Total Synthesis of Quinine and Quinidine. I

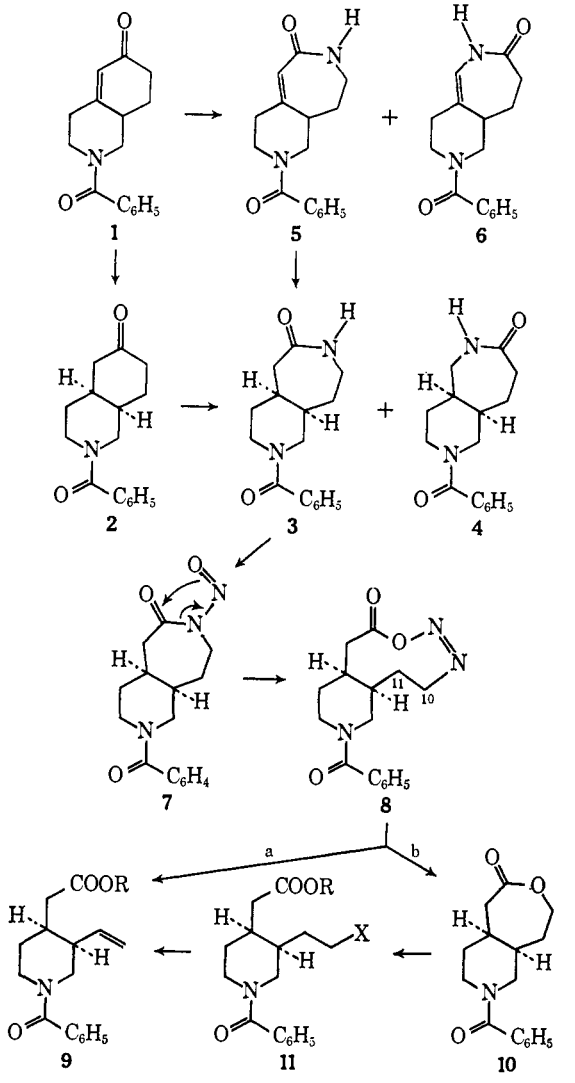
Sir:

Despite continuing interest in the biological properties of the classical Cinchona alkaloids, quinine and quinidine, no recent synthetic endeavors have been made in this field.[1] In this and the subsequent communication, we wish to report a novel synthesis of these alkaloids in which the quinuclidine part of quinine and quinidine is derived from the elements of *cis*-3-vinyl-4-piperidineacetic acid. The 3(*R*),4(*S*) enantiomer of this compound is known as meroquinene, a degradation product of quinine.[2] Until now its synthesis has not been reported. This communication describes a stereoselective four-step synthesis of racemic N-benzoylmeroquinene (**9**, R = H).

Hydrogenation of the easily accessible N-benzoylhexahydroisoquinolone **1** in ethanolic hydrochloric acid over a rhodium on alumina catalyst gave predominantly (>60%) the *cis*-isoquinolone **2**.[3] In order to create the acetic acid and vinyl side chains present in **9**, several methods for the fragmentation of the carbocyclic ring of **2** were investigated (see Scheme I). Thus, treatment of the ketone **2** with sodium azide in polyphosphoric acid at 60° for 16 hr gave quantitatively a 2:1 mixture of the seven-membered lactams **3** and **4** (**3**, mp 167–168.5°; **4**, mp 188–190°),[4] which were separated by tedious fractional crystallization. The structure assignment for the desired lactam **3** emerged from an investigation of the Schmidt rearrangement of the unsaturated ketone **1**. In this case, the conjugated lactam **5** [mp 219–221°; λ_{max} 223–225 mμ (ε 20,000); $\gamma_{max}^{CHCl_3}$ 3422 cm^{-1} (N–H), 1663 (lactam), 1630 (amide); δ^{CDCl_3} 5.87 (s, olefinic proton); molecular ion at *m/e* 270] was obtained by direct crystallization in 67% yield. The enamino lactam **6** [mp 194–196°; λ_{max} 245 mμ (ε 17,000); $\nu_{max}^{CHCl_3}$ 3410 cm^{-1} (N–H), 1670 (lactam), 1625 (amide); δ^{CDCl_3} 7.70 (d, *J* = 6 Hz, N–*H*), 5.73 (d, *J* = 6 Hz, =C*H*–)] was isolated as a minute by-product by column chromatography of the mother liquors. Hydrogenation of **5** over rhodium on alumina catalyst gave exclusively the desired *cis*-lactam **3**.

