

# PHOSPHONIC ACIDS AND ESTERS—XVIII<sup>1</sup>

## PREPARATION OF $\beta,\gamma$ -UNSATURATED PHOSPHONATES BY THE STOBBE CONDENSATION WITH DIETHYL $\beta$ -CARBETHOXYETHYLPHOSPHONATE; STEREOCHEMICAL DEPENDENCIES OF HOMOALLYLIC $^{31}\text{P}$ — $^1\text{H}$ SPIN-SPIN COUPLING CONSTANTS<sup>2</sup>

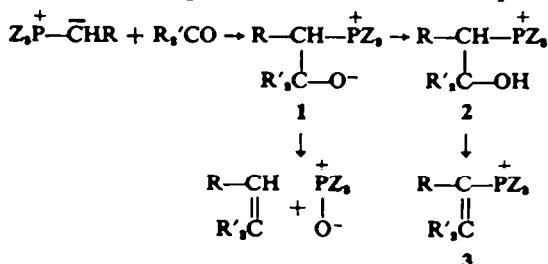
D. J. MARTIN, M. GORDON<sup>3</sup> and C. E. GRIFFIN

Department of Chemistry, University of Pittsburgh,  
Pittsburgh, Pennsylvania 15213

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**Abstract**—The base catalyzed condensation of the title compound (4) with benzaldehyde and a variety of ketones follows a normal Stobbe course yielding  $\beta,\gamma$ -unsaturated phosphonates, i.e. ethyl hydrogen  $\beta$ -carbethoxy- $\gamma$ -substituted allylphosphonates (5). Despite the unsymmetrical nature of 4, condensation is specific at the position adjacent to the carbethoxy function; neither the isomeric  $\alpha,\beta$ -unsaturated phosphonates nor the dephosphonated (Wittig) products,  $\beta,\gamma$ -unsaturated carboxylates, are observed. The specificity presumably reflects the greater stabilization afforded an  $\alpha$ -anion by a carbonyl function than by a dialkoxyphosphono function. Condensations with unsymmetrical carbonyl components (acetophenone, benzaldehyde) yield mixtures of *cis*- and *trans*-5 in a non-stereoselective manner. Gross structures and stereochemical relationships were assigned on the basis of PMR spectroscopy. In 5 derived from acetophenone and acetone, a long-range (five bond)  $^{31}\text{P}$ — $^1\text{H}$  coupling is observed. Based upon studies of these and model compounds (dimethyl  $\gamma,\gamma$ -dimethylallylphosphonate), it was shown that the *transoid*  $^3J_{\text{PH}}$  is of larger magnitude than the corresponding coupling involving *cisoid* geometry.

ALTHOUGH base-catalyzed condensation reactions constitute one of the primary general synthetic methods of organic chemistry, relatively few applications of such reactions have been reported for the preparation of organophosphorus compounds. The primary reason for the lack of utilization of condensation procedures in this guise is the propensity of the readily formed  $\alpha$ -anions of organophosphorus compounds to undergo condensation with carbonyl compounds with the loss of the phosphorus grouping. The Wittig reaction constitutes the best known example of this general process.<sup>4</sup> The initial condensation adducts (1) form readily, but a strong thermodynamic drive exists for their collapse to form an olefin and a phosphoryl compound.



<sup>1</sup> Part XVII: W. M. Daniewski and C. E. Griffin, *J. Org. Chem.* **31**, 3236 (1966).

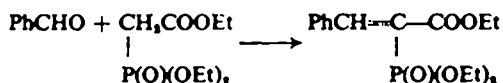
<sup>2</sup> Presented in part at the 150th National Meeting of the American Chemical Society. Abstracts p. 58S. Atlantic City, New Jersey, Sept. 16 (1965).

<sup>3</sup> National Science Foundation Cooperative Graduate Fellow, 1961–1964.

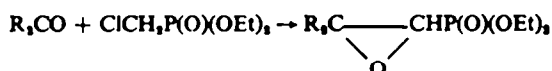
<sup>4</sup> For recent discussions, see: \* A. Maercker, *Org. Reactions* **14**, 270 (1964); \* R. F. Hudson, *Structure and Mechanism in Organo-Phosphorus Chemistry* pp. 223–232. Academic Press, New York, N.Y. (1965).

Consequently, these adducts rarely exist sufficiently long for protonation to occur and the simple phosphorus containing products (2 and 3) are not normally observed. Olefin formation is generally observed in the reactions of the  $\alpha$ -anions of phosphonium salts,<sup>4a</sup> phosphonates,<sup>5</sup> and phosphine oxides.<sup>5a,6</sup>

Products of types 2 and 3 have been obtained in a limited number of cases.  $\beta$ -Hydroxyalkylphosphorus structures (2) have been reported in reactions involving the  $\alpha$ -anions of phosphonium salts<sup>7</sup> and phosphine oxides<sup>5a,6,8</sup> with aldehydes and ketones. A successful Knoevenagel-type condensation of benzaldehyde with diethyl carbethoxymethylphosphonate has been carried out,<sup>9</sup> but attempted extension of the reaction to *p*-nitrobenzaldehyde led to the normally encountered dephosphonation<sup>8</sup>

