The orientation, the optic axial angle, and the refractive indices α and β are so similar in the two forms that measurements of γ were required to establish the essential optical difference. Even then a knowledge that the fine-grained preparations contained no disturbing contaminant was necessary. One preparation from water contained both needles and blades. Refractive index β of the needles was definitely the higher. The immersion liquids used between 1.74 and 1.79 were saturated solutions of sulfur in mixtures of methylene iodide and iodobenzene.

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The Photochemical Reaction between Quinine and Dichromic Acid. III. Quinine Derivatives and Utilization of Absorbed Quanta

BY GEORGE S. FORBES AND LAWRENCE J. HEIDT

Two recent papers[1,2] from this Laboratory support the view previously advanced[3] that quinine activated by light is oxidized by non-activated chromic acid. One activated quinine molecule appears to react with one of chromic, as distinguished from dichromic acid. Hydrogen ion in excess has little effect upon the kinetic pattern.

The present study indicates that ten quinine derivatives conform to this same reaction scheme. In all cases the quinoline group can be held chiefly responsible for the absorption of light, and the secondary hydroxyl on carbon atom 4 of Fig. 2 for the reduction of chromic acid. There follows an attempt to correlate structural variations with the efficiency of energy transmission from the absorbing group to the reactive group, also with the purely steric factors of the oxidation reaction.

Our experimental methods have been described.[1,2] The mixtures were irradiated by monochromatic light of several wave lengths in the same trapezoidal quartz cell, capacity 11.5 cc. Radiometric and analytical precautions were not relaxed. Extinctions, to be discussed more in detail in a later paper, were here measured by spectroradiometer with thermopile. These absorptions were approximately 50%. Light absorbed by solutions photolyzed was properly apportioned between each quinine derivative and the chromate which acted as an inner light filter. The quantum yield, ϕ_q, represents half the (oxidation) equivalents of chromate reduced per Einstein absorbed by the quinine *derivative*, after correction for the dark reaction which was always measured separately in a parallel experiment.

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[1] Forbes, Heidt and Boissonnas, THIS JOURNAL, **54**, 960 (1932).

[2] Forbes, Heidt and Brackett, *ibid.*, **55**, 588 (1933).

[3] Luther and Forbes, *ibid.*, **31**, 770 (1909).

The latter never exceeded 5% of the total reaction except in the case of quinicine, where in one experiment it reached 20%.

Materials

We are greatly indebted to Dr. Walter A. Jacobs[4] for supplying us with hydroquinine hydrochloride, quinicine dihydrochloride and hydrocupreine (base). We purchased quininic acid (Eastman), quinidine sulfate (Mallinckrodt U. S. P.), also cinchonidine sulfate U. S. P.-X, cinchonine sulfate NF-V, optochin, eucupin and vuzin dihydrochloride, all from Merck. So far as possible, purification and tests for impurities followed the procedure for quinine,[1] and were carried out with much care, since traces of readily oxidizable impurities would have proved disastrous. The melting points of the bases thus obtained agreed within ±2° of those given in Allen,[5] except hydrocupreine, which melted at 259°, probably because of the preponderance of sulfate present.

Quinicine was precipitated as the base from the dihydrochloride. The yellow oil, washed free from alkali and chloride, was dissolved in 95% ethanol and then evaporated at 50° until about half the base reappeared as a colorless oil. The calculated amount of 95% reagent sulfuric acid added, produced, upon scratching at 0° and addition of an excess of ether, a white voluminous crystalline precipitate. After several washings with ether and drying *in vacuo* over concentrated sulfuric acid, it softened on heating at 120–130° and melted at 175° with decomposition. According to Allen, Hesse prepared the sulfate and disulfate but attempts by others to repeat this work have been unsuccessful.[6] The white crystals were then dissolved in an excess of 5% sulfuric acid at 25°. Quinicine separated as a colorless oil on addition of alkali and was purified as described for quinine. On drying *in vacuo* over sulfuric acid it solidified. It melted at 62°.

The other alkaloids purchased as hydrochlorides were first freed from chloride by washing the precipitated bases free from alkali and chloride before recrystallization as the acid sulfate. In the case of hydrocupreine an excess of alkali, in which the base would be soluble, was avoided. Eucupin in 5% sulfuric acid forms a white gel which synerized on standing. Recrystallization was therefore impossible, and purification was limited to repeated precipitation and washing of the base, m. p. 153–154°. The sources and purification of the other reagents as well as the standardization of solutions, have been described.[1]

Tables and graphs give concentrations in moles per liter and λ in mμ. The extinction coefficient, K_q, of any quinine derivative is $(1/cd) \log_{10} (I_0/I)$. The quanta per minute absorbed by quinine in the first centimeter of reaction mixture, E, was varied by changing the concentration of the derivative and again by stopping down one monochromator lens. The total photochemical reaction proved to be a function of E alone, other variables fixed, as is shown in Curve A, Fig. 1, where points corresponding to the regulation of E by both methods lie on the same curve. Thereupon, the same rule was postulated for all the derivatives as well, and E was controlled through the concentration of the derivative while holding constant the total incident radiation flux. Each point graphed represents the average of two or three experimental values of ϕ_q. Two to four such points were determined for each of the monochromatic radiations by which

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(4) Heidelberger and Jacobs, THIS JOURNAL, **41**, 817 (1919).

