Dihydrocytosines and Cytosines from 3-Aminopropionitriles

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The synthesis of dihydrocytosines **4** from 3-aminopropionitriles **1** has been broadened and the dihydrocytosines themselves have now been successfully converted to cytosines **9**. Unsubstituted 3-(H, alkyl or aryl) aminopropionitriles (**1**, X = H) convert with cyanate to 1-(H, alkyl or aryl)-1-(2-cyanoethyl)ureas (**2**, X = H), which in turn easily cyclize with anhydrous strong acid or base to 1-(H, alkyl or aryl)-5,6-dihydrocytosines (**4**, X = H). The 1-arylaminopropionitriles (**1**, X = H) which are poorly reactive with cyanic acid combine readily with benzoylureas to form 3-benzoyl-1-(2-cyanoethyl)-1-arylureas (**3**, X = H). These benzoylureas likewise cyclize with strong acid or base but with simultaneous elimination of the benzoyl moiety to yield the 1-aryldihydrocytosines **4** (X = H). Amines have successfully been added to 2-chloroacrylonitrile to yield 2-chloro-3-(amino and substituted amino)propionitriles (**1**, X = Cl). These 2-chloropropionitriles also could be converted with cyanate or benzoylisocyanate to ureas and benzoylureas, respectively (1-(H or alkyl)-1-(2-chloro-2-cyanoethyl)ureas (**2**, X = Cl) or 1-(H or alkyl)-1-(2-chloro-2-cyanoethyl)-3-benzoylureas (**3**, X = Cl). The chlorine substituted ureas were unstable especially to base and to heat but with anhydrous acid were cyclized in high yield to 1-(H or alkyl)-5-chloro-5,6-dihydrocytosines (**4**, X = Cl). Direct chlorination of unsubstituted dihydrocytosines **4** (X = H) did not afford these same 5-chlorodihydrocytosines **4** (X = Cl) under any conditions investigated. 1-Ethyl-5,6-dihydrocytosine (**4b**) as the cation (hydrobromide) is converted directly in good yield to 1-ethylcytosine hydrobromide (**7**) by bromine in nitrobenzene at 140-160° in a concomitant bromination dehydrobromination reaction. 1-(Alkyl or aryl)-5,6-dihydrocytosines (**4**, X = H) are halogenated at low temperature in the presence of base to form (N^3 or N^4)halogenodihydrocytosines (**8**, R = H). The *N*-chlorodihydrocytosines **8** are stable. The *N*-bromo and *N*-iodo compounds isomerize spontaneously to 5-halogeno-5,6-dihydrocytosines (**4**, X = Br, I; R = H). The 5-halogeno-5,6-dihydrocytosines **4** (X = Cl, Br, I) whether from cyclization or direct halogenation are readily dehydrohalogenated to the corresponding cytosines **9**.

A practical conversion of dihydrocytosines to cytosines has been an objective of this laboratory for some time (1). This conversion is new and will be treated in detail later in this paper. First the work will be presented which deals with making the dihydrocytosines themselves easily and cheaply available.

Synthesis of Dihydrocytosines by Cyclization.

The synthetic routes developed in this work are outlined in Scheme I. The pivotal step is a ring closure to dihydrocytosines of substituted cyanoethylureas (**2** and **3**) by basic or acidic catalysis. The non-halogenated ureas were prepared by procedures which can be varied widely but the corresponding chlorine-containing intermediates often are inherently unstable and the experimental procedures must be followed closely.

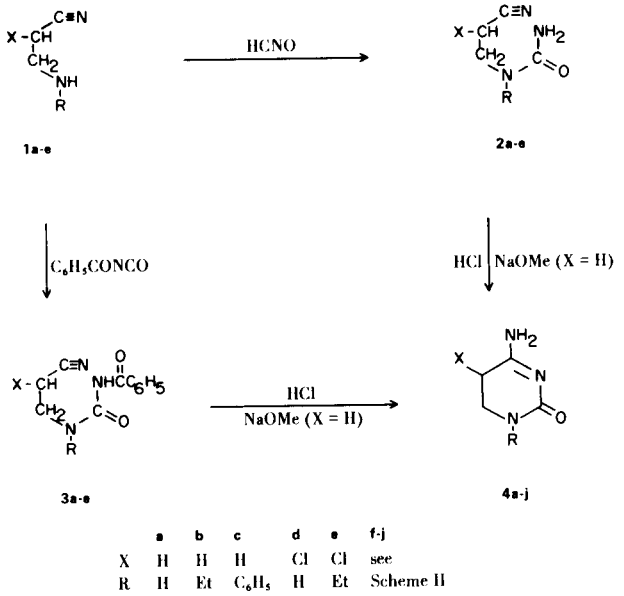
Well along in the course of this investigation Cheng and Lewis (2) published their work on the base catalyzed ring closure of simple cyanoethylureas (**2**, X = H, R = alkyl). Consequently, in the experimental section of the present paper only one such example has been described--synthesis of the new compound 1-ethyl-5,6-dihydrocytosine (**4b**). The practicability of the process is attested to by the 67% yield of **4b** in two steps from the easily available 3-ethylaminopropionitrile (**1b**).

It was found that 1-alkyl-1-cyanoethylureas also cyclize readily with strong acid. However the resulting dihydrocytosine (**4**) salts hydrolyze with extraordinary ease to the corresponding dihydrouracils (3). Cheng and Lewis (2) prepared 1-alkyl-5,6-dihydrouracils in good yield by refluxing the substituted cyanoethylureas (**2**, R = alkyl, X = H) in dilute aqueous acid. Doubtless this reaction goes through a dihydrocytosine stage which easily loses its amino group in aqueous acid.

An acid cyclization of these cyanoethylureas to dihy-

drocytosines with high concentrations of anhydrous hydrochloric acid takes place readily under mild conditions, typically at room temperature for a few hours or overnight. The choice of solvent is severly restricted to those solvents incapable of producing water by action of strong acid. Dry acetonitrile seems most suitable; nitrobenzene affords product but because of the low solubility of hydrochloric acid in this solvent the gas should be bubbled in continuously during the reaction. When methanol, dioxane or tetrahydrofuran were used, the major product often was the dihydrouracil resulting from hydrolysis of the amino group from the corresponding dihydrocytosine **4**.

