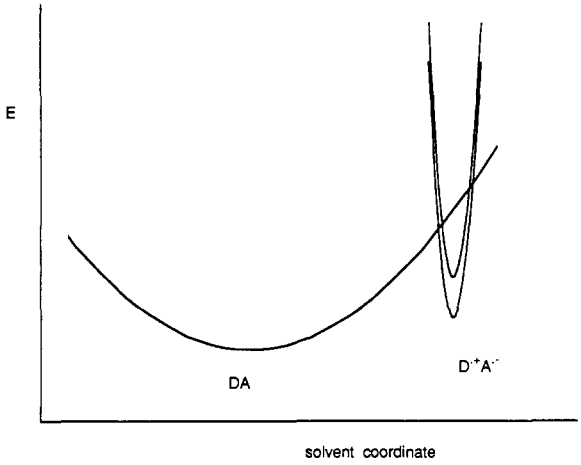


Figure 5. Possible potential energy diagram of a charge-separation ET reaction.

the DA complex should be flat. On the other hand, the solvent movement around the $D^{\bullet+}A^{\bullet-}$ complex is restricted and hence the potential energy curve of the $D^{\bullet+}A^{\bullet-}$ complex should be very sharp as illustrated in Figure 5. In such a case, the TS (intersecting point) lies late along the solvent coordinate regardless of the exothermicity of the reaction, and a perturbation which stabilizes $D^{\bullet+}A^{\bullet-}$ complex results in only a minor stabilizing effect at the TS. Therefore, the ET rate can be relatively insensitive to the change in E_{red} of the acceptor, A.

In summary, the present results indicate that all the reactions of aromatic carbonyl compounds with RLi studied proceed via the same mechanism, namely the ET mechanism in which the rate-determining step is the initial ET step.

Experimental Section

Materials. Diethyl ether was dried over $LiAlH_4$ and distilled before use. Cyclohexane was dried over CaH_2 and distilled. Pentane was dried over Na and distilled. Commercial solution of PhLi (cyclohexane–ether 7:3, Merck), allyllithium (ether, Alfa), and *t*-BuLi (pentane, Aldrich) were standardized by using 2,5-dimethoxybenzyl alcohol as described in the literature.[8] Substituted benzophenones and benzophenone-*carbonyl*-^{14}C were prepared as described previously.[1a] All substituted benzaldehydes were commercially available and purified either by distillation or recrystallization before use. Benzaldehyde-*carbonyl*-^{14}C was synthesized by the tributyltin hydride reduction[9] of benzoyl-7-^{14}C chloride which was obtained by chlorination of benzoic-7-^{14}C acid (NEN) with thionyl chloride.

Reactions. All reactions with PhLi and allyllithium gave the normal 1,2-adduct exclusively except one case, 2,4,6-trimethylbenzophenone + PhLi, in which 1,4-adduct was obtained as a minor product. All products were isolated and identified by IR and NMR. The material balance was confirmed for the unsubstituted carbonyl compounds and found excellent. The reaction of benzophenone with *t*-BuLi gave four products (1,2-adduct, 65%; 1,6-adduct, 28%; benzhydrol, 5%; structure not determined, 2%).

The relative reactivities of the substituted benzophenones and benzaldehydes were determined at 0.0 °C by the competition experiments as described previously,[1a] and the carbonyl carbon-^{14}C KIEs for reactions 1–3 were measured in a usual manner.[4]

Acknowledgment. We are indebted to the Material Analysis Center of ISIR for the elemental analyses and NMR measurements.

(8) Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. *J. Chem. Soc., Chem. Commun.* **1980**, 87.
(9) Four, P.; Guibe, F. *J. Org. Chem.* **1981**, *46*, 4439.

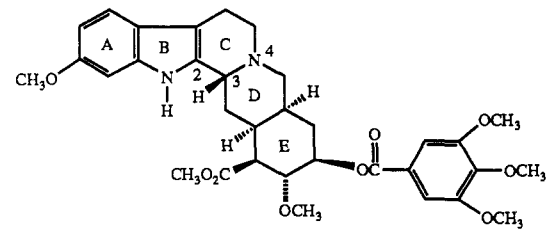
Reinvestigation of the Mechanism of the Acid-Catalyzed Epimerization of Reserpine to Isoreserpine

Lin-Hua Zhang, Ashok K. Gupta, and James M. Cook*

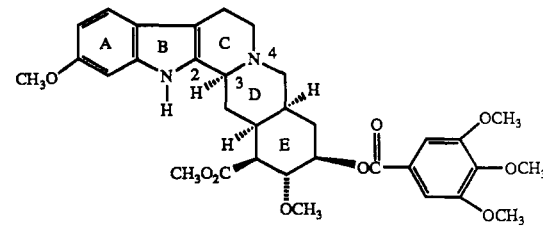
Department of Chemistry, University of Wisconsin—Milwaukee, Milwaukee, Wisconsin 53201

