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REACTION OF TRIALKYL PHOSPHITES WITH AROMATIC ALDEHYDES

CARBON–CARBON CONDENSATIONS FROM THE REACTION OF *p*-NITROBENZALDEHYDE AND OF *o*-NITROBENZALDEHYDE WITH TRIALKYL PHOSPHITES—NEW ROUTES TO GLYCOL PHOSPHATES[1]

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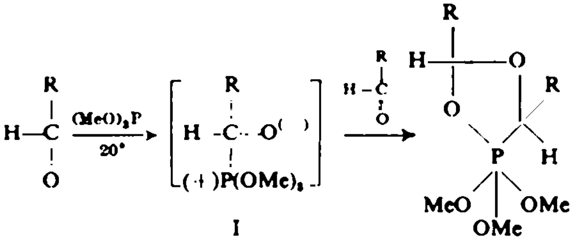
Abstract—Trialkyl phosphites induced a carbon–carbon condensation reaction in *p*-nitrobenzaldehyde and in *o*-nitrobenzaldehyde, at 20°. The products were 2,2,2-*trialkoxy*-4,5-*di*(*nitrophenyl*)1,3,2-*dioxaphospholanes*. Both diastereomers at carbon were produced; the major isomer had the *meso*-configuration. The phospholanes were hydrolyzed to glycol phosphotriesters of known configuration. The phospholanes were converted into dinitrostilbene oxides of known configuration by hot alcohol. *m*-Nitrobenzaldehyde, the chlorobenzaldehydes, and aromatic aldehydes with electron-releasing groups, failed to react with trialkyl phosphites at 20°. A previous report of the course of these reactions was shown to be in error.

INTRODUCTION

A RECENT study[3] of the reaction of trialkyl phosphites with unsubstituted *aliphatic* aldehydes[4] disclosed that the phosphorus of the phosphite attacked the carbon atom of the carbonyl function at 20°. The 1:1-adduct I, however, could not be detected since it reacted further with more aldehyde to give a 2,2,2-*trialkoxy*-1,4,2-*dioxaphospholane* (II).



I

R = Alkyl

II, $\delta P^{31} = +34$ ppm *vs.* H_3PO_4

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[1] ᵃ *Organic Compounds with Pentavalent Phosphorus*, Part XXV; ᵇ Part XXIV: F. Ramirez, S. B. Bhatia and C. P. Smith, *J. Org. Chem.* **31**, 4105 (1966).

[2] This investigation was supported by Public Health Service Grant No. CA-04769-07 from the National Cancer Institute and by the National Science Foundation (GP 3341).

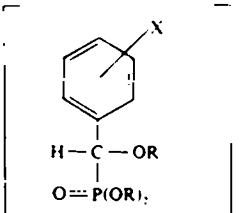
[3] F. Ramirez, A. V. Patwardhan and S. R. Heller, *J. Am. Chem. Soc.* **86**, 514 (1964).

[4] For earlier literature see: ᵃ V. S. Abramov, *Dokl. Akad. Nauk. U.S.S.R.* **95**, 991 (1954); ᵇ V. A. Ginsburg and A. Ya. Yakubovich, *J. Gen. Chem. U.S.S.R.* **30**, 3936 (1960); ᶜ *Zh. Obsch. Khim.* **30**, 3987 (1960).

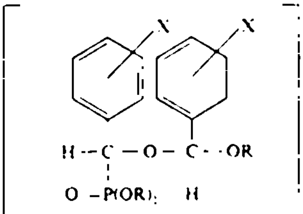
Unsubstituted aromatic aldehydes are said[4,5] to be inert toward trialkyl phosphites at 20°. At elevated temperatures, this reaction afforded small amounts of olefins, produced by a reductive dimerization of the aldehyde.[5,6]

Unsubstituted aliphatic and aromatic monoketones did not react with trialkyl phosphites at 20°.[5,7] At elevated temperatures, aromatic ketones were converted into diarylmethylphosphonic esters by certain types of trialkyl phosphites.[7]

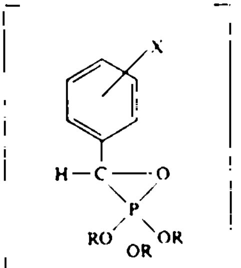
Kukhtin and Kirillova[8] claimed to have isolated the α-alkoxyphosphonates, III, IV, and the acetal-phosphonates V, VI, from the reaction of trialkyl phosphites with *p*-nitro- and *o*-nitrobenzaldehydes. They concluded that these products were formed *via* 1:1 and 2:1 *adducts* of type VII, VIII, and IX, X, respectively. In fact, they described the isolation and characterization of one of these 2,2,2-trialkoxy-1,4,2-dioxaphospholanes, X.



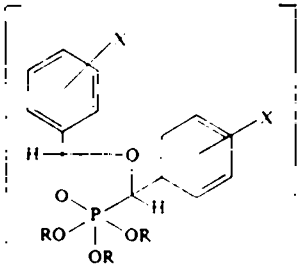
III, $X = p-NO_2$
IV, $X = o-NO_2$



V, $X = p-NO_2$
VI, $X = o-NO_2$



VII, $X = p-NO_2$
VIII, $X = o-NO_2$



IX, $X = p-NO_2$
X, $X = o-NO_2$

The results described by the Russian investigators[8] would lead to the conclusion that the phosphorus of the phosphites added to the carbonyl-carbon of the nitrobenzaldehydes, just as it added to the carbonyl-carbon of unsubstituted aliphatic monoaldehydes.[3] However, there is now a great deal of evidence showing that phosphites tend to attack the oxygen atom of a carbonyl function *whenever the latter is surrounded*

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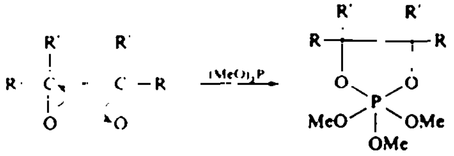
[4] A. Arbuzov and V. M. Zoroastrova, *Izv. Akad. Nank. U.S.S.R., Otd. Khim. Nauk.* 1030 (1960).

[6] The reductive dimerization of phthalic anhydride to biphthalyl by triethyl phosphite at elevated temp, has been reported. This reaction was much faster when the anhydride carried electron-withdrawing groups. Cf. F. Ramirez, H. Yamanaka and O. H. Basedow, *J. Org. Chem.* **24**, 1838 (1959); *Ibid. J. Am. Chem. Soc.* **83**, 173 (1961).

[7] A. C. Poshkus and J. E. Herweh, *J. Org. Chem.* **29**, 2567 (1964).