SCHEME I

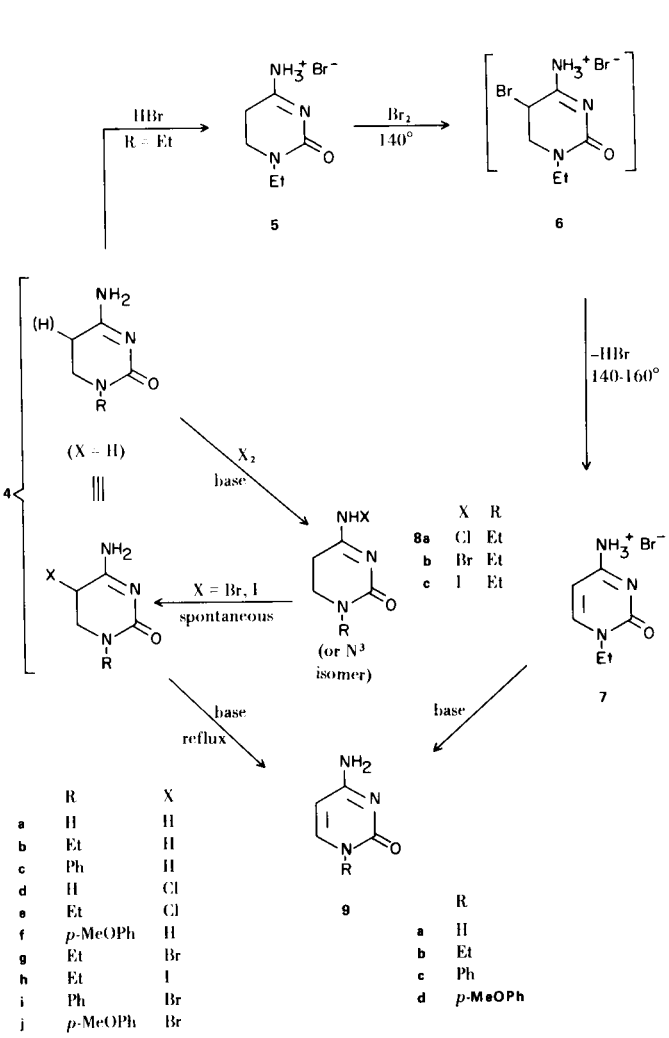


These contrasting cyclizations can be illustrated using as example the ring closure of 1-(2-cyanoethyl)-1-ethylurea (**2b**). The alkoxide catalyzed cyclization of **2b** gives *ca.* 80% yield of **4b** (1-ethyl-5,6-dihydrocytosine) and the acid catalyzed reaction gives *ca.* 90% yield of **4b** (hydrochloride salt).

A modification of the synthesis has been developed for unreactive aminopropionitriles. This is illustrated by 3-anilinopropionitrile (**1c**). This compound which reacts with cyanic acid very poorly, combines energetically with benzoyl isocyanate (4) to give a quantitative yield of 1-phenyl-1-(2-cyanoethyl)-3-benzoylurea (**3c**). The urea **3c** can be cyclized by methoxide catalysis to **4c** in 84% yield. The benzoyl group simultaneously is eliminated as methyl benzoate.

Since a primary goal of this research was the synthesis of cytosines we were interested in the possibility of producing halogen substituted dihydrocytosines. Dehydrohalogenation would then lead directly to cytosines.

SCHEME II



It was found that the starting 2-chloro-3-ethylaminopropionitrile (**1e**) is easily formed in the cold by addition of ethylamine to 2-chloroacrylonitrile (5). The product **1e** can be converted to the hydrochloride which is stable. This salt either can be converted directly to the unstable urea **2e** by reacting with alkali cyanate, or it can be isolated and stored as such. Alternatively, **1e** can be directly converted to the fairly stable benzoyl urea derivative **3e** and isolated.

Both the benzoylurea **3e** and (particularly) the urea **2e** must be handled carefully otherwise ring closure by nucleophilic displacement of chlorine occurs, probably to yield five membered heterocycles rather than the desired dihydrocytosines. 1-Ethyl-1-(2-chloro-2-cyanoethyl)-3-benzoylurea (**3e**) can be stored for months without decomposition. However, heating in pyridine at 100° for 15 minutes converts **3e** in good yield to the by-product

derivative which might be formulated as 3-benzoyl-4-cyano-1-ethyl-2-imidazolidinone or its oxazolidone isomer. The non-benzoylated urea 1-ethyl-1-(2-cyanoethyl)urea (**2e**) is less stable but can be isolated if care is taken to avoid elevated temperatures. The solid product **2e** can be dried *in vacuo* at room temperature during several days and then used satisfactorily in the subsequent reaction **2e** to **4e**. However, if **2e** is merely refluxed in acetonitrile it is converted into a new by-product compound for which a probable structure is 4-cyano-1-ethyl-2-imidazolidinone hydrochloride or its oxazolidone isomer.

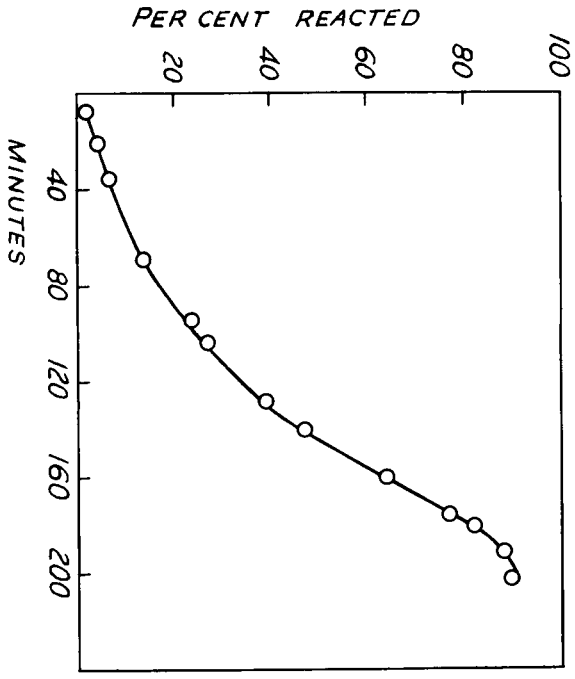


Figure: Isomerization of *N*-bromo-1-ethyl-5,6-dihydrocytosine (**8b**) to 5-bromo-1-ethyl-5,6-dihydrocytosine (**4g**), 0.125 molar in 0.25 molar methanolic triethylamine acetate at 0°.

The chlorine substituted urea **2e** and benzoylurea **3e** could be cyclized to 5-chloro-1-ethyl-5,6-dihydrocytosine (**4e**) easily by acid catalysis. The yields were excellent and the method makes available these previously inaccessible compounds. The cyclization reaction to **4e** is mildly exothermic and proceeds at a temperature below where the unwanted closure to a five-membered ring occurs. In the course of the ring closure of **3e**, the benzoyl group is eliminated as benzoyl chloride (or equivalent reactive species). This was demonstrated by isolating benzanilide in 67% yield after adding excess aniline to the reaction filtrate.

It is of interest now to turn to the special case where in **1**, R = H. Application of these syntheses *via* **2a** or **2d** would lead to the series parent, 5.6-dihydrocytosine, (**4a**) or to 5-chloro-5,6-dihydrocytosine, (**4d**). The compounds **4a** and **4d** are of special interest as possible precursors for synthesis of the naturally occuring biochemical, cytosine.

Methoxide treatment of (2-cyanoethyl)urea (**2a**) inexplicably gave impure 5,6-dihydrocytosine (**4a**). That **4a** substantially was the expected product we judge from the absorption at 243 mμ and from its conversion to 5,6-dihydrouracil (6) upon dilute acid hydrolysis. More successful was the preparation of 5-chloro-5,6-dihydrocytosine (**4d**). The acid catalyzed cyclization of 1-(2-chloro-2-cyanoethyl)urea (**2d**) proceeded smoothly, and the product was pure. The overall yield of **4d** hydrochloride through three steps was 25% of theory, satisfactory in view of the cheapness of the starting ammonia and 2-chloroacrylonitrile.

Halogenation and Dehydrohalogenation of Dihydrocytosines.

Dihydrouracils can be converted easily and in good yields to uracils by a sequential halogenation and dehydrohalogenation (6,7). The straightforward application of these reactions to effect the conversion of the dihydrocytosines **4** to cytosines **9** fails in our experience and, apparently, in the experience of others (2). However variations on the procedure have now been found which are successful.

