Table IV. Crystal Data and Experiment Parameters

	N-5 isomer	N-1 isomer
formula	$C_{11}H_{12}N_4O_4$	$C_{11}H_{12}N_4O_4$
space group	$P2_12_12_1$	$P2_1$
a	7.507 (1) Å	8.651 (5) Å
b	9.015 (5)Å	7.031 (3) Å
c	16.907 (7) Å	10.133 (7) Å
β	90°	97.79 (5)°
V, Å^3	1148.8	611.1
Z	4	2
d_{meas}, g/cc	1.53	1.44
μ, cm^{-1}	0.76	0.76
max 2θ	45°	50°
cut off for obsd reflection	2.5σ (F)	2σ (F)
measured data	1059	2559
observed data	822	2254

a $\theta - 2\theta$ scan technique with variable scan rates. No absorption correction was made for either compound as $\mu = 0.76$ cm^{-1}. The experimental data are summarized in Table IV.

Both structures were solved by using the direct methods program of the SHELX-76 program package.[15] In both structures the major portion of the non-hydrogen atoms were apparent in the first E map and the remaining heavy atoms were located using Fourier techniques. Refinement proceeded normally with all twelve hydrogen atoms of each isomer eventually located in difference maps. Non-hydrogen atoms were refined anisotropically while hydrogen atoms were refined isotropically. The quantity minimized was $\sum w(|FO| - |F_c|)^2$ with w being calculated from counting statistics. The final residual values are, for **16**, $R = 0.050$ and $R_w = 0.023$ and, for **10**, $R = 0.046$ and 0.031. The final difference map for both structures showed no significant features.

(15) Sheldrick, G. M. SHELX-76 "A program for X-Ray Crystal Structure Determination", 1976, University of Cambridge, England.

Acknowledgment. We are grateful to Drs. Charles R. Petrie for ^{13}C NMR spectrum, Richard L. Snow, and James L. Bills for molecular orbital calculations.

Registry No. **1**, 91296-17-2; **2**, 91296-18-3; **3**, 91296-19-4; **4**, 91296-20-7; **5**, 91296-21-8; **6**, 91296-34-3; **7**, 91296-36-5; **8**, 14215-97-5; **9**, 91296-22-9; **10**, 91296-23-0; **11**, 91311-06-7; **12**, 91296-24-1; **13**, 91311-07-8; **14**, 91296-25-2; **15**, 91296-26-3; **16**, 91296-27-4; **17**, 91296-28-5; **19**, 91296-30-9; **18**, 91296-29-6; **20**, 91296-31-0; **21**, 91296-32-1; 2-hydrazinoacetaldehyde diethyl acetal, 42351-81-5; (ethoxymethylene)malononitrile, 123-06-8.

Supplementary Material Available: Tables of positional and thermal parameters of the atoms of **10** and **16** (V and VI), bond lengths and angles for the two isomers (VII), least-squares planes of the heterocyclic portion of each isomer (VIII), and hydrogen bond data for the two isomers (IX) (5 pages). Ordering information is given on any current masthead page.

The Rugulovasines: Synthesis, Structure, and Interconversions

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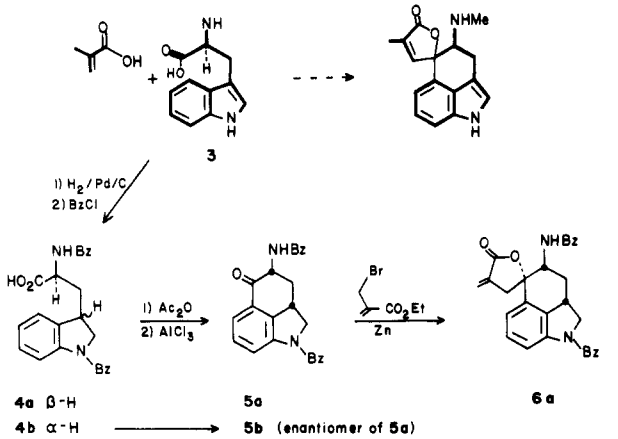
Experimental details are provided for the synthesis of the rugulovasine alkaloids from tryptophan. Optically active rugulovasine A is prepared for the first time and details concerning its conformation, racemization, and isomerization to rugulovasine B are presented.

It was not until X-ray crystallographic analysis[1] established rugulovasine A to be *racemic* that the remarkable behavior of these naturally occurring substances was fully exposed. First obtained[2] from *Pennicillium concavo-rugulosium*, and then[3] from *Pennicillium islandicum*, these alkaloids were formulated[4] as **1** and **2** on the basis of chemical and spectroscopic evidence. Their *interconversion*, combined with their racemic form was efficiently described by the ingenious mechanism shown[1] (Figure 1). Our access to optically active ergot alkaloids through synthesis from L-tryptophan[5] put us in a unique position to study these isomerization so we felt obliged to do so. This is an account of our experiences.

Synthesis

The combination of tryptophan and methacrylate provided the necessary skeletal features of the rugulovasines (Scheme I), while the stereochemical details emerged from the high selectivities of the reactions involved. Specifically, hydrogenation[6] of tryptophan followed by benzoylation led to the diastereomeric **4a** and **4b** each of which gave a single enantiomer of the tricyclic ketone **5** on Friedel–Crafts reactions of the corresponding azalactones. Reformatsky[7] reaction produced the methylene lactone **6**.

