

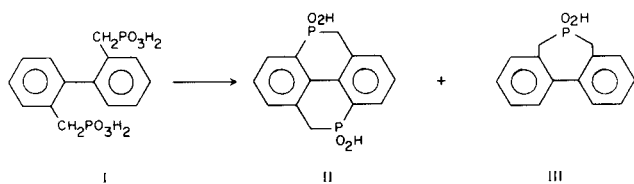
The Thermal Cyclization of Arenylphosphonic Acids. III The Synthesis of 1,3-Dihydro-2-hydroxyisophosphindole 2-Oxide (I)

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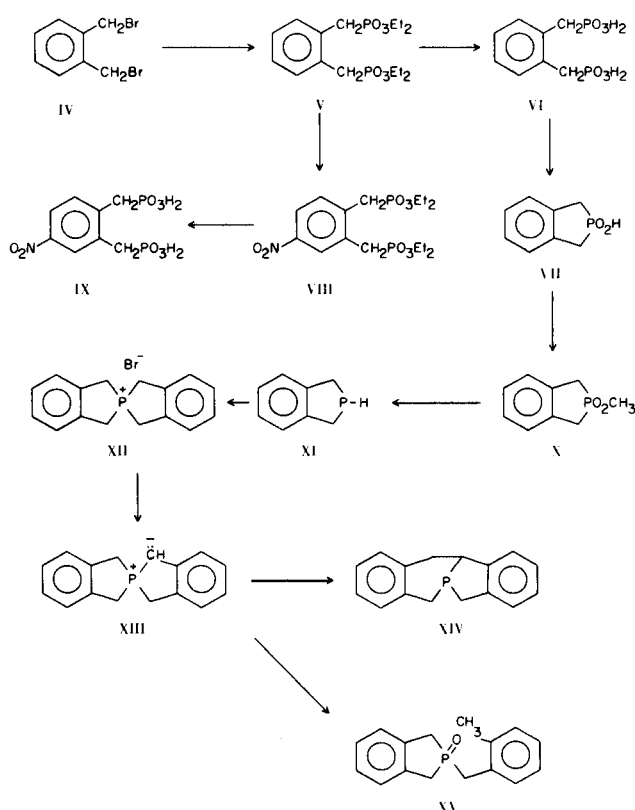
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We have previously reported that (2,2'-biphenylene-dimethylene)diphosphonic acid (I) undergoes an unusual cyclization to form 6,7-dihydro-6-hydroxy-5*H*-dibenzo-[*c,e*]phosphepin 6-oxide (III) as the major product along with smaller amounts of 4,9-dihydroxy-4,5,9,10-tetrahydrophosphapyrene 4,9-dioxide (II) (1*a*). The formation of III has led us to an investigation of the possibility that other heterocyclic compounds might be prepared by this method. In this article we have examined the possibility of varying the ring size.



o-Xylylene dibromide (IV), prepared by the method of Stephenson (3), was converted into *o*-xylylenediphosphonic acid (VI) by hydrolysis of the ester, V, formed in the Arbusov reaction. Attempts to induce cyclodephosphonation of VI under the same conditions used for I (heating the acid to 350-370°/1.25 mm.) were unsuccessful. It was found, however, that grinding the acid thoroughly with equimolar quantities of iron powder (4) and conducting the reaction in a sublimation apparatus resulted in sublimation of the desired product, 1,3-dihydro-2-hydroxyisophosphindole 2-oxide (VII). Lower yields of VII resulted when copper powder was used to effect cyclodephosphonation. The formation of this isophosphindole derivative along with the formation of the phosphepin derivative reported on earlier (1*a*) indicates that this method can be useful, with some modification, in the synthesis of phosphorus heterocyclic compounds of varying ring size. Other allowable structural variations must be examined, however, before one can determine how general the reaction might be.

The mechanism of this reaction has not yet been determined. However, in an attempt to determine the effect of electron withdrawing groups, tetraethyl *o*-xylylenediphosphonate (V) was nitrated and the nitro



ester, VIII, was hydrolyzed to 4-nitro-*o*-xylylenediphosphonic acid (IX). Attempts to effect cyclization of the free acid, IX, and of its sodium salt in DMSO at 180° were unsuccessful. Heating the acid with iron at temperatures up to 230° was also unsuccessful in inducing cyclodephosphonation; at 275° this reaction mixture exploded.

