

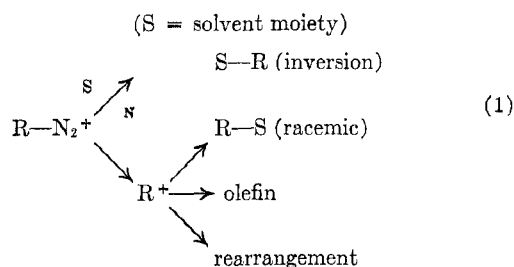
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA]

**An Interpretation of the Reaction of Aliphatic
Primary Amines with Nitrous Acid**

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Although the reaction of aliphatic primary amines with nitrous acid has long been known to yield a variety of products including those resulting from solvolysis, elimination, and rearrangement, no comprehensive attempt has been made to account for all of these reactions in terms of a complete theory. By analogy with the reactions of aromatic primary amines with nitrous acid, an alkyldiazonium ion has been considered to be an important intermediate.¹ The mechanism of the reaction usually given in texts² is that of a solvolytic displacement reaction in which the diazonium ion decomposes into nitrogen and a carbonium ion which can subsequently react with solvent, eliminate a proton, or rearrange (Equation 1). To account for the partial inversion of configuration frequently observed when optically active amines are used^{3,4} a competing reaction is considered to be a direct displacement (S_N2) by solvent.



A major difficulty with this mechanism is that rearrangements are frequently observed which have no counterpart in related solvolytic reactions. For example, *n*-alkylamines yield substantial amounts of secondary alkyl products,⁵ the results of a hydrogen rearrangement. Yet, solvolyses of *n*-alkyl halides or sulfonate esters give at most small amounts of rearranged products; e.g., prolonged refluxing of *n*-propyl tosylate in acetic acid gives <3% of isopropyl acetate.⁶ Rearrangements of *n*-alkyl halides to secondary alkyl derivatives generally occur only when the nucleophilic reagents available for reaction with the intermediate carbonium ion are so weak that such reaction is slower than the rearrangement. Such conditions are obtained, for example, in alkylations with aluminum chloride or boron fluoride.

Consequently, the hypothesis has been presented

(1) L. P. Hammett, *Physical Organic Chemistry*, p. 295, McGraw-Hill Book Company, Inc., New York, N. Y., 1940.

(2) (a) C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, p. 397, Cornell University Press, Ithaca, N. Y., 1953. (b) M. J. S. Dewar, *Electronic Theory of Organic Chemistry*, p. 210, Oxford University Press, London, 1949. (c) P. H. Hermans, *Theoretical Organic Chemistry*, p. 246, Elsevier Publishing Co., Amsterdam, 1954. (d) E. E. Royals, *Advanced Organic Chemistry*, p. 226, Prentice-Hall Publishing Co., New York, N. Y., 1954. (e) E. R. Alexander, *Principles of Ionic Organic Reactions*, p. 49, J. Wiley and Sons, Inc., New York, 1950.

(3) P. Brewster, F. Hiron, E. O. Hughes, C. K. Ingold, and P. A. D. S. Rao, *Nature*, **166**, 179 (1950).

(4) K. B. Wiberg, Dissertation, Columbia University, July, 1950.

(5) (a) D. W. Adamson and J. Kenner, *J. Chem. Soc.*, 838 (1934). (b) V. Meyer and F. Forster, *Ber.*, **9**, 535 (1876). (c) V. Meyer, J. Barbieri, and F. Forster, *Ber.*, **10**, 130 (1877). (d) P. C. Ray and J. N. Rashkit, *J. Chem. Soc.*, **101**, 141 (1912). (e) F. C. Whitmore and D. P. Langlois, *J. Am. Chem. Soc.*, **54**, 3441 (1932). (f) F. C. Whitmore and R. S. Thorpe, *J. Am. Chem. Soc.*, **63**, 1118 (1941). (g) J. D. Roberts and M. Halmann, *J. Am. Chem. Soc.*, **75**, 5759 (1953).

(6) R. Huisgen and C. Ruchardt, *Ann.*, **601**, 1 (1956).

that the carbonium ion formed in the decomposition of an alkyldiazonium ion is a "hot", "high-energy", or "unsolvated" carbonium ion^{6,7-13} which has properties different from the carbonium ions formed in the solvolysis of a halide or sulfonate ester. However, this hypothesis fails to explain why diastereomeric amines in cyclic systems generally yield different sets of products (*vide infra*). In terms of this mechanism diastereomeric amines should yield the same carbonium ion.

The hypothesis has recently been proposed¹⁴ that the diazonium ion rather than a carbonium ion is the branching point of the competing reactions. According to the theory presented, the great stability of the leaving nitrogen molecule implies that the activation energy required for the decomposition of an aliphatic diazonium ion is rather small—perhaps of the order of 3–5 kcal./mole. Consequently, the range of energies required for a number of competing reactions is compressed. To illustrate, if in the solvolysis of a halide two competing reactions of carbonium ion formation and a concerted rearrangement have activation energies of, respectively, 25 and 30 kcal./mole, in the corresponding amine-nitrous acid reaction the respective activation energies might be 5 and 6 kcal./mole. (In both cases the ratio of the activation energies is considered to be the same to a first approximation.) In the solvolysis reaction these values mean that rearrangement accounts for only 0.02% of the product; in the amine reaction, rearrangement would account for about 16% of the product. Consequently, a mode of reaction not observed in solvolyses may be important in amine-nitrous acid reactions.

In the present paper this theory and its corollaries are used to interpret many of the varied observations pertaining to the amine-nitrous acid reaction. The point of view of this presentation is to determine how well these observations are in accord with one unified theory, although, clearly, in individual cases alternative explanations are possible. In some of the relatively few cases which are not satisfactorily explained by this theory, the theory is probably deficient and may require future modification; in others, published data are contradictory.

(7) D. J. Cram and J. E. McCarty, *J. Am. Chem. Soc.*, **79**, 2866 (1957).

(8) L. S. Ciereszko and J. G. Burr, *J. Am. Chem. Soc.*, **74**, 145 (1952).

(9) P. S. Bailey and J. G. Burr, *J. Am. Chem. Soc.*, **75**, 2591 (1953).

(10) J. D. Roberts, C. C. Lee, and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **76**, 4501 (1954).