[8a] V. A. Kukhtin and K. M. Kirillova, *J. Gen. Chem. U.S.S.R.* **31**, 2078 (1961); [b] *Ibid. Zh. Obsch. Khim.* **31**, 2226 (1961).

by groups which are capable of stabilizing a negative charge at the carbonyl-carbon.[9] In general, the reaction of a trialkyl phosphite with an *activated* carbonyl function followed two extreme patterns. In reactions of type I, two molecules of the same carbonyl compound XI were converted into a 2,2,2,-trialkoxy-1,3,2-dioxaphospholane (XII) without detectable intermediates.[10–12]



XI XI XII, δp^{31} = +50 to +52 ppm

In reactions of type II one molecule of the carbonyl compound XIII was converted into a 1,3,2-*dioxaphospholene* (XIV). The latter could then be condensed with the same, or with a different carbonyl compound to give the 1,3,2-dioxaphospholane XV.[13–19]

The two types of oxyphosphorane condensation differ only in the relative rates of the two steps involved. The reactivity of a phospholene XIV toward a given carbonyl compound is related to the tendency of the phosphorus to acquire pentacovalency.[20] A rather stable phospholene will display a comparatively low reactivity toward a carbonyl compound, and *vice-versa*. Several factors appear to contribute to the stability of the phospholenes XIV,[21] one of them being the stereoelectronic

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[9a] F. Ramirez and S. Dershowitz, *J. Org. Chem.* **22**, 956 (1957); [b] *Ibid.* **22**, 1282 (1957); [c] *Ibid.* **23**, 778 (1958); [d] *Ibid. J. Am. Chem. Soc.* **81**, 587 (1959); [e] F. Ramirez, E. H. Chen, and S. Dershowitz, *J. Am. Chem. Soc.* **81**, 4338 (1959); [f] E. A. C. Lucken, F. Ramirez, V. P. Catto, D. Rhum and S. Dershowitz, *Tetrahedron* **22**, 637 (1966).

[10] F. Ramirez and N. Ramanathan, *J. Org. Chem.* **26**, 3041 (1961).

[11] F. Ramirez, N. B. Desai and N. Ramanathan, *Tetrahedron Letters* No. 5, 323 (1963).

[12a] F. Ramirez, C. P. Smith, A. S. Gulati and A. V. Patwardhan, *Tetrahedron Letters* No. 19, 2151 (1966). [b] E. M. Rokhlin, Yu. V. Zeifman, Yu. A. Cheburkov, N. P. Gambaryan and I. L. Knunyants, *Dokl. Akad. Nauk. S.S.S.R.* **161**, (6), 1356 (1965); Proceedings p. 393.

[13a] F. Ramirez and N. B. Desai, *J. Am. Chem. Soc.* **82**, 2652 (1960); [b] F. Ramirez, N. Ramanathan and N. B. Desai, *Ibid.* **84**, 1317 (1962); [c] F. Ramirez and N. B. Desai, *J. Am. Chem. Soc.* **85**, 3252 (1963); [d] F. Ramirez, N. Ramanathan and N. B. Desai, *Ibid.* **85**, 3465 (1963).

[14] The formation of 1:1 adducts (but not of 2:1 adducts) from the reaction of biacetyl with trialkyl phosphites was reported also by two other groups of investigators: [a] G. H. Birum and J. L. Dever, *Abstracts, Division of Organic Chemistry, 135th National Meeting of the American Chemical Society*, p. 101. Chicago, Ill. Sept. (1958); [b] G. H. Birum and J. L. Dever, *U.S. Patents* **2**, 961, 455 (1960); [c] V. A. Kukhtin, *Dokl. Akad. Nauk. S S.S.R.* **121**, 466 (1958); [d] V. A. Kukhtin and K. M. Orekhova, *J. Gen. Chem. U.S.S.R.* **30**, 1229 (1960); [e] V. A. Kukhtin, K. Kirillova and R. R. Shagidullin, *Zh. Obsch. Khim.* **32**, 649 (1962); [f] V. A. Kukhtin and K. M. Kirillova, *J. Gen. Chem. U.S.S.R.* **32**, 2755 (1962).

[15a] F. Ramirez, A. V. Patwardhan and C. P. Smith, *J. Org. Chem.* **30**, 2575 (1965); [b] *Ibid.* **31**, 474 (1960).

[16] F. Ramirez, A. V. Patwardhan, N. Ramanathan, N. B. Desai, C. V. Greco and S. R. Heller, *J. Am. Chem. Soc.* **87**, 543 (1965).

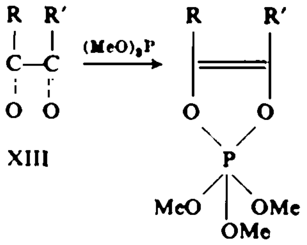
[17] F. Ramirez, A. V. Patwardhan and C. P. Smith, *J. Org. Chem.* **31**, 3159 (1966).

[18] F. Ramirez, A. V. Patwardhan, N. B. Desai, N. Ramanathan and C. V. Greco, *J. Am. Chem. Soc.* **85**, 3056 (1963).

[19] F. Ramirez, H. J. Kugler and C. P. Smith, *Tetrahedron Letters* No. 4, 261 (1965).

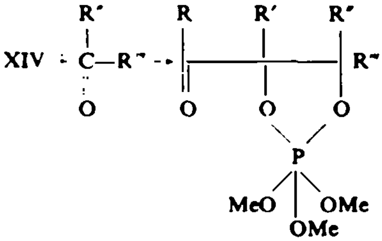
[20a] F. Ramirez, *Pure and Appl. Chem.* **9**, 337 (1964); [b] F. Ramirez, *Bull. Soc. Chim. Fr.* No. 6, 2443 (1966).

[21a] F. Ramirez, A. V. Patwardhan and C. P. Smith, *J. Am. Chem. Soc.* **87**, 4973 (1965); [b] F. Ramirez, A. V. Parwardhan, H. J. Kugler and C. P. Smith, *Tetrahedron Letters* No. 26, 3053 (1966).



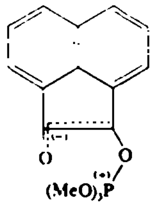
XIII

XIV, $\delta P^{31} = -44$ to $+50$ ppm

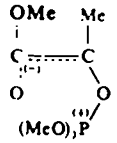


XV, $\delta P^{31} = +46$ to $+55$ ppm

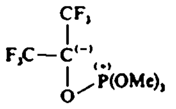
characteristics of the carbonyl compounds. The high reactivity of the 1:1-adducts derived from acenaphthenequinone,[10] methyl pyruvate[11] and hexafluoroacetone[12] suggests that these adducts have open dipolar structures, XVI, XVII and XVIII.



XVI



XVII



XVIII

Evidently, the report by Kukhtin and Kirillova was not in accord with these views; consequently, we reexamined the reaction of the nitrobenzaldehydes with trialkyl phosphites.

RESULTS

Reaction of trialkyl phosphites with p-*nitrobenzaldehyde*

Trimethyl phosphite reacted with *p*-nitrobenzaldehyde at 20°. Slightly more than one mole of phosphite was required to cause the disappearence of two mole of the aldehyde. The main products were the *meso*- and the *racemic* forms of 2,2,2-*trimethoxy*-4,5-*di*-p-*nitrophenyl*-1,3,2-*dioxaphospholane*, (XIXa and XIXb).

