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Pyrimidines. XIV. Synthesis of 1-Substituted 5,6-Dihydrocytosines and an Improved Synthesis of 1-Substituted Uracils (1)

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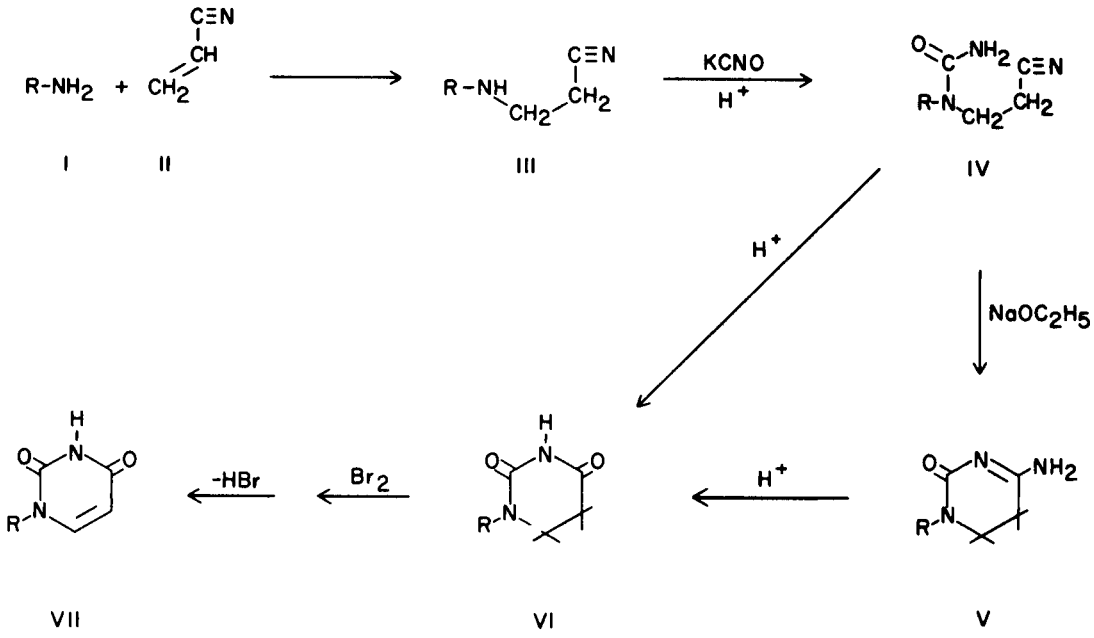
1-Substituted 5,6-dihydrouracils (VI) and 1-substituted 5,6-dihydrocytosines (V) were prepared by cyclization of N-substituted N-β-cyanoethyl ureas (IV) in acid and basic medium, respectively. Compounds IV were synthesized from cyanic acid and β-(substituted amino)propionitriles (III), the latter in turn were prepared from primary amines (I) and acrylonitrile (II).

Preparations of 1-substituted uracils (VII) from VI were carried out by known procedures.

It is well known that certain dihydropyrimidines, such as dihydroorotate, are important intermediates in the biosynthesis of pyrimidine nucleotides (2). This fact, together with the report that dihydrocytidylic acid was isolated from liver (3), has led Cohen and co-workers (4) to postulate that some dihydrocytosines might be precursors of cytidine derivatives.

At present the only reported method for the preparation of dihydrocytosines is the catalytic hydrogenation of cytosine and related compounds (4a, 5). In addition to limitations in application, this method has other drawbacks. When hydrogenation was carried out with a rhodium catalyst, for example, the cytosine compounds - unlike the uracils and thymines which absorbed only one mole of hydrogen to give quantitative formation of the 5,6-dihydro derivatives (6) - did not stop at the dihydro stage but hydrogenated further. Green and Cohen (4a) had attempted to terminate the reduction by filtration from the catalyst and isolation of the reaction product after the uptake of one equivalent of hydrogen, only to find that the reaction mixture was composed of the desired dihydrocytosine, material which had been reduced past the dihydro stage, and 4-13% of the original starting material. For further metabolic study of dihydropyrimidines, development of a new and unambiguous synthesis of dihydrocytosines, especially 1-substituted dihydrocytosines of which the position 1 is the important site for ribosidation and phosphorylation, is definitely in need.

