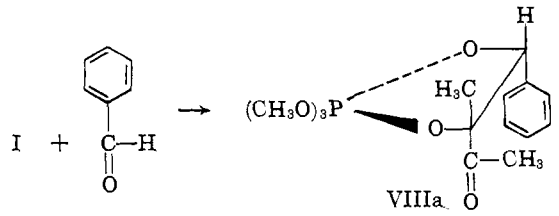


VIIIa

field of 85% H_3PO_4, like other related compounds.[2] We have described the partial hydrolysis of oxyphosphoranes to cyclic phosphate esters.[3]

The configurations shown for the predominant adducts and for the cyclic phosphates are highly probable but not definitive. They are based on comparisons between the H^1 n.m.r. spectra and the corresponding spectra in the series of *meso* and DL 2:1 biacetyl–phosphite[3] and 2:1 methyl pyruvate–phosphite adducts[4] and cyclic phosphates.[3]

The adduct I and the methyl pyruvate were mixed in a 3:1 mole ratio and kept 90 hr. at 20° with stirring (N_2). The excess of I was removed *in vacuo*, and the colorless residue (88% yield; $n^{25}D$ 1.4465; infrared similar to that of pure IIa) was dissolved in ether and allowed to crystallize at −10°. Crystalline IIa (m.p. 33–35°, *ca.* 60%) separated out. *Anal.* Calcd. for $C_{11}H_{21}O_8P$: C, 42.3; H, 6.8; P, 9.9. Found: C, 42.2; H, 7.0; P, 10.3. Bands at 5.76 (ester C=O), 5.84 (ketone C=O), and 9.2–9.3 μ ($POCH_3$) (in CCl_4). Singlet at 6.35 ($COOCH_3$), doublet at 6.52, J_{HP} = 13 c.p.s. ($POCH_3$), singlet at 7.83 (acetyl), and singlets at 8.57 and 8.76 τ (CH_3C—) (in CCl_4 *vs.* TMS).

The cyclic phosphate IIIa had m.p. 81–83° (ether). *Anal.* Calcd. for $C_9H_{15}O_7P$: C, 40.6; H, 5.7; P, 11.6. Found: C, 40.7; H, 5.9; P, 11.7. Bands at 5.74 (ester C=O), 5.84 (ketone C=O), 7.70 (P=O), and 9.52 μ ($POCH_3$) (in CCl_4). The H^1 n.m.r. spectrum in $CDCl_3$ is complex; two sets of peaks are observable, the stronger set consists of a singlet at 6.20 ($COOCH_3$), doublet at 6.17, J_{HP} = 12.5 c.p.s. ($POCH_3$), singlet at 7.68 (acetyl), and two singlets at 8.28 and 8.38 τ (CH_3C—). The weaker set has a singlet at 6.25 τ ($COOCH_3$), under the high field component of the strong $POCH_3$ doublet; a doublet at 6.08, J_{HP} = 12.5 c.p.s. ($POCH_3$), a singlet at 7.64 (acetyl), and singlets at 8.32 and 8.35 τ (CH_3C—). (A stereomutation at phosphorus in the *meso*-cyclic phosphate derived from the 2:1 biacetyl–phosphite adduct, which doubles the number of peaks, has been mentioned.)[3]

α,β-Dihydroxylevulinate (IVa) had m.p. 72–73° (cyclohexane). *Anal.* Calcd. for $C_8H_{14}O_5$: C, 50.6; H, 7.4. Found: C, 50.5; H, 7.4. Bands at 2.92 (broad OH), 5.83–5.88 μ (broad ester and ketone C=O) (in $CHCl_3$). Singlet at 6.1 (OH), 6.20 ($COOCH_3$), 7.71 (acetyl), and 8.57 and 8.61 τ (CH_3C—).

The adduct I and propionaldehyde (dried over Drierite) (1:3 mole ratio) were stirred 88 hr. at 20°. The oxyphosphorane Va ($n^{25}D$ 1.4356; 60% yield) was collected at 88–89° (1.5 mm.) using a 12-in. spinning band column.[4a] In addition, some cyclic phosphate VIa ($n^{25}D$ 1.4381; 20%) was collected at 90–93° (0.5 mm.). The latter was identical with the product of the hydrolysis of Va with one mole of water in benzene. The dihydroxyketone VIIa had $n^{25}D$ 1.4489; b.p. 50–51° (0.3 mm.).

