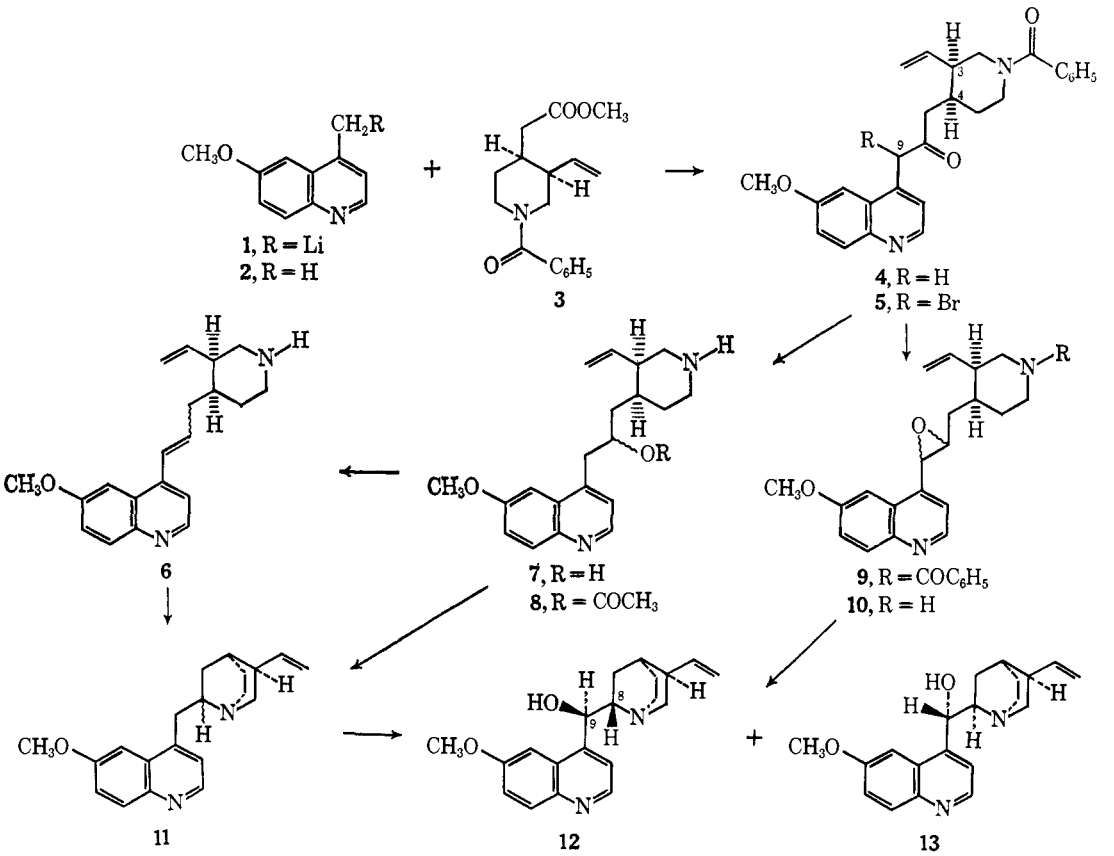
Scheme I



sium *t*-butoxide in an atmosphere of oxygen resulted in rapid uptake of 1 equiv of oxygen affording a mixture of **12** and **13**. Separation by a combination of crystallization and chromatography gave 32% of quinine [**12**; neutral (+)-tartrate monohydrate, mp and mmp 207–209°, dec > 200°; $[\alpha]^{25}D$ −154.1° (*c* 0.8, MeOH); the free base was spectroscopically identical with natural quinine], 41% of quinidine [**13**; mp and mmp 170–171°; $[\alpha]^{25}D$ 259° (*c* 1.0, EtOH); spectroscopically identical with natural quinidine], and 15% of a mixture of epiquinine and epiquinidine.

