Direct Conversion of Terpenylalkanolamines to Ethylidyne N-Nitroso Compounds

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A series of mono- and diterpenylalkanolamines bearing isopropylidene functionality on the terpene group was reacted with sodium nitrite in aqueous acetic acid to yield ethylidyne N-nitroso analogues. The key feature of this direct conversion involved intial N-nitrosation followed by apparent elimination of a "CH_4" unit (not necessarily methane) from the isopropylidene double bond. The product distribution data for ethylidyne nitrosamines derived from tertiary terpenyl alkanolamines reflect the conformational outcome of the nitrosative dealkylation process. For β,γ-unsaturated allylic diterpenylethanolamines, electronic effects appeared to be important for controlling the product distribution of ethylidyne nitrosamines in light of the highly selective α-cleavage observed in the nitrosation reactions.

In studies directed toward the quantitative assessment of the occurrence of nitrosamines in tissues treated with fishery chemicals,[1,2] it was discovered that *N*-(2-hydroxyethyl)digeranylamine (1), an experimental fish toxicant, reacted with sodium nitrite in aqueous acetic acid to give exclusively *N*-nitroso-*N*-(2-hydroxyethyl)geranylamine (2) in high yield. When 1 was nitrosated in a usual manner with a large excess of sodium nitrite (amine/nitrite = 1/11) for an extended period of about 4 h at 90 °C, a new nitrosamine product was obtained in moderate yield. The structure of this compound was subsequently determined to be 2-nitroso-(3′-methyl-2′-octen-6′-ynyl)aminoethanol (4) by independent synthesis, carbon-13 NMR spectrometry, and mass spectrometry. The formation of 4 from 1 is unusual. This hitherto unknown reaction presents the first direct C=C → C≡C conversion under conventional nitrosation conditions. As a result of our continuing efforts to uncover the mystery of this seemingly bizarre reaction, the general applicability of the reaction to a number of structurally related alkanolamines has been demonstrated. In this paper we report the details of the confirmation study on the structure of 4 and the extension of the 1 → 4 conversion to a series of mono- and diterpenyl alkanolamines.

Results and Discussion

As illustrated in Scheme I, nitrosation of 1 yielded quantitatively 2, which constituted the sole nitrosamine product isolated from the reaction mixture. Attempts to identify other nitrosation products by combined high-performance liquid chromatography (HPLC)–thermal energy analysis[3] failed to produce any evidence of the formation of *N*-nitrosodigeranylamine (3), which would have been formed from the nitrosative dealkylation at the C_2–N bond with the resultant removal of the hydroxyethyl group. The result is illustrative of a highly selective α-cleavage of a C_1–N bond of 1 by nitrous acid. Nitrosation studies carried out on a series of related β,γ-unsaturated allylic terpenyl ethanolamines (Table I, type I compounds) show a similar and remarkable selectivity in the dealkylation processes.

On the contrary, the reaction of 5, the octahydro analogue of 1, with nitrous acid under identical conditions as above proved rather nonselective and afforded a mixture of nitroso compounds 6 and 7 in respective yields of 47% and 53% (Scheme II). Generally, it seems that compounds devoid of β,γ-unsaturated allylic groups, such as those in type II compounds (Table I), follow a relatively nondiscriminative pattern for undergoing C–N bond cleavage. Nevertheless, the data in Table I clearly show substantial deviation in the relative yield values of the nitrosamine products for both type I and II compounds from the statistical values of 67% A (from the C_1–N cleavage) and 33% B (from the C_2–N cleavage) on the basis of random attacks at the C–N bonds. We feel that the favorable formation of B from type II compounds may be partially due to the steric influence of the terpenyl hydrocarbon chain on the reaction course, notwithstanding the absence of any substituents on the α-carbons. On the other hand, the preferential formation of A from type I compounds can be explained in terms of allylic stabilization of the transition state leading to an immonium ion intermediate.[4] To attest the hypothesis of allylic involvement in the nitrosative dealkylation of type I compounds, we examined the nitrosation reactions of a pure isomer of 1 at various temperatures. Each of the reactions was found to occur with concomitant isomerization of the β,γ-double bond yielding a mixture of cis and trans nitrosamine 2 (compounds depicted in Scheme I are the

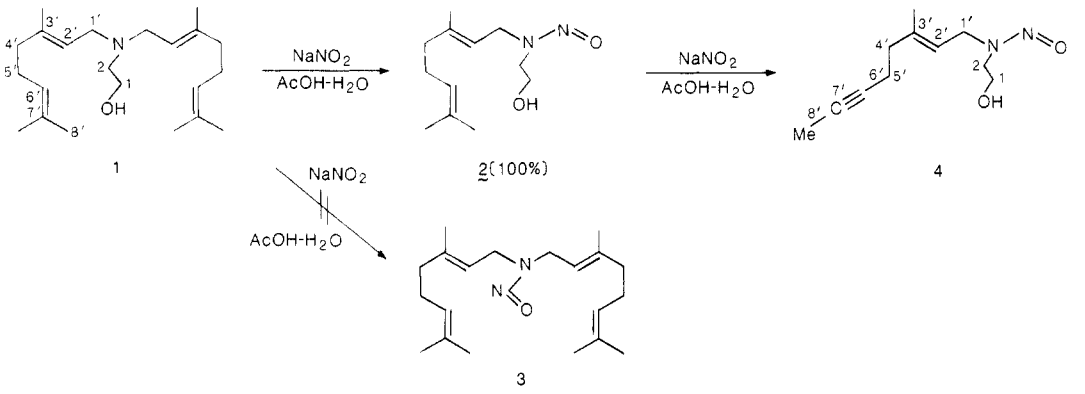
Table I. Nitrosation of Some Terpenylethanolamines[a]

compound	nitrosamine isolated (%)[b]
Type I[c]	
(2-hydroxyethyl)digeranylamine (1)	A (100), B (0)
bis(2-hydroxyethyl)geranylamine	A (95), B (5)
(2-hydroxyethyl)bis(6′,7′-dihydrogeranyl)amine	A (100), B (0)
(2-hydroxyethyl)dilinalylamine	A (99), B (1)
Type II[d]	
(2-hydroxyethyl)bis(3′,7′-dimethyloctyl)amine (5)	A (47), B (53)
bis(2-hydroxyethyl)(3′,7′-dimethyloctyl)amine	A (16), B (84)
(2-hydroxyethyl)bis(3′,7′-dimethyl-6′-octenyl)-amine	A (45), B (55)
(2-hydroxyethyl)dilanduylamine	A (41), B (59)

