IR (film) 3457, 1736, 1436, 1374, 1246, 1060, 1047, 1022, 967 cm^{-1}; MS for $C_{26}H_{44}SiO_3$ (M^+ – HOAc for Me_3Si derivative) *m/e*(calcd) 432.3060, *m/e*(found) 432.3059 (other ions at *m/e* 417, 390, 372, 300, 282, 175, 133, 132, 131, 129, 117); TLC R_f 0.50 in 50% ethyl acetate in Skellysolve B. For **44** (0.39 g, 29%): NMR δ 0.90 (t, J = 5 Hz, 3 H), 0.8–2.83 (m, 24 H), 1.98 (s, 3 H), 2.04 (s, 3 H), 3.65 (t, J = 6 Hz, 2 H), 4.55–5.67 (m, 5 H); IR (film) 3456, 1736, 1456, 1436, 1372, 1242, 1066, 1025, 969 cm^{-1}; MS for $C_{26}H_{44}SiO_3$ (M^+ – HOAc for Me_3Si derivative) *m/e*(calcd) 432.3060, *m/e*(found) 432.3050 (other ions at *m/e* 417, 390, 372, 300, 282, 175, 133, 132, 131, 129, 117); TLC R_f 0.54 in 50% ethyl acetate in Skellysolve B.

(5*E*,15*R*)-6a-Carbaprostaglandin I_2 (45) was prepared in 49% yield from alcohol **43** (0.63 g, 1.50 mmol) in the same manner used in the preparation of **4**. The chromatographically pure sample of **45** was initially a colorless oil which partially solidified to a white semisolid on standing at −19 °C. Attempts to recrystallize this material were not successful: NMR δ 0.92 (t, J = 5 Hz, 3 H), 0.75–2.65 (m, 23 H), 3.52–4.32 (m, 2 H), 5.13–5.73 (m, 3 H), 5.23 (s, 3 H); IR (film) 3500, 3050, 2700, 1710, 1620, 1260, 1150, 1090, 1030, 980 cm^{-1}; MS for $C_{29}H_{55}Si_3O_4$ (M^+ – CH_3 for the tris(trimethylsilyl) derivative) *m/e*(calcd) 551.3408, *m/e*(found) 551.3387 (other ions at *m/e* 495, 476, 461, 405, 386, 379, 360, 173, 117); $[\alpha]_D$ +61° (*c* 0.8485, CH_3OH); TLC R_f 0.44 in the A-IX solvent system.[29]

(5*Z*,15*R*)-6a-Carbaprostaglandin I_2 (46) was prepared in 63% yield from alcohol **44** (0.39 g, 0.93 mmol) in the same manner used in the preparation of **4**. The chromatographically pure sample of **46** was a colorless oil: NMR δ 0.88 (t, J = 5 Hz, 3 H), 0.70–2.75 (m, 23 H), 3.52–4.28 (m, 2 H), 5.08–5.75 (m, 3 H), 5.46 (s, 3 H); IR (film) 3400, 1710, 1450, 1370, 1250, 1080, 1050, 970 cm^{-1}; MS for $C_{29}H_{55}Si_3O_4$ (M^+ – CH_3 for the tris(trimethylsilyl) derivative) *m/e*(calcd) 551.3408, *m/e*(found) 551.3420 (other ions at *m/e* 566, 495, 476, 461, 405, 386, 379, 360, 199, 173, 117); $[\alpha]_D$ +20° (*c* 0.675, CH_3OH); TLC R_f 0.45 in the A-IX solvent system.[29]

(5*E*)-6a-Carbaprostaglandin I_2 (4) and (5*Z*)-6a-Carbaprostaglandin I_2 (36). A solution of 75.83 mmol of sodium methylsulfinylmethide (prepared from 3.19 g (75.83 mmol) of a 57% NaH dispersion and 50 mL of Me_2SO in the usual manner[30]) was cooled to 10–15 °C and treated with stirring with 16.81 g (37.92 mmol) of (4-carboxybutyl)triphenylphosphonium bromide under nitrogen. The red solution containing ylide **47** was stirred at 25 °C for 15 min and then treated with a solution of 1.68 g (6.31 mmol) of ketone diol **16** in 25 mL of Me_2SO. The reaction mixture was stirred at 35 °C for 10 h, cooled to 15 °C, quenched with 15 mL of water, and diluted with 1 N aqueous NaOH. The aqueous solution was washed with diethyl ether (2 times), acidified to pH 3 with 0.5 M aqueous potassium bisulfate, and extracted with diethyl ether (2 times). The combined ethereal extracts were washed with brine (2 times), dried over sodium sulfate, and concentrated in vacuo to give 3.90 g of crude **4** and **36** as a yellow oil. This material was chromatographed over 350 g of silica gel, eluting with 30% acetone in methylene chloride. Fractions were combined based on TLC homogeneity to give 1.83 g (83%) of a mixture of **4** and **36**. The identities of **4** and **36** were established by TLC comparison with authentic samples of each pure isomer in several solvent systems.

