Benzo[*b*]thiophene Derivatives. XXIII. Derivatives of 5,6-Dihydroxy-3-benzo[*b*]thienylacetic Acid (1)

E. Campaigne, E. Homfeld and Dale E. Mais (2)

Chemistry Laboratories, Indiana University, Bloomington, Indiana 47401

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A series of 5,6-disubstituted benzo[*b*]thiophenes have been synthesized for biological evaluation. These include analogs of tryptamine, melatonin and harmaline types, having hydroxy, methoxy, methoxymethyloxy, or isopropylidenedioxy groups at both the 5- and 6- positions. In order to synthesize these, the appropriate mercaptoguaiacols were prepared, and condensed with chloroacetoacetic esters to the 4-arylthioacetoacetic esters. Cyclization of these ketones was best accomplished when the free phenolic groups were masked by methoxymethyl groups. The benzo[*b*]thienylacetic esters were then converted to corresponding amides, reduced to tryptamine analogs, acetylated to melatonin analogs, and cyclized to harmaline analogs. *N*-Acetyltryptamine and 1-methylmelatonin were also synthesized for comparison. Preliminary bioassay results on the melatonin analogs, which showed activity, are reported.

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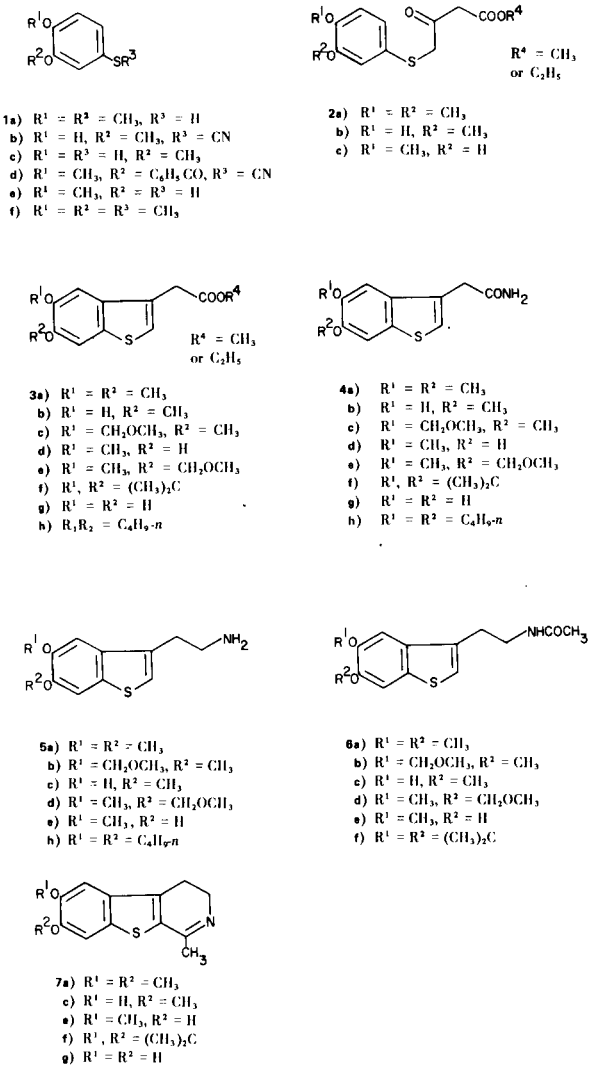
The report (3) that 5,6-dihydroxytryptamine had a long lasting, depleting effect on serotonin levels in the mammalian central nervous system prompted us to synthesize and examine the biological activity of the sulfur isoster of this compound, 3-β-aminoethyl-5,6-dihydroxybenzo[*b*]thiophene (5,6-DHST) (4). It was found that norepinephrine levels in the rat were decreased both peripherally and centrally, but serotonin levels remained relatively unchanged, upon administration of 5,6-DHST, either intraperitoneally or intracerebrally. The qualitative difference in activity of these two analogs suggests that the active agents may be metabolites of the two compounds, which may differ in structure. Furthermore, it was shown (4) that the 5,6-isopropylidene derivative of 5,6-DHST also had biological activity. For these reasons it was desireable to synthesize a variety of derivatives related to 5,6-DHST, in which one or both of the hydroxy groups are blocked by alkyl groups, and to convert these compounds to sulfur analogs of melatonin and harmaline, since compounds of these types have also been shown to have interesting pharmacological properties (5).

The general synthetic approach was that used previously (4), in which an appropriately substituted thiophenol (**1**) was condensed with γ-chloroacetoacetic ester and the keto-sulfide (**2**) so obtained then cyclized with polyphosphoric acid to give the corresponding benzo[*b*]-thienylacetate **3** (Scheme I). The esters were converted to the corresponding amides **4** with alcoholic ammonia and reduced with diborane to the amines **5**. Acetylation of the amines led to the melatonin analogs **6** and these in turn could be cyclized, using Bischler-Napieralski conditions, to the desired harmaline analogs **7**. Compound **5a**, 3-β-aminoethyl-5,6-dimethoxybenzo[*b*]thiophene, has previously been prepared *via* this scheme by Sauter and Stutz (6).

Scheme I



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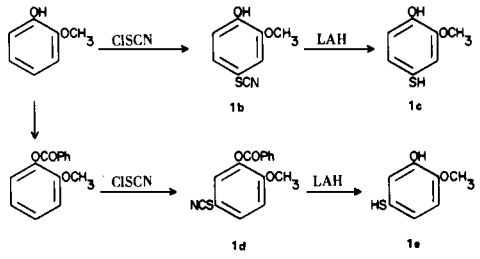
This synthetic scheme requires the corresponding thiols, **1a**, **1c**, and **1e**. 3,4-Dimethoxythiophenol (**1a**), utilized in the initial synthesis (6), was prepared by the method of Fries, Koch and Stückenbrock (7), who obtained **1a** by chlorosulfonation of veratrole and reduction of the sulfonyl chloride, in an overall 37.5% yield. In order to prepare the mercaptophenols **1c** and **1e**, it was necessary to use a milder reagent, and thiocyanogen chloride served quite well, as we had shown for the preparation of 3,4-isopropylidenedioxythiophenol (4). Veratrole was converted to **1a** in approximately 55% yield by thiocyanation followed by reduction with lithium aluminum hydride (LAH).

The synthesis of the isomeric mercaptoguaiacols **1c** and **1e** (Scheme II) was accomplished by deactivation of

Scheme II



the directing influence of the phenolic group by conversion to a benzoate in the one case. Direct thiocyanation of guaiacol gave **1b**, comparable in properties to the compound previously reported (8), and reduction gave thiol **1c**. Conversion of guaiacol to its benzoate, followed by thiocyanation and reduction with excess LAH gave a different thiol, assigned structure **1e**. Although the two thiols, **1c** and **1e** differed by only two degrees in melting point, they gave distinctly different nmr spectra. The relative orientation of all three functional groups in **1c** and **1e** was confirmed by methylation, giving 4-methylthioveratrole (**1f**) in each case, identical to the product obtained by methylation of **1a**.

