Free Radical Rearrangements in Uracil Derivatives

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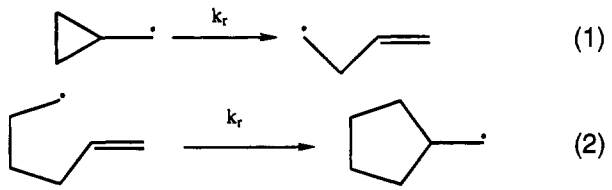
As part of an effort to develop general probes for radical reactions involving DNA bases, several uracil derivatives were synthesized. The rates of the cyclopropyl carbinyl rearrangement in these systems were evaluated by means of competition experiments. The results indicate that when a cyclopropyl group is substituted in the 5-position of uracil, the rearrangement occurs very slowly—with a rate constant of $<2.5 \times 10^4$ s^{-1}. On the other hand, the analog of the 5-hexenyl radical cyclization onto the 5,6-double bond of uracil derivatives occurs with rates which were similar to the parent process: $(4.0-8.9) \times 10^4$ s^{-1}. The experimental results along with semiempirical calculations show that radicals **23** and **25** are unusually stable species. These results explain why no rearrangements are observed when a cyclopropyl-substituted thymine dimer is cleaved by reductive single electron transfer.

Introduction

Free radical species are intermediates in a wide variety of chemical and biological processes.[1] Over the past several years a number of free radical rearrangement reactions have been explored for use as mechanistic probes or so-called "radical clocks".[2] A radical clock is a functional group which is incorporated into a molecule suspected of undergoing free radical reactions. When the radical center is generated, the clock group rearranges in competition with a subsequent reactions of the radical intermediate. Not only are radical intermediates detected by this method, but it is possible to estimate rate constants for the radical reactions based on the relative yields of the rearranged and unrearranged products.

The two canonical radical clock reactions are the cyclopropylcarbinyl to homoallylic radical rearrangement (eq 1) and the 5-hexenyl radical to cyclopentylmethyl radical rearrangement (eq 2). These rearrangements



(1)

(2)

have been employed in the study of a variety of chemical and biochemical processes. For example, the intervention of free radicals in the enzymatic oxidation of hydrocarbons by cytochrome P-450 was determined by means of a cyclopropylcarbinyl rearrangement[3] (eq 1). In this, case the rearrangement of the cyclopropyl carbinyl radical to the homoallylic radical competes with oxygen transfer to the radical ("oxygen rebound"). The 5-hexenyl radical cyclization has been used to probe for radical intermediates in the oxidation of alkyltriarylborates[4] and the reduction of alkyl halides.[5] In the latter cases the cyclization reaction (eq 2) competes with hydrogen atom transfer to the primary radical.[6]

For such tools to be generally useful in probing reactions of biological interest, several properties are desirable: (1) the probe group must be easily and selectively incorporated into the biological substrate; (2) the probe group must be as small as possible so as not to interfere with biomolecular recognition (e.g., enzyme–substrate binding); (3) the probe group must be inert to the conditions experienced by the substrate other than the free radical reaction (for example, a probe for redox chemistry must not itself be redox active); and (4) the probe group must rearrange with a rate constant that is predictable. The latter point is of special importance. If incorporation of the probe group into the biological system significantly retards the rearrangement reaction, then erroneous interpretations of the experiment can result. An observation of no rearrangement might lead to the conclusion that no radicals are formed during the reaction, or that their lifetimes are vanishingly short.

There are a wide variety of free radical process that occur with DNA molecules. Many of the biological effects of ionizing radiation occur as a result of DNA reactions with hydroxyl radicals or through the direct ionization of DNA bases.[7] These processes initiate a complex series of free radical reactions that involve both the bases and deoxyribose groups in the DNA polymer. Hydroxyl radical cleavage DNA has been used to determine the sequence specificity of drug binding to DNA.[8] Enediyne anticancer drugs such as neocarzinostatin and calicheamicin initiate free radical cleavage of DNA, apparently by H-atom transfer from deoxyribose portions of the polymer.[1b]

Our interest in DNA–radical chemistry is motivated

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(1) For reviews see: (a) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237–1286. (b) Stubbe, J. A. *Biochemistry* **1988**, *27*, 3893–3900. (c) Pryor, W. A. In *Free Radicals in Biology*; Pryor, W. A., Ed.; Academic Press: New York, 1976; Chapter 1. (d) Stubbe, J. A. *Ann. Rev. Biochem.* **1989**, *58*, 257–285.

(2) (a) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151–1176. (b) Bowry, V. W.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1991**, *113*, 5687–5698.

(3) Bowry, V. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1991**, *113*, 5699–5707.

(4) Schuster, G. B. *Pure. Appl. Chem.* **1990**, *62*, 1565–1572.

(5) Newcomb, M.; Varick, T. R.; Choi, S.-Y. *J. Org. Chem.* **1992**, *57*, 373–378.

(6) For other recent examples of enzymatic mechanism determination through the use of radical clocks see: (a) Branchaud, B. P.; Montague-Smith, M. P.; Kosman, D. J.; McLaren, F. R. *J. Am. Chem. Soc.* **1993**, *115*, 798–800. (b) Liu, K. E.; Johnson, C. C.; Newcomb, M.; Lippard, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 939–947.

(7) For reviews see: (a) Sonntag, C. v. *The Chemical Basis of Radiation Biology*; Taylor & Francis: New York, 1987. (b)Ward, J. F. In *Advances in Radiation Biology*; Lett, J. T., Adler, H., Ed.; Academic Press: New York, 1976; v. 5.

(8) Tullius, T. D.; Dombroski, B. A. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 5469–5473.

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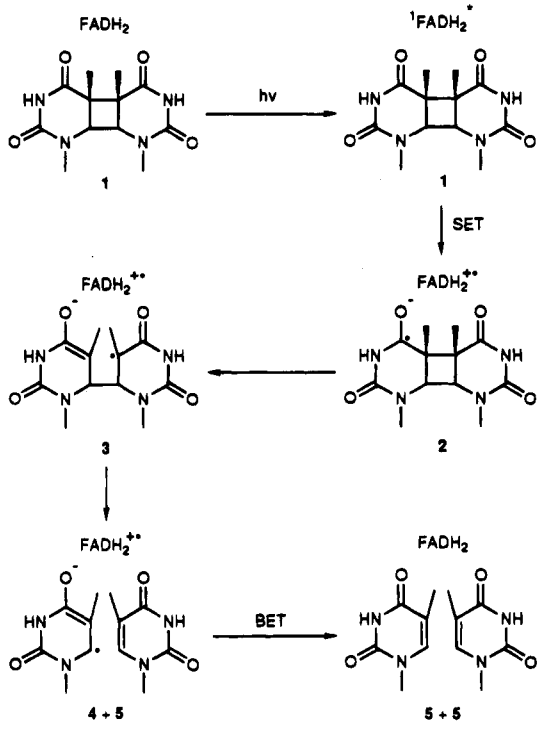
Scheme 1



by efforts to understand the catalytic mechanism of DNA photolyase enzymes. These unique proteins use visible light to mediate the repair of pyrimidine dimers in damaged DNA.[9] Although the mechanistic details of the repair process are not completely understood, it is becoming increasingly clear that absorption of a photon by the enzyme initiates an electron-transfer step. There is considerable evidence which suggests that the electron flows from $FADH_2$ in the enzyme (in the singlet exited state) to the substrate, resulting in a dimer anion radical.[10] The dimer anion radical fragments rapidly to give a momoner and a monomer anion radical.[11] The latter transfers an electron back to the enzyme and the DNA is repaired. A summary of this mechanistic pathway is illustrated in Scheme 1. One interesting question involves the intermediacy and lifetime of the distonic ion radical **2**. Kinetic isotope effect studies by Begley provide some evidence for this.[12]

The present study focuses on free radical clock reactions on pyrimidine bases. Both 5-hexenyl cyclization and the cyclopropyl carbinyl rearrangement involving uracil have been examined. The former occurs with a rate of about 5×10^4 s^{-1} which is comparable to that of the parent hydrocarbon (10^5 s^{-1}). The latter occurs very slowly, if at all. Competition experiments show that it occurs with a rate constant $<10^3$ s^{-1}.

