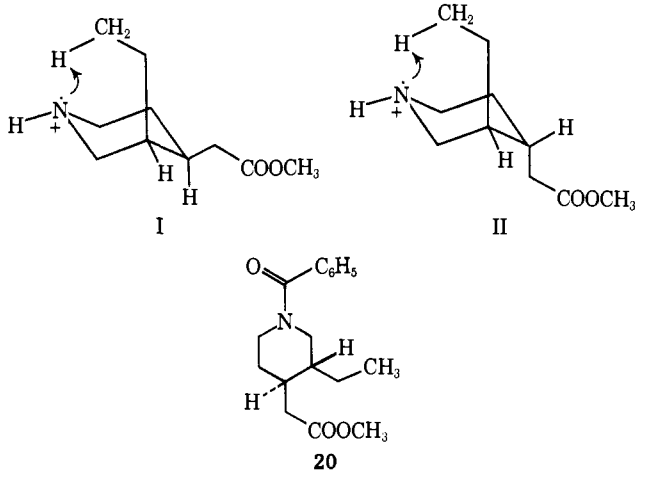
gave the imino ether **4**, which on reduction with sodium borohydride[9] furnished the racemic *trans*-ethyl ester **6** in nearly quantitative overall yield [bp 91–92° (bath) (0.5 mm); nmr ($CDCl_3$) δ 0.85 (distorted t, 3 H, $-CH_2CH_3$), 1.26 (t, 3 H, J = 7 Hz, OCH_2CH_3), 1.71 (s, 1 H, NH), 4.13 (q, 2 H, J = 7 Hz, OCH_2CH_3); mass m/e 199 (M^+)]. Saponification and reesterification with methanolic hydrogen chloride gave the methyl ester **7**.

Photolysis of the *trans*-*N*-chloramine **9**, followed by benzoylation, resulted in only 35% yield of the desired rearranged product **13** [oil, mass m/e 323 (M^+), 288 (M − Cl), 105 (base peak)]. Competitive photolytic dechlorination[10] followed by benzoylation led to racemic *trans*-*N*-benzoyl-3-ethyl-4-piperidineacetic acid methyl ester (**20**) in 25% yield [mass m/e 289 (M^+)].

Scheme II

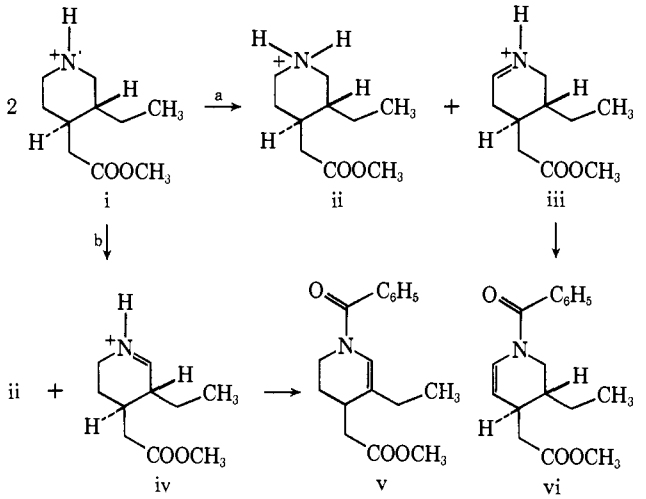


The low rearrangement yield in this case is due to a higher energy transition state in the hydrogen abstraction step, which involves chair conformation II with two axial substituents. This is contrasted with chair conformation I for the corresponding transition state in the cis series, which bears only one axial substituent (Scheme II). It was noted on the basis of several experiments that lower temperatures during photolysis favored dechlorination instead of rearrangement.

