3-(*m*-Trifluoromethylanilino)isonicotinic Acid. Method D.—A mixture of 3-iodoisonicotinic acid[11] (2.5 g), *m*-trifluoromethylaniline (4.0 g), K_2CO_3 (2.8 g), reduced copper powder (0.3 g), water (5 ml), and 1-pentanol (12 ml) was stirred under N_2 for 24 hr. The dark mixture was steam distilled, treated with charcoal, and acidified with concentrated HCl. The precipitate was removed by filtration and recrystallized from ethanol yielding the required acid (300 mg, 11%), mp 280–282°.

6-(*m*-Trifluoromethylanilino)nicotinic Acid. Method E.—6-Chloronicotinamide (6.0 g) and *m*-trifluoromethylaniline (15 ml) were stirred at 170–180° for 4 hr. The cooled reaction mixture was equilibrated between two 100-ml portions of benzene and two 50-ml portions of 2 *N* NaOH, and the combined organic solutions were washed with water, dried (Na_2SO_4), and evaporated under reduced pressure to yield a yellow solid (9.0 g). A portion of this solid (1.0 g), ethanol (25 ml), and 4 *N* NaOH (10 ml) were heated at 100° for 7 hr. Most of the solvent was removed by distillation, and water (25 ml) was added to the residue. The clear solution was neutralized with 4 *N* HCl and the precipitate was removed by filtration, washed with a small amount of water, and recrystallized from aqueous ethanol. The product was thus obtained as light yellow crystals (600 mg), mp 243–246°.

8,9-Dimethylpyrido[2,3-*b*]quinol-5-one. Method F.—2-(2,3-Dimethylanilino)nicotinic acid (1.0 g) and polyphosphoric acid (10 ml) were stirred at 160° for 75 min, poured onto crushed ice (30 g), and neutralized by the addition of 4 *N* NaOH. The solid which separated was removed by filtration, washed with a small amount of cold water, and recrystallized from ethanol yielding **4** as yellow needles (0.75 g, 81%), mp 243–244° dec.

Acknowledgment.—We thank Dr. S. S. Szinai for valuable discussion and Miss R. A. K. Finucane for technical assistance. The mefenamic and flufenamic acids used in the biological tests were kindly supplied by Dr. H. O. J. Collier, Parke, Davis and Company, Hounslow, Middlesex, England.

(11) K. Palát, M. Čeladník, L. Nováček, and R. Urbančik, *Rozhledy Tuberk.*, **19**, 716 (1959).

2,4,7-Triamino-6-*ortho*-substituted Arylpteridines. A New Series of Potent Antimalarial Agents

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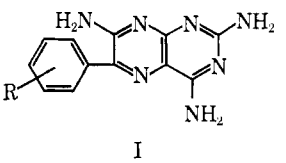
Activity against the experimental malarias caused by *Plasmodium berghei* in mice and *P. gallinaceum* in chicks has been demonstrated for several 2,4,7-triamino-6-*ortho*-substituted arylpteridines. The *o*-methyl and *o*-chloro derivatives were the most active compounds in the systems examined. A toxicity study in rats and dogs revealed that 2,4,7-triamino-6-*o*-tolylpteridine is sufficiently nontoxic to be administered in effective doses to humans.

From time to time reports of antimalarial activity in the pteridine series have appeared in the literature.[1-6] To the present, however, no compound of this type has achieved clinical significance in the treatment or prophylaxis of the disease. The present study originated in the observation that 2,4,7-triamino-6-*o*-tolylpteridine (I, R = *o*-CH_3)[7] was highly active against *Plasmodium berghei* infections in mice and that this activity was coupled with a relatively low toxicity in this species.



I

Results.—The activity of several of the most interesting 2,4,7-triamino-6-arylpteridines is compared with the standard antimalarial agents quinine sulfate and chloroquine diphosphate in Table I.

From the table it can be seen that the activity of the compounds at 160 mg/kg falls in the following order taking quinine sulfate as 1: I, R = 2-CH_3 (7.7 Q) > I, R = 2-Cl (5.3 Q) = I, R = 2,6-$(Cl)_2$ (5.3 Q) > chloroquine diphosphate (5.0 Q) > I, R = H (2.8 Q). However the first three compounds differ from the remainder in that they are able to cure the infection. Similar results were obtained against *P. gallinaceum* in chicks. It should be noted that while the compounds fall in the expected order with respect to activity the quantitative value of the activity (Q) is probably not comparable with that obtained by other antimalarial tests against experimental infection,[8] where the intensity of parasitemia rather than death is taken as the criterion.

