

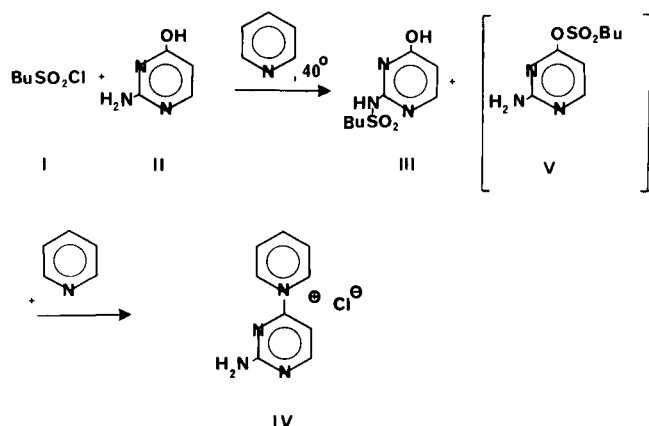
The Base Catalyzed Ring-Opening Reaction of
N-(2-Amino-4-pyrimidinyl)pyridinium Chloride

E. Patrick Lira

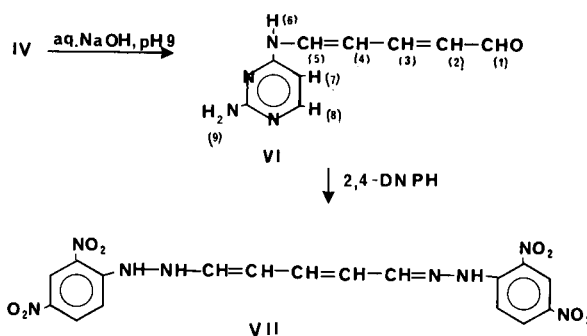
International Minerals & Chemical Corporation, Libertyville, Illinois 60048

Received January 14, 1972

While investigating the reaction of sulfonyl halides with various hydroxyl substituted heterocyclic compounds, we discovered that butanesulfonyl chloride (I) reacts with 2-amino-4-hydroxypyrimidine (II, isocytosine) in pyridine to form, in addition to the expected sulfonamide III, the pyridinium chloride IV (1). This product is apparently formed through the intermediate sulfonate V by a displacement reaction with pyridine. The salt IV precipitated from the reaction media in preference to the corresponding butanesulfonate salt because of its relative insolubility. When compound III was treated with pyridine under similar conditions, it was recovered in 80% yield.



The reaction of pyridinium salts with nucleophilic reagents has been studied intensively (2,3,4). The nature of the quaternizing group is one of the important factors in determining the course of the reaction (2). Therefore, because the 2-amino-4-pyrimidinyl group is not a typical quaternizing function, we treated an aqueous solution of pyridinium salt IV with 2 *N* aqueous sodium hydroxide. A transient reddish coloration appeared at pH 8.5 followed by the precipitation of a yellowish-brown solid at pH 8.7. This solid was established to be the open chain amino aldehyde VI by elemental, infrared, and nuclear magnetic resonance analyses (5). The hydrazone VII was prepared from VI by treatment with 2,4-dinitrophenylhydrazine (2,4-DNPH).



Amino aldehydes similar to VI have been prepared previously (5,6,7,8), but a quaternizing group containing both electron attracting and electron donating functions has not been reported in these reactions. The increase in electron density of the pyrimidine ring due to the 2-amino group is apparently not sufficient to offset the electron attracting effect of the two ring nitrogens and therefore, the ring opening reaction of the pyridinium salt occurs.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus or a Fisher-Johns melting point apparatus and are uncorrected. The ultraviolet spectra were determined in aqueous solution on a Beckman DK-2A ratio recording spectrophotometer. The infrared spectra were determined on a Perkin-Elmer Model 521 spectrophotometer. The nuclear magnetic resonance spectra were determined in deuterium oxide or deuterated DMSO at 60 Mc/sec on a Varian Associates A-60 spectrometer at Simon Research Laboratory, Elgin, Illinois, by Dr. W. Simon. The microanalyses were performed by our analytical department.

