.98
50	*o*-F-C_6H_4	H	$C_{10}H_6FN_5$	B(d)	0	52	171-173.5	C-6H	9.62	C	55.82	55.71
										H	2.81	2.98
										N	32.54	32.85
										F	8.83	9.18
51	*o*-F-C_6H_4	Me	$C_{11}H_8FN_5$	B	0	70	227-229	C-3Me	3.02	C	57.64	57.49
								C-6H	9.60	H	3.52	3.64
										N	30.55	30.80
										F	8.29	8.56
52	*o*-F-C_6H_4	NH_2	$C_{10}H_7FN_6$	A	76	34	234-236	C-6H	9.18	C	52.18	52.07
								C-7H	9.27	H	3.06	2.98
										N	36.50	36.37
										F	8.25	8.52
53	*o*-F-C_6H_{14}	NH_2	$C_{10}H_7FN_6$	B	0	77	296-300	C-6H	9.16	C	52.18	52.09
										H	3.06	3.23
										N	36.50	36.22
										F	8.25	8.46

Table I continued

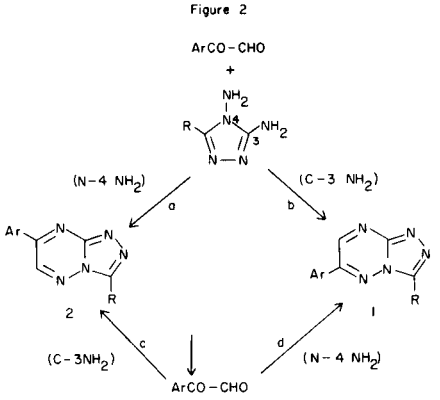
Compound No.	Ar	R	Formula	Method of Preparation	%1	Yield (a) (%)	M.p. °C	Pertinent Pmr Signals (b)		Analysis	Calcd.	Found
54	*o*-Cl-C_6H_4	H	$C_{10}H_6ClN_5$	A	0	8	164-166	C-6H	9.54	C	51.85	52.02
										H	2.61	2.68
				B	0	44	162-165	C-6H	9.56	N	30.23	30.21
										Cl	15.30	15.38
55	*o*-Cl-C_6H_4	Me	$C_{11}H_8ClN_5$	B(d)	0	79	192-196.5	C-3Me	3.04	C	57.64	57.49
								C-6H	9.53	H	3.52	3.64
										N	30.44	30.80
										Cl	8.29	8.56
56	*o*-Cl-C_6H_4	NH_2	$C_{10}H_7ClN_6$	A	20	46	237.5-240.5	C-6H	9.06	C	48.69	48.56
								C-7H	9.16	H	2.86	2.78
										N	34.08	33.67
										Cl	14.37	14.28
57	*o*-Cl-C_6H_4	NH_2	$C_{10}H_7ClN_6$	B	0	81	296-299	C-6H	9.06			
58	3,4-Cl_2-C_6H_3	H	$C_{10}H_5Cl_2N_5$	A	5	36	280-295	C-6H	9.50	C	45.14	45.04
								C-7H	9.60	H	1.89	1.90
										N	26.65	26.58
										Cl	26.32	26.07
59	3,4-$Cl_2C_6H_3$	Me	$C_{11}H_7Cl_2N_5$	A	0	26	275-280.5	C-3Me	2.98	C	47.17	47.11
								C-6H	9.47	H	2.52	2.55
										N	25.00	25.01
										Cl	25.31	25.31

(a) When only isomer **2** was formed, as evidenced by tlc or pmr, the product was recrystallized from ethanol-hexane. Mixtures were washed with hexane for purification. (b) In trifluoroacetic acid; chemical shifts (δ) are in ppm relative to tetramethylsilane internal standard. (c) Recrystallized from chloroform-methanol. (d) No reaction by Method A.

selenium dioxide (5) gave the arylglyoxals **11** which were not isolated, but were used in solutions to condense with the 3,4-diamino-4*H*-1,2,4-triazoles **4**,**12a** and **12b**. These condensations were not always regiospecific and varying amounts of 6-aryl isomer **1** were formed. The results are summarized in Table I.

The formation of the two regioisomers **1** and **2** by method A may be explained on the basis of four distinct mechanistic pathways (Figure 2).

