Steric Fixation of Bromovinyluracil: Synthesis of Furo[2,3-*d*]pyrimidine Nucleosides

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A new synthetic procedure for the preparation of 5,6-dihydrofuro[2,3-*d*]pyrimidin-2(3*H*)-one (**3**) and its deoxyriboside **8** is reported. Compound **3** undergoes nucleophilic reactions with various agents to yield 5-substituted uracil derivatives. The dehydro derivative of **3**, furo[2,3-*d*]pyrimidin-2(3*H*)-one (**18**) was synthesized by cyclization of BVU **15**, which made us develop a reproducible and high yield method for the synthesis of BV(D)U. Starting from **18**, the α-deoxyriboside **20** and the β-riboside **22** were prepared.

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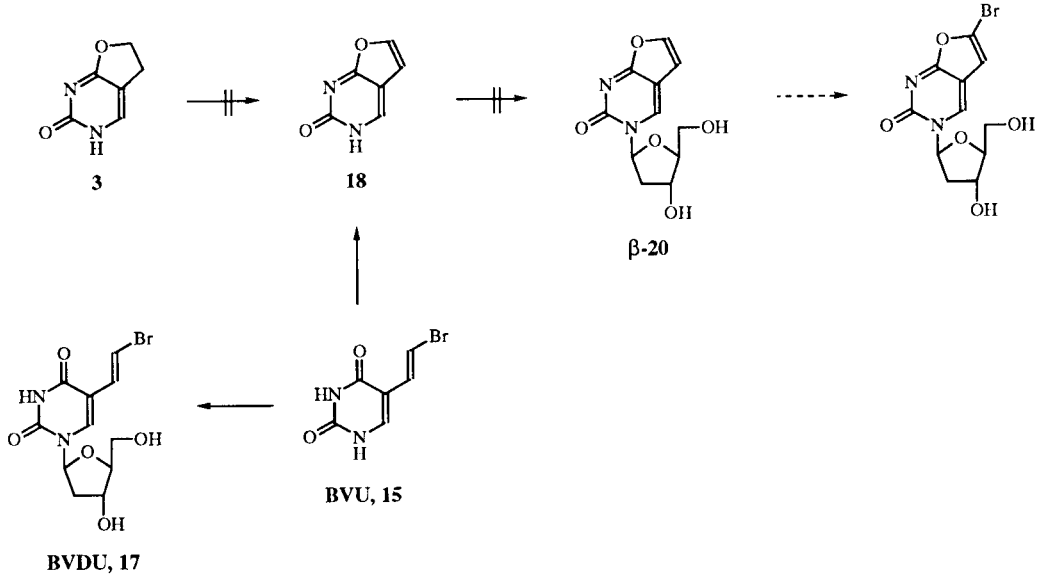
Introduction.

E-Bromovinyldeoxyuridine (BVDU, **17**) is known to be one of the most active pyrimidine nucleosides against herpes simplex virus type 1 (HSV-1) [1]. In our investigations concerning structure-activity relationships of **17** [2] we were interested in the synthesis of a sterically rigid derivative of BVDU (Scheme 1), which should be accessible by bromination of β-**20**. We planned to prepare β-**20** by deoxyribosidation of furo[2,3-*d*]pyrimidin-2(3*H*)-one (**18**).

Scheme 1



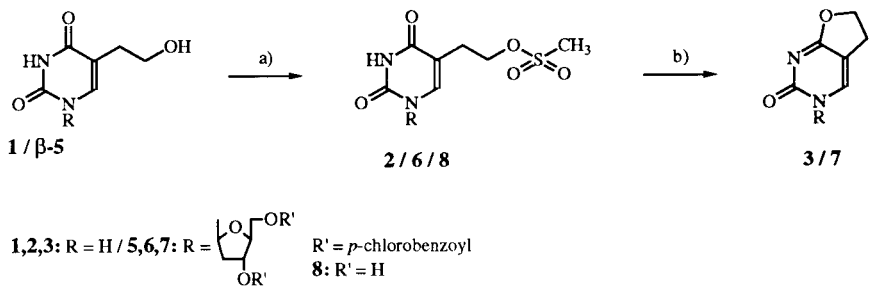
The aglycone, **18**, was synthesized by Bleackley *et al.* in 1976 [3], but the yield of this sequence was not satisfactory for our purposes. We planned to prepare **18** by the dehydration of 5,6-dihydrofuro[2,3-*d*]pyrimidin-2(3*H*)-one (**3**, Scheme 1, R = H), which is accessible by literature methods in moderate yields [4,5]. We were not able to dehydrate **3**, instead we discovered that **3** can easily be attacked by nucleophilic agents, which gives an access to 5-substituted uracil derivatives. Finally we obtained **18** by cyclization of bromovinyldeoxyuracil (BVU, **15**). The subsequent deoxyribosidation yielded selectively only α-**20** (Scheme 7), which showed no activity against HSV-1 in the biological screening. The same was true for the β-riboside **22** (Scheme 7). Unfortunately all efforts to obtain β-**20** from **18** failed.

Synthesis of 5,6-Dihydrofuro[2,3-*d*]pyrimidin-2(3*H*)-one (**3**) and its Desoxyriboside **5**.

Fissekis *et al.* [4,5] prepared **3** in 4 steps, starting from valerolactone. A big handicap of this sequence was the poor overall yield, which made us search for another approach. We reacted 5-(2-hydroxyethyl)uracil [4,5] (**1**) with methanesulphonyl chloride to **2** (Scheme 2), which was subsequently cyclized to **3** with the aid of diazabicycloundecane (DBU).

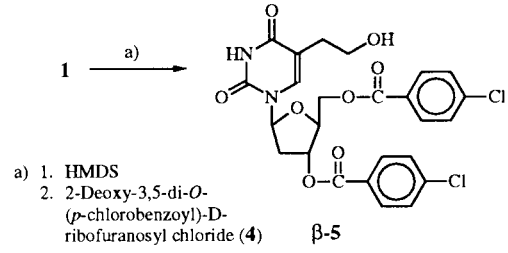
Griengl *et al.* [6] and Hassan [7] prepared the deoxyriboside of **1** by activating **1** with hexamethylenedisilazane (HMDS). We used a variation of their procedure

Scheme 2



in order to obtain the deoxyriboside of **3**. Instead of using *p*-toluoyl-protected deoxyribofuranosyl chloride we found it more advantageous to use 2-deoxy-3,5-di-*O*-(*p*-chlorobenzoyl)-D-ribofuranosyl chloride (**4**, Scheme 3), which—in contrast to the oily *p*-toluoyl derivative—is crystalline and easy to handle [2].

