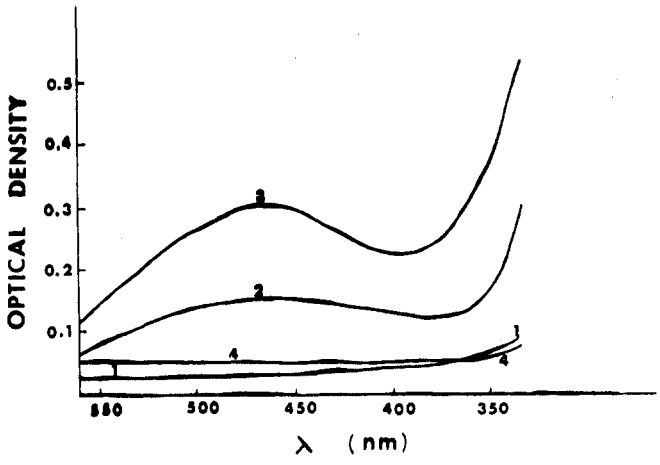

Figure 2. Oxidation of tyrosine peptides by the Cu^{2+}/H_2O_2 system: curve 1, L-tyrosyl-L-leucine at zero time; curve 2, L-tyrosyl-L-leucine after 45 min at room temperature; curve 3, L-tyrosyl-L-leucine after 3.75 hr at room temperature; curve 4, DL-leucyl-DL-tyrosine after 6 hr at room temperature.

Dukler, *et al.*,[4] reported that their dopachrome (**2**, R = CH_3), formed by the action of Fremy salt in a buffered solution (pH 8) on tyrosine methyl ester, on long standing in the presence of the reagents was converted into a dihydroxyindole. It is known that the rearrangement of dopachromes to dihydroxyindoles is catalyzed by acid and by alkali.[5,6] The rearrangement observed by Dukler, *et al.*, was therefore probably due to the alkalinity of the solution. A similar rearrangement was not observed in the present study when the reaction mixture containing the dopachrome was held at room temperature for 8 hr, since the pH of the solution was 5.0 and the dopachrome is known to be stable at this pH.[6]

The presence of dopachrome as a product of the reaction, indicated by the absorption maxima observed, was confirmed by its conversion to the known methyl 5,6-dimethoxyindole-2-carboxylate (**3**, R = Me) by the method of Dukler, *et al.*[4,7] The formation of dopachrome involves introduction of an oxygen ortho to the OH group, dehydrogenation, and intramolecular cyclization through a Michael-type addition reaction; this process evidently requires the hydrogen acceptor Pt black in the case of free tyrosine.

Spectroscopic Studies of the Oxidation of Tyrosine Peptides with the Cu^{2+}/H_2O_2 System. As is the case with other oxidizing agents, the effect of the Cu^{2+}/H_2O_2 system on tyrosine peptides depends on the position of the tyrosine moiety in the peptides.

With the NH_2-terminal tyrosine peptide, L-tyrosyl-L-leucine (**1**, R = leucine moiety), the Cu^{2+}/H_2O_2 system gave an absorption spectrum (Figure 2, curves 1, 2, and 3) similar to that found by Dukler, *et al.*,[4] when tyrosylglycylglycine was oxidized by potassium nitrosodisulfonate (maximum at 475 nm). Dukler, *et al.*, have attributed the spectrum to the fact that the N-terminal peptide was oxidized by a dopachrome mechanism, forming an aminochrome; analogously, the present product may be regarded as an aminochrome (**2**, R = leucine moiety). At room temperature and with excess Cu^{2+}/H_2O_2 the aminochrome absorption at 475 nm increased up to 4 hr, and then slowly began to decline. With neither potassium nitrosodisulfonate nor the present Cu^{2+}/H_2O_2 system was treatment with Pt black required for aminochrome formation from NH_2-terminal tyrosine peptides. Addition of Pt black produced no significant changes in the spectrum other than reduction of the end absorption at shorter wavelengths.

