8-Hydroxyquinoline Derivatives. Synthesis and Biological Evaluation of Arylglyoxal *N*-7-Amino-5-substituted 8-Hydroxyquinoline Hemiacetals and 5-Phenylglyoxylidenamino-8-hydroxyquinolines

E. MASSARANI, D. NARDI, R. POZZI, L. DEGEN, AND M. J. MAGISTRETTI

Research Division, Recordati s.a.s., Milan, Italy

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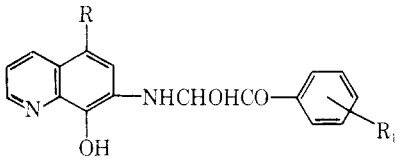
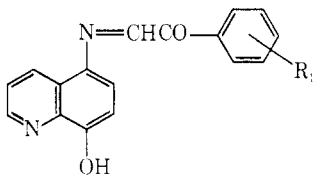
A series of phenylglyoxal *N*-7-amino-5-substituted 8-hydroxyquinoline hemiacetals and of 5-phenylglyoxylidenamino-8-hydroxyquinolines was synthesized and evaluated for their pharmacological, microbiological, and antiviral activity. The importance of the phenylglyoxal moiety on the antiviral activity and the influence of the nature of 8-hydroxyquinoline moiety on toxicity and antibacterial, antifungal, and antiinflammatory activities are discussed.

The purpose of this paper was to describe the synthesis of a series of compounds with the following structures in order to study their antiviral activities, since such properties are found in derivatives of arylglyoxals,[1-3] and their antimicrobial properties as they are observed for 8-hydroxyquinoline derivatives.



I



II

R = H, Cl, SO_3H

Chemistry.—*N*,*O*-Acetals (I) were obtained by condensing the 7-amino-8-hydroxyquinolines with the substituted phenylglyoxals, whereas only Schiff's bases (II) were obtained by condensing the 5-amino-8-hydroxyquinoline.

While preparing I, we also isolated condensation products (particularly at higher reaction temperature) to which we could attribute the structure of Schiff's bases on the basis of analytical data.

The ir spectra of these compounds did not contain C=O and O–H bands in contrast to those of compound I. This may be attributed to intramolecular H bond involving OH. An analogous phenomenon was observed by Durant, *et al.*,[4] for 4-biphenylglyoxal derivatives. Nmr spectra could not be determined because of the low solubility of these compounds.

Biological Results.—The acute toxicity was determined intraperitoneally in mice for all compounds. Most compounds showed low toxicity, except the derivatives of 8-hydroxyquinoline-5-sulfonic acid.

All compounds were tested for bacteriostatic activity *in vitro* on the following microorganisms: *Escherichia coli* 100, *Pseudomonas aeruginosa* H2, *Proteus vulgaris* OX, *Micrococcus pyogenes* SG 511, *Streptococcus pyogenes* A 88, *Bacillus subtilis* ATCC 9466, *Mycobacterium tuberculosis* H_{37} Ra, *Trichophyton mentagrophytes* 1236, and *Candida albicans* 28. All compounds were also tested on embryonated eggs infected with A-PR8 and vaccinia virus. The results are summarized in Table I.

Some derivatives of 7-amino-8-hydroxyquinoline exhibited antibacterial activity *in vitro* against *E. coli*, *M. pyogenes*, *B. subtilis*, and *M. tuberculosis*. Compound **2** was also tested for its prophylactic activity on *E. coli* peritonitis in mice, and was found active intraperitoneally but inactive orally; no activity was shown against *M. tuberculosis* infection in mice.

The derivatives of 5-chloro-7-amino-8-hydroxyquinoline exhibited antibacterial activity against *E. coli*, *M. pyogenes*, and *B. subtilis*, though in lower degree. They were found active against *T. mentagrophytes* but inactive against *M. tuberculosis*.

The derivatives of 7-amino-8-hydroxyquinoline-5-sulfonic acid and of 5-amino-8-hydroxyquinoline showed no relevant antibacterial activity.

All compounds showed antiviral activity against A-PR8 virus, some also against vaccinia virus.

Most derivatives of 5-amino-8-hydroxyquinoline showed antiinflammatory activity. This activity was found also in two derivatives of 7-amino-8-hydroxyquinoline-5-sulfonic acid (**18**, **20**), and in two derivatives of 7-amino-8-hydroxyquinoline (**2**, **6**). No analgetic activity was shown by these products in Randall and Selitto's test.