Scheme 3



The reaction of silylated pyrimidines with α-halogeno sugars yields a mixture of the α- and β-nucleosides, which usually are separated by column chromatography. We found that α-**5** could be extracted by stirring the mixture of products in ether at room temperature for two hours. As the remaining β-**5** can then be filtered off as practically pure crystals the yield of the reaction is greatly increased.

Analytical differentiation between α- and β-configurated nucleosides is possible by means of nmr spectroscopy, comparing the chemical shifts and coupling constants of the sugar protons. In α-isomers H-1' appears as a doublet, whereas in β-compounds the same atom shows resonance as a triplet [8]. The width of the multiplet of H-2' in α-isomers [9] usually is much larger (>1 ppm) than in β-nucleosides (<0.7 ppm). In addition the chemical shift of H-4' is a good indicator for the configuration of nucleosides [10]; H-4' in α appears downfield with respect to β-nucleosides. With these findings in mind, the isolated nucleoside can readily be identified as β-**5**.

The protected deoxyriboside **7** (Scheme 2) was obtained *via* the same reaction sequence as given above for the aglycone **3**. Reacting β-**5** with methanesulphonyl chloride yields crystalline **6**, which is transformed to the protected dihydrofuropyrimidine nucleoside **7** by refluxing **6** with DBU. Deprotection of **7** with sodium ethoxide led to a partial decomposition of the reaction mixture. Less aggressive but equally effective was a saturated methanolic solution of ammonia, which yielded **8** (R' = H).

Nucleophilic Attacks on **3**:

As our aim was to prepare furo[2,3-*d*]pyrimidin-2(3*H*)-one (**18**) by dehydrogenation of **3**, we tried out various dehydrating methods given in the literature. 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) was used for the dehydrogenation of dihydrofurans by Piozzi *et al.* [11]. The application of this reagent led to the decomposition of **3**, maybe due to the poor solubility of **3** in organic solvents. When we performed the reaction in hot glacial acetic acid, we isolated the acetate **9** (Scheme 4), which was formed by a nucleophilic attack of the acid. Nickel peroxide [12] as an oxidizing agent led to the formation of **1**. In 1984 Palomo *et al.* reported on a new dehydrogenating agent, formed by the reaction of DMF and thionyl chloride [13]. Again, **3** was not dehydrogenized, but the product isolated proved to be **10**, which is known since 1986 from the works of Streicher, Werner, and Rosenwirth [14]. Eger dehydrogenized tetrahydroindolopyrimidines by heating the compounds with ethanolic nitric acid [15]. Applying this agent we again were not able to isolate **18**; instead we obtained **11**.

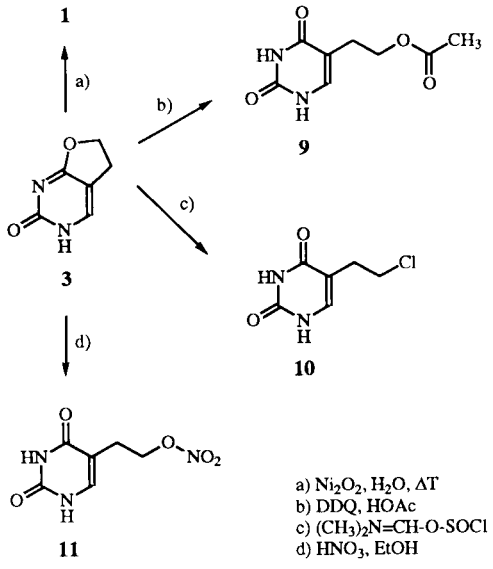
The facility of nucleophilic attacks upon the dihydrofuropyrimidine system allows the preparation of different 5-substituted uracil derivatives.

Preparation of **18** by Cyclization of BVU (**15**).

Since we were not able to obtain **18** *via* dehydrogenation of **3** we searched for another approach. We attempted the cyclization of BVU (**15**), which in fact was successful.

BVDU (**17**) was developed independently in Belgium [16,17] and in the German Democratic Republic [18] in 1979. Since then, several sequences for the preparation of

Scheme 4



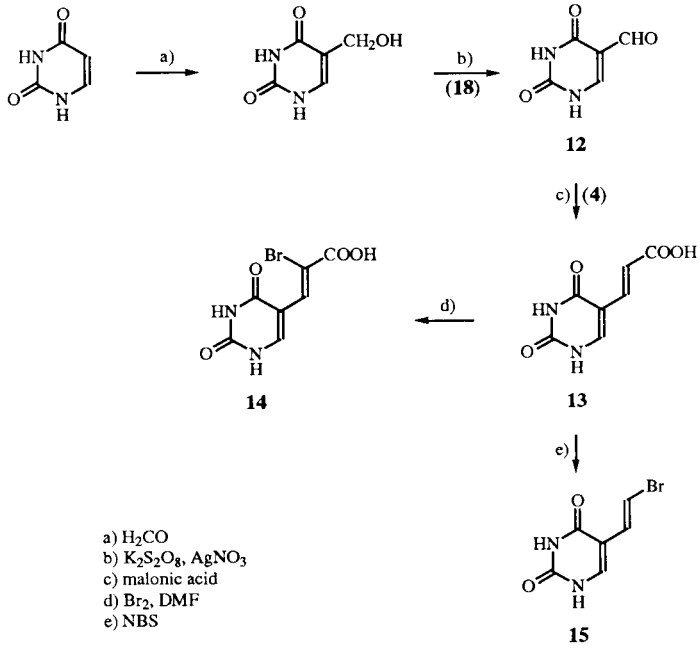
BVU/BVDU have been proposed, all of them turned out to have poor yields or not to be reproducible in our laboratory.

One promising reaction sequence started from uracil, which was converted to hydroxymethyluracil and subsequently oxidized to 5-formyluracil (**12**) with potassium peroxodisulphate [19]. We also prepared **12** by the oxidation of **1** with the same oxidizing agent (Scheme 5). As described by Fissekis and Sweet [4] **12** was reacted with malonic acid in a Knoevenagel condensation reaction to yield 5-(2-carboxyvinyl)uracil (**13**).

