extract were combined and evaporated to give 1 as an oil: yield 21.0 g (75.0%). A crystalline fumarate salt of 1 was obtained from MeOH-Et_2O; yield 19.5 g (55.0 %); mp 253-254° dec. The salt was recrystallized twice from MeOH-Et_2O and the analytical sample of 1 was obtained: yield 14.5 g (41.7%); mp 260-261° dec. *Anal.* ($C_{13}H_{21}NO_3{\cdot}0.5C_4H_4O_4$) C, H, N.

3-[2-(*tert*-Butylamino)-1-hydroxyethyl]-5-hydroxybenzoic Acid (12). An ethanolic solution (200 ml) containing 6.00 g (16.2 mmol) of **6** was hydrogenated over 2.5 g of 10% Pd/C catalyst at room temperature until H_2 uptake had ceased. The mixture was filtered through a Celite pad and the ethanolic filtrate was evaporated *in vacuo* to the crude **12** as the HCl salt. The analytical sample was obtained by recrystallization from EtOH-Et_2O: yield 2.15 g (44.4%); mp 188-191° dec. *Anal.* ($C_{13}H_{19}NO_4{\cdot}HCl{\cdot}0.5H_2O$) C, H, N, Cl.

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Notes

Isosteres of Natural Phosphates. 3. Synthesis of the Dilithium Salt of 4,4-Diethoxy-3-hydroxybutyl-1-phosphonic Acid, an Isostere of Glyceraldehyde 3-Phosphate

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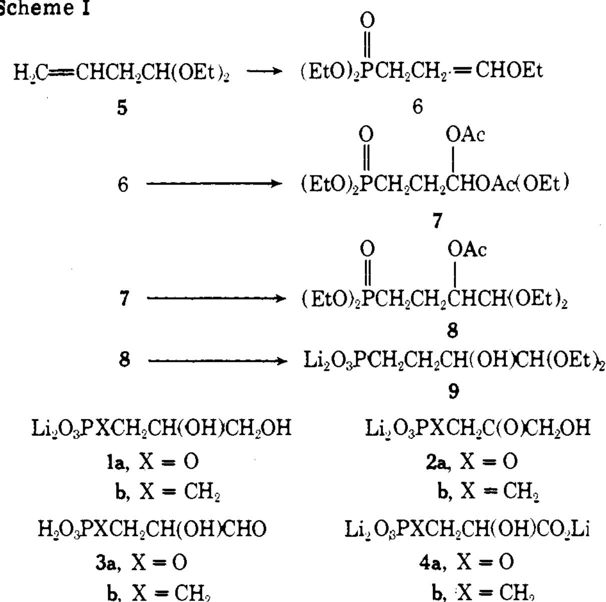
This laboratory has been engaged in the examination of the role of phosphonic acid analogs of natural organic phosphates as possible chemotherapeutic reagents which function by affecting specific biochemical pathways. We have previously reported the synthesis of 3,4-dihydroxybutyl-1-phosphonate (**1b**),[1] an analog of glycerol 3-phosphate (**1a**), and 4-hydroxy-3-oxobutyl-1-phosphonate (**2b**),[2] an analog of dihydroxyacetone phosphate (**2a**). The present report concerns the synthesis of a closely related compound, 3-hydroxy-4-oxobutyl-1-phosphonate (**3b**), an analog of glyceraldehyde 3-phosphate (**3a**). It was also expected that a precursor of **3b** would be converted readily to 3-carboxy-3-hydroxypropyl-1-phosphonate (**4b**), an isostere of 3-phosphoglyceric acid (**4a**), thereby providing a sample of this material for preliminary testing before determining whether a different, more efficient route to this isostere need be found. An alternative synthesis of **4b** has recently been reported.[3]

Results

The overall synthetic route is illustrated in Scheme I. 1,1-Diethoxy-3-butene (**5**) was chosen as a starting material because it was readily available from ethyl vinyl ether and it appeared that the four carbon unit could properly be functionalized. The initial route for the incorporation of the phosphorous group involved hydroboration and formation of the tosyl ester of the resulting alcohol, followed by an Arbuzov reaction. However, low yields and intermediates which were difficult to purify eliminated this route.

