SYNTHESIS OF 1-(5'-DEOXY-\(\beta\)-D-ERYTHROPENT-4'-ENOFURANOSYL) ISOCYTOSINE AND 2-N,5'-ANHYDROISOCYTIDINE

Vinko Škarić\(^{X}\), Jasenka Matulić-Adamić, and Djurdja Škarić

Laboratory of Stereochemistry and Natural Products,
Institute "Rudjer Bošković", 41001 Zagreb, Croatia, Yugoslavia

The synthesis of 2-N-benzoyl-1-(2',3'-O-isopropylidene-5'-deoxy-\(\beta\)-D-erythropent-4'-enofuranosyl)-isocytosine (VII) and its conversion into 5'-deoxy-\(\alpha\)-L-lyxopentofuranosyl-\(\alpha\)-isocytosine (XVI) and 2-N,4'-anhydro-1-(5'-deoxy-5'-bromo-\(\alpha\)-L-lyxopentofuranosyl)-isocytosine (XVIII), is described. Treatment of 5'-deoxy-5'-iodo-(X) or 5'-O-p-toluenesulphonyl-isocytidine (IV) with potassium phthalimide in dioxan has afforded 2',3'-O-bis-benzoyl-5'-anhydroisocytidine (VI) in high yields.

Nucleoside antibiotics are important biochemical tools in the elucidation of complex cellular reactions, especially in reading the genetic message on ribosomes\(^1\). The antibiotic Angustmycin A, possessing significant antibacterial and antitumor activity\(^2\), stimulated our search toward isocytidine analogs bearing the 4',5'-double bond\(^3\). Thus, our continued interest in isocytidine chemistry led us to consider the synthesis of 2-N,5'-anhydroisocytidine and its furanoid vinyl ether derivative.

In a previous article\(^4\) we reported that the acylation of 2',3'-O-isopropylidene isocytidine\(^5,6\) with 1 equiv. of acylating reagent offered a selective route to the preparation of 2-N-acyl isocytidines. This paper deals with the preparation of 2',3'-O-isopropylidene-2-N-benzoyl-isocytidine (I) and a minor by-product identified as 2-N,5'-O-bis-benzoyl derivative (II). The nmr spectrum of the latter clearly showed a marked influence of the 5'-O-benzoyl group on the chemical shift.
of the C-6 proton, providing a very simple technique for the distinction of benzoylated products. It is worth noting that the benzoylation of 2',3'-O-isopropylidene-5,6-dihydroisocytidine with 1 equiv. of benzoic anhydride afforded 2-N-benzoyl-derivative (III) in higher yields than the corresponding isocytidine. 2-N-Benzoyl-isocytidines (I) and (III) thus obtained were then tosylated to give the corresponding 5'-O-tosyl derivatives (IV) and (V).

The tosyl derivative (IV) reacted rapidly with t-BuOK (path i) at room temperature, yielding 2-N-benzoyl-2-N,5'-anhydro-2',3'-O-isopropylidene isocytidine (VI) and lesser amounts of 2-N-benzoyl-1-(2',3'-O-isopropylidene-5'-deoxy-β-D-erythropent-4'-enofuranosyl)-isocytosine (VII). However, extended treatments of compound (IV) with t-BuOK (path ii) at room temperature or at 60°C (path iii) promoted the reaction to give mainly 4',5'-unsaturated compound (VII). The nmr spectrum of the latter showed the aromatic protons as multiplets at δ 1.58-1.81 and 2.43-2.65, the 4'-methylene group as a pair of doublets (J = 2.8 Hz) at δ 5.13 and 5.37 and the anomeric (1') proton as a singlet at δ 3.53. The hydrolysis of 2-N-benzoyl-1-(2',3'-O-isopropylidene-5'-deoxy-β-D-erythropent-4'-enofuranosyl)-isocytosine (VII) (path iv) gave the debenzoylated product (VIII) showing 4'-exo-methylene proton resonances at δ 5.25 and 5.48 (J = 2.5 Hz) and a shift of the anomeric proton to δ 4.22.

At this stage it appeared highly desirable to have an unambiguous method for the preparation of 2,5'-anhydropyrimidine nucleosides in order to evaluate the factors inducing the formation of 4',5'-unsaturated nucleosides. We found that both 5'-deoxy-5'-ido- and 5'-O-p-toluenesulphonyl-2',3'-O-isopropylidene uridine could be converted into 2,5'-anhydro-2',3'-O-isopropylidene uridine (IX) in very high yields by a reaction with potassium phthalimide (path v). Analogously, 2',3'-O-isopropylidene-2-N-benzoyl-2-N,5'-anhydroisocytidine (VI) was prepared from either 5'-ido-(X) or 5'-O-p-toluenesulphonyl isocytidine (IV).

