Synthesis and Antiviral Evaluation of Several 6-(Methylene-carbomethoxy)pteridine-4,7(3*H*,8*H*)-diones

S. Molina, J. Cobo, A. Sánchez, and M. Nogueras
Departamento de Química Inorgánica y Orgánica, Universidad de Jaén, 23071 Jaén, Spain

E. de Clercq

Rega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium
Received October 12, 1998

The reactions of 5,6-diaminopyrimidin-4(3*H*)-one derivatives **1a-h**, with dimethyl acetylenedicarboxylate are discussed in this paper. 6-Amino-5-(*E*)(1',2'-dicarbomethoxyvinyl)aminopyrimidines, **2**, and 6-(methylenecarbomethoxy)pteridinones, **3**, have been obtained as main the products, which can be explained on the basis of a Michael addition on pyrimidine derivatives, and cyclization. Those compounds were evaluated for their *in vitro* antiviral activity.

J. Heterocyclic Chem., **36**, 435 (1999).

Introduction.

Polyaza-heteroaromatic analogues of those occurring naturally as pteridines have a great biological interest due to their widely pharmaceutic applications *i.e.* inhibitors of folate biosynthesis [1], anti-allergic [2], anti-inflammatory [3], anthelmintic [4], and in the treatment of hypotensive shock, Alzheimer's disease, atherosclerosis [5], *etc.*

We have focused our efforts on the preparation of pteridine derivatives starting from 5,6-diaminopyrimidines. Different 5,6-diaminopyrimidines reacting with aldehyde derivatives [6], α-ketoesters [6]; and 6-amino-5-nitro(or 5-phenylazo)-pyrimidines [7,8] with dimethyl acetylenedicarboxylate, have been previously reported for the synthesis of pteridine derivatives. However, there are no bibliographic references to be found starting from diaminopyrimidines and dimethyl acetylenedicarboxylate.

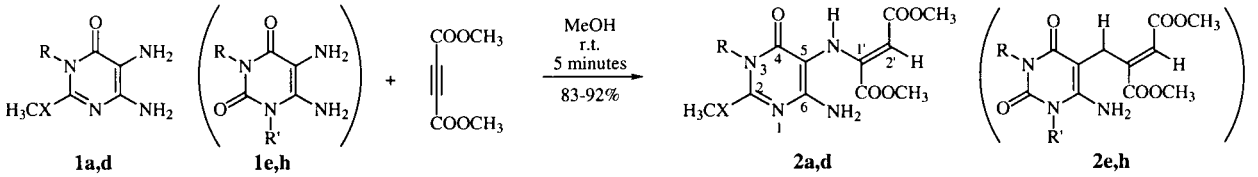
In this work, we present an efficient and facile procedure for the synthesis of several pteridine-4,7(3*H*,8*H*)-diones starting from 5,6-diaminopyrimidin-4(3*H*)-ones and dimethyl acetylenedicarboxylate. These reactions have two points of interest: first, to obtain and test new derivatives with potential biological applications and second to explore the reactivity of 5,6-diaminopyrimidin-4(3*H*)-ones with electron-deficient alkynyl compounds. In previous papers, we reported a study on the reactivity of several 6-amino and 6-glycosylaminopyrimidin-4(3*H*)-ones towards dimethyl acetylenedicarboxylate [9], resulting in 2-amino and 2-glycosylaminopyridines as the main products, which were formed from Diels-Alder/Retro Diels-Alder reactions. These pyridine derivatives were used to prepare several pyrrolo[3,4-*c*]pyridine-1,3(2*H*)-dione and pyrido[3,4-*d*]-pyridazine-1,4(2*H*,3*H*)-dione derivatives [10].

Results and Discussion.

The synthesis of the pteridine derivatives was carried out starting from several 5,6-diaminopyrimidines. These were 5,6-diamino-2-methoxy- and 2-methylthiopyrimidin-4(3*H*)-one **1a,b** and their *N*(3)-methyl derivatives **1c,d**, as

Scheme 1

Reaction of 5,6-Diaminopyrimidin-4(3*H*)-one Derivatives **1a-h** with Dimethyl Acetylenedicarboxylate and Cyclization of 6-Amino-5-(*E*)(1,2-dicarbomethoxyvinyl)aminopyrimidines **2a-h** to 6-(Methylenecarbomethoxy)pteridine-4,7(3*H*,8*H*)-diones **3** in Refluxing Methanol



1-3	R	X	R'
a	H	O	-
b	H	S	-
c	CH_3	O	-
d	CH_3	S	-
e	H	-	H
f	CH_3	-	H
g	CH_3	-	CH_3
h	H	-	CH_3

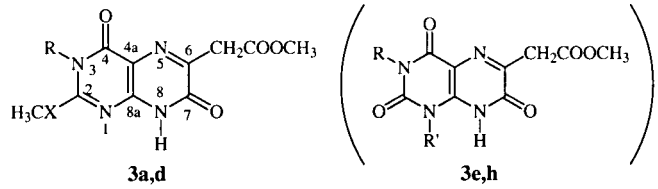


Table 1

Analytical and Spectroscopic Data for 6-Amino-5-(*E*)(1,2-dicarbomethoxyvinyl)aminopyrimidines Derivatives **2**

