[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORY OF POLAROID CORPORATION AND THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

The Total Synthesis of Quinine

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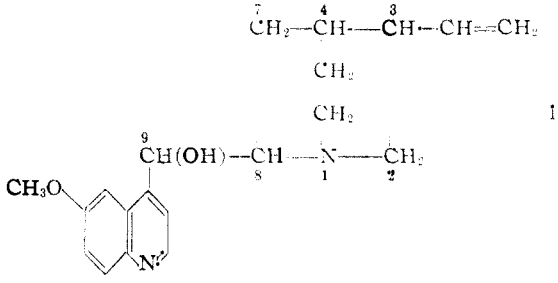
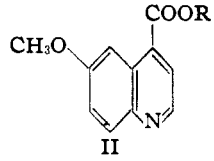
The culmination of the structural investigations on quinine in the proposal of the correct structure (I) in 1908[1] may be considered the point at which rational efforts toward total synthesis could be

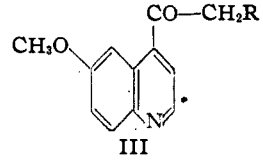


I

initiated.[2] These efforts first took the form of an attack on the synthesis of substances containing the quinoline moiety of the quinine molecule. First success was achieved independently by Pictet and Misner,[3a] and by Kaufmann and Peyer,[3b] in 1912 with the synthesis of quininic acid (II, R = H); since that time a number of other methods have been described for the synthesis of this and related quinoline 4-carboxylic acids.[3c-h] It was then shown[4] that quininic acid, in the form of its esters, could be condensed with esters of the type RCH_2COOEt to produce substances

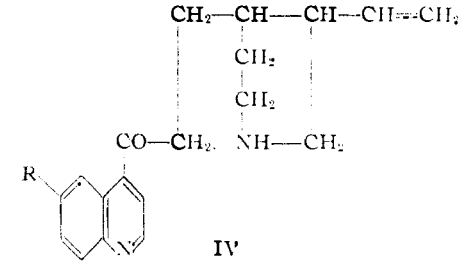


II



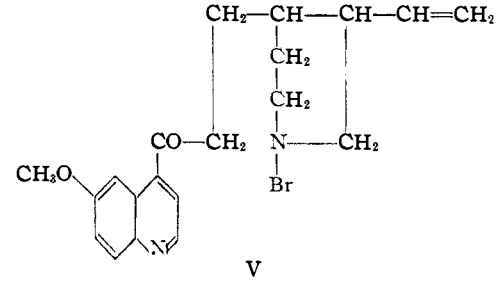
III

easily transformable by hydrolysis and decarboxylation to molecules of the class (III), containing various groupings attached to the quinoline ring through a carbonyl function. This observation, not in itself of exceptional interest,[5] took on prime importance in consequence of the success of a correlative line of investigation. Pasteur had shown[6] in 1853 that the cinchona alkaloids, on heating with tartaric or sulfuric acid, were transformed into isomeric substances, *e. g.*, cinchotoxine (cinchonicine) and quinotoxine[7] (quinicine) from cinchonine and quinine, respectively. Subsequent investigations by other workers resulted in the verification of these early results,[8] in improvements in the mode of effecting the isomerization,[9] and in the successful formulation[10] of quinotoxine as (IV, R = OCH_3) and cinchotoxine as (IV, R = H). It was now apparent that these

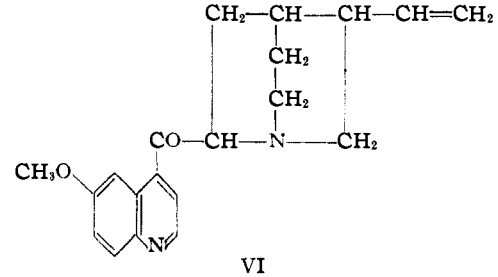


IV

substances fell into the general category (III) and that their synthesis might be effected along the lines adumbrated in the model experiments on ester condensation involving ethyl quininate. It was then found that it was possible to effect the



V



VI

(1) Rabe, *Ber.*, **41**, 62 (1908).

(2) Earlier attempts had been made, notably that of Perkin, who attempted to convert allyl toluidine to quinine by oxidation. An interesting account of this work, which led directly to the establishment of the coal tar color industry, and thence of the organic chemical industry, is given by Perkin himself in the Hofmann Memorial Lecture, *J. Chem. Soc.*, **69**, 603 (1896).

(3) (a) Pictet and Misner, *Ber.*, **45**, 1800 (1912); (b) Kaufmann and Peyer, *ibid.*, **45**, 1805 (1912); (c) Kaufmann, *ibid.*, **51**, 116 (1918); **55**, 614 (1922); (d) Halberkann, *ibid.*, **54**, 3079, 3090 (1921); (e) Thielepape, *ibid.*, **55**, 127 (1922); **71**, 387 (1938); (f) Rabe, Huntenburg and Selikin, *ibid.*, **64**, 2492 (1931); (g) Thielepape and Fulde, *ibid.*, **72**, 1432 (1939); (h) Ainley and King, *Proc. Roy. Soc.* (London), **125B**, 83 (1938).

(4) Rabe and Pasternack, *Ber.*, **46**, 1032 (1913).

(5) *E. g.*, certain compounds of this class may be obtained easily in other ways, notably by the action of Grignard reagents on 4-cyanoquinolines: *cf.* Kaufmann, Peyer and Kunkler, *Ber.*, **45**, 3090 (1912); Rabe and Pasternack, *ibid.*, **45**, 1026 (1913).

(6) Pasteur, *Compt. rend.*, **36**, 110 (1853).

(7) The isolation of quinotoxine directly from the mixed alkaloids of cinchona bark was subsequently reported [Howard, *J. Chem. Soc.*, **24**, 61 (1871); **25**, 101 (1872)], but it is not entirely clear whether the substance is a *bona fide* natural product, or is formed from quinine during the isolation processes.

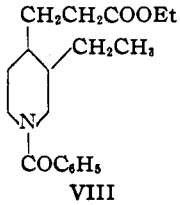
(8) Hesse, *Ann.*, **166**, 276 (1873); **178**, 244 (1875).

(9) Von Miller and Rohde, *Ber.*, **28**, 1064 (1895); von Miller, Rohde and Fussenegger, *ibid.*, **33**, 3228 (1900).

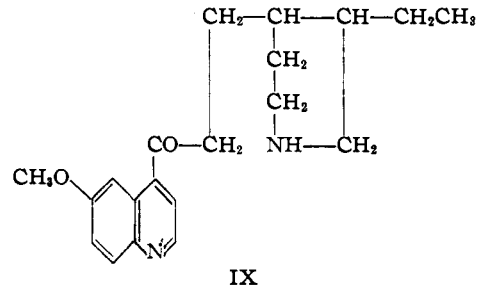
(10) Rabe, *Ann.*, **350**, 180 (1906); **365**, 366, 377 (1909).

reconversion, first of cinchotoxine,[11] and later, of quinotoxine,[12] into cinchonine and quinine. Quinotoxine was converted by the action of sodium hypobromite into N-bromoquinotoxine (V), which was cyclized by alkali, with loss of hydrogen bromide, to give quininone (VI). Reduction of the ketone (VI) with aluminum powder and ethanol in the presence of sodium ethoxide gave a mixture of stereoisomeric alcohols, from which both quinine (I) and quinidine were isolated.[13]

At this point it seemed likely that by condensation of ethyl quininate with appropriate esters, substances of the cinchona toxine class could be prepared, and transformed by the processes described above into the cinchona alkaloids. The difficulty lay in procuring the apposite esters, which contained the skeleton of the quinuclidine part of the cinchona alkaloid molecule. In initial experiments along this line, Rabe was able to demonstrate the validity of the general scheme by utilizing the ethyl ester of N-benzoylhomocincholoipon (VIII), which had been prepared by Kaufmann[14] by degradation of natural dihydrocinchonine. The condensation proceeded smoothly, and the product, on hydrolysis and decarboxylation gave dihydroquinotoxine (IX).[15]

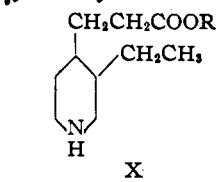


VIII

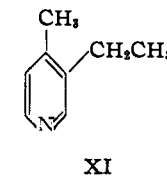


IX

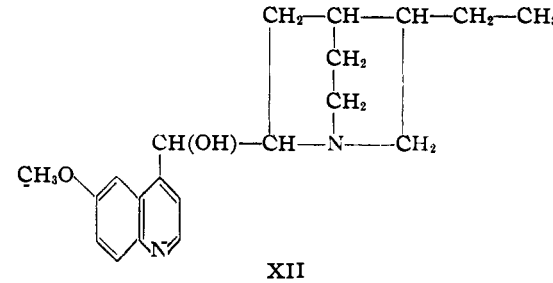
Subsequently, Koenigs was successful in preparing racemic homocincholoipon (X, R = H) synthetically from β-collidine (XI),[16] which was itself first synthesized by Ruzicka,[17] and later by many other workers.[18] Finally, Rabe was able, using Koenigs' method, to prepare a sufficient quantity of homocincholoipon ethyl ester (X, R = C_2H_5) to permit resolution through the corresponding *d*-tartrates, and this achievement, coupled with the earlier work,[14,16] constituted a total synthesis of dihydroquinine[19] (XII).



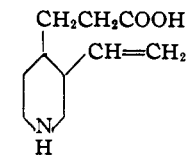
X



XI



XII



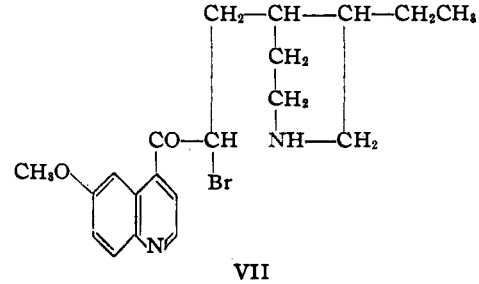
XIII

There remained the task of carrying out a total synthesis of quinine.[20] The problem had been simplified by the work described above to one of the synthesis of quinotoxine (IV, R = OCH_3). Further, at the outset of our work it seemed highly probable, in view of the conversion by Rabe of homocincholoipon (dihydrohomomeroquinene) (X, R = H) to dihydroquinotoxine,[16] that homomeroquinene (XIII) would be transformable to quinotoxine, and accordingly our efforts were directed toward the synthesis of (XIII). This further simplification of the synthetic objective was subsequently established by Prelog,[21] who

(11) Rabe, *Ber.*, **44**, 2088 (1911).

(12) Rabe and Kindler, *ibid.*, **51**, 466 (1918).

(13) An alternate and somewhat smoother method for the conversion of cinchona toxines proceeds through the C-bromo derivatives (*e. g.*, VII), but is applicable only to the dihydro series (ethyl, rather than vinyl at C. 3).



VII

(14) Kaufmann, Rothlin and Brunnschweiler, *Ber.*, **49**, 2302 (1916).

(15) Rabe and Kindler, *ibid.*, **52**, 1843 (1919); *cf.* also Rabe and Kindler, *ibid.*, **51**, 1360 (1918).

(16) E. Koenigs and Ottmann, *ibid.*, **54**, 1343 (1921); *cf.* also Koenigs, "Dissertation," Breslau, 1912.

(17) Ruzicka and Fornasir, *Helv. Chim. Acta*, **2**, 338 (1919).

(18) Rabe and Jantzen, *Ber.*, **54**, 925 (1921); Tschitschibabin, Moschkin and Tjaschelowa, *J. prakt. Chem.*, [2] **107**, 132 (1924); E. Koenigs and Hofmann, *Ber.*, **58**, 194 (1925); Tschitschibabin and Oparina, *ibid.*, **60**, 1877 (1927); Prelog and Komzak, *ibid.*, **74**, 1705 (1941).

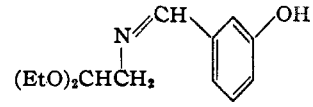
(19) Rabe, Huntenburg, Schultze and Volger, *ibid.*, **64**, 2487 (1931).

(20) For the preliminary announcement of the completion of the synthesis see THIS JOURNAL, **66**, 849 (1944).

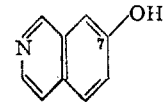
(21) Prostenik and Prelog, *Helv. Chim. Acta*, **26**, 1965 (1943).

prepared homomeroquinene by the degradation of natural cinchonine, and converted it, by Rabe's method, to quinotoxine.[21a]

We chose as the starting point of our investigations 7-hydroxyisoquinoline (XV), which contains almost the complete carbon–nitrogen skeleton of homomeroquinene (XIII). The phenol had been prepared by Fritsch by the action of sulfuric acid on *m*-hydroxybenzylideneaminoacetal (XIV).[22] We subjected this method to careful



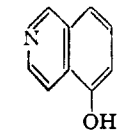
XIV



XV

scrutiny. The condensation of *m*-hydroxybenzaldehyde[23] with aminoacetal[23] to give (XIV) proceeded smoothly and in practically quantitative yield. As demonstrated in the earlier investigation, success in the cyclization of (XIV) was sharply dependent on the sulfuric acid concentration. The optimum yield of cyclized material from the pure crystalline Schiff base was obtained with 76% sulfuric acid (method I). From the practical point of view, the observation that the cyclization could be carried out directly on the reaction mixture resulting from the condensation of *m*-hydroxybenzaldehyde and aminoacetal was of considerable importance. In that case, adjustment of the acid concentration (to 80%) was necessary in order to compensate for water formed concomitantly in the condensation, and further, the introduction of benzene as solvent resulted in smoother reaction and higher yields (method II).

