

The Chemistry Laboratories of Indiana University

3-Substituted Thiophenes. XII.

Bromination of β -3-Thienylacrylic Acid (1)

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Bromination of β -3-thienylacrylic acid in glacial acetic acid gave β -(2-bromo-3-thienyl)-acrylic acid with an equivalent of bromine, and β -(2,5-dibromo-3-thienyl)- α,β -dibromopropionic acid with excess bromine. In hot carbon tetrachloride, an excellent yield of the stable olefinic addition product, β -3-thienyl- α,β -dibromopropionic acid, was obtained, and its structure was confirmed by conversion to β -bromo-3-thienylethylene in base. 3-Thienaldehyde underwent a Darzen's Glycidic Ester condensation to produce ethyl β -3-thienyl- α,β -epoxypropionate, but treatment of this ester or the salt of its derived acid with hydrogen bromide led to the formation of unstable products. The structure of the bromo-acids and derivatives were confirmed by unequivocal syntheses and/or by nuclear magnetic resonance spectra.

Cinnamic acid smoothly adds bromine in glacial acetic acid, chloroform or carbon disulfide to produce β -phenyl- α,β -dibromopropionic acid in high yield (2). β -2-Thienylacrylic acid adds bromine in hot carbon tetrachloride to produce β -(2-thienyl)- α,β -dibromopropionic acid, which readily loses hydrogen bromide in refluxing acetic acid to form β -(2-thienyl)- α -bromoacrylic acid (3). When β -2-thienylacrylic acid was treated with bromine in refluxing acetic acid, the product was β -(5-bromo-2-thienyl)- α -bromoacrylic acid, showing that bromination of the thiophene ring, as well as addition of bromine and elimination of hydrogen bromide, had occurred (3).

The thiophene ring with an acrylic acid side chain in the 3-position is more readily substituted in the 2- and 5-positions, and the dibromo adduct, β -3-thienyl- α,β -dibromoacrylic acid (III) seems more stable than its 2-thienyl isomer. Bromination of β -3-thienylacrylic acid (I) in glacial acetic acid, using a molar ratio of bromine, produced β -(2-bromo-3-thienyl) acrylic acid (II) as the main product. The structure of II was confirmed by comparison with an authentic specimen prepared by a Knoevenagel condensation of 2-bromo-3-thienaldehyde (4).

Treatment of I in hot carbon tetrachloride with an equimolar amount of bromine gave an excellent yield of the adduct III, which proved to be a relatively stable compound with sharp melting point, in contrast to the reported behavior of its 2-thienyl isomer (3). The structure of III was confirmed by its nuclear magnetic resonance spectrum, which showed a multiplet of three aromatic protons and two aliphatic protons as doublets splitting each other on adjacent carbon atoms, and by its conversion to β -bromo-3-thienylethylene (IV) in base. III did not readily lose

hydrogen bromide, even in refluxing acetic acid. Under these conditions a small amount of II was isolated from the initial tars. This may indicate some reversal of the initial bromine addition, followed by substitution of I to II.

Treatment of I with excess bromine in glacial acetic acid yielded the tetrabromo derivative, β -(2,5-dibromo-3-thienyl)- α,β -dibromopropionic acid (V). The same tetrabromide was obtained by addition of bromine to 2,5-dibromo-3-thienylacrylic acid (VI) prepared from 2,5-dibromo-3-thienaldehyde VII. Both II and III were converted to V by excess bromine in glacial acetic acid.

At attempt was made to synthesize III by an alternate route. Condensing ethyl chloroacetate with 3-thienaldehyde in the typical Darzen's manner (5), yielded ethyl β -(3-thienyl)- α,β -epoxypropionate (VIII). Treatment of VIII with hydrogen bromide in cold ether (6) gave a liquid which decomposed during vacuum distillation. VIII was saponified with sodium in ethyl alcohol, giving the sodium salt of β -(3-thienyl)- α,β -epoxypropionic acid, which was treated with hydrogen bromide in dry ether, to prepare the bromohydrin (5). The oily solid, suspected to be β -(3-thienyl)- β -bromo- α -hydroxypropionic acid (IX), was found to be extremely sensitive to both acidic and basic reagents. 3-Thienyl bromides are reported to be unstable under acidic conditions (7), and Johnson and co-workers have shown that β -halo- α -hydroxy acids readily decarboxylate and dehalogenate in base to give carbonyl compounds (5). Indeed, treatment of IX with pyridine and semicarbazide hydrochloride gave the semi-carbazone of 3-thienylacetaldehyde (X). Since IX was unstable to either acidic or basic reagents, it could not be converted to the desired dibromide III.

