University of Illinois, Urbana, for final deuterium analysis of tropilidene, to Professor J. Jonas, Department of Chemistry, University of Illinois, Urbana, for the determination of the deuterium distribution, and to Professor E. T. Kaiser, Department of Chemistry, University of Chicago, for the use of the mass spectrometer.

The Reaction of 4-Chloro-8-methoxyquinoline with Hydrogen Peroxide[1a]

TAKESHI FUJITA[1b] AND J. M. PRICE[1c]

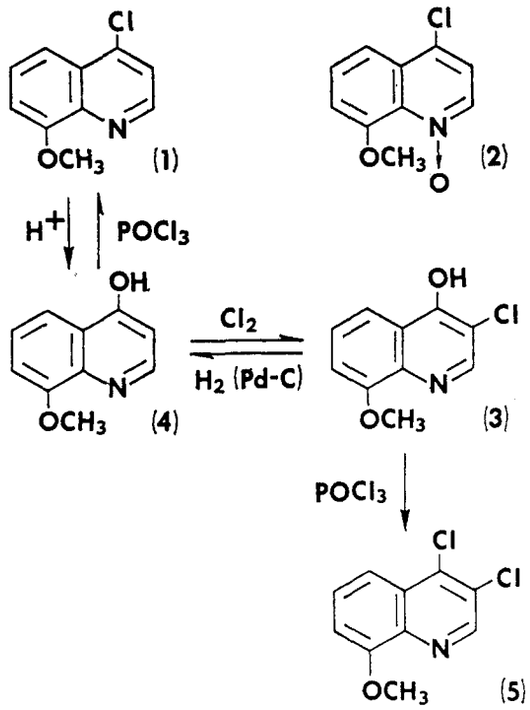
Division of Clinical Oncology, University of Wisconsin Medical School, Madison, Wisconsin 53706

Received January 9, 1967

In the course of an attempt to synthesize 4-chloro-8-methoxyquinoline 1-oxide by the treatment of 4-chloro-8-methoxyquinoline (**1**) with hydrogen peroxide, the resulting product failed to show the properties expected of the desired 1-oxide (**2**), but instead appeared to be 3-chloro-8-methoxy-4-quinolinol (**3**). The proposed structure (**3**) was considered as a possible product because it had an ultraviolet spectrum nearly identical with that of 8-methoxy-4-quinolinol (**4**), and because **3** was converted into **4** by reduction with palladium on charcoal in methanol containing hydrogen chloride (Scheme I). Furthermore, **3** was prepared from **4** and chlorine in acetic acid, and treatment of **3** with phosphorus oxychloride produced 3,4-dichloro-8-methoxyquinoline (**5**) in high yield. The nmr spectrum of **5** showed no doublet downfield expected of **2**, but did show a singlet at τ 1.27, which was assigned to the proton at the C_2 position.

The bromination of 4-quinolinol[2] and 4-quinolinol 1-oxide[3] afforded the respective 3-bromo derivatives of these compounds. Brobański[4] reported that 4-chloroquinoline was converted into 4-quinolinol by acid hydrolysis. Robison and Robison[5] found that 4-chloroisocarbostyril was obtained in the reaction of 1-chloroisoquinoline with aqueous peracetic acid. Therefore, the hydrolysis of **1** in aqueous acetic acid followed by the halogenation of the resultant **4** by the chlorine produced from hydrogen chloride by hydrogen peroxide would explain the conversion of **1** into **3** instead of the desired **2**. This mechanism was demonstrated by the experiments reported here.

SCHEME I



Experimental Section[6]

3-Chloro-8-methoxy-4-quinolinol (**3**).—8-Methoxy-2-carboxy-4-quinolinol was prepared according to the method of Furst and Olsen,[7] and decarboxylated[8] in refluxing Dowtherm A at 250° to yield **4** which was converted into **1** by refluxing for 1 hr in phosphorus oxychloride, mp 80–81° (lit.[8] mp 79–80°).

