oped with petroleum ether (bp 30–60°)–ether (2:1)] to give two fractions in addition to additional pure **2d** (total recovery 52%).

The first of these was a mixture (nmr)[3] of syn alcohol **1d** (~10% yield by nmr) and anti formate **2g** (30% yield) which have nearly identical R_f values. The anti formate, which was unknown, was purified by recrystallization of this mixture from chloroform–petroleum ether (bp 60–90°): nmr ($CDCl_3$) δ 8.19 (1, s, O_2CH), 8.19–7.58 (4, m, aromatic H), 6.23 (1, X portion of ABX, $J_{AX} + J_{BX}$ = 16 Hz, q, CHO_2CH), 3.75–0 (broad m, 18, bridge CH_2).

Anal. Calcd for $C_{20}H_{24}NO_2Cl$: C, 69.45; H, 6.99; N, 4.05. Found: C, 69.68; H, 7.01; N, 4.04.

The mother liquor from this recrystallization contained (tlc and nmr) syn alcohol **1d**, anti formate **1d**, and trace amounts of another material assumed to be syn formate **1g**.

The other fraction (5.5 mg, 6% yield) was reduced pyridinophane **1c** (mp and mmp[4b] of picrate 173–174°).

Thermal Stability of Syn and Anti Bromides (1b and 2b). A. A solution of syn **1b** (50.5 mg, 0.133 mmol) in xylene (ACS grade, 0.5 ml) was heated at the reflux temperature under nitrogen for 220 hr. Xylene was removed (*in vacuo*) from the brown, tarry mixture; the residue showed (nmr) unchanged **2a** (δ 6.06) and no epimer **2b** (δ 5.42). The sample was dissolved in chloroform and washed with dilute sodium bicarbonate and the product was recrystallized from petroleum ether to give 41.6 mg (82.3% recovery) of **2a**, mp 141–142°, mmp 143–144° with material melting at 144–145°.

B. A sample of anti **2b** (65.8 mg, 0.173 mmol) was treated in xylene as described above. The nmr spectrum of the crude product showed no **2b** (δ 5.42) or **2a** (δ 6.06) and was quite similar to that of **1c**. The product was decolorized as above and purified by preparative tlc [silica gel, petroleum ether–ether (3:1)] to give 26 mg (50% yield) of **1c** (mp and mmp 78–79°).

Registry No. **1a**, 37781-25-2; **1b**, 25859-37-4; **1d**, 25866-36-8; **1g**, 42880-43-3; **2a**, 37781-31-0; **2b**, 42880-45-5; **2d**, 25907-82-8; **2g**, 42962-81-2.

References and Notes

(1) Support by the National Science Foundation, Grant GP 35429.
(2) Address correspondence to Paul Gross Chemical Laboratory, Duke University, Durham, N. C. 27706.
(3) W. E. Parham, K. B. Sloan, K. R. Reddy, and P. Olson, *J. Org. Chem.*, **38**, 927 (1973).
(4) (a) W. E. Parham, K. B. Sloan, and J. B. Biasotti, *Tetrahedron*, **27**, 5767 (1971); (b) W. E. Parham, R. W. Davenport, and J. B. Biasotti, *J. Org. Chem.*, **35**, 3775 (1970).
(5) Alkylsulfonates normally undergo carbon–oxygen scission under these conditions; the authors are unaware of related acid-catalyzed S–O bond cleavage.
(6) 2- and 4-methylpyridines undergo hydrogen–deuterium interchange on the methyl group, presumably through a carbanion intermediate, under rather mild conditions; *cf.* K. Schofield, "Hetero-Aromatic Nitrogen Compounds," Butterworths, London, 1967, pp 324–327, and references cited therein.
(7) Sulfur–oxygen bond cleavage of alkylsulfonates by base is uncommon, since substitution or elimination at carbon generally occurs. However, arylsulfonates readily undergo S–O bond cleavage by nucleophiles: *cf.* W. D. Closson and P. Wriede, *J. Amer. Chem. Soc.*, **88**, 1581 (1966).
(8) Reactions of **1a** and **1b** with KBr in hot dimethylformamide and in dimethyl sulfoxide were also studied with similar results. The principal products were unchanged starting materials along with complex mixtures which were not examined.
(9) In view of the parallel in reactivity of tosylates **1a** and **2a**, coupled with the fact that the anti bromide **2b** is difficult to obtain in quantity, only selected reactions of both epimers **1b** and **2b** were carried out.
(10) Reduction of alkyl halide by strong base is uncommon but not unknown. Iodoform, for example, is reduced to methylene iodide by base, and the reaction is thought to involve nucleophilic attack at halogen; *cf.* S. Bagnara, *Eng. Mining J.-Press*, **116**, 51 (1923).
(11) Reduction of aryl halides by alkoxide is well known; *cf.* J. F. Bunnet and R. R. Victor, *J. Amer. Chem. Soc.*, **90**, 810 (1968). Formation of low yields of syn and anti ethers under these drastic conditions is not interpreted as evidence for SN2 reactions, since a variety of routes can be postulated for their formation.
(12) Triphenylcarbinol, for example, is efficiently reduced to triphenylmethane; *cf.* H. Kauffmann and P. Pannwitz, *Chem. Ber.*, **45**, 766 (1912).
(13) W. E. Parham, "Synthesis and Reactions in Organic Chemistry," Wiley, New York, N. Y., 1970, pp 258–259.