Figure 2

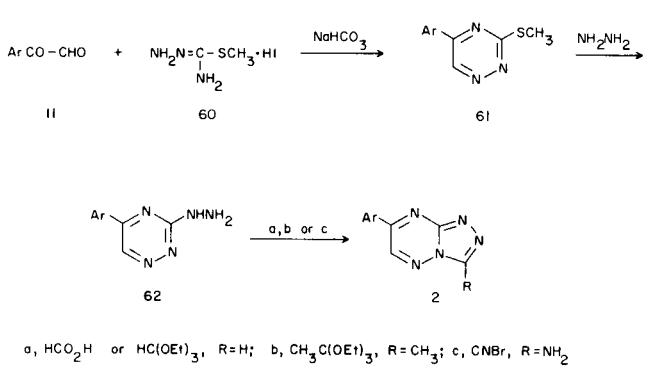


In agreement with the experimental results, the most favorable pathway should be path a (Figure 2), as the more reactive carbonyl group (aldehyde) would be expected to react with the more reactive 4-amino group (6) of the triazole, to give the 7-aryl isomer **2**. However, there are factors which may decrease the reactivity of the 4-amino group, such as increasing the steric bulk of the C-5 substituent (R). The results in Table I tend to support this explanation. Of the fifteen examples involving condensation with the triazole **4** (R = H), only three examples (**17**,**22** and **58**) were non-regiospecific. On the other hand, of the nine reactions with the 5-methyl triazole **12a**, four examples were non-regiospecific. The increase in bulk about the 4-amino group in the triazoles **12a** and **12b** would favor an increase in reaction by path b to give enhanced amounts of the C-6 isomer **1**. In the case of 3,4,5-triamino-4*H*-1,2,4-triazole (**12b**), there are two equivalent NH_2 groups (at C-3 and C-5) and thus an increased statistical probability of reaction by path b.

A second factor to be considered in the isomer distribution is the electronic effect of the aryl moiety on the ketone carbonyl in the aryl-glyoxaldehydes **11**. If the aryl group is electron withdrawing, then the ketone carbonyl will be more positively charged and increased amounts of the 6-aryl derivative will be formed (path d). While this pathway may be operative, the results in Table I are not definitive. Finally, reaction of the less reactive 3-amino group at the ketone carbonyl (path c) is considered to be a minor factor in determining the proportions of isomers **1** and **2** formed.

In order to obtain pure 7-aryl isomers, an alternative synthetic pathway was investigated. This route which is depicted in Scheme III (Method B) utilized procedures described by Paudler for preparing the parent 3-hydrazino-5-phenyl-1,2,4-triazine (**7**) (4,7). The results are described in Table I, and the intermediates are listed in Table II. It is clear from those examples in Table I which

Scheme III
Method B

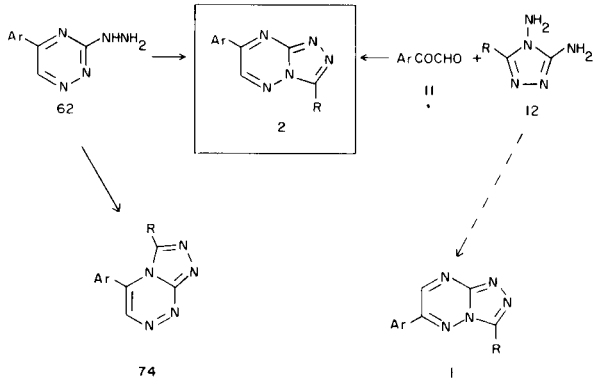


a, HCO_2H or $HC(OEt)_3$, R=H; b, $CH_3C(OEt)_3$, R=CH_3; c, CNBr, R=NH_2

were prepared by both methods that the pmr signals are useful in assigning structures. In all cases, the C-6 proton in 7-aryl derivatives **2** occurred at higher field than the C-7 proton in the 6-aryl derivatives **1**. More interestingly, the C-3 methyl group in the methyl derivatives had quite predictable chemical shifts, with the methyl signal in the C-7 isomers occurring at $\leq$ 3.0 ppm and the methyl in the C-6 isomers at lower field.

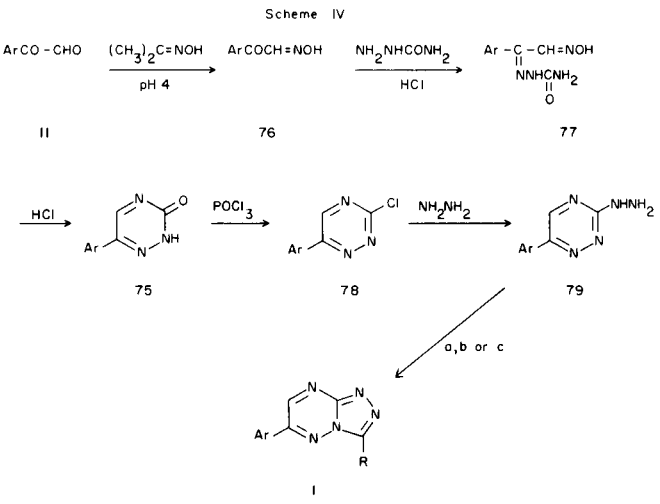
The cyclization of the 3-hydrazino-5-aryl-1,2,4 triazines **62** to give the compounds **2** merits some comment, since it is conceivable that instead of cyclization on N-2, cyclization on N-4 could occur to give the isomeric 1,2,4-triazolo-[3,4-*c*]-1,2,4-triazines (**74**) (Figure 3). That this does not occur is shown by the fact that only structure **2** can be formed by the two methods, A and B. In addition, Stevens has argued (8) that formation of a species such as **74** is unfavored on electronic grounds.

