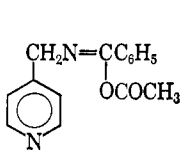
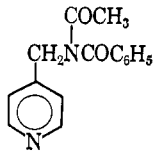
Cohen and Fager[6] have suggested that the N–O bond of **1** might cleave *heterolytically* to produce an acetate anion and a picolyl cation. The latter could then be attacked by internal or external acetate (or acetic acid), thereby accounting for products from both routes *via* a single mode of cleavage of **1**. The production of substantial ester in the reation of the related 2-picoline N-oxide with phenylacetic[6,7] and trichloroacetic[7] anhydrides has been interpreted as supporting a picolyl cation mechanism in that case, although quite similar experimental results[4] in the case of 4-picoline N-oxide have been used to support the radical-pair mechanism.

We have attempted to trap the intermediate picolyl species by performing the reaction of 4-picoline N-oxide with acetic anhydride in the solvents anisole and benzonitrile, and in a 1:1 mixture of the two. The anisole experiment produced a 20% yield of a mixture of three picolylanisoles in addition to the usual ester product. The *m*- and *p*-(4-picolyl)anisoles were identified by comparison with independently prepared samples.[8] The *meta*:*para* ratio, 0.25, is consistent with cationic attack on a ring bearing an *ortho,para*-directing substituent but not with alkyl radical attack, which gives a ratio varying between 5.6 and about 1.4, depending upon the particular radical.[11]

Radical attack is known[11] to occur readily on the benzonitrile ring system, whereas cations attack the nitrogen.[12] In this solvent, the picolyl group was found to attack the nitrogen almost exclusively, producing the imide **5** (11% yield by nmr), probably by way of the intermediate **4**. The merest trace of material which



4



5

could result from attack of a picolyl group on the nucleus was detected by vpc–mass spectrometry. The structure of **5** was determined by vpc–mass spectrometry and by comparison with a specimen prepared by treatment of the benzamide with sodium hydride followed by acetic anhydride.

Corresponding results were obtained in the direct competition between anisole and benzonitrile. Although the latter is known to be much more susceptible to radical substitution than the former,[11] essentially all the substitution occurred in the anisole ring. The only other product involving the solvent was **5**.

While these experiments clearly demonstrate that the reaction of 4-picoline N-oxide with acetic anhydride generates a substantial portion of picolyl cations, it is conceivable that this is a side reaction and that ester formation proceeds by an independent radical-pair process in which recombination is so remarkably efficient that picolyl radicals cannot be trapped by the solvent. However, this possibility must be regarded as highly unlikely, especially in view of the strong contrary evidence in the case of 2-picoline N-oxide.[6,7]

The synthetic implications of this simple method of generation of picolyl cations is now under investigation.

Acknowledgment. We wish to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work. We also thank the National Institutes of Health for a grant used to purchase the LKB 9000 combined gas chromatograph–mass spectrometer used in this work and Dr. Charles Sweeley for help in determining and interpreting the mass spectra.

Theodore Cohen, Gary L. Deets
Department of Chemistry, University of Pittsburgh
Pittsburgh, Pennsylvania 15213
Received May 16, 1967

(6) T. Cohen and J. H. Fager, *J. Am. Chem. Soc.*, **87**, 5701 (1965).
(7) T. Koenig, *ibid.*, **88**, 4045 (1966).
(8) The *para* isomer was prepared by reduction of *p*-(4-picolyl)-nitrobenzene[9] and thermal decomposition in methanol of the corresponding diazonium salt. A mixture of the *meta* and *para* isomers was prepared by the benzyne method, which involves the reaction of *p*-bromoanisole with sodium amide and 4-picoline.[10]
(9) A. J. Nunn and K. Schofield, *J. Chem. Soc.*, 583 (1952).
(10) P. H. Dirstine and F. W. Bergstrom, *J. Org. Chem.*, **11**, 55 (1946).
(11) J. R. Shelton and C. W. Uzelmeier, *J. Am. Chem. Soc.*, **88**, 5222 (1966).
(12) R. M. Lusskin and J. J. Ritter, *ibid.*, 72, 5577 (1950).

