Synthesis of 5,5′-[[3-(Dimethylamino)propyl]imino]bis[3-(trichloromethyl)-1,2,4-thiadiazole] and Related Thiadiazoles as Antimalarial Agents (1,2)

Edward F. Elslager, Judith Johnson, and Leslie M. Werbel*

Department of Chemistry, Research and Development Division, Parke, Davis and Company, Ann Arbor, Michigan 48106

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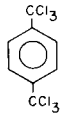
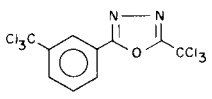
The condensation of 5-chloro-3-(trichloromethyl)-1,2,4-thiadiazole (VIII) with *N,N*-dimethyl-1,3-propanediamine gave 5-[[3-(dimethylamino)propyl]amino]-3-(trichloromethyl)-1,2,4-thiadiazole (**5**) and 5,5′-[[3-(dimethylamino)propyl]imino]bis[3-(trichloromethyl)-1,2,4-thiadiazole] (**14**), together with 5,5′-[(3-[methyl[3-(trichloromethyl)-1,2,4-thiadiazol-5-yl]amino]propyl)-imino]bis[3-(trichloromethyl)-1,2,4-thiadiazole] (**17**) which was formed *via* an unusual displacement of the distal methyl group of **14**. The remarkable antimalarial activity of **14** prompted the synthesis of an array of 5-amino-3-(trichloromethyl, methyl, and 3,4-dichlorophenyl)-1,2,4-thiadiazoles and 5,5′-[[(dialkylamino)alkyl]imino]bis[3-(trichloromethyl, methyl, and 3,4-dichlorophenyl)-1,2,4-thiadiazoles] from an amine and the requisite 5-chloro-3-substituted-1,2,4-thiadiazoles, which were prepared from the appropriate amidine and trichloromethylsulfenyl chloride. 5-[[3-[(Diethylamino)methyl]-*p*-anisidino]-3-(trichloromethyl)-1,2,4-thiadiazole (**13**) was active against a chloroquine-resistant line of *Plasmodium berghei* in the mouse, and compound **14**, the most promising member of the series overall, was designated for expanded antimalarial and toxicological studies. Structure-activity relationships against *P. berghei* in mice and *P. gallinaceum* in chicks are discussed.

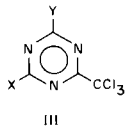
It has been demonstrated that α,α,α,α′,α′,α′-hexachloro-*p*-xylene (I) (Hetol®) and related halogenated hydrocarbons possess strong suppressive antimalarial activity against *Plasmodium berghei* in mice, *P. gallinaceum* in chicks, and *P. cynomolgi* and *P. knowlesi* in monkeys (3,4). Heterocyclic systems containing the trichloromethyl group also have been shown to exhibit significant antimalarial activity. Thus a group of 2-(trichloromethyl)-5-(α,α,α-trichlorotolyl)-1,3,4-oxadiazoles, exemplified by 2-(trichloromethyl)-5-(α,α,α-trichloro-*m*-tolyl)-1,3,4-oxadiazole (II), displayed activity against *P. berghei* comparable with Hetol® (I) (5).



I

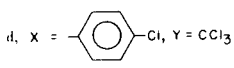


II

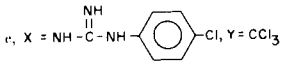


III

a, X = Y = CCl_3
b, X = CCl_3, Y = OH
c, X = CCl_3, Y = Cl

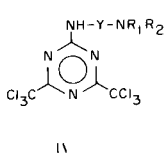


d, X = Cl, Y = CCl_3

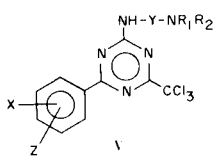


e, X = NH-C(=NH)-NH, Cl, Y = CCl_3

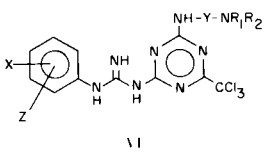
In the *s*-triazine series, simple derivatives such as 2,4,6-tris(trichloromethyl)-*s*-triazine (IIIa), 4,6-bis(trichloromethyl)-*s*-triazin-2-ol (IIIb), 2-chloro-4,6-bis(trichloromethyl)-*s*-triazine (IIIc), 2-(*p*-chlorophenyl)-4,6-bis(trichloromethyl)-*s*-triazine (IIId), and 1-[4,6-bis(trichloromethyl)-*s*-triazin-2-yl]-3-(*p*-chlorophenyl)guanidine (IIIe) lacked appreciable antimalarial effects against *P. berghei* in mice or *P. gallinaceum* in chicks at high dose levels (6). However, the introduction of a basic side chain into such molecules afforded an array of 2-[[(dialkylamino)alkyl]-amino]-4,6-bis(trichloromethyl)-*s*-triazines (IV), 2-phenyl-4-[[(dialkylamino)alkyl]amino]-6-(trichloromethyl)-*s*-triazines (V), and 1-phenyl-3-(4-[[(dialkylamino)alkyl]amino]-6-(trichloromethyl)-*s*-triazin-2-yl)guanidines (VI) that



IV



V



VI

possessed noteworthy antimalarial activity (6-8). These promising results led to further investigations in these laboratories concerning basically-substituted trichloromethyl heterocycles. One aspect of these studies, namely the synthesis and antimalarial properties of 5-amino-3-(trichloromethyl)-1,2,4-thiadiazoles and related aminothiadiazoles, is the subject of the present communication.

Chemistry.

Initial experiments were directed toward the synthesis of the prototype 5-[[3-(dimethylamino)propyl]amino]-3-(trichloromethyl)-1,2,4-thiadiazole (**5**) (Scheme I). Treatment of trichloroacetonitrile with liquid ammonia provided trichloroacetamidine (VII) (9) (82%), which was condensed with trichloromethanesulfenyl chloride to give 5-chloro-3-(trichloromethyl)-1,2,4-thiadiazole (VIII) (10) (53%). A solution of one equivalent of VIII in benzene was treated with a benzene solution of two equivalents of *N,N*-dimethyl-1,3-propanediamine, and the mixture was stirred overnight at room temperature and then at 40° for 3 hours. This afforded a mixture of products from which only a compound m.p. 110-113° was isolated in low yield (7%). Elemental analyses (C, H, N, Cl, S) were in agreement with the empirical formula $C_{11}H_{12}Cl_6N_6S_2$ and structure **14** was tentatively assigned. The nmr spectrum showed a 2 proton triplet at 4.4 δ assigned to the CH_2 attached to the thiadiazole amine. The remaining protons appeared as a complex absorption at 2.0-2.7 δ (relative integration 10) and included a strong peak at 2.25 δ (relative integration 6 protons) which was assigned to the CH_3 groups. Repetition of this reaction utilizing 0.50 mole of VIII and 0.93 mole of the diamine at 30° for 1 hour increased the yield of **14** to 37%.

Early antimalarial test results with this substance against *P. berghei* in mice and *P. gallinaceum* in chicks were highly promising (*vide infra*) (11-14). Therefore, it was of interest to explore the scope of this reaction in greater depth, and to elucidate the structures of the products obtained from this reaction under various experimental conditions.

