The Synthesis of 6-Substituted Thieno[3,2-*b*]pyrroles. Analogs of Tryptophan, Tryptamine, and Indoleacetic Acid[1,2]

A. J. HUMPHRIES, RONALD L. KEENER,[3] KUNIHIKO YANO, F. S. SKELTON, EDWARD FREITER, AND H. R. SNYDER*

School of Chemical Sciences, University of Illinois at Urbana-Champaign, Roger Adams Laboratory, Urbana, Illinois 61801

Received November 15, 1971

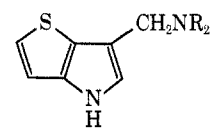
The conversions of 6-piperidinomethylthieno[3,2-*b*]pyrrole to the thieno[3,2-*b*]pyrrole analogs of tryptophan, tryptamine, indoleacetic acid, indoleacetic acid methyl ester, the ethyl ester of *N*-acetyltryptophan, and *N*-acetyltryptophan are reported. The thieno[3,2-*b*]pyrrole compounds are much less stable than the corresponding indole derivatives.

In a preceding paper[4] we reported practical syntheses of 6-piperidinomethylthieno[3,2-*b*]pyrrole (**1a**) and 6-dimethylaminomethylthieno[3,2-*b*]pyrrole (**1b**), substances which, by analogy with the similar indole compounds, *e.g.*, gramine,[5] were expected to serve conveniently in the synthesis of many 6-substituted thieno[3,2-*b*]pyrroles analogous to naturally occurring indole compounds but having the benzene ring of the indole system replaced by a thiophene unit. The synthesis of the analog **7** of the amino acid tryptophan was of particular interest because of the possibility that the greater chemical reactivity of the thienopyrrole nucleus, as compared to the indole nucleus, might greatly alter the biochemical function of a peptide containing a unit of the new amino acid in a position normally occupied by a tryptophan residue.

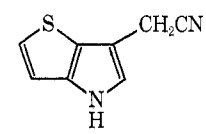
In the present work the tertiary amine **1a** and its methiodide were found to have the expected activity as alkylating agents. Thus, good yields of the nitrile **2**, the alkylated amidomalonates **3a** and **3c**, and the cyano ester **3d** were readily obtained from the methiodide of **1a**. Reaction of the amine **1a** with diethyl acetamidomalonate gave **3a** in lower yield. Reduction of the nitrile **2** with lithium aluminum hydride gave the amine **4**. Alkaline hydrolysis of the nitrile **2** produced the acid **5a**, but attempts to obtain it in the pure crystalline state were unsuccessful; however, the pure methyl ester **5b** was readily isolated after methylation of the crude acid with diazomethane.

In the hydrolysis and decarboxylation of the malonic acid derivatives **3a** and **3c** the intermediates proved to be very much more unstable than anticipated. In general, the compounds were highly sensitive to acid, heat, and air, and some of them to light, especially if traces of acid were present. In acidic media, except under strict pH control, those thienopyrroles lacking a stabilizing 5-carboethoxy group rapidly formed complex dark-colored mixtures, usually initially purple. However, it has been possible to isolate the amido ester **6a** by half-saponification of **3a**, followed by thermal decarboxylation of the acid ester **3b**.

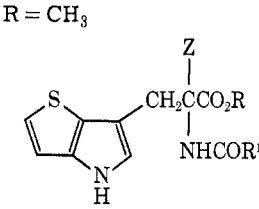
The amidomalonate **3a** underwent saponification and decarboxylation on heating in aqueous ethanolic sodium hydroxide. The small amount of the corresponding malonic acid, concurrently formed with the amido acid **6b**, was decarboxylated when the reaction



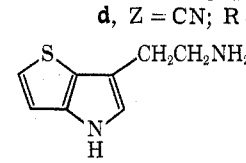
1a, $R_2 = (CH_2)_5$
b, $R = R = CH_3$



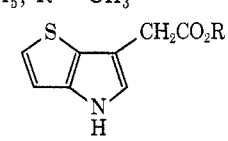
2



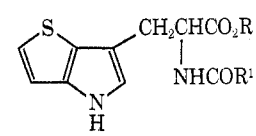
3a, $Z = CO_2C_2H_5$; R = C_2H_5; $R^1 = CH_3$
b, $Z = CO_2H$; $R = C_2H_5$; $R^1 = CH_3$
c, $Z = CO_2C_2H_5$; $R = C_2H_5$; $R^1 = H$
d, $Z = CN$; $R = C_2H_5$; $R^1 = CH_3$