In connection with our continued study in the field of nucleic acid chemistry it became necessary to examine the preparation of 1-substituted uracils and related compounds. One method, initiated by Fischer and Roeder (7) and modified by Johnson and Livak (8), Brown, Hoerger and Mason (9), and Binkley *et al.*, (10) involves the preparation of a substituted β-alanine, cyclization to a 1-substituted dihydrouracil, followed by bromination and dehydrobromination to yield the desired compound. This route is a preferred one because of its unambiguity. How-



ever, the isolation of 1-substituted dihydrouracils and related compounds frequently gave much difficulty and in most cases a high vacuum distillation of the dihydropyrimidine from the syrupy reaction mixture was necessary (11). This presented a practical problem since during the operation the distilled or sublimed dihydropyrimidine quickly condensed and solidified in the distilling head and condenser. Thus, occasional local heating at different parts of the distillation unit is required. Consequently, an improved synthesis of 1-substituted uracils as well as a new synthesis of 1-substituted dihydrocytosines has been developed in our laboratory.

Many compounds containing labile hydrogen atoms readily reacted with acrylonitrile to form derivatives with a cyanoethyl moiety (12). When acrylonitrile (II) was added to a primary amine (I) at low temperature and the resulting β-alkylaminopropionitrile (III) treated with potassium cyanate in mineral acid, an N-substituted N-β-cyanoethyl urea (13) (IV) was readily formed. Cyclization of IV in refluxing absolute ethanol in the presence of sodium ethoxide gave a 1-substituted 5,6-dihydrocytosine (14,15) (V) in good yield. Acid cyclization of IV, on the other hand, smoothly yielded the 1-substituted 5,6-dihydrouracil (VI). Compound VI could also be prepared by acid hydrolysis of V. Compounds of type VI prepared by these routes were readily isolated and purified. Preparation of the desired 1-substituted uracil (VII) from VI was carried out by known procedures (7, 8, 9, 10). Attempts to convert V into the corresponding 1-substituted cytosine are, as yet, unsuccessful. The lability of the amino group of the dihydrocytosine derivatives, as reported by Green and Cohen (4a), has also been demonstrated with 1-substituted dihydrocytosines.

EXPERIMENTAL (16)

β-Alkylaminopropionitriles (III).

These compounds were prepared by the addition of acrylonitrile to the appropriate primary amines (12,17). It was found that rapid addition of acrylonitrile at lower reaction temperature (-10°) gave better yields of III than higher reaction temperature (20-30°) and slower addition, as reported by other investigators (17).

β-Methylaminopropionitrile.

This compound was obtained in 93% yield (b.p. 67-68°/10 mm.) (17d,e).

β-*Iso*propylaminopropionitrile.

This compound was obtained in 72% yield, b.p. 80-83°/13.5 mm.
Anal. Calcd. for $C_6H_{12}N_2$: C, 64.3; H, 10.7; N, 25.0. Found: C, 64.0; H, 11.0; N, 24.7.

β-Benzylaminopropionitrile.

This compound was obtained in 58% yield, b.p. 167-169°/13.3 mm.
Anal. Calcd. for $C_{10}H_{12}N_2$: C, 75.0; H, 7.5; N, 17.5. Found: C, 75.2; H, 7.6; N, 17.1.

β-Butylaminopropionitrile and β-Cyclohexylaminopropionitrile.

β-Butylaminopropionitrile (b.p. 103°/12.5 mm., 98% yield) and β-cyclohexylaminopropionitrile (b.p. 131-134°/13 mm., 74% yield) were prepared by known procedures (17b,e).

N-Alkyl-N-(β-cyanoethyl)urea (IV).

A solution of 0.5 mole of III in 150 ml. of water and 50 ml. of concentrated hydrochloric acid was added dropwise to a solution of 56.7 g. (0.7 mole) of potassium cyanate in 100 ml. of water. The clear solution was stirred at room temperature for 12 hr. and then evaporated to dryness under reduced pressure. The resulting solid was extracted repeatedly with ethanol and the ethanol extract evaporated to dryness. All the products showed a strong -C≡N band at 2220 cm^{-1}.

