3-Hydroxypyridopyrimidine-2,4(1*H*,3*H*)diones

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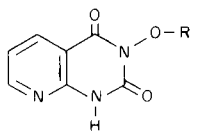
Current interest in the chemistry (1) and stated antitumor activity (2) of pyridouracils, prompts us to report the synthesis of the four isomers, **1-4**.



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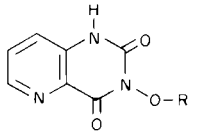

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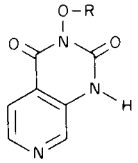

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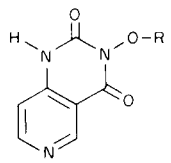

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where, in series, a, R = $C_6H_5SO_2$; b, R = H.

The starting materials for the syntheses of **1** and **2** was ethyl 2,3-pyridinedicarboxylate (3), which was converted to the corresponding bishydroxamate (4). The modified Lossen rearrangement of this hydroxamate with benzenesulfonyl chloride (4) produced a mixture of **1a** and **2a** (5:1). Hydrolysis of **1a** and **2a** with dilute sodium hydroxide (95°, 5 minutes) afforded **1b** and **2b**, respectively. Hydrolysis of **1b** with 6*N* hydrochloric acid at 180° furnished 2-aminonicotinic acid, which establishes the structure of isomers **1** and **2**.

A similar reaction sequence from methyl 3,4-pyridinedicarboxylate (5), gave rise to **3a** and **4a** (1:1). Proof of their structures was realized when each was hydrolyzed to the corresponding aminopyridinecarboxylic acid.

EXPERIMENTAL (6)

3-Benzenesulfonyloxypyrido[2,3-*d* and 3,2-*d*]pyrimidine-2,4(1*H*, 3*H*)diones, **1a** and **2a**, respectively.

To a stirred suspension of dry 2,3-pyridinedicarbohydroxamate (30.4 g.) in tetrahydrofuran (490 ml.) was added dropwise a solution of benzenesulfonyl chloride (46 g., 0.26 mole) in tetrahydrofuran (230 ml.) at a rate so as to maintain the temperature below 20° (0.5 hour). The mixture was stirred 0.5 hour longer, then sodium acetate trihydrate (24 g.) was added and stirring continued for 2 hours. After standing at 25° for 18 hours, the solid was filtered off and washed with several 50 ml.-portions of tetrahydrofuran. The combined tetrahydrofuran solution was concentrated to 10 ml. *in vacuo*.

The residue was partitioned between petroleum ether, (b.p. 30-60°, 300 ml.) and water (300 ml.) and the solid was filtered and washed with cold ethanol (20 ml.). The product was a mixture of **1a** and **2a**, and weighed 20.9 g. (51.6%, based on the original ester used).

Crystallization of the mixture (3.4 g.) from aqueous dioxane (1:1) produced first **1a**, (1.80 g.). The mother liquor was concentrated *in vacuo* to about 5 ml. to produce a fraction which was crystallized again from aqueous dioxane (1:1). A second batch of **1a** was obtained (0.58 g.), m.p. 254-256° dec.; tlc, solvent A (Rf = 0.36); ir (Nujol) 1710, 1760 cm^{-1} (C=O); pmr (DMSO), δ 9.00 (dd, H-7) 8.61 (dd, H-5) 7.60 (dd, H-6) ($J_{5,6}$ = 8.0, $J_{6,7}$ = 5.0 $J_{5,7}$ = 1.6 Hz) 8.43-7.78 (m, C_6H_5); mass spectrum m/e (rel. intensity) 319 (10), 255 (9), 163 (10), 141 (62), 120 (21), 94 (10), 93 (20), 92 (22), 91 (13), 77 (100), 65 (19), 64 (11), 51 (25).

Anal. Calcd. for $C_{13}H_9N_3O_5S$: C, 48.90; H, 2.84; N, 13.16. Found: C, 49.08; H, 2.84; N, 13.16.