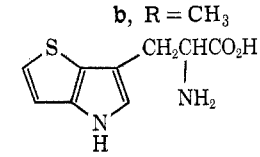
4



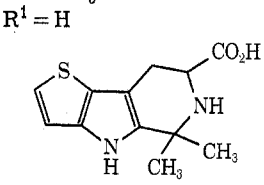
5a, R = H
b, $R = CH_3$



6a, $R = C_2H_5$; $R^1 = CH_3$
b, R = H; $R^1 = CH_3$
c, R = H; $R^1 = H$



7



8

mixture was boiled after the pH was adjusted to and maintained at 6. The isolation of the amido acid **6b** was accomplished by an extractive–azeotropic distillation with nitromethane, which conveniently freed it from reaction solvents and sodium chloride. No **6b** was detected on attempted hydrolysis of the amido ester **6a** or the cyano ester **3d**.

The amino acid **7** has been obtained by hydrolysis and decarboxylation of the formamidomalonate **3c** followed by deformylation without isolation of inter-

(1) Supported in part by a research grant (CA-8663) from the National Cancer Institute, U. S. Public Health Service.

(2) Abstracted in part from a thesis submitted by R. L. Keener to the Graduate College of the University of Illinois in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 1967.

(3) (a) National Science Foundation Summer Fellow, 1964; (b) Phillips Petroleum Company Fellow, 1964–1966.

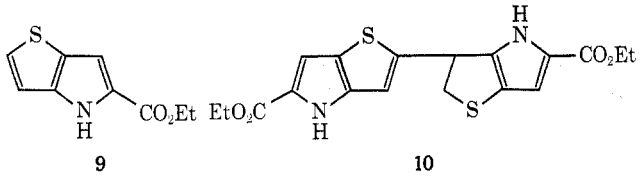
(4) R. L. Keener, F. S. Skelton, and H. R. Snyder, *J. Org. Chem.*, **33**, 1355 (1968).

(5) E. E. Howe, A. J. Zambito, H. R. Snyder, and M. Tishler, *J. Amer. Chem. Soc.*, **67**, 38 (1945).

mediates. One of the problems in the isolation of the amino acid **7** lay in the complete removal of sodium chloride from the very soluble crude reaction product. The purification of **7** was finally achieved by the aid of a series of Amberlite and DEAE–cellulose columns; the experimental procedures developed may prove useful in the conversion of other amidomalonates to amino acids.

The failure to obtain the amino acid **7** from the amido acid **6b** led to a large number of attempts, all unsuccessful, to circumvent the final hydrolytic deacylation by utilizing intermediates derived from various carbobenzyloxy-protected amidomalonates, nitromalonic ester, and chloroacetamidomalonic ester,[6] which might permit the introduction of the free α-amino group in a nonhydrolytic step, *e.g.*, reduction or reaction with thiourea.[6] In a search for a nonhydrolytic deacylation which might be applied to **6b**, it was found that, in the presence of small amounts of its dihydrochloride, hydrazine is effective in the conversion of several amido acids to the amino acids (see Experimental Section). When **6b** was subjected to the action of hydrazine the reaction mixture developed much less color than had been observed in the hydrolysis attempts. However, some destruction of the thienopyrrole nucleus was indicated by the formation of hydrogen sulfide, especially when the mixture was heated. Furthermore, when the reaction mixture was poured into acetone to consume the excess hydrazine and precipitate the amino acid, under conditions that were quite satisfactory in the conversion of *N*-acetyltryptophan to tryptophan, the solid obtained proved to be a mixture of the amino acid **7** and a compound for which the mass spectrum [molecular ion at *m/e* 250.0772 ($C_{12}H_{14}N_2SO_2$) and chief fragment ions at *m/e* 235.0536 (loss of CH_3) and 189.0481 (loss of CH_3 and HCO_2H)] and the nmr spectrum in DMSO-d_6 (two singlet nonequivalent methyl groups and only an AB pattern for the thiophene protons) strongly suggest the tricyclic structure **8**.

A key intermediate in the earlier described synthesis of the tertiary amines **1a** and **1b** is 5-carboethoxythieno[3,2-*b*]pyrrole (**9**), obtained in about 50% yield by the reductive cyclization of ethyl 3-nitro-2-thienylpyruvate with stannous chloride and hydrochloric acid. A major by-product (*ca.* 25% yield) was a dimer of **9** which could be largely converted to **9** by treatment with acid and for which the structure **10** was tentatively sug-



9 10

gested.[4] In the present work the dimer was aromatized by the action of chloranil in boiling xylene. The nmr spectrum of the product confirms the previous formulation **10** of the dimer.

