Synthesis of 6-Benzyl- and 6-Phenethyl-2,4-diamino-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidines (1)

Thomas J. Delia and Salah M. Sami*

Malcolm H. Filson Laboratories, Department of Chemistry, Central Michigan University, Mt. Pleasant, MI 48859

Received March 2, 1981

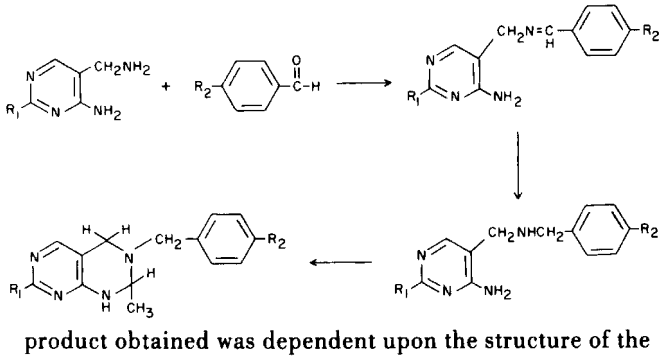
The preparation of ten aralkyl derivatives of 2,4-diamino-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidines (**6**) has been accomplished. The title compounds were prepared in a simple one step reaction from 2,4,6-triaminopyrimidine (**4**), formaldehyde (**2**), and either substituted benzylamines (**1a-d**) or substituted phenethylamines (**1e-j**). This modified Mannich reaction has been shown to be a general method for such derivatives. Elemental analysis, ^{1}H nmr and mass spectral data have confirmed the proposed structures. None of the compounds exhibited either antimalarial or antitrypanosomal activity.

J. Heterocyclic Chem., **18**, 929 (1981).

Considerable interest has developed in fused pyrimidine ring systems because of similarities to folic acid. Such compounds may be potential inhibitors of enzymes within the biochemical processes involving the folate mechanism (2). Movement of one or both ring nitrogen atoms in the pyrazine portion of the pteridine system has been attempted with the hope of achieving inhibitory activity, especially of dihydrofolate reductase. One example of such a modification which has not been seriously examined is the tetrahydropyrimido[4,5-*d*]pyrimidine system. Most of the recent compounds containing this ring system have involved the oxo group in either or both of the rings and are usually fused uracil derivatives (3-6). Our interest was directed at analogs which maintained the aromaticity of one ring while permitting substitution at various locations in the reduced ring.

This paper describes a facile synthesis of the title compounds in a one step process involving readily available starting materials. A report by Harmon and coworkers (7) suggested a simple and direct route in which a 4-amino-5-aminomethylpyrimidine derivative was cyclized by means of an appropriate aldehyde to provide a derivatized tetrahydropyrimido[4,5-*d*]pyrimidine (Scheme1). However, the

Scheme I



product obtained was dependent upon the structure of the aldehyde. While extension of this approach was possible we envisioned a simpler approach based on our earlier work involving the aminoalkylation of uracil (8).

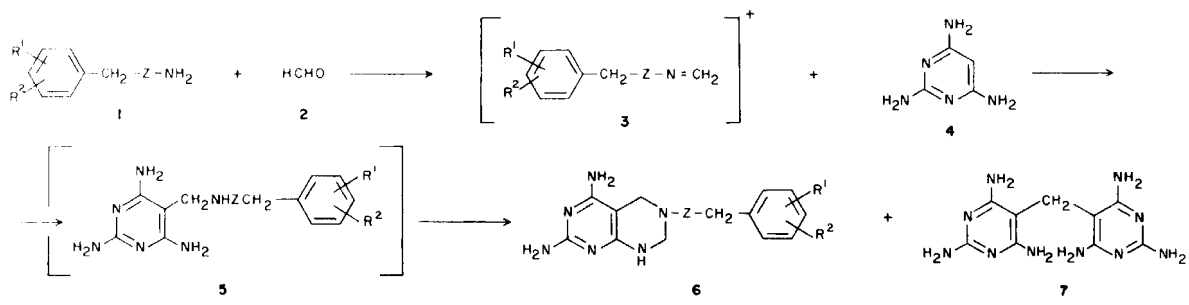
The direct aminoalkylation at position 5 of a suitable substituted pyrimidine would provide, we reasoned, a facile method for obtaining the desired products without isolation of intermediates. A pyrimidine already bearing an amine function at position 4 (6) provides the opportunity for *in situ* ring closure and would be suitable for this purpose. Thus, 2,4,6-triaminopyrimidine (**4**) quite ideally fulfilled the role of providing two identical amine functions adjacent to C-5 while precluding the formation of isomers. The reaction sequence is shown in Scheme 2.

