A Facile Synthesis of [1,2,4]Triazino[3,2-*f*]purines and [1,2,4]Triazepino[3,2-*f*]purines

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[1,2,4]Triazino[3,2-*f*]purines **3a-e** and [1,2,4]triazepino[3,2-*f*]purine **5** were synthesized by the reaction of 7,8-diamino-1,3-dimethylxanthine **1** with diketones such as glyoxal, diacetyl, dibenzoyl, pyruvic aldehyde dimethyl acetal, phenylglyoxal or acetylacetone in acetic acid in the presence of boric acid or polyphosphoric acid.

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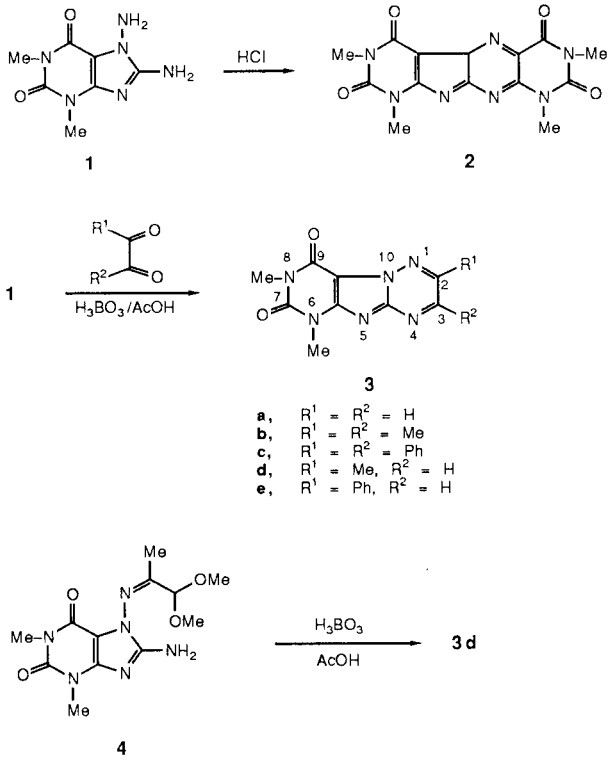
Previously we reported the synthesis of 2,4,7,9-tetramethylpurino[7,8-*g*]-6-azapteridine-1,3,8,10(2*H*,4*H*,7*H*,9*H*)-tetrone **2** by the reaction of 7,8-diamino-1,3-dimethylxanthine **1** with hydrochloric acid [2]. The mechanism of the formation of **2** was explained by the reaction of **1** with alloxan which was generated in part by hydrolysis and oxidation of **1**. Biological testing showed that compound **2** was active against P-388 leukemia. In connection with that work we were interested to synthesize [1,2,4]triazino[3,2-*f*]purines and [1,2,4]triazepino[3,2-*f*]purines which constitute a partial structure of **2**.

Scheme 1

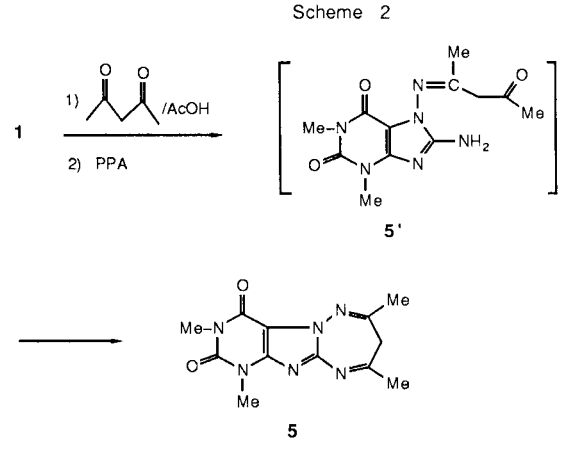


a, $R^1 = R^2 = H$
b, $R^1 = R^2 = Me$
c, $R^1 = R^2 = Ph$
d, $R^1 = Me$, $R^2 = H$
e, $R^1 = Ph$, $R^2 = H$

