added over 2 h via a mechanical syringe to the CsF suspension maintained at 65 °C. The reaction mixture was stirred at 65 °C for an additional 12 h, treated with 15 mL of H_2O, and extracted with 25 mL of CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solvents were evaporated and the crude mixture was chromatographed on Brockmann 3 neutral alumina (40% ethyl acetate–hexane for elution) to give 211 mg (70%) of the tetracyclic erythrinane **10** as an oil: NMR ($CDCl_3/SiMe_4$) δ 1.58 (m, 2 H, CH_2), 1.87 (m, 3 H, overlapping CH_2), 2.19 (m, 1 H, CH_2), 2.31 (m, 1 H, CH_2), 2.36 (m, 1 H, CH_2), 2.74 (m, 1 H, CH), 2.90 (m, 2 H, overlapping CH_2), 3.00 (m, 2 H, CH_2), 3.26 (ddd, 1 H, J = 9.3, 7.0, 7.0 Hz, CH_2), 3.83 (s, 3 H, CH_3), 3.85 (s, 3 H, CH_3), 6.55 (s, 1 H, Ar CH), 6.60 (s, 1 H, Ar CH); IR cm^{-1} (film) 3100–2900 (CH envelope), 1710 (C=O). Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69. Found: C, 71.92; H, 7.76.

4-Oxo-6,7-didehydro-15,16-dimethoxyerythrinane (21). A flame-dried, round-bottomed flask equipped with a nitrogen inlet adaptor, rubber septum, and magnetic stirring bar was charged with 300 mg of CsF (2.0 mmol) and 4 mL of diglyme. In a separate flask, 161 mg of the dihydroisoquinoline **8c** (0.57 mmol) was alkylated with 267 mg of trimethylsilylmethyl triflate (1.14 mmol) in 3 mL of CH_2Cl_2 for 48 h at 25 °C. After removal of the CH_2Cl_2, the excess trimethylsilylmethyl triflate was evaporated in vacuo. The residue was dissolved in 2 mL of diglyme and added over 2 h via a mechanical syringe to the CsF suspension maintained at 110 °C. The reaction mixture was stirred at 110 °C for an additional 12 h, treated with 15 mL of H_2O, and extracted with 25 mL of CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solvents were evaporated and the crude mixture was chromatographed on Brockmann 3 neutral alumina (40% ethyl acetate–hexane for elution) to give 71 mg (42%) of the tetracyclic erythrinane **21** as an oil: NMR ($CDCl_3/SiMe_4$) δ 1.83 (1 H, m, CH_2), 2.23 (1 H, m, CH_2), 2.48 (1 H, ddd, J = 14.3, 3.8, 3.8 Hz, CH_2), 2.79 (6 H, complex m, CH_2), 3.41 (1 H, d with fine splitting, J = 12.5 Hz, CH_2), 3.79 (1 H, d with fine splitting, J = 12.8, CH_2), 3.85 (2 H, m, CH_2), 3.86 (3 H, s, CH_3O), 3.89 (3 H, s, CH_3O), 5.71 (1 H, br s, vinyl CH), 6.66 (1 H, s, Ar CH), 7.01 (1 H, s, Ar CH); IR (film) cm^{-1} 3150–2860 (CH envelope), 1715 (C=O); high resolution mass spectrum calcd for $C_{18}H_{21}NO_3$ M^+ = 299.1516, found M^+ = 299.1522.

Hydrogenation of 4-Oxo-6,7-didehydro-15,16-dimethoxyerythrinane (21). To an oven-dried, round-bottomed flask equipped with an gas inlet adapter and magnetic stirring bar was added 2 mg of 10% palladium on charcoal. The system was purged with nitrogen and charged with 5.0 mg of the erythrinane **21** (0.017 mmol) in 4 mL of absolute EtOH. The system was flushed with hydrogen and the mixture was stirred under a hydrogen atmosphere for 3 h at 25 °C. The reaction mixture was subsequently filtered through Celite and the solvent was evaporated to give a quantitative yield of a single hydrogenated product.

The hydrogenation product was shown to be identical with the erythrinane **10** in all respects (300-MHz NMR, IR, and mass spectra, capillary GC, and HPLC).

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Registry No. **4a**, 63609-01-8; **4a** (formamide), 14301-36-1; **4b**, 100571-63-9; **4b** (formamide), 98547-33-2; **4c**, 100571-65-1; **4c** (formamide), 100571-66-2; **4d**, 100571-64-0; **4d** (formamide), 6502-82-5; **5** (X = Cl, R = $CH(CH_3)_2$), 79-30-1; **5** (X = Cl, R = C_6H_5), 98-88-4; **5** (X = Cl, R = $(CH_2)_2CO_2Me$), 1490-25-1; **5a**, 3282-30-2; **5b**, 36394-07-7; **5c**, 55183-45-4; **5d**, 78283-59-7; **5e**, 2941-64-2; **8a**, 100571-70-8; **8b**, 100571-68-4; **8c**, 100571-69-5; **8d**, 100571-71-9; **8d** (acid), 54717-84-9; **8e**, 100571-72-0; (±)-**10**, 100571-78-6; **15**, 100571-73-1; **17a**, 100571-74-2; **17b**, 100571-75-3; **18**, 100571-67-3; **19**, 100571-76-4; **20**, 100571-77-5; (±)-**21**, 100571-79-7; $EtO_2C(CH_2)_2COMe$, 539-88-8; $HS(CH_2)_2SH$, 540-63-6; 2-(2-furyl)ethylamine, 1121-46-6.

Stereoselective Reductions of a Vinylogous Urethane Structure in a Highly Substituted Indolo[2,3-*a*]quinolizidine

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Stereoselective reductions of the vinylogous urethane **1** are described. Reduction of **1** with sodium cyanoborohydride in acetic acid gave a 81:19 mixture of isomers **2** and **3**; tributyltin hydride in 0.7 M trifluoroacetic acid solution in methylene chloride reversed the ratio of **2**–**3** to 17:83. Reduction of **1** with triethylsilane in trifluoroacetic acid yielded a mixture of isomers **2**, **3**, and **4** in a ratio of 19:17:64. The structure and stereochemistry of **4** were established by X-ray crystallography.

The indolo[2,3-*a*]quinolizidine system is part of the carbon skeleton of many indole alkaloids, e.g., ajmalicin or corynanthein. For the selective generation of the stereocenters in the quinolizidine substructure the reduction of the double bond of a vinylogous urethane moiety seems suitable. This reduction generates two new stereocenters and thereby determines the nature of the annelation of the rings in the quinolizidine. However, the usual reagent (sodium borohydride in acetic acid)[1,2] for this reduction often shows little stereoselectivity or produces an undesired isomer. New reducing agents offering a greater degree of control upon the stereochemical outcome of this reduction thus seem desirable.

Results and Discussion

We describe here a study on the stereoselective reduction of the vinylogous urethane **1**. The use of various reducing agents led to the formation of the isomers **2**–**4** (Scheme I) in varying ratios (Table I).

