3-(Cyanomethyl)-4′,7-dimethoxyflavone (10d). This was isolated as a byproduct (17%) in the above preparation of **9d** (X = CN). Also see the enolate preparation below. The analytical sample melted at 202–204 °C. **10d**: IR ($CHCl_3$) 2250 cm^{-1} (CN), 1625 cm^{-1} (flavone CO); ^1H NMR ($CDCl_3$) δ 3.62 (s, 2, methylene H), 3.93 (s, 6, $ArOCH_3$), 6.9–8.4 (m, 7, ArH); UV max (CH_3CN) 209 nm (log ε 4.25), 244 (4.13), 225 (4.23). Anal. Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.70; N, 4.36. Found: C, 71.25; H, 5.15; N, 4.34.

Enolate of 9b (X = CN). A solution of 1.5 g (4.1 mmol) of **4b**, 0.27 g (4.1 m mol) of KCN, 15 mL of EtOH, and 5 mL of H_2O was refluxed for 1.5 h. The red solution was cooled, and 0.10 g (8%) of the decarboxylated byproduct **10b** separated. After the removal of **10b**, the filtrate was evaporated, yielding the enolate **9b** as a red powdery residue. This enolate was supended in ether and collected by filtration, 1.48 g (90%), mp 165–167 °C. An analytical sample was not obtained. **9b**: IR (mull) 2164 cm^{-1} (CN), 1620; UV max (CH_3CN) 295 nm (log ε 4.25), 241 (4.26), 220 (4.69).

Enolate of 9d. The same procedure as for the enolate of **9b** (0.62 g (1.5 mmol) of **4d**, 0.12 g (1.9 mmol) of KCN, 25 mL of EtOH, 25 mL of H_2O, reflux 1.5 h) yielded 0.08 g (17%) of the decarboxylated byproduct **10d** (see above) and 0.53 g (80%) of the enolate, mp 167–174 °C. An analytical sample was not obtained. **9d**: IR (mull) 2160 cm^{-1} (CN), 1610–1630 (2 bands); UV max (CH_3CN) 297 nm (log ε 4.29), 246 (4.20), 226 (4.28).

3-(1-Carbethoxy-1-cyanoethyl)-4′-methoxyflavone (11b). The (carbethoxycyanomethyl)flavone **9b** (X = CN) was methylated (1 g (2.7 mmol) of **9b**) in refluxing acetone (5 mL, 8 h) with 0.48 g (3.4 mmol) of iodomethane in the presence of 0.35 g (4.2 mmol) of sodium bicarbonate. After the inorganics were filtered, the solvent was removed and the residue taken up in Et_2O. After filtration followed by evaporation, the Et_2O solution left a gum. Upon trituration with a little ether, the gum changed to a yellow solid, 0.85 g (82%) of crude **11b**, mp 120–135 °C. A single recrystallization (EtOH) raised the melting point to 138–142 °C. The analytical sample melted at 143–145 °C. **11b**: IR ($CHCl_3$) 2225 cm^{-1} (CN), 1745 (ester CO), 1640 (flavone CO); ^1H NMR ($CDCl_3$) δ 1.24 (t, 3, OCH_2CH_3), 1.77 (s, 3, CCH_3), 3.90 (s, 3, $ArOCH_3$), 4.26 (q, 2, OCH_2CH_3), 6.9–8.4 (m, 8, ArH); UV max (CH_3CN) 295 nm (log ε 4.14), 240 (4.19). Anal. Calcd for $C_{22}H_{19}NO_5$: C, 70.02; H, 5.07; N, 3.71. Found: C, 70.17; H, 5.23; N, 3.63. This substance was also prepared by refluxing 1.0 g (2.5 mmol) of the enolate of **9b** and 0.53 g (3.7 mmol) of MeI for 9 h in dry acetone. The resulting solution was worked up as above, affording 0.72 g (76%), of **11b**, mp 133–137 °C.

3-(1-Carbethoxy-1-cyanoethyl)-4′,7-dimethoxyflavone (11d). This was prepared from the enolate of **9b** by refluxing the enolate (0.45 g, 1.0 mmol) with 0.22 g (1.5 mmol) of MeI in 5 mL of dry acetone for 8 h. This was then worked up following the procedure for **11b** from **9b** above, yielding 0.16 g (40%) of **11d**, mp 151–156 °C. The analytical sample melted at 154.5–157 °C (EtOH). **11d**: IR ($CHCl_3$) 2230 cm^{-1} (CN), 1745 (ester CO), 1615 (flavone CO); ^1H NMR ($CDCl_3$) δ 1.25 (t, 3, OCH_2CH_3), 1.75 (3, s, CCH_3), 3.89 (s, 6, $ArOCH_3$), 4.24 (q, 2, OCH_2CH_3), 6.8–8.4 (m, 7, ArH); UV max (CH_3CN) 293 nm (log ε 4.16), 245 (4.20), 226 (4.30). Anal. Calcd for $C_{23}H_{21}NO_6$: C, 67.80; H, 5.19; N, 3.44. Found: C, 67.74; H, 5.12; N, 3.47.

Acknowledgment. Partial support from the Camille and Henry Dreyfus Foundation is gratefully acknowledged.

Registry No. 3a, 1603-46-9; **3b**, 1808-05-5; **3c**, 2047-54-3; **3d**, 1808-02-2; **3e**, 80907-12-6; **4a**, 80907-13-7; **4b**, 80907-14-8; **4c**, 80907-15-9; **4d**, 80907-16-0; **4e**, 80907-17-1; **5a**, 50526-01-7; **5a** (Et = H), 80907-18-2; **5b**, 80907-19-3; **5b** (Et = H), 80907-20-6; **5d**, 80907-21-7; **5e**, 80907-22-8; **5e** (Et = H), 80907-23-9; **9a** (X = Br), 80907-24-0; **9a** (X = CN), 80907-25-1; **9b** (X = Br), 80907-26-2; **9b** (X = CN), 80907-27-3; **9b** enolate (X = CN), 80907-28-4; **9c** (X = CN), 80907-29-5; **9d** (X = CN), 80907-30-8; **9d** enolale (X = CN), 80964-96-1; **9e** (X = Br), 80907-31-9; **9e** (X = CN), 80907-32-0; **10b**, 80907-33-1; **10d**, 80907-34-2; **11b**, 80907-35-3; **11d**, 80907-36-4; **12**, 1099-45-2.

Synthesis of 5-Fluorouracil Derivatives Having *N*-Acylazacycloalkanes and Lactams[1]

Takashi Nishitani, Hiroshi Horikawa, Tameo Iwasaki,* Kazuo Matsumoto, Ichizo Inoue, and Muneji Miyoshi

Department of Synthetic Chemistry, Research Laboratory of Applied Biochemistry, Tanabe Seiyaku Co., Ltd., 3-16-89 Kashima, Yodogawa-ku, Osaka 532, Japan

Received October 6, 1981

5-Fluorouracil derivatives have been synthesized, in 41–84% yield, by the Lewis acid catalyzed condensation of 2,4-bis(trimethylsilyl)-5-fluorouracil with *N*-acyl-2-methoxyazacycloalkanes; the latter have been prepared by anodic oxidation of either *N*-acylprolines and *N*-acylpipecolic acids in methanolic sodium methoxide or *N*-acylperhydroazepines and *N*-acylmorpholines in methanolic tetraethylammonium perchlorate. The method has been extended to the synthesis of the 5-fluorouracil derivatives having five-, six-, and seven-membered lactams.

Chemical modifications of 5-fluorouracil (5-FU)[2] have been investigated extensively during the last two decades in search for effective nontoxic antitumor agents.[3] Interest in this area has been further stimulated by the recent finding that the derivatives represented by 1-(tetrahydrofuran-2-yl)-5-fluorouracil,[4] 1-(hexylcarbamoyl)-5-fluorouracil[5] and 5′-deoxy-5-fluorouridine[6] show significant antitumor activities as well as therapeutic advantages over 5-FU. Of prime importance for the design of new 5-FU derivatives would be the choice of the substituents and of the binding sites of 5-FU onto the substituents, both of which sway the pharmacokinetic properties of the 5-FU derivatives. We have recently directed our attention, as one of our research programs,[7] to the 5-FU derivatives

(1) Synthetic Electroorganic Chemistry. 14. A part of this work was presented at 29th Annual Meeting of the Kinki Branch, Pharmaceutical Society of Japan, Kyoto, Japan, Nov 11, 1979.

