

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

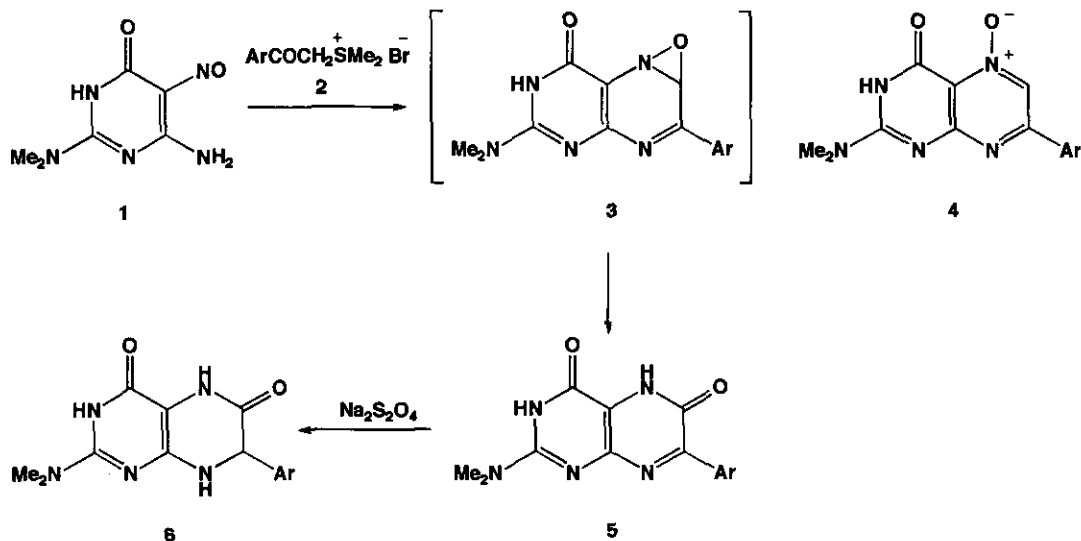
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Abstract- 6-Amino-2-dimethylamino-5-nitrosopyrimidin-4(3*H*)-one (**1**) was condensed with a series of dimethylphenacylsulfonium bromides (**2**) in pyridine to yield 7-aryl-2-dimethylamino-3,4,5,6-tetrahydropteridine-4,6-diones (xanthopterin derivatives) (**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-aminopterin 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-dimethylumazines,⁴ while condensation with phenacylidetriphenylphosphorane gives 7-substituted 1,3-dimethylumazines *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(8H)-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(3H)-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 ^1H 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 ^1H 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 ₆ H ₅	44	204-205 (MeOH)	C ₁₄ H ₁₃ N ₅ O ₂	59.23 (59.34)	4.76 (4.63)	24.82 (24.73)
5b	4-BrC ₆ H ₄	46	262-264 (MeOH-pyridine)	C ₁₄ H ₁₂ N ₅ O ₂ Br	46.40 (46.43)	3.52 (3.34)	19.37 (19.34)
5c	4-ClC ₆ H ₄	59	259-261 (MeOH-pyridine)	C ₁₄ H ₁₂ N ₅ O ₂ Cl	52.80 (52.92)	4.00 (3.81)	22.10 (22.04)
5d	4-MeOC ₆ H ₄	49	231-233 (MeOH-pyridine)	C ₁₅ H ₁₅ N ₅ O ₃	57.50 (57.50)	5.00 (4.83)	22.40 (22.35)
5e	4-MeC ₆ H ₄	46	232-234 (MeOH-pyridine)	C ₁₅ H ₁₅ N ₅ O ₂	60.58 (60.60)	5.11 (5.09)	23.57 (23.56)
6a	C ₆ H ₅	80	199-201 (iso-PrOH)	C ₁₄ H ₁₅ N ₅ O ₂	58.86 (58.94)	5.26 (5.30)	24.36 (24.55)
6b	4-BrC ₆ H ₄	70	211-212 (iso-PrOH)	C ₁₄ H ₁₄ N ₅ O ₂ Br	45.99 (46.17)	3.98 (3.90)	18.98 (19.23)
6c	4-ClC ₆ H ₄	52	195-196 (iso-PrOH)	C ₁₄ H ₁₄ N ₅ O ₂ Cl	52.46 (52.58)	4.57 (4.41)	21.82 (21.90)
6d	4-MeOC ₆ H ₄	66	200-202 (iso-PrOH)	C ₁₅ H ₁₇ N ₅ O ₃	57.21 (57.14)	5.59 (5.43)	21.99 (22.21)
6e	4-MeC ₆ H ₄	48	192-194 (iso-PrOH)	C ₁₅ H ₁₇ N ₅ O 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 **17** (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	3.10 (s, 6H), 7.52-7.70 (s, 5H), 8.30 (s, 1H), 8.33 (s, 1H) (DMDO-d ₆)
		1610	1540	1455	
5b	361	3325	1625	1580	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 ₃ COOH)
		1545	1505	1480	
5c	317	3340	1620	1580	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 ₃ COOH)
		1545	1500	1480	
5d	313	3320	1630	1615	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 ₃ COOH)
		1590	1550	1480	
5e	297	3465	3330	1620	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 ₃ COOH)
		1540	1490	1405	
6a	285	3460	3345	1640	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)
		1590	1550	1540	
6b	362	3420	3280	1630	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)
		1610	1550	1530	
6c	319	3450	3310	1640	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)
		1615	1560	1535	
6d	315	3500	3340	1640	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)
		1610	1570	1550	
6e	299	3490	3340	1640	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)
		1620	1565	1540	