(11) A. W. Fort and J. D. Roberts, *J. Am. Chem. Soc.*, **78**, 584 (1956).

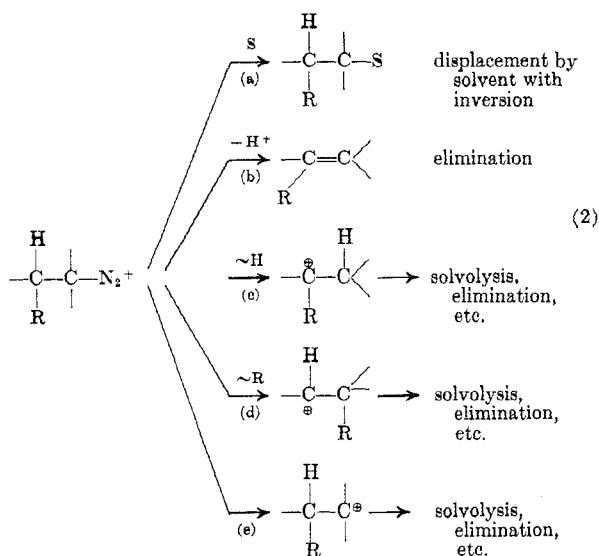
(12) J. G. Burr and L. S. Ciereszko, *J. Am. Chem. Soc.*, **74**, 5431 (1952).

(13) D. Y. Curtin and M. C. Crew, *J. Am. Chem. Soc.*, **76**, 3719 (1954).

(14) A. Streitwieser, Jr., and W. D. Schaeffer, *J. Am. Chem. Soc.*, **79**, 2888 (1957).

It has been emphasized¹⁴ that because the driving force for the decomposition of an alkyldiazonium ion is the elimination of nitrogen, the rearranging group should not be regarded as providing only anchimeric assistance in the reaction, i.e., a *push*, but also that it is being *pulled* over by the positive field being generated at the α -carbon atom. A further implication of the facility with which nitrogen is lost is that the transition state of each of the various reactions may resemble the diazonium ion in important respects.^{7,14,15}

The reactions which appear to compete more or less successfully in various systems are given in Equation 2.



ACYCLIC SYSTEMS

Reaction 2a: Direct Displacement. One of the reactions which can compete with normal carbonium ion formation is direct displacement by solvent. The hypothesis that the structure of the transition state resembles the reactants carries the implication that the bond to the attacking solvent molecule at transition state for displacement is long and weak. Steric hindrance effects are reduced and relatively small stereochemical differences are to be expected between various systems. The 1-butyl-1-*d* acetate obtained from the reaction of 1-aminobutane-1-*d* with nitrous acid in acetic acid is 69% inverted and 31% racemized.¹⁴ The *sec*-butyl acetate similarly obtained from *sec*-butylamine is 28% inverted and 72% racemized.⁴ Although *sec*-butyl and α -phenylethyl cations differ markedly in stability, the stereochemical outcomes of the reactions of the corresponding amines with nitrous acid do not differ greatly. In aqueous media *sec*-butylamine gives *sec*-butyl alcohol with 22% net inversion;⁴ α -phenylethylamine gives α -phen-

(15) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

ylethyl alcohol with 6–12% net inversion.¹⁶ The proportion of reaction by direct displacement decreases along the series, *n*-butyl > *sec*-butyl > α -phenylethyl, in agreement with theoretical expectations although the differences are comparatively small.

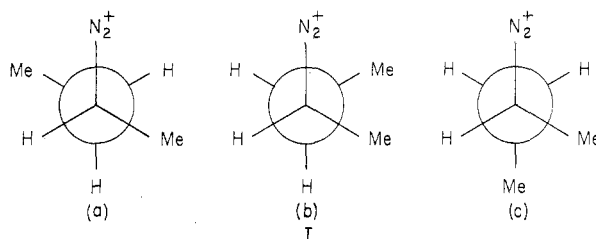
Since the bond to solvent at the transition state is weak, the nucleophilicity of the solvent would be expected to play a small role. Consequently, the stereochemical results with *sec*-butylamine in water and in the less nucleophilic acetic acid differ but little (and actually, in the wrong direction from a simple expectation).

The stereochemical results of racemization and inversion for the reactions of a number of secondary alkylamines have also been reported by Brewster, *et al.*³ although complete details were not given. The partial net retention of configuration reported¹⁷ for the reaction of α -phenylethylamine with nitrous acid in acetic acid requires an additional mode of reaction which may depend on ion-pair phenomena in acetic acid. However, additional results would be required to warrant further discussion.¹⁸

Reaction 2b. Elimination. The olefin obtained from *sec*-butylamine in aqueous nitrous acid consists of 25% 1-butene, 19% *cis*-2-butene and 56% *trans*-2-butene.¹⁴ The composition of this mixture which would not be expected to change significantly in acetic acid differs greatly from that of the butene mixture obtained from the acetolysis of *sec*-butyl tosylate:¹⁹ 10% 1-butene, 43% *cis*-2-butene, and 47% *trans*-2-butene. Not only does the amount of 1-butene differ considerably in the two reactions but the *cis/trans* ratios of the 2-butenes differ importantly. In the solvolysis reaction the olefin is considered to arise from an intermediate carbonium ion because in several such systems the olefin composition is independent of the nature of the leaving group.²⁰ The fact that a different olefin composition is obtained in the amine-nitrous acid reaction means that at least part of this olefin does not come from an intermediate carbonium ion.

An independent competing reaction, 2b, has been shown to explain the experimental results.¹⁴ Generally such concerted eliminations result in the removal of hydrogens *trans* to the leaving group. Because the activation energy required for reaction 2b is presumed to be comparable to the energy required for rotation about a C—C bond (3–4 kilo-

calories per mole for the central bond in *n*-butane),²¹ the decomposition of the diazonium ion will be of comparable rate to such rotation; *i.e.*, conformational effects will be important. In the case of 2-butylamine, three conformations are important, Ia, b, and c. Ib is expected to be less populated than Ia and Ic. Only Ia and Ib can eliminate a



trans-3-hydrogen; hence, consistent with the observed results, *cis*-2-butene which would arise from Ib is expected to be formed in smaller amount than *trans*-2-butene which arises from Ia. In elimination from a carbonium ion, the two types of hydrogen are conformationally equivalent and comparable amounts of the *cis* and *trans* olefins may be anticipated. Ic, which is relatively highly populated cannot give a 2-butene by *trans*-elimination. All three conformations (*i.e.*, the entire population of diazonium ions) can give rise to 1-butene; only a fraction of the entire population of diazonium ions (that part in Ia and Ib) can generate 2-butene; therefore, even if the specific rate constant for formation of 1-butene is somewhat lower than that for the more stable 2-butenes, a relatively large amount of 1-butene is produced in the reaction.

