on silica gel with chloroform–methanol (20:1) as an eluent. N^1,N^3-Disubstitution product 1,3-bis(*N*-butyl-5-oxopyrrolidin-2-yl)-5-fluorouracil: colorless prisms; mp 135–137 °C (ethyl acetate–hexane); R_f 0.62; IR (Nujol) 3080, 1691, 1655 cm^{-1}; NMR (Me_2SO-d_6) δ 0.6–1.7 (m, 14 H), 1.7–3.7 (m, 12 H), 5.8–6.2 (m, 1 H), 6.2–6.6 (m, 1 H), 8.02 (d, J = 6.0 Hz, 1 H); UV (MeOH) λ_{max} 272 nm (ϵ 7930). Anal. Calcd for $C_{20}H_{29}FN_4O_4$: C, 58.81; H, 7.15; F, 4.65; N, 13.72. Found: C, 58.84; H, 7.20; F, 4.49; N, 13.64. N^1-Substitution product **3l**: colorless needles (ethyl acetate–hexane); R_f 0.53; IR (Nujol) 3190, 3150, 3040, 1735, 1695, 1675, 1661 cm^{-1}; UV (MeOH) λ_{max} 268 nm (ϵ 9160). Anal. Calcd for $C_{12}H_{16}FN_3O_3$: C, 53.52; H, 5.99; F, 7.06; N, 15.61. Found: C, 53.54; H, 6.02; F, 6.92; N, 15.47. N^3-Substitution product 3-(*N*-butyl-5-oxopyrrolidin-2-yl)-5-fluorouracil: colorless powder; mp 155.5–156.5 °C (ethyl acetate–hexane); R_f 0.48; IR (Nujol) 3060, 1726, 1664, 1645 cm^{-1}; NMR (Me_2SO-d_6) δ 0.6–1.7 (m, 7 H), 1.8–3.6 (m, 6 H), 6.2–6.6 (m, 1 H), 7.83 (d, J = 5.6 Hz, 1 H), 10.3–11.5 (br, 1 H); UV (MeOH) λ_{max} 271 nm (ϵ 6730). Anal. Calcd for $C_{12}H_{16}FN_3O_3$: C, 53.52; H, 5.99; F, 7.06; N, 15.61. Found: C, 53.46; H, 6.03; F, 7.15; N, 15.57.

Compound 8. To a stirred solution of compound **2m** (1.49 g, 6 mmol) and $(Me_3Si)_2$-5-FU (1.37 g, 5 mmol) in 30 mL of acetonitrile was added dropwise a solution of $SnCl_4$ (0.46 mL, 4 mmol) in 2 mL of dichloromethane at −40 °C under vigorous stirring. The reaction temperature was raised gradually to −10 °C for 30 min, and then the reaction was quenched by the same procedure as that described in the preparation of compound **3a**. The filtrate was evaporated to dryness in vacuo. To the residue was added 30 mL of chloroform, and the insoluble materials were filtered off. The filtrate was evaporated to dryness in vacuo. The crystals were triturated with isopropyl ether and collected by filtration. Recrystallization from ethanol gave colorless needles of pure compound 8: yield 1.27 g (73%); mp 144 °C dec; IR (Nujol) 3370, 3170, 1728, 1712, 1528 cm^{-1}; NMR (Me_2SO-d_6) δ 1.8–2.6 (m, 4 H), 3.55 (s, 3 H), 5.05 (s, 2 H), 5.7–6.1 (m, 1 H), 7.31 (s, 5 H), 7.77 (d, 1 H, J = 7.0 Hz), 7.9–8.4 (m, 1 H), 11.69 (br s, 1 H); UV (MeOH) λ_{max} 268 nm (ϵ 8130). Anal. Calcd for $C_{17}H_{18}FN_3O_6$: C, 53.82; H, 4.78; F, 5.01; N, 11.08. Found: C, 53.66; H, 4.66; F, 4.96; N, 11.04.

Compound 12. To a stirred solution of compound 11 (0.56 g, 3 mmol) and $(Me_3Si)_2$-5-FU (0.69 g, 2.5 mmol) was added dropwise a solution of $SnCl_4$ (0.14 mL, 1.25 mmol) in 2 mL of dichloromethane at 5–10 °C. After the stirring was continued for 2 h at the same temperature, the reaction mixture was treated by the same procedure as described above to afford compound 12 in 62% yield. Recrystallization from ethanol gave colorless needles of pure compound 12: mp 156–157 °C; IR (Nujol) 3160, 3100, 3020, 1723, 1692, 1664, 1632 cm^{-1}; NMR (Me_2SO-d_6) δ 1.0–3.0 (m, 8 H), 3.22 (s, 3 H), 4.8–5.3 (m, 1 H), 4.97 and 5.31 (AB q, 2 H, J = 13.5 Hz), 7.94 (d, 1 H, J = 6.8 Hz), 11.84 (s, 1 H); UV (MeOH) λ_{max} 267 nm (ϵ 8730). Anal. Calcd for $C_{12}H_{16}FN_3O_4$: C, 50.52; H, 5.65; F, 6.66; N, 14.73. Found: C, 50.41; H, 5.60; F, 6.66; N, 14.70.

