group as well as a 5-cycle spin coupling between themselves. The spectrum was obtained by Varian Associates.

Compound IV exhibited no absorption in the ultraviolet between 220–420 mμ at a concentration of $10^{-3}$ *M*, infrared spectrum (potassium bromide): 697, 758, 851, 926, 954, 1062, 1136, 1188, 1250, 1290, 1435, 1543, 2994, 3049, 3165 cm.$^{-1}$

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# The Preparation of Some Alkoxybenzothiophene Derivatives[1]

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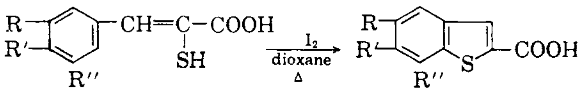
In connection with earlier studies in this laboratory,[3,4] several mono-, di- and trialkoxyphenyl-α-mercaptoacrylic acids were prepared. Subjection of these compounds to mild ring-closure conditions (iodine in dioxane) provided, in most instances, the corresponding alkoxybenzothiophene-2-carboxylic acids.



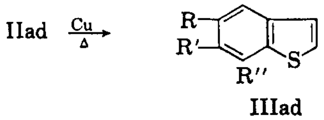
Iabcd IIabcd

a. R = $CH_3O$, R′ = H, R″ = H
b. R = H, R′ = $CH_3O$, R″ = H
c. R = $C_2H_5O$, R′ = $C_2H_5O$, R″ = H
d. R = $CH_3O$, R′ = $CH_3O$, R″ = $CH_3O$

The β-aryl-α-mercaptoacrylic acids (Ia–Id) were obtained by alkaline hydrolysis of the corresponding 5-(benzylidene)rhodanines.[3] Treatment of β - (3,4 - diethoxyphenyl)- and β - (3,4,5-trimethoxyphenyl)-α-mercaptoacrylic acids (Ic and Id) with an excess of iodine in dioxane at 70° for several hours afforded 5,6-diethoxybenzothiophene-2-carboxylic acid (IIc) and 5,6,7-trimethoxybenzothiophene-2-carboxylic acid (IId) in fair to moderate yields. Interestingly enough, when β-(4-ethoxyphenyl)-α-mercaptoacrylic acid was subjected to ring-closure conditions only tars were obtained. Similarly, β-(2,4-dimethoxyphenyl) - α - mercaptoacrylic acid gave resinous material. The 4-methoxy derivative (Ib) produced the desired 6-methoxybenzothiophene-2-carboxylic acid (IIb) in extremely poor yield, while the 3-methoxy analog (Ia) produced a moderate yield of 5-methoxybenzothiophene-2-carboxylic acid (IIa).

Thus, it appears that the ring closure is related to direction of orientation of the substituent rather than degree of activation of the aryl ring. Apparently, intermolecular condensation becomes predominant when orientation is to the 3- and 5-positions, particularly in the highly activated 2,4-dialkoxy derivative. On the other hand, ring closure is facilitated by electron-releasing groups in the 3-position, which can activate the point of ring closure (*para*) to electrophilic attack.

In two cases (IIa and IId) the decarboxylated derivatives (IIIa and IIId) were prepared in almost quantitative yields using copper in quinoline.



IIIad

## EXPERIMENTAL

*Preparation of the 5-(alkoxybenzylidene)rhodanine derivatives.* The procedure previously employed[3] was used to prepare the three new rhodanine derivatives described below.

*5-(3,4,5-Trimethoxybenzylidene)rhodanine* (IV). Twenty-five grams (0.128 mole) of 3,4,5-trimethoxybenzaldehyde (Aldrich) was refluxed for 30 min. with 17 g. of rhodanine in 150 ml. of glacial acetic acid using 40 g. of fused sodium acetate as catalyst. The hot mixture was poured into 1 l. of water and stirred. The precipitate was collected and dried in air to give 37 g. (93%) of material which was recrystallized from ethanol-dioxane as orange prisms melting at 202–203°.

*Anal.* Calcd. for $C_{13}H_{13}NO_4S_2$: S, 20.61. Found: S, 20.66.

*5-(4-Ethoxybenzylidene)rhodanine* (V). Five grams (0.033 mole) of *p*-ethoxybenzaldehyde was condensed with 5 g. of rhodanine in 40 ml. of glacial acetic acid using 10 g. of fused sodium acetate as described above. Isolating in the normal manner gave 8 g. (91%) of material which was recrystallized from ethanol as yellow needles melting at 225–226°.

*Anal.* Calcd. for $C_{12}H_{11}NO_2S_2$: S, 24.15. Found: S, 24.19.

*5-(2,4-Dimethoxybenzylidene)rhodanine* (VI). Twenty-five grams (0.156 mole) of 2,4-dimethoxybenzaldehyde (Eastman) and 20 g. of rhodanine were refluxed in 125 ml. of glacial acetic acid with 37 g. of fused sodium acetate as described above for the trimethoxy derivative. Isolating as before gave 40 g. (95%) of material melting at 269–270°. The analytical sample was recrystallized from ethanol-dioxane as yellow-orange needles melting at 271–272°.