One reaction path which could be used was the sequence **4** through **7** (see Scheme II) as applied to 1-ethyl-5,6-dihydrocytosine (**4b**). It works well for bromination but fails with chlorination. Central to this approach is the conversion of **4b** entirely to the cation **5** before commencing bromination. This insures that the brominated and dehydrobrominated products also exist as cations. These product cations should be even more resistant to nucleophilic attack than the starting cation **5** and thus minimize the risk of overbromination. Additionally, in a strongly acid medium the formation of *N*-bromo compounds is no problem.

It was found that nitrobenzene at 120-140° adequately dissolves the cation **5**. This solvent cannot give the elements of water with hydrobromic acid; consequently, the cations **5** and **6** do not deaminate. Nitrobenzene is suitably high boiling and is itself resistant to bromination so that the temperature could be raised above 140° to induce bromination of the resistant cation **5**. Beginning at this temperature and becoming rapid by 160° dehydrobromination also occurred. Thus in the operating range 140-160° both reactions occurred concurrently and perforce sequentially. The yield of 1-ethylcytosine hydrobromide (**7**) over the two sequential steps was above 70%. This bromination, despite the unusual conditions, we found to be surprisingly smooth and easy to carry out.

In a similar procedure using hydrochloric acid and chlorine, only 5-chloro-1-ethylcytosine in less than 1% yield and much starting material could be isolated.

If the dihydrocytosines are halogenated at low temperatures in the presence of an acid binding agent, thereby avoiding salt formation, one obtains (N^4 or N^3)halogeno-5,6-dihydrocytosines **8** in good yield. The use of chlorine with **4b** gives the *N*-chloro compound **8a** which was relatively stable. It could be crystallized from hot solvents, and it could be stored for months at room temperature. In contrast, the *N*-bromo compound **8b** is unstable at room temperature and can be isolated only if the temperature is kept low throughout the isolation procedure. Beginning just below room temperature **8b** in methanol solution changes in a mildly exothermic reaction nearly quantitatively into the insoluble 5-bromo-1-ethyl-5,6-dihydrocytosine **4g**. The structure **4g** is assigned by analogy with the product of bromination of hydrouracil (6,7). Isolated and stored as the solid, **8b** also changes to **4g** but does it much more slowly. The course of conversion of **8b** in buffered solution is shown in the Figure. A sharp break in the curve for the conversion in soluuion occurs at 80-90% reaction and comes from precipitation of solid **4g** carrying with it occluded **8b**. The early part of this plot curves upward and describes an accelerating reaction.

As a method of producing 1-substituted cytosines this route promises to be superior to the concurrent bromination-debromination described earlier in this paper. It avoids the high temperature and high acidity of that reaction and thus broadens markedly the variety of dihydrocytosines that can be submitted to bromination. There is another important advantage. The dihydrocytosines can be brominated directly in the cooled alkoxide solution in which they are formed and need not be isolated. By using a full equivalent of alkoxide in the cyclization of the urea one arrives after bromine addition at a substantially neutral solution of the *N*-bromo compound **8** which then converts to the 5-bromo compound (**4**), often exothermically as the solution is warmed. Frequently the 5-bromo compounds are insoluble and can be isolated by filtration directly in good yield from this telescoped reaction.

These 5-halogeno compounds **4** depicted in Scheme I and II are a new class of compounds. Besides being of interest in their own right as relatives of biologically important cytosines, these dihydrocytosines can be readily converted into cytosines. A variety of methods can effect this dehydrohalogenation (*e.g.* 50-90% yield using alcoholic alkali hydroxide or triethylamine).

This new bromination reaction failed when applied to the (impure) parent 5,6-dihydrocytosine (**1a**). The bromination works well with the 1-alkyl and 1-aryldihydrocytosines **4b** and **4c**.

N-Bromination and isomerization proceeds smoothly and in good yield when the side chain in position 1 of the dihydrocytosine is *p*-anisyl (compound **4f**). Since the *p*-anisyl group is easily brominated but not affected in the conversion **4f** to **4j** to **9d** one can conclude that bromination in side chains is not likely to be a serious general limitation. Consequently the method may have wide scope in the number and types of allowable substitutions.

Although the *N*-chloro dihydrocytosine **8a** does not rearrange to the 5-chloro isomer, it was found that the 1-ethyl-*N*-iodo-5,6-dihydrocytosine (**8c**) *does* isomerize. The change occurs in a mildly exothermic reaction with precipitation of the 5-iodo compound **4h**. This product could be judged to contain **4h** (co-precipitated with *N*-iodo compound) because it could be converted in small yield into 1-ethylcytosine (**9b**).

It is uncertain whether the isomerization of *N*-bromo-1-substituted-5,6-dihydrocytosines (**8**) to the corresponding 5-bromo compounds (**4g,i,j**) is intra- or intermolecular. Attempts to get suitable kinetic data to settle this point have been balked by an inexplicable variability. The course of the reaction in methanolic buffer is complex as presented in the characteristic isolated experiment of the Figure and varies somewhat from experiment to experiment. The reaction is slower in pure solvents. The accelerating portion of the curve could arise as from a simple autocatalytic "isomerization" in the sense **8** yields (**4g-j**) in Scheme II or from the vagaries of buildup of intermediates in a sequential multistep process.

Whether the isomerization *N* to C^5 is merely a loose intermolecular halogenation or a reaction with a structurally defined intermediate complex is a point which must be left unsettled. That the isomerizat on **8** to **4g-j** often proceeds briskly in solution at 20-30° and slowly even at 0-10° suggests that it *may* be importantly different in mechanism from the bromination of 1-substituted-5,6-dihydrouracils which Gabel and Binkley chose to perform in refluxing acetic acid (7). The C^5 bromination reaction can be initiated using *N*-bromosuccinimide (NBS) directly with 1-substituted-5,6-dihyd ocytosines instead of bromine and a base. However the high probability that NBS can itself give rise to **8** diminishes its significance as an indicator of reaction mechanism. Also equivocal to mechanism is the pattern of performance of the halogens in this reaction (bromine and iodine isomerize, chlorine does not).

It was of particular interest to prepare the parent biochemical, cytosine (**9a**), by our new series of reactions. The parent 5,6-dihydrocytosine (**4a**) was prepared in poor purity by the methods of Scheme I: this impure product could not be brominated. However 5-chloro-5,6-dihydrocytosine hydrochloride (**4d** HCl) can be obtained in good yield (Scheme I). The product **4d** HCl can be converted to cytosine in 68% yield by refluxing it in ethanolic triethylamine. This sequence of reactions promises to make

this expensive biochemical more cheaply available.

EXPERIMENTAL (8)

1-(2-Cyanoethyl)-1-ethylurea (**2b**).

With stirring and cooling to keep below 34°, 898.5 g. (9.16 moles) of 3-(ethylamino)propionitrile (**1b**) (9) was neutralized by the careful addition of concentrated hydrochloric acid (753 ml.). Then 755 g. of potassium cyanate (of 98% purity) was added in four approximately equal portions over three hours, the temperature being brought to and maintained at 48° for 16 hours after the first addition. It was then evaporated dry on the steam bath *in vacuo*. The residue was boiled with 2.2 l. of 2-propanol and filtered hot from potassium chloride. The product **2b** separated on cooling, yield 1082.5 g. (83.7%), m.p. 88-89.5°. The product was crystallized from ethanol, m.p. 89-90.5°.

