

Synthesis of 1,3-Benzoxathiole-2-acetic Acid Derivatives (I)

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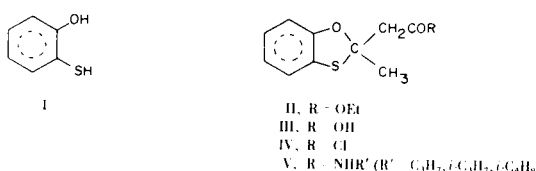
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The preparation and the study of five-membered ring oxygen heterocycles containing O-M-O and O-M-S grouping, where M = carbon, silicon and boron, has been previously reported (2). This note describes the synthesis of the hitherto unknown 1,3-benzoxathiole derivatives II-V for their potential pharmaceutical activity.

Phosphorus pentoxide or dry hydrogen chloride promoted condensation of 2-hydroxythiophenol with ethyl acetoacetate gave compound II. This product was easily hydrolyzed to give the corresponding acid III, which with thionyl chloride afforded the chloride IV. Reaction with amines converted IV to the corresponding amides V.

The reactions performed are shown in scheme I. All the obtained compounds gave correct elemental analyses, and the spectral (ir and nmr) data were consistent with the assigned structures.

Scheme I



EXPERIMENTAL

The infrared spectra were obtained on a Perkin Elmer model 325 spectrophotometer using either potassium bromide mulls or neat liquids between sodium chloride plates. Nmr spectra were determined on a JEOL C-60 HL spectrometer working at 60 MHz and using hexamethyldisiloxane as internal standard. Melting points were uncorrected and obtained on a Tottoli apparatus. All boiling points were uncorrected and obtained from distillation or with a boiling point apparatus.

2-Hydroxythiophenol (I).

This compound was obtained by the literature procedure from 2-hydroxyaniline (3).

2-Methyl-1,3-benzoxathiole-2-acetic Acid, Ethyl Ester (II).

Method A.

To a warm (50°) stirred solution of 2-hydroxythiophenol (0.23

mole) and ethyl acetoacetate (0.25 mole), phosphorus pentoxide (50 g.) was added during 30 minutes. When the addition was complete, the mixture was stirred at 50-55° for 1 hour, then at room temperature for 6 hours. The resulting mixture was diluted with diethyl ether and filtered to remove the gummy residue (phosphoric acids). The ether phase was washed with water, dried on calcium chloride, filtered, and the solvent evaporated. The crude product was chromatographed on a silica gel column, using petroleum ether-benzene (3:1) as eluent, to give a yellow liquid. Yield 45%; b.p. 163-165° (4 mm); n_D^{26} 1.5471; ir (neat), 1740 cm^{-1} (C=O); nmr (carbon tetrachloride): δ 1.25 (t, 3 H, CH₃-CH₂-OCO-), 1.95 (s, 3 H, CH₃-C=), 3.00 (s, 2 H, -CH₂-COOC₂H₅), 4.05 (q, 2 H, CH₃-CH₂-OCO-) and 6.85 ppm (m, 4 H arom).

Anal. Calcd. for C₁₂H₁₄O₃S: C, 60.48; H, 5.92; S, 13.45. Found: C, 60.30; H, 5.92; S, 13.34.

Method B.

A stirred solution of 2-hydroxythiophenol (0.28 mole) and ethyl acetoacetate (0.25 mole) was saturated during 3 hours with dry hydrogen chloride. The resulting mixture was allowed to stand for 12 hours, then poured into 10% sodium hydroxide (250 ml.), extracted with diethyl ether and worked up as in Method A, yield 49%; ir and nmr spectral data were identical with the product obtained by Method A.

2-Methyl-1,3-benzoxathiole-2-acetic Acid (III).

A mixture of II (0.02 mole), ethanol (40 ml.) and 40% sodium hydroxide was refluxed for 2 hours. The solution was concentrated *in vacuo* (40°) and the concentrate was acidified with 10% hydrochloric acid. The white precipitate was filtered off, washed thoroughly with water and *vacuum* dried. After recrystallization from (1:1) hexane-benzene the compound had m.p. 145-147°, yield 50%; ir (potassium bromide): 3460 (OH) and 1680 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.30 (s, 3 H, CH₃), 5.05 (s, 2 H, -CH₂-), 7.00 (m, 4 H arom) and 7.40 ppm (s, 1H, COOH, deuterium oxide exchanged).

