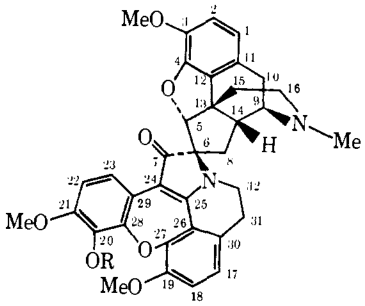
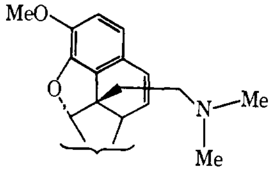
To deduce the structure of cancentrine from **5** it is necessary (a) to show that the transformation **1** → **5** involves only the opening of the nitrogen containing bridge and (b) to locate the nitrogen terminus of the bridge and the OH function of **1**.

Compounds **1**, **2**, **3**, **4**, and **5** are all bright yellow with very similar uv spectra and in every case an ir band at $\nu_{max}^{CHCl_3}$ 1665 ± 5 cm^{-1}. All pmr spectra have a sharp singlet at δ 5.0 ± 0.2 attributed to C_5–H and three AB quartets accounting for six aromatic protons. An additional AB quartet (vinylic, H_9–H_{10}) is present in the spectrum of **4**. Thus, it is clear that in the conversion **1** → **4** → **5** only the simple expected changes have taken place.

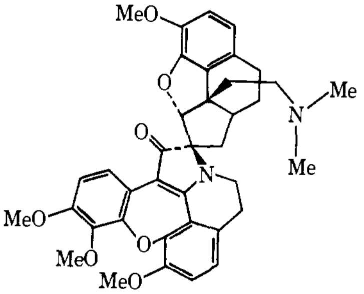
The terminus of the bridge was established through pmr examination of **1** and comparison of its spectrum with that of codeine, **6**.[8] The splitting patterns and the chemical shifts of the protons C_9–C_{10} in the two systems are very similar. Thus $H_{10\beta}$ (δ 3.18) in **1** is coupled to $H_{10\alpha}$ (δ 2.43) ($J_{10\alpha,10\beta}$ = 18.5 Hz) but is only weakly coupled to H_9 (δ 3.43; $J_{H_{10\beta},H_9}$ = 1.0 Hz). In the spectrum of cancentrine, $H_{10\alpha}$ is partially obscured although it has been observed in the morphine systems,[8] while H_9 appears as a multiplet in both coupled as it is to $H_{10\alpha}$, $H_{10\beta}$, and H_{14} with coupling constants in **1** of $J_{H_9,H_{10\alpha}}$ = 6.0 Hz, $J_{H_9,H_{10\beta}}$ = 1.0 Hz, and $J_{H_9,H_{14}}$ = *ca.* 1.5 Hz. The couplings for codeine are virtually identical[8] suggesting the same steric arrangement in the two systems as shown in the structures. A spectrum completely different from that of codeine would have resulted for the protons at C_9 and C_{10} in cancentrine had the nitrogen been joined to C_{14} as in hasubanonine,[9] or to C_{10}, which is biogenetically unlikely.



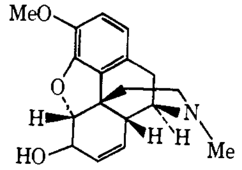
1, R = H
2, R = Me
3, R = COMe



4, R = H



5



6

The site of the acetoxy group in **3** and, therefore, of the OH group in **1** has been established by pmr examination of **1** and **3**. The aromatic protons appear as three AB quartets with one proton at lower field than the rest. This proton is centered at δ 7.51 and 7.88 in **1** and **3**, respectively. A shift of this order upon acetylation is characteristic of a proton para to a phenolic OH group.[10] This places the OH group of **1** and the acetoxy group of **3** at C_{20} in agreement with observed nuclear Overhauser effects[11] of 25, 25, and 24% in the aromatic signals at δ 6.83, 6.68, and 6.98 when the methoxyl signals at δ 3.91, 3.76, and 3.85, respectively, in **1** were irradiated—a result only possible if the phenolic OH group in **1** is located at C_{20} where it is not vicinal to any aromatic protons.

Thus, cancentrine is the first member of a new class of dimeric benzylisoquinoline alkaloids, unique both in the nature of the individual benzylisoquinoline units (morphine and cularine[12]), and in the manner of their linkage. Three more alkaloids of the cancentrine family have been isolated from the same source. Their structures will be the subject of a subsequent publication.

Acknowledgments. This investigation was supported by grants from the National Research Council of Canada.