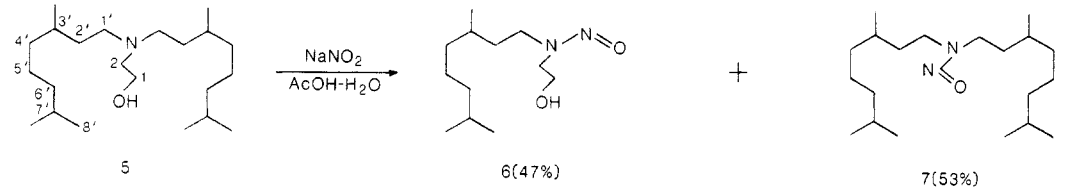
[a] Reaction conditions: 50 °C; amine/nitrile = 1/5; phosphate buffer, pH 5; 70% aqueous DMF; period, 2 h. [b] Relative yields based on nitrosamine products. A and B represent nitrosamines obtained from cleavage of the C_1–N and C_2–N bonds, respectively. [c] β,γ-Unsaturated allylic terpenylethanolamines. [d] Terpenylethanolamines without β,γ-unsaturation.

(1) Abidi, S. L.; Idelson, A. L. *Anal. Chem. Symp. Ser.* **1982**, *11*, 563-569.
(2) Abidi, S. L. *Anal. Chem.* **1982**, *54*, 510-516.
(3) Fine, D. H.; Rufeh, F.; Lieb, D.; Roundbehler, D. P. *Anal. Chem.* **1975**, *47*, 1188-1191.
(4) Smith, P. A. S.; Loeppky, R. N. *J. Am. Chem. Soc.* **1967**, *89*, 1147-1157.

Scheme I



Scheme II



Scheme III

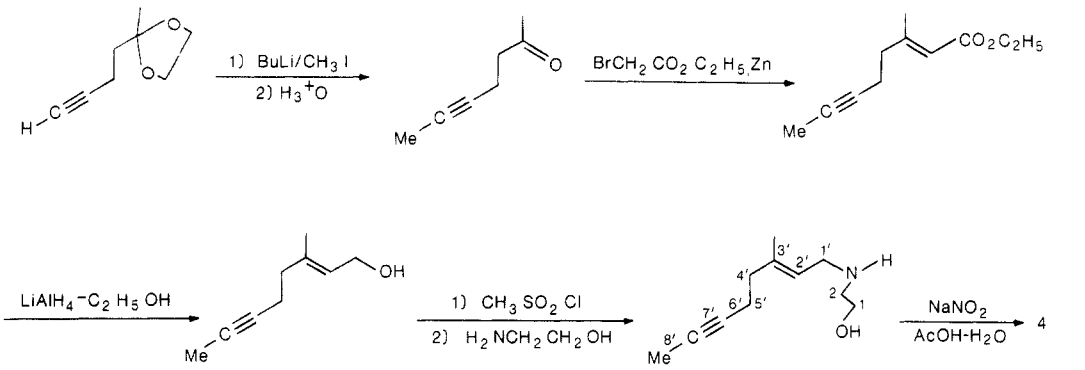


Table II. Cis-Trans Isomerization of Nitrosamine 2[a]

	control standard[b]				nitrosation product, nitrosamine 2	
	amine 1		nitrosamine 2			
temp, °C	cis, %	trans, %	cis, %	trans, %	cis, %	trans, %
30	0.0	100	1.7	98.3	11.1	88.9
50	0.0	100	10.0	90.0	29.3	70.7
65	0.0	100	11.9	88.1	36.6	63.4
85	0.0	100	16.4	83.6	50.0	50.0

[a] Nitrosation conditions are same as in Table I except different temperatures were used to show the extent of temperature effects on cis-trans ratios of 2. [b] Pure trans isomers of 1 and 2 were used as reference standards in control experiments when the reactions were run in the absence of nitrite.

trans isomers). Table II summarizes the results of the study and includes the data from control experiments.

In view of the absence of any acetylenic ethanolamine (containing no nitroso group) in the nitrosation products from 1, it is evident that 4 was formed via a stepwise reaction sequence going from initial N-nitrosation to apparent elimination of an overall "CH_4" unit (not necessarily methane) from the isopropylidene moiety in the last step: 1 → 2 → 4. Experimentally, we observed the sequential appearance (2 and 4) and disappearance (1 and 2) of relevant chromatographic peaks during monitoring the reaction course. The result of the preliminary study showed that the nitrosative elimination reaction appeared to be unique for the isopropylideneterpenyl structure. We were unable to isolate any compounds similar to 4 from the nitrosation of 5 and 6 (the saturated analogues of 1 and 2, respectively) in separate experiments. This suggests that the allylic double bond is not necessary and only the olefinic 6′,7′-unsaturation in the terpenyl moiety is a structural prerequisite for the elimination reaction to take place.

To establish the structural identity of 4 unequivocally, we synthesized the authentic compound from 5-hexyn-2-one (Scheme III), which was prepared by the method of Gelin and Hablot.[5] Ketalization of this starting material with ethylene glycol and *p*-toluenesulfonic acid in benzene was followed by sequential methylation and acid hydrolysis to give 5-heptyn-2-one in 85% overall yield. Subsequent Reformatsky condensation of this ketone with ethyl bromoacetate and zinc yielded the trans α,β-unsaturated

(5) Gelin, R.; Hablot, J. C. *C. R. Seances Acad. Sci. Ser. C* **1967**, *264*, 1966–1968.