Nitration and Bromination of Isocytosine-6-acetic Acid. Some Corrections[1]

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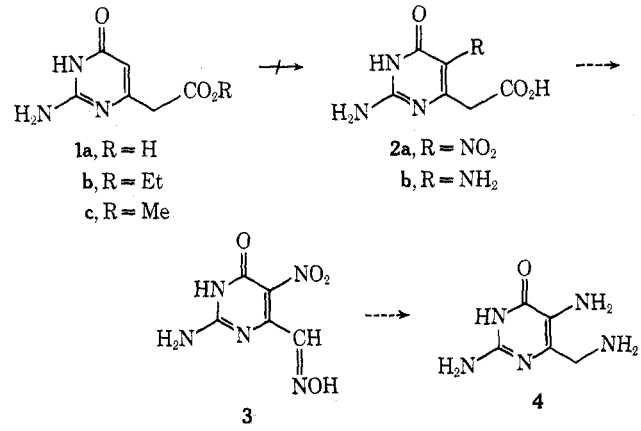
The reported nitration and bromination of isocytosine-6-acetic acid (**1a**) was reinvestigated. Under nitration conditions, oxidation of **1a** occurred to give isocytosine-6-carboxylic acid (**12a**), instead of the reported 5-nitroisocytosine-6-acetic acid (**2a**). Consequently, the reported reduction of **2a** to 5-aminoisocytosine-6-acetic acid (**2b**) may not have occurred. The nitrosation of **1a** produced 6-hydroxyiminomethylisocytosine (**11**), which could also be oxidized to **12a** by nitric acid. By a modification of the reported preparation of **1a**, the direct preparation of ethyl isocytosine-6-acetate (**1b**) was accomplished. Bromination of **1a** at room temperature gave 5-bromoisocytosine-6-acetic acid (**13**) hydrobromide. However, the reported **13** could not be obtained without decarboxylation of **13** to 5-bromo-6-methylisocytosine (**14**). Bromination of **1a** could also be controlled to give di- and tribromo derivatives of **14**.

The preparation of 5-nitroisocytosine-6-acetic acid[2] (**2a**) and the subsequent reduction to 5-aminoisocytosine-6-acetic acid[3] (**2b**) had been reported by Worrall. We desired **2a** as a precursor for 5-amino-6-aminomethylisocytosine (**4**, Scheme I) which we had intended to use as the key intermediate in an improved synthesis of an isomer of ethyl pteroate.[4] Consequently, our isolation of the product from our attempted nitration of **1a** other than the reported **2a** was quite disappointing. We report here our reinvestigation of the nitration of isocytosine-6-acetic acid (**1a**), as well as its bromination as reported by Worrall.[2,3]

