2-Phenyl-5-(trichloromethyl)-1,3,4-oxadiazoles, A New Class of Antimalarial Substances (1,2)

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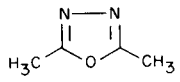
An investigation of hybrids of 2,5-dimethyl-1,3,4-oxadiazole (I) and α,α,α,α′,α′,α′-hexachloro-*p*-xylene (Hetol®) (II) as potential antimalarial agents led to the synthesis of representative 2-phenyl-5-(trichloromethyl)-1,3,4-oxadiazoles (VIa-f, VIII-X) and related trichloromethyl 1,2,4-oxadiazole, 1,3,4-oxadiazoles, and 1,3,4-thiadiazole (VII, XIII-XV). Treatment of the appropriately substituted benzoic acid hydrazides (IVa-f) with trichloroacetic anhydride afforded the intermediate 1-benzoyl-2-(trichloroacetyl)hydrazines (Va-f) which were cyclized to the desired 5-(chlorophenyl, tolyl, or α,α,α-trifluorotolyl)-2-(trichloromethyl)-1,3,4-oxadiazoles (VIa-f) (44-66%) *in situ* utilizing phosphorous oxychloride. Chlorination of the 5-tolyl-2-(trichloromethyl)-1,3,4-oxadiazoles (VId-f) afforded 2-(trichloromethyl)-5-(α,α,α-trichloro-*m*- and *p*-tolyl)-1,3,4-oxadiazole (VIII and IX) and 2-(α,α,α,α′,α′,α′-hexachloro-3,5-xylyl)-5-(trichloromethyl)-1,3,4-oxadiazole (X) in 23-56% yield. Each of the 2-phenyl-5-(trichloromethyl)-1,3,4-oxadiazoles (VIa-f, VIII-X) was active against *Plasmodium berghei* in mice when administered in single 160 or 640 mg./kg. subcutaneous doses or given orally by drug-diet for 6 days at doses of 29-336 mg./kg./day. The 2-(trichloromethyl)-5-(α,α,α-trichlorotolyl)-1,3,4-oxadiazoles (VIII-X) were the most active compounds prepared and exhibited activity against *P. berghei* comparable with Hetol®. Structure-activity relationships are discussed.

A review of accomplishments by the pharmaceutical industry in Germany during the period 1939-1945 (3) disclosed that Meiser and co-workers at Elberfeld investigated the antimalarial effects of various oxadiazole derivatives and discovered that 2,5-dimethyl-1,3,4-oxadiazole (I) possessed "prophylactic" antimalarial activity in birds.

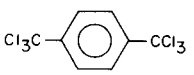


I

More recently the literature has been peppered with reports on the biological activity of other oxadiazole derivatives (4-15), namely anabolic (7), analgetic (8), anthelmintic (9), antibacterial (10,11), antispasmodic (8), fungicidal (12), hypoglycemic (13), insecticidal (12), muscle relaxant (14), nematocidal (12), and sedative (15) effects.

To enable further evaluation of the potential usefulness of oxadiazole derivatives in malaria chemotherapy, an authentic sample of 2,5-dimethyl-1,3,4-oxadiazole was resynthesized (16) for antimalarial testing. As might have been anticipated, 2,5-dimethyl-1,3,4-oxadiazole lacked appreciable suppressive activity against the erythrocytic phase of *Plasmodium berghei* in mice (17,18) or *Plasmodium gallinaceum* in chicks (19) when administered in a single, subcutaneous dose of 640 and 240 mg./kg., respectively. Moreover, the drug did not suppress oocysts or sporozoites of *P. gallinaceum* when fed to infected mosquitoes (*Aedes aegypti)* at a concentration of 0.1% in sucrose (20).

