2,3-Dichloro-5,5-dimethyl-2-cyclohexenone (8): 0.11 g (2%); mp 60.5–62 °C (petroleum ether, bp 60–80 °C) [lit.[24] mp 63 °C]; ^{1}H NMR ($CDCl_3$) δ 1.13 (s, 6 H), 2.43 (s, 2 H, C-6), 2.80 (s, 2 H, C-4); mass spectrum, m/e (relative intensity) 194 (19), 192 (29), 164 (29), 136 (100), 108 (17).

In addition, 2,2'-thiobisdimedone (**4a**; 0.26 g, 5%) was also isolated.

(B) Isolation of 15a. The reaction was carried out in benzene in the usual manner but stopped after 1 h. Filtration yielded dimedone (3.11 g, 62%). Evaporation and column chromatography (SiO_2, CH_2Cl_2) afforded first a small amount (0.05 g) of impure **7**, followed by the major fraction (1.23 g, 58%) consisting of a yellow solid (**15a**) which was recrystallized from dichloromethane–cyclohexane: mp 183–183.5 °C (lit.[16] mp 176–178 °C); ^{1}H NMR ($CDCl_3$) δ 0.87 (s, 3 H), 1.15 (s, 6 H), 1.22 (s, 3 H), 2.28 (s, 2 H), 2.45 (d, 2 H, ^2J = 14 Hz), 2.56 (s, 2 H), 3.03 (d, 2 H, ^2J = 14 Hz), in excellent agreement with the previously published ^{1}H NMR spectrum.[16]

Reaction of 1 with Methanesulfenyl Chloride. Isolation of 9 and 10. Chlorine (20.72 g, 0.296 mol) was slowly bubbled into dimethyl disulfide (27.84 g, 0.296 mol) in diglyme (60 mL). Vacuum distillation of 25 °C, with a receiver cooled in a dry ice–acetone bath, yielded methanesulfenyl chloride: 15.86 g (33%); ^{1}H NMR ($CDCl_3$) δ 2.82 (s) [lit.[10] (CCl_4) δ 2.91 (s)].

Reaction with dimedone was carried out by the standard procedure. Filtration yielded dimedone (3.63 g, 73%). Evaporation yielded a white solid. Recrystallization from petroleum ether (bp 60–80 °C) yielded 2-chloro-2-(methylthio)dimedone (**9**); 1.50 g (70%); mp 93–94 °C; ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 3 H), 1.22 (s, 3 H), 2.21 (s, 3 H), 2.58 (d, 2 H, ^2J = 14 Hz), 3.28 (d, 2 H, ^2J = 14 Hz); IR ($CHCl_3$) ν_{max} 1740, 1755 cm^{-1} (C=O); mass spectrum, m/e (relative intensity) 222 (9), 220 (24), 186 (17), 130 (14), 83 (100).

Anal. Calcd for $C_9H_{13}ClO_2S$: C, 48.98; H, 5.94; Cl, 16.06; S, 14.53. Found: C, 48.86; H, 5.84; Cl, 16.24; S, 14.45.

The residual filtrate from the recrystallization was evaporated, yielding a clear oil. Purification by thick-layer chromatography (SiO_2, CH_2Cl_2) yielded 2,2-bis(methylthio)dimedone (**10**): 0.24 g (11%; mp 59–60 °C (petroleum ether, bp 60–80 °C); ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 6 H), 2.10 (s, 6 H), 2.78 (s, 4 H); mass spectrum, m/e (relative intensity) 232 (46), 149 (24), 107 (18), 106 (10), 83 (100).

Anal. Calcd for $C_{10}H_{16}O_2S_2$: C, 51.69; H, 6.94; S, 27.60. Found: C, 51.89; H, 7.00; S 27.39.

Reaction of 10 with Methanesulfenyl Chloride. Methanesulfenyl chloride (0.10 g, 1.2 mmol) and compound **10** (0.15 g, 0.6 mmol) in chloroform (2 mL) were stirred for 18 h. Evaporation of the solvent yielded **9** (0.13 g, 93%).

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Registry No. **1**, 126-81-8; **4a**, 3359-52-2; **5**, 7298-89-7; **6**, 7298-86-4; **7**, 17530-69-7; **8**, 79255-35-9; **9**, 79255-36-0; **10**, 79255-37-1; **15a**, 56995-07-4; disulfur dichloride, 10025-67-9; sulfur dichloride, 10545-99-0; sulfuryl chloride, 7791-25-5; thionyl chloride, 7719-09-7; methanesulfenyl chloride, 5813-48-9.

(23) Coke, J. L.; Williams, H. J.; Natarajan, S. *J. Org. Chem.* **1977**, *42*, 2380.
(24) Hinkel, L. E.; Williams, W. D. *J. Chem. Soc.* **1922**, 2498.

Iminium Salts from α-Amino Acid Decarbonylation. Application to the Synthesis of Octahydroindolo[2,3-*a*]quinolizines

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Iminium salts, formed regiospecifically by the decarbonylation of tertiary α-amino acids, have been applied to the synthesis of substituted tetrahydro-β-carbolines. In this manner the octahydroindolo[2,3-*a*]quinolizines **5–8** were prepared. Several useful methods for the synthesis of the requisite tertiary pipecolic acids **1–4** were developed. These include alkylation of secondary α-amino esters with tryptophyl bromide and alkylation of tryptophan methyl ester with α,ω-dibromo esters. Following deprotection, the resulting tertiary α-amino acids were heated breifly in phenylphosphonic dichloride to give the cyclized products in good yield. The presence of other substituents α or β to the basic nitrogen induces stereoselectivity in the ring closure. When this substituent is an α-carboxylic acid, it can be replaced by hydrogen through decarbonylation followed by reduction of the resulting iminium salt.

The tetrahydro-β-carboline nucleus is a structural feature present in many indole alkaloids. The most common methods for its synthesis are the Bischler–Napieralski and Pictet–Spengler reactions.[2] Application of the latter, however, is limited by the difficulty of regiospecifically generating the necessary iminium salt.

Recently we developed a convenient and regiospecific method for the preparation of iminium salts from tertiary α-amino acids.[3] Application to the synthesis of berbines,[4] a homotropane (anatoxin a),[5] and 1-azabicyclic systems[6] has demonstrated its value for the synthesis of nitrogen heterocylces. In this report we described the application of tertiary α-amino acid decarbonylation to the synthesis of some substituted tetrahydro-β-carbolines. Specifically, treatment of the tertiary pipecolic acids **1–4** with phenylphosphonic dichloride has resulted in the formation in high yield of the octahydroindolo[2,3-*a*]quinolizines **5–8**.

Results and Discussion

Synthesis of Tertiary Pipecolic Acids 1–4. Two conceptually different methods were used to synthesize the

(1) Fellow of the Royal Norwegian Council for Scientific and Industrial Research.
(2) ApSimon, J., Ed. "The Total Synthesis of Natural Products"; Wiley: New York, 1977; Vol. 3, p 283.
(3) Dean, R. T.; Padgett, H. C.; Rapoport, H. *J. Am. Chem. Soc.* **1976**, *98*, 7448.
(4) Dean, R. T.; Rapoport, H. *J. Org. Chem.* **1978**, *43*, 2115, 4183.
(5) Bates, H. A.; Rapoport, H. *J. Am. Chem. Soc.* **1979**, *101*, 1259.
(6) Csendes, I. G.; Lee, Y. Y.; Padgett, H. C.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 4173.

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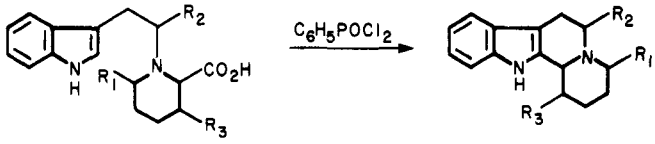
pipecolic acids 1–4, namely, (a) alkylation of a pipecolic



