[CONTRIBUTION FROM THE BEN MAY LABORATORY FOR CANCER RESEARCH, UNIVERSITY OF CHICAGO]

SUBSTITUTED THENOIC ACIDS

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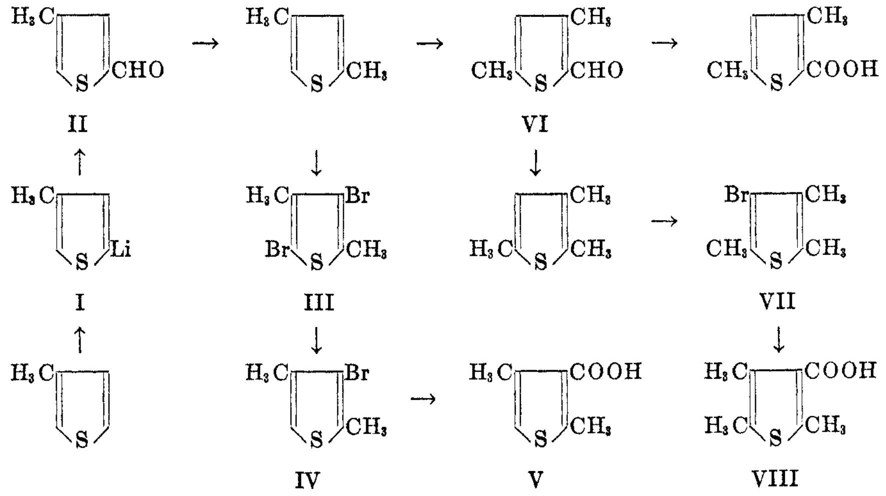
The displacements of the absorption bands of some substituted thenoic acids (1) are not readily understandable. In an attempt to correlate these shifts, the ultraviolet spectra of the methylthenoic acids and the thiophenedicarboxylic acids have been determined. The preparation of the yet undescribed substances of this series is reported in this communication.

These acids were obtained by carbonation of the proper thienylmetallo compounds as indicated in the chart for one sequence. 2,4-Dimethylthiophene was prepared by Wolff-Kishner reduction of 4-methyl-2-thenaldehyde (II) obtained by a modified Bouveault synthesis (1), from 4-methyl-2-thienyllithium (2).



The most practical approach to the unknown thiophene-3,4-dicarboxylic acid is through a halogen-lithium interconversion. Aromatic compounds containing two lithium atoms, although not on adjacent carbon atoms, have been prepared by this reaction (3). It was found that 3,4-diiodothiophene reacted at low temperature with butyllithium to give the expected diacid in good yield (74%). This dicarboxylic acid was readily dehydrated to the corresponding anhydride, as was its isomer (4). The anhydride was characterized by conversion to the imide.

Esterification of thiophene-2,3-dicarboxylic acid gave a dimethyl ester melting at *ca.* 30° below the temperature recorded in the literature (4); this ester may exist under two dimorphic forms.

The spectral absorption of these substances will be discussed elsewhere.

EXPERIMENTAL

The melting points were determined in evacuated capillaries and were corrected; the boiling points were not corrected. The organometallic reactions were kept under an inert atmosphere. The microanalyses were performed by Mr. W. Saschek.

4-Methyl-2-thenaldehyde (II). 3-Methylthiophene[1] (29 g.) was added at room temperature, in a slow stream, to a solution of butyllithium (0.33 mole) in 500 ml. of ether. The reaction was exothermic and it proceeded with evolution of gas. The mixture was stirred for two additional hours and then slowly added (45 min.) to an ice-cold solution of dimethylformamide (30 ml., 0.39 mole) in ether (100 ml.). The yellow suspension was stirred overnight and then poured onto ice. The solvent layer was washed with water, dilute hydrochloric acid, aqueous sodium bicarbonate, and again with water. The dried solution was concentrated; the residue distilled as a colorless liquid (25.6 g., 61%), b.p. 84–86° (8 mm.); n_D^{20} 1.5740, d_4^{20} 1.160.