Solvents were removed from mother liquor of second batch, *in vacuo*, and the residue was crystallized from dioxane. There was obtained pure **2a**, (0.47 g.), m.p. 244° dec.; tlc, solvent A (Rf = 0.10); ir (Nujol) 1750, 1725 cm^{-1} (C=O); pmr (DMSO), δ 8.71 (m, H-6), 7.66-8.34) (m, H-7, H-8, and C_6H_5) mass spectrum m/e (rel. intensity), 319 (5), 255 (4), 163 (53), 161 (100), 158 (45), 135 (35), 129 (12), 120 (27), 119 (13), 105 (28), 94 (57), 93 (10), 92 (52), 91 (17), 76 (26), 77 (90), 71 (12), 66 (18), 65 (38), 64 (19), 57 (23), 53 (23), 51 (44), 50 (18).

Anal. Calcd. for $C_{13}H_9N_3O_5S$: C, 48.90; H, 2.84; N, 13.16. Found: C, 48.89; H, 2.76; N, 13.35.

The ratio of **1a** to **2a** from pmr spectra and fractional crystallization is estimated to be 5:1.

3-Hydroxypyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione (**1b**).

A solution of **1a** (1 g.) in 5% sodium hydroxide solution (10 ml.) was heated on the steam bath for 5 minutes, cooled, and acidified with concentrated hydrochloric acid at 5° to *p*H 2. The precipitate was collected and recrystallized from water to afford **1b** (0.5 g., 89% as light yellow needles, m.p. 338.5° dec.; ir (Fluorolube) 3070, 2800 (NH and N-OH), 1765, 1645 cm^{-1} (C=O); pmr (DMSO), δ 8.72 (dd, H-7), 8.40 (dd, H-5) 7.31 (dd, H-6) ($J_{5,6}$ = 8.0, $J_{6,7}$ = 5.0, $J_{5,7}$ = 1.6 Hz), mass spectrum, m/e (rel. intensity) 179 (78), 163 (17), 147 (100), 120 (16), 119

(31), 93 (25), 92 (15), 91 (15), 64 (12).

Anal. Calcd. for $C_7H_5N_3O_3$: C, 46.93; H, 2.81; N, 23.46. Found: C, 46.68; H, 2.69; N, 23.45.

3-Hydroxypyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)dione (**2b**).

The hydrolysis of **2a** (1.0 g.) as described for **1a** afforded **2b**, (0.5 g., 89%), small white needles, m.p. 360° dec.; ir (Fluorolube) 3200, 2750 (broad, NH, NOH), 1690, 1750 cm^{-1} (C=O); pmr (DMSO) consisted of a complex pattern for the three ring protons (AB_2 system); the multiplet centered at δ 8.58 integrated for one proton (H-6) and the two-line pattern at δ 7.69 and 7.64 arose from H-7, H-8; mass spectrum m/e (rel. intensity) 180 (10), 179 (100), 164 (10), 163 (95), 147 (48), 135 (12), 121 (19), 120 (48), 119 (43), 93 (11), 92 (79), 91 (20), 78 (17), 66 (14), 65 (33), 64 (18).

Anal. Calcd. for $C_7H_5N_3O_3$: C, 46.93; H, 2.81; N, 23.46. Found: C, 46.84; H, 2.74; N, 23.60.

Structure Proof for **1b**.

Hydrolysis of **1b** with 14% aqueous sodium hydroxide at 170° for 4 hours produced 2-aminonicotinic acid in poor yield. Better results were obtained when **1b** (0.25 g.) was heated in a sealed tube with 6*N* hydrochloric acid (3 ml.) at 180° for 4 hours. The residue was dissolved in 3 ml. of water and the *p*H adjusted to 5 with dilute ammonium hydroxide (1:1) to produce 2-aminonicotinic acid, (0.120 g., 62%) m.p. 303° dec., identical (ir) to a sample, prepared from 2-amino-3-picoline (7), lit. (8) m.p. varied 290-310°; mass spectrum, m/e (rel. intensity) 139 (8), 138 (100), 120 (25), 94 (30), 93 (63), 92 (25), 67 (12), 66 (19), 65 (15).

3-Benzenesulfonyloxypyrido[3,4-*d* and 4,3-*d*]pyrimidine-2,4-(1*H*-3*H*)diones, **3a** and **4a**, respectively.