EXPERIMENTAL

β -(2-Bromo-3-thienyl)acrylic Acid (II). A. From 2-Bromo-3-thienaldehyde.

Freshly distilled 2-bromo-3-thienaldehyde (4) (9.55 g., 0.05 mole) was condensed with 10.4 g. (0.10 mole) of malonic acid following the procedure of Raich and Hamilton (9), yielding 8.1 g. (70%) of II melting at 224–227° after one recrystallization from 50% ethanol. Further recrystallization gave fine white needles melting at 225–226°, ν max (KBr), 2800–3000 (carboxylic O-H), 1670 (α, β -unsat. carboxylic C=O), and 1610 cm^{-1} (conj. C=C).

Anal. Calcd. for $\text{C}_7\text{H}_6\text{O}_2\text{BrS}$: Br, 34.28; S, 13.76; N.E., 233. Found: Br, 34.72; S, 13.69; N.E., 236.

B. By Bromination of β -3-thienylacrylic acid.

A solution of 1.0 g. (6.5 mmoles) of I (9) in 10 ml. of glacial acetic acid was warmed on a steam bath, while 1.04 g. (6.5 mmoles) of bromine in 8 ml. of glacial acetic acid was added dropwise to the solution. After the addition was complete, the solution was warmed an additional 15 min., then bisulfite was added to reduce any unreacted bromine. Pouring the solution into 100 ml. of cold water yielded 1.24 g. (80%) of a pale orange solid. After two recrystallizations from 50% ethanol, the white crystals melted at 224–226°, and did not depress the melting point of authentic II. The infrared spectra of both samples were identical.

2,5-Dibromo-3-thienaldehyde, VII.

2,5-Dibromo-3-methylthiophene (10) was converted to the hexamine salt of 2,5-dibromo-3-thienyl bromide (m.p. 179–181°) in 75% yield by the method of Campaigne and LeSuer (4). The salt was refluxed in 50% acetic acid for three hours, 25 ml. of concentrated hydrochloric acid was then added, and the solution was heated an additional ten minutes. The oily solution was extracted three times with ether, and the combined ether layers evaporated at reduced pressure. The residue was poured into 100 ml. of ice-water and the pale yellow oily solid

which separated was collected and then dried under vacuum at room temperature. A total of 7.1 g. (62%) of crude aldehyde was isolated, melting at 47–49°. VII was characterized by its 2,4-dinitrophenylhydrazone prepared in the usual manner (11), which melted at 244–246° (dec.).

Anal. Calcd. for $\text{C}_{11}\text{H}_8\text{Br}_2\text{N}_4\text{O}_4\text{S}$: C, 29.36; H, 1.34; N, 12.45. Found: C, 29.60; H, 1.45; N, 12.38.

A sample of VII was oxidized to the known 2,5-dibromo-3-thenoic acid by silver oxide (4). After one recrystallization from water, the sample melted at 176–178°, and a mixture melting point with an authentic specimen (12) melting at 178–179° showed no depression.

β -(2,5-Dibromo-3-thienyl)acrylic acid, VI.

VI was prepared via the Knoevenagel condensation (9), from 4.0 g. (0.014 mole) of VII and 3.08 g. (0.03 mole) of malonic acid. A total of 3.7 g. (80%) of fine yellow crystals was obtained, melting at 220–221° after three recrystallizations from ethanol, ν max (KBr), 2800, 1680, and 1610 cm^{-1} . A mixed melting point with II showed a depression of 40°.

Anal. Calcd. for $\text{C}_7\text{H}_4\text{O}_2\text{Br}_2\text{S}$: C, 26.94; H, 1.29; S, 10.28; N.E., 312. Found: C, 27.23; H, 1.36; S, 10.10; N.E., 310.

β -(2,5-Dibromo-3-thienyl)- α, β -dibromopropionic acid, V.

In a 50 ml. flask equipped with reflux condenser was placed 1.0 g. (6.5 mmoles) of I, 25 ml. of glacial acetic acid, and 3.1 g. (20 mmoles) of bromine. The solution was heated on a steam bath for 24 hours, then bisulfite was added to reduce unreacted bromine, and the solution was poured into ice-water. The pale yellow solid which precipitated was collected and recrystallized from benzene, yielding 1.4 g. (45%) of a pale white powder melting at 196–197°, ν max (KBr), 2800–3000 (carboxylic O-H), and 1720 cm^{-1} (carboxylic C=O).