The dimerization of **9** and the reaction of **7** with acetone under very mild conditions indicate that unsubstituted 5 and 2 positions in thieno[3,2-*b*]pyrroles are much more reactive than corresponding positions in indoles. The tendency of many of the reactions mentioned above to give very complex mixtures, especially if exposed to strong acid, air, and light, may result from attack at these sites by electrophilic species supplied either inter- or intramolecularly or by free-radical species generated in the reaction mixtures, yielding intermediates comparable to **8** and **10** and capable of generating various further products by elimination, oxidation, condensation, etc. It is hoped that further study will elucidate some of these reactions.

(6) M. Masaki, T. Kitihara, H. Kurita, and M. Ohta, *J. Amer. Chem. Soc.*, **90**, 4508 (1968).

Experimental Section

Melting points were determined with a Kofler microstage apparatus and are uncorrected. A Perkin-Elmer 521 infrared spectrophotometer was used for the ir spectra. Microanalyses were performed by Mr. J. Nemeth and associates. Routine nmr spectra were recorded on a Varian A-56/60 or A-60A spectrometer; 100-MHz and 220-MHz spectra were recorded by Mr. R. L. Thrift and associates on a Varian HA-100 and HR-220[7] spectrometer, respectively. Mass spectra were recorded by Mr. J. Wrona and associates on an Atlas CH4 mass spectrometer at 70 eV. Exact mass measurements were obtained by Mr. J. Carter Cook and associates with the peak-matching technique on an MAT SM-1B high-resolution mass spectrometer[8] and are within 0.0004 amu of values calculated for the indicated ion compositions.

6-Piperidinomethylthieno[3,2-*b*]pyrrole Methiodide.—Excess methyl iodie (9.2 ml) was added dropwise and under anhydrous conditions to a stirred solution of 6-piperidinomethylthieno[3,2-*b*]pyrrole[4] (**1a**, 3.83 g, 17.4 mmol) in anhydrous ether (80 ml). The mixture was left stirring overnight and then cooled to 0° for 1 hr. The methiodide of **1a** was collected, washed with ether, and dried. The yield was 4.04 g (62.5%), mp 166–167°.

Anal. Calcd for $C_{13}H_{19}N_2SI$: C, 43.13; H, 5.29; N, 7.74. Found: C, 43.05; H, 5.42; N, 7.62.

A further crop was obtained on concentrating the mother liquors (total yield 90–99%).

6-Cyanomethylthieno[3,2-*b*]pyrrole (**2**).—A stirred mixture of the methiodide of **1a** (250 mg, 0.69 mmol) and potassium cyanide (200 mg, 3.07 mmol) in water (12 ml) was refluxed for 1.5 hr. The nitrile **2** was extracted into ether (100 ml) and dried ($MgSO_4$). Evaporation of the ether *in vacuo* afforded 75 mg (67%) of **2** as a pale yellow oil, ir ($CHCl_3$) 3500 (NH), 2250 cm^{-1} (CN).

Methyl 6-Thieno[3,2-*b*]pyrrolylacetate (**5b**).—A solution of crude **2** (450 mg) in 10% alcoholic sodium hydroxide (60 ml) was refluxed for 12 hr. The cooled reaction mixture was made slightly acidic (pH 5) by the addition of dilute hydrochloric acid. The liberated 6-thieno[3,2-*b*]pyrrolylacetic acid (**5a**) was extracted into ether (150 ml) and washed with water (25 ml), and the dried (Na_2SO_4) solution[9] was concentrated *in vacuo* to approximately 50 ml and then treated dropwise with a slight excess of diazomethane in ether. The solution was left at room temperature for 30 min. Excess diazomethane was removed by gently warming the solution on a steam bath and the remaining solution was evaporated under reduced pressure. The residual oil was distilled *in vacuo* to afford 350 mg (65%) of **5b** as a pale yellow oil: bp 120° (0.1 mm); $n^{25}D$ 1.5876; ir ($CHCl_3$) 1750 cm^{-1} (ester); nmr (CCl_4) δ 3.46 (s, 2 H, CH_2), 3.55 (s, 3 H, CH_3), 6.40 (s, 1 H, H-5), 6.55 (d, 1 H, $J_{2,3}$ = 5.0 Hz, H-3), 6.85 (d, 1 H, $J_{2,3}$ = 5.0 Hz, H-2). The absorptions due to H-2 and H-5 were further split by $J_{2,5}$ = 1.3 Hz.

