5-Vinyl Pyrimidines. I. Synthesis

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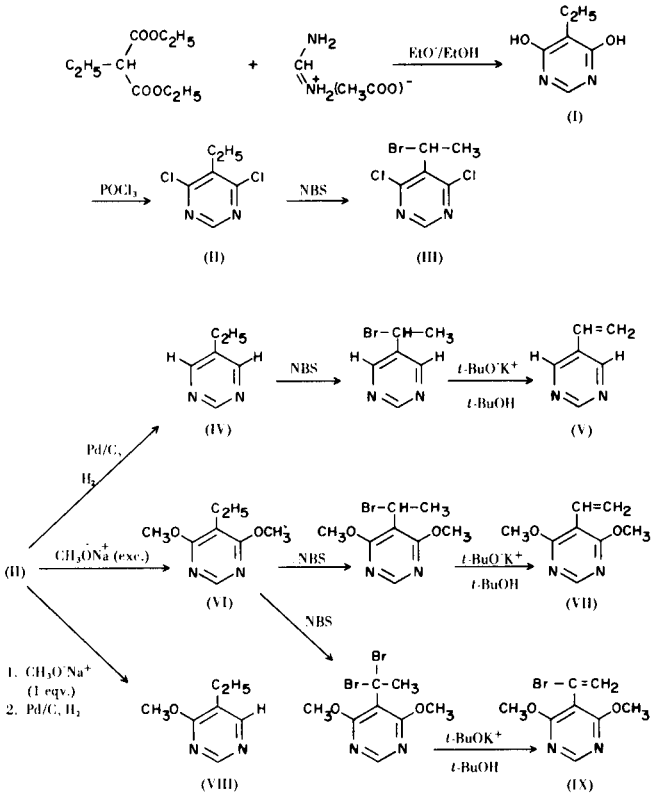
A total synthesis of 5-vinyl pyrimidine and some of its substituted derivatives is described. The following vinyl pyrimidines have been prepared: 5-vinyl pyrimidine, 5-vinyl-4,6-dimethoxy pyrimidine, 5-(α-bromo) vinyl-4,6-dimethoxy pyrimidine.

The electrical properties of polymeric complexes (1-5) of 5-ethylpyrimidine with transition metal ions, have been studied in this laboratory (6). It was of interest, in this connection, to prepare a related complex-forming polymer - poly-5-vinylpyrimidine.

5-Vinyl pyrimidine (V), 4,6-dimethoxy-5-vinyl pyrimidine (VII) and 5-(α-bromo)vinyl pyrimidine (IX) were obtained from the corresponding 5-ethyl derivatives by bromination with *N*-bromosuccinimide followed by dehydrobromination. Excess of potassium *t*-butoxide in *t*-butyl alcohol was reacted with the 5-(α-bromo)ethyl-pyrimidines to effect the dehydrobromination. Heating of the 5-(α-bromo)ethylpyrimidines or reaction with tertiary amines such as *N,N*-dimethylaniline, *N*-ethyldi-isopropyl amine and NBD (1.5diazabicyclo[4.3.0]on-5-ene) were not effective in the dehydrobromination. The reaction mixture either polymerized or the starting materials recovered.

5-(α-Bromo)vinyl-4,6-dimethoxypyrimidine (IX) was obtained from the 5-(α,α-dibromo)ethyl derivative on reacting it with either an excess or an equivalent amount of potassium *t*-butoxide. 5-(α-bromo)ethyl-4,6-dichloro-pyrimidine (III) could not be dehydrobrominated even when heated with excess of potassium *t*-butoxide in dimethylsulfoxide. This might be due to the combined inductive (-I) effects of the pyrimidine ring and the chlorine atoms. Bromination of 4-methoxy-5-ethylpyrimidine (VIII) with NBS followed by dehydrobromination of the crude α-bromo derivative, resulted in 40-50% yield of 4-methoxy-5-vinylpyrimidine. This was evident from nmr and vpc measurements carried out with the crude reaction product. No attempt was made to purify the crude reaction product.

