# The Chemistry of Some 5-(2-Hydroxyalkyl)uracil Derivatives and a Synthesis of 5-Vinyluracil[1]

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From 5-(2-hydroxyethyl)uracil, its 2-*O*-methanesulfonate or 2′-*O*-*p*-toluenesulfonate, treated with acid or base, a variety of substitution or elimination products can be obtained, depending on the conditions used. Mechanisms for inter- and intramolecular nucleophilic substitutions, and their competition with elimination of the C-2′ groups, are discussed. The decarboxylation of *trans*-3-(5-uracilyl)propenoic acid to 5-vinyluracil is described, and the effects of association of the vinylic and propenoic acid side chains with the uracil ring on both the p$K_a$ values and ultraviolet and infrared absorption spectra are interpreted. The chemical consequences of these finds in biologically active compounds are considered.

Pyrimidines with lipophilic substituents at position 5 display substantial biological activity.[2-4] In another line of investigation a number of *N*-vinyl derivatives of purines or pyrimidines,[5-10] and some *O*-acryloyl nucleosides[11-15] have been useful for studies of intramolecular forces in nucleic acid[16-19] and for chromatographic separation of nucleic acid components.[20-23]

We have now extended our synthetic approach to the 5-substituted pyrimidines[24] to 5-vinyluracil, which is of interest to both of the above areas of investigation. The van der Waals radius of the 5-vinyl substituent is expected to be nearer to that of the methyl of thymine than is that of the ethyl of 5-ethyluracil, which is a thymine analog.[25-27]

The presence of the 5-vinyl substituent should leave the hydrogen-bonding properties of the pyrimidine ring essentially unchanged, so that a polymer of this compound could be uniquely useful as a chromatographic medium selective for natural poly A sequences,[28,29] and a complex of poly A and poly (5-vinyl U) should also be of interest.[30]

Few 5- or 6-vinylpyrimidines[31] are known. In addition to 4-vinylpyrimidine and its 2-dimethylamino derivative,[32,33] it has been reported, although no experimental details were given, that 4-alkylamino-5-(2-chloroethyl)pyrimidines give 5-vinyl derivatives in ethanolic alkali.[34]

Dehydration of 5-(2-hydroxyethyl)uracil (**3**)[34,35] with potassium hydroxide,[32] which had proven satisfactory for dehydration of 4-(2-hydroxyethyl)pyrimidine, was tried unsuccessfully. The dehydration of **3** in concentrated $H_2SO_4$ at 90–100° proceeded to give 2*H*,3*H*,-5(7)*H*-furano[2,3]pyrimidin-6-one (**4**) (Scheme I). The structure of **4** was supported by nmr and ir data and its ultraviolet absorption properties (Table I).

TABLE I

| Compd | pH | Charge | $\lambda_{max}$, nm ($\epsilon \times 10^{-3}$) | | Apparent p$K_a$ values (±) |
|---|---|---|---|---|---|
| **4** | 7 | 0 | 280 (4.6) | 206 (17.5) | |
| | 13 | −1 | 290 (6.6) | 226 (8.1) | 10.90 (0.03) |
| **13** | 1 | 0 | 296 (18.5) | 270 sh (13.6) | |
| | 6 | −1 | 293 (13.5) | 260 (13.6) | 4.33 (0.06) |
| | 11.5 | −2 | 319 (17.8) | 278 (12.5) | 9.01 (0.06) |
| **14** | 7 | 0 | 286 (6.82) | 238 (11.4) | |
| | 11.5 | −1 | 307 (8.06) | 251 (12.2) | 9.14 (0.05) |
| **22** | 1 | 0 | 305 (19.4) | 270 sh (12.9) | |
| | 7.4 | −1 | 301 (15.0) | 261 (13.7) | 4.32 (0.05) |
| | 12.0 | −2 | 301 (9.33) | 265 (8.95) | 9.76 (0.04) |

Under the experimental conditions the $H_0$ value of the acid solution is ~−9.0.[36,37] The protonation p$K_a$ of **3** should be similar to that of uracil (−3.38),[38,39] since the ionization p$K_a$'s of **3** and uracil, 9.68[35] and

(1) This investigation was supported in part by funds from the National Cancer Institute (Grant No. CA 08748) and the American Cancer Society (Grant No. P 295).

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(36) $H_0$ values of 98 and 99% $H_2SO_4$ at 90° have been calculated to be −8.82 and −9.26, respectively.[37]

(37) C. D. Johnson, A. R. Katritzky, and S. A. Shapiro, *J. Amer. Chem. Soc.*, **91**, 6654 (1969).

