A Novel Synthetic Approach to Reserpine Based upon Amino-Claisen Rearrangements of Zwitterionic *N*-Vinylisoquinuclidenes

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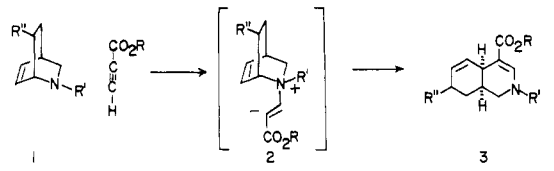
Studies focused on the development of a general hydroisoquinoline synthetic methodology based upon amino-Claisen rearrangements of zwitterionic *N*-vinylisoquinuclidenes are described. The tertiary amine containing *N*-(indolylethyl)isoquinuclidenes **9** and **16** undergoes reactions with ethyl propiolate to afford the corresponding cis-fused hydroisoquinolines **17** and **18** in synthetically useful yields. Mechanisms involving reversible formation of dipolar *N*-vinylisoquinuclidenes and stepwise conversion to isoquinolines are discussed. The overall synthetic utility of this process coupled with Wenkert cyclization of the hydroisoquinoline β-enamino esters in routes to the Rauwolfia alkaloid reserpine is demonstrated by the preparation of the pentacyclic systems **26** and **27**, which possess the basic skeleton of members of this natural product family.

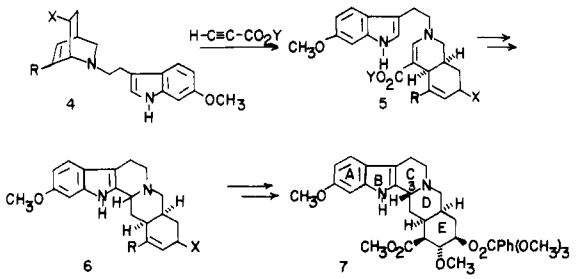
In earlier studies,[1,2] we have demonstrated that amino-Claisen rearrangements of *N*-vinylisoquinuclidenium salts, generated in situ from the corresponding tertiary amines, serve as mild and efficient methods for preparation of cis-fused hydroisoquinolines. An alternate approach was developed to expand the versatility of this methodology and involves the use of acid-catalyzed rearrangements of *N*-(β-ketovinyl)isoquinuclidenes to produce hydroisoquinolines.[1,2] We have pointed out how the latter strategy can be employed to construct substances possessing the tetracyclic structure found in members of the lycorine natural product family.[3,4] Our continuing studies in this area are focused on the development of another general hydroisoquinoline synthetic methodology based upon amino-Claisen rearrangments of zwitterionic *N*-vinylisoquinuclidenes **2**. We envisaged that dipolar intermediates **2**, generated by reversible addition of tertiary isoquinuclidenes **1** to acetylenic esters, would be capable of undergoing rearrangement to the corresponding cis-fused hydroisoquinolines **3** via concerted or stepwise mechanistic pathways (Scheme I).[5]

Our studies designed to test this strategy are part of a larger effort targeted at the development of general procedures for construction of members of the Rauwolfia indole alkaloid class, typified by reserpine **7**. Reserpine, previously synthesized by three elegantly conceived routes,[6] contains five contiguous chiral centers in its highly functionalized cis-fused hydroisoquinoline DE-ring system. In addition, a 6-methoxyindolylethylene unit spans the isoquinoline N-4 and C-3 positions. The zwitterionic amino-Claisen rearrangement process depicted in Scheme I, with its attendant structural and stereochemical manifestations, appears to present a potentially interesting solution to the problems inherent in a reserpine synthesis. An approach, incorporating this strategy (Scheme II), would employ rearrangement of the dipolar intermediate arising by reaction of isoquinuclidene **4** with propiolic acid esters, to construct the *N*-(indolylethyl)isoquinoline **5**. Cyclization to install the C ring of the pentacyclic system

Scheme I



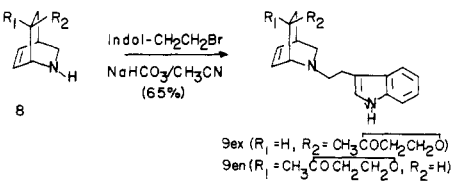
Scheme II



6 would then be accomplished by use of the well-known β-enamino ester annelation procedure developed by Wenkert.[7] The remaining steps in a sequence based upon this design would attend to the adjustment of E-ring functionality and C-3 stereochemistry.

In this paper, we disclose the results of our preliminary investigations with two easily prepared, model *N*-(indolylethyl)isoquinuclidenes devised to examine several key features of the strategy embodied in Scheme II. Importantly, we have demonstrated that the zwitterionic version of the amino-Claisen rearrangement shown in Scheme I is a viable process and that Wenkert cyclization of β-enamino esters like **5** is applicable to the construction of systems having the pentacyclic reserpine skeleton.

The *N*-tryptophylisoquinuclidenes **9** and **16** required for these studies were conveniently prepared from secondary amine precursors. Accordingly, alkylation of a C-7 epimeric mixture of the known[2] 7-dioxolanylisoquinuclidene **8** with tryptophyl bromide[8] provides the isoquinuclidenes **9**.[9] The endo epimer **9**-en can be obtained in pure form