We decided to use the vinylogous urethane **1** as a model compound because it has the same ring system as several indole alkaloids and can be obtained in a simple two-step synthesis (Scheme II). The 1,4-dihydropyridine derivative **5** was prepared in 42% yield from tryptamine, benzaldehyde, and ethyl propiolate.[3] Acid-catalyzed cyclization

(1) Djerassi, C.; Monteiro, H. J.; Walser, A.; Durham, L. J. *J. Am. Chem. Soc.* **1966**, *88*, 1792–1798.

(2) (a) Thielke, D.; Wegener, J.; Winterfeldt, E. *Chem. Ber.* **1975**, *108*, 1791–1802. (b) Ernst, H.; Hauser, B.; Winterfeldt, E. *Chem. Ber.* **1981**, *114*, 1894–1906.

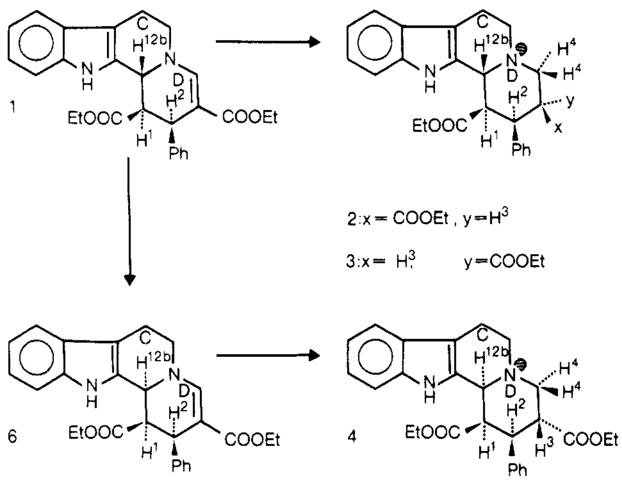
0022-3263/86/1951-1165$01.50/0

Table I. Ratio of Isomers 2-4 under Various Reduction Conditions

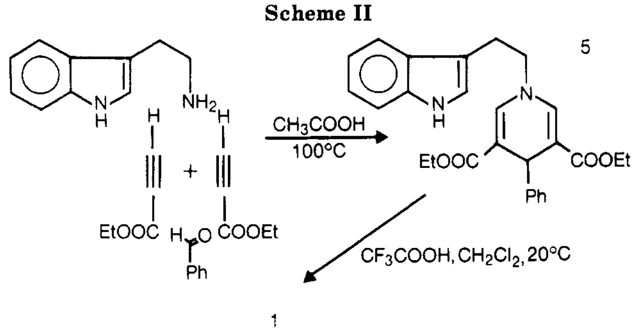
entry	reducing agent	equiv	solvent	temp, °C	time, h	ratio of 2:3:4[a]
1	$NaBH_4$	15	CH_3COOH/CH_2Cl_2[b]	20	18	75:25:0
2	$NaCNBH_3$	2.5	CH_3COOH/CH_2Cl_2[b]	0	1.5	81:19:0
3	$NaCNBH_3$	2	CF_3COOH	0	1	7:76:17
4	Et_3SiH	2	CF_3COOH	20	1.5	19:17:64
5	Et_3SiH	2	CH_3COOH	20	18	no reduction
6	Et_3SiH	2	CF_3COOH/CH_2Cl_2[c]	20	1	no reduction[d]
7	$(CH_3)_2PhSiH$	3	CF_3COOH	20	18	46:44:10
8	Ph_3SiH	3	CF_3COOH	20	18	no reduction[e]
9	Bu_3SnH	4	CF_3COOH/CH_2Cl_2[c]	20	0.15	17:83:0
10	Bu_3SnH	4	CH_3COOH	20	18	no reduction

[a] See ref 4. [b] 20 vol % of dichloromethane in acetic acid. [c] 0.7 M solution of trifluoroacetic acid in dichloromethane. [d] Decomposition of triethylsilane. [e] Decomposition of starting material 1.

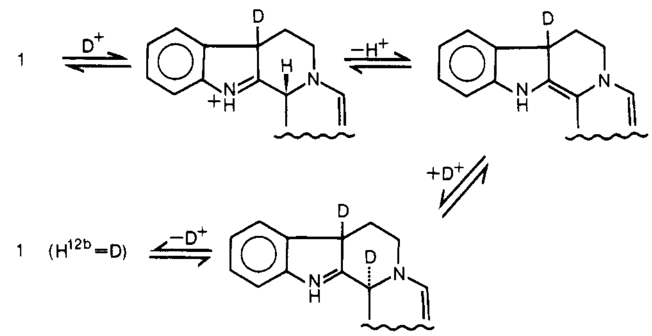
Scheme I



Scheme II



Scheme III



of 5 with 10% trifluoroacetic acid in methylene chloride gave model compound 1 in 80% yield. The ^1H NMR spectrum of 1 shows a 12-Hz coupling constant between H12b (δ 4.95) and H1 (δ 2.95) and a 5-Hz coupling constant between H1 and H2 (δ 4.42), which is consistant only with configuration 1 depicted in Scheme I.

Reduction of 1 with sodium cyanoborohydride in acetic acid at 0 °C gave a mixture of the isomeric amino esters 2 and 3 in a ratio of 81:19[4] (Scheme I). From this mixture the major isomer 2 was obtained analytically pure by simple crystallization from methanol. The shift value for H12b (δ 4.54)[5] in isomer 2 and the absence of Bohlmann bands[6] in the IR prove the cis fusion of the rings C and D; the 11-Hz coupling constant of H12b with H1 (δ 3.27), the 6-Hz coupling constant of H3 (δ 3.36) with H2 (β 4.02) and the 12-Hz coupling constant of H3 with the axial H4 (δ 3.48) indicate the cis configuration of all substituents in ring D in relation to H12b. The assignment of the observed ^1H NMR signals to the protons in the rings C and D was accomplished by an homonuclear shift correlation experiment (COSY 45); see Figure 1.

However, reduction of 1 by tributyltin hydride in 0.7 M trifluoroacetic acid solution in methylene chloride gave a mixture of the isomers 2 and 3 with a reversed ratio of 17:83.[4] From this mixture isomer 3 was isolated by simple crystallization from petroleum ether in 54% yield. As with isomer 2 the shift value of H12b (δ 4.60)[5] in isomer 3 and the absence of Bohlmann bands[6] in the IR indicate a cis annelation of the rings C and D. The only apparent difference between the isomers 2 and 3 exists in the configuration of carbon-3, which was confirmed by base-catalyzed (DBN) isomerization of 2 to 3 (66% isolated yield of 3). The coupling constant of the protons at ring D (derived from a COSY 45 spectrum, see Figure 2) are in agreement with the postulated stereochemistry of 3 when a half-chair conformation of ring D is assumed.

Changing the reduction conditions from a mildly acidic medium as in entries 1, 2, 4 and 7 in Table I to the strongly acidic medium trifluoroacetic acid led to a further complication due to the configurational instability at carbon 12b of compound 1 in strongly acidic media. An isomerization of compound 1 to its isomer 6 (Scheme I) was achieved in 70% yield by treating 1 with trifluoroacetic acid at room temperature for 1.5 h. This inversion of configuration at carbon 12b occurred under exchange of proton H12b, as could be shown by performing the isomerization in deuterated trifluoroacetic acid. A possible mechanism is depicted in Scheme III. Reduction of 1 with triethylsilane[7] in trifluoroacetic acid at room temperature gave a new major isomer 4 together with the isomers 2 and 3 in a ratio of 64:19:17[4] (Scheme I). However, the vinylogous urethane 6 yielded 4 exclusively under these con-

(3) Analogous to a procedure described in: Chennat, T.; Eisler, U. *J. Chem. Soc., Perkin Trans. 1* **1975**, 926–929.