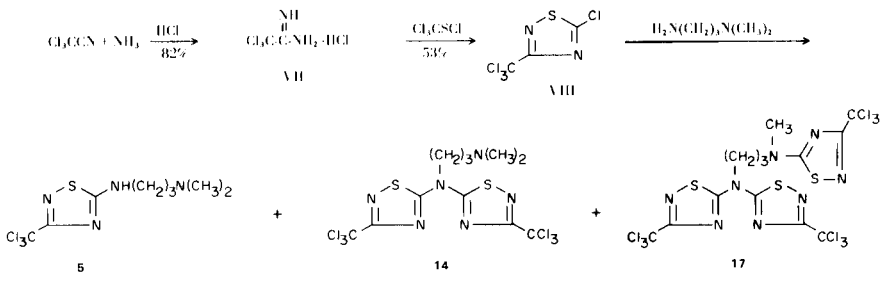
When three equivalents of *N,N*-dimethyl-1,3-propanediamine were allowed to react with one equivalent of VIII in benzene at 5-10° for 1.5 hours and the reaction mixture was chromatographed on alumina, 5-[[3-(dimethylamino)propyl]amino]-3-(trichloromethyl)-1,2,4-thiadiazole (**5**) was obtained as the hydrochloride salt in 12% yield. The condensation of one equivalent of VIII with 1.5 equivalents of the diamine in benzene at 60-80° for one hour afforded yet a third product, m.p. 162-164°, in 10% yield which analyzed correctly (C, H, N, Cl, S) for the empirical formula $C_{13}H_9Cl_9N_8S_3$ and was postulated to be 5,5′-[(3-[methyl[3-(trichloromethyl)-1,2,4-thiadiazol-5-yl]amino]propyl)imino]bis[3-(trichloromethyl)-1,2,4-thiadiazole] (**17**).

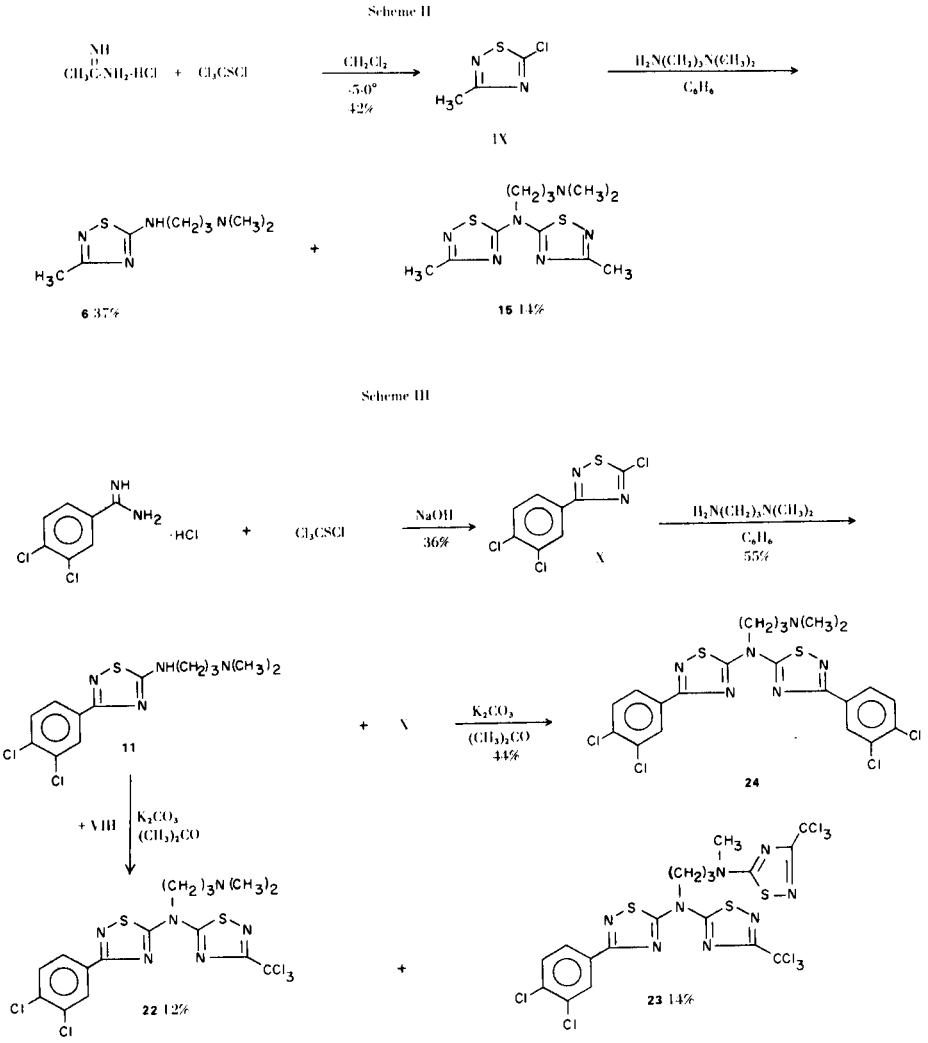
Confirmation of the proposed structure for **17**, which presumably arises from an unusual displacement of a methyl group from **14**, was obtained by comparing the nmr spectra. The spectrum of **17** showed no shift of the triplet from the CH_2 attached to the thiadiazole amine, nor the multiplet from the middle CH_2 at 2.0-2.7 δ. However, the triplet from the remaining CH_2 and the 3 proton singlet from the CH_3 group were shifted downfield to 3.9 and 3.2 δ, respectively, reflecting their proximity to the third thiadiazole ring.

In view of the overall promise of **14** as an antimalarial drug, a variety of aminothiadiazoles related to **5** and **14** were synthesized (Tables I, II) and submitted for antimalarial evaluation (Tables III, IV). Generally the simple 5-[[(dialkylamino)alkyl]amino]-3-(trichloromethyl)-1,2,4-thiadiazoles (Table I) could be isolated directly from the reaction of one equivalent of 5-chloro-3-(trichloromethyl)-1,2,4-thiadiazole with two equivalents of the appropriate amine in benzene at 30-60° for 0.3-2 hours (**2-4**, **7**, **8**, **10**, **12**, **13**, Table I) (11-60%), although in one instance (**9**) column chromatography on alumina was required to obtain pure product (33%). 5-Amino-3-(trichloromethyl)-1,2,4-thiadiazole (**1**, Table I) was obtained in 63% yield when VIII was heated at 50° under 60 p.s.i.g. of ammonia for 12 hours.

Among five 5,5′-[[(dialkylamino)alkyl]imino]bis[3-

Scheme I





(trichloromethyl)-1,2,4-thiadiazole] analogs of **14** that were prepared (**16**, **18-21**, Table II), two (**18**, **21**) were obtained directly by treating two equivalents of VIII with one equivalent of the diamine in acetone in the presence of potassium carbonate (19, 10%). Alternatively, compounds **16**, **19**, and **20** were obtained in 12-47% yield by alkylation of the corresponding performed 5-amino-3-(trichloromethyl)-1,2,4-thiadiazole (Table I) by VIII in acetone in the presence of potassium carbonate.

To determine whether or not the trichloromethyl group at position 3 of the 1,2,4-thiadiazole nucleus was essential for antimalarial activity, representative 5-amino-3-(methyl and 3,4-dichlorophenyl)-1,2,4-thiadiazoles were synthesized (Schemes II and III). 5-Chloro-3-methyl-1,2,4-thiadiazole (IX) was obtained in 42% yield by the condensation of acetamidine hydrochloride with trichloromethanesulfenyl chloride according to the method of Goerdeler *et al.* (15). Treatment of one equivalent of IX with two equivalents of *N*,*N*-dimethyl-1,3-propanediamine afforded a mixture from which 5-[[[3-(dimethylamino)propyl]amino]-3-methyl-1,2,4-thiadiazole hydrochloride (**6**, Table I) and 5,5'-[[[3-(dimethylamino)propyl]imino]bis[3-methyl-1,2,4-thiadiazole] hydrochloride (**15**, Table II) were isolated in 37% and 14% yield, respectively (Scheme II).

