Benzo[*b*]thiophene Derivatives. XXI. On the Proof of Structure of the Sulfur Isostere of Psilocin (1).

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Differences in the characteristics of several common compounds reported in two independent syntheses of the sulfur analog of psilocin required re-examination of our products. Additional evidence supporting the structures previously reported by us is presented. This includes proof of 3-substitution in 4-methoxy-3-β-dimethylaminoethylbenzo[*b*]thiophene by deuterium exchange of the 2-proton, demonstration that the intermediate 4-methoxy-*N*,*N*-dimethyl-3-benzo[*b*]-thienylglyoxamide is different from the 2-isomer, and confirmation of the structure of 4-methoxy-3-methylbenzo[*b*]thiophene, an intermediate in one of the reported syntheses, by three different synthetic methods.

Recently we reported the synthesis of the sulfur analog of psilocin (SAP), 3-(β-dimethylaminoethyl)-4-hydroxybenzo[*b*]thiophene (**1a**), and several of its methylated and demethylated derivatives (2). Since our initial report Chapman, Scrowston, and Sutton (3) have published an independent synthesis of SAP and some of its derivatives. Since the physical constants of several of the common compounds reported in the two papers are different, we report now additional evidence supporting the structure of the various compounds synthesized as previously reported (2).

The starting material for our synthesis was 3-bromo-4-methoxybenzo[*b*]thiophene (2). This was subsequently converted to 3-lithio-4-methoxybenzo[*b*]thiophene (**2**) *via* halogen-metal exchange with *n*-butyllithium. Compound **2** was condensed with an electrophile to give a 3-substituted-4-methoxybenzo[*b*]thiophene. Additional operations on the 3-substituent gave the various sulfur psilocin derivatives. Since Dickinson and Iddon had previously shown that under certain conditions 3-lithiobenzo[*b*]thiophene undergoes rearrangement and decomposition (5), we were careful to show that using our reaction conditions, the structural integrity of **2** was maintained. This structural proof from our original paper is summarized in Chart I.

One of the compounds reported in both papers is 3-(β-dimethylaminoethyl)-4-methoxybenzo[*b*]thiophene (**1b**). The reported melting points of the hydrochloride of **1b** are 202-205° (2) and 152-154° (3). In addition, we reported (2) complete nmr data on **1b** which is reproduced in Tables I and II. The nmr data coupled with the fact

