Benzo[*b*]thiophene Derivatives. XX. The Sulfur Isostere of 5,6-Dihydroxytryptamine (1).

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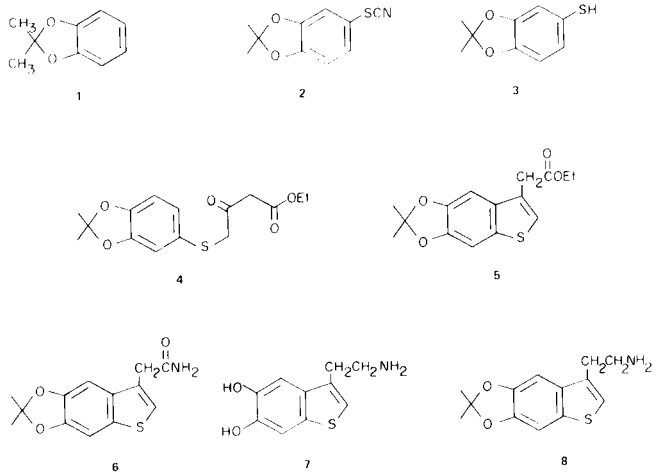
Received June 26, 1973

3-β-Aminoethyl-5,6-dihydroxybenzo[*b*]thiophene, the sulfur bioisostere of 5,6-dihydroxytryptamine, a selective neurotoxin, has been synthesized and shown to have significant effect on biogenic amine levels both centrally and peripherally. A derivative, 3-β-aminoethyl-5,6-isopropylidenedioxybenzo[*b*]thiophene, showed significant but opposite activity. The syntheses and preliminary pharmacology are reported.

The importance of benzo[*b*]thienyl isosteres of biologically active indoles has clearly been established (2). This is particularly true of the isosteres of CNS active agents such as tryptamine (3), serotonin (4) and harmaline (5). Recently, an effective neurotoxin has been reported to have a preferential degenerative effect on central indoleamine-containing neurons. Intraventricular injection of this compound, 5,6-dihydroxytryptamine (5,6-DHT), in the rat, depleted brain and spinal cord 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid, but increased tyrosine hydroxylase activity. These pharmacological observations suggest a preferential action of 5,6-DHT on tryptaminergic neurons (6,7). This interesting activity of an indole derivative prompted the investigation of the sulfur bioisostere.

We have synthesized 3-(β-aminoethyl)-5,6-dihydroxybenzo[*b*]thiophene (**7**) for the purpose of examining its potential as a serotonin blocker, analogous to 5,6-DHT. Thus, 1,2-isopropylidenedioxybenzene (**1**) was converted to 3,4-isopropylidenedioxythiophenol (**3**) *via* lithium aluminum hydride reduction of the intermediate thiocyanate (**2**). Condensation of **3** with ethyl γ-chloroacetoacetate followed by intramolecular cyclization of the resulting keto-ester **4** with polyphosphoric acid gave ethyl 5,6-isopropylidenedioxy-3-benzo[*b*]thienylacetate (**5**). Ethanolic ammonia converted **5** to the corresponding amide **6** which, after reduction with diborane and an acidic work-up, gave the desired **7**. Compound **6** could also be reduced directly to the 3-β-aminoethyl-5,6-isopropylidenedioxybenzo[*b*]thiophene (**8**), isolated as its oxalate salt.



1 2 3 4 5 6 7 8

Biological Evaluation.

As an initial screen for biological activity, the effects of these sulfur bioisosteres of 5,6-DHT, **7** and **8**, on biogenic amine levels peripherally and centrally in the rat were investigated. Two routes of administration were employed in separate experiments, intraperitoneal and intracerebral injections.

When given peripherally, 40 mg./kg. i.p., **7**·HCl (5,6-DHST) decreased norepinephrine (NE) in the heart and spleen, but not 5-HT in the latter tissue. In contrast, the isopropylidene derivative **8**, at the same dosage, decreased 5-HT in the spleen, and to a lesser statistically insignificant extent, NE in the heart and spleen. Also in contrast to the less lipid-soluble **7**, **8** decreased NE in the brain.

Injected intracerebrally into the lateral ventricles (100 μg/rat) **7** decreased NE levels in the whole brain of the rat, while leaving 5-HT and its principal metabolite levels unchanged. More like 5,6-DHT itself, **8** decreased 5-HT levels in the whole rat brain, while NE levels remained unchanged. A slight decrease in 5-hydroxyindoleacetic acid levels was also observed.

The toxicity of **8** was considerably greater than **7**. Behaviorally, those rats injected i.p. with **7** exhibited signs of excitation (exophthalmos and piloerection) while **8** caused a depression compared to controls. Behavioral manifestations following intracerebral injections were more or less reversed. The isopropylidene derivative **8** increased spontaneous motor activity and excitement in the rats while **7** caused an immobile, rigid though alert, stance compared to controls.