Figure 3



The remaining objective in this synthetic study was the regiospecific preparation of the 6-aryl isomers **1**. The key intermediates were the 6-aryl-1,2,4-triazin-3(2*H*)ones (**75**) (9). Their preparation and subsequent conversion to 6-aryl-1,2,4-triazolo[4,3-*b*]-1,2,4-triazines (**1**) are shown in Scheme IV.

Scheme IV



a, HCO_2H or $HC(OEt)_3$, R=H; b, $CH_3C(OEt)_3$, R=CH_3; c, CNBr, R=NH_2

The oximino ketones **76** are conventionally prepared by the nitrosation of an acetophenone derivative (10). In our hands, this procedure was unsatisfactory, for in addition to the poor yields (*ca.* 30%), this method would have necessitated the frequent use of large quantities of alkyl nitrites. We were able to circumvent these difficulties by using the oxime exchange procedure originally described by Taylor and Jacobi for a pteridine synthesis (11). The desired 6-aryl heterocycles **1** are described in Table III, and the intermediates are listed in Tables IV-VI.

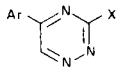
X-Ray Structure Proof of **1**.

While the structure of the 7-phenyl isomers **2** were shown to be correct beyond reasonable doubt according to the two methods of synthesis (Figure 3), it was of interest to confirm the structure of the 6-phenyl isomers **1**. To accomplish this, a sample of the parent compound **5** (entry 1, Table III) was subjected to x-ray study.

Crystals of this compound grown from ethanol/chloroform mixture are orthorhombic space group Pcab. The unit cell dimensions a = 7.440(4), b = 21.476(10), c = 10.981(4)A were determined by least-squares fit of the values of diffraction angles for 25 reflections in the range $20° < \theta < 45°$. The observed density determined by flotation in a carbon tetrachloride/hexane mixture is 1.475 g. cm^{-3}; the calculated value for 8 formula units/unit cell is 1.489 g. cm^{-3}. A crystal with approximate dimensions of 450 × 250 × 40 μm was used for three dimensional data collection on a CAD-3 Enraf-Nonius automatic diffractometer using the $\theta / 2\theta$ scan method with nickel filtered CuKα radiation. Of the 1299 independent reflections measured in the range $3 > \theta > 60$, 892 were classed as observed $I < 2.0\sigma(I)$; standard deviations of intensities were based on counting statistics. No absorption corrections were applied.

Table II

5-Aryl-1,2,4-triazines (a)

