Variable Reaction Pathways for the Action of Polysulfide on Michael Acceptors

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α,β-Unsaturated enones and cinnamaldehyde are treated with ethanolic sodium polysulfide and the product mixtures are analyzed to ascertain the types of products. 2'-Methoxychalcone reacts to give a thiolane wherein C-2 of one chalcone unit forms a carbon–carbon bond with C-1 of the second unit. The structure of the product follows from spectral evidence and an X-ray diffraction study. Similarly chalcone in ethylene glycol gives a predominant amount of the same type of thiolane. This alternative mode of combining enone units is contrasted with the normal mode of combination wherein C-2 of one unit combines with C-3 of a second to give a thiolane. Two phenyl vinyl ketone units combine in the normal mode with sulfur from polysulfide to give *trans*-2,4-dibenzoylthiolane and 2,4-dibenzoylthiophene. Evidence for the stereochemistry of the thiolane is provided by the ^1H NMR study. The non-chalcones, cinnamaldehyde and 4-phenylbutenone, combine in the alternative mode giving thiophenes. Terminal olefinic enones 1,2-diphenylpropenone and 1-phenyl-2-methylpropenone produce mixtures of polysulfides.

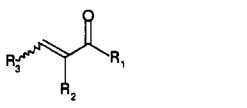
Introduction

The treatment of variously substituted chalcones with polysulfide results in the formation of a thiolane wherein the carbon–sulfur framework is assembled as depicted in **1**, Scheme I.[1,2] In each case a fair to good yield of a single diastereomeric thiolane results when monohydroxylic alcohols are used as solvents. ^1H NMR studies of these thiolanes showed from the values of the $^3J_{H-H}$ couplings that three contiguous thiolane hydrogens, located at C-3, C-4, and C-5, were trans-anti.[2] The relative configuration of the C-2 hydrogen could not be ascertained because of the somewhat lower value of its $^3J_{H-H}$ coupling to the C-3 proton.

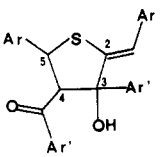
More recent analyses of the minor products obtained from chalcones and an extension of the study to non-chalcone Michael acceptors have been attempted in order to learn more about the scope of the reaction and the nature of the products, including their stereochemistry. This paper is concerned with findings which demonstrate that two types of sulfur-containing pentacycles are formed. The second contains the Michael acceptor units joined as depicted in **2**, Scheme I. This paper also presents new evidence which further defines the stereochemistry of both types of thiolanes.

Results

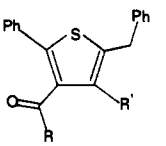
The treatment of 2'-methoxychalcone, **3**, with an ethanolic solution saturated with sodium polysulfide produced **4** in low yield as the only isolable product. Its structure is in accord with the compound's ^1H and ^{13}C NMR, MS, and IR spectra. The X-ray model, in which hydrogens are omitted for clarity, is shown in Figure 1. The anti-periplanar disposition of the vicinal protons accounts, therefore, for the large $^3J_{H-H}$ value (11.2 Hz) of the AB doublet of doublets.



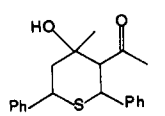
3: R_1 = 2-$CH_3OC_6H_4$; R_2 = H; R_3 = Ph
5: R_1 = R_3 = Ph; R_2 = H
7: R_1 = R_2 = H; R_3 = Ph
17: R_1 = CH_3; R_2 = H; R_3 = Ph
18: R_1 = Ph; R_2 = H; R_3 = CH_3
19: R_1 = t-C_4H_9; R_2 = H; R_3 = Ph
20: R_1 = Ph; R_2 = R_3 = H
21: R_1 = R_2 = Ph; R_3 = H
22: R_1 = Ph; R_2 = CH_3; R_3 = H



4: Ar = C_6H_5; Ar' = 2-$CH_3OC_6H_4$
6: Ar = Ar' = C_6H_5



8: R = R' = H
9: R = OC_2H_5; R' = H
10: R = OH; R' = H
26: R = R' = CH_3



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Chalone **5** was treated with a saturated ethylene glycol solution of sodium polysulfide. The analytical HPLC analysis of a mixture of the products revealed that the known normal thiolane, whose structure corresponds to **1**, and a new isomer, **6**, were formed in low conversion in a ratio of 1:4. In contrast, the same reaction carried out in ethanol, as is the usual procedure,[3] resulted in the high conversion to products in which the normal thiolane **1** predominated and the new isomer was present in less than 5%. The spectral properties of **6** were similar to those of **4**, including the AB coupling constant (11.2 Hz), again

(1) Reinecke, M. G.; Morton, D. W.; Del Mazza, D. *Synthesis* **1983**, 160.
(2) LaLonde, R. T.; Horenstein, B. A.; Schwendler, L.; Fritz, R. C.; Florence, R. A. *J. Org. Chem.* **1983**, *48*, 4049.
(3) Fromm, E.; Hubert, E. *Liebigs Ann. Chem.* **1912**, *394*, 301.

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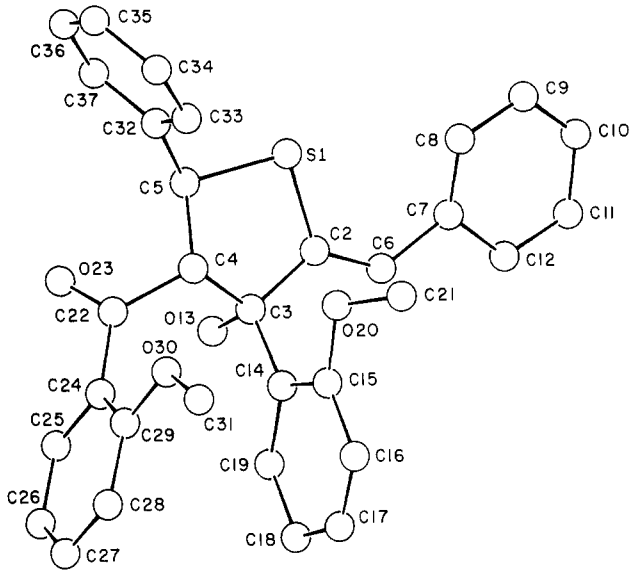
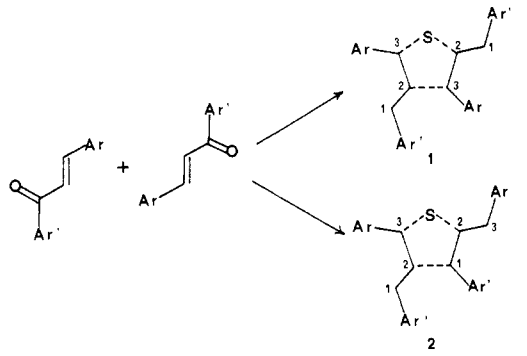


Figure 1. A computer generated drawing of **4**. Hydrogens are omitted.

