Schleyer's group at Princeton.[38] In this case, 1-adamantylcarbene ring-expands to 3-homoadamantene (**24**). The structure of **24** was inferred from the formation of appropriate dimers.

Most of the experimental skill and much of the conceptual input for the work just described were provided by an exceptionally skilled group of young coworkers. Drs. William Baron, Mark DeCamp, Michael Hendrick, and Ronald Levin all did portions of this work as part of their Ph.D. Theses at Princeton. Dave Richardson's A.B. Thesis concerned the gas-phase pyrolysis of diazomalonic ester and Tom Berdick successfully worked out the formation of xylenes from **16**. *Dr. V. V. Kane was instrumental in making the synthetic efforts feasible, and Dr. Anthony Wolf carried out the paracyclophane and bridgehead olefin isolations and labeling experiments with great skill.*

It has been a pleasure to collaborate with Professors Philip Shevlin of Auburn University, Peter Gaspar of Washington University, and Paul Schleyer at Princeton. Over the years conversations with Professor Gaspar, who is ever critical and insightful, have been especially stimulating and encouraging.

(38) M. Farcasiu, D. Farcasiu, R. T. Conlin, M. Jones, Jr., and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **95**, 8207 (1973).

Some Chemistry of Alkanediazotates

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Received April 24, 1974

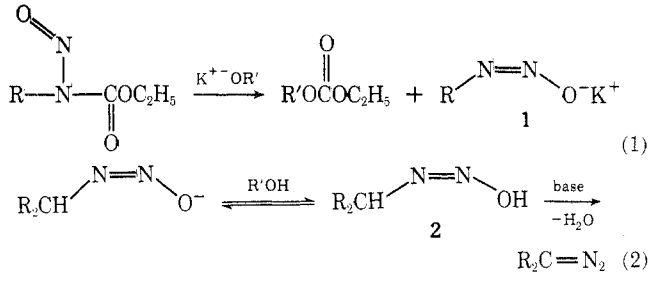
The structure and chemistry of *arene*diazotates, $ArN{=}NO^-$, have long been of interest, and, from 1894 to 1912, were the subject of heated controversy between A. Hantzsch and E. Bamberger.[1a] They can be formed by the action of hydroxide ions on arenediazonium ions.

The importance of the latter in azo coupling reactions was an early driving force for the study of the diazotates. Today, there is intense interest in the rates and equilibria of the reactions of arenediazonium ions with nucleophiles,[1b] and the related chemistry of the arenediazotates is still being developed.

Alkyldiazonium ions are much less stable than their aryl counterparts, are seldom isolated, and rarely participate in azo coupling reactions. Accordingly, the chemistry of *alkane*diazotates, $RN{=}NO^-$, is not accessible *via* the diazonium ions. Although alkanediazotates have been known for a long time, the development of their chemistry has been somewhat haphazard.

We therefore initiated a broad study of alkanediazotates, and have found that their chemistry has important mechanistic and synthetic features. This Account will explore those aspects. We also make brief note of the past and present context of alkanediazotate chemistry.

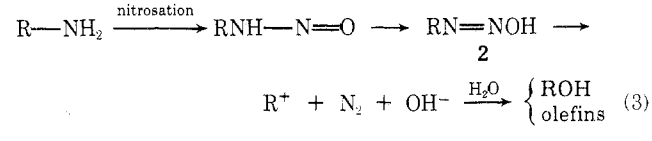
A Brief History of Alkanediazotates. Alkanediazotates, **1**, may be generated by the basic cleavage of *N*-alkyl-*N*-nitrosourethanes (eq 1). In alcoholic KOH, **1**, when possessing an α proton, can afford a diazoalkane (eq 2). The intermediacy of **1** in Pechmann's diazomethane synthesis[2] was established by Hantzsch,[3] who cleaved *N*-methyl-*N*-nitrosourethane with ethereal KOC_2H_5, isolating solid potassium methanediazotate (**1**, R = CH_3), which gave diazomethane upon addition of base and wet ether. Similar behavior was observed for **1**, R = $C_6H_5CH_2$.



(1)

(2)

The conjugate acid of **1**, diazotic acid (**2**), is a key intermediate in the nitrosative deamination of primary carbinamines[4] (eq 3). The centrality of **2** in diazoalkane synthesis (eq 2) and in deaminative reactions was implicit in observations that **1** (R = $C_6H_5CH_2$) gave rise to benzyl alcohol, benzyl methyl ether, and phenyldiazomethane in aqueous metha-



(3)

Robert A. Moss was born in Brooklyn, N. Y. He received a B.S. degree from Brooklyn College, and M.S. and Ph.D. degrees from the University of Chicago, where he studied with Professor G. L. Closs. After a postdoctoral year at Columbia with Professor Ronald Breslow, he joined the School of Chemistry at Rutgers University (1964), where he is now Professor of Chemistry. Dr. Moss has been National Institutes of Health Special Postdoctoral Fellow and Visiting Scientist at M.I.T., and a Fellow of the A. P. Sloan Foundation. Besides diazotate and deamination chemistry, he is interested in carbenes, the synthesis of azoxyalkanes, and micellar organic chemistry.

(1) (a) Historical and chemical considerations appear in H. Zollinger, "Azo and Diazo Chemistry," Interscience, New York, N.Y., 1961; (b) H. Zollinger, *Accounts Chem. Res.*, 6, 335 (1973).

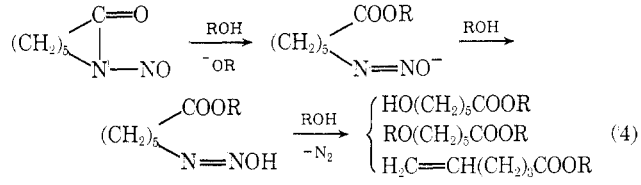
(2) H. v. Pechmann, *Chem. Ber.*, **27**, 1888 (1894); **28**, 855 (1895).

(3) A. Hantzsch and M. Lehmann, *Chem. Ber.*, **35**, 897 (1902). The $CH_3N{=}NOK$ was probably contaminated with potassium ethyl carbonate. Pure material can be prepared from CH_3NH_2, NOCl, and CH_3OK: E. Müller, H. Haiss, and W. Rundel, *Chem. Ber.*, **93**, 1541 (1960).

