yielded 35 mg of white solid, mp 120–125°. Repeated recrystallizations from petroleum ether (bp 65–100°) raised the melting point to 133–135°; λ_{max} 234 mμ (ε 16,500); infrared bands at 1770 (γ-lactone), 1705 (cyclopentenone), and 1644 cm^{-1} (double bonds).

Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60; O, 19.65. Found: C, 73.58; H, 7.06; O, 19.68.

Chromium Trioxide Oxidation of Ivaxillarin.—A solution of 100 mg of **3** in 4 ml of pyridine was added at 0° to a stirred solution of 1 g of chromium trioxide in 10 ml of pyridine and left overnight at room temperature. The mixture was poured into ice and extracted thoroughly with ether. The ether extract was was washed with sodium bicarbonate solution, water, dilute hydrochloric acid, and then water, and dried. The residue obtained by the removal of the solvent was chromatographed over silicic acid (8 g). The residue obtained from the chloroform–benzene (1:1) eluate was recrystallized from petroleum ether (bp 65–100°) to yield a white solid, mp 130–133°, identical in all respects with anhydroivaxillarin (**6**). Elution with chloroform and recrystallization of the product from methanol–benzene yielded 60 mg of unchanged ivaxillarin.

Anhydrodihydroivaxillarin (7).—A solution of 80 mg of **4** in 1.5 ml of pyridine was treated at 0° with 0.3 ml of methanesulfonyl chloride and left at room temperature for 24 hr. The mixture was poured into ice–water and worked up and the product was chromatographed over 10 g of silicic acid. The residue obtained from the chloroform–benzene (1:1) eluates was recrystallized once from chloroform–hexane and again from chloroform–ether as white needles: 35 mg; mp 209–211°; λ_{max} 236 mμ (ε 16,900), infrared bands at 1780 (lactone), 1705 (cyclopentenone), and 1665 cm^{-1} (double bond).

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37; O, 19.49. Found: C, 73.20; H, 6.97; O, 19.54.

Reduction of Anhydroivaxillarin.—A solution of 100 mg of **6** in 50 ml of ethanol and 0.5 ml of acetic acid was hydrogenated with 100 mg of platinum oxide at 30 psi for 8 hr. The residue obtained by the removal of the solvent from the filtered solution was dissolved in sodium bicarbonate solution, the aqueous solution was extracted with chloroform, and the chloroform extract was rejected. The bicarbonate solution was acidified with hydrochloric acid and again extracted with chloroform. The residue (65 mg) obtained on evaporation of the solvent was chromatographed over 15 g of silicic acid. Elution with benzene–ether (2:1) and recrystallization of the product from ether–petroleum ether (bp 60–100°) yielded acid **8**: mp 142–144°, $[\alpha]^{25}D$ −91.5° (*c* 0.9), infrared bands at 1745 (cyclopentanone) and 1710 cm^{-1} (COOH).

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86; O, 19.17. Found: C, 72.49; H, 8.60; O, 19.23.

Reduction of Axivalin.—A solution of 80 mg of axivalin (**9**) in 50 ml of ethanol was hydrogenated with 50 mg of 5% palladized charcoal at 30 psi for 3 hr. The catalyst was filtered, the solvent was removed from the filtrate, and the residue was chromatographed over 6 g of siliicic acid. The residue obtained from the benzene–chloroform (2:1) eluates was recrystallized from chloroform–hexane to yield **5b**: 55 mg, mp 140–142°, identical in nmr, infrared, tlc, and melting point with an authentic sample of acetyltetrahydroivaxillarin.

Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85; O, 25.94. Found: C, 65.84; H, 8.0; O, 25.85.

Dehydrogenation of Acetyltetrahydroivaxillarin (5b).—To a stirred slurry of lithium aluminum hydride (1 g) in 50 ml of tetrahydrofuran was added dropwise a solution of 250 mg of **5b** in 50 ml of tetrahydrofuran. The mixture was refluxed for 7 hr and cooled, the excess reagent was decomposed with ethyl acetate, and water was added to decompose the complex. The organic layer was dried (Na_2SO_4) and the solvent was removed. The residue was suspended in 15 ml of Nujol and dehydrogenated with 1 g of 10% palladium on charcoal at 340° for 15 min. The acid extract was diluted with water and the aqueous solution was extracted thoroughly with hexane. The azulene obtained by the removal of solvent was chromatographed over 50 g of acid-washed Merck alumina and eluted with hexane. The blue azulene (approximately 20 mg) had a visible spectrum identical with that of guaiazulene, melting point of trinitrobenzene complex 148–150°, mixture melting point of trinitrobenzene complex with guaiazulene undepressed.

Acknowledgment.—We wish to thank the Florida State University Research Council for a grant in aid to help defray the cost of plant collections, and Miss June McCaskill and Dr. P. C. Tueller for arranging the collections.

Phosphonic Acids and Esters. XVII. Formation, Aromatization, and Reduction of Diels–Alder Adducts of Vinyl- and Chlorovinylphosphonates[1]

W. M. DANIEWSKI AND C. E. GRIFFIN

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

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Diethyl vinylphosphonate has been shown to undergo Diels–Alder reactions in acceptable yields with butadiene, 1,3-pentadiene, isoprene, 2,3-dimethylbutadiene, 1-methoxybutadiene, cyclopentadiene, and hexachlorocyclopentadiene. Mixtures of positional isomers are formed in reactions with 1,3-pentadiene and isoprene; reaction with 1-methoxybutadiene is apparently directionally specific. The adducts from butadiene, 1,3-pentadiene, isoprene, and 1-methoxybutadiene can be aromatized to the corresponding arylphosphonates by the use of nitrobenzene in the presence of a palladium catalyst. Similarly, adducts are formed by the reactions of diethyl α-chlorovinylphosphonate with butadiene, diethyl *trans*-β-chlorovinylphosphonate with butadiene and cyclopentadiene, and diethyl *cis*-β-chlorovinylphosphonate with cyclopentadiene. Mixtures of *endo* and *exo* isomers are obtained in reactions leading to the formation of norbornenylphosphonates.

