Synthesis of Phosphonate Analogues of Thymidine Di- and Triphosphate from 5′-*O*-Toluenesulfonylthymidine

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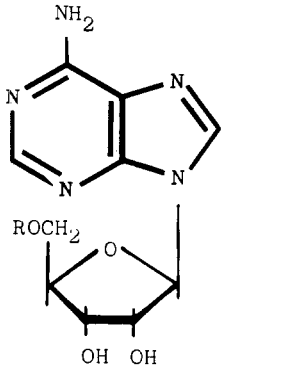
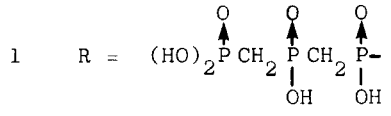
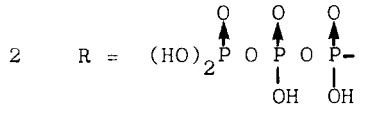
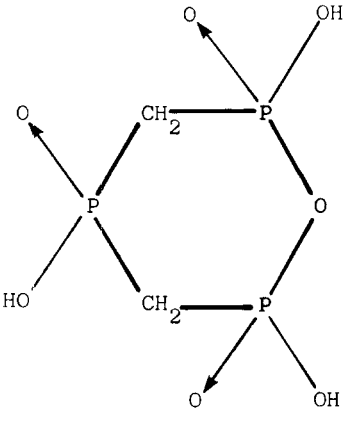
Analogue 1 of adenosine triphosphate (2) has been prepared[1] by an acid-catalyzed reaction between 2′,3′-isopropylideneadenosine and the cyclic anhydride 3, with subsequent removal of the blocking group. No other nucleoside derivative of type 1 has been described.





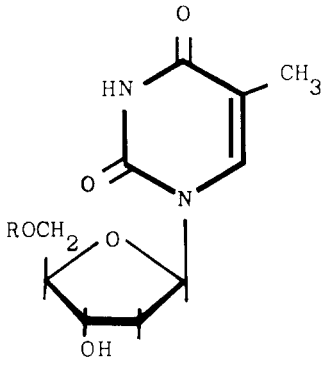


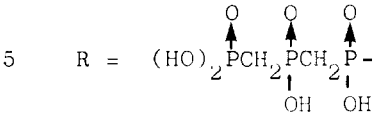


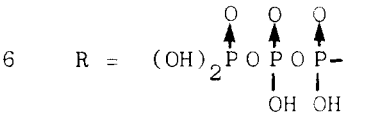
3

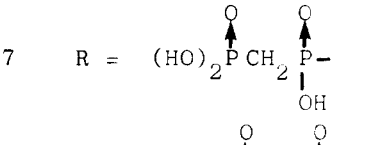
In an attempt in this laboratory to prepare the corresponding analogue 5 of thymidine triphosphate (6), the condensation of 3′-*O*-benzylthymidine with 3 did not proceed satisfactorily. Attempts to condense bis(dihydroxyphosphinomethyl)phosphinic acid (10) with 3′-*O*-benzylthymidine through the mediation of dicyclohexylcarbodiimide or triisopropylbenzenesulfonyl chloride—reagents commonly used[2] in nucleotide chemistry—were also unpromising.

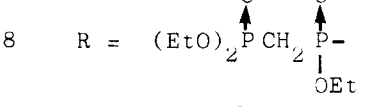
The nucleophilic displacement of *O*-sulfonyl groups, such as *O*-toluenesulfonyl, is well-known but does not appear to have been exploited for the preparation of phosphate or phosphonate esters. This paper describes the successful application of the method to the synthesis of 5 and of the corresponding analogue 7 of thymidine diphosphate and its triethyl ester 8. A small-scale ex-

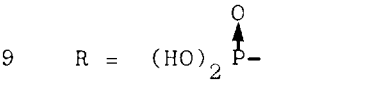












periment indicated that thymidine monophosphate (9) could be synthesised in a similar way from phosphoric acid. The yield of 5 was low (10%) but was comparable to that of the ATP analogue in the experiments of Trowbridge et al.[1]

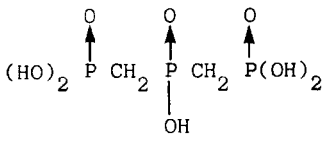
In general, 5′-*O*-tosylthymidine (4) was heated for a few hours in dimethylformamide (DMF) with the appropriate acid (in excess, except for the monoanion 11, to minimize di- or polysubstitution) and a base. The solubility of salts of the acids in DMF decreased sharply with increasing negative charge, so lipophilic bases were used: tri-*n*-octylamine with the acid 10, and tri-*n*-butylamine with methylenediphosphonic acid; triethyl methylenediphosphonate was readily soluble as the sodium salt 11.

