was obtained before the residue in the distilling flask polymerized. The picrate, prepared in the usual fashion,[6] melted at 141–142° (dec.).

B. By reducing 9 g. of 2-pyrrolalmethylamine[5] in absolute alcohol with sodium in the usual manner, 1.5 g. of very impure product boiling at 95–110° (20 mm.), was obtained; m. p. of the picrate was 139–140° (dec.).

Anal. Calcd. for $C_{12}H_{13}N_5O_7$: N, 20.64. Found: N, 20.73.

C. 1.27 g. of the Schiff base was dissolved in 20 ml. of ethanol and reduced at room temperature with hydrogen at atmospheric pressure, using 60 mg. of platinum oxide catalyst. After the calculated volume of hydrogen had been absorbed, the solution was filtered, decolorized with a little charcoal and used directly to prepare the picrate in 80% yield (based on the starting Schiff base), m. p. 140° (dec.).

Anal. Calcd. for $C_{12}H_{13}N_5O_7$: N, 20.64. Found: N, 21.18.

Mixed melting points of the picrates from A, B and C showed no depression.

(6) Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1940, p. 149.

Summary

The preparation of monosubstituted derivatives of pyrrole by the Mannich reaction, under conditions where excess pyrrole is treated with a mixture of formaldehyde and the hydrochlorides of a number of primary and secondary amines, is described. The structure of 2-methylaminomethylpyrrole is proved, and the properties of the compounds are given.

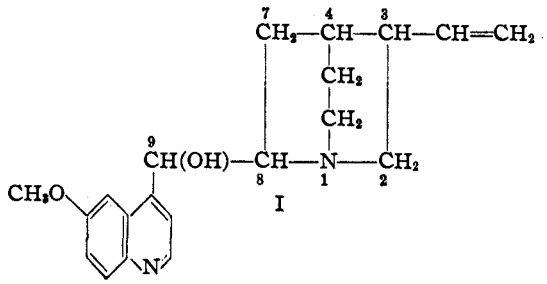
BOULDER, COLORADO RECEIVED FEBRUARY 4, 1947

[CONTRIBUTION FROM THE CHANDLER LABORATORY, COLUMBIA UNIVERSITY]

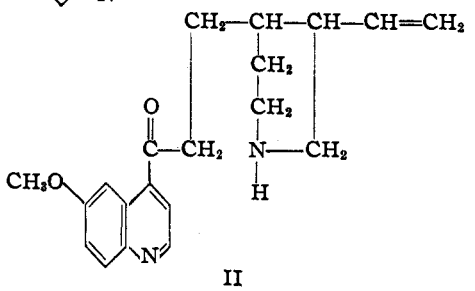
Partial Racemization of Quinine[1]

BY W. E. DOERING, GLORIA CORTES AND L. H. KNOX

Using a reaction known to effect racemization or inversion of an asymmetric secondary hydroxyl group[2,3] in general and specifically to have converted cinchonine into cinchonidine (5% yield),[4] Rabe has converted quinine to an equilibrium mixture of the four stereoisomeric alkaloids (III, IV, V and VI).[5a,5b,6]



I



II

On boiling quinine for forty-eight hours in a solution of potassium hydroxide in amyl alcohol there is isolated a mixture from which quinine (7%), quinidine (10–15%), and the two epibases (15–20% each) are obtained. From the fact that

(1) This work was carried out under Government Contract WPB-191 between the Office of Production Research and Development and the Division of War Research, Columbia University.

(2) Erlenmeyer and Hell, *Ann.*, **160**, 303 (1871); Willstätter, *Ber.*, **29**, 944 (1896).

(3) For further references, see Hückel, "Theoretische Grundlagen der organischen Chemie," Akademische Verlagsgesellschaft, Leipzig, 2nd ed., 1934, vol. I, pp. 286–288.

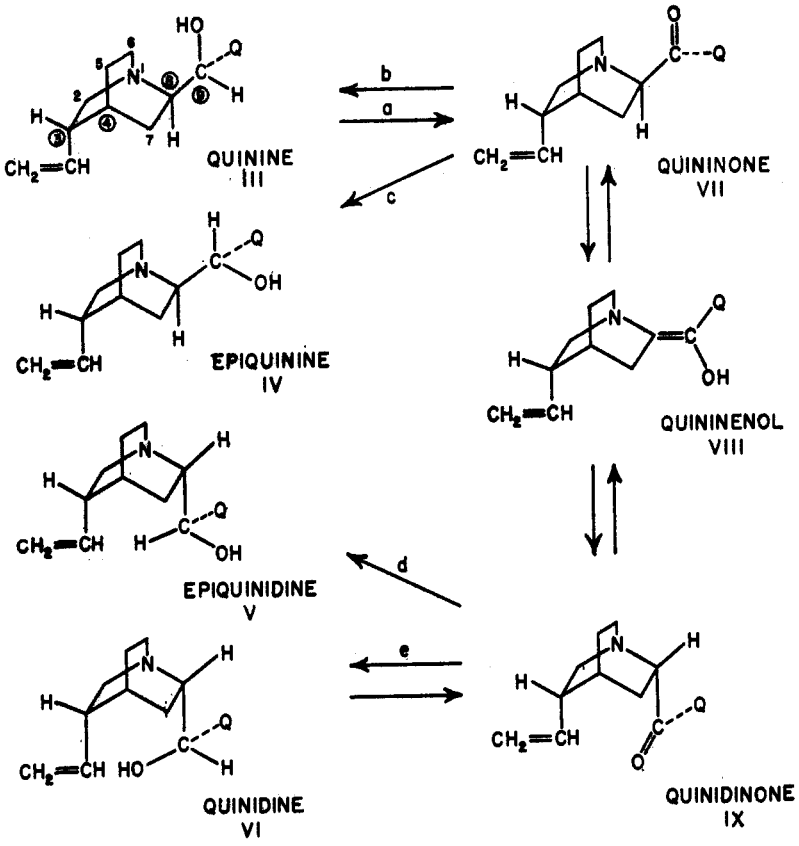
(4) Koenigs and Husmann, *Ber.*, **29**, 2185 (1896).

(5) (a) Rabe, Kolbe and Hochstätter, *Ann.*, **492**, 258 (1931); (b) Rabe and Höter, *J. prakt. Chem.*, **154**, 66 (1939).

(6) In molecules having structure I there are centers of asymmetry at carbon atoms 3, 4, 8 and 9. The four known isomers are all related to quinotoxine (II) and are, therefore, C.8 and C.9 epimers[7] [Pasteur, *Compt. rend.*, **36**, 26 (1853)]. Stereochemical configurations are assigned to III, IV, V, and VI on the basis of the following considerations. (1) Prelog and Zalan [*Helv. Chim. Acta*, **27**, 535 (1944)] have proved the C.7–C.8 bridge to be *cis* to the C.3 vinyl group. (2) Quinine and quinidine are C.8 epimers since they are degraded to two different C.9 desoxy alkaloids of negative and positive rotation, respectively. (3) From the specific rotation of the alkaloids (quinine, −158°; epiquinine, +43°; epiquinidine, +102°; and quinidine, +265°) application of the rule of superposition or additivity of specific rotation of individual asymmetric centers coupled with fact (2) indicates that quinine and epiquinine are epimeric at C.9, as are quinidine and epiquinidine, the two pairs differing at C.8 [for details *cf.* Henry, "The Plant Alkaloids," 3rd ed., Blakiston, London, 1939, p. 424]. (4) The direct epimerization of quinidine to epiquinidine by way of the *p*-toluene sulfonate [Sussko and Szelag, *Chem. Zentr.*, **108**, I, 464 (1937)] confirms conclusion (3). (5) The C.9 hydroxyl group and the C.3 vinyl group in quinidine react to form a cyclic ether [Henry, Solomon and Gibbs, *J. Chem. Soc.*, 592 (1937)] whereas no cyclic ether has ever been formed from quinine. Since a model of the cyclic ether can only be constructed if the C.3 and C.8 hydrogen atoms are *cis*, it follows that C.9 and the C.3 vinyl group must be *cis* in quinidine and epiquinidine, *trans* in quinine and epiquinine. (6) Woodward, *et al.*,[8] have shown that dihydroquininone is reduced catalytically predominantly to dihydroquinidine. Dihydroquininone, therefore, has the quinidine configuration at C.8 and might be named more appropriately dihydroquinidinone. If one assumes that dihydroquinidinone (dihydro IX) with the quinoline ring extended away from the quinuclidine ring is adsorbed on the catalyst in the least hindered position [Linstead, *et al.*, THIS JOURNAL, **64**, 1985 (1942)], that is, with the C.3 ethyl group away from the catalyst, reduction would lead to the isomer in which the hydroxyl group at C.9 is close to the C.3 ethyl group (the quinoline ring being oriented away from the quinuclidine ring) or to the isomer in which looking along the C.8–C.9 bond, the hydrogen, hydroxyl and quinoline ring are encountered in that order reading clockwise (the C.3 configuration arbitrarily being written as in III).

