A STUDY OF THE CONDENSATION OF ARENEDIOLS WITH PHENYLPHOSPHONIC DICHLORIDE

THE PROCESS OF RING OPENING IN CERTAIN BICYCLIC PHOSPHONATES LEADING TO SUBSTITUTED O-HYDROXYARYL HYDROGEN PHENYLPHOSPHONATES^{1,2}a

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Abstract—Phenylphosphonic dichloride condenses with 4-chlorocatechol, 3,4-dihydroxypropiophenone, and 2,3-naphthalenediol to give strong acids *via* hydrolytic ring-cleavage involving the corresponding intermediate bicyclic phosphonates. Proof of structure for the two acids in the catechol series consisted of degradation to derivatives of guaiacol. A nucleophilic attack by water on phosphorus is postulated as the initial step in the hydrolysis.

BICYCLIC organophosphorus compounds which contain an aromatic nucleus are of current interest in view of the biological activity of certain examples,^{3,4} and because of theoretical considerations^{2a,5,6} in reactions involving the heterocyclic ring. 2-Chloro-1,3,2-benzodioxaphosphole (Ia) has been prepared from catechol and phosphorus trichloride in wet ether.⁷ Similarly, the corresponding oxide IId⁸ and other fused systems such as IIa^{2a} IIIa,⁴ IIIb,⁹ IV,¹⁰ V¹¹ and VI¹² are recent additions to the literature. It was reported from this Laboratory that phenylphosphonous dichloride and catechol condense in boiling bromobenzene to give 2-phenyl-1,3,2-benzodioxaphosphole (Ib).^{2a} Oxidation of the bicyclic phosphonite Ib is extremely facile and

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- ^{3a} For the preceding article describing preliminary observations, K. D. Berlin and M. Nagabhushanam, J. Org. Chem. 29, 2506 (1964); ^b Post-doctorate, 1963–65.
- ⁸⁶ H. G. Khorana, Some Recent Developments In The Chemistry of Phosphate Esters of Biological Interest. J. Wiley, New York (1961); ^b D. M. Brown, Phosphorylation in Advances In Organic Chemistry Vol. 3; p. 75. Interscience, New York (1963).
- ⁴ D. C. Schroeder, P. O. Corcoran, C. L. Holden and M. A. Mulligan, J. Org. Chem. 27, 1098 (1962).
- ⁸ R. S. Edmundson, Chem & Ind. 1770 (1962).
- R. L. Dannley and D. A. Zazaris, Abstracts of the 140th National Meeting of the American Chemical Society, p. 62Q, September (1962).
- ⁷⁶ L. Anschutz, W. Broeker, and A. Ohnheiser, Ber. Dtsch. Chem. Ges. 77B, 439 (1944); ^b L. Anschutz and W. Marquardt, Chem. Ber. 89, 1119 (1956).
- ⁸ L. Anschutz, H. Bodeker, W. Broeker and F. Wenger, Leibig's Ann. 454, 71 (1927).
- * R. L. Dannley and P. L. Wagner, J. Org. Chem. 26, 3995 (1961).
- ¹⁰ I. G. M. Campbell and J. K. Way, J. Chem. Soc. 5034 (1960).
- ¹¹ K. Pilgram and F. Korte, Tetrahedron 19, 137 (1963).
- ¹⁹ J. H. Lister and G. M. Timmis, Chem & Ind. 819 (1963).



leads to the phosphonate IIa which was purified and completely characterized. With one molar equivalent of water the ester IIa is quantitatively converted to a strong acid, o-hydroxyphenyl hydrogen phenylphosphonate (VII). Without the benefit of an anhydrous oxygen-free atmosphere during the purification stage phenylphosphonous dichloride and catechol produce VII quantitatively.^{2a} Synthesis of the bicyclic



phosphonate IIa was achieved from the reaction of phenylphosphonic dichloride with catechol.