(5) Allen, "Commercial Organic Analysis," P. Blakiston's Son and Co., Philadelphia, fifth edition, Vol. VII.

(6) Ref. 5, p. 498.

each derivative was rayed, making about 270 complete experiments in all. We exemplify the uniformly linear character of the plots involving E and ϕ_q in Fig. 1, where quinine and quinidine appear. In all cases maximum deviation of ϕ_q from the "best" lines was less than 10%, showing in addition that the derivatives play the same kinetic part in the reaction as quinine. To facilitate comparisons we next interpolated round values of E and ϕ_q from these plots and the others (not given), and listed them in Tables I and II. It will be noted that ϕ_q at λ 405 mμ is uniformly independent of K_q of the derivatives. This relation will be further discussed in a later paper.

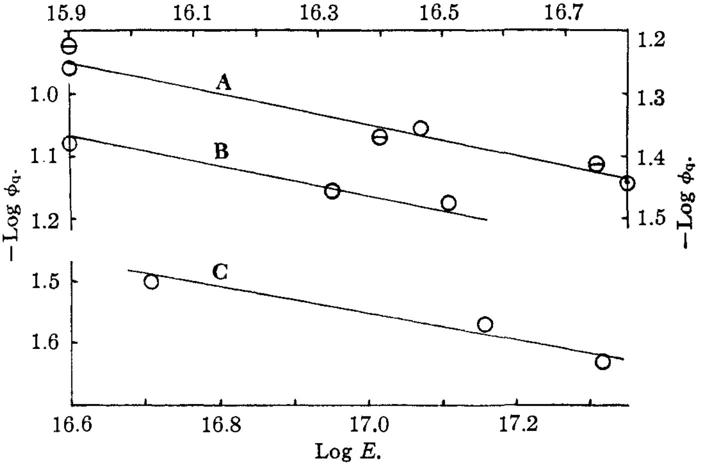

Fig. 1.—⊖, values obtained by variation of E_0; ○, values obtained by variation of [Q].

	Curve	λ in mμ	$[H_2SO_4]$	$[K_2Cr_2O_7]$	Compound	Concn. $\times 10^5$	$E_0 \times 10^{-17}$	Temp., °C.
Top scale	A	366	0.8	0.00004	Quinine	25	0.1–0.8	5±2
Bottom scale	B	313	.9	.00016	Quinidine	25–100	1.4	24±2
Bottom scale	C	405	.9	.00016	Quinidine	100–1000	2.6	24±2

We have mentioned[1] the tendency of ϕ_q to rise and fall with the molar extinction of dichromic acid, K_c, when both are plotted against λ. Vuzin differs from our other derivatives in that K_{436} is large enough to allow measurement of ϕ_q in light of this wave length. We find $\phi_{q436}/\phi_{q405} = 0.84$ and $(\log K_c)_{436}/(\log K_c)_{405} = 1.0$, showing that the tendency in question persists over the range λ 405 to 436 mμ.

Identification of the Group Photochemically Oxidized.—Rabe[7] states that the secondary hydroxyl on carbon (4) Fig. 2, is first oxidized in the dark. Our working hypothesis—that the same holds for the photochemical reaction[8]—can be tested to some extent by the data in Table I. For in-

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(7) Rabe, *Ann.*, **365**, 353 (1909).

(8) Ref. 1, p. 972.

TABLE I

Temp., 24 ± 2°; $[K_2Cr_2O_7]$, 0.00016; $[H_2SO_4]$, 0.9; E, 1.5×10^{17} quanta/min.