The crystalline isomers were formed in the approximate proportion of 70:30, XIXa:XIXb. The major isomer is thought to be the *meso*-form XIXa with two hydrogen atoms in *cis*- relationship. This assignment of configuration is based on the ^{1}H NMR data given in Table 1. The two equivalent protons in the phospholane ring of the major isomer were at significantly lower magnetic field than the corresponding protons of the minor isomer. Therefore, the latter protons are probably

TABLE 1. NMR SHIFTS[a] OF 2,2,2-TRIALKOXY-1,3,2-DIOXAPHOSPHOLANES FROM THE REACTION OF TRIALKYL PHOSPHITES WITH *p*-NITRO- AND *o*-NITROBENZALDEHYDES

		Major diastereomer[b]						Minor diastereomer[c]					
Substituents	R in $(RO)_3P$	No.	δP^{31}	τ_H[d]	J_H[d]	τ_R[e]	J_R[e]	No.	δP^{31}	τ_H[d]	J_H[d]	τ_R[e]	J_R[e]
p-NO_2	Me	XIXa	+49·6	4·60	11·8	6·25	12·6	XIXb	+50·2	5·30	2·2	6·28	12·8
p-NO_2	Et	XXa	+52·4	4·59	11·6	5·85[f]	7·5	XXb	+53·4	5·32	2·3	5·8	7·5
o-NO_2	Me	XXIa	+50·1	3·83	11·5	6·25	12·8	XXIb	...	4·55	5·2	6·30	12·8
o-NO_2	Et	XXIIa	+52·8	3·82	11·6	5·85[g]	7·5	XXIIb	...	4·52	6·20	6·0	7·5

[a] δP^{31} at 40·5M c/s in ppm *vs* H_3PO_4. ^1H NMR at 60M c/s in ppm *vs* TMS = 10 (τ values). J_{H-P} in c/s. Solvents: CH_2Cl_2 for ^{31}P; $CDCl_3$ for ^1H NMR.

[b] Assumed to be *meso* (*cis* H/H) from ^1H NMR.

[c] Assumed to be *racemic* (*trans* H/H).

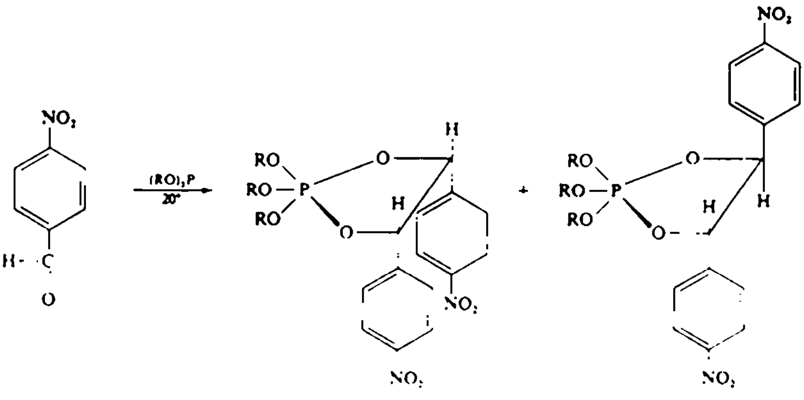
[d] Protons on dioxaphospholane ring.

[e] Protons on α-carbon of phosphite.

[f] Doublet, J_{HP} = 7·5 c/s, of quartets, J_{HH} = 7·5 c/s. The CH_3 of CH_3CH_2— gave a doublet, J_{HP} = 1·7 c/s, of triplets, J_{HH} = 7·5 c/s.

[g] Doublet, J_{HP} = 7·5 c/s, of quartets, J_{HH} = 7·5 c/s. The CH_3 of CH_3CH_2— gave a doublet, J_{HP} = 1·8 c/s, of triplets, J_{HH} = 7·5 c/s.

adjacent to the aromatic ring, as in *racemic*-XIXb.[15-20] The ring-protons of the *meso* form XIXa were more effectively coupled with the phosphorus than the ring-protons of the *racemic* form XIXb. Apparently, the dihedral angles between the planes defined by the atoms H—C—O and P—O—C are rather different in the two isomers.[15,16,22c]



XIXa, R = Me
XXa, R = Et

XIXb, R = Me
XXb, R = Et

The ^{31}P NMR signal of the major isomer XIXa was at slightly lower magnetic field than that of the minor isomer XIXb. The signals were strongly positive relative to H_3PO_4 (Table 1). The evidence linking a positive ^{31}P NMR shift with quintuply-connected phosphorus in these compounds has been presented elsewhere.[23]

Our results are quite different from those reported by Kukhtin *et al.*[8,24] who claimed the isolation of dimethyl *p*-nitro-α-methoxybenzylphosphonate (III, R = Me), m.p. 132–134°, from trimethyl phosphite and *p*-nitrobenzaldehyde. We can offer no explanation for this wide discrepancy.

The reaction of triethyl phosphite with *p*-nitrobenzaldehyde was analogous in all respects to the reaction of trimethyl phosphite and gave over 80% of the *meso*-XXa and the *racemic*-XXb phospholanes in the proportion of 70:30. Kukhtin *et al.*[8,24] claimed the isolation of *p*-nitrobenzyl-*p*-nitrobenzoate, m.p. 171–172° and of diethyl *p*-nitro-α-(*p*′-nitro-α′-ethoxybenzyloxy) benzylphosphonate (V, R = Et), from the reaction of triethyl phosphite with *p*-nitrobenzaldehyde.

Reaction of trialkyl phosphites with o-*nitrobenzaldehyde*

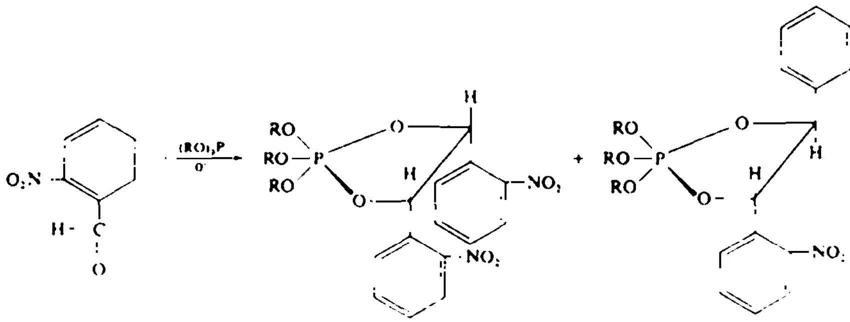
The reaction of trimethyl phosphite with *o*-nitrobenzaldehyde gave the *meso*-form of 2,2,2-*trimethoxy*-4,5-*di*-o-*nitrophenyl*-1,2,3-*dioxaphospholane* (XXIa) in about 70% yield. Small amounts of the *racemic*-form XXIb were also detected. The spectral data are given in Table 1.

