# Synthesis of 1,3,4,9-Tetrahydro-1-alkylthiopyrano[3,4-*b*]indole-1-acetic Acids. The Sulfur Isoster of Prodolic Acid.

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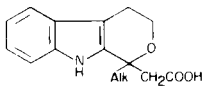
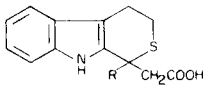
The condensation of thiotryptophol with β-ketoesters and successive hydrolysis of the intermediates afforded the title compounds which represent a novel ring system. The reaction of thiotryptophol with ethyl propiolate in the presence of sodium methoxide gave the unstable 1,3,4,9-tetrahydrothiopyrano[3,4-*b*]indole-1-acetic acid. One of the described products is the sulfur isoster of the potent antiinflammatory agent, prodolic acid. The sulfur compounds of the present study displayed lower antiinflammatory activities than the corresponding oxygen analogs. A simple preparation of thiotryptophol is described.

A recent report (1) from these laboratories has described the synthesis of 1-substituted 1,3,4,9-tetrahydropyrano-[3,4-*b*]indole-1-acetic acids I which exhibit strong antiinflammatory activities. It was reasonable to expect that variations of this novel ring system, in the framework of isosterism, might lead to an improvement or a modification of the activity. We now communicate our studies on the synthesis of corresponding thiopyrano[3,4-*b*]indole derivatives II.




I




II, R = Alk or H

Dreiding molecular models of I and II indicate that the replacement of the oxygen by the bulkier sulfur atom changes the conformation of the dihydropyrano ring considerably. We propose that this ring adopts the half-chair conformation (Fig. 1) in I, whereas the sofa conformation (Fig. 2) seems to be the likely one for the dihydrothiopyrano ring in II. Thus, there are five nearly coplanar atoms, and the apical sulfur atom projects out of the plane. Steric repulsions of the quasi-axial substituents of the dihydrothiopyrano ring tend to flatten the ring.

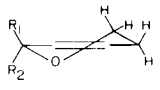


Fig. 1

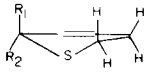
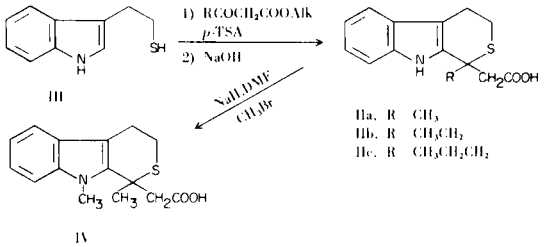


Fig. 2

The key to the synthesis of the thiopyrano[3,4-*b*]indoles II was the acid-catalyzed condensation of thiotryptophol III with β-ketoesters followed by direct hydrolysis of the

SCHEME 1



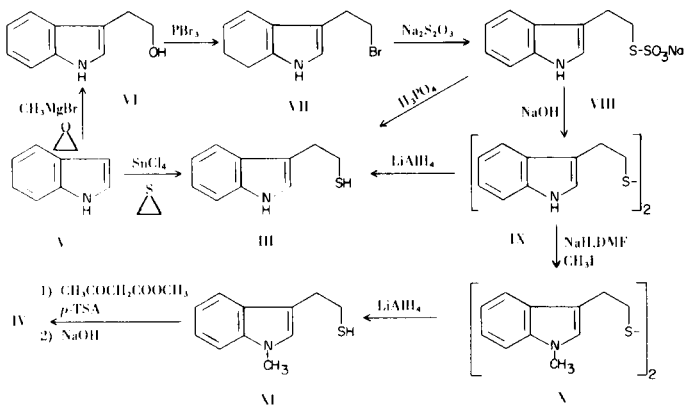

III

IV

intermediate esters (Scheme 1). The resultant acids could be *N*-alkylated with alkyl bromides in the presence of sodium hydride (IIa → IV).

