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.

Milan Uskoković, Jürg Gutzwiller, Thomas Henderson
Chemical Research Department, Hoffmann-La Roche, Inc.
Nutley, New Jersey 07110
Received November 14, 1969

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]

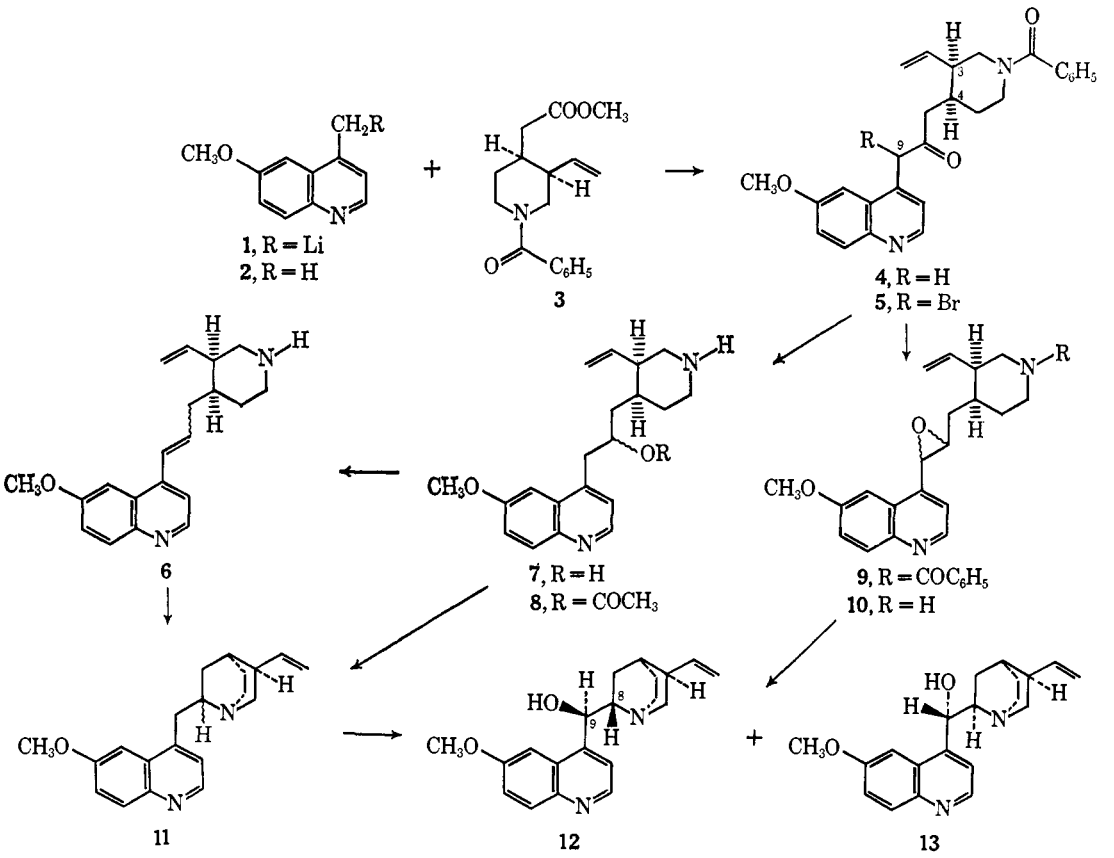
Heating the 3(*R*),4(*S*)-amino alcohols **7** with benzene–acetic acid (4:1) at reflux for 4.5 days furnished a mixture of desoxyquinine–desoxyquinidine (**11**) in 45% yield. This cyclization presumably proceeds *via* dehydration and subsequent intramolecular addition of the amino group to the vinylquinoline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

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)].

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

Jürg Gutzwiller, Milan Uskoković
Chemical Research Department
Hoffmann-La Roche, Incorporated
Nutley, New Jersey 07110
Received November 14, 1969

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.