With the COOH-terminal tyrosine peptide DL-leucyl-DL-tyrosine, the absorption spectrum obtained on addition of excess Cu^{2+}/H_2O_2 gave no indication of formation of an aminochrome (maxima at 305 and 475 nm) or of an *o*-quinone (maximum at 390 nm) after 6 hr at room temperature (Figure 2, curve 4). Similar results were obtained with another COOH-terminal tyrosine peptide, glycyl-L-tyrosine. Even after 14 hr at room temperature, followed by treatment with Pt black, no spectral evidence that the COOH-terminal tyrosine peptides were oxidized by either an aminochrome mechanism or a dopaquinone pattern was obtained. The dopaquinone pattern of oxidation of COOH-terminal tyrosine peptides occurs on enzymatic oxidation[2] and on oxidation with potassium nitrosodisulfonate.[4]

Experimental Section

L-Tyrosyl-L-leucine, glycyl-L-tyrosine, and DL-leucyl-DL-tyrosine were obtained from Nutritional Biochemicals Corp., Cleveland, Ohio, and tyrosine from Matheson Coleman and Bell, Cincinnati, Ohio. The 3% H_2O_2 was prepared by dilution of 30% unstabilized H_2O_2 (Fisher Scientific Co.).

Tyrosine or the tyrosine peptide (0.3 mmol) was added to 50 ml of freshly prepared $CuSO_4$ (5×10^{-4} *M*)/H_2O_2 (3% unstabilized) (44.1 mmol of H_2O_2), and the mixture was allowed to stand at room temperature. At intervals aliquots were withdrawn from the solutions, and their absorption spectra were determined after dilution with distilled water (one part reaction mixture to 35 parts water for the spectra shown in Figure 1, and 1:3 for the spectra shown in Figure 2), using a Beckman DB spectrophotometer and reading against a $CuSO_4$ blank of the same concentration as the diluted solution. When Pt black was added to the diluted solution, the mixture was centrifuged to remove the metal after catalytic decomposition of the peroxide was complete, and the absorption spectrum of the supernatant was determined.

For confirmation of the identity of dopachrome produced in the oxidation of tyrosine, the reaction mixture on a preparative scale, after 4 hr at room temperature followed by treatment with Pt black, was allowed to stand overnight at room temperature with $Na_2S_2O_4$ and extracted with ethyl acetate, and the product obtained was converted by ethereal diazomethane to **3**, R = Me, mp 117–119°.

Anal. Calcd for $C_{12}H_{13}NO_4$: N, 5.96. Found: 5.99.

Registry No.—**1** (R = H), 60-18-4; **1** (R = leucine moiety), 17355-10-1; **3** (R = Me), 28059-24-7; $CuSO_4$, 10124-44-7.

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(7) Dukler, *et al.*, state that the conversion of a dopachrome to a dihydroxyindole by $Na_2S_2O_4$ is a reduction; however, the reaction is not a reduction but a catalyzed rearrangement.[5]

Hydrolysis and Alcoholysis of Orthothio Esters

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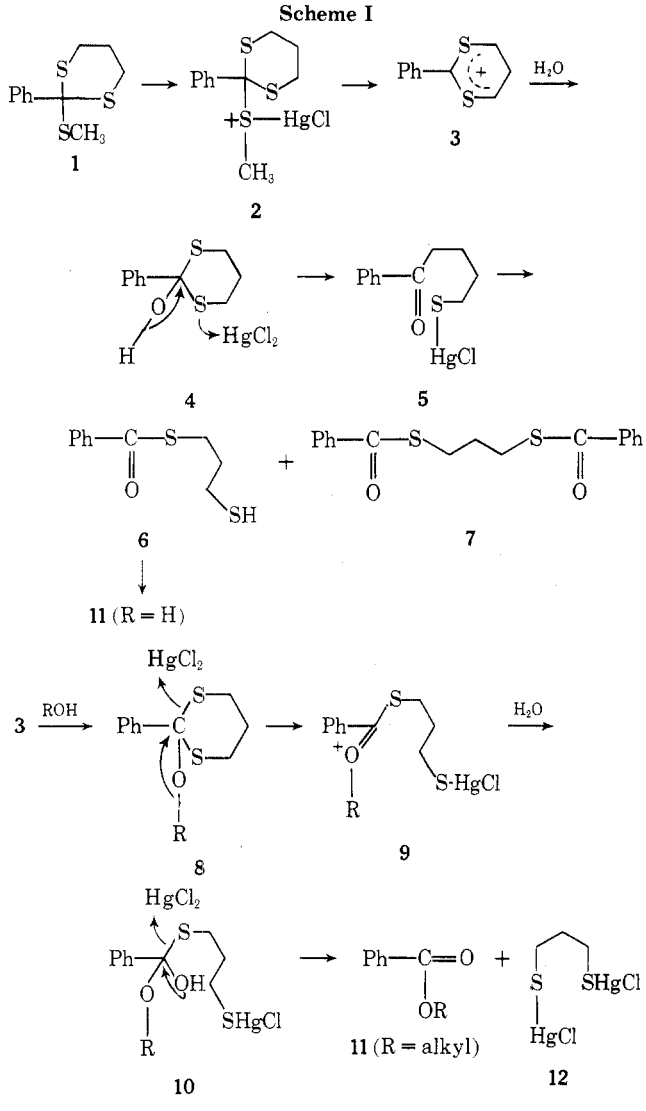
Recently we reported a convenient oxidation of aldehydes to esters and acids *via* 1,3-dithiane derivatives.[1] The hydrolysis to produce the carboxylic acids proceeded less efficiently and in poorer yield than alcoholysis and, unlike the latter, has now been found to give several neu-