The direction of cyclization of (XIV) is not unambiguous. While Fritsch had obtained only the 7-hydroxy isomer (XV), we found that the crude phenolic product contained both possible isomers, 7-hydroxyisoquinoline (XV) and 5-hydroxyisoquinoline (XVI). The two phenols were separated and purified by crystallization of their sodium salts, that of (XVI) being the more soluble.



XVI

Final purification was best effected by sublimation and subsequent recrystallization. Pure 7-hydroxyisoquinoline had m. p. 229.5–230.5°, and was obtained in *ca.* 60% yield by either method (*vide supra*). Pure 5-hydroxyisoquinoline, obtained in *ca.* 5% yield, had m. p. 227–229°,[24] and was identical with a sample of the phenol obtained by alkaline fusion of isoquinoline-5-sulfonic acid.[25] The phenols were further characterized by the preparation of the corresponding acetyl derivatives, 7-acetoxyisoquinoline, m. p. 73–75°, and 5-acetoxyisoquinoline, m. p. 59–60°, respectively.

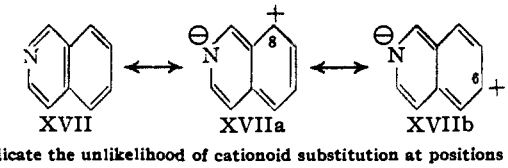
7-Hydroxyisoquinoline condensed readily in warm methanol solution with formaldehyde and piperidine, and the product, 7-hydroxy-8-piperidinomethylisoquinoline (XVIII), was easily separated and purified through its *sodium salt*. The pure substance, m. p. 81.5–82.5°, was obtained in 62% yield. Initial attempts to effect reductive cleavage of the piperidino-group, *e. g.*, by catalytic hydrogenation, and through the use of various chemical reducing agents, were not successful. The compound (XVIII) was remarkably resistant

(21a) Although our synthesis of homomeroquinene was complete at the time Prelog's paper describing the preparation of homomeroquinene from natural sources became available to us (Received March 3, 1944), we could not establish identity by a direct comparison of the properties of our substance with that of Prelog, since our synthetic sample was racemic, whereas the material obtained by degradation of natural cinchonine was the active (*d*) isomer. Consequently, we adhered to our original plan of proceeding by Rabe's method (which was in any event that used by Prelog) to quinotoxine, and effecting resolution and establishment of identity at that point.

(22) Fritsch, *Ann.*, **286**, 10 (1895).

(23) The published procedures for the preparation of these two intermediates are unsatisfactory, and particularly in the case of the latter, much ambiguity exists in the literature [*cf.* Wohl, *Ber.*, **21**, 616 (1888); **39**, 1951 (1906); Wolff, *ibid.*, **21**, 1481 (1888); **26**, 1830 (1893); *Ann.*, **363**, 169 (1908); Marckwald, *Ber.*, **25**, 2355 (1892); Böeseken and Felix, *ibid.*, **62**, 1311 (1929); Hartung and Adkins, THIS JOURNAL, **49**, 2517 (1927); Buck and Wrenn, *ibid.*, **51**, 3612 (1929); Allen and Clark, *Org. Syn.*, **24**, 3 (1944)]. The details of reproducible methods for preparing *m*-hydroxybenzaldehyde [*via m*-nitrobenzaldehyde and *m*-aminobenzaldehyde, *cf.* Tiemann and Lndwig, *Ber.*, **15**, 2054 (1882); Rieche, *ibid.*, **22**, 2348 (1889)] and aminoacetal (from chloroacetal and ammonia) may be found in the experimental section.

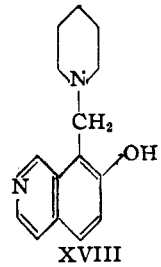
(24) An equimolecular mixture of the two isomeric phenols melted quite sharply at 184°. An *x*-hydroxyisoqninoline, m. p. 184°, has been obtained [Claus and Raps, *J. prakt. Chem.*, [2] **45**, 244 (1892)] by the alkaline fusion of an isoquinoline-*x*-sulfonic acid, formed by the direct high-temperature sulfonation of isoquinoline [Claus and Seelemann, *J. prakt. Chem.*, [2] **52**, 2 (1899)]. Substitution theory indicates (*cf.* the mesomeric forms XVII ⟷ XVII*a* ⟷ XVII*b*, which

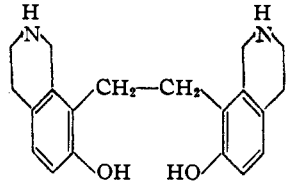


XVII XVIIa XVIIb

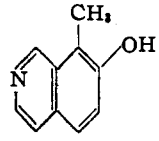
indicate the unlikelihood of cationoid substitution at positions 6- or 8-) that direct substitution in the isoquinoline nucleus should take place at the 5- (*cf.* note 25, below) and the 7-positions. These considerations suggest that the *x*-derivatives are mixtures of 5- and 7-substituted compounds, and that in particular the *x*-hydroxyisoquinoline is a eutectic of 5-hydroxy- and 7-hydroxyisoquinoline. It seems possible that the development of these observations might lead to a more simple and direct method of preparation of 7-hydroxyisoquinoline than the Fritsch synthesis upon which we have relied.

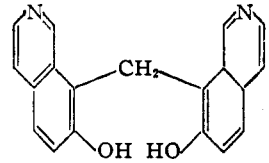
(25) Hoogewerff and van Dorp, *Rec. trav. chim.*, **5**, 308 (1886); Weissgerber, *Ber.*, **47**, 3179 (1914); *cf.* also ref. 24, and Fieser and Martin, THIS JOURNAL, **57**, 1840 (1935). For the orientation of this acid, and the substances related to it by direct interconversions, *viz.*, 5-nitro-, 5-bromo-, 5-amino-, 5-cyano-, and 5-hydroxyisoquinoline, see Tyson, THIS JOURNAL, **61**, 183 (1939). *Cf.* also Le Févre and Le Févre, *J. Chem. Soc.*, 1470 (1935). Since Fritsch had provided a proof of structure for his 7-hydroxyisoquinoline, the identity of the other product of the cyclization of *m*-hydroxybenzylideneaminoacetal (which can only be the 5-hydroxy-isomer) with the phenol from the sulfonic acid of Hoogewerff and van Dorp provides independent confirmation of the assignment of the 5-substituted configuration to the predominant direct substitution products of isoquinoline. It is worthy of note that this result conforms to modern substitution theory, in that substitution would be expected in the benzenoid ring, and preferably in the 5- or 7-position (*cf.* note 24, above).


XVIII


XIX

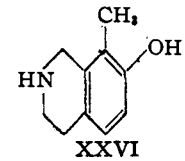
to reduction over platinum[26] in a variety of solvents, and the products which could be isolated after long-continued treatment, *e. g.*, a (phenolic) *compound*, $C_{20}H_{24}O_2N$, m. p. 158.5–159.5°, probably *sym-bis*-(7-hydroxy-1,2,3,4-tetrahydro-8-isoquinolinyl)-ethane (XIX), and a non-phenolic, strongly basic oil, which gave a crystalline *carbonate*, m. p. 105–110° (dec.), were not of the desired character. The piperidino compound (XVIII) was first successfully converted, in small yield, into 7-hydroxy-8-methylisoquinoline (XX) by heating at elevated temperatures over a dehydrogenation catalyst. This method was of some theoretical interest, but of no practical importance. On the other hand, on heating for ten hours at 220° in methanolic sodium methoxide,[27] 7-hydroxy-8-piperidinomethylisoquinoline was converted smoothly into 7-hydroxy-8-methylisoquinoline (XX). In order to separate the major product

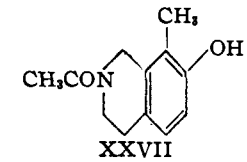

XX


XXI

(XX) and some regenerated 7-hydroxyisoquinoline[28] from phenolic material of higher molecular weight, *e. g.*, bis-(7-hydroxy-8-isoquinolinyl)-methane (XXI),[28] the crude reaction product was sublimed *in vacuo*. Further purification was effected by taking advantage of the preferential formation by 7-hydroxyisoquinoline (XV) of an alcohol-soluble *barium salt*. In this way, pure 7-hydroxy-8-methylisoquinoline (XX), m. p. 232–233,5°, was obtained in 64% yield. It was further found that the isolation in the pure state of the intermediate (XVIII) was unnecessary, and that in fact the over-all yield in the conversion of 7-hydroxyisoquinoline (XV) into the 7-hydroxy-8-methyl compound (XX) was considerably improved (40% → 60%) when the crude reaction mixture from the condensation of (XV) with piperidine and formaldehyde was submitted directly to the reductive cleavage reaction.

We may comment at this point that with the synthesis of the intermediary piperidino compound (XVIII) a substance had been obtained which contained all of the carbon atoms and the nitrogen atom of the homomeroquinene skeleton, and that subsequent operations were designed to effect changes in the desired direction in the nature of the attached atoms and groups.[29] On hydrogenation in acetic acid over platinum, the phenol (XX) was converted readily into 7-hydroxy-8-methyl-1,2,3,4-tetrahydroisoquinoline (XXVI), m. p. 246–250°. The same product was


XXVI

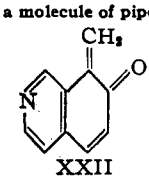

XXVII

obtained, less smoothly, through the use of chemical reducing agents, *e. g.*, tin and hydrochloric acid, or by high pressure hydrogenation over Raney nickel. In the case of the platinum hydrogena-

(26) The resistance to hydrogenation over platinum catalysts of substances containing within the same molecule a strongly basic nitrogen atom and a phenolic function was noticed elsewhere in our work (*vide infra*), and is deserving of special comment.

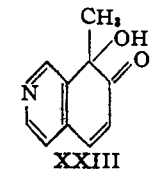
(27) *Cf.* Conforth, Conforth and Robinson, *J. Chem. Soc.*, 682 (1942), who developed this method for the reduction of piperidinomethyl phenols.

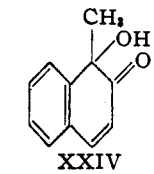
(28) 7-Hydroxy-8-piperidinomethylisoquinoline (XVIII) is a labile substance which appears to undergo reversible decomposition fairly readily, into 7-hydroxyisoquinoline (XV), formaldehyde and piperidine. (XV) may then participate in condensation with (XVIII), or an equivalent intermediate (such as [XXII]) derived from (XVIII) by loss of a molecule of piperidine, with the formation


XXII

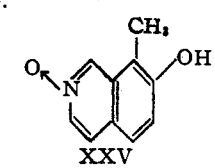
of (XXI), or alternately. (XXII) may undergo self-condensation to give products of double (*cf.* the results described under the hydrogenation of [XVIII], above) or higher molecular weight.

(29) It will be evident that a necessary general change was the cleavage at some stage of the carbocyclic ring between carbon atoms 7 and 8. In the completed synthesis, the cleavage was effected at a stage some steps removed from the phenol (XX) (*vide infra*). In some parallel experiments, a study was made of the oxidation of 7-hydroxy-8-methylisoquinoline, with particular regard to the possibility of preparing the quinol (XXIII), which should be subject to ready scission (say by periodic acid) in a predictable manner. A *substance*, m. p. 135.5–136.5°, which was almost certainly the latter compound, was indeed formed, but in impracticable yield, by the direct chromic acid or sodium persulfate oxidation of the phenol.


XXIII

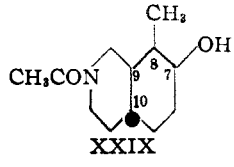

XXIV

It was then found that the transformation of the model compound, 1-methyl-2-naphthol, into the corresponding quinol (XXIV) could be effected smoothly and in excellent yield by peracetic acid. On the other hand, peracetic acid attacked the heterocyclic phenol (XX) only slowly, and the sole isolable product was the N-oxide (XXV), m. p. 256–257° (dec.).

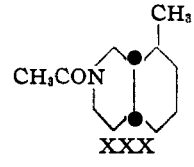

XXV

tion, absorption of hydrogen stopped sharply at two moles; moreover, the pure tetrahydro compound (XXVI) could not be reduced further over this catalyst in any solvent.[26] On acetylation with acetic anhydride in methanol, (XXVI) was converted quantitatively into N-acetyl-7-hydroxy-8-methyl-1,2,3,4-tetrahydroisoquinoline (XXVII), m. p. 187–198°, which was peculiar in that analytically pure samples, many times recrystallized, exhibited the same large melting point range.[30] It was unnecessary to isolate (XXVI), in the pure state. Experiments in which the crude tetrahydro- compound, directly from the hydrogenation, was acetylated, resulted in 95% over-all conversion ([XX] → [XXVII]).