Anal. Calcd. for $C_6H_{11}N_3O$: C, 51.05; H, 7.85; N, 29.76. Found: C, 51.16; H, 7.64; N, 29.76.

1-Ethyl-5,6-dihydrocytosine (**4b**) *via* Alkoxide Catalysis.

Compound **4b** was obtained in *ca.* 80% yield by a procedure essentially identical to that described by Cheng and Lewis (2), m.p. 188-190.5° dec., λ max (*p*H 7), 242 mμ (ε, 5,360).

Anal. Calcd. for $C_6H_{11}N_3O$: C, 51.05; H, 7.85; N, 29.76. Found: C, 51.08; H, 7.80; N, 29.80.

1-Ethyl-5,6-dihydrocytosine (**4b**) Hydrochloride -- *via* the Acid Catalyzed Cyclization.

An approximately 4 *M* solution of hydrochloric acid in dry acetonitrile was prepared by passing the gas into acetonitrile held at −30° in a dry ice bath. To 12.5 ml. (0.05 mole) of this solution at −30° was added 1.76 g. (0.0125 mole) of 1-(2-cyanoethyl)-1-ethylurea (**2b**). The resulting solution was allowed to stand at room temperature for 26 hours then evaporated to dryness at room temperature under reduced pressure. The resulting solid was transferred to a sintered glass filter with 10 ml. of acetonitrile and washed with 10 ml. of ether; it was dried *in vacuo* over potassium hydroxide, yield, 2.06 g. (90.4%), m.p. 194-196°, λ max (*p*H 7), 242 mμ (ε, 5,450). A sample of hydrochloride prepared from the pure **4b** from the base catalyzed ring closure, m.p. 200-201.5° dec., λ max (*p*H 7), 242 mμ (ε, 5,135).

If only one or two *M* hydrochloric acid-acetonitrile was used as above, the hydrochloric acid adduct of starting urea, m.p. 110.5-112°, was isolated.

The above procedure accords a good yield of **4b** hydrochloride if nitrobenzene is substituted for acetonitrile. To avoid freezing the nitrobenzene the lowest temperature should be *ca.* 5°; because the hydrogen chloride gas is only slightly soluble it must be bubbled in throughout the main part of the reaction (during 4-5 hours.

When methanol, *p*-dioxane, or tetrahydrofuran were substituted for acetonitrile the major product frequently was 1-ethyl-5,6-dihydrouracil, m.p. 132-134° (crystallized from methanol).

Anal. Calcd. for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.54; H, 7.38; N, 20.07.

3-Benzoyl-1-(2-cyanoethyl)-1-phenylurea (**3c**).

To a cooled solution of 52.3 g. (0.357 mole) of 3-anilinopropionitrile (10) in 200 ml. of ethylene chloride was slowly added 53.6 g. (0.357 mole) of benzoyl isocyanate (4) in 75 ml. of 1,2-dichloroethane. The internal temperature was kept below 10° during this addition. The solvent was removed *in vacuo*, in a 60° bath. The product **3c** weighed 104.6 g. (quantitative) and melted at 97.5-110°. (Subsequent experience showed that filtering the thick slurry in 1,2-dichloroethane before it goes to dryness can give up to 97% yield of pure material without recrystallization.) Crystallized from acetonitrile it melted at 110.5-112.3°, λ max (methanol), 231 mμ (ε, 17,600).

Anal. Calcd. for $C_{17}H_{15}O_2N_3$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.86; H, 5.18; N, 14.73.

1-Phenyl-5,6-dihydrocytosine (**4c**).

To a solution of 1.725 g. (0.075 g.-atom) of sodium in 75 ml. of methanol at 40° was added 22 g. (0.075 mole) of 3-benzoyl-1-(2-cyanoethyl)-1-phenylurea (**3c**). The solution was refluxed for 30 minutes (precipitation starts in 3 minutes). The suspension was neutralized with glacial acetic acid (4.4 ml.), refluxed again, and then filtered at *ca.* 40°. (Later experience showed the neutralization is unnecessary. A 97% yield of pure product can be filtered off idrectly.) The dry product **4c**, m.p. 257-259° dec., weighed 11.90 g. (83.8% yield). Crystallization from a 1:1 mixture of acetonitrile and water gave a 70% recovery of **4c**, m.p. 262-264° dec., (greatly variable depending on rate of heating); λ max (methanol), 251 mμ (ε, 10,630).

Anal. Calcd. for $C_{10}H_{11}N_3O$: C, 63.47; H, 5.86; N, 22.21. Found: C, 63.48; H, 6.09; N, 22.42.

The filtrate from the reaction mixture was fractionally distilled. The probable presence of methyl benzoate in the fraction distilling at 110-112° at 8 mm. was shown by the formation of benzhydrazide by refluxing the fraction with hydrazine in ethanol, m.p. 113.4-115°, unaltered on admixture with authentic benzhydrazide.

2-Chloro-3-(ethylamino)propionitrile (**1e**) Hydrochloride.

Ethylamine at 0° (6.38 ml., 0.1 mole measured at 0°) in 50 ml. of acetonitrile at 0° was cooled to −20° in a dry ice bath and 8.04 ml. (0.1 mole) of 2-chloroacrylonitrile (5) was added rapidly. The temperature of the exothermic reaction was held below 10° until complete. The reaction solution cooled (dry ice bath) to 0° was neutralized to *ca. p*H 6 with 2 *N* aqueous hydrochloric acid. (In later runs dry ethanolic hydrochloric acid was used and the precipitated pure product separated by filtration; yield 63%, m.p. 158-159°; second crop, yield 21%, m.p. 155.157°.) The solution was evaporated (*in vacuo*, 40°) to a syrup which solidified. It was crystallized successively from ethanol, then acetonitrile (with charcoal). The yield of pure product was 8.55 g. (51%), m.p. 158-159°.

Anal. Calcd. for $C_5H_{10}Cl_2N_2$: C, 35.52; H, 5.96; N, 16.57; Cl (total), 49.95; Cl (ionic), 20.97. Found: C, 35.81; H, 5.96; N, 16.57; Cl (total), 42.11; Cl (ionic), 21.40.

1-(2-Chloro-2-cyanoethyl)-1-ethylurea (**2e**).

A stirred solution of 16.9 g. (0.1 mole) of **1e** hydrochloride in 30 ml. of cold water was cooled in an ice bath. Potassium cyanate of 98% purity (8.27 g., 0.1 mole) and *ca.* 1 g. of dry ice was added. The initially clear solution was allowed to warm to 15°. An oil deposited which soon crystallized. The suspension was held at 12-14° for 1 hour and then stored overnight at 0°. The white product **2e** was filtered off, washed with two 5 ml. portions of ice water and dried to constant weight in a vacuum desiccator over phosphorus pentoxide with constant pumping. The yield of crude **2e** suitable for further reactions was 16.64 g. (95%), m.p. 85-86°.

An analytically pure sample could be prepared with 50% recovery by dissolving crude **2e** at room temperature in a mixture of 1 part of water--2.5 parts of acetone to about 30% solution. Insoluble material was filtered off and discarded. Two volumes of water were added to the filtrate. The white solid was separated

by filtration, washed with a little cold water and then ether and dried as above. The pure **2e** melted at 90-90.6°.