These results led to the conclusion that toxicity and antibacterial, antifungal, and antiinflammatory activities are connected with the position and the nature of substituents in the 8-hydroxyquinoline ring, whereas the antiviral activity, shown by the glyoxals, was not affected by such substitution.

No activity was found for the Schiff's bases listed in Table II. This observation points out the importance of free OH of 8-hydroxyquinoline derivatives for their biological activity, which involves intramolecular hydrogen bond formation.

(1) G. Cavallini, *Int. Symp. Chemother. 2nd, Naples, 1961*, **2**, 36 (1963).
(2) G. Cavallini, E. Massarani, and D. Nardi, *Farmaco Ed. Sci.*, **19**, 610 (1964).
(3) G. Cavallini, E. Massarani, D. Nardi, F. Tenconi, and L. Mauri, *ibid.*, **19**, 751 (1964).
(4) G. J. Durant, H. F. Ridley, and R. G. W. Spickett, *J. Med. Chem.*, **9**, 792 (1966).

Table I

Antimicrobial,[a] Antifungal, Antiviral, and Antiinflammatory Activity of 8-Hydroxyquinoline Derivatives

	Minimal inhibitory concentration (γ/ml)						Embryonated eggs				
								Virucidal activity			
No.	*E. coli*	*B. subtilis*	*M. pyogenes*	*S. pyogenes*	*T. mentagrophytes*	C. *albicans*	MTD[b] μmoles/egg	A-PR8	Vaccinia	LD_{50} mg/kg ip	Antiinflammatory activity[c] mg/kg
1	40	80	80	0[d]	0	0	1.25	1[e]	0	>3000	*f*
2	5	40	160	0	160	0	20	>2	1	>3000	100
3	20	80	160	160	0	0	0.62	1	0	>3000	
4	10	80	20	0	80	160	*g*			>3000	
5	20	20	20	160	0	0	5	3	0	>3000	
6	5	20	40	0	80	0	5	>2	2	>3000	50
7	0	160	160	0	0	160	1.25	2	1	>3000	
8	160	80	80	0	160	0	10	3	0	3000	
9	80	10	20	160	40	80	1.25	2	2	1000	
10	40	40	40	160	80	0	5	>3	0	>3000	
11	80	80	80	80	40	160	5	2	0	>3000	
12	160	20	20	0	80	0	2.5	>3	0	>3000	
13	160	20	20	0	0	0	5	3	0	>3000	
14	80	5	10	160	160	40	1.25	2	0	>3000	
15	160	80	80	160	20	160	5	>3	0	>3000	
16	0	160	160	160	0	0	1.25	0	0	500	
17	0	160	160	160	0	0	10	>2	0	750	100
18	0	160	160	160	160	160	5	1	0	240	
19	0	80	80	80	0	160	10	>2	0	250	60
20	160	80	80	160	160	0	1.25	>2	1	1200	
21	0	80	40	160	0	160	20	2	0	>3000	50
22	0	0	0	0	0	0	20	1	0	2000	100
23	0	0	0	0	0	0	20	3	0	3000	100
24	160	0	80	0	160	0	20	2	0	>3000	200
25	0	0	160	0	0	160	20	0	0	3000	
26	0	0	160	0	0	0	10	0	1	3000	40
27	0	0	0	0	0	0	20	2	0	>3000	
28	0	0	0	0	0	0	20	>2	2	2400	100
29	0	0	0	0	0	80	20	1	0	1800	50

[a] All compounds except **4, 6, 20, 21, 25,** and **26** were inactive against *Ps. aeruginosa* (at 40, 160, 160, 40, 160, and 80 μg/ml, respectively). All compounds except **9, 15, 20,** and **21** were inactive against *P. vulgaris* (at 80, 160, 160, and 40 μg/ml, respectively). All compounds except **2. 4, 6, 18, 19,** and **20** were inactive against *M. tuberculosis* (at 10, 10, 40, 80, 80, and 40 μg/ml, respectively). [b] Maximal tolerated dose. [c] Dose which provoked a statistically significant diminution of edema over 3 hr. [d] The number zero indicates no activity under 160 μg/ml. [e] The numbers represent the difference between log EID_{95} of control and log EID_{95} of treated. [f] No effect. [g] Toxic.

