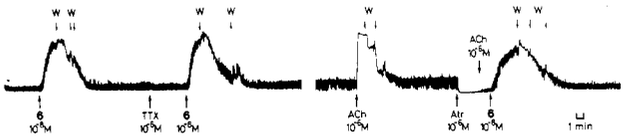

Figure 3. Comparison of contractile response of the isolated rabbit duodenum in a longitudinal axis to **6** and acetylcholine (ACh) in vitro. The contractile response induced by **6** (10^{-8} M) was phasic with a gradual tonal increase while that induced by ACh (10^{-6} M) was a rapid tonic contraction. The effect of **6** on smooth muscle contraction was not inhibited by the pretreatment of the muscle preparation with tetrodotoxin (TTX, 10^{-6} M) or atropine (Atr, 10^{-6} M). The minimum effective concentration of **6** measured in this system was found to be 10^{-9} M. W with arrows indicates repeated washing of preparation.

among the derivatives as shown in Table I, the qualitative characteristics of the contractile patterns induced by these derivatives were quite similar to each other; namely, all these derivatives induced a series of contractions in the gastrointestinal tract which were quite similar to the natural interdigestive contractions. The in vitro study, moreover, indicated that **6** caused contractions of the rabbit duodenum in a concentration of 10^{-9} M (the minimum effective concentration).[13] The contractile pattern induced by **6**, as shown in Figure 3, was quite different from that caused by acetylcholine, and the contractions produced by this compound were not blocked by pretreatment with tetrodotoxin (10^{-6} M) and atropine (10^{-6} M). The EM derivatives illustrated here may be useful to modulate the contractile activity in the gastrointestinal tract. Such agents may alone be useful tools to study the physiology and controlling mechanism of gastrointestinal motility.

(13) Strunz, U.; Domschke, W.; Mitznegg, P.; Domschke, S.; Shubert, E.; Wunsch, E.; Jaeger, E.; Delming, L. *Gastroenterology* **1975**, *68* 1485–1491.

Registry No. **1**, 33396-29-1; **2**, 110205-60-2; **3** (X = I^-), 110205-61-3; **4** (X = I^-), 110205-62-4; **5** (X = Br^-), 110205-63-5; **6** (X = Br^-), 110205-64-6; **7** (X = I^-), 110205-65-7; **8** (X = Br^-), 110205-66-8; **9** (X = Br^-), 110205-67-9; EM-A, 114-07-8; 8,9-dihydroerythromycin A 6,9-epoxide, 42853-24-7.

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Received June 8, 1987

Articles

Antimalarial Activity of 2-(Substituted amino)-4,6-bis(trichloromethyl)-1,3,5-triazines and *N*-(Chlorophenyl)-*N'*-[4-(substituted amino)-6-(trichloromethyl)-1,3,5-triazin-2-yl]guanidines[1,2]

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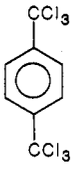
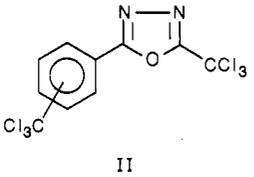
A series of 2-[[(dialkylamino)alkyl]amino]-4,6-bis(trichloromethyl)-1,3,5-triazines (III) and *N*-(4-chlorophenyl)-*N'*-[4-[[(dialkylamino)alkyl]amino]-6-(trichloromethyl)-1,3,5-triazin-2-yl]guanidines (IV) were prepared from 2,4,6-tris(trichloromethyl)-1,3,5-triazine and 2-chloro-4,6-bis(trichloromethyl)-1,3,5-triazine. Compounds of type III showed modest antimalarial activity while XIa with the camoquin side chain was more potent. Analogues of type IV broadly exhibited modest antimalarial activity.

The continuing problem of drug resistance in the successful treatment of malaria mandates further exploratory studies for novel structural classes that exhibit even moderate antimalarial activity.

The importance of the trichloromethyl group has been implicated in several instances in conferring antimalarial activity on a molecular species. Thus both aromatic and heterocyclic structures (I, II) have been shown to possess strong suppressive activity against the malaria parasite.[3-5]



I



II

In the course of these investigations patents[6,7] came to our attention indicating that certain trichloromethyl-

(1) This is paper 64 of a series on antimalarial drugs. For paper 63, see: Werbel, L. M.; Degnan, M. J. *J. Med. Chem.* **1987**, *30*, 2151.

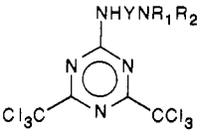
(2) This investigation was supported in part by U.S. Army Medical Research and Development Command Contract DA-49-193-MD-2754. This is Contribution No. 1815 to the U.S. Army Drug Development Program.

(3) Jacobus, D. P. Presented before the Division of Medicinal Chemistry at the 153rd National Meeting of the American Chemical Society, Miami Beach, FL, April 1967.

