The FT 200-MHz ^1H NMR spectral data of these compounds are given in Table IV. Inspection of the data in this table reveals that the three spectra are identical and—like the melting points—indicative of a single compound in each case. Thus these three compounds have the same basic structure, which—based on the analysis below—is consistent with that of the Markovnikov addition product, **4**. The assignments of the signals (all sharp and well-defined) given in Table IV are as follows. Peaks number 1 are assigned to the aromatic protons. Peaks number 2 are attributed to the benzylic proton. The signal given by this proton appears as a triplet, rather than a quartet, because the coupling constants between this proton and the two adjacent diastereotopic protons, H_5 and H_6, are very similar. Peak number 3 is due to the protons on the *p*-MeO group of that particular derivative. Peaks number 4 are assigned to the protons on the α-MeO group. Peaks numbers 5 and 6 are ascribed to the two diastereotopic methylene protons. The resonances of these protons occur in the region where protons α to mercury are expected.[23] Protons H_2, H_5, and H_6 from an ABX system; therefore, H_5 and H_6 experience both geminal and vicinal couplings and should appear as quartets. The only other signals present in these spectra were the low-intensity ^{199}Hg satellites of peaks number 2, 5, and 6. In all cases, $J_{^{199}Hg-H_2} \gg J_{^{199}Hg-H_6} > J_{^{199}Hg-H_5}$, with the average values (hertz) being 266.1 ± 7.7, 202.6 ± 0.9, and 192.3 ± 2.1, respectively.

Iododemercurations. The methoxymercuration reactions were quenched by the addition of an excess volume of an ice-cold saturated aqueous solution of KI and $KHCO_3$ to the reaction flasks. Within a few minutes, a slight excess of an aqeuous solution of I_2 and KI was added. After at least 1 h, each reaction mixture was diluted with 50 mL of water; the excess I_2 was destroyed by the dropwise addition of a dilute $Na_2S_2O_3$ solution, and then the solution was extracted with one 10-mL portion of CH_2Cl_2 followed by one 15-mL portion of pentane. The combined extracts were washed with water and dried over anhydrous Na_2SO_4. GC–MS analyses of these extracts showed that only one product—the expected 2-methoxy-2-arylethyl iodide, **5**—was formed in each case. The mass spectrum of each of these products showed a weak (0.2–3%) M^+ peak at the correct *m/e* and a weak (2%, in all cases) peak at *m/e* 141 (ICH_2^+). The other major distinguishing peaks—at *m/e* corresponding to the indicated losses (abundances are given in parentheses)—appeared at M – CH_3O (0.2%, in all cases), M – Ar (0.2–20%), M – I (15–30%), and M – CH_2I (100%, in all cases). Below the base peak, the spectra of these compounds were almost identical with those (below M – 15) of the corresonding 1-methoxy-1-arylethanes. Evaporation of the extracts gave essentially quantitative yields of **5**. The MeO and H derivatives of **5** are liquids, while the NO_2 derivative is a white solid, mp 69.5–70 °C.

Acknowledgment. We are deeply indebted to Professors Peter Hambright and Carlyle B. Storm of this Deparment for both the loan of some of their equipment and their assistance in carrying out this work.

Registry No. 2 (X = MeO), 637-69-4; **2** (X = Me), 622-97-9; **2** (X = H), 100-42-5; **2** (X = F), 405-99-2; **2** (X = Br), 2039-82-9; **2** (X = COOMe), 1076-96-6; **2** (X = Ac), 10537-63-0; **2** (X = CN), 3435-51-6; **2** (X = NO_2), 100-13-0; **4** (X = MeO), 76584-15-1; **4** (X = H), 72887-18-4; **4** (X = NO_2), 67083-12-9; **5** (X = NO_2), 76584-16-2; $Hg(OAc)_2$, 1600-27-7.

(23) Brownstein, S. *Discuss. Faraday Soc.* **1962**, *34*, 25.

Photochemistry of 2,3,6-Trialkyl-4-pyrimidinones in Liquid Ammonia–Ether Solution. Chemistry of Dewar 4-Pyrimidinones

Shun-ichi Hirokami, Tamiko Takahashi, and Masanori Nagata

Laboratory of Chemistry, Toyama Medical and Pharmaceutical University, Sugitani, Toyama 930-01, Japan

Yoshiro Hirai and Takao Yamazaki*

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani, Toyama 930-01, Japan

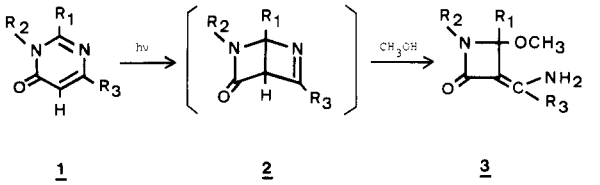
Received October 28, 1980

Irradiation of the 2,3,6-trialkyl-4-pyrimidinones **4** and **18** in liquid ammonia–ether (7:3) solution at −40 °C gave the corresponding Dewar 4-pyrimidinones, **5** and **19**, which decomposed in inert solvents at room temperature and did not revert to the corresponding 4-pyrimidinones. The first-order rate constants for disappearance of **5** and **19** were measured at 10–54 °C. The solvolysis reactions of **5** and **19** occur in methanol to give the α-(aminoethylidene)-β-methoxy-β-lactams **6** and **20**, respectively, whereas treatment of **5** and **19** in methanol containing sodium methoxide gave the imino ether **7** and the ketal **23**, respectively. The reactions of **5** and **19** in methylamine–ether (1:4) solution afforded the imine derivatives **9** and **24**, respectively. Furthermore, treatment of **5** in methanol-*d* containing sodium methoxide gave *N*-methyl-3-[(methoxyethylidene)amino]-2-butenamide-2-*d* (**7D**$_1$) and *N*-methyl-3-[(methoxyethylidene)amino]-2-butenamide-2,4-d_2 (**7D**$_2$) as the major components. The imino ether **7** did not give the deuterated imino ether under similar conditions. The products (**7**, **9**, **23**, **24**, and **27**) formed in basic solutions are discussed in terms of abstraction of the methine proton by base from the Dewar 4-pyrimidinone or in terms of addition of nucleophile to the imino group of Dewar 4-pyrimidinone.

In the previous papers,[1] we reported the photochemical reactions of 4-pyrimidinones in alcoholic solution and in methylamine–ether solution. Irradiation of 2,3,6-trialkyl-4-pyrimidinone **1** in methanol gave the corresponding α-(aminoalkylidene)-β-methoxy-β-lactam **3** (see Scheme I).

A Dewar 4-pyrimidinone intermediate **2** was postulated for the formation of **3**, but no decisive evidence for this intermediate was available. A preliminary experiment

Scheme I



1 **2** **3**

R_1, R_2, R_3 = alkyl

showed that the assumed Dewar 4-pyrimidinone was unstable at room temperature. Then, we undertook the

(1) (a) Yamazaki, T.; Nagata, M.; Hirokami, S.; Hirai, Y.; Date, T. *Heterocycles* **1978**, *9*, 505. (b) Hirokami, S.; Hirai, Y.; Nagata, M.; Yamazaki, T.; Date, T. *J. Org. Chem.* **1979**, *44*, 2083. (c) Hirai, Y.; Yamazaki, T.; Hirokami, S.; Nagata, M. *Tetrahedron Lett.* **1980**, *21*, 3067.

0022-3263/81/1946-1769$01.25/0

Scheme II

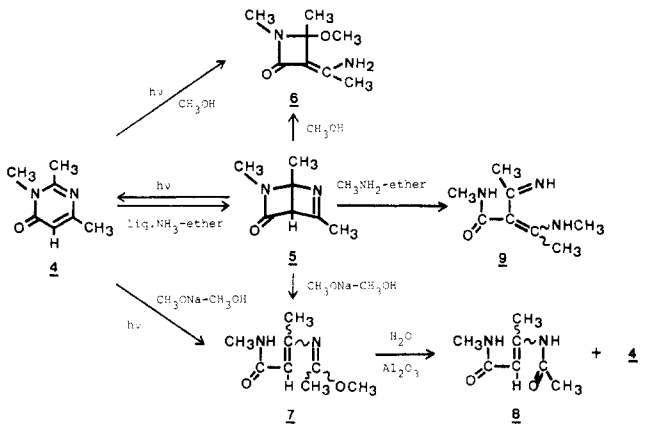


Table I. ^{13}C NMR Spectral Data for 2,3,6-Trimethyl-4-pyrimidinone (4) and the Dewar 4-Pyrimidinone 5

4-pyrimidinone 4		Dewar 4-pyrimidinone 5	
signals[a]	assignment	signals[a]	assignment
23.3 (q)	2-CH_3 or 6-CH_3	14.3 (q)	3-CH_3
23.6 (q)	2-CH_3 or 6-CH_3	20.8 (q)	1-CH_3
30.7 (q)	NCH_3	26.9 (q)	NCH_3
110.0 (d)	C-5	64.7 (d)	C-4
158.7 (s)	C-6	74.2 (s)	C-1
162.4 (s)	C-2 or C-4	165.3 (s)	C-3
162.5 (s)	C-2 or C-4	187.5 (s)	C-5

[a] Chemical shifts are given in δ units from internal tetramethylsilane and measured in $CDCl_3$ at −10 °C.

photolysis of 2,3,6-trialkyl-4-pyrimidinone at low temperature in the expectation that the Dewar 4-pyrimidinone might be isolable and more stable to the present systematic study. In this report we describe the irradiation of 2,3,6-trialkyl-4-pyrimidinones (4 and 18) in liquid ammonia–ether (7:3) solution at −40 °C to form the Dewar 4-pyrimidinones (5 and 19, respectively) and their reactions in methanol and in basic solutions. The photochemical electrocyclization of 1,3,5,6-tetramethyl-2-pyrazinone[2] and 2-pyrimidinones[3] and the photolysis of 2-pyridazinones[4] which undergoes type I cleavage have recently been reported.

