with 1 N HCl (aqueous) and saturated NaCl (aqueous), dried over $MgSO_4$, filtered, and then evaporated to give 38 g of thick oil **13**. Analysis by gas chromatography indicated 92.2% purity with the major impurity being benzyl alcohol: ^1H NMR ($CDCl_3$) δ 11.0 (s, 1 H), 7.25 (s, 5 H), 5.0 (s, 2 H), 2.5 (s, 2 H), 1.4 (br s, 10 H).

Benzyl 2-(L-Boc-amino)-5-[1-(carbobenzoxymethyl)-cyclohexyl]pentanoate (10L). Sodium (0.15 g) was added to a large metal beaker containing methanol (200 mL) followed by pyridine (80 mL), 1,1-cyclohexanediacetic acid monobenzyl ester (**13**) (35 g, 121 mmol), and *N*-α-Boc-L-Glu-α-benzyl ester (**14**) (25 g, 74 mmol) dissolved in methanol (40 mL). The solution was electrolized with vigorous mechanical stirring at 100 V and 2.5 A between two platinum plates (25 × 50 mm) spaced 2-mm apart. The temperature of the reaction was kept between 20 and 25 °C by the aid of a 2-propanol/dry ice bath. After 9 h, TLC indicated most of **14** was reacted. The reaction mixture was evaporated to give a brown oil which was taken into 1:1 ethyl acetate/*n*-hexane. The precipitate was filtered off and the filtrate was washed two times with dilute HCl (aqueous), two times with 1 N Na_2CO_3 (aqueous), and once with saturated NaCl (aqueous), dried over $MgSO_4$, filtered, and evaporated to give an oil. The majority of the impurities were removed by flash chromatography (silica gel, 5–10% ethyl acetate/*n*-hexane). Final purification was achieved on a 3.0 × 100 cm silica gel gravity column eluted with 7% ethyl acetate/*n*-hexane. A pure fraction contained 7.17 g (18%) of **10L**. This material was identical with the racemic material **10** except that it was optically active: $[\alpha]_D$ −14.7° (*c* = 0.1025 g/mL, methanol).

2-(Boc-amino)-5-[1-(carbobenzoxymethyl)cyclohexyl]-pentanoic Acid (3L). The optically pure Boc diester **10L** was hydrolyzed under the same conditions as **10** to give material that was identical with racemic **3** except that it was optically active: $[\alpha]_D$ +0.40° (*c* 0.1008 g/mL, methanol). Anal. Calcd for $C_{25}H_{37}NO_6$: C, 67.09; H, 8.33, N, 3.13. Found: C, 66.87; H, 8.33; N, 3.07.

Chiral GC Analysis of 3L. The optical purity of **3L** was confirmed by chiral gas chromatographic analysis. In order to analyze the protected amino acid **3L** by GC, it was necessary to convert **3L** to its *N*-pentafluoropropionyl, diisopropyl ester **15L**. Hydrolysis of **10L** with 6 N HCl at 100 °C for 18 h gave after evaporation the HCl salt of **2L**. The amino acid salt **2L** was esterified with HCl/2-propanol at 100 °C for 30 min, evaporated, and then aceylated with pentafluoropropionic anhydride in CH_2Cl_2 at 100 °C for 15 min to give **15L**. The D,L standard **15** was prepared in a similar manner from **2**. GC analysis of **15L** on the Chirasil-Val III column (isothermal, 175 °C) showed only a single enantiomer.

Acknowledgment. We acknowledge Lewis B. Killmer, Jr. of the Department of Physical and Structural Chemistry for the mass spectra and Edith A. Reich of the Department of Analytical Chemistry for elemental analysis.

Registry No. **2**, 113009-17-9; **3**, 113009-18-0; **3L**, 113084-43-8; **4**, 4630-82-4; **5**, 113009-19-1; **6a**, 113009-20-4; **6b**, 113009-26-0; **6c**, 113009-27-1; **7**, 113009-21-5; **8**, 113009-22-6; **9**, 113009-23-7; **10**, 113009-24-8; **10L**, 113084-42-7; **11**, 4355-11-7; **12**, 1010-26-0; **13**, 113009-25-9; **14**, 30924-93-7; CH_2=$CH(CH_2)_3I$, 7766-48-5.

An Unusual Substituent Effect on Elimination vs Fragmentation Reactions of the Dianions of 5-Fluorouracil–Alkene Photoadducts. Preparation of Cyclobutane-Annelated Uracils

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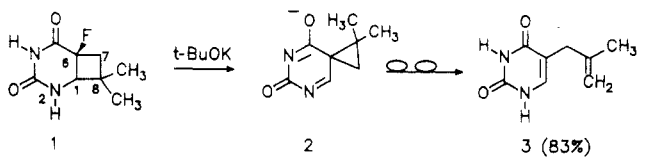
Acetone-sensitized photocycloadditions of 5-fluorouracil to methyl vinyl ether, 2-methoxypropene, and ketene dimethyl acetal give good yields of the respective 8,8-disubstituted-6-fluoro-2,4-diazabicyclo[4.2.0]octane-3,5-diones. Whereas the dianions of cycloadducts of 5-fluorouracil and alkyl-substituted alkenes afford high yields of 5-substituted uracils, the products from 2-methoxypropene and ketene dimethyl acetal give predominantly cyclobutane-annelated uracils derived from syn elimination of hydrogen fluoride. Deuterium labeling studies support the proposed mechanism of elimination. Heating 8,8-dimethoxy-2,4-diazabicyclo[4.2.0]oct-1(6)-ene-3,5-dione, obtained from hydrogen fluoride elimination of the 5-fluorouracil–ketene dimethyl acetal photoadduct, in the presence of *N*-phenylmaleimide or dimethyl acetylenedicarboxylate, gives Diels–Alder adducts derived from trapping the thermally generated diene.