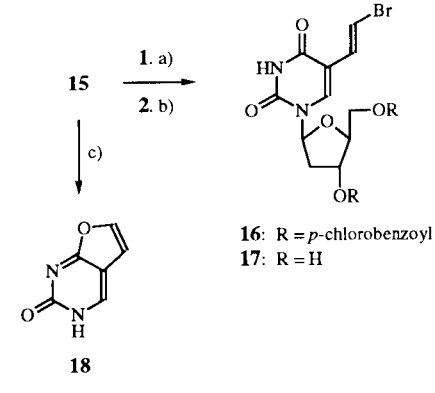
The most hazardous step in the synthesis of BVU is introducing a bromine atom while retaining the vinyl functionality and exchange of the carboxyl group. Thus, by reacting **13** with bromine in DMF [20] we did not obtain BVU, but 5-(2-bromo-2-carboxyvinyl)uracil (**14**). In analogy to De Clercq *et al.* [21] we finally exchanged the carboxyl group with bromine using NBS as a donor of bromine, thus obtaining BVU (**15**) in good yields.

In order to prepare BVDU (**17**), **15** was silylated and reacted with the protected α-halogeno sugar **4** to the *p*-chlorobenzoyl protected nucleoside **16** (Scheme 6, R = *p*-chlorobenzoyl). As we already found in case of **5** the separation of the anomers α-**16** and β-**16** can be accomplished by stirring the products in ether at room temperature. Again, the α-isomer was in solution whereas β-**16** was selectively filtered off; the structural idendity was confirmed by nmr spectroscopy. The deprotection of β-**16** to **17** (Scheme 6, R = H) was achieved with 0.1 *M* sodium methoxide at room temperature.

Scheme 5



Scheme 6



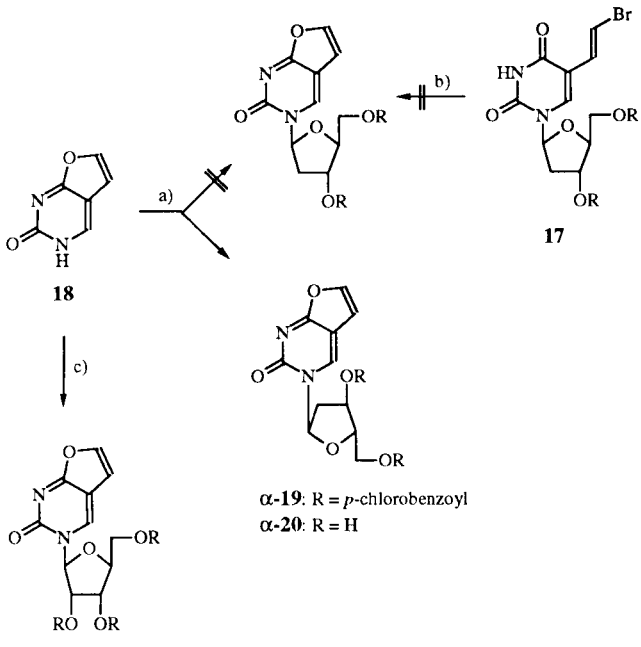
The cyclization of **15** to the furanopyrimidinone **18** was possible using potassium *tert*-butylate as a base, whereas less bulkier bases led to decomposition of the reaction mixture.

Preparation of Glycosides from **18**.

As usual **18** was silylated with HMDS and reacted with the protected sugar **4**. After 30 minutes, a clouding of the clear solution was observed. About 50% of the starting compound precipitated from the mixture, whereas the other 50% reacted to the protected α-nucleoside **19** (Scheme 7). This result was reproducible even on varia-

tion of catalysts, protecting groups or solvents. The classical method for the preparation of nucleosides, the reaction of the pyrimidine bases with sodium hydride in DMSO with subsequent treatment with protected 1-halogeno sugars, also yielded no trace of β-**19**. Natural and artificial nucleosides with biological activity mostly are β-nucleosides. Thus it was no surprise to us that **20**, which was won from **19** by deprotection with methanolic ammonia, had no effect against HSV-1. As an alternative route to obtain β-**20**, we tried to cyclize BVDU with potassium *tert*-butylate, unfortunately without success (Scheme 7).

Scheme 7



21: R = acetyl
22: R = H

a) 1. HMDS,
2. 2-deoxy-3,5-di-*O*-(*p*-chlorobenzoyl)ribose (**4**)
b) K-*tert*-butylate
c) Tetraacetylribose, $SnCl_4$

Eger *et al.* [22] used a modification of the Hilbert-Johnson procedure for the preparation of nucleosides [23] in order to force glycosides of barbituric acid into the β-configuration. Tetraacetylribose forms a complex with tin tetrachloride, which allows the nucleophilic attack of the pyrimidine base only from the upper side of the sugar, thus forming a β-nucleoside. We used this procedure to prepare a β-riboside of **18**. We obtained the reaction product **21** (Scheme 7) in 48% yield only. Deprotection of **21** with methanolic ammonia yielded **22**, which also showed no antiviral activity against HSV-1. Several attempts to introduce a bromine atom in the position 2 of the furan moiety, to obtain a steric fixed BVDU-analog were unsuccessful.

EXPERIMENTAL

Biological Methods.

The compounds were added to mice embryo cell cultures in concentrations of 0.5, 5, 50, and 500 μg/ml and incubated for 3 days. Subsequently the cell plaques were controlled macro- and microscopically. Growth inhibition or disruption of noninfected cells indicated cytotoxicity. As a parameter for antiviral effects the reduction or inhibition of cell destruction of HSV-1 infected plaque assays was used. *E*-BVDU was used as a reference.

Apparatus.

Melting points were determined on a Büchi 510 melting point apparatus, and are uncorrected. The ir spectra (potassium bromide) were recorded on a Perkin Elmer 1750 FTIR spectrometer. The ^1H and ^{13}C-nmr spectra were measured on a Bruker AC80 spectrometer using tetramethylsilane as an internal standard. For the resonance signals the following abbreviations are used: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; m, multiplet; br, broad. In all cases the solvent was DMSO-d_6. The structural assignment derived from the spectra was confirmed by comparison to literature data. The mass spectrum of **18** was obtained on a Finnigen MAT 711A spectrometer (modified by AMD Intectra GmbH) using a direct inlet system. It was recorded by the Abteilung Massenspektroskopie, Organisch-Chemisches Institut der Universität Tübingen. Elemental analysis was performed by the Abteilung Elementaranalyse, Anorganisch-Chemisches Institut der Universität Tübingen.