CHART I

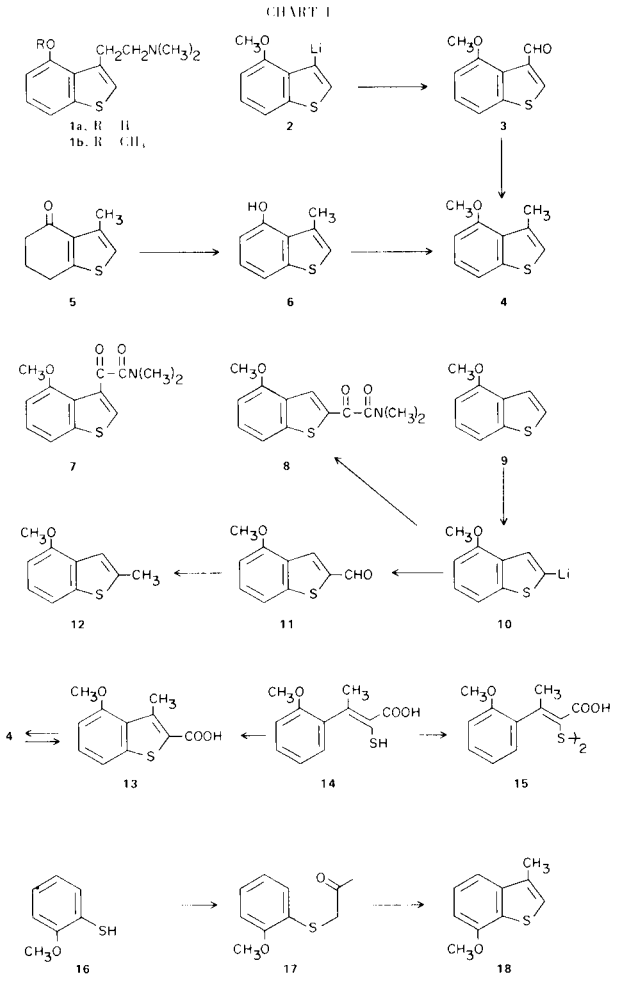

TABLE I

Chemical Shift Values (δ) (a) for Some Substituted Benzo[*b*]thiophenes

Compd.	H_2	H_3	H_4	H_5	H_6	H_7	4-OCH_3	7-OCH_3	2-CH_3	3-CH_3
1b	6.92(s)	----	----	6.65(d of d)	7.17(q)	7.33(d of d)	3.84(s)	----	----	----
4(b)	6.76(m)	----	----	6.60(d of d)	7.16(q)	7.32(d of d)	3.79(s)	----	----	2.56(d)
4(c)	6.80(q)	----	----	(d)	(d)	(d)	3.85(s)	----	----	2.60(d)
12	----	~7.06(m)	----	6.55(d of d)	7.10(q)	7.24(d of d)	3.76(s)	----	2.44(d)	----
18	6.98(m)	----	~7.27	~7.27	6.71(m)	----	----	3.93(s)	----	2.38(d)
3	8.29(s)	----	----	6.85(d of d)	7.34(q)	7.46(d of d)	3.98(s)	----	----	----
11	----	8.10(s)	----	6.70(m)	7.32(m)	7.32(m)	3.94(s)	----	----	----

(a) Taken using deuteriochloroform as solvent and tetramethylsilane as a reference. (b) E. Campaigne and R. B. Rogers, *J. Heterocyclic Chem.*, **10**, 297 (1973). (c) N. B. Chapman, R. M. Scrowston and J. M. Sutton, *J. Chem. Soc.*, 3011 (1972). (d) Not reported.

TABLE II

Coupling Constants (Hz) for Some Substituted Benzo[*b*]thiophenes

Compound	$J_{2,3'}$	$J_{2',3}$	$J_{5,6}$	$J_{5,7}$	$J_{6,7}$
1b	----	----	7.5	1.6	7.5
4(a)	1.2 ± 0.1	----	7.8	1.0	7.8
4(b)	0.8	----	(c)	(c)	(c)
12	----	1.0	7.8	1.0	8.0
18	1.1	----	(d)	(d)	----

(a) E. Campaigne and R. B. Rogers, *J. Heterocyclic Chem.*, **10**, 297 (1973) report $J_{2,3'}$ = 1.4. (b) N. B. Chapman, R. M. Scrowston and J. M. Sutton, *J. Chem. Soc.*, 3011 (1972). (c) Not reported. (d) Not measured.

that our synthesis started with an authentic sample of 4-hydroxybenzo[*b*]thiophene (4) demonstrate that the β-dimethylaminoethyl side chain must be attached to either carbon 2 or 3 of the ring system. Attachment at carbons 5, 6, or 7 would yield a pair of doublets for H_2 and H_3, and a simpler pattern for the benzene ring protons. Only a singlet corresponding to one proton on the thiophene ring is observed, with a characteristic ABX pattern for the benzene ring (9).

It is well documented that H_2 of the benzo[*b*]thiophene ring system is a fairly acidic proton (5, 6a, 6b). Thus, if the side chain is attached to C_3, then treating the compound with butyllithium and quenching the resulting lithiobenzo[*b*]thiophene with deuterium oxide should give **1b** deuterated at C_2. This would be readily observable by the disappearance of the singlet at 6.92 δ in the nmr spectrum of this compound (6b). H_3 would not be expected to exchange with butyllithium. After performing this exchange on **1b**, the nmr spectrum of the resulting compound showed complete disappearance of the signal at 6.92 δ with the remainder of the spectrum being unchanged.

An intermediate in our synthesis of **1b** was the glyoxamide **7** (2). The isomeric glyoxamide **8** was synthesized by condensing 2-lithio-4-methoxybenzo[*b*]thiophene (**10**) (from butyllithium and 4-methoxybenzo[*b*]thiophene, **9**) with tetramethyloxamide. The melting points, infrared and nmr spectra of **7** and **8** were different.

Chapman *et al.* used 4-methoxy-3-methylbenzo[*b*]-thiophene (**4**, m.p. 49.5-50°) as the starting point for their synthesis (3). As shown in Chart I, we prepared **4** (m.p. 57-58°) by two independent routes (2). Treatment of **2** with dimethylformamide gave 4-methoxybenzo[*b*]-thiophene-3-carboxaldehyde (**3**) which was reduced to 3-methyl-4-methoxybenzo[*b*]thiophene (**4**). Alternatively, an authentic sample of 3-methyl-6,7-dihydro-5*H*-benzo-[*b*]thiophene-4-one (**5**) (4) was aromatized to 4-hydroxy-3-methylbenzo[*b*]thiophene (**6**) and this phenol methylated to **4**. The nmr data are given in Tables I and II. Again, the nmr spectrum shows that the methyl group is either attached to C_2 or C_3 and coupled to either H_3 or H_2.

