The Role of Pentaco-ordinate Species in the Mechanism of the Arbusov Reaction

By **C. L. Bodkin** and **P. Simpson,*** School of Molecular Sciences, University of Sussex, Brighton BN1 9QJ

The Arbusov reaction between *cis*- and *trans*-2-ethoxy- and 2-isopropoxy-4-methyl-1,3,2-dioxaphosphorinan and alkyl iodides is non-stereospecific. In general, the amount of stereomutation appears to depend upon the nature of the alkoxy groups on the reactant P^{III} ester. Unchanged 2-alkoxy-4-methyl-1,3,2-dioxaphosphorinan recovered from interrupted Arbusov reactions shows that some of the less stable *cis*-phosphite has been converted to the *trans*-isomer, demonstrating that the Arbusov reaction pathway provides a route for this isomerisation. Pentacovalent intermediates are postulated to account for these observations. An approximate model of the conventional two-step mechanism for this reaction, which involves no pentaco-ordinate species, was set up and shown to proceed stereospecifically.

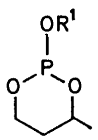
We have reported[1] that the reactions of certain 2-alkoxy-4-methyl-1,3,2-dioxaphosphorinans with ethyl and methyl iodides are of low stereospecificity, and have suggested a possible modification to the generally-accepted mechanism for the Arbusov reaction [equations (1) and (2)] to account for this. We now describe our findings more fully, and present further evidence in support of our mechanistic interpretation.

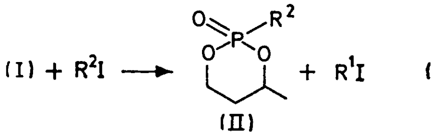
$$(R^1O)_3P + R^2I \longrightarrow (R^1O)_3\overset{+}{P}R^2 + I^- \qquad (1)$$

$$I^- + (R^1O)\overset{+}{P}(OR^1)_2R^2 \longrightarrow R^1I + (R^1O)_2P(O)R^2 \qquad (2)$$

Arbusov reactions were carried out between the cyclic phosphites (I; $R^1 = Et$ or Pr^i) and methyl or ethyl iodide. The reaction mixtures were analysed by g.l.c. (see Experimental section). In these reactions, the dealkylation step [equation (2)] can occur either at the exocyclic alkoxy-group to give a cyclic phosphonate product [equation (3)], or at C-4 or -6, resulting in an acyclic product. Using methyl or ethyl iodides in the ratio of ten equiv. of iodide to one equiv. of phosphite, and carrying out the reactions under reflux, the alkyl iodide R^1I formed did not effectively compete with the original reactant R^2I, and essentially only one pair of cyclic phosphonate isomers (II; $R^2 = Me$ or Et) was formed in any one reaction. Some acyclic products were observed in each case, however, particularly when the isopropyl phosphites (I; $R^1 = Pr^i$) or ethyl iodide [equation (3); $R^2 = Et$] were used.

(I)





(3)

Conversion of the phosphites (I) into their sulphides by the addition of sulphur provides a convenient method of determining their isomeric composition, using g.l.c.[2] In the present study, a comparison of the isomeric composition of the starting phosphites with that of the phosphonates (II) (determined from g.l.c. of the crude products) was undertaken. In no case were the two compositions the same (see ref. 1).

We have recently reported[3] the configurations and conformations of some 2-alkoxy-4-methyl-1,3,2-dioxaphosphorinans and their 2-thio-adducts, but in the present study we were unable to assign the configurations of the cyclic phosphonates (II; $R^2 = Me$ or Et) largely because pure samples of both isomers were not available for either compound, and because of the difficulty of predicting dipole moments of such species. In particular, it is not clear what is the appropriate value to choose for the phosphorus–oxygen bond moment. A calculation, using a value assumed by Mingaleva *et al.*[4] does not yield a predicted dipole moment in agreement with the observed value of $4{\cdot}25 \pm 0{\cdot}03$ D for the isomer obtained pure from the reaction of the *trans*-ethyl phosphite (I; $R^1 = Et$) and ethyl iodide. If a value used by Verkade *et al.*[5] for a bicyclic phosphite is assumed, similar dipole moments are predicted for both configurations, and these are close to that which we have observed for our single, pure isomer. It is therefore impossible to decide from the evidence obtained in this study whether the reaction proceeds with predominant inversion or retention of configuration at phosphorus, although the latter seems most likely, particularly as two related reactions have been shown[6,7] to proceed with retention of configuration at phosphorus.

