FACILE SYNTHESIS OF 6-ARYL-1,3-DIMETHYL-5*H*-PYRIMIDO-[4,5-*b*][1,4]DIAZEPINE-2,4(1*H*,3*H*)-DIONES

Shahriyar TAGHAVI-MOGHADAM, Rüdiger STUMPF, Helmut FISCHER[1] and Wolfgang PFLEIDERER[2,*]

Faculty of Chemistry, University of Constance, P.O. Box 5560, D-78434 Constance, Germany; e-mail: [1] hfischer@dgG.chemie.uni-konstanz.de, [2] wolfgang.pfleiderer@uni-konstanz.de

Received September 4, 1998
Accepted December 12, 1998

In the memory of Dr Miroslav Protiva and in admiration of his contributions to heterocyclic chemistry.

A facile procedure for the preparation of 6-aryl-1,3-dimethyl-5*H*-pyrimido[4,5-*b*][1,4]diazepine-2,4(1*H*,3*H*)-diones **8**, **9** from 6-amino-5-arylideneamino-1,3-dimethyluracils **1**, **2** and triethyl orthoacetate (**3**) in a two-step reaction *via* 6-aryl-8-ethoxy-6,7-dihydro-1,3-dimethyl-5*H*-pyrimido[4,5-*b*][1,4]diazepine-2,4(1*H*,3*H*)-diones **6**, **7** is described. Condensation of **1** with diethoxymethyl acetate (**10**) resulted in the formation of (1,3-dimethyl-2,6-(1*H*,3*H*)-dioxopurin-7-yl)(phenyl)methyl acetate (**11**) and a small amount of 1,3-dimethyl-6-phenyl-pyrazino[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**12**). The structures of **6** and **11** were unambiguously confirmed by single-crystal X-ray diffraction analysis.

Key words: Orthoester condensation; Crystal structure; Purines; Pyrimidines; Pteridines; Pyrimido[4,5-*b*][1,4]diazepines.

The pyrimido[4,5-*b*][1,4]diazepine ring system occurs rarely in nature and has not been studied very extensively so far. Two types of this natural heterocyclic system have been discovered, both in *Drosophila melanogaster*. These studies show that the 6-acetyl-2-amino-7,8-dihydro-9*H*-pyrimido-[4,5-*b*][1,4]diazepin-4(3*H*)-one (6-acetyldihydrohomopterin)[1–4] functions as a biogenetic precursor of the more complex pentacyclic red eye pigments known as drosopterin[5], aurodrosopterin[6] and neodrosopterin[7]. The first synthesis of a pyrimido[4,5-*b*][1,4]diazepine based on condensation of a 4,5-diaminopyrimidine with ethyl acetoacetate was reported by Cheng *et al.*[8] in 1965. A photochemical approach using 6-azido-1,3-dimethyl uracil was developed by Senda[9], but the classical synthetic route involves condensations of 4,5-diaminopyrimidines with 1,3-dicarbonyl compounds[10] analogous to the Gabriel–Isay pteridine synthesis[11]. Problems regarding the

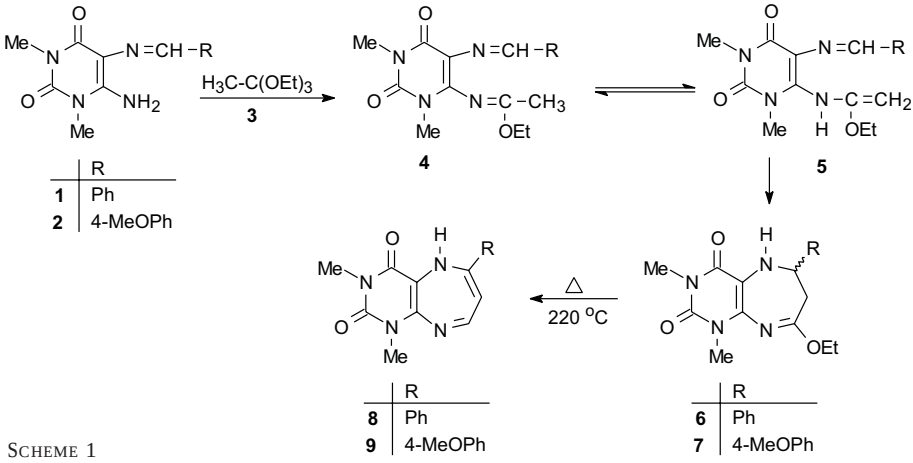
regioselectivity arise in condensations with unsymmetrical 1,3-dicarbonyl derivatives leading commonly to 6- and 8-substituted isomeric mixtures. Unambiguous approaches were demonstrated by Ayling *et al.*[12] as well as by Boyle[4] applying a Polonovski–Boon[11] type method.

