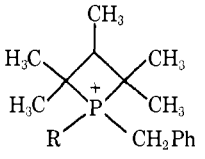
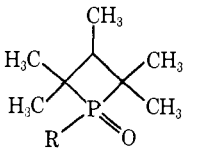
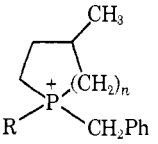
astereomers of the six-membered ring analog **9**[4] can now best be explained in terms of the operation of two simultaneous mechanisms, the "McEwen mechanism" leading to inverted product, and a mechanism of the type observed for the base decomposition of the diastereomers of **5** and **6** yielding the oxide of retained configuration.



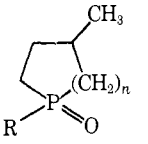
1, R = CH_3
2, R = Ph



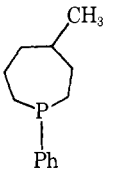
3, R = CH_3
4, R = Ph



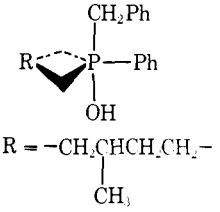
5, R = CH_3; $n = 1$
6, R = Ph; $n = 1$
9, R = Ph; $n = 2$
11, R = Ph; $n = 3$



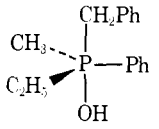
7, R = CH_3; $n = 1$
8, R = Ph; $n = 1$
10, R = Ph; $n = 2$
12, R = Ph; $n = 3$



13



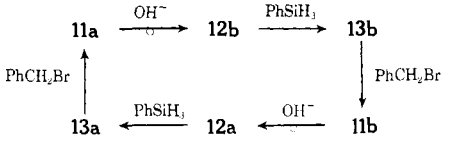
14, R = $-CH_2CHCH_2CH_2-$ (CH$_3$)



15

The stereochemical cycle shown in Scheme I was followed beginning with **11a**, estimated to be 92 ± 5% isomerically pure. Phenylsilane has previously been shown to reduce phosphine oxides with complete retention of configuration,[2,3] and quaternization of phosphines is also known to be accompanied by retention of configuration at phosphorus.[7,8] Both are high-yield reactions as shown in Table I.

Scheme I



The properties of **11a**, obtained after the six consecutive reactions shown, were found to be essentially identical with those of the starting **11a**. The compounds designated **a** belong to the same diastereomeric family and are converted to the **b** family by inversion of configuration at phosphorus by base cleavage of **11a**. Treatment of **11a** with phenyllithium and benzaldehyde (Wittig reaction) gave an oxide identical with **12a** as expected.[9] The diastereomer **11b** was prepared separately from the cycle shown in Scheme I and was found to be identical with **11b** prepared in the cycle. Elemental analyses on all compounds were satisfactory, and ^1H nmr spectra were consistent with assigned structures. A summary of characteristics of phosphepanes and derivatives employed in this study are given in Table I.

Table I. Characteristics of Phosphepanes and Their Derivatives

Compd	Mp (bp), °C	Yield,[a] %	$\delta^{31}P$ nmr[b]	Purity,[c] %
11a	187.5–189		+110.13	92
11a[d,e]	182.5–183.5	97	+110.15	94
12b	80–82	98	+98.85	92
13b	115 (0.05 mm)	91		
11b[e]	161.5–163	100	+109.96	92
12a[f]	80.5–81.5	88	+99.18	89
13a	97 (0.03 mm)	97		

[a] From the preceding step in the cycle (Scheme I). [b] Determined on a 220-MHz Varian spectrometer at a resonance frequency of 89 MHz and expressed as parts per million from trimethyl phosphite, used as an external standard. The chemical shift of trimethyl phosphite relative to 85% phosphoric acid is reported as −139.6 ppm [J. G. Verkade, R. W. King, and C. W. Heitsch, *Inorg. Chem.*, **3**, 884 1964)]. [c] Expressed as the principal isomer and determined by integration of proton-decoupled ^{31}P nmr signals; estimated to be accurate within ±5%. [d] Crude salt obtained by quaternization of **13a** from the fifth step of the cycle (Scheme I). [e] Unrecrystallized. [f] Although **12a** and **12b** have very similar melting points and δ values, mixtures of the two provide a proton-decoupled ^{31}P nmr spectrum consisting of two separated signals of δ values reported in Table I.