An alternative synthetic route carried out with semisynthetic 3(*R*),4(*S*)-N-benzoylmeroquinene methyl ester (**3**)[5] proceeded nonstereoselectively. It involved direct conversion of a mixture of the diastereomeric aminoepoxides **10** to quinine (**12**), quinidine (**13**), epiquinine, and epiquinidine by construction of the quinuclidine ring with concommitant formation of the hydroxyl function. Thus, ketone **4** [3(*R*),4(*S*) enantiomer, $[\alpha]^{24}D$ +27.3° (*c* 1.0, $CHCl_3$)] was converted into a mixture of diastereomeric N-benzoyl epoxides **9** [40%; glass; $[\alpha]^{25}D$ +12.4° (*c* 1.3, $CHCl_3$); δ^{CDCl_3} 3.90 (s, OCH_3); 3.6, 4.1, and 4.4 (2 H, *HCOCH*), 5.1 (m, $=CH_2$), 5.7 (m, $-CH=$), 7.34 and 7.38 (2 s, phenyl)] by bromination (N-bromosuccinimide in CCl_4–*hν*) followed by sodium borohydride reduction of the resulting crude α-bromo ketone **5**. Reductive debenzoylation with 1 mol equiv of diisobutylaluminum hydride in toluene at −78° furnished a mixture of diastereomeric amino epoxides **10** [63% yield; oil; molecular ion at *m/e* 324]. Treatment of **10** with toluene–ethanol (19:1) at reflux for 12 hr and separation of the reaction mixture by preparative layer chromatography afforded 13% of quinine [**12**; neutral (+)-tartrate monohydrate, mp and mmp 207–209°, dec >200°; $[\alpha]^{25}D$ −153.3° (*c* 0.9, MeOH)], 24% of quinidine [**13**; mp and mmp 170–171°; $[\alpha]^{25}D$ +256.0° (*c* 0.8, EtOH)], 18% of epiquinine[11] [neutral dibenzoyl-(+)-tartrate, mp and mmp 149–152°; $[\alpha]^{25}D$ −21.1° (*c* 1.0, MeOH)], and 18% of epiquinidine[11] [neutral dibenzoyl-(+)-tartrate, mp 167–168°; $[\alpha]^{25}D$ +2.4° (*c* 0.9, EtOH–$CHCl_3$ 4:1)].

Acknowledgment. We thank Professor M. Gates, Dr. A. Brossi, and Dr. W. Leimgruber for fruitful discussions. We are indebted to Dr. P. Bommer and his staff for spectra and microanalyses and to Mr. A. Swigar for experimental assistance in certain phases of this work.

(11) P. Rabe, *Ann.*, **492**, 242 (1931).

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Syntheses in the Cinchona Alkaloid Series

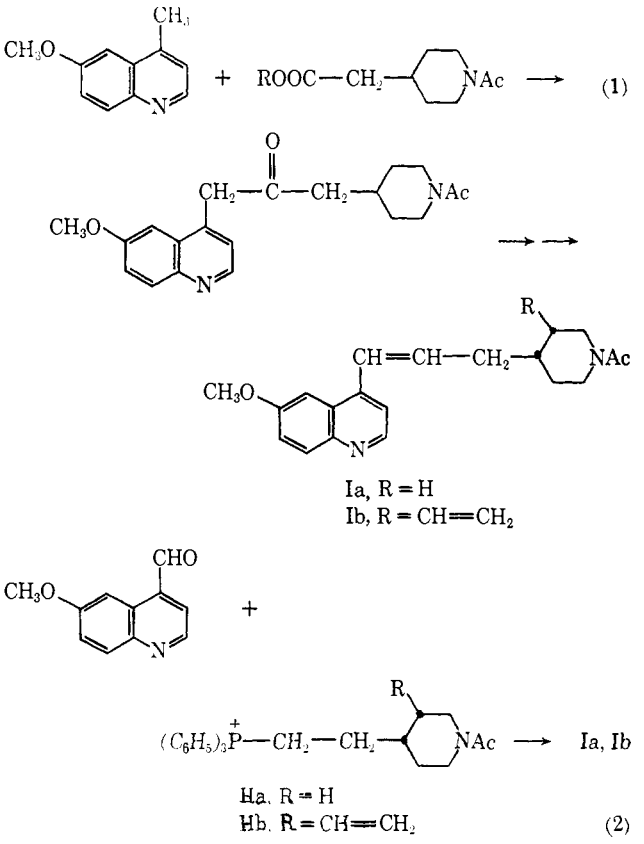
Sir:

We have been able to construct the carbon–nitrogen skeleton of the cinchona alkaloids by making use of the facile nucleophilic addiition[1] of appropriately constituted secondary amine functions to the β-carbon atom of substituted 4-vinylquinoline systems.

The requisite intermediates have been synthesized[2] by either of two methods: (1) the condensation of N-acetyl-4-piperidineacetic acid esters with 6-methoxy-

(1) W. E. Doering and R. A. N. Weil, *J. Amer. Chem. Soc.*, **69**, 2461 (1947).
(2) All new substances have been characterized by concordant elemental analyses and show the expected spectral properties.

lepidine followed by reduction of the ketone so produced and dehydration of the resulting alcohol with acetic anhydride or (2) the Wittig reaction of quininaldehyde with the quaternary phosphonium compound derived from N-acetyl-2-(4-piperidyl)ethyl bromide (IIa) or from the corresponding bromide derived from meroquinene alcohol[3] (IIb).