(4) Reviews include: (a) R. A. Moss, *Chem. Eng. News*, 49 (48), 28 (1971); (b) J. T. Keating and P. S. Skell in "Carbonium Ions," Vol. II, G. A. Olah and P. v. R. Schleyer, Ed., Interscience, New York, N.Y., 1970, p 573 ff; (c) L. Friedman in ref 4b, p 655 ff; (d) E. H. White and D. J. Woodcock in "The Chemistry of the Amino Group," S. Patai, Ed., Interscience, New York, N.Y., 1968, pp 440–483.

nol.[2] In the acidic media typical of nitrous acid deaminations, the diazotate itself is not involved. However it is clear that an isolated diazotate could, by protonation, be made to enter sequence 3 at the diazotic acid stage. The consequences of such an entry are discussed below.

Despite early reports, alkanediazotates appeared infrequently in the literature over the succeeding half-century. Renewed interest was generated by the contributions of Newman,[5] who examined the basic cleavage of *N*-nitrosooxazolidones, and of Huisgen[6a] and Müller,[6b] who studied a similar reaction of *N*-nitrosocaprolactam (eq 4). In both cases, diazotates or diazotic acids were key intermediates.

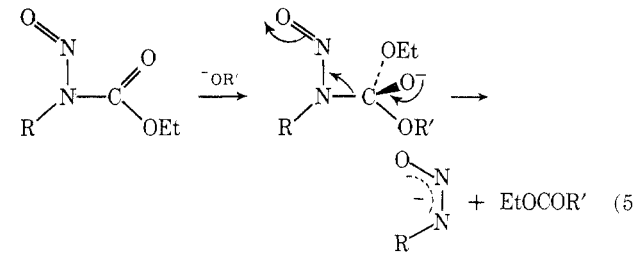


(4)

Thereafter, diazotates were encountered in diazoalkane syntheses, where they also afforded carbonium ion products, *cf.* eq 2 and 3. Gutsche reexamined Hantzsch's study of 1 (R = $C_6H_5CH_2$), clearly establishing the interrelation of diazotate, diazotic acid, diazoalkane, and the derivative carbonium ion.[7] Analogous interrelations were discovered for cyclohexanediazotate[8] and cyclobutanediazotate.[9]

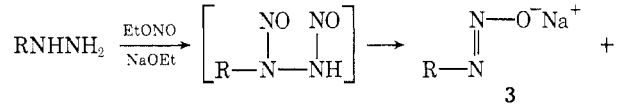
The Stereochemistry of Alkanediazotates. The configuration of the diazotates obtained according to eq 1 appears to be syn, *cf.* **1.** This has been established for methanediazotate by X-ray studies[10] and nmr spectroscopy[11] and for 1-phenylethanediazotate by nmr.[12] The reason behind this stereochemical result is not firmly established, but must have to do with the orientation adopted by the nitroso group in the tetrahedral intermediate formed when alkoxide attacks the nitrosourethane's carbonyl carbon (see eq 5).

The negative charge in methanediazotate is delocalized; both N-N (1.32 Å) and N-O (1.29 Å) linkages are intermediate between single and double bonds.[10] However, rotation about N-N is sufficiently



(5)

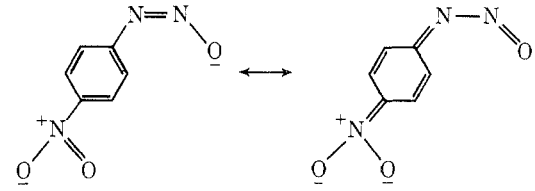
1



(6)

restricted to prevent facile syn → anti isomerism: *syn-* and *anti*-diazotates, **3**,[12,13] can be separately obtained, the latter from monoalkylhydrazines (eq 6).

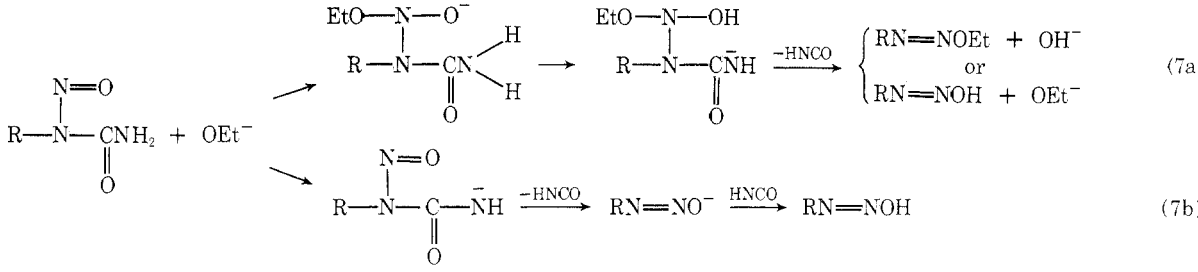
The *anti*-diazotates prepared *via* eq 6 include examples with R = methyl,[13] benzyl,[13] and 1-phenylethyl.[12] They are less reactive than their syn isomers and can be dissolved in *cold* water without reaction; heating induces diazoalkane and carbonium ion formation. Conceivably, anti → syn isomerization precedes the latter reaction, although such behavior is not expected at ~25°.[14] Even *syn-p*-nitrobenzenediazotate (4), in which double bond character at the



4

N-N bond is weakened by extended resonance, has ΔG^* ~20 kcal/mol for syn → anti at 300 K.[15] ΔG^* should be greater for alkanediazotates, in which such resonance is impossible.

Other Routes to Alkanediazotates. Diazotates can be formed by addition of N_2O across the C-Li bond of alkyl- or aryllithiums;[16,17] however, subse-



(7a)

(7b)

(5) M. S. Newman and A. Kutner, *J. Amer. Chem. Soc.*, **73**, 4199 (1951); M. S. Newman and W. M. Edwards, *ibid.*, **76**, 1840 (1954).

(6) (a) R. Huisgen and J. Reinertshofer, *Justus Liebigs Ann. Chem.*, **575**, 174 (1952); (b) G. Nischk and E. Müller, *ibid.*, **576**, 232 (1952).

(7) C. D. Gutsche and H. E. Johnson, *J. Amer. Chem. Soc.*, **77**, 109 (1955).

(8) F. W. Bollinger, F. N. Hayes, and S. Siegal, *J. Amer. Chem. Soc.*, **72**, 5592 (1950); K. Heyns and A. Heins, *Justus Liebigs Ann. Chem.*, **604**, 133 (1957).

(9) D. E. Applequist and D. E. McGreer, *J. Amer. Chem. Soc.*, **82**, 1965 (1960).