*Anal.* Calcd. for $C_{12}H_{11}NO_3S_2$: S, 22.80. Found: S, 22.62.

*Preparation of the β-(alkoxyphenyl)-α-mercaptoacrylic acids. β-(3,4-Diethoxyphenyl)-α-mercaptoacrylic acid* (Ic). Thirty-five grams (0.113 mole) of 5-(3,4-diethoxybenzylidene)rhodanine[5] (m.p. 199°) was stirred into a solution of 25 g. of sodium hydroxide in 160 ml. of water. The mixture was stirred at 70° for 30 min., chilled, filtered (Norit) and acidified by pouring into excess cold 10% hydrochloric acid. The precipitated material was collected and air-dried to give 27 g. (72%) of product which was recrystallized from petroleum ether (b.p. 30–60°) as orange prisms melting at 128–130°.

*Anal.* Calcd. for $C_{13}H_{16}O_4S$: S, 11.95. Found: S, 11.88.

*β-(3,4,5-Trimethoxyphenyl)-α-mercaptoacrylic acid* (Id). Thirty-five grams (0.11 mole) of 5-(3,4,5-trimethoxybenzylidene)rhodanine (IV) was hydrolyzed with 25 g. of sodium hydroxide in 160 ml. of water on the steam bath for 0.5 hr. Isolation and recrystallization from benzene gave 25 g. (82%) of orange needles melting at 158–159°.

*Anal.* Calcd. for $C_{12}H_{14}O_5S$: S, 11.85. Found: 11.80.

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(1) Contribution No. 977 taken from a portion of a thesis submitted by W. E. K. in partial fulfillment of the requirements for the Ph.D. degree at Indiana University, June, 1960.

(2) Lubrizol Fellow, 1959–1960.

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(4) E. Campaigne and W. E. Kreighbaum, *J. Org. Chem.*, **26**, 359, 363 (1961).

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*2,2'-Dithiobis(3,4,5-trimethoxyphenyl)acrylic acid.* Id (2.7 g., 0.01 mole) was dissolved in 35 ml. of absolute ethanol and cooled to 0°. A stoichiometric amount of iodine (1.27 g., 0.005 mole) was added and the solution stirred at 0° for 2 hr. After dilution with 500 ml. of water, the precipitate was recrystallized from aqueous methanol and then from ethanol-benzene to give 2.5 g. (92%) of fine yellow leaflets melting at 186–187° dec.

*Anal.* Calcd. for $C_{24}H_{26}O_{10}S_2$: S, 11.86. Found: S, 11.88.

*β-(4-Ethoxyphenyl)-α-mercaptoacrylic acid.* Eight grams (0.019 mole) of 5-(4-ethoxybenzylidene)rhodanine (V) was hydrolyzed in 100 ml. of 10% sodium hydroxide on the steam bath for 0.5 hr. Isolation and recrystallization from acetone-ethanol gave 5 g. (62%) of orange prisms melting at 181–183° with gas evolution.

*Anal.* Calcd. for $C_{11}H_{12}O_3S$: S, 14.30. Found: S, 14.35.

*β-(2,4-Dimethoxyphenyl)-α-mercaptoacrylic acid.* Forty grams (0.144 mole) of 5-(2,4-dimethoxybenzylidene)rhodanine (VI), hydrolyzed with a warm solution of 40 g. of sodium hydroxide in 500 ml. of water gave 24 g. (65%) of material which melted at 221–222° dec. after one recrystallization from ethanol.

*Anal.* Calcd. for $C_{11}H_{12}O_4S$: S, 13.34. Found: S, 13.32.

*Preparation of the alkoxybenzothiophene-2-carboxylic acids. 5,6-Diethoxybenzothiophene-2-carboxylic acid* (IIc). Twenty-two grams (0.082 mole) of β-(3,4-diethoxyphenyl)-α-mercaptoacrylic acid (Ic) was dissolved in 750 ml. of dioxane and 30 g. (0.118 mole) of iodine was added. The solution was heated at 60–70° for 22 hr. and then poured into 6 l. of water, decolorized with saturated sodium bisulfite solution and stirred vigorously for a few minutes. The crude material was collected and dissolved in about 100 ml. of warm 10% sodium hydroxide solution. The strongly alkaline solution was treated with Norit and filtered to give a deep red solution (color due to impurities). Upon standing in the refrigerator overnight, 7 g. of pale pink crystals formed. The mother liquor was concentrated under an air stream and cooled to give an additional 2 g. of the sodium salt of 5,6-diethoxybenzothiophene-2-carboxylic acid. The salt was dissolved in 200 ml. of water and precipitated with dilute hydrochloric acid to give 7 g. (31%) of acid which was recrystallized from 95% ethanol as fine white needles melting at 245–246°.

