Vinyl Compounds and Other Monomers Containing Heterocyclic Moieties of Nucleic Acids

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This review deals with recent developments in the preparation and polymerization of new monomeric compounds containing heterocyclic moieties of nucleic acids:
1. N-Vinyl and related compounds containing nucleic bases
2. Epoxy compounds containing nucleic bases
3. Amino acids containing nucleic bases

Es wird eine Übersicht gegeben über neuere Entwicklungen in der Herstellung und Polymerisation monomerer Verbindungen, die heterocyclische Komponenten von Nucleinsäuren enthalten:
1. N-Vinyl-Verbindungen und ähnliche Verbindungen, die Nucleinbasen enthalten
2. Epoxyverbindungen, die Nucleinbasen enthalten
3. Aminosäuren, die Nucleinbasen enthalten

The chemistry of polymerizable and polycondensable compounds containing heterocyclic moieties has recently received considerable attention, and numerous works have been devoted to the preparation and polymerization of these new monomeric species. These monomers and polymers, particularly those containing purines, pyrimidines, nucleosides, and nucleotides, are not only of interest to the field of N-heterocyclic chemistry, but also to that of biochemical investigations.

1. N-Vinyl and Related Compounds Containing Nucleic Bases

1.1. Vinyl Compounds with Purines

1.1.1. Preparation

The general preparative route to N-vinyl monomers is illustrated by the following scheme, where Z·N denotes a heterocyclic moiety:

\[
\begin{array}{c}
Z \cdot N \\
H \\
\rightarrow \\
CH_2\text{-}CH_2OH \\
\rightarrow \\
CH_2\text{-}CH_2Cl \\
\rightarrow \\
CH=CH_2
\end{array}
\]

Hydroxymethylation of purine bases can be carried out by treating the bases with ethylene carbonate in dimethylformamide solution in the presence of a trace of sodium hydroxide. The hydroxyethyl compounds thus obtained can be readily chlorinated by heating with thionyl chloride. Finally, the N-chloroethyl compounds are converted to the corresponding N-vinyl compounds by treatment with sodium methoxide in dioxane at room temperature.

The N-vinyl compounds of adenine, theophylline, 6-chloro-9-vinyl- and 2,6-dichloro-9-vinylpurine have been synthesized using this procedure.

9-Vinyladenine (3):

\[
\begin{array}{c}
\text{NH}_2 \\
\text{N} \\
\text{H} \\
\text{C} \equiv \text{C} \\
\text{H}_2\text{-CH}_2\text{OH} \\
\rightarrow \\
\text{NH}_2 \\
\text{N} \\
\text{H} \\
\text{C} \equiv \text{C} \\
\text{H}_2\text{-CH}_2\text{Cl} \\
\rightarrow \\
\text{NH}_2 \\
\text{N} \\
\text{H} \\
\text{C} \equiv \text{C} \\
\text{H}_2
\end{array}
\]

9-(2-Hydroxyethyl)-adenine (1): A solution of adenine (1.4 g, 0.01 mol) and ethylene carbonate (1.0 g, 0.01 mol) in dimethylformamide (40 ml) containing a trace of sodium hydroxide is boiled for 1 hr; after cooling, the solvent is removed completely under reduced pressure. The solid residue is recrystallized from ethanol; yield: 1.06 g (54%); m. p. 238–239°.

9-(2-Chloroethyl)-adenine (2): A mixture of 9-(2-hydroxyethyl)-adenine (1.04 g, 0.0025 mol) and thionyl chloride (10 ml) is heated on a water bath for 40 min. After removal of excess thionyl chloride under reduced pressure, the residue is dissolved in water (50 ml) and the solution is neutralized by adding a saturated sodium carbonate solution; the precipitate formed is filtered off, dried, and recrystallized from ethanol; yield: 0.79 g (75%); m. p. 204–205°, colorless needles.

