Reaction of 4,5-Diaminopyrimidines with 2,5-Hexanedione

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Reaction of 2,5-hexanedione with various 4,5-diaminopyrimidines was found to lead to the formation of 5-(*N*-pyrryl)-4-aminopyrimidines. Structural assignments for the products obtained were made on the basis of nmr, ir, uv and mass spectral data.

In a 4,5-diaminopyrimidine, the two amino groups, because of their different positions with respect to the nitrogen atoms in the ring, possess very different nucleophilic potential. Since the 5-amino group is more nucleophilic than the 4-amino group, the former is therefore expected to undergo condensation with a carbonyl group much faster than the latter. The vast number of 5-substituted aminopyrimidines prepared from the condensation of 4,5-diaminopyrimidines and carbonyl compounds are indications of this feature (2).

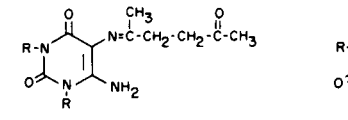
Condensation of 4,5-diaminopyrimidines with a 1,2-dicarbonyl compound is a general procedure for the synthesis of pteridines (3). The mode of reaction involves condensation of the two carbonyls with the two amino groups leading to a six-membered ring closure.

Recent reports (4) on the reaction of 4,5-diaminopyrimidines with a 1,3-dione indicates that a 5-*N*-substituted condensed product was obtained rather than a seven-membered ring.

We therefore decided to investigate the reaction of a 1,4-dione, 2,5-hexanedione, with various 4,5-diaminopyrimidines. This reaction was expected first to lead to an open chain intermediate **1** which may then cyclize. The cyclization may occur in three possible ways; 1) by the interaction of the 4-amino group with the side chain imine function to form a substituted purine **2**; 2) condensation of the 4-amino group and the side chain carbonyl to lead to eight-member ring formation **3**, or its isomers due to rearrangement of the double bonds; 3) interaction of the imine and carbonyl functions to form a 5-substituted-*N*-pyrrylpyrimidine **5**, **7**.

Refluxing a solution of 1,3-dimethyl-5,6-diaminouracil (**4a**) (5) and 2,5-hexanedione in a mixture of ethanol acetic acid for 3 hours led to 65% of a crystalline substance, m.p. 290-292°. The elemental analysis consistently showed the loss of two moles of water. The infrared spectrum lacked the expected bands in the region 1700-1750 cm^{-1} due to a saturated carbonyl group. The nmr spectrum in deuterated chloroform showed two similar methyl groups at δ 1.84 and two similar olefinic hydrogen atoms at δ 5.50. The two *N*-methyl groups in the pyrimidine ring appeared at δ 3.24 and δ 3.45. The signal at δ 5.72 which is due to a primary amine group exchanged rapidly with deuterium when the compound was treated with deuterium oxide.

Although the foregoing collected physical property data favors the structure **5a** over **1**, **2**, and **3**; nevertheless, it does not permit a definite structural assignment for the product obtained. To remove any doubt concerning the



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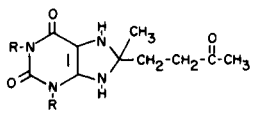

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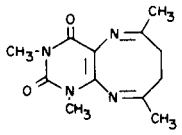

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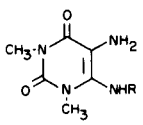
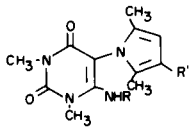
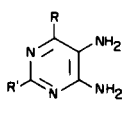


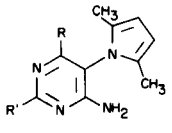
4a R = H
b R = CH_3



5a R = H, R' = H
b R = CH_3, R' = H
c R = H, R' = $\overset{O}{\overset{\|}{C}}-CH_3$



6a R = OH, R' = C_6H_5
b R = H, R' = H
c R = OH, R' = H
d R = OH, R' = CH_3



7a R = OH, R' = C_6H_5
b R = H, R' = H
c R = OH, R' = H
d R = OH, R' = CH_3

structure **5a**, the substance was further subjected to certain chemical reactions. Acylation with acetic anhydride and boron trifluoride etherate at room temperature gave the corresponding monoacetylated product **5c**, m.p. 321-323°. The nmr spectrum of this compound in hexadeuterodimethylsulfoxide indicated seven singlets at δ 1.89 (3H), 2.17 (3H), 2.28 (3H), 3.12 (3H), 3.34 (3H), 6.31 (1H) and 6.75 (2H, which exchanges with deuterium when treated with deuterium oxide) due to methyl ketone, 5-methylpyrryl, 2-methylpyrryl, 1-*N*-methylpyrimidine, 3-*N*-methylpyrimidine, olefinic hydrogen and primary amine, respectively. In the infrared spectrum the principal features are 3350 (NH); 2930 (CH); 1700 (carbonyl); 1610, 1580 and 1520 (C = N, C = C). Hydrogenation of **5a** using Pd/C as catalyst gave only the unchanged material.