Analysis (tlc) was performed on silica gel F_{254} (Merck) alumina plates. For column chromatography separations silica gel 0.05-0.2 mm (Merck) was used.

Solvents for the reaction of silylated pyrimidines with protected sugars were carefully purified. Acetonitrile was refluxed with phosphorus-(V) oxide for 5 hours, distilled and stored on potassium carbonate. Prior to usage it was again refluxed with phosphorus-(V) oxide and fractionated on a 20 cm Vigreux column. 1,2-Dichloroethane and dichloromethane were refluxed with phosphorus-(V) oxide (20 g/l) for two hours, distilled and stored over molecular sieves (4Å). Dimethylformamide was refluxed with calcium hydride for 8 hours and then fractionated *in vacuo*. Pyridine was refluxed with solid potassium hydroxide (100 g/l) and then fractionated on a 20 cm Vigreux column at normal pressure (114-115°).

5-(2-Carboxyvinyl)uracil [4], 5-formyluracil [19] and its precursor 5-(2-hydroxyethyl)uracil [4,5] were prepared from uracil by literature procedures. Commercially available chemicals were purchased from E. Merck, Fluka, and Aldrich Chemie, Germany.

5-(2-Methylsulfonyloxyethyl)uracil (**2**).

A solution of 0.31 g (2 mmoles) of 5-(2-hydroxyethyl)uracil (**1**) in 20 ml of absolute pyridine was cooled to 0°. After adding 0.45 g (4 mmoles) of methanesulphonyl chloride the mixture was stirred at 0° for 5 hours, 0.2 ml of water was added and the mixture was again stirred for 30 minutes at 0°, poured on crushed ice and the precipitate was collected by suction and

washed neutral with ice water, yield 0.44 g (95%), mp 195-200°; ir: ν 1320, 1174 (SO_2), 1715, 1645 (lactam) cm^{-1}; ^{1}H-nmr (δ [ppm]): 2.60 (t, 2H, CH_2-CH_2O), 3.14 (s, 3H, CH_3), 4.26 (t, 2H, CH_2-CH_2-O), 7.30 (d, 1H, *H*-6, J = 5.7 Hz), 10.7 (d, br, 1H, N*H*-1), 11.1 (s, 1H, N*H*-3).

Anal. Calcd. for $C_7H_{10}N_2O_5S$ (234.08): C, 35.91; H, 4.27; N, 11.96; S, 13.69. Found: C, 35.82; H, 4.25; N, 11.95; S, 13.71.

5,6-Dihydrofuro[2,3-*d*]pyrimidin-2(3*H*)-one (**3**) [4,5].

To a suspension of 0.234 g (1 mmole) of **2** in 30 ml of absolute THF, 0.153 g (1 mmole) of DBU was added and the mixture was refluxed. The termination of the reaction was indicated by the formation of a white precipitate, which was collected by filtration and washed until neutral with cold water. Recrystallization from methanol gave a yield of 0.11 g (85%), mp 270-305° dec; ir: ν 1230, 1020 (ether) cm^{-1}; ^{1}H-nmr: (δ [ppm]): 2.97 (t, 2H, CH_2-CH_2, J = 8.1 Hz), 4.58 (t, 2H, CH_2-CH_2-O, J = 8.1 Hz), 7.43 (s, 1H, C=C*H*-N), 10.36 (s, br, 1H, N*H*).

Anal. Calcd. for $C_6H_6N_2O_2$ (138.04): C, 52.20; H, 4.34; N, 20.28. Found: C, 52.14; H, 4.32; N, 20.35.

2-Deoxy-3,5-di-*O*-(*p*-chlorobenzoyl)-D-ribofuranosyl Chloride (**4**).

To a solution of 8.4 g (62 mmoles) of deoxy-D-ribose in 160 ml of absolute methanol 8.4 ml of 1% methanolic hydrogen chloride was added and the mixture was stirred at room temperature. After 45 minutes the solution was neutralized with 42 ml of absolute pyridine and the solvent was removed *in vacuo*. In order to purify the oily product from traces of methanol, 20 ml of dry pyridine was added to the residue and the solvent was again evaporated. The oily sugar was dissolved in 50 ml of absolute pyridine. Under cooling and exclusion of moisture 20 ml of *p*-chlorobenzoyl chloride was added. The internal temperature must not exceed 30°. The reaction mixture was stirred at room temperature over night. The precipitate was filtered off, dissolved in 20 ml of dichloromethane and the excess *p*-chlorobenzoyl chloride was hydrolized with 125 ml of water. The aqueous layer was reextracted with 60 ml of dichloromethane. The combined organic fractions were washed twice with each 120 ml of a cold, saturated solution of sodium bicarbonate, water, cold 3*N* sulfuric acid, and again with water. After drying with sodium sulfate the solvent was removed *in vacuo*.

The oily residue was dissolved in 30 ml of absolute toluene and evaporated *in vacuo* in order to remove traces of water as an azeotrope. The product was then dissolved in 36 ml of toluene and stored at 0° for one hour. The precipitate was filtered off and washed with toluene. The combined filtrates were concentrated to a syrup and then dissolved in 48 ml of glacial acetic acid. The product precipitated from the solution after addition of 90 ml of a cold saturated solution of dry hydrogen chloride in absolute acetic acid with cooling in an ice bath. The precipitation was completed after 20 minutes. The product was filtered off and washed with absolute ether until the filtrate was neutral; **4** was dried over potassium hydroxide *in vacuo* (>1 mbar), yield 20.2 g (76%), mp 125-126°; ^{1}H-nmr: (δ [ppm]) 2.75-2.87 (m, 2H, *H*-2,2'), 4.65 (m, 2H, *H*-5,5'), 4.85 (m, 1H, *H*-4), 5.53 (m, 1H, *H*-3), 6.40 (dd, 1H, *H*-1), 7.25-8.10 (2x m, 2x 4H, 2x *p*-chlorobenzoyl).

Anal. Calcd. for $C_{19}H_{15}O_5Cl_3$ (429.6): C, 53.11; H, 3.49; Cl, 24.78. Found: C, 53.21; H, 3.51; C1, 25.02.

5-(2-Hydroxyethyl)-1-[2'-deoxy-3',5'-di-*O*-(*p*-chlorobenzoyl)-β-D-ribofuranosyl]uracil (**5**) [6,7].