Following demonstrations that α,α,α,α′,α′,α′-hexachloro-*p*-xylene (II) (Hetol®) was active against *Fasciola hepatica*

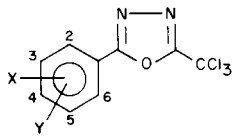


II

in rodents, sheep, and cattle (21) and was useful in the treatment of clonorchiasis and opisthorchiasis (22), it was discovered that this drug and related α,α,α,α′,α′,α′-hexachloroxylene derivatives also exhibited strong suppressive antimalarial activity against *P. berghei* in mice, *P. gallinaceum* in chicks, and *Plasmodium cynomolgi* and *Plasmodium knowlesi* in monkeys (23,24). The latter observations stimulated an investigation of hybrids of 2,5-di-

TABLE I

2-Phenyl-5-(trichloromethyl)-1,3,4-oxadiazoles

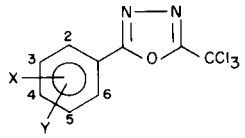


Compound No.	X, Y	M.p., °C	Yield, %	Purification Solvent (a)	Method	Formula	Analyses					
							Carbon, %		Hydrogen, %		Nitrogen, %	
							Calcd.	Found	Calcd.	Found	Calcd.	Found
VIa	3,4-Cl_2	94-95	53	A	I	$C_9H_3Cl_5N_2O$	32.52	32.73	0.91	1.07	8.43	8.12
VIb	4-Cl	88-90	58	A	I	$C_9H_4Cl_4N_2O$ (b)	36.27	36.03	1.35	1.59	9.40	9.22
VIc	4-CF_3	88-90	62	A	I	$C_{10}H_4Cl_3F_3N_2O$	36.22	36.02	1.21	1.26	8.45	8.14
VIII	3-CCl_3	114-116	56	A	II	$C_{10}H_4Cl_6N_2O$	31.53	31.59	1.06	1.12	7.35	7.33
IX	4-CCl_3	111-113	38	B	II	$C_{10}H_4Cl_6N_2O$	31.53	31.82	1.06	1.17	7.35	7.39
VId	3-CH_3	90-93	66	A	I	$C_{10}H_7Cl_3N_2O$	43.27	43.46	2.54	2.68	10.09	10.05
VIe	4-CH_3	93-95	64	A	I	$C_{10}H_7Cl_3N_2O$	43.27	43.06	2.54	2.68	10.09	10.04
X	3,5-$(CCl_3)_2$	115-116	23	A	II	$C_{11}H_3Cl_9N_2O$	26.52	26.70	0.60	0.83	5.63	5.55
VIf	3,5-$(CH_3)_2$	78-80	44	A	I	$C_{11}H_9Cl_3N_2O$	45.31	45.10	3.11	3.21	9.61	9.49

(a) A, aqueous ethanol; B, 2-propanol. (b) Chlorine, %: calcd. 47.59; found, 47.31.

TABLE II

Comparative Antimalarial Effects of 2-Phenyl-5-(trichloromethyl)-1,3,4-oxadiazoles and α,α,α,α′,α′,α′-Hexachloro-*p*-xylene Against *Plasmodium berghei* in Mice



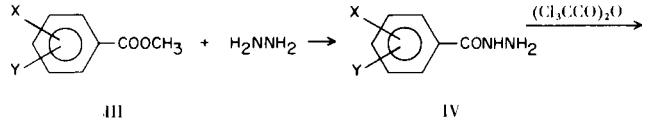
Compound No.	X, Y	Drug diet, 6 days: No. of mice	Drug diet, 6 days: SD_{90} (a), mg./kg./day	Drug diet, 6 days: Q (b)	Single s.c. dose: ΔMST; T or C (c) after mg./kg.: 640	320	160	80
VIa	3,4-Cl_2	14	105	0.7	5.6	4.4	4.2	1.6
VIb	4-Cl	14	105	0.7	T5	5.5	3.3	1.5
VIc	4-CF_3				9.3; T1 8.3; T1	6.4	3.4 3.8	1.0
VIII	3-CCl_3	21	29	2.6	22.8; C4 27.3; C3	7.0	5.8 6.0	1.4
IX	4-CCl_3				23.9; C3 23.9; C4	19.4, Cl	9.7 9.5	1.5
VId	3-CH_3	14	>73	<1.0	5.0 5.2	4.8	0.6 0.4	0.2
VIe	4-CH_3	14	336	0.2	7.3 6.9	4.9	2.1 1.3	0.5
X	3,5-$(CCl_3)_2$	21	32	2.3	9.6; Cl 8.1; Cl	8.2	4.8 4.6	3.0
VIf	3,5-$(CH_3)_2$	14	110	0.7	7.6 6.8	3.2	1.8 0.8	1.0
α,α,α,α′,α′,α′-Hexachloro-*p*-xylene (Hetol®)		28	36	2.1	C5 C5	8.9	6.7 6.9	0.3

(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 6.5 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 post infection and termed "cured"; data to establish parasitological cure based on sub-inoculation is unavailable. Each entry at each dose level represents results with a 5 animal group.