Scheme I



A free-radical addition of diethyl phosphite across the terminal double bond of the butene appeared promising. This addition was initiated by benzoyl peroxide at 85°, but it proved necessary to use a large amount of the peroxide, probably due to the presence of trace amounts of mercury in the butene. The product from this reaction was not the expected diethyl 4,4-diethoxybutyl-1-phosphonate but rather the corresponding enol ether **6**. This compound probably arises from an acid (benzoic acid) catalyzed pyrolysis of the acetal during the distillation. The enol ether was converted to diacetate **7** with the addition of bromine across the double bond followed by acetate displacement of bromide.

The diacetate **7** was subjected to vigorous acidic hydrolysis and the nmr spectrum of the resulting material indi-

cated that the derived α-hydroxyaldehyde had quantitatively rearranged to the corresponding α-hydroxy ketone (the free isostere **2b** of dihydroxyacetone phosphate). Since neither the diacetate nor the free aldehyde would be stable to alkaline hydrolysis, it was necessary to convert **7** to the acetal **8**. This was accomplished in ethanol with sulfuric acid as a catalyst. The acetal **8** was then hydrolyzed under basic conditions to yield the diethyl acetal **9** of the isostere of glyceraldehyde 3-phosphate (**9**). The acetal **8** was also treated with formic acid and hydrogen peroxide and the resulting carboxylic acid hydrolyzed to yield the isostere of 3-phosphoglyceric acid, 3-carboxy-3-hydroxypropyl-1-phosphonate (**4b**).

For biochemical testing the acetal **9** was converted to the free aldehyde **3b** by washing with Dowex 50 in the acid form. The free aldehyde content was calculated on the basis of amount of analyzed acetal converted.

Discussion

3-Hydroxy-4-oxobutyl-1-phosphonate (**3b**) was synthesized for a variety of reasons. The availability of the phosphonic acid analog of glyceraldehyde 3-phosphate affords an important substrate analog for examining the specificity of several of the glycolytic enzymes and possibly for the biochemical synthesis of some of the isosteric analogs of intermediates of glycolysis. We have determined that 3-hydroxy-4-oxobutyl-1-phosphonate (**3b**) is a substrate for rabbit muscle glyceraldehyde-3-phosphate dehydrogenase.† DL-3-Hydroxy-4-oxobutyl-1-phosphonate (**3b**) at a concentration of 2.5 m*M* completely inhibits the growth of *Escherichia coli* strains 7 and 8 cultured on the synthetic medium of Garen and Levinithal[4] supplemented with potassium succinate.‡ This analog has little effect when glucose replaces the succinate as the carbon source. This may be the result of catabolite repression. The analog of dihydroxyacetone phosphate (**2a**), 4-hydroxy-3-oxobutyl-1-phosphonate (**2b**), does not appear to inhibit the growth of *E. coli* with either carbon source.§

The studies of Hyashi, Kock, and Lin[5] indicated that DL-glyceraldehyde 3-phosphate could inhibit the transport of L-glycerol 3-phosphate whereas dihydroxyacetone phosphate appeared to be without effect upon the L-glycerol 3-phosphate transport system. These findings are consistent with an assumption that the L-glycerol 3-phosphate transport system can transport glyceraldehyde 3-phosphate but not dihydroxyacetone phosphate. This assumption would certainly explain the failure of 4-hydroxy-3-oxobutyl-1-phosphonate (**2b**) to affect the growth of *E. coli*. Although according to the above assumption the analog of glyceraldehyde 3-phosphate might be expected to be transported by the L-glycerol 3-phosphate transport system, a further problem must be considered. If, as appears likely, it is the L form of 3-hydroxy-4-oxobutyl-1-phosphonate which enters *E. coli* through the L-glycerol 3-phosphate transport system, then how does this optical isomer interfere with cell growth? Several possibilities may be considered: (i) the L form is converted to D-3-hydroxy-4-oxobutyl-1-phosphonate which has the same configuration as the normal intermediate of glycolysis, (ii) the L form acts in a pathway other than the glycolytic pathway either as a substrate or inhibitor, and (iii) the D form can enter the cell by the L-glycerol 3-phosphate transport system or some other transport systems such as that used for glucose 6-phosphate uptake. These questions are currently under investigation.