Table III. Catalytic Hydrogenation of 4

entry	reduction condition	product composition (%)
1	Raney Ni, 1000 psi, 30 °C, 2 h	(2-hydroxyethyl)-3-methyloctylamine (43); (2-hydroxyethyl)-3-methyloctylhydrazine (18); other unidentified products
2	Raney Ni, 1,000 psi, 60 °C, 24 h	(2-hydroxyethyl)-3-methyloctylamine (94%)
3	Rh/alumina (5%), 20 psi, 25 °C, 2 h, 10% catalyst	6′,7′-dihydro analogue of 4 (55) [^{13}C NMR δ 129.11 (6′C), 124.23 (7′C)]; 6′,6′,7′,7′-tetrahydro analogue of 4 (45)
4	Rh/alumina (5%), 50 psi, 25 °C, 24 h, 20% catalyst	2′,3′,6′,6′,7′,7′-hexahydro analogue of 4 (56); 6′,6′,7′,7′-tetrahydro analogue of 4 (30); 6′,7′-dihydro analogue of 4 (14)

ester (47–71%). The ester was then quantitatively converted to the corresponding acetylenic alcohol by mild reduction with $LiAlH_4$–EtOH (1:1) in ether. Fractional distillation of the crude product afforded pure 3-methyl-2-octen-6-yn-1-ol. Its chloride was readily prepared from methanesulfonyl chloride as described by Bunton and co-workers.[6] Finally, this acetylenic chloride was utilized for the alkylation of 1 equiv of ethanoalmine[7] to give the desired monosubstituted acetylenic ethanolamine, which was then nitrosated to 4 in 75–95% yield. A sample of this nitrosamine product showed spectral characteristics identical with those of 4 obtained from 2 in a single step.

In spite of the earlier detection of the acetylenic nitrosamine 4 from the nitrosation of 1, the fact that the terpenyl nitrosamine 2 was quantitatively converted into 4 under the same reaction conditions should preclude the possibilities that 1 might participate in the reaction leading to 4. Since the one-step transformation of an alkenyl nitrosamine to an alkynyl analogue, 2 → 4, represents the first example of novel elimination reaction, we deemed it worthwhile to corroborate the presence of an ethylidyne triple bond in 4 by hydrogenation experiments. As shown in Table III, catalytic hydrogenation of 4 produced a diversity of products, depending largely on the conditions employed. When hydrogenation was carried out over Raney Ni, the major product isolated was (2-hydroxyethyl)-3-methyloctylamine. On the other hand, hydrogenation of 4 over 5% rhodium-on-alumina afforded mainly the partially saturated nitrosamines and the N—N=O group was not reduced. However, exhaustive catalytic hydrogenation of 4 over Raney Ni at 60 °C for 24 h produced (2-hydroxyethyl)-3-methyloctylamine in 94% yield. Nitrosation of this amine with sodium nitrite in AcOH–H_2O readily gave the 2′,3′,6′,7′-hexahdyro analogue of 4 (98%). This product was identical with the major product obtained from selective hydrogenation of 4 (entry 4, Table III).

In a recent paper,[2] we documented a detailed NMR spectral analysis of the precursor nitrosamine 2. Because there were few structural changes associated with the conversion of 2 to 4, it came as no surprise to find the striking similarity of their spectra. Although IR spectral information (C≡C, 2215 cm^{-1}) gave some indication of the presence of an acetylenic bond in 4, the large upfield shift of the 8′-methyl carbon resonance from 25.81 to 2.93 ppm as a result of the 2 → 4 transformation provided crucial clue to the elucidation of the alkyne structure 4. As a cis–trans mixture of the ethylidyne nitrosamine 4 was used in obtaining the spectra (Table IV), the chemical shift assignments were made on two sets of isomers: a cis–trans pair and an *E*–*Z* pair (in the *E* rotamer the nitroso oxygen is cis to the hydroxyethyl group). As anticipated, the α-, β-, and γ-carbons (C_1, C_2, $C_{1'}$, $C_{2'}$, and $C_{3'}$) of the *E* rotamer exhibit resonances sufficiently distinguishable from those of the *Z* rotamer. In the cis–trans pair, there are only two carbons, the 4′-methylene and the 3′-methyl, that show marked differences in chemical shift values. Upon O-methylation, both C_1 and C_2 carbons experience respective paramagnetic and diamagnetic shifts, and the chemical shifts of carbons at 6′, 7′, and 8′ positions remain predictably unchanged (Table IV). The isolation of a pure geometrical isomer (cis or trans) and a pure configurational isomer (*E* or *Z*) by preparative HPLC aided in further confirmation of unambiguous NMR spectral determination of 4. The elemental microanalysis was performed on a sample of its *O*-methyl ether because 4 was not distillable.

Additionally, spectral properties of other ethylidyne nitrosamines prepared directly from (isopropylideneterpenyl)alkanolamines were likewise ascertained. Structural elucidation of all these compounds was accomplished on the basis of much informative NMR and mass spectral data. Although proton NMR spectra were not instructive, the carbon-13 NMR spectrum of each of these compounds clearly displayed a signal in the high-field region (δ 2.75–3.22) attributable to the ethylidyne methyl carbon and two additional signals near δ 75.4–78.6 due to the couple of acetylenic carbons, along with other signals of much less diagnostic value. Of these absorptions, the ethylidyne methyl carbon resonance proved to be most revealing in consideration of only a limited number of known compounds having absorptions in the high-field region (δ 2–4). Moreover, no carbon resonance was observed within the δ 0–15 range in each of the spectra of all substrates investigated. Examination of mass spectral data for samples of ethylidyne nitrosamines including 4 revealed significant mass fragments consistent with the proposed ethylidyne nitrosamine structures. In every case studied, the mass spectrum of a pure ethylidyne compound in the respective monalkynyl (compounds under A′ and B′ columns, Table V) and dialkynyl nitrosamine series (compounds under B″ column, Table V) exhibited a molecular ion signal at 16 and 32 mass units less than that of the corresponding isopropylidene olefinic nitrosamine.

