Synthesis of 1,3-Dimethyl-7-amino-6-substituted-2,4-pteridinediones

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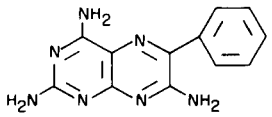
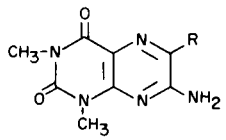
2,4,7-Triamino-6-phenylpteridine (I) (generically named triamterene) has been shown to have effective diuretic activity (1,2). As a part of a program for the synthesis of diuretic agents in this laboratory, compound I was modified

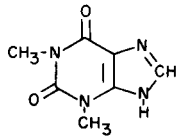


I

by replacing the 2,4-diaminopyrimidine ring of compound I by a 1,3-dimethyl-2,4-pyrimidinedione ring, resulting in the general pteridinedione structure II. The 1,3-dimethyl-2,4-dioxopyrimidine ring is also a part of the structure of thiophylline (III), which is also an effective diuretic agent.



II



III

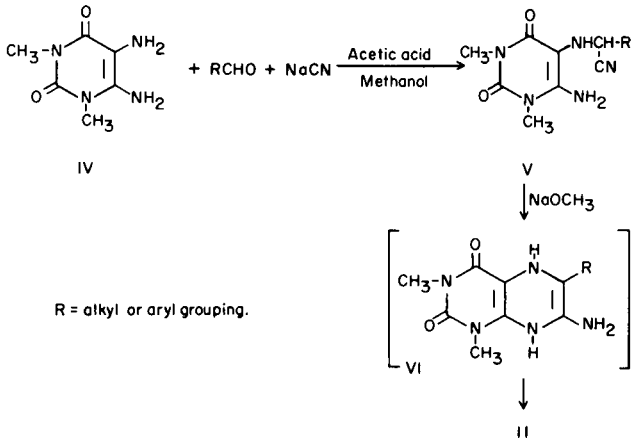
Only one member of this series, 7-amino-1,3-dimethyl-2,4-pteridinedione (II, R = H) has been reported in the literature (3).

The general procedure of Pachter *et al.*, (4) and other workers (5,6) for the synthesis of substituted pteridines was used for the synthesis of the desired pteridinediones. In the present work 5,6-diamino-1,3-dimethyl uracil (7) (IV) was suspended in methanolic acetic acid, treated with aqueous sodium cyanide and then with various aldehydes. 6-Amino-1,3-dimethyl-5-(α-cyanoalkylamino)-uracils (V) formed readily and crystallized from solution.

The uracils (V) in which R = aryl could not be purified for microanalysis because partial cyclization of these compounds to the corresponding pteridinediones occurred on boiling the sample in any solvent. Pure analytical samples of the alkyl analogs were prepared without difficulty (Table I). On treatment with methanolic sodium methoxide the aryl analogs of compound V cyclized to the corresponding substituted pteridinediones (II) (Table II), but this cyclization could not be effected with the alkyl analogs.

The dihydro intermediate VI could not be isolated. Consequently, it was not found necessary to use an oxidizing agent, although previous workers (4) have reported the use of hydrogen peroxide in such reactions for the isolation of the final product. It was concluded that the cyclization of compound V to the dihydro derivative VI was followed by immediate air oxidation to the desired product II.

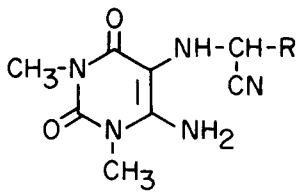
The pharmacological results will be published elsewhere.

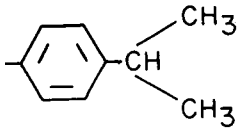


The assignment of the aromatized structure II to the final products was supported by the precise determination by mass spectrum of the molecular weight of compound IX and the fact that the two extra protons of structure VI were not detectable in the nmr spectra of compounds VIII and IX (8).