(7) Dirscherl and Thron, *Ann.*, **521**, 57 (1936).

(8) Woodward, Wendler and Brutschy, THIS JOURNAL, **67**, 1425 (1945).



quinidine is converted to the same mixture when similarly treated, Rabe has concluded that the mixture is the result of an equilibration. We have reinvestigated these experiments of Rabe in an effort to develop a practical method for converting quinine to quinidine.

In all our work on the partial racemization of quinine we have used the excellent method of separation developed by Rabe.[5a] The method is mentioned briefly in order that there be no misunderstanding of the accuracy and significance of the results reported later. Quinine is removed first as the neutral tartrate, the crude salt containing 90–95% quinine. The quinidine is next removed as the acid tartrate from water (80% pure), one recrystallization giving pure salt. Since quininone, too, forms an acid tartrate that may be crystallized from alcohol, the presence of quininone might be expected to interfere with the separation of quinidine, but does so only when an appreciable quantity is present. Attempts to isolate quinidine without first removing quinine are not successful for large quantities of quinine acid tartrate are occluded in the quinidine acid tartrate thus prepared. Furthermore quinidine cannot be obtained by direct crystallization from a mixture of the alkaloids because appreciable amounts of quinine contaminate the quinidine thus obtained.

Isolation of the epibases[5a] as the dihydrochloride is not very satisfactory, for the dihydrochloride is apparently a sparingly soluble double salt similar to the double sulfate. The dihydrochlorides of *pure* epiquinine and epiquinidine are much more soluble than the double salt, which can, therefore, only be used for the separation of epibases from mixtures containing approximately equal quantities of the epibases. As an analytical method Rabe's dibenzoyl-*d*-tartrate procedure is much to be preferred.

A complicating factor in the equilibration reaction has been pointed out by Tishler and Pearson.[9] These workers have confirmed Rabe in finding that the optical rotation rises from −158° (quinine) to *ca.* + 60° (apparent equilibrium) and have discovered the remarkable fact that the amount of quinidine present passes through a maximum during the course of the reaction. In Table I one of our experiments in which the partial racemization is carried out in a boiling solution of sodium *n*-hexylate in *n*-hexyl alcohol is reported as an illustration of the phenomenon.

TABLE I

PARTIAL RACEMIZATION IN ABSOLUTE *n*-HEXANOL

Hours	$[\alpha]^{25}D$	Quinine, %	Quinidine, %
0	−158	100	0
1.00	− 11	45.2	16.5
1.25	+ 3	44.7	19.6
2.00	+ 40	21.6	16.5
4.00	+ 58	6.8	11.2
8.00	+ 66	1.6	4.0

The amount of quinidine rises rapidly, reaches a maximum and then decreases gradually until a small amount of quinidine remains. This phenomenon is observed when quinine is boiled with sodium alcoholate in absolute *n*-butanol, *n*-pentanol, isoamyl alcohol, *n*-hexanol or heptanol-2. For the purpose of converting quinine to quinidine it is desirable to stop the reaction shortly before the maximum amount of quinidine has been formed, for during the ensuing periods there is a large decrease in the amount of recovered quinine uncompensated by a commensurate increase in quinidine content (compare the one and two hour result in Table I).

The partial racemization procedure does not, in fact, lead to a true equilibrium as proposed by Rabe. There are side reactions which lead to

(9) Tishler and Pearson, private communication.

unidentifiable products. Thus the longer the heating is continued, the smaller is the yield of the four alkaloids. In *n*-butanol, for example, after twenty-four, thirty-six and forty-eight hours, the sums of the yields of the four stereoisomers is 74.5, 67.9 and 52.1%, respectively. Only to a rough approximation does the reaction lead to equilibrium.

Another characteristic of the partial racemization is brought to light by the use of certain alcohols purified by treatment first with zinc dust and alkali,[10] then with sodium metal, and finally by distillation under nitrogen. Figure 1, illustrating the rate of change of optical rotation when quinine is equilibrated in isoamyl alcohol purified as described above, shows that the reaction possesses an induction period. The rate is slow at the beginning of the reaction, increases to a maximum and finally approaches (to a first approximation) equilibrium.

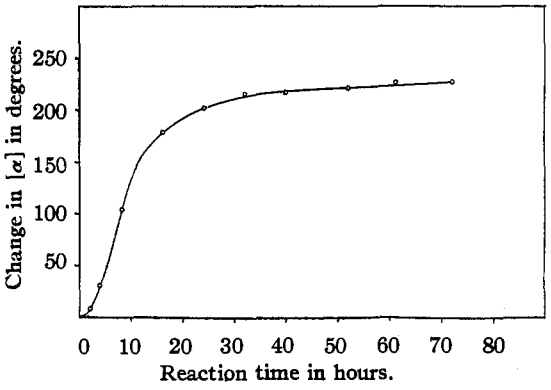


Fig. 1.—Change in specific rotation of total crude alkaloid product as a function of time in hours when quinine is boiled with sodium isoamylate in purified isoamyl alcohol under nitrogen.

The mechanism which we have found to be in accord with the experiments is identical in some respects to that proposed independently by Wagner-Jauregg[11] and Hückel.[3] These authors assume an oxidation–reduction mechanism initiated by dehydrogenation of the alcohol and carried on by the alkali-catalyzed oxidation–reduction of the ketone-alcohol system, each molecule of alcohol being at least once in the enolizable ketone state. This mechanism is in agreement with the facts that racemization occurs only at the carbinol group and the adjacent carbon atoms, that tertiary alcohols are not racemized, and that the ketone corresponding to the alcohol being racemized has actually been isolated in one case by Hückel.[12] We shall describe the hypothetical mechanism using quinine as an example, and show that its validity is strengthened by consistency with our experimental evidence.

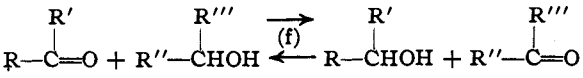
(10) Dubovitz, *Chem.-Ztg.*, **46**, 654 (1922).

(11) Wagner-Jauregg in Freudenberg, "Stereochemie," Franz Deuticke, Leipzig, 1932, pp. 866–867.

(12) Hückel and Naab, *Ber.*, **64**, 2137 (1931).

The first step of the partial racemization or equilibration is assumed to involve the oxidation of quinine to quininone (step a). By this reaction the asymmetry of the two centers that are inverted in the equilibration is destroyed, the one at C.9 by conversion of the secondary alcohol group to carbonyl and the one at C.8 by base-catalyzed establishment of the equilibrium between quininone (VII) and quinidinone (IX) by way of quininenol (VIII).

The oxidation of quinine under conditions fairly close to those prevailing in the equilibration has been effected by Woodward, *et al.*[8] These workers found quinine to be unaffected by the usual Oppenauer conditions, but were able to oxidize it quantitatively to quininone on boiling with a solution of potassium *t*-butylate and benzophenone in benzene. This is another example of the reaction involving establishment of equilibrium between two alcohol–ketone systems by alkoxide ion as catalyst.[13] The fact that the oxidation can also be effected in *t*-butyl alcohol as solvent in



place of benzene, dispels all doubt that the alcohol used as solvent in the equilibration might interfere with the oxidation of quinine.

The second step of the mechanism proposed for the partial racemization involves reduction of the quininone–quinidinone system by reversal of the forward step involved in the equilibrium (f). In the reduction of quininone the asymmetry at C.9 is reëstablished leading to the formation of both quinine (III) and epiquinine (IV) [equations (b) and (c) above]. Similarly quinidinone (IX) may be reduced to quinidine (VI) and epiquinidine (V) [equations (e) and (d) above].

