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 J. Gutzwiller of these laboratories (unpublished results).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

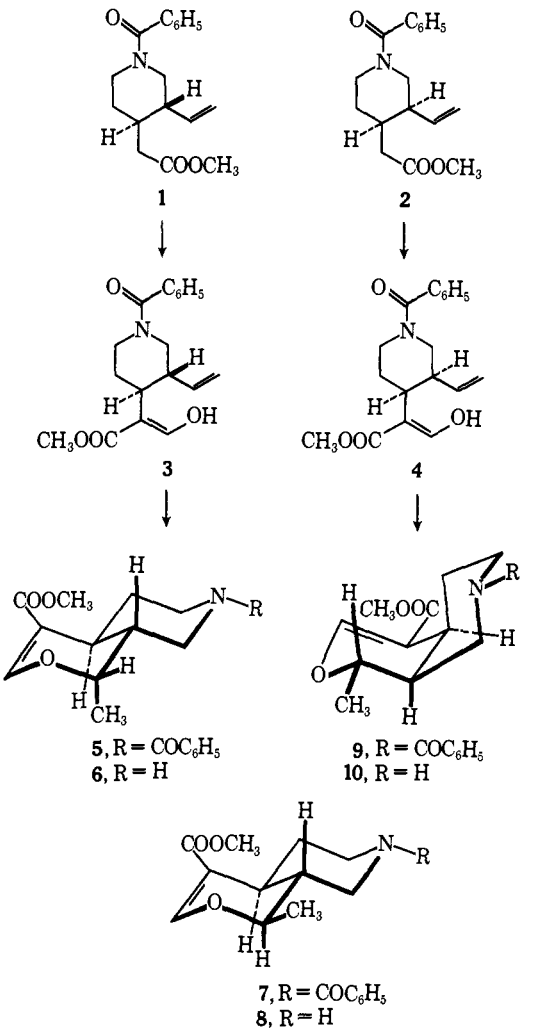
Sir:

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



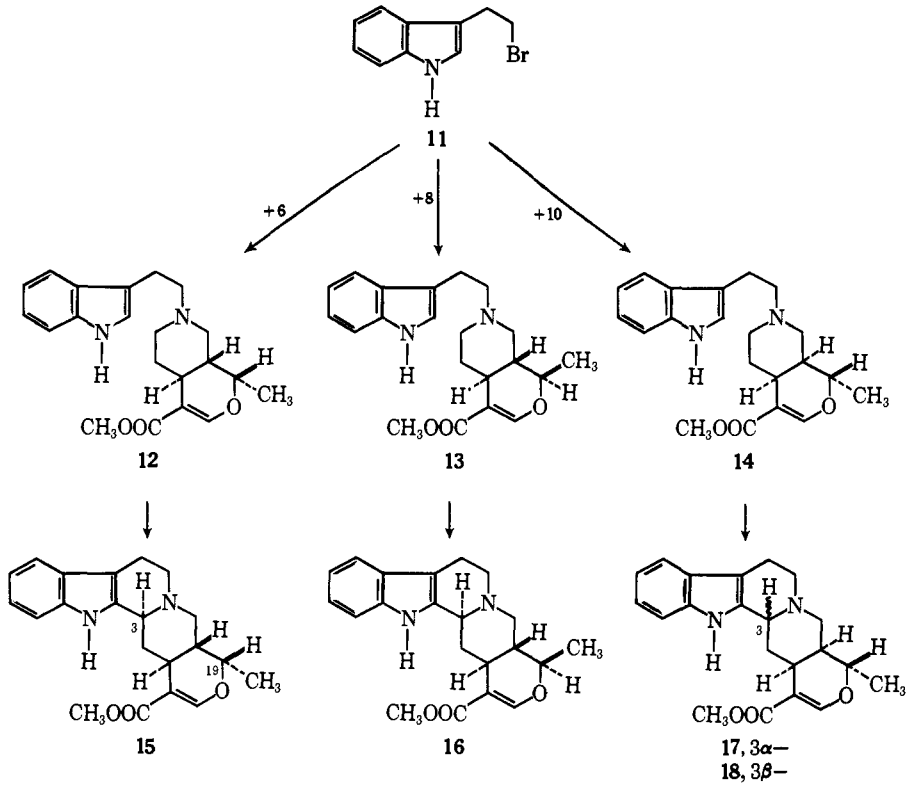
(1) M. Hesse, "Indolalkaloide in Tabellen," Springer-Verlag, Berlin-Göttingen-Heidelberg, 1964; Ergänzungswerk, 1968; R. E. Woodson, Jr., H. W. Youngken, E. Schlittler, and J. A. Schneider, "Rauwolfia," Little, Brown and Co., Boston, Mass., 1957, Chapter 3.

(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).