(2) Heidelberger, C.; Chaudhuri, N. K.; Danneberg, P.; Mooren, D.; Griesbach, L.; Duschinsky, R.; Schnitzer, R. J.; Pleven, E.; Scheiner, J. *Nature (London)* **1957**, *179*, 663.

(3) (a) Cook, A. F.; Holman, M. J. *J. Med. Chem.* **1980**, *23*, 852. (b) Kametani, T.; *et al. Ibid.* **1980**, *23*, 1324 and references cited therein.

(4) Yasumoto, M.; Yamawaki, I.; Marunaka, T.; Hashimoto, S. *J. Med. Chem.* **1978**, *21*, 738.

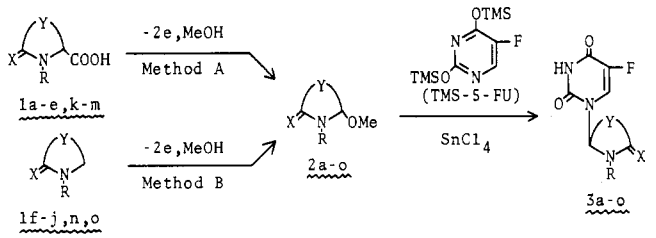
(5) Ozaki, S.; Ike, Y.; Mizuno, H.; Ishikawa, K.; Mori, H. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2406.

(6) Cook, A. F.; Holman, M. J.; Kramer, M. J.; Trown, P. W. *J. Med. Chem.* **1979**, *22*, 1330.

(7) For the synthesis of the 5-FU derivatives having oxacycloalkanes, see: Iwasaki, T.; Nishitani, T.; Horikawa, H.; Inoue, I. *Tetrahedron Lett.* **1981**, 1029.

0022-3263/82/1947-1706$01.25/0

Scheme I



a, X=H2; Y=(CH2)2; R=CH3CO
b, X=H2; Y=(CH2)2; R=CH3(CH2)2CO
c, X=H2; Y=(CH2)2; R=PhCH2OCONHCH2CO
d, X=H2; Y=(CH2)3; R=PhCH2OCO
e, X=H2; Y=(CH2)3; R=PHCH2OCONHCH2CO
f, X=H2; Y=CH2OCH2; R=CH3CO
g, X=H2; Y=CH2OCH2; R=PhCO
h, X=H2; Y=CH2OCH2; R=C2H5OCO
i, X=H2; Y=(CH2)4; R=CH3CO
j, X=H2; Y=(CH2)4; R=PhCO
k, X=O; Y=(CH2)2; R=H
l, X=O; Y=(CH2)2; R=C4H9
m, X=O; Y=(CH2)2; R=PhCH2OCO
n, X=O; Y=(CH2)3; R=H
o, X=O; Y=(CH2)4; R=H

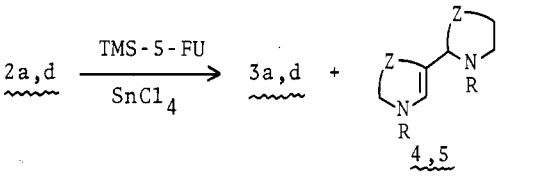
having *N*-acylazacycloalkanes wherein geminal diamine moieties[8,9] are involved.

The strategy for the synthesis of these nucleosides so far reported involves the preparation of the functionalized *N*-acylazacycloalkanes, followed by making of the nitrogen–carbon bonds between the *N*-acylazacycloalkanes and nucleic acid bases. The prominent method is exemplified by that reported by Szarek et al.;[10] the nucleosides were synthesized by the treatment of an appropriate heterocycle such as a *N*-acylmorpholine with *tert*-butyl peracetate–cuprous chloride, followed by the condensation of the *N*-acyl-3-hydroxymorpholine with nucleic acid bases by using the diethyl azodicarboxylate–methyldiphenylphosphine system. On the other hand, we have recently developed a viable synthetic route to the 5-FU derivatives bearing geminal diamine skeletons based on an electrochemical approach[11] and applied the method to the synthesis of the amino acids having 5-FU at the 2-positions of the amino acids.[8,9] We herein report a new synthesis of a novel class of 5-FU derivatives having *N*-acylazacycloalkanes [(5-fluorouracil-1-yl)azacycloalkanes] using *N*-acylazacycloalkane-2-carboxylic acids or *N*-acylazacycloalkanes as starting materials. The synthetic method consists of the anodic methoxylation of *N*-acylazacycloalkane-2-carboxylic acids or *N*-acylazacycloalkanes, followed by Lewis acid catalyzed condensations of the *N*-acyl-2-methoxyazacycloalkanes with 2,4-bis(trimethylsilyl)-5-fluorouracil [$(Me_3Si)_2$-5-FU] to give the (5-fluorouracil-1-yl)azacycloalkanes. The method has been further extended to the synthesis of the 5-FU derivatives having five-, six-, and seven-membered lactams (5-FU lactams, Scheme I).

(5-Fluorouracil-1-yl)azacycloalkanes

2-Functionalized azacycloalkanes such as *N*-acyl-2-methoxypyrrolidines from which the acylimmonium ion can be generated invariably, have been found to be synthetic intermediates of high potential in organic syntheses,[12] especially in the biogenetic-type syntheses of several categories of alkaloids.[13] The methods for preparing the functionalized azacycloalkanes include the oxidation of azacycloalkane-2-carboxylic acid derivatives induced by *m*-chloroperbenzoic acid,[14] thermal treatment[15] of azacycloalkane-2-carbonyl chlorides,[16] and pH-controlled sodium borohydride reduction of succinimide derivatives.[17] Most recently, two substantially new procedures based on electrochemical approaches have been reported by us[18] and other workers;[19a–d] the one involves the regioselective introduction of a methoxyl group by anodic oxidation of *N*-acylazacycloalkane-2-carboxylic acids, while the other involves the direct anodic methoxylation of *N*-acylazacycloalkanes. For the preparation of the *N*-acyl-2-methoxyazacycloalkanes, we have employed the former method involving the anodic replacement of the carboxyl group by a methoxyl group. The latter method involving the direct methoxylation has also been utilized when the starting materials, *N*-acylazacycloalkane-2-carboxylic acids, are not readily available.

Scheme II

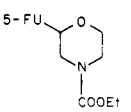


2a,d → 3a,d + 4,5

4, Z=CH2; R=CH3CO
5, Z=(CH2)2; R=PhCH2OCO

Thus, *N*-acyl-2-methoxypyrrolidines and *N*-acyl-2-methoxypiperidines were prepared in almost quantitative yields with good current efficiencies by anodic oxidation of *N*-acylprolines and *N*-acylpipecolic acids, respectively, in methanol containing 0.025 molar equiv of sodium methoxide.[11c,18] In the preparation of *N*-acyl-2-methoxymorpholines and *N*-acyl-2-methoxyperhydroazepines, *N*-acylmorpholines and *N*-acylperhydroazepines were used

