$[\alpha]^{25}D$ −64.45° (*c* 0.568, benzene), $\nu_{max}^{CCl_4}$ 1710, 1650, 1250, and 1080 cm^{-1}; λ_{max}^{EtOH} mμ (ε) 218 (10,630); nmr ($CDCl_3$) δ 0.83–0.93 (9 H), 3.70 (3 H, singlet), and 6.93 (1 H, broad singlet); mass spectrum *m/e* 266 (M^+), 234, 167, and 134 (base peak). The ord and cd spectra are shown in Figures 3 and 4.

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.21; H, 10.13.

(2*R*)-[1-Methyl-7-oxabicyclo[4.1.0]heptan-(4*R*)-yl]-6-methyl-4-heptanone (20). (2*R*)-[4-Methyl-3-cyclohexen-(1*R*)-yl]-6-methylheptan-4-one (**10**, 6.65 g, 0.03 mole) in 45 ml of dichloromethane was placed in a 500-ml flask, fitted with magnetic stirrer, thermometer, condenser, and dropping funnel. *m*-Chloroperbenzoic acid (6.4 g, 0.033 mole) in 90 ml of dichloromethane was added dropwise at 23–25° over a 30-min period. The reaction mixture was allowed to stir at this temperature for 2 hr. The excess *m*-chloroperbenzoic acid was destroyed with 35 ml of 10% sodium sulfite solution until a negative test was obtained with starch–iodide paper. The mixture was extracted with three 50-ml portions of dichloromethane and the extracts were washed with 5% sodium bicarbonate and water, and dried with anhydrous sodium sulfate. Evaporation of the solvent and distillation at 104–106° (0.2 mm) gave 5.1 g of epoxide **20**: $[\alpha]^{25}D$ +47.85° (*c* 1.30, benzene); $\nu_{max}^{CHCl_3}$ 1710 and 840 cm^{-1}; nmr ($CDCl_3$) δ 0.80–0.95 (9 H), 1.30 (3 H, singlet), 2.96 and 3.05 (broad singlets, ratio 1:2, 1 H); and mass spectrum *m/e* 238 (M^+), 138 (base peak), 127, 111, 95, 85, and 57.

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.23; H, 11.26.

(+)-Juvabione from Epoxide 20. To an ice-cold solution of diethylamine (4.9 g, 0.067 mole) in 75 ml of dry tetrahydrofuran was added 45.0 ml of a 1.48 *M* solution of *n*-butyllithium in hexane. The entire reaction was carried out in an atmosphere of nitrogen. The reaction mixture was stirred for 30 min and then a solution of 4.1 g (0.0167 mole) of epoxide **20** in 35 ml of dry tetrahydrofuran was added. The mixture was heated to reflux for 3 hr, cooled, and poured into 100 ml of ice water. The mixture was saturated with sodium chloride and the layers were separated. The aqueous layer was extracted with ether and the ether extracts were washed with saturated sodium chloride solution and dried with anhydrous sodium sulfate. Evaporation of the solvent gave 3.9 g of an alcohol mixture containing the desired product **12**.

The alcohol mixture was oxidized with sodium dichromate as described previously. The crude keto aldehyde **14** so obtained was further oxidized to (+)-todomatuic acid with basic silver oxide. The crude (+)-todomatuic acid (0.15 g) was converted to the ester by treatment with an ethereal solution of diazomethane. Column chromatography and distillation at 150–160° (bath temperature) and 0.25 mm gave 20 mg of (+)-juvabione, $[\alpha]^{25}D$ +80° (*c* 1.0, benzene). The ord and cd spectra were identical with those of the natural material.

Acknowledgment. We thank the Physical Chemistry Department, Hoffmann-La Roche Inc., directed by Dr. P. Bommer, for spectral measurements and microanalyses. We are grateful to Professor M. Matsui, University of Tokyo, for samples of (±)-juvabione and (±)-todomatuic acid.

Cyclization of Tryptophan and Tryptamine Derivatives to 2,3-Dihydropyrrolo[2,3-*b*]indoles

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Received July 7, 1969

Abstract: N-Acetylated derivatives of tryptophan and tryptamine (**1–4**) in phosphate buffer at pH 9 with N-bromosuccinimide (NBS) or in methylene chloride containing triethylamine with *t*-butyl hypochlorite give acid-labile tricyclic dihydropyrrolo[2,3-*b*]indoles (**5–8**) characterized by λ_{max} 308 mμ. These cyclizations presumably occur *via* β-haloindolenines, which ring close to β-haloindolines. On standing, the products arise by spontaneous or base-catalyzed dehydrohalogenation. Excess *t*-butyl hypochlorite converts the 2,3-dihydropyrroloindoles to *methyl* and *ethyl* 1-*acetyl*-3*a*-*chloro*-2,3,3*a*,8*a*-*tetrahydropyrrolo*[3,2-*b*]*indolenine*-2-*carboxylate* which on refluxing in aqueous methanol (or ethanol) gave *methyl* (and *ethyl*) *pyrrolo*[2,3-*b*]*indole*-2-*carboxylates* ($\lambda\lambda_{max}$ 332, 272 mμ) as the first synthetic representatives of "anhydrodethiosporidesmin," the dehydration and desulfurization product from sporidesmin. The tetracyclic system present in the sporidesmins was synthetically approached by *t*-BuOCl oxidation of N-methyl-L-alanyl-L-tryptophan diketopiperazine.

N-Acetyl-L-tryptophan ethyl ester (**1**) or N-acetyl-L-tryptophanamide (**3**) with 1 equiv of NBS in aqueous buffers at pH 8–9 yields a product with strong absorption at 308 mμ which is stable above pH 7, but below this pH[2] rapidly changes to that of an oxindole (λ_{max} 250 mμ). The new chromophore was not observed with skatole, indole-3-propionic acid, or N-acetyltryptophan, indicating some participation reaction of the indole side chain. The present work clarifies the structure and transformations of the products with the unusual absorption at 308 mμ.[3]

The minimum requirement for the formation of products possessing the new chromophore was a 3-(2-acetamidoethyl) side chain or, in the case of tryptophan derivatives, a carboxyl-blocked, N_α-acetylated derivative. N-Benzyloxycarbonyltryptophan, N-trifluoroacetyltryptophan, tryptophan methyl ester, N-acetylhomotryptamine, and tryptamine all failed to produce the chromophore with the addition of 1 equiv of NBS. N-Acetyltryptamine (**4**) was found to produce the chromophore, but at a rate much slower than **1** or **2**; about 15 min were required for the development of maximum intensity.

