Decarboxylation of 2,6-Disubstituted Pyrimidine-4-acetic Acids

Carlton E. Turner, John H. Bedenbaugh (1), and Charles E. Lane, Jr.

Department of Chemistry, University of Southern Mississippi
Hattiesburg, Mississippi 39401

Received April 20, 1970 - Revised September 13, 1971

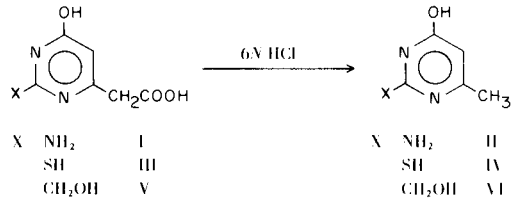
Oxidation of a side chain to a carboxyl group, followed by decarboxylation, constitutes an effective way to remove an alkyl group from pyrimidines. For example, the decarboxylation of pyrimidine-4-carboxylic acid was once an important preparative method for the production of pyrimidine; furthermore, Schlenker (2) decarboxylated 5-methylpyrimidine-4-carboxylic acid to obtain 5-methylpyrimidine. Although the decarboxylation procedure has been successfully employed many times in the case of carboxyl groups attached directly to the ring, relatively little has been published about the decarboxylation of pyrimidine-4-acetic acids to the corresponding methylpyrimidines. The inadvertent decarboxylation of 6-hydroxy-2-thiopyrimidine-4-acetic acid (III) during a recrystallization procedure led to this investigation of the decarboxylation of pyrimidine-4-acetic acids. 4-Methylpyrimidines are made more conveniently by condensation reactions involving ethyl acetoacetate (3); however, knowledge of the decarboxylation reaction is important to avoid converting pyrimidine-4-acetic acids to 4-methylpyrimidines during isolation and recrystallization procedures.

Wheeler and Little (4), to our knowledge, reported the first example of the decarboxylation of a pyrimidine-4-acetic acid, the decarboxylation of 2-ethylmercapto-6-hydroxypyrimidine-4-acetic acid at 170°. Recently, Shvachkin, *et al.* (5,6) reported that 2,6-dihydroxypyrimidine-4-acetic acid was stable in hot alkalies, but could be decarboxylated in 100% yield to 6-methylpyrimidine-2,4-diol when refluxed for 8 hours with 2*N* hydrochloric acid. Shvachkin stated that the decarboxylation is readily explained on electronic grounds, and that the actual decarboxylation proceeds *via* initial protonation of one hetero atom to produce a pyrimidinium structure.

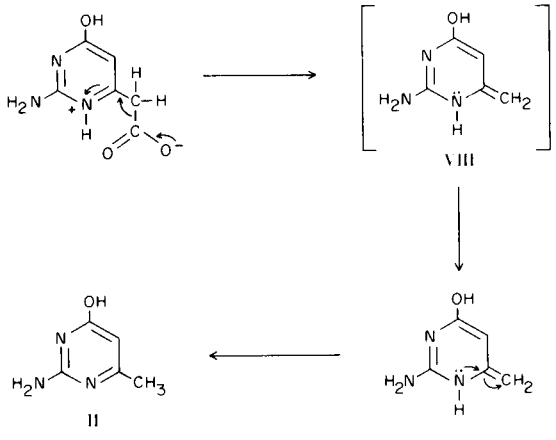
Recent findings in these laboratories show that the decarboxylation of 2,6-dihydroxypyrimidine-4-acetic acid by Shvachkin was not an isolated reaction but only one example of the general tendency of appropriate 2,6-disubstituted pyrimidine-4-acetic acids to decarboxylate.

2-Amino-6-hydroxypyrimidine-4-acetic acid (I) was successfully decarboxylated to produce 2-amino-6-methyl-4-pyrimidinol (II) by boiling 8 hours in 6*N* hydrochloric acid. Furthermore, 6-hydroxy-2-thiopyrimidine-4-acetic acid (III) and 2-hydroxymethyl-6-hydroxypyrimidine-4-acetic acid (V) were decarboxylated in the same way to give the methyl derivatives. Yields were comparable to those reported by Shvachkin, *et al.:* nearly quantitative.