Anal. Calcd for $C_9H_9NO_2S$: C, 55.42; H, 4.64; N, 7.17. Found: C, 55.67; H, 4.91; N, 7.23.

6-(2-Aminoethyl)thieno[3,2-*b*]pyrrole (**4**).—A solution of crude **2** (500 mg) in anhydrous ether (25 ml) was added dropwise to a

(7) We gratefully acknowledge a grant to the School of Chemical Sciences of the University of Illinois at Urbana-Champaign from the National Science Foundation, which helped to make the purchase of the HR-220 possible.

(8) We gratefully acknowledge NIH Grants GM-16864 and CA-11388 to the School of Chemical Sciences of the University of Illinois at Urbana-Champaign, which helped to make purchase of the SM-1B possible.

(9) In one experiment the ethereal extracts were evaporated to dryness, affording a 36% yield of the crude acid **5a**: mp 134–138°; ir (KBr) 1695–1725 cm^{-1} (broad). Attempted recrystallization from water or from 50% aqueous methanol resulted in the decomposition of the sample.

stirred dispersion of excess lithium aluminum hydride (120 mg) in anhydrous ether (25 ml). The mixture was stirred for 15 min at room temperature and then the excess hydride was destroyed by the cautious addition of water. The ethereal layer was separated and the aqueous layer was shaken with chloroform (100 ml). The combined organic extracts were dried ($MgSO_4$) and then evaporated to leave a pale yellow oil. Distillation in a microsublimation apparatus gave 300 mg (59%) of the amine **4** as pale yellow prisms: mp 84–86°; nmr (acetone-d_6) δ 2.86 (t, 2 H, J = 7 Hz, CH_2CH_2), 3.27 (s, 2 H, NH_2), 3.52 (t, 2 H, J = 7 Hz, CH_2CH_2), 6.82 (s, 1 H, H-5), 6.90 (d, 1 H, $J_{2,3}$ = 5.0 Hz, H-3), 7.06 (d, 1 H, $J_{2,3}$ = 5.0 Hz, H-2). The absorptions due to H-2 and H-5 were further split by $J_{2,5}$ = 1.3 Hz.

Anal. Calcd for $C_8H_{10}N_2S$: C, 57.87; H, 6.02; N, 16.86. Found: C, 57.94; H, 5.97; N, 16.57.

Ethyl 2-Acetamido-2-carboethoxy-3-(6-thieno[3,2-*b*]pyrrolyl)-propionate (3a). Method 1.—The solution formed by reaction of sodium (149.5 mg, 6.5 mmol) with dry ethanol (10 ml) was added under anhydrous conditions and a nitrogen atmosphere to a stirred solution of diethyl acetamidomalonate[10] (1.41 g, 6.5 mmol) in dry ethanol (5 ml). The methiodide of **1a** (2.354 g, 6.5 mmol) was added in small portions over a 10-min period, and the resulting heterogeneous mixture was left stirring for 3.5 hr at room temperature. The solid was collected, washed with cold dry ethanol, and dried to give 1.734 g (76%) of **3a**, mp 198.5–200.5°. A further 215 mg of **3a** was obtained by concentrating the filtrate and adding water (total yield 86%). One recrystallization from ethanol produced the analytical sample: mp 199–200°; ir (KBr) 1645 (amide), 1730, with a shoulder at 1750 cm^{-1} (ester carbonyl); nmr (DMSO-d_6) δ 1.16 (t, 6 H, J = 7 Hz, OCH_2CH_3), 2.00 (s, 3 H, CH_3), 3.50 (s, 2 H, CH_2), 4.18 (q, 4 H, J = 7 Hz, OCH_2CH_3), 6.76 (s, 1 H, H-5), 6.93 (d, 1 H, $J_{2,3}$ = 5.0 Hz, H-3), 7.14 (d, 1 H, $J_{2,3}$ = 5.0 Hz, H-2), 8.00 (s, 1 H, NH), 10.97 (s, 1 H, NH). The absorptions due to H-2 and H-5 were further split by $J_{2,5}$ = 1.3 Hz.

Anal. Calcd for $C_{16}H_{20}N_2O_5S$: C, 54.59; H, 5.73; N, 7.96. Found: C, 54.59; H, 5.68; N, 7.74.

Method 2.—A mixture of **1a** (315 mg, 1.43 mmol), diethyl acetamidomalonate[10] (311 mg, 1.43 mmol), and powdered sodium hydroxide (17 mg) in toluene (3 ml) was refluxed for 53 hr under nitrogen. On cooling overnight the solution deposited **3a** (275 mg). A 23-mg recovery of **1a** was obtained from the filtrate. The yield of **3a** after allowing for recovered **1a** was 59%. Recrystallization from ethanol gave 194 mg (48%) of **3a**.