Received April 4, 1989

Reserpine (1) was originally isolated from the Indian snake root *Rauwolfia serpentina* Benth.[1,2] It is the preeminent member of the yohimboid class of indole alkaloids because of its structural complexity coupled with its clinical importance as a hypotensive agent. This base also exhibits significant activity as a sedative and tranquilizer.[3] Over the years, reserpine has formed the subject of extensive chemical and synthetic investigations.[4] It has been reported that the epimerization of reserpine (1) to isoreserpine (2) can be effected either under acidic or basic



1



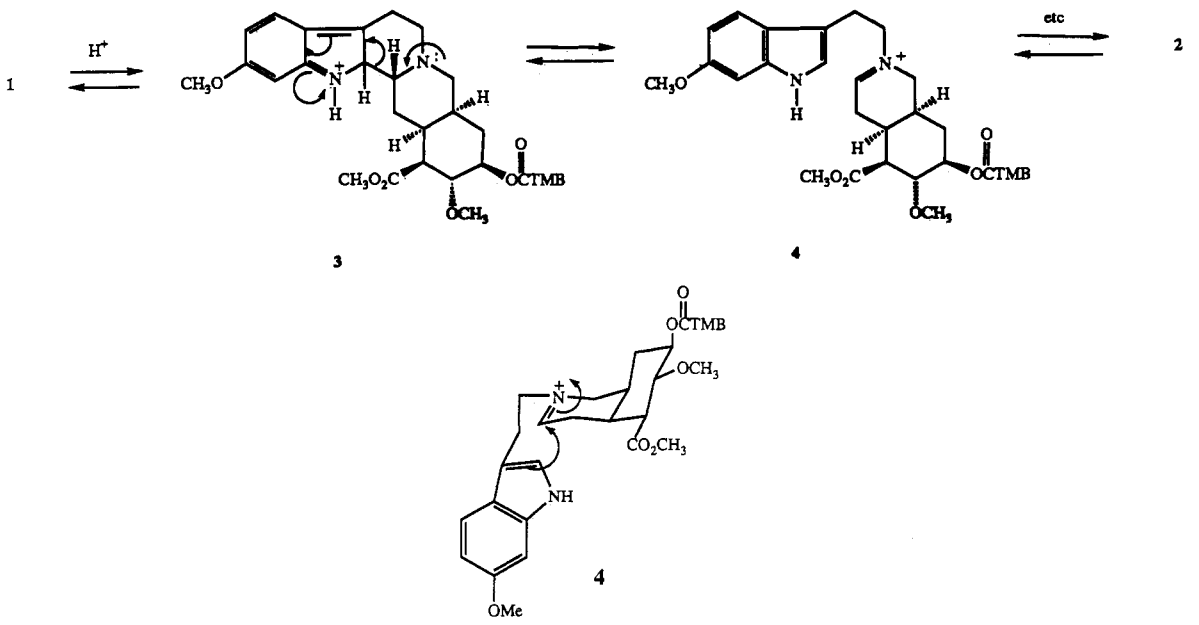
2

conditions; moreover, under acidic conditions (Δ, HOAc), 2 has been found to predominate over 1 in a ratio of 3.5:1.[4] Several mechanisms have been suggested to account for this equilibration.[2,4,5] Joule, however, concluded that the mechanism involving initial protonation at C(2) followed by reverse Mannich fission of the C(2)–C(3) bond was responsible for the isomerization between 1 and 2, as illustrated in Scheme I.[6a] This series of steps is related to