Introduction

The availability of functionalized benzocyclobutenes coupled with the cycloaddition reactions of their thermally generated *o*-quinodimethane forms has made these compounds useful synthetic intermediates.[1] Heterocyclic analogues of benzocyclobutenes and their respective *o*-quinodimethane forms are less common. Although the pyridine analogues of benzocyclobutenes have been prepared via pyrolysis routes,[2] their chemistry has not been extensively studied.

Several years ago we envisioned a preparation of pyrimidine analogues of benzocyclobutenes from an elimination reaction of the readily available cycloaddition products of 5-fluorouracil and alkenes. However, reaction of these photoaddition products with excess KO-*t*-Bu gave 5-substituted uracils (i.e., **1** → **3**) in excellent yields,[3] not the expected cyclobutenes. Labeling and kinetic studies favored rearrangement of the dianion of **1** to form a spirocyclic intermediate **2** which then yielded **3**.



(1) (a) For some leading references, see: Oppolzer, W. *Synthesis* **1978**, 793. (b) Kametani, T.; Kato, Y.; Honda, T.; Fukumoto, K. *J. Am. Chem. Soc.* **1976**, *98*, 8185.

(2) (a) Thummel, R. P. "Carbocyclic Annelated Pyridines" In *Pyridines and Derivatives*, Supp. 2; Newkome, G. R., Ed.; John Wiley & Sons: New York, 1984; Vol. 14, Part V, p 253. (b) Thummel, R. P. *Acc. Chem. Res.* **1980**, *13*, 70. (c) Trahanovsky, W. S.; Mullen, P. W. *J. Am. Chem. Soc.* **1972**, *94*, 5911. (d) Trahanovsky, W. S.; Riemann, J. M. *Tetrahedron Lett.* **1977**, 1867.

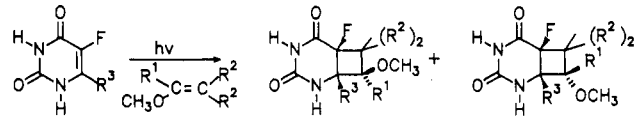
(3) Kaminski, V. V.; Wexler, A. J.; Balchunis, R. J.; Swenton, J. S. *J. Org. Chem.* **1984**, *49*, 2738 and references cited therein.

0022-3263/88/1953-1530$01.50/0

We report herein that the cycloaddition products from 5-fluorouracil with 2-methoxypropene and ketene dimethyl acetal react with KO-*t*-Bu to afford bicyclic cyclobutenes. A mechanistic study of this reaction and some preliminary results on the cycloaddition chemistry of the dienes generated by thermolysis of these cyclobutenes are presented.

Results and Discussion

Photocycloaddition Studies. Acetone-sensitized cycloaddition of 5-fluorouracil and 2-methoxypropene afforded two compounds (77% yield) in the ratio 1.8:1 as determined by ^{1}H NMR spectroscopy. These products were separated by silica gel chromatography, and spectroscopic and analytical data established that the compounds were 1:1 adducts of 5-fluorouracil and 2-methoxypropene. The ^{1}H NMR spectrum of the major photoadduct **5a** showed a one-hydrogen doublet of doublets at 3.99 ppm (hydrogen on C-1) with coupling constants of 3.7 and 24 Hz. Irradiation of the proton signal at 8.37 ppm (hydrogen on N-2) resulted in the collapse of the signal at 3.99 ppm into a doublet with a coupling constant of 24 Hz. This pattern is consistent only with a head-to-tail adduct such as **5a**: the hydrogen on C-1 coupled to the fluorine on C-6 and the proton on N-2. The ^{1}H NMR spectrum of the minor adduct was similar and this product is assigned as stereoisomeric head-to-tail cycloadduct **6a** (see following discussion).

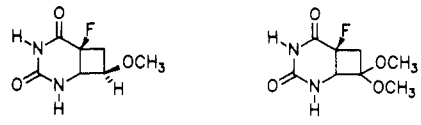


4 5a–c 6a–c

a, $R^1 = CH_3$, $R^2 = R^3 = H$; **b**, $R^1 = CH_3$, $R^2 = H$, $R^3 = D$; **c**, $R^1 = CD_3$, $R^2 = D$, $R^3 = H$

The stereochemistry of the adducts at C-8 was assigned by using literature precedent.[3] Earlier chemical and spectroscopic studies of the 1,3-dimethyluracil–isopropenylacetate photoadducts established that the absorptions for the endo methyl groups in cycloadducts occurred at higher field in the ^{1}H NMR spectrum than those for the corresponding exo methyl groups.[3] The methyl hydrogen signals in the major adduct **5a** appeared at 1.07 ppm; those in the minor adduct **6a** appeared at 1.32 ppm. Consequently, the major isomer was assigned as having an endo methyl group.

The photocycloaddition products from 5-fluorouracil plus methyl vinyl ether, **7**, and 5-fluorouracil with ketene dimethyl acetal, **8**, were also prepared. For the former system, the major cycloaddition product **7** was obtained (54%) by fractional crystallization of the crude irradiation mixture. The stereochemistry at C-8 was not rigorously established; however, the product has been assigned as **7** since in these cycloadditions the major stereoisomer is usually that having the larger group in the exo position. Spectroscopic and combustion analysis data detailed in the Experimental Section strongly support the head-to-tail regiochemistry of the products.