Acknowledgments. The authors gratefully acknowledge the technical assistance of Mr. J. L. Thompson. We also than Mr. P. A. Meulman and Mr. R. J. Wnuk for infrared and mass spectra. We especially acknowledge with gratitude Dr. H. A. Karnes and associates for the preparation of intermediates, Mr. C. F. Lawson and co-workers for gerbil colon and rat blood presure results, and Dr. E. E. Nishizawa and co-workers for blood platelet inhibition results.

Registry No. 4, 69552-46-1; **4** tris(Me_3Si) derivative, 70398-64-0; **5**, 39521-44-3; **6** isomer A, 70398-67-3; **6** isomer B, 70428-02-3; **7**, 70398-65-1; **8**, 70398-66-2; **9** isomer A, 70398-62-8; **9** isomer B, 70428-01-2; **10** isomer A, 70398-63-9; **10** isomer B, 70469-90-8; **11** isomer A, 70398-68-4; **11** isomer B, 70428-03-4; **12** isomer A, 70398-69-5; **12** isomer B, 70428-04-5; **13** isomer A, 70398-70-8; **13** isomer B, 70428-05-6; **13** Me_3Si derivative isomer A, 70398-71-9; **13** Me_3Si derivative isomer B, 70428-06-7; **14**, 70398-72-0; **15**, 70398-73-1; **16**, 69552-54-1; **16** bis(Me_3Si) derivative, 70398-74-2; **17**, 70428-07-8; **17** bis(Me_3Si) derivative, 70428-08-9; **18**, 70398-75-3; **19**, 70428-09-0; **20**, 70398-76-4; **21**, 70398-77-5; **24**, 30004-67-2; **25**, 31608-22-7; **26**, 70398-78-6; **28**, 70470-13-2; **29**, 70470-14-3; **30**, 70398-79-7; **31**, 70428-10-3; **32**, 70398-80-0; **33**, 70428-11-4; **34**, 70398-81-1; **34** Me_3Si derivative, 70398-82-2; **35**, 70428-12-5; **35** Me_3Si derivative, 70428-13-6; **36**, 69609-77-4; **36** tris(Me_3Si) derivative, 70470-15-4; **37**, 70398-83-3; **38**, 70428-14-7; **39**, 70428-15-8; **40**, 70428-16-9; **41**, 70428-17-0; **42**, 70428-18-1; **43**, 70428-19-2; **43** Me_3Si derivative, 70428-20-5; **44**, 70428-21-6; **44** Me_3Si derivative, 70428-22-7; **45**, 69609-79-6; **45** tris(Me_3Si) derivative, 70428-23-8; **46**, 69609-80-9; **46** tris(Me_3Si) derivative, 70428-24-9; **47**, 41723-91-5; hexyltriphenylphosphonium bromide, 4762-26-9; sodium methylsulfinylmethide, 15590-23-5; methylmagnesium bromide, 75-16-1; (4-carboxybutyl)triphenylphosphonium bromide, 17814-85-6.

Carbon-13 Nuclear Magnetic Resonance Study of Benzo[*b*]thiophenes and Benzo[*b*]thiophene *S*-Oxides and *S*,*S*-Dioxides

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The ^{13}C NMR spectra of benzo[*b*]thiophenes and a series of benzo[*b*]thiophene *S*-oxides and *S*,*S*-dioxides of well-defined structure were recorded. A comparison between benzothiophenes and the sulfoxide and sulfone derivatives permits the characterization of the effect of the sulfoxide and sulfone moieties on ^{13}C chemical shifts in this heteroaromatic system. A comparison of the ^{13}C resonances of benzothiophene *S*-oxides and *S*,*S*-dioxides with the corresponding derivatives of 2,3-dihydrobenzothiophene shows a decrease in aromaticity on going from the benzo[*b*]thiophene to the *S*-oxide and *S*,*S*-dioxide systems, the sulfoxide being more aromatic than the sulfone.

The chemical literature contains a number of reports on ^{13}C NMR studies of substituted thiophenes[1-9] and methylbenzothiophenes[10,11] but the corresponding sulfoxides and sulfones have largely been ignored.

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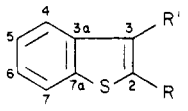
Chart I



1, R = H, R′ = H
2, R = CH_3, R′ = H
3, R = Cl, R′ = H
4, R = Br, R′ = H
5, R = Ph, R′ = H
6, R = $CHOHCH(CH_3)_2$, R′ = H
7, R = $C(=CH_2)CH_3$, R′ = H
8, R = H, R′ = CH_3
9, R = H, R′ = Cl
10, R = H, R′ = Br
11, R = H, R′ = Ph with Ph =
12, R = CH_3, R′ = CH_3
13, R = Cl, R′ = Cl

In the course of our studies[12-14] on the reactivity of these compounds we have recorded ^{13}C NMR spectra of 2- and/or 3-substituted benzothiophenes and the corresponding sulfoxides and sulfones in order to determine the effect of the sulfoxide and sulfone functions on the carbon resonances in these heteroaromatic systems.