The synthetic method employed for the synthesis of the 5-vinylpyrimidines is outlined in the following scheme:

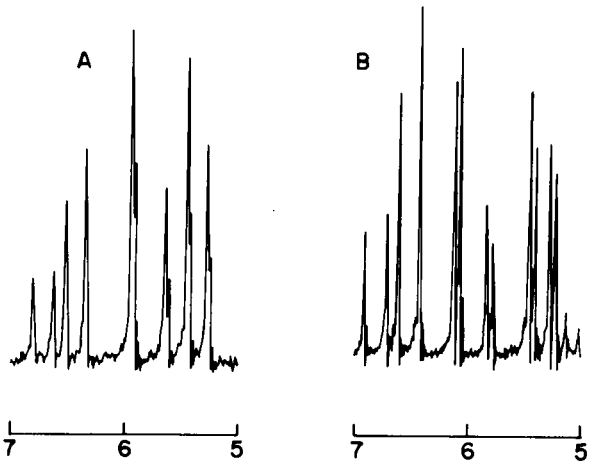


EXPERIMENTAL

Synthesis of Pyrimidine Derivatives.

4,6-Dihydroxy-5-ethylpyrimidine (I).

Ethyl diethylmalonate (98 g., 0.52 mole) was added to a solution of sodium (24.5 g., 1.04 mole) in 400 ml. absolute ethanol under anhydrous conditions. This was followed by addition of formamidine acetate (54 g., 0.52 mole). The reaction



A. Nmr spectrum of 5-vinylpyrimidine: 5-7 ppm (vinyl hydrogens (9), 3H), 8.73 ppm (2H), 9.05 ppm (1H).

B. Nmr spectrum of 4,6-dimethoxy-5-vinylpyrimidine: 3.98 ppm (s, 6H), 5-7 ppm (vinyl hydrogens (9), 3H), 8.20 ppm (1H).

mixture was stirred for 24 hours, the precipitate filtered off and washed with ethanol. The filtrate was evaporated to dryness and the combined precipitates were dissolved in 500 ml. of hot water. The aqueous solution was then cooled to room temperature and acidified with glacial acetic acid. The white precipitate formed was filtered, washed with water and then ethanol, and recrystallized from ethanol (63 g., 87%); nmr: 1.2 ppm (t, J = 6.9 cps, 3H); 2.69 ppm (q, J = 6.9 cps, 2H); 9.24 ppm (s, 1H).

Anal. Calcd. for $C_6H_8N_2O_2$: C, 51.43; H, 5.75; N, 19.98. Found: C, 51.42; H, 5.92; N, 19.88.

4,6-Dichloro-5-ethylpyrimidine (II).

A mixture of 4,6-dihydroxy-5-ethylpyrimidine (43 g., 0.308 mole) and 260 ml. of phosphoryl chloride was refluxed for 1 hour. A yellow-orange homogeneous solution was formed. The excess of phosphorus oxychloride was distilled under vacuum and the residue was poured, with stirring, onto crushed ice (500 g.) and left overnight in the cold. This was followed by extraction with chloroform. A fraction of b.p. 106-110°/20 mm was recovered (46 g., 65%); nmr: 1.23 ppm (t, J = 7.5 cps, 3H); 2.88 ppm (q, J = 7.5 cps, 2H); 8.52 ppm (s, 1H); ir: 760, 780, 815 cm^{-1} (C-Cl).

Anal. Calcd. for $C_6H_6Cl_2N_2$: C, 40.71; H, 3.42; N, 15.82. Found: C, 40.87; H, 3.49; N, 16.03.

5-(α-Bromo)ethyl-4,6-dichloropyrimidine (III).

5-Ethyl-4,6-dichloropyrimidine (5 g., 0.028 mole) was added to a solution of *N*-bromosuccinimide (5 g., 0.028 mole) and benzoylperoxide (0.4 g.) in carbon tetrachloride (150 ml.). The reaction mixture was heated under reflux for 2.5-3 hours. It was then cooled to room temperature, filtered, the solvent evaporated from the filtrate and the residue distilled to yield a fraction of b.p. 102°/0.25 mm (6.1 g., 85%); nmr: 2.12 ppm (d, J = 7.5 cps, 3H); 5.75 ppm (q, J = 7.5 cps, 1H); 8.62 ppm (s, 1H).