1	$R_1=R_2=R_3=H$	5
2	$R_2=R_3=H$, $R_1=CO_2CH_3$	6
3	$R_1=R_3=H$, $R_2=CO_2CH_3$	7
4	$R_1=R_2=H$, $R_3=CO_2CH_3$	8

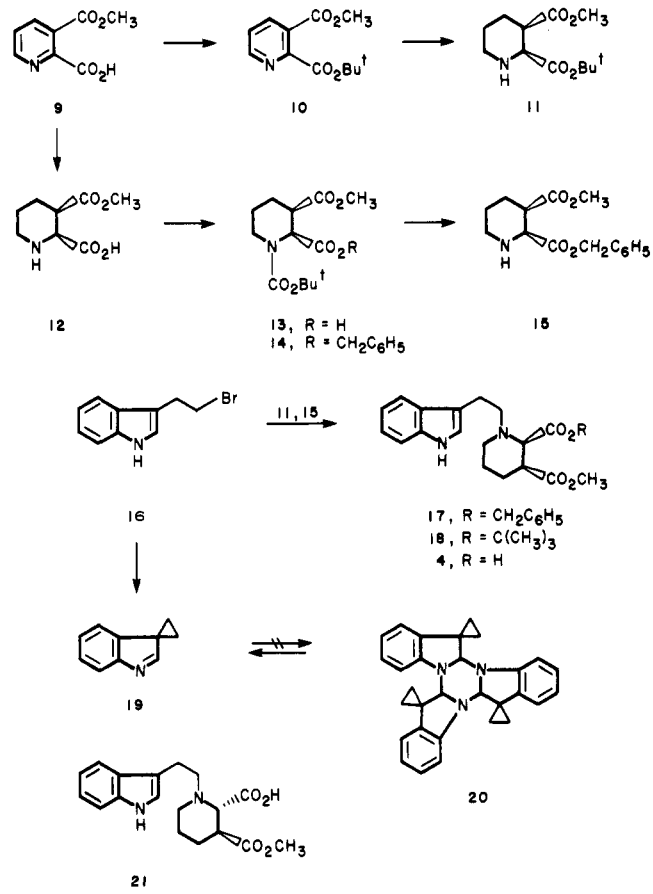
acid derivative with a tryptophyl bromide or (b) alkylation of tryptophan methyl ester or tryptamine with a 2,6-dihalohexanoic acid derivative.

The first method is illustrated in Scheme I by the synthesis of amino acid **4**. For this route a piperidine 2,3-diester was needed in which the esters were differentiated. Thus hydrogenation of methy 2-carboxynicotinate (**9**)[7] gave the amino acid **12**. Protection as the *N-tert*-butyloxycarbonyl derivative, followed by esterification with *O*-benzyl-*N,N'*-diisopropylisourea[8] and removal of the protecting group with trifluoroacetic acid (TFA), gave the desired diester **15** in 95% yield from **9**.

For an alternative approach we desired the corresponding mixed piperidine methyl *tert*-butyl diester **11**. Acid-catalyzed esterification of **9** with isobutylene[9] failed due to limited solubility. Attempted esterification using *tert*-butyl alcohol with oxalyl chloride/DMF[10] or *p*-toluenesulfonyl chloride/pyridine[11] gave only low yields of **10**, together with a highly colored side product. This side product, which could be formed exclusively by omission of *tert*-butyl alcohol from the reaction mixture, is still under investigation. Use of a large excess of *tert*-butyl alcohol was found to favor the formation of the desired ester **10**, producing it in 95% yield. Hydrogenation gave the crystalline piperidine diester **11**.

The next step was to alkylate the piperidine diester (**11** or **15**) with tryptophyl bromide (**16**)[12] to give the indole diesters **17** and **18**. Initially we employed conditions similar to those used before,[6] refluxing **15** and **16** in benzene over solid K_2CO_3 for 8 h. This gave variable and poor yields which were generally around 30%. Further investigation showed that tryptophyl bromide alone reacts with K_2CO_3 in CH_3CN at reflux, being totally converted to a new compound after 8 h. Isolation gave an 85% yield of crystalline spiro[cyclopropane-1,3'-indolenine] (**19**), first described as an oil.[13] Contrary to similar indolenines,[14] **19** exists in solution solely as the monomer (as determined by NMR spectroscopy), rather than the trimer **20**. This is probably due to stabilization of the imine by cyclopropyl conjugation.[15] Alkaline solutions of **19** in water or ethanol are indefinitely stable, but acidification (acetic acid) causes rapid conversion to indolic compounds, as shown by UV absorption.

Scheme I. Synthesis of Tertiary Pipecolic Acid 4 by Alkylation of 2,3-Piperidinedicarboxylates 11 and 15 with Tryptophyl Bromide (16)



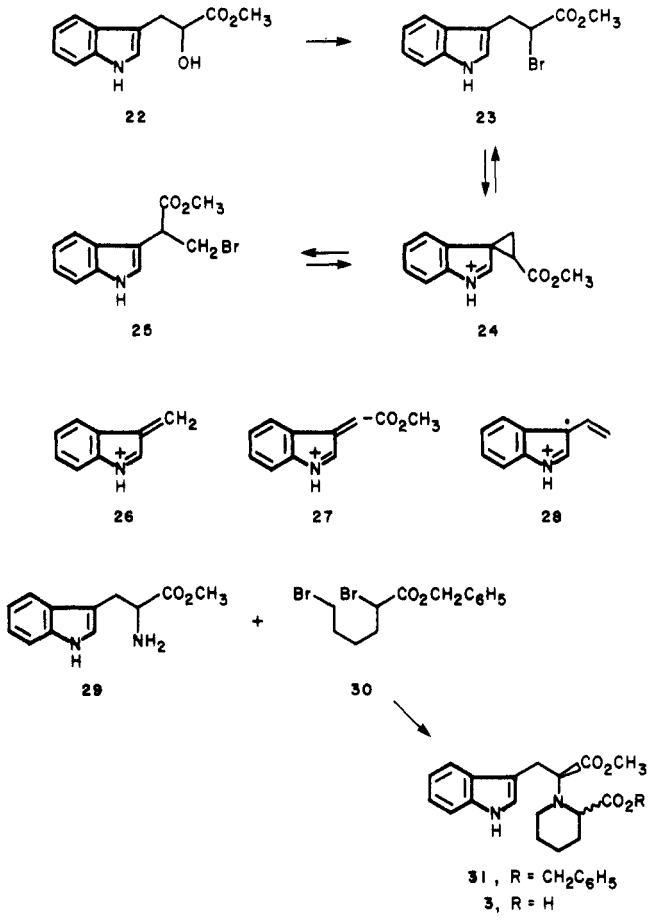
Since tryptophyl bromide was converted to the cyclopropyl derivative **19** only very slowly when $NaHCO_3$ was substituted for K_2CO_3, bicarbonate was used for the alkylation of piperidine diesters **11** and **15**. The indole diesters **17** and **18** were produced in 85% and 90% yields, respectively. Hydrogenolysis of benzyl methyl diester **17** gave amino acid **4**, which was also produced by treating **18** with TFA. The product from this cleavage with TFA showed several small *tert*-butyl peaks in the proton NMR, suggesting that the intermediate *tert*-butyl cation had attacked the indole ring. Also, the strong acid used gave a dark product.

To avoid these problems, we developed a superior process for cleavage of the *tert*-butyl ester which consisted of refluxing **18** in water/*n*-propanol/acetic acid (5/5/1) for 4 h, cleanly giving a quantitative yield of **4**. Without water or acetic acid, no reaction occurred, and the purpose of *n*-propanol was to increase the solubility of the diester. When **18** was refluxed in glacial acetic acid, a 1/3 mixture of **4** and a very similar compound we believe to be the trans compound **21** was produced. This appears to be occurring through formation of a mixed anhydride, since water inhibits this isomerization.

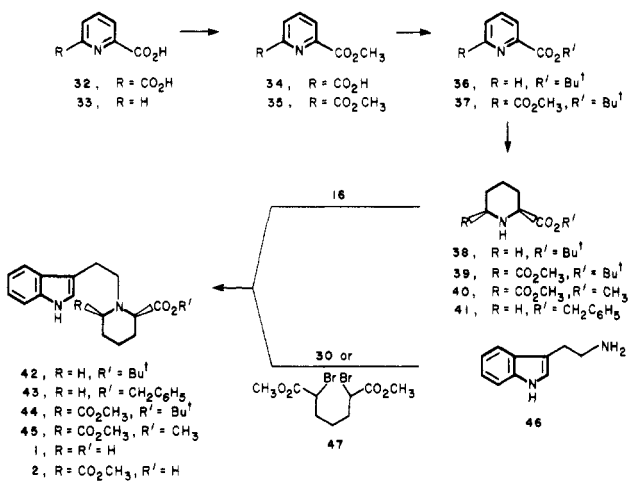
Originally we intended to synthesize amino acid **3** by the same method used for **4**. Thus we undertook the preparation of substituted tryptophyl bromide **23** from the alcohol **22**[16,17] (Scheme II). A mixture of isomeric bromides **23** and **25** was produced, and when it was allowed to stand, the branched chain bromide **25** became the predominant

(7) Thunus, L.; Dejardin-Duchene, M. *J. Pharm. Belg.* **1969**, *24*, 3.
(8) Mathias, L. J. *Synthesis* **1979**, 561.
(9) Anderson, G. W.; Callahan, F. M. *J. Am. Chem. Soc.* **1960**, *82*, 3359. Roeske, R. *J. Org. Chem.* **1963**, *28*, 1251.
(10) Stadler, P. A. *Helv. Chim. Acta* **1978**, *61*, 1675.
(11) Brewster, J. H.; Ciotti, C. J., Jr. *J. Am. Chem. Soc.* **1955**, *77*, 6214. Blotny, G.; Biernat, J. F.; Taschner, E. *Justus Liebigs Ann. Chem.* **1963**, *663*, 194.
(12) Neumeyer, J. L.; Moyer, U. V.; Leonard, J. E. *J. Med. Chem.* **1969**, *12*, 450.
(13) Closson, W. D.; Roman, S. A.; Kwiatkowski, G. T.; Corwin, D. A. *Tetrahedron Lett.* **1966**, 2271.
(14) Fritz, H.; Pfaender, *Chem. Ber.* **1965**, *98*, 989. Jackson, A. H.; Smith, P. *Tetrahedron* **1968**, *24*, 2227.
(15) Hoffman, R. *Tetrahedron Lett.* **1965**, 3819.
(16) Gortatowski, M. J.; Armstrong, M. D. *J. Org. Chem.* **1957**, *22*, 1217.
(17) Suvorov, N. N.; Buyanov, V. N. *Khim. Geterotsikl. Soedin.* **1970**, 377.