A close parallelism in regard to ring opening in IIa to give VII is observed in the hydrolysis of esters of ethylene hydrogen phosphate. Strain of approximately 9 K cal in the five-membered ring is suggested to explain the rate of hydrolysis which is many times faster than that of a straight-chain analog or the six-membered ring counterpart.¹³⁻¹⁷ Attack of water on phosphorus accompanied by cleavage of a phosphorus-oxygen bond in the ester has been postulated in the case of IIa and the ethylene glycol phosphate esters.^{16,17}

In order to assess electronic influence on the direction of ring cleavage in certain 1,3,2-benzodioxaphosphole 2-oxides, two substituted derivatives of catechol were selected as coreactants with phenylphosphonic dichloride. Since phenylphosphonic dichloride is hygroscopic, the actual condensations were performed under nitrogen. A stoichiometric quantity of hydrogen chloride was evolved when X (or XI) was treated with phenylphosphonic dichloride in boiling bromobenzene. Immediate IR analyses of the hot oils from the two reaction mixtures showed the absence of a hydroxyl

¹⁸ J. Kumamoto, J. R. Cox, Jr. and F. H. Westheimer, J. Amer. Chem. Soc. 78, 4858 (1956).

¹⁴ J. R. Cox, Jr., R. E. Wall and F. H. Westheimer, Chem. & Ind. 929 (1959).

¹⁵ P. C. Haake and F. H. Westheimer, J. Amer. Chem. Soc. 83, 1102 (1961).

¹⁶ R. E. Davis, J. Amer. Chem. Soc. 84, 599 (1962).

¹⁷ F. Covitz and F. H. Westheimer, J. Amer. Chem. Soc. 85, 1773 (1963).



band indicating the bicyclic ring was intact in each case. Upon cooling in air, the oils solidified and the solids were recrystallized. As reported previously,^{2a} the bicyclic phosphonate IIa absorbed moisture from the atmosphere. Similarly, from IIb and IIc only acids VIII and IX were isolated in yields of 86 and 83%, respectively.

Potentially two isomeric acids could result from phosphorus-oxygen bondseverance in the bicyclic precursor IIb. The powerful inductive effect of the chlorine atom might be expected to facilitate rupture of the nearer phosphorus oxygen linkage as was actually observed. Apparently, intranuclear delocalization of the charge on the phenoxide ion XII is less with a chlorine atom in the *para* position. Comparison



of pK_a values of the three isomeric chlorophenols reveals *p*-chlorophenol to be the weakest acid¹⁸ which may be a result of reduced stability of the conjugate base.

Scheme I illustrates the route followed in determination of the structure for acid VIII. Methylation with diazomethane in methylene chloride-methanol¹⁹ afforded



¹⁸ R. T. Morrison and R. N. Boyd, Organic Chemistry p. 586, Allyn and Bacon, Boston (1959).

¹⁹ The procedure was patterned after that of M. Neeman and Y. Hashimoto, *Tetrahedron Letters* No. 5, 183 (1961); see also M. Neeman, M. C. Caserio, J. D. Roberts and W. S. Johnson, *Tetrahedron* 6, 36 (1959). a new acid XIII. Hydrolysis of XIII with dilute acid gave phenylphosphonic acid and 4-chloroguaiacol in high yields. 4-Chloroguaiacol was converted to 4-chloro-2methoxyphenoxyacetic acid (XIV) by standard procedure.²⁰ With authentication of XIV the direction of ring opening with respect to the chlorine atom in IIb is established.

As in the previous example, two isomers are predictable from hydrolysis of IIc which results from reaction of 3,4-dihydroxypropiophenone with phenylphosphonic dichloride. In contrast to the behaviour of IIb, the bond-breaking process in IIc took a different course to give IX. If attack of water is envisioned as follows, the charge on the anion XVI can be distributed over the oxygen atom in the acyl group



in addition to three carbon atoms of the ring. An analogy is again found in examination of the marked acidity of phenols with an electron-withdrawing group in the *para* position. Increased stability of the conjugate base is most reasonably explained by participation of the electron-withdrawing substituent in resonance stabilization of the phenoxide ion.²¹ In the initial attack of water on IIc as depicted, no implication of the exact molecular geometry around phosphorus in XV is intended. Models imply that approach of water is difficult whether the attack on phosphorus is at an angle of 90° or 180° with respect to the O—P bond. It appears that the backside of the phosphorus atom (if a near tetragonal configuration is assumed) is protected by the phenyl group. To be sure the exact attack angle remains in obscurity.

