SYNTHESIS OF 7-ARYL-2-DIMETHYLAMINO-3,4,5,6-TETRAHYDROPTERIDINE-4,6-DIONES

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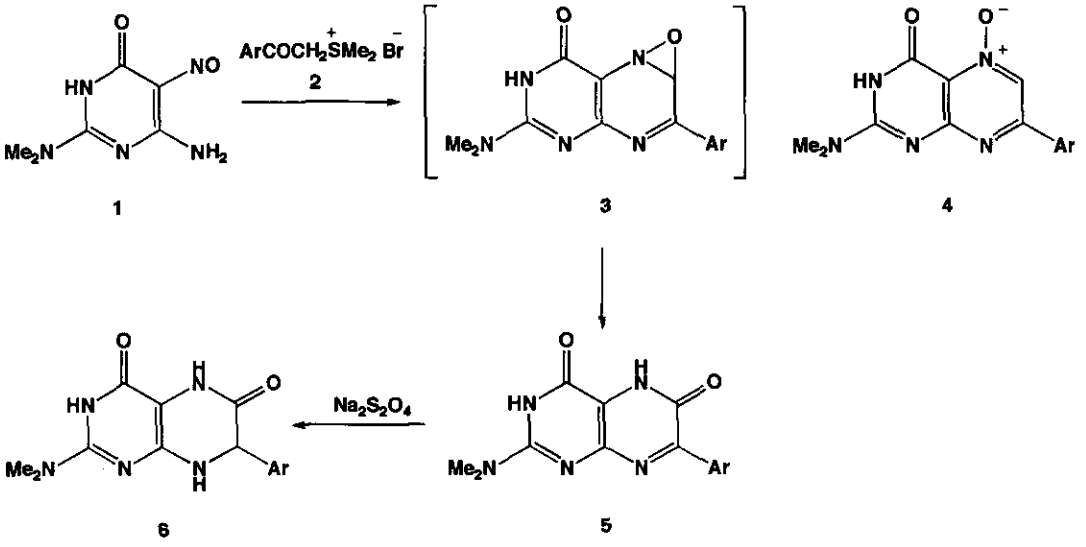
Abstract- 6-Amino-2-dimethylamino-5-nitrosopyrimidin-4(3*H*)-one (**1**) was condensed with a series of dimethylphenacylsulfonium bromides (**2**) in pyridine to yield 7-aryl-2-dimethylamino-3,4,5,6-tetrahydropteridine-4,6-diones (xanthopterin derivatives) (**5**) which were reduced to yield the corresponding 7,8-dihydro derivatives (**6**).

4-Amino-5-nitrosopyrimidines are important starting materials for the synthesis of pteridines, and their preparation and reactions have been thoroughly reviewed.[1,2] In certain cases, pteridine 5-oxides are formed directly from these precursors. For example, treatment of 4,6-diamino-5-nitrosopyrimidines with acylpyridinium halides in the presence of base, or with α-cyanobenzyl benzenesulfonate in the presence of pyridine, leads to 4-aminopteridine 5-oxides.[3] These reactions apparently proceed by attack of the *in situ*-generated *N*-ylides to the nitroso group to give an intermediate nitrone, which undergoes a subsequent dehydrative cyclization. By contrast, the reaction of 6-amino-1,3-dimethyl-5-nitrosouracil with phenacylpyridinium halides is reported to give 6-hydroxy-1,3-dimethyllumazines,[4] while condensation with phenacylidenetriphenylphosphorane gives 7-substituted 1,3-dimethyllumazines *via* intermediate pyrimidine



anils.[5] Similarly, 2-phenyl-4,6-diamino-5-nitrosopyrimidine condenses with diethyl phosphonate carbanions, prepared from α-bromo-esters, -nitriles or -ketones, to give pteridin-7(8*H*)-ones, 7-aminopteridines, and 7-alkyl or arylpteridines respectively, again *via* intermediate anils.[6]

