

Stereospecific Formation of a Vinyl Sulphide *via* a Sulphonium Ylide–Salt Coupling Reaction †

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The identification of tetramethyl 1-(methylthio)hexa-1,5-diene-2,3,4,5-tetracarboxylate (X), formed in low yield during attempted oxidation of dimethyl α -(bromomethyl)fumarate (IV) by dimethyl sulphoxide in the presence of a weak base, is described. It is shown that the production of the vinyl sulphide (X) under these conditions takes place *via* the intermediate (2,3-bismethoxycarbonylprop-2-enyl)dimethylsulphonium bromide (XIV), which undergoes a stereospecific Michael addition reaction with the derived sulphonium ylide (XX).

RECENT contributions² from this and another laboratory demonstrated that hydroxy- and methoxy-butenolides (I) could be utilized successfully in Wittig olefinations. As an extension of these investigations, the preparation of the methoxybutenolide (II), as a possible intermediate in the synthesis of a series of cross-conjugated diesters (III) by the Wittig condensation, was investigated.

During one of our efforts to synthesize the methoxybutenolide (II), oxidation of dimethyl α -(bromomethyl)fumarate (IV) with dimethyl sulphoxide³ was attempted under various conditions. However, heating the bromo-ester (IV) in an excess of Me₂SO without the addition of base led to the formation of a mixture of products from which the crystalline butenolide (V)⁴ (30%) and a small quantity of the hydroxy-ester (VI) were separated, but no methoxybutenolide (II) was detected. Although the formation of the related butenolide (VII), by heating the corresponding bromo-ester (IV), has been reported⁵ before, we believe that the ready transformation of dimethyl α -(bromomethyl)fumarate (IV) into the butenolide (V) in Me₂SO took place *via* the intermediate formation of the alkoxysulphonium salt (VIII). Displacement of Me₂SO from the sulphonium ion (VIII), due to nucleophilic attack by water at the γ -carbon atom, could furthermore account for the formation of the hydroxy-ester (VI). The isolation of the alkoxysulphonium salt (VIII) as its crystalline tetraphenylborate (IX) in low yield from the reaction mixture can be regarded as additional evidence in favour of these assumptions.^{3,6}

Longer reaction times (24 h) and lower temperatures (60°) led to a substantial increase in the yield of the butenolide (V) (50%), with the concomitant crystallization in high yield of trimethylsulphonium bromide from the reaction mixture.

Attempted oxidation of the bromo-ester (IV) with

† A preliminary account of a part of this work was published jointly with Baldwin and Walker.¹ This paper describes details of our independent investigations.

¹ J. E. Baldwin, J. A. Walker, A. J. H. Labuschagne, and D. F. Schneider, *Chem. Comm.*, 1971, 1382.

² (a) G. Pattenden, B. C. L. Weedon, C. F. Garbers, D. F. Schneider, and J. P. van der Merwe, *Chem. Comm.*, 1965, 347; (b) C. F. Garbers, D. F. Schneider, and J. P. van der Merwe, *J. Chem. Soc. (C)*, 1968, 1982; (c) G. Pattenden and B. C. L. Weedon, *ibid.*, p. 1984.

³ W. W. Epstein and F. W. Sweat, *Chem. Rev.*, 1967, **67**, 247.