2⁸ (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 CHCl₃ 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 Na₂S₂O₄ (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 CHCl₃ (3 x 30 ml). The extract was dried over anhyd. MgSO₄ and evaporated *in vacuo*, and the residue was recrystallized to give **6**.

REFERENCES

1. (a) D. J. Brown, "The Pyrimidines", Vol. 16 of "The Chemistry of Heterocyclic Compounds", ed. by A. Weissberger, Interscience, New York, 1962; (b) D. J. Brown, "The Pyrimidines, Supplement I", Vol. 16 of "The Chemistry of Heterocyclic Compounds", ed. by A. Weissberger and E. C. Taylor, Wiley-Interscience, New York, 1970; (c) D. J. Brown, "The Pyrimidines; Supplement II", Vol. 16 of "The Chemistry of Heterocyclic Compounds", ed. by A. Weissberger and E. C. Taylor, John Wiley & Sons, New York, 1985.
2. D. J. Brown, "Fused Pyrimidines. Part Three. Pteridines", Vol. 24 in "The Chemistry of Heterocyclic Compounds", ed. by E. C. Taylor, John Wiley and Sons, New York, 1988.
3. (a) I. J. Pachter, P. E. Nemeth, and A. J. Villani, *J. Org. Chem.*, 1963, **28**, 1197; (b) I. J. Pachter, in "Pteridine Chemistry. Proceedings of the 3rd International Symposium", ed. by W. Pfeleiderer and E. C. Taylor, MacMillan, New York, 1964, 47-64.
4. K. Senga, K. Shimizu, and S. Nishigaki, *Heterocycles*, 1977, **6**, 1907.
5. K. Senga, H. Kanazawa, and S. Nishigaki, *J. Chem. Soc., Chem. Commun.*, 1976, 588.

6. E. C. Taylor and B. E. Evans, *J. Chem. Soc., Chem. Commun.*, 1971, 189.
7. B. Roth, J. M. Smith, Jr., and M. E. Hultquist, *J. Amer. Chem. Soc.*, 1951, **73**, 2864.
8. H. Böhme and W. Krause, *Ber.*, 1949, **82**, 426.
9. ^{13}C Nmr spectrum of **5c** (DMSO- d_6): δ 36.97 (CH₃), 108.66, 128.47 (CH), 132.10 (CH), 133.91, 138.53, 150.05, 157.36, 161.15, 165.90, 176.73.
10. A. W. Johnson and R. T. Amel, *J. Org. Chem.*, 1969, **34**, 1240.
11. A. W. Johnson, *J. Org. Chem.*, 1963, **28**, 252.
12. W. Pfeleiderer, *J. Heterocycl. Chem.*, 1992, **29**, 583.
13. ^{13}C Nmr spectrum of **6b** (DMSO- d_6): δ 36.88 (CH₃), 68.11 (CH), 106.18, 120.90, 128.66 (CH), 131.14 (CH), 139.68, 155.92, 157.93, 159.84, 166.29.
14. S. Kano and Y. Yuasa, *Heterocycles*, 1981, **16**, 1449.
15. M. Takahashi and M. Hatazaki, *Heterocycles*, 1995, **41**, 1667. In this paper, various 1,3-disubstituted 5-amino-4-nitrosopyrazoles were condensed with dimethylphanacylsulfonium bromides in boiling pyridine to give pyrazolo[3,4-*b*]pyrazin-5(4*H*)-ones and/or pyrazolo[3,4-*b*]pyrazine 4-oxides.

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