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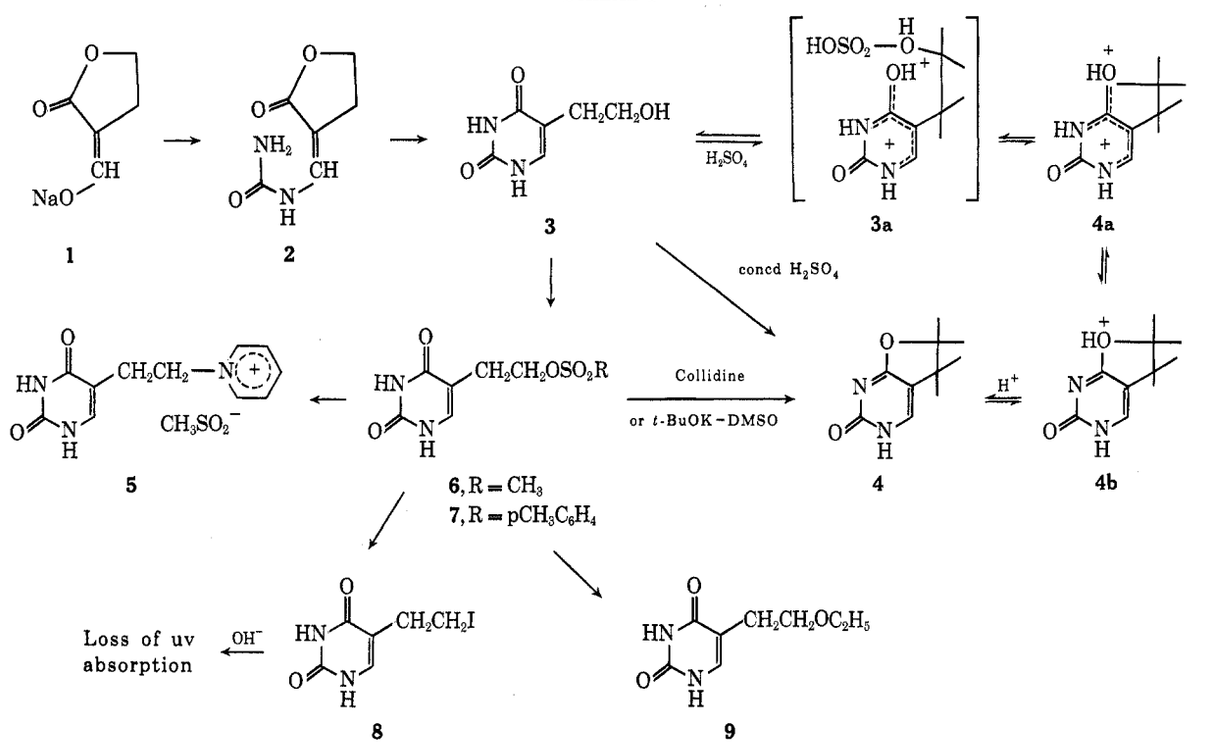
SCHEME I




9.5,[40,41] differ but slightly. Therefore the pyrimidine moiety of **3** must exist as a monocation and in further analogy to uracil, protonation would occur at the C-4 carbonyl,[42] to form the resonance-stabilized cation **3a**. Nucleophilic intramolecular displacement of the 2′-*O*-sulfate followed by deprotonation would lead to **4**. Under conditions that promote sulfation of the side chain but preclude formation of the pyrimidine cation (*i.e.*, 30% $H_2SO_4$, 90–100°, $H_0 = -1.4$[37]) **4** could not be detected in the reaction mixture. In 70 or 80% $H_2SO_4$ ($H_0 = -4.8$ and $-6.1$, respectively[37]) the presence of **4** could again be demonstrated. These experiments suggest that protonation of the pyrimidine is a prerequisite for the cyclization (Scheme I). The conversion of **3** to **4** is reversible, as demonstrated by the quantitative conversion of **4** to **3** on a Dowex-50 ($H^+$) column eluted with $H_2O$. This acid lability is comparable to that of the analogous C-4, O-5′ "cyclonucleoside" derived from pseudouridine.[43]

When 5-(2-methanesulfonyloxyethyl)uracil (**6**) is treated with an organic base, it undergoes bimolecular nucleophilic substitution rather than elimination. Refluxing **6** in pyridine yields the crystalline methanesulfonate of the 5-(2-pyridiniumethyl)uracil (**5**) in quantitative yield. When steric effects prevent bimolecular substitution, as in the case with 2,4,6-collidine, **6** undergoes the alternative intramolecular reaction to give **4**. This base-catalyzed cyclization of **6** to **4** is analogous to the formation of the cyclopseudouridine derivative mentioned above.[43] Attempted conversion of **6** to the olefin **14** with excess potassium *tert*-butoxide (*t*-BuOK) in dimethyl sulfoxide (DMSO) also led to the cyclized oxetane derivative **4** in 70% yield. The latter reaction, used for the direct introduction of unsaturation into the carbohydrate moiety of nucleosides, proceeds through either an E2 mechanism[44] involving a cyclic intermediate analogous to **4**, or an E1cB mechanism.[45] A considerable degree of carbanion character would reside on the C-1′ atom of **6** or **4** if the base-promoted E2 elimination reaction mechanism as proposed for β-phenylethyl compounds[46] or the E1cB mechanism were to be operative. In either case the formation of a stable pyrimidine dianion would hinder the formation of the respective conjugate bases and inhibit the elimination reactions. The difficulty of establishing a negative charge on C-1′ of **4**, compounded with the relatively poor leaving group character of the uracilyl moiety, might account for the stability of **4** toward the *t*-BuOK–DMSO reagent.

The apparent difference between **6** and the related sulfonates **10a** and **10b**, which could be converted to the respective olefins 5-(1-cyclopentenyl)uracil (**11a**)[47] and 5-(3-methoxy-1-cyclopentenyl)uracil (**11b**) (Scheme II) by potassium *tert*-butoxide in dimethyl sulfoxide,[48] can be rationalized, since in the latter instances the respective sulfonlyl group is restricted to a position cis to the pyrimidine, rendering impossible the formation of an oxetane derivative by an SN2 nucleophilic attack by the C-4 carbonyl. Thus the elimination reaction to the olefin **11b** could take place. The observed differences in the products of the reaction (*i.e.*, 2′,1′ elimination *vs.* 2′,4 substitution) could also be the result of differences in the kinetic rate of the formation of the product **4** from the anion of **6** as

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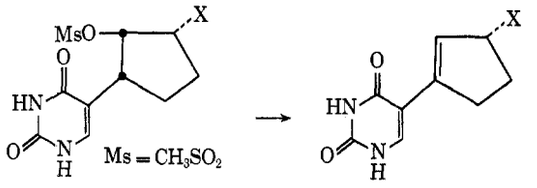
SCHEME II



10a, X = H
b, X = $OCH_3$

11a, X = H
b, X = $OCH_3$

opposed to the attraction (E2) or abstraction (ElcB) of C-1′ proton from the same anion.