It was conceivable that the product isolated from the reaction between tosylthymidine and compound 10 was formed by esterification at the central, rather than the terminal, P atom. That the structure of the product is

(1) D. B. Trowbridge, D. M. Yamamoto, and G. L. Kenyon, *J. Am. Chem. Soc.*, **94**, 3816 (1972).

(2) T. M. Jacob and H. G. Khorana, *J. Am. Chem. Soc.*, **86**, 1630 (1964); R. Lohrmann and H. G. Khorana, *ibid.*, **88**, 829 (1966).

0022-3263/79/1944-3997$01.00/0



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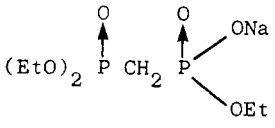
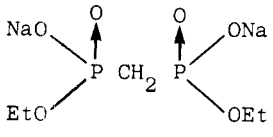


11

represented by formula **5** was demonstrated by the ^{31}P NMR spectrum which showed three signals of equal intensity; the isomer with a symmetrical, branched phosphonate chain would be expected to give two ^{31}P peaks of relative intensity 2:1.

The structure was further confirmed by comparison with a sample provided by Dr. Andrzej Okruszek, who has applied[3] the method of Trowbridge et al.[1] to 3′-*O*-acetylthymidine, with subsequent removal of the acetyl group from the product.

The intermediate salt **11** was prepared by hydrolysis of tetraethyl methylenediphosphonate with 1 equiv of sodium hydroxide. The symmetrical disodium salt **12** was formed

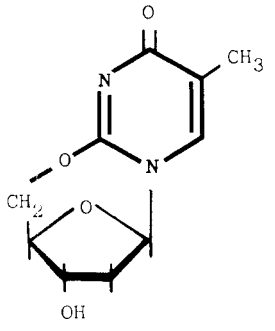


12

as a minor product in the reaction. Compound **11** has also been reported[4] as a product of the base-catalyzed reaction of the pentaethyl ester of **10** with benzaldehyde.

The proximal phosphorus atom in the ester **8** is chiral, and resolution of the two epimers occurred during preparative high-pressure LC although no separation was seen on TLC.

An alternative potential method of preparing nucleoside phosphonates was suggested by the ability of pyrimidine cyclonucleosides to alkylate phosphate ions.[5] Examination by TLC of small-scale reaction mixtures indicated, however, that the use of O^2,5′-cyclothymidine (**13**) offered



13

no advantage over the more readily available **4** in reaction with anions derived from methylenediphosphonic acid or from **10**. The cyclothymidine **13** could be an intermediate in the reaction of **4** with phosphate or phosphonate ions, although these reaction mixtures darkened far less than those in which **13** was used as starting material.

In the present work, it was found that the Epstein reagent, 4-(4-nitrobenzyl)pyridine,[6] commonly used for the estimation or detection of alkylating agents, particularly 2-chloroethylamines, was useful for the detection of neutral esters of phosphonic acids on TLC plates. The ferric chloride–sulfosalicylic acid reagent[7] conveniently located ionic phosphonates on TLC and TLE (volatile buffer) plates.

