Anal. Calcd. for $C_{12}H_{15}N_3O_2$: C, 62.32; H, 5.67; N, 18.17. Found: C, 62.00; H, 5.64; N, 18.25.

1,3-Dimethyl-6,7-diphenyl-7H-2,4(1H,3H)pyrrolo[2,3-*d*]pyrimidinedione (6).—An intimate mixture of 2.3 g. (0.01 mole) of 1,3-dimethyl-6-anilinouracil and 3.1 g. (0.011 mole) of phenacylpyridinium bromide was heated in an oil bath at 215°, under a strong stream of nitrogen, for 3 hr. The resultant brown glass was dissolved by boiling with *ca.* 15 ml. of ethanol. After overnight refrigeration, filtration gave 0.5 g. (15%) of a cream-colored solid, m.p. 219–221°. Recrystallization from ethanol yielded white needles, m.p. 223–224°.

Anal. Calcd. for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.82; H, 5.36; N, 12.71.

1,3-Dimethyl-5-nitro-6-(*p*-methoxy)styryluracil (7a).—A mixture of 4.0 g. (0.02 mole) of 1,3,6-trimethyl-5-nitrouracil, 2.8 g. (*ca.* 0.02 mole) of anisaldehyde, 2 ml. of piperidine, and 90 ml. of ethanol was heated to reflux with magnetic stirring. Solution occurred shortly after the reflux temperature was reached. After 1.5 hr. a yellow solid began to separate, and after 20 hr. of heating the suspension was filtered hot to give a canary yellow solid, m.p. 186–187°. Concentration of the filtrate to a small volume yielded a yellow solid which was washed thoroughly with boiling ethanol. The combined yield was 5.2 g. (82%). Recrystallization from 1-butanol gave yellow needles, m.p. 186–187°.

Anal. Calcd. for $C_{15}H_{15}N_3O_5$: C, 56.78; H, 4.77; N, 13.24. Found: C, 56.72; H, 4.59; N, 13.20.

1,3-Dimethyl-5-nitro-6-(*p*-dimethylamino)styryluracil (7b).—A suspension of 2.0 g. (0.01 mole) of 1,3,6-trimethyl-5-nitrouracil, 1.5 g. (0.01 mole) of *p*-dimethylaminobenzaldehyde, 1 ml. of piperidine, and 45 ml. of ethanol was heated, with stirring, to reflux. The resulting deep red solution was heated under reflux for 20 hr. and then filtered hot to give 2.5 g. of orange-red crystals, m.p. 205–207° dec. Concentration of the filtrate to a small volume gave a red solid which after recrystallization from ethanol–benzene yielded 0.3 g. of additional product; total yield 2.8 g. (85%). Recrystallization from aqueous dimethylformamide gave bright red plates, m.p. 207–208° dec.

Anal. Calcd. for $C_{16}H_{18}N_4O_4$: C, 58.17; H, 5.49; N, 16.96. Found: C, 58.42; H, 5.71; N, 16.80.

1,3-Dimethyl-6-(*p*-dimethylaminophenyl)-5H-2,4(1H,3H)pyrrolo[3,2-*d*]pyrimidinedione (8b).—A mixture of 1.65 g. (0.005 mole) of 1,3-dimethyl-5-nitro-6-(*p*-dimethylamino)styryluracil and 5 ml. (large excess) of freshly distilled triethylphosphite was refluxed under nitrogen for 5.5 hr. After standing overnight at room temperature, the mixture was filtered to give an amber-colored solid, m.p. >300°. Distillation of the filtrate under reduced pressure (*ca.* 0.1 mm.) gave a red sticky mass which when triturated with ethanol yielded a few milligrams of additional product. Recrystallization of the combined solids from dimethylformamide followed by vacuum sublimation at 240–250° (0.05 mm.) gave 0.9 g. (60%) of pale yellow solid, m.p. 310–318° dec., ν_{max}^{Nujol} 3225 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78. Found: C, 64.33; H, 5.99; N, 18.79.