Reaction 2c: Migration of hydrogen. Instead of eliminating, a *trans*-hydrogen may migrate instead in a 1,2-shift and generate a new carbonium ion as in reaction 3. The reaction apparently takes place to



an important extent, however, only when the resulting carbonium ion is more stable than that which would arise by elimination of nitrogen without rearrangement, hence the β -carbon must be distributing an important share of the positive charge. Ethylamine-1-C¹⁴ gives ethanol which contains only 1.5% of the rearrangement product, ethanol-2-C¹⁴,²² although *n*-propyl-, *n*-butyl-, and *n*-amylamines, etc., yield important amounts of secondary carbinol.^{5,6} 3-Aryl-1-propylamine gives 18–19% of 1-aryl-2-propyl alcohol.¹¹ Several cases are known in which no product of the rearrangement of a hydrogen is observed although such rearrangement would generate a more stable carbonium ion. For example, no diphenylmethylcarbinol is obtained

(21) K. S. Pitzer, *Discussions Faraday Soc.*, 10, 66 (1951).

(22) J. D. Roberts and J. A. Yancey, *J. Am. Chem. Soc.*, 74, 5943 (1952).

(16) Calculated from the data of W. Marckwald and R. Meth, *Ber.*, 38, 801 (1905), and B. Holmberg, *Ber.*, 45, 999 (1912).

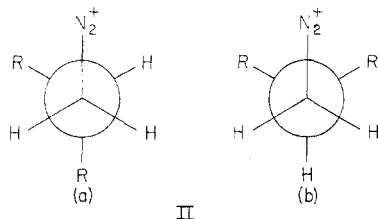
(17) (a) E. Ott, *Ann.*, 488, 186 (1931). (b) R. Huisgen and C. Rüdhardt, *Ann.*, 601, 21 (1956).

(18) However, see page 869.

(19) H. C. Brown and M. Nakagawa, *J. Am. Chem. Soc.*, 77, 3614 (1956).

(20) For a review, cf. A. Streitwieser, Jr., *Chem. Revs.*, 56, 571 (1956).

from 2,2-diphenylethylamine,²³ although more or less tertiary alcohol is obtained from isobutylamine,^{24,25} 2-methyl-1-octylamine,²⁶ 2-phenyl-1-propylamine,²⁷ and cyclopentyl- and cyclohexyl-carbinylamines.²⁸ An explanation for these apparently discordant results may again be found in reactions and populations of different conformations. The diazonium ions corresponding to these amines can exist in two types of conformation, IIa,



in which the diazonium function is *gauche* to only one of the carbon functions, R, and IIb, in which it is *gauche* to both R groups. Only IIb, the less populated conformation, can lead to rearrangement of a hydrogen. Consequently, as both R groups become more bulky, the population in IIb decreases and the amount of hydrogen-rearranged product (in these cases, R_2COHCH_3) decreases.

Although *n*-amylamine yields substantial amounts of 2-pentanol,^{5a} no 3-pentanol is observed;²⁹ the 2-pentyl cation formed in the rearrangement does not further rearrange. Analogously, the acetolysis of 2-pentyl brosylate is reported to yield no observable amounts of 3-pentyl acetate.¹⁹ Furthermore, 3-phenyl-1-propylamine gives no 1-phenyl-1-propyl derivatives.¹¹

It should be mentioned that reactions 2b and 2c, elimination and rearrangement of a *trans*-hydrogen, may actually be a single reaction leading to a hydrogen-bridged intermediate which can subsequently eliminate a proton or complete the rearrangement.

Reaction 2d: Rearrangement of a carbon function. As in the rearrangement of hydrogen, the rearrangement of a carbon function has conformational requirements and is important only when the resulting carbonium ion is more stable than that which would arise without rearrangement;^{29b,30a} hence,

(23) L. Hellerman, M. L. Cohn, and R. E. Hoen, *J. Am. Chem. Soc.*, **50**, 1716 (1928).

(24) (a) E. Linnemann, *Ann.*, **162**, 12 (1872). (b) L. Henry, *Compt. rend.*, **145**, 899 (1907).

(25) (a) L. G. Cannell and R. W. Taft, Jr., *J. Am. Chem. Soc.*, **78**, 5812 (1956). (b) E. H. White, *J. Am. Chem. Soc.*, **77**, 6011 (1955).

(26) M. Freund and F. Schönfeld, *Ber.*, **24**, 3350 (1891). (27) P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **103**, 373 (1933).

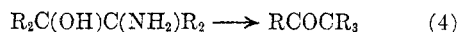
(28) (a) P. A. S. Smith and D. R. Baer, *J. Am. Chem. Soc.*, **74**, 6135 (1952). (b) P. A. S. Smith, D. R. Baer, and S. N. Ege, *J. Am. Chem. Soc.*, **76**, 4564 (1954).

(29) A. Streitwieser, Jr., and D. van Sickle, unpublished results.

(30) (a) A. Brodhag and C. R. Hauser, *J. Am. Chem. Soc.*, **77**, 3024 (1955). (b) W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **78**, 6127 (1956).

the rearranging group and the β -carbon atom are distributing an important share of the positive charge. In the reaction of *n*-butylamine, no ethyl group rearrangement is observed.¹⁴ The 3,3-dimethyl-1-butanol obtained from the corresponding amine shows less than 1% of *t*-butyl group rearrangement.^{30b} Similarly, the reactions of 3-phenyl-1-propylamine and 3-anisyl-1-propylamine give no rearrangement of a benzyl group or an anisylmethyl group, respectively.¹¹ It has been suggested^{30b} that the 8.5% methyl rearrangement reported⁶ in the *n*-propyl alcohol from *n*-propylamine is a high result due to experimental difficulties.