Derivative	Concn. $\times 10^5$	λ in mμ	K_q	ϕ_q	$\phi\alpha$
Quinine	10,000	436	<1		
	100–2000	405	43	0.027	<0.1
	1–25	366	3450	.070	<0.1
	1–25	313	3600	.065	<0.1
Hydroquinine	600	436	<2		
	100–1000	405	47	.030	
	10	366	4200		
	2.5–100	313	3700	.070	
Quininic acid	100	570	<1		
	50–1000	436	127	.004	
	50	405	950		
	2.5–100	366	4000	.002	
	5–100	313	4800	.005	
Quinicine	8.5–85	436	297	.043	
	8.5–85	405	1450	.039	
	85	366	4300		
	2.1–85	313	3010	.036	
Quinidine	60	436	<1		
	100–1000	405	39	.025	
	10	366	3310		
	2.5–100	313	3845	.070	

stance, ϕ_q is practically unchanged under corresponding conditions when quinine is transformed to hydroquinine by hydrogenating the vinyl group marked (1) in Fig. 2. If, on the other hand, everything to the right of the dotted line is replaced by carboxyl, quininic acid is obtained and ϕ_q becomes negligibly small. Apparently neither the vinyl group nor the unsaturated tertiary nitrogen (5) nor the methoxyl group (6) is an efficient reducing agent. Upon converting the secondary hydroxyl on (4) to carbonyl oxygen, and transferring the two hydrogens to carbon (3) and nitrogen (2), the customary formula of quinicine results, but ϕ_q still remains half as large as for quinine. The fact that the carbonyl group of quinicine ought to resist oxidation does not, however, demand transfer of photochemical activity elsewhere—to saturated nitrogen (2) for in-

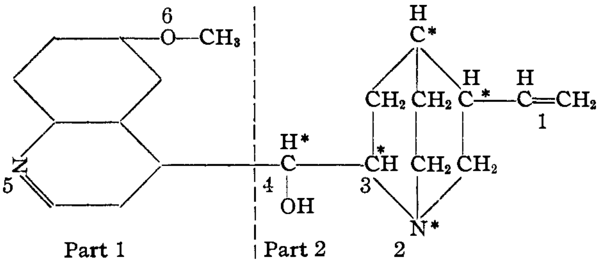

Fig. 2.—Structural formula of quinine.

stance. For as carbon (4) adjoins the hydrogenated aliphatic carbon (3), partial enolization might be expected, providing a double bond between (3) and (4). This configuration, even if representing much less than half the total quinicine present, might well prove sufficiently reactive to account for the observed value of ϕ_q and also for the large dark reaction of quinicine with dilute chromic acid, mentioned above. So far, then, our working hypothesis appears to be consistent with the facts.

The Stability of Quinine in Light.—Among the possible reasons for the low values of ϕ_q are (1) the consumption of quanta in direct decomposition of alkaloid molecules and (2) steric and time factors influencing the secondary reaction. Absorption and fluorescence will be considered in a subsequent paper. The optical rotations of 0.01 and 0.001 molar solutions of quinine bisulfate in water and in 0.9 *m* sulfuric acid were measured using a large Schmidt and Haensch polarimeter kindly lent by Professor J. B. Conant. The probable error of reading its scale was 0.02°. Using the green mercury line and a 4-decimeter tube at a temperature of 25 ± 1°, no change was detected in the specific rotation $[\alpha]$ of any of the solutions after absorption of about 10^{22} quanta of light of any of several wave lengths. The maximum quantum yield, ϕ_α, of any reaction producing optically inactive decomposition products comes out less than 0.1 as seen in Table I, last column. Pyrolysis is known to break quinine at (3) Fig. 2, with formation of quinicine and almost complete loss of optical activity.[4] Granting that photolysis would have the same effect, it appears that the low efficiency of photochemical reduction of chromic acid is not due to loss of quanta in direct decomposition of quinine, or, by inference, of quinine derivatives.[9]

Optical Isomers and Quantum Yields.—Quinidine is an optical isomer of quinine, the sole difference residing in asymmetric carbon (3). Under corresponding conditions ϕ_q (Table I) is the same for both isomers, within experimental error, over considerable concentration ranges. Cinchonidine is similarly related to cinchonine, and Table II shows that ϕ_q, again, is the same for both. This outcome, while no doubt predictable, was reassuring, as tending to show that our purifications, in these four cases at least, were adequate, and the experimental work internally consistent.

Energy Transfer within Molecules.—Table II compares ϕ_q for hydroquinine and derivatives differing from it only in group 6 as given in the second column. Wave lengths and concentrations vary in corresponding fashion. Values of K_q would indicate that absorbed light fell in comparable regions of the several absorption curves. A study of these curves,

(9) Dietzel and Söllner, (a) *Pharm. Ztg.*, **75**, 955 (1930); (b) *Arch. Pharm.*, **268**, 629 (1930), exposed to ultraviolet light water solutions of quinine hydrochloride, Q·HCl, and found $[\alpha]$ unchanged except after sixty days' exposure. Upon acidifying, $[\alpha]$ approached a limiting value when $[\mathrm{Q\cdot HCl}]/[\mathrm{HCl}] = 1$. We have found $[\alpha] = 107$ (unit concn., one molar) for quinine bisulfate in water and 107 in 0.9 molar sulfuric acid. Mather and Bhatnagar, *Indian J. Physics*, **3**, 37 (1928), report that sunlight in five hours expedites a measurable atmospheric oxidation of quinine sulfate both in water and in presence of sodium hydroxide and gelatine, but Weigert and Savenu, Nernst Festschrift, 464 (1912) state that acid strongly inhibits this oxidation.