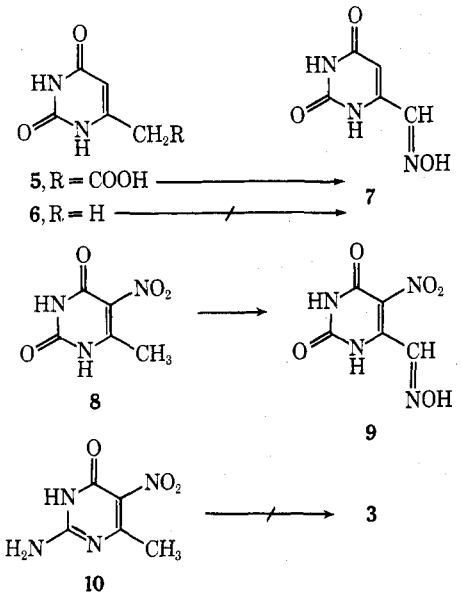
The selection of this mode of preparation of **4** was based on similar reactions on pyrimidine substrates of slightly different structures (see Scheme II). Uracil-6-acetic acid (**5**) had been shown to nitrosate and spontaneously decarboxylate to give **7**.[5] Similarly, the 6-methyl group activated by the 5-nitro group of 5-nitrouracil (**8**) could also be

Scheme I



nitrosated to give **9**, while nitrosation of 6-methyuracil (**6**) had failed.[6] The known deactivating effect of a 2-amino group was sufficient to prevent our attempted nitrosation of 5-nitro-6-methylisocytosine (**10**) under the same conditions (**10** ↛ **3**). However, we hoped that the combined activating effects of the 5-nitro and the carboxyl groups would overcome the deactivating effect of the 2-amino group and permit the nitrosation and decarboxylation of **2a** to obtain **3**. Subsequent reduction of **3** would afford **4**.

Scheme II



We prepared **1a** from diethyl acetonedicarboxylate with 2 equiv of guanidine by Worrall's procedure.[2,3] We also found that, by using only 1 equiv of guanidine, the ethyl ester **1b** was easily obtained.

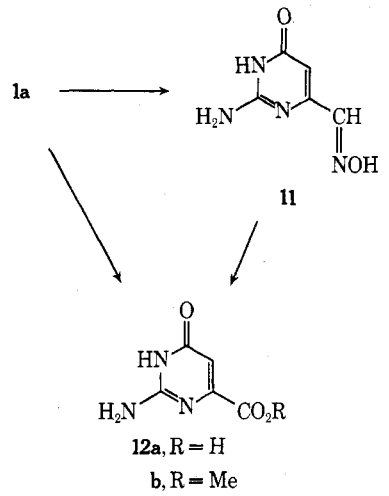
The nitration of **1a** was carefully performed according to the procedure of Worrall (70% nitric acid at 70°).[2] Although the nmr of the isolated material showed several new peaks, the bulk of this material was the starting acid **1a**.[7]

The nitration procedure of Wempen, *et al.*[8] (concentrated sulfuric acid and potassium nitrate), which we had successfully used to prepare **10**, was applied to **1a** and we obtained a new product A, free of starting material. The highest mass of significance in the mass spectrum was *m/e* 155, with the parent peak at *m/e* 44 (CO_2). Repeated attempts to obtain a reasonable analysis were unsuccessful. Attempts to calculate an empirical formula from the obtained analysis gave carbon to nitrogen ratios between 6:4 and 5:3. The ir of A indicated that a carboxylic acid was still present, as had the mass spectrum.

Some nitrations are known to proceed by nitrosation, followed by oxidation of the nitroso group to the nitro group.[9] The procedure of Wempen employed in the "nitration" of **1a** was repeated in a modified manner; the addition of 1 equiv of potassium nitrate to the sulfuric acid solution of **1a** was preceded by the addition of 1 equiv of potassium nitrite. The yield of A increased from 24 to 56%.

Concurrently we had nitrosated **1a** in dilute acid and had obtained 6-hydroxyiminomethylisocytosine (**11**) hydrochloride (Scheme III). This identity was also confirmed by the synthesis of **11**·HCl from 6-diethoxymethylisocytosine.[10] Since nitrosation had strongly been implicated in the preparation of A, we subjected **11** to the "nitration" conditions and indeed obtained A. This reaction established the number of carbons in A at five, and the crude analysis obtained had suggested a possible 5:3 carbon to nitrogen ratio. This and the ir and mass spectral data mentioned earlier suggested the product to be isocytosine-6-carboxylic acid (**12a**). Comparison of the physical properties of A and its methyl ester (**12b**) with authentic samples confirmed this identity. That our product A was **12a**, rather than 5-nitroisocytosine-6-carboxylic acid, was consistent with Shepard's unsuccessful attempts to nitrate **12a**.[11]

