Synthesis of 6-(Arylthio)- and 6-[(Arylmethyl)thio]-1,2,4,5-tetrazin-3-amines and *N*-Phenyl- and *N*-(phenylmethyl)-1,2,4,5-tetrazine-3,6-diamines (1) as Potential Antimalarial Agents

*Judith L. Johnson, Barbara Whitney and Leslie M. Werbel**

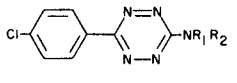
Warner-Lambert/Parke-Davis, Pharmaceutical Research Division, Department of Chemistry, Ann Arbor, Michigan 48105

Received September 10, 1979

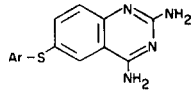
Alkylation of tetrahydro-1,2,4,5-tetrazine-3,6-dithione with iodomethane and 1,2-dichloro-4-(chloromethyl)benzene, respectively (Scheme I, **4**) followed by oxidation afforded 3,6-bis(methylthio)- and 3,6-bis[[(3,4-dichlorophenyl)methyl]thio]-1,2,4,5-tetrazines (**6**, **15**). The reaction of **15** with amines provided the 6-[(arylmethyl)thio]-1,2,4,5-tetrazin-3-amines (**16**) while sequential displacement of both methylthio groups in **6** afforded the tetrazine-diamines **8** and **10**. Hydrolysis of *N*,*N*-dimethyl-6-(methylthio)-1,2,4,5-tetrazin-3-amine (**11**) with potassium hydroxide afforded the tetrazin-3-ol (**12**) which was chlorinated and then treated with 4-chlorobenzenethiol to provide **13**. The target 6-substituted-1,2,4,5-tetrazin-3-amines displayed negligible antimalarial activity.

J. Heterocyclic Chem., **17**, 501 (1980).

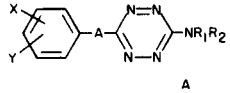
The disclosure (2) of the antimalarial properties of 6-(4-chlorophenyl)-*N*-methyl-1,2,4,5-tetrazin-3-amine (**1a**) and its *N*,*N*-dimethyl analog (**1b**) prompted the exploration of a series of related analogs which we have recently described (3). In addition we felt it would be desirable to examine the preparation of a series of analogs in which a hetero atom spacer was introduced between the tetrazine ring and the aryl group. Use of such groupings had been particularly successful (4) in attaining high antimalarial activity among a series of diamino quinazolines (**2**). In this communication we describe the synthesis of 1,2,4,5-tetrazin-3-amines in which amino (**3a**), methylamino (**3b**), thio (**3c**) and methylthio (**3d**) spacers were introduced between the aryl group and the tetrazine moiety.



	NR_1R_2
1a	$NHCH_3$
b	$N(CH_3)_2$



2



	A
3a	NH
b	CH_2NH
c	S
d	CH_2S

Chemistry.