(8) Nishitani, T.; Iwasaki, T.; Mushika, Y.; Miyoshi, M. *J. Org. Chem.* **1979**, *44*, 2019.
(9) Nishitani, T.; Iwasaki, T.; Mushika, Y.; Inoue, I.; Miyoshi, M. *Chem. Pharm. Bull.* **1980**, *28*, 1137.
(10) See, for example: (a) Pinto, B. M.; Vyas, D. M.; Szarek, W. A. *Can. J. Chem.* **1977**, *55*, 937 and references cited therein. For the other synthetic method, see: (b) Jones, A. S.; Walker, T. *Carbohydr. Res.* **1973**, *26*, 255.
(11) (a) Horikawa, H.; Iwasaki, T.; Matsumoto, K.; Miyoshi, M. *Tetrahedron Lett.* **1976**, 191. (b) Iwasaki, T.; Horikawa, H.; Matsumoto, K.; Miyoshi, M. *J. Org. Chem.* **1977**, *42*, 2419. (c) Iwasaki, T.; Horikawa, H.; Matsumoto, K.; Miyoshi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 826.
(12) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172 and references cited therein.
(13) (a) Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron Lett.* **1975**, 3963, 4035. (b) Schoemaker, H. E.; Speckamp, W. N. *Ibid.* **1978**, 1515. (c) Evans, D. A.; Thomas, E. W. *Ibid.* **1979**, 411. (d) Hart, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 397.
(14) Lucente, G.; Pinnen, F.; Zanotti, G. *Tetrahedron Lett.* **1978**, 3155.
(15) (a) Dean, R. T.; Padgett, H. C.; Rapoport, H. *J. Am. Chem. Soc.* **1976**, *98*, 7448. (b) Dean, R. T.; Rapoport, H. *J. Org. Chem.* **1978**, *43*, 4183.
(16) Adesogan, E. K.; Alo, B. I. *J. Chem. Soc., Chem. Commun.* **1979**, 673.
(17) Wijnberg, J. B. P. A.; Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 179.
(18) Iwasaki, T.; Horikawa, H.; Matsumoto, K.; Miyoshi, M. *J. Org. Chem.* **1979**, *44*, 1552.
(19) (a) Nyberg, K.; Servin, R. *Acta Chem. Scand., Ser. B* **1976**, *B30*, 640. (b) Eberson, L.; Nyberg, K. *Tetrahedron* **1976**, *32*, 2185. (c) Shono, T.; Hamaguchi, H.; Matsumura, Y. *J. Am. Chem. Soc.* **1975**, *97*, 4264. (d) Mitzlaff, M.; Warning, K.; Jensen, H. *Justus Liebigs Ann. Chem.* **1978**, 1713. (e) The formation of *N*-acyl-3-methoxymorpholines was not observed. This was substantiated by treating the crude electrolysis products with $(Me_3Si)_2$-5-FU under the Lewis acid catalyzed conditions; under these reactions, 5-FU derivatives wherein 5-FU is attached to the 3-position of the *N*-acylmorpholines[20] were not formed at all.
(20) For example, the regioisomer **13** (mp 184–185 °C) was prepared according to the method reported previously.[7]



13

as starting materials. The anodic oxidation of *N*-acylmorpholines was carried out in methanol containing tetraethylammonium perchlorate by using a graphite anode and cathode in a nondivided cell to provide the corresponding *N*-acyl-2-methoxymorpholines[19e] in 60–85% yields. *N*-Acyl-2-methoxyperhydroazepines were also obtained in 56–75% yields on passing 1.5 times the theoretical amount of electricity; in these reactions, the starting materials remained unaltered.

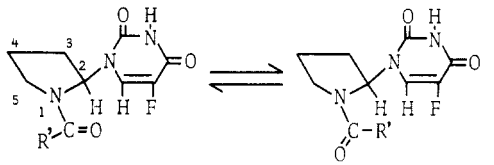
The condensation of the *N*-acyl-2-methoxyazacycloalkanes with $(Me_3Si)_2$-5-FU was examined under Lewis acid catalyzed conditions.

It is well-known[21] that *N*-(α-methoxyalkyl) amides amidoalkylate a wide variety of nucleophiles, through *N*-acyl imines and/or *N*-acyl immonium ions, under Lewis acid-catalyzed conditions. On the other hand, as illustrated by Vorbrüggen et al.,[22] the Friedel–Craft-catalyzed silyl Hilbert–Johnson reaction, wherein the electrophilic sugar carbonium ions are generated, is usually effective for the nucleoside syntheses.[23] It is anticipated that the highly reactive *N*-acyl immonium ions generated by the treatment of *N*-acyl-2-methoxy-azacycloalkanes with a Lewis acid undergo the silyl Hilbert–Johnson reaction to provide the corresponding nucleosides. Thus, we have employed the methodology based on the Hilbert–Johnson reaction for the synthesis of the 5-FU derivatives having *N*-acylazacycloalkanes.

We treated *N*-acetyl-2-methoxypyrrolidine (**2a**) with $(Me_3Si)_2$-5-FU under the conditions (using 1 molar equiv of $SnCl_4$ at 5–10 °C) that had worked well for the condensations of the sugar components and $(Me_3Si)_2$-5-FU.[7,24] In no case, however, did we observe a clear solution; the dimerization product (**4**) was formed in 32% yield instead of the desired N^1-substitution product **3a** (36% yield, Scheme II). The dimerization product (**4**) is most probably formed by the action of the Lewis acid on the elimination product, *N*-acetyl-2,3-dehydropyrrolidine.[25] The formation of the byproduct could be simply suppressed by working under the same conditions at lower reaction temperatures and employing longer reaction times. Thus, on treatment of **2a** with $(Me_3Si)_2$-5-FU in acetonitrile at −15 °C and 1 molar equiv of $SnCl_4$, the 5-FU derivative **3a** was obtained in 81% yield; a small amount of the byproduct (12% yield) was formed. The other *N*-acyl-2-methoxypyrrolidines **2b,c** were also treated with $(Me_3Si)_2$-5-FU to give the corresponding 5-FU derivatives **3b,c** in 72–78% yields. In order to obtain a water-soluble 5-FU derivative, we carried out the hydrogenolysis of the compound **3c** in methanol containing 1 molar equiv of HCl in dioxane using 10% palladium on charcoal at atmospheric pressure to provide *N*-glycyl-2-(5-fluorouracil-1-yl)pyrrolidine hydrochloride in 88% yield.

The synthesis of the 5-FU derivatives containing *N*-acylpiperidines was also carried out under conditions similar to those described above. In the reactions of compounds **2d,e** with $(Me_3Si)_2$-5-FU at −40 to −45 °C for 10 min with 1 molar equiv of $SnCl_4$, the desired N^1-substitution products **3d,e** were obtained in 54% and 41% yields, respectively. The N^1-substitution products are so unstable under the reaction conditions that these undergo decomposition by elimination of the 5-FU moiety. For example, when the above reaction mixture was kept for 1 h at the same temperature, the desired product **3d** disappeared completely, resulting in the formation of the dimerization product **5** (Scheme II). Most recently, it has been documented that under the conditions of amidoalkylations, *N*-benzoyl-2-methoxypiperidine tends to eliminate mainly to *N*-benzoyl-2,3-dehydropiperidine.[26]

Scheme III



3A 3B

In contrast to the 5-FU derivatives bearing *N*-acyl piperidines described above, the derivatives having *N*-acylmorpholines are quite stable under the Lewis acid catalyzed conditions. When *N*-acetyl-2-methoxymorpholine (**2f**) was allowed to react with $(Me_3Si)_2$-5-FU in the presence of 1.5 molar equiv of $SnCl_4$ at −20 to −25 °C for 24 h, the N^1-substitution product **3f** was formed in 60% yield. The reactions of the other *N*-acyl-2-methoxymorpholines and *N*-acyl-2-methoxyperhydroazepines with $(Me_3Si)_2$-5-FU were also carried out under the conditions similar to those described above to provide the corresponding 5-FU derivatives (**3g–j**) in 70–84% yields.

The yields and characterization of *N*-acyl-2-methoxyazacycloalkanes and the 5-FU derivatives are summarized in Table I.

The structural assignments of these products were made on the basis of the NMR and mass spectra and elemental analyses. The position of substitution of the *N*-acylazacycloalkanes on 5-FU was determined by the UV spectra obtained in the neutral and basic media by use of the same method as reported previously.[8]

The NMR spectra of the 5-FU derivatives containing *N*-acylpyrrolidines[27] described above exhibited an interesting aspect due to the hindered rotation of the amide bonds.[28] Two conformational isomers, **3A** and **3B**, are possible which undergo interconversion at a rate slow on the NMR time scale (Scheme III). In the H^1 NMR spectrum of the *N*-formyl derivative,[29] the distinct difference of the chemical shifts between one set of the signals given by the C-2 proton on the pyrrolidine ring was observed in Me_2SO-d_6 at ambient probe temperature. These signals show multiplets at 5.91 and 6.15 ppm; the ratio of the former to the latter was determined by integration of the spectrum to be 4.7:5.3. The ratio increases as the size of the substituent R′ on the carbonyl group increases. When R′ is a methyl or propyl group, the ratio is 7.5:2.5 and 8.0:2.0, respectively, whereas only the lower field signal (6.15 ppm) is observed in the case when R′ is a phenyl group.[29] This trend may be explained in terms of simple steric repulsion[30] between the 5-FU moiety and the sub-

(21) (a) Zaugg, H. E.; Martin, W. B. *Org. React.* **1965**, *14*, 52. (b) Zaugg, H. E. *Synthesis* **1970**, 49.