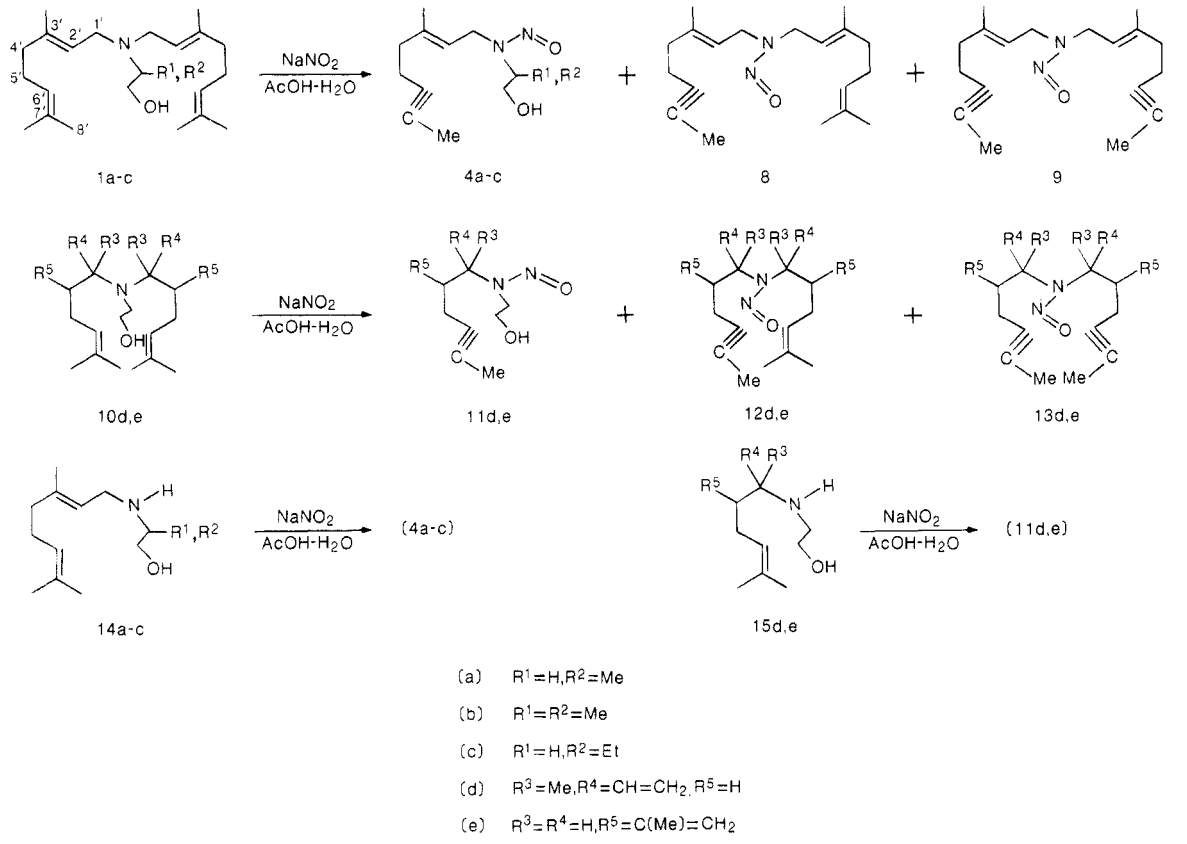
To gain further insight into the influence of substrate structures on the reaction, the scope of the proposed nitrosative elimination reaction was extended to a series of mono- and diterpenylalkanolamines including the saturated and partially saturated counterparts. The terpenylalkanolamines chosen for study are *N*,*N*-digeranylalkanolamines 1 and **1a–c**, *N*,*N*-dilinalylethanolamine (**10d**), *N*,*N*-dilavandulylethanolamine (**10e**), and the corresponding monoterpenylalkanolamines **14**, **14a–c**, and **15d,e** (Chart I). The perhydro analogues in the series failed to yield any products other than those formed by the usual nitrosative dealkylation pathway.[4] Analogously, saturation of all the isopropylidene double bonds of substrates (dihydro or tetrahydro analogues) led only to products devoid of the ethylidyne structures. On the other hand, without exception ethylidyne nitrosamines were produced in moderate to good yield from the alkanolamines where at least one requisite isopropylidene olefinic bond was present in each of the terpenyl groups (Table

(6) Bunton, C. A.; Hachey, D. L.; Leresche, J. P. *J. Org. Chem.* **1972**, *37*, 4036–4039.
(7) Abidi, S. L.; Idelson, A. L. *J. Labelled Compd. Radiopharm.* **1981**, *18*, 1215–1225.

Table IV. Carbon-13 NMR Spectral Data (δ) for Nitrosamine 4 and Its *O*-Methyl Ether

	nitrosamine 4				*O*-methyl ether			
	cis		trans		cis		trans	
C	*E*	*Z*	*E*	*Z*	*E*	*Z*	*E*	*Z*
1	58.84	60.20	58.84	60.20	68.76	70.71	68.76	70.71
2	45.89	53.42	45.89	53.42	42.20	50.72	42.20	50.72
1′	51.03	41.94	51.03	41.94	50.54	41.67	50.54	41.67
2′	119.36	117.47	118.22	116.60	119.68	117.90	118.55	116.92
3′	142.58	140.02	141.46	140.44	142.61	140.73	141.50	140.53
4′	31.05	31.05	38.47	38.47	31.05	31.05	38.47	38.47
5′	17.23	17.23	17.23	17.23	17.34	17.34	17.34	17.34
6′	78.07	78.07	78.07	78.07	78.12	78.12	78.12	78.12
7′	76.03	76.03	76.03	76.03	75.95	75.95	75.95	75.95
8′	2.93	2.93	2.93	2.93	2.97	2.97	2.97	2.97
3′-CH_3	22.92	22.92	15.87	15.87	22.90	22.90	15.93	15.93
O-CH_3					58.50	58.50	58.50	58.50

Chart I



(a) R^1=H,R^2=Me

(b) R^1=R^2=Me

(c) R^1=H,R^2=Et

(d) R^3=Me,R^4=CH=CH_2,R^5=H

(e) R^3=R^4=H,R^5=C(Me)=CH_2

V). The β,γ- and γ,δ-saturated analogues of the same series were similarly converted into the acetylenic compounds. These results clearly indicate that the isopropylidene group is all that is required for the elimination to occur.

Nitrosative elimination of analogous series of secondary terpenyl alkanolamines **14**, **14a–c**, and **15d,e** (Chart I) produced the corresponding ethylidyne nitrosamines **4**, **4a–c**, and **11d,e** in a straightforward manner (Table V). The yields were generally greater than those derived from tertiary diterpenylalkanolamines. In addition, we studied the elimination reaction with the diterpenylamines 1-DA, **10d**-DA, and **10e**-DA. As expected, the corresponding acetylenic products **8**, **12d**, and **12e** were obtained in moderate yield, whereas the yields of additional acetylenic products **9**, **13d**, and **13e** were notably lower (Table V). It is noteworthy that formation of latter compounds can be boosted by increasing the reaction time and temperature as shown in the example in the table (entry 19 vs. entry 22). The pure ethylidyne nitrosamines obtained from experiments 13–22 were also used to verify the structures of those furnished by experiments 1–6.

