PREPARATION OF ACYL DERIVATIVES OF PYRIMIDIN-2-ONE NUCLEOSIDES BY THE SILYL VARIANT OF THE HILBERT–JOHNSON REACTION*

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Reaction of pyrimidin-2-one (*II*) with hexamethyldisilazane afforded 2-trimethylsilyloxypyrimidine (*III*) which was converted to 1-(peracyl-β-D-glycosyl)pyrimidin-2-ones *V* by reaction with the corresponding peracetyl- or perbenzoylhalogenose *IV* in acetonitrile. The following *V* were prepared: 1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)- (*Va*), 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)- (*Vb*), 1-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)- (*Vc*), 1-(2,3,5-tri-O-benzoyl-β-D-xylofuranosyl)- (*Vd*), 1-(2,3,4-tri-O-benzoyl-β-D-ribopyranosyl)- (*Ve*), and 1-(2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl)pyrimidin-2-one (*Vf*). Methanolysis of compounds *Vb* and *Vc*, resp., yielded 1-(β-D-ribofuranosyl)- (*Ia*) and 1-(β-D-xylofuranosyl)pyrimidin-2-one (*Ib*). Simplified preparations of 1,2,3,5-tetra-O-acetyl-D-xylofuranose and 1,2,3,5-tetra-O-benzoyl-α-D-xylofuranose are also described.

1-(β-D-Ribofuranosyl)pyrimidin-2-one (*Ia*) is an efficient inhibitor of DNA biosynthesis *de novo* in bacteria[1]. As demonstrated in this Laboratory, the mechanism of action consists in coversion of compound *Ia* to the corresponding 2'-deoxyribonucleoside which is phosphorylated with the formation of the 5'-deoxyribonucleotide acting as a specific reversible inhibitor of thymidylate-synthetase[2,3]. In view of the biochemical interest, some further nucleoside derivatives of pyrimidin-2-one with a modified sugar moiety have been now prepared.

The existing preparations of pyrimidin-2-one nucleosides mainly consist in condensation of the sugar halogenose with the chloromercuri salt of pyrimidin-2-one in the presence of mercuric bromide[4], desulfurisation of 4-thiouracil derivatives with Raney nickel[5], condensation of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose with 2-trimethylsilyloxypyrimidine in the presence of stannic chloride[6] or cleavage of 4-hydrazinopyrimidin-2-one nucleoside derivatives in the presence of metal catalysts[7]. In these methods, salts of heavy metals are used that interfere with biochemical assays even when present in trace amounts. This drawback is circumvented by the present alternative glycosidation of pyrimidin-2-one.

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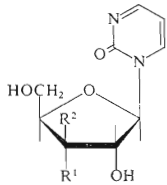
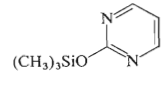
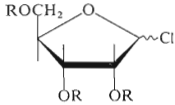
II



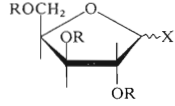
Ia: R^1 = OH. R^2 = H
Ib: R^1 = H. R^2 = OH



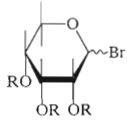
III



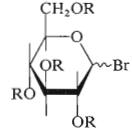
IVa: R = $COCH_3$
IVb: R = COC_6H_5



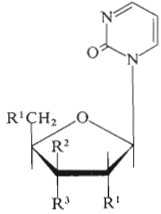
IVc: R = $COCH_3$, X = Cl
IVd: R = COC_6H_5, X = Br



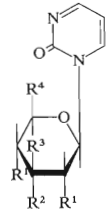
IVe: R = COC_6H_5



IVf: R = COC_6H_5



Va: $R^1 = R^3 = OCOCH_3$, R^2 = H
Vb: $R^1 = R^3 = OCOC_6H_5$, R^2 = H
Vc: $R^1 = R^2 = OCOCH_3$, R^3 = H
Vd: $R^1 = R^2 = OCOC_6H_5$, R^3 = H