Preparation of the requisite thiotryptophol was recently described by Suvorov and Buyanov (2). We repeated this preparation (Scheme 2, VI → VII → VIII → IX → III) in the overall yield of 53%, however, some serious scaling-up difficulties were encountered. Our modified three-step route alleviated these problems: tryptophol VI was treated with phosphorus tribromide in methylenechloride, the resultant bromoethylindole VII was heated with a solution of sodium thiosulfate, and the Bunte salt VIII was recrystallized. Hydrolysis of VIII with 50% phosphoric acid or with deaerated 10% hydrochloric acid yielded directly thiotryptophol III. Although the reaction conditions were not necessarily optimized in every step, the overall yield was over 62%. An alternative synthesis of thiotryptophol (3) which comprises indolization of 4-(phenylmethylthio)-butanal and debenzylation of the resultant 3-[(2-phenylmethylthio)ethyl]indole does not seem to be practical. As starting material for our syntheses, tryptophol VI was prepared from indole V. The metalation of V with a Grig-

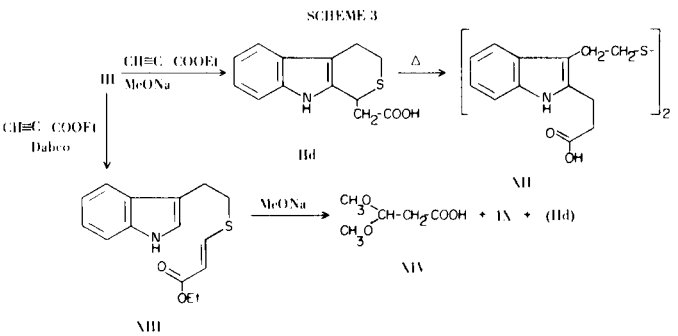
SCHEME 2



nard reagent was followed by treatment with ethylene oxide (4). Similarly, mercaptoethylation of indole with episulfide would be an ideal procedure for preparing thiotryptophol, however, it has been well documented that organometallics eliminate sulfur from episulfides (5). Therefore, we carried out the reaction of indole with episulfide in the presence of stannic chloride. Thiotryptophol III was obtained in a 10% yield along with smaller amounts of disulfide IX and a variety of side products. Methylation of IX and subsequent reduction of X afforded *N*-methyl thiotryptophol XI. Being less stable than thiotryptophol, XI was immediately condensed with methyl acetoacetate and the intermediate product was hydrolyzed to the crystalline acid IV.

In view of the successful synthesis of IIa-c, it was of interest to investigate preparative routes to the carboxylic acid IId which is not alkyl-substituted in the β-position. Our approach (Scheme 3) made use of the addition-cyclization reaction of thiotryptophol III with ethyl propiolate. A mixture of both components was treated with methanolic sodium methoxide to give the desired acid IId in one step (54% yield). The action of Dabco catalyst on the same mixture produced the trans-(β-substituted)acrylate XIII. The structure is supported by the nmr spectrum which shows two vinyl proton doublets centered at δ 5.75 and 7.70 with a large coupling constant of 15 Hz. Treatment of XIII with 1 mole of sodium methoxide in methanol at

SCHEME 3



25° gave no reaction, whereas refluxing XIII with methanolic sodium methoxide (2 moles) for 4 hours led to a mixture of IX and malonaldehydic acid dimethyl acetal XIV. Mild hydrolysis of XIII with sodium hydroxide in aqueous methanol yielded IId as a minor by-product.

The carboxylic acid IId was found to be unstable. When crystallized from benzene, IId underwent ring opening and oxidation to yield XII.

The antiinflammatory properties of IIa-d were less pronounced than those of the corresponding isosteric acids in the pyrano[3,4]indole series (1). The most potent of the series, compound IIb, was several times less active than prodolic acid (6). It seems that the perturbation of the molecular shape induced by the O → S replacement (*vide supra*) produces a molecule which does not fulfill the steric requirements associated with a strong antiinflammatory effect (1).

## EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Ir spectra were measured with a Perkin-Elmer 225 spectrometer. All pmr spectra were recorded on a Varian A-60A instrument with TMS as internal standard.

Indole-3-ethanethiol (Thiotryptophol), III.

a) To a stirred solution of 140 g. of indole-3-ethanol (tryptophol), VI, in 2900 ml. of methylene chloride was added dropwise a solution of 24 ml. of phosphorus tribromide in 100 ml. of the same solvent at 0°. The reaction mixture was stirred at ambient temperature overnight and poured onto crushed ice. The organic layer was separated, washed quickly with cold 10% sodium bicarbonate, then with water, dried over magnesium sulfate, and evaporated to dryness. There was obtained 160 g. (82%) of practically pure 3-(2-bromoethyl)indole, VII, a pale yellow solid, m.p. 97-98° (reported m.p. 98.5-99° (7)).

A solution of 194 g. of sodium thiosulfate in 1.2 l. of water and 2 l. of ethanol was poured onto 160 g. of VII. The reaction mixture was heated under reflux for 4 hours, allowed to cool, and evaporated under reduced pressure. The residue was slurried in 0.5 l. of 2-propanol and the solvent was removed in a rotating evaporator. The crude solid was recrystallized from 1.7 l. of 2-propanol (insoluble material filtered off) to give 240 g. of crystalline material, sodium (3-indolyl)ethyl thiosulfate, VIII, containing approximately 30% of inorganic salts. This material was used directly in the next step.

Fifty g. of the foregoing sodium salt VIII was suspended in 1000 ml. of 50% phosphoric acid and 300 ml. of ether. The heterogeneous mixture was stirred at room temperature overnight, in a nitrogen atmosphere. The organic layer was separated, 300 ml. of fresh ether was added to the aqueous phase, and stirring was continued at reflux temperature (35-40°) for 12 hours. The reaction mixture was allowed to cool, the ethereal extracts were combined, washed with water, dried over magnesium sulfate, filtered, and evaporated. The product (20 g.) was homogeneous on tlc ($R_f$ 0.85 on silica plate in chloroform), and solidified in the fridge. Crystallization from ether-petroleum ether afforded an analytical sample, m.p. 35-36°, lit. m.p. 34-36° (2); ir (chloroform): 3460 (vs, NH), 2570 (w, SH), and 1625 $cm^{-1}$; pmr (deuteriochloroform): δ 1.42 (t, J = 7 Hz, 1H, SH), 3.00 (m, 4H, $CH_2$), 6.99 (d, J = 2.5

Hz, 1H, =CH-), 7.26 (m, 3H, ArH), 7.66 (m, 1H, ArH-7), 7.86 (b, 1H, NH).

*Anal.* Calcd. for $C_{10}H_{11}NS$: C, 67.76; H, 6.26; N, 7.91; S, 18.08. Found: C, 67.59; H, 6.13; N, 7.88; S, 18.14.

b) To a cold (-10°) solution of indole (2.34 g.) and ethylene sulfide (1.2 g.) in carbon tetrachloride (20 ml.) was added a cold solution of stannic chloride (5.22 g.) in carbon tetrachloride (25 ml.) during 2 hours. The reaction mixture was diluted with some chloroform, washed with icy water, and evaporated. Chromatography on silica gel gave 1 g. of starting indole, and further elution with chloroform afforded 0.36 g. (10%) of thiotryptophol, identical with the material prepared by the foregoing procedure in every respect.

General Procedure for the 1,3,4,9-Tetrahydro-1-alkylpyrano[3,4-*b*]-indole-1-acetic Acids.