Reduction of ketones by alcohols is well known, for the reaction is identical to the previously discussed oxidation, the difference lying in point of emphasis. In addition to the extensive literature on the Meerwein–Ponndorf reduction with aluminum isopropylate,[14] there are a number of references in which sodium alkoxides effect reduction of ketones.[15] The possibility of reducing quininone in the proposed manner has been realized in several experiments. It has been found that many alcohols in the presence of their corresponding alcoholates are capable of carrying out the reduction of quininone to a mixture of the four stereoisomers.

The rates of reduction vary widely depending on the structure of the alcohol effecting reduction. Isopropanol, *n*-butanol, pentanol-3, and cyclohex-

(13) Ponndorf, *Z. angew. Chem.*, **39**, 138 (1926).

(14) Wilds, "Organic Reactions," Vol. II, J. Wiley and Sons, New York, N. Y., 1944, p. 178.

(15) Sagumeni, *Ber.*, **9**, 276 (1876); Diels and Rhodius, *ibid.*, **42**, 1072 (1909); Schicht, German Patent 327,510 (1920); Montagne, *Rec. Trav. Chim.*, **41**, 703 (1922); Verley, *Bull. soc. chim.*, [4] **37**, 537, 871 (1925); **41**, 788 (1927); Rubin, THIS JOURNAL, **66**, 2075 (1944).

anol reduce quininone at reasonable rates. Diisopropylcarbinol effects reduction at a barely observable rate and Woodward has reported no reduction with benzhydrol.[16] These results parallel the observations of Baker and Adkins[17] in their study of the establishment of equilibrium between pairs of alcohol–ketone systems by aluminum alkoxides (Oppenauer oxidation—Meerwein–Ponndorf reduction). The observation of these workers that diisopropyl ketone and benzophenone are among the most slowly reacting ketones clarifies the failure noted above.

A critical test of the validity of the proposed oxidation–reduction mechanism is to be found in the behavior of quinine and quininone toward tertiary alcohols. As anticipated from the previous discussion, ketones should be incapable of reduction by tertiary alcohols, the latter being incapable of oxidation by the ketones. In accord with this conclusion, quininone has been found to be completely stable in a solution of potassium *t*-butylate in *t*-butyl alcohol boiling under nitrogen. The more important further prediction is that quinine should not be partially racemized in tertiary alcohols, in which solvents the first step of the postulated mechanism may take place, but the second step, the reduction of quininone, is prohibited. This prediction has been substantiated. When quinine is boiled with a solution of potassium in triethylcarbinol a reaction product is obtained in which no epiquinine, quinidine or epiquinidine can be detected.

In the discussion of the oxidative phase of the equilibration mechanism, the catalytic nature of the action of carbonyl compounds has not been emphasized. The oxidation of only a small amount of quinine to quininone is required, for during the subsequent reduction of quininone, which may occur only in an oxidizable alcohol (primary or secondary), an equivalent quantity of carbonyl compound is regenerated. Therefore, theoretically only a catalytic amount of carbonyl compound is required to effect the partial racemization of quinine, although in practice some carbonyl intermediates may be lost through condensation.

One accordingly predicts that quinine should be stable and remain unequilibrated in primary and secondary alcohols free of carbonyl compounds because the first step of the proposed mechanism may not take place. In such an experiment it is imperative to exclude air meticulously since alkoxides of primary and secondary alcohols are oxidized by air to the corresponding carbonyl compounds. An experiment designed to realize this prediction has already been reported and clearly failed (see Fig. 1). In subsequent experiments no matter what pains were taken to free the solvent of carbonyl compounds and to work in the absence of oxygen, the equilibration could not be prevented from occurring.

(16) Woodward, private communication.

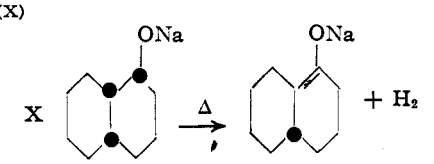
(17) Baker and Adkins, THIS JOURNAL, **62**, 3305 (1940).

The resolution of the discrepancy depends on the observation that quinine is converted to quininone in a purely base-catalyzed reaction. In the previously described reaction in which quinine is boiled with a solution of potassium in carefully purified triethylcarbinol under nitrogen the main isolable product (41.2%) is quininone. No evidence bearing on the mechanism of this novel reaction has been brought to light. It seems probable that quininone is formed at the expense of either one half or one equivalent of quinine leading in the latter case to a dihydroquinine.[18] Attempts to obtain the reduction product pure and crystalline have failed. In any event it has been demonstrated experimentally that quinine is convertible to quininone in the absence of oxidizing agent by a type of disproportionation reaction that is apparently catalyzed by strong base. It is reasonable to assume that the same disproportionation may be catalyzed by primary and secondary alkoxides although the possibility of observing the formation of quininone directly is excluded by the reducing action of these agents on quininone.

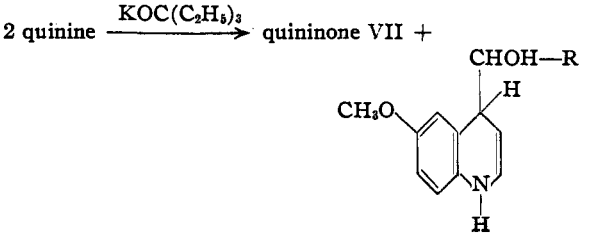
The phenomenon of the induction period is now explainable. In the pure ketone-free solvent, the equilibration may not, in fact, be initiated, but the formation of quininone by the base-catalyzed disproportionation does proceed at a slow rate. Therefore at the beginning of the reaction in ketone-free alcohol quinine is being converted gradually to quininone. Quininone is, however, a carbonyl compound capable of catalyzing the equilibration reaction so that this reaction proceeds at an increasing rate as the concentration of carbonyl compound increases, until finally the reaction is identical to a normal equilibration reaction initiated by carbonyl impurities in the alcohol solvent.

Further support for the oxidation–reduction mechanism is afforded by realization of the expectation that added oxidant should obliterate the in-

(18) Hückel[3] has proposed that the carbonyl compound required by the mechanism is formed by the dehydrogenation of the alcohol and cites as evidence the isolation of decalone in the racemization of decalol (X)



and the formation of hydrogen in the Guerbet reaction. Because the reaction has been observed only at temperatures much higher than those employed in the usual conditions (120–150°) of the equilibration reaction, we do not believe that the large amounts of quininone found here have been formed in this way.



duction period. According to the proposed theory, the rate of quinine disappearance in ketone-free alcohol solvent increases, finally reaching a maximum, because of the introduction by the disproportionation side-reaction of carbonyl compound in the form of quininone. If carbonyl compound is added at the beginning, no induction period should be observed for the equilibration may be initiated at once.

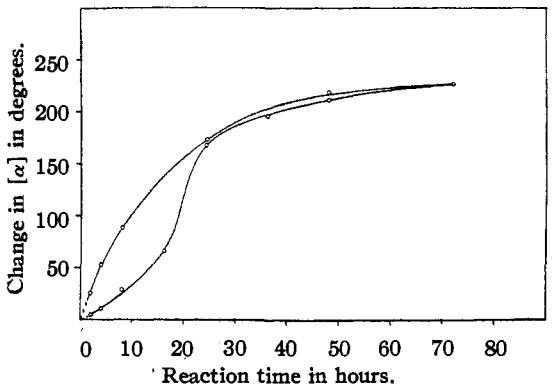


Fig. 2.—Curve 1 (upper) shows the relation of change in $(\alpha)_D$ with time when quinine is boiled with sodium butoxide in carefully purified butyl alcohol under nitrogen. Curve 2 (lower) shows the result of a similar experiment in which one-tenth of an equivalent (of the quinine used) of benzophenone has been added.

Figure 2 shows the results of two experiments: the one in which quinine is treated with sodium butoxide in *n*-butyl alcohol in the absence of carbonyl compound shows the induction period; the other in which one-tenth of an equivalent of benzophenone is added shows no trace of induction period. The fact that the rate of equilibration with oxidant added is at a maximum at the beginning of the experiment demonstrates in a striking fashion the obliteration of the induction period by adding a small amount of oxidant and affords strong support for the mechanism of the equilibration.

The reduction of quininone by alcoholates having been established, the effect of structural variation in the alcohol on the stereochemical course of the reduction has been investigated. The accuracy of the data on the composition of the reduction products of quininone is not high, the very conditions of reduction being those which effect equilibration. Accordingly the figures given in Table II represent only in a very approximate fashion the composition of the reduction mixture of quininone in the alcohol–alcoholate combination indicated. The period of time reported is close to that at which no more quininone remains and short enough to be minimally affected by equilibration.