The literature contains only a limited number of references to the utilization of phosphorus-containing dienes and dienophiles in the Diels–Alder reaction. The readily available diethyl vinylphosphonate[2,3] (**1**) has been reported to form adducts (**2**) with butadiene,[4] 2,4-hexadiene,[5] 1,3-pentadiene,[5] cyclopentadiene,[6] and hexachlorocyclopentadiene[7] in acceptable yields although the adducts were not fully characterized in all cases. On the basis of comparative studies, the dienophilic reactivity of **1** was reported to be less than that of α,β-unsaturated carbonyl compounds and nitriles.[5] To the best of our knowledge, the aromatization of **2** to the corresponding arylphosphonates (**3**)

(1) Part XVI: J. B. Plumb, R. Obrycki, and C. E. Griffin, *J. Org. Chem.*, **31**, 2455 (1966). This study was supported in part by the Directorate of Chemical Sciences, Air Force Office of Scientific Research under Grant No. AF-AFOSR-470-64.

(2) A. H. Ford-Moore and J. H. Williams, *J. Chem. Soc.*, 1465 (1947).

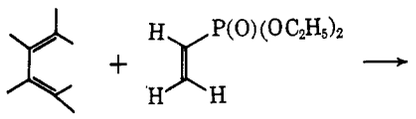
(3) G. M. Kosolapoff, *J. Am. Chem. Soc.*, **70**, 1971 (1948).

(4) J. B. Dickey, H. W. Coover, Jr., and N. H. Shearer, Jr., U. S. Patent 2,550,651 (April 24, 1951); *Chem. Abstr.*, **45**, 8029 (1951).

(5) A. N. Pudovik and M. G. Imaev, *Izv. Akad. Nauk SSSR Otd. Khim. Nauk*, 916 (1952).

(6) E. C. Ladd, U. S. Patent 2,611,784 (Sept 23, 1952); *Chem. Abstr.*, **47**, 9355 (1953).

(7) E. C. Ladd, U. S. Patent 2,622,096 (Dec 16, 1952); *Chem. Abstr.*, **47**, 9344 (1953).



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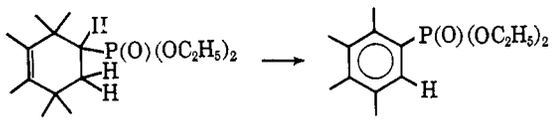
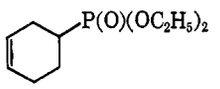


2 3

has not been reported. Because of the ease of synthesis of **1** and other vinylphosphonates,[8] the sequence **1** → **3** is attractive as a potential mode of entry to **3**.[9] The synthetic utility of this sequence has now been investigated by a study of the reactions of **1** and its chloro analogs[10] with representative dienes and the aromatization of certain of the resulting adducts.

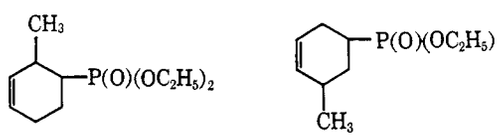
Reaction of **1** with excess butadiene at 160° for 10 hr gave diethyl 3-cyclohexen-1-ylphosphonate (**4**,



4

67%); the structure **4**, as well as the structures of other adducts obtained in this study, was substantiated by infrared and pmr spectra and elemental analysis. Attempted aromatization of **4** with a 5% palladium-on-charcoal catalyst in refluxing *p*-cymene or decalin gave a quantitative yield of the disproportionation products, diethyl cyclohexyl- (**5**) and phenylphosphonates (**6**); disproportionation of cyclohexene is observed under similar conditions.[11,12a] Aromatization of **4** was achieved by the use of nitrobenzene as a hydrogen acceptor;[12b] a near-quantitative yield of **6** was obtained by refluxing a solution of **4** and nitrobenzene in the presence of the palladium catalyst for 24 hr. In view of the ease of catalytic disproportionation of **4**, its reduction with cyclohexene[11,12a] was attempted; a 2-hr reflux of a solution of **4** in excess cyclohexene over the palladium catalyst gave **5** (80%).

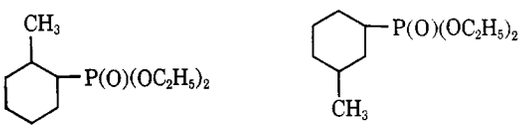
In view of the ease of formation of **4** and its successful conversion to **6**, the reactions of **1** with other dienes were examined. Reaction of 1,3-pentadiene (**7**) and **1** at 170° gave a 68% yield of product. This reaction had been examined previously by Pudovik and Imaev[5] who reported the formation of a single product, diethyl 2-methyl-3-cyclohexen-1-ylphosphonate (**8**); formation



8 9

of a single isomer was attributed to the polarization of the diene system by the inductive effect of the methyl substituent.[5] However, in view of the lack of orientational specificity normally observed in reactions of **7** and other alkyl-substituted dienes with nonsymmetrical dienophiles,[13] the formation of a mixture of the positional isomers **8** and **9** would be anticipated. In support of this expectation, the pmr spectrum of the product from **1** and **7** showed two $CHCH_3$ doublets (τ = 8.87 and 8.99 ppm, J_{HH} = 6.8 cps) and glpc analysis indicated the presence of two materials (1:1 ratio). Aromatization of the product by the nitrobenzene procedure gave two arylphosphonates (1:1 ratio by pmr and glpc analysis); preparative-scale glpc led to the isolation of diethyl *o*- and *m*-tolylphosphonates,[14] the aromatization products of **8** and **9**, respectively.