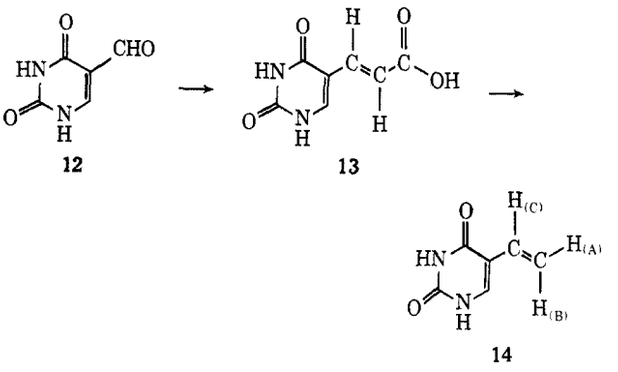
When the crude **7** is heated in ethanol, 5-(2-ethoxyethyl)uracil (**9**) is formed, possibly through an anhydro derivative such as **4**. This is consistent with a variety of analogous nucleophilic openings of the oxetane ring of "anhydronucleosides."[49] When **4** is heated under reflux in an ethanolic solution for several hours, no ring opening occurs, but in the presence of *p*-toluenesulfonic acid the conversion to **9** is quantitative. In the overall conversion of **7** to **9** 1 equiv of acid is liberated from **7** which is available for catalysis. Conceivably the bridged oxygen becomes protonated as in ethers, to give the pyrimidyl oxonium moiety **4b** which is a better leaving group.[50] Comparable examples in the "cyclonucleoside" series have been reported.[51,52] The overall reaction from **6** to **5** very likely also proceeds through the cyclic derivative **4**, which undergoes opening of the oxetane ring. This is supported by the fact that **4** is the main product of the reaction of **6** with collidine. Since **4** is a model of "cyclopseudonucleosides," the above reactions provide evidence that the vast experience with pyrimidine nucleoside transformations *via* anhydro nucleosides[49] is applicable to the "pseudonucleoside" series.

The sulfonate **6** can be converted to the corresponding 5-(2-iodoethyl)uracil (**8**) by the procedure of Pfitzner and Moffat.[53] In dilute aqueous sodium hydroxide at room temperature, the iodo compound undergoes a selective loss of ultraviolet absorption above 220 nm within 30 min. Under the same conditions the monoanion of **3** is stable.

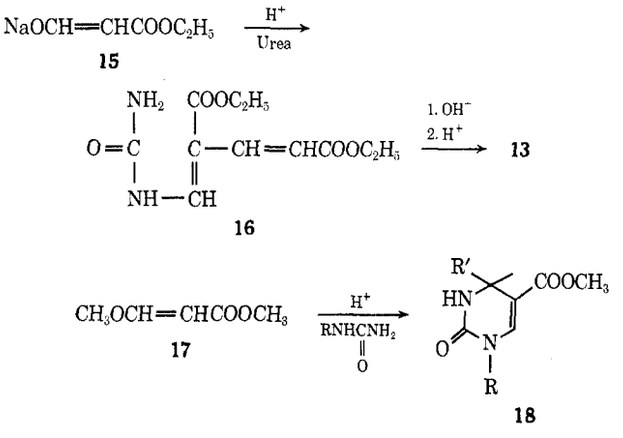
Our failure to effect the direct dehydration of **3** to the vinyl derivative **14** led us to investigate 3-(5-uracilyl)propenoic acid (**13**, Scheme III) as an alternative intermediate for the synthesis of 5-vinyluracil. The preparation of the above acid has been mentioned in a footnote,[54] which described that **13** was obtained by base-catalyzed cyclization of the intermediate ureide **16** (Scheme IV) which had been obtained in crystalline form when a solution of 2 mol of urea and the sodium formylacetic ester from 10 g of sodium was treated with 150 cc of concentrated hydrochloric acid. We attempted to condense methyl β-methoxyacrylate (**17**)[55] with ureas in the respective stoichiometric ratio of 2:1. The only isolated products from these reactions under a variety of conditions were 1,2,3,4-tetrahydropyrimidin-2-ones **18** (R′ = $CH_2COOH$ or $CH_3$). The mechanism and the scope of this reaction will be the subject of a future report. The propenoic acid derivative **13** was synthesized by the condensation of 5-formyluracil (**12**)[56] with malonic acid, to give exclusively the trans isomer as evidenced by nmr data. The coupling constant of the vicinal vinyl protons on the side chain is $J_{\alpha\beta}$ = 16 Hz, similar to that found in trans cinnamates ($J_{\alpha\beta\ trans}$ = 16.2, $J_{\alpha\beta\ cis}$ = 13.2 Hz),[57] and the *trans*-3(6-uracilyl)propenoates ($J_{\alpha\beta\ trans}$ = 16.5, $J_{\alpha\beta\ cis}$ = 13 Hz).[31,58] The acid **13** was decarboxylated to 5-vinyluracil (**14**) by heating it in quinoline at 200–210° under nitrogen. The structure of **14** was established by ultraviolet and nmr spectroscopy and elemental analysis. There is a striking similarity between the ultraviolet spectral characteristics of **14** and those[47] of the 2,4-dihydroxy-5-(1-cyclopentenyl)pyrimidine (**11a**). Moreover, the nmr spectrum of **14** shows the typical first-order ABX pattern of the vinyl group, with coupling constants of $J_{AB} \cong 3$, $J_{AC} \cong 10.5$, and $J_{BC} \cong 17.5$ Hz, similar to corresponding values reported for styrene.[59]

Association of the 5-vinyl group with the pyrimidine ring of uracil is expected to result in overlap of the ring π orbitals with that of the 5 substituent. This is evidenced by a bathochromic shift of the $B_{2u}$ (259 nm,

