39. *Perkow* Reaction Induced C,C-Bond Formation

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Summary

The reaction of a cinnamoyl chloride with excess trimethyl phosphite gives a substituted 1,5-hexadiene, in which C,C-bond formation has taken place between the β-C-atoms of the two α,β-unsaturated carbonyl moieties.

Introduction. – The *Perkow* reaction [1] [2] affords dialkyl vinyl phosphate esters by the reaction of a trialkyl phosphite with an α-halo carbonyl compound. There are further reactions known, where the attack of the trialkyl phosphite takes place at the O-atom [3]. We wish to report a reaction of trimethyl phosphite with the O-atom of an α,β-unsaturated carbonyl system, which leads to a reversal of the polarity of the double bond permitting a C,C-bond formation between the β-C-atoms of two α,β-unsaturated carbonyl moieties.

We planned to prepare *p*-chlorocinnamoyl phosphonate by the *Michaelis-Arbusow* reaction [4]. *Welter et al.* [5] obtained dimethyl cinnamoyl phosphonate ester in 38% yield by dissolving the acylchloride in benzene and adding the trimethyl phosphite. Aiming at an improved yield we added the acylchloride to an excess of trimethyl phosphite without a further solvent and obtained a crystalline material which is formally the trimer of the expected acyl phosphonate ester.

$$(p\text{-Cl})\text{-}C_6H_4CH{=}CH\text{-}CO\text{-}Cl \xrightarrow{P(OCH_3)_3} \underset{\mathbf{1}}{(C_{11}H_{12}ClO_4P)_3}$$

Structure determination. – The structure of **1** has been determined by ^{1}H-, ^{13}C- and ^{31}P-NMR. spectroscopy. An outline of this determination follows. The ^{1}H-NMR. spectrum shows six different methyl groups, three different *AA'BB'*-systems for the aromatic protons and six different other protons. Since the elemental analysis gave a formula of $(C_{11}H_{12}ClO_4P)_n$, n had to be at least 3. This was proven by molecular weight determination (found 830, calc. 823.9). The ^{1}H-NMR. spectrum shows, furthermore, that one cinnamoyl moiety is still intact (protons at 7.63 and 6.42 ppm with $^3J_{H,H}$ of 16 Hz and no P,H-coupling). The ^{13}C-NMR. spectrum indicates that the structural element $-\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{P}}-$ is not present in the molecule, since there are no signals below 163.1 ppm. Consequently the trimer is not an endproduct of the *Michaelis-Arbusow* reaction. Exhaustive decoupling of the remaining four of the six other protons mentioned above showed that they are positioned in a chain with a coupling of 10 Hz between vicinal protons. The protons

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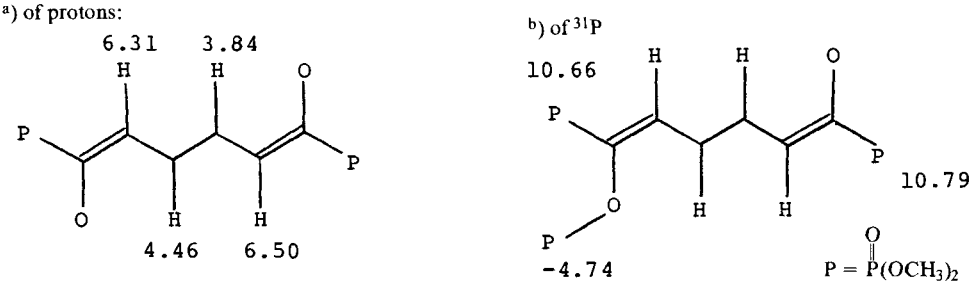
Scheme 1. *Chemical shifts* (ppm) *of* **1**



