SYNTHESIS OF 6,7-DISUBSTITUTED PTERIDINE-2,4-DIONES

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Abstract- *The reaction of pyrimido[5,4-c][1,2,5]oxadiazin-3(5H)-one (1) with carbon nucleophiles afforded pteridine-2,4-diones (3) bearing a variety of substituents unequivocally positioned in the pyrazine ring.*

One of the major difficulties in the pteridine synthesis is to devise simple and efficient strategies which allow unambiguous positioning of the pyrazine side-chains. Aimed at this goal, many alternatives to the classical Isay method have been reported,[1] including the fundamental procedures by Taylor and coworkers.[2]

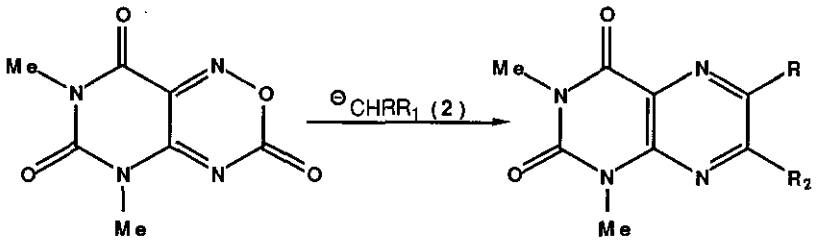
Earlier work in our laboratories had shown that fused 1,2,5-oxadiazinones are suitable starting materials to construct annulated pyrazines.[3,4] The key element in this synthetic approach was the use of pyrimido[5,4-*c*][1,2,5]oxadiazin-3(5H)-one (**1**), a bicyclic system readily available by reacting 4-amino-5-nitrosouracil with phosgene[5] or with trichloromethyl chloroformate.[4] The oxadiazinone moiety of **1** was shown to be susceptible to the attack by β-dicarbonyl carbanions, affording 6,7-disubstituted pteridine-2,4-diones.[4]

As a development of these findings, the present paper describes a new route to a series of 6,7-disubstituted pteridine-2,4-diones, which could be useful for its simplicity and positional selectivity.

The pyrimido-oxadiazinone (**1**) was allowed to react with carbanions derived from compounds containing a methylene group activated by two different electron-withdrawing functions. For this purpose β-ketophosphonates (**2a,b**), triethyl phosphonoacetate (**2c**), nitro ketone (**2d**) and nitro ester (**2e**), sulfonylacetate (**2f**) and N-acetoacetylglycine (**2g**) were employed. The reactants (**2**) were choosen in

order to functionalize the positions 6 and 7 of the pyrazine ring with convenient substituents, which can be hardly inserted by the known methods.

In a typical reaction, a solution of **1** in tetrahydrofuran was added dropwise to a solution of **2a** in the same solvent in the presence of a strong base. After 2 h stirring at room temperature, **1** was converted into a sole reaction product, which was characterized as the pertinent 6,7-disubstituted pteridine-2,4-dione (**3a**) (Scheme 1).



1 **3**

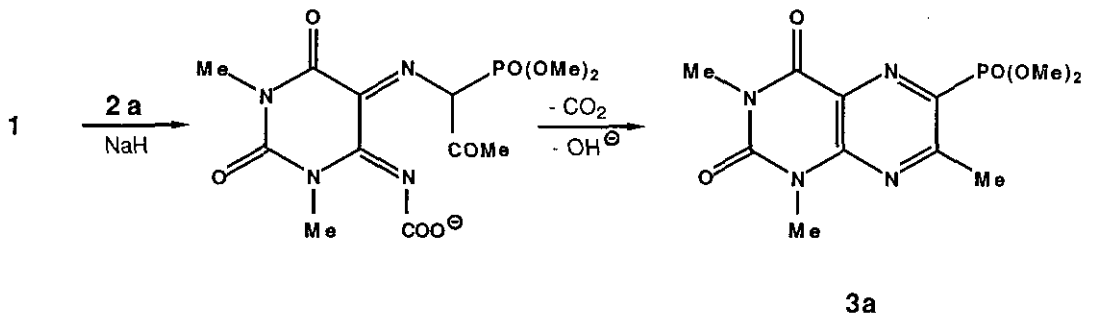
2 **3**

	R	R_1	R	R_2
a	$PO(OMe)_2$	COMe	$PO(OMe)_2$	Me
b	$PO(OMe)_2$	CO n-Pentyl	$PO(OMe)_2$	n-Pentyl
c	$PO(OEt)_2$	COOEt	$PO(OEt)_2$	OH
d	NO_2	COPh	NO_2	Ph
e	NO_2	COOMe	NO_2	OH
f	SO_2Ph	COOMe	SO_2Ph	OH
g	$CONHCH_2COOH$	COMe	$CONHCH_2COOH$	Me