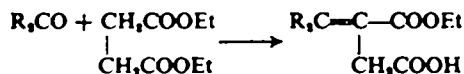


and the formation of ethyl *p*-nitrocinnamate.<sup>9b</sup> An analog of the Darzens glycidic ester synthesis represents the only remaining reported example of this general class of condensation reaction. Epoxyphosphonates are readily prepared by the reaction of the  $\alpha$ -anion of diethyl chloromethylphosphonate with aldehydes and ketones;<sup>10</sup>

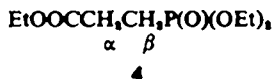


in this reaction, elimination of chloride ion from the initial adduct 1 ( $\text{R} = \text{Cl}$ ) competes successfully with elimination of a phosphoryl structure and olefin formation.

In an effort to realize some of the synthetic advantages of conventional condensation reactions in organophosphorus chemistry, we have undertaken the study of a number of such reactions<sup>10b</sup> which might be expected to lead to the formation of phosphorus containing products. One such reaction is the Stobbe condensation which



has been demonstrated to be of wide applicability in organic synthesis.<sup>11</sup> The monophosphonate analog (diethyl  $\beta$ -carbethoxyethylphosphonate, 4) of diethyl succinate,



the normal active hydrogen component of the Stobbe condensation, is readily available through the reaction of triethyl phosphite and  $\beta$ -propiolactone.<sup>12</sup>

<sup>4a</sup> L. Horner, H. Hoffman, H. G. Wippel and G. Klahre, *Chem. Ber.* **92**, 2499 (1958); <sup>b</sup> W. S. Wadsworth, Jr. and W. D. Emmons, *J. Am. Chem. Soc.* **83**, 1733 (1961); <sup>c</sup> D. H. Wadsworth, O. E. Schupp, E. J. Seus and J. A. Ford, Jr., *J. Org. Chem.* **30**, 680 (1965).

<sup>5</sup> L. Horner, H. Hoffman and H. G. Wippel, *Chem. Ber.* **91**, 61 (1958).

<sup>7</sup> G. Wittig and U. Schöllkopf, *Chem. Ber.* **87**, 1315 (1954) and Ref 4b, p. 224.

<sup>8</sup> F. Hein and H. Hecker, *Chem. Ber.* **93**, 1339 (1960).

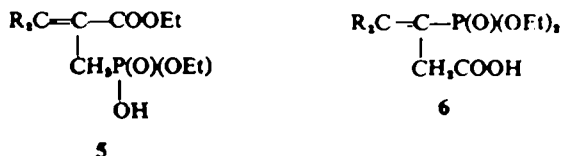
<sup>9a</sup> A. N. Pudovik and N. M. Lebedeva, *Dokl. Akad. Nauk SSSR* **90**, 709 (1953); <sup>b</sup> S. Patai and A. Schwartz, *J. Org. Chem.* **25**, 1232 (1960).

<sup>10a</sup> V. F. Martynov and V. E. Timofeev, *J. Gen. Chem. USSR* **32**, 3383 (1962); <sup>b</sup> R. H. Churi and C. E. Griffin, *J. Amer. Chem. Soc.* **88**, 1824 (1966) and unpublished results.

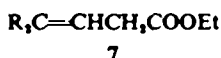
<sup>11</sup> W. S. Johnson and G. H. Daub, *Org. Reactions* **6**, 1 (1951).

<sup>12</sup> R. L. McConnel and H. W. Coover, Jr., *J. Amer. Chem. Soc.* **78**, 4453 (1956).

Three primary products could be formed in the base-catalyzed condensation of a carbonyl compound with 4. Because of its unsymmetrical nature, condensation could occur at either the  $\alpha$ - or  $\beta$ -carbon atoms of 4 leading to the formation of  $\beta,\gamma$ - (5) or  $\alpha,\beta$ - (6) unsaturated phosphonates, respectively; the structures postulated for 5 and 6 assume the operation of the mechanism accepted for the conventional Stobbe



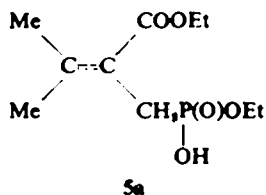
condensation.<sup>11</sup> The third product to be considered was the dephosphonated olefin 7, which would result from condensation at the  $\beta$ -position followed by the loss of the



phosphonate function in analogy to other results with phosphonate anions.<sup>5,12</sup>

Treatment of 4 with acetone in the presence of sodium hydride gave an exothermic reaction. A colorless acidic liquid (40%) with an elemental analysis corresponding to either 5 or 6 was isolated, indicating that reaction had proceeded with retention of the phosphonate function. The IR spectrum of this product showed carbonyl ( $1721\text{ cm}^{-1}$ ) and phosphoryl ( $1283\text{ cm}^{-1}$ ) bands. The carbonyl absorption is within the ranges cited for both  $\alpha,\beta$ -unsaturated esters ( $1730\text{--}1715\text{ cm}^{-1}$ ) and saturated aliphatic acids ( $1725\text{--}1700\text{ cm}^{-1}$ ).<sup>13</sup> These data are consequently consistent with both structures 5 and 6 ( $\text{R} = \text{Me}$ ).

