under nitrogen for 3 h. The reaction mixture was then cooled, poured into water, and extracted with ether. Acidification of the aqueous phases, extraction with ether, drying, and removal of the solvent in vacuo gave as an oil 126 mg (93%) of the corresponding carboxylic acid.

A solution containing 74 mg (0.41 mmol) of this acid and 10 ml of anhydrous ether was treated at 0 °C under nitrogen with 0.63 ml (3.2 equiv) of MeLi (2.06 M). The resulting solution was stirred at room temperature for 19 h and then worked up as above to give 68 mg (93%) of **12d**. An analytical sample was obtained by VPC on column C: IR 3110 (w), 2970 (s), 2930 (s), 1710 (s), 1640 (w), 890 cm^{-1} (s); NMR (60 MHz) δ 1.07, 1.20 (d, s, J = 7 Hz, 6 H), 1.23–2.06 (m, 7 H), 2.08 (s, 3 H), 2.55 (s, 2 H), 4.62 (m, 2 H); mass spectrum m/e 180.1497 (M^+, calcd for $C_{12}H_{20}O$, 180.1513).

2,*t*-6-Dimethyl-*r*-2-(2′-oxoprop-1′-yl)-1-cyclohexanone (9d). A solution containing 55 mg (0.31 mmol) of ketone **11d** and 6 ml of spectroquality hexane was cooled to −78 °C. Ozone was then passed slowly through the solution for 75 min after which 95 mg of triphenylphosphine was added. After warming to room temperature the resulting suspension was filtered and the filtrate chromatographed on silica gel. Elution with ether–hexane (1:1) gave 46 mg (82%) of **9d**. A pure sample prepared by VPC on column C possessed the IR and NMR data listed below, which were identical with those reported for *trans*-2,6-dimethyl-2-(2-oxoprop-1-yl)cyclohexan-1-one by Muller and Jager:[5] IR 2975 (s), 2940 (s), 1720 (s, br), 1360 (s), 1015 (s), 975 (w), 950 cm^{-1} (w); NMR (60 MHz) δ 0.99, 1.02 (d, s, J = 6 Hz, 6 H), 1.13–2.67, 2.04 (m, s, 10 H), 2.70 (s, 2 H); (220 MHz) δ 0.98–1.91, 0.99, 1.02 (m, d, s, J = 6 Hz, 10 H), 1.92–2.36, 2.05 (m, s, 5 H), 2.56–2.82, 2.70 (m, dd, J = 16 Hz, 3 H).

2,*c*-6-Dimethyl-*r*-2-(2′-oxoprop-1′-yl)-1-cyclohexanone (10d). In a manner similar to the above, 29 mg (0.16 mmol) of **12d** was ozonized to give 29 mg (94%) of **10d**. A pure sample of **10d** prepared by VPC on column C possessed the IR and NMR data listed below which were identical with those reported for *cis*-2,6-dimethyl-2-(2-oxoprop-1-yl)cyclohexan-1-one by Muller and Jager:[5] IR 2975 (s), 2940 (s), 1710 (s, br), 1360 (s), 1168 (s), 1142 (s), 1125 (s), 1000 (s), 978 (m), 955 cm^{-1} (w); NMR (60 MHz) δ 1.02 (d, J = 6 Hz, 3 H), 1.20 (s, 3 H), 1.50–2.16, 2.09 (m, s, 9 H), 2.16–2.75, 2.51 (m, dd, J = 17 Hz, 3 H); (220 MHz) δ 0.99 (d, J = 6 Hz, 3 H), 1.18 (s, 3 H), 1.20–2.13, 2.09 (m, s, 9 H), 2.42, 2.48 (m, dd, J = 17 Hz, 3 H).

Acknowledgments. It is a pleasure to acknowledge the support of this investigation by the Research Corporation and by the donors of the Petroleum Research Fund, administered by the American Chemical Society. In addition, we thank Mr. S. T. Bella for the microanalyses, Mr. Michael Czarniecki and Dr. Edward Hagaman for discussion and aid in determining the ^{13}C NMR spectra, The Rockefeller University Mass Spectrometry Laboratory (NIHDRR RR00862) for the high-resolution mass spectra, and the Middle Atlantic Regional NMR Facility (NIH RR542) at the University of Pennsylvania where the 220-MHz NMR spectra were obtained.

Registry No.—**8**, 17990-00-0; **10c** free acid, 61140-34-9; **11b** free acid, 61140-35-0; **11b** acid chloride, 61140-36-1; **12b** free acid, 61140-37-2; **12b** acid chloride, 61140-38-3; **13**, 61140-39-4; 2,6-dimethylcyclohexanone, 2816-57-1; allyl bromide, 106-95-6.

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Analogues of Phosphoenol Pyruvate. 3.[1] New Synthetic Approaches to α-(Dihydroxyphosphinylmethyl)acrylic acid and Unequivocal Assignments of the Vinyl Protons in Its Nuclear Magnetic Resonance Spectrum

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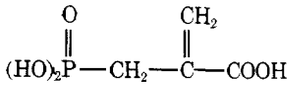
Three new synthetic routes to α-(dihydroxyphosphinylmethyl)acrylic acid (**1**), the phosphonic acid analogue of phosphoenolpyruvic acid, have been developed. One of these routes was devised so that a carbon-13 label could be introduced specifically in the carboxylate carbon position of **1**. By measurement of $^3J_{^1H-^{13}C}$ coupling constants in the NMR spectrum of **1**, unequivocal assignments for the vinyl protons have been made.