(10) E. Müller, W. Hoppe, H. Hagenmaier, H. Haiss, R. Huber, W. Rundel, and H. Suhr, *Chem. Ber.*, **96**, 1712 (1963); E. Müller, W. Rundel, H. Haiss, and H. Hagenmaier, *Z. Naturforsch. B*, **15**, 751 (1960).

(11) H. Suhr, *Chem. Ber.*, **96**, 1720 (1963).

(12) E. H. White, T. J. Ryan, and K. W. Field, *J. Amer. Chem. Soc.*, **94**, 1360 (1972).

(13) J. Thiele, *Chem. Ber.*, **41**, 2806 (1908); *Justus Liebigs Ann. Chem.*, **376**, 239 (1910).

(14) White has argued against such a possibility; see ref 12, note 11.

(15) V. A. Ketlinskii and I. L. Bagal, *J. Org. Chem. USSR*, **9**, 1915 (1973); C. D. Ritchie and J. D. Wright, *J. Amer. Chem. Soc.*, **93**, 2425 (1971); E. S. Lewis and M. P. Hanson, *ibid.*, **89**, 6268 (1967), and references therein. Resonance in 4 is decreased by the inability of diazotate and phenyl groups to be coplanar in the syn isomer because of steric hindrance between diazotate oxygen and ortho hydrogen atoms.

(16) F. M. Beringer, J. A. Farr, Jr., and S. Sands, *J. Amer. Chem. Soc.*, **75**, 3984 (1953).

(17) R. Meier, *Chem. Ber.*, **86**, 1483 (1953); R. Meier and W. Frank, *ibid.*, **89**, 2747 (1956).

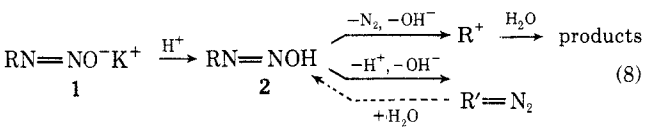
quent reactions transform the diazotate to azo and hydrazo compounds.

The action of alkoxides on *N*-alkyl-*N*-nitrosoureas appears not to occur by attack at the carbonyl group. Suggested mechanisms for these reactions include those of Jones[18] and Hecht,[19] eq 7a and 7b. Further work is required to establish the scope of these mechanisms.[20] In neither case are diazotates isolated in high yield.

With *N*-alkyl-*N*-nitrosourethanes (or amides), attack at the nitrosyl group can sometimes take precedence over attack at carbonyl (eq 1), especially when LiOEt is the base.[18] Again, as in eq 7a and 7b, diazotates are not isolated.

The Solvolysis of Alkanediazotates. Alkanediazotates can be obtained as solid salts by the potassium *tert*-butoxide cleavage of ethereal *N*-alkyl-*N*-nitrosourethanes. For the purpose of subsequent reaction, the solid diazotates can be slurried in such solvents as ether or methylene chloride, or dissolved in hexamethylphosphoric triamide (HMPA).

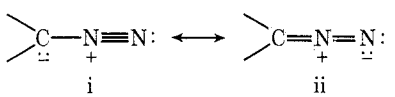
Our work began with a study of the hydrolytic partitioning of alkanediazotates, **1**, into diazoalkanes and carbonium ions (eq 8).[21] With R = secondary



(8)

alkyl (or 2,3-dipropylcyclopropenylmethyl[21,22]), relatively stable alkyl cations formed to the near exclusion of diazoalkanes; with R = primary alkyl, a rather even partition into cationic products (alcohols, alkenes) and diazoalkanes was observed;[21,23] and with R = methyl,[3] benzyl,[3] or allyl,[24] the diazoalkanes dominated. Note that diazoalkane formation is first order in base[24,25] and that the above results pertain to ~3 *M* aqueous hydroxide.

The dependence of the kinetically controlled partition, eq 8, on the structure of R is mainly governed by those factors which determine the stability of diazoalkanes, for example the presence of a primary or a vinyl- or aryl-conjugated α carbon atom (*cf.* the "carbanionic" α carbon in the resonance hybrid i ↔ ii).[21] The partition is less strongly affected by struc-



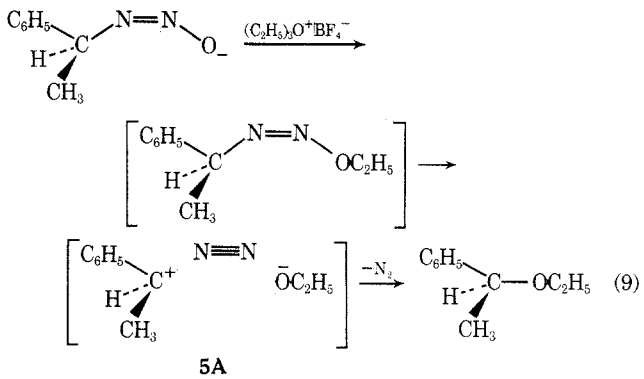
tural features which pertain to carbonium ion stability, because the fragmentation of diazotic acid (**2**) is a low activation energy process.[4]

In the case of *sec*-alkyl R groups, the carbonium ion branch of eq 8 is largely followed. Deuterium labeling experiments prove that any diazoalkane which does form cannot return and enter the carbonium ion pool.[21]

The importance of sequence 8 is that we have in hand a way of *generating alkyl cations in strongly basic* (3 *M* OH^-) or *nucleophilic* media. This can also be accomplished by the anodic oxidation of alkanecarboxylate ions[26] or by the "deoxidation" of alcohols,[27] but the unique feature of the diazotate route is its ability to directly generate ion pairs and ion triplets.

Nitrogen-Separated Ion Pairs and Ion Triplets. The possible intervention of ion pairs in the solvolytic reactions of *sec*-alkyl substrates is basic to the understanding of solvolysis reactions; it is also contentious in the extreme.[28] It is not our purpose to explore this issue here, but rather to exhibit new reactions which do generate ionic species in easily varied environments. Delineation of the properties of these latter species may be useful for the analysis of solvolytic reactions.

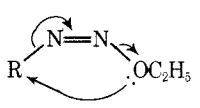
A simple example of ion-pair formation from diazotates occurs in the ethylation of 1-phenylethanediazotate with $Et_3O^+BF_4^-$ in CH_2Cl_2, which affords the nitrogen-separated[29] ion pair **5A**[30] (eq 9). In the



(9)

absence of a nucleophilic solvent, *return* of ethoxide ion dominates, and 1-phenylethyl ethyl ether is formed with 70% net retention (−50°).