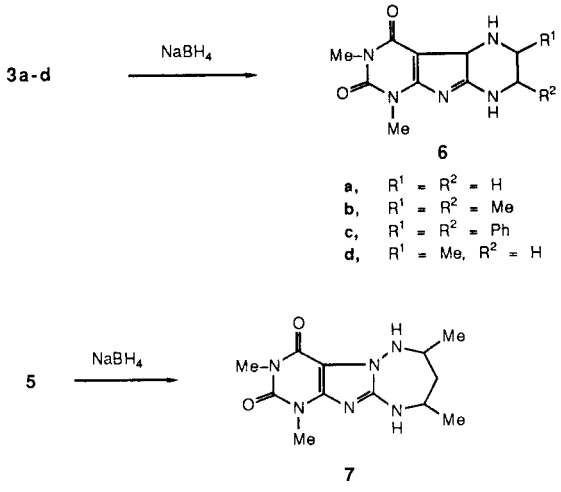
We report here a facile synthesis of [1,2,4]triazino[3,2-*f*]-purines and [1,2,4]triazepino[3,2-*f*]purines [3] by the reaction of **1** with diketones such as glyoxal, diacetyl, dibenzoyl, pyruvic aldehyde dimethyl acetate, phenylglyoxal or acetylacetone.

The reaction of **1** with glyoxal in acetic acid in the presence of boric acid [4] gave 6,8-dimethyl[1,2,4]triazino-[3,2-*f*]purine-7,9(6*H*,8*H*)-dione **3a** in 77% yield. Similarly, the reaction of **1** with diacetyl, dibenzoyl, pyruvic aldehyde dimethyl acetal or phenylglyoxal was carried out to give 2,3-disubstituted 6,8-dimethyl[1,2,4]triazino[3,2-*f*]-purine-7,9(6*H*,8*H*)-diones **3b-d** in 46-96% yields. The proton nmr, ir, and mass spectra as well as analytical data agreed well with the assigned structures. Compound **3d** was also obtained from 8-amino-7-(2-dimethoxy-1-methylethylideneamino)-1,3-dimethylxanthine **4** [2] and this reaction confirmed that *C*-methyl group was substituted at C_2-position. As for the reaction of **1** with phenylglyoxal we failed to isolate the intermediate. However, we recognized previously that 7-amino group of **1** was more reactive than 8-amino group [2]. Thus, phenyl group of **3e** seems to be at the C_2-position. The reaction of **3a** with benzoylperoxide

Scheme 2



Scheme 3



in benzene also gave **3e**. Physicochemical and spectral data are listed on Table I and II.

As for the synthesis of [1,2,4]triazepino[3,2-*f*]purines, the initial reaction of **1** with acetylacetone in acetic acid in the presence of boric acid gave 2,4,7,9-tetramethyl-3*H*-[1,2,4]-triazepino[3,2-*f*]purine-8,10(7*H*,9*H*)-dione **5** in a trace amount. The major product seemed to be 8-amino-7-(1-methyl-3-oxobutylidene)amino-1,3-dimethylxanthine **5'** from the measurement of mass spectra [m/z, 292 (M^+)]. However attempt to purify **5'** for the analytical grade was failure. Thus, compound **5'** was used to the next reaction without further purification. Treatment of **5'** with polyphosphoric acid (PPA) [5] gave **5** in 61% yield. The proton nmr, ir, and mass spectra as well as elemental analyses agreed well with the assigned structure.

Compounds **3a-d** were readily hydrogenated with sodium borohydride in dioxane to give 2,3-disubstituted

Table I

2,3-Disubstituted 6,8-Dimethyl[1,2,4]triazino[3,2-*f*]purine-7,9(6*H*,8*H*)-diones **3**

Compound No.	Mp °C	Yield (%)	Molecular Formula	Analyses (%) Calcd. C	H	N	Found C	H	N
3a	286-288 [a]	77	$C_9H_8N_6O_2$ 232.20	46.55	3.47	36.20	46.46	3.32	36.56
3b	269-272 [a]	61	$C_{11}H_{12}N_6O_2$ 260.25	50.76	4.65	32.30	51.00	4.42	32.43
3c	270 dec [b]	46	$C_{21}H_{16}N_6O_2$ 384.39	65.62	4.20	21.87	65.67	3.95	21.88
3d	211-215 [b]	70	$C_{10}H_{10}N_6O_2$ 246.23	48.78	4.09	34.14	48.63	3.85	34.43
3e	>290 [c]	96	$C_{15}H_{12}N_6O_2$ 308.29	58.44	3.92	27.26	58.15	3.70	26.99

[a] Recrystallized from 2-propanol. [b] Recrystallized from ethanol. [c] Recrystallized from chloroform.