The reaction of 3,4-dichlorobenzonitrile and absolute ethanol gave 3,4-dichlorobenzimidic acid ethyl ester hydrochloride (90%), which was converted to 3,4-dichlorobenzamidine hydrochloride (16) (41%) by treatment with ammoniacal ethanol. Ring-closure utilizing trichloromethylsulfenyl chloride afforded 5-chloro-3-(3,4-dichlorophenyl)-1,2,4-thiadiazole (X) in 36% yield. The condensation of one equivalent of X with two equivalents of *N*,*N*-dimethyl-1,3-propanediamine in benzene once again produced a complex mixture of products from which 3-(3,4-dichlorophenyl)-5-[[[3-(dimethylamino)propyl]ami-

no]-1,2,4-thiadiazole (**11**, Table I) was isolated in 55% yield by column chromatography. When equimolar amounts of **11** and 5-chloro-3-(3,4-dichlorophenyl)-1,2,4-thiadiazole (X) were allowed to react in a benzene-acetone mixture in the presence of potassium carbonate, 5,5'-[[3-(dimethylamino)propyl]imino]bis[3-(3,4-dichlorophenyl)-1,2,4-thiadiazole] (**24**, Table II) was isolated directly in 44% yield. However, when **11** was condensed with an equimolar amount of 5-chloro-3-(trichloromethyl)-1,2,4-thiadiazole (VIII) under similar conditions and the reaction mixture was subjected to column chromatography, both the expected 3-(3,4-dichlorophenyl)-3'-(trichloromethyl)-5,5'-[[3-(dimethylamino)propyl]imino]-bis-1,2,4-thiadiazole (**22**, Table II) (12%) and the curious product 3-(3,4-dichlorophenyl)-3'-(trichloromethyl)-5,5'-[(3-[methyl[3-(trichloromethyl)-1,2,4-thiadiazol-5-yl]-amino]propyl)imino]bis-1,2,4-thiadiazole (**23**, Table II) (14%) were obtained (Scheme III). Spectral data (ir, uv, nmr) were in agreement with the structures assigned for each of the 5-amino-3-(trichloromethyl, methyl, and 3,4-dichlorophenyl)-1,2,4-thiadiazoles.

Suppressive Antimalarial Screening in Mice.

The 5-amino-3-(trichloromethyl, methyl, and 3,4-dichlorophenyl)-1,2,4-thiadiazoles (**1-10**, **12**, and **13**, Table I), 5,5'-[[(dialkylamino)alkyl]imino]bis[3-(trichloromethyl, methyl, and 3,4-dichlorophenyl)-1,2,4-thiadiazoles] (**14-24**, Table II), and 5-chloro-3-(3,4-dichlorophenyl)-1,2,4-thiadiazole (X) described in the present communication were tested initially against a normal drug-sensitive strain of *P. berghei* in mice by the parenteral route (11,12). The compounds were dissolved or suspended in sesame or peanut oil and were administered to mice in a single subcutaneous dose 72 hours post infection. Extension of the mean survival time of the treated mice is interpreted as evidence of antimalarial activity (12). 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 to 6.3 days. Results are summarized in Tables III and IV.

Fourteen of these 5-amino-1,2,4-thiadiazoles (**2-9**, **11-14**, **18**, and **20**) (Tables I and II) were also evaluated orally against another normal drug-sensitive strain of *P. berghei* in mice (13,14). The drugs were given continuously in the diet of mice for 6 consecutive days, and all drug doses were calculated as free base equivalent. Results (Tables III and IV) are expressed both in terms of the SD_{90} (daily dose required for 90% suppression of the parasitemia in treated mice relative to control mice) and the quinine equivalent Q (the ratio of the SD_{90} of quinine hydrochloride to the SD_{90} of the test substance under comparable experimental conditions).

Both oral and parenteral baseline data for the reference drugs quinine, Hetol® (I), and 2-(trichloromethyl)-5-(α,α,α-trichloro-*m*-tolyl)-1,3,4-oxadiazole (II) are included for reference purposes (Table III).

Overall Results and Structure-Activity Relationships in Mice.

Although each of the 5,5'-[[(dialkylamino)alkyl]imino]-bis[3-(trichloromethyl)-1,2,4-thiadiazoles] (**16**, **18-21**) exhibited significant parenteral activity against *P. berghei* (Table IV) and compounds **18** and **20** were active orally, ironically none was more promising than the original lead compound **14**. Analysis of the overall results with the other congeners enables the following generalizations concerning structure-activity relationships against *P. berghei* in mice relative to **14**:

(1) Activity is retained when one of the trichloromethyl groups is replaced by a 3,4-dichlorophenyl group (**22**, Table IV).

(2) Replacement of both of the trichloromethyl functions with methyl or 3,4-dichlorophenyl groups results in a loss of activity (**15**, **24** *vs.* **14**, Table IV).

(3) Substitution of a [3-(trichloromethyl)-1,2,4-thiadiazol-5-yl] function for one of the distal methyl groups destroys antimalarial activity (**17**, **23** *vs.* **14**, **22**, Table IV).

(4) Activity is abolished when one of the [3-(trichloromethyl)-1,2,4-thiadiazole] moieties is removed from the proximal nitrogen [**5** (Table III) *vs.* **14** (Table IV)].

(5) Other secondary 5-amino-3-(trichloromethyl, methyl, and 3,4-dichlorophenyl)-1,2,4-thiadiazole analogs (**1-4**, **6-13**, Table III) of **14** possess only weak antimalarial effects or are inactive.

(6) The chlorothiadiazole precursor X was inactive.

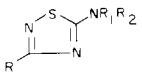
Suppressive Antimalarial Effects in Chicks.

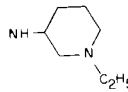
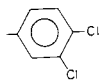
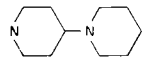
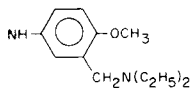
5-Chloro-3-(3,4-dichlorophenyl)-1,2,4-thiadiazole (X) and four of the 5-amino-1,2,4-thiadiazoles (**11**, **14**, **18**, **21**) were also tested for suppressive antimalarial effects against *P. gallinaceum* infections in white Leghorn cockerels (Tables III, IV) (11,12). The drugs were administered to infected chicks in a single subcutaneous dose in peanut oil. In this test, as in the parenteral mouse assay, the antimalarial activity of candidate compounds was assessed by comparing the mean survival times of treated malaria-infected chicks with the survival times of untreated malaria-infected chicks. A compound was arbitrarily considered to be active against malaria if it produced survival times of treated chicks that were at least 100% greater than the survival times of untreated infected control animals.

