SYNTHESIS OF THE HILBERT–JOHNSON GLYCOSYLATION PRODUCTS BY OTHER METHODS*

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2-Deoxyribofuranosylations of 4-methoxy-2(1*H*)-pyrimidinone (*I*) and its 5-methyl derivative *II* were performed by the silylation and mercuri procedures leading exclusively to anomeric nucleosides, and the steric course was examined. Ribofuranosylation and glucopyranosylation when performed according to the mercuri process, lead to mixtures of N^1- and O^2-glycosyl derivatives; the steric course is explained by involvement of the subsequent O → N transglycosylation.

In connection with investigations on utilization of the Hilbert–Johnson reaction as a complementary nucleosidation method, attention has been paid to the preparation of versatile Hilbert–Johnson products by some other procedures such as the silylation and mercuri process. In systematic investigations on the silylation method, Wittenburg[1] also used 5-methyl-4-ethoxy-2(1*H*)-pyrimidinone, the glycosylation of which affords nucleosides in fair yields. Glycosylations of 4-alkoxy-2(1*H*)-pyrimidinones by the mercuri procedure were reported by other authors[2–4].

The preparation of protected 1-glycosyl-4-methoxy-2(1*H*)-pyrimidinones was performed with the use of 4-methoxy-2(1*H*)-pyrimidinone (*I*) and its 5-methyl derivative *II* as the starting material. In 2-deoxyribofuranosylations according to the silylation method, the pyrimidinones *I* and *II* were converted into the 4-methoxy-2-trimethylsilyloxypyrimidines *III* and *IV*, resp., which were treated with one equivalent of 3,5-di-O-*p*-toluyl-2-deoxy-D-ribofuranosyl chloride (*V*) in acetonitrile in the presence of mercuric acetate. Within several minutes at room temperature, the pyrimidine *III* afforded a 45% yield of nucleosides *VI* and *VIII* in the anomeric ratio α/β equal to 0·8. From the pyrimidine *IV*, the nucleosides *VII* and *IX* (anomeric ratio, 0·75) were obtained in 57% yield. In both cases, the yields of anomeric pairs are higher and the anomeric ratios are more favourable with respect to the formation of the β-anomer than in 2-deoxyribofuranosylations of 2,4-dimethoxypyrimidines in the presence of mercuric salts[5]; similar results have been reported by Wittenburg[1].

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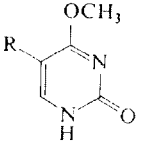
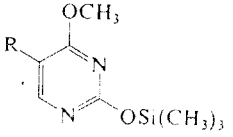
2-Deoxyribofuranosylations of pyrimidinones *I* and *II* by the mercuri process in toluene or acetonitrile at room temperature afford fair yields of anomeric nucleosides, the ratio of which is similar to that of nucleosides obtained by the silylation method.

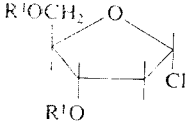
In the following glycosylations of the chloromercuri salts of pyrimidinones *I* and *II*, the character of products was strongly dependent upon the polarity of the solvent. Thus in poorly polar toluene, an equimolar mixture of 4-methoxy-2(1*H*)-pyrimidinone chloromercuri salt and the benzoylated D-ribofuranosyl chloride *X* afforded a mixture of the O^2-ribofuranosyl derivative *XI* and N^1-ribofuranosyl derivative *XIII* while in the



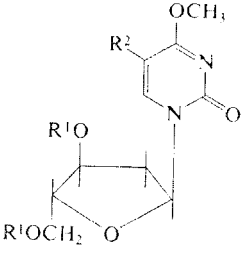
I, R = H
II, R = CH_3



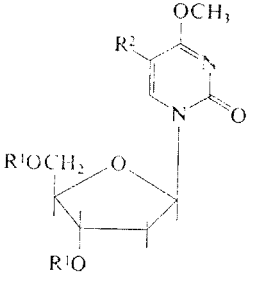
III, R = H
IV, R = CH_3



V

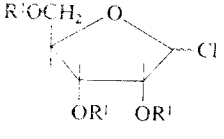


VI, R^2 = H
VII, R^2 = CH_3

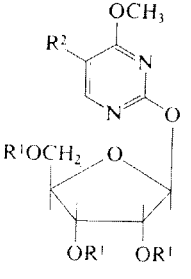


VIII, R^2 = H
IX, R^2 = CH_3

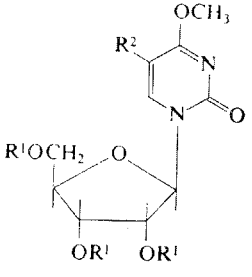
In formulae *V*—*IX*, R^1 = *p*-$CH_3C_6H_4CO$