N-Methyl-N-(β-cyanoethyl)urea.

This compound was obtained in 76% yield after recrystallization from propanol. White fine needles, m.p. 119-121°.
Anal. Calcd. for $C_5H_9N_3O$: C, 47.2; H, 7.1; N, 33.1. Found: C, 47.0; H, 7.3; N, 33.3.

N-*Iso*propyl-N-(β-cyanoethyl)urea.

This compound was obtained in 43% yield after recrystallization from ethyl acetate, m.p. 117-119°.
Anal. Calcd. for $C_7H_{13}N_3O$: C, 54.2; H, 8.4; N, 27.1. Found: C, 53.8; H, 8.6; N, 26.9.

N-Butyl-N-(β-cyanoethyl)urea.

This compound was obtained in 79% yield after recrystallization from butanol followed by a mixture of ethanol and *iso*propyl ether (1:6), m.p. 69-71°.
Anal. Calcd. for $C_8H_{15}N_3O$: C, 56.8; H, 8.9; N, 24.9. Found: C, 56.5; H, 9.0; N, 24.6.

N-Cyclohexyl-N-(β-cyanoethyl)urea.

This compound was obtained in 55% yield after recrystallization from benzene, m.p. 108-109°.
Anal. Calcd. for $C_{10}H_{17}N_3O$: C, 61.5; H, 8.7; N, 21.6. Found: C, 61.5; H, 8.8; N, 21.4.

N-Benzyl-N-(β-cycloethyl)urea.

This compound was obtained in 92% yield after recrystallization from ethyl acetate, m.p. 75-78°.
Anal. Calcd. for $C_{11}H_{13}N_3O$: C, 65.1; H, 6.4; N, 20.7. Found: C, 64.8; H, 6.6; N, 20.5.

N-Methyl-N-(β-cyanoethyl)thiourea.

This thio analog was similarly prepared by the procedure already described for the preparation of the urea derivative except that the potassium thiocyanate was used in place of potassium cyanate. The crude product was extracted with butanol and then, after evaporation of the extract to dryness, recrystallized from methanol to give a 43% yield of pure product as white platelets, m.p. 124-125°.
Anal. Calcd. for $C_5H_9N_3S$: C, 42.0; H, 6.3; N, 29.4. Found: C, 41.8; H, 5.9; N, 29.6.

1-Methyl-5,6-dihydrocytosine (V. R = CH_3).

A mixture of 6.3 g. (0.05 mole) of N-methyl-N-(β-cyanoethyl)urea and 1.0 g. of sodium methoxide was dissolved in 60 ml. of boiling absolute ethanol. The solution was refluxed, with stirring, for 30 min., at which time a precipitate had gradually formed. The reaction mixture was cooled and the solid was collected by filtration and washed with cold ethanol. It was recrystallized from ethanol to give 5.3 g. (84% yield) of analytically pure product. It melted at 223-225° with decomposition. U. V. λ max (pH 11), 245 mμ (ε, 7,600).
Anal. Calcd. for $C_5H_9N_3O$: C, 47.2; H, 7.1; N, 33.1. Found: C, 47.1; H, 7.3; N, 33.0.

1-Butyl-5,6-dihydrocytosine (V. R = CH_3-$(CH_2)_3$).

A mixture of 8.5 g. (0.05 mole) of N-butyl-N-(β-cyanoethyl)urea, 1 g. of sodium methoxide and 80 ml. of absolute ethanol was refluxed for 2 hr. The clear solution was evaporated to *ca.* 20 ml. under reduced pressure and the resulting solid was filtered and washed with cold ethanol. Recrystallization of the product from ethanol gave 7.1 g. (84% yield) of white needles, m.p. 188-189° dec. U. V. λ max (pH 11), 239 mμ (ε, 3,800).
Anal. Calcd. for $C_8H_{15}N_3O$: C, 56.8; H, 8.9; N, 24.9. Found: C, 57.0; H, 9.2; N, 24.8.

1-Substituted 5,6-Dihydrouracil (VI).

