THE ALKALOIDS

Chemistry and Physiology

VOLUME III

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THE ALKALOIDS

Chemistry and Physiology

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PREFACE

Again we take this opportunity to express our thanks for the reception which chemists have accorded our efforts to review for them the chemistry of the alkaloids. We are acutely conscious of the almost unprecedented activity in this field and aware that the volumes as published often and inevitably cannot include the most recent material. We hope to publish a supplement which will take care of such matters, and we invite authors of papers on alkaloids to send us reprints of all material which has not been included in the printed volumes.

The continued efforts and cooperation of the contributors to this series are gratefully acknowledged.

R. H. F. M.
H. L. H.

June, 1953

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CHAPTER 16

The Chemistry of the Cinchona Alkaloids

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Harvard University, Cambridge, Massachusetts

The cinchona alkaloids are found in the bark of *Cinchona* and *Remijia* species, which are indigenous to the high (5000–8000 feet) eastern slopes of the Andes from 10° N to 20° S latitude (1). The great demand

for the alkaloids in medicine has led to extensive and successful cultivation and breeding in India, Ceylon, and the Dutch East Indies (2).

Cinchona preparations were introduced into medical use in Europe in the early seventeenth century, and were popularized through the efforts of the wife of the then Spanish Viceroy of Peru, the Countess of Chinchon, who in 1638 was successfully treated for malaria through administration of the hitherto little known remedy. Almost two hundred years later, one of the most intensive chemical investigations of the nineteenth century began, with the isolation of a crude mixture of crystalline alkaloids from the bark by Gomes in Portugal in 1810, and of pure quinine and cinchonine by Pelletier and Caventou in 1820 (3). Subsequently, upwards of two dozen further bases have been isolated from *Cinchona* and *Remijia* species; of these only quinidine (van Hejningen, 4) and cinchonidine (Winckler, 5) need be mentioned here.

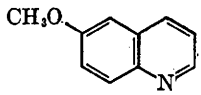
I. Determination of Structure

The investigations which culminated in the determination of the structures of the cinchona alkaloids have long been established as a classic of organic chemistry. It is worthy of note that much of our knowledge of the chemistry of quinoline and pyridine derivatives, and thence, of heterocyclic compounds in general, had its inception in the results of degradative studies on quinine and its congeners. Then, as now, the study of natural products enriched the body of general knowledge in the science, and pointed the way to new departures in the theory and practice of organic chemistry.

Strecker is credited with having first established the empirical formula $C_{20}H_{24}N_2O_2$ for quinine (6). Later, Skraup showed that cinchonine possesses the formula $C_{19}H_{22}N_2O$ (7). Both alkaloids were shown to be diacidic through analyses of salts. The nitrogen atoms were shown to be tertiary by the preparation of isomeric tertiary ethiodides (6, 8, 9). Hesse showed that quinine and cinchonine, as well as quinidine and cinchonidine, are converted by warm acetic anhydride into monoacetyl derivatives which are hydrolyzed by alcoholic potash to the original bases (10). When it became clear that both nitrogen atoms were tertiary these experiments demonstrated the presence of an hydroxyl group in the alkaloids. This conclusion was confirmed by the transformation of the alkaloids into chlorides (OH $\rightarrow$ Cl) through the action of phosphorus pentachloride in chloroform (11–14). The cinchona bases were shown to be rapidly attacked by permanganate, and to form addition products with halogen acids (14–21) and bromine (12, 14, 22, 23). These indications of the presence of a double bond were confirmed, and the function was shown to be incorporated as a vinyl group, through oxidation of the

alkaloids to carboxylic acids (—CH=CH_2 → —COOH) and formic acid (24–31).