5,5'-[[3-(Dimethylamino)propyl]imino]bis[3-(trichloromethyl)-1,2,4-thiadiazole] (**14**) and 5,5'-[[4-(diethyl-

TABLE I

5-Amino-3-(trichloromethyl, methyl, and 3,4-dichlorophenyl)-1,2,4-thiadiazoles

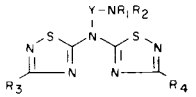


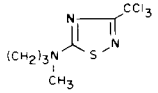
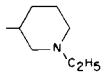
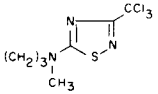
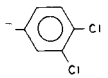
No.	NR_1R_2	R	M.p., °C	Yield, %	Purification Solvent	Formula	Analyses Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	NH_2	CCl_3	187-189	63 (a)	C_6H_6-MeCN (3:1)	$C_3H_2Cl_3N_3S$	16.49	16.69	0.92	0.96	19.23	19.44
2		CCl_3	255-260 dec.	35	EtOH	$C_7H_9Cl_3N_4S$·HCl	25.94	26.26	3.11	3.16	17.29	17.24
3	$N(C_2H_5)_2$	CCl_3	52-54 (b)	50	Petroleum ether	$C_7H_{10}Cl_3N_3S$	30.61	30.84	3.67	3.67	15.30	15.42
4		CCl_3	252-254 dec.	52	EtOH	$C_8H_{11}Cl_3N_4S$·HCl (c)	28.42	28.66	3.58	3.50	16.57	16.63
5	$NH(CH_2)_3N(CH_3)_2$	CCl_3	175-177	12	2-PrOH	$C_8H_{13}Cl_3N_4S$·HCl (d)	28.25	28.40	4.15	4.24	16.47	16.46
6	$NH(CH_2)_3N(CH_3)_2$	CH_3	180-184 (j)	37		$C_8H_{16}N_4S$·2.33 HCl·0.8H_2O (e)	32.05	32.21	6.70	7.06	18.69	18.40
7	$NH(CH_2)_2N(C_2H_5)_2$	CCl_3	128-130	41	2-PrOH	$C_9H_{15}Cl_3N_4S$·HCl	30.52	30.82	4.55	4.68	15.82	15.80
8		CCl_3	220-222	26	MeCN-2-PrOH (80:1)	$C_{10}H_{15}Cl_3N_4S$·HCl	32.80	32.89	4.41	4.11	15.30	15.34
9	$N(CH_3)(CH_2)_3N(C_2H_5)_2$	CCl_3	130-137	33	(f)	$C_{11}H_{19}Cl_3N_4S$·HCl (g)	34.57	34.64	5.27	5.19	14.66	14.70
10	$NH(CH_2)_5N(C_2H_5)_2$	CCl_3	115.5-118	11 (h)	2-PrOH-Et_2O	$C_{12}H_{21}Cl_3N_4S$·HCl	36.37	36.33	5.60	5.50	14.14	14.31
11	$NH(CH_2)_3N(CH_3)_2$		78-80	55	MeCN (i)	$C_{13}H_{16}Cl_2N_4S$	47.13	47.16	4.87	4.99	16.91	16.95
12		CCl_3	113-115	60	MeCN	$C_{13}H_{19}Cl_3N_4S$	42.23	42.27	5.18	5.10	15.15	15.39
13		CCl_3	244-247	52 (h)	EtOH-2-PrOH (1:1)	$C_{15}H_{19}Cl_3N_4OS$·HCl	40.37	40.26	4.52	4.52	12.56	12.65

(a) Heated in 2-propanol at 50° under 60 p.s.i.g. of ammonia for 12 hours, evaporated to dryness, and taken up in chloroform. (b) Literature (10) reports m.p. 55°. (c) Cl^-: calcd., 10.49; found, 10.50. (d) Cl^-: calcd., 10.43; found, 10.29. (e) Cl^-: calcd., 27.59; found, 27.76. Water: calcd., 4.81; found, 4.72. (f) Chromatography on alumina with chloroform, fractions $R_f \cong 0.15$ were evaporated to dryness, taken up in ether, and treated with 25% hydrogen chloride in 2-propanol. (g) Cl^-: calcd., 9.28; found, 9.41. (h) Reaction run at room temperature overnight. (i) After chromatography on alumina with ethyl acetate. (j) With prior softening.

TABLE II

5,5′-[[(Dialkylamino)alkyl]imino]bis[3-(trichloromethyl, methyl, and 3,4-dichlorophenyl)-1,2,4-thiadiazoles]

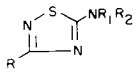


No.	-Y-NR$_1$R$_2$	R$_3$	R$_4$	M.p., °C	Yield, %	Purification Solvent	Formula	Analyses Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
14	$(CH_2)_3N(CH_3)_2$	CCl_3	CCl_3	110-113	7, 37	Hexane	$C_{11}H_{12}Cl_6N_6S_2$ (a)	26.15	26.43	2.40	2.47	16.64	16.60
15	$(CH_2)_3N(CH_3)_2$	CH_3	CH_3	70-72	14		$C_{11}H_{18}N_6S_2 \cdot 0.25HCl$ (b)	42.96	43.38	5.98	5.78	27.33	27.43
16	$(CH_2)_2N(C_2H_5)_2$	CCl_3	CCl_3	190-192	47	2-PrOH	$C_{12}H_{14}Cl_6N_6S_2 \cdot HCl$	25.94	26.17	2.72	2.87	15.13	15.12
17		CCl_3	CCl_3	162-164	10	MeCN	$C_{13}H_9Cl_9N_8S_3$ (c)	22.54	22.94	1.31	1.43	16.18	16.37
18		CCl_3	CCl_3	225-227 dec.	19	MeCN (d)	$C_{13}H_{14}Cl_6N_6S_2 \cdot HCl$	27.51	27.87	2.66	2.70	14.81	14.95
19	$(CH_2)_3N(C_2H_5)_2$	CCl_3	CCl_3	80-82	12	MeCN-2-PrOH (e)	$C_{13}H_{16}Cl_6N_6S_2$	29.28	29.56	3.03	3.06	15.76	15.71
20	$CH(CH_3)CH_2N(C_2H_5)_2$	CCl_3	CCl_3	216-219 dec.	23	2-PrOH (d)	$C_{13}H_{16}Cl_6N_6S_2 \cdot HCl$	27.41	27.68	3.01	3.08	14.75	14.65
21	$(CH_2)_4N(C_2H_5)_2$	CCl_3	CCl_3	141-143	10	2-PrOH (d)	$C_{14}H_{18}Cl_6N_6S_2 \cdot HCl$	28.81	29.13	3.28	3.36	14.40	14.30
22	$(CH_2)_3N(CH_3)_2$	CCl_3		248-250 dec.	12		$C_{16}H_{15}Cl_5N_6S_2 \cdot HCl$	33.76	33.95	2.83	2.99	14.77	14.60
23		CCl_3		139-143	14	MeCN	$C_{18}H_{12}Cl_8N_8S_3$ (f)	30.02	30.11	1.68	1.75	15.56	15.67
24	$(CH_2)_3N(CH_3)_2$			198-200	44	C_6H_6	$C_{21}H_{18}Cl_4N_6S_2$	45.01	44.93	3.24	3.31	15.00	15.04

(a) Cl: calcd., 42.12; found, 42.05. S: calcd., 12.69; found, 12.69. (b) Cl^-: calcd., 2.89; found, 2.89. S: calcd., 20.86; found, 20.94. (c) Cl: calcd., 46.08; found, 46.08. Cl^-: calcd., 0.00; found, 0.00. S: calcd., 13.89; found, 14.04. (d) After chromatography on alumina with benzene, removal of the solvent, solution in ether, and addition of hydrogen chloride in 2-propanol. (e) After chromatography on alumina with benzene. (f) Cl: calcd., 39.39; found, 39.09.