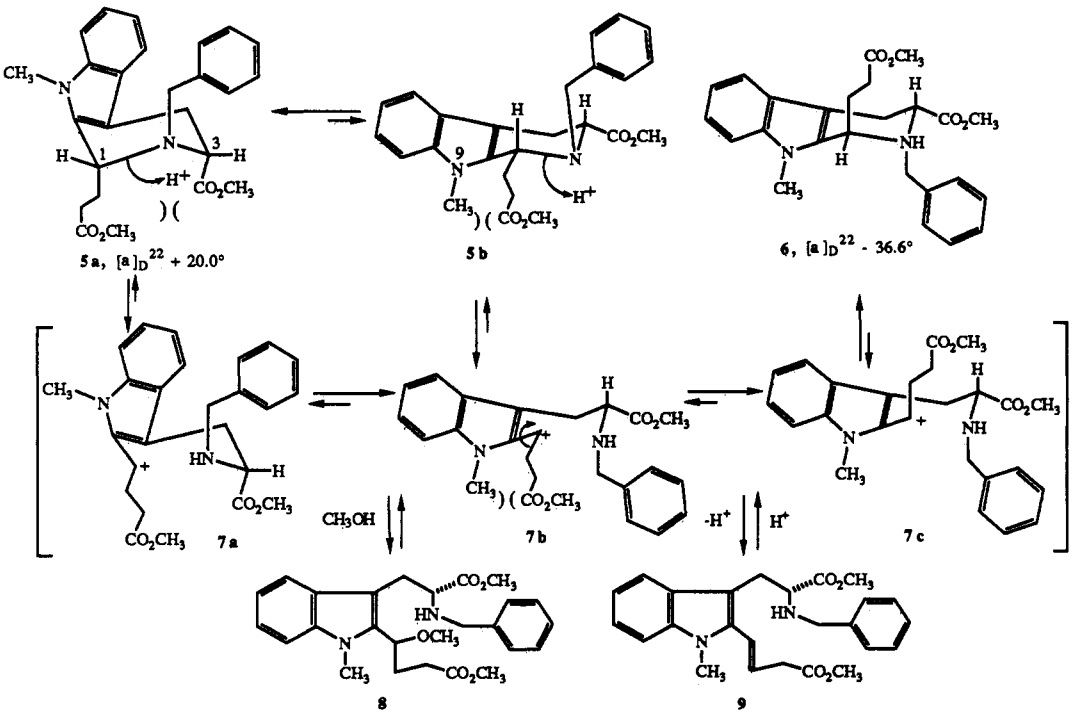
(1) Chatterjee, A. *Fortschr. Chem. Org. Naturst.* **1953**, *10*, 390. Chatterjee, A.; Pakrashi, S. C.; Werner, G. *Fortschr. Chem. Org. Naturst.* **1956**, *13*, 346. Schlittler, E.; Schneider, J. A.; Plummer, A. J. *Angew. Chem.* **1954**, *66*, 386. Saxton, J. E. *Quart. Rev. Chem. Soc.* **1956**, *10*, 128.
(2) Müller, J. M.; Schlittler, E.; Bein, H. J. *Experimenta* **1952**, *8*, 338.
(3) Dorfman, L.; Huebner, C. F.; MacPhillamy, H. B.; Schlittler, E.; St. André, A. F. *Experimenta* **1953**, *9*, 368.
(4) (a) Woodward, R. B.; Bader, F. E.; Bader, H.; Frey, A. J.; Kierstead, R. W. *J. Am. Chem. Soc.* **1956**, *78*, 2023 and 2657; *Tetrahedron* **1658**, *2*, 1. (b) Pearlman, B. A. *J. Am. Chem. Soc.* **1979**, *101*, 6398 and 6404. (c) Wender, P. A.; Schaus, J. M.; White, A. W. *J. Am. Chem. Soc.* **1980**, *102*, 6157; *Heterocycles* **1987**, *25*, 263. (d) Martin, S. F.; Rueger, H.; Williamson, S. A.; Grzejszczak, S. *J. Am. Chem. Soc.* **1987**, *109*, 6124.
(5) Dorfman, L.; Furlenmeier, A.; Huebner, C. F.; Lucas, R.; MacPhillamy, H. B.; Müller, J.; Schlittler, E.; Schwyzer, R.; St. André, A. F. *Helv. Chem. Acta* **1954**, *37*, 59. MacPhillamy, H. B.; Dorfman, L.; Huebner, C. F.; Schlittler, E.; St. André, A. F. *J. Am. Chem. Soc.* **1955**, *77*, 1071. Wenkert, E.; Liu, L. H. *Experimenta* **1955**, *11*, 302. MacPhillamy, H. B.; Huebner, C. F.; Schlittler, E.; St. André, A. F.; Ulshafer, R. E. *J. Am. Chem. Soc.* **1955**, *77*, 4335. Janot, M. M.; Goutarel, R.; Amin, M. *C. R. Acad. Sci., Paris* **1950**, *230*, 2541.

0022-3263/89/1954-4708$01.50/0

Scheme I



Scheme II



a retro Pictet–Spengler process.[7] In addition, Sakai and Oikawa investigated the ring scission of 1 under conditions related to Eschweiler–Clarke reduction.[6b]

