from EtOH and dioxane to give 1.8 g (64%) of **16** as reddish gray needles, mp 210° dec.

The 3-Me analog **17** and the 5-(5-nitro-2-furylacrylidene-thiazolidene-2,4-diones **21-25** were prepd similarly.

5-(2-Furylidene)-2-methylrhodanine (27).—A soln of 3.0 g (0.02 mole) of 3-methylrhodanine, 2.0 g (0.02 mole) of furfural, and 0.5 ml of piperidine was heated under reflux in 30 ml of 95% EtOH for 30 min. The cryst which formed on cooling were collected, dried, and recrystd from 95% EtOH to give 4.25 g (95%) of **27** as long golden yellow needles, mp 142-143°.

5-(2-Furylidene)rhodanine (**26**) and the thiazolidine-2,4-diones **28** and **29** were prepd similarly.

5-(2-Furylacrylidene)thiazolidene-2,4-dione (31).—A mixt of 1.2 g (0.01 mole) of thiazolidine-2,4-dione, 1.2 g (0.01 mole) of 2-furylacrolein, and 0.5 ml of piperidine in 30 ml of 95% EtOH was refluxed for 1 hr. The mixt was allowed to cool overnight causing the pptn of a yellow solid which was collected, dried, and recrystd from EtOH and dioxane to give 1.5 g (71%) **30** as reddish brown needles, mp 217-218°.

Acknowledgments.—The authors express their gratitude to Professor A. H. Beckett for providing all facilities for this research and for many fruitful discussions. The authors also acknowledge Mr. Tattersale of Smith and Nephew Laboratories for performing the antimicrobial tests.

Antimalarials. "Distal" Hydrazine Derivatives of 7-Chloroquinoline

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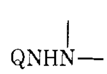
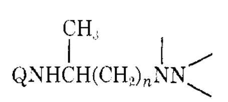
Twenty-six derivatives of 7-chloroquinoline have been prepared which incorporate a hydrazine feature in the side chain attached at position 4. They were tested for their antimalarial activity against *Plasmodium berghei* in mice. They ranged in activity from extremely toxic to highly curative.

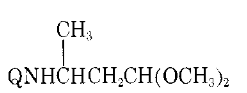
In a previous publication[1] we reported quinoline derivatives with a "proximal" hydrazine feature as shown in the generic structure I. We are now reporting some derivatives with a "distal" hydrazine feature as represented by the generic structure II. Compounds



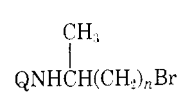
I



II

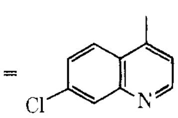


III



IV

$n = 1, 2$ Q =



21-26 (Table I) contain both the proximal and the distal hydrazine moieties. Compounds **12-14** and **16** incorporate a hydrazinium bromide feature. These compounds, although found active or curative, were also quite toxic.

Chemistry.—The intermediate III was prepared by the reaction of 4,7-dichloroquinoline and β-aminobutyraldehyde dimethyl acetal. It was hydrolyzed *in situ* to the aldehyde and reacted with the appropriate hydrazine for the preparation of hydrazones **1-4**. These hydrazones were intended for reduction to the corresponding hydrazine derivatives. But our efforts to reduce them catalytically or chemically did not prove successful. Fragmentation of the molecule generally took place accompanied, sometimes, by the reduction of the quinoline ring or removal of the ring Cl. The Br intermediate IV, $n = 2$, the preparation of which was reported by us before,[2] proved to be very useful and gave rise to **5**, and **7-14**. Similarly the Br intermediate IV, $n = 1$, was made and used for the preparation of **15** and **16**. For **17-20** and **21-26**, piperazine and 1,4-diaminopiperazine were used to react with 4,7-dichloroquinoline. The intermediates, thus formed, led to final compounds through 1 or 2 steps without much difficulty.

Biological Tests.—All compounds except **20** were tested for their antimalarial activity against *Plasmodium berghei* in mice by Dr. L. Rane according to the procedure already published.[3] The results are given in Table II.

In general, the hydrazones **1-4** were extremely toxic. Test results of hydrazine derivatives with an unsubstituted end NH_2 were mixed, showing activity as well as toxicity except for **15** which showed excellent curative activity without being toxic. Toxicity seemed to disappear with substitution on the end NH_2. Compd **22** appears to be the best, in which the end NH_2 is substituted by a second molecule of 7-chloroquinoline. It showed curative activity with as low a dose as 40 mg/kg, and no toxicity even up to the maximum dose of 640 mg/kg.

