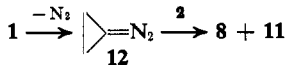
of olefinic products which might be expected if a carbene is involved. We favor an alternate mechanism for the formation of **8** and **11** as shown in Scheme II.

Scheme II



1,3-Bisdiazopropane (**1**) may lose nitrogen forming diazocyclopropane[12] (**12**) which could then react with cyclohexanone (**2**) to form both **8** and **11** in a fashion well documented for diazoalkanes.[13,14] Further work is in progress to differentiate between these two mechanistic possibilities and to determine whether diazocyclopropane is formed from **1**.

Acknowledgment. We thank the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

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(13) C. D. Gutsche, *Org. React.*, 8, 364 (1954).
(14) NOTE ADDED IN PROOF. Support for the mechanism proposed in Scheme II is found in the recent observation that products derived from diazocyclopropane are formed when 1,3-bisdiazopropane is prepared from 1,3-bis(N-nitrosoureido)propane (W. Kirmse and B. Brinkmann, *Chem. Ber.*, in press.

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A Potential Transition State Analog for Adenosine Deaminase[1]

Sir:

Stable molecules, with binding properties resembling those of highly reactive intermediates approaching the transition state, are expected to be unusually potent enzyme inhibitors.[2-5] Adenosine deaminase catalyzes hydrolytic displacement of nitrogen, halogen, oxygen, and sulfur leaving groups from purine ribonucleosides,[6-10] and indirect evidence suggests that the transition state is reached during formation of a tetrahedral intermediate in nucleophilic substitution by water or by enzyme.[11,12] Stable purine analogs with a tetrahedral carbon at C-6 have therefore seemed desirable for testing the possibility of direct water attack. We wish to report an unusually potent reversible inhibitor of adenosine deaminases, with space-filling properties strikingly similar to those of the proposed tetrahedral intermediate for water attack, but quite different from those of the substrate and product.

The synthetic method employed was similar to that of Linschitz and Connolly, who have recently reported the photoaddition of alcohols to unsubstituted purine.[13] When purine ribonucleoside (I), the most powerful reversible adenosine deaminase inhibitor previously known,[12,14] was irradiated with ultraviolet light (254 mμ) in methanol, the crude product mixture was found to be very much more inhibitory than the parent compound. Three major products were isolated as solids by preparative thin-layer chromatography on silica gel PF (Brinkman Instruments Co.) with 30% methanol in chloroform (two developments). The products of lowest mobility, II (R_f = 0.11) and II′ (R_f = 0.05), were recovered in 25 and 29% yield, respectively. These compounds showed ultraviolet spectra similar to each other (II, λ_{max} 293 mμ, log ϵ_M 3.62 at pH 7; II′, λ_{max} 291 mμ, log ϵ_M 3.67 at pH 7) and similar to those reported for 1,6-dihydropurine[15] and for products of methanol photoaddition to purine.[13] Tentative identification of compounds II and II′, as diastereomers of 1,6-dihydro-6-hydroxymethylpurine ribonucleoside, was confirmed by mass spectrometry, showing in each case a parent peak at *m/e* 284. Major peaks in the mass spectra corresponded to fragments resulting from loss of OH (267), loss of CH_2OH (253), and loss of ribose (151); the other major fragments were also readily accounted for in terms of these structures.

The product of highest mobility, III, was somewhat slower moving (R_f = 0.22) than purine ribonucleoside (R_f = 0.35), but showed an ultraviolet absorption spectrum (λ_{max} 263 mμ, log ϵ_M 3.78 at pH 7) similar to that of purine ribonucleoside, indicating the presence of the fully aromatic purine nucleus. The mass spectrum (parent *m/e* = 282), as well as nmr and ir spectra, indicated that III was 6-hydroxymethylpurine ribonucleoside, presumably arising by air oxidation of the primary products II and II′. When II and II′ were individually treated with hydrogen peroxide in the presence of either ultraviolet light or ferrous sulfate catalyst, each was found by thin-layer chromatography and ultraviolet spectroscopy to be converted quantitatively to III, reinforcing the structure assignment of all three products (Scheme I).