(9) For a review see: Sancar, A.; Sancar, G. B. *Ann. Rev. Biochem.* **1988**, *57*, 29–67.

(10) (a) Jorns, M. S.; Baldwin, E. T.; Sancar, G. B.; Sancar, A. *J. Biol. Chem.* **1987**, *262*, 486–491. (b) Sancar, G. B.; Jorns, M. S.; Payne, G.; Fluke, D. J.; Rupert, C. S.; Sancar, A. *J. Biol. Chem.* **1987**, *262*, 492–498. (c) Payne, G.; Heelis, P. F.; Rohrs, B. R.; Sancar, A. *Biochemistry* **1987**, *26*, 7121–7127. (d) Kim, S.-T.; Sancar, A.; Essenmacher, C.; Babcock, G. T. *J. Am. Chem. Soc.* **1992**, *114*, 4442–4443. (e) Jorns, M. S. *J. Am. Chem. Soc.* **1987**, *109*, 3133–3136. (f) Hartman, R. F.; VanCamp, J. R.; Rose. S. D. *J. Org. Chem.* **1987**, *52*, 2684–2689.

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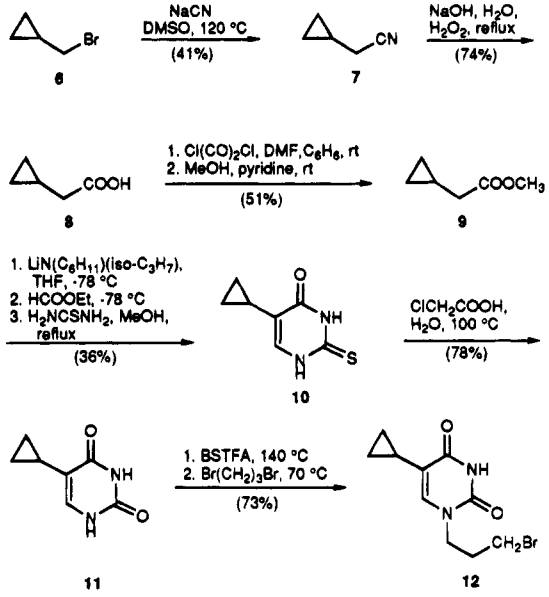
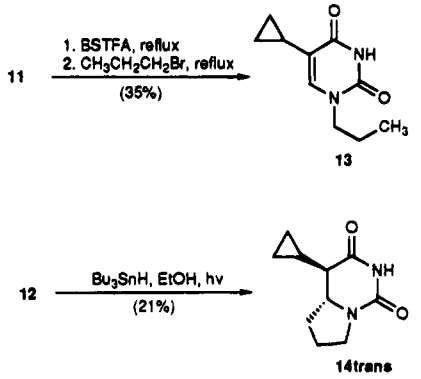
Scheme 2



Scheme 3



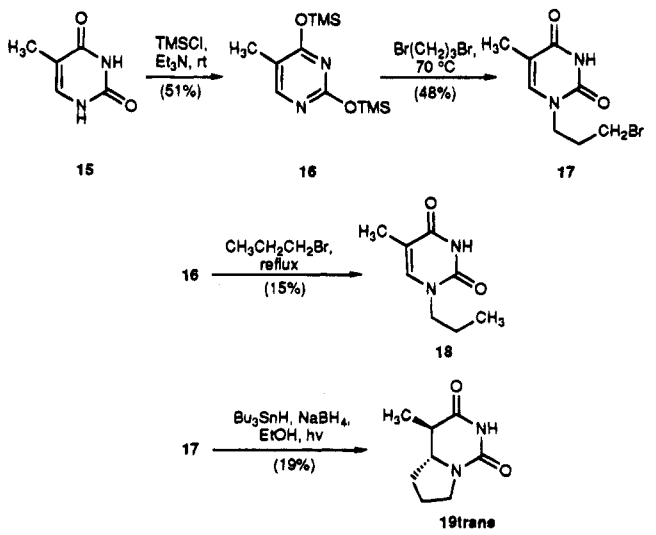
Results and Discussion

Synthesis. The synthesis of 1-(3-bromopropyl)-5-cyclopropyluracil (**12**) is illustrated in Scheme 2. Starting with 1-(bromomethyl)cyclopropane, reaction with sodium cyanide gives cyclopropylacetonitrile (**7**) in 41% yield. Base-catalyzed hydrolysis of **7** gives cyclopropylacetic acid (**8**) in 74% yield which is esterified by conversion to the acid chloride (not isolated) and then the methyl ester **9** in 51% yield. Conversion to 2-thio-5-cyclopropyluracil (**10**) is carried out using a modified procedure of Basnak and Farkas.[13] Compound **9** is condensed with ethyl formate to give the lithium enolate of methyl 2-cyclopropyl-2-formylacetate which, in its crude state, is allowed to react with thiourea to give 2-thio-5-cyclopropyluracil (**10**) in 36% yield. Hydrolysis with chloroacetic acid in water[13] gives 5-cyclopropyluracil (**11**) in 78% yield. 5-cyclopropyluracil (**11**) is then silylated by reaction with bis(trimethylsilyl)triflouroacetamide (BSTFA) to give bis-(trimethylsilyl)-5-cyclopropyluracil (not isolated). The latter is heated with 1,3-dibromopropane to give 1-(3-bromopropyl)-5-cyclopropyluracil (**12**) in 73% yield.

HPLC standards of the radical cyclization products are prepared as illustrated in Scheme 3. Reaction of 5-cyclopropyluracil **11** with BSTFA and then 1-bromopropane gives 1-propyl-5-cyclopropyluracil (**13**) in 35% yield.

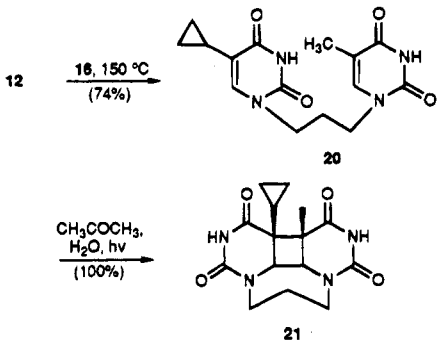
(13) Basnak, I.; Farkas, J. *Collect. Czech. Chem. Commun.* **1976**, *41*, 311–316.

Scheme 4



15 16 17 18 19trans

Scheme 5



12 20 21

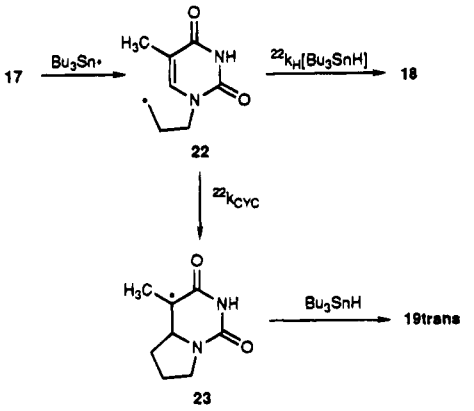
Photoinduced free radical cyclization of **12** gives (4*RS*,-5a*RS*)-4-cyclopropyl-4a,5,6,7-tetrahydro-1,3-dioxopyrrolo-[1, 2-*c*]pyrimidine **14-trans** in 21% yield.