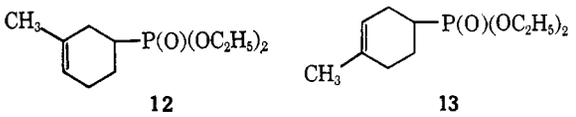
An essentially quantitative reduction of the mixture of **8** and **9** was achieved with cyclohexene over the palladium catalyst; the rate of reduction was somewhat slower than that of **4**. The pmr spectrum of the product showed it to be free of **8**, **9**, and aromatics and indicated the sole constituents of the mixture to be diethyl 2-methyl- (**10**) and 3-methylcyclohexylphosphonates (**11**, $CHCH_3$, τ = 8.96 and 9.08 ppm, J_{HH} =



10 11

6.8 cps). However, glpc analysis indicated the presence of two major and two minor products, the latter having retention times only slightly greater than those of the respective major components; the retention times of all four peaks fall in the range characteristic of cyclohexylphosphonates. These observations are suggestive of the presence of both the *cis* and *trans* forms of **10** and **11**.[15]

Reaction of **1** and isoprene led to the formation of a product (73%) which showed two $=CCH_3$ singlets (τ = 8.38 and 8.36 ppm) suggestive of the presence of both possible positional isomers (**12** and **13**); glpc



12 13

analysis showed two products in a 2.3:1.0 ratio. A similar lack of orientational specificity has been observed in other reactions of isoprene with unsymmetrical dienophiles.[13] This assignment was confirmed by nitrobenzene aromatization of the product which yielded a mixture (22%) of the anticipated products, diethyl *m*- (**14**) and *p*-tolylphosphonates[14] (**15**) in a 1.0:1.4 ratio. The ratio (**12**:**13**) of unreacted starting materials in this reaction mixture was 1.0:4.3.

(8) E. L. Gefter, "Organophosphorus Monomers and Polymers," G. M. Kosolapoff, Transl., Associated Technical Services, Inc., Glen Ridge, N. J., 1962, pp 3–21.

(9) For summaries of the methods available for the synthesis of **3**, see ref 1 and L. D. Freedman and G. O. Doak, *Chem. Rev.*, **57**, 479 (1957).

(10) W. M. Daniewski, M. Gordon, and C. E. Griffin, *J. Org. Chem.*, **31**, 2083 (1966).

(11) E. A. Braude, R. P. Linstead, P. W. D. Mitchell, and K. R. H. Wooldridge, *J. Chem. Soc.*, 3595 (1954).

(12) (a) E. A. Braude, R. P. Linstead, and P. W. D. Mitchell, *ibid.*, 3578 (1954); (b) *ibid.*, 3586 (1954).

(13) A. S. Onishchenko, "Diene Synthesis," Israel Program for Scientific Translations, Jerusalem, Israel, 1964, pp 24–29, 131–156.

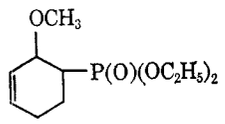
(14) Prepared by the same method utilized for the preparation of the corresponding methyl esters: C. E. Griffin, R. B. Davison, and M. Gordon, *Tetrahedron*, **22**, 561 (1966).

(15) Alternatively, these observations may indicate the presence of stable conformers of a single preferred geometrical isomer of **10** and **11**. No investigations of geometrical isomerism or conformational stability in monosubstituted cyclohexylphosphorus compounds have been reported to date. Further investigations of the stereochemistry of **10** and **11** are in progress.

The near equivalence in the amounts of **14** and **15** formed and the difference between the ratios of **12** to **13** before and after aromatization indicate **12** to be aromatized more readily than **13**.

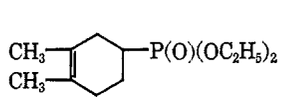
Reduction of the mixture of **12** and **13** to a mixture of 3- (**11**) and 4-methylcyclohexylphosphonates was also successful, although the rate of reduction was significantly less than that of **4** or **8** and **9**. This observation is consistent with the earlier reports[12a] that 1- or 1,2-substituted cyclohexenes undergo reduction by this procedure with more difficulty than do cyclohexenes substituted at positions 3–6.

1-Methoxybutadiene and **1** similarly gave an adduct (32%) which showed two methoxyl singlets (τ = 6.40 and 6.30 ppm) in a 3.6:1.0 ratio; glpc analysis showed the presence of two materials with similar retention times. However, aromatization of this product led to the formation of diethyl *o*-anisylphosphonate as the sole product indicating that the reaction of **1** and methoxybutadiene is probably directionally specific, yielding adduct **16**. A similar directional



16

specificity has been reported in the reaction of acrolein with this diene.[16] The pmr and glpc observations are probably the result of either geometrical isomerism or conformational stability as in the case of **8** and **9**. Adduct **16** was also reduced with cyclohexene to the corresponding cyclohexyl derivative. 2,3-Dimethylbutadiene and **1** reacted to yield adduct **17** (31%). This adduct failed to undergo aromatization with nitrobenzene or other dehydrogenation agents such as chloranil even under severe conditions. Cyclopentadiene reacted readily with **1** to yield an adduct (**18**)



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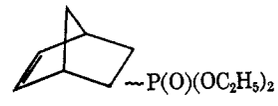
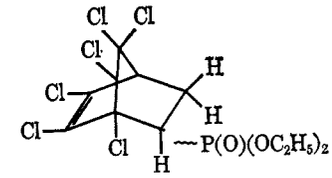


18

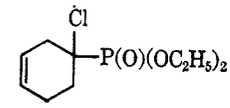
in 76% yield with physical properties similar to those reported by Ladd.[6] The pmr spectrum of the product was consistent with structure **18**. The observed chemical shifts for the ring protons were in the ranges cited for other substituted norbornene derivatives,[17] although the complexity of the spectrum precluded complete analysis. The presence of two OCH_2CH_3 triplets of comparable intensity indicated the presence of two isomers, presumably *endo* and *exo* **18**. Glpc analysis confirmed the presence of two materials, but attempted preparative-scale separation was accompanied by partial decomposition and the structures of the isomers could not be assigned. Hexachlorocyclopentadiene also reacted readily with **1** to yield **19**; this product had been obtained previously in an impure state by Ladd.[7] The adduct underwent extensive decomposition on attempted distillation, but was ob-



19

tained in an analytically pure state by column chromatography. Its thermal stability was too low for glpc analysis, but its pmr spectrum was consistent with structure **19** and indicated the presence of both *endo* and *exo* **19**. Two doublets of quartets (τ = 5.87 and 5.90 ppm, J_{PH} = 8.1 cps and J_{HH} = 6.9 cps) were observed for the $POCH_2$ protons; the ring proton signals consisted of the ABC portions (τ = 6.65–8.00 ppm) of two overlapping ABCX spectra.