Experimental Section

^1H NMR spectra were taken on a Bruker HFX 90 MHz Fourier transform instrument (King's College, London; compounds **5**, **7**, and **8**) or a Perkin-Elmer R12B 60-MHz spectrometer. Tetramethylsilane was used as internal standard in $CDCl_3$ and CF_3CO_2H and sodium 3-(trimethylsilyl)propanesulfonate in D_2O. ^{31}P NMR spectra were run at 40 MHz on a JEOL FX-100 Fourier transform spectrometer (Imperial Chemical Industries Corporate Laboratory, Runcorn, Cheshire), with 85% aqueous H_3PO_4 as external standard. The mass spectra of the *R* and *S* epimers of compound **8** were run on an AEI MS12 spectrometer (ion source temperature 150 °C; 70 eV; trap current 100 μA). Optical rotations (**8**, *R* and *S*) were determined on a Perkin-Elmer Model 141 polarimeter. Thin-layer electrophoresis (TLE) was performed on a Shandon-Southern TLE apparatus (Mark II) with a variable-voltage (1000 V max) power pack; cellulose-coated glass plates with fluorescent indicator (Anachem Avicel F; thickness 250 μm) were used (buffers: A, 0.10 M NH_4HCO_3, pH 8; B, 0.05 M citrate, pH 3.8). Preparative high-pressure LC was carried out on a Jobin-Yvon Chromatospac Prep 10 coupled to a Cecil 212A UV monitor set at 250 nm and a Kelvin Servoscribe recorder. Silica column chromatography, other than preparative high-pressure LC, was carried out on Merck Kieselgel 60 (Art 7734). Thin-layer chromatograms were run on fluorescent silica on plastic film (Camlab Polygram Sil G/UV_{254}); the corresponding Merck product was not generally used because it inhibited the development of spots with the $FeCl_3$/sulfosalicylic acid reagent. Ion-exchange chromatography was carried out on Bio-Rad resins. Dimethylformamide (DMF) was distilled from CaH_2 and stored over molecular sieves (type 4A; British Drug Houses Ltd). The elemental analyses were performed by Butterworth Laboratories Ltd., Teddington, Middlesex, England.

Detection on TLC and TLE Plates. (a) Examination under UV light (Hanovia "Chromatolite") for thymidine and derivatives; (b) cysteine (0.5% as hydrochloride in 2 M H_2SO_4)[8] for thymidine and derivatives, including phosphonates (sprayed plates heated at 100 °C for a few minutes); (c) 4-(4-nitrobenzyl)pyridine (Epstein reagent;[6] 1% in EtOH) for neutral esters (sprayed plates heated at 100 °C for 2 h or more, then sprayed with 3% ethanolic KOH; blue or purple spots, usually transient); (d) ferric chloride–sulfosalicylic acid[7] (Fe/SSA) for P^V anions (0.5% $FeCl_3 \cdot 5H_2O$, then 0.2% sulfosalisylic acid, each in 4:1 EtOH–H_2O).

5′-Thymidinyl P^1 Ester of Bis(dihydroxyphosphinomethyl)phosphinic Acid (5). Bis(dihydroxyphosphinomethyl)phosphinic acid[9] (**10**; 730 mg, 2.88 mmol), tri-*n*-octylamine (5.00 mL, 11.5 mmol), and 5′-*O*-tosylthymidine[10] (**4**; 570 mg, 1.44 mmol) were heated in DMF (15 mL) in a stoppered flask at 120 °C for 6 h. TLC (*i*-PrOH–6 N aqueous NH_3, 1:1) showed little residual **4**, the major product (UV and Fe/SSA positive) having R_f ca. 0.25. The reaction mixture was evaporated under vacuum to small volume and the residue evaporated with toluene (2×) and then chromatographed on silica (42 × 3.7 cm; eluant *i*-PrOH–6 N aqueous NH_3, 1:1; 10-mL fractions). Fractions 29–44 contained

(3) Personal communication from Dr. A. Okruszek, Polish Academy of Sciences, Centre of Molecular and Macromolecular Studies, 90-362 Lodz, Boczna 5, Poland.
(4) W. F. Gilmore and J. W. Huber, *J. Org. Chem.*, **38**, 1423 (1973).
(5) J. Zemlicka and J. Smrt, *Tetrahedron Lett.*, 2081 (1964); J. Nagyvary and J. S. Roth, *ibid.*, 617 (1965).
(6) J. Epstein, R. W. Rosenthal, and R. J. Ess, *Anal. Chem.*, **27**, 1435 (1955).
(7) H. E. Wade and D. M. Morgan, *Biochem. J.*, **60**, 264 (1955).
(8) J. G. Buchanan, *Nature (London)*, **168**, 1091 (1951).
(9) L. Maier, *Helv. Chim. Acta*, **52**, 827 (1969).
(10) E. J. Reist, A. Benitez, and L. Goodman, *J. Org. Chem.*, **29**, 554 (1964).