The first insight into the nature of the main framework of the alkaloidal structures was obtained through the study of the products resulting when the bases were subjected to destructive fusion with caustic potash. Quinoline was obtained for the first time when cinchonine was so treated (32, 33). The correct structure for the key degradation product was suggested by Körner (34), and established through syntheses of the base by Koenigs (35), by Baeyer (36, 37), and by Friedländer (38). From quinine, by similar methods, an oxygenated base was obtained (39), which was shown to be 6-methoxyquinoline (I) (40). The attachment of a substituent in the γ-position of the quinoline nucleus in these alkaloids was indicated by the isolation (33) and proof of structure (41–45) of lepidine (II). The formation of β-ethylpyridine (39, 46) (III) and β-collidine (47, 48) (IV) in the alkali degradations stimulated work on the chemistry of pyridine bases.



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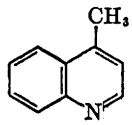
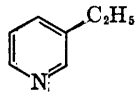


II



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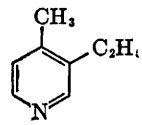
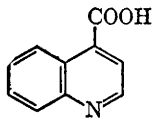
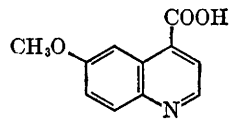


IV

The oxidation of the cinchona alkaloids also led to quinoline and pyridine derivatives. From cinchonine, and cinchonidine, by oxidation with nitric, or chromic acid, cinchoninic acid (V) was obtained (16, 49–51) and related to lepidine (41, 42). Similarly, quinine and quinidine were converted to quininic acid (52, 53), which was shown to have the structure (VI). Further oxidation of the quinoline acids was shown to lead

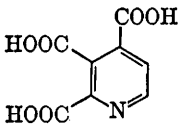


V

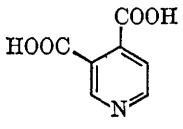


VI

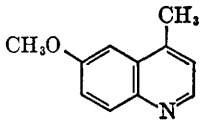
to pyridine-2,3,4-tricarboxylic acid (VII) (16, 51, 52, 53) and cinchomeronic acid (VIII), which were also obtained directly from the alkaloids under drastic oxidative conditions (54, 55).



VII



VIII



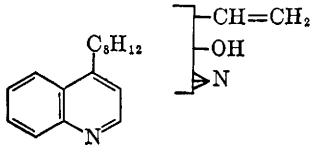
IX

The isolation of quinoline and its congeners from oxidation and drastic alkali degradations suggested the presence in the alkaloids of an intact quinoline nucleus, but other evidence was needed to exclude the possibility that the fully aromatic nuclei arose from hydroaromatic precursors by oxidative or dehydrogenative processes When the chlorides derived from cinchonine and cinchonidine were dehydrohalogenated by alcoholic potash, a new base, cinchene, $C_{19}H_{20}N_2$, was formed (12, 56); in a similar manner, the base quinene, $C_{20}H_{22}N_2O$, was formed from quinine and quinidine. When quinene and cinchene, or their salts, were heated with water or acids under carefully controlled conditions, 6-methoxylepidine (IX) and lepidine (II), respectively, were obtained (57). Later, it was found that the cleavage proceeded sufficiently smoothly when the anhydro bases were heated with 20% aqueous phosphoric acid at 170–180° to permit isolation of a fragment which contained all of the atoms of the original alkaloids in excess of those which appeared as quinoline derivatives (58). The same substance, $C_9H_{15}NO_2$, was obtained from quinine and from cinchonine; it was named meroquinene (Gr. μερος, a part), and became a key substance in the elucidation of the constitution of the non-aromatic "second half" of the cinchona bases. It was clear that the cleavage of quinene and cinchene had followed the course A,

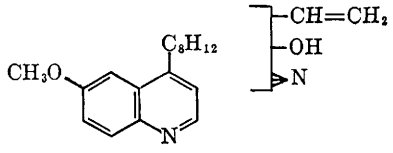
A $$(CH_3O)C_{19}H_{19}N_2 + 2H_2O \rightarrow (CH_3O)C_{10}H_8N + C_9H_{15}NO_2$$

Lepidine(s) Meroquinene

and that for the first time, strong positive evidence was available for the presence of an intact quinoline ring in the alkaloids themselves. Confirmation of this view was soon obtained when the hydrogen-rich meroquinene was found among the products of the direct oxidation of cinchonine (59). It was now possible to ascribe to cinchonine and quinine the structures (X) and (XI) with confidence.