One would expect to see an ABC pattern in the nmr for both compounds **1c** and **1e**. In fact, all three aromatic protons in **1c** by coincidence absorbed at δ 6.70 to give a sharp singlet. However, in **1e** the pattern was more predictable. Both singlets at δ 6.92 and δ 6.77 were somewhat broad with shoulders well enough indicated to show that an ABC system was present. The methoxy groups in **1c** and **1e** absorb at δ 3.70 and δ 3.80, respectively. The difference here was evidently due to the combined electronic effects of both the thiol and hydroxy groups since the dimethoxythiophenol (**1a**) gave a sharp singlet at δ 3.78 instead of two singlets which one might expect if the thiol or hydroxy group alone was determining the chemical shift.

The several thiols **1a**, **1c**, and **1e** were allowed to react with either the ethyl or methyl esters of 4-chloroacetoacetic acid in pyridine to produce the keto-esters (2) in high yields, and the crude products cyclized in a refluxing solvent containing polyphosphoric acid, phosphorous pentoxide and celite, as previously described (4). The solvent had to be very dry, as traces of moisture decreased the yield. Use of toluene, rigorously dried by refluxing over phosphorous pentoxide for several hours, gave superior yields over the benzene system previously reported (4). Furthermore, addition of celite and phosphorus pentoxide to the mixture before addition of polyphosphoric acid gave a cleaner granular reagent, easier to separate when the reaction was completed.

Treatment of the dimethoxy ester **3a** with ammonia in methanol gave the amide **4a** in satisfactory yield, but the phenolic esters **3b** and **3d** gave poor yields. Protection of the free hydroxyl group with chloromethyl methyl ether gave the amides **4c** and **4e** in satisfactory yields, however. In order to complete this series, 5,6-dihydroxy-3-benzo[*b*]thienylacetamide (**4g**) was also synthesized from the known (4) 5,6-isopropylidenedioxy-3-benzo[*b*]thienylacetamide. To enhance lipid solubility, we also desired the 5,6-di-*n*-butoxy derivatives. The 5,6-dihydroxy ester, **3g**, obtained by acid cleavage of the isopropylidenedioxy derivative, **3f**, was alkylated with butyl bromide to **3h** and converted to the desired amide, **4h**.

These amides were reduced cleanly with diborane, using a simple modification of the technique previously reported (9). As described, the reaction was hard to reproduce. However, if the dry nitrogen was bubbled through the tetrahydrofuran for five minutes before adding the diborane, excellent and reproducible yields were obtained. Evidently dissolved oxygen or unstable peroxides in the THF were removed by this treatment. Addition of dry hydrogen chloride to ether solutions of the crude reduction products precipitated the desired amines, **5**, as hydrochlorides, with cleavage of the protecting methoxymethyl group in the case of **5b** and **5d**.

It has been reported (10) that cyclization of keto-sulfides with polyphosphoric acid may result in rearrangement, to produce the 2-substituted benzo[*b*]thiophenes. Although this rearrangement does not usually occur with aliphatic ketones, it was desireable to confirm the orientation of the acetic acid side chain in an acetoacetic ester cyclization. Taking advantage of the acidic proton in position 2 of the benzo[*b*]thiophene nucleus, which may be selectively deuterated (11), we treated the dimethoxy ethylamine **5a** with butyllithium followed by deuterium oxide. Compound **5a** exhibited three singlets for aromatic portons at δ 7.2, 6.95 and 6.8, and after deuterium exchange, only a trace of the 6.8 proton was retained, thus confirming that cyclization of keto-sulfides,

such as **2**, are cyclized to 3-substituted benzo[*b*]-thiophenes. The proton at position 2 of 3-alkylbenzo[*b*]-thiophenes have been shown to occur in the range of 7.67-6.98 (11).

The several acetamides **6** were prepared by direct acetylation of the appropriate amines **5**. In the case of the phenolic derivatives, **6c** and **6e**, the acetylation was carried out on the methoxymethyl ethers **5b** and **5d**, to obtain the corresponding acetamides **6b** and **6d**, which were then cleaved in dilute acid to provide the phenolic amides **6c** and **6e**. The amides were cyclized, using Bischler-Napieralski conditions (9), to the corresponding 6,7-disubstituted 3,4-dihydro-1-methylbenzothieno[2,3-*c*]-pyridines **7**. Yields in the cyclizations of **6c** and **6e** were very poor, but adequate yields of **7c** and **7e** were obtained by cyclizing **6b** and **6d**. Cyclizing conditions resulted in cleavage of the phenol protecting group to give the desired *S*-harmaline derivatives **7**, in the case of **6b** and **6d**. However, cyclization of the isopropylidenedioxy derivative **6f** with phosphorus pentoxide and phosphorus oxychloride in refluxing toluene did not cleave the protecting group, and the isopropylidenedioxy derivative **7f** could be isolated as a hydrochloride salt, which was cleaved to **7g** on heating in aqueous acid. All of the harmaline analogs **7** were isolated and characterized as salts.

For comparison of melatonin activity, three related indole derivatives were also synthesized. *N*-acetyltryptamine was first reported by Spath and Lederer (18). 1-Methylmelatonin has apparently not been prepared. Taborsky, *et al.*, (19) studied the synthesis and pharmacology of some 1-methylindoles and reported that the melatonin analog, methylated in the 1-position, had been prepared by direct methylation of melatonin in liquid ammonia. However, they later noted that the only indole compound which did not methylate at the 1-position was melatonin; the product isolated may have been the chain *N*-methylated derivative. We, therefore, prepared 1-methylmelatonin by an alternate route. 5-Methoxy-1-methyl-3-(2′-nitrovinyl) indole has previously been reported (21). It was readily reduced with lithium aluminum hydride, and the resulting 5-methoxy-1-methyltryptamine, identical to that reported by Taborsky (19) was acetylated to the desired 1-methylmelatonin. The physical constants of this compound are very similar to those reported (19). The mass spectrum of the compound prepared by the method of Taborsky (19) was consistent with that of the 1-methyl compound (20). 6-Hydroxymelatonin was obtained from Regis Chemical, and methylated to form 6-methoxymelatonin.

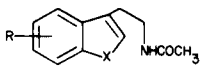
Biological Evaluation.

Preliminary studies on certain of the 3-β-aminoethyl derivatives (**5**) have been reported (5) and a more complete study (16) has been reported elsewhere. The high activity of sulfur isosteres of harmaline has been shown (17) and similar studies on the analogs **7** are currently under way.

Reed (22) has demonstrated a very specific bioassay of melatonin, based on its ability to produce distinctive night coloration in the Australian Pencil fish. Preliminary assay of a number of our melatonin analogs, **6**, and related

Table I

Comparison of Effects of Melatonin and Related Structures on Pencil Fish Melanophores (a)



Compound		MED μg/fish
Melatonin	R = 5-CH_3O, X = NH	0.0001
SAM (d)	R = 5-CH_3O, X = S	0.001
Acetyl-4-Methoxy-SAT (e)	R = 4-CH_3O, X = S	0.1
Acetyl-6-Methoxy-SAT (f)	R = 6-CH_3O, X = S	1.0
6a	R = 5,6-di-CH_3O, X = S	0.1
6f	R = 5,6-isopropylidenedioxy, X = S	10.0 (b)
Acetyl-SAT (g)	R = H, X = S	10.0 (b)
Acetyltryptamine	R = H, X = NH	10.0 (c)
1-Methylmelatonin	R = 5-CH_3O, X = NCH_3	0.01
6-Hydroxymelatonin (h)	R = 5-CH_3O, 6-OH X = NH	0.1
6-Methoxymelatonin	R = 5,6-di-CH_3O, X = NH	0.1

