

JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

VOLUME 67

SEPTEMBER 13, 1945

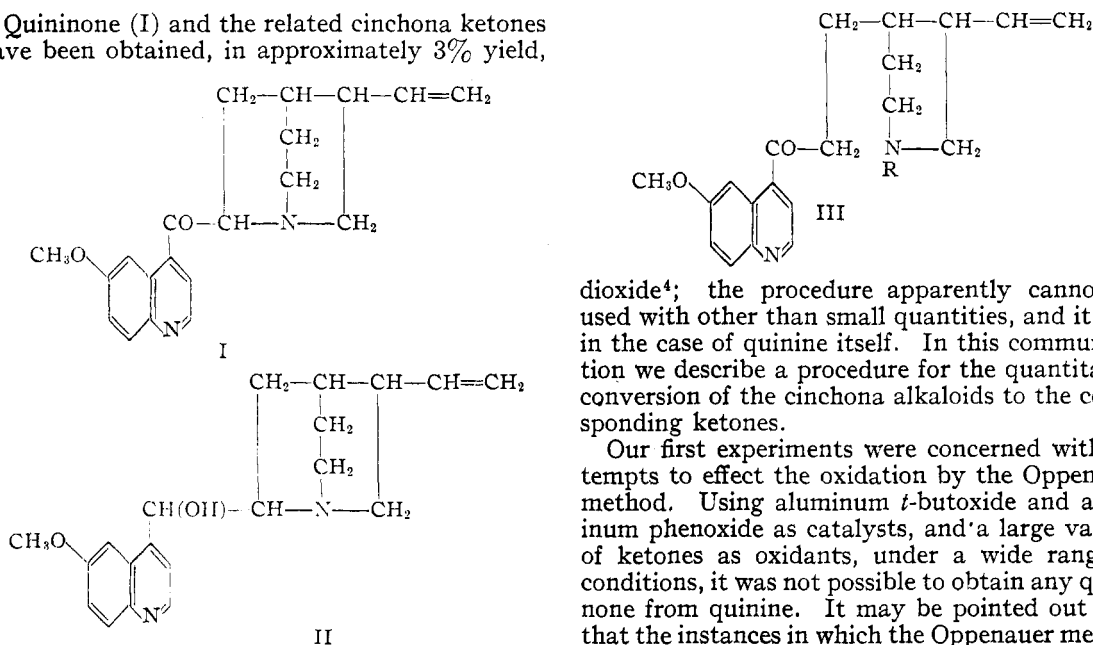
NUMBER 9

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Quininone¹

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Quininone (I) and the related cinchona ketones have been obtained, in approximately 3% yield,



by chromic acid oxidation, under carefully controlled conditions, of the corresponding secondary alcohols, *viz.*, quinine (II) and the other cinchona alkaloids.² An alternative method³ for the preparation of the ketones is illustrated by the sequence quinine (II) → quinotoxine (III, R = H) → N-bromoquinotoxine (III, R = Br) → quininone (I). From the preparative point of view, the length of this process presents obvious disadvantages, and the percentage conversion does not exceed 20%. Recently, dihydroquinine has been oxidized to dihydroquininone in poor yield by selenium

dioxide⁴; the procedure apparently cannot be used with other than small quantities, and it fails in the case of quinine itself. In this communication we describe a procedure for the quantitative conversion of the cinchona alkaloids to the corresponding ketones.

Our first experiments were concerned with attempts to effect the oxidation by the Oppenauer method. Using aluminum *t*-butoxide and aluminum phenoxide as catalysts, and a large variety of ketones as oxidants, under a wide range of conditions, it was not possible to obtain any quininone from quinine. It may be pointed out here that the instances in which the Oppenauer method has been used for the oxidation of substances containing basic nitrogen atoms are very small in number.⁵ It seems probable that the failure of the reaction, in our case, as undoubtedly in others, is due to the acidic nature of the catalyst, which contains an aluminum atom with an open sextet of electrons. In the presence of a base, complexes of the type $R_3N^+ : AlR_3^-$ can be formed, which may remove the catalyst from the sphere of action. This sequence of events is supported by our experiments, in that in the majority of cases, insoluble precipitates appeared at once on admixture of the reactants; on the other hand, in some cases in

(1) This investigation was carried out under Contract WPB-187 of the Office of Production Research and Development.

(2) Rabe and Kuliga, *Ann.*, **364**, 346 (1909).