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Reactions of the Nitrosonium Ion. I. The Reaction of Alkyl Azides with Nitrosonium Salts. A New Method for the Production of Carbonium Ions

Sir:

Interest in the reaction between azides and various sources of the nitrosonium ion has existed since Curtius attempted to produce hydrogen azide from hydrazine and nitrous acid.[1] Only recently, however, has the reaction between the azide ion and nitrous acid been

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(1) T. Curtius, *Ber.*, **26**, 1263 (1893).

studied in some detail.[2] The nitrosonium ion reacts with azide ion to form nitrosyl azide, an unstable but isolable compound,[2b] which subsequently decomposes to nitrogen and nitrous oxide (eq 1). Treatment of

$$N_3^- + NO^+ \longrightarrow NNNNO \longrightarrow N_2 + N_2O \qquad (1)$$

$$A\text{-}N_3 + NO^+ \longrightarrow [AN_4O]^+ \longrightarrow A^+ + N_2 + N_2O \qquad (2)$$

substituted azides (eq 2) with nitrosonium compounds offers the means by which cations may be produced without concomitant formation of a substance which would interfere with this process, as when an equimolar amount of water is formed as a by-product in the deamination of primary amines by nitrous acid.[3] Indeed, transition metal azides have been treated with nitrous acid with formation of nitrogen, nitrous oxide, and metal complexes with coordination number one less than the reactant.[4] Surprisingly, however, there has been no report of reaction between organic azides and any source of the nitrosonium ion.

We wish to report that alkyl azides react rapidly and efficiently with stable nitrosonium salts, such as $NO^+BF_4^-$, $NO^+PF_6^-$, and $NO^+SbF_6^-$,[5] to produce carbonium ions. Thus triphenylmethyl azide, when treated with $NO^+BF_4^-$ in acetonitrile at 10°, quantitatively produced nitrogen, nitrous oxide, and triphenylmethyl tetrafluoroborate. Nitrous oxide was collected in a cold trap and identified from its characteristic infrared spectrum. Triphenylmethyl tetrafluoroborate was identified from its melting point and infrared, ultraviolet, and pmr spectra.

Similar treatment of benzhydryl azide, prepared from benzhydrol,[6] with nitrosonium salts followed by quenching with water yielded, along with nitrogen and nitrous oxide, an unexpectedly large number of products. In a typical experiment, $NO^+BF_4^-$ (10.6 mmol) in 20 ml of acetonitrile was added[7] over a period of 30 min to a stirred solution of benzhydryl azide (9.6 mmol) in 10 ml of acetonitrile[8] maintained at 7°. Total gas evolution was measured. After complete addition, the reaction mixture was quenched by addition of water and worked up in the usual way.

The organic products obtained from the reaction between benzhydryl azide and $NO^+BF_4^-$ in acetonitrile include (relative yields given in parentheses) benzhydrol (26%), (*N*-diphenylmethyl)acetamide (53%), benzophenone (13%), benzaldehyde (8%), and benzenediazonium tetrafluoroborate (8%). Preparative thin-layer chromatography was used to separate the components of the reaction mixture, and each component was identified from its physical properties and through comparison with an authentic sample. The total recovery of products was nearly quantitative. Reactions of benzhydryl azide with nitrosonium salts in other nitrile solvents show analogous results.

$$(C_6H_5)_2CH\text{-}N_3 \xrightarrow[CH_3CN]{NO^+BF_4^-} \xrightarrow{H_2O} (C_6H_5)_2CH\text{-}OH + (C_6H_6)_2CH\text{-}NHCOCH_3 + (C_6H_5)_2C{=}O + C_6H_5CHO + C_5H_5N_2^+BF_4^-$$

That the benzhydryl cation is produced in this reaction is shown by the formation of benzhydrol and the corresponding amide, produced by N alkylation of the nitrile solvent. The relative amounts of alcohol and amide formed are independent of reaction times but are dependent on the concentration of reactants and on the reaction temperature, as would be expected from the equilibrium

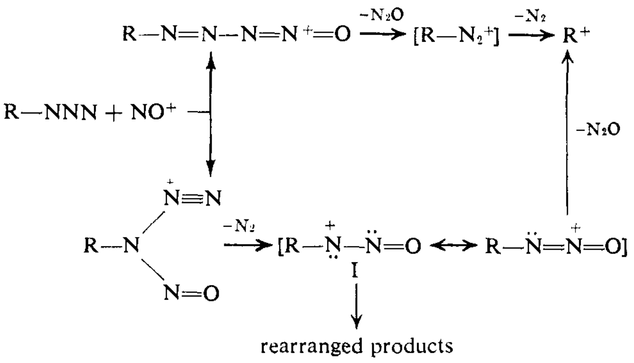
$$(C_6H_5)_2CH^+ + CH_3CN \rightleftarrows (C_6H_5)_2CH{-}N^+{\equiv}CCH_3$$

Trapping of the benzhydryl cation by trialkylsilanes[9] produced the expected diphenylmethane.