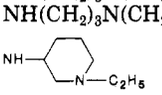
(4) Elslager, E. F.; Hutt, M. P.; Werbel, L. M. *J. Med. Chem.* **1970**, *13*, 542.

0022-2623/87/1830-1943$01.50/0

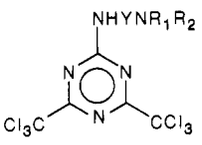
Table I. 2-[[(Dialkylamino)alkyl]amino]-4,6-bis(trichloromethyl)-1,3,5-triazines



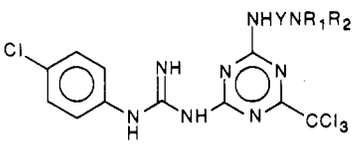
III

compd no.	$NHYNR_1R_2$	mp, °C	yield purified, %	purifn solvent	formula	anal.
IIIa	$NH(CH_2)_3N(CH_3)_2$	123–124	83	$MeOH-H_2O$	$C_{10}H_{13}Cl_6N_5$	C, H, N, Cl
IIIb	$NH(CH_2)_3N(CH_2)_4$	132–135	62		$C_{12}H_{15}Cl_6N_5$	C, H, N, Cl
IIIc		97–98	69	$MeOH-H_2O$	$C_{12}H_{15}Cl_6N_5$	C, H, N
IIId	$NH(CH_2)_4N(CH_2)_4$	103–106	47		$C_{13}H_{17}Cl_6N_5$	C, H, N
IIIe	$NH(CH_2)_5N(CH_2)_4$	136–139	60	$EtOH-H_2O$	$C_{14}H_{19}Cl_6N_5$	C, H, N

substituted triazines (III, IV) also had potent activity against *Plasmodium berghei* infections in the mouse.

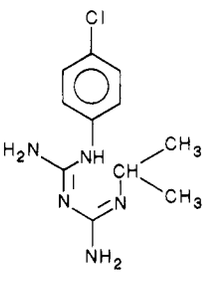


III

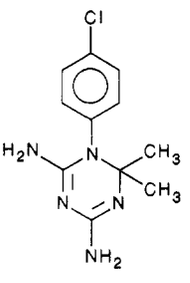


IV

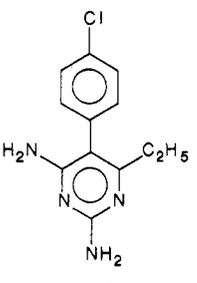
Generally, structural requirements for potent antimalarial activity in the chlorguanide (V), cycloguanil (VI), and pyrimethamine series (VII) are rather specific and parallel to each other. Furthermore, strains of malarial parasites resistant to one of these drugs are usually cross-resistant to the other two substances.



V



VI



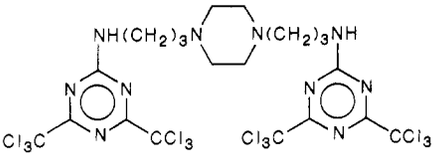
VII

The tacit assumption is often made that antimalarial substances related to compounds V–VII would be cross-resistant. However, there is a good possibility that certain types of related compounds may act by different mechanisms and thus escape this liability.

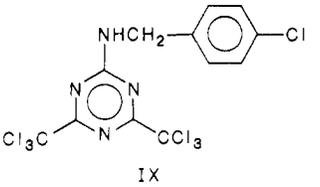
For example, 5-[(4-nitrophenyl)methyl]-2,4-pyrimidinediamine is virtually as active against a strain of *Plasmodium gallinaceum* 64-fold resistant to pyrimethamine as to the parent strain.[8] The closely related 5-[(3,4,5-trimethoxyphenyl)methyl]-2,4-pyrimidinediamine (trimethorprim) is active against pyrimethamine-resistant *Plasmodium falciparum*.[10] Furthermore, *N*-(4-chlorophenyl)-*N'*-[4-[[2-(diethylamino)ethyl]amino]-6-methyl-2-pyrimidinyl]guanidine is fully effective against chlorguanide-resistant *P. gallinaceum*, cycloguanil-resistant *P. berghei*, chlorguanide-resistant *P. knowlesi*, and pyrimethamine-resistant *Plasmodium knowlesi*.[11,13]

Thus it was of interest to reexplore the (trichloromethyl)triazines. The parent compounds were shown to be curative against *P. berghei* infections in mice. Expansion of these series was then undertaken and it is this work that is the subject of the present paper.

