showed, in one case, no vinyl absorption but internal unsaturation and methyl absorption; the other material examined showed absorptions corresponding to a methyl group and both vinyl and internal unsaturation. The spectra were otherwise similar to that of 4-vinylcyclohexene. Thus both addition and substitution products are found. Acetone was also found to be produced in these reactions showing that some cleavage of *t*-butoxy radical to form $CH_3\cdot$ must also have occurred.

### Experimental

**Reagent.**—Di-*t*-butyl peroxide (Shell) was distilled at reduced pressure before use. The 4-vinylcyclohexene (Cities Service) was passed through an activated alumina column immediately before use.

All experiments were performed in a 1-l., three-necked, round-bottom flask equipped with a quartz test tube in the center neck. A length of hypodermic tubing was inserted through a serum cap attached to one of the flask necks. Samples were removed by placing evacuated sample vials onto this tubing and withdrawing approximately 1 ml. of solution. The reactions were stirred at all times by a magnetic stirring bar.

4-Vinylcyclohexene (165 g., 1.5 moles) was heated in the flask described above, and di-*t*-butyl peroxide (36 g., 0.25 mole) was heated simultaneously under nitrogen in a dropping funnel attached to the flask. When both were at the desired temperature (80 or 115°) the peroxide was added. Samples were withdrawn at appropriate time intervals. In those reactions involving cupric chloride, 0.3 g. of cupric chloride (dihydrate) was added to the 4-vinylcyclohexene before heating. The photolysis reactions were performed using a G.E. H85A3/UV lamp inserted into the quartz test tube mentioned above.

*t*-Butyl peroxide concentration was measured by gas chromatography at 75° on a 6-ft. silicone gum rubber column. Product analysis was also carried out by gas chromatography on a 6-ft. Carbowax (20M) column, programming from 100–250°. Product identification was by infrared spectroscopy. The following absorptions were observed in the 4-vinylcyclohexenyl ethers: 3090 $cm.^{-1}$ vinyl unsaturation, 3030 $cm.^{-1}$ *cis*-internal unsaturation, the typical aliphatic C–H absorptions around 2900 $cm.^{-1}$, 1640 $cm.^{-1}$ vinyl unsaturation, 1390 $cm.^{-1}$ and 1360 $cm.^{-1}$ assigned to *t*-butyl, 1155 $cm.^{-1}$ typical of ethers, 997 $cm.^{-1}$ and 915 $cm.^{-1}$ vinyl unsaturation, and 690 $cm.^{-1}$ assigned to internal unsaturation. The dehydrodimers showed the following absorptions: 3080 $cm.^{-1}$ vinyl unsaturation, 3030 $cm.^{-1}$ *cis*-internal unsaturations, aliphatic C–H absorptions between 3000 and 2800 $cm.^{-1}$, 1640 $cm.^{-1}$ vinyl unsaturation, 997 and 910 $cm.^{-1}$ vinyl unsaturation, 660 $cm.^{-1}$ internal unsaturation. The over-all infrared spectrum of the dehydrodimer showed the presence of all the major absorptions of 4-vinylcyclohexene, the only marked exception being the moderately strong 4-vinylcyclohexene peak at 1140 $cm.^{-1}$ (unassigned) absent in the dehydrodimer.

Comparison with previous work,[2] in which both the ether and dehydrodimer were isolated and characterized by infrared, hydrogenation, and elemental analysis, further confirmed the identification.

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## Dibenzyl Carbethoxy Phosphate

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Several anhydrides of phosphoric acid with carboxylic acids of the type $RCO{-}O{-}PO(OH)_2$ have been described,[1] in which R is a simple alkyl or aryl group. Much interest has been directed to the chemical and biological properties of acetyl phosphate.[2] No anhydride of phosphoric acid with a monoalkyl carbonic acid, in which R = alkoxy, has been described.

In the present work, dibenzyl carbethoxy phosphate was prepared by reaction of dibenzyl silver phosphate with ethyl chloroformate.

$$(C_7H_7O)_2POOAg + ClC(O)OC_2H_5 = (C_7H_7O)_2P(O)OC(O)OC_2H_5 + AgCl$$

The product is colorless oil, which is stable at 0°.