Results and Discussion

Benzo[*b*]thiophenes. The chemical shifts for the benzo[*b*]thiophene carbons are given in Table I. Asterisks in the table indicate that peak assignments are uncertain and may be interchanged. The assignments for benzothiophene 1 (see Chart I) and its methyl derivatives **2**, **8**, and **12** are based on assignments in the literature[10,11] and were confirmed by deuteration of benzothiophene in positions 2 and 3, respectively, and of 3-methylbenzothiophene in position 2.[12] For the remaining benzothiophenes the peaks for the quaternary carbons C_{3a} and C_{7a} of the ring junctions are readily identified since they are less intense and almost invariant. These peaks are also somewhat less intense than quaternary C_2 or C_3 signals.[11] An unequivocal distinction of C_{3a} and C_{7a} resonances is difficult. The assignments of the C_2 and C_3 signals are based on chemical shifts for C_2 and C_3 in 2-methyl- and 3-methylthiophene, on substituent effects in the thiophene series,[1a,7] and on heavy-atom effects of Cl and Br.[15] Table I also contains shift differences between benzothiophene

Table I. ^{13}C Chemical Shifts (ppm) in Benzo[*b*]thiophene and 2- and/or 3-Substituted Benzo[*b*]thiophenes with Carbon Shieldings Relative to Benzothiophene[a] in Parentheses

compd	substituent	C_2	C_3	C_4	C_5	C_6	C_7	C_{3a}	C_{7a}	C_x
1	none	126.4	124.0	123.8	124.3	124.4	122.6	139.8	139.9	
2	2-Me	140.7	121.7	122.6	124.1	123.4	122.0	140.7	139.9	15.9 (CH_3)
		(+14.3)	(−2.3)	(−1.2)	(−0.2)	(−1.0)	(−0.6)	(+0.9)	(0.0)	
3	2-Cl	124.5	122.9*	122.8*	124.5**	124.8**	121.7	138.5	138.5	
		(−1.9)	(−1.1)	(−1.0)	(+0.2)	(+0.4)	(−0.9)	(−1.3)	(−1.4)	
4	2-Br	115.4	126.5	122.7	124.4*	124.7*	121.5	140.9	139.5	
		(−11.0)	(+2.5)	(−1.1)	(+0.1)	(+0.3)	(−1.1)	(+1.1)	(−0.4)	
5	2-Ph	144.3	119.4	123.5	124.3*	124.5*	122.2	140.7	139.5	134.4 (C_1'), 126.5 (C_2'),
		(+17.9)	(−4.6)	(−0.3)	(+0.0)	(+0.1)	(−0.4)	(+0.9)	(−0.4)	128.9 (C_3'), 128.2 (C_4')
6	2-CHOHCH-$(CH_3)_2$	148.5	120.8	123.4	124.2*	124.1*	122.4	139.5	139.5	76.4 (C_8), 35.7 (C_9), 19.0
		(+22.1)	(−3.2)	(−0.4)	(−0.1)	(−0.3)	(−0.2)	(−0.3)	(−0.4)	and 18.1 (C_{10} and C_{11})
7	2-CH=C-$(CH_3)_2$	141.7	122.0*	123.0	124.2	123.7	122.1*	139.8	139.5	119.0 (C_8), 137.6 (C_9),
		(+15.3)	(−2.0)	(−0.8)	(−0.1)	(−0.7)	(+0.5)	(0.0)	(−0.4)	20.9 (C_{10}), 27.3 (C_{11})
8	3-Me	121.8	131.9	122.8	124.0*	124.2*	121.8	139.9	140.1	13.8 (CH_3)
		(−4.6)	(+7.9)	(−0.1)	(−0.3)	(−0.2)	(−0.8)	(+0.1)	(+0.2)	
9	3-Cl	120.6	121.1	122.7	125.1*	124.7*	121.7	136.1	138.4	
		(−5.8)	(−2.9)	(−1.1)	(+0.8)	(+0.3)	(−0.9)	(−3.7)	(−1.5)	
10	3-Br	123.4	107.7	122.9*	125.2**	124.9**	122.6*	137.5	138.5	
		(−3.0)	(−16.3)	(−0.9)	(+0.9)	(+0.5)	(0.0)	(−2.3)	(−1.4)	
11	3-Ph	122.8	137.9*	123.3**	124.3	124.3	122.8**	138.0*	140.7	136.0 (C_1'), 128.65 (C_2'
		(−3.6)	(+13.9)	(−0.5)	(0.0)	(−0.1)	(+0.2)	(−1.8)	(+0.8)	and C_3'), 127.5 (C_4')
12	2,3-$(Me)_2$	133.6	127.0	121.0	123.7*	123.4*	121.9	141.0	138.1	13.7 (CH_3-C_2),
		(+7.2)	(+3.0)	(−2.8)	(−0.6)	(−1.0)	(−0.7)	(+1.2)	(−1.8)	11.2 (CH_3-C_3)
13	2,3-$(Cl)_2$	119.7	126.1	121.9*	125.7**	125.4**	121.6*	135.3	135.5	
		(−6.7)	(+2.1)	(−1.9)	(+1.4)	(+1.0)	(−1.0)	(−4.5)	(−4.4)	

[a] For C_i $\Delta(\delta) = \delta$(substituted benzothiophene) − δ(benzothiophene).