Scheme 4 outlines the synthesis of the compounds used for the kinetic studies of the cyclization of 1-(3-bromopropyl)thymine **17**. Silylation of thymine with trimethylsilyl chloride[14] gives bis(trimethylsilyl)thymine (**16**) in 51% yield. Compound **16** is either allowed to react with 1,3-dibromopropane to give 1-(3-bromopropyl)thymine (**17**) in 48% yield or allowed to react with 1-bromopropane giving 1-propylthymine (**18**) in 15% yield. Photoinduced free radical cyclization of **17** gives (4*RS*,5a*RS*)-4-methyl-4a,5,6,7-tetrahydro-1,3-dioxopyrrolo[1,2-*c*]pyrimidine **19-trans** in 19% yield.

The synthesis of 1-[3-(thym-1-yl)propyl]-5-cyclopropyluracil photodimer (**21**) is illustrated in Scheme 5 and is based on the work of Golankiewicz,[15] Leonard,[16] and Nishimura.[14] Heating 1-(3-bromopropyl)-5-cyclopropyluracil (**12**) in a neat solution of bis(trimethylsilyl)thymine (**16**) gives 1-[3-(thym-1-yl)propyl]-5-cyclopropyluracil (**20**) in 74% yield. Photolysis of this material in an aqueous acetone solution affords 1-[3-(thym-1-yl)propyl]-5-cyclopropyluracil photodimer **21** in 100% yield.

Free Radical Cyclization. Few examples of carbon-centered free radical additions to the 5–6 double bond of uracil derivatives are known.[17] Therefore, it was of interest to determine if radical **22** would cyclize as illustrated in Scheme 6. The latter radical was generated by means of tri-*n*-butyltin hydride mediated chain reaction, initiated by UV irradiation. This method of cyclization has been extensively described.[18] The *n*-$Bu_3Sn^•$ radicals generated in the initiation step abstract a Br-atom from the alkyl group. The alkyl radical thus generated either cyclizes to give a tertiary radical **23** (and ultimately **19-trans**) or abstracts a H-atom from *n*-Bu_3-SnH to give **18**.

Scheme 6



17 18 22 23 19trans

Treatment of **17** with Bu_3SnH and UV irradiation gives the expected radical cyclization product pyrrolopyrimidine **19-trans** and the reduction product **18** in reasonable yields. Although only 12–15% of product **19-trans** was isolated, HPLC analysis of the reaction mixture showed that the pyrrolopyrimidine was formed in >80% yield (see below). The low isolated yields are due to losses in the purification procedure, which was not optimized. Similar treatment of cyclopropyl derivative **12** with Bu_3SnH and UV irradiation gives pyrrolopyrimidine **14-trans** and 1-propyl-5-cyclopropyluracil (**13**) in a combined yield of 80–95%. Scheme 7 illustrates the hypothetical intermediates and products which could occur upon cyclization of **12**. Surprisingly, no cyclopropyl rearranged products (such as **27**) were observed.

An interesting feature of these reactions is that the addition occurs to give exclusively the *trans* products. NMR spin–spin decoupling experiments on **19-trans** give a coupling constant for the C5–C6 ring protons of 12.3 Hz (Figure 1). The large coupling constant observed is typical for vicinal diaxial protons and thus indicates a *trans* orientation for the C5–C6 protons.[19,20] Similar ^1H NMR decoupling experiments revealed that free radical cyclization of **12** yielded only a *trans*-pyrrolopyrimidine product (**14-trans**).

The exclusive formation of products with *trans* stereochemistry seemed to warrant further investigation. Previous work on the formation of 5–6 fused ring systems

(14) Nishimura, T.; Iwai, I. *J. Chem. Pharm. Bull. Jpn.* **1964**, *12*, 352–356.
(15) Kazmierczak, F.; Langer, J.; Golankiewicz, K. *Rocz. Chem.* **1973**, *47*, 1943–1948.
(16) Browne, D. T.; Eisinger, J.; Leonard, N. J. *J. Am. Chem. Soc.* **1968**, *90*, 7302–7323.
(17) Itahara, T.; Seto, Y. *Chem. Lett.* **1988**, 1441–1442.
(18) For reviews see: (a) Newmann, W. P. *Synthesis* **1987**, 665–683. (b) Curran, D. P. *Synthesis*, **1988**, 417–439. (c) Giese, B. In *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds (Organic Chemistry Series; v. 5)* Baldwin, J. E., Series Ed.; Permangon Press: New York, 1986.
(19) Lambert, J. B.; Shurvell, H. F.; Lightner, D.; Cooks, R. G. *Introduction to Organic Spectroscopy*; Macmillan: New York, 1987; pp 76–79.
(20) This assignment is further supported by AM1 geometry optimization of the two possible stereoisomers of **19-trans**. These calculations predict dihedral angles between the vicinal C5–C6 protons of 43° for the *cis* isomer and 164° for the *trans* isomer. The Karplus equation predicts the *cis* isomer to have a maximum coupling constant of 7.5 Hz whereas the *trans* isomer would have a maximum coupling contant of 12.9 Hz.

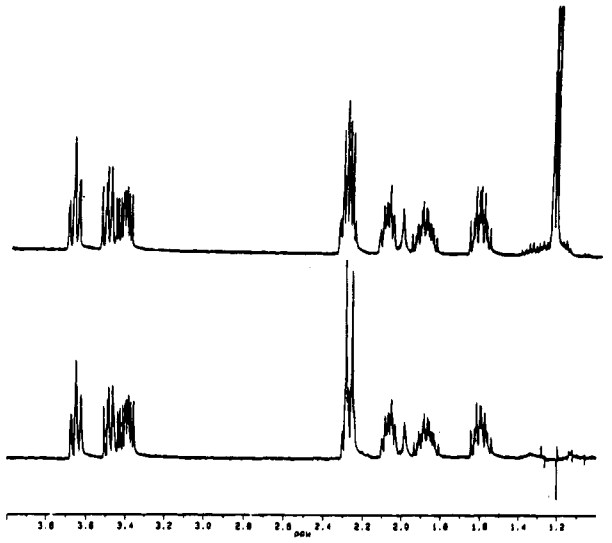
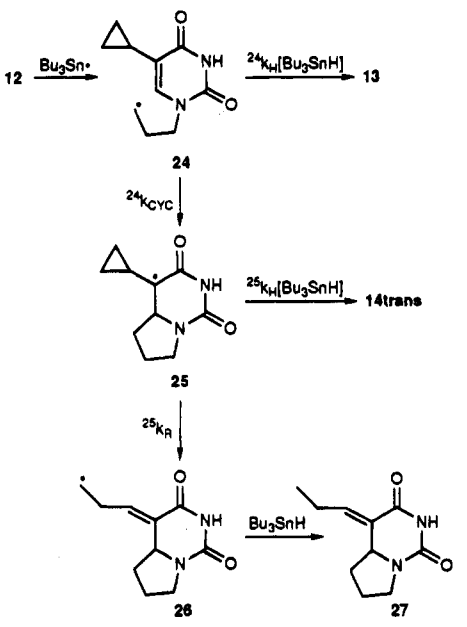


Figure 1. 400-MHz ^{1}H NMR spectrum of **19-trans** without decoupling (top) and with decoupling of the 5-methyl group at 1.20 ppm (bottom). This causes the C5 hydrogen (2.25 ppm) to resolve to a doublet with a coupling constant of 12.3 Hz for the C5–C6 ring protons. This strongly implies an eclipsed or antiperiplanar configuration of these hydrogens.

Scheme 7



via intermolecular radical addition to double bonds suggest that hydrogen atom transfer from tributyltin hydride should come from the less hindered face of intermediate radical species **23** and **25**, thus resulting in formation of the *cis* product.[21] This does not appear to be the case for our system. We considered the possibility that C5 of the intermediate radical species **23** and **25** was pyramidalized, thus favoring *trans* products. Geometry minimization of the intermediate radical species **23** using AM1/UHF calculations predicts a planar geometry at C5, as well as an overall "bowl-shaped" conformation of the molecule (Figure 3). AM1/UHF calculations on radical **25** yielded similar results (data not shown). From these studies it would appear that hydrogen atom donation is coming from the more hindered side (inside of the "bowl").[22]

(21) Stork, G. *Bull. Soc. Chim. Fr.* **1990**, *127*, 675–680.