Results and Discussion

Irradiation of 2,3,6-Trimethyl-4-pyrimidinone (4).[5a] When a liquid ammonia–ether (7:3) solution (liquid NH_3–ether) of 2,3,6-trimethyl-4-pyrimidinone (4) [λ_{max} (MeOH) 274 (ϵ 4000), 224 nm (5330)] at −40 °C under nitrogen atmosphere was irradiated through quartz, changes occurred in its NMR and IR spectra which suggested that a mixture of 4 and 5 was formed (Scheme II).

New signals in the ^1H NMR (C_6D_6) appeared at δ 1.32 (s, 3 H), 1.75 (s, 3 H), 2.48 (s, 3 H), and 3.69 (s, 1 H), while that of 4 showed four singlets at δ 1.82 (3 H), 2.03 (3 H), 2.85 (3 H), and 6.18 (1 H) which were assigned to the 2-methyl, 6-methyl, *N*-methyl, and olefinic proton, respectively. The shifts of the 2-methyl and olefinic proton of 4 to higher field at δ 1.32 and 3.69 for 5, respectively, indicated that a new chemical bond is formed between the positions 2 and 5 of 4. The ^{13}C NMR spectrum of 5 confirmed the presence of three methyl carbons, one methine carbon, one quarternary carbon (sp^3), one olefinic carbon, and a carbonyl carbon (see Table I). In the IR spectrum, the carbonyl band at 1665 cm^{-1} for 4 and a new carbonyl band at 1750 cm^{-1} were observed. This new carbonyl band at 1750 cm^{-1} for 5 is attributed to formation of the β-lactam moiety. From these data, the structure of 5 was assigned to 1,3,6-trimethyl-5-oxo-2,6-diazabicyclo[2.2.0]hex-2-ene (Dewar 4-pyrimidinone).

Table II. Effect of Irradiation Time on the Fraction of Dewar 4-Pyrimidinones 5 and 19

Dewar 4-pyrimidinone 5[a]		Dewar 4-pyrimidinone 19[b]	
time, h	fraction, %	time, h	fraction, %
0	0	0	0
1.5	12	1.0	8
3.0	23	2.5	20
4.5	27	4.0	23
6.0	31	6.0	26
8.0	32	8.0	26
9.0	32	8.5	26

[a] Photolysis of 2,3,6-trimethyl-4-pyrimidinone (4; 0.073 M) was carried out in liquid NH_3–ether (7:3) solution at −40 °C under a nitrogen atmosphere. The fractions of 4 and 5 were estimated by integration of the peak areas of the ^1H NMR spectra at 35 °C. [b] Photolysis of the fused 4-pyrimidinone 18 (0.055 M) was carried out in liquid NH_3–ether (7:3) solution at −40 °C under a nitrogen atmosphere. The fractions of 18 and 19 were estimated by integration of the peak areas of the ^1H NMR spectra at 35 °C.

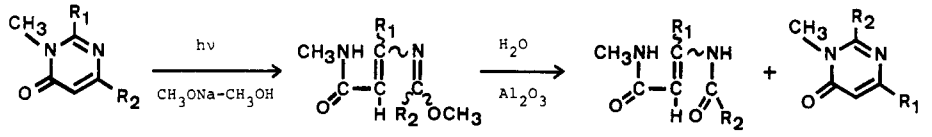
In the ^1H NMR spectrum, the intensities of the new signals increased with irradiation time while the intensities of the signals in the spectrum of 4 decreased. After 6–8 h of irradiation, the ^1H NMR signals could be accounted for by the presence of an equilibrium mixture of 4 (68%) and 5 (32%) (Table II). The fraction of 5 in photoequilibrium did not vary with the concentration of 4. One possible explanation for the photoequilibrium between 4 and 5 under irradiation could be an efficient photoreverse reaction of 5 to 4.

However, the Dewar 4-pyrimidinone 5 was not stable in inert solvents at room temperature. The intensity measurements of 5 by the ^1H NMR spectrum in benzene-d_6 showed a first-order decrease (2.57×10^{-5} s^{-1}; half-life time 450 min) at 34 °C. On the other hand, the relative intensities of 4 to those of a reference compound (benzene-d_5 as the isotope impurity in benzene-d_6 solvent) remained unchanged. After measurement, a brown tarry material was observed on the surface of the NMR tube. The results indicated that 5 did not thermally revert to 4. To determine optimum conditions for measurements of the physical properties of 5, the first-order rate constants for disappearance of 5 at 25, 34, 45, and 54 °C were measured (see Experimental Section).

Chemistry of Dewar 4-Pyrimidinone 5. The reactions of 5 were carried out with a mixture in which the starting material 4 was present, because 5 could not be separated from the reaction mixture. Treatment of 5 with methanol at room temperature for 1 h gave a crystalline β-lactam 6 (*E* form determined by X-ray data) in a yield of 48%.[5b] The same product was previously obtained

(2) Furrer, H. *Chem. Ber.* **1972**, *105*, 2780.
(3) Nishio, T.; Kato, A.; Kashima, C.; Omote, Y. *J. Chem. Soc., Perkin Trans. 1* **1980**, 607.
(4) Tsuchiya, T.; Hasebe, M.; Arai, H.; Igeta, H. *Chem. Pharm. Bull.* **1974**, *22*, 2276.
(5) (a) Irradiation of 4-pyrimidinones (4 and 18) in isopentane or *n*-pentane solution at −20 °C also gave the corresponding Dewar 4-pyrimidinones (5 and 19), but these methods were not readily applicable to the preparation of gram quantities needed in our experiment, because of insufficient solubilities of 4-pyrimidinones at low temperature. (b) The yields reported here stand for the conversion yields, because almost all the experiments were not carried out until the starting materials were completely consumed by irradiation (see Experimental Section).

Scheme III



4a (R_1=C_2H_5, R_2=CH_3) 7a (R_1=C_2H_5, R_2=CH_3) 8a (R_1=C_2H_5, R_2=CH_3) 4b

4b (R_1=CH_3, R_2=C_2H_5) 7b (R_1=CH_3, R_2=C_2H_5) 8b (R_1=CH_3, R_2=C_2H_5) 4a

(58%) by irradiation of **4** in methanol (Scheme II).[1b]

The reaction of **5** and the photochemistry of **4** in methanol solution containing sodium methoxide (0.04–0.15 M) markedly differed from those in the absence of sodium methoxide. When irradiation of **4** was performed in methanol solution in the presence of sodium methoxide (0.087 M) at 20 °C, a crystalline imino ether **7** (44%) was obtained.[6] Treatment of **5** in methanol solution containing sodium methoxide (0.101 M) at 10 °C for 0.5 h gave the same product **7** (42%).[6] However, both reactions did not give the β-lactam product **6**. The structure of **7** was assigned to *N*-methyl-3-[(methoxyethylidene)amino]-2-butenamide from its spectral data. Further supportive evidence for the structural assignment was obtained by using a chemical method. Hydrolysis of **7** on alumina gave 3-(acetylamino)-*N*-methyl-2-butenamide (**8**, 57%) and 4-pyrimidinone **4** (18%). Structural confirmation of **8** was achieved by acetylation of 3-amino-*N*-methyl-2-butenamide[7] with acetic anhydride.

Analogous photolysis of 2,6-dialkyl-3-methyl-4-pyrimidinones **4a** and **4b** under the similar conditions led to the formation of the imino ethers **7a** and **7b**, respectively (Scheme III). Hydrolysis of the reaction mixture, **4a** and **7a**, on alumina gave 3-(acetylamino)-*N*-methyl-2-pentenamide (**8a**, 34%) and a mixture of 4-pyrimidinone **4b** (19%; determined by ^{1}H NMR) and **4a**. From the mixture of **4b** and **7b** were obtained *N*-methyl-3-(propionylamino)-2-butenamide (**8b**, 15%) and a mixture of **4a** (15%; determined by ^{1}H NMR) and **4b**. The structures of **8a** and **8b** were assigned from their spectral data. Confirmation of **8b** by synthesis was achieved by the reaction of 3-amino-*N*-methyl-2-butenamide[7] with propionic anhydride. The results indicated clearly that methanol adds to the imine bond of the Dewar 4-pyrimidinone **5**.