Anal. Calcd. for $C_6H_{10}ClN_3O$: C, 41.03; H, 5.74; N, 23.93; Cl (total), 20.19; Cl (ionic), 0.0. Found: C, 41.30; H, 5.72; N, 23.86; Cl (total), 20.57; Cl (ionic), 0.0.

Compound **2e** is intrinsically unstable, presumably converting slowly to the five-membered heterocycle (below). The decomposition at room temperature of the dry solid is reflected in a rise in ionic chloride when checked daily from 0% through four days, 4.44% at 10 days, 7.75% at 15 days and 13.65% ionic chloride at 29 days (complete decomposition would have given 20.57% ionic chlorine).

If the temperature is allowed to rise to *ca.* 45° during the formation above, or the isolated urea **2e** is refluxed in acetonitrile approximately 40% yield can be obtained of a product which presumably is 4-cyano-1-ethyl-2-imidazolidinone hydrochloride (or isomeric oxazolidone). The product was crystallized from acetonitrile, m.p. 161-162°. The infrared spectrum had a strong carbonyl peak at 1720 cm^{-1}; however as characteristic of salts no cyano peak was evident.

Anal. Calcd. for $C_6H_{10}ClN_3O$: C, 41.03; H, 5.74; N, 23.93; Cl (ionic), 20.19. Found: C, 41.46; H, 5.73; N, 24.16; Cl (ionic), 20.43. *Mass spectrum* (on a Finnigan 1015 quadropole mass spectrometer) as mass and relative intensity for prominent peaks followed by identification where significant 139 (25) (M–HCl), 124 (4), 113 (3) (M–HCl–CN), 101 (9), 96 (14), 81 (22), 68 (36), 56 (100), 55 (23), 54 (94).

3-Benzoyl-1-(2-chloro-2-cyanoethyl)-1-ethylurea (**3e**).

A stirred solution of 12.76 ml. (0.2 mole at 0°) of anhydrous ethyl amine in 100 ml. of dry acetonitrile at 0° was cooled to -30° in a dry ice bath and 61.1 ml. (0.20 mole) of 2-chloroacrylonitrile (precooled to 0°) was added rapidly in one portion. The temperature rose quickly to 0°. After a few minutes the solution was cooled back to -25° and 25.5 ml. (0.20 mole) benzoyl isocyanate (4) was added rapidly. The cooling bath was removed and the temperature was allowed to rise to 15° during 10 minutes. A solid was obtained, m.p. 117.7-120°, 35.94 g. (64.3% yield). Crystallization from ethanol gave pure **3e**, m.p. 122-123°, λ max (methanol), 231 mμ (ε, 15,700).

Anal. Calcd. for $C_{13}H_{14}ClN_3O_2$: C, 55.82; H, 5.05; N, 15.04; Cl, 12.67. Found: C, 55.94; H, 5.14; N, 15.01; Cl, 12.71.

The benzoylurea **3e** on 15 minutes heating in pyridine on the steam bath was converted in 73% yield into a product presumably 3-benzoyl-4-cyano-1-ethyl-2-imidazolidinone (or oxazolidone isomer). Crystallized from ethyl acetate, m.p. 136-139°, λ max (methanol) 237 mμ (ε, 12,850), strong band at 2250 cm^{-1} for CN.

Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.39; N, 17.27. Found: C, 64.09; H, 5.34; N, 17.51. *Mass Spectrum* (Finnigan 1015 quadropole mass spectrometer) (70 ev), principal peaks mass (relative intensity) (interpretation): 243 (10) (mol. ion), 215 (15) (M–HCN?), 113 (28), 104 (45), 77 (100).

5-Chloro-1-ethyl-5,6-dihydrocytosine Hydrochloride (**4e** Hydrochloride).

Dry hydrogen chloride was passed into 127 ml. of dry acetonitrile cooled in a dry ice bath to a weight gain of 19.5 g. (0.5 mole). To this solution at 0° (in an ice bath) was added 35.5 g. (0.127 mole) of the benzoylurea **3e**. With ice bath removed the temperature rose (exothermically) to about 35° when precipitation of white solid began. The suspension stood three days at room temperature, was then cooled to 0° and the solid separated by filtration. The product was washed with acetonitrile (3 x 20 ml.) then with ether and dried to constant weight *in vacuo* over potassium hydroxide. The yield of **4e** hydrochloride was 23.07 g. (85.6%), m.p. 216° dec., λ max (*p*H 7), 224 mμ (ε, 8,150); infl λ 250 mμ (ε *ca.* 6,500).

Anal. Calcd. for $C_6H_{11}Cl_2N_3O$: C, 33.98; H, 5.23; N, 19.81; Cl (total), 33.44; Cl (ionic), 16.71. Found: C, 34.23; H, 4.81; N, 19.71; Cl (total), 33.47; Cl (ionic), 16.67.

The probable presence of benzoyl chloride in the above acetonitrile filtrate after partial evaporation was shown by the isolation of 69% yield of benzanilide after adding excess aniline (identical with an authentic sample by m.p. and mixed m.p.).

5-Chloro-1-ethyl-5,6-dihydrocytosine hydrochloride (**4e**, hydrochloride) was also prepared in the same way from the simpler urea **2e**. The yield of product, m.p. 210° dec., was 91%. The hydrochloride salt (2.0 g.) was converted to free base **4e** by adding it to methanol (20 ml.) containing 1 1/2 equivalents (2 ml.) of triethylamine. The **4e** was filtered off, washed with a little chilled water, ethanol and ethyl ether. The yield of **4e** was 1.17 g. (71%), m.p. 184° dec. On crystallization from ethanol it melted at 180-190° dec.

Anal. Calcd. for $C_6H_{10}ClN_3O$: C, 41.03; H, 5.74; N, 23.93; Cl, 20.19. Found: C, 41.09; H, 5.64; N, 23.82; Cl, 20.38.

(2-Cyanoethyl)urea (**2a**) and Conversion to Impure 5,6-Dihydrocytosine (**4a**).

The compound **2a** was prepared (11) from potassium cyanate and 3-aminopropionitrile (12). Crystallized from methanol it was obtained in 79% yield, m.p. 110-111.5°.

Anal. Calcd. for $C_4H_7N_3O$: C, 42.47; H, 6.23; N, 37.15. Found: C, 42.65; H, 6.09; N. 37.15.

Refluxing **2a** in methanolic sodium methoxide and isolation as usual gave impure **4a**, m.p. 213-214° dec., λ max (methanol), 235 mμ (E_1^1 681). It was not improved, even worsened, by repeated crystallization from a variety of solvents. On hydrolysis in dilute acid it yielded pure 5,6-dihydrouracil, m.p. 280-281° identical by m.p. mixed m.p. and infrared spectrum to an authentic sample (6).

3-Amino-2-chloropropionitrile Hydrochloride (**1d**, Hydrochloride).