If we rule out[31] a completely concerted, front-side conversion of $RN{=}NOC_2H_5$ to ROC_2H_5 (see iii),



(18) W. M. Jones and D. L. Muck, *J. Amer. Chem. Soc.*, **88**, 3798 (1966); W. M. Jones, D. L. Muck, and T. K. Tandy, Jr., *ibid.*, **88**, 68 (1966); T. K. Tandy, Jr., and W. M. Jones, *J. Org. Chem.*, **30**, 4257 (1965).

(19) S. M. Hecht and J. W. Kozarich, *Tetrahedron Lett.*, 5147 (1972); *J. Org. Chem.*, **38**, 1821 (1973).

(20) Equation 7a appears to hold for R = cyclopropyl;[18] eq 7b pertains to R = methyl.[19]

(21) R. A. Moss, *J. Org. Chem.*, **31**, 1082 (1966).

(22) A. E. Feiring and J. Ciabattoni, *J. Org. Chem.*, **37**, 3784 (1972).

(23) W. Kirmse and G. Wächterhäuser, *Justus Liebigs Ann. Chem.*, **707**, 44 (1967).

(24) The allyl case has been thoroughly studied by H. Hart and J. L. Brewbaker, *J. Amer. Chem. Soc.*, **91**, 716 (1969). Methanolyses of substituted cinnamyl diazotates showed that withdrawing substituents favored diazoalkane formation over nitrogen loss; donating substituents had the opposite effect. Similar conclusions were reached in comparative examination of allyl, methallyl, and crotyl diazotates.

(25) Unpublished work of R. A. Moss with neopentane diazotate.

(26) J. T. Keating and P. S. Skell, *J. Amer. Chem. Soc.*, **91**, 695 (1969); P. S. Skell and P. H. Reichenbacher, *ibid.*, **90**, 2309 (1968).

(27) P. S. Skell and I. Starer, *J. Amer. Chem. Soc.*, **81**, 4117 (1959).

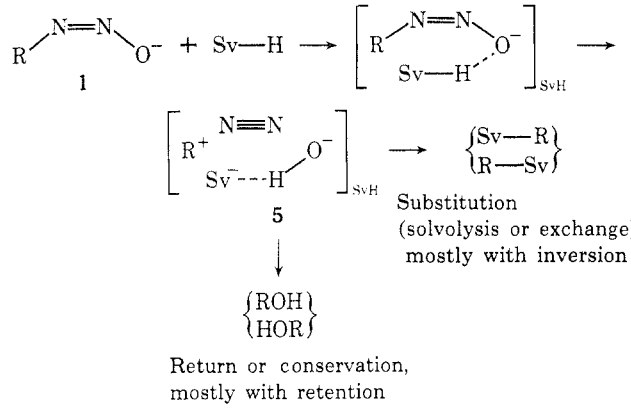
(28) A recent negative vote: V. F. Raaen, T. Juhlke, F. J. Brown, and C. J. Collins, *J. Amer. Chem. Soc.*, **96**, 5928 (1974). The positive case is summarized in R. A. Sneen, *Accounts Chem. Res.*, **6**, 46 (1973). See also: J. B. Lambert and G. J. Putz, *J. Amer. Chem. Soc.*, **95**, 6313 (1973); R. A. Sneen and H. M. Robbins, *ibid.*, **94**, 7868 (1972). See *contra:* D. J. Raber, J. M. Harris, R. E. Hall, and P. v. R. Schleyer, *ibid.*, **93**, 4821 (1971); B. J. Gregory, G. Kohnstam, M. Paddon-Row, and A. Queen, *Chem. Commun.*, 1032 (1970). Many leading references are cited in these articles.

(29) E. H. White, R. H. McGirk, C. A. Aufdermarsh, Jr., H. P. Tiwari, and M. J. Todd, *J. Amer. Chem. Soc.*, **95**, 8107 (1973).

(30) R. A. Moss and M. J. Landon, *J. Amer. Chem. Soc.*, **92**, 5755 (1970).

(31) L. Tenud, S. Farooq, J. Seibl, and A. Eschenmoser, *Helv. Chim. Acta*, **53**, 2059 (1970).

Scheme I



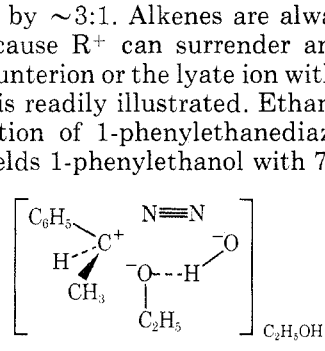
then the stereochemical retention observed in eq 9 demands that an ion pair such as **5A**, and not an alkyldiazonium ion, be the immediate product precursor.

A more complicated situation is encountered in the *solvolysis* of alkane diazotates. A general scheme is presented, which we have found to be paradigmatic for the ethanolysis,[30] hydrolysis,[32,33] ammonolysis,[34] hydrazinolysis,[35] and lithium ion catalyzed[36] decompositions of chiral *sec*-alkanediazotates.

In Scheme I, Sv–H represents a protic solvent, and Sv^- represents the corresponding lyate ion. The reaction of **1** with a protic solvent gives the key intermediate, **5**, a nitrogen-separated ion triplet. Collapse of **5** by *return*, or *conservation*, affords an alcohol with net stereochemical retention, although some inverted alcohol can form if R^+ rotates within **5** prior to collapse.[4d] *Capture* of R^+ occurs mainly from the rear, affording an inverted *substitution* product, Sv–R. However, a lyate ion is hydrogen bonded to the counterion of **5**, making possible a front-side collapse (*exchange*) to the stereochemically retained substitution product, R–Sv. Complete inversion in the substitution process is therefore unlikely.

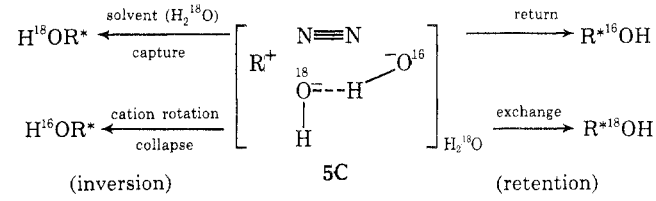
The overall ratio, substitution/return, can be readily obtained from the product ratio R–Sv/R–OH. In general we have found that substitution exceeds return by ~3:1. Alkenes are always major byproducts because R^+ can surrender an α proton to either the counterion or the lyate ion within **5**.