Unlike the free secondary amine (XXVI), N-acetyl-7-hydroxy-8-methyl-1,2,3,4-tetrahydroisoquinoline (XXVII) readily absorbed hydrogen in acetic acid solution over a platinum catalyst. Under these conditions, however, the saturation of the aromatic ring was largely concomitant with loss of the hydroxyl group. Not more than 10% of the starting material was converted to N-acetyl-7-hydroxy-8-methyldecahydroisoquinoline (XXIX[31]), m. p. 126–128°, which was separated from the major product by extraction from ether



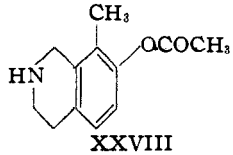
XXIX



XXX

solution by 2 *N* hydrochloric acid.[32] The large *acid-insoluble*[32] fraction, containing N-acetyl-8-methyldecahydroisoquinoline (XXX[31]), gave, after acid hydrolysis of the amide link, the oily 8-methyldecahydroisoquinoline (XXXI[31]), purified through the crystalline *bicarbonate*, m. p. 78–84° (dec.), and characterized as the extremely volatile *hemihydrate*, m. p. 41–43°. The phenol (XXVII) could not be hydrogenated in neutral ethanol over platinum, and while the addition of small amounts

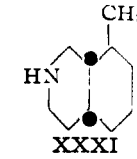
(30) This exceptional behavior may have been due to gradual establishment at elevated temperatures of equilibrium between (XXVII) and the O-acetyl isomer (XXVIII).



XXVIII

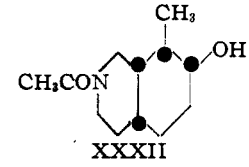
(31) In all of the decahydroisoquinoline derivatives described in this paper, the ring-locking configurations (9/10) only are known. No evidence is available as to the configurations at C.7 and C.8, and the formulas XXIX–XXXI are not meant to contain implications in regard to that portion of the molecule.

(32) The striking difference in acid-solubility between (XXIX) and (XXX) cannot be attributed to the greater basicity of the former. Rather it is a consequence of the hydrophilic nature of the hydroxyamide, and the fact that the ratio of acid solubilities of two equally (weakly) basic substances must be proportional to the ratio of their solubilities in pure water. The latter ratio may be large, even though individually both compounds may be so slightly soluble as to be described in usual terms as "insoluble."

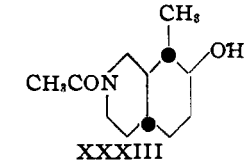


XXXI

of hydrogen chloride initiated fairly rapid reduction, the product composition was essentially that described above. Generalized experience with platinum-catalyzed room-temperature hydrogenations[33] indicates strongly that the major product (XXX) had the *cis* ring-locking configuration.[34] On the other hand, evidence detailed in a subsequent section points equally clearly to the *trans* configuration for the by-product (XXIX),[35] in which the hydroxyl has been retained. It has been assumed that the predominance of *cis*-addition of hydrogen under these conditions is a consequence of adsorption on the catalyst followed by complete saturation of the double bond, aromatic ring, or other unsaturated center by transfer of a sufficient number of hydrogen atoms in a single act (type *a* hydrogenation). Alternately, to the extent that by-products are formed under these conditions whose configuration does not conform to the above picture, and in general in non-stereo-specific hydrogenations, the process is a more random one of successive additions, *e. g.*, of one or more hydrogen atoms at a time to individual unsaturated centers of the system (type *b* hydrogenation). In the light of these considerations, the correlation between configuration and oxygen cleavage suggested by our results might be interpreted in one of two ways. (1) The major proportion of the initial product is formed by type *a* hydrogenation, and has the all *cis* configuration (XXXII), while a lesser amount of material re-



XXXII



XXXIII

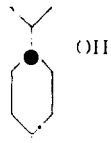
sults from type *b* hydrogenation, and has a 7/8 *trans* configuration, *e. g.* (XXXIII). Experience in the case of the similar pair, menthol (XXXIV) and *d-neo*-menthol (XXXV)[36] suggests that the *trans* isomer (XXXIII) would be stable, and that the *cis* isomer (XXXII) would undergo very ready dehydration (and subsequent hydrogenation) under the influence of the (necessarily) acidic solvent. (2) The not-uncommon carbon–oxygen cleavage reactions observed in the hydrogenation

(33) Linstead, *et al.*, THIS JOURNAL, **64**, 1985 (1942).

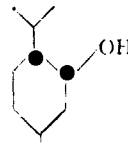
(34) The convention (*cf.* formulas XXIX and XXX) is that of Linstead [*Chemistry and Industry*, **56**, 510 (1937)], the dot indicating that the attached hydrogen atom lies above the plane of the paper.

(35) In our preliminary communication (ref. 20), this substance was inadvertently reported as having the *cis* ring-locking configuration.

(36) *E. g.*, *d-neo*-menthol is readily dehydrated on contact with formic acid, while menthol is unchanged, or is converted into the formate [Zeitschel and Schmidt, *Ber.*, **59**, 2298 (1926)].

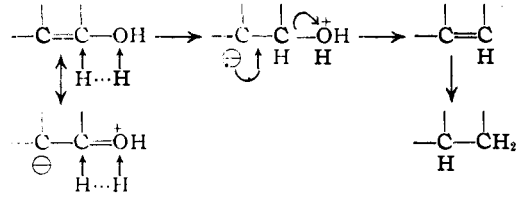


XXXIV

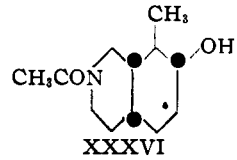


XXXV

of many substances containing the system —C=C—O —[37] may proceed only by type *a* hydrogenation, with simultaneous hydrogenolytic carbon–oxygen bond scission *and* addition of hydrogen to the unsaturated system in the case of multiply unsaturated substances such as the phenols. In the simplest case the reaction can be represented by the following sequence



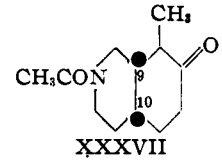
Neither scheme precludes the formation of small amounts of stable isomers, *e. g.* (XXXVI), having the *cis* ring-locking configuration, and the stable *trans* CH_3/OH relationship, but (1) would not be



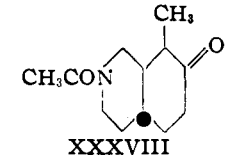
XXXVI

applicable in those cases in which carbon-oxygen cleavage is observed in the absence of an adjacent tertiary hydrogen atom. Finally, the observation that no cleavage takes place (*vide infra*) in high temperature Raney nickel hydrogenations, which are non-stereospecific, and therefore of type *b*, lends further support to alternative (2).

On hydrogenation in ethanol solution over Raney nickel at 150° under 3000 pounds pressure, N-acetyl-7-hydroxy-8-methyl-1,2,3,4-tetrahydroisoquinoline (XXVII) was almost quantitatively converted into a mixture of stereoisomeric N-acetyl-7-hydroxy-8-methyldecahydroisoquinolines, which was purified by distillation in a high vacuum. On standing, the crystalline *trans*-isomer (XXIX), m. p. 126–128°, identical with the alcohol from the platinum hydrogenation, separated in *ca.* 50% yield. Direct oxidation by chromic acid[38] in acetic acid of the total mixed isomers gave a mixture of isomeric N-acetyl-7-keto-8-methyldecahydroisoquinolines, from which the pure *cis*-isomer (XXXVII) was isolated in 23–36% yield as the crystalline *hydrate*, m. p. 80.5–82.5°. Similar oxidation of the *trans*-alcohol (XXIX) gave the oily *trans*-ketone (XXXVIII),



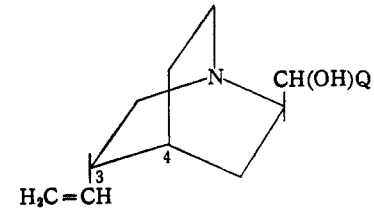
XXXVII



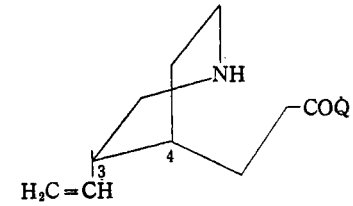
XXXVIII

which did not form a crystalline hydrate, and was not further characterized. Oxidation of the residual oily alcohol after removal of the crystalline *trans*-alcohol (XXIX) gave the hydrate of the *cis*-ketone (XXXVII) in 70% yield.

At this point, it is necessary to consider the stereochemistry of quinine in relation to that of the above decahydroisoquinoline derivatives. It has been suspected for some time[39] and there is now no doubt[40] that in quinine itself, and in quinotoxine, which retains asymmetry only at carbon atoms 3 and 4 (and consequently can exist only in two racemic modifications), the vinyl group and the —CH_2CH—CH(OH)Q (or —CH_2CH_2COQ) side chains are attached in the *cis* position with respect to the piperidine ring (*cf.* the space formulas [XXXIX] and [XL]. It will be evi-



XXXIX



XL

dent from the sequel that the 3 and 4 positions of the alkaloid molecules correspond to the 9 and 10 positions, respectively, of the synthetic decahydroisoquinoline derivatives, *e. g.* (XXXVII), described above. Consequently, the *cis*-isomer (XXXVII) was the one desired for further synthetic work, and conversely the configurations

(37) *Cf., e. g.*, Hückel, *Ann.*, **441**, 16 (1925); Jacobs and Scott, *J. Biol. Chem.*, **87**, 601 (1930); **93**, 139 (1931); Leuchs and Overberg, *Ber.*, **66**, 951 (1933); Butenandt and Westphal, *Z. physiol. Chem.*, **223**, 150 (1934); Long and Burger, *J. Org. Chem.*, **6**, 852 (1941); Martin and Robinson, *J. Chem. Soc.*, 492 (1943).

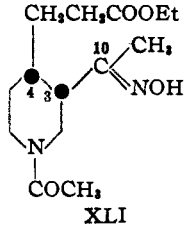
(38) N-Acetyl-7-hydroxy-8-methyldecahydroisoquinoline (XXIX) has four asymmetric carbon atoms (7, 8, 9 and 10), and may exist in eight racemic modifications, all of which might have been present in the mixture resulting from a non-stereospecific hydrogenation of the type described above. Consequently, in initial experiments, the entire mixture was oxidized directly, since this process would result directly in the reduction of the number of asymmetric carbon atoms by one (>*CHOH → >C=O), and indirectly by two, since the system (>*CH—C=O) would assume, by facile interconversion through the enol, whatever configuration was most stable.

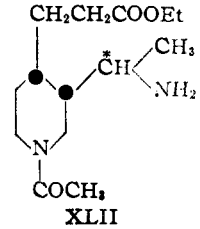
(39) Kenner, *Ann. Rep. Chem. Soc.*, **18**, 157 (1922). The same conclusion is reached by consideration of the relative stabilities of α- and β-cincholoiponic acids [Wohl and Losanitsch, *Ber.*, **40**, 4698 (1907); Wohl and Maag, *ibid.*, **42**, 627 (1909)].

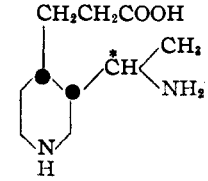
(40) Prelog and Zalan, *Helv. Chim. Acta*, **27**, 535 (1944).

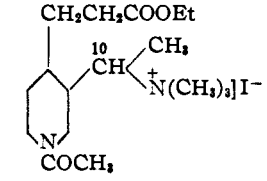
assigned above were based ultimately on the successful conversion of the apposite isomer into synthetic alkaloids of known stereochemical character. All of the substances described subsequently in this paper are *cis*-3,4-disubstituted piperidine derivatives obtained from the *cis*-ketone (XXXVII).

cis-N-Acetyl-7-keto-8-methyldecahydroisoquinoline (XXXVII), obtained from the crystalline hydrate by evaporation of its solution in benzene, was converted on treatment in absolute ethanol solution with sodium ethoxide and fresh, dry ethyl nitrite into N-acetyl-10-oximinodihydrohomomeroquinene ethyl ester[41] (XLI) in 68% yield.[42] The latter substance crystallized in two polymorphic modifications, a *labile*, m. p. 96–98°, and a *stable* form, m. p. 108.5–109°.[43] Hydrogenation of the oximino-ester (XLI) in acetic acid over platinum at room temperature gave the corresponding amino-compound (XLII). The crude oily product was probably a mixture of stereoisomeric amine acetates derived from (XLII), since a new asymmetric center (starred) was generated during reduction, and there was no reason to anticipate steric selectivity. However, since in a proximate later stage of the synthesis, the new asymmetric center was destroyed, it was not necessary to effect a separation of isomers at this point. The material was characterized by the isolation, after acid hydrolysis, of a crystalline 10-aminodihydrohomomeroquinene *dihydrate* (XLIII), m. p. 186.5–188°. It was necessary to handle the amino-esters (XLII) with care, since heat brought about changes which rendered the material useless for further synthetic work, probably through inter- and intramolecular condensations involving the amino and the carbethoxyl groups.

