Mamoru Igarashi, Tohru Kambe, and Masaru Tada*

Department of Chemistry, School of Science and Engineering,
Waseda University, Okubo, Shinjuju, Tokyo 169, Japan
Received August 3, 1995

Folic acid models, 1,3-dimethyl-6-(*N*-acylarylamino)methyllumazines **9**, were synthesized from 6-bromomethyl-1,3-dimethyllumazine (**6**), which was derived from 5,6-diamino-1,3-dimethyluracil (**1**) by the condensation with 1,3-dihydroxyacetone, followed by bromination. The bromide **6** was also prepared by the cycloaddition between 3,6,8-trioxo-5,7-dimethyl-5,6,7,8-tetrahydro-3H-pyrimido[5,4–*c*][1,2,5]oxadiazine (**4**) and 1-propenyl trimethylsilyl ether followed by bromination. The folic acid models **9** were also directly synthesized from the oxadiazine **4** and 3-(*N*-acylaryl)amino-1-propenyl trimethylsilyl ether **8** by cycloaddition.

J. Heterocyclic Chem., **33**, 341 (1996).

Tetrahydrofolic acid is a C_1-unit carrier in a biological system [1], which is important in nucleic acid metabolism [2], and the control of the C_1-transfer is an important means of cancer therapy [3]. So far model reactions of C_1-transfer - transfer to uracil [4], transfer to a cobalt complex [5], and transfer to sulfur [6] - have been carried out using the models having no pteridine structure or the pteridine models lacking an anilinomethyl group.

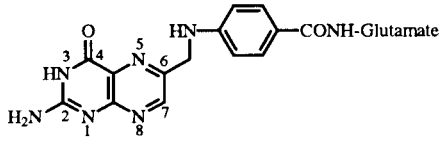


Figure 1. Structure of Folic Acid

Folic acid has a (4-glutamidylanilino)methyl group at the 6-position of the pteridine ring. The site of the C_1-carrier in tetrahydrofolate is the ^5N, ^{10}N, and ^5N- ^{10}N bridge [7]. These structural features of folic acid prompted us to synthesize 6-(arylamino)methyllumazines as folic acid models.

Baugh and Shaw have reported that 4-oxo-2,5,6-triamino-3,4-dihydropyrimidine reacts with 1,3-dihydroxyacetone to give 4-oxo-2-amino-7-hydroxymethyl-1,3-dimethylpteridine and 4-oxo-2-amino-6-hydroxymethyl-1,3-dimethylpteridine [8]. The regiospecificity to give the 6- or 7-hydroxymethylpteridine derivative is controlled by the reaction conditions. Thus, the selective synthesis of 1,3-dimethyl-6-hydroxymethyllumazine (**3**) [9] from 5,6-diamino-1,3-dimethyluracil (**1**) and 1,3-dihydroxyacetone enables the transformation of **1** into a folic acid model.