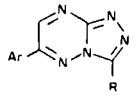


Compound	Ar	X	Formula	Recrystallization Solvent	Yield (%)	M.p. °C		Analysis Calcd.	Found
63	C_6H_5	SMe	$C_{10}H_9N_3S$	Ethanol-Water	88	93-97 (b)	C	59.09	59.18
							H	4.46	4.50
							N	20.67	20.54
							S	15.77	15.67
7	C_6H_5	$NHNH_2$	$C_9H_9N_5$	Ethanol-Hexane	33	149-150.5 (c)	C	57.74	57.57
							H	4.85	4.74
							N	37.40	37.13
64	*p*-F-C_6H_4	SMe	$C_{10}H_8FN_3S$	Ethanol-Water	100	138-140	C	54.29	54.65
							H	3.64	3.68
							N	18.99	18.62
							S	14.49	14.69
							F	8.59	8.86
65	*o*-Cl-C_6H_4	SMe	$C_{10}H_8ClN_3S$	Ethanol-Water	68	71-74.5	C	50.53	50.65
							H	3.39	3.52
							N	17.68	17.73
							Cl	14.91	15.00
							S	13.49	13.58
66	*o*-Cl-C_6H_4	$NHNH_2$	$C_9H_8ClN_5$	Ethanol-Hexane	96	169-172	C	48.77	48.59
							H	3.64	3.66
							N	31.60	31.82
							Cl	15.99	16.19
67	*o*-F-C_6H_4	SMe	$C_{10}H_8FN_3S$	Ethanol-Water	69	84-86	C	54.29	54.29
							H	3.64	3.73
							N	18.99	19.03
							F	8.59	8.52
							S	14.49	14.86
68	*o*-F-C_6H_4	$NHNH_2$	$C_9H_8FN_5$	Ethanol-Hexane	72	140.5-143.5	C	52.68	52.27
							H	3.93	4.00
							N	34.13	34.42
							F	9.26	9.26
69	2-Thienyl	SMe	$C_8H_7N_3S_2$	Ethanol-Water	70	108-110.5	C	45.91	45.46
							H	3.37	3.46
							N	20.08	20.12
							S	30.64	30.55
70	2-Thienyl	$NHNH_2$	$C_7H_7N_5S$	Ethanol-Hexane	79	185.5-189.5	C	43.51	43.21
							H	3.65	3.72
							N	36.24	36.42
							S	16.59	16.79
71	*m*-CF_3-C_6H_4	SMe	$C_{11}H_8F_3N_3S$	Ethanol-Water	43	125.5-129	C	48.71	43.39
							H	2.97	2.94
							N	15.49	15.62
							F	21.01	21.15
							S	11.82	12.17
72	*m*-CF_3-C_6H_4	$NHNH_2$	$C_{10}H_8F_3N_5$	Ethanol-Hexane	89	151-153	C	47.06	46.96
							H	3.16	3.19
							N	27.44	27.40
							F	22.33	23.04
73	*p*-Cl-C_6H_4	SMe	$C_{10}H_8ClN_3S$	Ethanol-Water	32	169.5-171.5	C	50.53	50.51
							H	3.39	3.62
							N	17.68	17.58
							Cl	14.91	15.11
							S	13.49	13.77

(a) Those intermediates to products listed in Table I which are not depicted were used as obtained without purification. (b) Lit. (4) m.p. 98-105°. (c) Lit. (7) m.p. 149-155°.

Table III

6-Aryl-1,2,4-triazolo[4,3-*b*]-1,2,4-triazines (1)

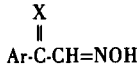


Compound No.	Ar	R	Formula	Yield (%)	M.p. °C	Pertinent Pmr Signals (b)			Analysis Calcd.	Found
5	C_6H_5	H	$C_{10}H_7N_5$	79	200-205	C-3H	9.50	C	60.90	60.50
						C-7H	9.65	H	3.58	3.79
								N	35.52	35.49
80	C_6H_5	Me	$C_{11}H_9N_5$	45	249-258	C-3Me	3.11	C	62.55	62.36
						C-7H	9.61	H	4.30	4.37
								N	33.26	33.26
81	C_6H_5	NH_2	$C_{10}H_8N_6 \cdot \frac{1}{2}H_2O$	40	274-276	C-7H	9.56	C	55.29	55.67
								H	4.18	3.92
								N	38.69	38.90
82	*p*-F-C_6H_4	H	$C_{10}H_6FN_5$	6	231-235	C-3H	9.52	C	55.82	56.06
						C-7H	9.65	H	2.81	2.93
								N	32.54	32.14
								F	8.83	8.62
83	*p*-F-C_6H_4	Me	$C_{11}H_8FN_5$	24	147-150	C-3Me	3.10	C	57.62	57.19
						C-7H	9.60	H	3.52	3.38
								N	30.57	30.41
								F	8.29	8.24
84	*o*-Cl-C_6H_4	H	$C_{10}H_6ClN_5$	72	145-148	C-7H	9.55	C	51.85	51.71
								H	2.61	2.74
								N	30.23	30.19
								Cl	15.30	15.22
85	*o*-Cl-C_6H_4	Me	$C_{11}H_8ClN_5$	75	172-175	C-3Me	3.08	C	53.78	53.52
						C-7H	9.47	H	3.28	3.32
								N	28.51	28.61
								Cl	14.43	14.41
86	*o*-Cl-C_6H_4	NH_2	$C_{10}H_7ClN_6$	59	251-254	C-7H	9.14	C	48.69	48.46
						C-3H	9.14	H	2.84	2.93
								N	34.08	33.79
								Cl	14.37	14.21
87	*o*-F-C_6H_4	H	$C_{10}H_6FN_5$	86	193-196	C-3H	9.56	C	55.82	55.60
						C-7H	9.62	H	2.81	2.95
								N	32.54	32.63
								F	8.83	8.73
88	*o*-F-C_6H_4	Me	$C_{11}H_8FN_5$	90	199.5-203.5	C-3Me	3.12	C	57.62	57.54
						C-7H	9.57	H	3.52	3.58
								N	30.57	30.69
								F	8.29	8.50
89	*o*-F-C_6H_4	NH_2	$C_{10}H_7FN_6$	52	242-246	C-7H	9.24	C	52.18	51.88
								H	3.06	3.20
								N	36.51	36.47
								F	8.25	8.60
90	*p*-CF_3-C_6H_4	H	$C_{11}H_6F_3N_5$	79	200-203	C-3H	9.58	C	49.82	49.84
						C-7H	9.68	H	2.28	2.62
								N	26.41	26.37
								F	21.49	21.17
91	*p*-CF_3-C_6H_4	Me	$C_{12}H_8F_3N_5$	85	226-228.5	C-3Me	3.12	C	51.62	51.37
						C-7H	9.64	H	2.89	3.05
								N	25.08	25.16
								F	20.41	20.42
92	*m*-CF_3-C_6H_4	H	$C_{11}H_6F_3N_5$	87	229-232	C-3H	9.56	C	49.82	49.68
						C-7H	9.68	H	2.28	2.17
								N	26.41	26.42
								F	21.49	21.45
93	*m*-CF_3-C_6H_4	Me	$C_{12}H_8F_3N_5$	93	265-268.5	C-3Me	3.12	C	51.62	52.10
						C-7H	9.65	H	2.84	3.03
								N	25.08	25.25
								F	20.41	20.70