A mixture of 10 g. of N-substituted N-(β-cyanoethyl)urea (IV), 50 ml. of methanol, and 100 ml. of 10% hydrochloric acid was refluxed for 2 hr. The resulting solution was evaporated to dryness under reduced pressure and the crude product was purified as follows:

1-Methyl-5,6-dihydrouracil.

This compound was obtained in 55% yield as long needles after recrystallization from *iso*propyl alcohol, m.p. 173° (9,10a,18).
This compound was also obtained in quantitative yield by refluxing 1.5 g. of 1-methyl-5,6-dihydrocytosine (V. R = CH_3) for 2 hr. with 40 ml. of 10% hydrochloric acid.

1-*Iso*propyl-5,6-dihydrouracil.

This compound was obtained in 81% yield after recrystallization from benzene, m.p. 143-144° (10a).

1-Butyl-5,6-dihydrouracil.

This compound was obtained in 83% yield as large hexagonal plates after recrystallization from a mixture of methanol and ethyl acetate, m.p. 78-79°.

Anal. Calcd. for $C_8H_{14}N_2O_2$: C, 55.5; H, 8.3; N, 16.5. Found: C, 55.4; H, 8.3; N, 16.5.

1-Cyclohexyl-5,6-dihydrouracil.

This compound was obtained in 67% yield after recrystallization from a mixture of methanol and water, m.p. 180-182°.

Anal. Calcd. for $C_{10}H_{16}N_2O_2$: C, 61.2; H, 8.2; N, 14.3. Found: C, 61.0; H, 8.3; N, 14.3.

1-Benzyl-5,6-dihydrouracil.

This compound was obtained in 63% yield after recrystallization from benzene, m.p. 125-127° (10a).

1-Methyl-2-thio-5,6-dihydrouracil.

This compound was obtained in 78% yield after recrystallization from water, m.p. 162-163°.

Anal. Calcd. for $C_5H_8N_2OS$: C, 41.6; H, 5.6; N, 19.4. Found: C, 41.6; H, 5.3; N, 19.5.

1-Substituted 5-Bromo-5,6-dihydrouracil.

These compounds were prepared by the known procedure (9,10).

1-Butyl-5-bromo-5,6-dihydrouracil.

This compound was obtained as white fluffy needles in 68% yield after rapid recrystallization from absolute ethanol, m.p. 165-167°.

Anal. Calcd. for $C_8H_{13}BrN_2O_2$: C, 38.6; H, 5.2; N, 11.2. Found: C, 38.4; H, 5.4; N, 11.2.

1-Cyclohexyl-5-bromo-5,6-dihydrouracil.

This compound was obtained in 54% yield after rapid recrystallization from ethyl acetate, m.p. 167-169°.

Anal. Calcd. for $C_{10}H_{15}BrN_2O_2$: C, 43.6; H, 5.5; N, 10.2. Found: C, 43.6; H, 5.6; N, 10.3.

1-Substituted Uracils (VII).

1-Methyluracil.

1-Methyluracil, (9,10a,18,19) m.p. 230-231°. U. V. λ max (*p*H 1). 267 mμ (ε, 8,900); λ max (*p*H 11), 265 mμ (ε, 7,000).

1-Butyluracil.

This compound was obtained in 88% yield after recrystallization from water, m.p. 100.5-102.5°. U. V. λ max (*p*H 1), 267 mμ (ε, 10,700); λ max (*p*H 11), 265 mμ (ε, 7,600).

Anal. Calcd. for $C_8H_{12}N_2O_2$: C, 57.0; H, 7.2; N, 16.7. Found: C, 56.9; H, 7.4; N, 16.6.

1-Cyclohexyluracil.

This compound was obtained in 74% yield after recrystallization from ethyl acetate, m.p. 217-218°. U. V. λ max (*p*H 1), 268 mμ (ε, 10,500); λ max (*p*H 11), 266 mμ (ε, 7,200).

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.9; H, 7.2; N, 14.4. Found: C, 62.2; H, 7.5; N, 14.1.

1-Benzyluracil.

1-Benzyluracil, (10a,20) m.p. 173-174°. U. V. λ max (*p*H 1), 265 mμ (ε, 9,700); λ max (*p*H 11), 264 mμ (ε, 7,100).

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