A solution of 0.5 g of **1** and 0.5 ml of hydrogen peroxide (30%) in 10 ml of glacial acetic acid was stirred for 3 hr at 65–70°. After another 0.5 ml of hydrogen peroxide was added to the solution, it was heated at 60–70° for 3 hr. Following evaporation of the acetic acid, the residue was dissolved in dilute aqueous sodium hydroxide and washed with ethyl ether, and the aqueous solution was neutralized with dilute hydrochloric acid. A yield of 0.21 g (39%) of colorless needles was obtained, mp 273–274°. In a second trial, 0.7 g (32%) of this product was obtained from 2.0 g of **1**. The infrared spectrum of this product showed no strong absorption of the N–O stretching frequency expected of the 1-oxide near 1210 but had a hydroxyl band at 2900–3200 cm^{-1}; uv showed λ_{max} 232 mμ (ϵ 32,530), 303 (8130), 327 (12,310), 340 (10,610) (in ethanol). *Anal.* Calcd for $C_{10}H_8NO_2Cl$: C, 57.30; H, 3.85; N, 6.68; O, 15.26; Cl, 16.91. Found: C, 57.52; H, 3.92; N, 6.52; O, 15.63; Cl, 16.21.

Reduction of 3-Chloro-8-methoxy-4-quinolinol (**3**).—Compound **3** (0.5 g) in 30 ml of aqueous hydrochloric acid (10%) was hydrogenated over 0.5 g of palladium on charcoal (5%) under 20-psi pressure. After removal of the catalyst, the filtrate was evaporated *in vacuo*. The residue was dissolved in a small amount of water and was neutralized with dilute aqueous sodium hydroxide to yield 0.145 g (34.6%) of white needles. After recrystallization from water, the melting point was 183–184° (with **4**, mmp 183–184°). The ultraviolet spectrum of this product was identical with that of **4** in 0.1 *N* hydrochloric acid, ethanol, and 0.1 *N* sodium hydroxide. The reduction product and **4** were also indistinguishable on paper chromatograms using the solvent system of Mason and Berg[9] containing 1% ammonia (R_f 0.90) or 1% acetic acid[10] (R_f 0.90) and 6% aqueous sodium acetate (R_f 0.50).

Chlorination of 8-Methoxy-4-quinolinol (**4**).—A mixture containing 2 g of **4**, 70 ml of glacial acetic acid, and 0.7 g of chlorine was kept for 12 hr at room temperature. A white

(1) (a) This work was supported by Grant No. CA-07817 from the National Institutes of Health, U. S. Public Health Service. (b) Eisai Research Laboratories, Koishikawa 4, Bunkyo-ku, Tokyo, Japan. (c) American Cancer Society–Charles S. Hayden Foundation Professor of Surgery in Cancer Research. To whom all correspondence should be addressed at Abbott Laboratories, North Chicago, Ill. 60064.

(2) B. Riegel, G. R. Lappin, C. J. Albinsetti, Jr., B. H. Adelson, R. M. Dodson, L. G. Ginger, and R. H. Baker, *J. Amer. Chem. Soc.*, **68**, 1229 (1946).

(3) E. Hayashi, *J. Pharm. Soc. Jap.*, **71**, 213 (1951).

(4) B. Brobański, *Ber.*, **69**, 1113 (1936).

(5) M. M. Robison and B. L. Robison, *J. Org. Chem.*, **23**, 1071 (1958).

(6) Analyses were by Huffman Microanalytical Laboratories, Wheatridge, Colo., and Eisai Research Laboratories, Tokyo, Japan. Melting points are uncorrected. Ultraviolet spectra were determined using a Beckman Model DU spectrophotometer. Infrared spectra were determined in potassium bromide disks with a Hitachi spectrophotometer Model EPI-2. Nmr spectra were determined in carbon tetrachloride with a Varian A-60 magnetic resonance spectrophotometer. All chemical shifts are given as τ values (tetramethylsilane as internal standard).

(7) A. Furst and C. J. Olsen, *ibid.*, **16**, 412 (1951).

(8) W. M. Lauer, R. T. Arnold, B. Tiffany, and J. Tinker, *J. Amer. Chem. Soc.*, **68**, 1268 (1946).

(9) M. Mason and C. P. Berg, *J. Biol. Chem.*, **188**, 783 (1951).