Compound	Yield (%)	mp [a] (°C)	Molecular Formula [b]	UV λ_{max} (log ε) MeOH	IR (potassium bromide) ν (cm^{-1})	MS m/z (%)
2a	88	225	$C_{11}H_{14}N_4O_6$	209 (4.23), 273 (4.14)	3480-2700, bs; 1740, s; 1680, s; 1615, s; 1440, s; 1276, s; 1218, s	298 (M^+, 23), 266 (61), 238 (52), 207 (100), 179 (76), 122 (44), 70 (63)
2b	91	220	$C_{11}H_{14}N_4O_5S$	214 (4.24), 229 (4.24) [c], 284 (4.11)	3500-2800, bs; 1738, s; 1680, s; 1647, s; 1323, w; 1276, s; 1219, s	313 (M^+, 3), 282 (78), 250 (100), 222 (94), 68 (55), 59 (50)
2e	90	212	$C_{12}H_{16}N_4O_6$	210 (4.27), 273 (4.08)	3500-2900, bs; 1742, s; 1671, s; 1628, s; 1560, s; 1440, w; 1276, s; 1224, s	312 (M^+, 62), 280 (33), 253 (78), 221 (100), 193 (70), 136 (43), 59 (43)
2d	91	210	$C_{12}H_{16}N_4O_4S$	220 (4.31), 293 (4.03)	3500-2900, bs; 1735, s; 1640, s; 1524, s; 1315, w; 1278, s; 1227, s	328 (M^+, 70), 296 (41), 269 (100), 237 (96), 209 (70), 59 (66)
2e	85	220	$C_{10}H_{12}N_4O_6$	203 (4.03), 271 (4.21)	3500-2900, bs; 1742, s; 1670, s; 1576, s; 1415, w; 1286, s; 1224, s	284 (M^+, 15), 252 (37), 220 (58), 207 (70), 78 (70), 59 (91), 43 (100)
2f	83	210	$C_{11}H_{14}N_4O_6$	208 (4.35), 275 (4.00), 328 (4.15)	3500-2900, bs; 1743, s; 1682, s; 1627, s; 1550, s; 1439, w; 1294, s; 1214, s	
2g	88	180	$C_{12}H_{16}N_4O_6$	211 (4.30), 277 (4.06), 328 (4.11)	3500-2900, bs; 1729, s; 1651, s; 1581, s; 1438, w; 1285, s; 1217, s	312 (M^+, 47), 280 (30), 253 (87), 221 (82), 193 (55), 57 (100), 42 (58)
2h	89	180	$C_{11}H_{14}N_4O_6$	212 (4.30), 279 (4.03), 327 (4.11)	3500-2900, bs; 1734, s; 1641, s; 1578, s; 1438, w; 1288, s; 1220, s	298 (M^+, 1), 266 (42), 234 (100), 207 (22), 78 (57), 63 (72), 45 (51)

[a] Decomposition point. [b] Molecular formula determined by elemental analysis and ms spectrum. [c] Shoulder.

Table 2

Selected ^{1}H- and ^{13}C-NMR Data for 6-Amino-5-(*E*)(1,2-dicarbomethoxyvinyl)aminopyrimidines **2a-h**