(22) Niedballa, U.; Vorbrüggen, H. *J. Org. Chem.* **1974**, *39*, 3654, 3660, 3664, 3668.

(23) (a) Vorbrüggen, H.; Niedballa, U.; Krolikiewicz, K.; Bennua, B.; Höfle, G. In "Chemistry and Biology of Nucleosides and Nucleotides"; Harmon, R. E., Robins, R. K., Townsend, L. B., Eds.; Academic Press: New York, 1978; p 251. (b) Vorbrüggen, H. In "Nucleoside Analogues"; Walker, R. T., De Clercq, E., Eckstein, F., Eds.; Prenum Press: New York, 1979; p 35.

(24) Vorbrüggen, H.; Krolikiewicz, K.; Niedballa, U. In "Chemistry, Biology, and Clinical Uses of Nucleoside Analogs"; Bloch, A., Ed.; The New York Academy of Sciences: New York, 1975; p 82.

(25) Horikawa, H. Ph.D. Thesis, Kytoto University, Kyota, Japan.

(26) Asher, V.; Becu, C.; Anteunis, M. J. O.; Callens, R. *Tetrahedron Lett.* **1981**, 141.

(27) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1965**, *5*, 495.

(28) Stewart, W. E.; Siddall, T. H. *Chem. Rev.* **1970**, *70*, 517.

(29) *N*-Formyl-2-(5-fluorouracil-1-yl)pyrrolidine (mp 181 °C dec) and *N*-benzoyl-2-(5-fluorouracil-1-yl)pyrrolidine (mp 216 °C dec) were synthesized under the same conditions as those employed in the preparation of compound **3a**.

Table I. Yields and Characterization of Compounds 2 and 3

	2[a]			3[b]		
	method	yield, %	bp, °C (mmHg)	yield, %	mp,[c] °C	NMR (Me_2SO-d_6), δ
a	A	*d*	*d*	81	182	1.6-2.4 (m,[e] 7 H), 3.1-4.1 (m, 2 H), 5.89 and 6.12 (2 m, 1 H), 7.73 and 7.84 (2 d, *J* = 6.8, 7.2 Hz, 1 H), 11.74 (br s 1 H)
b	A	*d*	*d*	78	171	0.8-1.1 (m, 3 H), 1.2-2.4 (m, 8 H), 3.2-4.1 (m, 2 H), 5.91 and 6.12 (2 m, 1 H), 7.74 and 7.78 (2 d, *J* = 6.6, 7.2 Hz, 1 H), 11.74 (br s, 1 H)
c	A	*d*	*d*	72	167	1.6-2.3 (m, 4 H), 3.2-4.3 (m, 2 H), 3.93 (d, 2 H), 5.03 (s, 2 H), 5.95 and 6.18 (2 m, 1 H), 6.9-7.6 (br, 1 H), 7.32 (s, 5 H), 7.81 (d, *J* = 7.2 Hz, 1 H), 11.77 (br s, 1 H)
d	A	*d*	*d*	54	148	1.1-2.3 (m, 6 H), 3.2-4.2 (m, 2 H), 4.94, 5.21 (AB q, *J* = 12.0 Hz, 2 H), 5.7-6.1 (m, 1 H), 7.26 (s, 5 H), 7.74 (d, *J* = 7.1 Hz, 1 H), 11.67 (br s, 1 H)
e	A	93	74-75[f]	41	139	1.1-2.1 (m, 6 H), 3.2-4.2 (m, 2 H), 3.96 (d, 2 H), 5.01 (s, 2 H), 5.6-6.1 (m, 1 H), 6.8-7.6 (br, 1 H), 7.31 (s, 5 H), 7.81 (d, *J* = 7.3 Hz, 1 H), 11.73 (br s, 1 H)
f	B	62	83-85 (0.9)	60	167	2.19 (s, 3 H), 3.0-4.3 (m, 6 H), 6.04 (m, 1 H), 7.7-8.4 (m,[g] 1 H), 11.84 (br s, 1 H)
g	B	60	131-133 (1.0)	71	192	3.0-4.4 (m, 6 H), 6.12 (m, 1 H), 7.47 (s, 5 H), 8.20 (d, *J* = 7.2 Hz, 1 H), 11.80 (br s, 1 H)
h	B	85	78-79 (1.0)	84	157	1.17 (t, 3 H), 3.1-4.4 (m, 6 H), 4.09 (q, 2 H), 6.04 (m, 1 H), 7.96 (d, *J* = 6.8 Hz, 1 H), 11.83 (br s, 1 H)
i	B	56	82-83 (2.0)	70	182	1.0-2.4 (m, 8 H), 2.06 and 2.12 (2 s, 3 H), 3.5-4.2 and 5.2-6.7 (2 m, 3 H),[h] 7.61 and 7.70 (2 d, *J* = 6.1, 7.1 Hz, 1 H), 11.68 (br s, 1 H)
j	B	75	138-140 (3.0)	73	191	0.9-2.3 (m, 8 H), 3.4-4.3 and 5.2-6.5 (2 m, 3 H),[h] 7.1-7.6 (m, 5 H), 7.77 and 8.00 (2 d, *J* = 7.2, 7.2 Hz, 1 H), 11.23 (br s, 1 H)
k	A	*d*	*d*	41	163	2.0-2.80 (m, 4 H), 5.8-6.1 (m, 1 H), 7.98 (d, *J* = 7.0 Hz, 1 H), 8.2 (br s, 1 H), 11.50 (br s, 1 H)
l	A	82	78-80 (0.9)	38	140	0.7-1.7 (m, 7 H), 1.8-3.7 (m, 6 H), 5.8-6.1 (m, 1 H), 7.91 (d, *J* = 6.8 Hz, 1 H), 11.82 (br s, 1 H)
m	A	84	138-140 (0.04)	*i*		
n	B	64	107-109[f]	40	190	1.4-2.6 (m, 6 H), 5.5-6.0 (m, 1 H), 7.85 (s, 1 H), 8.08 (d, *J* = 7.5 Hz, 1 H), 11.73 (br s, 1 H)
o	B	65	65-67[f]	36	183	1.1-2.7 (m, 8 H), 5.5-5.9 (m, 1 H), 7.74 (m, 1 H), 8.02 (d, *J* = 7.4 Hz, 1 H), 10.76 (m, 1 H)

[a] Satisfactory elemental analyses were obtained for compounds **2c-e**. The elemental analyses of the other compounds showed the following limit of error due to their hygroscopic or volatile properties: C, ±1.50%; H, ±0.41%; N, ±0.38%. [b] All new compounds gave satisfactory elemental analyses. [c] All the compounds listed here decompose at the temperatures of the melting points. [d] The boiling points and yields of these compounds were reported previously (see ref 18). [e] The multiplet contains a distinct singlet at 2.03 ppm which may be assigned to be an acetyl group. [f] Melting point. [g] The resonance due to the C-6 proton of the 5-FU moiety is observed as multiplet only in this compound, although the C-6 protons of the other 5-FU derivatives that we have synthesized exhibit distinct doublets. [h] These resonances contain those due to the C-2 and C-7 protons of the perhydroazepine ring. [i] Compound **3m** was not obtained, but compound **8** was formed in 73% yield.

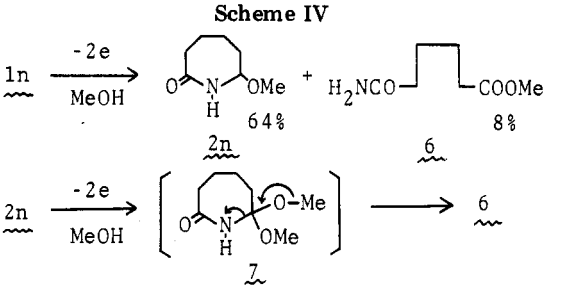
stituents R′ on the carbonyl groups attached to the pyrrolidine ring. Thus, we assigned[31] the higher field signal to that of the conformer **3B**, while the lower field signal was assigned to that of the conformer **3A**.

5-Fluorouracil Lactams

The synthetic method described above also enabled the synthesis of the 5-FU derivatives having lactams.