Footnote:
9-Vinyladenine (3): To a solution of 9-(2-chloroethyl)-adenine (0.60 g, 0.003 mol) in dioxan (50 ml) is added a methanolic solution of sodium methoxide prepared from 4 ml of methanol and 0.4 g (0.018 g-atom) of sodium. The mixture is stirred at room temperature for 24 hr. and water is added until solution results. This solution is treated with Dowex 50 (H⁺) until neutral, and evaporated to dryness. Recrystallization of the residue from ethanol/benzene gives colorless plates; yield: 0.29 g (60.0% yield); m.p. 196-197°.

A vinyl compound containing the hypoxanthine moiety (5) was prepared by a somewhat modified procedure; the chloroethylhypoxanthine 4 is obtained from the corresponding adenine derivative (2) and is converted into 9-vinylhypoxanthine (5) by treatment with sodium methoxide in dioxan.

In the synthesis of 9-vinyladenine, an improved procedure not requiring chromatographic purification was used, wherein the 6-amino group was first protected by a benzoyl group (compound 6), which renders the adenine moiety more soluble in vinyl acetate. The N-benzoyl derivative 6 was subjected to the reaction with vinyl acetate in the presence of mercury(II)-acetate. Treatment of the 6-benzoyl-9-vinyladenine (7; m.p. 168-170°) thus obtained (65%) with methanolic ammonia afforded 9-vinyladenine.

6-Chloro-9-vinylpurine: A solution of conc. sulfuric acid (0.1 ml) in ethyl acetate (2 ml) is added to a suspension of mercuric acetate (0.5 g) in vinyl acetate (100 ml) in a pressure flask. A clear and colorless solution is formed. This procedure avoids the discoloration of vinyl acetate resulting from the direct addition of acid. Then, powdered 6-chloropurine (2 g) is added followed by another 50 ml of vinyl acetate. After flushing with nitrogen for 10 min., the flask is cooled and left in a bath at 45-50° with occasional agitation for 5 days. Dry sodium acetate is then added, the mixture stirred for 10 min., and filtered. The filtrate is evaporated in vacuo and the residue dissolved in chloroform. This solution is extracted with cold 1 N sodium hydroxide; occasional centrifugation of the mixture is necessary to facilitate the removal of the aqueous layer. The chloroform is then dried with magnesium sulfate and evaporated. The residue is purified by recrystallization and sublimation in vacuo; yield: 1.6 g (70%); m.p. 166-167°.

The N-(2-methacryloyloxethyl) derivatives of theophylline and 2-chloro-6-methylpurine are synthesized by an alternate scheme:

An alternative method of obtaining the N-vinyl derivatives directly from the corresponding heterocyclic parent compounds involves a vinyl-exchange reaction of the unsubstituted heterocyclic systems with vinyl acetate, catalyzed by mercury(II)acetate and sulfuric acid. This procedure has been used to prepare 9-vinylpurine and 2,6-dichloro-9-vinylpurine.

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2. N. Ueda, K. Kondo, M. Kono, K. Takemoto, M. Imoto, Makromol. Chem. 120, 13 (1968).


unsuitability for other bases because of the low yields obtained with it, has therefore been adopted for the synthesis of the adenine compound:

\[
\begin{align*}
\text{N} & \quad \text{NaH} \\
\text{CH}_2\text{-CH}_2\text{OH} & \quad \rightarrow \\
\text{N} & \quad \left[\begin{array}{c}
\text{N} \\
\text{CH}_2\text{-CH}_2\text{ONa}
\end{array}\right] \\
\text{CH}_3 & \quad \rightarrow \\
\text{N} & \quad \text{CH}_2\text{-CH}_2\text{O-CH}_2\text{-CH}_2
\end{align*}
\]

The following compounds have been prepared by this method:

51% yield (step 2) m.p. 150–152°

50% yield (step 2) m.p. 90°

30% yield (step 2) m.p. 201–203°

2-Chloro-6-methyl-9-(2-methacryloyloxyethyl)-purine\(^7\): 2-Chloro-6-methyl-9-(2-hydroxyethyl)-purine (1 mmol) is dissolved in dimethylformamide (10 ml). The solution is cooled to −50° and methacryloyl chloride (1 mmol) is added with stirring. The mixture is stirred at room temperature for 2 hr and the solvent distilled off under reduced pressure. The product is isolated by column chromatography [silica gel containing 3% of water, elution with benzene/ethanol (8/1)]; yield: 50%; m.p. 90°, colorless needles.