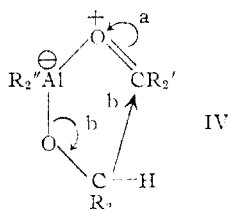
(3) Rabe and Kindler, *Ber.*, **51**, 466 (1918).

(4) McKee and Henze, *THIS JOURNAL*, **66**, 2020 (1944).

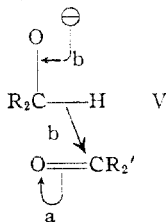
(5) Cf. Witkop, *Ann.*, **554**, 83 (1943); Burger, Alfried and Deinet, *THIS JOURNAL*, **66**, 1327 (1944).

which such complexes did not separate, and in general, when the reaction was carried out under conditions sufficiently drastic to effect eventual dissolution of the precipitated complexes, oxidation still did not occur. In the case at hand, in view of the susceptibility of quinine to cleavage to quinotoxine under the influence of acidic catalysts,⁶ it seems likely that the latter reaction supervened when drastic conditions were used in the effort to force the oxidation under the unfavorable circumstances arising from complex formation. Probably for the same reason, an attempt to circumvent these difficulties by using a salt of quinine, and thereby suppressing the basic character of the nitrogen atoms, was unsuccessful.⁷

While it is general practice to use aluminum alkoxides as catalysts in hydrogen transfer reactions such as the Oppenauer oxidation or the Meerwein-Ponndorf reduction, there are a number of evidently related cases, *e. g.*, the Cannizzaro reaction and the reduction of nitro compounds by sodium methoxide, in which hydrogen transfer is effected in the presence of alkali hydroxides or alkoxides. Further, on mechanistic grounds, while the aluminum atom may at the same time facilitate proton release (IV, process b), and increase

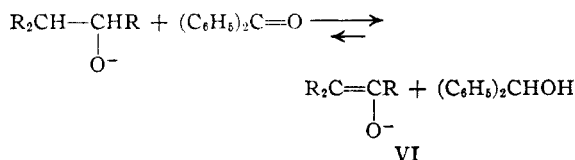


the acceptor capacity of the carbonyl carbon (IV, process a), its function would not seem to be unique; the same driving forces in favor of proton transfer are available, if possibly to lesser degree, in any system containing (primary or secondary) alkoxide ions and carbonyl compounds (V, processes a and b). We were led by these



considerations to attempt the oxidation of quinine in the presence of a hydrogen acceptor and an alkali alkoxide. When the alkaloid was heated fifteen hours in benzene solution with 5 moles of benzophenone in the presence of 3 moles of

potassium *t*-butoxide, quinone was formed in quantitative yield. Under otherwise similar conditions the use of 1 mole of oxidant gave approximately 80% of quinone. It seems probable that the preponderance of quinone in the equilibrium is a consequence of the relatively strongly acidic properties of the ketone, and the resultant formation of a stable potassium enolate (VI).



The oxidation procedure further was used with equal success for the conversion of quinidine to quinone, dihydroquinine to dihydroquinone, and dihydrocinchonine to dihydrocinchonone. It seems probable that the procedure will be of general applicability, particularly in the case of basic substances, where the aluminum alkoxide procedure fails, or gives poor results. On the other hand, the strong capacity of alkali alkoxides for the initiation of condensation reactions will preclude the use of the method in many cases in which the product is a carbonyl compound capable of self-condensation. The same factor prevents the use of certain ketones as oxidants; cyclohexanone, for example, condensed readily with itself under the reaction conditions, the water which was formed removed from the originally anhydrous sphere of action all of the basic catalyst, and the reaction ceased. With cyclohexylidene-cyclohexanone, condensation is possible, but was sufficiently slow that the oxidation was substantially complete before quenching of the reaction occurred, and reasonably good yields (85%) of oxidized product were obtained.

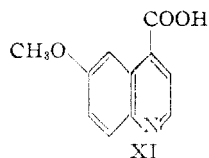
The converse process of reduction was also possible under similar alkaline conditions. When quinone was heated for six hours in toluene with 10 moles of sodium isopropoxide, quinine and quinidine were formed in yields of 30 and 60%, respectively.⁸ The only previous successful reduction of the carbonyl group of quinone was that of Rabe,⁹ who obtained 12% of quinine and 6% of quinidine by reducing the ketone with aluminum and ethanol in the presence of sodium ethoxide. It is worthy of note that this reaction constitutes the last step in the total synthesis of the cinchona alkaloids,⁹ which has thus been noticeably improved. Further, the oxidation-reduction sequence described here makes possible

(6) Pasteur, *Compt. rend.*, **36**, 110 (1853); Hesse, *Ann.*, **166**, 276 (1873); **178**, 244 (1875); von Miller and Rohde, *Ber.*, **28**, 1064 (1895); von Miller, Rohde and Fussenegger, *ibid.*, **33**, 3228 (1900).