Anal. Calcd for $C_{16}H_{20}N_2O_5S$: C, 54.59; H, 5.73; N, 7.96. Found: C, 54.83; H, 5.79; N, 7.65.

Ethyl 2-Acetamido-2-cyano-3-(6-thieno[3,2-*b*]pyrrolyl)propionate (3d).—This was prepared from ethyl acetamidocyanoacetate and the methiodide of **1a** by the procedure given for **3a** (method 1). The yield (first crop) was 40%; mp 192–193° (from ethanol); ir (KBr) 1660 (amide), 1740 (ester), 2240 cm^{-1} (CN); nmr (DMSO-d_6) δ 1.00 (t, 3 H, J = 7 Hz, OCH_2CH_3), 1.98 (s, 3 H, CH_3), 3.46 (s, 2 H, CH_2), 4.07 (q, 2 H, J = 7 Hz, CH_2CH_3), 6.97 (d, 1 H, $J_{2,3}$ = 5.0 Hz, H-3), 7.05 (s, 1, H, H-5), 7.17 (d, 1 H, $J_{2,3}$ = 5.0 Hz, H-2), 9.20 (s, 1 H, NH), 11.15 (s, 1 H, NH). The absorptions due to H-2 and H-5 were further split by $J_{2,5}$ = 1.3 Hz.

Anal. Calcd for $C_{14}H_{15}N_3O_5S$: C, 55.13; H, 4.96; N, 13.78. Found C, 55.20; H, 4.97; N, 13.46.

Ethyl 2-Acetamido-2-carboxy-3-(6-thieno[3,2-*b*]pyrrolyl)propionate (3b).—A mixture of **3a** (2.456 g, 7.0 mmol), 1 *N* sodium hydroxide (7.2 ml), water (18 ml), and ethanol (50 ml) was stirred under nitrogen for 4.5 hr at room temperature. The mixture was diluted with 1 *N* sodium hydroxide (0.3 ml) and ethanol (15 ml) and stirred for 11 hr. The resulting solution was concentrated to *ca.* 10 ml under reduced pressure with very little heat. Unreacted **3a** (310 mg) was collected after the solution had cooled to 0°. The filtrate was diluted to about 25 ml with water, cooled to 0°, and carefully acidified with 1 *N* hydrochloric acid (8 ml). The copious white precipitate which formed was left at 0° for 24 hr. The half-ester **3b** was collected and washed well with ice-cold water. Decomposition of **3b** was minimized by adding the wash water before the last trace of acidic solution was filtered. The white, granular, slightly hygroscopic solid was dried to give 1.42 g (72% based on reacted **3a**) of analytically pure **3b**: mp 103–107°; ir (KBr) 1610–1650 (amide, carboxylic acid), 1720–1730 cm^{-1} (ester).

Anal. Calcd for $C_{14}H_{16}N_2O_5S$: C, 51.90; H, 4.98; N, 8.65. Found: C, 52.15; H, 4.98; N, 8.80.

Ethyl 2-Acetamido-3-(6-thieno[3,2-*b*]pyrrolyl)propionate (6a).—A thin film of **3b** (1.26 g, 3.9 mmol) was deposited on the walls of a 100-ml round-bottom flask by evaporating a solution of **3b** in ethanol to dryness on a rotary evaporator. The flask was filled with nitrogen and heated for 1 hr at 110–115° in an oil bath. Water (30 ml) was added and the aqueous mixture was refluxed for 4 hr until the evolution of carbon dioxide had ceased. The crude product was extracted into ethyl acetate. Evaporation of the extracts under reduced pressure left a viscous yellow oil which slowly solidified to give 0.994 g of a highly hygroscopic solid. The solid was purified by column chromatography (silica gel, ethyl acetate) to give 0.602 g (55%) of **6a** as an amber, highly hygroscopic solid: ir (KBr) 1625–1645 (amide), 1705–1715 cm^{-1} (ester); nmr ($CDCl_3$) δ 1.23 (t, 3 H, J = 7 Hz, OCH_2CH_3), 1.98 (s, 3 H, CH_3), 3.16 (d, 2 H, J = 5.0 Hz, CH_2CH), 4.17 (q, 2 H, J = 7 Hz, OCH_2CH_3), 4.88 (broad m, 1 H, CH_2CHNH), 6.25 (d, 1 H, J = 7 Hz, NHCH), 6.73 (s, 1 H, H-5), 6.87 (d, 1 H, $J_{2,3}$ = 5.4 Hz, H-3), 7.04 (d, 1 H, $J_{2,3}$ = 5.4 Hz, H-2), 8.87 (s, 1 H, H-4). The absorptions due to H-2 and H-5 were further split by $J_{2,5}$ = 1.2 Hz.