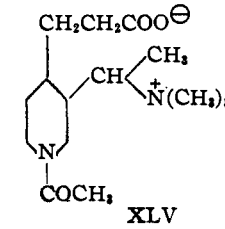

XLI


XLII

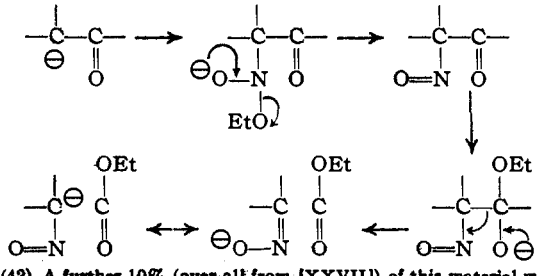

XLIII


XLIV

N-Acetyl-10-aminodihydrohomomeroquinene ethyl ester (XLII) was converted in 90% yield into N-acetyl-10-trimethylammoniumdihydrohomomeroquinene ethyl ester iodide (XLIV) on heating with excess methyl iodide in ethanol solution over potassium carbonate. The quaternary salt was obtained as a colorless analytically pure glass. This material, like the amino derivative from which it was obtained was probably a mixture of epimers differing in configuration at C. 10. With silver oxide, or with dilute alkalies, it was very rapidly converted to the stable betaine (XLV), but on treatment with very concentrated alkali hydroxides, normal Hofmann elimination took place. With 60% sodium or potassium hydroxide, vigorous evolution of trimethylamine commenced at 140°, and with simultaneous hydrolysis of the ester group and the amide link, homomeroquinene (XLVI)[45] was formed.[46] At-


XLV

(41) For instances of similar cleavage reactions, *cf.* Clarke, Lapworth and Wechsler. *J. Chem. Soc.*, **93**, 30 (1908). The cleavage reaction clearly proceeds by the following mechanism, to which attention has not hitherto been directed:

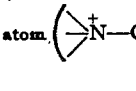


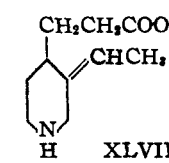
(42) A further 10% (over-all from [XXVII]) of this material was obtained on subjecting to the cleavage reaction the mixed ketones left after removal by means of the crystalline hydrate of as much *cis*-ketone (XXXVII) as possible from the mixture resulting from oxidation of the total hydrogenation product of (XXVII).

(43) The fact that the compound (XLI) retains the *cis* configuration is worthy of comment. Had we been dealing with the corresponding ketone, inversion would undoubtedly have taken place under the strongly alkaline reaction conditions, with formation of a *trans* compound. The stability of (XLI) is a consequence of the acidity of the oximino-group, since the distributed negative charge in the system

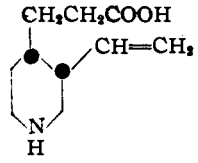
(*cf.* note 41) places a high barrier in the way of proton release from C. 3.

(44) Knorr, *Ber.*, **22**, 184 (1889); Willstätter, *ibid.*, **28**, 3288 (1895); Straus, *Ann.*, **401**, 374 (1912).

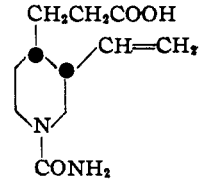
(45) We were able to proceed with the synthesis of (XLIV), with confidence that the elimination would take place in the desired direction, with the introduction of a vinyl group and formation of homomeroquinene, rather than with the formation of the ethylidene isomer (XLVIII), on the basis of a large body of evidence relating to decomposition of quaternary hydroxides $R_4N^+]OH^-$. The *Hofmann Rule* in its original form stated that in such decompositions ethylene was eliminated, if possible, in preference to any other olefin. More generally, it has been found subsequently that the olefin most readily eliminated is derived from that group containing the largest number of hydrogen atoms on the carbon atom β to the nitrogen atom.  These results indicate clearly that within


XLVIII

tempts to isolate the free acid directly from the reaction mixture were not successful, but when the reaction product was warmed for a short time in neutral aqueous solution with a slight excess of potassium cyanate, subsequent acidification resulted in the separation of pure N-uramidohomomeroquinene (XLVII), m. p. 165.2–165.8° (dec.). The over-all yield in the conversion of



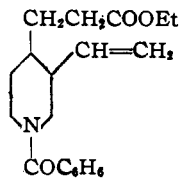
XLVI



XLVII

the crystalline oximino ester (XLI) to (XLVII) was 42%.

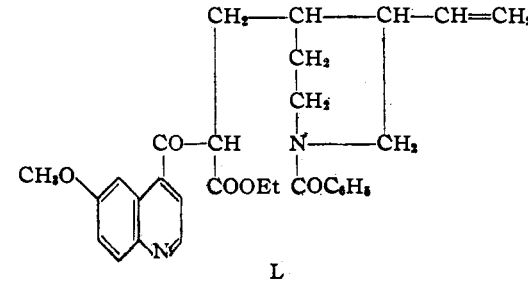
N-Uramidohomomeroquinene (XLVII) was readily converted in quantitative yield into a mixture of homomeroquinene hydrochloride and ammonium chloride on boiling with aqueous 0.1 *N* hydrochloric acid.[47] From the former, by treatment with silver oxide, followed by hydrogen sulfide, pure *dl-cis*-homomeroquinene (XLVI), m. p. 219–220°, was obtained. For synthetic purposes, the crystalline mixed chlorides, directly from the cleavage reaction, were treated with dilute ethanolic hydrogen chloride. Direct benzoylation in chloroform solution of the resulting *dl-cis* homomeroquinene ethyl ester hydrochloride with benzoyl chloride and potassium carbonate paste gave N-benzoylhomomeroquinene ethyl ester (XLIX), which was purified by molecular



XLIX

distillation, and was obtained in 96% yield (overall from [XLVII]) as a clear, colorless, viscous oil.

Condensation of the N-benzoyl ester (XLIX) with excess ethyl quininate (II, R = C_2H_5) was effected by heating the fused mixture of reactants with dry sodium ethoxide.[16,21] The crude intermediate β-keto ester (L), obtained as an alkali-



L

soluble oil, gave, on hydrolysis with boiling 6 *N* hydrochloric acid, crude *dl*-quinotoxine (IV, R = OCH_3) as an orange oil in 50% yield (from XLIX). Attempts to resolve the racemic alkaloid through its salts with *d*-tartaric acid were unsuccessful,[48] but the dibenzoyl-*d*-tartrates were readily separable by crystallization from methanol, that of the dextrorotatory isomer being the less soluble. Pure *d*-quinotoxine dibenzoyl-*d*-tartrate, m. p. 185.5–186°, showed no depression in melting point on admixture with the salt of the natural alkaloid. On regeneration from the salt, pure synthetic *d*-quinotoxine was obtained as a very light yellow viscous oil, $[\alpha]_D$ +43°. For further characterization, the synthetic base was converted to the beautifully crystalline *d*-quinotoxine-*d*-tartrate *hexahydrate*, m. p. 55–63°, and from the latter, by crystallization from absolute ethanol, to the *anhydrous* *d*-quinotoxine acid *d*-tartrate, m. p. 150–153°. The melting points of these two salts were not depressed on admixture with samples of the corresponding salts from natural quinotoxine. Table I recapitulates the com-

a single group, elimination should take place in the direction of the most heavily hydrogen-substituted β-carbon atom, and this conclusion has been verified experimentally in a number of cases. For a very interesting and thorough, if not entirely convincing, discussion of these points from the theoretical point of view, *cf.* Hughes and Ingold, *Trans. Faraday Soc.*, **37**, 657 (1941). It is not out of place to point out here that other elimination reactions involving a substituent (*e. g.*, Br, OH) on the 10-position would have given (XLVIII).

(46) It is evident that this reaction is the point at which, with the introduction of the double bond, the asymmetry at C. 10 is destroyed, and that the two possible epimers of (XLIV) differing in configuration at that center, give the same stereochemically homogeneous *cis*-homomeroquinene.

(47) Quantitative studies of the cleavage of simple ureas [*e. g.*, *cf.* Fawsitt, *Z. physik. Chem.*, **41**, 610 (1902); *J. Chem. Soc.*, **87**, 494 (1905)] on which this procedure was based indicate that the reaction is not a direct hydrolysis of the amide link, but rather, an isomerization to a substituted ammonium cyanate, followed by hydrolysis of the cyanate ion ($CNO^- + H_2O + H^+ \rightarrow CO_2 + NH_3$). The ease with which the uramido group is both introduced and removed suggests that it should be of general value in the separation and characterization of amino compounds. It has hitherto seen limited use in work with *α-amino acids* [*cf.* Dakin, *Am. Chem. J.*, **44**, 48 (1910)] in which case the situation is complicated by the tendency of the corresponding uramido derivatives to pass readily into hydantoins.

(48) This in spite of the fact that *dl*-tartaric acid is smoothly resolvable by natural *d*-quinotoxine. It is a little known albeit historically an important fact, that this, and the similar resolution by cinchotoxine were the first examples [Pasteur, *Compt. rend.*, **37**, 162 (1853)] of the now universally used method of resolution of a racemic compound by combination with an active material, followed by separation of the resulting diastereomers. Confusion seems to have resulted from the fact that quinotoxine and cinchotoxine (which were discovered by Pasteur [ref. 6]) were in 1853 known as quinicine and cinchonicine, and the resemblance to cinchonidine has led some to believe that the latter alkaloid was the first resolving agent [*cf.* Lowry, "Optical Rotatory Power," Longmans, Green and Co., 1935. p. 34] while others have assumed that the well-known alkaloids quinine and cinchonine were used. Further, Pasteur gave no experimental details of his work; in fact the original note to the French Academy was largely concerned with other matters, and the discovery is mentioned only in passing, there, and later, in the course of a series of lectures summarizing his work on molecular asymmetry ["Researches on the Molecular Asymmetry of Natural Organic Products," (1860); "Alembic Club Reprints," No. 14, p. 41]. Further, the published information elsewhere with regard to the tartrates of quinotoxine is fragmentary at best (*cf.* ref. 7. Even Beilstein contains no reference to Pasteur's work). A description of our experiences with the above resolution and with the characterization of the quinotoxine tartrates will be found in the Experimental Part of this paper.

parison of the natural and synthetic alkaloids and their derivatives.

TABLE I

	d-Quinotoxine (*natural*)	*d*-Quinotoxine (*synthetic*)
$[\alpha]_D$	+44°[a]	+43°
d-Tartrate *hexahydrate*	55 – 63°[b]	55 – 63°
Anhydrous *d*-tartrate	152 –155°	150 –153°
Dibenzoyl *d*-tartrate	185.5–186°	185.5–186°

[a] Hesse, *Ann.*, 178, 260 (1875). [b] *Cf.* ref. 7.

Crystallization of the dibenzoyl-*l*-tartrates[49] from the crude quinotoxine regenerated from the mother liquors of the above resolution gave pure *l*-quinotoxine dibenzoyl-*l*-tartrate, m. p. 185–186°, from which pure *l*-quinotoxine, $[\alpha]_D$ –43°, was obtained.

In view of the established conversion of quinotoxine to quinine,[12] with the synthesis of quinotoxine the total synthesis of quinine was complete.

Experimental

Aminoacetal.[28,50]—Into a solution of 38.2 g. of chloroacetal (b. p. 154.4–156.2°) in one liter of absolute methanol cooled to 0° dry ammonia was passed until 283 g. had been absorbed. The reaction mixture was then heated ten hours at 140° in the autoclave. The colored solution was concentrated on the steam-bath to 500 cc., 100 cc. of 5% aqueous potassium hydroxide was added, and concentration was continued until the vapors no longer burned. The solution was saturated with sodium chloride, treated with 100 cc. of 50% aqueous potassium hydroxide and extracted continuously with ether overnight. Concentration of the ether extract gave an oil from which on fractionation *in vacuo* 24.1 g. (72.5%) of **aminoacetal** (b. p. 99–103° [100 mm.]) was obtained.

Using twice the quantity of chloroacetal and the same quantities of methanol and ammonia, 40.0 g. of aminoacetal (60%) was obtained. By fractionation of the higher boiling material from fourteen such double runs through a two-foot column packed with glass rings, 83 g. (10%) of **diacetalylamine** (b. p. 189.0–189.4° (100 mm.); **oxalate**, m. p. 172.0–172.6° dec.) was obtained.

***m*-Hydroxybenzaldehyde.**—To a solution of *pure* stannous chloride (450 g.) in 600 cc. of concentrated hydrochloric acid cooled to 5°, 100 g. of *m*-nitrobenzaldehyde was added in one portion. The temperature rose slowly at first, and then very rapidly. The reaction was quenched (by immersion in an ice–salt-bath) at such time that the maximum temperature attained by the reaction-mixture was *ca.* 100° (the proper time for quenching depended on the size of the run, and the efficiency of stirring and cooling). During this period vigorous mechanical stirring was necessary. After quenching, the mixture was stirred very slowly for one and one-half hours. The orange-red paste of *m*-aminobenzaldehyde stannichloride was collected on a sintered glass funnel, sucked dry as possible, and suspended in 600 cc. of concentrated hydrochloric acid. While the reaction mixture was stirred continuously, a solution of 46 g. of sodium nitrite in 150 cc. of water was added gradually from a separatory funnel whose stem dipped below the surface of the solution; the rate of addition was regulated to keep the temperature of the reaction mixture between 4 and 5°. Stirring was continued further for one hour; the precipitated diazonium stannichloride was then collected on a glass funnel, sucked dry, and decomposed by addition in portions to 1700 cc. of boiling water (in a large vessel). During reaction, water lost by evaporation was replaced. The solution was then clarified with Norit (4 g.) and filtered hot. Overnight 48–52 g. (59–64%) of ***m*-hydroxybenzaldehyde** separated as orange or tan crystals, m. p. 99–101°. Further purification was effected by crystallization after solution in *ca.* one liter of boiling benzene, clarification with Norit, and concentration to 600 cc. (41–45 g. [51–56%], m. p. 101–102°).