2-Methoxy-5-pyrrolidone (**2k**) was obtained in 94% yield by anodic oxidation of 5-pyrrolidone-2-carboxylic acid (**1k**) in methanol containing 0.025 molar equiv of sodium methoxide.[18] Methoxylation of *N*-butyl- and *N*-(benzyloxycarbonyl)-5-pyrrolidone-2-carboxylic acids (**1l,m**) also proceeded smoothly under the same conditions as described above to yield the corresponding 2-methoxy-5-pyrrolidone derivatives (**2l,m**) in nearly quantitative yields.

Scheme IV



In the methoxylation of the six- and seven-membered lactams,[33] 2-piperidone (**1n**) and caprolactam (**1o**) were used as the starting materials. The methoxylation of these lactams was achieved in methanol containing tetraethylammonium perchlorate by passing 4–5 F/mol of electricity, which is enough to consume the starting materials completely. Under the reaction conditions, the desired methoxylated products (**2n,o**) were obtained in 64–65%

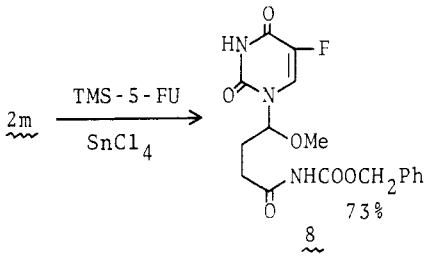
(30) See, for example: (a) LaPlanche, L. A.; Rogers, M. T. *J. Am. Chem. Soc.* **1964**, *86*, 337. (b) Staab, H. A.; Lauer, D. *Chem. Ber.* **1968**, *101*, 864.

(31) The conclusion concerning the structural assignment described here is in disagreement with that obtained in *N*-acyl-2-methoxypyrrolidines reported previously which is derived on the basis of the Paulsen and Todt criterion[32] which in turn is based on the magnetic anisotropy of amides. In the NMR spectra of *N*-acyl-2-methoxypyrrolidines, the C-2 proton cis to the carbonyl oxygen shows a larger downfield shift due to the anisotropic effect of the carbonyl group. To our present knowledge, no satisfactory explanation is given for these conflicting results. A detailed study is currently under investigation.

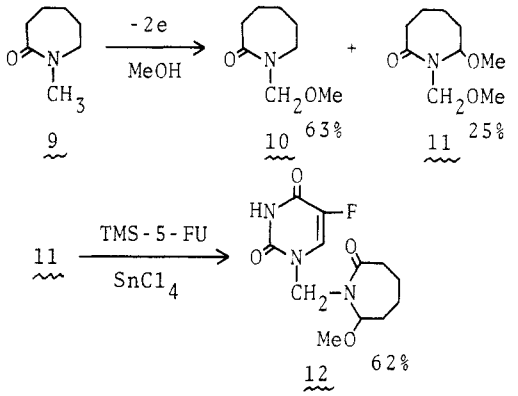
(32) (a) Paulsen, H.; Todt, K. *Angew. Chem., Int. Ed. Engl.* **1965**, *5*, 899. (b) *Chem. Ber.* **1967**, *100*, 3385, 3397.

(33) Warning, K.; Mitzlaff, M. *Tetrahedron Lett.* **1979**, 1563.

Scheme V



Scheme VI



yields. In the oxidation of caprolactam, the concomitant formation of the ring-opened product **6** was observed, which is probably formed via the overoxidation product, 2,2-dimethoxycaprolactam (**7**, Scheme IV). The anodic oxidation of *N*-methylcaprolactam (**9**) was also carried out with twice the theoretical amount of electricity in methanol–tetraethylammonium perchlorate to afford a mixture of monomethoxylated (**10**) and dimethoxylated (**11**) products (Scheme VI). Compound **11** is most probably formed by the oxidation of compound **10**, since no 2-methoxy-*N*-methylcaprolactam was formed at all in the course of the reaction. It seems likely that in the anodic oxidation of *N*-alkylcaprolactams, the exocyclic carbon α to the nitrogen is more susceptible to oxidation than the endo one under the reaction conditions.[34]

The methoxylated lactams **2k,l,n,o** underwent reaction with $(Me_3Si)_2$-5-FU in the presence of $SnCl_4$ to give the corresponding 5-FU derivatives (**3k,l,n,o**) containing lactams in 36–41% yields; in the reaction of **2l** with $(Me_3Si)_2$-5-FU, the N^3-substitution and N^1,N^3-disubstitution products were formed concomitantly. Two interesting observations are noted in the reactions with the compounds **2m** and **11**. Treatment of **2m** with $(Me_3Si)_2$-5-FU resulted in the formation of the ring-opened material **8** in 73% yield (Scheme V). In the reaction of compound **11** with $(Me_3Si)_2$-5-FU, the substitution reaction occurred only onto the exocyclic carbon α to the nitrogen to afford the 5-FU derivative **12** in 62% yield (Scheme VI).

The antitumor activities of the 5-FU derivatives described here were evaluated against Sarcoma 180 in mice. Of these, the N^3-substitution product, 3-(*N*-butyl-5-oxopyrrolidin-2-yl)-5-fluorouracil showed significant activity at 100 mg/kg/day × 7 (ip). However, the other compounds were inactive at the 100 mg/kg level.

Experimental Section

Equipment. Melting points were measured by using a Yamato melting point apparatus and were uncorrected. IR spectra were recorded on a Shimadzu IR-27G infrared spectrometer. NMR spectra were obtained by using a Hitachi Perkin-Elmer R-20 high-resolution NMR spectrometer with tetramethylsilane as an internal standard. UV spectra were measured on a Hitachi EPS-3T spectrometer. Mass spectra were taken with a Hitachi M-60 mass spectrometer. Anodic oxidations were carried out by using a Hokuto PGS 2000 (2 A, 120 V) or PGS 2500 (2.5 A, 60 V) potentiogalvanostat attached to a Hokuto HA 108A coulometer.

Typical Electrolysis Procedure. Method A. Methoxylation of the *N*-acylazacycloalkane-2-carboxylic acids was carried out on a 0.1-mol scale in the same manner as that described in the previous reports.[11c,18] Typical procedure was exemplified by the anodic oxidation of *N*-(benzyloxycarbonyl)glycylpipecolic acid (**1e**). Compound **1e** (32 g, 0.1 mol) was dissolved in 150 mL of methanol containing 2.5 mL of N sodium methoxide. The anodic oxidation was carried out at 10–20 °C at a constant current of 200 mA/cm^2 by using graphite anode and cathode in a nondivided cell. The reaction was discontinued when 2 F/mol of electricity was passed. The reaction mixture was evaporated to dryness in vacuo below 20 °C. The resulting residue was dissolved in ethyl acetate, washed with water, dried over magnesium sulfate, and then evaporated to dryness in vacuo to afford colorless crystals of compound **2e** in 93% yield. Recrystallization from ethyl acetate–petroleum ether gave the pure **2e** as colorless prisms: IR (Nujol) 3320, 3060, 3030, 3000, 1710, 1644, 1530 cm^{-1}; NMR ($CDCl_3$) δ 1.2–2.1 (m, 6 H), 2.6–3.5, 3.8–4.6 (2 m, 2 H, CH_2CH_2N), 3.22 (s, 3 H), 4.04 (d, 2 H), 5.13 (s, 2 H), 5.72 (m, 1 H), 5.90 (m, 1 H), 7.33 (s, 5 H). Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.43; H, 7.18; N, 9.08.

The compounds **2a–d,k–m** were prepared by the same method as above. The spectral data of compounds **2a–d,k** have already been reported in the previous paper.[18] The NMR and mass spectra of compounds **2l,m** are as follows. Compound **2l**: NMR ($CDCl_3$) δ 0.7–1.8 (m, 7 H), 1.8–2.7 (m, 4 H), 2.8–3.8 (m, 2 H), 3.29 (s, 3 H), 4.87–5.11 (m, 1 H); mass spectrum, *m/e* 171 (M$^+$), 156, 140, 128. Compound **2m**: NMR ($CDCl_3$) δ 1.7–2.8 (m, 4 H), 3.33 (s, 3 H), 5.20 (s, 2 H), 5.1–5.4 (m, 1 H), 7.0–7.5 (m, 5 H); mass spectrum, *m/e* 249 (M$^+$), 218, 217, 201, 189, 174, 173, 157, 142, 111, 107.