The most likely explanation of the stereomutation observed in these reactions appears to be the intervention at some stage of a pentaco-ordinate intermediate such as (III). The importance of such intermediates in other reactions of organophosphorus compounds is rapidly being recognised.[8]

---

[1] C. L. Bodkin and P. Simpson, *Chem. Comm.*, 1970, 1579.

[2] G. Aksnes, R. Eriksen, and K. Mellingen, *Acta Chem. Scand.*, 1967, **21**, 1028.

[3] C. L. Bodkin and P. Simpson, *J. Chem. Soc.* (*B*), 1971, 1136; *Chem. Comm.*, 1969, 829.

[4] K. S. Mingaleva, B. I. Ionin, and A. A. Petrov, *J. Gen. Chem.* (*U.S.S.R.*), 1968, **38**, 545.

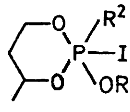
[5] A. C. Vandenbroucke, jun., E. J. Boros, and J. G. Verkade, *Inorg. Chem.*, 1968, **7**, 1469.

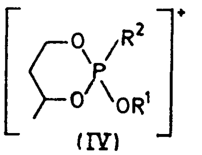
[6] G. R. Van den Berg, D. H. J. M. Platenburg, and H. P. Benschop, *Chem. Comm.*, 1971, 606.

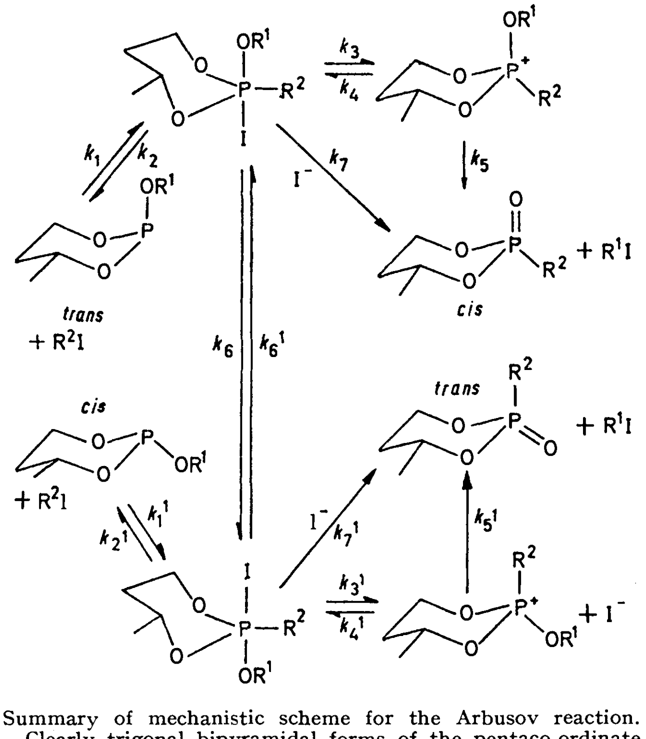
[7] W. G. Bentrude and J. H. Hargis, *J. Amer. Chem. Soc.*, 1970, **92**, 7136.

[8] (*a*) D. Z. Denney, G. Y. Chen, and D. B. Denney, *J. Amer. Chem. Soc.*, 1969, **91**, 6838; (*b*) F. H. Westheimer, *Accounts Chem. Res.*, 1968, **1**, 70; (*c*) K. E. DeBruin and K. Mislow, *J. Amer. Chem. Soc.*, 1969, **91**, 7393; (*d*) J. H. Finley and D. B. Denney, *ibid.*, 1970, **92**, 362.