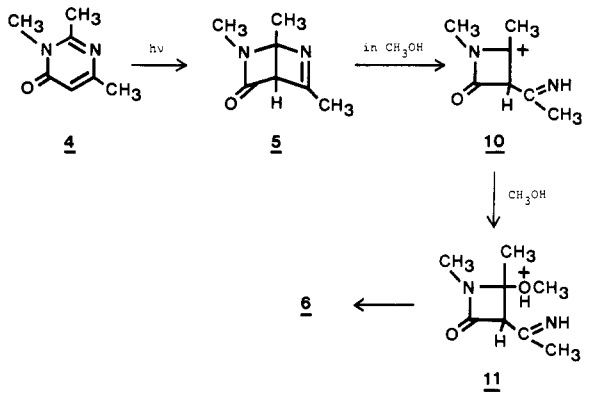
The reaction of **5** in a methylamine–ether (1:4) solution at −20 °C for 9 days gave a crystalline imine product **9** (72%), which was previously obtained (13.5%) by irradiation of **4** in methylamine–ether (1:5) solution at 0 °C (Scheme II).[1c]

The formation of the β-lactam **6** from the Dewar 4-pyrimidinone **5** may be explained by the reaction in Scheme IV.

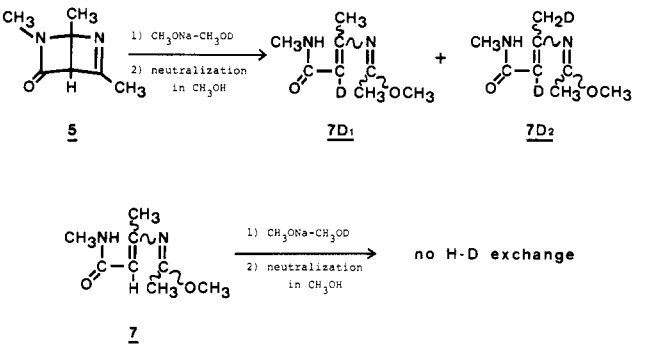
Irradiation of **4** gives an excited molecule which leads to an electrocyclic reaction to form **5**. The Dewar 4-pyrimidinone **5** undergoes the solvolysis reaction (S_N1) in methanol to give the β-lactam **6**.

The more important mechanistic question concerns the nature of the pathway from **5** to the imino ether **7** or to the imine **9**. The rate of solvolysis of **5** in methanol was

Scheme IV



Scheme V



completely reduced by the presence of methoxide anion. The structures of the products, **7** and **9**, indicated the cleavage of C(1)–N(6) bond of **5** and the formation of the conjugated double bond. These observations suggested that the reaction of **5** takes place by attack of a base (CH_3O^- or CH_3NH_2) on the methine hydrogen with concomitant formation of a double bond and breaking of the C(1)–N(6) bond.

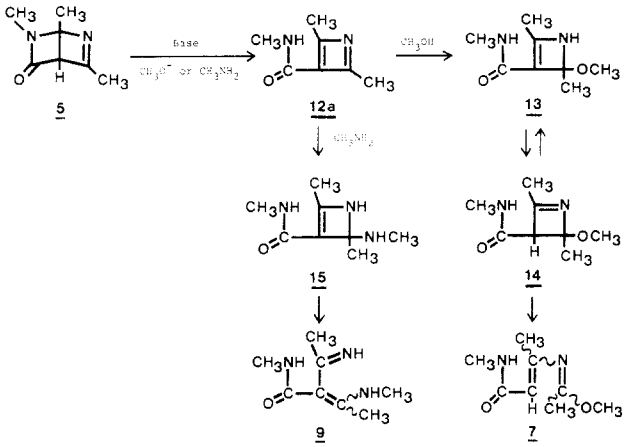
In order to examine the above mechanism (E2 or E1cB), we undertook an experiment on the reaction of **5** in methanol-*d* containing sodium methoxide. The mechanism would predict the deuterium atom to be found as the vinyl proton of **7** (see Scheme VIII).

The C–H/C–D exchange measurements of **7** by ^{1}H NMR in methanol-d_4 containing sodium methoxide-d_3 (0.057–0.64 M) were performed. Benzene was present in solutions as an internal reference compound. The chemical shifts and the integrated areas of three methyls (δ 1.88, 2.18, and 2.75), one methoxy (δ 3.67), and a vinyl proton (δ 5.08) relative to those of benzene remained unchanged for 0.5 h. The observations indicated that no C–H/C–D exchange of the imino ether **7** occurred in the basic solution. Furthermore, when **7** was treated in methanol-*d* containing sodium methoxide (0.30 M), **7** was recovered

(6) The low yield of **7** may be due to the destruction of **7** in the process of neutralization by the ion-exchange resin in methanol (see Experimental Section).

(7) Kato, T.; Yamanaka, H.; Kawamoto, J.; Shimomura, H. *Chem. Pharm. Bull.* **1969**, *17*, 1889.

Scheme VI



in 52% yield after N–H/N–D exchange of the amino group with methanol. The ^1H NMR and the mass spectrometric analysis of **7** showed that no deuterium atom was incorporated (Scheme V).

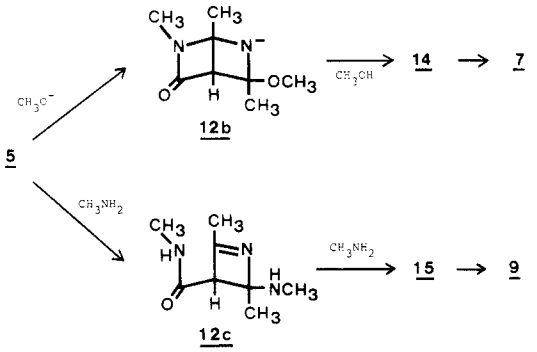
The Dewar 4-pyrimidinone **5** was treated with methanol-*d* containing sodium methoxide (0.17 M) at 10 °C for 0.5 h. The deuterated imino ether was isolated in 51% yield after N–H/N–D exchange of the amino group with methanol. The ^1H NMR analysis of the product indicated that the deuterium atoms were incorporated as the vinyl proton (85 ± 1%) and in the methyl group (C-4, 14 ± 1% assumed as CD_3). Mass spectrometric analysis showed this to be 9 ± 1% $C_8H_{14}N_2O_2$, 48 ± 2% $C_8H_{13}DN_2O_2$, 30 ± 1% $C_8H_{12}D_2N_2O_2$, 10 ± 2% $C_8H_{11}D_3N_2O_2$, and 3 ± 1% $C_8H_{10}D_4N_2O_2$. The major components were *N*-methyl-3-[(methoxyethylidene)amino]-2-butenamide-*2-d* (**7D$_1$**) and *N*-methyl-3-[(methoxyethylidene)amino]-2-butenamide-*2,4-d$_2$* (**7D$_2$**; Scheme V).

The incorporation of the deuterium atom as the vinyl proton of **7** may indicate that the methine proton of Dewar 4-pyrimidinone **5** was abstracted by methoxide anion and/or a relatively stable intermediate(s) in the reaction process could exchange hydrogen for deuterium, although the possibility of rapid C–H/C–D exchange of the reactive Dewar 4-pyrimidinone **5** could not be excluded before any further reaction occurred. The presence of the imino ether-d_3 and -d_4 and the increase in the fractions of these components at higher concentration (0.73 M) of sodium methoxide suggested that the deuterium (methyl hydrogen) at C-4 position of **7** might be incorporated by the C–H/C–D exchange with the solvent deuterium through an imine–enamine tautomerization.

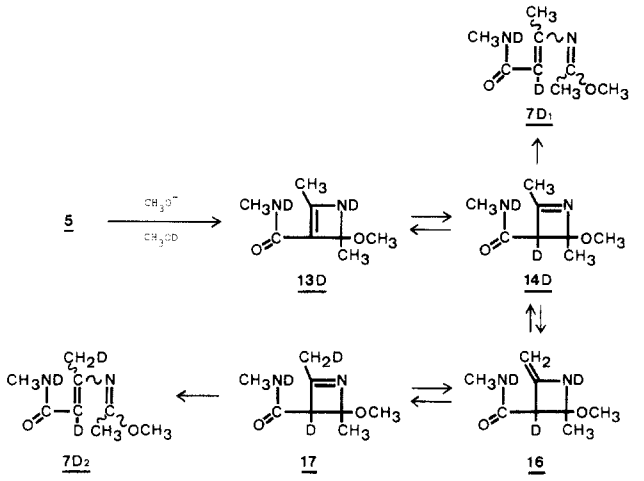
In a preliminary communication, the formation of the product **9** from the photolysis of **4** in methylamine–ether (1:5) solution was tentatively explained by the solvolysis of an assumed Dewar 4-pyrimidinone from analogy to the solvolysis of that in methanol. However, the present experimental results indicated that methoxide anion could react with **5** as a base or a nucleophile and completely reduce the rate of the solvolysis reaction of **5** in methanol. Then, we could assume that methylamine in ether also serves as a base or a nucleophile.

The initial stage of the reaction in the basic solution would be the attack of the base on the methine proton of the Dewar 4-pyrimidinone **5** or would be addition of the nucleophile to the imino group of **5**. If the initial abstraction of the methine proton by base is assumed for **5**, 2,4-dimethyl-3-(*N*-methylcarbamoyl)-1-azacyclobutadiene (**12a**) may then be a transient intermediate as shown in Scheme VI.

Scheme VII



Scheme VIII



The preparation and reactivity of azacyclobutadiene derivatives[8] and of diaminocyclobutadiene esters (push–pull cyclobutadiene)[9] have recently been reported. The reactions worthy of our serious consideration are the addition of nucleophiles (such as water, mthanol, and methylamine) to the benzazetes or the push–pull cyclobutadienes which give the ring-opened products.[8,9] Accordingly, the intermediate **12a** may react with methanol to give the azetine **13**. The azetine **13** isomerizes to **14**, which gives the open-chain product **7**. Analogous addition of methylamine to **12a** gave the azetine **15**, which leads to the formation of the imine **9**.