Anal. Calcd. for $\text{C}_7\text{H}_4\text{O}_2\text{Br}_4\text{S}$: Br, 67.75; S, 6.80; N.E., 472. Found: Br, 67.48; S, 6.78; N.E., 475.

When either II, III or VI was treated as above, the same product, V, was obtained as shown by mixture melting point and identity of infrared spectra.

β -(3-Thienyl)- α, β -dibromopropionic acid, III.

Following the procedure of Nord and co-workers (3), a solution of 4.15 g. (27 mmoles) of I in 175 ml. of carbon tetrachloride was treated with 4.0 g. (25 mmoles) of bromine in 20 ml. of carbon tetrachloride. A precipitate formed in solution and after all the bromine color had disappeared, the mixture was cooled and the precipitate was collected. A total of 6.57 g. (84% yield) of crude solid melting at 156–162° was isolated. Recrystallization from a carbon tetrachloride-chloroform pair (Norite) gave white needles, melting at 160–161°, ν max (KBr), 2800–3000 (carboxylic O-H) and 1725 cm^{-1} (carboxylic C=O); n.m.r. (deuteroacetone) $\tau = 4.90$ d ($J = 12$ cps), 4.34 d ($J = 12$ cps), 2.22–2.73 m; ratio, 1:1:3.

Anal. Calcd. for $\text{C}_7\text{H}_6\text{Br}_2\text{O}_2\text{S}$: C, 26.78; H, 1.93; Br, 50.91; S, 10.21. Found: C, 27.03; H, 1.99; Br, 51.06; S, 10.17.

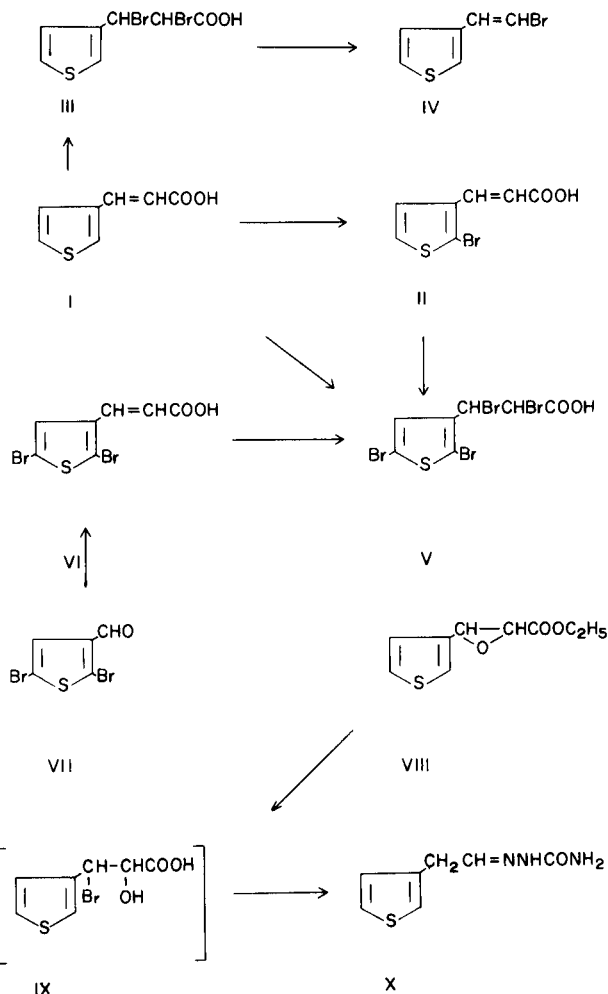
A sample of III was treated with 10% potassium hydroxide as reported by Nord, *et al.* (3), yielding β -bromo-3-thienylethylene (IV), b.p. 69–71°/1 mm, $N_D^{25} 1.6288$, ν max (liq. film), 3095 (C-H stretch), 1610 (C=C stretch), and 932 cm^{-1} (C-H bend).

Anal. Calcd. for $\text{C}_8\text{H}_5\text{BrS}$: C, 38.11; H, 2.66; Br, 42.26. Found: C, 38.60; H, 2.66; Br, 42.02.