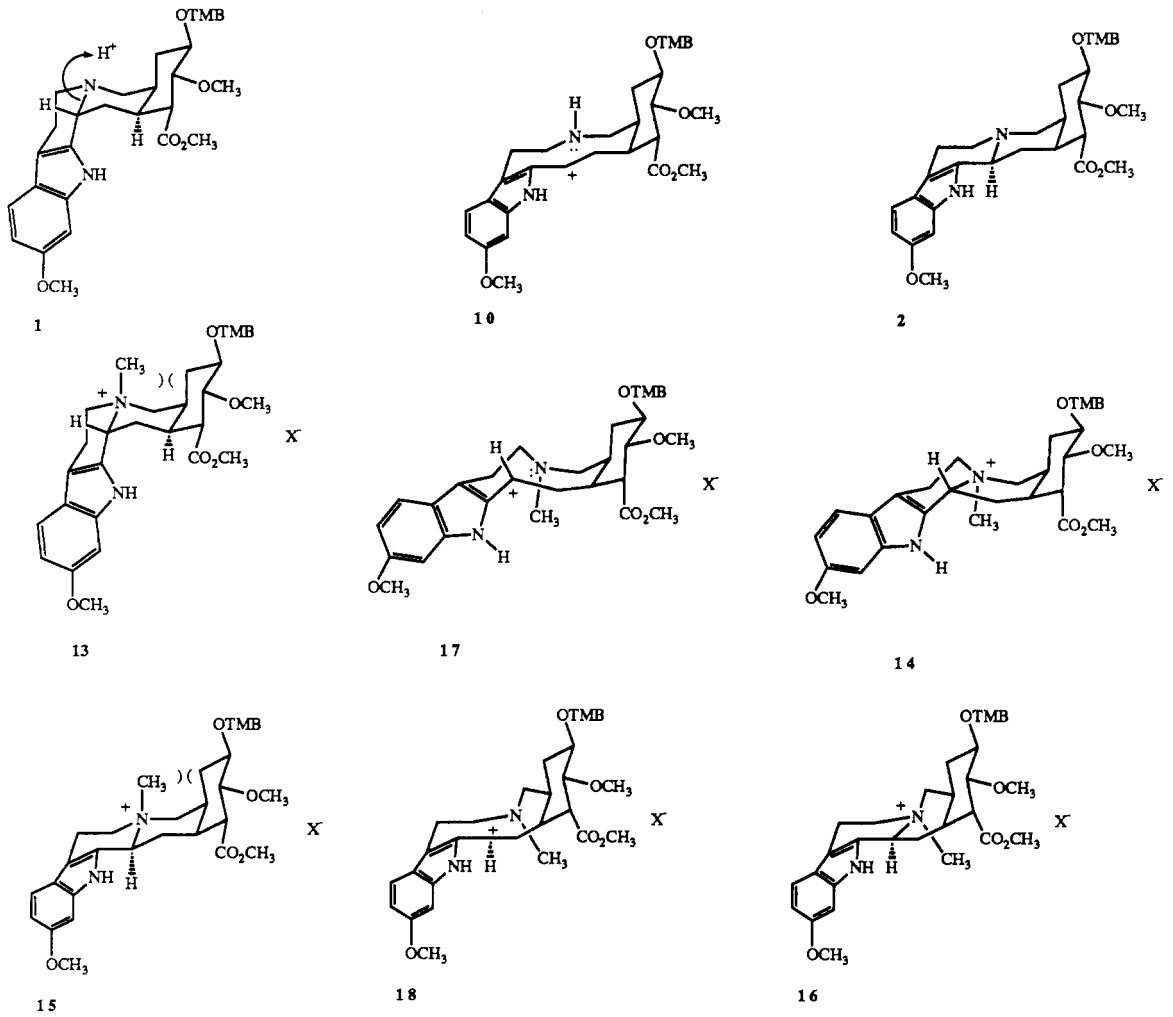
Recent observations by Martin[4d] during the synthesis of 1 have prompted a reinvestigation of the equilibration. In brief, he found that cyclization of the immonium ion 4 proceeded via a half-chair/chair conformation as depicted at the bottom of Scheme I to provide reserpine (1) as the major product (4.3:1).[4d] If 4 was indeed an intermediate in the conversion of 1 into 2, as proposed earlier by Joule, then isoreserpine should in contrast have been isolated by Martin[4d] and Sakai[6c] as the major product in a ratio of 3.5:1.[6a] Intermediate 4 therefore cannot be the predominant species in the acid-catalyzed isomerization of 1 into 2. Recent results from our laboratory bear on this issue. When the *cis*-1,3-disubstituted-1,2,3,4-tetrahydro-β-carboline (5) was heated in methanolic hydrogen chloride it was converted into the thermodynamically more stable trans isomer 6 via bond cleavage across the C(1)–N(2) bond followed by intramolecular recyclization.[8] As illustrated in Scheme II, the driving force for this acid-catalyzed ring scission at the C–N bond is presumed to result from relief of the 1,3-diaxial interactions (repulsion) between substituents at C(1) and C(3) in the diaxial conformer **5a** or release of A(1,2) strain[9] between the substituents located

(6) (a) Gaskell, A. J.; Joule, J. A. *Tetrahedron* **1967**, *23*, 4053. (b) Sakai, S.; Ogawa, M. *Chem. Pharm. Bull.* **1978**, *26*, 678. (c) Sakai, S.; Ogawa, M. *Heterocycles* **1978**, *10*, 67.

(7) For a review of the Pictet–Spengler reaction, see: Ungemach, F.; Cook, J. M. *Heterocycles* **1978**, *9*, 1089.

(8) Zhang, L. H.; Cook, J. M. *Heterocycles* **1988**, *27*(6), 1357.

Scheme III

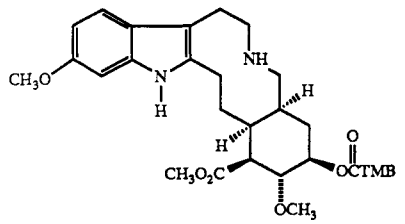


at C(1) and C(9) in the diequatorial conformer **5b**. Support for protonation of **5** across the C(1)–N(2) bond followed by ring scission and recyclization to **6** was obtained by isolation of intermediates **8** and **9** (Scheme II). When **8** and **9** were heated in methanolic hydrogen chloride, **6** was generated in optically pure form presumably via carbocation **7**.