The adduct I and benzaldehyde (1:3 mole ratio) were stirred 112 hr. at 20°. The oxyphosphorane VIIIa ($n^{25}D$ 1.4935, 80% yield) was collected at 95–102° (1 mm.). Under certain conditions VIIIa loses trimethyl phosphate and forms a β-diketone enol. All structures given are consistent with the analytical data and the infrared and H^1 n.m.r. spectra.

Acknowledgment.—We are grateful to Dr. J. Lancaster (American Cyanamid Co.) for P^{31} n.m.r. spectra and to Dr. E. M. Banas (American Oil Co.) for Professor E. Eliel (University of Notre Dame) for aid in H^1 n.m.r. spectroscopy.

Mc./sec. showed 16 of the 20 lines expected for the P^{31} nucleus coupled with nine methoxyl protons (J_{PH} = 12.6 c.p.s.) and with one methine proton (J_{PH} = 6.3 c.p.s.); the center of this multiplet was at +51.27 ± 0.03 p.p.m *vs.* H_3PO_4. A much weaker multiplet, possibly due to a diastereomer, was centered at +48.9 ± 0.1 p.p.m. (measurements by Mr. S. R. Heller of this Department).

(3) F. Ramirez, N. B. Desai, and N. Ramanathan, *J. Am. Chem. Soc.*, **85**, 1874 (1963).

(4) New data on mixtures of DL plus *meso* 2:1 methyl pyruvate-trimethyl phosphite adducts show that the carbomethoxy group of the DL form is at lower field than that of the *meso* form (see ref. 2b).

(4a) NOTE ADDED IN PROOF.—A small amount (<15%) of a by-product with $n^{25}D$ 1.4313 was also obtained from the reaction of the biacetyl adduct I with propionaldehyde; its structure will be described in the forthcoming paper.

(5) Alfred P. Sloan Fellow, 1961–1963.

DEPARTMENT OF CHEMISTRY
STATE UNIVERSITY OF NEW YORK
AT STONY BROOK,
STONY BROOK, N. Y.

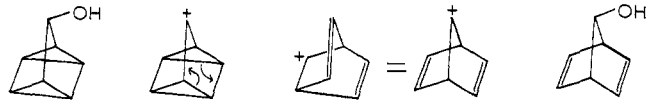
FAUSTO RAMIREZ[5]
A. V. PATWARDHAN
N. B. DESAI
N. RAMANATHAN
C. V. GRECO

RECEIVED JUNE 14, 1963

Quadricyclo[2.2.1.0^{2,6}.0^{3,5}]heptan-7-ol (Quadricyclanol)

Sir:

We have prepared quadricyclo[2.2.1.0^{2,6}.0^{3,5}]heptan-7-ol (quadricyclanol, I). Carbonium ion II that might form directly from I or its derivatives could isomerize



I II III IV

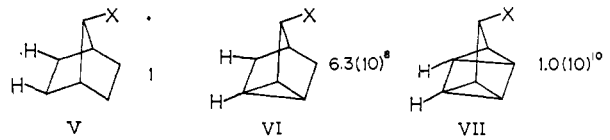
readily, as shown by the arrows, to the 7-norbornadienyl cation III thought to be remarkably stable.[1,2] Alternatively, II and III might represent resonance structures of a hybrid ion formed directly from both the quadricyclic and dienylic systems. The product of acetolysis of the β-naphthalenesulfonate ester of I contains approximately 20% of the acetate of I, 70% of the acetate of IV, and 10% of unidentified material (though the quadricyclic acetate was shown to be far less stable by its quantitative isomerization to the dienylic acetate on attempts at g.p.c.). In contrast, Winstein and Ordronneau reported[1] that hydrolysis of 7-norbornadienyl chloride or trifluoroacetate gave only IV and Story and Saunders[2] that acetolysis of the fluoroborate of III gave only the acetate of IV. Therefore, different intermediates (presumably II and III) must be formed initially in solvolysis reactions of these quadricyclic and dienylic derivatives. A solution of I in 96% sulfuric acid has λ_{max} 350 mμ (ϵ 5000), the same absorption reported for IV in sulfuric acid, suggesting formation of the same absorbing species from I and IV. The slow rate of formation of this absorption from solutions of I in less concentrated acid suggests that this species is not II or III.

The acetolysis rate of naphthalenesulfonate VII is 8.9×10^{-5} sec.$^{-1}$ at 25°. This rate is 10^{10} times that

(1) S. Winstein and C. Ordronneau, *J. Am. Chem. Soc.*, **82**, 2084 (1960).