Anal. Calcd. for $C_6H_5BrCl_2N_2$: C, 28.10; H, 1.95; N, 10.90; Cl, 27.80; Br, 31.20. Found: C, 28.25; H, 2.21; N, 10.56; Cl, 27.40; Br, 31.74.

5-Ethylpyrimidine (IV).

A mixture of 4,6-dichloro-5-ethylpyrimidine (17.7 g., 0.1 mole), anhydrous sodium acetate (17 g., 0.21 mole) and 1 g. of Pd/C (10%) in 150 ml. absolute ethanol were hydrogenated at room temperature using a Paar apparatus for 5-6 hours. The reaction mixture was then filtered. Ethanol was distilled away from the filtrate, and ether was added to the residue followed by a saturated solution of sodium bicarbonate until no evolution of carbon dioxide was observed. The ether fraction was washed with a little water and dried. A fraction of b.p. 84-86°/60 mm (8) (8.6 g., 80%) was recovered from the etheral solution; nmr: 1.25 ppm (t, J = 7.5 cps, 3H); 2.65 ppm (q, J = 7.5 cps, 2H), 8.62 ppm (s, 2H); 8.87 ppm (s, 1H).

5-Vinylpyrimidine (V).

5-Ethylpyrimidine (5.6 g., 0.05 mole) was added to a solution of NBS (10 g., 0.056 mole) and benzoylperoxide (0.2 g.) in 150 ml. of carbon tetrachloride. The mixture was refluxed under the light of a lamp for 90 minutes. It was then cooled to room temperature and filtered. The filtrate was evaporated under vacuum. The residue which contained 80-85% of 5-(α-bromo)-ethylpyrimidine as evident from vpc and nmr measurements, was further used without any purification. The nmr spectrum of this crude product contained the characteristic bands of 5-(α-bromo)-ethylpyrimidine as follows: 2.04 ppm (d, J = 7.5 cps, 3H); 5.11 ppm (q, J = 7.5 cps, 1H); 8.73 ppm (s, 2H); 9.06 ppm (S, 1H). The crude bromination product was dissolved in 50 ml. of *t*-butyl alcohol and this solution was added dropwise into a hot solution of potassium *t*-butoxide (11.2 g., 0.1 mole) in *t*-butyl alcohol (150 ml.). A precipitate was immediately formed. The reaction mixture was refluxed for an additional 2 hours and left overnight at room temperature and then filtered. Most of the solvent was evaporated, water added and the mixture was extracted with carbontetrachloride. A fraction of b.p. 86°/45 mm (2.1 g., 40%) was recovered from the extracts. The nmr spectrum of the vinyl group of 5-vinylpyrimidine (V) and 5-vinyl-4,6-dimethoxypyrimidine (VII) is of the ABC type and is very similar to that of 4-vinylpyridine (9) (see Figure).

Anal. Calcd. for $C_6H_6N_2$: C, 67.90; H, 5.70; N, 26.40. Found: C, 67.64; H, 5.61; N, 26.72.

4,6-Dimethoxy-5-ethylpyrimidine (VI).

A solution of 4,6-dichloro-5-ethylpyrimidine (17.7 g., 0.1 mole) in 50 ml. of methanol was added dropwise to a solution of sodium (11.5 g., 0.5 mole) in 150 ml. of methanol under anhydrous conditions. A white precipitate was formed. The reaction mixture was refluxed for 2 hours with stirring, cooled to room temperature and filtered. The precipitate was washed with a little cold ethanol. The combined filtrates were evaporated to dryness and water was added, followed by extraction with ether. The ether solution was dried and the ether evaporated. The residue crystallized to give a product of m.p. 34-35° (13.7 g., 81%); nmr: 1.04 ppm (t, J = 7.5 cps, 3H); 2.49 ppm (q, J = 7.5 cps, 2H); 3.90 ppm (s, 6H); 8.20 ppm (s, 1H).

Anal. Calcd. for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.65. Found: C, 57.13; H, 7.17; N, 16.58.

5-Vinyl-4,6-dimethoxypyrimidine (VII).