Ve: $R^1 = R^2 = OCOC_6H_5$, $R^3 = R^4$ = H
Vf: $R^1 = R^3 = OCOC_6H_5$, R^2 = H,
$R^4 = CH_2OCOC_6H_5$

The present method is based on a silyl variant of the Hilbert-Johnson reaction. Thus, 2-trimethylsilyloxypyrimidine (*III*) obtained by reaction of compound *II* with hexamethyldisilazane is allowed to react with the halogenose *IV*, preferably in acetonitrile. The reaction mixture is decomposed with water and the crude product crystallised or chromatographed on silica gel to afford pure pyrimidin-2-one peracylglycosyl derivatives *V* from which the free nucleosides *I* are prepared by alcoholysis[4]. In addition to the absence of heavy metals in the whole reaction sequence, the advantage of the method also consists in accessibility of both the halogenoses and compound *III* which is stable enough to make possible work-up in air and storage for a long period of time without any considerable change. The literature[6] reports on the use of compound *II* but does not mention the properties and reaction conditions of the preparation.

The applicability of the present method was demonstrated with the use of halogenoses derived from D-ribofuranose (*IVa, b*), D-xylofuranose (*IVc, d*), D-ribopyranose (*IVe*), and D-glucopyranose (*IVf*) and protected by two types of acyl (acetyl and benzoyl) groups. From the thus-obtained 1-(peracyl-β-D-glycosyl)pyrimidin-2-ones *V*, the acetyl derivatives *Va, c* have been examined as potential depot models of the active substance that increase the penetration through the cell wall as well as the stability of the whole molecule. On the other hand, a direct acetylation of pyrimidin-2-one nucleosides is known to be accompanied by destruction of the nucleoside. The present method[8,9] is also suitable for preparations on a larger scale and is more advantageous from the preparative point of view than the existing[4,6] types of nucleosidation reactions.

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block). The b.p. and m.p. data are not corrected. Solutions were taken down on a rotatory evaporator at 40°C/15 Torr. Substances were dried over phosphorus pentoxide at 0·1 Torr. Paper chromatography was performed on paper Whatman No 3 MM in the solvent system S_1, 2-propanol–conc. aqueous ammonia–water (7 : 1 : 2). Thin-layer chromatography was performed on ready-for-use Silufol UV_{254} (Kavalier Glassworks, Votice, Czechoslovakia) silica gel sheets in solvent systems S_2, chloroform; S_3, chloroform–ethanol (95 : 5); and S_4, chloroform–ethanol (9 : 1). Paper electrophoresis was performed by the reported[10] technique at 40 V/cm for 1 h in 0·1M triethylammonium borate (pH 7·5). Column chromatography was performed on the Pitra (30–60 μm) silica gel (150 g) in chloroform (30 ml fractions). Preparative chromatography on loose layers (50 × 16 × 0·3 cm) was performed on a fluorescent-indicator-containing silica gel produced by Service Laboratories of this Institute. The UV spectra were taken in aqueous solutions on a Zeiss Specord apparatus. The ^{1}H-NMR spectra were recorded in deuteriochloroform (hexamethyldisiloxane as internal standard) on a Varian 100 apparatus; chemical shift values are expressed in ppm, the coupling constants in Hz.

2-Trimethylsilyloxypyrimidine (*III*)

A stirred mixture of pyrimidin-2-one[11] (*II*; 30 g; 0·31 mol), hexamethyldisilazane (80 ml), and crystalline ammonium sulfate (0·1 g) was refluxed (bath temperature, 150°C) under a calcium chloride tube for 2 h and then distilled under diminished pressure to afford 52 g (100%) of compound *III*, b.p. 93°C/10 Torr.