(1) Mariano, P. S.; Dunaway-Mariano, D.; Huesmann, P. L.; Beamer, R. *Tetrahedron Lett.* **1977**, 4299.
(2) Mariano, P. S.; Dunaway-Mariano, D.; Huesmann, P. L. *J. Org. Chem.* **1979**, *44*, 124.
(3) Chen, Y.; Mariano, P. S.; Little, G. M.; O'Brien, D.; Huesmann, P. L. *J. Org. Chem.* **1981**, *46*, 4643.
(4) Chen, Y.; Huesmann, P. L.; Mariano, P. S. *Tetrahedron Lett.* **1983**, 1021.
(5) Singh, A.; Archer, S.; Hoogsteen, K.; Hirshfield, J. *J. Org. Chem.* **1983**, *48*, 173. Hayakawa, K.; Fujii, I.; Kanematsu, K. *J. Org.* Chem. **1983**, *48*, 166.
(6) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *Tetrahedron* **1958**, *2*, 1. Pearlman, B. *J. Am. Chem. Soc.* **1979**, *101*, 6398, 6404. Wender, P. A.; Schaus, J. M., White, A. W. *Ibid.* **1980**, *102*, 6157.
(7) Wenkert, E.; Dave, K. G.; Haglid, F. *J. Am. Chem. Soc.* **1965**, *87*, 5461. Lownasmaa, M.; Jokela, R. *Tetrahedron* **1978**, *34*, 1841.
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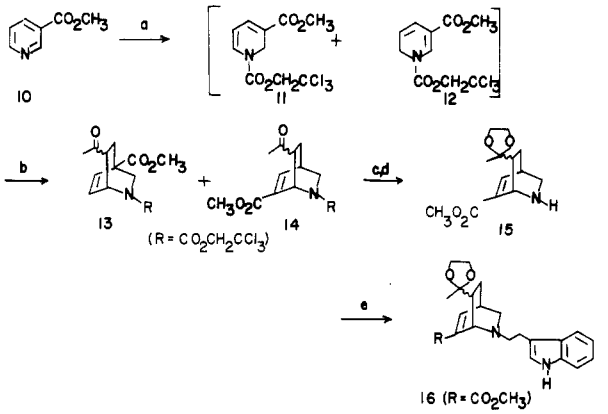
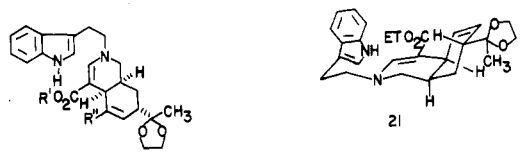
Scheme III[a]



[a] (a) $ClCO_2CH_2CCl_3$, $NaBH_4$, EtOH, Et_2O, −78 °C; (b) MVK, C_6H_6, 80 °C, 3 days; (c) $HOCH_2CH_2OH$, C_6H_6, *p*-TsOH, ref, 3 h; (d) Zn, CH_3OH, ref, 1 h; (e) tryptophyl bromide, $NaHCO_3$, CH_3CN, ref.

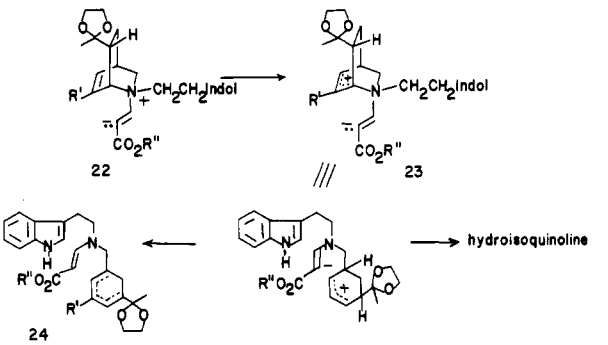
from this mixture by silica gel chromatography. The secondary amine precursor of **16** is produced by a sequence beginning with methyl nicotinate (**10**). Reaction of **10** with trichloroethyl chloroformate and sodium borohydride under the familiar Fowler conditions[10] furnishes a 1:1 mixture of the 1,2- and 1,6-dihydropyridines (**11** and **12**), which are directly converted to the regioisomeric isoquinuclidenes **13** and **14** by Diels–Alder reaction with methyl vinyl ketone (Scheme III). Separation by large-scale (ca. 15 g) flash chromatography on silica gel then yields the desired isoquinuclidene **14** in a acceptable overall yield (from **10**) of 24%. The amino ester **15**, generated from **14** by ketalization and N-deblocking, is transformed to a separable mixture of the C-7-epimeric tertiary amines by alkylation with tryptophyl bromide.[9]

With routes for large-scale production of the *N*-tryptophylisoquinuclidenes in hand, attention turned to studies of the zwitterionic amino-Claisen rearrangement of these systems. In the manner anticipated, reaction of **9-en** with ethyl propiolate occurred smoothly in refluxing acetonitrile to generate the *N*-tryptophylisoquinoline **17** (60%). The cis-ring-fusion stereochemistry and preferred conformation with the bulky dioxolane substituent equatorial as depicted in **21** was demonstrated by comparison of characteristic ^1H NMR data for **17** with those of analogous substances prepared in our earlier studies.[2] In a similar fashion, the C-6 functionalized isoquinuclidenes **16en** follows an analogous reaction pathway when treated with ethyl propiolate to yield the cis-fused hydroisoquinoline **18** (68%).

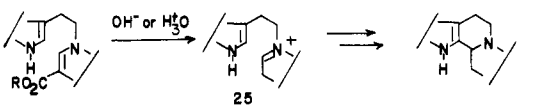


17 (R' = Et, R'' = H)
18 (R' = Et, R'' = CO_2CH_3)
19 (R' = t-Bu, R'' = H)
20 (R' = t-Bu, R'' = CO_2CH_3)

Information about the mechanism responsible for conversion of the dipolar intermediate **22** to hydroisoquinoline products is found in the observation that reaction of the *N*-tryptophylisoqunuclidene **9-en** with *tert*-butyl propiolate fails to form the hydroisoquinoline **19**.[17] In this case an uncyclized cyclohexadiene product (e.g., **24**) is formed in high yield. In contrast, the isoquinuclidene ester **16** is converted to hydroisoquinoline **20**, albeit in low yield, when reacted with *tert*-butyl propiolate. These results suggest that stepwise pathways involving interconversion of the initially formed **22** and secondary **23** dipolar intermediates are followed in the rearrangement reactions and that perhaps subtle steric and electronic factors influence the relative rates of the ring closure vs. proton transfer.[11,17]