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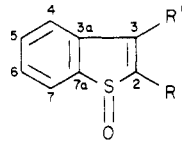
Table II. ^{13}C Chemical Shifts (ppm) in 2- and/or 3-Substituted Benzo[*b*]thiophene *S*-Oxides

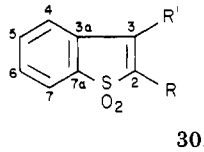
compd	substituent	C_2	C_3	C_4	C_5	C_6	C_7	C_{3a}	C_{7a}	C_x
14	2-Me	150.6	128.7	127.6	132.0	123.7	126.1	138.2	144.8	12.8 (CH_3)
15	2-Cl	143.5	129.9	128.4	132.3	124.0	126.1	136.0	143.6	
16	2-Br	131.5	134.3	128.4	132.3	123.9	126.2	137.2	145.1	
17	2-Ph	152.3	126.4	128.3	132.2	124.5	126.6	137.7	144.1	130.8 (C_1'), 127.0 (C_2'), 129.1 (C_3'), 129.5 (C_4')
18	3-Me	132.1	145.2	128.7	131.8	122.5	125.8	138.5	145.9	14.1 (CH_3)
19	3-Cl	132.4	139.2	130.2	132.1	123.2	126.2	135.2	144.7	
20	3-Br	135.4	128.4	130.1	132.3	124.5	125.9	136.2	144.0	
21	3-Ph	132.6	148.4	129.0	131.7	124.4	126.6	137.2	146.6	129.9 (C_1'), 128.0 (C_2'), 129.0 (C_3'), 129.9 (C_4')
22	2,3-$(Me)_2$	143.7	136.5	127.6	131.9	121.6	125.7	139.9	142.9	10.6 (CH_3-C_2), 11.6 (CH_3-C_3)
23	2,3-$(Cl)_2$	131.1	134.1	129.9	132.8	122.4	126.2	134.5	141.8	

Chart II



14, R = CH_3, R′ = H
15, R = Cl, R′ = H
16, R = Br, R′ = H
17, R = Ph, R′ = H
18, R = H, R′ = CH_3
19, R = H, R′ = Cl
20, R = H, R′ = Br
21, R = H, R′ = Ph
22, R = CH_3, R′ = CH_3
23, R = Cl, R′ = Cl

Chart III



24, R = H, R′ = H
25, R = CH_3, R′ = H
26, R = Cl, R′ = H
27, R = Br, R′ = H
28, R = Ph, R′ = H
29, R = $CHOHCH(CH_3)_2$, R′ = H
30, R = H, R′ = CH_3
31, R = H, R′ = Cl
32, R = H, R′ = Br
33, R = H, R′ = Ph
34, R = CH_3, R′ = CH_3

derivatives and benzothiophene itself. These shift increments were used for the assignments of the C_4, C_5, C_6, and C_7 resonances. We will return to these assignments after the discussion of the sulfoxide and sulfone results. The phenyl carbon resonances in 2-phenyl- and 3-phenylbenzothiophene, **5** and **11**, are readily distinguished from the aromatic benzothiophene carbons on the basis of their intensities (there are two 2′ and two 3′ carbons) and of substituent effects in the benzene ring.[1b,16] The shift increments due to the replacement of a benzene hydrogen by benzothiophene are included in Table VI. Carbon signals 10 and 11 of **7** were assigned on the basis of molecular planarity, as shown by photoelectron spectroscopy.[17]

Benzo[*b*]thiophene *S*-Oxides. The ^{13}C chemical shifts for the benzothiophene *S*-oxides (see Chart II) are given in Table II. Benzothiophene *S*-oxide itself could not be isolated[13] and its chemical shifts are therefore not found in Table II. In the ^{1}H NMR spectra of the sulfoxides no aromatic proton signal is sufficiently separated to permit the identification of the corresponding carbon signal by selective decoupling. The assignments are based principally on the displacements of the signals upon Pr(fod)$_3$ addition, which complexes with the sulfoxide function[18] according to the method described for organic monofunctional compounds.[19]

Oxidation of the sulfide to the sulfoxide shifts the signals of carbons 2–5, 7, and 7a to low field and of 3a to high field (Table IV). A very small chemical shift range is observed for C_6.

The large downfield shift of the C_2 and also the C_{7a} signal could be a consequence of the increased electronegative character of the sulfoxide group compared to that of the sulfide group. The deshielding effect at C_3, C_7, and C_5 could indicate an increase in mesomeric acceptor character of the sulfoxide group, relative to that of sulfide. However, without any further calculations it is not possible to determine the effects responsible for the observed chemical shifts.[20]

The effect of the sulfoxide group on the phenyl carbons in 2-phenyl- and 3-phenylbenzothiophene is quite small (Table VI).

Benzo[*b*]thiophene *S*,*S*-Dioxides. The chemical shifts for benzothiophene *S*,*S*-dioxide and its derivatives (see Chart III) are given in Table III.

The assignments are again supported by the pattern of shift increments observed upon addition of Pr(fod)$_3$, which presumably forms a bidentate complex with the sulfone.[21,22] These increments are substantially smaller in the sulfone series compared to those for the corresponding sulfoxides, which is presumably due to both a change in complex structure and complexation equilibrium.