TABLE III

Effects of 5-Amino-3-(trichloromethyl, methyl, and 3,4-dichlorophenyl)-1,2,4-thiadiazoles Against *Plasmodium berghei* in Mice and *Plasmodium gallinaceum* in Chicks



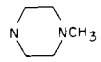
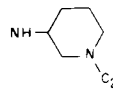
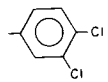
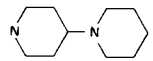
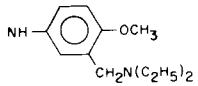
No.	NR_1R_2	R	*P. berghei* Diet, 6 days: No. of mice	SD90 (a), mg./kg./day	Q (b)	*P. berghei* Single s.c. dose: ΔMST; T or C (c) after mg./kg.: 640	320	160	80	40	20	*P. gallinaceum* Single s.c. dose: mg./kg.	ΔMST; T or C (d)
1	NH_2	CCl_3				T5	T5	1.9	1.1	0.7	0.7		
2		CCl_3	7	230	0.3	T5	1.8; T2 1.9; T3 2.8; T3	0.8 0.9 1.8; T3	0.2 0.3 0.8; T1	0.2 0.3 0.6	0.2 0.3 0.4		
3	$N(C_2H_5)_2$	CCl_3	7	>187	<0.4	0.1	0.1	0.1	0.1	0.1	0.1		
4		CCl_3	7	>40	<1.9	0.3	0.3	0.1	0.1	0.1	0.1		
5	$NH(CH_2)_3N(CH_3)_2$	CCl_3	7	>41	<1.9	0.4	0.4	0.2	0.2	0.2	0.0		
6	$NH(CH_2)_3N(CH_3)_2$	CH_3	7	>148	<0.5	0.3	0.3	0.1	0.1	0.1	0.1		
7	$NH(CH_2)_2N(C_2H_5)_2$	CCl_3	14	185	0.4	T5	4.8 5.0	3.8 3.6	0.4 0.4	0.2 0.4	0.2 0.2		
8		CCl_3	14	195	0.4	0.8	0.4	0.2	0.2	0.2	0.0		
9	$N(CH_3)(CH_2)_3N(C_2H_5)_2$	CCl_3	14	140	0.5	T5	T5	0.3	0.1	0.1	0.1		
10	$NH(CH_2)_5N(C_2H_5)_2$	CCl_3				0.1	0.1	0.1	0.1	0.1	0.1		
11	$NH(CH_2)_3N(CH_3)_2$		21	>243	<0.3							320 80	T5 0.0
12		CCl_3	7	>51	<1.5	T5	0.9; T1	0.5	0.3	0.3	0.3		
13		CCl_3	7	>158	<0.5	3.2	3.0 3.0	1.2 1.0	0.4 0.4	0.2 0.2	0.2 0.2		
	Quinine (e)		224	74.5	1.0	5.4	3.2	2.0	1.4	1.0	0.2		
	I Hetol®		28	36	2.1	C5 C5	8.9	6.7 6.9	0.3	0.3	0.1	120	0.8
	II		15	29	2.6	22.8; C4 27.3; C3	7.0	5.8 6.0	1.4	0.2 0.4	0.2	120	0.3

TABLE III – Footnotes

(a) SD_{90} represents the daily dose (mg./kg.) required for 90% suppression of the parasitemia in treated mice relative to control mice. The SD_{90} was estimated graphically using semi-logarithmic paper. (b) The quinine equivalent Q is the ratio of the SD_{90} of quinine hydrochloride (74.5 mg. base/kg./day) to the SD_{90} of the test substance under comparable experimental conditions. (c) ΔMST 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 6.3 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 post infection and termed "cured"; data to establish parasitological cure based on sub-inoculation are unavailable. (d) ΔMST is the mean survival time (days) of treated chicks (MSTT) minus the mean survival time (days) of control chicks (MSTC). In the present study the MSTC ranged from 3.9 to 4.0 days. C designates the number of chicks surviving to 30 days post infection and termed "cured"; data to establish parasitological cure based on sub-inoculation are unavailable. T indicates the number of deaths occurring within 48 hours after infection which are attributed to drug action and are counted as toxic deaths. Control birds do not die before 48 hours. Each entry at each dose level represents results with a 5 animal group. (e) Tested parenterally as the sulfate and orally as the hydrochloride.

amino)butyl]imino]bis[3-(trichloromethyl)-1,2,4-thiadiazole] (**21**), in contrast to the reference drugs Hetol® (I) (3,4) and 2-(trichloromethyl)-5-(α,α,α-trichloro-*m*-tolyl)-1,3,4-oxadiazole (II) (5), exhibited marked suppressive activity against *P. gallinaceum* when administered in single subcutaneous doses ranging from 80 to 320 mg./kg. (Table IV). Compounds **11**, **12**, and X lacked appreciable antimalarial effects in chicks at subcutaneous doses of 80-320 mg./kg.

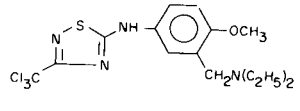
Evaluation of Prophylactic Action in Chicks.

Nine of the 5-amino-1,2,4-thiadiazoles (**6**, **14-20**, **24**) were evaluated for prophylactic action in chicks (11,17). White Leghorn cockerels were parasitized by the intrajugular injection of *P. gallinaceum* sporozoites. All control chicks die between 6 and 11 days post-infection. In the present study, the mean survival time of control animals ranged from 7.0 to 9.6 days. A drug is considered active if the mean survival time of treated chicks is at least twice as long as that of untreated control chicks, or if any of the chicks survive to 30 days.

The above drugs were suspended in peanut oil and were administered subcutaneously in a single dose on the day of infection. Each compound was tested in groups of 5 chicks at one to six dose levels ranging from 5 to 640 mg./kg. None of the aminothiadiazoles tested possessed prophylactic activity based on the above criteria.

Drug Resistance Studies in Mice.

To determine whether or not the 5-amino-3-(trichloromethyl)-1,2,4-thiadiazoles represented a unique chemical class with regard to apparent mode of action relative to chloroquine, one member of the series, namely 5-[[3-[(diethylamino)methyl]-*p*-anisidino]-3-(trichloromethyl)-1,2,4-thiadiazole (**13**), was evaluated in parallel against the parent (P) drug-susceptible strain of *P. berghei* and line C which was 77-fold resistant to chloroquine (13,14).

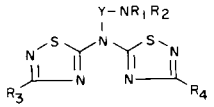


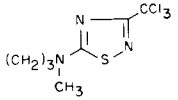
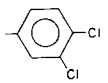
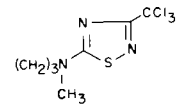
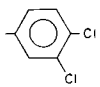
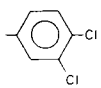
13

The drug was administered continuously in the diet of mice at levels of 0.0125, 0.050, and 0.1% for five days to groups of seven mice infected with each strain. The SD_{90} was estimated to be 115 mg./kg./day for the chloroquine-resistant line C and 114 mg./kg./day for the parent (P) drug-susceptible strain. These results indicate that there is no cross-resistance between **13** and chloroquine, and suggest that the 5-amino-3-(trichloromethyl)-1,2,4-thiadiazoles possess a unique mode of action relative to chloroquine.