(a) Data supplied by Drs. B. Reed and B. C. Finnin, Victoria College of Pharmacy. (b) Inactive and nontoxic at this dose. (c) Slight activity at this dose, toxic at 100 μg/fish. (d) E. Campaigne and A. Dinner, *J. Med. Chem.*, **13**, 1205 (1970). (e) E. Campaigne and R. B. Rogers, *J. Heterocyclic Chem.*, 10, 297 (1973). (f) T. R. Bosin, *et al.*, *J. Heterocyclic Chem.*, 9, 1265 (1972). (g) W. Herz, *J. Am. Chem. Soc.*, 72, 4999 (1950). (h) Regis Chemical Co.

compounds by this method are reported in Table I (23). It appears from this data that the indolic nitrogen is not the critical moiety for activity. Both the sulfur analog and 1-methylmelatonin show significant activity. Evidently the methoxy group at the 5 position is essential and changing the position of this group or omitting it greatly decreases the activity. Also the presence of two groups tends to diminish activity as can be seen for compounds **6a**, and **6f**. The presence of an additional 6-hydroxy or 6-methoxy group in melatonin itself also decreased activity one thousand-fold.

EXPERIMENTAL

Melting points were obtained on a Mel-Temp capillary melting point apparatus and are uncorrected for stem exposure. Infrared spectra were obtained on a Perkin Elmer Model 137 infrared spectrometer. Nmr spectra were measured on Varian Associates A-60 and HA-100 instruments using deuteriochloroform as a solvent and tetramethylsilane as a reference. Mass spectra were measured on Varian Associates MAT CH-7 spectrometer or on Associated Electrical Industries MS-9 spectrometer at 70 eV. Microanalysis were obtained courtesy of Midwest Microlab, Ltd., Indianapolis, Indiana.

4-Thiocyanoveratrole.

Thiocyanogen chloride (0.23 mole) was prepared from lead thiocyanate and chlorine in 500 ml. of glacial acetic acid, according to the method described by Bacon and Guy (12). To this solution was added 31.7 g,(0.23 mole) of veratrole all at once. The solution was stirred at room temperature for 1 hour and the lead chloride filtered. The filtrate was poured into 3 l. of ice water and allowed to stand over night. The colorless product was filtered to give 40 g. (90%) of essentially pure product. Recrystallization from hexane gave white needles melting at 46-47° [lit. 42-45° (13)].

5-Thiocyanatoguaiacol (**1b**).

Thiocyanogen chloride (approximately 91 mmoles) was prepared as before and 9.05 g. (73 mmoles) of guaiacol added all at once. The work up, as above, yielded 8.1 g. (62%) of essentially pure **1b**. Recrystallization from hexane gave white needles, m.p. 103-104° [lit. 105-106° (**8a**) and 104-105° (**8b**)]; nmr (deuteriochloroform): δ 7.1-7.3 (m, 3H), 6.0 (s, 1H), 3.96 (s, 3H).

5-Thiocyano-2-methoxyphenyl Benzoate (**1d**).

Guaiacol was esterified with benzoyl chloride in dry pyridine to yield the benzoate in 94% yield, melting at 52-53° after recrystallizing from hexane [lit. m.p. 51-52° (14)]. This ester (17.1 g., 75 mmoles) was added to 75 mmoles of thiocyanogen chloride, prepared as above. After work-up, the white precipitate was recrystallized from hexane, giving 14.9 g. (70%) of **1d** melting at 72-73°.

Anal. Calcd. for $C_{15}H_{11}NO_3S$: C, 63.14; H, 3.85; S, 11.23. Found: C, 62.87; H, 3.96; S, 10.89.

3,4-Dimethoxythiophenol (**1a**).

Into a stirred solution of LAH (0.6 g., 15 mmoles) in 100 ml. of ether was slowly dropped 2.5 g (12 mmoles) of 4-thiocyanoveratrole. When the addition was complete, the ether was brought to reflux for 1 hour after which it was carefully quenched by cautiously adding 6 ml. of water, and enough 6*N* hydrochloric acid to dissolve the inorganic salts. The ether phase was separated and the aqueous phase extracted with 3 x 50 ml. portions of ether and the combined ether layers were dried over magnesium sulfate. Evaporation of the ether left a yellow oil which was distilled at 124-127°/2 mm. [lit. 136°/12 mm. (6)] to give 1.3 g. (60%) of a clear oil.

4-Hydroxy-3-methoxythiophenol (**1c**).

Reduction of 4.0 g. (22 mmoles) of **1b** with 0.86 g. (44 mmoles) of LAH was worked up as above. Evaporation of the dried ether yielded an oil which was distilled at 74-76°/0.075 mm. to give 1.8 g. (53%) of a clear oil which solidified and melted at 43-44°; ir (silver chloride): 3.0 μ (OH), 3.9 μ (SH); nmr (deuteriochloroform): δ 6.7 (s, 3H), 5.9 (s, 1H), 3.7 (s, 3H), 3.35 (s, 1H).

Anal. Calcd. for $C_7H_8O_2S$: C, 53.82; H, 5.16; S, 20.52. Found: C, 53.95; H, 5.30; S, 20.80.

3-Hydroxy-4-methoxythiophenol (**1e**).

Reduction of 4.0 g. (14 mmoles) of the benzoate **1d** with 1.12 g. (28 mmoles) of LAH, as above, yielded an oil which was distilled at 110-115°/1.5 mm. to give 2.0 g. (92%) of a clear oil which solidified on standing and melted at 41-42°: ir (silver chloride): 3.0 μ (OH), 3.9 μ (SH); nmr (deuteriochloroform): δ 6.7-7.0 (m, 3H), 5.8 (s, 1H), 3.8 (s, 3H), 3.5 (s, 1H). A mixture of **1e** and **1c** melted in the range 32-36°.

Anal. Calcd. for $C_7H_8O_2S$: C, 53.82; H, 5.16; S, 20.52. Found: C, 54.10; H, 5.37; S, 20.30.

3,4-Dimethoxythioanisole (**1f**).

A. From 3,4-Dimethoxythiophenol.

Into 50 ml. of acetone was added 0.5 g. of potassium carbonate, 1.2 g. (8 mmoles) of **1a** and one equivalent (8 mmoles) of methyl sulfate. The reaction mixture was refluxed over night, filtered, and evaporated to give an oil which was distilled at 85-87°/0.075 mm. in a Hickman apparatus to give 0.8 g. (70%) of **1f**: ir (silver chloride): no thiol band at 3.9 μ; nmr (deuteriochloroform): δ 6.9 (s, 3H), 3.85 (s, 6H), 2.48 (s, 3H).

B. From 3-Mercaptoguaiacol and 4-Mercaptoquaiacol.

In the same way, **1c** and **1e** were alkylated with two equivalents of methyl sulfate to give products identical in all respect to the above oil, in 75% yield in each case (15).

3,4-Disubstituted Phenylthioacetoacetates (**2**).

To a cold stirred solution of the appropriate thiol (**1**) (0.03 mole) in 30 ml. of pyridine was added 0.03 moles of ethyl or methyl 4-chloroacetoacetate (Aldrich). Within 10 minutes a white precipitate formed, after which the mixture was heated on a steam bath for 15 minutes, cooled and diluted with about 50 ml. of water and acidified to *p*H 5. The soluiton was extracted with three 50 ml. portions of ether, the ether dried over magnesium sulfate and evaporated to give 75-90% yields of yellow oils, which were used without further purification. The crude products showed no thiol band in the ir at 3.9 μ, and gave appropriate parent ions in the mass spectrum. In this way, compounds **2a** ($R^4 = C_2H_5$), **2b** ($R^4 = CH_3$ and C_2H_5) and **2c** ($R^4 = CH_3$) were obtained.