In this paper, we would like to report a new approach to the regioselective synthesis of 6-aryl-1,3-dimethylpyrimido[4,5-*b*][1,4]diazepine-2,4(1*H*,3*H*)-diones starting from simply accessible 6-amino-5-benzylideneaminopyrimidines.

During our studies of new variations in the pteridine synthesis[13], we investigated the possibility of condensing a one-carbon unit with a 6-amino-5-arylideneaminopyrimidine to form the corresponding 6-arylpteridine derivative in a regioselective manner. This condensation, termed according to early findings in Japan[15] the Yoneda reaction[14], works especially well in the 6-amino-5-arylideneamino-1,3-dimethyluracil series with orthoesters and amide acetals, to give 6-aryl-1,3-dimethylpyrazino-[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones. An analogous condensation between 6-amino-5-arylideneamino-1,3-dimethyluracils (**1**) and triethyl orthoacetate (**2**) described by Yoneda and Higuchi[15] proceeds in a similar manner. The first isolated reaction product was assigned an open-chain 6-(1-ethoxyethylideneamino)uracil structure **4** due to the fact that the thermal cyclizations allegedly resulted in the formation of 6-aryl-1,3,7-trimethylpyrazino[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones. Unfortunately, only melting points and elemental analyses were reported whereas common analytical tools such as ^{1}H NMR and UV spectra clearly indicated that the constitutions of the proposed intermediates **4** and the end products have to be revised. Their spectroscopic properties are consistent with the isomeric 8-ethoxy-6,7-dihydro-1,3-dimethyl-6-phenyl-5*H*-pyrimido[4,5-*b*][1,4]-diazepine-2,4(1*H*,3*H*)-dione (**6**) structure, which can be explained by the primary formation of 5-arylmethylenamino-6-(1-ethoxyethylideneamino)uracil (**4**), followed by tautomerization to the enamine form **5** and subsequent cyclization to pyrimido[4,5-*b*][1,4]diazepines **6**, **7** by enamine addition across the neighbouring imine double bond at position 5. Furthermore, single crystal X-ray diffraction analysis of compound **6** unambiguously confirmed the proposed new structure (Fig. 1, Scheme 1).

Heating of the pyrimido[4,5-*b*][1,4]diazepines **6**, **7** to 220 °C for 1 h led to elimination of EtOH and formation of stable heteroaromatic 6-aryl-1,3-dimethyl-5*H*-pyrimido[4,5-*b*][1,4]diazepines **8**, **9**. The structural assignment of these compounds was based on NMR evidence. The ^{1}H NMR spectra of **8** and **9** in DMSO-d_6 showed the presence of one NH as a singlet signal at 13.50–13.70 ppm which was proved by a deuterium exchange ex-

periment. This clearly indicates that compounds **8** and **9** exist in solution in the 5*H* and not the 9*H* tautomeric form and also excludes the 6-methylene tautomers as stated by Fukushima *et al.*[16] for 6,8-disubstituted pyrimido[4,5-*b*][1,4]diazepines. A straighforward assignment of the pyrimido[4,5-*b*][1,4]diazepines structure could be achieved by 2D HMQC NMR spectra from which the heteronuclear coupling of C–H nuclei in the diazepine ring can be depicted unambiguously (Fig. 2).