Scheme I

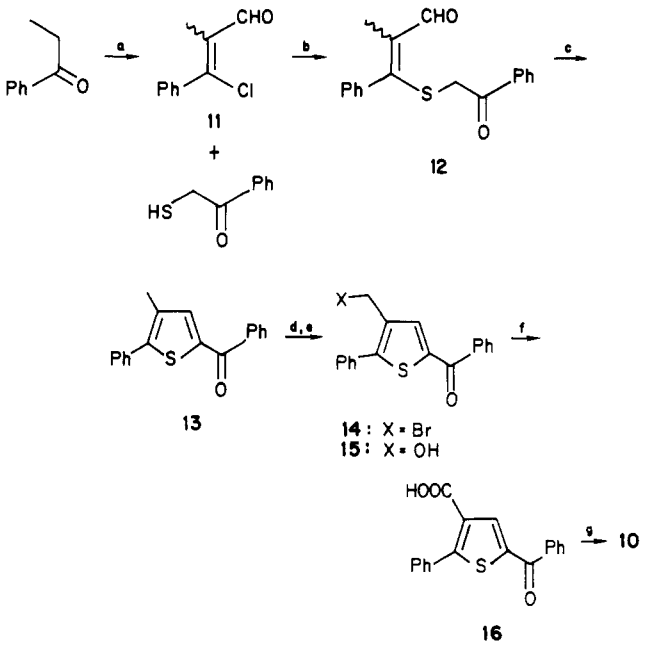


resulting from the protons at C-4 and C-5.

The action of polysulfide on some non-chalcone Michael acceptors also leads to heterocycles possessing the alternative arrangement of Michael acceptor units (**2**, Scheme I). Thus the treatment of cinnamaldehyde, **7**, with an ethanolic solution saturated in sodium polysulfide gave a complex product mixture from which the thiophene carboxaldehyde **8** and ethyl ester **9** were isolated by chromatography. Oxidation of aldehyde **8** with silver oxide produced the carboxylic acid **10**, the same acid obtained by the hydrolysis of the isolated ethyl ester **9**. The acid **10** proved to be identical, by spectral and melting point comparisons, with a sample independently synthesized as summarized in Scheme II. Important structural evidence pointing to the acid to be synthesized was obtained by determining the ^{1}H NMR of **8** and **9** in deuteriobenzene. When this solvent was used in place of deuteriochloroform, the triplet attributed to the single proton attached to the thiophene ring of **8** and **9** was no longer obscured by the envelope of aromatic resonances and its coupling to the benzylic methylene could be demonstrated by homonuclear decoupling. Thereby the 2–3 or 2–4 relation of methylene and single ring proton was indicated in accord with well-established data for long-range coupling in thiophenes.[4,5] Similarly the lack of long-range coupling of the aldehydic proton indicated the 2–5 or 3–5 attachments of aldehyde and single ring proton could be eliminated from further consideration.

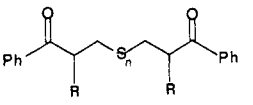
(4) Hoffman, R. A.; Gronowitz, S. *Ark. Kemi* **1960** *16*, 515.
(5) Hoffman, R. A.; Gronowitz, S. *Ark. Kemi* **1960**, *16*, 563.

Scheme II[a]



[a] (a) $POCl_3$, DMF, 0 °C; (b) pyridine-triethylamine, 20 °C, (c) HOAc, N_2, 120 °C; (d) NBS, CCl_4, $h\nu$; (e) $AgNO_3$, acetone-H_2O, 25 °C; (f) CrO_3, H_2SO_4, acetone-water, 10 °C; (g) Zn, concentrated NH_4OH, 100 °C then Zn, HOAc, 120 °C.

In the course of our investigation, a report appeared[1] which indicated that polysulfide treatments of non-chalcone Michael acceptors **17** and **18** gave uncharacterizable mixtures while the mixture resulting from **19** showed evidence of containing mono-, di-, and trisulfides. Phenyl vinyl ketone, **20**, was reported to undergo polymerization. The results of our investigations of these and similar compounds are in general agreement with what was reported yet details differ in some significant respects. In agreement with the earlier report,[1] we found the polysulfide in ethanol treatment of 1-phenyl-2-buten-1-one, **18**, resulted in a crude product whose MS and ^{1}H NMR pointed to the presence of a thiolane, but because the mixture was so complex no attempt was made to isolate it. The crude product resulting from 2,2-dimethyl-5-phenylpenten-3-one, **19**, gave no evidence for the presence of thiolanes or thiophenes by MS or ^{1}H NMR. Similarly 1,2-diphenylpropenone, **21**, and 1-phenyl-2-methylpropenone, **22**, gave no thiolanes although MS and ^{1}H NMR analysis of product mixtures and partially purified products indicated the formation of polysulfide **23** and **24**.



23: R = Ph
24: R = CH_3

4-Phenylbuten-2-one, **17**, in ethanolic sodium polysulfide also gave a complex mixture which, unlike that of the earlier report,[1] yielded pure products. One was the known thiane **25** which was identified by comparing its spectral properties with those reported. This product had been obtained earlier by the action of sodium sulfide on the enone **17**.[6] In addition to **25**, the tetrasubstituted

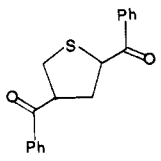
(6) Del Mazza, D.; Reinecke, M. G. *J. Org. Chem.* **1981**, *46*, 128.

Table I. ^{1}H NMR Values in Hertz for the Saturated Ring of 2,4-Dibenzoylthiolane, 27, Determined in $CDCl_3$ Solution Relative to Me_4Si (0.0 Hz) at 360 MHz

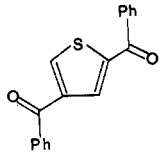
position	ν	H–H	$^3J_{H-H}$
2	1759.8	2–3e	1.9
		2–3a	6.3
3a	819.2	3a–3e	−12.3
		3a–4a	9.6
3e	1074.8	3e–4a	5.2
4a	1591.4	4a–5a	9.4
		4a–5e	5.9
5a	1198.7	5a–5e	−10.5
5e	1132.5		

thiophene **26** was isolated by chromatography. Evidence for the structure of this product comes from its spectral characteristics in comparison with those of aldehyde **8**.

Although phenyl vinyl ketone did indeed undergo polymerization when treated with ethanolic polysulfide, it also was transformed in small part to 2,4-dibenzoylthiolane, **27**, and 2,4-dibenzoylthiophene, **28**, both of which were



27

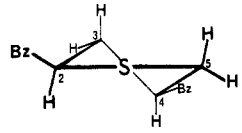


28

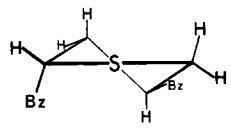
isolated by chromatography. The former was of special interest since the additional protons located at C-3 and C-5 held the promise of giving more stereochemical information about adjacent substituents through NMR analysis than had resulted from similar previous analyses[2] of the tetrasubstituted thiolanes. Such a consideration was significant in view of our persistent failure to obtain crystals of tetrasubstituted thiolanes appropriate for X-ray determinations or, alternatively, more than a single diastereomer that could be used for comparing $^3J_{H-H}$ values.