Method B. *N*-Acetylmorpholine (**1f**; 25.8 g, 0.2 mol) was dissolved in 150 mL of methanol containing 2.6 g of tetraethylammonium perchlorate. The solution was electrolyzed at 10–20 °C by passing a constant current of 2.5 A (current density 330 mA/cm^2). The reaction was discontinued when 2.4 F/mol of electricity was passed. The solution was evaporated to dryness in vacuo, and the residue was dissolved in 300 mL of ethyl acetate. The solution was washed with 30 mL of water, dried ($MgSO_4$), and then evaporated in vacuo to give a colorless oil. Distillation of the oil under reduced pressure yielded the pure methoxylated product **2f**: NMR (CCl_4) δ 1.98 and 2.07 (2 s, 3 H), 3.24 (s, 3 H), 2.6–4.3 (m, 6 H), 4.74 and 5.35 (2 br s, 1 H); mass spectrum, *m/e* 159 (M$^+$), 149, 129, 128, 118, 114, 102, 101.

The compounds **2g–j** were prepared under the same conditions as shown above. In the preparation of the compound **2n**, a 10 F/mol of electricity was passed. The NMR and mass spectra of these methoxylated compounds are as follows. Compound **2g**: NMR (CCl_4) δ 3.16 (s, 3 H), 3.0–4.0 (m, 6 H), 4.8–5.2 (m, 1 H), 7.34 (s, 5 H); mass spectrum, *m/e* 221 (M$^+$), 207, 206, 191, 190, 176, 164, 148, 122, 116, 106, 105. Compound **2h**: NMR (CCl_4) δ 1.27 (t, 3 H), 2.9–4.4 (m, 6 H), 3.25 (s, 3 H), 4.13 (q, 2 H), 5.00 (br s, 1 H); mass spectrum, *m/e* 189 (M$^+$), 174, 159, 158, 144, 130, 116, 102. Compound **2i**: NMR ($CDCl_3$) δ 1.11 (br s, 8 H), 2.08 and 2.18 (2 s, 3 H), 3.1–4.2 (m, 5 H), 4.93 and 5.74 (2 t, 1 H). Compound **2j**: NMR (CCl_4) δ 0.8–2.6 (m, 8 H), 2.7–4.4 (m, 5 H), 4.5–5.4 (m, 1 H), 7.29 (s, 5 H); mass spectrum, *m/e* 233 (M$^+$), 231, 218, 202, 201. Compound **2n**: NMR ($CDCl_3$) δ 1.1–2.6 (m, 6 H), 3.36 (s, 3 H), 4.4–4.7 (m, 1 H), 8.0–8.7 (m, 1 H). Anal. Calcd for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.85. Found: C, 55.74; H, 8.46; N, 10.73.

Anodic Oxidation of Compound 1o. Compound **1o** (5 g, 44.2 mmol) was dissolved in 100 mL of methanol containing 0.5 g of tetraethylammonium perchlorate. The solution was electrolyzed by using graphite electrodes at 10–20 °C by passing a constant current of 2.0 A (current density 100 mA/cm^2). After 7 times the theoretical amount of electricity was passed, the solution was evaporated to dryness in vacuo. To the residue was added 100

(34) A similar result concerning the hydroxylation of *N*-alkyl lactams by anodic oxidation has been reported. See: Okita, M.; Wakamatsu, T.; Ban, Y. *J. Chem. Soc., Chem. Commun.* **1979**, 749.

mL of ethyl acetate, and the solution was treated with 2 g of activated charcoal. The insoluble materials were filtered off, and the filtrate was evaporated to dryness in vacuo. To the residue was added 30 mL of ether, and the crystals were collected by filtration. Recrystallization from ethyl acetate–hexane gave colorless leaflets of compound **7** (0.53 g, 7.5% yield).

The filtrate was evaporated to dryness in vacuo, and the residue was purified by chromatography on silica gel with chloroform–acetone (10:3) as an eluent to afford colorless crystals of compound **2o** (4.1 g, 61%). Compound **7**: mp 92–93 °C; IR (Nujol) 3350, 3180, 1731, 1665, 1628 cm^{-1}; NMR ($CDCl_3$) δ 1.3–2.0 (m, 4 H), 2.1–2.6 (m, 4 H), 3.66 (s, 3 H), 5.8–6.6 (br s, 2 H). Anal. Calcd for $C_7H_{13}NO_3$: C, 52.82; H, 8.23; N, 8.80. Found: C, 52.74; H, 8.23; N, 8.75. Compound **2o**: IR (Nujol) 3200, 3100, 1736, 1665 cm^{-1}; NMR ($CDCl_3$) δ 1.1–3.0 (m, 8 H), 3.35 (s, 3 H), 4.6–5.0 (m, 1 H), 7.6–8.3 (br, 1 H).

Anodic Oxidation of Compound 9. Compound **9** (10 g) was electrolyzed in 80 mL of methanol containing 1.0 g of tetraethylammonium perchlorate under the same conditions as those employed in the oxidation of compound **1o**. After twice the theoretical amount of electricity was passed, the solvent was evaporated under reduced pressure, and the residue was dissolved in 100 mL of ethyl acetate. The solution was washed with brine, dried ($MgSO_4$), and evaporated to dryness in vacuo. The residue was purified by chromatography on silica gel with chloroform–acetone (10:1) as an eluent to afford 7.78 g (63%) of compound **10** and 3.83 g (26%) of compound **11**. Compound **10**: syrup; IR (film) 3290, 2920, 2860, 1650 (br) cm^{-1}; NMR (CCl_4) δ 1.45–1.95 (m, 6 H), 2.25–2.65 (m, 2 H), 3.20 (s, 3 H), 3.2–3.5 (m, 2 H), 4.65 (s, 2 H); mass spectrum, *m/e* 157 (M^+), 143, 142, 127, 126, 115, 114. Compound **11**: syrup; NMR (CCl_4) δ 1.2–2.8 (m, 8 H), 3.26 (s, 3 H), 3.32 (s, 3 H), 4.4–4.7 (m, 1 H), 4.47 and 4.96 (AB q, 2 H, J = 10.5 Hz); mass spectrum, *m/e* 187 (M^+), 172, 156, 142, 128, 127, 113, 104.

Compounds 3a–c. Compound **2a** (1.43 g, 10 mmol) and $(Me_3Si)_2$-5-FU (2.74 g, 10 mmol) were dissolved in 30 mL of acetonitrile. To the solution was added dropwise a solution of $SnCl_4$ (1.15 mL, 10 mmol) dissolved in 2 mL of dichloromethane at −13 to −15 °C under vigorous stirring. After the reaction was continued for 3 h at the same temperature, the reaction mixture was poured into a mixture of 15 mL of water, 100 mL of acetonitrile, and 30 g of sodium hydrogen carbonate under vigorous stirring. The insoluble materials were filtered off. The filtrate was dried over magnesium sulfate and evaporated to dryness in vacuo. To the residue was added 30 mL of chloroform, and the insoluble materials were filtered off. Most of 5-FU can be removed by this procedure. The filtrate was evaporated to dryness in vacuo. To the residue was added 10 mL of ethanol, and the crystals that appeared were collected by filtration to give 1.95 g (81%) of compound **3a**. Recrystallization from methanol afforded colorless needles of the pure compound **3a**: IR (Nujol) 3180, 3060, 1720, 1700, 1662, 1639 cm^{-1}; UV (MeOH) λ_{max} 272 nm (ϵ 8620). Anal. Calcd for $C_{10}H_{12}FN_3O_3$: C, 49.79; H, 5.01; F, 7.88; N, 17.42. Found: C, 49.79; H, 5.01; F, 7.78; N, 17.20.

The filtrate was evaporated to dryness in vacuo. The residue was purified by chromatography on silica gel with chloroform–ethanol (10:1) as an eluent to give the dimerization product **4**. Recrystallization from ethyl acetate afforded colorless prisms of compound **4**: yield 0.6 g (12%); mp 128–129 °C; IR (Nujol) 3080, 1648, 1620 cm^{-1}; NMR (Me_2SO-d_6) δ 1.6–2.9 (m, 12 H), 3.2–4.1 (m, 4 H), 4.52 (m, 1 H), 6.45 (m, 1 H); UV (MeOH) λ_{max} 248 nm (ϵ 20 720); mass spectrum, *m/e* 222 (M^+), 179, 137, 120, 112, 109, 108. Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.73; H, 8.24; N, 12.84.