Scheme I is readily illustrated. Ethanolysis[30] of an HMPA solution of 1-phenylethanediazotate affords **5B** which yields 1-phenylethanol with 73% net retention (return) and 1-phenylethyl ethyl ether with



5B

Scheme II



~29% net inversion (substitution). The latter is formed mainly by inverting solvolysis, with competition from front-side exchange of ethoxide (retention). The 1-phenylethanol is largely formed by front-side return of hydroxide (retention), in competition with a quite minor contribution of rotation-collapse.[4d,37]

Note that the stereochemical properties of the substitution and conservation products enable us to chart *in detail* the various fates of ionic triplet **5B**. This combination of stereochemical examination of the products and determination of product ratios is *generally* applicable to reactions of the ion triplets **5**, generated as in Scheme I.

We should note, however, that some loss of stereospecificity in the formation of conservation and substitution products can be attributed to alkyl cations which escape from **5** and become symmetrically solvated. This is likely to be a minor process because **5** is highly reactive and most certainly short-lived. Thus, **5** (R = 2-Oct) selects between water and azide ion in a near-statistical manner when **1** is treated with 7 *M* aqueous NaN_3.[32b] This implies that [2-Oct$^+$N≡N$^-$OH] is extremely unselective in water, and that its quenching must be very rapid, behavior quite different from that of more stable carbonium ions, which strongly select azide over water.[38]

Remarkably, Scheme I can be extended to the *hydrolysis* of octane-2-diazotate. Now, however, both the substitution *and* the conservation products are *identical* (2-octanol), and a "double labeling" approach must be used to differentiate them;[32,33] see Scheme II.

Hydrolysis of the optically active diazotate (R*N=N^{16}O$^-$) with $H_2{}^{18}O$ produces **5C**, which can collapse with either stereochemical retention *and* conservation of the "original" oxygen atom (to R* ^{16}OH) or with retention and front-side exchange (to R* ^{18}OH). Cation rotation-collapse would give inverted H^{16}OR* (and H^{18}OR*), whereas substitution *via* rear-side capture would afford H^{18}OR*.

The actual experiment was done by adding an HMPA *solution* of **1** (R = 2-Oct*) to 20% ^{18}O-enriched water. The isolated 2-octanol was resolved by conversion to the diastereomeric 2-octyl L-acetyllactates, followed by glpc separation.[32a,33] From the overall stereochemical course of the reaction and the separate ^{16}O:^{18}O content of each diastereomer (mass spectrometry), it was possible to evaluate the "fates" of **5C**: retention/^{16}O return = 16.5%, retention/^{18}O exchange = 18.9%, inversion/^{16}O conservation = 6.0%, and inversion/^{18}O capture = 58.5%.[33] The overall substitution:conservation (^{18}O:^{16}O) ratio was directly measured as 73:27.

The stereochemistry of the conservation process

(32) (a) R. A. Moss, D. W. Reger, and E. M. Emery, *J. Amer. Chem. Soc.*, **92**, 1366 (1970); (b) R. A. Moss and S. M. Lane, *ibid.*, **89**, 5655 (1967).

(33) R. A. Moss, A. W. Fritz, and E. M. Emery, *J. Org. Chem.*, **36**, 3881 (1971).

(34) R. A. Moss, P. E. Schueler, and T. B. K. Lee, *Tetrahedron Lett.*, 2509 (1973).

(35) R. A. Moss and C. E. Powell, in preparation.

(36) R. A. Moss and P. E. Schueler, *J. Amer. Chem. Soc.*, **96**, 5792 (1974).

(37) A related methanolysis study has been described by W. Kirmse and H. Arold, *Chem. Ber.*, **103**, 3722 (1970).

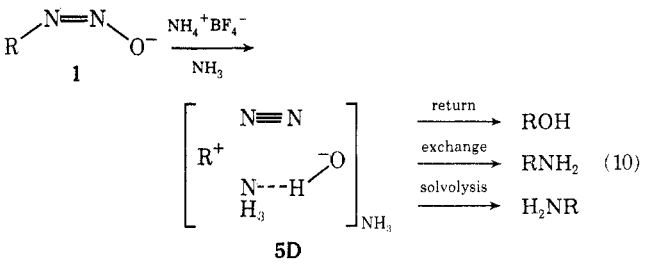
(38) C. D. Ritchie, *Accounts Chem. Res.*, **5**, 348 (1972).

(^{16}O, 73% overall retention) may be compared to that of the collapse of **5B** to 1-phenylethanol (87% overall retention). The stereochemistry of the substitution pathway (^{18}O, 76% overall inversion) may be compared to that of the ethanolysis of **5B** to 1-phenylethyl ethyl ether (65% overall inversion). Gross similarities are readily apparent.

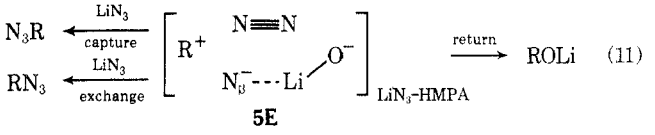
The stereochemistry of the hydrolysis of **1** ($H_2{}^{18}O$ capture of **5C**) can also be compared with that of the aqueous nitrous acid (pH 4) deamination of 2-aminooctane, which, in the absence of alkylammonium ion micelles,[39] affords 2-octanol with 62% overall inversion, probably with no front-side return of the original diazotic acid oxygen.[40] In contrast, hydrolysis of **1** *via* **5C** gives 76% overall inverted 2-octanol (substitution pathways only), accompanied by 27% of ^{16}O-conserving pathways. Clearly, *there is more integrity to (RN=NOH) in the highly nucleophilic and basic medium of diazotate hydrolysis;* we observe more inversion in substitution, and substantial counterion return. The substitution does not involve SN2 trapping of octane-2-diazotic acid, however, for it does not exhibit a dependence of inversion on $[OH^-]$.

