for virus-induced cytopathogenic effects (CPE) and the amount of reduction in CPE caused by the test compound was determined. A virus rating (VR) was calculated for each compound tested against each virus by use of a modification of the method of Ehrlich, *et al.*,[10] which has been described previously.[11] The results are shown in Table I. As can be seen, the 1-(methylbenzyloxy)adenosines exhibited significant antiviral activity against HSV and VV *in vitro* with VR's ranging from 1.5 to 2.4 and, except for the 2-methylbenzyloxy compound, at one-third the molar concentration of the 1-benzyloxyadenosine. The 1-(fluorobenzyloxy)adenosines likewise demonstrated definite *in vitro* activity against these two DNA viruses, but 1-(*p*-nitrobenzyloxy)adenosine was inactive. Thus, it would appear, on the basis of this limited data, that groups capable of donating electrons to the benzene ring by resonance may enhance antiviral activity, whereas groups that withdraw electrons destroy activity. These interesting preliminary findings are being pursued. No significant activity was noted with any of these compounds against Ad, PIV, or influenza virus. Moderate antiviral activity was observed against RV with 1-(4-methylbenzyloxy)adenosine and 1-(4-fluorobenzyloxy)adenosine.

Experimental Section

Melting points were determined with a Mel-Temp apparatus and are not corrected. Uv were determined in aqueous solution with a Cary Model 14 spectrophotometer. The pmr spectra were determined in DMSO-d_6 (TMS) with a Varian XL-100 spectrometer. All compounds were tlc homogeneous on silica gel plates developed in $CHCl_3$–MeOH (3:1).

1-(Aralkyloxy)adenosine Fluoborates. A solution of adenosine 1-oxide[1] and the aralkyl bromide (4 mol/mol of adenosine 1-oxide) in DMA (20 ml/mol of adenosine 1-oxide) was stirred 3–5 days at ambient temperature. Evaporation of the DMA *in vacuo* gave a residue which was triturated with ether before it was dissolved in methanol. The methanol solution was filtered, diluted with ethyl acetate, and chilled overnight. The solid that crystallized was dissolved in water, and the solution was filtered before it was treated with 1 equiv of silver fluoborate. After removal of the silver bromide, the solution was treated with KI to precipitate silver iodide, which was removed by filtration before the solution was concentrated to a small volume *in vacuo* and refrigerated overnight. The crude fluoborate salt was recrystallized from water. The ultraviolet spectra of all these compounds were essentially identical with that of 1-benzyloxyadenosine,[3] except that of the 1-(4-nitrobenzyloxy)adenosine, which exhibited hyperchromicity. Details for individual compounds are given in Table II.

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Isosteres of Natural Phosphates. 2. Synthesis of the Monosodium Salt of 4-Hydroxy-3-oxobutyl-1-phosphonic Acid, an Isostere of Dihydroxyacetone Phosphate

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In this laboratory's continuing examination of the effect of phosphonic acid isosteres (substituting CH_2 for O in the ester linkage of naturally occurring phosphates) on phospholipid synthesis in *Escherichia coli*, the synthesis of 4-hydroxy-3-oxobutyl-1-phosphonic acid (3), the analog of dihydroxyacetone phosphate, was undertaken. Concurrently, a route for the synthesis of 3,4-dihydroxybutyl-1-phosphonic acid (8) was sought which would be readily applicable to the incorporation of a radioactive label (tritium) into the molecule. These two routes are described below.

The monosodium salt of 4-hydroxy-3-oxobutyl-1-phosphonic acid (4) serves as a substrate for rabbit muscle L-glycerol 3-phosphate:NAD oxidoreductase and for the biosynthetic L-glycerol 3-phosphate dehydrogenase from *E. coli* which was initially described by Kito and Pizer.[1,†] The herein described compound is of use in determining the mode of action of 3,4-dihydroxybutyl-1-phosphonic acid which affects the synthesis of phospholipids, primary precursors for which are the natural phosphates, glycerol 3-phosphate and dihydroxyacetone phosphate. These isosteres may thereby serve as metabolic regulators and probes of biochemical mechanisms. The overall synthetic scheme is outlined in Scheme I.

Experimental Section

Acetoxymethyl Vinyl Ketone (1). The procedure of Hennon and Kupiecki[2] was followed. 2-Butyne-1,4-diol (1 mol) was treated with acetic anhydride (2.5 mol). The resulting solution was treated with mercuric oxide and sulfuric acid and the product isolated by distillation. The yield of 1 was 90 g (78%). This material was prepared immediately prior to use.