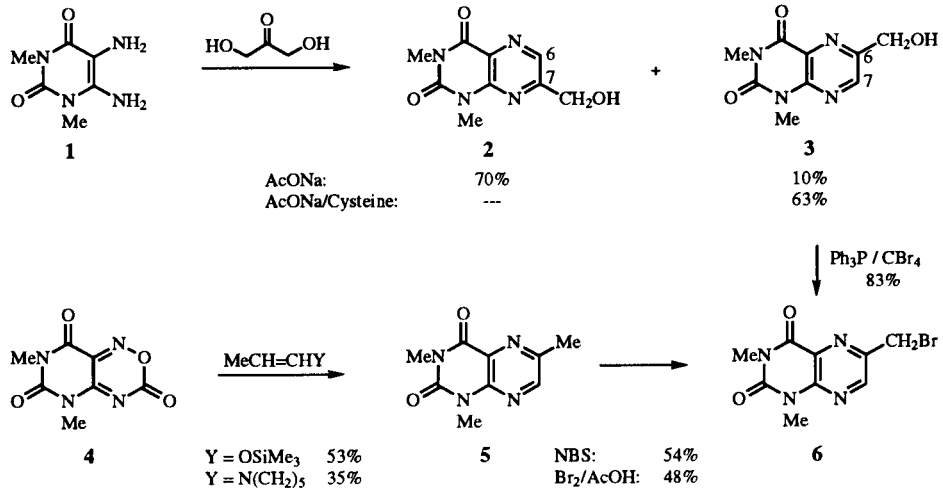
On the other hand, we have reported the reverse electron demanding Diels-Alder addition of 3,6,8-trioxo-5,7-dimethyl-5,6,7,8-tetrahydro-3*H*-pyrimido[5,4–*c*]-[1,2,5]oxadiazine (**4**) [10] with enamines [11] or silylenol ethers [12]. These cycloadditions produce regiospecifically 6-alkyl substituted lumazines and their conversion to folic acid models is a second possibility. A similar type of cycloaddition of **4** with the silylenol ethers **8** having an (*N*-acylarylamino)methyl group is a third possibility. In this paper are described these three independent syntheses of the folic acid models, 1,3-dimethyl-6-(*N*-acylarylamino)methyllumazines **9**.

5,6-Diamino-1,3-dimethyluracil (**1**) [13] and dihydroxyacetone were reacted in aqueous solution by the catalysis of sodium acetate under bubbling air. This process gave a mixture of lumazine derivatives **2** and **3** in 70 and 10% yield, respectively. On the other hand, product **3** was obtained as a major product in 63% yield when cysteine was added to the reaction system and the product **2** was not found under the latter reaction conditions. The effect of cysteine to exclude the formation of the 7–hydroxymethyl derivative **2** is not definitely explained but it must be related to the inhibition of the autoxidation of dihydroxyacetone. The use of cysteine, which was first introduced by Baugh and Shaw [8], is a convenient practical procedure for the synthesis of 1,3-dimethyl-6-hydroxymethyllumazine (**3**). Treatment of **3** with triphenylphosphine and tetrabromomethane gave 6-bromomethyl-1,3–dimethyllumazine (**6**) [9] in 83% yield. The structure of **6** was confirmed by ^{1}H-nmr and mass spectra.

The bromide **6** [9] was also obtained from 1,3,6-trimethyllumazine (**5**), which was prepared by the Diels-Alder addition of **4** and the trimethylsilyl enol-ether [14] or pyrrolidyl enamine [15] of propionaldehyde. Thus, treatment of **5** with *N*-bromosuccinamide in tetrachloromethane or with bromine in acetic acid gave the bromide **6** in 54 and 48% yields, respectively.

The bromide **6** was then treated with sodium *N*-acylarylamide to give the 1,3-dimethyl-6-(*N*-acylarylamino)methyllumazines **9**. This bimolecular substitution proceeds more efficiently with formanilide and form(4-methoxycarbonyl)anilide (74-77%) than acetoanilide and aceto(4-methoxycarbonyl)anilide (37-40%) for an unknown reason. Structures of these lumazines **9** are confirmed by the addition of the ^{1}H-nmr and ^{13}C-nmr signals due to (*N*-acylarylamino)methyl groups to the signals of the bromide **6**.