X



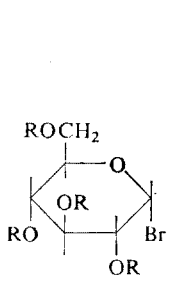
XI, R^2 = H
XII, R^2 = CH_3



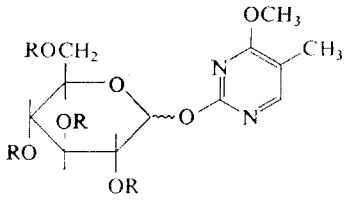
XIII, R^2 = H
XIV, R^2 = CH_3

In formulae *X*—*XIV*, R^1 = C_6H_5CO

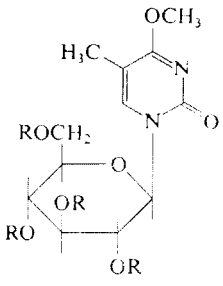
dipolar acetonitrile only *XIII* was obtained. Ribofuranosylation of the pyrimidinone *II* chloromercuri salt occurred analogously; the ribofuranoside *XII* was obtained by reaction in toluene only. An appreciable excess (500%) of the pyrimidinone *II* chloromercuri salt was necessary in both solvents to obtain the ribofuranoside *XII* as the main product. Glucopyranosylation of 5-methyl-4-methoxy-2(1*H*)-pyrimidinone by the mercuri process afforded a mixture of the O^2-glucopyranosyl derivative *XVI* and N^1-glucopyranosyl derivative *XVII* both in toluene and acetonitrile.



XV



XVI



XVII

In formulae *XV*—*XVII*, R = CH_3CO

The course of ribofuranosylations of 4-methoxy-2(1*H*)-pyrimidinone (*I*) and its 5-methyl derivative *II* performed according to the mercuri process is analogous to the reaction of isomeric 4-benzyloxy-6(1*H*)-pyrimidinones[6]. In ribofuranosylations of pyrimidinones by the mercuri process, their ambident anion or a complex with the corresponding Lewis acid is assumed to participate (*cf.*[7]). Regardless the polarity of the solvent, substitutions take place on the more electronegative center of the ambident anion in reactions obeying the S_N1 mechanism; in our case, a primary formation of the O-ribofuranosyl derivatives should be expected while the isomeric N-ribofuranosyl derivatives should be formed by the subsequent O → N transribofuranosylation. The primary formation of the O^2-ribofuranosyl derivatives was proved by performance of the reaction with a great excess of the pyrimidinone *II* chloromercuri salt, *i.e.*, under conditions which markedly suppress the O → N transribofuranosylation; a similar evidence has been presented in glycosylations of 4-alkoxy-6(1*H*)-pyrimidinones. The primary formation of glycosides appears as a characteristic feature in the preparation of pyrimidine nucleosides by the mercuri process. As inferred from numerous papers, glycosylations of aglycones derived from other heterocyclic systems proceed similarly.

The solvent polarity effect on composition of glycosylation mixtures asserts itself in the subsequent O → N transglycosylation. As inferred from our earlier investiga-

tions[8], the O → N transribofuranosylation of for example 4-benzyloxy-6-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyloxy)pyrimidine is strongly dependent on the polarity of the solvent. In acetonitrile with a marked ionisation effect as solvent, the concentration of the ribosylium cation (derived from the halogenose *X*) as the glycosylation agent proper is obviously higher than concentration of the dissolved salt (especially when equimolar amounts of reaction components are used); consequently, the O-ribofuranosylation and the otherwise subsequent O → N transribosylation may proceed simultaneously.

The course of O → N transglycosylations has been some time ago interpreted[8] in terms of an analogy of the Hilbert–Johnson glycosylation, *i.e.*, as an intermolecular process. Our idea has been later confirmed by results of mixed O → N transglycosylations[4]. Another contribution to this problem may be regarded in transformation of 5-methyl-4-methoxy-2-(2,3,4,6-tetra-O-acetyl-D-glucopyranosyloxy)pyrimidine (*XVI*) into the N^1-ribofuranosyl derivative *XIV* by the action of the halogenose *X* in acetonitrile in the presence of mercuric acetate. Furthermore, the O → N transribofuranosylation of ribofuranosides *XI* and *XII* afforded a high yield of nucleosides *XIII* and *XIV* under otherwise analogous conditions. All these results favour a similar mechanism in glycosylations of pyrimidine bases by the mercuri process and the Hilbert–Johnson method. Similar conclusions have been recently reported by Fox and coworkers in a comprehensive survey[7].