(4) Determined by HPLC from a worked up sample of the reaction mixture.

(5) (a) Lounasmaa, M.; Tolvanen, A.; Kan, S. K. *Heterocycles* **1985**, *23*, 371–375. (b) Uskoković, M.; Bruderer, H.; von Planta, C.; Williams, T.; Brossi, A. *J. Am. Chem. Soc.* **1964**, *86*, 3364–3367.

(6) Crubb, T. A.; Katritzky, A. R. *Adv. Heterocyclic Chem.* **1984**, *36*, 3–175.

(7) Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633–651.

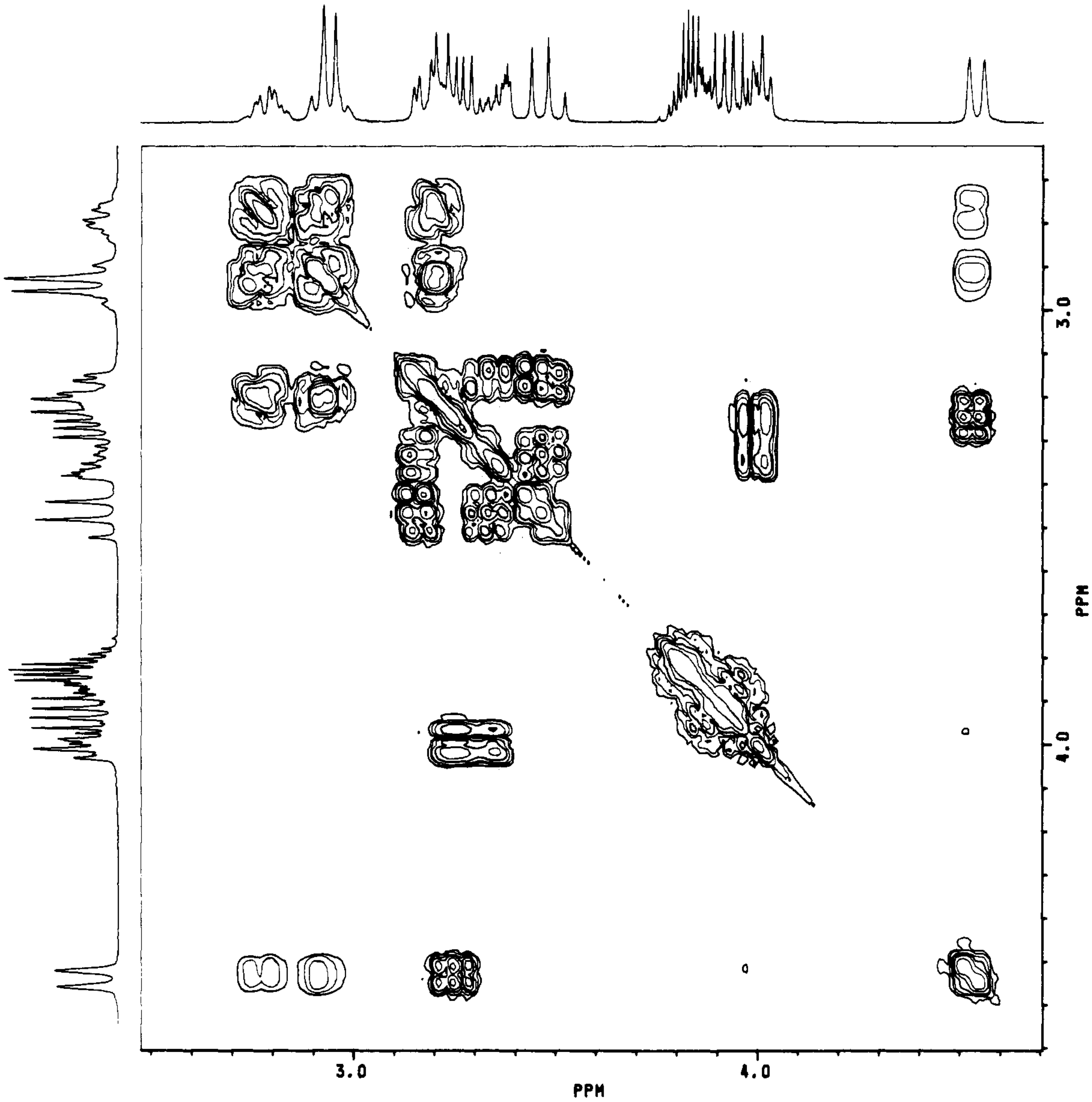


Figure 1. COSY 45 spectrum of isomer 2 showing the region from 2.6 to 4.7 ppm.

ditions. The reduction of compound 1 in deuterated trifluoroacetic acid with triethylsilane gave compound 4 deuterated in the positions 12b and 3.[8] Therefore it seems reasonable to assume that isomer 4 originates from 6 formed in situ whereas the concomitantly produced isomers 2 and 3 arise from the reduction of 1.

Compound 6 as the real precursor of 4 implicates the cis relationship of protons H12b and H1 in 4. The shift value of H12b (δ 3.80)[5,9] together with the presence of Bohlmann bands[6] in the IR (2700–2800 cm^{-1}) showed a trans annelation of the rings C and D. Under the assumption of a chair conformation for ring D, the 11-Hz coupling constant of H3 (δ 4.28) with the axial H4 (δ 2.65) was only in agreement with a trans arrangement of protons H3 and H2 (Figure 3).

The structure of amino ester 4 as shown in Scheme I was confirmed by a single-crystal X-ray diffraction analysis. An ORTEP[13] plot of the structure is shown in Figure 4. The rings C and D are trans fused, ring D exists in a chair conformation in which one ester group (at carbon 1) occupies an axial position, and the other substituents are equatorial.

(8) Reduction of 1 in deuterated acetic acid with sodium cyanoborohydride gave 2 with only one deuterium at carbon 3. Likewise, reduction with tributyltin hydride and 0.7 M trifluoroacetic acid solution in methylene chloride gave 3 with one deuterium incorporated at carbon 3. It can therefore be assumed that under these mildly acidic conditions no inversion of configuration at carbon 12b occurs prior to reduction.

(9) Assignment of the ^{1}H NMR signals to the protons in ring D was accomplished by a COSY 45 experiment.

Experimental Section

General Aspects. Proton nuclear magnetic spectra (^{1}H NMR) were recorded on a Bruker AM 300 spectrometer in $CDCl_3$ solution. All spectra were recorded with an internal lock on tetramethylsilane. Infrared spectra were obtained with a Perkin-Elmer 281 infrared spectrometer. Mass spectra were obtained on a Kratos MS 80 mass spectrometer. Melting points were determined on a Büchi 510 melting point determinator, and are uncorrected. Analytical thin-layer chromatography (TLC) was conducted on Merck glass plates precoated with 0.25 mm of silica gel 60 F-254. Analytical high-pressure liquid chromatography (HPLC) was performed on a Hewlett-Packard hp 1084 instrument equipped with an UV detector. The stationary phase used was Lichrosorb Si 60, 7 μm, from Merck in a 4 × 250 mm column. Elution was done by a linear gradient of n-hexane with 0.8–1.5% propan-2-ol over 20 min with a flow rate of 2 mL/min.