Scheme 1



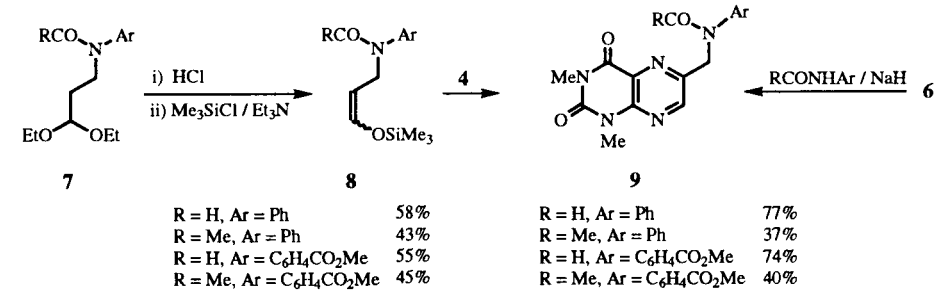
Next, we tried the cycloaddition between the oxadiazine **4** and 3-(*N*-acylarylamino)-1-propenyl trimethylsilyl ethers **8** to get the folic acid models **9** directly from **4**. In this procedure, the purification of the silyl enol ether was difficult due to the higher boiling points, and it was used without purification. Thus, the silyl enol ethers were prepared from 3-(*N*-acylarylamino)propanal dimethyl acetal **7** first by acid hydrolysis followed by treatment with chlorotrimethylsilane and triethylamine. The reaction mixture was distilled under reduced pressure and the residues were further concentrated under reduced pressure. The cycloaddition of the enol ethers **8** thus obtained and **4** gave the desired products **9** (Scheme 2). Though the yields of these cycloadditions were modest due to the impurities of the residue containing **8**, this is a preferable procedure to synthesize **9** due to the short process. In these cycloadditions, formanilide derivatives again gave the products in better yields due to unspecified reasons.

Folic acid has a (4-glutamidylanilino)methyl substituent on the pteridine ring and we introduced the methoxycarbonyl group in the present model compound as an analog to the amidyl group in folic acid. The carbonyl group at the anilino moiety must affect the chemical properties of tetrahydrofolic acid in harvesting the C_1-unit from formic acid and its congener and in the stepwise reductive transformations of the ^5N- or ^{10}N-formyl group into the ^5N-methyl group. We plan to clarify the relation between the structural feature of terahydrofolic acid and the biochemical function, namely intramolecular transfer of the ^{10}N-formyl group to the ^5N-formyl group, its transformation into the $^5N,^{10}N$-methylene bridge, and further transformation into the ^5N-methyl group. The syntheses of the folic acid models described here are helpful in these studies.

EXPERIMENTAL

The ir spectra were recorded using a Perkin Elmer 1640 spectrometer. The ^{1}H-nmr spectra were recorded using a Hitachi R–90H sectrometer (90 MHz), JEOL EX-270 (270 MHz), and JEOL GSX-400 (400 MHz) spectrometer. The ^{13}C-nmr spectra were recorded using a JEOL EX-270 (68 MHz) and GSX-400 (100 MHz) spectrometer. Chemical shifts are given in δ (ppm) relative to internal tetramethylsilane and coupling constants are recorded in Hz. Mass spectra were measured using a JEOL JMN-AUTOMASS150 spectrometer and a JEOL JMS-DX300 spectrometer (high resolution mass). Melting points were mea-

Scheme 2



sured by a Yamato MP-21 apparatus and are uncorrected. Elemental analyses were performed at the Material Characterization Center of Waseda University.

Condensation of 5,6-Diamino-1,3-dimethyluracil (**1**) with 1,3-Dihydroxyacetone.

5,6-Diamino-1,3-dimethyluracil (**1**) [13] (520 mg, 3.0 mmoles), 930 mg (5.2 mmoles) of the 1,3-dihydroxyacetone dimer, and 2.10 g (12 mmoles) of L-cysteine hydrochloride were dissolved in 100 ml of an aqueous solution of sodium acetate (3.0 mole/l). This mixture was heated at 65° for 20 hours with gentle bubbling of air. After cooling the solution, it was extracted four times with 30 ml of dichloromethane, and the extract was dried over sodium sulfate. After evaporation of the solvent, the product was purified by silica gel chromatography (50-60 mesh, 3.2 (ϕ) x 6.0 cm) eluted with ethyl acetate. Recrystallization of the product from ethanol gave 420 mg (63%) of 1,3-dimethyl-6-hydroxymethyllumazine (**3**) which decomposed at 209-210° (lit 211-212°) [9]; ^{1}H-nmr (270 MHz, deuteriochloroform): δ 2.71 (1H, t, J = 5.9), 3.56 (3H, s), 3.74 (3H, s), 4.97 (2H, d, J = 5.9), 8.77 (1H, s).