1,2,3,5-Tetra-O-acetyl-D-xylofuranose[12]

A mixture of 1,2 : 4,5-di-O-isopropylidene-α-D-xylofuranose[13] (92·5 g; 0·4 mol), 50% aqueous methanol (500 ml), and Dowex 50X 8 (H^+) ion exchange resin was stirred at room temperature for 2 h, *i.e.*, until the starting compound disappeared (thin-layer chromatography in the solvent system S_3, detection by iodine vapours). The mixture was then filtered, the filtrate evaporated under diminished pressure, and the residue coevaporated with four 50 ml portions of pyridine. The residual monoisopropylidene derivative (R_F 0·10 in S_3) was kept in a mixture of pyridine (400 ml) and acetic anhydride (150 ml) at room temperature overnight, the whole evaporated at 80°C/0·1 Torr, and the residue diluted with chloroform (500 ml). The chloroform solution was washed with water, two portions of dilute (1 : 10) hydrochloric acid, aqueous sodium hydrogen carbonate, and water again (200 ml each), dried over anhydrous magnesium sulfate, filtered, and the filtrate evaporated under diminished pressure. A mixture of the residual 1,2-O-isopropylidene-3,5-di-O-acetyl-α-D-xylofuranose (R_F 0·25 in S_2), acetic acid (800 ml), and acetic anhydride (200 ml) was treated dropwise under external ice-cooling with conc. sulfuric acid (70 ml) at 10°C over 30 min. The mixture was kept at room temperature overnight, poured onto ice (2 kg), and the whole extracted with three 500 ml portions of chloroform. The extract was washed with three 200 ml portions of water, dried over anhydrous magnesium sulfate, filtered, and the filtrate evaporated under diminished pressure. The residue was coevaporated with four 50 ml portions of toluene at 40°C/0·1 Torr and finally dried at 80°C/0·1 Torr to afford 102 g of 1,2,3,5-tetra-O-acetyl-D-xylofuranose which was directly used in the condensation step.

1,2,3,5-Tetra-O-benzoyl-α-D-xylofuranose

The above mentioned crude 1,2-O-isopropylidene-α-D-xylofuranose (0·4 mol; R_F 0·10 in S_3) was dissolved in pyridine (300 ml) and the solution was treated portionwise with benzoyl chloride (140 g; 1 mol) under external ice-cooling. The mixture was kept at room temperature overnight, taken down under diminished pressure, and the residue treated with methanol (50 ml) and diluted with chloroform (1000 ml). The solution was washed with water (200 ml), dilute (1 : 10) hydrochloric acid (up to the acid reaction), water (200 ml), saturated aqueous sodium hydrogen carbonate (two 100 ml portions), and water again (200 ml), dried over anhydrous magnesium sulfate, filtered, and the filtrate evaporated under diminished pressure. The residual oil was heated in 50% aqueous formic acid (200 ml) at 100°C for 1 h; as shown by thin-layer chromatography in S_2, the reaction was quantitative (R_F value of the starting compound, 0·30; R_F of the product, 0·05). The mixture was evaporated under diminished pressure, the residue dissolved in chloroform (500 ml), and the solution washed with water, four portions of saturated aqueous sodium hydrogen carbonate, and water again (100 ml each), dried over anhydrous magnesium sulfate, filtered, and the filtrate evaporated under diminished pressure. The residue was dissolved in pyridine (300 ml) and the solution treated with benzoyl chloride (121 g; 86 mmol) under external ice-cooling. The mixture was kept at room temperature overnight, treated with methanol (50 ml), and processed analogously to the above first benzoylation. The resulting mixture of anomers (R_F 0·70 in S_2) was crystallised from ethanol (easy formation of oversaturated solutions). Yield, 40 g (17·7%) of

1,2,3,5-tetra-O-benzoyl-α-D-xylofuranose, m.p. 165°C (ethanol) (reported[14], m.p. 165—166°C), $[\alpha]_D^{20}$ +154·3° (*c* 1; dimethylformamide). ^{1}H-NMR spectrum: 4·62 (d, 2 H, $J_{5,4} = J_{5',4} = 5·0$) 2 H_5; 5·07 (m, 1 H) H_4; 5·94 (dd, 1 H, $J_{2,1} = 4·4$, $J_{2,3} = 6·0$) H_2; 6·21 (dd, 1 H, $J_{3,2} = 6·0$, $J_{3,4} = 6·5$) H_3; 6·94 (d, 1 H, $J_{1,2} = 4·4$) H_1; and 7·25—8·15 (m, 20 H) arom. protons. The mother liquor afforded a mixture of anomers (120 g; 52%).