TABLE II

Temp., 24 ± 2°; [$K_2Cr_2O_7$], 0.00016; [H_2SO_4], 0.9; E, 1.5 × 10^{17} quanta/min.

Derivative	Group attached to carbon atom 6, Fig. 2	Concn. × 10^5	λ in mμ	K_q	ϕ_q
Cinchonine	Hydrogen	10,000	405	0.0	
		2.5–100	366	63	0.005
		2.5–100	313	7000	.002
Cinchonidine	Hydrogen	10,000	405	0.0	
		2.5–100	366	117	.005
		2.5–100	313	6900	.002
Hydrocupreine	Hydroxyl	10,000	436	0.0	
		100–1000	405	85	.012
		10–100	366	3665	.012
		10–100	313	3520	.013
Hydroquinine	Methoxyl	600	436	<2	
		100–1000	405	47	.030
		10	366	3700	
		2.5–100	313	4200	.070
Optochin	Ethoxyl	600	436	<4	
		100–1000	405	66	.035
		10	366	3780	
		2.5–100	313	3970	.060
Eucupin	Isoamoxyl	540	436	<0.5	
		91–9100	405	61	.030
		9.1	366	3080	
		2.3–91	313	2920	.072
Vuzin	Isooctoxyl	76–228	436	<12	.021
		76–228	405	169	.025
		7.6	366	4150	
		3.8–76	313	3560	.060

between 20,000 and 45,000 cm.$^{-1}$, to be published later, has verified this indication.

The relatively small values of ϕ_q for cinchonine and cinchonidine as compared with those for quinine and derivatives might in themselves suggest that hydroxyl or alkyloxyl group in position 6 was the photochemically active one. The very low value of ϕ_q for quininic acid, which has a methoxyl group in position 6, discredits such a conclusion. Granting now that the secondary hydroxyl (position 4) is photochemically active in all these four cases, it is clear that even a large group replacing hydrogen in position 6 does not serve as an energy trap, but rather aids in transfer of energy across the quinoline group. The efficiency increases from hydrogen to hydroxyl, reaches a maximum with methoxyl, remains about constant through ethoxyl and isoamoxyl, and declines but slightly with isooctoxyl. In any case it is hard to generalize such results in terms of a classical building up of energy in a particular bond. The effect might be visualized in terms of a resonance phenomenon by which the energy absorbed by the quinoline group was transferred to the secondary hydroxyl only in the presence of some degree of molecular symmetry of groups attached to the quinoline group. With maximum lack of balance the quantum might be dissipated chiefly as thermal energy, and without activation of the secondary hydroxyl. A less plausible alternative is that the quinoline group absorbs most of the quanta but that these may not be effectively transmitted to the secondary hydroxyl. On the other hand, all the groups studied in position 6, hydrogen excepted, though appropriating but a small fraction of all quanta absorbed, may transmit these across the quinoline group with efficiency great enough to account for the admittedly small quantum yield. Work is now in progress to decide between these alternatives.

Summary

The photochemical reactions of ten quinine derivatives with chromic acid have been studied quantitatively at various wave lengths and concentrations and compared with that of quinine.

The logarithm of the quantum yield of quinine or of its derivatives is a linear function of the logarithm of the concentration of excited alkaloid molecules.

Within the limits of observation the rotatory power of quinine bisulfate in water and 0.9 molar sulfuric acid remains constant on absorption of 10^{22} quanta of light of λ 405, 366 or 313 mμ. This indicates that the low values of ϕ_q are not due to loss of quanta decomposing quinine molecules directly.

The secondary hydroxyl group of quinine appears to be chiefly responsible for the reduction of chromic acid, and the same holds for all the derivatives containing it.

Effective transmission of absorbed quanta to the reactive hydroxyl occurs only when various photochemically inactive groups are substituted for hydrogen on the opposite side of the quinoline group. This transmission may be a resonance phenomenon dependent merely upon due balancing of the quinoline structure, or it may involve quanta originally absorbed in the substituting group itself.

Values of ϕ_q at λ 405 and 436 mμ are uniformly independent of the molar extinction coefficient of the derivative.

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