The PMR spectrum of this product, however, allowed an unequivocal assignment of structure 5a. The spectrum showed a triplet ( $-\text{CH}_2-\text{CH}_3$ ) at  $\tau = 8.75$ , two

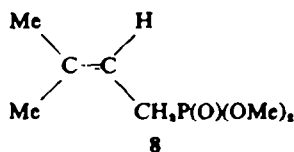


doublets ( $=\text{C}-\text{CH}_2$ ) at  $8.12$  ( $^5J_{\text{PH}} = 4.1$ ) and  $7.95$  ( $^5J_{\text{PH}} = 5.8$ ), a doublet ( $\text{P}-\text{CH}_2$ ) at  $7.13$  ( $^3J_{\text{PH}} = 21.8\text{ c/s}$ ), a doublet of quartets ( $\text{P}-\text{O}-\text{CH}_2-\text{CH}_3$ ) at  $6.05$ , a quartet ( $\text{C}-\text{O}-\text{CH}_2-\text{CH}_3$ ) at  $5.92$  and a broad singlet ( $-\text{OH}$ ) at  $-1.03\text{ ppm}$ . Three features of this spectrum provide strong support for structure 5a. The multiplets at  $\tau = 6.05$  and  $5.92\text{ ppm}$  indicate the presence of two non-equivalent ethyl ester functions; the isomeric 6 ( $\text{R} = \text{Me}$ ) would be expected to give rise to a pair of superimposable doublets of quartets since the  $\text{P}-\text{O}-\text{Et}$  groups would be magnetically equivalent. The coupling constant of  $21.8\text{ c/s}$  observed for the  $\text{P}-\text{CH}_2$  group is in excellent agreement with the observation of  $^3J_{\text{PH}} = 22.0 \pm 1.0\text{ c/s}$  for a wide variety of model benzyl and allyl phosphonates.<sup>14</sup> For example, a  $^3J_{\text{PH}}$  of  $21.6\text{ c/s}$  is observed

<sup>13</sup> C. N. R. Rao, *Chemical Applications of Infrared Spectroscopy*. Academic Press, New York, N.Y. (1963).

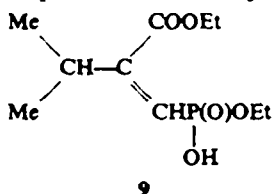
<sup>14</sup> M. Gordon, Ph.D. Thesis, University of Pittsburgh (1965).

in the model compound dimethyl  $\gamma,\gamma$ -dimethyl allylphosphonate (8). The corresponding three bond phosphorusmethylene coupling in 6 would be expected to be



smaller.<sup>15</sup> Similarly, the long-range coupling constants ( $^5J_{\text{PH}}$ ) observed for the  $=\text{C}-\text{CH}_2$  groups of 5a are in good agreement with those observed in 8 (4.2, 5.4 c/s).<sup>16</sup> In the isomeric 6 (R = Me), the phosphorus-methyl coupling would be through four bonds and allylic couplings of this type have been demonstrated to be smaller than the homoallylic couplings of 5a and 8,<sup>14</sup> e.g., in diethyl  $\beta,\beta$ -dimethylvinylphosphonate [ $\text{Me}_2\text{C}=\text{CHP}(\text{O})(\text{OEt})_2$ ],  $^4J_{\text{PH}} = 1.2, 3.2$  c/s.<sup>17</sup>

A careful examination of the reaction mixture failed to yield any evidence for the formation of products of gross structures 6 or 7. Additionally, no evidence was obtained for the existence of 9, a possible base-catalyzed isomerization product of 5a.



Ionin and Petrov<sup>18</sup> have shown the existence of a base-catalyzed equilibrium between  $\beta,\gamma$ - and  $\alpha,\beta$ -unsaturated (butenyl) phosphonates with the former isomer predominating. The reaction does not appear to be general, e.g. cinnamylphosphonate fails to isomerize.<sup>18</sup> Similarly, 5a failed to undergo detectable (PMR) isomerization to 9 on treatment with one equivalent of sodium ethoxide in ethanol for 24 hr.

This condensation reaction was found to be applicable to a variety of carbonyl compounds yielding  $\beta,\gamma$ -unsaturated phosphonates (5) as the sole isolable product in each case. Reactions with benzophenone, cyclohexanone, cyclopentanone, 9-fluorenone, acetophenone and benzaldehyde gave 5b-5i; reaction times and yields are listed in Table 1. The structure assigned to each of these products was supported by IR (Table I), PMR (Table 2) and UV spectra. Again, no evidence was obtained for the formation of structures 6, 7 and 9. The same general PMR characteristics cited for 5a are also observed in 5b-5i. Ethyl ester non-equivalence is demonstrated by the observation of separate  $\text{P}-\text{O}-\text{CH}_2$  and  $\text{C}-\text{O}-\text{CH}_2$  resonances in 5e-5g and separate  $\text{C}-\text{CH}_2$  resonances for 5b, 5d-5g. The chemical shifts and  $^3J_{\text{PH}}$  observed for the  $\text{P}-\text{CH}_2$  groups of 5b-5i and the long-range couplings ( $^5J_{\text{PH}}$ ) of 5f and 5g are quite similar to those of 5a.