An alternative mechanism can be formulated by postulating the addition of methoxide anion to the imine bond of **5**. The initially formed intermediate is the bicyclic anionic intermediate **12b**. The reaction of **12b** with methanol gives the azetine **14**, which leads to the formation of product **7** (Scheme VII). The reaction of **5** with methylamine gives the azetine **12c**, which isomerizes to **15**. The intermediate **15** gives the product **9** by cleavage of the C–N bond (Scheme VII).

A possible mechanism for observed deuterium incorporation of the imino ether product is outlined in Scheme VIII. Deuteration of the methyl and vinyl hydrogens could be explained by the usual imine–enamine equilibria

(8) (a) Seybold, G.; Jersak, U.; Gompper, R. *Angew. Chem.* **1973**, *85*, 918; *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 847. (b) Adger, B. M.; Keating, M.; Rees, C. W.; Storr, R. C. *J. Chem. Soc., Chem. Commun.* **1973**, 19. (c) Rees, C. W; Storr, R. C.; Whittle, P. J. *Tetrahedron Lett.* **1976**, 4647. (d) Chambers, R. D.; Maslakilwicz, J. R. *J. Chem. Soc., Chem. Commun.* **1976**, 1005.

(9) (a) Neuenschwander, M.; Niederhauser, A. *Helv. Chim. Acta* **1970**, *53*, 519. (b) Gompper, R.; Seybold, G. "Aromaticity, Pseudo-Aromaticity, Antiaromaticity"; Bergman, E. D., Pullman, B., Eds.; The Israel Academy of Science and Humanities: Jerusalem, 1971; p 215.

Scheme IX

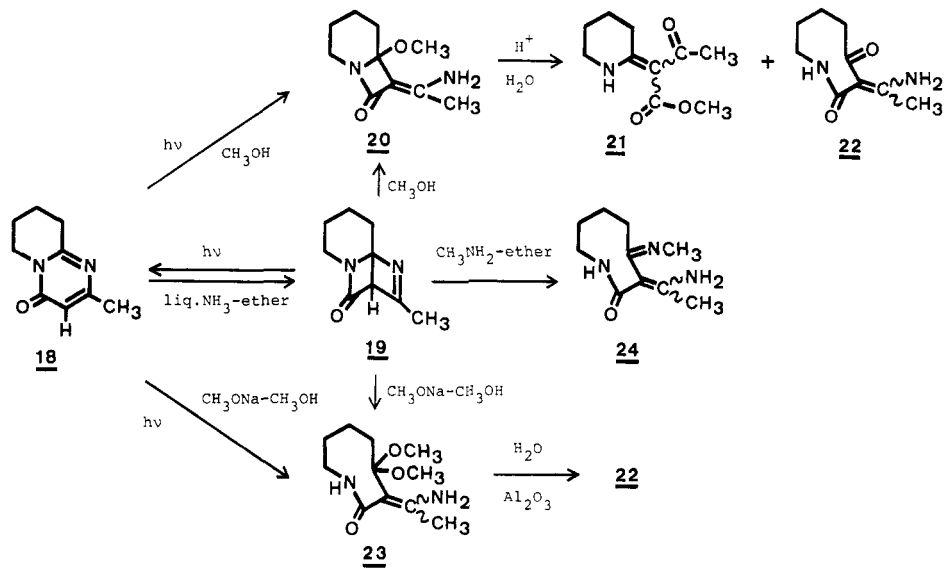


Table III. ^{13}C NMR Spectral Data for the Fused 4-Pyrimidinone 18 and the Dewar 4-Pyrimidinone 19

4-pyrimidinone 18		Dewar 4-pyrimidinone 19	
signals[a]	assignment	signals[a]	assignment
19.1 (t)	C-8	15.3 (q)	CH_3
21.7 (t)	C-7	20.9 (t)	C-3
23.6 (q)	CH_3	23.5 (t)	C-4
31.5 (t)	C-9	25.6 (t)	C-2
42.5 (t)	C-6	38.4 (t)	C-5
109.6 (d)	C-3	66.1 (d)	C-8
158.8 (s)	C-2	71.5 (s)	C-1
162.3 (s)	C-9a or C-4	161.5 (s)	C-9
162.5 (s)	C-9a or C-4	188.3 (s)	C-7

[a] Chemical shifts are given in δ units from internal tetramethylsilane and measured in $CDCl_3$ at −20 °C.

of the intermediates, **14** and **16**, if C–H/C–D exchange of the Dewar 4-pyrimidinone **5** in the presence of base is excluded.

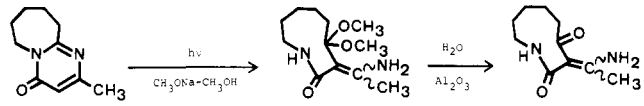
Irradiation of Fused 4-Pyrimidinone 18. The photolysis of **18** [λ_{max} (MeOH) 274 (ϵ 5280), 228 nm (6800)] in liquid NH_3–ether (7:3) solution at −40 °C paralleled closely that of the 4-pyrimidinone **4** (Scheme IX).

The ^1H NMR spectrum showed new signals at δ 1.72 (s, 3 H) and 3.80 (s, 1 H), which could be assigned to the methyl and methine protons of the Dewar 4-pyrimidinone **19**. The ^{13}C NMR spectrum of **19** revealed the presence of four methylene groups, one methyl group, one methine carbon, one quarternary carbon (sp^3), one olefinic carbon, and a carbonyl carbon (Table III). The main chemical shifts of **5** and **19** were nearly identical. The infrared spectrum showed a new carbonyl absorption at 1745 cm^{-1} due to the β-lactam carbonyl. From these data, the structure of **19** was assigned to 9-methyl-7-oxo-6,10-diazatricyclo[4.4.0.$0^{1,8}$]dec-9-ene.

The chemical properties of **19** were similar to those of **5**. After 6–8 h of irradiation, a mixture of **18** (74%) and **19** (26%) was formed (Table II). The first-order rate constants for disappearance of **19** at 10, 20, 31, and 38 °C were measured (see Experimental Section).

Chemistry of Dewar 4-Pyrimidinone 19. The Dewar 4-pyrimidinone **19** could not be separated from the reaction mixture. The various reactions were carried out with mixture in which the starting material **18** was present. The treatment of **19** with methanol at room temperature for 0.3 h gave a crystalline fused β-lactam **20** (*E* form determined by X-ray data) in a yield of 32%, which was the same product previously obtained (66%) by irradiation of **18** in methanol.[1] Hydrolysis of **20** in acidic ethanol solution (11% water and 1% acetic acid) at room temperature gave **21** (67%) and **22** (24%) (Scheme IX).[10]

Scheme X



Irradiation of **18** and treatment of **19** in methanol containing sodium methoxide (0.10 M) gave the crystalline ketal derivative **23** in yields of 40% and 32%, respectively. The structure of **23** was assigned to 2-(aminoethylidene)-3,3-dimethoxy-7-heptanelactam from the spectral data. Hydrolysis of **23** on alumina gave **22** (about 100%) as expected from the structure (Scheme IX).

The reaction of **18** in methylamine–ether (1:4) solution at −20 °C for 10 days gave the crystalline imine derivative **24** (89%). The product **24** was previously obtained (30%) by irradiation of **18** in methylamine–ether (1:5) solution at 0 °C (Scheme IX).[1c]

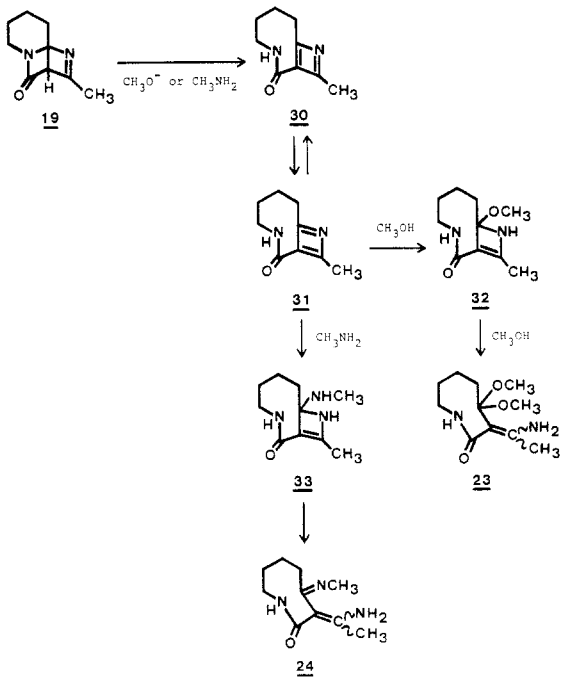
Analogous photolysis of the fused 4-pyrimidinone **25** in methanol containing sodium methoxide (0.085 M) gave the ketal **26** (41%, Scheme X). Hydrolysis of **26** on alumina gave the enamino ketone derivative **27** (81%), which was the same product as that obtained from the hydrolysis of 8-(aminoethylidene)-7-methoxy-9-oxo-1-azabicyclo-[5.2.0]nonane in acidic ethanol solution (11% water and 1% acetic acid) at room temperature.[10] The experimental results suggest that the reactivity of the Dewar 4-pyrimidinones formed from the fused 4-pyrimidinones in methanol–sodium methoxide solution do not vary with the additional methylene unit in the ring.