SCHEME III



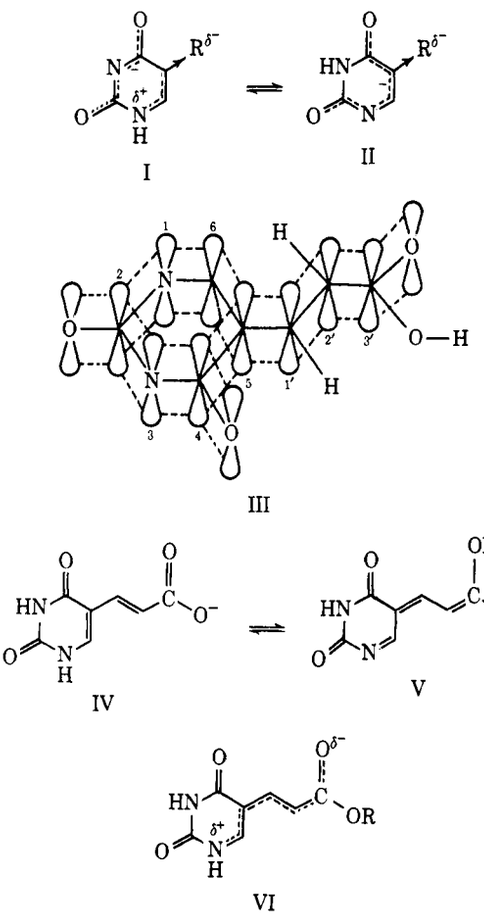
SCHEME IV



(49) For a review, see J. J. Fox, *Pure Appl. Chem.*, **18**, 223 (1969).
(50) J. March, "Advances in Organic Chemistry," McGraw-Hill, New York, N. Y., 1968, p 290.
(51) J. J. Fox and N. C. Miller, *J. Org. Chem.*, **38**, 936 (1963).
(52) N. Miller and J. J. Fox, *ibid.*, **29**, 1772 (1964).
(53) K. E. Pfitzner and J. G. Moffat, *ibid.*, **29**, 1508 (1964).
(54) D. Davidson and O. Baudisch, *J. Amer. Chem. Soc.*, **48**, 2379 (1926).
(55) The use of this ester was considered preferable to that of **15**, since the purity of preparations of the latter was highly questionable.
(56) R. Brossmer and D. Ziegler, *Tetrahedron Lett.*, 5253 (1966).
(57) M. C. Cagaleiro and M. D. Johnson, *J. Chem. Soc. B*, 565 (1967).
(58) It is also interesting that the only product of the condensation reaction of 3-formyl-2-pyridone with malonic acid is the trans isomer of (carboxy-2-vinyl)-3-hydroxy-2-pyridine: D. Bonnetand, G. Queguiner, and P. Pastour, *J. Heterocycl. Chem.*, **9**, 165 (1972).
(59) T. Yoshino, Y. Manabe, and Y. Kikuchi, *J. Amer. Chem. Soc.*, **86**, 4670 (1964).

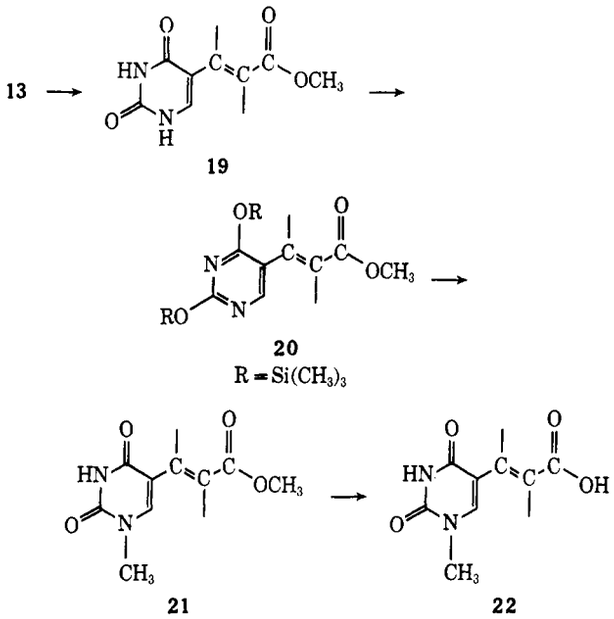
$\epsilon$ 8100) and $E_{1ua}$ (202 nm, $\epsilon$ 8800) bands of uracil[60] to 286 ($\epsilon$ 6820) and 238 nm ($\epsilon$ 11,400), respectively, at pH 7 (Table I). This shift is most likely due to a combination of effects[61] generated by the vinylic side chain in **14**. The significant increase in $\epsilon$ of the $E_{1ua}$ band parallels that of the respective band observed in benzene and styrene.[62] The vinyl substituent appears to exert a net electron-withdrawing effect upon the pyrimidine ring, since the acidity of **14** ($pK_a$ = 9.14 ± 0.05) is increased relative to uracil ($pK_a$ = 9.5).[40,41] The effect of the 5-propenoyl group in **13** upon the ionization and spectral properties of the uracil base is of interest.[63] As with **14**, an acid-strengthening effect is also observed in **13**, which exhibits $pK_a$'s of 4.33 ± 0.06 and 9.01 ± 0.06, the first for the side chain carboxyl group. The ring anion probably contains a mixture of the two anionic species I and II (Scheme V) of the

SCHEME V



pyrimidine.[41,64] The diminished value for the second $pK_a$ of **13**, along with the further bathochromic displacement of the $B_{2u}$ band of uracil to 296 nm (for the neutral molecule) and the ultraviolet absorption change associated with the ionization of the side chain carboxyl group, indicate that the $\pi$-electron system of the pyrimidine ring is extended through the entire side chain (III, Scheme V). Intramolecular interaction between the side chain carboxyl group and the pyrimidine ring, such as an H bond, is precluded by the trans configuration. To study this phenomenon more fully the compounds **19** and **22** were synthesized as described in Scheme VI. The acid **13** was esterified

SCHEME VI



with methanol in the presence of sulfuric acid and the obtained ester was converted to the bis-*O*-trimethylsilyl derivative **20**. This derivative was selectively methylated with $CH_3I$[65] to give **21**, which was then saponified to the N-1 methyl derivative **22**.