Methylation of IX was unsuccessful with diazomethane in the presence of boron trifluoride or methanol.¹⁹ The use of dimethyl sulfate in a basic medium with normal procedures was unsatisfactory because of the labile nature of the phosphorus-oxygen bonds. However, when a solution of IX in acetone and dimethyl sulfate was treated dropwise with dilute sodium hydroxide, an oil was obtained which lacked absorption in the IR spectrum for the hydroxyl group. Two acidic hydrogens destroy the base

²⁰ J. P. Brown and E. B. McCall, J. Chem. Soc. 3681 (1955). Since the chloroacetic acid derivatives of 4-choroguaiacol and 5-chloroguaiacol have only a five-degree m.p. differential, both compounds were prepared and compared with authentic samples which were kindly supplied by Dr. Brown.

²¹ For a discussion of this see, J. Hine, *Physical Organic Chemistry* Chap. 2. McGraw-Hill, New York (1962).

to give a dibasic salt which is promptly methylated. It would be expected that the sodium salt of the acid might be esterified to give XVII. Once XVII is formed the phosphorus-oxygen linkages are essentially unaffected by the basic medium at room temperature. Treatment of XVII with dilute (water-ethanol) hydrochloric acid gave



phenylphosphonic acid and XVIII.²² Identification of XVIII confirms the structure IX as that of 2-hydroxy-5-propionylphenyl hydrogen phenylphosphonate.

2,3-Naphthalenediol and phenylphosphonic dichloride reacted smoothly to give an oil which solidified on standing. When the solid was recrystallized from toluene (in air), only crystals of XIX were obtained. A sample of the pure acid XIX was hydrolyzed rapidly by concentrated acid to phenylphosphonic acid and 2,3-naphthalenediol.



Causes of inherent strain in the bicyclic phosphonates II are difficult to evaluate. In the analogous ethylene hydrogen phosphate system, 1,3-non-bonded interactions between the oxygen atoms is estimated as moderate from LCAO-MO calculations on an appropriate model.¹⁶ Apparently bulky substituents on phosphorus in certain 1,3,2-benzodioxaphospholes retard hydrolysis. For example, 2-trityl-1,3,2-benzodioxaphosphole is converted to tritylphosphonic acid and catechol by dilute hydrochloric acid at 180° in a sealed tube.²³ The implication is that the approach to phosphorus by a water molecule in a nucleophilic attack is hampered by the large group on the phosphorus atom. This information, coupled with the UV absorption data for IIa (spectrum nearly identical to that of catechol), implies that electronic delocalization via $d\pi$ -p π overlap between the phosphoryl group and the attached benzene ring is small. Analogously in triphenylphosphine oxide the benzenoid spectra are only slightly perturbed and are definitely recognizable.²⁴ Since the UV spectrum of IIa is similar to that of catechol, contributions of the species XX to the actual hybrid may be significant. Consequently nucleophilic attack by water would be enhanced because of an increased electronic deficit on phosphorus. In addition, the presumed double bond character of the C-O linkage could impart new geometric requirements on the heterocyclic ring causing distortion through alterations of the

²² I. A. Pearl, J. Amer. Chem. Soc. 78, 4433 (1956). We express our thanks to Dr. I. A. Pearl for supplying an authentic sample of 4-propionylguaiacol.

²⁸ A. E. Arbuzov and F. G. Valitova, Zh. Obsch. Khim. 22, 1479 (1952); Chem. Abstr. 47, 9290 (1953).

²⁴ For a discussion of the UV spectra of organophosphorus compounds, H. H. Jaffe and M. Orchin, *Theory and Application of Ultraviolet Spectroscopy* Chap. 17. J. Wiley, New York (1962).