In the condensations of 4 with unsymmetrical carbonyl compounds (acetophenone and benzaldehyde), the formation of both *cis* and *trans* isomers could be anticipated.

<sup>15</sup> F. Ramirez, O. P. Madan and C. P. Smith, *J. Amer. Chem. Soc.* **86**, 5339 (1964).

<sup>16</sup> Similar two- and five-bond phosphorus-proton couplings have been reported for the diethyl analog of 8: V. Mark, 147th National Meeting of the American Chemical Society, Abstracts p. 29L Philadelphia, Pennsylvania, April 9 (1964).

<sup>17</sup> D. C. Wysocki and C. E. Griffin, unpublished results.

<sup>18</sup> B. I. Ionin and A. A. Petrov, *J. Gen. Chem.* **33**, 426 (1963).

TABLE 1. FORMATION AND INFRARED ABSORPTIONS OF  $\beta,\gamma$ -UNSATURATED PHOSPHONATES

$  \begin{array}{c}  R_1 \quad \quad COOEt \\  \diagdown \quad \diagup \\  C=C \\  \diagup \quad \diagdown \\  R_2 \quad \quad CH_2P(O)(OEt) \\  \quad \quad \quad   \\  \quad \quad \quad OH  \end{array}  $ 5						
Compd	R <sub>1</sub>	R <sub>2</sub>	Reaction Time (hr)	Yield (%)	$\nu_{CO}$	$\nu_{PO}$
a	Me	Me	16	40	1721	1283
b	Ph	Ph	18	65	1718	1263
c	—(CH <sub>2</sub> ) <sub>5</sub> —		16	66	1724	1215
d	—(CH <sub>2</sub> ) <sub>6</sub> —		16	45	1721	1239
e	—C <sub>6</sub> H <sub>4</sub> —C <sub>6</sub> H <sub>4</sub> — <sup>a</sup>		16	41	1733	1272
f	Me	Ph	17	51 <sup>b</sup>	1715	1238
g	Ph	Me			1715	1258
h	Ph	H				
i	H	Ph	12	70 <sup>b</sup>	1724	1271

<sup>a</sup> From 9-fluorenone.<sup>b</sup> Mixture of *cis* and *trans* isomers.TABLE 2. PMR SPECTRA OF  $\beta,\gamma$ -UNSATURATED PHOSPHONATES

$  \begin{array}{c}  R_1 \quad \quad COOEt \\  \diagdown \quad \diagup \\  C=C \\  \diagup \quad \diagdown \\  R_2 \quad \quad CH_2P(O)(OEt) \\  \quad \quad \quad   \\  \quad \quad \quad OH  \end{array}  $ 5									
Chemical Shifts and Coupling Constants <sup>a</sup>									
Compd	R <sub>1</sub>	R <sub>2</sub>	$\tau$ C—CH <sub>3</sub>	$\tau$ R <sub>1</sub>	$\tau$ R <sub>2</sub>	$\tau$ PCH <sub>2</sub>	$\tau$ POCH <sub>3</sub>	$\tau$ COCH <sub>3</sub>	$\tau$ OH <sup>b</sup>
a	CH <sub>3</sub>	CH <sub>3</sub>	8.75 t	7.95 d (5.8)	8.12 d (4.1)	7.13 d (21.8)	6.05 dq	5.92 q	-1.03 s
b <sup>c</sup>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	9.15 t 8.72 t	2.62–2.82 m		6.98 d (22.6)	6.02 m		-2.78 s
c	—(CH <sub>2</sub> ) <sub>5</sub> —		8.75 t	8.42–8.72 m		7.13 d (22.0)	6.02 m		-1.45
d <sup>c</sup>	—(CH <sub>2</sub> ) <sub>6</sub> —		8.72 t 8.68 t	7.08–8.50 m		7.03 d (21.2)	5.88 m		-0.62
e	—C <sub>6</sub> H <sub>4</sub> —C <sub>6</sub> H <sub>4</sub> —		8.88 t 8.73 t	2.00–3.08 m		6.47 d (23.4)	5.90 dq	5.57 q	-2.20
f	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	8.75 t 8.68 t	7.77 d (5.6)	2.82 m	7.35 d (21.9)	5.85 dq	6.00 q	—
g	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	9.23 t 8.90 t	2.92 m (4.4)	7.87 d	7.02 d (21.6)	6.28 dq	6.00 q	—
h	C <sub>6</sub> H <sub>5</sub>	H	8.75 t	2.35–2.85 m		6.94 d	5.87 m		-1.50
i	H	C <sub>6</sub> H <sub>5</sub>	8.70 t			(22.7)			

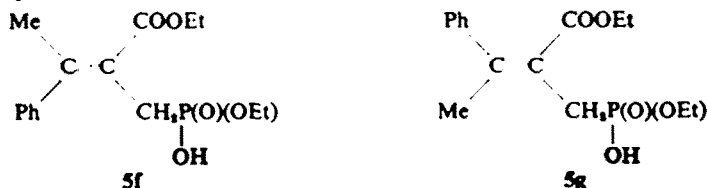
<sup>a</sup> Peak multiplicities are indicated by letters: s = singlet, d = doublet, t = triplet, q = quartet, dq = doublet of quartets, m = unresolved multiplet. Phosphorus-proton coupling constants (c/s) are given in parentheses. Spectra were determined in CCl<sub>4</sub> unless otherwise noted.