Ia, R = H
Ib, R = CH=CH$_2$

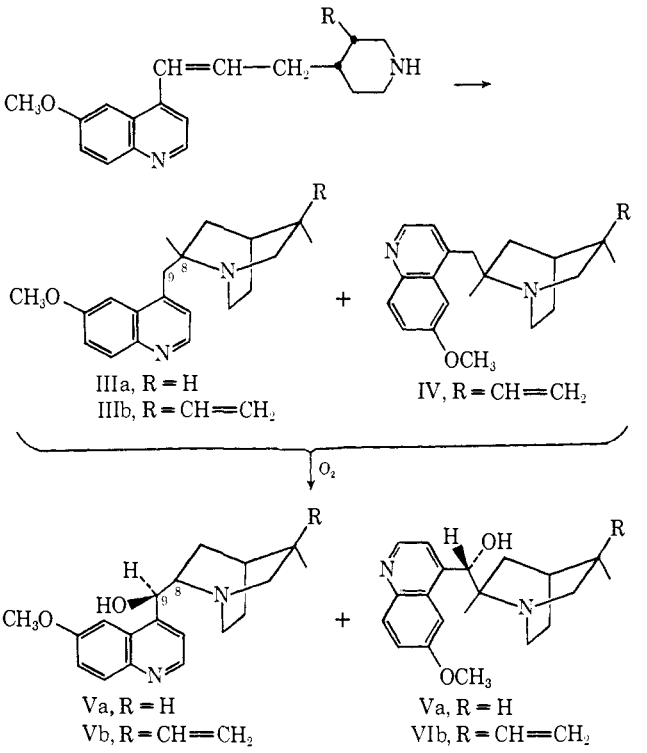
IIa, R = H
IIb, R = CH=CH$_2$ (2)

The olefin Ia, mp 115–116°, produced by the first method appears to be essentially completely *trans* ($J_{\text{vinyl H}}$ = 16 Hz); those (Ia and Ib) from the second method are *cis,trans* mixtures; these mixtures can be converted to all *trans* material (*trans*-Ib picrate mp 155.5–156.5°) by treatment with acetic acid, and *trans* material can be converted largely to *cis* photochemically ($J_{\text{vinyl H}}$ = 9 Hz).

The cyclization of the secondary amines produced by hydrolysis of olefins Ia and Ib to give the carbon–nitrogen skeleton of the cinchona alkaloids is easily accomplished in the presence of either acid or base or by simply refluxing in aqueous alcohol. Thus alkaline hydrolysis of olefin Ia yields racemic 6-methoxyrubane (IIIa) (dipicrate mp 191–193° dec) in 67% yield. The use of the optically active olefin Ib leads to a difficultly separable mixture of desoxyquinine (IIIb) and its C_8 epimer desoxyquinidine IV in 85% yield.

Oxidation of racemic 6-methoxyrubane and the desoxyquinine–desoxyquinidine mixture with molecular oxygen in the presence of potassium *t*-butoxide and triphenylphosphine[4] in dimethylformamide–*t*-butyl alcohol allowed the introduction of hydroxyl at C_9. In the former case racemic 6-methoxyrubanol (Va) (hydrate mp 84–91°, anhydrous 191–192.5°) (*erythro*) was obtained along with the diasteromeric *threo* isomer (oil) in a 5:1 ratio.[5]

In the latter case a readily separable[6] mixture of quinine (Vb) (26% as neutral (+)-tartrate, mp 202–206° dec), quinidine (VIb) (28% as acid (+)-tartrate), and epiquinine (4.1%, dibenzoyl-(+)-tartrate, mp 153–155°) was obtained. Thus, this oxidation in every case tried (6-methoxyrubane, desoxyquinine, desoxyquinidine) gives predominantly the *erythro* configuration at carbon atoms 8 and 9 characteristic of the naturally occurring cinchona alkaloids.