The ^{13}C NMR of **27** was uniquely consistent with a dibenzoylthiolane lacking C_2 or C_s symmetry since four thiolane ring resonances and two ketone resonances were revealed. The chemical shift and $^3J_{H-H}$ values, determined from the 360-MHz spectra, for the six-spin ^{1}H system of the thiolane ring are summarized in Table I. Assignments of protons bonded to saturated carbon were made with the assistance of a 2D ^{1}H NMR contour plot. The reference point for making resonance assignments was the C-2 proton, which was assigned to the lowest field resonance in the region because the carbon to which it was attached also was attached to both a sulfur and a benzoyl group and its splitting resulted from the coupling to two other protons.

Experiment has confirmed the results of earlier calculations that thiolane is a strongly inhibited, highly puckered pseudorotator possessing a barrier of nearly 3 kcal/mol between the more stable half-chair (C_2) and less stable envelope (C_s) conformations.[7] The appearance of two pairs of $^3J_{H-H}$ values (9.6 and 5.2 Hz, 9.4 and 5.9 Hz), resulting from the five protons located at C-3, C-4, and C-5, corresponded to two axial–axial and two equatorial–axial interactions in a single half-chair conformation. Had a third pair of $^3J_{H-H}$ values of similar magnitude been observed, the cis-2,4 configuration **27a** could have been assigned. Instead, the observed third pair of $^3J_{H-H}$ values (1.9 and 6.3 Hz), resulting from C-2 and C-3 proton interactions, was different from the other two. It corresponded to the H–C(3)–C(2)–H dihedral angles[8,9] in the half-chair conformation of *trans*-2,4-dibenzoylthiolane, **27b**, but not to that of the cis-2,4 isomer **27a**. Justification for the axial C-2 benzoyl group would seem to rest in a similar anomeric effect that favors the axial disposition of the carbomethoxy group in 2-carbomethoxy-1,3-dithiane.[10] By analogy, the previously studied tetrasubstituted thiolanes[2] would possess a cis,trans,trans configuration rather than the all trans configuration, which rested on ^{1}H NMR couplings and MS evidence.[6]



27a



27b

The ^{13}C NMR of the dibenzoylthiophene, **28**, revealed two ketone resonances and thus indicated a thiophene lacking C_2 symmetry. A sample of **28** was prepared for direct comparison by a route somewhat different from that previously reported.[11] Thus 3-thiophenecarboxaldehyde was converted to its oxime, which was dehydrated to the nitrile with hot acetic anhydride. In turn the nitrile was treated with phenylmagnesium bromide to obtain 3-benzoylthiophene, which was acylated with benzoyl chloride and aluminum chloride to give the 2,4-dibenzoylthiophene, **28**. Samples originating from synthesis and the action of polysulfide on phenyl vinyl ketone proved to be identical by mixture melting point determination, ^{13}C NMR, IR, and analytical HPLC. Little doubt remains that the conversion of phenyl vinyl ketone to thiophene **28** involves the 2,4-dibenzoylthiolane, **27**, which undergoes dehydrogentation by sulfur.

Conclusions and Discussion

The detection and isolation of the reaction products described in the previous section demonstrates that the combination of Michael acceptors occurs as depicted in both **1** and **2**. Chalcone and non-chalcone Michael acceptors alike are capable of combining in both modes under the normal conditions of employing a saturated ethanolic sodium polysulfide solution. In the case of chalcone, however, the importance of the alternative pathway leading to **2** can be enhanced by changing the solvent from ethanol to ethylene glycol. The sensitivity of product composition to changes in solvents has previously been noted in connection with the reaction of chalcone and polysulfide in glyme solution.[12] To date all evidence points to the formation of single diastereomeric products when chalcones are transformed to either **1** or **2**.

(7) Fuchs, B. In "Topics in Stereochemistry"; John Wiley: New York, 1978; p 68.

(8) The H_{3a}–C–C–H_{2e} and H_{3e}–C–C–H_{2e} dihedral angles (ϕ) were 64° and 40°, respectively, when estimated from the observed coupling constants 1.9 and 6.3 Hz using the Karplus relation $^3J_{H-H} = A\cos^2\phi - 0.3$. These dihedral angles correspond to angles 80° and 40° measured from a Dreiding model of thiolane held in a highly puckered half-chair conformation. The coefficient A = 11.2 Hz was evaluated from observed $^3J_{H-H}$ values for type **1** and **2** thiolanes and the X-ray determined dihedral angles of **4**.

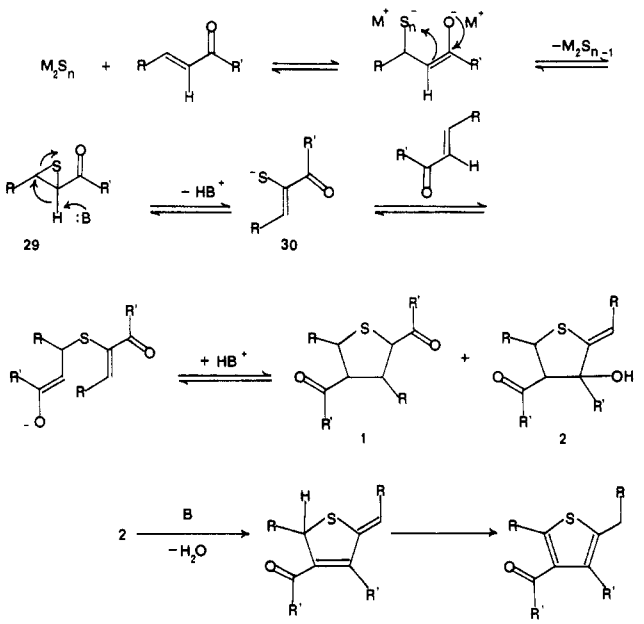
(9) Possibly one might argue that the third pair of $^3J_{H-H}$ values results from an equatorial benzoyl group at C-2 as well as C-4. However, this conformation would mean the effect of the electronegativity and orientation of the equatorial benzoyl group is different when attached to C-2 than when it is attached to C-4, a difference which seems unlikely since C-3 and C-5 do not experience such a difference as a result of diequatorial aryl substitution in any of the 2,4-dibenzoyl-3,5-diarylthiolanes analyzed by high-resolution ^{1}H NMR.[2]

(10) Arai, K.; Iwamura, H.; Oki, M. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3319.

(11) Yakubov, A. P.; Belen'kii, L. I.; Gol'dfarb, Y. A. *Zh. Org. Khim.* **1973**, *9*, 1959; *Chem. Abstr.* **1974**, *80*, 14801a.

(12) LaLonde, R. T. *J. Chem. Soc., Chem. Commun.* **1982**, 401.

