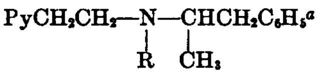
TABLE I



$$PyCH_2CH_2\text{—}\underset{R}{\underset{|}{N}}\text{—}\underset{CH_3}{\underset{|}{C}}HCH_2C_6H_5{}^{a}$$

No.	R	M.P.[b,c] or B.P., (Mm.)	Yield,[d] %	Formula	Carbon,[e] % Calcd.	Carbon,[e] % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	H	120 (0.05)	66^{g}	$C_{16}H_{20}N_2$	80.0	80.1	8.4	8.2	11.7	12.0
2	CH_3CO—	170–179 (0.16)	87	$C_{18}H_{22}N_2O$					9.9	10.1
3	[f]	$151\text{–}152^{c_1}$	85	$C_{19}H_{25}IN_2O$	53.8	54.0	5.9	6.0	6.6	6.8
4	p-$CH_3OC_6H_4CO$—	238–242 (0.03)	39	$C_{24}H_{26}N_2O_2$	77.0	77.0	7.0	6.7	7.5	7.0
5	o-$C_2H_5OC_6H_4CO$—	226–229 (0.03)	47	$C_{25}H_{28}N_2O_2$					7.2	6.8
6	TMB[h]	$117\text{–}118^{c_2}$	58	$C_{26}H_{30}N_2O_4$	71.9	71.7	7.0	7.2	6.5	6.0
7^{a_1}	H	128–134 (0.08)	53^{g}	$C_{16}H_{20}N_2$	80.0	79.5	8.4	8.4	11.7	11.7
8^{a_1}	o-$C_2H_5OC_6H_4CO$—	$103\text{–}106^{c_2}$	57	$C_{25}H_{28}N_2O_2$	77.3	77.4	7.3	7.1	7.2	6.9
9^{a_2}	H	148–150 (0.4)	46^{g}	$C_{18}H_{24}N_2$	80.6	80.7	9.0	9.1	10.4	9.8

[a] Py = 2-pyridyl unless otherwise indicated; [a1] Py = 4-pyridyl; [a2] Py = 5-ethyl-2-pyridyl. [b] Melting points are not corrected and were established on a Fisher-Johns melting point block. [c] Recrystallizing solvent; [c1] ethyl acetate; [c2] hexane-benzene. [d] Yields are expressed as recrystallized or distilled product. [e] Analyses are by Weiler and Strauss, Oxford, England. [f] Compound is methiodide of compound 2. [g] $[\alpha]_D^{20}$ in methanol: compound 1, +21.40; compound 7, +24.30; compound 9, +22.30. [h] TMB = 3,4,5-trimethoxybenzoyl.

(41.5 g.) was obtained, b.p. 148–150° (0.4 mm). The fore-run, upon trituration with hexane, gave 2.4 g. (4.1%), m.p. 126–127°, not depressing the melting point of authentic *d*-α-methylphenethylacetamide.[16]

Compounds 1 and 7 were similarly prepared.

Acetamide of compound 1 (Compound 2). A mixture of 9.6 g. (0.04 mole) of compound 1 and 10 ml. of acetic anhydride was heated under reflux for 1 hr. When cool, after addition of 100 ml. of water, and treatment with base, the formed oil was extracted with 100 ml. of benzene and the product was obtained by distillation, 9.77 g. (87%), b.p. 170–179° (0.16 mm.).

A solution of 2.8 g. (0.01 mole) of this compound in 25 ml. of acetonitrile and 2 ml. of methyl iodide was refluxed for 2 hr., and upon cooling, yielded 3.6 g. (85%) of the methiodide (compound 3). Attempted hydrogenation[17] with rhodium on carbon afforded only unconverted reactant.

3,4,5-Trimethoxybenzamide of compound 1 (Compound 6). A solution of 9.6 g. (0.04 mole) of compound 1 in 35 ml. of benzene was added dropwise under stirring over 1 hr. to a solution of 4.6 g. (0.02 mole) of 3,4,5-trimethoxybenzoyl chloride in 65 ml. of benzene while maintaining the temperature at 25–30°. When addition was complete, the reaction mixture was heated under reflux for 1 hr. and then stored at 20° for 24 hr. After extraction with dilute hydrochloric acid, and treatment with base, 8.6 g. (98%) of product was separated and recrystallized.