The final aspect of these preliminary studies concerns Wenkert cyclization of *N*-tryptophylisoquinolines, which is of crucial importance to the success of a reserpine synthesis based upon the strategy outlined in Scheme II. In his pioneering work in this area,[7] Wenkert uncovered two related procedures for cyclization of systems of this type, both of which proceed via iminium cation intermediates related to **25**. The applicability of the base-induced annulation methodology to the current problem has been confirmed by observations made in our studies with the hydroisoquinoline **17**. Accordingly, treatment of **17** under the suggested conditions[7] (25% KOH, 1:1 EtOH-H_2O, 85 °C, 4 days) followed by chromatographic purification on silica gel leads to isolation of two products, characterized as the pentacyclic substances **26** and **27** in a ratio of 9:1.[12]



The spectroscopic properties of the major isomer **26** are in full accord with the assigned structure and C-3 stereochemistry. Both the presence of strong Bohlmann bands[13] in the IR spectrum of **26** at 2780 and 2830 cm^{-1} and the close agreement between the ^{13}C NMR chemical shifts of C-5 (53.3 ppm) and C-6 (21.5 ppm) with those for closely related substances[14] possessing the epialloyohimbane nucleus strongly suggest that the major cyclization product has the trans C-3 stereochemistry and exists preferentially in the *trans*-quinolizidine conformation represented by **28**. Indeed, this stereochemical assignment to the major pentacyclic product is also consistent with steric and stereoelectronic[15] controls of the iminium cation cyclization.[16]

(9) The conditions used for this alkylation are those suggested in Johansen, J. E.; Christie, B. D.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 4914.

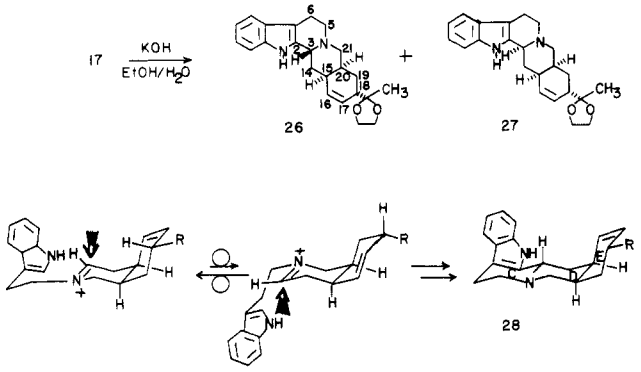
(10) Fowler, F. *J. Org. Chem.* **1972**, *37*, 1321.

(11) It should be noted that similar, diene-forming proton-transfer processes have been observed in the acid-catalyzed amino-Claisen rearrangement[2,4] and in allylamine–propiolate reactions in the thebaine series.[5]

(12) The pathway for iminium cation formation involves base saponification of the ester and decarboxylation of the intermediate vinylogous carboxamidic acid.

(13) Bohlmann, F. *Chem. Ber.* **1958**, *91*, 2157; **1959**, *92*, 1798. Crabb, T. A.; Newton, R. F.; Jackson, D. *Chem. Rev.* **1971**, *71*, 109. E. Wenkert, D. K.; Roychaudhuri, C. *J. Am. Chem. Soc.* **1956**, *78*, 6147.

(14) An excellent general discussion of ^{13}C NMR chemical shift correlations within members of the stereochemistry different classes of the yohimbanes is found in Wenkert, D.; Chang, C. J.; Chawala, H. P. S.; Cochran, D. W.; Hagamen, E. W.; King, J. C.; Orito, K. *J. Am. Chem. Soc.* **1976**, *98*, 3645.



It is evident from the results uncovered thusfar that the combined use of zwitterionic amino-Claisen rearrangements and Wenkert-type cyclizations offers efficient synthetic entry into the pentacyclic skeleton found in members of the Rauwolfia alkaloid family. Studies are continuing with the aim of uncovering additional and more efficient procedures for Wenkert-cyclization and E-ring functionality adjustment.

Experimental Section

General Procedures. ^1H NMR spectra were recorded by using Varian EM-360 (60 MHz) or XL-100 and Brucker WP-200 spectrometers with $(CH_3)_4Si$ as an internal standard. Chemical shifts are recorded in parts per million (δ) relative to $(CH_3)_4Si$. ^{13}C NMR spectra were recorded by using a Varian XL-100 or a Brucker WP-200 spectrometer with $(CH_3)_4Si$ as an internal standard. Chemical shifts are recorded in parts per million relative to $(CH_3)_4Si$. Mass spectra were obtained on a Dupont 492 spectrometer (low resolution) or at the Penn State Mass Spectrometry Center (high resolution). IR spectra were obtained on a Perkin-Elmer 298 spectrophotometer. UV spectra were obtained on a GCA/McPherson EU-700 series spectrophotometer. Preparative chromatographic separations were accomplished by using the following absorbants; for TLC, E. Merck 60 GF 254 silica gel; for flash chromatography, E. Merck 60 silica gel (230–400 mesh); for Florisil chromatography (100–200 mesh), for silica gel chromatography, Fisher (100–200 mesh), and for alumina chromatography, MCB Alcoa Type F-20 (100–200 mesh).

Analyses were performed by Dr. F. Kassler at the University of Maryland. Drying of organic extracts during the workup of reactions was performed over Na_2SO_4.