In the alcohols investigated the reduction of quininone leads to a preponderance of quinine and quinidine over the two epibases. This result contrasts the equilibration experiments in which

TABLE II

Alcohol	Temp., °C.	Time, hours	Quinine, %	Quinidine, %	Epibases, %
Propanol-2	80	48	15.5	36	[a]
Propanol-2[b]	80	26	10.5	10.9	8.5
Diisopropylcarbinol	110	48	12.5	2.1[c]	[a]
Pentanol-3	117	4	51	18.8	[a]
Butanol-1	117	3	34.6	16.4	8.9
Cyclohexanol	160	1/4	26	16	3.9

[a] Undetermined. [b] Aluminum isopropoxide as catalyst. [c] Considerable quininone remained.

the epibases are highly favored over quinine and quinidine at equilibrium. The ratio of quinine to quinidine formed in the reduction varies markedly and advantageously from one reducing alcohol to the next. Thus pentanol-3 is the solvent of choice for the reduction of quininone to quinine, the ratio of quinine to quinidine being two and a half. On the other hand for the preparation of quinidine from quininone, isopropyl alcohol is indicated for the ratio is seven to three in favor of quinidine. The preparative implications of these results are obvious.[8]

The final problem remaining in connection with the oxidation–reduction mechanism of the equilibration reaction is the explanation of the phenomenon of the maximum in the yield of quinidine. The origin of the epibases requires comment in this connection. The very reasonable hypothesis that they are formed in the reduction of quininone along with quinine and quinidine, is supported by the results of three experiments.

Three hours of boiling in *n*-butanol is required to effect substantially complete reduction of quininone to a mixture containing 8.9% of the epibases. Boiling quinine for eight hours under the same conditions leads to 10.8% epibases. Were the epibases in the reduction of quininone being formed from quinine by an extraneous reaction also occurring in the equilibration, much less than 8.9% would have been formed since in the eight hour reaction starting with pure quinine only 10.8% epibases is formed. One concludes that the epibases are formed directly in the reduction.

The results of an experiment in which a similar reduction of quininone is carried out lead to the same conclusion. The reduction of quininone by aluminum isopropoxide in isopropyl alcohol proceeds slowly, giving a poor yield of epibases (see Table II). Since no equilibration of quinine may be effected by aluminum alkoxide catalyst, it is clear that the formation of epibases could only have arisen during the reduction of quininone, not as the result of a side reaction of the quinine or quinidine once formed.[19]

(19) The inability to equilibrate quinine with aluminum alkoxide is understandable, since the first step of the reaction, the oxidation of quinine to quininone, cannot be carried out.[8] Since the complete reversibility of the aluminum (primary and secondary) alkoxide catalyzed oxidation–reduction system has been established in many cases,[17] it is surprising to find the Oppenauer oxidation of quinine to quininone impossible of realization, while the Meerwein–Ponndorf reduction proceeds, although poorly. We have no suggestion to explain the anomaly [*cf.* reference (8)].

Finally attention may be recalled to the experiment in which quinine is treated with the potassium salt of triethylcarbinol, a solvent in which the oxidation–reduction mechanism of equilibration may not operate. Since no epibases are formed, the possibility of converting quinine to the epibases by a purely base-catalyzed reaction is excluded. Therefore with a high degree of probability, the epibases arise only by the reduction of quininone, no matter whether the reduction is being carried out explicitly, or implicitly as part of the oxidation–reduction mechanism of the equilibration.

Further information required to elucidate the origin of the maximum in the yield of quinidine concerns the relative rates of oxidation of the four stereoisomeric alkaloids. We have no precise quantitative data on the subject but the rough data available is sufficient. Both quinine and quinidine are oxidized in quantitative yield by benzophenone in benzene containing potassium *t*-butylate.[8] Treated under the same conditions, the epibases are recovered substantially unchanged, even though the reaction time is quadrupled. One may freely conclude that the pair quinine–quinidine is oxidized very much faster than the pair epiquinine–epiquinidine.

The above experiment gives the erroneous indication that quinine and quinidine differ qualitatively rather than quantitatively from the epibases with respect to ease of oxidation. If the oxidizing agent used is fluorenone, found by Adkins[17] to oxidize about one hundred fold faster than benzophenone despite a lower oxidation potential, the epibases may be oxidized with ease. Thus pure epiquinidine is oxidized to quininone in 79% yield by boiling with fluorenone in a benzene solution of potassium butylate. The practical significance of this observation lies in the possibility of transforming the large quantity of epibases present in quinoidine[7] to either quinine or quinidine by way of quininone.

The maximum in the yield of quinidine occurs in the following way. The quininone formed in the first step in the equilibration is reduced to a mixture consisting predominantly of quinine and quinidine together with a small amount of the epibases. Therefore the concentration of quinidine increases faster than that of the epibases. Superimposed on this simple picture is the complication that quinidine and the epibases once formed are subject to the same oxidizing conditions as is the starting quinine. Accordingly quinidine and the epibases are reoxidized, but at quite different rates; quinidine is oxidized rapidly to quininone, while the epibases remain substantially unchanged. Consequently the concentration of the epibases gradually increases as quinine and quinidine are preferentially reoxidized to quininone and partially reconverted by reduction to the more slowly oxidized epibases. The concentration of quinidine therefore reaches a maximum concentration considerably higher than the equilibrium concentration, the variation of composition of the equilibration mixture with time being determined by two factors: first, the reduction of quininone favoring quinine and quinidine, and, second, the relative rates of oxidation of the four stereoisomers. It is this last factor which determines the position of the final equilibrium and favors a high concentration of the epibases.

The phenomenon is similar to that observed in many competitive reactions. A clear example has been studied by Kohler.[19a] A mixture of one equivalent of cinnamaldehyde and one equivalent of sodium bisulfite reacts rapidly to give a quantitative yield of cinnamaldehyde bisulfite addition product but on long standing is converted to β-phenyl-β-sulfopropionaldehyde.

On the basis of the oxidation–reduction mechanism of the equilibration, one would expect the addition of oxidant (ketone) to the alcoholic sodium alkoxide solution to have no effect on the maximum yield of quinidine. To a first approximation only the rate of attaining the point of maximum quinidine yield would be accelerated. More subtle consideration leads to the anticipation of a somewhat higher position of the maximum. It has been established that there are two ways by which quinine may be converted to quininone, reduction of which initiates equilibration. The first of these is the base-catalyzed oxidation in which another molecule of quinine serves as hydrogen acceptor, probably being irreversibly reduced, and thereby destroyed in so far as contributing to the final yield as a stereoisomeric alkaloid is concerned. This undesirable participation of quinine as hydrogen acceptor may be prevented by encouraging the second method of quininone formation in which an extraneous ketone acts as hydrogen acceptor. By this means added ketonic oxidant would be expected to improve the over-all yield of stereoisomers in general and of quinidine in particular. A series of experiments in heptanol-2 exhibits improvement in yield upon adding oxidant. Boiled for one hour with 0.1, 4.7 and 18.75 equivalents of benzophenone in a solution of sodium heptylate in heptanol-2, quinine is converted to quinidine in yields of 19.5, 22.0 and 27.4%, respectively. When treated in the same way with 10.0 equivalents of the rapid oxidizing agent fluorenone in place of benzophenone, 29.2% yield of quinidine is obtained.