Table I

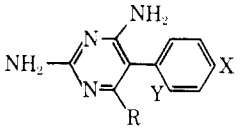
Compd	MTD, mg/kg[a]	Increase in mean survival time at MTD, days	Min. dose giving cure, mg/kg (cured/treated)	Increase in survival time at 160 mg/kg[b]
I, R = 2-CH_3	>1280	(Cure)[c]	320 (6/10)	15.6
I, R = 2-Cl	>1280	(Cure)	320 (3/10)	10.5
I, R = 2,6-Cl_2	>1280	(Cure)	320 (1/5)	10.6
I, R = H	160[d]	5.6	...	5.6
Quinine	640	5.4	...	2
Chloroquinine	160	10	...	10

[a] Maximum tolerated dose = dose at which no toxic deaths occur. [b] MTD of chloroquinine. [c] Cure defined as a survival of 30 days or more. [d] The MTD for this compound varied greatly in different tests as did the increase in MST (mean survival time).

(1) M. D. Potter and T. Henshall, *J. Chem. Soc.*, 2000 (1956).
(2) W. R. Boon, *ibid.*, 2146 (1957).
(3) H. O. J. Collier and M. Phillips, *Nature*, **174**, 180 (1954).
(4) A. Bishop, *Parasitology*, **44**, 450 (1954).
(5) J. Thurston, *ibid.*, **44**, 99 (1954).
(6) J. Greenberg, *J. Pharmacol. Exptl. Therap.*, **97**, 484 (1949).
(7) R. G. W. Spickett and G. M. Timmis, *J. Chem. Soc.*, 2887 (1954).
(8) P. B. Russell in "Medicinal Chemistry," A. Burger, Ed., 2nd ed, Interscience Publishers, Inc., New York, N. Y., 1960, p 814.

The Influence of Structure on Antimalarial Activity.—The effect of substitution on the antimalarial activity of a series of 27 2,4,7-triamino-6-arylpteridines is shown in Table II. The parent compound of the series, 2,4,7-triamino-6-phenylpteridine, a compound which finds clinical application as a diuretic,[9] is weakly antimalarial. Table I indicates that it is perhaps three times as active as quinine against *P. berghei* in mice; it is also active against *P. gallinaceum* in chicks. A study of the effects of substitution in the 6-phenyl group was conducted and an interesting pattern of activity emerged. In general, substitution in the *meta* or *para* position of the 6-phenyl group appeared to eliminate the activity but substitution in the *ortho* position by methyl, ethyl, chlorine, or bromine appeared greatly to increase the antimalarial activity of the resulting compound. Indeed substitution in the *ortho* position by either methyl or chlorine rendered the compound curative as did disubstitution in the 2,6 positions. Certain other *ortho*-substituted groups in the 6 position, *e.g.*, 1-naphthyl or 2-diphenylyl, gave compounds of the same or slightly greater order of activity as the parent compound. Disubstituted compounds with methyl or chlorine in the *ortho* position and a chlorine at the *para* position were inactive or about as active as the parent compound. Substitution in the *ortho* position by fluorine gave an inactive compound which had some toxicity, the *o*-iodo compound on the other hand, although toxic, possessed some activity. Substitution at the *ortho* position with a methoxy group gave a toxic but inactive compound.

There are certain striking similarities between the structural-activity relationship of the pteridine antimalarials outlined above, and those which exist in the pyrimidine antimalarials of the pyrimethamine (II) series;[10] on the other hand there are some equally



II (pyrimethamine), R = C_2H_5; X = Cl; Y = H

significant differences. For high activity in the latter series the substituent R in the 6 position of the pyrimidine ring of II must be alkyl; in pyrimethamine it is ethyl. In the pteridine series the presence of an *o*-methyl group in the aromatic nucleus gives rise to high activity, the *o*-ethyl compound is somewhat less active. In the pyrimidine series substitution with chlorine in the *meta* or *para* position of the aromatic nucleus increases activity while *ortho* substitution appears to diminish it. Yet, in contrast, substitution by chlorine in the pteridine series is only effective when the substituent is in the *ortho* position. It has been shown that substitution by an alkyl group in the 6 position of a 5-phenylpyrimidine gives rise to a nonplanar configuration of the pyrimidine and benzene rings.[11] While the absorption spectra of the arylpteridines do not show clearly the nonplanarity of pteridine and aromatic rings in the *ortho*-substituted compounds, models demonstrate that this must nevertheless be the case. Lack of coplanarity is not, however, the sole requirement for high antimalarial activity in the pyrimethamine series, for absorption spectra demonstrate that the pyrimidine and aromatic rings are not planar in 2,4-diamino-5-(2-chlorophenyl)pyrimidine,[11] yet this compound is an antimalarial of relatively low potency.[10]