Ethyl 5,6-Dimethoxy-3-benzo[*b*]thienylacetate (**3a**) ($R^4 = C_2H_5$).

Into a mechanically stirred mixture of 180 ml. of refluxing benzene, 7.5 g. of celite and 1.5 g. of phosphorus pentoxide was added 5.4 g. of polyphosphoric acid. The mixture was allowed to reflux for an additional 30 minutes at which time 5.0 g. (17 mmoles) of **2a** in 50 ml. of benzene was added all at once. The mixture was refluxed for one hour and then filtered. The benzene solution was washed with 100 ml. of 0.1 *N* sodium hydroxide and

dried over magnesium sulfate. Evaporation of the benzene yielded a yellow oil which was distilled at 175-178°/0.05mm. [lit. 165-170°/0.001 mm. (6)] to give 3.0 g. (65%) of a clear oil which solidified on standing. Recrystallization from hexane afforded colorless rods, m.p. 76°; ir (solid melt): ν 1730 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 1.23 (t, 3H, ester CH_3), 3.80 (s, 2H, $ArCH_2$), 3.97 (s, 6H, OCH_3), 4.17 (q, 2H, ester CH_2), 7.23 (m, 3H, ArH) ppm; ms: m/e 280 (base, M^+), 207 (M^+ -CO_2Et).

Ethyl 5-Hydroxy-6-methoxy-3-benzo[*b*]thienylacetate (**3b**, R^4 = C_2H_5).

Into a mechanically stirred mixture of 180 ml. of dry refluxing toluene was added 7.5 g. of celite and 1.5 g. of phosphorus pentoxide. Upon addition of these, 5.4 g. of polyphosphoric acid was added and the mixture was refluxed for 30 minutes at which time 4.75 g. (16.6 mmoles) of **2b** (R^4 = C_2H_5) in 50 ml. of toluene was added all at once. The mixture was refluxed for 1 hour and then filtered. Evaporation of the toluene gave a yellow oil which solidifide on standing. Recrystallization from hexane afforded colorless meedles (3.4 g., 75%), m.p. 79°; ir (solid melt): ν 1725 (C=O), 3450 (broad, OH) cm^{-1}; nmr (deuteriochloroform): δ 1.27 (t, 3H, ester CH_3), 3.77 (s, 2H, $ArCH_2$), 3.90 (s, 3H, $ArOCH_3$), 4.20 (q, 2H, ester CH_2) 5.83 (s, 1H, OH, exchangeable with deuterium oxide), 7.23 (m, 3H, ArH) ppm; ms: m/e 266 (M^+), 193 (base, M^+ -CO_2Et).

Anal. Calcd. for $C_{13}H_{14}O_4S$: C, 58.62; H, 5.29; S, 12.04. Found: C, 58.40; H, 5.35; S, 11.88.

Methyl 5-Hydroxy-6-methoxy-3-benzo[*b*]thienylacetate (**3b**, R^4 = CH_3).

Similarly, **2b** (R^4 = CH_3) was converted to **3b** (R^4 = CH_3) in 78% yield, obtained as a clear oil which solidified to give a solid melting at 76-77°: ir (potassium bromide): 2.9-3.0 μ (OH), 5.77 μ (C=O); nmr (deuteriochloroform): δ 7.23 (s, 1H), 7.15 (s, 2H), 6.12 (s, 1H), 3.79 (s, 3H), 3.72 (s, 2H), 3.62 (s, 3H).

Anal. Calcd. for $C_{12}H_{12}O_4S$: C, 57.94; H, 4.76; S, 12.91. Found: C, 57.78; H, 4.78; S, 12.88.

Ethyl 5-Methoxymethyloxy-6-methoxy-3-benzo[*b*]thienylacetate (**3c**, R^4 = C_2H_5).

Into 25 ml. of DMF was placed 0.5 g. (2 mmoles) of **3b** R^4 = C_2H_5) and 0.08 g. (2 mmoles) of sodium hydride. This solution was stirred for 1 hour at room temperature at which time 0.3 g. (4 mmoles) of chloromethyl methyl ether was added all at once. This mixture was stirred at room temperature for 3 hours and then poured over 100 ml. of crushed ice. Filtration of the solid followed by recrystallization from petroleum ether afforded 0.4 g. (70%) of white crystals melting at 69-71°: nmr (deuteriochloroform): δ 7.60 (s, 1H), 7.40 (s, 1H), 7.30 (s, 1H), 5.35 (s, 2H), 4.25 (q, 2H), 4.00 (s, 3H), 3.85 (s, 2H), 3.60 (s, 3H), 1.33 (t, 3H).

Anal. Calcd. for $C_{15}H_{18}O_5S$: C, 58.04; H, 5.84; S, 10.33. Found: C, 58.04; H, 5.89; S, 10.13.

Methyl 5-Methoxymethyloxy-6-methoxy-3-benzo[*b*]thienylacetate (**3c**, R^4 = CH_3).

Into 35 ml. of DMF was placed 0.082 g. (2 mmoles) of sodium hydride and 0.5 g. (2 mmoles) of **3b** (R^4 = CH_3). The reaction was allowed to stir at room temperature for 30 minutes at which time 0.31 g. (4 mmoles) of chloromethyl methyl ether was added all at once. The mixture was stirred at room temperature for an additional 3 hours and then poured into 50 ml. of ice water. Filtration of the precipitate followed by recrystallization from petroleum ether yielded 0.42 g. (72%) of white crystals melting at 67-68°: nmr (deuteriochloroform): δ 7.61 (s, 1H), 7.40 (s, 1H), 7.29 (s, 1H), 5.35 (s, 2H), 3.98 (s, 3H), 3.81 (s, 2H), 3.70 (s, 3H), 3.60 (s, 3H).

Anal. Calcd. for $C_{14}H_{16}O_5S$: C, 56.75; H, 5.40; S, 10.80. Found: C, 56.71; H, 5.21; S, 11.09.

Methyl 5-Methoxy-6-hydroxy-3-benzo[*b*]thienylacetate (**3d**, R^4 = CH_3).

Into a mechanically stirred solution of 200 ml. of refluxing toluene, 6.25 g. of celite and 1.6 g. of phosphorus pentoxide was added 4.5 g. of polyphosphoric acid. This mixture was refluxed for 30 minutes and 3.9 g. (14 mmoles) of **2c** (R^4 = CH_3) in 50 ml. of toluene added all at once. This solution was refluxed for 1 hour and then filtered. Evaporation of the toluene yielded an oil which solidified on standing. Recrystallization from hexane afforded 2.1 g. (60%) of white plates melting at 77-78°: nmr (deuteriochloroform): δ 7.30 (s, 1H), 7.10 (s, 2H), 6.25 (s, 1H), 3.80 (s, 3H), 3.70 (s, 2H), 3.63 (s, 3H).

Anal. Calcd. for $C_{12}H_{12}O_4S$: C, 57.14; H, 4.76; S, 9.52. Found: C, 57.25; H, 4.53; S, 9.78.