Table 1. Calculated and Experimental Bond Dissociation Energies for Compounds Used in This Study

RH	R•	BDE (kcal/mol)	method
19-trans	**23**	76.8	AM1/UHF
		77.5	PM3UHF
19-cis	**23**	75.1	AM1/UHF
		77.3	PM3/UHF
14-trans	**25**	76.5	AM1/UHF
		73.1	PM3/UHF
14-cis	**25**	77.1	AM1/UHF
		68.4	PM3/UHF
CH_3COCH_3	CH_3COCH_2•	88.2	AM1/UHF
		87.8	PM3/UHF
		91.7	experiment[a]
R_3SnH	R_3Sn•	74	experiment[b]

[a] Reference 35. [b] Reference 24.

To understand the thermodynamics of these reactions and the origin of the exclusive formation of trans products, AM1 and PM3 semiempirical calculations were performed to predict C5–H bond dissociation energies (BDE) and relative stabilities of the products. The calculations provide the heat of formation, ΔH_f for the radicals (R•) and the parent compounds (RH). BDE's are determined from the difference between these quantities along with the heat of formation of the H-atom (eq 3).

$$\mathrm{BDE} = [\Delta H_f(\mathrm{R}^\bullet) + \Delta H_f(\mathrm{H}^\bullet)] - \Delta H_f(\mathrm{RH}) \qquad (3)$$

The BDE's thus calculated for the each of the cis and trans isomers of **19** and **14** are listed in Table 1. Included in Table 1 are similar calculations carried out for the acetonyl radical $CH_3C(O)CH_2$•. This species is of interest because it is a carbonyl-substituted radical for which experimental BDE's are available. Calculated BDE's for the C5-dihydrouracil radicals range from 68 to 77 kcal/mol, compared with 88.2–87.8 for the acetonyl radical. As reported previously, the UHF wave functions exaggerate the stabilization of the radicals somewhat.[23] The calculated BDE's for acetonyl radical are 3.5–3.9 kcal/mol lower than the experimental value. Despite this, it is clear from comparison of the calculated values that the C5-dihydrouracil radicals enjoy considerably more resonance stabilization compared with the acetonyl radical.

The stereochemistry of the hydrogen transfers can be explained by the Hammond postulate. The semiempirical calculations predict high stabilities for radicals **25** and **23**. Therefore, H-atom transfer from n-Bu_3SnH to these radicals should be less exothermic than for typical alkyl radicals. In this case, the transition state should occur later and reflect the stabilities of the products. It follows then that the more stable trans products would be preferred. The low values for the BDE's make it tempting to speculate that the H-atom transfer from n-Bu_3SnH is reversible, especially considering that the Sn–H BDE for the latter is known from experiment to be 74 kcal/mol.[24] However, such a conclusion would be unwarranted. The UHF wavefunctions in semiempirical cal-

(22) We also considered the possibility that radicals **23** and **25** are strongly oxidizing radicals which are reduced by the solvent (ethanol), thus giving an anion at C5 and, after protonation from the solvent, giving the more thermodynamically stable *trans* product. However, photolysis of **17** using EtOD as the solvent shows no deuterium incorporation in the final product **19-trans**, thus ruling out this possibility.

(23) Tupper, K. J.; Gajewski, J. J.; Counts, R. W. *THEOCHEM* **1991**, *236*, 211–217.

(24) Burkey, T. J.; Majewski, M.; Griller, D. *J. Am. Chem. Soc.* **1986**, *108*, 2218–2221.

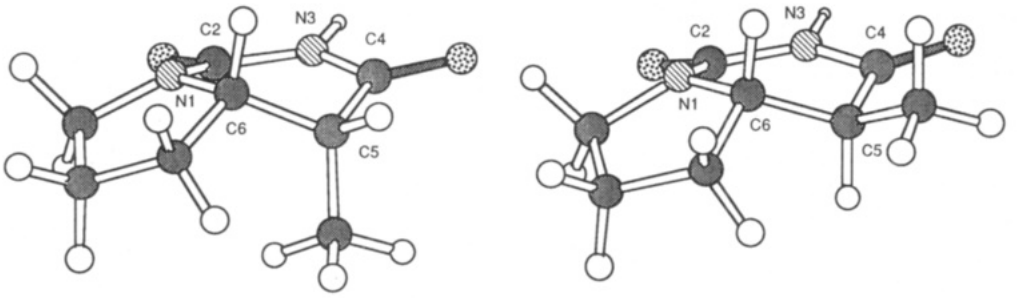


Figure 2. AM1/UHF-minimized structures of the two possible isomers which can result from free radical cyclization of **17**. The *trans* isomer **19-trans** (observed) is on the right and the *cis* isomer **19-cis** (not observed) is on the left. The dihedral angles between the vicinal 5−6 protons for the *trans* and *cis* isomers are calculated to be 164° and 43°, respectively.

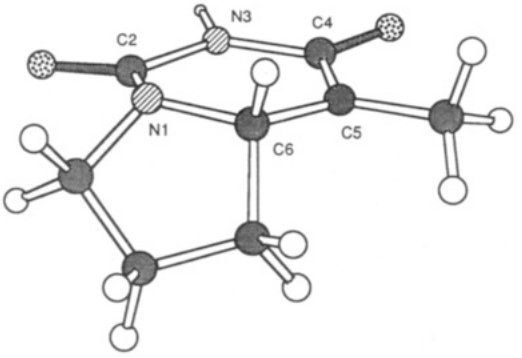


Figure 3. AM1/UHF-minimized structure of radical intermediate **23** which occurs upon free radical cyclization of **17**. Note the planar geometry at C5.

culations are known to overestimate radical stabilities. A more thorough computational study of these types of radicals would be necessary before the calculated BDE's could be meaningfully compared with experimental values.

Rate Constants for Cyclization. The unusually high stability of radicals **23** and **25** led us to investigate the rates of intramolecular free radical cyclization **22** and **24**. This was accomplished by means of competition experiments. Photoinitiated free radical cyclization of **17** in the presence of 10 molar equiv of tribuyltin hydride yielded uncyclized product **18** and cyclized product **19-trans** as the only products observed by HPLC and ^{1}H NMR analysis. The reaction was run at various concentrations of tributyltin hydride, and the relative yields of **18** and **19-trans** were determined by HPLC. In all cases, yields of **18** and **19-trans** ($Y_{18} + Y_{19trans}$) were 90% of the theoretical yield.

The relative yields were analyzed using the kinetic scheme shown in Scheme 6. Cyclization competes with H-atom transfer to primary radical **22**. Assuming that cyclization to form the pyrrollopyrimidine is irreversible, the relative rates of k_H and k_{cyc} are given by the ratio reduced product **18** to cyclized product **19-trans** (eq 4).

$$\frac{Y_{18}}{Y_{19\text{-trans}}} = \frac{^{22}k_H[Bu_3SnH]}{^{22}k_{cyc}} \qquad (4)$$

A plot of [Bu_3SnH] vs the ratio of reduced to cyclized product yields gives a straight line with a slope of $^{22}k_H/^{22}k_{cyc}$ (Figure 4). This gives a relative rate of hydrogen atom abstraction to ring closure of 61.8 for **22**.