Scheme III



The fact that thiolanes and thiophenes are formed even in low conversion from non-chalcone enones is an encouraging sign that other types of Michael acceptors also will undergo similar dimerizations with the incorporation of a sulfur atom. However, limitations of the reaction are emerging from the results reported here and elsewhere.[1] To date, no Michael acceptor lacking an α-hydrogen has been converted to a thiolane, a failure which might be ascribed to steric crowding during thiolane formation. Certainly the importance of steric factors cannot be lightly dismissed since chalcones possessing bulky groups fail to undergo thiolane formation.[2] Another explanation may be that thiolane and thiophene formations proceed by a mechanism necessitating the presence of an α-hydrogen, a mechanism differing from the one originally proposed.[6,13] An alternative is offered in Scheme III, the first two steps of which amount to the sulfur analogue of the well-known conversion of Michael acceptors to epoxides with alkaline hydrogen peroxide. A similar example may be taken from recent carbon chemistry. Thus the reaction of Michael acceptors with sulfoxonium ylides yields cyclopropanes.[14,15] Here, as with the group VIB elements, the initially nucleophilic atom later becomes an electrophilic center from which a leaving group is displaced by the carbon terminus of the intramolecular enolate. As a consequence of its nucleoelectrophilic mode of reactivity,[16] a single atom provided by the reagent becomes bonded to two different carbon atoms provided by a Michael acceptor.

An analogy for removal of a proton from the proposed thiirane intermediate **29** is the facile based-catalyzed conversion of epoxychalcone to the α-diketone, 1,3-diphenylpropane-1,2-dione and its enol form.[17] Because of the body of evidence[18] supporting the greater acidity of α-hydrogen in sulfides as opposed to ethers, the removal of α-hydrogen from **29** would be even more facile. According to Scheme III, the influence of sulfur in mediating carbon–carbon bond formation stems from the generation of α-thioenolate **30** and the high potential of the latter, like other nucleophilic thiating agents, to add to Michael acceptors. Thus through **30** two Michael acceptors are brought together for later carbon–carbon bond formation. Subsequent Michael reaction of the second enolate leads to thiolane type **1** whereas an aldol reaction leads to thiolane type **2**. As for the formation of type **2** thiophenes, the aldol product undergoes base-promoted dehydration and then a [1,5]-shift of hydrogen in its transformation to the thiophene. The failure of chalcone products **4** and **6** to undergo dehydration under normal conditions can be attributed to the difficulty in achieving coplanarity of the bulky substituents attached to C-3 and C-4.

The preparation of 2,4-disubstituted thiolanes and thiophenes often involves the stepwise construction of the carbon–sulfur skeleton from acyclic precursors or the substitution of 3-substituted thiophenes, which are not always readily available. The multistep preparations of **10** and **28** described above are examples of the routes involved. In contrast to such routes, the polysulfide–Michael acceptor route leads to the preparation of these compounds in a single step.

Experimental Section

Spectra. ^{1}H NMR were determined in $CDCl_3$ solution, except were noted otherwise, in 5-mm tubes by employing Bruker WM 360, Varian XL-100, or Varian EM 360 spectrometers. Totally decoupled and off-resonance decoupled ^{13}C NMR were determined in $CDCl_3$ solution in 5- or 12-mm tubes on a Varian XL-100 spectrometer. Chemical shifts are relative to Me_4Si (δ 0.0). The signs of the $^3J_{H-H}$ and $^2J_{H-H}$ values of **27** were ascertained through computer assisted simulations of the determined 360-MHz ^{1}H NMR. EI or CI MS were obtained from a Finnigan 4021 spectrometer. IR were determined in $CHCl_3$ solution, except where noted otherwise, on Perkin-Elmer 137 and 1310 spectrometers.

TLC. TLC was performed on Baker-flex silica gel 1B2-F strips, 7.5 × 2.5 cm with low boiling petroleum ether (PE) and ethyl acetate (EtOAc) mixed in the proportions indicated within the parentheses appearing after the designation "TLC".

Michael Acceptors. Chalcones **3** [bp 177–179 °C (0.45 mmHg) (lit.[19] bp 214–215 °C (8 mmHg)] and **5** [mp 55–57 °C (lit.[20] mp 55–57 °C)], 4-phenyl buten-2-one, **17** [mp 37–40 °C (lit.[21] mp 40–42 °C)], and 2,2-dimethyl-5-phenyl penten-3-one, **19** [mp 40–42 °C (lit.[22] mp 41–42 °C)], were prepared by common hydroxide ion catalyzed condensations of benzaldehyde and the appropriate ketone. 1-Phenyl-2-buten-1-one, **18** [bp 84–87 °C (2 mmHg) (lit.[23] bp 90–95 °C (2 mmHg)], was obtained by the aluminum chloride catalyzed acylation of benzene by crotonyl chloride. Phenyl vinyl ketone, **20** [bp 93 °C (8 mmHg) (lit.[24] bp 114–116 °C (18 mmHg))], 1,2-diphenylpropen-1-one, **21** [mp 28–29 °C (lit.[25] mp 29 °C)], and 1-phenyl-2-methylpropen-1-one, **22** [bp 67–69 °C (4 mmHg) (lit.[24] bp 60 °C (3 mmHg))] were prepared respectively from acetophenone, desoxybenzoin, and propiophenone through acid- and

(13) Wong, C. F.; LaLonde, R. T. *Experientia* **1975**, *31*, 15.
(14) Lehmann, H. G.; Muller, H.; Wiechert, R. *Chem. Ber.* **1965**, *98*, 1470.
(15) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1971**, *93*, 3773.
(16) Both the mechanism proposed earlier[6,13] and the one proposed here require polysulfide to function as a nucleoelectrophilic thiating agent. Besides the added requirement for the presence of α-hydrogen, the alternative mechanism of Scheme III differs in the sequence of the carbon–sulfur and carbon–carbon bond-forming steps leading to a five-membered ring. The earlier mechanism proposed bond-forming steps in the order carbon–sulfur, carbon–carbon, and carbon–sulfur. The alternative mechanism of Scheme III proposes bond-forming steps in the order carbon–sulfur, carbon–sulfur, and carbon–carbon.
(17) Widman, O. *Chem. Ber.* **1916**, *49*, 477.
(18) Block, E. "Reactions of Organosulfur Compounds"; Academic Press: New York, 1978; pp 36–90.
(19) Enebeck, C.; Gripenberg, J. *Acta Chem. Scand.* **1957**, *11*, 866.
(20) Kohler, E. P.; Chadwell, H. M. In "Organic Synthesis", 2nd ed.; Gilman, H., Ed.; Wiley: New York, 1941; Collect. Vol. 1, pp 78–80.
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(22) Webb, C. N. In "Organic Synthesis", 2nd ed.; Gilman, H., Ed.; Wiley: New York, 1941; Collect. Vol. 1, pp 81–82.
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base-catalyzed Mannich reactions of the appropriate ketone with formaldehyde in the presence of piperidine. ^{1}H NMR and IR spectra of the prepared enones were determined and were found to be consistent with the structures. Cinnamaldehyde, **7**, was obtained from a commercial source and was distilled immediately before use.