Acknowledgments. The author wishes to thank Dr. Frank Lin for ^{31}P nmr spectra determinations, California Institute of Technology for use of the nmr spectrometer, and the National Science Foundation for its sponsorship of this work under Grant No. GP-25479.

(9) W. E. McEwen, *ibid.*, 2, 3 (1965).

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Concerning the Stereochemistry of Deoxygenation of Ribonucleotides. The Specifically 2′-Monodeuterated 2′-Deoxycytidines

Sir:

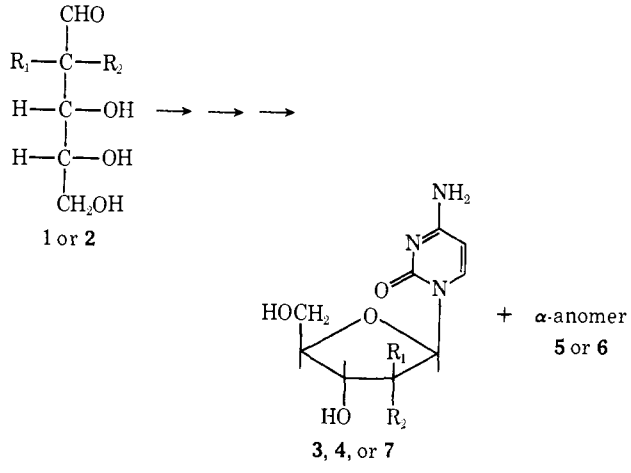
In the biosynthesis of deoxyribonucleic acids (DNA), the reduction of ribonucleotides to deoxyribonucleotides constitutes a critical step which might be susceptible to regulation.[1] In view of this possibility, the mechanism of the reduction has received well-warranted attention,[1–8] and several features of the process have

(1) P. Reichard, *Eur. J. Biochem.*, 3, 259 (1968).
(2) S. R. Anand, *J. Sci., Ind. Res.*, 26, 428 (1967).
(3) P. Reichard, A. Baldesten, and L. Rutberg, *J. Biol. Chem.*, 236, 1150 (1961); L. E. Bertani, A. Haggmark, and P. Reichard, *ibid.*, 236, PC 67 (1961); P. Reichard, *ibid.*, 237, 3513 (1962); A. Holmgren, P. Reichard, and L. Thelander, *Proc. Nat. Acad. Sci. U. S.*, 54, 830 (1965).
(4) R. L. Blakley, R. K. Ghambeer, P. F. Nixon, and E. Vitols, *Biochem. Biophys. Res. Commun.*, 20, 439 (1965), and previous papers by R. L. Blakley.
(5) R. J. Abrams, *J. Biol. Chem.*, 240, PC 3697 (1965), and previous papers by R. J. Abrams.
(6) A. Larsson and J. B. Neilands, *Biochem. Biophys. Res. Commun.*,

(6) K. F. Kumli, W. E. McEwen, and C. A. VanderWerf, *J. Amer. Chem. Soc.*, 81, 3805 (1959).
(7) L. D. Quin and T. P. Barket, *ibid.*, 92, 4303 (1970).
(8) W. E. McEwen, *Top. Phosphorus Chem.*, 2, 23 (1965).

been revealed. The reduction occurs at the di-[3] or tri-[4,5] phosphate level of the nucleotide, without sugar–base bond rupture,[6] and without intervention of olefinic intermediates.[7] When the reaction was studied in heavy water, the isotope was incorporated exclusively at carbon 2 of the sugar residue.[7,8] In an attempt to determine the stereochemistry of the product, Reichard and coworkers studied the enzymic reduction of cytidine diphosphate in deuterium oxide in the hope that the deuterated deoxynucleoside produced would be amenable to proton magnetic resonance (nmr) analysis.[9] In fact, analysis of the spectrum only allowed the conclusion that the reduction had occurred stereospecifically, and although the stereochemistry could not be determined unequivocally, the authors did venture a tentative suggestion that deoxygenation had occurred with retention of configuration.