the required product (R_f now ca. 0.02[11]). Electrophoresis of small samples of the residue from the combined fractions showed contamination by both acid **10** (buffer A) and a minor UV-absorbing, higher mobility impurity (buffer B). Anion-exchange chromatography (AG1X2 HCO_3^- form; 33 × 2.5 cm; stepwise elution with 250-mL volumes of 0.10, 0.15, 0.20, 0.40, 0.60, 0.80 and 1.00 M Et_3NHHCO_3) followed by cation exchange (AG50WX4; Na^+ form), gave **5** as the Na salt (170 mg), still contaminated with the UV-absorbing impurity (electrophoresis). Further anion-exchange chromatography (AG1X2; HCO_3^- form; 0.60 M NH_4HCO_3 as eluant) of the bulk (110 mg) of the Na salt rendered the product homogeneous. Cation exchange (AG50WX4; Na^+ form) and subsequent precipitation from aqueous solution (1 mL) with ethanol (15 mL) gave, after drying (P_2O_5), the colorless tetrasodium salt of **5** as its trihydrate (64 mg; equivalent to 10% yield based on **4**): ^1H NMR (D_2O) δ 1.93 (3 H, d, 5-CH_3, coupled to H6), 1.98–2.60 (6 H, complex, H2′, H2″, PCH_2P), 3.98–4.27 (3 H, complex, H4′, H5′), 4.61 (1 H, m, H3′), 6.33 (1 H, t, H 1′), 7.73 (1 H, d, H6, coupled to C-5 CH_3); ^{31}P NMR (three equal peaks) δ 28.16 (βP), 17.53 (αP), 15.50 (γP) [integration: βP, 57; αP + γP (incompletely separated), 119]. Anal. Calcd for $C_{12}H_{17}N_2O_{12}P_3Na_4 \cdot 3H_2O$: C, 23.24; H, 3.74; N, 4.52; P, 14.98. Found: C, 23.66; H, 3.95; N, 4.49; P, 14.65. In comparative tests, the major UV-absorbing component of the sample provided by Dr. Okruszek had electrophoretic mobilities (buffers A and B) and an R_f value (TLC; *n*-PrOH–2 N aqueous NH_3, 1:1) identical with those of **5**.

5′-Thymidinyl Ester of Methylenediphosphonic Acid (7).[12] Methylenediphosphonic acid[13] (176 mg, 1.00 mmol), 5′-*O*-tosylthymidine (198 mg, 0.50 mmol), and tri-*n*-butylamine (0.95 mL, 4.00 mmol) were heated in DMF (5 mL) in a stoppered flask for 4.5 h at 120 °C. The clear, amber solution was taken to small volume and eluted with water from AG50WX4 resin (NH_4^+ form), and the residue from evaporation of the combined UV-positive fractions was chromatographed on silica (34 × 2.4 cm; *n*-PrOH–2 N aqueous NH_3, 1:1). The required product (cysteine-reagent and Fe/SSA positive), isolated initially as the homogeneous (TLC, *n*-PrOH–NH_3 as above) gummy NH_4 salt, was converted in the usual way (AG50WX4) to the Na salt. Addition of excess ethanol to an aqueous solution (0.5 mL) of the salt and storage of the turbid mixture at 0 °C gave the diphosphonate **7** as the solid trisodium salt dihydrate (85 mg, 34% based on **4**): ^1H NMR (D_2O) δ 1.78–2.51 (7 H, complex; C5 CH_3, H2′, H2″, PCH_2P), 4.11 (3 H, apparent d, H4′ H5′), 4.61 (1 H, m, H3′), 6.32 (1 H, t, H1′), 7.71 (1 H, d, H6, coupled to C5 CH_3). Anal. Calcd for $C_{11}H_{15}N_2O_{10}Na_3 \cdot 2H_2O$: C, 26.30; H, 3.81; N, 5.58; P, 12.34; Na, 13.73. Found: C, 26.49; H, 4.13; N, 5.45; P, 11.95; Na, 13.53.