To a stirred solution of 47 g. (2.76 moles) of ammonia gas in 1 l. of methanol at 1-2° was added quickly 32.2 ml. (0.40 mole) of 2-chloroacrylonitrile (5). A mildly exothermic reaction ensued which lasted about five minutes. After about 20 minutes the solution was evaporated under reduced pressure and internal temperature below ambient by cooling if necessary. This effectively removes excess ammonia. The residual solution was cooled in a dry ice bath to -45° and acidified with a slight excess of cold (-30°) approximately 25% methanolic hydrochloric acid, using an external indicator and keeping below -32°. The solution was removed from the cooling bath and 700 ml. of ether was added. The deposited syrup slowly crystallized. The yield of crude product (**1d** hydrochloride) dried *in vacuo* at room temperature was 31.4 g. (55.8%), m.p. 142-149°, suitable for the next step. Crystallization from methanol gave pure **1d** hydrochloride, m.p. 154-155°.

Anal. Calcd. for $C_3H_6Cl_2N_2$: C, 25.5; H, 4.29; N, 19.87; Cl (total), 50.29; Cl (ionic), 25.15. Found: C, 25.46; H, 3.86; N, 19.66; Cl (total), 50.86; Cl (ionic), 25.90.

(2-Chloro-2-cyanoethylurea (**2d**).

A solution of 24.7 g. (0.175 mole) of above crude **1d** hydrochloride in 52.5 ml. of water was brought to approximately *p*H 5 with solid sodium bicarbonate (*ca.* 0.5 g.). The solution was

cooled to 2° in an ice bath and carbon dioxide was passed in. After five minutes 14.5 g. (0.175 mole) of potassium cyanate was added. Powdered solid carbon dioxide was added as needed to keep the slightly exothermic reaction mixture below 8-10°. The solution was stored overnight at 0° and extracted with ethyl acetate (3 x 60 ml.). The extract was dried with magnesium sulfate and evaporated (*in vacuo* at room temperature) to a syrup which slowly crystallized. Yield of crude **2d** (dried over phosphorus pentoxide *in vacuo*) was 22.2 g. (86%), m.p. 58-60°. Redissolution in ethyl acetate, washing with water, redrying and evaporating as above gave a syrup which crystallized. This crystalline solid on dispersion into 10 volumes of ether and separation by filtration gave pure **2d**, m.p. 62-68°.

Anal. Calcd. for $C_4H_6ClN_3O$: C, 32.55; H, 4.10; N, 28.48; Cl, 24.03. Found: C, 32.89; H, 3.80; N, 28.34; Cl, 23.87.

5-Chloro-5,6-dihydrocytosine Hydrochloride (**4d** Hydrochloride).

A solution of 23.6 g. (0.647 mole) hydrogen chloride gas in 122 ml. of dry acetonitrile was cooled to 4° and added to 17.93 g. (0.122 mole) of the above crude urea **2d**. The solution was warmed spontaneously to 28° then was stirred for three days at room temperature. The resulting suspension was cooled in an ice bath for two hours, filtered and the solid product washed with acetonitrile followed by ether. The product **4d** hydrochloride, m.p. 182-183° dec., was 11.50 g. (51.7% yield) and was pure; λ max (*p*H 7), 222 mμ (ε, 8,070); infl 240 mμ (ε, 7,250).

Anal. Calcd. for $C_4H_7Cl_2N_3O$: C, 26.11; H, 3.83; N, 22.84; Cl (total), 38.54; Cl (ionic), 19.27. Found: C, 26.01; H, 3.75; N, 22.76; Cl (total), 38.00, 38.43; Cl (ionic), 19.90.

All attempts to crystallize the product lowered its purity. The hydrochloride salt (5.53 g.) was converted to free base **4d** by adding it to methanol (25 ml.) containing 1 equivalent of triethylamine. The **4d** crystallized from the initially clear solution and after cooling was separated by filtration. The yield of **4d** was 3.55 g. (80% recovery) m.p. 179° dec., after drying to constant weight over phosphorus pentoxide with constant pumping. On crystallizing from methanol it melted at 177-178° dec.

Anal. Calcd. for $C_4H_6ClN_3O$: C, 32.55; H, 4.10; N, 28.48; Cl (total), 24.03; Cl (ionic), 0.0. Found: C, 32.54; H, 4.17; N, 28.46; Cl (total), 23.92; Cl (ionic), 0.0.

1-Ethylcytosine (**9b**) by Concurrent Bromination -- Dehydrobromination of Cationic Species **5**.

Dry hydrogen bromide was rapidly passed into a stirred suspension of 525 g. (3.72 moles) of 1-ethyl-5,6-dihydrocytosine (**4b**) in 3.72 l. of nitrobenzene. External heating was used in addition to the heat of neutralization to bring the internal temperature to approximately 140°, at which point solution was complete. Hydrogen bromide addition was continued until absorption ceased. With the temperature of the nitrobenzene solution held at 140°, 625 g. (5% excess) of bromine was added portionwise at a rate allowing safe escape of the hydrogen bromide which is evolved in 30-60 seconds following each addition due to the bromination-dehydrobromination reaction. After the bromine addition was complete the temperature was raised in the course of about an hour to 160° when hydrogen bromide evolution had practically ceased. The reaction mixture was cooled to 5° and the crude tan product collected by filtration; it was washed with nitrobenzene then ether, m.p. 197-203°. The damp cake was crystallized from 6.5 l. of anhydrous ethanol, yield 620 g. of **7** (76%), m.p. 207-209° dec.; λ max (*p*H 7 buffer), 273 mμ (ε, 8,297). This material converted to the free base **9b** with dilute alkali and crystallized from ethanol melted at 245-246° dec.; λ max (*p*H 7 buffer), 274 mμ (ε, 8.350).

Anal. Calcd. for $C_6H_9N_3O$: C, 51.76; H, 6.52; N, 30.20. Found: C, 52.07; H, 6.60; N, 30.03.

Chlorination-Dehydrochlorination of 1-Ethyl-5,6-dihydrocytosine (**4b**) Failure to Yield 1-Ethylcytosine.

A similar run to above but substituting hydrochloric acid for hydrobromic acid and chlorine for bromine gave a mixture containing mainly starting material. Precipitation of the free base from dilute water solution with alkali and crystallization from alcohol yielded *ca.* 0.7% of theory of a compound presumed to be 5-chloro-1-ethylcytosine, m.p. 194-196° dec.; λ max (*p*H 7 buffer), 289 mμ (ε, 7,000).

Anal. Calcd. for $C_6H_8ClN_3O$: N, 24.21; Cl, 20.43. Found: N, 23.93; Cl, 20.16.

(N^3 or N^4)-Chloro-1-ethyl-5,6-dihydrocytosine (**8a**).

To a solution of 14.1 g. (0.1 mole) of 1-ethyl-5,6-dihydrocytosine (**4b**) and 5.68 g. (0.1 mole) of sodium methylate (95% pure) in 100 ml. methanol cooled to −12° was added 7.1 g. (0.1 mole) of chlorine over 30 minutes. The mixture after standing two days at room temperature was filtered to remove sodium chloride. The total volume was 128 ml.; 108 ml. of the filtrate was evaporated to dryness (bath 75°). Yield of crude white solid 16.23 g. which on crystallization from 50 ml. of boiling 2-propanol (filtered from sodium chloride) yielded 10.63 g. (72% based on aliquot) (containing a trace of ionic chloride) m.p. 108-140° dec.; λ max (*p*H 7 buffer), 220 mμ (ε, 11,900).

Anal. Calcd. for $C_6H_{10}ClN_3O$: C, 41.03; H, 5.74; N, 23.92; Cl, 20.19. Found: C, 41.45; H, 5.71; N, 23.83; Cl, 20.20.

