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Benzo[*b*]thiophene Derivatives I. 6-Methoxybenzo[*b*]thiophene Analogs of Plant Growth Regulators (1)

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The acid catalyzed ring closure of an appropriately substituted phenyl ketoester sulfide served as the initial reaction in the synthesis of several 3,4- and 3,6-disubstituted benzo[*b*]thiophenes. One of these compounds, 4-methoxybenzo[*b*]thienyl-3-acetic acid, showed marked plant growth enhancement.

The plant growth regulating properties of indole-3-acetic acid (IAA) are well documented. Benzo[*b*]thiophene-3-acetic acid has been tested in several biological systems and found to have a pronounced auxin-like activity (2). The synthesis of 3,6-disubstituted benzo[*b*]-thiophenes by Tilak *et al.*, (3) suggested a synthetic approach for the preparation of 6-methoxybenzo[*b*]thiophene analogs of IAA.

Accordingly, 3-methoxythiophenol was alkylated with ethyl 4-chloro-3-oxobutyrate to obtain the sulfide, ethyl 4-(3-methoxyphenylmercapto)-3-oxobutyrate. Cyclization of the sulfide by refluxing it in chlorobenzene with polyphosphoric acid produced a mixture of the esters ethyl (4-methoxybenzo[*b*]thienyl-3)acetate (I) and ethyl (6-methoxybenzo[*b*]thienyl-3)acetate (II). Fractional distillation of the mixture failed to separate the esters.

The mixture of esters was subjected to ammonolysis to form the amides, 4-methoxybenzo[*b*]thienyl-3-acetamide (III) and 6-methoxybenzo[*b*]thienyl-3-acetamide (IV). The mixture of isomeric amides was readily separated by crystallization and chromatography.

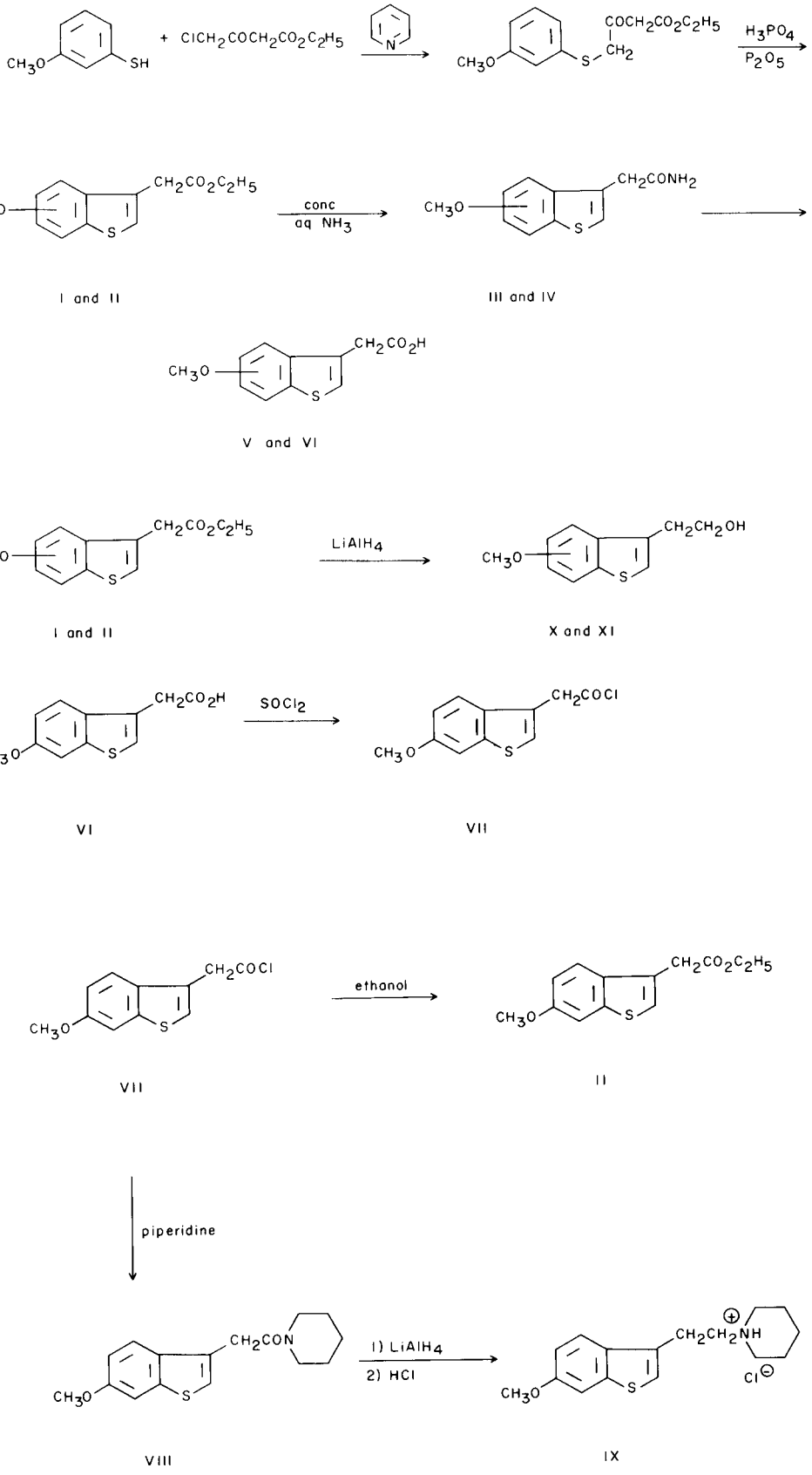
Each amide was hydrolyzed to its parent acid, 4-methoxybenzo[*b*]thienyl-3-acetic acid (V) and 6-methoxybenzo[*b*]thienyl-3-acetic acid (VI) respectively. The acid isomers were distinguished by desulfurizing with Raney nickel then oxidizing the residue with alkaline permanganate. The acid which melted from 141-142° yielded anisic acid after such treatment.

