Nitrogen Photochemistry. V. A New Photochemical Reduction of the Cinchona Alkaloids,[1] Quinine, Quinidine, Cinchonidine, and Cinchonine

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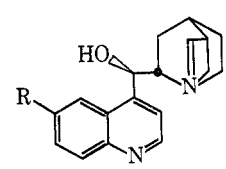
The cinchona alkaloids cited in the title undergo a new type of photoreduction to the corresponding 9-deoxy compounds. The reduction, which also proceeds with the parent compounds, 2- and 4-hydroxymethylquinoline, is shown to proceed *via* the triplet state, $T^1_{(\pi,\pi^*)}$. Contrary to earlier reports, the $S^1_{(\pi,\pi^*)} \rightarrow T^1_{(\pi,\pi^*)}$ process for quinoline is viable under these conditions. These results have implications concerning the use of quinine as a fluorescence standard.

The photochemistry of alkaloid systems is intriguing because of the possibility of developing new molecular structures for pharmacologically active compounds, and the rigid structure of many of the alkaloids is excellent for stereochemical analysis of photochemical reactions. Our initial studies concentrated on the photochemistry of the cinchona alkaloids because of indirect evidence which has been presented indicating the presence of new antimalarial agents among the photochemical products of quinine (I) and quinidine (II).[2-10] To ultimately prove the point concerning the antimalarial agents, the photoproducts had to be isolated and tested for antimalarial activity. In a preliminary communication,[1d] the quinine and quinidine reaction products were reported. We now wish to fully describe this work and further studies on this series of alkaloids.

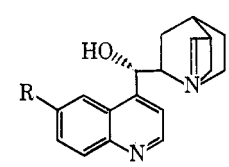
Concerning the biological activity of irradiated quinine, Macht and Teagarden[11] stated that ultraviolet light renders the solutions more active pharmacologically. Conflicting reports have appeared regarding the effect of irradiated quinine on *Paramecium*. There are several accounts recording increased toxicity accompanying the irradiation[12-14] while others observe no significant difference on this organism.[15,16] Federov[17] and Nitta[18] found that irradiation increased the action of quinine on infusoria and tissue cultures, respectively. Two research groups have reported increased antimalarial activity by irradiated quinine solutions.[19,20]

Results and Discussion

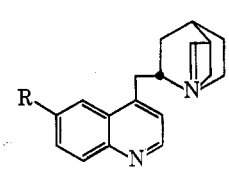
Quinine (I), quinidine (II), cinchonine (III), and cinchonidine (IV), all members of the cinchona family of alkaloids, give the corresponding 9-deoxy derivatives (V–VIII) when their aqueous acid solutions are irradiated with a broad spectrum uv lamp through quartz. This novel reduction is of a new type in photochemistry and potentially points the way to other analogous photochemical reductions. No products of the quinotoxine type structure could be found.



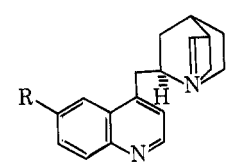
I, R = OCH_3
IV, R = H



II, R = OCH_3
III, R = H



V, R = OCH_3; deoxyquinine
VIII, R = H; deoxycinchonidine



VI, R = OCH_3; deoxyquinidine
VII, R = H; deoxycinchonine

The quantitative data for the reductions are summarized in Table I. The structures of the deoxy compounds were determined from their elemental analyses, uv, ir, nmr spectra, and finally comparison with independently synthesized materials.

The mechanism which has been proposed for the reduction is reproduced in Scheme I. For the initial steps, this scheme borrows heavily from those proposed by Stermitz, *et al.*, for the photochemical alkylation of the aromatic nitrogen heterocycles in alcohol solutions.[21-23] The intermediate, IX, is analogous to one proposed for the alkylation reaction of quinoline in acidified alcohols.[21] It appears the present reduction provides a facile alternate reaction pathway to alkylation for the excited state quinoline moiety when the CHROH group is attached to C_4 of the heterocyclic ring. These alkaloid reaction mixtures were scrutinized for the presence of alkylated products to no avail.

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(1) (a) Part I is regarded to be V. I. Stenberg and D. J. Holter, *J. Org. Chem.*, **29**, 3420 (1964). (b) Part II: D. Elad, D. V. Rao, and V. I. Stenberg, *ibid.*, **30**, 3252 (1965). (c) Part III: V. I. Stenberg, P. A. Barks, D. Bays, D. D. Hammargren, and D. V. Rao, *ibid.*, **33**, 4402 (1968). (d) Part IV: V. I. Stenberg, E. F. Travecedo, and W. E. Musa, *Tetrahedron Lett.*, 2031 (1969).

(2) F. Weigert, *J. Chem. Soc.*, **102**, 1120 (1912).

(3) R. Dietzel and K. Söllner, *Pharm. Ztg.*, **75**, 955 (1930).

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(5) G. C. Kyker, W. E. Cornatzer, and M. M. McEwen, *J. Biol. Chem.*, **162**, 353 (1946).

(6) M. Giordani, *Ann. Chim. Appl.*, **18**, 239 (1928).

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(8) W. Scoville, *J. Amer. Pharm. Ass.*, **4**, 590 (1915).

(9) L. Pasteur, *C. R. Acad. Sci., Ser. C*, **37**, 110 (1853).

(10) H. C. Biddle, *J. Amer. Chem. Soc.*, **34**, 500 (1912).

(11) D. I. Macht and E. J. Teagarden, *J. Pharmacol.*, **22**, 21 (1923).

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(13) G. Roskin and K. Romanova, *ibid.*, **62**, 147 (1929).

(14) Z. S. Shishlyaeva and A. P. Muratova, *Zh. Microbiol., Epidemiol. Immunitaetsforsch. (USSR)*, **16**, 847 (1936).