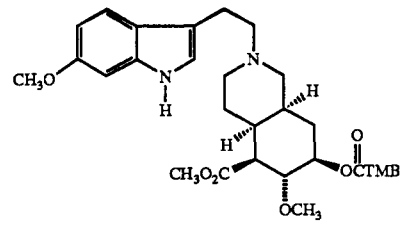
Encouraged by these results, we heated reserpine (**1**) in methanolic hydrogen chloride (1%) for 72 h, under conditions analogous to those employed to convert **5** into **6**, to provide a mixture of isoreserpine (**2**) and **1** with **2** predominating in a ratio of 2.6:1. Moreover, when **2** was heated in methanolic hydrogen chloride it remained the major alkaloid isolated from this equilibration in agreement with its thermodynamic stability.[6a] As illustrated in Scheme III, protonation of the N_b-nitrogen function of **1** followed by ring scission [C(3)–N(4)] would generate the carbocation **10** and release the 1,3-diaxial interaction inherent in **1**. This same interaction, however is not present in isoreserpine (**2**), and ring scission via **10** would be expected to occur at a slower rate. In agreement with this hypothesis heating **1** in methanolic hydrogen chloride for only 12 h resulted in 56% conversion into **2**, while the analogous experiment with isoreserpine (**2**) resulted in only 8% conversion into reserpine (**1**). If immonium ion **4** had indeed been an intermediate in the conversion of **2** into **1** the equilibration to a mixture of reserpine–isoreserpine from **2** would have occurred more rapidly than observed since Martin has already shown that **4** cyclized predominantly to **1** rather than isoreserpine.[4d] This is contrary to the results observed here. Clearly **1** undergoes ring scission more rapidly than **2**, the driving force of which was described above and implicates carbocation **10** as a viable intermediate in this process rather than **4**.

Joule elegantly demonstrated that the reaction of reserpine in acetic acid with zinc provided dihydroreserpines **11** and **12** in a ratio of 60:1.[6a] Dihydroreserpine **11** arises by cleavage across the C(3)–N(4) bond followed by reduction, whereas **12** originates from scission at C(2)–C(3). Although scission across the C(3)–N(4) bond (see **11**) occurred in excess of 97% when compared to C(2)–C(3) cleavage (**12**), Joule concluded that scission across the C(2)–C(3) bond accounted for the isomerization of reserpine to isoreserpine (Scheme I). This hypothesis was based on epimerization experiments executed on the two quaternary methacetates **13** and **15** (see Scheme III; X = $\bar{O}$Ac). As illustrated in Scheme I, participation of the lone pair of electrons on N(4) is necessary for the reverse Mannich reaction to proceed to the immonium ion **4**. Joule et al.[6a] blocked involvement of this lone pair of electrons by methylation of **1**, the result of which was to prevent equilibration of **1** (**13**) to **2** (**15**) (see ref 6a for details) at C(3). In brief, heating the two methacetates **13** or **14** in acetic acid resulted in epimerization (**13** → **14**, **15** → **16**) only at N(4) and not at C(3), consequently Joule concluded that C(2)–C(3) bond fission, not C(3)–N(4) cleavage, repre-

(9) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.



11



12

sented a mechanism consistent with these results. However, based on the experiments in methanolic hydrogen chloride and the energetics of these conversions, we have arrived at an alternative explanation for the reactivity of **13** and **15** consistent with the C(3)–N(4) scission mechanism proposed here for conversion of **1** into **2** (see below).

Reserpine (**1**) is approximately 1 kcal/mol less stable than isoreserpine via a standard calculation[10] based on the equilibrium constant.[6a] The driving force for the isomerization of **1** is the release of steric strain between the bulky indole group (axial) at C(3) and ring D, as suggested above the result of which is to provide **2**, wherein the indole group occupies the equatorial position[6a] (see Scheme III). Methylation of **1** increases the potential energy of **13** by about 7–8 kcal/mol[10] relative to **1**. This increase in energy is due to the 1,3 diaxial repulsion of the *N*(4)-methyl group with the axial carbon–carbon bond in the E ring. This γ-gauche effect increases the probability for the axial methyl group at N(4) to epimerize (see **14** and **17**) and it becomes the predominant interaction in this system rather than epimerization of **13** at C(3). In other words, energy considerations in going from the β-*N*-methyl group in **13** to the α-*N*-methyl group in **14** (via **17**) outweigh the interactions at C(3) in **13**. Further support for this hypothesis arises from the epimerization at N(4) of isoreserpine methacetate (**15** → **16**), which further illustrates that **14** is more stable than **15**. Combining enthalpy and entropy considerations,[11,12] we suggest that the results obtained with **13** and **15** (via **18**) by Joule arise because the D rings in **14** and **16** exist in boat conformations[13] since the three substituents on the E ring prefer to occupy the equatorial position.[4,8] Similar phenomena were also observed by Woodward et al. and employed in the total synthesis of yohimbine alkaloids.[4a]