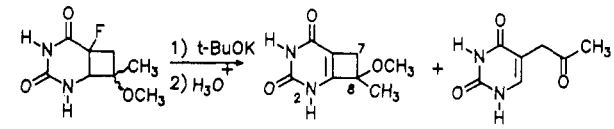
7 8

Elimination/Fragmentation Reactions of Photoadducts. Unexpectedly, reaction of the stereoisomeric mixture of products obtained from 5-fluorouracil and 2-methoxypropene with 3.1 equiv of KO-*t*-Bu at reflux followed by acidic workup did not give exclusively the expected fragmentation product **10** but gave instead a ca. 1:1 mixture of **10** and a second product, **9**. The new product showed in the ^{1}H NMR spectrum singlets at 3.23 and 1.48 ppm (3 H) and an AB quartet (2 H) at 2.7 ppm. The ^{1}H NMR data together with the UV spectrum of the product (λ_{max} 267 nm, ϵ 4140; λ_{max} 212 nm, ϵ 4160) suggested that the product was a fused uracil arising from elimination of hydrogen fluoride from the photoadducts.

Table I. Reaction of 5 and 6 with KO-*t*-Bu To Form 9 and 10

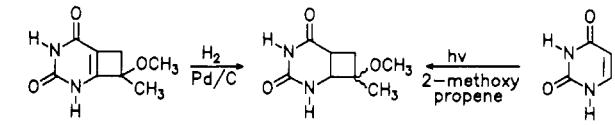
entry	reactant	equiv KO-*t*-Bu	9:10	k_H/k_D
1	**5a**	3	1:0.7	
2	**6a**	3	1:4.0	
3	**5a**	10	1:0.5	
4	**5a**	20	1:0.3	
5	**5b**[a]	3	1:1.4	$\simeq 2$
6	**6b**	3	1:8.0	$\simeq 2$
7	**5c**[b]	3	$1:0.6_5$	$\simeq 1$
8	**6c**	3	1:4	$\simeq 1$

[a] **5b** was >95% deuteriated at C-1. [b] **5c** had 0.5 H (ca. 16% hydrogen) in the CD_3 group from ^{1}H NMR analysis.



5a (OCH_3 exo)
6a (OCH_3 endo) 9 10

The combusion and spectroscopic data noted above provided strong support for the structural assignment. However, in view of the rearrangement reaction noted in earlier studies[3] on these systems, we wished to exclude the 7,7-disubstituted isomer of **9** as a possible structure.



9 11

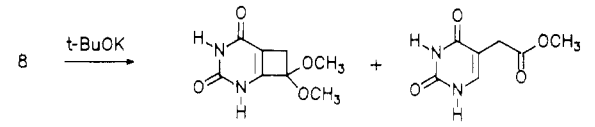
Hydrogenation of the double bond of **9** and comparison of the resulting isomeric products with those obtained from acetone-sensitized cycloaddition of uracil with 2-methoxypropene confirmed the structural assignment of **9**. Thus, in contrast to the reactions of cycloadducts analogous to **1** with KO-*t*-Bu, the mixture of cycloadducts **5** and **6** gives major amounts of the corresponding cyclobutene.

A more detailed study revealed that the ratio of **9** to **10** formed in this reaction is a function of the stereochemistry of the groups at C-8 and the number of equivalents of base (Table I). The reaction of **5a** with KO-*t*-Bu gave a 1.0:0.7 ratio of **9** to **10**; this reaction with **6a** gave a 1.0:4.0 ratio of the same products (entries 1 and 2). Increasing the equivalents of KO-*t*-Bu used in the reaction of **5** favored the formation of **9** over **10** (entries 1, 3, and 4). Isotope effect studies also furnished information on the mechanism of formation of **9** and **10**. The 1-deuterio derivative **5b** was obtained from the photocycloaddition of 5-fluorouracil-*6-d* with 2-methoxypropene. The photoadduct **5c** was prepared from an analogous reaction using 2-methoxypropene-d_5 as the olefinic component. The required alkene was prepared by pyrolysis of the dimethyl acetal of acetone-d_6. Reaction of **5b** with KO-*t*-Bu gave **9** and **10**-*d* (complete retention of deuterium by ^{1}H NMR spectroscopy). As shown in the table (entries 5 and 6), deuterium substitution at C-1 favored formation of the fragmentation

product **10**. Assuming that deuterium substitution at C-1 does not effect the rate of formation of **10**, then k_H/k_D for formation of **9** $\simeq$ 2. This value is in the range of other base-promoted syn eliminations,[4] although the magnitude of the isotope effect is known to depend upon the leaving group and the base.[4]

The reaction of **5c** with KO-*t*-Bu again afforded a mixture of **9**-d_5 (complete retention of deuterium) and **10**. The fragmentation product **10** had virtually no loss of deuterium from the CD_3 group, but the methylene group showed nearly complete loss of deuterium. Exchange reactions of the methylene group during acidic workup would account for the complete loss of deuterium at the methylene position. In contrast to the results above, the isotope effect on the formation of **10** was negligible, assuming that deuterium incorporation at C-7 does not effect the rate of formation of **9**.