Recognizing the requirement of a high molar ratio of nitrite to amine for effecting direct conversion of alkenylalkanolamines to alkynyl nitrosamines, we employed the nitrosation reactants in an optimum ratio of 1/15 (amine/nitrite) for all the reactions listed in Table V. Under conditions specified in the table, reaction with **1** gave very small amounts of **8** and **9**, which were undoubtedly formed via intermediate **3**. The latter compound, as demonstrated earlier, was not detected in products obtained from N-nitrosation of **1** using conditions stated in Table I (note, amine/nitrite = 1/5). When *N,N*-digeranylalkanolamines **1a**, **1b**, and **1c**, in which the α-carbons at the C_2 positions were attached to various alkyl substituents shown in Chart I, were subjected to the nitrosative elimination conditions (Table V), acetylenic nitrosoalkanolamines **4a**, **4b**, and **4c** were formed with yields slightly but definitely higher than that of **4** produced from **1** (entry 1, Table V). However, neither **8** nor **9** was found in the reaction products (entries 2–4, Table V). The results

Table V. Nitrosative Elimination of Terpenylalkanolamines[a]

entry	compound[b]	reaction temp, °C	ethylidyne nitrosamine product (yield, %)[c] A′	B′	B″
1	1	60	4 (75)	8 (4)	9 (2)
2	1a	60	4a (79)	8 (0)	9 (0)
3	1b	60	4b (80)	8 (0)	9 (0)
4	1c	60	4c (78)	8 (0)	9 (0)
5	10d	60	11d (60)	12d (19)	13d (9)
6	10e	60	11e (41)	12e (39)	13e (18)
7	1-DH	60	4-DH (22)	8-DH (50)	9-DH (25)
8	1a-DH	60	4a-DH (65)	8-DH (13)	9-DH (10)
9	1b-DH	60	4b-DH (73)	8-DH (17)	9-DH (6)
10	1c-DH	60	4c-DH (70)	8-DH (15)	9-DH (9)
11	10d-DH	60	11d-DH (35)	12d-DH (41)	13d-DH (17)
12	10e-DH	60	11e-DH (38)	12e-DH (45)	13e-DH (11)
13	14	45	4 (92)		
14	14a	45	4a (95)		
15	14b	45	4b (90)		
16	14c	45	4c (87)		
17	15d	45	11d (78)		
18	15e	45	11e (73)		
19	1-DA	50		8 (66)	9 (24)
20	10d-DA	50		12d (71)	13d (20)
21	10e-DA	50		12e (63)	13e (27)
22	1-DA	70		8 (31)	9 (58)

[a] Reaction conditions: amine/nitrite = 1/15; amine concentration, 0.1 M; 60% aqueous AcOH; period, 4 h. [b] DH = β,γ- or γ,δ-dihydro analogue. DA = diterpenylamine. [c] A′, B′, and B″ designations are analogous to A and B in Table I. B″ is for diacetylenic nitrosamines.

imply that steric factors must play a significant role during the rate-determining step in the initial N-nitrosation to be accountable for the observed differences in product analysis (ethylidyne nitrosamines) between the C_2-substituted and unsubstituted *N,N*-digeranylalkanolamines (**1** vs. **1a**, **1b**, or **1c**). Interestingly, α-substitition at the $C_{1'}$ position, such as those in **10d**, tended to shift the reaction, only to a small extent, in favor of the formation of **12d** and **13d** by dealkylation at the C_2–N bond of **10d**, even though ethylidyne nitrosoethanolamine **11d** was produced predominantly from **10d** through initial removal of the allylic linalyl group. The product distribution data (Table V) for ethylidyne nitrosamines derived frm other diterpenylalkanolamines including the β,γ- and γ,δ-tetrahydro analogues (entries 6–12) reflect the conformational outcome of the nitrosative dealkylation process. In conformity with the results reported by Smith and co-workers,[4] the conformational effects associated with the nitrosative elimination of **10e** and the β,γ- and γ,δ-dihydrocompounds 1-DH (**1a–c**)-DH, and (**10d–e**)-DH appear to be of steric origin. Despite the absence of α-substituents, the terpenyl hydrocarbon chains in these compounds may exert steric influence on the N-nitrosation processes which in turn dictate the product ratios of ethylidyne nitrosamines for the elimination reactions. The findings are in consistence with those observed in our preliminary study described earlier.

In order to gather useful information on the relationship between nitrosation conditions and the specificity of nitrosative elimination reactions, extensive nitrosation studies were conducted under various conditions using diterpenylethanolamines **1**, **10d**, and **10e** as substrates. Of the numerous solvent systems studied, 60% aqueous DMF in acetate buffer (pH 4.5) was found to be the best medium for specific N-nitrosation. A 60% aqueous methane sulfonic acid–phosphate buffer (pH 4.5) system yielded comparable results but the yields of N-nitrosation products (containing no acetylenic groups) were somewhat inferior in this case. Thus, treatment of **1**, **10d**, and **10e** separately with sodium nitrite (amine/nitrite = 1/10) in either above medium for 5 h at 70 °C afforded respective alkenyl nitrosamines **2** (88–99%), **15d**–NA (70–78%, NA = nitrosamine), and **15e**-NA (40–45%). The latter two compounds were accompanied with the corresponding diterpenyl nitrosamines **10d**–NA (20–27%) and **10e**–NA (53–60%). None of the related alkynyl nitrosamines **4**, **8**, **9**, **11d,e**, **12d,e**, and **13d,e** were produced from these reactions. By virtue of the favorable conditions employed, the reactions described above apparently proceeded with a high degree of specificity for the N-nitrosation step that the direct conversions to the alkynyl nitrosamines were aborted in the elimination step. With modifications of solvent systems, however, it was possible to render the reaction specific for the formation of alkynyl nitrosamines as only isolable products. Thus, when **1**, **10d**, and **10e** were reacted individually with sodium nitrite in 60% aqueous acetic acid (pH 1.5–4.5, phosphate buffer) under otherwise conditions identical with those described above, direct conversions to the corresponding alkynyl nitrosamines were realized in all cases without isolation of intermediary alkenyl nitrosamines. The product distribution patterns for the alkynyl nitrosamines obtained in this fashion are similar to those illustrated in Table V (entries 1, 5, and 6), although the overall yields of the end products were relatively lower in each case. The conversion efficiency appeared to be adversely affected by the lower nitrite content of reaction mixtures (note a ratio of amine–nitrite = 1/10 was used in above reactions).