Methyl 6-Methoxymethyloxy-5-methoxy-3-benzo[*b*]thienylacetate (**3e**, R^4 = CH_3).

Into 25 ml. of dry DMF was added 0.08 g. (1.8 mmoles) of sodium hydride and 0.5 g. (1.8 mmoles) of **3d** (R^4 = CH_3). The solution was stirred for 30 minutes and then 0.3 g. (3.6 mmoles) of chloromethyl methyl ether added all at once. The mixture was stirred at room temperature for 3 hours and poured over 100 ml. of crushed ice. Filtration of the precipitate followed by recrystallization from petroleum ether gave 0.43 g. (75%) of white crystals melting at 74-75°: nmr (deuteriochloroform): δ 7.60 (s, 1H), 7.20 (s, 2H), 5.25 (s, 2H), 3.92 (s, 3H), 3.77 (s, 2H), 3.66 (s, 3H), 3.50 (s, 3H).

Anal. Calcd. for $C_{14}H_{16}O_5S$: C, 56.74; H, 5.44; S, 10.82. Found: C, 56.47; H, 5.53; S, 10.47.

Ethyl 5,6-Isopropylidenedioxy-3-benzo[*b*]thienylacetate (**3f**, R^4 = C_2H_5).

This compound was previously reported (4) as a crude product. The oil was distilled, b.p. 140°/0.1 mm. after which it solidified. Recrystallization from pentane afforded a white powder, m.p. 36°; ir (liquid Melt): ν 1740 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 1.27 (t, 3H, ester CH_3), 1.70 [s, 6H, $(CH_3)_2C$], 3.75 (s, 2H, $ArCH_2$), 4.18 (q, 2H, ester CH_2), 7.13 (m, 3H, ArH); ms: m/e 292 (base, M^+), 277 (M^+ -CH_3), 219 (M^+ -CO_2Et).

Anal. Calcd. for $C_{15}H_{16}O_4S$: C, 61.62; H, 5.52; S, 10.97. Found: C, 61.81; H, 5.50; S, 11.08.

Ethyl 5,6-Dihydroxy-3-benzo[*b*]thienylacetate (**3g**, R^4 = C_2H_5).

A mixture of 5,6-isopropylidenedioxy-3-benzo[*b*]thienylacetate (**3f**) (1.5 g., 5.13 mmoles) and phosphoric acid (15 ml.) was stirred at room temperature for one hour. The solution was diluted with chilled water and extracted twice with ether. The combined ethereal extracts were dried (sodium sulfate) and the solvent was evaporated, affording an oil (1.20 g., 93%) which crystallized from carbon tetrachloride as colorless prisms, m.p. 108-109°; ir (solid melt); ν 3300 (OH), 1700 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 1.27 (t, 3H, ester CH_3), 3.77 (s, 2H, $ArCH_2$), 4.23 (q, 2H, ester CH_2), 6.43 [s, (broad), 2H, ArOH, exchangeable with deuterium oxide], 7.13 (m, 3H, ArH) ppm; ms: m/e 252 (M^+), 179 (base, M^+ -CO_2Et).

Anal. Calcd. for $C_{12}H_{12}O_4S$: C, 57.13; H, 4.80; S, 12.71. Found: C, 56.84; H, 4.80; S, 12.68.

Ethyl 5,6-Di-*n*-butoxy-3-benzo[*b*]thienylacetate (**3h**, R^4 = C_2H_5).

Into 50 ml. of dry acetone was added 4.0 g. (15.8 mmoles) of ester **3g** (R^4 = C_2H_5), 1.5 g. of potassium carbonate and 8.76 g.

(64 mmoles) of *n*-butyl bromide. This mixture was refluxed for two days and then poured over 100 g. of crushed ice. Extraction with chloroform followed by drying and evaporation gave 5.46 g. (95%) of crude product. Recrystallizaiton from methanol gave pure **3h** ($R^4 = C_2H_5$) melting at 36-38°: nmr (deuteriochloroform): δ 7.27 (s, 1H), 7.13 (s, 1H), 7.10 (s, 1H), 4.30-3.90 (m, 6H), 3.68 (s, 2H), 2.12-1.90 (m, 17H).

Anal. Calcd. for $C_{20}H_{28}O_4S$: C, 65.90; H, 7,74; S, 8.80. Found: C, 65.65; H, 7.46; S, 8.52.

5,6-Di-*n*-butoxy-3-benzo[*b*]thienylacetic Acid (**3h**, $R^4 = H$).

Into 25 ml. of a 20% sodium hydroxide solution was placed 2.0 g. (5.5 mmoles) of **3h** ($R^4 = C_2H_5$) and enough ethanol to dissolve the ester. The solution was refluxed overnight and then poured over 100 g. of crushed ice and made acidic. Filtration of the crude acid followed by recrystallization from hexane afforded 1.66 g. (90%) of white crystals melting at 110-111°: nmr (deuteriochloroform): δ 8.45 (s, 1H), 7.35 (s, 1H), 7.25 (s, 2H), 4.10 (t, 4H), 3.82 (s, 2H), 2.10-1.85 (m, 14H).

Anal. Calcd. for $C_{18}H_{24}O_4S$: C, 64.28; H, 7.14; S, 9.52; Found: C, 64.05; H, 7.25; S, 9.78.

5,6-Dimethoxy-3-benzo[*b*]thienylacetamide (**4a**).

Into 40 ml. of methanol saturated with ammonia was placed 2.5 g. (9 mmoles) of **3a** ($R^4 = C_2H_5$) and the solution allowed to stir for 5 days at room temperature. After the alloted time, the precipitate was filtered and recrystallized from methanol to give 1.8 g. (80%) of white needles melting at 208-210° [lit. 211-212° (6)].

5-Hydroxy-6-methoxy-3-benzo[*b*]thienylacetamide (**4b**).

Into 20 ml. of methanol saturated with ammonia was placed 0.5 g. (2 mmoles) of the ester **3b** ($R^4 = C_2H_5$). The solution was stirred for 5 days after which the brown precipitate was filtered and recrystallized from hexane to give 0.2 g. (45%) of **4b**, melting at 174-176°: nmr (hexadeuteriodimethyl sulfoxide): δ 9.08 (s, 1H), 7.25-7.52 (m, 4H), 6.97 (s, 1H), 3.87 (s, 3H), 3.53 (s, 2H).

Anal. Calcd. for $C_{11}H_{11}NO_3S$: C, 55.67; H, 4.67; N, 5.90; S, 13.51. Found: C, 55.35; H, 4.73; N, 5.89; S, 13.65.

5-Methoxymethyloxy-6-methoxy-3-benzo[*b*]thienylacetamide (**4c**).

The use of either the ethyl or methyl esters **3c** ($R^4 = CH_3$ or C_2H_5) gave nearly identical results in yields. A solution of 1.0 g. (3 mmoles) of **3c** in 45 ml. of methanol saturated with ammonia was stirred at room temperature for 5 days, filtered and the precipitate recrystallized from methanol to give 0.72 g. (80%) of **4c** melting at 180-182°: nmr (hexadeuteriodimethyl sulfoxide): δ7.60 (s, 1H), 7.55 (s, 1H), 7.50 (s, 1H), 7.32 (s, 1H), 7.00 (s, 1H), 5.20 (s, 2H), 3.88 (s, 3H), 3.60 (s, 2H), 3.44 (s, 3H).

