iodide, and 30 mL of acetone and refluxed for 42 h. NMR spectra of aliquots withdrawan at intervals indicated that this amount of time is required for essentially complete reaction. 100 mL of benzene were added, the mixture filtered, and the filtrate distilled, first at 1 atm and then at 4.5 torr. The fraction boiling between 75 and 81 °C (mostly 77–79 °C) consisted of 14.2 g (90%) of **7** sufficiently pure to be used to prepare the substituted barbituric acid: ^{1}H NMR (12%, $CDCl_3/Me_4S$:) δ 4.22 (q, J = 7 Hz, 4 H); 2.86 (q, J = 11.2 Hz, 2 H); 2.13 (q, J = 7.5 Hz, 2 H); 1.25 (t, J = 7 Hz, 6 H); 0.87 (t, J = 7.5 Hz, 3 H); ^{19}F NMR ϕ* −62.24 (t, J = 11.2 Hz).

Diethyl Isoamyl(2,2,2-trifluoroethyl)malonate (8). This was prepared from 23.3 g (96 mmol) of **3** and 60.4 g (400 nmol) of 1-bromo-3-methylbutane essentially as above, except that the mixture was refluxed for 12 days. A fraction boiling between 90 and 103 °C (mostly 100–103 °C) at 4.5 torr consisted of 25 g (84%) of nearly pure **8**: ^{1}H NMR (12%, $CDCl_3/Me_4Si$) δ 4.21 (q, J = 7 Hz, 4 H), 2.84 (q, J = 11 Hz, 2 H), 2.07 (complex multiplet, 2 H), 0.9–1.9 (complex multiplet, 3 H), 1.24 (t, J = 7 Hz, 6 H), 0.89 (d, J = 6 Hz, 6 H); ^{19} F NMR ϕ* −62.18 (t, J = 11 Hz).

5-Ethyl-5-(2,2,2-trifluoroethyl)barbituric Acid (Trifluorobarbital). A 5.0-g (83 mmol) sample of urea, 3.6 g (157 mmol) of sodium, and 47 mL of dry ethanol were mixed and heated until homogeneous. Then, 14.2 g (52 mmol) of **7** and 5 mL of ethanol were added, and the mixture was heated under reflux with an oil bath at 105 °C for 10 to 12 h. Ethanol was removed from the cooled mixture at reduced pressure and 75 mL of water added to the yellow residue. The solution was washed 3 times with 30 mL of ether, the combined ether solutions were extracted twice with 25 mL of water, and the combined aqueous layers were neutralized by dropwise addition of concentrated hydrochloric acid. A total of 9.8 g (78%) of crude solid product was obtained from the chilled solution and recrystallized from hot water. The NMR spectra of trifluorobarbital and trifluoroamobarbital were observed by using 0.08 g of material dissolved in 0.6 mL of trifluoroacetic acid containing 2 vol % tetramethylsilane: ^{1}H NMR δ 3.11 (q, J = 9.7 Hz, 2 H), 2.26 (q, J = 7.5 Hz, 2H), 1.07 (t, J = 7.5 Hz, 3 H); ^{19}F NMR ϕ* −65.52 (t, J = 9.7 Hz); Anal. Calcd for $C_8H_9F_3N_2O_3$: C, 40.34; H, 3.81. Found: C, 40.02; H, 3.88.

5-Isoamyl-5-(2,2,2-trifluoroethyl)barbituric Acid (Trifluoroamobarbital). By essentially the same procedure, 16.5 g (76%) of this product were prepared from 24.3 g (78 mmol) of **8** and recrystallized from water/ethanol: ^{1}H NMR δ 3.11 (q, J = 9.7 Hz, 2 H), 2.2 (complex multiplet, 2 H), 1.0 to 1.8 (complex multiplet, 3 H), 0.91 (d, J = 6 Hz, 6 H); ^{19}F NMR ϕ* −65.63 (t, J = 9.7 Hz). Anal. Calcd for $C_{11}H_{15}F_3N_2O_3$: C, 47.14; H, 5.40. Found: C, 47.53; H, 5.13.