1,3-Dimethyl-6-(*p*-methoxyphenyl)-5H-2,4(1H,3H)pyrrolo-[3,2-*d*]pyrimidinedione (8a). Method A.—A mixture of 1.4 g. (0.0044 mole) of 1,3-dimethyl-5-nitro-6-(*p*-methoxy)styryluracil and 4 ml. of triethylphosphite was refluxed for 7 hr. under nitrogen. After standing overnight at room temperature, the mixture was filtered and the solid was washed with ether. Distillation of the filtrate gave a red viscous oil which when treated with ethanol gave a few additional milligrams. Recrystallization of the combined solids from aqueous dimethylformamide followed by vacuum sublimation at 250° (0.05 mm.) gave 0.5 g. (40%) of white crystals, m.p. 304–306° dec., ν_{max}^{Nujol} 3200 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.03; H, 4.84; N, 14.74.

Method B.—A solution of 0.2 g. of 1,3-dimethyl-5-nitro-6-(*p*-methoxy)styryluracil in 30 ml. of warm triethylphosphite in a quartz tube was degassed by bubbling in nitrogen for a few minutes, and the tube was stoppered and irradiated for 114 hr. at 3500 Å. in a Rayonet photochemical chamber. During this time a very small amount of solid separated. Filtration and washing with ether gave a few milligrams of a yellow solid, m.p. 300° dec., which was shown to be identical with the product obtained by method A above by a comparison of infrared spectra and by a mixture melting point determination.

Organic Disulfides and Related Substances. XIII. Oxidation of Some Aryl Disulfides[1a-c]

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A conversion of aliphatic disulfides to aliphatic thiolsulfonates (RSO_2SR) has been developed by Douglass and Farah which affords an elegant and valuable synthesis of aliphatic thiolsulfonates.[2] The procedure involves chlorinolysis in the presence of acetic acid and then treatment with water. The sequence of events is shown by these equations.[2]

$$RSSR + CH_3CO_2H + 2Cl_2 \longrightarrow \underbrace{RSOCl + RSCl + CH_3COCl} + HCl$$

$$\downarrow 2H_2O$$

$$RSO_2SR + CH_3CO_2H + 3HCl$$

To some extent, we extended this method earlier to the aromatic series, obtaining good results with *p*-tolyl,[3] *m*-carboxyphenyl, and *o*-carboxyphenyl disulfide (and its ester).[1c] Further assessment of steric and electronic factors which might affect results with aryl disulfides remained of interest, however. The present paper reports extension of the Douglass–Farah method to phenyl, *p*-chlorophenyl, and *p*-nitrophenyl disulfide. The total picture now makes it evident that the method provides a rather general and quite useful synthesis of aromatic thiolsulfonates, as well as of aliphatic ones. For preparation of symmetrical aryl arenethiolsulfonates, we consider the Douglass–Farah procedure to be much the method of choice.

Table I summarizes the results. It shows that pure products were obtained in high yields with or without use of solvent, that a thiol can be used (since it is easily

TABLE I

OXIDATION TO THIOLSULFONATES USING CHLORINE

Reactant	Reactant, moles	Chlorine, moles	Solvent (ml.)	Yield, %[a]	M.p., °C. Product[a]	M.p., °C. Lit.
$(C_6H_5S)_2$	0.45	0.90[b]	None	84	42–44	45–46[c]
$(p\text{-}CH_3C_6H_4S)_2$	0.32	0.64[b]	None	89	74–76	78.5–79.5[c]
$p\text{-}ClC_6H_4SH$	0.30	0.45[d]	CH_2Cl_2 (35)	84	134–136	137–138[e]
$(p\text{-}NO_2C_6H_4S)_2$	0.05	0.12[b,f]	CH_2Cl_2 (20)	75	180–182	180–180.5[e]

[a] After recrystallization from methanol. Crude yields were nearly quantitative. [b] $(RS)_2 + 2Cl_2(+ CH_3CO_2H) + 2H_2O \rightarrow RSO_2SR (+ CH_3CO_2H) + 4HCl$. [c] L. Field, *J. Am. Chem. Soc.*, **74**, 394 (1952). [d] $2RSH + 3Cl_2 (+ CH_3CO_2H) + 2H_2O \rightarrow RSO_2SR (+ CH_3CO_2H) + 6HCl$. [e] G. Bulmer and F. G. Mann, *J. Chem. Soc.*, 680 (1945). [f] This amount of chlorine was necessary to convert the suspension to a solution ($RSSR \rightarrow 2RSCl$).

