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SYHTHESIS OF THE TETRAHYDROPTERIDINE-2,4-DIONE HAVING A SUBSTITUTED METHYL GROUP AT 6-POSITION

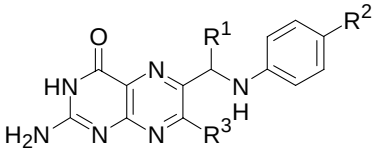
Masaru Tada,* Tomoyuki Shimamura, and Takeaki Suzuki

Department of Chemistry, School of Science and Engineering,
Waseda University, Shinjuku, Tokyo 169-8555, Japan

Abstract – Lewis acid treatment of 5-amino-6-(*N*-2,3-epoxypropyl-*N*-tosyl)amino-1,3-dimethyluracil (**3**) gave the diazepine (**4**) fused to uracil ring, and the tosylate (**5**) from **4** underwent ring transformation to provide tetrahydropteridinediones (**7** and **8**) depending on the reaction conditions. Thus, heating in dry acetonitrile led to 6-tosyloxymethyl-tetrahydropteridine-2,4-dione (**7**) whereas that in wet acetonitrile to 6-hydroxymethyl derivative (**8**).

Introduction

The majority of naturally occurring pteridines possess carbon substituents at position 6 as can be seen in folic acid,[1] methanopterin[2] and biopterin.[3] The coenzyme forms are actually their reduced products, mostly 5,6,7,8-tetrahydro derivatives, whose nitrogen atom at position 5 is reactive site of those molecules in C_1-unit metabolism. Numerous synthetic methods for pteridine have been reported[4] while the direct synthesis of the 5,6,7,8-tetrahydropteridine derivatives is quite limited.[5-8] In this paper we report a successful synthesis of 6-substituted tetrahydropteridines starting from uracil derivatives.



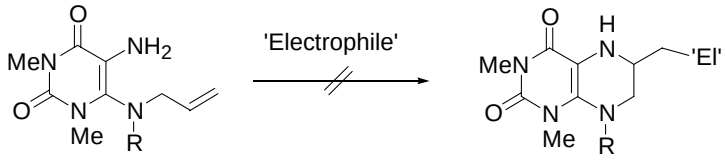
Folic acid
[R^1=H, R^2=CONHCH(COOH)-$(CH_2)_2$COOH, R^3=H]

Methanopterin
[R^1=CH_3, R^2=$CH_2(CHOH)_3CH_2$-ribose-OP(O)(OH)-OCH(COOH)-$(CH_2)_2$COOH, R^3=CH_3]

Figure1. Natural pteridine derivatives

Results and discussion

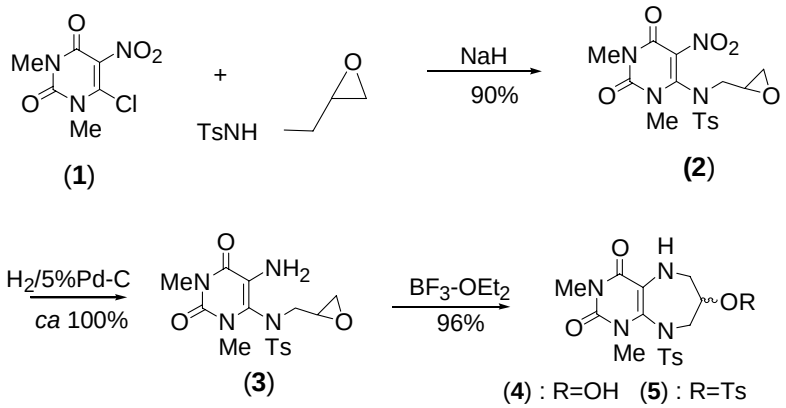
We first attempted the transformation of 6-allylamino-5-aminouracil into tetrahydropteridinedione by treatment with electrophiles such as iodine or NBS, expecting the successive cyclization of the resulting adduct by nucleophilic attack of the 5-amino group of the pyrimidine ring. However, the halogenonium ion might react with the 5-amino functionality to result in only the formation of undesirable products (Scheme 1).