Anal. Calcd. for $C_{13}H_{15}NO_4S$: C, 55.49; H, 4.97; N, 5.37; S, 11.30. Found: C, 55.47; H, 5.02; N, 5.53; S, 11.13.

6-Methoxymethyloxy-5-methoxy-3-benzo[*b*]thienylacetamide (**4e**).

A solution of 1.0 g. (3.4 mmoles) of **3e** ($R^4 = CH_3$) in 50 ml. of methanol saturated with ammonia was allowed to stir at room temperature for 4 days. The precipitate was recrystallized from methanol to give 0.75 g. (78%) of white plates melting at 163-165°: nmr (hexadeuteriodimethyl sulfoxide): δ 7.57 (s, 1H), 7.48 (s, 1H), 7.33 (s, 1H), 7.28 (s, 1H), 6.90 (s, 1H), 5.15 (s, 2H), 3.78 (s, 3H), 3.52 (s, 2H), 3.33 (s, 3H).

Anal. Calcd. for $C_{13}H_{15}NO_4S$: C, 55.49; H, 5.37; N, 4.97. Found: C, 55.89; H, 5,67; N, 4.73.

5,6-Dihydroxy-3-benzo[*b*]thienylacetamide (**4g**).

A mixture of 5,6-isopropylidenedioxy-3-benzo[*b*]thienylacetamide (4) (2.5 g., 9.5 mmoles) and phosphoric acid (30 ml.) was stirred at room temperature for one hour. The solution was diluted with chilled water (150 ml.), affording the amide **4g** (2.0 g., 94%) as colorless needles, m.p. 214-215° (from water); ir (potassium bromide disc): ν 3200 (broad, OH, NH), 1660 (C=O) cm^{-1}; nmr (hexadeuteriodimethylsulfoxide): δ 3.55 (s, 2H, CH_2), 6.93 (s, 1H, NH), 7.18 (m, 3H, ArH), 7.40 (s, 1H, NH), 8.97 (s, 2H, OH); ms: m/e 223 (M^+), 179 (base, $M^+ - CONH_2$).

Anal. Calcd. for $C_{10}H_9NO_3S$: C, 53.80; H, 4.06; N, 6.27. Found: C, 53.52; H, 4.10; N, 6.56.

5,6-Di-*n*-butoxy-3-benzo[*b*]thienylacetamide (**4h**).

A solution of 4.0 g. (10.9 mmoles) of **3h** ($R^4 = C_2H_5$) in 20 ml. of methanol saturated with ammonia was stirred for 5 days at room temperature and then filtered. Recrystallization from methanol gave 2.55 g. (70%) of amide **4h**, which melted at 135-137°: nmr (deuteriochloroform): δ 7.44 (s, 1H), 7.40 (s, 1H), 7.30 (s, 1H), 5.63 (s, 2H), 4.18 (t, 4H), 3.90 (s, 2H), 2.18-1.15 (m, 14H).

Anal. Calcd. for $C_{18}H_{25}NO_3S$: C, 64.44; H, 7.51; N, 4.18. Found: C, 64.72; H, 7.27; N, 4.60.

3-β-Aminoethyl-5,6-dimethoxybenzo[*b*]thiophene (**5a**).

To a slurry of 1.63 g. (6.5 mmoles) of **4a** in dry THF, after having bubbled dry nitrogen into the solution for 5 minutes, was added a THF solution of diborane (16 ml. of 1*M* in borane). The mixture was heated at reflux for 5 hours and then carefully quenched by adding 40 ml. of 6*N* hydrochloric acid. Evaporation of the reaction mixture yielded 1.4 g. (80%) of a solid, **5a** hydrochloride, melting at 247-249° dec. (6).

The hydrochloride salt proved to be hygroscopic, so the oxalate salt was prepared and recrystallized from methanol/ethyl acetate to give white needles melting at 161-163°.

Anal. Calcd. for $C_{14}H_{17}NO_6S$: C, 51.36; H, 5.24; N, 4.28; S, 9.79. Found: C, 51.60; H, 5.34; N, 3.94; S, 9.45.

3-β-Aminoethyl-5-hydroxy-6-methoxybenzo[*b*]thiophene (**5c**) Hydrochloride.

Into a slurry of 30 ml. of dry THF and 0.25 g. (0.9 mmole) of **4c** purged with dry nitrogen for 5 minutes was injected 3 ml. (3 mmoles) of 1*M* borane in THF. This solution was allowed to reflux for 5 hours. At the end of this time, 12 ml. of brine was slowly added and the resulting mixture allowed to stir overnight at room temperature in order to decompose all boron salts. Separation of the two layers followed by drying over magnesium sulfate and evaporation of the solvent yielded the amine **5b** as an oily free base. Bubbling dry hydrogen chloride into an ether solution of the free base gave the desired **5c** hydrochloride. Recrystallization from methanol/ethyl acetate gave 0.2 g. (80%) of the amine hydrochloride melting at 238-240° dec.: nmr (deuterium oxide): δ 7.48 (s, 1H), 7.27 (s, 1H), 7.20 (1, 1H), 3.90 (s, 3H), 3.60 (t, 2H), 3.22 (t, 2H).

Anal. Calcd. for $C_{11}H_{14}ClNO_2S$: C, 50.96; H, 5.40; N, 5.40; S, 12.35. Found: C, 51.30; H, 5.61; N, 5.45; S, 11.99.

3-β-Aminoethyl-5-methoxy-6-hydroxybenzo[*b*]thiophene (**5e**) Hydrochloride.

Into a slurry of dry THF and 0.75 g. (2.7 mmoles) of the amide **4e** purged with dry nitrogen for 5 minutes was injected 6.8 ml. (6.8 mmoles) of 1*M* borane in THF and the solution allowed to reflux for 5 hours. Work-up as above gave the oily free base **5d**, which was taken up in ether and the hydrochloride of **5e** precipitated. Recrystallization from methanol/ethyl acetate afforded 0.51 g. (72%) of a white powder melting at 289-291°:

nmr (deuterium oxide) δ 7.53 (s, 1H), 7.42 (s, 1H), 7.35 (s, 1H), 4.02 (s, 3H), 3.60-3.10 (m, 4H).

Anal. Calcd. for $C_{11}H_{14}ClNO_2S$: C, 50.86; H, 5.43; N, 5.39; S, 12.34. Found: C, 51.08; H, 5.68; N, 5.32; S, 12.04.

3-β-Aminoethyl-5,6-dimethoxybenzo[*b*]thiophene-2-D.

Into 50 ml. of dry THF was added 0.5 g. (2.1 mmoles) of the free base of amine **5a**, the solution cooled to -78°, and 3 ml. of 1*M* solution of *n*-butyllithium (3 mmoles) was injected. The solution was stirred for 30 minutes and quenched by adding 5 ml. of deuterium oxide. Work-up with water and extraction with chloroform followed by evaporation yielded an oil: nmr (deuteriochloroform) δ 7.2 (s, 1H), 6.95 (s, 1H), 3.8 (s, 6H), 2.5 (m, 4H). Free base **5a**, isolated by neutralizing a solution of the hydrochloride, ether extraction, drying (magnesium sulfate) and evaporation of the ether, gave nmr (deuteriochloroform) δ 7.2 (s, 1H), 6.95 (s, 1H), 6.8 (s, 1H), 3.8 (s, 6H), 2.5 (m, 4H).