<sup>b</sup> Shift cited is center of broad multiplet.

<sup>c</sup> Spectrum determined in CDCl<sub>3</sub>.

<sup>d</sup> Spectrum determined on mixture of *cis* and *trans* isomers.

Examination of the PMR spectrum of the crude product (**5f** + **5g**) from the acetophenone condensation showed the presence of two  $\text{CH}_3\text{—C=}$  doublets ( $\tau = 7.77, 7.87$  ppm) and two  $\text{—CH}_2\text{—P}$  doublets ( $\tau = 6.98, 7.32$  ppm). Silicic acid chromatography led to the separation of the *cis* (**5f**) and *trans* (**5g**) isomers. Stereochemical assignments



were made on the basis of the chemical shifts of the  $\text{CH}_3\text{—C=}$  groups; the Me group *cis* to the carbethoxy group should be deshielded ( $\tau = 7.77$  ppm in **5f**) relative to the methyl group *trans* to the carbonyl function ( $\tau = 7.87$  ppm in **5g**).<sup>19</sup> The anisotropy of the carbethoxy group has been shown to be much greater than that of the  $\text{—CH}_2\text{—P(O)—}$  function.<sup>14</sup> Further evidence for the validity of these assignments is found in the chemical shifts of the  $\text{P—CH}_2\text{—}$  protons. The methylene protons *cis* to the phenyl ring (in **5f**) are shielded ( $\tau = 7.35$  ppm) relative to the methylene protons *trans* to the phenyl ring ( $\tau = 7.02$  ppm in **5g**). The preferential shielding in the *cis* isomer must arise from a tilting of the phenyl ring out of the plane of the double bond; the methylene group would then lie above the plane of the ring in a region of anisotropic shielding.<sup>20</sup> A similar shielding effect ( $\tau = 6.98$  ppm) is observed in the  $\gamma,\gamma$ -diphenyl compound (**5b**) in which the methylene group must be *cis* to a phenyl ring. A marked difference is observed in the chemical shift of the methylene protons of the fluorenylidene derivative (**5e**). In this compound, the aromatic rings are constrained to the plane of the double bond and the methylene group must lie in that plane, a region of strong anisotropic deshielding ( $\tau_{\text{PCH}_2} = 6.47$  ppm).

The postulation of non-coplanarity for the phenyl ring in **5f** is supported by a comparison of the ultraviolet spectra of the two isomers. The *cis* isomer (**5f**) exhibits a maximum at  $240\text{ m}\mu$ , while the *trans* isomer (**5g**) has a maximum at  $245\text{ m}\mu$ .  $\beta$ -Methylcinnamic acid [*cis*,  $\lambda_{\text{max}} = 247\text{ m}\mu$ ; *trans*,  $\lambda_{\text{max}} = 256\text{ m}\mu$ ]<sup>21</sup> is an appropriate model system. Since **5f** is a *trans*- $\alpha$ -substituted- $\beta$ -methylcinnamate, it would be expected to absorb at a longer wave length than **5g**, which contains a *cis*-cinnamate chromophore. The anomalous ultraviolet absorption of **5f** can be explained on the basis of non-coplanarity of the phenyl ring.

The demonstration of the stereochemistry of **5f** and **5g** allows an assignment of the stereochemical dependencies of the observed long-range ( $^5J_{\text{PH}}$ ) couplings. The larger coupling constant ( $5.6\text{ c/s}$ ) observed in **5f** is associated with the *transoid* geometry of the  $\text{H—C—C—CP}$  system, while the smaller coupling constant ( $4.4\text{ c/s}$ ) is associated with *cisoid* geometry. These stereochemical dependencies are parallel to those observed in homoallylic proton-proton couplings; for a variety of butenyl derivatives,  $^5J_{\text{HH}}$  of  $1.2\text{--}1.8\text{ c/s}$  are observed with the *transoid* geometry giving coupling constants about  $0.5\text{ c/s}$  larger in any given stereoisomeric pair.<sup>22</sup> The same dependency

<sup>19</sup> L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, p.121. Pergamon Press, New York, N.Y. (1959).

<sup>20</sup> Ref. 19, pp. 125–129.

<sup>21</sup> A. Mangini and F. Montanari, *Gazz. Chim. Ital.* **88**, 1081 (1958).

<sup>22</sup> S. Sternhell, *Rev. Pure Appl. Chem.* **14**, 15 (1964).

is observed for  $^1J_{PH}$  in **5a** (*transoid*, 5.8 c/s; *cisoid*, 4.1 c/s)<sup>25</sup> and **8** (*transoid*, 5.4 c/s; *cisoid*, 4.2 c/s). Similar long-range couplings ( $^3J_{PH}$  = 1.5, 3.0 c/s) have been reported by Bentrude and Witt<sup>24</sup> in a vinyl phosphite system:  $Me_2C=C(R)OP(OR)_2$ . Although no assignments of stereochemistry were made, it is probable that the larger coupling is that of the *transoid* system.