The shift differences between the sulfones and the corresponding sulfides are given in Table IV. As in the case of sulfoxides, it can be seen that carbons 3–5 are substantially deshielded whereas carbon 3a is shielded. The upfield shift of the C_{7a} signals and the small downfield shift of the C_2 peak could indicate that the SO_2 group is less electron attracting than the SO group.

The effect of the SO_2 group on the phenyl carbons in 2-phenyl- and 3-phenylbenzothiophene *S*,*S*-dioxides are given in Table VI.

A comparison with the Pr(fod)$_3$-assisted assignments in the sulfoxide and sulfone series lends support to the assignments in the benzothiophene series.

In order to further support the assignments and conclusions concerning the carbons of the homocycle in the benzothiophenes and their sulfoxide and sulfone derivatives, we determined the chemical shifts for a number of

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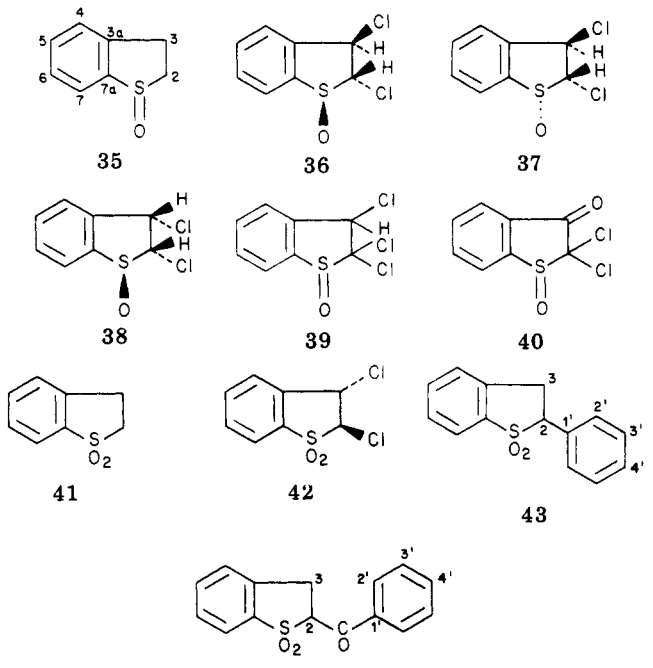
Table III. ^{13}C Chemical Shifts (ppm) in Benzo[*b*]thiophene *S,S*-Dioxide and 2- and/or 3-Substituted Benzo[*b*]thiophene *S,S*-Dioxides with Carbon Shieldings Relative to Benzothiophene *S,S*-Dioxide[a] in Parentheses

compd	substituent	C_2	C_3	C_4	C_5	C_6	C_7	C_{3a}	C_{7a}	C_x
24	none	130.8	130.8	132.5	133.7	125.6	121.3	131.3	136.9	
25	2-Me	140.4	125.8	129.0	133.4	124.2	120.9	131.3	136.1	8.6 (CH_3)
		(+9.6)	(−5.0)	(−3.5)	(−0.3)	(−1.4)	(−0.4)	(0.0)	(−0.8)	
26	2-Cl	129.7	126.5	130.2	134.1	124.9	121.9	134.4	134.9	
		(−1.1)	(−4.3)	(−2.3)	(+0.4)	(−0.7)	(+0.6)	(+3.1)	(−2.0)	
27	2-Br	122.7	130.9	130.1	134.0	124.8	122.1	131.3	135.6	
		(−8.1)	(+0.1)	(−2.4)	(+0.3)	(−0.8)	(+0.8)	(0.0)	(−1.3)	
28	2-Ph	142.6	123.6	129.8	133.5	125.0	121.4	131.1	137.1	127.1 (C_1'), 126.5 (C_2'),
		(+11.8)	(−7.2)	(−2.7)	(−0.2)	(−0.6)	(+0.1)	(−0.2)	(+0.2)	129.1 (C_3'), 130.3 (C_4')
29	2-CHOHCH-$(CH_3)_2$	146.3	127.2	129.8	133.7	125.0	121.2	130.7	137.2	71.7 (C_8), 32.5 (C_9), 19.2
		(+15.5)	(−3.6)	(−2.7)	(0.0)	(−0.6)	(−0.1)	(−0.6)	(+0.3)	and 16.0 (C_{10} and C_{11})
30	3-Me	125.8	142.9	130.4	133.5	122.4	120.8	133.1	137.5	13.7 (CH_3)
		(−5.0)	(+12.1)	(−2.1)	(−0.2)	(−3.2)	(−0.5)	(+1.8)	(+0.6)	
31	3-Cl	125.9	140.1	131.6	133.7	122.8	120.9	130.2	137.5	
		(−4.9)	(+9.3)	(−0.9)	(0.0)	(−2.8)	(−0.4)	(−1.1)	(+0.6)	
32	3-Br	129.9	129.6	131.7	133.9	124.8	120.9	131.3	137.3	
		(−0.9)	(−1.2)	(−0.8)	(+0.2)	(−0.8)	(−0.4)	(0.0)	(+0.4)	
33	3-Ph	125.7	145.9	130.5	133.2	124.3	121.6	131.9	138.2	131.0 (C_1'), 127.9 (C_2'),
		(−5.1)	(+15.1)	(−2.0)	(−0.5)	(−1.3)	(+0.3)	(+0.6)	(+1.3)	129.1 (C_3'), 130.5 (C_4')
34	2,3-$(Me)_2$	134.1	133.9	129.1	133.5	121.6	120.8	133.9	136.0	6.8 (CH_3-C_2),
		(+3.3)	(+3.1)	(−3.4)	(−0.2)	(−4.0)	(−0.5)	(+2.6)	(−0.9)	10.9 (CH_3-C_3)

[a] For C_i $\Delta(\delta) = \delta$ (substituted benzothiophene *S,S*-dioxide) − δ (benzothiophene *S,S*-dioxide).