3-β-Aminoethyl-5,6-di-*n*-butoxybenzo[*b*]thiophene (**5h**) Monooxalate.

Dry nitrogen was bubbled for 5 minutes into 50 ml. of dry THF containing 1.0 g. (2.9 mmoles) of amide **4h** and then 10 ml. of 1*M* borane in THF (10 mmoles) was injected. The solution was refluxed for 5 hours followed by careful quenching at 0° with brine. Extraction of the mixture with ether followed by drying and evaporation yielded the crude amine **5h** which was taken up in dry ether and an equivalent of anhydrous oxalic acid added. Recrystallization from methanol/ethyl acetate gave 0.9 g. (75%) of **5h**, monooxalate melting at 147-149°: nmr (deuteriochloroform): δ 7.31 (s, 1H), 7.25 (s, 1H), 7.12 (s, 1H), 4.15 (t, 4H), 3.65 (t, 2H), 2.98 (t, 2H), 2.10-1.95 (m, 14H).

Anal. Calcd. for $C_{20}H_{29}NO_6S$: C, 58.39; H, 7.05; N, 3.40. Found: C, 58.25; H, 6.95; N, 3.65.

3-β-Acetaminoethyl-5,6-dimethoxybenzo[*b*]thiophene (**6a**).

A solution of 2.0 g. (7.3 mmoles) of **5a** hydrochloride in 25 ml. of water was stirred with 3.0 g. (30 mmoles) of acetic anhydride, then 2.5 g. (30 mmoles) of sodium acetate in 10 ml. of water was added. The solution was then poured over ice and the white crystals collected and recrystallized from petroleum ether/ethyl acetate to give 1.8 g. (90%) of **6a** melting at 135-136°: nmr (deuteriochloroform): δ 7.3 (s, 1H), 7.25 (s, 1H), 7.0 (s, 1H), 5.68 (s, 1H), 3.92 (s, 6H), 3.52 (t, 2H), 2.95 (t, 2H), 1.9 (s, 3H).

Anal. Calcd. for $C_{14}H_{17}NO_3S$: C, 60.18; H, 6.13; N, 5.01. Found: C, 60.01; H, 6.32; N, 4.84.

3-β-Acetaminoethyl-5-methoxymethyloxy-6-methoxybenzo[*b*]thiophene (**6b**).

To the crude amine **5b** (2.0 g.) was added 10 ml. of acetic anhydride and the mixture allowed to sit at room temperature for 15 minutes, then poured into 100 ml. of hexane. Filtration of the solid afforded 2.1 g. (90%) of **6b** which was recrystallized from hexane to give white crystals melting at 104-105°: nmr (deuteriochloroform): δ 7.60 (s, 1H), 7.42 (s, 1H), 7.38 (s, 1H), 7.10 (s, 1H), 5.31 (s, 2H), 4.00 (s, 3H), 3.70 (t, 2H), 3.60 (s, 3H), 3.10 (t, 2H), 2.00 (s, 3H).

Anal. Calcd. for $C_{15}H_{19}NO_4S$: C, 58.23; H, 6.19; N, 4.53. Found: C, 58.12; H, 6.26; N, 4.53.

3-β-Acetaminoethyl-5-hydroxy-6-methoxybenzo[*b*]thiophene (**6c**).

To a solution of 0.5 g. (1.6 mmoles) of amide **6b** in 10 ml. of ethanol was added 10 drops of concentrated hydrochloric acid. Evaporation of the solvent yielded 0.42 g. (100%) of a white solid recrystallized from hexane to give **6c** melting at 150-152°: nmr (deuteriochloroform): δ 7.25 (s, 2H), 7.00 (s, 1H), 5.00 (s, 2H), 3.95 (s, 3H), 3.50 (t, 2H), 2.90 (t, 2H), 2.10 (s, 3H).

Anal. Calcd. for $C_{13}H_{15}NO_3S$: C, 58.84; H, 5.69; N, 5.28. Found: C, 58.84; H, 5.54; N, 5.10.

3-β-Acetaminoethyl-6-methoxymethyloxy-5-methoxybenzo[*b*]thiophene (**6d**).

The amine **5d** (2 g.) was treated with 10 ml. of acetic anhydride and the solution worked up as before, to yield 2.0 g. (86%) of **6d**, recrystallized from hexane as white crystals melting at 106-108°: nmr (deuteriochloroform): δ 7.70 (s, 1H), 7.35 (s, 1H), 7.11 (s, 1H), 5.80 (s, 1H), 5.33 (s, 1H), 4.05 (s, 3H), 3.60 (s, 3H), 3.59 (t, 2H), 3.10 (t, 2H), 2.05 (s, 3H).

Anal. Calcd. for $C_{15}H_{19}NO_4S$: C, 58.23; H, 6.19; N, 4.53. Found: C, 58.02; H, 6.05; N, 4.67.

3-β-Acetaminoethyl-6-hydroxy-5-methoxybenzo[*b*]thiophene (**6e**).

Treatment of 0.8 g. (2.5 mmoles) of amide **6d** in 10 ml. of ethanol with 10 drops of concentrated hydrochloric acid yielded 0.68 g. (100%) of a pinkish solid, recrystallized from water to give white needles, which melted at 54-56°: nmr (hexadeuteriodimethyl sulfoxide): δ 8.03 (s, 1H), 7.32 (s, 1H), 7.28 (s, 1H), 7.10 (s, 1H), 4.70 (s, 1H), 3.88 (s, 3H), 3.35 (t, 2H), 2.80 (t, 2H), 1.80 (s, 3H).

Anal. Calcd. for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.69; N, 5.28. Found: C, 59.10; H, 5.51; N, 5.42.

3-β-Acetaminoethyl-5,6-isopropylidenedioxybenzo[*b*]thiophene (**6f**).

Acetylation of 2.0 g. (8 mmoles) of 3-β-aminoethyl-5,6-isopropylidenedioxybenzo[*b*]thiophene (4) in 5 ml. of acetic anhydride gave 2.2 g. (95%) of white crystals melting at 122-124° after recrystallization from hexane: nmr (deuteriochloroform): δ 7.27 (s, 1H), 7.10 (s, 1H), 7.00 (s, 1H), 5.72 (s, 1H), 3.60 (q, 2H), 3.00 (t, 2H), 2.00 (s, 3H), 2.72 (s, 6H).

Anal. Calcd. for $C_{15}H_{17}NO_3S$: C, 61.83; H, 5.88; N, 4.81; S, 11.00. Found: C, 61.62; H, 5.72; N, 4.91; S, 10.78.

6,7-Dimethoxy-3,4-dihydro-1-methylbenzothieno[2,3-*c*]pyridine (**7a**) Hydrochloride.

A mixture of 200 ml. of dry xylene, 1.0 g. (3.6 mmoles) of **6a**, 2.0 g. of phosphorus pentoxide and 2.0 g. of phosphorus oxychloride was refluxed for 90 minutes. The cooled mixture was diluted with 100 ml. of water and the aqueous layer separated, washed with ether, made basic with sodium hydroxide and extracted with 3 x 100 ml. portions of ether. The combined basic ether extracts were dried over sodium sulfate and saturated with dry hydrogen chloride gas to give 0.89 g. (83%) of bright yellow product. Recrystallization from methanol/ethyl acetate afforded yellow needles melting at 254-256°: nmr (deuteriochloroform): δ 7.32 (s, 1H), 7.25 (s, 1H), 4.00 (s, 6H), 3.9 (s, 2H), 2.9 (s, 2H), 2.4 (s, 3H).