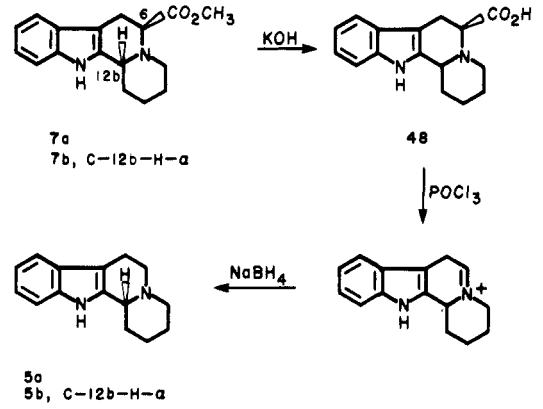
Scheme II. Synthesis of Tertiary Pipecolic Acid 3



Scheme III. Synthesis of Tertiary Pipecolic Acids 1 and 2



Scheme IV. Synthesis of Optically Active 1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-a]quinolizine (8a)



isomer. We propose that this transformation is realized so easily through the assistance of the indole ring to give the intermediate spirocyclopropane **24**. Bromides **23** and **25** can be distinguished by their proton NMR absorptions and mass spectra. Thus **23** and **25** have geminal coupling constants of 14.4 and 9.8 Hz, respectively, which are typical values for each system.[18] While alcohol **22** shows the fragment **26** as its base peak in the mass spectrum, **25** fragments to give **27** and **28**, with only a minor peak corresponding to **26**.

Thus a different route was required and was developed for the synthesis of tertiary pipecolic acid **3** as shown in Scheme II. Tryptophan methyl ester (**29**)[19] was alkylated with benzyl 2,6-dibromohexanoate (**30**), readily prepared from 6-bromohexanoic acid,[20] to give the diester **31** as a mixture of diastereomers. Hydrogenolysis gave the amino acid **3**.

The remaining indole amino acids **1** and **2** could be made by either of the two procedures (Scheme III). Controlled esterification of 2,6-pyridinedicarboxylic acid (**32**) gave the monomethyl ester **34** in 40% yield.[21] This was converted to the methyl *tert*-butyl diester **37**, hydrogenated, alkylated with tryptophyl bromide, and treated with acid, as before, to give the indole amino acid **2** in 66% overall yield from **34**. Alkylation of tryptamine (**46**) with dimethyl 2,6-dibromopimelate (**47**)[22] or alkylation of dimethyl 2,3-piperidinedicarboxylate (**40**) with tryptophyl bromide, followed by a controlled hydrolysis of the resulting **45**, also gave **2**.

The same sequences, using picolinic acid (**33**) instead of **32** and benzyl 2,6-dibromohexanoate (**30**) in place of **47**, gave the amino acid **1** in 56% overall yield. This could also be made by alkylation of benzyl pipecolate (**41**)[23] with tryptophyl bromide to give **43**, followed by hydrogenolysis to **1**.

Cyclizations to Octahydroindolo[2,3-*a*]quinolizines. The four octahydroindolo[2,3-*a*]quinolizines **5–8** were obtained in 99%, 60%, 83%, and 62% isolated yields, respectively, by treating the appropriate acids **1–4** with phenylphosphonic dichloride ($PhPOCl_2$) at 105 °C for 1–2 min. No other products were observed as judged by TLC, HPLC, and NMR.

The tryptophan derivative **7** was obtained as a 4/1 mixture of the two possible diastereomers, which were readily separated by TLC. Since (*S*)-tryptophan was the precursor to **7**, both diasteriomers have the *S* configuration at C-6. The major isomer was hydrolyzed to acid **48** and treated with phosphorous oxychloride to generate the iminium salt which was reduced directly to give the tetrahydro-β-carboline **5** (Scheme IV). The product thus obtained had $[\alpha]^{20}_D$ +89°, opposite to that of known **5b** ([α]

(18) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon: Oxford, 1969; p 271.

(19) Peter, H.; Brugger, M.; Schreiber, J.; Eschenmoser, A. *Helv. Chim. Acta* **1963**, *46*, 577.

(20) Chen-e, Y.; Shchukina, M. N. *J. Gen. Chem. USSR (Engl. Transl.)* **1955**, *25*, 1917.

(21) Other methods to make **34**, based on 2,6-disubstituted pyridines, are as follows: Ooi, G. K. S.; Magee, R. J. *Inorg. Nucl. Chem.* **1970**, *32*, 3315. Mathes, W.; Sauermilch, W.; Klein, T. *Chem. Ber.* **1953**, *86*, 584. Matsumoto, J.; Tomimoto, K. Japan Kokai 73 80570; *Chem. Abstr.* **1974**, *80*, 108385. Vasa, V. B.; Parameswaran, V. K.; Khorana, M. L.; Tipnis, H. P. *Indian J. Pharm.* **1968**, *30*, 282. See also ref 7.

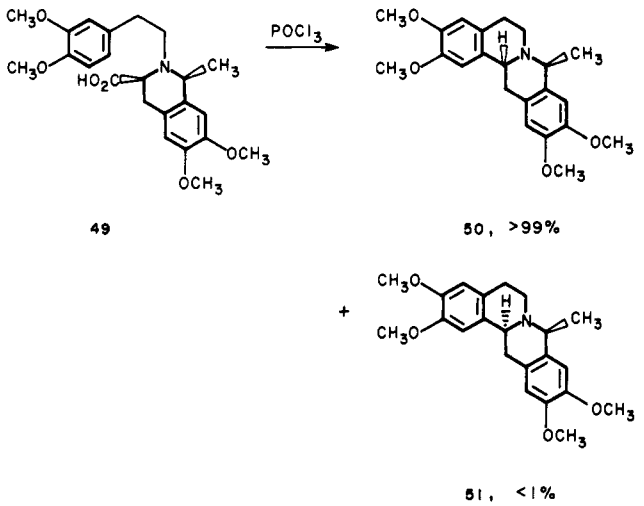
(22) Fehnel, E. A.; Oppenlander, G. C. *J. Am. Chem. Soc.* **1953**, *75*, 4660.

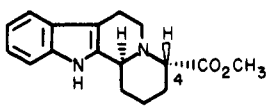
(23) Padgett, H. C.; Csendes, I. G.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 3492.

−86°, −84°).[24] Thus the absolute stereochemistry of the major product is represented by **7a**. This result parallels that of similar cyclizations of tryptophan derivatives.[25]

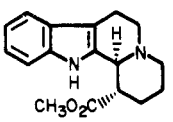
In the case of the transformation **2** → **6**, diastereomers were obtained in a ratio of 3/1. These could be separated by chromatography on alumina, and the isomers were identified by NMR. The major isomer proved to be **6a** (equatorial C-4 H at 4.5 ppm) and the minor isomer **6b** (axial C-4 H at 3.2 ppm).

An interesting comparison can be made between this cyclization and a similar one in the tetrahydroisoquinoline series. When amino acid **49** was treated with $POCl_3$, followed by an acid treatment, the product **50** was obtained.[3] Although the relative stereochemistry of the major product is the same as in our indole cyclization, the stereoselectivity is much better, giving <1% of the minor isomer **51**. This difference may be due to the greater reactivity of the indole compared to the dimethoxybenzene. Also, the indole cyclization product may be partially isomerizing under the reaction conditions to give more of **6b** (presumably the thermodynamically favored product).[26]



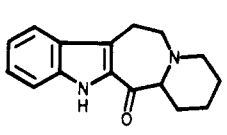


6a
6b, C-4-H-α

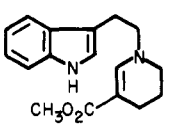


8a
8b, C-12b-H-β

In a preliminary reaction using $POCl_3$ rather than $PhPOCl_2$ as the reaction medium for the decarbonylation of **1**, the product was a 4/1 mix of **5** and **52**, in which Friedel–Crafts acylation by the acid chloride had taken place competitively with decarbonylation. It was felt that an increased temperature would favor decarbonylation, so the higher boiling $PhPOCl_2$ was tried. Suprisingly, both at 100 °C as well as 175 °C the product was only **5**. Thus, not only the temperature but also the choice of reagent seems to determine the reaction products.