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Alkylating Properties of Phosphate Esters. 1. Oxygen → Nitrogen Methyl Transfer in Dimethyl 2-Pyridylmethyl Phosphate

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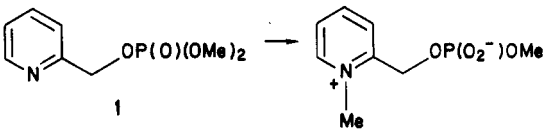
The growing interest in nucleophilic displacement at the carbon atom of phosphate esters stems from at least two sources. First, alkylation of nucleotides by trialkyl phosphates[1] is related to studies on alkylated nucleosides which have been found in nucleic acids. Second, the "triester method" for the synthesis of oligonucleotides involves cleavage of the methyl phosphotriester intermediate by nitrogen[2] or sulfur[3] nucleophiles. In phosphates containing both a nucleophilic center and an electrophilic carbon in the phosphate ester group, alkyl transfer results in isomerization and formation of the zwitterionic product. This reaction has been employed[4] in the synthetic approach to phospholipid analogues where the *O*-methyl is transferred to the β-dimethylamino group in a phosphate triester. Although this isomerization is believed[4] to be inter-not intramolecular, no evidence for the mechanism was given. For the decomposition of 2-(dimethylamino)ethyl phosphates, Manninen[5] claimed, on the basis of "the effect of the different concentrations" and "the appearance of the intermediate products" in the ^{1}H NMR spectra of the reaction mixture, that the methyl transfer is a bimolecular process.

In continuation of our interest in the electrophilic reactivity of phosphate esters,[6] we report the results of our study on the isomerization of dimethyl 2-pyridylmethyl phosphate (**1**) to the corresponding zwitterionic derivative **2**.



1 2 (1)

The triester **1** was chosen as a model substrate because not only should its reactions be free of any intermediate formation of the aziridinium ion, observed for aliphatic β-aminoalkyl esters,[5] but also because, in view of a recent report on selectivity in dealkylation of phosphate esters,[7] competing alkylation by the 2-pyridylmethyl group, is not expected. We found that **1** is not a reactive methylating agent with respect to the 2-pyridyl nitrogen; it is unchanged after 4 months at room temperature (in pure form or in Me_2SO-d_6) or after refluxing for several hours in $CDCl_3$, $(CD_3)_2CO$, or CD_3CN. The low reactivity of **1** contrasts with that of the β-(dimethylamino)ethyl analogue, in which the isomerization was complete after 28 days at 20 °C.[4] Since the Swain–Scott parameters n for triethylamine and 2-picoline differ by only 0.34 unit,[8] the difference in reactivity of **1** and the β-(dimethylamino)-ethyl substrate results not from the difference in the nucleophilicity of nitrogen atoms but probably from steric hindrance offered by the bulky 2-[(dimethoxylphosphoryl)oxy]methyl substituent in **1**. Isomerization of **1** can however be easily achieved in aqueous media.[9] When a solution of **1** (1.7 M) in D_2O is refluxed for 2 h, all substrate disappears, and **2** is formed as the major (spectral yield, 88%) product.

The conversion of **1** into **2** is easily seen in the ^{1}H NMR spectra of the solution taken before and after the reaction. The only other product observed was methanol (ca. 12%), formed by the hydrolysis of **1** and/or **2**.[10] If the isomer-

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(9) We have observed that alkylating properties of trialkyl phosphates are greatly enhanced in hydroxylic solvents (particularly in water) relative to other solvents of comparable polarity. This medium effect is currently being investigated in our laboratory.

(10) Under the same conditions, trimethyl phosphate (TMP) yields a similar quantity of methanol.

