A Novel Improved Synthesis of 3-Aminopyrazine-2-carboxylic Acid

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A three step synthesis of 3-aminopyrazine-2-carboxylic acid (**1**) starting from pyrazine-2,3-dicarboxylic acid (**5**) is described. Diacid **5** is converted *via* the anhydride **6** into the ammonium salt of the half acid amide **7** which on Hofmann rearrangement gives the title compound in 55% overall yield.

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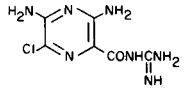
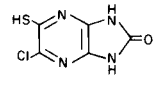
Introduction.

3-Aminopyrazine-2-carboxylic acid is used in the synthesis of compounds possessing useful diuretic activity, one of them, *N*-amidino-3,5-diamino-6-chloropyrazinecarboxamide is in clinical use and is known as Amiloride. The amino-acid is also used to prepare a series of 1*H*-imidazo[4,5-*b*]pyrazin-2-ones which have antihypertensive as well as diuretic activity (1).

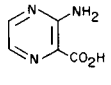


Amiloride



An Antihypertensive

3-Aminopyrazine-2-carboxylic acid (**1**) was first prepared (2) from pyrazine-2,3-dicarboxamide (**2**) by means of a Hofmann rearrangement involving the use of one equivalent of hypobromite. The yield of the amino-acid however was



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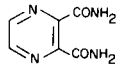

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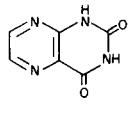
not stated and the reaction appeared to be complicated in that use of two equivalents of hypobromite gave lumazine **3** in 40% yield.

The second published synthesis (3) which apparently has remained the only practical method for preparing amino-acid **1** involved the preparation of lumazine from diaminouracil (**4**) (4) and its subsequent hydrolysis.



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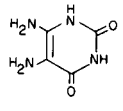

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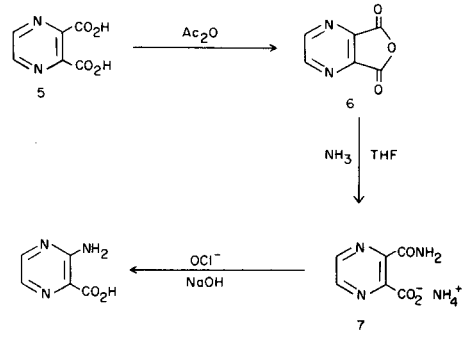
Lumazine hydrate and diaminouracil hydrochloride are now both commerically available (5) but are expensive. Also, the hydrolysis of lumazine is somewhat involved in that it requires a high temperature (190°) and thus facilities for carrying out the reaction under pressure. It was therefore thought worthwhile to investigate a simpler and cheaper alternative synthesis of amino-acid **1**.

Results and Discussion.

The synthetic route chosen is outlined in Scheme 1. Pyrazine-2,3-dicarboxylic acid is commerically available



5 6 7

Scheme I

(5) and is approximately half the cost of the uracil **4**. Dicarboxylic acid **5** was refluxed with acetic anhydride for 10 minutes and on cooling, pure anhydride **6** was conveniently found to crystallize out in 83% yield. This was collected, washed with ether, dried, dissolved in tetrahydrofuran, and ammonia gas passed through the solution until no further precipitation occurred (10 minutes). The white ammonium salt of the half acid amide **7** was collected, washed with ether and dried. The yield of this material which was analytically pure was 95%. Finally compound **7** was added to a sodium hydrochlorite and sodium hydroxide solution, heated for 5 minutes at 80°, cooled, and hydrolysed with 7.5-*M* hydrochloric acid to give amino-acid **1** in 67% yield.

EXPERIMENTAL

Melting points are uncorrected. The pmr spectra were recorded on a JEOL FX 100 Fourier Transform Model. Infra-red spectra were recorded on a Perkin-Elmer Model 257 spectrometer. Elemental analyses were performed by the Auxiliary Services Laboratory, Kodak Limited Research Laboratories. Infra-red samples were submitted in the form of potassium bromide discs and abbreviations included in the spectral data are (vs) very strong, (s) strong, (m) medium, (w) weak and (br) broad. Under pmr data (s) stands for singlet, (d) doublet, (br) broad and (m) multiplet.