The ultraviolet spectrum of **19** displays no changes over the range of pH 2–6, and coincides with that of the *neutral* species of **13**, obtained at pH < 2. Therefore the spectral changes of **13** between pH 2–6 are not likely to reflect a shift in the tautomeric equilibrium toward the 4-enol form caused by the strong electron-withdrawing effect of the 5 substituent analogous to that suggested for 5-bromouracil.[66] Moreover, the similar ultraviolet spectral changes of the N-1 methyl derivative **22** in the range of pH 2–6 rules out the possibility of the tautomeric shift IV ⇄ V (Scheme V) in **13**. The first ionization $pK_a$ (4.32 ± 0.05) due to the carboxyl group is identical with the corresponding one of **13**. The second $pK_a$ (9.76 ± 0.04), corresponding to the monoanion I above, is comparable to that of 1-methyluracil (9.77,[41] 9.72[67]) but is higher than the second $pK_a$ (9.06) of **13**. From these results it is clear that, in compounds **13** and **20**, the influence of the 5-propenoyl substituent is exerted exclusively upon the N-1 of the uracil as represented by the conjugated system VI (Scheme V). Such conjugation would be expected to increase the acidity of the N-1 proton, as is actually observed. It should render any nucleosidic bond at this position more labile to

(60) L. B. Clark and I. Tinoco, Jr., *J. Amer. Chem. Soc.*, **87**, 11 (1965).

(61) For a discussion of these effects, see A. R. Katritzky and R. D. Topsom, *Angew. Chem., Int. Ed. Engl.*, **9**, 87 (1970).

(62) For benzene $E_{1ua}$ 202 nm ($\epsilon$ 6900), $B_{2u}$ 255 nm ($\epsilon$ 224); and for styrene $E_{1ua}$ 244 nm ($\epsilon$ 12,000), $B_{2u}$ 282 nm ($\epsilon$ 450). E. A. Brande, in E. A. Brande and F. C. Nachod, Ed., "Determination of Organic Structures by Physical Methods," Vol. I, Academic Press, New York, N. Y., 1955, p 151.

(63) This uracil derivative is closely related to the 3-[5-(6-methyl)uracilyl]propenoic acid, isolated from the antibiotic sparsomycin: P. F. Wiley and F. A. Mackellar, *J. Amer. Chem. Soc.*, **92**, 417 (1970).

(64) K. L. Wierzchowski, E. Litonska, and D. Shugar, *ibid.*, **87**, 4621 (1965).

(65) E. Wittenburg, *Chem. Ber.*, **101**, 1095 (1968).

(66) A. R. Katritzky and A. J. Waring, *J. Chem. Soc.*, 1521 (1962).

(67) J. Jonas and J. Gut, *Collect. Czech. Chem. Commun.*, **27**, 716 (1962).

acid hydrolysis, and it may not be coincidental that the antibiotic sparsomycin[63] has not been isolated in the nucleoside form.

Additional evidence supporting the existence of resonance interaction between the side chain and pyrimidine $\pi$-system in compounds **13** and **14** is obtained from their ir spectra. In the high-frequency region of multiple bonds uracil exhibits two intense bands which are split and centered at 1715 and 1750 $cm^{-1}$ [41,68] due to the C=O and C=C functions. No bands are observed between 1500 and 1600 $cm^{-1}$.[69] In contrast, **14** shows, in addition to two similar uracil bands at 1740 and 1670 $cm^{-1}$, a third narrow, medium-intensity band at 1590 $cm^{-1}$, and **13** displays a broad band at 1680 $cm^{-1}$ due to the carbonyl groups and another strong band at 1600 $cm^{-1}$. Probably the 1590-$cm^{-1}$ band exists in the spectrum of uracil, but is too weak to be detected. However, the appearance of this band in the spectra of **13** and **14** is indicative of extended exocyclic conjugation.[70]

## Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. The nmr spectra were obtained using a Varian A-60 spectrometer with tetramethylsilane as an internal reference. Ultraviolet and infrared spectra were determined using a Unicam SP 800 and an Infracord spectrophotometer, respectively. All solvents were removed in a Büchler flash evaporator under reduced pressure, unless otherwise indicated. Drying of all solids was accomplished under reduced pressure over $P_2O_5$ at suitable temperatures. The $pK_a$'s were determined by methods described[71] spectrophotometrically in 0.01 *M* buffers with a Beckman DU spectrophotometer or electrometrically with 0.001 *M* solutions. For tlc, Eastman chromagram silica gel sheet was used with the solvent systems indicated.

**α-(1-Carbamyliminomethylene)-8-butyrolactone (2).**—To a solution of 30 g (0.5 mol) of urea in ~200 ml of cold 3 *N* HCl was added 34 g (0.25 mol) of the sodium derivative of α-hydroxymethylene-γ-butyrolactone[35] in small portions. After stirring overnight in the cold, the precipitated product (23 g, 59%) was collected, washed with cold water, and dried. Recrystallization from $H_2O$–EtOH gave fine needles melting at 246–247°:[72] nmr τ 7.2 (pair of t, 2, $J_{3,4}$ = 7.5, $J_{1',3}$ = 2 Hz, $-CH{=}CCH_2-$), 5.65 (t, 2, $J_{4,3}$ = 7.5 Hz, $-CH_2CH_2O-$), 3.59 (s, 2, exch), 7.68 (pair of t, 1, $J_{1',3}$ = 2, $J_{1',2'}$ = 12 Hz, $-NHCH{=}CCH_2-$), 0.64 (d, 1, $J_{2',1'}$ = 12 Hz, exch).

**5-(2-Hydroxyethyl)uracil (3).**—To an alcoholic solution of $C_2H_5ONa$ (2.18 g, 9.46 × $10^{-2}$ mol of Na in 250 ml of EtOH) was added 13.4 g (8.6 × $10^{-2}$ mol) of **2**. The mixture was heated under reflux for 6 hr, during which time a solid separated. The solvent was removed and the residue was dissolved in 400 ml of water. The resulting solution was passed through a heated (*ca.* 60°) Amberlite IRC-50 ($H^+$) column (2.5 × 14 cm) which was washed well until the eluent showed negligible uv absorption at 265 nm. The combined eluents were concentrated to ~500 ml, then treated with Norit and filtered, and the filtrate was further concentrated to ~250 ml and cooled. The product (12.4 g, 92%) was collected, washed with EtOH, and dried. It melted at 264–265°:[73] nmr τ 7.64 (t, 2, $J_{1',2'}$ = 7 Hz, $-CH_2CH_2OH$), 6.48 (t, 2, $J_{2',1'}$ = 7 Hz, $-CH_2CH_2OH$), 5.44 (broad s, 1, exch), 2.72 (d, 1, $J_{6,1}$ = 5.5 Hz), −0.66 (d, 1, $J_{1,6}$ = 5.5 Hz, exch), −1.0 (s, 1, exch).

