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.

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

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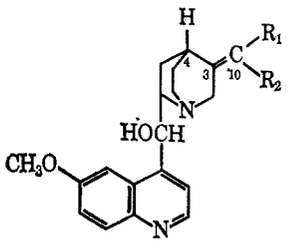
Dihydroquinine, which occurs naturally in Cinchona bark in very small quantities, is a useful antimalarial agent possessing slightly higher activity than quinine.[2] Commercially, it is prepared by hydrogenation of quinine with Pd–C in ethanol. In the commercial samples examined, we consistently found 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.

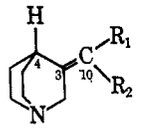
(5) T. A. Henry, W. Solomon, and E. M. Gibbs, *J. Chem. Soc.*, 592 (1937).

(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).

methyl resonance to the α-isoquinine (**1a**) and the higher field methyl resonance to the β-isoquinine (**1b**).



2a, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$

The formation of these isoquinines during the hydrogenation of quinine with Pd–C resulted from a catalytic isomerization of the Δ_{10-11} (quinine) to Δ_{3-10} (α,β-isoquinine). Once formed, these isoquinines cannot be reduced to dihydroquinine under the conditions normally employed for the commercial preparation of the latter compound. However, we found that, by substituting PtO_2 for Pd–C, these isoquinines are readily reduced to dihydroquinine.[3]

Experimental Section

Infrared spectra were determined as Nujol mulls on a Perkin-Elmer 137 spectrometer. Optical rotations were obtained on a Perkin-Elmer 141 polarimeter. Pmr spectra were recorded as $CDCl_3$ solutions on a Varian HA-100 spectrometer equipped with a C-1024 time-averaging computer; chemical shifts are reported on a τ scale from internal tetramethylsilane (τ = 10.00 ppm). Melting points were obtained on a Fisher-John melting point apparatus. Tlc solvent systems are (a) methanol, (b) methanol–triethylamine 25:1 v/v, and (c) acetone–water 9:1 v/v.

Isolation of α- and β-Isoquinines.—Commercial dihydroquinine[9] (45 mg dissolved in 2 ml of chloroform) was applied to a 200 × 200 × 1 mm SiO_2–H plate, which was developed with methanol. The respective α- and β-isoquinine bands from numerous plates were isolated, combined, and extracted with methanol. The methanol solutions were filtered and evaporated to dryness, and the residues were extracted with chloroform. The chloroform solutions were concentrated to minimal volumes and the materials were rechromatographed until each isomer was chromatographically pure. The α-isoquinine, **1a**, had mp 178–181°, $R_{f(a)}$ 0.50. The β-isoquinine, **1b**, had mp 167–170°, $R_{f(a)}$ 0.55.

Hydrogenation of α- and β-Isoquinines.—The isoquinines were individually hydrogenated with PtO_2 (1:1 isoquinine–PtO_2) in absolute ethanol at room temperature, 1 atm, for 1 hr. The catalyst was removed by filtration and the filtrate was concentrated to dryness. The residue, which was shown to be chromatographically homogeneous and identical with dihydroquinine, was crystallized from ethyl acetate. The product[3] melted at 173–175° and was identical with authentic dihydroquinine according to mixture melting point, pmr, and infrared comparisons.

Synthesis of α- and β-Isoquinines.—The procedure employed was that reported by Suszko[8] except for the method of isolation of the isoquinines. Quinine was heated in 18 *N* sulfuric acid at 145° for 6 hr. The solution was cooled and made alkaline with sodium hydroxide. Carbon dioxide was added until a pH of 8 was obtained. The precipitate was collected, washed with water, and dried. The material was dissolved in methanol and treated with an ethereal solution of diazomethane for 16 hr. The isolation of the respective isoquinines was achieved by preparative tlc. The procedure gave an over-all yield of 24% α-isoquinine,[10] mp 177–179°, $[\alpha]^{22}D$ −184 ± 4° (*c* 0.26, EtOH), and 1% β-isoquinine,[8] mp 166–170°, $[\alpha]^{22}D$ −185 ±4° (*c* 0.21, EtOH). The equivalence of these samples to those isolated from commercial dihydroquinine samples was established by tlc, pmr, infrared, and hydrogenation comparisons.

Registry No.—**1a**, 16935-07-9; **1b**, 16934-08-0; dihydroquinine, 522-66-7.

(9) Samples of commercial dihydroquinine were generously provided by Dr. Thomas R. Sweeney of the Walter Reed Institute of Research, Department of the Army, Washington, D. C.

(10) Although the melting points for these isoquinines agree with those for samples isolated from commercial dihydroquinine, they do not agree with those cited by Henry[4] (α = 196.5°, β = 183–185°) or by Suszko[8] (β = 186–187°). When Suszko's procedure for the isolation of the isoquinines was followed exactly, the recrystallized material obtained was shown by tlc to be a mixture of four components, α- and β-isoquinines, dihydroquinine, and an unknown. This may explain why the physical constants they reported differ from ours, which were obtained on materials that are chromatographically homogeneous and are supported by unambiguous spectral data.