The formation of such an intermediate during the reaction can occur either directly from the starting phosphite and alkyl halide (see ref. 9, p. 5798), with subsequent dissociation into phosphonium and halide ions (see Figure), or by the association of an initially-formed phosphonium salt (IV). In order to obtain evidence as to which of these alternatives was adopted by the reaction we treated each stereoisomer of phosphite (I; $R^1 = Et$ or Pr^i) with trityl fluoroborate, and decomposed the resulting phosphonium salt with iodide ion [equations (4) and (5)]. The isomers of the tritylphosphonate product (VI) could be separated by preparative scale t.l.c., and the isomeric compositions of the products could be determined by measuring the relative u.v. absorbances of the two stereoisomers.


(III)

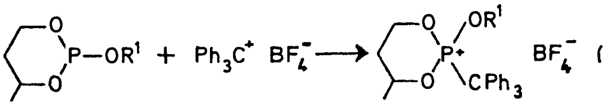

(IV)



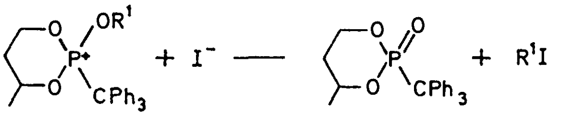
Summary of mechanistic scheme for the Arbusov reaction. Clearly trigonal bipyramidal forms of the pentaco-ordinate species, other than those shown, are also involved, and that formed initially may be different from the one shown

The ^1H n.m.r. spectra of the *cis*- and *trans*-stereoisomers of (VI) are not identical, and the resonances of the 4-methyl group in particular show significant differences. In one isomer [derived from the *trans*-phosphites (I)] this resonance has the appearance of a pair of doublets (J 2 and 6 Hz) due to couplings with phosphorus and with 4-H respectively. The spectrum of this compound is very similar to others which we have recently interpreted, of related compounds,[3] and is, we believe, suggestive of a conformationally fixed, approximately chair-shaped ring with the methyl group equatorial.

In the ^1H n.m.r. spectrum of the other stereoisomer of (VI) derived from the *cis*-phosphites, however, the resonance of the 4-methyl group appears as a pair of unresolved triplets (J 6 and $2 \times J$ *ca.* 0·5 Hz). We interpret this as signifying that the 4-methyl group adopts the axial conformation in this compound and the two small couplings of *ca.* 0·5 Hz are presumably to the axial 5-proton and to phosphorus.[10] If the assumption is made that the trityl group adopts the equatorial conformation in both molecules, then in the latter isomer the 4-methyl group must be *trans* to the trityl group, and in the former it must be *cis*.



(4)



(5)

Table 1 shows the isomeric composition of the cyclic tritylphosphonates (VI) formed from the phosphites (I) of different isomeric purity. From the results in this Table it is clear that the overall reaction represented in equations (4) and (5) proceeds with complete stereospecificity, and with retention of configuration at phosphorus (in the sense that the spatial arrangement of the oxygen atoms remains the same relative to the 4-methyl group). This observation suggests (though by no means proves) that no pentaco-ordinate intermediate is formed during either stage of this reaction, and since any association of the phosphonium ion (V) with iodide

TABLE 1

Isomeric composition of the tritylphosphonates (VI) obtained from phosphites (I)

R^1 in (I)	*cis* : *trans* * in phosphite (I)	% *cis* * in product (VI)
Et	4 : 96	†
Et	3 : 2	40 ± 3
Et	58 : 42	45 ± 2
Pr^i	8 : 92	†
Pr^i	1 : 1	51 ± 2
Pr^i	1 : 1	53 ± 6

* In the case of the phosphites, *cis* : *trans* refers to the relationship between the methyl and the alkoxy-group. In the case of the phosphonates, the relationship is between the methyl and the trityl group. † Too small for quantiative assessment.

---

[9] W. A. Henderson and S. A. Buckler, *J. Amer. Chem. Soc.*, 1960, **82**, 5794.