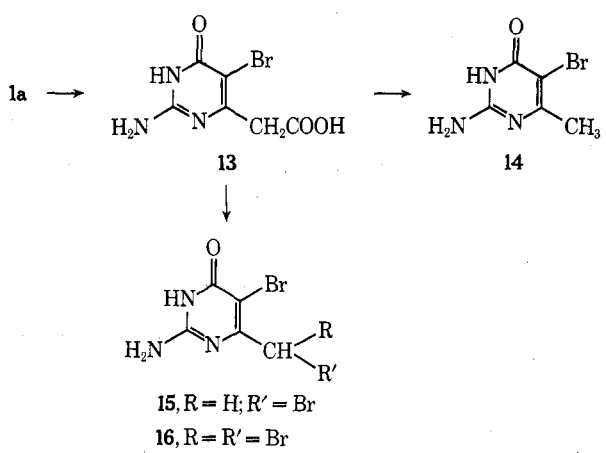
Scheme III



Worrall also had reported[3] the reduction of the alleged nitro acid **2a** to 5-aminoisocytosine-6-acetic acid (**2b**) (*Anal.* Calcd for $C_6H_8N_4O_3$: C, 39.1; H, 4.3. Found: C, 38.7; H, 4.5.). However, since it is unlikely that he prepared **2a**, perhaps he subjected an impure sample of **12a** to the reduction conditions and recovered a purified **12a** (*Anal.* Calcd for $C_5H_5N_3O_3$: C, 38.72; H, 3.25.). Thus it would seem that Worrall's reported **2b** was actually **12a**, and that **2b** has not yet been prepared.

The bromination of **1a** had also been reported by Worrall[3] to produce 5-bromoisocytosine-6-acetic acid (**13**) hydrobromide (Scheme IV) as well as the hydrobromide-free

Scheme IV



13 after treatment with base and repeated recrystallization to avoid a high bromine analysis. We found that, even in the presence of 3 equiv of bromine, monobromination occurred quickly at room temperature in acetic acid. Dilution of the reaction mixture with acetone removed the excess bromine and an analytically pure **13** · HBr precipitated. We were unable to obtain pure **13** by neutralizing the hydrobromide. Nmr indicated that the decarboxylation easily occurred at room temperature and we apparently obtained a mixture of **13** and 5-bromo-6-methylisocytosine (**14**). We also obtained the decarboxylated dibromo and tribromo derivatives, **15** and **16**, in refluxing ace-

tic acid in low yields; however, no attempt was made to maximize the yields. Keana and Mason have recently prepared several mono-, di-, and trihalo derivatives of the 2-acetyl derivative of **1c**.[12]

Experimental Section

The elemental analyses were carried out by Micro-Tech Laboratories, Skokie, Ill. Samples were dried *in vacuo* at 100° over phosphorus pentoxide. Melting points were taken on a Fisher-Johns melting point apparatus or in sealed capillaries on an aluminum block, and are uncorrected. Ir spectra were recorded on a Perkin-Elmer 257 grating infrared spectrophotometer and calibrated with reference to polystyrene peaks at 3027 and 1601 cm^{-1}. Nmr spectra were determined on a Varian Model A-60 spectrometer or on a Jeol Model JNM-C60HL spectrometer, employing TMS as internal reference.[13,15] Low-resolution mass spectra were obtained on a Hitachi RMU-62 mass spectrometer. The high-resolution mass spectrum was determined on a AEI MS 902 mass spectrometer at The Research Triangle Center for Mass Spectrometry, Research Triangle Park, N. C., supported under Grant RP-330 from the Biotechnology Resources Branch of the Division of Research Resources of the National Institutes of Health.