Sodium Triethyl Methylenediphosphonate (11). A solution of tetraethyl methylenediphosphonate[14] (1.31 g, 4.55 mmol) in 1 N NaOH (4.60 mL) and water (10 mL) was heated for 15 min on a steam bath, evaporated under vacuum to a smaller volume, cooled, and passed through a cation-exchange column (AG50WX4, NH_4^+ form). The fractions containing the major reaction product (TLC, *n*-PrOH–6 N aqueous NH_3, 9:1; Epstein and Fe/SSA positive) were combined and taken to dryness. Chromatography of the residual gum on silica (35 × 3.5 cm), with the above PrOH–NH_3 mixture as eluant, gave the homogeneous (TLC), gummy NH_4 salt corresponding to **11** (810 mg, after drying over P_2O_5; 64%): ^1H NMR (CF_3CO_2H) δ 1.44 (9 H, t, CH_3), 2.92 (2 H, t, PCH_2P), 4.36 (6 H, m, ethyl CH_2), 6.68 (4 H, t, 1:1:1, NH_4^+). The NH_4 salt was converted (AG50WX4, Na^+ form) to the colorless, solid Na salt **10**. Anal. Calcd for $C_7H_{17}O_6P_2Na$: C, 29.78; H, 6.07; P, 21.96. Found: C, 30.08; H, 6.26; P, 22.06. A minor, slower running product of the hydrolysis was identical (TLC *n*-PrOH–NH_3; Fe/SSA positive) with the dianion **12** (see below).

Disodium Diethyl Methylenediphosphonate (12). The method of preparation from the tetraethyl ester (864 mg, 3.00 mmol) resembled that of **11**, except that 2 molar equiv of NaOH was used. The hydrolysate was chromatographed on an anion-exchange column (26 × 2.8 cm; AG1X2, HCO_3^- form; gradient elution with NH_4HCO_3, 0.1–0.3 M, total volume 1 L). The major product (Fe/SSA positive) was isolated, after trituration with EtOH, as the homogeneous solid diammonium salt (240 mg, 30%) corresponding to **12**: ^1H NMR (D_2O) δ 1.23 (6 H, t, CH_3), 2.10 (2 H, t, PCH_2P), 3.91 (4 H, m, ethyl CH_2). Cation exchange (AG50WX4, Na^+ form) gave the solid disodium salt **12**. Anal. Calcd for $C_5H_{12}O_6P_2Na_2$: C, 21.75; H, 4.38; P, 22.44. Found: C, 21.92; H, 4.46; P, 22.57. The earlier anion-exchange fractions yielded triethyl methylenediphosphonic acid, isolated as the Na salt **11** (227 mg, 27%) described in the previous section.