Diverse reaction and products from 5,6-dihydropyrimidine nucleoside derivatives by the potassium phthalimide route remained to be examined. Namely, preliminary treatments of 2-N-benzoyl-5'-O-p-toluenesulphonyl-(V) and 2-N-benzoyl-5'-deoxy-5'-ido-5,6-dihydroisocytidine (XII) afforded several products

(180)
Reagents: i: t-BuOK in t-BuOH/py (1:1), 8 min; ii: t-BuOK in t-BuOH/py (1:1), 24 h; iii: t-BuOK/t-BuOH, 2 h; iv: NH$_3$/MeOH; v: Ph-SK/O(CH$_2$CH$_2$)$_2$O; vi: t-BuOK/DMSO; vii: [H$_2$], 5% Rh/C in MeOH; viii: [H$_2$], 5% Pd/C in MeOH; ix: [H$_2$], 5% Pd/C in 1N NaOH/EtOH; x: Br$_2$ in CHCl$_3$. 
and only low yields of 2-N, 5'-anhydro-5,6-dihydroisocytidine (XI) and its 2-N-benzoyl derivative (XIII), the latter being evidenced by the nmr spectrum.

The debenzoylation of 2-benzamido compound (VI) (path vi) smoothly proceeded into 2',3'-O-isopropylidene-2-N,5'-anhydroisocytidine (XIV) which, on hydrogenation (path vii), furnished 2',3'-O-isopropylidene-2-N,5'-anhydro-5,6-dihydroisocytidine (XI), characterized as hydrochloride (XV). 2-N,5'-Anhydro-5,6-dihydroisocytidine (XI) was also prepared from 5'-O-p-toluenesulphonyl-5,6-dihydroisocytidine (V) by the aforementioned phthalimide method. Compound (XI) showed the characteristic singlet at $\delta 5.01$ attributed to the anomeric (1') proton, two quartets at $\delta 6.03$ and 6.75 ($J = 14.5$ Hz) corresponding to the geminal 5'protons, and two triplets centred at $\delta 6.30$ and 7.50 ($J = 7.0$ Hz) corresponding to the C-6 and C-5 protons. It is interesting to note that the 4',5'-unsaturated compound (VII) was stereospecifically hydrogenated (path viii) into 2-N-benzoyl-1-(2',3'-O-isopropylidene-5'-deoxy-\(\alpha\)-L-lyxopentofuranosyl) isocytosine (XVI), $[\alpha]_D^{21} = 13.5^\circ$, by the procedure described in the conversion of the analogous uridine derivative\(^\text{14}\). The stereoisomeric 5'-deoxy-2',3'-O-isopropylidene-2-N-benzoylisocytidine (XVII), $[\alpha]_D^{18} = 57.0^\circ$, was obtained from 2',3'-O-isopropylidene-5'-deoxy-5'-ido-2-N-benzoyl-isocytidine (X) by catalytic hydrogenation in a basic ethanolic solution\(^\text{15}\) (path ix).

On view of the reported preparation of 2,4'-anhydropyrimidine nucleoside and N\(^3\),4'-purine cyclonucleoside\(^\text{2,16}\) we envisaged the synthesis of the hitherto unknown 2-N-benzoyl-2-N,4'-anhydro-1-(2',3'-O-isopropylidene-5'-deoxy-5'-bromo-\(\alpha\)-L-lyxopentofuranosyl) isocytosine (XVIII). However, treatment of 4',5'-unsaturated compound (VII) with bromine (path x) generated the hydrobromide of 2-N-benzoylisocytosine as a product of the N1 - C1' cleavage and a small amount of 2,4'-anhydro derivative (XVIII), the latter being evidenced by the absorption maximum at $\lambda 237$ nm and in the nmr spectrum by a characteristic sharp singlet at $\delta 4.42$ attributed to anomeric (1') proton and two doublets centred at $\delta 5.76$ and 6.10 ($J = 12$ Hz) corresponding to the 5'-geminal protons.
EXPERIMENTAL

The same techniques and apparatus were used as described previously. In addition optical rotations were measured for solutions in anhydrous ethanol (1 = 1 dm) unless otherwise stated, using a Zeiss-Winkel 179707 apparatus, nmr spectra for solutions in deuteriochloroform, and uv spectra in 95% ethanol.

Benzoylation of 2',3'-O-isopropylideneisocytidine. - To a solution of 2',3'-O-isopropylideneisocytidine (15 g, 53 mmol) in anhydrous pyridine (218 ml) benzoic anhydride (13.2 g, 57.5 mmol) was added, stirred at room temperature for 18 hr and then evaporated to dryness. The residue was chromatographed in methylene chloride on a silica gel (190 g) column affording 2',3'-O-isopropylidene-2-N,5'-O-bis-benzoyl isocytidine (II) (3.87 g, 14.9%), Rf ca. 0.75 [methylene chloride-acetone (10:1)]; mp 138-139°C (from methylene chloride - n-hexane); [α] D

