mmol) of 1. Upon dissolution, 4.41 g (20 mmol) of 3,5-di-*tert*-butyl-*o*-benzoquinone was added, the reaction stirred 1 h, an additional 4.41 g (20 mmol) of the quinone added, and stirring continued for 30 min. The reaction was partitioned between ice water and diethyl ether, the pH was adjusted to 8, the layers were separated, and the aqueous phase was extracted three more times with ether. The combined ethyl acetate extracts were dried (Na_2SO_4), filtered, and concentrated at reduced pressure to yield 8.07 g (67%) of 4:[3] NMR (acetone-d_6, internal Me_4Si) δ 8.27 (broad s, 1 H), 7.48 (d, J = 2 Hz, 1 H), 7.28 (d, J = 2 Hz, 1 H), 5.91 (broad s, 2 H), 5.12 (s, 1 H), 4.86 (AB center, J = 13 Hz, 2 H), 3.82 (s, 3 H), 3.48 (broad s, 5 H), 3.07 (broad t, 2 H), 2.16–2.75 (complex m, 4 H), 1.47 (s, 9 H), 1.35 (s, 9 H); mass spectrum (methyl ester), *m/e* 616 (M^+, 11), 615 (26), 555 (61), 554 (100).

Registry No.—**1**, 64162-09-0; **3**, 3383-21-9; **4**, 64130-72-9; **6**, 64130-73-0; **7**, 64147-38-2; **8**, 64130-74-1; alanine, 56-41-7; β-phenylalanine, 63-91-2; aminoadipic acid, 542-32-5.

References and Notes

(1) A. Schöenberg, R. Moubasher, and A. Mostafa, *J. Chem. Soc.*, 176 (1948), and references therein.
(2) A. Strecker, *Justus diebigs Ann. Chem.*, **123**, 363 (1862).
(3) All products were in agreement with ^1H and ^{13}C NMR as well as combustion analyses and mass spectroscopy.
(4) E. J. Corey and K. Achiwa, *J. Am. Chem. Soc.*, **91**, 1429 (1969). For a list of other methods available for the formation of benzoxazoles see J. W. Cornforth, in "Heterocyclic Compounds", Vol. V, R. C. Elderfield, Ed., Wiley, New York, N.Y., 1957, Chapter 6.
(5) The ^{13}C NMR chemical shifts and ^1H–^{13}C coupling constants of **6** allow unequivocal assignment of the substitution pattern. Although substituent effects are not strictly additive, especially when ortho groups are present, the predicted chemical shifts using benzoxazole and *tert*-butylbenzene as models correlated well for a 5,7-disubstituted benzoxazole when used in conjunction with ^1H–^{13}C coupling data. Long-range ^1H–^{13}C coupling constants can be structurally useful especially in aromatic systems where the most significant long-range coupling is via a three-bond pathway.[6] In **6**, the aromatic carbons bearing hydrogen (113.7 and 118.7 ppm) can easily be determined from the large one-bond couplings, and they each exhibit a single three-bond coupling. The carbon resonanances at 147.2 and 133.4 ppm must be assigned to those bearing *tert*-butyl groups, due to long range couplings with the *tert*-butyl hydrogens. Of the two remaining aromatic signals, the one at 141.8 ppm shows no long-range coupling, while the signal at 147.2 ppm is a triplet ($J \cong$ 10 Hz), demanding two ring hydrogens which are at a distance of three bonds. The predicted chemical shift values (see Figure 1) clearly support the 5,7 isomer while ruling out 4,6 disubstitution.
(6) (a) F. J. Weigert and J. D. Roberts, *J. Am. Chem. Soc.*, **89**, 2967 (1967); (b) L. Ernst, V. Wray, V. A. Chertkov, and N. M. Sergeyev, *J. Magn. Reson.*, **25**, 123 (1977).

Photoproducts of Thymine and Uracil. Syntheses of the Four Bipyrimidine Combinations

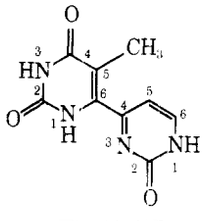
Jerry D. Bryant and Nelson J. Leonard*

School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801

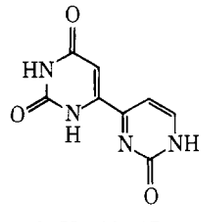
Received June 27, 1977

Convenient first syntheses have been devised for the following bipyrimidines: 6-(2-hydroxypyrimidin-4-yl)thymine, Thy(6-4)Pyo (**1**); 6-(2-hydroxypyrimidin-4-yl)uracil, Ura(6-4)Pyo (**2**); 6-(2-hydroxy-5-methylpyrimidin-4-yl)thymine, Thy(6-4)m^{5}Pyo (**3**); and 6-(2-hydroxy-5-methylpyrimidin-4-yl)uracil, Ura(6-4)m^{5}Pyo (**4**). The first three of these are among the non-cyclobutane photoproducts resulting from DNA or from frozen aqueous solutions of thymine, thymidine, uracil, or uridine under appropriate conditions. The synthetic methodology involved (1) the combination of 6-lithiopyrimidines with β-alkoxyacroleins, (2) oxidation to the corresponding masked β-dicarbonyl intermediates, (3) condensation of these with guanidine carbonate to form substituted aminobipyrimidines, and (4) diazotization and hydrolysis to furnish the desired products **1–4**. The spectroscopic properties, especially the ultraviolet excitation and fluorescence emission, are of special interest within the series and in comparison with the photoproducts of natural origin.

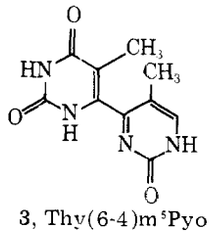
Considerable interest has been displayed in the isolation and identification of photoproducts of DNA as a means of investigating possible photobiological implications. Along with the familiar pyrimidine photodimers of the cyclobutane structure,[1] a series of bipyrimidine photoproducts has been accumulated by Wang and Varghese, exemplified by formulas **1–3**.[2] (As drawn, these formulas are not intended to portray a preferred torsional geometry.) The first of these, Thy(6-4)Pyo (**1**),[3] was identified as a product from the trifluoroacetic acid hydrolysates of DNA irradiated with far-UV light[4–6] and from photolysis of a frozen solution of thymine and uracil.[7] Ura(6-4)Pyo (**2**) was isolated from the UV irradiation of uracil in frozen aqueous solution[8] and from the acid hydrolysates of uridine irradiated in frozen aqueous solution.[9] Thy(6-4)-m^{5}Pyo (**3**) was obtained from the UV irradiation of frozen solutions of thymine[10,11] and of thymidine,[12] followed by acid treatment.