Scheme I



There are no stereochemical challenges here, since cis *hetero*atoms in the methylene lactone **6** lead to rugulo-

(1) Cole, R. J.; Kirksey, J. W.; Clardy, J.; Eickman, N.; Weinreb, S. M.; Singh, P.; Kim, D. *Tetrahedron Lett.* **1976**, 3849–3852.
(2) Abe, M.; Ohmomo, S.; Ohashi, T.; Tabuchi, T. *Agric. Biol. Chem.* **1969**, *33*, 469–471.
(3) Cole, R. J.; Kirksey, J. W.; Cutler, H. G.; Wilson, D. M.; Morgan-Jones, G. *Can. J. Microbiol.* **1976**, *22*, 741–744.
(4) Yamatodani, S.; Asahi, Y.; Matsukura, A.; Ohmomo, S.; Abe, M. *Agric. Biol. Chem.* **1970**, *34*, 485–487.
(5) Rebek, J., Jr.; Shue, Y. K. *J. Am. Chem. Soc.* **1980**, *102*, 5426–5427.
(6) Daly, J. W.; Mauger, A. N.; Yonemitsu, O.; Antonov, V. K.; Takase, K.; Witkop, B. *Biochemistry* **1967**, *6*, 648–654.
(7) Ohler, E.; Reininger, K.; Schmidt, U. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 457–458.

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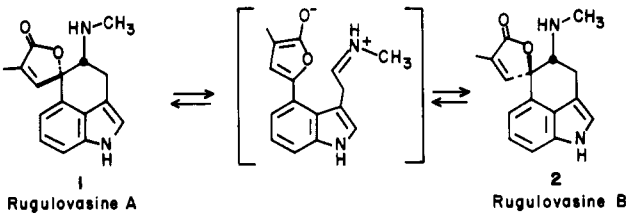


Figure 1.

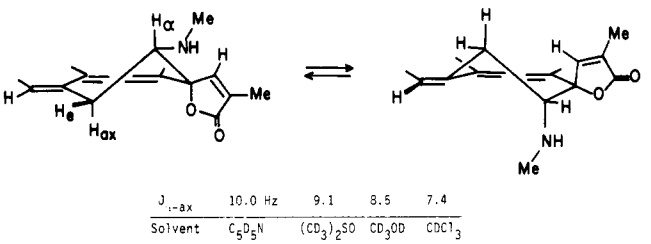
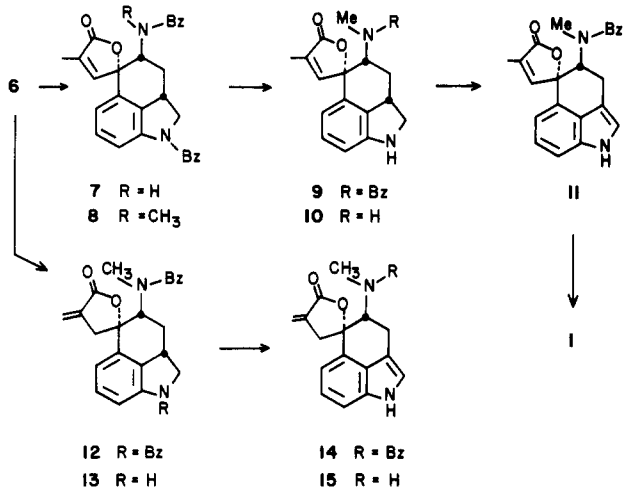
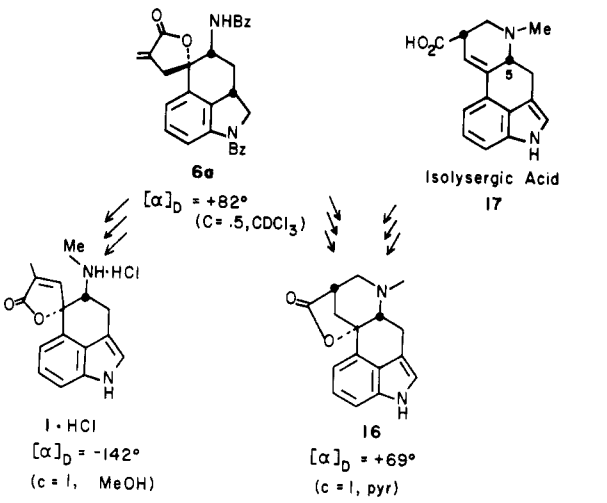


Figure 2.

Scheme II



Scheme III



vasine A, while trans heteroatoms lead to rugulovasine B. The selectivity of the Friedel–Crafts cyclization permits the synthesis of either enantiomer from L-tryptophan. Asymmetry is bestowed by the α-carbon to the γ-carbon during hydrogenation but returned to the α-carbon of the ketone **5** through the rapid epimerization of the azalactone during cyclization. Ultimately, the repository of asymmetry at the γ-carbon disappears on regeneration of the indole. Experimental details for the synthesis of **6** are provided elsewhere.[8]

The remaining steps of the synthesis were relatively uneventful (Scheme II). Isomerization to the butenolide **7** was accomplished with $RhCl_3 \cdot 3H_2O$[9] and then alkylation with NaH/MeI gave the *N*-methyl derivative **8**. The order of this sequence was dictated by the failure of **12** (the *N*-methyl derivative of **6**) to isomerize with the Rh reagent. This observation suggests binding between the 2° amide of **6** and the metal center occurs to facilitate the isomerization. Mild hydrolysis with base exposed the indoline function as **9**, from which **11** was obtained by MnO_2 oxidation.[10] The overall yield from **4** was 25–30%, in either the racemic or optically active series. In addition, **6** was taken through the sequence to **14** by mere osmission of the isomerization step.