C26H25N3O7 requires C, 63.53; H, 5.13; N, 8.55%; λmax 228, 248, 268, and 294 br nm (log ε 4.27, 4.16, 4.22, and 4.35), λmin 218 and 256 nm (log ε 4.24 and 4.12); ηmax 2994, 2967, 1721, 1701, 1689, 1631, 725 and 714 cm⁻¹; δ [1.45-1.86(2H, m), 1.89-2.12(2H, m), and 2.35-2.67 (6H, m), aromatic], 2.26 (1H, d, 6-H; J6,5 8.3 Hz), 3.55 (1H, d, 1'-H; J1',2,1,9 Hz), 4.33 (1H, d, 5-H; J5,6 8.3 Hz), 8.29 and 8.60 (3H each, 2s, C(CH₃)₂). Methylene chloride - methanol (10:1) eluted 2',3'-O-isopropylidene-2-N-benzoyl isocytidine (1) (13.1 g, 64%), Rf ca. 0.16; mp 178-179°C (from ethanol); [α] D

C19H21N3O6 requires C, 58.91; H, 5.46; N, 10.60%. λmax 248, 269 sh, and 296 br nm (log ε 4.12, 4.18 and 4.31), λmin 227 and 256 nm (log ε 3.90 and 4.09); ηmax 3436, 2985, 2941, 1718, 1706 sh, 1686 br, 1653, 1626 and 725 cm⁻¹; δ [1.51-1.72 (2H, m) and 2.42-2.63 (3H, m), aromatic], 1.83 (1H, d, 6-H; J6,5 8.3 Hz), 4.13 (1H, d, 5-H; J5,6 8.3 Hz), 8.31 and 8.60 (3H each, 2s, C(CH₃)₂).

2',3'-O-Isopropylidene-2-N-benzoyl-5,6-dihydroisocytidine (III). - A solution of 2',3'-O-isopropylidene-5,6-dihydroisocytidine (100 mg, 0.35 mmol) in an-
hydrous pyridine (2 ml) was treated with benzoic anhydride (87 mg, 0.384 mmol), stirred at room temperature for 3.5 hr, and then evaporated to dryness. Preparative tlc [methylene chloride - acetone (10:1); recovery with acetone] gave the product (110 mg, 81%), \( R_f \) ca. 0.17; mp 158-160\(^\circ\)C (from ethanol); \( [\alpha]_D^{25} \) -26.8\(^\circ\) (c 0.63 in methylene chloride) (Found: C, 58.80; H, 6.22; N, 11.06. \( C_{19}H_{23}N_3O_6 \) requires C, 58.60; H, 5.95; N, 10.79%); \( \lambda_{\text{max}} \) 247, 279 and 294sh nm (log\( \varepsilon \) 4.14, 4.36 and 4.23), \( \lambda_{\text{min}} \) 222 and 258 nm (log\( \varepsilon \) 3.84 and 4.09); \( \gamma_{\text{max}} \) 3436br, 2985, 1730br, 1618sh, 1605sh, 1590br, and 709 cm\(^{-1}\); \( \varepsilon \) 1.68-1.90 (2H, m), 2.46-2.68 (3H, m), aromatic], 3.41 (1H, m, J \( \sim \) 3.0 Hz), 6.27 (2H, t, 6-H; J \( \sim \) 6.7 Hz), 7.33 (2H, t, 5-H; J \( \sim \) 6.7 Hz), 8.35 and 8.63 (3H each, Z, s, C(CH\(_3\))\(_2\)).

2',3'-O-Isopropylidene-5'-O-p-toluenesulphonyl-2-N-benzoyl-isocytidine (IV). - To a solution of 2',3'-O-isopropylidene-2-N-benzoyl isocytidine (I) (1.1 g, 2.84 mmol) in anhydrous pyridine (20 ml) toluene-p-sulphonyl chloride (725 mg, 3.79 mmol) was added, stirred at 3\(^\circ\)C for 18 hr and then evaporated to an oil. This oily product was dissolved in methylene chloride and chromatographed on a silica gel (30 g) column. Methylene chloride - acetone (10:1) eluted the product (1.0 g, 66%), \( R_f \) ca. 0.77 [methylene chloride - acetone (10:1)]; mp 169-171\(^\circ\)C (from methylene chloride - n-hexane); \( [\alpha]_D^{25} + 78^\circ \) (c 0.82 in methylene chloride) (Found: C, 57.87; H, 5.24; N, 7.92; S, 5.63. \( C_{26}H_{27}N_3O_8 \) requires C, 57.66; H, 5.03; N, 7.76; S, 5.92%); \( \lambda_{\text{max}} \) 220, 247, 267br, 288, and 297sh nm (log\( \varepsilon \) 4.32, 4.16, 4.11, 4.17, and 4.17), \( \lambda_{\text{min}} \) 238, 260, 274 nm (log\( \varepsilon \) 4.13, 4.10, and 4.11); \( \gamma_{\text{max}} \) 3436br, 2994, 1736sh, 1704sh, 1689, 1634, and 725 cm\(^{-1}\); \( \varepsilon \) 1.61-1.81 (2H, m), 2.17-2.31 (2H, m), 2.50-2.73 (5H, m), aromatic], 2.42 (1H, d, 6-H; J \( \sim \) 8.3 Hz), 3.54 (1H, d, 1'-H; J \( \sim \) 1.9 Hz), 4.23 (1H, d with secondary splitting, 5-H; J \( \sim \) 8.3 Hz), 7.56 (3H, s, C(CH\(_3\))\(_2\)), 8.35 and 8.64 (3H each, 2s, C(CH\(_3\))\(_2\)).