9-(2-Methacryloyloxyethyl)-adenine\(^8\): A mixture of sodium hydride (50 wt. 2%, 0.1 g), 9-(2-hydroxyethyl)-adenine (0.36 g, 2 mmol), and dimethylformamide (30 ml) is stirred at room temperature until the evolution of hydrogen ceases. The mixture is then cooled in an ice bath to 3–4°, and methacryloyl chloride (2 mmol) is added dropwise and with stirring. After the mixture has been stirred for 2 hr, the solvent is removed under reduced pressure. Recrystallization of the residue from water gives colorless needles; yield: 30%; m.p. 201–203°.

1.2. Vinyl Derivatives of Pyrimidines

1.2.1. Preparation

A convenient synthetic route to 4-vinylpyrimidine (9) and 2-dimethylamino-4-vinylpyrimidine consists of conversion of the corresponding methylpyrimidine into the 4-(2-hydroxyethyl) derivative (8) followed by dehydration using solid potassium hydroxide:

[Chemical equation]

4-(2-Hydroxyethyl)-pyrimidine (8): A sealed tube containing 4-methylpyrimidine (10 g, 0.106 mol) and paraformaldehyde (3.9 g, 0.1 mol) is heated at 165° for 3.5 hr. The contents of the tube are then transferred using ether for rinsing to a 10 ml distillation

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flask. The solvent is removed, and the residue distilled to give 6 g (60%) 4-methylpyrimidine (b. p. 140–141/760 mm) and 4.0 g 8 (87% based on recovered 4-methylpyrimidine; b. p. 132–139/10 mm). The 4-(2-hydroxyethyl)-pyrimidine (8) is purified by distillation; yield: 3.5 g (76%); b. p. 125–127/9 mm. The product is a viscous liquid with a rancid odor.

4-Vinylpyrimidine (9): The apparatus used for the dehydration consists of a cylindrical stainless-steel vessel fitted with a dropping funnel attached to a copper tube leading to the bottom of the cylinder and an outlet tube attached to a condenser and a receiver. The receiver is cooled with Dry-ice/methanol and connected to a water pump so that the whole system can be evacuated. The reactor is one-half filled with potassium hydroxide pellets (~250 g), evacuated to 10 mm, and heated at 160°C. Then, 4-(2-hydroxyethyl)-pyrimidine (10 g, 0.085 mol) containing p-t-butylecatacol (3.5,7,3-tetrahydroxy-4-butyloxylavlan, 0.1 g) is added dropwise over a period of 3 min. The mixture of water and 4-vinylpyrimidine which distils is collected in the receiver and extracted with ether (3 × 15 ml). The combined extracts are dried over sodium sulfate for 24 hr. The drying agent and solvent are removed, and the product is distilled under reduced pressure to give a colorless product; yield: 2 g (23%); b. p. 56–58/10 mm.

For the synthesis of 1-vinyluracil (15, R = H), a procedure similar to that used in the preparation of N-vinyl compounds containing purine bases can be applied: 1-(2-hydroxyethyl)-uracil (10) is first prepared by treating uracil with ethylene carbonate and separating the product from the accompanying disubstituted derivative by chromatography. Compound 10 is then chlorinated; dehydrochlorination of the 1-(2-chloroethyl) derivative thus obtained affords 1-vinyluracil4. In order to avoid the chromatographic separation of the product mixture at the first stage of the reaction, an alternative method, affording only 1-(2-hydroxyethyl)-uracil and starting from 2,4-dithoxyopyrimidine (11)2, was proposed:

\[
\begin{align*}
\text{Cl} & \rightarrow \text{HN} - \text{N} - \text{H} \\
& \rightarrow \text{HN} \downarrow \text{N} \uparrow \text{OH} \\
& \rightarrow \text{HOCH}_2\text{CH}_2\text{OH} \\
& \rightarrow \text{OC}_2\text{H}_5
\end{align*}
\]