The generality of this elimination reaction has led us to explore its applicability to other types of isopropylidene olefins.[8,9] Although the reaction of certain olefins with various nitrosating agents has been reported previously,[10] the unprecedented alkene–alkyne transformation is noteworthy and may find potential synthetic utility in structural modifications of terpenes and related compounds. We are continuously challenged by the novelty and mechanistic obscurity of the elimination reaction. At this stage of work there is too little experimental evidence to designate a mechanism to the reaction in question. On the basis of a mechanistic rationale set forth most recently by Marchesini and collaborators[11] in their study on the formation of alkynes from diazotization of 5-aminoisoxazoles with sodium nitrite in AcOH–H_2O, we suspect that a radical process may be involved in the ultimate net loss of an overall "CH_4" unit (not necessarily methane) from a hypothetical adduct of an isopropylidene substrate (donor) with nitrosating species (acceptor). The intermediary species postulated by these authors for the diazotization reaction may have some bearing on the nature of reactive intermediates for the present reaction despite the apparent irrelevance of the two different reactions. Further, a charge-transfer complex may be invoked to better describe the reactive adduct in light of the transient appearance of green-blue color solution at the outset of the elimination reaction of the title amines. This coloration phenomenon was also observed in all reactions with sub-

(8) Presented in part at the 188th National Meeting of the American Chemical Society, Philadelphia, PA, August 26–31, 1984.
(9) Abidi, S. L. *Tetrahedron Lett.*, in press.
(10) Ranganathan, S.; Kar, S. K. *Tetrahedron* **1975**, *31*, 1391–1398.
(11) Beccalli, E. M.; Manfredi, A.; Marchesini, A. *J. Org. Chem.* **1975**, *50*, 2372–2375.

strates that contain no amine functionality.[9]

We plan to undertake ESR and kinetic studies along with low-temperature experiments in nonaqueous systems that provide concrete information on the mechanism of the reaction. The fate of isopropylidene CH_3 is being explored.

Experimental Section

Elemental analysis were performed on a Hewlett-Packard 185B CHN analyzer. High-resolution mass spectra were determined on an AEI MS-902 instrument and low-resolution mass spectra on a Varian MAT 112 magnetic-sector, double focusing mass spectrometer equipped with a dual electron impact/chemical ionization source. IR spectra were obtained on neat samples with a Perkin-Elmer 337 spectrophotometer. FT ^{13}C NMR spectra were determined on a JEOL FX-90(22.5) spectrometer with Me_4Si as an internal standard in $CDCl_3$. Analytical GC employed a Varian 3711 chromatograph interfaced with a Varian CDS 111 data system. A glass column (200 cm × 2 mm i.d.) packed with 5% Carbowax 20M on 100/120 Supelcoport was used in all GC analyses. Nitrosamine analyses were also performed on a Thermo Electron 502 thermal energy analyzer for confirmation purposes.

Analytical and preparative HPLC separations were carried out on a Varian LC 5020 instrument. The full details of HPLC mobile and stationary phase systems including operational conditions have been described.[12] Flash chromatography was performed with silica gel 60 (EM reagents).[13]

All reagents and solvents were checked for purity prior to use. Terpene precursors were supplied by Bedoukian Research Institute (Danbury, CT). Terpenyl alkanolamines were products of SCM Corporation and were freshly redistilled before use. The compounds were also prepared by a published method.[7] Satisfactory ^{13}C NMR spectral data were obtained for all reactant alkanolamines and intermediate nitrosamines in their subsequent conversion to alkyne products.

General Procedure for the Preparation of Ethylidyne *N*-Nitroso Compounds. To a stirred solution of a terpenyl-alkanolamine (2 mmol) in 60% aqueous acetic acid (20 mL), sodium nitrite (30 mmol) was added portionwise over a period of about 0.5 h. The mixture was stirred at 60 °C for 3–4 h until completion of reaction as indicated by the absence of both reactant and intermediate peaks on GC chromatograms of aliquot samples withdrawn. The mixture was cooled to room temperature. Water (100 mL) and crushed ice were then added. Extraction with CH_2Cl_2 (3 × 25 mL) followed by washing the resultant organic layer successively with 5% $NaHCO_3$ and water, drying, and concentrating afforded the crude product. This material was analyzed for various alkyne nitrosamines present (Table V) by GC and HPLC. To obtain pure alkyne components, the crude product was purified by flash chromatography to give fractions enriched with an alkyne component, which was further purified by distillation of its *O*-methyl ether under high vacuum. In flash chromatography, the crude material was chromatographed onto a 100-mL (bed volume) column and eluted sequentially with the following solvents (100 mL each): hexane, hexane–ether (4:1, 2:1, 1:1, 1:2, and 1:4), ether, ether–CH_2Cl_2 (4:1, 2:1, 1:1, 1:2, and 1:4), and CH_2Cl_2. In some cases where separations of heterogeneous products were difficult, preparative HPLC techniques[12] were utilized to resolve the crude mixtures into distinct components and eventually isolate individual products. Cis–trans isomers were separated either by silica gel column chromatography or by preparative HPLC, whereas mixtures of *E*–*Z* isomers were resolvable only by preparative HPLC. *O*-Methyl ethers of alkanol nitrosamine products were prepared by a standard CH_3I–Ag_2O–DMF method.[14] Yields of ethylidyne nitrosamine products are compiled in Table V.

2-[Nitroso(3′-methyl-2′-octen-6′-ynyl)amino]ethanol (4): ^{13}C NMR spectral characteristics of this compound are detailed in Table III; IR 3400, 2215, 1662, 1445, 1300, 1050 cm^{-1}; mass spectrum, *m/e* 210 (M^+), 193, 180, 121; HRMS, *m/e* 210.2735 (calcd for $C_{11}H_{18}N_2O_2$ *m/e* 210.2754). It decomposed upon distillation.

O-methyl ether of **4**: 89% yield; bp 118–119 °C (0.1 mm); ^{13}C NMR (see Table III); IR 2820, 2215, 1660, 1447, 1330, 1115, 1060, 1010 cm^{-1}; mass spectrum, *m/e* 224 (M^+), 207, 194, 121. Anal. Calcd for $C_{12}H_{20}N_2O_2$: C, 64.29; H, 8.93; N, 12.50. Found: C, 64.18; H, 9.02; N, 12.59. This material was identical with that obtained from nitrosative elimination of the *O*-methyl ether of **2** (Scheme I).