(1) Associate in the visiting program of the U.S. Public Health Service, 1967–1968.

(2) N. M. Green and B. Witkop, *Trans. N. Y. Acad. Sci., Ser. II*, **26**, 659 (1964).

(3) *Cf.* M. Ohno, T. F. Spande, and B. Witkop, *J. Amer. Chem. Soc.*, **90**, 6521 (1968).

A homogeneous, optically active, bromine-free crystalline product, with strong absorption at 308 mμ, was isolated in 30% yield when a vigorously stirred, very dilute solution of **1** in 0.04 *M* phosphate buffer (pH 9.2) was treated rapidly with 1 equiv of a dilute aqueous solution of NBS at room temperature and the reaction mixture extracted immediately with ether. Although yields based on product isolated were modest, conversions in solution approached 60% based on the molar extinction coefficient (ϵ_{308} 15,700) of pure product.

Combustion analyses and a high-resolution mass measurement of the molecular ion established the composition, $C_{12}H_{16}N_2O_3$ (calculated mol wt, 272.1161, found 272.1166), for the NBS oxidation product of **1**. A low-resolution mass spectrum (Figure 1) showed the following principal peaks: (*m/e*), 230 ($M^+ - CH_2{=}C{=}O$); 157 [$M^+ - (CH_2{=}C{=}O + EtO + CO)$]; 156 [$M^+ - (CH_2{=}C{=}O + EtOH + CO)$]; 130[$M^+ - (CH_2{=}C{=}O + EtO + CO + HCN)$]; and 129 [$M^+ - (CH_2{=}C{=}O + EtOH + CO + HCN)$]. No fragmentations involving the loss of NHAc and NH_2Ac from the molecular ion, a pathway characteristic of the starting material **1**, were observed.

The ir spectrum ($CHCl_3$) had principal absorption bands at 3470 (indole N–H), 1740 (saturated ester C=O), 1660 (tertiary amide), and 1590 cm^{-1} (phenyl).

The nmr spectrum (100 MHz; $CDCl_3$) established the structure **5**, *i.e.*, **ethyl 1-acetyl-2,3-dihydropyrrolo-[2,3-*b*]indole-2-carboxylate,** for the NBS-oxidation product of **1**. It displayed a well-resolved ABX-type 12-line spectrum with one-proton quartets centered at $\delta_A = 3.29$, $\delta_B = 3.65$, and $\delta_X = 5.15$ ppm. Coupling constants were $J_{AX} = 3.4$, $J_{BX} = 10.1$, and $|J_{AB}| = 14.6$ Hz. In addition to signals expected for the carbethoxy group, the acetamido group, and the aromatic ring (see Experimental Section), a broad one-proton signal at 9.3–9.4 ppm, disappearing with D_2O and assigned to a hydrogen-bonded (donor) indole N–H, was observed.

Structure **5** is supported by the facile hydrolysis to an oxindole in dilute acid, in analogy to the acid lability of 2-acetamidoindoles[4] with which they have in common the characteristic uv absorption.

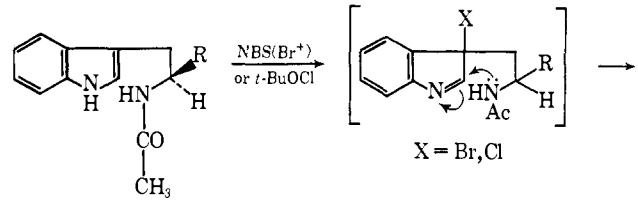
NBS oxidation of the amide **3** followed immediately by extraction with ethyl acetate gave the analogous **1-acetyl-2,3-dihydropyrrolo[2,3-*b*]indole-2-carboxamide** (**7**) (λ_{max}^{EtOH} 308 mμ (ϵ 14,500)) in 30% yield.

A more efficient oxidation procedure used 1 equiv of *t*-butyl hypochlorite in triethylamine-buffered methylene chloride and produced **5** in 80% yield. From N-acetyltryptophan methyl ester **2** the analogous tricyclic methyl ester (**6**) was obtained in 78% yield. Although **1-acetyl-2,3-dihydropyrrolo[2,3-*b*]indole (8)** could not be isolated by the NBS procedure, *t*-butyl hypochlorite oxidation of **4** followed by the addition of 1 equiv of ethanolic NaOH produced **8** (λ_{max}^{EtOH} 308 mμ (ϵ 15,200)) in a yield of 63%.

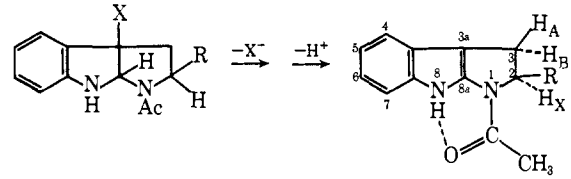
So far only tetrahydropyrrolo[2,3-*b*]indole derivatives have been obtained with quaternary methyl groups in the 3a position. Two different synthetic[5,6] approaches to physostigmine involve similar 3-methylindolenine intermediates and treatment of 2,3-dimethyl-3-cyanomethylindolenine with dry HCl in ethanol affords 1,2-dehydro-2-ethoxy-8a-methylbisnordeoxyeseroline.[7]

(4) J. Kebrle and K. Hoffmann, *Helv. Chim. Acta*, **39**, 116 (1956).
(5) T. Hoshino and T. Kobayashi, *Ann.*, **516**, 81 (1934).
(6) J. Harley-Mason and A. H. Jackson, *J. Chem. Soc.*, 3651 (1954).

However, a simple oxidative one-step cyclization of a tryptophan derivative to the pyrrolo[2,3-*b*]indole systems **5–8** has so far not been possible and for the first time makes this type of tricyclic compound easily accessible.