The non-quantitative nature of the separation of **5f** and **5g** does not allow a determination of specific quantities of the two isomers, but the PMR spectrum of the crude mixture indicates approximately equivalent quantities to be present. A similar non-stereoselectivity was observed in the condensation of benzaldehyde with **4**. The PMR spectrum of the product from this reaction indicated the presence of both *cis* (**5i**) and *trans* (**5h**) isomers in a ca. 1:1 ratio. However, in this case, attempted separation of the isomers by column chromatography was unsuccessful.

The isolation of **5** as the sole product from the condensations of carbonyl compounds with **4** is probably the result of either preferential or exclusive anion formation *alpha* to the carbethoxy function. Although acidity studies<sup>26</sup> indicate the inductive effects ( $\sigma^*$ ) of carboalkoxy and dialkoxyphosphono groups to be comparable, a lone phosphono group is apparently incapable of activating an  $\alpha$ -CH function sufficiently for effective anion formation. The examples of successful utilization of  $\alpha$ -anions of phosphonates all involve compounds in which a second activating group (e.g., carboalkoxy, cyano, phenyl) is substituted at the  $\alpha$ -position.<sup>5,9,10,26</sup> The ineffectiveness of a phosphono function in stabilizing an  $\alpha$ -anionic charge is presumably due to the relative weakness of  $d\pi$ - $p\pi$  bonding<sup>27</sup> as compared to the simpler *p*-orbital bonding in the  $\alpha$ -anions of carbonyl compounds. Evidence relevant to this point was provided by two studies. In our hands, methyl acetate was found to undergo  $\alpha$ -deuteration with NaOMe in MeOD at 37° at least 100 times more rapidly than dimethyl methylphosphonate.<sup>28</sup> An attempted exchange study with **4** was unsuccessful; some exchange was observed (PMR integration), but the position of deuteration could not be determined because of the overlap of the  $\alpha$ - and  $\beta$ -methylene resonances. Attempted deuteration and alkylation of the anion of **4** (formed by NaH reaction) was similarly inconclusive; higher boiling materials, presumably self-condensation products of **4**, were isolated. Attempted condensation of benzophenone with  $(EtO)_2P(O)CH_2CH_2P(O)(OEt)_2$ <sup>29</sup> under the Stobbe conditions employed with **4** was unsuccessful (70% of the ester was recovered), providing further indication that

<sup>25</sup> Assignments of the stereochemistry of the homoallylic systems in **5a** are made in the same manner as the structural assignments of **5f** and **5g**, i.e. on the basis of the deshielding of the  $CH_2-C\equiv$  by *cis* carbethoxy. For a discussion of the stereochemical relationships involved in **8**, see the Experimental Section.

<sup>24</sup> W. G. Bentrude and E. R. Witt, *J. Amer. Chem. Soc.* **85**, 2522 (1963).

<sup>23</sup> D. J. Martin and C. E. Griffin, *J. Org. Chem.* **30**, 4034 (1965).

<sup>10</sup> G. Kosolapoff and J. S. Powell, *J. Amer. Chem. Soc.* **72**, 4198 (1950); G. Kosolapoff, *ibid.*, **75**, 1500 (1953); A. N. Pudovik, L. P. Shchelkina and L. A. Bashirova, *Zh. Obshch. Khim.* **27**, 2367 (1957); L. E. Tammelin and L. Fagerlin, *Acta. Chem. Scand.* **14**, 1353 (1960).

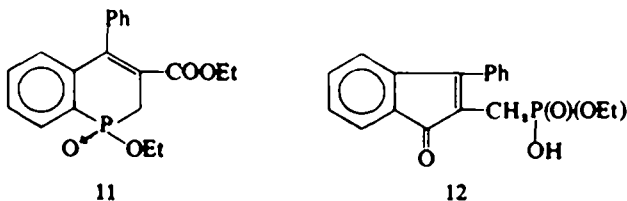
<sup>27</sup> Ref. 4b, pp. 46-89.

<sup>11</sup> Optically active diethyl 2-octylphosphonate has been shown by D. J. Cram, R. D. Trepka and P. St. Janiak, *J. Amer. Chem. Soc.* **86**, 2731 (1964) to undergo only 18-20% exchange with  $t-C_4H_9OK$  in  $t-C_4H_9OD$  (100°, 20 hr). No absolute rate data were given for this reaction, but the analogous sulfonate underwent exchange ca. 100 times more rapidly at 25°.

<sup>26</sup> A. H. Ford-Moore and J. H. Williams, *J. Chem. Soc.* 1465 (1947).

anion formation is quite unfavorable at an unactivated methylene  $\alpha$  to a phosphono function.

