two crops of **10** (methoxyethyl 1,2-dihydro-3-hydroxy-2-methyl-1,2-benzisothiazole-3-chloroacetate 1,1-dioxide) weighing 2.1 g. The combined yield of crystalline **10** was 65%. This material was recrystallized to a constant melting point from dichloromethane/hexane to yield pure **10**: mp 133–133.5 °C; IR (KBr) 3250, 1754 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.6–8.2 (5 H, m), 5.1 (1 H, s), 4.0 (2 H, m) 3.3 (2 H, m), 3.1 (3 H, s), 2.7 (3 H, s); ^{13}C NMR (Me_2SO-d_6) δ 23.0 (q), 58.1 (q), 60.6 (d), 65.0 (t), 69.2 (t),88.0 (s), 120.4 (d), 126.1 (d), 131.1 (d), 133.3 (d), 134.3 (s), 136.7 (s), 165.8 (s). Anal. Calcd for $C_{13}H_{16}O_6SNCl$: C, 44.64; H, 4.61; N, 4.00; S, 9.17; Cl, 10.14. Found: C, 44.29; H, 4.65; N, 3.98; S, 9.00; Cl, 10.48.

Isolation of the Chlorohydrin 10 (R = OCH_3). In an analogous fashion to the example above, *N*-methylsaccharin (15.7 g, 0.08 mol) and methyl chloroacetate (8.67 g, 0.08 mol) were reacted with NaH (0.20 mol) in THF to yield, after the workup, 21.0 g of an amber oil. NMR and TLC analysis of this oil indicated it to be the desired chlorohydrin **10** (86%) along with traces of *N*-methylsaccharin and the benzothiazine ester **3** (R = OCH_3; see below). Attempts to purify this oil by column chromatography on silica gel led to decomposition. However, when a portion of the crude oil was set aside for several days, a white solid separated from the remaining oil. This material was filtered, washed with isopropyl alcohol, and dried to yield pure **10** (R = OCH_3): mp 122–125 °C; mass spectrum, *m/e* 305, parent; IR (KBr) 3279, 1739 cm^{-1}; ^1H NMR δ 8.1–7.6 (5 H, m), 5.05 (1 H, s), 3.45 (3 H, s), 2.7 (3 H, s). Anal. Calcd for $C_{11}H_{12}O_5NSCl$: C, 43.31; H, 3.96; N, 4.58; S, 10.49; Cl, 11.60. Found: C, 43.10; H, 3.97; N, 4.56; S, 10.49; Cl, 11.62.

Reaction of the Chlorohydrin 10 (R = $OCH_2CH_2OCH_3$) with NaH in THF. To the chlorohydrin **10** (R = OCH_2CH_2O-CH_3; 1.72 g, 0.049 mol) in 10 mL of THF was added 99% NaH (Alpha; 0.12 g, 0.50 mol), and the reaction mixture was stirred at room temperature for 30 min. TLC showed good conversion to *N*-methylsaccharin (**8**). The reaction was then quenched by addition of the mixture to 50 mL of cold 5% HCl, and this was extracted with CH_2Cl_2. GC analysis of this extract showed that 0.41 g of **9** (R = $OCH_2CH_2OCH_3$) was present (54%). The CH_2Cl_2 extract was concentrated and the residue extracted into 5 mL of DMF. This solution was in turn added to cold 5% HCl. Upon filtration, 0.60 g of *N*-methylsaccharin (61%) was isolated.

Reaction of the Chlorohydrin 10 (R = $OCH_2CH_2OCH_3$) with NaOH in H_2O. To the chlorohydrin **10** (R = OCH_2CH_2-OCH_3; 0.65 g, 0.00186 mol) in 10 mL of H_2O was added 1.85 mL of 1 N NaOH solution. After the mixture was stirred for 3 h, TLC showed complete conversion of **10** to *N*-methylsaccharin (**8**). Filtration of the solids after cooling yielded 0.27 g (74%) of *N*-methylsaccharin.