Trifluoroacetic acid was dried by standing over molecular sieves (3 Å); acetic acid-d (98%) and trifluoroacetic acid-d (99%) were purchased from Aldrich.

COSY experiments were carried out as described by Bax and Freeman.[10]

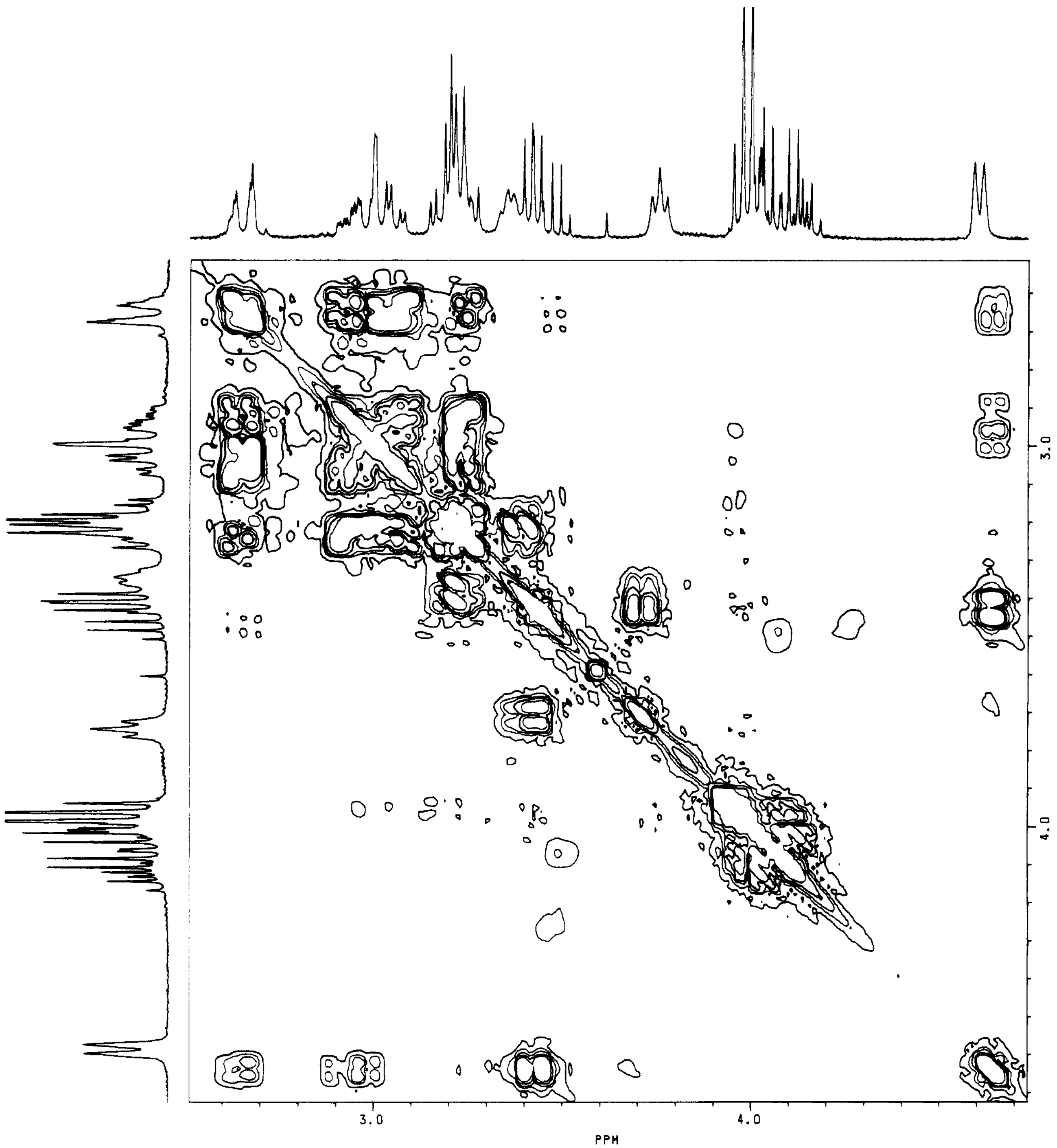


Figure 2. COSY 45 spectrum of isomer 3 showing the region from 2.5 to 4.75 ppm.

Diethyl 1,4-Dihydro-1-[2-(3-indolyl)ethyl]-4-phenylpyridine-3,5-dicarboxylate (5). To a suspension of 16 g (0.1 mol) of tryptamine in 28 mL of acetic acid were added under stirring and slight cooling 19.6 g (0.2 mol, 20.2 mL) of ethyl propiolate and 10.6 g (0.1 mol, 11.1 mL) of benzaldehyde. The reaction mixture was heated for 15 min at 100 °C. After cooling, the reaction mixture was poured into 400 mL of 10% sulfuric acid and extracted twice with ethyl acetate. The combined organic layers were washed twice with 10% sulfuric acid and twice with 10% sodium hydroxide and were dried with Na_2SO_4. The residue obtained after evaporation of the solvent crystallized from ether to yield 19 g (42.3%) of 1,4-dihydropyridine 5 (mp 162–164 °C): IR (KBr) ν_{max} 3350 (N-H), 1700 (C=O), 1680 (C=C), 1580 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.15 (t, 6 H, J = 7 Hz, $COOCH_2CH_3$), 3.18 (t, 2 H, J = 7 Hz, CH_2 indole), 3.75 (t, 2 H, J = 7 Hz, CH_2N), 4.00–4.20 (m, 4 H, $COOCH_2CH_3$), 4.85 (s, 1 H, proton in 4-position of the dihydropyridine ring), 7.00 (d, 1, J = 2 Hz, indole H), 7.1–7.30 (m, 9 H, Ar H), 7.37 (d, 1 H, J = 6 Hz, indole H), 7.64 (d, 1 H, J = 6 Hz, indole H), 8.20 (s br, 1 H, NH); mass spectrum, m/e (relative intensity) 444 (M^+, 38), 415 (5), 399 (6), 367 (44), 144 (100), 130 (40). Anal. Calcd for $C_{27}H_{28}N_2O_4$: C, 73.0; H, 6.3; N, 6.3. Found: C, 72.8; H, 6.5; N, 6.3.

Diethyl *r*-1,*c*-2,6,7,12,*t*-12b-Hexahydro-2-phenylindolo[2,3-*a*]quinolizine-1,3-dicarboxylate (1). To a solution of 5 g (11.26 mmol) of 5 in 50 mL of CH_2Cl_2 was added under nitrogen 5 mL of trifluoroacetic acid. After the mixture stood for 3 h at room temperature 200 mL of CH_2Cl_2 were added, and this solution was washed twice with 10% sodium hydroxide. The organic layer was dried with Na_2SO_4 and the solvent evaporated. The residue crystallized from methanol to yield 4 g (80%) of the cyclization product 1 (mp 187 °C): IR (KBr) 3430 (N-H), 1720 (C=O), 1680

(10) Bax, A.; Freeman, R. *J. Magn. Reson.* **1981**, *44*, 542. Bax, A. "*Two Dimensional Nuclear Magnetic Resonance in Liquids*"; Delft University and Reidel: Dordrecht, Boston, London, 1982.