Acknowledgment. The authors wish to thank Dr. G. Ungar and his staff for the pharmacological results herein reported.

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(16) Ref. (1) reports m.p. 123–125°.

(17) S. L. Shapiro, K. Weinberg, T. Bazga, and L. Freedman, *J. Am. Chem. Soc.*, 81, 5146 (1959).

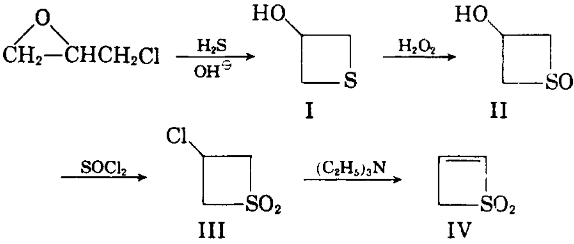
Thiete Sulfone[1]

DONALD C. DITTMER AND MARCIA E. CHRISTY

Received August 17, 1960

The synthesis and properties of five- and six-membered cyclic unsaturated sulfones have been described[2,3] but the four-membered cyclic unsaturated sulfones have been unreported.

The most simple four-membered cyclic unsaturated sulfone, thiete sulfone (thiete 1,1-dioxide), has been prepared according to the following reaction sequence:



Starting material, 3-thiethanol, (I),[4] was obtained by the addition of epichlorohydrin to a barium hydroxide solution saturated with hydrogen sulfide.[5] Oxidation of I in glacial acetic acid at room temperature gave the sulfone II in 56% yield. If the oxidation is carried out at 90–100°, the product is dimethyl sulfone which also is obtained by oxidation of I with potassium permanganate in acetone at 0°. The dimethyl sulfone probably arises from methylsulfonylacetic acid which is known to decarboxylate readily.[6]

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(1) Presented at the 137th Meeting, American Chemical Society, Cleveland, Ohio, April, 1960.

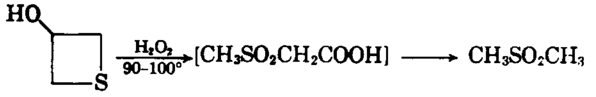
(2) For a brief review see A. Schöberl and A. Wagner, *Methoden der Organischen Chemie*, Vol. IX, Schwefel-, Selen-, Tellur-Verbindungen, E. Müller, ed., Georg Thieme, Stuttgart, 4th Ed., 1955, p. 236.

(3) L. Bateman and R. W. Glazebrook, *J. Chem. Soc.*, 2834 (1958); R. C. Krug, G. R. Tichelaar, and F. E. Didot, *J. Org. Chem.*, 23, 212 (1958); R. C. Krug and T. Yen, *J. Org. Chem.*, 21, 1441 (1956); E. A. Fehnel and P. A. Lackey, *J. Am. Chem. Soc.*, 73, 2473 (1951); R. F. Naylor, *J. Chem. Soc.*, 2749 (1949).

(4) B. Sjöberg, *Svensk. Kem. Tid.*, 50, 250 (1938).

(5) Modification of the method of B. Sjöberg, *Ber.*, 75, 13 (1941).

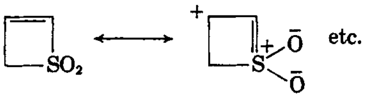
(6) E. Baumann and G. Walter, *Ber.*, 26, 1131 (1893).



Conversion of II to III proceeded in good yield with thionyl chloride in 2,4,6-collidine. Yields were considerably lower in pyridine, presumably because of a greater amount of dehydrohalogenation by the stronger base. The chlorosulfone, III, is readily dehydrohalogenated by triethylamine at room temperature to yield the unsaturated sulfone, IV.

The structure of IV was confirmed by hydrogenation to the known thietane sulfone. Its NMR spectrum is in agreement with the structure.