The demonstration of the feasibility of Stobbe condensations with **4** provides a new synthetic route to  $\beta,\gamma$ -unsaturated phosphonates of relatively complicated structure which may serve as useful starting materials for further syntheses. Two such conversions have been carried out. Alkaline hydrolysis of **5b** led to formation of the corresponding free acid,  $\text{Ph}_2\text{C}=\text{C}(\text{COOH})\text{CH}_2\text{P}(\text{O})(\text{OH})_2$  (**10**); no rearrangement or decarboxylation<sup>30</sup> was observed. Recent studies in this laboratory have shown that suitably substituted **5** undergo cyclization readily.<sup>31</sup> Thus, **5b** can be cyclized at either the phosphonate or carbethoxy functions to yield **11** or **12**. Further studies in this area are in progress.



## EXPERIMENTAL<sup>32</sup>

*Reactions of carbonyl compounds with diethyl  $\beta$ -carbethoxyethylphosphonate (4).* The following general procedure, with the noted exceptions, was followed in all reactions. NaH (10 mmoles as a 55% dispersion in mineral oil) was placed in a 3-neck flask and was washed with 3 portions of n-pentane to remove the mineral oil. The flask was fitted with a reflux condenser, magnetic stirrer, N inlet and dropping funnel. The system was flushed thoroughly with N prior to use and an atm of N was maintained throughout the duration of the reaction. A soln of 10 mmoles of **4** and 10 mmoles of the carbonyl compound (20 mmole for acetone) in 10 ml dry benzene containing 3 drops abs EtOH was added dropwise to the NaH. In general a slightly exothermic reaction occurred; in the cases of cyclopentanone and benzaldehyde, a vigorous exothermic reaction occurred which required ice bath cooling to maintain a gentle reflux. After the exothermic reaction had subsided, the reaction mixture was stirred at room temp for the periods indicated in Table 1. The reaction mixture was treated with 40 ml water followed by 10 ml glacial AcOH and then extracted with ether. The ethereal soln was separated and extracted repeatedly with 5%  $\text{NaHCO}_3$  aq; the alkaline soln was separated and acidified with conc HCl and extracted with chf. After drying over  $\text{Na}_2\text{SO}_4$  or  $\text{MgSO}_4$ , the chf soln was reduced in volume under reduced press (rotary evaporator) to yield the product.

The product **5b** separated as a colorless crystalline solid, which was recrystallized 3 times from a mixture of EtOH and water to yield analytically pure material, m.p. 141–142°. The remaining products separated as colorless or yellow oils and were purified by column chromatography.<sup>33</sup> The analytically pure products were eluted as colorless oils with a mixture of 98% chf and 2% MeOH;

<sup>30</sup> The lack of decarboxylation is not unexpected, since it has been shown that only those  $\alpha,\beta$ -unsaturated acids which can undergo rearrangement to the corresponding  $\beta,\gamma$ -isomer decarboxylate readily: R. T. Arnold, O. C. Elmer and R. M. Dodson, *J. Amer. Chem. Soc.* **72**, 4359 (1950).

<sup>31</sup> C. E. Griffin and W. L. Bryant, unpublished results.

<sup>32</sup> IR spectra were recorded with a Perkin-Elmer Model 21 spectrometer using dil chf or  $\text{CCl}_4$  solns in 0.1 mm NaCl cells. Details of the IR spectra are given in the Ph.D. Thesis of D. J. Martin University of Pittsburgh, 1965. UV absorption spectra were recorded on a Cary Model 14 spectrophotometer. PMR spectra were determined at 37° (probe temp) with a Varian Associates A-60 spectrometer using TMS as an internal standard; chemical shifts are given on the  $\tau$ -scale in ppm relative to TMS ( $\tau = 10.00$ ) and are accurate to  $\pm 0.015$  ppm. The coupling constants, obtained from 50 c/s. sweep width spectra, are the average of at least three determinations and are accurate to  $\pm 0.15$  c/s. Column chromatography was carried out on 50 g silicic acid columns (2.5  $\times$  18 cm) All m.p.s are uncorrected.



5e was eluted with a 95:5 mixture of the same solvents. Results of elemental analyses are given in Table 3. The yields cited in Table 1 are for materials of analytical purity; it must be pointed out that no attempts were made to optimize reaction conditions or yields.

Separation of isomers 5f and 5g was achieved by repeated column chromatography on silicic acid using a mixture of 99% chf and 1% MeOH as eluant. The progress of the separation was followed by UV spectroscopy with the early fractions (5f) having  $\lambda_{\max} = 240 \text{ m}\mu$  and the later fractions (5g) having  $\lambda_{\max} = 245 \text{ m}\mu$ . No true inflection was observed, but an arbitrary division was made and both the early and later fractions were rechromatographed using a larger ratio (125:1) of silicic acid to compound.<sup>22</sup> Both isomers were separated as colorless oils in this manner and