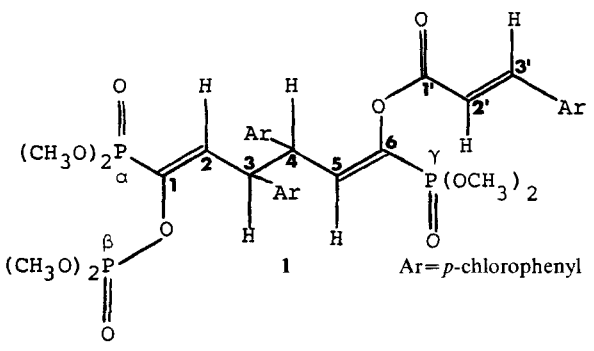
at 6.31 and 6.50 ppm are additionally coupled by 10 Hz to a phosphorus nucleus (see *Scheme 1a*). This coupling is a $^3J_{cis}$, which is reduced from the normal value of ca. 22 Hz [6] by electronegative substitution. The signal at 6.31 ppm has a long range coupling [2] of 2 Hz, which is absent in the signal at 6.50 ppm. The ^{31}P proton-noise-decoupled NMR. spectrum consists of three signals at 10.79, 10.66 and −4.74 ppm, the last two of which are coupled with each other, $J = 6.1$ Hz. Given the elemental composition of the molecule, these data extend the chain of *Scheme 1a* to that of *Scheme 1b*. In the ^{13}C-NMR. spectrum, we find a signal at 163.1 ppm with a $J_{C,P}$ of 1 Hz and only two H–C signals ($J_{C,P} = 11$ and 12 Hz) besides the methyl groups in the aliphatic region (above 115 ppm). Taken together, these data result in the structure given in *Scheme 2*. Since the vicinal coupling between H–C(2), H–C(3), H–C(4) and H–C(5) amounts to 10 Hz, these protons assume a s-*trans* conformation to each other.

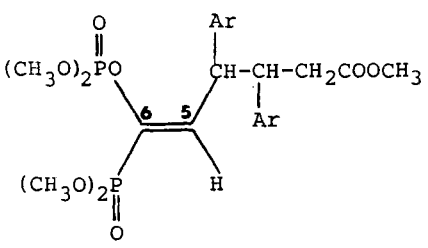
The structure of **1** was corroborated by chemical degradation. Methanolysis in the presence of aqueous NaOH-solution yielded methyl *p*-chlorocinnamate and **6**.

Methanolysis under the same conditions with more base present produced dimethyl 3,4-di(*p*-chlorophenyl)-adipate besides *p*-chlorocinnamic acid and methyl *p*-chlorocinnamate.

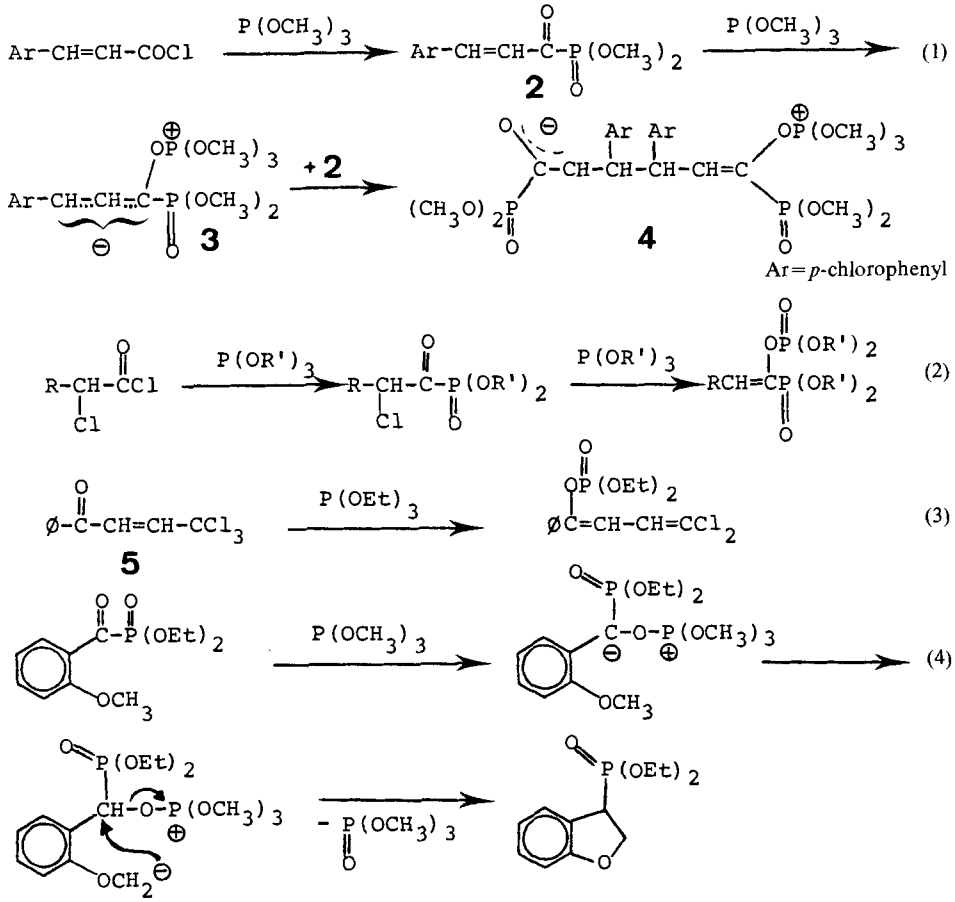
Discussion of the reaction mechanism. – We propose the following mechanism of the formation of **1** *(Scheme 3)*. The first step gives rise to an intermediary *Michaelis-Arbusow* product **2**, which, in turn, is attacked at the carbonyl O-atom by a second phosphite in a *Perkow* reaction, as it is known for α-halo-acylhalides [7] (eqn. 2); the intermediate **3** reacts with another molecule of **2** in a *Michael* addition (this step is analogous to the *Perkow* reaction of **5** (eqn. 3) [8]); the enolate **4** finally