[22a] F. Ramirez, N. B. Desai and N. Ramanathan, *J. Am. Chem. Soc.* **85**, 1874 (1963); [b] F. Ramirez, O. P. Madan, N. B. Desai, M. Neyerson and E. M. Banas, *Ibid.* **85**, 2681 (1963); [c] F. Ramirez, A. V. Patwardhan, N. B. Desai and S. R. Heller, *J. Am. Chem. Soc.* **87**, 549 (1965).

[23] W. C. Hamilton, S. J. La Placa and F. Ramirez, *J. Am. Chem. Soc.* **87**, 127 (1965).

[24] The formula $(o\text{-}O_2NC_6H_4CHO)_2P(OEt)_3$ given in *Chem. Abstr.* **56**, 3707g (1962) does not appear in the original Russian article of Ref. 8. Kukhtin *et al.* referred explicitly to 2,2,2-*trialkoxy*-1,4,2-*dioxaphospholanes*, IX and X, with a P—C bond, and did not mention the 2,2,2-*trialkoxy*-1,3,2-*dioxaphospholane* structure.

Triethyl phosphite behaved like trimethyl phosphite toward *o*-nitrobenzaldehyde. The *meso*-form of the dioxaphospholane XXIIa was isolated in 75% yield.



XXIa, R = Me
XXIIa, R = Et

XXIb, R = Me
XXIIb, R = Et

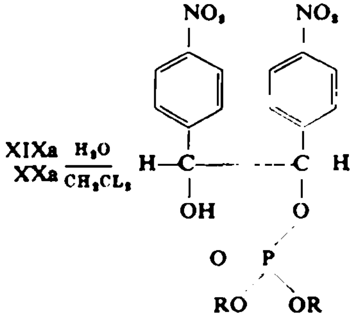
Kukhtin *et al.*[8] reported the formation of the phosphonate IV (R = Me) from the reaction of trimethyl phosphite with *o*-nitrobenzaldehyde. They claimed the isolation of the 1,4,2-*dioxaphospholane* X (R = Et) and of the phosphonate VI (R = Et) in the case of triethyl phosphite. We found no evidence for the formation of these substances.

Behaviour of other aldehydes toward trialkyl phosphites

m-Nitrobenzaldehyde gave no evidence of reaction with trimethyl phosphite after 48 hr at 20°; some reaction was noted after 8 hr at 100°. Benzaldehyde and *p*-chloro-, *o*-chloro-, *p*-methoxy- and *p*-acetamidobenzaldehyde, as well as furfural, failed to react at 100° (48 hr).

Hydrolysis of 1,3,2-*dioxaphospholanes to glycol phosphates*

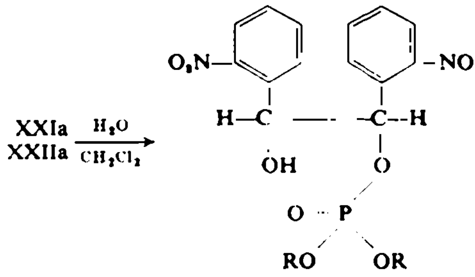
The major isomer obtained from *p*-nitrobenzaldehyde and trimethyl phosphite, XIXa, was converted into a crystalline, neutral glycol phosphotriester XXIIIa, by water in methylene chloride at 20°. The elemental analysis, the ^{31}P NMR shift and the IR spectrum support the phosphate structure. Since the hydrolysis was very mild, the glycol phosphate probably has the *erythro*-configuration, XXIIIa.



XXIIIa, R = Me; $\delta P^{31} = +0{\cdot}8$ ppm
XXIVa, R = Et

The triethyl phosphite-adduct XXa gave the corresponding glycol phosphate XXIVa, on hydrolysis.

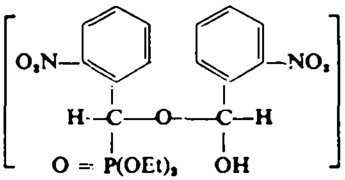
The adducts XXIa and XXIIa derived from *o*-nitrobenzaldehyde, were converted into the corresponding phosphates, XXVa and XXVIa, by one or two mole equivalents of water.



XXVa, R = Me; δP^{31} = −0·1 ppm
XXVIa, R = Et

There was no evidence for the formation of 5-membered cyclic phosphates in the hydrolyses of these 1,3,2-dioxaphospholanes.[22]

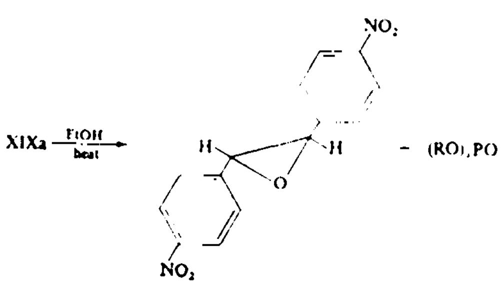
Kukhtin and Kirillova[8] reported the formation of a hemiacetalphosphonate, XXVII, from the hydrolysis of the 1,4,2-dioxaphospholane, X. Since the latter structure is incorrect, the hemiacetal phosphonate XXVII, if at all formed, could not have resulted in the manner indicated by the Russian authors.[8]



XXVII

Conversion of 1,3,2-*dioxaphospholanes to dinitrostilbene oxides in boiling alcohol*

The major diastereomer XIXa, made from *p*-nitrobenzaldehyde and trimethyl phosphite, was converted into trans-p,p′-*dinitrostilbene* oxide XXVIII, m.p. 202–203°, by hot ethanol.



XXVIII

Both diastereomers of the epoxide have been reported;[25] the *trans*-isomer was said to melt at 201–202°, and the *cis*-isomer at 153–154°. Since the dioxaphospholane

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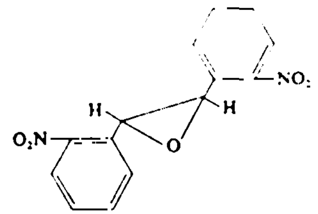
[24] F. Barrow and E. D. Griffiths, *J. Chem. Soc.* 212 (1921); [25] E. Bergmann and J. Harvey, *Ber. Dtsch. Chem. Soc.* **62B**, 893 (1929); [26] S. Bodforss, *Liebigs Ann.* **534**, 243 (1938); [27] S. B. Hanna, Y. Iskander and J. Riad, *J. Chem. Soc.* 217 (1961).

XIXa had the *meso*-configuration, and since epoxide formation is probably a *trans*-substitution, the formation of the *trans*-epoxide XXVIII is reasonable.

The adducts, XXIa and XXIIa, derived from *o*-nitrobenzaldehyde were converted into a diastereomer XXIX, of *o,o'*-dinitrostilbene oxide, m.p. 169–170°, by hot ethanol.