[10] See for example (*a*) D. Gagnaire, J. B. Robert, and J. Verrier, *Bull. Soc. chim. France*, 1968, 2392; (*b*) D. W. White, R. D. Bertrand, G. K. McEwen, and J. G. Verkade, *J. Amer. Chem. Soc.*, 1970, **92**, 7125; (*c*) L. D. Hall and R. B. Malcolm, *Chem. and Ind.*, 1968, 92.

ion to give a pentaco-ordinate species would almost certainly lead to a loss of stereospecificity similar to that described above, we take this to support our suggestion that in the ' normal ' Arbusov reaction with alkyl iodide the pentaco-ordinate species is formed initially, and subsequently dissociates to phosphonium salt or is dealkylated (Figure).

It will be seen from the Figure that a consequence of our proposal would be a route for the conversion of one phosphite isomer into the other during the reaction provided, as seems reasonable, that the pentaco-ordinate species forms reversibly from the reactants. We have demonstrated that such a route exists by analysing the phosphite remaining unchanged at various stages in an Arbusov reaction between the ethyl phosphites (I; $R^1 = Et$) and methyl iodide at 0 °C. Aliquot portions of a mixture of the phosphite and methyl iodide were removed at intervals and treated with an excess of sulphur in carbon disulphide, the resulting mixture of sulphides and phosphonates being analysed by g.l.c. The results are summarised in Table 2. It will be seen that the figures do show a reproducible increase in the *amount* of *trans*-phosphite present in the mixture. We therefore interpret this as (*a*) further evidence that a pentaco-ordinate species is involved, (*b*) evidence that this intermediate forms reversibly from the reactants, and (*c*) evidence that it probably forms before the intervention of any phosphonium intermediates which we would expect to dealkylate more rapidly than they could revert to phosphite and alkyl halide.

TABLE 2

Weight (g) of the *trans*-ethyl phosphite (I; $R^1 = Et$) in a sample (1 ml) withdrawn from the reaction mixture at time *t* (min) during the Arbusov reaction with methyl iodide at 0 °C

Run	$t = 0$	$t = 30$	$t = 60$	$t = 120$	$t = 180$	$t = 240$
a	0·058	0·078	0·100	0·106	0·107	0·106
b	0·063	0·096	0·109	0·120	0·121	0·115
c	0·060	0·086	0·105	0·115	0·116	0·112

Amounts and compositions of the phosphite samples used to make up the initial reaction mixtures were run a: 3·11 g, 26% *trans*; run b: 3·02 g, 31% *trans*; run c: 3·16 g, 27% *trans*.

It is noticeable that in the Arbusov reactions with alkyl iodides (see ref. 1) a greater degree of stereomutation is observed with the isopropyl phosphites (I; $R^1 = Pr^i$) than with the ethyl phosphites (I; $R^1 = Et$). It is probable that this is a consequence of the mechanism of the dealkylation stage of the reaction which, if an S_N2 process, may be expected to be slower at isopropyl than at ethyl. If this is so, the pentaco-ordinate intermediates in the isopropyl case will be longer-lived and can undergo more pseudorotations before dealkylation occurs. After the inception of this work, two reports [6,7] of stereospecific or nearly stereospecific Arbusov reactions have appeared in the literature, in one of which dealkylation took place at a methyl,[7] and in the other at a trimethylsilyl group.[6] Since either dealkylation would be more rapid than that at ethyl, it is consistent with the present findings that a large degree of stereomutation is not observed in these cases. The spatial requirements of the alkoxy-group may also be important in controlling pseudorotation.

Our findings [1] also show that the *cis*-isomers react with less stereospecificity than do the *trans*. The reason for this is less clear. If, as seems probable, the formation of the pentaco-ordinate species from the phosphite occurs by a valency expansion process,[9] then from either phosphite isomer as many as nine enantiomeric pairs of intermediates may be formed. Of these, several contain the unfavourable [8b,11] arrangement of more than one electronegative oxygen atom in an equatorial position, and two of these structures, with one pseudorotation, can yield a species of lower energy,[12] and lead to phosphonate of inverted configuration. One may suppose either that more of these less stable species is formed from the *cis*-phosphite isomers than the *trans*, or that the set of intermediates obtained from the *trans*-phosphites is of higher energy than the *cis*. [Arguments similar to these have recently been applied [8d] to the reaction of (I; $R^1 = Me$) with neopentyl hypochlorite, in which the two phosphite isomers also react with different stereospecificities.]