SCHEME 1

Additionally, we have also been interested in the reaction of 6-amino-5-benzylideneamino-1,3-dimethyluracil (**1**) with diethoxymethyl acetate (**10**) as a more reactive reagent for the preparation of lumazine derivatives under mild reaction conditions. Diethoxymethyl acetate (**10**) was

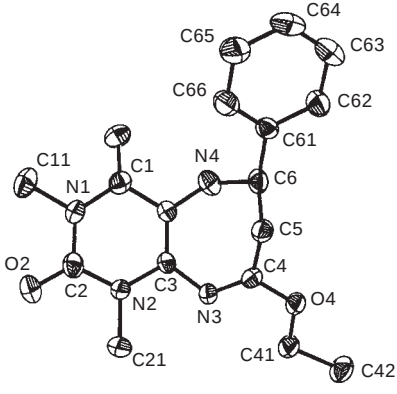
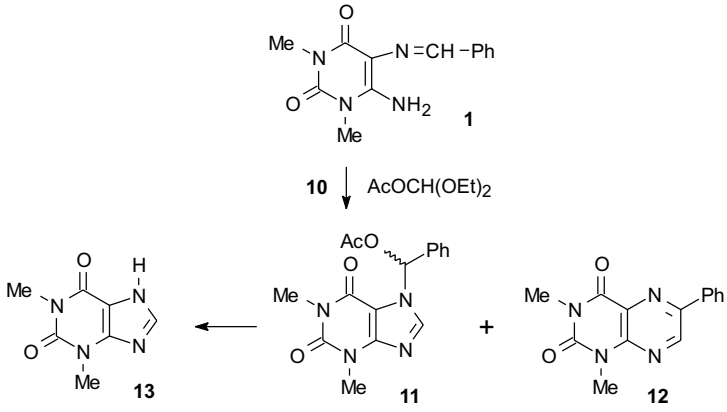


FIG. 1
ORTEP representation of 8-ethoxy-6,7-dihydro-1,3-dimethyl-6-phenyl-5*H*-pyrimido[4,5-*b*][1,4]-diazepine-2,4(1*H*,3*H*)-dione (**6**)

already used by Montgomery and Temple[13,14] for the cyclization of 4,5-diaminopyrimidines to purines. Reaction of 6-amino-5-benzylideneamino-1,3-dimethyluracil (**1**) with diethoxymethyl acetate (**10**) afforded a mixture giving (1,3-dimethyl-2,6(1*H*,3*H*)-dioxopurin-7-yl)(phenyl)methyl acetate (**11**) in 71% yield and 1,3-dimethyl-6-phenylpyrazino[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**12**) as a by-product in 5% yield. Compound **11** could also be obtained in 73% isolated yield on treatment of **1** with an excess of a mixture of triethyl orthoformate and acetic anhydride (Scheme 2).



SCHEME 2

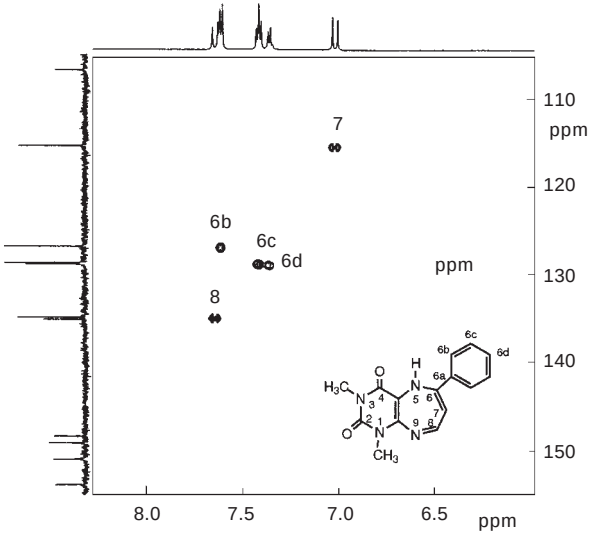


FIG. 2
2D HMQC NMR spectrum ((DMSO-d_6) of 1,3-dimethyl-6-phenyl-5*H*-pyrimido[4,5-*b*][1,4]-diazepine-2,4(1*H*,3*H*)-dione (**8**)