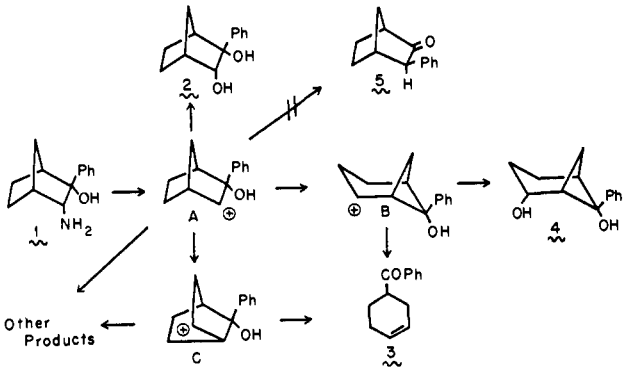
Anomalous Behavior of 3-*endo*-Hydroxy-3-*exo*-phenyl-2-*endo*-norbornylamine during Deamination[1]

Sir:

An explanation based on torsional effects has recently been advanced[2] to account for the "remarkable stereospecificity of 3,2 shifts" in rearrangements of derivatives of bicyclo[2.2.1]heptane. The stereospecificity requirements are so stringent that 3-*endo*-hydrogens[3] or methyl groups[4] must become *exo* through circuitous routes[3] involving Wagner–Meerwein and 6,1-hydride shifts before they can migrate to the adjacent (*exo*-2) position. The phenyl is another group which is unable to migrate 3 → 2 or 2 → 3 in an *endo–endo* fashion.[3,5] To our surprise, however, there also does not seem to be an example of *exo–exo* migration of phenyl during solvolyses of substituted norbornyl derivatives.[3,5,6]

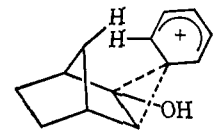
It is well known that during deamination of aliphatic amines the energy profiles of the various processes which can occur are so compressed that pathways which are unlikely during ordinary solvolyses often become important.[7-9] In 3-*endo*-hydroxy-3-*exo*-phenyl-2-*endo*-

(1) Research sponsored by the U. S. Atomic Energy Commission under contract with the Union Carbide Corp.
(2) P. von R. Schleyer, *J. Am. Chem. Soc.*, **89**, 699 (1967).
(3) C. J. Collins, Z. K. Cheema, R. G. Werth, and B. M. Benjamin, *ibid.*, **86**, 4913 (1964); see also the several pertinent references given in ref 2.
(4) J. D. Roberts and J. A. Yancey, *ibid.*, **75**, 3165 (1953); W. R. Vaughan and R. Perry, Jr., *ibid.*, **75**, 3168 (1953); A. M. T. Finch, Jr., and W. R. Vaughan, *ibid.*, **87**, 5520 (1965).
(5) B. M. Benjamin, B. W. Ponder, and C. J. Collins, *J. Am. Chem. Soc.*, **88**, 1558 (1966); B. M. Benjamin and C. J. Collins, *Tetrahedron Letters*, **45**, 5477 (1966); C. J. Collins and B. M. Benjamin, *J. Am. Chem. Soc.*, **89**, 1652 (1967).
(6) Dr. D. C. Kleinfelter and his co-workers have subjected the four 3-phenyl-2-norbornyl tosylates to exhaustive solvolytic examination. Although isotopic experiments will be required to rigidly exclude the possibility of phenyl migration, neither the kinetic data nor the products isolated on solvolysis require phenyl migration in their interpretation. See also D. C. Kleinfelter, E. S. Trent, J. E. Mallory, and T. E. Dye, *J. Am. Chem. Soc.*, **88**, 5350 (1966).
(7) R. Huisgen and Ch. Rüchardt, *Ann.*, **601**, 1 (1956).
(8) H. Stetter and P. Goebel, *Chem. Ber.*, **96**, 550 (1963).
(9) B. M. Benjamin, P. Wilder, Jr., and C. J. Collins, *J. Am. Chem. Soc.*, **83**, 3654 (1961); B. M. Benjamin and C. J. Collins, *ibid.*, **83**, 3662 (1961).



norbornylamine (**1**) the C_3–phenyl bond is *trans* (although about 60° away from coplanarity) with the C_2–N bond, a situation as conducive as possible for phenyl migration in the norbornane skeleton. Further, since migration of phenyl during deamination of **1** should lead to 3-*exo*-phenylnorbornanone-2 (**5**), one might suspect a powerful driving force for ketone formation. Accordingly we synthesized and deaminated **1** in order to determine whether—even under these favorable conditions—phenyl is still unable to undergo *exo–exo* shift to an adjacent carbon.