(7) The substantial correctness of the above picture is indicated by the observation (private communication from Dr. N. L. Drake) that in certain cases the Oppenauer method has been applied successfully to the salts of basic substances which themselves could not be oxidized by that method.

(8) In this reduction, we had not anticipated the observed marked steric selectivity, the possibility of which first became apparent as the result of a careful investigation by Dr. W. E. Doering, *et al.*, of the mechanism of the direct equilibration of the cinchona alkaloids [cf. Rabe, *J. prakt. Chem.*, **154**, 66 (1939); *Ann.*, **492**, 253 (1932)]. The results of that work, including a thorough discussion of the reducing action on quinone of (primary and secondary) alcohols in the presence of the corresponding alkoxides will appear in a forthcoming paper from Dr. Doering's laboratory.

(9) Woodward and Doering, *THIS JOURNAL*, **67**, 860 (1945).



Experimental

Quinone (I).—Potassium *t*-butylate (0.25 mole) was prepared by dissolving 10 g. of freshly cut potassium metal in 200 cc. of anhydrous *t*-butyl alcohol contained in a 1-liter flask equipped with a reflux condenser connected to a mercury blow-off trap. The excess *t*-butyl alcohol was removed *in vacuo*, and the solid cake broken up and heated *in vacuo* until a dry mobile powder was obtained.

To the potassium *t*-butylate was added 500 cc. of anhydrous benzene, 32.4 g. of dry quinine (0.1 mole) and 91 g. of dry benzophenone (0.5 mole). The system was flushed with dry nitrogen, connected to a mercury blow-off trap, and the mixture refluxed for fifteen to eighteen hours on the steam-bath. The reaction mixture was then cooled, poured onto ice and extracted with 10% hydrochloric acid until the acid extract was nearly colorless (*ca.* four to five times). The combined acid extracts were washed twice with ether and then dripped with stirring into an excess of ammonium hydroxide-ice. The quinone precipitated as a pale yellow semi-solid which was extracted with ether. The aqueous layer was salted and re-extracted three to four times. The combined ether extracts were washed neutral with salt solution, dried and evaporated in a stream of dry air until the major portion of the quinone crystallized. After chilling, the quinone was removed and washed with a small amount of cold ether; wt. 29–30 g. The mother liquors were evaporated to dryness, and the residue was recrystallized as above. Weight of second and third crops was 1–2 g.; total yield 30–32 g., m. p. 106–108° (pale yellow needles); yield, 95–98%. For analysis, a sample was crystallized twice from ether; long, pale yellow needles, m. p. 107–108.5°.

Anal. Calcd. for $C_{20}H_{20}O_2N_2$: C, 74.53; H, 6.83. Found: C, 74.51; H, 6.51.

Quinone Enol Benzoate (VIII, R = $-\text{COC}_6\text{H}_5$).—A solution of quinone (1 g.) in benzoyl chloride (10 cc.) was heated in a closed flask for one hour on the steam-bath (crystalline material separated). The contents of the flask were poured into ice-water and the excess benzoyl chloride was removed with ether. The quinone enol benzoate was precipitated as a colorless semi-solid by dripping the aqueous solution into ice and ammonia water with stirring. The solution of the precipitated product in ether was washed neutral with water, dried and evaporated to a colorless oil, which solidified on standing overnight. Crystallization from ether-petroleum ether afforded colorless small prisms, m. p. 114–115°; wt. 1–1.2 g.

Anal. Calcd. for $C_{27}H_{26}O_3N_2$: C, 76.06; H, 6.10. Found: C, 76.28; H, 5.95.

The enol benzoate gives a yellow solution with acids. A small sample warmed with alcoholic potassium hydroxide was hydrolyzed quantitatively to quinone.