Conversion of 2′-Methoxychalcone 3 to 4. A 14.4-mmol quantity of **3** was added in one portion to a stirred 95% ethanolic solution saturated with sodium polysulfide which had been prepared by treating 225 mmol of $Na_2S{\cdot}9H_2O$ with 270 mmol of sulfur. Within 4 h a precipitate resulted. Continued stirring for an additional 14 h and standing another 24 h, followed by filtration, washing the solid repeatedly with 20% aqueous ammonium sulfide, and drying the refiltered solid at 25 °C for 3 days resulted in 3.05 g of white powder, from which 500 mg was taken for recrystallization from acetic acid then chlorobenzene. Thus obtained was 183 mg (28%) of crystalline **4**: mp 212–214 °C; IR (KBr), 3440, 1657 cm^{-1}; MS, m/e 508 (M^+), 355, 271, 270, 269, 255, 239, 238, 237, 135 (base peak), 91, 77; ^{13}C NMR δ 54.0 (d), 55.0 (q), 55.9 (q), 65.6 (d), 88.3 (s); ^{1}H NMR δ 3.45 (s, OCH_3), 3.75 (s, OCH_3), 3.96 (s, exchanged with D_2O, OH), 5.56 (ABdd, J = 11.2 Hz, H-4 and 5), 5.96 (s, C=CH). Anal. Calcd for $C_{32}H_{28}O_4S$: C, 75.57; H, 5.55; S, 6.30. Found: C, 75.70; H, 5.43; S, 6.17.

Conversion of Chalcone 5 to 6. The general procedure for converting chalcones to thiolanes was employed except that 225 mmol of $Na_2S{\cdot}9H_2O$ was dissolved in 25 mL of warm ethylene glycol. Sulfur (250 mmol) was added and the dark red-brown solution was allowed to cool to 25 °C. A 14.4 mmol quantity of chalcone was added and the resulting slurry was stirred for 2 days at 25 °C then filtered. The solid was washed repeatedly with 20% aqueous ammonium sulfide and then with water and dried under a gentle stream of air to give 1.55 g of powder, from which a 400-mg portion was taken for a recrystallization from PE–EtOAc to remove the bulk of the unconverted chalcone. Reversed-phase HPLC (9.4 mm × 25 cm, 5% C_{18} on Partisil 10, MeOH–H_2O, 70:30 at 3.2 mL/min) showed the ratio of 2,4-dibenzoyl-3,5-diphenylthiolane and **6** to be 1:4 in the 182 mg (11%) of the once recrystallized mixture. A 125 mg was first chromatographed at medium pressure (SiO_2, PE–EtOAc, 4:1). HPLC (9.4 mm × 25 cm, Partisil 10, PE–EtOAc, 6:1) of fractions enriched in **6** gave 5.2 mg of pure **6**, which was similarly obtained in additional 5- to 8-mg amounts starting from 400-mg quantities of the crude product mixture. Compound **6**: mp 172.5–173.5 °C; IR 3410, 1707, 1652 cm^{-1}; MS, m/e 448 (M^+), 325, 241, 240, 239, 209, 208, 207, 105 (base peak), 77; ^{13}C NMR δ 55.0, 65.7, 89.8, 202.6; ^{1}H NMR δ 4.62 (d, J = 11.2 Hz, H-4), 5.03 (s, exchanged with D_2O, OH), 5.48 (d, J = 11.2 Hz, H-5), 6.10 (s, C=CH). Anal. Calcd for $C_{30}H_{24}O_2S$: C, 80.33; H, 5.39; S, 7.15. Found: C, 80.04; H, 5.37; S, 7.23.

Conversion of Cinnamaldehyde 7 to Thiophenes 8 and 9. A 14.4-mmol amount of freshly distilled **7** was treated with 22.5 mmol of $Na_2S{\cdot}9H_2O$ and 250 mmol of sulfur in 20 mL of 95% EtOH according to the standard reaction and CH_2Cl_2–aqueous $(NH_4)_2S$ workup procedures. The removal of CH_2Cl_2 solvent at reduced pressures left 3 g of foam which was chromatographed repeatedly on alumina (Act II) with PE–Et_2O (3:2) to obtain a 57-mg (1.6%) sample of liquid **9**: TLC (4:1) R_f 0.54; MS, m/e 322 (M^+) (base peak), 293, 277, 249, 215, 149, 115, 91, 77; ^{1}H NMR (C_6D_6) δ 0.85 (t, J = 7 Hz, CH_3), 3.75 (d, J = 0.7 Hz, CH_2Ph), 3.97 (q, J = 7 Hz, CCH_2O), 7.36 (t, J = 0.7 Hz, thiophene C-3H); IR 1709 cm^{-1} also obtained was 135 mg (6.7%) of faintly yellow liquid **8**: TLC (4:1) R_f 0.49; IR 2832, 2740, 1669, 1605, 1490, 1443 cm^{-1}; MS, m/e 278 (M^+), 217, 215, 202, 173, 115, 105, 91 (base peak) 77; MS (CI, methane) 279 (base peak) (M^+ + 1), 307 (M^+ + 29), 319 (M^+ + 41); ^{13}C NMR δ 35.1 (t, CH_2Ph), 184.9 (d, CHO); ^{1}H NMR δ 4.14 (d, J = 0.8, CH_2Ph), 7.2–7.5 (11 H), 9.80 (s, CHO); ^{1}H NMR (C_6D_6) δ 3.65 (d, J = 0.7 Hz, CH_2Ph), 7.37 (t, J = 0.7 Hz, thiophene C-3H, s when δ 3.65 signal was irradiated), 9.82 (s, CHO).

Conversion of Aldehyde 8 and Ester 9 to Carboxylic Acid 10. To a 2.25-mmol quantity of silver oxide suspended in alkaline THF–water (2:1) was added 0.54 mmol of **8** with vigorous stirring. The resulting mixture was stirred at 30–40 °C for 3 days, the mixture was centrifuged, the solids were washed repeatedly with THF–water (2:1), and the washings were combined with the original supernatant, then filtered, concentrated by vacuum evaporation, diluted with MeOH, and then filtered again. Organic solvents were removed at reduced pressure and the resulting alkaline aqueous mixture was extracted with CH_2Cl_2 to remove neutrals. The aqueous layer was acidified and then extracted with CH_2Cl_2. Evaporation of the solvent at reduced pressure yielded 120 mg of yellow solid which was recrystallized from 4 mL of CCl_4 to obtain 71 mg (45%) of crystalline **10**: mp 152–156 °C; mp (EtOH–H_2O) 157–158 °C; TLC (2:1) R_f 0.52; MS, m/e 294 (M^+) (base peak), 249, 217, 171, 121, 115, 91, 77; IR 3500–2500, 1692 cm^{-1}; ^{1}H NMR δ 4.10 (s, CH_2Ph); ^{1}H NMR (C_6D_6–$CDCl_3$, 5:1) δ 3.71.