In a typical experiment, a solution of thiotryptophol, III, (1.5 g.) and methyl acetoacetate (1.2 g.) in dry benzene (50 ml.) was heated at 60-70° for 20-30 minutes, thereafter, *p*-toluenesulfonic acid (0.15 g.) was added, and the reaction mixture was refluxed under a Dean-Stark water separator for 12 hours. After cooling, the solution was washed with 10% aqueous sodium bicarbonate, followed by water. Removal of the solvent gave a semi-solid residue which was dissolved in 200 ml. of methanol and 10 ml. of 20% sodium hydroxide. The mixture was stirred at room temperature overnight, and then shortly heated under reflux. Methanol was removed with a rotavapor, the aqueous solution was diluted, washed with ether, filtered, acidified with 6*N* hydrochloric acid, and extracted with chloroform. The combined extracts were washed successively with water and saturated brine solution, dried over magnesium sulfate, filtered, and evaporated. Recrystallization of the residue from benzene and benzene-hexane mixture yielded 2.1 g. of IIa which melted at 110°, resolidified and melted again at 147-149°. According to the pmr spectrum, this material was a benzene solvate. Upon thorough drying at 110°/ 1mm Hg for 24 hours, the sample (1.5 g., 68%) exhibited one melting point 147-149°; ir (chloroform): 3470, 3410, and 1704 with an infelxion at 1765 $cm^{-1}$; pmr (deuteriochloroform): δ 1.86 (s, 3H, $CH_3$), 3.05 and 3.13 (s, 6H, $CH_2$), 7.35 (m, 4H, ArH), 8.71 (b, 1H, NH), 10.31 (b, 1H, COOH).

*Anal.* Calcd. for $C_{14}H_{15}NO_2S$: C, 64.35; H, 5.70; N, 5.35; S, 12.26. Found: C, 64.68; H, 5.98; N, 5.47; S, 12.21.

The above procedure was effective in condensation of III with ethyl β-oxovalerate to yield IIb (45%); m.p. 138° (benzene-hexane); ir (chloroform): 3460 and 1705 $cm^{-1}$; pmr (deuteriochloroform): δ 0.95 (t, J = 7 Hz, 3H, $CH_3$), 2.21 (q, J = 7 Hz, 2H, $CH_2$), 3.00 (s, 4H, $CH_2$-$CH_2$-S), 3.11 (s, 2H, $CH_2$-CO), 7.28 (m, 4H, ArH), 8.70 (b, 1H, NH), 10.50 (s, 1H, COOH).

*Anal.* Calcd. for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22; N, 5.09; S, 11.65. Found: C, 65.55; H, 6.16; N, 5.27; S, 11.71.

In a similar manner, using ethyl β-oxocaproate, the sulfur isoster of prodolic acid was obtained IIc (30%); m.p. 127-129° (methanol-water); ir (chloroform): 3460, 2960, and 1705 $cm^{-1}$; pmr (deuteriochloroform): δ 0.88 (t, J = 7 Hz, 3H, $CH_3$), 1.50 (m, 2H, -$CH_2$-), 2.17 (t, J = 7 Hz, 2H, -C-$CH_2$-), 3.02 (s, 4H, $CH_2$-$CH_2$-S), 3.12 (s, 2H, $CH_2$-CO), 7.27 (m, 4H, ArH), 8.72 (b, 1H, NH), 9.60 (b, 1H, COOH).

*Anal.* Calcd. for $C_{16}H_{19}NO_2S$: C, 66.41; H, 6.62; N, 4.84; S, 11.08. Found: C, 66.18; H, 6.63; N, 4.96; S, 11.05.

Bis-[*N*-methyl-(3-indolyl)ethyl]disulfide, X.

Crude sodium (3-indolyl)ethyl thiosulfate, VIII (6.4 g.), was suspended in ethanol (140 ml.) and 15% aqueous sodium hydroxide (60 ml.). The mixture was heated under reflux for 3 hours, ethanol was removed in a rotavapor, the residue was diluted with water and extracted with ether. The combined extracts were washed with water, dried over magnesium sulfate, filtered, and stripped of the solvent. After recrystallization from benzene-hexane, the product (3 g.), IX, had m.p. 120-121; lit. (2) m.p. 120-121.5°.