2-*n*-Butanesulfonamido-4-hydroxypyrimidine (III) and *N*-(2-Amino-4-pyrimidinyl)pyridinium Chloride (IV).

To a warm (40°), stirred milky suspension of 11.2 g. (0.1 mole) of dry 2-amino-4-hydroxypyrimidine (II) in 250 ml. of dry pyridine was added dropwise 15.8 g. (0.1 mole, 13 ml.) of *n*-butanesulfonyl chloride (I). The stirred mixture was heated (40°) overnight and then cooled at approximate 5° over the weekend, filtered and dried to yield 8.2 g. (39%) crude pyridinium salt IV, sinters at 60°, m.p. 150-170° dec. Crude IV was crystallized from absolute ethanol to yield pure IV, m.p. 167-169° dec.; ir

(potassium bromide) 3.0 (broad, H-bonding) 6.2 and 6.5 (C=C, C=N); $\text{uv } \lambda \text{ max (water) pH 1 225.5 } (\epsilon = 20,960)$, 267.0 ($\epsilon = 4,330$) and 330.0 $\text{m}\mu$ ($\epsilon = 2,790$); $\text{pH 7 225.5 } (\epsilon = 21,400)$ 264.0 ($\epsilon = 5,030$) and 332.0 $\text{m}\mu$ ($\epsilon = 2,790$); nmr (deuterium oxide) δ 7.18 (d, 1H, $J_{AB} = 5.5$ cps, pyrimidine ring H), 8.20 (m, 2H β), 8.48 (d, 1H, $J_{BA} = 5.5$ cps, pyrimidine ring H), 8.75 (m, 1H δ), 9.36 (m, 2H α).

Anal. Calcd. for $\text{C}_9\text{H}_9\text{ClN}_4\cdot\text{H}_2\text{O}$: C, 47.69; H, 4.89; N, 24.72; Cl 15.64. Found: C, 47.86; H, 4.94; N, 25.00; Cl 15.5.

The above filtrate was evaporated under vacuum and purged twice with toluene under vacuum to afford reddish-brown solids which were triturated with hot isopropyl alcohol (175 ml.) to yield pure III (3.6 g., 15.5%), m.p. 249.5-250.5°. The alcohol solution was cooled to yield crude III (4.7 g.) which was crystallized from methanol to afford additional III (3.0 g., 13%), m.p. 246-248°. A sample was recrystallized (2X) from methanol to yield analytically pure III, m.p. 251.5-252.5°, ir (potassium bromide) 3.2 (N-H), 5.9 (C=O), 8.2 and 8.7 μ (SO_2N); $\text{uv } \delta \text{ max (water) pH 1 225 m}\mu$ ($\epsilon = 7,020$), $\text{pH 7/260 } (\epsilon = 3,750)$ and 285 $\text{m}\mu$ ($\epsilon = 23,310$), $\text{pH 10 273.5 m}\mu$ ($\epsilon = 5,270$), nmr (deuterium oxide) δ 0.93 (t, 3H, $J = 7$ cps, CH_3), 1.62 (m, 4H, 2 CH_2), 2.98 (t, 2H, $J = 7$ cps, S- CH_2), 6.10 (d, 1H, $J_{AB} = 7.5$ cps, pyrimidine ring H), and 7.70 (d, 1H, $J_{BA} = 7.5$ cps, pyrimidine ring H).

Anal. Calcd. for $\text{C}_8\text{H}_{13}\text{N}_3\text{O}_3\text{S}\cdot\text{H}_2\text{O}$: C, 38.55; H, 6.07; N, 16.85; S, 12.85. Found: C, 38.72; H, 6.15; N, 16.93; S, 12.55.

N-(2-Amino-4-pyrimidinyl)-5-amino-2,4-pentadienal (VI).