Isocytosine-6-acetic acid (1a).[2,3] Diethyl acetonedicarboxylate and 2 equiv of guanidine carbonate were condensed according to Worrall[2,3] to obtain **1a** in 44% yield. For analysis, a sample was recrystallized once from water: mp (sealed capillary) frothing at 185–190°, remelts at 295–300° (same as 6-methylisocytosine); ir (KBr) 3475, 3400–2500 (broad), 1710, 1660 cm^{-1} (sh); nmr (TFA) τ 6.50 (s, 2, CH_2), 3.67 (s, 1, H-5), 1.88 (s, 2, NH_2); mass spectrum (70 eV), *m/e* (rel intensity) 125 (73), 97 (13), 96 (7), 84 (15), 68 (7), 44 (100), 43 (14), 42 (10). With the exception of *m/e* 44, the spectrum is identical with that of 6-methylisocytosine.

Anal. Calcd for $C_6H_7N_3O_3 \cdot H_2O$: C, 38.51; H, 4.85; N, 22.45. Found: C, 38.15: H, 4.95; N, 22.63.

Ethyl Isocytosine-6-acetate (1b). This was prepared in the same manner as **1a**, except that only 1 equiv of guanidine carbonate was employed. For analysis, a 10-g sample was stirred at room temperature for 1 hr with 200 ml of water, recovering, after drying, 5.1 g of pure **1b**: mp 178° dec (frothing); ir (KBr) 1727, 1687–1605 cm^{-1}; nmr (DMSO-d_6) τ 8.80 (t, 3, J = 7 Hz, CH_3CH_2O), 6.60 (s, 2, CH_2CO_2), 5.85 (q, 2, J = 7 Hz, CH_3CH_2O), 4.45 (s, 1, H-5), 2.7 and 3.1 (two broad overlapping singlets, 3, NH_2, possibly some guanidine impurity, analysis shows high nitrogen). On addition of D_2O, the peaks at 2.7 and 3.1 disappear immediately, while the methylene protons at τ 6.6 exchange more slowly.

Anal. Calcd for $C_8H_{11}N_3O_3$: C, 48.73; H, 5.62; N, 21.31. Found: C, 48.80; H, 5.56; N, 21.83.

5-Nitro-6-methylisocytosine (10). Wempen's procedure[8] for the nitration of monooxopyrimidines was adapted for the preparation of **10**. Addition of 4.3 g (0.043 mol) of potassium nitrate to a suspension of 5.36 g (0.043 mol) of 6-methylisocytosine in 40 ml of concentrated sulfuric acid produced a rapid temperature rise to 80–100°. After cooling to room temperature, the acid solution was carefully poured into 1500 ml of rapidly stirred ether. The ether was decanted and fresh ether was added; this sequence was repeated twice. The precipitated pyrimidine salt was dissolved in 200 ml of water and made basic with 50% sodium hydroxide, and the solution was cooled in an ice bath. Any precipitate was collected and discarded. Acidification with acetic acid precipitated the product, which after drying at room temperature yielded 5.4 g (67%) of $10 \cdot H_2O$, mp >300°.

Anal. Calcd for $C_5H_6N_4O_3 \cdot H_2O$: C, 31.92; H, 4.29: N, 29.78. Found: C, 31.61; H, 4.22; N, 30.61.

If $10 \cdot H_2O$ is dried at 100°, or stirred in glacial acetic acid overnight, water of hydration is lost. The analytical sample below was stirred with glacial acetic acid, filtered, and dried at 100°, nmr (DMSO-d_6) τ 7.70 (s, 3, CH_3), 2.5 (broad s, 2, NH_2).

Anal. Calcd for $C_5H_6N_4O_3$: C, 35.30; H, 3.55; N, 32.93. Found: C, 34.31; H, 3.47; N, 33.33.

Attempted Preparation of 5-Nitro-6-hydroxyiminomethylisocytosine (3). Attempted nitrosation in acetic or formic acid by the procedure of Davis, *et al.*,[6] resulted in only the recovery of starting material. However, a suspension of 0.85 g (5.0 mmol) of **10** in 10 ml of 8 *N* perchloric acid, followed by addition of 0.345 g (5.0 mmol) of sodium nitrite in 2 ml of water, produces a vigorous exothermic reaction. The reaction mixture was immediately cooled. A small amount of a light yellow precipitate was collected. This was dissolved in a few ml of water, made basic with concentrated ammonium hydroxide, and acidified with acetic acid. There was no immediate precipitate, but crystals did form after several days. Yellow crystals (30 mg) were thus collected. From the above filtrate, 0.35 g of starting material was recovered. After drying, the yellow crystals (sealed capillary) decomposed at *ca.* 181°: ir (KBr) very sharp spectrum, 3402 (s), 3380 (s), 3265 (m), 3242 (m), 1701 (m), 1682 (m), 1660 (m), 1575 (m), 1528 (m), 1482 (m), 1455 (m), 1410 (m), 1370 (m) 1260 (s), 1225 (m), 1142 (m), 1085 (m), 892 (w), 810 (w), 778 (w), 760 (w), 725 cm^{-1} (w); mass spectrum, sample decomposes.

