# Benzo[*b*]thiophene Derivatives. XVIII. The Sulfur Isosteres of Harmaline, Harmine and Related Isomers (Ia,b)

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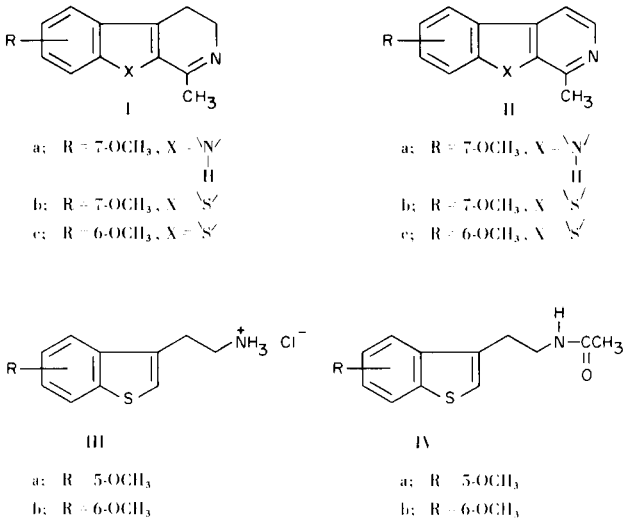
The sulfur analogs of harmaline, 7-methoxy-3,4-dihydro-1-methyl[1]benzothieno[2,3-*c*]-pyridine (Ib), harmine, 7-methoxy-1-methyl[1]benzothieno[2,3-*c*]pyridine (IIb), and corresponding 6-methoxy isomers (Ic and IIc) have been synthesized for pharmacological evaluation as monoamine oxidase inhibitors.

In 1958, Freter, *et al.* reported that harmana L. alkaloids were active reversible inhibitors of monoamine oxidase (MAO) (3). Subsequently, Undenfriend and coworkers reported a study on the *in vivo* and *in vitro* inhibition of MAO by harmaline and a number of related carboline structures, and concluded that harmaline (4,9-hydro-7-methoxy-1-methyl-3*H*-pyrido[3,4-*b*]indole) (Ia) and harmine (7-methoxy-1-methyl-9*H*-pyrido[3,4-*b*]indole) (IIa) are the most potent of the series (4). More recently, McIsaac and Estevez have studied a larger series of β-carbolines and described the structure-activity relationships of various substituents and degrees of unsaturation (5).

In continuing our studies of the syntheses and pharmacological properties of benzo[*b*]thiophene isosteres of biologically active indole derivatives (6,7) we have now synthesized the sulfur analog of harmaline (SAH), 7-methoxy-3,4-dihydro-1-methyl[1]benzothieno[2,3-*c*]-pyridine hydrochloride (Ib) the corresponding harmine analog (IIb) and, for comparative purposes, analogs bearing a methoxy group at the 6-position (Ic and IIc), derived from 5-methoxybenzo[*b*]thiophenes. β-Carboline isosteres of this type without methoxy substituents were first reported by Herz (8) but no biological data were presented. Recently, sulfur analogs of 3,4-dihydro-β-carboline and β-carboline have been described (9), but no biological data were reported.

Our syntheses depend on the ready availability of 5-methoxy-3-(β-aminoethyl)benzo[*b*]thiophene (IIIa), previously reported (6), and 6-methoxy-3-(β-aminoethyl)-benzo[*b*]thiophene (IIIb) which we obtained in better yield by a slight modification of the reduction reported by Schuetz, *et al.* (10) in the synthesis of this material.




Each of these amines were converted to its acetamide (IVa and IVb) and cyclized by the Bischler-Napieralski method to the corresponding 3,4-dihydro-1-methyl[1]-benzothieno[2,3-*c*]pyridines (Ib and Ic). Dehydrogenation over palladium in xylene gave excellent yields of the harmine analogs (IIb and IIc).

A pharmacological study of Ib and IIb has been completed and is the subject of a separate communication (11).

## EXPERIMENTAL

Melting points were measured on a Mel-Temp capillary melting point apparatus and are uncorrected. Ir spectra were determined on a Perkin-Elmer Model 137 Infracord, and were as expected. Uv data were determined on a Bausch and Lomb Spectronic 505 spectrometer in methanol solution. Nmr spectra were determined

on a Varian Associates Model HA-100 spectrometer. Microanalyses were performed by Midwest Microlabs, Inc., Indianapolis, Indiana.