Hydrolysis of **13** afforded quantitatively the chloro acid **15** [mp 122–124°; ir ($CHCl_3$) 3520, 1716 cm^{-1}; mass m/e 309 (M^+)]. Subsequent elimination then gave racemic *trans*-*N*-benzoylmeroquinene [**18**; mp 137–141°; nmr ($CDCl_3$) δ 4.9–5.8 (m, 3 H, $CH{=}CH_2$), 7.36 (s, 5 H, phenyl); mass spectrum m/e 273 (M^+)] in 97% yield. The methyl ester **19** was obtained in high yield on treatment with diazomethane [oil, nmr ($CDCl_3$) δ 3.64 (s, 3 H, $-OCH_3$), 4.9–5.8 (m, 3 H, $CH{=}CH_2$), 7.37 (s, 5 H, phenyl); mass m/e 287 (M^+)]. This ester was utilized in the synthesis of ajmalicine and **19**-epiajmalicine.[4,11]

(9) R. F. Borch, *Tetrahedron Lett.*, 61 (1968).

(10) Dechlorination is probably due to disproportionations a and b of the intermediate aminium radical i



Compounds v and vi were isolated from the benzoylation reaction, and their structures were supported by spectra. The yield of v and vi together was equal to the yield of **20**, which resulted from the benzoylation of ii.

(11) Correct analytical figures have been obtained for all compounds for which physical and spectral data are given.

M. Uskoković,* C. Reese, H. L. Lee
G. Grethe, J. Gutzwiller
Chemical Research Department, Hoffman-La Roche Inc.
Nutley, New Jersey 07110
Received August 6, 1971

Synthesis of Cinchona Alkaloids *via* Quinuclidine Precursors

Sir:

We report a new total synthesis of the cinchona alkaloids quinine, quinidine, and their dihydro analogs. It differs from previous syntheses[1] in that quinuclidine derivatives properly functionalized at C-2 and C-5 are used as intermediates. These compounds were prepared from 1,1-dichloro-3-piperidinylpropan-2-ols synthesized by two complementary methods (Scheme I).

In method A, applicable only to the dihydro series, β-collidine (**1**)[2] was condensed with chloral[3] and the crystalline reaction product was subsequently resolved with *l*- and *d*-tartaric acid into the enantiomers **2** [mp 132–134° (ether); $[\alpha]^{25}D$ −43.6° (*c* 1.123, EtOH)][4] and **3** [mp 132–134° (ether); $[\alpha]^{25}D$ +43.2° (*c* 1.1075, EtOH)]. Hydrogenation of **2** in 5% aqueous hydrochloric acid over a platinum catalyst gave after fractional crystallization the diastereoisomers **4** [mp 169–171° (acetone); $[\alpha]^{25}D$ −25.2° (*c* 0.931, MeOH); ir (KBr) 3340 cm^{-1} (OH); nmr (D_2O) δ 4.54 (m, 1, CHOH), 6.52 (d, 1, J = 3 Hz, $CHCl_2$)] and **5** [mp 232–233° (EtOH); $[\alpha]^{25}D$ −28.3° (*c* 1.024, MeOH); ir (KBr) 3390 cm^{-1} (OH); nmr (D_2O) δ 4.52 (m, 1, CHOH), 6.49 (d, 1, J = 3 Hz, $CHCl_2$)]. Under identical conditions the enantiomer **3** yielded **6** [mp 169–171° (acetone); $[\alpha]^{25}D$ +25.3° (*c* 1.014, MeOH)] and **7** [mp 232–233° (EtOH); $[\alpha]^{25}D$ +29.6° (*c* 1.095, MeOH)]. The hydrogenation yields were high, and none of the trans isomers was isolated. The cis configuration of the products **4**–**7** was