Phosphoenolpyruvic acid (PEP) is one of the most important biological substances with a high phosphate group-transfer potential.[4] In 1972, Stubbe and Kenyon reported the synthesis of the nonhydrolyzable phosphonate analogue of PEP, α-(dihydroxyphosphinylmethyl)acrylic acid (**1**). This analogue has been found to replace PEP as a substrate in the enolase reaction[1,5] and to serve as a weak competitive inhibitor of rabbit muscle pyruvate kinase.[6] In the case of both enzymes,

distance measurements between enzyme-bound Mn(II) at the active sites and fixed protons of bound 1 were made using



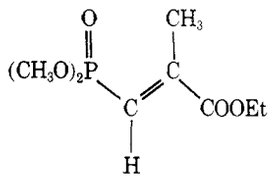
1

NMR techniques. The distance values obtained permitted models to be constructed of the enzyme–Mn(II)–inhibitor ternary complexes.[5,6] Although the tentative NMR assignments made to the vinyl protons of 1 were not crucial to the arguments made in either paper, there was disagreement about these assignments.[5,6] In this paper we present unequivocal assignments for these two vinyl protons, assignments which support the arguments of James and Cohn,[6] and which do not support those of Nowak, Mildvan, and Kenyon.[5]

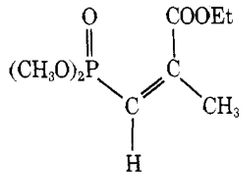
In addition, new, more efficient synthetic approaches to 1 and some related compounds are presented.

Results and Discussion

One synthetic approach to phosphonate analogues of phosphoenolpyruvic acid which was explored used the Wadsworth–Emmons–Horner (modified Wittig) reaction.[7,8] When the preformed α anion of bis(dimethoxyphosphinyl)methane (2) was treated with ethyl pyruvate in a manner similar to the procedure of Huff et al.,[9] a 50:50 mixture of (*E*)- and (*Z*)-ethyl (α-methyl-β-dimethoxyphosphinyl)acrylates (*E*- and *Z*-4) was isolated in 91% yield. In an analogous fashion using bis(diethoxyphosphinyl)methane (3), a 50:50 mixture of (*E*)- and (*Z*)-ethyl (α-methyl-β-diethoxyphosphinyl)acrylates (*E*- and *Z*-5) was generated in 88% yield (Scheme I).



E-4



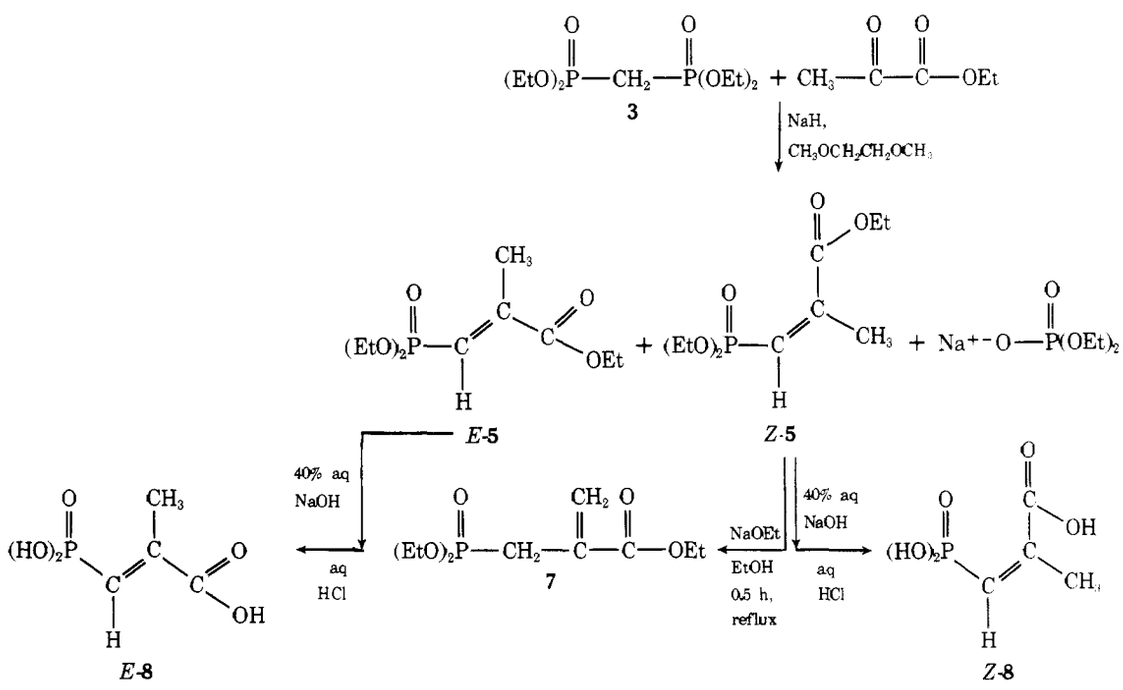
Z-4

When the former reaction was conducted with an excess of sodium hydride, substantial amounts of the known itaconate analogue, ethyl (α-dimethoxyphosphinylmethyl)acrylate[1] (6), were formed along with *E*- and *Z*-4, as judged by examining the NMR spectrum of the product mixture. This type of base-catalyzed rearrangement was also observed when a 40:60 mixture of *E*- and *Z*-5 was treated with refluxing sodium ethoxide in ethanol. The course of the rearrangement was followed by NMR spectroscopy, and it was observed that *only* isomer *Z*-5 readily rearranged to ethyl α-(diethoxyphosphinylmethyl)acrylate (7) (see Scheme I). Isomer *E*-5 remained unchanged. Presumably, the driving force for this stereoselective *Z*-5 → 7 conversion is release of relatively unfavorable steric interactions between the cis ethoxycarbonyl and diethoxyphosphinyl substituents of the *Z*-5 molecule. In compound *E*-5 these bulky substituents are trans to one another.