Conversion of this compound into N-benzoylmeroquinene and its ester **9** was accomplished by two routes. Ethanolysis of **3** in boiling ethanolic hydrogen chloride led to the amino ester **11** (R = C_2H_5; X = NH_2), which on methylation with a formic acid–formaldehyde mixture gave the dimethylamino ester **11** [R = C_2H_5; X = $N(CH_3)_2$]. Pyrolysis of the corresponding N-oxide furnished racemic N-benzoylmeroquinene ethyl ester [**9**, R = C_2H_5; mp 67–68°; $\nu_{max}^{CHCl_3}$ 1730 cm^{-1} (ester), 1625 (amide), 1000 and 930 (vinyl); δ^{CDCl_3} 7.39 (s, phenyl), 5.90 (m, –*H*C=), 4.80–5.30 (m, =CH_2), 4.15 (q, *J* = 7 Hz, CH_2 of ethyl), 1.25 (t, *J* = 7 Hz, CH_3 of ethyl); molecular ion at *m/e* 301]. The spectral properties of this product were identical with those of optically active N-benzoylmeroquinene ethyl ester, which was obtained as an oil by degradation of cinchonine.[2] A more efficient conversion of the lactam **3** into racemic N-benzoylmeroquinene (**9**, R = H) was achieved *via* pyrolysis of the N-nitrosolactam **7**. This compound, an unstable yellow powder, was obtained in quantitative yield by treatment of **3** with dinitrogen tetroxide. When heated at 125°, it rearranged to the diazolactone **8**,[5] which fragmented with extrusion of nitrogen to give a mixture of racemic N-benzoylmeroquinene [**9**, R = H; oil; $\nu_{max}^{CHCl_3}$ 1713 cm^{-1} (carboxyl), 1625 (amide), 1000 and 930 (vinyl); δ^{CDCl_3} 10.20 (s, COO*H*), 7.38 (s, phenyl), 5.80 (m, –C*H*=), 4.90–5.30 (m, =CH_2); molecular ion at *m/e* 273] and the seven-membered lactone **10** in 50 and 30% yield, respectively. In order to rationalize the formation of these products, two different concerted fragmentation paths are as-

Scheme I

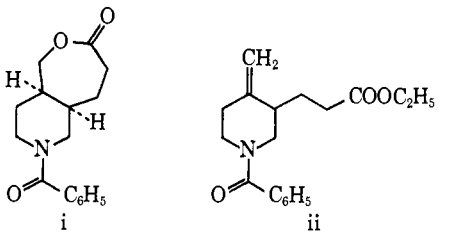


(1) (a) R. B. Turner and R. B. Woodward, *Alkaloids*, 3, 1–63 (1953); (b) P. Rabe and K. Kindler, *Ber.*, 51, 466 (1918); (c) R. B. Woodward and W. E. Doering, *J. Amer. Chem. Soc.*, 67, 860 (1945).

(2) W. E. Doering and J. D. Chanley, *ibid.*, 68, 586 (1946).

(3) R. L. Augustine, *J. Org. Chem.*, 23, 1853 (1958).

(4) The reaction of ketone **3** with *m*-chloroperbenzoic acid in benzene yielded exclusively the undesired lactone **i** resulting from the migration of the carbon adjacent to the ring junction. The structure of **i** was proven by degradation into the olefinic ester **ii**, which was also obtained from lactam **4**, the by-product in the Schmidt rearrangement.