Experimental Section[5]

The phenylglyoxals were prepared by known procedures[6-11] from acetophenones by SeO_2 oxidation, from α,α-dichloroacetophenones by treatment with NaOMe followed by acid hydrolysis, and from α-ketotriphenylphosphazines by reaction with HNO_2.

5-Amino-8-hydroxyquinoline[12] and **7-amino-8-hydroxyquinoline**[13] were prepared by known procedures. 7-Amino-8-hydroxyquinoline-5-sulfonic acid was prepared by catalytical hydrogenation of an aqueous solution of 7-benzolazo-8-hydroxyquinoline-5-sulfonic acid monosodium salt on 10% Pd–C at 5 atm. This substance crystallized from aqueous dilute HCl.

5-Chloro-7-amino-8-hydroxyquinoline.—To a suspension of 5.6 g (0.02 mol) of 5-chloro-7-nitro-8-hydroxyquinoline in 50 ml of concentrated HCl was added 22.5 g (0.08 mol) of $SnCl_2 \cdot H_2O$. A vigorous reaction took place and the temperature rose to 110°. The reaction mixture was left to cool down to room temperature and the separated solid was collected. The salt was treated with 40% aqueous NaOH, and the separated base was filtered, washed with 10% aqueous NaOH and 10% aqueous NH_4Cl, dried, and crystallized from C_6H_6–ligroin. Attempts to use this material, as isolated, for further reaction usually gave impure products, but it could be purified by sublimation at 130° (15 mm). The sublimate, washed with H_2O, gave 3.1 g (77%), mp 162–163° (lit.[14])

We prepared this product also by catalytical hydrogenation of 5-chloro-7-nitro-8-hydroxyquinoline suspended in HCl (H_2O–MeOH) on 10% Pd–C at normal pressure The hydrogenation was stopped when the theoretical amount of H_2 was adsorbed. If more H_2 was adsorbed, we obtained 7-amino-8-hydroxyquinoline.

Arylglyoxal *N*-7-Amino-5-substituted 8-Hydroxyquinoline Hemiacetals. Method A.—To a solution, cooled to 10°, of 0.01 mol of α-ketoaldehyde in 60 ml of dioxane was first added, under N_2, a solution of 0.01 mol of NaOAc in 30 ml of H_2O, then a solution cooled to 10° of 0.01 mol of 7-amino-8-hydroxyquinoline·HCl in 30 ml of H_2O. The mixture was stirred for 8 hr at 10° under N_2. The separated crystals were collected and washed with Et_2O (see Table III). When the reaction was carried out at 50–60°, a Schiff's base was isolated (see Table II). If the reaction was carried out between 30 and 50° a mixture of *N,O*-acetal and Schiff's base was obtained.

Method B.—7-Amino-8-hydroxyquinoline·HCl (0.01 mol) was dissolved in 100 ml of H_2O, and the solution was made alkaline with Na_2CO_3 under N_2. The base was extracted with Et_2O (three times with 150 ml). After drying on Na_2SO_4 and filtering, a solution of 0.01 mol of α-keto aldehyde in 15 ml of dioxane was added to the Et_2O solution. The mixture was kept at

(5) Melting points were uncorrected and were determined in open capillaries in an oil bath. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(6) S. Steinbach and E. J. Beker, *J. Amer. Chem. Soc.*, **76**, 5808 (1954).

(7) L. Mauri and D. Nardi, *Farmaco Ed. Prat.*, **18**, 651 (1963).

(8) G. Cavallini, *J. Med. Chem.*, **7**, 255 (1964).

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(10) B. D. Tiffany, J. B. Wright, R. B. Moffet, R. V. Heinzelman, R. E. Strube, B. D. Aspergren, E. H. Lincoln, and J. L. White, *J. Amer. Chem. Soc.*, **79**, 1682 (1957).

(11) H. J. Bestmann, O. Klein, L. Göthlich, and H. Buckschenwski, *Chem. Ber.*, **96**, 2259 (1963).

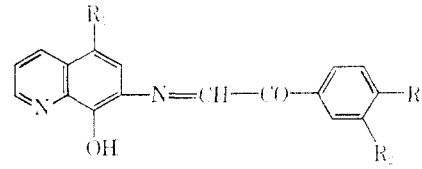
(12) A. F. Helin and C. A. Vanderwerf, *J. Org. Chem.*, **17**, 229 (1952).

(13) K. Matsumura, *J. Amer. Chem. Soc.*, **49**, 810 (1927).