Too, in other respects a similarity exists between the 6-arylpteridine (I) and the 5-arylpyrimidine (II) antimalarials. Both series of compounds have been shown to inhibit the reduction of folic acid to the citrovorum factor,[12,13] yet in both instances the antimalarial activity against *P. berghei* in mice is not reversed by either of these compounds. The pteridine I (R = 2-CH_3) reduces the toxicity of folic acid to mice yet its antimalarial activity is undiminished. The same compound when given to rats in doses of 5 mg/day ip for 1 month is said to cause a leucopenia which is reversed by the simultaneous administration of 200 μg of folic acid or of 100 μg of the citrovorum factor per day.[12] In the toxicity studies reported below rats receiving 0.1 and 0.05% of the pteridine in the diet did not show any evidence of leucopenia over 7 and 5.5 weeks, respectively. No leucopenia was observed in toxicity studies conducted in other laboratories;[14] these studies in general confirmed those reported below but it was noticed that the animals which died during the course of the study, both rats and dogs, developed the gastrointestinal lesions sometimes associated with folic acid deficiency.

2,4,7-Triamino-6-*o*-tolylpteridine. A. Toxicity Study.—2,4,7-Triamino-6-*o*-tolylpteridine (I, R = 2-CH_3) was selected for toxicity studies. In mice the acute LD_{50} by the oral route was >5071 mg/kg and by the intraperitoneal route 3720 mg/kg. In rats the corresponding figures were 1800 and 1260 mg/kg, respectively. In subacute studies, with the drug incorporated in the diet, rats survived for 7 weeks at a level of 0.1% (approximately 100 mg/kg). At higher levels the animals commenced to die during the second or third week. Animals at the 0.1% level did not reveal evidence of specific organ injury due to the drug. A further study in which the animals received 0.05% drug in diet was conducted. All animals survived the 5.5-week treatment period; no specific organ injury was visible in these animals and statistical analysis of the mean group values for hematology did not reveal differences between control and drug-treated groups.

While dogs receiving 5 mg/kg orally survived a 5-week treatment period, animals receiving 30 mg/kg and up died. In the 5-mg/kg group, the mean values for hematology did not show differences from the control and no specific organ injury related to the drug treatment was observed on histopathological examination. The mechanism of death in the higher dose animals was not apparent.

B. Other Biological Properties.—The compound was observed to be active against leishmania *in vitro* by Dr. Daricarrere of the Vargas Hospital in Caracas, Venezuela. This work will be published elsewhere. The *o*-tolyl derivative also showed marked antitumor activity against the Ca775 and L1210 mouse tumors.

(9) Triamterene (Dyrenium®, Smith Kline and French Laboratories).

(10) E. A. Falco, L. G. Goodwin, G. H. Hitchings, I. M. Rollo, and P. B. Russell, *Brit. J. Pharmacol.*, **6**, 185 (1951).

(11) P. B. Russell, *J. Chem. Soc.*, 2951 (1954).

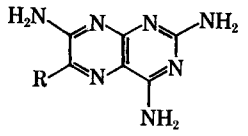
(12) G. H. Hitchings, *Clin. Pharmacol. Therap.*, **1**, 570 (1960).

(13) V. M. Doctor, *J. Biol. Chem.*, **232**, 617 (1958).

(14) Private communication from Dr. D. Jacobus.