This material was dissolved in 15 ml. of anhydrous dimethylformamide, and 1.16 g. of sodium hydride (54% oil suspension) was added. The mixture was stirred 1 hour at ambient temperature, 1.5 g. of methyl iodide was added and stirring was continued overnight. The solvent was removed under reduced pressure, and the residue partitioned between water and chloroform. The organic layer was evaporated and the residual oil was filtered through a column of silica gel with benzene as eluant. A major fraction (homogeneous on tlc) was collected as a colorless oil; 2.8 g. (86%); pmr (deuteriochloroform): δ 3.06 (m, 8H, $CH_2$-$CH_2$-S), 3.59 (s, 6H, N-$CH_3$), 6.78 (s, 2H, =CH-), 7.18 (m, 6H, ArH), 7.53 (m, 2H, ArH-7).

1,3,4,9-Tetrahydro-1,1-dimethylthiopyrano[3,4-*b*]indole-1-acetic Acid, IV.

a) Three g. of IIa was dissolved in 100 ml. of dry dimethylformamide and 20 ml. of benzene. To remove traces of moisture, benzene was distilled off, the solution was cooled to room temperature, and 0.44 g. of sodium hydride (54% oil suspension) was added. After stirring for 30 minutes, the same portion of sodium hydride was added, and stirring was continued for 1 hour. The resultant yellow solution was chilled to 0°, and 1.5 g. of methyl bromide in 10 ml. of dry dimethylformamide was added dropwise (15 minutes). The reaction mixture was stirred at 0° for 4 hours, poured onto 100 g. of ice containing 2 ml. of concentrated hydrochloric acid, and extracted with chloroform. The combined extracts were washed with saturated brine solution, dried over magnesium sulfate, filtered, and thoroughly evaporated to dryness under reduced pressure. The residue was stripped with two 100 ml. portions of benzene, and chromatographed on silica gel. Elution with chloroform afforded 2.4 g. (75%) of IV; m.p. 145-146° (benzene-hexane); ir (chloroform): 1710 with an inflexion at 1745 $cm^{-1}$; pmr (deuteriochloroform): δ 1.92 (s, 3H, $CH_3$), 3.05 (m, 6H, $CH_2$), 3.78 (s, 3H, N-$CH_3$), 7.22 (m, 4H, ArH), 10.95 (s, 1H, COOH).

*Anal.* Calcd. for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22; N, 5.09; S, 11.65. Found: C, 65.23; H, 6.15; N, 5.00; S, 11.72.

b) A solution of X (1.9 g.) in 60 ml. of ether-tetrahydrofuran (5:1) was added dropwise to a stirred slurry of lithium aluminum hydride (0.8 g.) in ether (100 ml.). The reaction mixture was stirred overnight, then heated at reflux for 3 hours and cooled. Water (3.4 ml.) was cautiously added dropwise, and the white precipitate was filtered off. Customary work-up of the filtrate afforded 1.4 g. (78%) of XI (homogeneous on tlc, less polar than the starting disulfide) which was used directly for the condensation. On exposure to air, XI was rapidly oxidized to X.

A mixture of XI (1.4 g.), methyl acetoacetate (1.2 g.), benzene (250 ml.), and *p*-toluenesulfonic acid (0.3 g.) was refluxed under a Dean-Stark water separator for 12 hours. Additional portion of methyl acetoacetate (1.2 g.) was added, and reflux conditions were maintained for 2 hours. After cooling, the reaction mixture was washed with 10% aqueous sodium bicarbonate, and benzene was removed in a rotavapor. The residual material was hydrolyzed with 10% aqueous sodium hydroxide (20 ml.) in methanol (200 ml.) at room temperature. The corresponding acid IV was isolated in the usual manner, and recrystallized from benzene-hexane, m.p. 145-146°. A mixed melting point of the products prepared by

both methods exhibited no depression; ir and pmr spectra were identical with the spectra of IV prepared above.