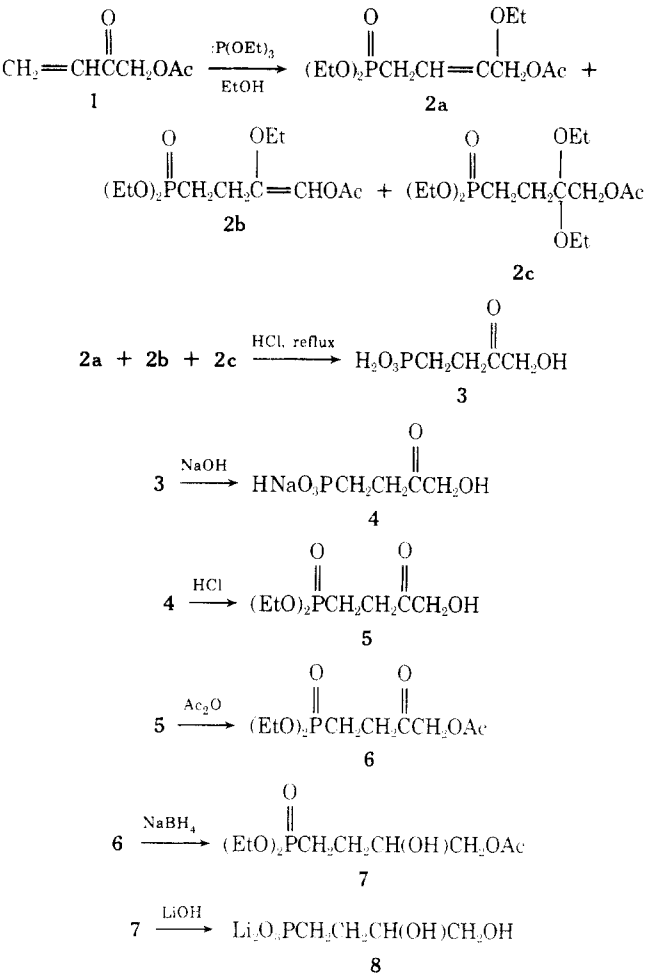
Diethyl 1-Acetoxy-2-ethoxybut-2-enyl-4-phosphonate (2a). To a cooled (0°) solution of 90 g (0.78 mol) of the ketone 1 and 130 g (2.8 mol) of absolute ethanol was added dropwise 133 g (0.80 mol) of triethyl phosphite.[3] The solution was stirred for 1 hr at 0° and overnight at room temperature. Upon fractional distillation there was obtained a colorless liquid, bp 145° (0.3 mm). The nmr and ir spectra of this material indicated that although it consisted primarily of **2a**, significant amounts of the isomeric enol ether **2b** and the ketal **2c** were also present. Further attempts at separation were unsuccessful. This mixture was considered suitable for the next stage in the synthesis. The yield, based on **2a**, was 140 g (70%).

Monosodium 4-Hydroxy-3-oxobutyl-1-phosphonate (4). A solution of 10 g (0.034 mol based on **2a**) of the mixture **2a–c**, 30 ml of concentrated HCl, and 70 ml of water was refluxed for 22 hr. The volatile components were removed under reduced pressure and the pale yellow oil was dissolved in water, treated with activated charcoal, and filtered. The water was evaporated and the ir and nmr spectra of the resulting oil were in accord with the proposed structure **3** for the phosphonic acid. The special data obtained for **3** are as follows: ir (film) 2.95, 3.60, 5.85, 7.17, 8.20, 9.45, 10.16, 10.22, 12.75, 14.13 μ; nmr (TFA) δ 2.22–3.16 (m, 4 H, PCH_2CH_2), 4.62 (s, 2 H, CH_2O).

This material was dissolved in water and titrated with 1 *N* NaOH to pH 4.0. The water was evaporated to yield a colorless semisolid to which was added 100 ml of absolute methanol. The mixture was sitrred until the product crystallized. The resulting white powder was isolated by filtration and the filtrate was concentrated to about 10 ml. The solution was added to 100 ml of absolute ethanol and the resulting second crop of white powder was isolated by filtration. The solids were combined and washed with

† P. J. Cheng, R. Engel, and B. E. Tropp, unpublished results of this laboratory.

Scheme I



absolute ethanol and then with anhydrous ether. The filtrate and wash solvents were combined and evaporated to give an oil which was retitrated. The powder was dried *in vacuo* over P_2O_5 and gave 6.0 g (93%) of pure **4**: ir (Nujol) 3.00, 5.90, 6.95, 7.90, 8.17, 8.80, 9.45, 9.97, 10.20, 11.20 μ; nmr (TFA) δ 2.15–3.10 (m, 4 H, PCH_2CH_2), 4.68 (s, 2 H, CH_2O). *Anal.* Calcd for $C_4H_8O_5NaP$: C, 25.26; H, 4.21. Found: C, 25.05; H, 4.51.‡