The Diels–Alder reactions of three chloro analogs of **1** were also investigated. Diethyl α-chlorovinylphosphonate[10] reacted readily with butadiene to yield adduct **20**. Diethyl *trans*-β-chlorovinylphosphonate[10]



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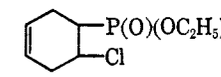
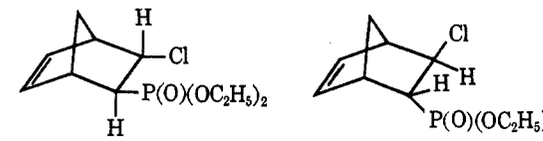


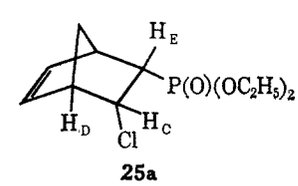
22

(**21**) was much less reactive than the α isomer and gave an unstable adduct (**22**) in low yield. The adduct could not be purified, but the nmr spectrum of the crude material was consistent with structure **22**. Cyclopentadiene and **21** reacted to give a relatively unstable adduct (**23**) which could be purified by column chromatography. As in the case of **18**, the pmr spectrum was consistent with the assigned structure and was indicative of the presence of two isomers.

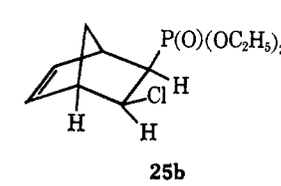


23

An anticipated, higher dienophilic reactivity was observed for diethyl *cis*-β-chlorovinylphosphonate (**24**).[10] Cyclopentadiene and **24** reacted readily to yield a stable adduct (**25**) in good yield. Glpc analysis showed the presence of two materials in approximately equal quantities. The pmr spectrum was completely consistent with the proposed structure and indicative of the presence of *endo* (**25a**) and *exo* (**25b**) isomers.



25a



25b

Primary pmr evidence for the presence of two isomers rested on the absorptions of the ester protons. Two triplets were observed for the OCH_2CH_3 protons (τ = 8.67 and 8.72 ppm, J_{HH} = 6.8 cps) and two doublets of quartets for the OCH_2CH_3 protons (τ = 5.93 and 5.98 ppm, J_{HH} = 6.8 cps and J_{PH} = 7.7 cps). The vinylic protons showed a typical AB pattern

(16) K. Alder, F. H. Flock, A. Hausweiler, and R. Reeber, *Chem. Ber.*, **87**, 1752 (1954).

(17) (a) P. Laszlo and P. R. Schleyer, *J. Am. Chem. Soc.*, **85**, 2709 (1963); (b) *ibid.*, **86**, 1171 (1964); (c) E. I. Snyder and B. Franzus, *ibid.*, **86**, 1166 (1964).

(τ = 3.67 and 3.83 ppm, J_{AB} = 5.4 cps) further coupled to the bridgehead protons (J = 2.6 and 2.7 cps). These peaks are only slightly broadened, indicating that the chemical shifts of the vinylic protons of **25a** and **25b** are nearly equivalent. Similar parameters (τ = 3.73 ppm, J = 5.55 and 2.85 cps) have been reported for the equivalent vinylic protons of *cis,endo*-5,6-dichloro-2-norbornene (**26**).[17b] Further evidence for the presence of the *cis,endo* isomer was provided by the appearance of a six-line signal (0.5 H) at τ = 5.27 ppm ascribed to H_C of **25a**. This multiplet arises from coupling to both of the vicinal protons and to the phosphorus (J_{CD} = 3.4 cps, J_{CE} = 7.8 cps; and J_{PH} = 7.8 cps). In the model compound (**26**), the analogous couplings (J_{CD} = 3.2 cps and J_{CE} = 7.5 cps) and chemical shift (τ = 5.40 ppm) are quite similar. This multiplet is attributed to H_C of the *cis,endo* isomer since it has been shown by Anet[18] that J_{CD} in 5,6-dihydroxy-2-norbornenes is extremely sensitive to stereochemical differences: *cis,endo*, J = 4.4 cps; *cis,exo*, J = 0 cps. The multiplets from the remaining protons were unresolved but their chemical shifts were characteristic of norbornene systems.[17]

In accord with the results of previous workers,[4-7] this study indicates that vinylphosphonates can serve as effective dienophiles in Diels–Alder reactions with a variety of dienes. The formation of mixtures of *endo* and *exo* isomers in the reactions of β-chlorovinylphosphonates with cyclopentadiene systems further indicates that the reaction may provide a useful entry to β-substituted phosphonates of rigid geometry suitable for stereochemical studies. The use of these Diels–Alder adducts as an entry to arylphosphonates is highly limited owing to the difficulty of aromatizing adducts which possess a substituent on the double bond. However, the procedure may possess certain virtues for the formation of 2,5-disubstituted phenylphosphonates, *i.e.*, by aromatization of adducts derived from 1,4-disubstituted butadienes. Further work in this general area, particularly the Diels–Alder reactions of butadienylphosphonates, is in progress.

Experimental Section[19]

Preparation of Vinylphosphonates.—Diethyl 2-bromoethylphosphonate was prepared in 70% yield by established procedures[2,3] and was dehydrohalogenated by the action of triethylamine in benzene[2] to yield diethyl vinylphosphonate (**1**), bp 69° (2.3 mm), in 85% yield. Diethyl α- and *cis*-β- and *trans*-β-chlorovinylphosphonates were prepared by a reported procedure.[10]

Diels–Alder Reactions of Diethyl Vinylphosphonate (1).—Unless otherwise noted, the same general procedure was followed in all of the Diels–Alder reactions reported below. A mixture of diene and dienophile was placed in a 75-ml stainless steel autoclave; 0.1–0.2 g of hydroquinone or pyrogallol was added to inhibit polymerization. The autoclave was closed, evacuated with suitable cooling, and heated in an oil bath to effect reaction. The progress of the reaction was commonly followed by observation of pressure drops. In general, products were isolated by direct vacuum distillation of the reaction mixture. Results of elemental analyses are given in Table I.