Scheme 2





Scheme 3



reacts with another molecule of cinnamoyl chloride. The chloride freed in this step reacts with the methyl group to form CH_3Cl. Other modes of stabilization of **4** are inhibited since there are no other electrophiles available in the solution (except **2** for chain propagation), and a nucleophilic attack at the C-atom carrying the $O\overset{\oplus}{P}(OCH_3)_3$ moiety similar to eqn. 4 [9] is prevented by the presence of the double bond.

The attack of the carbonyl O-atom of the α,β-unsaturated acyl phosphonate by the trimethyl phosphite leads, as we have shown, to a reversal of the usual polarity of the double bond, making the β-C-atom nucleophilic.

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Experimental Part

The ^{1}H-NMR. spectra were recorded on a *Varian* HA 100- and a *Bruker* HX 360-, the ^{13}C-NMR. spectra on a *Bruker* HX 360- and the ^{31}P-NMR. spectra on a *Bruker* WP-80 NMR. spectrometer.

Preparation of 6-(p-chlorocinnamoyl)-3,4-bis(p-chlorophenyl)-1-(dimethylphosphato)-1,6-bis(dimethylphosphono)-1,5-hexadien (**1**). Crystalline *p*-chlorocinnamoylchloride (30.2 g, 0.15 mol) was added with

stirring in *ca.* 2 g portions to trimethylphosphite (37.2 g, 0.3 mol). The exothermic reaction was controlled by cooling, keeping the temperature below 35°. A slow stream of N_2 swept out the evolved CH_3Cl. After about 2/3 of the acylchloride had been added the reaction mixture became a viscous pasty liquid. After completion of the addition of the acylchloride the yellow mixture was stirred for 3 h at RT. and another 2 h at 70°. Excess trimethylphosphite was removed i.V. at 100°. Dilution with 150 ml of ether afforded a suspension of a crystalline product which was collected by suction, 15.2 g (36.9%), m.p. 153–9°. The crude product was recrystallized from ethyl acetate and hexane, 13.9 g, m.p. 160–2°. – ^{1}H-NMR. ($CDCl_3$): 7.63 (*d*, J = 16, H–C(3')); 7.40–7.55 (one *AA'BB'*-system, aromatic protons of the cinnamoyl moiety); 7.15–7.35 (two *AA'BB'*-systems, the remaining aromatic protons); 6.50 (*t*, $J_{4,5}=J_{5,P(\gamma)}=10$, H–C(5)); 6.42 (*d*, J = 16, H–C(2')); 6.31 (*t* × *d*, $J_{2,3}=J_{2,P(\alpha)}=10$, $J_{2,P(\beta)}=2$, H–C(2)); 4.46 (*t* × *d*, $J_{2,3}=J_{3,4}=10$, $J_{3,P(\alpha)}=1.5$, H–C(3)); 3.84 (*m*, $J_{3,4}=J_{4,5}=10$, $J_{4,P(\gamma)}=2$, H–C(4)); 3.82, 3.73, 3.58, 3.56, 3.45 and 3.33 (*6d*, J = 11,6 OCH_3). – ^{13}C-NMR. ($CDCl_3$): 163.1 (*d*, $J_{C,P}=1$, C(1')); 146.3 (*s*, C(3')); 128.8–139.5 (complex pattern, aromatic and the remaining olefinic C-atoms); 116.2 (*s*, C(2')); 55.1, 53.1, 53.0, 52.8 and 52.6 (5 *d*, J = 5, OCH_3); 48.4 and 46.6 (2 *d*, J = 12 and 11 resp., C(3) and C(4)). – ^{31}P-NMR. (C_6D_6 against H_3PO_4 external, proton noise decoupled): 10.79 (*s*, P(γ)); 10.66 (*d*, J = 6,1, P (α)); –4.74 (*d*, J = 6.1, P(β)). – ^{31}P-NMR. ($CDCl_3$): 11.07 (P(γ)); 11.01 (P(α)); –4.56 (P(β)):