1,3,4,9-Tetrahydrothiopyrano[3,4-*b*]indole-1-acetic Acid, IId.

A solution of sodium (0.52 g.) in anhydrous methanol (100 ml.) was added at once to a mixture of III (4 g.) and ethyl propiolate (3 g.). The exothermic reaction set in immediately, the resulting solution was stirred for 15 minutes, diluted with 10 ml. of water, and heated under reflux for 90 minutes. The mixture was concentrated to *ca.* 20 ml., diluted with 50 ml. of water, and extracted several times with ether. The aqueous phase was acidified with 10% hydrochloric acid upon cooling and extracted with ether. The combined ethereal extracts were dried over magnesium sulfate and filtered. Removal of the solvent *in vacuo* left 3 g. (54%) of crystalline solid (homogeneous on silica plates). The compound could not be purified by crystallization; ir (chloroform): 3480 and 1700 $cm^{-1}$; pmr (deuteriochloroform): δ 2.93 (m, 6H, $CH_2$), 4.37 (t, J = 7 Hz, 1H, CH-S), 6.9-7.6 (m, 4H, ArH).

3,3′-Dithiodiethylenebis(indole-2-acrylic Acid), XII.

The foregoing acid was repeatedly crystallized from hot benzene; m.p. 171-172°; ir (Nujol): 3430, 3380, and 1655 $cm^{-1}$; uv λ max (methanol): 299 nm (ε, 33,200) and 281 nm (ε, 36,700); pmr (DMSO-$d_6$): δ 3.05 (s, 3H, $CH_2$-$CH_2$-S), 5.78 (d, J = 10 Hz, 2H, =CH-CO), 7.33 (d, J = 10 Hz, 2H, -CH=), 6.7-7.8 (m, 8H, ArH), 10.95 (b, 4H, NH and COOH).

*Anal.* Calcd. for $C_{26}H_{24}N_2O_4S_2$: C, 63.39; H, 4.91; N, 5.69. Found: C, 63.14; H, 5.05; N, 5.44.

Ethyl β-[[(3-Indolyl)ethyl]thio]acrylate, XIII.

To a solution of III (1 g.) and ethyl propiolate (0.56 g.) in benzene (10 ml.) was added a catalytic amount of Dabco. The reaction mixture was stirred at 5° for 45 minutes, washed with water, and evaporated under reduced pressure. The residue was chromatographed on silica using benzene-chloroform (1:1) as the eluent to give 1.1 g. (70%) of a colorless oil; ir (chloroform): 3485 and 1700 $cm^{-1}$; pmr (deuteriochloroform): δ 1.26 (t, J = 7 Hz, 3H, $CH_3$), 3.11 (s, 4H, $CH_2$-$CH_2$-S), 4.18 (q, J = 7 Hz, 2H, $CH_2$), 5.75 (d, J = 15 Hz, 1H, =CH-CO), 7.70 (d, J = 15 Hz, 1H, S-CH=), 6.9-7.7 (m, 5H, ArH), 8.15 (b, 1H, NH).

Attempted Cyclization of XIII.

A solution of XIII (2.75 g.) in anhydrous methanol (30 ml.) was added to a solution of sodium (0.46 g.) in the same solvent (70 ml.) and the mixture was heated under reflux for 4 hours. Five ml. of water was added, and heating was continued for 2 hours. The reaction mixture was concentrated, diluted with water, and extracted with ether. Evaporation of the solvent yielded crude IX (1.2 g.) which was recrystallized from benzene-hexane; m.p. 120-121°. The aqueous phase was acidified with 10% hydrochloric acid upon cooling and extracted with ether. Usual work-up of the combined extracts gave 0.9 g. of XIV as an oil (8); pmr (deuteriochloroform): δ 2.67 (d, J = 6 Hz, 2H, $CH_2$), 3.40 (s, 6H, $CH_3O$), 4.86 (t, J = 6 Hz, 1H, CH), 9.42 (s, 1H, COOH).

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