We first utilized a series of benzylamines in this sequence. The treatment of two equivalents of 3,4-dichlorobenzylamine (**1a**) and two equivalents of formaldehyde (**2**) in ethanol at room temperature for approximately 15-30 minutes permitted the formation of the reactive intermediate (**3**). This was followed by addition of one equivalent of **4** in ethanol and the mixture heated to reflux for 24 hours. Workup of the reaction mixture (see Experimental) provided an excellent yield of the desired 6-(3,4-dichlorobenzyl)-2,4-diamino-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidine (**6a**). The structure was assigned on the basis of elemental analysis, ^{1}H nmr spectral data and mass spectrum (see Tables I and II). In particular the presence of ^{1}H nmr signals for the methylene groups at C_5 and C_7 were instrumental in determining the assignment (Table II).

When the ratio of **3**:**4** was 1:1 some of the desired product (**6a**) was obtained although in considerably lower yield (30%). A second product was isolated in this situation in substantial quantity (*ca* 50%). ^{1}H nmr and mass spectrum analysis of this material suggested the structure **7**. Significant quantities of this bis-(2,4,6-triaminopyrimidyl)methane were also isolated when **1** and **2** were not premixed or when **1a**·HCl was used. Apparently attack by the intermediate reagent, **3**, occurs easily followed by a

0022-152X/81/050929-03$02.25

Scheme 2



	Z	R^1	R^2
a	—	3-Cl	4-Cl
b	—	2-Cl	4-Cl
c	—	4-Cl	H
d	—	3-CF_3	H
e	CH_2	2-Cl	H
f	CH_2	4-Cl	H
g	CH_2	3-Cl	H
h	CH_2	3-CF_3	H
i	CH_2	2-Cl	4-Cl
j	CH_2	2-Cl	6-Cl

Table I. Physical and Chemical Data for **6**

Compound	R_1	R_2	Z	Yield,	Crystallization Solvent	Mp °C	Empirical Formula	Analysis Calcd. C	H	N	Found C	H	N
6a	3-Cl	4-Cl	-	98	MeOH	194-196° (a)	$C_{13}H_{14}Cl_2N_6$	48.00	4.33	25.82	47.80	4.02	25.69
6b	2-Cl	4-Cl	-	92	$CHCl_3$ or DMSO-H_2O	155-157° (b)	$C_{13}H_{14}Cl_2N_6 \cdot H_2O$	45.50	4.70	24.50	45.98	4.81	24.69
6c	4-Cl	H	-	97	EtOH	240-241° (c)	$C_{13}H_{15}ClN_6 \cdot 2HCl$	42.92	4.68	23.10	42.99	5.01	22.53
6d	3-CF_3	H	-	98	$CHCl_3$ or DMSO-H_2O	213-215° (d)	$C_{14}H_{15}Cl_3N_6 \cdot 2HCl \cdot 2H_2O$	38.79	4.80	19.40	38.55	4.26	19.23
6e	2-Cl	H	CH_2	62	MeOH or MeOH-Et_2O	186-188° (e)	$C_{14}H_{17}ClN_6 \cdot CH_3OH$	53.48	6.28	24.95	53.37	6.25	25.09
6f	4-Cl	H	CH_2	76	MeOH	187-193° (f)	$C_{14}H_{17}ClN_6 \cdot CH_3OH$	53.48	6.28	24.95	53.82	6.31	25.07
6g	3-Cl	H	CH_2	96	MeOH	104-105.5° (g)	$C_{14}H_{17}ClN_6 \cdot CH_3OH$	53.48	6.28	24.95	53.33	6.21	24.28
6h	3-CF_3	H	CH_2	80	MeOH or MeOH-H_2O	112-114°	$C_{15}H_{17}F_3N_6$	51.89	5.75	22.70	51.44	5.72	22.93
6i	2-Cl	4-Cl	CH_2	80	$CHCl_3$ or DMSO-H_2O	186-188°	$C_{14}H_{16}Cl_2N_6$	49.75	4.74	24.69	49.73	4.77	24.72
6j	2-Cl	6-Cl	CH_2	76	MeOH-EtOH	200-202°	$C_{14}H_{16}Cl_2N_6$	49.75	4.74	24.69	49.57	4.75	24.78