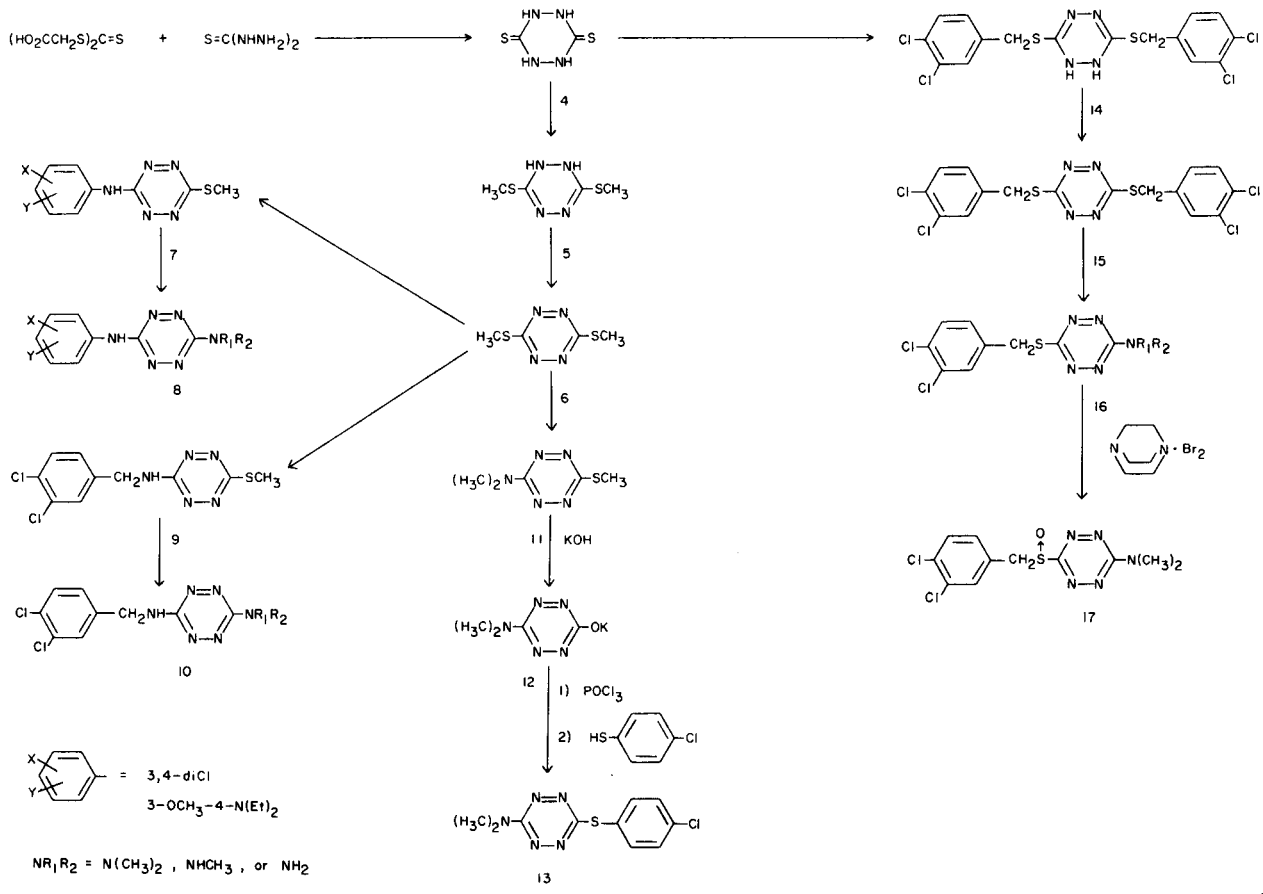
The synthetic approach to the desired 1,2,4,5-tetrazin-3-amines is outlined in Scheme I (5). Tetrahydro-1,2,4,5-tetrazine-3,6-dithione (or *p*-dithiourazine) (**4**), the common precursor, was prepared according to Sandström (6) from carbonothioic dihydrazide and mercaptoacetic acid diester with carbonotrithioic acid (7) in 45% yield. Alkylation of the dithione with methyl iodide and with 1,2-dichloro-4-(chloromethyl)benzene afforded the corresponding 1,2-dihydro-3,6-bis(methylthio)-1,2,4,5-tetrazine (**5**) (6,8) and 3,6-bis[[(3,4-dichlorophenyl)methyl]thio]-1,2-dihydro-1,2,4,5-tetrazine (**14**). These compounds autooxidized and generally were not purified prior to the oxidation with ferric chloride to the more stable 3,6-bis(methylthio)-1,2,4,5-tetrazine (**6**) and 3,6-bis[[(3,4-dichlorophenyl)methyl]thio]-1,2,4,5-tetrazine (**15**).

Displacement of one thiomethyl group on 3,6-bis(methylthio)-1,2,4,5-tetrazine (**6**) with a benzenamine or a benzenemethanamine afforded the corresponding *N*-phenyl-6-(methylthio)-1,2,4,5-tetrazin-3-amine (**7**) or *N*-(phenylmethyl)-6-(methylthio)-1,2,4,5-tetrazin-3-amine (**9**). A second displacement with ammonia, methylamine, and dimethylamine afforded the desired 1,2,4,5-tetrazine-3,6-diamines **8** and **10**.