The availability of **11** in its racemic form permitted us to assess the optical purity of the enantiomeric forms. Using the chiral shift reagent eufacam[11] and the *N*-methyl resonance, it could be shown that the enantiomers of **11** contained <1% of the racemate. The results of deblocking procedures and the isomerization experiments involving rugulovasine A could also be evaluated by rebenzoylation to **11** followed by shift reagent analysis.

Our original method of generating **1** from **11** involved debenzoylation by the Gassman[12] procedure (*t*-BuOK, H_2O/THF). Despite the harshness of these conditions, the stereochemical features were maintained in this reaction, a fact that was established by rebenzoylation of the product **1** and analysis as described above. The yield, however, was sufficiently low that alternatives were sought. This led us to the application of the Hanessian[13] sequence (Et_3O^+, H_3O^+) which gave generally excellent results. Debenzoylation of **11** gave rugulovasine A in 75% yield with this method; again, no racemization was detected when optically active **11** was the substrate. In addition, the method gave **10** directly from **8** and also provided access to **15**, *an isomer of rugulovasine A*, through debenzoylation of **14**.

Structure

(a) Absolute Stereochemistry. Rugulovasine A may be unique among indole alkaloids in that it has been obtained in optically active form through chemical synthesis rather than biosynthesis. The absolute stereochemistry of this material follows from that of the lactone **6**, one enantiomer of which has been converted[8] to a substance of known stereochemistry. Specifically, **6a** (Scheme III) led to the lactone **16** which showed the specific rotation and other physical properties[14] of the compound derived from isolysergic acid **17**. The configuration of the latter at C_5 is as shown. Since **6a** also gave optically active

(8) Rebek, J.; Tai, D. F.; Shue, Y. Y. *J. Am. Chem. Soc.* **1984**, *106*, 1813–1819.
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(13) Hanessian, S. *Tetrahedron Lett.* **1967**, 1549–1552. King, S. W.; Riordan, J. M.; Holt, E. M.; Stammer, C. H. *J. Org. Chem.* **1982**, *47*, 3270–3273.
(14) Bernardi, L.; Bosisio, G.; Geoffredo, O.; Patelli, B. *Gazz. Chim. Ital.* **1965**, *95*, 384–392.

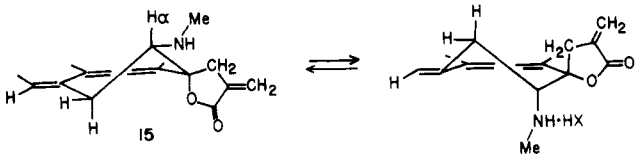


Figure 3.

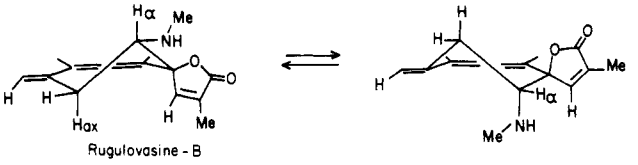


Figure 4.

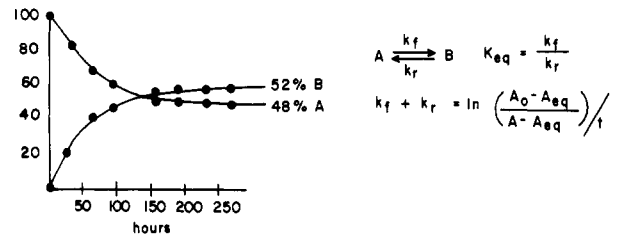


Figure 5.

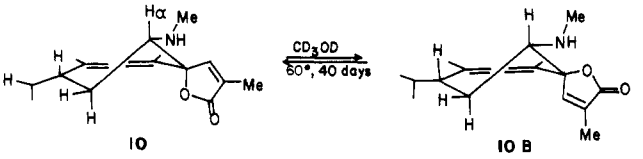


Figure 6.

rugulovasine A hydrochloride the absolute stereochemistry of this material must be as shown.

It has suggested that the rugulovasines may be artifacts of the isolation procedure rather than natural products.[1] Given the facile isomerizations described later in this paper, it is probable that optically active rugulovasine A would indeed racemize during the rigors of isolation. Perhaps, in vivo, the alkaloid enjoys a relatively nonpolar environment, say, bound to a membrane. If so, a rapid, low-temperation procedure would yield optically active material, the stereochemistry of which can be predicted to be the one shown in Scheme III. This configuration at C_5 is shared by all of the ergolines as well as the tricyclic chanoclavines.[15]

(b) Conformation. The crystalline state of rugulovasine A features an equatorial nitrogen[1], but its NMR spectra in different solvents suggests that substantial amounts of the axial conformation can be present in solution (Figure 2). Specifically, the range of values observed for the H_α–H_{ax} coupling points to a rapidly interconverting system in which both species are well represented. Assuming a maximum J of 14 Hz, as is seen in the N-benzoyl derivative 11, the values of Figure 2 can be translated into 30% axial N-Me in C_5D_5N to about 60% in $CDCl_3$.

Protonation shifts this equilibrium further to the right. When either the free base or its hydrochloride was dissolved in CF_3CO_2D, a new spectrum rapidly emerged. In this solvent the geminal protons collapse to a narrow triplet showing small (J = 1.5 Hz) coupling to the α and indole C–H protons. (Ultimately, the indole resonance disappears as the acid-catalyzed exchange with solvent proceeds). A similar spectrum is shown by the trifluoroacetate in $CDCl_3$ and by the hydrochloride in CD_3OD. In the latter case the geminal protons appear as a well-defined AB system with further coupling to the α-H (J = 4 Hz). The reduced coupling in all of these cases is indicative of an orientation of the protonated amine function which is almost exclusively *axial*.