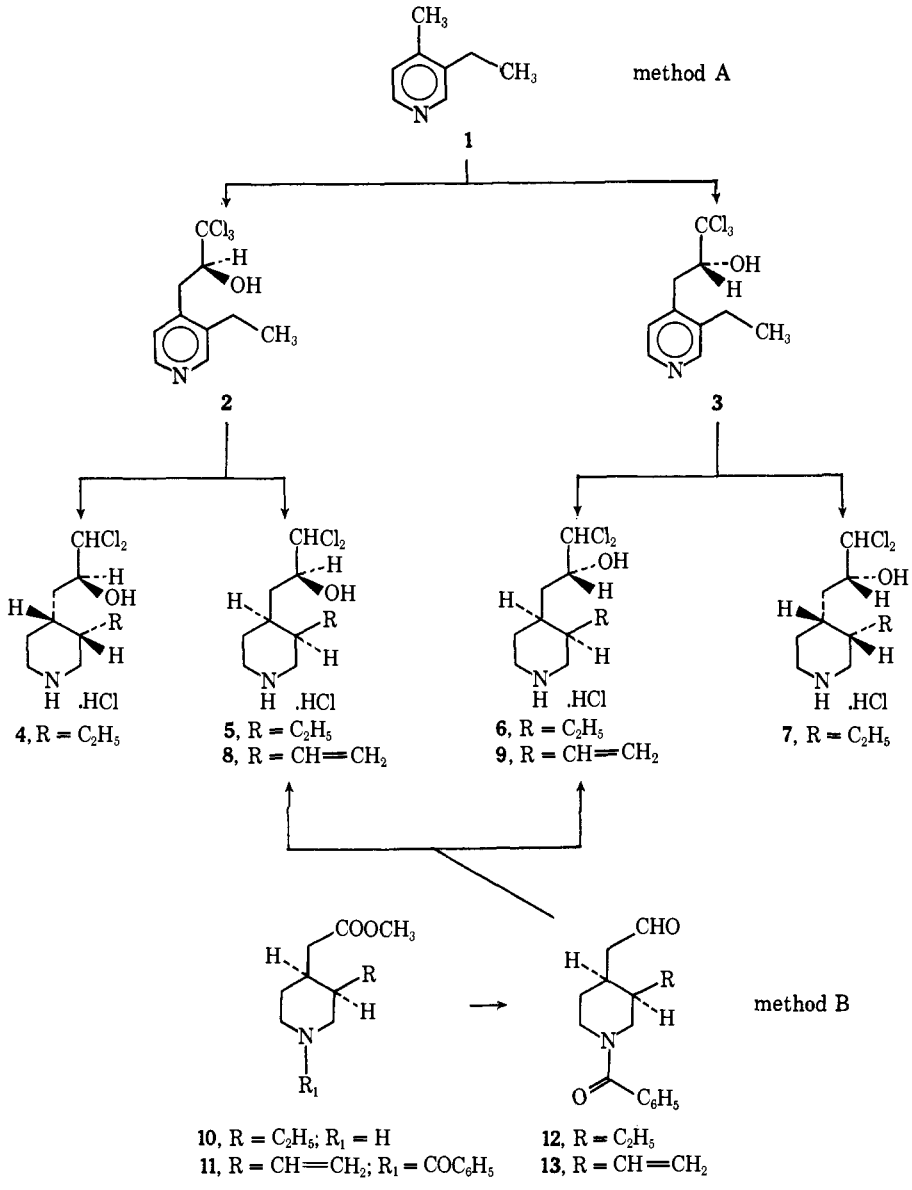
(1) (a) P. Rabe, W. Huntenberg, A. Schultze, and G. Vogler, *Chem. Ber.*, **64**, 2487 (1931); (b) M. Prošenik and V. Prelog, *Helv. Chim. Acta*, **26**, 1965 (1943); (c) R. B. Woodward and W. E. Doering, *J. Amer. Chem. Soc.*, **67**, 860 (1945); (d) M. Uskoković, T. Henderson, and J. Gutzwiller, *ibid.*, **92**, 203 (1970); J. Gutzwiller and M. Uskoković, *ibid.*, **92**, 204 (1970); (e) M. Gates, B. Sugavanam, and W. E. Schreiber, *ibid.*, **92**, 205 (1970); (f) G. Grethe, J. Gutzwiller, H. L. Lee, and M. Uskoković, to be published.

(2) An efficient three-step synthesis of β-collidine has been developed in these laboratories (unpublished results).

(3) E. Koenigs and W. Ottmann, *Chem. Ber.*, **54**, 1343 (1921).

(4) All new compounds gave correct microanalyses and their structural assignments were supported by physical data.

Scheme I



confirmed by an X-ray structure analysis[5] of the hydrobromide of **5** [mp 223–224° (EtOH); $[\alpha]^{25}D$ −24.8° (*c* 0.949, MeOH)] and by the results obtained by method B.