Scheme 1

Similarly the reaction of **1** with each reactant (**2b-f**) proceeded smoothly, yielding the pertinent reaction product (**3b-f**). Also the reaction of **1** with the carbanion derived from N-acetoacetylglycine (**2g**), which contains two different carbonyl groups, gave a single reaction product (**3g**). The structure of the compounds (**3**) was supported by analytical (Table 1) and spectral data (Experimental).

A rational mechanism for these reactions is reported in Scheme 2.



3a

Scheme 2

The attack of the carbanion, for example the carbanion generated in situ by treating dimethyl 2-oxopropylphosphonate (**2a**) with sodium hydride, on the nitrogen atom linked to oxygen leads to the cleavage of the N-O bond with formation of an unstable ring opened intermediate. The cyclisation of this intermediate to **3a** takes place by the attack of the carboxyimine nitrogen on the carbonyl group, with loss of carbon dioxide and formation of only one product.[6]

The results obtained indicate that pyrimido[5,4-*c*][1,2,5]oxadiazin-3(5H)-one (**1**) can be a suitable intermediate for an alternative synthesis of substituted pteridine derivatives. The reaction of **1** with each reactant (**2**) proceeds smootly under mild conditions and allows selected substitutions of the pyrazine moiety.

EXPERIMENTAL

Melting points were determined using a Büchi capillary apparatus and are uncorrected. The ir spectra were recorded from potassium bromide discs on a Perkin-Elmer 299B spectrophotometer. The ^{1}H-nmr and ^{13}C-nmr spectra were recorded on a Bruker AC 2OO spectrometer; chemical shift (δ) are given in parts per million (ppm) relative to tetramethylsilane as internal standard. Coupling constants are in Hz; J is referred to the usual constants (J_{HH} and J_{CH}) while J_{HP} and J_{CP} are referred to the constants of ^{1}H and ^{13}C with ^{31}P. Thin layer chromatography was performed on the pre-coated silica gel 60 F-254 plates manufactured by Merck, Darmstad, Germany. Column chromatography was carried out using Merck 7734 silica gel.

General Procedure for Pteridine-2,4-diones (3a-f).

A solution of **1** (0.84 g, 4 mmol) in anhydrous tetrahydrofuran (24 ml) was added dropwise under a nitrogen atmosfere to a stirred solution of the pertinent reactant **2a-f** (4.4 mmol) in anhydrous tetrahydrofuran (8 ml), previously treated with a 55% sodium hydride dispersion in mineral oil (0.2 g, 4.4 mmol). Upon completation of the addition the mixture was stirred for 2 h, the solvent was removed in vacuo and the residue was poured into water (20 ml) and acidified with 2N hydrochloric acid. The resulting precipitate was collected, or alternatively the suspension was extracted with ethyl acetate, the extracts were dried (magnesium sulfate) and evaporated to dryness. The crude product was recrystallized or chromatographed on a silica gel column (Table 1).

Table 1. Analytical Data of 1,3-Dimethylpteridine-2,4-diones (3a-g).

Comp.	yield (%)	mp(°C) (a)	formula	Elemental analysis	C	H	N
3a	67	137-38	$C_{11}H_{15}N_4O_5P$	Calcd	42.05	4.81	17.83
		(A)		Found	41.92	5.04	17.86
3b	70	71-72	$C_{15}H_{23}N_4O_5P$	Calcd	48.65	6.26	15.13
		(B)		Found	48.49	6.46	14.97
3c	69	173-175	$C_{12}H_{17}N_4O_5P$	Calcd	41.62	5.53	16.18
		(C)	$\cdot H_2O$	Found	41.73	5.31	15.99
3d	88	243-244	$C_{14}H_{11}N_5O_4$	Calcd	53.68	3.54	22.36
		(D)		Found	53.55	3.60	22.23
3e	87	255-57	$C_8H_7N_5O_5$	Calcd	37.95	2.79	27.66
		(D)		Found	37.88	2.82	27.55
3f	68	295-297	$C_{14}H_{12}N_4O_5S$	Calcd	48.27	3.47	16.08
		(D)		Found	48.36	3.52	16.28
3g	64	225-227	$C_{11}H_{11}N_5O_6$	Calcd	42.72	3.59	22.65
		(D)		Found	42.52	3.45	22.54