Formation of Methyl 2-Methyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-Dioxide (3, R = OCH_3) from the Chlorohydrin 10 (R = OCH_3). To pentane-washed NaH (50% dispersion; 0.63 g, 0.0013 mol) in 8.0 mL of Me_2SO under an N_2 atmosphere was added a solution of **10** (R = OCH_3; 0.40 g, 0.0013 mol) in 8.0 mL of Me_2SO (dropwise addition over 10 min). The internal temperature rose to 34 °C. The reaction mixture was stirred at this temperature for 1.5 h. TLC showed no starting **10** and a good conversion to the ester **3** (R = OCH_3). Isolation by quenching by addition of the mixture to 80 mL of 5% HCl followed by heating and filtration yielded 0.28 g (80%) of the ester **3**, mp 162–163 °C (lit.[5] mp 162–165 °C). This material was identical in its chromatographic and spectral properties with a sample of **3** (R = OCH_3) made via the procedure of Lombardino.[5]

Formation of Methoxyethyl 2-Methyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-Dioxide (3, R = $OCH_2CH_2OCH_3$) from the Chlorohydrin 10 (R = $OCH_2CH_2OCH_3$). Following the procedure above, the ester **3** (R = $OCH_2CH_2OCH_3$) was isolated: 82% yield; mp 101–105 °C; IR (KBr) 3475, 1680 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.0 (4 H, m), 4.5 (2 H, m), 3.7 (2 H, m), 3.34 (3 H, s), 2.90 (3 H, s). Anal. Calcd for $C_{13}H_{15}O_6NS$: C, 49.83; H, 4.83; N, 4.47; S, 10.23. Found: C, 49.97; H, 4.71; N, 4.48; S, 10.24.

Replacement of Me_2SO by DMF resulted in a 67% isolated yield of **3** (R = $OCH_2CH_2OCH_3$) by using the above conditions.

(5) Lombardino, J. G.; Wiseman, E. H.; McLamore, W. M. *J. Med. Chem.* **1971**, *14*, 1171.

Formation of Methyl 2-Methyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-Dioxide (3, R = OCH_3) from *N*-Methylsaccharin (8) and Methyl Chloroacetate (9, R = OCH_3). To a solution of *N*-methylsaccharin (**8**; 3.0 g, 0.15 mol) and methyl 2-chloroacetate (**9**, R = OCH_3; 9.8 g, 0.09 mol) in 15 mL of Me_2SO (or DMF) at 40 °C was added over 2 h 0.81 g (0.33 mol) of sodium hydride 99% (Alpha). Stirring was continued for an additional 2 h while maintaining a temperature of 40–50 °C. The reaction was then quenched by addition of the mixture described above, and 3.07 g (76%) of the benzothiazine ester **3** (R = OCH_3) was isolated. Comparable results were obtained in the methoxyethyl series.

Control Experiments. Controlled Quenching with 1 Equiv of Acetic Acid. In a flame-dried flask under N_2 was placed 1.18 g (0.02 mol) of sodium hydride (50% dispersion in mineral oil). The mineral oil was removed by pentane washing and decantation. Dry THF (15 mL) was added, followed by *N*-methylsaccharin (1.97 g, 0.01 mol), and this mixture heated to 35 °C. To the resultant reaction mixture was added dropwise a solution of methoxyethyl chloroacetate (**9**, R = $OCH_2CH_2OCH_3$; 1.52 g, 0.01 mol) in 10 mL of THF. An exothermic reaction resulted, accompanied by gas evolution and foaming. After the addition of **9** was completed (30 min), the reaction mixture was stirred at 40–45 °C for an additional 2 h. At this point, quenching of an aliquot of the reaction mixture by addition into dilute cold HCl and analysis by TLC and GC showed the absence of appreciable amounts of **9** and **8** and a good conversion to the chlorohydrin **10**. Next a solution of 0.6 g of HOAc (0.01 mol) in 5 mL of THF was slowly added to the reaction mixture, and the mixture was stirred another 30 min. Quenching of another aliquot by addition into dilute HCl followed by GC and TLC analysis showed appreciable quantities of the starting materials **8** and **9**. The workup of the remainder of the reaction with 100 mL of cold 5 N HCl and filtration yielded 0.90 g (46%) of *N*-methylsaccharin (**8**).