Deamination of the hydrochloride of **1**[10] in water led to all of the products previously[5] isolated during hydrolysis of 3-*exo*-*p*-toluenesulfonoxy-2-*endo*-phenylnorborneol-2, plus the three additional products **2**[11] (6%), **3**[11] (23%), and **4**[12] (22%). There was no evidence for the formation of 3-*exo*-phenylnorbornanone-2 (**5**).[13] Thus 7,2 Wagner–Meerwein rearrangement to form ion B and thence **4** is an easier pathway than *exo–exo* migration of phenyl.[14] Since the diol **4** is a major product of the deamination (22% yield) the ratio of 7,2 shift to phenyl migration (2,3-*exo–exo*) is at least 20:1 and may be much greater depending upon how much of the ketone **3** is produced through ion B. The reasons for this remarkable behavior do not appear to lie in the slightly unfavorable dihedral angle between the C_2–N and C_3–phenyl bonds, for this factor does not prevent the migration of hydrogen[3] or methyl[4] when similarly situated. We propose that in the transition state (D) for phenyl migration the σ-hydrogen of the



D

phenyl and the 7-*syn*-hydrogen of the norbornane skeleton interfere with each other to such an extent that phenyl migration is excluded.

(15) Atomic Energy Commission Postdoctoral Fellow, 1963–1965.

Clair J. Collins, Vernon F. Raaen
Ben M. Benjamin, Irving T. Glover[15]
Chemistry Division, Oak Ridge National Laboratory
Oak Ridge, Tennessee
Received May 8, 1967

The Pepsin-Catalyzed Hydrolysis of Sulfite Esters

Sir:

Beginning with the pioneering work of Fruton and Bergmann in 1939, a number of investigations have shown that the proteolytic enzyme pepsin catalyzes the hydrolysis of a limited class of N-acyl-L-dipeptides and N-acyl-L-tripeptides.[1-7] Recently it has been established that pepsin also catalyzes the hydrolysis of selected esters of β-phenyl-L-lactic acid.[8,9] We wish to report that certain organic sulfite esters are excellent substrates for pepsin.[10]

(1) J. S. Fruton and M. Bergmann, *J. Biol. Chem.*, **127**, 627 (1939).
(2) L. E. Baker, *ibid.*, **193**, 809 (1951); **211**, 701 (1954).
(3) M. S. Silver, J. L. Denburg, and J. J. Steffens, *J. Am. Chem. Soc.*, **87**, 886 (1965).
(4) A. J. Cornish-Bowden and J. R. Knowles, *Biochem. J.*, **96**, 71P (1965).
(5) W. T. Jackson, M. Schlamowitz, and A. Shaw, *Biochemistry*, **4**, 1537 (1965).
(6) E. Zeffren and E. T. Kaiser, *J. Am. Chem. Soc.*, **88**, 3129 (1966).
(7) K. Inouye, I. M. Voynick, G. R. Delpierre, and J. S. Fruton, *Biochemistry*, **5**, 2473 (1966).
(8) L. A. Lokshina, V. N. Orekhovich, and V. A. Sklyankina, *Nature*, **204**, 580 (1964).
(9) K. Inouye and J. S. Fruton, *J. Am. Chem. Soc.*, **89**, 187 (1967).
(10) Preliminary report presented at the Pacific Slope Biochemical Conference, Eugene, Ore., Aug 25–27, 1966. This research was supported in part by Grant GM 13446, U. S. Public Health Service. Kinetic constants for the enzymic hydrolysis of methyl phenyl sulfite were obtained by following the initial rate of production of phenol at 270 mμ using a Gilford 2000 spectrophotometer. The concentration of pepsin (twice recrystallized, Worthington Biochemical Corp.) was estimated from the absorbance at 278 mμ assuming a molar absorptivity of 50,900 l. mole^{-1} cm^{-1} determined by G. E. Perlmann (*J. Biol. Chem.*, **241**, 153 (1966)). The total enzyme concentration in these experiments was $[E_T] = 1.5 \times 10^{-5}$ *M*; initial substrate concentration was varied from $[S]_0 = 0.6$ to 3.8 m*M*. Buffers (0.10 *M* glycine hydrochloride) were adjusted to an ionic strength of 0.50 *M* with sodium chloride. The $\Delta\epsilon$ for complete hydrolysis of methyl phenyl sulfite is 1.14 ± 0.02 $\times 10^3$ at pH 2.0 and pH 4.0.