(14) K. Matsumura and M. Ito, *J. Org. Chem.*, **25**, 853 (1960). By this procedure we were not able to obtain constant yields.

TABLE II

7-ARYLGLYOXILIDENAMINO-8-HYDROXYQUINOLINES AND 5-CHLORO-7-ARYLGLYOXYLIDENAMINO-8-HYDROXYQUINOLINES

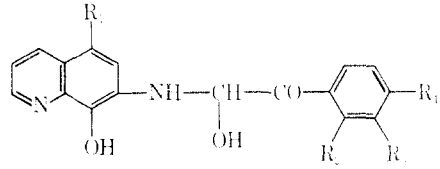


R_1	R_2	R_3	Method	Mp, °C[a]	Yield, %	Formula[b]
H	NO_2	H	A	271	36	$C_{17}H_{11}N_3O_4$
H	H	NO_2	A	279	56	$C_{17}H_{11}N_3O_4$
H	Cl	H	A	260–262		$C_{17}H_{11}ClN_2O_2$
H	H	Cl	A	268	58	$C_{17}H_{11}ClN_2O_2$
H	NO_2	Cl	A	282	56	$C_{17}H_{10}ClN_3O_4$
H	H	C_6H_5	B	280–281		$C_{23}H_{16}N_2O_2$
Cl	NO_2	H	C	280	55	$C_{17}H_{10}ClN_3O_4$
Cl	H	NO_2	C	275	62	$C_{17}H_{10}ClN_3O_4$
Cl	Cl	H	C	279	58	$C_{17}H_{10}Cl_2N_2O_2$
Cl	H	Cl	C	290	52	$C_{17}H_{10}Cl_2N_2O_2$
Cl	NO_2	Cl	C	284	51	$C_{17}H_9Cl_2N_3O_4$

[a] With decomposition. [b] All compounds were analyzed for C, H, N.

TABLE III

ARYLGLYOXAL *N*-7-AMINO 5-SUBSTITUTED 8-HYDROXYQUINOLINE HEMIACETALS



No.	R_1	R_2	R_3	R_4	Method	Mp, °C	Yield, %	Formula[a]
1	H	H	NO_2	H	A	235 dec	47	$C_{17}H_{13}N_3O_5$
2	H	H	H	NO_2	A,B	180 dec	88	$C_{17}H_{13}N_3O_5$
3	H	H	Cl	H	A[b]	205 dec	52	$C_{17}H_{13}ClN_2O_3$
4	H	H	H	Cl	A,B	185 dec	79	$C_{17}H_{13}ClN_2O_3$
5	H	H	NO_2	Cl	A[c]	218	47	$C_{17}H_{12}ClN_3O_5$
6	H	H	H	C_6H_5	A,B[d]	143	51	$C_{23}H_{18}N_2O_3$[f]
7	Cl	H	NO_2	H	C[e]	175	62	$C_{17}H_{12}ClN_3O_5$
8	Cl	H	H	NO_2	C[g]	206 dec	96	$C_{17}H_{12}ClN_3O_5$
9	Cl	Cl	H	H	D	127 dec	77	$C_{17}H_{12}Cl_2N_2O_3$
10	Cl	H	Cl	H	C	173 dec	89	$C_{17}H_{12}Cl_2N_2O_3$
11	Cl	H	H	Cl	C[g]	166 dec	75	$C_{17}H_{12}ClN_2O_3$
12	Cl	H	NO_2	Cl	C	210	84	$C_{17}H_{11}Cl_2N_3O_5$
13	Cl	Cl	H	NO_2	C	153 dec	59	$C_{17}H_{11}Cl_2N_3O_5$
14	Cl	H	OCH_3	H	C	148 dec	79	$C_{18}H_{15}ClN_2O_4$
15	Cl	H	H	C_6H_5	C[h]	150	90	$C_{23}H_{17}ClN_2O_3$
16	SO_3H	H	H	H	E	260–261	68	$C_{17}H_{13}N_2O_7S\cdot 2H_2O$
17	SO_3H	H	H	NO_2	E	254	56	$C_{17}H_{13}N_3O_8S\cdot 3H_2O$
18	SO_3H	H	H	OC_6H_5	E	254	49	$C_{23}H_{18}N_2O_7S$
19	SO_3H	H	H	SC_6H_5	E	234 dec	57	$C_{23}H_{18}N_2O_6S_2\cdot H_2O$
20	SO_3H	H	H	C_6H_5	E[b]	242	53	$C_{23}H_{18}N_2O_6S\cdot H_2O$

[a] All compounds were analyzed for C, H, N. [b] Double amount of solvent was used. [c] The reaction was carried out for 24 hr. [d] The reaction was carried out at 25°. [e] The reaction was carried out at 10° for 8 hr in 120 ml of dioxane and 40 ml of H_2O. [f] H_2O (40 ml) was used. [g] Reaction time, 4 hr. [h] Dioxane (60 ml) was used. [i] C: calcd, 74.58; found, 73.98.