In aqueous dioxan (1:1 by volume), dibenzyl carbethoxy phosphate undergoes hydrolysis and dibenzyl hydrogen phosphate is formed. The progress of hydrolysis can be followed by neutralizing the acid as it is produced, using an automatic pH-stat titrator. The reaction observed first-order kinetics. At a constant pH of 6.0 and 37°, $k = (3.53 \pm 0.02) \times 10^{-5}\ sec.^{-1}$, using initial concentrations of 2 to 9 mmoles of the anhydride.

Attempts were made to remove the benzyl groups and to obtain carbethoxy phosphate, $C_2H_5O\ C(O)OPO(OH)_2$. Various debenzylating agents were tried, but in each case extensive decomposition occurred and carbon dioxide was evolved.

### Experimental

**Dibenzyl Carbethoxy Phosphate.**—Ethyl chloroformate (8 ml., freshly distilled) was added to a suspension of silver dibenzyl phosphate[3] (m.p. 213°, 1.05 g., prepared from dibenzyl phosphorochloridate[4]) in dry dioxan (30 ml.). A precipitate formed instantly. The mixture was stirred for 2 hr. at room temperature and the precipitate of silver chloride was then filtered off. The solvents were evaporated by high vacuum distillation, yielding 0.94 g. (98%) of a colorless viscous oil, which was stored in the cold.

*Anal.* Calcd. for $C_{17}H_{19}O_6P$: C, 58.2; H, 5.44; P, 8.9%. Found: C, 57.8; H, 5.46; P, 9.1.

The infrared absorption of the product was measured in carbon tetrachloride solution, using a Perkin-Elmer Model 12 spectrometer. Strong absorption bands occurred at 1024 $cm.^{-1}$ (due to the POC vibration[5]), at 1235 $cm.^{-1}$ (phosphoryl stretching), at 1372 $cm.^{-1}$ (methyl group vibration), at 1459 $cm.^{-1}$ (benzyl group vibration), at 1731 $cm.^{-1}$ (carbonyl stretching), and at 2955 $cm.^{-1}$ (C–H vibration).

**Hydrolysis.**—Dibenzyl carbethoxy phosphate (about 100 mg.) was dissolved in aqueous dioxan (100 ml.; 1:1 by volume) in a beaker fitted with a magnetic stirrer and covered by a rubber stopper. This stopper had three holes, through which the glass and calomel electrodes as well as the capillary glass outlet of a magnetic valve-operated buret led into the solution. The beaker was placed into a thermostat at 37.0°, above a rotating permanent magnet enclosed in a brass can. The electrodes were connected to a Radiometer Model TTT 1a automatic pH meter, which was set to keep a constant pH of 6.00 ± 0.05. The buret contained standard 0.10 *N* sodium hydroxide solution and titrated the dibenzyl hydrogen phosphate as it was formed. In a separate experiment, the end point in the titration of dibenzyl hydrogen phosphate had been shown to be pH = 6.0. Example of a kinetic experiment: dibenzyl carbethoxy phosphate (initially 1.9 mmoles) at 37.0°.

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| | | | | |
|---|---|---|---|---|
| Time (sec.) | 0 | 780 | 3600 | 5400 |
| x = mmoles NaOH | 0.585 | 0.635 | 0.785 | 0.89 |
| Time (sec.) | 7200 | 9000 | 10800 | Infinity |
| x = mmoles NaOH | 0.98 | 1.07 | 1.15 | 2.34 |

From the slope of a plot of log (a–x) against time, the first-order rate was derived $k_1 = 3.55 \times 10^{-5}$ sec.$^{-1}$.

**Hydrogenation of dibenzyl carbethoxy phosphate** in dry ethanol in the presence of a 10% palladium catalyst (on carbon powder) yielded after several hours shaking at 30–40 lbs./sq. in. pressure of hydrogen an equivalent amount of carbon dioxide (collected in barium hydroxide). Similar results were obtained by treatment of the material with barium iodide in acetone,[6] and hydrogen bromide in acetic acid.[7]

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# Potential Inhibitors of Cancerous Growth. III. Dibenzyl Acetals as Synthetic Intermediates

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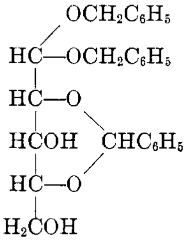
In the attempted synthesis of N,N-bis(2-chloroethyl)-3,5-cyclophosphamido-D-ribose, the corresponding dimethyl acetal[1] was hydrolyzed in dilute mineral acid. Although the cyclic phosphamide structure was apparently retained, the removal of the acetal grouping was unsatisfactory under these conditions. In a typical run, using 0.01 *N* hydrochloric acid in 50% aqueous dioxane, the amount of liberated aldehyde, estimated by the quantitative Benedict procedure, initially increased to 70% of the calculated value and then decreased for some unknown reason.