Chemistry. The 2-[[(dialkylamino)alkyl]amino]-4,6-bis(trichloromethyl)-1,3,5-triazines III (Table I) were prepared by stirring 2,4,6-tris(trichloromethyl)-1,3,5-triazine[14] (Xa) with an aliphatic diamine in ethyl acetate at room temperature. *N,N'*-[1,4-Piperazinediylbis(1,3-propanediyl)]bis[4,6-bis(trichloromethyl)-1,3,5-triazin-2-amine] (VIII) was obtained similarly by utilizing 2 equiv of Xa and 1 equiv of 1,4-piperazinedipropanamine. The [(4-chlorophenyl)methyl]amino derivative IX was obtained by mixing Xa and 4-chlorobenzenemethanamine in benzene at ice-bath temperature.



VIII

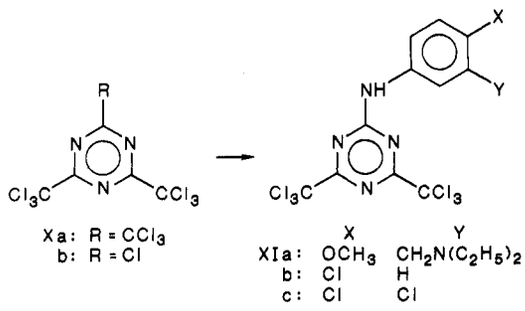


IX

Displacement of the trichloromethyl group by less basic aromatic amines was unsuccessful. Xa was therefore hydrolyzed in aqueous triethylamine to the triethylamine salt of 4,6-bis(trichloromethyl)-1,3,5-triazin-2-ol, which was then converted to 2-chloro-4,6-bis(trichloromethyl)-1,3,5-triazine[15] (Xb) with phosphorus oxychloride. Treatment with 5-amino-*N,N*-diethyl-2-methoxybenzenemethanamine, 4-chlorobenzenamine, and 3,4-dichlorobenzenamine in benzene provided XIa–c.

The reaction between Xb and 4-chlorobenzoic acid hydrazide in acetonitrile at room temperature furnished 4-chlorobenzoic acid 2-[4,6-bis(trichloromethyl)-1,3,5-

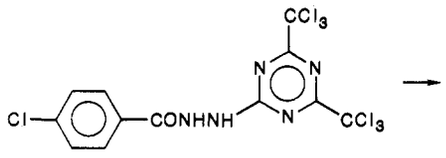
(5) Hutt, M. P.; Elslager, E. F.; Werbel, L. M. *J. Heterocycl. Chem.* **1970**, *7*, 511.
(6) Birtwell, S.; Hepworth, W. British Patent 767 848, 1957.
(7) Birtwell, S.; Hepworth, W.; Stacey, G. J. British Patent 767 749, 1957.
(8) Greenberg, J.; Bond, H. W. *J. Parasitol.* **1954**, *40*, 472.
(9) Martin, D. C.; Arnold, J. D. *J. Clin. Pharmacol.* **1967**, *7*, 336.
(10) Martin, D. C.; Arnold, J. D. *J. Am. Med. Assoc.* **1968**, *203*, 476.
(11) Williamson, J.; Lourie, E. M. *Am. J. Trop. Med. Parasitol.* **1947**, *41*, 278.
(12) Singh, I.; Ray, A. P.; Basu, P. C.; Nair, C. P. *Trans. R. Soc. Trop. Med. Hyg.* **1952**, *46*, 639.
(13) Singh, J.; Nair, C. P.; Ray, A. P. *Indian J. Malariol.* **1954**, *8*, 187.
(14) Norton, T. R. *J. Am. Chem. Soc.* **1950**, *72*, 3527.
(15) Kober, E. *J. Org. Chem.* **1960**, *25*, 1728.



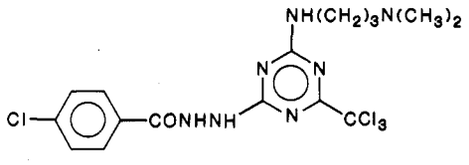
Xa: R = CCl_3
b: R = Cl

	X	Y
XIa:	OCH_3	$CH_2N(C_2H_5)_2$
b:	Cl	H
c:	Cl	Cl

triazin-2-yl]hydrazide (XII). Heating XII in acetonitrile with *N,N*-dimethyl-1,3-propanediamine provided 4-chlorobenzoic acid 2-[4-[[3-(dimethylamino)propyl]-amino]-6-(trichloromethyl)-1,3,5-triazin-2-yl]hydrazide (XIII).