To further demonstrate that in a 4,5-diaminopyrimidine the involvement of the 5-amino group in Schiff's base formation is the preferred reaction, 1,3-dimethyl-5-amino-6-methylaminouracil (**4b**) was prepared (6) and reacted under the same reaction conditions as **4a** with 2,5-hexanedione. The elemental analysis, nmr, ir and uv spectra of the product isolated were consistent with the structure **5b**. The nmr spectrum in deuteriochloroform revealed two similar methyl groups at δ 2.0, one *N*-methyl at δ 2.31, two *N*-methylpyrimidine at δ 3.29 and δ 3.44, and a broad band due to two olefinic hydrogen and one secondary amino group at δ 5.91.

In a similar manner, **7a**, **7b**, **7c** and **7d** were obtained from the reaction of 2,5-hexanedione and 2-phenyl-4,5-diamino-6-hydroxypyrimidine (**6a**), (7), 4,5-diaminopyrimidine (**6b**), (8) 4,5-diamino-6-hydroxypyrimidine (**6c**) (9) and 2-methyl-4,5-diamino-6-hydroxypyrimidine (**6d**) (10), respectively.

EXPERIMENTAL (11)

1,3-Dimethyl-5-(2,5-dimethyl-*N*-pyrryl)-6-aminouracil (**5a**).

A solution of 500 mg. of **4a**, 1 g. of 2,5-hexanedione, 3 ml. of acetic acid and 30 ml. of ethanol was refluxed for 3 hours. After removal of the solvent, it was diluted with ether, filtered and the residue was chromatographed over 30 g. of alumina. Elution with tetrahydrofuran gave 650 mg. (65%) of **5a** which was crystallized from dichloromethane-ether to lead to pure **5a**, m.p. 290-292°; uv λ max 218 mμ (ε, 11,700, shoulder), 267 mμ (ε, 16,700); nmr (deuteriochlorofrom) 1.84 (s, 6), 3.24 (s, 3), 3.45 (s, 3), 5.50 (s, 2), 5.75 (s, 2 disappears on addition of deuterium oxide); ir ν max 3310, 1620, 990, 812 and 745 cm^{-1}.

Anal. Calcd. for $C_{12}H_{16}N_4O_2$: C, 58.05; H, 6.50; N, 22.57. Found: C, 58.15; H, 6.62; N, 22.15.

Acylation of **5a**.

A mixture of 100 mg. of **5a**, 1 ml. of acetic anhydride and two drops of etherated boron triflouride was stirred at room temperature for 5 minutes. It was then diluted with ether, the residue was filtered, washed with 5% sodium bicarbonate and then water. It was then dried and crystallized from methanol-dichloromethane to give pure **5c**, m.p. 321-323°; ir ν max 3350, 2930, 1700, 1610, 1580, 1520, 1395, 1220, 1010, 946, 838, 780, 755 cm^{-1}; uv λ max 205 mμ (ε, 20,200), 265 (ε, 18,700); 290 (ε, 7,740); nmr δ 1.89 (s, 3H), 2.17 (s, 3H), 2.28 (s, 3H), 3.12 (s, 3H), 3.34 (s, 3H), 6.31 (s, 1H) and 6.75.

Anal. Calcd. for $C_{14}H_{18}N_4O_3$: C, 57.92; H, 6.25. Found: C, 57.46; H, 6.27.

1,3-Dimethyl-6-methylamino-5-(2,5-dimethyl-*N*-pyrryl)uracil (**5b**).

A solution of 200 mg. of **4b**, 0.5 g. of 2,5-hexanedione, 1.2 ml. of acetic acid in 10 ml. of ethanol was refluxed for 2 hours. It was then cooled and filtered to give 109 mg. (39%) of **5b**, m.p. 245-247°, which was crystallized from ethanol, m.p. 246-248°; ir ν max 3320, 1710, 1620, 1540, 1430, 1382, 1330, 1160, 992, 760 cm^{-1}; uv λ max 207 mμ (ε, 26,600) and 272 (ε, 16,200); nmr (deuteriochloroform) δ 2.0 (s, 6), 2.31 (s, 3), 3.29 (s, 3), 3.44 (s, 3) and 5.91 (broad s, 3).

Anal. Calcd. for $C_{13}H_{18}N_4O_2$: C, 59.53; H, 6.92; N, 21.36. Found: C, 59.32; H, 6.99; N, 21.30.

2-Phenyl-4-amino-5-(2,5-dimethyl-*N*-pyrryl)-6-hydroxypyrimidine (**7a**).