(a) All compounds were recrystallized from or washed with ethanol-hexane. (b) In trifluoroacetic acid with tetramethylsilane internal standard.

Table IV

Arylglyoxaldoximes (**76**) and Semicarbazones (**77**) (a,b)



Compound No.	Ar	X	Formula	M.p., °C	Yield (%)		Analysis Calcd.	Found
94	*p*-FC_6H_4	NNHCNH$_2$	$C_9H_8FN_4O_2$	179-182 dec	55	C	48.43	48.99
						H	3.61	3.78
						N	25.10	25.46
						F	8.51	8.69
95	*m*-$CF_3C_6H_4$	O	$C_9H_6F_3NO_2$	91.5-94.5	66	C	49.78	49.81
						H	2.78	2.69
						N	6.45	6.73
						F	26.45	26.13
96	*m*-$CF_3C_6H_4$	NNHCNH$_2$	$C_{10}H_9F_3N_4O_2$	209-211 dec	84	C	43.80	43.83
						H	3.31	3.41
						N	20.43	20.34
						F	20.78	21.00
97	*o*-F-C_6H_4	NNHCNH$_2$	$C_9H_9FN_4O_2$	176-179 dec	64	C	48.22	47.70
						H	4.05	4.22
						N	24.94	24.92
						F	8.47	8.81
98	*o*-Cl-C_6H_4	NNHCNH$_2$	$C_9H_9ClN_4O_2$	207-210 dec	71	C	44.92	44.84
						H	3.77	3.82
						N	23.28	23.43
						Cl	14.73	14.88
99	*o*-Cl-C_6H_4	O	$C_7H_6ClNO_2$	oil	78	C	52.33	52.40
						H	3.29	3.53
						N	7.62	7.42
						Cl	19.31	19.33

(a) Other intermediates not depicted were used without purification. (b) All products recrystallized from ethanol-hexane.

A complete trial structure was obtained using the automatic phase determining program MULTAN (12). After isotropic least-squares refinement with all non-hydrogen atoms treated as carbons, the five nitrogen atoms were assigned as the atoms with the lowest temperature parameters. An isotropic refinement (to R = 0.091) yielded a difference map in which peaks corresponding to the seven hydrogens could be identified. Further refinement, isotropic for hydrogen and anisotropic for non-hydrogens, led to a final discrepancy factor of 0.063 for the observed reflections. All calculations were made using the XRAY76 set of programs (13). An ORTEP plot of the molecule is shown in Figure 4.

The two significant features of the x-ray structure of **5** are the position of the phenyl at C-6 and the ring juncture of the heterocycle confirming the direction of cyclization (on N-2) of 3-hydrazino-6-phenyl-1,2,4-triazine (**106**).