Experimental Section

7-Chloro-4-(2-dimethylacetal-1-methylethylamino)quinoline (III).—A mixt of 4,7-dichloroquinoline (50.0 g, 0.25 mole), β-aminobutyraldehyde dimethyl acetal (67.0 g, 0.5 mole), KI (0.2 g), and 200 ml of ethoxyethanol was heated under reflux for 24 hr. Ethoxyethanol was then removed under reduced pressure, the residue was basified with 30% NaOH and extd with Et_2O, and the ext was dried (K_2CO_3), filtered, and concd. The residue was distd at 125-135° (5×10^{-4} mm) to give 34.0 g (46.2%) of the product which was crystd twice from Et_2O, mp 138-141°. *Anal.* ($C_{15}H_{19}ClN_2O_2$) C, H, N.

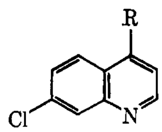
General Preparation of 1-4.—A soln of III (0.02 mole) in 100 ml of EtOH was added to an ice-cold soln of the required hydrazine

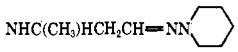
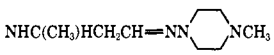
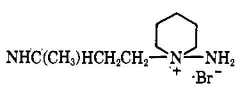
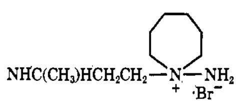
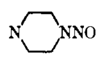
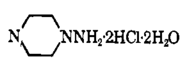
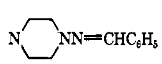
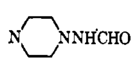
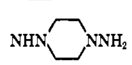
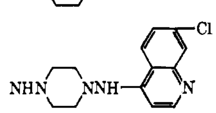
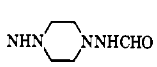
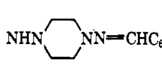
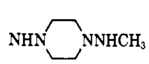
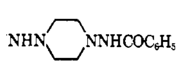
(1) T. Singh, R. G. Stein, and J. H. Biel, *J. Med. Chem.*, **12**, 801 (1969).

(2) T. Singh, R. G. Stein, J. F. Hoops, J. H. Biel, W. K. Hoya, and D. R. Cruz, *ibid.*, **14**, 283 (1971).

(3) T. S. Osdene, P. B. Russell, and L. Rane, *ibid.*, **10**, 431 (1967).

TABLE I



No.	R	Yield, %	Crystn solvent	Mp, °C, or bp, °C (mm)[a]	Formula[b]
1	NHC(CH_3)HCH_2CH=NN(CH_3)$_2$	91.2	Cyclohexane	120–122	$C_{15}H_{19}ClN_4$
2	NHC(CH_3)HCH_2CH=NN(C_2H_5)$_2$	84.3	Cyclohexane	118–120	$C_{17}H_{23}ClN_4$
3		83.0	Et_2O	145–147	$C_{18}H_{23}ClN_4$
4		9.5	Et_2O	123–126	$C_{18}H_{24}ClN_5$
5	NHC(CH_3)HCH_2CH_2N(CH_3)NH_2	56.0	Et_2O	98–100	$C_{14}H_{19}ClN_4$
6	NHC(CH_3)HCH_2CH_2N(CH_3)NHCOCH_3	66.7	Et_2O	153–156	$C_{16}H_{21}ClN_4O$
7	NHC(CH_3)HCH_2CH_2N(CH_3)NHCH_3	68.2	*n*-Heptane	119–121	$C_{15}H_{21}ClN_4$
8	NHC(CH_3)HCH_2CH_2N(CH(CH_3)$_2$)NH_2	29.8	Et_2O	105–107	$C_{16}H_{23}ClN_4$
9	NHC(CH_3)HCH_2CH_2N($C_6H_5CH_2$)NH_2	39.6	Et_2O	112–114	$C_{20}H_{23}ClN_4$
10	NHC(CH_3)HCH_2CH_2N(*o*-Cl$C_6H_4CH_2$)NH_2	40.0	Et_2O	128–130	$C_{20}H_{22}Cl_2N_4$
11	NHC(CH_3)HCH_2CH_2N($C_6H_5CH_2CH_2$)NH_2	50.8	Et_2O	125–128	$C_{21}H_{25}ClN_4$
12	NHC(CH_3)HCH_2CH_2(CH_3)$\overset{+}{N}$(CH_3)NH_2 ·Br^-	76.0	EtOH–PhMe	222–224	$C_{15}H_{22}BrClN_4$
13		53.9	MeOH–EtOAc	239–241	$C_{18}H_{26}BrClN_4$
14		44.7	*i*-PrOH	222–223	$C_{19}H_{28}BrClN_4$
15	NHC(CH_3)HCH_2N(CH_3)NH_2	47.0	C_6H_6	198–200	$C_{13}H_{17}ClN_4$
16	NHC(CH_3)HCH_2(CH_3)$\overset{+}{N}$(CH_3)NH_2 ·Br^-	52.0	EtOH	231–232 dec	$C_{14}H_{20}BrClN_4$
17		89.5	Et_2O	122–124	$C_{13}H_{13}ClN_4O$
18			MeOH	245–248	$C_{13}H_{21}Cl_3N_4O_2$
19			C_6H_6	165–167	$C_{20}H_{19}ClN_4$
20			EtOH	208–211	$C_{14}H_{15}ClN_4O$
21		72.0	C_6H_6	205–208	$C_{13}H_{16}ClN_5$
22[c]			AcOH	336–338 dec	$C_{22}H_{20}Cl_2N_6$
23		82.0	EtOH	287–290	$C_{14}H_{16}ClN_5O$
24		61.5	EtOAc	261–263	$C_{20}H_{20}ClN_5$
25		10.5	C_6H_6	210–214	$C_{14}H_{18}ClN_5$
26		52.7	EtOH	300–305	$C_{20}H_{20}ClN_5O$