Scheme 1

Next we searched another route of ring closure by using an allylamino group equivalent and we selected *N*-(2,3-epoxypropyl)tosylamide. Thus 6-chloro-5-nitro-1,3-dimethyluracil[7] (**1**) was reacted with sodium *N*-(2,3-epoxypropyl)tosylamide to produce 5-nitro-6-(*N*-tosyl-*N*-2,3-epoxypropyl)amino-1,3-dimethyl-uracil (**2**) in a high yield, and the nitro group was reduced by the hydrogenation over Pd-C to produce 5-amino-6-(*N*-tosyl-*N*-2,3-epoxypropyl)amino-1,3-dimethyluracil (**3**) (Scheme 2). Uracil derivatives (**2**) and (**3**) were *ca* 1:1 mixtures of two diastereomers due to the atropisomerism[9] of the *N*-tosyl group and the asymmetry of the epoxy group. The atropisomerism originates from the hindered rotation of the bulky *N*-(2,3-epoxypropyl)tosylamide group by the steric repulsion with the *N*-methyl group.

The epoxy derivative (**3**) was treated with BF_3-etherate, expecting the formation of 6-hydloxymethyl-5,6,7,8-tetrahydro-2,4-(1*H*,3*H*)-pteridinedione (**8**), but the structure of the cyclization product (**4**) was concluded to possess a diazepine ring.



Scheme 2

The product (**4**) was again a 1:1 mixture of diastereomers by the same reason cited above but due to the asymmetric secondary hydroxyl group instead of the epoxy group.

Tosylation of the 1:1 diastereomeric mixture of **4**, however, gave tosylate (**5**) as a single isomer in high yield (>80%). This fact suggests that the compound (**4**) or (**5**) isomerizes at the atrophic center under the conditions of tosylation to give the more stable isomer or the tosylate (**5**) is relieved from the flipping barrier of the tosyl group. Detailed analysis of the ^{1}H-NMR spectrum of the tosylate (**5**) by ^{1}H-^{1}H COSY (see Figure 2) convinced us the seven membered structure and lack of the tosyloxymethyl group (CH_2OTs), which was required by the expected structure (**7**). Exclusive formation of the diazepinoid product (**4**) must be a consequence of the geometric requirement of the transition state of the ring closure. The reaction proceeds by attack of the amino group on the less hindered terminal site of the epoxide group.

Fortunately the compound (**4**) was easily transformed into the tetrahydropteridinedione derivative (**7**) through its tosylate (**5**). Thermal treatment of the tosylate (**5**) under varying conditions produced 5,6,7,8-tetrahydro-2,4-(1*H*,3*H*)-pteridinedione derivatives. Thus heating in dry acetonitrile produced 6-tosyloxymethyl-5,6,7,8-tetrahydro-2,4-(1*H*,3*H*)-pteridinedione (**7**) in 70% yield and heating in acetonitrile-water (2:1) produced 6-hydroxymethyl-5,6,7,8-tetrahydro-2,4-(1*H*,3*H*)-pteridinedione (**8**) in 47% yield (Scheme 3). Structures of **7** and **8** were unequivocally assigned from ^{1}H-NMR spectral data as shown in Figure 3. Compounds (**2**, **3**, and **4**) are diastereomeric mixtures but tosylate (**5**) consists of a single isomer, and the products (**7** and **8**) formed by the skeletal rearrangement of **5** were single isomers.

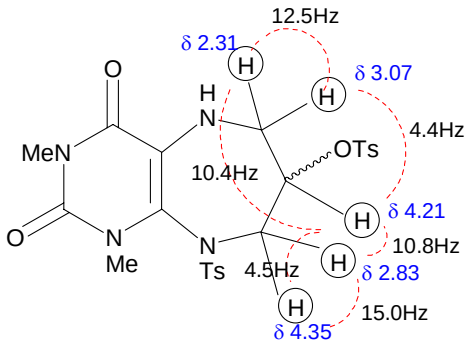


Figure 2. Chemical shifts and coupling constants of tosylate (**5**) from ^{1}H-^{1}H COSY