Table II

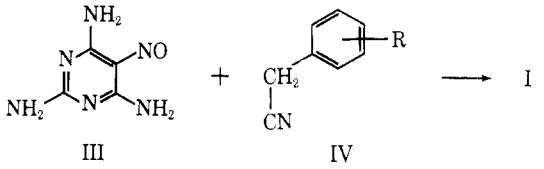
2,4,7-Triamino-6-arylpteridines



Compd	R	Mp, °C	Recrystn solvent[a]	Yield, %	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found	Halogen, % Calcd	Halogen, % Found	Antimalarial[c] *P. berghei*	Antimalarial[c] *P. gallinaceum*
1	C_6H_5[b]	327	A	72	$C_{12}H_{11}N_7$	56.91	56.72	4.38	4.23	38.72	38.5			+	+
2	2-$CH_3C_6H_4$	344	A	77	$C_{13}H_{13}N_7$	58.41	58.38	4.90	4.97	36.69	36.41			++++	++++
3	3-$CH_3C_6H_4$	321–322 dec	A, C		$C_{13}H_{13}N_7$	58.41	58.64	4.90	5.14	36.69	36.47			0	−
4	4-$CH_3C_6H_4$	344–345	A, C	85	$C_{13}H_{13}N_7$	58.41	58.50	4.90	5.09	36.69	36.25			0	0
5	2-$C_2H_5C_6H_4$	316	A, C	98	$C_{14}H_{15}N_7$	59.76	59.64	5.38	5.30	34.86	34.48			++	+++
6	4-$(CH_3)_2CHC_6H_4$	>360	A, C	57	$C_{15}H_{17}N_7$	61.00	61.23	5.80	5.70	33.20	33.15			0	0
7	3,4-$(CH_3)_2C_6H_3$	354	A, C	92	$C_{14}H_{15}N_7$	59.76	59.88	5.38	5.53	34.86	34.75			0	0
8	1-Naphthyl[b]	>360	A, C	94	$C_{16}H_{13}N_7$	63.35	63.36	4.32	4.44	32.33	31.98			++	−
9	2-$C_6H_5C_6H_4$	362	A, C	21	$C_{18}H_{15}N_7$	65.64	65.19	4.59	4.70	29.77	29.61			+	0
10	4-$C_6H_5C_6H_4$	>360	A	95	$C_{18}H_{15}N_7$	65.64	65.42	4.59	4.27	29.77	29.81			0	−
11	2-$CH_3OC_6H_4$[b]	339 dec	A	66	$C_{13}H_{13}N_7O$	55.11	55.08	4.63	4.63	34.61	34.13			0	0
12	3,4-$(CH_3O)_2C_6H_3$	330–331 dec	A, C	86	$C_{14}H_{15}N_7O_2$	53.66	53.52	4.83	4.66	31.30	31.30			0	0
13	4-$H_2NC_6H_4$	>360	A, C	54	$C_{12}H_{12}N_8$	53.72	53.84	4.51	4.58	41.77	41.66			0	0
14	4-$(HOCH_2CH_2)_2NC_6H_4$	310–312	D, E	63	$C_{16}H_{20}N_8O_2$	53.92	53.86	5.66	5.73	31.44	31.50			0	0
15	2-FC_6H_4	338	B, C	64	$C_{12}H_{10}FN_7$	53.13	53.03	3.72	3.39	36.15	35.85	7.00	6.7	0	−
16	4-FC_6H_4[b]	>360	A	37	$C_{12}H_{10}N_7F$	53.13	52.83	3.72	3.80	36.15	35.88	7.00	6.08	0	0
17	2-ClC_6H_4[b]	349	A, C	74	$C_{12}H_{10}N_7Cl$	50.09	50.36	3.50	3.49	34.08	33.93	12.32	12.2	++++	++++
18	3-ClC_6H_4[b]	>360	A, C	70	$C_{12}H_{10}N_7Cl$	50.09	50.16	3.50	3.62	34.08	33.95	12.32	12.2	0	0
19	4-ClC_6H_4[b]	>360	A	88	$C_{12}H_{10}N_7Cl$	50.09	50.05	3.50	3.60	34.08	34.02	12.32	12.32	0	0
20	3,4-$Cl_2C_6H_3$	>360	A	78	$C_{12}H_9N_7Cl_2$	44.73	45.04	2.82	2.98	30.44	30.28	22.01	21.9	0	0
21	2,4-$Cl_2C_6H_3$	330	B, C	85	$C_{12}H_9N_7Cl_2$	44.73	44.92	2.82	2.82	30.44	30.15	22.01	21.7	0	0
22	2,6-$Cl_2C_6H_3$	353	A, C	41	$C_{12}H_9N_7Cl_2$	44.73	44.85	2.82	2.83	30.44	30.10	22.01	21.9	++++	
23	2-CH_3-4-ClC_6H_3	330	A, C	57	$C_{13}H_{12}N_7Cl$	51.74	51.41	4.01	3.94	32.49	32.64	11.75	11.9	+	−
24	2-BrC_6H_4	320 dec	B, C	41	$C_{12}H_{10}N_7Br$	43.39	43.24	3.03	3.00	29.52	29.23	24.06	24.04	++	+++
25	4-BrC_6H_4	>360	D, E	68	$C_{12}H_{10}N_7Br$	43.39	43.52	3.03	2.99	29.52	29.78	24.06	24.1	0	0
26	2-IC_6H_4	331	D, E	33	$C_{12}H_{10}N_7I$	38.01	38.30	2.66	2.54	25.86	25.51	33.47	33.7	+	−
27	4-IC_6H_4	>360	D, E	67	$C_{12}H_{10}N_7I$	38.01	38.30	2.66	2.75	25.86	25.41	33.47	33.5	0	0