A suspension of 1.2 g (7.7 mmoles) of 5-(2-hydroxyethyl)-uracil in a mixture of 20 ml of HMDS and 0.2 ml of chlorotrimethylsilane was heated to 140°. After 8 hours a clear, colorless solution resulted. The excess of HMDS was removed by distillation *in vacuo* (20 mbar, 60°). The residue was dissolved in 30 ml of absolute 1,2-dichloroethane, and a solution of 3.2 g (7.5 mmoles) of **4** in 40 ml of absolute 1,2-dichloroethane was added. The mixture was stirred for 20 hours at room temperature, then the solvent was evaporated, and the residue was dissolved in 50 ml of chloroform. The organic solution was extracted 3x with 20 ml of a cold, saturated solution of sodium bicarbonate, then 3x with 20 ml of water. In order to increase the yield, the combined aqueous layers were reextracted with 4x 30 ml of chloroform. The organic layer was dried over sodium sulfate, filtered off, and the solvent was evaporated. The resulting amorphous foam was suspended in ether. After stirring for 2 hours at room temperature the α-isomer was dissolved in ether, whereas the β-isomer was filtered off and washed with ether. The yield was 1.7 g (90%), mp 125-126°; ^{1}H-nmr: (δ [ppm]) 2.33 (t, 2H, CH_2-CH_2O, J = 6.4 Hz), 2.56 (m, 2H, *H*-2',2"), 3.43 (t, 2H, CH_2OH, J = 6.4 Hz), 4.47-4.60 (m, 3H, *H*-4',5',5"), 5.6 (m, 1H, *H*-3'), 6.3 (t, 1H, *H*-1', J = 7.1 Hz), 7.51-8.08 (m, 9H, *H*-6, 2x *p*-chlorophenyl), 11.32 (s, br, 1H, N*H*-3).

Anal. Calcd. for $C_{25}H_{22}Cl_2N_2O_8$ (549.36): C, 54.66; H, 4.04; Cl, 12.91; N, 5.10. Found: C, 54.38; H, 3.98; Cl, 13.13; N, 5.07.

5-(2-Methanesulfonyloxyethyl)-1-[2'-deoxy-3',5'-di-*O*-(*p*-chlorobenzoyl)-β-D-ribofuranosyl]uracil (**6**).

A solution of 1.09 g (2 mmoles) of β-**5** in 12 ml of absolute pyridine was cooled to 0° in an ice bath. After addition of 0.2 ml of methanesulphonyl chloride the mixture was stirred at 0° overnight. The reaction was terminated by the addition of 0.2 ml of water and stirring for 30 minutes, 50 ml of ice water was added and the solution was extracted 4x with 30 ml of chloroform. The combined organic layers were washed with 70 ml each of cold, 2*N* sulfuric acid and a solution of 2% sodium bicarbonate, respectively, dried, filtered off, and evaporated *in vacuo*; **6** was obtained as white crystals, yield 1.2 g (96%), mp 75-78°; ^{1}H-nmr: (δ [ppm]) 2.51-2.89 (m, 4H, CH_2-CH_2O, *H*-2',2"), 3.13 (s, 3H, CH_3), 4.20-4.25 (m, 2H, CH_2O), 4.50-4.60 (m, 3H, *H*-4', *H*-5',5"), 5.63 (m, 1H, *H*-3'), 6.31 (t, 1H, *H*-1', J = 6.1 Hz), 7.39-8.08 (m, 9H, *H*-6, 2x *p*-chlorophenyl), 11.50 (s, br, 1H, N*H*-3).

Anal. Calcd. for $C_{26}H_{24}Cl_2N_2O_{10}S$: C, 49.79; H, 3.82; Cl, 11.30; N, 4.46; S, 5.11. Found: C, 49.60; H, 3.79; Cl, 11.45; N, 4.42; S, 5.19.

3-(2'-Deoxy-3',5'-di-*O*-(*p*-chlorobenzoyl)-β-D-ribofuranosyl)-5,6-dihydrofuro[2,3-*d*]pyrimidin-2(3*H*)-one (**7**).

To a solution of 0.62 g (1 mmole) of **6** in 20 ml of absolute THF 0.15 g (1 mmole), DBU was added. The mixture was refluxed for 1 hour. The resulting precipitate was collected by filtration and washed with cold acetone. Due to the poor solubility of **7** the nmr spectrum was measured at 100°, yield 0.43 g (87%), mp 270-274°; ^{1}H-nmr: (δ [ppm]) 2.60 (m, 2H, *H*-2',2"), 2.95-3.08 (m, 2H, CH_2-CH_2O), 4.51-4.71 (m, 5H, CH_2-O, *H*-4', *H*-5',5"), 5.60 (m, 1H, *H*-3'), 6.20 (t, 1H, *H*-1', J = 6.6 Hz), 7.45-8.04 (m, 9H, C=C*H*-N, 2x *p*-chlorophenyl).

3-(2'-Deoxy-β-D-ribofuranosyl)-5,6-dihydrofuro[2,3-*d*]pyrimidin-2(3*H*)-one (**8**).

After suspending 0.5 g (1 mmole) of **7** in 200 ml of absolute methanol with cooling in an ice bath the mixture was saturated with gaseous ammonia within 5 minutes and then stirred at room temperature. The course of the reaction was followed by tlc (chloroform + ethanol = 4 + 1 and 1 + 4). The reaction was terminated after 6 hours; the solvent was removed *in vacuo* and the residue was suspended in ether. The product was filtered off and purified by column chromatography (chloroform + methanol = 94 + 6), yield 0.18 g (73%), mp 195-200°; ir: ν 3379 (OH), 1685-1651 (lactam), 1230, 1020 (COC) cm^{-1}; ^{1}H-nmr: (δ [ppm]) 1.93-2.20 (m, 2H, *H*-2',2"), 3.01 (t, 2H, CH_2-CH_2O, J = 7.9 Hz), 3.60 (m, 2H, *H*-5',5"), 3.82 (m, 1H, *H*-4'), 4.21 (m, 1H, *H*-3'), 4.64 (t, 2H, CH_2O, J = 7.9 Hz), 5.00 (t, 1H, O*H*-5', J = 4.8 Hz), 5.20, (d, 1H, O*H*-2', J = 4.3 Hz), 6.14 (t, 1H, *H*-1', J = 6.6 Hz), 8.09 (s, 1H, C=C*H*-N).