(15) O. Jirovec and V. Bouse, *Z. Immunitaets.*, **78**, 100 (1933).

(16) E. Milanesi, *Arch. Farmacol. Sper. Sci. Affini*, **46**, 29 (1928).

(17) B. T. Federov, *Bull. Soc. Natur. Moscou, Sect. Biol.*, **44**, 119 (1935).

(18) B. Nitta, *Folia Pharmacol. Jap.*, **17**, 72 (1938).

(19) G. Roskin and K. Romanova, *Z. Immunitaets.*, **72**, 445 (1931).

(20) G. C. Kyker, M. M. McEwen, and W. E. Cornatzer, *Arch. Biochem.*, **12**, 191 (1947).

(21) F. R. Stermitz, C. C. Wei, and W. H. Huang, *Chem. Commun.*, 482 (1968).

(22) F. R. Stermitz, R. Pau, and H. Vyas, *ibid.*, 326 (1967).

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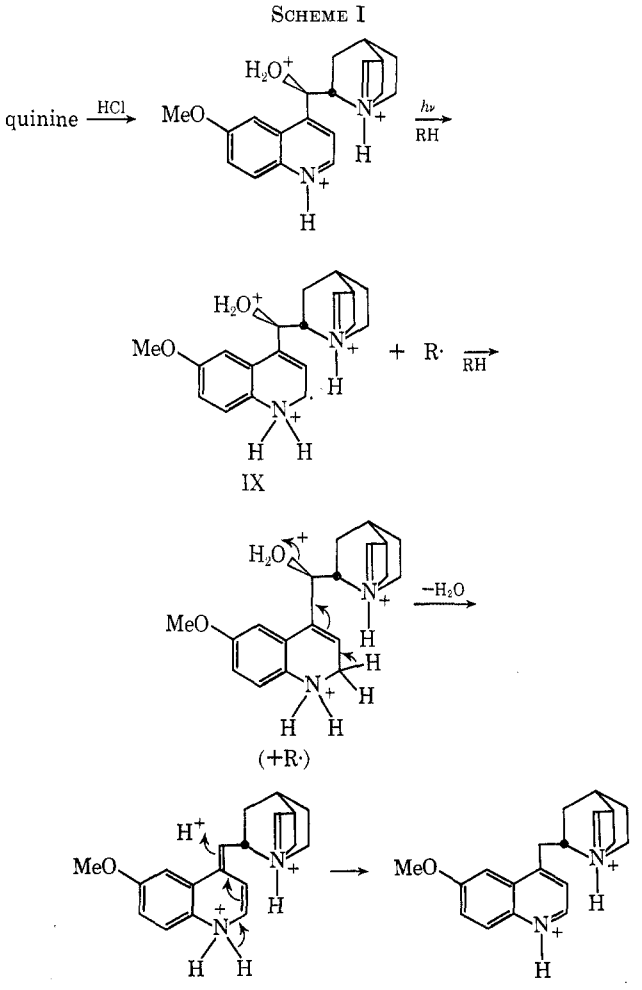
TABLE I
SUMMARY OF IRRADIATION DATA

Compd	Solvent	Filter	Irradiation time, hr	Recovered starting material, %	Yield of reduced product, %[a]
Quinine	2 *M* HCl	Quartz	70	50	10
	2 *M* HCl–2-propanol	Quartz	24	50	33
	2 *M* HCl–2-propanol	Pyrex	24	70	23
	pH 5.1	Quartz	70	10	1
	pH 3.0	Quartz	22	20	4
	pH 5.0–2-propanol	Quartz	22	21	2
	pH 2.7–2-propanol	Quartz	22	Trace	6
Hydroquinine	2 *M* HCl	Quartz	70	50	22
	2 *M* HCl–2-propanol	Pyrex	24	60	16
Quinidine	2 *M* HCl–2-propanol	Quartz	24	63	23
Cinchonine	2 *M* HCl–2-propanol	Pyrex	24	20	49
	2 *M* HCl–2-propanol	Pyrex	5	36	43[b]
	2 *M* HCl–2-propanol with benzophenone	Pyrex	5	Trace	74[b]
Cinchonidine	2 *M* HCl–2-propanol	Pyrex	24	17	49
	2 *M* HCl–2-propanol	Quartz	24	0	42
4-Hydroxymethyl-quinoline	2 *M* HCl–2-propanol	Quartz	2.5	0	44
2-Hydroxymethyl-quinoline	2 *M* HCl–2-propanol	Quartz	4	0	42
	2 *M* HCl–2-propanol	Pyrex	5	0	57

[a] Based on total amount of starting material. [b] Obtained with 350-nm low pressure lamps. The Hanovia 550-W medium pressure lamps were used for the others.

SCHEME I



Therefore, the reduction route is taken in preference to the alkylation route when the appropriate functional group is present.

The mechanism illustrated in Scheme I for the observed reduction is supported by a number of observations. First, if this were the mechanism, the elimination of water during step 3 should be favored by increased acidity of the medium. This is indeed in accordance with the actual observations (Table I). Irradiation of the monohydrochloric salt of quinine dissolved in aqueous solution, pH 5.1, rapidly decomposed to give only trace amounts of V and mainly polymeric materials. The dihydrochloride salt in aqueous solution, pH 3.0, gave analogous results, although the yield of V increased to 4%. The yield of V is increased to 10% in 2 *M* HCl solution. Since the nonbonding electrons on the nitrogen are bound by a proton in the strong acid conditions, it is the $\pi \rightarrow \pi^*$ excitation which gives rise to the observed reduction; and the $n \rightarrow \sigma^*$ and $n \rightarrow \pi^*$ transitions, which may occur in neutral solutions, ultimately produce other products.