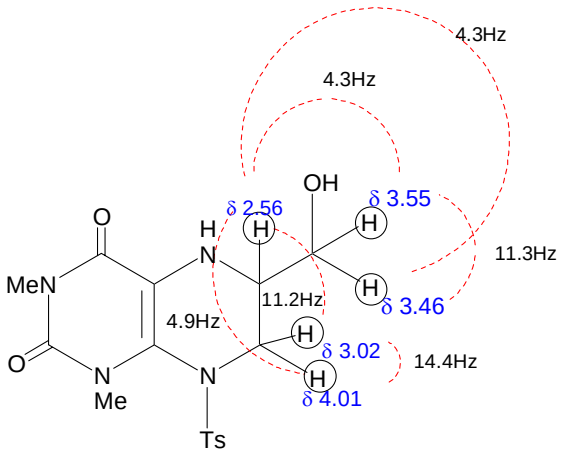
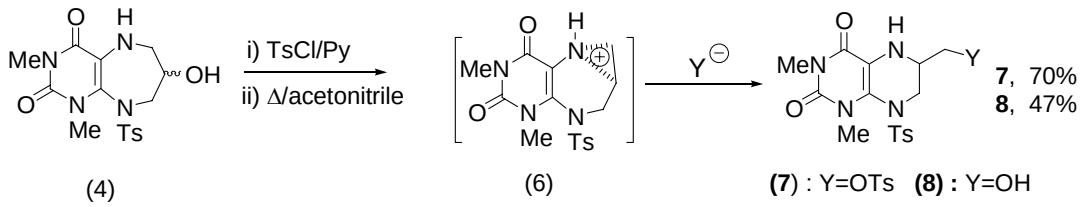


Figure 3. Chemical shifts and coupling constants of **8**

Though we must remove the *N*-tosyl group after the introduction of alternative group for the 6-tosyloxymethyl group, tosylate (**7**) is a versatile intermediate for the convergent syntheses of



(4) (6) **(7)** : Y=OTs **(8) :** Y=OH

Scheme 3

6-substituted 5,6,7,8-tetrahydro-2,4-(1*H*,3*H*)-pteridinediones, which are analogues of folic acid, methanopterin and related bioactive molecules. In addition, the modified tetrahydrofolic acid derivatives having diazepine structure must be valuable candidates for biological test as folic acid analogues. The procedure described in this paper should be a convenient means for the preparation of such analogues due to its simplicity.

EXPERIMENTAL

Synthesis of N-(2,3-epoxypropyl)tosylamide

In a nitrogen flushed flask were placed tosyl chlroride (2.44 g, 12.8 mmol) and 10 mL of dry dichlroromethane, and to the mixture was slowly added 5 mL of allylamine. After stirring for 30 min at rt, 1M HCl was added and the mixture was extracted with 100 mL of dichloromethane, and the dichloromethane solution was treated with *m*-CPBA (3.73 g, 21.6 mmol). After stirring for 24 h at rt, the condensate was subjected to column chromatography (Al_2O_3, EtOAc) to produce *N*-(2,3-epoxypropyl)tosylamide (2.46 g, 85%), mp 65-66^{o}C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.43 (3H, s), 2.63-2.65 (1H, m), 2.75-2.77 (1H, m), 3.00-3.09 (2H, m), 3.31-3.36 (1H, m), 4.90 (1H, br s, NH), 7.31 (2H, d, *J*=8.3), 7.75 (2H, d, *J*=8.3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 21.45, 44.33, 45.12, 50.29, 127.0 (2C), 129.7 (2C), 136.7, 143.6; IR ($CHCl_3$) 3395, 1339, 1161 cm^{-1}; HRMS(FAB) *m/z*=226.0680. Calcd for ($C_{10}H_{13}NO_3S$ + H) *m/z*=226.0694.

Anal. Calcd for $C_{10}H_{13}NO_3S$: C, 52.85; H, 5.77; N, 6.16. Found: C, 52.75; H, 5.72; N, 6.07.