Halides and sulfonates which solvolyze with participation of a neighboring carbon function and consequent rearrangement also demonstrate analogous rearrangements when the corresponding amines are treated with nitrous acid provided that conformational requirements are met. Parallels of this sort in the rearrangement products obtained from solvolytic reactions and amine-nitrous acid reactions are given by neopentyl,^{30a,31} β,β -diarylethyl,^{8,23,32} and β,β,β -triarylethyl^{23,32b,33} systems. The formation of some *sec*-butyl alcohol from isobutylamine²⁵ and the numerous⁵ examples of the Demjanow ring expansion³⁴ and semipinacolic demininations (Equation 4) are additional examples of this mode of reaction. In the latter cases, the rearrangement competes effectively because a relatively stable carbonium ion, a protonated carbonyl group, is produced.



The conformational requirements have been elegantly demonstrated by Cram and McCarty⁷ by the reactions of *erythro*- and *threo*-3-phenyl-2-butylamine. Both diastereomers gave evidence of phenyl group rearrangement, but the phenyl group rearrangement was much more prevalent in the *erythro* isomer. The population of that conformation in which the phenyl group is *trans* to the nitrogen function is expected to be greater than that in which the methyl group is *trans* for the *erythro* isomer. The reverse is expected to be true for the *threo* isomer.⁷

Studies of migration aptitudes are interesting. In the acetolysis of β -phenyl- β -tolylethyl tosylate, rearrangement of the *p*-tolyl group occurs three

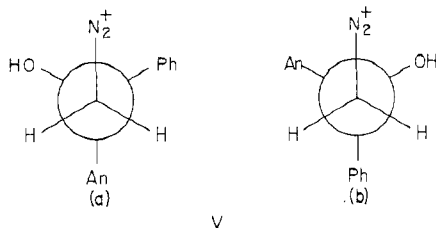
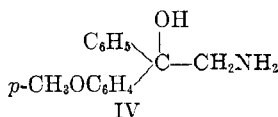
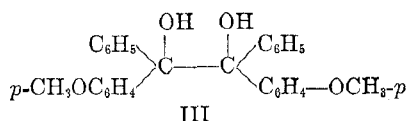
(31) (a) M. Freund and F. Lenze, *Ber.*, **23**, 2865 (1890); **24**, 2150 (1891). (b) M. L. Tissler, *Compt. rend.*, **112**, 1065 (1891). (c) F. C. Whitmore, E. C. Wittle, and A. H. Popkin, *J. Am. Chem. Soc.*, **61**, 1586 (1939). (d) I. Dostrovsky and E. D. Hughes, *J. Chem. Soc.*, 166 (1946).

(32) (a) J. G. Burr, *J. Am. Chem. Soc.*, **75**, 5008 (1953). (b) S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber, and J. Corse, *J. Am. Chem. Soc.*, **74**, 1113 (1952).

(33) J. C. Charlton, I. Dostrovsky, and E. D. Hughes, *Nature*, **167**, 986 (1951).

(34) For a review of N. J. Demjanow's results cf. *Uspekhi Khim.*, **3**, 493 (1934); for a recent comprehensive study cf. ref. 28.

times as readily as the phenyl group.^{32a} In the reaction of the corresponding amine with nitrous acid, the two groups rearrange almost equally.^{3,33} More striking differences are observed in the comparison of the products of pinacol rearrangements with those of semipinacolic deaminations. For example, in the rearrangement of a 1,2-diphenyl-1,2-di-*p*-anisylethylene glycol, III, with acid the relative rate of anisyl to phenyl rearrangement is 500:1.³⁶ In the analogous reaction of 1-phenyl-1-*p*-anisyl-2-aminoethanol, IV, with nitrous acid, the anisyl:phenyl migration ratio is only 1.56:1.¹⁹ On the basis of these results, Curtin and Crew¹³ concluded that the rearranging group is not participating appreciably in the rearrangement in the amine reaction. Yet, the fact that the rearrangement occurs in this case to the virtual exclusion of other possible reactions demonstrates that the migrating group is participating to an important extent as far as the amount of positive charge distributed is concerned. However, the low activation required for decomposition of the intermediate diazonium ion which would exist almost entirely in only two conformations, Va and b, equally populated is hypothesized to be comparable to that required for rotation about



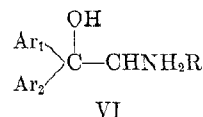
the carbon-carbon bond.³⁷ In the absence of any such rotation equal amounts of phenyl and anisyl rearrangement would be expected; because some rotation probably does occur, a small excess of anisyl rearrangement is observed. Correspondingly, both diastereomers of a number of amines of the type VI have been treated with nitrous acid. The ketone which is produced principally or exclusively,

(35) P. S. Bailey and J. G. Burr, *J. Am. Chem. Soc.*, **75**, 2951 (1953); B. M. Benjamin and C. J. Collins, *J. Am. Chem. Soc.*, **78**, 4952 (1956).

(36) W. E. Bachman and F. H. Moser, *J. Am. Chem. Soc.*, **74**, 1124 (1932).

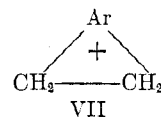
(37) Compare with J. Hine, *Physical Organic Chemistry*, p. 314, McGraw-Hill Book Co., New York, N. Y., 1956, and W. G. Dauben and K. S. Pitzer in *Steric Effects in Organic Chemistry*, M. S. Newman, Ed., p. 10, J. Wiley and Sons, Inc., New York, N. Y., 1956.

depending on the size of R, is that which results from migration of the group *trans* to the nitrogen



function in the most stable conformation.³⁸ The stereospecificity of the rearrangement of the *trans* group has also been demonstrated in the reaction of several steroidal amines.³⁹