It may be noted that the signal for the *beta* olefinic proton is at lower field than the *alpha* olefinic proton which suggests less electron density at the β- than the α-carbon. This may be a result of delocalization of the electrons in the system of the double bond and the sulfone group.



The infrared spectrum shows a C—H stretching frequency at 3165 cm.$^{-1}$ and a C=C stretching frequency at 1543 cm.$^{-1}$

Further work on the reactivity of IV is in progress.

EXPERIMENTAL[7]

3-Thietanol (I). A modified procedure of Sjöberg was used.[5] A mixture of 315 g. (1 mole) of barium hydroxide octahydrate and 1.8 l. of water was stirred and saturated with hydrogen sulfide at room temperature. The mixture was cooled in ice with continuous stirring and passage of hydrogen sulfide, and 92.53 g. (1 mole) of epichlorohydrin was added dropwise over 2 hr. After another hour at 50–55°, carbon dioxide was introduced until the precipitation of barium carbonate was complete. The precipitate was collected and washed with water. The combined filtrates and washings from four 1-mole runs were concentrated *in vacuo* on the steam-bath until oil began to separate. The oil was taken up in ether, and after drying and removal of the solvent, it was fractionated *in vacuo*. The 3-thietanol (142 g.; 39%), was collected at 51–52°/0.9 mm., $d_{25°}$ 1.2129, $n_D^{25°}$ 1.5408 (lit.[4] b.p. 57°/1.3 mm., $d_{20°}$ 1.2130, $n_D^{20°}$ 1.5433). A sample from a comparable preparation, b.p. 61–62°/2 mm., $n_D^{20°}$ 1.5476, gave the following analysis:

Anal. Calcd. for C_3H_6OS: C, 39.97; H, 6.71; S, 35.57. Found: C, 39.69; H, 6.73; S, 35.44.

The *3,5-dinitrobenzoate* melted at 112–113° after repeated crystallizations from 95% ethanol.

Anal. Calcd. for $C_{10}H_8O_6N_2S$: C, 42.25; H, 2.84; N, 9.86. Found: C, 41.99; H, 2.86; N, 9.72.

Treatment with excess methyl iodide in benzene in the cold gave *dimethyl 2-hydroxy-3-iodopropylsulfonium iodide* which melted at 110–110.5° after repeated crystallizations from absolute ethanol.

Anal. Calcd. for $C_5H_{12}OI_2S$: C, 16.05; H, 3.23; I, 67.86. Found: 16.28; H, 3.26; I, 67.88.

3-Thietanol 1,1-dioxide (II). To a stirred and ice cold solution of 22.5 g. (0.25 mole) of 3-thietanol in 75 ml. of glacial acetic acid, hydrogen peroxide, 58 g. (0.51 mole) of 30%, was added rapidly dropwise. After another 15 min. in the cold and 1 hr. at room temperature, the reaction was quenched with 450 ml. of water and the solution evaporated to dryness on the steam-bath. The residual oily, colorless solid afforded 17.3 g. (56.5%) of colorless needles, m.p. 99.5–102°, after two crystallizations from ethyl acetate. An analytical sample melted at 101–102°.

Anal. Calcd. for $C_3H_6O_3S$: C, 29.50; H, 4.96; S, 26.25. Found: C, 29.61; H, 4.71; S, 26.33.

The *3,5-dinitrobenzoate* melted at 197–198° after two crystallizations from 95% ethanol.

Anal. Calcd. for $C_{10}H_8O_8N_2S$. C, 37.98; H, 2.55; N, 8.86. Found: C, 38.08; H, 2.59; N, 8.82.

The *p-toluenesulfonate* was obtained as colorless prisms, m.p. 129–131°, from ethyl acetate.

Anal. Calcd. for $C_{10}H_{12}O_5S_2$: C, 43.46; H, 4.38; S, 22.90. Found: C, 43.55; H, 4.49; S, 23.25.

