and the analogy with other known cases of attack at the quinoline N[15,16] support the assignment of propiolate addition to the tautomeric quinoline ring N–H. Two *trans*-vinyl proton resonances from the propiolate portion (J = 14 Hz) could be observed at 4.79 and 7.72 ppm in the nmr. These not only rule out the possibility that the compound is a stable charge-transfer entity but also support the conclusion that NH to triple bond addition had occurred.

Antimalarials. 4-"Proximal" Hydrazino Derivatives of 7-Chloroquinoline

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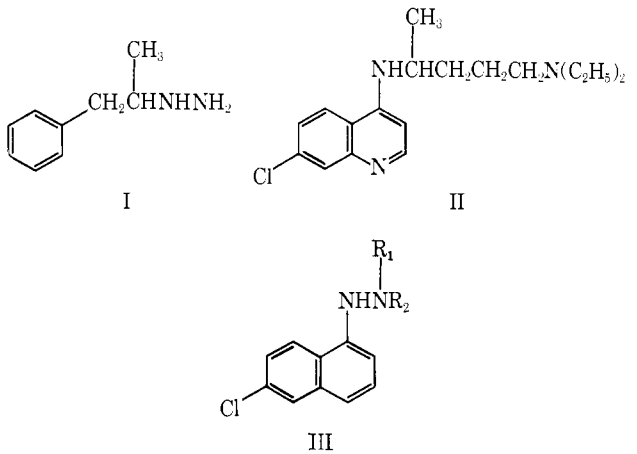
Sixteen "proximal" hydrazino derivatives of 7-chloroquinoline of the general structure III have been prepared and tested as antimalarials. Three of these have shown curative activity without toxic deaths up to doses of 640 mg/kg sc.

In our earlier work[1,2] with drugs bearing a hydrazine moiety, as in α-methylphenethylhydrazine (I), it was found that, in contrast to the parent amines, drug resistance did not develop to the corresponding hydrazines, thereby affording a long duration of action without decrease in efficacy on repeated administration. On this basis, it was considered worthwhile to incorporate a hydrazine moiety in the chloroquine (II) side chain in the hope of obtaining antimalarial drugs which would be effective in chloroquine-resistant malarial strains of *Plasmodium falciparum*. Accordingly, we prepared the "proximal" hydrazino derivatives of chloroquine represented by the generic structure III where R_1 is H, CH_3, and C_2H_5; R_2 is dialkylaminoalkyl; and R_1 and R_2 being the same part of a hydrazone derivative as in compounds **2**, **3**, **5**, **7**, **9**, and **10** (Table I).