TABLE 3. ELEMENTAL ANALYSES

Compd	Molecular Formula	Calculated			Found		
		% C	% H	% P	% C	% H	% P
5a	C <sub>10</sub> H <sub>11</sub> O <sub>3</sub> P	48.00	7.65	12.38	48.04	7.98	12.44
					47.96	8.03	12.60
5b	C <sub>10</sub> H <sub>11</sub> O <sub>3</sub> P	64.17	6.15	8.29	64.05	6.10	8.32
					63.98	6.19	8.44
5c	C <sub>11</sub> H <sub>13</sub> O <sub>3</sub> P	53.78	10.68	7.99	54.00	10.73	8.03
					54.01	10.80	8.09
5d	C <sub>11</sub> H <sub>13</sub> O <sub>3</sub> P	52.17	7.66	11.21	52.01	7.73	11.18
					51.97	7.77	11.15
5e	C <sub>10</sub> H <sub>11</sub> O <sub>3</sub> P	64.52	5.68	8.32	64.58	5.81	8.41
					64.37	5.77	8.38
5f + 5g*	C <sub>11</sub> H <sub>13</sub> O <sub>3</sub> P	57.68	6.78	9.92	57.41	6.88	10.11
					57.39	6.91	10.16
5h + 5i*	C <sub>14</sub> H <sub>19</sub> O <sub>3</sub> P	56.37	6.42	10.39	56.40	6.52	10.39
					56.44	6.47	10.38
8	C <sub>7</sub> H <sub>13</sub> O <sub>3</sub> P	47.19	8.49	17.39	46.89	8.53	17.44
					46.97	8.59	17.53
10	C <sub>16</sub> H <sub>21</sub> O <sub>3</sub> P	60.38	4.75	9.73	60.14	4.92	9.53

\* Mixture of *cis* and *trans* isomers

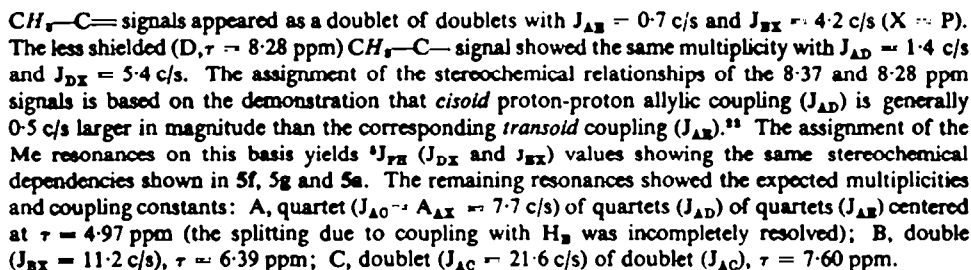
shown to be pure by IR and PMR spectra. Attempted separation of isomers 5h and 5i was unsuccessful. No material was eluted from the column using 100% chf or 99% chf-1% MeOH. Using solvent mixtures with higher (2-3%) MeOH contents, the product was eluted, but all fractions were shown to be virtually identical by PMR and UV spectroscopy.

UV absorption spectra of  $\beta,\gamma$ -unsaturated phosphonates (5). Spectra were determined on  $4.35 \times 10^{-4}$  -  $2.16 \times 10^{-4}$  molar solns in abs EtOH with the exception of the spectra of 5f and 5g which were determined in 95% EtOH. The following values [compound:  $\lambda_{\max}$  ( $\epsilon_{\max}$ );  $\lambda_{\min}$  ( $\epsilon_{\min}$ )] were observed. 5a: 222.5 (7,900); no minimum. 5b: 222, 263 (14,600, 9,600); 246 (8,100). 5c: 225 (6,600); no minimum. 5d: 230 (3,800); no minimum. 5e: 224, 252, 259, 302, 315 (21,500, 22,000, 30,500, 8,700, 9,300); 238, 254, 294, 307 (13,800, 21,200, 7,200, 8,500). 5f: 240 (8,600); 224 (7,800). 5g: 245 (7,000); 228 (6,400). 5h + 5i: 268 (15,100); 230 (3,600).

Hydrolysis of ethyl hydrogen  $\beta$ -carboxy- $\gamma,\gamma$ -diphenylallylphosphonate (5b). A mixture of 535 mg (1.43 mmole) of 5b and 50 ml water containing 10 g NaOH was refluxed for 3 hr. After cooling to room temp, the soln was acidified with conc HCl and was extracted with chf. The combined chf extracts were dried over MgSO<sub>4</sub> and the solvent was removed under reduced press to give a colorless crystalline solid (343 mg, 75%). The solid was recrystallized 3 times from a mixture of chf and cyclohexane and dried over P<sub>2</sub>O<sub>5</sub> *in vacuo* at room temp to give the product,  $\beta$ -carboxy- $\gamma,\gamma$ -diphenylallylphosphonic acid (10), m.p. 179-181°. PMR spectrum (CF<sub>3</sub>COOH soln): P-CH<sub>2</sub>—, doublet,  $\tau$  = 6.62 ppm,  $J_{PH}$  = ca. 22 c/s.; C<sub>6</sub>H<sub>5</sub>—, complex multiplet centered at  $\tau$  = 2.77 ppm.

<sup>22</sup> Chromatographic purifications employed normally used 25-50:1 ratios of silicic acid to compound.

The PMR spectrum of **8** ( $\text{CCl}_4$ ) showed extensive coupling which could be related readily to the stereochemistry of the interacting systems. The more shielded (E,  $\tau = 8.37$  ppm) of the two



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