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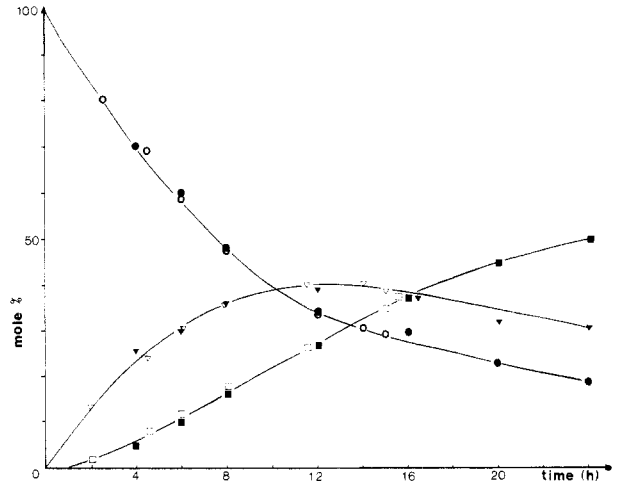

Figure 1. Reaction of 1 in D_2O at 60 °C: composition of the mixture at different times: (○, ●) 1; (□, ■) 2; (▽, ▼) 3 + 4. Open and full symbols correspond to data obtained by ^{13}C and ^1H NMR analysis, respectively.

ization of 1 was a bimolecular process, two additional phosphates, the N-methylated substrate 3 and O-demethylated substrate 4 should appear in the reaction mixture as intermediates. The formation of 3 and 4 was demonstrated when a more dilute solution of 1 (0.9 M) in D_2O was heated under reflux for 2 h. In addition to the signals corresponding to unreacted 1 (ca. 12%), 2 (ca. 63%), and methanol (ca. 15%), the ^1H NMR spectrum of the solution revealed signals that could reasonably be assigned to the monocation 3 and monoanion 4. For example, the *O*-methyl groups of 3 and 4 appear as doublets at δ 3.85 (J = 11.5 Hz) and 3.64 (J = 11 Hz), respectively.[11] When a 1.97 M solution of 1 in D_2O was kept at 60 °C and the reaction progress examined periodically by ^1H NMR spectroscopy, changes in concentrations of individual species with time gave a plot typical for systems involving the transient formation of intermediates. The intermolecular mechanism for reaction 1 was also supported by ^{13}C NMR spectra of the reaction mixtures. As in the ^1H NMR spectra, isomerization of 1 results in shifts of the signals of the individual atoms. For example, the *O*-methyl and the methylene carbon atoms in 2 gave rise to signals shifted upfield (2.1 and 7.1 ppm, respectively), relative to the corresponding signals in 1, while the intermediate formation of 3 can be demonstrated by the transient appearance of additional signals such as that of the CH_3 ester group shifted 0.7 ppm *downfield* and the CH_2 group shifted 5.3 ppm upfield relative to 1. The appearance of a new signal, for the N^+Me group in 2 (45.7 ppm), is preceeded by the transient formation of a signal at 46.2 ppm—the N^+Me absorption of 3. The plots of concentrations of substrate, product, and reaction intermediates as a function of time, based on the intensity of the corresponding signals in the ^{13}C and the ^1H NMR spectra of the mixture, are shown in Figure 1.

Although the initial formation of the ionic intermediates 3 and 4, followed by their disappearance, demonstrates qualitatively the bimolecular nature of the isomerization, it is kinetic measurements, and in particular the effect of substrate concentration on the reaction rate, which provide quantitative evidence for the intermolecular mechanism. ^1H NMR spectroscopy was used to measure the rates of the conversion of 1 into 2 in D_2O at 60 °C for four different initial concentrations of 1. The first- and second-order rate constants were determined for each run, and the results are summarized in Table I.

