phosphorochloridate (2.5 ml) in $CCl_4$ and anhydrous pyridine; 3.8 g of an orange oil was isolated. The free amine, obtained by removal of the *tert*-butoxycarbonyl function with boron trifluoride, was precipitated from ether with an ethereal solution of tosic acid. The crude tosic acid salt (2 g) was filtered from the ether after standing overnight in the cold. The yield for each step was difficult to calculate owing to the fact that none of the intermediates could be crystallized. However, starting with 3.5 g (29 mmol) of DL-homoserine, 4.5 g (7.3 mmol) of the crude tosic acid salt was isolated which represents an overall yield of 25%. The crude tosic acid salt can be twice crystallized from alcohol and ether with a 70% recovery to give crystals with a melting point of 110–112°.

*Anal.* Calcd for $C_{30}O_9NSPH_{32}$: C, 58.7; N, 2.29; H, 5.23. Found: C, 59.20; N, 2.39; H, 5.33.

Conversion of L-homoserine to the corresponding tosic acid salt (mp 109–110°) was effected in a similar yield.

**L-Homoserine Phosphate.**—*O*-Diphenylphosphoro-L-homoserine benzyl ester tosylate (122 mg) was converted to the free amine and dissolved in 2 ml of distilled acetic acid; 100 mg of $PtO_2/C$ was added and the reaction mixture was subjected to hydrogenolysis at room temperature and pressure. The progress of the reaction was monitored by assaying the phosphate content of an aliquot of the reaction mixture[16] treated with alkaline phosphatase; it was found that the reaction required 4 days to go to completion. Homoserine phosphate was isolated in quantitative yield; the material cochromatographs with homoserine phosphate prepared enzymically, is ninhydrin and phosphate positive,[17] and, after alkaline phosphatase treatment, cochromatographs with homoserine. In both cases one-dimensional chromatography was performed with Whatman Chromatography Paper No. 1 with phenol–water (80:20) as the developing solvent.[1]

**Racemization Assay.**—In order to determine the degree of racemization accompanying our synthesis of L-homoserine phosphate we made use of the auxotroph, *E. coli* M-145.[18] This organism can utilize L-homoserine in the place of three of its required amino acids, methionine, threonine, and isoleucine. It cannot, however, utilize homoserine phosphate as such owing to the impermeability of this anion. Thus, in order to assay the material for its optical purity, it was dephosphorylated with alkaline phosphatase.[19] The enzymic reaction produced homoserine in virtually quantitative yield (paper chromatography); any remaining homoserine phosphate will not interfere with the biological assay, as it cannot be utilized by the bacterium. As shown in Table I, the homoserine from L-homoserine phosphate

TABLE I
GROWTH YIELD OF M-145 ON HOMOSERINE AND HOMOSERINE PHOSPHATE

| Sample | Klett units per micromoles of material |
|---|---|
| L-Homoserine | 530 |
| DL-Homoserine | 270 |
| L-Homoserine phosphate[a] | 430 |
| DL-Homoserine phosphate[a] | 270 |

[a] The number of micromoles of phosphate released by the alkaline phosphatase is taken to be the number of micromoles of homoserine available to the organism to support its growth. See Experimental Section for details.

is 81% as effective as an L-homoserine standard in supporting growth of the auxotroph, indicating that 19% of the synthetic material is D-homoserine phosphate.

**Registry No.**—*N*-*tert*-Butoxycarbonyl-DL-homoserine, 38308-92-8; DL-homoserine, 1927-25-9; triethylamine, 121-44-8; *tert*-butoxycarbonyl azide, 1070-19-5; *N*-*tert*-butoxycarbonyl-DL-homoserine benzyl ester, 38308-93-9; 1-benzyl-3-*p*-tolyltriazene, 17683-09-9; *O*-diphenylphosphoro-DL-homoserine benzyl ester tosylate, 38308-95-1; *O*-diphenylphosphoro-DL-homoserine benzyl ester, 38308-96-2; diphenylphosphorochloridate, 2524-64-3; L-homoserine phosphate, 4210-66-6; *O*-diphenylphosphoro-L-homoserine benzyl ester tosylate, 38308-98-4.

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(16) P. S. Chen, T. Y. Toribara, and H. Warner, *Anal. Chem.*, **28**, 1756 (1956).