2',3'-O-Isopropylidene-5'-O-p-toluenesulphonyl-2-N-benzoyl-5,6-dihydro-isocytidine (V). - A solution of 2',3'-O-isopropylidene-2-N-benzoyl-5,6-dihydro-isocytidine (III) (100 mg, 0.257 mmol) in anhydrous pyridine (2 ml) was treated with toluene-p-sulphonyl chloride (100 mg, 0.52 mmol) at room temperature for
18 hr and then evaporated to an oil. Preparative tlc [in methylene chloride - acetone (10 : 1); recovery with acetone] afforded the product (108 mg, 78%);

R_f ca. 0.8; mp 106-108°C (from ethanol); [α]_D^25 - 6.20° (c 0.79 in acetone)

(Found: C, 57.50; H, 5.66; N, 7.93; S, 5.88. C_{26}H_{29}N_{3}O_{8}S requires C, 57.45; H, 5.38; N, 7.73; S, 5.90%);

λ_max 224, 248, 278, and 293sh nm (log ε 4.31, 4.17, 4.43 and 4.27), λ_min 212, 238, and 256 nm (log ε 4.25, 4.09, 4.16); ν_max 3436br, 2994, 1742sh, 1621sh, 1595br, and 712 cm\(^{-1}\); ζ [1.68-1.87 (2H,m), 2.09-2.32 (2H,m), 2.46-2.71 (5H,m), aromatic], 3.38 (1H,m, 1'-H), 6.16-6.56 (2H,m, 6-H), 7.33 (2H,t, 5-H; J 6.7 Hz), 7.56 (3H,s, CH\(_3\)), 8.36 and 8.64 (3H each, 2s, C(CH\(_3\))\(_2\)).

2',3'-O-Isopropylidene-2-N-benzoyl-2-N,5'-anhydroisocytidine (VI). - To a solution of 2',3'-O-isopropylidene-5'-O-toluenesulphonyl-2-N-benzoyl-isocytidine (IV) (150 mg, 0.278 mmol) in anhydrous pyridine (9 ml) and t-BuOH (9 ml) freshly prepared 0.25 N solution of t-BuOK (5.5 ml) was added and stirred at room temperature for 8 min. This solution was triturated with silica gel (0.5 g) in ethanol (30 ml) and then filtered. The filtrate was evaporated to dryness, extracted with chloroform, and again evaporated to dryness. Preparative tlc [in methylene chloride - acetone (10 : 1), recovery with methanol], separated the starting material (37 mg), a fraction identified as 2-N-benzoyl-1-(2',3'-O-isopropylidene-5'-deoxy-\(\beta\)-D-erythropent-4'-enofuranosyl)-isocytosine (VII), (15 mg, 15%) and the product (60 mg, 59%), R_f ca. 0.12; mp 285-286°C (dec.) (from methylene chloride - n-hexane); [α]_D^28 + 66.7° (c 0.72 in methanol) (Found: C, 61.93; H, 5.43; N, 11.66. C_{19}H_{19}N_{3}O_{5} requires C, 61.78; H, 5.19; N, 11.38%); λ_max 222sh and 243 nm (log ε 4.22 and 4.30), λ_min 211 nm (log ε 4.20); ν_max 3436br, 2994, 1686, 1658, 1645br, 1603, and 702 cm\(^{-1}\); 2' 2.59 (1H,d,6-H, J 6.5 7.8 Hz), 2.63 (5H,s,aromatic), 4.01 (1H,d,5-H, J 5,6 7.8 Hz), 4.51 (1H,s,1'-H), 4.70-5.30 (4H,m, 5'-H, 4',3', and 2'-H), 6.83 (1H,d with secondary splitting, 5'-H; J 5,6 15 Hz), 8.48 and 8.68 (3H each, 2s, C(CH\(_3\))\(_2\)).

