7-Deazapurines V. Synthesis and Reactions of 7-Amino-5,7-dihydro-4-methyl-2-phenyl-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one

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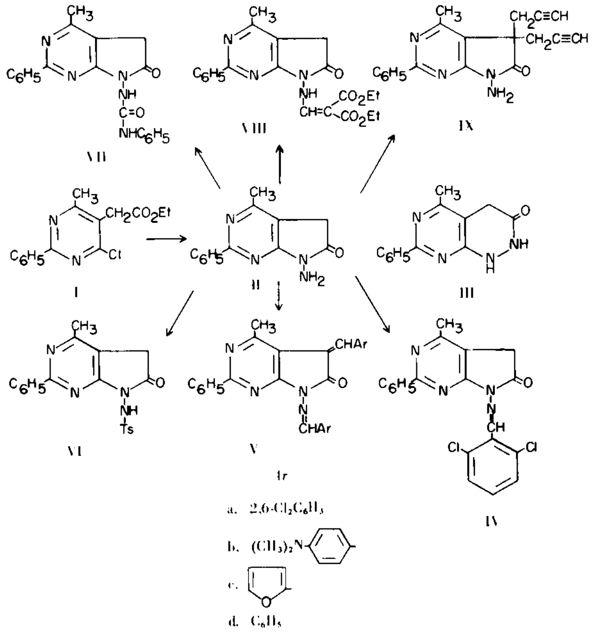
Considerable effort in recent years has been directed towards methods of synthesizing various classes of biologically significant pyrrolo[2,3-*d*]pyrimidines (7-deazapurines). Earlier reports from this laboratory have described the syntheses and chemical transformations of several pyrrolo[2,3-*d*]pyrimidines (1a-d). Bisagni and co-workers (2) have shown that either 7-aminopyrrolo[2,3-*d*]pyrimidines or isomeric dihydropyrimido[4,5-*c*]pyridazines can be formed from the reaction of 5-acetonyl-4-chloropyrimidines with hydrazine, depending on the type of substituents present on the pyrimidine nucleus. These as well as other synthetic methods have been reviewed recently (3). The preparation of 7-aminopyrrolo[2,3-*d*]pyrimidines from 4-chloro-5-pyrimidineacetates and hydrazine has not been reported. This note describes the reaction of ethyl 4-chloro-6-methyl-2-phenyl-5-pyrimidineacetate (I) with hydrazine in refluxing ethanol and the resultant formation of 7-amino-5,7-dihydro-4-methyl-2-phenyl-6*H*-pyrrolo-[2,3-*d*]pyrimidin-6-one (II) in 75% yield (Scheme I). The infrared spectrum of the product shows a characteristic NH_2 absorption pattern at 3.04, 3.11 μ. The carbonyl absorption at 5.76 μ is in good agreement with the value expected for a 5-membered ring lactam derivative. A compound having a 6-membered ring amidic carbonyl group such as the dihydropyrimido[4,5-*c*]pyridazine III would be expected to absorb at 6.0-6.1 μ. Although none of this isomer was isolated from the reaction mixture, the possibility of its initial formation and subsequent rearrangement to II remains a point for consideration. This possibility, however, appears somewhat remote in view of the results obtained by Winters and co-workers (4) who studied this type of rearrangement with analogous compounds. These workers have shown that an analog of III, tetrahydrocinnolin-3-one rearranges readily in boiling dilute hydrochloric acid to form 1-amino-2-indolinone while under basic conditions the rearrangement did not take place. The isomers were readily distinguishable on the basis of their ir carbonyl absorptions. In the present study, the generation of II from III, therefore, seems less likely since such a rearrangement process would not be favored by the existing alkaline reaction conditions. The pmr spectrum of II is not available because of its poor solubility characteristics.



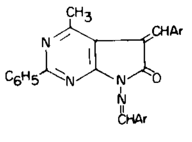
Scheme I

Several chemical transformations involving the primary amino function or methylene group in II were carried out and are as follows.