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Pyrazine-2,3-dicarboxylic Acid Anhydride (**6**).

The dicarboxylic acid **5** (58.5 g., 0.35 mole) and acetic anhydride (200 ml.) were refluxed for 10 minutes and the resulting red solution cooled to 0° with swirling. The white crystalline material was collected, washed well with ether, and dried to give the anhydride 43.6 (83%) m.p. 221° dec., (lit. (2) dec. > 170°); ν max (cm^{-1}) 1880 (s), 1820-1750 (vs, br), 1392 (m), 1316 (s), 1297 (m), 1160 (s), 1130 (vs), 930-890 (vs, br), 870 (s), 722 (vs), 715 (vs); pmr (DMSO-d_6): δ 8.17 (s).

Anal. Calcd. for $C_6H_2N_2O_3$: C, 48.0; H, 1.3; N, 18.7. Found: C, 47.6; H, 1.4; N, 18.7.

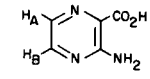
Ammonium 3-Carbamoylpyrazine-2-carboxylate (**7**).

Ammonia gas was passed rapidly with stirring through a solution of the anhydride (10 g., 0.067 mole) in tetrahydrofuran (500 ml.) for 10 minutes at room temperature. The solid was collected, washed with ether, dried at 50° under vacuum for 1 hour to give the product **7**, 11.7 g. (95%); ν max (cm^{-1}) 3410 (m), 3350-2600 (vs, br), 1675 (vs, br), 1650-1550 (vs, br), 1342 (s), 1195 (w), 1167 (w), 1105 (m), 1066 (w), 875 (m); pmr (trifluoroacetic acid with DMSO-d_6 as lock): δ [6.5 br (s), 7.04 br (s) and 7.5 br (s)] (NH_4^+), 8.24 br (s, $CONH_2$), 8.7-8.85 (m, arom).

Anal. Calcd. for $C_6H_8N_4O_3$: C, 39.1; H, 4.4; N, 30.4. Found: C, 38.9; H, 4.2; N, 30.3.

3-Aminopyrazine-2-carboxylic Acid (**1**).

Sodium hydroxide (3.61 g., 0.09 mole) in water (10 ml.) was added to a 10-14% sodium hypochlorite solution (6) (15 ml., 0.02 mole assuming 10%) at 0°. The finely powdered amide (7) (3.1 g., 0.016 mole) was added in one portion with swirling, resulting in immediate effervescence and a temperature rise of 30°. The mixture was warmed on a steam bath and at 50° a clear yellow solution was obtained. At 80° the solution solidified to a solid mass and after a further 5 minutes at 80°, the mixture was cooled to 0° and acidified with 7.5-*M* hydrochloric acid (15 ml.). After heating briefly at 50°, when a clear solution was obtained, the mixture was cooled, adjusted to *p*H 2.5 and the product collected, washed with a little water and dried to give the amino-acid **1**, 1.49 g. (67%) m.p. 204° dec. (lit. 201°) (3). This material was found to analyse reasonably well and a pmr spectrum indicated no organic impurities; pmr (DMSO-d_6): δ 7.45 (br s, 2H, NH_2); 7.95 (d, 1H, probably H_A); 8.31 (d, 1H, probably H_B); 12.52 (v.br s, 1H, CO_2H);



ν max (cm^{-1}) 3470 (s), 3335 (s), 1720 (vs), 1609 s (br), 1355 (vs), 1230-1070 (s), 849 (w).

Anal. Calcd. for $C_5H_5N_3O_2$: C, 43.2; H, 3.6; N, 30.2. Found: C, 42.4; H, 3.5; N, 30.4.

REFERENCES AND NOTES

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(6) Available from B.D.H. Chemicals.