1-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)pyrimidin-2-one (*Va*)

A solution of 1,2,3,4-tetra-O-acetyl-β-D-ribofuranose[15] (8·0 g; 25 mmol) in 1,2-dichloroethane (100 ml; dried over phosphorus pentoxide) was saturated at 0° with hydrogen chloride, kept at room temperature for 2 days, and evaporated under diminished pressure. The residue was coevaporated with four 50 ml portions of toluene under analogous conditions, the final residue dissolved in acetonitrile (50 ml), and the solution treated with compound *III* (5 g; 30 mmol). The whole was refluxed with stirring for 8 h, evaporated under diminished pressure, the residue dissolved in chloroform (100 ml), the solution washed with two 50 ml portions of water, dried over anhydrous magnesium sulfate, filtered, and the filtrate evaporated under diminished pressure. The residue was chromatographed on a column of silica gel in chloroform. The product-containing fractions (*Va*, R_F 0·29 in S_4) were pooled, evaporated, and the residue dried under diminished pressure. Yield, 7·0 g (79%) of the amorphous compound *Va*, $[\alpha]_D^{25}$ +49·5° (*c* 0·5; dimethylformamide). For $C_{15}H_{18}N_2O_8$ (354·3) calculated: 50·84% C, 5·12% H, 7·91% N; found: 50·47% C, 4·98% H, 7·35% N. ^{1}H-NMR spectrum: 2·08 + 2·12 + 2·13(3 × s, 3 × 3 H) acetyl group; 4·10—4·55 (m, 3 H), $H_{4'}$ + 2 $H_{5'}$; 5·20—5·60 (m, 2 H) $H_{2'}$ + $H_{3'}$; 6·07 (d, 1 H, $J_{1',2'} = 3·0$) $H_{1'}$; 6·39 (dd, 1 H, $J_{5,6} = 7·0$, $J_{5,4} = 4·0$) H_5; 8·02 (dd, 1 H) H_6; 8·63 (dd, 1 H, $J_{4,5} = 4·0$, $J_{4,6} = 2·5$) H_4. R_F value, 0·29 in S_4.

1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)pyrimidin-2-one (*Vb*)

The solution of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (25 mmol) was converted to the halogenose analogously to the case *Va*. The residue was dissolved in acetonitrile (70 ml), the solution treated with compound *III* (5 g; 30 mmol), and the whole refluxed with stirring for 4 h. The mixture was evaporated under diminished pressure, the residue dissolved in chloroform (200 ml), the solution washed with water (50 ml), dried over anhydrous magnesium sulfate, filtered, and the filtrate evaporated under diminished pressure. The residue was crystallised from ethanol and light petroleum (until turbid) to afford 10·5 g (78%) of compound *Vb*, m.p. 154°C (reported[4], m.p. 152—155°C), $[\alpha]_D^{25}$ +9·5° (*c* 0·5; dimethylformamide). Thin-layer chromatography in S_3: R_F 0·42 (identical with an authentic specimen). ^{1}H-NMR spectrum: 4·80 (m, 3 H) $H_{4'}$ + 2 $H_{5'}$; 5·86 (m, 2 H) $H_{2'}$ + $H_{3'}$; 6·22 (dd, 1 H, $J_{5,6} = 7·0$, $J_{5,4} = 4·0$) H_5; 6·39 (d, 1 H, $J_{1',2'} = 3·0$) $H_{1'}$; 7·20—7·65 and 7·80—8·15 arom. protons; 8·05 H_6 (overlapped by arom. protons); 8·58 (br t, 1 H, $J_{4,5} = 4·0$, $J_{4,6} = 2·0$) H_4.