Syntheses of 6-Bromomethyl-1,3-dimethyllumazine (**6**).

i) From 1,3-Dimethyl-6-hydroxymethyllumazine (**3**).

A tetrahydrofuran solution (10 ml) containing 110 mg (0.49 mmole) of **3**, 147 mg (0.56 mmole) of triphenylphosphine, and 187 mg (0.56 mmole) of tetrabromomethane was stirred at room temperature for 10 hours. The filtrate of the reaction mixture was concentrated *in vacuo* and the residue was subjected to silica gel chromatography (60-80 mesh, 2.1 (ϕ) x 4.0 cm) eluted with ethyl acetate. Recrystallization of the eluate from 2-butanone gave 105 mg (74%) of bromide **6** which decomposed at 225-226° dec (lit [9] 228° dec); ^{1}H-nmr (90 MHz, deuteriochloroform): δ 3.55 (3H, s), 3.72 (3H, s), 4.71 (2H, s), 8.80 (1H, s); ms: (70 eV) m/z (relative intensity) 285 (M^+ + 2, 100%), 283 (M^+, 100%).

ii) Bromination of 1,3,6-Trimethyllumazine (**5**) with *N*-Bromosuccinimide.

A mixture of 520 mg (2.5 mmoles) of **5** [13], 1.34 g (7.5 mmoles) of *N*-bromosuccinimide and 100 mg (0.4 mmole) of dibenzyol peroxide in 20 ml of tetrachloromethane was refluxed for 6 hours. After cooling the mixture, 25 ml of water was added and extracted three times with 30 ml of chloroform. Evaporation of the extract after drying over sodium sulfate gave the mixture of 6-bromomethyl-1,3-dimethyllumazine (**6**), 6-dibromomethyl-1,3-dimethyllumazine and the recovered **5**, which were separated by silica gel column chromatography eluted first with benzene/ethyl acetate (9/1) to afford 520 mg (27%) of 6-dibromomethy-1,3-dimethyllumazine. Further elution with benzene/ethyl acetate (4/1) afforded 370 mg (53%) of **6**.

ii) Bromination of 1,3,6-Trimethyllumazine (**5**) with Bromine.

In 15 ml of glacial acetic acid was dissolved 520 mg (2.5 mmoles) of **5**. To the solution 0.25 ml (5 mmoles) of bromine was then added dropwise. The mixture was refluxed for 3 hours. It was then treated with 30 ml of chloroform and washed with water. Evaporation of the organic layer after drying over sodium sulfate gave the mixture of **5**, **6**, and 6-dibromomethyl-1,3-dimethyllumaine. The mixture was separated by the same procedure as in the case of the reaction with *N*-bromosuccinimide.

Synthesis of Lumazine Derivatives **9** from Bromide **6** and *N*-Acylarylanime.

Lumazine derivatives **9a-9d** were prepared by the general procedure exemplified in the following by the synthesis of **9a**. Formanilide (34 mg, 0.25 mmole) in 1 ml of dry THF was treated under nitrogen with sodium hydride (60% mineral oil dispersion, 10 mg, 0.25 mmole) which was washed twice with hexane. After refluxing for 1 hour, the mixture was treated with a catalytic amount of tris[2-(2-methoxyethoxy)ethyl]amine (0.01 ml, 0.03 mmole) and sodium iodide (10 mg, 0.06 mmole), and 70 mg (0.25 mmole) of bromide **6**. The mixture was refluxed for 24 hours, and then 10 ml of water was added and extracted three times with 10 ml of chloroform. Evaporation of the extract after drying over sodium sulfate gave the crude product, which was purified by preparative tlc on a silica gel plate (20 cm x 20 cm, 2 mm thickness) using the chloroform/ethyl acetate (1/1) mixed solvent.