52



53

Cyclization of **4** gave only **8a**, with no evidence for the presence of isomer **8b**. This product was identical with that prepared by the acid-catalyzed cyclization of **53** as described earlier.[27] Decarbonylation of **4** with *p*-toluenesulfonyl chloride in pyridine[28] produced only the tetrahydropyridine **53** and no cyclization. This reaction failed to give any recognizable product when applied to amino acid **1**.

In summary, this process represents a new method for the synthesis of the octahydroindolo[2,3-*a*]quinolizine ring system present in a large number of indole alkaloids. The ready access to a large number of optically active amino acids makes for broad flexibility in synthetic design. We are currently applying this methodology to the synthesis of naturally occurring indole alkaloids.

Experimental Section[29]

Methyl 2-[(*tert*-Butyloxy)carbonyl]nicotinate (10). To a solution of methyl 2-carboxynicotinate (**9**,[7] 25 g) in *tert*-butyl alcohol (250 mL) and pyridine (75 mL), cooled in an ice bath, was added *p*-toluenesulfonyl chloride (62 g) in one portion. After being stirred for 2 h, the mixture was poured into saturated $NaHCO_3$ (1 L), and the resulting deep red solution was stirred 1 h at room temperature, followed by extraction with Et_2O (5 × 250 mL). The combined Et_2O fractions were washed with saturated NaCl (250 mL), the NaCl solution was back-extracted with Et_2O (100 mL), and the combined Et_2O fractions were dried ($MgSO_4$), evaporated, and distilled [110 °C (0.3 mm)] to give 31.14 g (95%) of **10**: IR 3050, 1740, 1565 cm^{-1}; ^1H NMR (90 MHz) δ 8.66 (dd, J = 1.6, 4.5 Hz, 1 H), 8.10 (dd, J = 7.5, 1.6 Hz, 1 H), 7.38 (dd, J = 4.5, 7.5 Hz, 1 H), 3.86 (s, 3 H), 1.61 (s, 9 H). Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.7; H, 6.4; N, 5.9. Found: C, 60.5; H, 6.3; N, 5.7.

***tert*-Butyl *cis*-3-(Methoxycarbonyl)pipecolate (11).** A solution of diester **10** (56.17 g) in MeOH (1.2 L) with 10% Pd/C (5.5 g) was hydrogenated for 3 days. The solution was filtered, the filtrate evaporated, and the residue recrystallized from hexanes (280 mL) to give 46.63 g (83%) of **11**: mp 72–73 °C; IR (Nujol) 3450, 1745, 1320 cm^{-1}; NMR (250 MHz) δ 3.63 (s, 3 H), 3.57 (d, J = 3.5 Hz, 1 H), 3.05–2.93 (m, 2 H), 2.74–2.62 (m, 1 H), 2.18–2.02 (m, 2 H), 1.87–1.70 (m, 1 H), 1.65–1.40 (m, 2 H), 1.45 (s, 9 H). Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.2; H, 8.7; N, 5.8. Found: C, 59.4; H, 8.8; N, 5.7.

3-(Methoxycarbonyl)pipecolic Acid (12). A solution of nicotinate **9** (11.1 g) in MeOH (200 mL) with 10% Pd/C (1.1 g) was hydrogenated for 48 h, diluted with 300 mL MeOH, heated to boiling, and filtered. The filtrate was evaporated to give 11.95 g (96%) of **12** as the hemimethanolate: mp 165, 216–218 °C dec; IR (KBr) 1750, 1620, 1435 cm^{-1}; ^1H NMR (D_2O, 90 MHz) δ 3.69 (d, J = 4 Hz, 1 H), 3.59 (s, 3 H), 3.42–3.16 (m, 2 H), 3.08–2.72 (m, 1 H), 2.20–1.20 (m, 4 H); ^{13}C NMR (D_2O, 25 MHz) δ 174.6, 171.7, 57.9, 52.6, 43.7, 39.8, 24.2, 18.5. Anal. Calcd for $C_8H_{13}NO_4 \cdot 0.5CH_3OH$: C, 50.2; H, 7.4; N, 6.9. Found: C, 50.2; H, 7.4; N, 6.9.

1-[(*tert*-Butyloxy)carbonyl]-3-(methoxycarbonyl)pipecolic Acid (13). To a suspension of **12**·0.5MeOH (5.0 g) in 50% aqueous dioxane (35 mL) and triethylamine (5.6 mL) was added 2-[[[(*tert*-butyloxy)carbonyl]oxy]imino]-2-phenylacetonitrile (Boc-ON, 8.06 g). After the mixture was stirred at room temperature for 16 h, water (45 mL) and EtOAc (60 mL) were added. The EtOAc phase was washed with water (25 mL), the combined

(24) Akimoto, H.; Okamura, K.; Yiu, M.; Shiori, T.; Kuramoto, M.; Kikugawa, Y.; Yamada, S.-I. *Chem. Pharm. Bull.* **1974**, *22*, 2614. Pospisek, J.; Koblicova, Z.; Trojanek, J. *Chem. Ind. (London)* **1969**, 25 and references therein.

(25) Ungemach, F.; Soerens, D.; Weber, R.; DiPierro, M.; Campos, O.; Mokry, P.; Cook, J. M. *J. Am. Chem. Soc.* **1980**, *102*, 6976.

(26) Ono, K.; Kawakami, H.; Katsube, J. *Heterocycles* **1980**, *14*, 411.

(27) Wenkert, E.; Dave, K. G.; Haglid, F. *J. Am. Chem. Soc.* **1965**, *87*, 5461.

(28) Sheehan, J. C.; Frankenfeld, J. W. *J. Org. Chem.* **1962**, *27*, 628.

(29) Evaporations were done under aspirator vacuum with a Berkeley rotary evaporator. Melting points were uncorrected, and IR spectra were recorded for liquid films, unless otherwise indicated. ^1H NMR spectra were recorded in $CDCl_3$ solution, in parts per million downfield from Me_4Si. ^{13}C NMR spectra were recorded relative to $CDCl_3$ solvent at 77.0 ppm. Pyridine, *tert*-butyl alcohol, and CH_3CN were distilled from CaH_2. Simple distillations were performed on a rotating bulb-to-bulb apparatus. Hydrogenations were done at 50 psi of H_2 on a Parr apparatus. Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley, CA.

water phases were washed with EtOAc (50 mL), and the EtOAc washing was reextracted once with water (25 mL). The combined water extracts were acidified with citric acid and extracted with Et_2O. The Et_2O extract was dried ($MgSO_4$) and evaporated to give **13** (7.05 g, 100%) which was used without further purification. An analytical sample was obtained by adding a concentrated $CHCl_3$ solution dropwise to hexane with rapid stirring: mp 156–157 °C cor; IR (KBr) 1760, 1680, 1410 cm^{-1}; NMR (90 MHz) δ 8.72 (br s, 1 H), 5.57–5.21 (m, 1 H), 4.17–3.80 (m, 1 H), 3.65 (s, 3 H), 3.0–1.3 (m, 6 H), 1.46 (s, 9 H). Anal. Calcd for $C_{13}H_{21}NO_6$: C, 54.3; H, 7.4; N, 4.9 Found: C, 54.1; H, 7.2; N, 4.8.

Benzyl *cis*-1-[(*tert*-Butyloxy)carbonyl]-3-(methoxycarbonyl)pipecolate (14). The acid **13** (7.05 g) and *N,N'*-diisopropyl-*O*-benzylisourea[8] (6.32 g) in dioxane (20 mL) were stirred at 50 °C for 16 h. Cooling, filtering, and evaporating left a residue which was heated at 120–130 °C (0.06 mm). The residual product (9.29 g, 100%) was used without further purification. An analytical sample was obtained by chromatography on silica gel with CH_2Cl_2/hexane (1/1) as the eluant: IR 1745 1705, 1400, 740, 635 cm^{-1}; ^1H NMR (60 MHz) δ 7.27 (s, 5 H), 5.68–4.92 (m, 3 H), 4.18–3.36 (m, 4 H), 2.94–1.20 (m, 15 H). Anal. Calcd for $C_{20}H_{27}NO_6$: C, 63.6; H, 7.2; N, 3.7. Found C, 63.9; H, 7.2; N, 3.6.