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Registry No. **1e**, 80953-60-2; **1f**, 1696-20-4; **1g**, 1468-28-6; **1h**, 6976-49-4; **1i**, 5809-41-6; **1j**, 3653-39-2; **1l**, 80953-61-3; **1m**, 80953-62-4; **1n**, 675-20-7; **1o**, 105-60-2; **2a**, 63050-21-5; **2b**, 68471-61-4; **2c**, 69352-22-3; **2d**, 66893-75-2; **2e**, 80953-63-5; **2f**, 77873-72-4; **2g**, 80953-64-6; **2h**, 80953-65-7; **2i**, 63050-23-7; **2j**, 73269-87-1; **2k**, 63853-74-7; **2l**, 80953-66-8; **2m**, 80953-67-9; **2n**, 63853-82-7; **2o**, 63853-81-6; **3a**, 73269-74-6; **3b**, 73269-75-7; **3c**, 73269-79-1; **3d**, 73269-82-6; **3e**, 73269-83-7; **3f**, 77948-25-5; **3g**, 77937-94-1; **3h**, 77937-95-2; **3i**, 80953-68-0; **3j**, 80953-69-1; **3k**, 74991-05-2; **3l**, 74991-07-4; **3n**, 74991-10-9; **3o**, 74991-11-0; **4**, 80953-70-4; **5**, 80953-71-5; **7**, 80953-72-6; **8**, 80953-73-7; **9**, 2556-73-2; **10**, 10291-81-3; **11**, 80953-74-8; **12**, 80953-75-9; $(Me_3Si)_2$-5-Fu, 17242-85-2; *N*-glycyl-2-(5-fluorouracil-1-yl)pyrrolidine hydrochloride, 80953-76-0; 1,3-bis(*N*-butyl-5-oxo-pyrrolidin-2-yl)-5-fluorouracil, 80953-77-1; 3-(*N*-butyl-5-oxopyrrolidin-2-yl)-5-fluorouracil, 80953-78-2; **6**, 40760-22-3; *N*-formyl-2-(5-fluorouracil-1-yl)pyrrolidine, 73269-73-5; *N*-benzoyl-2-(5-fluorouracil-1-yl)pyrrolidine, 73269-78-0.

Mechanism of Formation of Cyclic Urea Nucleosides. Evidence for an O- to N-Transglycosylation

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The mechanism of formation of cyclic urea nucleosides under mercury catalysis (HgO and $HgBr_2$) was studied by using persilylated tetramethyleneurea (**1**) as a model aglycon. Evidence is presented to suggest that the desired N-nucleoside **9** arises via an intermolecular O → N transglycosylation rather than by a direct N-nucleosidation mechanism. Mercuric oxide catalyzes the formation of the intermediate silylated O-nucleoside **4** which later in the presence of $HgBr_2$ rearranges to the more thermodynamically stable N-nucleoside **9**. This rearrangement is brought about by either $HgBr_2$ or red HgO provided that there is excess of halogenose **2** and that the intermediate O-nucleoside remains silylated. When red HgO is employed, the required $HgBr_2$ is generated by the reaction between HgO and the $(CH_3)_3SiBr$ liberated during the condensation reaction. The intermediate O-nucleoside **5** was isolated and characterized. When resilylated to **4**, it rearranged rapidly to **9** under identical reaction conditions. The use of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl iodide (**2b**) instead of the corresponding bromo sugar (**2a**) shortened the reaction time, and in the presence of red HgO it gave exclusive formation of N-nucleoside **9**. The overall yield of this two-step transformation is 31%, and the desired compound **9** is easily separated by chromatographic means.

In the synthesis of pyrimidine nucleosides, the silylated version of the Hilbert–Johnson reaction, catalyzed by stannic chloride and other Friedel–Crafts catalysts, has become the method of choice.[1,2] This method has also proven useful with nonaromatic aglycons such as 6-oxadihydrouracil[3] and 5-methyl-5-azadihydrouracil.[4] How-

(1) Vorbruggen, H. F.; Niedballa, U.; Krolikiewicz, K.; Bennua, B.; Hofle, G. In "Chemistry and Biology of Nucleosides and Nucleotides"; Harmon, R. E., Robins, R. K., Townsend, L. B., Eds; Academic Press: New York, San Francisco, London, 1978; pp 251–265.

(2) Vorbruggen, H. In "Nucleoside Analogues. Chemistry, Biology and Medical Applications"; Walker, R. T., De Clercq, E., Eckstein, F., Eds.; Plenum Press: New York and London, 1979; pp 35–69.

(3) Berkowitz, P. T.; Robins, R. K.; Dea, P.; Long, R. A. *J. Org. Chem.* 1976, *41*, 3128.

(4) Skulnick, H. *J. Org. Chem.* 1978, *43*, 3188.

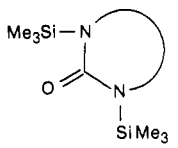
0022-3263/82/1947-1712$01.25/0

Table I. Reaction Conditions for the Synthesis of O- and N-Nucleosides: RX + 1 → 5 + 9

entry[e]	X of R[a]-X	RX/1 ratio	solvent	catalyst	time, h	TLC[b] (1 h) 5 (O-nucl)	TLC[b] (1 h) 9 (N-nucl)	yield,[c] % 5 (O-nucl)	yield,[c] % 9 (N-nucl)
1	Br	1.25	benzene		14				
2	Br	1.25	benzene	$HgBr_2$	14				
3	Br	1.25	benzene	HgO(r)	14	major	minor	38	13
4	Br	1.25	benzene	HgO(r), $HgBr_2$	14	major	minor	10	40
5	Br	1.25	benzene	HgO(y)	14	major		51	
6	Br	2.0	benzene	HgO(r), $HgBr_2$	14	minor	major	traces	23
7	Br	2.0	benzene	HgO(r)	4		major		22
8	Br	1.0	benzene	HgO(r)	4	major	minor	33	7
9	Br	2.0	benzene	HgO(y)	14	major	minor	15	4
10	Br	1.25	CH_3CN	HgO(r), $HgBr_2$	14				
11	I	2.0	benzene	HgO(r)	2	major[d]		traces	31
12	I	2.0	benzene	HgO(y), $HgBr_2$	2	major[d]	traces	17	9

[a] R = 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl. [b] Silica gel, methanol (4%) in methylene chloride. [c] In cases where mixtures were obtained, the yields were calculated by NMR. These yields are based on the starting aglycon 1. [d] These observations were made after the addition of 1 equiv of halogenose. [e] The temperature was 80 °C in all cases.