The solvolysis reaction of the Dewar 4-pyrimidinone **19** is analogous to that of Scheme IV.

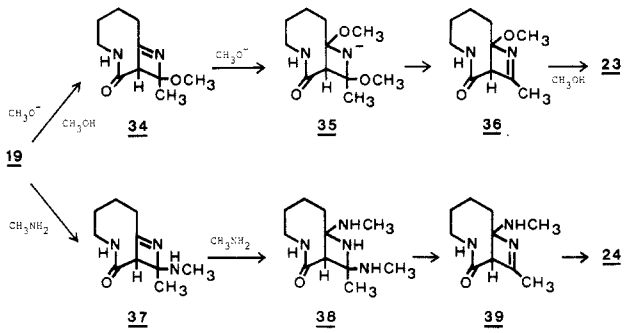
The formation of the fused β-lactam **20** from **19** was completely suppressed in methanol containing sodium

(10) Hirai, Y.; Hirokami, S.; Nagata, M.; Morita, M.; Yamazaki, T. *J. Org. Chem.* **1980**, *45*, 936.

Scheme XI



Scheme XII



methoxide. Instead, the ketal derivative **23** was formed. Then, the ketal **23** might be produced by the reaction of methoxide anion with the fused β-lactam **20** formed after the solvolysis of **19** in methanol. However, treatment of **20** with methanol containing sodium methoxide (0.083 M) did not give any product, and **20** was quantitatively recovered. Then, we can rule out the fused β-lactam **20** as a transient intermediate.

One of the plausible mechanisms for the formation of **23** is shown in Scheme XI which is analogous to Scheme VI.

The abstraction of the methine proton by methoxide anion results in the formation of an azacyclobutadiene **30** as an intermediate. By analogy with the reaction of **5** in basic solution, we presume that **30** and its isomeric form **31** are the logical precursors of **23**. The addition of methanol to **31** gives **32**, which then leads to the formation of **23**. A similar mechanism can be applied to the formation of **24** as that described in Scheme XI.

An alternative reaction mechanism analogous to Scheme VII is shown in Scheme XII. The 1,4-addition of methanol to **19** in the presence of methoxide anion gives a fused azetine **34**. The addition of methoxide anion to the bridgehead carbon of **34** leads to the formation of an anionic intermediate **35**, which undergoes elimination of the methoxy group and cleavage of the C–N bond with addition of methanol to give the product **23**. The reaction of the Dewar 4-pyrimidinone with methylamine could also be rationalized by similar intermediates (**37**, **38**, and **39**).

The reaction mechanisms of Schemes VI and XI indicate the abstraction of the methine proton by base from the Dewar 4-pyrimidinones in the initial process. The other mechanisms (Schemes VII and XII) represent the addition of nucleophile to the imine bond of the Dewar 4-pyrimidinone in the presence of base. However, the present results do not distinguish clearly between the two mechanisms.

Experimental Section

Melting points were measured with a Yanako micro melting point apparatus and are uncorrected. Hitachi 215 grating infrared and Hitachi Model 200-10 spectrophotometers were used, respectively, to determine IR and UV spectra. Mass spectrum was measured with JEOL-OISG-2 spectrometer at 70 eV. The ^1H and ^{13}C NMR spectra were measured with Me_4Si as an internal standard on Varian EM-390 90-MHz and Varian XL-200 spectrometers, respectively. The preparation of 4-pyrimidinones and preparative irradiation of 4-pyrimidinone solutions at 0–30 °C are given in the literature.[1b] Irradiation of 4-pyrimidinone in liquid NH_3–ether (7:3) solution at −40 °C under a nitrogen atmosphere was conducted in an apparatus consisting of a Nikko Seiki 100-W high-pressure mercury lamp in an immersion well surrounded by the solution being irradiated. The immersion well was made with a double quartz layer evacuated inside to insulate heat conduction from the lamp. Taiyo Sanso research-grade NH_3 (99.99%) was used without further purification. The methanol solution containing sodium methoxide was neutralized by an ion-exchange resin (Amberlite IRC-50) in methanol. Column chromatography was performed on alumina (activity II–III, Merck) and on Sephadex LH-20 (Pharmacia Fine Chemicals AB). The temperature was monitored by a thermocouple (constantan–copper).

Kinetic Measurements. Kinetic studies of the Dewar 4-pyrimidinones were made by using ^1H NMR measurement in benzene-d_6 solution. The disappearance of **5** and **19** was monitored by the decrease in the integration of the peak areas and the peak heights of the ^1H NMR spectrum, and the unreacted 4-pyrimidinone **4** or **18** was used as a reference compound. A least-squares computer program was used to calculate first-order rate constants.

Dark Reaction. A solution of 2,3,6-trimethyl-4-pyrimidinone (**4**) (108 mg) in 3 mL of methanol containing sodium methoxide (0.84 M) was stirred for 5 h at room temperature. After neutralization of the solution, unreacted starting material was recovered quantitatively.

Irradiation of 2,3,6-Trimethyl-4-pyrimidinone (4) in Methanol–Sodium Methoxide Solution. A solution of **4** (1.270 g, 9.20 mmol) in 320 mL of methanol containing sodium methoxide (8.56×10^{-2} M) was irradiated under a nitrogen atmosphere at 20 °C for 5.5 h. After neutralization of the irradiated solution, the photolysate was concentrated under vacuum, giving a pale yellow oil. The oily residue was dissolved in 10 mL of water. The reaction mixture was extracted with benzene containing ammonia (10 mL × 9). Evaporation of the solvent gave 0.682 g (44%) of *N*-methyl-3-[(methoxyethylidene)amino]-2-butenamide (**7**) as an oil which crystallized on standing. Recrystallization from hexane–ether gave colorless prisms: mp 107–108.5 °C; IR (KBr) 3340, 1660, 1610 cm^{-1}; UV (MeOH) λ_{max} 249 nm (ϵ 12 700); NMR ($CDCl_3$) 1.92 (s, 3 H, N=CCH_3), 2.30 (s, 3 H, C=CCH_3), 2.87 (d, J = 4.5 Hz, 3 H, NCH_3), 3.70 (s, 3 H, OCH_3), 5.03 (s, 1 H, CH), 5.80 (br, 1 H, NH); mass spectrum, m/e 170 (M^+).

Anal. Calcd for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.42; H, 8.50; N, 16.34.

Neutralization of Methanol–Sodium Methoxide Solution Containing 7. A solution of **7** (409 mg, 2.41 mmol) in 50 mL of methanol containing sodium methoxide (0.296 M) was stirred for 4 h. After neutralization and evaporation of the solvent, the residue was chromatographed on Sephadex LH-20 (60 g), using acetone as an eluent, and collected as three main fractions. Fraction 1 (221 mg, 54%) was recovered **7**. Fraction 2 (34 mg, 10%) was **4**. Fraction 3 (48 mg, 18%) was 3-amino-*N*-methyl-2-butenamide, which was found to be identical (spectra) with the authentic sample.[7]

Hydrolysis of 7 on Alumina. The imino ether **7** (379 mg, 2.23 mmol) was adsorbed on alumina (20 g) for 23 h and was

collected as two fractions. Fraction 1 (268 mg), eluted with benzene, was a mixture of two compounds. After removal of the solvent, benzene–hexane was added to the oily residue. Crude crystals of 3-(acetylamino)-*N*-methyl-2-butenamide (**8**; 192 mg, 55%) were separated on cooling and were collected by filtration. Recrystallization of **8** from benzene–hexane gave colorless needles: mp 132–133 °C; IR (KBr) 3350, 1615 cm^{-1}; UV (MeOH) λ_{max} 269 nm (ϵ 20 400); NMR ($CDCl_3$) 2.13 (s, 3 H, $COCH_3$), 2.35 (s, 3 H, CH_3), 2.85 (d, J = 4.5 Hz, 3 H, NCH_3), 4.78 (s, 1 H, CH), 6.18 (br, 1 H, NH), 12.13 (br, 1 H, NH); mass spectrum, m/e 156 (M^+).

Anal. Calcd for $C_7H_{12}N_2O_2$: C, 53.83; H, 7.74; N, 17.94. Found: C, 54.08; H, 7.61; N, 17.67.

Evaporation of the solvent from the filtrate gave an oily residue. The ^1H NMR analysis indicated that the oily mixture contained 91% **4** (56 mg) and 9% **8** (6 mg). The yields of **8** and **4** were 57% and 18%, respectively. Fraction 2 (24 mg, 6 w/w %), eluted with benzene–methanol (3%), was an unidentified product.

Synthesis of 8. To a solution of 3-amino-*N*-methyl-2-butenamide (1.00 g, 8.77 mmol) in 5 mL of chloroform at 0 °C was added dropwise with stirring a slight excess of acetic anhydride (1.40 g, 13.7 mmol). After the solution was heated under reflux for 1 h, the solvent and excess acetic anhydride were evaporated under reduced pressure to give an oily residue. Crystallization of the residual oil from ethyl acetate gave 1.06 g (77%) of 3-(acetylamino)-*N*-methyl-2-butenamide which was found to be identical (spectra) with **8** obtained from hydrolysis of **7** on alumina.