TABLE IV

Effects of 5,5′-[[(Dialkylamino)alkyl]imino]bis[3-(trichloromethyl, methyl, and 3,4-dichlorophenyl)-1,2,4-thiadiazoles] Against *Plasmodium berghei* in Mice and *Plasmodium gallinaceum* in Chicks



No.	-Y-NR$_1$R$_2$	R$_3$	R$_4$	Diet, 6 days: No. of mice	Diet, 6 days: SD_{90} (a), mg./kg./day	Diet, 6 days: Q (a)	*P. berghei* Single s.c. dose: ΔMST; T or C (a) after mg./kg.: 640	320	160	80	40	20	*P. gallinaceum* Single s.c. dose: mg./kg.	*P. gallinaceum* Single s.c. dose: ΔMST; T or C (a)
14	$(CH_2)_3N(CH_3)_2$	CCl_3	CCl_3	14	29	2.6	C5 C5 C5	21.9; C4 C5 C5	16.2; C2 10.9; C3 14.6; C2 15.2; C2	3.5 11.7 11.5	2.5 2.3 3.3 3.3	0.1 1.3 1.1	100	4.7
15	$(CH_2)_3N(CH_3)_2$	CH_3	CH_3				0.7	0.5	0.3	0.3	0.1	0.1		
16	$(CH_2)_2N(C_2H_5)_2$	CCl_3	CCl_3				10.8; C3	7.6 7.5	6.4 6.3	1.2 1.3	0.8 1.1	0.2 0.3		
17		CCl_3	CCl_3				1.1 0.7	0.5 0.7	0.5 0.5	0.3 0.3	0.3 0.3	0.3 0.1		
18		CCl_3	CCl_3	21	46	1.6	12.3	10.5 10.7	4.9 4.9	0.7 0.5	0.5 0.5	0.3 0.3	320	0.0
19	$(CH_2)_3N(C_2H_5)_2$	CCl_3	CCl_3				C5	C5 C5	11.8; C3 16.5; C2	7.8 7.8	7.0 7.0	1.4 1.6		
20	$CH(CH_3)CH_2N(C_2H_5)_2$	CCl_3	CCl_3	21	142	0.5	7.8	6.8 7.0	2.0 2.0	0.4 0.6	0.4 0.4	0.2 0.2		
21	$(CH_2)_4N(C_2H_5)_2$	CCl_3	CCl_3				C5	16.6; C2 16.9; C2	6.9 6.9	1.3 1.1	0.3 0.5	0.3 0.5	320 160 80 40	6.2 5.6 4.8 3.2
22	$(CH_2)_3N(CH_3)_2$	CCl_3					C5	11.6; C2	6.9 7.1	2.9 3.1	0.5 0.7	0.3 0.5		
23		CCl_3					0.1	0.1	0.1	0.1	0.1	0.1		
24	$(CH_2)_3N(CH_3)_2$						0.3	0.3	0.3	0.1	0.1	0.1		

(a) See footnotes a-d, Table III.

In view of the overall promise of these novel substances, the most promising member of the series, namely 5,5′-[[3-(dimethylamino)propyl]imino]bis[3-(trichloromethyl)-1,2,4-thiadiazole] (**14**), has been designated for expanded antimalarial and toxicological evaluation.

EXPERIMENTAL (18)

Trichloroacetamidine Hydrochloride (VII).

Gaseous ammonia was passed through a metal coil immersed in a dry ice-acetone bath, and the liquid was collected in a three-neck flask equipped with a stirrer and a dry ice-2-propanol condenser. To about 400 ml. of liquid ammonia collected in this manner was added dropwise 105 g. (0.727 mole) of trichloroacetonitrile. The ammonia was allowed to evaporate until the mixture became a light pink slush. This was taken up in 4 l. of hexane, dried over anhydrous potassium carbonate, and filtered. Hydrogen chloride was bubbled through the filtrate until no more precipitate formed. The white precipitate was collected, washed with hexane, and dried overnight at 45° to give 118 g. (82%) of the product, m.p. 220° dec. Literature (9) reports m.p. 223°.

5-Chloro-3-(trichloromethyl)-1,2,4-thiadiazole (VIII).

A solution of 130 g. (3.25 moles) of sodium hydroxide in 260 ml. of water was added dropwise with stirring to a mixture of 148 g. (0.75 mole) of trichloroacetamidine hydrochloride and 186 g. (0.75 mole) of trichloromethanesulfenyl chloride in 1 l. of dichloromethane. The temperature was maintained between -4° and 2° with an ice-salt bath. After the addition was complete, the mixture was allowed to warm slowly to room temperature and filtered to remove the precipitated salt. The salt was washed with dichloromethane, and the wash was combined with the filtrate. The dichloromethane layer was separated, washed twice with 100 ml. portions of water, dried over anhydrous sodium sulfate, filtered, and the solvent was removed *in vacuo*. The residual oil was distilled to give 95 g. (53%) of the product, b.p. 60-63° (0.2-0.3 mm.); $n_D^{24.5}$ 1.5690. Literature (10) reports n_D^{21} 1.5720.

5,5′-[[3-(Dimethylamino)propyl]imino]bis[3-(trichloromethyl)-1,2,4-thiadiazole] (**14**, Table II).

To a solution of 7.0 g. (0.0294 mole) of 5-chloro-3-(trichloromethyl)-1,2,4-thiadiazole (VIII) (10) in 15 ml. of benzene was added dropwise a solution of 6.0 g. (0.059 mole) of *N,N*-dimethyl-1,3-propanediamine in 20 ml. of benzene. The mixture was stirred overnight at room temperature and then at 40° for 3 hours. The solvent was removed *in vacuo* and the residue was washed with petroleum ether and recrystallized first from acetonitrile and then from hexane to give 0.5 g. (7%) of the product, m.p. 110-113°.

To obtain larger quantities of **14** the following modification was utilized. To a solution of 119 g. (0.5 mole) of 5-chloro-3-(trichloromethyl)-1,2,4-thiadiazole (VIII) in 400 ml. of benzene was added dropwise a solution of 95 g. (0.933 mole) of *N,N*-dimethyl-1,3-propanediamine in 100 ml. of benzene while the temperature was maintained at 30° with external cooling. The mixture was stirred for 1 hour after the addition was complete, filtered, and the solid discarded. The filtrate was washed successively with water, dilute sodium hydroxide, and water. It was dried over potassium carbonate and the solvent was removed *in vacuo*. To the oily residue was added 100 ml. of acetonitrile. The solid thus obtained was collected and recrystallized from acetonitrile to provide 46 g. (37%) of the product, m.p. 113-115°.

5-[[3-(Dimethylamino)propyl]amino]-3-(trichloromethyl)-1,2,4-thiadiazole Monohydrochloride (**5**, Table I).

A solution of 6.0 g. (0.025 mole) of 5-chloro-3-(trichloromethyl)-1,2,4-thiadiazole (VIII) (10) in 20 ml. of benzene was added dropwise to a cold (5-10°), stirred solution of 7.8 g. (0.076 mole) of *N,N*-dimethyl-1,3-propanediamine in 30 ml. of benzene. The reaction mixture was stirred at ice bath temperature for 1.5 hours, allowed to warm to room temperature, filtered to remove a small amount of solid, and evaporated to dryness *in vacuo*. The residue was taken up in a small amount of benzene and the solution was applied to a 20 x 5 cm. alumina column (Alcoa, F-20 Chromatographic Alumina) which had been equilibrated with benzene. The column was eluted with 1.05 l. of benzene and then with 1.4 l. of chloroform; the eluate was collected in 100 ml. fractions. Those fractions containing the desired product, as determined by thin layer chromatography (alumina-benzene; R_f = 0.07), were combined and evaporated to dryness *in vacuo*. The residue was dissolved in ether and 2 ml. of 25% hydrogen chloride in 2-propanol was added. The hydrochloride salt was collected, recrystallized from 2-propanol, and dried to give 0.7 g. of the product, m.p. 175-177°. An additional 0.3 g. was obtained by concentrating the mother liquor by one-half. Total yield, 12%.

