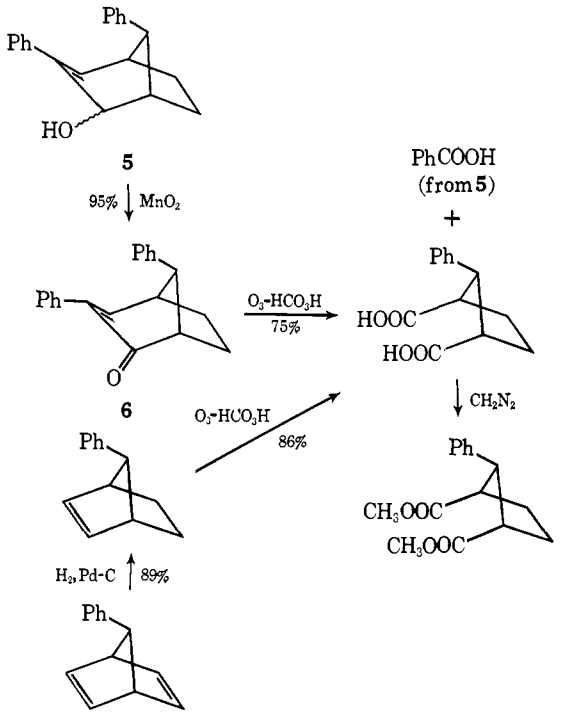
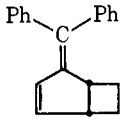


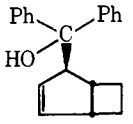

epimers); *m/e* fragments of 276 (parent), the *separated* phenyl fragments 159 (base peak, $CH_2{=}CH{-}C^+(OH){-}C(Ph){=}CH_2$) and 117 ($PhCH{=}CH{-}CH_2^+$).[10]

The important intermediate ketone **6**[3] was the *only* product of oxidation of **5** with manganese dioxide, a fact which supports the epimeric constitution of **5**. As evidence for its structure aside from the ozonolysis shown, ketone **6**, mp 107–108°, *m/e* 274 (parent), exhibited $\lambda_{KBr}$ 6.03 $\mu$ and $\lambda_{max}$ (EtOH) 265 m$\mu$ ($\epsilon$ 4460), indicative of an $\alpha,\beta$-unsaturated ketone. Also, upon reduction with lithium aluminum hydride **6** re-formed **5**, although as a different mixture of epimers now richer in the *exo*.

From **2**-OTs at least four products are formed, among them the epimeric alcohols **5** (29.5%). The other products have tentatively been assigned structures **7** (22.5%) and **8** (43%) from their spectra. Thus, **7**

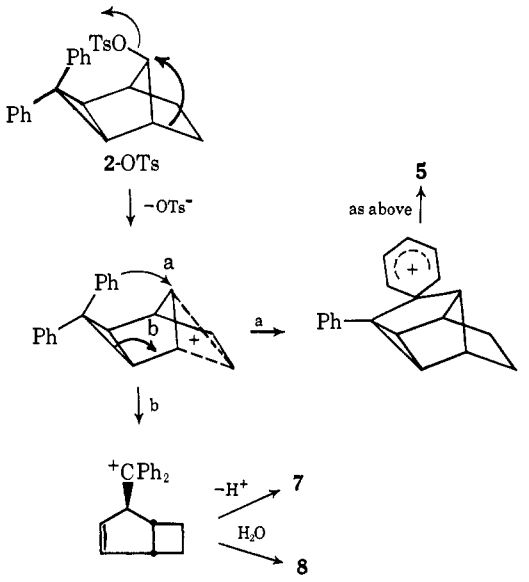



**7**




**8**

possessed $\lambda_{max}$ (EtOH) 242 ($\epsilon$ 9650) and 294 m$\mu$ ($\epsilon$ 21,800)[11] as well as two vinyl protons at $\delta$ 6.36 d and 6.06 m (AB portion of an ABX pattern). Compound **8** was apparently a tertiary alcohol, ir (neat) 2.83 and 8.6 $\mu$ with two vinyl protons at $\delta$ 5.85 m and 5.37 m (AB portion of an ABX pattern) and an OH at $\delta$ 1.95 s. Such products may be rationalized as shown. This scheme combines $\sigma$ participation by a ring bond (*à la syn*-7-norbornenyl tosylate[13]) and a facile cyclopropylcarbinyl rearrangement (b)[14] in competition




with the transannular phenyl migration (a) observed with **1**-OTs.

