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 λ_{max} mμ/ε: 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 λ_{max} mμ/ε: 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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INDIANA UNIVERSITY
BLOOMINGTON, IND.

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

E. CAMPAIGNE AND W. E. KREIGHBAUM[2]

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

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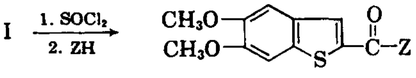
(1) Contribution No. 976, taken from a portion of a thesis submitted by W. E. K. in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Indiana University, June, 1960.

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

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

dioxybenzothiophene-2-carboxylic acids (I and II) were prepared. Three ester and amide derivatives of I (IIIabc) were submitted for pharmacological testing.[4] Although the anticipated antiserotonin activity of these substances was slight or nil in all three cases,

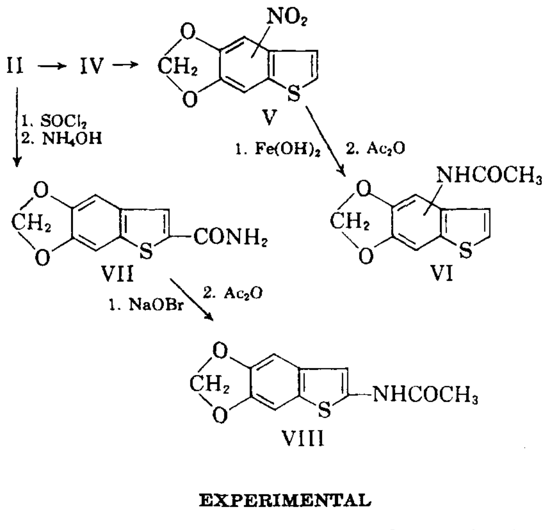


IIIabc

a. Z = N—(CH$_2$)$_4$—CH$_2$
b. Z = NHCH$_2$CH$_2$—N(C$_2$H$_5$)$_2$.HCl
c. Z = OCH$_2$CH$_2$—N(C$_2$H$_5$)$_2$.HCl

IIIa and IIIb were found to exhibit analgetic activity greater than that of aspirin, while IIIb but not IIIa showed diuretic activity in dogs. None of the compounds tested showed activity in bacteriological or antiviral screening.

Nitration of 5,6-methylenedioxybenzothiophene (IV),[3] the decarboxylated derivative of II, with nitric acid in acetic acid-acetic anhydride mixture gave a crystalline mononitro derivative (V) in nearly quantitative yield. Substitution did not occur at the expected 2-position (*cf.* Ref. 3). This was shown by conversion of V to the corresponding acetamide derivative (VI) and mixed melting point comparison of VI with an authentic sample of 2-acetamido-5,6-methylenedioxybenzothiophene (VIII) which was prepared unequivocally by the Hofmann rearrangement of II (VII).



EXPERIMENTAL

5,6-Dimethoxybenzothiophene-2-carbonyl chloride. A mixture of 16.5 g. (0.069 mole) of the acid (I),[3] 35 ml. of purified thionyl chloride and 375 ml. of dry benzene was refluxed for 3 hr. The acid dissolved slowly to form a clear amber solution which was then filtered through a Norit pad to remove traces of insoluble material. The benzene solution was chilled and the yellow crystals of the acid chloride were collected and dried in air. Concentration of the filtrate gave additional material. The total yield was 14 g. (79%) of odorless yellow needles melting at 171–172°.

Anal. Calcd. for $C_{11}H_9O_3SCl$: Cl, 13.81. Found: Cl, 13.89.

Preparation of the amides and ester of I. The acid chloride of I repeatedly demonstrated rather sluggish reactivity. This was first exemplified by the relatively high melting point of the odorless product, and later by the uncommonly vigorous conditions necessary to obtain some of the derivatives.

1-(5,6-Dimethoxy-2-benzothenoyl)piperidine (IIIa). A mixture of 2.4 g. (0.010 mole) of the acid (I) and 5 g. of purified thionyl chloride was suspended in 200 ml. of anhydrous ether. The mixture was allowed to stand for 2 days in a 250-ml. round bottomed flask fitted with a drying tube. The acid eventually dissolved to form a clear amber solution of the acid chloride. The ether was removed under vacuum; 50 ml. of benzene was added and removed in the same fashion until the odor of thionyl chloride had disappeared. The crude material thus obtained was treated with 2 g. (0.023 mole) of piperidine in 150 ml. of water containing 10 ml. of 10% sodium hydroxide solution. After the mixture had been shaken vigorously for 2 min., the precipitate was collected and recrystallized twice from aqueous ethanol to give 2.0 g. (65%) of transparent flakes which melted at 163–164°.