† D. Klein, R. Engel, and B. Tropp, unpublished results of this laboratory.

‡ M. Connolly, C.-T. Tang, R. Engel, and B. Tropp, unpublished results of this laboratory.

§ R. Salamon, S. Goldstein, R. Engel, and B. Tropp, unpublished results of this laboratory.

Experimental Section

1,1-Diethoxy-3-butene (5). The method of Hoaglin, *et al.*,[6] was followed. Ethyl vinyl ether (500 g, 7 mol) was added to a mixture of 8.4 ml of 50% BF_3-Et_2O, 35 g of mercuric acetate, and 70 ml of diethyl ether. When the reaction had ceased to be exothermic the mixture was stirred for an additional 10 min and then treated with 35 g of sodium carbonate in 350 ml of water. This mixture was stirred for 20 min and filtered through Celite, and the aqueous layer was separated. The organic layer was distilled until the material boiling below 100° was removed. The distillate was then cooled, treated with magnesium sulfate (anhydrous), and filtered through Celite. The filtrate was fractionated through a 35-cm Vigreux column and gave 375 g (75%) of pure **5**: bp 146–148° [lit.[6] bp 62–68° (50 mm)].

Diethyl 1-Ethoxybut-1-enyl-4-phosphonate (6). A solution of 72 g (0.5 mol) of acetal **5** and 138 g (1.0 mol) of diethyl phosphite was deoxygenated with a stream of dry nitrogen for 5 min and 6 g of benzoyl peroxide was added. The solution was heated to 85°, at which point the reaction became exothermic and the heat was removed. The reaction was maintained between 80 and 85° with the application of heat as necessary for 24 hr. During this period, at 3-hr intervals, two additional 3-g portions of benzoyl peroxide (12 g, 0.05 mol) were added to the reaction mixture. Unreacted starting material was removed under reduced pressure, and the remaining material was distilled *in vacuo*. The material boiling between 80 and 130° (0.5 mm) was collected, at which point benzoic acid began to solidify in the condenser. The distillate was dissolved in ether, the ether being washed with several portions of saturated sodium bicarbonate solution, and dried over Na_2SO_4. The ether was evaporated and the crude product was fractionally distilled to yield 65 g (55%) of pure **6**: bp 91–92° (0.02 mm); ir (film) 3.33, 3.42, 6.02, 7.24, 8.03, 9.07, 9.52, 9.76, 10.53, 12.90 μ; nmr (CCl_4) δ 1.05–1.40 (m, 9 H, CH_3), 1.40–2.55 (m, 4 H, PCH_2CH_2), 3.40–4.15 (m, 6 H, OCH_2), 4.25–4.90 (m, 1 H, =CH–), 5.80–6.40 (m, 1 H, =CHO–). *Anal.* ($C_{10}H_{21}O_4P$) C, H.