Based on the cyclization of **4** reported by Martin[4d] and Sakai,[6c] the above experiments, and stereochemical considerations, it is felt that the epimerization of reserpine at C(3) occurs via the pathway outlined in Scheme III.[14] Protonation of **1** at N(4) followed by ring scission of the C(3)–N(4) bond would afford the carbocation intermediate **10**. This carbocation can then cyclize to furnish isoreserpine **2**, the thermodynamically more stable molecule with the indole group in an equatorial position relative to ring C. In similar fashion **13** is converted into **14** and **15** into **16** via methyleneindoleninium ions (carbocations) **17** and **18**, respectively. Evidence for the existence of **10** was obtained earlier by Joule (see **11**) and by analogy to our work in methanolic hydrogen chloride.[8] Numerous attempts have been made to trap the intermediate at various temperatures during the reserpine–isoreserpine conversion (CH_3OH/HCl), but the isomerization under these conditions occurs too rapidly. It is felt this supports the mechanism of C(3)–N(4) cleavage for had the Mannich intermediate **4** been involved, presumably methanol would have added to the imine or effected cleavage (decomposition) before the Pictet–Spengler reaction took place. Since only **1** and **2** were obtained in the experiment in CH_3OH/HCl, evidently as soon as the methyleneindoleninium ion **10** is generated, it cyclizes to the more stable **2**.[15] Finally, the use of methanolic hydrogen chloride for conversion of **1** into **2** provides a simple procedure for preparation of isoreserpine **2** on multigram scale (see below).

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Proton NMR spectra were recorded on a Bruker 250-MHz or GE 500-MHz NMR spectrometer. IR spectra were taken on a Matteson Polaris instrument while mass spectral data were obtained on a Hewlett-Packard 5895 GC–mass spectrometer. Microanalysis were performed on an F and M Scientific Corp. Model 185 carbon, hydrogen, and nitrogen analyser. Analytical TLC plates employed were Kieselgel 60 F_{254} plates on plastic. Reserpine was purchased from Aldrich Chemical Co., Milwaukee, WI.

(–)-3-Isoreserpine (2). A solution of (–)-reserpine (**1**) (30 g, 49 mmol) in dry methanol (600 g) which contained 1% HCl(g) was heated at reflux under N_2 for 72 h until the equilibrium was established. The reaction was monitored by TLC (samples were withdrawn and each sample analyzed). The solvent was removed in vacuo, and the residue was brought to pH 8 with cold aqueous NH_3 (14%). The aqueous phase was extracted with $CHCl_3$ (4 ×

(10) Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962.

(11) Allinger, N. L. *J. Am. Chem. Soc.* **1959**, *81*, 5727. Howlett, K. E. *J. Am. Chem. Soc.* **1957**, 4353. Hendrickson, J. B. *J. Am. Chem. Soc.* **1961**, *83*, 4537.

(12) Johnson, W. S.; Bauer, V. J.; Margrave, J. L.; Frisch, M. A.; Dreger, L. H.; Hubbard, W. N. *J. Am. Chem. Soc.* **1961**, *83*, 606. Allinger, N. L.; Freiberg, L. A. *J. Am. Chem. Soc.* **1960**, *82*, 2393.

(13) Huffman, J. W. *J. Org. Chem.* **1959**, *24*, 447. Barton, D. H. R.; Lewis, D. A.; McGhie, J. F. *J. Chem. Soc.* **1957**, 2907. Djerassi, C.; Finch, N.; Cookson, R. C.; Bird, C. W. *J. Am. Chem. Soc.* **1960**, *82*, 5488. Holker, J. S. E.; Whalley, W. B. *Proc. Chem. Soc.* **1961**, 464.

(14) Under conditions ($HCONH_2$, HCO_2H, 210 °C) similar to those of Eschweiler–Clarke reductions, Sakai isolated a 53% yield of **12**;[6b] however, it is felt that immonium ion **4** had formed to a small extent (as in Joule's work[6a]) and has been reduced (irreversibly) to the ring-cleaved product **12**. As this process continues, **12** builds up at the expense of **1** and **2** which resulted in the yield observed by Professor Sakai.[6b] Alternatively it is possible that reserpine (**1**) undergoes ring sission via methyleneindoleninium ion (carbocation) **10** while isoreserpine underwent ring cleavage by way of immonium ion **4**; however, recent results in our laboratory indicate that both alkaloids open up to the same intermediate. When either **1** or **2** was treated with Zn/AcOH under the conditions of Joule the ratio (3:1) of **11** [C(3)–N(4)] to **12** [C(2)–C(3)] was almost identical (see experimental) in both experiments. It is felt that equilibration between **1** and **2** in both cases, therefore, occurs by **10** rather than immonium ion **4**.