Quinone Enol *p*-toluenesulfonate (VIII, R = $-\text{SO}_2\text{C}_6\text{H}_4$).—A mixture of quinone (1 g.) and of *p*-toluenesulfonyl chloride (10 g.) was heated in a closed flask for three-quarters of an hour on the steam-bath. The melt was treated with water and the aqueous extract washed with ether to remove excess *p*-toluenesulfonyl chloride. The aqueous layer was neutralized with ammonia, the product was extracted with ether and the ether extract was washed neutral, dried and evaporated to dryness. The solid was crystallized several times from ether; hard lustrous prismatic clusters or spurs, m. p. 133.5°, wt. 0.3–0.4 g.

Anal. Calcd. for $C_{27}H_{26}O_4N_2S$: C, 68.07; H, 5.88. Found: C, 68.36; H, 5.87.

The enol *p*-toluenesulfonate gives a yellow solution with acids but unlike the enol benzoate is stable to hot alcoholic potassium hydroxide.

Catalytic Hydrogenation of Quinone.—Quinone (1.6 g.) in 50 cc. of absolute ethanol was hydrogenated at room temperature and atmospheric pressure using 0.1 g. of platinum oxide catalyst. Absorption of the first mole of hydrogen (corresponding to saturation of the ethylenic side chain) proceeded rapidly (ten minutes). The second mole was absorbed in *ca.* three-quarters of an hour; completion of the reduction was accompanied by disappearance of the characteristic yellow color of solutions of quinone. The catalyst was removed and the solution was evaporated to a light colored glass. A few cc. of alcohol was added; scratching and seeding then induced crystallization. The chilled product was filtered and recrystallized from alcohol; glittering crystals, m. p. 170–171° undepressed with known dihydroquinidine; wt. 0.6 g. Evaporation of the mother liquors and reprocessing of the concentrate afforded an additional 0.1 g. of dihydroquinidine. From the residue, using the tartrate separation method of Rabe,¹⁵ only 5% of dihydroquinone was isolated.

The hydrogenation of quinone in dilute acid, and also that using palladium chloride as catalyst leads to essentially the same results. The similar reduction of dihydroquinone gave dihydroquinidine in 50% yield.

11-Bromodihydroquinone (VII, R' = H, R = Br).—A solution of 1.6 g. of quinone in 25 cc. of 48% aqueous hydrogen bromide containing 0.01 g. of hydroquinone was saturated at -10° with gaseous hydrogen bromide, and allowed to stand at room temperature for twenty-four hours; it was then poured into ice and ammonia water, and the product was extracted with ether. The ether solution was washed, first with aqueous sodium hydroxide, then with water until neutral, dried and evaporated to a solid. The latter was crystallized from alcohol; buff colored microscopic needles, m. p. 151–151.5° (dec.), with previous darkening; wt. 1.5 g.

Anal. Calcd. for $C_{20}H_{22}O_2N_2Br$: C, 59.55; H, 5.71. Found: C, 59.67; H, 5.55.

A repetition of this experiment, substituting ascaridole for hydroquinone, gave a bromide with the same melting point (no depression on admixture).

11,12-Dibromoquinone (VII, R' = Br, R = Br).—Quinone (6.44 g.) was dissolved in 35 cc. of 80% acetic acid and 5 cc. of 48% hydrobromic acid. To the chilled acid solution was added dropwise and with swirling 3.2 g. of bromine in 10 cc. of 80% aqueous acetic acid. During addition, incipient turbidity (perbromide?) developed which disappeared when the solution was agitated. The acid solution was poured with vigorous stirring onto ice and concentrated ammonia water: the dibromoquinone separated as a well-defined solid, which was filtered, washed with water and dried *in vacuo* over potassium hydroxide. The dried product (9.5 g.) was leached of impurities in the cold, successively with alcohol and acetone. A light yellow product (6–7 g.) was obtained. A small sample was crystallized from a large volume of ethanol: microscopic needles, m. p. 172–173° (dec.) with previous darkening.

Anal. Calcd. for $C_{20}H_{22}O_2N_2Br_2$: C, 49.79; H, 4.57. Found: C, 50.31; H, 4.65.

Conversion of Dibromoquinone to Quinone.—A suspension of 2 g. of dibromoquinone in 50 cc. of acetone containing 5 g. of sodium iodide was refluxed for one hour on the steam-bath. The acetone was removed in a current of air and the dark residue was treated with 25% potassium hydroxide solution and extracted with ether. The ether washings were extracted with dilute hydrochloric acid, the acid extract was neutralized with ammonia, and the free quinone was taken up in ether. The washed ether solution, after being dried and evaporated, gave a pale yellow oil that crystallized spontaneously. Recrystallization from ether afforded 1.2–1.3 g. of quinone, m. p. 101–102° (undepressed on admixture with authentic material).