Compound	^{1}H-NMR (dimethyl-d_6 sulfoxide) δ (ppm)	^{13}C-NMR (dimethyl-d_6 sulfoxide) δ (ppm)
2a	3.61 (s, 6H, COOC*H*$_3$), 3.80 (s, 3H, -OC*H*$_3$), 5.13 (s, 1H, C=C*H*), 6.55 [a] (s broad, 2H, -N*H*$_2$), 8.51 [a] (s broad, 1H, C_5-N*H*), 11.5 [a] (s broad, 1H, N(3)-*H*)	50.6 (C_2-COO*C*H$_3$), 52.2 (C_1-COO*C*H$_3$), 54.3 (-O*C*H$_3$), 87.6 (C=*C*H), 95.8 (C-5), 151.7 (*C*=CH), 154.4 (C-2), 156.9 (C-6), 159.7 (C-4), 163.1 (C_2-*C*OOCH$_3$), 169.41 (C_1-*C*OOCH$_3$)
2b	2.45 (s, 3H, -SC*H*$_3$), 3.62 (s, 6H, COOC*H*$_3$), 5.17 (s, 1H, C=C-*H*), 6.60 [a] (s broad, 2H, -N*H*$_2$), 8.56 [a] (s broad, 1H, C_5-N*H*), 11.8-12.2 [a] (s broad, 1H, N(3)-*H*)	12.7 (-S*C*H$_3$), 50.6 (C_2-COO*C*H$_3$), 52.2 (C_1-COO*C*H$_3$), 88.0 (C=*C*H), 98.1 (C-5), 150.9 (*C*=CH), 155.9 (C-6), 159.2 (C-4), 163.0 (C_2-*C*OOCH$_3$), 166.9 (C-2), 169.3 (C_1-*C*OOCH$_3$)
2c	3.05 (s, 3H, N(3)-C*H*$_3$), 3.56 (s, 6H, COOC*H*$_3$), 3.83 (s, 3H, -OC*H*$_3$), 5.13 (s, 1H, C=C*H*), 6.41 [a] (s broad, 2H, -N*H*$_2$), 8.49 [a] (s broad, 1H, C_5-N*H*)	27.9 (N(3)-*C*H$_3$), 51.1 (C_2-COO*C*H$_3$), 52.6 (C_1-COO*C*H$_3$), 55.5 (-O*C*H$_3$), 91.9 (C=*C*H), 97.7 (C-5), 151.9 (*C*=CH), 154.5 (C-2), 156.2 (C-6), 160.6 (C-4), 163.9 (C_2-*C*OOCH$_3$), 170.4 (C_1-*C*OOCH$_3$)
2d	2.48 (s, 3H, -SC*H*$_3$), 3.24 (s, 3H, N(3)-C*H*$_3$), 3.59, 3.61 (2s, 3H, 3H, COOC*H*$_3$), 5.18 (s, 1H, C=C*H*), 6.56 [a] (s broad, 2H, -N*H*$_2$), 8.60 [a] (s broad, 1H, C_5-N*H*)	14.2 (-S*C*H$_3$), 29.6 (N(3)-*C*H$_3$), 50.7 (C_2-COO*C*H$_3$), 52.4 (C_1-COO*C*H$_3$), 88.3 (C=*C*H), 97.7 (C-5), 151.0 (*C*=CH), 154.5 (C-6), 157.8 (C-2), 158.6 (C-4), 163.1 (C_2-*C*OOCH$_3$), 164.4 (C_1-*C*OOCH$_3$)
2e	3.63 (s, 6H, COOC*H*$_3$), 5.13 (s, 1H, C=C*H*), 6.32 [a] (s broad, 2H, -N*H*$_2$), 8.37 [a] (s broad, 1H, C_5-N*H*), 9.70-10.40 [a] (s broad, 2H, N(1,3)-*H*)	51.1 (C_2-COO*C*H$_3$), 52.7 (C_1-COO*C*H$_3$), 88.7 (C=*C*H), 90.6 (C-5), 149.8 (C-2), 149.8 (C-4), 156.8 (*C*=CH), 161.7 (C-6), 163.6 (C_2-*C*OOCH$_3$), 169.7 (C_1-*C*OOCH$_3$)
2f	3.01 (s, 3H, N(3)-C*H*$_3$), 3.63 (s, 6H, COOC*H*$_3$), 5.16 (s, 1H, C=C*H*), 6.96 [a] (s broad, 2H, -N*H*$_2$), 8.41 [a] (s broad, 1H, C_5-N*H*), 10.63 [a] (s broad, 1H, N(1)-*H*)	26.6 (N(3)-*C*H$_3$), 51.8 (C_2-COO*C*H$_3$), 52.5 (C_1-COO*C*H$_3$), 88.7 (C=*C*H), 90.3 (C-5), 149.2 (C-2), 149.6 (C-4), 152.5 (*C*=CH), 160.8 (C-6), 163.2 (C_2-*C*OOCH$_3$), 169.4 (C_1-*C*OOCH$_3$)
2g	3.12 (s, 3H, N(3)-C*H*$_3$), 3.37 (s, 3H, N(1)-C*H*$_3$), 3.68 (s, 6H, COOCH$_3$), 5.25 (s, 1H, C=C*H*), 7.03 [a] (s broad, 2H, -N*H*$_2$), 8.51 [a] (s broad, 1H, C_5-N*H*)	27.5 (N(1)-*C*H$_3$), 29.9 (N(3)-*C*H$_3$), 50.6 (C_2-*C*OOCH$_3$), 52.3 (C_1-*C*OOCH$_3$), 88.9 (C=*C*H), 90.7 (C-5), 150.1 (C-2), 151.0 (C-4), 152.9 (*C*=CH), 159.1 (C-6), 163.1 (C_2-*C*OOCH$_3$), 169.3 (C_1-*C*OOCH$_3$)
2h	3.23 (s, 3H, N(1)-C*H*$_3$), 3.62 (s, 6H, COOC*H*$_3$), 5.16 (s, 1H, C=C*H*), 6.96 [a] (s broad, 2H, -N*H*$_2$), 8.41 [a] (s broad, 1H, C_5-N*H*), 10.63 [a] (s broad, 1H, N(1)-*H*)	29.0 (N(1)-*C*H$_3$), 50.6 (C_2-COO*C*H$_3$), 52.3 (C_1-COO*C*H$_3$), 88.5 (C=*C*H), 90.8 (C-5), 149.6 (C-2), 149.9 (C-4), 152.1 (*C*=CH), 159.5 (C-6), 163.1 (C_2-*C*OOCH$_3$), 169.3 (C_1-*C*OOCH$_3$)

[a] Deuterium exchangeable.

well as the uracil derivatives 5,6-diaminopyrimidine-2,4(1*H*,3*H*)-dione **1e** and its N(1)- and/or *N*(3)-methyl derivatives **1f-h** (Scheme 1).