5′-Thymidinyl Triethyl Methylenediphosphonate (8; *R* and *S* Epimers). 5′-*O*-Tosylthymidine (317 mg, 0.80 mmol) and sodium triethyl methylenediphosphonate (**11**; 190 mg, 0.67 mmol) were heated in DMF (2 mL) in a stoppered flask for 4 h at 120 °C under N_2.[15] The major UV-absorbing product (TLC; $CHCl_3$–EtOH, 9:1) was Epstein positive. Concentration of the reaction mixture and subsequent drying over P_2O_5 gave a viscous residue, which was chromatographed (high-pressure LC; 140 g Merck TLC Kieselgel 60H (Art 11695); elution with 9:1 $CHCl_3$–EtOH at a flow rate of approximately 30 mL/min). The major product eluted as a double peak (33–55 min), homogeneous on TLC. Rechromatography of the mixed epimers as before, but with Merck LiChroprep Si60 (Art 9336) silica (140 g), removed traces of fast-running impurities but gave only partial resolution. The mixture (137 mg, 42% based on **11**) was rechromatographed as in the first run (140 g of 60H silica). Essentially complete resolution of the epimers was achieved. Faster running epimer: *R* or *S* about P; 52 mg colorless gum; $[\alpha]^{21}_D$ +15° (*c*, 5.3 mg/mL EtOH); ^1H NMR ($CDCl_3$) superimposed triplets at δ 1.34 (3 H, ethyl CH_3) and 1.36 (6 H, ethyl CH_3), 1.93 (3 H, d, ring CH_3), 2.21–2.83 (4 H, complex, H 2′, H2″, PCH_2P), 3.83–4.61 (10 H, complex, ethyl CH_2, H3′, H4′, H5′, H5″), 6.22 (1 H, q, H1′), 7.43 (1 H, d, H6); mass spectrum, *m/e* 484 (M^+). Anal. Calcd for $C_{17}H_{30}N_2O_{10}P_2$: C, 42.15; H, 6.24; N, 5.78. Found: C, 42.50; H, 6.32; N, 5.74. Slower running epimer: *S* or *R*; 60 mg of colorless gum; $[\alpha]^{21}_D$ +9.5° (*c*, 10.5 mg/mL EtOH); ^1H NMR ($CDCl_3$) δ 1.36 (9 H, t, ethyl CH_3), 1.95 (3 H, d, ring CH_3), 2.19–2.84 (4 H, complex, H 2′, H2″, PCH_2P), 3.84–4.61 (10 H, complex, ethyl CH_2, H3′, H4′, H5′, H5″), 6.28 (1 H, t, H1′), 7.34 (1 H, d, H6); mass spectrum, *m/e* 484 (M^+). Anal. Found: C, 42.12; H, 6.34; N, 5.77.

Thymidine 5′-Monophosphate (9). Crystalline H_3PO_4 (23 mg, 0.23 mmol), tri-*n*-butylamine (86 mg, 0.46 mmol), and 5′-*O*-tosylthymidine (31 mg, 0.08 mmol) were heated in DMF (0.25 mL) in a closed tube at 120 °C for 3 h. TLC (*n*-PrOH–2 N aqueous NH_3, 7:3) showed the formation of several UV-absorbing products, the major one (Fe/SSA and cysteine-reagent positive) having the same R_f and electrophoretic mobility (buffer A) as authentic thymidine monophosphate.

3′-*O*-Benzylthymidine.[15b] Powdered KOH (6 g) and benzyl chloride (0.85 mL, 7.4 mmol) were added to a solution of 5′-*O*-tritylthymidine[16] (3.00 g, 6.2 mmol) in a mixture of dry benzene (25 mL) and dry dioxane (10 mL), and the stirred mixture was heated under reflux ($CaCl_2$ guard tube) for 2 h, cooled, and filtered. The combined filtrate and washings (benzene, then dioxane) were taken to dryness under vacuum and the residue was heated under reflux with HOAc–H_2O (4:1) for 30 min. The solution was taken to dryness and the residue evaporated with $CHCl_3$ (3 × 30 mL)

(11) The presence of **10** markedly increased the TLC mobility of **5** in *i*-PrOH–NH_3 mixtures.

(12) The isolation of **7** in 33% yield as its trilithium salt tetrahydrate after a carbodiimide condensation of 3′-*O*-acetylthymidine with methylenediphosphonate has been described in the patent literature by S. Fujii and H. Ito, Japanese Kokai 74, 87, 685 (1974); *Chem. Abstr.*, **82**, 98348 (1975). The report of an earlier preparation of **7** by a similar method gave no elemental analytical data (P. T. Englund, J. A. Huberman, T. M. Jovin, and A. Kornberg, *J. Biol. Chem.*, **244**, 3083 (1969).

(13) G. Schwarzenbach and J. Zurc, *Monatsh. Chem.*, 81, 202 (1950). The impure methylenediphosphonic acid obtained from the tetraethyl ester by heating under reflux with concentrated HCl (2 days) was purified by anion-exchange chromatography (AG1X2; HCO_3^- form; eluted with $Et_3NH \cdot HCO_3$, 0.1–0.4 M), the final product being homogeneous on TLC (cellulose; MeOH–6 N aqueous NH_3, 6:4). It has since been found that the compound can be more easily purified by crystallization from glacial acetic acid to which about 2% water has been added.

(14) J. A. Cade, *J. Chem. Soc.*, 2266 (1959).