An 0.055-mmol amount of **9** was warmed in alkaline EtOH–H_2O for 1 h. The mixture was cooled and extracted with CH_2Cl_2. The aqueous layer was acidified and extracted with CH_2Cl_2. After drying the combined extracts, the solvent was removed at reduced pressure. The residue was recrystallized from EtOH–H_2O giving 12 mg (74%) of **10**: mp 156–158 °C; TLC (2:1) R_f 0.51; IR 3500–2500, 1690 cm^{-1}.

Conversion of 4-Phenylbuten-2-one, 17, to Thiane 25 and Thiophene 26. Under an atmosphere of N_2, a 20.5-mmol amount of **17** in anhydrous EtOH was added dropwise to a vigorously stirred, saturated solution of polysulfide which had been prepared by adding 109.4 mmol of sulfur to 23.1 mmol of anhydrous sodium sulfide in anhydrous EtOH. After stirring an additional 30 min, the mixture was allowed to stand 48 h at 25 °C. The bulk of the solvent was removed at the rotary evaporator and the residue was taken up in ether. The resulting mixture was then washed repeatedly with 20% aqueous ammonium sulfide and then with small portions of water. The ether solution was dried briefly over $MgSO_4$. Concentration of the ethereal solution with the rotary evaporator resulted in precipitation of 213 mg of a light tan solid which when crystallized from EtOAc–hexane gave 158 mg (4.7%) of **25**: mp 186–189 °C (lit.[6] mp 184.5–186 °C); TLC (hexane–EtOAc, 2:1, 2×) R_f 0.41; IR, ^{1}H NMR, and MS identical with those reported.[6] Removal of all the solvent with the rotary evaporator left 2.2 g of a dark residue which was stirred with 60 mL of PE at 25 °C for 3 days. Removal of the PE from the supernatant gave 1.2 g of an orange-yellow oil whose TLC (2:1), R_f 0.55, showed enrichment of the most mobile component of the original ethereal solution. Flash chromatography (silica gel 60, PE–EtOAc, 2:1) of one 213 mg portion of the orange-yellow oil produced several fractions of which one, 14 mg (2.5%), consisted of pure liquid **26**: TLC (2:1) R_f 0.55; MS, m/e 306 (M^+), 291 (base peak), 263, 128, 91; IR 1681 cm^{-1}; ^{1}H NMR δ 2.08 (s, $COCH_3$), 2.21 (s, thiophene-CH_3), 4.08 (s, CH_2Ph); ^{1}H NMR (C_6D_6) δ 1.85 (s, $COCH_3$) 2.18 (s, thiophene-CH_3), 3.76 (s, CH_2Ph).

Treatment of 2,2-Dimethyl-5-phenylpenten-3-one, 19, with Sodium Polysufide. The treatment of 16 mmol of **19** with anhydrous sodium polysulfide, according to the procedure used in the conversion of **17** to **26**, yielded a red-brown mixture whose TLC, ^{1}H NMR (60 MHz), and MS showed no evidence that thiolane or thiophene products had been formed.

Preparation of 2-Methyl-3-chloro-3-phenylpropenal, 11. The procedure of Arnold and Zemlicka[26] for preparing β-chlorocinnamaldehydes was followed. Thus under vigorous stirring, 123 mmol of $POCl_3$ was added to 150 mmol of DMF cooled to 0 °C. The syrupy mixture was stirred at 25 °C for 40 min and cooled again to 0 °C. A 50-mM quantity of propiophenone was added dropwise with vigorous stirring. Thereafter the mixture was warmed at 40–45 °C for 3 h and allowed to stand at 25 °C overnight. The workup procedure followed the general one reported.[26] Vacuum distillation of the crude product gave 28 mmol (56%) of pure **11**: bp (1.2 mm) 87–88 °C; TLC (5:1.5) R_f 0.63; IR 1672 cm^{-1}; ^{1}H NMR δ 2.1 (s, CH_3), 7.4 (s, 5 ArH), 10.0 (s, CHO).

Preparation of 2-Methyl-3,6-diphenyl-4-thia-6-oxo-2-hexenal, 12. A 33-mmol amount of phenacylmercaptan, prepared according to the literature,[27] and 27 mmol of **11** were dissolved in 28 mL of freshly distilled dry pyridine. The resulting solution was cooled to 15 °C and 4.05 g of triethylamine was added at such a rate so as to maintain the temperature at 15–20 °C. Thereafter the solution was allowed to stand at 25 °C for 1 h. A 10-mL

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amount of 48% KOH was added dropwise while cooling the stirred mixture. The resulting mixture was diluted with 300 mL of water and the white precipitate was collected by filtration. **12** was obtained (25.3 mmol, 94%: mp 124–125 °C (EtOH); TLC (5:1.5) R_f 0.46; MS, m/e 296 (M^+), 278, 268, 177, 176, 148, 115, 105 (base peak), 77; IR 1675, 1650 cm^{-1}; ^1H NMR δ 2.08 (s, CH_3), 3.82 (s, CH_2Ph), 9.22 (CHO); ^{13}C NMR δ 12.5, 38.8, 190.1, 193.6.

Preparation of 2-Phenyl-3-methyl-5-benzoylthiophene, 13. A 15.3-mmol quantity of **12** was heated in refluxing glacial acetic acid solution for 0.5 h. Thereafter eight drops of concentrated HCl was added and the solution heated again to reflux for 0.5 h. Cooling to room temperature resulted in the formation of a 15.2-mmol (99%) quantity of crystalline **13**: mp 104–105 °C (EtOH); TLC R_f 0.54; MS, m/e 278 (M^+), 201 (base peak), 171, 129, 115, 105, 77, IR 1625 cm^{-1}; ^1H NMR δ 2.35 (s, CH_3). Anal. Calcd for $C_{18}H_{14}OS$: C, 77.66; H, 5.07; S, 11.52. Found: C, 77.62; H, 5.11; S, 11.35.

Preparation of 2-Phenyl-3-(hydroxymethyl)-5-benzoylthiophene, 15. A 2.014-mmol quantity of **13** and 2.022 mmol of freshly recrystallized and dried *N*-bromosuccinimide were dissolved in 25 mL of CCl_4 distilled from P_2O_5. The resulting solution was irradiated 2 h, was cooled, and then filtered. The solvent was removed by evaporation at reduced pressures and the residue was dissolved in 6 mL of acetone. To the resulting solution was added 3.02 mmol of silver nitrate in 5 mL of water with vigorous stirring. The resulting mixture was stirred at 25 °C for 1 h and then filtered. The acetone was removed from the filtrate with the rotary evaporator, and additional water was added to the residue and then CH_2Cl_2. The CH_2Cl_2 layer was washed with water and then dried. The solvent was removed with the rotary evaporator to obtain 716 g of a tan semisolid of which 45 mg was purified by flash chromatography (silica gel, PE–EtOAc 4:1) to obtain 0.11 mmol (87%) of semisolid **15**: TLC (3:1) R_f 0.15; MS, m/e (M^+) (base peak), 277, 265, 217, 189, 128, 115, 105, 77; IR 3600, 3480–3300, 1760 cm^{-1}; ^1H NMR δ 4.62 (s, CH_2O).