Anal. Found: C, 19.14, 19.06; H, 2.55, 2.68; N, 36.74, 36.17.

The extremely high proportion of nitrogen and oxygen indicated that this was other than the desired product **3**. This material could probably be prepared in good yield by increasing the nitrite ratio; however, *the explosive nature of the reaction mixture and/or product should be considered.*

Attempted Nitration of Isocytosine-6-acetic Acid (1a). A. By the Procedure of Worrall.[2] **1a** ("guanidine salt") (0.7 g) prepared by Worrall's procedure was added in small amounts to 4 ml of 70% nitric acid and warmed to 70° for 0.5 hr. No precipitation of six-sided plates (or any precipitate) was observed. The mixture was poured into five volumes of water; no precipitate was observed. Ammonium hydroxide was employed to adjust the pH to 7, followed by addition of acetic acid. Crystals formed slowly over a weekend. After drying, 0.120 g of white needles were obtained. Nmr (TFA) showed that this was predominately starting material.

B. With Potassium Nitrate in Concentrated Sulfuric Acid. The procedure of Wempen, *et al.*[8] was used. **1a** (4 g, 0.022 mol) was dissolved in 20 ml of concentrated sulfuric acid. Upon addition of 2.15 g (0.0215 mol) of potassium nitrate, a vigorous exothermic reaction occurred. After cooling, the sulfuric acid solution was poured into 800 ml of ether. The ether was decanted and the residue was washed with fresh ether several times. The yellow solid was dissolved in 200 ml of water, 50% sodium hydroxide was added until the solution was alkaline, and acetic acid was added to precipitate the product. After drying, 0.820 g (24%) of product A subsequently identified as isocytosine-6-carboxylic acid (**12a**) was obtained.

C. With Potassium Nitrite and Potassium Nitrate in Concentrated Sulfuric Acid. Procedure B was followed carefully, with the exception that 1.85 g (0.0215 mol) of potassium nitrite was added, immediately followed by the addition of the potassium nitrate. The product A weighed 1.87 g (56%).

The products A from procedures B and C above were identical and also identical with the product obtained by the attempted nitration of 6-hydroxyiminomethylisocytosine (**11**). The physical data and proof of structure for A as isocytosine-6-carboxylic acid (**12a**) are given below with that procedure.

Nitrosation of Isocytosine-6-acetic Acid (1a) to Prepare 6-Hydroxyiminomethylisocytosine (11). Cautiously, 4.00 g (0.058 mol) of sodium nitrite was added to 8.95 g (0.050 mol) of **1a** in 50 ml of 3 *M* hydrochloric acid. The solution was heated on a steam bath for 30 min. After standing overnight, the product was collected and dried to give 5.20 g (55%) of $11 \cdot HCl$: ir (KBr) 3400, 1680, 1670, 986 cm^{-1} (characteristic of hydroxyiminomethylpyrimidines); nmr (DMSO-d_6) τ 3.60 (s, 1, 5-H), 1.92 (s, 1, CH=N), 1.34 (broad s, 2, NH_2), −2.75 (very broad singlet, probably a combination of some or all of the labile NOH, N-3 H, and N-1 H^+ hydrogens).

Anal. Calcd for $C_5H_6N_4O_2 \cdot HCl$: C, 31.51; H, 3.70; N, 29.40. Found: C, 31.41; H, 3.63; N, 28.54.

The free base **11** was obtained by dissolving $11 \cdot HCl$ in water, adjusting the pH to 8 with potassium carbonate, and collecting the precipitate: ir (KBr) 3420, 1700–1655, 995 cm^{-1}; nmr (DMSO-d_6) τ 4.20 (s, 1, 5-H), 3.20 (broad s, 2, NH_2), 2.30 (s, 1, CH=N), −1.7 (broad s, 1, NOH).