To obtain the desired phenylthio analog, 3,6-bis(methylthio)-1,2,4,5-tetrazine (**6**) was allowed to react first with dimethylamine to afford *N*,*N*-dimethyl-6-(methylthio)-1,2,4,5-tetrazin-3-amine (**11**) (8) and then treated with a solution of potassium hydroxide in ethanol to give 6-(dimethylamino)-1,2,4,5-tetrazin-3-ol,

0022-152X/80/030501-06$02.25

Scheme I



monopotassium salt (**12**). Chlorination with phosphorus oxychloride followed by treatment with 4-chlorobenzenethiol in the presence of potassium carbonate afforded the desired 6-[(4-chlorophenyl)thio]-*N*,*N*-dimethyl-1,2,4,5-tetrazin-3-amine (**13**).

Reaction of 3,6-bis[[(3,4-dichlorophenyl)methyl]thio]-1,2,4,5-tetrazine (**15**) with ammonia, methylamine, or dimethylamine produced the desired 6-[[(3,4-dichlorophenyl)methyl]thio]-1,2,4,5-tetrazin-3-amines (**16a,b,c**). Oxidation of **16a** with the bromine complex of 1,4-diazabicyclo[2.2.2]octane (9) produced 6-[[*N*-(3,4-dichlorophenyl)methyl]sulfinyl]-*N*,*N*-dimethyl-1,2,4,5-tetrazin-3-amine (**17**). Attempts to oxidize further to the sulfone with 30% hydrogen peroxide in acetic acid resulted in apparent decomposition.

The antimalarial potency of these tetrazines (**6-17**) were evaluated parenterally against a normal drug sensitive strain of *P. berghei* in mice (10,11). The drugs were dissolved or suspended in sesame or peanut oil and were administered in a single subcutaneous dose 72 hours after infection.

Generally these compounds were inactive in this test system. Only two compounds (**16b,c**) were equivalent to the lead compound **1a** producing an extension of survival time of 8-10 days at the highest dose used (640 mg./kg.). Thus the use of a hetero atom spacer in this system does not provide an advantage in terms of increased biological activity.

EXPERIMENTAL (12)

Tetrahydro-1,2,4,5-tetrazine-3,6-dithione (4).

The procedure of Sandström (6) was followed. Carbonothioic dihydrazide (31.9 g., 0.3 mole) was taken up in 1 l. of boiling water and filtered into a solution of 67.9 g. (0.3 mole) of mercaptoacetic acid, diester with carbonotrithioic acid (7) in 650 ml. of 1*N* sodium hydroxide solution. The mixture was allowed to remain at room temperature for three days and filtered. The filter cake was washed with a little cold water and dried *in vacuo* at 40° to afford 22 g. (45%) of the desired product, m.p. 194° dec. [lit. m.p. 176° (6)]; uv (methanol): λ 300 ϵ = 20,400 which is identical with that reported in the literature (6).

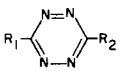
Anal. Calcd. for $C_2H_4N_4S_2$: C, 16.21; H, 2.72; N, 37.81; S, 43.27. Found: C, 15.97; H, 2.96; N, 38.03; S, 43.45.

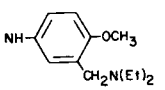
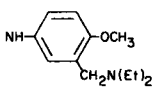
1,2-Dihydro-3,6-bis(methylthio)-1,2,4,5-tetrazine (5).

Under nitrogen, a solution of 1.42 g. (0.01 mole) of iodomethane in 5 ml. of 95% ethanol was added to a stirred solution of 0.74 g. (0.005 mole) of tetrahydro-1,2,4,5-tetrazine-3,6-dithione (**4**) in 10 ml. of 1 *N* sodium hydroxide, and the mixture