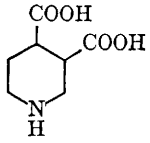


X

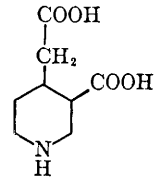


XI

The arrangement of atoms in the non-aromatic portion of the molecules was deduced from the study of meroquinene, and three other products which had previously been isolated from the complex mixtures obtained by oxidation of the alkaloids. The first of these was cincholoipon, $C_9H_{17}O_2N$, obtained by oxidation of cinchonine (60); it was not realized until later that the degradation product was in fact derived from dihydrocinchonine present in the natural base (61, 62). The second was cincholoiponic acid, $C_8H_{13}NO_4$ (60, 63), and the third, loiponic acid, $C_7H_{11}NO_4$ (62). Cincholoipon was found to contain an imino and a carboxyl group, and was transformed on distillation with zinc dust to β-ethyl pyridine (III). Cincholoiponic acid and loiponic acid were iminodicarboxylic acids. Meroquinene resembled cincholoipon in containing an imino and a carboxyl group (58). It was transformed smoothly into β-collidine (IV) when it was treated with dilute hydrochloric acid at 240°, and was oxidized by cold dilute acidic permanganate to cincholoiponic acid. By reduction with zinc and fuming hydriodic acid, it was converted into cincholoipon. Finally, cincholoiponic acid was converted directly by oxidation with permanganate to loiponic acid (62). Thus, all of these degradation products were interrelated, and shown to be 3,4-disubstituted piperidine derivatives, a view which was confirmed when loiponic acid, the simplest of them, was shown to be epimerized by potash at 200° to a hexahydrocinchomeronic acid (XII) available by synthesis (65). The most direct deduction from these facts was that

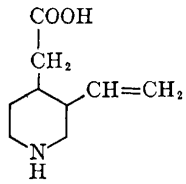


XII

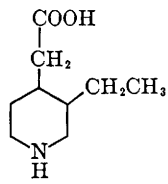


XIII

cincholoiponic acid, meroquinene, and cincholoipon could be formulated as (XIII), (XIV) and (XV), respectively. Unfortunately, the conver-

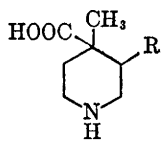


XIV

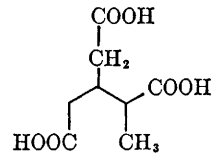


XV

sion of cincholoiponic acid to loiponic acid had proceeded in so low a yield that the possibility could not be excluded that the simpler acid had been derived from an impurity in the cincholoiponic acid, or by unusual processes. Consequently, it was not possible to dismiss rigorously structures such as (XVI, R = C_2H_5, C_2H_3 or COOH) for the degradation products (66). The degradation of cincholoiponic acid by exhaustive methylation and potash fusion to the acid (XVII), whose structure was proven by synthesis, afforded further support for the structure (XIII) (67), although the reaction sequence was sufficiently unusual to warrant some skepticism about the value of the evidence in structural arguments.



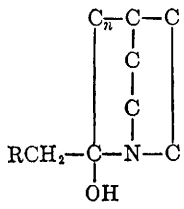
XVI



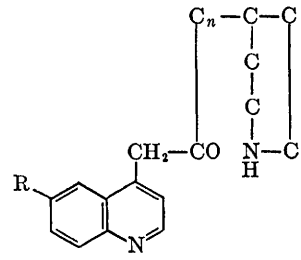
XVII

None the less the expressions (XIII), (XIV) and (XV) had gained general acceptance shortly after the turn of the century, and were finally shown conclusively to be correct through the synthesis of cincholoiponic acid by an unambiguous route (68, 69).

