Synthesis and Antimalarial Effects of *N,N*-Dialkyl-6-(substituted phenyl)-1,2,4,5-tetrazin-3-amines (1,2)

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The synthesis of a series of *N,N*-dialkyl-6-(substituted phenyl)-1,2,4,5-tetrazin-3-amines (IV) by two routes is described. The first route (Scheme I) involved the oxidative cyclization of formazans (II) to 3-bromo-6-(substituted phenyl)-1,2,4,5-tetrazines (III), followed by treatment with amines. The second (Scheme II) utilized the treatment of 3-(methylthio)-6-(substituted phenyl)-1,2,4,5-tetrazines (VII) with amines to provide the desired products. The intermediate 3-(methylthio)-6-(substituted phenyl)-1,2,4,5-tetrazines (VII) were obtained by thiobenzoylation of hydrazinecarbohydrazonothioic acid methyl ester with [[(substituted phenyl)thioxomethyl]thio]-acetic acids (V) to afford the 1,2-dihydro-3-(methylthio)-6-(substituted phenyl)-1,2,4,5-tetrazines (VI). Oxidation with bromine in acetic acid provided the desired intermediates. The target 6-(substituted phenyl)-1,2,4,5-tetrazin-3-amines (IV) displayed modest antimalarial activity.

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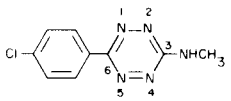
A brief patent (3) recently disclosed that 6-(4-chlorophenyl)-*N*-methyl-1,2,4,5-tetrazin-3-amine (**2**, Table I) and 6-(4-chlorophenyl)-*N,N*-dimethyl-1,2,4,5-tetrazin-3-amine (**3**, Table I) exhibit suppressive antimalarial activity against both sensitive and chloroquine- or pyrimethamine-resistant *Plasmodium berghei* infections in mice.



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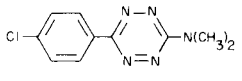


3

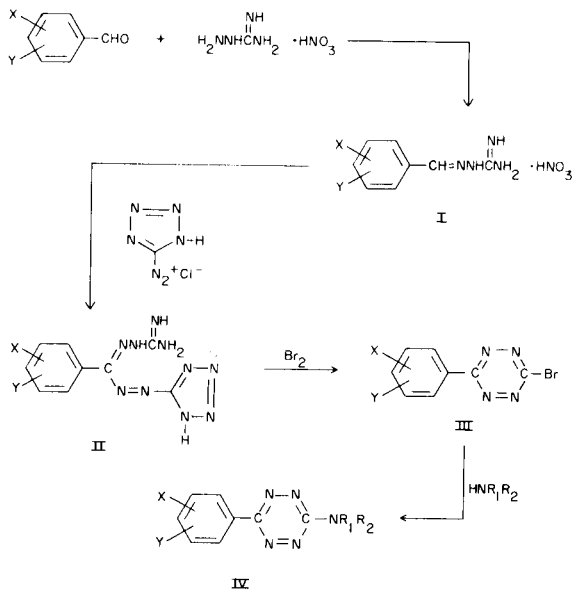
Novel structural types are of particular interest in the continuing search for drugs to combat the increasing problem of drug resistance in the treatment of malaria (4,5). Therefore we felt it important to investigate in some detail the structural ramifications of this apparently unique system. To this end we have now prepared and tested an array of compounds (**1-68**, Tables I and II) relating to **2** and **3** in an effort to delineate the structural requirements of this system for optimum antimalarial activity. Two major areas were explored in this work: (1) variations of the 3-amine substituent; and (2) the substitution pattern on the 6-phenyl group, and these will be described in this communication.

Chemistry.

The majority of 1,2,4,5-tetrazines which have been reported are 3,6-symmetrically disubstituted, obtained from the treatment of nitrile derivatives with hydrazine or aldehydes with substituted hydrazines (6,7). The synthesis of unsymmetrically disubstituted 1,2,4,5-tetrazines is considerably more difficult, and varies depending upon the nature of the substituent desired (8,9).

Heretofore the sole pathway to *N,N*-dialkyl-6-(substituted phenyl)-1,2,4,5-tetrazine-3-amines such as **2** and **3** was the poorly understood sequence shown in Scheme I

Scheme I



(10). During the course of our studies, the availability of a novel route to 3-(methylthio)-6-phenyl-1,2,4,5-tetrazine (11) (VII, Scheme II, X = Y = H) provided us with the key to an alternative, much improved synthesis for the desired compounds. The *N,N*-dialkyl-6-(substituted phenyl)-1,2,4,5-tetrazin-3-amines prepared early in this study were obtained *via* Scheme I and are summarized in Table I, while those prepared later by Scheme II are compiled in Table II.

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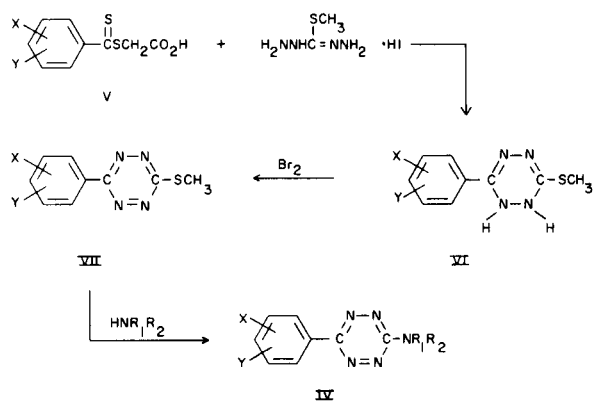
Scheme II



Thus to obtain compounds **1-31** (Table I), the appropriately substituted benzaldehydes were allowed to condense with hydrazinecarboximidamide mononitrate to provide the 2-[(substituted phenyl)methylene]hydrazinecarboximidamide mononitrates (I, Scheme I) in 81-95% yield. Treatment with the diazonium salt of 1*H*-tetrazol-5-amine then gave the 3-(substituted phenyl)-1-(1*H*-tetrazol-5-yl)-5-formazancarboximidamides (II, Scheme I), which were not purified or characterized but were allowed to react directly with bromine to provide the corresponding 3-bromo-6-(substituted phenyl)-1,2,4,5-tetrazines (III, Scheme I) in 16-27% yield (overall from I). Treatment of the bromo compound with the appropriate amines then provided the desired products in 13-99% yield.

This sequence suffered from several disadvantages. Firstly, it is hazardous. In one instance a cold, stirred solution of the diazonium salt of 1*H*-tetrazol-5-amine detonated. Thereafter the experimental manipulations were carried out by remote control behind a reinforced concrete wall. The intermediate formazans (II) are heat sensitive (10). As a precaution these compounds were collected from the aqueous reaction mixtures and used promptly without drying in the next step. In every successful isolation of a 3-bromo-6-(substituted phenyl)-1,2,4,5-tetrazine (III) there was also isolated a significant amount of an insoluble solid which is reported to be explosive (10).

Secondly, the scope of this sequence was limited. When, for example, 2-[[4-(dimethylamino)phenyl]methylene]-hydrazinecarboximidamide mononitrate (I, Scheme I, X = 4-N(CH$_3$)$_2$, Y = H) was allowed to react with the diazonium salt of 1*H*-tetrazol-5-amine, no corresponding formazan (II) could be isolated. Furthermore, when

Scheme III

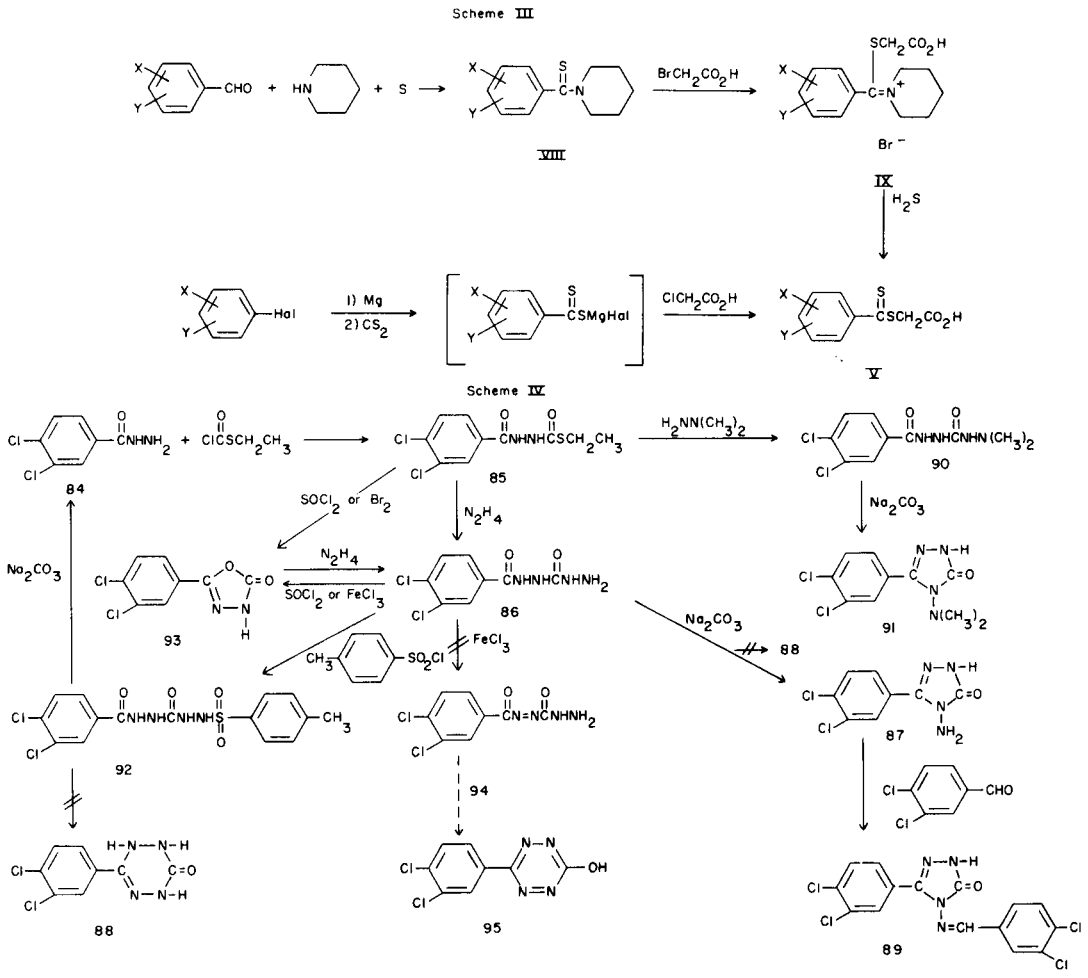
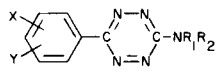


Table I

Synthesis of *N,N*-Dialkyl-6-(substituted phenyl)-1,2,4,5-tetrazin-3-amines IV, Prepared by Scheme I and Effects Against Trophozoite-Induced *Plasmodium berghei* in Mice