As it may be inferred from comparison of glycosylations of pyrimidines *I* and *II* under analogous conditions, the subsequent O → N transglycosylation asserts itself particularly in the case of reactive glycosides. In view of the very easy conversion of 2-deoxyribofuranosides to nucleosides, they are difficult to isolate as intermediates. Only in a single case the isolation was accomplished, namely with anomeric 2-(3,5-di-O-*p*-toluyl-2-deoxy-D-ribofuranosyloxy)pyridines[9]. The ribofuranosides undergo readily the O → N transribofuranosylation while a competitive anomerisation may take place in the case of glucopyranosides under analogous conditions. Composition of glycosylation mixtures may be explained (regardless the obvious effect of the solvent polarity) by the different stability of the glycosidic bond as well as by the different reactivity of the corresponding glycosylium cations in the course of the O → N transglycosylation.

In the preparation of pyrimidinones *I* and *II*, the known procedure was modified[10]; this modification has been several times used in these Laboratories (see *e.g.*[11]).

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block). Analytical samples were dried at 20°C/0·1 Torr for 10 h. NMR spectra were recorded on a Varian HA-100 spectrometer in deuteriochloroform. Chromatographies were performed on neutral alumina (Brockmann activity II–III).

4-Methoxy-2(1*H*)-pyrimidinone (*I*)

A solution of 2,4-dimethoxypyrimidine (2·80 g; 20·0 mmol) in acetyl chloride (15 ml) was kept at room temperature for 2 days, evaporated, the residue coevaporated with two 20 ml portions of toluene, and finally dissolved in 1M methanolic sodium methoxide (25 ml). The mixture was kept at 45°C for 1 h, neutralised with acetic acid, evaporated under diminished pressure, and the residue extracted with three 20 ml portions of boiling chloroform. The extracts were combined, evaporated, the residue crystallised from methanol, and the mother liquors processed as usual. Yield, 57% of the pyrimidinone *I*, m.p. 215–216°C, undepressed on admixture with a product[12] of the acidic cleavage of 2,4-dimethoxypyrimidine. For $C_5H_6N_2O_2$ (126·1) calculated: 47·62% C, 4·80% H, 22·21% N; found: 47·87% C, 4·88% H, 22·12% N.

Chloromercuri salt. A solution of the pyrimidinone *I* (1·26 g; 10·0 mmol) in 0·5M-NaOH (20 ml) was added to a hot solution of mercuric chloride (2·72 g; 10·0 mmol) in water (50 ml). The precipitate was collected with suction and washed with two 30 ml portions of water to afford 3·49 g (97%) of the required salt. For $C_5H_5ClHgN_2O_2$ (361·2) calculated: 7·76% N; found: 7·43% N.

5-Methyl-4-methoxy-2(1*H*)-pyrimidinone (*II*)

Analogously to *I*, there was obtained 82% of the pyrimidinone *II*, m.p. 225–227°C (methanol); reported[10], m.p. 220–221°C.

Chloromercuri salt. Analogously to the salt of compound *I*, there was obtained 94% of pyrimidinone *II* chloromercuri salt. For $C_6H_7ClHgN_2O_2$ (375·2) calculated: 7·47% N; found: 7·11% N.

Reaction of 4-Methoxy-2-trimethylsilyloxypyrimidine (*III*) with 3,5-Di-O-*p*-toluyl-2-deoxy-D-ribofuranosyl Chloride (*V*)

A mixture of the pyrimidinone *I* (252 mg; 2·0 mmol), hexamethyldisilazane (4 ml), and ammonium sulfate (15 mg) was refluxed for 2 h and the resulting solution evaporated under diminished pressure. The residue was coevaporated with two 10 ml portions of toluene and finally dissolved in acetonitrile (50 ml). To a solution (5 ml) of the crude silyl derivative *III*, there was added the halogenose *V* (78 mg; 0·20 mmol) and mercuric acetate (38 mg; 0·12 mmol). The mixture was stirred at room temperature for 10 min, decomposed with methanol (1 ml), and evaporated under diminished pressure. The residue was coevaporated with two 10 ml portions of benzene and finally chromatographed on a thin layer (17 × 43 cm) of loose alumina in 3 : 1 benzene–ethyl acetate. The UV-extinguishing band (R_F 0·25) afforded 20% of the α-anomer *VI*, m.p. 198–199°C, undepressed on admixture with an authentic specimen[13]. Work-up of the R_F 0·45 band yielded 25% of the β-anomer *VIII* identical with the known[13] nucleoside.