In this sequence, cincholoipon methyl ester (**10**)[6] and *N*-benzoylmeroquinene methyl ester (**11**)[6] were used as the starting materials. Reduction of **10** and **11** with diisobutylaluminum hydride and subsequent benzoylation of the crude reaction products gave in 70% yield the liquid aldehydes **12** [bp 180° (0.001 mm);[7] $[\alpha]^{25}D$ +2.14° (*c* 1.123, MeOH); ir ($CHCl_3$), 2730, 1722 (CHO), 1620 cm^{-1} (CON); nmr ($CDCl_3$) δ 9.72 (s, 1, CHO); *m/e* 259, M^+] and **13**[8] [bp 170° (0.005 mm); $[\alpha]^{25}D$ +46.4 (*c* 1.111, MeOH); ir ($CHCl_3$) 2840, 2740, 1728 (CHO), 1627 (CON), 1008, 933 cm^{-1} ($CH=CH_2$); nmr ($CDCl_3$) δ 9.74 (s, 1, CHO); *m/e* 257, M^+]. A solution of aldehyde **12** in anhydrous tetrahydrofuran was treated at −70° with 2 equiv of dichloromethyllithium[9] to give the two diastereoisomers **5** and **6** identical in all aspects with specimens obtained by method A. Under the same reaction conditions aldehyde **13** yielded a mixture of the diastereoisomeric 1,1-dichloro-3-[(3*R*)-vinyl-(4*S*)-piperidinyl]propan-2-ols **8** [mp 225–225.5° (EtOH); $[\alpha]^{25}D$ −13.3° (*c* 1.02, MeOH); ir (KBr) 3395 (OH), 1010, 938 cm^{-1} ($CH=CH_2$)] and **9** [mp 165–167° (acetone); $[\alpha]^{25}D$ +30.7° (*c* 1.00, MeOH); ir (KBr) 3330 (OH), 1010, 935 cm^{-1} ($CH=CH_2$)]. The configuration of **8** and **9** was established by catalytic hydrogenation of **8** which gave dihydro derivative **5**.

The formation of the desired quinuclidine derivatives was achieved by treating the dichloropropanols **5**, **6**, **8**, and **9** with methanolic potassium hydroxide or preferably with 2 *N* aqueous potassium hydroxide in a benzene suspension (Scheme II). Thus, **5** and **6** or a mixture of both gave in 65% yield a mixture of the liquid epimeric carboxaldehydes **14** [bp 80° (0.1 mm); $[\alpha]^{25}D$ +102.6° (*c* 1.168, MeOH); ir ($CHCl_3$) 2820,

(5) We are indebted to Dr. J. F. Blount of these laboratories for carrying out the X-ray analysis.

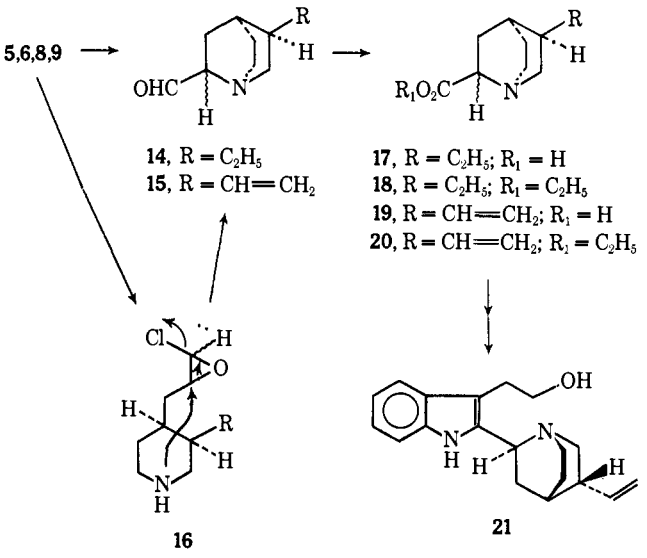
(6) See the accompanying communication: M. Uskoković, C. Reese, H. L. Lee, G. Grethe, and J. Gutzwiller, *J. Amer. Chem. Soc.*, **93**, 5902 (1971).

(7) Evaporative bulb-to-bulb distillation using a Büchi kugelrohrofen.

(8) This compound was first prepared by Dr. J. Gutzwiller in these laboratories (unpublished results).