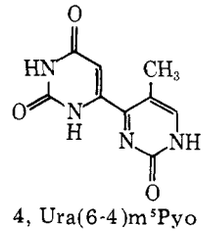
1, Thy(6-4)Pyo



2, Ura(6-4)Pyo



3, Thy(6-4)m^{5}Pyo



4, Ura(6-4)m^{5}Pyo

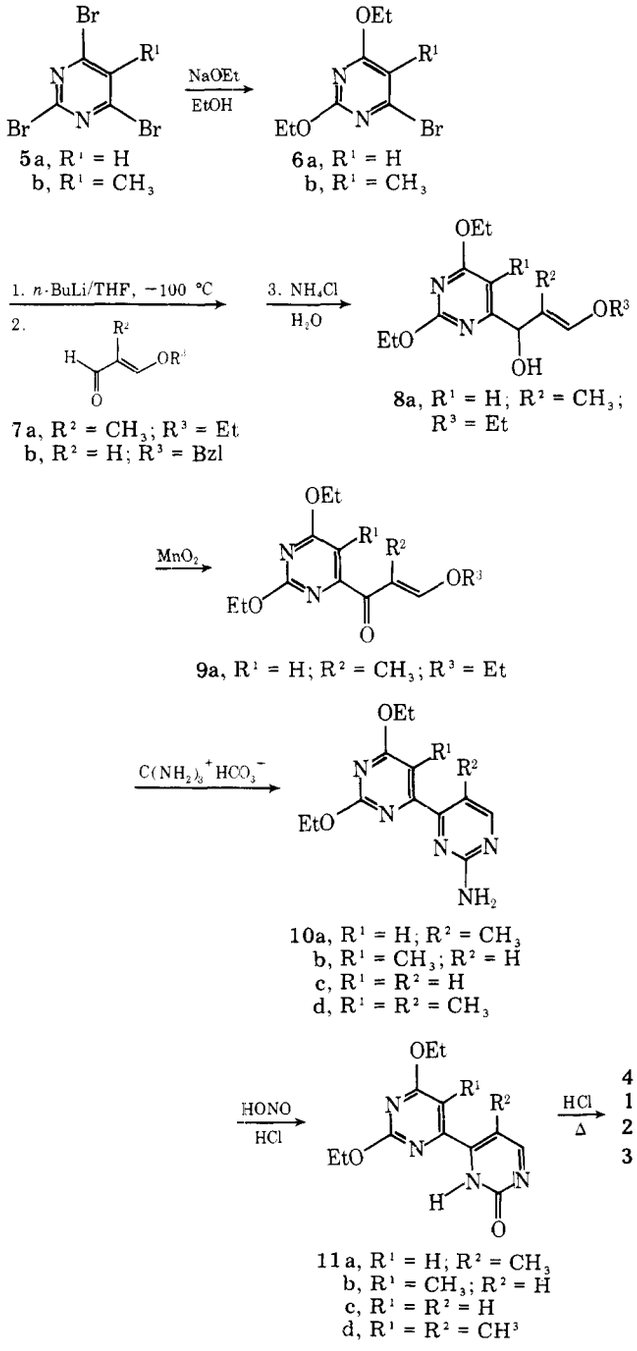
As part of our continuing interest in the structure determination and synthesis of nucleic acid radiation products,[13–17] we have devised unequivocal syntheses of compounds **1–3** which also provide independent confirmation of their assigned structures. We have also synthesized Ura(6-4)m^{5}Pyo (**4**) as a potential photoproduct which is theoretically accessible by a photoadduction pathway similar to that suggested for Ura(6-4)Pyo.[9]

An examination of the literature discloses several synthetic routes to bipyrimidines. Symmetrical 2,2′-, 4,4′-, and 5,5′-bipyrimidines have been obtained via an Ullmann or a Busch coupling reaction.[18,19] Symmetrical 4,4′- and 5,5′-bipyrimidines have also been prepared via construction of the carbon backbone followed by condensation with 2 equiv of a urea derivative.[20–23] Unsymmetrical 2,2′- and 2,4′-bipyrimidines

0022-3263/78/1943-0511$01.00/0

were obtained via the condensation of β-dicarbonyl compounds with 2- or 4-amidinopyrimidines.[24] 5-Lithiopyrimidines were found to undergo self-reaction to form 4,5′-bipyrimidines,[25] with attendant restriction of the substitution pattern in the two rings.

Recent work in our laboratory has demonstrated the applicability of methods employing the attachment of a carbonyl backbone for a second pyrimidine ring to an existing pyrimidine ring.[15] This route was adopted in the present work. In outline, it was envisaged that the ring closure of a β-alkoxy(α-alkyl)acryloyl moiety with guanidine[26] could lead to bipyrimidines that were two simple steps removed from the desired products. The major synthetic problem thus involved the attachment of a masked β-dicarbonyl precursor to the 6 position of an appropriately substituted pyrimidine ring. The approach through a combination of 6-lithiopyrimidines[27] with β-alkoxyacrylates[28] was not pursued because of anticipated difficulties with a competing Michael reaction or a diaddition of the lithio derivative. Such difficulties could be avoided through reaction of the readily available β-alkoxyacroleins with the 6-lithiopyrimidines and subsequent oxidation of the intermediate carbinols.



5a, R^1 = H
b, R^1 = CH_3

6a, R^1 = H
b, R^1 = CH_3

7a, R^2 = CH_3; R^3 = Et
b, R^2 = H; R^3 = Bzl

8a, R^1 = H; R^2 = CH_3; R^3 = Et

9a, R^1 = H; R^2 = CH_3; R^3 = Et

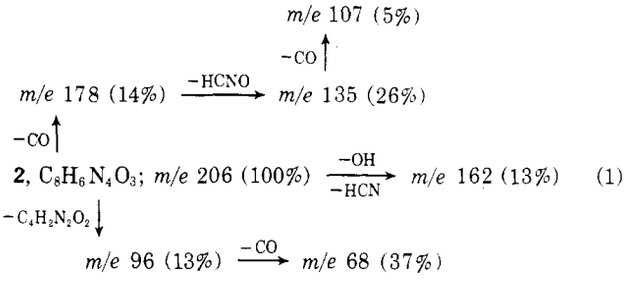
10a, R^1 = H; R^2 = CH_3
b, R^1 = CH_3; R^2 = H
c, R^1 = R^2 = H
d, R^1 = R^2 = CH_3

11a, R^1 = H; R^2 = CH_3
b, R^1 = CH_3; R^2 = H
c, R^1 = R^2 = H
d, R^1 = R^2 = CH^3

4
1
2
3

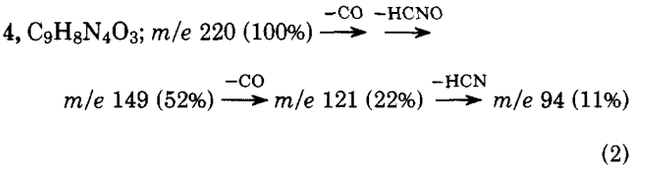
Langley[27] previously synthesized 6-bromo-2,4-diethoxypyrimidine (4-bromo-2,6-diethoxypyrimidine, **6a**) from 2,4,6-tribromopyrimidine (**5a**) and described conditions for the generation of the corresponding lithio derivative by halogen–metal interchange using *n*-butyllithium. Using similar conditions, we obtained 6-bromo-2,4-diethoxy-5-methylpyrimidine (**6b**) from 5-methyl-2,4,6-tribromopyrimidine (**5b**) and likewise observed halogen–metal interchange with *n*-butyllithium at low temperature. Each of the two 6-lithiopyrimidines was treated separately with β-ethoxy-α-methylacrolein (**7a**)[29] and β-benzyloxyacrolein (**7b**)[30,31] to yield the corresponding carbinol derivatives **8** after quenching with 20% aqueous NH_4Cl solution. The pyrimidinecarbinols **8** were oxidized with activated MnO_2[32] to the corresponding acryloylpyrimidines **9**, and these were condensed with guanidine carbonate to form the substituted aminobipyrimidines **10.** It was unnecessary to isolate the intermediates **8** and **9** in pure form, although this was done in the **a** series as a control. Diazotization of compounds **10a–d** followed by hydrolysis of the intermediates **11a–d** furnished the desired products **1–4.**

At every stage in the unequivocal synthetic process the compounds were fully characterized by elemental analyses and by ultraviolet, nuclear magnetic resonance, and mass spectrometry. The properties of the final products could be compared with those previously reported for the corresponding photoproducts. The mass spectra determined at either 70 or 10 eV showed a predominant molecular ion for **1–4.** The fragmentation pattern for Thy(6-4)Pyo (**1**) matched very closely the fragment ions and relative intensities in the spectrum of the photoproduct as reported by Fenselau and Wang.[33] The same was generally true for the sample of Thy(6-4)m^{5}Pyo (**3**) from synthetic and photolytic sources. The fragmentation pattern for synthetic Ura(6-4)Pyo (**2**) exhibited parallel behavior to the fragmentations recorded for **1** and **3,** as shown in eq 1.