It remained to establish the manner of linkage of the two portions of the molecule represented by the known cleavage products. von Miller and Rohde had rediscovered a reaction first observed by Pasteur (70), namely, that the bitertiary bases cinchonine and quinine were converted under acidic conditions into ketones, designated as toxines, which contained a secondary amine function, and in order to explain these observations, made the fruitful suggestion that the non-aromatic moiety of the alkaloid molecules contained a bicyclic system with nitrogen at the

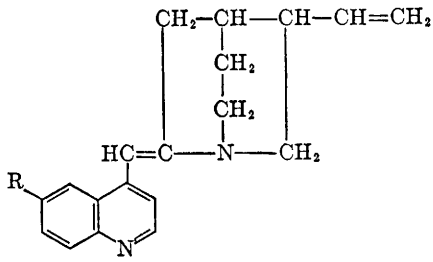


XVIII



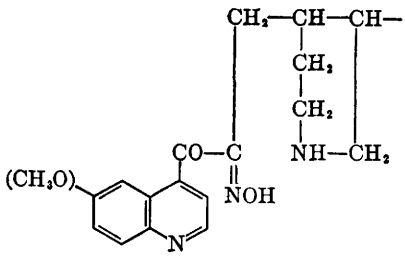
XIX

bridgehead, as in XVIII (n = 0 or 1) (71). Thus, the toxines were represented by the structure (XIX). Koenigs accepted this view (72), and pointed out that it was consistent with the formulation of cinchene and quinene as alkylidene lepidines (XX, R = H or OCH_3); the latter expressions, which are now known to be correct, were in accord with the smooth hydrolytic cleavage of the anhydro bases to lepidines and

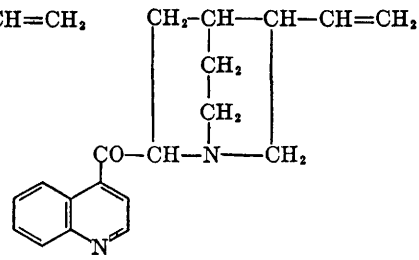


XX

meroquinene (73). The first strong evidence that the oxygen atom of the cinchona toxines, and thence presumably that of the alkaloids themselves, was not attached to a carbon atom penultimate to the aromatic ring was forthcoming when Rabe showed that the α-isonitrosotoxines were best formulated as XXI, since they were converted under the conditions of the Beckmann rearrangement to quinoline-4-carboxylic acids and meroquinene nitrile (74). Then, the widely held view that the alkaloids were tertiary alcohols was doomed when Rabe succeeded

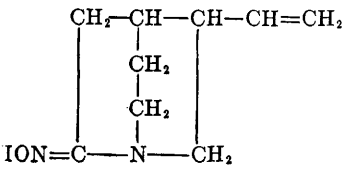


XXI

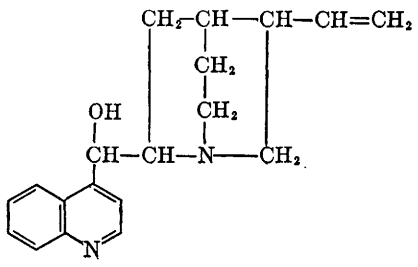


XXII

in oxidizing cinchonine directly to a ketone (75). Further, the structure of this ketone, cinchoninone (XXII), was demonstrated through cleavage by amyl nitrite and sodium ethoxide to cinchoninic acid (V) and an oximino compound (XXIII) which was hydrolyzed to meroquinene and hydroxylamine. Finally, it was possible to effect the



XXIII



XXIV

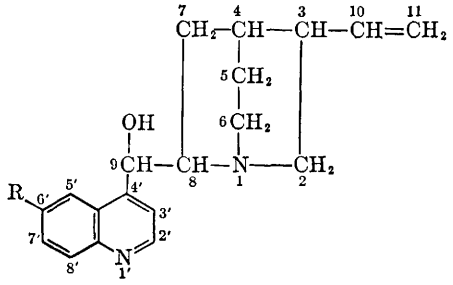
reconversion of cinchoninone, albeit in small yield, into cinchonine by reduction. These experiments showed conclusively that cinchonine possessed the structure XXIV.