(15) (a) The solution nevertheless darkened within 2 h, and about as rapidly as in a comparable experiment omitting N_2. (b) The author has recently found that the preparation of 3′-*O*-benzylthymidine by essentially the same method was described by B. E. Griffin and A. Todd, *J. Chem. Soc.*, 1389 (1958), but their synthesis is not recorded in *Chem. Abstr.*

(16) J. P. Horwitz, J. A. Urbanski, and J. Chua, *J. Org. Chem.*, **27**, 3300 (1962).

and then chromatographed on silica (40 × 3.8 cm; $CHCl_3$–MeOH, 19:1). The benzyl derivative emerged as the major product and crystallized in colorless needles (1.39 g; mp 151–151.5 °C) after addition of petroleum ether (bp 40–60 °C) to a solution in $CHCl_3$–EtOH. Rechromatography of early contaminated fractions gave a further quantity (80 mg; total yield 71%) of crystalline product, mp 151–152 °C. Anal. Calcd for $C_{17}H_{20}N_2O_5$: C, 61.43; H, 6.07; N, 8.43. Found: C, 61.37; H, 6.12; N, 8.05.

Comparison by TLC of 5′-*O*-Tosylthymidine and O^2,5′-Cyclothymidine as Precursors of Thymidine 5′-Phosphonates. Experiments were carried out on a 0.03–0.10 mmol scale.

A. Reaction with Bis(dihydroxyphosphinomethyl)-phosphinic Acid (10). (i) Acid **10** (24 mg, 0.09 mmol), tri-*n*-octylamine (95 mg, 0.27 mmol), and 5′-*O*-tosylthymidine (12 mg, 0.03 mmol) were heated in DMF (0.3 mL) in a closed tube at 120 °C. No substantial darkening occurred. Samples were taken at 2.5 and 4 h. (ii) The procedure was the same as in (i), but with O^2,5′-cyclothymidine[17] (13; 7 mg, 0.03 mmol) in place of **4**. The solution darkened within a few minutes of the start of heating.

Reaction mixtures (i) and (ii) gave similar patterns on TLC (*n*-PrOH–2 N aqueous NH_3, 7:3), compound **5** being a major product in both cases. There was no significant difference between the 2.5- and 4-h samples.

B. Reaction with Methylenediphosphonic Acid. Conditions were similar to those described in A, but with tri-*n*-butylamine as base (2 or 4 mol/mol of diphosphonic acid) and a heating time of 2.5 h. Compound **7** was formed in each case as a major product; the proportion of base was not critical. TLC (as in A) showed that the cyclothymidine reaction produced an additional, though minor, UV-absorbing product moving just ahead of **7**; in other respects the TLC patterns were closely similar.

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Registry No. **4**, 7253-19-2; **5** tetrasodium salt, 71370-59-7; **7** trisodium salt, 71370-60-0; (*R*)-**8**, 71393-23-2; (*S*)-**8**, 71425-91-7; **9**, 365-07-1; **10**, 22401-27-0; **11** ammonium salt, 71370-61-1; **11** sodium salt, 38379-51-0; **12** diammonium salt, 71370-62-2; **12** disodium salt, 71370-63-3; **13**, 15425-09-9; methylenediphosphonic acid, 1984-15-2; tetraethyl methylenediphosphate, 1660-94-2; phosphoric acid, 7664-38-2; 3′-*o*-benzylthymidine, 63593-01-1; benzyl chloride, 100-44-7; 5′-*o*-tritylthymidine, 7791-71-1.

(17) A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 816 (1955).

Synthesis and Thermal Reactions of 5,5-Diphenylcyclopentadiene[1]