TABLE I

ELEMENTAL ANALYSES

Compd	Formula	Calcd, % C	Calcd, % H	Calcd, % P	Found, % C	Found, % H	Found, % P
4	$C_{10}H_{19}O_3P$	55.08	8.78	14.20	55.29	8.70	14.30
10, 11[a]	$C_{11}H_{23}O_3P$	56.39	9.89	13.22	56.49	10.03	13.15
12, 13[a]	$C_{11}H_{21}O_3P$	56.88	9.12	13.34	57.09	9.40	13.41
16	$C_{11}H_{21}O_4P$	53.23	8.50	12.48	53.19	8.24	12.47
17	$C_{12}H_{23}O_3P$	58.60	9.43	12.57	58.69	9.55	12.67
18	$C_{11}H_{19}O_3P$	57.38	8.32	13.46	57.17	8.41	13.57
19	$C_{11}H_{12}Cl_6O_3P$	30.31	3.04	7.07	30.49	3.07	6.96
20	$C_{10}H_{18}ClO_3P$	47.50	7.18	12.23	47.37	7.23	12.19
23	$C_{11}H_{18}ClO_3P$	49.90	6.87	11.71	50.11	7.03	11.79
25	$C_{11}H_{18}ClO_3P$	49.90	6.87	11.71	50.09	7.09	11.97

[a] Mixture of positional isomers.

(**A**) **Butadiene.**—Reaction of a mixture of 30.0 g (183 mmoles) of **1** and 246 mmoles of butadiene at 160° for 10 hr gave 13.0 g (43.3% recovery) of **1** and 17.0 g (70 mmoles, 67.3%) of **diethyl 3-cyclohexen-1-ylphosphonate** (**4**), bp 114–115° (1.5 mm).

(**B**) **1,3-Pentadiene.**—Reaction of 20.0 g (122 mmoles) of **1** and 25.0 g (368 mmoles) of 1,3-pentadiene at 170° for 15 hr gave 12.0 g (48.0% recovery) of the diene, 3.8 g (29 mmoles) of 1,3-pentadiene dimers, bp 32–37° (0.3 mm) [lit.[20a] bp 77–80° (47 mm)], 7.5 g (37.5% recovery) of **1**, and 13.2 g (52 mmoles, 68.4%) of a mixture of **diethyl 2-methyl-3-cyclohexen-1-ylphosphonate** (**8**) and **diethyl 5-methyl-3-cyclohexen-1-ylphosphonate** (**9**), bp 97–99° (0.3 mm) [lit.[5] bp 118–119° (3 mm)]. Glpc analysis showed two peaks (1:1 ratio) with retention times of 21 and 23 min; at 150°, the peaks were completely resolved (30 and 34 min).

(**C**) **Isoprene.**—Reaction of 20.0 g (122 mmoles) of **1** and 25.0 g (368 mmoles) of isoprene at 180–190° for 15 hr gave 12.0 g (87 mmoles) of isoprene dimers, bp 60–68° (11 mm) [lit.[20b] bp 67° (18 mm)], unreacted **1**, and 22.8 g (90 mmoles, 73.8%) of a mixture of **diethyl 3-methyl-3-cyclohexen-1-ylphosphonate** (**12**) and **diethyl 4-methyl-3-cyclohexen-1-ylphosphonate** (**13**), bp 97–103° (0.3 mm). Glpc analysis showed two peaks (1:2.3 ratio) with retention times of 27 and 29 min.

(**D**) **1-Methoxybutadiene.**—Reaction of 20.0 g (122 mmoles) of **1** and 5.0 g (68 mmoles) of 1-methoxybutadiene at 180° for 24 hr gave 3.0 g (15.0% recovery) of **1** and 5.9 g (22 mmoles, 32.4%) of **diethyl 2-methoxy-3-cyclohexen-1-ylphosphonate** (**16**), bp 102–105° (0.3 mm). Glpc analysis showed two peaks (3:1 ratio) with retention times of 15 and 18 min.[21]

(**E**) **2,3-Dimethylbutadiene.**—Reaction of 20.0 g (122 mmoles) of **1**, 5.0 g (61 mmoles) of 2,3-dimethylbutadiene, and 20 ml of toluene at 150° for 7 hr gave 15.0 g (75.0% recovery) of **1** and 5.0 g (18 mmoles 58.6%) of **diethyl 3,4-dimethyl-3-cyclohexen-1-ylphosphonate** (**17**), bp 103–107° (0.3 mm). Glpc analysis showed a single peak with a retention time of 37 min.

(**F**) **Cyclopentadiene.**—Reaction of 40.0 g (244 mmoles) of **1** and 8.0 g (121 mmoles) of cyclopentadiene at 175° for 16 hr gave 24.2 g (92 mmoles, 76.0%) of a mixture of **diethyl** *endo*- and *exo*-**5-norbornen-2-ylphosphonates** (**18**), bp 88–91° (0.3 mm) [lit.[6] bp 88–89° (0.2 mm)]. Glpc analysis showed two peaks (1:1 ratio) with retention times of 24 and 27 min.

(**G**) **Hexachlorocyclopentadiene.**—Reaction of 24.0 g (146 mmoles) of **1** and 20.0 g (73 mmoles) of hexachlorocyclopentadiene at 150° for 9 hr gave 31.0 g (67 mmoles, 91.8%) of the adduct (**19**) as a brown residue. Unreacted starting materials were removed from the reaction mixture by vacuum distillation; pot temperatures were maintained below 120°. The crude adduct decomposed on attempted distillation, but was purified by chromatography on neutral alumina. The sample was applied to the column as a solution in hexane and the analytically pure **19** was eluted with chloroform as a slightly yellow, viscous liquid.