***m*-Hydroxybenzylideneaminoacetal (XIV).**—To 70.0 g. of *m*-hydroxybenzaldehyde was added 80.0 g. of aminoacetal. The reaction mixture became warm and homogeneous, and was warmed one-half hour on the steam-bath, 300 cc. of benzene was added, and water was removed by filtration through solid anhydrous sodium sulfate. Sufficient ligroin (70–90°) was added at 35° to cloud the solution, which on scratching and seeding, deposited long silky needles of *m*-hydroxybenzylideneaminoacetal, m. p. 67.2–67.8°. On long standing, the needles changed to a heavy prismatic form of the same melting point. From the concentrated mother liquor a second crop of pure material was obtained. The total yield was 128.4 g. (94%).

7-Hydroxyisoquinoline (XV). (Method 1.)—*m*-Hydroxybenzylideneaminoacetal (50 g.) was dissolved as rapidly as possible by shaking and stirring in 118 cc. of 76.0% sulfuric acid previously cooled to 0°. The reaction mixture was allowed to stand twelve hours at 3°, and then thirty-six hours at room temperature. After pouring onto ice (700 g.) the brown solution was neutralized with ammonia and buffered with sodium carbonate. The precipitated crude 7-hydroxyisoquinoline (30 g., *dry*) was sublimed in five batches at 2 mm. (bath temperature 160°). The sublimate (27 g.) on crystallization from 95% ethanol (36 g./10 g. phenol) gave 20 g. (64%) of nearly pure 7-hydroxyisoquinoline as very faintly yellow plates, m. p. 227–229°.

Alternately the crude phenol could be purified through its *sodium salt*. In a typical experiment, 32 g. (dry) of the crude material was dissolved in 160 cc. of water containing 64 g. of sodium hydroxide. The yellow plates of the sodium salt which separated from the cooled solution were collected and recrystallized from three to four times their (wet) weight of water containing one to two times their (wet) weight of sodium hydroxide. On regeneration (24 g. obtained) and recrystallization (Norit) from methanol (*ca.* 500 cc.), 21 g. (60%) of quite pure, very light tan 7-hydroxyisoquinoline, m. p. 229–231°, was obtained in two successive crops.

Method 2.—*m*-Hydroxybenzaldehyde (10 g.) and aminoacetal (11.4 g.) were heated on the steam-bath for half an hour. The reaction mixture was dissolved in benzene, most of the water was removed (by anhydrous sodium sulfate, or by filtration through benzene-wetted paper), and the remainder driven off by evaporation twice with excess benzene, the last time to a volume of 20–30 cc. To the cooled benzene solution, 25 cc. of 80% sulfuric acid (previously cooled to 0°) was added with vigorous swirling or shaking. The reaction mixture was allowed to stand overnight in the cold room (3–5°) and then for twenty-four hours at room temperature (with occasional cooling if the temperature rose). The acid layer was then separated, combined with an aqueous washing of the benzene layer, and neutralized and buffered to precipitate the crude phenol, which was purified through the sodium salt as above (*cf.* method 1). The pure phenol (7.6 g., 64%) was obtained as light yellow plates, m. p. 229.3–230.4°.

Under otherwise comparable conditions, variation in the strength of the acid used gave the following results (10-g. runs):

Acid strength, %	72	76	78	80	82	84
Yield, %	30	43	59	64	44	31

With larger runs (100 g. of *m*-hydroxybenzaldehyde) better results were obtained with 82% sulfuric acid. In nineteen runs (50–100 g.) using method 2 (82% acid) and

(49) Dibenzoyl-*l*-tartaric acid was prepared from *l*-tartaric acid [Haskins and Hudson, THIS JOURNAL, 61, 1266 (1939)] by the method used for the preparation of the *d*-isomer [Butler and Cretcher, *ibid.*, 55, 2605 (1933); Zetzsche and Hubacher, *Helv. Chim. Acta*, 9, 291 (1926)].

(50) We are indebted to Dr. L. P. Kyrides and the Monsanto Chemical Co. who placed at our disposal approximately two kilos of aminoacetal, presumably prepared by the method described here, or an adaptation of it.

the sodium salt method of purification, pure 7-hydroxyisoquinoline was obtained in an average yield of 60%.

The purest samples of 7-hydroxyisoquinoline melted at 229.5–230.5°. A small sample was converted to the acetyl derivative by treating with excess acetic anhydride, blowing off excess reagent, and crystallizing the residue from ether. Pure **7-acetoxyisoquinoline** has m. p. 73–75°.

5-Hydroxyisoquinoline (XVI).—The mother liquor after removal of the sodium salt of 7-hydroxyisoquinoline from 32 g. of the crude mixed phenols was neutralized and buffered. When the very crude precipitate (5.9 g.) was sublimed at 2 mm. (bath 160°), 1.6 g. of light yellow crystalline material was obtained. The solution of the latter in 8 cc. of water containing 3.2 g. of sodium hydroxide, when seeded with the sodium salt of 5-hydroxyisoquinoline, deposited pure material, from which on neutralization 1.20 g. (*ca.* 5%) of 5-hydroxyisoquinoline, m. p. 227–232°, was obtained. This material did not depress the melting point of authentic[25] 5-hydroxyisoquinoline; mixed with an equal weight of 7-hydroxyisoquinoline, it melted quite sharply at 184–185°.[24] Further crystallization from methanol of the 5-hydroxy isomer raised the melting point to 231–233°, and acetylation (as above) gave **5-acetoxyisoquinoline**, m. p. 59–60°. A mixture of the 5- and 7-acetoxy compounds melted below room temperature. Neither of the acetates was stable on standing for long periods, and both were readily hydrolyzed on shaking with aqueous 2 *N* sodium hydroxide.

7-Hydroxy-8-piperidinomethylisoquinoline (XVIII).—To a solution of 6.0 g. of 7-hydroxyisoquinoline and 3.5 g. of piperidine in 30 cc. of 95% ethanol, 3.7 g. of 35% aqueous formaldehyde was added. The solution was heated for six hours on the steam-bath, and then evaporated to "dryness." The ethereal solution of the dark red oil was filtered from a small amount of ether-insoluble material, and diluted with petroleum ether. From the seeded solution, yellow crystals separated which gave pure material (1.1 g., 11%) on one recrystallization from hexane.

The combined mother liquors were concentrated and treated with 40 cc. of aqueous 2 *N* sodium hydroxide. The warm solution was decolorized (Norit) and cooled; a mold-like mat of extremely fluffy yellow needles of the *sodium salt* separated. The salt was dissolved in water, the resulting solution was neutralized, and the colorless oily product was extracted with ether. The ether was evaporated; crystallization of the residue from hexane gave a further 3.6 g. (36%) of the pure piperidinomethyl derivative. Further crops were obtained by combining the residue from the hexane mother liquors with material regenerated from the sodium salt mother liquors, and putting the total material through a fresh sodium salt–hexane purification. In this way a total of 61% of pure 7-hydroxy-8-piperidinomethylisoquinoline was obtained as beautiful stout glistening blocks, m. p. 81.5–82.5°.

Anal. Calcd. for $C_{15}H_{18}ON_2$: C, 74.36; H, 7.49; N, 11.57. Found: C, 73.79, 75.18; H, 7.65, 7.55; N, 11.86.

The substance was reduced very slowly and incompletely in ethanol over Adams platinum catalyst. The combined material from several long-continued hydrogenations was dissolved in aqueous 2 *N* sodium hydroxide. Ether extraction gave an acid-soluble oil, insoluble in strong aqueous base, which gave a crystalline **carbonate**, recrystallized from alcohol–ether, m. p. 103–110° (dec.).

Anal. Found: C, 69.59; H, 8.37.

The residual alkaline solution on seeding deposited much sodium salt of 7-hydroxy-8-piperidinomethylisoquinoline, which was removed. Neutralization of the residual solution precipitated an oil, sparingly soluble in ether. On long standing the oil crystallized in part. The solid material (probably XIX), m. p. 155.5–156.5°, on recrystallization from ethanol, separated in needles, m. p. 158.5–159.5°.

Anal. Calcd. for $C_{20}H_{24}O_2N_2$: C, 74.04; H, 7.46. Found: C, 74.18; H, 7.44.

7-Hydroxy-8-methylisoquinoline (XX): (a) By Hydrogen Exchange.—7-Hydroxy-8-piperidinomethylisoquinoline (0.45 g.) in 10 cc. of methylnaphthalene was boiled for twenty-two hours over 0.07 g. of 30% palladium–charcoal catalyst. Seventy-three cc. of hydrogen was evolved. The catalyst was removed, the solution was extracted with dilute acid, the acid extract was made basic and extracted with ether. The alkaline solution was neutralized, and extracted twice with ether. The extracts were evaporated, the residue was dissolved in alcohol, and treated with formaldehyde (to convert any 7-hydroxyisoquinoline present into unsublimable material of high molecular weight). The alcohol was removed; sublimation (2 mm.) of the residue gave a small amount of crystalline material, which on recrystallization from methanol separated in shiny platelets, m. p. 227–228°, which did not depress the melting point of an authentic sample of 7-hydroxy-8-methylisoquinoline (b or c, below); mixed with 7-hydroxyisoquinoline, m. p. <196°.

(b) **From 7-Hydroxy-8-piperidinomethylisoquinoline.**—To a solution of 10.0 g. of 7-hydroxy-8-piperidinomethylisoquinoline in 50 cc. of fresh absolute methanol (distilled from magnesium methoxide), a solution of 12.0 g. of sodium in 100 cc. of absolute methanol was added. The reaction mixture was heated for sixteen hours at 220° in the autoclave. Water was added, the solution was concentrated and acidified and the remaining alcohol was boiled off. Addition of excess aqueous 2 *N* sodium carbonate precipitated 5.10 g. of crude phenolic material. When the latter was sublimed *in vacuo* (2 mm., bath at 160°) 4.3 g. (65%) of light yellow crystalline 7-hydroxy-8-methylisoquinoline, m. p. 229–231°, was obtained. This material depressed the melting points both of 5- and 7-hydroxyisoquinoline below 196°. Recrystallized twice from methanol, pure 7-hydroxy-8-methylisoquinoline, m. p. 232.0–233.5°, was obtained as shining platelets.

Anal. Calcd. for $C_{10}H_9ON$: C, 75.44; H, 5.70; N, 8.80. Found: C, 73.96; H, 5.51; N, 8.94.

The phenol formed a nicely crystalline **acid oxalate dihydrate**, flat needles, s. 205–210°, m. p. 227° (dec.).

Anal. Calcd. for $C_{13}H_{13}O_7N$: C, 50.52; H, 5.30. Found: C, 50.95; H, 5.23.

(c) **Directly from 7-Hydroxyisoquinoline.**—To a solution of 30 g. of 7-hydroxyisoquinoline in 700 cc. of commercial absolute methanol, 21 cc. (18 g.) of piperidine was added. The solution was cooled to *ca.* 15°, 25 cc. of aqueous 33% formaldehyde solution was added, and the reaction mixture was allowed to stand for *ca.* twelve hours at room temperature. The orange solution was then evaporated to "dryness." During concentration it was advisable to filter once or twice to remove 1–2 g. of crude bis-(7-hydroxy-8-isoquinolyl)-methane (XXI) (see below) which separated, in order to avoid severe bumping. The thick red-orange residue was evaporated once or twice with a small quantity of acetone (20–30 cc.) and heated for two to three hours *in vacuo* on the steam-bath to remove the last traces of water. The separately collected dimer (XXI) was added, the combined material was taken up in 700 cc. of commercial absolute methanol containing 190 g. of dry sodium methoxide (fresh Mathieson alkoxide was satisfactory, while other commercial products were not) and heated at 220° for ten to twelve hours in the autoclave; 500 cc. of dilute (1:5) hydrochloric acid was added to the cooled reaction mixture, the methanol was removed by concentration (to *ca.* 300 cc.), the dark green-brown solution was made slightly acid with *ca.* 150 cc. of concentrated hydrochloric acid, and then neutralized by adding excess aqueous sodium carbonate. The precipitated light gray-brown crude phenol was collected, dried and sublimed *in vacuo* (2–5 mm.). The light yellow crystalline sublimate (26 g., 80%, m. p. 231–233°, with previous softening) was recrystallized from methanol, a first crop (17 g., 51%) separating as nearly colorless plates, m. p. 231–233°. The loss on direct crystallization was considerable; rather than take out further crops, the mother liquors from several runs were usually combined and concentrated; the residue was taken up in boiling methanol, and to the hot concentrated solution, saturated aqueous barium hydroxide was added until clouding was initiated. The material which separated was collected and recrystallized once from

methanol. In this way an average further yield of 12% per run of pure 7-hydroxy-8-methylisoquinoline, m. p. 231–233°, was obtained. The total yield of pure phenol was therefore 63%. These figures are based on a sequence of eleven typical 20–30 g. runs.

