1023. *A Model for the Natural Synthesis of Allenes.*[1]

By J. Cymerman Craig and M. Moyle.

The closest available model for a β-polyketone, acetonedicarboxylic ester, was transformed into dimethyl penta-2,3-dienedioate through its enol phosphate which was decomposed by aqueous alkali in 10 sec. at 0°. The enol phosphate of γ-phenylacetoacetic ester needed 24 hr. for complete elimination. The reaction requires activation in both the groups R and R′ in $\text{R}\cdot\text{CH}_2\cdot\text{CO}\cdot\text{CH}_2\text{R}'$, in a manner similar to that in natural β-polyketones. A possible mechanism for the concurrent formation of acetylenes and allenes in Nature is proposed.

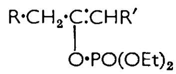
Acetylenes and allenes occur widely in Nature [2] and there is experimental evidence for the derivation of two polyacetylenes (nemotinic acid [3] and matricaria ester [4]) from acetate units by head-to-tail linkage. It was recently shown [5] that the dehydration step, $-\text{CO}\cdot\text{CH}_2-$ to $-\text{C}\vdots\text{C}-$, can be carried out by treating the enol phosphates with sodamide in liquid ammonia, and a synthesis of acetylenic acids has been reported [6] by the action of alkali on the enol arenesulphonates of certain substituted diethyl malonates. Both these reactions [5,6] required activation by a double bond in conjugation with the olefinic linkage in the enol. If the enol phosphate contained a methylene group adjacent to the central carbon–carbon double bond, then allenic products were obtained.[5] These findings suggested that a natural β-polyketone, in which each methylene group is doubly activated, should be transformed into an acetylene or allene *in vitro* under even milder conditions.

The closest available model for a β-polyketone was acetonedicarboxylic ester (Ia). This was converted by standard methods [7] into the enol phosphate (IIa) and the effect of base on the latter was examined. Reaction in ether with aqueous sodium hydroxide at 0° for 10 seconds gave 42% of dimethyl penta-2,3-dienedioate [8] (IIIa) (" glutinic ester "), and the same product (70%) was obtained after 90 minutes at 25° with aqueous sodium carbonate, and (12%) after 4 hours at 25° with sodium hydrogen carbonate in aqueous dioxan. In each case the absence of recovered enol phosphate indicates the occurrence of a competing substitution, with displacement of phosphate by hydroxyl ion.

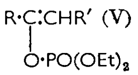
(I) $\text{R}\cdot\text{CH}_2\cdot\text{CO}\cdot\text{CH}_2\text{R}'$

$\text{R}\cdot\text{CH}_2\cdot\text{C}\vdots\text{CR}'$ (IV)

(II)



$\text{R}\cdot\text{CH}_2\cdot\text{C}(\text{O}\cdot\text{PO}(\text{OEt})_2)\text{:CHR}'$



$\text{R}\cdot\text{C}(\text{O}\cdot\text{PO}(\text{OEt})_2)\text{:CHR}'$

(V)

(III) $\text{R}\cdot\text{CH:C:CHR}'$

$\text{R}\cdot\text{C}\vdots\text{C}\cdot\text{CH}_2\text{R}'$ (VI)

	R	R′		R	R′
(a)	CO_2Me	CO_2Me	(e)	Ph	H
(b)	Ph	CO_2Et	(f)	$n\text{-C}_5\text{H}_{11}$	CO_2H
(c)	Ph	CO_2H	(g)	Me	CO_2H
(d)	H	CO_2Et			

Replacing one of the activating methoxycarbonyl groups by a phenyl group in the keto-ester (Ia) led to ethyl β-oxo-γ-phenylbutyrate (Ib), which was converted into diethyl *trans*-1-benzyl-2-ethoxycarbonylvinyl phosphate (IIb), shown to have this structure from its ultraviolet spectrum (rising end-absorption only). This had greatly diminished reactivity to base. Some unchanged enol phosphate (IIb) was still present after reaction with sodium hydroxide for 16 hours, and only after 24 hours was the reaction complete, giving an acidic fraction (65%), the infrared spectrum of which showed strong absorption at 1960 cm.$^{-1}$ (C:C:C) and no absorption at 2222 cm.$^{-1}$ ($\text{C}\vdots\text{C}$), and also phenylacetone (16%). The nuclear magnetic resonance (n.m.r.) spectrum of the total acidic material showed it to

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[1] Cf. *Proc. Chem. Soc.*, 1963, 56.