*Synthesis of 6-[N-(2,3- epoxypropyl)-N-tosyl]amino-5-nitro-1,3-dimethyluracil (**2**)*

In a dried and nitrogen flushed flask were placed *N*-(2,3-epoxypropyl)tosylamide (91 mg, 0.4 mmol), 50% sodium hydride-mineral oil dispersion (20 mg, 0.4 mmol) and 5 mL of dry THF, and the mixture was treated with 6-chloro-5-nitro-1,3-dimethyluracil[7] (88 mg, 0.4 mmol). After stirring for 1.5 h at rt, the reaction mixture was acidified with the saturated solution of tartaric acid and extracted with dichloromethane. The condensate of the extract was subjected to silica gel chromatography eluted with ethyl acetate to yield the yellow solid of the substitution product (**2**) (148 mg, 90%). The product was a 1:1 mixture of diastereomers and the effort to separate by TLC, column chromatography or fractional

crystallization was unsuccessful. The following ^{1}H-NMR spectral data were assigned from the data of the chromatography fractions consisting predominantly of one of the two components, and ^{13}C-NMR, IR, HRMS spectrum and elemental analysis were collected from the1:1 mixture.

2a, ^{1}H-NMR (600 MHz, $CDCl_3$) δ 2.48 (3H, s), 2.55 (1H, dd, *J*=4.6 and 2.4), 2.91 (1H, dd, *J*=4.6 and 4.6), 3.14 (1H, dd, *J*=15.9 and 9.3), 3.43 (3H, s), 3.53 (1H, dddd, *J*=9.3, 4.6, 2.4, and 2.0), 3.75 (3H, s), 4.19 (1H, dd, *J*=15.9 and 2.0), 7.37(2H, d, *J*=8.3), 7.72(2H, d, *J*=8.3).

2b, ^{1}H-NMR (600 MHz, $CDCl_3$) δ 2.48 (3H, s), 2.62 (1H, dd, *J*=4.6 and 2.4), 2.85 (1H, dd, *J*=4.6 and 4.4), 3.26 (1H, dddd, *J*=8.3, 4.4, 3.0, and 2.4), 3.44 (3H, s), 3.45 (1H, dd, 13.2 and 8.3), 3.58 (3H, s), 3.88 (1H, dd, *J*=13.2 and 3.0), 7.38 (2H, d, *J*=8.3), 7.70 (2H, d, *J*=8.3).

(**2a** + **2b**), ^{13}C-NMR (150 MHz, $CDCl_3$) δ 21.81, 21.82, 29.33, 29.37, 33.87, 34.03, 45.86, 46.28, 47.62, 50.22, 54.24, 57.11, 127.9, 128.0, 130.3, 134.1, 134.2, 144.3, 145.9, 146.3, 146.4, 149.5, 155.2, 155.5 (the signals at 130.3, 144.3, and 145.9 are common to **2a** and **2b**); IR ($CDCl_3$) 3030, 1728, 1680, 1539, 1362, 1167 cm^{-1}; HRMS(FAB) *m/z*=411.1019. Calcd for ($C_{16}H_{18}N_4O_7S$ + H) *m/z*=411.0974.

Anal. Calcd for $C_{16}H_{18}N_4O_7S$: C, 46.83; H, 4.42; N, 13.65. Found: C, 46.55; H, 4.27; N, 13.66.

*Reduction of the nitrouracil derivative(**2**) followed by cyclisation of the aminouracil derivative (**3**) into the diazepine derivative (**4**)*

The nitro derivative (**2**) (mixture of two diastereomers) (346 mg, 0.84 mmol) dissolved in 25 mL of ethyl acetate was hydrogenated over 5% Pd-C (86 mg) at the atmospheric pressure for 2.5 h. Filtration and condensation gave the aminouracil derivative (**3**) in quantitative yield as a violet solid. The product (**3**) was a 1:1 mixture of diastereomers but no separation was made due to its instability, and it was used directly for the next cyclization. The following ^{1}H-NMR spectral data of **3** were tentatively assigned from ^{1}H-^{1}H COSY of the 1:1 mixture of the diastereomers.