Methyl phenyl sulfite was prepared by the method of P. Carré and D. Libermann, *Compt. Rend.*, **195**, 799 (1926); bp 65–66° (1.2 mm). *Anal.* Calcd for $C_7H_8O_3S$: C, 48.84; H, 4.68; S, 18.62. Found: C, 49.09; H, 4.77; S, 18.21.

Phenyl sulfite was synthesized by the method of A. Green, *J. Chem. Soc.*, 500 (1927); bp 130° (0.45 mm). *Anal.* Calcd for $C_{12}H_{10}O_3S$: C, 61.52; H, 4.30; S, 13.68. Found: C, 61.73; H, 4.34; S, 13.98.

p-Bromophenyl sulfite was prepared from *p*-bromophenol and thionyl chloride; mp 62.5–63.5°. *Anal.* Calcd for $C_{12}H_8Br_2O_3S$: C, 36.76; H, 2.06. Found: C, 37.01; H, 2.20.

N-Diazoacetyl-DL-norleucine methyl ester was prepared according to the method of Rajagopalan, *et al.*;[11] mp 52.5–56.5°. *Anal.* Calcd for $C_9H_{15}O_3N_3$: C, 50.79; H, 7.09. Found: C, 49.41; H, 6.94.

N-Carbobenzoxy-L-phenylalanyl-L-tyrosine was purchased from Cyclo Chemical Corp. and recrystallized from methanol–water. *Anal.* Calcd for $C_{26}H_{26}N_2O_6$: C, 67.52; H, 5.66. Found: C, 67.02; H, 5.99.

(11) T. G. Rajagopalan, W. H. Stein, and S. Moore, *J. Biol. Chem.*, **241**, 4295 (1966).

(10) The synthetic route employed was

$$\text{2,3-norbornanedione} \xrightarrow{\text{PhMgBr}} \text{3-keto-2-phenylnorborneol-2 oxime} \xrightarrow{\text{LiAlH}_4} \mathbf{1}$$

Elemental analyses and nmr and infrared spectra were all consistent with the assigned structure.

(11) The diol **2** was synthesized independently by lithium aluminum hydride reduction (in small yield) of 3-keto-2-*exo*-phenylnorborneol-2. Ketone **3** was prepared by the addition of phenylmagnesium bromide to 3-cyclohexenylcarboxaldehyde followed by oxidation with CrO_3 in pyridine.

(12) P. Yates and R. J. Crawford, *J. Am. Chem. Soc.*, **88**, 1561 (1966), obtained 2β-hydroxybicyclo[3.1.1]heptan-6-one through the acid-catalyzed rearrangement of 3-diazonorcamphor. A sample of this ketone, on treatment with phenylmagnesium bromide, was converted to the diol **4**, thus confirming its structure. We are indebted to Professor Yates, who kindly supplied us with a sample of his ketone.

(13) Compound **5**, which we had prepared previously,[3] could have been detected in yields of 1%.

(14) The α-terpineol isolated upon deamination of 2-*endo*-bornylamine [W. Hückel and F. Nerdel, *Ann.*, **528**, 57 (1937)] and α-fenchylamine (2-*endo*) [W. Hückel and U. Ströle, *ibid.*, **585**, 182 (1954)] can also be formulated as arising from 7,2 shift to give an intermediate similar to B.