An interesting difference in rate of reaction is observed when sodium is compared with lithium. The half-life of quinine when boiled with sodium heptylate in heptanol-2 containing 4.7 equivalents of benzophenone is 0.7 hour. On replacing the sodium by lithium heptylate, the half-life increases to 3.0 hours. Since the equilibration requires the catalytic action of strong bases, the decreased rate in the presence of lithium ion may be ascribed to

(19a) Kohler, *Am. Chem. J.*, **38**, 523 (1907).

the greater acidity of Li^+ in comparison with the more metallic Na^+.[20]

Substantiation of the mechanism of the equilibration has made it possible to carry out the partial racemization under conditions which confirm in a clear, explicit manner the nature of the reaction. In the inert solvent, toluene, quinine is stable to boiling with sodium butylate under nitrogen for eighteen hours. There was recovered 82.8% of the unchanged quinine, along with a small amount (1.7%) of quininone. The disproportionation occurs, but at a slow rate. When there is added to the system 0.1 equivalent of the oxidant fluorenone in order to establish the necessary oxidation–reduc ion system (quinine as the secondary alcohol and fluorenone as the ketone) equilibration occurs leading to 28% yield of quinidine at the maximum, an amount which is 2.8 times the equivalent of oxidant added. At the four and eighteen hour points (*cf.* experiment with no oxidant added) the yields of quinine and quinidine are 71 and 4.2% and 52 and 14.5%, respectively. When the concentration of the oxidation–reduction system is increased by using 0.2 equivalent of fluorenone and 0.5 equivalent of fluorenol in the boiling toluene solution of quinine and sodium *t*-butylate, the rate of the equilibration is increased markedly. After four hours the reaction mixture consists of 40% quinine and 20% quinidine, a marked increase over the four hour point of the previous experiment. After eighteen hours equilibrium is substantially attained, at which point only traces of quinine and quinidine can be isolated while a 61% yield of the epibases is obtained.

While the experiments in toluene do not prove that the racemizations carried out in alcoholic solution require carbonyl compounds, either added, present as impurities, or formed by the air oxidation of the solvent, the results possibly suggest that the formation of carbonyl compounds by dehydrogenation[18] may not be of primary importance in reactions carried out at temperatures below about 150°. This problem of the initial formation of requisite carbonyl compounds, investigation of which is continuing, is important because the two theories of the initiation lead to the prediction of different sets of optimum conditions for the racemization. Hückel, *et al.*, for example, have failed to effect the epimerization of the fenchyl alcohols by using conditions which should accelerate dehydrogenation[21] (sodium metal in boiling decahydronaphthalene). It is probable that the reaction failed not for want of the formation of fenchone, but rather because of the sluggish nature of the fenchone–fenchyl alcohol system. We encountered a similar failure in an attempt to racemize quinine in benzene containing potassium *t*-butylate and 0.1 equivalent of quininone. On the basis of the present work one would attempt explicitly to establish a rapidly reacting oxidation–reduction system in order to obtain racemization in difficult cases.

(20) Pauling, "The Nature of the Chemical Bond," 2nd ed., Cornell University Press, Ithaca, N. Y., 1944, pp. 58–65.

(21) Hückel, Kindler and Wolowski, *Ber.*, **77B**, 220 (1944).

Experimental

General Procedure for Partial Racemization.—Quinine (10 g.) was boiled gently under reflux in a solution prepared by dissolving three equivalents of alkali metal in 175 cc. of alcohol. The alcohols were purified by boiling under reflux with zinc dust and 50% potassium hydroxide for half an hour and subsequently distilling.[10] The distilled alcohol was then boiled under reflux with sodium under nitrogen and distilled in an atmosphere of nitrogen. In certain experiments quinine was added to a solution of the alkali alkoxide in alcohol containing a definite amount of an oxidant (benzophenone, fluorenone, etc.). All operations were carried out under nitrogen in a wholly glass apparatus specially designed to permit the withdrawal of aliquot portions without opening the system to air or interrupting the heating. At definite intervals, aliquot portions were removed, rapidly cooled, diluted with an equal volume of ether and extracted with successive portions of 20% sulfuric acid solution. The combined acid layers were washed with small portions of ether to remove any alcohol. The acid solution was then made alkaline with 20% sodium hydroxide solution and exhaustively extracted with ether. The combined ether layers were washed with several portions of saturated salt solution to remove traces of alkali, dried over anhydrous magnesium sulfate and evaporated. To remove the last traces of solvent, it was necessary to heat the residue on a steam-bath under reduced pressure. Depending on the extent of racemization, the residue of alkaloids varied in appearance from a colorless or pale yellow flaky solid to an amber, highly viscous glass.

The rate of partial racemization was followed polarimetrically using solutions of the product in absolute ethanol (1.5–2 g. of base in 100 cc.).

Analysis of Reaction Product: Quinine Tartrate $(C_{20}H_{24}O_2N_2)_2 \cdot C_4H_4O_6 \cdot 2H_2O$.—The crude mixture of bases was dissolved in hot 95% ethanol (1 g. in 1.6 cc.) and treated with a hot solution of *d*-tartaric acid (0.232 g. per g. of base). Colorless needles of quinine tartrate crystallized overnight and were filtered, washed with a little cold 95% ethanol and air dried. In general the crude salts melted at 193–202° with decomposition although samples were isolated which melted at 185–195° with decomposition.

Recrystallization from hot 95% ethanol gave a sample of quinine tartrate which melted at 198–206° with decomposition.

Quinidine Acid Tartrate $C_{20}H_{24}O_2N_2 \cdot C_4H_4O_6 \cdot 3H_2O$.—To the alcoholic filtrate remaining after removal of quinine tartrate was added a hot solution of *d*-tartaric acid (0.232 g. per g. of remaining free base) in 95% ethanol. The ethanol was blown off on a steam-bath and the last traces removed under reduced pressure. The light brown frothy residue was dissolved in hot water (4 cc. per g. of residue). On standing overnight in the cold, the solution deposited colorless needles of the quinidine acid tartrate.

The crystals were filtered, washed with a small amount of cold water and air dried. The crude salt melted at 110–125° with decomposition.

A sample recrystallized from hot water melted at 124–131° with decomposition.

Pure quinidine was obtained from a recrystallized sample of the acid tartrate by regeneration with 20% sodium hydroxide and ether extraction. Recrystallized from either alcohol or ether, quinidine was obtained, m. p. 167–168°, $[\alpha]_D$ +254° (in ethanol).

Epiquinine and Epiquinidine Dihydrochlorides $[(C_{20}H_{24}O_2N_2) \cdot 2HCl]_2$.—The residual alkaloids were recovered from the tartaric acid filtrate by regeneration with 20% sodium hydroxide and ether extraction. The solvent-free bases were dissolved in absolute ethanol (1.4 g. in 1 cc. of ethanol) and the solution was adjusted to *p*H 2 with dry hydrogen chloride. On scratching and standing in the

cold for several days, the solution gave the mixed crystalline dihydrochloride, m. p. 190–195° with decomposition.[22]

Epiquinine and Epiquinidine Neutral Dibenzoyl-*d*-tartrate $(C_{20}H_{24}O_2N_2)_2 \cdot C_{18}H_{14}O_8$.—As an analytical method of estimating the epibases, Rabe's dibenzoyl-*d*-tartrate method[5a] was found to be more satisfactory than the dihydrochloride procedure given above. To a mixture of the solvent-free mixed bases in warm acetone (1 g. in 8.7 cc. of acetone) a warm solution of dibenzoyl-*d*-tartaric acid (0.58 g. per g. of base) in an equal volume of acetone was added. On standing two days in the cold, the solution deposited the mixture of the neutral dibenzoyl-*d*-tartrates as colorless crystals.

The mixed dibenzoyl-*d*-tartrates may be separated by refluxing the mixed salts with acetone (1 g. in 10 cc.) for one hour and filtering hot. The undissolved epiquinine neutral dibenzoyl-*d*-tartrate is filtered and air dried, m. p. 157–159°. From the acetone filtrate on concentration, the epiquinidine dibenzoyl-*d*-tartrate may be isolated.

Epiquinidine Monothiocyanate $C_{20}H_{24}O_2N_2 \cdot HSCN$.—Epiquinidine was separated from its mixed salts using a modification of a procedure due to Rabe.[5b] The mixture of solvent-free epibases was obtained from either the mixed dihydrochlorides or the dibenzoyl-*d*-tartrates by regeneration with 20% sodium hydroxide solution and ether extraction. The mixture of epibases was dissolved in hot absolute ethanol (1 g. of base in 7 cc.) and treated with a hot solution of ammonium thiocyanate (0.236 g. per g. of base) in absolute ethanol (10 cc. per g. of ammonium salt). The solution was concentrated to one fourth of its original weight. On seeding and standing in the cold for two days, the solution deposited colorless crystals of epiquinidine monothiocyanate, m. p. 188°.

Epiquinidine was obtained by suspending the monothiocyanate in a little water and adding sufficient 20% sulfuric acid to effect solution. The free base was liberated with 20% sodium hydroxide and extracted with ether. From the dried, concentrated ether extract, epiquinidine slowly crystallized. Further concentration of the mother liquor yielded additional crops of the free base, m. p. 112–113°.