TABLE I

6-Amino-1,3-dimethyl-5-(α-cyanoalkylamino)-uracils

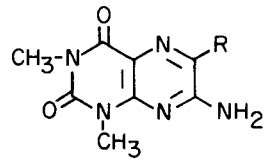


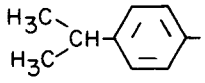
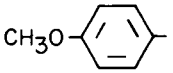
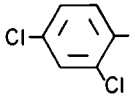
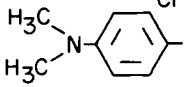
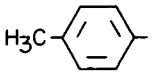
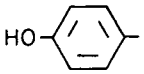
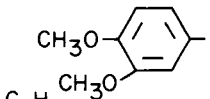
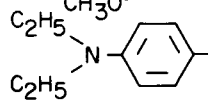
Compound	R	Yield %	M.p., °C (d)	Formula	ANALYSES C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found	O Calcd.	O Found
I	CH_3-$(CH_2)_5$- (b)	85	162	$C_{14}H_{23}N_5O_2$	57.31	56.65	7.90	7.64	23.87	23.82		
II	CH_3-$(CH_2)_8$- (b)	70	152	$C_{17}H_{29}N_5O_2$	60.86	60.65	8.71	8.62	20.88	20.79	9.53	9.62
III	CH_3-$(CH_2)_9$- (a)	80	152	$C_{18}H_{31}N_5O_2$	61.85	61.94	8.94	9.03	20.04	19.95	9.15	9.07
IV	CH_3-$(CH_2)_{10}$- (c)	70	152	$C_{19}H_{33}N_5O_2$	62.77	62.97	9.15	9.29	19.26	19.25	8.80	8.70
V	 (a)	75	173	$C_{17}H_{21}N_5O_2$	62.36	62.17	6.46	6.51	21.39	21.96	9.77	10.40

(a) Crystallized from methanol. (b) Crystallized from acetone. (c) Crystallized from methanol and acetone mixture. (d) Melting points of analytical samples.

TABLE II

1,3-Dimethyl-7-amino-6-substituted-2,4-pteridinediones



Compound	R		Yield % (a)	M.p., °C (c)	Formula	ANALYSES C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
VII		(b)	70	305	$C_{17}H_{19}N_5O_2$	62.75	62.54	5.88	5.94	21.52	21.38
VIII		(b)	33	344-345	$C_{14}H_{13}N_5O_2$	59.35	59.49	4.62	4.58	24.72	24.84
IX		(b)	50	327	$C_{15}H_{15}N_5O_3$	57.49	57.69	4.82	4.83	22.35	22.32
X		(b)	50	280-283	$C_{14}H_{11}Cl_2N_5O_2$	47.74	47.81	3.14	3.44	19.88	19.45
XI		(b)	80	345	$C_{16}H_{18}N_6O_2$	58.88	58.82	5.55	5.58	25.75	25.90
XII		(b)	60	370	$C_{15}H_{15}N_5O_2$	60.59	60.53	5.08	5.22	23.55	23.57
XIII		(b)	50	360	$C_{14}H_{13}N_5O_3$	56.18	56.33	4.37	4.39	23.40	23.34
XIV		(b)	60	310	$C_{16}H_{17}N_5O_4$	55.96	55.88	4.99	4.89	20.39	20.43
XV		(b)	70	315-320	$C_{18}H_{22}N_6O_2$	60.90	60.84	6.20	6.46	23.71	23.51

(a) Yield based on crude aminonitriles. (b) Crystallized from DMF. (c) Melting points of analytical samples.

EXPERIMENTAL

All melting points were taken with the Thomas Hoover capillary melting point apparatus. Microanalyses were prepared at the Microanalytical Laboratories of Abbott Laboratories, North Chicago, Illinois.

6-Amino-1,3-dimethyl-5-(α-cyanoalkylamino)-uracils (Table I).

General Procedure.

A solution of 5,6-diamino-1,3-dimethyluracil in methanolic acetic acid mixture (1 ml. acetic acid per 5 ml. methanol) was added first to an equimolecular aqueous solution of sodium cyanide and then to an equimolecular methanolic solution of an aldehyde. The mixture was allowed to stand at room temperature for about 4 hours. The product was filtered and recrystallized (see Table I).

1,3-Dimethyl-7-amino-6-substituted 2,4-pteridinediones (Table II).

General Procedure.

To a solution of sodium methoxide in dry methanol was added an equivalent weight of the 5-(α-cyanoalkylamino)-uracil derivative (V). The solution was refluxed for 15 minutes and filtered. On standing, a yellow precipitate was obtained. The product was filtered and recrystallized (see Table II).

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(4) Irwin J. Pachter and Piroska E. Nemeth, *J. Org. Chem.*, **28**, 1187 (1963); Irwin J. Pacter, *ibid.*, **28**, 1191 (1963); Irwin J. Pachter, Piroska E. Nemeth and A. J. Villani, *ibid.*, **28**, 1197 (1963); Irwin J. Pachter, and Piroska E. Nemeth, *ibid.*, **28**, 1203 (1963).

(5) H. Zondler, H. S. Forrest, and J. M. Lagowski, *J. Heterocyclic Chem.*, **4**, 124 (1967).

(6) T. S. Osdone, A. A. Santilli, L. E. McCardle and M. E. Rosenthale, *J. Med., Chem.*, 10, 165 (1967).

(7) This intermediate was bought from Aldrich Chemicals, Milwaukee, Wisconsin, U.S.A.

(8) The n.m.r. studies were done by Mr. R. Egan of the Chemical Physics Laboratory, Abbott Laboratories, North Chicago, Illinois. Mass spectra was taken by Morgan Schaffer Corporation, Montreal, Canada.

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