The identical procedure described above was followed, but after the initial 2-h reaction time the THF was removed from the reaction in vacuo (15 mm) and replaced with 20 mL of Me_2SO. Then, 0.6 g of HOAc (0.01 mol) was added dropwise in 5 mL of Me_2SO and the reaction mixture stirred for an additional 30 min at 40 °C. The reaction was quenched by addition of the mixture to 100 mL of cold 5% HCl, and it was stirred at 5 °C for 1 h. Filtration yielded 1.60 g (51%) of the benzothiazine ester **3** (R = $OCH_2CH_2OCH_3$).

Acknowledgment. We acknowledge helpful discussions with Professor D. S. Kemp and Dr. J. G. Lombardino.

Registry No. **3** (R = OCH_3), 35511-15-0; **3** (R = $OCH_2CH_2OCH_3$), 80201-74-7; **8**, 15448-99-4; **9** (R = $OCH_2CH_2OCH_3$), 13361-36-9; **9** (R = OCH_3), 96-34-4; **10** (R = OCH_3), 85727-15-7; **10** (R = $OCH_2CH_2OCH_3$), 85727-14-6.

Synthesis of Di-*tert*-butyl Methylenemalonate, a Sterically Hindered 1,1-Dicarbonyl Alkene

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Methylenemalonate esters are potentially useful electrophilic alkenes in important synthetic reactions, i.e., the Michael and Diels–Alder reactions. Their utility, however, has been restricted by their rapid polymerization. During our work on tetracarbonyliron complexes of alkenes,[1] we required a methylenemalonate ester, the ester groups of which could be readily cleaved in subsequent transfor-

(1) (a) Roberts, B. W.; Wong, J. *J. Chem. Soc., Chem. Commun.* **1977**, 20. (b) Baar, M. R.; Roberts, B. W. *Ibid.* **1979**, 1129. (c) Roberts, B. W.; Ross, M.; Wong, J. *Ibid.* **1980**, 428.

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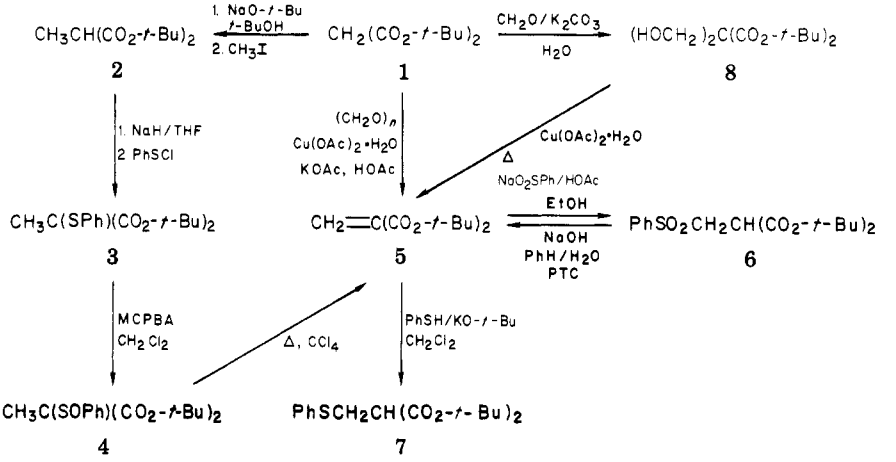
Scheme I



mations. Consideration of various candidates led us to explore the preparation of the di-*tert*-butyl ester **5**. As we report here, the latter can be prepared conveniently in multigram quantities and, in contrast to structurally simpler analogues, has been found to be essentially shelf stable and amenable to controlled synthetic study.