**5-(2-Methanesulfonyloxyethyl)uracil (6).**—To a cold suspension of 1.56 g (10 mmol) of **3** in 20 ml of pyridine was added 1.54 ml (2.28 g, 20 mmol) of methanesulfonyl chloride.[74] After the solution was stirred in the cold overnight a few drops of water were added and the mixture was chilled for several hours. The solvent was removed and the residue was suspended in 25 ml of cold water. A tan precipitate was collected, washed well with cold water, and dried [2.0 g (87%)]. This material was recrystallized from MeOH. The product melted at 180–182°: nmr τ 6.8 (s, 3), 5.76 (t, 2, $J_{2',1'}$ = 7.5 Hz, $-CH_2CH_2O-$); ir $\lambda_{max}^{KBr}$ 1315 ($\nu_{as}$ $SO_2$), 1168 $cm^{-1}$ ($\nu_s$ $SO_2$).[70]

*Anal.* Calcd for $C_7H_{10}N_2O_5S$: N, 11.96; S, 13.69. Found: N, 11.90; S, 13.58.

**2*H*,3*H*,5(7)*H*-Furano[2,3*d*]pyrimidin-6-one (4). Method A.**—A solution of 0.5 g (3.2 mmol) of **3** in 5 ml of concentrated $H_2SO_4$ was heated at 100° for 1 hr. Then it was cooled and added, with stirring, to 1 l. of ether. After 1 hr at 4° the ether phase was decanted from the precipitate, which was washed with 250 ml of ether. The residue was dissolved in 300 ml of cold water and the solution was passed through a small Amberlite IR-45 ($OH^-$) column which then was washed well with water. The neutral eluent (1 l.) was concentrated to give a white, crystalline solid which was collected, washed with a small volume of methanol, and dried. The product [310 mg (70%)] decomposes gradually to a glass between 260 and 315°: nmr τ 6.92 (t, 2, $J_{1',2'}$ = 8 Hz, $-CH_2CH_2O-$), 5.30 (t, 2, $J_{2',1'}$ = 8 Hz, $-CH_2CH_2O-$), 2.41 (s, 1); ir $\lambda_{max}^{KBr}$ 1015 $cm^{-1}$ ($\nu_s$ COC), 1230 $cm^{-1}$ ($\nu_{as}$ = COC).[75]

*Anal.* Calcd for $C_6H_6N_2O_2$: C, 52.17; H, 4.38; N, 20.28. Found: C, 51.97; H, 4.35; N, 20.10.

Similar reaction mixtures in 80, 70, or 30% $H_2SO_4$ were diluted with cold water and neutralized with 60 ml of Dowex-1 (20 to 30 mesh, $HCO_3^-$) in the cold with stirring. Then the resin was washed in a column with 1.6 l. of water when the eluent no longer showed uv absorption. The solvents were removed *in vacuo* and the residues were chromatographed on tlc plates (chromagram, silica gel; $C_6H_6$–MeOH, 2:8). Individual bands were eluted with water and the uv spectral shifts of the solutions at several pH's were recorded and compared with those of the starting material **3** and anticipated product **4**. In 80 or 70% $H_2SO_4$ small amounts of **4** were detected, and none in 30% $H_2SO_4$.

**Method B.**—A solution of 468 mg (2 mmol) of the methanesulfonate **6** in 25 ml of freshly distilled 2,4,6-collidine was heated in a bath at 125–130° for 30 min and then was lyophylized. The residue was treated with EtOH and the mixture was again lyophylized. Finally the residue was dissolved in ~50 ml of MeOH, the solution was treated with Norit and filtered, and the filtrate was concentrated until a solid began to separate. After chilling the product was collected, washed twice with ether, and dried, yield 80 mg (29%).

**Method C.**—The methanesulfonate **6** (468 mg, 2 mmol) was dissolved in 10 ml of DMSO (freshly distilled from CaH) and 673 mg (6 mmol) of *t*-BuOK was added. After standing for 6 days at room temperature the mixture was added to a suspension of 10 ml of Amberlite IRC-50 ($H^+$) in cold water. The neutral mixture was transferred on a small column and the resin was eluted with water (~1.1 l.). The combined eluates were concentrated and the residual DMSO was removed in a lyophylizer. The residue was suspended in 200 ml of boiling EtOH, the mixture was filtered, and the filtrate was taken to dryness. The residue was recrystallized from MeOH as described in method B, yield 195 mg (70%).

**5-(2-Pyridiniumethyl)uracil Methanesulfonate (5).**—A solution of 234 mg (1 mmol) of **6** in 25 ml of dry pyridine was heated under reflux for 72 hr. After standing at room temperature for a few hours the crystals which separated were collected, washed twice with EtOH and then several times with ether, and dried: yield 280 mg (89%); mp 207–209°; nmr τ 7.10 (t, 2, $J_{1',2'}$ = 6.5 Hz, $-CH_2CH_2N{\lessdot}^+$), 5.24 (t, 2, $J_{2',1'}$ = 6.5 Hz, $-CH_2CH_2N{\lessdot}^+$).

*Anal.* Calcd for $C_{12}H_{15}N_3O_5S$: C, 46.00; H, 4.82; N, 13.41; S, 10.23. Found: C, 46.13; H, 4.77; N, 13.44; S, 10.18.