Of these products, II was found to be an exceptionally powerful competitive inhibitor of adenosine deaminases, with K_i values approximately 40-fold lower than K_m values for adenosine, and more than 200-fold lower than K_i values for the substrate for the reverse reaction, inosine (Table I). These observations suggested that the binding properties of this inhibitor might resemble those of a highly reactive intermediate in the enzyme-catalyzed reaction. Examination of space-filling models shows that by rotation of the hydroxymethyl group II can adopt a structure very similar to that of the proposed intermediate IV, the exocyclic methylene group taking the place of the variable leaving group in substrates. The relative ineffectiveness of diastereomer II′ as an inhibitor is understandable if the

(1) Supported by Research Grant No. GM-12725 from the National Institutes of Health, U. S. Public Health Service. B. E. was supported by a predoctoral fellowship from the National Science Foundation. Inquiries should be addressed to R. W., at the Department of Biochemistry, University of North Carolina, Chapel Hill, N. C. 27514.
(2) L. Pauling, *Amer. Sci.*, **36**, 51 (1948).
(3) W. P. Jencks in "Current Aspects of Biochemical Energetics," N. O. Kaplan and E. P. Kennedy, Ed., Academic Press, New York, N. Y., 1966, p 273.
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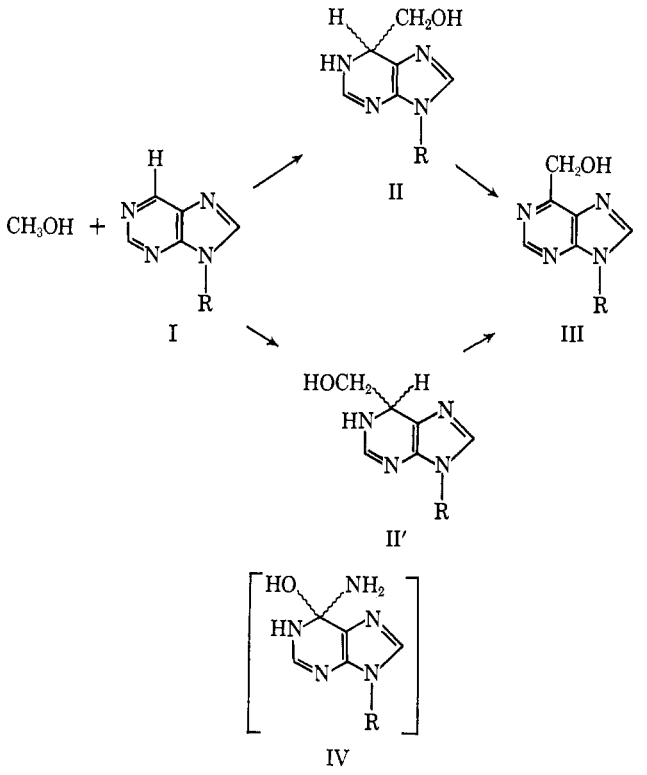
Scheme I



enzymatic reaction involves stereospecific attack from only one side of the purine ring. The absolute stereochemistry of II remains to be determined; however it may be noted that both the fungal and the mammalian enzyme are inhibited far more effectively by II than by II′ (Table I). This suggests that water attack is mounted from the same side of the ring in enzymes from both sources, which differ from each other very much in size and amino acid composition.[16]

Table I. Apparent Dissociation Constants for Adenosine Deaminases in Potassium Phosphate Buffer[a]

Enzyme	Calf duodenum	*Aspergillus oryzae*
Adenosine (K_m)[b]	31×10^{-6}	240×10^{-6}
Inosine[c]	160×10^{-6}	1800×10^{-6}
I	9.3×10^{-6}	37×10^{-6}
II	0.76×10^{-6}	6.5×10^{-6}
II′	12.5×10^{-6}	140×10^{-6}
III	9.4×10^{-6}	29×10^{-6}

[a] pH 7.50, 0.05 *M*; at 25°, moles/liter. [b] Reference 12. [c] Reference 11.