Table I

3,6-Disubstituted Tetrazines



No.	R_1	R_2	M.p., °C	Purified Yield, %	Purification Solvent	Formula	Analyses Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
6	SCH_3	SCH_3	80-81°	84	Hexane	$C_4H_6N_4S_2$ (a)	27.57	27.75	3.47	3.61	32.16	32.16
7a	SCH_3	NH C_6H_3-3,4-Cl_2	202-204°	33	Toluene	$C_9H_7Cl_2N_5S$	37.51	37.54	2.45	2.82	24.31	24.68
7b	SCH_3		104-106°	56	2-PrOH	$C_{15}H_{22}N_6OS$ (b)	53.87	53.94	6.63	6.72	25.13	25.14
8a	$N(CH_3)_2$	NHC_6H_3-3,4-Cl_2	253-256°	28	$CHCl_3$:EtOH (5:1)	$C_{10}H_6Cl_2N_6$	42.12	41.82	3.54	3.49	29.47	29.20
8b	$NHCH_3$	NHC_6H_3-3,4-Cl_2	264° dec.	37	EtOH	$C_9H_8Cl_2N_6$	39.87	39.95	2.97	3.10	31.00	30.93
8c	NH_2	NHC_6H_3-3,4-Cl_2	260° dec.	40	CH_3CN	$C_8H_6Cl_2N_6$	37.17	37.19	2.35	2.75	32.68	32.28
8d	$N(CH_3)_2$		137-139°	37	2-PrOH	$C_{16}H_{25}N_7O$	57.98	58.18	7.60	7.52	29.59	29.65
9	SCH_3	$NHCH_2C_6H_3$-3,4-Cl_2	128-130°	45	EtOH	$C_{10}H_9Cl_2N_5S$	39.74	39.76	3.00	3.29	23.18	23.40
10a	$N(CH_3)_2$	$NHCH_2C_6H_3$-3,4-Cl_2	142-143°	22	(c)	$C_{11}H_{12}Cl_2N_6$	44.16	44.08	4.04	4.06	28.09	28.25
10b	$NHCH_3$	$NHCH_2C_6H_3$-3,4-Cl_2	124-126°	21	EtOH	$C_{10}H_{10}Cl_2N_6$	42.12	41.85	3.54	3.79	29.48	29.24
11	$N(CH_3)_2$	SCH_3	38-40°	30	Pet. ether	$C_5H_9N_5S$	35.07	35.01	5.30	5.61	40.91	40.81
12	$N(CH_3)_2$	OK	300° dec.	62	(c)	$C_4H_6N_5OK$ (d)	26.80	26.06	3.38	3.98	39.08	38.00
13	$N(CH_3)_2$	SC_6H_4-4-Cl	76-78°	32	2-PrOH	$C_{10}H_{10}ClN_5S$	44.86	44.85	3.76	3.90	26.16	26.13
15	-SCH_2-C_6H_3-3,4Cl_2	$SCH_2C_6H_3$-3,4-Cl_2	132-133°	63	Toluene	$C_{16}H_{10}Cl_4N_4S_2$	37.51	37.74	2.45	2.74	24.31	24.45
16a	$N(CH_3)_2$	$SCH_2C_6H_3$-3,4-Cl_2	103-105°	74	2-PrOH:hexane (4:1)	$C_{11}H_{11}Cl_2N_5S$	41.78	41.67	3.51	3.72	22.15	22.07
16b	$NHCH_3$	$SCH_2C_6H_3$-3,4-Cl_2	113-116°	53	Cyclohexane	$C_{10}H_9Cl_2N_5S$	39.74	39.68	3.00	3.13	23.18	23.26
16c	NH_2	$SCH_2C_6H_3$-3,4-Cl_2	141-142°	21	C_6H_6-heptane, toluene	$C_6H_7Cl_2N_5S$ (e)	37.51	37.74	2.45	2.74	24.31	24.45
17	$N(CH_3)_2$	$SOCH_2$-C_6H_3-3,4Cl_2	145-147°	83	2-PrOH	$C_{11}H_{11}Cl_2N_5OS$	39.77	39.54	3.34	3.45	21.08	21.11

(a) Calcd. for S, 36.80; Found, 37.10. (b) Calcd. for S, 9.57; Found, 9.56. (c) Crystallized from reaction mixture. (d) Calcd. for K, 21.82; Found, 21.83. Although the C,H,N analysis of this material was not within 0.4%, the assigned structure was confirmed by ir and nmr spectra and by the preparation of analytically pure (**13**) from this material. (e) Calcd. for S, 11.13; Found, 11.31.

was allowed to stir for 3 hours. The precipitate that formed was collected and washed with water to give 0.46 g. (52%) of product, m.p. 195-198°. Recrystallization from ethanol afforded 0.38 g. (43.2%), m.p. 196-198° [(lit. m.p. 192-193° (6) and 196-198° (8)].