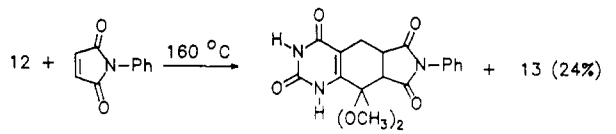
The photocycloaddition products **7** and **8** were also reacted with KO-*t*-Bu. Reaction of **7** with KO-*t*-Bu under a variety of experimental conditions produced a complex mixture of products. Chromatography of the reaction mixture afforded an impure solid (<5%) which appeared to be the cyclobutene analogous to **9**;[5] however, this was not rigorously established. By contract, reaction of **8** with 3.1 equiv of KO-*t*-Bu in *tert*-butyl alcohol at 100 °C for 3 h yielded two UV-active compounds which were easily separated by silica gel chromatography. The faster eluting compound was assigned as **12** (54%) and the slower eluting compound as **13** (14%) based on their spectroscopic and combustion analysis data.



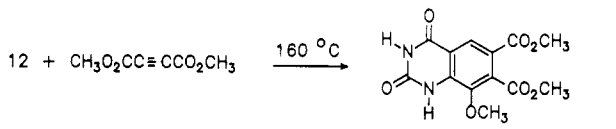
12 (54%) 13 (14%)

Having the cyclobutene **12** available, the thermal generation and trapping of the ring-opened diene was examined. Heating a tetrahydrofuran solution of **12** at 165 °C with *N*-phenylmaleimide for 3.2 h gave two UV-active products. Silica gel chromatography gave **15** (52%), **13** (24%), and recovered **12** (17%). The ^1H NMR spectrum of **15** showed the presence of two methoxyl groups at 3.62 and 3.29 ppm, two amide hydrogens at 11.2 and 10.4 ppm, aromatic hydrogens between 7.46 and 7.15 ppm, and four multiplets, each integrating to one hydrogen at 4.00, 3.54, 3.24, and 2.57 ppm, respectively.

When a less reactive dienophile, dimethyl acetylenedicarboxylate, was reacted with **12** (165 °C for 5 h), **17** (24%) was obtained. The ^1H NMR spectrum of **17** showed three closely spaced methoxyl groups at 3.86, 3.83, and 3.74 ppm, in addition to a single aromatic proton at 8.22 ppm, and two amide hydrogens at 11.6 and 11.3 ppm. These data are consistent with those of the quinazoline structure **17** which could be formed from aromatization of the initially



14 15 (52%)



16 17 (24%)

formed cycloadduct by loss of methanol. The low yield of cycloadduct obtained with dimethyl acetylenedicarboxylate was not unexpected since this dienophile was reported to be unsatisfactory in its reaction with the ring-opened form of α,α-dimethoxybenzocyclobutene at 170 °C.[8] An attempt to trap the ring-opened form of **9** at 175 °C with *N*-phenylmaleimide yielded after 3 h a complex mixture of 11 UV-active products,[9] which were not characterized.

Discussion. The formation of major amounts of elimination products from the reaction of **5** and **8** with KO-*t*-Bu is in marked contrast to the exclusive formation of 5-substituted uracils from 8,8-dialkyl-substituted derivatives such as **1**. This is especially surprising since the only difference between **1** and **5** is the replacement of one methyl group by a methoxyl group. The dependence of the product ratio on the equivalents of KO-*t*-Bu and the effect of isotopic substitution on product ratio support the contention that the formation of **9** and **10** from **5** arise via different reaction pathways.

Previous kinetic studies established that the fragmentation reaction pathway (**1** → **3**) involved the dianion of **1**, and intermediates analogous to **19** and **20** were invoked to explain the reactivity and products. The results reported herein are not inconsistent with a similar sequence of steps for the conversion of **5** and **6** to **10**. Trapping of **19** with *tert*-butyl alcohol and subsequent hydrolysis of the ketal during workup would afford **10**. Alternatively,

(4) Saunders, W. H., Jr.; Cockerill, A. F. *Mechanisms of Elimination Reactions*; John Wiley & Sons: New York, 1973, pp 78–82.

(5) The poor yield of cyclobutene product from this reaction could be due to the labile nature of the monomethoxy cyclobutene derivative and not to the β-elimination reaction. Sammes[6] has shown that α-methoxybenzocyclobutene undergoes electrocyclic ring opening to the α-methoxy-*o*-xylylene at a much enhanced rate in comparison to the parent benzocyclobutane. The formation of benzocyclobutadiene from α-methoxybenzocyclobutene in basic media has also been observed at 80 °C via a facile elimination of methanol,[7] and the analogous elimination could be occurring with the monomethoxycyclobutane-fused uracil.

(6) Sammes, P. G.; Arnold, B.; Wallace, T. W. *J. Chem. Soc., Perkin Trans. 1*, **1974**, 409.

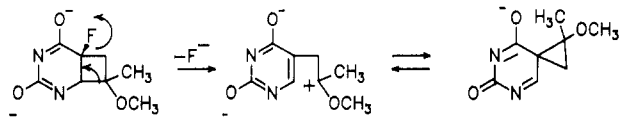
(7) Moss, R. J.; Rickborn, B. *J. Org. Chem.* **1984**, *49*, 3694.

(8) Moss, R. J.; White, R. D.; Rickborn, B. *J. Org. Chem. 50*, **1985**, 5132.

(9) The low yield of cycloaddition products from **9** could arise from a 1,5-hydrogen shift in the thermally generated diene to give methyl ester of 5-methylorotic acid. Such 1,5-hydrogen shifts are known in thermal reactions of *p*-ethylbenzoyl chlorides.[10]

(10) Schiess, P.; Heitzmann, M. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 469. Schiess, P.; Radimerski, P. *Helv. Chim. Acta* **1974**, *57*, 2583.