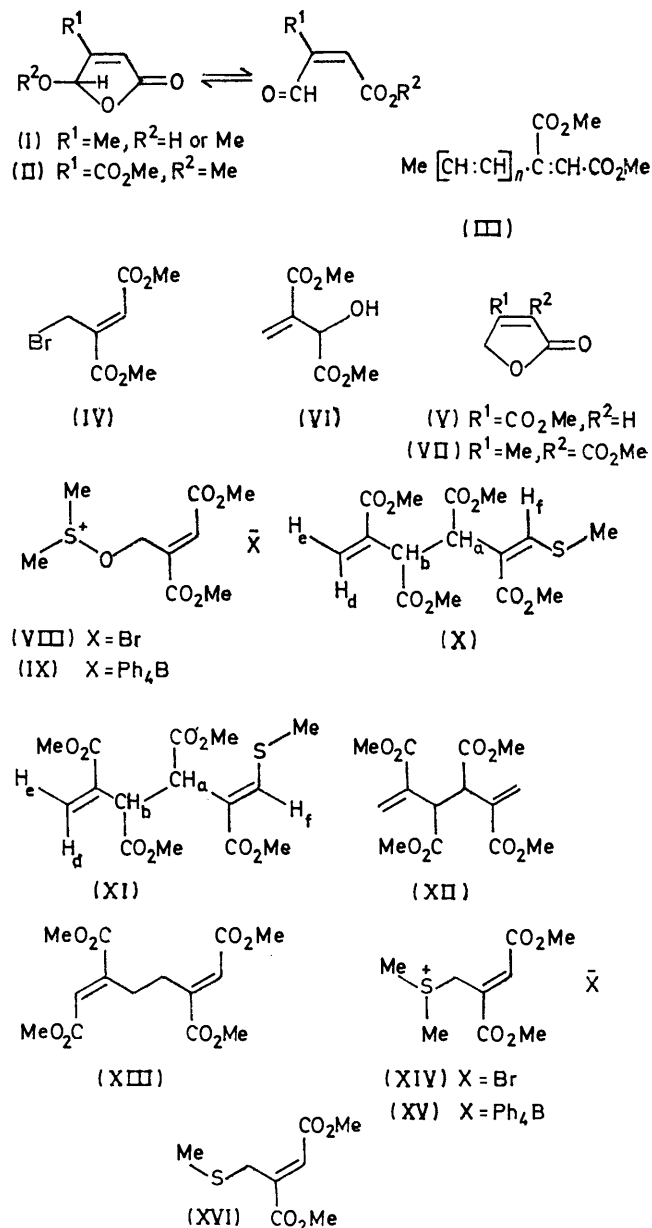
⁴ N. R. Campbell and J. H. Hunt, *J. Chem. Soc.*, 1947, 1176.

⁵ W. Haefliger and T. Petrzilka, *Helv. Chim. Acta*, 1966, **49**, 1937.

⁶ K. Torssell, *Acta Chem. Scand.*, 1967, **21**, 1.

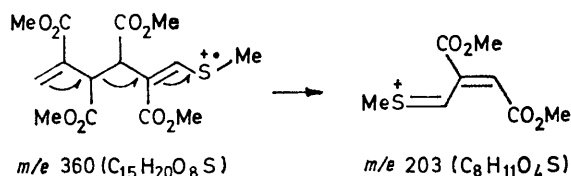
⁷ N. Kornblum, W. J. Jones, and G. J. Anderson, *J. Amer. Chem. Soc.*, 1959, **81**, 4113.

Me₂SO in the presence of sodium hydrogen carbonate⁷ again did not give the methoxybutenolide (II), but a crystalline compound was produced in low yield to



which the vinyl sulphide structure (X) was ascribed on the basis of physical and chemical evidence. The u.v.

spectrum could be interpreted as a combination of two chromophores, an α -alkylacrylic ester, λ_{\max} 207 nm (ϵ



8127),⁸ and an α -alkyl- β -alkylthio- $\alpha\beta$ -unsaturated carbonyl system, λ_{\max} 295 nm (ϵ 13,350).⁹ High resolution mass spectrometry established the molecular formula and the composition of the base peak (m/e 203), which resulted from γ -fission of the molecular ion (m/e 360). The 1H n.m.r. spectrum exhibited four methoxycarbonyl groups in two environments (δ 3.60 and 3.78), a methylthio-group (δ 2.39), three olefinic protons [δ 5.88 (H_d), 6.38 (H_e), and 7.23 (H_f)], and an AB quartet centred at δ 4.24 [δ_{H_a} 4.29, δ_{H_b} 4.19 (calc.¹⁰)].