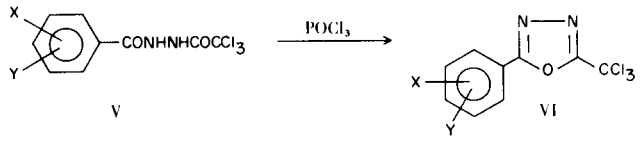
methyl-1,3,4-oxadiazole (I) and α,α,α,α′,α′,α′-hexachloro-*p*-xylene (II) as potential antimalarial agents. The present communication describes the synthesis and antimalarial properties of 2-phenyl-5-(trichloromethyl)-1,3,4-oxadiazoles and related trichloromethyl 1,2,4-oxadiazoles and 1,3,4-thiadiazoles, several of which exhibit noteworthy antimalarial activity.

The 2-phenyl-5-(trichloromethyl)-1,3,4-oxadiazoles VI a-f (Table I) were synthesized according to Scheme I. The appropriate substituted benzoic acids were converted to the corresponding methyl esters IIIa-f, which upon treatment with hydrazine afforded the benzoic acid hydrazides IVa-f (25-27). Condensation of IVa-f with trichloroacetic anhydride afforded the crude 1-benzoyl-2-trichloroacetylhydrazines (Va-f) which were not purified but were ring-closed to the desired 2-phenyl-5-(trichloromethyl)-1,3,4-oxadiazoles (VIa-f) *in situ* utilizing phosphorous oxychloride (44-66% yield, method I). The experimental conditions outlined previously for the synthesis of 2-phenyl-5-(trichloromethyl)-1,3,4-oxadiazole (12) were gen-

SCHEME I



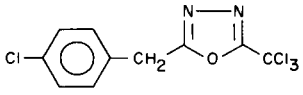
III IV



V VI

a,X,Y = 3,4-Cl_2
b,X,Y = 4-Cl
c,X,Y = 4-CF_3
d,X,Y = 3-CH_3
e,X,Y = 4-CH_3
f,X,Y = 3,5-$(CH_3)_2$

erally satisfactory. 2-(*p*-Chlorobenzyl)-5-(trichloromethyl)-1,3,4-oxadiazole (VII) was obtained (21%) in a similar



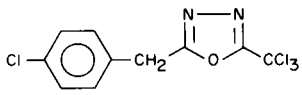
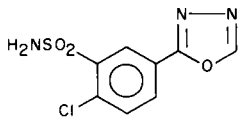
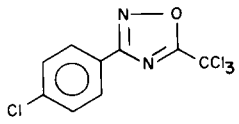
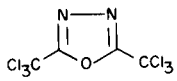
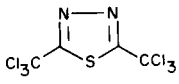
VII

manner from (*p*-chlorophenyl)acetic acid hydrazide (28), trichloroacetic anhydride, and phosphorous oxychloride.

2-Phenyl-1,3,4-oxadiazole analogs of Hetol® having trichloromethyl groups attached both to the benzene and the oxadiazole rings were of special interest. Chlorination of compounds VId-f with gaseous chlorine in a vessel irradiated with a 75 watt floodlight afforded 2-(trichloromethyl)-5-(α,α,α-trichloro-*m*-tolyl)-1,3,4-oxadiazole (VIII)

TABLE III

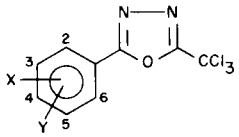
Antimalarial Effects of Miscellaneous 1,2,4-Oxadiazoles, 1,3,4-Oxadiazoles, and 1,3,4-Thiadiazoles Against *Plasmodium berghei* in Mice

Compound No.	Structure	Drug diet, 6 days: No. of mice	Drug diet, 6 days: SD_{90} (a), mg./kg./day	Drug diet, 6 days: Q (a)	Single s.c. Dose: ΔMST; T or C (a) after mg./kg.: 640	320	160	80
VII		14	248	0.3	5.7 4.1	2.1	2.7 1.5	0.7
XI					5.3		3.7 1.1	0.7
XIII		7	> 79	<0.9	2.9 1.3	0.7	0.7 0.3	0.3
XIV		7	>106	<0.7	T5		1.3, T1	
XV		7	>145	<0.5	T5	T5	1.4, T3	0.3

(a) See footnotes a-c, Table II.