Reaction of Diethyl α-Chlorovinylphosphonate with Butadiene.—Reaction of 6.9 g (35 mmoles) of the dienophile, 203 mmoles of butadiene, and 10 ml of toluene at 150° for 18 hr gave, after a forerun (to 103°), 3.0 g (12 mmoles, 34.3%) of **diethyl 1-chloro-3-cyclohexen-1-ylphosphonate** (**20**), bp 103–105° (0.3 mm).

(18) F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961).

(19) Infrared spectra were determined as films on a Beckman IR-8 spectrophotometer calibrated with a polystyrene film. Pmr spectra were determined on a Varian Associates A-60 spectrometer at 37° (probe temperature). Chemical shifts are reported on the τ scale from internal tetramethylsilane (τ = 10.00 ppm) and are accurate to at least +0.015 ppm. Glpc analyses were performed on an F & M Model 500 gas chromatograph using helium as carrier gas. Unless otherwise noted, glpc analyses were carried out on a 10 ft × 0.25 in. stainless steel column packed with a mixture of 15% Carbowax 20M and 5% Carbowax 1500 on Chromosorb P, column temperature 175°, flow rate 80 ml/min.

(20) (a) I. N. Nazarov, N. V. Kuznetsov, and A. I. Kuznetsova, *Zh. Obshch. Khim.*, **25**, 370 (1955); (b) I. N. Nazarov, A. I. Kuznetsova, and N. V. Kuznetsov, *ibid.*, **25**, 307 (1955).

(21) This analysis was carried out on a 6 ft × 0.25 in. stainless steel column packed with 18% silicone oil 710 on Chromosorb P, column temperature 175°, flow rate 50 ml/min.

Glpc analysis showed one peak (retention time 40 min). A polymeric residue (3.0 g) remained after distillation.

Reaction of Diethyl *trans*-β-Chlorovinylphosphonate (21) with Cyclopentadiene.—Reaction of 5.0 g (25 mmoles) of **21** and 1.4 g (21 mmoles) of cyclopentadiene in a 35-ml stainless steel autoclave at 180° for 20 hr gave 1.1 g (22.0% recovery) of **21** and two higher boiling fractions, bp 112–117°, 2.5 g (fraction 1), and bp 117–135°, 0.5 g (fraction 2), both at 0.5 mm. Glpc analysis[22] of fraction 1 showed two peaks with retention times of 43 and 53 min (ratio 6:1); fraction 2 showed the same peaks in a 1:1 ratio as well as about 20% of higher boiling materials. The pmr spectra of both of these fractions were consistent with the presence of the two isomers of adduct **23**. Preparative-scale glpc of these two fractions led to the isolation of impure materials. The yield of the adduct was 52% (based on cyclopentadiene). An analytically pure sample of **23** was isolated by chromatography on a silicic acid column (elution with benzene). No separation of the *endo* and *exo* isomers was achieved.

Reaction of Diethyl *cis*-β-Chlorovinylphosphonate (24) with Cyclopentadiene.—A mixture of 1.7 g (8.6 mmoles) of **24** and 0.5 g (7.6 mmoles) of cyclopentadiene was heated in a 10-ml stainless steel autoclave at 170° for 20 hr. Distillation of the reaction mixture gave the following fractions: (1) bp 77–95° (0.15 mm), 0.3 g, 72% **24** and unidentified impurities; (2) bp 95–105° (0.15 mm), 0.2 g, 65% **24**, 24% compound A (retention time 53 min), and 11% compound B (62 min); (3) bp 105–125° (0.15 mm), 1.2 g, compounds A and B in a 1:1 ratio with a trace of impurities.[22] The pmr spectrum of fraction 3 indicated it to consist of a mixture of **25a** and **25b** (see discussion) and an elemental analysis was obtained on this fraction. The total yield of the adducts was 62%.

Aromatization of Adducts. (A) Diethyl 3-Cyclohexen-1-ylphosphonate (4).—A mixture of 1.0 g (4.6 mmoles) of **4**, 3.0 g (24 mmoles) of nitrobenzene, 15 ml of anhydrous ethanol, and 0.5 g of a 5% palladium-on-charcoal catalyst (American Platinum Works) was refluxed for 24 hr. The catalyst was removed by filtration and the reaction mixture was distilled to yield a forerun of ethanol, nitrobenzene, and aniline and a fraction, bp 95–100° (0.1 mm), identified by glpc comparisons (retention time 34 min) with an authentic sample as **diethyl phenylphosphonate** (**6**, 98%). No diethyl cyclohexylphosphonate (**5**) was detected.

(B) Diethyl 2- and 5-Methyl-3-cyclohexen-1-ylphosphonates (8 and 9).—A mixture of adducts **8** and **9** (3.0 g, 13.6 mmoles), 7.0 g (57 mmoles) of nitrobenzene, 40 ml of anhydrous ethanol, and 1.0 g of the catalyst was heated at 150° in a rocking autoclave for 24 hr. The catalyst was removed by filtration; ethanol, nitrobenzene, and aniline were removed by distillation. Glpc analysis of the residue showed the presence of unreacted starting material (21 and 25 min) and two peaks with retention times 35 and 43 min. Glpc comparisons with authentic samples identified the latter two peaks as **diethyl *o*- and *m*-tolylphosphonates**, respectively. These products were also isolated by preparative-scale glpc; their pmr spectra were identical with those of known samples.[14] The total yield of aromatic products was 36% in a 1:1 ratio. When aromatization was carried out using the procedure of experiment A (refluxing solution), significantly lower yields of product were obtained.

(C) Diethyl 3- and 4-Methyl-3-cyclohexen-1-ylphosphonates (12 and 13).—A mixture of adducts **12** and **13** (1.0 g, 4 mmoles), 2.0 g (8.7 mmoles) of nitrobenzene, 30 ml of anhydrous ethanol, and 1.0 g of the catalyst was refluxed for 72 hr. The products were isolated and identified as in experiment B. **Diethyl *m*-(14) and *p*-tolylphosphonates (15)** (retention times 42 and 47 min) were isolated in 22% yield (1:1.4 ratio).