Such axial preferences for more electronegative substituents are not unknown[16] and are quite reasonable in the case at hand. The sp^2 centers of the carbocycle remove the usual 1,3 interactions, and access of solvents to the ammonium function may be easier in the axial orientation than in the equatorial one. While reasonable, the conformational preferences remain unpredictable, and the additional possibility of intramolecular hydrogen bonding may further confuse the issue. The related methylene lactone **15** showed only exchange-broadened spectra in CD_3OD, $(CD_3)_2CO$, or $CDCl_3$ while its hydrochloride showed exclusively the axial N-orientation (Figure 3). It thus appears that the very least one can conclude is that both axial and equatorial NHMe conformations are energetically accessible in this series.

Rugulovasine B or its salts were found to exist as a roughly equal mixture of the two conformations of Figure 4. To be sure, some of these salts proved unstable, but even during their rearrangements, no shift of the equilibrium toward the trans, diaxial arrangement of N and O substituents was observed.

Isomerizations

The curious interconversions of rugulovasine A dn B had been noted by others and we determined that the same mixture (ca. 48% A; 52% B) could be obtained from either pure isomer in CD_3OD. Equilibrium is attained in about 6 days at 25 °C in this solvent; in Me_2SO-d_6 interconversion is slower and occurs at an appreciable rate only at about 60 °C. Our many experiments can be summarized as follows:

(a) *The isomerization follows closely the kinetics of a first-order, reversible reaction* (Figure 5). The rates can be deduced from the equation shown and the equilibrium constant; this gives $k_f = (3.1 \times 10^{-6})/s$ and k_r as $(2.9 \times 10^{-6})/s$ in CD_3OD at 25 °C.

(b) *The butenolide function is required for the interconversion.* The methylene lactone isomer **15** of rugulovasine A failed to isomerize under any of these conditions. The only reaction observed was slow conversion to a lactam in MeOH. In contrast, the dihydro derivative with an intact butenolide **10**, (Figure 6) isomerized, albeit at a much reduced rate. Specifically, the equilibrium mixture of **10** (55%) and **10B** (25%) was attained after 40 days at 60 °C in CD_3OD. Two other compounds were also present (20%) but their structures could not be determined.

(c) *Isomerization occurs without the removal of carbon-bound hydrogen.* Thus, no exchange with solvent was observed during the isomerization of A to the equilibrium mixture in CD_3OD, or of **10** to its mixture in the same solvent. Only in CF_3CO_2D was such C–H exchange observed, but these reactions were confined to the aromatic and indole rings; the carbocycle or butenolide remained unaffected.

(d) *Rugulovasine B converts to A in CF_3CO_2D.* This reaction had already been noted by Abe[4], and we observed that conversion to A was complete within 2 h if B or its hydrochloride was dissolved in CF_3CO_2D.

(e) *The racemization of rugulovasine A is faster than its conversion to the B isomer.* We had intended to follow the racemization of optically active rugulovasine A by polarimetry since stable, sizable rotations could be ob-

(15) Floss, H. G. *Tetrahedron*, **1976**, *32*, 873–912.
(16) Cremer, D.; Binkley, J. S.; Pople, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 9836–6839.

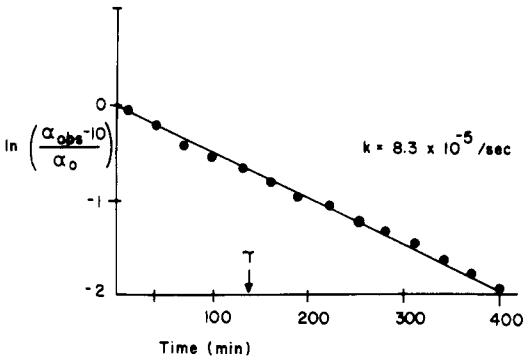


Figure 7.

served for its hydrochloride. The free base, however, darkened rapidly in solution giving polarimetry readings which fluctuated erratically. Even when great care was taken in sample preparation, some problems persisted.

Debenzoylation of 11 (derived from **6a**) gave samples of 1 which showed an initially large rotation (ca. +50°; MeOH, *c* 0.5) which decreased rapidly and stabilized at +10° after several hours. After 20 h, NMR indicated that the mixture consisted of 80% A and 20% B. However, benzoylation and shift reagent analysis of the recovered A isomer showed that *complete racemization of rugulovasine A had occurred.* The residual rotation is apparently due to a small amount (not detectable by NMR) of a substance with a large positive rotation which arises from the action of MeOH on rugulovasine A, e.g., a lactam or methyl ester. Assuming that this unknown material forms quickly and irreversibly, it is possible to use the polarimetric data to estimate the rotation for rugulovasine A in MeOH as +43° (for material derived from **6a**) and the half-life for its racemization as $2^1/_2$ h.

Figure 7 shows a plot of the data for racemization from which it can be seen that first-order behavior is followed for several half-lives. The extent of racemization was confirmed at various times through benzoylation of aliquots followed by shift reagent analysis. These methods indicate that racemization of rugulovasine A is about 25 times faster than its conversion to the B isomer. Its isolation from natural sources in racemic form is therefore not surprising.