TABLE IV

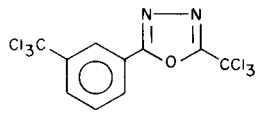
Comparative Antimalarial Effects of 2-Phenyl-5-(trichloromethyl)-1,3,4-oxadiazoles and α,α,α,α′,α′,α′-Hexachloro-*p*-xylene Against *Plasmodium gallinaceum* in Chicks



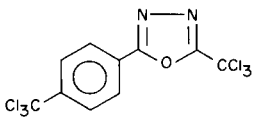
Compound No.	X, Y	Single s.c. dose (mg./kg.)	MST of Chicks (days) Treated	Control	ΔMST (a)	No. of Chicks Cured (b)	Toxic (c)
VIb	4-Cl	120	12.5	3.8	8.17	1	0
		240	20.5	3.8	16.7	3	0
VIc	4-CF_3	120	10.0	3.9	6.1	0	0
VIII	3-CCl_3	120	4.0	3.7	0.3	0	0
VId	3-CH_3	120	4.0	3.7	0.3	0	0
VIe	4-CH_3	100	4.0	3.7	0.3	0	0
X	3,5-$(CCl_3)_2$	480	4.0	3.9	0.1	0	0
VIf	3,5-$(CH_3)_2$	120	4.0	3.7	0.3	0	0
α,α,α,α′,α′,α′-Hexachloro-*p*-xylene (Hetol®)		120	4.0	3.2	0.8	0	0

(a) ΔMST is the mean survival time (days) of treated chicks (MSTT) minus the mean survival time (days) of control chicks (MSTC). (b) Chicks surviving to 30 days post infection are termed "cured"; data to establish parasitological cure based on sub-inoculation is unavailable. (c) Deaths occurring within 48 hours after infection 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.

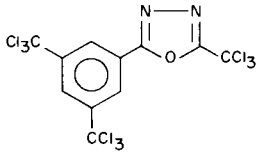
(56%), 2-(trichloromethyl)-5-(α,α,α-trichloro-*p*-tolyl)-1,3,4-oxadiazole (IX) (38%), and 2-(α,α,α,α′,α′,α′-hexachloro-3,5-xylyl)-5-(trichloromethyl)-1,3,4-oxadiazole (X) (23%),



VIII



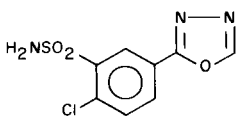
IX



X

respectively. The progress of the chlorination was monitored by NMR spectroscopy and the reaction was terminated upon the disappearance of all aliphatic proton absorption.

In an attempt to prepare sulfonamide derivatives of the 2-phenyl-5-(trichloromethyl)-1,3,4-oxadiazoles, 2-(*p*-chlorophenyl)-5-(trichloromethyl-1,3,4-oxadiazole (VIb) was treated successively with chlorosulfonic acid and liquid ammonia. The only product isolated from the reaction mixture analyzed correctly (C,H,N) for 2-chloro-5-(1,3,4-oxadiazol-2-yl)benzenesulfonamide (XI) (38%), and the physical properties of the product were in agreement with

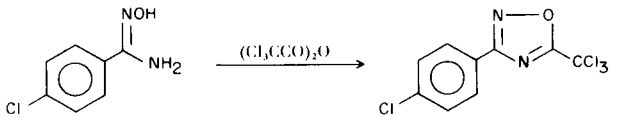


XI

those reported previously by Millard *et al.* (29) for an authentic sample of XI. The starting material VIb was recovered unchanged when treated with liquid ammonia

under similar conditions. It therefore appears that a carbon-carbon bond rupture occurred during the chlorosulfonation reaction.

In view of the interesting antimalarial activity exhibited by the 2-phenyl-5-(trichloromethyl)-1,3,4-oxadiazoles, a sample of the isomeric 3-(*p*-chlorophenyl)-5-(trichloromethyl)-1,2,4-oxadiazole (XIII) was prepared in 71% yield



XII XIII

by condensing *p*-chlorobenzamidoxime (9) with trichloroacetic anhydride in trichloroacetic acid utilizing the general procedure of Sousa *et al.* (12).