(17) I. Smith and J. G. Feinberg, "Paper and Thin Layer Chromatography and Electrophoresis," Shandon Science Educational Manuals, London, 1965, p 231.

(18) C. Gilvarg, *J. Biol. Chem.*, **237**, 482 (1962).

(19) L. A. Heppel, D. R. Harkness, and R. J. Hilmoe, *ibid.*, **237**, 843 (1962).

## Base-Catalyzed Condensation of Aldehydes with Ethyl Bis(diethylphosphonomethyl)phosphinate[1]

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As a possible synthesis of ethyl (diethylphosphonomethyl)vinylphosphinates **4** we have explored the base-catalyzed condensation of aldehydes with ethyl bis(diethylphosphonomethyl)phosphinate (**2**). Based on previously reported results[2] as well as our experience, the base-catalyzed condensation of tetraethyl methylenediphosphonate (**1**) with aldehydes is an excellent synthetic method for vinylphosphonates. We therefore expected that, during the course of the base-catalyzed reaction of **2** with aldehydes, diethyl phosphate ion would be eliminated with the formation of **4**. Instead, **5** was eliminated with the formation of **3**. The course of the reaction was the same when a number of solvents (benzene, ethanol, DMSO, ether, 1,2-dimethoxyethane) and a number of bases (sodium hydride, sodium ethoxide, potassium *tert*-butoxide) were used. The reaction is stereoselective with formation of predominantly the *trans*-vinylphosphonates. The stereochemistry was assigned on the basis of the nmr spectra and gas chromatograms.[3]

In order to change the electronic and steric properties of the central phosphorus atom, phenyl bis(diethylphosphonomethyl)phosphinate and isopropyl bis(diisopropylphosphonomethyl)phosphinate were prepared and reacted with isobutyraldehyde. The results were the same as with **2**. No attempt has been made to maximize these factors. From our very limited study we cannot indicate why the C–P bond of a phosphinate is cleaved in preference to a C–P bond of a phosphonate. Examination of models of possible transition states and intermediates has not lead us to an explanation.

One practical utilization of this reaction is the synthesis of compounds such as **5**. Such compounds are

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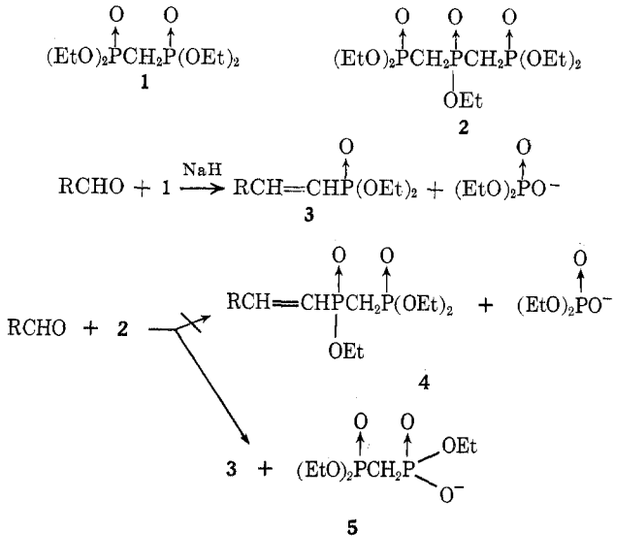
(2) (a) W. S. Wadsworth and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961); (b) T. L. Hullar, *J. Med. Chem.*, **12**, 58 (1969).

(3) (a) F. A. Carey and A. S. Court, *J. Org. Chem.*, **37**, 939 (1972); (b) C. E. Griffin and T. D. Mitchell, *ibid.*, **30**, 1935 (1965).

not easily prepared without the use of some unsymmetrical intermediate.