2-N-Benzoyl-1-(2',3'-O-isopropylidene-5'-deoxy-\(\beta\)-D-erythropent-4'-enofuranosyl)-isocytosine (VII). - (a) Into a solution of 2',3'-O-isopropylidene-5'-O-p-toluenesulphonyl-2-N-benzoyl isocytidine (IV) (200 mg, 0.37 mmol) in an-
hydrous pyridine (10 ml) and t-BuOH (10 ml). A 0.25 N solution of t-BuOK in t-BuOH (10 ml) was added, stirred at room temperature for 24 hr and then triturated with ion exchange resin [Amberlite IRC-50 (H-form), 3 g] in ethanol (40 ml). The resin was filtered off, the filtrate evaporated to dryness, and the residue dissolved in boiling chloroform (3 x 30 ml). Chromatography on a silica gel (10 g) column in methylene chloride - acetone (20:1), afforded the product (120 mg, 88%), Rf ca. 0.72 [methylene chloride - acetone (10:1)]; mp 163-164°C (from methylene chloride - n-hexane); [α]_D^{21} + 144.2° (c 0.60 in methanol) (Found: C, 61.69; H, 5.32; N, 11.44. \( \text{C}_{19}^\text{H}_{19}^\text{N}_{3}^\text{O} \) requires C, 61.78; H, 5.19; N, 11.38%); \( \lambda_{\text{max}} \) 248, 270sh, and 289br nm (log ε 4.18, 4.26, and 4.37), \( \lambda_{\text{min}} \) 228 and 255 nm (log ε 4.0 and 4.17); \( \nu_{\text{max}} \) 3363br, 2994, 1739, 1709, 1672, 1629, 1575br, and 725 cm\(^{-1}\); \( \nu_{\text{min}} \) [1.58-1.81 (2H,m), 2.43-2.65 (3H,m)], 5.22 (1H,d, 6-H; J_6,5 8.2 Hz), 3.53 (1H,s,1'-H), 4.14 (1H,d,5-H; J_5,6 8.2 Hz), 5.13 (1H,t,5'-H_b; J_b,a 2.8 Hz), 5.37 (1H,d,5'-H_a; J_a,b 2.8 Hz), 8.38 and 8.59 (3H each, 2s, C(CH_3)_2).

(b) Treatment of compound (IV) (220 mg, 0.407 mmol) in t-BuOH (8 ml) with 0.25 N t-BuOK in BuOH (8 ml) at 60°C for 2 hr yielded a product (120 mg, 80%), mp 162-164°C, identical (mixed mp, ir and nmr spectra) with that obtained under (a).

1-(2',3'-O-Isopropylidene-5'-deoxy-\( \beta \)-D-erythropent-4'-enofuranosyl)-iso-cytosine (VIII). - A solution of 2-N-benzoyl-1-(2',3'-O-isopropylidene-5'-deoxy-\( \beta \)-D-erythropent-4'-enofuranosyl)-iso-cytosine (VII) (50 mg, 0.136 mmol) in saturated methanolic ammonia (6.5 ml) was set aside for 10 days at room temperature, and then evaporated to dryness. Preparative tlc [in methylene chloride - methanol (10:1); recovery with acetone] afforded the product (29 mg, 84%), Rf ca. 0.15; mp 116-118°C (from methylene chloride - n-hexane); [α]_D^{25} + 41.7° (c 0.72 in methanol) (Found: C, 54.51; H, 6.00; N, 16.09. \( \text{C}_{12}^\text{H}_{15}^\text{N}_{3}^\text{O} \) requires C, 54.33; H, 5.70; N, 15.84%); \( \lambda_{\text{max}} \) 207, 228sh, and 256sh nm (log ε 4.28, 3.98, and 3.68), \( \nu_{\text{max}} \) 3333, 3125, 2985, 1681sh, 1658, and 1629 cm\(^{-1}\); \( \nu_{\text{min}} \) 2.90 (1H,d,6-H; J_6,5 8.2 Hz), 4.22 (1H,d,1'-H; J_1',2,1.9 Hz), 4.31 (1H,d,5-H; J_5,6 8.2 Hz), 5.25 (1H, d with secondary splitting, 5'-H_b; J_{b,a} 2.5 Hz), 5.48 (1H,d,5'-H_a; J_{a,b} 2.5 Hz), 8.47 and 8.62 (3H each, 2s, C(CH_3)_2).
Preparation of 2,5'-Anhydronucleosides by the Potassium Phthalimide Method. - General procedure. To a solution of either 2',3'-O-isopropylidene-5'-deoxy-5'-iodo- or 5'-O-p-toluenesulphonyl uridine, as well as of corresponding 2-N-benzoylisocytidine derivatives (X) and (IV) (0.1 mmol) in anhydrous dioxan (25 ml) potassium phthalimide (0.1 mmol) was added and heated under reflux for 3 hr. The solution was cooled and the precipitate filtered off. The filtrate was evaporated to dryness, dissolved in methylene chloride, and triturated with a minimal amount of finely grounded sodium thiosulphate (in the case when 5'-iodo compounds were used as starting material). Filtration and evaporation of the filtrate afforded crystalline products, purified by crystallization. The products were identical (ir, uv, nmr, and mixed melting points) with the authentic samples.

2',3'-O-Isopropylidene-2,5'-anhydrouridine (IX). - From 5'-iodouridine a 88.5% yield and from 5'-O-p-toluenesulphonyl uridine a 85% yield of this compound were obtained, mp 180-181°C (from methylene chloride - ether); Rf ca. 0.52 [in methylene chloride - methanol (9:1)].