Epiquinine Dibenzoyl-*d*-tartrate $(C_{20}H_{24}O_2N_2)_2 \cdot C_{18}H_{14}O_8$.—The solvent-free residue obtained by regeneration from the thiocyanate filtrate was converted to the neutral dibenzoyl-*d*-tartrate according to the procedure previously described. There crystallized epiquinine dibenzoyl-*d*-tartrate, m. p. 157–159°.

Partial Racemization of Quinine: A. Isoamyl Alcohol.—The results of the partial racemization in purified isoamyl alcohol (700 cc., b. p. 127–129°) containing 42.0 g. of quinine and 8.6 g. of sodium in a nitrogen atmosphere are shown in Table III and Fig. 1.

TABLE III

Time, hours	Crude base, rec. g.	$[\alpha]^{25}D$	Quinine, %	Quinidine, %
2	5.17	−149.1	90.7	..
4	5.25	−126.5	82.9	..
8	5.26	− 52.2	58.1	12.0
16	5.27	+ 20.2	33.5	18.3
24	5.20	+ 44.0	23.2	14.7
32	5.07	+ 57.1	13.1	15.3
40	2.50	+ 58.8	8.9	13.3
52	6.55	+ 62.3	6.9	11.1

B. *n*-Amyl Alcohol.—The results of applying the general procedure described above to quinine (20.0 g.) in a purified *n*-amyl alcoholic solution (350 cc., b. p. 135–136°) are given in Table IV.

C. *n*-Hexyl Alcohol.—Table I shows the course of the partial racemization of quinine (35.0 g.) in purified *n*-hexyl alcohol (600 cc., b. p. 155–156) containing sodium (7.2 g.). The general procedure was followed.

TABLE IV

Time, hrs.	Crude base, rec. g.	$[\alpha]^{25}D$	Quinine, %	Quinidine, %
8	2.59	− 5.2	42.0	15.6
20	2.32	+51.3	12.5	13.4
40	2.43	+67.1	5.9	5.9
48	12.02	+70.0	4.6	8.8

D. Pentanol-3.—A solution of 6.3 g. of sodium in 300 cc. of commercial purified pentanol-3, b. p. 113–117°, was prepared in a nitrogen atmosphere. Slightly below the boiling point, 30 g. of quinine in 225 cc. of hot pentanol-3 was added protected by a stream of nitrogen. The usual procedure was followed from this point, the results being indicated in Table V.

TABLE V

Time, hrs.	Crude base, rec. g.	Quinine, %	Quinidine, %	Epibases,[a] %
8	10.0	50.1	18.4	9.3
16	9.8	34.6	20.9	9.4
29	9.9	24.6	19.0	...

[a] Obtained as dihydrochlorides.

E. *n*-Butanol.—Table VI shows the results of applying the usual procedure to quinine (33.0 g.) and sodium (6.72 g.) in purified *n*-butanol (320 cc., b. p. 115–116°) in an atmosphere of nitrogen.

TABLE VI[a]

Time, hr.	Crude base, rec. g.	$[\alpha]^{25}D$	Quinine, %	Quinidine, %	Epibases mixed, %	Epiquinidine,[b] %	Epiquinine,[c] %
2	1.08	−153.4	90.7	..	..	...	..
4	1.07	−147.0	83.2	..	..	...	..
8	2.50	−127.8	88.0	5.2	..	...	..
16	2.61	− 92.2	75.9	7.7	5.7	...	..
24	2.23	+ 11.2	37.7	16.6	20.2	6.7	9.0
36	2.12	+ 37.8	22.6	16.5	28.8	5.7	18.9
48	2.29	+ 53.0	14.8	12.6	24.7	6.7	..
72	17.17	+ 68.0	12.8	11.4	28.7	8.4	15.1

[a] *Cf.* Fig. 2. [b] Epiquinidine was isolated as the monothiocyanate. [c] Epiquinine was isolated as the neutral dibenzoyl-*d*-tartrate.

Partial Racemization of Quinine with Added Oxidant: A. *n*-Butanol.—The general procedure used above was applied to 15 g. of quinine in 175 cc. of carefully purified *n*-butanol containing 3.15 g. of sodium and 0.84 g. of benzophenone (0.10 equiv.). Great care was used to prevent air from coming in contact at any stage. The results of the experiment are indicated in Table VII and Fig. 2.

TABLE VII

Time, hr.	Crude base, rec. g.	$[\alpha]^{25}D$	Quinine, %	Quinidine, %	Epibases, %	Epiquinidine, %	Epiquinine %
2	0.93	−131.6	85.0	4.6	..	...	..
4	0.96	−106.0	78.1	6.4	..	...	..
8	2.14	− 69.6	65.0	12.2	10.8	1.4	7.0
16	9.75	− 28.7	45.2	14.8	20.1	7.3	9.5
24.5	2.42	+ 15.1	30.6	16.5	24.4	5.4	16.2
48	1.73	+ 59.7	12.7	12.7	30.1	6.4	13.3
72	5.93	+ 68.0	4.2	5.7	20.7	3.9	10.0

B. Pentanol-3.—The results of experiment in pentanol-3 are contained in Table VIII.

(22) After removal of the mixed dihydrochlorides, the residue obtained from filtrate by regeneration with alkali and ether extraction gave an additional quantity of the epibases as the dibenzoyl-*d*-tartrates.

TABLE VIII

Time, hr.	Crude base, rec. g.	$[\alpha]^{25}D$	Quinine, %	Quinidine, %	Epibases, %
	1. 0.05 equiv. benzophenone[a]				
16	19.53	−42.3	57.6	15.4	8.3[d]
	2. 1.00 equiv. pentanone-3[b]				
8	6.67	....	52.2	16.2	6.0[d]
16	6.60	....	37.7	23.3	13.3[d]
24	6.33	....	32.8	22.1	15.5[d]
	3. 2.00 equiv. pentanone-3[c]				
24	49.87	....	39.2	19.6	17.7

[a] Twenty g. of quinine, 2.84 g. of sodium, 0.54 g. of benzophenone in 200 cc. of pentanol-3. [b] Twenty g. of quinine, 3.98 g. of sodium, 5.52 g. of pentanone-3 in 300 cc. of pentanol-3. [c] Fifty g. of quinine, 10.67 g. of sodium, 26.6 g. of pentanone-3 in 500 cc. of pentanol-3. [d] Isolated as dihydrochloride.

C. **Heptanol-2.**—The results of equilibrations in purified heptanol-2, b. p. 156–157° (Carbide and Carbon) with different amounts of added oxidant are contained in Table IX.

TABLE IX

Time, hr.	Crude base, rec. g.	$[\alpha]^{25}D$	Quinine, %	Quinidine, %	Epibases %
	1. 0.1 equiv. benzophenone[a]				
1	18.95	+46.0	21.2	19.4	22.5[b]
	2. 4.7 equiv. benzophenone[b]				
0.25	8.88	−80.5	69.6	8.5	..
.50	9.18	−48.9	58.1	13.7	..
.75	9.09	0.0	44.3	20.2	..
1.25	9.26	+34.1	33.3	23.7	..
2.00	8.64	+48.5	23.3	24.3	..
4.00	10.75	+57.6	14.7	16.7	..
	3. 18.75 equiv. benzophenone[c]				
1.00	4.83	....	27.4	27.4	19.8[b]
	4. 10.0 equiv. fluorenone[d]				
1.00	5.00	....	39.2	29.2	..
	5. 4.7 equiv. benzophenone (lithium)[e]				
0.75	4.81	....	81.5	6.0	..
1.25	4.91	....	77.6	9.6	..
2.00	4.93	....	63.5	11.2	..
4.00	3.81	....	38.5	16.3	..

[a] Twenty g. of quinine, 3.10 g. of sodium, 1.13 g. of benzophenone in 350 cc. of heptanol-2. [b] Two runs of 40.0 g. of quinine, 6.2 g. of sodium, 105 g. of benzophenone in 700 cc. of heptanol-2. [c] Five g. of quinine, 1.1 g. of sodium, 52.5 g. of benzophenone in 175 cc. of heptanol-2. [d] Five g. of quinine, 1.1 g. of sodium, 27.7 g. of fluorenone in 90 cc. of heptanol-2. [e] Twenty g. of quinine, 1.28 g. of lithium, 52.5 g. of benzophenone in 300 cc. of heptanol-2. [f] Isolated as the dihydrochlorides.