$(C_{11}H_{12}ClO_4P)_3$ Calc. C 48.1 H 4.4 Cl 12.9 P 11.3%
Found „ 48.1 „ 4.4 „ 12.8 „ 11.3%

Degradation of **1**. a) A solution of **1** (5mmol, 4.12 g) in 100 ml MeOH was added to aqueous 1N NaOH (5 ml) and allowed to stand at RT. overnight. The clear and colorless reaction mixture was evaporated to dryness i.V. maintaining the temperature of the bath below 50°. The residue (5.1 g, viscous oil) was stirred in 30 ml of water for 2 h. Part of the oily residue crystallized (3.7 g) and melted in a range of 70 to 104°. The crude product was chromatographed on a silica gel column (100 g, *Merck AG*). Elution with ethyl acetate furnished a crystalline fraction (0.8 g), m.p. 71–78°, and another more polar fraction (2.1 g), m.p. 106–112°. Distillation of the low melting fraction at 85°/0.05 Torr afforded 0.7 g of distillate, m.p. 73–75°. Elemental analysis and ^{1}H-NMR. spectrum identified this material as methyl *p*-chlorocinnamate. The high melting fraction (2.1 g, m.p. 106–112°) eluted from the column was recrystallized from acetone and hexane to give 1.55 g of colorless crystals, m.p. 113–115° (**6**, methyl *3,4-bis(*p*-chlorophenyl)-6-(dimethylphosphato)-6-(dimethylphosphono)-hex-5-enoate).* – ^{1}H-NMR. ($CDCl_3$): 7.1–7.4 (*AA'BB'*-system, aromatic protons); 6.30 (*t* br. J = 10, H–C(5)); 4.35 (*t* br., J = 10, H–C(4)); 3.82, 3.71, 3.56 and 3.35 (4 *d*, J = 11, OCH_3); 3.45 (*s*, $COOCH_3$); *ca.* 3.4 (*m* overlapping with CH_3 signals, H–C(3)); 2.48 (*d* br., CH_2).

$C_{23}H_{28}Cl_2O_9P_2$ (581.33) Calc. C 47.5 H 4.9 Cl 12.2% Found C 47.4 H 5.0 Cl 11.9%

b) A solution of **1** (5 mmol, 4.12 g) in 100 ml MeOH and 10 ml aqueous NaOH deposited 1.1 g crystalline dimethyl 3,4-di-(*p*-chlorophenyl) adipate, m.p. 175–178°. After recrystallization from ethyl acetate (1.0 g): m.p. 176–177°. ^{1}H-NMR. ($CDCl_3$): 7.1–7.4 (*AA'BB'*-system, aromatic protons); 3.45 (*s*, $COOCH_3$); 3.2–3.5 (2 H) and 2.2–2.6 (4 H) ((*ABX*)$_2$-system, CH_2CH). – MS. (m/z): 394 (*M*).

$C_{20}H_{20}Cl_2O_4$ (395.28) Calc. C 60.8 H 5.1 Cl 17.9% Found C 60.8 H 5.1 Cl 18.2%

From the filtrate of the main reaction product 0.6 g of methyl *p*-chlorocinnamate and 49 mg of *p*-chlorocinnamic acid have been isolated.

REFERENCES

[1] *F. W. Lichtenthaler,* Chem. Rev. *61*, 607 (1961).

[2] *I.J. Borowitz, K.C. Yee & R.K. Crouch,* J. org. Chemistry *38*, 1713 (1973).

[3] *B.J. Walker,* 'Organophosphorus Chemistry', vol. 9, chap. 5, 86–90, ed. S. Trippett, The Chemical Society, London 1978, and earlier volumes in this series.

[4] *K. Sasse,* in Houben-Weyl, «Methoden der Organischen Chemie», 4th. edn., ed. E. Müller, vol. 12/1, 453, G. Thieme Verlag Stuttgart 1963.
R.G. Harvey & E.R. De Sombre, 'Topics in Phosphorus Chemistry' *1*, 57 (1964), ed. M. Grayson & E.J. Griffith Interscience, New York 1964.

[5] *W. Welter, A. Hartmann & M. Regitz,* Chem. Ber. *111*, 3068 (1978).

[6] *C. Benezra, S. Nšeič & G. Ourisson,* Bull. Soc. chim. France *1967*, 1140.

[7] Ref. 1, p. 613 and references cited there.

[8] *J.F. Allen & O.H. Johnson,* J. Amer. chem. Soc. *77*, 2871 (1955).

[9] *G.P. Chiusoli, G. Cometti & V. Bellotti,* Chem. Commun. *1977*, 216.