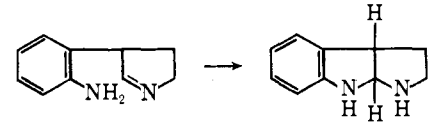
1, R = $CO_2CH_2CH_3$
2, R = CO_2CH_3
3, R = $CONH_2$
4, R = H



5, R = $CO_2CH_2CH_3$; mp 164–165°
6, R = CO_2CH_3; mp 175–177°
7, R = $CONH_2$; mp 243–244°
8, R = H; mp 243–244°

This facile entry into the ring system common to physostigmine (eserine), chimonanthine,[8] and the sporidesmins[9] presumably involves an initially formed 3-haloindolenine which closes to a 3-haloindoline. The consecutive loss of halide ion and a proton (a concerted *trans* dehydrohalogenation is impossible in the *cis*-fused 3-haloindoline) would rearomatize the system and produce the observed products.

A related intramolecular addition has been postulated in the synthesis of tryptamine from phenylhydrazine and γ-chlorobutyraldehyde.[10] The presumed intermediate

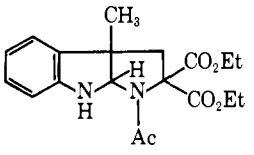


9 10

9 is believed to ring close to the cyclic tautomer of tryptamine,[10] the synthesis of which is under investigation.[11]

Even the acetamido group readily undergoes intramolecular cyclization: the tricyclic deoxyeseroline derivative **11** is found during Fischer-indole synthesis in refluxing glacial acetic acid.[12] Participation of the acetamido ethyl side chain of **1–4** under the *alkaline* conditions of the NBS oxidation would be expected to be even more facile.

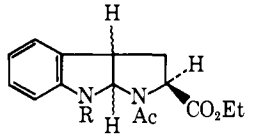
(7) M. Nakazaki, *Bull. Chem. Soc. Jap.*, **32**, 588 (1959).
(8) H. F. Hodson, B. Robinson, and G. F. Smith, *Proc. Chem. Soc.*, 4651 (1961).
(9) D. Brewer, R. Rahman, S. Safe, and A. Taylor, *Chem. Commun.*, 1571 (1968); R. Rahman and A. Taylor, *ibid.*, 1032 (1967); R. Hodges and J. S. Shannon, *Aust. J. Chem.*, **19**, 1059 (1966); J. W. Ronaldson, A. Taylor, E. P. White, and R. J. Abraham, *J. Chem. Soc.*, 3172 (1963); J. Fridrichsons and A. McL. Mathieson, *Tetrahedron Lett.*, 1265 (1962); A. F. Beecham. J. Fridrichsons, and A. McL. Mathieson, *ibid.*, 3131 (1966).
(10) L. I. Grandberg, T. I. Zujanova, N. I. Afonina, and T. A. Ivanova, *Dokl. Akad. Nauk SSSR*, **176**, 583 (1967); *Chim. Geterocikl. Soed.*, 875 (1968).
(11) T. Spande, H. Aoyagi, and B. Witkop, in preparation.
(12) B. Witkop and R. K. Hill, *J. Amer. Chem. Soc.*, 77, 6592 (1955).



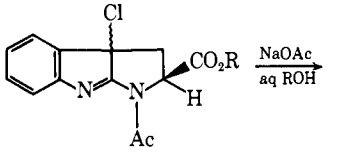
11

The tricyclic ester **5** was slowly hydrogenated over 3 days with a rhodium-on-alumina catalyst in ethyl acetate to **ethyl 1-acetyl-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2-carboxylate (12)** in 30% yield (after silica chromatography). The nmr spectrum showed a sharp doublet at 5.70 ppm (J = 7 Hz), assigned to the 8a proton, which was absent when **5** was reduced with deuterium. Acid or alkali converted **12** to N-acetyltryptophan ester (**1**) or N-acetyltryptophan. Acetylation of **12** with pyridine–acetic anhydride afforded **ethyl 1,8-diacetyl-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2-carboxylate (13)** in 60% yield. The configuration at 3a and 8a relative to the carbethoxy group at C-2 is not known. Although both **12** and **13** appeared to be homogeneous by tlc assay, the possibility of a mixture of diastereoisomers in both materials cannot be excluded.

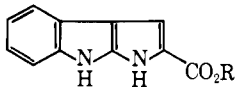
A 50% excess of *t*-butyl hypochlorite in buffered methylene chloride[13] converted **5** or **6** to the unstable **ethyl** and **methyl 1-acetyl-3a-chloro-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indolenine-2-carboxylates (14** and **15)** in 32 and 38% yields, respectively.



12, R = H; mp 104–105°
13, R = Ac; mp 204–205°



14, R = CH_2CH_3; mp 120–122° (dec)
15, R = CH_3; mp 133–134° (dec)



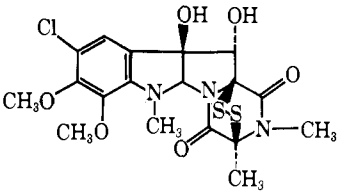
16, R = CH_2CH_3; mp 186–188°
17, R = CH_3; mp 229–231°

The chloroindolenines **14** and **15,** on refluxing in aqueous ethanol (**14**) or methanol (**15**) containing an excess of NaOAc, aromatized with deacetylation to the acid-stable **ethyl** and **methyl pyrrolo[2,3-*b*]indole-2-carboxylates (16** and **17)** ($\lambda\lambda_{max}$ 332, 272 mμ) in 40% yields.[11]

A delocalization energy of 6.18 β units was calculated for the parent molecule (HMO method using h_N = 1.5 and k_{C-N} = 0.8).[14]

This 14-π-electron system has so far not been synthesized, although a substituted pyrrolo[2,3-*b*]indole moiety is present in "anhydrodethiosporidesmin," **19,** a degradation product of sporidesmin (**18**).[15]

Catalytic oxygenation of **5** with O_2–PtO_2 in ethyl acetate,[16] followed by catalytic hydrogenation, or the



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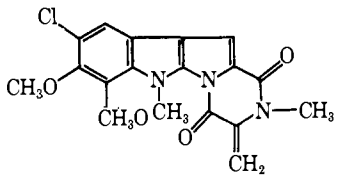


19

recently introduced singlet-oxygen system, triphenyl phosphite–ozone,[17] followed by borohydride reduction of the expected intermediary indolenine-3a-hydroperoxide **20,** failed to yield isolable **ethyl 1-acetyl-3a-hydroxy-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2-carboxylate (21).**

One equivalent of lead tetraacetate[18] in methylene chloride for 10 min at room temperature converted **5** to **ethyl 1-acetyl-3a-acetoxy-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indolenine-2-carboxylate (22).** After chromatography on neutral alumina and rechromatography on silica a 23% yield was obtained.