Reaction of 5-Methyl-4-methoxy-2-trimethylsilyloxypyrimidine (*IV*) with the Halogenose *V*

The pyrimidinone *II* was converted to the silyl derivative *IV* analogously to the transformation of *I* to *III*. A mixture of the crude silyl derivative *IV* (0·20 mmol), halogenose *V* (80 mg; 0·20 mmol), mercuric acetate (32 mg; 0·10 mmol), and toluene (5 ml) was stirred at room temperature for 2 h, washed with 25% aqueous potassium iodide (3 ml), dried, and evaporated. The residue was chromatographed on a thin layer (17 × 40 cm) of loose alumina in 1 : 1 benzene–ethyl acetate. The absorbing bands (R_F, 0·20 and 0·41) were processed as usual to afford 24·5% of the α-anomer *VII*, m.p. 165–167°C, and 32·5% of the β-anomer *IX*, m.p. 137–138°C; the anomers were identical

with those obtained from 5-methyl-2,4-dimethoxypyrimidine by the Hilbert–Johnson reaction[13]. Under otherwise identical conditions but in acetonitrile as solvent, there were obtained 22% of compound *VII* and 30% of compound *IX*.

Reaction of the Pyrimidinone *I* Chloromercuri Salt with the Halogenose *V*

A mixture of the title salt (362 mg; 1·00 mmol), halogenose *V* (399 mg; 1·025 mmol), and toluene (10 ml) was stirred at room temperature for 30 min, washed with 30% aqueous potassium iodide (5 ml), dried, and evaporated. The residue was chromatographed on a thin layer (18 × × 48 cm) of alumina in 3 : 1 benzene–ethyl acetate to afford 18% of the α-anomer *VI* and 22% of the β-anomer *VIII*. In acetonitrile as solvent, the reaction mixture was maintained for 3 min to afford after the usual work-up 21% of compound *VI* and 29% of compound *VIII*.

Reaction of the Pyrimidinone *II* Chloromercuri Salt with the Halogenose *V*

A mixture of the title chloromercuri salt (375 mg; 1·00 mmol), halogenose *V* (395 mg; 1·01 mmol), and acetonitrile (10 ml) was maintained at room temperature for 5 min, evaporated, the residue dissolved in benzene (10 ml), the solution washed with 30% aqueous potassium iodide (10 ml), dried, and evaporated. Thin-layer chromatography on loose alumina afforded the anomeric nucleosides *VII* and *IX* in 22% and 27% yields, resp.

Reaction of the Pyrimidinone *I* Chloromercuri Salt with 2,3,5-Tri-O-benzoyl-D-ribofuranosyl Chloride (*X*)

A suspension of the pyrimidinone *I* chloromercuri salt (360 mg; 1·00 mmol) in a 0·10M toluene solution of the halogenose *X* (10 ml; 1·0 mmol) was refluxed for 6 min and passed through a column of alumina (30 g) in 4 : 1 benzene–ethyl acetate (150 ml). The effluent was evaporated and the residue chromatographed on a thin layer (18 × 48 cm) of loose alumina in 3 : 1 benzene–ethyl acetate. The R_F 0·5 band afforded 18% of the N^1-ribofuranosyl derivative *XIII*, m.p. 200 to 201°C (ethanol), undepressed on admixture with an authentic sample[14]. Rechromatography of the R_F 0·8 band in 20 : 1 benzene–ethyl acetate afforded 60% of the O^2-ribofuranosyl derivative *XI*, m.p. 131–132°C (ether). NMR spectrum: δ 6·74 (s, 1′-H), 5·95–6·15 (m, 2′-H, 3′-H), 4·55 to 4·95 (m, 4′-H, 2 × 5′-H), 3·89 (s, CH_3O), 6·40 (d, 5-H, $J_{5,6}$ = 6·0 c.p.s.) and 8·17 p.p.m. (d, 6-H). For $C_{31}H_{26}N_2O_9$ (570·5) calculated: 65·26% C, 4·59% H, 4·91% N; found: 65·59% C, 4·80% H, 4·65% N. In refluxing acetonitrile (5 min), there was obtained under otherwise analogous conditions only the nucleoside *XIII* in 72% yield.