Benzyl *cis*-3-(Methoxycarbonyl)pipecolate (15). Compound **14** (8.94 g) was dissolved in 70% aqueous TFA and kept for 7 h at 0 °C. After evaporation at 50 °C, a K_2CO_3 solution and EtOAc were added to the cooled residue. The alkaline aqueous phase was extracted with EtOAc, and the EtOAc extracts washed with saturated NaCl, dried ($MgSO_4$), and evaporated to give crude **15** (6.50 g, 99%), which was used as such. An analytical sample was obtained by distillation: bp 140–160 °C (0.04 mm); IR 2940 1730, 1445, 775, 700 cm^{-1}; ^1H NMR (90 MHz) δ 7.30 (s, 5 H), 5.12 (s, 2 H), 3.64 (d, J = 4 Hz, 1 H), 3.52 (s, 3 H), 3.1–1.3 (m, 8 H). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 65.0; H, 6.9; N, 5.1. Found: C, 64.7; H, 6.9; N, 5.2.

Benzyl *cis*-3-(Methoxycarbonyl)-1-[2-(3-indolyl)ethyl]pipecolate (17). A mixture of tryptophyl bromide (**16**,[12] 1.00 g), pipecolate **15** (1.24 g), $NaHCO_3$ (1.35 g), and CH_3CN (2.8 mL) was refluxed with vigorous stirring for 24 h. The mixture was diluted with water and extracted twice with CH_2Cl_2. The CH_2Cl extracts were dried (Na_2SO_4) and evaporated, and the residue was chromatographed on silica (18 g, elution with 20% EtOAc in CH_2Cl_2) to give 1.59 g (85%) of **17**: IR 1730 1445, 1425, 725, 685 cm^{-1}; ^1H NMR (250 MHz) δ 8.06 (br s, 1 H), 7.57 (d, J = 7.8 Hz, 1 H), 7.37–7.26 (m, 6 H), 7.17 (td, J = 7.5, 1.0 Hz, 1 H), 7.08 (td, J = 7.5, 1.0 Hz, 1 H), 6.91 (d, J = 2.2 Hz, 1 H), 5.23 (d, J = 12.5 Hz, 1 H), 5.07 (d, J = 12.5 Hz, 1 H), 4.11 (d, J = 4.8 Hz, 1 H), 3.50 (s, 3 H), 3.03–2.73 (m, 7 H), 2.00–1.88 (m, 2 H), 1.82–1.50 (m, 2 H). Anal. Calcd for $C_{25}H_{28}N_2O_4$: C, 71.4; H, 6.7; N, 6.7. Found: C, 71.3; H, 6.7; N, 6.6.

***tert*-Butyl *cis*-3-(Methoxycarbonyl)-1-[2-(3-indolyl)ethyl]pipecolate (18).** Following exactly the procedure for the preparation of benzyl ester **17**, the *tert*-butyl ester **18** was prepared in 90% yield: ^1H NMR (250 MHz) δ 7.97 (br s, 1 H), 7.64 (d, J = 7.7 Hz, 1 H), 7.35 (d, J = 7.7 Hz, 1 H), 7.19 (td, J = 7.4, 1.2 Hz, 1 H), 7.11 (td, J = 7.4, 1.2 Hz, 1 H), 7.04 (d, J = 2.1 Hz, 1 H), 4.00 (br s, 1 H), 3.69 (s, 3 H), 3.04–2.75 (m, 7 H), 2.0–1.4 (m, 4 H), 1.44 (s, 9 H); ^{13}C NMR (25 MHz) δ 173.2, 170.0, 136.2, 127.5, 121.5, 118.8, 118.6, 114.0, 111.0, 81.2, 62.0, 56.2, 51.3, 46.6, 44.2, 28.0, 24.5, 23,8, 22.0. Anal. Calcd for $C_{22}H_{30}N_2O_4$: C, 68.4; H, 7.8; N, 7.3. Found: C, 68.5; H, 7.7; N, 7.3.

Spiro[cyclopropane-1,3'-indolenine] (19). A mixture of tryptophyl bromide[12] (**16**, 2.00 g), K_2CO_3 (8.2 g, pretreated by heating at 400 °C), and CH_3CN (40 mL) was refluxed under N_2 for 8 h. The mixture was filtered, the filtrate evaporated, and the residue distilled [75 °C (0.3 mm)] to give 1.09 g (85%) of cyclopropane **19**: mp 50–52 °C; IR (Nujol) 1630 1600, 1525, 1465, 770, 750 cm^{-1}; ^1H NMR (250 MHz) δ 7.86 (s, 1 H), 7.75 (d, J = 7.7 Hz, 1 H), 7.36 (td, J = 7.5, 1.1 Hz, 1 H), 7.24 (td, J = 7.4, 0.8 Hz, 1 H), 7.04 (d, J = 7.3 Hz, 1 H), 2.04–1.93 (m, 2 H), 1.87–1.75 (m, 2 H); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 173.4, 155.4, 139.4, 126.0, 124.7, 120.8, 117.1, 36.5, 14.9; UV (hexane) λ_{max} 256 nm (ϵ 39 000), 285 (18 000), 296 (11 000). Anal. Calcd for $C_{10}H_9N$: C, 83.9: H, 6.3; N, 9.8. Found: C, 83.9; H, 6.4; N, 9.7.

3-(Methoxycarbonyl)-1-[2-(3-indolyl)ethyl]pipecolic Acid (4). (a) From Benzyl Ester 17. A solution **17** (2.06 g) in MeOH (200 mL) with 10% Pd/C (190 mg) was hydrogenated for 15 h. The mixture was diluted to 2 L with MeOH, heated to boiling, filtered, cooled, and evaporated to give 1.58 g (98%) of acid **4**: mp 225 °C dec (from MeOH); IR (KBr) 1750, 1610, 1450, 730 cm^{-1}. Anal. Calcd for $C_{18}C_{22}N_2O_4$: C, 65.4; H, 6.7; N, 8.5. Found: C, 65.2; H, 6.7; N, 8.4.

(b) From *tert*-Butyl Ester 18. A solution of **18** (5.27 g) in *n*-propanol (50 mL), water (50 mL), and acetic acid (10 mL) was refluxed for 5 h. The solution was evaporated and heated (75 °C) in vacuum to give 4.57 g (100%) of **4** identical with that prepared from **17**.

Methyl 3-bromo-2-(3-indolyl)propionate (25) was prepared as directed for the preparation of **23**.[17] This gave an 8/1 mixture of **25** and **23**: ^1H NMR (of **25**, 250 MHz) δ 8.20 (br s, 1 H), 7.72 (d, J = 7 Hz, 1 H), 7.39 (d, J = 7 Hz, 1 H), 7.33–7.08 (m, 3 H), 4.36 (dd, J = 10.7, 5.1 Hz, 1 H), 4.03 (t, J = 9.8 Hz, 1 H), 3.75 (s, 3 H), 3.65 (dd, J = 9.8, 5.1 Hz, 1 H); ^{13}C NMR (25 MHz) δ 172.5, 135.9, 125.6, 122.6, 122.2, 119.8, 118.3, 111.4, 110.8, 51.9, 45.9, 31.8; mass spectrum, m/e (relative intensity) 283 (24), 281 (24), 224 (30), 222 (31), 188 (32), 143 (100), 130 (22), 115 (36).

Benzyl 2,6-Dibromohexanoate (30). A solution of 6-bromohexanoic acid[20] (19.75 g) in $SOCl_2$ (10 mL) was refluxed for 2 h. Excess $SOCl_2$ was removed under reduced pressure, the last traces being removed by entrainment with $CHCl_3$. The residual oil was treated with Br_2 (8.0 mL) at 100 °C for 3 h, evaporating the excess Br_2 and fractionally distilling the residue to give 18.09 g of product, bp 101 °C (0.4 mm). A 10.27-g portion of this mixture of acid chloride and bromide was added dropwise to benzyl alcohol (4 mL) with stirring and cooling (ice bath). The product was distilled, giving 8.74 g (68%) dibromo ester **30**: bp 120–140 °C (0.05 mm); ^1H NMR (250 MHz) δ 7.38 (s, 5 H), 5.21 (s, 2 H), 4.26 (t, J = 7.3 Hz, 1 H), 3.37 (t, J = 6.6 Hz, 2 H), 2.27–1.78 (m, 4 H), 1.73–1.40 (m, 2 H). Anal. Calcd for $C_{13}H_{16}HBr_2O_2$: C, 42.9; H, 4.4. Found: C, 42.6; H, 4.3.