Anal. Calcd. for $C_4H_8N_4S_2$: C, 27.26; H, 4.57; N, 31.79; S, 36.38. Found: C, 27.43; H, 4.47; N, 31.74; S, 36.20.

3,6-Bis[[(3,4-dichlorophenyl)methyl]thio]-1,2-dihydro-1,2,4,5-tetrazine (**14**).

The procedure was the same as that for **5**, using 3.9 g. (0.02 mole) of 1,2-dichloro-4-(chloromethyl)benzene and 1.5 g. (0.01 mole) of tetrahydro-1,2,4,5-tetrazine-3,6-dithione (**4**). The crude product (3.8 g.) was recrystallized from ethanol/water to afford 2 g. (43%) of product.

Anal. Calcd. for $C_{16}H_{12}Cl_4N_4S_2$: C, 41.21; H, 2.60; N, 12.02; S, 13.75. Found: C, 41.27; H, 2.78; N, 11.98; S, 13.92.

3,6-Bis(methylthio)-1,2,4,5-tetrazine (**6**).

To a hot solution of 8.1 g. (0.046 mole) of 1,2-dihydro-3,6-bis(methylthio)-1,2,4,5-tetrazine (**5**) in 400 ml. of ethanol was added 46 ml. of 2 *N* ferric chloride. The resulting red solution was allowed to stand one hour, diluted with 275 ml. of water and chilled to afford 6.7 g. (84%) of red crystalline product, m.p. 79-80°. Recrystallization of 2 g. from hexane gave 1.57 g. m.p. 80-81° [lit. m.p. 83.5-84° (6,8)].

3,6-Bis[[(3,4-dichlorophenyl)methyl]thio]-1,2,4,5-tetrazine (**15**).

This compound was prepared in the same manner as was **6**.

N-(3,4-Dichlorophenyl)-6-(methylthio)-1,2,4,5-tetrazin-3-amine (**7a**).

A mixture of 5.4 g. (0.031 mole) of 3,6-bis(methylthio)-1,2,4,5-tetrazine (**6**), 5.6 g. (0.034 mole) of 3,4-dichlorobenzenamine, and 25 ml. of dimethylsulfoxide was heated to an internal temperature of 165°. With the continued application of the same amount of heat during 6 hours, the temperature fell to 106°. The mixture was allowed to remain at room temperature for two weeks. The dark precipitate which accumulated was collected, washed with ethanol and recrystallized from toluene (charcoal) to give 2.94 g. (33%) of the desired product, m.p. 202-204°.

N-[3-[(Diethylamino)methyl]-4-methoxyphenyl]-6-(methylthio)-1,2,4,5-tetrazin-3-amine (**7b**).

A solution of 14.1 g. (0.05 mole) of 5-amino-*N*,*N*-diethyl-2-methoxybenzenemethanamine, dihydrochloride (13) in water was made basic with 10% sodium hydroxide solution and extracted with chloroform. The chloroform extract was washed with water, dried over anhydrous sodium sulfate and concentrated *in vacuo* to dryness. A mixture of the residual oil and 8 g. (0.046 mole) of 3,6-bis(methylthio)-1,2,4,5-tetrazine (**6**) in 85 ml. of ethanol was heated under reflux for 9 hours, allowed to cool, filtered to remove a small amount of dark precipitate and concentrated *in vacuo* to dryness. The residue was dissolved in benzene and applied on a 950 g. column of alumina (Alcoa F-20). The column was eluted first with 3 l. of benzene, then with 1 l. each of 5%, 10% and 15% ethyl acetate in benzene to elute impurities and finally with 6 l. of 25% ethyl acetate in benzene to elute the product ($R_f \cong 0.4$, alumina-30% ethyl acetate/benzene). The product-containing eluant was evaporated *in vacuo* to give 8.8 g. (57%) of dark purple powder. Recrystallization of 3.6 g. from 2-propanol afforded 2.0 g. (55.6% recrystallization yield) of the title compound, m.p. 104-106° with prior sintering.

N'-(3,4-Dichlorophenyl)-*N*,*N*-dimethyl-1,2,4,5-tetrazine-3,6-diamine (**8a**).