[a] A = dimethylformamide, B = 2-ethoxyethanol, C = water, D = glacial acetic acid, E = concentrated NH_4OH. [b] Spickett and Timmis[7] reported compounds **1**, **8**, **11**, **16**, **17**, **18**, and **19**, with melting points of 316, 384, 334, 362, 342, 353, and 362°, respectively. [c] − = insufficient compound for test. Activity scale: ++++ = curative, +++ = greater than 100% increase in survival time but not curative, ++ = greater than 100% increase in survival time but not curative, + = 100% increase in survival time (MST control = 6.8 ± 0.5 days), 0 = no activity.

Chemical Methods.—The compounds were prepared essentially by the method of Spickett and Timmis[7] *i.e.*, the condensation of 2,4,6-triamino-5-nitrosopyrimidine (III) with the corresponding arylacetonitrile (IV) in hot 2-ethoxyethanol in the presence of 1 equiv of sodium. The analyses and melting points are given in Table II.



III IV

Experimental Section

All melting points were determined on a Thomas–Hoover capillary melting point apparatus and are corrected.

Arylacetonitriles.—When not commercially available these compounds were prepared, for the most part, by the action of KCN on the corresponding benzyl halides as described by Kharasch and Brown.[15] The known nitriles, prepared in this manner which were not commercially available are the following: 2-ethylphenylacetonitrile,[16] 4-isopropropylphenylacetonitrile,[16] 3,4-xylylacetonitrile,[17] 2-biphenylylacetonitrile,[18] 2-methoxyphenylacetonitrile,[19] 2-chlorophenylacetonitrile,[20] 3,4-dichlorophenylacetonitrile,[21] 2,4-dichlorophenylacetonitrile,[21] 2-bromophenylacetonitrile.[22]

p-[Bis(2-hydroxyethylamino)]phenylacetonitrile was prepared by the reaction of 4-aminophenylacetonitrile with ethylene oxide.[23]

4-Chloro-2-methylbenzyl Alcohol.—To a stirred mixture of 6.1 g of $LiAlH_4$ in 200 ml of dry tetrahydrofuran (THF) was added dropwise a solution of 43.5 g of ethyl 4-chloro-*o*-toluate in 50 ml of THF. After the addition was complete (30 min), the reaction mixture was heated under reflux for 45 min then cooled in ice. The excess hydride and aluminum complex were decomposed by the cautious addition of 40 ml of 50% aqueous THF solution followed by 40 ml of 40% NaOH solution. The reaction mixture was filtered and the filtrate was taken to dryness in a rotary evaporator under vacuum. The residual oil (36.2 g) was used directly in the next step without purification.

4-Chloro-2-methylbenzyl Chloride.—Over the course of 35 min, 36 g of 4 chloro-2-methylbenzyl alcohol was added dropwise to 50 ml of $SOCl_2$. The reaction mixture was stirred and boiled under reflux for 1 hr. The excess $SOCl_2$ was removed *in vacuo*. The residual oil was dissolved in 50 ml of ethyl acetate and washed with water (50 ml), two 100-ml portions of 10% $NaHCO_3$ solution, and finally with water (50 ml). The acetate layer was dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo* and the residual oil distilled through a Vigreux column. The portion distilling at 118–121° (10 mm) amounted to 19.7 g.

Anal. Calcd for $C_8H_8Cl_2$: Cl, 40.51. Found: Cl, 40.8.

4-Chloro-*o*-tolylacetonitrile.—To a boiling stirred solution of 13.9 g of KCN in 100 ml of water was added dropwise a solution containing 19.7 g of 4-chloro-2-methylbenzyl chloride in 60 ml of ethanol. The reaction mixture was heated under reflux for 2 hr. The ethanol was then allowed to distil out of the reaction mixture. The product was extracted from the aqueous reaction mixture with 50 ml of benzene. The benzene layer was washed with two 50-ml portions of water and dried ($MgSO_4$). The benzene was removed by evaporation and the residual oil was distilled through a semimicro Vigreux column. The product amounted to 20 g, bp 140° (0.25 mm).