Hydrogenation of Dibromoquinone.—A solution of 1.5 g. of dibromoquinone in 40–50 cc. of 10% hydrochloric acid containing 0.1 g. of palladium chloride was hydrogenated at ordinary temperature and pressure. Three moles

(15) Rabe, *Ann.*, **492**, 242 (1932).

of hydrogen were taken up at a fairly rapid and continuous rate (one to two hours). The yellow color of the solution was not discharged until the third mole had been absorbed. The catalyst was removed and the solution was neutralized, extracted with ether, and the extract was worked up in the usual way. The solid remaining after evaporation of the solvent was crystallized several times from ethanol, m. p. 169–170°; wt. 0.3–0.4 g.; mixed m. p. with hydroquinidine, 169–170°; Beilstein test negative.

Hydrogenation of the above ketone in dioxane with platinum oxide, palladium chloride or Raney nickel likewise resulted in the absorption of 3 moles of hydrogen per mole of ketone.

Isobutylquinidine (IX, R = $-\text{CH}_2\text{CH}(\text{CH}_3)_2$).—Isobutylmagnesium bromide (0.1 mole) was prepared from 2.43 g. of magnesium and 14–15 g. isobutyl bromide in 100–125 cc. of ether. A solution of 3.2 g. of quinone in 100 cc. of benzene was added dropwise with swirling to the Grignard solution at room temperature. The reaction mixture was allowed to stand one hour, and then hydrolyzed with ice and hydrochloric acid. The acid extract was washed with ether, neutralized and the precipitated bases were taken up in ether. The ether solution was washed neutral with water, dried and evaporated to a dark oil. After standing several days this oil showed indications of crystallization. A few cc. of ethanol was added; trituration then caused the oil to crystallize in part. The solid was recrystallized from alcohol, wt. 1.4–1.5 g.; needles, m. p. (after drying in the pistol *in vacuo* at 100°) 146–147.5°.

Isobutylquinidine crystallizes with alcohol of crystallization. An air-dried sample was analyzed.

Anal. Calcd. for $\text{C}_{24}\text{H}_{32}\text{O}_2\text{N}_2 \cdot \text{C}_2\text{H}_5\text{OH}$: C, 73.24; H, 8.92. Found: C, 73.64; H, 8.59.

A sample dried at 100° *in vacuo* was analyzed.

Anal. Calcd. for $\text{C}_{24}\text{H}_{32}\text{O}_2\text{N}_2$: C, 75.79; H, 8.42. Found: C, 75.99; H, 8.13.

The specific rotation of the air-dried material was determined in ethanol: $[\alpha]^{25}_D + 148^\circ$ (50 mg./10 cc., $\alpha = 1.48^\circ$).

Methylquinidine (IX, R = $-\text{CH}_3$).—To methylmagnesium iodide (0.1 mole) in 100 cc. of dry ether, a solution of 3.2 g. of quinone in 100 cc. of dry benzene was added dropwise with swirling. After one to two hours at room temperature, the reaction mixture was hydrolyzed with ice and hydrochloric acid, the acid layer was washed with ether and dripped into ice and ammonia water. A colorless well-defined solid separated, which was readily filtered and washed. On crystallization from dilute aqueous ethanol (50%) 3.2–3.5 g. of methylquinidine separated as scintillating needles. Attempts to dry this product at 60° or 100° caused the compound to liquefy, with loss of solvent of crystallization. The air-dried product was analyzed.

Anal. Calcd. for $\text{C}_{21}\text{H}_{26}\text{O}_2\text{N}_2 \cdot 2\text{H}_2\text{O}$: C, 67.38; H, 8.02. Found: C, 67.51; H, 7.71.

The specific rotation of the air-dried material was determined in ethanol: $[\alpha]^{25}_D + 168^\circ$ (50 mg./10 cc., $\alpha = 1.68^\circ$).