Although the major pathway for reaction of alkyl azides with the nitrosonium ion leads to the formation of carbonium ions, a significant amount of product, benzophenone, benzaldehyde, and benzenediazonium tetrafluoroborate, is due to rearrangement of the alkyl group. In fact, when the reaction between $NO^+BF_4^-$ and benzhydryl azide is carried out at 55°, the relative amounts of benzaldehyde and benzophenone total 35%. When the same reaction is performed at −30°, less than 10% rearranged products are observed. Thus, the rearrangement process appears to lend itself to effective control.

Substituted azides, unlike the azide ion, may undergo attack by a Lewis acid on either the internal substituted nitrogen or on the external nitrogen (Scheme I). As with protonic decomposition of azides (the Curtius rearrangement) only attack on the internal nitrogen will yield rearranged products.[10] In the reaction of alkyl azides with the nitrosonium ion, attack at the external nitrogen will, through loss of nitrous oxide and nitrogen which may be concurrent,[4b] only yield the carbonium ion. However, if attack is at the internal nitrogen, loss of a nitrogen molecule will yield a species which has a contributing resonance form that may be formally written as a nitroso-substituted nitrenium ion (I).[11] If the rate of migration is comparable to or

Scheme I



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[2] (a) G. Stedman, *J. Chem. Soc.*, 2943 (1959); (b) H. W. Lucien, *J. Amer. Chem. Soc.*, 80, 4458 (1958); (c) F. Seel, R. Wolfle, and G. Zwarg, *Z. Naturforsch. B*, 13, 136 (1958); (d) P. A. Klaus Clusius and H. Knopf, *Chem. Ber.*, 89, 681 (1956).

[3] For a review of deamination reactions see R. J. Baumgarten, *J. Chem. Educ.*, 43, 398 (1966).

[4] (a) A. Hiam and H. Taube, *Inorg. Chem.*, 2, 1199 (1963); (b) R. B. Jordan, A. M. Sargeson, and H. Taube, *ibid.*, 5, 1091 (1966); (c) D. A. Buckingham, I. I. Olsen, A. M. Sargeson, and H. Satrapa, *ibid.*, 6, 1027 (1967); (d) R. C. Thompson and E. J. Kaufmann, *J. Amer. Chem. Soc.*, 92, 1540 (1970).

[5] These salts are commercially available and were dried prior to use over phosphorus pentoxide.

[6] C. H. Gudmundsen and W. E. McEwen, *J. Amer. Chem. Soc.*, 79, 329 (1957).

[7] Product formation is neither a function of the rate nor mode of addition.

[8] All solvents were of reagent grade quality and were dried by distilling from calcium hydride before use.

[9] F. A. Carey and H. S. Tremper, *J. Amer. Chem. Soc.*, 91, 2967 (1969), and previous articles in this series.

[10] P. A. S. Smith in "Molecular Rearrangements," P. deMayo, Ed., Wiley, New York, N. Y., 1963, Chapter 8.

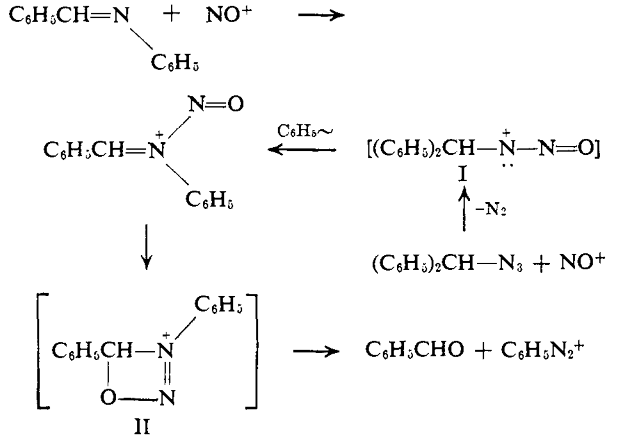
[11] Current research on nitrenium ions has been recently reviewed by P. G. Gassman, *Accounts Chem. Res.*, 3, 26 (1970).

faster than the rate of loss of nitrous oxide, migration will occur.

The formation of benzaldehyde and benzenediazonium tetrafluoroborate can be rationalized by phenyl migration and has ample analogy with the protonic decomposition of benzhydryl azide.[12] We have observed that benzhydryl azide yields benzaldehyde and benzenediazonium tetrafluoroborate even when water and oxygen are rigorously excluded. This result, which was supported by our inability to effectively trap the expected benzylideneaniline intermediate by sodium borohydride reduction,[13] suggested that imines are labile to diazotization by the nitrosonium cation.