In a first instance, we accomplished the reaction of compounds **1** with dimethyl acetylenedicarboxylate at room temperature in different solvents, both protic (methanol, ethanol) and aprotic solvents (acetonitrile), yielding in all cases the 6-amino-5-(*E*)(1,2-dicarbomethoxyvinyl)aminopyrimidine derivatives **2**, which were isolated directly by filtration of the reaction medium. Compounds **2** arise from Michael addition by attack of the highly nucleophilic 5-amino group with dimethyl acetylenedicarboxylate.

The best results (Table 1) were found using methanol as the solvent. In Table 1, we can see that the reaction with

the uracil derivatives **1e-h** gave lower yields than those with derivatives **1a-d**, due to greater instability than the former compounds, which must be prepared from their hydrochlorides [11].

Compounds **2a-h** were completly characterized by spectroscopic methods (Tables 1 and 2). By analysis of the nmr spectra we observed that a polar solvent such as dimethyl-d_6 sulfoxide permits the conversion of compounds **2** into pteridine derivatives. Hence the isolation of compounds **2a-h** was possible due to their insolubility in methanol at room temperature.

Once the 6-amino-5-(*E*)(1,2-dicarbomethoxyvinyl)-aminopyrimidine derivatives **2** had been obtained, they were converted to the desired 6-(methylenecarbomethoxy)pteridine-4,7(3*H*,8*H*)-dione derivatives **3** in methanol under reflux (Scheme 1 and Table 3).

As shown in Table 3, greater reaction times were required for compounds with R = H than for those with R = CH_3. Pteridine derivatives **3** were prepared directly from the 5,6-diaminopyrimidines **1** and dimethyl acetylenedicarboxylate in methanol at reflux, giving yields similar or slightly higher than the total yields by the isolation of the intermediates **2**.

Shorter reaction times were observed when acidic or basic medium (refluxing methanol) were used in the cyclization of compounds **2** to pteridine derivatives **3**, *i.e.* when the reaction time was 8 hours, the yield was 83% in sodium methoxide. The yield was 88% during 24 hours without basic medium for **3f**, and 56% during 14 hours in trifluoroacetic acid, while the yield was 72% without an acid medium for **3c** during a 24 hour reaction period.

Compounds **3a-h** were also characterized by spectroscopic methods (Tables 3 and 4).

Pteridines **3b,d** were isolated together with their tautomers **3'b,d** (Scheme 2) which were observed mainly by nmr analysis; the ^{1}H-nmr measurement of the **3:3'** ratio for compound **3d** (R = CH_3) was 2:1 and 18:1 for **3b** (R = H). Pteridines **3'** are intermediates in providing the final pteridines **3**, after cyclization.

Biological Results.

The antiviral activity was determined for compounds **2a,b,c,d,g** and **3a,b,c,d,f,g,h** by previously established procedures [12]. At the highest concentration tested (varying from 100 to 400 μg/ml, depending on the assay), all compounds were inactive against the following viruses: human immunodeficiency virus type 1 (HIV-1, strain III_B) and type 2 (HIV-2, strain ROD) in CEM cells.

EXPERIMENTAL

Melting Points were determined in a Electrothermal IA9000 series, Digital Melting Points Apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded with Bruker DPX-300, the following, abbreviations are used to described signal coupling: s = singlet; bs = broad singlet. Ultraviolet (uv) and

Scheme 2

Tautomerism in the Pteridine Derivatives **3**

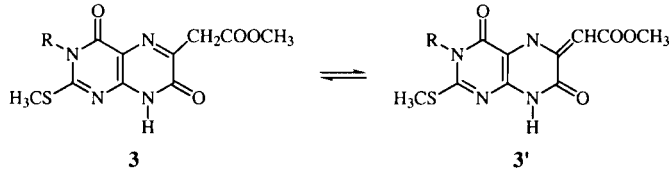


Table 3

Analytical and UV Spectroscopic Data of 6-(Methylenecarbomethoxy)pteridine-4,7(3*H*,8*H*)-dione **3**