Methylquinidine under Conditions of Equilibration.—A solution of methylquinidine (1.9 g.) in 15 cc. of isoamyl alcohol containing 0.84 g. of potassium hydroxide was refluxed for eighteen to twenty hours (oil-bath at 140°). The reaction mixture was treated with ice and hydrochloric acid and the amyl alcohol was removed with ether. The colorless acid solution was dripped into ice and ammonia water with stirring, thus precipitating unchanged methylquinidine. The air-dried product crystallized from dilute ethanol as characteristic colorless needles identical with the starting material (1.8–1.9 g.), $[\alpha]^{25}_D + 170^\circ$ (50 mg./10 cc., $\alpha = 1.70^\circ$).

Oxidation of the Potassium Enolate of Quinone.—Dry potassium *t*-butylate (from 1.3 g. of potassium and 30 cc. of *t*-butyl alcohol) was suspended in 50 cc. of dry benzene containing 3 g. of quinone. The resultant red suspension of the potassium enolate of quinone was aerated with a slow stream of dry air while the solution was heated under reflux for three hours. The reaction mixture was acidified, washed with ether and then made basic. Ether ex-

traction of the alkaline solution afforded 0.3 g. of quinone (10%). The aqueous layer was brought to pH 7 and evaporated to near dryness in a current of dry air. The solid residue was crystallized twice from dilute hydrochloric acid and once from a large volume of ethanol; 0.9–1.0 g. of quininic acid, tan needles, m. p. 284° (dec.); was obtained.

Reduction of Quinone by Sodium Isopropoxide.—Sodium isopropoxide (0.1 mole) was prepared from 2.3 g. of freshly cut sodium and 100–150 cc. of dry isopropyl alcohol. The excess alcohol was removed *in vacuo*.

To the sodium isopropoxide was added 100 cc. of dry toluene, and 3 g. of quinone. The mixture was refluxed (mercury-trap attachment) in an oil-bath at 120° for six hours. The reaction mixture was cooled under nitrogen, poured onto ice and extracted thoroughly with dilute hydrochloric acid. The combined acid extracts were washed with ether and dripped into an excess of ammonium hydroxide-ice with stirring; the colorless reduced alkaloids separated as a finely divided solid, which was extracted with ether. The aqueous layer was saturated with salt and extracted three to four times with generous portions of ether. The combined ether extracts were washed neutral with saturated salt solution, dried over potassium carbonate, filtered and evaporated to dryness in a current of dry air. The semi-solid residue was freed from last traces of solvent by heating *in vacuo* at 60°; wt. 3–3.2 g. The residue was dissolved in 5 cc. of 95% ethanol and the solution was cooled and seeded; quinidine separated as hard, colorless crystals, which were filtered, washed with a few cc. of cold 95% ethanol and air dried; wt. 1.52–1.55 g. (50–51%); m. p. 170–171°.

The filtrate from the quinidine separation was evaporated to dryness (wt. 1.5 g.); the residue was dissolved in 2.5 cc. of 95% ethanol, and treated with a solution of 0.38 g. (0.5 equivalent) of *d*-tartaric acid in 2.5 cc. of 95% ethanol. Quinine neutral tartrate separated in highly crystalline condition while the solution was still warm. The solution was chilled for some time; the solid was filtered, washed with a few cc. of 95% ethanol and air dried; wt. 1.05 g. \approx 0.85 g. of quinine (28%).

The filtrate from the above quinine separation was evaporated to dryness; the residue was dissolved in four times its weight of water and treated with 0.5 equivalent of *d*-tartaric acid. Seeding caused quinidine acid tartrate to separate as good crystals. The solution was chilled for some time, the acid tartrate was filtered, washed with a few cc. of cold water and dried at 40–50°; wt. 0.42 g. \approx 0.28 g. of quinidine (9–10%).

Evaporation of the mother liquors from the acid tartrate separation afforded 0.3–0.4 g. of thick oily residue. Upon carrying the residue through the tartrate separation a further small quantity of quinine tartrate was obtained.

Summary

A new procedure for the selective oxidation of alcohols to ketones is described. The method, which is probably of general applicability and may be of particular value for substances with basic properties, is exemplified in the case of quinine, which has been converted to quinone in quantitative yield. The reactions of quinone have been investigated, in particular the addition of hydrogen bromide, bromine and Grignard reagents, the formation of enol esters, catalytic hydrogenation, and reduction by sodium isopropoxide to quinine and quinidine. The latter reaction is the last step in the total synthesis of the cinchona alkaloids, and the new procedure constitutes a marked improvement over previous methods for effecting the change.

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RECEIVED FEBRUARY 28, 1945