Scheme I



tral intermediates which may be isolated as side products along with the acid. Further examination of this reaction using 2-methylthio-2-phenyl-1,3-dithiane (1) has permitted us to characterize, at least qualitatively, the mechanism of this reaction.

1 was prepared from 2-lithio-2-phenyl-1,3-dithiane[2] and methyl disulfide as previously described.[1] Reaction of 1 in refluxing acetone–water (2:1) in the presence of excess $HgCl_2$ for 24 hr resulted in a 63.2% yield of benzoic acid. When the reaction was conducted at 25° in acetone–water (12.5:1) for 66 hr, no acid was recovered but rather an oily mixture containing equal amounts of 6 and 7 (see Scheme I) which could be separated by preparative tlc. Both compounds displayed a carbonyl band in the ir spectrum at 6.02 μ and a broad band at 10.9 μ attributable to the methylene protons α to sulfur.

Confirmation of the assigned structures was obtained by spectroscopic and tlc comparison with authentic samples prepared synthetically. At reflux in acetone–water (12.5:1) but for only 4.5 hr, both 6 and 7 were recovered along with some benzoic acid (5.5:2:2.5, respectively). To further test that 6 and/or 7 were intermediates in the hydrolysis, the mercuric chloride salt of 6 (5) was prepared and exposed to $HgCl_2$ in refluxing acetone–water (2:1) for 24 hr. Benzoic acid was isolated in 52.4% yield. Similarly, at 25° for 71.5 hr, 5 gave a substantial amount of a 1:1 mixture of 6 and 7. Treatment of 7 under the same conditions at 25° for 20 hr gave only recovered starting material.

In contrast to hydrolysis, the ethanolysis of 1 proceeds smoothly. Complete reaction requires 1 equiv of $HgCl_2$ for each sulfur atom, as evidenced by the presence of starting material in reaction mixtures with $[HgCl_2]/[orthothioformate] < 3$. In the case of ratios ≥ 3, nmr analysis indicated complete reaction in a few minutes. However, when 1 was refluxed with $HgCl_2$ in *tert*-butyl alcohol–water (12:1) for 74 hr, the only isolable product was benzoic acid, which was isolated in 60% yield. *tert*-Butyl benzoate was prepared and found to be inert to these reaction conditions.[1] Thus benzoic acid may form directly from 1 and this suggests steric hindrance to the approach of the alcohol. In the case of the *n*-butyl or cinnamyl analogs of 1 the *tert*-butyl esters are formed in good yield, albeit after comparatively long reaction times.

When reactions were conducted using solvent mixtures consisting of two alcohols each having different steric bulk (1:1 v/v), the ester from the less bulky alcohol was formed either predominantly or exclusively. Thus, nmr analysis of products formed from mixtures of methanol with ethanol, isopropyl alcohol, *sec*-butyl alcohol, and *tert*-butyl alcohol gave ester ratios of 2.1:1, 2.9:1, 9:1, and infinity, respectively.

The mechanism we propose is outlined in Scheme I and is reminiscent of that described for ortho esters.[4] Comparison of reactions 4 → 5 and 8 → 9 (R = alkyl) shows why thio esters are obtained in the case of hydrolysis whereas only esters are derived from alcoholysis. Generation of thio esters like 6 and 7 has been encountered during the hydrolysis of ketene thioacetals.[5]

Experimental Section

General. Infrared spectra were recorded on a Beckman IR-5A spectrometer. Nmr spectra were recorded on a Varian A-60A spectrometer and chemical shifts were recorded in parts per million (δ) from internal tetramethylsilane. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. The preparation of orthothioformates and of *tert*-butyl benzoate was described in the previous paper.[1]

Hydrolysis of Phenyl Orthothioformate (1). At Reflux. Phenyl orthothioformate 1 (238 mg, 1 mmol) was dissolved in 35% aqueous acetone (27 ml) with $HgCl_2$ (1.14 g) and HgO (353 mg) and refluxed for 24 hr. The reaction was cooled and worked up as previously described.[1] The only product was benzoic acid (80 mg), mp 122°. When the same quantities were refluxed for 4.5 hr there was isolated, in addition to benzoic acid (9 mg), an oily mixture (26 mg) of two neutral compounds (6 and 7) which are further characterized below.