Compound **9a** was recrystallized from ethanol and melted at 185.0-185.6°; ^{1}H-nmr (90 MHz): δ 3.52 (3H, s), 3.69 (3H, s), 5.27 (2H, s), 7.12-7.53 (5H, m), 8.59 (1H, s), 8.71 (1H, s); ^{13}C-nmr (100 MHz): δ 29.0, 29.4, 48.6, 123.7, 126.5, 127.3, 129.9, 140.5, 147.3, 147.4, 147.9, 150.5, 159.8, 162.6; ir (chloroform): 3006, 2890, 1723, 1675, 1596 cm^{-1}; ms: (70 eV) m/z (relative intensity) = 325 (M+, 21%), 297 (98%), 120 (100%).

Anal. Calcd. for $C_{16}H_{15}N_5O_3$: C, 59.07; H, 4.65; N, 21.53. Found: C, 58.83; H, 4.37; N, 21.18.

Compound **9b** was recrystallized from ethanol and melted at 162.2-163.5°; ^{1}H-nmr (90 MHz): δ 1.93 (3H, s), 3.52 (3H, s), 3.71 (3H, s), 5.13 (2H, s), 7.03-7.57 (5H, m), 8.81 (1H, s); ^{13}C-nmr (100 MHz): δ 22.5, 29.0, 29.4, 52.5, 126.3, 128.0, 128.4, 129.9, 142.9, 147.1, 148.0, 149.0, 150.6, 160.0, 171.1; ir (chloroform): 3018, 3010, 2957, 1721, 1674, 1596 cm^{-1}; ms: (70 eV) m/z (relative intensity) = 339 (M+, 16%), 297 (100%).

Anal. Calcd. for $C_{17}H_{17}N_5O_3$: C, 60.17; H, 5.05; N, 20.64. Found: C, 60.15; H, 5.18; N, 20.38.

Compound **9c** was recrystallized from 2-butanone and melted at 213.1-213.9°; ^{1}H-nmr (270 MHz): δ 3.53 (3H, s), 3.69 (3H, s), 3.91 (3H, s), 5.30 (2H, s), 7.41 (2H, d, J = 8.8), 8.07 (2H, d, J = 8.8), 8.72 (1H, s), 8.73 (1H, s); ^{13}C-nmr (100 MHz): δ 29.1, 29.5, 48.1, 52.3, 122.2, 126.5, 128.5, 131.4, 144.4, 147.3, 147.4, 147.5, 150.5, 159.7, 162.1, 166.0; ir (chloroform): 3026, 3018, 2954, 1723, 1677, 1606 cm^{-1}; ms: (70 eV) m/z (relative intensity) = 383 (M^+, 16%), 205 (93%), 120 (100%).

Anal. Calcd. for $C_{18}H_{17}N_5O_5$: C, 56.40; H, 4.47; N, 18.27. Found: C, 56.06; H, 4.22; N, 17.97.

Compound **9d** was recrystallized from methanol and melted at 205.5-206.7°; ^{1}H-nmr (90 MHz): δ 1.95 (3H, s), 3.52 (3H, s), 3.71 (3H, s), 3.92 (3H, s), 5.12 (2H, s), 7.40 (2H, d, J = 8.6), 8.09 (2H, d, J = 8.6), 8.80 (1H, s); ^{13}C-nmr (100 MHz): δ 22.5, 29.0, 29.4, 52.3, 52.4, 126.4, 128.0, 129.9, 131.3, 146.9, 147.2, 147.9, 148.5, 150.6, 159.9, 166.0, 170.5; ir (chloroform): 3018, 2953, 1722, 1673, 1605 cm^{-1}; ms: (70 eV) m/z (relative intensity) = 397 (M^+, 17%), 120 (100%).