Preparation of 2-Phenyl-5-benzoyl-3-thiophenecarboxylic Acid, 16. An 0.11-mmol amount of alcohol **15** in 2 mL of acetone was treated with 0.2 mL of 3.2 mM chromic acid in sulfuric acid–water at 0 °C and under N_2. After stirring at 0 °C for 5 min, the mixture was allowed to come to 25 °C over a period of 15 min. Isopropyl alcohol was added to destroy excess chromic acid and acetone was removed with the rotary evaporator. Water was added to dissolve the salts and the mixture was extracted with ether. The combined ether extracts were washed with aqueous sodium bicarbonate. The bicarbonate solution was acidified and the resulting white floculent precipitate was taken up in CH_2Cl_2. After drying the solution, the solvent was removed with the rotary evaporator to obtain 0.075 mmol (68%) of crystalline **16**: TLC (2:1) R_f 0.41; MS, m/e 308 (M^+) (base peak), 263, 231, 115, 105, 77; IR 3500–2500, 1690 cm^{-1}; ^1H NMR δ 7.8–8.0 (ArH). When **16** was heated in a melting point tube, it contracted at 197 °C and began to darken and decompose at 205 °C.

Preparation of 2-Phenyl-5-benzyl-3-thiophenecarboxylic Acid, 10. According to the literature,[28] 0.089 mmol of **16** was dissolved in 5 mL of concentrated NH_4OH. To the solution was added 70 mg of zinc dust and a catalytic amount of $CuSO_4$. The vigorously stirred mixture was heated to reflux under N_2 for 4 h. Thereafter and at subsequent 8-h intervals over a period of 2 days additional 2-mL amounts of concentrated NH_4OH and 50-mg quantities of zinc dust were added. The mixture was cooled and filtered, and the filtrate was acidified with concentrated H_2SO_4. The floculent white solid was collected by filtration then dissolved in 2 mL of glacial acetic acid. A 250-mg quantity of zinc powder was added and the vigorously stirred mixture was heated to reflux overnight. The solids were removed by filtration, the filtrate was diluted with water, and the resulting solid was collected by filtration. Obtained after drying at 25 °C and recrystallization from EtOH–water was 0.041 mmol (46%) of **10**: mp 158–159 °C; mp (admixed with **10** originating from cinnamaldehyde) 157–158 °C; TLC (2:1) R_f 0.52; MS, m/e 294 (M^+), 249 (base peak), 217, 171, 121, 115, 91, 77; IR 3500–2500, 1690 cm^{-1}. The spectrum was superimposable with the spectrum from **10** originating from cinnamaldehyde. Anal. Calcd for $C_{18}H_{14}O_2S$: C, 73.44; H, 4.79; S, 10.89. Found: C, 73.27; H, 4.88; S, 10.77.

Conversion of Phenyl Vinyl Ketone, 20, to Thiolane 27 and Thiophene 28. The addition of a 14.4-mmol quantity of **20** to 22.5 mmol of $Na_2S{\cdot}9H_2O$ and 250 mmol of sulfur in 30 mL of 95% ethanol resulted in the warming of the flask and the gradual change to a rust color. After stirring 24 h the resulting mixture was allowed to stand for an additional 24 h, and ethanol was removed with the rotary evaporator. The residue was treated according to the normal procedure[2] to obtain 2.2 g of a dark red gum of which 90 mg when rectified first by medium-pressure HPLC (silica gel 60, $CHCl_2$–10% EtOH) and then by HPLC (Whatman Partisil M 9, PE–EtOAc, 4:1) yielded 10 mg (5.8%) of **27**: mp 106–108 °C; TLC (4:1) R_f 0.44; MS, m/e 296 (M^+), 191, 107, 105 (base peak), 77; IR 1686 cm^{-1}; ^{13}C NMR δ 35.2 (t), 35.5 (t), 48.4 (d), 50.4 (d), 196.7 (s), 199.6 (s). Anal. Calcd for $C_{18}H_{16}O_2S$: C, 72.94; H, 5.44. Found: C, 72.68, H, 5.20.

Also obtained by HPLC was 20 mg of **28**: mp 82–83 °C; TLC (4:1) R_f 0.37; MS, m/e 292 (M^+) (base peak), 215, 187, 115, 105, 77; IR 1630 cm^{-1}; ϵ_{252} (EtOH) 30 000; ^{13}C NMR δ 188.2, 189.7, 128–145.

Treatment of 1-Phenyl-2-buten-1-one, 18, with Polysulfide. The treatment of 11 mmol of **18** with 17 mmol of $Na_2S{\cdot}9H_2O$ and 189 mmol of sulfur in 23 mL of 95% ethanol according to the usual procedure,[2] followed by the normal workup, gave 1.84 g of dark brown oil whose MS showed m/e 324 and whose ^1H NMR showed resonance in the δ 3.0–4.7 region.

Treatment of 1-Phenyl-2-methylpropenone, 22, with Polysulfide. From 20.5 mmol of **22**, 32 mmol of $Na_2S{\cdot}9H_2O$, and 356 mmol of sulfur in 43 mL of 95% ethanol was obtained 3.42 g of green oil whose MS showed peaks at m/e 358 and 390. ^1H NMR δ 1.20 (d, J = 7.5 Hz, CH_3) and 1.23 (d, J = 5 Hz, CH_3).

Treatment of 1,2-Diphenylpropenone, 21, with Polysulfide. From 10 mmol of **21**, 15.6 mmol of $Na_2S{\cdot}9H_2O$, and 188 mmol of sulfur in 14 mL of 95% ethanol was obtained 2.48 g of viscous red oil. Medium-pressure chromatography on silica gel 60 (PE–EtOAc, 5:1) gave 57 mg of yellow oil, which on HPLC gave **23** (n = 2): MS, m/e 482 (M^+); ^1H NMR δ 5.0 (two overlapping dd, J = 14, 6 Hz and J = 9, 6 Hz), also 2.8–4.4.