In aqueous base, (RN=NOH) proceeds to **5C**, and its fate is settled there; little R^+ escapes to the symmetrically hydrated state. With a more stable cation, *e.g.*, cyclopropylcarbinyl, escape to hydrated carbonium ions is facilitated: hydrolysis of **1** (R = *c*-$C_3H_5CH_2$) with $H_2{}^{18}O$ gives cyclopropylcarbinol and cyclobutanol with, respectively, 11.9 and 14.7% return of the original ^{16}O.[41] This compares with 27% return for R = 2-octyl. A complete merging of HNO_2 deamination and diazotate hydrolysis was not observed in the cyclopropylcarbinyl system. Scrambling of the methylene groups of (*c*-$C_3H_5CH_2^+$) was ~1.6 times *less* efficient in the diazotate hydrolysis than in the deamination of the corresponding amine. Related effects have been observed in the methanolyses of methallyl and crotyl diazotates.[24]

Synthetic Applications of Diazotate Decomposition. The hydrolysis and ethanolysis reactions, which we have just described, involve much inverting solvolysis (see Scheme I), and we wondered whether such reactions could serve as the basis of an SN2-like *substitution* chemistry of aminoalkanes. Conversion of $-NH_2$ to $-N(SO_2CF_3)_2$ has recently been exploited for this purpose.[42] Would conversion of $-NH_2$ to $-N{=}NO^-$ also serve? As a test, we examined the ammonolysis of **1**, which should pass through **5D**, affording an alcohol by return and an amine by solvolysis or exchange pathways (eq 10).[34] With R = 1-phenylethyl, the expected amine (37%) formed with 47% net inversion, whereas the alcohol (12%) formed with 60% net retention. With R = 2-octyl, 2-aminooctane (18%) formed with 70% net inversion, and 2-octanol (6%) formed with 30% net retention. Styrene (14%) and 2-octenes (32%) were also isolated in the respective reactions. "Inversion of amines" *via* the diazotates, albeit in low yield, is an approach to amine substitution chemistry. In a related reaction, hydrazinolysis of **1** (R = 1-phenylethyl) afforded the corresponding monoalkylhydrazine (40%) with ~54% net inversion.[35]

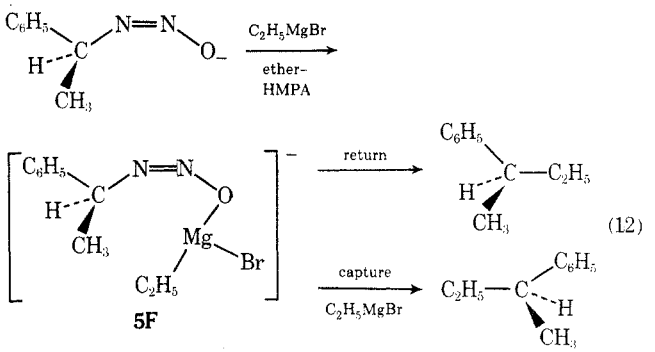


Similarly, lithium azide catalyzed decomposition of octane-2-diazotate[36] (10 equiv of LiN_3 in HMPA), probably *via* **5E**, gives 2-azidooctane (17%) with 73% net inversion and 2-octanol (from 2-Oct-OLi) with 24% net retention (eq 11). Addition of *n*-$Bu_4N^+N_3^-$



does not increase the inversion of the azide, which suggests that we are not observing a rate-determining displacement by N_3^- on a covalent precursor of **5E**. In this reaction, electrophilic Li^+ labilizes the diazotate.

The magnesium of Grignard reagents can function analogously: *sec*-butylbenzene can be obtained with ~60% net inversion from 1-phenylethanediazotate and ethyl Grignard, presumably *via* the ate complex, **5F** (eq 12).[43] Note that the substitution pathway



dominates, just as it does in the solvolytic reactions of alkanediazotates; the *sec*-butylbenzene is formed with net inversion. The conversion of C–N to C–C bonds by the reaction of alkanediazotates with organometallic reagents is a matter of intense interest in our laboratory.

The Integrity of Nitrogen-Separated Ion Pairs and Ion Triplets. The hallmark of a reactive intermediate is that its behavior in varied circumstances is both consistent and comprehensible. That this is true for nitrogen-separated ion pairs and triplets can be seen by quantitative stereochemical comparisons

(39) R. A. Moss, C. J. Talkowski, D. W. Reger, and C. E. Powell, *J. Amer. Chem. Soc.*, **95**, 5215 (1973); R. A. Moss and C. J. Talkowski, *ibid.*, **94**, 4767 (1972); R. A. Moss and D. W. Reger, *ibid.*, **91**, 7539 (1969).

(40) D. L. Boutle and C. A. Bunton, *J. Chem. Soc.*, 761 (1961).

(41) R. A. Moss, F. C. Shulman, and E. M. Emery, *J. Amer. Chem. Soc.*, **90**, 2731 (1968).

(42) P. J. DeChristopher, J. P. Adamek, G. D. Lyon, J. J. Galente, H. E. Haffner, R. J. Boggio, and R. J. Baumgarten, *J. Amer. Chem. Soc.*, **91**, 2384 (1969); R. S. Glass, *Chem. Commun.*, 1547 (1971); N. H. Andersen and H. Uh, *Syn. Commun.*, **2**, 297 (1972); J. B. Hendrickson, R. Bergerson, A. Giga, and D. Sternbach, *J. Amer. Chem. Soc.*, **95**, 3412 (1973).

(43) R. A. Moss and J. Banger, *Tetrahedron Lett.*, 3549 (1974). C–C bond formation also occurred in the phenolysis of butane-2-diazotate, which gave *o-sec*-butylphenol with 75–80% net inversion. Here, however, the phenolic proton was the labilizing electrophile: R. A. Moss and G. H. Temme, III, *Tetrahedron Lett.*, 3219 (1968).

Table I
Stereochemistry of Return Pathways of Deaminative Reactions

R	X	See intermediate	Solvent	% retn	% invn
$C_6H_5CHCH_3$	$OOCC_{10}H_{17}$		CH_3COOH	81	19[a]
$C_6H_5CHCH_3$	OH		CH_3COOH	79	21[b]
$C_6H_5CHCH_3$	OH	5B	C_2H_5OH	87	13
$C_6H_5CHCH_3$	OC_2H_5	5A	CH_2Cl_2	82	18
$C_6H_5CHCH_3$	OH	5D	NH_3	80	20
$C_6H_5CHCH_3$	OH		H_2NNH_2	83	17[c]
$C_2H_5CHCH_3$	$OOCC_6H_5$		CH_3COOH	68	32[d]
n-$C_6H_{13}CHCH_3$	OH	5C	$H_2{}^{18}O$–HMPA	73	27
n-$C_6H_{13}CHCH_3$	OH	5D	NH_3–HMPA	65	35
n-$C_6H_{13}CHCH_3$	OLi	5E	LiN_3–HMPA	62	38

[a] E. H. White and C. A. Aufdermarsh, Jr., *J. Amer. Chem. Soc.*, **83**, 1179 (1961). [b] R. Huisgen and C. Rüchardt, *Justus Liebigs Ann. Chem.*, **601**, 21 (1956). [c] Reference 35. [d] E. H. White, *J. Amer. Chem. Soc.*, **77**, 6014 (1955).

within the conservation and substitution branches of their reactions (see Scheme I).