(9) G. Köbrich, K. Flory, and W. Drischel, *Angew. Chem.*, **76**, 536 (1964), and subsequent papers; G. Köbrich, *Bull. Soc. Chim. Fr.*, **9**, 2712 (1969).

Scheme II



2730, 1730 cm^{-1} (CHO); nmr ($CDCl_3$) δ 9.78 (s, 1, CHO), 0.89 and 0.81 (t, 3, J = 7 Hz, CH_2CH_3, ratio 1:1); *m/e* 167, M^+, *m/e* 138, base peak]. Similarly, a mixture of **8** and **9** yielded the liquid vinyl analog **15** [bp 60° (0.05 mm); $[\alpha]^{25}D$ +154.9° (*c* 0.896, $CHCl_3$); ir ($CHCl_3$) 2820, 2730, 1732 (CHO), 994, 920 cm^{-1} ($CH=CH_2$); nmr ($CDCl_3$) δ 9.76 (s, 1, CHO); *m/e* 165, M^+, *m/e* 136, base peak]. The quinuclidine-2-carboxaldehydes are presumably formed by an intramolecular nucleophilic reaction of the secondary amine at the epoxide ring[10] of the intermediate α-chloro epoxides **16**.[11]

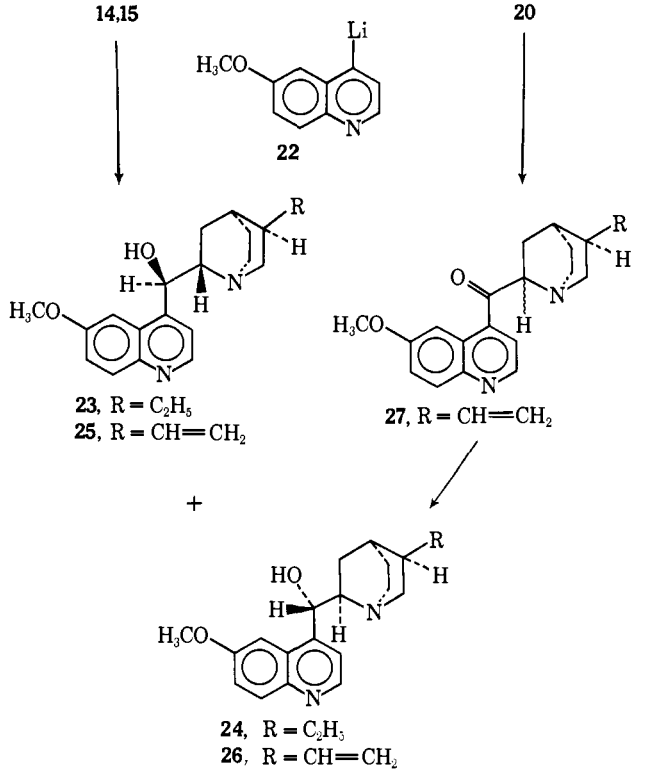
The aldehydes were found to be very labile compounds reverting on standing to a glassy polymer from which they could be partially recovered by vacuum distillation. However, the corresponding acids or esters which could be prepared readily proved to be stable. Mixtures of **5** and **6** as well as **8** and **9** were treated with methanolic potassium hydroxide and the aldehydes **14** and **15**, respectively, were oxidized *in situ* with freshly prepared silver oxide. In the dihydro series, esterification of the resulting crude epimeric acids **17** gave after distillation in 60% yield the epimeric esters **18** [bp 95–97° (0.05 mm); $[\alpha]^{25}D$ +77.3° (*c* 1.049, MeOH); ir ($CHCl_3$) 1730 cm^{-1} (ester); nmr ($CDCl_3$) 0.89 and 0.85 (t, 3, J = 7 Hz, CH_2CH_3, ratio 1:1); *m/e* 211, M^+, *m/e* 138, base peak]. Esterification of the hygroscopic vinyl acids **19** [sublimed at 165–170° (0.15 mm); $[\alpha]^{25}D$ +23.4° (*c* 1.07, $CHCl_3$), $[\alpha]^{25}D$ +40.4° (*c* 1.12, 1 *N* NaOH)[12]] yielded the epimeric mixture of liquid esters **20**[13,14] [bp 70° (0.04 mm); $[\alpha]^{25}D$ +82.1° (*c* 1.074, MeOH); ir ($CHCl_3$) 1732 (ester), 995, 920 cm^{-1} ($CH=CH_2$); *m/e* 209, M^+, *me/e* 136, base peak]. Without isolation of any of the intermediates, **20** was obtained from **13** in 40% overall yield.