Preparation of 2,4-Dibenzoylthiophene, 28, from Thiophene-3-carboxaldehyde. According to the method of Campaigne and Thomas,[29] thiophene-3-carboxaldehyde was converted to its oxime which in turn was dehydrated with acetic anhydride to give 3-cyanothiophene. This nitrile was treated with phenylmagnesium bromide to obtain 3-benzoylthiophene. A 5.3-mmol sample of the ketone was heated at 105 °C under nitrogen for 19 h with an equimolar amount of benzoyl chloride and 13 mmol of aluminum chloride. The solid mass resulting upon cooling was broken into small pieces which were stirred with dilute aqueous hydrochloric acid and ether. The ether layer was removed, washed successively with water, dilute aqueous sodium bicarbonate, and water, and then dried over anhydrous $MgSO_4$. Upon removal of the ether with the rotary evaporator, a 1.40-g quantity of brown semisolid was obtained, of which an 80-mg portion was chromatographed at medium pressure on silica gel 60 (PE–EtOAc, 4:1) to obtain 62 mg (70%) of **28**: TLC (4:1) R_f 0.38; mp 81–82 °C (EtOH–H_2O); mp admixed with sample originating from phenyl vinyl ketone, 82–83 °C; MS, m/e 292, 215, 187, 105 (base peak), 77; IR 1630 cm^{-1}; ^{13}C NMR δ 188.3, 189.8, and 128–145. Anal. Calcd for $C_{18}H_{12}O_2S$: C, 73.95; H, 4.14; S, 10.97. Found: C, 73.89; H, 4.19; S, 10.90.

Single-Crystal X-ray Analysis of 4. Preliminary X-ray photographs showed only monoclinic symmetry and accurate lattice constants of a = 9.973 (3) Å, b = 11.561 (3) Å, c = 13.063 (4) Å, α = 77.65 (2), β = 77.83 (2), and γ = 64.49 (3)° were determined from a least-squares fit of fifteen diffractometer measured 2θ values. A crystal density indicated that two molecules of composition $C_{32}H_{28}O_4S_1$ formed the unit cell. The space group was assumed to be $P\bar{1}$ and the successful solution and refinement validate this choice. All unique diffraction maxima with $20° \leq 114°$ were surveyed on a computer controlled diffractometer using a variable speed, 1° ω-scan and graphite monochromated Cu K$\bar{\alpha}$ X-rays (1.54178 Å). After correction for Lorentz, polarization, and background effects, 3254 of the 3806 reflections were judged

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observed ($|F_0| \geq 3\sigma(F_0)$). A multisolution sign-determining procedure revealed all of the non-hydrogen atoms uneventfully.[30] All hydrogens were located in a subsequent difference electron density synthesis. Block-diagonal least-square refinements with anisotropic non-hydrogen atoms and isotropic hydrogens have converged to a conventional R of 0.059 for the observed reflections.

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Additional crystallographic details are available and are described in the paragraph at the end of this paper on Supplementary Material.

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Registry No. **3**, 6948-61-4; **4**, 92670-41-2; **5**, 94-41-7; **6**, 92670-42-3; **7**, 104-55-2; **8**, 92670-43-4; **9**, 92670-44-5; **10**, 92670-45-6; **11**, 35811-93-9; **12**, 92670-47-8; **13**, 92670-48-9; **15**, 92670-49-0; **16**, 92670-50-3; **17**, 122-57-6; **18**, 495-41-0; **19**, 538-44-3; **20**, 768-03-6; **21**, 4452-11-3; **22**, 769-60-8; **23** (n = 2), 92670-52-5; **25**, 92760-85-5; **26**, 92670-46-7; **27**, 92670-51-4; **28**, 50460-02-1; $C_6H_5COCH_2SH$, 2462-02-4; propiophenone, 93-55-0; thiophene-3-carboxaldehyde, 498-62-4; sodium polysulfide, 1344-08-7.

Supplementary Material Available: Tables of fractional coordinates, thermal parameters, bond distances, and bond angles for compound 1 (6 pages). Ordering information is given on any current masthead page.

dl-Isoserine and Related Compounds

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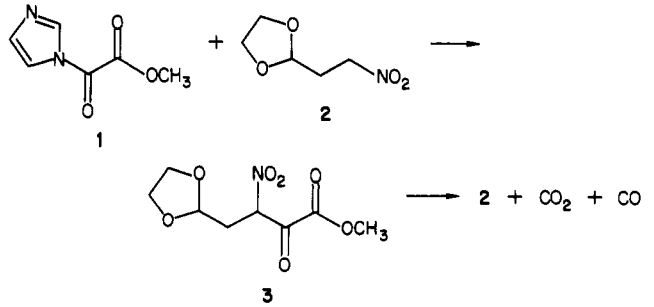
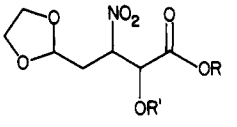
Syntheses of *dl*-isoserine (3-amino-2-hydroxypropanoic acid, **7**) and further functionalized derivatives are described. Reaction of glyoxylic acid with nitromethane gives the known 2-hydroxy-3-nitropropanoic acid (**8**), which upon hydrogenolysis affords *dl*-isoserine in high yield. The comparable nitro-aldol reaction of 3-nitropropanal ethylene acetal (**2**) with glyoxylic acid produces 2-hydroxy-3-nitro-5-oxopentanoic acid ethylene acetal (**4a**) as a mixture of erythro and threo isomers. The methyl esters of hydroxy acid **4a** are chromatographically separable as the *tert*-butyldimethylsilyl ethers. Catalytic reduction (Pd/C) of these nitro compounds gives the corresponding methyl 3-amino-2-hydroxy-5-oxopentanoate ethylene acetals **9**. Ethyl 2-hydroxy-3-phthalimidopropanoate (**22**) and ethyl 2-oxo-3-phthalimidopropanoate (**23**) were also prepared along with several other N-protected β-amino-α-oxy esters related to isoserine.

Nitrocarbonyl compounds are useful intermediates in the synthesis of polyfunctional compounds.[1] An α-nitro ketone with protected aldehyde and carboxylic acid functions having structure **3** was synthesized[2] as a possible intermediate in a projected convergent synthesis of tetrodotoxin.[3,4] However, the esters of this tetrafunctionalized compound could not be converted to the free acid nor would they undergo transesterification reactions; acid or base catalysis resulted in regeneration of 3-nitropropanal ethylene acetal (**2**) with concommitant gas evolution (presumably carbon dioxide and carbon monoxide).



A key feature of structure **3** is the double activation of position 3 to aldol-type condensations by virtue of the carbonyl adjacent to the nitro group. Presumably this double activation accounts for its great sensitivity and requires modification. Obvious alternatives were to retain the 3-nitro group as represented by **4** or the 2-oxo group as represented by **5**.



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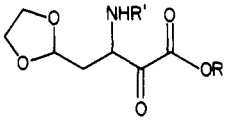

5

This paper deals with the results from studies directed at the syntheses of **4** and **5**, which diverged somewhat from the original goals, becoming interrelated with previous work on the synthesis of the amino acid isoserine and related compounds.

L-Isoserine (3-amino-2-hydroxypropanoic acid, **7**) is a biologically active β-amino acid[5] and a constituent of the pentapeptide antibiotic edeine.[6] Chemically modified butirosin, in which isoserine replaces 4-amino-2-hydroxybutanoic acid, exhibits enhanced antibiotic activity.[7]

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