2-Tryptophyl-*endo*-7-[1,1-(ethylenedioxy)ethyl]-2-azabicyclo[2.2.2]oct-5-ene (9en). A suspension of 0.504 g (6.0 mmol) of $NaHCO_3$ in 10 mL of anhydrous CH_3CN containing 0.390 g (2.0 mmol) of *endo*- and *exo*-7-[(1,1-(ethylenedioxy)ethyl]-2-azabicyclo[2.2.2]oct-5-ene[2] and 0.448 g (2.0 mmol) of tryptophyl bromide was stirred at reflux for 24 h, cooled to 25 °C, and poured into water. The water layer was extracted with $CHCl_3$. The combined extracts were washed with water, dried, and concentrated in vacuo, giving an oil, which was purified by flash column chromatography on silica gel (utilizing a gradual increase in concentration of eluant from 4% to 7% methanol–chloroform), yielding 0.270 g (45%) of **9en**: ^1H NMR ($CDCl_3$) δ 8.0 (br s, 1 H, indole NH), 7.0–7.6 (m, 5 H, aromatic), 6.3 (t, 1 H, H-5), 6.2 (t, 1 H, H-6), 3.9 (s, 4 H, ethylenedioxy CH_2), 3.7 (d, 1 H, H-1), 2.9 (m, 4 H, H-3, NCH_2 of tryptophyl group), 2.5–2.6 (m, 3 H, H-4 and benzylic Hof indole ring), 1.75 (m, 3 H, H-8, H-7), 1.15 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) 110.9, 127.6, 118.8, 119.0, 121.7, 111.0, 136.4, 121.7 (indole ring), 132.0, 131.0 (C-5, C-6), 53.6 (C-1), 53.5 (C-3), 46.1 (C-4), 31.4 (C-7), 27.7 (C-8), 22.5 (CH_3), 114.4 (OCO), 58.3, 24.5 (indole NCH_2CH_2); IR ($CHCl_3$) 3500 (strong, NH), 1625 cm^{-1}; mass spectrum, *m/e* (relative intensity) 338.0 (P, 1.49), 223 (0.90), 208 (90.8), 146 (9.12), 144 (10.34), 130 (9.37), 115 (2.11), 87 (100); high-resolution mass spectrum, *m/e* 338.1990 ($C_{21}H_{26}N_2O_2$ requires 338.1977).

Methyl 1-[(2,2,2-Trichloroethoxy)carbonyl]-1,6- and -1,2-dihydronicotinates (12 and 11). The general procedure described by Fowler[10] for the preparation of analogous substances was employed. To a mixture of 27.4 g (0.2 mol) of methyl nicotinate and 7.4 g (0.2 mol) of sodium borohydride in 200 mL of absolute ethanol at −78 °C under N_2 was added 56 mL (0.4 mol) of 2,2,2-trichloroethyl chloroformate in 40 mL of anhydrous ethyl ether. After stirring for an additional 3 h at −78 °C under N_2, the reaction mixture was poured into 300 mL of ice water. The ethereal layer was separated, washed with water, dried, and concentrated in vacuo to give 75.0 g of a thick oil, which was shown by ^1H NMR analysis to contain a 1:1 mixture of the desired 1,6- and the undesired 1,2-dihydronicotinates **12** and **11**: ^1H NMR ($CDCl_3$) δ 7.80 (m, 1 H, H-2 of 1,6-isomer), 7.00 (m, 2 H, H-4, H-6 of 1,2-isomer), 4.8 (s, 2 H, CH_2 α to CCl_3), 4.8–4.0 (m, 3 H, H-4, H-5 of 1,6-isomer, H-5 of 1,2-isomer), 3.8 (s, 3 H, methoxy).

2-[(Trichloroethoxy)carbonyl]-6-carbomethoxy-7-acetyl-2-azabicyclo[2.2.2]oct-5-ene (14). A mixture of 62.6 g (0.2 mol) of methyl 1-[(trichloroethoxy)carbonyl]-1, 2- and -1,6-dihydronicotinate (**12** and **11**) and 34 mL (0.4 mol) of methyl vinyl ketone in 100 mL of dry benzene was heated at 80 °C for 24 h under N_2. Another 34 mL of methyl vinyl ketone was added and the reaction mixture was stirred at 80 °C for another 48 h. Removal of the benzene under reduced pressure yielded a brown oil, which was subjected to rapid preliminary purification by column chromatography on silica gel (utilizing a gradual increase in the concentration of eluant from 15% to 40% ether–petroleum ether), giving 40 g of a mixture of the regioisomeric **13** and **14**. Final separation by flash chromatography on silica gel (utilizing a gradual increase in the concentration of eluant from 20% to 50% ether–petroleum ether) yielded 12.0 g (24%) of **14** as an oil: ^1H NMR ($CDCl_3$) δ 7.3 (d, 1 H, H-5), 5.8 (m, 1 H, H-1), 4.9–4.6 (m, 2 H, CH_2 α to CCl_3), 3.8 (s, 3 H, methoxy), 3.5–3.0 (m, 4 H, H-3, H-4, H-7), 2.2 (s, 3 H, methyl), 2.0–1.8 (m, 2 H, H-8); IR ($CHCl_3$) 3030, 2960, 1710, 1410, 1280, 1130 cm^{-1}; high-resolution mass spectrum, *m/e* 383.0089 ($C_{14}H_{16}Cl_3NO_5$ required 383.0084).

Anal. Calcd for $C_{14}H_{16}Cl_3NO_5$: C, 43.72; H, 4.19; N, 3.64; Cl, 27.65. Found: C, 43.68; H, 4.39; N, 3.58; Cl, 27.50.