EXPERIMENTAL

The infrared spectra were obtained on a Perkin-Elmer model 137-B infracord spectrometer using either potassium bromide mulls or 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 on 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. Elemental analyses were performed by Midwest Microlab of Indianapolis, Indiana.

1,2-Isopropylidenedioxybenzene (**1**).

This compound was prepared from catechol and acetone in 65% yield by the method of Slooff (8).

1-Thiocyano-3,4-Isopropylidenedioxybenzene (**2**).

Thiocyanogen chloride (approx. 0.09 mole) in anhydrous acetic acid (500 ml.) was prepared from lead thiocyanate and chlorine according to the method of Bacon and Guy (9). To this solution, compound **1** (10.98 g., 0.073 mole) was added all at once. The solution was stirred at room temperature for one hour, then filtered to remove the lead chloride. The filtrate was then poured into 3 liters of ice water and the mixture allowed to stand in the refrigerator for 2 hours. The colorless product was filtered to yield 13.6 g. (89%) of essentially pure **2**. Recrystallization from aqueous ethanol gave an analytical sample: m.p. 69-70°; ir (potassium bromide): 4.63 (C≡N) μ; nmr (deuteriochloroform): δ 1.64 (s, 6H), 6.68 (d, 1H, $J_{5,6}$ = 8 Hz, H-5), 6.86-7.04 (m, 2H, H-2, 6).

Anal. Calcd. for $C_{10}H_9NO_2S$: C, 57.97; H, 4.35; S, 15.46; M.W. 207. Found: C, 58.09; H, 4.57; S, 15.70; M.W. m/e 207.

3,4-Isopropylidenedioxythiophenol (**3**).

Into a stirred solution of LAH (3.65 g., 0.096 mole) in ether (100 ml.) was slowly dropped a solution of **2** (18 g., 0.087 mole) in ether (200 ml.). The addition required approximately 30 minutes after which the mixture was heated at reflux for an additional 30 minutes and quenched by cautiously adding 15 ml. of water, then sufficient 6 *N* hydrochloric acid to dissolve the inorganic salts. The ether layer was immediately separated and the aqueous phase extracted with ether (3 x 100 ml.). The combined ether layers were dried (magnesium sulfate), and the solvent evaporated leaving a yellow liquid. The liquid was distilled (66-68°, 0.5 mm) to give 10.4 g. (66%) of **3**: ir (silver chloride): 3.90 (S-H) μ; nmr (deuteriochloroform): δ 1.58 (s, 6H), 3.28 (s, 1H, SH), 6.46-6.76 (m, 3H).

Anal. Calcd. for $C_9H_{10}O_2S$: C, 59.31; H, 5.49; S, 17.58; M.W. 182. Found: C, 59.28; H, 5.53; S, 17.71; M.W. m/e 182.

Ethyl 4-(3,4-Isopropylidenedioxythiophenoxy)acetoacetate (**4**).

To a cold (0°), stirred solution of **3** (9.1 g., 0.05 mole) in pyridine (45 ml.) was added over a 10 minute period ethyl γ-chloroacetoacetate (10) (10.36 g., 0.063 mole). During the addition period a white precipitate appeared. After the addition, the mixture was heated on a steam bath for 15 minutes during which time the solid dissolved and the mixture turned dark red. The solution was cooled to 0°, 6 *N* hydrochloric acid added until *p*H 5 was attained, and the resulting mixture extracted with ether (3 x 100 ml.). The combined ether phases were extracted with ice-cold 6 *N* hydrochloric acid (3 x 50 ml.), then with water (2 x 50 ml.), dried (magnesium sulfate), filtered, and the solvent evaporated to give a viscous, yellow-red oil (14 g., 94%): nmr (deuteriochloroform): δ 1.24 (t, 3H, J = 6.5 Hz), 1.63 (s, 6H), 3.60 (s, 2H), 3.64 (s, 2H), 4.14 (q, 2H, J = 6.5 Hz), 6.59 (d, 1H, $J_{5,6}$ = 8 Hz, H-5), 6.74-6.94 (m, 2H); M.W. Calcd. 310.0875. Found: m/e 310.0858. This material was used directly without further purification.

Ethyl 5,6-Isopropylidenedioxy-3-benzo[*b*]thienylacetate (**5**).