The compound 12, formed as an intermediate, can be isolated from the by-products by fractional recrystallization and converted into 1-(2-hydroxyethyl)-uracil by treatment with dilute hydrochloric acid.

Synthesis of 1-(2-Hydroxyethyl)-uracil (10) from Uracil (89.6 g) and its monosodium salt (2 g) is dissolved in dry, hot dimethylformamide (1300 mL). To the boiling, stirred solution, ethylene carbonate (72 g) in dimethylformamide (150 ml) is added dropwise. After boiling for 1 hr, the solution is evaporated in vacuo at 60°C. Ethanol is added to the residue and the mixture is repeatedly evaporated in vacuo to remove remaining dimethylformamide. The residue is dissolved in hot water (700 mL); addition of Dowex 50 W (10 form) brings the solution to pH = 5. The solution is filtered, the solvent removed in vacuo and the residue extracted with boiling ethanol (100 mL); most of the uracil remains undissolved. The extract is filtered; evaporation of the filtrate gives colorless crystals of 10, 1,3-bis[2-hydroxyethyl]-uracil, and a small quantity of uracil. By extracting this mixture with ethyl acetate in a Soxhlet apparatus, a crystalline mixture of 10 and the bis-hydroxyethyl compound is obtained. This mixture is separated by column chromatography on cellulose (1:50 weight ratio of substance to cellulose); 1-(2-hydroxyethyl)-uracil (10), m. p. 138°; 1,3-bis[2-hydroxyethyl]-uracil, m. p. 154°.

Synthesis of 1-(2-Hydroxyethyl)-uracil (10) from 2,4-Dithoxyopyrimidine: A mixture of 2,4-diethoxyopyrimidine (11) and 2-bromoethanol (2 equivalents) is heated at 50–60°C for 4–5 days. Unreacted 2-bromoethanol and 2,4-dithoxyopyrimidine are removed at reduced pressure, and the residual solution is diluted with benzene to 4–5 times its original volume. The resultant clear solution is cooled to 5°C, and a seed crystal of 2-oxo-4-ethoxy-1-(2-hydroxyethyl)-dihydrooxypyrrolidine (12), purified by column chromatography (silica gel containing 3% water, eluant: 5%; methanol in benzene) added. The solution is allowed to stand; the crystals formed are separated by filtration. Recrystallization of the product from benzene gives two oxo-4-ethoxy-1-(2-hydroxyethyl)-dihydrooxypyrrolidine (12) as colorless needles; yield: 20%; m. p. 82–83°. Compound 12 is converted into 1-(2-hydroxyethyl)-uracil (10) by heating with dilute hydrochloric acid. The product obtained is recrystallized from ethanol; colorless needles, m. p. 136.5–137.5°.

Still another method may be used to prepare 1-vinyluracil (15, R = H); in this procedure5, 2,4-bis[5-trimethylsilyl-oxy]-pyrimidine (13, bis-[O-trimethylsilyl]-uracil) is heated with 1,2-dichloroethane for two days at 110°C to yield 1-(2-hydroxyethyl)-uracil (14), which is dehydrohalogenated with an excess of potassium t-butoxide in tetrahydrofuran at 25°C to give 1-vinyluracil:

A third method of synthesis of L-vinuracil (15, R = H) involves the cyclization of N-vinyl-N’-(3-ethoxyacryloyl)urea (16) in aqueous ethanolic sodium hydroxide. Compound 16 is obtained by the reaction of β-ethoxyacrylamide with vinyl isocyanate. However, this approach is not convenient because of the greater number of steps involved and the need for chromatographic purification in the final stage.