O—P—O bond angle which would be relieved by ring opening. In view of the work of Arbuzov and Valitova,²³ however, the molecular geometry around the highly electron-deficient phosphorus atom in Ha-c must also permit a rapid attack by water.²⁵ Although models suggest the fused rings in the bicyclic phosphonates are strained and have all atoms in the rings nearly coplanar, an X-ray examination of a suitable example in the series will likely be required before the postulate can be evaluated.

Compound	N.E. (M.W Calc.)	p <i>K</i> _a 2∙45	M.P. °C 110–12°	Yield % 86	Analysis Calc. Found		KBr λ _{max} cm ⁻¹	
	289·3 (284·5)				$C = 50.61 \\ H = 3.50 \\ P = 10.90 \\ Cl = 12.49$	C = 50.16 H = 3.96 P = 10.79 Cl = 12.59	3425(O—H), 1180(P→ O)	1445(P—C ₆ H ₅),
IX	310·9 (306)	2.45	163-4·5°	83	C = 58.82 H = 4.90 P = 10.13	$C = 58 \cdot 39$ $H = 5 \cdot 0$ $P = 9 \cdot 65$	3425(O-H), 1182(P \rightarrow O)	1445(P—C ₆ H _b)
XIX	304·1 (300)	2.65	146-7 ·5 °	90	C = 64.00 H = 4.33 P = 10.33	$\begin{array}{rcl} C = 63.80 \\ H = & 4.57 \\ P = & 9.85 \end{array}$	3333(O—H), 1220(P → O)	1445(P→C ₆ H ₅)

TABLE. SUBSTITUTED O-HYDROXYARYL HYDROGEN PHENYLPHOSPHONATES

EXPERIMENTAL²⁶

Hydrolysis of IIa with one mole equivalent of water. To a stirred suspension of catechol (5.5 g, 0.05 mole) in 100 ml bromobenzene was added a solution of phenylphosphonic dichloride (9.7 g, 0.05 mole) in 50 ml bromobenzene under N₂, and the mixture was heated to reflux for 6 hr during which time the stoichiometric amount of HCl was evolved. Removal of 140 ml bromobenzene left an oil the IR spectrum of which was superimposable on that of the pure IIa reported;² $\lambda_{max}^{C_{2}H^{SOH}}$ 272 m μ (log ε , 3.47). One ml water was added to the oil and the mixture was left overnight at room temp. The acid VII, which precipitated, was filtered and purified by recrystallization from bromobenzene; yield, quantitative.

2-Hydroxy-4-chlorophenyl hydrogen phenylphosphonate (VIII). To a stirred suspension of 4chlorocatechol (14.45 g, 0.10 mole) in 200 ml bromobenzene was added dropwise phenylphosphonic dichloride (19.5 g, 0.10 mole) in 100 ml bromobenzene under N₃. The mixture was heated to reflux for 6 hr during which period the evolution of HCl gradually subsided. Removal of solvent gave an

- ²⁶ The corresponding amine analogs, such as IIIa, are reported to undergo rapid hydrolysis (acid and base catalyzed) to give acids of the type discussed but the bicyclic derivatives of 1,3,2-diazaphosphole could be isolated and purified in air.⁹ Since a variety of functional groups were reported to have little influence on the stability of the derivatives, the implication is that a steric factor may be operative. Hydrolysis of certain five-membered cyclic phosphotriesters with one mole equivalent of water in aprotic solvents at room temp has been studied recently; see F. Ramirez, O. P. Madan, N. B. Desai, S. Meyerson and E. M. Banas, J. Amer. Chem. Soc. 85, 2681 (1963). Preservation of the ring structure containing phosphorus was observed. The suggestion was made that an oxyphosphorane intermediate may be present as a result of hydration of the phosphoryl group. Such a possibility cannot be discounted in our work but additional evidence in regard to the structures of hydrates of organophosphorus compounds seems necessary before a definite statement can be made.
- ³⁴ All m.p. are corrected. The micronanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. Petroleum ether of boiling range 40–60° was used. IR spectra were recorded on a Beckman IR-5 spectrophotometer.

oily material [the bicyclic phosphonate IIb, $\lambda_{\text{max}}^{\text{max}}$ 1445 (P—C₄H₄), 1235 (P \rightarrow O), and 689 cm⁻¹ (monosubstituted benzene)] which on cooling yielded VIII which was recrystallized from n-hexane; yield: 24.5 g.