Table I. Rates of the O → N Methyl Transfer in Dimethyl 2-Pyridylmethyl Phosphate (D_2O, 60 °C)

a_0, M	10^5k_1, s^{-1}	r	10^5k_2, M^{-1} s^{-1}	r
1.97	1.83	0.9888	2.73	0.9984
1.50	1.80	0.9924	3.08	0.9987
1.17	1.53	0.9878	3.05	0.9924
0.55	1.03	0.9841	3.43	0.9958
av	1.55 ± 0.37	0.9883 ± 0.0035	3.07 ± 0.29	0.9963 ± 0.0029

The isomerization of 1 is described much better by the second-order than by the first-order rate law; the values of k_1 not only show a greater standard deviation than the k_2 values (24% vs. 9%), but they decrease steadily with the decrease in a_0, and, for all runs, the first-order plots showed distinct curvatures. The second-order kinetics of the isomerization was further tested by plotting the values of the half-lives for the reaction vs. the $1/a_0$ values.[12] A good straight line was obtained (r = 0.9989) and the value of $k_2 = 3.78 \times 10^{-5}$ M^{-1} s^{-1} determined from the slope agrees reasonably well with the average value obtained from the kinetic runs. We have found that ^{13}C NMR spectroscopy can also be successfully used for measuring the rate of the isomerization reaction. The rate of reaction 1 was followed in D_2O at 60 °C by measuring the intensity of the CH_2 signal in 1, and for a_0 = 2.04 M, the obtained value of $k_2 = 3.10 \times 10^{-5}$ M^{-1} s^{-1} (r = 0.9910) is in excellent agreement with the value determined by means of the ^1H NMR spectroscopy. A third possible approach by which to investigate the isomerization 1 → 2 and to observe the participation of the intermediates 3 and 4 could be based on ^{31}P NMR spectroscopy. Our reaction could be followed qualitatively by this method, because as the isomerization progressed, the substrate's signals (−9.26 ppm) was initially replaced by an upfield signal at δ −15.03 (probably the absorption of the anionic intermediate 4, which subsequently gave way to the signal of the product 2 (−12.85 ppm). However, since the bonding characteristics at phosphorus do not change significantly upon isomerization, and since the ^{31}P chemical shift is rather insensitive to the chemical identity of the groups bonded to the phosphate oxygens,[13] the ^{31}P signals observed are too close to each other to allow accurate determination of the concentrations of the respective species. The ^{31}P NMR spectra were therefore not suitable for rate determinations.

Experimental Section

^1H NMR spectra were recorded with a Varian XL100 spectrometer with DSS as internal standard.

^{13}C NMR spectra were obtained in 10-mm tubes at 22.03 MHz with a Bruker HS-90 FT spectrometer. All shifts are quoted relative to external dioxane in D_2O at δ −67.7 relative to Me_4Si.

^{31}P NMR spectra were obtained at 36.44 MHz in 10-mm tubes with a Bruker HS-90 spectrometer. All shifts are quoted relative to neat TMP present in a 2-mm coaxial capillary.

1 was prepared by adding sodium 2-pyridylmethoxide in C_6H_6 to a solution of $(MeO)_2P(O)Cl$ in Et_2O at 8 °C under N_2. After filtration and evaporation of solvent, the product was purified by column chromatography (silica gel, 4:1 $CHCl_3$/EtOH): pale yellow oil, 53%; MS, m/e 217 (M^+); ^1H NMR (D_2O) δ 3.77 (d, 6 H, J = 11 Hz, 2 × OCH_3), 5.08 (d, 2 H, J = 9 Hz, CH_2), 7.47 (m, 2 H, 3-, 5-H), 7.83 (m, 1 H, 4-H); 8.53 (d, 1 H, J = 4 Hz, 6-H). Anal. Calcd for $C_8H_{12}NO_4P$: C, 44.25; H, 5.57; N, 6.45. Found: C, 44.40; H, 5.60; N, 6.55. 2: ^1H NMR (D_2O) δ 3.68 (d, 3 H, J

(11) The same *O*-methyl group signals were observed when 1 was treated with Me_2SO_4 (*N*-methylation) or with NaI (O-demethylation), respectively.