Chart IV

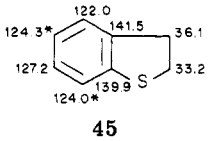


2,3-dihydrobenzothiophene *S*-oxides and *S,S*-dioxides. (Table V and Chart IV).

2,3-Dihydrobenzothiophene *S*-Oxides and *S,S*-Dioxides. In the ^1H NMR spectra of the 2,3-dihydro derivatives the hydrogen signals at positions 2 and 3 are clearly separated from the aromatic proton resonances and selective decoupling may be used in the assignment of the carbon resonances. This technique was used in the case of *trans-syn*-2,3-dichloro-2,3-dihydrobenzothiophene *S*-oxide (**37**), where protons 2 and 3 give rise to an AB system.[12] Signal assignments for the homocycle in the 2,3-dihydrobenzothiophene *S*-oxides and *S,S*-dioxides were supported by $Pr(fod)_3$ experiments with substrates **35** and **41**. The 2,3-dihydrobenzothiophene substituent effects on the phenyl carbon resonances of **43** and **44** are indicated in Table VI.

In the 2,3-dihydrobenzothiophene series the chemical shifts for carbons 4–6 are virtually identical for the sulfoxides and sulfones, whereas C_7 and C_{3a} are substantially deshielded in the sulfoxides, relative to the sulfones.

However, comparison of the benzothiophene *S*-oxides with the 2,3-dihydro derivatives (Table II) shows that the carbon signals for the homocycle in the 2,3-dihydro derivatives are deshielded (Table V) and that this shift is more pronounced for carbon 6. This remark is also valid for 2,3-dihydrobenzothiophene, where carbons 6 and 7 are substantially deshielded by 2.8 and 1.4 ppm, respectively, relative to 1 due to the lack of the participation of the double bond to the aromaticity. In the sulfone series, on the other hand, reduction of the C_2–C_3 bond results in only small downfield shifts of the C_6 and C_7 signals (Tables III and V).



45

The observation that the reduction of the C_2–C_3 bond affects the carbon resonances for the homocycle in the sulfide and sulfoxide series and not the sulfones indicates that the double bond of the heterocycle plays a more

Table IV. ^{13}C Chemical Shifts (ppm) of 2- and/or 3-Substituted Benzo[*b*]thiophene *S*-Oxides and *S,S*-Dioxides Relative to the Corresponding Sulfides[a]

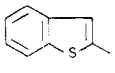
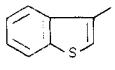
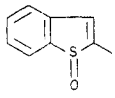
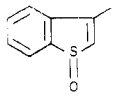
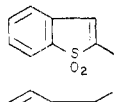
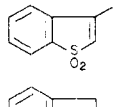
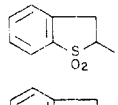
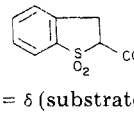
substituent	compd	ΔC_2	ΔC_3	ΔC_4	ΔC_5	ΔC_6	ΔC_7	ΔC_{3a}	ΔC_{7a}
none	sulfone **24**	+4.4	+6.8	+8.7	+9.4	+1.2	−1.3	−8.5	−3.0
2-Me	sulfoxide **14**	+9.9	+7.0	+5.0	+7.9	+0.3	+4.1	−2.5	+4.9
	sulfone **25**	−0.3	+4.1	+6.4	+9.3	+0.8	−1.1	−9.4	−3.8
2-Cl	sulfoxide **15**	+19.0	+7.0	+5.6	+7.8	−0.8	+4.4	−2.5	+5.1
	sulfone **26**	+5.2	+3.6	+7.4	+9.6	+0.1	+0.2	−4.1	−3.6
2-Br	sulfoxide **16**	+16.1	+7.8	+5.7	+7.9	−0.8	+4.7	−3.7	+5.6
	sulfone **27**	+7.3	+4.4	+7.4	+9.6	+0.1	+0.6	−9.6	−3.9
2-Ph	sulfoxide **17**	+8.0	+7.0	+4.8	+7.9	0.0	+4.4	−3.0	+4.6
	sulfone **28**	−1.7	+4.2	+6.3	+9.2	+0.5	−0.8	−9.6	−2.4
2-CHOHCH$(CH_3)_2$	sulfone **29**	−2.2	+6.4	+6.4	+9.5	+0.9	−1.2	−8.8	−2.3
3-Me	sulfoxide **18**	+10.3	+13.3	+5.9	+7.8	−1.7	+4.0	−1.4	+5.8
	sulfone **30**	+4.0	+11.0	+7.6	+9.5	−1.8	−1.0	−6.8	−2.6
3-Cl	sulfoxide **19**	+11.8	+18.1	+7.5	+7.0	−1.5	+4.5	−0.9	+6.3
	sulfone **31**	+5.3	+19.0	+8.9	+8.6	−1.9	−0.8	−5.9	−0.9
3-Br	sulfoxide **20**	+12.0	+20.7	+7.2	+7.1	−0.4	+3.3	−1.3	+5.5
	sulfone **32**	+6.5	+21.9	+8.8	+8.7	−0.1	−1.7	−6.2	−1.2
3-Ph	sulfoxide **21**	+9.8	+10.5	+5.7	+7.4	+0.1	+3.8	−0.8	+5.9
	sulfone **33**	+2.9	+8.0	+7.2	+8.9	0.0	−1.2	−6.1	−2.5
2,3-$(Me)_2$	sulfoxide **22**	+10.1	+9.5	+6.6	+8.2	−1.8	+3.8	−1.1	+4.8
	sulfone **34**	+0.5	+6.9	+8.1	+9.8	−1.8	−1.1	−7.1	−2.1
2,3-$(Cl)_2$	sulfoxide **23**	+11.4	+8.0	+8.0	+7.1	−3.0	+4.6	−0.8	+6.3