(10) P. Duhamel, L. Duhamel, and J. Gralak, *Chem. Ber.*, 3641 (1970).
(11) A. Kirrmann, P. Duhamel, and R. Nouri-Bimorghi, *ibid.*, 3264 (1964).
(12) The quinuclidine carboxylic acid obtained by oxidative degradation of cinchonamine [R. Goutarel, M. M. Janot, V. Prelog, and W. I. Taylor, *Helv. Chim. Acta*, **33**, 150 (1950)] showed $[\alpha]^{28}D$ +81° after mutarotation in 1 *N* NaOH.
(13) The (2*S*) isomer was obtained by degradation of quininone by R. P. Evstigneeva, Ch'en Ch'an-pai, and N. A. Preobrazhenskii, *J. Gen. Chem. USSR*, 30 495 (1960).
(14) See also R. L. Augustine and S. F. Wanat, *Syn. Commun.*, in press.

Preobrazhenskii and coworkers have previously synthesized cinchonamine (**21**)[15] from ethyl (5*R*)-vinyl-(4*S*)-quinuclidine-(2*S*)-carboxylate obtained by degradation.[13] Therefore, the preparation of **20** formally completes the first total synthesis of this indole cinchona alkaloid.

The synthesis of quinine and quinidine and their dihydro analogs was completed by combining the aldehydes **14** and **15** with an appropriate quinoline derivative (Scheme III). Thus, condensation of the

Scheme III



aldehydes **14** at −70° with 6-methoxy-4-quinolyllithium (**22**), prepared from 4-bromo-6-methoxyquinoline and *n*-butyllithium at −65° in ether–tetrahydrofuran (1:1),[16] and separation of the reaction mixture by chromatography on silica gel afforded 13% of dihydroquinine (**23**) [mp and mmp[17] 170–171°; $[\alpha]^{25}D$ −144.5° (*c* 0.935, 95% EtOH)], 22% of dihydroquinidine (**24**) [mp and mmp 169–170°, $[\alpha]^{25}D$ +222° (*c* 0.970, EtOH)], and 8% of a mixture of 9-epidihydroquinine and 9-epidihydroquinidine. The latter was isolated from the mixture in the form of its neutral dibenzoyl-*d*-tartrate[18] [mp 163–165° (benzene); $[\alpha]^{25}D$ −13.7° (*c* 0.970, EtOH–$CHCl_3$ (4:1)]. Dihydroquinine and dihydroquinidine were spectroscopically identical with reference samples prepared by Rabe's procedure.[1a]

Under the same reaction conditions, condensation of the unsaturated aldehyde **15** with **22** yielded 20% of quinine (**25**) [neutral *d*-tartrate, mp and mmp[17] 211–212°; $[\alpha]^{25}D$ −159.5° (*c* 1.00, MeOH); ir (KBr) identical with that of an authentic sample[1d]], 23% of quinidine (**26**) [mp 172–173°, mmp 171–172.5°, $[\alpha]^{25}D$ +265.6° (*c* 1.07, 95% EtOH); spectroscopically identical with

(15) Ch'en Ch'an-pai, R. P. Evstigneeva, and N. A. Preobrazhenskii, *Dokl. Akad. Nauk SSSR*, **123**, 707 (1958).
(16) H. Gilman and T. S. Soody, *J. Org. Chem.*, **23**, 1584 (1958).
(17) Mixture melting points were obtained with natural materials.
(18) P. Rabe, *Justus Liebigs Ann. Chem.*, **492**, 242 (1932).

natural quinidine], and 12% of a mixture of 9-epidihydroquinine and 9-epidihydroquinidine.