Anal. Calc'd for C_6H_6OS: C, 57.11; H, 4.79; $[R]_D$ 34.76.

Found: C, 57.22; H, 5.12; $[R]_D$ 35.90.

The *p-nitrophenylhydrazone* crystallized from ethanol in red needles, m.p. 179–181°.

Anal. Calc'd for $C_{12}H_{11}N_3O_2S$: N, 16.08. Found: N, 16.05.

The *ethylene acetal*, obtained in 88% yield by the usual procedure (5), distilled from sodium at 121–122° (12 mm.); n_D^{22} 1.5372, d_4^{22} 1.200.

Anal. Calc'd for $C_8H_{10}O_2S$: C, 56.44; H, 5.92; $[R]_D$ 45.07.

Found: C, 56.56; H, 6.03; $[R]_D$ 44.32.

This aldehyde was converted upon oxidation by silver oxide to the known (2) 4-methyl-2-thenoic acid, m.p. 123–124° after recrystallization from hexane.

The *hydrazone* of II decomposed at 120° in a solution of potassium hydroxide in ethylene glycol (6) to give an 85% yield of 2,4-dimethylthiophene,[2] b.p. 139° (740 mm., 50 plate column); n_D^{24} 1.5120.

2,4-Dimethyl-3,5-dibromothiophene (III). To an ice-cold solution of 2,4-dimethylthiophene (11.22 g.) in dry carbon disulfide (60 ml.) was added dropwise a solution of bromine (32.0 g., 2 moles) in carbon disulfide (20 ml.). The orange mixture was left to stir overnight, then evaporated on the steam-bath. The brown residue was refluxed during four hours with 6 g. of potassium hydroxide and 6 ml. of methanol and the resulting mixture was steam-distilled. The organic layer was separated and gave by distillation 21.86 g. of a colorless liquid, b.p. 104–106° (7 mm.). This material was taken up in 40 ml. of hexane and was cooled to −60°. The crystalline precipitate was decanted and redistilled, b.p. 106–107° (8 mm.); n_D^{21} 1.6049, d_4^{21} 1.894.

Anal. Calc'd for $C_6H_6Br_2S$: Br, 59.20; $[R]_D$ 50.27.

Found: Br, 59.24; $[R]_D$ 49.13.

2,4-Dimethyl-3-bromothiophene (IV). A Grignard reagent was prepared from 7.0 g. of magnesium, 15.0 ml. of ethyl bromide, and 21.0 g. of the raw III in 50 ml. of ether; the mixture was stirred overnight and poured onto ice. The residue left by evaporation of the solvent, after the usual work up, was steam-distilled. The organic layer gave by distillation a colorless liquid (8.65 g.), b.p. 67–68° (8 mm.); n_D^{21} 1.5640, d_4^{21} 1.486.

Anal. Calc'd for C_6H_7BrS: Br, 41.82; $[R]_D$ 42.51.

Found: Br, 41.18; $[R]_D$ 41.80.

2,4-Dimethyl-3-thenoic acid (V). A Grignard reagent was prepared from 0.97 g. of magnesium, 2.0 ml. of ethyl bromide, and 2.80 g. of IV. The mixture was stirred overnight and then refluxed for two hours. The residue (0.46 g.) left after the usual work up was crystallized from hexane and sublimed at 60° under a high vacuum, giving colorless needles, m.p. 165–166°. $\lambda_{max.}^{H_2O}$ 2430 Å (ϵ 6,300).

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[1] Generously supplied by the Socony-Vacuum Laboratories, Paulsboro, N. J.

[2] Hartough and Dickert stated (private communication) n_D^{20} 1.5130 for this compound, instead of the value reported (7).

Anal. Calc'd for $C_7H_8O_2S$: C, 53.82; H, 5.16.