(1) (a) Reported in part at the Southeastern Regional Meeting of the American Chemical Society, Gatlinburg, Tenn., Nov. 1–3, 1962. This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contract No. DA-49-193-MD-2030. Abstracted from a portion of the Ph.D. Dissertation of T. F. P.[1b] (b) T. F. Parsons, Ph.D. Dissertation, Vanderbilt University, May 1964. (c) Paper XII: R. R. Crenshaw and L. Field, *J. Org. Chem.*, **30**, 175 (1965). (d) Du Pont Postgraduate Teaching Assistant, 1962–1963.

(2) I. B. Douglass and B. S. Farah, *J. Org. Chem.*, **24**, 973 (1959).

(3) L. Field, T. C. Owen, R. R. Crenshaw, and A. W. Bryan, *J. Am. Chem. Soc.*, **83**, 4414 (1961).

oxidized to the disulfide), and that a nitro group (unlike 2-pyridinium)[4] does not deplete electron density on the sulfur atom sufficiently to be damaging (a slightly lower yield of 75% can be ascribed to excess chlorine used to ensure destruction of all of the difficultly separable nitrodisulfide). It is worth adding that commercial *p*-nitrophenyl disulfide was purified by recrystallizing it from chloroform–methanol and acetone–methanol (the melting point rose from 140–155° to 179–181°), a method which is simpler than earlier ones.[5]

Heretofore our only poor results with the Douglass–Farah route as applied to ring compounds have been with 2-pyridyl disulfide dihydrochloride[4] and *p*-carboxyphenyl disulfide.[1c] We now report failure of the method with 2,4,6-triisopropylphenyl disulfide (**1**). After attempts to oxidize disulfide **1** at 0 or 30° without solvent, or at 0° in methylene chloride with a stoichiometric amount or excess of chlorine, **1** was recovered in good yield. Steric hindrance associated with the four *o*-isopropyl groups seems the most probable cause of the failure even though *t*-butyl disulfide, which might also be thought to be hindered, can be cleaved to *t*-butylsulfenyl chloride under mild conditions.[6]

Efforts then were made to convert the disulfide **1** to 2,4,6-triisopropylphenyl 2,4,6-triisopropylbenzenethiolsulfonate (**2**) with a peroxide. Hydrogen peroxide in glacial acetic acid at about 40° converted **1** only to 2,4,6-triisopropylphenyl 2,4,6-triisopropylbenzenethiolsulfinate (**3**, 78% yield). Excess hydrogen peroxide in acetic acid at about 70° evidently oxidizes **3** rather quickly to the sulfonic acid, because when the disulfide **1** was submitted to these conditions the only material which could be isolated was the disulfide (**1**, 49%) and the product was strongly acidic. Interestingly, the thiolsulfinate **3** showed no change after two years at room temperature, a degree of stability which seems unusual for the class[7] and probably has its origin in steric factors. Attempted oxidation of the thiolsulfinate **3** to the thiolsulfonate **2** with hydrogen peroxide in acetic acid at 80° permitted only recovery of **3** (42%), although there were indications of the presence of a little **2** (and also of the disulfide **1**).