Compounds **3b,c** were prepared under the same conditions as above.

Hydrogenolysis of Compound 3c. Compound **3c** (1.17 g, 3.0 mmol) was dissolved in 100 mL of methanol containing 0.55 g of 20% HCl in dioxane. The solution was subjected to hydrogenolysis with 0.2 g of 10% palladium on charcoal at atmospheric pressure. After the reaction was over, the catalyst was filtered off, and the filtrate was evaporated to dryness in vacuo. To the residue was added 10 mL of ethanol, and the crystals were collected by filtration. Recrystallization from methanol–ether gave colorless crystals of pure *N*-glycyl-2-(5-fluorouracil-1-yl)pyrrolidine hydrochloride: yield 0.81 g (88%); mp 205 °C dec; IR (Nujol) 3150, 1690, 1670, 1650 cm^{-1}; UV (MeOH) λ_{max} 272 nm (ϵ 7160). Anal. Calcd for $C_{10}H_{14}ClFN_4O_3$: C, 38.91; H, 4.57; Cl, 11.98; F, 6.16; N, 18.15. Found: C, 38.94; H, 4.71; Cl, 11.52; F, 6.11; N, 18.14.

Compounds 3d,e. The procedure is exemplified by the preparation of compound **3d**. Compound **2d** (5.48 g, 22 mmol) and $(Me_3Si)_2$-5-FU (5.48 g, 20 mmol) were dissolved in 50 mL of acetonitrile. To the solution was added dropwise a solution of $SnCl_4$ (2.54 mL, 22 mmol) dissolved in dichloromethane for 2 min at −40 to −45 °C under vigorous stirring. After the stirring was continued for 10 min at the same temperature, the reaction was quenched by pouring the reaction mixture into the sodium hydrogen carbonate solution as described in the preparation of compound **3a**. The insoluble materials were filtered off, and the filtrate was evaporated to dryness in vacuo. To the residue was added 75 mL of chloroform and the insoluble materials were filtered off. The filtrate was evaporated to dryness in vacuo. To the residue was added 30 mL of ether, and the crystals were collected by filtration. Recrystallization from ethanol gave colorless needles of pure compound **3d**: yield 3.75 g (54%); IR (Nujol) 3160, 3090, 3030, 1713, 1690, 1680, 1665, 1650 cm^{-1}; UV (MeOH) λ_{max} 270 nm (ϵ 7460). Anal. Calcd for $C_{17}H_{18}FN_3O_4$: C, 58.78; H, 5.22; F, 5.47; N, 12.10. Found: C, 58.67; H, 5.29; F, 5.19; N, 12.25.

Compound **5** was isolated from the above filtrate in 12% yield as a syrup by chromatography on silica gel with toluene–ethyl acetate (10:1) as an eluent. Compound **5**: syrup; NMR ($CDCl_3$) δ 1.3–2.2 (m, 10 H), 2.4–3.1 (m, 1 H), 3.52 (t, 2 H), 3.8–4.2 (m, 1 H), 4.81 (br s, 1 H), 5.13 and 5.16 (2 s, 4 H), 6.6–6.9 (m, 1 H), 7.28 (s, 10 H). Anal. Calcd for $C_{26}H_{30}N_2O_4$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.57; H, 7.21; N, 6.25.

Compounds 3f–j. Compound **2f** (1.91 g, 12 mmol) and $(Me_3Si)_2$-5-FU (2.74 g, 10 mmol) were dissolved in 30 mL of acetonitrile. To this was added dropwise 1.73 mL of $SnCl_4$ dissolved in 2 mL of dichloromethane at −8 to −10 °C under vigorous stirring. The reaction mixture was allowed to stand for 24 h in a refrigerator (−20 to −25 °C). The reaction was quenched by the same procedure as that described in the preparation of compound **3a**. The filtrate was evaporated to dryness in vacuo. To the residue was added chloroform, and the insoluble materials were filtered off. The filtrate was evaporated to dryness in vacuo. The residue was washed with 30 mL of ether and then 30 mL of ethanol. The crystals (1.54 g, 60%) were collected by filtration. Recrystallization from ethanol afforded colorless needles of pure compound **3f**: IR (Nujol) 3200, 3060, 1721, 1696, 1660 cm^{-1}; UV (MeOH) λ_{max} 269 nm (ϵ 9400). Anal. Calcd for $C_{10}H_{12}FN_3O_4$: C, 46.69; H, 4.71; F, 7.39; N, 16.33. Found: C, 46.78; H, 4.73; F, 7.59; N, 16.33.

Compounds **3g–j** were prepared under the same conditions as above.

Compounds 3k,n,o. Compound **2n** (1.55 g, 12 mmol) and $(Me_3Si)_2$-5-FU (2.74 g, 10 mmol) were dissolved in 75 mL of acetonitrile. To this was added dropwise $SnCl_4$ (0.58 mL, 5 mmol) in 2 mL of dichloromethane at 0–5 °C under vigorous stirring. After the stirring was continued for 6 h at room temperature, the reaction was quenched by the same procedure as above. The filtrate was dried over magnesium sulfate and evaporated to dryness in vacuo. The crystals were triturated with ether and collected by filtration. Recrystallization from methanol–water gave colorless crystals of pure compound **3n**: yield 0.91 g (40%); IR (Nujol) 3160, 3030, 1725, 1695, 1673, 1651 cm^{-1}; UV (MeOH) λ_{max} 269 nm (ϵ 8850). Anal. Calcd for $C_9H_{10}FN_3O_3$: C, 47.58; H, 4.44; F, 8.36; N, 18.49. Found: C, 47.65; H, 4.50; F, 8.33; N, 18.58.

Compounds **3k,o** were prepared under the same conditions as above.

Compound 3l. Compound **2l** (1.88 g, 11 mmol) and $(Me_3Si)_2$-5-FU (2.74 g, 10 mmol) were dissolved in 30 mL of acetonitrile. To this was added dropwise a solution of $SnCl_4$ (0.58 mL, 5 mmol) in 2 mL of dichloromethane at −30 °C under vigorous stirring. After continuing for 6 h at −20 to −25 °C, the reaction was quenched by the same procedure as that described in the preparation of compound **3a**. The insoluble materials were filtered off. The filtrate was evaporated to dryness in vacuo. TLC (Merck, silica gel 60 F-254) of the residue with chloroform–methanol (10:1) as a developing solvent showed three spots at R_f values of 0.62, 0.53, and 0.48. The products were separated by chromatography

on silica gel with chloroform–methanol (20:1) as an eluent. N^1,N^3-Disubstitution product 1,3-bis(*N*-butyl-5-oxopyrrolidin-2-yl)-5-fluorouracil: colorless prisms; mp 135–137 °C (ethyl acetate–hexane); R_f 0.62; IR (Nujol) 3080, 1691, 1655 cm^{-1}; NMR (Me_2SO-d_6) δ 0.6–1.7 (m, 14 H), 1.7–3.7 (m, 12 H), 5.8–6.2 (m, 1 H), 6.2–6.6 (m, 1 H), 8.02 (d, J = 6.0 Hz, 1 H); UV (MeOH) λ_{max} 272 nm (ϵ 7930). Anal. Calcd for $C_{20}H_{29}FN_4O_4$: C, 58.81; H, 7.15; F, 4.65; N, 13.72. Found: C, 58.84; H, 7.20; F, 4.49; N, 13.64. N^1-Substitution product **3l**: colorless needles (ethyl acetate–hexane); R_f 0.53; IR (Nujol) 3190, 3150, 3040, 1735, 1695, 1675, 1661 cm^{-1}; UV (MeOH) λ_{max} 268 nm (ϵ 9160). Anal. Calcd for $C_{12}H_{16}FN_3O_3$: C, 53.52; H, 5.99; F, 7.06; N, 15.61. Found: C, 53.54; H, 6.02; F, 6.92; N, 15.47. N^3-Substitution product 3-(*N*-butyl-5-oxopyrrolidin-2-yl)-5-fluorouracil: colorless powder; mp 155.5–156.5 °C (ethyl acetate–hexane); R_f 0.48; IR (Nujol) 3060, 1726, 1664, 1645 cm^{-1}; NMR (Me_2SO-d_6) δ 0.6–1.7 (m, 7 H), 1.8–3.6 (m, 6 H), 6.2–6.6 (m, 1 H), 7.83 (d, J = 5.6 Hz, 1 H), 10.3–11.5 (br, 1 H); UV (MeOH) λ_{max} 271 nm (ϵ 6730). Anal. Calcd for $C_{12}H_{16}FN_3O_3$: C, 53.52; H, 5.99; F, 7.06; N, 15.61. Found: C, 53.46; H, 6.03; F, 7.15; N, 15.57.