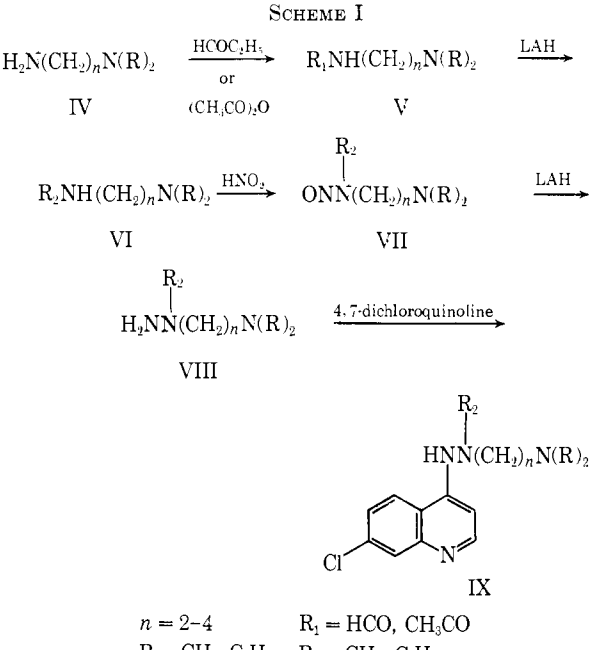


I II III

The key intermediate for the preparation of **2–10** was 7-chloro-4-hydrazinoquinoline (**1**) which was obtained according to the procedure of Surrey and Cutler.[3] The hydrazones were prepared by the reaction of 4-hydrazinoquinoline with appropriate aldehyde or the diethyl acetal of the aldehyde in the conventional manner. The hydrazines **4**, **6**, and **8** were obtained by catalytic (Pt) hydrogenation of the corresponding hydrazones in EtOH at room temperature and atmospheric pressure. Because of the premature poisoning of the catalyst, it had to be changed once or twice to complete the hydrogenation.

For the preparation of **11–16**, the hydrazino-side-chain amines were first prepared and then put on 4,7-dichloroquinoline according to the sequence of reactions outlined in Scheme I.

SCHEME I



IV V VI VII VIII IX

n = 2–4 R_1 = HCO, CH_3CO

R = CH_3, C_2H_5 R_2 = CH_3, C_2H_5

For **13**, the side chain could also be prepared by the alkylation of methylhydrazine with dimethylaminopropyl chloride according to the procedure of Elslager, *et al.*[4]

Biological Activity.—The compounds were tested for their antimalarial activity against *Plasmodium berghei* in mice. The screening was carried out by Dr. L. Rane of the University of Miami, Miami, Fla. The screening procedure is described by T. S. Osdene, *et al.*[5] Compound **1** was toxic. It killed one animal at 40 mg/kg and all five at 160 mg. Compounds **6–10** were inactive. Compounds **2–5** were slightly active, showing an increase in mean survival time of about 7.4 days.

(1) J. H. Biel, A. E. Drukker, T. F. Mitchell, E. P. Sprengeler, P. A. Nuhfer, A. C. Conway, and A. Horita, *J. Amer. Chem. Soc.*, **81**, 2805 (1959).

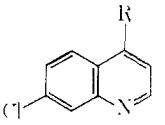
(2) J. H. Biel, A. Horita, and A. E. Drukker in "Psychopharmacological Agents," Vol. I, M. Gordon, Ed., Academic Press, New York, N. Y., 1964, p 366.

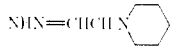
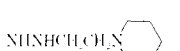
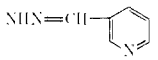
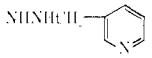
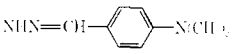
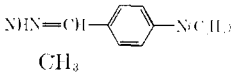
(3) A. R. Surrey and R. A. Cutler, *J. Amer. Chem. Soc.*, **68**, 2570 (1946).

(4) E. F. Elslager, E. A. Weinstein, and D. F. Worth, *J. Med. Chem.*, **7**, 493 (1964).

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

TABLE I



No.	R	Yield, %	Bp, °C (mm)	Mp, °C[a]	Crystn solvent	Formula[b]
1	$NHNH_2$	59.0		215–217[c]	EtOH	
2	$NHN{=}CHCH_2N(CH_3)_2$	72.0		181–182	EtOH	$C_{12}H_{15}ClN_4$
3	$NHN{=}CHCH_2N(C_2H_5)_2$	74.0		174–175	EtOH	$C_{15}H_{19}ClN_4$
4	$NHNHCH_2CH_2N(C_2H_5)_2$	72.0		170–171 dec	EtOH–H_2O	$C_{15}H_{21}ClN_4$
5		47.0		163–164	EtOH	$C_{16}H_{15}ClN_4$
6	 ·2HCl	33.0		194–196		$C_{16}H_{21}ClN_4$
7		60.0		245–246	EtOH–H_2O	$C_{15}H_{11}ClN_4$
8		45.0		238–240	EtOH–H_2O	$C_{15}H_{13}ClN_4$
9		42.0		259–261	EtOH–H_2O	$C_{18}H_{15}ClN_4$
10		44.0		244–246	EtOH	$C_{20}H_{21}ClN_4$
11	$NHNCH_2CH_2N(CH_3)_2$ CH_3	40.0	130–160 (0.07)	130–132	Cyclohexane	$C_{14}H_{19}ClN_4$
12	$NHNCH_2CH_2N(CH_3)_2$ C_2H_5	57.0	110–120 (0.001)			$C_{15}H_{21}ClN_4$
13	$NHN(CH_3)(CH_2)_3N(CH_3)_2$	50.0		137.5–138	Cyclohexane	$C_{15}H_{21}ClN_4$
14	$NHN(C_2H_5)(CH_2)_3N(CH_3)_2$	53.0	160–170 (0.34)			$C_{16}H_{23}ClN_4$
15	$NHN(CH_3)(CH_2)_3N(C_2H_5)_2$	66.0	135–150 (0.05)	124–125	Cyclohexane	$C_{17}H_{25}ClN_4$
16	$NHN(CH_3)(CH_2)_4N(C_2H_5)_2$	14.0	140–165 (0.05)	118.5–120	Cyclohexane	$C_{18}H_{27}ClN_4$