(2) P. R. Story and M. Saunders, *ibid.*, **82**, 6199 (1960); **84**, 4876 (1962).

observed for a 7-norbornyl derivative V.[3,4] An explanation of the effect of introducing two cyclopropyl rings into a 7-norbornyl derivative must also accommodate the observation that most of this dramatic rate enhancement occurs[4,6] on introducing only one cyclopropyl ring to give the nortricyclyl system VI.



V VI VII

The low solvolytic reactivity of the 7-norbornyl system has been attributed to (1) the small C-1–C-7–C-4 angle, resulting in increased strain on going to the cation, (2) steric hindrance by the hydrogens on C-2 and C-3 to solvation of the cation, and (3), probably most important, unfavorable orientation of the C-1 and C-4 hydrogens for hyperconjugation.[7] In going from V to VI to VII, the orientation of the C-1 and C-4 hydrogens does not change, and though the C-1–C-7–C-4 angle probably increases slightly, only a minor rate increase could be attributed to this factor. Hindrance by the C-2 and C-3 hydrogens to solvent approach is diminished considerably in VI and somewhat more in VII; however, acetolyses of secondary arylsulfonates would not be expected[8] to be extremely sensitive to hindrance to solvation. Stabilization of carbonium ion formation by cyclopropyl rings is an attractive explanation for the large part of the rate enhancement not otherwise accounted for. The dilemma remains that, despite its similar geometric placement, the second cyclopropyl ring has much less effect than the first, contrary to experience in other systems.[9] The attachment of two cyclopropyl rings together or their face-to-face proximity may reduce their ability to delocalize positive charge.

The acetate[10] of I, b.p. 68–70° (2 mm.), m.p. 33–35°, was prepared by photolysis of the acetate[11] of IV using a procedure similar to that described for synthesis of quadricyclo[2.2.1.$0^{2,6}$.$0^{3,5}$]heptane (quadricyclane).[12] The acetate was saponified to I, b.p. 52° (2 mm.); *p*-nitrobenzoate, m.p. 147.5–149°; β-naphthalenesulfonate, m.p. 96–97.5°. The acetolysis rate was measured by a standard procedure[13] in acetic acid containing 1% of acetic anhydride and 0.1 *M* in potassium acetate. The solvolysis product was obtained by addition of water followed by extraction with carbon disulfide; its components were identified and their amounts estimated by their absorptions in the n.m.r. and infrared spectra.[14]

N.M.R. SPECTRA[a] IN CS_2

H-values at	I	Acetate	Naphthalenesulfonate
C-7	5.4 (1)	4.6 (1)	4.7 (1)
C-1–C-6	8.2–8.9 (6)	8.3–8.6 (6)	8.2–8.7 (6)
Other positions	7.3 (1)[b]	8.0 (3)[c]	1.6–2.6 (7)[d]

[a] Chemical shifts are in p.p.m. relative to tetramethylsilane as 10.0. The numbers in parentheses are approximate peak area ratios. Spectra were taken at 60 Mc. [b] Assigned to the hydroxyl H. [c] Assigned to the methyl H's. [d] Assigned to the naphthalene H's.

Acknowledgment.—The support of this work by the National Science Foundation is gratefully acknowledged.

(3) The acetolysis rate of the *p*-toluenesulfonate is 6.36 × 10^{-15} sec.$^{-1}$ extrapolated from data at higher temperatures (S. Winstein, M. Shatavsky, C. Norton, and R. B. Woodward, *J. Am. Chem. Soc.*, **77**, 4183 (1955)).

(4) Relative acetolysis rates of *p*-bromobenzenesulfonates, β-naphthalenesulfonates, and *p*-toluenesulfonates are taken as 9:4:3 (ref. 5 and R. A. Sneen, K. M. Lewandowski, I. A. I. Taha, and B. R. Smith, *J. Am. Chem. Soc.*, **83**, 4843 (1961)).

(5) S. Winstein and M. Shatavsky, *ibid.*, **78**, 592 (1956).

(6) The acetolysis rate of the *p*-bromobenzenesulfonate is about 1.2 × 10^{-5} sec.$^{-1}$ (ref. 5 and S. Winstein, H. W. Walborsky, and K. Schreiber, *J. Am. Chem. Soc.*, **72**, 5795 (1950)).