[2] Bohlmann and Mannhardt, *Progr. Chem. Org. Nat. Prod.*, 1957, **14**, 1; Jones, *Proc. Chem. Soc.*, 1960, 199; Sörensen, *ibid.*, 1961, 98.

[3] Bu'lock and Gregory, *Biochem. J.*, 1959, **72**, 322.

[4] Bu'lock, Allport, and Turner, *J.*, 1961, 1654.

[5] Craig and Moyle, *Proc. Chem. Soc.*, 1962, 149; *J.*, 1963, 3712.

[6] Fleming and Harley-Mason, *Proc. Chem. Soc.*, 1961, 245; *Chem. and Ind.*, 1962, 560.

[7] Lichtenthaler, *Chem. Rev.*, 1961, **61**, 607.

[8] Jones, Mansfield, and Whiting, *J.*, 1954, 3208.

be a mixture composed of 66% of 4-phenylbuta-2,3-dienoic acid (IIIc) and 33% of 4-phenylbut-3-ynoic acid (VIc). In this spectrum, the allenic protons appeared as two doublets with chemical shifts $\delta = 5{\cdot}94$ and 6·58 p.p.m. (*J* 6·5 c./sec.) and the methylene group as a singlet with $\delta = 3{\cdot}47$ p.p.m. The similarly located methylene group in pent-3-ynoic acid (VIg) was found at δ 3·26 p.p.m. and in phenylallene the single proton was at δ 5·82 p.p.m. (triplet, $J = 6{\cdot}7$ c./sec.) and the terminal protons at 4·75 p.p.m. (doublet, $J = 6{\cdot}7$ c./sec.). Long-range spin–spin coupling across the allene system has been previously observed.[9]

The same mixture of the acids (IIIc) and (VIc) in the ratio of 3 : 2 was obtained [10] when the 3-ynoic acid (VIc) was equilibrated with 18% potassium carbonate at 40°. Conversion of the acetylenic acid (IVc) into the allenic acid (IIIc) appears to be irreversible.

Since the crude product was completely soluble in alkali but on acidification afforded the acids (IIIc) and (VIc) and phenylacetone, the latter arose by decarboxylation of β-oxo-γ-phenylbutyric acid, formed either by total alkaline hydrolysis of the enol phosphate (IIb) or possibly from the allenic acid (IIIc), which has been reported [10] to give phenylacetone with alkali at 90°.

Further removal of activating groups from the ester (Ib) left acetoacetic ester (Id) and phenylacetone (Ie). Their enol phosphates, diethyl *trans*-2-ethoxycarbonyl-1-methylvinyl phosphate [11] (IId) and diethyl 1-benzylvinyl phosphate [5] (IIe), afforded no allene or acetylene with aqueous alkali even after 24 hours.

Successful elimination with aqueous base at room temperature therefore requires the presence of activating groups on both sides of the three-carbon system in the enol phosphate (II), *i.e.*, in both R and R′, in a manner similar to that obtaining in a natural β-polyketone. It should be recalled, however, that in the enol phosphate (V), which lacks the methylene group adjacent to the enol double bond, only hydrolysis occurred with aqueous alkali [5] even if both R and R′ were activating groups (*e.g.*, Vb), emphasizing the greater ease of elimination in enol phosphates of type (II) possessing a central three-carbon system analogous to a natural β-polyketone.

Formation of the allene (III) could take place from the enol phosphate (II) either by loss of the olefinic proton to give the acetylene (IV) which then undergoes rapid isomerization to the allene, or by direct loss of a proton from the methylene group adjacent to the enol double bond to produce the allene directly. Whereas only glutinic ester (IIIa) is expected [8] from acetonedicarboxylic ester (Ia), in the case of ethyl β-oxo-γ-phenylbutyrate (Ib) the product could be the allene (IIIc) or the acetylene (IVc). Since 4-phenylbut-2-ynoic acid (IVc) on identical treatment gave a mixture of 66% of the allene (IIIc) and 33% of the acetylenic acid (VIc), it is not possible to say whether or not formation of the allene proceeded through the intermediate acetylene (IVc). In the same conditions non-2-ynoic acid (IVf) was recovered unchanged. Since this acid gave the allene (IIIf) and the acetylenic acid (VIf) on treatment [12] with sodamide in liquid ammonia, this confirms the need for activation on both sides of the three-carbon system in the acetylenes (IV) [*e.g.*, (IVc)] for allene formation to occur with aqueous alkali. These requirements are thus identical for the enol phosphates (II) and the acetylenes (IV).