XXIa
XXIIa

$\xrightarrow[\text{heat}]{\text{EtOH}}$



(RO)$_3$PO

XXIX

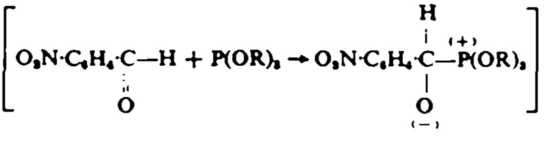
Kukhtin and Kirillova[8] reported that the adduct prepared by them from *o*-nitrobenzaldehyde and triethyl phosphite, and to which they ascribed the 1,4,2-dioxaphospholane structure X, R = Et, was converted into an *o,o'*-dinitrostilbene oxide, m.p. 163–165°. The formation of an epoxide from a 1,4,2-dioxaphospholane would require the cleavage of a phosphorus-carbon bond. Although, in principle, such a P—C bond cleavage is not impossible, our experiments show that, in the present case, the epoxide is derived from a 1,3,2-dioxaphospholane, *in which the carbon-carbon bond of the epoxide had already been established.* For the reasons given above, the formation of the *trans*-epoxide, XXIX from the *meso*-1,3,2-dioxaphospholanes is reasonable.

The Russian authors[8] reported the isolation of the epoxide XXIX when triethyl phosphite was added to *o*-nitrobenzaldehyde in hot ethanol solution. Evidently, their interpretation of the formation of the epoxide in this reaction is in error.

DISCUSSION

o-Nitrobenzaldehyde was more reactive than *p*-nitrobenzaldehyde toward trialkyl phosphites. In both cases, 1,3,2-dioxaphospholanes, XIX–XXII, were produced in high yields. The ratio of *meso* to *racemic* isomers was significantly higher in the *o*-nitro than in the *p*-nitro case; in fact, little *racemic*-dioxaphospholanes, XXIb and XXIIb, were formed from *o*-nitrobenzaldehyde. *m*-Nitrobenzaldehyde did not react with the trialkyl phosphites under comparable conditions (20°). The chlorobenzaldehydes, and aromatic monoaldehydes with electron-releasing substituents were also inert to trialkyl phosphites below 100°.

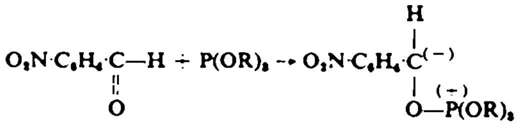
The present investigation does not exclude the possibility that the phosphorus of the phosphites could have added, reversibly, to the carbonyl-*carbon* of the nitrobenzaldehydes.



$$\left[O_2N\cdot C_6H_4\cdot \underset{\overset{\|}{O}}{C}-H + P(OR)_3 \rightarrow O_2N\cdot C_6H_4\cdot \underset{\underset{(-)}{\overset{|}{O}}}{\overset{\overset{H}{|}}{C}}-\overset{(+)}{P}(OR)_3\right]$$

XXX

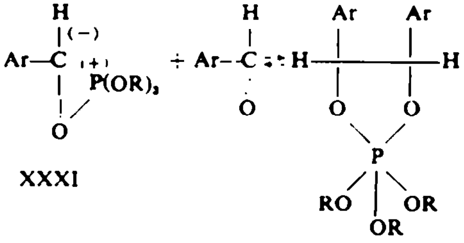
However, the data show conclusively that the *first observable products of these reactions are derived from intermediates which were formed by an attack by phosphorus on carbonyl-oxygen;* i.e., XXXI.



$$O_2N{\cdot}C_6H_4{\cdot}\underset{\underset{O}{\parallel}}{C}{-}H + P(OR)_3 \rightarrow O_2N{\cdot}C_6H_4{\cdot}\overset{\overset{H}{|}}{C}{}^{(-)}{-}O{-}\overset{(+)}{P}(OR)_3$$

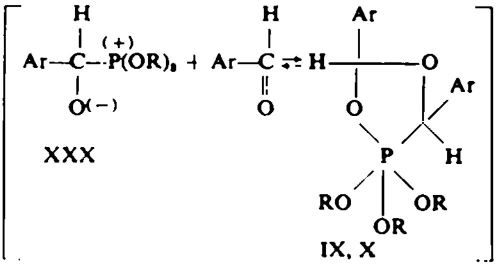
XXXI

The 1:1-adducts, XXXI, appeared to be too reactive for detection. They added to a second molecule of the aldehyde and gave the 1,3,2-dioxaphospholanes with a new carbon-carbon bond, XIX-XXII. It is conceivable that 1:1-adduct XXX with a carbon-phosphorus bond could rearrange to a 1:1-adduct XXXI, with an oxygen-phosphorus bond, either directly or *via* an intermediate with a three-membered ring. It should be emphasized, however, that in the case of the reaction of *aliphatic* monoaldehydes with trialkyl phosphites,[3] where the phosphorus did attack the carbonyl-carbon, a rearrangement of the 1:1-adduct analogous to XXX did not take place. Therefore, it seems very probable that the initial attack was on oxygen in the case of the nitrobenzaldehydes. This matter could be more complicated than these statements might imply. At the present state of these investigations, it is safest to assume that changes in the structure of the carbonyl compound and of the phosphite, as well as variations in the nature of the solvent, could alter the relative rates and equilibria of the steps that might be involved in the reaction of trialkyl phosphites with carbonyl compounds, namely, the attacks by phosphorus on carbon or oxygen, and the formation of 1,4,2-dioxaphospholanes or of 1,3,2-dioxaphospholanes.



XXXI

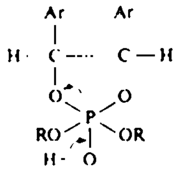
XIX-XXII



XXX

IX, X

The hydrolysis of the five-membered cyclic pentaoxyphosphoranes gave exclusively open-chain glycol phosphotriesters. No cyclic phosphates were obtained, in contrast to the behavior of other pentaoxyphosphoranes[13,22] of type XV in which one or two carbonyl functions were attached to the 1,3,2-dioxaphospholane ring. These hydrolyses could proceed *via* an intermediate of type XXXII. Possible reasons for the differences in the final products that are obtained in the hydrolyses of the various types of oxyphosphoranes are being investigated.



XXXII

Another difference between the 4,5-diaryl-1,3,2-dioxaphospholanes XIX–XXII and the 4,5-diacetyl- or 4-acetyl-5-alkyl(aryl)-1,3,2-dioxaphospholanes, such as XV, is the tendency of the former to form epoxides and trialkyl phosphates when heated in alcohol. Compounds of type XV, including 4,5-diaroyl- and 4,5-dicarbomethoxy-1,3,2-dioxaphospholanes, showed little or no tendency to give epoxides under similar conditions. A number of reasons could contribute to these differences. (1) Steric interference to the intramolecular substitution required in the formation of epoxides. (2) Electronic effects associated with the "benzylic" positions of the phospholane. (3) Differences in stability in the phospholane rings. (4) The existence of other solvolytic pathways in the case of carbonyl-containing phospholanes. Some of these possibilities are being explored.

EXPERIMENTAL

Analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y.