(11) Melting points were taken in a Thomas-Hoover Unimelt apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 282B grating spectrometer in the indicated phase. ^1H NMR spectra were recorded at 80 MHz on an IBM NR 80 instrument and at 500 MHz on a Bruker AM 500 instrument by Dr. Charles Cottrell. ^{13}C NMR spectra were recorded at 125 MHz on a Bruker AM 500 instrument. ^{19}F NMR spectra were recorded at 75.3 MHz on an IBM NR 80 instrument by Carl Engelman. UV measurements were made on a Beckman DU-7 spectrophotometer. Mass spectra and exact mass measurements were obtained by C. Weisenberger on a Kratos MS-30 mass spectrometer connected to a DS-55 data system. Combustion analyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark. Column chromatography was performed on silica gel (E. Merck, 230–400 mesh) and thin-layer chromatography was performed on aluminum plates coated with silica gel 60. HPLC analyses were performed on an Altex Model 110A solvent pump with a 10 × 250 Lichrosorb Si60-10 column using an Altex Model 153 Analytical UV Detector at 254 nm. The *tert*-butyl alcohol (*t*-BuOH) was dried over and distilled from calcium hydride. It is essential that dry *t*-BuOH be employed in the elimination reactions. Stock solutions of potassium *tert*-butoxide (KO-*t*-Bu) were prepared by dissolving potassium in *t*-BuOH under a nitrogen atmosphere. All irradiations were conducted in a standard immersion apparatus with Cortex-filtered light from a Hanovia 450-W medium-pressure source.



18 19 20

direct demethylation of **19** by KO-*t*-Bu would also account for the deuterium distribution of **10** from **5c**.

The simplest explanation for formation of the cyclobutenes **9** and **12** is syn elimination of hydrogen fluoride from the corresponding fluoride. This reasonably would occur from the dianion of the starting material, and the effect of base concentration on the yields of **9** and **10** from **5** would derive from a different order for KO-*t*-Bu concentration in the rate expressions for formation of **9** and **10**. Likewise, the estimated isotope effect supports an E_2-type mechanism.

The interesting unanswered mechanistic question is why the simple substitution of a methyl for a methoxyl group increases the importance of the elimination vs the fragmentation pathway. One possibility is that acidity of the hydrogen attached to C-1 is increased by virtue of the inductive effect of the methoxyl group, thus favoring the elimination reaction at the expense of the fragmentation pathway. A number of rationales would account for the higher percentage of elimination from **5** vs **6**; however, in the absence of rate data, such a discussion would be premature.

Summary. The acetone-sensitized photocycloaddition of 5-fluorouracil to 2-methoxypropene and ketene dimethyl acetal affords cycloadducts which upon reaction with KO-*t*-Bu give cyclobutane-fused uracils **9** and **12**; this ring system was previously unreported. This two-step sequence from commercially available 5-fluorouracil and vinyl ethers constitutes a convenient preparation of this ring system. The reason for the contrasting chemistry of the KO-*t*-Bu reactions reported herein and those reported earlier for the 8,8-dialkyl-substituted compounds remains unanswered. Finally, a brief survey of the thermal generation of the diene from **12** and its subsequent trapping via the Diels–Alder reaction indicates that cyclobutene **12** could serve as an intermediate for the polycyclic ring systems containing the pyrimidine moiety.

Experimental Section

Photocycloadditions. 5-Fluorouracil to 2-Methoxypropene. A solution of 5-fluorouracil (500 mg, 3.84 mmol), 2-methoxypropene (10 mL, 104 mmol), and acetone (200 mL) in a standard immersion apparatus with a quartz well was irradiated with Corex-filtered light from a 450-W Hanovia medium-pressure source for 2.5 h. The solution was concentrated in vacuo to a white solid; the ^{1}H NMR spectrum of the crude solid showed two isomers in the ratio 1.9:1. The crude solid was washed with Et_2O (2 × 20 mL) and dried under vacuum to yield a mixture of **5a** and **6a** (600 mg, 77%). The isomers (150 mg) were separated by column chromatography (silica gel, 3.5 × 12 cm) as follows: 0.5% (95%) EtOH/Et_2O (200 mL); 0.5% (95%) EtOH/Et_2O (200 mL), 71 mg of **5a**. Recrystallization from EtOAc yielded product (46 mg, 31%): mp 213–214 °C (sealed capillary); IR (KBr) 1720 (s), cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.7 (br s, 1 H), 8.37 (br s, 1 H), 3.99 (dd, J = 3.7, 24 Hz, 1 H), 3.14 (s, 3 H), 2.48 (overlapping DMSO), 2.37 (d, of AB q, J = 13.5, 21.3 Hz, 1 H), 1.07 (s, 3 H); ^{19}F NMR δ −146.10, −146.24, −146.36, −146.42, −146.49, −146.58, −146.82; UV (CH_3OH) λ_{max} 209 nm (ϵ 2.62 × 10^3). Anal. Calcd for $C_8H_{11}N_2O_3F$: C, 47.23; H, 5.48. Found: C, 47.31; H, 5.48.