The proposed mechanism leads to the prediction that hydrogen atom donor solvents should favor the reduction. The hydrogen atom abstraction process is expected to be unfavorable in aqueous 2 *M* HCl. The prediction is substantiated by the yield increase, *i.e.*, to 33% of the photoreduction in the presence of the hydrogen donor, 2-propanol (bond dissociation energy is 90.3 kcal/mol).[24] The identification of acetone in the irradiated solution confirmed that 2-propanol was, at least partially, acting as hydrogen donor although the rate and yield enhancement might well be attributed to a solvent effect.

The reaction also proceeded with a Pyrex-filtered light eliminating the known photodecomposition of 2-propanol by 184.9-nm light as a functioning mechanism under these conditions.[25] As with the aqueous acid solutions, the efficiency of the quinine reduction in the aqueous acid–2-propanol solutions increased with lowering of the pH.

The relatively low yield of deoxyquinine during the irradiation of quinine in *aqueous* HCl together with the

(24) R. Walsh and S. W. Benson, *J. Amer. Chem. Soc.*, **88**, 3480 (1966).
(25) N. C. Yang, D. P. C. Tang, D. M. Thap, and J. S. Sallo, *ibid.*, **88**, 2851 (1966).

fact that polymeric material is formed accounting for a large portion of the remainder of products indicated the vinyl group participated in the reaction by radical polymerization. To evaluate this possibility, dihydroquinine was irradiated under comparable conditions to that of the quinine irradiation. In accordance with the expectation, hydroquinine produced a higher yield of photoproduct than did quinine, and less polymeric material was obtained.

Since marked changes of the excited states of quinoline are known to occur when heteroatoms are attached to the ring,[26] it was of interest to irradiate cinchonine (III) and cinchonidine (IV). These molecules have all the structural features of quinidine and quinine, respectively, except they do not have the 6′-methoxy group. These molecules gave significantly higher yields of the corresponding reduced products, VII and VIII, than did quinidine and quinine (Table I). Thus, the presence of the methoxy group in quinine and hydroquinine has a detrimental effect on the reduction process possibly because of enhanced radiative decay.

On the basis of model studies it is evident that the quinuclidine superstructure of the cinchona alkaloids restricts the orientation of the 9-OH group. To determine the influence of this restriction, the reduction of 4-hydroxymethylquinoline, a molecule which does not have as much restriction on the movement of the CH_2OH group and probably has a predominance of the 90° dihedral angle conformer, was done for comparison. The reaction proceeded as expected producing 4-methylquinoline, but the reaction was complicated by side reactions which resulted in lower yields of the reduction product. Thus, the quinuclidine side chain has the effect of hindering the side reactions from occurring possibly because of steric factors. However, no conclusions can be made concerning the stereochemical implications of the OH orientation.

The postulated mechanism of Scheme I predicts the reaction should be successful for 2-hydroxymethylquinoline also. This was tried and indeed the reaction proceeded. The slower time of reaction of 2-hydroxymethylquinoline may be attributed to steric hindrance offered by the $-CH_2OH$ group to the approaching hydrogen donor during the initial step of hydrogen abstraction.

The proposed mechanistic Scheme I is consistent with the fact that no isomerization of the remaining optically active centers, *i.e.*, those at C_3,C_4, and C_8, occurs during the irradiation. The optical rotations of the deoxy compounds V and VI obtained from quinine and quinidine were the same as those for the corresponding deoxy bases synthesized by classical methods (Table II).

Recently, Padwa, *et al.*,[27] reported that the $-C{=}N-$ bond of imines was reduced by ground-state reaction of the imine with a ketyl radical arising from carbonyl impurities in the irradiation medium. This suggests the alternative pathway for the quinine reduction illustrated in Scheme II.

Such a possibility is unlikely because no carbonyl compounds were detected in the starting material. However, the acetone generated from 2-propanol during the irradiation could have caused the mechanism illustrated in Scheme II to operate. To test this, acetone was added to the reaction mixture prior to irradiation and no effect could be detected on the reaction results. Further, ketyl radicals were thermally generated from benzopinacol[27] in an aqueous acid–alcoholic solution of cinchonine. No reduction product was observed.

(26) K. N. Nurmukhametov, *Russ. Chem. Rev.*, **36**, 693 (1967), and references cited therein.

(27) A. Padwa, W. Bergmark, and D. Pashayan, *J. Amer. Chem. Soc.*, **91**, 2653 (1969).

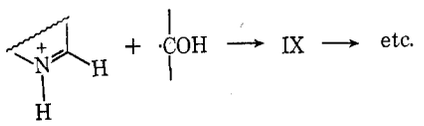
TABLE II

OPTICAL ROTATIONS OF IRRADIATION PRODUCTS

Compd	$[\alpha]_D$ obtained from the irradiations,[a] deg	Lit.[b] $[\alpha]^{26}D$, deg
Deoxyquinine	−99.1	−97.7
Deoxyquinidine	+210.7	+211.1
Deoxyhydroquinine	−78.6	−77.5
Deoxycinchonidine	−27.3	−29.9
Deoxycinchonine	+179.3	+176.5

[a] The small deviations are due to temperature and concentration effects. [b] For the specific literature references, see the Experimental Section.

SCHEME II



The Nature of the Excited States Involved in the Reduction.—There are four possible chromophoric groups in the molecule, the quinoline ring, the vinyl groups, and the two different nitrogens. The available evidence clearly points to the quinoline moiety as responsible for the light absorption which ultimately leads to reduction. The two sets of lone pair electrons on the nitrogens are adequately bound as the ammonium salt by the strong acid of the medium effectively preventing n,π^* and n,σ^* transitions from occurring.