D. **Toluene.**—The equilibration was carried out in the inert solvent, toluene, at the boiling point under the oxidative–reductive conditions as summarized in Table X.

Oxidation of Quinine in Triethylcarbinol.—Triethylcarbinol was prepared from ethylmagnesium bromide (large excess) and diethyl carbonate.[23] The fraction collected at 143.0°, $n^{25}D$ 1.4272, was employed in the following experiment. To a hot solution prepared by dissolving 3.61 g. (0.092 mole) of clean potassium metal in 100 cc. of triethylcarbinol under nitrogen, 10 g. (0.0381 mole) of quinine in 60 cc. of warm triethylcarbinol was introduced in a current of nitrogen. The mixture was rapidly brought to gentle boiling. On introduction of the quinine, the colorless alcoholic solution of the alkoxide immediately became yellow, then reddish orange, and in less than ten minutes, a deep red. After boiling for forty-five minutes, the mixture was rapidly cooled in ice and water under nitrogen, diluted with an equal volume of ether, and extracted with one 50-cc. and three 25-cc. portions of ether. The combined acid layers were washed with small portions of ether to remove alcohol and the free bases liberated by dropping the aqueous solution into a mixture of 150 cc. of 20% sodium hydroxide solution and 100 g. of crushed ice. The brown oil was extracted with one 50-cc. and three 25-cc. portions of ether. The ether solution was washed with small portions of a saturated sodium chloride solution to remove alkali, dried over anhydrous sodium sulfate and evaporated. Removal of the last traces of solvent gave 8.76 g. of a viscous brown oil.

TABLE X

Time, hr.	Crude base, rec. g.	Quinine, %	Quinidine, %	Quininone, %	Epibases, %
	1. Blank determination[a]				
18	9.24	82.8	0.0	1.7	0.0
	2. 0.1 equiv. fluorenone[b]				
4	4.39	71.0	4.2	..	...
18	4.25	52.0	14.5	..	...
42	4.40	19.1	28.0	..	...
68	5.67	4.9	4.1	..	...
3.	0.2 equiv. fluorenone; 0.5 equiv. fluorenol.[c]				
4	9.83	40.1	19.9	4.76	5.3[d]
18	9.70	0.0	0.6	0.0	60.6[e]

[a] Ten g. of quinine, 2.96 g. of sodium *t*-butoxide in 150 cc. of toluene under nitrogen. [b] Twenty g. of quinine, 5.92 g. of sodium *t*-butoxide, 1.12 g. of fluorenone in 300 cc. of toluene. [c] Twenty g. of quinine, 5.92 g. of sodium *t*-butoxide, 2.28 g. of fluorenone, 5.70 g. of fluorenol in 300 cc. of toluene under nitrogen. [d] Isolated as mixed dihydrochlorides. [e] 47.5% isolated as the dihydrochlorides and 13.1% obtained as the dibenzoyl-*d*-tartrates from dihydrochlorides mother liquor.

The recovered alkaloid was taken up in 14.0 cc. of hot 95% ethanol and treated with a solution of 2.03 g. of *d*-tartaric acid in 14.0 cc. of hot 95% ethanol. On standing in the cold, 1.00 g. of a pale yellow crystalline solid was obtained melting at 170° with decomposition and consisting of a mixture of quininone acid tartrate and quinine neutral tartrate. After three recrystallizations from 95% alcohol the melting point was raised to 198–201°. The white crystalline solid did not depress the melting point of an authentic sample of quinine neutral tartrate.

To the tartaric acid filtrate was added a solution of 1.86 g. of *d*-tartaric acid in 10 cc. of 95% ethanol. On seeding and standing at room temperature, quininone acid tartrate, 6.14 g. (41.19%), crystallized; m. p. 193–195°. After recrystallization from 50% ethanol, m. p. 198–201°.

Quininone was obtained from the acid tartrate with 20% sodium hydroxide solution and ether extraction. Recrystallized from 75% ethanol and dried over sulfuric acid, the free base melted at 95–98°, mixed melting point with an authentic sample, 92–99°. Initial $[\alpha]^{25}D$ +119.5° (0.1088 g. in 100 cc. absolute ethanol). Final (after sixteen hours) $[\alpha]^{25}D$ +73.5°.

Reduction of Quininone and Analysis of Products.—Following the general procedure for partial racemization, quininone[8] was gently refluxed in a solution of sodium alkoxide (3 moles of sodium per mole of quininone) in the corresponding alcohol. The reaction mixture which initially showed the characteristic cherry red color of basic

(23) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, N. Y., 1943, p. 602.

solutions of quininone in organic solvents became perceptibly lighter as the reduction proceeded. At definite intervals, aliquot portions were removed and analyzed according to the general procedure. Before proceeding to the separation of the epibases, the solvent-free residual bases obtained on regeneration from the quinidine acid tartrate filtrate were dissolved in absolute ethanol (1 g. in 1 cc.). On seeding and standing in the cold for one or two days, any unreduced quininone crystallized; air dried, m. p. 99–101°. A mixed melting point with an authentic sample of quininone showed no depression.

The alcoholic filtrate was then treated by the usual procedure to isolate the mixed dihydrochlorides of the epibases.

A. Butanol-1.—Quininone (18 g.) and sodium (4 g.) in *n*-butyl alcohol purified according to general procedure (270 cc., b. p. 115–116°) were boiled under reflux in nitrogen leading to results tabulated in Table XI.

TABLE XI

Time, hours	Crude base, rec. g.	Quinine, %	Quinidine, %	Quininone, %	Epibases,[a] %
1/2	1.68	9.8	5.4	26	..
1 1/2	1.62	20.2	8.5	2.1	4.1
3	1.77	34.6	16.4	..	8.9
6	1.82	33.1	17.9	..	23.6
9	1.72	21.4	29.7	..	27.8
12	1.80	22.5	21.6	..	28.0
18	1.85	21.6	18.8	..	30.5
24	1.91	9.3	20.0	..	32.0
48	1.78	4.6	9.4	..	28.0

[a] Isolated as the dihydrochlorides.

B. Propanol-2.—Quininone (15 g.) and sodium (3.2 g.) in isopropyl alcohol dried with aluminum isopropoxide and distilled (225 cc., b. p. 80–81°) were boiled under nitrogen.

TABLE XII[a]

Time, hours	Crude base, rec. g.	Quinine, %	Quinidine, %
1	0.98	1.8	0.8
4	2.12	1.8	2.2
9	2.47	6.4	14.0
24	2.40	14.5	22.0
48	2.42	15.5	36.0

[a] Experiment by J. D. Chanley.

A mixture of 2 g. of quininone, 8 g. (20 equivs.) of aluminum isopropoxide and 120 cc. of dry isopropyl alcohol was boiled under nitrogen for twenty-six hours. A portion of the solvent (*ca.* 40 cc.) was distilled off very slowly until the distillate no longer gave a precipitate with 2,4-dinitrophenylhydrazine.

The residue in the flask was immediately poured into ice and 20% sulfuric acid solution. The isopropyl alcohol was distilled off and the aqueous acid solution of the crude bases was analyzed by the usual procedure. From 1.61 g. of crude base there was obtained quinine in 10.5%, quinidine in 10.9% and epibases in 8.5% of the theoretical yield.

C. Diisopropylcarbinol.—Quininone (10 g.) was added to a solution of 2.2 g. of sodium in 150 cc. of di-isopropylcarbinol. The reaction mixture was heated in a constant temperature apparatus employing toluene vapors (b. p. 110–111°).

Analysis of the first three aliquot portions gave no quinine neutral tartrate. The alkaloid of each sample was converted to the acid tartrate in order to precipitate quinidine. After two days none appeared. After a week, a light yellow crystalline precipitate was obtained from each portion. The crystals of quininone acid tartrate were filtered, washed with a little cold water and dried, m. p. 197–199° with decomposition.

Recrystallization from hot 50% ethanol gave faintly yellow crystals, m. p. 198–201° with decomposition.

Anal. Calcd. for $C_{20}H_{22}O_2N_2 \cdot C_4H_6O_6$: C, 61.04; H, 5.97. Found: C, 61.37; H, 5.77.

A mixed melting point with a sample of quininone acid tartrate prepared from an authentic sample of quininone showed no depression.

The results of the experiment are shown in Table XIII.