The rate constant for hydrogen atom transfer to *n*-butyl radical is 2.47×10^6 s^{-1}.[25] These rate constants are generally insensitive to chain length.[17b] Therefore, we

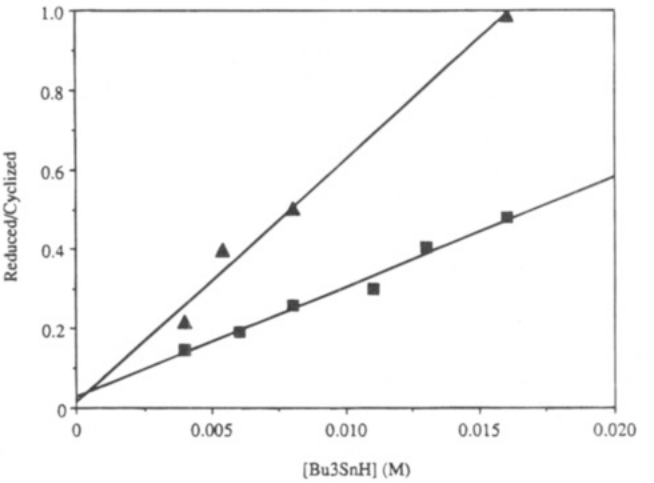


Figure 4. Product ratios from free radical cyclization of thymine derivitives vs n-Bu_3SnH concentration. Ratios are **18**/**19-trans** for starting material **17** (triangles, see Scheme 6) and **13**/**14-trans** for starting material **12** (squares, see Scheme 7).

take 2.47×10^6 M^{-1} s^{-1} as an estimate for $^{22}k_H$. The rate of ring closure was calculated (from eq 4) to be 4.0×10^4 s^{-1} for this radical. The interesting conclusion from this result is that the rate at which cyclization occurs for our system is reasonably close to the rate reported for 5-hexenyl radical[26] which is 1×10^5 s^{-1}.

A similar series of experiments was carried out with cyclopropyl derivative **12** in order to deduce the reactivity of its C5—C6 double bond toward intramolecular free radical addition. The only products of photoinitiated free radical cyclization observed (by HPLC and ^{1}H NMR analysis) were **13** and **14-trans**. The yields of **13** + **14-trans** were 85% of the theoretical yield. The plot of [n-Bu_3SnH] vs $Y_{13}/Y_{14trans}$ was linear, similar to that observed for **17** (Figure 4). The slope gave $^{24}k_H/^{24}k_{cyc} = 27.8$. The rate constant for cyclization was determined to be $^{24}k_{cyc} = 8.9 \times 10^4$ s^{-1} by taking the rate constant of hydrogen atom transfer from n-Bu_3SnH to primary radical **24** to be 2.47×10^6 M^{-1} s^{-1}. Again, this indicates that the C5-C6 bond has a similar rate of reactivity toward radical addition as an unactivated carbon—carbon double bond.

Cyclopropylcarbinyl Rearrangement. With compound **12** there is the additional issue of cyclopropyl ring opening (**25** → **26**, Scheme 7). In principle, it is possible that following cyclization, tertiary radical **25** partitions

(25) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739−7742.
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between H-atom transfer from n-Bu_3SnH (giving **14-trans**) and ring opening. However, even when the Bu_3SnH concentrations were brought to very low levels, no cyclopropyl ring rearranged products were detected by ^1H NMR or HPLC.[27]

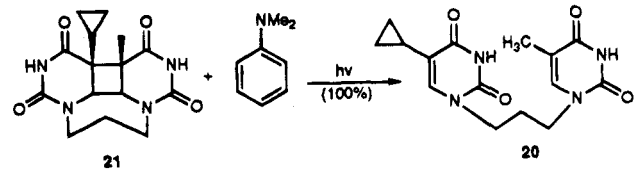
It is possible that some ring-opened products are formed in very low yields and escaped detection—mass balances from the HPLC determinations ranged from 85 to 90%. Four observations argue against this possibility. (1) The unaccounted mass appears to be the result of secondary photolysis of products **13** and **14-trans**. A plot of the yield of **13** + **14-trans** (based on converted starting material) vs irradiation time shows that the percentage of unaccounted material increases directly with irradiation time. (2) The loss of material was observed to approximately the same extent during reactions with thymine derivative **17** (where cyclopropyl ring-opening is not possible). (3) According to Scheme 7, ring-opening competes with H-atom transfer from n-Bu_3SnH. If ring-opening resulted in undetected products, then the material balance should decrease with decreasing [n-Bu_3SnH]. A plot of material balance vs [n-Bu_3SnH] showed no discernable correllation. (4) A plot of product ratio (**13**: **14-trans**) vs [n-Bu_3SnH] gives a straight line with a nearly zero intercept (Figure 4). If cyclopropyl ring opening were occuring at a kinetically significant rate, this would not be the case.[28]

In the absence of any detectable products from cyclopropylcarbinyl rearrangement, it is impossible to determine the rate constant for that process ($^{25}k_R$). However, on the basis of the yield of unrearranged products (**13** and **14-trans**), it is possible to estimate an upper limit for $^{23}k_R$. The assumption is that the yield of rearranged products is less than or equal to the unaccounted mass from the reactions. In this case, the ratio of unaccounted mass to the yield of **14-trans** is given by the ratio of the rate constants times the tributyltin hydride concentration (eq 5).

$$\frac{^{25}k_H[Bu_3SnH]}{^{25}k_r} \geq \frac{Y_{14\text{-trans}}}{1 - Y_{14\text{-trans}} - Y_{13}} \qquad (5)$$

The yields from reactions at varying [n-Bu_3SnH] can be analyzed using inequality 5. Although a plot of the ratio of the yield of **14-trans** to the unaccounted mass vs [n-Bu_3SnH] gives very poor correlation, the best-fit slope has a value of 79. Assuming that the upper limit of the rate of hydrogen atom transfer to the unrearranged intermediate is at best close to that of *tert*-butyl radical ($^{25}k_H \leq 1.7 \times 10^6\ M^{-1}\ s^{-1}$),[29] the rate of cyclopropyl carbinyl rearrangement is estimated to be $^{25}k_r \leq 2.5 \times 10^4\ s^{-1}$. The actual k_r is probably much lower than this value for two reasons. First, as discussed above, the unaccounted mass is largely due to secondary photolysis rather than cyclopropylcarbinyl rearrangement. Second, the stability of tertiary radical **25** predicted from the AM1 calulations indicates that $^{25}k_H$ is significantly lower than that for the *tert*-butyl radical.

Scheme 8



21 20

The interesting conclusion of these results is that although the stability of radical **25** is greater than expected, the rate of cyclization **24** → **25** is very close to that of the model 5-hexenyl system. One might have predicted that if **25** is such a stable radical species, then the process **24** → **25** would be much faster than the 5-hexenyl radical system. This is not necessarily the case. We propose that any rate enhancement that is gained through resonance stabilization of radical product **25** is lost by the fact that formation of the new bond breaks the pseudoaromaticity of the uracil ring. These two effects cancel each other out. Therefore, the barrier to cyclization is approximately the same as for the 5-hexenyl radical. However, once the intermediate radical species **25** is formed, the barrier to cyclopropylcarbinyl rearrangement to form **26** is much higher than it is for the cyclopropyl methyl radical since radical **25** is stabilized by resonance. Thus, little or no cyclopropyl carbinyl rearrangement is observed for our system.

Photoinduced Electron-Transfer Splitting of 21. Dimethylaniline (DMA)-photosensitized cleavage of **21** gave **20** in 100% yield as determined by HPLC and ^1H NMR analysis (Scheme 8). The conversion of **21** to **20** was linear with irradiation time. Attempts at trapping intermediate radical species by the addition of thiols failed due to the fact that the thiols quench the singlet excited state of DMA.

We did consider the possibility that **21** was splitting via a pathway not involving SET. Irradiation of a solution of **21** without DMA showed no reaction after 6 h irradiation time. Likewise, irradiation of a solution of **20** yielded no dimer after 6 h irradiation, therefore ruling out the possibility of redimerization after the initial cleavage. DMA-photosensitized cleavage of cis-syn dimethylthymine dimer (DMT dimer) is known to occur via a SET mechanism.[11] Due to the structural similarity of **21** with DMT dimer, an alternative mechanism of dimer cleavage is highly unlikely.