(a) Purified by recrystallisation: A= ethyl ether/light petroleum; C= dimethylformamide/water; D= ethanol.
B= purified by column chromatography; eluent ethyl acetate/ light petroleum (9/1).

By this procedure the following compounds were obtained:

3a (R= $PO(OMe)_2$; R_2= Me): obtained from dimethyl 2-oxopropylphosphonate (**2a**):

Ir (potassium bromide): 1725, 1680, 1540, 1260, 1040 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 2.93 (d, J_{HP}=1 Hz, 3H, Me), 3.55 (s, 3H, NMe), 3.72 (s, 3H, NMe), 3.98 (d, J_{HP}=10.8 Hz, 6H, 2 OMe); ^{13}C-nmr (DMSO-d_6): δ 23.36 (q, J=129 Hz, Me), 28.91 (q, J=141.7 Hz, NMe), 29.31 (q, J=142.1 Hz, NMe), 54.30 (dq, J=147.8 Hz, J_{CP}=6.7 Hz, two OMe), 124.73 (d, J_{CP}=20.1 Hz, C-4a), 141.11 (d, J_{CP}=229.0 Hz, C-6), 147.80 (s, C-8a), 150.50 (s, CO), 159.00 (s, CO), 162.30 (d, J_{CP}=30.3 Hz, C-7)

3b (R= $PO(OMe)_2$; R_2= n-pentyl): obtained from dimethyl 2-oxoheptylphosphonate (**2b**):

Ir (potassium bromide): 1730, 1680, 1550, 1260, 1040 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 0.92-0.97 (m, 3H, Me), 1.38-1.44 (m, 4H, $2CH_2$), 1.60-1.90 (m, 2H, CH_2), 3.25 (dt, J=7.6 Hz, J_{HP}=0.8 Hz 2H, CH_2), 3.52 (s, 3H, NMe), 3.72 (s, 3H, NMe), 3.97 (d, J_{HP}=10.8 Hz, 6H, two OMe); ^{13}C-nmr (DMSO-d_6): δ 13.97 (q, J=123.1 Hz, Me), 22.45 (t, J=117.2 Hz, CH_2), 28.21 (t, J=126.1 Hz, CH_2), 28.88 (q, J=141.7 Hz, NMe), 29.26 (q, J=142.0 Hz, NMe), 31.56 (t, J=123.3 Hz, CH_2), 35.47 (t, J=128.5 Hz, CH_2), 54.25 (dq, J=147.7 Hz, J_{CP}=6.7 Hz, two OMe), 124.60 (d, J_{CP}=20 Hz, C-4a), 140.90 (d, J_{CP}=228.8 Hz, C-6), 147.88 (s, C-8a), 150.60 (s, CO), 159.10 (s, CO), 166.10 (d, J_{CP}=31Hz, C-7).

3c (R= $PO(OEt)_2$; R_2= OH): obtained from triethyl phosphonoacetate (**2c**):

Ir (potassium bromide): 3420, 3300 br, 1720, 1660, 1500, 1245, 1220, 1005 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.30 (t, J=6.9 Hz, 6H, 2Me), 3.29 (s, 3H, NMe), 3.47 (s, 3H, NMe), 4.08-4.23 (m, 4H, $2CH_2$); ^{13}C-nmr (DMSO-d_6): δ 16.10 (dq, J=126 Hz, J_{CP}=6.0 Hz, 2 Me), 28.10 (q, J=141 Hz, NMe), 28.98 (q, J=141 Hz, NMe), 62.85 (dt, J=147 Hz, J_{CP}=6.0 Hz, two OCH_2), 62.97 (t, J=147 Hz, CH_2),119.80 (d, J_{CP}=20.1 Hz, C-4a), 129.80 (d, J_{CP}=232 Hz, C-6), 149.90 (s, C-8a), 150.50 (s, CO), 158.50 (s, CO), 162.30 (d, J_{CP}=24.8 Hz, C-7).