Mechanism

The usual result of mechanistic studies is the exclusion of plausible alternatives, and those alternatives that involve many intermediates are particularly vulnerable to the culling process. Here, the lack of exchange with solvent-bound deuterium excludes those pathways which involve ionization at the appropriate C–H bond. Another mechanism that could convert A to B, ionization at the C–O bond, fails to account for the racemization observed. Ionization at the C–C bond, as originally proposed by Clardy, Weinreb, and Cole,[1] provides a pathway consistent with the above and only minor refinements of this mechanism are necessary to accommodate most of the facts.

The single intermediate proposed by this mechanism arises from the spontaneous heterolysis of a C–C bond. Such processes can be motivated by extensive delocalization of charge, as in the recent dramatic examples described by Arnett,[17] and the present case would seem to have ample stabilization of both charges, as well as sufficient solvation in MeOH. That this intermediate fails to show exchange (iminium ion ⇄ enamine) during the

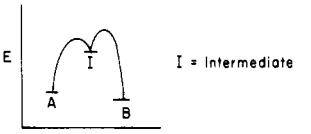
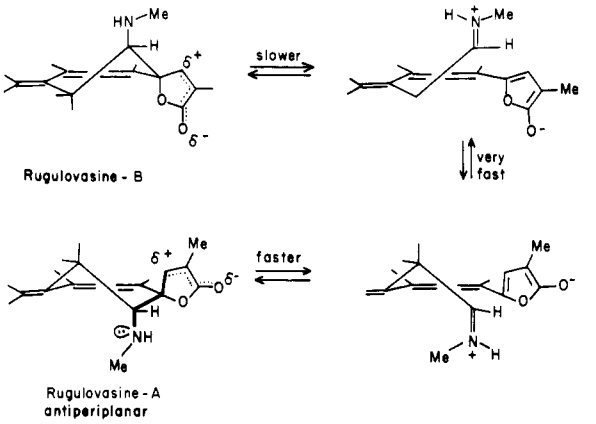


Figure 8.

Scheme IV



isomerizations appears to result from faster cyclization than deprotonation of the intermediate. The racemization requires only simple rotations about a few bonds of this intermediate and the facility of this process can be rationalized with the aid of Scheme IV. Heterolysis may be regarded as an example of a Grob[18] fragmentation for which the optimum stereoelectronics are antiperiplanar. This requires an axial orientation of the NHMe group, an arrangement that is readily accessible for either the A or B isomer. However, if the β-carbon of the butenolide be regarded as the electrofuge in the fragmentation, the B isomer can never achieve the antiperiplanar arrangement. The formation and fragmentation of B is slower than the corresponding process for A; racemization of A is therefore faster than its conversion to B.

A frequent result of mechanistic studies is the emergence of new problems or unanswered questions. This work is no exception. We have already mentioned the curious conformational preferences of the rugulovasines, but the related question of the driving force for the B → A conversion in CF_3CO_2D is even more puzzling. Mannich reactions are known to be catalyzed by acids, and if this mechanism holds for the reaction in CF_3CO_2D, one would expect A to racemize in this solvent. However, optically active A was recovered unchanged after 2–3 h in CF_3CO_2D. If the conversion of B to A in this medium involves mere ionization at the C–O bond, followed by its reformation on the opposite face, then no racemization would be involved. This mechanism can be tested when optically active rugulovasine B is available. In the meantime, Figure 8 summarizes our observations. For the free bases, return of the intermediate to rugulovasine A in either of its conformations (racemization) is faster than its conversion to rugulovasine B.

Summary

Tryptophan has been shown to be an excellent source of atoms and chirality for ergot alkaloid synthesis, as exemplified through the first synthesis of optically active rugulovasine A. Our related successful experiences with the conversion of hydroxyproline to a mitosene suggest

(17) Arnett, E. M.; Troughton, E. G.; McPhail, A. T.; Molter, K. E. *J. Am. Chem. Soc.* **1983**, *105*, 6172–6173.

(18) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535–546. Grob, C. A.; Schiess, A. *Ibid.* **1967**, *6*, 1–15.

that amino acids in general should not be overlooked as starting materials suited for the total synthesis of natural products. The availability of rugulovasine A in optically active form permitted the study of its racemization and conversion to its diastereomer, rugulovasine B. The evidence is generally in support of the incisive reverse-Mannich mechanism originally proposed by Clardy, Weinreb, and Cole[1] for the isomerizations.

Experimental Section

4-(Methylbenzamido)-1,2,2a,3,4,5-hexahydro-5-hydroxy-α-methylbenz[*c*,*d*]indole-5-acrylic Acid, γ-Lactone (9). A solution of *N*-methyl butenolide[8] **8** (230 mg, 0.48 mmol) in 10 mL of EtOH was treated with 10 mL of 20% NaOH under nitrogen and heated to 75 °C for 1 h. The reaction mixture was cooled in an ice bath and the pH adjusted to 1.00. After stirring for 4 min, the pH was readjusted to 13 by using 2% NaOH. This was immediately extracted with $CHCl_3$. The organic phase was dried over Na_2SO_4 and then evaporated to give a solid which was recrystallized from EtOH. This gave 162 mg (90%), mp 278–280 °C dec. From (+)-**8** the dextrorotary form of **9** was prepared in an identical fashion. The product was recrystallized from ethanol, mp 264–266 °C. (+)-**9**: $[\alpha]^{25}_D$ +184° (*c* 0.5, $CHCl_3$); IR (KBr) 3300, 1743, 1604 cm^{-1}; NMR 300 MHz ($CDCl_3$) 2.03 (d, 3 H, *J* = 1.62 Hz), 2.23 (q, 1 H, *J* = 12 Hz), 2.24–2.32 (br s, 1 H), 2.79 (s, 3 H), 3.39–3.51 (m, 1 H), 3.30 (dd, 1 H, *J* = 7.7 Hz, 12.5 Hz), 3.80 (t, 1 H, *J* = 7.7 Hz), 3.83–3.93 (br s, 1 H), 5.37 (dd, 1 H, *J* = 12 Hz, 3.2 Hz), 7.23 (d, *J* = 1.62 Hz), 6.42 (d, 1 H, *J* = 7.7 Hz), 6.65 (d, 1 H, *J* = 7.3 Hz), 7.05 (t, 1 H, *J* = 7.5 Hz), 7.20–7.30 (m, 3 H), 7.37–7.44 (m, 2 H). Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.59; H, 6.10; N, 7.42.