The reactions of β -arylethylamines are particularly interesting. Rearrangement of the aryl group would produce a bridged ion, VII, which is probably



more stable than the isomeric β -arylethyl cation.²⁰ From the reaction of 2-phenylethylamine-1-C¹⁴ with nitrous acid in acetic acid, 2-phenylethyl-C¹⁴ acetate is obtained in 70% yield⁴⁰ and is partially rearranged.^{40,41} This product may be considered, to a first approximation, to arise from a competing displacement (reaction 2a) and phenyl rearrangement to a bridged ion. Because almost all of the diazonium salt is expected to be in that conformation in which the bulky phenyl ring is *trans* to the nitrogen function, hydrogen rearrangement and elimination are expected to be but minor reactions. In the corresponding saturated system, 2-cyclohexylethylamine, the bridged ion does not form, hence the other reactions, which require prior rotation about the carbon-carbon bond, are more important. Primary and secondary alcohol and olefin are isolated in this case.⁴² The observation of 27% rearrangement from β phenylethylamine⁴¹ would indicate that 54% of the reaction occurred by rearrangement to VII and 46% occurred directly with solvent.⁴³ The rate of rearrangement relative to displacement is 1.2. The corresponding relative rate for rearrangement of a *p*-anisyl group is 9.0. Since the rate for displacement on the diazonium salt from β -phenylethylamine is probably very similar to that on the diazonium salt from β -*p*-anisylethylamine, these

(38) (a) P. I. Pollack and D. Y. Curtin, *J. Am. Chem. Soc.*, **72**, 961 (1950). (b) D. Y. Curtin and P. I. Pollack, *J. Am. Chem. Soc.*, **73**, 992 (1951). (c) D. Y. Curtin, E. H. Harris, and P. I. Pollack, *J. Am. Chem. Soc.*, **73**, 3453 (1951). (d) D. Y. Curtin and M. C. Crew, *J. Am. Chem. Soc.*, **77**, 354 (1955). (e) A. McKenzie and A. K. Mills, *Ber.*, **62**, 284 (1929). (f) A. McKenzie and A. D. Wood, *Ber.*, **71**, 358 (1938).

(39) F. Ramirez and S. Stafiej, *J. Am. Chem. Soc.*, **77**, 134 (1955); **78**, 644 (1956).

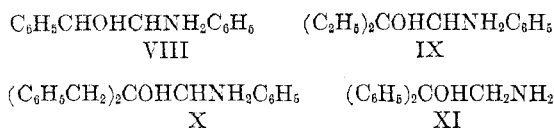
(40) C. C. Lee and J. W. T. Spinks, *Can. J. Chem.*, **31**, 761 (1953).

(41) J. D. Roberts and C. M. Regan, *J. Am. Chem. Soc.*, **75**, 2069 (1953).

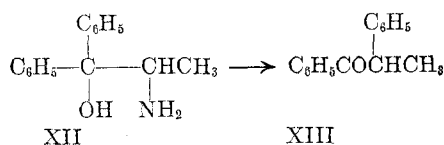
(42) O. Wallach, *Ann.*, **359**, 312 (1899).

(43) This hypothesis is currently under stereochemical investigation.

relative rates indicate that the anisyl group tends to participate eight times as readily as a phenyl group. This "migratory aptitude" demonstrates that the migrating group bears a significant amount of positive charge⁴⁴ and reiterates the conclusion reached above that the *p*-anisyl:phenyl ratio of 1.56:1 measured directly from the reaction of 1-phenyl-1-*p*-anisyl-2-aminoethanol is due in large measure to the relative populations of different conformations. These conclusions are further supported by the observation that compounds VIII, IX, and X give a mixture of glycol and rearranged ketone in aqueous nitrous acid although XI and XII give only ketone.⁴⁶ In the former cases, displacement by solvent to form glycol apparently competes favorably with the rearrangement of an alkyl group or hydrogen but such displacement in the latter cases competes less effectively with rearrangement of an aryl group. In solvolytic displacements aryl groups generally give greater neighboring group participation than alkyl groups or hydrogen.

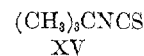
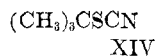


It should be mentioned that the present hypothesis which assumes a concerted rearrangement and expulsion of nitrogen is consistent with the stereochemical results of Bernstein and Whitmore⁴⁷ who found that optically active 1,1-diphenyl-2-aminopropanol, XII, gave optically active phenyl α -phenylethyl ketone, XIII.



Reaction 2e: Carbonium ion formation. One of the competing modes of decomposition of the diazonium ion is the direct formation of a carbonium ion by loss of nitrogen. Unlike the "high energy" carbonium ion which has been postulated from such a reaction (*vide supra*) the carbonium ion is here considered to be "normal", *i.e.*, directly comparable to carbonium ions which are produced in other reactions such as solvolytic displacements of alkyl halides and sulfonates.

The *t*-butyl cation reacts with thiocyanate ion to give a mixture of *t*-butyl thiocyanate, XIV, and isothiocyanate, XV. The similarity of the ratio of



XIV to XV for the mixture obtained from different sources of the *t*-butyl cation, isobutylamine, 1,9, *t*-butylamine, 1,9, *t*-butyl chloride, 2,5, demonstrates that essentially the same cation is produced from the three sources.⁴⁸ The reactions with aqueous nitrous acid of crotylamine, α -methylallylamine, α,α -dimethylallylamine, and γ,γ -dimethylallylamine yield, respectively, the same mixtures of isomeric allylic alcohols as the silver ion catalyzed aqueous solvolyses of the corresponding chlorides.^{49,50} The reactions of cyclopropylcarbinylamine and cyclobutylamine with aqueous nitrous acid to give similar mixtures of cyclobutyl alcohol, cyclopropyl carbinol, and allyl carbinol have been interpreted on the basis of the same intermediate cation.⁴⁹

The racemic portions of the 1-butyl-1-*d* acetate, 2-butyl acetate, 2-butyl alcohol, and α -phenylethyl alcohol obtained from the reactions of the corresponding amines with nitrous acid in acetic acid or water (*vide supra*) undoubtedly result from the respective carbonium ions.

Neighboring group participation. To reactions 2a-e may be added a sixth competing reaction, reaction 5, when the β -carbon contains a suitable heteroatomic function. An example is found in the



reaction of α -aminoacids with nitrous acid. Although the esters yield product with predominant inversion of configuration, the aminoacids produce a net retention of configuration^{2a,3} presumably because of the formation of an α -lactone by reaction 5 with one inversion followed by reaction of the α -lactone with solvent water to yield the hydroxyacid with a second inversion. In suitable cyclic cases oxides have been obtained from β -aminoalcohols (*vide infra*).