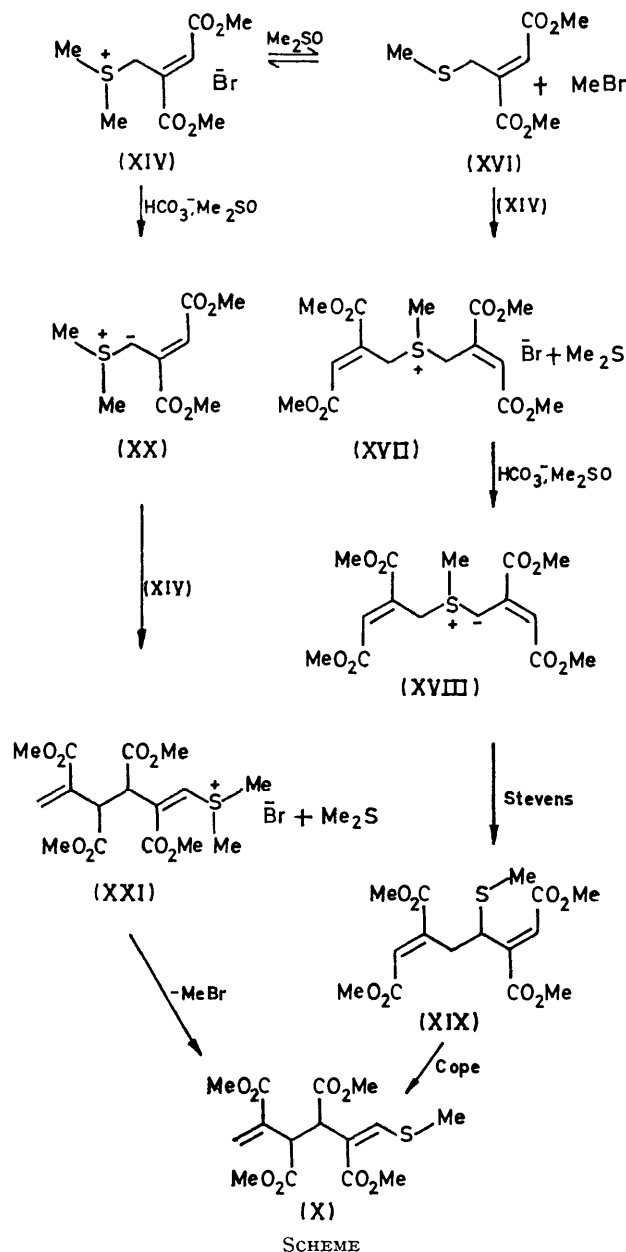
Thermolysis (200°; 14 h) of the vinyl sulphide (X) in a sealed tube under nitrogen produced a mixture from which unchanged starting material and a small quantity of an isomer [λ_{\max} 207 and 286 nm (ϵ 7450 and 15,670)] were separated by chromatography on silica gel and repeated fractional crystallization. Comparison of the 1H n.m.r. data for this isomer with those of the vinyl sulphide (X) revealed that the signals due to the vinylic proton at C-6 (H_f) and H_a were shifted to lower field [δ_{H_f} 7.71, δ_{H_a} 4.65 (calc.¹⁰)], and the methylthio-group was also more deshielded (δ 2.48). These spectral differences could readily be accounted for by assuming that the isomers were the *E*- and *Z*-vinyl sulphides (XI) and (X), respectively. The observed stereomutation could have resulted from a double Cope rearrangement,¹ although, in view of the drastic reaction conditions, a thermally induced geometric isomerization without rearrangement cannot be ruled out.

Further proof of structure (X) was provided by mild desulphurization with Raney nickel, which produced the crystalline tetraester (XII) as the major cleavage product together with a small quantity of the tetraester (XIII), probably formed from a Cope rearrangement of compound (XII).