A mixture of 1.79 g. (0.006 mole) of *N*-(3,4-dichlorophenyl)-6-(methylthio)-1,2,4,5-tetrazin-3-amine (**7a**), 15 ml. of 40% aqueous dimethylamine and 175 ml. of ethanol was heated under reflux for 5 hours, cooled and filtered to afford 0.51 g. of purple precipitate. The filtrate was evaporated *in vacuo* and the residue was triturated with chloroform to give 0.15 g. The two crops were combined, treated with 125 ml. of a boiling chloroform:ethanol (5:1) mixture and filtered to collect about 0.1 g. of product, m.p. 253-256°. The filtrate afforded an additional 0.37 g., m.p. 253-256°, which was combined with the first crop (total yield = 0.47 g., 28%).

N'-[3-[(Diethylamino)methyl]-4-methoxyphenyl]-*N*,*N*-dimethyl-1,2,4,5-tetrazine-3,6-diamine (**8d**) and *N'*-[(3,4-Dichlorophenyl)-methyl]-*N*,*N*-dimethyl-1,2,4,5-tetrazine-3,6-diamine (**10a**).

These compounds were similarly prepared by allowing the requisite (methylthio)tetrazine (**7b** and **9**) to react with dimethylamine.

N-(3,4-Dichlorophenyl)-*N'*-methyl-1,2,4,5-tetrazine-3,6-diamine (**8b**).

A mixture of 1.15 g. (0.004 mole) of *N*-(3,4-dichlorophenyl)-6-(methylthio)-1,2,4,5-tetrazin-3-amine (**7a**), 1 ml. of 40% aqueous methylamine and 80 ml. of ethanol was heated under reflux for 6 hours. After each hour, an additional 1-2 ml. of aqueous 40% methylamine was added. At the end of 6 hours tlc (silica-benzene) indicated that the reaction mixture contained primarily product (R_f = 0.04, violet color) and very little starting material (R_f = 0.28, pink color). The reaction mixture was filtered hot and cooled to afford 0.7 g. of crude product. Recrystallization from ethanol gave 0.4 g. (37%), m.p. 262-264° dec.

N-[(3,4-Dichlorophenyl)methyl]-*N'*-methyl-1,2,4,5-tetrazine-3,6-diamine (**10b**) and 6-[[(3,4-Dichlorophenyl)methyl]thio]-*N*-methyl-1,2,4,5-tetrazin-3-amine (**16b**).

These two compounds were prepared analogously.

N-(3,4-Dichlorophenyl)-1,2,4,5-tetrazine-3,6-diamine (**8c**).

A mixture of 1.4 g. (0.049 mole) of *N*-(3,4-dichlorophenyl)-6-(methylthio)-1,2,4,5-tetrazin-3-amine (**7a**) and 5 g. of ammonia in 150 ml. of ethanol was shaken in a bomb at 100° for 17 hours, allowed to cool and filtered to collect 0.4 g. of crude product. Concentration of the filtrate to 30 ml. afforded an additional 0.3 g. The two crops were combined and recrystallized from acetonitrile to give 0.5 g. (40%) of the title compound, m.p. 260° dec.

N-[(3,4-Dichlorophenyl)methyl]-6-(methylthio)-1,2,4,5-tetrazin-3-amine (**9**).

A mixture of 5.0 g. (0.0287 mole) of 3,6-bis(methylthio)-1,2,4,5-tetrazine (**6**) and 5.25 g. (0.0299 mole) of 3,4-dichlorobenzenemethanamine in 70 ml. of ethanol was heated under reflux for 5 hours and cooled to afford 4.76 g. (54.9%) of product, m.p. 124-126°. The filtrate was combined with an additional gram of 3,4-dichlorobenzenemethanamine, heated under reflux for 5 hours and cooled to give 0.9 g., m.p. 122°, total crude yield = 65%. Recrystallization from ethanol afforded red crystals m.p. 128-130°.

N,*N*-Dimethyl-6-(methylthio)-1,2,4,5-tetrazin-3-amine (**11**).