1,3,4,5-Tetrahydro-5-hydroxy-α-methyl-4-(methylbenzamido)benz[*c*,*d*]indole-5-acrylic Acid, γ-Lactone (11). A solution of indoline **9** (250 mg, 0.668 mmol) in 20 mL of anhydrous methylene chloride was treated with 2.2 g of Attenburrow MnO_2[10] and stirred at room temperature for 2 h. The solids were separated by filtration and washed thoroughly with $CHCl_3$. Evaporation of the solvent gave a pale yellow solid, which was recrystallized from ethyl acetate and hexane to give 219 mg (88%) of a white solid, mp 237–238 °C dec. Dextrorotatory *N*-benzoyl rugulovasine A **11** was prepared in an identical fashion from (+)-**9**. The product was recrystallized from ethyl acetate: mp >260 °C. (+)-**11**: $[\alpha]^{25}_D$ + 346° (*c* 0.5, $CHCl_3$); Ir (KBr) 3300, 1743, 1608 cm^{-1}; NMR (300 MHz, $CDCl_3$) 2.12 (d, 3 H, *J* = 1.62 Hz), 3.06 (s, 3 H), 3.14 (dd, 1 H, *J* = 13.5 Hz, 4.8 Hz), 3.64 (dt, *J* = 13.5 Hz, 1.4 Hz), 5.54 (dd, *J* = 13.5 Hz, 4.8 Hz), 6.84 (d, 1 H, *J* = 7.0 Hz), 7.05 (br s, 1 H), 7.17 (t, 1 H, *J* = 7.5 Hz), 7.34 (df, 1 H, *J* = 8.0 Hz), 7.23–7.30 (m, 3 H), 7.40–7.75 (m, 2 H), 8.28 (br s, 1 H). Anal. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 73.99; H, 5.66; N, 7.33.

4-(Methylbenzamido)-1,2,2a,3,4,5-hexahydro-5-hydroxy-α-methylenebenz[*c*,*d*]indole-5-propionic Acid, γ-Lactone (13). A solution of the *N*-methyl derivative[8] **12** (240 mg, 0.5 mmol) in 10 mL of methanol was treated with 10 mL of 1 N HCl under nitrogen and heated to 70 °C for 13 h. The reaction mixture was cooled and neutralized by saturated $NaHCO_3$, extracted with chloroform, and chromatographed on silica gel (50% EtOAc:Hx(Hx = hexane) to Et_2OAc), giving 95 mg (50%) of **13**: NMR (300 MHz, $CDCl_3$) 2.10–2.35 (m, 2 H), 2.96 (s, 3 H), 3.24 (dd, 1 H, *J* = 7 Hz, 11.5 Hz), 3.36–3.41 (m, 2 H), 3.65–3.81 (m, 3 H), 5.44 (dd, 1 H, *J* = 4 Hz, 11.5 Hz), 5.74 (t, 1 H, *J* = 2.4 Hz), 6.33 (t, 1 H, *J* = 2.8 Hz), 6.64 (d, 1 H, *J* = 7.8 Hz), 6.70 (d, 1 H, *J* = 7.8 Hz), 7.12 (t, 1 H, *J* = 7.8 Hz), 7.26–7.5 (m, 5 H): mp ((+)-**13** 216–217 °C; [α] +236 ($CHCl_3$, *c* 1); IR 3150, 1758, 1626, 1605; *m/e* calcd for $C_{23}H_{22}N_2O_3$ 374.1629, found 374.1630.

4-(Methylbenzamido)-1,3,4,5-tetrahydro-5-hydroxy-α-methylenebenz[*c*,*d*]indole-5-propionic Acid, Lactone (14). A solution of **13** (200 mg, 0.5 mmol) in 20 mL of methylene chloride was treated with 2 g of activated MnO_2, as described above. A pale yellow solid, 160 mg (80%), mp 252–253 °C, was obtained: $[\alpha]^{25}_D$ +280, (*c* 1, $CHCl_3$); NMR (300 MHz, $CDCl_3$) 3.0 (s, 3 H), 3.09 (dd, *J* = 4.5, 12 Hz), 3.45–3.73 (m, 3 H), 5.54 (dd, *J* = 4.5 Hz, 12 Hz), 5.85 (s, 1 H), 6.39 (s, 1 H), 6.96 (s, 1 H), 7.08 (d, 1 H, *J* = 7.7 Hz), 7.19 (t, 1 H, *J* = 7.7 Hz), 7.31 (d, 1 H, *J* = 7.7 Hz), 7.3–7.5 (m, 5 H), 8.36 (s, 1 H); IR 3500, 1760, 1626, 1600; *m/e* calcd for $C_{23}H_{20}N_2O_3$ 372.1473, found 372.1474.