We now report that condensation of 6-amino-2-dimethylamino-5-nitrosopyrimidin-4(3*H*)-one (**1**)[7] with a series of dimethylphenacylsulfonium bromides (**2**)[8] in pyridine under reflux leads to the formation of 7-aryl-2-dimethylamino-3,4,5,6-tetrahydropteridine-4,6-diones (**5**) rather than the isomeric 5-oxides (**4**). Physical and spectral properties of these new xanthopterin derivatives (**5**) are given in Tables 1 and 2. The structures of the condensation products (**5**) were assigned on the basis of ^{1}H and ^{13}C nmr spectra;[9] noteworthy is the absence of resonances for the proton and the tertiary carbon at position 6 of the alternative pteridine 5-oxide structures (**4**). Although the reaction of sulfonium ylides with nitroso groups is reported to yield nitrones *via* oxaziridine intermediates,[10,11] it appears here that the initial oxaziridine (**3**) rearrange to give the observed pteridin-6-ones (**5**).

Reduction of **5** proceeded smoothly with sodium dithionite to give 7,8-dihydro derivatives (**6**). These results are in accord with the known susceptibility of the 7,8-position of xanthopterin to the addition of nucleophiles, and to covalent hydration.[12] The structures of the product (**6**) are in accord with their ^{1}H nmr spectra, which clearly show coupling

Table 1. Physical Properties of Compounds (**5**) and (**6**)

	Ar	Yield %	Mp (°C) (Solvent)	Molecular Formula	Found % (Calcd %) C	H	N
5a	C_6H_5	44	204-205 (MeOH)	$C_{14}H_{13}N_5O_2$	59.23 (59.34)	4.76 (4.63)	24.82 (24.73)
5b	4-BrC_6H_4	46	262-264 (MeOH-pyridine)	$C_{14}H_{12}N_5O_2Br$	46.40 (46.43)	3.52 (3.34)	19.37 (19.34)
5c	4-ClC_6H_4	59	259-261 (MeOH-pyridine)	$C_{14}H_{12}N_5O_2Cl$	52.80 (52.92)	4.00 (3.81)	22.10 (22.04)
5d	4-$MeOC_6H_4$	49	231-233 (MeOH-pyridine)	$C_{15}H_{15}N_5O_3$	57.50 (57.50)	5.00 (4.83)	22.40 (22.35)
5e	4-MeC_6H_4	46	232-234 (MeOH-pyridine)	$C_{15}H_{15}N_5O_2$	60.58 (60.60)	5.11 (5.09)	23.57 (23.56)
6a	C_6H_5	80	199-201 (iso-PrOH)	$C_{14}H_{15}N_5O_2$	58.86 (58.94)	5.26 (5.30)	24.36 (24.55)
6b	4-BrC_6H_4	70	211-212 (iso-PrOH)	$C_{14}H_{14}N_5O_2Br$	45.99 (46.17)	3.98 (3.90)	18.98 (19.23)
6c	4-ClC_6H_4	52	195-196 (iso-PrOH)	$C_{14}H_{14}N_5O_2Cl$	52.46 (52.58)	4.57 (4.41)	21.82 (21.90)
6d	4-$MeOC_6H_4$	66	200-202 (iso-PrOH)	$C_{15}H_{17}N_5O_3$	57.21 (57.14)	5.59 (5.43)	21.99 (22.21)
6e	4-MeC_6H_4	48	192-194 (iso-PrOH)	$C_{15}H_{17}N_5O_2$	60.23 (60.19)	5.71 (5.72)	23.44 (23.40)

between the C-7 and N-8 protons.[13]

The condensation of dimethylphenacylsulfonium iodide with *o*-phenylenediamine is known to give quinoxalines.[14] The present work constitutes an expansion of our previous observation that the reaction of dimethylphenacylsulfonium bromide with heterocyclic *o*-nitrosoamines can provide a convenient route to condensed pyrazinones.[15]

EXPERIMENTAL

7-Aryl-2-dimethylamino-3,4,5,6-tetrahydropteridine-4,6-diones (5):

General Procedure. A mixture of **1**[7] (1.0 mmol, 183 mg) and the corresponding

Table 2. Spectral Data of Compounds (**5**) and (**6**)