[a] All melting points are uncorrected. [b] Compds 1–11, **13–17**, **19**, **21**, **23–26** were analyzed for C, H, N and **12**, **18**, **20**, and **22** for N. All anal. were within ±0.4% of calcd values. [c] While this work was in progress, the prepn of this compd was reported by E. F. Elslager, F. H. Tendick, L. M. Werbel, and D. F. Worth, *J. Med. Chem.*, **12**, 970 (1969).

(0.2 mole) in 50 ml of concd HCl and 100 ml of EtOH. The mixt was allowed to stand at room temp for 48 hr. It was strongly basified with 40% NaOH with cooling, EtOH was evapd under reduced pressure, and the residue was extd with CH_2Cl_2. The ext, after usual work-up, gave the product.

7-Chloro-4-(3-bromo-1-methylpropylamino)quinoline (IV, *n* = 2) was made according to the procedure previously[2] reported.

General Preparation of 5, 7–11.—A mixt of IV (0.03 mole), the required hydrazine (0.3 mole), and 100 ml of EtOH was refluxed for 12 hr. EtOH was evapd under reduced pressure, and the residue was treated with K_2CO_3 soln and extd with Et_2O. The ext, on usual work-up, gave the crude product.

General Preparation of 12–14.—A mixt of IV (0.03 mole), the required hydrazine (0.15 mole), and 100 ml of EtOH was refluxed for 4 hr The vol of the mixt was reduced to half and the product was pptd by the addn of Et_2O. If gummy, further trituration with Et_2O gave a cryst solid which was further purified by crystn.

TABLE II

No.[a]	D[b]	Antimalarial activity C	TD	$T - C$	Remarks[c]
1	40	0	5		Toxic
	160	0	5		Toxic
	640	0	5		Toxic
2	40	0	5		Toxic
	160	0	5		Toxic
	640	0	5		Toxic
3	40	0	5		Toxic
	160	0	5		Toxic
	640	0	5		Toxic
4	40	0	0	0.0	
	160	0	0	0.0	
	640	0	3		Toxic
5	40	0	0	8.6	Active
	80	0	0	11.8	Active
	160	2	0		Curative
	320	2	3		Curative; toxic
	640	0	5		Toxic
6	40	0	0	0.2	
	160	0	0	4.0	
	640	0	0	6.6	Active
7	40	0	0	6.1	Active
	80	0	0	6.9	Active
	160	0	0	13.1	Active
8	10	0	0	0.8	
	40	0	0	4.0	
	160	0	3	13.8	Active; toxic
9	40	0	0	0.6	
	160	0	3	3.8	Toxic
	640	0	5		Toxic
10	40	0	0	0.6	
	160	0	0	5.4	
	640	0	3	8.8	Active; toxic
11	40	0	0	0.7	
	160	0	3	5.4	Toxic
	640	0	5		Toxic
12	40	0	0	4.7	
	160	1	0		Curative
	640	2	3		Curative; toxic
13	40	0	0	1.3	
	160	0	2	2.9	Toxic
	640	0	5		Toxic
14	40	0	0	1.3	
	160	0	0	8.1	Active
	640	0	2		Toxic
15	40	0	0	4.2	
	160	0	0	13.2	Active
	320	3	0		Curative
	640	4	0		Curative
16	40	0	0	10.6	Active
	160	0	0	15.4	Active
	640	2	2		Curative; toxic
17	40	0	0	0.2	
	160	0	0	0.6	
	320	0	0	1.0	
18	40	0	0	0.5	
	160	0	0	2.9	
	320	0	0	3.9	
	640	0	5		Toxic
19	40	0	0	0.4	
	160	0	0	1.8	
	640	0	0	3.4	
21	40	0	0	4.0	
	160	0	0	15.0	Active
	640	0	5		Toxic
22	40	1	0		Curative
	160	3	0		Curative
	320	5	0		Curative
	640	5	0		Curative
23	40	0	0	3.8	
	160	0	0	17.2	Active
	320	3	0		Curative
	640	3	0		Curative
24	40	0	0	2.8	
	160	0	0	17.6	Active
	320	1	0		Curative
	640	2	0		Curative
25	40	0	0	6.9	Active
	160	3	0		Curative
	640	5	0		Curative
26	40	0	0	0.5	
	160	0	0	6.5	Active
	640	2	0		Curative