The vinyl group which absorbs at about 180 nm is not considered an active chromophoric group in the 200–400-nm region which is available in the quartz filters used. Additional evidence on this point is that the reduction also proceeds with Pyrex filters which only allow light of wavelength greater than 285 nm to enter the sample.

By process of elimination, the quinoline ring must be responsible for the light absorption. Direct evidence on this point can be seen by observing the detrimental effect the 6′-methoxy group on the quinoline ring has on the yields of the reduction; *cf.* the yield of quinine (I) and quinidine (II) with those of cinchonine (III) and cinchonidine (IV) as recorded in Table I. The presence of –OR, –SR, and $-NR_2$ are known to cause marked changes in the uv spectra and hence the electronic states of quinoline when the heteroatom is conjugated with the ring.[26,28]

The energy level diagram for the quinoline ring is constructed in Figure 1. This is a construct from the several reports in literature[26,29–31] all converted to the kcal/einstein energy scale. The $S^1_{(\pi,\pi^*)}$ band is a diffuse band whereas the $S^1_{(n,\pi^*)}$ band is sharp. Fluorescence from S^1 is only observed in polar solvents and has been attributed to a change in the relative positions of the $S^1_{(\pi,\pi^*)}$ and $T^1_{(n,\pi^*)}$ levels.[29] Under the influ-

(28) S. P. Popli and M. M. Dhar, *J. Sci. Ind. Res., Sect. B*, **19**, 29 (1960).

(29) M. A. El-Sayed and M. Kasha, *Spectrochim. Acta*, **15**, 758 (1959).

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(31) V. L. Ermolaev, *Sov. Phys. Usp.*, **80**, 333 (1963) (English translation), and references cited therein.

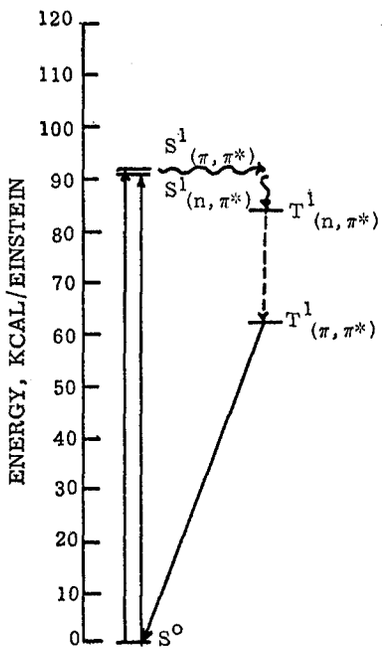

Figure 1.—Energy diagram for quinoline in neutral nonpolar solution.

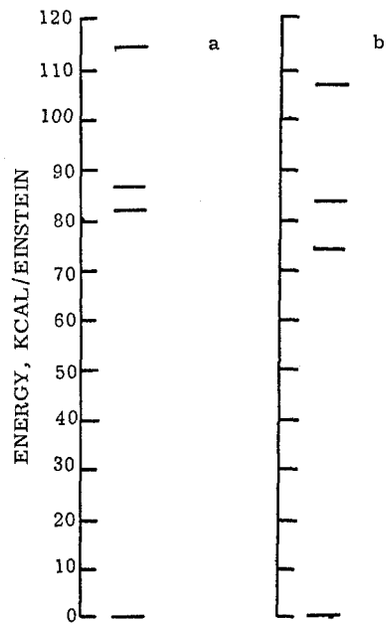

Figure 2.—Singlet energy states for (a) cinchonine and (b) quinine in 20% 2-propanol–2 *M* HCl.

ence of the polar solvents, particularly those which can hydrogen bond intermolecularly, the energy of the $S^1_{(n,\pi^*)}$ and $T^1_{(n,\pi^*)}$ levels is raised, and they occupy a position above the $S^1_{(\pi,\pi^*)}$ level of quinoline.

The $T^1_{(n,\pi^*)}$ level is estimated at approximately 9 kcal below that of the $S^1_{(n,\pi^*)}$ state in nonpolar media on the basis of an analogy to the corresponding levels of pyridine. No phosphorescence has been observed from this state. The $S^1_{(n,\pi^*)}$ or $S^1_{(\pi,\pi^*)}$ state is believed to degrade *via* $T_{(n,\pi^*)}$ to $T_{(\pi,\pi^*)}$ from where phosphorescence is observed.[30] The radiative lifetime of $S^1_{(\pi,\pi^*)}$ is estimated at 10^{-7}–10^{-8} sec and the intersystem crossing rate at 8×10^7 sec^{-1}.[29]

In acid solution, the energy level diagrams for cinchonine and quinine are illustrated in Figure 2. Since the reduction occurs with Pyrex filters, the $S^1_{(\pi,\pi^*)}$ and $S^2_{(\pi,\pi^*)}$ state are populated during the irradiation.

We have been successful in sensitizing the photoreduction of cinchonine with benzophenone (E_t = *ca.* 68 kcal/einstein) using 360-nm low pressure lamps. The reaction proceeds to a higher yield, *i.e.*, 74%, with the sensitizer than without (43%). This, together with the known fact that the phosphorescence of quinoline can be sensitized by benzophenone,[31] is strong evidence that the reaction proceeds *via* the $T^1_{(\pi,\pi^*)}$ state. The conclusion reached by El-Sayed that the intersystem crossing of quinoline is "...attributed to the triplet (n,π^*) state which is located between the lowest singlet and triplet (π,π^*) states in quinoline" needs to be reevaluated.[30] Since the $T^1_{(n,\pi^*)}$ state is predicted to be of high energy in the quinoline ammonium salt, these results point to the intersystem crossing path of $S^1_{(\pi,\pi^*)} \rightarrow T^1_{(\pi,\pi^*)}$ as a viable one.