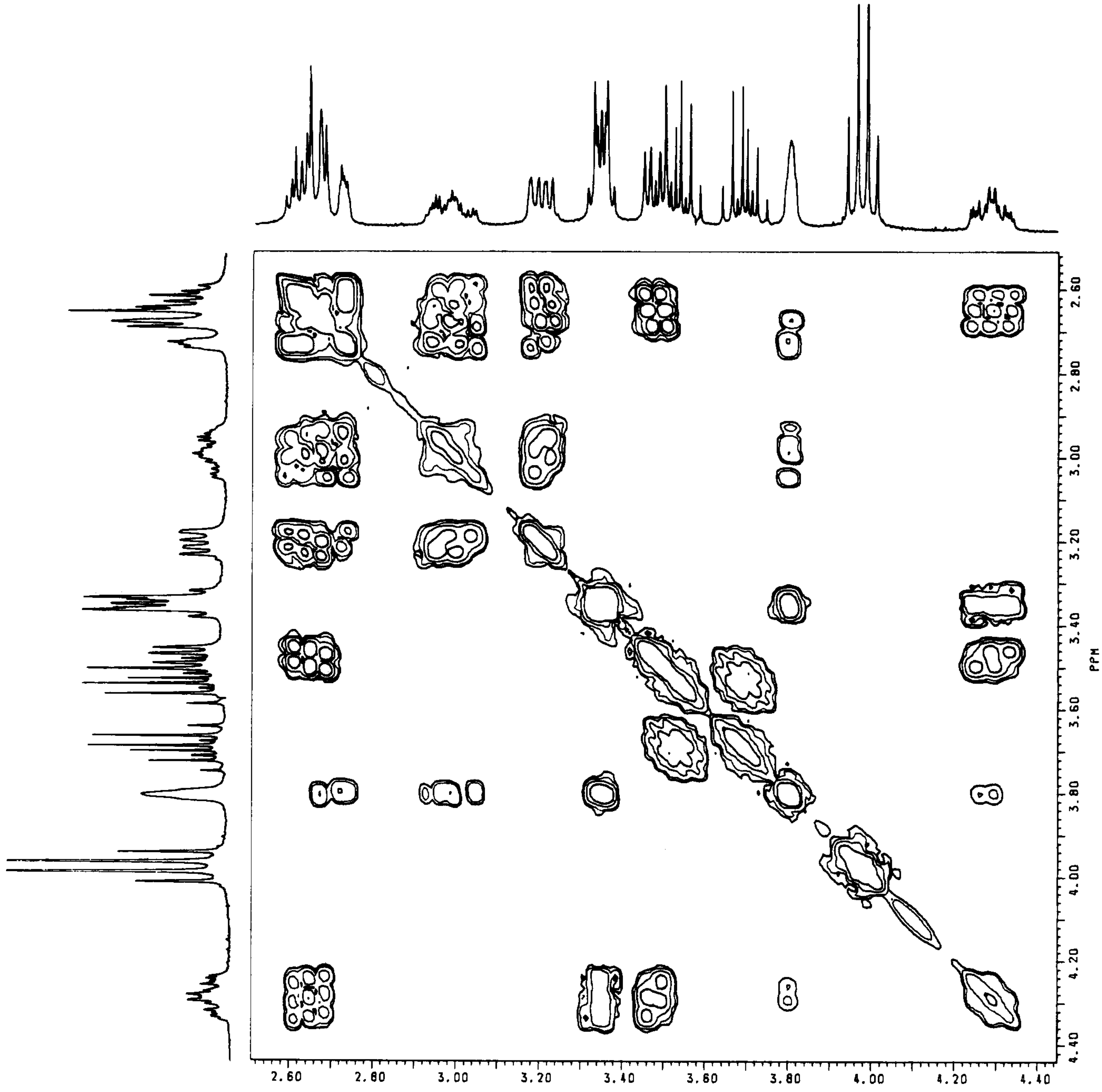


Figure 3. COSY 45 spectrum of isomer 4 showing the region from 2.5 to 4.35 ppm.

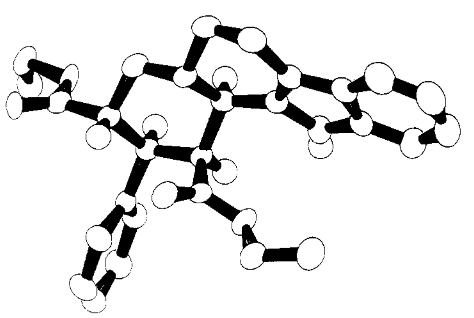


Figure 4. An ORTEP[13] plot showing the structure of 4 in the solid state from single-crystal X-ray analysis.

(C=C—C=O), 1610, 1580 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.15 (t, 3 H, J = 7 Hz, $COOCH_2CH_3$), 1.35 (t, 3 H, J = 7 Hz, $COOCH_2CH_3$), 2.70–3.05 (m, 2 H, CH_2 indole), 2.95 (dd, 1 H, J = 11 and 15 Hz, $CHCOOCH_2CH_3$), 3.55–3.85 (14-line m, 2 H, CH_2NCH=C), 3.95–4.27 (m, 4 H, $COOCH_2CH_3$), 4.42 (d, 1 H, J = 5 Hz, CH phenyl), 4.95 (d, 1 H, J = 11 Hz, CHNCH=C), 7.00–7.40 (m, 2 H, Ar H), 7.46 (d, 1 H, J = 6 Hz, indole H), 7.80 (s, 1 H, NCH=C), 8.40 (s br, 1 H, NH); mass spectrum, m/e (relative intensity) 444 (M^+, 75), 415 (50), 399 (10), 371 (90). Anal. Calcd for $C_{27}H_{28}N_2O_4$: C, 73.0; H, 6.3; N, 6.3. Found: C, 72.8; H, 6.4; N, 6.4.