A sample was crystallized from hot water, 70% recovery, m.p. 111-112°, titrated iodometrically 98.3% pure **8a** pure by TLC silica gel (87% propanol), 10% isooctane, 3% concentrated ammonia). Stability: the solid is stable at room temperature for months. After four years m.p. 77-100° indistinct. After refluxing **8a** in methanol for 16 hours the solution no longer gave a positive starch-iodide test but by TLC the product was largely 1-ethyl-5,6-dihydrocytosine (**4b**). On heating **8a** in dimethylformamide at *ca.* 100° overnight, TLC gave evidence for some 5-chloro-1-ethylcytosine.

(N^3 or N^4)-Bromo-1-ethyl-5,6-dihydrocytosine (**8b**).

A solution of 1-ethyl-5,6-dihydrocytosine (**4b**) was formed by refluxing 14.1 g. (0.1 mole) of 1-(2-cyanoethyl)-1-ethylurea (**2b**) with 1 molar equivalent of sodium methoxide in 50 ml. of methanol. This solution was cooled to and kept at 0° while 16.3 g. (0.102 mole) of bromine was added over 10 minutes. The intensely yellow neutral solution was evaporated to dryness under reduced pressure using a water bath below room temperature, the final portions of solvent being taken off in a cold water bath (*ca.* 10-15°). The solid was extracted with 200 ml. of chloroform, the solution filtered from insoluble matter and the filtrate washed twice with cold water. The chloroform extract was dried for a few minutes at room temperature over magnesium sulfate and evaporated to dryness again using a cool water bath. The syrupy residue crystallized, yield 19.9 g. (90.8%) m.p. 75°. This was dissolved in 30 ml. of acetonitrile (slight warming) and cooled to 0°. The crystallized solid was isolated by filtration, washed with ether and dried at room temperature by evacuation to *ca.* 0.1 mm. for 2 hours. It was stored under refrigeration, yield 12.24 g. (55%) m.p. 90° dec.; λ max (methanol), 221 mμ (ε, 13,300).

Anal. Calcd. for $C_6H_{10}BrN_3O$: C, 32.75; H, 4.58; N, 19.10; Br, 36.33. Found: C, 32.94; H, 4.69; N, 19.13; Br, 36.20. Purity by iodometric titration 99.7%.

Stability of the Solid **8b**.

Time	Temp.	Content by Iodometric Titration
Start	---	99.7%
3 days	approx. 25°	97.2
21 days	approx. 25°	19.4
21 days	-3°	98.3
17 months	-3°	94.9

Stability of a 0.5 Molar Chloroform Solution of **8b**.

.75 hours	25°	94.5
5.5 hours	25°	88.9
21 hours	25°	5.8

Stability of 0.125 Molar **8b** in Methanol.

45 min.	0°	99.6
185 min.	0°	99.6

Stability of 0.125 Molar **8b** in 0.25 Molar Methanolic Triethylamine Acetate.

8 min.	0°	98
190 min.	0°	11.7

(Other points in the Figure.)

5-Bromo-1-phenyl-5,6-dihydrocytosine (**4i**).

Rapidly, in one portion, 60.5 g. (0.32 mole) of 1-phenyl-5,6-dihydrocytosine (**4c**) was added to a stirred solution of 7.36 g. (0.32 g.-atom) of sodium in 320 ml. of methanol at about 40°. The solution was cooled (external dry ice bath) to 0°. Over four minutes 51.2 g. (0.32 mole) of bromine was added, maintaining the internal temperature at 0-2°. The resulting light yellow solution reacts with and bleaches acidified starch-iodide paper. The cooling bath was removed and the solution was allowed to warm spontaneously over four hours. The temperature rose to 35° and a white precipitate formed. After stirring overnight at room temperature the slurry was refluxed for seven minutes, then cooled and the product filtered off. It was washed with methanol then ether, yield of **4i**, 73.7 g. (86%) m.p. 172° dec., λ max (methanol), 231 mμ (ε, 11,270).

Anal. Calcd. for $C_{10}H_{10}BrN_3O$: C, 44.79; H, 3.76; N, 15.67; Br, 29.81. Found: C, 45.06; H, 3.47; N, 15.57; Br, 29.81.

5-Bromo-1-ethyl-5,6-dihydrocytosine (**4g**) by Direct Bromination in the Presence of Triethylamine.

In 100 ml. of methanol was dissolved 14.1 g. (0.1 mole) of 1-ethyl-5,6-dihydrocytosine (**4b**) and 13.84 ml. (0.1 mole) of dry triethylamine. The bromination was performed using 15.98 g. (0.1 mole) of bromine as in the bromination of **4c** above, yield of **4g** after overnight standing 18.13 g. (82%), m.p. 146° dec.; λ max (*p*H 7 buffer), 230 mμ (ε, 6,670); infl 260 mμ (ε *ca.* 5,780).

5-Bromo-1-ethyl-5,6-dihydrocytosine (**4g**) by Bromination with *N*-Bromosuccinimide.

In 10 ml. of methanol at room temperature were combined 0.176 g. (0.00125 mole) of 1-ethyl-5,6-dihydrocytosine (**4b**) and 0.223 g. (0.00125 mole) of *N*-bromosuccinimide and the product filtered off as above after 24 hours, yield of **4g** 0.1 g. (36%), m.p. 134°; λ max (*p*H 7 buffer), 230 mμ (ε, 6, 340).

5-Bromo-1-ethyl-5,6-dihydrocytosine (**4g**) by Cyclization and Bromination in One Step.

A solution of sodium methoxide was made by dissolving 27.6 g. (1.2 g.-atom) of sodium in 1.2 l. of methanol. To this was added 169.4 g. (1.2 moles) of 1-(2-cyanoethyl)-1-ethylurea (**1b**) and the mixture refluxed 30 minutes. The solution was then cooled to 0° and 192 g. (1.2 moles) of bromine was added over 14 minutes, keeping below 5° by external cooling (dry ice bath). The resulting clear solution was approximately *p*H 7 (indicator paper) and strongly positive to acidified sodium iodide-starch paper. It was allowed to warm spontaneously by removing the cooling bath. As the temperature rose to about 15-20° a mild exothermic reaction set in which carried the temperature to approximately 35° during which time precipitation started. The reaction mixture was allowed to stand two days at room temperature. The suspension was cooled to 4° and the white solid filtered off; the cake was washed with methanol and ether. Dried at 60° *in vacuo* overnight the product **4g** weighed 224 g. (85%), m.p. 140° resolidifies, remelts 198-206° dec.; λ max (*p*H 7 buffer), 230 mμ (ε, 6,798 broad inflection 260 mμ). For analysis later assorted lots were combined and crystallized twice from methanol, m.p. 145°; λ max (*p*H 7 buffer), 229 mμ (ε, 6,468).

Anal. Calcd. for $C_6H_{10}BrN_3O$: C, 32.75; H, 4.58; N, 19.10; Br, 36.33; Br (ionic), 0.0. Found: C, 32.92; H, 4.61; N, 19.48, 19.57; Br, 36.19; Br (ionic), 0.0.

1-Ethylcytosine (**9b**).

Method A. Dehydrobromination.