Ene diester **5** was initially approached via a multistep strategy based on sulfoxide elimination (Scheme I).[2,3] However, the tediousness of this approach for preparing multigram quantities prompted us to explore a more direct approach based on Knoevenagel-type condensation of **1** with formaldehyde. Among several reports in the literature on the preparation of simpler methylenemalonate esters in this fashion,[4] the thorough study by Bachman and Tanner[4a] was selected as a departure point for adapting the reaction to the *tert*-butyl analogue. Fortunately little modification was necessary. Thus, heating **1** with paraformaldehyde, potassium acetate, and cupric acetate in acetic acid (Scheme I) and direct distillation of product from the reaction mixture afforded crude **5** with no indication that the tertiary ester was any less suitable to these conditions.

^{1}H NMR spectroscopic analysis of **5** obtained in this fashion indicated the presence of small amounts of starting ester **1** and bis(hydroxymethyl) derivative **8** (vide infra) as contaminants. The latter was removed by a second distillation to give an overall yield of 53% of **5** containing a trace of **1**. In our experience, the presence of **1** has presented no interference to reactions of **5**, and there has been no necessity for further purification.

5 was obtained as a mobile, clear liquid, the stability of which contrasts sharply with that of simpler methylenemalonate esters. Thus freshly prepared samples have been kept at room temperature for up to 4 weeks with no observable change as indicated by ^{1}H NMR spectroscopy. Infrequently, however, some samples have developed a cloudiness, and as a routine precaution, we have preferred to store the compound under nitrogen in the refrigerator.

Chemical characterization of **5** was achieved by conversion (77%) to crystalline sulfone **6** through addition of the elements of benzenesulfinic acid ($C_6H_5SO_2Na$/HOAc). The sulfone could be converted back to **5** in 80% yield through base-promoted sulfone elimination under conditions of phase-transfer catalysis. The product contained again a trace of starting ester **1**, possibly generated via conjugate addition–retroaldolization under the aqueous basic conditions. **5** also underwent addition of thiophenol under base catalysis to give adduct **7** in high yield as indicated by ^{1}H NMR spectroscopic analysis. However, this material was unstable to heat, forming **5** and unidentified compounds upon attempted distillation, and was not investigated further.[3]

5 was also prepared by cupric acetate catalyzed breakdown of bis(hydroxymethyl) derivative **8** according to the method of Kunichika et al.[5] Because of the inferior yield (40%), however, this approach was not pursued further.[3]

Di-*tert*-butyl ester **5** is to our knowledge the first methylenemalonate ester sufficiently stable for conventional synthetic study. The ready availability of the compound now permits full exploration of its synthetic utility. Preliminary studies on Michael reactivity have revealed that **5** is a highly reactive acceptor that, in its most useful applications, is capable of combining with nucleophilic olefins with or without Lewis acid catalysis. Details of these findings will be the subject of a forthcoming report.

Experimental Section

Boiling points are uncorrected. Infrared data were obtained on a Perkin-Elmer Model 137 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker WM-250 and IBM WP-200 spectrometers, respectively. Chemical shifts are reported in parts per million downfield from internal tetramethylsilane. Elemental analysis was performed by Robertson Laboratory, Florham Park, NJ.

Di-*tert*-butyl Methylenemalonate (5). A one-necked, 100-mL, round-bottomed flask was fitted with a reflux condenser attached to a drying tube ($CaCl_2$) and with a magnetic stirrer. The flask was charged with 15.0 g (69.4 mmol) of diester 1,[6] 4.20 g (140 mmol) of paraformaldehyde, 0.70 g (7.13 mmol) of potassium acetate, 0.70 g (3.51 mmol) of cupric acetate monohydrate, and 30 mL of acetic acid. The mixture was heated with stirring

(2) Cf. (a) An unsuccessful attempt to prepare the methylene derivative of Meldrum's acid: Brown, R. F. C.; Eastwood, F. W.; McMullen, G. L. *Aust. J. Chem.* **1977**, *30*, 179 and (b) Hoye, T. R.; Caruso, A. J.; Magee, A. S. *J. Org. Chem.* **1982**, *47*, 4152.