1-(2,3,5-Tri-O-acetyl-β-D-xylofuranosyl)pyrimidin-2-one (*Vc*)

The above crude 1,2,3,5-tetra-O-acetyl-D-xylofuranose (8·0 g; 25 mmol) was converted to the halogenose analogously to the case *Va*. A mixture of the resulting product, acetonitrile (70 ml), and compound *III* (5·0 g; 30 mmol) was refluxed for 7 h and then processed analogously to the preparation of compound *Va*. Yield, 4·5 g (51%) of the amorphous compound *Vc*; R_F in S_4, 0·29. For $C_{15}H_{18}N_2O_8$ (354·3) calculated: 50·84% C, 5·12% H, 7·91% N; found: 50·53% C, 5·33% H, 7·73% N. Optical rotation: $[\alpha]_D^{25}$ +41·9° (*c* 0·5; dimethylformamide).

1-(2,3,5-Tri-O-benzoyl-β-D-xylofuranosyl)pyrimidin-2-one (*Vd*)

A solution of the above 1,2,3,5-tetra-O-benzoyl-β-D-xylofuranose (14·2 g; 25 mmol) in 1,2-dichloroethane (50 ml) was treated with 35% hydrogen bromide in acetic acid (50 ml), the mixture kept at room temperature for 1 h, evaporated under diminished pressure, the residue coevaporated with three 50 ml portions of toluene, and the final residue dissolved in acetonitrile (70 ml). Compound *III* (5·0 g; 30 mmol) was then added to the solution, the whole refluxed with stirring for 5 h, evaporated, and the residue dissolved in chloroform (200 ml). The solution was washed with two 50 ml portions of water, dried over anhydrous magnesium sulfate, filtered, the filtrate evaporated, and the residue chromatographed on silica gel in chloroform. The product-containing fractions (R_F in S_3, 0·25) were pooled, evaporated, and the residue crystallised from ethanol to afford 9·0 g (67%) of compound *Vd*, m.p. 101—103°C, $[\alpha]_D^{25}$ + 148·9° (*c* 0·5, dimethylformamide). For $C_{30}H_{24}N_2O_8$ (540·5) calculated: 66·66% C, 4·47% H, 5·18% N; found: 66·02% C, 4·48% H, 5·04% N. ^{1}H-NMR spectrum: 4·45—4·90 (m, 2 H) 2 H_5; 4·90—5·10 (m, 1 H) $H_{4'}$; 5·80 (m, 2 H) $H_{2'}$ + $H_{3'}$; 6·20 (br s, 1 H, $J_{1',2'}$ = 1·0) $H_{1'}$; 6·40 (dd, 1 H, $J_{5,4}$ = 4·0, $J_{5,6}$ = 7·0) H_5; 8·41 (dd, 1 H, $J_{6,5}$ = 7·0, $J_{6,4}$ = 3·0) H_6; 8·68 (m, 1 H) H_4; 7·20—8·20 (m, 15 H) arom. protons. R_F value in S_3, 0·42.

1-(2,3,4-Tri-O-benzoyl-β-D-ribopyranosyl)pyrimidin-2-one (*Ve*)

A solution of 1,2,3,4-tetra-O-benzoyl-β-D-ribopyranose[16,17] (14·0 g; 25 mmol) in 1,2-dichloroethane (50 ml) was treated with 30% hydrogen bromide in acetic acid (50 ml), the whole kept at room temperature for 1 h, and evaporated under diminished pressure. The residue was coevaporated with four 50 ml portions of toluene under analogous conditions and dissolved in acetonitrile (70 ml). Compound *III* (5·0 g; 30 mmol) was then added, the whole refluxed for 5 h, and processed analogously to the preparation of compound *Vd*. Yield, 3·6 g (27%) of compound *Ve*, m.p. 216—217°C (ethanol); $[\alpha]_D^{20}$ −38·2° (*c* 0·5; dimethylformamide); R_F value in S_3, 0·42. For $C_{30}H_{24}N_2O_8$ (540·5) calculated: 66·66% C, 4·47% H, 5·18% N; found: 66·92% C, 4·43% H, 5·26% N. ^{1}H-NMR spectrum: 4·20—4·50 (m, 2 H) 2 $H_{5'}$; 5·48 (dd, 1 H; $J_{2',3'}$ = 3·0, $J_{2',1'}$ = = 9·5) $H_{2'}$; 5·58 (m, 1 H; $J_{4',3'}$ = 2·5, $J_{4',5'}$ = 6·0, $J_{4',5''}$ = 10·0) $H_{4'}$; 6·31 (t, 1 H, $J_{3',2'}$ = 3·0, $J_{3',4'}$ = 2·5) $H_{3'}$; 6·36 (dd, 1 H; $J_{5,4}$ = 4·0, $J_{6,5}$ = 7·0) H_5; 6·78 (d, 1 H; $J_{1',2'}$ = 9·5) $H_{1'}$; 7·96 (dd, 1 H; $J_{6,5}$ = 7·0, $J_{6,4}$ = 2·5) H_6; 8·53 (dd, 1 H; $J_{4,5}$ = 4·0, $J_{4,6}$ = 2·5) H_4; 7·20—7·70 (m, 9 H) and 7·75—8·25 (m, 6 H) arom. protons.