To a solution of 6.35 g. (0.1 mole) of 86% potassium hydroxide in 135 ml. of methanol cooled to 5° was added 22 g. (0.1 mole) of 5-bromo-1-ethyl-5,6-dihydrocytosine (**4g**). The stirred suspension was allowed to warm spontaneously (removed from bath). A maximum temperature of about 35° was reached. The stirred mixture was brought to reflux for a few minutes then allowed to stand overnight. It was evaporated to dryness (*ca.* 20 mm. pressure, 80° bath). The white residue was dissolved in 23.1 ml. of water at 80° and the solution refrigerated at 0° overnight. The crystalline product **9b** was separated by filtration, pressed dry, washed twice with 1-2 ml. of ice water, then washed with ether; it was dried *in vacuo* at 60° overnight; λ max (*p*H 7 buffer) 273 mμ (ε, 8,140) (approximately 97.5% pure), yield of crude product 12.63 g. (88%), m.p. 224-241°.

Method B. Dehydrochlorination.

A similar treatment of **4e** with two moles of potassium hydroxide afforded a 56% yield of 1-ethylcytosine (**9b**), m.p. 237-242° dec.; λ max (*p*H 7) 274 mμ (ε, 8,200) approximately 98% pure. Recrystallization first from ethanol then acetonitrile yielded pure 1-ethylcytosine (**9b**), m.p. 244-247° dec.

1-Phenylcytosine (**9c**).

A solution of 1.93 g. (0.03 mole) of 87% potassium hydroxide in 40 ml. of ethanol was prepared. To this stirred solution at 52° was added 8.04 g. (0.03 mole) of 5-bromo-1-phenyl-5,6-dihydrocytosine (**4i**). The temperature rose to 62° over a few minutes following which the solution was refluxed for one minute. The product was filtered from the cooled solution, washed with ethanol, hot methanol and finally with ether. The dry product

was washed with much water and again with methanol. It was dried at 60° *in vacuo*, yield 4.97 g. (89%) m.p. 299-300° dec. This product on crystallizing twice as the hydrochloride (1 g. per 10 ml. of 1 *N* hydrochloric acid, each time followed by reconverting to the free base with 5% aqueous ammonia) then finally crystallizing from methanol gave a 40% recovery of pure **9c**, m.p. 337-339° dec., (dried at 100°); λ max (methanol) 238 mμ (ε, 14,500); 279 mμ (ε, 14,100).

Anal. Calcd. for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 63.61; H, 4.58; N, 22.41.

1-Ethylcytosine (**9b**) *via* Iodination and Dehydroiodination of 1-Ethyl-5,6-dihydrocytosine (**4b**).

Finely ground crystalline iodine 25.3 g. (0.1 mole) was stirred at 0° in a solution of 14.1 g. (0.1 mole) 1-ethyl-5,6-dihydrocytosine (**4b**) and 0.1 mole sodium methoxide in 100 ml. of methanol. The cooling bath was removed and stirring was continued. During 45 minutes the temperature increased exothermically to 34° as the iodine completely dissolved and precipitation of the yellow 5-iodo compound started. The iodo compound was filtered off after 20 hours at room temperature, yield 15.4 g., m.p. 161-162° dec. This crude **4h** contained much (>50%) *N*-iodo compound **8c** judged by iodometric titration but was shown to contain some **4h** by conversion with methanolic potassium hydroxide to 1-ethylcytosine which, after crystallization from water using sodium sulfite to destroy residual *N*-iodo compound, was obtained in small yield, m.p. 245-246°; λ max (*p*H 7 buffer), 273 mμ (ε, 8,380).

Anal. Calcd. for $C_6H_9N_3O$: C, 51.76; H, 6.52; N, 30.20. Found: C, 51.39; H, 6.46; N, 30.33.

1-(2-Cyanoethyl)-1-(*p*-methoxyphenyl)urea.

3-*p*-Anisidinopropionitrile (13) (123.35 g., 0.70 mole) was dissolved in 567 ml. of absolute alcohol. This solution was neutralized with 700 ml. of 1 *N* hydrochloric acid, keeping below 30°. To this suspension was added 62.5 g. (0.77 mole) of potassium cyanate. The reaction mixture was brought to approximately 50° when complete solution ensued. It was allowed to stand at room temperature overnight when precipitated dicyanoethylation byproduct was removed by filtration. The mother liquor was concentrated to 200 ml., cooled and the precipitated solid collected. The product was washed with cold water and dried. On crystallization from methanol (250 ml.), then acetonitrile (180 ml.) and finally acetone (250 ml.), it yielded 52.3 g. (34%), m.p. 134-137.5°; λ max (methanol), 229.5 mμ (ε, 10,080); 280 mμ (ε, 1,228).

Anal. Calcd. for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.42; H, 6.02; N, 19.38.

1-(*p*-Methoxypehnyl)cytosine (**9d**) from 1-(2-Cyanoethyl)-1-(*p*-methoxyphenyl)urea by Bromination and Dehydrobromination.

To a solution of 0.184 mole of sodium methoxide (from 4.23 g. of sodium) in 300 ml. of methanol was added 39.5 g. (0.18 mole) of 1-(2-cyanoethyl)-1-(*p*-methoxyphenyl)urea and brought to reflux. A precipitate formed in the initially clear hot solution. After five minutes refluxing the mixture was removed to a dry ice bath and cooled to −10°. Over 8 minutes to the stirred suspension held at approximately −10° was added 29.95 g. (0.188 mole) of bromine. The now yellow suspension after being allowed to warm to room temperature was brought carefully to reflux. The yellow precipitate dissolved and was replaced by a white solid. After 2 minutes of refluxing the suspension was cooled, the solid collected and dried at 50° *in vacuo* overnight. The yield of crude **4i**, m.p. 158° dec., was 41.4 g. (77%). This crude product was refluxed in a mixture of 205 ml. of dimethylformamide and 56 ml. of triethylamine for five minutes. The suspension was cooled and at 80° two volumes of water was added. The suspension after cooling was filtered and the solid dried (18.8 g., m.p. 310°). It was purified by dissolution in 350 ml. of warm dilute hydrochloric acid (*ca.* 0.6 *N*), filtering with charcoal and neutralizing with excess ammonia; yield of **9d** dried *in vacuo* 17.4 g. (57% based on crude bromo compound **4j**), m.p. 316° dec.; λ max (*p*H 7 buffer), 272 mμ (ε, 9,740). The product was crystallized with 85% recovery from 75% dimethylformamide-water mixture, then washed with methanol and ether, m.p. 332-335°; λ max (*p*H 7 buffer), 271 mμ (ε, 10,600).

Anal. Calcd. for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.11; N, 19.35. Found: C, 60.65; H, 5.24; N, 19.34.

Cytosine (**9a**).

A suspension of 36.8 g. (0.20 mole) of 5-chloro-5,6-dihydrocytosine hydrochloride (**4d** HCl) in 200 ml. of ethanol and 111 ml. of triethylamine was refluxed with stirring overnight. The suspension was then evaporated to dryness *in vacuo* on a steam bath (residue 89.66 g.). This residue was dissolved in 110 ml. of hot water, treated with charcoal and filtered. After cooling in an ice bath the product was collected, washed twice with 10 ml. of cold water, thrice with 10 ml. of cold ethanol and finally with ether; yield of crude **9a** 15.10 g. (68% of theory), m.p. 308-310° dec.; λ max (methanol), 268 mμ (ε, 5,720); authentic analytically pure cytosine, λ max 268 mμ (ε, 5,720); m.p. 313-315° dec.

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