Table I summarizes the overall stereochemical courses of *conservation or return* pathways, eq 13, for

$$R{-}N{=}N{-}X \xrightarrow{\text{solvent}} R{-}X + N_2 \qquad (13)$$

various deaminative processes. In most cases, the key intermediate, a nitrogen-separated ion triplet, was generated by the solvolysis of an alkanediazotate as discussed above. (References are given to the numbered intermediates which appear in the text.) The behavior of several nitrogen-separated ion pairs is also summarized. These were generated by the thermolysis of *N*-alkyl-*N*-nitrosoamides, an elegant method largely developed by White.[4]

Retention is always observed in these return reactions. Its extent depends mainly on cation identity, and less strongly on the nature of solvent or counterion. Retention seems higher in the α-phenylethyl cases than in the *sec*-alkyl examples. An extension of Whiting's hypothesis[44] can rationalize this: cleavage of C–N and N–X bonds is more closely concerted for the more stable nascent cation (1-phenylethyl); X^- is generated closer to R^+; return is more efficiently stereoconservative, and more retention is observed. For the less stable *sec*-alkyl cations, cleavage of N–X is somewhat more in advance of C–N cleavage; X^- is generated further away from R^+; there is more chance for cation escape or rotation; capture of X^- is not as stereoconservative.

In Table II, we summarize the overall stereochemistry of the companion *substitution* pathways for several diazotate solvolyses (eq 14).

$$R{-}N{=}N{-}O^- + Sv{-}H \longrightarrow OH^- + N_2 + Sv{-}R \qquad (14)$$

Inversion is always observed in substitution; its extent appears to increase as the substrate's alkyl group is less able to support a positive charge and as the capturing reagent becomes more nucleophilic. The process assumes the stereochemical trappings of

(44) M. C. Whiting, *Chem. Brit.*, **2**, 482 (1966); M. Maskill, R. M. Southam, and M. C. Whiting, *Chem. Commun.*, 496 (1965).

Table II
Stereochemistry of Substitution Pathways of Deaminative Reactions

R	See intermediate	SvH	% invn	% retn
$C_6H_5CHCH_3$	5B	C_2H_5OH–HMPA	66	34
$C_6H_5CHCH_3$	5D	NH_3–HMPA	73	27
$C_6H_5CHCH_3$		H_2NNH_2	77	23[a]
n-$C_6H_{13}CHCH_3$	5C	$H_2{}^{18}O$–HMPA	76	24
n-$C_6H_{13}CHCH_3$	5D	NH_3–HMPA	85	15
n-$C_6H_{13}CHCH_3$	5E	LiN_3–HMPA	86	14

[a] Reference 35.

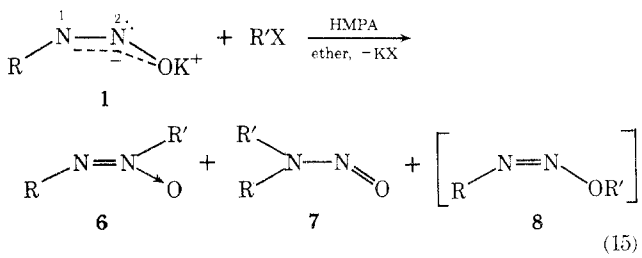
the SN2 reaction, although 100% inversion is never realized—probably because of front-side exchange with the lyate ion, which affords some retained capture product (see Scheme I).

Relation to Solvolytic Ion Pairs. The nitrogen-separated ion pairs and triplets clearly exhibit a characteristic chemistry. How does this chemistry relate to that ascribed to solvolytic ion pairs? Nitrogen-separated ion pairs or triplets could lead to intimate ion pairs similar to those associated with solvolysis reactions, if the former could survive long enough to lose nitrogen and adjust the interionic separation. We do not know what fraction of simple, *sec*-alkyl, nitrogen-separated ion pairs can achieve the intimate ion pair state. Certainly, from $[R^+N_2X^-]$ with X = OH, OR′, or OLi, an "intimate ion pair" would collapse to product quickly and irreversibly. Such pairs could not be solvolytically generated from alcohols, ethers, or lithium alkoxides.

Despite this uncertainty, there may be an important relation between nitrogen-separated and solvolytically generated *sec*-alkyl ionic species. Thus, although the intermediacy of ion pairs in the solvolysis of *sec*-alkyl substrates is still contentious,[28] it is worth noting that azide capture of solvolytically generated 2-octyl methanesulfonate "ion pairs" gave ~80% net inverted 2-azidooctane,[45] a very similar result to the 73% net inversion which we observed in the azide capture of **5E**.

The Synthesis of Azoxyalkanes. During the course of our solvolysis studies, we discovered a unique route to azoxyalkanes. These compounds are difficult to obtain by other methods, and are of considerable biological interest.