Anal. Calcd for $C_{15}H_{16}N_2O_3S$: C, 56.76; H, 5.76; N, 10.01. Found: C, 56.03; H, 5.89; N, 9.95.

2-Acetamido-3-(6-thieno[3,2-*b*]pyrrolyl)propionic Acid (6b).—A stirred mixture of **3a** (1.775 g, 5 mmol), ethanol (50 ml), 1 *N* sodium hydroxide (7.50 ml), and water (42.5 ml) was refluxed under nitrogen with minimum exposure to light. A slow flow of nitrogen was passed through the apparatus and into a trap containing a saturated aqueous solution of barium hydroxide. The trap was periodically changed in order to follow the progress of the decarboxylation. The mixture became homogeneous almost immediately and carbon dioxide evolution started within 1 hr. The solution was refluxed until carbon dioxide evolution had ceased (approximately 14 hr). The cooled reaction solution was adjusted to pH 6 by the careful addition of 1 *N* hydrochloric acid. Boiling was continued and carbon dioxide was rapidly evolved. The pH was 8 after 1 hr. Hydrochloric acid was again added until the pH was 6, and this procedure was repeated until carbon dioxide evolution had ceased and the pH of the resultant solution remained constant. The cooled solution was treated with charcoal and then acidified, with stirring, to pH 3 by the addition of 1 *N* hydrochloric acid (5.40 ml). Nitromethane (1 l.) was added, and with efficient stirring the two-phase system was heated in a distillation apparatus. The ethanol and water were distilled along with the nitromethane and gradually a homogeneous solution was formed. Toward the end of the distillation a suspension of sodium chloride appeared. The distillation was continued until the refractive index of the distillate was identical with that of nitromethane. The heterogeneous mixture was filtered through a fluted filter paper and the colorless filtrate was concentrated to *ca.* 150 ml under reduced pressure, when **6b** usually started to separate. The mixture was left at −15° overnight. The white crystals were collected and redissolved in a minimum volume of acetone (*ca.* 40 ml).[11] High-boiling petroleum ether was added to the cloud point (*ca.* 30 ml). Gentle warming on a steam bath gave a homogeneous solution, which was cooled to room temperature and then to −15°. The extremely hygroscopic white crystals of **6b** that were deposited amounted to 0.556 g (43.6%): mp 191–194°; mass spectrum *m/e* 252.0569 ($C_{11}H_{12}N_2O_3S$), 193 (M − CH_3CONH_2), 136.0220 (C_7H_6NS); ir (Nujol mull) 1700 (carboxylic acid), 1592, 1545 (amide), 1460, 1377, 1225, 825 cm^{-1}; ir (DMSO) 1720 (carboxylic acid), 1662, 1545 (amide), 1222, 830 cm^{-1}; nmr (DMSO-d_6) δ 1.87 (s, 3 H, CH_3), 3.00 (d, 2 H, J = *ca.* 8 Hz, CH_2CH), 4.50 (m, 1 H, CH_2CHNH), 7.09 (m, 3 H, 6-substituted thieno[3,2-*b*]pyrrole), 8.06 (d, 1 H, J = *ca.* 8 Hz, NHCH), 10.78 (broad s, 1 H, H-4).

Anal. Calcd for $C_{11}H_{12}N_2O_3S$: C, 52.37; H, 4.79; N, 11.10. Found: C, 52.65; H, 5.03; N, 11.01.

A second crop of 138 mg (10.9%) of **6b** was obtained by concentrating the mother liquors.

The amido acid **6b** was soluble in DMSO, DMF, ethanol, nitromethane, and *n*-butyl alcohol. It was very soluble in acetone or THF only when a trace of water was present.

Ethyl 2-Formamido-2-carboethoxy-3-(6-thieno[3,2-*b*]pyrrolyl)-propionate (3c).—Sodium hydride (110.4 mg, 2.76 mmol)[12] was

(10) Dow Chemical Co.

(11) If this solution was colored, it was treated with charcoal.