(d) From **Bis-(7-hydroxy-8-isoquinolyl-)-methane (XXI)**.—A quantity of this material, the separation of which is described under (c) above, was collected from a considerable number of runs. It was not sublimable, and was characterized as a beautifully crystalline canary yellow infusible *sulfate*. Twenty grams of the crude substance was treated in the usual way with 128 g. of sodium methoxide in 550 cc. of absolute methanol. When the reaction product was worked up directly after sublimation by the barium hydroxide method, 3.2 g. (29%) of pure 7-hydroxy-8-methylisoquinoline was obtained.

Oxidation of 7-Hydroxy-8-methylisoquinoline.—A solution of 0.92 g. of chromic anhydride in 30 cc. of cold acetic acid was added to a solution of 1.00 g. of 7-hydroxy-8-methylisoquinoline. A precipitate appeared immediately and remained on standing overnight. The reaction mixture was heated for a day at 45°, the excess reagent was decomposed by ethanol, and the solvent was removed *in vacuo*. The residue was made just alkaline with aqueous 2 *N* sodium hydroxide and extracted twice with ether. The extracts were evaporated and the residue was sublimed; the glassy sublimate of the quinol (XXIII) crystallized readily from ether as shiny yellow plates, m. p. 135.5–136.5°.

When 1 g. of the phenol, dissolved in 2 *N* sodium hydroxide, was treated with 6.0 g. of sodium peroxydisulfate in 20 cc. of water, a red, cloudy solution was obtained rapidly, from which ether extracted material which on working up as above gave a small quantity of the identical quinol, m. p. 135.5–136.5°.

One gram of 7-hydroxy-8-methylisoquinoline was treated with 50.0 cc. of 0.503 N peracetic acid. One atom of oxygen was consumed in 140 hours. The solvent was removed *in vacuo*. The residue was dissolved in water, treated with alkali and extracted with ether, which removed no material. The material which separated on neutralization of the aqueous solution was leached with boiling methanol, from which 0.22 g. of 7-hydroxy-8-methylisoquinoline, m. p. 232–233°, separated on cooling. The residual material on crystallization from 95% ethanol gave 90 mg. of the **N-oxide** (XXV), needles, m. p. 256–257° (dec.).

Anal. Calcd. for $C_{10}H_9O_2N$: C, 68.56; H, 5.18. Found: C, 68.80; H, 5.37.

The oxide was sparingly soluble in water, as was its hydrochloride. On sublimation it lost oxygen and reverted to 7-hydroxy-8-methylisoquinoline.

7-Hydroxy-8-methyl-1,2,3,4-tetrahydroisoquinoline (XXVI).—(a) 7-Hydroxy-8-methylisoquinoline (1.6 g.) in 100 cc. of glacial acetic acid absorbed two moles of hydrogen in approximately one hour over 0.5 g. of Adams catalyst. No further absorption took place on shaking for three hours more. The solvent was removed *in vacuo*, the residual crystalline acetate was dissolved in water, and the phenol was precipitated by bringing the solution to *p*H 8. The crude material was collected, dried, sublimed *in vacuo*, and crystallized from 40 cc. of methanol. 7-Hydroxy-8-methyl-1,2,3,4-tetrahydroisoquinoline (XXVI) separated (1.1 g.) as prismatic crystals, m. p. 246–250°.

Anal. Calcd. for $C_{10}H_{13}ON$: C, 73.59; H, 8.03; N, 8.58. Found: C, 72.95; H, 8.38; N, 8.48.

(b) 7-Hydroxy-8-methylisoquinoline (1.0 g.) in 30 cc. of 5 *N* hydrochloric acid was boiled for two hours with excess mossy tin. The stannichloride which separated on cooling was collected, dissolved in water, and treated with hydrogen sulfide. Precipitated stannic sulfide was removed, and the solution was made just alkaline to litmus; the precipitated material was recrystallized twice from methanol; it then weighed 0.11 g., had m. p. 248–250°, and was identical with the phenol described under (a, above).

Anal. Found: C, 73.41; H, 8.26; N, 8.63.

(c) Four grams of 7-hydroxy-8-methylisoquinoline was hydrogenated overnight at 130° and 3700 lb. pressure in 20 cc. of absolute ethanol containing 2 g. of Raney nickel. The reaction mixture contained crystalline material, which was dissolved in excess alcohol and combined with the original solution from which the catalyst had been removed. Concentration of the combined solutions gave two crops (1.83 g., 45%) of pure 7-hydroxy-8-methyl-1,2,-3,4-tetrahydroisoquinoline, m. p. 248–250°, identical with the material described above. Further complete removal of solvent left an oily residue from which an ether-insoluble *carbonate*, and, after successive treatment with acetic anhydride and 2 *N* hydrochloric acid, a crystalline material, m. p. 151.5–155.5°, were obtained. These materials were not further investigated.

N-Acetyl-7-hydroxy-8-methyl-1,2,3,4-tetrahydroisoquinoline (XXVII).—(a) One gram of 7-hydroxy-8-methyl-1,2,3,4-tetrahydroisoquinoline was suspended in 10 cc. of methanol and treated with 0.7 cc. of acetic anhydride. The solution became warm and clear; the material which separated on cooling on recrystallization from methanol gave 0.83 g. of prismatic needles, m. p. 187–198°. Four recrystallizations failed to raise or change the melting point.

Anal. Calcd. for $C_{12}H_{15}O_2N$: C, 70.22; H, 7.35; N, 6.83. Found: C, 70.54; H, 7.20; N, 7.03.

Evaporation of the combined mother liquors, solution of the residue in 2 *N* sodium hydroxide, and acidification to congo red gave a further 0.21 g. of the derivative, m. p. 187–198°.

(b) **Direct Method.**—Twenty grams of 7-hydroxy-8-methylisoquinoline was hydrogenated in 200 cc. of glacial acetic acid over 0.6 g. of Adams catalyst under *ca.* 60 lb. pressure. The theoretical amount of hydrogen was absorbed in *ca.* eighteen hours. The solvent was removed *in vacuo* at 40–50°, the residual acetate was taken up in 140 cc. of methanol, and 16 cc. of acetic anhydride was added to the hot solution. When the cooled solution was seeded or scratched, the acetyl derivative separated in large colorless plates or prisms. The filtrate from the first crop was evaporated, the residue was taken up in aqueous 10% sodium hydroxide and acidified to congo red with concentrated hydrochloric acid; the separated material was recrystallized from *ca.* 20 cc. of methanol (Norit). The total yield of pure N-acetyl-7-hydroxy-8-methyl-1,2,3,4-tetrahydroisoquinoline in a typical run was 24.5 g. (95%).

Platinum Catalyzed Hydrogenation of N-Acetyl-7-hydroxy-8-methyl-1,2,3,4-tetrahydroisoquinoline.—Four grams of N-acetyl-7-hydroxy-8-methyl-1,2,3,4-tetrahydroisoquinoline in 50 cc. of glacial acetic acid was shaken with hydrogen at 60 lb. initial pressure over 0.5 g. of (relatively unreactive) Adams catalyst. In sixteen hours the hydrogenation was complete, and about 3.8 moles had been absorbed. The solvent was removed *in vacuo*, and the residual oil was treated with 5 cc. of 2 *N* hydrochloric acid and extracted with ether; the residue from the ether extract (3.75 g.) was boiled three hours with 25 cc. of 2 *N* hydrochloric acid. The solution was made basic and extracted with ether; 2.06 g. (70%) of crude oily **8-methyldecahydroisoquinoline (XXXI)** was obtained from the extracts. The amine was further purified by conversion into the crystalline **bicarbonate** (1.20 g.) by passing wet carbon dioxide into an ethereal solution of the substance. The salt crystallized in needles, m. p. 78–84° (dec.).

Anal. Calcd. for $C_{11}H_{21}O_3N$: C, 61.36; H, 9.83; N, 6.51. Found: C, 60.93; H, 10.15; N, 6.51.

On regeneration from the crystalline bicarbonate, followed by distillation (b. p. 100° (12 mm.)), the amine was obtained as the very volatile **hemihydrate**, which on recrystallization from 1–2 volumes of ether at −10°, or from a larger volume at −70°, separated in needles, m. p. 41–43°.

Anal. Calcd. for $C_{10}H_{19}N\cdot\frac{1}{2}H_2O$: C, 74.01; H, 12.43; N, 8.64. Found: C, 73.90, 73.54, 73.74; H, 12.08, 11.65, 11.60; N, 8.82, 8.99, 8.96.

The amine was recovered unchanged after treatment with chromic acid in acetic acid for twenty-four hours.

The (ether extracted) hydrochloric acid solution of the initial reduced material was made basic and again extracted with ether; evaporation of the extracts left a partially crystalline residue (0.46 g.), from which on recrystallization from alcohol–ether, *trans*-**N-acetyl-7-hydroxy-8-methyldecahydroisoquinoline** (XXIX) separated in rosets of needles, m. p. 126–128°, identical with the material described below.

Anal. Calcd. for $C_{12}H_{21}O_2N$: C, 68.20; H, 10.02; N, 6.63. Found: C, 68.64; H, 10.83; N, 6.59.

Similar reductions with fresh, active Adams catalyst were complete in as little as three hours. In ethanol, no reduction took place until a small amount of concentrated hydrochloric acid was added, when slow hydrogenation occurred. In all cases, however, the product composition was essentially that described above.

Nickel Catalyzed Hydrogenation of N-Acetyl-7-hydroxy-8-methyl-1,2,3,4-tetrahydroisoquinoline.—(a) A solution of 1.63 g. of N-acetyl-7-hydroxy-8-methyl-1,2,3,4-tetrahydroisoquinoline in 10 cc. of absolute ethanol over 1 g. of Raney nickel was shaken with hydrogen at 3000 lb. pressure at 150° for sixteen hours. The catalyst was removed, the solution was evaporated to dryness, and the residue was distilled *in vacuo*.[51] The resulting mixture of isomeric **N-acetyl-7-hydroxy-8-methyldecahydroisoquinolines**, obtained in quantitative yield, was a very viscous oil, slightly soluble in ether, and completely soluble in aqueous 2 *N* hydrochloric acid. A portion was analyzed directly.

Anal. Calcd. for $C_{12}H_{21}O_2N$: C, 68.20; H, 10.02. Found: C, 68.06; H, 9.75.

On standing, such mixtures gradually deposited *ca.* 50% of crystalline *trans*-**N-acetyl-7-hydroxy-8-methyldecahydroisoquinoline** (XXIX), recrystallized, m. p. 126–128°, identical with the alcohol obtained in small yield by platinum reduction (above), mixed m. p. 126–128°. The initial separation was facilitated by seeding, or by the addition of a small amount of ether.

Anal. Calcd. for $C_{12}H_{21}O_2N$: C, 68.20; H, 10.02; N, 6.63. Found: C, 68.38; H, 9.48; N, 6.93.

Hydrolysis of 0.15 g. of the mixed alcohols by boiling for eighty minutes with 2 *N* sodium hydroxide gave an ether-extractable oil. When damp carbon dioxide was passed into the ethereal solution, the *carbonate* separated, from which after regeneration and crystallization from a small quantity of ether, a crystalline 7-hydroxy-8-methyldecahydroisoquinoline of undetermined configuration, m. p. 130–132°, was obtained.

Anal. Calcd. for $C_{10}H_{19}ON$: C, 70.95; H, 11.31. Found: C, 70.38; H, 10.83.

(b) **Preparative Method.**—See (a) under N-acetyl-7-keto-8-methyldecahydroisoquinoline, below.

N-Acetyl-7-keto-8-methyldecahydroisoquinolines (XXXVII and XXXVIII).—(a) N-Acetyl-7-hydroxy-8-methyl-1,2,3,4-tetrahydroisoquinoline (40 g.) was hydrogenated in 400 cc. of commercial absolute ethanol over 7 g. of Raney nickel at a starting pressure of 3000 lb. at 160° in twelve to eighteen hours. After removal and washing with methanol of the catalyst, the combined alcohol solutions were evaporated in a current of air, and the yellow viscous oily residue was placed *in vacuo* to remove the last traces of solvent. The crude mixture of alcohols was taken up directly in 280 cc. of hot glacial acetic acid, and divided into eight aliquots. To each portion, after cooling in an ice-bath, 34 cc. of a cooled chromic anhydride solution (0.0597 g./cc. in 1:4 water–glacial acetic acid; the amount of oxidant used was 20% in excess of the theoretical) was added. Shortly after addition of the oxidant, a heavy dark brown precipitate appeared which gradually dissolved on standing for two to three hours in the ice-bath. The reaction mixtures were then allowed to stand overnight at room temperature, and were subsequently warmed to 50° for one hour; the solution was then clear green. The aliquot portions were then combined and the solvents were removed as completely as possible *in vacuo* at 50–60°. The residue was dissolved in *ca.* 15 cc. of hot methanol, and 1000 cc. of ether was added with vigorous shaking. The ether solution was poured off, and the residue was extracted with a new portion of ether. The combined extracts were boiled to coagulate chromic salts, filtered and evaporated in a stream of air. Residual acetic acid was removed from the residue by heating *in vacuo* at 50–60°, and the resulting dark green oil was transferred to the still,[51] where it was left overnight *in vacuo* (water pump) at 60–70° to remove the last traces of solvents. The pressure was then carried from about 0.1 mm. to 0.03 mm. while the bath temperature rose from 100° to 170°. Three fractions were taken: 1F, 100–130°, 2 g. colorless mobile oil; 2F, 130–150°, 27 g. somewhat viscous oil; 3F, 150–170° + washings from cold finger; 5 g. somewhat viscous oil.