1-(2,3,5,6-Tetra-O-benzoyl-β-D-glucopyranosyl)pyrimidin-2-one (*Vf*)

A solution of 1,2,3,5,6-penta-O-benzoyl-α-D-glucopyranose[17] (15·5 g; 22 mmol) in 1,2-dichloroethane (50 ml) was treated with 30% hydrogen bromide in acetic acid (50 ml), the mixture stirred at room temperature for 1 h, evaporated under diminished pressure, and the residue coevaporated with four 50 ml portions of toluene. A mixture of the final residue, acetonitrile (50 ml), and compound *III* (3·5 g; 21 mmol) was then refluxed for 8 h, and processed analogously to the preparation of compound *Vd*. Yield, 6·7 g (48%) of compound *Vf* which does not melt up to 260°C (ethanol); $[\alpha]_D^{20}$ + 62·4° (*c* 0·5; dimethylformamide). For $C_{38}H_{30}N_2O_{10}$ (674·6) calculated: 67·65% C, 4·48%H, 4·15% N; found: 68·03% C, 4·32% H, 4·32% N. ^{1}H-NMR spectrum: 4·35—4·70 (m, 3 H) $H_{5'}$ + 2 $H_{6'}$; 5·73 (t, 1 H; $J_{2',1'}$ = 9·0, $J_{2',3'}$ = 10·0) $H_{2'}$; 5·85 (*m*, 1 H) $H_{4'}$; 6·15 (t, 1 H; $J_{3',2'}$ = $J_{3',4'}$ = 10·0) $H_{3'}$; 6·42 (dd, 1 H; $J_{5,6}$ = 7·0, $J_{5,4}$ = 4·0) H_5; 6·58 (d, 1 H; $J_{1',2'}$ = = 9·0) $H_{1'}$; 8·03 (dd, 1 H); $J_{6,5}$ = 7·0, $J_{6,4}$ ~ 2·0) H_6; 8·52 (m, 1 H) H_4; 7·15—7·60 (m, 12 H) and 7·70—8·15 (m, 8 H) arom. protons.

1-(β-D-Xylofuranosyl)pyrimidin-2-one (*Ib*)

A solution of compound *Vc* (1·4 g; 4 mmol) in 0·05M methanolic sodium methoxide (20 ml) was kept at room temperature overnight, neutralised with Dowex 50X 8 (H^+) ion exchange resin, filtered, and the resin washed with methanol. The filtrate and washings were combined and evaporated under diminished pressure to afford 0·9 g (98·5%) of the amorphous compound *Ib*, homogeneous on chromatography in S_1 (R_F of *Ib*, 0·69; R_F of *Ia*, 0·67) and electrophoresis ($E_{urd} = 0·90$). UV spectrum (water): λ_{max} 308 nm (ε_{max} 5000). For $C_9H_{12}N_2O_5$ (228·2) calculated: 47·36% C, 5·30% H, 12·28% N; found: 47·12% C, 5·48% H, 12·56% N.

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