Methylation of VIII. To an ice-cold solution of diazomethane (ca. 5.04 g) in 200 ml ether, prepared from nitrosomethylurea (18 g) and a 40% NaOH aq, were added VIII (3.6 g, 0.0265 mole) in 50 ml methanol and 100 ml methylene chloride. The mixture was allowed to stand in the cold for 30 min with occasional shaking. Excess diazomethane was destroyed by treatment with dil. acetic acid aq. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were washed thoroughly with water and dried (MgSO₄) for 6 hr. Removal of solvent gave 3.5 g crude methyl ether XIII which showed no absorption in the hydroxy region of IR spectrum, thus indicating that the phenolic group has been methylated, $\lambda_{\rm max}^{\rm time}$ 1445 (P—C₆H₈), 1267 (aryl ether

 $= \dot{C} - OCH_s$) and 1195 cm⁻¹ (P \rightarrow O).

Hydrolysis of the methylated product XIII. A solution of 3.0 g XIII, 30 ml 95% ethanol, and 120 ml 1:1 HCl aq was heated at reflux for 20 hr with stirring under N₂. After cooling to room temp, the solution was neutralized with NaHCO₃ and extracted with ether. Removal of ether gave an oil (4-chloroguaiacol) which did not solidify on standing at 0° for 2 days, λ_{max}^{flim} 3510 (O–H) and 1266 cm⁻¹

(aryl ether $= C - OCH_{a}$).

The bicarbonate solution was acidified with dil. HCl aq, and the resulting solution was extracted with ether. Evaporation of ether left a crystalline product, m.p. 155–158°. Recrystallization from benzene-n-heptane gave pure phenylphosphonic acid.

Preparation of the phenoxyacetic acid derivative of 4-chloroguaiacol. A solution of the crude 4chloroguaiacol (1·2 g), monochloroacetic acid (4·2 g), NaOH (3·0 g), and water (20 ml) was heated at 90-95° on a steam bath for 2 hr. When the hot solution was poured into 15 ml 32% HCl aq, an oil separated which did not solidify. Extraction of the oil with a solution of benzene and ether and evaporation of the solvents left an oil (1·2 g) which resisted all attempts at crystallization, λ_{\max}^{11m} 3484

(O—H), 1748 (carboxyl C=O) and 1266 cm⁻¹ (aryl ether = \dot{C} —OCH_a). Chromatography of the material on a column of silica gel was performed and the fraction eluted with ether gave a crystalline material, m.p. 129–133°. Repeated crystallizations from benzene gave an analytical sample of XIV,

m.p. 135-136.5°, $^{12} \lambda_{max}^{KBr}$ 3480 (O—H), 1748 (carboxyl C—O), and 1258 cm⁻¹ (aryl ether —C—OCH₃). A mixture m.p. determination with 2-methoxy-5-chlorophenoxyacetic acid, m.p. 137-138.5°, was 115-118° (nearly 20° depression), and there were some differences in the IR spectrum for 2-methoxy-5-chlorophenoxyacetic acid, λ_{max}^{KBr} 3448 (O—H), 1739 (carboxyl C—O), and 1250 cm⁻¹ (aryl ether

<u>—Ċ</u>—ОСН").

2-Hydroxy-5-propionylphenyl hydrogen phenylphosphonate (IX). To a slurry of 3,4-dihydroxypropiophenone (16.0 g 0.10 mole) in 200 ml bromobenzene was added with stirring a solution of phenylphosphonic dichloride (19.5 g, 0.10 mole) in 100 ml of bromobenzene under N₂. The mixture was boiled for 6 hr and the HCl evolved (0.20 mole; quantitative) was passed into water and titrated with 1.0N NaOH. The clear yellow solution was distilled until nearly all bromobenzene had been removed and an oil remained, λ_{max}^{11m} 1667 (carbonyl C=O), 1445 (P=C₆H₅), 1250 (P \rightarrow O), and 694 cm⁻¹ (monosubstituted benzene). The residual oil, which showed no peak in the hydroxyl region of the IR spectrum (thus indicating the presence of IIc), solidified when it was triturated with 10 ml ethyl acetate, m.p. 153–155.5°. After recrystallization from ethyl acetate, the acid IX melted at 163– 164.5°; yield, 25.4 g.