Found: C, 53.89; H, 5.23.

3,5-Dimethyl-2-thenaldehyde (VI). This substance was obtained in 69% yield by following the procedure described for II. It was a colorless liquid, b.p. 101–102° (8 mm.); n_D^{23} 1.5797, d_4^{23} 1.138.

Anal. Calc'd for C_7H_8OS: C, 59.96; H, 5.75; $[R]_D$ 39.37.

Found: C, 60.00; H, 5.90; $[R]_D$ 40.94.

The *p-nitrophenylhydrazone* crystallized from ethanol in red needles, m.p. 221–223°.

Anal. Calc'd for $C_{13}H_{13}N_3O_2S$: N, 15.26. Found: N, 15.31.

This aldehyde (VI) furnished upon oxidation by silver oxide the known (8) 3,5-dimethyl-2-thenoic acid, m.p. 173–174° after crystallization from benzene.

The hydrazone of VI decomposed at 125° in a solution of potassium hydroxide in ethylene glycol to give a 77% yield of 2,3,5-trimethylthiophene (6), b.p. 162.5° (746 mm., 50 plate column); n_D^{26} 1.5101. $\lambda_{max.}^{pentane}$ 2370 Å (ϵ 6,700).

2,4,5-Trimethyl-3-bromothiophene (VII). The procedure previously described for III gave a 51% yield of colorless liquid, b.p. 84–85° (8 mm.); n_D^{19} 1.5608, d_4^{19} 1.429.

Anal. Calc'd for C_7H_9BrS: Br, 38.96; $[R]_D$ 47.13.

Found: Br, 38.66; $[R]_D$ 46.46.

2,4,5-Trimethyl-3-thenoic acid (VIII). A Grignard reagent prepared from VII gave a 31% yield of this acid, m.p. 167–168°, after crystallization from benzene-hexane and sublimation at 90° under a high vacuum. $\lambda_{max.}^{H_2O}$ 2410 Å (ϵ 6,900).

Anal. Calc'd for $C_8H_{10}O_2S$: C, 56.44; H, 5.92.

Found: C, 56.27; H, 6.02.

4,5-Dimethyl-2-thenoic acid. One ml. of 2,3-dimethylthiophene (6) was metalated with 50 ml. of a 0.2 *M* solution of butyllithium in ether, and then carbonated. Crystallization from benzene and sublimation at 100° under a high vacuum gave 0.71 g. of material m.p. 210–212°. $\lambda_{max.}^{H_2O}$ 2500 and 2840 Å (ϵ 7,400 and 8,000).

Anal. Calc'd for $C_7H_8O_2S$: C, 53.82; H, 5.16.

Found: C, 53.54; H, 5.31.

4,5-Dimethyl-2,3-dibromothiophene. The procedure used for the preparation of III was followed exactly and gave 18.40 g. of a colorless liquid, b.p. 110–111° (8 mm.); n_D^{19} 1.6068, d_4^{19} 1.867.

Anal. Calc'd for $C_6H_6Br_2S$: Br, 59.20; $[R]_D$ 50.27.

Found: Br, 59.26; $[R]_D$ 49.95.

4,5-Dimethyl-3-thenoic acid. A Grignard reagent was prepared from the preceding dihalide, and then was hydrolyzed as previously described for IV, but the product (4.12 g., b.p. 66–68° (7 mm.)) was not homogenous and gave low analytical values for bromine. It was then converted to the acid by the usual procedure. Colorless crystals were obtained, m.p. 144–145°, after crystallization of the material (0.86 g.) from hexane and sublimation at 70° under a high vacuum. $\lambda_{max.}^{H_2O}$ 2450 Å (ϵ 7,100).

Anal. Calc'd for $C_7H_8O_2S$: C, 53.82; H, 5.16.

Found: C, 53.78; H, 5.28.