Conclusions

The 5,6 double bond in uracil derivatives is reactive toward 5-*exo-trig* radical cyclization. For example, the 3-(1-thyminyl)-1-propyl radical **22** undergoes efficient cyclization with a rate constant similar to that for the parent 5-hexenyl radical cyclization. On the other hand, no radical rearrangement is detected when a cyclopropyl group is incorporated into the 5-position of a uracil and a radical center is generated at that site (radical **25**). Semiempirical calculations suggest that 5,6-dihydrouracil-5-yl radicals (e.g., **23** and **25**) experience considerably more resonance stabilization than expected for a simple carbonyl-substituted radical, such as acetonyl radical. The cyclopropylcarbinyl rearrangement is often

(27) Considering the stability of radical **25**, a reviewer suggested that its cyclopropyl carbinyl rearrangement may be reversible. In this case, we would still expect to observe products from the more reactive primary radical **26**. For example, see ref 30b.

(28) A plot of the yield of **13**/**14-trans** vs Bu_3SnH concentration (Figure 4) for the kinetic system depicted in Scheme 7 can be described by the equation:

$$\frac{\mathbf{13}}{\mathbf{14\text{-trans}}} = \frac{^{24}k_H}{^{24}k_{CYC}}[Bu_3SnH] + \frac{^{24}k_H\,^{25}k_R}{^{24}k_{CYC}\,^{25}k_H}$$

(29) Johnston, L. J.; Lusztyk, J.; Wayner, D. D. M.; Abeywickreyma, A. N.; Beckwith, A. L. J.; Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 4594.

used as a mechanistic probe for free radicals. The results from this study show that it should not be assumed that these rearrangements will invariably occur rapidly. Other work in the current literature supports this generalization.[30] Caution should be applied when interpreting negative results from these types of experiments.

Experimental Section

General. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. All distillations were performed under a dry N_2 atmosphere unless otherwise stated. THF and benzene were distilled from Na/benzophenone ketyl. DMSO was distilled from CaH_2. Pyridine, MeOH, diisopropylamine, and Et_3N were distilled from Na. Ethyl formate was allowed to stand over K_2CO_3 overnight and then distilled from P_2O_5. 1,3-Dibromopropane and 1-bromopropane were distilled from P_2O_5. (Bromomethyl)-cyclopropane was obtained from Aldrich chemicals. Boiling points were obtained during short path distillations and are uncorrected. ^1H NMR J values are given in Hz.

Preparative photolysis reactions were performed using an Ace-Hanovia medium-pressure Hg vapor lamp. Unless otherwise noted, no filters were used.

Photochemical Cleavage of 5-Cyclopropyluracil–Thymine Photodimer (21). A quartz cuvette was charge with 2 mL of a 3×10^{-3} M aqueous 5-cycloproyluracil–thymine dimer **21** solution which was saturated with *N,N*-dimethylaniline. The cuvette was sealed with a rubber septum and purged with N_2. The sample was irradiated with a 400-W Xe arc lamp through a 310-nm cutoff filter and analyzed by reversed-phase HPLC. Chromatograms were obtained using an isocratic 4:1 H_2O:CH_3CN mobile phase, a C18 stationary phase, and a detector wavelength of 222 nm. Percent yield of the photoproducts was determined from their peak areas by comparison to concentration curves derived from authentic samples.

Kinetic Studies. To 5 mL of an ethanolic 1.7×10^{-3} M solution of 1-(3-bromopropyl)-5-cyclopropyluracil (**12**) or 1-(3-bromopropyl)thymine (**17**) was added 23 mL (10 equiv) of n-Bu_3SnH. The solution was diluted with varying amounts of EtOH, placed in a 5-mL quartz test tube, and purged of O_2 with N_2. Several samples were prepared in the same manner, and all were irradiated in parallel with a medium-pressure Hg vapor lamp for 10 min and analyzed by reversed-phase HPLC. Chromatograms were obtained using an isocratic 3:1 H_2O:CH_3CN mobile phase, a C18 stationary phase, and a detector wavelength of 222 nm. Percent yield of the photoproducts was determined from their peak areas by comparison to concentration curves derived from authentic samples.

Computer Modeling. Semiempirical molecular orbital calculations were carried out on a Silicon Graphics Personal IRIS workstation using version 1.0 of the Spartan software package, available from Wavefunction, Inc., Irvine, CA. Geometry optimization and heats of formation were calculated using the AM1[31a] and PM3[31b,c] semiemperical methods. UHF wavefunctions were used for both radicals and closed shell species.

Cyclopropylacetonitrile (7). A solution of 11.3 g (230 mmol) of NaCN in 120 mL of dry DMSO was heated to 100 °C. To this stirred solution was added 25 g (185 mmol) of (bromomethyl)cyclopropane slowly so that the solution temperature did not exceed 140 °C. The solution was allowed to cool to room temperature whereupon it solidified. The solid was dissolved in 250 mL of water and extracted with four 100-mL portions of ether. The ether layers were combined and dried over $MgSO_4$. The solvent was removed by rotary evaporation to give 15.3 g of crude **7** as a yellow liquid which was purified by vacuum distillation to give 6.2 g (41%) of **7** as a clear liquid: bp 58 °C (15 mmHg); ^1H NMR ($CDCl_3$) δ 0.32 (m, 2H), 0.65 (m, 2H), 1.07 (m, 1H), 2.37 (d, $J = 6.4$, 2H); ^{13}C NMR ($CDCl_3$) δ 118.8, 21.8, 6.8, 4.6; IR (neat) 3084 (s), 3002 (s), 2238 (s), 1420 (s); low-resolution mass spectrum, m/z (rel intensity) 81 (M^+, 64), 80 (74), 54 (100); high-resolution mass spectrum, m/z 81.0586 (C_5H_7N requires 81.0579)

Cyclopropylacetic Acid (8). To a cooled (ice bath) solution of 72 g (1.8 mol) of NaOH in 90 mL of water was slowly added 90 mL (870 mmol) of 30% aqueous H_2O_2. The ice bath was removed, and 15 g (185 mmol) of **7** was added to the solution. The solution was allowed to stir at room temperature until most of the foaming subsided (about 30 min). The solution was slowly brought to reflux and was allowed to stir for 44 h. The solution was then cooled to room temperature and extracted once with $CHCl_3$ to remove any unreacted starting material. The solution was then acidified to pH 0 with HCl, allowed to cool, and extracted thoroughly with $CHCl_3$. The $CHCl_3$ layers were combined and dried over $MgSO_4$. The solvent was removed by rotary evaporation to give 13.8 g (74%) of **8** as a yellow liquid which was judged to be >95% pure by ^1H NMR: bp 110 °C (15 mmHg) (lit.[32] bp 90 °C (15 mmHg)); ^1H NMR ($CDCl_3$) δ 0.19 (m, 2H), 0.58 (m, 2H), 1.06 (m, 1H), 2.27 (d, $J = 7.1$, 2H), 9.70 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 179.8, 39.2, 6.6, 4.4; IR (neat) 3007 (br s), 1708 (vs); low-resolution mass spectrum, m/z (rel intensity) 100 (M^+, 14), 60 (13), 55 (100); high-resolution mass spectrum, m/z 100.0523 ($C_5H_8O_2$ requires 100.0524).