The free fractions were crystallized separately by taking up in twice their volume of ether, adding the theoretical amount of water (to form the monohydrate), shaking, and seeding or scratching. After the solution had stood overnight in the cold room, the crystalline material was collected by centrifugation. In all 13.3 g. (30% over-all from the tetrahydro compound [XXVII]) of *cis*-**N-acetyl-7-keto-8-methyldecahydroisoquinoline hydrate** (XXXVII) was obtained as beautiful large clear prisms. The substance was recrystallized by evaporating with benzene to remove water, taking up the residual oily anhydrous ketone in 75 cc. of ether, adding the theoretical quantity of water, and adding a few drops of methanol to the boiling solution to achieve homogeneity. On seeding the cooled solution deposited 11.6 g. (88% recovery, 26% over-all from [XXVII]) of absolutely pure ketone hydrate, m. p. 80.5–82.5°. On drying *in vacuo*, the hydrate lost water, and the pure oily ketone was formed. For analysis the ketone hydrate was dried in air.

Anal. Calcd. for $C_{12}H_{19}O_2N \cdot H_2O$: C, 63.40; H, 9.32. Found: C, 63.34; H, 8.85.

The above procedure was a typical run. In a sequence of thirteen runs, the over-all yield from XXVII of the recrystallized ketone hydrate varied from 24–36%; the average yield was 28%.

(b) When 1.43 g. of the oily *cis*-N-acetyl-7-hydroxy-8-methyldecahydroisoquinoline, from which as much as possible of the crystalline *trans*-alcohol (XXIX) had been removed by crystallization and centrifugation, was oxidized as above (a), the crystalline hydrate of the *cis*-ketone (XXXVII), m. p. 80.5–82.5°, identical with that described above, was obtained in 70% yield.

(c) Oxidation as above (a) of the crystalline *trans*-alcohol (XXIX), m. p. 126–128°, gave after fractionation *in vacuo* the liquid *trans*-ketone (XXXVIII), which unlike XXXVII did not form a crystalline hydrate.

(d) The mother liquors from the separation of the *cis*-ketone hydrate by the procedure described in (a) gave on evaporation and redistillation an oily mixture of ketones in which the *trans*-isomer (XXXVIII) predominated, but which still contained, on the basis of the experiments described below (under N-acetyl-10-oximinodihydrohomomeroquinene ethyl ester), at least 17% of the *cis*-isomer (XXXVII).

N-Acetyl-10-oximinodihydrohomomeroquinene Ethyl Ester (XLI).—Pure *cis*-N-acetyl-7-keto-8-methyldecahydroisoquinoline hydrate (19 g.) was taken up in benzene, which was boiled off in order to remove water. The residual anhydrous oily ketone was taken up in *ca.* 100 cc. of *anhydrous* ethanol (freshly distilled from magnesium ethylate), protected with a calcium chloride drying tube and cooled to 0° in an ice-bath. A cold solution of carefully cleaned and dried sodium metal (1.94 g., the theoretical quantity) in *anhydrous* ethanol was added, the volume was brought to 300 cc. by addition of more absolute ethanol, and 7.25 cc. of *anhydrous* ethyl nitrite was added (the ethyl nitrite was freshly prepared, distilled, dried over solid potassium hydroxide, and redistilled from potassium hy-

(51) This and other high vacuum distillations described subsequently were very conveniently carried out in short-path stills built on the cold finger principle, with central take-offs so placed as to allow the condensate drops to fall directly into the receiver.

droxide immediately prior to use). The reaction mixture was allowed to stand in the cold-room at +3 to +5° for eighteen hours. Carbon dioxide was then bubbled through the yellow-orange solution for three to four hours. Filter-aid and charcoal were then added, and the solution was heated to boiling, filtered, and evaporated to dryness on the steam-bath. The oily residue was taken up in 200 cc. of ether, decolorized with Norit, and filtered to remove the latter and a small quantity of ether-insoluble material. When the solution was concentrated to *ca.* 50 cc., scratched, and allowed to stand overnight in the cold, the major portion of the beautifully crystalline, gleaming, highly refractive oximino-ester separated. From the mother liquor, a second crop was taken; in all 18 g. (78%) of N-acetyl-10-oximinodihydrohomomeroquinene ethyl ester (XLI), m. p. 107.5–108.5°, was obtained. The ester was recrystallized by taking up in 5 cc. of methanol, and adding 50 cc. of boiling ether. In two crops, 16.5 g. (71% overall, 92% recovery) of the recrystallized ester was obtained as glass-clear, large hexagonal, highly refractive blocks, m. p. 108.5–109°.

Anal. Calcd. for $C_{14}H_{24}O_4N_2$: C, 59.14; H, 8.51; N, 9.85. Found: C, 59.39; H, 8.24; N, 10.02.

The run described was a typical one. In a sequence of eight runs, the yield of *recrystallized* oximino-ester varied from 58–76%; the average yield was 68%.

When the oximino-ester was first prepared, and in numerous subsequent runs, a *labile* crystalline form, m. p. 96–98°, was isolated. This form survived recrystallization until the stable form, m. p. 108.5–109°, first appeared in the laboratory. All subsequent runs gave the stable form, and further, subsequent recrystallizations of the labile form, under any conditions, gave only the stable form, m. p. 108.5–109°. A mixture of the two solid forms sintered momentarily at *ca.* 96°, and then melted at 108–109°.

When 5 g. of the distilled mixed ketones (see [d] above) from the mother liquors after separation of the *cis*-ketone hydrate, m. p. 80–82°, was subjected to the above procedure (0.55 g. of sodium metal, 1.75 cc. of ethyl nitrite, 85 cc. of absolute ethanol), it was possible to isolate 0.87 g. of the *cis*-oximino-ester, m. p. 107.5–108.5°, identical with that described above. Assuming that the yield in the reaction could not have exceeded 76%, this experiment demonstrated that the ketone mixture used still contained at least 17% of the *cis*-isomer (XXXVII), or (less likely) a comparable amount of an isomeric ketone having the *cis*-ring locking configuration, but differing from XXXVII in the stereochemical relationships at C. 8.

N-Acetyl-10-trimethylammoniumdihydrohomomeroquinene Ethyl Ester Iodide (XLIV).—N-Acetyl-10-oximinodihydrohomomeroquinene ethyl ester (5 g.) absorbed the theoretical quantity of hydrogen on shaking at 1–3 atmospheres in 150 cc. of glacial acetic acid over 1.0–1.5 g. of Adams catalyst in twenty to forty hours. When the hydrogenation was complete, the major part of the solvent was removed *in vacuo* at *room temperature* (it was extremely important not to warm the reaction mixture or to allow it to stand for long periods of time), the residue was taken up in some 250 cc. of commercial absolute ethanol, and heated (*oil-bath*) under reflux with 50 g. of anhydrous potassium carbonate and 50 g. of freshly distilled methyl iodide. From time to time, further quantities of carbonate and methyl iodide were added (25–50 g. of each, in all). After forty-eight hours under reflux, the reaction-mixture was cooled, filtered from potassium carbonate and iodide, and concentrated *in vacuo*. The residue was taken up in chloroform, filtered from residual inorganic salts and again concentrated *in vacuo*. The residue of **N-acetyl-10-trimethylammoniumdihydrohomomeroquinene ethyl ester iodide (XLIV)** after drying *in vacuo* at 100° until no further loss of weight occurred was either a pale yellow glass, or a white solidified froth of bubbles, and weighed 7.1 g. (91%). For analysis a sample was dissolved in water, the aqueous solution was extracted continuously overnight with ether (practically no material was removed), the aqueous solution was concentrated, the residue was taken up in chloroform, filtered, the chloroform was removed, and the colorless glassy residue was dried *in vacuo* for some hours.

Anal. Calcd. for $C_{17}H_{33}O_3N_2I$: C, 46.45; H, 7.55; N, 6.35. Found: C, 46.67; H, 7.14; N, 6.18.

The average yield in a sequence of ten runs was 90%. No disadvantage was introduced when the methylation was carried out on a much larger scale. The quaternary iodide gave off no trimethylamine on boiling with dilute aqueous bases, and was rapidly transformed by silver chloride and silver oxide to the corresponding quaternary chloride and the betaine (XLV), respectively. Aqueous solutions of the latter were stable on long boiling, alone or in the presence of dilute base.

When the amino compound (XLII) resulting directly from the hydrogenation of the oximino-ester (XLI) was hydrolyzed either with 20% aqueous sodium hydroxide, or with 1:1 aqueous hydrochloric acid, small quantities of a 10-aminodihydrohomomeroquinene dihydrate (XLIII), m. p. 186.5–188°, were obtained.

Anal. Calcd. for $C_{10}H_{20}O_2N_2 \cdot 2H_2O$: C, 51.20; H, 10.24; N, 11.86. Found: C, 50.83; H, 9.90; N, 12.04.

N-Uramidohomomeroquinene (XLVII).—The quaternary iodide (XLIV) (1.45 g.) was taken up in approximately an equal quantity of water, and heated (oil-bath) in a platinum or nickel crucible with vigorous stirring with 2.5 cc. of a solution of 5 g. of sodium (or potassium) hydroxide in 4 cc. of water. Vigorous evolution of trimethylamine commenced at 140°. The temperature was gradually raised to 165–180° while stirring was continued and water was dropped in from time to time to replace that lost by evaporation. When the evolution of trimethylamine had ceased (one half to one hour), the reaction mixture was allowed to cool, and the excess aqueous sodium hydroxide solution (which contained no organic matter) was pipetted from the upper layer of reaction product, which was usually a light tan granular layer of solid or semi-solid material. The latter was taken up in *ca.* 3 cc. of water; the solution was just neutralized to litmus with concentrated hydrochloric acid, decolorized with Norit, filtered, and treated with 0.35 g. of potassium cyanate in a small quantity of water. After heating for half an hour on the steam-bath, the solution was acidified to congo red with concentrated hydrochloric acid while hot. On cooling, **N-uramidohomomeroquinene (XLVII)** crystallized (0.30 g., 38%) in small shining prisms, m. p. 163–164° (dec.). Occasionally it was necessary to scratch and triturate the material which separated initially in order to effect complete crystallization. The derivative crystallized beautifully from pure water, but the loss was considerable, due to dissociation of the urea grouping, and it was preferable to purify the substance by dissolving it in water, adding slightly more than the theoretical quantity of potassium cyanate, warming for twenty to thirty minutes on the steam-bath and acidifying to congo red, when the substance separated in large, pretty, bold prisms, m. p. 165.2–165.8° (dec.).

Anal. Calcd. for $C_{11}H_{18}O_3N_2$: C, 58.40; H, 8.02; N, 12.39; CH_3-C, nil. Found: C, 58.13; H, 7.45; N, 12.39; CH_3-C, nil.

N-Uramidohomomeroquinene decolorized bromine and permanganate instantly in aqueous solution. No trouble was experienced in carrying out the above reaction in batches as large as 7 g. of the quaternary iodide. In a sequence of eleven runs (1–7 g. of quaternary iodide) the average yield (over-all from the oximino-ester [XLI]) was 40%.

From the uramido compound there was obtained a **cinchonidine salt**, which after crystallization from boiling acetone containing a trace of methanol had m. p. 155–157°.

In an early run carried out in a closed system, the reaction mixture was evaporated several times with water; from the combined aqueous distillate, 63% of the theoretical quantity of trimethylamine was isolated as the sparingly soluble **aurichloride**, m. p. 248–250° (dec.).[44]

***dl*-Homomeroquinene (XIII or XLVI).**—N-Uramidohomomeroquinene (XLVII) (81 mg.) was heated under reflux with 13 cc. of 0.1 *N* aqueous hydrochloric acid

for thirty-four hours. The solution was then shaken with 0.21 g. of silver oxide, filtered, saturated with hydrogen sulfide, filtered, concentrated *in vacuo*, centrifuged, separated from a further small quantity of silver sulfide, and evaporated to dryness *in vacuo*. In this way, 65 mg. (100%) of crystalline free ***dl*-homomeroquinene**, m. p. 214–215° (dec.), was obtained. On recrystallization from methanol, the acid separated in stout white blocks, m. p. 219–220° (dec.).

Anal. Calcd. for $C_{10}H_{17}O_2N$: C, 65.52; H, 9.35; N, 7.64. Found: C, 65.15; H, 9.14; N, 8.23.

The *dl*-homomeroquinene gave a neutral **dibenzoyl-*d*-tartrate**, m. p. 166–168°, which was very soluble in methanol, and crystallized from that solvent on the addition of acetone in beautiful glistening rectangular plates.