[a] All melting points are uncorrected. [b] All compounds were analyzed for C, H, N. All analytical results were within ±0.4% except for **6** (H: calcd, 6.14; found, 5.63) and for **8** (H: calcd, 4.60; found, 4.08). [c] Lit.[3] mp 220–221°.

The results for the compounds **11–16** are given in Table II. Compound **15**, which is an N isostere of chloroquine is toxic at 320 and 640 mg killing two and five mice, respectively. This toxicity is similar to chloroquine but less severe. The curative activity of the compounds **11–13** is noteworthy as they produced no toxic deaths even at the maximum dose of 640 mg/kg sc.

Experimental Section

N-(2-Dimethylaminoethyl)-N-methylnitrosoamine (VII, R = CH_3, n = 2, R_2 = CH_3).—A solution of N-(2-dimethylaminoethyl)-N-methylamine (50.0 g, 0.5 mol), concentrated H_2SO_4 (80.0 g, 0.8 mol), and 400 ml of H_2O was cooled to 0°. A solution of $NaNO_2$ (42.0 g, 0.6 mol) in H_2O was added dropwise over a period of 2 hr. The mixture was left to stand for 2 hr and then concentrated to dryness. The residue was dissolved in a minimum amount of H_2O, cooled, and basified with KOH pellets. The product was extracted with Et_2O (three 200-ml portions), the Et_2O extract was dried (KOH), filtered, and concentrated to an oil which was distilled at 108° (15 mm), yield 50.0 g (76.3%). *Anal.* ($C_5H_{13}N_3O$) C, H, N.

N-(2-Dimethylaminoethyl)-N-methylhydrazine (VIII, R = CH_3, n = 2, R_2 = CH_3).—A solution of N-(2-dimethylaminoethyl)-N-methylnitrosoamine (39.3 g, 0.3 mol) in 100 ml of anhydrous Et_2O was added dropwise to an ice-cold mixture of LAH (13.2 g) in 1 l. of anhydrous Et_2O over a period of 2 hr. The mixture was stirred for another 1 hr at ice-bath temperature and then carefully decomposed by the successive dropwise addition of 126 ml of H_2O, 12.6 ml of 15% NaOH solution, and 37.8 ml of H_2O. Stirring was continued for another 12 hr and then the inorganic salts were filtered and washed with Et_2O. The filtrate and washings were combined, dried (NaOH), filtered, and concentrated to an oil which distilled at 140–145° (760 mm), yield 15.0 g (42.9%). The liquid was very hygroscopic and used as such in the next step.