Irradiation of 2-Ethyl-3,6-dimethyl-4-pyrimidinone (4a) in Methanol–Sodium Methoxide Solution. A solution of **4a** (1.300 g, 8.52 mmol) in 350 mL of methanol containing sodium methoxide (7.03×10^{-2} M) was irradiated under a nitrogen atmosphere at 20 °C for 4 h. After a similar workup as before, 1.128 g of a pale-yellow oil was obtained. The ^1H NMR analysis showed that the resulting oil contained 66% *N*-methyl-3-[(methoxyethylidene)amino]-2-pentenamide (**7a**), 17% 6-ethyl-2,3-dimethyl-4-pyrimidinone (**4b**), and 17% **4a**. The observed ^1H NMR spectrum[11] of **7a** in $CDCl_3$ was δ 1.06 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 1.92 (s, 3 H, CH_3), 2.84 (d, J = 4.5 Hz, 3 H, NCH_3), 3.72 (s, 3 H, OCH_3), 4.89 (s, 1 H, CH), 5.73 (br, 1 H, NH).

The reaction mixture (1.128 g) was adsorbed on alumina (80 g) for 24 h. Hydrolysis and separation of the reaction mixture gave 3-(acetylamino)-*N*-methyl-2-pentenamide (**8a**; 0.495 g, 34%) as crude crystals and a mixture (0.431 g, 33%) of 4-pyrimidinones (**4a** and **4b**). The ratio of **4a** and **4b** was 42:58 (by ^1H NMR). The calculated yield of **4b** was 19%. Recrystallization of **8a** from benzene–hexane gave colorless needles: mp 98–99 °C; IR (KBr) 3360, 1640 cm^{-1}; UV(MeOH) λ_{max} 269 nm (ϵ 20 200); NMR ($CDCl_3$) 1.13 (t, J = 7.3 Hz, 3 H, CH_2CH_3), 2.13 (s, 3 H, CH_3), 2.78 (q, J = 7.3 Hz, 2 H, CH_2CH_3), 2.86 (d, J = 4.5 Hz, 3 H, NCH_3), 4.78 (s, 1 H, CH), 5.70 (br, 1 H, NH), 12.12 (br, 1 H, NH); mass spectrum, m/e 170 (M^+).

Anal. Calcd for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.70; H, 8.35; N, 16.23.

Irradiation of 6-Ethyl-2,3-dimethyl-4-pyrimidinone (4b) in Methanol–Sodium Methoxide Solution. A solution of **4b** (1.109 g, 7.30 mmol) in 350 mL of methanol containing sodium methoxide (6.06×10^{-2} M) was irradiated under a nitrogen atmosphere at 20 °C for 3 h and workup as before gave 0.876 g of a pale yellow oil. The ^1H NMR analysis showed that the resulting oil contained 59% *N*-methyl-3-[(methoxypropylidene)amino]-2-butenamide (**7b**) and 41% **4b**. The observed ^1H NMR spectrum[11] of **7b** in $CDCl_3$ was δ 1.12 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 2.32 (s, 3 H, CH_3), 2.85 (d, J = 4.5 Hz, 3 H, NCH_3), 3.70 (s, 3 H, OCH_3), 5.03 (s, 1 H, CH), 5.88 (br, 1 H, NH).

The reaction mixture (0.876 g) was adsorbed on alumina (80 g) for 22 h. Hydrolysis and separation of the reaction mixture gave *N*-methyl-3-(propionylamino)-2-butenamide (**8b**; 0.189 g, 15%) as crude crystals and a mixture (0.438 g, 39%) of 4-pyrimidinones (**4a** and **4b**). The ratio of **4a** and **4b** was 38:62 (by ^1H NMR). The calculated yield of **4a** was 15%. Recrystallization of **8b** from benzene–hexane gave colorless prisms: mp 96.5–97.5 °C; IR (KBr) 3370, 1690, 1625 cm^{-1}; UV (MeOH) λ_{max} 270 nm (ϵ 22 400); NMR ($CDCl_3$) δ 1.22 (t, J = 7.3 Hz, 3 H, CH_2CH_3), 2.38 (s, 3 H, CH_3), 2.40 (q, J = 7.3 Hz, 2 H, CH_2CH_3), 2.87 (d, J = 4.5 Hz, 3 H, NCH_3), 4.78 (s, 1 H, CH), 5.83 (br, 1 H, NH), 12.18 (br, 1 H NH); mass spectrum, m/e 170 (M^+).

Anal. Calcd for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.74; H, 8.34; N, 16.32.

Synthesis of 8b. To a solution of 3-amino-*N*-methyl-2-butenamide (0.902 g, 7.90 mmol) in 10 mL of chloroform at 0 °C was added dropwise with stirring a slight excess of propionic anhydride (1.11 g, 8.53 mmol). After the solution was heated under reflux for 1 h, the solvent and excess propionic anhydride were evaporated under reduced pressure to give an oily residue. The residue was chromatographed on alumina (50 g) with benzene to give 0.743 g (55%) of *N*-methyl-3-(propionylamino)-2-butenamide which was found to be identical (spectra) with **8b** obtained from hydrolysis of **7b**.

Irradiation of 4 in Liquid Ammonia–Ether Solution at −40 °C. Formation of 1,3,6-Trimethyl-5-oxo-2,6-diazabicyclo[2.2.0]hex-2-ene (5). A solution containing 2.300 g (16.7 mmol) of **4** in 230 mL of liquid NH_3–ether (7:3) solution was irradiated under a nitrogen atmosphere at −40 °C for 9 h. The ^1H NMR analysis showed that the solution contained 68% **4** and 32% **5**. Evaporation of the solvent gave a mixture of **4** and **5** from which the following properties were deduced: IR ($CHCl_3$) 1750 cm^{-1} (CO); ^1H NMR (C_6D_6) δ 1.32 (s, 3 H, 1-CH_3), 1.75 (s, 3 H, 3-CH_3), 2.48 (s, 3 H, NCH_3), 3.69 (s, 1 H, methine); the ^{13}C NMR spectral data in $CDCl_3$ at −10 °C and the effect of irradiation time on the fraction of **5** are listed in Tables I and II. The temperature dependence of the first-order disappearance rate constants, and the activation parameters are (1.58 ± 0.09) $\times 10^{-5}$ s^{-1} (25 °C), (2.57 ± 0.08) $\times 10^{-5}$ s^{-1} (34 °C), (1.04 ± 0.04) $\times 10^{-4}$ s^{-1} (45 °C), (3.03 ± 0.10) $\times 10^{-4}$ s^{-1} (54 °C), E_a = 20.3 ± 2.5 kcal, and log A = 10.0 ± 1.8.

Reaction of 5 with Methanol. A solution of 1.494 g (10.8 mmol) of **4** in 230 mL of liquid NH_3–ether (7:3) solution was irradiated under a nitrogen atmosphere at −40 °C for 7.5 h. After evaporation of the solvent, the residue was dissolved in 100 mL of methanol and stirred at 20 °C for 1 h. After removal of solvent, ether was added to an oily residue. When the solution was cooled, crude crystals were separated and collected by filtration. Recrystallization of the crude crystals from ether–methanol gave 282 mg (15.4%) of *N*-methyl-3-(aminoethylidene)-4-methoxy-4-methyl-2-azetidinone (**6**), identical (spectra) with the material obtained by irradiating **4** in methanol.[1b] The starting material **4** (1.00 g, 67%) was recovered by column chromatography of the filtrate on alumina (60 g), using benzene as an eluent. The conversion yield of **6** was 48% of the photoequilibrium state of product **5**.

Reaction of 5 in Methanol–Sodium Methoxide Solution. A solution of 2.030 g (14.7 mmol) of **4** in 230 mL of liquid NH_3–ether solution was irradiated at −40 °C for 8 h. After evaporation of the solvent, the residue was dissolved in 70 mL of methanol containing sodium methoxide (0.101 M) and stirred at 10 °C for 0.5 h. After neutralization of the reaction mixture, the solvent was evaporated. The residue was dissolved into 10 mL of water. The reaction mixture was extracted with benzene containing ammonia (10 × 10 mL). After evaporation of the solvent, the residue was chromatographed on Sephadex LH-20 (65 g), using acetone as eluent, to give two main fractions. Fraction 1 (331 mg, 13.3%) was the imino ether **7**, identical (spectra) with material obtained by irradiating **4** in methanol–sodium methoxide solution. Fraction 2 (890 mg, 44%) was recovered **4**. The starting material (0.510 g, 25%) was recovered from the aqueous solution. The recovered **4** was 1.40 g (69%). The conversion yield of **7** was 42% of the photoequilibrium product **5**.