CYCLIC SYSTEMS

Cyclohexyl systems. Concerted rearrangements and eliminations with loss of nitrogen from diazonium ions in cyclohexyl systems have been proposed by several authors⁵¹ but no attempt has previously been made to relate these proposals to a

(44) For comparison, the migratory aptitude of *p*-anisyl relative to phenyl in the acid-catalyzed rearrangement of β,β -diarylethanol is 21.⁴⁶

(45) J. G. Burr and L. S. Ciereszko, *J. Am. Chem. Soc.*, **74**, 5426 (1952).

(46) H. Felkin, *Compt. rend.*, **226**, 819 (1948).

(47) H. I. Bernstein and F. C. Whitmore, *J. Am. Chem. Soc.*, **61**, 1324 (1939).

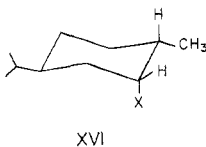
(48) L. G. Cannell and R. W. Taft, Jr., Abstracts of the 129th meeting of the AMERICAN CHEMICAL SOCIETY, Dallas, Tex., April 12, 1956, p. 46N.

(49) J. D. Roberts and R. H. Mazur, *J. Am. Chem. Soc.*, **73**, 2509 (1951).

(50) W. G. Young and C.-H. Shih, unpublished results reported in W. G. Young and R. H. DeWolfe, *Chem. Revs.*, **56**, 753 (1956).

(51) (a) M. Mousseron, *Bull. soc. chim. France*, 1008 (1956). (b) R. J. W. Cremlyn, D. L. Garmaise, and C. W. Shoppee, *J. Chem. Soc.*, 1847 (1953). (c) R. Anliker, O. Rohr, and H. Heuser, *Helv. Chim. Acta*, **38**, 1171 (1955).

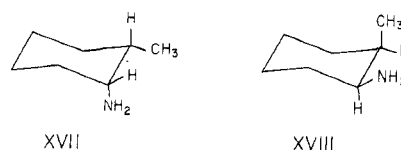
general theory. Cyclohexylamines have been shown to provide a striking demonstration of the importance of conformational considerations in the amine-nitrous acid reaction.^{52,53} In general, equatorial amines yield equatorial (retained) alcohol with little or no olefin; axial amines yield large amounts of olefin together with a small amount of alcohol which is predominantly the equatorial (inverted) alcohol.⁵⁴ In terms of the present hypothesis, equatorial amines would undergo reaction 2e almost exclusively and the resulting carbonium ion would react with solvent along an equatorial path and may be expected to produce exclusively equatorial alcohol. This point has been discussed in greater detail by Dauben, *et al.*^{53a,55} The axial diazonium ion can react by migration or elimination of a neighboring *trans*- (axial) hydrogen, by direct displacement by solvent, and in part by reaction 2e, carbonium ion formation. This carbonium ion, as in the equatorial case, should yield only equatorial alcohol. Other alcohols are generally also produced in small amount from axial amines but these have frequently been characterized either inadequately or not at all.⁵⁶ It seems clear, however, that in at least some of these cases, traces of the corresponding axial alcohols are formed.⁵⁷ According to the present hy-



pothesis, these alcohols could not be formed from the carbonium ion from reaction 2e but could arise from the reaction with solvent of a hydrogen-bridged intermediate.⁵⁵ Cyclohexylamine, which gives 80% cyclohexanol and 16% cyclohexene,^{56,58} would then be considered to be reacting about 80%

as an equatorial amine and 20% as an axial.⁵⁹ Direct displacements are not expected to be important in cyclohexyl systems because typical S_N2 reactions on cyclohexyl derivatives are about 100 times slower than on other secondary carbonyl systems.²⁰

The 2-methylcyclohexylamine system is an important case. The *trans*-isomer, which exists almost exclusively in the conformation in which both the methyl group and the amino group are equatorial, yields, as expected, *trans*-2-methylcyclohexanol.⁶⁰ The *cis*-amine is expected to exist in comparable amounts in the equatorial-methyl, axial-amino (XVII) and axial-methyl, equatorial-amino (XVIII) conformations. The former should yield olefin, *trans*-2-methylcyclohexanol, and the product of the migration of the tertiary *trans* (axial) hydrogen, (reaction 2c), 1-methylcyclohexanol. The



latter conformation, XVIII, should yield only 2-methylcyclohexyl cation which by rotation to the methyl-equatorial cation and equatorial reaction with solvent would lead to *trans*-2-methylcyclohexanol. Experimentally, the *cis*-amine yields mostly *trans*-2-methylcyclohexanol, some 1-methylcyclohexanol and olefin, and only a trace of *cis*-2-methylcyclohexanol,^{60c} in complete accord with the present theory. A mechanism involving a frontside displacement of nitrogen by solvent has been proposed to explain the retention of configuration observed with equatorial amines.^{52b} On this basis, XVIII should yield *cis*-2-methylcyclohexanol. The formation of only traces of this alcohol provides an argument against this mechanism. Similarly, these results are not consistent with the "hot" carbonium ion theory (*vide supra*).

In the case of equatorial amines, the *trans*-group is a ring carbon. As expected from the discussion developed in reaction 2d, rearrangement with ring contraction would be expected to be a significant competing reaction when a more stable carbonium ion would result from such rearrangement. Examples are the reaction of *trans*-2-phenylcyclohexylamine which gives a good yield of phenylcyclopent-

(52) (a) A. K. Bose, *Experientia*, **9**, 256 (1953). (b) J. A. Mills, *J. Chem. Soc.*, 260 (1953).

(53) (a) W. G. Dauben, R. C. Tweit, and C. Manner-skantz, *J. Am. Chem. Soc.*, **76**, 4420 (1954). (b) W. G. Dauben and J. Jiu, *J. Am. Chem. Soc.*, **76**, 4426 (1954). (c) W. G. Dauben, R. C. Tweit, and R. L. MacLean, *J. Am. Chem. Soc.*, **77**, 48 (1955).

(54) The recent report of C. W. Shoppee, D. E. Evans and G. H. R. Summers, *J. Chem. Soc.*, 97 (1957), that some axial steroid amines yield olefin and *axial* (retained) alcohol is in complete apparent contradiction to all of the other results cited with cyclohexyl systems. Clearly, additional work is required to determine why these amines differ from the others; no explanation can be offered at this time.

(55) Cf. also W. H. Saunders, Jr., in ref. 53a, footnote 36.

(56) For example, see the summary of other references cited in W. Hüchel, *Ann.*, **533**, 1 (1937).