In view of the relative acid lability of cyclic phosphamides[2] and certain phosphate esters,[3] it seemed desirable to investigate the possibility of using an aldehyde blocking group in the above synthesis which could be removed by some reaction that does not involve the use of acid. The cleavage of O- and N-benzyl compounds by catalytic hydrogenation is a well known and widely used reaction in other fields for similar purposes.[4,5] In the carbohydrate field the cleavage of benzyl β-D-glycosides with hydrogen and metal catalysts has been described.[6] The dibenzyl acetal derivatives of D-ribose therefore appeared to be suitable intermediates for our projected synthesis, particularly in view of the reported stability of phosphate esters toward hydrogenolysis.[7] However, the dibenzyl acetals of D-ribose and its derivatives do not appear to have been described or used as synthetic intermediates. We have, therefore, prepared the dibenzyl acetal of D-ribose as well as that of D-ribose tetraacetate and 2,4-O-benzylidene-D-ribose.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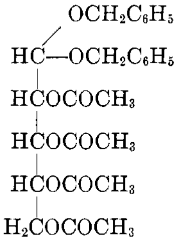
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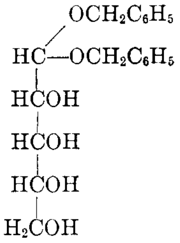
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In order to determine the suitability of dibenzyl acetals as synthetic intermediates, we have studied the behavior of these compounds toward hydrogenation. By choice of a suitable catalyst,[6] O-benzyl groups can be removed selectively by hydrogenation. In the case of the above-mentioned dibenzyl acetals, 10% palladized charcoal was found to be a suitable catalyst for the preparation of the corresponding free aldehyde compounds by hydrogenolysis.

## Experimental[18]

**2,4-O-Benzylidene-D-ribose dibenzyl Acetal** (I).—Yellow mercuric oxide (3.24 g., 15 mmoles) and anhydrous calcium sulfate (5 g.) were added to a solution of 2,4-O-benzylidene-D-ribose di-*n*-propyl dithioacetal[9] (1.86 g., 5 mmoles) in 68 ml. of pure anhydrous benzyl alcohol in a 500-ml. three-necked flask fitted with a mercury-sealed mechanical stirrer and a calcium chloride tube. The mixture was stirred vigorously with the flask submerged in a water bath maintained at 70°. A solution of 3.4 g. of mercuric chloride in 68 ml. of anhydrous benzyl alcohol was added slowly from a dropping funnel over a period of 5 min. Stirring was continued for a further 3 hr., the mixture filtered under suction onto 0.5 g. of yellow mercuric oxide, and the residue washed thoroughly with anhydrous benzyl alcohol. The benzyl alcohol was then removed from the combined filtrates as completely as possible in a rotary vacuum evaporator (0.5 mm., 65°). The residue was taken up in 100 ml. of chloroform, filtered, and washed with five 100-ml. portions of 10% aqueous potassium iodide and then with water until the washings were free from iodide ions. The chloroform solution was then dried over anhydrous sodium sulphate and evaporated to dryness. The remaining oil crystallized immediately on addition of 50 ml. of dibutyl ether. The crystals were filtered off and recrystallized from dibutyl ether; yield 1.6 g. (73%), m.p. 96–97°, $[\alpha]^{20}\text{D}$ +18.6 (*c* 8.75, methanol); $\lambda_{\max}^{CH_3OH}$ 258 mμ ($a_m$ 570); $\lambda_{\max}^{KBr}$ 2.93, 9.05 μ.

*Anal.* Calcd. for $C_{26}H_{28}O_6$: C, 71.55; H, 6.46. Found: C, 71.34; H, 6.34.

**Hydrogenolysis of 2,4-O-Benzylidene-D-ribose Dibenzyl Acetal.**—Two grams of 10% palladized charcoal[10] was saturated with hydrogen in 50 ml. of methanol. A solution of 2,4-O-benzylidene-D-ribose dibenzyl acetal (200 mg.) in 10 ml. of methanol was added and the hydrogenation continued. After approximately 3 hr., the calculated volume of hydrogen had been taken up. The catalyst was filtered off, washed with four 25-ml. portions of

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