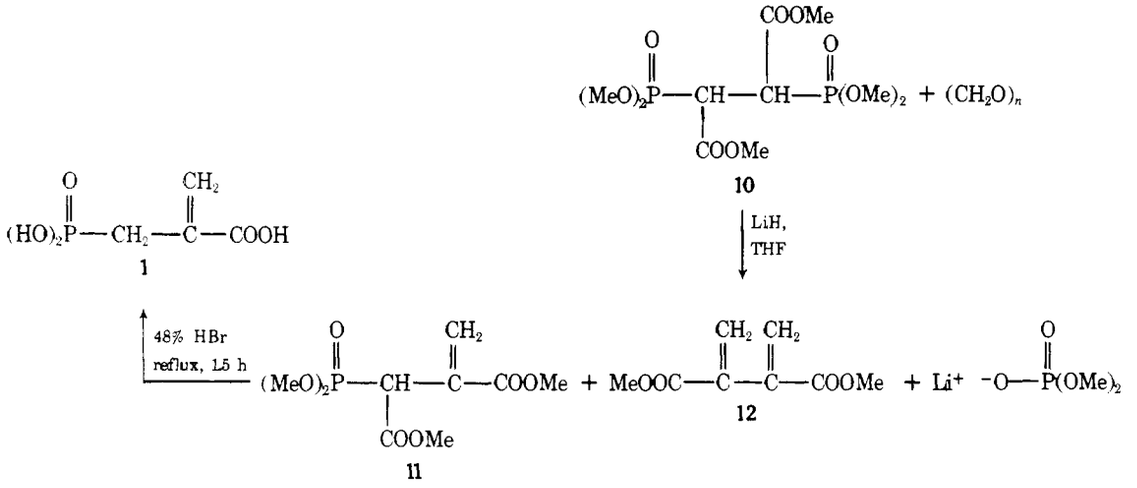
A definitive assignment of the geometries of *E*- and *Z*-5 has been made on the basis of the following observations (Scheme I). A 40:60 mixture of *E*- and *Z*-5 was stirred for 3 days at room temperature in an aqueous solution containing 1 molar equiv of NaOH; the solution was then acidified with HCl to pH 2 and thoroughly extracted with CH_2Cl_2. The aqueous layer was found to contain only *Z*-8 in the amount consistent with essentially its quantitative production from *Z*-5. The CH_2Cl_2 layer, in contrast, was found to contain only *E*-(α-methyl-β-diethoxyphosphinyl)acrylic acid (*E*-9) in the amount consistent with its production from *E*-5. Compound *E*-9 could be hydrolyzed to unesterified *E*-8 in 71% yield by heating at reflux for 36 h in 6 N HCl. The relatively rapid conversion of *Z*-5 to *Z*-8 at room temperature is strongly indicative of carboxyl group participation in the hydrolysis of the phosphonate ethyl ester groups via intramolecular nucleophilic catalysis.[10,11] Only the *Z* isomer of 5, with the carboxylate and phosphonate substituents cis to one another, would be expected to exhibit this hydrolytic behavior. Precedents for such intramolecular carboxyl-group participation leading to accelerated rates of hydrolysis of phosphonate esters may be found in the work of both Gordon et al.[12] and Blackburn and Brown.[13]

Observations of anisotropic deshielding effects in the ^1H NMR spectra[14] of both *E*- and *Z*-5 also support the given

Scheme I



Scheme II



structural assignments. For example, as predicted, the vinyl proton of *E*-**5** resonates at a lower field than the vinyl proton of *Z*-**5**, presumably owing to its cis relationship to an ethoxycarbonyl group.[14] Also, the allylic methyl protons of *E*-**5** resonate at a lower field than those of *Z*-**5**, again presumably owing to their cis relationship to a diethoxyphosphinyl group.

By treatment with aqueous HBr, esters of the type **6** and **7** may be hydrolyzed to the free α-(dihydroxyphosphinylmethyl)acrylic acid (**1**).[1] In the present study, **6** was converted to **1** in 54% isolated yield.

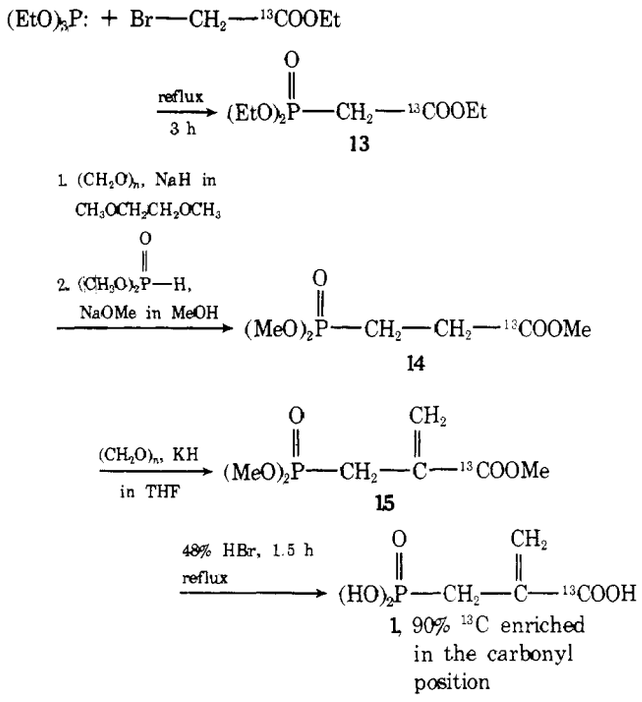
In Scheme II is outlined another modified Wittig reaction examined as a synthetic route to **1**. In this case the known compound dimethyl α,β-bis(dimethoxyphosphinyl)succinate[15] (**10**) was treated with formaldehyde under strongly basic conditions. A mixture of what appeared to be both dimethyl (α-methylidene-β-dimethoxyphosphinyl)succinate (**11**) and the known compound dimethyl α,β-bis(methylidene)succinate (**12**) was generated. Compound **12** was always the major product regardless of the conditions (e.g., base, temperature, reaction time, sequence of addition, solvent, stoichiometry) employed. Upon hydrolysis, **11** underwent decarboxylation without apparent double-bond rearrangement to give a 36% yield of **1**.

Still another synthetic approach to **1**, outlined in Scheme III, was developed so that selective carbon-13 enrichment could be made in the carboxyl carbon position. The finding of a commercial source of ethyl bromoacetate, 90% ^{13}C enriched in the carbonyl carbon position, led to the adoption of this scheme.