(57) One of the best examples is the reaction of neocarcovomethylamine (XVI, X = NH₂) from which a small amount of neocarcovomethylol (XVI, X = OH) was obtained and characterized *via* the 3,5-dinitrobenzoate. [R. G. Johnston and J. Read, *J. Chem. Soc.*, 1138 (1935)].

(58) W. Huckel and R. Kupka, *Ber.*, **89**, 1694 (1956).

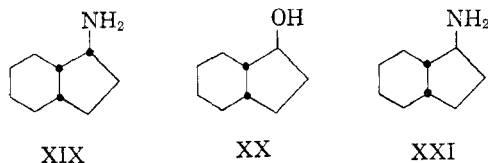
(59) These values correspond to an energy difference (A value) of the two conformations of the nitrogen function of 0.8 kcal./mole, a not unreasonable value inasmuch as the A value for the hydroxyl group is 0.8 kcal./mole [S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955)].

(60) (a) P. Anziani and R. Cornubert, *Compt. rend.*, **221**, 103 (1945). (b) P. Anziani and R. Cornubert, *Bull. soc. chim. France*, **15**, 857 (1948). (c) M. Claudon, P. Anziani and R. Cornubert, *Bull. soc. chim. France*, 150 (1956).

tylcarbinol⁶¹ and the formation of phenyl cyclopentyl ketone from *trans*-2-amino-1-phenylcyclohexanol.⁶² Analogous results are obtained with some steroidal amines.^{51b,c}

Trans-2-aminocyclohexanol yields only cyclopentylaldehyde although the *cis*-aminoalcohol yields both cyclopentylaldehyde and cyclohexanone;⁶³ cyclohexyl systems in which an amino function and a hydroxyl function occupy adjacent axial positions yield epoxides.^{51a,b} In these positions, neighboring group participation is geometrically most favorable (reaction 5). Similar reactions with other functions have been summarized by Mousseron.^{51a}

Cyclopentyl systems. Both carbonium ion formation and direct displacement reactions are expected to be important with cyclopentyl amines. When *trans*-hydrogens are available, elimination and rearrangement are to be anticipated. Cyclopentylamine itself yields equal amounts of cyclopentene and cyclopentanol.^{56,64a} The alcohol from *trans*-2-cyclopentyl-1-cyclopentylamine is almost pure *cis*-2-cyclopentyl-1-cyclopentanol and the alcohol from the *cis* amine is mostly *trans*. In both cases a net inversion of configuration predominates.^{64b} Olefin is also obtained in both cases. Analogously, *cis*-1-amino-*cis*-hydrindane, XIX, yields more of the corresponding *trans*-alcohol, XX, than does the *trans*-amine, XXI.



On the other hand, *cis*-2-methylcyclopentylamine is reported^{64a} to yield an alcohol mixture of 70% *cis*-2-methylcyclopentanol and 30% *trans*-2-methylcyclopentanol and an olefin mixture consisting of about equal amounts of 1-methylcyclopentene and 2-methylcyclopentene although the *trans*-amine yields an alcohol mixture consisting of about equal parts of these *cis* and *trans* alcohols and olefin which is essentially pure 1-methylcyclopentene. These results are in direct contrast to those obtained in the other systems cited above and from those expected by the theory, and suggest further investigation.

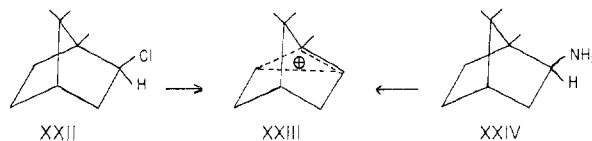
(61) (a) D. V. Nightingale and M. Maienthal, *J. Am. Chem. Soc.*, **72**, 4823 (1950). (b) D. V. Nightingale, J. D. Kerr, J. A. Gallagher, and M. Maienthal, *J. Org. Chem.*, **17**, 1017 (1952); *trans*-2-cyclohexylcyclohexylamine does not rearrange in this way probably because a secondary carbonium ion would result which is no more stable than that formed without rearrangement.

(62) D. Y. Curtin and S. Schumkler, *J. Am. Chem. Soc.*, **77**, 1105 (1955).

(63) G. E. McCasland, *J. Am. Chem. Soc.*, **73**, 2293 (1951).

(64) (a) W. Hüchel and R. Kupka, *Ber.*, **89**, 1694 (1956). (b) W. Hüchel, A. Gross, and W. Doll, *Rec. trav. chim.*, **57**, 555 (1938).

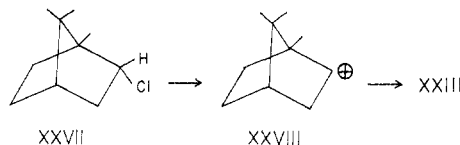
Bridged bicyclic systems. In the bicyclo[2.2.1]heptyl system a comparison of the amine-nitrous acid reaction with solvolytic displacement reactions is especially pertinent because nonclassical bridged ions have been shown to be important intermediates in the latter reactions.²⁰ The solvolysis of isobornyl chloride, XXII, to yield the bridged ion, XXIII, shows such substantial rate enhancement that in the reaction of the corresponding amine, XXIV, the decomposition of the diazonium salt to yield XXIII is expected to be the only important mode of reaction. In aqueous base, XXIII yields



camphene hydrate, XXV. The products of the reaction of XXIV with sodium nitrite in dilute acetic acid are camphene hydrate, XXV, and camphene, XXVI,^{64a} consistent with expectations. On the other hand, bornyl chloride, XXVII, cannot yield XXIII by a concerted neighboring group rear-

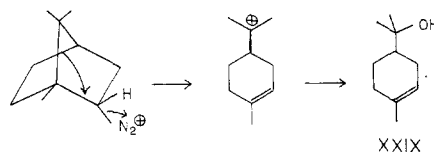


rangement but does so in a comparatively slow reaction presumably by way of the bornyl cation, XXVIII. In the reaction of bornylamine, therefore, two modes of decomposition of the diazonium ion are important.