Reaction of p-*nitrobenzaldehyde with trimethyl phosphite*

(a) *In the absence of solvent.* Trimethyl phosphite (7·56 g, 61·7 m-moles) was added to *p*-nitrobenzaldehyde (9·33 g, 61·7 m-moles) at 20° under N_2. An exothermic reaction was noted after 10–15 min. The mixture was stirred for 20 hr at 20°, during which time pale yellow crystals separated. The excess of phosphite was removed at 20° (1 mm), and the residue was crystallized from benzene–hexane. The first crop of crystals (8·6 g, 66% yield, m.p. 120–133°) consisted of a mixture of *meso*- and *racemic* phospholanes XIXa and XIXb, in about 80:20 proportion, according to the ^{1}H NMR in $CDCl_3$. One recrystallization from benzene–hexane gave meso-2,2,2-*trimethoxy-4,5-di*-p-*nitrophenyl-1,3,2-dioxaphospholane* (XIXa), m.p. 138–139° (6·0 g, 46%). (Found: C, 47·7; H, 4·2; N, 6·30; P, 7·2. $C_{17}H_{19}O_9N_2P$ requires: C, 47·9; H, 4·5; N, 4·5; P, 7·3%.) The ^{1}H and ^{31}P NMR shifts are given in Table 1; the aromatic protons gave a multiplet at ca. τ 2·4. The IR spectrum had bands at 6·25 (w), 6·56 (s), 7·43 (s), 8·50 (w), 9·40 (v.s.) and 9·15 (shoulder) μ (in CH_2Cl_2). The mother liquid, from which *meso*-XIXa was removed, was concentrated somewhat and was allowed to stand, yielding racemic-2,2,2-*trimethoxy-4,5-di*-p-*nitrophenyl*-1,3,2-*dioxaphospholane* (XIXb), m.p. 131–132° (1·0 g, 8%). (Found: C, 48·1; H, 4·5; N, 6·3%. P, 7·6) The ^{1}H and the ^{31}P NMR shifts are given in Table 1; the aromatic protons gave a multiplet at ca. τ 2·2. The IR spectrum had bands at 6·25 (w), 6·56 (s), 7·43 (s), 8·50 (w), 9·40 (v.s.), and 9·15 (shoulder) μ (in CH_2Cl_2). There were some differences in the IR spectrum of *meso*-XIXa and *racemic*-XIXb in the 11·5–12·5 μ-region.

When two moles of trimethyl phosphite were added to one mole of *p*-nitrobenzaldehyde at 20°, similar results were obtained. The crystalline mixture of *meso* + *racemic* 2:1 adducts XIXa + XIXb was obtained in about 60–65% yield.

(b) *In methylene chloride.* One mole of trimethyl phosphite was added to two moles of *p*-nitrobenzaldehyde in 0·5M CH_2Cl_2 soln at 20°, under N_2. The IR spectrum of an aliquot was examined after 48 hr and after 6 days; both spectra were identical and showed the presence of small amounts of unreacted aldehyde (C=O band at 5·90 μ). The CO band due to aldehyde completely disappeared when more trimethyl phosphite (ca. 0·5 mole) was added. Therefore, in CH_2Cl_2 soln, it takes between 1·0 and 1·5 moles of phosphite to cause the complete disappearance of 2·0 moles of *p*-nitrobenzaldehyde.

Reaction of p-*nitrobenzaldehyde with triethyl phosphite*

(a) *In diethyl ether.* Triethyl phosphite (7·5 g, 45·1 m-moles) was added to a suspension of *p*-nitrobenzaldehyde (7·0 g, 46·5 m-moles) in anhydrous ether (100 ml), at 20°, under N_2. The mixture was stirred for 20 hr at 20°, and the resulting colorless crystals of meso-*2,2,2-triethoxy-4,5-di-*p-*nitrophenyl-*1,3,2-*dioxaphospholane* (XXa) (3·2 g, 30%, m.p. 130–138°) were filtered. The ^1H NMR showed the presence of one diastereomer. One recrystallization from benzene–hexane (1:2) gave *meso*-XXa of m.p. 138–140° (25% yield). (Found: C, 51·4; H, 5·5; N, 6·2; P, 6·6; mol. wt. 546 (isothermal distillation.) $C_{20}H_{25}O_9N_2P$ requires: C, 51·3; H, 5·3; N, 6·0; P, 6·6%; mol. wt. 468). The NMR shifts are given in Table 1; the aromatic protons gave a multiplet at ca. τ 2·4. The IR spectrum had bands at 6·25 (w), 6·50 (s), 7·44 (s), 9·56 (v.s.) with shoulders at 9·10, 9·30 and 9·94 μ (in CH_2Cl_2). The ether filtrate, from which 30% of *meso*-XXa had been removed, was concentrated to ca. 50 ml, yielding 5·3 g (51%) of a mixture of XXa + XXb. The ^1H and ^{31}P NMR spectra showed that the proportion of the isomers was roughly 40:60, XXa:XXb. The shifts are included in Table 1. One recrystallization from benzene–hexane gave 4·45 g (40%, m.p. 100–110°) of a mixture of XXa + XXb, similar to the previous one (by ^1H NMR). No further attempt was made to separate the diastereomer. Therefore, this reaction afforded ca. 81% of XXa + XXb, in the *approximate* proportion of 70:30, of which about 30% of *meso*-XXa was obtained in pure form.

The ether mother liquid had three P-nuclei: XXa, $\delta P^{31} = +52·5$ ppm (4 parts), XXb, $\delta P^{31} = +53·4$ ppm (1 part), and a phosphate ester (*vide infra*), $\delta P^{31} = +1·1$ ppm (5 parts).

(b) *In methylene chloride.* Triethyl phosphite (4·8 g, 28·8 m-moles) was added to a clear soln of *p*-nitrobenzaldehyde (7·9 g, 52·5 m-moles) in CH_2Cl_2 (85 ml). The course of the reaction was followed by means of IR spectra. After one hr there was some aldehyde left unreacted (5·88 μ-band). The aldehyde continued to disappear and was nearly absent after 5 hr. The H^1 NMR of the residue obtained after 24 hr at 20° showed the signals due to *meso*-XXa and *racemic*-XXb, in about 70:30 proportion. It was estimated that, in CH_2Cl_2 soln, it takes between 1·0 and 1·2 moles of phosphite to cause the complete disappearance of 2·0 moles of *p*-nitrobenzaldehyde.

Reaction of o-*nitrobenzaldehyde with trimethyl phosphite*

(a) *In the absence of solvent.* The addition of two moles of trimethyl phosphite to one mole of *o*-nitrobenzaldehyde at 20°, under N_2, led to a very exothermic reaction. The mixture reached its b.p. within a few sec. The black viscous gum thus obtained was not investigated further. (Compare this reaction with the milder one of *p*-nitrobenzaldehyde with trimethyl phosphite.)