For example, treatment of II with 2,6-dichlorobenzaldehyde in hot acetic acid gave the Schiff base IV. Lack of absorption in the NH_2 region of the ir spectrum indicates the product is indeed a Schiff base rather than a benzylidene derivative. The lactam carbonyl band is present at 5.76 μ. A second product, the Schiff base-benzylidene derivative Va, also was isolated from the reaction mixture. Formation of this material apparently results through a Knoevenagel type reaction between the aldehyde and activated methylene group of the pyrrole ring. Other Schiff base-benzylidene type derivatives, Vb-d, were prepared by treatment of II with 2 equivalents of appropriately substituted aldehydes. Tosylation of II in pyridine afforded the substituted *p*-toluenesulfonamide VI. Interaction of II with phenyl isocyanate in refluxing THF gave the substituted phenyl-

Table I

Schiff base-Benzilidene Derivatives of 7-Amino-5,7-dihydro-4-methyl-2-phenyl-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one



Compound	M.p., °C	Recrystallization Solvent (a)	Formula	Analysis Calcd. C	H	N	Found C	H	N
Va	257-259	A	$C_{27}H_{16}Cl_4N_4O$	58.51	2.91	10.11	58.34	3.02	10.20
Vb	261-264	A	$C_{31}H_{30}N_6O$	74.08	6.02	16.72	73.70	6.00	16.54
Vc	219-222	A	$C_{23}H_{16}N_4O_3$	69.69	4.07	14.14	69.42	4.23	13.92
Vd	184-187	A	$C_{27}H_{20}N_4O$	77.86	4.84	13.45	77.83	4.92	13.50

(a) A = ethanol-dimethylacetamide.

urea derivative VII. The reaction of II with diethyl ethoxymethylenemalonate in refluxing ethanol gave the expected enamine VIII. Finally, when II was alkylated with propargyl bromide in refluxing ethanol in the presence of sodium carbonate, dialkylation at the C_5-position resulted instead of at the amino nitrogen giving the dipropynyl derivative IX. The absence of a methylene resonance in the pmr spectrum of the product and the presence of a two proton singlet which vanishes on deuteration confirms C_5 as the cite of alkylation.

EXPERIMENTAL

Melting points were determined in capillary tubes (Thomas-Hoover melting point apparatus) and are uncorrected. Ir spectra were obtained in potassium bromide discs 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.

Ethyl 4-Chloro-6-methyl-2-phenyl-5-pyrimidineacetate (I).

A stirred mixture of 41.2 g. of ethyl 4-hydroxy-6-methyl-2-phenyl-5-pyrimidineacetate in 350 ml. of phosphorus oxychloride was heated under reflux for 5 hours. The excess phosphorus oxychloride was removed *in vacuo* in a rotary evaporator. The residue was poured onto crushed ice. The precipitate which resulted was collected on a filter, washed with water and dried in a vacuum desiccator. The product amounted to 43.0 g. (98%) m.p. 99-102°. The analytical sample (m.p. 102-104°) was obtained by recrystallization from ethanol.

Anal. Calcd. for $C_{15}H_{15}ClN_2O_2$: C, 62.18; H, 5.22; N, 9.67. Found: C, 62.06; H, 5.19; N, 9.68.

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

A stirred mixture of 20.2 g. of I, 7.4 g. of sodium carbonate and 7.09 g. of 98% hydrazine hydrate in 200 ml. of ethanol was heated under reflux for 24 hours. The mixture was filtered and the filter cake washed with warm water to give 12.5 g. (75%) of product m.p. 233-236°. Recrystallization from ethanol-dimethylacetamide afforded the analytical sample, m.p. 234-237°; ir (potassium bromide): μ 3.04, 3.11 (NH_2), 5.76 (lactam C=O).

Anal. Calcd. for $C_{13}H_{12}N_4O$: C, 64.98; H, 5.03; N, 23.32. Found: C, 64.72; H, 5.03; N, 23.41.