Wittig (5) has shown that di-*o*-xylylene ammonium bromide undergoes a Stevens rearrangement on treatment with base (corresponding to the nitrogen isosteres of XII → XIV). In order to investigate the possibility of a similar rearrangement of the spiro phosphonium salt, 1,3-dihydro-2-hydroxyisophosphindole-2-oxide (VII) was converted into its methyl ester, X, with diazomethane and the ester was reduced to isophosphindoline (XI) with diphenylsilane. This phosphine, XI, was treated with *o*-

xylylene dibromide (IV) to produce the phosphonium salt, XII. When the salt, XII, was treated with base in aqueous acetone, the product formed was 1,3-dihydro-2-*o*-methylbenzylisophosphindole 2-oxide (XV) rather than the Stevens rearrangement product, XIV. The oxide, XV, could be formed either by hydrolysis of the ylide, XIII or by direct attack of hydroxide ion on the phosphorus atom of XII with subsequent cleavage of one of the P-CH₂ bonds.

EXPERIMENTAL

Melting points were determined using a Mel-Temp capillary melting point apparatus and are uncorrected. Elemental analyses were performed by M-H-W Laboratories, Garden City, Michigan.

o-Xylylenediphosphonic Acid (VI).

A mixture of 132 g. (0.5 mole) of *o*-xylylene dibromide and 200 g. (1.2 moles) of triethyl phosphite was refluxed for four hours. The excess of triethyl phosphite was removed under reduced pressure (water aspirator) and the remaining oil was distilled at 187-192°/0.25 mm. to give 122.5 g. (64.6 percent) of tetraethyl *o*-xylylenediphosphonate (V); nmr (carbon tetrachloride): δ 7.25 (s, 4, ArH), 3.95 (m, 8, P-O-CH₂), 3.4 (d, 4, $J = 20$ Hz, Ar-CH₂-P), 1.2 (t, 12, O-CH₂-CH₃). This ester (122.5 g. = 0.0324 mole) was added to 400 ml. of concentrated hydrochloric acid and the solution was refluxed for twelve hours and allowed to cool. The precipitate that formed was recrystallized from water to give 69 g. of the diphosphonic acid (VI): m.p., 347-349°; ir (potassium bromide): 1260 (P=O) and 975 cm⁻¹ (P-OH); nmr (DMSO-d₆) δ 7.8 (s, 4, Ar-H), 3.51 (d, 4, $J = 20$ Hz, Ar-CH₂-P).

Anal. Calcd. for C₈H₁₂O₆P₂: C, 36.11; H, 4.55; P, 23.28. Found: C, 36.13; H, 4.69; P, 23.36.

1,2-Dihydro-2-hydroxyisophosphindole 2-Oxide (VII).

A finely pulverized mixture of 20 g. (0.075 mole) of *o*-xylylenediphosphonic acid and 4 g. of iron powder was placed in a sublimation apparatus. The apparatus was evacuated for 15 minutes and placed in a Wood's metal bath at 370° for 12 hours. The sublimate was dissolved in methanol and the solution was evaporated to dryness to give 3.5 g. (28 percent) of 1,2-dihydro-2-hydroxyisophosphindole 2-oxide: m.p. (recrystallized from water) 142-148°; ir (potassium bromide): 1240 (P=O) and 975 cm⁻¹ (P-OH); nmr (deuteriochloroform): δ 11.28 (s, 1, POH), 7.15 (s, 4, Ar-H), 3.17 (d, 4, $J = 14$ Hz, Ar-CH₂-P).

Anal. Calcd. for C₈H₉O₂P: C, 57.15; H, 5.39; P, 18.42. Found: C, 57.33; H, 5.47; P, 18.23.

4-Nitro-*o*-xylylenediphosphonic Acid (IX).

Eighty-five g. (0.225 mole) of tetraethyl *o*-xylylenediphosphonate was added dropwise over a period of 30 minutes to 146 ml. of fuming nitric acid at 35-45°. The reaction mixture was stirred an additional 1.5 hours after the addition was complete and the reaction was quenched by pouring it into 500 ml. of ice water. The resulting solution was extracted with three 150-ml. portions of benzene which were combined and washed with 200 ml. of water, three 100-ml. portions of 10 percent sodium bicarbonate, and an additional 100 ml. of water. The benzene layer was dried over potassium carbonate and the solvent evaporated over a steam cone. Eighty-six g. (88.3 percent) of product was obtained. A portion of the product decomposed explosively

when distillation under nitrogen at 0.5 mm. of mercury was attempted. A mixture of 20 g. (0.047 mole) of the crude nitro ester and 50 ml. of concentrated hydrochloric acid was refluxed for 4 hours and cooled to give 10.5 g. (63 percent from V) of the solid 4-nitro-*o*-xylylenediphosphonic acid: m.p. (recrystallized from water) = 268-270°; ir (potassium bromide): 1260 (P=O) and 965 cm⁻¹ (P-OH); nmr (deuterium oxide saturated with sodium carbonate): δ 8.15 (m, 3, Ar-H), 3.55 (d, 4, $J = 21$ Hz, Ar-CH₂-P).