2-[(Trichloroethoxy)carbonyl]-6-carbomethoxy-7-[1,1-(ethylenedioxy)ethyl]-2-azabicyclo[2.2.2]oct-5-ene. A solution of 11.0 g (0.03 mol) of **14**, 31.2 mL (0.53 mol) of ethylene glycol, and 175 mg (0.9 mmol) of *p*-toluenesulfonic acid in 500 mL of anhydrous benzene was stirred at reflux under N_2 for 3 h in an apparatus equipped with a Dean–Stark trap. The reaction mixture was cooled to 25 °C, washed with saturated $NaHCO_3$, dried, and concentrated in vacuo to yield 12.0 g (ca. 100%) of the ketal as an oil: ^1H NMR ($CDCl_3$) δ 7.3 (m, 1 H, H-5), 5.4 (m, 1 H, H-1), 4.9–4.5 (m, 2 H, CH_2 α CCl_3), 4.0–3.8 (m, 4 H, ethylenedioxy CH_2), 3.8 (s, 3 H, methoxy), 3.4 (m, 1 H, H-7), 3.1–2.9 (m, 2 H, H-3), 2.5 (dt, 1 H, H-4), 2.0–1.7 (m, 2 H, H-8), 2.4 and 2.2 (d, 3 H, diastereomeric methyls); high-resolution mass spectrum, *m/e* 337.1515 ($C_{16}H_{20}NO_6Cl_3$ requires 337.1525).

6-Carbomethoxy-7-[1,1-(ethylenedioxy)ethyl]-2-azabicyclo[2.2.2]oct-5-ene (15). To a suspension of 16.4 g (251 mmol) of activated (with HOAc) zinc in 100 mL of anhydrous methanol was added 4.7 g (11.2 mmol) of the above ketal. The resulting mixture was then stirred at reflux under N_2 for 1 h, cooled to 25 °C, and filtered through Celite. The filtrate was diluted with chloroform to give approximately a 3:7 methanol–chloroform mixture and percolated through an alumina (Alcoa F-20, 100–200 mesh) column followed by washing with three bed volumes of 3:7 methanol–chloroform. The combined eluant was concentrated in vacuo, yielding 2.8 g (100%) of an oil containing C-7 epimeric mixture of the deblocked isoquinuclidines **15**: ^1H NMR ($CDCl_3$) δ 7.2 (d, 1 H, H-5), 4.2 (m, 1 H, H-1), 3.9 (m, 4 H, ethylenedioxy CH_2), 3.7 (s, 3 H, methoxy), 2.9 (br s, 2 H, H-3), 2.4 (m, 1 H, H-4), 1.9 (dt, 1 H, H-7), 1.2 (s, 3 H, CH_3); IR (liquid film) 3300, 2940, 2880, 1710, 1430, 1250, 1090, 750 cm^{-1}; UV max (absolute EtOH) 308 nm (ϵ 11 600).

(15) Beaulieu, N.; Dickinson, R. A.; Deslongchamps, P. *Can. J. Chem.* **1980**, *58*, 2531 and publication cited in ref 15.

(16) Surprisingly, Wenkert-type cyclization of the hydroisoquinoline ester **18** under the basic conditions used for the transformation **17** → **26** + **27** is unsuccessful.

(17) **Note Added in Proof**: Recent observations we have made suggest that the reaction of **9en** with *tert*-butyl propiolate is very sensitive to the conditions used. Accordingly, we have demonstrated that this process is successful for generation of **19** when run under the proper conditions and that **19** serves as an ideal precursor for pentacyclic systems related to **26** and **27**. These observations will be described in a future publication.

Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.96; H, 7.32; N, 5.60.

2-Tryptophyl-6-carbomethoxy-7-[1,1-(ethylenedioxy)ethyl]-2-azabicyclo[2.2.2]oct-5-ene (16). A suspension of 3.60 g (43 mmol) of $NaHCO_3$ in 15 mL of anhydrous CH_3CN containing 3.60 g (14.2 mmol) of isoquinuclidene **15** and 3.20 g (14.3 mmol) of tryptophyl bromide was stirred at 60 °C for 12 h. The mixture was cooled to 25 °C, poured into water, and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed with water, dried, and concentrated in vacuo, giving an oil, which was purified by flash column chromatography on silica gel (increase from 1% to 3.5% CH_3OH–$CHCl_3$), yielding 2.62 g (46.5%) of the C-7 epimeric isoquinuclidenes **16**. These diastereomers can be separated by preparative TLC on silica gel. ^1H NMR ($CDCl_3$) δ 8.7 (br s, 1 H, indole NH), 7.7–7.0 (m, 5 H, aromatic), 6.9 (m, 1 H, H-5), 4.3 (m, 1 H, H-1), 3.9 (m, 4 H, ethylenedioxy CH_2), 3.7 (s, 3 H, methoxy), 3.2–2.3 (m, 6 H, H-3 and ethylene of tryptophyl group), 1.9 (dt, 1 H, H-7), 1.2 (s, 3 H, CH_3); endo epimer ^{13}C NMR ($CDCl_3$) 164.9 (C=O), 143.1 (C-5), 136.1 (C-6), 136.3, 127.5, 121.5, 121.9, 118.8, 118.5, 113.6, 111.1 (indole), 113.6 (OCO), 64.7, 64.7 (OCH_2CH_2O), 54.1 (NCH_2), 58.7 (C-3), 51.4 (OCH_3), 53.3 (C-1), 32.2 (C-4), 46.6 (C-7), 23.8 (C-8), 23.5 (CH_2), 21.9 (CH_3); mass spectrum, *m/e* (relative intensity) 396 (P, 0.5), 298 (5.8), 267 (15.9), 266 (100), 152 (50.2), 144 (13.3), 130 (10.2), 87 (78.4); high-resolution mass spectrum, *m/e* 396.2048 ($C_{23}H_{28}N_2O_4$ requires 396.2049; exo epimer ^{13}C NMR ($CDCl_3$) δ 165.2 (C=O), 141.5 (C-5), 134.6 (C-6), 136.2, 127.4, 121.7, 121.4 118.8, 118.6, 111.0 (indole), 110.0 (OCO), 64.4, 63.9 (OCH_2CH_2O), 52.5 (NCH_2), 58.0 (C-3), 51.2 (OCH_3), 52.5 (C-1), 31.8 (C-4), 46.3 (C-7), 24.1 (C-8), 26.6 (CH_2), 21.9 (CH_3); mass spectrum, *m/e* (relative intensity) 396 (0.04), 298 (3.2), 267 (9.2), 266 (57.5), 144 (7.0), 130 (6.3), 87 (100); high-resolution mass spectrum, *m/e* 396.2050 ($C_{23}H_{28}N_2O_4$ requires 396.2049).