Attempts to prepare 2,5-bis(trichloromethyl)-1,3,4-oxadiazole (XIV) by cyclization of 1,2-bis(trichloroacetyl)-hydrazine with phosphorous oxychloride or polyphosphoric

XIV XV

acid or by chlorination of 2,5-dimethyl-1,3,4-oxadiazole (I) were unsuccessful. However, XIV was obtained in poor yield (8%) by the ring-closure of 1,2-bis(trichloroacetyl)hydrazine with phosphorous pentachloride according to the procedure of Yiannios *et al.* (30). 2,5-Bis-(trichloromethyl)-1,3,4-thiadiazole (XV) was prepared in 19% yield by chlorination of 2,5-dimethyl-1,3,4-thiadiazole in chloroform with irradiation.

In preliminary antimalarial studies the compounds described in the present communication were administered subcutaneously in a single dose to mice infected with *Plasmodium berghei* (17,18). Each of the 2-phenyl-5-(trichloromethyl)-1,3,4-oxadiazoles (VIa-f, VIII-X) caused an increase in the mean survival time of treated mice ranging from 5.0 to 27.3 days at doses of 160 or 640 mg./kg. (Table II). The three 2-(trichloromethyl)-5-tolyl-(or xylyl)-1,3,4-oxadiazoles VIII-X cured some mice at doses of 160 and 640 mg./kg. and thus exhibited activity comparable with Hetol®. Compounds VIa, b, d-f, VII, VIII, X, and XIII-XV were also given continuously by drug-diet for 6 days to mice infected with another normal drug-sensitive strain of *P. berghei* (31,32) (Tables II and III). Seven compounds (VIa, b, e, f, VII, VIII, and X) were active at daily doses ranging from 29-336 mg./kg., and the oral structure-activity relationships exhibited a strong correlation with the previous subcutaneous results *(vide supra)*. Thus 2-(trichloromethyl)-5-(α,α,α-trichloro-*m*-tolyl)-1,3,4-oxadiazole (VIII) (SD_{90} = 29 mg./kg./day, Q = 2.6) and 2-(α,α,α,α′,α′,α′-hexachloro-3,5-xylyl)-5-(trichloromethyl)-1,3,4-oxadiazole (X) (SD_{90} = 32 mg./kg./day, Q = 2.3) were the most active compounds tested and each substance was comparable with Hetol® (II) in potency.

Compounds VIb-f, VII, VIII, X, XIII, and XV were also evaluated against *P. gallinaceum* infections in white Leghorn cockerels (19). Chicks were given an intravenous injection of 0.2 ml. of heparinized blood infected with *P. gallinaceum* and having a minimum of 80-90% parasitized red blood cells. The parasitized blood was drawn by cardiac puncture from donor birds infected 72 hours earlier with *P. gallinaceum*. Donor strains were maintained in separate groups of chicks, 14-16 days old, that also received inoculations of heparinized infected blood. In every experiment 100% of the untreated control birds died within 72-96 hours post-infection. Candidate substances were administered to chicks in a single subcutaneous dose in peanut oil immediately after infection. In this test, as in the mouse test, the antimalarial activity of candidate compounds was assessed by comparing the maximum survival times of treated malaria-infected chicks with the survival times of untreated malaria-infected controls. A compound was arbitrarily considered to be active against malaria if it produced increases in the survival times of treated chicks that were at least 100% over the survival times of untreated controls. Surprisingly, 2-(*p*-chlorophenyl)-5-(trichloromethyl)-1,3,4-oxadiazole (VIb) and 2-(trichloromethyl)-5-(α,α,α-trifluoro-*p*-tolyl)-1,3,4-oxadiazole (VIc), which exhibited minimal activity against *P. berghei*, were the only two compounds active against *P. gallinaceum* in chicks based on these criteria (Table IV). In contradistinction, the 2-(trichloromethyl)-5-tolyl(or xylyl)-1,3,4-oxadiazoles VIII and X, which showed strong oral and parenteral activity against *P. berghei* in mice *(vide supra)*, were ineffective against *P. gallinaceum* in chicks (Table IV). At present no satisfactory explanation of this discrepancy is apparent. None of the compounds tested (VIa-c, e, VII, IX, X, and XV) suppressed oocysts or sporozoites of *P. gallinaceum* when fed to infected mosquitoes *(Aedes aegypti)* at a concentration of 0.1% in sucrose (20).