The conditions required for the transformation acetylene $\longrightarrow$ allene were examined in order to discover a base which might cause elimination of the phosphate from the enol (II) without also bringing about the acetylene $\longrightarrow$ allene isomerization. For this purpose, ethyl 4-phenylbut-2-ynoate (IVb) was subjected to a range of bases of decreasing pK_a under identical conditions (6 hours in boiling benzene). With triethylamine (pK_a 10·74),[13] complete disappearance of the acetylenic ester was observed, and the product (which in the

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[9] Snyder and Roberts, *J. Amer. Chem. Soc.*, 1962, **84**, 1582.
[10] Jones, Mansfield, and Whiting, *J.*, 1956, 4761.
[11] Schrader, *Angewandte Chemie*, Monograph No. 62, 1952, Verlag Chemie, Weinheim.
[12] Craig and Moyle, *J.*, **1963**, 4402.
[13] Hall, *J. Phys. Chem.*, 1956, **60**, 63.

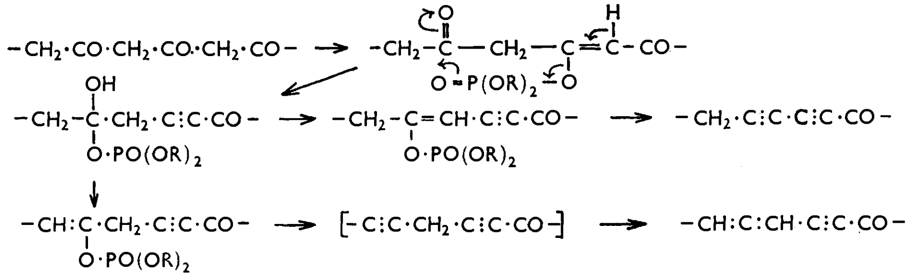
infrared spectrum showed only allenic absorption) consisted of 30% of ethyl 4-phenylbut-3-ynoate (VIb) and 70% of the allene ester (IIIb), as determined from the n.m.r. spectrum. The conversion of the acetylenic ester (IVb) into the allene (IIIb) was extremely rapid, since the infrared spectrum showed only allenic absorption after 5 minutes when the ester (IVb) was treated with triethylamine under the same conditions.

When benzyldimethylamine (pK_a 8·93)[13] and 4-methylmorpholine (pK_a 7·41)[13] were used, the acetylenic absorption in the infrared spectrum was completely replaced by the allene band, while with diethylaniline (pK_a 6·56) the acetylene (IVb) was recovered quantitatively.

The enol phosphate (IIb) under the same conditions gave 75% elimination when triethylamine was used (complete elimination required 8 hours); 4-methylmorpholine afforded only recovered phosphate. It therefore follows that any base of $pK_a > 7{\cdot}4$ (necessary for the elimination) will also cause the rearrangement to the allene (and subsequently to the 3-ynoic ester), and that the acetylene intermediate, if present, can never be isolated from the reaction.

Chlorination of ethyl β-oxo-γ-phenylbutyrate and reaction of the resulting ethyl α-chloro-β-oxo-γ-phenylbutyrate with triethyl phosphite[14] gave diethyl *cis*-2-ethoxycarbonyl-1-benzylvinyl phosphate (IIb), showing an ultraviolet spectrum (rising end-absorption only) almost identical with that of its *trans*-isomer. It should be noted that the *cis*- and *trans*-enol phosphates (IIb) had $\nu_{max.}$ 1129 and 1208 cm.$^{-1}$ (=C–O–), respectively, in agreement with the observed values of 1136 and 1215 cm.$^{-1}$, respectively, for the *cis*- and *trans*-isomers of dimethyl 2-methoxycarbonyl-1-methylvinyl phosphate[15] and $\nu_{max.}$ 1217 cm.$^{-1}$ for the *trans*-enol phosphate (IId). The *cis*-enol phosphate (IIb) reacted with triethylamine in boiling benzene to give not more than 5% elimination [from spectroscopic estimation of the allene (IIIb) produced], compared with 75% of such elimination from the *trans*-isomer (IIb) by the same method.