A Michaelis–Arbusov reaction of the labeled ethyl bromoacetate with triethyl phosphite gave labeled ethyl (diethoxyphosphinyl)acetate (**13**) in 96% yield. The modified Wittig procedure with formaldehyde then generated labeled ethyl acrylate. This ethyl acrylate was next treated without isolation with an excess of dimethyl phosphite in the presence of 1 molar equiv of sodium methoxide in methanol, following the procedure of Pudovik and Kitaev,[16] to generate labeled dimethyl β-methoxycarbonylethylphosphonate (**14**) in 62% yield. This in turn was converted to labeled methyl α-(dimethoxyphosphinylmethyl)acrylate (**15**) by treatment with KH in tetrahydrofuran followed by condensation with formaldehyde. Martin et al.[17] had earlier shown that such Stobbe condensations of diethyl β-ethoxycarbonylethylphosphonate with a variety of ketones gave a series of β,γ-unsaturated phosphonates. No evidence was observed for subsequent base-catalyzed rearrangement to α,β-unsaturated phosphonates.[17]

Compound **15** was converted to labeled **1** by acid-catalyzed

Scheme III



hydrolysis. The ^1H NMR spectra showing the vinyl proton regions of both labeled and unlabeled **1** are illustrated in Figure 1. In unlabeled **1** each of the vinyl proton signals is split by $^4J_{^1H-^{31}P}$ couplings of 4.3 and 4.7 Hz for the downfield and upfield protons, respectively. The smaller splitting of each peak is due to geminal ^1H–^1H coupling.[5] These ^1H–^{31}P and ^1H–^1H vinyl proton couplings were verified earlier by Nowak et al.[5] using both heteronuclear and homonuclear spin decoupling experiments. In the ^{13}C-labeled sample of **1** additional $^3J_{^1H-^{13}C}$ couplings of 6.7 and 11.5 Hz were observed for the downfield and upfield vinyl protons, respectively. Similarly, for the trimethyl ester precursor **15** $^3J_{^1H-^{13}C}$ values of 7.0 and 13.5 Hz were observed for the corresponding vinyl protons in the spectrum.

For spin–spin coupling between two nuclei substituted directly on the carbons of a carbon–carbon double bond it has been shown experimentally *without exception*[18] that *J* trans > *J* cis. This observation has also received some theoretical justification.[19] Thus it is clear from Figure 1 that the vinyl proton which is cis to the ^{13}C-enriched carboxyl group in both **1** and **15** resonates at a lower field (relative to tetramethylsilane) than that which is trans.

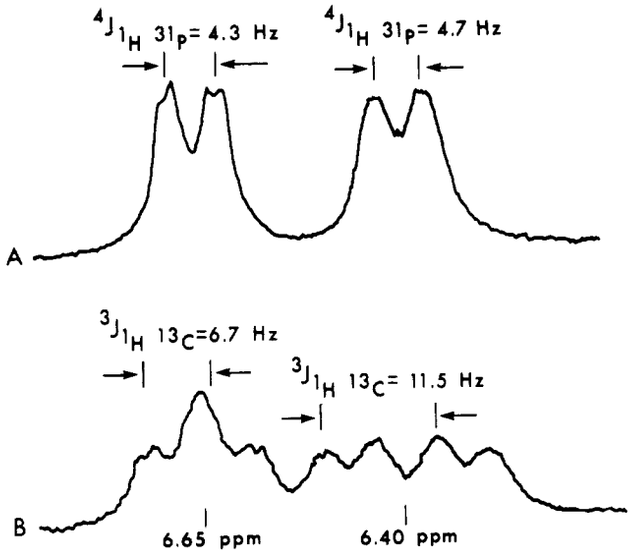


Figure 1. A: the ^1H NMR spectrum in D_2O at 60 MHz showing the vinyl proton region of the dilithium salt of **1**. B: the same, with 90% ^{13}C enrichment in the carboxyl carbon position.

Nowak, Mildvan, and Kenyon[5] had earlier made a tentative assignment of these vinyl protons in **1** on the basis of the observed differences in the $^4J_{^1H-^{31}P}$ values. It was pointed out that trans coupling is often greater than cis coupling in such systems, but known exceptions were noted,[20] and it was stated that there was "uncertainty in the assignments of the vinyl protons".[5]

James and Cohn[6] later made the opposite tentative assignments of the vinyl protons of **1** based on analogy to the well-established vinyl proton assignments made earlier for phosphoenolpyruvic acid.[21] In phosphoenolpyruvic acid the vinyl proton cis to the carboxyl group resonates downfield relative to the corresponding trans vinyl proton. James and Cohn argued that the same should probably be true for **1**. Indeed, many examples are known where the anisotropic deshielding effect of a carbonyl group substituted on a carbon–carbon double bond results in the vinyl proton substituted cis to be downfield from the geometrical isomer with the corresponding vinyl proton substituted trans.[14] The results in Figure 1 support the assignments of James and Cohn,[6] and, at least for this limited number of cases, show that the anisotropic deshielding of a vinyl proton by a carboxyl group attached to a carbon–carbon double bond is greater than that of a phosphinylmethyl group similarly attached to such a double bond.

The most efficient synthesis of unlabeled **1** which emerges from these studies is to prepare unlabeled **14** and then to carry out the last two steps of Scheme III. Alternatively, diethyl β-ethoxycarbonylethylphosphonate, the triethyl ester related to **14**, can be prepared by the method of Garner et al.[22] and used in the same sequence.

Experimental Section

General. All melting and boiling points are uncorrected. NMR spectra were determined at 60 MHz using either a Varian Model A-60A or Perkin-Elmer R12B spectrometer; δ values are relative to Me_4Si. IR spectra were recorded on a Beckman Acculab 4 spectrometer. Microanalyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley.

Bis(dimethoxyphosphinyl)methane (2) was prepared by the methods of Roy[23] and Nicholson et al.,[24] bp 80–85 °C (0.02 Torr) [lit.[24] bp 87–90 °C (0.05 Torr)]. The method of Roy[23] was also employed for the synthesis of **bis(diethoxyphosphinyl)methane (3)**, bp 85–90 °C (0.02 Torr) [lit.[24] bp 90–94 °C (0.1 Torr)].