(5) R. Huisgen and J. Reinertshofer, *Ann.*, 575, 174 (1952); 575, 197 (1952).

sumed.[6] Path a, probably initiated by abstraction of the C-11 hydrogen by either one of the ester oxygens, leads to the formation of the acid **9** (R = H). Path b, which must be envisaged as a nucleophilic attack of one of the ester oxygens on the C-10 carbon, gives the lactone **10**. Under the conditions of separation, which included the treatment of the crude pyrolysis product with potassium hydroxide followed by neutralization with hydrochloric acid, opening of the lactone **10** occurred to give the hydroxycarboxylic acid **11** (R = H; X = OH).

Compounds **9** (R = H) and **11** (R = H; X = OH) were chemically interrelated. Esterification of the crude hydroxy acid **11** (R = H; X = OH) with diazomethane gave the hydroxy methyl ester **11** [R = CH_3; X = OH; oil; $\nu_{max}^{CHCl_3}$ 3615 cm^{-1} (O–H), 1735 (ester), 1625 (amide); δ^{CDCl_3} 7.37 (s, phenyl), 3.63 (s, OCH_3); molecular ion at *m/e* 305], which was converted into the tosyloxy ester **11** (R = CH_3; X = OTs; oil) on treatment with *p*-toluenesulfonic acid anhydride in pyridine. Substitution of the tosyloxy group with iodine proceeded smoothly with sodium iodide in acetone. Elimination of hydrogen iodide was effected at room temperature by treatment with silver fluoride in pyridine. The racemic olefinic methyl ester **9** [R = CH_3; mp 57–58° $\nu_{max}^{CHCl_3}$ 1733 cm^{-1} (ester), 1623 (amide), 1000 and 930 (vinyl); δ^{CDCl_3} 7.40 (s, phenyl); 5.89 (m, $-CH=$), 4.80–5.40 (m, $=CH_2$), 3.68 (s, OCH_3); molecular ion at *m/e* 287) thus obtained was identical with the product formed by esterification of **9** (R = H). In addition, the ir, nmr, and mass spectra of both products were identical in all respects with those of optically active N-benzoylmeroquinene methyl ester.[2,7]

Acknowledgment. We are grateful to Professor G. Büchi, Dr. A. Brossi, and Dr. W. Leimgruber for helpful discussions. We also wish to thank Dr. P. Bommer and his colleagues for spectra and analyses.

(6) E. H. White, *J. Amer. Chem. Soc.*, 77, 6014 (1955).
(7) Compounds **1**–**6** and **9** (R = H, CH_3, C_2H_5) and **11** (R = CH_3; X = H, OTs) gave correct microanalyses.

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Total Synthesis of Quinine and Quinidine. II

Sir:

In the preceding communication[1] we have described the stereoselective synthesis of racemic N-benzoylmeroquinene methyl ester (**3**), a potential precursor of the quinuclidine moiety of the Cinchona alkaloids. We now report its conversion into quinine (**12**) and quinidine (**13**) by employing 6-methoxylepidine[2] (**1**) as the precursor of the quinoline portion of the molecule. This completes a new nine-step total synthesis of these alkaloids starting from readily available materials.

Ester **3** was treated with 6-methoxylepidyllithium (**2**; from **1** and lithium diisopropylamide) in tetrahydrofuran to give the racemic N-benzoyl ketone **4**[3] [64%; oil; $\nu_{max}^{CHCl_3}$ 1720 cm^{-1} (ketone), 1630 (amide), 1000 and 920 (vinyl)]. This key intermediate contains all the functionality necessary for cyclization to the quinuclidine ring and for introduction of oxygen at C-9. Transformation of ketone **4** to the desired alkaloids was achieved either *via* the quinuclidine **11** or the amino epoxide **10**. In either case the N-benzoyl group, which could not be cleaved satisfactorily by hydrolysis, was removed readily under mild reductive conditions (see Scheme I).