The products obtained by the above procedure were also prepared from 6-diethoxymethylisocytosine[16] by the procedure of Bedenbaugh,[10] *via* the reaction of isocytosine-6-carboxaldehyde hydrochloride with hydroxylamine hydrochloride.

Attempted Nitration of 6-Hydroxyiminomethylisocytosine (11). Preparation of Isocytosine-6-carboxylic Acid (12a). The oxime **11** (1.65 g, 0.0107 mol) was dissolved in 10 ml of sulfuric acid. After addition of 1.07 g (0.0107 mol) of potassium nitrate, the mixture was heated at 100° for 30 min. After cooling, the solution was poured into ether, the ether was decanted, and the residue was triturated with fresh ether. The residue was made basic with 50% sodium hydroxide, and the product was precipitated with acetic acid. After drying at 100°, 0.35 g of isocytosine-6-carboxylic acid (**12a**) was obtained: mp >300°; ir (KBr) 1685 cm^{-1};

mass spectrum (70 eV) *m/e* (rel intensity) 155 (7), 111 (20), 44 (100), 43 (86).

Anal. Calcd for $C_5H_5N_3O_3$: C, 38.72; H, 3.25; N, 27.09. Found: C, 37.44; H, 3.40; N, 27.35.

A sample of authentic methyl isocytosine-6-carboxylate (**12b**) prepared in this laboratory by Shepard[11] was hydrolyzed at room temperature with 0.1 *M* potassium hydroxide. The ir and mass spectra of this acid were identical with those reported above, obtained from the oxime **11**. The sample is insoluble in most standard solvents for nmr.

However, since the analysis of the product from the acid **1a**, and the oxime **11**, was not acceptable, 10 g of the product prepared by the above method from the oxime was esterified with 400 ml of absolute methanol containing 35 ml of sulfuric acid according to Shepard's procedure.[11] The solution volume was reduced to about 100 ml by rotary evaporation and the solution was diluted with an equal volume of water. Careful adjustment to pH 6 with ammonium hydroxide resulted in precipitation of the product. Recrystallization from DMF–water afforded 3.34 g (28%) of a light brown powder. A second recrystallization, preceded by treatment with activated charcoal, produced 2.47 g of cream needles of methyl isocytosine-6-carboxylate (**12b**), mp >270° dec, principally 290–300° (lit.[11] mp 293–294° dec). The ir and nmr spectra were identical with those of the authentic sample of **12b** prepared by Shepard:[11] ir (KBr) 2910, 2755, 1750, 1665, 1590, 1560, 1495, 1445, 1395, cm^{-1}; nmr (TFA) τ 5.86 (s, 3, CH_3), 3.07 (s, 1, 5-H), 1.84 (br s, 2, NH_2); mass spectrum (70 eV) *m/e* (rel intensity) 169 (49), 154 (4), 139 (11), 138 (8), 137 (4), 112 (9), 111 (100), 110 (25).

Anal. Calcd for $C_6H_7N_3O_3$: C, 42.61; H, 4.17; N, 24.84. Found: C, 42.64; H, 4.20; N, 25.14.

5-Bromoisocytosine-6-acetic Acid (13) Hydrobromide. Approximately 3 equiv (1.35 mol) of bromine was added to 1 g of isocytosine-6-acetic acid (**1a**) suspended in 4 ml of acetic acid. The pyrimidine appeared to dissolve and promptly reprecipitated. The mixture was stirred for 9 hr, becoming a very pasty suspension. The mixture was diluted with 10 ml of acetone to remove the excess bromine (*caution: the bromoacetone formed is a strong lachrymator*) and stirred for 2 hr. The precipitate was collected and dried, yielding 1.5 g (87%) of **13** · HBr: mp 230–232° dec; ir (KBr) 3220, 2880, 1701, 1685, 1668, 1603, 1202 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 205 (11), 203 (11), 164 (2), 162 (2), 82 (23), 81 (80), 80 (23), 79 (86), 44 (100). With the exception of the peaks at *m/e* 44 and the increase in 82–79 the mass spectrum of **13** · HBr was essentially the same as that of 5-bromo-6-methylisocytosine (**14**).