IIIa, R = H
IIIb, R = CH=CH$_2$

IV, R = CH=CH$_2$

Va, R = H
Vb, R = CH=CH$_2$

Va, R = H
VIb, R = CH=CH$_2$

An interesting aspect of the above cyclization is that it can be reversed essentially quantitatively. Thus, racemic 6-methoxyrubane and desoxyquinine on refluxing with acetic anhydride are completely converted into the corresponding olefins Ia and Ib.[7] This observation was made during an unsuccessful attempt to introduce an acetoxyl function into IIIa by the action of selenium dioxide in acetic anhydride. We had originally hoped to make use of the action of acetic anhydride on the aromatic N-oxides of IIIa and IIIb to intro-

(3) Our initial samples of optically active meroquinene esters from which we prepared the corresponding alcohol and bromide were obtained by the degradation of quinidinone as described by Doering and Chanley (W. E. Doering and J. D. Chanley, *J. Amer. Chem. Soc.*, **68**, 586 (1946)). We are grateful to Dr. Philip Kumler for carrying out this degradation for us. Later samples of the *t*-butyl ester of meroquinene were generously provided by Dr. Milan Uskoković of Hoffmann-La Roche, who with his colleagues has developed an elegant new synthesis of meroquinene (see the accompanying communications).

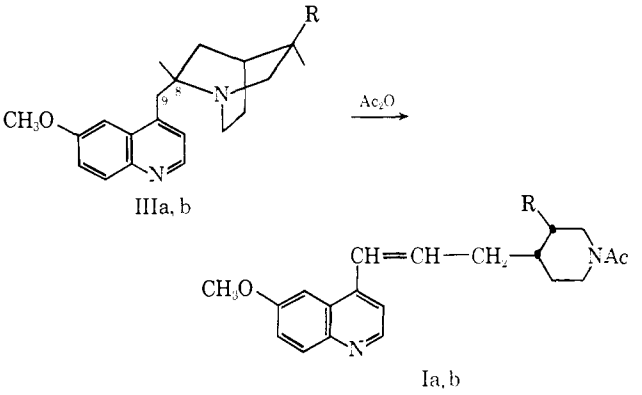
(4) The use of molecular oxygen and butoxide ion to introduce oxygen at C_9 was disclosed to us by Dr. Milan Uskoković. His group however used dimethyl sulfoxide to convert the intermediate hydroperoxide to the alcohol (*cf.* the accompanying communication).

(5) These substances were first synthesized and resolved by P. Rabe and his coworkers (P. Rabe, K. Kindler, and O. Wagner, *Ber.*, **55**, 532 (1922); P. Rabe and G. Hagen, *ibid.*, **74**, 636 (1941); P. Rabe and W. Shuler, *ibid.*, **76**, 318 (1943).

(6) P. Rabe, F. Kolbe, and W. Hochstatter, *Ann.*, **492**, 258 (1931); W. E. Doering, G. Cortes, and L. H. Knox, *J. Amer. Chem. Soc.*, **69**, 1700 (1947).

(7) A related reaction was observed many years ago by J. von Braun and K. Weissbach (*Ber.*, **64**, 1864 (1931)) who found that several desoxyquinine derivatives on refluxing in hydrocinnamic acid gave low yields of the hydrocinnamides of the corresponding ring-opened olefins.

duce acetoxyl at C_9,[8] but this facile ring opening precludes the use of this method.



The sequence of reactions outlined constitutes a synthesis of racemic 6-methoxyrubanol and partial syntheses of quinine and quinidine.

Acknowledgment. This work was supported in large part by the U. S. Army Medical Research and Development Command under Contract No. DA-49-193-MD-2956. We are grateful to Dr. Milan Uskoković and his colleagues and to Dr. Philip Kumler for a number of helpful discussions.

(8) See, for example, the production of 4-acetoxypicoline from 4-picoline N-oxide: V. Boekelheide and W. J. Linn, *J. Amer. Chem. Soc.*, **76**, 1286 (1954).

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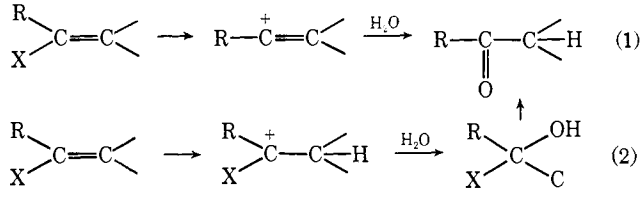
Hydration *vs.* Solvolysis of an Activated Vinyl Halide

Sir:

It has been recently proposed that hydrolysis of "activated" vinyl halides proceeds *via* SN1 solvolysis to a vinyl carbonium ion, eq 1.[1] Equally plausible under some, but not all, of the conditions used is hydrolysis *via* protonation of the alkene, as in eq 2 (*cf.* ref 1f).