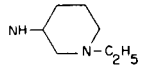
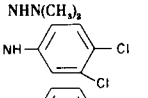
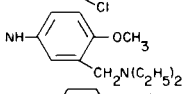
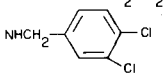
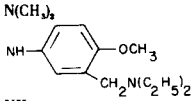
Compound Number	X,Y	NR_1R_2	M.p., °C	Recrystallization Solvent	Yield, % (a)	Molecular Formula	Analysis, %, C	H	Calcd./ N	Found Cl	Suppressive Antimalarial Effects in Mice Single s.c. Dose Δ MST, T or C^k after Mg./Kg. 640	320	160
1	4-Cl	NH_2	238-241 (e)	Ethanol	89.5	$C_8H_6ClN_5$	46.27	2.91	33.73	17.08	3C	7.5	4.7
							45.95	3.18	33.69	17.10			
2	4-Cl	$NHCH_3$	205-207 (b)	Ethanol	92	$C_9H_8ClN_5$	48.77	3.64	31.60				3.9
							48.76	3.78	31.84				
3	4-Cl	$N(CH_3)_2$	173.5-174.5 (c)	Ethanol	99	$C_{10}H_{10}ClN_5$	50.96	4.28	29.72		8.6	4.4	4.0
							50.97	4.38	29.60				
4	4-Cl	NHC_2H_5	186-187	Acetonitrile	78	$C_{10}H_{10}ClN_5$	50.96	4.28	29.72	15.04	0.9		0.5
							50.53	4.49	29.52	15.48			
5	4-Cl	$N(C_2H_5)_2$	141-143	Ethanol	73	$C_{12}H_{14}ClN_5$	54.65	5.35	26.56	13.44	6.1	3.2	
							54.68	5.27	26.64	13.67			
6	4-Cl	$N(CH_2CH_2CH_3)_2$	81-82	Ethanol	46	$C_{14}H_{18}ClN_5$	57.63	6.22	24.00	12.15	0.5		0.3
							57.48	6.34	23.97	12.29			
7	4-Cl		174-175	Ethanol	81	$C_{13}H_{13}ClN_6$	53.70	5.20	28.90		7.3	1.9	0.5
							53.99	5.31	29.14				
8	4-Cl	$N(CH_3)_4$	202-203	Ethanol	81	$C_{12}H_{12}ClN_5$	55.07	4.62	26.76	13.55	0.5		0.3
							54.76	4.76	26.86	13.61			
9	4-Cl	$N(CH_3)_3$	132-133	Ethanol	92	$C_{11}H_{14}ClN_5$	56.63	5.12	25.40	12.86	5.3	4.3	2.5
							56.46	5.13	25.59	12.99			
10	4-Cl		212-213	Ethanol	81	$C_{12}H_{12}ClN_5O$	51.90	4.36	25.22	12.76	0.3		0.3
							52.01	4.47	25.24	12.88			
11	4-Cl	$NH(CH_2)_3N(C_2H_5)_2$	117-119	Ethanol-Water	56	$C_{14}H_{19}ClN_6$	54.81	6.24	27.40	11.55	7.4	4.9	2.2
							54.89	6.17	27.56	11.69			
12	4-Cl		110-112	Acetonitrile	69	$C_{15}H_{19}ClN_6$	56.51	6.01	26.36	11.12	6.1	3.9	1.5
							56.57	6.04	26.49	11.42			
13	4-Cl	$N(CH_3)CH_2CH_2N(C_2H_5)_2$	67-68	Ethanol-Water	88	$C_{15}H_{21}ClN_6$	56.15	6.60	26.20	11.05	1.1		0.7
							56.08	6.67	25.95	11.09			
14	4-Cl	$NHNH_2$	201-203 (f,g)	Ethanol	61	$C_8H_7ClN_6$	43.16	3.17	37.75	15.92	6.4	4.6	2.8
							43.01	3.42	37.82	16.21			
15	4-Cl	$NHN(CH_3)_2$	176-178	Ethyl Acetate; Xylene	43	$C_{10}H_{11}ClN_6$	47.91	4.42		14.14	0.5		0.3
							47.90	4.62		14.42			
16(l)	4-Cl		275-278 (f)	Ethyl Acetate	23	$C_{14}H_8Cl_3N_5$	47.69	2.29	19.86	30.16			1
							47.56	2.41	19.96	30.05			
17	4-Cl		138-140	Ethanol-Water	13	$C_{20}H_{23}ClN_4O$	60.22	5.81	21.07	8.89		9.1	4.3
							60.04	6.10	21.29	8.99			
18	4-Cl		183-185	Acetonitrile	59	$C_{15}H_{10}Cl_3H_5$	49.14	2.75	19.10	29.01	0.1		0.1
							49.14	2.92	19.14	29.04			
19	3,4-	$NHCH_3$	164-166	Methanol; Ethyl Acetate	53	$C_{13}H_{11}N_5$	65.81 (d)	4.67	29.52		0.7	0.3	0.3
							65.63	4.71	29.40				
20	3,4-	$N(CH_3)_2$	171-172	Ethanol; Methanol; Ethyl Acetate	50	$C_{14}H_{13}N_5$	66.92 (d)	5.21	27.87		1.3	0.5	0.5
							66.63	5.26	27.77				
21	3,4-		141-143	95% Ethanol	83	$C_{17}H_{18}N_6$	66.65 (d)	5.92	27.43		1.5	0.3	0.3
							66.71	6.00	27.43				
22	3,4-	$NHCH_2CH_2N(C_2H_5)_2$	96-98	Ethanol-Water	64	$C_{16}H_{22}N_6$	67.06 (d)	6.88	26.07		3.4	0.3	0.3
							66.81	6.86	26.10				
23	3-Br	$NHCH_3$	149-151	Ethanol	70	$C_9H_8BrN_5$ (h)	40.62	3.03	26.33		5.7	3.1	0.5
							40.58	3.43	26.62				
24	3-Br	$N(CH_3)_2$	160-163	Ethanol	71.5	$C_{10}H_{10}BrN_5$ (i)	42.87	3.60	25.00		4.7	2.7	
							42.58	3.64	24.94				
25	3-Br		139-141	Acetonitrile	45	$C_{20}H_{23}BrN_6O$ (j)	54.18	5.23	18.96		0.5		0.3
							54.35	5.35	18.92				
26	3,4-Cl_2	NH_2	268-269	Acetonitrile; Benzene	31	$C_8H_5Cl_2N_5$	39.69	2.08	28.93	29.29		3C (12.9)	9.3
							39.75	2.24	29.22	29.17			
27	3,4-Cl_2	$NHCH_3$	229-231	Methanol; Ethyl Acetate	83	$C_9H_7Cl_2N_5$	42.21	2.76	27.34		2C	6.9	5.2
							42.30	2.68	27.61				

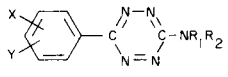
Table I continued

Compound Number	X,Y	NR_1R_2	M.p., °C	Recrystallization Solvent	Yield, % (a)	Molecular Formula	Analysis, %, C	H	Calcd./ N	Found Cl	Suppressive Antimalarial Effects in Mice Single s.c. Dose Δ MST, T or C[k] after Mg./Kg. 640	320	160
28	3,4-Cl_2	$N(CH_3)_2$	157-158.5	95% Ethanol	86	$C_{10}H_9Cl_2N_5$	44.47	3.36	25.93		5C	2C	8.5
							44.26	3.41	26.18				
29	3,4-Cl_2		154-155.5	Ethanol	57	$C_{13}H_{14}Cl_2N_6$	48.01 (d)	4.34	25.84		1.1		0.7
							48.10	4.33	25.89				
30	3,4-Cl_2	$NH(CH_2)_2N(C_2H_5)_2$	98-100	Ethanol	85	$C_{14}H_{18}Cl_2N_6$	49.28 (d)	5.32	24.63		6.9	3.7	1.7
							49.47	5.34	24.87				
31	3,4-Cl_2	$N(CH_3)[CH(CH_3)_2]$	129-131	Ethanol	57	$C_{12}H_{13}Cl_2N_5$	48.33	4.39	23.49	23.78	7.1	5.7	4.1
							48.16	4.36	23.37	23.68			

(a) Yields are of isolated, analytically pure materials, calculated from the corresponding 3-bromo-6-(substituted phenyl)-1,2,4,5-tetrazines. (b) Lit. (10) m.p. 205-207°. (c) Lit. (10) m.p. 174-174.5°. (d) Elemental analysis by the usual procedures gives incomplete combustion. The correct analysis was obtained using a tungsten oxide catalyst and a two minute combustion time. (e) Lit. (10) m.p. 243-244°. (f) Melts with decomposition. (g) Lit. (10) m.p. 200-201° dec. (h) *Anal.* Calcd. for Br: 30.04. Found: 29.96. (i) *Anal.* Calcd. for Br: 28.53. Found: 28.54. (j) *Anal.* Calcd. for Br: 18.03. Found: 17.78. (k) Δ MST is the mean survival time (days) of treated mice (MSTT) minus the mean survival time (days) of control mice (MSTC). In the present study the MSTC ranged from 6.1 to 6.5 days. T signifies the number of toxic deaths occurring on days 2-5 after infection which are attributed to drug action. C indicates the number of mice surviving at 60 days postinfection and termed "cured." (l) Test results not available for compound 16.

Table II

Synthesis of *N,N*-Dialkyl-6-(substituted phenyl)-1,2,4,5-tetrazin-3-amines IV, Prepared by Scheme II and Effects Against Trophozoite-Induced *Plasmodium berghei* in Mice