(b) *In methylene chloride.* Trimethyl phosphite (2·2 g, 17·7 m-moles) was added to a soln of *o*-nitrobenzaldehyde (5·37 g, 35·6 m-moles) in CH_2Cl_2 (35 ml), at 0°, under N_2. The soln was allowed to reach 20° within 3 hr and was stirred for 18 hr at 20°. The IR spectrum of an aliquot showed small amounts of unreacted *o*-nitrobenzaldehyde (band at 5·90 μ). The soln was stirred for 24 hr at 20° and was then evaporated at 20° (20 mm, 1 mm). The thick oil was crystallized from benzene–hexane to give meso-*2,2,2-trimethoxy-4,5-di-*o-*nitrophenyl-*1,3,2-*dioxaphospholane* (XXIa) (5·1 g, 67%, m.p. 108–114°). The ^1H NMR showed the presence of one diastereomer. One crystallization from benzene–hexane gave the colorless *meso* m.p. 120–121° (60%). (Found: C, 48·1; H, 4·5; N, 6·1; P, 7·6. $C_{17}H_{19}O_9N_2P$ requires: C, 47·9; H, 4·5; N, 6·6; P, 7·3%.) The NMR shifts are given in Table 1; the aromatic protons gave a multiplet at ca. τ 2·4. The IR spectrum had bands at 6·23 (w), 6·35 (w), 6·54 (s), 6·85 (w), 6·92 (w), 7·41 (s), 7·70 (w), 9·48 (v.s.) with shoulders at 9.30 and 9·62 μ (in CH_2Cl_2). The benzene–hexane filtrate from which 67% of *meso*-XXIa had been removed, showed the presence of very small amounts of *racemic*-XXIb. The NMR shifts of the latter are included in Table 1; no attempt was made to isolate this isomer. There was evidence for the formation of small amounts of a phosphate ester (*vide infra*).

When one mole of trimethyl phosphite was added to one mole of *o*-nitrobenzaldehyde in CH_2Cl_2 at 0–10°, similar results were obtained. Most of the aldehyde had been consumed after 30 min; no aldehyde was left unreacted after 20 hr at 20°. The ^1H NMR spectrum of the crude product showed the two diastereomers *meso*-XXIa and *racemic*-XXIb in roughly 90:10 proportion. Meso-XXIa was obtained pure in about 60–65% yield.

(c) *In ether.* Trimethyl phosphite (2·5 g, 20·2 m-moles) was added to a clear pale yellow soln of *o*-nitrobenzaldehyde (3·0 g, 20 m-moles) in *anhydrous* ether (50 ml). No significant color change was noted. No ppt was observed within 24 hr (Kukhtin and Kirillova[8] reported the formation of a precipitate after 50 min). The IR spectrum had a weak CO band at 5·90 μ after 24 hr; there was no aldehyde left after 48 hr. The soln was evaporated and the crystalline residue was examined by ^{1}H NMR-spectroscopy. The majority of the product was the *meso*-XXIa, but there was evidence of very small amounts of *racemic*-XXIb plus a phosphate ester (*vide infra*).

Reaction of o-*nitrobenzaldehyde with triethyl phosphite*

(a) *In methylene chloride.* Triethyl phosphite (2·4 g, 14·3 m-moles) was added to a soln of *o*-nitrobenzaldehyde (4·4 g, 28·7 m-moles) in CH$_2$Cl$_2$ (30 ml), at 0°, under N$_2$. The soln was stirred for 4 hr at 10° and 48 hr at 20°. The IR spectrum showed very small amounts of aldehyde (5·90 μ). The solvent was removed (20°, at 20 mm). The crystalline residue was recrystallized from benzene–hexane giving meso-*2,2,2-triethoxy-4,5-di-*o*-nitrophenyl-1,3,2-dioxaphospholane* (XXIIa) (4·2 g, 65%, m.p. 116–127°). One recrystallization from benzene–hexane gave the *meso*-XXIIa of m.p. 133–134° (55%). (Found: C, 51·5; H, 5·6; N, 5·6; P, 6·1. $C_{20}H_{25}O_9N_2P$ requires: C, 51·3; H, 5·3; N, 5·9; P, 6·6%.) The NMR shifts are given in Table 1. The aromatic protons gave a multiplet at ca. τ 2·4. The IR spectrum had bands at 6·56 (s), 7·41 (s), 9·50 (v.s.) with shoulders at 9·17 and 9·62 μ (in CH$_2$Cl$_2$). No effort was made to isolate the racemic-XXIIb, which was formed in small amounts according to the ^{1}H NMR spectrum.

(b) *In ether.* Triethyl phosphite (7·5 g, 45·2 m-moles) was added to a soln of *o*-nitrobenzaldehyde (7·0 g, 46·3 m-moles) in anhydrous ether (80 ml), at 20°, under N$_2$. The exothermic reaction brought the soln to its reflux temp. The soln was stirred for 24 hr at 20°; the crystals that precipitated were found to be *meso*-XXIIa (6·5 g, 60%, m.p. 122–132°). The ^{1}H and ^{31}P NMR spectra showed the presence of one diastereomer only. One crystallization from benzene–hexane gave *meso*-XXIIa, m.p. 134–135°. The ether filtrate was evaporated giving a residue which was shown to contain a mixture of *meso*-XXIIa + *racemic*-XXIIb in roughly 70:30 proportion. The NMR signals of the isomers are given in Table 1. One recrystallization from benzene–hexane gave *meso*-XXIIa (1·6 g, 15%, m.p. 127–135°). The reaction, therefore, afforded 75% of *meso*-XXIIa and an estimated 5–10% of *racemic*-XXIIb, which was not isolated.

Hydrolysis of the p-*nitrobenzaldehyde-trimethyl phosphite adduct* (*meso*-XIXa)

Five mole equivs (0·6 g) water was added to a 0·18M soln of the *meso*-XIXa (2·812 g) in CH$_2$Cl$_2$ (40 ml) at 20°. The mixture was stirred for 18 hr at 20°, and the pale yellow crystals (ca. 2·4 g) which precipitated were filtered off. One recrystallization from EtOH–water gave a first crop (1·24 g, m.p. 179–180°) and a second crop (0·6 g, m.p. 175–180°; total yield, 67%) of erythro-*dimethyl (2-hydroxy-1,2-di-*p*-nitrophenyl)ethyl phosphate* or erythro-*dimethyl phosphodihydro*(p,p′-*dinitro*)*benzoin* (XXIIIa). (Found: C, 46·8; H, 4·2; N, 7·0; P, 7·5. $C_{16}H_{17}O_9N_2$ requires: C, 46·6; H, 4·1; N, 6·8; P, 7·5%.)

The phosphate was sparingly soluble in CH$_2$Cl$_2$ acetone, acetonitrile and cold MeOH. The spectral characteristics were: bands at 3·1, 6·25, 6·60, 7·43, 8·1–8·2 (broad), ca. 8·8 (broad) and 9·50 μ (in Nujol mull). $\delta P^{31} = +0{\cdot}8$ ppm (in dimethyl formamide).