An independent study of the adenosine → deoxyadenosine conversion in D_2O by Blakley and coworkers also failed to give an unambiguous answer to the steric course of reduction.[8] However, a subsequent computer-assisted first-order analysis of the complex methylene pattern in the 60-MHz spectrum of deoxyadenosine[10] was used as a basis for suggesting the configuration of the deuterated deoxynucleoside obtained earlier.[8a] The suggestion[10] and Reichard's simultaneous guess[9] agree, but in order to place this vital issue on a more secure base, we now report the preparation of the two possible deuterated deoxycytidines, **3** and **4**, which allow for direct comparison with the substance from Reichard's *in vitro* experiment.



1, **3**, and **5**, $R_1 = D$; $R_2 = H$
2, **4**, and **6**, $R_1 = H$; $R_2 = D$
7, $R_1 = R_2 = H$

The specifically 2-monodeuterated 2-deoxy-D-riboses **1** and **2** recently prepared in this laboratory[11] were converted to the deoxycytidines **3** and **4**, respectively, and the corresponding α anomers **5** and **6**, by the excellent method of Fox and coworkers.[12] Physical constants for the deuterated deoxycytidines[13] were: for **3**, mp 208–210°; $[\alpha]^{23}D$ +78° (*c* 0.41, 1 *N* NaOH); for **4**, mp 203–205; $[\alpha]^{23}D$ +65.6° (*c* 0.44, 1 *N* NaOH); for 2′-deoxycytidine itself[14] (**7**), mp 211–213°; $[\alpha]^{23}D$ +84.7° (*c* 0.45, 1 *N* NaOH); for the picrates of **3**, **4**, and **7**, respectively, mp 198, 202, 191°,[15] all with decomposition.

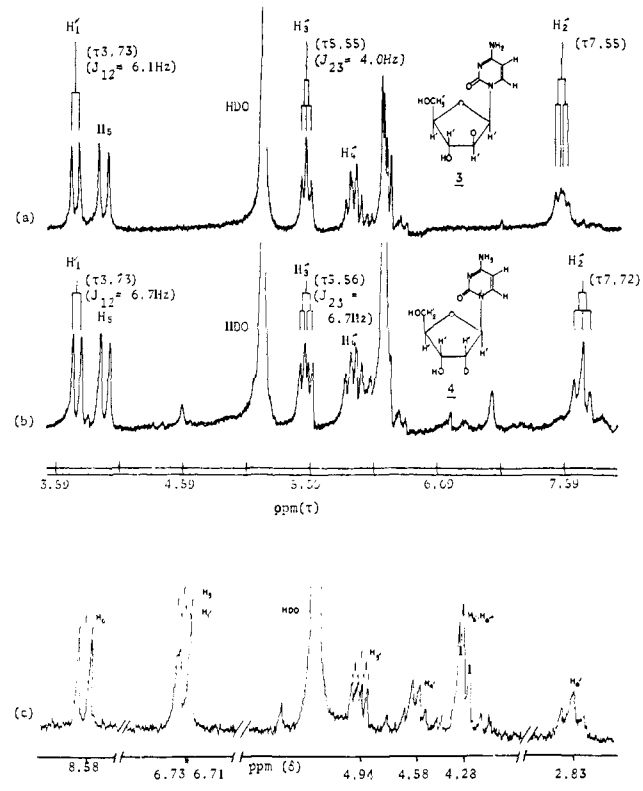


Figure 1. 100-MHz nmr spectra of 2′-deoxycytidines in D_2O. For (a) and (b) TSP (sodium trimethylsilyl-2,2,3-tetradeuteriopropionate) was used as internal reference, the probe temperature was 31 ± 0.5°, and the sweep width was 500 Hz. The parameters shown in parentheses were read directly from 220 MHz spectra (250-Hz sweep width) of the same solutions. The pH of both solutions was 7.75 ± 0.03. For (c) TMS was used as external reference.[9]

The 100-MHz nmr spectra of the deuterated deoxycytidines **3** and **4**[16] are shown in Figure 1 (a and b, respectively) along with the spectrum (Figure 1c)[17] reported by Reichard and coworkers for the substance from their *in vitro* experiment.[9] With the exception of relatively minor details,[18] Figures 1b and 1c are iden-

25, 222 (1966); O. Karlström and A. Larsson, *Eur. J. Biochem.*, 3, 164 (1967).