(a) Mp of HCl salt is 230-233° dec.; (b) Mp of HCl salt is 214-216° dec.; (c) Mp of free base is 197-199°; (d) Mp of free base is 158-159°; (e) Mp of HCl salt is 212-217° dec.; (f) Mp of HCl salt is 212-217° dec.; (g) Mp of HCl salt is 206-210°.

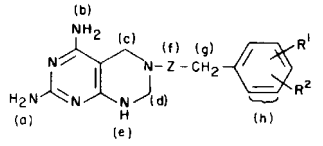
competitive reaction between cyclization (if excess **3** is available) and alkylation of a second molecule of **4** (if excess **3** is not available).

Other benzylamines were employed in this reaction with equal success. These included the 2,4-dichloro- (**1b**), 4-chloro- (**1c**) and 3-trifluoromethyl- (**1d**) derivatives. All of these materials were available commercially. Product characterization for these reactions may also be found in Tables I and II.

In an effort to extend the scope of this reaction to include a more aliphatic amine several phenethyl derivatives were prepared. Treatment of 4-chlorophenethylamine (**1f**) under similar conditions provided, after workup, a good yield of the expected product **6f**. The material was likewise identified through elemental analysis, ^1H nmr data and the mass spectrum (Tables I and II). The requisite phenethylamines were either available commercially or prepared by standard reduction methods from the corresponding benzyl cyanides. In this way 2-chloro- (**6e**), 3-chloro- (**6g**), 2,4-dichloro- (**6i**), 2,6-dichloro- (**6j**) and 3-trifluoromethyl- (**6h**) derivatives were prepared. With this series the use of free bases for both **4** and **1** were necessary to avoid undesirable side products, such as **7**. Even so, small amounts of **7** were formed even when a slight excess of the 2:1 ratio of **3** to **4** was used.

All of the compounds described have been screened for antimalarial activity (9). None have shown activity in this test system. In addition, compounds **6b**, **6f**, **6g**, **6j**, have been subjected to antitrypanosomal screening. None of these compounds exhibited activity in the Rane/Ager test system (10).

Table II NMR and Mass Spectral Data for 6



	Nmr Spectral Data (β)								Mass Spectral Data Mol. Wgt. (M^+)	
6	a (a)	b (a)	c (a)	d (a)	e (b)	f	g	h	calcd.	found
a	5.40	5.60	3.45	4.00	6.38	-	4.00 (s, 2H)	7.3-7.7 (m, 3H)	325	324/326 (c)
b	5.40	5.60	3.50	4.03	6.40	-	4.03 (s, 2H)	7.4-7.7 (m, 3H)	325	324/326 (c)
c	5.38	5.52	3.50	3.95	6.30	-	3.95 (s, 2H)	7.40 (s, 4H)	291	290
d	5.31	5.63	3.50	4.00	6.32	-	4.00 (s, 2H)	7.5-7.8 (d, 4H)	324	-
e	5.50	5.70	3.50	4.00	6.40	2.8 (broad, 4H)		7.20 (s, 4H)	305	304
f	5.26	5.53	3.41	3.90	6.25	2.8 (s, 4H)		7.28 (s, 4H)	305	304
g	5.17	5.47	3.40	3.90	6.17	2.7 (s, 4H)		7.20 (s, 4H)	305	304
h	5.32	5.60	3.45	3.93	6.26	2.8 (broad, 4H)		7.47 (s, 4H)	338	-
i	5.37	5.60	3.47	3.96	6.30	2.6-3.0 (m, 4H)		7.25-7.55 (m, 3H)	339	338
j	5.37	5.60	3.52	4.02	6.30	2.5-2.9 (broad, 2H)	2.90-2.33 (broad, 2H)	7.23-7.50 (m, 3H)	339	338

(a) All values are singlets. (b) All values are broad singlets. (c) Ratio for Cl^{35}:Cl^{37} is in agreement with structure.