Diethyl *r*-1,*c*-2,*c*-3,4,6,7,12,*t*-12b-Octahydro-2-phenylindolo[2,3-*a*]quinolizine-1,3-dicarboxylate (2) (Entry 2 in Table I). To a suspension of 2 g (4.5 mmol) of 1 in a mixture of 20 mL of acetic acid and 4 mL of CH_2Cl_2 was added at once 0.709 g (11.25 mmol) of sodium cyanoborohydride at 0 °C. After the mixture was stirred for 1.5 h at 0 °C a clear solution had formed which was diluted by 200 mL of ethyl acetate. This ethyl acetate solution was extracted twice with water and once with 10% sodium hydroxide. After the organic layer was dried over Na_2SO_4 and evaporation of the solvents the residue crystallized from methanol to yield 1.57 g (78.5%) of the amino ester 2 (mp 112–116 °C): IR ($CHCl_3$) ν_{max} 3450 (N-H), 1720 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3 H, J = 7 Hz, $COOCH_2CH_3$), 1.10 (t, 3 H, J = 7 Hz, $COOCH_2CH_3$), 2.72–2.85 (m, 1 H, indole CH_2), 2.88–3.02 (m, 2 H, indole CH_2 and NCH_2 in ring C), 3.18–3.28 (m, 1 H, NCH_2 in ring C), 3.19 (dd, 1 H, J = 12 and 4 Hz, NCH_2

in ring D), 3.27 (dd, 1 H, J = 11 and 6 Hz, $HCCOOCH_2CH_3$), 3.36 (ddd, 1 H, J = 12, 6, and 4 Hz, $HCCOOC_2H_5$), 3.48 (t, 1 H, J = 12 Hz, NCH_2 in ring D), 3.78–4.03 (m, 4 H, $COOCH_2CH_3$), 4.02 (t, 1 H, J = 6 Hz, HC phenyl), 4.54 (d, 1 H, J = 11 Hz, NCH indole), 7.05–7.45 (m, 8 H, Ar H), 7.50 (d, 1 H, J = 8 Hz, indole H), 8.45 (s br 1 H, NH); mass spectrum, m/e (relative intensity) 446 (M^+, 58), 401 (8), 373 (5), 270 (50), 184 (30), 170 (100). Anal. Calcd for $C_{27}H_{30}N_2O_4$: C, 72.6; H, 6.8; N, 6.3. Found: C, 72.6; H, 6.9; N, 6.3.

Diethyl [*c*-3-^{2}H]-*r*-1,*c*-2,*c*-3,4,6,7,12*t*-12b-Octahydro-2-phenylindolo[2,3-*a*]quinolizine-1,3-dicarboxylate (2). The reduction of 1 to 2 was carried out as described above in acetic [^{2}H]acid: ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3 H, J = 7 Hz, $COOCH_2CH_3$), 1.10 (t, 3 H, J = 7 Hz, $COOCH_2CH_3$), 2.72–2.85 (m, 1 H, indole CH_2), 2.88–3.02 (m, 2 H, indole CH_2 and NCH_2 in ring C), 3.18–3.28 (m, 1 H, NCH_2 in ring C), 3.19 (d, 1 H, J = 12 Hz, NCH_2 in ring D), 3.27 (dd, 1 H, J = 11 and 6 Hz, $HCCOOCH_2CH_3$), 3.48 (d, 1 H, J = 12 Hz, NCH_2 in ring D), 3.78–4.03 (m, 4 H, $COOCH_2CH_3$), 4.02 (d, 1 H, J = 6 Hz, HC phenyl), 4.54 (d, 1 H, J = 11 Hz, NCH indole), 7.05–7.45 (m, 8 H, Ar H), 7.50 (d, 1 H, J = 8 Hz, indole H), 8.45 (s br, 1 H, NH); mass spectrum, m/e (relative intensity) 448 (17), 447 (M^+, 42), 446 (16) 402 (10), 374 (6), 271 (54), 270 (38), 184 (33), 170 (100).

Diethyl *r*-1,*c*-2,*t*-3,4,6,7,12,*t*-12b-Octahydro-2-phenylindolo[2,3-*a*]quinolizine-1,3-dicarboxylate (3) (Entry 9 in Table I). To a solution of 1.78 g (4 mmol) of 1 in 40 mL of dichloromethane was added 3.19 g (28 mmol, 2.16 mL) of trifluoroacetic acid. During a period of 15 min, 4.66 g (16 mmol, 4.3 mL) of tributyltin hydride was dropped under stirring into the reaction mixture (slight cooling). The reaction mixture was stirred for additional 15 min at room temperature and then diluted with 200 mL of ethyl acetate. The ethyl acetate solution was extracted twice with 10% sodium hydroxide, dried over Na_2SO_4, and evaporated. The residue crystallized from petroleum ether to yield 0.96 g (54%) of the amino ester 3 (mp 194–196 °C): IR ($CHCl_3$) ν_{max} 3450 (N–H), 1725 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.00 (t, 3 H, J = 7 Hz, $COOCH_2CH_3$), 1.15 (t, 3 H, J = 7 Hz, $COOCH_2CH_3$), 2.60–2.70 (m, 1 H, indole CH_2), 2.90–3.10 (m, 2 H, indole CH_2 and NCH_2 in ring C), 3.16–3.27 (m, 1 H, NCH_2 in ring C), 3.18 (dd, 1 H, J = 12 and 4 Hz, NCH_2 in ring D), 3.25 (dd, 1 H, J = 12 and 6 Hz, NCH_2 in ring D), 3.35 (td, 1 H, J = 6 and 4 Hz, $CHCOOCH_2CH_3$), 3.42 (dd, 1 H, J = 7 and 6 Hz, $CHCOOCH_2CH_3$), 3.76 (t, 1 H, J = 6 Hz, CH phenyl), 3.98 (q, 2 H, J = 7 Hz, $COOCH_2CH_3$), 3.94–4.18 (m, 2 H, $COOCH_2CH_3$), 4.60 (d, 1 H, J = 7 Hz, NCH indole), 7.05–7.40 (m, 8 H, Ar H), 7.50 (d, 1 H, J = 8 Hz, indole H), 8.40 (s br, 1 H, NH); mass spectrum, m/e (relative intensity) 446 (M^+, 47), 401 (8), 373 (4), 270 (49), 184 (22), 170 (100). Anal. Calcd for $C_{27}H_{30}N_2O_4$: C, 72.6; H, 6.8; N, 6.3. Found: C, 72.7; H, 6.9; N, 6.1.

Diethyl [*t*-3-^{2}H]-*r*-1,*c*-2,*t*-3,4,6,7,12,*t*-12b-Octahydro-2-phenylindolo[2,3-*a*]quinolizine-1,3-dicarboxylate (3). The reduction of 1 to 3 was carried out as described above in a 0.7 M solution of trifluoroacetic [^{2}H]acid in methylene chloride: ^{1}H NMR ($CDCl_3$) δ 1.00 (t, 3 H, J = 7 Hz, $COOCH_2CH_3$), 1.15 (t, 3 H, J = 7 Hz, $COOCH_2CH_3$), 2.60–2.70 (m, 1 H, indol CH_2), 2.90–3.10 (m, 2 H, indole CH_2 and NCH_2 in ring C), 3.16–3.27 (m, 1 H, NCH_2 in ring C), 3.18 (d, 1 H, J = 12 Hz, NCH_2 in ring D), 3.25 (d, 1 H, J = 12 Hz, NCH_2 in ring D), 3.42 (dd, 1 H, J = 7 and 6 Hz, $CHCOOCH_2CH_3$), 3.76 (d, 1 H, J = 6 Hz, CH phenyl), 3.98 (q, 2 H, J = 7 Hz, $COOCH_2CH_3$), 3.94–4.18 (m, 2 H, $COOCH_2CH_3$), 4.60 (d, 1 H, J = 7 Hz, NCH indole), 7.05–7.40 (m, 8 H, Ar H), 7.50 (d, 1 H, J = 8 Hz, indole H), 8.40 (s br, 1 H, NH); mass spectrum, m/e (relative intensity) 448 (4), 447 (M^+, 25), 446 (17), 402 (6), 374 (3), 271 (37), 270 (39), 184 (23), 170 (100).