Anal. Calcd. for $C_{19}H_{19}N_5O_5$: C, 57.43; H, 4.82; N, 17.62. Found: C, 57.07; H, 4.51; N, 17.29.

Syntheses of 3-(*N*-Acylarylamino)-1-propenyl Trimethylsilyl Ethers **8** from Diethylacetals **7a-7d**.

i) Synthesis of Diethylacetals **7a-7d**.

Compounds **7a-7d** were prepared by the general procedure exemplified below by the synthesis of **7a**.

Formanilide (0.67 g, 5 mmoles) in 10 ml of dry THF was added under nitrogen to sodium hydride (60% mineral oil dispersion, 200 mg, 5 mmoles) which was washed twice with hexane. After refluxing for 1 hour, the mixture was treated with tris[2-(2-methoxyethoxy)ethyl]amine (0.3 ml, 1 mmole), sodium iodide (0.08 g, 0.5 mmole) and 3-chloro-1,1-diethoxypropane (0.83 ml, 5 mmoles). The mixture was refluxed for 48 hours, and then 25 ml of water was added and extracted three times with 40 ml of chloroform. Evaporation of the extract after drying over sodium sulfate gave the crude product, which was purified by silica gel column chromatography with hexane/ethyl acetate (1/1) to elute **7a**.

Compounds **7a-7d** were unstable upon heating and decomposed by distillation *in vacuo*. They were purified by column chromatography and directly used for the next reaction.

Compound **7a** gave the following spectroscopic data; ^{1}H-nmr (400 MHz): δ 1.17 (6H, t, J = 7.3), 1.89 (2H, td, J = 8.8, 5.9), 3.42 (2H, qd, J = 9.5, 7.3), 3.61 (2H, qd, J = 9.5, 7.3), 3.91 (2H, t, J = 8.8), 4.51 (1H, t, J = 5.9), 7.15-7.21 (2H, m), 7.23-7.35 (1H, m), 7.35-7.46 (2H, m), 8.37 (1H, s); ^{13}C-nmr (68 MHz): δ 15.2, 32.0, 41.3, 61.5, 100.9, 124.1, 126.8, 129.6, 141.0, 162.2; ir (tetrachloromethane): 3068, 3043, 2977, 2930, 1689, 1597 cm^{-1}; ms: (70 eV) m/z (relative intensity) = 251 (M^+, 11%), 103 (100%); hrms: Calcd. for $C_{14}H_{21}NO_3$: m/z = 251.1521. Found: m/z = 251.1568.

Compound **7b** gave the following spectroscopic data; ^{1}H-nmr (400 MHz): δ 1.16 (6H, t, J = 7.3), 1.83 (3H, s), 1.86 (2H, td, J = 9.2, 5.9), 3.45 (2H, qd, J = 9.5, 7.3), 3.61 (2H, qd, J = 9.5, 7.3), 3.78 (2H, t, J = 9.2), 4.54 (1H, t, J = 5.9), 7.16-7.21 (2H, m), 7.31-7.38 (1H, m), 7.38-7.45 (2H, m); ^{13}C-nmr (68 MHz): δ 15.2, 22.7, 32.0, 45.3, 61.2, 101.2, 127.8, 128.1, 129.6, 143.1, 170.2; ir (tetrachloromethane): 3065, 3038, 2977, 2930, 1662, 1596 cm^{-1}; ms: (70 eV) m/z (relative intensity) = 265 (M^+, 4%), 103 (100%); hrms: Calcd. for $C_{15}H_{23}NO_3$: m/z = 265.1678. Found: m/z = 265.1671.