The structure of theophylline derivative **11** was confirmed by usual spectroscopic methods (^{1}H NMR, UV and MS) and elemental analysis. Basic and acid hydrolysis of **11** at room temperature afforded theophylline (**13**) due to the sensitive acylated hemiacetal structure of the 7-substituent. Additionally, the structure of compound **11** was again confirmed by a single-crystal X-ray diffraction analysis (Fig. 3).

Crystallographic data of compounds **6** and **11** are summarized in Table I.

EXPERIMENTAL

Melting points were measured on a Gallenkamp apparatus and are uncorrected. UV/VIS spectra were recorded on a Perkin–Elmer Lambda 5 spectrometer, λ_{max} in nm ($\log \varepsilon$). ^{1}H NMR spectra were measured on Brucker AC 250 and DRX 600 instruments using TMS or residual $CHCl_3$ and DMSO as internal standards. Chemical shifts are given in ppm (δ-scale) and coupling constants (*J*) in Hz. Flash chromatography (FC) was performed on silica gel (Baker, 30–60 μm) and TLC on precoated silica gel TLC sheets (Schleicher and Schüll, FS 1500 254).

8-Ethoxy-6,7-dihydro-1,3-dimethyl-6-phenyl-5*H*-pyrimido[4,5- *b*][1,4]diazepine-2,4(1*H*,3*H*)-dione (**6**)

To a solution of 6-amino-5-benzylideneamino-1,3-dimethyluracil[19] (**1**; 1.3 g, 5.0 mmol) in dry DMF (10 ml), triethyl orthoacetate (**2**; 8.10 g, 50 mmol) was added and the mixture was refluxed for 8 h. The solvent was evaporated under reduced pressure and the residue crystallized from EtOH (5 ml). The light-yellow precipitate was collected, washed with Et_2O, and dried to give 1.0 g (60%) of chromatographically pure material, m.p. 187–189 °C (ethanol). For $C_{17}H_{20}N_4O_3$ (328.4) calculated: 62.18% C, 6.14% H, 17.06% N; found: 62.18% C, 6.29% H, 17.27% N. UV (MeOH): 222 (4.29), 345 (3.88). ^{1}H NMR ($CDCl_3$): 7.34 m, 5 H (arom. H); 5.13 m, 1 H (H-6); 4.30 q, 2 H, *J* = 7.2 ($CH_3C\mathbf{H}_2O$); 4.21 s, 1 H (NH); 3.45 s, 3 H, (Me–N(1)); 3.44 s, 3 H (Me–N(3)); 2.78 m, 1 H, (H-7); 2.62 m, 1 H, (H-7); 1.34 t, 3 H, *J* = 7.2 ($C\mathbf{H}_3CH_2O$).

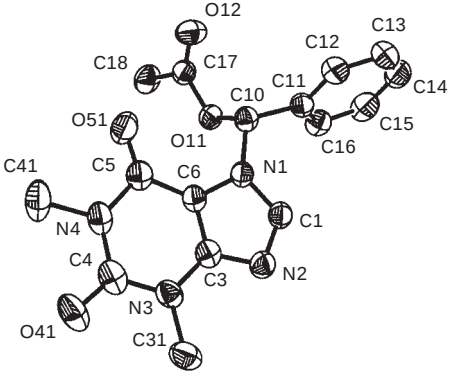


FIG. 3
ORTEP representation of (1,3-dimethyl-2,6(1*H*,3*H*)-dioxopurin-7-yl)(phenyl)methyl acetate (**11**)

8-Ethoxy-6,7-dihydro-6-(4-methoxyphenyl)-1,3-dimethyl-5*H*-pyrimido[4,5-*b*][1,4]-diazepine-2,4(1*H*,3*H*)-dione (**7**)

