Although the quantitative aspects of the phenomena are confused by the high instability of the "active" N_2 fixing species, the side reaction of O_2 with naphthalide, and the operation of a two-phase (gas–liquid) reaction, our results nevertheless demonstrate clearly, and for the first time, the nonbiological reaction of a compound with N_2 as a component of air.[7]

In fixation experiments with air, the general method described above was employed, and the active fixation agent (A) was prepared either under argon before exposure to air or under air from the beginning. In the former case yields of fixed ammonia were lower, probably because of the temporal instability of A: ~2% of ammonia was formed with air, as contrasted with ~6% with pure nitrogen, both experiments being carried out under otherwise virtually identical conditions with 4.0 equiv of sodium naphthalide.[8] When both preparation of A and reaction with N_2 were executed under air, ammonia yields of 21% (3 equiv of naphthalide) and 44% (10–12 equiv of naphthalide) were realized. In comparable experiments carried out with pure N_2, 43 and 71% yields, respectively, were observed.[9]

Acknowledgment. This research was supported financially by a National Institutes of Health grant (GM 13797).

(7) L. S. Nelson (*Science*, 148, 1594 (1965)) has reported partitioning of aerial N_2–O_2 in reaction with molten zirconium metal at *ca.* 3000 K.

(8) In this preparation of A, no naphthalide was present, as indicated by esr measurement (authors are grateful to Professor H. M. McConnell, Stanford University, for the determination).

(9) The structural nature of A remains undefined but is under investigation in these laboratories.

(10) Max Kade Foundation, Inc., Fellow, 1967–1968.

(11) National Science Foundation Fellow, 1966–present.

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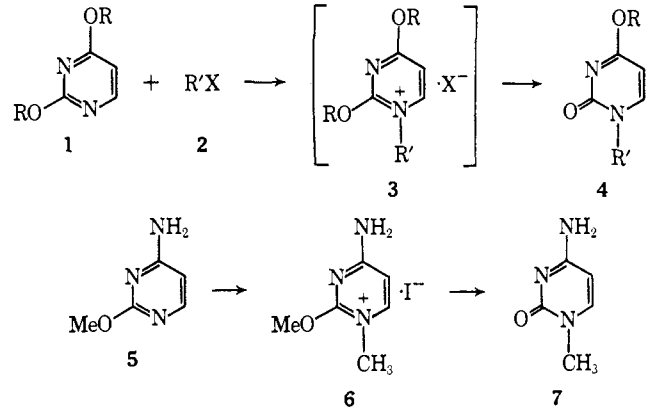
On the Hilbert–Johnson Procedure for Pyrimidine Nucleoside Synthesis

Sir:

We wish to report direct evidence for the presence of an intermediate glycosylpyrimidinium salt in the Hilbert–Johnson procedure for pyrimidine nucleoside synthesis and the extension of this procedure to a general method for the synthesis of 2-oxo-, 2-thio-, and 2-aminopyrimidine nucleosides of potential biochemical interest.

The Hilbert–Johnson precedure[1] has been an excellent method for the synthesis of various 2-oxopyrimidine nucleosides starting from a 2,4-dialkoxypyrimidine (**1**) and a protected glycosyl halide (**2**). Although the 1-substituted pyrimidinium salt **3** as an intermediate had not been detected, its existence had been suggested by the fact[4] that 4-amino-2-methoxypyrimidine (**5**) with methyl iodide gives the 1-methiodide **6** which, in turn, is converted to 1-methylcytosine (**7**).[2,3] The synthesis of 1-glycosylcytosines by the use of **5**, however, has not been successful (see Scheme I).

Scheme I



2,4-Diethoxypyrimidine (**1**, R = Et)[5] was treated with methyl iodide in acetonitrile at room temperature and the course of the reaction was followed by tlc. After 5 hr ether was added to furnish a precipitate (**3**, R = Et; R′ = Me; X = I), mp 56.5–58.5°, in *ca.* 35% yield. Prolongation of the reaction time afforded **4** (R = Et; R′ = Me) as the major product. The structure of **3** (R = Et; R′ = Me; X = I) was confirmed by elemental analysis (*Anal.* Calcd for $C_9H_{15}N_2O_2I$: C, 34.85; H, 4.88; N, 9.03. Found: C, 35.02; H, 4.98; N, 8.73), by uv and nmr spectra, and by its conversion to **4** (R = Et; R′ = Me) and then to 1-methyluracil by acid hydrolysis. By a similar method 2,4-diethoxy-5-methylpyrimidine[6,7] was converted to the corresponding 1-methiodide, mp 77.5–78°. *Anal.* Calcd for $C_{10}H_{17}N_2O_2I$: C, 37.05; H, 5.25; N, 8.61. Found: C, 37.17; H, 5.41; N, 8.33.