In either case, it is probably true to say that similar arguments will apply to the Arbusov reactions of differently substituted 2-alkoxy-1,3,2-dioxaphosphorinans. From the compositions of phosphonate mixtures derived from reaction between methyl iodide and the isomers of 2-methoxy-5-t-butyl-1,3,2-dioxaphosphorinan [7] it is possible to calculate that if one phosphite isomer reacts with complete stereospecificity then the other does so with *ca.* 10% loss of stereospecificity (*i.e. ca.* 10% of this isomer leads to phosphonate of inverted configuration).

EXPERIMENTAL

N.m.r. spectra were recorded on a Varian Associates HA100 instrument. G.l.c. was performed on a Pye 104 model 64 chromatograph: the column used for analysis of the interrupted reaction mixtures was 9 ft long and 4 mm i.d. packed with 5% Carbowax 20M on 100—120 mesh silanised Chromosorb G. The other reaction mixtures were analysed on a similar column of length 5 ft. In both cases the flow-rate of nitrogen carrier gas was 50 ml min^{-1} and the oven temperature 200°.

U.v. spectra were recorded on a Unicam SP 800 ultraviolet spectrophotometer. M.p.s were measured on a Kofler block, and are uncorrected. Silica gel (60—120 mesh) was used for column chromatography, and Kieselgel G, treated with a u.v. activator, for t.l.c.

The cyclic phosphites (I) were prepared by methods described previously.[3]

2-*Ethyl*-4-*methyl*-1,3,2-*dioxaphosphorinan*-2-*one* (II; $R^2 = Et$) was prepared by heating together for 2 h under reflux *trans*-2-ethoxy-4-methyl-1,3,2-dioxaphosphorinan (9·6 g, 0·06 mol) and ethyl iodide (5·7 g, 0·037 mol). Removal of volatile materials at atmospheric pressure was followed by

---

[11] E. A. Dennis and F. H. Westheimer, *J. Amer. Chem. Soc.*, 1966, **88**, 3431/32.

[12] C. L. Bodkin, D. Phil. Thesis, University of Sussex, 1971.

fractionation under reduced pressure using a 1 ft long Vigreux column to give the *phosphonate* (6·1 g, 62%), b.p. 87—90° at 0·4 mmHg, n_D^{21} 1·4492 (Found: C, 43·6; H, 8·0. $C_6H_{13}O_3P$ requires C, 43·9; H, 8·0%).

Other Arbusov reactions were carried out in a similar way by heating together the phosphite and 10 mol. equiv. of the alkyl iodide under reflux in an atmosphere of dry nitrogen. As the temperatures of these mixtures was slowly raised ebullition began quite suddenly, quickly became vigorous, and then subsided within a few min. We took this as signifying that the reaction reaches completion rapidly at the temperature of the boiling halide. Nevertheless, heating of the reaction mixtures was in each case continued for a total of 90 min. The resultant mixtures of phosphonates and alkyl iodides were analysed directly by g.l.c. The reaction was repeated several times with each phosphite isomer.

The isomers of the cyclic phosphonates (II; R^2 = Me or Et) were identified as the pair of peaks in the chromatograms which for a given alkyl iodide did not change retention time when the group R^1 of the reactant phosphite was changed. For the cyclic ethylphosphonate isomers this pair of peaks was shown by combined g.l.c.–m.s. to arise from isomeric compounds, one of which was shown to have a retention time identical with that of a sample of pure 2-ethyl-4-methyl-1,3,2-dioxaphosphorinan-2-one prepared from (I; R^1 = Et) and ethyl iodide.

The chromatogram of the products of each of the reactions carried out in almost every case contained two further peaks; these were assumed to arise from the products of ring opening. In each case the total intensity of these peaks was less than that of the peaks from the pair of cyclic phosphonate products, and was found to be essentially independent of which isomer (*cis* or *trans*) of the phosphite starting material was used.