20–25° for 40 hr, and the separate crystals were collected and washed with Et_2O (see Table III).

Method C.—H_2O (60 ml) was added to a solution of 0.01 mol of 5-chloro-7-amino-8-hydroxyquinoline and 0.01 mol of α-keto aldehyde in 60 ml of dioxane, and the mixture was kept at 20–25° for 24 hr. Then the separated crystals were collected and washed with Et_2O (see Table III). When the reaction was carried out at 50–60° in anhydrous dioxane the Schiff's base was obtained (see Table II).

2-Chlorophenylglyoxal *N*-7-Amino-5-chloro-8-hydroxyquinoline Hemiacetal. Method D.—To a solution of 1.68 g (0.01 mol) of 2-chlorophenylglyoxal in 15 ml of DMF at 10°, a solution cooled to 10° of 1.94 g (0.01 mol) of 5-chloro-7-amino-8-hydroxyquinoline in 15 ml of DMF and 60 ml of H_2O were added. After standing for 8 hr, the separated crystals were collected and washed with H_2O (see Table III).

Phenylglyoxal *N*-7-Amino-5-sulfo-8-hydroxyquinoline Hemiacetals. Method E.—To a solution of 0.01 mol of 7-amino-8-hydroxyquinoline-5-sulfonic acid and of 0.02 mol of NaOAc in 60 ml of H_2O, 0.01 mol of α-keto aldehyde dissolved in 30 ml of dioxane was added and the mixture was kept at 20–25° for 4 hr. After filtering with charcoal, the solution was acidified with 20 ml of 1 *N* HCl. After cooling, the crystals were collected and washed with Et_2O (see Table III).

5-Phenylglyoxylidenamino-8-hydroxyquinolines. Method F.—To a solution cooled to 10°, of 0.01 mol of 5-amino-8-hydroxyquinoline·2HCl in 25 ml of H_2O, a solution of 0.02 mol of NaOAc in 25 ml of H_2O was added. To this solution was added a solu-

tion cooled to 10° of 0.01 mol of α-keto aldehyde in 50 ml of dioxane. The mixture was stirred at 10° for 4 hr and the separated crystals were collected and crystallized (see Table IV).

Pharmacological Methods.—For all tests NMRI albino mice (18–20 g) and Wistar albino rats (200–250 g) were used.

Acute Toxicity.—LD_{50} values were determined in mice intraperitoneally, and the mortality over 48 hr was recorded. The animals were also observed for behavior and objective symptoms according to the Irwin scheme.[15]

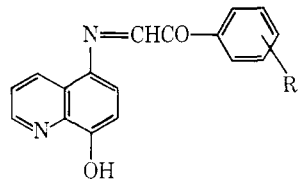
Other Tests.—All compounds were screened also for their antispasmodic activity *in vitro* following the methods described by Setnikar and Tirone,[16] and for their coronary vasodilatator activity on the isolated rabbit heart following the method of Setnikar, *et al.*[17]

Antimicrobial and antifungal activity *in vitro*, peritonitis with *E. coli* 100 in mice, antiviral activity, anticonvulsant activity, and antiinflammatory activity were determined according to the methods previously described [18]

Infection with *M. tuberculosis.*—A group of 25 female mice (16–18 g) was challenged intravenously with 0.2 ml of a suspension of *M. tuberculosis murium* SG 851 Vole strain, in buffered saline solution at pH 7.2 containing 10 LD_{95} (lethal dose 95 calculated at day 40) The infected mice and control groups of 10 mice were treated subcutaneously 1 day after infection and daily for 40 days with a suspension 10% arabic gum of 0.4 mmol/kg per 10 ml of the compound. The increase in weight and mortality of the animals was recorded.