Compound	Yield %	mp [a] (°C)	Molecular Formula [b]	UV λ_{max} (log ε) MeOH	IR (potassium bromide) ν (cm^{-1})	MS m/z (%)
3a	91	212	$C_{10}H_{10}N_4O_5$	209 (4.23), 273 (4.14)	3500-2500, bs; 2961, s; 1727, s; 1657, s; 1590, s; 1528, s; 1282, w	266 (M^+, 61), 234 (43), 207 (100), 179 (25), 59 (60)
3b	92	220	$C_{10}H_{10}N_4O_4S$	214 (4.24), 229 [c] (4.24), 284 (4.11)	3500-2900, bs; 1731, s; 1641, s; 1541, w; 1354, s; 1275, w	282 (M^+, 78), 250 (90), 222 (100), 59 (100)
3c	72	205	$C_{11}H_{12}N_4O_5$	210 (4.27), 273 (4.08)	3500-2500, bs; 2957, s; 1720, s; 1667, s; 1571, w; 1275, w; 1227, w	280 (M^+, 67), 248 (61), 221 (100), 193 (24), 59 (27)
3d	85	220	$C_{11}H_{12}N_4O_4S$	220 (4.31), 293 (4.03)	3500-2900, bs; 1712, s; 1636, s; 1609, s; 1314, w; 1291, w; 1215, w	296 (M^+, 70), 264 (92), 237 (100), 59 (24)
3e	90	215	$C_9H_8N_4O_5$	214 (4.21), 277 (4.03), 327 (4.18)	3500-2900, bs; 1719, s; 1669, s; 1626, s; 1432, w; 1285, w; 1226, w	252 (M^+, 16), 220 (65), 208 (5), 78 (77), 63 (100), 45 (69)
3f	88	210	$C_{10}H_{10}N_4O_5$	209 (4.17), 276 (4.04), 328 (3.98)	3500-2900, bs; 1710, s; 1645, s; 1500, s; 1439, w; 1281, w; 1221, w	266 (M^+, 32), 234 (100), 221 (21), 207 (23)
3g	75	210	$C_{11}H_{12}N_4O_5$	216 (4.34), 279 (3.99), 330 (4.22)	3500-2900, bs; 1730, s; 1636, s; 1580, s; 1439, w; 1292, w; 1219, w	280 (M^+, 54), 248 (100), 220 (37), 207 (9), 191 (11), 81 (49), 59 (50)
3h	66	200	$C_{10}H_{10}N_4O_5$	206 (4.23), 273 (4.11), 327 (3.96)	3500-2900, bs; 1696, s; 1620, s; 1578, s; 1478, w; 1282, w; 1218, w	266 (M^+, 42), 234 (100), 207 (23) 67 (28), 42 (13)

[a] Decomposition point. [b] Molecular formula determined by elemental analysis and ms spectrum. [c] Shoulder.

Table 4
Selected ^{1}H- and ^{13}C-NMR Data for 6-(Methylenecarbomethoxy)pteridine-4,7(3*H*,8*H*)-diones **3a-h**

Compound	^{1}H-NMR (dimethyl-d_6 sulfoxide) δ (ppm)	^{13}C-NMR (dimethyl-d_6 sulfoxide) δ (ppm)
3a	3.61 (s, 3H, COOCH_3), 3.70 (s, 2H, CH_2), 3.95 (s, 3H, -OCH_3), 12.50-13.00 [a] (s broad, 2H, N(3)-*H* N(8)-*H*)	38.6 (-CH_2), 51.7 (-COOCH_3), 55.5 (-OCH_3), 112.4 (C-4a), 149.0 (C-8a), 149.3 (C-6), 156.3 (C-7), 157.3 (C-2), 159.0 (C-4), 169.6 (-COOCH$_3$)
3b	2.56 (s, 3H, -SCH_3), 3.66 (s, 3H, COOCH_3), 3.72 (s, 2H, -CH_2), 12.80-13.20 [a] (s broad, 2H, N(3)-*H*, N(8)-*H*)	14.0 (-SCH_3), 39.7 (CH_2), 52.7 (-COOCH_3), 114.3 (C4a), 149.0 (C-8a), 151.6 (C-6), 157.2 (C-7), 159.3 (C4), 170.0 (C-2), 170.5 (-COOCH$_3$)
3c	3.32 (s, 3H, N(3)-CH_3), 3.64 (s, 3H, COOCH_3), 3.72 (s, 2H, -CH_2), 4.07 (s, 3H, -OCH_3), 12.80-13.20 [a] (s broad, 1H, N(8)-*H*)	28.4 (N(3)-CH_3) 39.1 (-CH_2), 52.2 (-COOCH_3), 56.9 (-OCH_3), 112.0 (C-4a), 147.9 (C-8a), 149.8 (C-6), 156.8 (C-7), 156.9 (C-2), 158.8 (C-4), 170.1 (-COOCH$_3$)
3d	2.62 (s, 3H, -SCH_3), 3.44 (s, 3H, N(3)-CH$_3$), 3.62 (s, 3H, COOCH_3), 3.74 (s, 2H, -CH_2), 12.96 [a] (s broad, 1H, N(8)-*H*)	14.8 (-SCH_3), 30.4 (N(3)-CH_3), 38.8 (-CH_2), 51.9 (-COOCH_3), 112.4 (C-4a), 146.4 (C-8a), 151.1 (C-6), 156.3 (C-7), 157.8 (C-4), 164.2 (C-2), 169.6 (-COOCH$_3$)
3e	3.60 (s, 3H, COOCH_3), 3.65 (s, 2H, -CH_2), 6.50-8.50 [a] (s broad, 2H, N(1,8)-*H*), 10.8-11.2 [a] (s, 1H, N(3)-*H*)	38.7 (-CH_2), 51.7 (-COOCH_3), 119.9 (C-4a), 142.8 (C-6), 148.4 (C-8a), 150.7 (C-2), 160.7 (C-4), 162.0 (C-7), 170.4 (-COOCH$_3$)
3f	3.20 (s, 3H, N(3)-CH_3), 3.60 (s, 3H, COOCH_3) 3.76 (s, 2H, -CH_2), 11.00-13.00 [a] (s broad, 2H, N(1,8)-*H*)	27.0 (N(3)-CH_3), 38.6 (-CH_2), 51.6 (-COOCH_3), 118.4 (C-4a), 138.3 (C-6), 146.1 (C-8a), 150.3 (C-2), 159.9 (C-4), 160.1 (C-7), 170.3 (-COOCH$_3$)
3g	3.25 (s, 3H, N(3)-CH_3), 3.40 (s, 3H, N(1)-CH_3), 3.60 (s, 3H, COOCH_3), 3.70 (s, 2H, -CH_2), 4.40-5.20 [a] (s broad, 1H, N(8)-*H*)	28.1 (N(3)-CH_3), 29.0 (N(1)-CH_3), 38.2 (-CH_2), 51.9, (-COOCH_3), 121.9 (C4a), 136.7 (C-6), 147.6 (C-8a), 150.7 (C-2), 159.2 (C-4), 160.6 (C-7), 170.1 (-COOCH$_3$)
3h	3.32 (s, 3H, N(1)-CH_3), 3.60 (s, 3H, COOCH_3), 3.67 (s, 2H, CH_2), 4.40-5.20 [a] (s broad, 1H, N(8)-*H*), 11.17 [a] (s, 1H, N(3)-*H*)	28.3 (N(1)-CH_3), 38.0 (CH$_2$), 52.0 (COOCH_3), 119.1 (C4a), 135.7 (C-6), 148.7 (C-8a), 150.3 (C-2), 159.5 (C4), 160.0 (C-7), 170.0 (COOCH$_3$)