*Anal.* Calcd. for $C_{13}H_{14}O_4S$: S, 12.04. Found: S, 11.89.

*5,6,7-Trimethoxybenzothiophene-2-carboxylic acid* (IId). A solution of 13.5 g. (0.05 mole) of β-(3,4,5-trimethoxyphenyl)-α-mercaptoacrylic acid (Id) and 20 g. (0.08 mole) of iodine in 400 ml. of dioxane was heated at 70° for 12 hr. with occasional swirling. The mixture was diluted with water to a volume of 2 l. and decolorized with 5% sodium bisulfite solution. After the mixture had been allowed to stand in the refrigerator for 4 days, the solid material was collected and recrystallized from dilute methanol to give 5 g. (37%) of flat rust-colored needles melting at 180–181°. Two additional recrystallizations from the same solvent failed to remove the color or change the melting point of the product.

*Anal.* Calcd. for $C_{12}H_{12}O_5S$: S, 11.87. Found: S, 11.75. Ultraviolet $\lambda_{max}$ $m\mu/\epsilon$: 235/20,400, 295/18,500.

*6-Methoxybenzothiophene-2-carboxylic acid* (IIb). Two grams (0.0095 mole) of β-(4-methoxyphenyl)-α-mercaptoacrylic acid (Ib)[6] was dissolved in 75 ml. of dioxane. Three grams (0.0118 mole) of iodine was added and the mixture was refluxed for 15 hr. By pouring the reaction mixture into 500 ml. of water containing 2 g. of sodium bisulfite and treating the resulting tars with acetone, a small amount of acid was isolated which was recrystallized once from ethanol to give 0.15 g. (7.5%) of silvery platelets which melted sharply at 251°. (Perold and van Lingen[7] reported a melting point of 248.5–249.0° for 6-methoxybenzothiophene-2-carboxylic acid.) Attempts to repeat this synthesis have failed completely, only tars being obtained.

*Anal.* Calcd. for $C_{10}H_8O_3S$: S, 15.40. Found: S, 15.40.

*5-Methoxybenzothiophene-2-carboxylic acid* (IIa). Twenty grams (0.095 mole) of β-(3-methoxyphenyl)-α-mercaptoacrylic acid (Ia)[8] and 30 g. (0.118 mole) of iodine were refluxed for 18 hr. in 500 ml. of dioxane. The solution was cooled to room temperature and poured into 3 l. of cold water containing 60 ml. of saturated sodium bisulfite solution. The mixture was stirred well and the tan precipitate was collected and recrystallized as the sodium salt from 30% sodium hydroxide solution. The salt was dissolved in water and acidified with 10% hydrochloric acid to give 8 g. (40%) of product melting at 215–216°. The analytical sample melted at the same temperature after one recrystallization from dilute acetic acid.

*Anal.* Calcd. for $C_{10}H_8O_3S$: S, 15.40. Found: S, 15.36.

*5,6,7-Trimethoxybenzothiophene* (IIId). Five grams (0.0186 mole) of 5,6,7-trimethoxybenzothiophene-2-carboxylic acid (IId) was heated with 1.0 g. of copper powder in 25 ml. of quinoline until the temperature rose to 180–195°. The mixture was cooled to room temperature and stirred well with 100 ml. of isopropyl ether. The solution was filtered to remove the solid material and stirred vigorously with dilute hydrochloric acid until acid to Congo red. The ether layer was separated, concentrated on the steam bath and distilled under vacuum to give 4.5 g. (99%) of a colorless oil boiling at 147–150° (1.5 mm.).

*Anal.* Calcd. for $C_{11}H_{12}O_3S$: S, 14.30. Found: S, 14.23. Ultraviolet $\lambda_{max}$ $m\mu/\epsilon$: 233/27,000; 262,269/8,750; 297,308/2,500.

Compound IIId forms a picrate, recrystallized from 95% ethanol as blood red needles, melting at 72.5°.

*Anal.* Calcd. for $C_{17}H_{15}N_3O_{10}S$: N, 9.26. Found: N, 9.38.

*5-Methoxybenzothiophene* (IIIa). Seven grams (0.084 mole) of the acid (IIa) was decarboxylated by heating with 0 5 g. of copper powder in 55 ml. of quinoline as described above. The crude material was isolated as before and steam-distilled to give 5.5 g. (99%) of beautiful white flakes melting at 43–44°.[9]

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## The Preparation of Some Derivatives of 5,6-Dimethoxy- and 5,6-Methylenedioxybenzothiophene[1]

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*Received August 11, 1960*

In connection with another problem,[3] several derivatives of 5,6-dimethoxy- and 5,6-methylene-

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(1) Contribution No. 976, taken from a portion of a thesis submitted by W. E. K. in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Indiana University, June, 1960.

(2) Schering Research Fellow, 1958–1959. Lubrizol Fellow, 1959–1960.

(3) E. Campaigne and W. E. Kreighbaum, *J. Org. Chem.*, 26, 359 (1961).