To a solution of 6-amino-5-(4-methoxybenzylideneamino-1,3-dimethyluracil[19] (**2**; 1.4 g, 4.86 mmol) in dry DMF (10 ml), triethyl orthoacetate (**3**; 8.10 g, 50 mmol) was added and the mixture was refluxed for 8 h. The mixture was evaporated to dryness in high vacuum and the residue was treated with Et_2O (15 ml) to form crystals. The yellowish powder was collected, washed with Et_2O, and dried to give 1.37 g (83%) of chromatographically pure material. A part of of the crude product (1.0 g) was recrystallized from ethanol (40 ml) to give 0.82 g of yellowish crystals, m.p. 152–156 °C. For $C_{18}H_{22}N_4O_4$ (358.4) calculated: 60.32% C, 6.19% H, 15.63% N; found: 60.58% C, 6.03% H, 15.87% N. UV (MeOH): 221 (4.35), 346 (3.97). ^{1}H NMR ($CDCl_3$): 7.27 d, 2 H (H-3′, H-5′); 6.87 d, 2 H (H-2′,H-6′); 5.05 m, 1 H (H-6); 4.30 q, 2 H, *J* = 7.1 ($CH_3C\mathbf{H}_2O$); 4.15 s, 1 H (NH); 3.80 s, 3 H (MeO); 3.45 s, 3 H (Me–N(1)); 3.43 s, 3 H (Me–N(3)); 2.78 m, 1 H (H-7); 2.62 m, 1 H (H-7); 1.34 t, 3 H, *J* = 7.1 ($C\mathbf{H}_3CH_2O$).

1,3-Dimethyl-6-phenyl-5*H*-pyrimido[4,5-*b*][1,4]diazepine-2,4(1*H*,3*H*)-dione (**8**)

Compound **6** (100 mg, 0.30 mmol) was heated in an oil bath to 220 °C for 2 h. The originally yellowish melt was slowly converted into a yellow-brownish solid. The residue was

TABLE I
Crystal data of compounds **6** and **11**

	6	**11**
Empirical formula	$C_{17}H_{20}N_4O_3$	$C_{16}H_{16}N_4O_4$
Color; habit	colorless needles	colorless needles
Crystal size, mm	0.3 × 0.3 × 0.3	0.5 × 0.5 × 0.5
Crystal system	orthorhombic	monoclinic
Space group	*Pbca*	$P2_1/n$
Unit cell dimensions	*a* = 31.495(6) Å	*a* = 12.012(4) Å
	b = 12.912(3) Å	*b* = 8.257(3) Å
	c = 7.8150(10) Å	*c* = 16.525(4) Å
		β = 110.11(2)°
Volume	3 177.9(10) Å^3	1 539.1(9) Å^3
Z	8	4
Formula weight	328.21	328.33
Density (calculated)	1.373 g cm^{-3}	1.417 g cm^{-3}
Absorption coefficient	0.090 mm^{-1}	0.098 mm^{-1}
F(000)	1 392	688

recrystallized from a mixture of DMF (4 ml) and water (1 ml) to give 44 mg (51%) of colourless solid **8**, m.p. >300 °C. For $C_{15}H_{14}N_4O_2$ (282.3) calculated: 63.82% C, 5.00% H, 19.85% N; found: 63.61% C, 5.06% H, 19.83% N. UV (MeOH): 262 (4.14), 340 (4.51). ^{1}H NMR (DMSO-d_6): 13.61 s (NH); 7.64 d, 1 H, *J* = 16.4 (H-8); 7.62 m, 2 H (arom. H); 7.40 m, 3 H (arom. H); 7.03 d, 1 H, *J* = 16.4 (H-7); 3.47 s, 3 H (Me–N(1)); 3.25 s, 3 H (Me–N(3)).