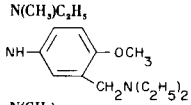
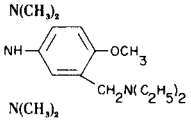
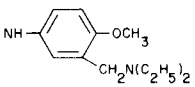
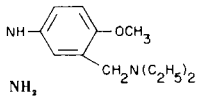
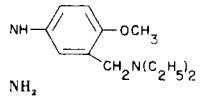
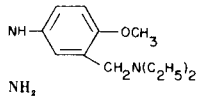
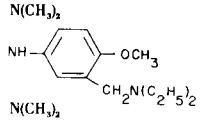
Compound Number	X,Y	NR_1R_2	M.p., °C	Recrystallization Solvent	Yield, % (a)	Molecular Formula	Analysis, %, C	H	Calcd./ N	Found	Suppressive Antimalarial Effects in Mice Single s.c. Dose Δ MST, T or C[l] after Mg./Kg. 640	320	160
32	3,4-Cl_2	$NH(CH_2)_2N(CH_3)_2$	126-129	Ethanol-Water	67	$C_{13}H_{16}Cl_2N_6$	47.72	4.93	25.68		5.1	1.1	0.3
							47.64	4.88	25.89				
33	3,4-Cl_2	$N(CH_3)C_4H_9$	55-56	95% Ethanol	44	$C_{13}H_{15}Cl_2N_5$	50.01	4.84	22.43		0.5		0.5
							49.98	4.70	22.18				
34	3,4-Cl_2	$N(CH_3)C_2H_5$	101-103	Ethanol-Water	57	$C_{11}H_{11}Cl_2N_5$	46.50	3.90	24.65		9.9	7.7	5.5
							46.32	4.06	24.60				
35	3,4-Cl_2		239 (g)	Ethanol	14	$C_{20}H_{22}Cl_2N_6O$ •HCl	51.13	4.93	17.89		0.1		0.1
							50.75	5.10	17.56				
36	4-Br	$N(CH_3)_2$	193-194	Ethanol	95	$C_{10}H_{10}BrN_5$	42.88	3.60	25.00		7.2	4.2	1.8
							43.21	3.62	24.90				
37	4-Br	$NHCH_3$	222-223	Ethanol	100	$C_9H_8BrN_5$	40.62	3.03	26.32		5.2	3.4	0.6
							40.56	3.03	26.24				
38	4-Br	NH_2	247 (g)	Ethanol	55	$C_8H_6BrN_5$	38.12	2.40	27.78		5.0	2.4	0.4
							38.09	2.55	27.57				
39	4-CH_3	NH_2	233-234	Ethanol	71	$C_9H_9N_5$	57.75	4.85	37.41		0.5		0.3
							58.00	4.86	37.67				
40	4-CH_3	$NHCH_3$	195-196	Ethanol	87	$C_{10}H_{11}N_5$	59.69	5.51	34.80		0.3		0.3
							59.18	5.51	34.85				
41	4-CH_3	$N(CH_3)_2$	146-147	Ethanol	70	$C_{11}H_{13}N_5$	61.38	6.09	32.53		3.5	2.7	1.5
							61.30	6.11	32.45				
42	4-CH_3		249 (g)	Ethanol	29	$C_{21}H_{26}N_6O$ •HCl (b)	60.79	6.56	20.25		0.3		0.3
							60.81	6.58	20.11				
43	4-NO_2	$N(CH_3)_2$	308-311	Benzene	45	$C_{10}H_{10}N_6O_2$	48.78	4.09	34.13		0.6		0.3
							48.03	4.02	33.74				
44	3,4,5-$(OCH_3)_3$	$NHCH_3$	191-193	Ethanol	66	$C_{12}H_{15}N_5O_3$	51.98	5.45	25.26		0.5		0.3
							51.86	5.44	25.38				
45	3,4,5-$(OCH_3)_3$	$N(CH_3)_2$	154-156	Ethanol	61	$C_{13}H_{17}N_5O_3$	53.60	5.88	24.04		0.5		0.3
							53.46	5.85	23.85				
46	3,4,5-$(OCH_3)_3$	NH_2	288-290	Ethanol	53	$C_{11}H_{13}N_5O_3$	50.19	4.98	26.60		0.5		0.3
							49.75	5.10	26.39				
47	3,4,5-$(OCH_3)_3$		128-130	Ethanol	29	$C_{23}H_{30}N_6O_4$ •HCl•H_2O (e)	54.27	6.53	16.51		0.5		0.5
							54.46	6.66	16.09				

Table II continued

Compound Number	X,Y	NR_1R_2	M.p., °C	Recrystallization Solvent	Yield, % (a)	Molecular Formula	Analysis, %, C	H	Calcd./ Found N	Suppressive Antimalarial Effects in Mice Single s.c. Dose Δ MST, T or C[l] after Mg./Kg. 640	320	160
48	3-CF_3	NH_2	217-218	95% Ethanol	69	$C_9H_6F_3N_5$	44.82 44.73	2.50 2.47	29.04 29.35	3C (-0.1)	3C (20.4)	8.3
49	3-CF_3	$NHCH_3$	176-177	Ethanol-Water	83	$C_{10}H_8F_3N_5$	47.07 46.97	3.16 3.24	27.44 27.37	8.7	5.9	4.3
50	3-CF_3	$N(CH_3)_2$	136-137	Ethanol-Water	73	$C_{11}H_{10}F_3N_5$	49.07 48.88	3.74 3.82	26.01 25.84	6.3	3.9	2.1
51	3-CF_3		157-159	Ethanol-Water	33	$C_{21}H_{23}F_3N_6O$ $\cdot O \cdot 1H_2O$ (f)	58.08 57.78	5.38 5.28	19.35 19.38	6.5	4.5	0.9
52	4-OCH_3	NH_2	257-259	Ethanol	82	$C_9H_9N_5O$ $\cdot O \cdot 05H_2O$ (h)	52.96 52.72	4.49 4.53	34.31 33.86	0.1		0.1
53	4-OCH_3	$NHCH_3$	179-182	Ethanol	87	$C_{10}H_{11}N_5O$	55.29 55.21	5.11 5.14	32.24 31.94	0.5		0.3
54	4-OCH_3	$N(CH_3)_2$	128-131 (k)	Ethanol	82	$C_{11}H_{13}N_5O$	57.13 56.68	5.66 5.72	30.28 29.96	0.3		0.1
55	4-OCH_3		223-224	Ethanol (c)	35	$C_{21}H_{26}N_6O_2$ $\cdot HCl$ (d)	58.53 58.23	6.31 6.54	19.50 19.33	0.3		-0.1
56	4-CF_3	NH_2	199-201	(i)	68	$C_9H_6F_3N_5$	44.82 44.62	2.51 2.56	29.04 29.09	1T (0.7)	2C (0.2)	4C (10.9)
57	4-CF_3	$NHCH_3$	193-195	Ethanol	67	$C_{10}H_8F_3N_5$	47.06 46.79	3.16 2.92	27.45 27.48	2T (0.2)	5C	2C (11.9)
58	4-CF_3	$N(CH_3)_2$	195-197	(i)	87	$C_{11}H_{10}F_3N_5$	49.07 48.85	3.74 3.74	26.01 25.97	3C (5.4)	4C (32.9)	2C (11.9)
59	4-CF_3		153-155	Isopropyl Alcohol-Water	35	$C_{21}H_{23}F_3N_6O$	58.32 58.36	5.36 5.31	19.44 19.60	4C, 1T	2.3	0.7
60	4-F	NH_2	240-242	Ethanol	82	$C_9H_6FN_5$	50.27 50.37	3.16 3.19	36.63 36.70	4T (-0.1)	3T (1.9)	1C (9.7)
61	4-F	$NHCH_3$	168-169	95% Ethanol	100	$C_9H_8FN_5$	52.68 52.52	3.93 4.08	34.13 33.95	5T	8.2	8.7
62	4-F	$N(CH_3)_2$	149-151	(i)	90	$C_{10}H_{10}FN_5$	54.79 54.73	4.60 4.71	31.94 32.10	5T	1T (7.7)	7.2
63	4-NHAc	$N(CH_3)_2$	214-218	Ethanol	91 (j)	$C_{12}H_{14}N_6O$	55.80 55.64	5.46 5.45	32.54 32.64	4.7	1.1	0.5
64	3-C_6H_5	NH_2	205-208 (k)	(i)	88	$C_{14}H_{11}N_5$	67.45 67.35	4.45 4.31	28.10 28.31	1.6		0.0
65	3-C_6H_5	$NHCH_3$	154-156	(i)	61	$C_{15}H_{13}N_5$	68.42 68.13	4.98 4.81	26.60 26.31	0.4		0.2
66	3-C_6H_5	$N(CH_3)_2$	121-123	(i)	63	$C_{16}H_{15}N_5$	69.29 69.14	5.45 5.27	25.26 24.97	1.4		0.0
67	3-C_6H_5		142-145	Isopropyl Alcohol-Water	26	$C_{26}H_{28}N_6O$	70.88 70.60	6.41 6.35	19.08 18.99	0.0		0.0
68	4-$N(CH_3)_2$	$N(CH_3)_2$	243-245	Ethanol	27	$C_{12}H_{16}N_6$	59.00 58.82	6.60 6.91	34.40 34.18	0.8		0.6

(a) Yields are of isolated, analytically pure materials, unless noted otherwise, calculated from the corresponding 3-(methylthio)-6-(substituted phenyl)-1,2,4,5-tetrazines. (b) *Anal.* Calcd. for Cl: 8.54. Found: 8.80. (c) After recrystallization this material was triturated in boiling ethyl acetate. (d) *Anal.* Calcd. for Cl: 8.23. Found: 8.30. (e) *Anal.* Calcd. for Cl: 6.96. Found: 6.86. *Anal.* Calcd. for H_2O: 3.54. Found: 3.08. (f) *Anal.* Calcd. for 0.1 H_2O: 0.41. Found: 0.52. (g) Melts with decomposition. (h) *Anal.* Calcd. for 0.05 H_2O: 0.44. Found: 0.20. (i) Material obtained from the reaction mixture and not recrystallized. (j) Crude yield. (k) With prior softening. (l) See footnote k of Table I.

2-[(3,5-dichlorophenyl)methylene]hydrazinecarboximidamide mononitrate (I, Scheme I, X = 3-Cl, Y = 5-Cl) was utilized, the only product isolated was 3-(3,5-dichlorophenyl)-6-methoxy-1,2,4,5-tetrazine in less than 1% yield. Both 3-thiophenecarboxaldehyde and 3-pyridinecarboxaldehyde have been reported to yield only explosive solids in this sequence and none of the desired 3-bromotetrazines (III) (10). Finally, the 3-bromo-6-(substituted phenyl)-1,2,4,5-tetrazines prepared in this manner were obtained in poor and erratic yields.

Because of these shortcomings, alternative routes to the desired tetrazines were explored. Although these efforts were abandoned at various stages of their development with the advent of Scheme II, it will be useful to summarize them here for the information of other investigators in these heterocyclic systems. The first alternative sequence (Scheme IV) required 3,4-dichlorobenzoic acid 2-(hydrazinocarbonyl)hydrazide (**86**) as its key intermediate. Its synthesis was achieved by treatment of 3,4-dichlorobenzoic acid hydrazide (**84**) with ethyl chlorothioformate to give 3,4-dichlorobenzoic acid 2-[(ethylthio)carbonyl]hydrazide (**85**, 54% yield), followed by the reaction with hydrazine to provide **86** in 77% yield. It was our hope that this material could be cyclodehydrated to give 6-(3,4-dichlorophenyl)-4,5-dihydro-1,2,4,5-tetrazin-3(2*H*)-one (**88**), which could be oxidized to 6-(3,4-dichlorophenyl)-

1,2,4,5-tetrazin-3-ol (**95**). Chlorination of **95** would then afford the direct precursor to the desired aminotetrazines.

Treatment of **86** with aqueous sodium carbonate, however, gave instead the isomeric 4-amino-5-(3,4-dichlorophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (**87**) in 59% yield. Confirmation of the triazole structure was obtained by: (a) formation of a benzylidene derivative (**89**, 53% yield); (b) lack of reactivity of the product with ferric chloride, which would have rapidly oxidized the dihydrotetrazine structure to the easily detectable tetrazine; (c) the similarity of the ultraviolet spectrum of **87** to that of **91** which was prepared analogously by the treatment of **90** with aqueous sodium carbonate, and which because of its substitution could cyclize only to the triazole structure and not to the tetrazine. Cyclization on oxygen to the alternative 2-hydrazino-1,3,4-oxadiazole structure was eliminated by the presence of the carbonyl band at 1700 cm^{-1} in the infrared spectrum, typical of the cyclic urea structure **87**.