Methylation of IX with dimethyl sulfate. To IX (2.2 g, 0.007 mole) in 20 ml acetone was added 70 ml dimethyl sulfate, and the mixture was stirred vigorously. An aqueous solution of 10% NaOH aq (50 ml) was added at such a rate that the temp was maintained at 45–50°. The mixture was stirred for 1 hr, and a solution of 30 ml dimethyl sulfate and 100 ml 10% NaOH aq was added dropwise while the temp was kept below 45°. The mixture was left overnight with stirring at room temp and was then extracted with an ether-benzene solution. Removal of solvent left an oil which contained dimethyl sulfate. Dimethyl sulfate was distilled at 60–80° (0.5 mm) and IR analysis of the residue (crude XVI; 1.5 g) indicated the absence of absorption in the hydroxyl region, λ_{max}^{rinm} 1684 (carbonyl C—O), 1445 (P—

 $C_{a}H_{a}$), 1266 (aryl ether $= \dot{C} - OCH_{a}$) and 1230 cm⁻¹ (P \rightarrow O).

A solution of the impure methyl ether XVI (1.5 g), 30 ml ethanol and 300 ml 1:1 dil. HCl aq was heated at reflux under N_1 for 20 hr and, on cooling, the solution was neutralized with NaHCO₃. Extraction with ether-benzene followed by evaporation of the solvents gave an oil which solidified on treatment with ether, m.p. 70–82°. Recrystallization of the solid from ether-pet ether gave pure XVII,

m.p. 90–91°, ³⁷ λ_{max}^{KBr} 3311 (O–H). 1672 (carbonyl C=O) and 1266 cm⁻¹ (aryl ether = C–OCH_s). The IR spectrum of the isomer, 4-propionylguaiacol, displayed some different peaks, λ_{max}^{KBr} 3401 (O–H), 1681

(carbonyl C=O), and 1266 cm⁻¹ (aryl ether = C-OCH₃). Since the 2,4-DNP of XVII was previously unrecorded, it was prepared by standard procedures, m.p. 209-211°. Found: N, 15-30. Calc. for $C_{16}H_{16}N_4O_6$: N, 15-55%.

3-Hydroxy-2-naphthyl hydrogen phenylphosphonate (XIX). A mixture of 2,3-naphthalenediol (8.0 g, 0.05 mole) in 100 ml bromobenzene and phenylphosphonic dichloride (9.75 g, 0.05 mole) in 50 ml bromobenzene was held at reflux for 6 hr with stirring under N_s. The resultant yellow solution after removal of bromobenzene gave an oily material [the bicyclic phosphonate, λ_{max}^{fiim} 1445 (P—C₆H₆), 1235 (P \rightarrow O), and 689 cm⁻¹ (monosubstituted benzene)] which solidified on standing for 30 min m.p. 145–147°. The crude solid was recrystallized from toluene-n-hexane to give 13.5 g pure XVIII.

Hydrolysis of XIX. A mixture of 2.25 g (0.0075 mole) of XIX and 20 ml conc. HCl aq was heated to reflux for 16 hr. After cooling, the reaction mixture was poured into 50 ml water and neutralized with NaHCO₃. The aqueous solution was extracted with ether-benzene solution and evaporation of solvents left a residue which was identified as 2,3-naphthalenediol (m.p. and mixture m.p.); yield, 0.62 g. The aqueous bicarbonate washings were acidified with dil. HCl aq and extracted with ether-benzene. Removal of solvents gave 0.105 g phenylphosphonic acid.

²⁷ The compound was prepared according to the method of C. E. Coulthard, J. Marshall and F. L. Pyman, J. Chem. Soc. 280 (1930).