3d (R= NO_2; R_2= Ph): obtained from benzoylnitromethane (**2d**):

Ir (potassium bromide): 1730, 1690, 1560, 1540, 1360 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 3.37 (s, 3H, NMe), 3.64 (s, 3H, NMe), 7.50-7.80 (m, 5H, Ph); ^{13}C-nmr (DMSO-d_6): δ 28.63 (q, J=141.4 Hz, NMe), 29.69 (q, J=142.2 Hz, NMe), 123.70 (s, C-4a), 128.40 (d, J=147 Hz, Ph), 128.98 (d, J=148 Hz, Ph), 131.36 (d, J=147 Hz, Ph,), 133.40 (s, Ph), 147.60 (s), 148.70 (s), 149.50 (s), 150.30 (s), 158.10 (s).

3e (R= NO_2; R_2= OH): obtained from methyl nitroacetate (**2e**):

Ir (potassium bromide): 3240, 1730, 1680, 1590, 1570, 1540, 1420, 1380 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 3.28 (s, 3H, NMe), 3.47 (s, 3H, NMe), 9.75 (br s, 1H, OH); ^{13}C-nmr (DMSO-d_6): δ 28.21 (q, J=141 Hz, Me), 29.57 (q, J=141 Hz, Me), 114.80 (s, C-4a), 138.02 (s), 149.90 (s), 150.30 (s), 155.40 (s), 157.80 (s).

3f (R= SO_2Ph; R_2= OH): obtained from methyl phenylsulfonylacetate (**2f**):

Ir (potassium bromide): 3350 br, 1720, 1660, 1550, 1380, 1160 cm^{-1}; ^1H-nmr (DMSO-d_6): δ 3.26 (s, 3H, NMe), 3.40 (s, 3H, NMe), 6.00 (br, 3H, OH+H_20), 7.62-7.73 (m, 3H, Ph), 7.94 (d, J=7.3 Hz, 2H, Ph); ^{13}C-nmr (DMSO-d_6): δ 28.37 (q, J=142.0 Hz,NMe), 29.52 (q, J=142.4 Hz, NMe), 118.40 (s, C-4a), 128.50 (d, J=168.0 Hz, Ph), 129.30 (d, J=165.9 Hz, Ph), 134.11 (d, J=163.9 Hz, Ph), 134.60 (s), 139.10 (s, Ph), 150.42 (s), 150.51 (s), 158.30 (s), 158.70 (s).

Synthesis of Compound 3g (R=$CONHCH_2COOH$, R_2=Me).

A solution of **1** (0.84 g, 4 mmol) in anhydrous tetrahydrofuran (24 ml) was added dropwise to a stirred mixture of N-acetoacetylglycine (**2g**) (0.7 g, 4.4 mmol) in tetrahydrofuran (8 ml) and 1N sodium hydroxide (4.4 ml). Upon completation of the addition the mixture was stirred for 2 h, the solvent was removed in vacuo and the residue was poured into water (20 ml) and acidified with 2N hydrochloric acid. The resulting precipitate was collected to yield 0.88 g, 64% of **3g**, mp 225-227°C (ethanol); ir (potassium bromide): 3400, 3100 br, 1760, 1730, 1670, 1560, 1200 cm^{-1}; ^1H-nmr (DMSO-d_6): δ2.86 (s, 3H, Me), 3.34 (s, 3H, NMe), 3.56 (s, 3H, NMe), 3.99 (d, J=6 Hz, 2H, CH_2), 8.81 (t, J=6 Hz, 1H, NH), 13.50 (br, 1H, COOH); ^{13}C-nmr (DMSO-d_6): δ 23.70 (q, J=128.8 Hz, Me), 28.49 (q, J=141.2 Hz, NMe), 29.07 (q, J=141.6 Hz, NMe), 41.09 (t, J=139 Hz, CH_2), 123.91 (s, C-4a), 138.30 (s), 147.59 (s), 150.41 (s), 157.90 (s, C-7), 159.01 (s), 163.90 (s), 171.00 (COOH).

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6 Evidence for the proposed mechanism had been obtained by the isolation of stable intermediates in the reaction of **1** with cyclic carbanions .[3,4]

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