Methyl Cyclopropylacetate (9). To a stirred solution of 38 mL (394 mmol) of oxallyl chloride in 460 mL of dry benzene was added 34.6 g (345 mmol) of **8** and 2 drops of DMF. The solution was stirred until the evolution of gas ceased (3 h), and the solvent was removed by rotary evaporation. The crude cyclopropylacetic acid chloride was added dropwise to a stirred solution of 56 mL (690 mmol) of pyridine in 580 mL of MeOH. The solution was stirred at room temperature overnight. The solution was poured into 600 mL of water and extracted with $CHCl_3$. The $CHCl_3$ layers were washed once with 10% aqueous HCl solution, once with water, once with saturated aqueous $NaHCO_3$ solution, and once again with water. The $CHCl_3$ layer was dried over $MgSO_4$ and the solvent removed by rotary evaporation to give the crude product as a yellow liquid. Purification by short path vacuum distillation gave 20.17g (51%) of **9** as a colorless liquid: bp 55 °C (15 mmHg); ^1H NMR, IR, and mass spectroscopic data matched that previously reported;[33] ^{13}C NMR ($CDCl_3$) δ 176.5, 51.5, 39.2, 6.9, 4.4.

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5-Cyclopropyl-2-thiouracil (10). To a solution of 5.8 mL (35 mmol) of *N*-isopropylcyclohexylamine in 30 mL of dry THF under dry N_2 was added 21 mL (35 mmol) of a 1.67 M n-BuLi in Hex solution. The solution was cooled to −78 °C, and 2 g (17.5 mmol) of **9** in 12 mL of dry THF were added dropwise with stirring over 1 h. The solution was allowed to stir at −78 °C for 1 h. A solution of 2.1 mL (26 mmol) of ethyl formate in 5 mL of dry THF was added to the reaction solution which was then allowed to stir at −78 °C for 1 h. The cold bath was removed, and the solution was allowed to stir for 1 h. A solution of 2 g (26 mmol) of thiourea in 16 mL of hot MeOH was added to the reaction solution which was then allowed to stir at reflux overnight. The solution was allowed to cool to room temperature, and the solvent was removed by rotary evaporation. The remaining solid was dissolved in 25 mL of water and extracted with two 25-mL portions of $CHCl_3$. The aqueous layer was acidified to pH 4 with AcOH and placed on an ice bath for 1 h. The resulting solid was purified by flash column chromatography (3:2 Hex:EtOAc). The resulting solid was recrystallized from water to give 950 mg (36%) of **10** as a white solid: mp 211−213 °C, (lit.[13] mp 211−212 °C); ^{1}H, IR, and mass spectroscopic data matched that previously reported;[13] ^{13}C NMR (d_6-DMSO) δ 174.4, 161.6, 135.6, 119.2, 7.8, 5.5.

5-Cyclopropyluracil (11). With use of the procedure of Basnak and Farkas,[12] 1.5 g (8.9 mmol) of **10** was converted to crude product which was recrystallized from water to give 1 g (78%) of **11** as white crystals: mp 214−217 °C; ^{1}H NMR, IR, and mass spectroscopic data matched that previously reported;[13] ^{13}C NMR (d_6-DMSO) δ 164.6, 151.0, 135.8, 113.6, 7.6, 5.9.

1-(3-Bromopropyl)-5-cyclopropyluracil (12). A suspension of 700 mg (4.6 mmol) of **11** in 17 mL (64.8 mmol) of BSTFA was stirred under N_2 at 140 °C until the solution turned clear (about 45 min). The solution was allowed to cool to room temperature, and the excess BSTFA was removed *in vacuo* leaving bis(trimethylsilyl)-5-cyclopropyluracil as an oil. To the flask was added 7.5 mL (74 mmol) of 1,3-dibromopropane. The solution was allowed to stir at 70 °C under N_2 for 6 h. The solution was allowed to cool to room temperature, poured into 45 mL of water, and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were dried over $MgSO_4$ and filtered and the solvent removed by rotary evaporation leaving the crude product in 1,3-dibromopropane. The 1,3-dibromopropane was removed by short path vacuum distillation (0.1 mmHg) leaving a solid residue which was recrystallized from $CHCl_3$:Hex to yield 925 mg (73%) of **12** as white crystals: mp 123−125 °C; ^{1}H NMR ($CDCl_3$) δ 0.52 (m, 2H), 0.87 (m, 2H), 1.72 (m, 1H), 2.25 (quintet, J = 6.3, 2H), 3.42 (t, J = 6.3, 2H), 3.88 (t, J = 6.3, 2H), 6.91 (d, J = 1.1, 1H), 9.14 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 164.0, 150.6, 139.5, 116.8, 47.4, 31.1, 29.9, 7.9, 5.7; IR (KBr) 3392 (w), 3169 (w), 3019 (m), 1684 (s); low-resolution mass spectrum, m/z (rel intensity) 274 (M + 2, 100), 272 (M^+, 99), 193 (21), 165 (11), 121 (51); high-resolution mass spectrum, m/z 272.0160 ($C_{10}H_{13}N_2O_2Br$ requires 272.0160).

1-Propyl-5-cyclopropyluracil (13). A solution of 462 mg (3 mmol) of **11** in 11 mL of BSTFA was stirred at reflux under a N_2 atmosphere until the solution became clear (about 1.5 h). The solution was allowed to cool, and the excess BSTFA was removed in vacuo (0.1 mmHg) leaving bis(trimethylsilyl)-5-cyclopropyluracil as a clear oil. To the oil was added 5 mL of dry 1-bromopropane. The solution was allowed to stir at reflux under N_2 for 18 h. The solution was allowed to cool, and 25 mL of water was added. The solution was extracted with $CHCl_3$. The organic layers were combined and dried over $MgSO_4$, and the solvent was removed by rotary evaporation leaving a greasy residue which was purified by flash column chromatography (3:2 EtOAc:Hex) to give 205 mg (35%) of **13** as a white solid: mp 160−162 °C; ^{1}H NMR ($CDCl_3$) δ 0.52 (m, 2H), 0.91 (m, 5H), 1.70 (m, 3H), 3.66 (t, J = 7.4, 2H), 6.80 (s, 1H), 9.04 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 164.1, 150.6, 139.3, 116.4, 50.3, 22.4, 10.9, 8.0, 5.6; IR ($CHCl_3$) 3394 (m), 3020 (s), 2969 (m), 2879 (w), 1681 (vs), 1469 (s); low-resolution mass spectrum m/z (rel intensity) 194 (M^+, 100), 179 (16), 165 (10), 152 (15), 137 (11), 122 (28), 109 (42), 94 (19), 80 (26), 66 (39), 53 (13); high-resolution mass spectrum, m/z 194.1064 ($C_{10}H_{14}N_2O_2$ requires 194.1055).

(4*RS*,5a*RS*)-4-Cyclopropyl-4a,5,6,7-tetrahydro-1,3-dioxopyrrolo[1, 2-*c*]pyrimidine (14-trans). A solution of 204 mg (0.75 mol) of **12** and 1.7 mL (6.4 mmol) of n-Bu_3SnH in 1600 mL of absolute EtOH was irradiated with a medium-pressure Hg vapor lamp for 1 h. The end of the reaction was indicated by a solution color change from clear to yellow. The solvent was removed by rotary evaporation leaving a yellow oil which was allowed to stand under vacuum (0.1 mmHg) for 2 h. The resulting yellow gum was purified by flash column chromatography (4:1 EtOAc:Hex, relevant fractions determined by HPLC analysis) to give an off-white semisolid which was recrystallized from $CHCl_3$:Hex to give 31 mg (21%) of **14-trans** as white crystals: mp 210−214 °C dec; ^{1}H NMR ($CDCl_3$) δ 0.22 (m, 1H), 0.42 (m, 1H), 0.54 (m, 1H), 0.77 (m, 1H), 0.83 (m, 1H), 1.52 (m, 1H), 1.61 (m, 1H), 1.89 (m, 1H), 2.08 (m, 1H), 2.08 (m, 1H), 2.46 (m, 1H), 3.41 (m, 1H), 3.63 (m, H), 7.32 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 171.7, 150.4, 59.2, 51.6, 44.7, 33.1, 23.4, 9.0, 4.2, 2.6; IR ($CHCl_3$) 3401 (m), 3087 (m), 3018 (s), 2876 (w), 699 (vs), 1459 (s); low-resolution mass spectrum, m/z (rel intensity) 194 (M^+, 13), 152 (31), 82 (33), 70 (100), 54 (32); high-resolution mass spectrum, m/z 194.1063 ($C_{10}H_{14}N_2O_2$ requires 194.1055).