Diethyl 3,4-Diacetoxy-4-ethoxybutyl-1-phosphonate (7). To a cooled (ice-water bath) mixture of 47.2 g (0.2 mol) of **6** and 42.8 g (0.4 mol) of anhydrous sodium acetate in 60 ml of acetic anhydride was added dropwise 32 g (0.2 mol) of bromine. The ice bath was removed and the mixture was stirred for 1 hr and then refluxed for 4 hr. The mixture was allowed to cool, treated with 100 ml of methylene chloride, and filtered, and the solvents were removed under reduced pressure. The residue was vacuum distilled through a short-path distillation apparatus. The material boiling between 120 and 175° (0.05 mm) was redistilled and gave 45 g (64%) of pure **7**: bp 147–149° (0.01 mm); ir (film) 3.36, 3.42, 5.78, 7.00, 8.20, 8.66, 9.17, 9.80, 10.64 μ; nmr (CCl_4) δ 0.95–1.40 (m, 9 H, CH_2CH_3), 1.55–2.65 [m, 10 H, $COCH_3$ (2.05) and PCH_2CH_2], 3.40–4.25 (m, 6 H, OCH_2), 4.65–5.40 (m, 1 H, CHO), 6.05 (d, J = 6 Hz, 1 H, CHO_2). *Anal.* ($C_{14}H_{27}O_8P$) C, H. (Note: this material was not very stable and soon yellowed on standing.)

Diethyl 3-Acetoxy-4,4-diethoxybutyl-1-phosphonate (8). A mixture of 20 g (57 mmol) of **7**, 200 ml of anhydrous ethanol, and 0.5 ml of concentrated sulfuric acid was refluxed for 3 hr. The solution was cooled, treated with excess potassium carbonate, and filtered, and the volatile components were removed under reduced pressure. The residue was vacuum distilled through a short-path distillation apparatus. The material boiling between 136 and 145° (0.02 mm) was redistilled and gave 13.5 g (70%) of pure **8**: bp 133–134° (0.02 mm); ir (film) 3.39, 3.48, 5.81, 7.44, 8.23, 9.76, 10.05, 10.81 μ; nmr (CCl_4) δ 1.00–1.45 (m, 12 H, CH_2CH_3), 1.45–2.30 [m, 7 H, $COCH_3$ (2.00) and PCH_2CH_2], 3.20–5.00 (m, 10 H, OCH_2 and CH). *Anal.* ($C_{14}H_{29}O_7P$) C, H.

Dilithium 4,4-Diethoxy-3-hydroxybutyl-1-phosphonate (9). A mixture of 10 g (29 mmol) of **8**, 1 ml of ethanol, and 10 ml of water was treated with 0.2 g of $NaBH_4$ to inhibit the formation of colored impurities. The mixture was then treated with 40 ml of water containing 5 g (200 mmol) of LiOH and heated in an autoclave for 12 hr at 120°. A white precipitate was isolated by filtration and washed with several portions of ethanol and then anhydrous ether. The resulting white powder was dried *in vacuo* and gave 5.9 g (79%) pure **9**: ir (KBr) 2.96, 3.41, 3.51, 7.21, 8.44, 9.80, 10.42 μ; nmr (D_2O) δ 1.30 (t, J = 4 Hz, 6 H, CH_3), 1.5–2.35 (m, 4 H, PCH_2CH_2), 3.55–4.15 (m, 5 H, OCH_2 and CHO), 4.60 (d, J = 3 Hz, 1 H, CHO_2). *Anal.* ($C_8H_{17}O_6PLi_2$) C, H.

Trilithium 3-Carboxy-3-hydroxypropyl-1-phosphonate (4b). A mixture of 6.8 g (20 mmol) of **8** and 5 ml of 30% H_2O_2 in 20 ml

of 80% formic acid was stirred and heated to 50° for 24 hr. Another 5 ml of 30% H_2O_2 was added and the heating and stirring were continued until an aliquot of the solution failed to give a positive Schiff test (another 24 hr). The volatile components were removed under reduced pressure and the residue was treated with 3.5 g (150 mmol) of LiOH in 35 ml of water. The resulting solution was heated in an autoclave at 120° for 12 hr. A white precipitate was isolated by filtration and washed with several portions of ethanol and then anhydrous ether. The resulting white powder was dried *in vacuo* to give 2.3 g (56%) of pure **4b**. The observed spectral and physical properties were in agreement with those previously reported for this compound.[3]

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14-Hydroxycodeinone. An Improved Synthesis

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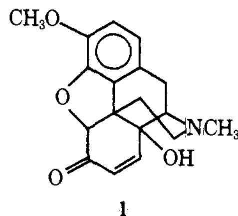
14-Hydroxycodeinone (1), an important synthetic intermediate for the preparation of several narcotic antagonists, is normally prepared by oxidation of thebaine with either hydrogen peroxide or potassium dichromate in acetic acid.[1] However, use of either of these oxidative procedures furnishes 1 in low to moderate yield and then only as a dark resinous material which must be further purified by repetitive recrystallization.