**5-[2-(*p*-Toluenesulfonyloxy)ethyl]uracil (7).**—To a solution of 312 mg (2 × $10^{-3}$ mol) of **3** in 10 ml of pyridine kept at −10° was added 419 mg (2.2 × $10^{-3}$ mol) of *p*-toluenesulfonyl chloride and the mixture was stirred (at −10°) for 3 days. After the solvent had been removed *in vacuo* at room temperature by means of a Dry Ice trap, 30 ml of crushed ice was added to the viscous residue, which immediately solidified. The solid was broken up

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(71) A. Albert and E. P. Serjeant, "Ionization Constant of Acids and Bases," Wiley, New York, N. Y., 1962, p 69.

(72) K. A. Chkhikvadze and O. Yu. Magidson, *Zh. Obshch. Khim.*, **34**, 2577 (1964).

(73) Reported mp 273–274[35] and 259–261°.[72]

(74) Comparable results are obtained if methanesulfonyl anhydride is used nstead of the chloride.

(75) K. Nakanishi, "Infrared Spectroscopy," Holden-Day, San Francisco, Calif., 1962, p 36.

and the mixture was left in the cold overnight. Then the product was collected, dried, and washed twice on the filter with small volumes of dry ether. It was chromatographically pure [tlc, chromagram silica gel, $C_6H_6$–EtOH (8:2) or $C_6H_6$–EtOAc–MeOH (8:1:1)]: yield 496 mg (80%); mp 170–173°; nmr $\tau$ 5.83 (t, 2, $J_{2',1'}$ = 6.5 Hz); ir $\lambda_{max}^{KBr}$ 1350 ($\nu_{as}$ $SO_2$), 1170, 1185 $cm^{-1}$ ($\nu_s$ $SO_2$).[70]

*Anal.* Calcd for $C_{13}H_{14}N_2O_5S$: N, 9.03; S, 10.33. Found: N, 8.97; S, 10.19.

**5-(2-Ethoxyethyl)uracil (9).**—A sample of the *p*-toluenesulfonate **7** was dissolved in EtOH and the solution was refluxed for several hours until tlc [$C_6H_6$–EtOAc–MeOH (8:1:1)] indicated the absence of starting material. After the solvent was removed the residue was chromatographed on a Dowex 50 column ($H^+$, 1 50 cm) which was eluted with water. The product-containing fractions were pooled and concentrated to dryness and the residue was recrystallized twice from EtOH to give a crystalline solid melting at 242–244°: nmr $\tau$ 8.92 (t, 3, $J$ = 6.5 Hz, $-OCH_2CH_3$), 7.62 (t, 2, $J$ = 6.5 Hz, $-CH_2CH_2O-$), 6.61 (9, 2, $J$ = 6.5 Hz, $-OCH_2-CH_3$), 6.60 (t, 2, $J$ = 6.5 Hz, $-CH_2CH_2O-$), 2.77 (s, 1); ir $\lambda_{max}^{KBr}$ 1240 $cm^{-1}$ ($\nu_{as}$ COC).[75]

*Anal.* Calcd for $C_8H_{12}N_2O_3$: C, 52.16; H, 6.56; N, 15.20. Found: C, 51.88; H, 6.57; N, 15.10.

**5-(2-Iodoethyl)uracil (8).**—A mixture of 937.0 mg (4 mmol) of the methanesulfonate **6**, 5.98 g (40 mmol) of NaI, and 180 ml of diglyme (freshly distilled from Na) was heated under reflux for 6 hr. After the solvent was removed the residue was triturated with cold water. The mixture was left in the cold for a few hours and then the solid product was collected, washed with water, and dried. It was recrystallized from ~200 ml of EtOH to yield 810 mg (76%) of crystals melting at 265°: nmr $\tau$ 7.29 (t, 2, $J_{1',2'}$ = 7 Hz, $-CH_2CH_2I$), 6.64 (t, 2, $J_{2',1'}$ = 7 Hz, $-CH_2CH_2I$), 2.65 (d, 1, $J_{6,1}$ = 5.5 Hz).

*Anal.* Calcd for $C_6H_7N_2IO_2$: N, 10.53; I, 47.70. Found: N, 10.53; I, 47.75.

In aqueous alkaline solutions, **8** seems to be unstable. Preliminary experiments have provided insight into several aspects of this reaction. When NaOD is added to a solution of **8** in DMSO-$d_6$, the vinylic signal ($C_6H$, $\tau$ 2.65) and those of the side-chain methylene protons ($C_{1'}$ H, $\tau$ 7.29; $C_{2'}$ H, $\tau$ 6.64) are almost completely quenched with simultaneous appearance of a broad signal centered at $\tau$ 8.8. No change other than a small downfield shift is noticed in the spectrum of **3** under the same conditions, even after several days. When an alkaline aqueous solution of **8** is allowed to stand for 1.5 hr at room temperature, until the absorption peak at 290 nm decreases by 95%, and then the solution is made strongly acid, the uv absorption is almost completely restored during a subsequent 24-hr period. A small amount of solid which separates during this period was found to be (melting point, nmr) starting material, **8**. Other products have not yet been identified.

**3-(5-Uracilyl)propenoic Acid (13).**—A mixture of 1.40 g ($1 \times 10^{-2}$ mol) of 5-formyluracil,[56] 2.08 g ($1 \times 10^{-2}$ mol) of malonic acid, and ~10 ml of dry pyridine was heated in a bath at 80–90° for 6 hr. The reaction mixture was evaporated to dryness, water was added to the residue, and again the mixture was taken to dryness, and the procedure was repeated twice more. The final residue was dissolved in 225 ml of boiling water, and the solution was acidified with 2 ml of glacial acetic acid and slowly cooled to room temperature. After further cooling at 4° the precipitated product was collected, washed with cold dilute acetic acid, and dried over $P_2O_5$ and KOH. The product (1.65 g, 90%) softens above 275° and melts with decomposition at 283–284°: nmr $\tau$ 3.19 (d, 1, $J_{2',1'}$ = 16 Hz, =CHCOOH), 2.6 (d, 1, $J_{1',2'}$ = 16 Hz, $-CH=CH-$), 1.96 (s, 1).

*Anal.* Calcd for $C_7H_6N_2O_4$: C, 46.16; H, 3.32; N, 15.38. Found: C, 46.05; H, 3.39; N, 15.36.