The synthesis of L-vinylthymine (15, R = CH₃) is more readily accomplished than that of L-vinuracil. Hydroxyethylation of thymine as well as cytosine gives no by-products, and no chromatographic separation is necessary.

1-(2-Hydroxyethyl)-thymine: A solution of thymine (1 g, 8 mmol), ethylene carbonate (0.7 g, 8 mmol), and a trace of sodium hydroxide in dimethylformamide (20 ml) is allowed to reflux for 6 hr. The solvent is removed under reduced pressure; ethanol is added to the residue, and the solution is cooled to separate unreacted thymine, which is filtered off. The filtrate is then evaporated to dryness, and recrystallized from ethanol; yield: 36%; m.p. 179–181 °C.

1-(2-Chloroethyl)-thymine: To a solution of 1-(2-hydroxyethyl)-thymine (1.0 g, 5.9 mmol) and a few drops of pyridine in dioxane (30 ml) is added a solution of thionyl chloride (2.0 g, 17 mmol) in dioxane (40 ml). The reaction mixture is refluxed for 35 min., and the solvent is then evaporated to dryness under reduced pressure. Recrystallization of the residue from ethanol gives colorless plates; yield: 94%; m.p. 203–205 °C (sealed tube).

1-Vinylthymine: A solution of sodium methoxide (0.25 g, 4.6 mmol) in methanol (3 ml) is added to a solution of 1-(2-chloroethyl)-thymine (0.46 g, 2.4 mmol) in dioxane (30 ml). The reaction mixture is stirred for 7 hr at room temperature, and water is added until a clear solution is obtained. This solution is treated with Dowex 50 (H⁺) until it becomes neutral and then evaporated to dryness in vacuo. The residue is recrystallized from water; yield: 47%; colorless needles, m.p. 205–207 °C (sublimes).

The N-(2-methacryloyloxyethyl) compounds of uracil and thymine are prepared in a manner similar to that for compounds containing purine bases: the corresponding N-(2-hydroxyethyl) compounds are treated with methacryloyl chloride.

Vinyl polymer containing uracil and thymine moieties as side groups can be used for a selective separation of nucleic bases from their mixtures.

1.2.2. Polymerization

Homopolymerization of 2-vinylpyrimidine and 2-dimethylamino-4-vinylpyrimidine, copolymerization with other each other, and of both monomers with 4,6-diamino-2-vinyl-1,3,5-triazine, can be achieved using radical catalysts such as azobisisobutyronitrile in toluene solution. The polymerization and copolymerization of N-vinyl and N-(2-methacryloyloxyethyl) derivatives of other pyrimidine bases, i.e., uracil and thymine, can be carried out in a similar manner to that used for purine bases.

Copolymerization of Vinylpyrimidines: A solution of 4-vinylpyrimidine (0.494 g, 4.4 mmol) and 2-dimethylamino-4-vinylpyrimidine (0.663 g, 4.6 mmol) in dry toluene (5 ml) is prepared, and azobisisobutyronitrile (0.0075 g) is added. The solution is transferred to a polymerization tube, degassed, sealed, and polymerized at 60 °C for 20 hr. No polymer is observed to precipitate from the solution during the reaction. The viscous content of the tube is poured out, and the copolymer precipitated using anhydrous ether. The copolymer is dissolved in benzene (8 ml) and reprecipitated with anhydrous ether. Two more precipitations and final freeze-drying from benzene affords a pure product; yield: 0.85 g (74% conversion).
In a similar manner, 4-vinylpyrimidine may be copolymerized in dimethylformamide solution with 4,6-diamino-2-vinyl-1,3,5-triazine.