(10) J. M. Price and L. W. Dodge, *ibid.*, **223**, 699 (1956).

precipitate (2.5 g) was collected and washed with hot water, and 1.5 g of **4** was recovered. The insoluble material was recrystallized from aqueous ethanol and 0.6 g (25% of **4**) was obtained as white needles, mp 272–274°. The melting point of an admixture with 3-chloro-8-methoxy-4-quinolinol (**3**) was 272–274°, and this product was identical with **3** in ultraviolet and infrared spectra and on paper chromatograms.

Treatment of 8-Methoxy-4-quinolinol (4) with Hydrochloric Acid and Hydrogen Peroxide in Acetic Acid.—A solution of 1.0 g of **4**, 1 ml of hydrochloric acid (35%), and 1 ml of hydrogen peroxide (30%) in glacial acetic acid was stirred for 3 hr at 65–70°. After another 1 ml of hydrogen peroxide was added to the solution, it was heated at 60–70° for 3 hr. The oily product, which resulted from evaporation of most of the solvent, was dissolved in dilute aqueous sodium hydroxide, and the alkaline solution was neutralized with dilute hydrochloric acid. A yield of 0.44 g of tan needles was obtained, mp 268–271°, undepressed on admixture with **3**.

Hydrolysis of 4-Chloro-8-methoxyquinoline (1).—Compound **1** (0.3 g) was treated under the same conditions as used in the attempted oxidation of **1** to **2** except that hydrogen peroxide was replaced by water. The residue, upon evaporation of the acetic acid, was dissolved in dilute aqueous sodium hydroxide and washed with ethyl ether. Neutralization of the alkaline solution gave 104 mg of colorless needles, mp 180–183° (undepressed on admixture with **4**). From the ethereal solution 82 mg of the starting material was recovered, mp 78–79° (admixture with **1** gave mp 78–80°).

3,4-Dichloro-8-methoxyquinoline (5).—**3** (0.3 g) in 5 ml of phosphorus oxychloride was refluxed for 3 hr. The solution was poured into ice water and then made basic with aqueous sodium hydroxide (20%) to yield 0.3 g of colorless precipitate, mp 113–116°. After recrystallization from aqueous ethanol, 0.19 g (61%) of 3,4-dichloro-8-methoxyquinoline (**5**) was obtained as colorless crystals: mp 115.0–115.5°; nmr (τ value), 1.27 (singlet) for C_2–H, 2.31 (quartet) for C_5–H, 2.55 (triplet) for C_6–H, 3.03 (quartet) for C_7–H, and 5.97 (singlet) for C_8–OCH_3 (J_{56} = 8.3, J_{67} = 7.2, and J_{57} = 2.0 cps). *Anal.* Calcd for $C_{10}H_7NOCl_2$: C, 52.66; H, 3.10; N, 6.14; Cl, 31.09. Found: C, 52.79; H, 3.11; N, 5.86; Cl, 30.90.

Registry No.—**1**, 16778-21-5; hydrogen peroxide, 7722-84-1; **3**, 16778-22-6; **5**, 16797-43-6.

Acknowledgments.—The authors wish to thank Mr. K. Sakaguchi from the Eisai Research Laboratories for valuable assistance with the nmr analyses.

Isolation and Identification of Contaminants Found in Commercial Dihydroquinine[1]

ANDREW P. CHEUNG, ALLEN BENITEZ, AND PETER LIM

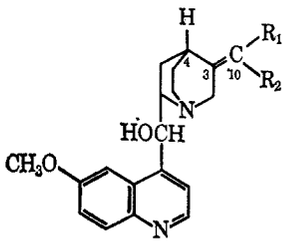
Life Sciences Research, Stanford Research Institute, Menlo Park, California 94025

Received March 19, 1968

Dihydroquinine, which occurs naturally in Cinchona bark in very small quantities, is a useful antimalarial agent possessing slightly higher activity than quinine.[2] Commercially, it is prepared by hydrogenation of quinine with Pd–C in ethanol. In the commercial samples examined, we consistently found two minor contaminants, which constituted 2–7% of the samples. In view of the current interest in malarial chemotherapy, it seems important that the structures of these impurities be known. This manuscript describes the isolation and identification of these contaminants.