When the oxidation of **5** or **6** with lead tetraacetate was carried out as above, subsequent reduction by sodium borohydride in methanol at 0° for 5 min produced **ethyl** and **methyl 1-acetyl-3a-acetoxy-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2-carboxylates (23** and **24)** which were isolated as oils (after silica chromatography) in 29 and 26% yields, respectively. Acetylation of **21** or **22** with pyridine and acetic anhydride at room temperature for 2 days afforded the O,N,N′-triacetates **25** and **26** in 47 and 57% yields, respectively.

The diketopiperazine **27,** synthesized from N-methyl-L-alanyl-L-tryptophan methyl ester, on oxidation with *t*-butyl hypochlorite at 0° in Et_3N-buffered methylene chloride–dimethoxyethane (2:1, v/v) gave the tetracyclic product **28** in 51% yield.[19] This reaction provides a simple method of constructing the basic skeleton of the recently characterized metabolites of *Pithomyces chartarum,* the sporidesmins.[9]

Experimental Section

All reactions were conducted in a semidarkened room. All melting points are uncorrected. Ultraviolet spectra were measured on Cary spectrophotometers, Models 11 or 14, or a Hitachi spectrophotometer, Model EPS-3T. Infrared spectra were obtained with Perkin-Elmer Models No. 237 ($CHCl_3$), 421 (KBr), or Hitachi Model EPI-2 ($CHCl_3$ and KBr). Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter or Yanagimoto polarimeter OR-20. The nmr spectra were obtained on Varian Associates Models A-60 or HA-100 spectrometers. Chemical shifts are reported as δ values (ppm) with tetramethylsilane (TMS) as an

(13) *Cf.* N. Finch and W. I. Taylor, *J. Amer. Chem. Soc.,* 84, 3871 (1962); G. Büchi and R. E. Manning, *ibid.,* 88, 2532 (1966).

(14) We are indebted to Dr. K. Kirk of this laboratory for these calculations; *cf.* A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley & Sons, Inc., New York, N. Y., 1961, p 135.

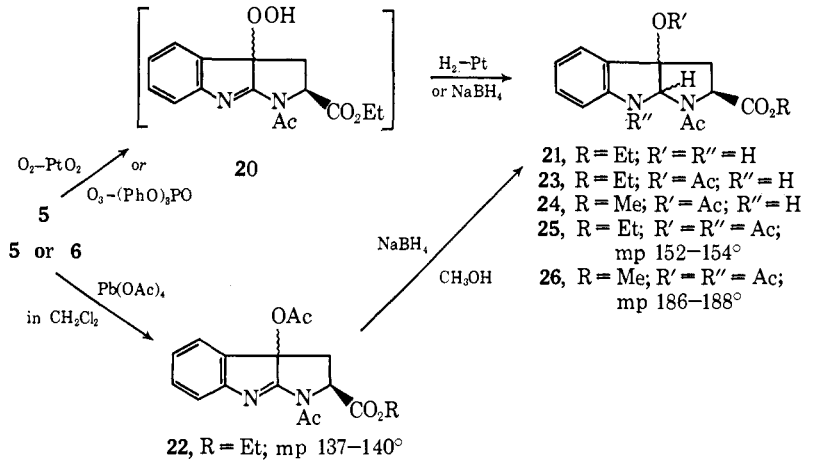
(15) R. Hodges, J. W. Ronaldson, J. S. Shannon, A. Taylor, and E. P. White, *J. Chem. Soc.,* 26 (1964).

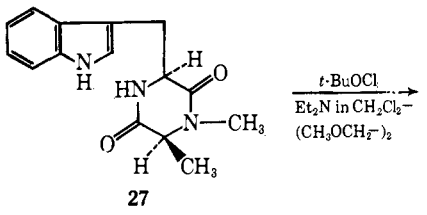
(16) B. Witkop and J. B. Patrick, *J. Amer. Chem. Soc.,* 73, 2188 (1951).

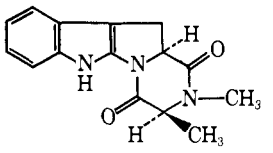
(17) R. W. Murray and M. L. Kaplan, *ibid.,* **90,** 537 (1968).

(18) N. Finch, C. W. Gemenden, I. H-C. Hsu, and W. I. Taylor, *ibid.,* 85, 1520 (1963); N. Finch, C. W. Gemenden, I. H-C. Hsu, A. Kerr, G. A. Sim, and W. I. Taylor, *ibid.,* 87, 2229 (1965).

(19) In a preliminary report (ref 3), the configuration of the alanyl moiety of **28** was inadvertently indicated as D. Dr. R. Nagarajan (Eli Lilly, Indianapolis) kindly informed us of this error and confirmed the L configuration by measuring the circular dichroism.







internal reference. High-resolution mass spectra were measured on an AEI MS-9 instrument (high-temperature direct inlet probe); low-resolution spectra with a double-focusing Hitachi RMU-6E spectrometer. Mallinckrodt silicic acid and Woelm alumina (neutral; activity grade 1) were used as adsorbants for chromatography. The N-bromosuccinimide (NBS) was Eastman practical grade; *t*-butyl hypochlorite was prepared according to Teeter and Bell.[20] N-Acetyl-L-tryptophan ethyl ester and amide, MA grade, were commercial samples (Mann). N-Acetyltryptamine was prepared from tryptamine hydrochloride and acetic anhydride. Petroleum ether refers to the fraction boiling between 30 and 60°. The rhodium–alumina catalyst was obtained from Engelhard Industries, Inc. Lead tetraacetate was supplied by Arapahoe Chemicals, Inc.

Unless described otherwise R_f values in tlc (silica gel G) refer to the system $CHCl_3$–CH_3OH (96:4 v/v). Spots were detected by a spray of 47% HBr followed by heating or by a spray of modified Ehrlich reagent (0.5% *p*-dimethylaminocinnamaldehyde solution in 0.5 *N* HCl).