The small amount of elimination observed with the *cis*-enol phosphate may be due to the presence of some of the *trans*-isomer, since it is known[7] that the Perkow reaction, while leading predominantly to the *cis*-enol phosphate, frequently produces some of the *trans*-compound as well. Some support for this assumption comes from the finding that extending the reaction of the *cis*-enol phosphate with triethylamine to 24 hours does not significantly increase the amount of allene present.



Since activating centres in both the groups R and R′ of the enol phosphate (II), apparently necessary for allene formation by aqueous base, confer additional acidity on the methylene protons as well as on the olefinic proton in phosphates (II), no clear distinction can be made between the two possible mechanisms of elimination.

The concurrent formation of acetylene and allene in Nature may be explained if formation of a triple bond is accompanied by intramolecular transphosphorylation giving an intermediate hemiketal phosphate. Dehydration of this could then give two different

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[14] Perkow, Ullerich, and Meyer, *Naturwiss.*, 1952, **39**, 352.

[15] Stiles, Reilly, Pollard, Tieman, Ward, Phillips, Soloway, and Whetstone, *J. Org. Chem.*, 1961, **26**, 3960.

enol phosphates leading, respectively, to a stable 1,2-diyne system (well known in Nature) or to an unstable 1,3-diyne, which is unknown while its rearrangement product, the allene-acetylene system, is relatively common.

EXPERIMENTAL

Ultraviolet spectra were determined for ethanol solutions on a Cary No. 11 recording spectrophotometer, and infrared spectra for KBr discs (solids) or films (liquids) with a Beckman I.R. 5 instrument. Analyses are by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley 4.

Diethyl trans-2-*methoxycarbonyl*-1-*methoxycarbonylmethylvinyl Phosphate* (IIa).—Dimethyl acetonedicarboxylate (21·8 g., 0·125 mole) was added to a stirred solution of sodium (2·3 g. 0·10 mole) in ethanol (100 ml.) at 0°. Diethyl phosphorochloridate (17·3 g., 0·10 mole) was added during 30 min. to the enolate, then the mixture was stirred for a further 30 min. at 0°. Ice–water (1 l.) was added and the products were isolated with ether. Triethyl phosphate and an excess of dimethyl acetonedicarboxylate were removed by distillation (bath to 160°/0·5 mm.). Fractionation of the residue afforded the *enol phosphate* (12·4 g., 40%), b. p. 127—129°/0·005 mm., n_D^{25} 1·4515 (Found: C, 42·3; H, 6·0. $C_{11}H_{19}O_8P$ requires C, 42·6; H, 6·1%), $\nu_{max.}$ 1666 cm.$^{-1}$ (—C=C—O).

Dimethyl Penta-2,3-*dienedioate* (IIIa).—(*a*) A solution of the preceding phosphate (12·4 g., 0·04 mole) in ether (250 ml.) at 0° was shaken for 10 sec. with an ice-cold solution of sodium hydroxide (10 g.) in water (250 ml.). The deep-red aqueous layer was separated and the ether solution washed with ice–water. Distillation of the dried (Na_2SO_4) ether layer gave dimethyl penta-2,3-dienedioate (2·6 g., 40%), b. p. 73—74°/0·3 mm., n_D^{25} 1·4840 (lit.,[16] b. p. 101°/6 mm., n_D^{19} 1·4878), $\nu_{max.}$ 1960 (C:C:C) and 1715 cm.$^{-1}$ (ester). No enol phosphate was recovered.

(*b*) A solution of the phosphate (3·1 g., 0·01 mole) in ether (100 ml.) was shaken with 10% aqueous sodium carbonate (25 ml.) for 15 min. at 25°. The orange aqueous layer was separated, and the ether layer washed with water, dried (Na_2SO_4), and evaporated. The course of the reaction was followed by observing the appearance of the allene band (1960 cm.$^{-1}$), the merging of the two ester peaks (1735, 1715 cm.$^{-1}$) of the enol phosphate into one (1715 cm.$^{-1}$) in the allene, and the disappearance of the enol peak (1666 cm.$^{-1}$). After six such treatments (total reaction time 90 min.), the reaction was complete and the product (1·1 g., 70%) had n_D^{25} 1·4840 and an infrared spectrum identical with that of dimethyl penta-2,3-dienedioate.