Treatment of **86** with dilute hydrochloric acid resulted only in hydrolysis to 3,4-dichlorobenzoic acid. Treatment of **86** with [(4-methylphenyl)sulfonyl] chloride provided **92** in 71% yield. It was hoped that treatment of this material with base would enable anion formation on the terminal nitrogen which could then effect the intramolecular cyclization to the desired tetrazine (**88**). Instead, treatment of **92** with aqueous sodium carbonate gave 3,4-dichlorobenzoic acid hydrazide (**84**, 30% yield) as the only isolable product. Other non-nucleophilic base systems were not investigated.

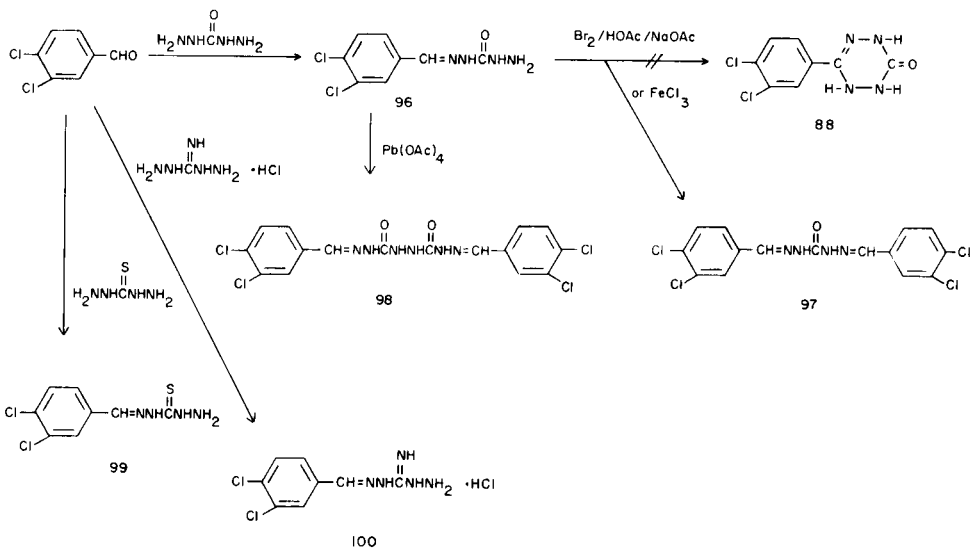
Attempted chlorination of both **85** and **86** with thionyl chloride resulted in the isolation only of 5-(3,4-dichlorophenyl)-1,3,4-oxadiazol-2-(3*H*)one (**93**, 19 and 27% yield, respectively), which could be reconverted to **86** by treatment with hydrazine (50% yield).

Since the formation of **87** in preference to **88** upon cyclodehydration might not be viewed as surprising upon examination of the energetics of the respective systems, it appeared advantageous to provide a higher oxidation state intermediate, *i.e.*, **94**. Cyclodehydration could then proceed only to the fully aromatic **95** with the exclusion of the 5-membered ring product. However, attempted oxidation of **86** with ferric chloride provided, instead of **94**, the oxadiazole **93** (19% yield). Other nonacidic oxidizing agents were not investigated.

Scheme V was explored briefly as another alternative route to the desired tetrazines (IV). It too involved a proposed cyclization to afford 6-(3,4-dichlorophenyl)-4,5-dihydro-1,2,4,5-tetrazin-3(2*H*)one (**88**), but the key intermediate this time was 2-[(3,4-dichlorophenyl)-methylene]carbonic dihydrazide (**96**) formed from 3,4-dichlorobenzaldehyde and carbonic dihydrazide in 93% yield. Treatment of **96** with bromine and sodium acetate in acetic acid in an effort to brominate at the benzylic position with concomitant cyclic dehydrobromination to afford **88** resulted only in the isolation of 2,2′-bis[(3,4-dichlorophenyl)methylene]carbonic dihydrazide (**97**, 14% yield). This material was also obtained upon treatment of **96** with ferric chloride (25% yield). The action of lead tetraacetate on **96** led to the formation of **98** in 30% yield. The sulfur and nitrogen analogs of **96** (**99** and **100**) both gave inseparable mixtures when they were allowed to react with bromine in acetic acid.

A report (12) that the hydrazinothioxomethylhydrazone of benzeneacetaldehyde exists in the cyclic tetrahydro-6-(phenylmethyl)-1,2,4,5-tetrazine-3(2*H*)thione form (**101**) rather than in the usual linear form in which the analogous hydrazinothioxomethylhydrazone of benzaldehyde exists, (*i.e.*, **99**) prompted effort on the development of Scheme VI. It was hoped that alkylation of the

Scheme V



Scheme VI

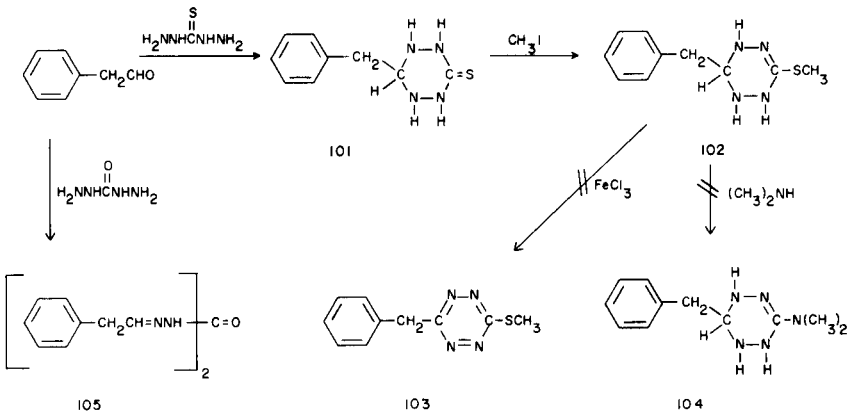
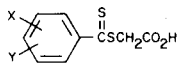


Table III

[[(Substituted phenyl)thioxomethyl]thio]acetic Acids (V)

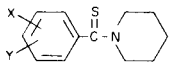


Compound No.	X,Y	M.p., °C	Recrystallization Solvent	Yield % (a)	Molecular Formula	Analysis, C	%, H	Calcd./ N	Found S
69	4-$N(CH_3)_2$	189-190 (c)	(b)	95	$C_{11}H_{13}NO_2S_2$	51.74	5.13	5.49	25.11
						51.52	5.13	5.53	24.90
70	3,4,5-$(OCH_3)_3$	122-124	Benzene-Petroleum Ether	41	$C_{12}H_{14}O_5S_2$	47.67	4.67		21.21
						47.68	4.76		21.15
71	4-CH_3	116-118 (d)	Toluene	72	$C_{10}H_{10}O_2S_2$	53.07	4.45		28.33
						53.19	4.63		28.46
72	4-OCH_3	124-125 (e)	Toluene	71	$C_{10}H_{10}O_3S_2$	49.57	4.16		26.46
						49.46	4.29		26.50
73	3-CF_3	85-87	Cyclohexane (f)	55	$C_{10}H_7F_3O_2S_2$	42.85	2.52		22.88
						42.80	2.56		23.02
74	2-CH_3	122-124 (g)	Toluene	33	$C_{10}H_{10}O_2S_2$	53.07	4.45		28.33
						53.14	4.44		28.13
75	4-NO_2	107-109 (h)	Toluene-Petroleum Ether	21	$C_9H_7NO_4S_2$	42.01	2.74	5.45	24.92
						42.01	2.73	5.52	24.42
76	4-F	122-123 (i)	Toluene	33	$C_9H_7FO_2S_2$	46.94	3.07		27.84
						47.03	2.97		27.74
77	4-CF_3	107-108	Toluene-*n*-Heptane	53	$C_{10}H_7F_3O_2S_2$	42.85	2.52		22.88
						42.67	2.72		23.18
78	4-Br	109-111	Benzene-*n*-Heptane	76 (j)	$C_9H_7BrO_2S_2$	l			
79	4-NHAc	203 (c,k)	(b)	94 (j)	$C_{11}H_{11}NO_3S_2$	l			
80	3-C_6H_5	111-113	Toluene	46	$C_{15}H_{12}O_2S_2$	62.47	4.20		22.24
						62.39	4.20		22.08
81	3,4-Cl_2	130-132	Benzene	71	$C_9H_6Cl_2O_2S_2$	38.44	2.15		
						38.40	2.11		
82	4-OH	190-193 (m)	(b)	90 (j)	$C_9H_8O_3S_2$	47.35	3.53		
						46.90	3.67		

(a) Yields are of isolated, analytically pure materials unless otherwise noted, calculated from the corresponding piperdinium bromide or from the halobenzene. (b) Material obtained from the reaction mixture and not recrystallized. (c) Melts with decomposition. (d) Lit. (13) m.p. 118-119°. (e) Lit. (13) m.p. 124-125°. (f) After recrystallization, this material was triturated in petroleum ether. (g) Lit. (13) m.p. 122-124°. (h) Lit. (16) m.p. 113-114°. (i) Lit. (16) m.p. 126-127°. (j) Yields are calculated from the corresponding thiopiperidide since the intermediate piperdinium bromides were hygroscopic and difficult to handle; yields are for slightly impure products. (k) Lit. (13) m.p. 206-208°. (l) Compound used without further purification. (m) Lit. (13) m.p. 194-197°.

Table IV

1-[(Substituted phenyl)thioxomethyl]piperidines (VIII)



X,Y	M.p., (h) °C	Recrystallization Solvent	Yield, (h) %	Molecular (i) Formula	Analysis, (g) C	%, H	Calcd./ N	Found S
4-$N(CH_3)_2$	148-149	Cyclohexane	94	$C_{14}H_{21}N_2S$	67.42	8.49	11.24	
					67.88	8.26	11.24	
3,4,5-$(OCH_3)_3$	80-84	Hexane	73					
4-CH_3	101-103	Heptane	72	$C_{13}H_{17}NS$	71.18	7.81	6.39	14.67
					71.03	7.73	6.52	14.49
4-OCH_3	104-106 (a)	Heptane-Toluene	80	$C_{13}H_{17}NOS$	66.34	7.28	5.95	13.62
					66.21	7.34	5.85	13.86
3-CF_3	78-81	Heptane	88	$C_{13}H_{14}F_3NS$	57.12	5.16	5.13	
					56.92	5.40	5.55	
4-NO_2	174-175.5 (b)	Toluene	78	$C_{12}H_{14}N_2O_2S$	57.58	5.64	11.19	
					57.50	5.71	11.31	
4-CF_3	109-112	Heptane	87	$C_{13}H_{14}F_3S$	57.13	5.16	5.12	
					57.03	5.46	5.08	
4-Br	105-108	Ethanol	90					
4-NHAc	(c)	(e)	64					
3-C_6H_5	115-118	(f)	85	$C_{18}H_{19}NS$	76.82	6.81	4.98	11.39
					76.66	6.87	4.90	11.60
3,4-Cl_2	79-83	Heptane	76					
4-OH	164-165 (d)	Toluene	87	$C_{12}H_{15}NOS$	65.12	6.83	6.33	
					64.79	6.78	6.24	

(a) Lit. (13) m.p. 104-106°. (b) Lit. (16) m.p. 176-178°. (c) M.p. not recorded; lit. (13) m.p. 201-202°. (d) Lit. (16) m.p. 168.5-170°. (e) Not recrystallized. (f) Chromatographed over silica gel with methylene dichloride. (g) Analytical data were not obtained for all compounds. (h) Melting points and yields are of isolated, analytically pure materials unless noted otherwise. (i) Molecular formula is given only if analytical results were obtained.

sulfur in **101** followed by oxidation would provide a suitable intermediate for a series of *N,N*-dialkyl-6-(substituted phenylmethyl)-1,2,4,5-tetrazin-3-amines. Treatment of **101** with iodomethane provided **102** in 96% yield. However, attempted oxidation of **102** with ferric chloride to give **103** was unsuccessful. A red liquid was isolated in poor yield, but not fully characterized. Microanalysis revealed the absence of sulfur. Moreover, thin layer chromatography indicated that **102** was converted into this same material merely on standing in solution. Efforts to replace the methylthio group of **102** with dimethylamine to give **104** resulted only in red decomposition products and unchanged starting material. Finally, efforts to prepare the oxo analog of **101** by allowing benzeneacetaldehyde to react with carbonic dihydrazide resulted only in the isolation of the bis product **105**.