[a] Numbers refer to those in Table I. [b] D, dose, mg/kg; C, cures; TD, toxic deaths when mice die 2-5 days postinfection, attributed to drug toxicity; $T - C$, increase in mean survival time of the treated mice over the control group. [c] A compd is active if the $T - C$ exceeds 6.1 days, and curative if one or more mice live for 60 days or more postinfection.

7-Chloro-4-(1-methyl-2-bromoethylamino)quinoline (IV, n = 1).—A mixt of 7-chloro-4-(2-hydroxy-1-methylethylamino)quinoline[4] (9.4 g), 25 ml of 48% HBr, and 5 ml of concd H_2SO_4 was heated at 160–170° for 3 hr. It was cooled to room temp when a gummy solid sepd. The aq layer was decanted and the gummy solid was triturated with 10% NH_4OH several times. The residue was boiled with C_6H_6 (3 × 150 ml), dried ($MgSO_4$), and concd to give 2.9 g (25%) of the product. The anal. sample was recrystd once, mp 132–133°. *Anal.* ($C_{12}H_{12}BrClN_2$) C, H, N. This Br intermediate was used to prepare the distal hydrazine **15** and the hydrazinium salt **16** according to the general procedures described for **5**, **7–11**, and **12–14**, resp.

7-Chloro-4-(4-nitroso-1-piperazinyl)quinoline (**17**).—A soln of 7-chloro-4-(1-piperazinyl)quinoline[3] (24.8 g, 0.1 mole) in 200 ml of H_2O and 100 ml of concd HCl was cooled to 0° and to this was added a cooled soln of $NaNO_2$ (21.0 g, 0.3 mole) in 75 ml of H_2O with stirring. After stirring for 0.5 hr after the addn of $NaNO_2$ soln, the mixt was allowed to come to room temp when a white ppt formed. After 2-hr stirring, the mixt was basified (pH 8–9) with cold NaOH soln and continuously extd with Et_2O. The ext was dried (K_2CO_3), filtered, and concd until crystn started; yield, 24.8 g. An anal. sample was recrystd once more.

7-Chloro-4-(4-amino-1-piperaziyl)quinoline (**18**) **and Its Derivatives 19 and 20.**—The nitroso derivative **17** (20.7 g, 0.075 mole) was dissolved in 50 ml of 50% AcOH and treated with Zn dust (14.7 g, 0.225 g-atom) in small portions with stirring, keeping the temp between 20 and 30°. After addn (0.5 hr), the mixt was warmed to 50° for 1 hr. Excess Zn was filtered off, the filtrate was concd *in vacuo* (bath temp 50°), and the residue was basified with excess of 50% NaOH with cooling and extd with CH_2Cl_2. The ext on work-up gave 18.5 g of crude product which was distd at 135–140° (10^{-3} mm). It was not pure enough to give satisfactory analyses. A portion was converted into the

(4) Rhone-Poulenc S. A., Belgian Patent 612,207; *Chem. Abstr.*, **58**, 9099*b* (1963); U. S. Patent 3,196,155. The prepn is given in the original, not in the Abstract.

hydrochloride which analyzed satisfactorily. The benzaldehyde hydrazone **19** was made in 50% AcOH at 50–60° and the formamido derivative **20** was prepd by refluxing the crude **18** with 97% HCO_2H for 0.5 hr. Excess HCO_2H was removed *in vacuo*, the residue was basified with cold dil NaOH soln, and the product was removed by filtration and purified by recrystn.