Preparation of Rugulovasine A (1) and Its Conversion to Rugulovasine B (2). A solution of **11**, (93 mg, .25 mmol) in 25 mL of CH_2Cl_2 was treated with 100 mg of Na_2CO_3 and a tenfold excess of $Et_3O^+BF_4^-$. After being stirred at room temperature for 2 h, the mixture was treated with 3% HOAc in H_2O (150 mL) and stirred for 30 min. The aqueous phase was neutralized with saturated $NaHCO_3$ and extracted with $CHCl_3$. Drying (Na_2SO_4) and then evaporation gave a crude product which was purified by chromatography on silica gel. Elution with 60% EtOAc/hexane removed the impurities and then elution with Me_2CO gave **1** as a light brown solid: 45 mg (75%), mp 135–137 °C. Optically active **1** could be prepared similarly from (+)-**11**: mp 120 °C; $[\alpha]^{25}_D$ ≈+43° (*c* 0.5, MeOH). Racemic **1** was dissolved in MeOH at room temperature for 2 days to give a mixture of rugulovasine A and B which were separated on silica gel. Mass spectrum for B (15 eV): *m/e* (relative intensity 268 M^+ (100), 225 (30), 197 (30), 183 (15). NMR (300 MHz, $CDCl_3$) of rugulovasine A: 2.05 (d, 3 H, *J* = 1.4 Hz), 2.49 (s, 3 H), 3.03 (br, dd, 1 H), 3.17 (dd, 1 H, *J* = 7.5 Hz, 4.0 Hz), 3.27 (br d, 1 H), 6.87 (d, 1 H, *J* = 7.0 Hz), 700 (br s, 1 H), 7.16 (t, 1 H, *J* = 7 Hz), 7.16 (d, 1 H, *J* = 1.4 Hz), 7.31 (d, 1 H, 8 Hz), 8.06 (br s, 1 H). NMR (300 MHz, $CDCl_3$) of rugulovasine B: 2.05 (d, 3 H, *J* = 1.6 Hz), 2.46 (s, 3 H), 3.04 (dd, 1 H), 3.22–3.27 (2 H), 6.87 (d, 1 H, *J* = 7.3 Hz), 7.03 (br s, 1 H), 7.18 (t, 1 H, *J* = 8.0 Hz), 7.32 (d, 1 H, *J* = 8.0 Hz), 7.37 (d, *J* = 1.6 Hz), 8.08 (br s, 1 H). Rugulovasine A hydrochloride salt was made by passing dry HCl to a solution of the base in ether: mp (racemic) 246 °C dec; mp (from (+)-rugulovasine A) 224 °C; $[\alpha]^{20}_D$–142° (*c* 1, MeOH), $[\alpha]^{20}_D$ +30° (*c* 0.5, Me_2SO).

4-(Methylamino)-1,3,4,5-tetrahydro-5-hydroxy-α-methylenebenz[*c*,*d*]indole-5-propionic Acid, Lactone (15). The same procedure as used to debenzoylate **11** was used on **14** and yielded 74% of theory: NMR (300 MHz, $CDCl_3$) 2.53 (s, 3 H), 3.03–3.7 (m, 5 H), 5.70 (t, 1 H, *J* = 2 Hz), 6.34 (t, 1 H, *J* = 2 Hz), 6.99 (d, 1 H, *J* = 7.7 Hz), 7.01 (s, 1 H), 7.18 (t, 1 H, *J* = 7.7 Hz), 7.31 (d, 1 H, *J* = 7.7 Hz), 8.31 (s, 1 H); *m/e* calcd for $C_{16}H_{16}N_2O_2$ 268.1212, found 268.1212.

Racemization Studies. Optically active **1** was prepared as described and the crude tan solid was dissolved in 2 mL of MeOH. One half of this solution was placed in a polarimeter cell and readings of rotation were taken with time (data for one of several runs is given below). The remaining solution was divided into four portions, one of which was quenched by benzoylation at each of four intervals. These aliquots were treated with enough $Eu(tfc)_3$ to cause separation of the H ortho to the indole N. (For (+)-A, δ 6.9 was found, and the enantiomer is at δ 7.1). Integration gave the enantiomeric excess values shown.

$[\alpha]_{obsd}$	time (min)	ee (NMR)
+48°	0	
44	40	
39	70	60% (120 min)
35.5	100	50% (150 min)
32.0	130	42% (180 min)
29.5	160	36% (210 min)
27.0	190	
25.0	220	
23.0	250	
21.4	280	
20.0	310	
18.6	340	
17.4	370	
16.0	400	
15.3	430	

Isomerization. (1) A solution of 6 mg of rugulovasine A in CD_3OD (0.3 mL) was stored at room temperature in an NMR tube. After given intervals (see Figure 5 for a typical run), the ratio of A to B was determined by integration of the *C*-methyl peaks: δ_A = 2.08 ppm; δ_B = 1.88 ppm. A purified sample of B was likewise treated and gave the same mixture at equilibrium.

(2) For the dihydro substance **10**[8] a sample (6 mg in 0.3 mL of CD_3OD) was maintained in a sealed NMR tube for 6 weeks at 60 °C. The new isomer which appeared during this time showed the following NMR characteristics in $CDCl_3$: 1.70 (q, 1 H, *J* = 11.7 Hz), 2.1 (d, 3 H), 2.51 (s, 3 H), 2.55 (dt, 1 H, *J* = 11.7 Hz, 2 Hz), 3.3 (m, 2 H), 3.42 (dd, H, *J* = 11.7 Hz, 2 Hz), 3.73 (t, 1 H,

J = 6 Hz), 6.35 (d, 1 H, J = 7.7 Hz), 6.56 (d, 1 H, J = 7.7 Hz), 8.1 (m, 1 H); mass spectrum (70 eV), m/e (relative intensity) 270 (10, 213 (100), 184 (10), 170 (20).