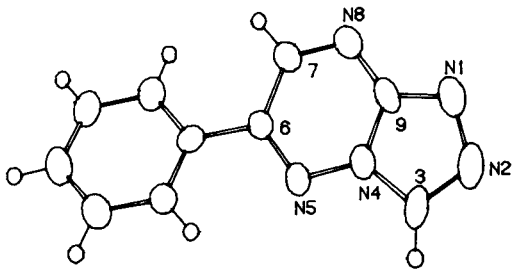
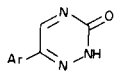


Figure 4: X-ray plot of 6-Phenyl-1,2,4-triazolo[4,3-*b*]-1,2,4-triazine (**5**)

Table V

6-Aryl-1,2,4-triazin-3(2*H*)ones (a,b) (**75**)

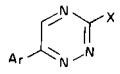


Compound No.	Ar	Formula	Yield (%)	M.p. °C
100	C_6H_5	$C_9H_7N_3O$	56	218-222 dec
101	*p*-F-C_6H_4	$C_9H_6FN_3O$	78	211.5 dec
102	*p*-$CF_3C_6H_4$	$C_{10}H_6F_3N_3O$	83	165-174 dec
103	*o*-F-C_6H_4	$C_9H_6FN_3O$	87	185-187 dec
104	*o*-ClC_6H_4	$C_9H_6ClN_3O$	64	191-195.5 dec

(a) Intermediates in this table and others not depicted were generally obtained as hydrates and were used without purification to analytical quality.
(b) All products were recrystallized from water-acetic acid and washed with ethanol.

Table VI

3-Substituted 6-Aryl-1,2,4-triazines (a) (**78** and **79**)



Compound No.	Ar	X	Formula	M.p. °C	Recrystallization Solvent	Yield (%)		Analysis Calcd.	Found
105	C_6H_5	Cl	C_9H_6Cl	138-140.5	Chloroform-Hexane	47	C	56.41	56.82
							H	3.16	3.09
							N	21.93	21.96
							Cl	18.50	18.49
106	C_6H_5	$NHNH_2$	$C_9H_9N_5$	196.5-199.5 (b)	Ethanol-Hexane	36	C	57.74	57.77
							H	4.85	4.79
							N	37.41	37.39
107	*o*-Cl-C_6H_4	Cl	$C_9H_4Cl_2N_3$	72-74	Chloroform-Hexane	35	C	47.82	47.52
							H	2.23	2.45
							N	18.59	18.63
							Cl	31.36	31.39
108	*o*-Cl-C_6H_4	$NHNH_2$	$C_9H_8ClN_5$	184-186	Ethanol-Hexane	83	C	48.77	48.59
							H	3.64	3.66
							N	31.60	31.82
							Cl	15.99	16.19
109	*o*-F-C_6H_4	$NHNH_2$	$C_9H_8FN_5$	146-148	Ethanol-Hexane	76	C	52.68	52.76
							H	3.93	4.10
							N	34.13	33.92
							F	9.26	9.25
110	*m*-CF_3-C_6H_4	$NHNH_2$	$C_{10}H_8F_3N_5$	157-160.5	Ethanol-Hexane	71	C	47.06	47.01
							H	3.16	3.23
							N	27.44	27.30
							F	22.33	22.62

(a) Intermediates not depicted in this table were characterized by their pmr spectra and used without purification. (b) Lit. (7) m.p. 197-199°.

EXPERIMENTAL

General.

Infrared spectra were determined on a Perkin-Elmer Spectrophotometer (Model 21). Pmr spectra were determined on a Varian HR-100 spectrometer. Melting points were taken on a Mel-Temp apparatus and are uncorrected. All solvents and reagents were used as is from commercial sources. 1,3-Diaminoguanidine hydrochloride was obtained from the Fine Chemicals Department, American Cyanamid Company.

3,4-Diamino-4*H*-1,2,4-triazole Hydrochloride (**4**).

A mixture of 1,3-diaminoguanidine hydrochloride (31.1 g., 0.25 mole) and 12.5 g. (0.25 mole) of 94% formic acid was heated on a steam bath

until a crystalline solid formed. The resulting slurry was filtered and the solid washed several times with ethanol to give 25.2 g. (74%) of a white solid, m.p. 234-236.5° dec.

Anal. Calcd. for $C_2H_4ClN_5$: C, 17.22; H, 4.46; N, 51.66; Cl, 26.15. Found: C, 17.37; H, 4.34; N, 51.47; Cl, 26.07.

3,4-Diamino-5-methyl-4*H*-1,2,4-triazole Hydrochloride (**12a**).

A mixture of 125 g. (1 mole) of 1,3-diaminoguanidine hydrochloride and 150 ml. of acetic acid was heated to reflux. A solution of 5 ml. of concentrated hydrochloric acid and 75 ml. of acetic acid was added and the mixture was refluxed overnight. On cooling, a white solid separated which was isolated by dilution with ethanol, cooling and filtration. There was obtained 90.5 g. (60%) of white crystals, m.p. 251-256° dec.

Anal. Calcd. for $C_3H_8ClN_5$: C, 24.09; H, 5.35; N, 46.82; Cl, 23.70. Found: C, 24.16; H, 5.33; N, 46.73; Cl, 23.33.

7-Phenyl-1,2,4-triazolo[4,3-*b*]-1,2,4-triazine (**6**).

a. Method A.