In the quaternary salt derivatives **3**, the 2-alkoxy group should be susceptible to substitution reactions, thus providing an extension of the Hilbert–Johnson reaction for nucleoside syntheses. In a model study, **3** (R = Et; R′ = Me; X = I) was rapidly converted to the known[8,9] 2,4-diaminopyrimidinium 1-methiodide by treatment with methanolic ammonia. When compound **1** (R = Et) was allowed to react with tri-O-benzoyl-D-ribofuranosyl chloride in acetonitrile for several days at 0–5° and the reaction mixture then treated with alcoholic ammonia, crude 2,4-diamino-1-(β-D-ribofuranosyl)pyrimidinium chloride (**8**) was obtained, identical with that afforded by an alternate route (see Scheme II).[10]

Attempts to introduce a thiono group on C-2 of **3** (R = Et; R′ = Me; X = I) by reaction of **3** with hydrogen sulfide resulted in the formation of **4** (R = Et; R′ = Me) which indicated that alkyl oxygen fission

(1) G. E. Hilbert and T. B. Johnson, *J. Am. Chem. Soc.*, **52**, 4489 (1930). For the recent reviews see ref 2 and 3.

(2) J. J. Fox and I. Wempen, *Advan. Carbohydrate Chem.*, **14**, 283 (1959).

(3) J. Pliml and M. Prystas, *Advan. Heterocyclic Chem.*, 8, 115 (1967).

(4) G. E. Hilbert, *J. Am. Chem. Soc.*, **56**, 190 (1934).

(5) G. E. Hilbert and T. B. Johnson, *ibid.*, **52**, 2001 (1930).

(6) W. S. Nickels and T. B. Johnson, *ibid.*, **52**, 4511 (1930).

(7) M. Roberts and D. W. Visser, *ibid.*, **74**, 668 (1952).

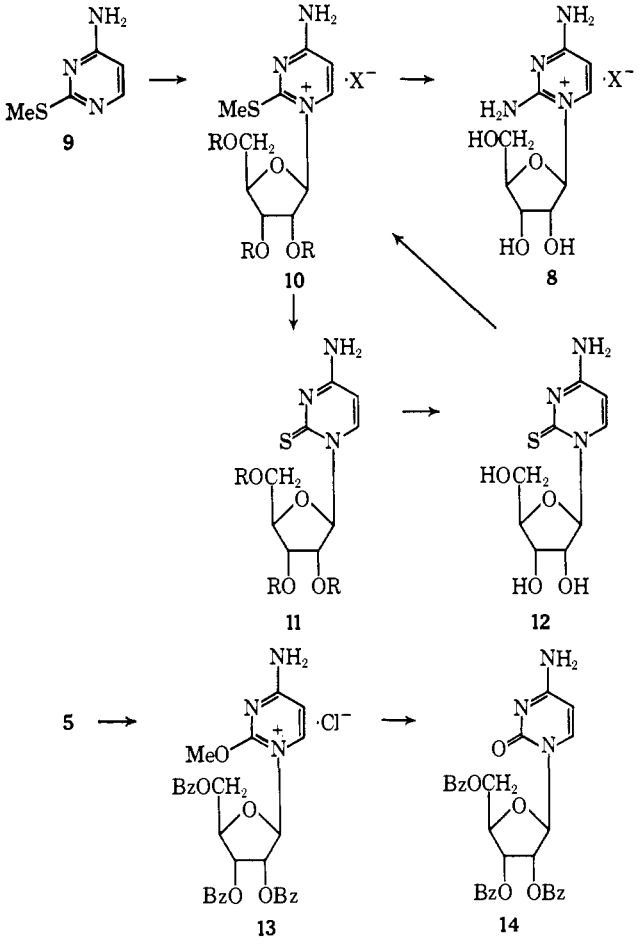
(8) D. J. Brown, E. Hoerger, and S. F. Mason, *J. Chem. Soc.*, 4035 (1955).