Quinine is known to have a high fluorescence quantum yield in polar solvents,[32,33] 0.55–0.58, which can account for the relative slowness of the reduction reaction. The presence of the 6′-methoxy group in quinine causes a marked reduction of the $S^1_{(\pi,\pi^*)}$ energy level (Figure 2) in accordance with the results of others.[26,28]

Quinine has been proposed as a fluorescence standard[32,33] and one of the given reasons for this recommendation is that it is not degraded by light during spectral measurements.[32] This must now be viewed with due caution. Fortunately, the isolated photoproduct has the same chromophore as the quinine, but it does not have the same reaction pathways available. Potentially, this might affect the fluorescence quantum yield. We also know there are as yet uncharacterizable materials present in the reaction solution which adds to the problem.

Results of Malarial Tests.—Various compounds obtained in the course of this investigation have been tested for antimalarial activity and the results thus far obtained are illustrated in Table III. These compounds have not demonstrated enough activity to merit further testing.

Experimental Section

All melting points are corrected and were taken in a silicone oil bath. Elemental analyses were done by Alfred Bernhard Laboratories, Elbach, West Germany. The infrared absorption spectra were determined on a Beckman IR-12 spectrophotometer. The ultraviolet absorption spectra were measured with a Cary 14 spectrophotometer. The nmr spectra were recorded on an A-60 Varian Associate spectrometer using tetramethylsilane as internal standard.

Reagents.—Quinine (J. T. Baker), cinchonidine (Fluka A. E., Chem. Fabr., Switzerland), cinchonine (K and K Laboratories), and quinidine (Aldrich) were used without further purification. The alkaloids were homogeneous (tlc). Hydroquinine was prepared by dissolving hydroquinine sulfate (Pfaltz and Bauer, Inc.) in water, and precipitating with 6 *N* NaOH. After washing, drying, and recrystallization from toluene, the melting point was 171–172° (lit.[34] 169–171°). The nmr spectrum[35] ($CDCl_3$) shows a doublet at τ 1.62 (1 H, $H_{2'}$, J = 4.5 Hz), doublet at 2.14 (1 H, $H_{8'}$, J = 10 Hz), doublet at 2.54 (1 H, $H_{3'}$, J = 4.5 Hz), multiplet at 2.60–2.90 (2 H, $H_{5'}$, $H_{7'}$), singlet at 4.46 (1 H, H_9), broad singlet at 3.30 (1 H, hydroxy hydrogen), broad pattern

(32) J. E. Gill, *Photochem. Photobiol.*, **9**, 313 (1969), and references cited therein.

(33) A. N. Fletcher, *ibid.*, **9**, 439 (1969).

(34) A. P. Cheung, A. Benitez, and P. Lin, *J. Org. Chem.*, **33**, 3005 (1968).

(35) T. Williams, R. G. Pitcher, P. Bommer, J. Gutzwiller, and M. Uskokovic, *J. Amer. Chem. Soc.*, **91**, 1871 (1969).

TABLE III
RESULTS OF MALARIA TESTS[a]

			MSTT,[b] days	MSTC,[c] days	Cures[d]
Deoxyquinidine	Mice[e]	*Plasmodium berghei*	6.3	6.1	0
Quininone	Mice[f]	*Plasmodium berghei*	6.9	6.1	0
Quinidinone	Mice[f]	*Plasmodium berghei*	6.3	6.2	0
Cinchoninone	Mice[f]	*Plasmodium berghei*	6.4	6.2	0
Deoxyquinine	Mice[e]	*Plasmodium berghei*	6.4	6.2	0
Uncharacterized benzene	Chick[g]	*Plasmodium gallinaceum*	4.0	3.1	0
Insoluble residue of quinine irradiation	Mice[e]	*Plasmodium berghei*	6.6	6.1	0

[a] All testing was done by the Department of Army, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D. C. 20012. [b] Mean survival time of treated animal. [c] Mean survival time of untreated animal. [d] Number of survivors at 30 days post infections. [e] ICR/H_a Swiss female mice. [f] ICR/H_a Swiss male mice. [g] White Leghorn cockerel.

at 6.20–7.80 (5 H, 2 H_6, 2 H_2, H_8), and a broad pattern at 7.90–9.50 (11 H, 2 H_5, 2 H_7, H_4, H_3, 2 H_{10}, 3 H_{11}). Eastman Spectro Grade 2-propanol was distilled at constant temperature 82° in a 2-ft Vigreux column.

Hydroxymethylquinolines.—Both 2- and 4-hydroxymethylquinolines were prepared by $LiAlH_4$ reduction at low temperature (Dry Ice–acetone) of the corresponding methyl and ethyl esters according to the procedure of Kaslow.[36] The method was modified in that the excess of $LiAlH_4$ was decomposed with a saturated solution of Na_2SO_4 to avoid the formation of gel-like precipitates of Li salts. Further purification of the hydroxymethyl compounds was achieved by forming the hydrochlorides (in anhydrous ether–HCl) and recrystallizing from absolute ethanol. The materials were homogenous on tlc. The esters of the quinoline carboxylic acids (K and K Laboratories) were prepared by refluxing with purified thionyl chloride and, after removal of the excess of thionyl chloride, reaction with the corresponding alcohol. Ethyl 4-quinoline carboxylate hydrochloride melts at 125–127° after recrystallization from benzene. The infrared spectrum (KBr) exhibits bands at 1732 (ester carbonyl) and 2300–2500 cm^{-1} (broad imonium band). Methyl 2-quinoline carboxylate melts at 76–78° after recrystallization from ether as the free base. Its infrared spectrum (CCl_4) shows a band at 1729 cm^{-1} (ester carbonyl group).