7-Chloro-4-[N′-(2-dimethylaminoethyl)-N′-methyl]hydrazinoquinoline (11).—A solution of N-(2-dimethylaminoethyl)-N-methylhydrazine (8.19 g, 0.07 mol), 4,7-dichloroquinoline (10.0 g, 0.05 mol), and PhOH (30.0 g) was heated at 140° for 8 hr. The mixture was cooled, poured into 10% KOH, and extracted with three 150-ml portions of $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried (K_2CO_3), and concentrated to an oil which was distilled at 130–160° (0.07 mm) to give 5.3 g (40%) of the product which solidified on standing. The solid was crystallized four times.

This is the typical, general method which also worked smoothly for compounds **12–16**.

N-(2-Dimethylaminoethyl)-N-ethylnitrosoamine (VII, R = CH_3, n = 2, R_2 = C_2H_5) was prepared from N,N-dimethyl-N′-ethylethylenediamine in 54.0% yield in the same manner as already described, bp 88–90° (8 mm). *Anal.* ($C_6H_{15}N_3O$) C, H, N.

N-(2-Dimethylaminoethyl)-N-ethylhydrazine (VIII, R = CH_3, n = 2, R_2 = C_2H_5) was prepared from N-(2-dimethylaminoethyl)-N-ethylnitrosoamine by LAH reduction in 70.0% yield. The colorless oil distilled at 172–174° and absorbed moisture and CO_2 from the atmosphere. Its purity was found to be 92.5% by glpc and was used as such to react with 4,7-dichloroquinoline to give **12**.

7-Chloro-4-[N′-(3-dimethylaminopropyl)-N′-methyl]hydrazinoquinoline (13).—The starting point for this compound was 3-dimethylaminopropylamine which was formylated and reduced to N-(3-dimethylaminopropyl)-N-methylamine according to the procedures of Krapcho, *et al.*[6] The latter was nitrosated accord-

(6) J. Krapcho, C. F. Turk, and E. J. Pribly, *J. Amer. Chem. Soc.*, **77**, 3632 (1955).

TABLE II

Compd	Antimalarial act.[b] D	C	TD	Increase in MST
11[a]	20	0	0	5.3
	40	0	0	7.1 (active)
	80	0	0	9.0 (active)
	160	0	0	12.0 (active)
	320	1	0	... (curative)
	640	4	0	... (curative)
12	20	0	0	3.5
	40	0	0	5.1
	80	0	0	7.3 (active)
	160	0	0	8.5 (active)
	320	4	0	... (curative)
	640	5	0	... (curative)
13	20	0	0	2.5
	40	0	0	3.9
	80	0	0	4.3
	160	0	0	8.3 (active)
	320	4	0	... (curative)
	640	5	0	... (curative)
14	40	0	0	4.1
	80	0	0	4.5
	160	0	0	5.1
	320	0	0	8.1 (active)
15	40	0	0	2.2
	80	0	0	3.0
	160	0	0	4.6
	320	0	2	8.8 (active, toxic)
	640	0	5	... (toxic)
16	20	0	0	2.5
	40	0	0	7.5 (active)
	80	0	0	9.5 (active)
	160	0	0	13.7 (active)
	320	2	0	18.6 (curative)
	640	2	3	... (curative, toxic)
Chloroquine	20	0	0	6.5 (active)
	40	0	0	7.5 (active)
	80	0	1	8.9 (active, toxic)
	160	0	3	... (toxic)
	320	0	5	... (toxic)

[a] Numbers refer to those in Table I. [b] D, dose in mg/kg of body weight; C, cures; MST, mean survival time of the treated mice; TD, toxic death when the mice die in 2–5 days after infection, which is attributed to drug toxicity. A compound is active if the increase in MST of the treated mice exceeds 6.2 days (the MST of the control group of mice) and curative if one or more mice live for 60.0 days or more postinfection.

ing to the procedure already described in 44.0% yield to give a yellow oil, bp 97–100° (7 mm). The nitroso compound was reduced with LAH in 64.0% yield to give N-(3-dimethylaminopropyl)-N-methylhydrazine, bp 56–57° (7 mm). This hydrazine was treated with 4,7-dichloroquinoline according to the procedure already described to give **13** in 50.0% yield, a white solid, which was recrystallized several times.