6-Methoxy-3-(β-aminoethyl)benzo[*b*]thiophene Hydrochloride (IIIb).

To a solution of diborane in tetrahydrofuran (12) (0.080 mole, 80 ml. of 1 *M* Borane, Alpha Inorganics, Beverly, Mass.) maintained under dry nitrogen (13) at 0° with stirring, was added 2.20 g. (10 mmoles) of 6-methoxybenzo[*b*]thiophene-3-acetamide (10) in one portion. The stirring mixture was allowed to reflux for 6 hours, then let stand under nitrogen overnight at room temperature. After cooling the solution to 0°, 10% hydrochloric acid was cautiously added until foaming ceased, then THF was removed at reduced pressure and the aqueous solution adjusted to *p*H 10. The product was extracted with ether, the combined ether extracts dried (magnesium sulfate) and dry hydrogen chloride gas was added, to precipitate 2.4 g. (80%) of IIIb hydrochloride melting at 215-217°.

*Anal.* Calcd. for $C_{11}H_{14}ClNOS$: C, 54.21; H, 5.75; S, 13.14. Found: C, 54.89; H, 5.46; S, 12.91.

6-Methoxy-3-(β-acetaminoethyl)benzo[*b*]thiophene (IVb).

A solution of 2.3 g. (9.5 mmoles) of IIIb in 20 ml. of water was shaken with 3.06 g. (30 mmoles) of acetic anhydride, then 2.46 g. (30 mmoles) of sodium acetate in 10 ml. of water was added. The mixture was diluted with ice water and the precipitate was filtered. Recrystallization from ethyl acetate-petroleum ether afforded 2.2 g. (92%) of white needles, m.p. 117-118°; ir (potassium bromide), μ 3.10 (NH), 6.1 (NHCO); uv λ max mμ (ε), 235 (28,400), 268 (6,600), 278 (6,400); nmr (deuteriochloroform), δ 1.89 (s, 3H, $COCH_3$), 2.97 (t, 2H, $ArCH_2$-), 3.55 (m, 2H, $CH_2N$-), 3.82 (s, 3H, $OCH_3$), 5.94 (broad s, 1H, NH), 6.93 (s, 1H, H-2), 6.96 (dd, 1H, H-5, $J_{4,5}$ = 8Hz, $J_{5,7}$ = 2Hz), 7.29 (d, 1H, H-7, $J_{5,7}$ = 2Hz), 7.60 (d, 1H, H-4, $J_{4,5}$ = 8Hz).

*Anal.* Calcd. for $C_{13}H_{15}NO_2S$: C, 62.65; H, 6.03; S, 12.85. Found: C, 62.65; H, 6.27; S, 12.99.

7-Methoxy-3,4-dihydro-1-methyl[1]benzothieno[2,3-*c*]pyridine Hydrochloride (Ib).

A mixture of 2.8 g. (11.2 mmoles) of IVb, 6 g. of phosphorus pentoxide and 6 g. of phosphorus oxychloride was allowed to reflux in 300 ml. of anhydrous xylene for 90 minutes. The cold mixture was diluted with 100 ml. of water and the aqueous layer was separated, washed with ether, made basic with concentrated sodium hydroxide and extracted with 3 x 100 ml. of portions of ether. The combined basic ether extracts were dried over sodium sulfate and saturated with dry hydrogen chloride gas to give 2.6 g. (87%) of bright yellow product. Recrystallization from methanol-ethyl acetate afforded bright yellow needles, m.p. 245-247°; ir (potassium bromide), μ 4.0 (broad, IV°NH), 6.1 (olefinic C=C); nmr (DMSO-$d_6$), δ 2.74 (s, 3H, $CH_3$-C), 3.40 and 3.96 (m, 4H, $-CH_2CH_2$-), 3.90 (s, 3H, $OCH_3$), 7.20 (dd, 1H, H-6, $J_{5,6}$ = 8Hz, $J_{6,8}$ = 2Hz), 7.81 (d, 1H, H-8, $J_{6,8}$ = 2Hz), 8.02 (d, 1H, H-5, $J_{5,6}$ = 8Hz); uv, λ max mμ (ε), 213 (10,000), 241 (10,800), 272 (6,133), 325 (6,000).