With regard to the mode of formation of the vinyl sulphide (X), we considered that the sulphonium bromide (XIV) was likely to be the key intermediate. To account for the formation of this salt (XIV) the generation of dimethyl sulphide in low yield *via* oxidation of the bromo-ester (IV) by Me_2SO is assumed. The isolation of the alkoxy-sulphonium salt (IX) is in accord with this assumption; several investigators have previously demonstrated that oxidation of bromomethyl compounds with Me_2SO proceeds *via* intermediate alkoxy-sulphonium salts.^{3,6}

Treatment of a pure sample of the sulphonium salt (XIV) with sodium hydrogen carbonate in Me_2SO in fact produced the vinyl sulphide (X) in 83% yield, but when 1 mol. equiv. of sulphide (XVI) or bromo-ester (IV)

was initially added to a similar reaction mixture, the weight of vinyl sulphide (X) obtained was increased by 50%. Furthermore, when the bromo-ester (IV) was treated with 1 mol. equiv. of dimethyl sulphide in Me_2SO in the presence of sodium hydrogen carbonate, the vinyl sulphide (X) was formed in 41% yield, but on the initial addition of 1 mol. equiv. of sulphide (XVI) to the same reaction mixture, the vinyl sulphide was produced in 60% yield. The sulphide (XVI) was synthesized in



high yield in a clean reaction by heating the sulphonium salt (XIV) or the bromo-ester (IV) directly with an excess of dimethyl sulphide.

⁹ H. Hermann and W. Lüttke, *Chem. Ber.*, 1971, **104**, 492.

¹⁰ R. H. Bible, 'Interpretation of N.M.R. Spectra,' Plenum Press, New York, 1965, p. 83.

⁸ A. I. Scott, 'Interpretation of the Ultraviolet Spectra of Natural Products,' MacMillan, London, 1964, p. 242.

The foregoing results, associated with the transformation of the sulphonium salt (XIV) into the vinyl sulphide (X), can be accommodated by a mechanism which proceeds *via* formation of the sulphonium salt (XVII) (Scheme), deprotonation, Stevens rearrangement of the resulting ylide (XVIII), and a Cope rearrangement of the sulphide (XIX). Formation of the vinyl sulphide (X) can also be rationalized as being the result of a stereospecific Michael addition of the ylide (XX) to the sulphonium bromide (XIV), followed by elimination of dimethyl sulphide and demethylation of the resulting salt (XXI) by bromide ion¹ (Scheme). The latter mode of formation can also account for the foregoing observations and, furthermore, appears to be strongly favoured by additional results.¹ Although further investigations¹¹ in this laboratory showed that related coupling reactions did in fact proceed *via* the intermediate sulphonium salt (XVII), rearrangement of the ylide (XVIII) did not lead to the generation of the vinyl sulphide (X). These results indirectly support the sulphonium ylide-salt pathway¹ for the formation of the vinyl sulphide (X).

EXPERIMENTAL

U.v. spectra were recorded for solutions in 96% ethanol with a Unicam SP 800 spectrophotometer; all quantitative measurements were obtained with a Zeiss PMQ 11 instrument. I.r. and mass spectra were determined with a Unicam SP 200 spectrophotometer and an A.E.I. MS 902 spectrometer, respectively. ¹H N.m.r. spectra were, unless otherwise indicated, recorded for solutions in [²H]chloroform with a Varian HA-60IL spectrometer and tetramethylsilane as internal standard.

Combustion analyses were performed by Dr. F. Pascher, Bonn, Germany; petroleum refers to the fraction of b.p. 40–60°. All operations were, as far as possible, carried out in a nitrogen atmosphere. Silica gel (0.05–0.2 mm; Merck) was used for column chromatography.

3-Methoxycarbonylbut-2-enolide (V) and Dimethyl 2-Hydroxy-3-methylenesuccinate (VI).—Dimethyl α -(bromomethyl)fumarate (IV) (9.48 g, 40 mmol) in Me₂SO (64 ml) was heated for 30 min at 100°. The mixture was cooled (room temp.), poured into an excess of water (200 ml), and repeatedly extracted with ether. The combined extracts were washed with water and dried (Na₂SO₄). On cooling (–15°) the residue from the ether extracts, the *butenolide* (V) (1.65 g, 29%) crystallized from the oily mixture; m.p. 83° (from ether) (lit.,⁴ 82°), ν_{\max} (CHCl₃) 1780 (C=O, ester), 1750 and 1740 (C=O, lactone), and 1640 (C=C) cm⁻¹, δ 6.70 (1H, t, *J* 2 Hz), 5.01 (2H, d, *J* 2 Hz), and 3.90 (3H, s), *m/e* 142 (*M*⁺) (Found: C, 51.0; H, 4.2. Calc. for C₆H₆O₄: C, 50.7; H, 4.25%).