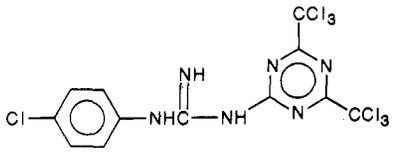


XII

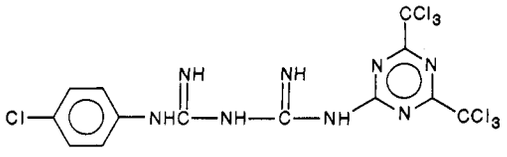


XIII

N-(4-Chlorophenyl)guanidine reacts with Xa to give *N*-[4,6-bis(trichloromethyl)-1,3,5-triazin-2-yl]-*N'*-(4-chlorophenyl)guanidine (XIV).[7] Brief heating of XIV with



XIV



XV

the appropriate diamine in benzene afforded the *N*-(4-chlorophenyl)-*N'*-[4-[[(dialkylamino)alkyl]amino]-6-(trichloromethyl)-1,3,5-triazin-2-yl]guanidines (**IV**) (Table II). The condensation of Xa with *N*-(4-chlorophenyl)imidodicarbonimidic diamide failed to give the desired *N*-(4-chlorophenyl)-*N'*-[4,6-bis(trichloromethyl)-1,3,5-triazin-2-yl]imidodicarbonimidic diamide (XV). This was obtained in poor yield, however, by allowing Xb to react with *N*-(4-chlorophenyl)imidodicarbonimidic diamide in acetonitrile at room temperature.

Antimalarial Effects. The compounds described were evaluated in mice infected with *P. berghei* sc[16] or by drug diet,[18] and against *P. gallinaceum* infections in white Leghorn cockerels[21] (Tables III and IV).

The 2-[[(dialkylamino)alkyl]amino]-4,6-bis(trichloromethyl)-1,3,5-triazines III displayed modest antimalarial activity, but none were considered sufficiently potent to warrant additional studies. It was surprising that structures of type III (Table III) lacked strong antimalarial effects against *P. gallinaceum* when given in a single sc dose. Neither bis-compound VIII nor the 4-chlorobenzenemethanamine analogue IX demonstrated antimalarial activity. Of the aromatic amine analogues, only the camoquin-like compound XIa showed activity and it was surprisingly potent with a *Q* of 1.5 (see footnote *b*, Table III) when given by drug diet, although it was quite toxic when given subcutaneously. The benzoic acid hydrazide derivatives XII and XIII were without antimalarial activity. The *N*-(chlorophenyl)-*N'*-[4-[[(dialkylamino)alkyl]amino]-6-(trichloromethyl)-1,3,5-triazin-2-yl]guanidines (Table IV) broadly exhibited modest activity but once again lacked sufficient potency for further consideration. Neither the intermediate guanidinobis(trichloromethyl)-triazine XIV nor the biguanide analogue XV possessed significant activity.

Conclusion. These studies, albeit limited, reveal limited antimalarial activity for the (trichloromethyl)triazines. Unless further work is able to increase dramatically the potency of these compounds, little potential is evident for the use of this novel structural class against resistant malaria.

Experimental Section

Melting points (corrected) were taken on a Thomas-Hoover capillary melting point apparatus. Where analyses are indicated by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

***N*-[5-(1-Pyrrolidinyl)pentyl]-4,6-bis(trichloromethyl)-1,3,5-triazin-2-amine (IIIe, Table I).** To a solution of 21.7 g (0.05 mol) of 2,4,6-tris(trichloromethyl)-1,3,5-triazine (Xa) in 100 mL of EtOAc cooled in an ice bath was added dropwise 7.8 g (0.05 mol) of 1-pyrrolidinepentanamine. The solid that formed in about 0.5 h was collected and recrystallized from EtOH–H_2O to give 14.2 g of the product.

***N,N'*-[1,4-Piperazinediylbis(3,1-propanediyl)]bis-4,6-bis(trichloromethyl)-1,3,5-triazin-2-amine (VIII).** To a solution of 21.7 g (0.05 mol) of Xa in 150 mL of EtOAc at 10 °C was added dropwise a solution of 5.0 g (0.025 mol) of 1,4-piperazinedipropanamine in EtOAc. The mixture was stirred at 10 °C for several hours, and the solid that formed was collected and recrystallized twice from EtOH to give 5.4 g (26%) of the product, which sintered at 167 °C, gradually darkened, began to shrink at 176 °C, and gradually melted with decomposition indefinitely to about 205 °C. Anal. ($C_{20}H_{22}Cl_{12}N_{10}$) C, H, N.

***N*-[(4-Chlorophenyl)methyl]-4,6-bis(trichloromethyl)-1,3,5-triazin-2-amine (IX).** To a solution of 21.8 g (0.05 mol) of Xa in 100 mL of C_6H_6 cooled in an ice bath was added dropwise 7.1 g (0.05 mol) of 4-chlorobenzenemethanamine. The mixture was stirred for 5 h and the solvent was removed in vacuo without heat. The residual oil was triturated with petroleum ether (bp 40–60 °C). Filtratiopn gave 2.2 g of the product, mp 92–94 °C. Concentration of the filtrate to half-volume gave an additional

(16) The parenteral antimalarial screening was carried out by Dr. Leo Rane of the University of Miami, and test results were provided 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. For a description of the test method, see ref 17.