The objective of the intensive structural investigations of more than a quarter of a century had been reached.

II. Reactions of the Alkaloids

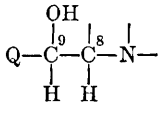
1. The C.8-C.9 System

We may turn now to a general consideration of the chemistry of the major cinchona alkaloids, in terms of the established structures, (XXV, R = H) for cinchonine and cinchonidine, and (XXV, R = OCH_3) for quinine and quinidine.



XXV

The major transformations undergone by the alkaloids devolve from the presence in the bases of the ethanolamine system (XXVI, Q = 4-quinolyl *or* 6-methoxy-4-quinolyl).

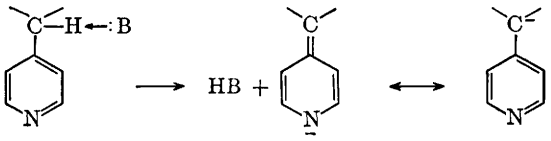


XXVI

We shall direct attention first to the special properties conferred on the system by its attachment at the γ-position of a quinoline nucleus. Any $-\overset{|}{\underset{|}{C}}=\overset{|}{N}$ double bond, in consequence of the presence of the strongly electron-attracting nitrogen atom as a bond partner, is polarized in the sense $-\overset{|}{\underset{|}{C}}=\overset{|}{N}$, and will stabilize directly attached anionoid centers (*cf.* XXVII*a* ↔ XXVII*b*). Thus a hydrogen atom α to such a group will be relatively easily removed by basic reagents, and the resulting anion may undergo the manifold reactions characteristic of such centers. These

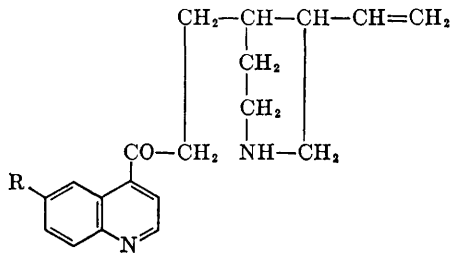
XXVII*a* XXVII*b*

characteristics of the carbon-nitrogen double bond may be transmitted through a series of attached double bonds, and thus to selected positions of an aromatic heterocyclic nucleus. The well-known reactivity of the methyl and methylene groups attached in the α and γ positions of pyridine and quinoline nuclei is explicable in these terms. It is clear then, that the attachment of C.9 of the cinchona bases to the γ-position



of a quinoline ring provides the key to an understanding of a large portion of the chemistry of the alkaloids.

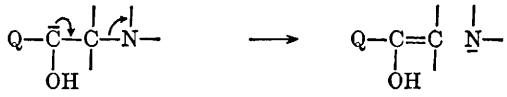
a. The Cinchona Toxines. One of the oldest and best-known reactions of the alkaloids is the conversion to the cinchona toxines, (70, 71, 77–79) cinchotoxine (XXVIII, R = H) and quinotoxine (XXVIII,



XXVIII

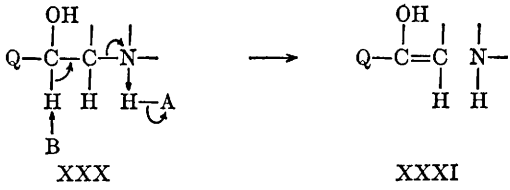
R = OCH_3). It may be noted that quinine and quinidine are converted to the same ketone, as are cinchonine and cinchonidine.

The considerations advanced above indicate that the C.9 hydrogen atom is susceptible to removal by bases; in the resulting fragment, the opportunity exists for the elimination of N (XXIX, arrows).