Schultz, Freyermuth, and Buc recently reported use of molybdenum, vanadium, and tungsten catalysts for oxidation with hydrogen peroxide of sulfides to sulfones.[8] Even though either the sulfide or the intermediate sulfoxide generally was soluble in water in this earlier work, one of these catalysts deserved trial with the refractory hindered disulfide **1**. No oxidation of **1** occurred, however, with excess hydrogen peroxide and tungsten trioxide in dioxane, even at elevated temperatures. Addition of acetic acid likewise was without effect. However, in the presence also of hydrochloric acid, which is known to catalyze peroxide oxidations,[9] the thiolsulfonate **2** could be obtained in 83% yield. Both the tungsten trioxide and the mineral acid are necessary. Use of hydrochloric or sulfuric acid in the absence of tungsten trioxide resulted in recovery of the disulfide **1** (75%), and use of the trioxide without the mineral acid gave impure product from which 40% of the **1** used was recovered. Adjustment of pH in formation of the catalyst[8] was unnecessary, tungsten trioxide itself being satisfactory. The structure of the thiolsulfonate **2** was established by its analysis and infrared spectrum, as well as by its conversion using 2-mercaptoethylamine to 2-aminoethyl 2,4,6-triisopropylphenyl disulfide hydrochloride (65% yield).[1b]

Seemingly, therefore, a powerful but selective oxidant which should prove useful in other instances is available in the combination of hydrogen peroxide with tungsten trioxide in an acidic solution.

Experimental[10]

Preparation of Thiolsulfonates by Chlorinolysis.—The general procedure, based on that of Douglass and Farah,[2] is exemplified by the oxidation of phenyl disulfide to phenyl benzenethiolsulfonate. Any variations are obvious from Table I.

Chlorine (64 g., 0.90 mole) was added, from a chilled container warmed occasionally by the hand, to a stirred solution of 98.6 g. (0.45 mole) of phenyl disulfide in 27.12 g. (0.45 mole) of glacial acetic acid at about −5° during about 1 hr. The mass changed from a white solid to a clear orange-brown liquid. Water (16.2 g., 0.90 mole) then was added slowly within 5 min.; hydrogen chloride evolved in large amounts. The cooling bath was removed and the mixture was stirred for 1.5 hr., at which time it was pale yellow. The mixture was washed with water by decantation to remove the acetic acid, and the thiolsulfonate remaining then was dried in a rotating-flask evaporator under reduced pressure to a constant weight of 111.7 g. (99%). This material was taken up in hot methanol. Chilling (Dry Ice–acetone) gave 94.7 g. (84%) of phenyl benzenethiolsulfonate as white prisms, m.p. 42–44°. The infrared spectrum contained characteristic strong $-SO_2-$ bands at 1340 and 1150 cm.$^{-1}$; the other thiolsulfonates of Table I showed these same bands with little variation and all gave a positive acidic thiolsulfonate test upon treatment with a thiol.[11] *p*-Tolyl *p*-toluenethiolsulfonate was prepared earlier by this general procedure, but no details were mentioned.[3]

2,4,6-Triisopropylphenyl 2,4,6-Triisopropylbenzenethiolsulfinate (3).—2,4,6-Triisopropylphenyl disulfide (**1**, m.p. 87–89°, 3.00 g.)[12] was suspended in 120 ml. of glacial acetic acid and was heated at 70° until a clear solution resulted. The solution was cooled to room temperature and hydrogen peroxide (1.44 ml. of 30% solution, plus 1.5 ml. of water) was added during 1 hr. The temperature had to be increased to 40° and 50 ml. more of acetic acid had to be added to keep the mixture homogeneous. The solution was stirred at room temperature for 24 hr., during which time 0.7 g. of solid crystallized and was removed by filtration, m.p. 128–131°, slight dec. The filtrate was poured into water (200 ml.); chilling overnight resulted in 1.70 g. more of solid, m.p. 127–131°, slight dec. Both solids had identical infrared spectra consistent with the thiolsulfinate **3** (78% yield, characteristic –SO– absorption at 1090 cm.$^{-1}$) but not the thiolsulfonate **2**. Combination of the two solids and recrystallization from methanol gave **3** as pale yellow needles having a constant m.p. 135–136° dec. (m.m.p. 84–115° with **1**).

Anal. Calcd. for $C_{30}H_{46}OS_2$: C, 74.00; H, 9.50; S, 13.17. Found: C, 73.65; H, 9.41; S, 13.22.