(15) In regard to suggestions by a referee to trap either **11** or **12** in methanolic hydrogen chloride (Pd/C, H_2), the following experiments were performed: Heating **1** in methanolic hydrogen chloride in the presence of Pd/C–H_2 furnished a mixture of **1** and **2**, but no evidence for the presence of either **11** or **12** was observed (TLC vs authentic samples of **11** and **12**). When the analogous reaction was conducted in the presence of $NaCNBH_3$, only starting **1** and **2** were observed for, as expected, the borohydride reagent reacted too rapidly with the medium. **Note Added in Proof.** When reserpine methacetate[6] was heated in methanolic HCl (1%) at 68 °C for 24 h, a new alkaloid was found that was identical by mixed TLC with that reported by Joule[6] on heating the methacetate in acetic acid in a sealed tube. Presumably, ring scission across the C(2)–C(3) bond has occurred followed by epimerization of the *N*-methyl group and reclosure to form the methacetate epimeric at N(4) not at C(3).[6] When reserpine methacetate was heated in methanol alone, no reaction occurred.

300 mL), and the combined extracts were washed with brine (2 × 50 mL). The organic layer was then dried (K_2CO_3) and concentrated under reduced pressure. The crude oil which resulted was purified by flash chromatography on silica gel (hexane/EtOAc, 1:3) to yield isoreserpine (2) (21 g, 95% yield based on recovered reserpine), accompanied by reserpine (1) (8 g) in a ratio of 2.6:1. The crude isoreserpine was crystallized from methanol to give pure 2 (18 g): mp 150–151 °C [lit.[4d] mp 148–150 °C]; $[\alpha]^{23}_D$ −165.1° (c = 1, $CHCl_3$); [lit.[5] $[\alpha]^{23}_D$ −163° ($CHCl_3$)]; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.75 (s, 1 H), 7.32 (d, J = 8.5 Hz, 1 H), 7.28 (s, 2 H), 6.83 (d, J = 2.0 Hz, 1 H), 6.75 (dd, J = 8.5, 2.0 Hz, 1 H), 5.09 (ddd, J = 12, 8.5, 5 Hz, 1 H), 3.89 (s, 3 H), 3.87 (s, 6 H), 3.84 (s, 3 H), 3.81 (s, 3 H), 3.79 (dd, J = 12, 9 Hz, 1 H), 3.45 (s, 3 H), 3.16 (br d, J = 10 Hz, 1 H), 2.75–3.0 (m, 3 H), 2.80 (dd, J = 11.5, 5 Hz, 1 H), 2.50–2.70 (m, 3 H), 2.32 (dd, J = 11.5, 12.5 Hz, 1 H), 2.31 (m, 1 H), 2.08 (m, 1 H), 1.98 (dddd, J = 12.5, 5, 4 Hz, 1 H), 1.86 (dd, J = 10, 12.5 Hz, 1 H), 1.75 (dd, J = 12.5, 4.0 Hz, 1 H).

The NMR spectrum of 2 was identical in all respects with that of a sample of synthetic 2 kindly provided by Professor Steve Martin. This reaction was run on a 70-g scale with no loss in yield.

Equilibration of Reserpine (1) in MeOH/HCl. Reserpine (1) (500 mg) was dissolved in anhydrous HCl–MeOH (50 g, conc = 1%) and was heated at 68 °C under a nitrogen atmosphere for 12 h. The solvent was removed in vacuo, and the residue was partitioned between dilute aqueous NH_3 and $CHCl_3$ (300 mL). The $CHCl_3$ layer was dried (K_2CO_3), and the solvent was removed in vacuo to provide a solid, which was purified by flash chromatography on silica gel. Elution was carried out with hexane–ethyl acetate (1:3) to provide a crystalline sample of 2 (280 mg, mp 149–150 °C) and reserpine (1) (200 mg, mp 247–252 °C dec) in the approximate ratio of 3:2.

Equilibration of Isoreserpine (2) in MeOH/HCl. Isoreserpine (2) (500 mg) was dissolved in HCl–MeOH (50 g, 1%) and was heated at 68 °C under nitrogen for 12 h. The reaction mixture was worked up as reported in the above experiment. Elution with hexane–EtOAc (1:3) gave pure isoreserpine (2) (435 mg) and reserpine (1) (40 mg) in the approximate ratio of 23:2.