(1)

The fragmentation pattern for synthetic Ura(6-4)m^{5}Pyo (**4**) was of interest vis-à-vis that of the isomeric monomethyl Thy(6-4)Pyo (**1**)[33] since neither exhibited an M − 15 peak, whereas the dimethyl compound Thy(6-4)m^{5}Pyo (**3**) lost a methyl radical. The major fragmentation pathway that we observed at 10 eV for Ura(6-4)m^{5}Pyo (**4**) is shown in eq 2.



(2)

The pair of monomethyl isomers **1** and **4** provided checks for the internal consistency of the NMR assignments throughout the synthetic series **1–4.** The NMR data for the synthetic products **1–3** were consistent with the published proton chemical shifts for the photoproducts if a correction

Table I. Corrected Fluorescence Data[a]

Compd	Registry no.	pH	Fluorescence excitation, nm	Fluorescence emission, nm[b] λ_{max}	$\lambda + \frac{1}{2}$	$\lambda - \frac{1}{2}$	Φ[c]
10a	64188-72-3	7.4	317, 278	465	522	421	0.20
b	64188-73-4	7.4	300, 272 sh	438	505	397	0.065
c	64188-74-5	7.6	312	445	500	407	0.10
d	64188-75-6	7.6	308, 275	435	505	393	0.11
11a	64188-76-7	7.6	328, 270	475	552	415	0.049
b	64188-77-8	7.7	320, 278 sh	445	525	390	0.087
c	64188-78-9	7.8	340 sh, 315	427	480	392	0.067
d	64188-79-0	7.5	310, 277 sh	405	454	373	0.045
4	64188-80-3	9.1	330, 277	513	598	454	0.015[d]
		9.1	330, 277	513	587	459	0.029[e]
1	18694-06-9	9.1	315	484[f]	551	430	0.016
2	35612-19-2	8.9	335, 303	471[g]	552	411	0.032
3	20545-68-0	8.8	315, 270	513[h]	597	450	0.014

[a] In water at 300 K. [b] Wavelengths representing half-heights on each side of the maximum are given. [c] Based on $\Phi = 0.70$[38] for quinine sulfate in 0.1 N H_2SO_4. [d] Excitation at 325 nm. [e] Excitation at 280 nm. [f] λ_{max} 456 nm reported.[36] [g] λ_{max} 444 nm reported.[36] [h] λ_{max} 387 nm reported.[36]

factor was applied to the latter, as had been shown to be necessary in other analogous comparisons.[17,34,35]

The ultraviolet absorption spectra of the four precursors represented by formula **10** and determined at the pH of their solutions in water and in strong acid are sufficiently complex so that unperturbed transitions are not readily assignable. The probability of more coplanarity (two coplanar conformations are possible) being achieved in **10c** than in **10d** is reflected in the molar extinction coefficients and in the wavelengths of the absorption maxima. The ring to which the methyl group is attached, i.e., its position in the monomethyl isomers **10a** and **10b**, has a greater influence than can be accounted for simply by the steric hindrance of one *o*-methyl group compared with two or none. Similar statements can be made for the set of precursors **11**. As for the final products, Hauswirth and Wang[36] have discussed the ultraviolet absorption spectra of compounds **1–3**. A comparison of the spectra of **1** with those of its position isomer **4** indicates that such discussion should take into consideration additional factors such as tautomeric forms, coplanar conformations, and ground-state and transition dipoles, as well as torsional angles relating to simple biphenyls.

The precursors **10** and **11** are all fluorescent, with emission maxima ranging from 405 to 475 nm and quantum yields ranging from 0.04 to 0.20. No consistent pattern over the dual **a–d** series was readily discernible. The data obtained at 300 K in water are assembled in Table I, along with the excitation, emission, and fluorescence yield characteristics of the highly purified, synthetic, bipyrimidines **1–4**. The corrected fluorescence excitation maxima match well with those reported by Hauswirth and Wang[36] for the photoproducts **1–3**. Our corrected emission maxima for **1** and **2** show some discrepancy (+ 27–28 nm) from those reported. The main point of difference is that we observe a fluorescence emission maximum at 513 nm for Thy(6-4)m^{5}Pyo (**3**) in place of the reported 387-nm value.[36] Since no synthetic precursor of **3** exhibits a fluorescence maximum at such long wavelength, since great care was taken in its purification, and since the determination was readily duplicated, we have confidence in the 513-nm value. Moreover, the fluorescence emission maximum observed for Ura(6-4)m^{5}Pyo (**4**) was 513 nm upon excitation at either 227 or 330 nm. As in the case of excitation, there are too many variables to be considered to define the relaxed fluorescing states (at 300 K) in simple terms. The quantum yield of fluorescence was greatest (0.032) for the unmethylated compound **2**, and the quantum yields for the mono- and dimethylated compounds **1**, **4**, and **3** were comparable and approximately half this value (Table I). Location of the methyl group on the pyrimidone ring, as in Ura(6-4)m^{5}Pyo (**4**) and in its precursors **10a** and **11a**, had the greatest effect on the fluorescence properties. Accordingly, the data for compound **4** must be included in any rationalization of the absorption and emission properties of the photoproduct series **1–3** recognized at this time.

Finally, in this work we have provided "improved methods" for preparing the photoadducts of thymine and uracil "in sufficient quantities for studying their possible biological importance." [2] The biological role of products such as **1–4** is not yet clear; the data permit the interpretation that either such photoproducts (i.e., from DNA) are not lethal or that they are lethal but can be repaired under certain conditions.[37] Compounds **1–4** showed no antibacterial activity at 0.1 mg/mL against *B. subtilis*, *E. coli*, and *P. atrovenatum* and no bacterial mutagenic activity in the Ames test.

Experimental Section

Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on Varian A-60, EM-390, or HA-100 spectrophotometers using tetramethylsilane as an internal standard. Mass spectra were run on a Varian MAT CH-5 spectrometer (10 and 70 eV), coupled with a 620i computer and a STATOS recorder. Ultraviolet absorption spectra were obtained on a Beckman Acta M VI spectrophotometer. Corrected fluorescence emission and excitation spectra were measured on a Spex Fluorolog spectrofluorometer. Microanalyses were performed by Mr. Josef Nemeth and his staff, who also weighed samples for quantitative ultraviolet absorption studies. Thin-layer chromatographs were run on EM silica gel f-254 plates (thickness, 0.25 mm).