Alternatively, quinine and quinidine were obtained in a combined yield of 20% by condensation of the ester **20** with 6-methoxy-4-quinolyllithium and subsequent stereoselective reduction of the resulting crude epimeric mixture of quininone and quinidinone (**27**) with diisobutylaluminum hydride in benzene.[19]

Acknowledgment. We thank Professor R. Augustine for informing us about the results of his work prior to its publication.

(19) This selective reduction was first observed by Dr. J. Gutzwiller of these laboratories (unpublished results).

Guenter Grethe,* Hsi Lin Lee
Toomas Mitt, Milan R. Uskoković
Chemical Research Department, Hoffmann-La Roche Inc.
Nutley, New Jersey 07110
Received August 6, 1971

A Novel Synthesis of Racemic Ajmalicine, 19-Epiajmalicine, Tetrahydroalstonine, and Akuammigine

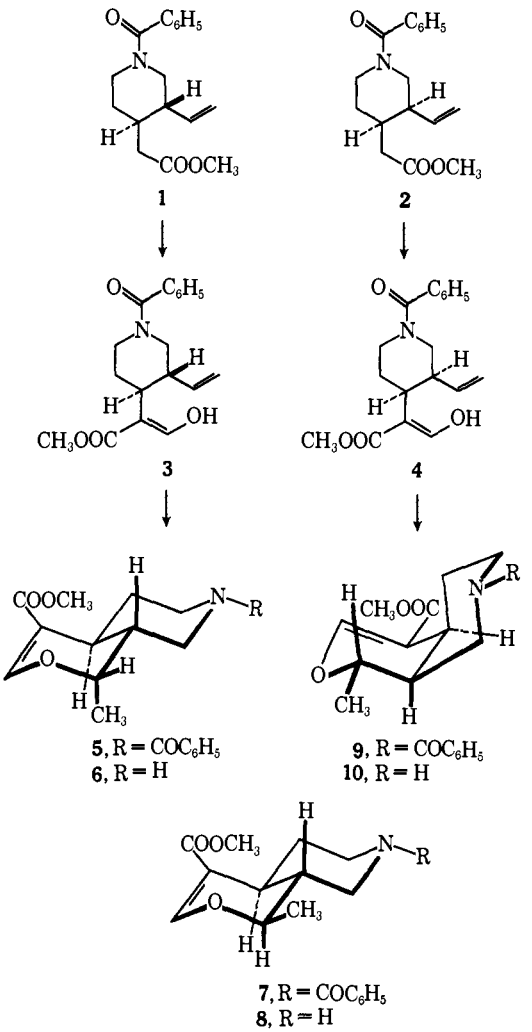
Sir:

In this communication we report convergent syntheses of the racemates of the four heteroyohimbine alkaloids[1,2] ajmalicine, 19-epiajmalicine, tetrahydroalstonine, and akuammigine. The D,E-ring moieties of these pentacyclic alkaloids were constructed from *trans*- and *cis*-3-vinyl-4-piperidineacetic acid methyl esters,[3] respectively. Alkylation with tryptophyl bromide and oxidative cyclization of the resulting seco intermediates completed the synthesis.