1.3. Vinyl Compounds with Nucleosides

1.3.1. Preparation

Recently, acryloyl compounds containing nucleoside groups such as 5'-O-acryloyluridine (17, R = H) and 3'-O-acryloyluridine (17, R = CH₃), as well as 2',3'-isopropylidene-5'-O-pentadienoyluridine, were synthesized. No general method for the production of acryloyl esters of nucleosides has been described, but the reaction using acryloyl anhydride and pyridine was found to be the most effective procedure in the cases of uridine and thymidine. Treatment of thymidine with one equivalent of acryloyl anhydride gives 5'-O-acryloylthymidine as the main product; two by-products, presumably 3'-O-acryloylthymidine and 3',5'-O-diacyloylthymidine, are also formed. Isopropylideneuridine reacts with acryloyl anhydride and pyridine to give the corresponding 5'-O-acryloyl derivative, which upon treatment with dilute acid gives 5'-O-acryloyluridine.  

1.3.2. Polymerization

Acryloyl compounds containing nucleoside groups have been homopolymerized, and copolymerized with acrylamide, in aqueous solutions using persulfate initiator; the polymers are soluble in water. Poly-[5'-O-pentadienoyluridine] produces a hypochromic effect of 5% with denaturated deoxyribonucleic acid in salt solution.  

Copolymerization of 5'-O-Acryloyluridine with Acrylamide: To a solution of 2'-O-acryloyluridine (20 mg, 0.067 mmol) and acrylamide (47.7 mg, 0.67 mmol) in 1.0 M acetic buffer (10 ml), pH: 5.2, is added a freshly prepared solution of ammonium persulfate (1%; 0.4 ml, 0.017 mmol). The solution is maintained at 60°C for 6 hr. It is exhaustively dialysed against distilled water and freeze-dried to isolate the polymer (60 mg). The product is analyzed for uridine by measuring the UV absorption.

Copolymerization of 5'-O-pentadienoyluridine with Acrylamide: To a solution of 4'-O-acryloyl-5'-pentadienoyluridine (160 mg, 0.44 mmol) in ethanol (10 ml) are added 0.01 M acetic buffer (pH 5.2, 40 ml), ammonium persulfate (1%; aqueous solution; 2 ml), and acrylamide (166 mg, 2.2 mmol), and the solution is heated at 80°C for 15 hr. The resultant suspension is dialysed against water and freeze-dried. The isopropylidene groups are removed by heating in 5% acetic acid at 90°C for 2 hr, after which time the solid has completely dissolved. The product is purified by dialysis and freeze-dried to give a water-soluble polymer (110 mg). The copolymer contains 7 uridine residues per 100 of total residues.

2. Epoxy Compounds Containing Nucleic Bases

The reaction of adenine with epichlorohydrin in acetic acid gives 9-(3-chloro-2-hydroxypropyl)-adenine (18), from which 9-(2,3-epoxypropyl)-adenine (19) can readily be prepared by treatment with aqueous alkali hydroxide:

9-(2,3-Epoxypropyl)-adenine (19)\(^1\)

To a dispersion of 9-(3-chloro-2-hydropropyl)-adenine (1 mmol) in water (5 ml) is added potassium hydroxide (1.5 mmol). After the mixture has been stirred for 2 hr at room temperature, the solid is separated by filtration and washed thoroughly with water (80\%). The compound 19 thus prepared is a colorless powder which is hygroscopic and difficultly soluble in common organic solvents; m.p. 205° (dec.).

The 9-(2,3-epoxypropyl)-adenine can be polymerized using boron trifluoride etherate as a catalyst; the reaction is carried out in dichloromethane at room temperature (24 hr) and affords a 60% yield. The polymer is hygroscopic, soluble in ethanol, and insoluble in ether.

3. Amino Acids Containing Nucleic Bases

The synthesis of \(\alpha\)-amino acids containing purine and pyrimidine side chains was investigated recently with the aim of preparing analogues of polynucleotides in which phosphodiester linkages are replaced by peptide linkages.

