7-Deazapurines VI. Syntheses and Reactions of 5,7-Dihydro-4-methyl-2-phenyl-7-substituted-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-ones

Arthur A. Santilli, Anthony C. Scotese and Dong Han Kim

Wyeth Laboratories Inc., Research and Development Division, Radnor, Pennsylvania 19087

Received October 1, 1975

In recent years emphasis has been placed on methods of synthesizing a variety of substituted pyrrolo[2,3-*d*]-pyrimidines because of their biological importance (1). In a previous paper of this series we reported the preparation of 7-amino-5,7-dihydro-4-methyl-2-phenyl-6*H*-pyrrolo-[2,3-*d*]pyrimidin-6-one, formed by the reaction of ethyl 4-chloro-6-methyl-2-phenyl-5-pyrimidineacetate (I) with hydrazine (2). There have been relatively few reports in the literature describing the syntheses of 6*H*-pyrrolo-[2,3-*d*]pyrimidin-6-ones, (3a-c). These generally have involved the cyclization of (4-aminopyrimidin-5-yl)acetic acid intermediates, and the resulting 6*H*-pyrrolo[2,3-*d*]-pyrimidin-6-ones thus formed are unsubstituted at the 7-position. With the exception of the previous paper in our series, only two reports have appeared which include examples of pyrrolo[2,3-*d*]pyrimidin-6-ones having substitution at the 7-position (4,5). The 7-substituent in these derivatives is either methyl or phenyl. In the present study we describe a facile synthesis for the preparation of a variety of 7-substituted pyrrolo[2,3-*d*]pyrimidin-6-ones having potential pharmacological interest. For example, the reaction of I with 2-methoxyethylamine in refluxing dimethylformamide directly afforded 5,7-dihydro-7-(2-methoxyethyl)-4-methyl-2-phenyl-6*H*-pyrrolo[2,3-*d*]-pyrimidin-6-one (IIa). Similarly, the pyrrolo[2,3-*d*]-pyrimidin-6-ones IIb-d (Table I) were prepared in one step from I and the appropriately substituted amines.

Several chemical transformations involving the activated methylene group of IIa were carried out. For example, treatment of IIa with an equivalent of 2,6-dichlorobenzaldehyde in refluxing acetic acid gave the 2,6-dichlorobenzylidene derivative (III). The reaction of IIa with phosphorus oxychloride and dimethylformamide under Vilsmeier conditions resulted in the formation of the 5-dimethylaminomethylene derivative (IV). Treatment of IIa with triethyl orthoformate in the presence of acetic acid gave the 5-hydroxymethylene derivative (V). Dichlorination was effected by allowing IIa to react with *N*-chlorosuccinimide in boiling carbon tetrachloride. The methylene resonance of the pyrrole ring is absent in the pmr spectrum of the product (VI), confirming the 5-position as the site of chlorination.

A recent report from this laboratory indicated that several substituted 2-pyrimidinylthioacetic acid derivatives have shown potent anti-hypercholesterolemic properties (6). One of the compounds showing good activity possesses a methyl group and a 4-chlorobenzylamino group as substituents on the pyrimidine nucleus. For purposes of comparative biological testing, it was of