The hydroxamate (5.5 g.) was reacted with benzenesulfonyl chloride (7.1 g.) as described for the synthesis of **1a** and **2a**. There was formed a mixture of **3a** and **4a** (3.7 g., 58% based on ester) which was separated as follows. A 5-g. sample was triturated with DMF (25 ml.) in which **4a** was insoluble. The DMF filtrate was evaporated, *in vacuo*, diluted with water and the solid recrystallized from methanol to give **3a**, (1.6 g.) as light yellow flakes; m.p. 228-229° dec.; tlc, solvent B (Rf = 0.33); ir (Nujol) 1760, 1720 cm^{-1} (C=O); pmr (DMSO δ 8.69 (s, H-8), 8.52 (d, H-6), 8.19-7.52 (6, m, C_6H_5 and H-5) ($J_{5,6}$ = 5.0 Hz); mass spectrum m/e (rel. intensity) 319 (22), 164 (27), 161 (43), 158 (13), 141 (98), 120 (20), 105 (10), 94 (18), 93 (22), 78 (14), 77 (100), 65 (15), 64 (10).

Anal. Calcd. for $C_{13}H_9N_3O_5S$: C, 48.90; H, 2.84; N, 13.16. Found: C, 48.94; H, 2.83; N, 13.14.

The DMF-insoluble solid (from above) was recrystallized from aqueous DMF (1:1) to furnish **4a** as light yellow needles, m.p. 238° dec., tlc solvent B, Rf = 0.21; ir (Nujol) 1760, 1725 cm^{-1} (C=O), pmr (DMSO) δ 9.05 (s, H-5), 8.64 (d, H-7), 8.02-7.55 (m, C_6H_5); 7.14 (d, H-8) ($J_{7,8}$ = 5.0 Hz) mass spectrum 319 (39), 163 (49), 161 (53), 158 (15), 141 (77), 120 (39), 105 (13), 94 (20), 93 (38), 78 (16), 77 (100), 65 (17), 64 (11).

Anal. Calcd. for $C_{13}H_9O_5N_3S$: C, 48.90; H, 2.84; N, 13.16. Found: C, 48.76; H, 2.94; N, 13.39.

3-Hydroxypyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)dione (**3b**).

A solution of **3a** (1.0 g.) in 5% sodium hydroxide solution (10 ml.) was heated on a steam bath for 1 minute. A heavy precipitate was formed. This suspension was cooled in an ice-bath and acidified with concentrated hydrochloric acid to *p*H 2. The solid was recrystallized from water to yield **3b** (0.3 g., 54%), brown prisms, m.p. 330° dec.; ir (Nujol) 3440 (N-OH), 2680 (N-H), 1725, 1680 cm^{-1} (C=O); pmr (DMSO) δ 8.72 (s, H-8), 8.55 (d, H-6), 7.80 (d, H-5) ($J_{5,6}$ = 5.0 Hz); (trifluoroacetic acid), δ 9.39 (s, b, H-8) 8.88 (s, b, H-5 and H-6); this type of AB_2 pattern in trifluoroacetic acid was also shown for the N-3 deoxy analog (1b), δ 8.61 (H-8), 8.25 (H-5 and 6); mass spectrum, m/e (rel. intensity) 179 (80), 163 (18), 147 (100), 120 (16), 119 (28), 93 (22), 91 (11), 65 (11), 64 (13).

Anal. Calcd. for $C_7H_5N_3O_3$: C, 46.93; H, 2.81. Found: C, 46.68; H, 2.90.

3-Hydroxypyrido[4,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione, (**4b**).

The hydrolysis of **4a** (0.6 g.) was carried out as for **3a**. After adjusting the *p*H to about 5, **4b** was collected and was crystallized from water to give 0.5 g. (90%), white needles; m.p. 340° dec.; ir (Nujol) 3350-2900 (N-OH), 2800-2100 (N-H), 1730, 1680 cm^{-1} (C=O); pmr (DMSO) δ 9.05 (s, H-5), 8.64 (d, H-7), 7.11 (d, H-8), ($J_{7,8}$ = 5.0 Hz); mass spectrum, m/e (rel. intensity) 179 (100), 163 (11), 149 (13), 147 (88), 120 (17), 119 (25), 93 (25), 91 (9), 64 (10).