The physical data for 2-hydroxymethylquinoline hydrochloride are mp 175–177° dec; ir (KBr) 3200 and 1070 (primary OH), 1640, 1610, 1530 (quinoline ring), 2580 cm^{-1} (broad C=N$^+$—H). The physical data for 4-hydroxymethylquinoline hydrochloride are mp 208–209° dec; ir (KBr) 3200 and 1085 (primary OH), 1630, 1595, 1540 (quinoline ring), 2530 cm^{-1} (broad C=N$^+$—H).

General Irradiation Procedure.—Irradiations were conducted in an immersion reactor using a Hanovia 550-W medium pressure lamp 673A36 with a quartz or Pyrex filter cooled by tap water. The solution was flushed with nitrogen for 20–30 min prior to irradiation and continued during the irradiation. The solution was stirred by a magnetic bar. The progress of the photolysis was monitored by tlc silica gel HF254 (Merck) employing a solvent mixture of *n*-hexane, acetone, and diethylamine (5:3:2). Spots were detected using a Mineralight lamp, UVSL-25 (Ultraviolet Products, Inc., San Gabriel, Calif.).

Irradiation of Quinine in 2 *M* HCl.—Quinine trihydrate (3.81 g, 0.010 mol) was dissolved in 700 ml of 2 *N* HCl and irradiated with a quartz filter. No nitrogen was used in this case in order to duplicate Kyker's conditions.[5,20] After a few hours a new spot, R_f 0.63, appeared on tlc. Quinine has R_f 0.42. After 70 hr the intensities of the spots were *ca.* 1:4, respectively. At this time the solution was made alkaline, pH 11, by addition of 240 ml of 6 *N* NaOH while cooling on an ice bath. The neutralized solution was extracted four times with 250-ml portions of chloroform. A brown, insoluble, powder-like material remained. After macerating twice with chloroform and drying, the residue weighed 0.9 g (27.8%). This material was insoluble in most of the organic solvents and smears on tlc which suggests that it is a polymer. The chloroform extracts were washed twice with 150-ml portions of water and dried over $CaSO_4$. After removal of the chloroform under reduced pressure, the brown residue, 2.4 g, was partially dissolved in benzene. The benzene-insoluble portion remained, 0.9 g, consisting mainly of quinine (85%, after alumina chromatography) and polymeric material (15%). The benzene extract was chromatographed on a 130 g of Al_2O_3 which was packed in 3% diethylamine–benzene and washed with benzene. A 1:1 benzene–chloroform solution eluted 0.32 g (10% yield, dry quinine basis) of deoxyquinine, R_f 0.63. More quinine (0.8 g) was recovered by elution with 5% CH_3OH–$CHCl_3$. Further elution with methanol gave 0.2 g of a tarry material which smears in tlc analysis.

Identical irradiations done under nitrogen in Pyrex gave less insoluble polymeric material, *i.e.*, 0.3–0.4 g (9–12%). Deoxyquinine yield was approximately 6% and the recovered starting material was higher. Further purification of deoxyquinine was done by preparative tlc, and microdistillation to collect the sticky, oily material on the cold finger of a small sublimator: $[\alpha]^{24}D$ (deoxyquinine) −99.1° (*c* 1.463, 90% alcohol) [lit.[37] $[\alpha]^{20}D$ −97.7° (*c* 2.201, 90% alcohol)].

Anal. Calcd for $C_{20}H_{24}N_2O$: C, 77.89; H, 7.84; N, 9.08. Found: C, 77.83; H, 7.93; N, 8.95.

The ir spectrum (neat, NaCl plates) is characterized by the missing of absorption bands of quinine (KBr) at 3170 (–OH) and 1095 cm^{-1} (hydroxylic C–O stretching). The ultraviolet spectrum has λ_{max} (95% alcohol) 206 nm (ϵ 24,500); 232 (31,500), 280 (3150), 320 (3700), and 332 (4260).

The nmr spectrum of deoxyquinine ($CDCl_3$) shows a doublet at τ 1.37 (1 H, $H_{2'}$, J = 4.5 Hz), a doublet at 1.97 (1 H, $H_{8'}$, J = 10 Hz), a doublet at 2.87 (1 H, $H_{3'}$, J = 4.5 Hz), a multiplet at 2.80–2.51 (2 H, $H_{5'}$, $H_{7'}$), a multiplet at 4.52–3.90, centered at 4.20, (1 H, H_{10}), multiplet at 5.25–4.78 (2 H, 2 H_{11}), singlet at 6.10 (3 H, OCH_3), broad pattern at 7.34–6.42 (7 H, 1 H_8, 2 H_2, 2 H_6, 2 H_9, and a broad pattern at 9.16–8.17 (6 H, 2 H_5, 2 H_7, 1 H_4, 1 H_3). The nmr spectrum ($CDCl_3$) of quinine shows a doublet at τ 1.67 (1 H, $H_{2'}$, J = 4.5 Hz), doublet at 2.16 (1 H, $H_{8'}$, J = 10 Hz), doublet at 2.55 (1 H, $H_{3'}$, J = 4.5 Hz), broad singlet at 3.65 (OH), multiplet at 3.98–4.50 (1 H, H_{10}), multiplet at 4.89–5.29 (2 H, 2 H_{11}), singlet at 6.11 (3 H, OCH_3), broad pattern at 6.70–7.80 (5 H, 2 H_2, H_8, 2 H_6), and broad pattern at 7.82–8.20 (6 H, H_3, H_4, 2 H_5, 2 H_7).

Quinine Irradiation in Aqueous HCl–2-Propanol Solution.—Quinine trihydrate (3.81 g) was dissolved in 700 ml of 23% (v/v) 2-propanol-2 *M* HCl and irradiated 24 hr in quartz. At the end of the irradiation, most of the 2-propanol was removed under reduced pressure, and the solution was made alkaline with 6 *M* NaOH. No insoluble material remaining upon extraction with chloroform. After removal of the chloroform, the residue was worked up in the usual way giving 3% of benzene insoluble material, 33% of deoxyquinine, and 50% of recovered quinine. Irradiation in Pyrex gave no benzene insoluble material and afforded 23% of deoxyquinine and 70% of recovered quinine.