Anal. Calcd for C_9H_8ClN: C, 65.25; H, 4.87. Found: C, 65.45; H, 5.12.

2,4,7-Triamino-6-(4-chloro-*o*-tolyl)pteridine.—Sodium (0.23 g) was dissolved in 200 ml of anhydrous 2-ethoxyethanol. The solution was heated with stirring to boiling under reflux and 1.8 g of 4-chloro-2-methylphenylacetonitrile was added followed by 1.5 g of 2,4,6-triamino-5-nitrosopyrimidine. The reaction mixture was boiled for 1.67 hr. The dark amber solution was evaporated to dryness *in vacuo* on a rotary evaporator. The residue was washed with 100 ml of water and removed by filtration. This product was recrystallized from aqueous DMF solution affording 1.7 g of yellow, crystalline product, mp 330°.

Biological Methods. A. Activity *vs. P. berghei* in Mice.—Mice of one sex weighing 15–18 g were housed in metal cages with plastic tops and given a standard laboratory diet and water *ad lib.* The animals were infected with an intraperitoneal injection of 0.5 ml of heparinized heart blood, containing a minimum of 90% parasitized cells, drawn from donor mice infected 1 week earlier with *P. berghei*. The donor strain is maintained by weekly passages in separate groups of mice inoculated with 0.5 ml of a 1:500 dilution of heparinized heart blood.

The test compounds were dissolved (or suspended) in peanut oil and a single dose was administered subcutaneously 72 hr after infection. In the primary test the drug was administered in three dilutions: 640, 160, and 40 mg/kg. A minimum of five animals per dilution was used. If the drug proved to be toxic lower dilutions were used. If the primary test gave a positive result, a confirmatory test was performed using five animals at six dilutions (1280, 640, 320, 160, 80, and 40 mg/kg).

A group of infected animals treated with pyrimethamine was included in every experiment as a positive control.

An increase in survival time of 6.8 ± 0.5 days (*i.e.*, 100%) is considered the minimum effective response (+) for an active compound. Compounds which increase the survival of the mice beyond 30 days are considered curative (++++). Intermediate survival is indicated by ++ and +++.

B. Activity *vs. P. gallinaceum* in Chicks.—White leghorn chicks were delivered to the laboratory when 1 day old; they were maintained under standard laboratory conditions on a nonmedicated diet until 9–12 days old. The birds then received an intravenous injection of 0.2 ml of heparinized blood infected with *P. gallinaceum* having a minimum of 80–90% parasitized red blood cells. The parasitized blood was drawn by cardiac puncture from donor chicks infected 72 hr earlier; the disease is fatal to 100% of untreated chicks within this period.

Drugs were prepared and administered in the same fashion as in the *P. berghei* test. The dose was given immediately following infection. Chicks surviving 30 days are considered cured. The drugs are rated as in the case of *P. berghei* above.

Acknowledgment.—The authors wish to thank Drs. Milton Wolf and A. Santilli for assistance in the preparation of this manuscript. One of them (L. R.) acknowledges the support of the Department of Defense under Contract No. DA-49-193-MD 22-2218. This paper is Contribution No. 152 from the Army Research Program on Malaria.

(15) M. S. Kharasch and H. C. Brown, *J. Am. Chem. Soc.*, **61**, 2142 (1939).

(16) G. S. Skinner, J. A. Gladner, and R. F. Heitmiller, *ibid.*, **73**, 2230 (1951).

(17) F. Benington, R. D. Morin, and L. C. Clark, Jr., *J. Org. Chem.*, **25**, 2066 (1960).

(18) J. von Braun and G. Manz, *Ann.*, **468**, 258 (1929).

(19) Z. Horii, J. Tsuji, and T. Inoi, *Yakugaku Zasshi*, **77**, 248 (1957); *Chem. Abstr.*, **51**, 8671 (1957).

(20) H. Mehner, *J. Prakt. Chem.*, **62**, 556 (1898).

(21) P. B. Russell and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 3763 (1951).

(22) C. L. Jackson and J. F. White, *Am. Chem. J.*, **2**, 316 (1881).

(23) R. M. Peck, R. K. Preston, and H. J. Creech, *J. Org. Chem.*, **26**, 3409 (1961).