Anal. Calcd. for $C_{11}H_{14}N_2O_5$ (245.06): C, 51.99; H, 5.51; N, 11.02. Found: C, 52.12; H, 5.50; N, 11.12.

5-(2-Acetoxyethyl)uracil (**9**).

Glacial acetic acid (100 ml) was heated to 100° and 0.14 g (1 mmole) of **3** was dissolved therein. After adding 0.45 g of DDQ the mixture was refluxed for 36 hours. The solvent was removed by evaporation and the product was purified by column chromatography (methylene chloride + methanol + cold saturated ethanolic ammonia = 15 + 4 + 1), yield 0.12 g (63%), mp 210°; ir: ν 1738 (acetyl-CO), 1707, 1670 (lactam), 1235 (C-O-C) cm^{-1}; ^{1}H-nmr: (δ [ppm]) 1.97 (s, 3H, CO-CH_3), 2.47 (t, 2H, CH_2-CH_2O, J = 6.7 Hz), 4.06 (t, 2H, CH_2-CH_2-O, J = 6.7 Hz), 7.29 (s, 1H, *H*-6), 10.68 (d, br, 1H, N*H*-1), 11.02 (s, br, 1H, N*H*-3).

Anal. Calcd. for $C_8H_{10}N_2O_4$ (198.04): C, 48.49; H, 5.09; N, 14.14. Found: C, 48.62; H, 5.21; N, 14.07.

5-(2-Chloroethyl)uracil (**10**) [14].

To 5 ml of absolute benzene 1 ml of absolute DMF and 0.8 ml of thionyl chloride was added. The solution was left at room temperature for 5 minutes, then it was cooled to 0°, and a suspension of 0.14 g (1 mmole) of **3** in 20 ml of absolute dichloromethane was added. The reaction was terminated within 30 minutes at room temperature. After pouring on crushed ice the precipitate was collected by suction, and washed until neutral with ice water, yield 0.12 g (70%), mp 265-270°; ^{1}H-nmr: (d [ppm]) 2.62 (t, 2H, CH_2-CH_2Cl, J = 7.0 Hz), 3.68 (t, 2H, CH_2-Cl, J = 7.0 Hz), 7.39 (d, 1H, *H*-6, J = 5.6 Hz), 10.72 (d, br, 1H, N*H*-1), 11.08 (s, br, 1H, N*H*-3).

Anal. Calcd. for $C_6H_7ClN_2O_2$ (174.53): C, 41.27; H, 4.04; Cl, 20.30; N, 16.04. Found: C, 41.54; H, 4.07; Cl, 20.17; N, 16.04.

5-(2-Nitryloxyethano)uracil (**11**).

A solution of 0.1 g (0.71 mmole) of **3** in a mixture of 0.2 g of nitric acid (65%) and 25 ml of ethanol was refluxed at 85° for 14 hours. The solvent was removed *in vacuo*. By treating the residue with water precipitation was induced, which was completed at 4°. The precipitate was collected by suction and washed until neutral with ice water, yield 0.1 g (70%), mp 188-193°; ir: ν 1731-1670 (lactam), 1282 (NO_2) cm^{-1}; ^{1}H-nmr: (δ [ppm]) 2.62 (t, 2H, CH_2-CH_2O, J = 6.1 Hz), 4.60 (t, 2H, CH_2-ONO_2, J = 6.1 Hz), 7.3 (d, 1H, *H*-6, J = 5.6 Hz), 10.78 (d, br, 1H, N*H*-1), 11.11 (s, br, N*H*-3).

Anal. Calcd. for $C_6H_7N_3O_5$ (201.01): C, 35.83; H, 3.51; N, 20.89. Found: C, 35.97; H, 3.52; N, 20.69.

5-Formyluracil (**12**) [19].

In 100 ml of water 3.1 g (20 mmoles) of hydroxyethyluracil, 0.1 g of silver nitrate and 10.8 g of potassium peroxodisulphate were dissolved, and stirred at 30-40°. After 3 hours the precipitate was collected by filtration and washed until neutral with ice water, yield 1.42 g (51%), mp >290° dec; ir: ν 1724 (CHO), 1706-1670 (lactam) cm^{-1}; ^{1}H-nmr: (δ [ppm]) 8.13 (s, 1H, *H*-6), 9.74 (s, 1H, C*H*O), 11.74, 11.83 (2x s, 2x 1H, N*H*-1, N*H*-3).

Anal. Calcd. for $C_5H_4N_2O_3$ (140.0): C, 42.86; H, 2.88; N, 20.00. Found: C, 42.96; H, 2.83; N, 20.20.

5-(2-Carboxy-2-bromovinyl)uracil (**14**).

To a solution of 0.6 g (3.3 mmoles) of 5-(2-carboxyvinyl)-uracil (**13**) [4] in 50 ml of absolute DMF, 0.52 g of bromine, dissolved in 10 ml of absolute DMF was added dropwise. The mixture was refluxed for 1 hour. After evaporation of the solvent the residue was suspended in water, the product was collected by filtration and washed with ice water. Recrystallization from water yielded 0.51 g (59%) of **14**, mp 275-280°; ir: ν 1710-1681 (lactam and COOH) cm^{-1}; ^{1}H-nmr: (δ [ppm]) 7.22 (s, 1H, C*H*=CBr), 7.90 (d, 1H, *H*-6, J = 5.7 Hz), 11.28 (br, 3H, N*H*-1, N*H*-3, COO*H*).

Anal. Calcd. for $C_7H_5BrN_2O_4$ (260.94): C, 32.21; H, 1.91; Br, 30.62; N, 10.73. Found: C, 32.25; H, 1.87; Br, 31.01; N, 10.69.

5-(2-Bromovinyl)uracil (**15**) [21].

A solution of 0.75 g (4.2 mmoles) of NBS in 15 ml of acetone was diluted with 15 ml of water and added within 90 minutes *via* a dropping funnel to a solution of 0.72 g (4 mmoles) of 5-(2-carboxyvinyl)uracil (**13**) [4] and 0.4 g of potassium acetate in 40 ml of boiling water. The reaction mixture was concentrated to half its volume *in vacuo* and cooled to 4° overnight. The resulting precipitate was collected by filtration and washed free from bromide ions with ice water, yield 0.7 g (81%), mp 218°; ir: ν 1714, 1657 (lactam) cm^{-1}; ^{1}H-nmr: (δ [ppm]) 6.82 (d, 1H, C*H*=CHBr, J = 13.5 Hz), 7.25 (d, 1H, CH=C*H*Br, J = 13.5 Hz), 7.65 (s, 1H, *H*-6), 11.18 (2H, N*H*-1, N*H*-3).