Iddon and Scrowston (7) have reported that the coupling between a proton at C_2 and a methyl group at C_3 ($J_{2,3'}$) falls in the range of 1.1-1.5 Hz while that between a proton at C_3 and a methyl group at C_2 ($J_{2',3}$) is between 0.8-1.0 Hz. In a series of 5-substituted-3-methylbenzo[*b*]thiophenes, Chapman *et al.* (8) reported that the coupling between H_2 and the 3-CH_3 was 1.1-1.2 Hz. However, in recent papers it has been reported that $J_{2,3'}$ is 0.8 Hz (3,9) or to be nonexistent (10). We have found $J_{2,3'}$ in **4** to be between 1.1-1.4 Hz (the measurements appear to be slightly different depending upon the sweep width of the instrument).

To circumvent these somewhat confused coupling constant ranges we have synthesized 4-methoxy-2-methyl-

benzo[*b*]thiophene (**12**) as shown on Chart I. The melting points, infrared and nmr spectra of **4** and **12** are completely different. In addition compound **12**, as expected, did not undergo lithiation as shown by its failure to incorporate deuterium. Compound **4** did undergo lithiation with *n*-butyllithium as shown by its conversion to 4-methoxy-3-methylbenzo[*b*]thiophene-2-carboxylic acid (**13**). The infrared spectrum of this acid was identical with that synthesized in a manner analogous to the method used by Chapman *et al.* (11). Decarboxylation of **13** (3) in quinoline regenerated **4**, with a slightly lower m.p. (53-55°) but nearly identical infrared spectrum. It should be noted that although Chapman, *et al.* (3) reported the m.p. of **4** to be 49.5-50°, their compound was later reported to be contaminated with some 7-chloro-4-methoxy-3-methylbenzo[*b*]thiophene (9). The mass spectrum of our sample (m.p. 53-55°), prepared by the chlorine cyclization, also showed the presence of a trace of impurity of mass 212, 214, presumably the 7-chloro derivative.

It should be noted that contrary to Chapman's results (11), the major product which we obtained from the chlorine-catalyzed cyclization of the mercaptoacrylic acid **14** was the disulfide **15** along with smaller amounts of the desired **13**.

For purposes of comparison, we have also prepared 7-methoxy-3-methylbenzo[*b*]thiophene (**18**) according to the method of R. Royer, *et al.* (12). This compound was quite different from either **4** or **12**. The nmr data for this compound are given in Tables I and II. Since it has been reported (13) that polyphosphoric acid catalyzed cyclizations, as in **17** → **18**, may give rearranged products, **18** was lithiated (butyllithium) then quenched with deuterium oxide to give **18** deuterated at C_2, thus confirming the substituent at C_3.

EXPERIMENTAL

The infrared spectra were obtained on a Perkin-Elmer model 137-B Infracord spectrometer using either potassium bromide mulls or as neat liquids between silver chloride or sodium chloride plates. Nmr spectra were determined on a Varian Associates Model HA-100 spectrometer. Mass spectra were determined either on a Varian MAT CH-7 spectrometer or an Associated Electrical Industries' MS-9 spectrometer at 70 eV. Melting points were obtained on a Mel-Temp capillary melting point apparatus and are uncorrected. The tetrahydrofuran (THF) used was distilled from lithium aluminum hydride immediately prior to use. All lithiation reactions were carried out using a dry ice-acetone cooling bath and a dry nitrogen atmosphere. The *n*-butyllithium was used as a 1.6 *M* hexane solution.

Deuteration of 3-(β-Dimethylaminoethyl)-4-methoxybenzo[*b*]thiophene.

A solution of **1b** (235 mg., 1 mmole) in THF (35 ml.) was cooled to -78° and *n*-butyllithium (1.25 ml., 2 mmoles) was added. The mixture was stirred for 30 minutes then deuterium oxide (1 ml.) added and the mixture allowed to warm to room temperature. After drying (magnesium sulfate) the solution, the solvent was removed to yield an oil. The nmr spectra of this compound was identical with that of **1b** as reported in Tables I and II with the exception that the singlet at 6.92 δ was no longer present.