[a] Exchangeable with deuterium oxide.

visible spectra were recorded in a GBC UV/VIS 911 spectrophotometer. Infrared spectra were recorded in a Perkin-Elmer 1760X FT-IR spectrophotometer (potassium bromide pellets). The following abbreviations are used to describe signal strength: b = broad; s = strong; w = weak. Mass spectra were recorded in a Hewlett-Packard HP-5989-B spectrometer. The analysis for C, H and N were performed in a Perkin-Elmer 240 C from "Servicios Técnicos de la Universidad de Granada". Reaction progress and purity of the products were monitored by thin layer chromatography (tlc) on Merck Silica Gel 60GF$_{254}$ (0.2 mm) aluminium precoated sheets with fluorescent indicator, the spots were visualized by ultraviolet irradiation. Dimethyl acetylenedicarboxylate (99%) was purchased from Aldrich, and directly used without further purification.

General Procedure to Obtain 6-Amino-5-(1,2-(*E*)-dicarbomethoxyvinyl)aminopyrimidinones **2**.

To a stirred mixture of the corresponding 5,6-diaminopyrimidinone **1** (3 mmoles) in absolute methanol (20 ml) at room temperature, dimethyl acetylenedicarboxylate was added (3.9 mmoles). After 5 minutes, the yellow solid precipitated was filtered and washed with fresh methanol to afford the desired products.

6-Amino-5-(1,2-(*E*)-dicarbomethoxyvinyl)amino-2-methoxypyrimidin-4(3*H*)-one **2a**.

From 5,6-diamino-2-methoxypyrimidin-4(3*H*)-one **1a**, **2a** was obtained (88%), tlc Rf = 0.49 (methylene chloride/methanol 9:1).

Anal. Calcd. for $C_{11}H_{14}N_4O_6$: C, 44.30; H, 4.73; N, 18.79. Found: C, 44.18; H, 4.64; N, 18.58.

6-Amino-5-(1,2-(*E*)-dicarbomethoxyvinyl)amino-2-methylthiopyrimidin-4(3*H*)-one **2b**.

From 5,6-diamino-2-methylthiopyrimidin-4(3*H*)-one **1b**, **2b** was obtained (91%), tlc Rf = 0.53 (methylene chloride/methanol 9:1).

Anal. Calcd. for $C_{11}H_{14}N_4SO_5$: C, 42.00; H, 4.49; N, 17.83; S, 10.20. Found: C, 41.87; H, 4.47; N, 17.73; S, 9.90.

6-Amino-5-(1,2-(*E*)-dicarbomethoxyvinyl)amino-3-methyl-2-methoxypyrimidin-4(3*H*)-one **2c**.

From 5,6-diamino-3-methyl-2-methoxypyrimidin-4(3*H*)-one **1c**, **2c** was obtained (90%), tlc Rf = 0.62 (methylene chloride/methanol 9:1).

Anal. Calcd. for $C_{12}H_{16}N_4O_6$: C, 46.10; H, 5.16; N, 17.94. Found: C, 46.04; H, 5.05; N, 17.40.

6-Amino-5-(1,2-(*E*)-dicarbomethoxyvinyl)amino-3-methyl-2-methylthiopyrimidin-4(3*H*)-one **2d**.

From 5,6-diamino-3-methyl-2-methylthiopyrimidin-4(3*H*)-one **1d**, **2d** was obtained (91%), tlc Rf = 0.73 (methylene chloride/methanol 9:1).

Anal. Calcd. for $C_{12}H_{16}N_4SO_5$: C, 43.90; H, 4.91; N, 17.06; S, 9.77. Found: C, 43.80; H, 4.91; N, 16.91; S, 9.55.

6-Amino-5-(1,2-(*E*)-dicarbomethoxyvinyl)aminopyrimidine-2,4(1*H*,3*H*)-dione **2e**.