(17) Osdene, T. S.; Russell, P. B.; Rane, L. *J. Med. Chem.* **1967**, *10*, 431.

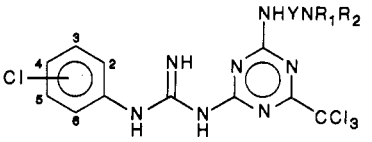
(18) Oral antimalarial screening against *P. berghei* in mice was carried out by Dr. Paul E. Thompson and co-workers, Department of Pharmacology, Parke, Davis and Co., Ann Arbor, MI. For a description of the test method, see ref 19 and 20.

(19) Thompson, P. E.; Bayles, A.; Olszewski, B. *Exp. Parasitol.* **1969**, *25*, 32.

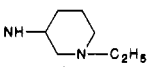
(20) Thompson, P. E.; Bayles, A.; Olszewski, B. *Am. J. Trop. Med. Hyg.* **1970**, *19*, 12.

(21) Antimalarial screening against *P. Gallinaceum* in chicks was carried out by Dr. Leo Rane at 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.

Table II. *N*-(Chlorophenyl)-*N'*-[4-[[(dialkylamino)alkyl]amino]-6-(trichloromethyl)-1,3,5-triazin-2-yl]guanidines

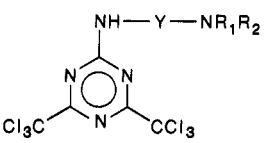


IV

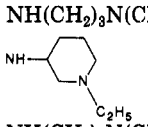
compd no.	$NHYNR_1R_2$	*x*-Cl	mp, °C	yield purified, %	purifn solvent	formula	anal.
IVa	$NH(CH_2)_3N(CH_3)_2$	3,4-Cl_2	209–211 dec	32		$C_{16}H_{19}Cl_5N_8$	C, H, N
IVb	$NH(CH_2)_3N(CH_3)_2$	4-Cl	193–195	50	alc–H_2O	$C_{16}H_{20}Cl_4N_8$	H, N, Cl; C[a]
IVc	$NH(CH_2)_3N(CH_2)_4$	4-Cl	169–170 dec	48		$C_{18}H_{22}Cl_4N_8$	C, H, N
IVd		4-Cl	148–151	20	MeCN	$C_{18}H_{22}Cl_4N_8$	C, H, N
IVe	$NH(CH_2)_4N(CH_2)_4$	4-Cl	153–155 dec	28	MeOH	$C_{19}H_{24}Cl_4N_8$	C, H, N
IVf	$NH(CH_2)_3N(CH_2)_5$	4-Cl	177–179 dec	46	EtOAc–MeCN	$C_{19}H_{24}Cl_4N_8$	C, H, N
IVg	$NH(CH_2)_5N(CH_2)_4$	4-Cl	171–172 dec	40	alc–H_2O	$C_{20}H_{26}Cl_4N_8$	C, H, N
IVh	$NH(CH_2)_3N(CH_2)_6$	4-Cl	171–172	34	alc	$C_{20}H_{26}Cl_4N_8$	C, H, N

[a] C: calcd, 41.22; found, 41.78.

Table III. Effects of 2-[[(Dialkylamino)alkyl]amino]-4,6-bis(trichloromethyl)-1,3,5-triazines against *P. berghei* in Mice and *P. gallinaceum* in Chicks



III

			P. berghei										*P. gallinaceum*	
			diet, 6 days			ΔMST; T or C[c] after single sc dose, mg/kg							single sc dose,	ΔMST; T
compd no.	$NHYNR_1R_2$	formula	no. of mice	SD_{90},[a] mg/kg per day	Q[b]	640	320	160	80	40	20		mg/kg	or C[d]
IIIa	$NH(CH_2)_3N(CH_3)_2$	$C_{10}H_{13}Cl_6N_5$	14	125	0.6	16.3; T3 17.7; T2	6.8; T3	4.0 4.7	2.2	2.0 2.1	1.2		240	0.3
IIIb	$NH(CH_2)_3N(CH_2)_4$	$C_{12}H_{15}Cl_6N_5$	14	86	0.9	3.8	1.6	1.0	0.2	0.0	0.0		240	0.3
IIIc		$C_{12}H_{15}Cl_6N_5$	14	91	0.8	C1		2.8		0.2			240	1.6
IIId	$NH(CH_2)_4N(CH_2)_4$	$C_{13}H_{17}Cl_6N_5$	14	80	0.9	C1 C1	4.2	2.8 2.1	0.4	0.2 0.3	0.2		60	0.1
IIIe	$NH(CH_2)_5N(CH_2)_4$	$C_{14}H_{19}Cl_6N_5$	14	34	2.2	C1 C1	8.6	3.0 2.3	0.4	0.4 0.5	0.0		120 60	4.6 1.2

[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 with semilogarithmic paper. [b] The quinine equivalent Q is the ratio of the SD_{90} of quinine hydrochloride (74.5 mg of base/kg per 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 that 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 subinoculation is 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 3.0 to 4.0 days. C designates the number of chicks surviving to 30 days post infection termed "cured"; data to establish parasitological cure based on subinoculation is unavailable. T indicates the number of deaths occurring within 48 h after infection that are attributed to drug action and are counted as toxic deaths. Control birds do not die before 48 h. Each entry at each dose level represents results with a five-animal group.