Treatment of *N*-benzylideneaniline with an equivalent amount of $NO^+BF_4^-$ in acetonitrile produces benzaldehyde and benzenediazonium tetrafluoroborate in nearly quantitative yields, as determined by chromatography and spectral properties. The pmr spectrum of benzylideneaniline before addition of the nitrosonium salt shows the C-hydrogen as a singlet at δ 8.51 relative to internal TMS.[14] Upon addition of $NO^+BF_4^-$ the C-hydrogen is observed at δ 9.37[15] which corresponds well to the change in chemical shift observed by Olah for the analogous protonated benzylideneaniline.[16] In addition, a new proton resonance due to benzaldehyde appears at δ 10.0 which increases in intensity with time at the expense of the δ 9.37 signal. These data support a mechanism in which nitrososation occurs prior to rearrangement (Scheme II). We speculate that the production of aldehyde and diazonium ion is preceded by rate-limiting formation of an N-substituted oxadiazetine ring (II), but have at present no evidence to support the existence of such an unusual compound. In general, *N*-aryl derivatives of benzylideneimine react readily with nitrosonium salts to produce aryldiazonium ions and benzaldehyde (eq 3), and *N*-alkyl derivatives of benzylideneimine produce carbonium ions, nitrogen, and benzaldehyde (eq 4).

Scheme II



$$C_6H_5CH{=}NAr + NO^+X^- \longrightarrow C_6H_5CHO + ArN_2^+X^- \quad (3)$$

$$C_6H_5CH{=}NR + NO^+X^- \longrightarrow C_6H_5CHO + N_2 + R^+X^- \quad (4)$$

Recently, Olah reported that alkyl and acyl sulfinylamines, isocyanates, and thioisocyanates react with nitrosonium salts to produce carbonium or oxocarbonium ions.[17] We have found that benzhydryl thioisocyanate and sulfinylamine react similarly, although at higher temperatures than we have used with the corresponding azides and without production of benzaldehyde. Adaption of the mechanism given in Scheme II to the reaction of nitrosonium salts with sulfinylamines, isocyanates, and thioisocyanates would explain the formation of carbonium ions, oxide gases, and nitrogen in those cases.

Production of benzophenone from benzhydryl azide occurs prior to quenching with water and may be explained by hydrogen migration or hydride abstraction from I. We have observed that benzhydrylidenimine reacts with $NO^+BF_4^-$ in anhydrous acetonitrile to produce an equal amount of benzophenone and nitrogen.

The reduction of alkyl azides with nitrosonium compounds represents a new and valuable route to the formation of carbonium ions. The cleavage of the carbon–nitrogen double bond of imines is also an efficient and useful method for diazotization. Whereas deamination of an amine requires a large excess of a particular nitrosonium compound[18] with resultant formation of water as a by-product, azides and imines react completely with 1 equiv of nitrosonium salt to produce carbonium ions. We are continuing investigations in these areas and into the reactions of nitrosonium compounds with other unsaturated systems.

Acknowledgment. We gratefully acknowledge the donors of the Research Corporation for partial support of this work.

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(12) C. H. Gudmundsen and W. E. McEwen, *J. Amer. Chem. Soc.*, **79**, 329 (1957).

(13) R. W. Layer, *Chem. Rev.*, **63**, 489 (1963).

(14) Spectra were taken on a Varian Associates Model A-60-A nmr spectrometer using acetonitrile as solvent and at a temperature of 35°.

(15) The expected change in position of phenyl patterns was also observed.[16]

(16) G. A. Olah and P. Kreienbuhl, *J. Amer. Chem. Soc.*, **89**, 4756 (1967).

(17) G. A. Olah, N. Friedman, J. M. Bollinger, and J. Lukas, *ibid.*, **88**, 5328 (1966).

(18) Benzhydrylamine, for example, requires more than 2 equiv of nitrosonium salt for complete reaction.

(19) National Science Foundation Undergraduate Research Participant, Summer 1969.

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Nuclear Relaxation at the Active Site of α-Chymotrypsin

Sir:

In a recent paper we described the irreversible inhibition of the enzyme α-chymotrypsin by a series of trifluoromethyl-substituted α-bromoacetanilides (Ia–c) and alluded to our plans to examine the resulting derivatized proteins by fluorine nuclear magnetic resonance spectroscopy.[1] We now wish to report the results of preliminary experiments with these materials which provide, for the first time, direct data regarding nuclear transverse relaxation times (T_2) at the active site of this enzyme.

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