Scheme II



Hz, 2-*H*), 7.51 (d, 1 H, $J \sim 1$ Hz, OC*H*=); mass *m/e* 354 (M^+)], and **14** [mp 156–158°; nmr ($CDCl_3$) δ 1.30 (d, 3 H, $J = 6$ Hz, CH_3), 4.47 (doublet of quartets, 1 H, $J = 10$ and 6 Hz, OC*H*CH_3), 6.96 (d, 1 H, $J \sim 2$ Hz, 2-*H*), 7.49 (s, 1 H, OC*H*=); mass *m/e* 354 (M^+)] (see Scheme II).

Oxidative cyclization to the pentacyclic alkaloids was achieved using excess 1:1 mercuric acetate–ethylenediaminetetraacetic acid disodio salt followed by reduction of the iminium intermediates with sodium borohydride. The resulting mixtures were separated by preparative thin-layer chromatography, and all pentacyclic products were identified on the basis of their spectral and microanalytical data. Thus, oxidative cyclization of **12** in 2.5% aqueous acetic acid afforded racemic ajmalicine [**15**; 28%; hemihydrate from methanol, mp 216–219° dec, loss of water with darkening at 110–120°; ir ($CHCl_3$) 2850–2750 (Bohlmann bands), 1700 (C=O), 1620 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.12 (d, 3 H, $J = 6.5$ Hz, CH_3), 3.66 (s, 3 H, OCH_3), 4.33 (m, 1 H, largest $J = 6.5$ Hz, OC*H*CH_3), *ca.* 7.0–7.6 (4 aromatic), 7.48 (d, 1 H, $J \sim 1$ Hz, OC*H*=), 8.21 (b, 1, N*H*); mass *m/e* 352 (M^+), 351 (M − 1), 184, 169, 156 (base peak)].[5,6] Under similar reaction conditions in aqueous ethanol **13** gave racemic 19-epiajmalicine [**16**; 20%; monohydrate after crystallization from methanol; mp 111–115°; ir ($CHCl_3$) 2850–2750 (Bohlmann bands), 1700 (C=O), 1620 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.33 (d, 3 H, $J = 6.5$ Hz, CH_3), 3.69 (s, 3 H, OCH_3), 3.81 (m, 1 H, largest $J = 10$ Hz, OC*H*CH_3) *ca.* 7.0–7.5 (4 H aromatic), 7.53 (d, 1 H, $J \sim 1$ Hz, OC*H*=), 8.1 (b, 1 H, N*H*); mass *m/e* 352 (M^+ and base peak), 351 (M − 1), 184, 170, 169, 156].[6] Analogous treatment of the cis compound **14** gave 43% of racemic 3,4,5,6-tetrahydroalstonine [**17**; mp 199.5–200.5°, crystallized from ethanol; ir ($CHCl_3$) 2850–2750, (Bohlmann bands), 1700 (C=O), 1635 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.35 (d, 3 H, $J = 6$ Hz, CH_3), 3.69 (s, 3 H, OCH_3), 4.46 (doublet of quartets, 1 H, $J = 10$ and 6 Hz, OC*H*CH_3), *ca.* 7.0–7.4 (4 H aromatic), 7.54 (s, 1, H, OC*H*=), 7.96 (b, 1 H, N*H*); mass *m/e* 352 (M^+ and base peak), 351 (M − 1), 337, 156],[7] 10% of the C-3 epimer, racemic akuammigine [**18**; hydrate from ethanol, mp 125–126°; ir ($CHCl_3$) no Bohlmann bands, 1690 (C=O), 1620 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.31 (d, 3 H, $J = 6$ Hz, CH_3), 4.39 (m, 1 H, OC*H*CH_3), 7.55 (s, 1 H, OC*H*=); mass *m/e* 352 (M^+ and base peak), 351 (M − 1), 337, 156].[7,8]

While the last reaction was fairly unselective, the shortness of the synthesis allowed us to prepare these pharmacologically interesting alkaloids in quantity.

(5) E. E. van Tamelen, C. Placeway, G. P. Schiemenz, and I. G. Wright, *J. Amer. Chem. Soc.*, **91**, 7359 (1969).
(6) E. Winterfeldt, A. J. Gaskell, T. Korth, H. E. Radunz, and M. Walkowiak, *Chem. Ber.*, **102**, 3558 (1969).
(7) E. Winterfeldt, H. Radunz, and T. Korth, *ibid.*, **101**, 3172 (1968).
(8) Correct analytical figures have been obtained for all compounds for which physical and spectral data are given.

J. Gutzwiller, G. Pizzolato, M. Uskoković*
Chemical Research Department, Hoffmann-La Roche Inc.
Nutley, New Jersey 07110
Received August 6, 1971

Synthesis with Zerovalent Nickel. Coupling of Aryl Halides with Bis(1,5-cyclooctadiene)nickel(0)

Sir:

Biaryls are commonly prepared by metal-promoted coupling of aryl halides, either directly with copper metal as in the Ullmann reaction[1] or by a two-step procedure involving the reaction of intermediate

(1) P. E. Fanta, *Chem. Rev.*, **38**, 139 (1946); **64**, 613 (1964).