A mixture of **(*E*) and (*Z*)-ethyl (α-methyl-β-dimethoxyphosphinyl)acrylates** (*E*- and *Z*-**4**) was prepared as follows. Sodium hydride (3.2 g of a 56% suspension in mineral oil, 75 mmol, Metal Hydrides, Inc.) was washed with hexane under N_2, and 100 ml of dimethoxyethane, freshly distilled from NaH, was added. Compound **2** (18.5 g, 92.5 mmol) dissolved in 25 ml of the distilled dimethoxyethane was added dropwise at 0 °C and allowed to stir for 2 h at room temperature under N_2. Freshly distilled ethyl pyruvate (9.3 g, 74 mmol, Aldrich) in 25 ml of dimethoxyethane was added dropwise at 0 °C, and the mixture was stirred for 0.5 h at 0 °C after addition was complete. Then cold, saturated aqueous KH_2PO_4 (50 ml) was added, and the reaction mixture was extracted thoroughly with five 100-ml portions of CH_2Cl_2. The extract was dried using Na_2SO_4 and filtered, and the solvent was removed in vacuo. Short-path distillation at 85–90 °C (0.03 Torr) gave 14.9 g (91% yield) of a 50:50 mixture of *E*- and *Z*-**4**. ***E*-4:** NMR ($CDCl_3$) δ 1.33 (t, J = 7 Hz, 3 H), 2.25 (d of d, $^4J_{H-H}$ = 1.3 Hz, $^4J_{H-^{31}P}$ = 3.6 Hz, 3 H), 3.73 (d, J = 11 Hz, 6 H), 4.25 (q, J = 7 Hz, 2 H), 6.6 (d of q, $^2J_{H-^{31}P}$ = 16.4, $^4J_{H-H}$ = 1.3 Hz, 1 H). ***Z*-4:** NMR ($CDCl_3$) δ 1.33 (t, J = 7 Hz, 3 H), 2.11 (apparent t, $^4J_{H-H}$ = 1.8, $^4J_{H-^{31}P}$ = 1.8 Hz, 3 H), 3.75 (d, $^3J_{H-^{31}P}$ = 11 Hz, 6 H), 4.25 (q, J = 7 Hz, 2 H), 5.8 (d of q, $^2J_{H-^{31}P}$ = 15, $^4J_{H-H}$ = 1.8 Hz, 1 H).

Anal. Calcd for $C_8H_{15}O_5P$: C, 43.25; H, 6.80. Found: C, 43.21; H, 6.77.

A mixture of **(*E*)- and (*Z*)-ethyl (α-methyl-β-diethoxyphosphinyl)acrylates** (*E*- and *Z*-**5**) was prepared in an analogous fashion using **3** instead of **2**. Short-path distillation at 100–110 °C (0.03 Torr) gave 16.2 g (88% yield) of an analytically pure sample of *E*- and *Z*-**5** in a 50:50 ratio. ***E*-5:** NMR ($CDCl_3$) δ 1.33 (t, J = 7 Hz, 3 H), 1.35 (t, J = 7 Hz, 6 H), 2.25 (d of d, $^4J_{H-H}$ = 1.0, $^4J_{H-^{31}P}$ = 3.6 Hz, 3 H), 4.15 (m, J = 7 Hz, 6 H), 6.58 (d of q, $^2J_{H-^{31}P}$ = 15.8, $^4J_{H-H}$ = 1.0 Hz, 1 H). ***Z*-5:** NMR ($CDCl_3$) δ 1.33 (t, J = 7 Hz, 3 H), 1.35 (t, J = 7 Hz, 6 H), 2.11 (apparent t, $^4J_{H-H}$ = 1.4, $^4J_{H-^{31}P}$ = 1.4 Hz, 3 H), 4.15 (m, J = 7 Hz, 6 H), 5.78 (d of q, $^2J_{H-^{31}P}$ = 14.6, $^4J_{H-H}$ = 1.4 Hz, 1 H).

Anal. Calcd for $C_{10}H_{19}O_5P$: C, 48.00; H, 7.65. Found: C, 47.68; H, 7.73.

Rearrangement of *E*- and *Z*-4 to ethyl α-(dimethoxyphosphinylmethyl)acrylate (6) could be achieved either by (1) conducting the reaction described above to prepare *E*- and *Z*-**4** with a 20% molar excess of NaH and stirring for 6 h at room temperature or (2) adding a 5.0-g mixture of isolated *E*- and *Z*-**4** dropwise to a 5% molar equivalent of hexane-washed NaH in 100 ml of dry dimethoxyethane at 0 °C and stirring for 6 h at room temperature before workup. With the second method 2.05 g (41% yield) of product **6** was obtained, bp 90–95 °C (0.03 Torr) [lit.[1] bp 103–105 °C (1 Torr)], with an NMR spectrum ($CDCl_3$) identical with that reported previously.[1]

Rearrangement of *E*- and *Z*-5 to ethyl α-(diethoxyphosphinylmethyl)acrylate (7) could be demonstrated by NMR spectroscopy. A 5.0-g mixture of *E*- and *Z*-**5** in a 40:60 ratio was treated with NaH using the second method described above. The product mixture distilled at bp 100–110 °C (0.03 Torr) giving 2.8 g (58% recovery) of approximately 65% **7** and 35% of unrearranged *E*- and *Z*-**5**, as judged by integration of the allylic proton region of the NMR spectrum. Compound **7** had the following NMR ($CDCl_3$): δ 1.33 (t, J = 7 Hz, 3 H), 1.35 (t, J = 7 Hz, 6 H), 2.94 (d, $^2J_{H-^{31}P}$ = 22 Hz, 2 H), 4.15 (m, J = 7 Hz, 6 H), 5.81 (d, J = 5 Hz, 1 H), 6.21 (d, J = 4 Hz, 1 H).