Anal. Calcd. for $C_{16}H_{19}NO_3S$: S, 10.50. Found: S, 10.45.

β-Diethylaminoethyl 5,6-dimethoxybenzothiophene-2-carboxamide hydrochloride (IIIb). Seven grams (0.027 mole) of the acid chloride of I and 3.2 g. (0.027 mole) of β-diethylaminoethylamine were refluxed overnight with 250 ml. of benzene. The cooled reaction mixture afforded a white precipitate which was collected and recrystallized from isopropanol to give 5 g. (47%) of light tan flakes melting at 185–186°.

Anal. Calcd. for $C_{17}H_{26}O_3N_2SCl$: Cl, 9.54. Found: Cl, 9.69.

β-Diethylaminoethyl 5,6-dimethoxybenzothiophene-2-carboxylate hydrochloride (IIIc). This compound was prepared from 7 g. (0.027 mole) of the acid chloride of I and 3.2 g. (0.027 mole) of β-diethylaminoethanol according to the procedure described in the preceeding experiment. Recrystallization from isopropyl alcohol gave 5 g. (49%) of colorless needles melting at 198–199°.

Anal. Calcd. for $C_{17}H_{24}O_4NSCl$: Cl, 9.48. Found: Cl, 9.42.

Nitration of 5,6-methylenedioxybenzothiophene. A solution of 3 g. (0.017 mole) of the benzothiophene (IV)[3] in 30 ml. of glacial acetic acid was added dropwise with stirring to a mixture of 50 ml. of acetic anhydride, 20 ml. of glacial acetic acid and 1.6 g. (0.018 mole) of 70% nitric acid maintained at 0–3°. The mixture was allowed to come to room temperature, whereupon 500 ml. of water was added with vigorous stirring. The yellow precipitate was collected, washed with ethanol and dried to give 3.7 g. (98%) of material melting at 234–235° (compound V). The analytical sample (golden-yellow threadlike needles from acetone) melted at 235–236°.

Anal. Calcd. for $C_9H_5O_4NS$: N, 6.27. Found: N, 6.38.

Reduction and acetylation of the mononitro-5,6-methylenedioxybenzothiophene (V). One gram (0.009 mole) of the finely divided nitro derivative was stirred into a suspension of ferrous hydroxide made by adding 30 ml. of concentrated ammonia to 20 g. of ferrous sulfate heptahydrate in a solution of 30 ml. of dioxane and 80 ml. of water. The mixture was stirred at 90–95° for 20 min. The resulting paste was filtered hot and the filtrate was treated with 20 ml. of acetic anhydride with vigorous stirring. The clear solution was chilled overnight to give a dark precipitate which was collected and recrystallized several times from dilute ethanol to give 0.3 g. (27%) of amber needles melting at 227–228° (compound VI).

Anal. Calcd. for $C_{11}H_9NO_3S$: N, 5.95; S, 13.62. Found: N, 6.16; S, 13.42.

5,6-Methylenedioxybenzothiophene-2-carboxamide (VII). Nine grams (0.04 mole) of I was converted to the acid chloride by refluxing 3 hr. with an excess (18 ml.) of thionyl chloride and 0.25 ml. of pyridine in 50 ml. of benzene. The benzene was removed under vacuum at room temperature; the crude acid chloride was dissolved in a small amount of

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[4] Testing was performed in the laboratories of the Schering Corp., Bloomfield, N. J.

dioxane and poured into excess concentrated ammonia. After the mixture had been allowed to stand overnight, the tan precipitate was collected and dried to give 8.5 g. (94%) of (VII) which melted at 240–241° after one recrystallization from absolute ethanol.

Anal. Calcd. for $C_{10}H_7NO_3S$: S, 14.50. Found: S, 14.23.

2-Acetamido-5,6-methylenedioxybenzothiophene (VIII). The amide prepared in the preceding experiment was subjected to the Hofmann hypobromite reaction according to the procedure of Vogel.[5] Eight grams (0.036 mole) of VII was treated with 30 ml. of a solution made by dissolving 8.4 ml. of bromine in 120 ml. of water containing 30 g. of sodium hydroxide. The mixture was warmed slightly until the reaction started and was then held at 80–90° for 45 min. The resulting suspension was diluted with 25 ml. of water and cooled to room temperature. Twenty milliliters (0.21 mole) of acetic anhydride was added with rapid stirring over a period of 20 min. and then the mixture was warmed at 60° for 0.5 hr. After the solution had been allowed to cool in the refrigerator overnight, the brown precipitate was collected and recrystallized from ethanol. The yield was 6 g. (70%) of red warty aggregates which melted at 241°. A mixed melting point with compound VI was depressed to 208–215°, and one with compound VII was depressed to 223–240°.