Esters **1** and **2** were formylated in high yield with bis(dimethylamino)-*tert*-butoxymethane[4] followed by acid-catalyzed hydrolysis of the intermediate vinylogous carbamates (Scheme I). Intramolecular oxymercuration of the oily *trans*-formyl ester **3** [ir ($CHCl_3$) 1700, 1670, 1620, 1600 cm^{-1} (carbonyl region); mass *m/e* 315 (M^+)] in dimethylformamide at 50° in the presence of 1.1 equiv of mercuric acetate and reduction with sodium borohydride in methanol afforded an inseparable amorphous mixture of the enol ethers **5** and **7** [69%, ratio *ca.* 1:2; ir ($CHCl_3$) 1690 (ester), 1610 cm^{-1} (amide, C=C); mass *m/e* 315 (M^+)]. Treatment of this epimeric mixture with 1 molar equiv of diisobutylaluminum hydride (toluene–THF, 9:1, −78°) gave the sensitive free amines **6** [15%; ir ($CHCl_3$) 1705 (C=O), 1620 cm^{-1} (C=C); uv max (EtOH) 239 nm (ε 11,080); nmr ($CDCl_3$) δ 1.1 (d, 3 H, J = 6.5 Hz, CH_3), 4.28 (doublet of quartets, 1 H, J = 6.5 and 3.5 Hz, $OCHCH_3$), 7.44 (d, 1 H, $J \sim 1$ Hz, $OCH{=}$); mass *m/e* 211 (M^+)] and **8** [31%; ir ($CHCl_3$) 1710 (C=O), 1630 cm^{-1} (C=C); uv max (EtOH) 239 nm (ε 10,780); nmr ($CDCl_3$) δ 1.28 (d, 3 H, J = 6.5 Hz, CH_3), 3.74 (doublet of quartets, 1 H, J = 10 and 6.5 Hz, $OCHCH_3$) 7.51 (d, 1 H, $J \sim 1$ Hz, $OCH{=}$); mass *m/e* 211 (M^+)], which were separated by preparative thin-layer chromatography. The oily *cis*-formyl ester **4** [ir ($CHCl_3$) 1740, 1720, 1670, 1620 cm^{-1} (carbonyl region)] was cyclized analogously to give only the crystalline enol ether **9**, the kinetically favored product [45%; mp 143–144°; ir ($CHCl_3$) 1700 (ester), 1630 cm^{-1} (amide, C=C); nmr ($CDCl_3$) δ 1.4 (b, 3 H, CH_3), 4.17 (doublet of quartets, 1 H, J = 10 and 6 Hz, $OCHCH_3$), 7.38 (s, 5 H, phenyl), 7.35 (s, 1 H, $OCH{=}$); mass *m/e* 315 (M^+)]. The configuration and the indicated conformation of **9** followed from the nmr spectrum. The benzoyl group was removed to give the cis free amine **10** [oil; ir ($CHCl_3$) 1700 cm^{-1} (C=O), 1630 (C=C); nmr ($CDCl_3$) δ 1.37 (d, 3 H, J = 6 Hz, CH_3), 4.50 (doublet of quartets, 1 H, J = 10 and 6 Hz, $OCHCH_3$), 7.50 (s, 1 H, $OCH{=}$), mass *m/e* 211 (M^+)].

Alkylation of the bicyclic amino esters **6**, **8**, and **10** with tryptophyl bromide (**11**) and potassium carbonate in dimethylformamide solution led in high yield to the respective seco compounds **12** [amorphous; nmr ($CDCl_3$) δ 1.11 (d, 3 H, J = 6.5 Hz, CH_3), 4.30 (m, 1 H, largest J = 6.5 Hz, $OCHCH_3$), 6.95 (d, 1 H, $J \sim 2$ Hz, 2-*H*), 7.47 (d, 1 H, $J \sim 1$ Hz, $OCH{=}$); mass *m/e* 354 (M^+)], **13** [amorphous, nmr ($CDCl_3$) δ 1.28 (d, 3 H, J = 6.5 Hz, CH_3), 3.83 (doublet of quartets, 1 H, J = 10 and 6.5 Hz, $OCHCH_3$), 6.98 (d, 1 H, J = 2

Scheme I



(1) M. Hesse, "Indolalkaloide in Tabellen," Springer-Verlag, Berlin-Göttingen-Heidelberg, 1964; Ergänzungswerk, 1968; R. E. Woodson, Jr., H. W. Youngken, E. Schlittler, and J. A. Schneider, "Rauwolfia," Little, Brown and Co., Boston, Mass., 1957, Chapter 3.

(2) E. Wenkert, B. Wickberg, and C. L. Leicht, *J. Amer. Chem. Soc.*, **83**, 5037 (1961); M. Shamma and J. B. Moss, *ibid.*, **83**, 5038 (1961); M. Shamma and J. M. Richey, *ibid.*, **85**, 2507 (1963).

(3) M. Uskoković, J. Gutzwiller, and T. Henderson, *ibid.*, **92**, 203 (1970); M. Uskoković, C. Reese, H. L. Lee, G. Grethe, and J. Gutzwiller, *ibid.*, **93**, 2902 (1971).

(4) H. Bredereck, G. Simchen, S. Reesdat, W. Kautlehner, P. Horn, R. Wahl, H. Hoffmann, and P. Grieshaber, *Chem. Ber.*, **101**, 41 (1968).