(9) D. J. Brown and N. W. Jacobsen, *ibid.*, 3172 (1962).

(10) The synthesis of 2,4-diamino-1-(β-D-arabinofuranosyl)pyrimidinium picrate and sulfate by anhydronucleoside procedure was recently reported [I. L. Doerr and J. J. Fox, *J. Org. Chem.*, **32**, 1462 (1967)].

had occurred. However, the desired 2-thiocytidine was obtained by treatment of 2-methylthio-4-aminopyrimidine (**9**)[9] with tri-O-benzoyl-D-ribosyl chloride in acetonitrile with a molecular sieve at 30°. A crude

Scheme II



ribosylpyrimidinium salt (**10**) was obtained which on reaction with H_2S in pyridine gave the tri-O-benzoate of 2-thiocytidine (**11**) in 40% over-all yield (*Anal.* Calcd for $C_{30}H_{25}N_3O_7S$: C, 63.03; H, 4.41; N, 7.35. Found: C, 62.95; H, 4.60; N, 7.43); mp 190–191°; $[\alpha]_D$ −27° (*c* 1.0, $CHCl_3$); uv λ_{max}^{EtOH} mμ (ε): 233 (49,900), 275 sh (19,000), 282 sh (18,000); $\lambda_{max}^{H^+}$ 233.5 (52,100), 278 (19,700). Debenzoylation of **11** afforded 2-thiocytidine (**12**) which was identical with an authentic sample prepared by an independent route,[11] thus establishing the β configuration. Methylation of **12** with methyl iodide gave a 4-amino-2-methylthio-1-(β-D-ribofuranosyl)pyrimidinium salt obtained as a crystalline chloride (**10**, R = H; X = Cl), mp 155–156° dec (*Anal.* Calcd for $C_{10}H_{16}N_3O_4SCl$: C, 38.75; H, 5.17; N, 13.57. Found: C, 38.89; H, 5.13; N, 13.34); uv $\lambda_{max}^{H_2O}$ mμ (ε) 246.5 (28,300), 275 sh (9000). Alkaline treatment converted **10** to cytidine. Treatment of **10** (R = H; X = I) with methanolic ammonia afforded **8** (X = I), mp 164.5–165° dec. (*Anal.* Calcd for $C_9H_{15}N_4O_4I$: C, 29.20; H, 4.08; N, 15.14. Found: C, 29.13; H, 4.36; N, 15.19); uv $\lambda_{max}^{H_2O}$ mμ (ε) 210.5 (36,100), 223 sh (8000); λ_{max}^{1NHCl} 212.5 (30,600), 223 sh (27,800), 266 sh (8000); λ_{max}^{1NNaOH} 228.5 (36,500), 291 (2800); $[\alpha]_D$ 5° (*c* 1.0, H_2O).

Though previous attempts[4] to utilize 4-amino-2-methoxypyrimidine in nucleoside synthesis were unsuccessful, we reinvestigated this reaction. Treatment of **5** with tri-O-benzoyl-D-ribosyl chloride in acetonitrile at 30° gave a syrup and a crystalline product. The latter was shown to be the hydrochloride salt of tri-O-benzoylcytidine (**14**), mp 202°. *Anal.* Calcd for $C_{30}H_{26}N_3O_8Cl$: C, 60.88; H, 4.43; N, 7.10. Found: C, 60.58; H, 4.45; N, 6.68. Debenzoylation of **14** with alcoholic ammonia gave cytidine. The syrup also contained appreciable amounts of **14** and some pyrimidinium salt (**13**) (as evidenced by tlc) which was gradually converted to **14**.

The 2-methylthio group provides an advantage over the 2-methoxy function in the Hilbert–Johnson reaction in that the reaction stops at the quaternization step to afford intermediates in which the 2 substituent may be replaced by other functions. This aspect provides an important extension of the Hilbert–Johnson reaction which was hitherto restricted to the synthesis of 2-oxopyrimidine nucleosides.

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(11) T. Ueda, Y. Iida, K. Ikeda, and Y. Mizuno, *Chem. Pharm. Bull.* (Tokyo), **14**, 666 (1966).

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