One is the formation of XXVIII, thence XXIII; the other is the elimination (or a rearrangement followed by elimination) of the *trans* group, the *gem*-dimethyl bridge (Equation 6). The products of the reaction in dilute acetic acid are not only camphene and camphene hydrate but also terpineol, XXIX.⁶⁵

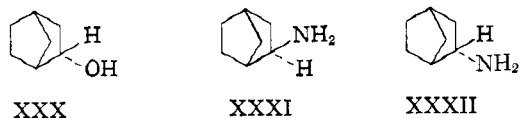
The reactions of the norbornylamines are directly comparable except that a reaction similar



to reaction 6 does not occur because a primary carbonium ion would result. The *exo*-norborneol, XXX,

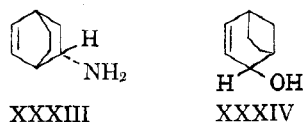
(65) W. Hüchel and F. Nerdel, *Ann.*, **528**, 57 (1937).

which is obtained from *exo*-norbornylamine, XXXI, is about 50% rearranged,¹⁰ apparently because of the almost exclusive direct formation of a bridged cation. The lesser amount of rearrangement¹⁰ found in the case of the *endo*-amine, XXXII, is

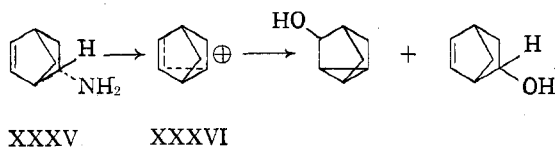


presumably due either to a reaction of the initial intermediate, the unbridged norbornyl cation, with solvent or by a competing direct displacement, or both. Similar arguments can be applied to the reaction products obtained from the epimeric fenethylamines⁶⁶ and from camphenylamine.⁶⁷

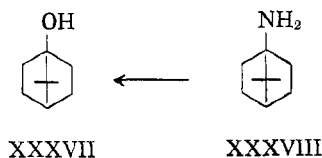
Although the reaction with nitrous acid of *endo*-2-aminobicyclo[2.2.2]octene-5, XXXIII, to yield bicyclo[3.2.1]oct-3-ene-2-ol, XXXIV,⁶⁸ is probably



best interpreted as a 2d reaction in which the ethylene bridge migrates as nitrogen is lost, the corresponding reaction of *endo*-2-amino-bicyclo[2.2.1]heptene-5, XXXV, on the basis of the present discussion probably occurs by way of the nonclassical ion, XXXVI.⁶⁹ The further rearrangement which the ion XXXVI can undergo has been detailed by Roberts, *et al.*^{69a}



The formation of apocamphanol-1, XXXVII, from 1-amino-apocamphane, XXXVIII,⁷⁰ accord-



ing to the present hypothesis is due to the formation of a carbonium ion at the bridgehead which in

(66) (a) W. Hüchel and H. Wolowski, *Ber.*, **80**, 39 (1947). (b) W. Hüchel and U. Ströle, *Ann.*, **585**, 182 (1954).

(67) S. Beckmann and R. Bamberger, *Ann.*, **574**, 65 (1951).

(68) W. C. Wildman and D. R. Saunders, *J. Am. Chem. Soc.*, **76**, 946 (1954).

(69) (a) J. D. Roberts, C. C. Lee, and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **77**, 3034 (1955). (b) W. E. Parham, W. T. Hunter, and R. Hanson, *J. Am. Chem. Soc.*, **73**, 5068 (1951).

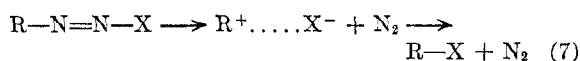
(70) P. D. Bartlett and L. H. Knox, *J. Am. Chem. Soc.*, **61**, 3184 (1939).

this case is the only mode of reaction available to the intermediate diazonium ion. Because of the higher energy of the tetrahedral carbonium ion⁷¹ this reaction should occur less readily than the decomposition of other alkyldiazonium ions but should occur at least as readily as the decomposition of an aryldiazonium ion which yields a similarly unstable aryl cation.⁷²

OTHER SYSTEMS

The transannular 1,5- and 1,6-hydride shifts which have been found to occur during the reaction of cyclodecylamine with nitrous acid⁷³ are presumably directly analogous to the 1,2-shifts represented as reaction 2c.

Finally, mention should be made of the several reactions of the amine-nitrous acid type in inert solvents. The reaction of optically active α -phenylethylamine with nitrosyl chloride in dioxane leads to the corresponding chloride with partial net retention of configuration.⁷⁴ The decomposition of 2-phenyl-2-*p*-tolylethylamine nitrite in dry ligroin or in dry butanol gave *carbinol*.³⁵ In both cases the results were attributed to an intramolecular reaction of the S_N1 ⁷⁵ type. However, like other such reactions, these results are consistent with the intermediate formation of an "intimate ion pair" or "p σ -complex" which collapses with predominant retention of configuration, reaction 7.^{76,77}



Further work may demonstrate the necessity of including reactions of this type among the competing modes of decomposition of alkyldiazonium salts.

Acknowledgment. The author is indebted to Professor William G. Dauben for many stimulating discussions on this subject.

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(71) Cf. W. E. Doering, M. Levitz, A. Sayigh, M. Sprecher, and W. P. Whelan, *J. Am. Chem. Soc.*, **75**, 1008 (1953).

(72) Cf. J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 273 (1951).

(73) V. Prelog, H. J. Urech, A. A. Bothner-by, and J. Würsch, *Helv. Chim. Acta*, **38**, 1095 (1955).

(74) H. Felkin, *Compt. rend.*, **236**, 298 (1953).

(75) W. A. Cowdrey, E. D. Hughes, C. K. Ingold, S. Masterman, and A. D. Scott, *J. Chem. Soc.*, 1252 (1937).

(76) (a) C. E. Boozer and E. S. Lewis, *J. Am. Chem. Soc.*, **75**, 3182 (1953). (b) D. J. Cram, *J. Am. Chem. Soc.*, **75**, 332 (1953). (c) A. Streitwieser, Jr., and W. D. Schaeffer, *J. Am. Chem. Soc.*, **79**, 379 (1957). (d) A. Streitwieser, Jr., and W. D. Schaeffer, *J. Am. Chem. Soc.*, **79**, 2893 (1957).

(77) The application of this explanation to the results of Bailey and Burr³⁵ is uncertain. Inadequate experimental details were given and one cannot tell if the first products were alkyl nitrites which hydrolyzed during work-up or whether an intermediate diazoalkane was formed.^{76d}