	Ms m/z (M^+)	Ir KBr, cm^{-1}	^{1}H-Nmr δ (Solvent)
5a	283	3480 3350 1640 1610 1540 1455	3.10 (s, 6H), 7.52-7.70 (s, 5H), 8.30 (s, 1H), 8.33 (s, 1H) (DMDO-d_6)
5b	361	3325 1625 1580 1545 1505 1480	3.45 (s, 6H), 7.55 (d, J=8.4 Hz, 2H), 8.13 (s, 2H), 8.25 (d, J=8.4 Hz, 2H) (CF_3COOH)
5c	317	3340 1620 1580 1545 1500 1480	3.45 (s, 6H), 7.60 (d, J=8.8 Hz, 2H), 8.13 (br s, 2H), 8.37 (d, J=8.8 Hz, 2H) (CF_3COOH)
5d	313	3320 1630 1615 1590 1550 1480	3.42 (s, 6H), 4.02 (s, 3H), 7.12 (d, J=8.8 Hz, 2H), 8.13 (br s, 2H), 8.42 (d, J=8.8 Hz, 2H) (CF_3COOH)
5e	297	3465 3330 1620 1540 1490 1405	2.53 (s, 3H), 4.47 (s, 6H), 7.50 (d, J=8.2 Hz, 2H), 8.17 (br s, 2H), 8.37 (d, J=8.2 Hz, 2H) (CF_3COOH)
6a	285	3460 3345 1640 1590 1550 1540	3.04 (s, 6H), 5.80 (d, J=5.0 Hz, 1H), 6.51 (d, J=5.0 Hz, 1H), 7.14 (s, 2H), 7.31-7.50 (m, 5H) (DMSO-d_6)
6b	362	3420 3280 1630 1610 1550 1530	3.05 (s, 6H), 5.81 (d, J=4.8 Hz, 1H), 6.61 (d, J=4.8 Hz, 1H), 7.12 (br s, 2H), 7.44 (d, J=8.3 Hz, 2H), 7.58 (d, J=8.3 Hz, 2H) (DMSO-d_6)
6c	319	3450 3310 1640 1615 1560 1535	3.03 (s, 6H), 5.82 (d, J=5.0 Hz, 1H), 6.57 (d, J=5.0 Hz, 1H), 7.03 (br s, 2H), 7.43 (s, 4H) (DMSO-d_6)
6d	315	3500 3340 1640 1610 1570 1550	3.06 (s, 6H), 3.75 (s, 3H), 5.75 (d, J=4.8 Hz, 1H), 6.37 (d, J=4.8 Hz, 1H), 6.92 (d, J=8.0 Hz, 2H), 7.06 (br s, 2H), 7.40 (d, J=8.0 Hz, 2H) (DMSO-d_6)
6e	299	3490 3340 1640 1620 1565 1540	2.29 (s, 3H), 3.04 (s, 6H), 5.74 (d, J=4.8 Hz, 1H), 6.41 (d, J=4.8 Hz, 1H), 7.09 (br s, 2H), 7.17 (d, J=7.9 Hz, 2H), 7.35 (d, J=7.9 Hz, 2H) (DMSO-d_6)

2[8] (1.3 mmol) in pyridine (10 ml) was heated under reflux for 2 h. After removal of the solvent, the residue was purified by column chromatography on silica gel with $CHCl_3$ as the eluent. Recrystallization gave yellow crystals of **5**.

7-Aryl-2-dimethylamino-3,4,5,6,7,8-hexahydropteridine-4,6-diones (6):

General Procedure. To a stirred mixture of **5** (1.0 mmol) in a mixed solvent (50 ml) of water/pyridine/MeOH (2:1:5), a solution of $Na_2S_2O_4$ (0.80 g) in a small amount of water was added dropwise at 60 °C. The color of the reaction mixture turned from yellow to lemon when the reaction was complete. After cooling, the mixture was acidified with 1N HCl and extracted with $CHCl_3$ (3 x 30 ml). The extract was dried over anhyd. $MgSO_4$ and evaporated *in vacuo*, and the residue was recrystallized to give **6**.

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9. ^{13}C Nmr spectrum of **5c** (DMSO-d_6): δ 36.97 (CH_3), 108.66, 128.47 (CH), 132.10 (CH), 133.91, 138.53, 150.05, 157.36, 161.15, 165.90, 176.73.

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13. ^{13}C Nmr spectrum of **6b** (DMSO-d_6): δ 36.88 (CH_3), 68.11 (CH), 106.18, 120.90, 128.66 (CH), 131.14 (CH), 139.68, 155.92, 157.93, 159.84, 166.29.

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Received, 2nd October, 1995