ever, as we reported recently, this procedure failed when applied to a series of saturated cyclic ureas which could not form the trimethylsilyloxy derivatives after silylation.[5] That this was the reason for its failure in those cases was shown by demonstrating the exclusive formation of the nonnucleophilic *N,N*-bis(trimethylsilyl) form (structure I).[5] Since no trimethylsilyloxy form (structure II) was



I

II

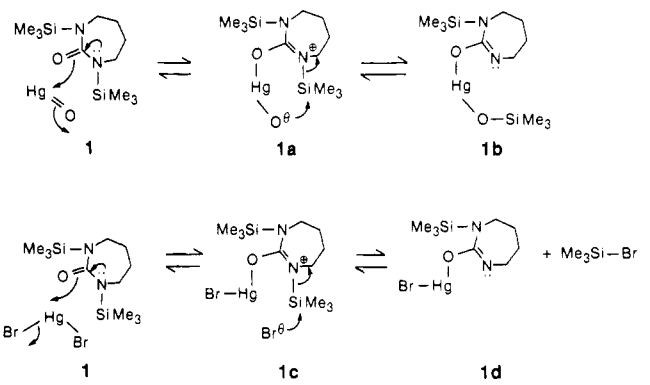
formed, no Hilbert–Johnson product could be isolated. This synthetic difficulty was circumvented by the use of mercury catalysts which produced useful yields of the desired target nucleosides.[5] The method initially appeared to be an extension of Wittenburg's procedure for nucleoside synthesis.[6] However, the mechanism of the reaction proceeded in a different fashion due to the nonaromatic nature of the aglycons employed here. The mechanism of nucleoside formation and the role of the mercury catalysts are the subject of the present paper.

Results and Discussion

Our initial efforts involved the search for a catalyst that would convert the N,N,-bis-silylated urea (I) into a reactive form similar to structure II and capable of reacting nucleophilically with a halo sugar. The rationale for the selection of the mercury catalysts is depicted in Scheme I, where the expected transformations are indicated by using silylated tetramethyleneurea (1) as an example.

Under Wittenburg's conditions, interaction between the silylated pyrimidines and the mercury catalysts is not necessary because the aromatic persilylated pyrimidines already exist in the nucleophilically reactive O-silylated form.[6-9] This observation is supported by the fact that in such cases the reaction works even in the absence of the mercury catalysts whose function is merely to facilitate the

Scheme I



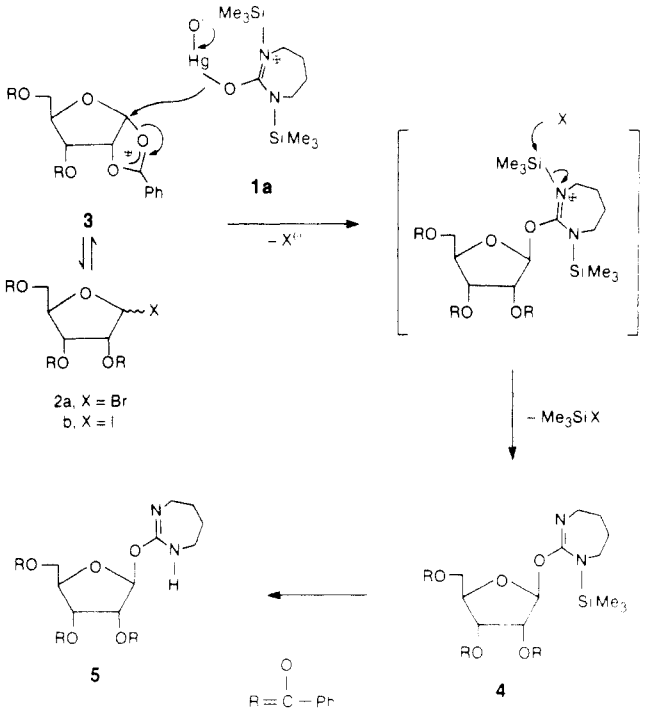
dissociation of the halogenose to the more reactive 1,2-acyloxonium cation.[6,10,11]

Concerning the use of the silylated, cyclic, nonaromatic ureas under $HgO/HgBr_2$ catalysis, the two initial questions appeared to be (a) how important was the catalytic mixture to the reaction's outcome and (b) which of the two mercury compounds was the more critical ingredient in the reaction. As seen in Table I (entry 1), no reaction took place between the halogenose and the persilylated cyclic urea 1 in the absence of the catalytic mixture. As to the second question, it became apparent that $HgBr_2$ alone (Table I, entry 2) was incapable of catalyzing the reaction, thus precluding the sort of interaction with the silylated urea indicated in Scheme I (structures **1c–d**). With red mercuric oxide, however, the reaction was successful. Besides the desired N-nucleoside product (**9**), an even higher yield of the O-nucleoside **5** was obtained (Table I, entry 3). When the two catalysts were combined, the yield of the desired N-nucleoside increased at the expense of that of the O-nucleoside (Table I, entry 4). The O-nucleoside appears to be the kinetically favored product which in the presence of a Lewis acid catalyst such as $HgBr_2$ is converted to the more thermodynamically stable N-nucleoside. Of the several ureas studied,[5] the seven-membered tetramethyleneurea was the only one in which the catalytic mixture afforded isolable yields of the O-nucleoside. It was for this reason that we selected it for our mechanistic studies.