12.1 g, mp 90–92 °C (total yield = 63%). Anal. ($C_{12}H_7Cl_7N_4$) C, H, N.

***N*-[3-[(Diethylamino)methyl]-4-methoxyphenyl]-4,6-bis(trichloromethyl)-1,3,5-triazin-2-amine Hydrochloride (XIa).** To a solution of 12 g (0.034 mol) of 2-chloro-4,6-bis(trichloromethyl)-1,3,5-triazine (Xb) in C_6H_6 was added 14.6 g (0.07 mol) of 5-amino-*N*,*N*-diethyl-2-methoxybenzenemethanamine,[22] and the mixture was stirred overnight at room temperature. The heavy yellow solid that formed was collected, washed with hot H_2O, and recrystallized from 2-PrOH to give 3.9 g of the product, mp 263–264 °C. The C_6H_6 filtrate was concentrated in vacuo, and the residue was taken up in Et_2O and treated with EtOH saturated with gaseous HCl to give an additional 3.7 g of the product, mp 262–263 °C (total yield = 19.2%). Anal. ($C_{17}H_{19}Cl_6N_5O$·HCl) C, H, N.

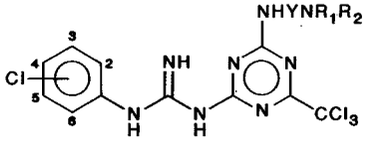
***N*-(4-Chlorophenyl)-4,6-bis(trichloromethyl)-1,3,5-triazin-2-amine (XIb).** A mixture of 3.6 g (0.01 mol) of Xb and 2.6 g (0.02 mol) of 4-chlorobenzenamine in 50 mL of C_6H_6 was heated under reflux for 0.5 h. The 4-chlorobenzenamine hydrochloride was filtered from the reaction mixture, and the filtrate was concentrated to an oil, which solidified upon addition of petroleum ether (bp 40–60 °C). Recrystallization from EtOH–H_2O gave 2.5 g (57%) of the product, mp 141–142 °C. Anal. ($C_{11}H_5Cl_7N_4$) C, H, N.

***N*-(3,4-Dichlorophenyl)-4,6-bis(trichloromethyl)-1,3,5-triazin-2-amine (XIc)** was prepared similarly in 73% yield, mp 171–173 °C (EtOH–H_2O). Anal. ($C_{11}H_4Cl_8N_4$) C, H, N.

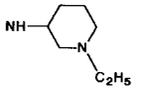
4-Chlorobenzoic Acid 2-[4,6-Bis(trichloromethyl)-1,3,5-triazin-2-yl]hydrazide (XII). To a stirred solution of 3.5 g (0.01

(22) Bent, R. L.; et al. *J. Am. Chem. Soc.* **1951**, *73*, 3100.

Table IV. Effects of *N*-(Chlorophenyl)-*N'*-[4-[[(dialkylamino)alkyl]amino]-6-(trichloromethyl)-1,3,5-triazin-2-yl]guanidines against *P. berghei* in Mice and *P. gallinaceum* in Chicks



IV

				P. berghei									*P. gallinaceum*	
				diet, 6 days			ΔMST; T or C[a] after single sc dose, mg/kg							
compd no.	$NHYNR_1R_2$	*x*-Cl	formula	no. of mice	SD_{90},[a] mg/kg per day	*Q*[a]	640	320	160	80	40	20	single sc dose, mg/kg	ΔMST; T or C[a]
IVa	$NH(CH_2)_3N(CH_3)_2$	3,4-Cl_2	$C_{16}H_{19}Cl_5N_8$	14	100	0.7	15.5; C2		12.3		1.3		100	0.2
							14.9; C2		12.6		1.6			
IVb	$NH(CH_2)_3N(CH_3)_2$	4-Cl	$C_{16}H_{20}Cl_4N_8$				C5		5.4		4.2			
							C5		6.5		4.6			
IVc	$NH(CH_2)_3N(CH_2)_4$	4-Cl	$C_{18}H_{22}Cl_4N_8$	14	235	0.3	10.1	7.5	3.7	1.9	0.5	0.5	240	14.4
							9.9		2.3		0.5		120	11.7; C2
IVd		4-Cl	$C_{18}H_{22}Cl_4N_8$	14	97	0.8	10.3; C1	5.3	4.7	4.1	0.7	0.3	100	9.5
							9.9; C1		2.3		1.1			
IVe	$NH(CH_2)_4N(CH_2)_4$	4-C1	$C_{19}H_{24}Cl_4N_8$	14	108	0.7	5.8; T2	4.8; T1	3.8; T1	2.2	0.4	0.2		
							5.3; T3		4.8; T1		1.0			
IVf	$NH(CH_2)_3N(CH_2)_5$	4-Cl	$C_{19}H_{24}Cl_4N_8$	14	208	0.4	7.9	5.5	3.1	2.7	1.7	0.3	120	9.1
							8.1		3.9		1.5			
IVg	$NH(CH_2)_5N(CH_2)_4$	4-Cl	$C_{20}H_{26}Cl_4N_8$	14	145	0.5	7.2	4.0	3.8	2.2	1.0	0.6	120	0.7
							7.0		4.2		1.2			
IVh	$NH(CH_2)_3N(CH_2)_6$	4-Cl	$C_{20}H_{26}Cl_4N_8$	14	240	0.3	7.5	4.5	2.7	1.7	1.1	0.7	240	7.2
							4.7		1.5		0.7		100	18.7; C3