TABLE XIII

Time, hours	Crude base, rec. g.	Quinine, %	Quinidine, %	Quininone,[a,b] %
1	1.75	..	...	67.0
4	1.80	..	...	52.4
9	1.75	..	...	41.5
24	1.50	2.3	2.3	..
48	0.60	12.5	2.1	..

[a] Isolated as quininone acid tartrate. [b] From no portion were epibases isolable.

D. Pentanol-3.—The reduction of 5.0 g. of quininone was effected by boiling in a solution of 1.1 g. of sodium in 95 cc. of purified pentanol-3, b. p. 115–117°. After four hours there was removed an aliquot portion containing 2.23 g. of crude base which give quinine in 51% and quinidine in 18.8% of the theoretical amount. The crude base (2.32 g.) remaining after eight hours gave quinine in 34%, quinidine in 37.0% and the epibases in 12.2% of the theoretical amount.

E. Cyclohexanol.—The reduction was investigated by boiling 5.0 g. of quininone in 75 cc. of purified cyclohexanol, b. p. 159–160°, containing 1.1 g. of sodium in a nitrogen atmosphere. After fifteen minutes, quinine (26%), quinidine (16%) and epibases (3.9%) were isolated from the reaction mixture. At the end of an hour the yields were 5.5, 10.0 and 13.0%, respectively.

Oxidation of Epiquinidine to Quininone.—To 2.60 g. (0.023 mole) of dry potassium *t*-butylate was added a solution of 3 g. (0.009 mole) of epiquinidine and 4.99 g. (0.028 mole) of fluorenone in 90 cc. of dry benzene. The mixture was boiled gently under reflux for forty-eight hours. The reaction mixture was cooled to about 5° and poured with stirring into a mixture of 30 g. of crushed ice and 30 cc. of 12% hydrochloric acid. The combined acid layers were washed with three 15-cc. portions of ether and made alkaline with cold, 20% sodium hydroxide solution. The liberated oil was extracted with three 15-cc. portions of ether. The combined ether layers were washed with two 15-cc. portions of ice-cold water, dried over anhydrous sodium sulfate and concentrated to about 10 cc. On cooling and seeding, 2.73 g. (79.0%) of almost pure quininone, m. p. 96–104°, was obtained in three successive crops.

In an attempted oxidation of a mixture of epibases obtained from the mixed dihydrochlorides using benzophenone as the oxidant, no quininone could be isolated and the epibases were recovered in substantial yield (experiment by J. D. Chanley).

Use of Buffer Extraction in Alkaloidal Residues.—The residual bases (12.15 g.), obtained after the separation of quinine and quinidine from a racemized sample, were dissolved in ether. This ethereal solution was then fractionally extracted with several portions of a phosphate buffer, *p*H 6.74 (equal amounts of *M*/10 sodium dibasic

TABLE XIV

Fraction	Buffer used	$[\alpha]D$	Crude bases	Quinine, %	Quinidine, %
1st	600 cc.	+69	6.09	None	
2nd	500 cc.	+70	2.20	isolated	
3rd	500 cc.	+56	1.98	1.0[a]	1.1[a]
4th	10% H_2SO_4	...[b]	0.09	...	...

[a] Based on 20 g. of quinine originally used in racemization. [b] Solution was too dark for observation.

phosphate and of $M/10$ sodium monobasic phosphate solutions) and finally with 10% sulfuric acid. Each individual acid extract was worked up according to the general procedure and analyzed for quinine and quinidine.

The method offered no significant improvement over the usual method of isolation.

Summary

The mechanism of the partial racemization of quinine to a mixture of quinine, epiquinine, quinidine and epiquinidine involves two steps: the alkoxide catalyzed oxidation of quinine to quininone by a ketone followed by the alkoxide catalyzed reduction of quininone to the stereoisomeric mixture by a primary or secondary alcohol. The dependence of the proportion of isomers in the reduction mixture on the nature of the alkoxide ion employed was investigated. It was found that sodium isopropoxide converted quininone to quinidine in good yield while sodium pentylate-3 reduced quininone predominantly to quinine. There was discovered the disproportionation of quinine to quininone in potassium *t*-alkoxides and the oxidation of the epibases to quininone by sodium *t*-butoxide and fluorenone.

A new and probably general method for the racemization or epimerization of secondary alcohols was developed: quinine was partially racemized in toluene by treating with sodium *t*-butoxide and an oxidation–reduction system such as fluorenone–fluorenol.

NEW YORK 27, N. Y. RECEIVED OCTOBER 24, 1946

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Alkyl Thiolsulfinates

BY LAVERNE D. SMALL, JOHN HAYS BAILEY AND CHESTER J. CAVALLITO

The antibacterial agent isolated from *Allium sativum* has been assigned the probable structure, $CH_2{=}CH{-}CH_2{-}\underset{\underset{O}{|}}{S}{-}S{-}CH_2{-}CH{=}CH_2$.[1]

This compound, allyl 2-propene-1-thiolsulfinate, represented the only known example of a derivative of the hypothetical thiolhyposulfurous acid, $H{-}\underset{\underset{O}{|}}{S}{-}S{-}H$.[2]

There is now described the preparation and properties of a series of synthetic alkyl thiolsulfinates. This new class of compounds of which the antibacterial agent of garlic represents the prototype, has the feature of possessing marked antimicrobial activity. This property is believed to be associated with the marked reactivity of the $-\underset{\underset{O}{|}}{S}{-}S-$ group toward biologically essential sulfhydryl groups.[1,3]

The following method for the preparation of thiolsulfinates proved to be unsatisfactory

$$R{-}MgCl + SOCl_2 \longrightarrow R{-}SO{-}Cl + MgCl_2$$
$$R{-}SO{-}Cl + R'{-}S{-}M \longrightarrow R{-}SO{-}S{-}R' + MCl$$

where M is H or Na. By using ethyl as R and R′ in a variety of solvents at several concentrations and temperatures, yields were obtained of less than 0.3% thiolsulfinate as shown by antibacterial assay.

The alkyl thiolsulfinates were satisfactorily prepared by oxidation of the corresponding disulfides with an organic per-acid in an appropriate solvent. A number of per-acids could be used, including peracetic, perbenzoic, perfuroic, perphthalic and percamphoric; perlauric acid was not as satisfactory. Perbenzoic or peracetic acid was the oxidizing agent of choice in the presently described work.

The solvent for the oxidation was not critical although chloroform was preferred. Ethanol, ether, acetone, acetaldehyde, acetic acid, acetonitrile, or carbon tetrachloride also could be used.

An equimolecular ratio of organic per-acid to disulfide gave the best yields of thiolsulfinate (20% to 65%), the yields decreasing with a deficiency or an excess of per-acid. The oxidation of normal disulfides from methyl through amyl proceeded readily, thirty minutes reaction time at 25° being sufficient for maximum yield. Secondary disulfides proceeded with more difficulty, isopropyl disulfide underwent oxidation more slowly and gave poorer yields than the normal compound. In the oxidation of the secondary isomer, peracetic was better than perbenzoic acid, and ultraviolet light irradiation improved the yield with perbenzoic acid. No measurable yield of thiolsulfinate could be obtained by the presently described procedures, from oxidation of di-tertiary disulfides such as *t*-butyl and *t*-hexyl disulfide. Since normal alkyl disulfides yielded a monoxide and the tertiary did not, it was of interest to extend the series to a mixed type such as *t*-butyl ethyl disulfide. The latter yielded a thiolsulfinate which was assigned the structure $C_2H_5{-}\underset{\underset{O}{|}}{S}{-}S{-}C(CH_3)_3$

in light of the hindrance to oxidation of the sulfur demonstrated by the tertiary group.

(1) Cavallito, Buck and Suter, THIS JOURNAL, **66**, 1950 (1944).

(2) Hinsberg, (*Ber.*, **41**, 2838 (1908)) postulated that a thiolsulfinate was formed by the oxidation of bis-(*p*-acetaminophenyl) disulfide with nitric acid; however later (*ibid.*, **42**, 1278 (1909)) he indicated that the product was an equimolecular mixture of disulfide and disulfoxide. Toennies (THIS JOURNAL, **56**, 2198 (1934)) and Toennies and Lavine (*J. Biol. Chem.*, **113**, 571 (1936)) believed that cystine, upon oxidation to the disulfoxide, went through the monoxide intermediate (thiolsulfinate) which could not be isolated.

(3) Cavallito, *J. Biol. Chem.*, **164**, 29 (1946).