6-Methoxybenzo[*b*]thienyl-3-acetic acid (V) was treated with thionyl chloride to form 6-methoxybenzo[*b*]thienyl-3-acetyl chloride (VII) which was allowed to interact with ethanol to form ethyl 6-methoxybenzo[*b*]thienyl-3-acetate (II) and with piperidine to yield the amide, *N*-(6-methoxybenzo[*b*]thienyl-3-acetyl)piperidine (VIII). The amide was reduced to the corresponding amine which was isolated as the hydrochloride, *N*-[β-(6-methoxybenzo[*b*]thienyl-3)ethyl]piperidine hydrochloride (IX).

The isomeric alcohols, β-(4-methoxybenzo[*b*]thienyl-3)ethanol (X) and β-(6-methoxybenzo[*b*]thienyl-3)ethanol (XI) were prepared by lithium aluminum hydride reduction of the mixture of isomeric esters obtained from the ring closure of ethyl 4-(3-methoxyphenylmercapto)-3-oxobutyrate. The alcohol X was obtained as a solid but all attempts to purify XI yielded an oil. The identity of the alcohols was established by lithium aluminum hydride reduction of V which yielded a solid alcohol identical with X; a mixture of the two solids gave no depression of the melting point.

The series of 3,4-disubstituted benzo[*b*]thiophenes can be distinguished from the 3,6-disubstituted isomers by the infrared spectra. A strong doublet was centered at 850 cm^{-1} in the case of the 3,4-disubstituted isomers. This peak was absent in the spectra of the 3,6-disubstituted isomers.

Bioassay of the acids using *Avena* coleoptile sections showed that at concentrations of 10^{-6} *M* to 10^{-4} *M*, 4-methoxybenzo[*b*]thienyl-3-acetic acid (V) was 70-100% as active as indole-3-acetic acid in promoting cell elongation. There was only slight activity at concentrations of 10^{-7} *M* and 10^{-8} *M*. The 6-methoxy acid (VI) was inhibitory at concentrations of 10^{-6} *M* to 10^{-8} *M* and was only slightly active at concentrations of 10^{-4} *M* and 10^{-5} M.


+ ClCH2COCH2CO2C2H5
COCH2CO2C2H5
CH2
H3PO4
P2O5
CH2CO2C2H5
conc
aq NH3
CH2CONH2
I and II
III and IV
CH2CO2H
V and VI
LiAlH4
CH2CH2OH
X and XI
SOCl2
CH2COCl
VI
VII
ethanol
piperidine
CH2CON
1) LiAlH4
2) HCl
CH2CH2NH
Cl⊖
VIII
IX

EXPERIMENTAL

Melting points were taken on a micro melting point block using a calibrated thermometer. Boiling points are uncorrected.

Ethyl 4-(3-Methoxyphenylmercapto)-3-oxobutyrate.