Δ^3,Δ^5-2-Tryptophyl-4-carbethoxy-7-[1,1-(ethylenedioxy)ethyl]hexahydroisoquinoline (17). A solution of 0.676 g (2.0 mmol) of isoquinuclidene **9en** and 0.392 g (8.0 mmol) of ethyl propiolate in 10.0 mL of acetonitrile was stirred at reflux for 12 h under N_2 and concentrated in vacuo to give an oil, which was purified by flash column chromatography on silica gel (1% MeOH–$CHCl_3$), yielding 0.523 g (60%) of **17**: ^1H NMR ($CDCl_3$) δ 8.0 (br s, 1 H, indole NH), 7.0–7.6 (m, 5 H, aromatic and H-3), 6.9 (d, H2, J = 2 Hz), 5.8 (d, 1 H, J = 10 Hz, H16), 5.5 (ddd, 1 H, J = 10, 2, 2 Hz, H17), 4.2 (q, OCH_2), 3.9 (m, 4 H, OCH_2CH_2O), 3.4 (m, 2 H, H5), 3.2 (br s, 1 H, H15), 3.1 (t, 1 H, J = 12 Hz, H21a), 3.0 (m, 2 H, H6), 2.8 (dd, 1 H, J = 12, 4 Hz, H21e), 2.2 (m, 2 H, H20, H18), 1.8 (m, 2 H, H19), 1.3 (t, 3 H, ethoxy CH_3), 1.2 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 168.5 (COEt), 145.9 (C3), 136.4 (C13), 133.0 (C17), 127.0 (C8), 122.2 (C11), 121.8 (C16), 119.2 (C10), 118.3 (C9), 112.1 (OCO), 111.5 (C7), 111.2 (C12), 64.7, 64.5 (OCH_2CH_2O), 58.7 (C5), 46.6 (C21), 40.2 (C15), 31.6 (C20), 29.9 (C18), 26.8 (C6), 20.8 (CH_3), 14.6 (ethoxy CH_3) ppm; IR ($CHCl_3$) 3500 (NH), 1670 (NC=CCO), 1615 cm^{-1}; mass spectrum, *m/e* (relative intensity) 43.6 (P, 18.56), 391 (12.30), 349 (1.54), 306 (32.35), 176 (0.3), 173 (1.77), 172 (2.55), 145 (3.66), 144 (21.05), 143 (6.32), 130 (6.51), 87 (100); high-resolution mass spectrum, *m/e* 436.2355 ($C_{26}H_{32}N_2O_4$ requires 436.2338).

Δ^3,Δ^5-2-Tryptophyl-4-carbethoxy-5-carbomethoxy-7-[1,1-(ethylenedioxy)ethyl]hexahydroisoquinoline (18). A solution of 0.106 g (0.266 mmol) of **16** and 0.034 g (0.346 mmol) of ethyl propiolate in 0.5 mL of CH_3CN was stirred at reflux for 12 h under N_2. Concentration in vacuo gave an oil, which was purified by TLC on silica gel (7.5% MeOH in $CHCl_3$), giving 0.09 g of **18** (68%): ^1H NMR ($CDCl_3$) δ 8.5 (br s, 1 H, NH), 7.7–7.0 (m, 6 H, aromatic and H-3), 6.9 (d, 1 H, H-17), 4.1 (q, 2 H, ethoxy CH_2), 3.9 (m, 4 H, ethylenedioxy CH_2), 3.7 (s, 3 H, methoxy), 3.5–2.8 (m, 5 H, H-21, H-5, H-15), 2.6–1.4 (m, 6 H, H-6, H-18, H-19, H-20), 1.3 (s, 3 H, O_2CCH_3), 1.2 (t, 3 H, ethoxy CH_3); ^{13}C NMR ($CDCl_3$) δ 168.9 (s, EtOCO), 168.5 (s, MeOCO), 145.2 (d, C-3), 136.9 (s, C-13 or C-16), 136.3 (s, C-16 or C-13), 134.2 (d, C-17), 127.0 (s, C-8), 122.4 (d, C-2 or C-10), 122.3 (d, C-10 or C-2), 119.4 (d, C-11), 118.4 (d, C-9), 112.1 (s, C-14), 111.5 (s, C-7), 111.3 (d, C-12), 94.7 (s, OCO), 64.8 (t, OCH_2CH_2O), 58.8 (t, C-5), 56.2 (t, ethoxyl CH_2O), 51.6 (q, methoxy), 48.4 (t, C-19), 41.7 (d, C-15), 30.5 (d, C-20), 29.4 (d, C-18), 25.0 (t, C-6), 24.3 (t, C-19), 21.9 (q, O_2CCH_3), 14.5 (q, ethoxyl CH_3); IR ($CHCl_3$) 3480, 2980, 2950, 2880, 1710, 1670, 1600, 1430, 1150, 1090, 1040 cm^{-1}; UV max (EtOH) 285 nm (ϵ 17 400); mass spectrum (70 eV), *m/e* (relative intensity) 494 (5), 462 (6), 448 (34), 364 (17), 144 (20), 87 (100); high-resolution mass spectrum, *m/e* 494.2410 ($C_{28}H_{34}N_2O_6$ requires 494.2417).