In the first route, ketone **4** was treated with 2 mol equiv of diisobutylaluminum hydride in toluene at −78° which removed the benzoyl group with concommitant reduction of the ketone function to give the amino alcohol **7** as a 3:2[4] mixture of C-8 epimers in 80% yield. Resolution with dibenzoyl-(+)-tartaric acid afforded a 3:2 mixture of these C-8 epimers with the natural 3(*R*),4(*S*) configuration as a sharp melting neutral dibenzoyl-(+)-tartrate [mp 190.5–191.5°; $[\alpha]^{25}D$ −25.9° (*c* 0.8, MeOH); corresponding base: oil; $[\alpha]^{25}D$ +39.0° (*c* 1.0, $CHCl_3$)]. This salt was identical with a sample prepared by the same route from semisynthetic, optically active meroquinene methyl ester.[5]

Heating the 3(*R*),4(*S*)-amino alcohols **7** with benzene–acetic acid (4:1) at reflux for 4.5 days furnished a mixture of desoxyquinine–desoxyquinidine (**11**) in 45% yield. This cyclization presumably proceeds *via* dehydration and subsequent intramolecular addition of the amino group to the vinylquinoline **6**.[6]

Cyclization proceeded more efficiently when the alcohol function of compound **7** was first acetylated. Thus, exposure of **7** to acetic acid containing 10% boron trifluoride etherate furnished quantitatively the amino acetate **8** as a mixture of C-8 epimers [oil; $[\alpha]^{25}D$ +21.4° (*c* 0.8, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 1730 and 1245 cm^{-1} (acetate); δ^{CDCl_3} 2.01 and 2.05 (2 s, ratio 3:2, CH_3COO-) 3.98 and 4.00 (2 s, ratio 3:2, $-OCH_3$)]. This product cyclized readily in boiling benzene–acetic acid–sodium acetate to give a mixture of desoxyquinine–desoxyquinidine [**11**; 80%; oil; $[\alpha]^{25}D$ +76°[7] (*c* 1.0, $CHCl_3$)], spectroscopically identical with a reference sample prepared from natural alkaloids.[8]

Base-catalyzed hydroxylation of the epimeric mixture **11** with molecular oxygen gave predominantly the *erythro* products, quinine (**12**) and quinidine (**13**).[9] Thus, stirring a 0.02 *M* solution of **11** in dimethyl sulfoxide–*t*-butyl alcohol (4:1)[10] containing 1.2 mol equiv of potas-

(1) See the accompanying communication: M. Uskoković, J. Gutzwiller, and T. Henderson, *J. Amer. Chem. Soc.*, 92, 203 (1970).
(2) K. N. Campbell and I. J. Schaffner, *ibid.*, 67, 86 (1945).
(3) All compounds described gave correct microanalyses.
(4) The epimer ratio was determined by nmr analysis of the corresponding O-acetates **8**.
(5) W. E. Doering and J. D. Chanley, *J. Amer. Chem. Soc.*, 68, 586 (1946).
(6) Experimental evidence in support of this mechanism was obtained as follows: olefin **6**, obtained from alcohol **7** by dehydration with thionyl chloride in pyridine, was exposed to boiling benzene–acetic acid (9:1) for 4 hr to give the quinuclidine **11** in good yield.
(7) This value suggests that the ratio of desoxyquinine to desoxyquinidine is 44:56.
(8) P. Rabe, E. Kuliga, O. Marshall, W. Naumann, and W. F. Russell, *Ann.*, 373, 85 (1910).
(9) Stereoelectronic factors resulting from electron repulsion of the lone pair of the quinuclidine nitrogen and the incoming O_2 species (O–O or O–O:$^-$)[10] may be responsible for the high stereoselectivity of this reaction.
(10) (a) For a review see: G. A. Russell, E. G. Janzen, A. G. Bemis, E. J. Geels, A. J. Moye, S. Mak, and E. J. Strom, "Oxidation of Hydrocarbons in Basic Solutions," Advances in Chemistry Series, No. 51, R. F. Gould, Ed., American Chemical Society, Washington, D. C., 1965, p 112; (b) G. A. Russell, A. G. Bemis, E. J. Geels, E. G. Janzen, and A. J. Moye, Advances in Chemistry Series, No. 75, American Chemical Society, Washington, D. C., 1968, p 174; (c) DMSO acts as the reductant of the intermediate peroxy anions as shown by the isolation of dimethylsulfone from the reaction mixture.