From 5,6-diaminopyrimidine-2,4(1*H*,3*H*)-dione **1e**, **2e** was obtained (63%), tlc Rf = 0.40 (methylene chloride/methanol 9:1).

Anal. Calcd. for $C_{10}H_{12}N_4O_6$: C, 42.25; H, 4.25; N, 19.71. Found: C, 41.96; H, 4.18; N, 19.66.

6-Amino-5-(1,2-(*E*)-dicarbomethoxyvinyl)amino-3-methylpyrimidine-2,4(1*H*,3*H*)-dione **2f**.

From 5,6-diamino-3-methylpyrimidine-2,4(1*H*,3*H*)-dione **1f, 2f** was obtained (61%), tlc Rf = 0.42 (methylene chloride/methanol 9:1).

Anal. Calcd. for $C_{11}H_{14}N_4O_6$: C, 44.21; H, 4.72; N, 18.75. Found: C, 44.00; H, 4.60; N, 18.51.

6-Amino-5-(1,2-(*E*)-dicarbomethoxyvinyl)amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **2g**.

From 5,6-diamino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **1g, 2g** was obtained (88%), tlc Rf = 0.44 (methylene chloride/methanol 9:1).

Anal. Calcd. for $C_{12}H_{16}N_4O_6$: C, 46.15; H, 5.16; N, 17.94. Found: C, 46.19; H, 5.13; N, 17.91.

6-Amino-5-(1,2-(*E*)-dicarbomethoxyvinyl)amino-1-methylpyrimidine-2,4(1*H*,3*H*)-dione **2h**.

From 5,6-diamino-1-methylpyrimidine-2,4(1*H*,3*H*)-dione **1h, 2h** was obtained (89%), tlc Rf = 0.36 (methylene chloride/methanol 9:1).

Anal. Calcd. for $C_{11}H_{14}N_4O_6$: C, 44.21; H, 4.72; N, 18.75. Found: C, 44.06; H, 4.58; N, 18.55.

General Procedure to Obtain of 6-Methylenecarboxymethylpteridinones **3**.

The corresponding 6-amino-5-(1,2-(*E*)-dicarbomethoxyvinyl)-aminopyrimidinone **2** (2 mmoles) was refluxed in methanol (20 ml) for the appropriate time. The final mixture was reduced by evaporation to half volume and methylene chloride was added to favour the desired solid crystallisation, which was filtered and washed with fresh methanol and methylene chloride.

6-Methylenecarboxymethyl-2-methoxypteridine-4,7(3*H*,8*H*)-dione **3a**.

From 6-amino-5-(1,2-(*E*)-dicarbomethoxyvinyl)amino-2-methoxypyrimidin-4(3*H*)-one **2a, 3a** was obtained as a pale yellow solid (91%) after a reflux time of 48 hours, tlc Rf = 0.27 (methylene chloride/methanol 9:1).

Anal. Calcd. for $C_{10}H_{10}N_4O_5$: C, 45.12; H, 3.79; N, 21.05. Found: C, 45.09; H, 3.67; N, 20.74.

6-Methylenecarboxymethyl-2-methylthiopteridine-4,7(3*H*,8*H*)-dione **3b**.

From 6-amino-5-(1,2-(*E*)-dicarbomethoxyvinyl)amino-2-methylthiopyrimidin-4(3*H*)-one **2b, 3b** was obtained as a yellow solid (92%) after a reflux time of 48 hours tlc Rf = 0.21 (methylene chloride/methanol 9:1).

Anal. Calcd. for $C_{10}H_{10}N_4SO_4$: C, 42.55; H, 3.57; N, 19.85; S, 11.35. Found: C, 42.33; H, 3.63; N, 19.74; S, 10.60.

6-Methylenecarboxymethyl-3-methyl-2-methoxypteridine-4,7(3*H*,8*H*)-dione **3c**.

From 6-amino-5-(1,2-(*E*)-dicarbomethoxyvinyl)amino-3-methyl-2-methoxypyrimidin-4(3*H*)-one **2c, 3c** was obtained as a pale yellow solid (92%) after a reflux time of 24 hours, tlc Rf = 0.19 (methylene chloride/methanol 9:1).

Anal. Calcd. for $C_{11}H_{12}N_4O_5$: C, 47.15; H, 4.32; N, 19.99. Found: C, 47.20; H, 4.41; N, 19.90.

6-Methylenecarboxymethyl-3-methyl-2-methylthiopteridine-4,7(3*H*,8*H*)-dione **3d**.

From 6-amino-5-(1,2-(*E*)-dicarbomethoxyvinyl)amino-3-methyl-2-methylthiopyrimidin-4(3*H*)-one **2d, 3d** was obtained as a pale yellow solid (85%) after a reflux time of 24 hours, tlc Rf = 0.25 (methylene chloride/methanol 9:1).

Anal. Calcd. for $C_{11}H_{12}N_4SO_4$: C, 44.59; H, 4.08; N, 18.91; S, 10.81. Found: C, 44.16; H, 3.96; N, 18.66; S, 9.92.

6-Methylenecarboxymethylpteridine-2,4,7(1*H*,3*H*,8*H*)-trione **3e**.