Alkylation of alkanediazotates gives azoxyalkanes (eq 15) by attack at the N-2 lone pair.[46,47] Yields of

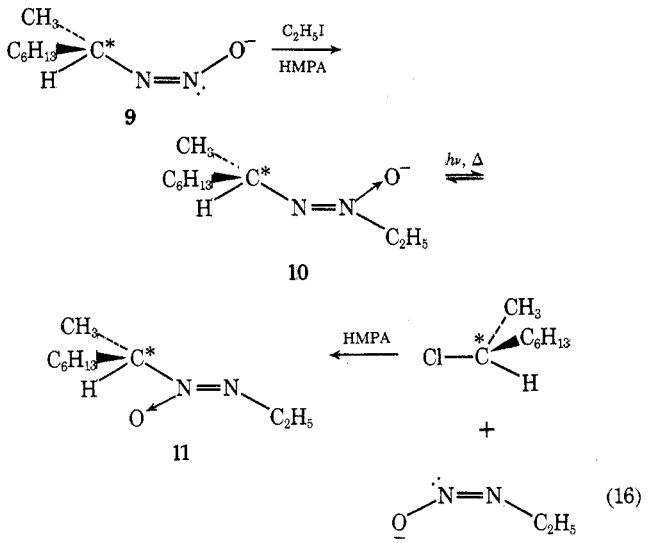


(15)

(45) H. Weiner and R. A. Sneen, *J. Amer. Chem. Soc.*, **87**, 287, 292 (1965).
(46) R. A. Moss and M. J. Landon, *Tetrahedron Lett.*, 3897 (1969).
(47) R. A. Moss, M. J. Landon, K. M. Luchter, and A. Mamantov, *J. Amer. Chem. Soc.*, **94**, 4392 (1972).

unsymmetrical **6** range from 30 to 60%. Alkylation at N-1 yields nitrosoamine **7**, whereas O-alkylation gives an unstable diazo ether, **8** (see **5A**). In dissociating solvents (HMPA), little **7** is formed; **8** is generated to ~50%. In less-polar solvents (ether–HMPA, 95:5), **1** is more ion paired and **7** becomes the dominant by-product at the expense of **8**. The yield of **6** is relatively invariant. These results contrast with the acylation or arylation of **1**, R = CH_3, which occur very largely at N-1, affording only **7**.[10]

Alkylation of **1** is a *regiospecific* synthesis of azoxyalkanes, in which only one position isomer is produced, and the location of the oxygen is certain. Many combinations of R and R′ can be chosen from primary and secondary alkyl groups.[47] Chirality can be accommodated at either α carbon atom (eq 16).[48]



9

10

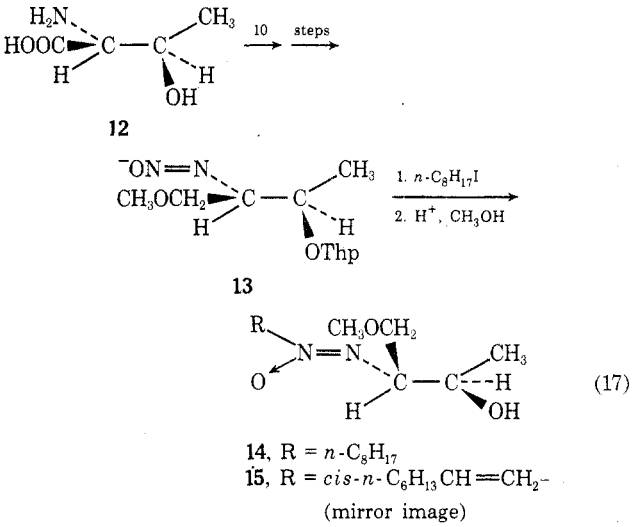
11

(16)

Optically pure (*R*)-**9** gave azoxyalkane (*R*)-**10**, which afforded isomer (*R*)-**11** by "photothermal" equilibration.[49] Azoxyalkane **11** could be prepared with equal rotation by the alkylation of ethanediazotate with optically pure (*S*)-2-chlorooctane. The latter reaction therefore represents SN2 attack of the N-2 diazotate lone pair on 2-chlorooctane.

The regiospecific and stereospecific azoxyalkane synthesis can be applied to the construction of more complicated molecules. From L-threonine (**12**), protected diazotate **13** was prepared. Alkylation with 1-iodooctane, followed by deprotection, gave L-dihydroelaiomycin (**14**; eq 17), analogous to an authentic (enantiomeric) sample produced by reduction of natural elaiomycin (**15**).[50]

Elaiomycin,[51] from *Streptomyces hepaticus*, is one



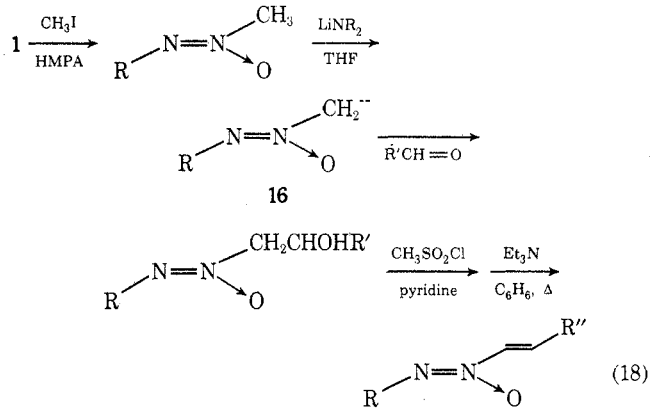
12

13

(17)

14, R = n-C_8H_{17}
15, R = *cis*-n-$C_6H_{13}CH{=}CH_2$–
(mirror image)

of only four[52] naturally occuring azoxyalkanes, and is of interest because of its antibiotic[53] and carcinogenic[54] properties. Its synthesis would require the construction of a cis-proximal α,β-unsaturated azoxyalkene functionality. We have thus far developed a synthesis of trans-proximal α,β-unsaturated azoxyalkenes[55,56] (eq 18). The intermediate anion, **16**, can



16

(18)

R = *sec*-C_8H_{17}, *sec*-C_4H_9; R″ = CH_3, n-C_6H_{13}

also be alkylated[55] and acylated.[56] Its chemistry is being intensively studied in our laboratory, with a view toward the synthesis of elaiomycin.

I owe more than I can adequately acknowledge to my collaborators, whose names are cited above. Together, we thank the National Science Foundation, the National Institutes of Health, the Petroleum Research Fund, and the A. P. Sloan Foundation for financial support of our research.

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(50) R. A. Moss and T. B. K. Lee, *J. Chem. Soc., Perkin Trans. 1*, 2778 (1973).
(51) C. L. Stevens, B. T. Gillis, and T. H. Haskell, *J. Amer. Chem. Soc.*, **81**, 1435 (1959), and references therein; T. H. Haskell, A. Ryder, and Q. R. Bartz, *Antibiot. Chemother.*, **4**, 141 (1954).
(52) For leading references, see ref 47.
(53) J. Ehrlich, *et al.*, *Antiobiot. Chemother.*, **4**, 338 (1954).
(54) R. Schoental, *Nature (London)*, **221**, 765 (1969).
(55) R. A. Moss and G. M. Love, *Tetrahedron Lett.*, 4701 (1973).
(56) R. A. Moss and R. Nahas, unpublished work.