1,3-Dimethyl-6-(4-methoxyphenyl)-5*H*-pyrimido[4,5-*b*][1,4]diazepine-2,4(1*H*,3*H*)-dione (**9**)

Compound **7** (100 mg, 0.28 mmol) was heated at 220 °C in an oil bath for 2 h. The resulting solid was recrystallized from DMF (4 ml) to give 42 mg (48%) of **9** as a yellowish crystal powder, m.p. >300 °C. For $C_{16}H_{16}N_4O_3$ (312.3) calculated: 61.53% C, 5.16% H, 17.94% N; found: 61.23% C, 5.38% H, 18.14% N. UV (MeOH): 269 (3.94), 340 (4.49). ^{1}H NMR (DMSO-d_6): 13.47 s (NH); 7.60 d, 1 H, *J* = 16.4 (H-8); 7.56 m, 2 H (arom. H); 6.97 m, 3 H (arom. H); 6.86 d, 12 H, *J* = 16.4 (H-7); 3.87 s, 3 H (MeO); 3.46 s, 3 H (Me–N(1)); 3.23 s, 3 H (Me–N(3)).

(1,3-Dimethyl-2,6(1*H*,3*H*)-dioxopurin-7-yl)(phenyl)methyl Acetate (**11**)

Method A: A mixture of 6-amino-5-benzylideneamino-1,3-dimethyluracil[19] (**1**; 0.3 g, 1.16 mmol) and diethoxymethyl acetate[17] (**10**; 3 ml) was stirred for 20 min at room temperature and then heated at 100 °C for 2 h. After evaporation, the residue was purified by FC (toluene–AcOEt 95 : 5 to 1 : 1) to give 16 mg (5%) of **12** as a yellowish powder, m.p. 258 °C (ref.[20]) and 0.27 g (71%) of **11** as a colourless material, m.p. 140–143 °C. For $C_{16}H_{16}N_4O_4$ (328.3) calculated: 58.53% C, 4.91% H, 17.06% N; found: 58.57% C, 5.03% H, 16.63% N. UV (MeOH): 275 (3.92). ^{1}H NMR (DMSO-d_6): 8.25 s, 1 H (CH–O); 8.10 s, 1 H (H-8); 7.45 m, 5 H (arom. H); 3.41 s, 3 H (Me–N(1)); 3.20 s, 3 H (Me–N(3)); 2.19 s, 3 H (OAc).

Method B: 6-Amino-5-benzylideneamino-1,3-dimethyluracil[19] (**1**; 1.0 g, 3.87 mmol) was added to a mixture of triethyl orthoformate (3.5 ml, 21 mmol) and acetic anhydride (2 ml, 21 mmol) and heated, first at 100 °C for 1 h followed by refluxing overnight. After cooling to room temperature, the mixture was evaporated to dryness and the residue crystallized from ethanol (5 ml) to give 0.92 g (73%) of **11**, m.p. 141–143 °C. The product was chromatographically and spectroscopically identical with the substance from method *A*.

Theophylline (**13**)

Method A: A suspension of compound **11** (0.5 g, 1.52 mmol) in a saturated solution of hydrogen chloride in methanol (15 ml) was stirred at room temperature overnight. The mixture was evaporated, the residue suspended in water (5 ml) and ethanol (1 ml) and then neutralized by 1 M aqueous ammonia. The resulting precipitate was collected, washed with water, and dried in a vacuum desiccator over phosphorus pentoxide to yield 0.21 (78%) of **13** as a colourless material, m.p. 270 °C. The product was identical in all respects with an authentic sample.

Method B: A suspension of compound **11** (0.5 g, 1.52 mmol) in a saturated solution of methanolic ammonia (15 ml) and was stirred overnight. The suspension was evaporated, the residue treated with water (5 ml) and ethanol (1 ml) and then neutralized by 2 M hydrochloric acid. The precipitate was collected, washed with water and dried at 100 °C to yield 0.19 (70%) of **13** as a colourless crystalline powder, m.p. 270 °C.