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are corrected. NMR spectra were determined on a Varian A-60 spectrometer in deuteriochloroform or carbon tetrachloride using tetramethylsilane as an internal standard.

2,5-Dimethyl-1,3,4-oxadiazole (I) (16).

A mixture of 46.4 g. (0.4 mole) of *sym*-diacetylhydrazine and

60 ml. (0.6 mole) of acetic anhydride was heated under reflux for 2 hours. Solvent was removed *in vacuo* and the residue was distilled to give 33.7 g. of crude product, b.p. 105-115°/70 mm. The infrared spectrum of this material indicated that some residual acetic acid and acetic anhydride were present. The crude product was combined with the crude product from a preceding 0.2 mole run and stirred with 100 ml. of concentrated ammonium hydroxide for 2 hours at room temperature. The mixture was extracted with four 100 ml. portions of ether. The combined extracts were dried over magnesium sulfate, and the ether removed by distillation, and the residue distilled to give 16.8 g. (29.5%) of product, b.p. 105°/60 mm., n_D^{25} = 1.4348.

Anal. Calcd. for $C_4H_6N_2O \cdot 1/6H_2O$: C, 47.51; H, 6.31; N, 27.71; H_2O, 2.96. Found: C, 47.53; H, 6.60; N, 27.93; H_2O, 2.83.

Benzoic Acid Hydrazides (IVa-f).

A mixture of 50.0 g. (0.33 mole) of 3,5-dimethylbenzoic acid and 150 ml. of thionyl chloride was heated under reflux for 4 hours. The excess thionyl chloride was removed *in vacuo*. To the crude acid chloride, cooled with an ice bath, was added 100 ml. of methanol and the solution was heated under reflux for 2 hours. The excess methanol was removed *in vacuo*. To the crude ester, 100 ml. of 85% hydrazine hydrate was added and the reaction mixture was heated under reflux for 2 hours. After cooling, the reaction mixture was diluted with water, and the crude hydrazide was collected by filtration. Recrystallization from 1.5 l. of water gave 39.8 g. (73%) of 3,5-dimethylbenzoic acid hydrazide, m.p. 136-137°.

Anal. Calcd. for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.94; H, 7.47; N, 17.06.

The following benzoic acid hydrazides were prepared in a similar fashion: 4-chloro-, m.p. 165-166° (25); 3,4-dichloro-, m.p. 169-171° (26); 4-trifluoromethyl-, m.p. 120-122° (27); 3-methyl-, m.p. 93-96° (25); and 4-methyl-, m.p. 112-115° (25).

2-Phenyl-5-(trichloromethyl)-1,3,4-oxadiazoles (VIa-f) (Method I).

To 0.04 mole of the substituted benzoic acid hydrazide was added 0.04 mole of trichloroacetic anhydride with stirring. After the exothermic reaction subsided, the reaction mixture was allowed to cool to room temperature at which point it usually solidified. Phosphorous oxychloride (30.0 g.) was added to the crude 1-(substituted benzoyl)-2-(trichloroacetyl)hydrazine, and the mixture was heated under reflux for 2-3 hours. The reaction mixture was cooled and added to a vigorously stirred mixture of ice and water. The crude product was separated by filtration and recrystallized from aqueous ethanol.

2-(*p*-Chlorobenzyl)-5-(trichloromethyl)-1,3,4-oxadiazole (VII).

(*p*-Chlorophenyl)acetic acid hydrazide (28) (18.5 g., 0.1 mole) was allowed to react with 30.9 g. (0.1 mole) of trichloroacetic anhydride and 100 ml. of phosphorous oxychloride utilizing the general procedure outlined above for the 2-phenyl analogs VIa-f. The crude product was crystallized successively from aqueous ethanol, methanol, and ethanol to give 6.4 g. (21%) of off-white crystals, m.p. 109-111°.

Anal. Calcd. for $C_{10}H_6Cl_4N_2O$: C, 38.49; H, 1.94; N, 8.98. Found: C, 38.85; H, 2.28; N, 8.98.