Isomerization of Amino Ester 2 to the Isomeric Amino Ester 3. 2 (0.45 g, 1 mmol) was refluxed in 2 mL of anhydrous ethanol together with 0.12 g (1 mmol, 0.12 mL) of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) under nitrogen for 16 h. After cooling, 0.3 g (67%) of amino ester 3 crystallized directly from the reaction mixture.

Diethyl *r*-1,*c*-2,*t*-3,4,6,7,12,*c*-12b-Octahydro-2-phenylindolo[2,3-*a*]quinolizine-1,3-dicarboxylate (4) (Entry 4 in Table I). To a solution of 5 g (11.26 mmol) of 1 in 20 mL of trifluoroacetic acid was added 2.62 g (22.6 mmol, 3.6 mL) of triethylsilane. After the mixture was stirred for 1.5 h at room temperature the trifluoroacetic acid was evaporated in vacuo. The residue was dissolved in ethyl acetate and washed twice with 10% sodium hydroxide. The organic layer was dried with Na_2SO_4 and evaporated. Crystallization of the residue from methanol gave 2.3 g (46%) of amino ester 4 (mp 200–205 °C): IR ($CHCl_3$) ν_{max} 3480 (NH), 2700–2800 (Bohlmann bands), 1730 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.55 (t, 3 H, J = 7 Hz, $COOCH_2CH_3$), 1.05 (t, 3 H, J = 7 Hz, $COOCH_2CH_3$), 2.58–2.76 (m, 2 H, indole CH_2 and NCH_2 in ring C), 2.65 (t, 1 H, J = 11 Hz, NCH_2 in ring D), 2.92–3.06 (m, 1 H, indole CH_2), 3.20 (dd, 1 H, J = 12 and 5 Hz, NCH_2 in ring C), 3.30–3.40 (m, 2 H, $CHCOOCH_2CH_3$ and CH phenyl), 3.48 (t, 1 H, J = 11 and 4 Hz, NCH_2 in ring D), 3.48–3.59 (m 1 H, $COOCH_2CH_3$), 3.64–3.75 (m, 1 H, $COOCH_2CH_3$), 3.80 (s br, 1 H, NCH indole), 3.98 (q, 2 H, J = 7 Hz, $COOCH_2CH_3$), 4.28 (dddd, 1 H, J = 11, 10.5, 4, and 2 Hz),7.05–7.30 (m, 8 H, Ar H), 7.50 (d, 1 H, J = 8 Hz, indole H), 7.90 (s br, 1 H, NH); mass spectrum, m/e (relative intensity) 446 (M^+, 33), 373 (12), 270 (47), 184 (26), 170 (100). Anal. Calcd for $C_{27}H_{30}N_2O_4$: C, 72.6; H, 6.8; N, 6.3. Found: C, 72.8; H, 6.9; N, 6.1.

Diethyl [*t*-3,*c*-12b-^{2}H$_2$]-*r*-1,*c*-2,*t*-3,4,6,7,12,*c*-12b-Octahydro-2-phenylindolo[2,3-*a*]quinolizine-1,3-dicarboxylate (4). The reduction of 1 to 4 was carried out as described above in trifluoroacetic [^{2}H]acid: ^{1}H NMR ($CDCl_3$) δ 0.55 (t, 3 H, J = 7 Hz, $COOCH_2CH_3$), 1.05 (t, 3 H, J = 7 Hz, $COOCH_2CH_3$), 2.58–2.76 (m, 2 H, indole CH_2 and NCH_2 in ring C), 2.65 (d, 1 H, J = 11 Hz, NCH_2 in ring D), 2.92–3.06 (m, 1 H, indole CH_2), 3.20 (dd, 1 H, J = 12 and 5 Hz, NCH_2 in ring C), 3.35 (s, 2 H, $CHCOOCH_2CH_3$ and CH phenyl), 3.48 (d, 1 H, J = 11 Hz, NCH_2 in ring D), 3.48–3.59 (m, 1 H, $COOCH_2CH_3$), 3.64–3.75 (m, 1 H, $COOCH_2CH_3$), 3.98 (q, 2 H, J = 7 Hz, $COOCH_2CH_3$), 7.05–7.30 (m, 8 H, Ar H), 7.50 (d, 1 H, J = 8 Hz, indole H), 7.90 (s br, 1 H NH); mass spectrum, m/e (relative intensity) 450 (8), 449 (32), 448 (M^+, 58), 447 (32), 446 (8), 375 (7), 274 (10), 273 (32), 272 (76), 270 (70), 186 (15), 185 (30), 184 (12), 173 (12), 172 (53), 171 (100), 170 (71).

Diethyl *r*-1,*c*-2,6,7,12,*c*-12b-Hexahydro-2-phenylindolo-[2,3-*a*]quinolizine-1,3-dicarboxylate (6). 1 (5 g, 11.26 mmol) was dissolved in 50 mL of trifluoroacetic acid under nitrogen and left standing at room temperature for 1.5 h. The reaction mixture was diluted with 200 mL of ethyl acetate and extracted twice with water and twice with 10% sodium hydroxide. The organic layer was dried with Na_2SO_4, and the solvents were evaporated. The residue crystallized from methanol to yield 3.5 g (70%) of the vinylogous urethane 6 (mp 252–254 °C): IR (KBr) ν_{max} 3380 (NH), 1730 (C=O), 1675 (C=C), 1605, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05 (t, 3 H, J = 7 Hz, $COOCH_2CH_3$), 1.45 (t br, 3 H, J = 7 Hz, $COOCH_2CH_3$), 2.85 (dd, 1 H, J = 15 and 4 Hz, indole CH_2), 3.05–3.55 (m, 1 H, indole CH_2), 3.64 (t, 1 H, J = 4.5 Hz, $CHCOOCH_2CH_3$), 3.85–4.05 (m, 3 H, NCH_2 and $COOCH_2CH_3$), 4.33 (m, 2 H, J = 7 Hz, $COOCH_2CH_3$), 4.47 (d, 1 H, J = 4.5 Hz, CH phenyl), 4.96 (s br, 1 H, CHN), 6.60 (m, 6 H,Ar H), 6.78 (m, 1 H, Ar H), 6.88 (d, 1 H, J = 6 Hz, Ar H), 7.00 (m, 2 H, Ar H), 7.40 (d, 1 H, J = 6 Hz, indole H), 7.80 (s, 1 H), CH=C), 8.40 (s br, 1 H, NH); mass spectrum, m/e (relative intensity) 444 (M^+, 88), 415 (47), 371 (100). Anal. Calcd for $C_{27}H_{28}N_2O_4$: C, 73.0; H, 6.3; N, 6.3. Found: C, 73.0; H, 6.3; N, 6.2.