(*c*) A mixture of the phosphate (3·1 g., 0·01 mole), sodium hydrogen carbonate (3 g.), water (20 ml.), and dioxan (20 ml.) was stirred under nitrogen at 25° for 4 hr., during which the mixture became orange. Water was added and the product isolated with ether. The infrared spectrum indicated that ~12% of the allene had been formed. When the reaction time was extended to 24 hr., no allenic material was isolated.

Diethyl trans-1-*Benzyl*-2-*ethoxycarbonylvinyl Phosphate* (IIb).—Ethyl γ-phenylacetoacetate [17] (20·6 g., 0·10 mole) was added to a solution from sodium (2·3 g.) in ethanol (100 ml.) at 0° and the mixture was stirred for 30 min. at 0°. Diethyl phosphorochloridate (17·3 g., 0·10 mole) was added during 1 hr. to the stirred enolate, then the mixture kept for a further 30 min. at 0°. Ice–water (1 l.) was added and the products were isolated with ether. Distillation gave a small forerun (4 g.), b. p. 45—47°/0·4 mm. (triethyl phosphate), and recovered ethyl γ-phenylacetoacetate (8·4 g.), b. p. 105—108°/0·4 mm. A cooled solution of the residue in ether (250 ml.) was washed with ice-cold N-sodium hydroxide, then water, dried (Na_2SO_4), and evaporated. Distillation afforded *diethyl* trans-1-*benzyl*-2-*ethoxycarbonylvinyl phosphate* (18·9 g., 55%), b. p. 156—158°/0·005 mm., n_D^{25} 1·4935 (Found: C, 56·1; H, 6·5. $C_{16}H_{23}O_6P$ requires C, 56·1; H, 6·8%), $\nu_{max.}$ 1666 (—C=C—O), 1208 cm.$^{-1}$ (=C—O), $\lambda_{max.}$ rising end-absorption only, inflexion at 226 mμ (ε 1170).

Reaction of Diethyl trans-1-*Benzyl*-2-*ethoxycarbonylvinyl Phosphate with Sodium Hydroxide in Aqueous Dioxan.*—Diethyl *trans*-1-benzyl-2-ethoxycarbonylvinyl phosphate (6·84 g., 0·02 mole) in dioxan (75 ml.), and a solution of sodium hydroxide (3 g.) in water (75 ml.), were stirred at 5° for 4 hr. during which the mixture became homogeneous. After a further 20 hr. at 5°, the bulk of the solvent was evaporated at 5° and the residue distributed between ether and

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[16] Makulec, Malachawski, and Maritus, *Chem. Zentr.*, 1929, 1328.

[17] Bowman, *J.*, 1950, 322.

water. Evaporation of the dried (Na_2SO_4) ether layer left no residue. An extract of the acidified aqueous layer was washed with water, saturated sodium hydrogen carbonate solution, and water, dried (Na_2SO_4), and evaporated. Phenylacetone (0·43 g., 16%) remained. The sodium hydrogen carbonate washings were acidified and the product was isolated with ether. Evaporation of the ether left 2·08 g. (65%) of acidic material, $\nu_{\text{max.}}$ 1960 cm.$^{-1}$, the n.m.r. spectrum of which showed it to be a mixture of 66% of 4-phenylbuta-2,3-dienoic acid (IIIc) and 33% of 4-phenylbut-3-ynoic acid (VIc). Crystallization from ether–light petroleum (b. p. 30—60°) gave 4-phenylbuta-2,3-dienoic acid, m. p. 90—93° (lit.,[10] 92—94°).

Isomerization of 4-*Phenylbut*-2-*ynoic Acid*.—A solution of 4-phenylbut-2-ynoic acid (0·80 g., 0·005 mole) in dioxan (30 ml.) was stirred with N-sodium hydroxide (30 ml.) for 4 hr. at 5°, then kept for a further 20 hr. at 5°. The acidic material, isolated as above, had infrared and n.m.r. spectra identical with those reported above.