Acetone was identified by distilling the Pyrex-irradiated reaction mixture with 2-propanol under reduced pressure, trapping the distillate in a dry ice trap and analyzing it by vpc with a flame detector gas chromatograph (Varian Aerograph Series 1200) equipped with a 15 ft by $^3/_8$ in. column containing 15% Carbowax on 20M Chromosorb W 60–80 mesh at an oven temperature of 80°. The retention times follow: acetone, 10.5 min and 2-propanol, 16 min; no acetone was detected in the 2-propanol used for the irradiation.

Irradiation of Hydroquinine.—Hydroquinine (3.36 g, 0.0104 mol), R_f 0.4, was dissolved in 700 ml of 2 *M* HCl and irradiated in quartz for 70 hr to give 22% of deoxyhydroquinine as an oil, R_f 0.56, and 50% of recovered hydroquinine. No chloroform or

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benzene insoluble polymeric material was found. Irradiation in 23% (v/v) 2-propanol–2 *N* HCl by Pyrex-filtered light for 24 hr gave 16% of deoxyhydroquinine and 60% of recovered starting material.

Deoxyhydroquinine was recrystallized from 50% aqueous acetone as the trihydrate: mp 63° (contracts), 68–70° milky liquid [lit.[38] 61° (contracts), 68–69° milky liquid]; $[\alpha]^{19}D$ −78.6° (*c* 1.397, absolute alcohol) [lit.[39] $[\alpha]^{24}D$ −77.5° (*c* 1.244, absolute alcohol)]. The infrared spectrum of the anhydrous base (net) shows no ir bands corresponding to the absorption bands of hydroquinine (KBr) at 3180 (–OH) and 1120 cm^{-1} (hydroxylic CO stretching). Nmr shows ($CDCl_3$) doublet at τ 1.37 (1 H, $H_{2'}$, J = 4.5 Hz), doublet at 1.80 (1 H, $H_{8'}$, J = 10 Hz), doublet at 2.82 (1 H, $H_{3'}$, J = 4.5 Hz), multiplet at 2.80–2.50 (2 H, $H_{5'}$, $H_{7'}$), singlet at 6.11 (3 H, OCH_3), broad pattern at 6.50–7.90 (7 H, 2 H_9, 2 H_6, 2 H_2, H_8), broad pattern at 8.10–9.05 (8 H, 2 H_5, 2 H_7, H_4, H_3, 2 H_{10}), and a triplet at 9.20 (3 H, CH_3).

Irradiation of Quinidine in Aqueous HCl–2-Propanol Solution.—Quinidine monohydrate (3.51 g, 0.0102 mol) was irradiated through quartz in 700 ml of 23% (v/v) 2-propanol–2 *M* HCl for 24 hr. The usual work-up afforded 0.710 g (22.5%) of anhydrous deoxyquinidine as an oil: $[\alpha]^{21}D$ 210.7° (*c* 1.393, 95% alcohol) [lit.[37] $[\alpha]^{20}D$ 211.1° (*c* 2.023, 99% alcohol)]; crystals of the dihydrate from 2:3 acetone:water, mp 80–82° (lit.[38] mp 82°). The infrared spectrum (KBr) shows no bands corresponding to the absorption of quinidine (KBr) at 3200 (–OH) and 1110 cm^{-1} (hydroxylic CO stretching). Nmr spectrum ($CDCl_3$) exhibits a doublet at τ 1.38 (1 H, $H_{2'}$, J = 4.5 Hz), a doublet at 2.0 (1 H, $H_{8'}$, J = 10 Hz), a doublet at 2.85 (1 H, $H_{3'}$, J = 4.5 Hz), a multiplet at 2.55–2.92 (2 H, 1 $H_{5'}$, 1 $H_{7'}$), a multiplet at 3.73–4.34 (1 H, 1 H_{10}), a multiplet at 4.75–5.15 (2 H, 2 H_{11}), singlet at 6.11 (3 H, OCH_3), broad pattern at 6.55–7.40 (7 H, 1 H_8, 2 H_2, 2 H_6, 2 H_9), and a broad pattern at 8.20–9.00 (6 H, 2 H_5, 2 H_7, 1 H_3, 1 H_4). The recovered starting material was 63%.

Synthesis of Deoxyquinine and Deoxyquinidine.—The deoxy bases were prepared by treatment of the bases, quinine and quinidine, respectively, with PCl_5 in $CHCl_3$ to form the 9-chloro bases followed by reduction with Fe–H_2SO_4 according to the procedure of Rabe.[37] The deoxy bases were purified by preparative tlc on silica gel HF254 using a mixed solvent composed of *n*-hexane, acetone, and diethylamine (6:3:1). The materials were identical (ir, uv, nmr, optical rotation) to the deoxy bases obtained from the irradiated solutions.

Photolysis of Cinchonidine.—Cinchonidine (3.005 g, 0.0102 mol) was dissolved in 700 ml of 23% (v/v) 2-propanol–2 *M* HCl and irradiated in quartz. After 24 hr, the solution was worked up and chromatographed as usual. It afforded 1.18 g (41.6%) of anhydrous deoxycinchonidine as an oil. Similar irradiations using Pyrex-filtered light for 24 hr gave 49% of deoxycinchonidine and 17% of recovered cinchonidine. Attempts to recrystallize the deoxy base were unsuccessful. The anhydrous deoxy base oil showed $[\alpha]^{19}D$ −27.3° (*c* 2.089, absolute alcohol) [lit.[39] $[\alpha]^{18}D$ −29.9° (*c* 2.006, 99% alcohol)]. Infrared spectrum (net) shows no bands corresponding to the absorption of cinchonidine (KBr) at 3200 (OH) and 1100 cm^{-1} (hydroxylic CO stretching).