XXIX

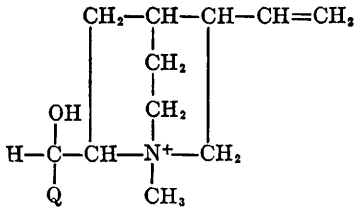
This process, however, will not be a ready one in the absence of factors which facilitate electron-accession to nitrogen. The most readily attainable such situation is the conference of a full positive charge on the nitrogen atom by salt formation. It is for this reason that the rate of toxine formation passes through a maximum as the acidity of the medium in which the change is brought about increases, and then decreases at higher acidities, as the suppression of loss of the C.9 hydrogen atom becomes dominant. For the overall reaction we may write a concerted process (XXX → XXXI) in which cooperation of acidic and basic catalysts is essential (80).



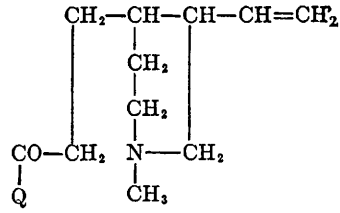
XXX XXXI

The transformation of the enol to the observed ketonic product is unexceptional.

This view of the nature of the process is confirmed by the behavior of the quaternary salts (XXXII) derived from the alkaloids (81–87). These substances very readily undergo transformation to *N*-alkyl toxines (XXXIII) in the presence of *bases* alone. In these cases, a full positive charge is fixed on the nitrogen atom, and the base-catalyzed removal of H-C.9 alone initiates reaction. It is of interest that base-

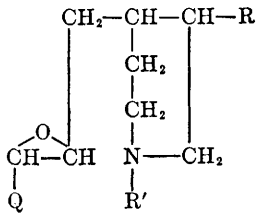


XXXII



XXXIII

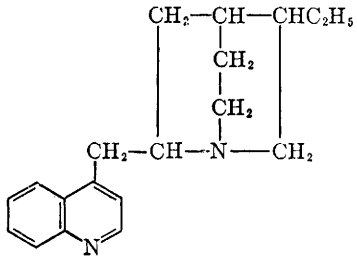
induced toxine formation from the quaternary derivatives is frequently accompanied by the formation of oxides (XXXIV), through the sequence (XXXV → XXXVI).



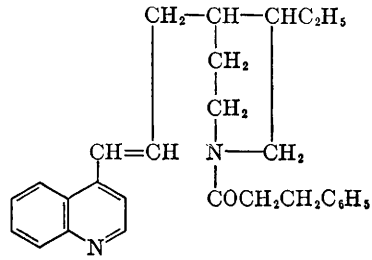
XXXIV

XXXV XXXVI

It may be noted that desoxydihydrocinchonine (XXXVII), when boiled with anhydrous hydrocinnamic acid furnishes XXXVIII, through changes essentially similar to those outlined above (88).



XXXVII

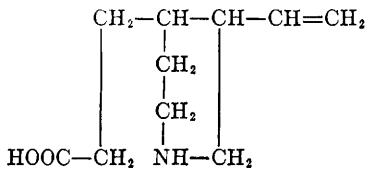


XXXVIII

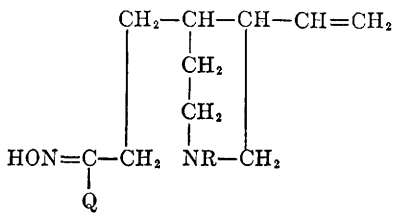
The reactions of the cinchona toxines are in general those to be expected of substances containing the structural features known to be present. The ready formation of α-isonitroso derivatives (XXI), and the cleavage of the latter to cinchoninic acid derivatives and meroquinene or its congeners has been mentioned in Section I. The interesting reactions which permit reconstitution of the cinchona alkaloid structure from the toxines are discussed in Section IV.