These preliminary experiments indicated that HgO was critical for the first stage of the reaction leading to the

(5) Liu, P. S.; Marquez, V. E.; Driscoll, J. S.; Fuller, R. W.; McCormack, J. J. *J. Med. Chem.* **1981**, *24*, 662.
(6) Wittenburg, E. *Chem. Ber.* **1968**, *101*, 1095.
(7) Wittenburg, E.; Etzold, G.; Langen, P. *Chem. Ber.* **1968**, *101*, 494.
(8) Wittenburg, E. *Chem. Ber.* **1968**, *101*, 1614.
(9) Wittenburg, E. *Chem. Ber.* **1968**, *101*, 2132.
(10) Nishimura, T.; Iwai, I. *Chem. Pharm. Bull.* **1964**, *12*, 352, 357.
(11) Holy, A. *Collect. Czech. Chem. Commun.* **1977**, *42*, 902.

Scheme II



O-nucleoside and that $HgBr_2$ was necessary for a possible O → N transglycosylation as the second and final transformation. This became more evident when we studied the effects of the different types of mercuric oxides on the ratio of O- and N-nucleosides. As mentioned previously, when red HgO was used as the sole catalyst, the O-nucleoside was the major product, although a significant amount of N-nucleoside was still formed. In contrast, when yellow HgO was present, only the O-nucleoside was isolated (Table I, entry 5). This experiment confirmed that HgO catalyzed the first step of the reaction leading to the O-nucleoside exclusively. Contrary to Wittenburg's reaction with aromatic aglycons, the interaction between the catalyst (HgO) and the silylated urea in this reaction appears critical, and, of all the equilibrium forms shown in Scheme I, structure **1a** is the most likely to lead to the O-nucleoside as shown in Scheme II.

Other mechanisms can be envisioned; however, a concerted nucleophilic attack of **1a** on the halogenose **2** or on the 1,2-acyloxonium intermediate **3** is in better agreement with the heterogeneous nature of the catalyst and with the fact that the reaction works only in nonpolar solvents (vide infra). Still, a puzzling question remains. How does the N-nucleoside arise from the red HgO catalyzed reaction? It could originate by the direct attack of an intermediate such as **1b**, or, alternatively, it could arise from an O → N interconversion catalyzed by a Lewis acid. Early TLC observations of the reaction mixture gave no evidence of direct N-nucleoside formation. As was the case when $HgBr_2$ and HgO were used in combination, the O-nucleoside was formed first (Table I, entries 3 and 4), and part of it was gradually transformed to the N-nucleoside as the reaction progressed. The required Lewis acid catalyst could be provided by a side reaction occurring between Me_3SiX (X = Br), liberated in the second step of the condensation, and mercuric oxide (Scheme III).[6]

Scheme III

$$2Me_3SiX + HgO \rightarrow Me_3SiOSiMe_3 + HgX_2$$

Since the reaction shown in Scheme III should not reside exclusively with red HgO, it is difficult to understand the differences observed between red and yellow mercuric oxide. Our hypothesis is that since yellow HgO is the more reactive form (finer particles),[12] the halogenose is rapidly consumed to form the O-nucleoside, and none of the halogenose necessary for the O → N transglycosylation (vide infra) is left. On the contrary, reaction in the presence of red HgO is much slower (TLC observations at different time intervals), and under such conditions the generated O-nucleoside finds sufficient halogenose to react in order to undergo the HgX_2-catalyzed intermolecular transformation. In support of this explanation, the N-nucleoside **9** was also formed in the reaction catalyzed by yellow HgO when an excess of halogenose was provided (Table I, entry 9).

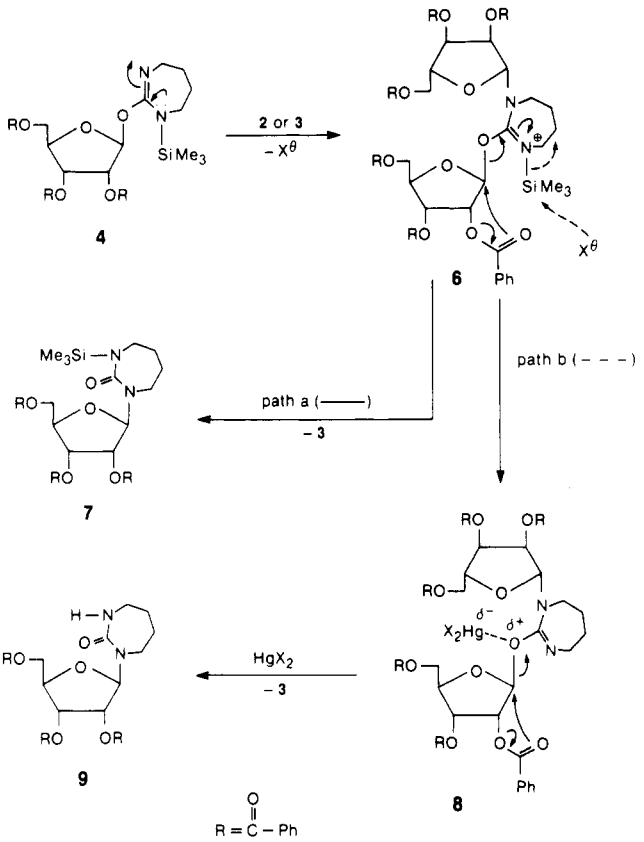
The intermediacy of the O-nucleoside is an interesting aspect of this reaction since normally O-nucleosides are not formed under Wittenburg's conditions when applied to the synthesis of pyrimidine nucleosides.[13,14] Wittenburg's reaction, as mentioned previously, is really a Hilbert–Johnson reaction where N-nucleosides are expected to form directly from the silylated aromatic pyrimidines. Indeed, only rarely have O-nucleosides been observed in a Hilbert–Johnson reaction.[15-17] The formation of urea N-nucleosides through intermediate O-nucleosides by our method is perhaps more similar to the heavy-metal method of pyrimidine nucleoside synthesis.[18] In such method, the ambident nucleophilic nature of the aromatic pyrimidine salts is responsible for both O- and N-nucleoside formation,[18-20] and, under the reaction conditions, the N-nucleosides arise through an intermolecular O → N transglycosylation.[21,22]

