

THE PREPARATION AND OPTICAL ROTATION OF PURE  
QUINIDINE.\*

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Quinidine is separated from the mixture of alkaloids extracted from cinchona bark after removal of quinine.<sup>3</sup> Since the hydrogenated derivatives of the four common cinchona alkaloids, quinine, quinidine, cinchonine and cinchonidine, also occur naturally, and since the solubilities of the reduced bases are quite similar to those of the unreduced substances, the preparation of absolutely pure alkaloids is sometimes exceedingly difficult. It is not surprising that ordinary commercial grades should be contaminated. Dawson<sup>4</sup> has listed the impurities which may be found in U. S. P. or B. P. grades of the common cinchona alkaloids. These are shown in Table I, and it will be noticed that the amount of impurity in ordinary quinidine may be quite large.

TABLE I.—POSSIBLE IMPURITIES IN U. S. P. OR B. P. CINCHONA ALKALOIDS.

Quinine*	Up to 2% each of cinchonidine and hydroquinine
Quinidine	6-30% of hydroquinidine
Cinchonine	10%, or even 15% according to Skraup, <sup>1</sup> of cinchonidine
Cinchonidine*	10% of quinine and 8% of hydrocinchonidine

\* From the stereochemical point of view it is interesting to note that quinine and cinchonidine appear as impurities with the bases which are believed to have the same stereochemical configuration, that is, with cinchonidine and quinine, respectively.

<sup>1</sup> Skraup, *Ann.*, 197 (1879), 374.

Study of the stereochemical rearrangement of quinine has been in progress in this Laboratory for some time. This reaction, as carried out by Rabe,<sup>5</sup> yields a separable mixture of bases containing quinidine. Rabe gives no account of the properties of quinidine from this source. Since the impurity in the U. S. P. quinine used as starting material is comparatively small in amount, it appeared feasible to prepare pure quinidine by means of this reaction. The preparation was undertaken at the suggestion of Professor W. T. Dawson of the University of Texas.

*Preparation of Pure Quinidine.*—Several batches of 200 Gm. of quinine were submitted to the action of gently boiling amyl alcoholic potassium hydroxide solution (90 Gm. KOH in 3 L. of amyl alcohol boiling at 127–129°). After removal of quinine from the rearrangement mixture as neutral tartrate, quinidine was isolated as acid tartrate. Ninety Gm. of the crude salt were washed by grinding in a mortar with enough cold water to make a thin paste. This was filtered and the washed salt was dissolved in 600 cc. of hot water. After treatment with

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<sup>3</sup> Henry, "Plant Alkaloids," Philadelphia, Blakiston's Son and Company, (1924), page 137.

<sup>4</sup> Dawson, *Internat. Clin.*, Series 40, Vol. 2 (1930), 121. (Reprinted in) *J. Roy. Army Med. Corps*, 56 (1931), 178.

<sup>5</sup> Rabe, *Ann.*, 492 (1932), 242.

a little nuchar, the solution was filtered. The yield of colorless quinidine acid tartrate obtained on cooling the solution was 60 Gm., melting point 130–132°. Fifty Gm. of the recrystallized salt were dissolved in hot water and the base was precipitated with ammonium hydroxide. The ammoniacal liquor was poured off and the product was washed with water. It was dissolved in hot alcohol and the solution was filtered. The free base with alcohol of crystallization separated on cooling in colorless crystals. Anhydrous quinidine of constant melting point 170–171° and rotation  $[\alpha]_D +262$  in alcohol, was obtained on drying over night at 100°. The yield was 25 Gm. Several Gm. more of base were obtained on concentrating the alcoholic mother liquor.

A comparison of the properties of quinidine thus prepared, with those of a sample of U. S. P. quinidine is shown in Table II. Oxidation experiments per-

TABLE II.—ROTATION AND MELTING POINT OF QUINIDINE.

Sample.	Observed Rotation.*	Solvent.	$[\alpha]_D$ .	Melting Point.
U. S. P. quinidine	+ 9.92°	Absolute alcohol	+248.0°	162–163° C.
Quinidine from	+10.48°	Absolute alcohol	+262.0°	170–171° C.
Quinine rearrangement	+12.95°	1.8 HCl solution	+323.8°	

\* NOTE: The length of tube was 2 dcm. and the concentration 2 Gm. per 100 cc. of solution in each case.

formed on our U. S. P. material by Dr. Alice G. Renfrew, of this Laboratory, indicated that it contained about 20% hydroquinidine.<sup>1</sup> Some data are available in the literature on the rotation of presumably pure alkaloid. Thus Emde<sup>2</sup> reported  $[\alpha]_D +265^\circ$  in 97% alcohol on a sample of practically pure quinidine supplied by Amsterdamsche Chininefabrik, Amsterdam, while Lewis and his associates<sup>3</sup> reported  $[\alpha]_D +323.12^\circ$  in dilute hydrochloric acid solution, on a sample containing not more than 0.5% impurity prepared by Blagden and Chick in the laboratory of Howard and Sons, Ilford, England. Our data agree well with these figures.

## NIGHT BLUE AS AN INDICATOR FOR USE IN VOLUMETRIC TITRATIONS OF ALKALOIDS WITH SILICOTUNGSTIC ACID.

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In their study of the use of silicoduodecitungstic acid as a volumetric reagent in the titration of alkaloids, North and Beal (4) used malachite green as an indicator. Malachite green gives a deep bluish green in water, but on the addition of hydrochloric acid the color changes gradually through olive-green, yellow, orange

<sup>1</sup> Hydroquinidine may be estimated by oxidizing at 0° C. with permanganate,<sup>4</sup> whereby quinidine is destroyed and hydroquinidine is unattacked. Allen, "Commercial Organic Analysis," Philadelphia, Blakiston's Son and Co., 5th Edition, Vol. 7 (1929), 466, 490.

<sup>2</sup> *Helv. Chim. Acta*, 15 (1932), 574.

<sup>3</sup> Lewis, Drury, Wedd and Ilescu, *Heart*, 9 (1922), 207.

<sup>4</sup> See reference 4, page 412.

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