Chart I

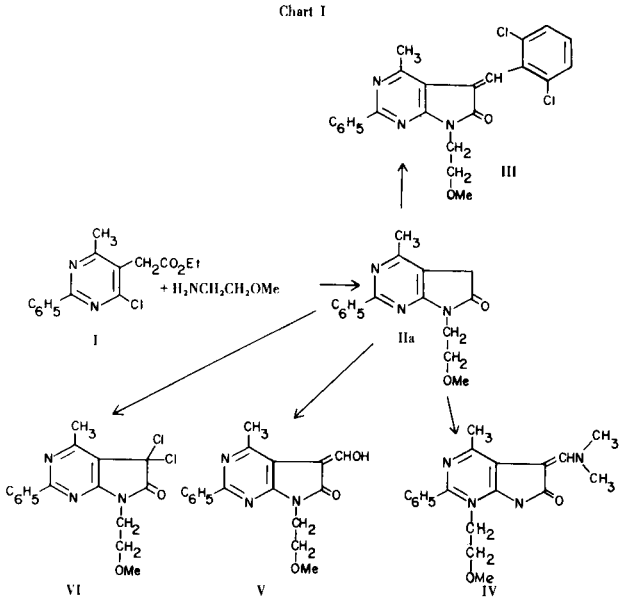


Chart II

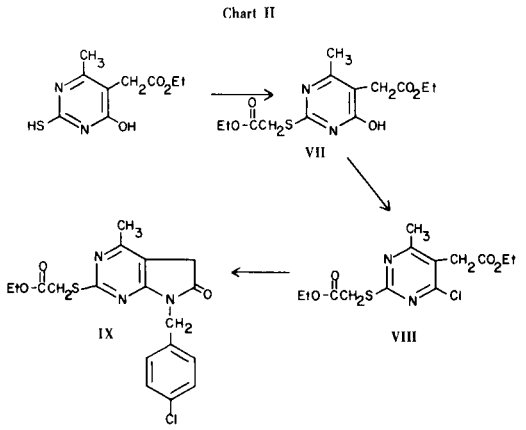
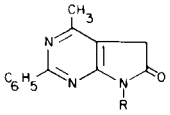
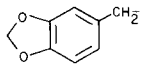


Table I

5,7-Dihydro-4-methyl-2-phenyl-7-substituted 6*H*-pyrrolo[2,3-*d*]pyrimidin-6-ones





Compound	R	M.p., °C	Recrystallization Solvent	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIa	$CH_3OCH_2CH_2$-	142.5-144	Ethanol	$C_{16}H_{17}N_3O_2$	67.82	6.05	14.83	67.79	6.14	15.07
IIb	2,6-$Cl_2C_6H_3CH_2$-	210-211	Ethanol-DMA	$C_{20}H_{15}Cl_2N_3O$	62.51	3.93	10.93	62.33	3.93	10.92
IIc		192-195	Ethanol-DMA	$C_{21}H_{17}N_3O_3$	70.18	4.77	11.69	70.01	4.87	11.99
IId	4-$ClC_6H_4CH_2$-	216-219	Ethanol-DMA	$C_{20}H_{16}ClN_3O$	68.67	4.61	12.01	68.68	4.69	12.01

interest to incorporate these structural features into a pyrrolo[2,3-*d*]pyrimidine system. One such structural variant which contains these groups is ethyl [7-(*p*-chlorobenzyl)-6,7-dihydro-4-methyl-6-oxo-5*H*-pyrrolo[2,3-*d*]-pyrimidin-2-ylthio]acetate (IX). Its synthesis parallels the one used for the preparation of II and is given in Chart II. Alkylation of the sodium salt of ethyl 4-hydroxy-2-mercapto-6-methyl-5-pyrimidineacetate with ethyl bromoacetate gave ethyl (5-carbethoxymethyl-4-hydroxy-6-methyl-2-pyrimidinylthio)acetate (VII). Treatment of VII with phosphorus oxychloride gave ethyl (2-carbethoxymethyl-4-chloro-6-methyl-2-pyrimidinylthio)acetate (VIII). The desired pyrrolo[2,3-*d*]pyrimidine was obtained by allowing VIII to react with *p*-chlorobenzylamine in refluxing ethanol for several hours.

The reaction of primary aliphatic amines with variously substituted 4-chloro-5-pyrimidineacetates appears to be rather general, and with proper selection of starting materials the synthesis of a wide selection of pyrrolo-[2,3-*d*]pyrimidin-6-ones is possible.

EXPERIMENTAL

Melting points were determined in capillary tubes (Thomas-Hoover melting point apparatus) and are uncorrected. Ir spectra were obtained in potassium bromide disks using a Perkin-Elmer (Model 21) spectrophotometer. Pmr spectra were obtained with a Varian A-60 spectrometer using deuteriochloroform or DMSO-d_6. Chemical shifts were measured in ppm (δ) with respect to tetramethylsilane. The observed spectra are in accord with the structural assignments.

5,7-Dihydro-7-(2-methoxyethyl)-4-methyl-2-phenyl-6*H*-pyrrolo-[2,3-*d*]pyrimidin-6-one (IIa).