Impetus to published studies was given by the work of Grob on hydrolysis of α-bromostyrenes.[1a] The postulated vinyl carbonium ion mechanism for this system was based largely on findings with α-bromo-*p*-aminostyrene. In 80% ethanol, the hydrobromide salt, with 0–5 equiv of triethylamine, hydrolyzed much more rapidly than the *p*-methoxy derivative, which in turn hydrolyzed faster than the parent α-bromostyrene. Our interest in the hydration of styrenes in general,[2] and of aminostyrenes in particular,[3] prompted us to examine the hydrolysis of α-bromo-*p*-aminostyrene in sufficient detail to allow a clearer delineation of mechanism. A study of the behavior of first-order rate constants in aqueous buffer and perchloric acid solutions establishes that the vinyl carbonium ion mechanism for this compound is definitely incorrect, and that hydrolysis most probably occurs *via* acid-catalyzed hydration, eq 3–8.

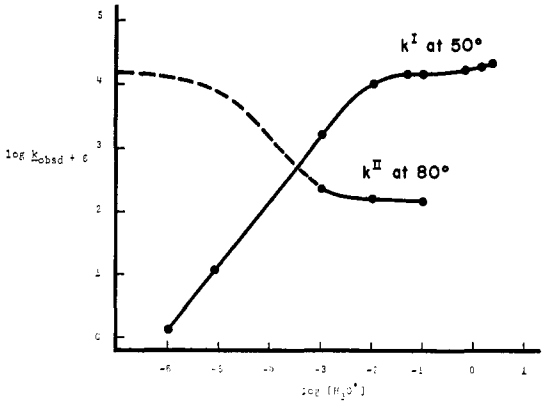


Figure 1. Plot of log k_{obsd}^{I} and log k_{obsd}^{II} against log $[H_3O^+]$.

Hydrolysis occurs in two stages. In solutions of higher acidity, the ultraviolet spectrum of the styrene disappears completely before any ketone spectrum appears, and is replaced by the spectrum of a metastable intermediate. The spectrum of this intermediate then slowly changes to that of the end product, *p*-aminoacetophenone. Rate constants for stage I (50°) and the much slower stage II (80°) were successively determined by quantitatively following changes in absorptivity at optimum wavelengths.

In solutions over a narrow pH range, around 4.5, stages I and II are competitive, and the spectrum of the intermediate builds up momentarily, then declines, while styrene disappears and ketone appears. In solutions of high pH, stage II was much faster than stage I, *i.e.*, the intermediate did not make its appearance, and the first-order rates of styrene disappearance and ketone appearance were identical.

The dependence of k_{obsd}^{I} (extrapolated values in buffers) on $[H_3O^+]$ over the entire acidity range is shown graphically in Figure 1. The acidity dependence of k_{obsd}^{I} unequivocally rules out the vinyl carbonium ion mechanism, since an opposite behavior is required by that mechanism. That is, the rate constant should remain unchanged in solutions of low acidity ($[S] \gg [SH^+]$) and be inversely dependent on $[H_3O^+]$ in solutions of high acidity ($[SH^+] \gg [S]$).

The behavior of k_{obsd}^{I} does correspond to that expected for the acid-catalyzed hydration of eq 3–5, as expressed in the rate eq 9 (k_4 and K_{SH^+}[c] are medium dependent constants). Indeed, it parallels that found in the hydration of unsubstituted *p*-aminostyrene to 1-*p*-aminophenylethanol.[3] Thus, k_{obsd}^{I} increases linearly with $[H_3O^+]$ in media of low acidity in which the ground state is essentially free α-bromo-*p*-aminostyrene, S (rate eq 9a). In media of higher acidity in which the ground state is essentially SH^+, N-protonated styrene, k_{obsd}^{I} is independent of the acidity (rate eq 9b). The

(1) (a) C. A. Grob and G. Cseh, *Helv. Chim. Acta*, **47**, 194 (1964); (b) L. L. Miller and D. A. Kaufman, *J. Amer. Chem. Soc.*, **90**, 7282 (1968); (c) C. A. Grob and R. Spear, *Tetrahedron Lett.*, 1439 (1969); (d) S. A. Sherrod and R. C. Bergman, *J. Amer. Chem. Soc.*, **91**, 2115 (1969); (e) M. Hanack and T. Bassler, *ibid.*, **91**, 2117 (1969); (f) S. J. Huang and M. V. Lessard, *ibid.*, **90**, 2432 (1968); (g) P. E. Peterson and J. M. Indelicato, *ibid.*, **91**, 6194 (1969); **90**, 6515 (1968).

(2) W. M. Schubert, B. Lamm, and J. R. Keeffe, *ibid.*, **86**, 4727 (1964); W. M. Schubert and B. Lamm, *ibid.*, **88**, 120 (1966).

(3) James L. Jensen, Ph.D. Thesis, University of Washington, 1967.