Compound **7c** gave the following spectroscopic data; ^{1}H-nmr (400 MHz): δ 1.17 (6H, t, J = 7.0), 1.92 (2H, td, J = 8.8, 5.9), 3.43 (2H, qd, J = 9.2, 7.0), 3.62 (2H, qd, J = 9.2, 7.0), 3.93 (3H, s), 3.96 (2H, t, J = 8.8), 4.51 (1H, t, J = 5.9), 7.26 (2H, d, J = 8.8), 8.09 (2H, d, J = 8.8), 8.52 (1H, s); ^{13}C-nmr (68 MHz): δ 15.2, 31.9, 40.9, 52.2, 61.6, 100.8, 122.2, 127.9, 131.2, 145.0, 161.8, 166.1; ir (tetrachloromethane): 3028, 2977, 2951, 1727, 1687, 1606 cm^{-1}; ms: (70 eV) m/z (relative intensity) = 309 (M^+, 2%), 103 (100%); hrms: Calcd. for $C_{16}H_{23}NO_5$: m/z = 309.1576. Found: m/z = 309.1568.

Compound **7d** gave the following spectroscopic data; ^{1}H-nmr (400 MHz): δ 1.15 (6H, t, J = 7.0), 1.87 (2H, td, J = 9.2, 5.9), 2.21 (3H, s), 3.43 (2H, qd, J = 9.2, 7.0), 3.61 (2H, qd, J = 9.2, 7.0), 3.83 (2H, t, J = 9.2), 3.94 (3H, s), 4.53 (1H, t, J = 5.9), 7.27 (2H, d, J = 8.6), 8.09 (2H, d, J = 8.6); ^{13}C-nmr (68 MHz): δ 15.2, 22.8, 32.1, 45.5, 52.3, 61.4, 101.1, 128.0, 129.5, 131.1, 147.2, 166.1, 169.7; ir (tetrachloromethane): 2977, 2952, 1728, 1669, 1606 cm^{-1}; ms: (70 eV) m/z (relative intensity) = 323 (M^+, 3%), 164 (100%), 103 (68%); hrms: Calcd. for $C_{17}H_{25}NO_5$: m/z = 323.1733. Found: m/z = 323.1699.

ii) Syntheses of Silylenol Ethers **8**.

Silylenol ethers **8a-8d** were prepared by the general procedure exemplified below by the synthesis of **8a**.

A solution of 52 mg (0.2 mmole) of **7a** in 2 ml of THF was treated with 1 ml of 1*N*-hydrochloric acid and stirred for 3 hours at room temperature. To the mixture was then added 10 ml of water, and it was extracted three times with 10 ml of chloroform. Evaporation of the extract after drying over sodium sulfate gave the crude aldehyde **8a**. The **8a** obtained above was dissolved in 1 ml dry *N,N*-dimethylformamide and to the solution was added 0.035 ml (0.28 mmole) of trimethylsilylchloride, 0.07 ml (0.55 mmole) of trimethylamine, and 1 ml of dry *N,N*-dimethylformamide. The mixture was then heated to 100° for 12 hours. After removal of most of the solvents and the excess reagents under reduced pressure, the residue was further concentrated by heating at 100° under reduced pressure (20 mm Hg) for 3 hours. The crude product thus obtained was directly used for the cycloaddition.

Cycloaddition of Silylenol Ethers **8** with Oxadiazine **4**.

The syntheses of folic acid models **9a-d** were carried out by the general procedure exemplified below by the synthesis of **9a**. The unpurified silylenol ether **8a** obtained from 0.2 mmole of **7a** (see preceding paragraph) was dissolved in 1 ml of dry THF and the solution was added to **4** (21 mg, 0.1 mmole) in 1 ml of dry THF, and then the mixture was refluxed for 12 hours. After cooling, to the reaction mixture was added 10 ml of water, and it was extracted three times with 10 ml of chloroform. Evaporation of the extract after drying over sodium sulfate gave the crude product, which was purified by preparative tlc on a silica gel plate (20 x 20 cm, 2 mm thickness) using the mixed solvent of chloroform/ethyl acetate (1/1). The products **9a-9d** obtained by similar methods were identical with those obtained from the bromomethyl-1,3-lumazine (**6**) in every spectroscopic characteristic.

Acknowledgement.