5-Methyl-2,4,6-tribromopyrimidine (5b). A mixture of phosphorus oxybromide (69.6 g, 0.24 mol), 5-methylbarbituric acid[39] (8.24 g, 0.058 mol), *N,N*-dimethylaniline (16 mL), and toluene (100 mL) in a 500-mL flask was heated at reflux for 5 h. The organic layer was separated, washed with H_2O, dried, and concentrated in vacuo to yellow solid **5b** (10 g, 52% yield). An analytical sample was obtained by recrystallization from absolute ethanol: mp 136–137.5 °C; NMR ($CDCl_3$) δ 2.52 (s, 3, CH_3); MS *m/e* (rel intensity) 328 (37), 330 (100), 332 (99), 334 (33).

Anal. Calcd for $C_5H_3Br_3N_2$: C, 18.14; H, 0.91; N, 8.47. Found: C, 18.35; H, 0.90; N, 8.51.

6-Bromo-2,4-diethoxy-5-methylpyrimidine (4-Bromo-2,6-diethoxy-5-methylpyrimidine, 6b). After the addition of **5b** (11.9 g, 0.036 mol) to benzene (40 mL) and stirring until dissolution was complete, absolute ethanol (35 mL) was added, and the reaction flask was cooled to 5 °C. During the next 60 min a sodium ethoxide solution generated from sodium (1.65 g, 0.072 g-atom) in absolute ethanol (35 mL) was dripped in, and the resulting mixture was stirred overnight. Following sodium bromide precipitation through the addition of anhydrous ethyl ether (50 mL), the mixture was filtered with the aid of additional ether (3 × 15 mL). Concentration of the filtrate in vacuo

left a white solid which was treated with anhydrous ethyl ether (100 mL) and then refiltered in order to remove residual salt. The removal of the filtrate solvent provided a white solid product (8.5 g, 91% yield). From examination of the MS, NMR, and microanalytical data, it was concluded that the reaction product was a mixture of **6b** and the isomeric 2-bromo-4,6-diethoxy-5-methylpyrimidine in a relative proportion of 77:23. Repeated fractional crystallization from 50% aqueous ethanol led to an enrichment of the major isomer **6b** to a purity of >98% (by NMR): 4.16 g, 44% yield; mp 75–76 °C; NMR ($CDCl_3$) δ 1.41 (t, J = 7 Hz, 6, OCH_2CH_3), 2.17 (s, 3, 5-CH_3), 4.42 and 4.48 (q, J = 7 Hz, 2 each, OCH_2CH_3); MS m/e 262, 260 (M^+).

Anal. Calcd for $C_9H_{13}BrN_2O_2$: C, 41.39; H, 5.02; N, 10.73. Found: C, 41.29; H, 4.94; N, 10.63.

That the structure of the isolated major isomer was in fact **6b** was proven through the following procedure. The major isomer (273 mg, 1.05 mmol), dissolved in freshly distilled THF (10 mL), was cooled to −100 °C under a positive nitrogen atmosphere. A dry ice cooled solution of n-butyllithium (1 mL of a 2.4 M solution in hexane, 2.4 mmol) was added to the mixture of THF and precipitated reactant, and the resultant reaction mixture was warmed quickly to −65 °C. At this temperature, an orange homogeneous solution resulted, and the cooling bath was replaced. After 20 min of stirring, the reaction solution was inversely quenched with a mixture of ethyl ether (50 mL) and a 20% aqueous NH_4Cl solution (50 mL). Following the extraction of the aqueous layer with ethyl ether (2 × 50 mL), the organic layers were combined, dried, and concentrated in vacuo to an oil (180 mg, 94%). Analyses of the product via NMR, TLC, and MS matched in all respects an authentic sample of 2,4-diethoxy-5-methylpyrimidine.

2,4-Diethoxy-6-(1-ethoxy-3-hydroxy-2-methylpropen-3-yl)pyrimidine (8a). A solution of 6-bromo-2,4-diethoxypyrimidine (4-bromo-2,6-diethoxypyrimidine, **6a**)[27] (2.0 g, 8.1 mmol) in freshly distilled THF (50 mL) was cooled to −100 °C under a positive nitrogen pressure. A solution of n-butyllithium (3.7 mL of a 2.4 M solution in hexane, 8.9 mmol) cooled in dry ice was added at such a rate that the internal temperature did not exceed −90 °C. The pyrimidine solution was stirred for 5 min, and a solution of β-ethoxy-α-methylacrolein (**7a**,[29] 1.39 g, 12.25 mmol) in THF (5 mL) was added over a 15-s interval. The solution was stirred at −70 °C for 50 min and then allowed to warm to −20 °C over the next 25 min. The reaction was quenched with a mixture of 50 mL of Et_2O and 75 mL of a 20% aqueous NH_4Cl solution. After separation of the organic layer, the aqueous layer was extracted with 50 mL of Et_2O, and the ether extracts were combined and dried over magnesium sulfate. After filtration, the solvent was removed in vacuo to leave a light orange oil. Addition of 25 mL of petroleum ether and refrigeration at −20 °C for 12 h afforded white crystals (0.95 g) which, on washing with excess petroleum ether, proved to be analytically pure. Removal of the petroleum ether in vacuo, addition of 25 mL of pentane, and refrigeration at −20 °C provided additional, slightly yellow crystals: 0.26 g, total yield 53%; mp 61–62.5 °C; NMR ($CDCl_3$) δ 1.27, 1.37, and 1.44 (t, J = 7 Hz, 3 each, OCH_2CH_3), 1.46 (d, J = 1 Hz, 3, $=CCH_3$), 4.2 (br s, 1, CH–OH), 3.85, 4.39, and 4.43 (q, J = 7 Hz, 2 each, OCH_2CH_3), 4.82 (br s, 1, CH–OH), 6.25 (q, J = 1 Hz, 1, CH=), 6.3 (s, 1, 5-H); MS m/e 282 (M^+).

Anal. Calcd for $C_{14}H_{22}N_2O_4$: C, 59.55; H, 7.85; N, 9.92. Found: C, 59.44; H, 7.70; N, 9.85.

2,4-Diethoxy-6-(3-ethoxy-2-methylacryloyl)pyrimidine (9a). To pyrimidinecarbinol **8a** (270 mg, 0.96 mmol) in benzene (1.5 mL) and petroleum ether (1.5 mL) was added activated MnO_2[32] (448 mg, 5.2 mmol), and the mixture was stirred at room temperature for 24 h. Additional MnO_2 (200 mg, 2.3 mmol) was then added. After 72 h, the reaction mixture was filtered with the aid of benzene (2 × 20 mL), and the filtrate was concentrated in vacuo. The residual oil (249 mg) solidified on standing. This crude product (<10% carbinol on the basis of NMR data) was used without purification in subsequent reactions. Analytical material could be obtained by allowing the reaction to proceed entirely to the ketone, as followed by TLC (silica gel; $CHCl_3$/absolute EtOH, 9:1) and recrystallization of this product from petroleum ether. This sequence typically required additional MnO_2 and 6–7 days reaction time: mp 74–74.5 °C; NMR ($CDCl_3$) δ 1.36, 1.41, and 1.45 (t, 3 each, OCH_2CH_3), 1.87 (d, J = 1 Hz, 3, $=CCH_3$), 4.14, 4.46, and 4.50 (q, 2 each, OCH_2CH_3), 6.69 (s, 1, 5-H), 7.84 (q, J = 1 Hz, 1, CH=); MS m/e 280 (M^+).