Anal. Calcd. for C₁₀H₁₀O₃S: C, 57.12; H, 4.79; S, 15.25. Found: C, 56.96; H, 4.88; S, 15.13.

2-Methyl-1,3-benzoxathiole-2-acetyl Chloride (IV).

A solution of III (0.014 mole) in dry benzene (30 ml.) was treated with thionyl chloride (0.015 mole) and refluxed for almost 3 hours. After solvent evaporation *in vacuo*, the obtained compound, which had a tendency to become a dark colored substance on heating, was used for the next reactions without further purification; ir (neat) 1780 cm^{-1} (C=O).

2-Methyl-1,3-benzoxathiole-2-(N-propyl)acetamide (Va).

The compound IV (0.014 mole) was added dropwise to a well

stirred suspension of *n*-propylamine (0.02 mole) and anhydrous sodium carbonate (0.01 mole) in chloroform (50 ml.). After refluxing for 3 hours, the mixture was filtered and the clear filtrate concentrated *in vacuo*. The crude product was chromatographed on a silica gel column, using petroleum ether-diethyl ether (3:1) as eluent, to give a white product, which was recrystallized from diisopropyl ether, yield 40%, m.p. 118-119°; ir (potassium bromide): 3340 (NH) and 1640 cm^{-1} (C=O); nmr (deuteriochloroform): δ 0.90 (t, 3 H, $\text{CH}_3\text{-CH}_2\text{-}$), 1.45 (m, 2 H, $\text{CH}_3\text{-CH}_2\text{-}$), 2.40 (s, 3 H, $\text{CH}_3\text{-C}\leq$), 3.15 (m, 4 H, $\text{-CH}_2\text{-CO-}$ and $\text{-CH}_2\text{-NH-}$), 6.55 (s, 1 H, NH, deuterium oxide exchanged) and 7.10 ppm (m, 4 H arom).

Anal. Calcd. for $\text{C}_{13}\text{H}_{17}\text{NO}_2\text{S}$: C, 62.12; H, 6.82; N, 5.57; S, 12.75. Found: C, 62.16; H, 6.90; N, 5.73; S, 12.64.

In the same manner starting from IV and isopropylamine or isobutylamine, respectively, the following compounds were obtained:

2-Methyl-1,3-benzoxathiole-2-(*N*-isopropyl)acetamide (Vb).

Yield 60%; crystallized from diisopropyl ether, m.p. 85°; ir (potassium bromide): 3320 (NH) and 1650 cm^{-1} (C=O); nmr (deuteriochloroform): δ 1.05 (d, 6 H, $(\text{CH}_3)_2\text{CH-}$), 1.90 (s, 3 H, $\text{CH}_3\text{-C}\leq$), 2.90 (s, 2 H, $\text{-CH}_2\text{-CO-}$), 4.00 (m, 1 H ($\text{CH}_3)_2\text{CH-}$), 5.90 (s, 1 H, NH, deuterium oxide exchanged) and 6.90 ppm (m, 4 H arom).

Anal. Calcd. for $\text{C}_{13}\text{H}_{17}\text{NO}_2\text{S}$: C, 62.12; H, 6.82; N, 5.57;

S, 12.75. Found: C, 61.85; H, 6.75; N, 5.69; S, 12.60.

2-Methyl-1,3-benzoxathiole-2-(*N*-isobutyl)acetamide (Vc).

Yield 80%; crystallized from dioxane, m.p. 117°; ir (potassium bromide): 3300 (NH) and 1635 cm^{-1} (C=O); nmr (deuteriochloroform): δ 0.80 (d, 6 H, $(\text{CH}_3)_2\text{CH-}$), 1.45 (m, 1 H, $(\text{CH}_3)_2\text{CH-}$), 1.85 (s, 3 H, $\text{CH}_3\text{-C}\leq$), 2.95 (m, 4 H, $\text{-CH}_2\text{-CO-}$ and $\text{-CH}_2\text{-NH-}$), 6.05 (s, 1 H, NH, deuterium oxide exchanged) and 6.80 ppm (m, 4 H arom).

Anal. Calcd. for $\text{C}_{14}\text{H}_{19}\text{NO}_2\text{S}$: C, 63.36; H, 7.22; N, 5.28; S, 12.08. Found: C, 63.31; H, 7.27; N, 5.18; S, 11.97.

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