This study was supported by the Grant-in-Aid for Scientific Research, Annual Project organized by Waseda University, and Sasagawa Science Research Grant (to M. I.).

REFERENCES AND NOTES

[1a] R. L. Blakely and S. J. Benkovic, eds, Folates and Pteridines, Vol **1**, Wiley, New York, 1984; Vol **2**, Wiley, New York, 1985.

[1b] H. C. S. Wood, Comprehensive Organic Chemistry, Vol **5**, E. Haslam, ed, Chapter 24.3, Pegamon, Oxford, 1979.

[1c] R. G. Mathew and J. T. Drummond, *Chem. Rev.*, **90**, 1275 (1990).

[2a] C. Staben and J. C. Rabinowitz, Folates and Pteridines, Vol **1**, R. L. Blakely and S. J. Ben, eds, Chapter 12, Wiley, New York, 1984.

[2b] M. Friedkin, *Ann. Rev. Biochem.*, **32**, 185 (1963).

[2c] D. W. Young, *Chem. Soc. Rev.*, 119 (1994).

[3a] J. K. Landquist, Comprehensive Heterocyclic Chemistry, Vol **1**, A. R. Katritzky and C. W. Rees, eds, Pergamon, Oxford, 1984, p 159.

[3b] E. C. Taylor, *J. Heterocyclic Chem.*, **27**, 1 (1990).

[3c] P. R. Marsham, *J. Heterocyclic Chem.*, **31**, 603 (1994).

[4a] J. W. G. Merssers and U. K. Pandit, *Tetrahedron Letters*, **33**, 2999 (1992).

[4b] J. R. Kagel, B. Wang and M. P. Mertes, *J. Org. Chem.*, **58**, 2738 (1993).

[4c] U. K. Pandit, *Pure Appl. Chem.*, **66**, 759 (1994).

[5a] J. M. Pratt, P. R. Norris, M. S. A. Hanza, R. Bolton and U. K. Pandit, *J. Chem. Soc., Chem. Cummun.*, 1323 (1994).

[5b] E. Hilhorst, A. S. Iskander, T. B. R. A. Chen and U. K. Pandit, *Tetrahedron Letters*, **34**, 4257 (1993); *Tetrahedron*, **50**, 8863 (1994).

[6a] E. Hilhorst, T. B. R. A. Chen and U. K. Pandit, *J. Chem. Soc. Chem. Commun.*, 881(1993).

[6b] E. Hilhorst, T. B. R. A. Chen, A. S. Iskander and U. K. Pandit, *Tetrahedron*, **50**, 7837 (1994).

[7a] C. Temple, Jr. and J. A. Montgomery, Folates and Pteridines, Vol **1**, R. L. Blakely and S. J. Benkovic, eds, Wiley, New York, 1984, Chapter 2.

[7b] W. Pfleiderer, Comprehensive Organic Chemistry, Vol **2**, A. Katritzky and C. W. Rees, eds, Pergamon, Oxford, 1984,p 325.

[8] C. M. Baugh and E. Shaw, *J. Org. Chem.*, **29**, 3610 (1964).

[9] Y. Kang, R. Soyka and W. Pfleiderer, *J. Heterocyclic Chem.*, **24**, 597 (1987).

[10] W. Pfleiderer and F. E. Kempter, *Angew. Chem., Int. Ed. Engl.*, **6**, 259 (1967); *Chem. Ber.*, **103**, 908 (1970).

[11] M. Igarashi and M. Tada, *J. Heterocyclic Chem.*, **32**, 807 (1995).

[12] M. Igarashi and M. Tada, *Synthesis*, under submission.

[13] F. F. Blicke and H. C. Godt, Jr., *J. Am. Chem. Soc.*, **76**, 2978 (1954).

[14] H. O. House, L. J. Czuba, M. Gall and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1069).

[15] G. Opitz, H. Hellman and H. W. Shubert, *Liebigs Ann. Chem.*, **623**, 112 (1959).