X-Ray Structure Analyses of **6** and **11**

Crystal data and parameters of the data collection are compiled in Table I. Single crystals were grown from $CHCl_3$–pentane (compound **6**), or from MeOH–Et_2O (compound **11**) and mounted in a glass capillary. All crystal data were collected on a Siemens R3m/V diffractometer (Wyckoff scan, scan range $4° < 2\theta < 54°$, scan speed variable, 2.0 to 29.3° min^{-1} in ω) with a graphite monochromator (MoKα, $\lambda = 0.71073$). The structures were solved by direct methods using the Siemens SHELXTL PLUS program package. The positions of the hydrogen atoms were calculated by assuming ideal geometry ($d_{C-H} = 0.96$ Å) and their coordinates were refined, together with the attached carbon atoms, as a "riding model". The positions of all other atoms were refined anisotropically by full-matrix least-squares techniques. Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC-115863 (**6**) and CCDC-115864 (**11**). Copies of the data can be obtained free of charge on application to CCDC, e-mail: deposit@ccdc.ca.ac.uk.

We thank Dr A. Geyer for the NMR spectroscopic studies and the interpretation of the spectra. We are also grateful to the Analytical Laboratory of the Department of Chemistry, University of Constance, for elemental analyses.

REFERENCES

1. Wilson T. G., Jacobson K. B.: *Biochem. Genet.* **1977**, *15*, 307.
2. Wiederrecht G. J., Paton D. R., Brown G. M.: *J. Biol. Chem.* **1981**, *256*, 10399.
3. Jacobson K. B., Dorsett D., Pfleiderer W., McCloskey J. A., Sethi S. K., Buchanan M. W.: *Biochemistry* **1982**, *21*, 5700.
4. Boyle P. H., Hughes E. M., Khattab H. A., Lockhart R. J.: *J. Chem. Soc., Perkin Trans. 1*, **1990**, 2071.
5. Theobald N., Pfleiderer W.: *Chem. Ber.* **1978**, *111*, 3385.
6. Yim J., Kim S., Walcher G., Pfleiderer W.: *Helv. Chim. Acta.* **1993**, *76, 1970.*
7. Rokos K., Pfleiderer W.: *Chem. Ber.* **1975**, *108*, 2728.
8. Nyberg W. H., Noell C. W., Cheng C. C.: *J. Heterocycl. Chem.* **1965**, *2*, 110.
9. Senda S., Hirota K., Asao T., Maruhashi K.: *J. Am. Chem. Soc.* **1977**, *99*, 7358.
10. Fryer R. I. in: *Bicyclic Diazepine, The Chemistry of Heterocyclic Compounds* (E. C. Taylor, Ed.), p. 325. Wiley, New York 1991.
11. Brown D. J. in: *The Chemistry of Heterocyclic Compounds* (E. C. Taylor, Ed.), Vol. 24, Part 3. Wiley, New York 1988.
12. Pike D. C., Hora M. T., Bailey S. W., Ayling J. E.: *Biochemistry* **1986**, *25*, 4762.
13. Pfleiderer W., Blank U.: *Angew. Chem.* **1968**, *80*, 534.
14. Taghavi-Moghadam S., El-Kalyoubi S., Pfleiderer W.: *Pteridines* **1997**, *8*, 50.
15. Yoneda F., Higuchi M.: *J. Chem. Soc., Perkin Trans. 1* **1977**, 1336.
16. Fukushima S., Ueno A., Noro K., Iwagaya K., Noro T., Morinaga K., Akahori Y., Ishihara H., Saiki Y.: *Yakugaku Zasshi* **1977**, *97*, 52; *Chem. Abstr.* **1977**, *87*, 68305.
17. Montgomery J. A., Temple C.: *J. Am. Chem. Soc.* **1958**, *80*, 409.
18. Montgomery J. A., Temple C.: *J. Org. Chem.* **1960**, *25*, 395.
19. Traube W., Nithak W.: *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 227.
20. Angier R. B.: *J. Org. Chem.* **1963**, *28*, 1398.