A stirred mixture of 10.1 g. of ethyl 4-chloro-6-methyl-2-phenyl-5-pyrimidineacetate (2), 3.95 g. of 2-methoxyethylamine and 3.6 g. of sodium carbonate in 35 ml. of *N*,*N*-dimethylformamide was heated under reflux for 1.5 hours and then filtered. On cooling the filtrate a precipitate was deposited which amounted to 5.4 g. The addition of water to the filtrate gave an additional 0.5 g. of product. Recrystallization of the combined products from ethanol gave 2.4 g. of product; ir: μ 5.84 (lactam C=O); pmr (deuteriochloroform): δ 2.41 (s, 3, C-Me), 3.38 (s, 5, OCH_3 + CH_2C=O), 3.80 (m, 2, NCH_2), and 4.01 (m, 2, OCH_2.

5-(2,6-Dichlorobenzylidene)-5,7-dihydro-7-(2-methoxyethyl)-4-methyl-2-phenyl-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one (III).

A stirred mixture of 7.0 g. of IIa and 5.2 g. of 2,6-dichlorobenzaldehyde in 75 ml. of glacial acetic acid was heated under reflux for 2.5 hours. The mixture was then cooled in ice and the resulting precipitate which formed was filtered. This material was recrystallized from ethanol giving 6.5 g. of product, m.p. 200-204°; ir: μ 5.78 (lactam C=O).

Anal. Calcd. for $C_{23}H_{19}Cl_2N_3O_2$: C, 62.74; H, 4.35; N, 9.54; Cl, 16.10. Found: C, 62.75; H, 4.36; N, 9.62; Cl, 16.06.

5-(Dimethylaminomethylene)-5,7-dihydro-7-(2-methoxyethyl)-4-methyl-2-phenyl-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one (IV).

To a solution containing 11.5 g. of phosphorus oxychloride in 6.5 g. of dimethylformamide was added 8.4 g. of IIa in 100 ml. of chloroform. The temperature of the reaction mixture was kept at 0-10° during the addition. The resulting yellow solution was stirred at room temperature for 3 hours and then poured onto 200 g. of ice. An additional 100 ml. of chloroform was added to the mixture. The chloroform phase was separated from the aqueous phase and evaporated to dryness in a rotary evaporator. The residue was dissolved in water and the *p*H of the solution was adjusted to 7 by the addition of sodium acetate. The resulting precipitate was collected and recrystallized from ethanol giving 3.5 g. of product, m.p. 141-144°; ir: μ 5.94 (lactam C=O) and 6.19 (C=C).

Anal. Calcd. for $C_{19}H_{22}N_4O_2$: C, 67.43; H, 6.55; N, 16.56. Found: C, 67.72; H, 6.65; N, 16.57.

5-(Hydroxymethylene)-5,7-dihydro7-(2-methoxyethyl)-4-methyl-2-phenyl-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one (V).

A stirred mixture of 1.4 g. of IIa, 2.96 g. of triethyl orthoformate and 5 drops of glacial acetic acid was heated to 150° for 5 hours. On cooling the reaction mixture in ice a precipitate was deposited. The reaction mixture was diluted with 95% ethanol and filtered. The precipitate thus obtained was recrystallized (2x) from ethanol, giving 0.3 g. of product, m.p. 233-235°; ir: μ 5.92 (lactam C=O) and 6.15 (C=C); pmr (DMSO-d_6): δ 3.71 (m, 2-NCH_2), 4.05 (m, 2-OCH_2), 8.54 (s, 1-CH) and 10.18 (broad s, 1-OH).

Anal. Calcd. for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.30; H, 5.51; N, 13.56.

5,5-Dichloro-5,7-dihydro-7-(2-methoxyethyl)-4-methyl-2-phenyl-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one (VI).

A solution of 6.6 g. of IIa and 5.3 g. of *N*-chlorosuccinimide in 250 ml. of carbon tetrachloride was heated under reflux with stirring for 4 hours and then allowed to cool to room temperature. The reaction mixture was filtered and the filtrate taken to dryness on a rotary evaporator, affording 7.1 g. of product, m.p. 82-91°. The analytical sample (m.p. 97-99°) was obtained by recrystallization from petroleum ether; ir: μ 5.66 (lactam C=O); pmr (deuteriochloroform): δ 2.70 (s, 3, C-Me), 3.30 (s, 3, OCH_3), 3.81 (m, 2, NCH_2), and 4.02 (m, 2, OCH_2).