A mechanically stirred mixture of benzene (600 ml.), polyphosphoric acid (18 g.), and phosphorus pentoxide (5 g.) was heated to reflux. To this mixture was added 25 g. of Celite filter-aid (11). After an additional 30 minutes of stirring and heating, compound **4** (17.8 g., 0.057 mole) in benzene (50 ml.) was added all at once. The resulting mixture was heated at reflux for one hour, then filtered. The filtrate was washed with 4 *N* sodium hydroxide solution, then with water, dried (magnesium sulfate), clarified (Norite) and the solvent evaporated to give 12.9 g. (77%) of the desired **5** which by thin layer chromatography [silica gel, acetone: petroleum ether (60-90°) (3:7)] was contaminated with a trace of **4**; ir (silver chloride): 5.75 μ (C=O); nmr (deuteriochloroform): δ 1.22 (t, 3H, J = 7.0 Hz), 1.65 (s, 6H), 4.68 (s, 2H), 5.12 (q, 2H, J = 7.0 Hz), 6.98-7.12 (m, 3H), M.W.: Calcd.: 292.0770. Found: m/e 292.0372.

5,6-Isopropylidenedioxy-3-benzo[*b*]thienylacetamide (**6**).

A solution of **5** (2.0 g., 6.85 mmoles) in methanol (50 ml.) was saturated with ammonia and the resulting mixture stirred at room temperature. After approximately 36 hours, a precipitate appeared. After 5 days the mixture was filtered and the solid recrystallized from methanol to give 1.25 g. (75%) of **6**, m.p. 214-216°; ir (potassium bromide): 3.05, 3.20 (NH), 6.05 (C=O) μ; nmr (DMSO-d_6): δ 1.65 (s, 6H), 3.54 (s, 2H), 6.85 (bs, 1H, NH), 7.14-7.28 (m, 3H), 7.40 (bs, 1H, NH).

Anal. Calcd. for $C_{13}H_{13}NO_3S$: C, 59.31; H, 4.94; S, 12.17. M.W. 263. Found: C, 59.19; H, 4.84; S, 12.41; M.W. m/e 263.

3-(β-Aminoethyl)-5,6-dihydroxybenzo[*b*]thiophene (**7**).

A slurry of **6** (1.7 g., 6.5 mmoles) in dry THF (75 ml.) was added to a THF solution of diborane (16 ml., 1*M* in BH_3). The amide dissolved immediately upon the additional of the diborane. The mixture was heated at reflux for 5 hours, then quenched by the careful addition of 6 *N* hydrochloric acid (50 ml.). The mixture was distilled until the temperature of the distillate was allowed to cool to room temperature whereupon a solid precipitated. This solid was collected and recrystallized from 3 *N* hydrochloric acid to yield 1.0 g. (63%) of colorless, crystalline needles (7·HCl), m.p. 268-270° dec.; nmr (deuterium oxide): δ 3.0-3.4 (m, 4H, $-CH_2-CH_2-$), 7.1 (s, 1H), 7.20 (s, 1H), 73.0 (s, 1H).

Anal. Calcd. for $C_{10}H_{12}ClNO_2S$: C, 48.87; H, 4.92; S, 13.06; M.W. 245.5. Found: C, 48.78; H, 4.88; S, 13.26; M.W. m/e 245, 247.

3-(β-Aminoethyl)-5,6-isopropylidenedioxybenzo[*b*]thiophene (**8**) Monohydrooxalate.

A reduction mixture of 1.7 g. (6.5 mmoles) of **6** with diborane, as described above, was heated at reflux for 5 hours, then quenched with 50 ml. of saturated salt water. After washing with ether, the combined organic phases were dried (magnesium sulfate) and filtered. An ether solution of anhydrous oxalic acid was added, and the gummy precipitate filtered and recrystallized from methanol/ethyl acetate to give 1.54 g. (70%) of the oxalate salt, m.p. 205.5-206° (with gas evolution).

Anal. Calcd. for $C_{15}H_{17}NO_6S$: C, 53.10; H, 5.02; S, 9.44. Found: C, 52.87; H, 5.06; S, 9.70.

An nmr spectrum of the free base, extracted from a bicarbonate solution of **8** monohydrooxalate, showed the following resonances: (deuteriochloroform): δ 1.67 (s, 6H), 2.76-3.12 (m, 4H), 6.90 (s, 1H), 6.99 (s, 1H), 7.08 (s, 1H).

The hydrochloride of **8** was precipitated from an ethereal solution of the free base, and recrystallized from methanol/ethyl acetate, m.p. 203-205°.

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(1) Contribution No. 2288, supported in part by U.S.P.H.S. Grant GM-10366-10, and in part by NS-90672. This paper was presented in part before the Fifth Central Regional Meeting, ACS, at Cleveland, Ohio, May 14, 1973. For part XIX of this series, see E. Campaigne and R. B. Rogers, *J. Heterocyclic Chem.*, **10**, 297 (1973).

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(11) We are indebted to Dr. A. I. Rachlin, Hoffman-LaRoche, Nutley, New Jersey for suggesting this procedure.