(7) J. D. Roberts, F. O. Johnson, and R. A. Carboni, *ibid.*, **76**, 5692 (1954); W. G. Woods, R. A. Carboni, and J. D. Roberts, *ibid.*, **78**, 5653 (1956); E. E. van Tamelen and C. I. Judd, *ibid.*, **80**, 6305 (1958); P. D. Bartlett and W. P. Giddings, *ibid.*, **82**, 1240 (1960); R. B. Woodward in "Perspectives in Organic Chemistry," A. Todd, Ed., Interscience Publishers, Inc., New York, N. Y., 1956, p. 177.

(8) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962.

(9) H. Hart and J. M. Sandri, *J. Am. Chem. Soc.*, **81**, 320 (1959); H. Hart and P. A. Law, *ibid.*, **84**, 2462 (1962); N. C. Deno, H. G. Richey, Jr., J. S. Liu, J. D. Hodge, J. J. Houser, and M. J. Wisotsky, *ibid.*, **84**, 2016 (1962).

(10) Satisfactory analyses for carbon and hydrogen were obtained for all new compounds.

(11) P. R. Story, *J. Org. Chem.*, **26**, 287 (1961).

(12) W. G. Dauben and R. L. Cargill, *Tetrahedron*, **15**, 197 (1961).

(13) S. Winstein, E. Grunwald, and L. I. Ingraham, *J. Am. Chem. Soc.*, **70**, 821 (1948).

(14) The acetates of I and IV were recovered unchanged from similar solutions.

(15) A portion of this work is contained in the Senior Thesis of N. C. B., the Pennsylvania State University, March, 1963.

DEPARTMENT OF CHEMISTRY HERMAN G. RICHEY, JR.
THE PENNSYLVANIA STATE UNIVERSITY NEIL C. BUCKLEY[15]
UNIVERSITY PARK, PENNSYLVANIA

RECEIVED AUGUST 5, 1963

The Structure of Dihydrofolic Acid Prepared by Dithionite Reduction of Folic Acid

Sir:

The widespread use of reduced forms of pteridine derivatives as intermediates in a variety of enzymic and microbiological systems has recently focused attention on the exact location of the hydrogen atoms on the pyrazine ring of dihydrofolate (folate-H_2). Folate-H_2 rather than folate is the initial compound formed in the biosynthesis *de novo* of this class of pteridine derivatives.[1] It is the precursor of tetrahydrofolate (folate-H_4) and is formed in stoichiometric amounts during the biosynthesis of thymidylate.[2] The results of chemical, physical, and enzymatic procedures described in this communication have convinced us that the 7,8-dihydro structure, the one originally suggested by O'Dell, *et al.*,[3] is the correct one rather than the 5,8-dihydro alternative recently put forth by Zakrzewski[4] and by Huennekens' laboratory.[5] The 5,6-dihydro formulation has been excluded on the basis that essentially all of the folate-H_2 is enzymatically convertible to a single diastereoisomer of folate-H_4.[6]

Tritium Incorporation Experiments.—The possibility of a 5,8-dihydro structure was tested by isotopic experiments in T_2O (1) by enzymatic conversion of folate-H_2 to folate-H_4 and (2) by dithionite reduction of folate to folate-H_2.[7,8] In neither case could the 5,8-dihydro assignment be substantiated.

We had previously shown that in the enzymic reduction of folate-H_2 one nonexchangeable hydrogen was incorporated into folate-H_4 from TPNH.[9] The second hydrogen for the reduction must come from the medium and, assuming the 5,8-dihydro structure, would also be nonexchangeable (reaction 1).

(1) G. M. Brown, R. A. Weisman, and D. A. Molnar, *J. Biol. Chem.*, **236**, 2534 (1961).

(2) A. J. Wahba and M. Friedkin, *ibid.*, **236**, PC11 (1961).

(3) B. L. O'Dell, J. M. Vandenbelt, E. S. Bloom, and J. J. Pfiffner, *J. Am. Chem. Soc.*, **69**, 250 (1947).

(4) S. F. Zakrzewski, *Federation Proc.*, **22**, 231 (1963).

(5) K. Smith, K. G. Scrimgeour, and F. M. Huennekens, *Biochem. Biophys. Res. Commun.*, **11**, 388 (1963).

(6) C. K. Mathews and F. M. Huennekens, *J. Biol. Chem.*, **235**, 3304 (1960).

(7) S. Futterman, *ibid.*, **228**, 1031 (1957).

(8) R. L. Blakley, *Nature*, **188**, 231 (1960).

(9) E. J. Pastore and M. Friedkin, *J. Biol. Chem.*, **237**, 3802 (1962).