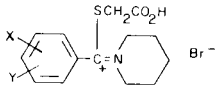
In the midst of these studies, the publication (11) of a novel synthesis (Scheme II) for 3-(methylthio)-6-phenyl-1,2,4,5-tetrazine allowed the preparation of our desired target molecules. Thus thiobenzoylation of hydrazinecarbohydrazonothioic acid methyl ester with [(phenylthioxomethyl)thio]acetic acid (V, Scheme II, X = Y = H) was reported to give 1,2-dihydro-3-(methylthio)-6-phenyl-1,2,4,5-tetrazine (VI, Scheme II, X = Y = H). Oxidation to the fully aromatic tetrazine (VII, Scheme II, X = Y = H) was effected with hydrogen peroxide.

We found that with slight modifications this sequence became a general route by which a variety of 3-(methylthio)-6-(substituted phenyl)-1,2,4,5-tetrazines could be prepared. More importantly, we found that the action of amines on these intermediates (21) readily provided the desired *N,N*-dialkyl-6-(substituted phenyl)-1,2,4,5-tetrazin-3-amines (**32-68**, Table II). Thus a safe and reproducible pathway to the tetrazin-3-amines evolved.

Most of the required [[(substituted phenyl)thioxomethyl]-thio]acetic acids (V, Table III) were synthesized readily from the corresponding benzaldehydes (Scheme III) (13). Thus, the appropriately substituted benzaldehydes were allowed to react with piperidine and sulfur to provide the 1-[(substituted phenyl)thioxomethyl]piperidines (VIII,

Table V

1-[[(Carboxymethyl)thio](substituted phenyl)methylene]piperidinium Bromides (IX)



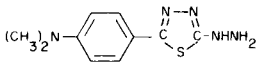
X,Y	M.p., (e) °C	Yield, (e) %	Molecular Formula (f)	Analysis, (g) C	%, H	Calcd./Found N
4-$N(CH_3)_2$	122-124	92	$C_{19}H_{29}BrN_2O_2S$	53.14	6.81	6.53
				52.64	6.36	6.56
3,4,5-$(OCH_3)_3$	a					
4-CH_3	159-160 (b)	76	$C_{15}H_{20}BrNO_2S$	50.28	5.63	3.91 (h)
				49.78	5.70	3.90
4-OCH_3	156-158 (b,c)	95				
3-CF_3	171-174	68	$C_{15}H_{17}BrF_3NO_2S$	43.70	4.16	3.40
				43.68	4.18	3.55
4-NO_2	173-175 (b,d)	89	$C_{14}H_{17}BrN_2O_4S$	43.19	4.40	7.20 (i)
				42.72	4.50	6.98
4-CF_3	175-176	93				
4-Br	(a)					
4-NHAc	(a)					
3-C_6H_5	148-153 (b)	100				
3,4-Cl_2	172-174	98	$C_{14}H_{16}BrCl_2NO_2S$	40.70	3.90	3.39
				40.64	3.82	3.53
4-OH	(a)					

(a) Obtained as a hygroscopic semisolid which was used directly in the next step without characterization. (b) Melts with decomposition. (c) Lit. (13) m.p. 156-159°. (d) Lit. (16) m.p. 167-169. (e) Melting points and yields are of unrecrystallized products, which were used without purification in the next reaction. (f) Molecular formula is given only if analytical results were obtained. (g) Analytical data were obtained only where listed. (h) Calcd. for Br: 22.31; S, 8.95. Found: Br, 22.35; S, 8.87. (i) Calcd. for S: 8.24. Found: S, 8.05.

Table IV, 64-94% yield).

Alkylation with bromoacetic acid then afforded the 1-[[(carboxymethyl)thio](substituted phenyl)methylene]-piperdinium bromides (IX, Table V, 68-100% yield). Thiohydrolysis with hydrogen sulfide gave the desired thioacetic acids (**69-73, 75, 77-82,** Table III, 21-95% yield). This sequence did suffer from some limitations however. For example, neither 2-chlorobenzaldehyde nor 2-methylbenzaldehyde resulted in the desired 1-[(substituted phenyl)thioxomethyl]piperidines (VIII, Scheme III) and 4-fluorobenzaldehyde could not be utilized in this route because of the known reactivity of the fluorine to displacement by amines. Alternatively, aromatic halides could be used as starting materials, converted to the Grignard reagent and treated successively with carbon disulfide and chloroacetic acid to provide the desired thioacetic acids (V, Scheme III) (13). The synthesis of [[(2-methylphenyl)thioxomethyl]thio]acetic acid (**74,** Table III, 33% yield) and [[(4-fluorophenyl)thioxomethyl]-thio]acetic acid (**76,** Table III, 33% yield) was accomplished in this manner. The synthesis of the 2-fluoro analog was unsuccessful, however.

The [[(substituted phenyl)thioxomethyl]thio]acetic acids (**70-73, 75-81,** Table III) were condensed with hydrazinecarbohydrazonothioic acid methyl ester to give the corresponding 1,2-dihydro-3-(methylthio)-6-(substituted phenyl)-1,2,4,5-tetrazines (VI, Table VI, 21-72% yield). The thiocondensation reaction in the case of the 2-methyl (**74**) and 4-hydroxy (**82**) analogs yielded none of the desired products and extensive decomposition of the starting materials was evident. From the 4-dimethylamino (**69**) analog, only 2-[4-(dimethylamino)phenyl]-5-hydrazino-1,3,4-thiadiazole (**83**) was isolated in 22% yield. Similar by-products were observed in minor amounts in analogous reactions.

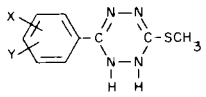


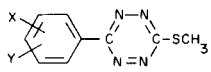
83

The dihydrotetrazines were easily oxidized to the fully aromatic tetrazines (VII, Table VI, 50-100% yield) by bromine in acetic acid. Treatment with a variety of amines then provided the final desired products (14-100% yield).

Table VI

1,2-Dihydro-3-(methylthio)-6-(substituted phenyl)-1,2,4,5-tetrazines (VI)
and 3-(Methylthio)-6-(substituted phenyl)-1,2,4,5-tetrazines (VII)





X,Y	M.p. (a,b), °C	Yield (a), %	M.p. (a), °C	Yield (a), %
3,4,5-$(OCH_3)_3$	220-222	47	133-141	94
4-CH_3	199-207	44	115-117	100
4-OCH_3	169-176	35	138-141 (d) (ethanol)	72
3-CF_3		36	(c)	97
4-NO_2		21	(c)	92
4-F		42	149-152	98
4-CF_3	176-179	48	152-154 (d,e) (2-propanol)	58
4-Br		72	184-187	61
4-NHAc		37	173-178	85
3-C_6H_5		58	104-106 (d,f) (2-propanol)	82
3,4-Cl_2		61	131-132 (d) (hexane)	50

(a) Unless otherwise noted, melting points and yields are of crude products, which were used without purification in the next reaction. (b) Upon heating, the dihydrotetrazines were oxidized to tetrazines as evidenced by the appearance of the characteristic red color of the tetrazines. This phenomenon made melting points impossible to determine for some dihydrotetrazines, and for those for which melting points are given, the melting point is preceded by softening and reddening. (c) Melting point not recorded. (d) Melting point and yield of recrystallized material. Recrystallization solvent in parenthesis. (e) *Anal.* Calcd. for $C_{10}H_7F_3N_4S$: C, 44.11; H, 2.59; N, 20.58. Found: C, 43.79; H, 2.53; N, 20.52. (f) *Anal.* Calcd. for $C_{15}H_{12}N_4S$: C, 64.26; H, 4.32; N, 19.99. Found: C, 63.84; H, 4.24; N, 19.59.

Suppressive Antimalarial Screening in Mice.

The *N,N*-dialkyl-6-(substituted phenyl)-1,2,4,5-tetrazin-3-amines (**1-68**, Tables I and II) described in the present communication were tested against a drug-sensitive strain of *P. berghei* in mice by the parenteral route (14,15). The compounds were dissolved or suspended in sesame or peanut oil and were administered to mice in a single subcutaneous dose 72 hours postinfection. Extension of the mean survival time of the treated mice is interpreted as evidence of antimalarial activity. Compounds are arbitrarily considered to be "active" when they produce at least a 100% increase in the mean survival time of treated mice. Animals that survive to 60 days are considered "cured." The mean survival time of infected control mice in the present study ranged from 6.1-6.5 days. Results are summarized in Tables I and II.

Suppressive Antimalarial Effects in Mice.

Of the sixty-five novel *N,N*-dialkyl-6-(substituted phenyl)-1,2,4,5-tetrazin-3-amines on which data has been received (**1, 4-15, 17-68**, Tables I and II), twenty three (**1, 7, 11, 14, 17, 26-28, 30, 31, 34, 36, 48-51, 56-62**) were active when administered to mice in a single subcutaneous dose ranging from 20-640 mg./kg., and most were well tolerated.

One lead compound, 6-(4-chlorophenyl)-*N,N*-dimethyl-1,2,4,5-tetrazin-3-amine (**3**, Table I) provided an extension of survival time of only 8.6 days even at 640 mg./kg. The other lead compound, 6-(4-chlorophenyl)-*N*-methyl-1,2,4,5-tetrazine-3-amine (**2**, Table I) provided an extension of survival time of 3.9 days at 160 mg./kg.; it was not tested at higher doses. Substantial enhancement of activity was obtained with 6-(3,4-dichlorophenyl)-1,2,4,5-tetrazin-3-amine (**26**, Table I) and the corresponding *N,N*-dimethyl analog (**28**, Table I) which were both curative at 320 mg./kg. and provided significant extension of survival time through 80 mg./kg. Similar enhancement was shown by 6-[3-(trifluoromethyl)phenyl]-1,2,4,5-tetrazine-3-amine (**48**, Table II) while the most active compounds were the 6-[4-(trifluoromethyl)phenyl] analogs (**56-58**, Table II) which were curative through 160 mg./kg. A wide variety of changes both of the phenyl substituents and the 3-amine provided no further advantage. Since other series appeared to have more promise, efforts to further improve the activity of this structural type were suspended.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ir and nmr spectra of all new compounds were consistent with their structures.

