sulfurization of III (1.5 g.) proceeded at 100° in a refluxing ethanol–Methyl Cellosolve solution in the presence of a 15-fold weight of catalyst to give 0.8 g. (67%) of crude 2′,3′-dideoxyadenosine. After three recrystallizations from ethanol, colorless crystals of IV (0.25 g.) were obtained, chromatographically homogeneous. Pure 2′,3′-dideoxyadenosine (IV) melted at 184–186°, $[\alpha]^{25}D$ −25.2° (*c* 1.01, H_2O); λ_{max}^{MeOH} 259.5 mμ (ε 14,800). *Anal.* Calcd. for $C_{10}H_{13}N_5O_2$: C, 51.1; H, 5.54; N, 29.8. Found: C, 50.9; N, 5.32; N, 29.6; R_f 0.45, $R_{Adenine}$ 1.80 (NH_4OH:DMF:*i*-PrOH, 10:25:65); R_f 0.36, $R_{Adenine}$ 1.19 (*n*-BuOH saturated with H_2O). The proton magnetic resonance spectrum of IV in D_2O showed a complex multiplet corresponding to four protons at δ 2.0 to 2.8 (C-2′ and C-3′ protons) and no absorption at δ 4.63 in the region of the C-3′ proton in 2′-deoxyadenosine in the same solvent.

These procedures are presently being applied to the preparation of other novel purine deoxy- and polydeoxynucleosides utilizing the commercially available deoxynucleosides obtained from DNA.

(21) Supported by an Arizona State University Foundation Graduate Research Fellowship, 1962–1963.

(22) Supported in part by research grant CA 04008-06 from the National Cancer Institute of the National Institutes of Health, Public Health Service.

ARIZONA STATE UNIVERSITY
DEPARTMENT OF CHEMISTRY
TEMPE, ARIZONA
MORRIS J. ROBINS[21]
ROLAND K. ROBINS[22]

RECEIVED June 22, 1964

Synthesis of Deoxyribonucleoside-3′,5′ Cyclic Phosphates by Base-Catalysed Transesterification

Sir:

Hydrolysis of *p*-nitrophenyl thymidine-3′ phosphate in *aqueous* sodium hydroxide produces both thymidine-3′ and thymidine-5′ phosphates, thymidine-3′,5′ cyclic phosphate being an intermediate in the reaction.[1] This communication describes the reaction of *p*-nitrophenyl esters of deoxyribonucleotides with base in *anhydrous* solvents where deoxyribonucleoside-3′,5′ cyclic phosphates are produced in excellent yields.

5′-O-Di-*p*-methoxytritylthymidine[2,3] was reacted with *p*-nitrophenyl phosphate and dicyclohexylcarbodiimide in dimethylformamide–pyridine[4] to yield, after acetic acid treatment, *p*-nitrophenyl thymidine-3′ phosphate. The nucleotide (20 μmoles) as its ammonium salt in dimethyl sulfoxide (2.0 ml.)[5] was treated with molar potassium *t*-butoxide in *t*-butyl alcohol (1.0 ml.)[6] at 20°. Immediately an intense yellow color developed and chromatography in isopropyl alcohol–concentrated ammonia–water (7:1:2) indicated that formation of thymidine-3′,5′ cyclic phosphate was quantitative and complete in less than 5 min. The nucleotide was isolated by ion-exchange chromatography on diethylaminoethyl cellulose[7] and characterized by its spectral properties, paper chromatography in three systems, electrophoresis at pH 7.5, and hydrolysis to thymine in molar hydrochloric acid at 50°.[7-9]

Although *p*-nitrophenyl uridine-5′ phosphate is not hydrolysed by aqueous alkali *via* the nucleoside-3′,5′ cyclic phosphate,[1] the reaction of *p*-nitrophenyl thymidine-5′ phosphate (sodium salt) was next examined. Under the conditions described above, conversion to thymidine-3′,5′ cyclic phosphate was complete in 60 min.[10] Similarly, *p*-nitrophenyl deoxyadenosine-5′ phosphate[11] was completely converted to deoxyadenosine-3′,5′ cyclic phosphate, although the reaction proceeded at about 80% of the rate of the thymidine-5′ nucleotide. Deoxyadenosine-3′,5′ cyclic phosphate was characterized by its ion-exchange, spectral, chromatographic, and electrophoretic properties, by its resistance to molar hydrochloric acid at 50°, and by its hydrolysis by the adenosine-3′,5′ cyclic phosphate diesterase of brain.[7,12]

When formamide was substituted for dimethyl sulfoxide as solvent,[13] there was no detectable reaction of *p*-nitrophenyl thymidine-5′ phosphate after 60 min. In dimethylformamide, thymidine-3′,5′ cyclic phosphate was produced at about 75% of the rate in dimethyl sulfoxide.