Ethyl 4-chloro-3-oxobutyrate (4) (70.0 g., 0.430 mole) was added dropwise to a stirred solution of 60.0 g. (0.430 mole) of 3-methoxythiophenol (5) in 300 ml. of pyridine maintained at 25-30°. After being set aside for 15 minutes, the mixture was heated on a steam bath for a similar period and then cooled. The pyridine was dissolved by the slow addition of 600 ml. of 8 *N* hydrochloric acid which caused the reaction mixture to separate into two layers. The aqueous layer was separated and extracted twice with ether. The ether extracts and product layer were combined, washed with water, and dried with anhydrous magnesium sulfate. After removal of the solvent, the crude product was distilled to yield 88.6 g. (0.330 mole, 77%) of the ketoester sulfide boiling at 100° (0.2 mm) to 170° (0.5 mm). The occurrence of some product decomposition during distillation was indicated by continually rising pressure in the distillation system.

Ethyl 4-Methoxybenzo[*b*]thienyl-3-acetate (I) and Ethyl 6-Methoxybenzo[*b*]thienyl-3-acetate (II).

A solution of 28.8 g. (0.107 mole) of ethyl 4-(3-methoxyphenylmercapto)-3-oxobutyrate in 200 ml. of chlorobenzene was heated at its reflux temperature for three hours with polyphosphoric acid (96 g., 0.678 mole of phosphorus pentoxide in 48 ml. of 85% phosphoric acid). The chlorobenzene was decanted and the remaining semisolid was heated at its reflux temperature for three hours with 200 ml. of benzene. The benzene was decanted and the combined aromatic solutions were washed first with aqueous sodium bicarbonate and then with two portions of saturated aqueous sodium chloride. The solvents were removed under reduced pressure and the residue was distilled to obtain 22.4 g. (0.0888 mole, 83%) of crude product b.p. 90-155° (0.1 mm). Fractionation of the crude product using a heated Vigreaux column yielded a mixture of I and II b.p. 120-164° (0.07 mm).

4-Methoxybenzo[*b*]thienyl-3-acetamide (III) and 6-Methoxybenzo[*b*]thienyl-3-acetamide (IV).

A 10.0 g. (0.036 mole) portion of the ester mixture of I and II was shaken with 200 ml. of concentrated ammonium hydroxide for a week. The crude amides (III and IV) weighing 6.6 g. (0.025 mole, 75%) were recovered by filtration. Recrystallization of crude amide from 95% ethanol gave pure IV, m.p. 192.8-193.3°.

Anal. Calcd. for $C_{11}H_{11}NO_2S$: C, 59.72; H, 5.01; N, 6.36; S, 14.47. Found: C, 60.21; H, 5.14; N, 6.22; S, 14.37.

The filtrate from the purification of amide IV was evaporated to dryness. Chloroform was used to transfer 0.4 g. of the residue to a 1 x 16" alumina column which was eluted with chloroform. The amide IV was removed first, followed by the amide III. Removal of the eluent from the latter solution and recrystallization of the residue from 95% ethanol gave pure amide III, m.p. 200.0-200.5°. The crude amide mixture yielded about 5% pure amide III.

Anal. Calcd. for $C_{11}H_{11}NO_2S$: C, 59.72; H, 5.01; N, 6.36; S, 14.47. Found: C, 59.83; H, 5.08; N, 6.47; S, 14.42.

4-Methoxybenzo[*b*]thienyl-3-acetic Acid (V).

A mixture of 0.5 g. (0.0023 mole) of amide III, 13 ml. of 10% sodium hydroxide, and 5 ml. of 95% ethanol was heated at its reflux temperature for two hours. The cooled mixture was acidified to Congo red with hydrochloric acid to precipitate quantitatively the free acid (V). This was recovered by filtration, and after recrystallization from an ethanol-water (1:1) mixture had a m.p. of 159.5-160.5°.

Anal. Calcd. for $C_{11}H_{10}O_3S$: C, 59.44; H, 4.54; S, 14.43. Found: C, 59.11; H, 4.71; S, 14.33.

6-Methoxybenzo[*b*]thienyl-3-acetic Acid (VI).

Amide IV was hydrolyzed quantitatively in the same manner as was amide III. The recrystallized acid (VI) melted at 141-142°. Its equivalent weight was determined to be 228 (calcd. 222). The structure of acid VI was determined by desulfurizing it with Raney nickel (6) followed by permanganate oxidation of the oil from the desulfurization to the known anisic acid. This acid melted at 181-184° and did not depress the melting point of authentic anisic acid.

Anal. Calcd. for $C_{11}H_{10}O_3S$: C, 59.44; H, 4.54; S, 14.43. Found: C, 59.37; H, 4.76; S, 14.33.

6-Methoxybenzo[*b*]thienyl-3-acetyl Chloride (VII).