3a, ^{1}H-NMR (600 MHz, $CDCl_3$) δ 2.50 (1H, dd, *J*=5.5 and 4.0), 2.77 (1H, t, *J*=4.5), 3.06-3.09 (1H, m), 3.24 (3H, s), 3.32-3.36 (1H, m), 3.39 (3H, s), 3.48 (1H, br s), 3.88 (1H, dd, *J*=14.5 and 4.0), 7.36 (2H, d, *J*=8.3), 7.78 (2H, d, *J*=8.3).

3b,^{1}H-NMR (600 MHz, $CDCl_3$) δ 2.45-2.47 (1H, m), 2.77-2.79 (1H, m), 3.19-3.21 (1H, m), 3.29-3.34 (1H, m), 3.38 (3H, s), 3.41 (3H, s), 3.49 (1H, br s), 3.85 (1H, dd, *J*=14.5 and 3.5), 7.36 (2H, d, *J*=8.3), 7.78 (2H, *J*=8.3).

(**3a** + **3b**), HRMS(FAB) *m/z*=381.1237. Calcd for ($C_{16}H_{20}N_4O_5S$ + H) *m/z*=381.1232.

In a dry and nitrogen flushed flask were placed the aminouracil derivative (**3**) obtained above and 20 mL of dry dichloromethane, and the mixture was treated with BF_3-etherate (0.11 mL, 0.84 mmol) by using a syringe. Then the mixture was stirred for 3 h at rt, quenched by adding water, and extracted with dichloromethane. The condensate of the extract was subjected to silica gel chromatography eluted by

ethyl acetate to produce a white solid of diazepine derivative (**4**) (306 mg, 96%). The product (**4**) was a non-separable mixture of two diastereomers and the following spectral data were collected from the1:1 mixture of diastereomers.

4, ^{1}H-NMR (600 MHz, $CDCl_3$) δ 1.60-1.63 (0.5H, br s), 2.08 (0.5H, d, *J*=11.6), 2.19 (0.5H, dd, *J*=10.0 and 12.3), 2.43 (3H, s), 2.50 (0.5H, dd, *J*=13.2 and 1.2), 2.68 (0.5H, dd, *J*=14.9 and 10.8), 3.04 (0.5H, dd, *J*=15.5 and 1.5), 3.08-3.15 (0.5H, m), 3.15-3.19 (0.5H, m), 3.42 (1.5H, s), 3.43 (1.5H, s), 3.48 (1.5H, s), 3.49 (1.5H, s), 3.46-3.52 (0.5H, br), 3.73 (0.5H, br d, *J*=7.8), 3.78 (0.5H, d, *J*=6.0), 3.85 (0.5H, br d, *J*=6.4), 4.32 (1H, m), 7.27 (1H, d, *J*=8.3), 7.28 (1H, d, *J*=8.3), 7.71 (1H, d, *J*=8.3), 7.74 (1H, d, *J*=8.3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 21.70, 21.71, 28.93, 33.11, 33.73, 51.06, 52.33, 52.66, 52.72, 66.72, 67.53, 124.4, 125.3, 128.2, 128.3, 129.6, 129.8, 133.3, 135.0, 136.8, 137.1, 145.0, 145.1, 149.9, 150.1, 161.4, 161.5 (the siganals at 28.93 and 133.3 are common to the two diastereomers); IR ($CHCl_3$) 3360, 1700, 1636, 1367, 1164 cm^{-1}; HRMS(FAB) *m/z*=381.1252. Calcd for ($C_{16}H_{20}N_4O_5S$ + H) *m/z*=381.1232. Anal. Calcd for $C_{16}H_{20}N_4O_5S$: C, 50.52; H, 5.30; N, 14.73. Found: C, 50.39; H, 5.04; N, 14.59.

*Ring contraction of the diazepine derivative (**4**) through its tosylate (**5**)*

In a dry and nitrogen flushed flask were placed diazepine derivative (**4**) (270 mg, 0.7 mmol), tosyl chloride (267 mg, 1.4 mmol), *p*-(dimethylamino)pyridine (342 mg, 2.8 mmol) and 10 mL of dry dichloromethane, and the mixture was stirred for 3 h at rt. The condensate of the reaction mixture was subjected to silica gel chromatography eluted by ethyl acetate and the tosylate (**5**) was obtained in 80% yield (304 mg). Although we started from the 1:1 mixture of the diastereomer (**4**), the tosylate obtained was a single product (**5**).