Anal. Calcd. for $C_6H_7N_3O_3Br_2$: C, 21.91; H, 2.15; N, 12.77; Br, 48.59. Found: C, 22.05; H, 2.14; N, 13.01; Br, 48.71.

An attempt was made to recover the free 5-bromoisoisocytosine-6-acetic acid (**13**) by adjusting the pH of 1 g of **13** · HBr in 25 ml of water to pH 8 with sodium carbonate and back to pH 4 with hydrochloric acid. The nmr of the 0.669 g of white powder, after drying, showed singlets at τ 6.55 (CH_2), and 7.75 (CH_3) (identical with an independently prepared sample of **14**) that indicated that this was a mixture of **13** and about 35% 5-bromo-6-methylisocytosine (**14**). The increased sensitivity of **13** to decarboxylation is an expected effect of the electron withdrawal by the 5-bromo group.

5-Bromo-6-bromomethylisocytosine (15). Bromine (1.1 ml, 0.02 mol) was added dropwise to 3.4 g (0.02 mol) of **1a** suspended in 20 ml of glacial acetic acid. The suspended pyrimidine dissolved as it reacted. A faint orange color persisted after addition of the bromine. An undissolved residue was removed by filtration, and the clear solution was heated overnight at 115°. A white precipitate separated. This was filtered after cooling to room temperature and washed with acetic acid. After drying, 1.5 g of product was obtained. This was heated in 250 ml of water for several hours and the insoluble residue was removed by filtration. The clear solution was allowed to cool slowly overnight. After drying at 100°, 0.39 g of 5-bromo-6-bromomethylisocytosine (**15**) were obtained: mp 200–210° dec; ir (KBr) 3435, 3320, 3090, 2870, 2730, 1660, 1604, 1560, 1475, 1405, 1215, 1150, 1095, 1028, 1005, 776, 668 cm^{-1}; nmr (DMSO-d_6) τ 5.70 (s, 2, CH_2Br), 3.15 (s, 2 NH_2).

Anal. Calcd for $C_5H_5N_3Br_2O$: C, 21.22; H, 1.78; N, 14.85; Br, 56.49; *m/e* 282.8778 for ^{81}Br ^{79}Br. Found: C, 22.19; H, 2.40; N, 15.29; Br, 55.63; *m/e* 282.8783.

Over a period of several days, the DMSO-d_6 nmr sample turned red. DMSO has been used to oxidize halomethyl compounds to aldehydes.

5-Bromo-6-dibromomethylisocytosine (16). Bromine (0.9 ml, 0.0175 mol) was added to 1.0 g (0.0056 mol) of **1a** suspended in 4 ml of acetic acid. The solution was heated overnight at 120°. Upon cooling, a product precipitated. The precipitate was collected and triturated with hot water and sufficient sodium bisulfite was added to remove the faint orange trace of bromine. The hot suspension was filtered and washed with water to give, after drying, 1.3 g of fine white crystals. This was redissolved in dilute sodium hydroxide and reprecipitated with dilute hydrobromic acid. After recrystallization from hot water, the 5-bromo-6-dibromomethylisocytosine (**16**) was dried: mp 240–247° dec; ir (KBr) 3550, 3390, 3310, 3200, 3080, 3015, 2915, 1655, 1628, 1585, 1468, 1369, 1218, 1152, 1102, 1021, 786, 735, 695, 642 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 365 (34), 363 (98), 361 (100), 359 (34).

Anal. Calcd for $C_5H_5N_3Br_3O$: C, 16.59; H, 1.40; N, 11.6; Br, 66.25. Found: C, 16.08; H, 1.77; N, 10.93; Br, 72.54.

Registry No. 1a, 42822-67-3; **1b**, 42822-68-4; **10**, 42822-69-5; **11**, 42822-70-8; **11** · HCl, 42822-71-9, **12a**, 34415-11-7; **12b**, 21615-64-5; **13** · HBr, 42822-74-2; **15**, 42822-75-3; **16**, 42822-76-4; diethyl acetone-dicarboxylate, 105-50-0; guanidine carbonate, 3425-08-9; potassium nitrate, 7757-79-1; 6-methylisocytosine, 5414-09-5; sodium nitrite, 7632-00-0; bromine, 7726-95-6.

References and Notes

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