Diethyl [*c*-12b-^{2}H]-*r*-1,*c*-2,6,7,12,*c*-12b-Hexahydro-2-phenylindolo[2,3-*a*]quinolizine-1,3-dicarboxylate (6). The isomerization of 1 to 6 was carried out as described above in trifluoroacetic [^{2}H]acid: ^{1}H NMR ($CDCl_3$) δ 1.05 (t, 3 H, J = 7 Hz, $COOCH_2CH_3$), 1.45 (t br, 3 H, J = 7 Hz, $COOCH_2CH_3$), 2.85 (dd, 1 H, J = 15 and 4 Hz, indole CH_2), 3.05–3.55 (m, 1 H, indole CH_2), 3.64 (d, 1 H, J = 4.5 Hz, $CHCOOCH_2CH_3$), 3.85–4.05 (m, 3 H, NCH_2 and $COOCH_2CH_3$), 4.33 (m, 2 H, J = 7 Hz, $COOCH_2CH_3$), 4.47 (d, 1 H, J = 4.5 Hz, CH phenyl), 6.60 (m, 6 H, Ar H), 6.78 (m, 1 H, Ar H), 6.88 (d, 1 H, J = 6 Hz, Ar H), 7.00 (m, 2 H, Ar H), 7.40 (d, 1 H, J = 6 Hz, indole H), 7.80 (s, 1 H, CH=C), 8.40 (s br, 1 H, NH); mass spectrum, m/e (relative intensity) 447 (22), 446 (71), 445 (M^+, 100), 444 (20), 417 (28), 416 (40), 373 (18), 372 (52), 371 (70).

Reduction of 6 by Et_3SiH. To a solution of 0.444 g (1 mmol) of 6 in 2 mL of trifluoroacetic acid was added 0.233 (2 mmol, 0.32 mL) of triethylsilane. The reaction mixture was stirred for 1 h at room temperature, diluted with 50 mL of ethyl acetate, and extracted twice with 10% sodium hydroxide. The organic phase was dried over Na_2SO_4 and evaporated. The residue crystallized from methanol to yield 0.36 g (81%) of amino ester 4. HPLC analysis of the mother liquor showed no other isomer present.

Other Reducing Agents. $NaBH_4$ in Acetic Acid (Entry 1 in Table I). Six portions of 95 mg (2.5 mmol) of sodium borohydride were added under slight cooling to a suspension of 0.444 g (1 mmol) of 1 in a mixture of 5 mL of acetic acid and 1 mL of dichloromethane during a period of 3 h. The reaction mixture was stirred for 18 h at room temperature. An aliquot of the reaction mixture was worked up (as described in the procedure for the preparation of amino ester **2**) and analyzed by HPLC.

$NaCNBH_3$ in Trifluoroacetic Acid (Entry 3 in Table I). To a stirred solution of 0.444 g (1 mmol) of 1 in 2 mL of trifluoroacetic acid was added 0.126 g (2 mmol) of sodium cyanoborohydride at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, and then an aliquot was worked up (as described in the procedure for the preparation of 4) and analyzed by HPLC.

$(CH_3)_2PhSiH$ in Trifluoroacetic Acid (Entry 7 in Table I). To a solution of 0.444 (1 mmol) of 1 in 5 mL of trifluoroacetic acid was added 0.409 g (3 mmol, 0.46 mL) of dimethylphenylsilane. The reaction mixture was stirred for 18 h at room temperature. An aliquot of the reaction mixture was worked up (as described in the procedure for the preparation of 4) and analyzed by HPLC.

Single-Crystal X-ray Structure Determination of Amino Ester 4. Crystals suitable for X-ray diffraction analysis were grown from ethanol. The crystal used for data collection was a colorless, transparent needle prism measuring 0.075 × 0.175 × 0.625 mm. Lattice constants and intensity data were measured at 297 K on an Enraf-Nonius Cad-4 automated diffractometer using graphite-monochromatized Cu Kα radiation. Unit cell dimensions were obtained by least-squares methods from the adjusted angular settings of 25 large-angle reflections. The crystal data are as follows: $C_{27}H_{30}N_2O_4$, $M_r = 446.55$; triclinic space group $P\bar{1}$; $a = 5.8241$ (6) Å, $b = 13.0620$ (20) Å, $c = 15.3812$ (16) Å, $\alpha = 95.990$ (11)°, $\beta = 93.392$ (9)°, $\gamma = 95.633$ (11)°, $V = 1155.24$ Å^3, $Z = 2$, $\rho_c = 1.284$ g/cm^3, μ(Cu Kα) = 6.6 cm^{-1}. Data collection was attempted to $\theta < 65°$ in the ω–2θ scanning mode. A total of 4083 reflections were collected (±h,±k,+l) yielding 4083 unique intensities and 3199 reflections with $I > 3.0\sigma(I)$. This set of reflections was used in the structure solution. Data reduction included corrections for background, Lorentz and polarization effects, extinction, and absorption by a semiempirical method.[11]

By direct methods (MULTAN)[12] 31 out of 33 non-hydrogen atoms were located, the missing two non-hydrogen atoms by difference Fourier methods. The positions of the hydrogen atoms were calculated geometrically or in the case of the methyl H atoms located from Fourier difference maps. Full-matrix least-squares refinement was carried out with anisotropic temperature factors for non-H atoms and isotropic factors for H atoms, using all reflections with $I > 3.0\sigma(I)$ and $\sin\theta/\lambda < 0.5$ Å^{-1}. The final R_1 (2160 reflections, 419 variables) was 0.037. The final difference Fourier map was featureless. The following programs were used: Enraf-Nonius SDP[13] and ORTEP.[14]

Supplementary Material Available: Tables of bond distances, bond angles, atomic positional parameters, and atomic thermal parameters for amino ester 4 (6 pages). Ordering information is given on any current masthead page.

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The Chemistry of *N*-Sulfonyl Enamines

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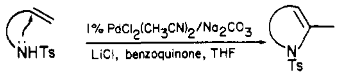
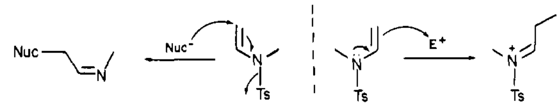
N-Tosyl enamines are available in multigram quantities using a palladium(II)-catalyzed cyclization process. This unusual class of compounds has limited nucleophilic character at the β-position, undergoing protonation and halogenation by *N*-halosuccinimides. The 3-iodo compound is subject to a number of palladium(0)-catalyzed insertion processes leading to conjugated dienes having an electron donor at one terminus and an electron acceptor at the other. *N*-Tosyl enamines are inert to nucleophilic attack at the β-position. The 3-iodo compound is cleaved to the alkyne by *n*-butyllithium.

Transition metal catalyzed processes have been developed for the synthesis of heterocyclic systems not readily available by conventional heterocyclic preparative methods.[1] One such class of heterocyclic compounds is the *N*-sulfonyl enamines, many of which are easily prepared by a palladium-catalyzed procedure (eq 1)[2] but not readily available by more standard synthetic routes. The recent



(1)

development of this cyclization reaction on a preparative scale (10–15 g)[3] made usable quantities of these compounds available for further study. *N*-Tosyl enamines are potentially "ambiphilic" and may be reactive toward both electrophiles (depending on the availability of the lone pair of electrons on nitrogen) and nucleophiles (depending on the ease of displacement of the sulfinate group) (eq 2).



(2)

Both modes of reactivity have been observed.[2] For example, both the acid-catalyzed hydrolysis to the *N*-tosyl amino ketone and the acid-assisted reduction by cyanoborohydride to the saturated *sulfonamide* clearly involved in-

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