Bis(trimethylsilyl)thymine (16). With use of the procedure described by Nishimura,[14] 12.6 g (82.6 mmol) of thymine was converted into crude product which was purified by vacuum distillation to afford 11.7g (51%) of **16** as a clear liquid which solidified upon standing at room temperature and readily reverted to thymine upon exposure to moisture: bp 80 °C (0.1 mmHg) (lit.[14] bp 123−125 °C (13 mm Hg)); mp 74−76 °C (lit.[14] mp 63−65 °C); ^{1}H NMR ($CDCl_3$) δ 0.25 (s, 9H), 0.31 (s, 9H), 1.95 (s, 3H), 8.07 (s, 1H).

1-(3-Bromopropyl)thymine (17). With use of the procedure outlined by Golankiewicz,[15] 1 g (3.7 mmol) of **16** in 6 mL of 1,3-dibromopropane (59 mmol) was stirred at 70 °C under an Ar atmosphere for 6 h. The solution was poured into 60 mL of water and extracted with $CHCl_3$. The organic layers were combined and dried over $MgSO_4$. The solvent was removed by rotary evaporation leaving **17** in 1,3-dibromopropane. The 1,3-dibromopropane was removed by vacuum distillation (bp 25 °C, 0.1 mmHg) leaving crude **17** as a white solid. Recrystallization from $CHCl_3$/Hex afforded 0.44 g (48%) of **17** as white crystals: mp 131−136 °C (lit.[16] mp 136−138 °C); ^{1}H NMR spectroscopic data matched that previously reported.[16]

1-Propylthymine (18). A solution of 1.5 g (9.8 mmol) of **16** in 14 mL of dry 1-bromopropane was stirred at reflux under N_2 for 20 h. The solution was poured into

50 mL of water and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$, and the solvent was removed by rotary evaporation leaving a brown residue. Recrystallization from $CHCl_3$:Hex afforded 250 mg (15%) of **18** as white crystals: mp 130–133 °C (lit.[16,34] mp 138 °C, 134–136 °C); ^1H NMR matched that previously reported.[34]

(4*RS*,5a*RS*)-4-Methyl-4a,5,6,7-tetrahydro-1,3-dioxopyrrolo[1,2-*c*]pyrimidine (19-trans). A solution of 1.45 g (6 mmol) of **17**, 930 mg (24.6 mmol) of $NaBH_4$, and 161 mL (0.6 mmol) of n-Bu_3SnH in 1000 mL of absolute EtOH was irradiated for 90 min with a medium-pressure Hg vapor lamp. The end of the reaction was indicated by a solution color change from clear to yellow-orange. The solution was poured into 1000 mL of water and acidified to pH 4 with AcOH. The solution was extracted with $CHCl_3$. The organic extracts were combined, washed with a saturated aqueous $NaHCO_3$ solution, washed with water, and dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The remaining residue was purified by flash column chromatography (4:1 EtOAc:Hex; the relevant fractions were determined by HPLC analysis) to give 185 mg (19%) of **19-trans** as a white solid: mp 188–192 °C; ^1H NMR ($CDCl_3$) δ 7.66 (s, 1H), 3.67 (m, 1H), 3.51 (m, 1H), 3.41 (m, 1H), 2.31 (m, 1H), 2.10 (m, 1H), 1.91 (m, 1H), 1.62 (m, 1H), 1.24 (d, J = 6.9, 3H); ^{13}C NMR ($CDCl_3$) δ 172.6, 150.4, 59.5, 45.1, 41.7, 32.6, 23.3, 11.2; IR ($CHCl_3$) 3406 (m), 3013 (m), 2981 (m), 2881 (w), 1700 (s), 1469 (m), 1338 (m), 1244 (m); low-resolution mass spectrum, m/z (rel intensity) 169 (M + 1, 6), 168 (M^+, 52), 167 (4), 149 (4), 140 (1), 129 (1), 124 (2), 105 (5), 97 (10), 84 (10), 77 (4), 70 (100), 56 (25); high-resolution mass spectrum, m/z 168.0901 ($C_8H_{12}N_2O_2$ requires 168.0899).

1-[3-(Thym-1-yl)propyl]-5-cyclopropyluracil (20). A flame-dried flask was charged with 250 mg (0.91 mmol) of **12** and 925 mg (3.42 mmol) of **16**. The solution was heated to 150 °C with stirring under N_2 for 6 h. The excess **16** was distilled off under vacuum (0.1 mmHg) and the remaining solid collected. The crude product was recrystallized from EtOH to give 214 mg (74%) of **20** as white crystals: mp 258–260 °C; ^1H NMR (d_6-DMSO) δ 0.51 (m, 2H), 0.67 (m, 2H), 1.53 (m, 1H), 1.72 (s, 3H), 1.86 (quintet, J = 6.8, 2H), 3.62 (t, J = 6.8, 4H), 7.30 (s, 1H), 7.50 (s, 1H), 11.22 (s, 2H); ^{13}C NMR (d_6-DMSO) δ 164.2, 164.1, 150.9, 150.1, 141.2, 139.6, 114.5, 108.5, 44.9, 44.7, 27.9, 11.9, 7.7, 5.5; UV–vis (H_2O) λ_{max} = 209, 270; IR (KBr) 3030 (s), 1676 (s), 1474 (m), 1360 (m), 1218 (m); low-resolution mass spectrum, m/z (rel intensity) 318 (M^+, 78), 220 (95), 201 (75), 192 (36), 182 (81), 167 (100); high-resolution mass spectrum, m/z 318.1319 ($C_{15}H_{18}N_4O_4$ requires 318.1328).

1-[3-(Thym-1-yl)propyl]-5-cyclopropyluracil Photodimer (21). To a solution of 100 mg (0.31 mmol) of **20** in 450 mL of water was added 50 mL of spectroscopic grade acetone. The solution was placed in an immersion well photolysis tube and purged of O_2 by bubbling N_2 through the solution. The solution was irradiated with a medium-pressure Hg vapor lamp with a 290-nm cutoff filter (Corex) for 1 h. The solvent was removed by rotary evaporation, and the remaining residue was washed with acetone and dried under vacuum to yield 100 mg (100%) of **21** as a white solid which was judged to be >95% pure by ^1H NMR: mp > 300 °C; ^1H NMR (400 MHz, d_6-DMSO) δ 0.12 (m, 1H), 0.46 (m, 1H), 0.68 (m, 2H), 1.30 (m, 2H), 1.47 (s, 3H), 1.84 (m, 2H), 2.73 (m, 2H), 3.59 (d, J = 6.5, 1H), 3.73 (d, J = 6.5, 1H), 4.04 (m, 2H), 10.27 (s, 1H), 10.39 (s, 1H); ^{13}C NMR (d_6-DMSO) δ 169.2, 169.1, 150.7, 150.6, 59.7, 53.3, 49.6, 46.6, 46.4, 45.0, 23.6, 19.7, 12.9, 11.8, 2.8, −0.9; UV–vis (H_2O) λ_{max} = 209; IR (KBr) 3201 (m), 1696 (s), 1484 (m), 1378 (m), 1284 (m), 12 08 (m); low-resolution mass spectrum, m/z (rel intensity) 318 (M^+, 39), 212 (10), 192 (29), 179 (11), 167 (100), 153 (21), 140 (22), 131 (64), 119 (35), 110 (31); high-resolution mass spectrum, m/z 318.1309 ($C_{15}H_{18}N_4O_4$ requires 318.1328).

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Supplementary Material Available: ^1H NMR spectra for compounds **12**, **13**, **14-trans**, **19-trans**, **20**, and **21** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the article, and can be ordered from the ACS; see any current masthead page for ordering information.

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