Dealkylation of the Tritylphosphonium Tetrafluoroborates.—To a solution of one of the ethyl phosphite isomers (I; R^1 = Et) in dichloromethane was added a solution of trityl tetrafluoroborate in the same solvent. This material was prepared by the method of Dauben *et al.*[13] and before use was recrystallised from 1,2-dichloroethane–acetone (3 : 1) and thoroughly washed with pentane and with ether. A few drops of triethylamine were added to the solutions of the *cis*-phosphites to prevent their isomerisation by traces of acid.

The resulting colourless solution was concentrated under reduced pressure, diluted with acetone, and mixed with an acetone solution of the equivalent amount of lithium iodide; all manipulations were performed in an atmosphere of dry nitrogen. The resulting red solution was chromatographed (40 × 2 cm column) using ethyl acetate–hexane as eluant, yielding (*a*) from the *trans*-ethyl phosphite: first fraction (ring opening product), *ethyl* 3-*iodo*-1-*methylpropyl triphenylmethylphosphonate* (48%), m.p. 124—125° (from hexane) (Found: C, 55·9; H, 5·3. $C_{25}H_{28}IO_3P$ requires C, 56·2; H, 5·3%); second fraction cis-4-*methyl*-2-*triphenylmethyl*-1,3,2-*dioxaphosphorinan*-2-*one* (37%), m.p. 194—195° (from chloroform–hexane) (Found: C, 72·5; H, 6·2. $C_{23}H_{23}O_3P$ requires C, 72·8; H, 6·4%); (*b*) from the *cis*-ethyl phosphite: first fraction, *ethyl* 3-*iodo*-1-*methylpropyl triphenylmethylphosphonate* [diastereoisomer of that obtained in (*a*)] (45%), m.p. 147—150° (from hexane) (Found: C, 56·4; H, 5·5%); second fraction, trans-4-*methyl*-2-*triphenylmethyl*-1,3,2-*dioxaphosphorinan*-2-*one* (34%), m.p. 190—192° (from chloroform–hexane) (Found: C, 73·1; H, 6·3%).

The u.v. spectra of the two cyclic triphenylmethylphosphonates (VI) were identical and showed absorption maxima (in methanol) at 255 (ε 520 ± 30 and 510 ± 20), 261 (600 ± 30 and 580 ± 30), and 267 nm (500 ± 30 and 490 ± 10).

For the quantitative analysis of mixtures of phosphonate isomers, obtained as above from mixtures of phosphite isomers, the reaction mixtures were concentrated somewhat and separated by t.l.c. (20 × 20 cm plate; 0·5 mm thickness) using methyl ethyl ketone–hexane–ethyl acetate (3 : 3 : 4) as eluant. To obtain a complete separation of the cyclic phosphonates elution had to be carried out in two dimensions. The spots were located by u.v. irradiation and extracted with methanol. The relative intensities of the u.v. absorptions of each isomer were used to determine their relative amounts in the mixture.

Interrupted Arbusov Reactions.—A weighed, known volume (*ca.* 3 ml, 3 g) of methyl iodide, contained in a two-necked flask fitted with a rubber 'Suba' seal and a calcium chloride guard tube, was allowed to come to the desired reaction temperature and a weighed, known volume (*ca.* 11 ml, 25 g) of the *cis*-ethyl phosphite (I; R^1 = Et) was introduced, using a hypodermic syringe in order to prevent contact of phosphite with moisture. At intervals, samples (1 ml) were removed from the flask, using the syringe, and added to an excess of sulphur dissolved in carbon disulphide. These mixtures were allowed to stand for *ca.* 1 h before being concentrated somewhat under reduced pressure and analysed by g.l.c.

Calculation of the results from the chromatograms requires a knowledge of the relative response of the detector to the cyclic methylphosphonate (II; R^2 = Me) and the sulphide of the ethyl phosphite. This was estimated by obtaining the chromatogram of a mixture of weighed amounts of distilled samples of both compounds.

The award of a S.R.C. research studentship (to C. L. B.) is gratefully acknowledged.

[2/863 *Received*, 19*th April*, 1972]

---

[13] J. H. Dauben, jun., L. R. Honnen, and K. M. Harmon, *J. Org. Chem.*, 1960, **25**, 1442.