At 22°. Phenyl orthothioformate (1, 475 mg) was dissolved in 8% aqueous acetone along with $HgCl_2$ (2.28 g) and stirred at room temperature for 66 hr. Upon work-up, no acidic material was detected. From the neutral fraction there was isolated a crude oil (172 mg) from which could be separated in low yield two compounds by preparative tlc on silica gel developed with benzene–ethyl acetate (10:1). The compound with higher R_f was shown to be chromatographically and spectroscopically identical with 6 which was prepared independently (see below). Similarly, the less polar compound was shown to be 7.

Preparation of Monothio Ester 6. Benzoyl chloride (1.26 g, 8 mmol) was added dropwise to a stirred solution of propanedithiol (2.01 ml, 20 mmol) in dry pyridine (10 ml). The resulting solution was refluxed for 30 min under nitrogen and then cooled to room temperature. Aqueous 5% $NaHCO_3$ (40 ml) was added and the solution was extracted with two 100-ml portions of CH_2Cl_2. The organic extracts were washed with aqueous NH_4Cl followed by aqueous NaCl, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to yield 6 as a clear oil (1.2 g, 72%) which was purified by distillation in a Kugelrohr apparatus: ir (neat) 6.01, 10.9 μ; nmr ($CDCl_3$) δ 1.33 (t, 1 H, J = 8.5 Hz), 1.98 (m, 2 H), 2.61 (m, 2 H), 3.13 (t, 2 H, J = 7.0 Hz). *Anal.* Calcd: C, 56.57; H, 5.70. Found: C, 56.63; H, 5.69.

Preparation of Bisthio Ester 7. Benzoyl chloride (7.56 g, 48 mmol) was added dropwise to a stirred solution of propanedithiol (1.75 ml, 17.4 mmol) in dry pyridine (10 ml). The reaction pro-

ceeded as described for the preparation of 6 to yield 7 as an oily solid which was purified by crystallization from hexane: mp 53–53.5°; ir (CCl_4) 6.00, 10.9 μ; nmr ($CDCl_3$) δ 2.10 (q, 2 H, J = 7.0 Hz), 3.15 (t, 4 H, J = 7.0 Hz). *Anal.* Calcd: C, 64.53; H, 5.10. Found: C, 64.64; H, 5.09.

Preparation of Salt 5. Monothio ester 6 (320 mg, 1.5 mmol) was dissolved in acetone–water (99:1, 35.5 ml). Addition of a solution of $HgCl_2$ (815 mg, 3 mmol) in acetone (5 ml) to the above solution immediately gave a white precipitate. After stirring for 15 min the reaction mixture was filtered and washed with cold acetone to yield a white power (510 mg). Evaporation of the filtrate followed by trituration with acetone–water gave additional, less pure powder (87 mg). The salt was insoluble in $CHCl_3$, acetone, and benzene but dissolved in warm THF, dioxane, or DMSO: ir (KBr) 6.01, 10.98 μ; nmr (DMSO-d_6) δ 1.92 (m, 2 H, J = 0 Hz), 3.21 (t, 2 H, J = 7 Hz).

Benzoic Acid from Salt 5. Salt 5 (223 mg) was refluxed under nitrogen with a solution of $HgCl_2$ (560 mg) and HgO (176 mg) in 35% aqueous acetone (27 mg) for 24 hr. The reaction mixture was filtered and the filtrate was diluted with H_2O and extracted with CH_2Cl_2. The organic layer was separated into acid and neutral fractions. From the acid fraction, after evaporation of the CH_2Cl_2, benzoic acid was isolated (32 mg, 52%), mg 122°.

Reaction of Salt 5 at 22°. Salt 5 (223 mg) was dissolved in acetone–H_2O (92:8, 12.5 ml) with $HgCl_2$ (560 ml) and stirred for 72 hr at 22°. The reaction mixture was filtered and the filtrate was worked up as above to give an oily solid (19 mg) which was shown to be mostly 7 by tlc and nmr.

Acknowledgment. We are grateful to the Graduate School of The University of Wisconsin, which supported this work.