### Experimental Section[4]

**Diethyl β-Styrylphosphonate (3, R = Phenyl).**—A solution of 15.8 g (0.04 mol) of **2**[5] in 25 ml of $C_6H_6$ was added dropwise to a stirred suspension of 1.7 g (0.04 mol) of sodium hydride (57% dispersion in mineral oil) in 50 ml of $C_6H_6$. When the solution had become clear, 4 g (0.038 mol) of benzaldehyde in 25 ml of $C_6H_6$ was added dropwise. Stirring was continued overnight. The $C_6H_6$ was washed with 100 ml of $H_2O$ in five portions and was concentrated to an oil, which after distillation afforded 3.7 g (41%) of the phosphonate: bp 122–126° (0.025–0.05 mm) [lit. bp 137–138° (0.03 mm),[5a] 125–126° (0.3 mm),[6b] 134° (1.5 mm),[6c] 116–118° (0.35 mm),[2a] 138° (2 mm)[6d]]; $n^{20}D$ 1.5250 [lit. $n^{20}D$ 1.5665,[6a] 1.5298,[6c] 1.5325[6d]]; nmr[6b] ($CCl_4$) δ 7.35–8.06 (m, 6, $C_6H_5CH$=), 6.3 (t, 1, $J$ = 18 Hz, C=CHP),[5b,7] 4.15 (m, 4, $J$ = 9 Hz, $POCH_2$), and 1.35 (t, 6, $J$ = 8 Hz, $POCH_2CH_3$); ir[6b] (neat) 690, 740 (phenyl), 1620 (CH=CH), 1160 (POC), and 1250 $cm^{-1}$ (P=O).

The aqueous extract was evaporated to obtain a glassy solid, which was dried under reduced pressure. The resulting solid was pulverized to obtain 8.07 g (76%) of the sodium salt **5**, mp 104–109°. A 1-g sample of the salt was dissolved in 100 ml of water and passed through an Amberlite IR-120 H. C. P. column (2 × 32 cm). Evaporation of the eluate gave 0.93 g of triethyl hydrogen methylenediphosphonate (**5**) as a gum: nmr ($CCl_4$) δ 12.05 (s, 1, POH), 4.22 (m, 6, $J$ = 8 Hz, $POCH_2$), 2.58 (t, 2, $J$ = 22 Hz, $PCH_2P$) and 1.39 (t, 9, $J$ = 8 Hz, $POCH_2CH_3$); ir (neat) 1240 (P=O) and 1170 $cm^{-1}$ (POC).

*Anal.* Calcd for $C_7H_{18}O_6P_2$: C, 32.31; H, 6.97; P, 23.81. Found: C, 32.19; H, 6.77; P, 23.98.

**Diethyl 3-Methyl-1-butenylphosphonate [3, R = $(CH_3)_2CH$].**—The procedure was the same as that described above. Evaporation of the $C_6H_6$ layer gave a yellow liquid, which was distilled under reduced pressure to obtain 4.7 g (57%) of diethyl 3-methyl-1-butenylphosphonate: bp 45° (0.025 mm); $n^{25}D$ 1.4372; ir (neat) 1640 (CH=CH), 1375, 1395 ($Me_2CH$), 1250 (P=O), and 1165, 1025 $cm^{-1}$ (POC); nmr[3c] ($CCl_4$) δ 6.84 (m, 1, $J_{HH}$ = 7, $J_{HH}$ = 18, $J_{HP}$ = 23 Hz, CH=CP), 5.65 (t, 1, $J_{HH}$ = $J_{HP}$ = 18 Hz, C=CHP), 4.13 (m, 4, $J$ = 7 Hz, $POCH_2$), 2.5 (m, 1, $Me_2CH$), 1.3 (t, 6, $J$ = 7 Hz, $POCH_2CH_3$), and 1.1 (d, 6, $J$ = 7 Hz, $CH_3CHCH_3$).

The nmr spectrum is consistent with that reported[3c] for the trans isomer.

Gc analysis indicates less than 1% of a compound with smaller retention volume than the major component. This minor component is believed to be the cis isomer.

**Registry No.**—**2**, 18033-91-5; *trans*-**3** (R = *i*-Pr), 33536-50-4; *cis*-**3** (R = *i*-Pr), 18689-34-4; **5**, 38379-50-9; **5** sodium salt, 38379-51-0.

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(4) Melting points were taken on a Mel-Temp melting point apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer. Nmr spectra were taken on a Jeolco Model C-60-HL spectrometer using tetramethylsilane as an internal standard. Gas chromatograms were obtained with a 5 ft × 0.25 in. column packed with 10% 20M Carbowax on 80–100 mesh Chromosorb W. The column was maintained at 200° in a Perkin-Elmer Model 900 chromatograph equipped with a flame ionization detector. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(5) (a) L. Maier, *Angew. Chem., Int. Ed. Engl.*, **7**, 385 (1968); (b) K. O. Knollmeuler, U. S. Patent 3,534,125 (1970); *Chem. Abstr.*, **74**, 53989ρ (1971).