Δ^3,Δ^5-2-Tryptophyl-4-carbo-*tert*-butoxy-5-carbomethoxy-7-[1,1-(ethylenedioxy)ethyl]hexahydroisoquinoline (20). A solution of 0.648 g (1.63 mmol) of **16**, 0.437 g (3.46 mmol) of *tert*-butyl propiolate in 2 mL of anhydrous CH_3CN was stirred at reflux under N_2 for 12 h. The mixture was cooled to 25 °C and concentrated in vacuo giving a residue that was purified by flash column chromatography on silica gel (gradual increase from 0% to 2% MeOH–$CHCl_3$), giving 0.199 g (23%) or 20: ^1H NMR ($CDCl_3$) δ 8.7 (br s, 1 H, NH), 7.6–6.5 (m, 7 H, aromatic and H-3, H-17), 4.0 (m, 4 H, OCH_2CH_2O), 3.7 (s, 3 H, methoxy), 3.5–2.8 (m, 5 H, H-21, H-5, H-15), 2.7–1.6 (m, 6 H, H-6, H-18, H-19, H-20), 1.4 (s, 9 H, *t*-Bu), 1.3 (s, 3 H, O_2CCH_3); ^{13}C NMR ($CDCl_3$) δ 168.6 (*t*-BuOCO), 168.0 (MeOCO), 144.3 (C-3), 137.1 (C-13 or C-16), 136.5 (C-16 or C-13), 133.2 or 134.5 (C-17), 127.1 (C-8), 122.5 (C-2 or C-10), 121.7 (C-10 or C-2), 119.0 (C-11 or C-9), 118.1 (C-9 or C-11), 111.9 (C-14 or C-7 or C-12), 11.3 (C-14, or C-7 or C-12), 96.9 (ketal OCO), 64.6 (OCH_2CH_2O), 56.0 (C-5 or Me_3CO), 55.9 (Me_3CO or C-5), 51.2 (methoxy), 48.1 (C-19), 41.5 (C-15), 30.9 or 30.6 or 29.9 (C-20 or C-18), 28.4 or 28.3 (($CH_3)_3C$), 25.2 or 25.0 or 24.9 or 24.5 (C-6 or C-19), 21.5 or 21.0 (O_2OCCH_3); IR ($CHCl_3$ 3480, 2980, 2880. 1710, 1670, 1610, 1450, 1370, 1150, 1090, 1040 cm^{-1}; UV max (EtOH) 290 nm (ϵ 17 600); mass spectrum (70 eV), *m/e* (relative intensity) 522 (P, 2), 448 (14), 336 (8), 292 (5), 144 (17), 87 (100); high-resolution mass spectrum, *m/e* 522.2696 ($C_{30}H_{38}N_2O_6$ requires 522.2730).

***N*-Tryptophyl-*N*-cyclohexadienylmethyleneamino Ester 24 (R′ = H, R″ = *t*-Bu).** A solution of 0.063 g (0.185 mmol) of **9en** and 0.093 g (0.74 mmol) of *tert*-butyl propiolate in 10.0 mL of CH_3CN was stirred at reflux for 12 h under N_2. Concentration in vacuo gave an oil, which was purified by flash column chromatography on silica gel, (1.5% MeOH–$CHCl_3$), yielding 26 mg (32%) of **24** (R′ = H, R″ = *t*-Bu):[17] ^1H NMR ($CDCl_3$) δ 8.4 (br s, 1 H, NH), 7.2–8.1 (m, 5 H, indole ring), 6.9 (m, 1 H, H-3), 5.5–6.1 (m, 3 H, H-15, H-16, H-17), 4.6 (d, 1 H, H-14), 3.9 (m, 4 H, OCH_2CH_2O), 3.4 (m, 2 H, H-21), 3.0 (m, 4 H, H-5, H-6), 1.5–2.5 (m, 3 H, H-18, H-19), 1.5 (m, 9 H, $(CH_3)_3C$), 1.3 (m, methyl); ^{13}C NMR ($CDCl_3$) δ 112, 127.5, 118, 119, 122.5, 111, 137.5, 125.0 (indole ring), 25 (indole CH_2), 56 (NCH_2), 151 (NCH=), 87 (NCH=CH), 56.0 (($CH_3)_3C$), 28.7 (($CH_3)_3$), 46 (NCH_2), 138.5, 146, 127, 133, 32.3, 29.0 (cyclohexadiene ring), 111 (0CO), 64 ($0CH_2CH_2O$), 23.6 (methyl); IR ($CHCl_3$) 3495 (NH), 1670 (enamino ester), 1600 cm^{-1}; mass spectrum, *m/e* (relative intensity) 464 (P, 11), 408 (6), 391 (5), 334 (9), 278 (28), 743 (58), 144 (100), 130 (23), 87 (78); high-resolution mass spectrum, *m/e* 464.2673 ($C_{28}H_{36}N_2O_4$ requires 464.2670).

18-[1,1-(Ethylenedioxy)ethyl]-Δ^{16}-dehydroepialloyohimbane (26). A solution of 55 mg (0.13 mmol) of the hydroisoquinoline **17** in 8 mL of 1:1 EtOH–H_2O containing 25% KOH was stirred at reflux under N_2 for 4 days. The mixture was cooled to 25 °C, poured into water, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried and concentrated in vacuo giving an oil that was purified by TLC on silica gel (4% CH_3OH–$CHCl_3$) to yield 15.0 mg (36%) of the epialloyohimbane **26** and 2 mg (4%) of its C-3 epimer **27**. **26**: ^1H NMR ($CDCl_3$) δ 7.8 (br s, 1 H, NH), 7.0–7.5 (m, 4 H, aromatic), 5.8 (d, 1 H, J = 10 Hz, H-16), 5.7 (d, 1 H, J = 10 Hz, H-17), 3.9 (m, 4 H, OCH_2CH_2O), 3.3 (dd, 1 H, H-3, J = 12, 1 Hz), 3.1 (dd, 1 H, H-21a, J = 12, 12 Hz), 2.8 (dd, 1 H, H-21e, J = 12, 4 Hz), 1.2 (s, 3 H, methyl); ^{13}C NMR ($CDCl_3$) δ 136.0 (C-13), 134.5 (C-2), 127.3 (C-8), 121.3 (C-11), 119 (C-10), 118.0 (C-9), 110.8 (C-12), 111.6 (C-7), 131.3 (Ch17), 128.0 (C-16), 108.3 (OCO), 55.4 (C-21), 55.2 (C-3), 53.3 (C-5), 40.9 (C-15), 35.4 (C-4), 27.6 (C-19), 32.6 (C-18), 21.5 (C-6), 21.1 (CH_3), 64.6 (OCH_2CH_2O), 33.1 (C-20); IR 2810, 2775, 3495 cm^{-1}; mass spectrum, *m/e* 364.0 (P, 35.05), 277, 197, 184, 169, 156, 130, 87 (100); high-resolution mass spectrum, *m/e* 364.2153 ($C_{23}H_{28}N_2O_{27}$ requires 364.2160).