Reaction of 5 in Methanol-*d* (CH_3OD)–Sodium Methoxide Solution. A solution of 2.105 g (15.3 mmol) of **4** in 230 mL of liquid NH_3–ether (7:3) solution was irradiated under a nitrogen atmosphere at −40 °C for 8.5 h. After evaporation of the solvent, the residue was dissolved in 20 mL of methanol-*d* (99%) containing sodium methoxide (0.169 M) and stirred at 10 °C for 0.5 h. After similar workup, 426 mg (16.2%) of the deuterated imino ether **7** was obtained and starting material **4** (1.52 g, 71%) was recovered. The conversion yield of **7** was 51% of the photoequilibrium product **5**. ^1H NMR analysis of the deuterated imino ether indicated that the D atoms were incorporated as the vinyl proton (85%) and in methyl group (hydrogen of C-4; 14% assumed

(11) The signal of the methylene protons of the ethyl group could not be distinguished from that of the starting material (**4a** or **4b**).

as CD_3). Mass spectrometric analysis showed that 7 was 9 ± 1% $C_8H_{14}N_2O_2$, 48 ± 2% $C_8H_{13}DN_2O_2$, 30 ± 1% $C_8H_{12}D_2N_2O_2$, 10 ± 2% $C_8H_{11}D_3N_2O_2$, and 3 ± 1% $C_8H_{10}D_4N_2O_2$. The spectral analysis indicated that the major components were *N*-methyl-3-[(methoxyethylidene)amino]-2-butenamide-2-*d* (**7D**$_1$) and *N*-methyl-3-[(methoxyethylidene)amino]-2-butenamide-2,4-d_2 (**7D**$_2$).

The ^{1}H NMR and mass spectrometric analyses of the recovered 4-pyrimidinone indicated that the D atoms were incorporated in the methyl group at 2 position. The predominant 4-pyrimidinone was 2-(trideuteriomethyl)-3,6-dimethyl-4-pyrimidinone.[12]

Treatment of 7 in Methanol-*d*–Sodium Methoxide Solution. A solution of 54 mg of **7** in 2 mL of methanol-*d* containing sodium methoxide (0.297 M) was stirred at 20 °C for 0.5 h. After workup, 28 mg (52%) of **7** was recovered. The ^{1}H NMR and mass spectrometric analyses showed that no D atom was incorporated.

Reaction of 5 in Methylamine–Ether Solution. A solution of 2.158 g (15.6 mmol) of **4** in 230 mL of liquid NH_3–ether (7:3) solution was irradiated at −40 °C for 8 h. After evaporation of the solvent, the residue was dissolved in about 300 mL (224 g) of methylamine–ether (1:4) solution and was stirred for 1 h at −30 °C. The solution was left in storage in the freezer at −20 °C for 9 days. After evaporation of the solvent, the residue was chromatographed on Sephadex LH-20 (65 g), using acetone as an eluent, to give two fractions. Fraction 1 (607 mg, 23.0%) was 3-amino-*N*-methyl-2-[1-(methylimino)ethyl]-2-butanamide (**9**), identical (spectra) with the material obtained by irradiating **4** in the methylamine–ether (1:5) solution at 0 °C.[1c] Fraction 2 (1.51 g, 70%) was recovered **4**. The conversion yield of **9** was 72% of the photoequilibrium product **5**.

Irradiation of 6,7,8,9-Tetrahydro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (18) in Methanol–Sodium Methoxide Solution. A solution of **18** (1.643 g, 10.0 mmol) in 300 mL of methanol containing sodium methoxide (9.77×10^{-2} M) was irradiated under a nitrogen atmosphere at 20 °C for 5 h. After neutralization and evaporation of the solvent, crude crystals of 2-(aminoethylidene)-3,3-dimethoxy-7-heptanelactam (**23**; 491 mg, 21.5%) were separated and collected by filtration. Recrystallization from benzene–methanol gave colorless needles: mp 153–155 °C; IR (KBr) 3460, 3260, 3180, 1600 cm^{-1}; UV (MeOH) λ_{max} 263 nm (ϵ 5720); NMR (Me_2SO-d_6) 1.00–2.33 (m, 6 H, 3 CH_2), 1.45 (s, 3 H, CH_3), 2.83–3.63 (m, 2 H, CH_2), 3.05 (s, 3 H, OCH_3), 3.17 (s, 3 H, OCH_3), 4.98 (s, 2 H, NH_2), 7.00 (t, J = 6.8 Hz, 1 H, NH); mass spectrum, m/e 228 (M^+).

Anal. Calcd for $C_{11}H_{20}N_2O_3$: C, 57.87; H, 8.83; N, 12.27. Found: C, 57.66; H, 8.71; N, 12.05.

The filtrate was chromatographed on alumina (17 g) with benzene as an eluent to give 451 mg (27.5%) of the starting material **18**. Further elution with methanol gave 331 mg (18.2%) of 2-(aminoethylidene)-3-oxo-7-heptanelactam (**22**) as the hydrolysis product of **23**. The total yield of **23** was about 40% on the basis of the result of the hydrolysis of **23** on alumina described below.

Hydrolysis of 23 on Alumina. The ketal **23** (356 mg, 1.56 mmol) was adsorbed on alumina (12 g) for 27 h. Elution with methanol gave 320 mg (107%) of **22** as colorless crystals, identical (spectra) with the compound obtained by the hydrolysis of the fused β-lactam **20** in acidic ethanol solution (11% water and 1% acetic acid).[10]

Irradiation of 18 in Liquid Ammonia–Ether Solution at −40 °C. Formation of 9-Methyl-7-oxo-6,10-diazatricyclo[4.4.0.0^{1,8}]dec-9-ene (19). A solution containing 2.068 g (12.6 mmol) of **18** in 230 mL of liquid NH_3–ether (7:3) solution was irradiated under a nitrogen atmosphere at −40 °C for 8.5 h. The ^{1}H NMR analysis showed that the solution contained 74% **18** and 26% **19**. Evaporation of the solvent gave a mixture of **18** and **19** from which the following properties were deduced: IR ($CHCl_3$) 1745 cm^{-1} (CO); ^{1}H NMR (C_6D_6) δ 1.72 (s, 3 H, CH_3), 3.80 (s, 1 H, methine) (signals of the methylene hydrogens could not be assigned because of overlapping with those of **18**); the ^{13}C NMR spectral data in $CDCl_3$ at −20 °C and the effect of irradiation time on the fraction of **19** are listed in Tables II and III. The temperature dependence of the first-order disappearance rate constants of **19** and the activation parameters are (6.37 ± 0.10) × 10^{-5} s^{-1} (10 °C), (8.62 ± 0.13) × 10^{-5} s^{-1} (20 °C), (1.39 ± 0.01) × 10^{-4} s^{-1} (31 °C), (2.93 ● 0.01) × 10^{-4} s^{-1} (38 °C), E_a = 9.1 ± 2.0 kcal, and log A = (2.74 ± 1.45).

Reaction of 19 with Methanol. A solution of 1.501 g (9.15 mmol) of **18** in 230 mL of liquid NH_3–ether (7:3) solution was irradiated at −40 °C for 9 h. After evaporation of the solvent, the residue was dissolved in 100 mL of methanol and stirred at 20 °C for 0.3 h. Ether was added to an oily residue obtained after evaporation of the solvent. When the solution was cooled, crude crystals of **20** were separated and collected by filtration. Recrystallization from ether–methanol gave 151 mg (8.4%) of 7-(aminoethylidene)-6-methoxy-8-oxo-1-azabicyclo[4.2.0]octane (**20**), identical (spectra) with the compound obtained by irradiating **18** in methanol.[1b] The starting material **18** (1.05 g, 70%) was recovered by column chromatography of the filtrate on alumina (60 g), using benzene as an eluent. The conversion yield of **20** was 32% of the photoequilibrium product **19**.

Reaction of 19 in Methanol–Sodium Methoxide Solution. A solution of 2.320 g (14.1 mmol) of **18** in 230 mL of liquid NH_3–ether (7:3) solution was irradiated at −40 °C for 8 h. After evaporation of the solvent, the residue was dissolved in 100 mL of methanol containing sodium methoxide (0.102 M) and stirred at 10 °C for 0.5 h. After neutralization and evaporation of the solvent, the residue was triturated with acetone to give pale yellow crystals. The crude crystals were collected by filtration. Recrystallization from ether–methanol gave 257 mg (8.0%) of **23**, identical (spectra) with the compound obtained by irradiating **18** in methanol–sodium methoxide solution. The filtrate was chromatographed on Sephadex LH-20 (65 g), using acetone as an eluent, to give two main fractions. Fraction 1 (11 mg, 0.3%) was the ketal **23**. Fraction 2 (1.68 g, 72%) was recovered **18**. The conversion yield of **23** was 32% of the photoequilibrium product **19**.

Reaction of 19 in Methylamine–Ether Solution. A solution of **18** (2.176 g, 13.3 mmol) in 230 mL of liquid NH_3–ether (7:3) solution was irradiated under nitrogen atmosphere at −40 °C for 8 h. After evaporation of the solvent, the residue was dissolved in about 420 mL (335 g) of methylamine–ether (1:4) solution and stirred for 1 h at −30 °C. The solution was left in storage in the freezer at −20 °C for 10 days. After evaporation of the solvent, the residue was chromatographed on Sephadex LH-20 (75 g), using acetone, to give two fractions. Fraction 1 (601 mg, 23.2%) was 2-(aminoethylidene)-3-(methylimino)-7-heptanelactam **24**, identical (spectra) with the compound obtained by irradiating **18** in methylamine–ether (1:5) solution at 0 °C.[1c] Fraction 2 (1.53 g, 70%) was recovered **18**. The conversion yield of **24** was 89% of the photoequilibrium product **19**.