Aliphatic and Heterocyclic Amines.

All of these intermediates were purchased from commercial sources except 5-amino-*N*-ethyl-2-methoxybenzenemethanamine dihydrochloride, which was prepared according to the cited literature (19).

The general procedure (10) for the preparation of *N,N*-dialkyl-6-(substituted phenyl)-1,2,4,5-tetrazin-3-amines (**1-31**, Table I) by Scheme I is illustrated here with the synthesis of 6-(3-bromophenyl)-*N*-methyl-1,2,4,5-tetrazin-3-amine (**23**, Table I).

2-[(3-Bromophenyl)methylene]hydrazinecarboximidamide Mononitrate (I, X = 3-Br, Y = H).

A solution of 25 g. (0.135 mole) of 3-bromobenzaldehyde in 300 ml. of ethanol at 50° was addded to a solution of 23.4 g. (0.135 mole) of hydrazinecarboximidamide mononitrate dihydrate in 100 ml. of water. The resulting solution was heated under reflux for 1 hour and cooled overnight. The solid that formed was collected, washed with cold ethanol and then with ether. Air drying gave 36.2 g. (89%) of the product as shiny white crystals, m.p. 210° dec.

Similarly prepared were the following 2-[(substituted phenyl)-methylene]hydrazinecarboximidamide mononitrates. The 3,4-dichlorophenyl derivative had m.p. 223° dec (92%). The 4-chlorophenyl derivative had m.p. 223° dec (81%).

Anal Calcd. for $C_8H_9ClN_4 \cdot HNO_3$: C, 37.00; H, 3.88; N, 26.97. Found: C, 37.00; H, 3.83; N, 27.28.

The 2-naphthalenyl derivative had m.p. 218-220° dec (84%).

Anal. Calcd. for $C_{12}H_{12}N_4 \cdot HNO_3$: C, 52.36; H, 4.76; N, 25.44. Found: C, 52.06; H, 4.74; N, 25.68.

The 4-(dimethylamino)phenyl derivative had m.p. 204-212° dec (81%) and the 3,5-dichlorophenyl derivative had m.p. 227° dec (95%).

3-(3-Bromophenyl)-1-(1*H*-tetrazol-5-yl)-5-formazancarboximidamide (II, X = 3-Br, Y = H).

A solution of 8.32 g. (0.12 mole) of sodium nitrite in 65 ml. of water was added by remote control to a cold solution of 12.16 g. (0.118 mole) of 1*H*-tetrazol-5-amine hydrate in 400 ml. of water and 29 ml. of concentrated hydrochloric acid. Addition took 2 minutes during which time the temperature rose from 0.9° to 3.5°. When addition was complete, the solution was stirred for an additional 8 minutes and rapidly transferred by suction into a stirred slurry of 36.2 g. (0.119 mole) of 2-[(3-bromophenyl)methylene]hydrazinecarboximidamide mononitrate in 1200 ml. of pyridine at -6°. The resulting orange slurry rapidly warmed to 19°. The slurry was stirred for 2 minutes and diluted by remote addition of 1600 ml. of water. The solid was then dissolved by manual addition of 10% sodium hydroxide. The resulting deep red solution was poured onto 2 kg. of ice and made acidic with concentrated hydrochloric acid. The solid that formed was collected and washed successively with water, methanol and ether. The resulting wet solid was used in the next step without purification.

Similarly prepared were the following 3-(substituted phenyl)-1-(1*H*-tetrazol-5-yl)-5-formazancarboximidamides: 3,4-dichlorophenyl, 4-chlorophenyl, 2-naphthalenyl and 3,5-dichlorophenyl. These formazans are unstable compounds (10) and were not characterized. They were not isolated dry but were used wet in the next reaction. When this reaction was attempted with 2-[[4-(dimethylamino)phenyl]methylene]hydrazinecarboximidamide mononitrate, no isolable product was obtained.

Caution! The diazonium salt of 1*H*-tetrazol-5-amine is explosive. On one occasion a cold, stirred solution of the salt detonated. Following this accident, the above formazan synthesis was carried out by remote control behind a reinforced concrete wall.

3-Bromo-6-(3-bromophenyl)-1,2,4,5-tetrazine (III, X = 3-Br, Y = H).

The wet solid 3-(3-bromophenyl)-1-(1*H*-tetrazol-5-yl)-5-formazancarboximidamide was added portionwise to a solution of 35 g. of bromine in 400 ml. of acetic acid at 55°, at a rate sufficient to maintain the temperature at 55-60°. When addition was complete the mixture was heated at 55° for 30 minutes and poured into water. The solid that formed was collected, air dried and extracted into ethyl acetate. The extracts were evaporated and the residue was recrystallized from a mixture of ethyl acetate and petroleum ether to give 6.6 g. (18%) of the product as a pink solid, m.p. 124-125°.

Anal. Calcd for $C_8H_4Br_2N_4$: C, 30.41; H, 1.28; N, 17.73. Found: C, 30.61; H, 1.32; N, 17.99.

Warming the filtrate and addition of more petroleum ether provided a second crop of 1.4 g. of the product, m.p. 123-125°. The mother liquors were evaporated and the residue triturated with petroleum ether to give 2.1 g. of the product suitable for use in the following reaction, m.p. 109-115°. (Total yield calculated over 2 steps from 2-[(3-bromophenyl)-methylene]hydrazinecarboximidamide mononitrate is 27%).

Similarly prepared were the following 3-bromo-6-(substituted phenyl)-1,2,4,5-tetrazines. Yields are calculated over two steps from the corresponding 2-[(substituted phenyl)methylene]hydrazinecarboximidamide mononitrate.

The 3,4-dichlorophenyl derivative had m.p. 150-153° (ethyl acetate), 18%. Analysis of this material established it to be an 80:20 mixture of 3-chloro-6-(3,4-dichlorophenyl)-1,2,4,5-tetrazine and 3-bromo-6-(3,4-dichlorophenyl)-1,2,4,5-tetrazine, suitable for use in the next reaction.

The 4-chlorophenyl derivative had m.p. 173-174.5° (ethyl acetate) (lit. (10) m.p. 176-177°), 25%.

Anal. Calcd. for $C_8H_4BrClN_4$: C, 35.39; H, 1.48; N, 20.64. Found: C, 35.68; H, 1.69; N, 20.86.

The 2-naphthalenyl derivative had m.p. 158-164° (ethyl acetate), 16%.

Anal. Calcd. for $C_{12}H_7BrN_4$: C, 50.20; H, 2.46; N, 19.51. Found: C, 50.43; H, 2.68; N, 19.63.

When this reaction was attempted with 2-[(3,5-dichlorophenyl)-methylene]hydrazinecarboximidamide mononitrate, the only product isolated was 3-(3,5-dichlorophenyl)-6-methoxy-1,2,4,5-tetrazine, m.p. 70-100° (ethanol), <1%.

Anal. Calcd. for $C_9H_6Cl_2N_4O$: C, 42.05; H, 2.35; Cl, 27.58. Found: C, 41.70; H, 2.56; Cl, 27.40.

6-(3-Bromophenyl)-*N*-methyl-1,2,4,5-tetrazin-3-amine (**23**, Table I).

To a solution of 2.53 g. (0.0095 mole) of 3-bromo-6-(3-bromophenyl)-1,2,4,5-tetrazine in 100 ml. of benzene was added with stirring 2.5 g. (0.032 mole) of 40% aqueous methanamine. The reaction was allowed to stir for 20 minutes and then evaporated to dryness on the steam bath with a stream of air passing over the surface. The residue was triturated with water, collected by filtration, and recrystallized from ethanol to give 1.2 g. (56%) of the product as a red solid, m.p. 149-151°.

The other *N,N*-dialkyl-6-(substituted phenyl)-1,2,4,5-tetrazin-3-amines (**1-31**) in Table I were prepared similarly.

The general procedure for the preparation of *N,N*-dialkyl-6-(substituted phenyl)-1,2,4,5-tetrazin-3-amines (**32-68**, Table II) by Scheme II is illustrated with the synthesis of *N,N*-dimethyl-6-[3-(trifluoromethyl)-phenyl]-1,2,4,5-tetrazin-3-amine (**50**, Table II).

1-[Thioxo[3-(trifluoromethyl)phenyl]methyl]piperidine (VIII, X = 3-CF_3, Y = H, Table IV) (13).

To a mixture of 52.2 g. (0.3 mole) of 3-(trifluoromethyl)benzaldehyde and 40 ml. (0.4 mole) of piperidine was added 12.8 g. (0.4 mole) of sublimed sulfur. The mixture was heated under reflux for 1 hour and the warm, dark syrup was poured into 400 ml. of vigorously stirred ice water containing 50 ml. of 2*N* hydrochloric acid. The resulting gum was induced to solidify by triturating in the acid. The *p*H was maintained at about 4 by addition of more acid as needed. The yellow solid was collected, washed with water and dried *in vacuo* at 50°. Recrystallization from heptane yielded 72.4 g. (88.3%) of the product as beige crystals, m.p. 78-81°.

Similarly prepared were the other 1-[(substituted phenyl)thioxomethyl]-piperidines in Table IV. In some instances the piperidines formed oils initially which were isolated by extraction rather than filtration.

1-[[(Carboxymethyl)thio][3-(trifluoromethyl)phenyl]methylene]piperidinium Bromide (IX, X = 3-CF_3, Y = H, Table V) (13).

To a solution of 71.3 g. (0.261 mole) of 1-[thioxo[3-(trifluoromethyl)-phenyl]methyl]piperidine in 300 ml. of dry benzene was added 41.7 g. (0.3 mole) of bromoacetic acid, and the mixture was stirred at room temperature for 20 hours. The white solid that separated was collected

and washed with ether to give 72.5 g. (67.5%) of the product, m.p. 171-174°.

Similarly prepared were the other 1-[[(carboxymethyl)thio](substituted phenyl)methylene]piperidinium bromides in Table V.

[[Thioxo[3-(trifluoromethyl)phenyl]methyl]thio]acetic Acid (**73**, Table III) (13).

Hydrogen sulfide was bubbled into a stirred, cooled solution of 72 g. (0.175 mole) of 1-[[(carboxymethyl)thio][3-(trifluoromethyl)phenyl]methylene]piperidinium bromide in 500 ml. of anhydrous ethanol for 3 hours. The red solution was allowed to remain at room temperature overnight. The solution was evaporated to a red gum which was treated with ether to extract the product from the insoluble piperidinium hydrobromide. The ether extract was concentrated to a red oil which was crystallized from cyclohexane. The crystalline material was triturated with petroleum ether to give 26.9 g. (55%) of the product, m.p. 85-87°.

Similarly prepared were the other [[(substituted phenyl)thioxomethyl]-thio]acetic acids (**69-72, 75, 77-82**) in Table III which were synthesized as shown in Scheme III.

[[(2-Methylphenyl)thioxomethyl]thio]acetic Acid (**74**, Table III) (13).