Diethyl 4-Acetoxy-3-oxobutyl-1-phosphonate (6). A mixture of 29.4 g (0.1 mol) of the mixture **2a–c** with 4 ml of 3% HCl was stirred overnight and heated at 60–70°. Volatile components were removed under reduced pressure and the resulting mixture of the keto alcohol **5** and keto acetate **6** was treated with 20 g (0.2 mol) of acetic anhydride. The solution was heated on a steam bath for 2 hr and distilled. The yield of pure **6** was 19 g (71%): bp 142° (0.3 mm); ir (film) 3.35, 3.42, 5.78, 7.10, 7.32, 8.25, 8.65, 9.90, 10.58, 12.10 μ; nmr (CCl_4) δ 1.18 (t, J = 7 Hz, 6 H, CH_3CH_2O), 1.50–2.90 [2 m and s (2.02), total 7 H, PCH_2CH_2 and $C(O)CH_3$], 3.92 (m, 4 H, CH_3CH_2O), 4.70 (s, 2 H, CH_2OAc). *Anal.* Calcd for $C_{10}H_{19}O_6P$: C, 45.12; H, 7.19. Found: C, 45.24; H, 7.44.

Dilithium 3,4-Dihydroxybutyl-1-phosphonate (8). To a solution of 1.59 g (6 mmol) of keto acetate **6** in 25 ml of anhydrous 2-propanol was added 76 mg (2 mmol) of $NaBH_4$. The mixture was heated at 50° for 1 hr and stirred overnight at room temperature. The solution was treated with 1 ml of 3 *N* HCl and the volatile components were removed under reduced pressure. To the residue was added 50 ml of water and 2.5 g (100 mmol) of LiOH, and the resulting solution was heated in an autoclave for 6 hr at 120°. A white precipitate was isolated by filtration, washed with absolute ethanol and anhydrous ether, and dried under vacuum to yield 0.88 g of **8**. This material was identical with that prepared by the route previously described[4] as indicated by ir and nmr spectra, tlc, and enzymatic assay.† This reaction was subsequently repeated on a smaller scale using tritium-labeled sodium borohydride yielding **8** labeled at the 3 position with tritium.

Biological Data. The ability of the monosodium salt of the 4-hydroxy-3-oxobutyl-1-phosphonic acid (**4**) to serve as a substrate for L-glycerol 3-phosphate:NAD oxidoreductase (EC 1.1.1.8) was determined by the procedure of Black.[5] Kinetic studies of **4** and dihydroxyacetone phosphate yielded K_m's of 182 and 133 μM, respectively. These values are similar to one another and relatively close to the value of 80 μM for dihydroxyacetone phosphate which was reported by Black. Preliminary evidence indicates that the phosphonic acid analog **4** can also serve as a substrate for the biosynthetic L-glycerol 3-phosphate dehydrogenase from *E. coli* which was initially described by Kito and Pizer.[1]

The 3,4-dihydroxybutyl-1-phosphonic acid (**8**) with tritium labeling at the 3 position was used to determine an apparent K_m for L-glycerol 3-phosphate CMP phosphatidyl transferase. A value of 1.8×10^{-5} M was determined,§ adding to our previous data on this compound.[6]

The data obtained substantiate the value of the synthesized compounds as analogs of natural substrates both for the investigation of biological action and as a metabolic regulator.

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Cyclization of Lactamimide Ketones to Imidazo[1,2-*a*]-azacycloalkanes with Hypoglycemic Activity

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We have prepared many lactamimides in order to evaluate their pharmacological properties, especially hypoglycemic effects.[1-3] When α-amino ketone hydrochlorides I were allowed to react with lactim ethers II, the resulting products were found to be imidazo[1,2-*a*]azacycloalkane hydrochlorides IV. These resulted from cyclization of the lactamimides III, which could be isolated in some instances. Compounds IV lacked the carbonyl absorption seen in the infrared spectra of III at 1700–1710 cm^{-1} and the benzoyl chromophore at 246 nm (ϵ 16,300) seen in the ultraviolet spectra of III. On treatment with concentrated hydrochloric acid, compounds IV dehydrated to the aromatic compounds V that showed the characteristic phenylimidazole ultraviolet chromophore at 234–237 nm (ϵ 11,700). The isomeric compound Vd has recently been described (Scheme I).[4]

Compounds III and IV are interconvertible and there appears to be a preference for one or the other form, which depends on the size of the azacycloalkane ring (n). Thus, the hydrochloride salts of the lactamimide ketones IIIa and IIIb were isolated from the reaction of the hydrochloride of Ia with lactim ethers IIa or IId, respectively. Ketone IIIa was stable to refluxing concentrated hydrochloric acid. When converted to free base, IIIa and IIIb spontaneously cyclized to IVa and IVd, respectively; IVa opened to IIIa in a solution of ethanol or deuteriochloroform, and thus only the infrared spectrum (KBr) provides evidence for its existence (*cf.* Table I). Compound IVd, on