A mixture of 2.25 g. (0.01 mole) of VI, 22 ml. of absolute diethyl ether and two drops of pyridine was cooled to 0°. Freshly distilled thionyl chloride (2 ml., 0.028 mole) was added to the mixture. After being set aside at room temperature for five hours, the reaction mixture was heated at its reflux temperature for 15 minutes then cooled, and the ether was removed under reduced pressure. The product was dissolved in 20 ml. of dry benzene which was then removed under reduced pressure. The red residual acid chloride, which contained traces of solvent, was used in additional syntheses without further purification.

Ethyl 6-Methoxybenzo[*b*]thienyl-3-acetate (II).

The acid chloride (VII) obtained from 2.25 g. (0.01 mole) of VI was esterified with 25 ml. of absolute ethanol to give a nearly quantitative yield of the crude ester (II) which after two distillations gave an oil, b.p. 140-145° (0.07 mm); n_D^{25} 1.5811.

N-(6-Methoxybenzo[*b*]thienyl-3-acetyl)piperidine (VIII).

The acid chloride (VII) obtained from 2.25 g. (0.01 mole) of VI was dissolved in 10 ml. of dry benzene and treated with a solution of 2 ml. (0.02 mole) of piperidine in 20 ml. of dry benzene. The reaction mixture was washed twice with 8% hydrochloric acid, twice with water, once with saturated sodium bicarbonate solution, and again twice with water. The benzene solution was dried with anhydrous magnesium sulfate. The solvent was evaporated and the amide residue (VIII), which contained traces of solvent, was used without further purification.

N-[β-(6-Methoxybenzo[*b*]thienyl-3)ethyl]piperidine Hydrochloride (IX).

A solution of the crude amide VIII, obtained from 2.25 g. (0.01 mole) of the acid chloride VII as described above, in 30 ml. of anhydrous diethyl ether was added dropwise to a stirred suspension of 0.68 g. (0.018 mole) of lithium aluminum hydride. After adding the amide VIII the reaction mixture was stirred for half an hour, then heated at its reflux temperature for half an hour, and then cooled to room temperature. The organo lithium complex was decomposed by the dropwise addition of 0.68 ml. of water, 0.68 ml. of 15% aqueous sodium hydroxide, and 2.04 ml. of water, followed by vigorous stirring for half an hour. The precipitate was removed by filtration and the filtrate was saturated with dry hydrogen chloride gas to precipitate the hydrochloride salt of the amine (IX). Two recrystallizations from absolute ethanol gave 1.5 g. (50%) of the hydrochloride which melted at 224.5-225.5°.

Anal. Calcd. for $C_{16}H_{22}ClNOS$: C, 61.61; H, 7.11; N, 4.49; S, 10.28; Cl, 11.37. Found: C, 61.77; H, 7.26; N, 4.23; S, 10.30; Cl, 11.10.

β-(4-Methoxybenzo[*b*]thienyl-3)ethanol (X) and β-(6-Methoxybenzo[*b*]thienyl-3)ethanol (XI).

A 30 g. (0.12 mole) quantity of the mixture of esters I and II was reduced using 5.28 g. (0.14 mole) of lithium aluminum hydride and diethyl ether as solvent.

The reduction reaction mixture was hydrolyzed with dilute sulfuric acid (15 ml. of concentrated acid in 90 ml. of water) to yield 19 g. (76%) of the combined alcohols. The oily residue of a mixture of the alcohols X and XI was fractionated. After being set aside for several weeks at room temperature crystallization occurred in the lower boiling fractions. The crystalline alcohol X was isolated and after recrystallization from benzene melted at 97.8-98.5°. The 3,5-dinitrobenzoate derivative of X melted at 194.5-199.5°. The alcohol X was identified as the 4-isomer by comparison of its infrared spectrum with those of the corresponding acid and amide.

Anal. Calcd. for $C_{11}H_{12}O_2S$: C, 63.43; H, 5.81; S, 15.40. Found: C, 63.59; H, 5.98; S, 15.12.

The alcohol XI was obtained as an oil; its 3,5-dinitrobenzoate derivative melted at 167.5-168°.

β-(4-Methoxybenzo[*b*]thienyl-3)ethanol (X).

A solution of 0.085 g. (0.00038 mole) of the acid V in 9 ml. of absolute ether was added dropwise to a suspension of 0.050 g. (0.0013 mole) of lithium aluminum hydride in 4 ml. of absolute ether. After the addition of the acid was complete the mixture was refluxed for 20 minutes then hydrolyzed using 12 ml. of dilute hydrochloric acid. The ether layer was separated and the aqueous layer was extracted with 4 ml. of ether. The ether was removed from the combined extracts to give a solid residue which after one crystallization from benzene melted at 95-97°. Yield was 0.042 g., 52% of theory.

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