2-[Nitroso(3′-methyl-2′-octen-6′-ynyl)amino]-2-methylethanol (4a): ^{13}C NMR δ 23.10 (2-CH_3), 17.89 (5′C), 78.11 (6′C), 76.09 (7′C), 2.95 (8′C); IR 3400, 2210, 1664, 1443, 1320, 1030 cm^{-1}; mass spectrum, *m/e* 224 (M^+), 207, 194, 121; HRMS, *m/e* 224.3018 (calcd for $C_{12}H_{20}N_2O_2$ *m/e* 224.3022).

O-Methyl ether of **4a**: 91% yield; bp 103–104 °C (0.05 mm); ^{13}C NMR δ 21.45 (2-CH_3), 17.91 (5′C), 78.21 (6′C), 76.00 (7′C), 2.98 (8′C), 58.89 (OCH_3); IR 2815, 2210, 1663, 1445, 1325, 1118, 1055, 1010 cm^{-1}; mass spectrum, *m/e* 238 (M^+), 221, 208, 121. Anal. Calcd for $C_{13}H_{22}N_2O_2$: C, 65.52; H, 9.30; N, 11.75. Found: C, 65.39; H, 9.41; N, 11.81.

2-[Nitroso(3′-methyl-2′-octen-6′-ynyl)amino]-2,2-dimethylethanol (4b): ^{13}C NMR δ 26.05 (2-CH_3), 17.97 (5′C), 78.25 (6′C), 76.14 (7′C), 2.99 (8′C); IR 3390, 2212, 1662, 1440, 1310, 1050 cm^{-1}; mass spectrum, *m/e* 238 (M^+), 221, 208, 121; HRMS, *m/e* 238.3280 (calcd for $C_{13}H_{22}N_2O_2$ *m/e* 238.3290).

O-Methyl ether of **4b**: 78% yield; bp 121–123 °C (0.15 mm); ^{13}C NMR δ 26.42 (2-CH_3), 17.99 (5′C), 78.30 (6′C), 76.11 (7′C), 3.01 (8′C), 59.25 (OCH_3); IR 2817, 2212, 1664, 1445, 1320, 1116, 1050, 1015 cm^{-1}; mass spectrum, *m/e* 252 (M^+), 235, 220, 121. Anal. Calcd for $C_{14}H_{24}N_2O_2$: C, 66.63; H, 9.59; N, 11.10. Found: C, 66.49; H, 9.62; N, 11.26.

2-[Nitroso(3′-methyl-2′-octen-6′-ynyl)amino]-2-ethylethanol (4c): ^{13}C NMR δ 27.13 (2-CH_2CH_3), 13.37 (2-CH_2CH_3), 18.20 (5′C), 78.17 (6′C), 76.10 (7′C), 2.97 (8′C); IR 3410, 2211, 1663, 1442, 1320, 1050 cm^{-1}; Mass spectrum, *m/e* 238 (M^+), 221, 208, 121; HRMS, *m/e* 238.3275 (calcd for $C_{13}H_{22}N_2O_2$ *m/e* 238.3290).

O-Methyl ether of **4c**: 84% yield; bp 110–111 °C (0.05 mm); ^{13}C NMR δ 27.38 (2-CH_2CH_3), 13.67 (2-CH_2CH_3), 18.25 (5′C), 78.03 (6′C), 76.05 (7′C), 3.00 (8′C), 59.01 (OCH_3); IR 2818, 2211, 1664, 1444, 1318, 1115, 1060, 1015 cm^{-1}; mass spectrum, *m/e* 252 (M^+), 235, 220, 121. Anal. Calcd for $C_{14}H_{24}N_2O_2$: C, 66.63; H, 9.59; N, 11.10. Found: C, 66.51; H, 9.64; N, 11.23.

2-[Nitroso(1′-methyl-1′-vinylhex-4′-ynyl)amino]ethanol (11d): ^{13}C NMR δ 13.62 (3′C), 78.24 (4′C), 75.83 (5′C), 3.09 (6′C); IR 3400, 2215, 1640, 1444, 1300, 1040 cm^{-1}; mass spectrum, *m/e* 210 (M^+), 195, 180, 121, 106; HRMS, *m/e* 210.2738 (calcd for $C_{11}H_{18}N_2O_2$ *m/e* 210.2754).

O-Methyl ether of **11d**: 73% yield; bp 102–104 °C (0.15 mm); ^{13}C NMR δ 13.65 (3′C), 78.31 (4′C), 75.75 (5′C), 3.11 (6′C), 52.13 (OCH_3); IR 2820, 2215, 1640, 1445, 1330, 1116, 1040, 1010 cm^{-1}; mass spectrum, *m/e* 224 (M^+), 209, 194 121, 106. Anal. Calcd for $C_{12}H_{20}N_2O_2$: C, 64.29; H, 8.93; N, 12.50. Found: C, 64.34; H, 9.05; N, 12.35.

2-[Nitroso-(2′-isopropenylhex-4′-ynyl)amino]ethanol (11e): ^{13}C NMR δ 20.50 (3′C), 77.25 (4′C), 75.41 (5′C), 3.20 (6′C); IR 3410, 2213, 1647, 1445, 1437, 1335, 1050 cm^{-1}; mass spectrum, *m/e* 210 (M^+), 193, 180, 179, 103; HRMS, *m/e* 210.2729 (calcd for $C_{11}H_{18}N_2O_2$ *m/e* 210.2754).

O-Methyl ether of **11e**: 77% yield; bp 109–110 °C (0.1 mm); ^{13}C NMR δ 20.54 (3′C), 77.38 (4′C), 75.40 (5′C), 3.21 (6′C); 58.33 (OCH_3); IR 2817, 2213, 1646, 1444, 1440, 1320, 1115, 1050, 1010 cm^{-1}; mass spectrum, *m/e* 224 (M^+), 207, 194, 179, 103. Anal. Calcd for $C_{12}H_{20}N_2O_2$: C, 64.29; H, 8.93; N, 12.50. Found: C, 64.41; H, 9.05; N, 12.55.

2-[Nitroso(3′-methyloct-6′-ynyl)amino]ethanol (4-DH): ^{13}C NMR δ 16.45 (5′C), 78.59 (6′C), 75.44 (7′C), 3.21 (8′C); IR 3400, 2215, 1445, 1300, 1050 cm^{-1}; mass spectrum, 212 (M^+), 195, 182, 181, 103; HRMS, *m/e* 212.2905 (calcd for $C_{11}H_{20}N_2O_2$ *m/e* 212.2912). Its *O*-methyl ether: yield, 95%; bp 115–116 °C (0.1 mm). Anal. Calcd for $C_{12}H_{22}N_2O_2$: C, 63.69; H, 9.80; N, 12.38. Found: C, 63.40; H, 9.91; N, 12.45.