Registry No.—1, 34858-82-7; 5, 51025-51-5; 6, 51021-88-6; 7, 51021-89-7; benzoic acid, 65-85-0; benzoyl chloride, 98-88-4; propanedithiol, 109-80-8; $HgCl_2$, 7487-94-7.

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2,2-Bis(methylsulfonyl)vinylamines. A New Class of Vinylamines

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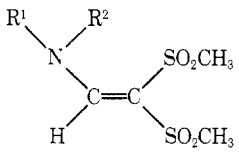
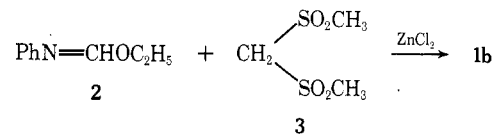
We were interested in preparing compounds of the general formula **1**. Surprisingly, compounds of this type appear not to be known, although many of the corresponding aminomethylene malononitrile and aminomethylene malonic ester derivatives have been reported.[1,2]

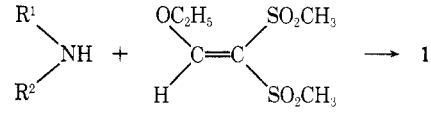


	R^1	R^2
1a	H	H
b	Ph	H
c	n-C_3H_7	H
d	C_2H_5	C_2H_5
e	PhNH	H
f	Ph	CH_3
g	H	O=CPh
h	H	O=CNHCH$_3$
i	H	Ts

N-[2,2-Bis(methylsulfonyl)vinyl]aniline (**1b**) was prepared in 20% yield by the zinc chloride catalyzed reaction of bis(methylsulfonyl)methane[3] (**3**) and ethyl N-phenylformimidate (**2**). A more efficient scheme for the preparation of bis(methylsulfonyl)vinylamines was the reaction of an amine with 2,2-bis(methylsulfonyl)vinyl ethyl ether (**4**), obtained by the reaction of **3** and triethyl orthoformate in the presence of acetic anhydride and zinc chloride. The reaction of **4** with amines proceeded under mild conditions to give the 2,2-bis(methylsulfonyl)vinylamines in 70–80% yield. The reaction of **4** with ammonia, propylamine, diethylamine, phenylhydrazine, or hydroxylamine proceeded without the addition of a catalyst. However, addition of acetic acid to the phenylhydrazine reaction gave a higher yield of **1e**. The reaction of **4** with aniline did not proceed smoothly without the addition of an acid catalyst.[5] N-Methylaniline would not condense with **4** directly; however, N-[2,2-bis(methylsulfonyl)vinyl]methylaniline (**1f**) could be prepared by the reaction of **1b** with dimethyl sulfate.

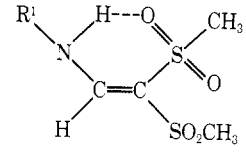


2 **3**

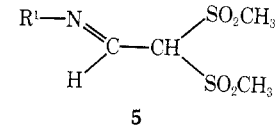


4

Infrared and pmr evidence indicate that the compounds **1a, 1b, 1c,** and **1e** exist mainly as the vinylamines and not as the tautomeric aldimines (**5**). This evidence includes a strong ir band at ~1600 cm^{-1} for the enamine sulfone system[4] of **1a, 1b, 1c,** and **1e,** as well as for **1d,** which cannot tautomerize, and an NH absorption for compounds **1b** and **1c.** The pmr evidence includes the large (J = 12–15 Hz) NHCH= coupling for compounds **1a, 1b, 1c,** and **1e.**

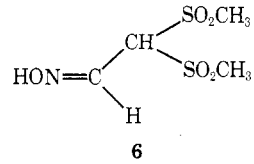


1a, b, c, e,



5

The reaction of hydroxylamine and **4** does not give N-[2,2-bis(methylsulfonyl)vinyl]hydroxylamine but rather, from ir (no 1600-cm^{-1} band) and pmr evidence, 2,2-bis(methylsulfonyl)acetaldehyde oxime (**6**). Although the melting point of **6** is sharp, its pmr in dimethyl sulfoxide-d_6 suggests a 2:1 mixture of the E and Z oximes.[7] 2,2-Bis(methylsulfonyl)vinylamine (**1a**) reacts as an amine with acylation-type reagents, benzoyl chloride, or methyl isocyanate, to yield the benzamide **1g** or methylurea **1h.** However, **1a** did not react with p-toluenesulfonyl chloride in the presence of triethylamine. Conversion to the anion (n-butyllithium) permitted preparation of the sulfonamide **1i.**



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