Benzyl 1-[1-(Methoxycarbonyl)-2-(3-indolyl)ethyl]pipecolate (31). Tryptophan methyl ester hydrochloride[19] (**29**, 1.00 g) was added over 15 min to a stirred solution of dibromo ester **30** (1.43 g) and K_2CO_3 (2.75 g) in DMF/benzene (5 mL, 1/1) at 90 °C. Stirring was continued for 4 h. The mixture was cooled, poured onto ice–water, and extracted with Et_2O (3 × 50 mL). The combined Et_2O extracts were dried ($MgSO_4$) and evaporated to give a residue which was purified by chromatography on silica (elution with cyclohexane/EtOAc, 7/3) to give 0.73 g (45%) of pipecolate **31**: IR (KBr) 1740, 1450, 1160, 730, 685 cm^{-1}; ^1H NMR (250 MHz) δ 7.96 (br s, 1 H), 7.66 (d, J = 8.0 Hz, 1 H), 7.37–7.02 (m, 9 H), 5.16 (d, J = 8.3 Hz, 1 H), 5.11 (d, J = 8.3 Hz, 1 H), 3.82 (dd, J = 10.3, 4.8 Hz, 1 H), 3.52 (s, 3 H), 3.46–3.23 (m, 3 H), 3.10 (dd, J = 14.0, 4.8 Hz, 1 H), 2.40–2.26 (m, 1 H), 1.96–1.24 (m, 6 H); mass spectrum, m/e (relative intensity) 420 (3.4), 291 (26), 290 (88), 285 (30), 160 (16), 143 (16), 140 (19), 130 (41), 92 (16), 91 (100), 85 (15), 84 (27), 69 (21), 57 (44), 56 (24), 55 (26), 44 (55), 43 (37), 42 (18), 41 (34), 39 (19); calcd for $C_{25}H_{28}N_2O_4$ m/e 420.2050, found m/e 420.2052.

1-[1-(Methoxycarbonyl)-2-(3-indolyl)ethyl]pipecolic Acid (3). The benzyl ester **31** (0.37 g) in 95% EtOH (25 mL) was shaken with hydrogen over 40 mg of 10% Pd/C for 5 h. The mixture was filtered, the solid washed thoroughly with hot EtOH, and the combined filtrate taken to dryness to give 0.25 g (86%) of **3**: mp 114–120 °C (from CH_2Cl_2); IR (KBr) 1740, 1625, 1430, 1200, 735 cm^1. Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.4; H, 6.7; N, 8.5. Found: C, 65.1; H, 6.7; N, 8.4.

6-(Methoxycarbonyl)picolinic Acid (34). A mixture of 6-carboxypicolinic acid (**32**, 20 g), water (100 mL), MeOH (100 mL), and H_2SO_4 (10 mL) was refluxed for 15 min and then stirred at room temperature for 10 h. The solution was poured into 1 L of saturated $NaHCO_3$ and extracted with $CHCl_3$. Evaporation of the $CHCl_3$ gave 6.0 g (25%) of methyl 6-(methoxycarbonyl)-picolinate (**35**). The aqueous phase was acidified with concentrated HCl and extracted with $CHCl_3$. Evaporation of the $CHCl_3$ gave 9.0 g (40%) of **34**: mp 147–148 °C (lit.[21] mp 147–148 °C); ^1H NMR (250 MHz) δ 8.42 (dd, J = 7.8, 0.5 Hz, 1 H), 8.37 (dd, J = 7.8, 0.5 Hz, 1 H), 8.13 (t, J = 7.8 Hz, 1 H), 7.24 (br s, 1 H), 4.04 (s, 3 H).

***tert*-Butyl 6-(Methoxycarbonyl)picolinate (37).** To a suspension of **34** (2.75 g) in *tert*-butyl alcohol (30 mL) and pyridine (10 mL) was added *p*-toluenesulfonyl chloride (5.8 g). After being stirred for 3 h, the homogeneous solution was poured into satu-

rated $NaHCO_3$ (100 mL), stirred 30 min, and extracted with $CHCl_3$ (3 × 100 mL). The $CHCl_3$ extracts were dried (Na_2SO_4) and evaporated, and the residue was distilled [150 °C (0.5 mm)] to give 3.51 g (97%) of **37**: mp 96–99 °C; IR (Nujol) 1720 1565, 1285, 765, 700 cm^{-1}; ^1H NMr (250 MHz) δ 8.28 (dd, J = 7.8, 1.2 Hz, 1 H), 8.22 (dd, J = 7.9, 1.2 Hz, 1 H), 7.98 (t, J = 7.8 Hz, 1 H), 4.02 (s, 3 H), 1.65 (s, 9 H). Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.7; H, 6.4; N, 5.9. Found: C, 60.7; H, 6.3; N, 5.8.

***tert*-Butyl *cis*-6-(Methoxycarbonyl)pipecolate (39).** A solution of **37** (3.35 g) in MeOH (70 mL) with 10% Pd/C (350 mg) was hydrogenated for 40 h. The mixture was filtered, evaporated, and distilled [120 °C (0.3 mm)] to give 3.30 g (96%) of **39**: IR 3400, 2970, 1735, 1435 cm^{-1}; ^1H NMR (250 MHz) δ 3.73 (s, 3 H), 3.38 (dd, J = 11.2, 2.1 Hz, 1 H), 3.24 (dd, J = 11.2, 2.1 Hz, 1 H), 2.35 (br s, 1 H), 2.03–1.92 (m, 3 H), 1.62–1.22 (m, 3 H), 1.47 (s, 9 H). Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.2; H, 8.7; N, 5.8. Found: C, 59.2; H, 8.6; N, 5.7.

***tert*-Butyl Picolinate (36)** was made as described for the preparation of **10** in 87% yield: bp 110 °C (3 mm); IR 2940 1725, 1705, 1589, 1430, 750, 710 cm^{-1}; ^1H NMR (250 MHz) δ 8.75 (dt, J = 4.7, 0.6 Hz, 1 H), 8.06 (d, J = 7.9 Hz, 1 H), 7.81 (t, J = 8.0 Hz, 1 H), 7.44 (dd, J = 7.6, 3.5 Hz, 1 H), 1.65 (s, 9 H). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.0; H, 7.3; N, 7.8. Found: C, 67.0; H, 7.3; N, 7.9.

***tert*-Butyl Pipecolate (38).** A solution of **36** (5.00 g) in MeOH (100 mL) and acetic acid (10 mL) with 10% Pd/C (500 mg) was hydrogenated for 48 h. The mixture was filtered, evaporated to 15 mL, added to saturated $NaHCO_3$ (200 mL), and adjusted to pH 9 with solid K_2CO_3. After extraction with Et_2O (3 × 50 mL), the Et_2O extracts were washed with saturated NaCl (50 mL), dried ($MgSO_4$), and evaporated, and the residue was distilled [70 °C (0.4 mm)] to give 4.83 g (93%) of **38** as an oil that partially solidified at room temperature: IR 3425, 2925, 1730, 1360 cm^{-1}; ^1H NMR (250 MHz) δ 3.23 (dd, J = 7.6, 2.4 Hz, 1 H), 3.08 (dt, J = 9.1, 2.4 Hz, 1 H), 2.65 (td, J = 8.6, 2.7 Hz, 1 H), 1.99–1.37 (m, 7 H), 1.46 (s, 9 H). Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.8; H, 10.3; N, 7.6. Found: C, 64.6; H, 10.4; N, 7.4.

***tert*-Butyl 1-[2-(3-Indolyl)ethyl]pipecolate (42).** A mixture of tryptophyl bromide (**16**, 1.00 g), *tert*-butyl pipecolate (**38**, 0.83 g), $NaHCO_3$ (1.35 g), and CH_3CN (2.8 mL) was refluxed for 23 h. The mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The CH_2Cl_2 extracts were dried (Na_2SO_4) and evaporated, and the residue was chromatographed on silica (20 g, eluted with $CHCl_2$/EtOAc, 2/1) to give 1.12 g (77%) of **42**: mp 151–153 °C; IR (Nujol) 1730, 1150, 1100, 740 cm^{-1}; ^1H NMR (250 MHz) δ 7.99 (br s, 1 H), 7.62 (d, J = 7.5 Hz, 1 H), 7.36 (d, J = 7.7 Hz, 1 H), 7.18 (td, J = 7.3, 1.0 Hz, 1 H), 7.09 (td, J = 7.3, 1.0 Hz, 1 H), 7.03 (d, J = 2.1 Hz, 1 H), 3.27–3.17 (m, 1 H), 3.10–2.88 (m, 4 H), 2.74–2.60 (m, 1 H), 2.39–2.28 (m, 1 H), 1.90–1.60 (m, 5 H), 1.46 (s, 9 H), 1.46–1.34 (m, 1 H). Anal. Calcd for $C_{20}H_{28}N_2O_2$: C, 73.1; H, 8.6; N, 8.5. Found: C, 72.9; H, 8.6; N, 8.4.