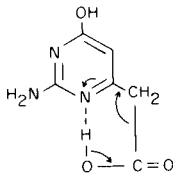
In each case, an admixture of the methyl derivatives obtained by decarboxylation did not depress the melting point of the methyl compounds obtained by the condensation of the substituted urea derivatives with ethyl acetoacetate. Moreover, a comparison of the infrared spectrum of each product of decarboxylation with that of the corresponding authentic methyl compound showed that the two were identical.



Decarboxylation of I also occurred under essentially neutral conditions by boiling in water for 8 hours. Apparently the neutral decarboxylation of I proceeds through a neutral enamine (VII) which could be formed *via* the transition state VIII or from IX. This is supported by results obtained by Doering and Pasternak (7). In light of the recent work by Stermitz and Huang (8) which



showed that 2- and 4-pyridylacetic acid thermally decarboxylate in water with equal ease and with a similar *p*H profile, it appears that transition state VIII is much more likely than IX.



IX

In view of the nature of the substituents in the 2 and 6 positions of the pyrimidine-4-acetic acids discussed, we propose that under acidic conditions decarboxylation of pyrimidine-4-acetic acids containing electron-donating substituents in the 2 and 6 position is a general occurrence.

EXPERIMENTAL

The melting points reported were determined on a Mel-Temp apparatus and are uncorrected. The microanalysis was performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

Infrared spectra were determined in potassium bromide disks with a Perkin-Elmer Model 257 spectrophotometer. Nmr spectra were determined on a Varian Model A-60D spectrometer with tetramethylsilane as an internal reference.

Compound I was prepared by the method of Worall (9,10), II by the procedure of Jaeger (11), and III by the method of Schueler, Grabhoefer and Ulrich (12). The structures of these compounds were confirmed by infrared and nuclear magnetic resonance spectra.

Compound IV and diethyl acetonedicarboxylate were obtained commercially and glycolamidine hydrochloride was prepared in 63% yield by a procedure described by Kim (13), m.p. 147-149°.

2-Hydroxymethyl-6-hydroxypyrimidine-4-acetic acid (V).

To a 13 ml. 2*N* solution of sodium hydroxide was added glycolamidine hydrochloride (2.75 g., 0.0240 mole) and diethyl acetonedicarboxylate (5.05 g., 0.0250 mole). The suspension was shaken for 4 hours followed by standing 14 hours at ambient temperature. Acidification to *p*H 5 with glacial acetic acid followed by cooling gave 1.53 g. (47%) of the sodium salt of V which melted at 236°. Acidification to *p*H 3 with hydrochloric acid gave the free acid. Ir ν max (potassium bromide) 3098 (sh), 2845 (w), 1840 (sh), 1692 (vvs), 1681 (vvs), 1593 (vvs, COO^-), 1480 (s), 1449 (m), 1411 (s), 1366 (vvs), 1280 (m), 1238 (w), 1190 (m, ring OH), 1173 (m), 1108 (s), 1018 (s, primary OH), 987 (vw), 958 (m), 930 (w), 918 (m), 862 (m), 828 (vw), 781 (w), 751 (m), 701 (w), and 635 cm^{-1} (vw); nmr (DMSO-d_6, max) τ 4.18 (s, 1, aromatic H), 5.77 (s, 2, -CH_2OH), and 7.92 (s, 2, -CH_2COO).

Anal. Calcd. for $C_7H_7N_2O_4Na$: C, 40.79; H, 3.43; N, 13.59. Found: C, 40.58; H, 3.39; N, 13.46.

The above procedure (14) will serve as an example for the preparation of the following compound.

2-Hydroxymethyl-6-methyl-4-pyrimidinol (VI).