Analogs **2-4**, **7**, **8**, **10**, **12**, and **13** (Table I) were prepared similarly in 10-60% yield by the condensation of one equivalent of 5-chloro-3-(trichloromethyl)-1,2,4-thiadiazole (VIII) with two equivalents of the requisite amine in benzene at 30-60° for 0.3-2 hours. The reaction mixtures were filtered to remove insoluble by-products, and the benzene filtrates were washed successively with dilute sodium hydroxide and water, dried over potassium carbonate, concentrated *in vacuo*, and the residue crystallized. One compound (**9**) was purified by column chromatography as above.

5-[[3-(Diethylamino)propyl]amino]-3-(trichloromethyl)-1,2,4-thiadiazole monohydrochloride, an intermediate for the preparation of **19**, was prepared similarly. Purification of the crude product by column chromatography on alumina with ethyl acetate, conversion to the hydrochloride, and recrystallization from acetonitrile afforded 5.7 g. (37%), m.p. 134-136°.

Anal. Calcd. for $C_{10}H_{17}Cl_3N_4S$·HCl: C, 32.62; H, 4.93; N, 15.22. Found: C, 32.71; H, 5.06; N, 15.27.

5,5′-[(3-[[Methyl[3-(trichloromethyl)-1,2,4-thiadiazol-5-yl]amino]-propyl)imino]bis[3-(trichloromethyl)-1,2,4-thiadiazole] (**17**, Table II).

One third of a solution of 7.7 g. (0.0753 mole) of *N,N*-dimethyl-1,3-propanediamine in 30 ml. of benzene was added rapidly dropwise to a stirred solution of 11.9 g. (0.05 mole) of 5-chloro-3-(trichloromethyl)-1,2,4-thiadiazole (VIII) (10) in 30 ml. of benzene. The exothermic reaction caused the mixture to reflux. The remaining amine solution was added slowly. The mixture was stirred at 60° for 1 hour, allowed to cool, and filtered. The filtrate was washed first with 5% aqueous sodium hydroxide and then with water. The benzene layer was dried over anhydrous potassium carbonate and evaporated to dryness *in vacuo*. The residual gum was washed three times with 30 ml. portions of hexane and then recrystallized from acetonitrile to give 1.2 g. (10%) of the product, m.p. 162-164°.

5-Amino-3-(trichloromethyl)-1,2,4-thiadiazole (**1**, Table I).

A solution of 10.0 g. (0.042 mole) of 5-chloro-3-trichloromethyl-1,2,4-thiadiazole (VIII) in 100 ml. of 2-propanol was heated at 50° under 60 p.s.i.g. of ammonia for 12 hours. The

mixture was filtered and the filter cake was washed with methanol. The filtrate and wash were combined and evaporated to dryness *in vacuo*. The greenish solid residue was shaken with a mixture of 200 ml. of water and 600 ml. of chloroform in a separatory funnel. A white precipitate accumulated at the interface. The chloroform layer was separated and filtered to collect the insoluble material. The water layer was extracted five times with 50-75 ml. portions of chloroform; each time the chloroform extract was filtered to collect additional solid. The water layer was discarded. The chloroform extracts were combined, dried over anhydrous potassium carbonate, filtered, and evaporated to dryness *in vacuo*. The residue was combined with the insoluble material and recrystallized from a benzene:acetonitrile mixture (3:1) to give 4.2 g. of product, m.p. 187-189°. Concentrating the mother liquor afforded an additional 1.6 g. of material, m.p. 187-189°. The total yield was 63%.

3-[[Bis[3-(trichloromethyl)-1,2,4-thiadiazol-5-yl]amino]-1-ethylpiperidine Monohydrochloride (**18**, Table II).

A solution of 16.0 g. (0.0673 mole) of 5-chloro-3-trichloromethyl-1,2,4-thiadiazole (VIII) in 40 ml. of acetone was added dropwise to a stirred mixture of 10.0 g. (0.072 mole) of powdered, anhydrous potassium carbonate and 4.3 g. (0.0336 mole) of 3-amino-1-ethylpiperidine in 50 ml. of acetone. The mixture was stirred overnight at room temperature and was then heated under reflux for 2 hours. It was allowed to cool and was filtered. The dark filtrate was treated with decolorizing charcoal, filtered through Supercel, and evaporated to dryness *in vacuo*. The residue was dissolved in benzene and applied to a 16 x 6.5 cm. column of alumina (Alcoa F-20 chromatographic) which had been equilibrated with benzene. The column was eluted with benzene and the eluate was collected in 100 ml. fractions. Those fractions containing the presumed product as determined by tlc (alumina-benzene; R_f = 0.47) were combined and evaporated to dryness *in vacuo* to give a yellow oil. The oil was dissolved in ether and the solution was filtered. To the filtrate was added 5 ml. of a 25% solution of hydrogen chloride in 2-propanol. The colorless solid that formed was collected, washed with ether, dried, and recrystallized from acetonitrile to give 3.7 g. (19%) of the title compound, m.p. 225-227° dec.

Compound **21** (Table II) was prepared similarly.

5,5'-[[2-(Diethylamino)ethyl]imino]bis[3-(trichloromethyl)-1,2,4-thiadiazole] Monohydrochloride (**16**, Table II).

A solution of 2.0 g. (0.005 mole) of 5-[[2-(diethylamino)-ethyl]amino]-3-(trichloromethyl)-1,2,4-thiadiazole monohydrochloride (**7**) in water was made strongly alkaline with 50% aqueous sodium hydroxide and extracted with chloroform. The extract was washed with a small amount of water, dried over anhydrous potassium carbonate, and the solvent was removed *in vacuo*. The residue was dissolved in 20 ml. of acetone, 1.4 g. (0.01 mole) of powdered anhydrous potassium carbonate and 1.2 g. (0.005 mole) of 5-chloro-3-(trichloromethyl)-1,2,4-thiadiazole (VIII) was added, and the mixture was heated under reflux for 2 hours and then stirred at room temperature for 48 hours. The mixture was filtered and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in benzene and applied to a 5 x 20 cm. alumina column (Alcoa, F-20) which had been equilibrated with benzene. The column was eluted with benzene and 100 ml. fractions were collected. Those fractions containing the product (tlc, alumina-benzene; R_f = 0.7) were combined and evaporated to dryness *in vacuo*. The residue was dissolved in ether and 1 ml. of 25% hydrogen chloride in 2-propanol was added. The white solid was collected, washed with ether, and recrystallized from 2-propanol to give 1.3 g. (47%) of the product, m.p. 190-192°.

Compounds **19** and **20** (Table II) were prepared similarly starting from VIII and the appropriate 5-[[(dialkylamino)alkyl]-amino]-3-(trichloromethyl)-1,2,4-thiadiazoles.

5-[[3-(Dimethylamino)propyl]amino]-3-methyl-1,2,4-thiadiazole Hydrochloride (**6**, Table I) and 5,5'-[[3-(Dimethylamino)propyl]-imino]bis[3-methyl-1,2,4-thiadiazole] Hydrochloride (**15**, Table II).