N-Benzoylhomomeroquinene Ethyl Ester (XLIX).—N-Uramidohomomeroquinene (XLVII), m. p. 159–161° (2.51 g.), was boiled under reflux with *ca.* 400 cc. of 0.1 *N* hydrochloric acid (3½ cc. concd. HCl in 400 cc. H_2O) for twenty-seven hours. The dilute hydrochloric acid was removed *in vacuo*, and the residue was evaporated three times with *ca.* 4% absolute ethanolic hydrogen chloride (6.5 g. of dry hydrogen chloride in 153 g. of alcohol). The residue was treated with 20 cc. of warm chloroform, the undissolved ammonium chloride was washed several times with 5–10 cc. portions of warm chloroform. The weight of dry ammonium chloride was 0.62 g. (calcd., 0.60 g.). Anhydrous potassium carbonate (7 g.) was made into a mush with 3.5 cc. of water (1.7 cc. excess over the quantity necessary to convert the anhydrous carbonate into $K_2CO_3 \cdot 2H_2O$). The combined chloroform extracts (from above) containing the homomeroquinene ester hydrochloride was poured over the carbonate mush, and stirred vigorously and boiled under reflux for half an hour. To the cooled reaction mixture, 2.0 cc. of freshly distilled (*in vacuo*) benzoyl chloride (2.4 g., = 50% excess over the theoretical amount) in 4 cc. of chloroform was added dropwise during ten minutes. The reaction mixture, which warmed somewhat spontaneously, was then boiled under reflux with vigorous stirring for two hours. The chloroform solution was decanted, the inorganic salts were washed with chloroform, and the combined chloroform extracts were evaporated to small volume and transferred to the molecular still. The remainder of the chloroform was removed, and the still was left on the water-pump vacuum for seven hours at 50° to remove the last traces of low-boiling material. The still was then put on the high vacuum pump, and the temperature was raised gradually. The following fractions were taken:

I, 0.08 g. red oil carried over mechanically before start of molecular distillation, during removal of chloroform.

II, 0.07 g. crystals and oil washed from cold finger, strong odor of benzoyl chloride.

III, 0.33 g. crystals and oil washed from cold finger, odor of benzoyl chloride quite strong, after solution in ether, extraction with aqueous K_2CO_3, and evaporation → 0.24 g. clear oil.

IV, 0.11 g. no crystals evident; benzoyl chloride odor *very* faint. Fraction IV was taken at *ca.* 129°, p = 0.2–0.1 mm.

V, 2.87 g. clear colorless odorless heavy viscous liquid. Fraction V was taken during eight to nine hours; the bath temperature rose very gradually during this time from 134° (initial) to 145° (final), while the pressure fell from 0.08 mm. (initial) to 0.01 mm. (final).

Fractions I, II, III, and IV were combined in ether solution, which after extraction with aqueous potassium carbonate was added to the residue remaining in the still after taking Fraction V. The molecular distillation was then resumed, and after a few preliminary fractions containing small amounts of benzoyl chloride were removed as above, a further fraction of N-benzoylhomomeroquinene ethyl ester was obtained.

VI, 0.50 g. clear colorless odorless heavy viscous liquid.

Total weight of **N-benzoylhomomeroquinene ethyl ester (XLIX)**, 3.37 g. = 96.3%.

***dl*-Quinotoxine** (IV, R = OCH_3).—N-Benzoylhomomeroquinene ethyl ester (2.70 g., 0.0086 mole) from Fraction V (above) was mixed with 4.0 g. of ethyl quininate (0.0173 mole = 100% excess). Absolutely dry pulverulent sodium ethoxide (1.4 g., 0.0207 mole = 140% excess, based on N-benzoylhomomeroquinene ethyl ester) was added, and the reaction mixture was heated to 80° with continuous stirring. As the ethyl quininate melted, and the materials became thoroughly mixed, the initial yellow color changed to brown and then gradually to deep red. The reaction mixture was maintained at *ca.* 82° for fourteen hours with continuous stirring. It was then cooled, and the resulting very hard dark red mass was decomposed with ice water and benzene. The (not entirely clear) combined aqueous layers were extracted with a small amount of ether. The clear deep red aqueous layer was then made just acid to litmus. The precipitated oil was taken up in ether. Evaporation of solvent, finally *in vacuo*, gave 2.56 g. of a red glass. The combined benzene and ether extracts from above, containing largely neutral material, were extracted with 10% aqueous sodium hydroxide. The alkaline extract was made just acid to litmus, and extraction with ether, followed by removal of solvent, gave a further small quantity of β-keto-ester, 0.16 g. Total weight of crude **N-benzoylquinotoxine carboxylic acid ethyl ester (L)**, was 2.72 g. = 63.4%.

N-Benzoylquinotoxine carboxylic acid ethyl ester (2.72 g.) was dissolved in 30 cc. of 1:1 aqueous hydrochloric acid. The clear reddish-orange solution was then boiled under reflux for four hours. The very dark reddish-brown solution was extracted with ether; from this extract 0.50 g. of benzoic acid was obtained on evaporation. The aqueous solution was then made strongly alkaline, and extracted with ether; 0.23 g. of ether-insoluble interface material was discarded. Removal of solvent from the above ether extract gave 1.39 g. (50%) of crude ***dl*-quinotoxine** as a reddish viscous oil.

Resolution of *dl*-Quinotoxine.—The above crude *dl*-quinotoxine (1.39 g.) was taken up in a small quantity of benzene, 1.00 cc. of water and 0.64 g. of *d*-tartaric acid were added, and the mixture was heated until the benzene was removed. The dark solution was allowed to stand overnight in the cold room, *ca.* 15 cc. of water was then added, and a certain amount of dark insoluble material was separated by decantation. The clear aqueous solution was made strongly alkaline and extracted with *ca.* 10 cc. of ether (some dark oily interface material was soluble in neither phase). The ether solution was allowed to stand until clear (fifteen minutes) and was then decanted and evaporated to dryness. The residue was triturated with 2–3 cc. of fresh ether, which was decanted and evaporated. The undissolved residue weighed 0.31 g., while the ether extract contained 0.56 g. of a viscous light orange-yellow oil. The latter was taken up in a very small amount of benzene, 0.26 g. of *d*-tartaric acid and 0.4 cc. of water were added, the benzene was removed by heating, the clear reddish-yellow solution was seeded with a trace of *d*-quinotoxine-*d*-tartrate . hexahydrate, and placed in the cold room at 5° overnight. Very fine canary-yellow needles of a *salt* separated, which was more soluble in and did not crystallize as well from water as natural *d*-quinotoxine-*d*-tartrate (see below). After four further recrystallizations, which were attended by serious losses, the salt, m. p. 40–55°, gave on treatment with base 44.4 mg. of partially resolved quinotoxine ($[\alpha]_D$ +13°). This material (43.5 mg.) was converted to the neutral dibenzoyl-*d*-tartrate by treatment with 25.2 mg. of dibenzoyl-*d*-tartaric acid in 150 mg. of methanol; 30.2 mg. of the nicely crystalline crude salt, m. p. 175–177°, separated, which after one further recrystallization from twice its weight of methanol separated in pure form (16.6 mg.), m. p. 184–185°, mixed with a sample of authentic *d*-quinotoxine dibenzoyl-*d*-tartrate, mixed m. p. 184–185°. The *d*-quinotoxine regenerated from the synthetic salt had $[\alpha]_D$ +43° (EtOH).

The mother liquors from the incomplete *d*-tartaric acid resolution were then arranged roughly according to degree of resolution, and from each the alkaloid was regenerated

and converted to the dibenzoyl-*d*-tartrate. Systematic fractional crystallization from methanol, involving thirty-two steps, then gave a total of 233 mg. (11% over-all from XLIX) of pure **d-quinotoxine dibenzoyl-d-tartrate**, m. p. 185.5–186.0°, mixed with a sample of the salt prepared from the natural alkaloid, mixed m. p. 185.5–186.0°. The pure synthetic *d*-quinotoxine regenerated from the salt was a very pale yellow viscous oil, $[\alpha]_D$ +44° (EtOH).

A sample of synthetic *d*-quinotoxine (29.4 mg.) was converted to the *anhydrous* acid *d*-tartrate by treatment with 13.6 mg. of *d*-tartaric acid in a minimum quantity of absolute ethanol; 31.7 mg. of anhydrous **d-quinotoxine acid d-tartrate**, m. p. 150–153°, was obtained. Mixed with the corresponding salt (m. p. 152–155°) from the natural alkaloid, the mixed m. p. was 151–154°.

Anal. Calcd. for $C_{24}H_{30}O_3N_2$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.75; H, 6.03; N, 5.93.

On recrystallization from 80 mg. of water, the synthetic anhydrous tartrate was converted into the characteristic **d-quinotoxine d-tartrate hexahydrate**, beautiful long stout canary-yellow needles (26.4 mg.), m. p. 55–63°, mixed with a sample of the corresponding pure salt (m. p. 55–63°) from the natural alkaloid, mixed m. p. 55–63°.

When 290 mg. of *l*-enriched quinotoxine regenerated from the mother liquors from the above resolution was treated with 168 mg. of dibenzoyl-*l*-tartaric acid in a minimum quantity of methanol, and the salt which separated was recrystallized directly five times from methanol, 34.6 mg. of pure *l*-quinotoxine dibenzoyl-*l*-tartrate, m. p. 185–186°, was obtained.

Resolution of *dl*-Tartaric Acid by *d*-Quinotoxine.—The resolution of *dl*-tartaric acid was readily effected through the *d*-quinotoxine *d*-tartrate hexahydrate described above; it is highly probable that this was the salt with which Pasteur worked in 1853.[48]

The pure (natural) *d*-quinotoxine regenerated from 2.00 g. of the pure anhydrous *d*-tartrate, m. p. 152–155°, was dissolved in a small quantity of benzene and treated with 0.708 g. of *dl*-tartaric acid (monohydrate) and 1.00 cc. of water. The solution was then heated to drive off the benzene, cooled, and seeded with the hexahydrate, m. p. 55–63° (seeding was not necessary to induce crystallization). The yellow needles of the salt which separated were filtered by centrifuging, and twice recrystallized from 1.2 cc. of water. The pure *d*-quinotoxine *d*-tartrate hexahydrate (0.71 g., 58%) was obtained in characteristic stout yellow needles, m. p. 55–63°, which did not depress the melting point of an authentic sample. The salt was soluble in water at room temperature to the extent of *ca.* 0.05 g./cc. The sample from the resolution was converted on crystallization from absolute ethanol into the anhydrous salt, m. p. 151–154°, identical with an authentic sample.

We wish to express our appreciation of the aid given us by our preparative assistants, Mr. Richard S. Corley throughout, and Mr. Donald B. Sparrow through the latter half of the program. The persistence, zeal, and efficiency with which these men carried out their duties made their participation an important factor in the successful completion of the work.

Summary

7-Hydroxyisoquinoline (XV) has been converted, in succession, through 7-hydroxy-8-piperidinomethylisoquinoline (XVIII), 7-hydroxy-8-methylisoquinoline (XX), 7-hydroxy-8-methyl-1,2,3,4-tetrahydroisoquinoline (XXVI), N-acetyl-7-hydroxy-8-methyl-1,2,3,4-tetrahydroisoquinoline (XXVII), N-acetyl-7-hydroxy-8-methyldecahydroisoquinoline (XXXVI), N-acetyl-7-keto-8-methyldecahydroisoquinoline (XXXVII), N-acetyl-10-oximinodihydrohomomeroquinene ethyl ester (XLI), N-acetyl-10-aminodihydrohomomeroquinene ethyl ester (XLII), N-acetyl-10-trimethylammoniumdihydrohomomeroquinene ethyl ester iodide (XLIV), homomeroquinene (XLVI), N-benzoylhomomeroquinene ethyl ester (XLIX), and N-benzoyl-8-carbethoxyquinotoxine (L), to *dl*-quinotoxine (IV, R = OCH_3). Resolution of the latter through its salts with dibenzoyl-*d*-tartaric acid gave *d*-quinotoxine, identical in all respects with the natural substance. This work, taken with Rabe's earlier conversion of *d*-quinotoxine to quinine, constitutes a total synthesis of the latter alkaloid.

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NOTES

The Action of Lead Tetraacetate on Acenaphthene and Acenaphthenyl Acetate[1]

BY RONALD F. BROWN AND LIM SING YEE[2]

Since we were in need of quantities of acenaphthoquinone for various purposes, it seemed worth while to investigate the action of lead tetraacetate on acenaphthene, even though the method of Graebe and Gfeller[3] has been used satisfactorily. Monti[4] has reported that lead tetraacetate in glacial acetic acid with acenaphthene yields acenaphthylene as the principal product either at room temperature or at 110°, although, at the latter temperature, some polyacenaphthylene and dinaphthylenecyclobutane were obtained. In no case was any acenaphthenediol diacetate formed, and no mention is made of acenaphthenyl acetate as a product. Fieser and Cason[5] have shown that acenaphthenyl acetate can be prepared in

(1) Abstracted from a thesis presented to the Graduate School of the University of Southern California in partial fulfillment of the requirements for the degree of Master of Science, May, 1943. Original manuscript received November 14, 1944.

(2) Present address: Firestone Tire and Rubber Company, Los Angeles, California.

(3) Graebe and Gfeller, *Ber.*, **25**, 652 (1892).

(4) Monti, *Gass. chim. ital.*, **68**, 608 (1938); *Chem. Abs.*, **33**, 1716 (1939); Monti, *Atti X° congr. intern. chim.*, **3**, 256 (1939); *Chem. Abs.*, **33**, 9316 (1939).

(5) Fieser and Cason, THIS JOURNAL, **62**, 432 (1940); Cason "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., Vol. 21, p. 1, 1941.