(7) A. Larsson, *Biochemistry*, 4, 1984 (1965).

(8) (a) R. L. Blakley, R. K. Ghambeer, T. J. Batterham, and C. Brownson, *Biochem. Biophys. Res. Commun.*, 24, 418 (1966); (b) M. M. Gottesman and W. S. Beck, *ibid.*, 24, 353 (1966).

(9) L. J. Durham, A. Larsson, and P. Reichard, *Eur. J. Biochem.*, 1, 92 (1967).

(10) T. J. Batterham, R. K. Ghambeer, R. L. Blakley, and C. Brownson, *Biochemistry*, 6, 1203 (1967).

(11) B. Radatus, M. Yunker, and B. Fraser-Reid, *J. Amer. Chem. Soc.*, 93, 3086 (1971).

(12) J. J. Fox, N. C. Yung, I. Wempen, and M. Hoffer, *ibid.*, 83, 4066 (1961).

(13) The physical constants of the α anomers **5** and **6** will be given in the full paper.

(14) 2′-Deoxycytidine was purchased from Raylo Chemicals Ltd., Edmonton, Alberta, Canada.

(15) L. A. Manson and J. O. Lampen, *J. Biol. Chem.*, 178, 431 (1951).

(16) We are indebted to Mr. Rick Hobson for obtaining these spectra on an instrument made available by our colleague Professor L. W. Reeves.

(17) Our Figure 1c is a reproduction of Figure 3 in ref 9.

(18) The discrepancy in the chemical shifts in Figures 1a and 1b *vs.* 1c is a result of the different reference standards used (see legend to Figure 1). The difference in the H-5–H-1 region in Figures 1b and 1c is due to the fact that Durham, *et al.*,[9] used the hydrochloride of their deuterated deoxycytidine. For example, commercial deoxycytidine, 2×10^{-4} *M* in D_2O, shows the following features at 60 MHz (TSP): τ 2.1 (H-6, d), 3.70 (H′-1, t), 3.90 (H-5, d). For a similar solution containing 1 equiv of HCl: τ 1.8 (H-6, d), 3.70 (H′-1, t), 3.72 (H-5, d).

tical, proving conclusively that the deuterated nucleoside obtained by Reichard in the *in vitro* reduction was indeed **4**, as suggested earlier.[9,10]

Enzymic reduction of ribonucleotides therefore occurs with retention of configuration at carbon 2′. It is interesting to note that this stereochemical outcome is reminiscent of catalytic hydrogenolysis of alcohols, which proceeds with predominant retention of configuration[19] and the opposite of ionic (hydride) deoxygenations which proceed in an SN2 manner.[20]

Acknowledgments. We express our gratitude to the National Research Council of Canada and Bristol Laboratories for financial support. We thank Professor Reichard and the Editor of The European Journal of Biochemistry for permission to reproduce Figure 1c.[9,17]

(19) E. W. Garbisch, Jr., *J. Org. Chem.*, **27**, 3363 (1962); W. A. Bonner, J. A. Zderic, and G. A. Casaletto, *J. Amer. Chem. Soc.*, **74**, 5086 (1952).

(20) E. R. Alexander, *ibid.*, **72**, 3796 (1950); L. W. Trevoy and W. G. Brown, *ibid.*, **71**, 1675 (1949).

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A New Synthesis of Ureas. The Reaction of Ammonia or Aliphatic Amines with Carbon Monoxide in the Presence of Selenium

Sir:

Early reports describe the synthesis of ureas from primary amines or ammonia and carbonyl sulfide[1-3] (or elemental sulfur and carbon monoxide[4-6]). In general high temperatures and pressures are required for primary amines, while secondary amines do not react. In this communication we report the general synthesis of ureas from aliphatic amines, carbon monoxide, and oxygen using selenium as a catalyst. The conditions required are mild and secondary amines can be used. The following procedure for the preparation of 1,3-di-*n*-butylurea is representative.