**5-Vinyluracil (14).**—A suspension of 364 mg (2 mmol) of **13** in 10 ml of dry quinoline was heated slowly to 220° (bath temperature) under nitrogen. The temperature of the reaction mixture was maintained between 175 and 200° for 20 min, and then the solvent was removed in a lyophylizer. Benzene was added to the residue and the solvent was removed as before. This treatment was repeated several times to remove as much of the quinoline as possible. The residue was chromatographed on either a silica gel column (30 g, 2.5 × 29 cm) which was eluted first with 200 ml of benzene and then with a mixture of benzene–ethanol (8:2) or a Dowex 50 ($H^+$) column (1 50 cm) which was eluted with water. In both cases, the combined fractions containing **14** were concentrated to dryness and the residue was recrystallized from ethanol (or methanol) to give 65 mg of product which decomposes between 230 and 270°: nmr $\tau$ 4.92 (pair of d, 1, $J_{AC}$ = 10.5, $J_{AB}$ = 3 Hz), 4.08 (pair of d, 1, $J_{BC}$ = 17.5, $J_{BA}$ = 3 Hz), 3.56 (pair of d, 1, $J_{CB}$ = 17.5, $J_{CA}$ = 10.5 Hz), 2.4 (s, 1).[76]

*Anal.* Calcd for $C_6H_6N_2O_2$: C, 52.17; H, 4.38; N, 20.28. Found: C, 51.90; H, 4.32; N, 20.28.

**Methyl 3-(5-Uracilyl)propenoate (19).**—A mixture of 1.82 g ($10^{-2}$ mol) of 3-(5-uracilyl)propenoic acid (**13**) and 30 ml of dry MeOH containing 2 drops of concentrated $H_2SO_4$ was heated under reflux for several days. Then about one half of the solvent was distilled, and the residual mixture was chilled. The product which separated was collected, washed with cold MeOH, and dried. It was found to be analytically pure. The average yield was over 90%: mp 288–289° dec; nmr $\tau$ 6.33 (s, 3, $OCH_3$), 3.20 (d, 1, $J_{2',1'}$ = 16 Hz, =CHCO), 2.61 (d, 1, $J_{1',2'}$ = 16 Hz, $-CH=CHCO$), 2.00 (s, 1).

*Anal.* Calcd for $C_8H_8N_2O_4$: C, 48.98; H, 4.11; N, 14.28. Found: C, 48.81; H, 4.09; N, 14.29.

**Methyl 3-[5-(2,4-Bis-*O*-trimethylsilyl)uracilyl]propenoate (20).**—A mixture of the ester **19** (4.12 g, $2.05 \times 10^{-2}$ mol), 30 ml of hexamethyldisilazane, and 0.4 ml of trimethylchlorosilane was heated in a bath at 155° for 16 hr. The solvents were removed *in vacuo* and the oily residue was fractionated. The product fraction was collected at 117–118° (34–35 × $10^{-3}$ mm) as a viscous oil, weighing 6.5 g (91%).

**Methyl 3-[5-(1-Methyl)uracilyl]propenoate (21).**—The above product **20** (6.5 g, $1.9 \times 10^{-2}$ mol) was dissolved in 50 ml of $CH_3I$ and the solution was gently heated under reflux for 6 hr. Then the solvent was boiled off and 50 ml of MeOH was added to the residue. The mixture was heated under reflux for 10 hr and then cooled at −20°. The product which precipitated was collected, washed with ether, dried, and then dissolved in 1 l. of boiling water. The solution was filtered and then sufficient solvent was removed by distillation to promote crystallization. After cooling, the product was collected, washed twice with cold water, and dried: yield 3.7 g (92%); mp 256–260°; nmr $\tau$ 6.72 (s, 3, $NCH_3$), 6.35 (s, 3, $OCH_3$), 3.27 (d, 1, $J_{2',1'}$ = 16 Hz, =CHCO), 2.7 (d, 1, $J_{1',2'}$ = 16 Hz, $-CH=CHCO$), 1.8 (s, 1).

*Anal.* Calcd for $C_9H_{10}N_2O_4$: C, 51.43; H, 4.80; N, 13.33. Found: C, 51.49; H, 4.80; N, 13.16.

**3-[5-(1-Methyl)uracilyl]propenoic Acid (22).**—Hydrolysis of **21** (424 mg, $2 \times 10^{-3}$ mol) was conducted in aqueous solution containing a stoichiometric amount of NaOH for 3 days at room temperature. The solution was chromatographed on a Sephadex G-10 column (1 16 cm) eluted with 0.05 *M* $NaH_2PO_4$ buffer at pH 7. The eluate containing the product was concentrated to a small volume, acidified to pH 1 with concentrated hydrochloric acid, and cooled. The crude product (327 mg, 82.5%) was recrystallized from $H_2O$ to give needles: mp 284–286° dec; nmr $\tau$ 6.7 (s, 3, $NCH_3$), 3.29 (d, 1, $J_{2',1'}$ = 16 Hz, =CHCO), 2.71 (d, 1, $J_{1',2'}$ = 16 Hz, $-CH=CHCO$), 1.91 (s, 1).

*Anal.* Calcd for $C_8H_8N_2O_4$: C, 48.98; H, 4.11; N, 14.28. Found: C, 49.13; H, 3.69; N, 14.31.

**Registry No.**—**4**, 37107-74-7; **5**, 37107-75-8; **6**, 37107-76-9; **7**, 37107-77-0; **8**, 37107-78-1; **9**, 37107-79-2; **13**, 37107-80-5; **14**, 37107-81-6; **19**, 37107-82-7; **20**, 37107-83-8; **21**, 37107-84-9; **22**, 37107-85-0.

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(76) NOTE ADDED IN PROOF.—Ions identical with **4b** and 5-vinyluracil (**14**) were observed in the mass spectrum of 5-(4',5'-dihydroxypentyl)uracil, a new pyrimidine from *Bacillus subtilis* phage SP-15 nucleic acid.[77]

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