Glycolamidine hydrochloride (2.76 g., 0.0250 mole), 2*N* sodium hydroxide (13 ml.), ethyl acetoacetate (3.17 g., 0.0260 mole) gave, after recrystallization from absolute ethanol, 1.73 g. (50%) of VI which melted at 197-203°; ir ν max (potassium bromide) 3180 (m), 2976 (m, CH_3), 2901 (m), 2826 (m-s), 1656 (vvs), 1619 (sh), 1475 (w), 1436 (w), 1409 (m), 1382 (vw), 1358 (m), 1272 (w), 1245 (vw), 1225 (w), 1188 (s, ring OH), 1102 (vs), 1039 (s, primary OH), 990 (sh), 974 (vs), 943 (m), 916 (m), 867 (m), 855 (s), 750 (vw), 695 (vw), and 688 cm^{-1} (vw); nmr (DMSO-d_6 max) τ 3.92 (s, 1, aromatic H), 5.65 (s, 2, -CH_2OH), and 7.82 (s, 3, -CH_3).

Decarboxylation of Pyrimidine-4-acetic Acids.

In each case, 1 g. of the pyrimidine was suspended in 6*N* hydrochloric acid (30 ml.), and refluxed for 8 hours, after which time, the *p*H was adjusted to 6.9 with concentrated ammonium hydroxide. Chilling, followed by filtration and recrystallization from absolute ethanol, gave, after drying *in vacuo*, a good yield of the known methyl derivatives. Decarboxylation of: I gave II, m.p. 289-293°, reported (15), m.p. 297-298°; III gave IV, m.p. 323° dec., purchased authentic compound, m.p. 322° dec.; V gave VI, m.p. 197-203°, unambiguously prepared compound (16) m.p. 197-203°.

Acknowledgment.

We are grateful to the Mississippi Research and Development Center for supporting this work.

Funds for the nmr spectrometer used in this investigation were provided in part by the National Science Foundation.

REFERENCES

(1) To whom all communications should be addressed.

(2) J. Schlenker, *Ber.*, **34**, 2812 (1901).

(3) D. J. Brown, "The Chemistry of Heterocyclic Compounds. Vol. XVI. The Pyrimidines", Interscience Publishers, Inc., New York, N. Y., 1962, pp. 48, 49.

(4) H. L. Wheeler and L. M. Little, *J. Am. Chem. Soc.*, **30**, 1156 (1908).

(5) Yu. P. Shvachkin, M. K. Berestenko, and G. P. Mishin, *Zh. Obshch. Khim.*, **34**, 1687 (1964); *Chem. Abstr.*, **61**, 5644c (1964).

(6) Yu. P. Shvachkin, M. K. Berestenko, and G. P. Mishin, *Biol. Aktivn. Soedin., Akad. Nauk. SSSR*, 63 (1965); *Chem. Abstr.*, **64**, 9720d (1965).

(7) W. Von E. Doering and V. Z. Pasternak, *J. Am. Chem. Soc.*, **72**, 143 (1950).

(8) F. R. Stermitz and W. H. Huang, *ibid.*, **93**, 3427 (1971).

(9) D. E. Worrall, *ibid.*, **40**, 1133 (1918).

(10) D. E. Worrall, *ibid.*, **65**, 2053 (1943).

(11) J. Jaeger, *Ann. Chem.*, **262**, 365 (1891).

(12) H. Schueler, H. Grabhoefer, and H. Ulrich, German Patent 1,163,142 (1964).

(13) D. H. Kim, Ph. D. Dissertation, The University of North Carolina, (1965), p. 38.

(14) G. E. McCasland and D. S. Tarbell, *J. Am. Chem. Soc.*, **68**, 2393 (1946).

(15) R. N. Lacey, *J. Chem. Soc.*, 843 (1954).

(16) Prepared by condensing glycolamidine hydrochloride and ethyl acetoacetate.