A solution of 5.0 g. (0.029 mole) of 3,6-bis(methylthio)-1,2,4,5-tetrazine (**6**) and 3.3 g. (0.029 mole) of 40% aqueous

dimethylamine in 40 ml. of ethanol was heated under reflux 1.5 hour and concentrated to dryness. The residue was dissolved in chloroform and the solution was washed with water, dried (magnesium sulfate) and concentrated to dryness *in vacuo*. The residue was extracted with hexane and the extract was concentrated to dryness. Two recrystallizations of the residue from petroleum ether afforded 1.5 g. (30%) of the product, m.p. 38-40° [lit. m.p. 38.5-40.5° (8)].

6-(Dimethylamino)-1,2,4,5-tetrazin-3-ol, Monopotassium Salt (**12**).

A solution of 3 g. (0.018 mole) of *N,N*-dimethyl-6-(methylthio)-1,2,4,5-tetrazin-3-amine (**11**) in 75 ml. of ethanol was treated with a solution of 3 g. of potassium hydroxide in 75 ml. of ethanol. The mixture was warmed on the steam bath for 10 minutes, cooled and filtered to collect 2 g. (62%) of the metallic red product, m.p. 300° dec.

6-[(4-Chlorophenyl)thio]-*N,N*-dimethyl-1,2,4,5-tetrazin-3-amine (**13**).

To 25 ml. of phosphorus oxychloride was added 2.5 g. (0.0139 mole) of 6-(dimethylamino)-1,2,4,5-tetrazin-3-ol, monopotassium salt (**12**). The mixture was heated under reflux for 1 hour, allowed to cool, filtered and concentrated *in vacuo*. The residual oil was dissolved in water, made basic with triethylamine, and extracted with dichloromethane. The extract was washed, dried over sodium sulfate and evaporated *in vacuo* to give 3 g. of crude 6-chloro-*N,N*-dimethyl-1,2,4,5-tetrazin-3-amine, R_f (silica gel - benzene) = 0.42, which was used immediately in the next step.

A mixture of 3 g. of crude 6-chloro-*N,N*-dimethyl-1,2,4,5-tetrazin-3-amine, 2 g. (0.014 mole) of 4-chlorobenzenethiol and 2 g. of potassium carbonate in 50 ml. of acetone was heated under reflux for 1 hour, cooled, filtered and concentrated to dryness *in vacuo*. The residue was extracted with benzene; the extract was concentrated *in vacuo* and chromatographed over 40 g. of silica gel with benzene. The product-containing eluant, as determined by tlc (silica gel-benzene, R_f = 0.13), was concentrated to dryness *in vacuo* and the residue recrystallized from 2-propanol to afford 1.2 g. (32% from **11**) of the title compound, m.p. 76-78°.

6-[[(3,4-Dichlorophenyl)methyl]thio]-*N,N*-dimethyl-1,2,4,5-tetrazin-3-amine (**16a**).

A mixture of 14.0 g. (0.03 mole) of 3,6-bis[[(3,4-dichlorophenyl)methyl]thio]-1,2,4,5-tetrazine (**15**), 7 ml. (0.06 mole) of 40% aqueous dimethylamine and 200 ml. of ethanol was heated under reflux for 2 hours and chilled to afford 5.3 g. of crude product, m.p. 97-100°. The filtrate was combined with 5 ml. of aqueous dimethylamine, heated under reflux for 2 hours and evaporated to dryness *in vacuo*. Thin layer chromatography (alumina-benzene) demonstrated two products: a colorless product with $R_f \cong 0.64$ and a red product with $R_f \cong 0.5$. The two were separated by chromatography over 400 g. of alumina, eluting with benzene. Fractions containing the colorless compound were combined and evaporated to give 5.3 g. of solid which was recrystallized from 2-propanol to give 3.5 g. of white crystals, m.p. 85-88°. Elemental analysis, nmr and ir demonstrated the colorless product to be 1,1'-[dithiobis(methylene)]bis[3,4-dichlorobenzene]. The fractions containing the red compound were combined and the solvent was removed *in vacuo*. The residue was combined with the 5.3 g. of crude obtained above and recrystallized from a 2-propanol:hexane mixture (4:1) to give 7 g. (74%) of the title compound as red needles, m.p. 103-105°.

6-[[(3,4-Dichlorophenyl)methyl]thio]-1,2,4,5-tetrazin-3-amine (**16c**).