Anal. Calcd for $C_{14}H_{20}N_2O_4$: C, 59.98; H, 7.19; N, 9.99. Found: C, 59.70; H, 6.99; N, 9.95.

6-(2-Amino-5-methylpyrimidin-4-yl)-2,4-diethoxypyrimidine (10a). The crude pyrimidinyl ketone **9a** (220 mg) mixed with guanidine carbonate (149 mg, 1.24 mmol) in 10 mL of absolute ethanol was heated at reflux for 16 h. The reaction mixture was filtered, and the filtrate was concentrated in vacuo to leave a light brown solid. Petroleum ether (20 mL) was added and decanted off after stirring for 5 min. The solid residue was then extracted, i.e., stirred and decanted, with anhydrous ethyl ether (2 × 20 mL), followed by chloroform (2 × 20 mL). Evaporation of the ether layer in vacuo yielded 127 mg of analytically pure white product. Evaporation of the chloroform extracts in vacuo yielded 13 mg of additional product (total yield 65%): mp 110–111 °C; UV λ_{max} (H_2O, pH 0.9) 325 nm (ϵ 5610), 292 sh (4900); (pH 8.9) 313 (5170), 271 (5140); NMR ($CDCl_3$) δ 1.42 and 1.46 (t, 3 each, OCH_2CH_3), 2.42 (s, 3, 5′-CH_3), 4.52 and 4.55 (q, 2 each, OCH_2CH_3), 5.35 (br s, 2, NH_2), 7.02 (s, 1, 5-H), 8.34 (s, 1, 6′-H); MS m/e 275 (M^+).

Anal. Calcd for $C_{13}H_{17}N_5O_2$: C, 56.71; H, 6.22; N, 25.44. Found: C, 56.43; H, 6.45; N, 25.17.

6-(2-Aminopyrimidin-4-yl)-2,4-diethoxypyrimidine (10c). The generation of 2,4-diethoxy-6-lithiopyrimidine from 6-bromo-2,4-diethoxypyrimidine (**6b**,[27] 2.0 g, 8.1 mmol) and n-butyllithium (3.5 mL of a 2.4 M solution in hexane, 8.4 mmol) in THF (50 mL) was accomplished in the manner previously described for **8a**. After the addition of β-benzyloxyacrolein **7b**[30,31] (1.4 g, 8.9 mmol) in THF (5 mL), the reaction solution was stirred and quenched as described for **8a**. The concentration of the $MgSO_4$-dried ether layers left a red oil which was subsequently oxidized with activated MnO_2 (1.5 g, 17 mmol) in 5 mL of petroleum ether/benzene (2:1). When no further oxidation was indicated by TLC (benzene/EtOAc, 4:1; I_2 visualization), the mixture was filtered with additional benzene, and the filtrate was concentrated in vacuo. The residual oil was mixed with guanidine carbonate (2.0 g, 16.7 mmol) in absolute ethanol (30 mL), and the mixture was heated at reflux for 16 h. After filtration and concentration in vacuo of the reaction mixture, the residual brown oil was extracted with anhydrous ethyl ether (2 × 100 mL). Concentration of the ether layers produced a brown residue which was subsequently extracted with petroleum ether (3 × 150 mL). On reduction of the volume of the petroleum ether extracts to 10 mL, **10c** (274 mg, 13% yield) precipitated from solution. Analytical material was obtained by recrystallization from ethyl ether/$CHCl_3$, following a decolorizing charcoal treatment: mp 137–138 °C; UV λ_{max} (H_2O, pH 0.9) 330 nm sh (ϵ 7130), 314 (7680), 302 sh (6850); (pH 9.1) 303 (6950); NMR ($CDCl_3$) δ 1.40 and 1.46 (t, 3 each, OCH_2CH_3), 4.43 and 4.47 (d, 2 each, OCH_2CH_3), 5.2 (s, 2, NH_2), 7.29 (s, 1, 5-H), 7.57 (d, J = 5 Hz, 1, 5′-H), 8.42 (d, J = 5 Hz, 1, 6′-H); MS m/e 261 (M^+).

Anal. Calcd for $C_{12}H_{15}N_5O_2$: C, 55.16; H, 5.79; N, 26.81. Found: C, 55.45; H, 5.49; N, 26.60.

6-(2-Aminopyrimidin-4-yl)-2,4-diethoxy-5-methylpyrimidine (10b). The generation of 2,4-diethoxy-6-lithio-5-methylpyrimidine from **6b** (522 mg, 2.0 mmol) and n-butyllithium (0.8 mL of a 2.4 M solution in hexane, 2.2 mmol) in THF (15 mL) was accomplished as previously described. A solution of β-benzyloxyacrolein (**7b**, 350 mg, 2.16 mmol) in THF (5 mL) was added, and the resultant reaction mixture was stirred at <−80 °C for 1.25 h. After being warmed to 0 °C over 30 min, the reaction solution was inversely quenched with a mixture of ethyl ether (50 mL) and a 20% aqueous NH_4Cl solution (50 mL). Following the extraction of the aqueous layer with additional ethyl ether (2 × 40 mL), the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to an oil. This oil was oxidized in the manner described for **10c**. On dissolution of the oxidation products in absolute ethanol (20 mL) and addition of guanidine carbonate (450 mg, 3.75 mmol), the reaction mixture was heated at reflux for 12 h. The treatment of these reaction products in a manner analogous to the procedure described for **10c** provided, on reduction of the volume of petroleum ether extracts to 10 mL, **10b** (136 mg, 25% yield). After treatment with decolorizing charcoal, recrystallization from $CHCl_3$/ethyl ether provided analytical material: mp 142.5–143.5 °C; UV λ_{max} (H_2O, pH 0.9) 312 nm (ϵ 7420), 278 sh (5040); (pH 8.9) 300 (6890), 278 sh (5950); NMR ($CDCl_3$) δ 1.40 (t, 6, OCH_2CH_3), 2.22 (s, 3, 5-CH_3), 4.40 and 4.47 (q, 2 each, OCH_2CH_3), 5.26 (br s, 2, NH_2), 7.06 (d, J = 5 Hz, 1, 5′-H), 8.41 (d, J = 5 Hz, 1, 6′-H); MS m/e 275 (M^+).

Anal. Calcd for $C_{13}H_{17}N_5O_2$: C, 56.71; H, 6.22; N, 25.44. Found: C, 56.64; H, 6.32; N, 25.21.

6-(2-Amino-5-methylpyrimidin-4-yl)-2,4-diethoxy-5-methylpyrimidine (10d). The 6-lithio derivative was prepared from **6b** (1.044 g, 4 mmol) and n-butyllithium (1.8 mL of a 2.4 M solution in hexane, 4.32 mmol) in THF (20 mL) as previously described. Following the addition of β-ethoxy-α-methylacrolein (**7a**, 479 mg, 4.2 mmol) in THF (5 mL), the reaction mixture was stirred at <−80 °C for 1.5 h, with gradual warming to 0 °C allowed over the next 40 min. The reaction solution was quenched, worked up, and oxidized in the manner of **10c**. After filtration and concentration of the oxidation products, the residual oil was dissolved in absolute ethanol (15 mL).