(12) As a 60.2% dispersion in mineral oil (Metal Hydrides Inc., Beverly, Mass.).

added to a stirred solution of diethyl formamidomalonate[13] (0.560 g, 2.76 mmol) in dry THF (50 ml) maintained under anhydrous conditions. The methiodide of **1a** (1.05 g, 2.9 mmol) was added in small portions and stirring was continued overnight at room temperature. The mixture was evaporated under reduced pressure. The crude product was taken up in chloroform, washed three times with water, and dried (Na_2SO_4). The chloroform was removed and the residual oil was purified by column chromatography (silica gel, ethyl acetate) and gave 0.700 g (76% based on malonate ester) of **3c**: mp 173–174°; a mass spectrum showed the molecular ion at *m/e* 338; nmr (acetone-d_6) δ 1.28 (t, 6 H, J = 7 Hz, OCH_2CH_3), 3.72 (s, 2 H, CH_2), 4.3 (q, 4 H, J = 7 Hz, OCH_2CH_3), 6.91 (s, 1 H, H-5), 6.97 (d, 1 H, $J_{2,3}$ = 5.2 Hz, H-3), 7.14 (d, 1 H, $J_{2,3}$ = 5.2 Hz, H-2), 7.80 (broad s, 1 H, NH), 8.28 (s, 1 H, CHO). On expansion of the aromatic portion, the absorptions due to H-5 and H-2 were found to be further split by $J_{2,5}$ = 1.25 Hz.[14]

Anal. Calcd for $C_{15}H_{18}N_2SO_5$: C, 53.25; H, 5.36; N, 8.28. Found: C, 53.44; H, 5.32; N, 8.39.

A similar yield of **3c** (75%) was obtained when the alkylation was carried out in anhydrous ethanol rather than in THF.

2-Amino-3-(6-thieno[3,2-*b*]pyrrolyl)propionic Acid (7).—A stirred mixture of **3c** (1.13 g, 3.34 mmol), ethanol (28 ml), 1 *N* sodium hydroxide (5 ml), and distilled water (24 ml) was gently refluxed under nitrogen with the minimum exposure to light. Nitrogen was passed slowly through the system and the exiting gases were passed through a trap containing a saturated aqueous solution of barium hydroxide. The trap was periodically changed in order that the progress of the decarboxylation might be followed. The mixture became homogeneous almost immediately and carbon dioxide evolution started within 1 hr. The pale yellow solution was refluxed for 26 hr, until carbon dioxide evolution had ceased. The pale brown solution was cooled to room temperature, 1 *N* hydrochloric acid (5 ml) was carefully added to bring the pH to a value between 2.5 and 3, and gentle refluxing was continued. Refluxing was stopped after 6 hr, when carbon dioxide evolution had ceased. The brown aqueous ethanolic solution was cooled and diluted with water (75 ml) and was then concentrated by heating the solution under s stream of nitrogen at atmospheric pressure until the volume was *ca.* 60 ml. The resulting aqueous solution was refluxed for 19 hr under nitrogen with the minimum exposure to light. A tlc of the reaction solution (methanol, silica gel) then showed the predominance of one component which had an R_f value practically identical with that of tryptophan and which gave a positive ninhydrin color. The dark brown reaction solution was cooled, becoming slightly cloudy. It was diluted with water (10 ml) and passed, at the rate of approximately 1 drop/sec, through Amberlite IR-4B (OH^- form, 100 ml of 20–50 mesh) made up into a column of length 18 cm and 2.9-cm internal diameter. The column was then washed with degassed distilled water and the eluate was collected in a vessel through which a slow stream of nitrogen was flowing. The product was in the first 750–850 ml. The solution was concentrated to *ca.* 10–15 ml under reduced pressure at near room temperature. A column of well-washed DEAE-cellulose[15] was made up measuring about 40 cm in length and 3.75 cm in internal diameter. A pressure head of degassed, distilled water was connected at the top of the column and the height was adjusted until the rate of flow was 30–66 ml/hr and then *ca.* 2–3 l. of water was passed through the column. The pressure head was disconnected and the water which remained above the DEAE-cellulose was drained until *ca.* 1–2 cm of water covered the surface. The dark-colored concentrate from the Amberlite IR-4B (OH^- form) column was placed at the top of the column and was then allowed to be absorbed by the DEAE-cellulose by applying a slightly positive nitrogen pressure such that the rate of flow was about the same as that above. The pressure head was reconnected and the column was eluted with degassed, distilled water. Fractions were collected and tested for chloride ion (silver nitrate) and for amino acid (ninhydrin). The first 256 ml was negative to both tests. Sodium chloride was contained in the next 182 ml of pale yellow eluate. The following 316 ml was again negative to both tests. The amino acid **7** was contained in the next 1124 ml. Further elution gave only a fraction negative to both tests. Dark decomposition products from the reaction were held at the top of the column. The fraction containing **7** was concentrated to *ca.* 5 ml under reduced pressure at about room temperature. Ethanol and then benzene were added and the remaining water was removed as the azeotrope under reduced pressure. The remaining ethanolic solution was about 20 ml in volume, and a small amount of dark solid was deposited when the solution was left overnight at room temperature. The dark yellow filtrate was diluted with ethanol, concentrated to 10–15 ml, and left at −15° for 5 days. Impure **7** separated and was collected, washed with cold dry ethanol followed by ether, and dried. A further yield of **7** was obtained on adding ether to the filtrate. The combined crops were rechromatographed on DEAE-cellulose. Work-up, as above, gave a concentrated ethanolic solution (10–15 ml) which deposited **7** (186.5 mg) on being left at −15° for several days. A further 212.5 mg of slightly less pure **7** was obtained on adding ether to the filtrate. The total yield, based on **3c**, was 56.9%. Recrystallization from ethanol gave a solid which decomposed between 240 and 245°: *m/e* 210.0463 ($C_9H_{10}N_2O_2S$), 136.0221 (C_7H_6NS); ir (KBr) 3425 (NH), 3300–2500 (broad), 1625, 1590 (amino acid), 1525, 1500 cm^{-1}; nmr (D_2O) δ 7.027 (s, 1 H, H-5), 7.050 (d, 1 H, $J_{2,3}$ = 5.2 Hz, H-3), 7.204 (d, 1 H, $J_{2,5}$ = 5.2 Hz, H-2). The absorptions due to H-2 and H-5 were further split by $J_{2,5}$ = 1.3 Hz. In addition, there was an ABX system with the X portion consisting of an apparent doublet of doublets with J_{app} = 5.1 Hz, centered at 4.004 and integrating for 1 H (CH_2-CH), and with the AB portion consisting of a multiplet centered at 3.245 and integrating for 2 H (CH_2CH).