[a] See footnotes *a–d*, Table III.

mol) of Xb in 35 mL of MeCN was added a slurry of 3.4 g (0.02 mol) of 4-chlorobenzoic acid hydrazide in 35 mL of MeCN. The mixture was stirred for 6.75 h at room temperature and the 4-chlorobenzoic acid hydrazide hydrochloride was removed by filtration. The filtrate was evaporated to dryness in vacuo and the residue was recrystallized from EtOH–H_2O to give 4.2 g (87%) of the product. Anal. ($C_{12}H_6Cl_7N_5O$) C, H, N.

4-Chlorobenzoic Acid 2-[4-[[3-(Dimethylamino)propyl]amino]-6-(trichloromethyl)-1,3,5-triazin-2-yl]hydrazide (XIII). To a solution of 1.7 g (0.0035 mol) of XII in 20 mL of MeCN was added 0.7 g (0.007 mol) of *N,N*-dimethyl-1,3-propanediamine and the solution was heated under reflux for 1 h. Filtration provided 1.4 g of a solid, which was recrystallized from EtOH to give 1.2 g (75%) of the product, mp 216–217 °C. Anal. ($C_{16}H_{19}Cl_4N_7O$) C, H, N.

***N*-(4-Chlorophenyl)-*N'*-[4-[[5-(1-pyrrolidinyl)pentyl]amino]-6-(trichloromethyl)-1,3,5-triazin-2-yl]guanidine (Compound IVg, Table II).** A mixture of 20.0 g (0.04 mol) of *N*-[4,6-bis(trichloromethyl)-1,3,5-triazin-2-yl]-*N'*-(4-chlorophenyl)guanidine and 12.5 g (0.08 mol) of 1-pyrrolidinepentanamine in 130 mL of C_6H_6 was heated under reflux for 30 min. The solution was allowed to cool to room temperature and the solid that formed was collected and recrystallized from EtOH–H_2O to give 8.4 g of the product.

(3,4-Dichlorophenyl)guanidine. A mixture of 10.0 g (0.05 mol) of 3,5-dimethylpyrazole-1*H*-carboxamidamide nitrate and 8.1 g (0.05 mol) of 3,4-dichlorobenzenamine was gradually heated to 120 °C and held there for 30 min. The mixture was cooled to room temperature and slurried in petroleum ether. The resulting solid was dissolved in hot MeOH, and the solution was cooled and poured into a large volume of Et_2O. Recrystallization of the precipitate from MeCN provided 10.8 g (80%) of the product as the nitrate salt, mp 198–200 °C. Anal. ($C_7H_7Cl_2N_3 \cdot HNO_3$) H, N; C: calcd, 31.48; found, 30.90.

A slurry of 9.5 g (0.035 mol) of the salt in 100 mL of warm H_2O was added to 100 mL of 50% NaOH solution. The warm mixture was stirred for 20 min and the solid was collected, washed with H_2O, and recrystallized from C_6H_6 to give 5.5 g (77%) of guanidine base.

***N*-[4,6-Bis(trichloromethyl)-1,3,5-triazin-2-yl]-*N'*-(3,4-dichlorophenyl)guanidine.** A solution of 5.5 g (0.027 mol) of (3,4-dichlorophenyl)guanidine and 11.8 g (0.027 mol) of Xa in 100 mL of C_6H_6 was heated under reflux for 8 h. The solvent was removed in vacuo and the residue was dried in vacuo at 25 °C for 24 h to provide 13.5 g (96.5%) of the product, mp 191–196 °C, which was used without further purification.