Under nitrogen, a solution of 68.5 g. (0.4 mole) of 2-bromotoluene in 250 ml. of ether was added slowly to 9.75 g. (0.4 mole) of magnesium turnings in 90 ml. of ether containing a crystal of iodine so that a steady relfux was maintained. The mixture was stirred and heated gently for 1 hour and then chilled with an ice bath. To the mixture was added dropwise, 34.2 g. (0.45 mole) of carbon disulfide. The mixture was allowed to come to room temperature overnight. Ice and water were added and the layers were separated. To the aqueous layer was added a solution of 37.7 g. (0.4 mole) of chloroacetic acid, neutralized with *ca.* 21 g. of sodium carbonate in 300 ml. of water. After remaining 24 hours at room temperature the mixture was acidified with concentrated hydrochloric acid. The resulting yellow-orange semisolid was rinsed with water and dissolved in ether. The solution was washed with water and with saturated sodium chloride solution, dried over sodium sulfate and concentrated to dryness *in vacuo*. Recrystallization from toluene afforded 29.7 g. (33%) of the product, m.p. 122-124° (lit. (13) 122-124°). An additional 2.6 g., m.p. 121-123°, was collected from the aqueous reaction mixture filtrate for a total yield of 32.3 g. (36%).

The 4-fluoro analog (**76**, Table III) was prepared similarly from 4-fluoroiodobenzene.

1,2-Dihydro-3-(methylthio)-6-[3-(trifluoromethyl)phenyl]-1,2,4,5-tetrazine (VI, X = 3-CF_3, Y = H, Table VI).

To a stirred mixture of 38.7 g. (0.156 mole) of hydrazinecarbohydrazonothioic acid methyl ester hydroiodide (17) in 750 ml. of pyridine, cooled to 0°, was added during 15 minutes a solution of 22.0 ml. (0.156 mole) of triethylamine in 75 ml. of pyridine. To the resulting yellow solution maintained at 0° was added during 110 minutes, a solution of 21.9 g. (0.078 mole) of [[thioxo[3-(trifluoromethyl)phenyl]methyl]-thio]acetic acid (**73**, Table III), 5.3 g. (0.078 mole) of 1*H*-imidazole (18) and 11.0 ml. (0.078 mole) of triethylamine in 375 ml. of pyridine. The resulting amber solution was stirred at 0° for 60 minutes and diluted with a large volume of ice water. Filtration gave 7.7 g. (36%) of the crude product as a light orange solid.

Similarly prepared were the other 1,2-dihydro-3-(methylthio)-6-(substituted phenyl)-1,2,4,5-tetrazines in Table VI.

3-(Methylthio)-6-[3-(trifluoromethyl)phenyl]-1,2,4,5-tetrazine (VII, X = 3-CF_3, Y = H, Table VI).

A mixture of 7.7 g. (0.028 mole) of 1,2-dihydro-3-(methylthio)-6-[3-(trifluoromethyl)phenyl]-1,2,4,5-tetrazine in 100 ml. of acetic acid was heated to 40°. To the yellow solution was added 31.0 ml. (0.031 mole) of a 1.0 *M* solution of bromine in acetic acid. The resulting red solution was stirred at room temperature for 1 hour and diluted with a large volume of ice water. Filtration gave 7.4 g. (97%) of the product as a red solid.

Similarly prepared were the other 3-(methylthio)-6-(substituted phenyl)-1,2,4,5-tetrazines in Table VI.

N,N-Dimethyl-6-[3-(trifluoromethyl)phenyl]-1,2,4,5-tetrazin-3-amine (**50**, Table II).

To a mixture of 1.8 g. (0.0066 mole) of 3-(methylthio)-6-[3-(trifluoromethyl)phenyl]-1,2,4,5-tetrazine in 10 ml. of ethanol was added 2.5 ml. (0.022 mole) of 40% aqueous dimethylamine. The resulting mixture was heated under reflux for 1 hour, becoming a red solution. Upon cooling, the solution deposited a red solid which was collected. The filtrate was diluted with water and filtered to give a second crop of crude product. The two crops were combined and recrystallized from ethanol-water to give 1.3 g. (73%) of the product as a shiny red solid, m.p. 136-137°.

The other *N,N*-dialkyl-6-(substituted phenyl)-1,2,4,5-tetrazin-3-amines (**32-67**) in Table II, were prepared similarly with the exception of compound **68**, which was synthesized as described below.

6-[4-(Dimethylamino)phenyl]-*N,N*-dimethyl-1,2,4,5-tetrazin-3-amine (**68**, Table II).

A solution of 2.0 g. (0.009 mole) of 6-(4-fluorophenyl)-*N,N*-dimethyl-1,2,4,5-tetrazin-3-amine (**62**, Table II) and 4.0 g. (0.09 mole) of anhydrous dimethylamine in 50 ml. of *N,N*-dimethylformamide was heated at 150° in a bomb for 20 hours. The solution was diluted with a large volume of ice water, and the scarlet solid was collected. Two recrystallizations from ethanol gave 0.6 g. (27%) of product, m.p. 243-245°.

5-[4-(Dimethylamino)phenyl]-2-hydrazino-1,3,4-thiadiazole (**83**).

Using the procedure for the synthesis of 1,2-dihydro-3-(methylthio)-6-[3-(trifluoromethyl)phenyl]-1,2,4,5-tetrazine, [[[4-(dimethylamino)phenyl]-thioxomethyl]thio]acetic acid (**69**, Table III) was condensed with hydrazinecarbohydrazonothioic acid methyl ester to give the title compound, m.p. 210-213°, 22%.

Anal. Calcd. for $C_{10}H_{13}N_5S$: C, 51.04; H, 5.56; N, 29.76. Found: C, 51.09; H, 5.80; N, 29.53.

3,4-Dichlorobenzoic Acid 2-[(Ethylthio)carbonyl]hydrazide (**85**).

To a solution of 25.0 g. (0.122 mole) of 3,4-dichlorobenzoic acid, hydrazide (20) in 125 ml. of dimethylsulfoxide, was added dropwise with cooling 16.7 g. (0.134 mole) of ethyl chlorothioformate. The brown solution was stirred overnight and diluted with water. The tan solid was filtered and recrystallized from benzene to give 19.2 g. (54%) of product, m.p. 111-138°. Recrystallization of 2.0 g. of this material from benzene (charcoal) gave 1.5 g. of product (75% recovery), m.p. 134-143°.

Anal. Calcd. for $C_{10}H_{10}Cl_2N_2O_2S$: C, 40.96; H, 3.43. Found: C, 40.89; H, 3.45.

3,4-Dichlorobenzoic Acid 2-(Hydrazinocarbonyl)hydrazide (**86**).

To a solution of 4.3 g. (0.015 mole) of 3,4-dichlorobenzoic acid, 2-[(ethylthio)carbonyl]hydrazide (**85**) in 50 ml. of ethanol was added 0.93 ml. (0.03 mole) of anhydrous hydrazine, and the resulting solution was heated under reflux overnight. After cooling, the white solid present was collected to give 3.0 g. (77%) of product, m.p. 197-204°. Recrystallization of 1.2 g. of this material from ethanol gave 1.0 g. (83% recovery) of analytical material, m.p. 198-199°.

Anal. Calcd. for $C_8H_8Cl_2N_4O_2$: C, 36.52; H, 3.06; N, 21.30. Found: C, 36.51; H, 3.16; N, 21.53.

4-Amino-5-(3,4-dichlorophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (**87**).

A mixture of 3.0 g. (0.011 mole) of 3,4-dichlorobenzoic acid 2-(hydrazinocarbonyl)hydrazide (**86**), 1.2 g. (0.011 mole) of sodium carbonate and 300 ml. of water was heated under reflux for 7 hours. The solution that resulted was allowed to remain at room temperature overnight and the solid that formed was collected. The filtrate was acidified with concentrated hydrochloric acid, cooled and filtered to give another crop of white solid. The two crops were combined and recrystallized from ethanol to give 1.6 g. (59%) of impure product. A second recrystallization of 1.2 g. of this material from ethanol gave 1.0 g. (83% recovery) of analytical material, m.p. 267° dec.

Anal. Calcd. for $C_8H_6Cl_2N_4O$: C, 39.21; H, 2.47; N, 22.86. Found: C, 39.16; H, 2.82; N, 22.84.

5-(3,4-Dichlorophenyl)-4-[[(3,4-dichlorophenyl)methylene]amino]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (**89**).

A mixture of 3.0 g. (0.012 mole) of 4-amino-5-(3,4-dichlorophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (**87**), 4.3 g. (0.024 mole) of 3,4-dichlorobenzaldehyde and 50 ml. of pyridine was heated under reflux overnight. The resulting dark brown solution was poured into water, and filtered. The crude product was recrystallized from ethanol to give 2.6 g. (53%) of analytical material, m.p. 274.5-275.5°.

Anal. Calcd. for $C_{15}H_8Cl_4N_4O$: C, 44.81; H, 2.00; N, 13.93. Found: C, 44.51; H, 2.35; N, 13.87.

3,4-Dichlorobenzoic Acid 2-[(2,2-Dimethylhydrazino)carbonyl]hydrazide (**90**).

To a solution of 10.0 g. (0.034 mole) of 3,4-dichlorobenzoic acid 2-[(ethylthio)carbonyl]hydrazide (**85**) in 100 ml. of ethanol, was added 2.8 ml. (0.037 mole) of 1,1-dimethylhydrazine and the resulting solution was heated under reflux overnight. The reaction mixture was diluted with water and filtered to give 7.3 g. of white solid which contained a significant amount of a by-product identified as 5-(3,4-dichlorophenyl)-1,3,4-oxadiazole-2(3*H*)-one (**93**), as well as the desired product. Recrystallization first from 95% ethanol, and then from ethanol gave 1.6 g. (16%) of analytically pure product, m.p. 211-213°.

Anal. Calcd. for $C_{10}H_{12}Cl_2N_4O_2$: C, 41.25; H, 4.16; N, 19.24. Found: C, 41.15; H, 4.21; N, 19.13.

5-(3,4-Dichlorophenyl)-4-(dimethylamino)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (**91**).

A mixture of 0.2 g. (0.0007 mole) of 3,4-dichlorobenzoic acid 2-[(2,2-dimethylhydrazino)carbonyl]hydrazide (**90**), 0.1 g. (0.001 mole) of sodium carbonate and 20 ml. of water was heated under reflux for 18 hours. The mixture was cooled and filtered to remove a small amount of solid which was discarded. The filtrate was acidified with concentrated hydrochloric acid, cooled and filtered. The white solid was recrystallized from ethanol to give the product, m.p. 226-228°.

Anal. Calcd. for $C_{10}H_{10}Cl_2N_4O$: C, 43.98; H, 3.69; N, 20.51. Found: C, 43.78; H, 3.87; N, 20.45.

3,4-Dichlorobenzoic Acid, 2-[2-[(4-Methylphenyl)sulfonyl]hydrazinocarbonyl]hydrazide (**92**).