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

To a solution of 0.48 g. of II in 20 ml. of hot acetic acid, 0.35 g. of 2,6-dichlorobenzaldehyde was added. The reaction mixture was heated on a steam bath for 15 minutes and was then filtered. On cooling the filtrate in ice, a precipitate was formed which was collected on a filter. Recrystallization of this material from ethanol-dimethylacetamide gave 0.20 g. of 5-(2,6-dichlorobenzylidene)-7-(2,6-dichlorobenzylideneamino)-5,7-dihydro-4-methyl-2-phenyl-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one (Va), Table I; ir (potassium bromide): μ 5.70 (lactam C=O). On cooling the filtrate of this recrystallization in ice, a precipitate was deposited which amounted to 0.10 g. Recrystallization from ethanol afforded the analytical sample (m.p. 217-220°) of IV, ir (potassium bromide): μ 5.76 (lactam C=O).

Anal. Calcd. for $C_{20}H_{14}Cl_2N_4O$: C, 60.47; H, 3.55; N, 14.10. Found: C, 60.38; H, 3.63; N, 13.89.

N-(5,6-Dihydro-4-methyl-6-oxo-2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-*p*-toluenesulfonamide (VI).

To a solution of 2.4 g. of II in 45 ml. of anhydrous pyridine, 1.9 g. of tosyl chloride was added. After 5 minutes the reaction mixture was diluted with water. A gummy solid was obtained which was recrystallized from ethanol, then from benzene and finally from ethanol. The product amounted to 0.50 g., m.p. 227-232° dec.

Anal. Calcd. for $C_{20}H_{18}N_4O_3S$: C, 60.90; H, 4.30; N, 14.20. Found: C, 60.56; H, 4.58; N, 14.62.

1-(5,6-Dihydro-4-methyl-6-oxo-2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidinyl-7-yl)-3-phenylurea (VII).

To a solution of 2.4 g. of II in 300 ml. of tetrahydrofuran, 1.2 g. of phenylisocyanate was added dropwise. The yellow-orange colored solution was heated under reflux for 28 hours. The solution was cooled and diluted with 600 ml. of petroleum ether. The resulting precipitate amounted to 2.5 g., m.p. 240-250° dec. Recrystallization of the product from ethanol gave 1.1 g. of pure product, m.p. 254-258°; ir (potassium bromide): μ 3.02 (NH), 5.66 (lactam C=O), 6.00 (urea C=O).

Anal. Calcd. for $C_{20}H_{17}N_5O_2$: C, 66.84; H, 4.77; N, 19.49. Found: C, 66.55; H, 4.78; N, 19.70.

Diethyl([5,6-Dihydro-4-methyl-6-oxo-2-phenyl-7*H*-pyrrolo[2,3-*d*]-pyrimidin-7-ylamino]methylene)malonate (VIII).

A stirred mixture of 16.8 g. of II and 21.6 g. of diethyl ethoxymethylenemalonate in 800 ml. of ethanol containing a sufficient amount of dimethyl acetamide for solubility was heated under reflux for 20 hours. The deep red mixture was diluted with 1 liter of water and filtered. The collected precipitate was recrystallized twice from ethanol giving 4.0 g. of product, m.p. 181-184°; ir (potassium bromide): μ 3.08 (NH), 5.66 (lactam C=O), 5.76 (ester C=O), 5.89 (lactam C=O).

Anal. Calcd. for $C_{21}H_{22}N_4O_5$: C, 61.45; H, 5.40; N, 13.65. Found: C, 61.51; H, 5.32; N, 13.40.

7-Amino-5,7-dihydro-4-methyl-2-phenyl-5,5-bis(2-propynl)-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one (IX).

A stirred mixture of 8.0 g. of II, 7.8 g. of propargyl bromide and 7.1 g. of sodium carbonate in 250 ml. of ethanol containing a sufficient amount of dimethyl acetamide for solubility was heated under reflux for 5 hours. The deep blue mixture was filtered and the filtrate diluted with water. The resulting precipitate was collected and recrystallized from ethanol giving 5.1 g. of product, m.p. 165-167°; ir (potassium bromide): μ 3.06 ($\equiv$CH), 5.75 (lactam C=O); pmr (deuteriochloroform): δ 1.86 (t, 2, C$\equiv$H), 2.62 (s, 3, CH_3), 2.88 (d, 4, CH_2), 4.58 (s, 2, NH_2) disappears on deuteration.

Anal. Calcd. for $C_{19}H_{16}N_4O$: C, 72.13; H, 5.10; N, 17.71. Found: C, 72.42; H, 5.16; N, 17.93.

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