Nmr spectrum ($CDCl_3$) shows a doublet at τ 1.17 (1 H, $H_{2'}$, J = 4.5 Hz), multiplet at 1.73–2.03 (2 H, $H_{8'}$, $H_{6'}$), multiplet at 2.15–2.54 (2 H, $H_{5'}$, $H_{7'}$), doublet at 2.74 (1 H, $H_{3'}$, J = 4.5 Hz), multiplet, eight lines, 3.88–4.50 (1 H, H_{10}), multiplet at 4.83–5.23 (2 H, 2 H_{11}), broad pattern at 6.48–7.67 (7 H, 2 H_9, 2 H_6, 2 H_2, 1 H_8), and a broad pattern at 7.80–9.15 (6 H, 2 H_7, 2 H_5, H_4, H_3).

Photolysis of Cinchonine.—Irradiation of 3.00 g (0.0102 mol) of cinchonine in 700 ml of 23% (v/v) 2 *M* HCl by Pyrex-filtered light for 24 hr afforded 1.40 g (49.4%) of deoxycinchonine and 20% of recovered starting material. Deoxycinchonine from *n*-hexane gave mp 90–91° (lit.[40] 90–91°), $[\alpha]^{21}D$ +176.5° (*c* 2.313, absolute alcohol) [lit.[37] $[\alpha]^{19}D$ +179.3° (*c* 2.025, 99% alcohol)]. Nmr spectrum ($CDCl_3$) shows a doublet at τ 1.18 (1 H, $H_{2'}$, J = 4.5 Hz), multiplet at 1.75–2.16 (2 H, $H_{6'}$, $H_{8'}$), multiplet at 2.20–2.71 (2 H, $H_{5'}$, $H_{7'}$), doublet at 2.83 (1 H, $H_{3'}$, J = 4.5 Hz), multiplet eight lines at 3.71–4.34 (1 H, H_{10}), multiplet at 4.75–5.18 (2 H, 2 H_{11}), broad pattern at 6.57–7.50 (7 H, 2 H_9, H_8, 2 H_2, 2 H_6), and a broad pattern at 7.59–9.15 (6 H, H_4, H_3, 2 H_2, 2 H_5). Infrared spectrum (net) shows no bands corresponding to the absorption of cinchonine (KBr) at 3200 (OH) and 1115 cm^{-1} (hydroxylic CO stretching).

Sensitized Irradiation of Cinchonine.—A solution of 0.20 g of benzophenone (Fisher) and 0.581 g of cinchonine in 131 ml of 50% (v/v) 2-propanol–2 *M* HCl was irradiated in the Srinivasan–Griffin–Rayonet reactor with the 350-nm lamps for 5 hr under oxygen-free nitrogen.[41] The amount of 2-propanol was increased to 50% to overcome the low solubility of benzophenone in aqueous solutions. The usual work-up procedure afforded 0.41 g (74%) of deoxycinchonine and traces of cinchonine. Irradiation of cinchonine without benzophenone, under the same conditions, gave 43% of deoxycinchonine and 36% of recovered cinchonine.

Thermal Decomposition of Benzopinacol in the Presence of Cinchonine.[27]—A solution of 12.2 mg of benzopinacol and 25.9 mg of cinchonine in 5 ml of 50% (v/v) 2-propanol–2 *M* HCl was sealed in a test tube and heated at 130–135° for 6 days. Tlc analysis of the resulting solution showed no deoxycinchonine to be present.

Irradiation of 2- and 4-Hydroxymethylquinolines.—The following procedure was used for both cases: the hydroxymethylquinoline hydrochloride (3.07×10^{-3} mol) was dissolved in 210 ml of 2 *M* HCl–20% 2-propanol and irradiated until the starting material disappeared. The course of the reaction was monitored by tlc on silica gel HF254 (Merck) with a solvent mixture of *n*-hexane, acetone, and diethylamine (5:3:2). By bubbling NH_3 (gas), the pH was raised to *ca.* 1; the solvents were removed under reduced pressure at 40°. The residue was made ammoniacal with excess NH_3 (gas) and extracted eight times with 80-ml portions of ether. The dried ether was distilled slowly through a 1-ft glass-packed column. To the residue, after the distillation of the ether, 0.1838 g of 4-methylquinoline or 2-methylquinoline, as the case may be, was added as internal standard and the volume diluted to 10 ml. Glpc analysis was done on a 7.5 ft × 1/4 in. 20% OV-I (Applied Science Labs) Chromosorb Q, mesh 60–80, column temperature at 178°, and the helium flow of 80 ml/min. The retention times were 2-methylquinoline, 5 min, and 4-methylquinoline, 6.5 min.

For identification purposes all the samples were collected by preparative vpc and their ir's compared to those of authentic materials, 2-methylquinoline (quinaldine) from Aldrich Chemical Company and lepidine (4-methylquinoline) from City Chemicals, N. Y.

Registry No.—I, 130-95-0; II, 56-54-2; III, 118-10-5; IV, 485-71-2; ethyl 4-quinoline carboxylate hydrochloride, 26316-04-1; methyl 2-quinoline carboxylate, 4491-33-2; 2-hydroxymethylquinoline hydrochloride, 26315-73-1; 4-hydroxymethylquinoline hydrochloride, 26315-74-2; V, 14528-51-9; VI, 14528-50-8; VII, 5808-37-7; VIII, 5949-01-9; deoxyhydroquinine, 26315-79-7; hydroquinine, 522-66-7.

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