(3) Details of these procedures are given as supplementary material.

(4) These preparations are widely scattered through the patent and primary literature. For methods used prior to 1940, see: (a) Bachman, G. B.; Tanner, H. A. *J. Org. Chem.* **1939**, *4*, 493 and references cited therein. Other reports from the primary literature include: (b) Vansheidt, A. A.; Itenberg, A. M.; Pazi, M. N. *Zh. Obshch. Khim.* **1945**, *15*, 574. (c) Takagi, Y.; Asahara, T. *J. Chem. Soc. Jpn., Ind. Chem. Sect.* **1953**, *56*, 901; *Chem. Abstr.* **1953**, *49*, 6836*d*. (d) Levina, R. Y.; Godovikov, N. N. *Zh. Obshch. Khim.* **1955**, *25*, 986. (e) Sakurai, A.; Midorikawa, H.; Aoyama, S. *J. Sci. Res. Inst., Tokyo* **1958**, *52*, 112; *Chem. Abstr.* **1959**, *53*, 15961*b*.

(5) Kunichika, S.; Oka, S.; Sugiyama, T.; Nakamura, K.; Fukui, K. *Nippon Kagaku Kaishi* **1972**, 596; *Chem. Abstr.* **1972**, *76*, 139905*m*.

(6) McCloskey, A. L.; Fonken, G. S.; Kluiber, R. W.; Johnson, W. S. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, p 261.

in an oil bath at 95–100 °C for 2 h. After cooling to room temperature, acetic acid was removed at room temperature and 1 mmHg. When essentially all acetic acid had been removed, the bath temperature was increased to 40–50 °C and the pressure was diminished to 0.1 mmHg to remove as much solvent as possible. The bath temperature was then increased to 140–150 °C, and a fraction of crude **5** (11.5 g), bp 82 °C (0.1 mmHg), was collected. This material was dissolved in 10 mL of ether, washed with saturated aqueous $NaHCO_3$ solution (3 × 10 mL), and extracted with ether (3 × 20 mL). The combined extracts were dried over $MgSO_4$, filtered, and distilled through a 20-cm Vigreux column to give 8.33 g (53%) of **5** as a clear liquid, bp 67 °C (0.1 mmHg): IR (neat film) 1720 (s) and 1650 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.51 (s, 18 H) and 6.25 (s, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 27.90 (q), 81.75 (s), 130.60 (t), 138.35 (s), and 163.65 (s). A higher boiling fraction (1.15 g), bp >75 °C (0.1 mmHg), was identified by ^1H NMR spectroscopy as a mixture of **5** and **8**.

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 62.81; H, 8.86.

Acknowledgment. We are pleased to acknowledge support of this work by the National Institutes of Health through Grant GM 25222.

Registry No. 1, 541-16-2; **5**, 86633-09-2; paraformaldehyde, 30525-89-4.

Supplementary Material Available: Experimental procedures for (a) preparation of sulfoxide **4** and diol diester **8** and conversion of each to **5**, (b) interconversion of **5** and sulfone **6**, and (c) conversion of **5** to sulfide **7** (5 pages). Ordering information is given on any current masthead page.