Benzyl 1-[2-(3-Indolyl)ethyl]pipecolate (43). A mixture of tryptophyl bromide (**16**, 1.00 g) and benzyl pipecolate (**41**, 0.97 g),[23] treated exactly as in the preparation of **42** above, gave 1.03 g (64%) of **43**: mp 104–105 °C; IR (KBr) 1725 1445, 1345, 735, 695 cm^{-1}; ^1H NMR (250 MHz) δ 7.93 (br s, 1 H), 7.57 (d, J = 7.7 Hz, 1 H), 7.37–7.24 (m, 6 H), 7.18 (td, J = 7.4, 1.2 Hz, 1 H), 7.09 (td, J = 7.4, 1.0 Hz, 1 H), 6.93 (d, J = 1.8 Hz, 1 H), 5.16 (d, J = 12.4 Hz, 1 H), 5.14 (d, J = 12.3 Hz, 1 H), 3.31–3.22 (m, 2 H), 3.04–2.85 (m, 3 H), 2.72–2.61 (m, 1 H), 2.42–2.31 (m, 1 H), 1.94–1.63 (m, 5 H), 1.47–1.34 (m, 1 H). Anal. Calcd for $C_{23}H_{26}N_2O_2$: C, 76.2; H, 7.2; N, 7.7. Found: C, 76.3; H, 7.3; N, 7.7.

1-[2-(3-Indolyl)ethyl]pipecolic Acid (1). (a) From Benzyl Ester 43. A solution of **43** (1.06 g) in 95% EtOH (70 mL) with 10% Pd/C (100 mg) was hydrogenated for 16 h. The catalyst was filtered off, refluxed with EtOH, and filtered again. The combined filtrates were evaporated to giive 0.73 g (92%) of **1**: mp 210–220 °C cor, dec. Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.6; H, 7.4; N, 10.3. Found: C, 70.3; H, 7.4; N, 10.2.

(b) From *tert*-Butyl Ester 42. A solution of **42** (1.13 g) in *n*-propanol (45 mL), water (45 mL), and acetic acid (10 mL) was refluxed for 4 h, the evaporated. The residue was triturated and boiled (5 min) with 50 mL of acetone, cooled to room temperature, and filtered to give 810 mg (86%) of **1**, identical with that prepared from **39**.

***tert*-Butyl *cis*-6-(Methoxycarbonyl)-1-[2-(3-indolyl)-ethyl]pipecolate (44).** A mixture of tryptophyl bromide (**16**, 1.00 g) and **39** (1.08 g) was treated exactly as in the preparation of **38** above, except that the residue was recrystallized from 95% EtOH (12 mL) to give 1.29 g (75%) of **44**: mp 157–161 °C; NMR (250 MHz) δ 8.04 (br s, 1 H), 7.58 (d, J = 7.9 Hz, 1 H), 7.34 (d, J = 7.6 Hz, 1 H), 7.17 (td, J = 7.5, 1.3 Hz, 1 H), 7.08 (td, J = 7.5, 1.3 Hz, 1 H), 6.93 (d, J = 2.3 Hz, 1 H), 3.74 (s, 3 H), 3.40 (dd, J = 8.0, 5.0 Hz, 1 H), 3.26 (dd, J = 9.8, 2.8 Hz, 1 H), 3.08–2.87 (m, 4 H), 1.96–1.72 (m, 5 H), 1.47 (s, 9 H), 1.47–1.34 (m, 1 H). Anal. Calcd for $C_{22}H_{30}N_2O_4$: C, 68.4; H, 7.8; N, 7.2. Found: C, 68.2; H, 7.7; N, 7.2.

Methyl 6-(Methoxycarbonyl)-1-[2-(3-indolyl)ethyl]pipecolate (45). Method a. A mixture of dimethyl 2,6-dibromopimelate (**47**,[22] 1.92 g), tryptamine hydrochloride (**46**, 1.00 g), K_2CO_3 (4.00 g), and DMF/benzene (1/1, 20 mL) was stirred at 90 °C for 10 h. The mixture was poured into ice water and extracted with Et_2O (3×). The Et_2O phase was extracted with 1 N HCl (3×), and the resulting solid and HCl solution were made alkaline with K_2CO_3 and extracted with Et_2O (3×) and $CHCl_3$. These extracts were washed with saturated NaCl, dried ($MgSO_4$), annd evaporated to give 1.62 g (93%) of a 1/1 mix of *cis*- and *trans*-**45**. Recrystallization from EtOH gave pure *cis*-**45**: mp 161–163 °C cor; IR (KBr) 1740, 1455, 1430, 750 cm^{-1}; ^1H NMR (250 MHz) δ 7.98 (br s, 1 H), 7.55 (d, J = 7.5 Hz, 1 H), 7.34 (d, J = 7.8 Hz, 1 H), 7.18 (td, J = 7.4, 1.0 Hz, 1 H), 7.10 (td, J = 7.4, 1.2 Hz, 1 H), 6.94 (d, J = 2.3 Hz, 1 H, 3.75 (s, 6 H), 3.44 (dd, J = 7.9, 4.6 Hz, 2 H), 2.95 (s, 4 H), 1.95–1.76 (m, 5 H), 1.49–1.36 (m, 1 H). Anal. Calcd for $C_{19}H_{24}N_2O_4$: C, 66.3; H, 7.0; N, 8.1. Found: C, 66.3; H, 7.1; N, 8.1.

Method b. A mixture of tryptophyl bromide (**16**, 1.00 g) and methyl 6-(methoxycarbonyl)pipecolate (**40**, 0.90 g) was treated as in the preparation of **44** above to give 1.24 g (82%) of *cis*-**45**, identical with that prepared above.

1-[2-(3-Indolyl)ethyl]-6-(methoxycarbonyl)pipecolic Acid (2). (a) From *tert*-Butyl Ester 44. A solution of **44** (105 mg) in *n*-propanol (4 mL), water (4 mL), and acetic acid (1 mL) was refluxed for 4 h. The solution was evaporated to a residue, which was dissolved in CH_2Cl_2, allowed to stand for 24 h, decanted from a small amount of precipitate, and evaporated to give 89 mg (94%) of *cis*-**2** as an amorphous solid hydrate: IR (KBr) 1745, 1630, 1200, 735 cm^{-1}; ^1H NMR (250 MHz) δ 8.04 (br s, 1 H), 7.52 (d, J = 7.5 Hz, 1 H), 7.37 (d, J = 7.5 Hz, 1 H), 7.20 (td, J = 7.5, 1.2 Hz, 1 H), 7.12 (td, J = 7.5, 1.2 Hz, 1 H), 7.02 (d, J = 1.8 Hz, 1 H), 5.52 (br s, 1 H), 3.67 (s, 3 H), 3.58–3.49 (m, 2 H), 3.06–2.97 (m, 4 H), 2.1–1.4 (m, 6 H). Anal. Calcd for $C_{18}H_{22}N_2O_4 \cdot H_2O$: C, 62.1; H, 6.9; N, 8.0. Found: C, 62.3; H, 6.6; N, 7.6.

(b) From Dimethyl Ester 45. A solution of **45** (0.3 g) in 2 N methanolic KOH (0.65 mL) was refluxed for 4 h. The solvent was evaporated at room temperature and the residue purified by TLC (developed with 12% CH_3OH in $CHCl_3$). This gave **2** (126 mg, 44%) together with recovered **45** (95 mg) and 43 mg of diacid.

1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine (5). The acid **1** (100 mg) was added to $PhPOCl_2$ (0.6 mL) at 105 °C and stirred for 90 s. After the mixture was cooled, dry K_2CO_3 (1.2 g) was added, and this suspension was diluted with water and extracted with $CHCl_3$ (3×). The $CHCl_3$ extracts were washed with water, and the water was back-extracted with $CHCl_3$. The combined $CHCl_3$ extracts were dried ($MgSO_4$) and evaporated to give 81 mg (99%) of **5**: mp 147–149 °C (on recrystallization from benzene/cyclohexane) (lit. mp 152–155 °C,[30] 149–150 °C[31]); IR (KBr) 2930, 735 cm^{-1}; ^1H NMR (250 MHz) δ 7.74 (br s, 1 H), 7.47 (d, J = 6.9 Hz, 1 H), 7.31 (d, J = 6.9 Hz, 1 H), 7.13 (td, J = 6.9, 1.8 Hz, 1 H), 7.08 (td, J = 6.9, 1.3 Hz, 1 H), 3.24 (d, J = 10 Hz, 1 H), 3.13–2.93 (m, 3 H), 2.78–2.57 (m, 2 H), 2.47–2.33 (m, 1 H), 2.14–2.03 (m, 1 H), 1.98–1.41 (m, 5 H).