On the addition of guanidine carbonate (1.0 g, 8.33 mmol), the mixture was heated at reflux for 18 h. Following a filtration with the aid of absolute ethanol (20 mL), the filtrate was concentrated in vacuo to a solid residue. The extraction of this residue with anhydrous ethyl ether (3 × 10 mL) and the subsequent concentration of the ether layer provided a lighter colored solid. Extraction of this solid with petroleum ether (4 × 5 mL) yielded white solid **10d** (285 mg, 25% yield) after partial concentration of the solvent. Analytical material was obtained by vacuum sublimation (6 mmHg, 155 °C): mp 152–153 °C; UV λ_{max} (H_2O, pH 0.9) 320 nm (ϵ 5150), 264 (5820); (pH 9.24) 305 (5190), 272 (6370); NMR ($CDCl_3$) δ 1.38 and 1.41 (t, 3 each, OCH_2CH_3), 1.91 and 2.0 (s, 3 each, Ar–CH_3), 4.35 and 4.47 (q, 2 each, OCH_2CH_3), 5.02 (br s, 2, NH_2), 8.23 (s, 1, 6′-H); MS *m/e* 289 (M^+).

Anal. Calcd for $C_{14}H_{19}N_5O_2$: C, 58.11; H, 6.62; N, 24.21. Found: C, 58.26; H, 6.45; N, 24.37.

2,4-Diethoxy-6-(2-hydroxy-5-methylpyrimidin-4-yl)pyrimidine (11a). To the ice-cooled bipyrimidine **10a** (360 mg, 1.31 mmol) was added 1 mL of H_2O, 1 mL of 6 M HCl, and 0.5 mL of concentrated H_2SO_4. Over a period of 10 min a solution of sodium nitrite (360 mg, 5.22 mmol) in H_2O (1 mL) was dripped in, and gas evolution was evident. The reaction was stirred at 25 °C for 3.5 h, after which time 20 mL of H_2O was added, and the mixture was extracted with chloroform (2 × 20 mL). The organic layer was dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated in vacuo to yield a yellow solid. The solid was transferred to a sintered glass funnel with 25 mL of petroleum ether and then washed with 5 mL of benzene to give the product (139 mg, 39% yield). An analytical sample was obtained by crystallization from petroleum ether/benzene: mp 162–163 °C; UV λ_{max} (H_2O, pH 1.0) 336 nm (ϵ 6570), 276 (4180); (pH 8.9) 321 (6420), 272 sh (3970); (pH 13.0) 316 (5810), 268 (5420); NMR ($CDCl_3$) δ 1.42 and 1.46 (t, 3 each, OCH_2CH_3), 2.37 (s, 3, 5′-CH_3), 4.51 and 4.53 (q, 2 each, OCH_2CH_3), 7.00 (s, 1, 5-H), 8.0–8.8 (br s, 1, OH), 8.22 (s, 1, 6′-H); MS *m/e* 276 (M^+).

Anal. Calcd for $C_{13}H_{16}N_4O_3$: C, 56.51; H, 5.84; N, 20.28. Found: C, 56.49; H, 5.84; N, 20.17.

2,4-Diethoxy-6-(2-hydroxypyrimidin-4-yl)pyrimidine (11c). To ice-cooled **10c** (75 mg, 0.29 mmol) was added 1 mL of H_2O, 0.3 mL of 6 N HCl, and 0.15 mL of concentrated H_2SO_4. Over a period of 10 min a solution of sodium nitrite (80 mg, 1.16 mmol) in H_2O (0.5 mL) was dripped in, and the reaction mixture was stirred for 1.5 h. After dilution with 20 mL of H_2O, an extraction with $CHCl_3$ (2 × 20 mL) was performed, and the resultant organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to a white solid. Washing with petroleum ether/benzene (5:1, 2 × 10 mL) provided nearly pure **11c** (53.4 mg, 71% yield). Analytical material was obtained by recrystallization from benzene/$CHCl_3$, after treatment with decolorizing charcoal: mp 223–223.5 °C; UV λ_{max} (H_2O, pH 0.9) 333 nm (ϵ 7000), 305 sh (7000), 293 (7200); (pH 8.9) 317 (8700); (pH 13) 318 (6600), 299 (6600); NMR ($CDCl_3$) δ 1.40 and 1.46 (t, 3 each, OCH_2CH_3), 4.47 and 4.49 (q, 2 each, OCH_2CH_3), 7.41 (s, 1, 5-H), 7.47 (d, J = 6 Hz, 1, 5′-H), 8.13 (d, J = 6 Hz, 1, 6′-H); MS *m/e* 262 (M^+).

Anal. Calcd for $C_{12}H_{14}N_4O_3$: C, 54.95; H, 5.38; N, 21.37. Found: C, 54.70; H, 5.25; N, 21.39.

2,4-Diethoxy-6-(2-hydroxypyrimidin-4-yl)-5-methylpyrimidine (11b). The diazotization–hydrolysis of **10b** was carried out essentially according to the directions for **11c**. The resulting solid (~200 mg) was washed with petroleum ether/benzene (5:1, 2 × 5 mL) and 2 mL of anhydrous ethyl ether to afford **11b** in 60% yield. Dissolution of this sample in hot benzene, treatment with decolorizing charcoal, filtration, and concentration gave analytically pure material: mp 181–182.5 °C; UV λ_{max} (H_2O, pH 0.9) 306 nm (ϵ 7700); (pH 8.8) 310 (8600), (pH 12.9) 300 (8030), 275 (6600); NMR ($CDCl_3$) δ 1.43 (t, 6, OCH_2CH_3), 2.37 (s, 3, 5-CH_3), 4.42 and 4.48 (q, 2 each, OCH_2CH_3), 7.04 (d, J = 5 Hz, 1, 5′-H), 8.16 (d, J = 5 Hz, 1, 6′-H), 9.9 (br s, 1, NH); MS *m/e* 276 (M^+).

Anal. Calcd for $C_{13}H_{16}N_4O_3$: C, 56.51; H, 5.84; N, 20.28. Found: C, 56.48; H, 5.87; N, 19.99.

2,4-Diethoxy-6-(2-hydroxy-5-methylpyrimidin-4-yl)-5-methylpyrimidine (11d). The diazotization–hydrolysis of sublimed **10d** was done in the manner of **11c** and, on similar workup, provided solid **11d** (150 mg, 70% yield). Analytical material was obtained by washing the product with petroleum ether (2 × 25 mL) and benzene (25 mL): mp 190.5–191.5 °C; UV λ_{max} (H_2O, pH 0.9) 326 nm (ϵ 6430), 267 (6830); (pH 8.9) 314 (6690), 268 (5180); (pH 12.6) 308 (6740), 270 (7180); NMR ($CDCl_3$) δ 1.37 and 1.41 (t, 3 each, OCH_2CH_3), 1.99 (s, 6, 5- and 5′-CH_3), 4.33 and 4.45 (q, 2 each, OCH_2CH_3), 7.99 (s, 1, 6′-H); MS *m/e* 290 (M^+).

Anal. Calcd for $C_{14}H_{18}N_4O_3$: C, 57.92; H, 6.25; N, 19.30. Found: C, 57.78; H, 5.98; N, 19.58.