7-Chloro-4-[N'-(3-dimethylaminopropyl)-N'-ethyl]hydrazinoquinoline (14).—The starting point for this compound was again 3-dimethylaminopropylamine which was acetylated with Ac_2O in 95.0% yield to give the acetamide, bp 140–144° (8 mm). It was reduced with LAH to give N,N-dimethyl-N'-ethylpropylenediamine in 59.0% yield, bp 155–157°. The nitroso derivative was prepared in 40.0% yield, bp 102–104° (7 mm), and was reduced to the hydrazine in 80.0% yield. The hydrazine, bp 82° (10–12 mm), reacted with 4,7-dichloroquinoline to give **14** in 53.0% yield as a viscous semisolid which was purified by distillation.

N-(3-Diethylaminopropyl)-N-methylnitrosoamine (VII, R = C_2H_5, n = 3, R_2 = CH_3).—3-Diethylaminopropylamine was formylated according to the procedure of Krapcho, *et al.*,[6] to give the formyl derivative in 94% yield, bp 135–140° (8 mm). This was reduced with LAH to give N-(3-diethylaminopropyl)-N-methylamine in 74% yield, bp 57–60° (8 mm). Munch, *et al.*,[7] who prepared this amine by a different procedure, have reported bp 58–60° (8 mm). This amine was nitrosated according to the procedure already described to give the nitroso derivative, bp 117–118° (8 mm), in 75% yield. *Anal.* ($C_8H_{19}N_3O$) C, H, N.

N-(3-Diethylaminopropyl)-N-methylhydrazine (VIII, R = C_2H_5, n = 3, R_2 = CH_3).—A solution of N-(3-diethylaminopropyl)-N-methylnitrosoamine (17.3 g, 0.1 mol) in 60 ml of glacial AcOH was slowly added to a rapidly stirring suspension of Zn dust (52.0 g, 0.8 g-atom) in 100 ml of H_2O. During the addition the temperature was maintained at 10–20° by external cooling. The mixture was stirred for another 2 hr, when it was slowly heated to 80° and maintained there for 0.5 hr. It was then filtered hot and the filter cake was washed with two 100-ml portions of hot 5% HCl solution. The combined filtrates were evaporated to give a gummy material which was dissolved in H_2O, basified to pH 12 with 50% NaOH, and extracted with Et_2O. The Et_2O extracts were combined, dried (KOH), and concentrated to give an oil in 70.0% yield, which distilled at 72–74° (6 mm).

This was treated with 4,7-dichloroquinoline to give **15**.

7-Chloro-4-[(N'-4-diethylaminobutyl)-N'-methyl]hydrazinoquinoline (16).—N-methyl-(4-diethylamino)butylamine (VI, R = C_2H_5, n = 4, R_2 = CH_3), bp 110° (60 mm), was prepared in 88.0% yield by the LAH reduction of the corresponding N-formyl compound. It was nitrosated to give N-(4-diethylaminobutyl)-N-methylnitrosoamine (VII, R = C_2H_5, n = 4, R_2 = CH_3), bp 129° (6 mm), in 76.0% yield. *Anal.* ($C_9H_{21}N_3O$) N. This was reduced to the corresponding hydrazine in 80.0% yield, bp 90° (8 mm). It proved to be 97.0+% pure by glpc and was treated as such with 4,7-dichloroquinoline in the usual manner to give **16**.

Acknowledgments.—This work was supported by the U. S. Army Medical Research and Development Command under the Research Contract No. DA-49-193-MD-2869. This is Contribution No. 566 from the Army Research Program on malaria.

(7) R. Munch, G. T. Thannhauser, and D. L. Cottle, *J. Amer. Chem. Soc.*, **68**, 1297 (1946).