Reduction of Reserpine (1) with Zn/AcOH. Reserpine (1) (1 g) and activated Zn powder (2.2 g) were heated in acetic acid (35 mL) at reflux under N_2 for 12 h. The solution was filtered and evaporated. The residue was partitioned between dilute aqueous NH_3 and $CHCl_3$. The chloroform layer was dried (K_2CO_3), and the solvent was removed in vacuo to provide a gummy solid, which was purified by flash chromatography on silica gel [EtOAc/hexane (3:1)–EtOAc]. This process yielded isoreserpine (2) (695 mg), 2,3-secoreserpine (12) (25 mg),[6b] reserpine (1) (200 mg), and compound 11 (72 mg), mp 236–237 °C (lit.[6a] mp 236–239 °C). The sample of 12 was identical with a sample of authentic material obtained by degradation of reserpine in the presence of formic acid and formamide.[6b]

Reduction of Isoreserpine (2) with Zn/AcOH. Isoreserpine (2) (1 g) and activated Zn powder (2.2 g) were heated in acetic acid (35 mL) at reflux under N_2 for 12 h. The solution was filtered and evaporated. The residue was partitioned between dilute aqueous NH_3 and $CHCl_3$, and the aqueous layer was extracted with chloroform (3 × 100 mL). The combined extracts were washed with brine (1 × 50 mL), dried (K_2CO_3), and concentrated under reduced pressure to furnish a gummy solid, which was purified by flash chromatography on silica gel (EtOAc/hexane (3:1)-EtOAc). This process gave isoreserpine (2) (680 mg), 2,3-secoreserpine (12) (22 mg), reserpine (1) (195 mg), and compound 11 (70 mg), mp 236–237 °C, in a nearly identical ratio with that reported in the previous experiment.

Acknowledgment. We wish to thank the NIH (NS 22287) and NIDA (DA-04963) for financial support. Our thanks go to Professor Steve Martin for a sample of isoreserpine, as well as to Frank Laib for the mass spectra. The 500-MHz NMR was purchased with funds from the NIH (BRSG) and NSF instrument programs. We also wish to acknowledge the helpful comments of Professor John Joule in regard to the present work. Initial support for this work was supplied by the Graduate School (UWM) and BRSG. Keith Krumnow and Liesl Schindler provided excellent technical assistance.

Counteranion Effects on Complexation of Cations

Kenneth M. Doxsee[1]

Department of Chemistry, University of Southern California, Los Angeles, California 90089-0744

Received March 27, 1989

In the twenty-odd years since Pedersen's first report of the formation of complexes between cyclic polyethers and cations,[2] an astounding number of complexation "hosts" have been designed, synthesized, and studied.[3] The vast majority of these hosts bind cationic "guests", though a rapidly increasing number of accounts report the selective complexation of anions and neutral molecules.[4] In the cationic complexes, the counteranion is generally assumed to be quite separated from the complexed cation. This "sequestration" of cations has been often demonstrated to have dramatic effects on the reactivity of the corresponding "naked" counteranions.[5]

This generalization, however, appears to be somewhat of an oversimplification. In particular, it has been noted in some cases that the binding affinity of a host for a chosen cation may be altered by changing the counteranion.[6] This effect has been most conveniently (and not unreasonably) explained by alteration of crystal lattice energies in the different salts; complexation must "pay the price" for disruption of the solid state of the guest, so solid salts of higher lattice energy disfavor formation of complexes. However, in a scattering of reports, anion effects have been noted even in homogeneous solution. For example, Cram observed[7] that enantiomeric discrimination of amino acid ester salts by a chiral macrocyclic polyether host was influenced by the counteranion, with hexafluorophosphate and perchlorate salts of amino acid esters providing high enantioselection in liquid–liquid extraction experiments, but bromide and picrate salts providing appreciably lower enantioselection.

In the latter example, the amino acid esters were complexed through their protonated amino groups. As structural studies demonstrate in such cases, complexation is effected through formation of three hydrogen bonds from the ammonium group to three oxygens of the polyether host. Such complexation of primary ammonium groups provides a simple and convenient route for the complexation of organic substrates even by very simple hosts such as 18-crown-6. The importance of this type of complexation, coupled with Cram's observation of a counteranion effect on the complexation of ammonium groups by cyclic polyethers, suggested a more detailed study in simple model systems was appropriate. Accordingly, we have examined the complexation of four salts of

(1) Address correspondence to the author at the University of Oregon, Department of Chemistry, Eugene, OR 97403.

(2) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 2495–2496.

(3) The Nobel Prize lectures given by Pedersen, Lehn, and Cram in 1987 provide a current survey of the state of the field of complexation chemistry: Pedersen, C. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1021–1028. Lehn, J.-M. *Ibid.* **1988**, *27*, 89–112. Cram, D. J. *Ibid.* **1988**, *27*, 1009–1020.

(4) See Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 362–86 for a recent overview of the complexation of neutral molecules.

(5) Liotta, C. L.; Grisdale, E. E.; Hopkins, H. P. *Tetrahedron Lett.* **1975**, 4205. Liotta, C. L. In *Synthetic Multidentate Macrocyclic Compounds*; Izatt, R. M., Christensen, J. J., Eds.; Academic Press: New York, 1978; pp 111–205.

(6) See, e.g., Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017–7036. Liotta, C. L., *op. cit.*, pp 114–115.

(7) Kyba, E. P.; Timko, J. M.; Kaplan, L. J.; de Jong, F.; Gokel, G. W.; Cram D. J. *J. Am. Chem. Soc.* **1978**, *100*, 4555–68.

0022-3263/89/1954-4712$01.50/0