27: ^1H NMR ($CDCl_3$) δ 7.0–7.4 (m, 4 H, aromatic), 5.8–6.0 (m, 2 H, vinyl), 3.9 (m, 4 H, OCH_2CH_2O), 1.3 (s, 3 H, methyl); IR 3495 (NH), 2815, 2780 cm^{-1}.

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Registry No. (±)-8 (R_2 = dioxolane), 87420-64-2; (±)-8 (R_1 = dioxolane), 87420-66-4; (±)-**9en**, 87371-63-9; **11**, 87371-65-1; **12**, 87371-64-0; **13**, 87371-72-0; **14**, 87371-67-3; **15**, 87393-28-0; (±)-*endo*-**16**, 87371-68-4; (±)-*exo*-**16**, 87420-63-1; (±)-**17**, 87371-69-5; (±)-**18**, 87393-29-1; (±)-**20**, 87371-70-8; **24** (R^1 = H; R'' = *t*-Bu), 87393-27-9; (±)-**26**, 87371-71-9; (±)-**27**, 87420-65-3; 2-[(trichloroethoxy)carbonyl]-6-carbomethoxy-7-(1,1-(ethylenedioxy)ethyl)-2-azabicyclo[2.2.2]oct-5-ene, 87371-66-2; tryptophyl bromide, 55982-76-8; methyl vinyl ketone, 78-94-4; ethyl propiolate, 623-47-2; *tert*-butyl propiolate, 13831-03-3; methyl nicotinate, 93-60-7.

Protonation of Anion Intermediates in Metal-Ammonia Reduction: 1,2- vs. 1,4-Dihydro Aromatic Products

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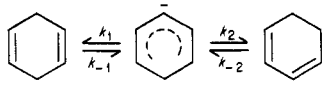
The competition between 1,3-cyclohexadienes and 1,4-cyclohexadienes during metal-ammonia reduction has been examined. The former is usually regarded as a thermodynamic product and the latter as a kinetic product although, in actuality, little thermodynamic difference exists between these two isomers. 1,4-Cyclohexadiene was found to undergo proton abstraction with potassium or sodium amide in ammonia at -50 °C but not with lithium amide. Similarly, 1,3-cyclohexadiene reacts only with potassium amide and not with sodium or lithium amide. Consequences relating to the formation of conjugated and nonconjugated products during metal-ammonia reduction are discussed. The reaction of dihydronaphthalenes with various amides is also presented and again there is considerable variation in behavior. This has led to improved synthetic schemes for the selective production of 1,2-dihydro- and 1,4-dihydronaphthalenes as well as tetralins. Finally, protonation sites in pentadienyl type anions are considered.

The Birch reduction and related metal-ammonia processes have become important methods for the preparation of dienes and dihydro aromatics[1] (Figure 1). Benzene itself affords 1,4-cyclohexadiene (**1**), which is regarded as a kinetic product, whereas 1,3-cyclohexadiene (**2**) has been considered to be the thermodynamic product[2,3] since it is a conjugated diene. It has been suggested[3] that conjugated products may result under equilibrium conditions such as illustrated in Scheme I (regioselectivity is determined by protonation of the final monoanion in Figure 1). However, Dewar has pointed out[4] that 1,3-cyclohexadiene cannot exist in an unstrained, planar conformation, and, in fact, experimental results[5,6] support little difference in thermodynamic stability between these dienes. We will show that thermodynamic arguments[3] may be unnecessary to explain conjugated products in light of additional information regarding the kinetics of these processes.

Protonation of the cyclohexadienyl anion (**3**) occurs most readily at the 3-position to produce **1** although a small amount (~1%) of **2** is also formed (i.e., $k_1 \gg k_2$). It becomes obvious from Scheme I that the relative amounts of **1** and **2** will be greatly affected by the values of k_{-1} and k_{-2}. For example, if protonation to form one isomer is reversible, and the other not, buildup of the latter may

Scheme I



1 3 2

occur. It is enlightening to consider the possible pathways 1-3. With pathway 1, an equilibrium exists and the ratio

nonconjugated product ⇌ anion ⇌ conjugated product (1)

nonconjugated product ⇌ anion → conjugated product (2)

nonconjugated product ← anion → conjugated product (3)

of products will indeed be dictated by the relative thermodynamic stabilities. In contrast, path 3 will produce products that simply reflect the relative protonation rates (k_1/k_2 in Scheme I). Path 2, however, will provide the conjugated product exclusively. As we will show below, it is, in fact, paths 2 and 3 that are most important for metal-ammonia reduction, and attention must be focused on the reverse (deprotonation) steps.

We have observed a considerable variation in the behavior of **1** and **2** toward deprotonation by amide in ammonia.[8] Moreover, we have noted substantial differences between lithium, sodium, and potassium as counterions[8b] (see Table I). KNH_2 is most effective at proton ab-

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