In order to confirm that the O-nucleoside **5** was an intermediate in our reaction, we set out to isolate it and rearrange it to the N-nucleoside **9**. The O-nucleoside **5** was isolated from the yellow HgO catalyzed reaction as a white foam which gave a positive Fehling reaction as expected for an O-nucleoside. In addition, **5** gave a NMR spectrum with nearly first-order resolution. The salient feature is the low-field doublet of the anomeric proton with a coupling constant of 4 Hz. The spectrum of the N-nucleoside, on the contrary, is quite different, with the anomeric proton appearing at a slightly higher field with a larger coupling constant (6 Hz). The NMR spectra of the isolated mixtures, therefore, proved very useful in determining product ratios by simple integration in the instances where both O- and N-nucleoside were obtained.

When the O-nucleoside **5** was refluxed in benzene in the presence of $HgBr_2$, the reaction produced only decomposed materials with disappearance of the starting O-nucleoside. The same result was observed when the reaction was performed in the presence of an extra equivalent of halogenose. Only when the isolated O-nucleoside was resilylated to **4** and reacted in the presence of excess halogenose **2** did the rearrangement occur rapidly under $HgBr_2$ catalysis (10–30 min). These experiments argue in favor of an intermolecular O → N transglycosylation which re-

(12) Cotton, F. A.; Wilkinson, G. In "Basic Inorganic Chemistry"; Wiley: New York, London, Sidney, Toronto, 1976; pp 324–359.
(13) Wittenburg, E. *Collect. Czech. Chem. Commun.* **1971**, *36*, 246.
(14) Lupke, U.; Seela, F. *Chem. Ber.* **1979**, *112*, 799.
(15) Hilbert, G. E.; Rist, C. E. *J. Biol. Chem.* **1937**, *117*, 1937.
(16) Visser, D. W., Goodman, I.; Dittmer, K. *J. Am. Chem. Soc.* **1948**, *70*, 1926.
(17) Lemieux, R. V.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2214.
(18) Watanabe, K. A.; Holemberg, D. H.; Fox, J. J. *J. Carbohydr., Nucleosides, Nucleotides* **1974**, *1*, 1.
(19) Wagner, G. *Z. Chem.* **1966**, *6*, 367 and references therein.
(20) Thacker, D.; Ulbricht, T. L. V. *J. Chem. Soc. C* **1968**, 333.
(21) Prystas, M. *Collect. Czech. Chem. Commun.* **1975**, *40*, 1786.
(22) Prystas, M.; Sorm, F. *Collect. Czech. Chem. Commun.* **1969**, *34*, 331, 2316.

Scheme IV



quires previous alkylation of the O-nucleoside 4 by the halogenose (Scheme IV). In agreement with an intermolecular reaction, the silylated O-nucleoside 4 failed to produce any N-nucleoside in the absence of halogenose when either $HgBr_2$ or red HgO was employed. Under the right conditions, the rearrangement occurred just as rapidly with red HgO, indicating that sufficient amounts of $HgBr_2$ were produced from the reaction between Me_3SiBr and HgO (Scheme III). We were able to show that half the equimolar amount of $HgBr_2$ (approximately half of the amount recommended in Wittenburg's procedure) was sufficient to catalyze the O → N interconversion starting with the O-nucleoside **5**. From the stoichiometry of the reactions (Schemes III and IV), this is precisely the amount of $HgBr_2$ that would be produced under mercuric oxide catalysis.

The role of the $HgBr_2$ catalyst in the O → N transglycosylation appears to be twofold. First, it facilitates initial formation of the more reactive 1,2-acyloxonium cation (**3**),[18,23] and second, it catalyzes the splitting of the bis-*O,N*-glycoside **8** to the desired N-nucleoside **9**. As seen in Scheme IV, the bis-*O,N*-glycoside cation **6** could also split spontaneously after alkylation due to the good leaving character of the positively charged ring (path a). Alternatively, $(CH_3)_3SiBr$ could be liberated first (path b), leading to a neutral species (**8**), which would require Lewis acid catalysis to rearrange to the N-nucleoside. The latter mechanism is favored by the fact that in the presence of red HgO, which also induces the O → N interconversion, prior elimination of Me_3SiX must take place in order to form the necessary HgX_2. The Lewis acid catalyst appears essential in this step since in its absence a thermal O → N rearrangement was not observed even with an excess of halogenose after 60 min of reflux. From Scheme IV it is evident that after the bis-*O,N*-glycoside splits by either path, an extra reactive 1,2-acyloxonium cation **3** is generated. Thus, theoretically, a very small amount of halogenose would be required as a primer for the reaction. This appears to be the case. On a small scale (0.5 mmol) the O-nucleoside is converted to the N-nucleoside in about 40% yield when either 1 or 0.25 equiv of halogenose is employed. However, since intermolecular rearrangements are concentration dependent, the overall reaction works best with a twofold excess of the halogenose with respect to the silylated tetramethyleneurea **1** to assure maximum O → N conversion (Table I, entries 6, 7, and 11). With other cyclic ureas, a 1.25 times excess of halogenose was sufficient for the transformation, indicating that possibly their O-nucleosides are less stable than that formed with **1**.[5]