To a solution of 2.7 g. (.02 mole) of 3,4-diamino-4*H*-1,2,4-triazole hydrochloride in 10 ml. of 2*M* sodium hydroxide, was added 3.04 g. (.02 mole) of phenyl glyoxal hydrate in 20 ml. of acetic acid. The mixture was heated on a steam bath for 15 minutes. Water was added, the mixture filtered to give 2.2 g. (56%) of tan crystals. Recrystallization from chloroform/methanol gave cream-colored plates, m.p. 257-260°.

b. Method B

Following the method of Fusco and Rossi (2a), a mixtue of 1.76 g. (9.4 mole) of **7** (4) and 3.5 ml. of 94% formic acid was refluxed for 2 hours. The mixture was cooled and diluted with water to give a pale green solid. Recrystallization from chloroform/methanol gave 0.6 g. (33%) of pale yellow plates, m.p. 258-260°. The pmr and tlc were identical to the product prepared by Method A (above), and a mixture had m.p. 258-262° (lit. (2) m.p. 252-253°).

3-Methyl-7-phenyl-1,2,4-triazolo[4,3-*b*]-1,2,4-triazine (**13**) (Method A).

By the method described in part a, above, 6.08 (0.04 mole) of phenylglyoxal hydrate was reacted with 5.98 g. (0.04 mole) of **12a** to give 4.8 g. (57%) of the product as yellow needles, m.p. 225-238°. Recrystallization from ethanol yielded yellow needles, m.p. 227-233°.

3-Amino-7-phenyl-1,2,4-triazolo[4,3-*b*]-1,2,4-triazine (**14**) (Method A).

To a solution of 3,4,5-triamino-4*H*-1,2,4-triazole (**12b**) (14) in 20 ml. of water, was added 6.08 g. (0.04 mole) of phenylglyoxal hydrate in 40 ml. of acetic acid and the mixture was heated on a steam bath. Within about 15 minutes, the solution turned deep red, followed by the precipitation of a thick solid. The product was filtered and washed with water and hot ethanol to afford 44 g. (52%) of red solid, m.p. 304-307° dec.

3-Methylthio-5-(*o*-chlorophenyl)-1,2,4-triazine (**65**).

A suspension of 22.2 g. (0.2 mole) of selenium dioxide in 150 ml. of dioxane and 4.5 ml. of water was heated to about 60° until the solid dissolved. A solution of 31.2 g. (0.2 mole) of *o*-chloroacetophenone in a little dioxane was added and the solution was refluxed overnight. The precipitated selenium was filtered and the filtrate was added to 200 g. of ice with external cooling. To this slurry was added 25.2 g. (0.3 mole) of sodium bicarbonate followed by 58.25 g. (0.25 mole) of 3-methylisothiosemicarbazide hydroiodide (**60**) (4). The mixture was stirred until a yellow solid separated and bubbling ceased. The solid was filtered and recrystallized from ethanol-water (with charcoal treatment) to give 32.2 g. (68%) of yellow needles, m.p. 71-74.5°.

3-Hydrazino-5-(*o*-chlorophenyl)-1,2,4-triazine (**66**).

A solution of 29.6 g. (0.125 mole) of **65** and 6.4 g. (0.19 mole) of 95% hydrazine in 100 ml. of methanol-THF was refluxed 2 days. On cooling, yellow needles separated which were filtered and washed well with ethanol-hexane to give a single product (tlc) which amounted to 26.5 g. (96%), m.p. 169-172°.

7-(*o*-Chlorophenyl)-1,2,4-triazolo[4,3-*b*]-1,2,4-triazine (**54**) (Method B).

A mixture of 6.65 g. (.03 mole) of **66** and 60 ml. of ethyl orthoformate was refluxed for 4 hours. After cooling, hexane was added and the mixture filtered to give a tan solid. Recrystallization from ethanol-hexane gave 2.9 (44%) of tan plates, m.p. 164-166°.

3-Methyl-7-(*o*-chlorophenyl)-1,2,4-triazolo[4,3-*b*]-1,2,4-triazine (**55**) (Method B).

In a similar manner as the preceding example, 6.65 g. (.03 mole) of **66** was heated with 60 ml. of ethyl orthoacetate. The mixture was diluted with hexane and filtered to yield 5.8 g. (72%) of yellow crystals, m.p. 192-196.5°.

3-Amino-7-(*o*-fluorophenyl)-1,2,4-triazolo[4,3-*b*]-1,2,4-triazine (**53**) (Method B).