Hydrolysis of 6 to form α-(dihydroxyphosphinylmethyl)acrylic acid (1) was achieved as follows. A mixture (5.0 g, 22.5 mmol) of **6**, *E*-**4**, and *Z*-**4** in a 60:20:20 ratio was heated at reflux for 1.5 h in 48% HBr according to the procedure of Stubbe and Kenyon.[1] Product **1** (1.21 g, 54% yield based on **6**) was isolated using fractional crystallization from water as white flakes, mp 168–170 °C (lit.[1] mp 118–120 °C). Samples would occasionally melt at 118–120 °C on recrystallization, suggesting that either polymorphism exists or that thermal dehydration to a cyclic anhydride is possibly occurring.[25] The NMR spectrum (D_2O) was identical with that previously reported for **1**.[1]

Stereoselective rearrangement of *Z*-5 to ethyl α-(diethoxyphosphinylmethyl)acrylate (7) was determined as follows. A mixture of *E*- and *Z*-**5** in the ratio 40:60 (1.0 g) was added dropwise to 40 ml of 0.1 M sodium ethoxide in ethanol, and the solution was heated at reflux for 0.5 h under N_2. The reaction mixture was then cooled to 0 °C, 225 ml of saturated aqueous KH_2PO_4 was added, and the solution was extracted with four 100-ml portions of CH_2Cl_2. After drying the solution over $MgSO_4$, the solvent was removed in vacuo. The NMR spectrum ($CDCl_3$) of the resulting yellow oil (0.76 g, 76% recovery) showed the presence of only *E*-**5** and **7** in a ratio of 40:60.

Hydrolysis of *Z*-5 to generate (*Z*)-(α-methyl-β-dihydroxyphosphinyl)acrylic acids (8) was carried out as follows. A mixture (5.0 g, 22.5 mmol) of *E*- and *Z*-**5** in the ratio of 40:60 was dissolved in 5 ml of H_2O and stirred at 0 °C while 2.0 g of 40% aqueous NaOH was added. The resulting mixture was stirred at room temperature for 48 h and then acidified with 12 N HCl to pH 2 and allowed to stir for an additional 3 h before extracting with five 25-ml portions of CH_2Cl_2.

The aqueous layer was observed to form a white, crystalline precipitate which was isolated by filtration. After recrystallization from water, 1.89 g of the hemihydrate of product *Z*-**8** (94% yield based on *Z*-**5**) was obtained as hygroscopic, colorless needles: mp 179–181 °C; IR (Nujol) 6.06, 7.6, 8.05, 8.53, 9.00, 9.86, 11.11 μ; NMR (D_2O) δ 2.02 (apparent t, $^4J_{H-H}$ = 1.4, $^4J_{H-^{31}P}$ = 1.4 Hz, 3 H), 6.11 (d of q, $^4J_{H-H}$ = 1.4, $^2J_{H-^{31}P}$ = 10.2 Hz, 1 H).

Anal. Calcd for $C_4H_7O_5P \cdot 0.5H_2O$: C, 27.44; H, 4.61. Found: C, 27.3; H, 4.93.

Hydrolysis of *E*-5 to generate (*E*)-(α-methyl-β-dihydroxyphosphinyl)acrylic acid (*E*-8) began with crude (*E*)-(α-methyl-β-diethoxyphosphinyl)acrylic acid (*E*-**9**, 1.65 g) which was obtained upon evaporating the CH_2Cl_2 layer from the preceding reaction. This ethyl ester *E*-**9** was heated at reflux for 36 h in 25 ml of 6 N HCl. Product *E*-**8** (1.06 g, 71% yield based on the crude *E*-**9**) was isolated by recrystallization from water as hygroscopic, colorless plates: mp 153–158 °C; IR (Nujol) 5.91, 7.88, 8.47, 9.71, 10.82 μ; NMR (D_2O) δ 2.13 (d of d, $^4J_{H-^{31}P}$ = 3.6, $^4J_{H-H}$ = 1.4 Hz, 3 H), 6.57 (d of q, $^4J_{H-H}$ = 1.4, $^2J_{H-^{31}P}$ = 16.4 Hz, 1 H).

Anal. Calcd for $C_4H_7O_5P \cdot 0.25H_2O$: C, 28.17; H, 4.43. Found: C, 28.21; H, 4.20.

Dimethyl α,β-bis(dimethoxyphosphinyl)succinate (10) was prepared by the method of Kirillova and Kukhtin,[15] bp 150–160 °C (0.03 Torr) [lit.[15] bp 208–210 °C (4 mm)].

Synthesis of 1 from 10 using a modified Wittig reaction with formaldehyde was achieved as follows. Compound **10** (30.0 g, 82.9 mmol), previously dried overnight over P_4O_{10}, was dissolved in 500 ml of dry tetrahydrofuran. Lithium hydride (1.0 g, 125 mmol) was added with stirring under N_2. The reaction mixture was then heated at reflux for 15 min. After cooling, 2.5 g (83.3 mmol) of paraformaldehyde (Eastman, previously dried in vacuo overnight) dissolved in 200 ml of tetrahydrofuran was added rapidly at room temperature. After 2 h of additional stirring, the reaction mixture was filtered, and the solvent was removed from the filtrate in vacuo at 25 °C. Short-path distillation at 65–85 °C (0.05 Torr) gave 8.45 g of a mixture of what appeared from examination of the NMR spectrum to be a 20:80 mixture of dimethyl (α-methylidene-β-dimethoxyphosphinyl)succinate (**11**) and dimethyl α,β-bis(methylidene)succinate[26] (**12**). This mixture could be partially resolved by further vacuum distillation, which yielded two fractions, bp 45–55 °C (0.1 Torr) and 100–110 °C (0.1 Torr). Judging from its NMR spectrum, the lower boiling fraction was mostly the dimethyl α,β-bis(methylidene)succinate [lit.[26] bp 52–65 °C (1 Torr)]. The higher boiling fraction, presumably mostly **11** (2.05 g, 9.3% yield), was then heated at reflux for 1.5 h in 20 ml of 48% HBr. After several recrystallizations from water, 0.46 g (36% yield based upon impure **11**) of **1** was obtained as white flakes, mp 168–170 °C. The NMR spectrum was identical with that previously reported.[1]