Of special interest are the methods which serve for the degradation of the ketones to derivatives of homomeroquinene (XXXIX). The Beckmann rearrangement of the toxine oximes (XL) proceeds in both

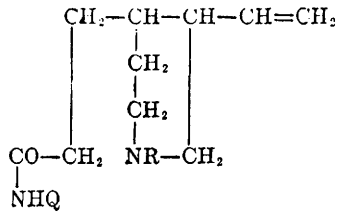
possible directions, to yield a mixture of the amides XLI and XLII (89, 90).



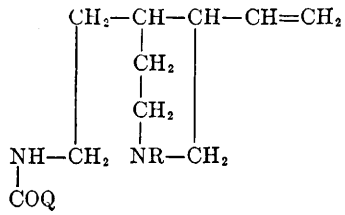
XXXIX



XL

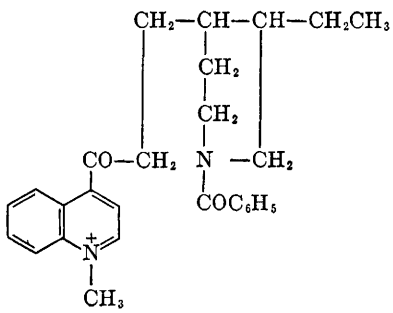


XLI

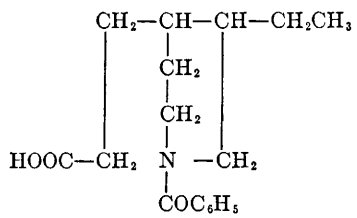


XLII

Direct oxidation of the ketones leads of course to the familiar cleavage between C.8 and C.9, but alkaline permanganate oxidation of *N*.1-benzoyldihydrocinchotoxine-*N*.1′-methiodide (XLIII) results in cleavage of the C.9-C.4′ bond, with the formation of *N*-benzoylhomocinchoploipon (XLIV) (91).

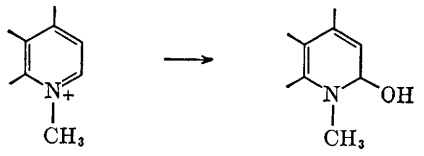


XLIII



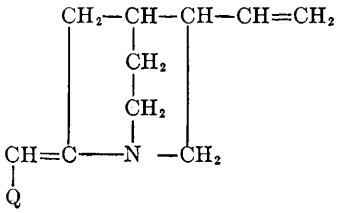
XLIV

The reaction sequence is explicable when it is realized that the aromatic ring, which is ordinarily very resistant to the attack of oxidizing agents, becomes very susceptible to oxidative degradation when the methiodide suffers the characteristic reaction of the class with hydroxide ions (XLV → XLVI).

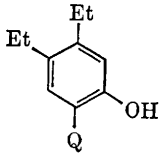


XLV XLVI

b. The Anhydro Bases. We have seen earlier that cinchene (XLVII, Q = 4-quinolyl) and quinene (XLVII, Q = 6-methoxy-4-quinolyl) are produced when the corresponding cinchona chlorides are treated with alcoholic potash.



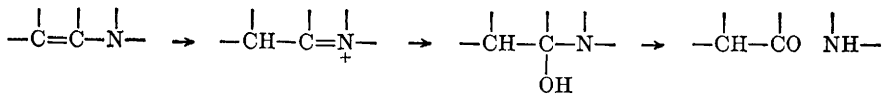
XLVII



XLVIII

The action of acids on these anhydro bases brings about, on the one hand, cleavage to meroquinene and the corresponding lepidine, and on the other, a complicated reaction leading to the new bases, *apo*cinchene and *apo*quinene (XLVIII) (13, 56, 58, 92, 93).

The cleavage reaction involves a point of special interest. Substances containing the system $-\overset{|}{C}=\overset{|}{C}-\overset{|}{N}-$ are ordinarily readily cleaved by aqueous acids, through the sequence (XLIX → LII).



XLIX L LI LII

In the case at hand, however, the formation of a conjugate acid of the general class (L) is unlikely to be a major factor in the initiation of the