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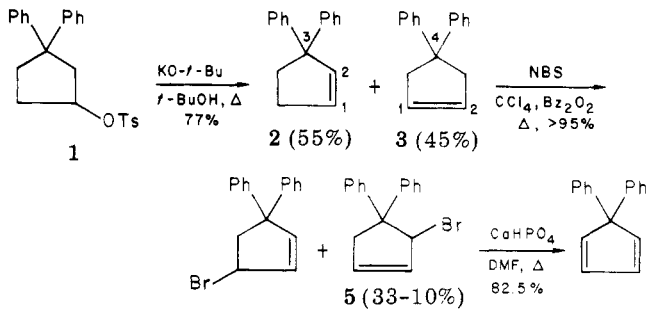
The *gem*-diphenyl function is not easily introduced into molecules. Probably, introduction of this function via diphenyldiazomethane or diphenylketene is most commonly employed. Because other work required *gem*-diphenyl functionality in bi- and tricyclic structures, we considered the possibility that 5,5-diphenylcyclopentadiene could serve usefully in the synthesis of such compounds. 5,5-Disubstituted cyclopentadienes of various types are indeed known. The alkyl examples, for instance, have a number of syntheses, proceeding from a cyclopentanone,[2] bicyclopentanes,[3] or cyclopentenones.[4] The 5,5-diphenyl analogue appears to be unreported previously, although the 1,4,[5] the 1,2,[6] and the 2,3[7] isomers, have been described. We report here the synthesis, characterization, thermal rearrangement, and Diels-Alder reactivity of this interesting diene.

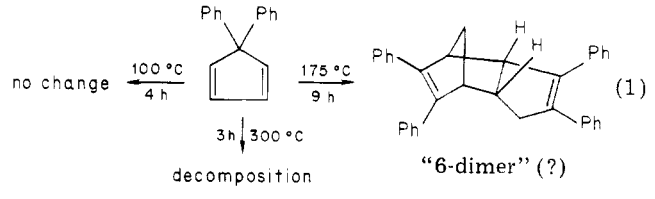
Scheme I



Results and Discussion

5,5-Diphenylcyclopentadiene (**6**) was prepared in a straightforward sequence from 3,3-diphenylcyclopentyl tosylate (**1**). These reactions are summarized in Scheme I.

Diene **6** showed no change in its NMR, IR, or UV spectra upon being heated neat under nitrogen at 100 °C for 4 h. A solution of **6** in hexadecane, when heated under nitrogen in a sealed tube at 300 °C for 3 h, underwent extensive degradation. Better control of the process was achieved by heating **6** in benzene-d_6 under nitrogen in a sealed NMR tube at 175 °C for 9 h, with NMR analysis being conducted each hour. No further change was observed after 3–4 h, however. Evaporation of the solvent left a solid, mp 136–138 °C dec, which exhibited *no vinyl proton* resonance in its NMR spectrum. Attempts to purify this crude solid by crystallization were unsuccessful, and the structure "**6**-dimer" for this material must be considered tentative (eq 1).[8]



(1) Taken from the M.S. Thesis of S.Z.A., 1978.

(2) C. F. Wilcox, Jr., and M. Mesirov, *J. Org. Chem.*, **25**, 1841 (1960).

(3) P. Eilbracht, P. Dahler, and W. Totzauer, *Tetrahedron Lett.*, 2225 (1976).

(4) R. Holder, J. Dahler, W. Baker, and R. Gilbert, Abstracts of Papers, 175th National Meeting of the American Chemical Society, Anaheim, Calif., March, 1978, paper ORGN 80.

(5) N. Drake and J. Adams, Jr., *J. Am. Chem. Soc.*, **61**, 1326 (1939). This is presumably the same diene as that prepared by W. Borsche and W. Menz, *Chem. Ber.*, **41**, 209 (1908), and believed by them to be the 1,3 isomer. Another preparation is due to M. Gonikberg and A. Gavrilova, *Zh. Obshch. Khim.*, **22**, 1384 (1952); *Chem. Abstr.*, **47**, 5901 (1953).

(6) G. Rio and M. Chariffi, *C. R. Hebd. Seances Acad. Sci., Ser C*, **268**, 1960 (1969).

(7) C. F. H. Allen, J. E. Jones, and J. A. Vanallan, *J. Org. Chem.*, **11**, 268 (1946). These authors name the diene "3,4-diphenylcyclopentadiene", but it is the 2,3 isomer.

(8) This dimer (mp 171–172 °C) was reported by Rio and Chariffi[6] to form along with others from 1,2-diphenylcyclopentadiene. Its structure was supported by (unreported) spectra. Compound "**6**-dimer" was not obtained in pure enough condition to make a comparison.

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