Preparation of Ethyl (Diethoxyphosphinyl)acetate (13) 90% ^{13}C Enriched in the Carbonyl Position. Ethyl bromoacetate (90% ^{13}C enriched in the carbonyl position, 5.0 g, 29.8 mmol, Koch Isotopes, Inc.) was heated at reflux for 3 h with 15 g (90.4 mmol) of freshly distilled triethyl phosphite (Aldrich). The ^{13}C-enriched product, ethyl (diethoxyphosphinyl)acetate (**13**, 6.45 g, 96% yield), was short-path distilled: bp 105–110 °C (1 Torr) [lit.[27] bp 142–145 °C (9 Torr)]; NMR ($CDCl_3$) δ 1.3 (t, J = 7 Hz, 3 H), 1.36 (t, J = 7 Hz, 6 H), 2.98 (d of d, $^2J_{H-^{13}C}$ = 7.5, $^2J_{H-^{31}P}$ = 21.7 Hz, 2 H), 4.2 (m, J = 7 Hz, 6 H).

Preparation of Dimethyl β-Methoxycarbonylethylphosphonate (14) 90% ^{13}C Enriched in the Carbonyl Position. A modified version of the procedure of Pudovik and Kitaev[16] was employed. Sodium hydride (1.44 g, 33.6 mmol, 56% suspension in mineral oil) was washed with hexane and placed in a 500-ml four-neck flask equipped with a mechanical stirrer, thermometer, 125-ml pressure-equalized addition funnel, and an N_2 bubbler. Dimethoxyethane (100 ml, freshly distilled from NaH) was added and the mixture was cooled to 0 °C. The ^{13}C-enriched **13** (6.45 g, 28.9 mmol) in 50 ml of the dry dimethoxyethane was added dropwise and allowed to stir for 1 h at 0 °C. The mixture was then cooled to −20 °C, 15 g (500 mmol) of paraformaldehyde (dried in vacuo overnight) was added rapidly, and the solution was allowed to stir at 0 °C. The reaction mixture, while still cold, was then filtered under an N_2 purge through a fine-fritted sintered glass filter into a 300-ml three-neck flask. The residue was washed with 25 ml of dry dimethoxyethane, and this solution was also added to the filtrate. Dimethyl phosphite (12 g, 109 mmol, Aldrich, freshly distilled from CaH_2) was added followed by the dropwise addition of 15 ml of 1 M sodium methoxide over 1 h at room temperature. After being stirred for an additional 1 h, the reaction mixture was cooled to 0 °C, 25 ml of saturated, aqueous KH_2PO_4 was added, and the solution was extracted with five 100-ml portions of CH_2CL_2/ After the extract was dried over Na_2SO_4, the solvent was removed in vacuo. The crude product was distilled, bp 95–103 °C (1 Torr) [lit.[16] bp 137–138 °C (10 Torr)], yielding 3.47 g of ^{13}C-enriched **14** (61% yield).

Preparation of Methyl α-(Dimethoxyphosphinylmethyl)-acrylate (15) 90% ^{13}C Enriched in the Carbonyl Position. Product **14** (3.44 g, 17.5 mmol) was dissolved in 60 ml of dry tetrahydrofuran and stirred under N_2 while potassium hydride (4.18 g of 25% suspension in mineral oil, 26.7 mmol) was added at room temperature. The mixture was allowed to stir at room temperature for 3 h. Paraformaldehyde (5.0 g, 16.7 mmol) was added to the mixture rapidly, and the slurry was stirred vigorously for 6 h. Excess paraformaldehyde was removed by filtration, and the solvent was removed in vacuo leaving a yellow oil which soon separated into two layers. The upper layer of mineral oil was removed by decantation leaving 1.43 g of product as a yellow oil. The NMR spectrum ($CDCl_3$) showed the presence of at least two products, compound **15** comprising better than 75% of the mixture. It was used in the next step of the synthesis without further purification. NMR ($CDCl_3$) δ 2.98 (d of d, $^2J_{H-^{31}P}$ = 22, $^3J_{H-^{13}C}$ = 4.6 Hz, 2 H), 5.95 (d of d, $^4J_{H-^{31}P}$ = 5.5 Hz, $^3J_{H-^{13}C}$ = 13.5 Hz, 1 H), 6.35 (apparent t, $^4J_{H-^{31}P}$ = 5.5, $^3J_{H-^{13}C}$ = 7.0 Hz, 1 H).

Preparation of Dilithium α-(Dihydroxyphosphinylmethyl)-acrylate (Dilithium Salt of 1) 90% ^{13}C Enriched in the Carbonyl Position. Impure ^{13}C-enriched **15** (1.43 g, 5.1 mmol) was heated at reflux for 1.5 h in 48% HBr (freshly distilled from $SnCl_2$). After removal of the solvent, an oil remained which was dissolved in 5 ml of H_2O. Barium acetate was then added until the pH was 4.3. Then 25 ml of absolute ethanol was added to yield 1.85 g of precipitated crude barium salt of **1**. This salt was suspended in water and subjected to ion exchange using a Dowex 50-W-X cation resin in the lithium form. The water was removed in vacuo leaving 0.95 g of crude dilithium salt of **1**. Recrystallization from aqueous ethanol gave 0.65 g of dilithium salt of ^{13}C-enriched **1**, the properties of which corresponded to those of the dilithium salt of **1** prepared from authentic, unlabeled **1**: NMR (D_2O) δ 3.19 (d of d, $^3J_{H-^{13}C}$ = 4, $^2J_{H-^{31}P}$ = 20.5 Hz, 2 H), 6.40 (d of d, $^3J_{H-^{13}C}$ = 11.5, $^4J_{H-^{31}P}$ = = 4.7 Hz, 1 H), 6.65 (apparent t, $^3J_{H-^{13}C}$ = 6.7, $^4J_{H-^{31}P}$ = 4.3 Hz, 1 H). The vinyl proton region of this spectrum is shown in Figure 1B.