Continued elution with 0.5% (95%) EtOH/Et_2O (200 mL) gave a mixture of **5a** and **6a** (38 mg); 5% (95%) EtOH/Et_2O (240 mL) gave **6a** (32 mg). Recrystallization from EtOAc yielded product (23 mg, 15%): mp 244–245 °C (sealed tube); IR (KBr) 1734 (s), 1710 (s), cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.4 (br s, 1 H), 7.88 (br s, 1 H), 3.96 (dd, J = 3.9, 19 Hz, 1 H), 3.08 (s, 3 H), 2.55 (d of AB q, J = 4.1, 13 Hz, 1 H), 2.12 (three-line m, 1 H), 1.32 (s, 3 H); ^{19}F NMR (DMSO-d_6, 73.5 MHz) δ −148.47, −148.53, −148.68, −148.73, −148.79, −148.99, −149.88; UV (CH_3OH) λ_{max} 208.5 nm (ϵ 4.19 × 10^3). Anal. Calcd for $C_8H_{11}N_2O_3F$: C, 47.23; H, 5.48. Found: C, 47.59; H, 5.58.

5-Fluorouracil and 1,1-Dimethoxyethylene. A solution of 5-fluorouracil (510 mg, 3.92 mmol), 1,1-dimethoxyethylene[12] (8.98 g, 102 mmol), and acetone (200 mL) was irradiated for 2 h as described above. At this time TLC analysis (10% $CH_3OH/CHCl_3$) showed a trace of 5-fluorouracil (R_f 0.26) and a 2537-Å light-sensitive compound (R_f 0.49). The acetone was removed in vacuo to yield a yellow oil which was dissolved in CH_3OH and adsorbed onto silica gel. Chromatography (3.5 × 12 cm column) proceeded as follows: 2% $CH_3OH/CHCl_3$ (340 mL), 2% $CH_3OH/CHCl_3$ (350 mL), 535 mg of a mixture of the cycloadduct (R_f 0.48, 10% $CH_3OH/CHCl_3$), and an unknown (R_f 0.44, 10% $CH_3OH/CHCl_3$). Recrystallization of the mixture from EtOAc gave **8** (395 mg, 46%): mp 247–249 °C (sealed tube); IR (KBr) 3333 (m), 1719 (s), 1690 (s), cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.6 (br s, 1 H), 8.19 (br s, 1 H), 4.17 (dd, J = 3.3, 20.7 Hz, 1 H), 3.17 (s, 3 H), 3.11 (s, 3 H), 2.75 (d of AB q, J = 5.16, 13.6 Hz, 1 H), 2.34 (d of AB q, J = 13.6, 17.8 Hz, 1 H); ^{19}F NMR (DMSO-d_6, 75.3 Hz) δ −153.83, −153.89, −154.06, −154.12, −154.16, −154.32, −154.40; UV (CH_3OH) λ_{max} 207 nm (ϵ 8140). Anal. Calcd for $C_8H_{11}N_2O_4F$: C, 44.04; H, 5.48. Found: C, 44.30; H, 5.22.

5-Fluorouracil and Methyl Vinyl Ether. A −5 °C solution of 5-fluorouracil (505 mg, 3.88 mmol), methyl vinyl ether (10 mL, 133 mmol), and acetone (200 mL) was irradiated for 2.5 h as described above. Concentration in vacuo gave a white solid, the ^{1}H NMR spectrum of which indicated two isomers in the ratio 3.8:1. The crude product was washed with Et_2O (2 × 20 mL), yielding a white solid (574 mg, 79%). Fractional recrystallization from EtOAc afforded the major adduct (394 mg, 54%): mp 231–232 °C (sealed tube); IR (KBr) 3230 (br, m), 3090 (br, m), 1740 (br s), 1304 (m), 1226 (m), 1207 (m), 1150 (m), 1072 (s) cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.7 (br s, 1 H), 8.49 (br s, 1 H), 3.92–3.86 (m, 1 H), 3.50–3.45 (m, 1 H), 3.25 (s, 3 H), 2.74–2.69 (m, 1 H), 2.16–2.07 (m, 1 H); UV (CH_3OH) λ_{max} 208 nm (ϵ 5420). Anal. Calcd for $C_7H_9N_2O_3F$: C, 44.68; H, 4.82. Found: C, 44.60; H, 4.85.

Uracil and 2-Methoxypropene. A solution of uracil (497 mg, 4.43 mmol), 2-methoxypropene (10 mL, 104.4 mmol), and 50% aqueous acetone (200 mL) was irradiated for 2 h as described above. The solution was concentrated in vacuo to an off-white solid which was recrystallized from EtOH, yielding a white solid which was a mixture of epimers at C-8 (252 mg, 30%): mp 195–203 °C; ^{13}C NMR (pyridine-d_5, 500 MHz) δ 173.8, 173.7, 155.2, 154.6, 81.8, 80.6, 54.8, 54.6, 50.2, 50.1, 35.5, 34.6, 32.4, 29.3, 21.3, 17.7.

Reactions of Photocycloaddition Products with KO-*t*-Bu. Formation of 9 and 10. To a mixture (1.8:1) of **5a** and **6a** (270 mg, 1.34 mmol) in a two-necked flask equipped with a reflux condensor and N_2 inlet was added a solution of KO-*t*-Bu (4.14 mmol) in *t*-BuOH (17.7 mL), and the resulting solution was heated at 100 °C (bath temperature) for 3.5 h. The slightly cloudy amber reaction mixture was cooled to room temperature and acidified with a 12 M HCl solution (0.50 mL) which caused a white solid to precipitate from solution. The resulting mixture was concentrated in vacuo to a white solid, CH_3OH (15 mL) was added, and the suspension was concentrated onto silica gel and chromatographed (silica gel, 2 × 10 cm column) as follows: 5% $CH_3OH/CHCl_3$ (50 mL), nil; 5% $CH_3OH/CHCl_3$ (36 mL), 120 mg (49%) of **9**. Recrystallization from EtOAc yielded product (90 mg, 37%): mp 173–175 °C; IR (KBr) (s), 1660 (s), cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.6 (br s, 1 H), 10.8 (s, 1 H), 3.29 (s, 3 H), 3.23 (s, 3 H), 2.87 (d, J = 11.2 Hz, 1 H), 2.54 (d, J = 11.2 Hz, 1 H), 1.48 (s, 3 H); UV (CH_3OH) λ_{max} 212 nm (ϵ 4140), 267 (4160). Anal. Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53. Found: C, 52.55; H, 5.59.