Practical Multigram Synthesis for 4(5)-Vinylimidazole

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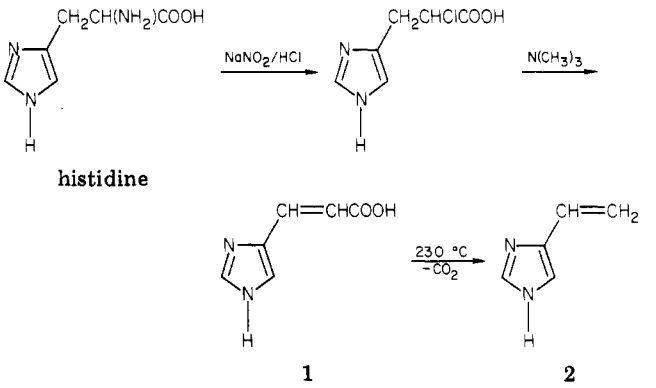
We plan to use 4(5)-vinylimidazole (**2**) as a starting material for the synthesis of derivatives of histamine and histidine. This material has also shown considerable promise as a polymer formulant.[1] The published procedure (Scheme I) for the synthesis of **2** from histidine, however, results in yields of only 9.7%. In addition, the final step in the synthesis, involving a high-vacuum thermal decarboxylation of urocanic acid (**1**), is impractical for quantities greater than 5 g unless liquid nitrogen traps are used to capture evolved CO_2.[1a]

We now report an improved multigram synthesis for **2**. This procedure (Scheme II) utilizes a Wittig reaction with the known compound 1-(triphenylmethyl)imidazole-4-carboxaldehyde (**7**)[3] to synthesize the desired vinyl group. Thus, protection of the imidazole nitrogen of 4(5)-hydroxymethylimidazole hydrochloride (**3**), obtained from fructose,[2] with triphenylmethyl chloride yields **4**.[3] Oxidation of alcohol **4** with activated MnO_2 in dioxane yields aldehyde **7**,[3] and reaction of **7** with triphenylmethylphosphonium bromide and the dimsyl anion yields the vinylimidazole (**11**).[4] The triphenylmethyl group is easily removed with mild acid hydrolysis, and **2** is isolated essentially pure in an overall yield of 36% from fructose.

Scheme I



The preceding steps are carried out with ease, and all intermediates are solids, easily purified and obtained in high yield. Protection of the ring nitrogen with the triphenylmethyl group yields only the 4-substituted product **4**,[3] presumably because of the steric bulk of the triphenylmethyl group. Only the products of the Wittig reaction need to be separated by chromatography. However, it proved necessary to use a large excess (2 equiv) of NaH and Ph_3PCH_3Br in the Wittig reaction in order to avoid significant reduction of the aldehyde **7** to alcohol **4**. Thus, reaction of the aldehyde **7** in dry Me_2SO with 1 equiv of Ph_3PCH_3Br and 1.3 equiv of NaH resulted in a 23% yield of the vinyl product **11**, 4.2% of unreacted aldehyde **7**, and 37% alcohol **4**. Use of 2 equiv of NaH/Ph_3PCH_3Br, however, resulted in an 82% yield of the vinyl product **11** with no discernible unreacted aldehyde **7** or alcohol **4**. The vinyl compound **11** prepared by this method is identical with that prepared by reacting 4(5)-vinylimidazole with triphenylmethyl chloride.[5] Attempts to similarly prepare 4(5)-vinylimidazole (**2**) from the unprotected 4(5)-imidazolecarboxaldehyde (**10**)[6] were unsuccessful, presumably due to the relatively acidic N–H on the imidazole ring.

A second synthetic route, utilizing the benzyl group to protect the ring nitrogen, was also explored. The alcohol **3**, when reacted with benzyl chloride, yielded an approximately 2:1 ratio of the *N*-benzyl protected 4- and 5-alcohols **5** (28.4%) and **6** (13.5%), respectively. Assignment of the structures for **5** and **6** is based upon comparison of the melting points of **6** and the known compound.[7]

Oxidation of **5** and **6** with activated MnO_2 in dioxane yielded the corresponding aldehydes **8** (73%) and **9** (94%). The aldehydes, under Wittig conditions, yielded the vinyl compounds **12** (70%) and **13** (59%), respectively. Again it proved necessary to use a large excess (2 equiv) of NaH and Ph_3PCH_3Br, since equivalent amounts resulted in the formation of alcohols **5** and **6** as primary products. This route, however, is less desirable since the benzyl-protected compounds were obtained in relatively low yields (8.2% and 4.2%, respectively, from fructose).

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