Experiments to determine the utility of this reaction in the synthesis of other deoxyribonucleoside-3′,5′ cyclic phosphates,[7] ribonucleoside-3′,5′ cyclic phosphates,[14] and internucleotide linkages are in progress.

(1) A. F. Turner and H. G. Khorana, *J. Am. Chem. Soc.*, **81**, 4651 (1959).
(2) H. Schaller, G. Wiemann, B. Lerch, and H. G. Khorana, *ibid.*, **85**, 3821 (1963).
(3) M. Smith, D. H. Rammler, I. H. Goldberg, and H. G. Khorana, *ibid.*, **84**, 430 (1962).
(4) This solvent system was first described by R. K. Ralph, W. J. Connors, H. Schaller, and H. G. Khorana, *ibid.*, **85**, 1983 (1963), and was used here because *p*-nitrophenyl phosphate is insoluble in anhydrous pyridine.
(5) Dimethyl sulfoxide is a useful solvent in nucleotide chemistry; see J. G. Moffatt, *Can. J. Chem.*, **42**, 599 (1964).
(6) R. B. Clayton, H. B. Henbest, and M. Smith, *J. Chem. Soc.*, 1982 (1957).
(7) G. I. Drummond, M. W. Gilgan, E. J. Reiner, and M. Smith, *J. Am. Chem. Soc.*, **86**, 1626 (1964).
(8) G. M. Tener, H. G. Khorana, R. Markham, and E. H. Pol, *ibid.*, **79**, 430 (1957).
(9) These criteria do not exclude the possibility of anomerization (at the glycosidic linkage). However, other experiments involving *t*-butoxide catalysis indicate that this is improbable. See R. Letters and A. M. Michelson, *J. Chem. Soc.*, 1410 (1961); A. M. Michelson and W. E. Cohn, *Biochemistry*, **1**, 490 (1962).
(10) Thymidylyl-(5′→3′)-thymidine is unaffected under the same conditions (unpublished results).
(11) Kindly donated by Dr. W. E. Razzell.
(12) G. I. Drummond and S. Perrot-Yee, *J. Biol. Chem.*, **236**, 1126 (1961).
(13) Formamide was used as solvent in the potassium *t*-butoxide catalysed transesterification of ribonucleic acid to ribonucleoside-2′,3′ cyclic phosphates; see D. Lipkin and P. T. Talbert, *Chem. Ind.* (London), 143 (1955).
(14) M. Smith, G. I. Drummond, and H. G. Khorana, *J. Am. Chem. Soc.*, **83**, 698 (1961).

FISHERIES RESEARCH BOARD OF CANADA
TECHNOLOGICAL RESEARCH LABORATORY
VANCOUVER 8, B. C., CANADA
MICHAEL SMITH

RECEIVED JUNE 24, 1964

Heat of Hydrogenation of Bicyclo[2.2.2]octa-2,5,7-triene

Sir:

In view of recent commentary on the question of delocalization energy in bicyclo[2.2.2]octa-2,5,7-triene ("barrelene"),[1] the author wishes to report the value obtained in this laboratory for the heat of hydrogenation of this substance. A purified sample, kindly provided by Dr. H. E. Zimmerman, was reduced in acetic acid solution at 25° with the uptake of 2.99 molar equivalents of hydrogen. The heat of hydrogenation was −93.78 ± 0.31 kcal./mole.

Since the heat of hydrogenation of bicyclo[2.2.2]-octa-2,5-diene is −56.21 ● 0.10 kcal./mole,[2] the heat evolved in reduction of the first double bond of barrelene

(1) H. E. Zimmerman and G. L. Grunewald, *J. Am. Chem. Soc.*, **86**, 1434 (1964), footnote 2.
(2) R. B. Turner, W. R. Meador, and R. E. Winkler, *ibid.*, **79**, 4116 (1957).