[a] $\Delta C = \delta$ [C(sulfoxide or sulfone)] − δ [C(sulfide)]; positive values are downfield.

Table V. ^{13}C Chemical Shifts (ppm) in 2,3-Dihydro Benzothiophene *S*-Oxides and *S,S*-Dioxides

compd	C_2	C_3	C_4	C_5	C_6	C_7	C_{3a}	C_{7a}	C_x
35	52.8	31.4	128.3	132.3	126.1	126.7	143.2	144.8	
36	83.3	61.9	131.4	133.4	126.9	127.1	139.2	142.7	
37	78.6	64.1	131.0	133.7	126.9	127.4	139.9	141.5	
38	78.9	64.2	131.1	133.9	127.1	127.7	140.1	141.8	
39	102.0	69.9	130.6	133.9	127.0	128.0	139.6	141.4	
40	93.9	191.3	138.2	134.4	128.7	128.7	138.2	148.6	
41	50.6	25.3	128.7	133.4	127.3	121.3	137.2	138.9	
42	65.7	65.7	131.3	135.2	126.9	123.5	133.8	134.4	
43	67.4	32.9	129.1	133.4	127.0	122.3	136.4	138.5	130.2 (C_1'), 129.0 (C_2), 129.3 (C_3' and C_4')
44	65.9	28.6	128.9	134.5*	127.3	121.7	136.3	137.5	188.5 (C_8), 136.2 (C_1') 129.0 (C_2'), 129.3 (C_3'), 133.9* (C_4')

Table VI. Aryl Carbon Shieldings (ppm), Relative to Benzene, for Phenyl-Substituted Benzothiophenes and Benzothiophene *S*-Oxides and *S,S*-Dioxides[a]

compd	substituent	C_i	ortho	meta	para
5		+5.7	−2.2	+0.2	−0.5
11		+7.3	−0.05	−0.05	−1.2
17		+2.1	−1.7	+0.4	+0.8
21		+1.2	−0.7	+0.3	+1.2
28		−1.6	−2.2	+0.4	+1.6
33		+2.3	−0.8	+0.4	+1.8
43		+1.5	+0.3	+0.6	+0.6
44		+7.5	+0.3	+0.6	+5.2

[a] $\Delta(\delta) = \delta$ (substrate) − δ (benzene).

important part in the aromaticity of the former systems than the latter. In other words, as postulated previously in thiophene series,[23] the double bond C_2–C_3 is more ethylenic in character in the sulfone than either in the sulfoxide or the sulfide.

Experimental Section

Sulfides **2–4**, **8–10**, **12**, and **13**, sulfoxides **14–16**, **18–20**, **22**, **23**, and **36–40**, and sulfones **24–27**, **30–32**, **34**, and **42** have already been described.[12,14] Benzothiophene **1** was a commercial product and was purified chromatographically on silica gel (petroleum ether eluent). The preparation of 2-phenyl- and 3-phenylbenzothiophene, **5** and **11**,[24,25] have already been described. 2,3-Dihydrobenzothiophene *S*-oxide **35** was readily prepared in two steps by reduction of **41** in **45** and oxidation to the sulfoxide.[14] Substrates **17**, **21**, **28**, **33**, **43**, and **44** were prepared by oxidation of **5** and **11**, by methods described previously.[14] Compounds **29**, **43**, and **44** were obtained by oxidation of the corresponding sulfides.

^{13}C NMR spectra of ca. 0.5 M solutions in $CDCl_3$, with Me_4Si as an internal standard, were recorded on an HX-90 Bruker NMR instrument, operating at 22.63 MHz in the Fourier transform mode. Spectra were generally recorded at 20 °C, using a sweep width of 4000 Hz (8K data memory). In compounds where peak separation was small, smaller sweep widths were employed.

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For studies with $Pr(fod)_3$, each experiment was run with three or four concentrations of shift reagent by addition of successive volumes of a shift reagent solution (c 0.25 M) to 1.0 mL of a substrate solution (c 0.5 M) up to a mole ratio [$Pr(fod)_3$]/[substrate] of 0.4.