Anal. Calcd for $C_9H_{10}N_2O_2S$: C, 51.41; H, 4.79; N, 13.32; S, 15.25. Found: C, 51.39; H, 4.82; N, 13.08; S, 14.99.

Hydrazinolysis by Hydrazine Hydrate Containing a Catalytic Quantity of Hydrazine Dihydrochloride.—A 69% yield of pure tryptophan resulted when a mixture of *N*-acetyltryptophan and hydrazine hydrate containing a trace of the dihydrochloride was boiled for 1 hr and then added to acetone. A 90% yield of pure glycine was obtained by reaction of the reagent with *N*-acetylglycine at room temperature for 58 hr and isolation as above.

Dehydrogenation of the Dimer 10.—A mixture of the dimer[4] **10** (300 mg, 1 mmol) and chloranil (300 mg, 1.2 mmol) in xylene (15 ml) was refluxed for 4 hr. A first crop of the dehydrogenated dimer was collected from the cooled solution. The filtrate was mixed with an equal volume of ether and washed with 1 *N* sodium hydroxide. The organic layer was dried ($MgSO_4$) and concentrated to *ca.* 5 ml. On cooling, a second crop of product was precipitated from the solution. The two crops were combined and washed with hot methylcyclohexane. Crystallization from aqueous methanol gave 180 mg (60%) of product: mp 205°; mixture melting point with **10** showed a depression; nmr (DMSO-d_6) showed aromatic absorptions at δ 7.12, 7.23, 7.64 and 7.73.

Anal. Calcd for $C_{18}H_{16}N_2O_4S_2$: C, 55.67; H, 4.13; N, 7.22. Found: C, 55.56; H, 4.11; N, 6.81.

Registry No.—**1a** methiodide, 36004-16-7; **3a**, 36004-17-8; **3b**, 36004-18-9; **3c**, 36004-19-0; **3d**, 36004-20-3; **4**, 36004-21-4; **5b**, 36004-22-5; **6a**, 36004-23-6; **6b**, 36004-24-7; **7**, 36004-25-8; **10** dehydrogenation product, 36004-26-9; tryptophan, 73-22-3; tryptamine 61-54-1; indoleacetic acid, 87-51-4.

(13) Aldrich Chemical Co., Inc., Milwaukee, Wis.

(14) R. J. Tuite, H. R. Snyder, A. L. Porte, and H. S. Gutowsky, *J. Phys. Chem.*, **65**, 187 (1961).

(15) Sigma Chemical Co., St. Louis, Mo.