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Registry No.—**1**, 4538-02-7; 1 dilithium salt, 61203-65-4; 1 ^{13}C derivative dilithium salt, 61203-61-0; **2**, 16001-93-7; **3**, 1660-94-2; *E*-**4**, 61203-62-1; *Z*-**4**, 61203-63-2; *E*-**5**, 34220-75-2; *Z*-**5**, 34220-74-1; **7**, 61203-64-3; *E*-**8**, 34220-77-4; *Z*-**8**, 34220-76-3; *E*-**9**, 61203-66-5; **10**, 2901-37-3; **11**, 61203-68-7; **12**, 38818-30-3; **13**, 61203-67-6; **14**, 61203-69-8; **15**, 61203-70-1; ethyl pyruvate, 617-35-6; ^{13}C-enriched ethyl bromoacetate, 61203-71-2; triethyl phosphite, 122-52-1.

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Acetylenic Analogues of the Cyanine Dyes. 2.[1] Synthesis of Isomeric Acetylenic Dyes

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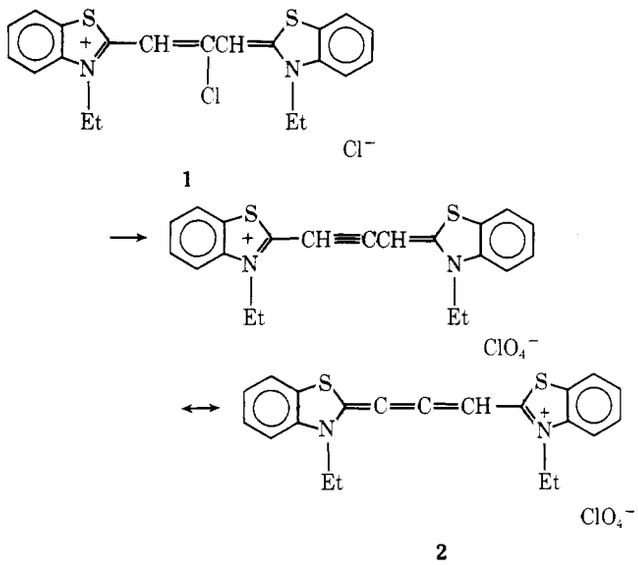
A new synthesis of acetylenic analogues of cyanine dyes is described, and the mechanism of the reaction is discussed in terms of ynenamines as reactive intermediates. This approach makes possible the separate synthesis of isomeric acetylenic dyes such as **4** and **5**.

The first examples of acetylenic cyanine analogues were described recently.[1] These compounds, which possess a formal triple bond in the conjugated system, were obtained through a reaction sequence in which the final step was the dehydrochlorination of a *meso*-chloro carbocyanine, as in the formation of **2** from **1**. This route leads to dyes of unambiguous structure only when the terminal heterocyclic nuclei are identical. In cases where this condition is not met, for example in **3**, elimination of hydrogen chloride can occur in two alternative modes to give the two isomeric dyes **4** and **5**.

We report here a new and more versatile approach, whereby dyes such as **4** and **5** may be obtained separately. One method[2] for the preparation of meso-substituted carbocyanines involves the reaction, under basic conditions, of a heterocyclic quaternary salt containing a 2-substituted propenyl group with a second quaternary salt having a suitable leaving group. Thus, reaction of the 2-chloropropenyl salt **6**[3] with the betaine **7**[4] in acetonitrile, using pyridine as condensing agent, gave the *meso*-chloro carbocyanine **1**. When triethylamine was used in place of pyridine, however, the product was the acetylenic dye **2**.[1,6]

Since **1** is not dehydrochlorinated under the conditions used to prepare **2**, it cannot be an intermediate in the formation of **2**. The reaction of 2-chloropropenyl salts with triethylamine in the absence of a second reactive quaternary salt proved to be highly illuminating. Although the reaction of **6** did not yield



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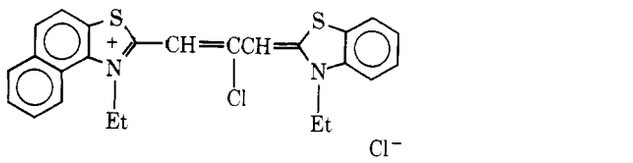

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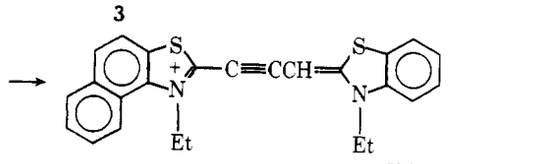

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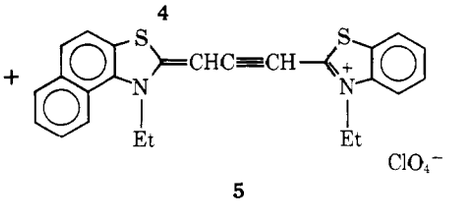

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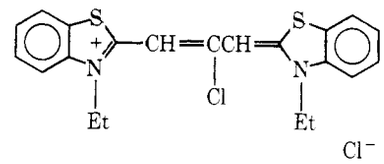

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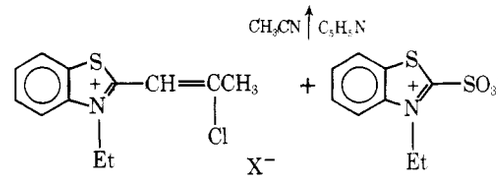
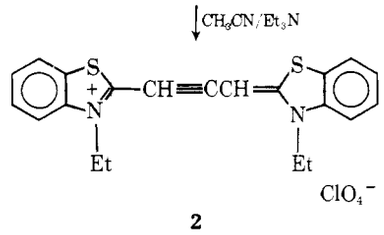


6 **7**



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