Work continues on the present system as well as on additional systems potentially susceptible to solvolytic participation combined with electrocyclic ring reactions. To our knowledge, this work is the first to describe such combined orbital symmetry and participation effects.

**Acknowledgment.** We thank Dr. Henry F. Dabek, Jr., for the mass spectral determinations.

(15) National Science Foundation Trainee, 1968–1970.

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## The Reaction of 1,3-Bisdiazopropane with Cyclohexane. The Possible Intermediacy of Diazocyclopropane

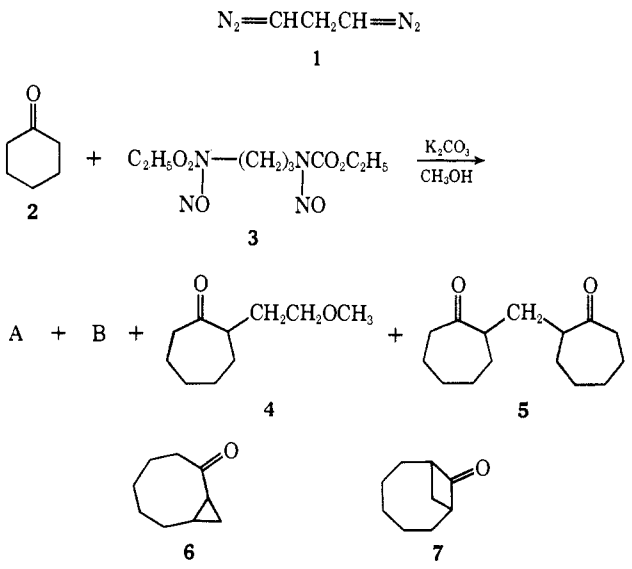
*Sir:*

We have reinvestigated the reaction of 1,3-bisdiazopropane (**1**) with cyclohexanone (**2**)[1] and have reassigned the structures of the two ketones which were formerly believed to arise by double expansion of the six-membered ring. Further, we have found a previously undetected product with a new ring system which rearranges to give one of the ketonic products. Diazocyclopropane is a possible intermediate in the reaction.

Gutsche and Smith reported that **1**, generated *in situ* from the bisnitroso urethane **3**, reacts with cyclohexanone (**2**) to give two isomeric ketones A and B along with the by-products **4** and **5**. Ketones A and B were isolated from the reaction mixture by column chromatography followed by distillation and a final purification by preparative vpc. The structures of A and B were assigned as **6** and **7** on the basis of analytical and spectral data.[1] In particular, A showed a carbonyl (1695 $cm^{-1}$) and cyclopropane hydrogens ($\tau$ 8.91 and 9.42) while **B** showed a four-membered ring ketone (1769 $cm^{-1}$) and low-field resonances in the nmr spec-

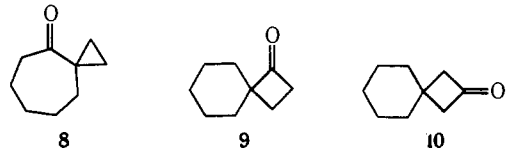
(10) The parent 1-OTs has for its base peaks the *geminal* phenyl fragments *m/e* 191, 192 ($Ph_2C^+{-}C{\equiv}CH$, $Ph_2C^+{-}CH{=}CH\cdot$).
(11) *Cf.* 1,1-diphenyl-1,3-butadiene: $\lambda_{max}$ (EtOH) 236 and 287 m$\mu$.[12]
(12) T. Holm, *Acta Chem. Scand.*, 17, 1441 (1963).
(13) S. Winstein and E. T. Stafford, *J. Amer. Chem. Soc.*, 79, 505 (1957).
(14) R. Breslow in "Molecular Rearrangements," P. de Mayo, Ed., Interscience, New York, N. Y., 1963, pp 259–276.