To a mixture of 1.0 g. (0.00034 mole) of 3,4-dichlorobenzoic acid 2-(hydrazinocarbonyl)hydrazide (**86**) in 50 ml. of pyridine at 40° was added 0.7 g. (0.0004 mole) of [(4-methylphenyl)sulfonyl]chloride. The resulting yellow solution was stirred at room temperature for 18 hours. Addition of ice water precipitated a cream solid which was collected to give 1.6 g. of crude product, m.p. 225-228° dec. Recrystallization from ethanol gave 1.0 g. (71%) of product, m.p. 232° dec. The nmr of this compound had four separate nitrogen proton absorptions, indicating that tosylation had indeed occurred on the terminal nitrogen.

Anal. Calcd. for $C_{15}H_{14}Cl_2N_4O_4S$: C, 43.18; H, 3.38; N, 13.43. Found: C, 43.23; H, 3.35; N, 13.29.

Hydrolysis of **92** to give **84**.

A mixture of 0.7 g. (0.002 mole) of 3,4-dichlorobenzoic acid 2-[2-(4-methylphenyl)sulfonyl]hydrazinocarbonyl]hydrazide (**92**) and 0.2 g. (0.002 mole) of sodium carbonate in 25 ml. of water was heated under reflux for 1 hour. The resulting yellow solution was cooled and filtered to give 0.1 g. (30%) of product. Recrystallization from water gave analytical material, m.p. 153-168° dec (lit (20) m.p. 169-171°). The ir of this product was identical to that of an authentic sample of 3,4-dichlorobenzoic acid hydrazide.

Anal. Calcd. for $C_7H_6Cl_2N_2O$: C, 41.00; H, 3.16; N, 13.66. Found: C, 40.86; H, 3.14; N, 13.62.

5-(3,4-Dichlorophenyl)-1,3,4-oxadiazol-2-(3*H*)one (**93**).

a) Preparation from **85**.

A solution of 4.0 g. (0.014 mole) of 3,4-dichlorobenzoic acid 2-[(ethylthio)carbonyl]hydrazide (**85**) in 50 ml. of thionyl chloride was heated under reflux for 15 hours. The residue obtained after evaporation *in vacuo* was recrystallized twice from benzene to give 0.6 g. (19%) of product, m.p. 193-195°.

Anal. Calcd. for $C_8H_4Cl_2N_2O_2$: C, 41.59; H, 1.74; N, 12.12. Found: C, 41.53; H, 2.03; N, 12.42.

b) Preparation from **86** with Thionyl Chloride.

The same product (**93**, identified by tlc and ir) was obtained in 27% crude yield by allowing **86** to react similarly with thionyl chloride.

c) Preparation from **86** with Ferric Chloride.

To a mixture of 1.5 g. (0.0057 mole) of 3,4-dichlorobenzoic acid 2-(hydrazinocarbonyl)hydrazide (**86**) in 100 ml. of ethanol cooled in an ice bath was added 7.5 ml. (0.015 mole) of a 2.0 *N* aqueous ferric chloride solution. After standing at room temperature for 45 minutes, the solution was diluted with ice water and filtered to give a grey solid. Recrystallization from 95% ethanol gave 0.25 g. (19%) of product, m.p. 185-193°. The ir of this product was identical to that of **93** as synthesized above.

Anal. Calcd. for $C_8H_4Cl_2N_2O_2$: C, 41.59; H, 1.74; N, 12.12. Found C, 41.25; H, 1.97; N, 12.30.

Treatment of **93** with Hydrazine.

A mixture of 0.2 g. (0.0009 mole) of 5-(3,4-dichlorophenyl)-1,3,4-oxadiazol-2-(3*H*)one (**93**) in 25 ml. of ethanol and 3.0 ml. (0.00095 mole) of a 1.0% ethanolic hydrazine solution was heated under reflux for 18 hours. The resulting solution was evaporated *in vacuo* and the residue recrystallized from ethanol to give 0.1 g. (50%) of white solid, m.p. 191-193°. The ir and nmr of this product were identical to that of **86** as synthesized above.

Anal. Calcd. for $C_9H_8Cl_2N_4O_2$: C, 36.52; H, 3.06; N, 21.30. Found: C, 36.16; H, 3.22; N, 20.90.

2-[(3,4-Dichlorophenyl)methylene]carbonic Dihydrazide (**96**).

A solution of 5.0 g. (0.029 mole) of 3,4-dichlorobenzaldehyde in 40 ml. of ethanol was added to a hot solution of 26.1 g. (0.29 mole) of carbonic dihydrazide in 200 ml. of water over a period of 1 hour. The reaction mixture was heated on a steam bath during the course of the addition. After cooling, the product was filtered to give 6.7 g. (93%), m.p. 218-219.5° dec.

Anal. Calcd. for $C_8H_8Cl_2N_4O$: C, 38.88; H, 3.26; N, 22.40. Found: C, 38.44; H, 3.38; N, 22.47.

The thio- and imino- analogs (**99** and **100**, respectively) were prepared similarly.

2-[3,4-Dichlorophenyl)methylene]carbonothioic Dihydrazide (**99**).

This compound had m.p. 212° dec, 74% crude yield.

Anal. Calcd. for $C_8H_8Cl_2N_4S$: C, 36.52; H, 3.06; N, 21.29. Found: C, 36.15; H, 3.40; N, 21.15.

2-[(3,4-Dichlorophenyl)methylene]carbonimidic Dihydrazide Hydrochloride (**100**).

This compound had m.p. 238-240° dec, 88% crude yield.

Anal. Calcd. for $C_8H_9Cl_2N_3 \cdot HCl$: C, 34.00; H, 3.57; N, 24.79. Found: C, 34.01; H, 3.66; N, 24.50.

2,2'-Bis[(3,4-dichlorophenyl)methylene]carbonic Dihydrazide (**97**).

a) From **96** with Bromine.

A mixture of 8.0 g. (0.032 mole) of 2-[(3,4-dichlorophenyl)methylene]-carbonic dihydrazide (**96**), 13.3 g. (0.16 mole) of anhydrous sodium acetate, and 100 ml. of acetic acid, cooled to room temperature by a water bath, was treated dropwise over 30 minutes with a solution of 1.8 ml. (0.032 mole) of liquid bromine in 10 ml. of acetic acid. The mixture was stirred for an additional hour and then diluted with 700 ml. of water. Filtration gave 7.0 g. of white solid, m.p. 185-200°. Recrystallization from ethanol gave 2.9 g., m.p. 210-213°. Another recrystallization from a methanol-ethanol mixture gave 1.35 g., m.p. 225-226°. A second crop of 0.4 g. was obtained. These two crops were combined, recrystallized from methanol, and dried *in vacuo* at 100° for 24 hours to give 0.9 g. (14%) of the product, m.p. 228-229°.

Anal. Calcd. for $C_{15}H_{10}Cl_4N_4O$: C, 44.59; H, 2.49; N, 13.87. Found: C, 44.24; H, 2.92; N, 13.97.

b) From **96** with Ferric Chloride.

To a mixture of 2.5 g. (0.01 mole) of 2-[(3,4-dichlorophenyl)methylene]-

carbonic dihydrazide (**96**) in 50 ml. of dimethylsulfoxide, cooled in an ice bath, was added 5.0 ml. (0.01 mole) of a 2.0*N* aqueous ferric chloride solution. An amber solution resulted, with evolution of gas. After standing at room temperature overnight, the solution was diluted with water and filtered to give 2.7 g. of solid. Trituration in hot methanol gave an insoluble solid which was discarded. Cooling the triturate gave 0.5 g. (25%) of product, m.p. 218-225°. The ir and nmr of this product were identical to that of **97** as synthesized above.

2-[(3,4-Dichlorophenyl)methylene]-2′-[[2-[(3,4-dichlorophenyl)methylene]-hydrazino]carbonyl]carbonic Dihydrazide Monohydrate (**98**).

To a stirred mixture of 1.0 g. (0.0041 mole) of 2-[(3,4-dichlorophenyl)-methylene]carbonic dihydrazide (**96**) in 100 ml. of acetic acid, cooled in an ice bath, was added portionwise 1.8 g. (0.0041 mole) of lead tetraacetate. A new white solid precipitated. The mixture was stirred for an additional 20 minutes while cooled by the ice bath, and then for 1 hour at room temperature. The mixture was diluted with water and filtered to give a white solid. Recrystallization gave 0.3 g. (30%) of product, m.p. 242-244°.

Anal. Calcd. for $C_{16}H_{12}Cl_4N_6O_2 \cdot H_2O$: C, 40.03; H, 2.94; N, 17.50; Cl, 29.54; H_2O, 3.75. Found: C, 40.07; H, 3.17; N, 17.71; Cl, 29.45; H_2O, 3.76.

Tetrahydro-6-(phenylmethyl)-1,2,4,5-tetrazine-3-(2*H*)thione (**101**).

To a stirred solution of 30.0 g. (0.28 mole) of carbonothioic dihydrazide in 200 ml. of hot water was added dropwise over 20 minutes, 34.0 g. (0.28 mole) of benzeneacetaldehyde in 100 ml. of ethanol. The reaction mixture was stirred and heated on a steam bath, without a condenser, during the course of the addition and for an additional 10 minutes. After cooling, the product was collected by filtration, and recrystallized from methanol to give 26.3 g. (45%) of white plates, m.p. 163-165° [lit. (12) m.p. 168-170° dec.].

Anal. Calcd. for $C_9H_{12}N_4S$: C, 51.90; H, 5.81; N, 26.90. Found: C, 51.96; H, 5.98; N, 27.17.

1,2,3,4-Tetrahydro-6-(methylthio)-3-(phenylmethyl)-1,2,4,5-tetrazine (**102**).

A solution of 4.5 ml. (0.048 mole) of iodomethane in 50 ml. of 95% ethanol was added dropwise to a mixture of 10.0 g. (0.048 mole) of tetrahydro-6-(phenylmethyl)-1,2,4,5-tetrazine-3-(2*H*)thione (**101**) in 48 ml. (0.048 mole) of 1.0*N* sodium hydroxide solution under nitrogen. The resulting mixture was stirred at room temperature for 4.5 hours under nitrogen. The mixture was filtered to give a white solid which was washed well with water. The product (10.2 g., 96%, m.p. 147-150°) slowly decomposed on standing to a red-brown oil. The product gave a stable diacetyl compound when treated with acetic anhydride, m.p. 174-176°. *Anal.* Calcd. for $C_{14}H_{18}N_4O_2S$: C, 54.88; H, 5.92; N, 18.29; S, 10.46. Found: C, 55.22; H, 6.00; N, 18.30; S, 10.62.

2,2′-Bis(2-phenylethylidene)carbonic Dihydrazide (**105**).

To a stirred solution of 5.0 g. (0.056 mole) of carbonic dihydrazide in 50 ml. of water heated under reflux was added dropwise over 40 minutes, 6.7 g. (0.056 mole) of benzeneacetaldehyde in 40 ml. of ethanol. The product precipitated as a white solid during the course of the addition. When the addition was complete, the mixture was cooled and filtered to give 7.8 g. of product. Recrystallization from ethanol gave 4.3 g. (53%) of analytical material, m.p. 187-189°.

Anal. Calcd. for $C_{17}H_{18}N_4O$: C, 69.37; H, 6.16; N, 19.03. Found: C, 69.28; H, 6.21; N, 18.77.

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