A solution of 10.6 g. (0.104 mole) of *N,N*-dimethyl-1,3-propanediamine in 15 ml. of benzene was added dropwise to a stirred solution of 7.0 g. (0.052 mole) of 5-chloro-3-methyl-1,2,4-thiadiazole (15). The mixture rapidly warmed to 60° and was cooled with an ice bath until the addition was complete. The reaction mixture was then stirred at 40° for 1 hour, cooled to room temperature, and filtered to remove diamine hydrochloride that had precipitated. The filtrate was washed first with 5% aqueous sodium hydroxide and then with water. The benzene layer was separated and used below. The sodium hydroxide and water washes were combined and extracted three times with chloroform. The extracts were dried and evaporated to dryness *in vacuo*. The residue was dissolved in ether and added to 200 ml. of ether containing 20 ml. of a 25% solution of hydrogen chloride in 2-propanol. The gum that formed was triturated with ether to give a white solid. The material was collected, immediately placed in a desiccator over Drierite and allowed to remain under vacuum for about an hour. It was then dried *in vacuo* at 40° overnight to give 5.8 g. (37%) of **6** as an extremely hygroscopic partial hydrochloride salt, m.p. 180-184° with preliminary softening.

The benzene layer from above was dried over magnesium sulfate, filtered, and evaporated to dryness. The residue was dissolved in a minimal amount of 1 *N* hydrochloric acid and the solution was extracted with chloroform. The aqueous layer was warmed briefly to remove residual chloroform, made basic with 50% aqueous sodium hydroxide, and chilled to give 1.1 g. (14%) of the partial hydrochloride salt **15**, m.p. 70-72°.

5-Chloro-3-(3,4-dichlorophenyl)-1,2,4-thiadiazole (X).

To a solution of 2.25 g. (0.01 mole) of 3,4-dichlorobenzamidine hydrochloride (16) in 50 ml. of water was added 1.86 g. (0.01 mole) of trichloromethylsulfenyl chloride. The mixture was cooled to 5° and to it was added 40 ml. of a 1 *N* sodium hydroxide solution (0.04 mole). The reaction mixture was stirred at 5° for 0.5 hour and then allowed to warm to room temperature. A white semi-solid formed which could not be filtered. The mixture was extracted with 300 ml. of dichloromethane, and the extract was washed with water, dried over magnesium sulfate, filtered, and evaporated to dryness *in vacuo*. The residue was dissolved in benzene and chromatographed on alumina with benzene. Those fractions containing the product as determined by tlc (alumina-benzene, R_f = 0.66) were combined and evaporated to dryness *in vacuo*. Recrystallization of the residue from acetonitrile gave 0.95 g. (36%) of the product, m.p. 84-85°.

Anal. Calcd. for $C_8H_3Cl_3N_2S$: C, 36.18; H, 1.14; N, 10.55. Found: C, 36.25; H, 1.20; N, 10.67.

3-(3,4-Dichlorophenyl)-5-[[3-(dimethylamino)propyl]amino]-1,2,4-thiadiazole (**11**, Table I).

A solution of 2.0 g. (0.02 mole) of *N,N*-dimethyl-1,3-propanediamine in 10 ml. of benzene was added dropwise to a stirred solution of 2.7 g. (0.01 mole) of 5-chloro-3-(3,4-dichlorophenyl)-1,2,4-thiadiazole (X) in 30 ml. of benzene. The mixture was stirred at 60° for 1 hour, allowed to cool to room temperature

overnight, and filtered to remove 0.8 g. of insoluble material. The filtrate was washed first with water and then with dilute sodium hydroxide, and again with water. The benzene layer was separated, dried over anhydrous potassium carbonate, filtered, and evaporated to dryness *in vacuo*. The residue was dissolved in ethyl acetate and applied to a 62 x 2.2 cm. alumina column (Alcoa F-20 chromatographic) which had been equilibrated with ethyl acetate. The column was eluted with ethyl acetate; fractions containing 25 to 50 ml. were collected. Those fractions containing the proposed product as determined by tlc (alumina-ethyl acetate, R_f = 0.3) were combined and evaporated to dryness *in vacuo*. The solid residue was recrystallized from acetonitrile to give 1.8 g. (55%) of the title compound, m.p. 78-80°.

3-(3,4-Dichlorophenyl)-3′-(trichloromethyl)-5,5′-[[3-(dimethylamino)propyl]imino]bis-1,2,4-thiadiazole Monohydrochloride (**22**, Table II) and 3-(3,4-Dichlorophenyl)-3′-(trichloromethyl)-5,5′-[(3-[methyl-[3-(trichloromethyl)-1,2,4-thiadiazol-5-yl]amino]propyl)-imino]bis-1,2,4-thiadiazole (**23**, Table II).

A solution of 2.9 g. (0.012 mole) of 5-chloro-3-trichloromethyl-1,2,4-thiadiazole (VIII) in 15 ml. of acetone was added dropwise to a stirred mixture of 4.0 g. (0.012 mole) of 3-(3,4-dichlorophenyl)-5-[[3-(dimethylamino)propyl]amino]-1,2,4-thiadiazole (**11**) and 3.3 g. (0.024 mole) of powdered anhydrous potassium carbonate in 25 ml. of acetone. The temperature of the reaction rose to 37° and additional white solid formed. The mixture was stirred for 2 hours and then filtered. The filter cake was washed well with chloroform and the filtrate and wash were combined and evaporated to dryness *in vacuo*. Thin layer chromatography (alumina-benzene) of the residue showed two major spots (R_f = 0.47, 0.21) and several minor ones. The residue was treated with benzene. The solution was decanted from the insoluble gum and was applied to a 2 x 58 cm. alumina column (Alcoa, F-20 chromatographic) equilibrated with benzene. The column was eluted with benzene. Fractions of 50 ml. were collected and those containing material with R_f = 0.47 were combined and evaporated to dryness *in vacuo*. The residue was recrystallized once from a cyclohexane:2-propanol mixture (1:1) and then from acetonitrile, and dried at 70° to give 0.6 g. (14%) of 3-(3,4-dichlorophenyl)-3′-(trichloromethyl)-5,5′-[(3-[methyl[3-(trichloromethyl)-1,2,4-thiadiazol-5-yl]amino]propyl)imino]bis-1,2,4-thiadiazole (**23**), m.p. 139-143°.

Elution with benzene was continued and those fractions containing material with R_f = 0.21 were combined and evaporated to dryness *in vacuo*. The residue was dissolved in ether and the solution was filtered. Three ml. of a 25% solution of hydrogen chloride in 2-propanol was added to the filtrate. The gelatinous precipitate that formed was collected and treated with 350 ml. of boiling 2-propanol. The hot mixture was filtered to collect the crude product. This was pulverized in ether and dried at 60° to give 0.8 g. (12%) of 3-(3,4-dichlorophenyl)-3′-(trichloromethyl)-5,5′-[[3-(dimethylamino)propyl]imino]bis-1,2,4-thiadiazole monohydrochloride (**22**), m.p. 248-250° dec.

5,5′-[[3-(Dimethylamino)propyl]imino]bis[3-(3,4-dichlorophenyl)-1,2,4-thiadiazole] (**24**, Table II).

A solution of 2.7 g. (0.0106 mole) of 5-chloro-3-(3,4-dichlorophenyl)-1,2,4-thiadiazole (X) in 30 ml. of benzene and 60 ml. of acetone was added dropwise to a stirred mixture of 3.5 g. (0.0106 mole) of 3-(3,4-dichlorophenyl)-5-[[3-(dimethylamino)propyl]-amino]-1,2,4-thiadiazole (**11**) and 2.8 g. (0.02 mole) of powdered anhydrous potassium carbonate in 50 ml. of acetone. The mixture was stirred overnight at room temperature, heated under reflux one hour, cooled, and filtered. The filter cake was washed with a small amount of acetone and was then extracted with 400 ml. of chloroform in a Soxhlet extractor for 4 hours. The extract was evaporated to dryness, and the residue was recrystallized from benzene to provide 2.8 g. (44%) of the product, m.p. 198-200°.

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