(1) C. D. Gutsche and T. D. Smith, *J. Amer. Chem. Soc.*, 82, 4067 (1960).



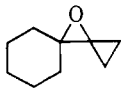
trum appropriate for hydrogens on a four-membered ring ($\tau$ 7.10, triplet, 2 H, and 8.46, triplet, 2 H).[1]

In our hands, the reaction products, after column chromatography and distillation, *but before vpc*, showed no evidence of compound B (assigned as **7**[1]) (no carbonyl between 1700 and 1800 $cm^{-1}$ and no low-field triplets). The low-boiling fraction[2a] showed the spectral characteristics of compound A (assigned as **6**[1]) along with a large symmetrical multiplet at $\tau$ 9.15 and a larger peak at 8.33 not reported by Gutsche and Smith. There were no protons in the vinyl region (*vide infra*). On injection of the low-boiling fraction into the gas chromatograph, two peaks were observed.[2b] The spectra of samples collected from the gas chromatograph revealed them to be ketones A and B isolated by Gutsche and Smith. Compound A, which had tentatively been assigned structure **6** by Gutsche and Smith[1] (although structure **8** was considered as a possibility—see footnote 30 of ref 1), was assigned structure **8** in accord with recently published nmr data on authentic material.[3,4] Similarly, we have revised the structure of compound B from the bridged structure **7** to spiro[3.5]nonan-1-one (**9**).



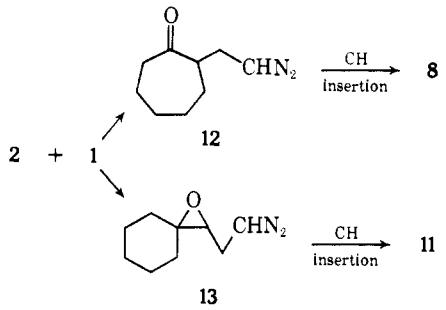
The nmr spectrum of B is more in accord with structure **9** than **7**. Furthermore, **7** has been prepared by another route and is clearly different from B.[5] Reaction of diazomethane with pentamethyleneketene (generated from cyclohexanecarbonyl chloride) produced ketones **9** and **10**.[6] Ketone **10** was also prepared from the reaction of dichloroketene[7] with methylenecyclohexane followed by reduction with zinc in acetic acid. Ketone **9** has spectra and gas chromatographic retention times identical with those of compound B prepared by the method of Gutsche and Smith[1] (after vpc).

The question of the origin of **9** was solved by identification of the labile compound in the chromatographed and distilled reaction mixture. The spectral characteristics required for this labile compound (peaks at $\tau$ 9.15, 8.33 in the nmr and no carbonyl) are in accord with 10-oxadispiro[2.0.5.1]decane (**11**).[8] Accordingly, **11** was synthesized by epoxidation of cyclopropylidenecyclohexane[9] with peroxybenzimidic acid.[10] The sensitive compound produced had all the spectral characteristics of the unstable compound in the low boiling fractions from the bisdiazopropane reaction, and it rearranged quantitatively to **9** on injection into the vpc.[11] The rearrangement may also be effected by heating **11** on a steam bath.



The question of the origin of **8** and **11** in the reaction of **1** with **2** is interesting. It is clear that the "double insertion reaction" of bis-1,3-diazocyclopropane fails. Compounds **4** and **5** are derived from single insertions into one and two molecules of cyclohexanone, respectively. Two schemes are presently entertained for the explanation of the origin of **8** and **11**.

**Scheme I**



Reaction of **2** with **1** (or its equivalent with only one functional group transformed into diazo) in each of the usual reaction paths for diazoalkanes with ketones should give **12** and **13**. Subsequent C–H insertions (possibly *via* a carbene) could give **8** and **11**. Arguing against this mechanistic scheme is the complete absence

(2) (a) The low-boiling fraction (bp 49–64°, 0.1 mm) was obtained in 38% yield (lit.[1] 26%). (b) The yields of A, B, and 4 were 27, 10, and 1%, respectively (standardized vpc response). Gutsche and Smith isolated 9% A, 9% B, and 2.4% 4 by preparative vpc. Differences in concentrations of reactants may be responsible for these differences in yields.