Anal. Calcd. for C₈H₁₁P₂O₈N: C, 30.89; H, 3.56; P, 19.91; N, 4.50. Found: C, 30.95; H, 3.49; P, 19.73; N, 4.29.

1,3-Dihydro-2-methoxyisophosphindole 2-Oxide (X).

A solution of 18.5 g. (0.112 mole) of 1,3-dihydro-2-hydroxyisophosphindole 2-oxide in 200 ml. of anhydrous methanol was treated with an ethereal solution of diazomethane until the bright yellow color persisted. The reaction mixture was allowed to stand overnight, the solvents were removed over a steam cone, and the residue was distilled at 150°/1.3 mm. to give 19.0 g. (94.5 percent) of the methyl ester. This ester solidified on standing at room temperature to give a white solid: m.p. (recrystallized from ligroin) = 37-47°; ir (neat) 1235 (P=O), 1030 (P-O-C), and 875 cm⁻¹ (P-O-C); nmr (carbon tetrachloride): δ 7.02 (s, 4, Ar-H), 3.60 (d, 3, $J = 11$ Hz, P-O-CH₃), 2.95 (d, 4, $J = 13$ Hz, Ar-CH₂-P).

Anal. Calcd. for C₉H₁₁PO₂: C, 59.31; H, 6.09; P, 17.01. Found: C, 59.15; H, 6.11; P, 16.86.

Isophosphindoline (XI).

A mixture of 10.2 g. (0.059 mole) of 1,3-dihydro-2-methoxyisophosphindole 2-oxide and 16.4 g. (0.089 mole) of diphenylsilane was refluxed under dry nitrogen for 3.5 hours. The reaction mixture was then distilled under reduced pressure under nitrogen to give 8.1 g. (98 percent) of isophosphindoline (XI): b.p. = 75°/2.5 mm.; ir (neat) 2270 cm⁻¹ (P-H); nmr (deuteriochloroform): δ 7.10 (s, 4, Ar-H), 3.20 (m, 4, Ar-CH₂-PH).

Anal. Calcd. for C₈H₉P: C, 70.61; H, 6.66; P, 22.76. Found: C, 70.69; H, 6.67; P, 22.46.

Di-*o*-xylylenephosphonium Bromide (XII).

A solution of 5.8 g. (0.022 mole) of *o*-xylylene dibromide in 75 ml. of tetrahydrofuran was added slowly to a solution of 4.0 g. (0.022 mole) of isophosphindoline in 75 ml. of tetrahydrofuran. The mixture was refluxed for four hours and allowed to cool to room temperature whereupon 7.2 g. of solid precipitated. Recrystallization of this (largely insoluble) material from water gave 1.0 g. (14.3 percent) of the salt, XII: m.p. = 338-345°; nmr (deuteriotrifluoroacetic acid): δ 7.23 (s, 8, Ar-H), 4.03 (d, 8, $J = 11$ Hz, Ar-CH₂-P).

Anal. Calcd. for C₁₆H₁₆BrP: C, 60.20; H, 5.05; P, 9.70. Found: C, 60.23; H, 4.93; P, 9.92.

1,3-Dihydro-2-*o*-methylbenzylisophosphindole 2-Oxide (XV).

To a solution of 0.537 g. (0.0017 mole) of di-*o*-xylylenephosphonium bromide in 36 ml. of 50% aqueous acetone was added 3 ml. of 1 N sodium hydroxide. The mixture was allowed to stand at room temperature for 36 hours and neutralized with 6 N hydrochloric acid. The acetone was evaporated over a steam cone and the remaining solution was extracted with three 25-ml. portions of chloroform. The chloroform extracts were combined, dried, and evaporated to give 0.489 g. of impure product which was purified by sublimation at 120°/0.5 mm.: m.p. = 111-113°; ir (potassium bromide): 1240 (P=O); nmr (deuteriochloroform): δ 7.57 and 7.65 (2 singlets, 8, Ar-H), 3.63 (d, 6, $J = 12$ Hz, Ar-CH₂-P), and 2.73 (s, 3, Ar-CH₃).

Anal. Calcd. for $C_{16}H_{17}OP$: C, 74.99; H, 6.69; P, 12.09.
Found: C, 75.08; H, 6.66; P, 12.17.

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