The next entries in Table I indicate the crucial nature of excess halogenose. In the case of red HgO, a twofold excess of sugar halide (entry 7) produced exclusively the N-nucleoside. When only 1 equiv was used (entry 8), the yield of N-nucleoside dropped, and the O-nucleoside became the major product. Conversely, when yellow HgO was used with about a 1.25 times excess of halogenose, exclusive formation of O-nucleoside was observed (entry 5), but with a twofold excess of halogenose (entry 9) O-nucleoside was not exclusive, and some N-nucleoside was formed. Under these circumstances, it is interesting to observe that as the yield of N-nucleoside increased (entries 6 and 7), the overall yield decreased. In addition, when a twofold excess of halogenose was used, the reaction times became shorter (entries 7 and 11). As we observed previously, tetramethylene urea (seven-membered aglycon) was the ideal candidate for this mechanistic study, but it had the disadvantage from a synthetic viewpoint in that it gave the lowest yields of N-nucleoside. With other cyclic ureas (five- and six-membered), the yields with this methodology were as high as 75%.[5]

Throughout the entire study, benzene was used exclusively as the reaction solvent, mainly because it was the solvent commonly used in Wittenburg's procedure. When the reaction was performed in polar solvents such as CH_3CN, only traces of products were observed on TLC, and the reaction gave mostly numerous uncharacterized decomposition products (Table I, entry 10). Contrary to the O → N transglycosylations with aromatic aglycons,[18,21,24,25] this reaction and rearrangement are favored by nonpolar solvents. When the O-nucleoside **5** was silylated to **4** and the rearrangement attempted as described previously, but with CH_3CN as the solvent, no O → N transformation was observed, and only decomposition products were formed. Other Lewis acid catalysts such as $SnCl_4$ failed to promote the O → N interconversion on starting with the silylated O-nucleoside **4** even in nonpolar solvents such as benzene. In summary, the overall mechanism would appear to be (a) a concerted attack of **1a** on the halogenose **2** followed by (b) an O → N intermolecular transglycosylation catalyzed by $HgBr_2$. The O → N reaction requires excess of halogenose, and it only occurs when the intermediate O-nucleoside is silylated.

In an effort to improve the yields of the reaction and to simplify the synthesis, we turned our attention to the use of the more reactive halogenose **2b**. This glycosyl iodide can be conveniently prepared by the adaptation of a recent procedure developed by Tocik et al. which employs iodotrimethylsilane to convert 1-O-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose to the desired halogenose.[26]

(23) Helferich, B.; Zirner, J. *Chem. Ber.* **1962**, *95*, 2604.

(24) Rogers, G. T.; Ulbricht, J. L. V. *J. Chem. Soc. C* **1970**, 1109.
(25) Prystas, M. *Collect. Czech. Chem. Commun.* **1967**, *33*, 1813.
(26) Tocik, Z.; Earl, R. A.; Beranek, J. *Nucleic Acids Res.* **1980**, *8*, 4755.

The method overcomes the tedious preparation of the glycosyl bromide **2a** which has to be freshly prepared each time.[27] In addition to the fact that the yields of pure N-nucleoside were higher and reaction times shorter with the iodo sugar **2b** (Table I, entry 11), the method gave some additional information concerning the reaction mechanism which tended to confirm our hypothesis. Under these conditions the benzene solution containing the glycosyl iodide and excess $(CH_3)_3SiI$ could not come in contact with the red HgO catalyst unless the latter had previously reacted with the silylated urea for some time. This happened when the solution containing the glycosyl iodide was added too fast, allowing the excess of $(CH_3)_3SiI$ to react with HgO to form HgI_2. The required HgO catalyst was depleted, and the reaction mixture gradually turned dark as in the case when $HgBr_2$ was used alone (Table I, entry 2). In this instance the amount of N-nucleoside as observed by TLC was negligible. If the glycosyl iodide was added gradually to the refluxing mixture of HgO and the silylated urea over a 1-h period, the reaction worked well. Moreover, after the addition of only 1 equiv of glycosyl iodide, the product was exclusively the O-nucleoside. After the complete addition of 2 equiv of glycosyl iodide, the reaction required heating for 30 min for conversion to the N-nucleoside. Under these conditions red HgO became a useful overall catalyst with no further improvement observed if $HgBr_2$ was added as a cocatalyst. Similarly, a combination of yellow HgO and $HgBr_2$ (Table I, entry 12) offered no improvement in the yields of N-nucleoside **9**.

The experiments with the glycosyl iodide also helped elucidate the nature of the catalysis required for the O → N interconversion. Such transglycosylation also could have been efficiently catalyzed by traces of protic acids as reported by others.[28,29] Despite extensive azeotropic distillation of the bromo sugar **2a** with toluene, we had no assurance that traces of HBr were completely removed from the bromo sugar. It could be reasoned, however, that if protic acid were responsible for this rearrangement, differences would not have been observed between the two mercuric oxides in catalyzing the O → N transglycosylation step. Under the conditions generating the glycosyl iodide **2b**, there is no likelihood of HI being present, and, therefore, the O → N transglycosylation should be catalyzed by the Lewis acid HgI_2 which appears to be as efficient as $HgBr_2$.

Experimental Section

General Methods. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Specific rotations were measured in a 1-dm cell with a Perkin-Elmer Model 141 polarimeter. Proton NMR spectra were determined on Varian T-60 or HA-100D instruments. Chemical shifts are given as δ values with reference to Me_4Si. Elemental analyses were carried out by the NIAMDD, NIH, and by Galbraith Laboratories, Inc., Knoxville, TN. Columns for chromatography were packed with silica gel (Bio-Sil A, 200–400 mesh, Bio-Rad Laboratories) and eluted with mixtures of ethyl acetate–hexane. The methodology of Still et al.,[30] also known as flash chromatography, was used throughout. Thin-layer silica gel plates (250 μm) were purchased from Analtech, Inc.