Ethyl 1-Acetyl-2,3-dihydropyrrolo[2,3-*b*]indole-2-carboxylate (5). A. By NBS. To 1 l. of 0.04 *M* phosphate buffer (Na_2HPO_4, pH 9.2), containing 137 mg (0.5 mmol) of **1** and 20 ml of ethanol, was quickly added with rapid stirring an aqueous solution of 89 mg of NBS (0.5 mmol) in 30 ml of water. The reaction mixture was immediately extracted with 300 ml of ether. The ether layer was washed with water and dried (Na_2SO_4). As the ether extract was concentrated (rotary evaporator), the product began to crystallize. The crystals, 45 mg (33%), which were washed with a small volume of ether and collected under ether–hexane (1:3, v/v) by centrifugation, had mp 164–165°; $[\alpha]^{20}D$ −101° (*c* 0.57, ethanol); λ_{max}^{EtOH} 308 (log ε 4.20), 290 mμ (log ε 4.09); $\nu_{max}^{CHCl_3}$ 3460, 1740, 1660, and 1590 cm^{-1}; R_f 0.71; nmr (100 MHz and 60 MHz, $CDCl_3$) 9.40 (broad, one proton, NH), 7.45–6.70 ppm (aromatic multiplet, four protons), ABX spectrum, with δ_A = 3.39 (quartet), δ_B = 3.50 (quartet), and δ_X = 5.50 ppm (quartet); $J_{AX} \cong 3.4$ Hz, $J_{BX} \cong 10$ Hz, and $|J_{AB}| \cong 14.6$ Hz; 4.28 ppm (quartet, J = 7 Hz, two protons, $-COCH_2CH_3$; 2.12 ppm (singlet, three protons, N-Ac); 1.28 (triplet, J = 7 Hz, three protons, $-COCH_2CH_3$). The signal at 9.40 ppm was absent after the solution was shaken with D_2O.

Anal. Calcd for $C_{15}H_{16}N_2O_3$ (mol wt 272.11608): C, 66.16; H, 5.92; N, 10.29. Found: C, 66.06; H, 6.11; N, 9.95 [molecular ion (M^+), 272.11660].

B. By *t*-Butyl Hypochlorite. A solution of 1.8 ml (15 mmol) of *t*-butyl hypochlorite in 20 ml of carbon tetrachloride was added dropwise over 30 min to a well-stirred solution of 4.05 g (15 mmol) of **1** in 250 ml of methylene chloride containing 8.4 ml (60 mmol) of triethylamine. After 2 hr the reaction mixture which was cooled in an ice–salt bath was allowed to warm up to room temperature. After standing overnight it was washed twice with cold water, dried (Na_2SO_4), and evaporated almost to dryness. An ether–hexane mixture (1:4, v/v) was added to the resulting crystals and the slurry was filtered to afford 3.27 g (81% yield) of colorless crystals, mp 163–164°, which after recrystallization from ethyl acetate–ether had mp 165–166°. The uv and ir spectra were identical with the NBS oxidation product.

Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.29; H, 5.78; N, 10.05.

Methyl 1-Acetyl-2,3-dihydropyrrolo[2,3-*b*]indole-2-carboxylate (6). This compound was prepared by the oxidation of N-acetyl-L-tryptophan methyl ester (**2**) with *t*-butyl hypochlorite in the same manner as **5**. The gelatinous solid resulting on evaporation of the ether was triturated with an ether–hexane mixture (1:2, v/v) and collected by filtration. The yield from 7.74 g of N-acetyl-L-tryptophan methyl ester (**2**) was 5.60 g (78%). After recrystallization from ethyl acetate–ether–hexane, 4.75 g (66%) of **6** was isolated, mp 175–177°; $[\alpha]D$ −97° (*c* 0.915, ethanol); λ_{max}^{EtOH} 308 (log ε 4.18), shoulder 290 mμ (log ε 4.02); $\nu_{max}^{CHCl_3}$ 3460, 1740, 1660, and 1590 cm^{-1}; M^+, 258; R_f 0.66.

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.06; H, 5.47; N, 10.58.

1-Acetyl-2,3-dihydropyrrolo[2,3-*b*]indole-2-carboxamide (7) by Oxidation of N-Acetyl-L-tryptophanamide (3) with NBS. This compound was prepared in the same manner as **5** except that two 200-ml portions of ethyl acetate were used for the extraction in place of ether. Crystals resulting on evaporation were washed with $CHCl_3$ and collected by centrifugation under ether. The yield from 116 mg of **3** was 35 mg (30%), mp 243–244°; $[\alpha]^{20}D$ −191° (*c*, 0.14, dimethylformamide); λ_{max}^{EtOH} 308 (log ε 4.13), shoulder 290 mμ (log ε 4.02); ν_{max}^{KBr} 3380 (broad), 1675, 1655, 1610, and 1520 cm^{-1}; M^+, 243 (low resolution mass spectrum); nmr (100 MHz, DMSO-d_6) 7.75 (broad, NH?), 7.42–6.90 (aromatic multiplet), 3.32 ppm ($-CONH_2$); ABX spectrum with $\delta_A \cong 2.98$ (quartet), $\delta_B \cong 3.55$ (quartet), and δ_X = 5.28 ppm (quartet); $J_{AX} \cong 4$ Hz, J_{BX} = 10 Hz, $|J_{AB}| \cong 15$ Hz; 2.00 ppm (singlet, N-Ac).

Anal. Calcd for $C_{12}H_{13}N_3O_2 \cdot 0.2C_4H_{10}O$ (diethyl ether): C, 64.50; H, 5.87; N, 16.31. Found: C, 64.81; H, 5.73; N, 16.21.

1-Acetyl-2,3-dihydropyrrolo[3,2-*b*]indole (8). To a cooled (−10°) and stirred solution of 1.21 g (6.0 mmol) of N-acetyltryptamine (**4**) in a mixture of 100 ml of methylene chloride and 3.36 ml (24 mmol) of triethylamine was added 26.4 ml (6.6 mmol) of a 0.25 *M* *t*-butyl hypochlorite solution in methylene chloride. The addition was carried out dropwise over 30 min and the solution stirred for another 2 hr at −10°. At this point the uv spectrum exhibited an absorption maximum at 290 mμ. The reaction mixture was cooled with an ice–salt mixture and a solution of 6.6 ml of 1.0 *N* NaOH and 40 ml of ethanol was added over 30 min. The uv

(20) H. M. Teeter and E. W. Bell, "Organic Syntheses," Coll. Vol. IV, N. Rabjohn, Ed., John Wiley & Sons, Inc., New York, N. Y., 1963, p 125.

spectrum of the reaction product now exhibited an absorption maximum at 308 mμ. The reaction mixture was diluted with 50 ml of methylene chloride, washed three times with water, dried, and concentrated nearly to dryness to afford fine crystals which were collected by filtration from ether–hexane (1:1), 0.76 g (63%). After recrystallization from methylene chloride–ether, 0.68 g of colorless crystals resulted, mp 243–244°; λ_{max}^{EtOH} 308 (log ε 4.18), shoulder 290 mμ (log ε 4.06); $\nu_{max}^{CHCl_3}$ 3460, 1650, 1610, and 1580 cm^{-1}; M$^+$, 200; R_f 0.71.

Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 70.86; H, 6.21; N, 13.84.

Ethyl 1-Acetyl-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2-carboxylate (12) by Catalytic Hydrogenation of 5. A solution of 0.20 g of **5** in 12 ml of ethyl acetate was stirred under hydrogen in the presence of 0.1 g of rhodium–alumina catalyst. After 24 hr another 0.1 g of catalyst was added. After an additional 24 hr the catalyst was removed and the filtrate washed with water, dried (Na_2SO_4), and evaporated to dryness. The residue was chromatographed over silica gel and eluted with $CHCl_3$–CH_3OH (96:4, v/v). Homogeneous fractions were combined and evaporated to dryness. Crystallization resulted on standing in an evacuated desiccator. The crystals were triturated with hexane–ligroin (1:1, v/v) and filtered to yield 52 mg of colorless crystals, mp 104–105°; $[\alpha]^{20}D$ +242° (*c*, 0.167, ethanol); $\lambda\lambda_{max}^{EtOH}$ 243 (log ε 3.87), 301 mμ (log ε 3.37); $\nu_{max}^{CHCl_3}$ 3440, 1740, and 1645 cm^{-1}; M$^+$, 274 (low resolution mass spectrum); R_f 0.45; nmr (60 MHz, $CDCl_3$) 7.26–6.48 (multiplet, four protons), 5.70 (doublet, one proton, J = 7 Hz, 8a proton), 5.1–4.8 (broad, one proton, N–H?), 4.45 (quartet, one proton (X)), $J_{AX} \cong$ 3 Hz, $J_{BX} \cong$ Hz, 4.25–3.25 (complex multiplet, four protons, multiplets from B and 3a protons and $-CO_2CH_2CH_3$ overlapping), 2.85–2.60 (multiplet, one proton (A)), 2.0 (three-proton singlet, N–Ac), 0.95 ppm (triplet, three protons, J = 7 Hz; $-CO_2CH_2CH_3$).

Anal. Calcd for $C_{12}H_{18}N_2O_3$: C, 65.69; H, 6.57; N, 10.22. Found: C, 65.77; H, 6.44; N, 10.31.

Ethyl 1-Acetyl-3a,8a-dideutero-2,3-dihydropyrrolo[2,3-*b*]indole-2-carboxylate. The reduction was carried out as described above in an atmosphere of deuterium: nmr (100 MHz, $CDCl_3$) 5.70 ppm doublet is absent. δ_A revealed a quartet ($J_{AX} \cong$ 2 Hz, $|J_{AB}| \cong$ 14 Hz) at 2.80 ppm. That the deuteration was incomplete and the labeling nonspecific was revealed, both by nmr and the mass spectrum: *m/e* for M$^+$ at 274, 275, 276, 277, 278; relative intensities 2:8.2:9.5:4.4:1.

Ethyl 1,8-Diacetyl-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2-carboxylate (13) by Acetylation of 12. A solution of 80 mg of **12** in 1 ml of dry pyridine and 0.3 ml of freshly distilled acetic anhydride was allowed to stand at room temperature for 2 days. The solvents were removed by evaporation under reduced pressure. The crystalline residue was dissolved in ethyl acetate, washed with water, and dried (Na_2SO_4), and the solvent removed at room temperature. The resulting crystals were collected by centrifugation under ether and washed once with ether to yield 58 mg of colorless crystals, mp 204–205°; $[\alpha]^{20}D$ +34° (*c* 0.113, methanol); λ_{max}^{EtOH} 244 (log ε 4.03), shoulder 283 mμ (log ε 3.16); $\nu_{max}^{CHCl_3}$ 1740, 1665, and 1600 cm^{-1}; M$^+$, 316; R_f 0.40.

Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.53; H, 6.33; N, 8.85. Found: C, 63.88; H, 6.09; N, 9.02.

Nmr spectrum (100 MHz and 60 MHz, $CDCl_3$) revealed 7.3–7.0 (four protons, multiplet), 6.35 (broad, 8a proton), 4.40 (multiplet, one proton, 2 position), 4.10 (quartet, J = 7 Hz, two protons $—CO_2CH_2CH_3$), 3.8–3.4 (multiplet, two protons), 3.18 (singlet (?), *ca.* one proton, 3a proton?), 3.65 (broad singlet, three protons, N(8)–Ac), 2.03 (broad singlet, three protons, N(1)-Ac), 0.93 ppm (triplet, J = 7 Hz, three protons, $-CO_2CH_2CH_3$), broad signals for N–Ac protons may indicate inhomogeneity, mixture of 3a,8a diastereoisomers is a possibility despite homogeneity on tlc.

Methyl 1-Acetyl-3a-chloro-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indolenine-2-carboxylate (15). To a stirred solution of 0.516 g (2 mmol) of **6** in 50 ml of methylene chloride and 0.5 ml of triethylamine was added dropwise at −10° 12 ml (3 mmol) of 0.2 *M t*-butyl hypochlorite in carbon tetrachloride over 20 min and stirring continued for an additional 40 min at −10°. The mixture was then washed with water, dried (Na_2SO_4), and evaporated. The residue containing crystals was triturated with 4 ml of methanol and 15 ml of hexane. The resulting crystals were collected by filtration and washed with hexane (0.223 g, 38%). Recrystallization from methylene chloride–methanol–hexane gave 0.196 g of fine crystals, mp 133–134° (dec); $[\alpha]^{20}D$ −322° (*c* 0.27, chloroform); $\lambda\lambda_{max}^{EtOH}$ 241 (log ε 4.33), 285 (log ε 3.45), 325 mμ (log ε 3.59); $\nu_{max}^{CHCl_3}$ 1764, 1737, 1706, 1624, and 1598 cm^{-1}; R_f 0.87.