A mixture of 4.6 g. (0.01 mole) of 3,6-bis[[(3,4-dichlorophenyl)methyl]thio]-1,2,4,5-tetrazine (**15**) and 2.5 ml. of 58% aqueous ammonium hydroxide in 500 ml. of ethanol was heated under reflux for 16 hours, then allowed to cool to room temperature and chilled in an ice bath. Filtration afforded 0.1 g. of unreacted 3,6-bis[[(3,4-dichlorophenyl)methyl]thio]-1,2,4,5-tetrazine. Solvent was removed from the filtrate under reduced pressure and the residue was recrystallized from a benzene-heptane mixture to give 1.0 g. of red crystals, m.p. 136-139°. Recrystallization from toluene gave 0.6 g. (21%) of the product, m.p. 141-142°.

6-[[(3,4-Dichlorophenyl)methyl]sulfinyl]-*N,N*-dimethyl-1,2,4,5-tetrazin-3-amine (**17**).

A mixture of 3.0 g. (0.0095 mole) of 6-[[(3,4-dichlorophenyl)methyl]thio]-*N,N*-dimethyl-1,2,4,5-tetrazin-3-amine (**16a**) and 2.1 g. (0.0049 mole) of the bromine complex of 1,4-diazabicyclo[2.2.2]octane (9) in 475 ml. of 70% aqueous acetic acid was stirred at room temperature for 20 hours, poured into 800 ml. of water and extracted with chloroform. The extract was washed with water, dried over anhydrous sodium sulfate, filtered, and allowed to evaporate to dryness overnight in an evaporating dish. Recrystallization of the residue from 2-propanol afforded 2.6 g. (82.5%) of red crystalline product, m.p. 145-147°. The ir (potassium bromide) of the product contained a new strong absorption maximum at 1055 cm^{-1} which is characteristic of the S=O group.

Acknowledgement.

The authors thank Mr. C. E. Childs and associates for the microanalyses, Dr. J. M. Vandenbelt and co-workers for determination of the spectral data, and Dr. A. L. Ager of the University of Miami for the antimalarial testing.

REFERENCES AND NOTES

(1) This is communication 46 of a series on antimalarial drugs. For paper 45 see E. F. Elslager, P. Jacob, J. Johnson, and L. M. Werbel, *J. Heterocyclic Chem.*, **16**, 129 (1980). This investigation was supported by U. S. Army Medical Research and Development Command Contract DADA-17-72-C-2077. This is contribution No. 1551 to the Army Research Program in Malaria.

(2) R. I. Hewitt, U. S. Patent 3,749,780, July 31, 1973.

(3) L. M. Werbel, D. J. McNamara, N. Colbry, J. L. Johnson, M. J. Degnan and B. Whitney, *J. Heterocyclic Chem.*, **16**, 881 (1979).

(4) E. F. Elslager, P. Jacob, J. Johnson, L. M. Werbel, D. F. Worth and L. Rane, *J. Med. Chem.*, **21**, 1059 (1978).

(5) A similar approach to unsymmetrical substituted tetrazines has been recently reported by A. Mangia, F. Bortesi, and U. Amendola, *J. Heterocyclic Chem.*, **14**, 587 (1977).

(6) J. Sandström, *Acta Chem. Scand.*, **15**, 1575 (1961).

(7) R. E. Strube, *Org. Synth. IV*, p. 967 (1963).

(8) U. S. Patent No. 3,166,400 (1965).

(9) S. Oae, Y. Ohnishi, S. Kozuka and W. Tagaki, *Bull. Chem. Soc., Japan*, **39**, 364 (1966).

(10) The parenteral antimalarial screening was carried out by Dr. Arba L. Ager of the University of Miami and test results were supplied through the courtesy of Dr. David P. Jacobus, Dr. T. R. Sweeney and Dr. E. A. Steck of the Walter Reed Army Institute of Research.

(11) For a description of the test method, see T. S. Osdene, P. B. Russell and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

(12) Melting points (corrected) were taken on a Thomas-Hoover capillary melting point apparatus. Ir and nmr spectra were obtained on all compounds cited and were consistent with the assigned structures.

(13) J. H. Burckhalter, F. H. Tendick, E. M. Jones, P. A. Jones, W. F. Holcomb, and A. L. Rawlins, *J. Am. Chem. Soc.*, **70**, 1363 (1948).