Elution was continued as follows: 8% $CH_3OH/CHCl_3$ (25 mL), nil; 8% $CH_3OH/CHCl_3$ (240 mL), **10** (114 mg, 50%). Recrystallization from EtOH yielded product (83 mg, 37%): mp 252–254 °C (lit.[3] mp 252–253 °C).

(12) Bass, J. D.; Corey, E. J.; LeMahieu, R. B.; Mitra, R. B. *J. Am. Chem. Soc.* **1964**, *86*, 5570.

A solution of **9** (26.8 mg, 0.147 mmol) in CH_3OH (4 mL) was hydrogenated at atmospheric pressure and room temperature over 5% Pd/C. After 40 min, TLC analysis (SiO_2, EtOAc) showed that **9** had been consumed and that one product had been formed, R_f 0.30. The reaction mixture was filtered through Celite; the filtrate was concentrated in vacuo to a white solid (27.8 mg) which was purified by sublimation (130 °C/0.2 mmHg), giving **10** (26.0 mg, 96%) which showed the identical ^{13}C NMR chemical shifts as those obtained from the material prepared from uracil.

Formation of 12 and 13. A solution (0.199 mmol) of potassium in *t*-BuOH (15 mL) was added to **8** (163 mg, 0.747 mmol) under N_2. The resulting clear solution was heated to reflux (bath temperature 100 °C) for 5 h. The progress of reaction was followed by diluting 2-μL aliquots of the solution with Na_2HPO_4/KH_2PO_4 buffer (pH 7.0, 2 mL) and observing the increase in absorbance at 268 nm. The reaction mixture was cooled to room temperature, acidified with 5% HCl to pH 3 (hydrion paper), and concentrated in vacuo to an amber solid. The solid was taken-up into CH_3OH, concentrated onto silica gel, and chromatographed (silica gel, 2 × 10 cm column) as follows: 5% $CH_3OH/CHCl_3$ (70 mL); 5% $CH_3OH/CHCl_3$ (40 mL), **12** (83.4 mg, 56%) which was recrystallized from EtOAc: mp 161.5–163.0 °C; IR (KBr) 3200 (m), 1720 (s), 1685 (s), cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 11.74 (br s, 1 H), 10.84 (br s, 1 H), 3.32 (s, 6 H), 2.79 (s, 2 H); UV (CH_3OH) λ_{max} 209 (ε 6760), 268 (4610). Anal. Calcd for $C_8H_{10}N_2O_4$: C, 48.09; H, 5.09. Found: C, 48.56; H, 5.09.

Elution was continued as follows: 5% $CH_3OH/CHCl_3$ (60 mL), **13** (19.2 mg, 14%) which was recrystallized from EtOAc: mp 233–234 °C; IR (KBr) 1740 (s), 1670 (s), 1655 (s), cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 11.6–10.4 (br, 2 H), 7.37 (s, 1 H), 3.58 (s, 3 H), 3.22 (s, 2 H); UV (CH_3OH) λ_{max} 206 nm (ε 8820), 261 (7565); mass spectrum, exact mass calcd for $C_7H_8N_2O_4$ *m/e* 184.0484, obsd *m/e* 184.0498.

6-Deuterio-5-fluorouracil. To a solution of Na (353 mg, 15.4 mmol) in D_2O under an N_2 atmosphere was added 5-fluorouracil (914 mg, 7.03 mmol), and the resulting solution was stirred for 7 h. The aqueous solution was acidified with a 12 M HCl solution to pH 3 (hydrion paper), and the resulting white precipitate was collected by filtration and washed with cold H_2O to yield the title compound (585 mg, 64%). Analysis for deuterium content by ^1H NMR (80 MHz, DMSO-d_6) using 1,3,6-trimethyluracil as standard indicated >95% deuterium incorporation.

2-Methoxypropene-d_6. To a solution of acetone-d_6 (10 mL, 0.136 mol), trimethylorthoformate (30 mL, 0.272 mol), and D_2O (1.2 mL, 0.0606 mol) in a 100-mL flask equipped with a condensor and drying tube ($CaSO_4$) was added *p*-toluenesulfonic acid (30 mg). Upon addition of the acid, an exothermic reaction occurred, and the solution was refluxed gently for 5 min. GLC (11 ft × $^1/_8$ in. column, 5% OV-101 on 120–140-mesh Chromosorb G at 30 °C) showed the reaction to be complete in 30 min with a product retention time of 4.5 min. To the solution was added NaOH (200 mg), and the solution was distilled through a column (1 × 25 cm) packed with glass helices to give product (ca. 8.6 g, bp 55–90 °C) which GLC analysis showed to be mostly the ketal: ^1H NMR ($CDCl_3$, 80 MHz) major peak at δ 3.13.