When the exothermic reaction with hydrogen peroxide was allowed to proceed without cooling and the solution then heated on the steam-bath for 3 hr., a 12% yield of *dimethyl sulfone* was isolated. The product was identical in melting point, 110.5–111.5°, (lit.[6] m.p. 109°), mixed melting point, 110–111°, and infrared spectrum with an authentic sample prepared by hydrogen-peroxide oxidation of dimethyl sulfide.

Oxidation with potassium permanganate in cold aqueous acetone resulted in a 2% yield of dimethyl sulfone.

3-Chlorothietane 1,1-dioxide (III). Thionyl chloride, 35.7 g. (0.3 mole), was added dropwise to a stirred suspension of 18.3 g. (0.15 mole) of II in 18.15 g. (0.15 mole) of dry *s*-collidine, the temperature being maintained at 25–30°. Stirring was discontinued after one-half of the reagent had been added when the mixture set to a solid mass. Most of the solid dissolved, when, after 45 min. at room temperature, the mixture was heated on the steam-bath for 30 min. The warm solution was poured onto ice and the solid product was collected, washed with cold water, and crystallized from water with decolorization with Norite; yield, 18.1 g. (86%) of large, colorless, prismatic needles, m.p. 136.5–137.5°.

Anal. Calcd. for $C_3H_5O_2ClS$: C, 25.63; H, 3.59; Cl, 25.22; S, 22.81. Found: C, 25.56; H, 3.96; Cl, 25.25; S, 23.51.

When the reaction was conducted under the same conditions using pyridine as the base, the yield of 3-chlorothietane 1,1-dioxide was 60%.

Thiete 1,1-dioxide (IV). A solution of 10.0 g. (0.071 mole) of III in 350 ml. of dry benzene at 40° was treated with 50 ml. of triethylamine. Triethylamine hydrochloride started to precipitate almost immediately and after 3 hr. at room temperature and overnight at 5°, the precipitate was collected and washed with benzene. Evaporation of the filtrate gave a very oily solid which was crystallized from ether containing a few milliliters of ethanol to obtain 6.0 g. (81%) of large, colorless needles, m.p. 48–50°. An analytical sample melted at 52–54°.

Anal. Calcd. for $C_3H_4O_2S$: C, 34.60; H, 3.87; S, 30.79. Found: C, 34.93; H, 4.07; S, 30.77.

Hydrogenation of IV in chloroform at 25 p.s.i. of hydrogen in the presence of 5% palladium on charcoal afforded *trimethylene sulfone*. The product was identical in melting point, 74–75° [lit.[8] m.p. 75°], mixed melting point, 74–76°, and infrared spectrum with an authentic sample prepared by hydrogen-peroxide oxidation of trimethylene sulfide.

The NMR spectrum of IV at 60 Mc. with tetramethylsilane as a standard shows a set of signals at 274 c.p.s. for the methylene (CH_2) protons which show about 2 cycle spin coupling to the adjacent olefinic proton and a little less than 1 cycle spin coupling to the other olefinic proton. The olefinic protons are at 408 (α) and 434 (β) c.p.s. and show a similar spin coupling to the protons of the methylene

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[7] All melting points are uncorrected. Microanalyses by Galbraith Laboratories, Knoxville, Tenn.

[8] E. Grishkevich-Trokhimovskii, *J. Russ. Phys. Chem. Soc.*, 48, 880 (1916); *Chem. Zentr.*, 1923 III, 773.

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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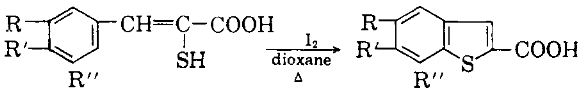
Received August 11, 1960

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.



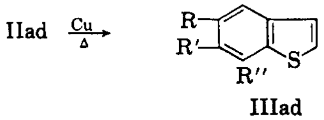
Iabcd IIabcd

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.

[3] E. Campaigne and R. E. Cline, *J. Org. Chem.*, **21**, 32, 39 (1956).

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

[5] F. C. Brown, C. K. Bradsher, S. M. Bond, and M. Potter, *J. Am. Chem. Soc.*, **73**, 2357 (1951).