Anal. Calcd. for $C_{14}H_{16}ClNO_2S$: C, 56.46; H, 5.41; S, 10.76; N, 4.70. Found: C, 56.58; H, 5.49; S, 10.55; N, 4.66.

6-Hydroxy-7-methoxy-3,4-dihydro-1-methylbenzothieno[2,3-*c*]pyridine (**7c**) Hydrochloride.

As above, 0.5 g. (1.6 mmoles) of amide **6b** was cyclized and the basic ether extract dried over mangesium sulfate. Evaporation of the ether yielded a light yellow oil which was taken up in dry ether and dry hydrogen chloride gas added to give the hydrochloride salt. Recrystallisation from methanol/ethyl acetate gave 0.25 g. (50%) of a yellow powder melting at 239-241° dec.: nmr (deuteriochloroform): δ 7.30 (s, 1H), 7.22 (s, 1H), 5.80 (s, 1H), 4.00 (s, 3H), 3.84 (t, 2H), 3.01 (t, 2H), 2.38 (s, 3H).

Anal. Calcd. for $C_{13}H_{14}ClNO_2S$: C, 55.02; H, 4.97; N, 4.94; S, 11.30. Found: C, 54.76; H, 4.19; N, 4.99; S, 10.98.

6-Methoxy-7-hydroxy-3,4-dihydro-1-methylbenzothieno[2,3-*c*]-pyridine (7e) Hydrochloride.

As above, 0.5 g. (.16 mmoles) of amide **6d** was cyclized. Drying the basic ether extract over magnesium sulfate and evaporation yielded a light yellow oil. This oil was taken up into dry ether and dry hydrogen chloride added to form the hydrochloride salt (0.08 g.) (16%) which melted at 252-254°. The very low yield for this reaction is very disappointing and the exact reason for it was not evident: nmr (deuteriochloroform): δ 7.32 (s, 1H), 7.24 (s, 1H), 5.75 (s, 1H), 5.75 (s, 1H), 3.95 (s, 3H), 3.82 (t, 2H), 3.05 (t, 2H), 2.40 (s, 3H).

Anal. Calcd. for $C_{13}H_{14}ClNO_2S$: C, 55.02; H, 4.97; N, 4.94. Found: C, 55.32; H, 5.05; N, 5.21.

6,7-Isopropylidenedioxy-3,4-dihydro-1-methylbenzothieno[2,3-*c*]-pyridine (7f) Hydrochloride.

The acid aqueous solution, obtained after cyclizing 2.0 g. (6.9 mmoles) of **6f** under Bischler-Napieralski conditions as above, was made basic by adding 50 ml. of aqueous sodium hydroxide and extracted with chloroform (3 x 100 ml.). The chloroform was dried with magnesium sulfate and evaporated to give a dark red oil which was taken up in ether and dry hydrogen chloride added. The crude hydrochloride was recrystallized from methanol/ethyl acetate to give 1.15 g. (55%) of **7f** hydrochloride at 266-268°: nmr (deuteriochloroform): δ 7.05 (s, 1H), 6.92 (s, 1H), 3.80 (t, 2H), 2.75 (t, 2H), 2.33 (s, 3H), 1.64 (s, 6H).

Anal. Calcd. for $C_{15}H_{16}ClNO_2S$: C, 58.15; H, 5.21; N, 4.52. Found: C, 57.85; H, 5.45; N, 4.58.

6,7-Dihydroxy-3,4-dihydro-1-methylbenzothieno[2,3-*c*]pyridine (7g) Hydrogen Sulfate.

A solution of 1.0 g. (3.25 mmoles) of **7f** hydrochloride in 20 ml. of 10% sulfuric acid was warmed over a steam bath for 4 hours and cooled to give 0.9 g. (85%) of needles melting at 221-223°: nmr (hexadeuteriodimethyl sulfoxide): δ 7.48 (s, 1H), 7.30 (s, 1H), 3.92 (t, 2H), 3.20 (t, 2H), 2.66 (s, 3H).

Anal. Calcd. for $C_{12}H_{13}NO_6S_2$: C, 43.50; H, 5.92; N, 4.22. Found: C, 43.75; H, 4.01; N, 4.25.

N-Acetyltryptamine.

Acetylation of 3.0 g. (15.3 mmoles) of tryptamine hydrochloride (Aldrich) with 5.0 g. of acetic anhydride and 6.9 g. of sodium acetate trihydrate in 20 ml. of water gave, after recrystallization from benzene, 2.8 g. (90%) of *N*-acetyltryptamine melting at 78-80° [lit. (18) gives 77°]; nmr (deuteriochloroform): δ 8.42 (s, 1H), 7.77-7.08 (m, 5H), 5.68 (s, 1H), 3.56 (t, 2H), 2.97 (t, 2H), 1.90 (s, 3H).

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.25; H, 6.97; N, 13.85. Found: C, 71.45; H, 7.23; N, 14.05.

1-Methylmelatonin (24).

Reduction of 5.0 g. (2.14 mmoles) of 5-methoxy-1-methyl-3-(2′-nitrovinyl)indole (21) with 16.4 g. of LAH in dry THF gave an oil which was extracted with ether, after dilution with water, dried and precipitated as the hydrochloride with anhydrous hydrogen chloride. The solid was recrystallized from methanol/ethyl acetate to give 2.32 g. (45%) of 5-methoxy-1-methyltryptamine hydrochloride, melting at 180-182°, in agreement with Taborsky (19). Acetylation by addition of sodium acetate solution to a mixture of this hydrochloride (0.5 g., 2.1 mmoles) in acetic anhydride gave a precipitate recrystallized from ethyl acetate and petroleum ether (b.p. 60-90°) to give 0.44 g. product (85%), m.p. 100-102°; ir (potassium bromide): 3.05 μ NH, 6.12 μ NHCO; nmr (deuteriochloroform): δ 1.87 (s, 3H), (CH_3CO), 2.85 (t, 2H, CH_2N), 2.48 (t, 2H, Ar-CH_2), 3.61 (s, 3H, CH_3N), 3.77 (s, 2H, CH_3O), 5.90 (s, 1H, NH), 6.74-7.12 (m, 4H, aromatics).

Anal. Calcd. for $C_{14}H_{18}N_2O_2$: C, 68.26; H, 7.35; N, 11.33; m.w. 246.1368. Found: C, 68.50; H, 7.24; N, 11.28; m/e 246.1388.

6-Methoxymelatonin.

A mixture of dry acetone (15 ml.), 6-hydroxymelatonin (Regis) (0.2 g.), potassium carbonate (0.2 g.) and 0.2 g. of dimethyl sulfate was refluxed for 24 hours and then poured over 200 g. of crushed ice. Filtration of the solid gave 0.14 g. (70%) melting at 176-178°: nmr (deuteriochloroform): δ 8.88 (s, 1H), 7.22 (s, 1H), 6.92 (s, 1H), 6.71 (s, 1H), 6.05 (s, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.42 (t, 2H), 2.80 (t, 2H), 1.78 (s, 3H).

Anal. Calcd. for $C_{14}H_{18}N_2O_3$: C, 64.88; N, 6.87; H, 6.87; N, 10.68. Found: C, 65.11; H, 6.58; N, 10.39.

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