Compound 8. To a stirred solution of compound **2m** (1.49 g, 6 mmol) and $(Me_3Si)_2$-5-FU (1.37 g, 5 mmol) in 30 mL of acetonitrile was added dropwise a solution of $SnCl_4$ (0.46 mL, 4 mmol) in 2 mL of dichloromethane at −40 °C under vigorous stirring. The reaction temperature was raised gradually to −10 °C for 30 min, and then the reaction was quenched by the same procedure as that described in the preparation of compound **3a**. The filtrate was evaporated to dryness in vacuo. To the residue was added 30 mL of chloroform, and the insoluble materials were filtered off. The filtrate was evaporated to dryness in vacuo. The crystals were triturated with isopropyl ether and collected by filtration. Recrystallization from ethanol gave colorless needles of pure compound 8: yield 1.27 g (73%); mp 144 °C dec; IR (Nujol) 3370, 3170, 1728, 1712, 1528 cm^{-1}; NMR (Me_2SO-d_6) δ 1.8–2.6 (m, 4 H), 3.55 (s, 3 H), 5.05 (s, 2 H), 5.7–6.1 (m, 1 H), 7.31 (s, 5 H), 7.77 (d, 1 H, J = 7.0 Hz), 7.9–8.4 (m, 1 H), 11.69 (br s, 1 H); UV (MeOH) λ_{max} 268 nm (ϵ 8130). Anal. Calcd for $C_{17}H_{18}FN_3O_6$: C, 53.82; H, 4.78; F, 5.01; N, 11.08. Found: C, 53.66; H, 4.66; F, 4.96; N, 11.04.

Compound 12. To a stirred solution of compound 11 (0.56 g, 3 mmol) and $(Me_3Si)_2$-5-FU (0.69 g, 2.5 mmol) was added dropwise a solution of $SnCl_4$ (0.14 mL, 1.25 mmol) in 2 mL of dichloromethane at 5–10 °C. After the stirring was continued for 2 h at the same temperature, the reaction mixture was treated by the same procedure as described above to afford compound 12 in 62% yield. Recrystallization from ethanol gave colorless needles of pure compound 12: mp 156–157 °C; IR (Nujol) 3160, 3100, 3020, 1723, 1692, 1664, 1632 cm^{-1}; NMR (Me_2SO-d_6) δ 1.0–3.0 (m, 8 H), 3.22 (s, 3 H), 4.8–5.3 (m, 1 H), 4.97 and 5.31 (AB q, 2 H, J = 13.5 Hz), 7.94 (d, 1 H, J = 6.8 Hz), 11.84 (s, 1 H); UV (MeOH) λ_{max} 267 nm (ϵ 8730). Anal. Calcd for $C_{12}H_{16}FN_3O_4$: C, 50.52; H, 5.65; F, 6.66; N, 14.73. Found: C, 50.41; H, 5.60; F, 6.66; N, 14.70.

Acknowledgment. We thank Dr. Ichiro Chibata, director of our laboratory, and Dr. Toshio Arai for their encouragement.

Registry No. **1e**, 80953-60-2; **1f**, 1696-20-4; **1g**, 1468-28-6; **1h**, 6976-49-4; **1i**, 5809-41-6; **1j**, 3653-39-2; **1l**, 80953-61-3; **1m**, 80953-62-4; **1n**, 675-20-7; **1o**, 105-60-2; **2a**, 63050-21-5; **2b**, 68471-61-4; **2c**, 69352-22-3; **2d**, 66893-75-2; **2e**, 80953-63-5; **2f**, 77873-72-4; **2g**, 80953-64-6; **2h**, 80953-65-7; **2i**, 63050-23-7; **2j**, 73269-87-1; **2k**, 63853-74-7; **2l**, 80953-66-8; **2m**, 80953-67-9; **2n**, 63853-82-7; **2o**, 63853-81-6; **3a**, 73269-74-6; **3b**, 73269-75-7; **3c**, 73269-79-1; **3d**, 73269-82-6; **3e**, 73269-83-7; **3f**, 77948-25-5; **3g**, 77937-94-1; **3h**, 77937-95-2; **3i**, 80953-68-0; **3j**, 80953-69-1; **3k**, 74991-05-2; **3l**, 74991-07-4; **3n**, 74991-10-9; **3o**, 74991-11-0; **4**, 80953-70-4; **5**, 80953-71-5; **7**, 80953-72-6; **8**, 80953-73-7; **9**, 2556-73-2; **10**, 10291-81-3; **11**, 80953-74-8; **12**, 80953-75-9; $(Me_3Si)_2$-5-Fu, 17242-85-2; *N*-glycyl-2-(5-fluorouracil-1-yl)pyrrolidine hydrochloride, 80953-76-0; 1,3-bis(*N*-butyl-5-oxo-pyrrolidin-2-yl)-5-fluorouracil, 80953-77-1; 3-(*N*-butyl-5-oxopyrrolidin-2-yl)-5-fluorouracil, 80953-78-2; **6**, 40760-22-3; *N*-formyl-2-(5-fluorouracil-1-yl)pyrrolidine, 73269-73-5; *N*-benzoyl-2-(5-fluorouracil-1-yl)pyrrolidine, 73269-78-0.

Mechanism of Formation of Cyclic Urea Nucleosides. Evidence for an O- to N-Transglycosylation

Victor E. Marquez,* Paul S. Liu, and Joanne K. Linevsky

Drug Design and Chemistry Section, Laboratory of Medicinal Chemistry and Biology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20205

Received November 23, 1981

The mechanism of formation of cyclic urea nucleosides under mercury catalysis (HgO and $HgBr_2$) was studied by using persilylated tetramethyleneurea (**1**) as a model aglycon. Evidence is presented to suggest that the desired N-nucleoside **9** arises via an intermolecular O → N transglycosylation rather than by a direct N-nucleosidation mechanism. Mercuric oxide catalyzes the formation of the intermediate silylated O-nucleoside **4** which later in the presence of $HgBr_2$ rearranges to the more thermodynamically stable N-nucleoside **9**. This rearrangement is brought about by either $HgBr_2$ or red HgO provided that there is excess of halogenose **2** and that the intermediate O-nucleoside remains silylated. When red HgO is employed, the required $HgBr_2$ is generated by the reaction between HgO and the $(CH_3)_3SiBr$ liberated during the condensation reaction. The intermediate O-nucleoside **5** was isolated and characterized. When resilylated to **4**, it rearranged rapidly to **9** under identical reaction conditions. The use of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl iodide (**2b**) instead of the corresponding bromo sugar (**2a**) shortened the reaction time, and in the presence of red HgO it gave exclusive formation of N-nucleoside **9**. The overall yield of this two-step transformation is 31%, and the desired compound **9** is easily separated by chromatographic means.

In the synthesis of pyrimidine nucleosides, the silylated version of the Hilbert–Johnson reaction, catalyzed by stannic chloride and other Friedel–Crafts catalysts, has become the method of choice.[1,2] This method has also proven useful with nonaromatic aglycons such as 6-oxadihydrouracil[3] and 5-methyl-5-azadihydrouracil.[4] How-

(1) Vorbruggen, H. F.; Niedballa, U.; Krolikiewicz, K.; Bennua, B.; Hofle, G. In "Chemistry and Biology of Nucleosides and Nucleotides"; Harmon, R. E., Robins, R. K., Townsend, L. B., Eds; Academic Press: New York, San Francisco, London, 1978; pp 251–265.

(2) Vorbruggen, H. In "Nucleoside Analogues. Chemistry, Biology and Medical Applications"; Walker, R. T., De Clercq, E., Eckstein, F., Eds.; Plenum Press: New York and London, 1979; pp 35–69.

(3) Berkowitz, P. T.; Robins, R. K.; Dea, P.; Long, R. A. *J. Org. Chem.* 1976, *41*, 3128.

(4) Skulnick, H. *J. Org. Chem.* 1978, *43*, 3188.

0022-3263/82/1947-1712$01.25/0