2,4,6-Triisopropylphenyl 2,4,6-Triisopropylbenzenethiolsulfonate (2).—The disulfide **1** (1.00 g.) was dissolved and tungsten trioxide (0.02 g.) was suspended in a mixture of 15 ml. of glacial acetic acid, 15 ml. of dioxane, and 5 ml. of 12 *N* hydrochloric acid at 65°. Hydrogen peroxide (0.7 ml. of 30% aqueous solution) was added during 1 hr. The mixture then was stirred for 24 hr. at 65° and let cool to *ca.* 25°. A trace of sodium sulfite was

(4) L. Field, A. Ferretti, R. R. Crenshaw, and T. C. Owen, *J. Med. Chem.*, **7**, 39 (1964).

(5) C. C. Price and G. W. Stacy, *J. Am. Chem. Soc.*, **68**, 498 (1946).

(6) W. A. Schulze, G. H. Short, and W. W. Crouch, *Ind. Eng. Chem.*, **42**, 916 (1950).

(7) *Cf.* D. Barnard, *J. Chem. Soc.*, 4675 (1957).

(8) H. S. Schultz, H. B. Freyermuth, and S. R. Buc, *J. Org. Chem.*, **28**, 1140 (1963).

(9) *Cf.* D. Barnard, L. Bateman, and J. I. Cunneen, "Organic Sulfur Compounds," Vol. 1, N. Kharasch, Ed., Pergamon Press, Inc., New York, N. Y., 1961, p. 229–247 (and references cited therein).

(10) Melting points are corrected. Analyses were by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Infrared spectra were obtained using a Perkin-Elmer Model 137 B spectrophotometer with Nujol mulls.

(11) *Cf.* L. Field, T. F. Parsons, and R. R. Crenshaw, *J. Org. Chem.*, **29**, 918 (1964).

(12) D. E. Pearson, D. Caine, and L. Field, *ibid.*, **25**, 867 (1960).

added to destroy any residual peroxide, and the solution was evaporated under reduced pressure to a yellow solid. Recrystallization (methanol) gave 0.88 g. (83%) of the thiolsulfonate 2, m.p. 105–107°, which after further recrystallization had constant m.p. 108.5–110°. The infrared spectrum contained strong bands (–SO_2–) at 1150 and 1340 cm.$^{-1}$.

Anal. Calcd. for $C_{30}H_{46}O_2S_2$: C, 71.63; H, 9.22; S, 12.76. Found: C, 71.59; H, 9.02; S, 12.91.

Preparation and Structure of Dimethyl α-Conidendrin-8-methyl Sulfonate

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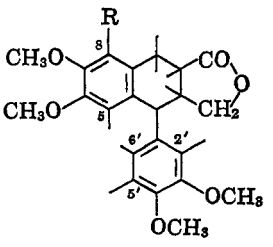
On the basis of Holmberg's preparation of α-conidendric acid in which concentrated sulfuric acid was used to open the lactone ring, a similar preparation of dimethyl α-conidendric acid from dimethyl α-conidendrin was attempted. Methylation of the product with diazomethane, however, failed to give the expected methyl dimethyl α-conidendrate and resulted instead in the 8-methyl sulfonate derivative of dimethyl α-conidendrin [2-naphthoic acid, 1,2,3,4-tetrahydro-3-hydroxymethyl-6,7-dimethoxy-4-(3,4-dimethoxyphenyl)-8-methyl sulfonate, γ-lactone or 3,4,3′,4′-tetramethoxy-2′-sulfonyl methyl-cyclolignan-olid (9.9′) by the proposed lignan nomenclature of Freudenberg and Weinges[3]], as shown by I. In view of these results Holmberg's reported α-conidendric acid[2] was probably the 8-sulfonic acid derivative.

Based on elemental analyses and a molecular weight determination an empirical formula of $C_{23}H_{26}O_9S$ was obtained for this compound. A ferric ferricyanide[4] color test for phenolic groups was negative. Since the infrared spectrum indicated that the lactone ring was intact and methoxyl analyses showed an additional methoxyl besides the four aromatic ring methoxyls expected, this fifth methoxyl group was apparently the methyl ester of a sulfonic acid group introduced into the compound. Although soluble in chloroform the new derivative was only moderately soluble in methanol, ethanol, and acetone, and was insoluble in water.