(3) P. Leriverend and J. M. Conia, *Bull. Soc. Chim. Fr.*, 121 (1966).

(4) In this reassignment we concur with the assignment made earlier by C. H. DePuy and J. L. Marshall, *J. Org. Chem.*, **33**, 3326 (1968).

(5) Bicyclo[5.1.1]nonan-8-one (**7**) has been prepared by W. F. Erman and H. C. Kretschmar, *J. Amer. Chem. Soc.*, **89**, 3842 (1967), who do not comment on the nonidentity of their compound with compound B described by Gutsche and Smith.[1]

(6) E. R. Buchman, D. H. Deutsch, and G. I. Fujimoto, *ibid.*, **75**, 6228 (1953). The procedure followed was adapted from N. J. Turro and W. B. Hammond, *Tetrahedron*, **24**, 6017 (1968).

(7) (a) H. C. Stevens, D. A. Reich, D. R. Brandt, K. R. Fountain, and E. J. Gaughan, *J. Amer. Chem. Soc.*, **87**, 5257 (1965); (b) L. Ghosez, R. Montaigne, and P. Mollet, *Tetrahedron Lett.*, 135 (1966); (c) R. W. Turner and T. Seder, *Chem. Commun.*, 399 (1966).

(8) To our knowledge the two syntheses of **11** herein reported provide the first example of this new ring system.

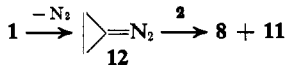
(9) E. E. Schweizer and J. G. Thompson, *Chem. Commun.*, 666 (1966); E. E. Schweizer, C. J. Berninger, and J. G. Thompson, *J. Org. Chem.*, **33**, 336 (1968).

(10) G. B. Payne, *Tetrahedron*, **18**, 763 (1962).

(11) Vpc conditions for rearrangement: 5 ft × 1/4 in. column of 6% carbowax on Chromosorb G; injector temperature, 175°; column temperature, 150°; detector temperature, 200°. Epoxide **11** could be purified satisfactorily using a 5 ft × 1/4 in. 20% carbowax on Chromosorb W containing 10% KOH; injector, 170°, column 120°, detector 150°.

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.

(12) W. Kirmse and H. Schütte, *Chem. Ber.*, **101**, 1674 (1968).
(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, $\lambda_{max}$ 293 mμ, log $\epsilon_M$ 3.62 at pH 7; II′, $\lambda_{max}$ 291 mμ, log $\epsilon_M$ 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 ($\lambda_{max}$ 263 mμ, log $\epsilon_M$ 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.
(4) R. Wolfenden, *Nature (London)*, **223**, 704 (1969).
(5) L. N. Johnson and R. Wolfenden, *J. Mol. Biol.*, **47**, 93 (1970).
(6) J. G. Cory and R. J. Suhadolnik, *Biochemistry*, **4**, 1733 (1965).
(7) R. Wolfenden, *J. Amer. Chem. Soc.*, **88**, 3157 (1966).
(8) H. Baer and G. I. Drummond, *Biochem. Biophys. Res. Commun.*, **24**, 584 (1966).
(9) B. M. Chassy and R. J. Suhadolnik, *J. Biol. Chem.*, **242**, 3655 (1967).
(10) R. Wolfenden and J. F. Kirsch, *J. Amer. Chem. Soc.*, **90**, 6849 (1968).
(11) R. Wolfenden, *Biochemistry*, **8**, 2409 (1969).
(12) R. Wolfenden, J. Kaufman, and J. B. Macon, *ibid.*, **8**, 2412 (1969).
(13) H. Linschitz and J. S. Connolly, *J. Amer. Chem. Soc.*, **90**, 2979 (1968).
(14) J. G. Cory and R. J. Suhadolnik, *Biochemistry*, **4**, 1729 (1965).
(15) D. L. Smith and P. J. Elving, *J. Amer. Chem. Soc.*, **84**, 1412 (1962).