(D) Diethyl 2-Methoxy-3-cyclohexen-1-ylphosphonate (16).—A mixture of 1.0 g (4 mmoles) of **16**, 2.0 g (8 mmoles) of nitrobenzene, 30 ml of anhydrous ethanol, and 1.0 g of the catalyst was refluxed for 74 hr. The product was isolated and identified as in experiment B. **Diethyl *o*-anisylphosphonate**[23] (30%, retention time 90 min) was the sole aromatic product isolated. Apparently, some isomerization of **16** (retention time 38 min) occurred during the reaction; two minor peaks (33 and 36 min) were observed in the reaction product.

(22) This analysis was carried out on a 6 ft × 0.25 in. stainless steel column packed with 15% silicone oil 710 on Anakrom ABS, column temperature 175°, flow rate 60 ml/min.

(23) An authentic sample of this compound was prepared by established procedures.[14] Details of its preparation will be given in the Ph.D. thesis of R. Obrycki, University of Pittsburgh, 1966.

Disproportionation of Diethyl 3-Cyclohexen-1-ylphosphonate (4).—A mixture of 5.0 g (23 mmoles) of **4**, 15 ml of *p*-cymene, and 1.5 g of the palladium catalyst was refluxed for 3 hr. After filtration of the catalyst and removal of solvent, the residue was distilled to yield 4.8 g of product, bp 90–110° (0.5 mm). Glpc analysis showed the product to consist of **diethyl cyclohexylphosphonate**[24] (**5**) and **diethyl phenylphosphonate** (**6**) in a 2:1 ratio (retention times 20 and 34 min). No unreacted **4** remained.

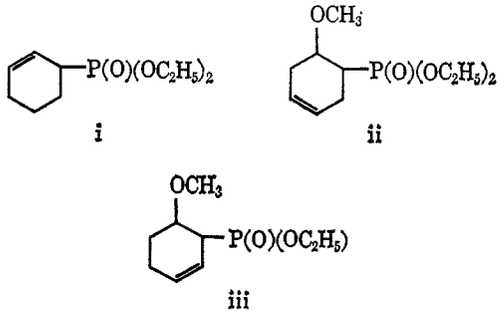
Cyclohexene Reduction of Adducts. (A) Diethyl 3-Cyclohexen-1-ylphosphonate (4).—A mixture of 1.0 g (4.6 mmoles) of **4**, 30 ml of cyclohexene, and 1.0 g of the catalyst was refluxed for 2 hr. Glpc analysis showed that all of the cyclohexene had disproportionated and that **diethyl cyclohexylphosphonate** (**5**) had been formed in 98% yield (retention time 20 min). The reduction product (**5**) was isolated, bp 82–84° (0.3 mm) [lit.[24] bp 87° (0.8 mm)], and identified by comparison with an authentic sample. Trace amounts of the aromatized product (**6**) were detected by glpc.

(B) Diethyl 2- and 5-Methyl-3-cyclohexen-1-ylphosphonates (8 and 9).—A mixture of 1.0 g (4 mmoles) of **8** and **9**, 15 ml of cyclohexene, and 1.0 g of the catalyst was refluxed for 2 hr. After removal of the catalyst, cyclohexane, and benzene, the same amounts of cyclohexene and catalyst were added to the residue and the reaction was repeated. Pmr analysis of the product showed it to be free of vinylic protons and glpc analysis showed four peaks with retention times of 19, 21, 25, and 27 min. The product (**10** and **11**) had bp 90–95° (0.3 mm).

(C) Diethyl 3- and 4-Methyl-3-cyclohexen-1-ylphosphonates (12 and 13).—A mixture of **12** and **13** (15 mmoles) was reduced in 60% yield as in experiment B. Glpc analysis showed three major (22, 24, and 30 min) and five minor (20, 26, 28, 42, and 46 min) peaks. The 28- and 30-min peaks were identified as unreacted **12** and **13**, while the 42- and 46-min peaks were due to aromatized materials (**14** and **15**). The remaining four peaks were attributed to the reduction products of **8** and **9**.

(D) Diethyl 2-Methoxy-3-cyclohexen-1-ylphosphonate (16).—Adduct **16** (8 mmoles) was reduced as in experiment B with the exception that the reduction was repeated four times; approximately 80% of the reduced product was obtained. Glpc analysis showed the presence of two materials (28 and 30 min). As in the case of aromatization of this adduct, two minor peaks (33 and 36 min) were observed, presumably arising from isomerization of **16**.

Proton Magnetic Resonance and Infrared Spectra.—The structures assigned to all of the monocyclic adducts (**4**, **8** + **9**, **12** + **13**, **16**, **17**, **20**) are supported by their pmr spectra; integrated intensities were in good agreement. For all of the adducts, typical $POCH_2CH_3$ absorptions were observed: τ_{CH_3} = 8.67–8.73 ppm (triplet), τ_{CH_2} = 5.88–6.09 ppm (doublet of quartets). Ring protons gave rise to essentially featureless multiplets (τ = 7.2–8.5 ppm). Vinylic absorptions were unresolved for **8** + **9** (τ = 4.48 ppm), **12** + **13** (τ 4.70 ppm), **16** (τ 4.22 ppm), and **20** (τ 4.43 ppm); for **4**, a partially resolved doublet (τ = 4.38 and 4.43 ppm) was observed. As required, compound **17** showed no vinylic absorption; a broadened $=CCH_3$ absorption at τ = 8.40 ppm was observed. It must be pointed out that the position of the double bond is not unequivocally established in these adducts with the exception of **17**; in this case, the integral (two $=CCH_3$ groups) and absence of vinylic signals eliminates the other possible positional isomers. In the remaining cases, at least one additional isomer would be compatible with the observed spectra, *e.g.*, i for **4** and ii and iii



(24) F. W. Hoffmann, T. C. Simmons, and L. J. Glunz, III, *J. Am. Chem. Soc.*, **79**, 3570 (1957).

for **16**. However, on the basis of the demonstrated structure of **17** and the known course of the Diels–Alder reaction, there is no apparent reason to challenge the postulated structures.