***N*-(4-Chlorophenyl)-*N'*-[4,6-bis(trichloromethyl)-1,3,5-triazin-2-yl]imidodicarbonimidic Diamide (XV).** To a solution of 3.5 g (0.01 mol) of Xb in 30 mL of MeCN was added a solution of 4.6 g (0.02 mol) of *N*-(4-chlorophenyl)imidodicarbonimidic diamide monohydrate in 65 mL of MeCN, and the mixture was stirred at room temperature for 3 h. Filtration removed the *N*-(4-chlorophenyl)imidodicarbonimidic diamide hydrochloride that formed, and the filtrate was concentrated in vacuo to a yellow semisolid. Recrystallization from EtOH–H_2O provided 0.8 g (15%) of the product, mp 217–219 °C. Anal. ($C_{13}H_9Cl_7N_8$) C, H, N.

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Registry No. IIIa, 101862-53-7; IIIb, 110045-46-0; IIIc, 110045-47-1; IIId, 110045-48-2; IIIe, 110045-49-3; IVa, 110045-50-6; IVb, 110045-51-7; IVc, 110045-52-8; IVd, 110045-53-9; IVe, 110045-54-0; IVf, 110045-55-1; IVg, 110045-56-2; IVh, 110045-57-3; VIII, 110045-58-4; IX, 110045-59-5; Xa, 6542-67-2; Xb, 30894-89-4; XIa, 110045-60-8; XIb, 3599-75-5; XIc, 30356-55-9; XII, 110045-61-9; XIII, 110045-62-0; XIV, 108845-44-9; XV, 110045-63-1; 4-$ClC_6H_4CH_2NH_2$, 104-86-9; 4-$ClC_6H_4NH_2$, 106-47-8; 3,4-$Cl_2C_6H_3NH_2$, 95-76-1; 4-$ClC_6H_4CO_2H$, 536-40-3; $H_2N(CH_2)_3N(CH_3)_2$, 109-55-7; 3,4-$Cl_2C_6H_3NHC(NH_2)$=NH, 65783-10-0; 3,4-$Cl_2C_6H_3NHC(NH_2)$=NH·HNO_3, 65783-11-1; 4-ClC_6H_4NHC(=NH)NHC(=NH)NH_2·HCl, 4022-81-5; 1-pyrrolidinepentamine, 71302-71-1; 1,4-piperazinedipropanamine, 7209-38-3; 5-amino-*N,N*-diethyl-2-methoxybenzenemethanamine, 50350-49-7; 3,5-dimethylpyrazole-1*H*-carboxamidamide, 38184-47-3; *N*-(4,6-bis(trichloromethyl)-1,3,5-triazin-2-yl)-*N'*-(3,4-dichlorophenyl)guanidine, 110045-64-2; 1-pyrrolidinepropanamine, 23159-07-1; 1-ethyl-3-piperidinamine, 6789-94-2; 1-pyrrolidinebutanamine, 24715-90-0; 1-piperidinepropanamine, 3529-08-6; hexahydro-1-azepinopropanamine, 3437-33-0.

Stereospecificity in Allergic Contact Dermatitis to Simple Substituted Methylene Lactone Derivatives

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The enantiomers of β,γ-dimethyl- and β-methyl-α-methylene-γ-butyrolactones have been synthesized stereospecifically from glutamic acid and β-hydroxy isobutyric acid, respectively. Guinea pigs have been sensitized (Freund complete adjuvant technique) and tested to them. Both enantiomers of β-methyl lactone as well as (+)-β,γ-dimethyl lactone induced enantiospecific allergic contact dermatitis (ACD); in turn, (−)-β,γ-dimethyl lactone showed no specificity. An interpretation is proposed.

Configuration–activity relationships in bioactive compounds have been demonstrated in pharmacology and enzymology. Specificity exhibited by the reactions involved has been generally related to high specificity in binding to receptors.[1]

Similarly, in allergic contact dermatitis (ACD), it can be imagined that clonal selection leads to a subpopulation of T-lymphocytes specific of a given allergen.[2] One can thus expect at least stereoselectivity in the allergic activity of two enantiomers.

In fact, such enantiospecificity has been described for the first time by Mitchell in 1980 in the case of ACD to usnic acid.[3] Few cases of such enantiospecificity have been reported; they include ACD to frullanolides[4] and Dalber-

† On leave from Kao Corporation.

(1) See, for example: Jones, J. B.; Sih, C. J.; Perlman, D. *Applications of Biochemical Systems in Organic Chemistry*; Wiley: New York, 1976; Parts I and II.
(2) For a review, see: Dupuis, G.; Benezra, C. *Allergic Contact Dermatitis to Simple Chemicals: A Molecular Approach*; Marcel Dekker: New York, 1982.
(3) Mitchell, J. C.; Shibata, S. *J. Invest. Dermatol.* **1969**, *52*, 517–520.

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