Anal. Calcd. for $C_6H_5BrN_2O_2$ (217.02): C, 33.20; H, 2.32; Br, 36.82; N, 12.90. Found: C, 33.07; H, 2.29; Br, 36.48; N, 12.72.

E-5-(2-Bromovinyl)-1-[2'-deoxy-3',5'-di-*O*-(*p*-chlorobenzoyl)-uridine (α-**16**, β-**16**).

In a solution of 15 ml of HMDS and 0.1 ml of chlorotrimethylsilane 1.8 g (8.3 mmoles) of **15** were refluxed for three hours. From the resulting clear solution the excess of HMDS was removed by distillation *in vacuo* (20 mbar, 60°). The residue was dissolved in 50 ml of absolute 1,2-dichloroethane, then a solution of 3.4 g (8 mmoles) of **4**, dissolved in 50 ml of absolute 1,2-dichloroethane was added. The mixture was stirred at room temperature under an argon atmosphere for 10 hours. The solvent was evaporated, the residue was suspended in ether and stirred at room temperature for 2 hours. The α-isomer was thus dissolved in ether whereas the precipitate consisted of the β-anomer, which was collected by filtration and washed with ether.

The α-anomer was purified by column chromatography (chloroform + methanol = 5 + 1) after evaporation of the solvent, yield 90% in total, 2.2 g (47% relative yield) of β-**16**, 2.1 g (43% relative yield) of α-**17**.

The analytical data for β-**16** is: mp 222-225°; ir: ν 1726 (CO), 1708-1684 (lactam) cm^{-1}; ^{1}H-nmr: (δ [ppm]) 2.66 (m, 2H, *H*-2',2"), 4.56 (m, 3H, *H*-4',5',5"), 5.65 (m, 1H, *H*-3'), 6.31 (t, 1H, *H*-1', J = 6.8 Hz), 6.76 (d, 1H, CH=CHBr, J = 13.5 Hz), 7.34 (d, 1H, =C*H*Br, J = 13.5 Hz), 7.51-8.03 (m, 9H, *H*-6, 2x *p*-chlorophenyl), 11.64 (s, br, 1H, N*H*-3).

The analytical data for α-**16** is: mp 170°; ir: ν 1726 (CO), 1705-1685 (lactam) cm^{-1}; ^{1}H-nmr: (δ [ppm]) 2.87 (m, 2H, *H*-2',2"), 4.46 (d, 2H, *H*-5',5", J = 5.0 Hz), 5.26 (t, 1H, *H*-4', J = 5.0 Hz), 5.61 (d, 1H, *H*-3', J = 4.9 Hz), 6.28 (d, 1H, *H*-1', J = 5.3 Hz), 6.80 (d, 1H, C*H*=CHBr, J = 13.5 Hz), 7.35 (d, 1H, CH=C*H*Br, J = 13.5 Hz), 7.42-8.09 (m, 9H, *H*-6, 2x *p*-chlorophenyl), 11.56 (s, br, 1H, N*H*-3).

E-5-(2-Bromovinyl)-2'-deoxyuridine (**17**).

A suspension of 0.6 g (1 mmol) of β-**16** in 15 ml of 0.1 *M* sodium methylate was stirred at room temperature for 6 hours. Within 10 minutes a clear, colorless solution was obtained. The solution was neutralized with strongly acidic ion exchange resin (Amberlyst® 15). The resin was filtered off and washed with methanol. The combined organic solutions were evaporated and the residue was suspended in ether. The product was collected by filtration and washed with ether, yield 0.3 g (93%), mp 158°; ir: ν 3500-3431 (OH), 1695, 1676 (lactam) cm^{-1}; ^{1}H-nmr: (δ [ppm]) 2.14 (t, 2H, *H*-2',2", J = 5.1 Hz), 3.60 (m, 2H, *H*-5,5"), 3.81 (m, 1H, *H*-4'), 4.20 (t, 1H, *H*-3', J = 4.6 Hz), 5.20 (br, 2H, 2x O*H*), 6.13 (t, 1H, *H*-1', J = 6.5 Hz), 6.80 (d, 1H, C*H*=CHBr, J = 13.5 Hz), 7.20 (d, 1H, CH=C*H*Br, J = 13.5 Hz), 8.07 (s, 1H, *H*-6), 11.39 (s, br, 1H, N*H*-3).

Anal. Calcd. for $C_{11}H_{13}BrN_2O_5$ (332.97): C, 39.67; H, 3.90; Br, 23.99; N, 8.40. Found: C, 39.47; H, 3.81; Br, 23.91; N, 8.41.

Furo[2,3-*d*]pyrimidin-2(3*H*)-one (**18**) [3].

To a solution of 0.5 g (2.3 mmoles) of **15** in 100 ml of absolute DMF 3.4 g (30 mmoles) of potassium *tert*-butylate (Aldrich Chemie, Germany; always store under reduced pressure) was added and the mixture was stirred at 50-55° under an argon atmosphere for 3 hours. The solids were filtered off, and the filtrate was neutralized with ethanolic hydrogen chloride. The solvent was removed *in vacuo*. The residue was suspended with water, filtered off, and washed with ice water, yield 0.28 g (89%), mp 260-262°; ms: (70 eV) m/z = 136 (M^+); ir: ν 1680 (lactam), 1640 (conjugated double bond) cm^{-1}; ^{1}H-nmr: (δ [ppm]) 6.72 (d, 1H, -C*H*=CH-O, J = 2.7 Hz), 7.67 (d, 1H, CH=C*H*-O, J = 2.7 Hz), 8.33 (s, 1H, C=C*H*-N), 12.16 (s, br, 1H, N*H*).

Anal. Calcd. for $C_6H_4N_2O_2$ (136.11): C, 52.94; H, 2.96; N, 20.58. Found: C, 52.89; H, 2.89; N, 20.47.

3-(2'-Deoxy-3',5'-di-*O*-(*p*-chlorobenzoyl)-α-D-ribofuranosyl)-furo[2,3-*d*]pyrimidin-2(3*H*)-one (**19**).