*Anal.* Calcd. for $C_{13}H_{14}ClNOS$: C, 58.32; H, 5.24; S, 11.96. Found: C, 58.60; H, 5.39; S, 12.00.

7-Methoxy-1-methyl[1]benzothieno[2,3-*c*]pyridine Hydrochloride (IIb).

A solution of 2.0 g. of the free base of Ib in 200 ml. of xylene and 0.8 g. of 30% palladium on carbon was allowed to reflux for 8 hours. The catalyst was filtered and the solvent removed *in vacuo* yielding a semi-solid. The oily solid was recrystallized from methanol giving 1.3 g. (67%) of the free base of IIb, melting at 124-126°. Solution in ether and addition of dry hydrogen chloride produced white needles of IIb hydrochloride, m.p. 259-260°; ir (potassium bromide) μ 4.2 (broad, IV°NH), 6.3 (aromatic C=C); nmr (DMSO-$d_6$, 100°), δ 2.96 (s, 3H, $CH_3$-C), 3.95 (s, 3H, $OCH_3$), 7.20-8.60 (m, 5H, aromatics); uv λ max mμ (ε), 215 (38,400) 242 (48,000), 275 (14,400), 297 (20,000).

*Anal.* Calcd. for $C_{13}H_{12}ClNOS$: C, 58.76; H, 4.52; S, 12.06. Found: C, 58.58; H, 4.76; S, 11.95.

6-Methoxy-3,4-dihydro-1-methyl[1]benzothieno[2,3-*c*]pyridine Hydrochloride (Ic).

This slightly hygroscopic material was made similarly to Ib from 2.0 g. of IVa, giving 1.45 g. (68%) of bright yellow needles (methanol-ether acetate), m.p., 209-210°, dependent on rate of heating; ir (potassium bromide) μ 3.8 (broad, IV°NH), 6.1 (olefinic C=C); nmr (DMSO-$d_6$, deuteriochloroform), δ 2.8 (s, 3H, $CH_3$-C), 3.38 (t, 2H, $-CH_2$), 3.90 (s, 3H, $OCH_3$), 4.04 (t, 2H, $-CH_2$), 7.28 (dd, 1H, H-7, $J_{7,8}$ = 8Hz, $J_{5,7}$ = 2Hz), 7.54 (d, 1H, H-5, $J_{5,7}$ = 2Hz), 8.03 (d, 1H, H-8, $J_{7,8}$ = 8Hz); uv, λ max mμ (ε), 216 (49,000), 248 (11,000), 352 (14,600).

*Anal.* Calcd. for $C_{13}H_{14}ClNOS$: C, 58.32; H, 5.24; S, 11.96. Found: C, 58.18; H, 5.10; S, 12.09.

6-Methoxy-1-methyl[1]benzothieno[2,3-*c*]pyridine Hydrochloride (IIc).

This material was made in 88% yield similar to IIb, as pale yellow needles, m.p. 235-237°; ir (potassium bromide) μ 4.0 (broad, IV°NH), 6.3 (aromatic C=C); nmr (DMSO-$d_6$, deuteriochloroform) δ 2.99 (s, 3H, $CH_3$-C), 3.94 (s, 3H, $OCH_3$), 7.44 (dd, 1H, H-7, $J_{7,8}$ = 8Hz, $J_{5,7}$ = 2Hz), 8.16 (d, 1H, H-8 $J_{7,8}$ = 8Hz), 8.27 (d, 1H, H-5, $J_{5,7}$ = 2Hz), 8.76 (s, 2H, H-3, and H-4).

*Anal.* Calcd. for $C_{13}H_{12}ClNOS$: C, 58.76; H, 4.52; S, 12.06. Found: C, 59.03; H, 4.78; S, 12.14.

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(12) It is important to use a fresh bottle of the Borane-tetrahydrofuran solution to get satisfactory results.

(13) Nitrogen must be bubbled through the solution during the entire reflux period.