Reaction of the Pyrimidinone *II* Chloromercuri Salt with the Halogenose *X*

A. A mixture of the chloromercuri salt of compound *II* (125 mg; 0·33 mmol) and the 0·10M toluene solution of the halogenose *X* (3·3 ml; 0·33 mmol) was refluxed for 10 min, cooled down, evaporated, and the residue chromatographed on a thin layer (17 × 43 cm) of loose alumina in 7 : 2 benzene–ethyl acetate. Work-up of the less mobile band (R_F 0·4) afforded the nucleoside *XIV* (45%), m.p. 137–139°C, undepressed on admixture with an authentic specimen[14]. The more mobile band (R_F 0·7) yielded 12% of the amorphous ribofuranoside *XII*; NMR spectrum: δ 6·71 p.p.m. (d, 1′-H, $J_{1',2'}$ = 0·5 c.p.s.). For $C_{32}H_{28}N_2O_9$ (584·6) calculated: 65·75% C, 4·83% H, 4·79% N; found: 65·98% C, 5·10% H, 4·56% N.

B. A suspension of the chloromercuri salt (2·25 g; 6·00 mmol) in 0·10M toluene solution of the halogenose *X* (10·0 ml; 1·00 mmol) was refluxed for 5 min and processed analogously to paragraph *A*. Yield, 77% and 7% of the O^2- and N^1-ribofuranosyl derivatives *XII* and *XIV*, resp.

C. A mixture of the chloromercuri salt (189 mg; 0·50 mmol) and the 0·10M acetonitrile solution of halogenose *X* (5·0 ml; 0·50 mmol) was refluxed for 6 min, cooled down, and evaporated. Thin-layer chromatography of the residue on loose alumina in 4 : 1 benzene–ethyl acetate yielded 75% of the nucleoside *XIV*.

D. A mixture of excess chloromercuri salt (1·12 g; 3·00 mmol) and the acetonitrile (5 ml) solution of the halogenose *X* (0·50 mmol) was refluxed and processed analogously to paragraph *C* to yield a mixture of the ribofuranoside *XII* (59%) and the nucleoside *XIV* (24%).

Reaction of the Pyrimidinone *II* Chloromercuri Salt with 2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl Bromide (*XV*)

A mixture of the title salt (375 mg; 1·00 mmol) and halogenose *XV* (410 mg; 1·00 mmol) in toluene (15 ml) was refluxed for 50 min, cooled down, diluted with ethyl acetate (5 ml), applied to a column of alumina (30 g) and eluted with 1 : 1 benzene–ethyl acetate (160 ml). The eluate was evaporated and the residue chromatographed on a thin layer (18 × 48 cm) of loose alumina in the above solvent mixture to afford 8% of the O^2-glucopyranosyl derivative *XVI* and 17% of the N^1-glucopyranosyl derivative *XVII*. Compound *XVI* melts between 95—105°C (ether–light petroleum) and its NMR spectrum indicates the presence of both anomers. For $C_{20}H_{26}N_2O_{11}$ (470·4) calculated: 51·06% C, 5·57% H, 5·95% N; found: 50·61% C, 5·86% H, 6·30% N. Compound *XVII* exhibits m.p. 150—152°C (ethanol) and the following NMR spectrum: δ 6·05 p.p.m. (d, 1′-H, $J_{1',2'} = 9{\cdot}0$ c.p.s.). For $C_{20}H_{26}N_2O_{11}$ (470·4) calculated: 51·06% C, 5·57% H, 5·95% N; found: 50·98% C, 5·70% H, 6·04% N. In acetonitrile as solvent, there were obtained 11% of the glucopyranoside *XVI* and 25% of the nucleoside *XVII*.

O → N Transribofuranosylation of the Ribofuranoside *XI* and *XII*

A mixture of the ribofuranoside *XI* (57 mg; 0·10 mmol), mercuric chloride (27 mg; 0·10 mmol), and a 0·05M acetonitrile solution of the halogenose *X* (2 ml; 0·10 mmol) was refluxed for 10 min, evaporated, and the residue chromatographed on a thin layer of loose alumina in 3 : 1 benzene–ethyl acetate to afford the nucleoside *XIII* in 67% yield. The analogous O → N transribofuranosylation of the ribofuranoside *XII* yielded 72% of the nucleoside *XIV*.

Mixed O → N Transglycosylation of the Glucopyranoside *XVI*

A mixture of the glucopyranoside *XVI* (47 mg; 0·10 mmol), mercuric chloride (27 mg; 0·10 mmol), and a 0·05M solution of the halogenose *X* (2·0 ml; 0·10 mmol) was refluxed for 12 min and processed analogously to the preceding paragraph. Yield, 68% of the nucleoside *XIV*, m.p. 137 to 138°C.

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