4-Methoxybenzo[*b*]thiophene-2-carboxaldehyde (**11**).

A solution of 4-methoxybenzo[*b*]thiophene (14) (1.64 g., 10 mmoles) in THF (40 ml.) was cooled to -78° and *n*-butyllithium (6.25 ml., 10 mmoles) added. The mixture was stirred for 30 minutes, then dry dimethylformamide (DMF) added all at once and the solution allowed to warm to room temperature. The mixture was poured into excess 2*N* hydrochloric acid and the resulting solid filtered and air dried. Recrystallization from hexane gave 1.35 g. (70%) of **11**, m.p. 96-97°; ir (potassium bromide): 5.98 (C=O) μ; nmr: Tables I and II.

Anal. Calcd. for $C_{10}H_8O_2S$: M.W. 192.0245. Found: M/e 192.0233.

4-Methoxy-2-methylbenzo[*b*]thiophene (**12**).

A solution of **11** (0.80 g., 4.16 mmoles), and 85% hydrazine hydrate (2.76 ml.) in diethyleneglycol (12 ml.) was heated for 10 minutes at 160°, cooled to 60° and finely ground potassium hydroxide (0.84 g., 14 mmoles) added. The mixture was heated at 170° for 2 hours then poured into 250 ml. of ice water. The resulting cloudy white suspension was extracted with ether, the combined organic phases dried (magnesium sulfate) and the solvent removed to yield an oil which solidified on standing. The compound was recrystallized by taking it up in hexane then cooling in a dry ice-acetone bath, m.p. 43-44°; nmr (deuteriochloroform): Tables I and II.

Anal. Calcd. for $C_{10}H_{10}O_2S$: M.W. 178.0453. Found: M.W. m/e 178.0442.

Attempted Deuterium Exchange with **12**.

The procedure used was identical with that used for the deuterium exchange as described for **1b**. The nmr spectrum of the resulting compound was identical to that of **12** before treatment, $J_{2'3} = 1.0$.

7-Methoxy-3-methylbenzo[*b*]thiophene (**18**).

This compound was synthesized by polyphosphoric acid catalyzed cyclization of **17** in about 25% yield as described by Royer *et al.* (12) after chromatography on silica gel, m.p. 76-77°; nmr (deuteriochloroform) see Tables I and II.

Deuterium Exchange with **18**.

The procedure was identical with that used for the deuterium exchange as described for **1b**. The nmr spectrum of the resulting compound showed that the multiplet at δ 6.98 had disappeared and the doublet at δ 2.38 had collapsed to a singlet.

4-Methoxy-3-methylbenzo[*b*]thiophene-2-carboxylic Acid (**13**).

A.

To a solution of **4** (0.051 g., 2.86 mmoles) in dry THF (3 ml.) cooled to -78° was added *n*-butyllithium (0.18 ml., 2.86 mmoles). The solution was allowed to stand for 30 minutes then excess carbon dioxide added and the resulting mixture allowed to warm to room temperature. Five drops of THF saturated with hydrogen chloride was added and the solvent evaporated to yield a colorless solid, m.p. 229-233°. Recrystallization from methanol gave a compound with a melting point of 238-242°. Additional purification was not attempted.

B.

The α-mercaptoacrylate **14** was prepared as previously described (11). A solution of chlorine (0.71 g., 0.01 mole) in carbon tetrachloride (10 ml.) was added all at once ot a stirred solution of **14** (2.24 g., 0.01 mole) in carbon tetrachloride (40 ml.). The mixture was stirred for 30 minutes then the precipitate filtered, recrystallized from benzene-methanol, and dried to give 1.60 g. (72%) of a compound identified as the disulfide **15**, m.p. 197-199°; nmr (DMSO-d_6, carbon tetrachloride) δ 2.19 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 6.68-7.04 (m, 3H), 7.11-7.34 (m, 1H).

Anal. Calcd. for $C_{22}H_{22}O_6S_2$: M.W. 446. Found: M.W. m/e 446.

Evaporating the solvent from the filtrate left a residue which, after two recrystallizations from methanol gave 0.45 g. (20%) of the acid **13**: m.p. 249-250° [lit. (11) m.p. 247-248°]; ir (potassium bromide): μ 3.7-4.1 (broad), 6.00 (C=O) μ.

The infrared spectra of the acid (**13**) as synthesized in methods A and B were identical.

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