Chromatography of the residual oil yielded the *alcohol* (VI) (0.63 g, 9%), eluted with ether-petroleum (4:1); b.p. 75–80° (air-bath temp.) at 0.05 mmHg, ν_{\max} (film) 3520 (OH), 1725 (C=O), and 1640 (C=C) cm⁻¹, δ 6.40 (1H, d, *J* 1 Hz), 5.96 (1H, d, *J* 1 Hz), 4.92 (1H, d, *J* 6.5 Hz), 3.80 (6H, s), and 3.48 (1H, d, *J* 6.5 Hz) (Found: C, 47.8; H, 5.85. C₇H₁₀O₅ requires C, 48.25; H, 5.8%).

* Despite several crystallizations from various solvents this salt did not give satisfactory analytical data owing to the presence of small quantities of coprecipitated sodium tetraphenylborate.

When a similar reaction mixture was heated for 24 h at 60°, the *butenolide* (V) was isolated in 50% yield.

(2,3-Bismethoxycarbonylprop-2-enyloxy)dimethylsulphonium Tetraphenylborate (IX).—A solution of dimethyl α -(bromomethyl)fumarate (IV) (4.8 g, 20 mmol) in Me₂SO (11 g, 140 mmol) was stirred for 5 h at room temp. An ice-cold solution of sodium tetraphenylborate (6.8 g, 20 mmol) in methanol-water (1:1) (60 ml) was then added dropwise to the stirred mixture during 15 min. Stirring was continued for a further 15 min and the resultant pale green precipitate was collected at the pump and washed with ice-cold methanol-ether (1:1). Recrystallization from methyl acetate gave the alkoxysulphonium tetraphenylborate (IX) (0.5 g, 8%), m.p. 146–147°, ν_{\max} (Nujol) 1710 (C=O), 1642, and 1580 (C=C) cm⁻¹, δ [(CD₃)₂SO] 7.40–6.60 (*ca.* 21H, m), 4.52 (2H, s), 3.76 (3H, s), 3.74 (3H, s), and 2.89 (6H, s).*

(Z)-Tetramethyl 1-(Methylthio)hexa-1,5-diene-2,3,4,5-tetracarboxylate (X).—Anhydrous sodium hydrogen carbonate (1.0 g) was added to a solution of dimethyl α -(bromomethyl)fumarate (IV) (2.37 g, 10 mmol) in Me₂SO (4.70 g, 60 mmol) and the stirred suspension was heated for 1.5 h at 80–90°. The cooled (room temp.) mixture was then added to an excess of water (20 ml) and the aqueous solution was repeatedly extracted with ether. Chromatography of the residue (0.94 g) from the combined extracts gave the *vinyl sulphide* (X) (100 mg) on elution with ether-petroleum (4:1); m.p. 113° (from ether), λ_{\max} 207 and 295 nm (ϵ 8127 and 13,350), ν_{\max} (CHCl₃) 1738 (C=O), 1638, and 1570 (C=C) cm⁻¹, δ 7.23 (1H, s), 6.38 (1H, s), 5.88 (1H, s), 4.24 [2H, ABq, *J*_{AB} 11 Hz, δ_{H_a} 4.29 and δ_{H_b} 4.19 (calc.¹⁰)], 3.78 (6H, s), 3.60 (6H, s), and 2.39 (3H, s), *m/e* 360.0896 (*M*⁺, 31%). C₁₅H₂₀O₈S requires *M*, 360.0879 and 203.0389 (*M*⁺ – C₇H₉O₄, 100%. C₈H₁₁O₄S requires 203.0378) (Found: C, 50.1; H, 5.55. Required: C, 50.0; H, 5.6%).