To a stirred 115 °C solution of succinic anhydride (15.01 g, 0.150 mol), benzoic acid (0.770 g, 0.0063 mol), pyridine (2.0 mL), and diglyme (17 mL) in a 50-mL three-necked, round-bottomed flask equipped with a pressure-equalizing addition funnel, thermometer, and a fractionating column (1.0 × 25 cm, packed with 5-mm glass helices) was added acetone-d_6 dimethyl ketal (0.136 mol) at a rate to maintain a head temperature of 44 °C. After all of the ketal was added (40 min), the head temperature climbed to 54 °C, and collection of the colorless distillate ceased. A mixture of the vinyl ether and ketone (8.4 g, ca. 5:1) was obtained.

Determination of Product Radios from Reactions of 5 and 6 with Potassium *tert*-Butoxide. A general procedure is as follows. To a photoadduct in a 10-mL round-bottomed flask equipped with a condensor and N_2 inlet was added KO-*t*-Bu (3.1 equiv) in *t*-BuOH. The resulting solution was heated at 100 °C for 3 h, cooled to room temperature, and acidified with a 12 M HCl solution. The resulting cloudy mixture was concentrated in vacuo to a white solid which was dissolved in CH_3OH (10 mL) with a known amount of 1,3-dimethyl-5-chlorouracil. The CH_3OH solution was analyzed by HPLC as described below. A 2-μL sample of the CH_3OH solution was chromatographed (8% $CH_3OH/CHCl_3$ as eluant, 1.2 mL/min flow rate). A standard solution of 1,3-dimethyl-5-chlorouracil, **9**, and **10** was also chromatographed, using the same parameters for calibration purposes. The areas of the peaks were determined and the yields of products were calculated.

Thermal Reaction of 12 and *N*-Phenylmaleimide. A solution of **12** (41 mg, 1.61 mmol) and THF (2 mL) was sealed in a glass tube and heated at 165 °C for 3.2 h. TLC analysis (8% $CH_3OH/CHCl_3$) showed two major products. The yellow THF solution was concentrated in vacuo to a yellow oil which was dissolved in CH_3OH and concentrated onto silica gel and chromatographed (silica gel, 1.5 × 12 cm column) as follows: 5% *i*-PrOH/$CHCl_3$ (39 mL); 5% *i*-PrOH/$CHCl_3$ (21 mL), 45 mg of a colorless oil which was dissolved in $CHCl_3$ and allowed to crystallize, yielding **15** (40 mg, 52%) as fine white needles: 170 °C dec; IR (KBr) 1717 (s), 1685 (sh), 1500 (m), 1386 (m), 1135 (m), 1055 (m) cm^{-1}; ^1H NMR (acetone-d_6, 500 MHz) δ 11.2 (br s, 1 H), 10.4 (br s, 1 H), 7.46–7.36 (m, 3 H), 7.17–7.15 (m, 2 H), 4.00 (d, *J* = 9.2 Hz, 1 H), 3.62 (s, 3 H), 3.54 (ddd, *J* = 2.1, 7.8, 9.1 Hz, 1 H), 3.29 (s, 3 H), 3.24 (dd, *J* = 2.1, 15.2 Hz, 1 H), 2.57 (dd, *J* = 7.8, 15.2 Hz, 1 H); UV (CH_3OH) λ_{max} 212 nm (ε 1.47 × 10^4), 271 (5622); mass spectrum, exact mass calcd for $C_{18}H_{17}N_3O_6$ *m/e* 371.1117, obsd *m/e* 371.1114.

Elution was continued: 5% *i*-PrOH/$CHCl_3$ (9 mL), 4 mg of a mixture of **15** and **12**; 5% *i*-PrOH/$CHCl_3$ (15 mL), 7.0 mg (17%) of **12**; 10% $CH_3OH/CHCl_3$ (25 mL), 9.0 mg (24%) of **13**.

Thermal Reaction of 12 and Dimethyl Acetylenedicarboxylate. A solution of **12** (32 mg, 0.162 mmol), dimethyl acetylenedicarboxylate (230 mg, 1.62 mmol), and nitrogen purged THF (2 mL) was sealed in a glass tube and heated at 165 °C for 5 h. TLC analysis (5% $CH_3OH/CHCl_3$) of the THF solution showed that starting material had been consumed and that a number of products were formed with R_f values of 0.40, 0.27, 0.20, 0.11, and 0.09. The amber THF solution was concentrated in vacuo to an oily solid (289 mg) which was dissolved in CH_3OH, concentrated onto SiO_2, and chromatographed (2 × 8 cm column) as follows: $CHCl_3$ (20 mL); 3% $CH_3OH/CHCl_3$ (25 mL); 4% $CH_3OH/CHCl_3$ (15 mL), amber oil; 6% $CH_3OH/CHCl_3$ (15 mL), 34 mg of a mixture of a beige solid and a yellow oil. The mixture was washed with a 50:50 solution of $CHCl_3/Et_2O$ (2 mL), yielding a beige solid (26 mg) which was recrystallized from $CH_3OH/CHCl_3$, giving **17** (12 mg, 24%): mp 298–300 °C (hot-stage apparatus); IR (KBr) 1715 (s), 1690 (s), 1620 (m), 1290 (s), cm^{-1}; ^1H NMR (DMSO-d_6, 80 MHz) δ 11.6 (br s, 1 H), 11.3 (br s, 1 H), 8.22 (s, 1 H), 3.86 and 3.83 (2 s, 6 H), 3.74 (s, 3 H); UV (CH_3OH) λ_{max} 234 (ε 3.31 × 10^4), 275 (1.49 × 10^4), 315 (4.13 × 10^3); mass spectrum, exact mass calcd for $C_{13}H_{12}N_2O_7$ *m/e* 308.0645, obsd *m/e* 308.0653.

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