2-(Trichloromethyl)-5-(α,α,α-trichlorotolyl)-1,3,4-oxadiazoles (VIII-X) (Method II).

Chlorine was bubbled into a solution of 10.0 g. (0.036 mole) of VId in 150 ml. of carbon tetrachloride heated under reflux for 17 hours. The apparatus was irradiated with a 75W floodlight. The reaction was monitored by NMR spectroscopy and was terminated upon the disappearance of all aliphatic proton absorption. The solution was evaporated to dryness *in vacuo* and the residue was recrystallized from ethanol and then from aqueous ethanol to give 7.6 g. (56%) of 2-(trichloromethyl)-5-(α,α,α-trichloro-*m*-tolyl)-1,3,4-oxadiazole (VIII), m.p. 114-116°

2-Chloro-5-(1,3,4-oxadiazol-2-yl)benzenesulfonamide (XI).

A mixture of 3.5 g. (0.012 mole) of 2-(*p*-chlorophenyl)-5-(trichloromethyl)-1,3,4-oxadiazole (VIb) and 10.0 g. (0.086 mole) of chlorosulfonic acid was heated with stirring at an oil bath temperature of 165-170° for 5 hours. The reaction mixture was poured onto crushed ice, and the solid was isolated by filtration and washed with water. The crude product was added with stirring to 20 ml. of liquid ammonia cooled to -70° in a 2-propanol-dry ice bath. Tetrahydrofuran (30 ml.) was added and the cooled mixture was stirred for 1 hour and then allowed to come to room temperature during 0.5 hour. The reaction mixture was filtered and the crude product was recrystallized from water to give 0.8 g. (38%) of XI, m.p. 197-200° (29).

Anal. Calcd. for $C_8H_6ClN_3O_3S$: C, 37.00; H, 2.33; N, 16.18. Found: C, 37.11; H, 2.38; N, 15.82.

3-(*p*-Chlorophenyl)-5-(trichloromethyl)-1,2,4-oxadiazole (XIII).

A mixture of 8.5 g. (0.05 mole) of *p*-chlorobenzamidoxime (9) and 32.7 g. (0.2 mole) of trichloroacetic acid was heated to 65° (oil bath temperature) to obtain a homogeneous melt. To the melt, 30.9 g. (0.1 mole) of trichloroacetic anhydride was added and the solution was heated at 110° (oil bath temperature) for 0.5 hour. The reaction mixture was poured into 500 ml. of water with stirring and extracted with 250 ml. of carbon tetrachloride. The carbon tetrachloride solution was washed with 500 ml. of water, 500 ml. of sodium bicarbonate solution, and 500 ml. of water, and then dried over sodium sulfate. The carbon tetrachloride was removed *in vacuo* to give 12.0 g. of crude product as an oil. Distillation of this oil gave 10.5 g. (71%) of the desired product, b.p. 91-94°/0.07 mm., which solidified on cooling, m.p. 43-45°.

Anal. Calcd. for $C_9H_4Cl_4N_2O$: C, 36.27; H, 1.35; N, 9.40. Found: C, 36.57; H, 1.42; N, 9.52.

2,5-Bis(trichloromethyl)-1,3,4-thiadiazole (XV).

Chlorine was bubbled into a refluxing solution of 6.5 g. (0.0625 mole) of 2,5-dimethyl-1,3,4-thiadiazole in 50 ml. of chloroform irradiated with a 75W floodlight for 32.5 hours. The reaction was monitored by NMR spectroscopy and was terminated upon the disappearance of all proton absorption from the spectrum. The reaction mixture was concentrated to dryness *in vacuo*, and the residue was recrystallized from aqueous ethanol to give 3.7 g. (19%) of XV, m.p. 145-147°.

Anal. Calcd. for $C_4Cl_6N_2S$: C, 14.98; Cl, 66.30; N, 8.73; S, 9.99. Found: C, 15.31; Cl, 65.23; N, 8.74; S, 10.25.

Acknowledgments.

The authors are indebted to Dr. Leo Rane of the University of Miami and to Dr. Paul E. Thompson of Parke, Davis and Company for the antimalarial testing. We also wish to thank Mr. C. E. Childs and associates for the microanalyses, and Dr. J. M. Vandenbelt and co-workers for determination of the spectral data.

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Received November 13, 1969 Ann Arbor, Michigan 48106