Anal. Calcd. for $C_{16}H_{15}Cl_2N_3O_2$: C, 54.56; H, 4.29; N, 11.93; Cl, 20.13. Found: C, 54.66; H, 4.17; N, 12.27; Cl, 20.11.

Ethyl (5-Carbethoxymethyl-4-hydroxy-6-methyl-2-pyrimidinylthio)acetate (VII).

To a solution of 0.84 g. of sodium bicarbonate in 50 ml. of water was added 2.3 g. of ethyl 4-hydroxy-6-methyl-2-mercapto-5-pyrimidineacetate (7). The mixture was warmed on a hot plate and 5 ml. of ethanol was added in order to obtain a clear solution. After the addition of 1.67 g. of ethyl bromoacetate, the reaction mixture was heated on a steam bath for 0.5 hours. The reaction mixture was filtered and the precipitate recrystallized from ethanol, giving 0.5 g. of product, m.p. 125-128.5°; ir: μ 5.78 (ester C=O).

Anal. Calcd. for $C_{13}H_{18}N_2O_5S$: C, 49.67; H, 5.77; N, 8.91. Found: C, 49.37; H, 5.79; N, 8.73.

Ethyl (5-Carbethoxymethyl-4-chloro-6-methyl-2-pyrimidinylthio)-acetate (VIII).

A stirred mixture of 18.4 g. of VII in 250 ml. of phosphorus oxychloride was heated under reflux for 4 hours. The excess phosphorus oxychloride was removed in a rotary evaporator *in vacuo*. The residue was poured onto 500 g. of ice and the mixture allowed to stand for several days. The precipitate thus formed was removed by filtration and recrystallized from ethanol-water, giving 9.3 g. of product. An analytical sample (m.p. 43-45°) was obtained by recrystallization from petroleum ether; ir μ 5.75 (ester carbonyl).

Anal. Calcd. for $C_{13}H_{17}ClN_2O_4S$: C, 46.91; H, 5.15; N, 8.42. Found: C, 46.61; H, 4.73; N, 8.04.

Ethyl [7-(*p*-Chlorobenzyl)-6,7-dihydro-4-methyl-6-oxo-5*H*-pyrrolo-[2,3-*d*]pyrimidin-2-ylthio]acetate (IX).

A stirred mixture of 9.3 g. of VIII, 4.0 g. of *p*-chlorobenzylamine and 3.0 g. of sodium carbonate in 150 ml. of ethanol was heated under reflux for 5 hours. The reaction mixture was filtered and the filtrate cooled in ice. The resulting precipitate amounted 6.7 g. Recrystallization from ethanol gave 3.0 g. of product, m.p. 132-135°; ir: μ 5.75 (ester and lactam C=O).

Anal. Calcd. for $C_{18}H_{18}ClN_3O_3S$: C, 55.17; H, 4.63; N, 10.73. Found: C, 55.05; H, 4.72; N, 10.57.

REFERENCES AND NOTES

(1) V. Amarnath and R. Madhav, *Synthesis*, 837 (1974).

(2) A. A. Santilli, A. C. Scotese and D. H. Kim, *J. Heterocyclic Chem.*, **12**, 1291 (1975).

(3a) T. B. Johnson, *J. Am. Chem. Soc.*, **33**, 758 (1911); (b) T. B. Johnson and E. F. Kohmann, *Am. Chem. J.*, **49**, 184 (1913); (c) Z. Földi, G. v. Fodor, I. Demjén, H. Szekeres and I. Halmos, *Chem. Ber.*, **75**, 755 (1942).

(4) P. Nesbitt and P. Sykes, *J. Chem. Soc.*, 3057 (1954).

(5) H. Ogura, M. Sakaguchi and K. Takeda, *Chem. Pharm. Bull.*, **20**, 404 (1972).

(6) Oral presentation before the Division of Medicinal Chemistry (Medi 49), 167th National American Chemical Society Meeting, Los Angeles, California, April 1974.

(7) H. Andersag and K. Westphal, *Chem. Ber.*, **70**, 2035 (1937).