6-(2-Hydroxy-5-methylpyrimidin-4-yl)uracil (4). A solution of **11a** (232 mg, 0.84 mmol) in 6 N HCl (30 mL) was heated at reflux for 1 h. Removal of the solvent in vacuo left a residue which, on crystallization from H_2O after a decolorizing charcoal treatment, yielded analytically pure **4**: 126 mg, 68% yield; 224–226 °C dec; UV λ_{max} (H_2O, pH 0.9) 320 nm (ϵ 6840); (pH 7.2) 319 (6980); (pH 12.9) 299 (9760); NMR [$(CD_3)_2SO$] δ 2.06 (s, 3, CH_3), 5.58 (s, 1, 5-H), 8.12 (s, 1, 6′-H); MS *m/e* 220 (M^+).

Anal. Calcd for $C_9H_8N_4O_3 \cdot 0.25H_2O$: C, 48.10; H, 3.81; N, 24.93. Found: C, 48.05; H, 3.91; N, 25.00.

6-(2-Hydroxypyrimidin-4-yl)thymine (1). A solution of **11b** (170 mg, 0.62 mmol) in 6 N HCl (15 mL) was heated at reflux for a period of 1.5 h. After removal of the solvent in vacuo, the residual solid was washed with $CHCl_3$ to afford **1** (76 mg, 56% yield). Analytical material was obtained by recrystallization from H_2O, following treatment with decolorizing charcoal: 273–275 °C dec; UV λ_{max} (H_2O, pH 0.9) 317 nm (ϵ 8980); (pH 7.2) 314 (8740); (pH 12.9) 303 (11 100); NMR [$(CD_3)_2SO$] δ 1.77 (s, 3, CH_3), 6.58 (d, J = 6 Hz, 1, 5′-H), 8.18 (d, J = 6 Hz, 1, 6′-H); MS *m/e* 220 (M^+).

Anal. Calcd for $C_9H_8N_4O_3$: C, 49.09; H, 3.66; N, 25.45. Found: C, 48.83; H, 3.56; N, 25.43.

6-(2-Hydroxypyrimidin-4-yl)uracil (2). A solution of **11c** (77 mg, 0.29 mmol) in 6 N HCl (10 mL) was heated at reflux for 1.5 h. Removal of the solvent in vacuo left solid **2** (50 mg, 84% yield). An analytical sample was obtained by recrystallization from H_2O, following a treatment with decolorizing charcoal: 242–243 °C dec; UV λ_{max} (H_2O, pH 0.9) 336 nm sh (ϵ 6970), 314 (9160), 303 (9360); (pH 7.2) 336 sh (6730), 314 (8300), 304 (8480); (pH 12.9) 325 (11 250); NMR [$(CD_3)_2SO$] δ 6.39 (s, 1, 5-H), 7.03 (d, J = 6 Hz, 1, 5′-H), 8.17 (d, J = 6 Hz, 1, 6′-H); MS *m/e* 206 (M^+).

Anal. Calcd for $C_8H_6N_4O_3$: C, 46.60; H, 2.93; N, 27.18. Found: C, 46.38; H, 2.82; N, 26.96.

6-(2-Hydroxy-5-methylpyrimidin-4-yl)thymine (3). A solution of **11d** (100 mg, 0.34 mmol) in 6 N HCl (10 mL) was heated at reflux for a period of 2 h. After concentration of the reaction solution to an oil, $CHCl_3$ (5 mL) was added, and the flask was left uncovered overnight. Evaporation of the solvent during the night left a solid yellow crystalline material, which was washed with 5 mL of anhydrous ether/absolute ethanol (4:1) to leave **3** (70 mg, 87% yield). Recrystallization from absolute ethanol provided analytical **3** as a white fluffy powder: 310–312 °C dec; UV λ_{max} (H_2O, pH 0.9) 322 nm (ϵ 7050), 255 (6500); (pH 7.2) 318 (7090), 258 (6250); (pH 12.9) 302 (12 970); NMR [$(CD_3)_2SO$] δ 1.57 and 1.93 (s, 3 each, CH_3), 8.14 (s, 1, 6′-H); MS *m/e* 234 (M^+).

Anal. Calcd for $C_{10}H_{10}N_4O_3 \cdot 0.25H_2O$: C, 50.31; H, 4.43; N, 23.47. Found: C, 50.35; H, 4.30; N, 23.58.

Acknowledgment. J.D.B. has held a Lilly Fellowship in Chemistry. This work has been supported by the National Science Foundation Research Grant CHE 76-23543.

Registry No.—**5b,** 64188-81-4; **6a,** 64188-82-5; **6b,** 64188-83-6; **7a,** 42588-57-8; **7b,** 4652-40-8; **8a,** 64188-84-7; **9a,** 64188-85-8; phosphorus oxybromide, 7789-59-5; 5-methylbarbituric acid, 2417-22-3; guanidine carbonate, 124-46-9.

References and Notes

(1) For review, see G. J. Fisher and H. E. Johns, in "Photochemistry and Photobiology of Nucleic Acids", Vol. I, S. Y. Wang, Ed., Academic Press, New York, N.Y., 1976, Chapter 5.
(2) For review, see S. Y. Wang in ref 1, Chapter 6.
(3) The symbolism employed for the bipyrimidines follows the system formally proposed for bipyrimidine photoproducts by Dr. Waldo E. Cohn, Secretary of the IUPAC–IUB Commission on Biochemical Nomenclature; see W. E. Cohn, N. J. Leonard, and S. Y. Wang, *Photochem. Photobiol.*, **19,** 89 (1974).
(4) A. J. Varghese and S. Y. Wang, *Science,* **156,** 955 (1967).
(5) S. Y. Wang and A. J. Varghese, *Biochem. Biophys. Res. Commun.,* **29,** 543 (1967).
(6) A. J. Varghese and M. H. Patrick, *Nature (London),* **223,** 299 (1969).
(7) D. F. Rhoades and S. Y. Wang, *Biochemistry,* **9,** 4416 (1970).
(8) M. N. Khattack and S. Y. Wang, *Science,* **163,** 1341 (1969).
(9) (a) A. J. Varghese, *Biochemistry,* **10,** 4283 (1971); (b) *ibid.,* **10,** 2194 (1971).
(10) A. J. Varghese and S. Y. Wang, *Science,* **160,** 186 (1968).
(11) A. J. Varghese and S. Y. Wang, *Biochem. Biophys. Res. Commun.,* **33,** 102 (1968).
(12) A. J. Varghese, *Biochemistry,* **9,** 4781 (1970).
(13) N. J. Leonard, D. E. Bergstrom, and G. L. Tolman, *Biochem. Biophys. Res. Commun.,* **44,** 1524 (1971).
(14) D. E. Bergstrom and N. J. Leonard, *Biochemistry,* **11,** 1 (1972).
(15) D. E. Bergstrom, I. Inoue, and N. J. Leonard, *J. Org. Chem.,* **37,** 3902 (1972).
(16) D. E. Bergstrom and N. J. Leonard, *J. Am. Chem. Soc.,* **94,** 6178