To a vigorously agitated solution of pyridinium salt IV (4 g., 0.0175 mole) in water (100 ml.) at ambient temperature was added cautiously sufficient aqueous 2 *N* sodium hydroxide to maintain the pH at 9. The yellowish-brown mixture was cooled and then neutralized to pH 7, filtered and the resulting yellowish-brown solids (VI) washed thoroughly with water. The solids were dried in vacuum at 55° to yield amino aldehyde VI (3.0 g., 90%), sintered at 130°, m.p. 270° dec., sealed capillary: sintered at 135° with condensate, m.p. 290° dec., ir (potassium bromide) 3.55 and 3.65 (aldehyde H), 6.00 μ (C=O); $\text{uv } \lambda \text{ max (water) pH 1 353.0 m}\mu$ ($\epsilon = 42,250$); nmr (deuterated DMSO) δ 5.88 (q, 1H, $\text{H}_{(2)}$), 6.08 (overlap, 1H, $\text{H}_{(7)}$), 6.15 (overlap, 1H, $\text{H}_{(4)}$), 6.43 (s, 2H, NH_2), 7.37 (q, 1H, $\text{H}_{(3)}$), 7.7-8.1 (diffuse, 2H, $\text{H}_{(5)}$, $\text{H}_{(8)}$), 9.34 (d, 1H, C-H $_{(1)}$) and 10.05 (diffuse, 1H, $\text{NH}_{(6)}$).

Anal. Calcd. for $\text{C}_9\text{H}_{10}\text{N}_4\text{O}$: C, 56.80; H, 5.26; N, 29.42. Found: C, 56.88; H, 5.37; N, 29.49.

Reaction of Amino Aldehyde VI and 2,4-Dinitrophenylhydrazine (2,4-DNPH).

To a vigorously stirred, hot acetic acid solution (2 ml.) of amino aldehyde VI (150 mg.) was added a hot acetic acid (2.5 ml.) solution of 2,4-DNPH (320 mg.) containing 3 drops concentrated hydrochloric acid. Water (1 ml.) and additional acetic acid (1.5 ml.) were added and the mixture was boiled for 30 minutes. Additional water (3 ml.) was added and then the solution reduced to half its volume, cooled, and the resulting brownish-orange solids separated by filtration, washed with water (3 x 10 ml.) and dried to yield crude VII (275 mg.) m.p. 190-193°. Repeated recrystallization from aqueous acetic acid (4X) gave analytically pure VII, m.p. 201-203°.

Anal. Calcd. for $\text{C}_{17}\text{H}_{14}\text{N}_8\text{O}_8\cdot 2\text{H}_2\text{O}$: C, 41.29; H, 3.67; N, 22.7. Found: C, 40.90; H, 3.58; N, 23.0.

Acknowledgment.

The author wishes to thank Dr. C. W. Huffman for his encouragement, Dr. M. Hamer and Dr. J. F. Kraemer for many interesting discussions and IMC's Analytical Department for the analytical results.

REFERENCES

- (1) B. K. Snell, *J. Chem. Soc. C*, 2358 (1968) previously reported the isolation of a pyridinium salt when 2-amino-5-n-butyl-4-hydroxy-6-methylpyrimidine and *p*-bromobenzenesulfonyl chloride were allowed to react.
- (2) D. Beke in "Advances in Heterocyclic Chemistry," Vol. 1, A. R. Katritzky, Ed., Academic Press, New York, N. Y., 1963, pp. 167-188.
- (3) R. A. Barnes in "Pyridine and Its Derivatives, Part One", E. Klingsberg, Ed., Interscience Publishers, New York, N. Y., 1960, pp. 57-60.
- (4) F. Krohnke, *Angew. Chem. Intern. Edit. Engl.*, 2, 280 (1963).
- (5) Y. Tamura, N. Tsujimoto, and M. Mano, *Chem. Pharm. Bull.*, 19, 130 (1971). The δ and splitting patterns for the 2,4-pentadienal hydrogens in compound VI were similar to those reported by these authors for 5-(2,4-dinitroanilino)-2,4-pentadienal.
- (6) D. Beke and C. Szantay, *Ann. Chem.*, 640, 127 (1961).
- (7) E. Koenigs and G. Jung, *J. Prakt. Chem.*, 137, 157 (1933).
- (8) E. Larrea and J. L. Leon, *An. Real Soc. Espan. Fis. Quim. (Univ. Madrid)*, 56B, 995 (1960).