General Procedure for the Condensation Reaction Using 2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl Bromide (2a). To a suspension of tetramethyleneurea (0.342 g, 3 mmol) stirred in dry acetonitrile (distilled over P_2O_5) at room temperature was added a sixfold excess (5 g, 19 mmol) of bis(trimethylsilyl)trifluoroacetamide (BSTFA). The mixture was stirred for 2 h at room temperature, and the excesses of reagent and solvent were removed in vacuo to leave a clear oil. The NMR spectrum revealed complete absence of NH signals. The oily persilylated tetramethyleneurea **1** was dissolved in 5 mL of dry benzene and added to a refluxing benzene (15 mL) suspension containing the catalyst(s) indicated in Table I ($HgBr_2$, 1.12 g; HgO, 1.12 g). After 10 min, a solution of the bromo sugar **2**[27] in benzene (10 mL), used in the molar ratio indicated in Table I, was rapidly added and refluxing continued for the time indicated (Table I). After cooling, the mixture was filtered through a bed of Celite, and the filter cake was washed with ethyl acetate. The combined organic filtrate and washings was extracted with solutions of saturated $NaHCO_3$ and water and then dried over anhydrous $MgSO_4$. The solution was then concentrated and purified on a silica gel column (200–400 mesh) by flash chromatography using ethyl acetate–hexane (3:2). In this solvent system both O-nucleoside **5** and N-nucleoside **9** migrated as a single band which was easily separable from the rest of faster moving unreacted sugar derivatives. In those instances where mixtures were obtained (Table I, entries 3, 4, 8, and 9), a TLC system consisting of a 4% methanol solution in methylene chloride allowed easy separation of the two spots. The slower moving spot corresponded to the O-nucleoside **5** (R_f 0.45), and the faster moving one corresponded to the N-nucleoside **9** (R_f 0.53). The relative yields were estimated from integration of the NMR signals corresponding to the anomeric protons of each isomer (Table I). When a single product was visualized in the methanol–methylene chloride system, it was isolated as a solid foam. From entries 6 and 11 (Table I) the N-nucleoside **9** was isolated and purified further by a second flash chromatography. The NMR and other physical properties agreed with those reported earlier by us; $[\alpha]^{23}_D$ −42° (*c* 0.102, $CHCl_3$). From entry 5 (Table I) the O-nucleoside **5** was isolated as a white amorphous foam: mp 62–70 °C; $[\alpha]^{23}_D$ +107.2° (*c* 0.109, $CHCl_3$). Anal. Calcd for $C_{31}H_{30}N_2O_8 \cdot 0.5H_2O$: C, 65.59; H, 5.32; N, 4.93. Found: C, 65.20; H, 5.49; N, 4.68.

General Procedure for the Condensation Reaction Using 2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl Iodide (2b). 2,3,5-Tri-*O*-benzoyl-1-*O*-acetyl-β-D-ribofuranose (3 g, 6 mmol) was dissolved in 20 mL of dry benzene and placed on an equilibrating dropping funnel. The funnel was kept in a nitrogen-filled glovebag and treated with 1.12 mL (8 mM) of iodotrimethylsilane. The solution was swirled occasionally and kept at room temperature for 8 min. The funnel was then placed on a 100-mL three-necked flask containing a refluxing benzene solution (30 mL) of the silylated tetramethyleneurea (Table I, entry 11) and the red mercury oxide (1.12 g) catalyst. The iodo sugar **2b** was added slowly to this mixture over the course of 1 h and refluxed further for the time shown in Table I. The workup and isolation procedure are identical with those of the previous experiment.

Conversion of O-Nucleoside 5 to the Corresponding N-Nucleoside 9. The O-nucleoside **5** (0.25 g, 0.45 mmol) was silylated in CH_3CN (3 mL) with 1 mL of BSTFA for 1 h at room temperature. The solvent was removed in vacuo and the remaining semisolid dissolved in 5 mL of benzene. To this solution were added $HgBr_2$ (0.09 g, 0.25 mmol) and 0.45 mmol of bromo sugar **2a** (1.80 mL of a 0.25 M solution in benzene), and the total volume was adjusted to 10 mL with benzene. This mixture was placed in a preheated bath (80 °C), and the reaction was followed by silica gel TLC plates developed with 4% methanol in methylene chloride. Samples were taken every minute for the first 10 min and then after 20 and 30 min, respectively. The starting bromo sugar (R_f 0.60) was observed throughout the reaction. Other faster moving spots were detected after the reaction started which corresponded to various decomposed sugar-derived materials. The O-nucleoside **5** (R_f 0.45) gradually disappeared, and after 6 min it was barely discernible. Formation of the N-nucleoside (R_f 0.53) became evident after 3 min and was the dominant spot at the end of 10, 20, and 30 min. From minutes 1–5 a new spot (R_f 0.39) was observed. It probably corresponded to the intermediate bis-*O*,*N*-glycoside **8**. The reaction mixture was purified as before by flash chromotography, and pure N-nucleoside **9** was isolated (0.105 g, 40%). When the reaction was performed with just 0.126 mmol of **2a**, it proceeded in an identical fashion, and 0.10 g (40%)

(27) Stevens, J. D.; Ness, R. K.; Fletcher, H. G. *J. Org. Chem.* **1968**, *33*, 1806.
(28) Schmidt, G.; Farkas, J. *Tetrahedron Lett.* **1967**, 4251.
(29) Schmidt, G.; Farkas, J. *Collect. Czech. Chem. Commun.* **1966**, *31*, 4442.
(30) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

of pure N-nucleoside 9 was isolated after flash chromatography. The reaction likewise proceeded similarly with 0.25 mmol of red HgO as the catalyst.

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Registry No. 1, 18023-41-1; **2a**, 16205-60-0; **2b**, 80963-16-2; **4**, 80963-17-3; **5**, 80963-18-4; **9**, 77249-70-8; $HgBr_2$, 7789-47-1; HgO, 21908-53-2; tetramethylene urea, 19055-93-7; 2,3,5-tri-*O*-benzoyl-1-*O*-acetyl-β-D-ribofuranose, 6974-32-9.