3,4-Dimethyl-2-thenoic acid. This substance was prepared by carbonation of the lithium derivative of 3,4-dimethylthiophene (4). It melted at 188–189° after crystallization from benzene-hexane and sublimation at 75° under a high vacuum. $\lambda_{max.}^{H_2O}$ 2530 Å (ϵ 9,600).

Anal. Calc'd for $C_7H_8O_2S$: C, 53.82; H, 5.16.

Found: C, 53.58; H, 5.13.

Thiophene-3,4-dicarboxylic acid. 3,4-Diiodothiophene (3 g.) (9) was added to a cold (−60°) solution of butyllithium (3 mol. eq.) in 100 ml. of ether. The mixture was stirred for 4 minutes and then treated all at once with an excess of powdered solid carbon dioxide. A white powder (1.16 g.) was obtained by the usual procedure. Recrystallization of this material from water gave colorless needles, m.p. 230–231°, $\lambda_{max.}^{H_2O}$ 2180 and 2400 Å (ϵ 27,300) and 6,100).

Anal. Calc'd for $C_6H_4O_4S$: C, 41.86; H, 2.34.

Found: C, 41.77; H, 2.46.

The *dimethyl ester*, prepared with diazomethane, crystallized from hexane in colorless prisms and melted at 59–60° after sublimation at 55° under a high vacuum.

Anal. Calc'd for $C_8H_8O_4S$: C, 47.99; H, 4.03.

Found: C, 48.04; H, 4.15.

The *anhydride* was prepared in 86% yield by refluxing the diacid for 4 hours with acetyl chloride. It crystallized from benzene in colorless needles and melted at 145–146° after sublimation at 70° under a high vacuum.

Anal. Calc'd for $C_6H_2O_3S$: C, 46.75; H, 1.31.

Found: C, 46.68; H, 1.32.

The *imide* was prepared in 72% yield by the usual procedure (10). It crystallized from acetone in colorless needles and melted at 293–294° after sublimation at 110° under a high vacuum.

Anal. Calc'd for $C_6H_3NO_2S$: N, 9.15. Found: N, 9.25.

Thiophene-2,3-dicarboxylic acid dimethyl ester. A solution of 0.69 g. of 3-methyl-2-thiophene carboxylic acid (11) in 15 ml. of 15% aqueous sodium hydroxide was treated with 1.55 g. of potassium permanganate. The mixture was shaken for 1 hour at room temperature and then was heated for 2 hours on the steam-bath. The reaction products were filtered, neutralized with hydrochloric acid, concentrated to *ca.* 10 ml., acidified, and cooled. The white precipitate was filtered off, dried (0.54 g.), and extracted with hot benzene. The insoluble fraction (0.37 g., 45%) was then treated with an excess of diazomethane and processed as usual. Colorless leaflets, m.p. 32–33°, crystallized from hexane; a distillation at 60° under a high vacuum did not change the m.p. $\lambda_{\text{max.}}^{\text{pentane}}$ 2540 Å (ϵ 9,200).

Anal. Calc'd for $C_8H_8O_4S$: C, 47.99; H, 4.03.

Found: C, 48.08; H, 4.14.

The pure dimethyl ester (40 mg.) was refluxed for 5 hours with 1.0 ml. of 10% aqueous barium hydroxide. The insoluble barium salt was separated from the cooled mixture and decomposed with dilute hydrochloric acid. Crystallization of the dicarboxylic acid from 0.5 ml. of water gave large colorless needles, m.p. 277–278° (dec.), reported (4) m.p. 270°. Its anhydride was prepared, m.p. 141–143°; reported (4) 140°. Treatment of the silver salt of this acid with methyl iodide (4), at reflux temperature or under pressure at 100°, gave a substance, m.p. 33–34°, identical with the one described above.

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SUMMARY

The following substances have been prepared: 4-methyl- and 3,5-dimethyl-2-thenaldehyde, thiophene-3,4-dicarboxylic acid, and the five unknown methylthenoic acids.

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