5-Ethyl-4,6-dimethoxypyrimidine (VI) (24 g., 0.143 mole) was added into a solution of *N*-bromosuccinimide (28.6 g., 0.160 mole) and benzoyl peroxide (1 g.) in 250 ml. of carbon tetrachloride. The reaction mixture was refluxed for 2 hours, cooled to room temperature and filtered. The filtrate was evaporated

under vacuum. The residue could not be purified by distillation due to side reactions. It contained 85% of 5-(α-bromo)ethyl-4,6-dimethoxypyrimidine as was evident from vpc and nmr measurements. This crude product was used without any further purification; nmr (carbon tetrachloride): 2.00 ppm (d, J = 7.5 cps, 3H); 3.49 ppm (s, 6H); 5.56 ppm (q, J = 7.5 cps, 1H); 8.27 ppm (s, 1H).

The crude 5-(α-bromo)ethyl-4,6-dimethoxypyrimidine (28.2 g., 0.114 mole) was dissolved in *t*-butyl alcohol (50 ml.) and added dropwise with stirring into a solution of potassium *t*-butoxide (28 g., 0.25 mole) in *t*-butyl alcohol (300 ml.) during 40 minutes. The reaction mixture was then refluxed for 2 hours and was left overnight at room temperature. It was evaporated under vacuum, water added and then extracted with ether. The residue left behind after evaporating the ethereal solution was distilled to give a fraction of b.p. 54-56°/0.25 mm Hg (10.5 g., 44%); nmr: see Figure.

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.60; H, 6.10; N, 16.84. Found: C, 57.34; H, 6.18; N, 16.60.

4-Methoxy-5-ethylpyrimidine (VIII).

A solution of sodium (2.3 g., 0.1 mole) in methanol was added dropwise with stirring to a solution of 4,6-dichloro-5-ethylpyrimidine (17.7 g., 0.1 mole) at room temperature. The reaction mixture was stirred for one hour after the end of the addition, and then filtered. The filtrate was evaporated to dryness, and water and ether were added. The ethereal layer was separated and dried, and the ether evaporated away. The residue was hydrogenated using Pd/C (10%) catalyst as described for the dichloro derivative. The crude liquid product recovered from the hydrogenation mixture was 94% pure (by vpc). It was distilled to yield a fraction of b.p. 114-116°/65 mm (9 g., 65%); nmr: 1.15 ppm (t, J = 7.5 cps, 3H); 2.50 ppm (q, J = 7.5 cps, 2H); 3.97 ppm (s, 3H); 8.17 ppm (s, 1H); 8.57 ppm (s, 1H).

Anal. Calcd. for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.27. Found: C, 60.32; H, 7.26; N, 19.93.

5-(α-Bromo)vinyl-4,6-dimethoxypyrimidine (IX).

A solution of 5-ethyl-4,6-dimethoxypyrimidine (5 g., 0.03 mole) in carbon tetrachloride was added into a solution of NBS (12 g., 0.067 mole) and benzoylperoxide (0.3 g.) in 200 ml. of carbon tetrachloride. The reaction mixture was refluxed for 2 hours under the light of a lamp, and then cooled to room temperature. The solvent was evaporated and the crude residue dissolved in *t*-butyl alcohol (25 ml.). The resulting solution was added dropwise into a hot solution of potassium *t*-butoxide (8 g., 0.071 mole) in 100 ml. of *t*-butyl alcohol. The reaction mixture was then refluxed for 2 hours and left overnight at room temperature. The solvent was then evaporated, and the residue dissolved in water and extracted with ether. The crude product obtained after evaporating the ether solidified on cooling. On recrystallization from ethanol yellow crystals were obtained (4.1 g., 56%) m.p. 107-108°; nmr (carbon tetrachloride): 3.97 ppm (s, 6H); 7.07 ppm (s, 2H); 8.14 ppm (s, 1H).

Anal. Calcd. for $C_8H_9BrN_2O_2$: C, 39.20; H, 3.70; N, 11.40; Br, 32.59. Found: C, 39.27; H, 3.85; N, 11.33; Br, 32.59.

Nuclear Magnetic Resonance.

Nmr spectra were recorded on a JEOL 60 MHz spectrometer employing 5-10% concentrations in deuteriochloroform. All chemical shifts are given in ppm from internal tetramethylsilane.

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