To a solution of 2.08 g. (0.01 mole) of 3-hydrazino-5-(*o*-fluorophenyl)-1,2,4-triazine (**68**) in 150 ml. of methanol was added 1.18 g. (.011 mole) of cyanogen bromide. Within minutes a red solid separated. The mixture was refluxed for 1 hour, cooled and poured into a slurry of ice and saturated sodium acetate. The mixture was filtered to give 1.8 g. (77%) of red plates m.p. 296-304°.

m-Trifluoromethylphenylglyoxaldoxime (**95**).

To a mixture of 29.5 g. (0.27 mole) of selenium dioxide in 6 ml. of water and 200 ml. of dioxane was added 50 g. (0.266 mole) of *m*-trifluoromethylacetophenone. The mixture was refluxed overnight, filtered twice through diatomaceous earth, diluted with water and adjusted to *p*H 4 with 5% sodium hydroxide solution. To this mixture was added 20.5 g. (0.28 mole) of acetone oxime and the mixture was stirred for 4 days. On dilution to 2 l. with water and chilling, a solid separated which was isolated by filtration and recrystallized from 50% ethanol to give 38.3 g. (66%) of yellow crystals, m.p. 91.5-94.5°.

m-Trifluoromethylphenylglyoxaldoxime Semicarbazone (**96**).

A solution of 35.6 g. (0.164 mole) of **95**, 18.3 g. (0.164 mole) of semicarbazide hydrochloride and 22.4 g. (0.164 mole) of sodium acetate trihydrate in 200 ml. of 50% ethanol was heated to 50° on a steam bath. The white crystalline solid which separated was isolated by filtration and recrystallized from ethanol-hexane to give 37.4 g. (84%) of colorless needles, m.p. 209-211° dec.

6-(*o*-Fluorophenyl)-1,2,4-triazin-3(2*H*)one (**103**).

A suspension of 61 g. (0.273 mole) of *o*-fluorophenylglyoxaldoxime semicarbazone (**97**) in 1.7 l. of 5% hydrochloric acid was heated to reflux and maintained at reflux for 1 hour, during which time the suspended solid changed from fluffy white needles to a tacky mass which hardened as the mixture cooled. The solid was isolated by filtration, washed well with water and then dissolved in 400 ml. of boiling acetic acid. The resulting solution was heated at reflux overnight, and the solvent was removed at reduced pressure. The residue was triturated with ethanol-hexane to give 49 g. (87%) of a yellow amorphous solid, m.p. 185-187° dec.

3-Chloro-6-(*o*-chlorophenyl)-1,2,4-triazine (**107**).

A mixture of 53 g. (0.255 mole) of 6-(*o*-chlorophenyl)-1,2,4-triazin-3(2*H*)one (**104**) and 5.3 g. of *N*,*N*-dimethylformamide in 800 ml. of 1:1 phosphorus oxychloride-chloroform was maintained at reflux overnight. The mixture was then concentrated at reduced pressure, diluted with methylene chloride and poured onto ice with stirring. When the ice melted the mixture was neutralized with sodium bicarbonate solution and filtered to remove a small amount of insoluble residue, and the layers were separated. The organic layer was dried and concentrated to a brown oil which was chromatographed through a small silica gel column to give 20.25 g. (35%) of colorless needles (from methylene chloride-hexane), m.p. 72-74°.

3-Hydrazino-6-(*o*-chlorphenyl)-1,2,4-triazine (**108**).

A solution of 19.8 g. (88 mmoles) of **107** in 120 ml. of dry (4A molecular sieves) pyridine was cooled in an ice bath and 15 ml. of hydrazine hydrate was added. The cooling was continued so as to keep the temperature below 30° at which time yellow needles separated. The mixture was then

heated to 65° and maintained for 0.5 hour at 65°. The mixture was cooled and poured into ice-water. Filtration gave 16.2 g. (83%) of yellow needles. A small sample recrystallized from ethanol-hexane had m.p. 184-186°.

Acknowledgement.

We would like to thank Mr. L. Brancone and staff for microanalytical data and Mr. W. Fulmor and staff for spectral interpretation. Special thanks are given to Mr. G. O. Morton for his interpretations of the pmr spectra in assigning isomer structures.

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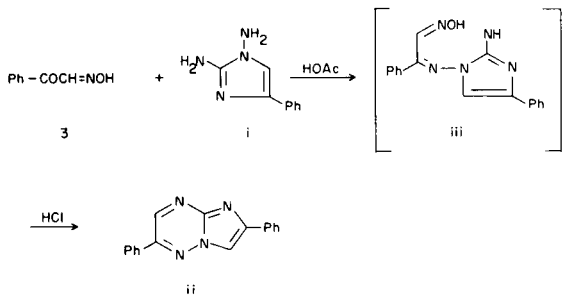

ii

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