Crude products of photoaddition of ethanol and isopropyl alcohol to purine ribonucleoside (presumably containing 1- and 2-methyl groups substituted for hydrogens on the 6-hydroxymethyl carbon[13]) were found to be at least two orders of magnitude less inhibitory than the mixed products of methanol photoaddition, providing a further indication of the close tolerance required for a good fit of inhibitors to the enzyme near the site at which the catalyzed reaction occurs.

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The present findings, in conjunction with earlier studies of bacterial cytidine deaminase,[4] suggest that tetrahedral analogs may prove to be useful inhibitors of a broad class of enzymes of this type. They also provide experimental evidence in support of speculations[17] that the catalytic power of some enzymes results from their strong powers of attraction for highly reactive intermediates.

(17) *Cf.* ref 2–4.

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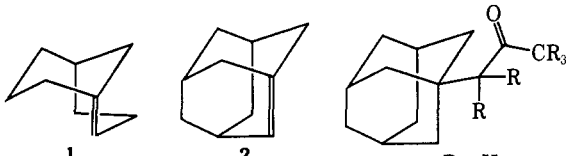
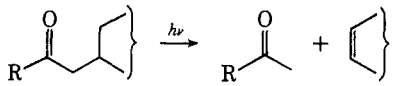
Photochemistry of 1-Adamantylacetone[1]

Sir:

Considerable recent interest in the synthesis of bicyclic compounds with bridgehead double bonds has resulted in the suggestion that such bicyclic compounds should be comparable in stability to the corresponding *trans*-monocyclic olefins.[2] Thus the bicyclononene, **1**, which has been synthesized by both Wiseman[2a] and Marshall[2b] can be correlated with the relatively stable *trans*-cyclooctene. By this line of reasoning, the interesting and elusive tricyclic bridgehead olefin, adamantene, **2**, should be similar in stability to *trans*-



cyclohexene, an exceptionally strained monocyclic olefin which has recently been postulated as a transient intermediate generated from photolysis of cyclohexenes.[3a] We wish to report the results of an attempt to generate adamantene, **2**, from adamantylacetone, **3**, by a Norrish type II photoelimination reaction (eq 1). If photoelimination were to occur from **3**, it could be detected easily by observing the production of acetone.



(1)

(1) Molecular Photochemistry. XXXIII. Paper XXXII: N. J. Turro and T.-J. Lee, *Mol. Photochem.*, **2**, 185 (1970). The authors thank the Air Force Office of Scientific Research (Grants 68-1381 and 70-1848) for their generous support of this work.

(2) (a) J. R. Wiseman, *J. Amer. Chem. Soc.*, **89**, 5966 (1967), and references therein; (b) J. A. Marshall and H. Faubl, *ibid.*, **89**, 5965 (1967); (c) J. R. Wiseman, H. F. Chan, and C. J. Ahola, *ibid.*, **91**, 2812 (1969); (d) J. R. Wiseman and J. A. Chong, *ibid.*, **91**, 7775 (1969); (e) J. A. Marshall and H. Faubl, *ibid.*, **92**, 948 (1970); (f) J. R. Wiseman and W. A. Pletcher, *ibid.*, **92**, 956 (1970).

(3) (a) J. A. Marshall, *Accounts Chem. Res.*, 2, 33 (1969). (b) Compound **9** exhibits the following spectral properties: nmr (CCl_4–TMS) δ 2.52 (broad s, 1 H), 2.20–1.85 with max 1.96 (m, 2 H), 2.05 (d, 2 H, J = 1.2 Hz), 1.85–1.35 with max 1.70 (m, 10 H), 1.58 (d, 3 H, J = 1.2 Hz). (c) Compound **10** exhibits the following spectral properties: ir $\nu_{max}^{CCl_4}$ 3020 (C=C), 1675 (C=C), 872 cm^{-1} (>=CH_2); nmr (CCl_4–TMS) δ 4.59 (m, 2 H), 2.53 (broad s, 2 H), 2.24 (broad s, 1 H), 2.15–1.50 with max 1.72 (m, 13 H). Further details of the structure proof for these compounds will be published in a full paper.