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= 11 Hz, OCH_3), 4.42 (s, 3 H, NCH_3), 5.38 (d, 2 H, J = 8 Hz, CH_2); 7.97-8.80 (m, 3 H, 3-, 4-, 5-H), 9.02 (d, 1 H, J = 6 Hz, 6-H).

The rates of disappearance of 1 were determined by measuring the decrease in the integrated area of the methylene doublet for the substrate (5.08 ppm) relative to the total integrated area for the methylene signals involved. All reactions were followed to 61-81% conversion. The values of k_1 and k_2 were calculated as slopes of the plots of the values of ln $(a_o/a_o - x_t)$ or x_t/a_o $(a_o - x_t)$ vs time.

Quantitatively meaningful integrals of ^{13}C signals were obtained by using 40° pulses, followed with a 6-8-s pulse delay, during which time the BB decoupler was gated off. In this way all ^{13}C signals except C-2 of the pyridine ring, yielded quantitative integrals to within ±5%. Typically 10^3 transients were collected, taking <1.8 h.

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Registry No. 1, 99668-67-4; 2, 99668-68-5; $(MeO)_2P(o)Cl$, 813-77-4; sodium 2-pyridylmethoxide, 99668-69-6.

The Conversion of Tetrahydroquinoline into Derivatives of 8*H*-Pyrido[3,2,1-*jk*][1,3]benzodiazepines via [2,3]-Sigmatropic Rearrangements

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Although pyridobenzodiazepines have been previously reported in the literature,[1] the pyrido[3,2,1-*jk*][1,3]-benzodiazepine ring system does not appear to be known. Recently, we described the use of tetrahydroquinoline as a starting material for the synthesis of derivatives of 4*H*-pyrrolo[3,2,1-*ij*]quinoline.[2] This transformation, which is exemplified by the conversion of **1** into **2**, utilized the general concept of [2,3]-sigmatropic rearrangements of ylides derived from aza sulfonium salts.[3] These rearrangements, which we have exploited in the synthesis of indoles[4] and oxindoles,[5] are widely applicable to a variety of ring systems bearing both electron-donating and electron-withdrawing substituents. Thus, it seemed reasonable that we should be able to apply this same methodology in the synthesis of the 8*H*-pyrido[3,2,1-*jk*][1,3]benzodiazepines, a class of compounds which is attractive because of its close relationship to pharmaceutically intriguing structures.[1]

Treatment of 2-(methylthio)-*N*-methylacetamide[6] with 0.95 equiv of chlorine at -78 °C gave the chlorosulfonium chloride salt **3**. Dropwise addition of **1** to a methylene chloride solution of **3**, followed by ylide formation using triethylamine as base, afforded a 71% yield of **4**. Raney nickel reduction of **4** produced **5** in 85% yield. When a benzene solution of **5** was refluxed with paraformaldehyde for 12 h, the cyclization product, 2-methyl-1,2,9,10-tetrahydro-8*H*-pyrido[3,2,1-*jk*][1,3]benzodiazepin-3(4*H*)-one (**6**) was obtained in 76% yield.

Reduction of **5** with lithium aluminum hydride gave an 84% yield (71% based on **4**) of **7** as an oil. When **7** was refluxed in benzene with 1 equiv of paraformaldehyde, a 91% yield of 1,2,3,4,9,10-hexahydro-2-methyl-8*H*-pyrido-[3,2,1-*jk*][1,3]benzodiazepine (**8**) was isolated. Refluxing **7** in tetrahydrofuran with 1 equiv of 1,1′-carbonyldiimidazole produced a 56% yield of the cyclic urea **9**.

The investigation outlined above makes the 8*H*-pyrido[3,2,1-*jk*][1,3]benzodiazepines readily available for the first time.

Experimental Section

α-(Methylthio)-α-(1,2,3,4-tetrahydroquinolin-8-yl)-*N*-methylacetamide (4). Chlorine (4.0 mL, 88 mmol) was con-

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