Table II

Mass, ^{1}H-NMR and IR Spectral Data of **3**

Compound No.	MS m/z (M^+)	^{1}H-NMR (δ ppm) [a] N_6-CH_3	N_8-CH_3	C_2-CH_3	C_3-CH_3	C_2-H	C_3-H	IR (cm^{-1}) CONH	
3a	232	3.42	3.52			8.62	8.62	1700,	1670
3b	260	3.48	3.68	2.70	2.70			1720,	1680
3c	384	3.52	3.68					1720,	1680
3d	246	3.48	3.72	2.68			8.52	1710,	1660
3e	308	3.54	3.64				9.12	1700,	1660

[a] Solvent, deuteriochloroform.

Table III

2,3-Disubstituted 6,8-Dimethyl-1,2,3,4-tetrahydro[1,2,4]triazino[3,2-*f*]purine-7,9(6*H*,8*H*)-diones **6**

Compound No.	Mp °C	Yield (%)	Molecular Formula	Analyses (%) Calcd. C	H	N	Found C	H	N
6a	263-266 [a]	65	$C_9H_{12}N_6O_2$ 236.23	45.76	5.12	35.58	45.88	5.01	35.19
6b	232-235 [b]	85	$C_{11}H_{16}N_6O_2$ 264.29	49.99	6.10	31.80	50.03	5.82	31.58
6c	197-198 [c]	85	$C_{21}H_{20}N_6O_2$ 388.42	64.93	5.19	21.64	64.79	4.88	21.91
6d	229-232 [c]	91	$C_{10}H_{14}N_6O_2$ 250.26	47.99	5.64	33.58	48.08	5.26	33.54

[a] Recrystallized from 2-propanol. [b] Recrystallized from 2-propanol-ether (1:1). [c] Recrystallized from ether-ethanol (1:1).

Table IV

Mass, ^{1}H-NMR and IR Spectral Data of **6**

Compound No.	MS m/z (M^+)	^{1}H-NMR (δ ppm) [a] N_6-CH_3	N_8-CH_3	C_2-CH_3	C_3-CH_3	IR (cm^{-1}) NH		CONH	
6a	236	3.20	3.36			3310,	3220	1770,	1640
6b	264	3.30	3.42	1.22	1.22	3300		1700,	1640
6c	388	3.32	3.52			3260,	3150	1690,	1640
6d	250	3.30	3.42	1.20		3210,	3320	1700,	1640

[a] Solvent, deuteriochloroform.

6,8-dimethyl-1,2,3,4-tetrahydro[1,2,4]triazino[3,2-*f*]-purine-7,9(6*H*,8*H*)-diones **6a-d** in 65-91% yields. Similarly, reduction of **5** with sodium borohydride in dioxane gave 2,4,7,9-tetramethyl-1,2,3,4,5-pentahydro[1,2,4]-triazepino[3,2-*f*]purine-8,10(7*H*,9*H*)-dione **7** in 75% yield.

Consequently synthesis of [1,2,4]triazino[3,2-*f*]purines and [1,2,4]triazepino[3,2-*f*]purines has been accomplished in a simple method.

Antitumor activity test on P-388 lymphocytic leukemia was carried out for **3a-d**. However none showed significant activity.

EXPERIMENTAL

All melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. The infrared spectra were measured with a JASCO IR-810 spectro photometer. Mass spectra were measured with a JEOL JMS-DX 300 spectrometer. Proton nuclear magnetic resonance spectra were recorded with a JEOL JNM-MH-100 or JNM-FX-100 spectrometer using tetramethylsilane as an internal standard. Abbreviations are as follows: s, singlet; d, doublet; q, quartet; br, broad; m, multiplet.

General Procedure for the Synthesis of 2,3-Disubstituted 6,8-Dimethyl-[1,2,4]triazino[3,2-*f*]purine-7,9(6*H*,8*H*)-diones **3a-e**.