2',3'-O-Isopropylidene-2-N-benzoyl-2-N,5'-anhydroisocytidine (VI). - From 2',3'-O-isopropylidene-5'-deoxy-5'-ido-2-N-benzoyl isocytidine (X) a 86% yield and from 5'-tosyl derivative (IV) (heated under reflux for 4 hr) a 70% yield of the product were obtained, mp 275-280°C.

2',3'-O-Isopropylidene-5'-deoxy-5'-ido-2-N-benzoyl isocytidine (X). - To a solution of 2',3'-O-isopropylidene-5'-O-p-toluenesulphonyl isocytidine (IV) (200 mg, 0.37 mmol) in butan-2-one (5 ml), protected from moisture, sodium iodide (150 mg, 1 mmol) was added and heated under reflux for 3 hr. The mixture was evaporated to dryness and the residue partitioned between methylene chloride and 5% sodium thiosulphate. From the organic layer a crystalline product separated (150 mg, 82%), Rf ca. 0.77 [methylene chloride - acetone (10:1)]; mp 125-126°C (from methanol); [α]18° + 72.5° (c 0.8 in acetone) (Found: C, 45.64; H, 4.33; N, 8.28; J, 25.31. C19H20N3O5J requires C, 45.89; H, 4.05; N, 8.45; J, 25.52%); λ_{max} 248, 268sh, and 290br nm (log ε 4.15, 4.24, and 4.34), λ_{min} 227 and 255 nm (log ε 3.95 and 4.14); 3413br, 3115, 2985, 1689, 1629, 1587, and
723 cm\(^{-1}\); \(2^*[1.59-1.77 \text{ (2H, m), 2.43-2.65 \text{ (3H, m), aromatic}]\), 2.08 (1H, d, 6-H; \(J_{6,5} 8.5\) Hz), 3.45 (1H, d, 1'-H; \(J_{1',2} 3.0\) Hz), 4.07 (1H, d, 5-H; \(J_{5,6} 8.5\) Hz), 8.31 and 8.61 (3H each, 2s, C(CH\(_3\))\(_2\)).

2',3'-O-Isopropylidene-2-N,5'-anhydro-5,6-dihydroisocytidine (XI). -
(a) A solution of 2',3'-O-isopropylidene-2-N,5'-anhydroisocytidine (XIV) (150 mg, 0.565 mmol) in anhydrous methanol (7 ml) containing 5% Rh/C (120 mg) was stirred in hydrogen atmosphere under 60 psi for 48 hr. The catalyst was filtered off, and the filtrate evaporated to a product which crystallized from ethanol (79.5 mg, 53%), \(R_f 0.16\) [in methylene chloride - methanol (20: 1)]; mp 287-289\(^{\circ}\)C (dec.); \([\alpha]_D^{19} +76.7^\circ\) (c 0.6 in methanol) (Found: C, 54.05; H, 6.73; N, 15.81. C\(_{12}\)H\(_{17}\)N\(_3\)O\(_4\) requires C, 53.92; H, 6.41; N, 15.72%); \(\lambda_{max}\) 224 sh and 247 nm (log\(\varepsilon\) 3.92 and 4.12); \(\nu_{max}\) 3497, 3226, 3021, 1664, 1608, and 1531 cm\(^{-1}\);
\(\delta 5.01\) (1H, s, 1'-H), 6.03 (1H, q, 5'-H\(_a\)); \(J_{a,b} 14.5\), \(J_{a,4} 3.0\) Hz), 6.30 (2H, t, 6-H; \(J_{a,b} 6.5\) 7.0 Hz), 6.75 (1H, q, 5'–H\(_b\)); \(J_{b,a} 14.5\), \(J_{b,4} 1.8\) 7.50 (2H, t, 5-H; \(J_{5,6} 7.0\) Hz), 8.53 and 8.72 (3H each, 2s, C(CH\(_3\))\(_2\)).

(b) A solution of 2',3'-O-isopropylidene-5'-O-p-toluenesulphonyl-2-N-benzoyl-5,6-dihydroisocytidine (V) (123 mg, 0.23 mmol) in anhydrous dioxan (25 ml) was heated with potassium phthalimide (60 mg, 0.34 mmol) under reflux for 20 hr, and then filtered and evaporated to a mixture of products (88 mg). Fractional crystallization from ethanol separated products with mp's: 176-178\(^{\circ}\)C (32 mg), and 282-286\(^{\circ}\)C (12 mg); the latter being identical (mixed mp, ir, and nmr spectra) with that obtained under (a), and 208-210\(^{\circ}\)C (13 mg).