Hydrolysis of the p-*nitrobenzaldehyde-triethyl phosphite adduct* (*meso*-XXa)

The hydrolysis was performed as described above for the Me analogue. The crude ppt (2·1 g, m.p. 90–120°) was recrystallized from aqueous–EtOH giving erythro-*diethyl phosphodihydro*(p,p′-*dinitro*)*benzoin* (XXIVa) (1·52 g, 57%, m.p. 130–145°). One more crystallization gave XXIVa of m.p. 149–150° (35%). (Found: C, 49·2; H, 4·7; N, 6·6; P, 7·2. $C_{18}H_{21}O_9N_2P$ requires: C, 49·1; H, 4·8; N, 6·4: P, 7·0%.) The spectral characteristics were: bands at 2·87, 3·10, 6·20, 6·68, 7·45, 7·8 (broad), 8·10 and 9·70 μ (in CH$_2$Cl$_2$). A 4H^1 multiplet at τ 2·0; a 4H^1 multiplet at τ 2·7; a 1H^1 doublet, $J_{HP} = 7{\cdot}2$ c/s, of doublets, $J_{HH} = 5$ c/s, at τ 4·40; a 1H^1 doublet, $J_{HH} = 5$ c/s at τ 4·80; a 1H^1 singlet at τ 5·60; a 4H^1 pair of doublets of quartets at τ ca. 6·0; a 3H^1 doublet, $J_{HP} = 1{\cdot}5$ c/s, of triplets, $J_{HH} = 7{\cdot}2$ c/s at τ 8·78, plus a second 3H^1 doublet, with similar couplings, at τ 8·85.

Hydrolysis of the o-*nitrobenzaldehyde-trimethyl phosphite adduct* (*meso*-XXIa)

One mole equiv water (0·14 g) was added to a 0·2M soln of the *meso*-XXIa (3·46 g) in CH$_2$Cl$_2$ (40 ml) at 20°. The mixture was stirred for 24 hr at 20°. The crude erythro-*dimethyl phosphodihydro*(o,o′-*dinitro*)*benzoin* (XXVa) (2·84 g, 85%, m.p. 158–165°) was recrystallized from EtOH giving *erythro*-XXVa of m.p. 169–170° (70%). (Found: C, 46·8; H, 4·2; N, 6·7; P, 7·6. $C_{16}H_{17}O_9N_2P$ requires: C, 46·6; H, 4·1; N, 6·8; P, 7·5%.) The spectral characteristics were: bands at 2·85, 3·1, 6·25, 6·35, 6·55, 7·45, 7·8 (broad) and 9·56 μ (in very dilute CH_2Cl_2). $\delta P^{31} = +0{\cdot}12$ ppm, a doublet, $J_{HP} = 8{\cdot}5$ c/s, of septets, $J_{HP} = 11{\cdot}3$ c/s, in DMF.

Hydrolysis of the o-*nitrobenzaldehyde-triethyl phosphite adduct* (*meso*-XXIIa)

Two mole equivs water (0·128 g) were added to a 0·12M soln of the *meso*-XXIIa (1·673 g) in CH_2Cl_2 (30 ml). The mixture was stirred for 24 hr at 20° and the solvent was removed at 20° (20 mm). The residue was crystallized from aqueous EtOH (1:1). The erythro-*diethyl phosphodihydro*(o,o′-*dinitro*)*benzoin* (XXVIa) (0·84 g, 52%, m.p. 120–141°) was recrystallized and gave *erythro*-XXVIa of m.p. 150–152° (35%). (Found: C, 49·1; H, 4·8; N, 6·5; P, 6·6. $C_{18}H_{21}O_9N_2P$ requires: C, 49·1; H, 4·8; N, 6·4; P, 7·0%.) The spectral characteristics were: bands at 3·85, 3·1, 6·25, 6·32, 6·55, 7·45, 7·8 (broad) and 9·70 μ (in CH_2Cl_2). An 8H^1 multiplet at τ 2·3; a 1H^1 doublet, $J_{HH} = 5{\cdot}5$ c/s, of doublets, $J_{HP} = 8{\cdot}5$ c/s, at τ 3·32; a 1H^1 doublet, $J_{HH} = 5{\cdot}5$ c/s, at τ 3·95; a 1H^1 singlet at τ 5·30; a 4H^1 pair of doublets of quartets as ca. τ 5·9 (unresolved); a 3H^1 doublet, $J_{HP} = 1{\cdot}2$ c/s, of triplets, $J_{HH} = 7$ c/s, at τ 8·75 and a second 3H^1 doublet of triplets with similar couplings at τ 8·92.

Reaction of the p-*nitrobenzaldehyde-trimethyl phosphite adduct* (*meso*-XIXa) *with hot ethanol*

A suspension of the *meso*-XIXa, (1·27 g) in EtOH (60 ml) was kept for 18 hr at reflux temp. The initial mixture became a clear soln within 20 min; the latter deposited a solid after 3 hr. The trans-p,p′-*dinitrostilbene oxide* (XXVIII) (0·77 g, 90%, m.p. 197–203°) was recrystallized from AcOEt giving colorless *trans*-XXVIII, of m.p. 202–203°. (Found: C, 58·8; H, 3·7; N, 9·5. $C_{14}H_{10}O_5N_2$ requires: C, 58·7; H, 3·5; N, 9·8%.) The spectral characteristics were: bands at 6·20 (w), 6·55 (v.s.) and 7·42 (v.s.) μ (in dil CH_2Cl_2). The epoxide is sparingly soluble in chf, acetone and DMSO.

Reaction of the o-*nitrobenzaldehyde-trimethyl phosphite adduct* (*meso*-XXIa) *with hot ethanol*

A suspension of the *meso*- XXIa, (4·9 g) in EtOH (70 ml) was kept for 18 hr at reflux temp. The suspension became clear and then deposited crystals of *trans*-XXIX (3·0 g, 94%, m.p. 159–164°). One recrystallization from EtOH gave *trans*-XXIX of m.p. 169–170°. (Found: C, 58·4; H, 3·7; N, 9·8. $C_{14}H_{10}O_5N_2$ requires: C, 58·7; H, 3·5; N, 9·8%.) The spectral characteristics were: bands at 6·20 (w), 6·32 (w), 6·56 (s), 7·45 (s) μ (in CH_2Cl_2). An 8H^1 multiplet at τ 1·9, 2·4; a 2H^1 singlet at τ 5·50 (in $CDCl_3$, in which it is sparingly soluble).

Reaction of the o-*nitrobenzaldehyde-triethyl phosphite adduct* (*meso*-XXIIa) *with hot ethanol*

A suspension of the *meso*-XXIIa (1·34 g) in EtOH (50 ml) was kept for 18 hr at reflux temp. The trans-o,o′-*dinitrostilbene oxide* (XXIX) (0·83 g, m.p. 164–166°) was recrystallized from EtOH giving XXIX of m.p. 169–170° (55% yield).