TABLE IV

5-ARYLGLYOXYLIDENAMINO-8-HYDROXYQUINOLINES



No.	R	Recrystn solvent[a]	Mp, °C	Yield, %	Formula[b]
21	H	A	158	47	$C_{17}H_{12}N_2O_2$
22	*p*-NO_2	D	234	56	$C_{17}H_{11}N_3O_4$
23	*p*-Cl	A	188	71	$C_{17}H_{11}ClN_2O_2$
24	*m*-Cl		175	87	$C_{17}H_{11}ClN_2O_2$
25	*p*-CH_3	A	160	49	$C_{18}H_{14}N_2O_2$
26	*p*-OCH_3	A	159	79	$C_{18}H_{14}N_2O_3$
27	*p*-OC_6H_5	A	142	55	$C_{23}H_{16}N_2O_3$
28	*p*-SC_6H_5	A	161	65	$C_{23}H_{16}N_2O_2S$
29	*p*-C_6H_5	A	178	58	$C_{23}H_{16}N_2O_2$

[a] A = EtOAc, D = dioxane. [b] All compounds were analyzed for C, H, N.

(15) This scheme was discussed informally by S. Irwin at a Gordon Research Conference, New London, N. H., 1959.

(16) I. Setnikar and P. Tirone, *Arzneimittel-Forsch.*, **16**, 1146 (1966).

(17) I. Setnikar, W. Murmann, and M. T. Ravasi, *Arch. Intern. Pharmacodyn.*, **131**, 187 (1961).

(18) E. Massarani, D. Nardi, L. Degen, and M. J. Magistretti, *J. Med. Chem.*, **9**, 617 (1966).

Potential Antimalarials. IV.[1,2] Quinoline-α,α-dialkylmethanols

J. B. WOMMACK, JR.,[3] AND D. E. PEARSON[4]

Department of Chemistry, Vanderbilt University, Nashville, Tennessee, 37203

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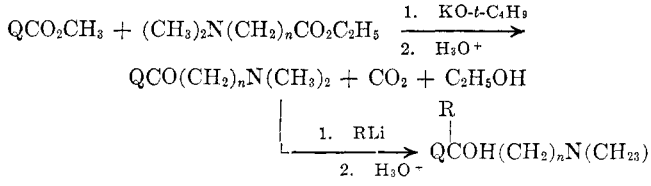
Quinoline-α,α-dialkylmethanols, tertiary alcohols, $QC(R)(OH)(CH_2)_nNR'_2$, have been made to compare their antimalarial activity with the corresponding secondary α-alkylmethanols, $QCHOH(CH_2)_nNR'_2$. Feasible routes for their synthesis are described: a mixed Claisen route for compounds where n is 3 or greater and an epoxidation route for compounds where $n = 1$. All quinoline-α,α-dialkylmethanols synthesized herein have greatly reduced antimalarial activity compared with the corresponding secondary alcohols and, in the 2-aryl-4-quinoline-α,α-dialkylmethanol family, retain their high phototoxicity.

Very few quinoline-α,α-dialkylmethanols have been made[5,6] and none has been compared rigorously with the highly active secondary quinoline-α-alkylmethanols. Model compounds were synthesized first to explore Grignard routes to quinoline-α,α-dialkylmethanols (see Table I and Experimental Section). They were not expected to have, nor did they have, antimalarial activity. More suitable quinoline-α,α-dialkylmethanols were then synthesized by the mixed Claisen route (see below) which served well to make the intermediate ketones (see Table II) as long as n was 3 or greater for reasons that the amino ketones with smaller chains ($n = 1$ or 2) were less stable under conditions of condensation.



The excellence of this route for aminoketones with $n \geq 3$ was ascribed to the more powerful catalyst used ($KO\text{-}t\text{-}C_4H_9$) and the very slow addition of the amino ester (to prevent self-condensation). Surprisingly, Grignard reagents would not add to these ketones, but alkyllithiums did (see Table III and Experimental Section). The antimalarial activity of compounds in Table III was quite low, the best having an increased survival time of only 1.8 days at 640 mg/kg. With the exception of methylquinine and dihydroquinine, a true comparison with the best of the highly active quinoline-*sec*-methanols had not been made (C side chains were too long, $n \geq 3$). Another route had to be devised to obtain shorter side chains ($n = 1$), a necessity which resulted in the development of the epoxidation route:

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(4) To whom correspondence should be addressed.

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