When 2.19 g. (7 mmoles) of III in 35 ml. of glacial acetic acid was refluxed for two hours, and cooled overnight in a refrigerator, 0.201 g. (12% yield) of solid precipitated from solution, melting at 215–220° and having an IR identical to that of authentic II. Recrystallization from ethanol yielded yellow needles, whose melting point did not depress that of II. Further work-up of the mother liquor only resulted in tarry products.

Ethyl β -(3-thienyl)- α, β -epoxypropionate, VIII.

The method used was that described by Johnson and co-workers (5). A 250 ml. flask fitted with thermometer, 125 ml. pressure-equalizing dropping funnel, and stirrer was charged with 11.2 g. (0.10 mole) of 3-thienaldehyde (4) and 14.0 g. (0.114 mole) of ethyl chloroacetate. A solution of 4.45 g. (0.114 mole) of freshly cut potassium metal in 125 ml. of dry *t*-butyl alcohol was put in the dropping funnel, and the entire system was swept with a stream of nitrogen for 15 minutes. The flask was then lowered into an ice-water bath, and the addition of *t*-butoxide solution was begun dropwise in order to maintain the temperature of the reaction below 10°. After completion of addition, which required two hours, the slurry was stirred for an additional 1.5 hours at 10°. Most of the *t*-butanol was removed on the steam bath at reduced pressure and the residue was taken up in ether, washed with water, then saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. Ether was evaporated and the glycidic ester was distilled at reduced pressure yielding a colorless liquid, b.p. 133–137° (1 mm.), $N_D^{25} 1.5271$, which weighed 13.8 g. (70%), ν max (liq. film), 1710 (ester C=O), 1120 and 890 cm^{-1} (cyclic ether).



Anal. Calcd. for $C_9H_{10}O_3S$: C, 54.52; H, 5.08; S, 16.18; M.W., 198. Found: C, 54.55; H, 5.16; S, 15.80; M.W. (methanol) 202.

Preparation of Sodium β -(3-thienyl)- α,β -epoxypropionate.

Following the procedure of Johnson and co-workers (5), 1.98 g. (0.01 mole) of VIII was added dropwise to a cold solution of 0.23 g. (0.01 mole) of sodium metal in 8 ml. of absolute ethanol maintained in an ice bath. One ml. of water was added dropwise and the resulting thick white, pasty suspension was allowed to stand overnight. The salt was collected, washed with dry ether and dried, yielding 1.79 g. (93%) of product.

Attempted Preparation of β -(3-thienyl)- β -bromo- α -hydroxypropionic acid, IX.

A 100 ml. flask was charged with 1.92 g. (0.01 mole) of the sodium salt (above) and 70 ml. of dry ether. Hydrogen bromide gas was bubbled into the cooled suspension with stirring (5). After 20 minutes addition of gas was stopped, the mixture poured into ice-water, and the ether layer separated, dried over anhydrous sodium sulfate and evaporated on the steam bath at reduced pressure. An oily liquid remained which solidified upon cooling to yield a bright yellow solid. This solid was washed with chloroform, but when dried under vacuum, it decomposed to a dark, greenish-black solid in a matter of a few hours. Repetition of this procedure yielded identical results, but an infrared spectrum was obtained on the partially dried yellow solid before complete decomposition could occur, ν max (KBr), 3500 (O-H), 3100-2800 (carboxylic O-H), and 1700-1670 cm^{-1} (carboxylic C=O).

3-Thienylacetaldehyde Semicarbazone, X.

Since the bromohydrin IX was an oily, unstable compound, no attempt was made to isolate it in the preparation of this semicarbazone. In a 250 ml. flask was placed 3.13 g. (0.0164 mole) of sodium β -(3-thienyl)- α,β -epoxypropionate and 100 ml. of ether. The solution was treated with hydrogen bromide gas in the same way as above, but the crude bromohydrin was immediately suspended in 5 ml. of water containing 1.98 g. (0.017 mole) of semicarbazide hydrochloride (5). Upon addition of 10 ml. of pyridine a violent evolution of gas was observed, but no solid separated from solution. After heating on a steam bath for 20 minutes, cooling, and adding a few drops of water to the solution a fine white solid precipitated, yielding 1.68 g. (56%, based on the sodium glycidate) of crude semicarbazone. The melting point of this crude solid was 120-127°, but recrystallization from aqueous ethanol yielded a pure white crystalline material melting at 145-146°.

Anal. Calcd. for $C_7H_8N_2OS$: C, 45.88; H, 4.95; N, 22.93. Found: C, 45.63; H, 5.01; N, 22.33.

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