A mixture of 15 ml of HMDS and 0.1 ml of chlorotrimethylsilane 0.54 g (4 mmoles) of **18** was refluxed for 45 minutes at 140°. The excess HMDS was removed from the resulting clear, colorless solution by distillation *in vacuo*. The solid residue was dissolved in 50 ml of absolute 1,2-dichloroethane, and 1.6 g (3.8 mmoles) of **4** in 50 ml of absolute 1,2-dichloroethane was added. After 30 minutes precipitation was observed. The reaction was terminated after 6 hours. The precipitated starting compound **18** was removed by filtration and the filtrate was evaporated to dryness. The residue was suspended in ether, the product collected by filtration and washed with ether, yield 0.92 g (44%), mp 230°; ir: ν 3118 (phenyl), 1727, 1670 (lactam, CO), 1640 (conjugated double bond) cm^{-1}; ^{1}H-nmr: (δ [ppm]) 2.90 (m, 2H, *H*-2',2"), 4.58 (m, 2H, *H*-5',5"), 5.29 (t, 1H, *H*-4', J = 5.0 Hz), 5.60 (d, 1H, *H*-3', J = 5.0 Hz), 6.24 (d, 1H, *H*-1', J = 6.2 Hz), 6.75 (d, 1H, C*H*=CH-O, J = 2.7 Hz), 7.34-8.11 (m, 9H, CH=C*H*-O, 2x *p*-chlorophenyl), 8.33 (s, 1H, C=C*H*-N), 11.56 (s, 1H, N*H*).

Anal. Calcd. for $C_{25}H_{18}Cl_2N_2O_7$ (529.16): C, 56.73; H, 3.40; Cl, 13.41; N, 5.29. Found: C, 56.43; H, 3.38; Cl, 13.22; N, 5.35.

3-(2'-Deoxy-α-D-ribofuranosyl)furo[2,3-*d*]pyrimidin-2(3*H*)-one (**20**).

A solution of 0.52 g (1 mmole) of **19** in 200 ml of methanol was saturated with gaseous ammonia under cooling in an ice bath for 5 minutes and then it was stirred at room temperature for 2 hours. The solvent was removed *in vacuo* and the residue was suspended in ether. The product was collected by filtration and washed with ether. Recrystallization with methanol yielded 0.2 g (80%) of **20**, mp 150-155°; ir: ν 3414 (OH), 1666 (lactam), 1639 (conjugated double bond) cm^{-1}; ^{1}H-nmr: (δ [ppm]) 2.10 (m, 2H, *H*-2',2"), 3.40 (m, 2H, *H*-5',5"), 4.25 (d, 1H, *H*-4', J = 5.2 Hz), 4.50 (t, 1H, *H*-3', J = 5.0 Hz), 5.10 (br, 2H, 2x O*H*), 6.10 (d, 1H, *H*-1', J = 5.3 Hz), 6.80 (d, 1H, C*H*=CH-O, J = 2.7 Hz), 7.70 (d, 1H, CH=C*H*-O, J = 2.7 Hz), 8.66 (s, 1H, C=C*H*-N).

Anal. Calcd. for $C_{11}H_{12}N_2O_5$ (252.06): C, 52.41; H, 4.76; N, 11.10. Found: C, 52.62; H, 4.71; N, 11.13.

3-(2',3',5'-Tri-*O*-acetyl-β-D-ribofuranosyl)furo[2,3-*d*]pyrimidin-2(3*H*)-one (**21**).

In a mixture of 15 ml of HMDS and 0.1 ml of chlorotrimethylsilane 0.28 g (2 mmoles) of **20** was refluxed at 140°. After 45 minutes a clear, colorless solution resulted. The excess of HMDS was removed by distillation *in vacuo* and the residue was dissolved in 100 ml of absolute acetonitrile. To this solution 0.58 g (1.8 mmoles) of tetraacetylribose and 0.5 ml (4 mmoles) of stannic chloride were added. The mixture was stirred at room temperature for 24 hours. The solvent was removed *in vacuo* and the residue was dissolved in 50 ml of chloroform. The organic solution was carefully extracted with 100 ml of a cold, saturated solution of sodium bicarbonate (*p*H must not exceed 7!). The aqueous layer formed an emulsion which was reextracted 3x with chloroform. The combined organic layers were dried on sodium sulfate, the drying agent was filtered off and the solvent was evaporated, yield 0.37 g (48%), amorphous foam, mp 95-100°; ir: ν 1751-1681 (CO, lactam) cm^{-1}; ^{1}H-nmr: (δ [ppm]) 2.07 (s, 9H, 3x $COCH_3$), 4.35 (m, 2H, *H*-5',5"), 5.30-5.60 (m, 3H, *H*-2',3',4'), 6.05 (d, 1H, *H*-1', J = 3.0 Hz), 6.87 (d, 1H, C*H*=CH-O, J = 2.7 Hz), 7.76 (d, 1H, CH=C*H*-O, J = 2.7 Hz), 8.66 (s, 1H, C=C*H*-N).

Anal. Calcd. for $C_{17}H_{18}N_2O_9$ (394.08): C, 51.80; H, 4.56; N; 7.10. Found: C, 51.61; H, 4.52; N, 7.13.

3-5-β-D-Ribofuranosylfuro[2,3-*d*]pyrimidin-2(3*H*)-one (**22**).

A solution of 0.39 g (1 mmole) of **21** in 200 ml of absolute methanol was saturated with gaseous ammonia for 5 minutes with cooling in an ice bath. After stirring at room temperature for 90 minutes the solvent was evaporated, and the residue was suspended in ether. The product was collected by filtration and recrystallized from dilute methanol (methanol + water = 5 + 1), yield 0.21 g (78%), mp 65-75°; ir: ν 1681-1617 (lactam) cm^{-1}; ^{1}H-nmr: (δ [ppm]) 3.25-4.00 (m, 4H, *H*-3',4',5',5"), 4.64 (d, 1H, *H*-2', J = 4.3 Hz), 4.99-5.53 (br, 3H, 3x O*H*), 5.90 (d, 1H, *H*-1',

J = 4.4 Hz), 6.80 (d, 1H, C*H*=CH-O, J = 2.7 Hz), 7.75 (d, 1H, CH=C*H*-O, J = 2.7 Hz), 9.00 (s, 1H, C=C*H*-N).

Anal. Calcd. for $C_{11}H_{12}N_2O_6$ (268.05): C, 49.28; H, 4.47; N, 10.44. Found: C, 49.42, H, 4.46; N, 10.35.

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