5, mp 129-133^{o}C (EtOAc-hexane). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 2.31 (1H, dd, *J*=12.5 and 10.4), 2.49 (3H, s), 2.50 (3H, s), 2.83 (1H, dd, *J*=15.0 and 10.8), 3.07 (1H, ddd, *J*=12.5, 4.4 and 1.8), 3.39 (3H, s), 3.44 (3H, s), 4.21 (1H, dddd, *J*=10.8, 10.4, 4.5, and 4.4), 4.35 (1H, ddd, *J*=15.0, 4.5 and 1.8), 7.32 (2H, d, *J*=8.3), 7.39 (2H, d, *J*=8.3), 7.68 (2H, d, *J*=8.3), 7.72 (2H, d, *J*=8.3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 21.70, 21.71, 28.86, 32.98, 49.66, 50.08, 53.34, 73.82,123.9, 127.8, 128.4, 130.0, 130.1, 133.4, 133.9, 136.7, 145.3, 145.5, 149.8, 161.2; IR ($CHCl_3$)1700, 1635, 1368, 1177, 1167 cm^{-1}; HRMS *m/z*=535.1285. Calcd for ($C_{23}H_{26}N_4O_7S_2$ + H) *m/z*=535.1321.

The tosyloxydiazepine derivative (**5**) (22.6 mg, 0.04 mmol) was heated at 70^{o}C for 5 h in 3 mL of acetonitrile (condition a) and at 60^{o}C for 3 h in 3 mL of acetonitrile-water (2:1) (condition b). The condensates of each fraction were subjected to silica gel chromatography eluted by ethyl acetate to yield 6-tolyloxymethyltetrahydropteridine-2,4-dione (**7**) in 70% (condition a) and 6-hydroxymethyltetra-hydropteridine-2,4-dione (**8**) in 47% (condition b). Compound (**8**) was correlated with **7** by tosylation.

7, ^{1}H-NMR (600 MHz, $CDCl_3$) δ 2.46 (3H, s), 2.47 (3H, s), 2.84 (1H, dd, *J*=14.5 and 10.8), 2.97 (1H,

dddd, *J*=10.8, 5.5, 4.8, and 4.8), 3.39 (3H, s), 3.49 (3H, s), 3.79 (1H, dd, *J*=10.4 and 5.5), 3.83 (1H, dd, *J*=10.4 and 4.8), 4.02 (1H, dd, *J*=14.5 and 4.8), 7.34 (2H, d, *J*=8.3), 7.36 (2H, d, *J*=8.3), 7.67 (2H, d, *J*=8.3), 7.74 (2H, d, *J*=8.3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 21.68, 21.75, 28.49, 33.85, 46.34, 46.86, 68.86, 115.2, 122.1, 127.9, 128.2, 130.1, 130.4, 132.0, 133.8, 145.5, 146.0, 149.7, 159.0; IR ($CHCl_3$) 1696, 1635, 1363, 1190, 1177 cm^{-1}; HRMS(FAB) *m/z*=535.1300. Calcd for ($C_{23}H_{26}N_4O_7S_2$ + H) *m/z*=535.1321.

8, ^{1}H-NMR (600 MHz, $CDCl_3$) δ 2.46 (3H, s), 2.56 (1H, dddd, *J*=11.2, 4.9, 4.3, and 4.3), 3.02 (1H, dd, *J*=14.4 and 11.2), 3.42 (3H, s), 3.46 (1H, dd, *J*=11.3 and 4.3), 3.52 (3H, s), 3.55 (1H, dd, *J*=11.3 and 4.3), 4.01 (1H, dd, *J*=14.4 and 4.9), 7.34 (2H, d, *J*=8.3), 7.70 (2H, d, *J*=8.3); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 21.71, 28.48, 33.90, 47.10, 48.99, 62.67, 116.2, 122.4, 128.2, 130.2, 134.3, 145.7, 149.7, 159.5; HRMS(FAB) *m/z*=380.1210. Calcd for ($C_{16}H_{20}N_4O_5S$ + H) *m/z*=380.1232.

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