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Registry No. 1, 95-15-8; 2, 1195-14-8; 3, 7342-85-0; 4, 5394-13-8; 5, 1207-95-0; 6, 70445-84-0; 7, 70445-85-1; 8, 1455-18-1; 9, 7342-86-1; 10, 7342-82-7; 11, 14315-12-9; 12, 4923-91-5; 13, 5323-97-7; 14, 33945-86-7; 15, 57147-28-1; 16, 57147-27-0; 17, 70445-86-2; 18, 51500-43-7; 19, 63724-95-8; 20, 57147-26-9; 21, 70445-87-3; 22, 70445-88-4; 23, 30834-33-4; 24, 825-44-5; 25, 6224-55-1; 26, 10133-41-2; 27, 5350-05-0; 28, 7420-84-0; 29, 70445-89-5; 30, 6406-91-3; 31, 21211-29-0; 32, 16957-97-4; 33, 27183-55-7; 34, 16958-01-3; 35, 26524-83-4; 36, 57147-29-2; 37, 57194-65-7; 38, 63783-25-5; 39, 63724-90-3; 40, 63724-93-6; 41, 14315-13-0; 42, 57147-30-5; 43, 70445-90-8; 44, 70445-91-9; 2,3-dihydro-2-phenylbenzo[b]thiophene, 54493-00-4; 2-benzoyl-2,3-dihydrobenzo[b]thiophene, 70445-92-0.

Synthesis of [3′,5′-$^{13}C_2$]Tyrosine and Its Use in the Synthesis of Specifically Labeled Tyrosine Analogues of Oxytocin and Arginine-Vasopressin and Their 2-D-Tyrosine Diastereoisomers[1,2]

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DL-[3′,5′-$^{13}C_2$]Tyrosine (91% ^{13}C enriched) was synthesized by a ten-step synthetic scheme in an overall yield of 22% (86+% per step) using [1,3-$^{13}C_2$]acetone as the source of label. The enantiomers were resolved by enzymatic methods, and the labeled DL amino acid or purified enantiomers readily converted to the N^{α}-Boc acids suitable for peptide synthesis. Boc-DL-[3′,5′-$^{13}C_2$]tyrosine was used for the total synthesis of the specifically labeled peptide hormone derivatives [2-DL-[3′,5′-$^{13}C_2$]tyrosine]oxytocin and [2-DL-[3′,5′-$^{13}C_2$]tyrosine,8-arginine]vasopressin by solid phase methods. The diastereoisomers were separated from each other by partition chromatography on Sephadex G-25 followed by gel filtration to give the following specifically labeled hormone derivatives: [2-[3′,5′-$^{13}C_2$]tyrosine]oxytocin, [2-D-[3′,5′-$^{13}C_2$]tyrosine]oxytocin, [2-[3′,5′-$^{13}C_2$]tyrosine,8-arginine]vasopressin, and [2-D-[3′,5′-$^{13}C_2$]tyrosine,8-arginine]vasopressin. The milk ejecting activities were determined.

Recently it has been found that ^{13}C-enriched amino acids, peptides, and proteins, enriched at specific carbon atoms, can be used for a variety of chemical–physical and biological studies related to structure, dynamics, metabolism, etc.[3-10] The use of high enrichment (85–95%) at a specific position in the molecule will generally ensure that the labeled carbon can be unambiguously identified above the natural abundance (1.1%) using nuclear magnetic resonance (NMR) spectroscopy or other physical methods. Some common amino acids can be obtained from hydrolysis of proteins obtained from microorganisms which are grown on ^{13}C-enriched carbonate or other ^{13}C-enriched sources,[11,12] but others are not obtained or are obtained only in small quantities. In addition, the amino acids so obtained usually are uniformly labeled. This is acceptable for some applications, and indeed a number of physical–chemical studies, especially using ^{13}C NMR, have appeared.[13-15] Unfortunately, uniformly labeled amino acids, whether free or as part of a peptide, give very complicated ^{13}C NMR spectra with the resonance line of each carbon greatly reduced in intensity due to splitting by adjacent and further removed ^{13}C nuclei. While in-

(1) Financial support from U.S. Public Health Service Grant AM-17420 and the National Science Foundation is gratefully acknowledged. We are also very grateful for the [1,3-$^{13}C_2$]acetone from the Stable Isotope Resource, which is supported by the U.S. Department of Energy and the National Institutes of Health, Grant No. RR-00962-01, which made this work possible.

(2) All amino acids except glycine are of the L configuration unless otherwise noted. Standard abbreviations for amino acids, protecting groups, and peptides as recommended by the IUPAC-IUB Commission on Biochemical Nomenclature [*J. Biol. Chem.*, **247**, 977 (1972)] are used. Other abbreviations include: DCC, dicyclohexylcarbodiimide; DIEA, diisopropylethylamine; DMB, 3,4-dimethylbenzyl; NMR, nuclear magnetic resonance; TFA, trifluoroacetic acid; HPLC, high performance (pressure) liquid chromatography; AVP, arginine-vasopressin.

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