4-(Methoxycarbonyl)-1,2,3,4,6,7,12,12b-octahydroindolo-[2,3-*a*]quinolizine (6). A mixture of acid **2** (250 mg) and $PhPOCl_2$ (2.5 mL) was heated at 105 °C for 75 s. The solution was cooled, mixed with 1 N HCl (25 mL), and heated at 70 °C for 5 min. The cooled mixture was made alkaline with K_2CO_3

(30) Wenkert, E.; Wickberg, B. *J. Am. Chem. Soc.* **1962**, *84*, 4914.
(31) Scherer, C. A.; Dorschel, C. A.; Cook, J. M.; LeQuesne, P. W. *J. Org. Chem.* **1972**, *37*, 1083.

and extracted three times with $CHCl_3$. The $CHCl_3$ extracts were dried ($MgSO_4$) and evaporated, and the residue was chromatographed on silica (elution with 5% CH_3OH in $CHCl_3$) to give **6**, 130 mg (60%), as an oil. Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.8; H, 7.1; N, 9.8. Found: C, 71.5; H, 7.1; N, 9.5.

In another experiment, 100 mg of **2** was cyclized as above and the crude product chromatographed on alumina (12 g, activity III, elution with CH_2Cl_2) to give 40 mg (46%) of **6a**, followed by 14 mg (16%) of **6b**. For **6a**: ^1H NMR (250 MHz) δ 7.77 (br s, 1 H), 7.47 (dd, J = 7.5, 1.9 Hz, 1 H), 7.28 (dd, J = 6.8, 1.9 Hz, 1 H), 7.12 (td, J = 6.8, 1.6 Hz, 1 H), 7.07 (td, J = 7.7, 1.5 Hz, 1 H), 4.56–4.46 (m, 1 H), 3.78 (m under CH_3, 1 H), 3.76 (s, 3 H), 3.22 (td, J = 11.3, 4.3 Hz, 1 H), 3.03–2.85 (m, 2 H), 2.70–2.59 (m, 1 H), 2.14–1.83 (m, 3 H), 1.75–1.52 (m, 3 H). For **6b**: ^1H NMR (250 MHz) 7.72 (br s, 1 H), 7.47 (d, J = 7.5 Hz, 1 H), 7.29 (d, J = 7.5 Hz, 1 H), 7.13 (t, J = 6.9 Hz, 1 H), 7.08 (t, J = 7.1 Hz, 1 H), 3.80 (s, 3 H), 3.41 (d, J = 10 Hz, 1 H), 3.18 (dd, J = 10.9, 3.4 Hz, 1 H), 3.13–2.96 (m, 2 H), 2.78–2.66 (m, 1 H), 2.59–2.47 (m, 1 H), 2.18–1.54 (m, 6 H).

6-(Methoxycarbonyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (7). The acid **3** (70 mg) was cyclized as described for **6**. The crude product (52 mg) was purified by silica TLC (developed with EtOAc/cyclohexane, 3/7) to give 40 mg (66%) of **7a**, followed by 10 mg (17%) of **7b**. For **7a**: $[\alpha]^{20}_D$ +97° (c 1, CH_3OH); ^1H NMR (60 MHz) δ 7.72 (br s, 1 H), 7.6–6.9 (m, 4 H), 4.40–4.04 (m, 1 H), 3.84 (dd, J = 4.8, 2.8 Hz, 1 H), 3.60 (s, 3 H), 3.3–2.9 (m, 4 H), 2.2–1.3 (m, 6 H); mass spectrum calcd for $C_{17}H_{20}N_2O_2$ m/e 284.1525, found m/e 284.1520. For **7b**: $[\alpha]^{20}_D$ −69° (c 1, CH_3OH); ^1H NMR (60 MHz) δ 7.88 (br s, 1 H), 7.5–6.9 (m, 4 H), 3.76 (s, 3 H), 3.7–1.4 (m, 12 H); mass spectrum calcd for $C_{17}H_{20}N_2O_2$ m/e 284.1525, found m/e 284.1522.

5a from 7a. A solution of **7a** (300 mg), KOH (220 mg) in CH_3OH (2 mL), and water (0.4 mL) was heated at 70 °C for 4 h. The mixture was evaporated, and the residue was dissolved in a minimum of water, filtered, and acidified with 6 N HCl until a precipitate formed. The mixture was cooled and decanted, and the precipitate was washed with water and dried to give 210 mg (74%) of **48**. This crude acid (120 mg) was added to $POCl_3$ (2 mL) at 100 °C, and the mixture was stirred for 75 s. The solvent was evaporated, and dioxane (10 mL) and $NaBH_4$ (205 mg) were added at 0 °C. The mixture was then stirred at room temperature for 5 h, diluted with water, and extracted three times with $CHCl_3$. The $CHCl_3$ fractions were dried ($MgSO_4$) and evaporated, and the residue was chromatographed on silica (elution with CH_2Cl_2/CH_3OH, 9/1) to give 17.0 mg of **5a**, identical (TLC, mass spectrum) with racemic **5** prepared from **1**: $[\alpha]_D$ + 89.2° (c 1.3, CH_3OH) [lit.[24] $[\alpha]_D$ −84°, −86.5 (c 1, CH_3OH) for **5b**].

1-(Methoxycarbonyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (8). The acid **4** (617 mg) was heated in $PhPOCl_2$ (12 mL) at 95 °C for 2.5 min. To this was added 1 N HCl (50 mL), and the resulting solution was stirred at 70 °C for 5 min. The cooled solution was made alkaline with K_2CO_3 and extracted with $CHCl_3$ (3×), the dried ($MgSO_4$) extracts were evaporated, and the residue was subjected to TLC (developed with EtOAc/cyclohexane, 2/3) to give 331 mg (62%) of **8**: mp 145–147 °C cor (on recrystallization from EtOAc) (lit. mp 133–134 °C,[27] 144–145 °C[32]); ^1H NMR (250 MHz) δ 8.16 (br s, 1 H), 7.47 (d, J = 7.5 Hz, 1 H), 7.27 (d masked by $CHCl_3$, 1 H), 7.13 (td, J = 7.5, 1.4 Hz, 1 H), 7.06 (td, J = 7.2, 1.3 Hz, 1 H), 3.82 (d masked by CH_3, 1 H), 3.80 (s, 3 H), 3.3–2.6 (m, 7 H), 2.20 (m, 1 H), 1.9–1.6 (m, 3 H). Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.8; H, 7.1; N, 9.8. Found: C, 71.7; H, 7.0; N, 9.8. This material was identical with a sample prepared by the literature method.[27]

Methyl 1-[2-(3-Indolyl)ethyl]-1,4,5,6-tetrahydronicotinate (53). To a suspension of amino acid **4** (100 mg) in *tert*-butyl alcohol (3 mL) and pyridine (3 mL) was added *p*-toluenesulfonyl chloride (115 mg). After being stirred at 0 °C for 90 min, the solution was added to saturated $NaHCO_3$ (20 mL) and stirred at room temperature for 5 h. It was then diluted with water and extracted with $CHCl_3$ (2 × 25 mL). The $CHCl_3$ extracts were dried ($MgSO_4$) and evaporated to give 70 mg (80%) of **53**, identical (TLC, NMR) with a sample prepared by the literature method.[26]

Registry No. **1**, 79233-55-9; **2**, 79233-56-0; **3**, 79233-57-1; **4**, 79233-58-2; (±)-**5**, 46798-86-1; **5a**, 15051-70-4; **6a**, 79233-59-3; **6b**, 79254-99-2; **7a**, 60873-74-7; **7b**, 79298-98-9; **8a**, 79255-00-8; **9**, 24195-02-6; **10**, 79233-60-6; **11**, 79233-61-7; **12**, 79233-62-8; **13**, 79233-63-9; **14**, 79233-64-0; **15**, 79233-65-1; **16**, 3389-21-7; **17**, 79255-01-9; **18**, 79233-66-2; **19**, 6243-48-7; **23**, 79233-67-3; **25**, 79233-68-4; **29**·HCl, 7524-52-9; **30**, 79233-69-5; **31** (isomer 1), 79233-70-8; **31** (isomer 2), 79233-71-9; **32**, 499-83-2; **34**, 7170-36-7; **35**, 5453-67-8; **36**, 79233-72-0; **37**, 79233-73-1; **38**, 71170-78-0; **39**, 79233-74-2; **40**, 59234-46-7; **41**, 38068-75-6; **42**, 79233-55-9; **43**, 79233-75-3; **44**, 79233-76-4; *cis*-**45**, 79233-77-5; *trans*-**45**, 79233-78-6; **46**·HCl, 343-94-2; **47**, 868-73-5; **48**, 79233-79-7; **49**, 79297-65-7; **50**, 79297-66-8; **53**, 4695-82-3; 6-bromohexanoic acid, 4224-70-8.

(32) Lounasmaa, M.; Jokela, R. *Tetrahedron* **1978**, *34*, 1841.