7-Chloro-4-(4-amino-1-piperazinylamino)quinoline (21) **and 1,4-Bis(7-chloro-4-quinolylamino)piperazine** (22).—A mixt of 4,7-dichloroquinoline (15.0 g, 0.075 mole), 1,4-diaminopiperazine dihydrate (30.4 g, 0.2 mole), 60 ml of ethoxyethanol, and a cryst of KI was refluxed overnight. The solvent was removed under reduced pressure, the residue was basified with NaOH soln, and the solid was collected by filtration and washed with H_2O. The solid was taken up in hot EtOH and filtered. The filtrate was evapd to dryness and the residue was recrystd.

The solid insol in EtOH (**22**) was crystd from AcOH, as it happened to be practically insol in all other solvents. The crystd product retained some AcOH which was difficult to remove. The anal. sample was dried at 110° under high vacuum for 24 hr.

7-Chloro-4-(4-formamido-1-piperazinylamino)quinoline (23).—A mixt of **21** (5.56 g, 0.02 mole), 100 ml of HCO_2Et, and 20 ml of 99% HCO_2H was refluxed for 4 hr. Excess HCO_2Et and HCO_2H were removed under reduced pressure (bath temp not exceeding 50°), the residue was treated with dil NaOH, and the white solid was collected by filtration and purified by crystn.

7-Chloro-4-(4-benzylideno-1-piperazinylamino)quinoline (24).—A mixt of **21** (5.56 g, 0.02 mole) and PhCHO (3.2 g, 0.03 mole) in 50 ml of 50% AcOH was warmed on a steam bath for 0.5 hr. The solvent was removed under reduced pressure and the residue was treated with dil K_2CO_3 soln. The aq layer was decanted. The semisolid mass, when triturated with Et_2O, gave a fine powder which was collected by filtration and crystd.

7-Chloro-4-(4-methylamino-1-piperazinylamino)quinoline (**25**).—**23** (1 g) was reduced with 1.0 g of LAH in 300 ml of anhyd Et_2O over a period of 18 hr. The color of the mixt turned greenish. The mixt was then refluxed for 5 hr more, decompd with satd Na_2SO_4 soln, and filtered and the filtrate, on evapn, gave 150 mg of cryst product which was purified by crystn.

7-Chloro-4-(4-benzoylamino-1-piperizinylamino)quinoline (**26**) was prepd in 52.7% yield from the reaction of **23** with BzCl using the usual Schotten–Baumann reaction condns.

***N*-Acetyl-*N'*-methyl-*N'*-[3-methyl-3-(7-chloro-4-quinolylamino)propyl]hydrazine** (**6**).—Compd **5** (3.0 g) was dissolved in 30 ml of Ac_2O at room temp and the soln was warmed at 60° for 5 min. Excess Ac_2O was removed under reduced pressure, keeping the bath temp below 60°. On addn of H_2O to the residue a clear soln was obtained. This was basified with cold NaOH soln and the product was extd with Et_2O. The ext was dried (K_2CO_3), filtered, and concd until crystn started.

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Antiviral Agents. 2.[1] Structure–Activity Relationships of Compounds Related to 1-Adamantanamine

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The antiviral activity toward influenza A S-14 (swine) of a number of compounds related to 1-adamantanamines has been determined. Among these compounds are N- and C-alkylated 1-adamantanamines, 1-adamantanemethylamines, and homoadamantanamines.

Extensive laboratory studies[2,3] and clinical reports[3,4] have established the prophylactic effect of 1-adamantanamine·HCl (amantadine·HCl) (**1**) toward influenza A virus strains. More recently, clinical investigators have found a therapeutic effect with amantadine·HCl[5,6] and with rimantadine·HCl[6] (α-methyl-1-adamantanemethylamine·HCl, **58**) in patients with naturally occurring influenza A_2 respiratory illness. Inhibition of rubella,[7] Rous sarcoma,[8,9] and Esh sarcoma viruses has also been reported. Amantadine·HCl more recently has been demonstrated to benefit patients suffering from Parkinson's disease.[10] Meanwhile, others[11] have disclosed results from drugs that include the adamantane moiety.

No systematic study of the effect of structural variations of 1-adamantanamine upon antiviral activity has

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