Anal. Calcd. for $C_7H_5N_3O_3$: C, 46.93; H, 2.81; N, 23.46. Found: C, 46.72; H, 2.77; N, 23.73.

Separation of **3b** and **4b**.

A mixture of **3a** and **4a** (10 g.) was hydrolyzed at 95° for 5 minutes with 5% sodium hydroxide (80 ml.), cooled, and brought to *p*H 2. The precipitate (2.7 g.) was pure **3b**. The *p*H was adjusted with sodium hydroxide to 5, when **4b** crystallized out (2.6 g.). The yield of hydrolysis was quantitative and the isomer ratio about 1:1.

Structure Proof of **3** and **4**.

A sample of **3a** (0.5 g.) was hydrolyzed first with 5 ml. sodium hydroxide solution to produce, on cooling, the *sodium salt* of **3b**. This salt was collected and then heated in a sealed tube with hydrochloric acid as that described for **1b**. After adjusting the *p*H to about 3.5 and maintaining the sample at 5° for several hours, 3-aminoisonicotinic acid (0.14 g.) 65% (based on **3a**) was collected, m.p. 303° dec., lit. (9), 295-297°; mass spectrum, m/e (rel. intensity), 138 (100), 120 (85), 93 (62), 92 (14), 66 (15), 65 (23).

A sample of **4a** (0.5 g.) was hydrolyzed first by sodium hydroxide and the sodium salt of **4b** was heated with hydrochloric acid as reported above for **3b**. After adjusting the *p*H to about 6,4-aminonicotinic acid (0.100 g., 46%) crystallized at 5°, after 18 hours at 5°; m.p. 324° dec., lit. m.p. (10) 336-337° dec.; mass spectrum, m/e (rel. intensity), 138 (100), 121 (11), 120 (95), 93 (62), 66 (20), 65 (12).

REFERENCES

(1a) W. J. Irwin, *J. Chem. Soc., Perkins* I, 353 (1972); (b) I. R. Gelling and D. G. Wibberley, *ibid.*, C, 931 (1969); (c) A. L. J. Beckwith and R. J. Hickman, *ibid.*, C, 2756 (1968) and papers quoted by those authors.

(2) B. H. Rizkalla, *Diss. Abstr., Int'l.*, B, 32, 5705 (1972).

(3) Prepared from 2,3-pyridinedicarboxylic acid (Aldrich Chemical Co.).

(4) The salt was generated by the method described previously; L. Bauer and C. S. Mahajanshetti, *J. Heterocylic Chem.*, **5**, 331 (1968) and references quoted in this paper.

(5) W. L. F. Armarego and R. F. Evans, *J. Appl. Chem.*, 12, 45 (1962).

(6) All m.p. are uncorrected and were determined on a Thomas Hoover Unimelt capillary melting point apparatus. Analyses for N were performed by Mr. Dvorak in this Department, those for C, H by Micro-Tech Lab., Inc., Skokie, Illinois. Infrared spectra were determined on a Perkin-Elmer 337 recording infrared spectrophotometer. Pmr spectra were determined by means of a Varian A-60 spectrometer and are recorded in ppm (δ), downfield from TMS. Mass spectra were obtained at 70 eV, using a Hitachi Perkin-Elmer RMU-6D single focusing mass spectrometer. Usually, ions with 10% of base peak or more are recorded only from m/e 60.

Thin layer chromatographs (tlc) were determined on silica gel with a fluorescent indicator (Eastman Chromagram Sheet 6060) using the following solvent systems, designed by letters: A, benzene-ethyl acetate, 1:1; B, ethyl acetate. Developing distance was 7.2 cm. for 15 minutes. Spots were detected by uv light.

(7) R. K. Robins and G. H. Hitchings, *J. Am. Chem. Soc.*, 77, 2256 (1955).

(8) C. D. Hurd and V. G. Bethune, *J. Org. Chem.*, 35, 1471 (1970).

(9) J. C. Crum and C. H. Fuchsman, *J. Heterocyclic Chem.*, 3, 252 (1966).

(10) A. G. Ismail and D. G. Wibberley, *J. Chem. Soc.*, C, 2613 (1967).