In a typical reaction, 0.1 mol of *n*-butylamine was dissolved in 100 ml of tetrahydrofuran; to the solution a 0.40-g sample (0.005 g-atom) of amorphous selenium[7] was added, and carbon monoxide was blown into the resultant suspension at a rate of 60 ml/min for about 5 min; the selenium dissolved completely. Thereafter, oxygen[8] was blown through the solution at a rate of 9 ml/min for 4 hr; the bubbling of carbon monoxide was also maintained. Finally the flow of carbon monoxide was stopped and oxygen flow was continued to precipitate the selenium. Removal of the recovered selenium and the solvent gave 1,3-di-*n*-butylurea in stoichiometric yield. An increase in the rate of oxygen addition during early stages of the reaction (20 ml/min) caused the deposition of elemental selenium and hence stopped the formation of the urea. Using a temperature of 20° and 1 atm of CO pressure, we prepared ureas from *n*-butylamine, *n*-hexylamine, *n*-octylamine, and cyclohexylamine in yields ranging from 95 to 99%. With ethylenediamine, benzylamine and piperidine, yields under these conditions were 14, 74, and 26%. Under more stringent conditions (T = 60°; CO, P_{atm} = 50; Se, 0.05 g-atom), ethylenediamine gave a 98% yield of 2-imidazolidone and 1,3-propylenediamine (T = 40°; CO, P_{atm} = 50; Se, 0.05 g-atom) gave a 96% yield of *N*,*N*′-trimethyleneurea.

Isolation of selenocarbamate salts as intermediates provides strong evidence that the process goes in at least two steps. These can be summarized by the equations

$$2RNH_2 + Se + CO \longrightarrow (RNH_3)^+(RHN{-}\overset{\overset{O}{\|}}{C}{-}Se)^-$$

$$(RNH_3)^+(RHN{-}\overset{\overset{O}{\|}}{C}{-}Se)^- + O_2 \longrightarrow (RNH)_2CO + H_2O + Se$$

The *N*-*n*-butyl selenocarbamate was very sensitive to oxidation while the *N*,*N*-pentamethylene selenocarbamate (or *N*-piperidyl selenocarboxylate) was significantly more stable. The latter compound would also react with excess piperidine to give the expected urea and piperidinium hydroselenide, $(C_5H_{12}N)^+(HSe)^-$.

Unsymmetrical urea can be synthesized from the intermediate salt. The reaction of the *N*-*n*-butyl selenocarbamate salt with piperidine in THF at 20° followed by air oxidation gave 98% yield of the expected unsymmetrical urea. Similarly, the reaction of the *N*,*N*-pentamethylene selenocarbamate with *n*-butylamine followed by air oxidation gave a stoichiometric yield of the unsymmetrical urea. The mechanism of mixed urea formation is being investigated. It is currently suggested that an intermediate anion of the form

$$\left(\begin{array}{c} OH \\ | \\ RHN{-}C{-}Se \\ | \\ HNR \end{array}\right)^-$$

may be important. It is also probable that carbonyl selenide (SeCO), prepared from CO and Se in the presence of a base such as pyridine, is an active intermediate. When CO and Se were combined in the presence of a pyridine solution and the issuing gas stream was introduced into a solution of *n*-butylamine, equimolar amounts of 1,3-di-*n*-butylurea and Se were isolated from the solution by air oxidation. No product was obtained without pyridine in the original solution. The data suggest that SeCO was formed in the pyridine solution and carried into the *n*-butylamine solution.

(1) M. Freund and E. Asbrand, *Ann.*, **A285**, 173 (1895).
(2) G. Hagelloch, *Chem. Ber.*, **83**, 258 (1950).
(3) R. J. Ferm, *Chem. Rev.*, **57**, 621 (1957).
(4) R. A. Franz and F. Applegath, *J. Org. Chem.*, **26**, 3304 (1961).
(5) R. A. Franz, F. Applegath, F. V. Morriss, and F. Baiocchi, *ibid.*, **26**, 3306 (1961).
(6) R. A. Franz, F. Applegath, F. V. Morriss, F. Baiocchi, and C. Bolze, *ibid.*, **26**, 3309 (1961).
(7) It was also possible to use metallic selenium; however, it dissolved more slowly into the solution.
(8) Air can also be used.

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