(6) (a) Ya. A. Levin and V. S. Galeev, *Zh. Obshch. Khim.*, **37**, 2736 (1967); (b) C. E. Griffin and T. D. Mitchell, *J. Org. Chem.*, **30**, 1935 (1965); (c) B. I. Ionin, K. S. Mingaleva, and A. A. Petrov, *Zh. Obshch. Khim.*, **34**, 2630 (1964); (d) K. K. Papok, K. N. Anisimov, B. S. Zuseva, and N. E. Kolobova, *Zh. Prikl. Khim.*, **32**, 656 (1959).

(7) A referee pointed out that the chemical shift we found is not consistent with that reported by Griffin.[3b] We have subsequently found that the chemical shift is concentration dependent and ranges from δ 6.28 (10%) to 6.75 (neat).

## Claisen Condensation. A Method for the Synthesis of Long Chain Dicarboxylic Acids

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Earlier syntheses of α,ω-dicarboxylic acids utilized the oxidation of α,ω-glycols, the hydrolysis of dinitriles, the malonic ester synthesis with α,ω-dibromides, and the Crum-Brown–Walker[2] application of the Kolbe[3] synthesis. Combinations of these procedures have provided pathways for the syntheses of α,ω-dioic acids in the range of 11 to 34 carbon atoms.[4-8] Newer methods have been developed by Lettré,[9] Hünig,[10-13] Buchta,[14,15] and others.[16-23] It was our purpose to utilize a compound which could give even- and odd-numbered dicarboxylic acids. Methyl *N*,*N*-dimethylsebacamate (**4**) might be condensed by Claisen and acyloin procedures to yield dicarboxylic acids of 19 and 20 carbon atoms, respectively. Only the former was successful.

(1) Abstracted from the M.S. thesis of R. W. Shubart, Roosevelt University, June, 1970.

(2) A. Crum-Brown and J. Walker, *Justus Liebigs Ann. Chem.*, **261**, 107 (1891).
(3) H. Kolbe, *ibid.*, **69**, 257 (1849).
(4) P. Chuit, *Helv. Chim. Acta*, **9**, 264 (1925).
(5) P. Chuit, *ibid.*, **12**, 850 (1929).
(6) K. Ziegler and W. Hechelhammer, *Justus Liebigs Ann. Chem.*, **528**, 114 (1937).
(7) L. Ruzicka, M. Stoll, and H. Schinz, *Helv. Chim. Acta*, **11**, 1174 (1928).
(8) D. A. Fairweather, *Proc. Roy. Soc. Edinburgh*, **45**, 283 (1925); *Chem. Abstr.*, **20**, 47 (1926).
(9) H. Lettré and A. Jahn, *Chem. Ber.*, **85**, 346 (1952).
(10) S. Hünig and E. Lücke, *ibid.*, **92**, 652 (1959).
(11) S. Hünig and W. Lendle, *ibid.*, **93**, 913 (1960).
(12) S. Hünig and H.-J. Buysch, *ibid.*, **100**, 4010 (1967).
(13) S. Hünig and H.-J. Buysch, *ibid.*, **100**, 4017 (1967).
(14) E. Buchta and W. Bayer *Naturwissenschaften*, **46**, 14 (1959).
(15) E. Buchta and C. Huhn, *Justus Liebigs Ann. Chem.*, **695**, 42 (1966).
(16) C. Wakselman, *C. R. Acad. Sci.*, **260**, 5056 (1965).
(17) Ng. Ph. Buu-Hoï, M. Sy, and N. Dat Xuong, *ibid.*, **240**, 442 (1955).
(18) A. Kreuchunas, *J. Amer. Chem. Soc.*, **75**, 3339 (1953).
(19) H. Stetter and W. Dierichs, *Chem. Ber.*, **85**, 290 (1952).
(20) H. Stetter and W. Dierichs, *ibid.*, **85**, 61 (1952).
(21) Hs. H. Günthard, S. D. Hinemann, and V. Prelog, *Helv. Chim. Acta*, **36**, 1147 (1953).
(22) V. Hnévosvá, V. Smělý, and I. Ernest, *Chem. Listy*, **50**, 573 (1956); *Chem. Abstr.*, **50**, 13749b (1956).
(23) J. C. Sauer, *J. Amer. Chem. Soc.*, **69**, 2444 (1947).