From 6-amino-5-(1,2-(*E*)-dicarbomethoxyvinyl)amino-3-pyrimidine-2,4(1*H*,3*H*)-dione **2e, 3e** was obtained as a pale yellow solid (90%) after a reflux time of 96 hours, tlc Rf = 0.06 (methylene chloride/methanol 9:1).

Anal. Calcd. for $C_9H_8N_4O_5$: C, 42.86; H, 3.19; N, 22.21. Found: C, 42.68; H, 3.09; N, 21.94.

6-Methylenecarboxymethyl-3-methylpteridine-2,4,7(1*H*,3*H*,8*H*)-trione **3f**.

From 6-amino-5-(1,2-(*E*)-dicarbomethoxyvinyl)amino-3-methylpyrimidine-2,4(1*H*,3*H*)-dione **2f, 3f** was obtained as a pale yellow solid (88%) after a reflux time of 24 hours, tlc Rf = 0.05 (methylene chloride/methanol 9:1).

Anal. Calcd. for $C_{10}H_{10}N_4O_5$: C, 45.11; H, 3.78; N, 21.04. Found: C, 44.88; H, 3.91; N, 20.83.

6-Methylenecarboxymethyl-1,3-dimethylpteridine-2,4,7(1*H*,3*H*,8*H*)-trione **3g**.

From 6-amino-5-(1,2-(*E*)-dicarbomethoxyvinyl)amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **2g, 3g** was obtained as a pale yellow solid (75%) after a reflux time of 24 hours, tlc Rf = 0.05 (methylene chloride/methanol 9:1).

Anal. Calcd. for $C_{11}H_{12}N_4O_5$: C, 47.14; H, 4.31; N, 19.99. Found: C, 46.69; H, 4.29; N, 20.12.

6-Methylenecarboxymethyl-1-methylpteridine-2,4,7(1*H*,3*H*,8*H*)-trione **3h**.

From 6-amino-5-(1,2-(*E*)-dicarbomethoxyvinyl)amino-1-methylpyrimidine-2,4(1*H*,3*H*)-dione **2h, 3h** was obtained as a pale yellow solid (66%) after a reflux time of 48 hours, tlc Rf = 0.04 (methylene chloride/methanol 9:1).

Anal. Calcd. for $C_{10}H_{10}N_4O_5$: C, 45.11; H, 3.78; N, 21.04. Found: C, 44.96; H, 4.12; N, 20.64.

REFERENCES AND NOTES

[1] A. Lang, C. Dunn, K. Paulini, L. Colin, M. Rice, and C. Suckling, *Pteridine*, **6**, 90 (1995).

[2] G. Ferrand, H. Dumas, J. Depin, and Y. Quentin, *Eur. J. Med. Chem.*, **31**, 273 (1996).

[3] H. B. Cottam, H. Shih, L. R. Tehrani, D. B. Wasson, and D. A. Carson, *J. Med. Chem.*, **39**, 2 (1996).

[4] C. Ochoa, J. Rodriguez, M. L. Lopez Garcia, and A. R. Martínez, *Arzneim.-Forsch.*, **46**, 643 (1996).

[5] W. Pfleiderer, H. Schmidt, and R. Henning, Patent DE 94-4,418,096 A1 30 Nov 1995.

[6] D. J. Brown, Fused Pyrimidines Part 3, Pteridines, John Wiley & Sons, New York, (1988).

[7] S. Nishigaki, K. Fukami, M. Ichiba, H. Kanazawa, K. Matsuyama, S. Ogusu, K. Senga, F. Yoneda, R. Koga, and T. Ueno, *Heterocycles*, **15**, 757 (1981).

[8] F. Yoneda, R. Koga, S. Nishigaki, and S. Fukuzawa, *J. Heterocyclic Chem.*, **19**, 949 (1982).

[9] J. Cobo, M. Melguizo, A. Sánchez, and A. Nogueras, *Synlett.*, 297 (1993); J. Cobo, C. García, M. Melguizo, A. Sánchez, and M. Nogueras, *Tetrahedron*, **50**, 10345 (1994); J. Cobo, M. Melguizo, A. Sánchez, M. Nogueras, and E. De Clercq, *Tetrahedron*, **52**, 5845 (1996); J. Cobo, M. Melguizo, A. Sánchez, M. Nogueras, J. A. Dobado, and M. Nonella, *Tetrahedron*, **52**, 13721 (1996).

[10] J. Cobo, A. Sánchez, M. Nogueras, and E. De Clercq, *Tetrahedron*, **53**, 8225 (1997).

[11] The 5,6-diaminouracil derivatives **1e,h** are stored as their hydrochloride derivatives, and they are released in aqueous solution before use, by neutralization with sodium bicarbonate and recovered by filtration. Some of the diaminouracil derivatives are decomposed during the filtration process, and the exact amount of compound is not controlled absolutely.

[12] E. De Clercq, in Minutes of the European Symposium on *in vitro* and *ex vivo* Test Systems to Rationalize Drug Design and Delivery, Editions de Santé, Paris, France, D. Crommelin, P. Couvreur, S. D. Duchêne eds, 1994 pp 108-125.