Irradiation of 6,7,8,9,10-Pentahydro-2-methyl-4*H*-pyrido[1,2-*a*]azepin-4-one (25) in Methanol–Sodium Methoxide Solution. Irradiation of **25** (1.596 g, 8.97 mmol) in 300 mL of methanol containing sodium methoxide (8.47×10^{-2} M) was conducted under a nitrogen atmosphere at 20 °C for 4.5 h. After neutralization of the irradiated solution, the photolysate was concentrated under vacuum to give a pale yellow oil. Ether was added to the oily residue. When the solution was cooled, crude crystals of 2-(aminoethylidene)-3,3-dimethoxy-8-octanelactam (**26**; 421 mg, 19.7%) were separated and collected by filtration. Recrystallization from ether–methanol gave colorless needles: mp 141–143 °C; IR (KBr) 3470, 3340, 3260, 3180, 1620 cm^{-1}; UV (MeOH) λ_{max} 256 nm (ϵ 4490); NMR (Me_2SO-d_6) 0.87–2.37 (m, 8 H, 4 CH_2), 1.45 (s, 3 H, CH_3), 2.80–3.43 (m, 2 H, CH_2), 3.07 (s, 3 H, OCH_3), 3.18 (s, 3 H, OCH_3), 4.77 (s, 2 H, NH_2), 7.02 (t, J = 6.8 Hz, 1 H, NH); mass spectrum, m/e 242 (M^+). Anal. Calcd for $C_{12}H_{22}N_2O_3$: C, 59.48; H, 9.15; N, 11.56. Found: C, 59.69; H, 9.09; N, 11.30.

The filtrate was chromatographed on alumina (40 g) with benzene as an eluent to give 196 mg (12.3%) of the starting material **25**. Further elution with benzene–methanol (5%) gave 393 mg (21.3%) of 2-(aminoethylidene)-3-oxo-8-octanelactam (**27**) as the hydrolysis product of **26**. The total yield of **26** was about 41% on the basis of the result of the hydrolysis of **26** on alumina.

Hydrolysis of 26 on Alumina. The ketal **26** (189 mg, 0.78 mmol) was adsorbed on alumina (10 g) for 16 h. Elution with methanol gave 124 mg (81%) of **27** as colorless crystals, identical (spectra) with the compound obtained by hydrolysis of 8-(ami-

(12) Detailed studies on the H/D exchange reaction of 4-pyrimidinones in the presence of base are now in progress.

noethylidene)-7-methoxy-9-oxo-1-azabicyclo[5.2.0]nonane in acidic ethanol solution (11% water and 1% acetic acid).[10]

Registry No. 4, 32363-51-2; **4a**, 32363-54-5; **4b**, 69912-33-0; **5**, 76599-91-2; **6**, 72611-06-4; **7**, 73645-42-8; **7a**, 76599-92-3; **7b**, 76599-93-4; **7**(D_1), 76599-94-5; **7**(D_2), 76599-95-6; **7**(D_3), 76599-96-7; **7**(D_4), 76599-97-8; **8**, 73645-43-9; **8a**, 76599-98-9; **8b**, 76599-99-0; **9**, 76600-00-5; **18**, 58156-40-4; **19**, 76600-01-6; **20**, 66849-14-7; **22**, 72611-26-8; **23**, 73645-44-0; **24**, 76227-55-9; **25**, 69912-22-7; **26**, 76600-02-7; **27**, 72611-27-9; 3-amino-*N*-methyl-2-butenamide, 24392276; CH_3OH, 67-56-1; acetic anhydride, 108-24-7; propionic anhydride, 123-62-6; CH_3OD, 4206-31-9; CH_3NH_2, 74-89-5.

Pyridopyrimidines. 12. Synthesis of 8-Deaza Analogues of Aminopterin and Folic Acid

Ananthachari Srinivasan and Arthur D. Broom*

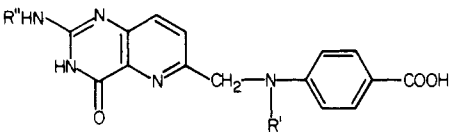
Department of Medicinal Chemistry, College of Pharmacy, University of Utah, Salt Lake City, Utah 84112

Received December 30, 1980

A new, general approach to the synthesis of numerous 8-deazafolate and 8-deazaaminopterin analogues is described. The key intermediate, 6-(acetoxymethyl)-2,4-dichloropyrido[3,2-*d*]pyrimidine, was prepared by chlorination of the 2,4-dioxo derivative which, in turn, resulted from the acetic anhydride induced rearrangement of 2,4-dioxopyrido[3,2-*d*]pyrimidine 5-oxide. Suitable nucleophilic displacements on the ring followed by activation of the side chain to the bromomethyl derivative gave 2,4-diamino- or 2-amino-4-oxo-6-(bromomethyl)pyrido-[3,2-*d*]pyrimidines which were reacted with a variety of *p*-substituted benzoylglutamates to give, after saponification, the target folate analogues.

Since the discovery that folate antagonists can be effectively used in the treatment of human neoplastic disease,[1] investigations have focused on the synthesis and biological evaluation of analogues of folic acid.[2] The successful use of methotrexate (MTX) in the treatment of certain forms of cancer[3] prompted the preparation of aminopterin analogues[4] which included modifications in the side chain. It has been reported that 8-deazafolic acid is as potent as methotrexate in the inhibition of certain bacterial cell lines and was active against some methotrexate-resistant strains.[5] The present report describes the synthesis of a series of 8-deaza analogues of aminopterin and folic acid having various isosteric substitutions at the 10 position.

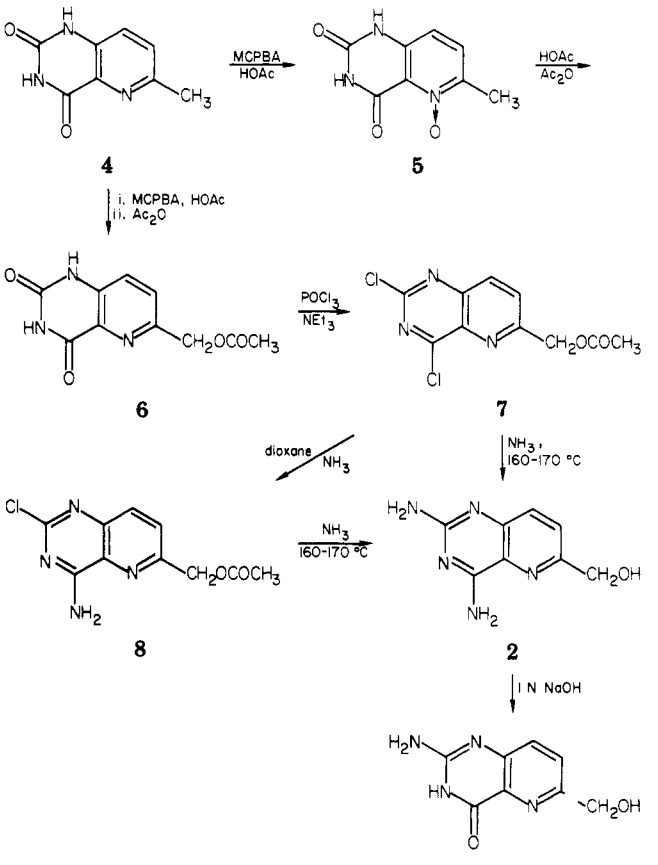
The synthetic procedure of DeGraw et al.[5] involves the preparation of protected 8-deazapteroic acid 1 followed by



1, R′ = $COCF_3$; R″ = $COCH_3$

introduction of glutamic acid by a mixed anhydride or solid-phase method to give 8-deazafolic acid. The intermediates used in the above scheme were not suitable for the preparation of a wide variety of aminopterin and folic acid analogues necessary to investigate structure–activity relationships. Since we were also interested in the effect of replacement of side-chain nitrogen in 8-deazaaminopterin and folic acid, a new general approach was developed.

Scheme I



The syntheses of 2,4-diamino-6-(hydroxymethyl)-pyrido[3,2-*d*]pyrimidine (**2**) and 2-amino-6-(hydroxymethyl)-4-oxopyrido[3,2-*d*]pyrimidine (**3**), the precursors of 8-deaza aminopterin and folic acid, respectively, are

(1) (a) Farber, S.; Diamond, L. K.; Mercer, R. D.; Slyvester, R. F.; Wolff, J. A. *N. Engl. J. Med.* **1948**, 238, 787. (b) Condit, P. T. *Ann. N.Y. Acad. Sci.* **1971**, *186*, 475.

(2) Sirotnak, F. M.; Chello, P. L.; Piper, J. R.; Montgomery, J. A.; DeGraw, J. I. In "Chemistry and Biology of Pteridines"; Kisliuk, R. L., Brown, G. M., Eds.; Elsevier: New York, 1978; p 587.

(3) Livingston, R. B.; Carter, S. K. "Single Agents in Cancer Chemotherapy"; IFI/Plenum: New York, 1970; p 130.

(4) (a) Nair, M. G.; Campbell, P. T. *J. Med. Chem.* **1976**, *19*, 825. (b) DeGraw, J. I.; Kisliuk, R. L.; Gaumont, Y.; Baugh, C. M.; Nair, M. G. *Ibid.* **1974**, *17*, 552. (c) Kim, Y. H.; Gaumont, Y.; Kisliuk, R. L.; Mautner, H. G. *Ibid.* **1975**, *18*, 776.

(5) DeGraw, J. I.; Kisliuk, R. L.; Gaumont, Y.; Baugh, C. M. *J. Med. Chem.* **1974**, *17*, 470.

0022-3263/81/1946-1777$01.25/0