2',3'-O-Isopropylidene-2-N,5'-anhydro-5,6-dihydroisocytidine, hydrochloride (XV) was obtained from the solution of 2',3'-O-isopropylidene-2-N,5'-anhydro-5,6-dihydroisocytidine (XI) (50 mg, 0.187 mmol) in anhydrous methanol (20 ml) and 6.5% methanolic hydrochloric acid (0.16 ml, 0.28 mmol) after it had been evaporated to a volume of 1 ml. The crystals separated (45 mg, 79%), mp 286-287\(^{\circ}\)C (dec.) (from ethanol); \([\alpha]_D^{21} +211^\circ\) (c 0.76 in methanol) (Found: C, 47.19; H, 6.26; N, 13.75; Cl, 11.78. C\(_{12}\)H\(_{17}\)N\(_3\)O\(_4\) CI requires C, 47.45; H, 5.97; N, 13.83; Cl, 11.67%); \(\lambda_{max}\) 213 and 245 nm (log\(\varepsilon\) 4.07 and 3.79),

(188)
A solution of 5'-O-p-toluenesulphonyl-5,6-dihydroisocytidine (V) (200 mg, 0.36 mmol) in butan-2-one (5 ml) was heated with sodium iodide (150 mg, 1 mmol) under reflux for 3 hr, and then worked up as described for compound (X). Yield 168% (91%), mp 167-168°C (from methylene chloride - n-hexane); [α]D<sup>23</sup> = 7.0° (c 1.0 in acetone) (Found: C, 45.99; H, 4.66; N, 8.65. C<sub>19</sub>H<sub>22</sub>N<sub>3</sub>O<sub>5</sub> requires C, 45.70; H, 4.44; N, 8.42%); λ<sub>min</sub> 351, 279, and 295 sh nm (log ε 4.20, 4.34, and 4.22), λ<sub>max</sub> 223 and 258 nm (log ε 3.78 and 4.18); γ<sub>max</sub> 3521, 3125, 3030, 1736, 1610, 1587 br, and 709 cm<sup>-1</sup>; 2 [1.68-1.91 (2H, m), 2.46-2.74 (3H, m), aromatic], 3.38 (1H, d, 1'-H; J<sub>1',2</sub> 4.0 Hz), 6.21 (2H, t, 6-H; J<sub>6,5</sub> 7.0 Hz), 7.27 (2H, t, 5-H; J<sub>5,6</sub> 7.0 Hz), 8.34 and 8.61 (3H each, 2s, C(CH<sub>3</sub>)<sub>2</sub>).

2',3'-O-Isopropylidene-2-N,5'-anhydroisocytidine (XIV). - To a solution of 2',3'-O-isopropylidene-2-N-benzoyl-2-N,5'-anhydroisocytidine (VI) (50 mg, 0.135 mmol) in DMSO (2 ml) a 0.25 N solution of freshly prepared t-BuOK (2 ml) was added and stirred at room temperature for 10 min. This solution was poured into a suspension of ion exchange resin [Amberlite IRC-50 (H-form), 1 g in ethanol (15 ml)] and stirred to a neutral reaction. The resin was then filtered off, the filtrate evaporated to dryness, and the residue extracted with chloroform. Preparative tlc [in methylene chloride - methanol (10:1), recovery with methanol] gave the product (34 mg, 95%), R<sub>f</sub> ca. 0.23; mp 285-287°C (dec.); [α]D<sup>24</sup> = 65° (c 0.60 in methanol) (Found: C, 54.17; H, 5.86; N, 15.66. C<sub>12</sub>H<sub>15</sub>N<sub>3</sub>O<sub>4</sub> requires C, 54.33; H, 5.70; N, 15.84%); λ<sub>max</sub> 3436, 3344, 1658, 1645, 1621, and 1603 cm<sup>-1</sup>; ν 2.80 (1H, d, 6-H; J<sub>6,5</sub> 7.8 Hz), 4.07 (1H, d, 5-H; J<sub>5,6</sub> 7.8 Hz), 4.63 (1H, s, 1'-H), 5.97 (1H, q, 5''-H<sub>a</sub>; J<sub>a,b</sub> 14.2, J<sub>a,a</sub> 2.5 Hz), 6.71 (1H, q, 5''-H<sub>b</sub>; J<sub>b,a</sub> 14.2, J<sub>b,b</sub> 2.0 Hz), 8.50 and 8.69 (3H each, 2s, C(CH<sub>3</sub>)<sub>2</sub>).
in anhydrous methanol (14 ml) containing 5% Pd/C (48 mg) was stirred in hydrogen atmosphere for 15 hr. The catalyst was filtered off, and the filtrate evaporated to a crystalline product (95 mg, 95%). \( R_f \) ca. 0.58 [methylene chloride - acetone (10:1)]; mp 128-129\(^\circ\)C (from methylene chloride - n-hexane); \([\alpha]_D^{21} + 13.5^\circ\) (c 0.88 in methanol) (Found: C, 61.37; H, 5.85; N, 11.46. \( C_{19} H_{21} N_3 O_5 \) requires C, 61.44; H, 5.70; N, 11.32%); \( \lambda_{\text{max}} \) 248, 270, and 297 br nm (log \( e \) 3.92, 4.0, and 4.14), \( \lambda_{\text{min}} \) 228, 256, and 273 nm (log \( e \) 3.69, 3.91, and 3.99); \( \gamma_{\text{max}} \) 3436 br, 2985, 1724 sh, 1704 sh, 1695, 1629, and 725 cm\(^{-1}\); \( \varepsilon \) [1.50-1.70 (2H, m), 2.47-2.69 (3H, m), aromatic], 2.51 (1H, d, 6-H; \( J_{6,5} \) 8.3 Hz), 4.06 br (1H, s, 1'-H), 4.16 (1H, d with secondary splitting, 5-H; \( J_{5,6} \) 8.3 Hz), 8.52 (3H, d, CH\(_3\); \( J_{CH_3,H} \) 6.5 Hz), 8.38 and 8.61 (3H each, 2s, C(CH\(_3\))\(_2\)).