As an example, D,L-D-amino acid (20, R = CH\(_3\), and 21, respectively) and D,L-β-(6-aminopurin-9-yl)-alanine (23) were prepared by treating the corresponding pyrimidines and adenine with bromoacetalddehyde diethyl acetal (2-bromo-1,1-diesthoxymethylene), followed by hydrolysis to give the aldehydes, and conversion of these by the Streeker synthesis into D,L-alanine derivatives\(^{19}\).

\[\text{HO} \quad \text{N} \quad \text{CH}_2\text{-CH} \quad \text{COOH} \quad \text{NH}_2\]

\[\text{HO} \quad \text{N} \quad \text{CH}_2\text{-CH} \quad \text{COOH} \quad \text{NH}_2\]

N-(2,3-Diethoxymethyl) Derivatives of Uracil, 4-N-Acetylcysteine, and Adenine\(^{15}\); Uracil, 4-N-acetylcysteine, or adenine is suspended in dry dimethylformamide (25 ml/g of base; 100 ml/g of base in the case of the acetylcysteine); dry potassium carbonate (1 equivalent) and bromoacetalddehyde diethyl acetal (1 equivalent) are added, and the mixture heated with stirring at 130° for 14 hr. The solution is then concentrated to dryness in vacuo. The uracil derivative is extracted with chloroform from the aqueous solution and is obtained as a crystalline solid in 60% yield by crystallization with ether. The 4-N-acetylcysteine derivative is also extracted with chloroform and deacetylated overnight by treatment with methanolic ammonia at room temperature to give 1-(2,2-diethoxymethyl)-cysteine; yield: 52%; m.p. 232–234°. The adenine derivative is crystallized from ethanol to give 2-(2,2-diethoxymethyl)-adenine; yield: 47%; m.p. 212°.

Hydrolysis of 1-(2,2-Diethoxymethyl)-uracil to 2-(2,4-Dioxo-1,2,3,4-tetrahydropryrimidin-1-yl)-acetalddehyde (24)\(^{20}\); A mixture of 1-(2,2-diethoxymethyl)-uracil (18.0 g), ammonium chloride (35 g), and water (150 ml) is heated on a steam bath for 3.5 hr. The resultant clear light yellow solution is cooled in ice and affords 9.3 g of the crystalline monohydrate of aldehyde 24, m.p. 206.5–206.5°. Use of the hydrolysis liquors as solvent for the above reaction gives an increased yield; 18.3 g of the acetal affords 10.5 g of the monohydrate; m.p. 213.5–214.5°. Repetition of this procedure using 14.0 g of the acetal affords 11.5 g of the acetal monohydrate; m.p. 213–214°; total yield of aldehyde monohydrate: 31.3 g (83%) from 50.3 g of the acetal.

Conversion of 1-(2,4-Dioxo-1,2,3,4-tetrahydropryrimidin-1-yl)-acetalddehyde (24) into \(\beta\)-(2,4-Dioxo-1,2,3,4-tetrahydropryrimidin-1-yl)-L-amino acid (20, R = H; Willardine)\(^{11}\); A solution of the aldehyde 24 (2.03 g) in water (7 ml) with aqueous ammonia (1.8 ml, d: 0.88), potassium cyanide (0.935 g), and ammonium chloride (0.79 g), is heated at 55–60° for 5 hr. The solution is mixed with 10 N hydrochloric acid (25 ml) and allowed to reflux for 1 hr (caution: HCN). It is then allowed to stand overnight. The solution is concentrated, mixed with 10 N hydrochloric acid (15 ml), and boiled under reflux for 3 hr. It is then evaporated to dryness in vacuo, the residue treated with water, and the mixture again evaporated in vacuo. The residue is dissolved in a small volume of water to give an acidic solution which is adjusted to pH 4 with aqueous ammonia and allowed to stand. A crystalline precipitate of D,L-willardine (1.58 g) soon appears. The amino acid is also obtained, as colorless needles, when the solution of the residue in aqueous ammonia is treated with charcoal, filtered, and adjusted to pH 4 with hydrochloric acid; m.p. 205–209° (dec.).

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