(3) A solution of 6 mg of optically pure rugulovasine A in 0.3 mL of CF_3CO_2H (TFA) was stored for 2 h and then the NMR spectrum was recorded at room temperature. After evaporation of the TFA, 0.3 mL of $CDCl_3$ was added and the spectrum was retaken. The solution was neutralized with saturated $NaHCO_3$, extracted into $CHCl_3$, dried, and evaporated. The residue was benzoylated and checked for optical purity by the shift reagent protocol; this showed <5% racemization: NMR (TFA), 2.1 (s, 3 H), 3.0 (s, 3 H), 3.7 (br t, 2 H), 4.0 (br t, 1 H), 7.0 (d, 1 H, J = 7 Hz), 7.4 (m, 2 H), 7.5 (d, 1 H, J = 7 Hz). The same spectrum was observed when a sample of rugulovasine B or a mixture of A and B were dissolved in TFA. TFA Salt in $CDCl_3$: 2.0 (s, 3 H), 2.9 (s, 3 H), 3.5 (t, 2 H, J = 3 Hz), 3.8 (t, 1 H, J = 3 Hz), 6.9 (d, 1 H, J = 7 Hz), 7.2 (m, 2 H), 7.4 (d, 1 H, J = 7 Hz), 8.4 (s, 1 H).

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Registry No. (±)-1, 26909-33-1; (+)-1, 91465-62-2; (+)-1·HCl, 91547-42-1; (+)-1·CF_3CO_2H, 91547-43-2; (±)-2, 26909-34-2; (±)-8. 74606-95-4; (+)-8, 88668-90-0; (±)-9, 91547-44-3; (+)-9, 91424-42-9; (±)-10, 88668-91-1; (±)-10B, 91465-63-3; (±)-11, 74644-92-1; (+)-11, 74606-96-5; (±)-12, 88668-95-5; (±)-13, 91424-43-0; (±)-14, 91424-45-2; (±)-15, 91424-44-1.

Occurrence of Electron Transfer in the Reduction of Organic Halides by $LiAlH_4$ and AlH_3

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A variety of methods have been utilized to detect the occurrence of a single electron transfer pathway in the reduction of alkyl halides by $LiAlH_4$ and AlH_3, i.e., (1) product studies of reduction of cyclizable alkyl halides containing the 5-hexenyl group, (2) trapping of intermediate radicals by dicyclohexylphosphine and other trapping agents, (3) direct EPR observation of the trityl radical in the reduction of trityl bromide, and (4) stereochemical studies of the reduction of secondary halides by lithium aluminum deuteride. The extent of electron transfer was found to be a function of the solvent, the substrate, the leaving group, and the hydride reagent. For alkyl iodides, and to a much lesser extent bromides, electron transfer was found to be the major reaction pathway; however, no evidence for electron transfer was found for the corresponding chlorides or tosylates. Reduction of (+)-2-octyl iodide by $LiAlD_4$ was found to be much less stereospecific than the corresponding reduction of bromide, chloride, or tosylate, indicating intermediate radical formation in the reduction of the secondary iodide.

In recent years numerous studies concerning the reduction of organic halides by $LiAlH_4$ have appeared in the chemical literature.[1] Lithium aluminum hydride has been considered to react as a nucleophilic reagent that donates a hydride ion to substrates such as alkyl halides.[1-3] However, a variety of mechanisms, including S_N2 and radical, have been proposed to describe this reduction reaction.[4-14] For example, Brown and co-workers have reported a number of rate–structure profile studies for a series of alkyl halides and $LiAlH_4$ and have proposed an S_N2 mechanism to describe these reactions.[4-6] However, bromobenzene is readily reduced to benzene by $LiAlH_4$ under mild conditions and yet bromobenzene is not considered a likely candidate for a facile S_N2 process. On the other hand, Chung and Chung have presented evidence for radical intermediates in the $LiAlH_4$ reduction of aryl bromides based on the cyclization of vinyl *o*-bromophenyl ether.[7] Nevertheless, in our hands this reaction took place in only 3% yield after 7 days and therefore the small amount of cyclization observed over such a long period of reaction time was not considered convincing. Chung has also suggested a radical pathway for the reduction of vinyl bromides by $LiAlH_4$, based on observations of cis–trans isomerization of the styryl group.[9] The formation of radical intermediates in an electron-transfer process has also been suggested for a variety of other reactions involving organic halides and metal hydrides.[10-14] Yet, the pioneering stereochemical study of Eliel[15] which showed that $LiAlD_4$ reacted with (+)-1-chloro-1-phenylethane with inversion of configuration generally has been interpreted as convincing evidence for an S_N2 mechanism for such reactions.

Since there seems to be some confusion concerning the mechanistic pathway describing the reaction of $LiAlH_4$ with alkyl halides, we decided to study this reaction in detail. The methodology used to study the model systems involve: (1) direct spectroscopic observation of radical intermediates, (2) the use of cyclizable radical probes in the alkyl halide, (3) trapping of intermediate radicals by hydrogen donor trapping agents, and (4) reduction of optically active alkyl halides and tosylates.

With respect to direct spectroscopic observation (1), EPR was used to detect the presence of stable radical intermediates. Thus, with alkyl halides that produce stable radicals, it was possible to observe by EPR radical intermediates produced by electron transfer. In the present

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