Anal. Calcd. for $C_{11}H_9NO_3S$: N, 5.95; S, 13.62. Found: N, 5.83; S, 13.98.

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BLOOMINGTON, IND.

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1-Thiadibenzo[*a,c*][3,6]cyclooctadiene and Other Cyclic *o,o′*-Bridged Diphenylmethanes[1]

DONALD D. EMRICK[2] AND WILLIAM E. TRUCE

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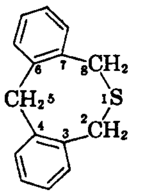
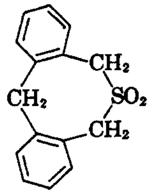
Regarding our studies on the preparation and geometry of various *o,o′*-bridged biphenyls and diphenylmethanes, it appears unlikely that further experimental work along these lines will be undertaken in the near future at this laboratory. Hence, the present data are being published in the hope that they may be of use to other workers, particularly since the stereochemistry of *o,o′*-bridged diphenylmethanes has yet to be demonstrated.

2,2′-Bis(bromomethyl)diphenylmethane, prepared from phthalic anhydride by the complex route of Bergmann and Pelchowicz,[3] was cyclized with methanolic sodium sulfide to the eight-membered ring 1-thiadibenzo[*a,c*][3,6]cyclooctadiene (I) approximately as readily as similar cyclization to the corresponding seven-membered sulfide in the biphenyl series occurred.[4] It was not necessary to use high dilution techniques in order to obtain good yields of the cyclic sulfide.



I



II

Oxidation of the sulfide (I) to the corresponding sulfone (II, 1-thiadibenzo[*a,c*][3,6]cyclooctadiene-1-dioxide) was readily accomplished with hydrogen peroxide in acetic acid. Alkylation of I with excess methyl iodide in ethanol produced a sublimable and water-insoluble coordination complex with an analysis corresponding to two g.-atoms of iodine per mole; the literature has described methyl iodide, haloform, and metal halide coordination complexes of sulfonium salts.[5]

Reduction of 2′-aminobenzophenone-2-carboxylic acid[6] to 2′-aminodiphenylmethane-2-carboxylic acid was accomplished *via* reduction by means of zinc dust (activated by copper) in ammonia.[7] Although stable indefinitely as carboxylate salts, the free 2′-aminodiphenylmethane-2-carboxylic acid cyclized slowly at room temperature (rapidly at 100°) to form the seven-membered ring cyclic lactam, indicating that this amino acid is more stable than 2′-aminobiphenyl-2-carboxylic acid and 2′-aminobiphenyl-2-acetic acid which have never been isolated, both cyclizing spontaneously to their six- and seven-membered cyclic lactams, respectively.[8]

EXPERIMENTAL[9]

1-Thiadibenzo[*a,c*][*3,6*]*cyclooctadiene* (I). A mixture of 10 g. (0.028 mole) of 2,2′-bis(bromomethyl)diphenylmethane,[3] 30 g. of sodium sulfide nonahydrate (0.125 mole), 80 ml. of water, and 1600 ml. of methanol were gently refluxed with stirring for 36 hr. The methanol was distilled and the residue was taken up in 500 ml. of cold water. The water-insoluble product was filtered off and recrystallized from a mixture of alcohol and benzene. The yield was 4.6 g. (72%), m.p. 194–195°.

Anal. Calcd. for $C_{14}H_{14}S$: C, 79.64; H, 6.19; mol. wt. 226. Found: C, 79.39; H, 6.14; mol. wt. 226.

A mercuric chloride coordination complex of the above sulfide was prepared by dissolving 1.00 g. of mercuric chloride in 10 ml. of hot absolute ethanol and adding quickly, with rapid stirring, a solution of 0.86 g. of the sulfide dis-

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(1) Abstracted from the doctoral thesis submitted to Purdue University in 1956 by Donald D. Emrick.

(2) Present address: Research Department, The Standard Oil Company (Ohio), Cleveland 28, Ohio.

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(9) Boiling and melting points reported are uncorrected.