A mixture of 550 mg. of **6a**, 1 g. of 2,5-hexanedione, 3 ml. of acetic acid and 35 ml. absolute ethanol was refluxed for 5 hours. After removal of the solvent, it was diluted with ether, filtered and the residue was chromatographed over 30 g. of alumina. Elution with tetrahydrofuran led to **7a** which was crystallized from tetrahydrofuran-ether to give 510 mg. (67%) of **7a**, m.p. 235-238°; uv λ max 203 mμ (ε, 9,100), 225 mμ (ε, 6,400), 278 mμ (ε, 1,775); ir ν max 3350, 1600, 765 and 695 cm^{-1}, nmr δ 1.99 (s, 6), 5.85 (s, 2), 6.2 (s, 2 exchanges with deuterium oxide) 7.62 and 8.24 (m, 4), and 12.25 (s, 1 exchange with deuterium oxide); mass spectrum, molecular ion, m/e 280.

Anal. Calcd. for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.75; N, 19.99. Found: C, 68.16; H, 6.04; N, 19.93.

4-Amino-5-(2,5-dimethyl-*N*-pyrryl)pyrimidine (**7b**).

A solution of 500 mg. of **6b**, 1 g. of 2,5-hexanedione, 3 ml. of acetic acid and 20 ml. of ethanol was refluxed for 5 hours. After workup as before, the residue was chromatographed over 30 g. of alumina. Elution with chloroform gave 550 mg. of **7b** which was crystallized from methanol-ether led to 450 mg. (53%) of **7b**, m.p. 206-209°; uv λ max 220 mμ (ε, 8,300) and 245 mμ (ε, 8,600); ir ν max 3300, 1650, 1600, 1400, 980, 790, 755 cm^{-1}; nmr δ 1.92 (s, 6), 5.9 (s, 2), 6.5 (s, 2 disappears on addition of deuterium oxide), 8.02 (s, 1) and 8.47 (s, 1); mass spectrum, molecular ion, m/e 188.

Anal. Calcd. for $C_{10}H_{12}N_4$: C, 63.81; H, 6.43; N, 29.76. Found: C, 64.44; H, 6.44; N, 30.31.

4-Amino-5-(2,5-dimethyl-*N*-pyrryl)-6-hydroxypyrimidine (**7c**).

A mixture of 340 mg. of **6c**, 1 g. of 2,5-hexanedione, 3 ml. of acetic acid and 15 ml. of ethanol was refluxed for 3 hours. After workup as before, it was chromatographed over 30 g. of alumina. Elution with 10% methanol-tetrahydrofuran gave **7c** which was crystallized from methanol-ether to give 180 mg. (33%) of **7c**, m.p. 288° dec.; uv λ max 215 mμ (ε, 30,800) and 261 mμ (ε, 12,600); ir ν max 3450, 1620 cm^{-1}; nmr δ 1.91 (s, 6), 5.75 (s, 2), 6.09 (s, 2 disappears on addition of deuterium oxide), 7.9 (s, 1) and 12.28 (s, 1 disappears on addition of deuterium oxide); mass spectrum molecular ion, m/e 204.

Anal. Calcd. for $C_{10}H_{12}N_4O$: C, 58.81; H, 5.92; N, 27.43. Found: C, 58.68; H, 6.07; N, 27.19.

2-Methyl-4-amino-5-(2,5-dimethyl-*N*-pyrryl)-6-hydroxypyrimidine (**7d**).

A solution of 550 mg. of **6d**, 1 g. of 2,5-hexanedione, 3 ml. of acetic acid and 30 ml. of ethanol was refluxed for 3 hours. After workup as before, the residue was chromatographed over 30 g. of alumina. Elution with 1:15 methanol-ether led to **7d** which was crystallized from tetrahydrofuran-ether to give 280 mg. (33%) of pure **7d**, m.p. 140-142° loss of water, 220-224°; uv λ max 210 mμ (ε, 30,600), 258 mμ (ε, 10,700); ir ν max 3500 and 1620 cm^{-1}; nmr δ 1.87 (s, 6), 2.18 (s, 3), 5.70 (s, 2), 5.85 (s, 2 disappears on addition of deuterium oxide) and 11.65 (s, 1 disappears on addition of deuterium oxide).

Anal. Calcd. for $C_{11}H_{14}N_4O \cdot H_2O$: C, 55.92; H, 6.83; N, 23.71. Found: C, 55.66; H, 6.70; N, 23.46.

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(11) Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected; infrared spectra were obtained on a Perkin-Elmer infrared spectrophotometer using the potassium bromide method; ultraviolet spectra on a CF 4 "OPPTICA" spectrophotometer in a *p*H 1 solution; nmr spectra on a Varian Model H-60 spectrometer using hexadeuterodimethylsulfoxide as solvent and tetramethylsilane as an internal reference; analysis were performed by the Microanalysis Laboratory, Hebrew University, Jerusalem, Israel; alumina active grade III was used in all chromatography columns.