The bicyclic structures showed typical norbornene spectra.[17] Compound **23** showed the following signals: vinylic, τ = 3.55 and 3.83 ppm (broadened AB, J_{AB} = 8 cps); C*H*Cl, τ = 5.3 ppm (broad); bridgehead, τ = 6.83 ppm (broad); and ring protons at τ = 7.95–8.5 ppm. Similar parameters were observed for **18**, although the vinylic AB (τ = 3.92 ppm) was not resolved. Ester absorptions were normal in each case and were doubled in the case of **18** due to the presence of *endo* and *exo* isomers.

Similarly, the postulated structures of reduction products were supported by their pmr spectra. The spectrum of the mixture of **10** and **11** is typical: $POCH_2CH_3$, τ = 5.98 and 8.72 ppm; $CHCH_3$, two doublets, τ = 8.96 and 9.08 ppm, J_{HH} = 6.8 cps; ring hydrogens, featureless multiplet, τ = 7.8–9.0 ppm.

The infrared spectra of the adducts showed the expected absorptions in the normal ranges: ν_{PO} 1228–1258, ν_{POC} 1022–1028, 1048–1060, ν_{POEt} 1147–1163, $\nu_{C=C}$ 1641–1655, and a band at 741–756 cm^{-1} tentatively assigned as the *cis*-olefinic out-of-plane C–H deformation.

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Nucleotide Synthesis. II. Nucleotide *p*-Nitrophenyl and 2,4-Dinitrophenyl Esters[1,2]

R. KEITH BORDEN[3] AND MICHAEL SMITH

Fisheries Research Board of Canada, Vancouver Laboratory, Vancouver 8, British Columbia, Canada

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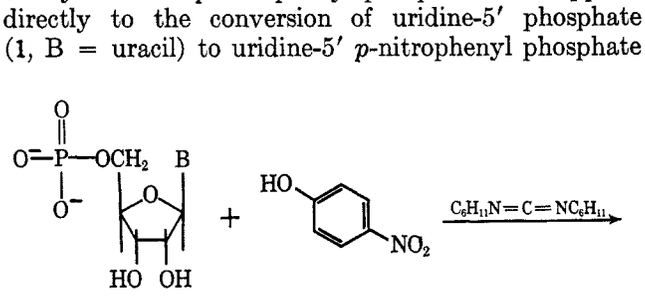
The syntheses of deoxyribonucleoside-5′ and ribonucleoside-5′ *p*-nitrophenyl phosphates by reaction of nucleoside-5′ phosphates with dicyclohexylcarbodiimide and *p*-nitrophenol are described. The reaction of *p*-nitrophenol phosphate and dicyclohexylcarbodiimide with suitably protected nucleosides proves a convenient new route to both nucleoside-5′ *p*-nitrophenyl phosphates and deoxyribonucleoside-3′ *p*-nitrophenyl phosphates. Nucleoside-5′ 2,4-dinitrophenyl phosphates are produced by reaction of nucleoside-5′ phosphates with dicyclohexylcarbodiimide and 2,4-dinitrophenol in the absence of pyridine. Where pyridine is present, the P^1,P^2-dinucleoside-5′ pyrophosphate is produced. The reactions of 2,4-dinitrofluorobenzene and related compounds with nucleoside-5′ phosphates are discussed.

Nucleoside-5′ and nucleoside-3′ *p*-nitrophenyl phosphates are effective and specific substrates for phosphodiesterases.[4–6] Recently it has been shown that both classes of diester are readily converted to nucleoside-3,′5′ cyclic phosphates on reaction with potassium *t*-butoxide in anhydrous solvent.[7] This reaction, which has been applied to the synthesis of both deoxyribonucleoside-3′,5′ and ribonucleoside-3′,5′ cyclic phosphates, also takes place when nucleoside-5′ 2,4-dinitrophenyl esters are treated with potassium *t*-butoxide in anhydrous solvent.[8]

A number of procedures have been applied to the synthesis of nucleotide *p*-nitrophenyl esters. Guanosine-5′ and uridine-5′ *p*-nitrophenyl phosphates have been prepared from suitably protected nucleosides using tetra-*p*-nitrophenyl pyrophosphate as phosphorylating agent.[9,10] Di-*p*-nitrophenyl phosphorochloridate has been used in the synthesis of uridine-5′ *p*-nitrophenyl phosphate[11] and the related reagent, *p*-nitrophenyl phosphorodichloridate,[12] has been used very successfully in the synthesis of deoxyadenosine-3′, deoxycytidine-3′, deoxyguanosine-3′, and thymidine-3′ *p*-nitrophenyl phosphates.[6,13] Thymidine-5′ *p*-nitrophenyl phosphate has been prepared by reaction of thymidine-5′ phosphate with dicyclohexylcarbodiimide *p*-nitrophenol in pyridine in the presence of triethylamine.[14] Because of the ready availability of nucleoside-5′ phosphates this last approach has been extended to other nucleoside derivatives in the present study. Thus, the reaction conditions employed in the synthesis of thymidine-5′ *p*-nitrophenyl phosphate were applied directly to the conversion of uridine-5′ phosphate (1, B = uracil) to uridine-5′ *p*-nitrophenyl phosphate



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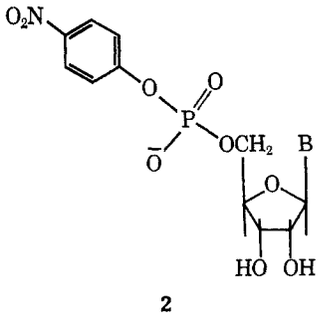

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(3) Part of this investigation was carried out by R. K. Borden in fulfillment of the requirements for a B.S. degree in Biochemistry from Cornell University, Ithaca, N. Y.

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