Total Synthesis of (±)-3-Deoxy-7,8-dihydromorphinone

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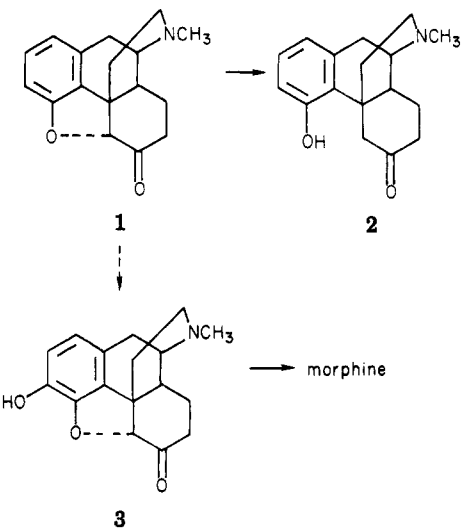
The total synthesis of (±)-3-deoxy-7,8-dihydromorphinone (1), starting from readily available [3,5-bis(benzyloxy)phenyl]acetic acid (4) is described. The amide 6, obtained from acid 4 and *m*-methoxyphenethylamine, was converted by Bischler–Napieralski cyclization to the dihydroisoquinoline hydrochloride 7. Birch reduction of 7 gave the dihydroxydihydroanisole 8, which was acid cyclized in situ and then converted to (±)-2,4-bis-[(methoxycarbonyl)oxy)]-17-(methoxycarbonyl)morphinan-6-one (10). The conversion of 7 to 10 was carried out without isolation of intermediates. Hydrolysis with THF/Et_2NH gave the 4-hydroxy compound 14. Reaction of 14 with cupric bromide followed by treatment with NaOH/$CHCl_3$ and hydrolysis gave 4,5-epoxy-2-hydroxymorphinan-6-one (16). The 2-oxygen function was removed by Li/NH_3 reduction of the phosphate ester 18 obtained by acylation of the ketal 17 with diethyl chlorophosphate. LAH reduction of the ketal 19 followed by acid hydrolysis gave the title compound (±)-3-deoxy-7,8-dihydromorphinone (1) in an overall yield (from 4) of 27%.

Our continuing interest in opioid chemistry and analgesics suggested to us that a total synthesis of (±)-3-deoxy-7,8-dihydromorphinone (1) will be of value, since it can be regarded as a key intermediate for carrying out further studies in this area. Thus, it can serve as a convenient source for the preparation of 4-hydroxymorphinanones, such as 2, which represent a relatively unexplored class of potent antinociceptive agents.[1,2] It can also potentially allow the synthesis of uniquely substituted morphine and morphinan structures and a study of their structure–activity relationships (SAR). In addition, it could lead to a novel synthesis of morphine (via 3) if a phenolic group could be successfully introduced at C-3. With these objectives in mind, we embarked on a total synthesis of 1. However, a recent communication by Hsu et al.,[3] who utilized the same materials and essentially the same strategy as ours (Grewe-type cyclization) for the synthesis of (±)-1, has prompted us to describe our own findings. Our synthesis differs clearly from theirs in the sequence and the method used for the removal of the 2-phenolic group and the formation of the 4,5-epoxy ring, for which we have devised a more efficient procedure. We describe in this paper the total synthesis of (±)-3-deoxy-7,8-dihydromorphinone (1) in an overall yield of 27% from readily available starting materials.

The basis of our synthesis strategy was the Grewe-type electrophilic cyclization of a (±)-1-benzylhexahydroisoquinoline[4] such as 8, which could be prepared from readily



available starting materials and which, upon acid cyclization, would furnish a single product 9, because of its symmetrical substitution in the benzyl radical. This dioxygenated morphinan 9, upon closure of the 4,5-epoxy bridge and removal of the 2-oxygen function, would then furnish the desired deoxydihydromorphinone (1). Hsu et al.[3] reached the same conclusion and used the same starting materials, but their intermediates and processes used were quite different from ours.

Our synthesis of the morphinan skeleton is shown in Scheme I. [3,5-Bis(benzyloxy)phenyl]acetic acid (4), prepared from 3,5-dihydroxybenzoic acid in six steps in an overall yield of 65%,[14] was condensed with *m*-meth-

(1) A. Manmade, H. C. Dalzell, J. F. Howes, and R. K. Razdan, *J. Med. Chem.*, **24**, 1437 (1981).

(2) (a) M. D. Rozwadowska, F. L. Hsu, A. E. Jacobson, K. C. Rice, and A. Brossi, *Can. J. Chem.* **58**, 1885 (1980); (b) F. L. Hsu, K. C. Rice, and A. Brossi, *Heterocycles*, **13**, 259 (1979); (c) J. Reden, M. F. Reich, K. C. Rice, A. E. Jacobson, A. Brossi, R. A. Streaty and W. Klee, *J. Med. Chem.* **22**, 256 (1979).

(3) F. L. Hsu, A. E. Jacobson, K. C. Rice, and A. Brossi, *Helv. Chim. Acta*, **63**, 2042 (1980).

(4) The problems associated with Grewe-type cyclization of (±)-1-benzylhexahydroisoquinolines substituted unsymmetrically, for the synthesis of various morphinans are well documented. See, for example, ref 5–13.

(5) (a) R. Grewe and A. Mondon, *Chem. Ber.*, **81**, 279 (1948); (b) R. Grewe, H. Fisher, and W. Fredrickson, *ibid.*, **100**, 1 (1967); (c) R. Grewe and W. Fredrickson, *ibid.*, **100**, 1550 (1967).

(6) G. C. Morrison, R. O. Waite, and J. Shavel, *Tetrahedron Lett.*, 4055 (1967).

(7) T. Kametani, T. Sugahara, H. Yagi, and K. Fukumoto, *Tetrahedron*, **25**, 3667 (1967).

0022-3263/82/1947-1717$01.25/0