Comparison of aromatic ring proton magnetic resonance spectra (p.m.r.) of dimethyl α-conidendrin (II)



I, R = SO_3CH_3.
II, R = H

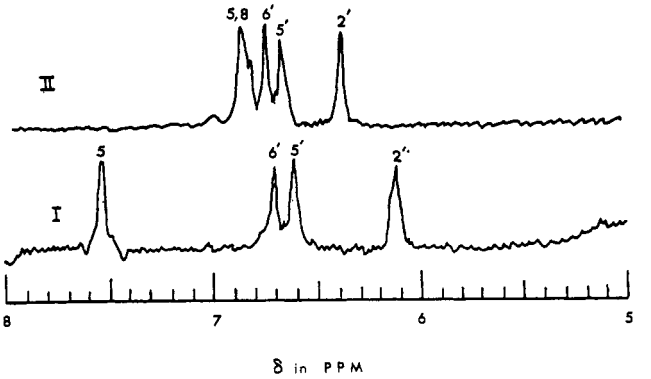


Figure 1.—Aromatic proton magnetic resonance spectra of dimethyl α-conidendrin-8-methyl sulfonate (I) and dimethyl α-conidendrin (II) in deuteriochloroform.

and this sulfur-containing derivative (Figure 1) together with stereochemical considerations strongly indicated that the sulfonic acid methyl ester group should be assigned to carbon 8.

Substitution of any one of the protons 2′, 5′, or 6′ by such a strong electron-withdrawing group as a sulfonic acid methyl ester would result in the displacement of the remaining two protons to higher δ-values. Since only one proton was so displaced, substitution must have involved protons 5 or 8. A choice between proton 8 and proton 5 was made on the basis of stereochemical models of the two possible structures (Courtauld atomic models). These models clearly indicated that substitution of a bulky sulfonic acid methyl ester group on carbon 5 would be restricted by the large aryl group on carbon 4.

Since the infrared spectrum of the monosulfonic acid intermediate showed it to be a mixture of the monosulfonic acids of both dimethyl and α-conidendric acids as well as their lactones, no rigorous purification of the intermediate was attempted. In any case, reaction of the intermediate with diazomethane produced only one crystalline end product I which was easily isolated. Undoubtedly, the 15-fold excess of diazomethane used in the reaction was involved in remethylation of free phenolic groups as well as combination with residual traces of sulfuric acids.

Experimental

Carbon, hydrogen, sulfur, and methoxyl analyses were performed by the Clark Microanalytical Laboratories, Urbana, Ill. Molecular weights were determined on the Mechrolab vapor pressure osmometer, Model 301A, using acetone as a solvent. P.m.r. spectra were recorded on a Varian, Model A-60, spectrometer in deuteriochloroform with tetramethylsilane as an internal standard. Infrared spectra were run in KBr disks on a Baird-Atomic infrared recording spectrophotometer, Model KM-1.

Preparation of the Monosulfonic Acid Intermediate.—Dimethyl α-conidendrin (4 g.) prepared by the method of Holmberg[5] was thoroughly mixed with concentrated sulfuric acid (12.6 ml.) and left at room temperature for 6 hr. Water (45 ml.) was then slowly added with stirring. The resultant precipitation was allowed to continue overnight at 4°. The excess acid solution was decanted and the product was recrystallized from water (35 ml.) by gentle warming. The slightly colored crystals (4.7 g.) melted with decomposition at 220–230°.

Dimethyl α-Conidendrin-8-methyl Sulfonate.—Dimethyl α-conidendrin-8-sulfonic acid (2 g.) in methanol (40 ml.) was added

(1) Research Officer, Vancouver Laboratory, FPRB.
(2) B. Holmberg, *Svensk. Kem. Tidskr.*, **32**, 56 (1920).
(3) K. Freudenberg and K. Weinges, *Tetrahedron*, **15**, 115 (1961).
(4) G. M. Barton, R. S. Evans, and J. A. F. Gardner, *Nature*, **170**, 249 (1952).
(5) B. Holmberg, *Chem. Ber.*, **54**, 2389 (1921).