2',3'-O-Isopropylidene-5'-deoxy-2-N-benzoyl-isocytidine (XVII). - Into a solution of 2',3'-O-isopropylidene-5'-deoxy-5'-ido-2-N-benzoyl-isocytidine (X) (100 mg, 0.2 mmol) in ethanol (10 ml) 1 N NaOH (0.4 ml) and 5% Pd/C (54 mg) were added and shaken in an atmosphere of hydrogen for 4 h. The solution was filtered and evaporated to dryness, and then partitioned between chloroform and water. The organic layer was washed with a solution of sodium thiosulphate, sodium hydrogen carbonate, and water. Preparative tlc [in methylene chloride - acetone (10:1); recovery with acetone] yielded the product (50 mg, 67%); \( R_f \) ca. 0.69; mp 143-145\(^\circ\)C; \([\alpha]_D^{18} + 57.9^\circ\) (c 0.7 in methanol) (Found: C, 61.49; H, 5.95; N, 11.19. \( C_{19} H_{21} N_3 O_5 \) requires C, 61.44; H, 5.70; N, 11.32%); \( \lambda_{\text{max}} \) 248, 268 sh, and 293 br nm (log \( e \) 4.18, 4.25 and 4.38), \( \lambda_{\text{min}} \) 227 and 256 nm (log \( e \) 3.97 and 4.16); \( \gamma_{\text{max}} \) 3448 br, 2985, 1695, 1672, 1621, 1570, and 720 cm\(^{-1}\); \( \varepsilon \) [1.55-1.71 (2H, m), 2.46-2.76 (3H, m), aromatic], 2.36 (1H, d, 6-H; \( J_{6,5} \) 8.3 Hz), 3.67 (1H, d, 1'-H; \( J_{1',2} \) 2.5 Hz), 4.12 (1H, d, 5-H; \( J_{5,6} \) 8.3 Hz), 8.56 (3H, d, CH\(_3\); \( J_{CH_3,H} \) 6.5 Hz), 8.32 and 8.62 (3H each, 2s, C(CH\(_3\))\(_2\)).

2-N-Benzoyl-2-N,4'-anhydro-1-(2',3'-O-isopropylidene-5'-deoxy-5'-bromo-\( \alpha \)-L-lyxopentofuranosyl)-isocytosine (XVIII). - A solution of 2-N-benzoyl-1-(2',3'-O-isopropylidene-5'-deoxy-\( \beta \)-D-erythropent-4'-enofuranosyl)-isocytosine (VII) (250 mg, 0.68 mmol) in anhydrous chloroform (28 ml) was treated with
a chloroform solution (12.5 ml) of bromine (0.034 ml, 0.72 mmol) at -10°C, and then stirred at 3°C for 18 hr. n-Hexane was added and the precipitate was purified on a tlc plate (five developments in methylene chloride - acetone (10:1); recovery with acetone). A component (30 mg) was identified as the hydrobromide of 2-N-benzoyl-isocytosine. The product, Rf ca. 0.1 (105 mg, 35%), was rechromatographed [in methylene chloride - methanol (20:1)] as a foam, Rf ca. 0.39; [α]D21 + 117° (c 0.47 in methanol) (Found: C, 50.87; H, 4.27; N, 9.35; C19H18N3O5Br requires C, 50.91; H, 4.05; N, 9.37%); λmax 208, 237, and 263sh nm (log ε 4.34, 4.25, and 4.15), λmin 224 nm (log ε 4.20); νmax 3448, 2994, 1684, 1639, 1592, 1577, and 709 cm⁻¹; δ [2.02-2.26 (2H, m), 2.43-2.71 (3H, m) aromatic], 2.89 (1H, d, 6-H; J6,5 7.5 Hz), 4.14 (1H, d, 5-H; J5,6 7.5 Hz), 4.42 (1H, s, 1′-H), 4.73 (1H, d, 2′-H; J2′,3′ 5.5 Hz), 5.15 (1H, d, 3′-H; J3′,2′ 5.5 Hz), 5.76 (1H, d, 5′-H₂; Jₐ₋ₐ′ 12.8 Hz), 6.10 (1H, d, 5′-Hₐ; Jₐ₋ₐ′ 12.8 Hz), 8.48 and 8.69 (3H each, 2s, C(CH₃)₂).

REFERENCES

17. V. Škarić, V. Turjak-Zebić, And Dj. Škarić, J.C.S. Perkin I, 1974, 1406.

Received, 15th June, 1977