(1972).
(17) N. J. Leonard and D. F. Wiemer, *J. Am. Chem. Soc.*, **98**, 8218 (1976).
(18) M. P. L. Caton, D. T. Hurst, J. F. W. McOmie, and R. R. Hunt, *J. Chem. Soc. C*, 1204 (1967), and references cited therein.
(19) J. J. Lafferty and F. H. Case, *J. Org. Chem.*, **32**, 1591 (1967).
(20) F. Effenberger, *Chem. Ber.*, **88**, 2260 (1965).
(21) R. Pater, *J. Heterocycl. Chem.*, **8**, 743 (1971).
(22) J. A. Otterstedt and R. Pater, *J. Heterocycl. Chem.*, **9**, 225 (1972).
(23) V. Krchnak and Z. Arnold, *Collect. Czech. Chem. Commun.*, **39**, 3327 (1974).
(24) B. A. Frit and A. Teuerstein, *J. Heterocycl. Chem.*, **10**, 47 (1973).
(25) L. Strekowski, *Rocz. Chem.*, **48**, 2157 (1974), and references cited therein.
(26) The use of guanidine with subsequent diazotization was considered superior to direct condensation with urea, which often results in low yields.
(27) B. W. Langley, *J. Am. Chem. Soc.*, **78**, 2136 (1956).
(28) V. D. Adams, *Synthesis*, **4**, 286 (1974).
(29) Tridom Chemical Co., U.S. representative of Fluka AG.
(30) N. N. Kalinina, V. T. Klimko, T. V. Protopopova, and A. P. Skoldinov, *J. Gen. Chem. USSR (Engl. Transl.)*, **32**, 2116 (1962).
(31) V. T. Klimko, T. V. Protopopova, N. V. Smirnova, and A. P. Skoldinov, *J. Gen. Chem. USSR (Engl. Transl.)*, **32**, 2913 (1962).
(32) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jensen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).
(33) C. Fenselau and S. Y. Wang, *Tetrahedron*, **25**, 2853 (1969).
(34) L. R. Subbaraman, J. Subbaraman, and E. J. Behrman, *J. Org. Chem.*, **38**, 1499 (1973).
(35) (a) B. S. Hahn and S. Y. Wang, *J. Am. Chem. Soc.*, **94**, 4764 (1972); (b) B. S. Hahn and S. Y. Wang, *ibid.*, **95**, 3082 (1973).
(36) W. Hauswirth and S. Y. Wang, *Photochem. Photobiol.*, **25**, 161 (1977).
(37) M. H. Patrick, *Photochem. Photobiol.*, **25**, 357 (1977).
(38) T. G. Scott, R. D. Spencer, N. J. Leonard, and G. Weber, *J. Am. Chem. Soc.*, **92**, 687 (1970).
(39) B. Doumas and H. G. Biggs, *J. Biol. Chem.*, **237**, 2306 (1962).

Notes

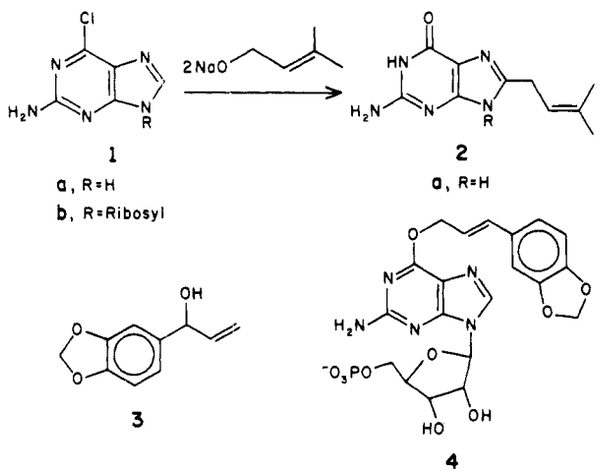
Rearrangement of Cinnamyl Groups from O^6 to C-8 in the Guanine Series

Brian N. Holmes[1] and Nelson J. Leonard*

Roger Adams Laboratory, School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801

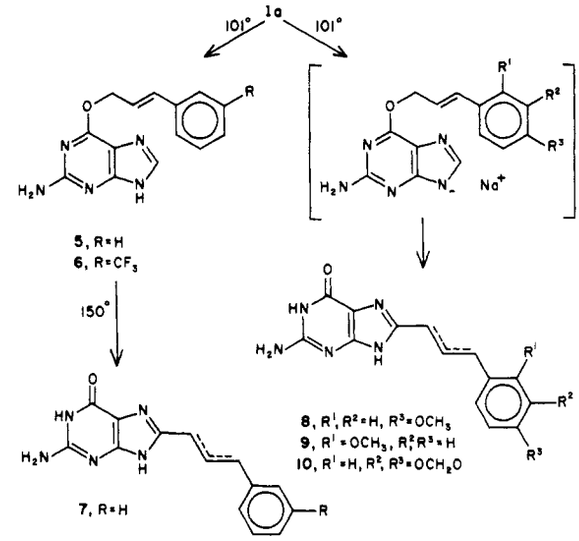
Received August 2, 1977

It was established in this Laboratory that displacement reactions of 2-amino-6-chloropurine (**1a**) with the sodium salts of allylic alcohols proceed through an O^6 ether to yield 8-substituted guanines (e.g., **2a**),[2] with the following stipulations: (a) the O^6 to C-8 rearrangement occurs with overall allylic retention and is partially controlled by the degree of methyl substitution of the allylic group and by the temperature, (b) the rearrangement proceeds with greatest facility through anionic species, and (c) it occurs intramolecularly and most logically by two [3,3]sigmatropic shifts via C-5.



Derivatives of allylbenzene and propenylbenzene are widely occurring plant constituents, and many which are present as major components of common spices and flavorings exhibit biological activity.[3] It has been shown that allylbenzene derivatives can be oxidized metabolically to give allylic alcohols.[4,5] More specifically, safrole (3,4-methylenedioxyallylbenzene), which is a hepatotoxin and a hepatocarcinogen, is oxidized in the liver, inter alia, to 1-(3,4-methylenedioxyphenyl)-2-propen-1-ol (**3**), a more potent carcinogen than the parent safrole.[5] Furthermore, a University of Wisconsin group has shown that the synthetic acetate of **3**, as a model for metabolic activation, reacts with guanosine monophosphate to give the O^6-allylic ether **4**. These reports led us to investigate the rearrangement of O^6-cinnamyl ethers of guanine.

Treatment of 2-amino-6-chloropurine (**1a**) with the sodium salt of either cinnamyl alcohol or *m*-trifluoromethylcinnamyl alcohol in refluxing dioxane (101 °C) for 4 h gave the corresponding O^6 ether **5** or **6**, respectively, of guanine. At 101 °C, no rearrangement product was detectable by thin-layer chromatography, even after heating at reflux for 24 h. However, when O^6-cinnamylguanine (**5**) was converted to its sodium salt with 1 equiv of sodium hydride and heated at 150 °C for 24 h in either anhydrous diglyme or dimethylformamide, rearrangement occurred to a mixture of 8-(3-phenyl-1-propenyl)guanine and 8-(3-phenyl-2-propenyl)guanine (**7**). When the *m*-trifluoromethyl compound **6** was treated under the same conditions at 150 °C, guanine was the only purine product that could be detected.



Electron-donating groups on the phenyl ring facilitated rearrangement. Thus, treatment of **1a** separately with the sodium salts of *p*-methoxycinnamyl alcohol,[6] *o*-methoxycinnamyl alcohol,[6] and 3-(3,4-methylenedioxyphenyl)-2-propen-1-ol[5] in refluxing dioxane (101 °C) gave the corresponding C-8 substituted guanines **8–10**. The product in each case was isolated as an approximately 1:1 mixture of the double-bond isomers. TLC analysis of the progress of the re-

0022-3263/78/1943-0516$01.00/0