EXPERIMENTAL

Melting points are uncorrected. ^1H nmr spectra were recorded in DMSO-d_6 on a Varian T-60 spectrometer with TMS as an internal standard. Elemental analysis were performed by Galbraith Laboratories, Knoxville, TN and Spang Microanalytical Laboratory, Eagle Harbor, MI. Mass spectra were performed by the Walter Reed Army Institute of Research. All the benzylamines used were available commercially. The phenethylamines used are known and were prepared by the sodium borohydride-cobaltous chloride reduction of the corresponding cyano compounds (11) or available commercially.

General Method for the Preparation of 6-Aralkyl-2,4-diamino-5,6,7,8-tetrahydropyrimido[4,5-6*d*]pyrimidines (**6a-j**).

A mixture of two equivalents of the appropriate amine (**1**) and two equivalents of formalin (**2**) (37%) was shaken at room temperature without solvent for 15 minutes. The gummy material obtained was then treated with a solution of one equivalent of 2,4,6-triaminopyrimidine (**4**) in ethanol. After refluxing for 24 hours the clear reaction mixture (12) was evaporated under reduced pressure and the gummy residue solidified upon washing once with petroleum ether (63° - 75°) followed by ether several times. In some cases, after washing with petroleum ether, the gummy material was dissolved in the least amount of methanol (**6f** and **6g**) or ether (**6j**) and the resulting solution was allowed to stand in the refrigerator for 24 hours to give a white crystalline material. Purification of the products was achieved by several crystallizations from the proper solvent or by silica gel column chromatography. Solvents used were chloroform:methanol (9:1), (8:2) or (7:3) followed by crystallization. Products isolated as hydrochlorides were prepared by dissolving the amine in absolute methanol and precipitated by addition of hydrogen chloride gas prior to recrystallization.

Acknowledgement.

This work was supported by the U. S. Army Medical Research and Development Command under Research Contract DAMD 17-78-C-8004. This paper has been designated as Contribution No. 1593 to the Army Research Program on Antiparasitic Drugs. The authors express their appreciation to Drs. Thomas Sweeney, Richard Strube and Hikmat Musallam for advice and encouragement throughout this work, and to Ms. Diane Kirt for her valuable technical assistance and discussions.

REFERENCES AND NOTES

(1) Presented, in part, at the 7th International Congress of Heterocyclic Chemistry, Tampa, FL, August 1979.

(2) W. Pfleiderer, "Chemistry and Biology of Pteridines", ed., Walter de Gruyter, Berlin and New York, 1975.

(3) F. Yoneda, T. Yano, M. Higuchi and A. Koshiro, *Chem. Letters*, 155 (1979).

(4) J. L. Bernier, A. Lefebvre, C. Lespagnol, J. Navarro and A. Perio, *Eur. J. Med. Chem. - Chim. Ther.*, **12**, 341 (1977).

(5) S. P. Gupta, R. K. Robins and R. A. Long, *J. Heterocyclic Chem.*, **12**, 1311 (1975).

(6) K. Grohe and H. Heitzer, *Ann. Chem.*, 2066 (1974).

(7) R. E. Harmon, J. L. Parsons and S. K. Gupta, *J. Org. Chem.*, **34**, 2760 (1969).

(8) T. J. Delia, J. P. Scovill, W. D. Munslow and J. H. Burckhalter, *J. Med. Chem.*, **19**, 344 (1976).

(9) T. S. Osdene, P. B. Russell and L. Rane, *ibid.*, **10**, 431 (1967).

(10) L. Rane, D. S. Rane and K. E. Kinnamon, *Am. J. Trop. Med. Hyg.*, **25**, 395 (1976).

(11) T. Satoh, S. Suzuki, Y. Suzuki, Y. Miyaji and Z. Imai, *Tetrahedron Letters*, 4555 (1969).

(12) In some cases when the reaction mixture was cooled to room temperature a white precipitate was observed; this was filtered and recrystallized from dimethylsulfoxide or water (sparingly soluble) and presumed to be 5,5-methylenebis-2,4,6-triaminopyrimidine (7) m.p. > 360°. The nmr spectrum indicted absorptions at 3.34 δ (2H, S, -CH_2-), 5.3 δ (2H, S, NH_2 at position 2), 5.6 δ (4H, S, NH_2 at positions 4 and 6). The mass spectrum showed major ions at m/e 262 (M^+), m/e 138, 125, and 110.