1

We have devised an alternate oxidation procedure, *m*-chloroperbenzoic acid in acetic acid–trifluoroacetic acid mixture, which furnishes high-purity 14-hydroxycodeinone in excellent yield. The initial product is nearly colorless and is of sufficient purity that it can be used directly for most synthetic purposes. A single recrystallization affords pure 14-hydroxycodeinone (1).

Experimental Section

Melting points were determined on a Kofler hot stage and are uncorrected. Nmr spectra were determined on a Varian HA-100 spectrophotometer ($CDCl_3$, TMS). Infrared spectra were taken on a Perkin-Elmer 267 spectrophotometer ($CHCl_3$).

14-Hydroxycodeinone (1). To a stirred solution of thebaine (30.1 g) in AcOH (120 ml) was added CF_3CO_2H (15 g) followed by *m*-chloroperbenzoic acid (12.5 g) added over 12 min. The reaction flask was placed in a preheated (95°) stirring wax bath for 15 min and then removed, and while stirring, additional *m*-chloroperbenzoic acid (10.3 g) was added over 18 min. The reaction was again placed in the heating bath for 20 min. After removing the flask from the wax bath, it was stirred an additional 10 min, cooled in an ice bath, and then poured into ice water (900 ml). After stirring for 30 min, the solid was removed by filtration. To the stirred, clear filtrate was added ice (500 g) and enough NH_4OH to make the solution basic. After 1 hr, the solution was filtered and the collected solid was washed with H_2O, 95% EtOH, and Et_2O. After drying, the nearly colorless product weighed 24.3 g (80%) and had mp 265–267° (lit. mp 275°). Recrystallization from EtOH containing a small amount of $CHCl_3$ gave 22.4 g (74%) with mp 274°.

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2-Aryl-3-dimethylphosphinylpropionic Acids as Potential Nonsteroidal Antiinflammatory Agents

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The literature of recent years contains many examples of 2-arylalkanoic acids which for the most part display potent antiinflammatory activity. Essentially all of these compounds can be thought of as arylacetic acids, with or without additional substitution in the α position. In general, substitution of these arylacetic acids in the α position by a small group (CH_3, C_2H_5, OH) leads to retention and, in many cases, enhancement of activity. The dimethylphosphinylmethyl (DPM) moiety has recently been shown[1] to be bioisosteric with methyl in the benzodiazepines, imparting, in addition, interesting changes in the activity profile. The decision was made to test the generality of this bioisosteric relationship by preparing several 2-aryl-3-dimethylphosphinylpropionic acids. It was anticipated that antiinflammatory activity would be enhanced or at least maintained in comparison to 2-arylpropionic acids, with perhaps useful changes in the physical (water solubility, biological distribution, etc.) properties and/or spectrum of activity. A similar approach involving phosphorus analogs of the analgetic methadone has recently been reported.[2]

Our initial synthetic goals, compounds 5–8 (Table I), were selected for two reasons. It was anticipated that the utility of the DPM moiety as a bioisosteric replacement for methyl could best be tested with compounds closely analogous to known potent antiinflammatory agents.† Furthermore, since it was expected that the DPM moiety would increase the water solubility of the target compounds with reference to methyl-substituted analogs, lipophilic phenyl substituents were deemed most desirable to maintain good partitioning ability. The phenyl substituents were thus selected[5] to give a π-value[6] range of 0.77–1.92, while σ[6] was allowed to vary from −0.32 to 0.23 in

†6 is related to naproxen;[3] 8 is similar to namoxyrate.[4]