Anal. Calcd for $C_{14}H_{13}N_2O_3Cl$: C, 57.44; H, 4.48; N, 9.57. Found: C, 57.18; H, 4.45; N, 9.51.

Ethyl 1-Acetyl-3a-chloro-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indolenine-2-carboxylate (14). This compound was prepared from **5** by oxidation with *t*-butyl hypochlorite in the same manner as described for **15**. The yield from 0.816 g (3 mmol) was 0.295 g (32%). Recrystallization from methylene chloride–ether–hexane yielded 0.251 g (27%), mp 120–122° dec; $[\alpha]^{20}D$ −297° (*c* 0.373, chloroform); $\lambda\lambda_{max}^{EtOH}$ 241 (log ε 4.33), 285 (log ε 3.45), 328 mμ (log ε 3.61); $\nu_{max}^{CHCl_3}$ 1754, 1727, 1706, 1635, and 1598 cm^{-1}; M$^+$, 306 (^{35}Cl) and 308 (^{37}Cl); R_f 0.87.

Anal. Calcd for $C_{15}H_{15}N_2O_3Cl$: C, 58.72; H, 4.89; N, 9.13. Found: C, 58.35; H, 4.86; N, 8.92.

Ethyl 1-Acetyl-3a-acetoxy-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indolenine-2-carboxylate (22). To a solution of 0.41 g (1.5 mmol) of **5** in 150 ml of methylene chloride was added 0.67 g (1.5 mmol) of crystalline lead tetraacetate and the solution stirred for 10 min at room temperature. The reaction mixture was washed twice with cold water, dried (Na_2SO_4), and evaporated. The residue was applied to a column of neutral Al_2O_3 and eluted with 4% (v/v) methanol in chloroform. The main fraction was rechromatographed on silica gel and eluted with the same solvent system. When homogeneous fractions were combined and evaporated, they left a residue which crystallized on trituration with hexane–petroleum ether to give 113 mg (23% yield) of colorless crystals, mp 137–140°; $[\alpha]^{20}D$ +177° (*c* 0.3, ethanol); $\lambda\lambda_{max}^{EtOH}$ 230 (log ε 4.38), 282 (log ε 3.52), 313 mμ (log ε 3.68); $\nu_{max}^{CHCl_3}$ 1745, 1695, 1640, and 1600 cm^{-1}; M$^+$, 330; R_f 0.80; nmr (60 MHz, $CDCl_3$) 7.7–6.9 (aromatic multiplet, four protons), 5.00 (quartet, one proton, δ_x of ABX system, $J_{AX} \cong$ 5.5 Hz, $J_{BX} \cong$ 10 Hz), 4.22 (quartet, two protons, J = 7 Hz, $CO_2CH_2CH_3$), 3.75–2.90 (eight-line multiplet, δ_A and δ_B quartets, $|J_{AB}| \cong$ 12–14 Hz), 2.65 (singlet, three protons, OCO–CH_3), 2.02 (singlet, three protons, N–Ac), 1.26 ppm (triplet, J = 7 Hz, protons, $-CO_2CH_2CH_3$).

Anal. Calcd for $C_{17}H_{18}N_2O_5$: C, 61.87; H, 5.50; N, 8.49. Found: C, 61.88; H, 5.30; N, 8.63.

Methyl 1-Acetyl-3a-acetoxy-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2-carboxylate (24). This compound was prepared from **6** by oxidation with lead tetraacetate and successive reduction with sodium borohydride. After oxidation of 2.32 g (9 mmol) of **6** with 4.0 g (9 mmol) of lead tetraacetate the reaction mixture was washed twice with cold water, dried (Na_2SO_4), and evaporated. The residue was dissolved in 50 ml of methanol and the solution was cooled with an ice–water bath. An excess (*ca.* 1.5 g) of sodium borohydride was added and the reaction mixture was stirred for 10 min, then diluted with 120 ml of ethyl acetate and washed three times with water, dried (Na_2SO_4), and evaporated. The residue was chromatographed on a silica gel column (3.0 × 54 cm) with 4% (v/v) methanol in chloroform. Homogeneous fractions (checked by thin-layer chromatography, sprayed with modified Ehrlich reagent) were combined and evaporated. Trituration of the oily residue (0.85 g) with hexane–petroleum ether gave 0.72 g (26%) of amorphous solid, mp < 65°; $[\alpha]^{20}D$ +133° (*c* 0.485, ethanol); $\lambda\lambda_{max}^{EtOH}$ 243 (log ε 3.87), 308 mμ (log ε 3.33); $\nu_{max}^{CHCl_3}$ 3420, 1735, and 1650 cm^{-1}; R_f 0.57.

Mass spectrometric analysis was unsuccessful because this compound was thermally unstable.

Ethyl 1-Acetyl-3a-acetoxy-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2-carboxylate (23). This compound was prepared from **5** by oxidation with lead tetraacetate and successive reduction with sodium borohydride. The reaction was carried out with 1.09 g (4 mmol) of **5**. The crude residue resulting on evaporation was applied to a silica gel column (2.0 × 50 cm) and eluted with 4% (v/v) methanol in chloroform. Homogeneous fractions were combined and evaporated leaving 0.384 g (29% from **5**) of an oily residue, $\lambda\lambda_{max}^{EtOH}$ 242, 308 mμ (OD_{242}/OD_{306} = 2.8); $\nu_{max}^{CHCl_3}$ 3420, 1735, and 1650 cm^{-1}; R_f 0.57.

Methyl 1,8-Diacetyl-3a-acetoxy-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2-carboxylate (26). A solution of 0.20 g (0.63 mmol) of **24** in 1.0 ml of dry pyridine and 2.0 ml of acetic anhydride was allowed to stand for 2 days at room temperature. The solvents were removed under reduced pressure at room temperature. The resulting crystals were dissolved in 15 ml of ethyl acetate and the solution was washed twice with water, dried (Na_2SO_4), and evaporated. The crystalline residue (0.10 g, 57%) after recrystallization from methanol–ether–hexane gave 0.089 g (40%) of colorless crystals, mp 186–188°, $[\alpha]^{20}D$ +172° (*c* 0.68, methanol); $\lambda\lambda_{max}^{EtOH}$ 244 (log ε 4.01), 283 mμ (log ε 3.14); $\nu_{max}^{CHCl_3}$ 1745 and 1670 cm^{-1}; M$^+$, 360; R_f 0.49.