4-*Phenylbut*-2-*ynoic Acid* (IVc).—A mixture of phenylallene and benzylacetylene was prepared from propargyl bromide and phenylmagnesium bromide as described by Gaudemar.[18] This mixture (23 g.) was added to ethylmagnesium bromide (from 2·4 g., 0·10 g.-atom of magnesium) in ether (100 ml.), then heated under reflux for 1 hr. The cooled mixture was poured over solid carbon dioxide (200 g.) and sealed overnight in an autoclave. The magnesium complex was decomposed with dilute sulphuric acid, and the product was isolated with ether. The ether was washed with water, saturated sodium hydrogen carbonate, and water, dried (Na_2SO_4), and evaporated. The infrared spectrum of the residue (14 g.) indicated that it was largely phenylallene. The sodium hydrogen carbonate washings were acidified and extracted with ether. Evaporation of the dried (Na_2SO_4) ether extracts and crystallization from hexane afforded 4-*phenylbut*-2-*ynoic acid* (7·8 g.) as leaflets, m. p. 50—51° (Found: C, 75·0; H, 5·0. $C_{10}H_8O_2$ requires C, 75·0; H, 5·0), $\nu_{\text{max.}}$ 2222 cm.$^{-1}$ ($C\vdots C$). Bourguel [19] reports this compound as a brown syrup.

Ethyl 4-*Phenylbut*-2-*ynoate* (IVb).—4-Phenylbut-2-ynoic acid (6·0 g.) and toluene-*p*-sulphonic acid (0·2 g.) in ethanol (120 ml.) were heated under reflux for 12 hr. The solvent was evaporated *in vacuo* and the residue diluted with ether and washed with water and saturated sodium hydrogen carbonate solution. Distillation of the dried (Na_2SO_4) ether solution afforded *ethyl* 4-*phenylbut*-2-*ynoate* (6 g.), b. p. 107—109°/0·8 mm., n_D^{25} 1·5230 (Found: C, 76·25; H, 6·3. $C_{12}H_{12}O_2$ requires C, 76·55; H, 6·4%), $\nu_{\text{max.}}$ 2222 cm.$^{-1}$ ($C\equiv C$).

Reaction of Diethyl trans-1-*Benzyl*-2-*ethoxycarbonylvinyl Phosphate with Triethylamine in Benzene*.—The phosphate (6·84 g., 0·02 mole), triethylamine (10·1 g., 0·1 mole), and benzene (50 ml.) were heated under reflux under nitrogen for 8 hr. The cooled solution was diluted with ether and washed with ice-cold dilute sulphuric acid, then water, dried (Na_2SO_4), and evaporated *in vacuo*. The infrared spectrum showed strong allenic absorption (1960 cm.$^{-1}$); the n.m.r. spectrum showed the total product to be a mixture of ethyl 4-phenylbuta-2,3-dienoate (IIIb) (70%) and 4-phenylbut-3-ynoate (VIb) (30%).

Isomerization of Ethyl 4-*Phenylbut*-2-*ynoate with Triethylamine in Benzene*.—Ethyl 4-phenylbut-2-ynoate (1·88 g., 0·01 mole), triethylamine (5·05 g., 0·05 mole), and benzene (25 ml.) were heated under reflux under nitrogen for 6 hr. The total product, isolated as above, had infrared and n.m.r. spectra identical with those reported above.

Diethyl cis-1-*Benzyl*-2-*ethoxycarbonylvinyl Phosphate* (IIb).—γ-Phenylacetoacetic ester (8·24 g., 0·04 mole) and sulphuryl chloride (6·1 g., 0·045 mole) in carbon tetrachloride (100 ml.) were stirred overnight at 25°. The solution was washed with saturated sodium hydrogen carbonate, then water, dried (Na_2SO_4), and evaporated *in vacuo*. The total residue was heated for 2 hr. at 100° with triethyl phosphite (9·9 g., 0·06 mole), then the excess of reagent was evaporated *in vacuo*. Distillation afforded *diethyl* cis-1-*benzyl*-2-*ethoxycarbonylvinyl phosphate* (9·8 g., 72%), b. p. 156—158°/0·01 mm., n_D^{23} 1·4950 (Found: C, 56·1; H, 6·6. $C_{16}H_{23}O_6P$ requires C, 56·1; H, 6·8%), $\lambda_{\text{max.}}$ rising end-absorption, inflexion at 226 mμ (ε 1180), $\nu_{\text{max.}}$ 1655 (–C=C–O), 1129 cm.$^{-1}$ (=C–O).

This work was supported by a grant from the National Institutes of Health, U.S. Public Health Service.

DEPARTMENT OF PHARMACEUTICAL CHEMISTRY, UNIVERSITY OF CALIFORNIA,
SAN FRANCISCO 22, U.S.A.

[*Received, March 4th,* 1963.]

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[18] Gaudemar, *Ann. Chim.* (*France*), **1956**, **1**, 161.

[19] Bourguel, *Ann. Chim.* (*France*), 1925, **3**, 388.