(E)-Tetramethyl 1-(Methylthio)hexa-1,5-diene-2,3,4,5-tetracarboxylate (XI).—The (Z)-vinyl sulphide (X) (1.6 g) was heated in a sealed tube for 14 h at 200° and the product was chromatographed to yield the (E)-*vinyl sulphide* (XI) (80 mg, 5%) after elution with ether-petroleum (1:1); m.p. 78° (from ether), λ_{\max} 207 and 286 nm (ϵ 7450 and 15,670), δ 7.71 (1H, s), 6.38 (1H, s), 5.92 (1H, s), 4.42 [2H, ABq, *J*_{AB} 11 Hz, δ_{H_a} 4.65 and δ_{H_b} 4.18 (calc.¹⁰)], 3.77 (3H, s), 3.72 (3H, s), 3.58 (3H, s), 3.56 (3H, s), and 2.48 (3H, s), *m/e* 360.0886 (*M*⁺, C₁₅H₂₀O₈S requires 360.0879) (Found: C, 50.0; H, 5.75; S, 9.05. Required: C, 50.0; H, 5.6; S, 8.9%).

Desulphurization of the (Z)-Vinyl Sulphide (X).¹²—The vinyl sulphide (X) (0.6 g) was added at room temp. to a stirred suspension of Raney nickel (*ca.* 1 g) in methanol (4 ml). After 3.5 h at room temp. the initial u.v. absorption maximum at 295 nm had completely disappeared. The mixture was filtered and the oily residue from the filtrate separated by preparative t.l.c. on silica gel GF₂₅₄ with ether-petroleum (1:1) as mobile phase to yield *tetramethyl hexa-1,5-diene-2,3,4,5-tetracarboxylate* (XII) (60 mg, 10%), m.p. 114° (from ether), λ_{\max} 212.5 nm (ϵ 7710), δ 6.41 (2H, s), 5.89 (2H, s), 4.28 (2H, s), 3.80 (6H, s), and 3.62 (6H, s), *m/e* 314.1001 (*M*⁺, C₁₄H₁₈O₈ requires *M*, 314.1002) (Found: C, 53.4; H, 5.85. Required: C, 53.5; H, 5.8%), and *tetramethyl hexa-1,5-diene-1,2,5,6-tetracarboxylate* (XIII) (25 mg, 4%), m.p. 58° (from ether-petroleum), λ_{\max} 221 nm (ϵ 20,550), δ 6.77 (2H, s), 3.82 (6H, s), 3.72 (6H, s), and 3.09 (4H, s), *m/e* 314.0991 (*M*⁺) (Found: C, 53.6; H, 5.8%).

¹¹ C. J. Meyer and D. F. Schneider, unpublished results.

¹² (a) G. R. Pettit and E. E. van Tamelen, *Org. Reactions*, 1962, **12**, 356; (b) L. F. Fieser and M. Fieser, 'Reagents for Organic Synthesis,' Wiley, New York, 1967, p. 729.

(2,3-Bismethoxycarbonylprop-2-enyl)dimethylsulphonium Bromide (XIV) and Tetraphenylborate (XV).—A solution of dimethyl α -(bromomethyl)fumarate (IV) (5.95 g, 25 mmol) and dimethyl sulphide (1.7 g, 27 mmol) in acetone (8 ml) was left for 20 h at room temp. The resulting suspension was filtered at the pump; the hygroscopic sulphonium salt (XIV) (5.4 g, 72%) was washed with acetone-ether (1 : 1) and dried at 0.5 mmHg. To a stirred solution of sodium tetraphenylborate (1.1 g, 3.3 mmol) in ice-cold methanol-water (1 : 1; 10 ml) the solid sulphonium bromide (XIV) (1.0 g, 3.3 mmol) was added in small portions. After 5 min the resulting yellow crystals were collected at the pump, washed with ice-cold methanol-water (1 : 1), and recrystallized from acetone to yield the tetraphenylborate (XV), m.p. 156°, ν_{\max} (KBr) 1710 (C=O), 1640, and 1580 (C=C) cm^{-1} , δ [(CD₃)₂CO] 7.55–6.75 (2H, m), 4.43 (2H, s), 3.79 (3H, s), 3.77 (3H, s), and 2.62 (6H, s) (Found: C, 73.55; H, 6.35; S, 6.4. C₃₃H₃₅BO₄S requires C, 73.6; H, 6.35; S, 5.95%).