The isolation was accomplished by preparative thin layer chromatography (tlc) with methanol on silica gel H. The pmr spectra of the individual contaminants clearly distinguished these compounds from quinine and dihydroquinine, the noteworthy difference being a doublet near τ 8.6 and a quadruplet near 4.4 (area ratio 3:1, respectively). These resonances strongly suggest the presence of a vinylmethyl group, $=CHCH_3$, in both compounds.

Hydrogenation of the individual contaminants with PtO_2 in absolute ethanol resulted in a single product,[3–5] which was shown to be dihydroquinine. This identity was established by comparison of pmr, tlc, and melting point with those of authentic dihydroquinine. The evidence presented strongly suggests that these contaminants are isomeric quinines of the following structures.[6,7]



1a, α-isoquinine;[6] $R_1 = CH_3$; $R_2 = H$
b, β-isoquinine;[6] $R_1 = H$; $R_2 = CH_3$

To provide further proof for the structures of these contaminants, α- and β-isoquinines were synthesized from quinine by the procedure reported by Suszko.[8] The final products were isolated not by the literature method, which called for tedious fractional crystallizations, but by preparative tlc, which was much simpler and far more specific. The equivalence of the synthetic materials to those isolated from samples of commercial dihydroquinine was established by infrared, pmr, tlc, and melting point comparisons.

Recent pmr studies[7] on the two isomeric 3-ethylidene-1-azabicyclo[2.2.2]octanes (3-ethylidenequinuclidines, **2a** and **2b**) have established that the protons of the methyl in **2a** resonate at a lower field than do the protons of the methyl in **2b**. Since the methyl signals from the respective isoquinines are centered at τ 8.51 and 8.60, we can, by analogy, assign the lower field

(1) This work was supported by US Army Medical Research and Development Command, Office of the Surgeon General, under Contract No. DA-49-193-MD-2753. This is Contribution No. 353 to the Army Research Program on Malaria.

(2) G. A. H. Buttle, T. A. Henry, and J. W. Trevan, *Biochem. J.*, **28**, 426 (1934); P. B. Marshall, *J. Pharmacol.*, **85**, 299 (1945).

(3) The catalytic hydrogenation of the Δ_{3-10} double bond in the α- and β-isoquinines produces a center of asymmetry, C_3, and should result in a pair of diastereomers, dihydroquinine and *epi*-C_3-dihydroquinine. According to Henry,[4,5] the former has mp 173.5° and $[\alpha]_D$ −235.7° (0.1 *N* H_2SO_4), and the latter has mp 169° and $[\alpha]_D$ −275° (0.1 *N* H_2SO_4). The dihydroquinine which we isolated from commercial samples has mp 169–171° and $[\alpha]^{21}_D$ −221 ± 6° (0.1 *N* H_2SO_4); the dihydroquinine which we obtained from the hydrogenation of α- and β-isoquinines has mp 173–175° and $[\alpha]^{21}_D$ −234 ± 5° (0.1 *N* H_2SO_4). A comparison of the $[\alpha]_D$ values for our dihydroquinine samples does suggest that the materials from the reduction of the isoquinines are mixtures of dihydroquinine and *epi*-C_3-dihydroquinine.

(4) T. A. Henry, "The Plant Alkaloids," The Blakiston Co., Philadelphia, Pa., 1949, p 429.

(5) T. A. Henry, W. Solomon, and E. M. Gibbs, *J. Chem. Soc.*, 592 (1937).

(6) The assignments of α to the C_4H–$C_{10}H$ transoid and of β to the C_4H–$C_{10}H$ cisoid are based on the assignments made for the 3-ethylene-1-azabicyclo[2.2.2]octanes.[7]

(7) J. C. Nouls, G. Van Binst, and R. H. Martin, *Tetrahedron Lett.*, **41**, 4065 (1967); G. Van Binst, J. C. Nouls, J. Stokes, C. Danheux, and R. H. Martin, *Bull. Soc. Chim. Belges*, **74**, 506 (1965).

(8) L. Jarzynski, R. Ludwiczakowna, and J. Suszko, *Rec. Trav. Chim.*, **52**, 839 (1933).