Anal. Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 60.21; H, 5.68; N, 7.71.

Ethyl 1,8-Diacetyl-3a-acetoxy-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole-2-carboxylate (25). This compound was prepared by acetylation of **23** as described above. Crystals resulting on evaporation were dissolved in ethyl acetate and the solution was washed twice with water, dried (Na_2SO_4), and evaporated. The residue was triturated with a mixture of ether–hexane. The yield from 0.192 g (0.578 mmol) of **23** was 0.103 g (47%), mp 144–145°. Recrystallization from ethyl acetate–ether–hexane gave 0.070 g of colorless crystals, mp 152–154°; $[\alpha]^{20}D$ +156° (*c*, 0.595, methanol); $\lambda\lambda_{max}^{EtOH}$ 244 (log ϵ 3.99), 283 mμ (log ϵ 3.13); $\nu_{max}^{CHCl_3}$ 1750 and 1670 cm^{-1}; M^+, 374; R_f 0.49.

Anal. Calcd for $C_{19}H_{22}N_2O_6$: C, 60.95; H, 5.92; N, 7.48. Found: C, 60.65; H, 6.15; N, 7.31.

Dicyclohexylamine N-Benzyloxycarbonyl-N-methyl-L-alaninate. To a cooled and stirred solution of 1.86 g (18 mmol) of N-methyl-L-alanine in 25 ml of water containing 6.05 g (72 mmol) of $NaHCO_3$, 4.6 ml (*ca.* 24 mmol) of benzyloxycarbonyl chloride was added in two equal portions at intervals of 15 min. The reaction mixture was stirred at 0° for 3 hr, then overnight at room temperature, and then extracted with ether, and the aqueous layer separated and acidified with citric acid. After extraction with three 30-ml portions of ethyl acetate, the combined ethyl acetate layers were dried (Na_2SO_4) and evaporated to give 2.2 g of an oil which failed to crystallize. The oil was dissolved in 10 ml of ether and dicyclohexylamine added. On evaporation, 2.45 g of a crystalline dicyclohexylammonium salt deposited and was filtered from a hexane slurry to yield, after recrystallization from ethyl acetate–ether–ligroin, 2.13 g of colorless crystals, mp 141–142°; $[\alpha]^{20}D$ −11.7° (*c* 1.61, ethanol).

Anal. Calcd for $C_{24}H_{38}N_2O_4$: C, 68.90; H, 9.09; N, 6.70. Found: C, 68.81; H, 8.83; N, 6.81.

N-Methyl-L-alanyl-L-tryptophan Diketopiperazine (27). Benzyloxycarbonyl-N-methyl-L-alanine was generated from its dicyclohexylamine salt as follows: a solution containing 1.88 g (4.47 mmol) of the salt in 30 ml of ethyl acetate was washed with three 35-ml portions of 1.0 *M* citric acid, once with water, dried (Na_2SO_4), and evaporated to give 1.08 g of colorless oil.

The oily benzyloxycarbonyl-N-methyl-L-alanine was dissolved in 5 ml of dimethoxyethane and mixed with a solution of 1.38 g (5.4 mmol) of L-tryptophan methyl ester hydrochloride in a solution of 10 ml of methylene chloride and 0.76 ml (5.4 mmol) of triethylamine. The solution was cooled in an ice–water bath and 0.93 g (4.5 mmol) of N,N′-dicyclohexylcarbodiimide was added. The mixture was stirred for 3 hr at 0°, then overnight at 10°. The residue resulting after evaporation was treated with ethyl acetate and filtered to remove insoluble material. The filtrate was washed successively with 0.5 *M* citric acid, saturated $NaHCO_3$ solution, and water, then dried (Na_2SO_4) and evaporated to afford 1.75 g of a homogeneous oil which was dissolved in 20 ml of methanol and stirred under hydrogen for 1 hr in the presence of 0.2 g of palladium black. After removal of the catalyst, the filtrate on evaporation afforded 1.20 g of a homogeneous oil, N-methyl-L-alanyl-L-tryptophan methyl ester, which was dissolved in 20 ml of methanol, saturated with dry NH_3 gas at 0°, and stored in a tightly glass-stoppered flask. After standing for 24 hr at room temperature, the solution was evaporated nearly to dryness. On addition of ether, the crystals were collected from an ether–hexane (2:1), v/v) slurry to afford 0.76 g of **27** which after recrystallization from methanol–ether gave 0.62 g, mp 180–181°; $[\alpha]^{20}D$ +22° (*c* 0.33, dimethylformamide); λ_{max}^{EtOH} 273 (log ϵ 3.68), 280 (log ϵ 3.70), 290 mμ (log ϵ 3.64).

Anal. Calcd for $C_{15}H_{17}N_3O_2$: C, 66.46; H, 6.27; N, 15.48. Found: C, 66.36; H, 6.36; N, 15.12.

Oxidation of N-Methyl-L-alanyl-L-tryptophan Diketopiperazine (27) with *t*-Butyl Hypochlorite to 28. To a well-stirred cooled (−10°) solution of 270 mg (1.0 mmol) of the diketopiperazine **27** in a mixture of 30 ml of methylene chloride, 15 ml of dimethoxyethane, and 1.4 ml (10 mmol) of triethylamine was added 4.4 ml (1.1 mmol) of 0.25 *M* *t*-butyl hypochlorite in carbon tetrachloride dropwise over 30 min. The mixture was stirred for 1 hr at −10°. After standing for 24 hr at room temperature, the solvents were evaporated and the residue was dissolved in 10 ml of methanol and 40 ml of methylene chloride. After washing twice with cold water and drying (Na_2SO_4) evaporation afforded 136 mg (51% yield) of **28** as colorless crystals, mp 233–235°; $[\alpha]^{20}D$ +55° (*c* 0.36, dimethylformamide), and after recrystallization from $CHCl_3$–Et_2O–hexane (20% yield), mp 245–249°; λ_{max}^{EtOH} 308 (log ϵ 4.17), shoulder 293 mμ (3.98); ν_{max}^{KBr} 3420 (broad), 1660, 1580, and 1525 cm^{-1}; M^+, at 269 and principal peaks at 224, 156, 143, and 130.

Anal. Calcd for $C_{12}H_{15}N_3O_2 \cdot H_2O$: C, 65.74; H, 5.67; N, 15.35. Found: C, 65.72; H, 5.87; N, 15.38.

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