(Z)-Tetramethyl 1-(Methylthio)hexa-1,5-diene-2,3,4,5-tetracarboxylate (X) from the Sulphonium Bromide (XIV).—A mixture of the sulphonium salt (XIV) (1.5 g, 5 mmol), Me₂SO (5 g), and anhydrous sodium hydrogen carbonate (1 g) was stirred for 90 min at room temp. and then heated for 90 min at 60°. The cooled (room temp.) mixture was poured into an excess of water (20 ml) and worked up as before. Recrystallization of the residue from the ether extracts gave the pure vinyl sulphide (X) (0.75 g, 83%), m.p. 113° (from ether).

When a similar reaction mixture was initially treated with dimethyl α -(bromomethyl)fumarate (IV) (1.2 g, 5 mmol) or dimethyl α -(methylthiomethyl)fumarate (XVI) (1.0 g, 5 mmol), an increased yield of vinyl sulphide (X) (1.1 g) was obtained under the same reaction conditions.

Dimethyl α -(Methylthiomethyl)fumarate (XVI).—A mixture of dimethyl α -(bromomethyl)fumarate (IV) (25 g, 0.105 mol) and dimethyl sulphide (32.8 g, 0.527 mol) was heated for 12 h at 60° in a pressure vessel. The resultant

trimethylsulphonium bromide was filtered off and washed with acetone-ether (1 : 1) to give the essentially pure salt (14 g, 84.5%), m.p. 198° (from acetone-methanol) (lit.¹³ 195°), δ (D₂O) 2.97 (9H, s) (Found: C, 23.15; H, 6.15. Calc. for C₃H₉BrS: C, 22.95; H, 5.75%). Distillation of the residue from the filtrate yielded the sulphide (XVI) (17 g, 79%), b.p. 86° at 0.6 mmHg, λ_{\max} 223 nm (ϵ 10,900), ν_{\max} 1725 (C=O) and 1645 (C=C) cm^{-1} , δ 6.75 (1H, s), 3.92 (2H, s), 3.84 (3H, s), 3.77 (3H, s), and 2.02 (3H, s), m/e 204.0473 (M^+ . C₈H₁₀O₄S requires M , 204.0456) (Found: C, 47.05; H, 5.9; S, 15.4. Required: C, 47.05; H, 5.9; S, 15.65%).

When a mixture of the sulphonium bromide (XIV) (12 g, 0.04 mol), dimethyl sulphide (19 g, 0.3 mol), and Me₂SO (19 g) was heated for 5 h at 60° in a pressure vessel, both the sulphide (XVI) and trimethylsulphonium bromide were produced as pure compounds in 100% yield.

Synthesis of the (Z)-Vinyl Sulphide (X) from Dimethyl α -(Bromomethyl)fumarate (IV) and Dimethyl Sulphide.—A mixture of the bromo-ester (IV) (2.4 g, 9.8 mmol), dimethyl sulphide (0.7 g, 11.3 mmol), Me₂SO (23 g), and sodium hydrogen carbonate (2 g, 24 mmol) was stirred for 5 h at room temp. in a stoppered flask. The mixture was worked-up in the usual way; recrystallization of the residue from the ether extracts produced the vinyl sulphide (X) (1.5 g, 41%). When the sulphide (XVI) (2 g, 9.79 mmol) was initially added to a similar reaction mixture, the yield of vinyl sulphide (X) was substantially increased (2.2 g, 60%) under identical conditions.

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¹³ P. Mamalis, *J. Chem. Soc.*, 1960, 4747.