A mixture of 7,8-diamino-1,3-dimethylxanthine **1** (2.5 mmoles), diketone (25 mmoles), boric acid (1.5 g) and acetic acid (30 ml) was heated at 100° for 5-30 minutes under stirring. The solvent was distilled off. Water was added to the residue and extracted with chloroform. The extract was dried and condensed to obtain crystals which were recrystallized from pertinent solvents (Table I).

Synthesis of **3d** from 8-Amino-7-(2-dimethoxy-1-methylethylideneamino)-1,3-dimethylxanthine **4**.

A mixture of **4** (60 mg), boric acid (120 mg) and acetic acid (2 ml) was heated at 100° for 7 minutes. Acetic acid was distilled off. Water was added to the residue and extracted with chloroform. The extract was dried over anhydrous magnesium sulfate. Chloroform was distilled off and the residue was purified by silica gel chromatography, yield 44 mg (92%).

Synthesis of **3e** from **3a**.

A mixture of **3a** (50 mg), benzoyl peroxide (60 mg) and benzene (3 ml) was refluxed for 16 hours. The solvent was distilled off and the residue was purified by preparative thin layer chromatography to give **3e**, yield 12 mg (18%).

2,4,7,9-Tetramethyl-3*H*-[1,2,4]triazepino[3,2-*f*]purine-8,10(7*H*,9*H*)-dione **5**.

A solution of **1** (0.5 g) and acetyl acetone (5 g) in acetic acid (10 ml) was heated at 100° for 10 minutes under stirring. The solvent was distilled off. The residue was washed with ether. Polyphosphoric acid (5 g) was added and the mixture was heated at 100° for 5 minutes with stirring. The reaction mixture was poured into ice-water and extracted with chloroform. The extract was dried over anhydrous magnesium sulfate. The solvent was distilled off and the residue was treated by column chroma-

tography on silica gel. Chloroform eluate was collected and the solvent was distilled off. The residue was recrystallized from ether-ethanol (1:1) to give pale yellow crystalline powder of mp 215° dec, yield 398 mg (61%); ir (potassium bromide): ν max 1710, 1660 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): δ 2.38 (3H, s, C-Me), 2.46 (3H, s, C-Me), 3.40 (3H, s, N-Me), 3.60 (3H, s, N-Me), 3.28 (2H, s, CH_2); ms: m/z 274 (M^+).

Anal. Calcd. for $C_{12}H_{14}N_6O_2$: C, 52.54; H, 5.15; N, 30.64. Found: C, 52.11; H, 4.87; N, 30.61.

General Procedure for the Synthesis of 2,3-Disubstituted 6,8-Dimethyl-1,2,3,4,-tetrahydro[1,2,4]triazino[3,2-*f*]purine-7,9(6*H*,8*H*)-diones **6a-d**.

Sodium borohydride (15 mmoles) was added to a solution of **3a-d** (1 mmole) in dioxane (80 ml). The mixture was stirred at 15-20° for 4 hours. The solvent was distilled off. Water was added to the residue, which was extracted with chloroform. The extract was dried and condensed to obtain crystals which were recrystallized from pertinent solvents.

2,4,7,9-Tetramethyl-1,2,3,4,5-pentahydro[1,2,4]triazepino-[3,2-*f*]-purine-8,10(7*H*,9*H*)-dione **7**.

Sodium borohydride (500 mg) was added to a solution of **5** (274 mg, 1 mmole) in dioxane (80 ml). The mixture was stirred for 4 hours at room temperature. The solvent was distilled off and water was added to the residue, which was extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and the solvent was distilled off. The residue was recrystallized from 2-propanol to give colorless prisms of mp 257-260°, yield 210 mg (75%); ir (potassium bromide): ν max 3300 cm^{-1} (NH), 1690, 1650 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): δ 1.24 (6H, s, 2x C-Me), 1.88 (2H, m, CH_2), 3.36 (3H, s, N-Me), 3.44 (3H, s, N-Me), 3.71 (2H, m, 2x -CH-), 4.68 (1H, b, NH), 6.04 (1H, b, NH); ms: m/z 278 (M^+).

Anal. Calcd. for $C_{12}H_{18}N_6O_2$: C, 51.78; H, 6.52; N, 30.20. Found: C, 51.76; H, 6.49; N, 30.39.

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REFERENCES AND NOTES

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[5] This reagent was purchased from Wako Co Ltd.