2-[Nitroso(3′-methyloct-6′-ynyl)amino]-2-methylethanol (4a-DH): ^{13}C NMR δ 22.73 (2-CH_3), 16.98 (5′C), 78.60 (6′C), 75.51 (7′C), 3.18 (8′C); IR 3400, 2210, 1444, 1325, 1030 cm^{-1}; mass spectrum, *m/e* 226 (M^+), 209, 196, 195, 117; HRMS, *m/e* 226.3167

(12) Abidi, S. L. *J. Chromatogr.* **1984**, *288*, 277–292.
(13) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.
(14) Walker, H. G.; McCready, R. M. *J. Org. Chem.* **1962**, *27*, 2100–2102.

(calcd for $C_{12}H_{22}N_2O_2$ *m/e* 226.3180). Its *O*-methyl ether: yield, 88%; bp 99–100 °C (0.05 mm). Anal. Calcd for $C_{13}H_{24}N_2O_2$: C, 64.97; H, 10.06; N, 11.66. Found: C, 65.03; H, 9.98; N, 11.81.

2-[Nitroso(3′-methyloct-6′-ynyl)amino]-2,2-dimethylethanol (4b-DH): ^{13}C NMR δ 25.11 (2-CH_3), 17.14 (5′C), 78.60 (6′C), 76.03 (7′C), 3.22 (8′C); IR 3400, 2212, 1440, 1320, 1045 cm^{-1}; mass spectrum, *m/e* 240 (M^+), 223, 210, 225, 209, 131; HRMS, *m/e* 240.3421 (calcd for $C_{13}H_{24}N_2O_2$ *m/e* 240.3448). Its *O*-methyl ether: yield, 80%; bp 117–118 °C (0.15 mm). Anal. Calcd for $C_{14}H_{26}N_2O_2$: C, 66.11; H, 10.30; N, 11.01. Found: C, 65.97; H, 10.38; N, 11.19.

2-[Nitroso(3′-methyloct-6′-ynyl)amino]-2-ethylethanol (4c-DH): ^{13}C NMR δ 26.00 (2-CH_2CH_3), 13.05 (2-CH_2CH_3), 17.59 (5′C), 78.45 (6′C), 75.98 (7′C), 3.15 (8′C); IR 3405, 2212, 1443, 1320, 1055 cm^{-1}; mass spectrum, *m/e* 240 (M^+), 223, 210, 209, 131, 211; HRMS, *m/e* 240.3419 (calcd for $C_{13}H_{24}N_2O_2$ *m/e* 240.3448). Its *O*-methyl ether: yield, 75%; bp 103–105 °C (0.05 mm). Anal. Calcd for $C_{14}H_{26}N_2O_2$: C, 66.11; H, 10.30; N, 11.01. Found: C, 66.15; H, 10.43; N, 11.13.

2-[Nitroso(1′-methyl-1′-ethylhex-4′-ynyl)amino]ethanol (11d-DH): ^{13}C NMR δ 13.44 (3′C), 77.15 (4′C), 76.66 (5′C), 3.13 (6′C); IR 3400, 2215, 1444, 1310, 1045 cm^{-1}; mass spectrum, *m/e* 212 (M^+), 195, 182, 181, 197, 183, 145; HRMS, *m/e* 212.2900 (calcd for $C_{11}H_{20}N_2O_2$ *m/e* 212.2912). Its *O*-methyl ether: yield, 80%; bp 98–99 °C (0.1 mm). Anal. Calcd for $C_{12}H_{22}N_2O_2$: C, 63.69; H, 9.80; N, 12.38. Found: C, 63.51; H, 9.95; N, 12.35.

2-[Nitroso(2′-isopropylhex-4′-ynyl)amino]ethanol (11e-DH): ^{13}C NMR δ 19.32 (3′C), 76.54 (4′C), 75.85 (5′C), 3.22 (6′C); IR 3410, 2215, 1444, 1340, 1050 cm^{-1}; mass spectrum, *m/e* 212 (M^+), 195, 182, 181, 103; HRMS, *m/e* 212.2905 (calcd for $C_{11}H_{20}N_2O_2$ *m/e* 212.2912). Its *O*-methyl ether: yield, 79%; bp 105–107 °C (0.1 mm). Anal. Calcd for $C_{12}H_{22}N_2O_2$: C, 63.69; H, 9.80; N, 12.38. Found: C, 63.71; H, 9.75; N, 12.42.

Nitrosogeranyl(3-methyl-2-octen-6-ynyl)amine (8) and 8-DH. 8: ^{13}C NMR δ 16.77 (5C), 77.75 (6C), 75.86 (7C), 2.86 (8C); IR 2215, 1440, 1330, 1050, 1662 cm^{-1}; mass spectrum, *m/e* 302 (M^+), 285, 272, 271, 137, 121; HRMS, *m/e* 302.4561 (calcd for $C_{19}H_{30}N_2O$ *m/e* 302.4588).

8-DH: ^{13}C NMR δ 16.15 (5C), 77.89 (6C), 75.40 (7C), 3.05 (8C); IR 2213, 1664, 1440, 1325, 1045 cm^{-1}; mass spectrum, *m/e* 306 (M^+), 289, 276, 275, 197, 181; HRMS, *m/e* 306.4897 (calcd for $C_{19}H_{34}N_2O$ *m/e* 306.4904).

Nitrosolinalyl(1-methyl-1-vinylhex-4-ynyl)amine (12d) and 12d-DH. 12d: ^{13}C NMR δ 13.23 (3C), 78.03 (4C), 75.66 (5C), 3.00 (6C); IR 2215, 1665, 1640, 1445, 1310, 1045 cm^{-1}; mass spectrum, *m/e* 302 (M^+), 285, 272, 271, 137, 121, 122, 106; HRMS, *m/e* 302.4544 (calcd for $C_{19}H_{30}N_2O$ *m/e* 302.4588).

12d-DH: ^{13}C NMR δ 12.87 (3C), 78.17 (4C), 75.42 (5C), 3.19 (6C); IR 2212, 1665, 1444, 1315, 1050 cm^{-1}; mass spectrum, *m/e* 306 (M^+), 289, 276, 275, 291, 277, 229, 225; HRMS, *m/e* 306.4889 (calcd for $C_{19}H_{34}N_2O$ *m/e* 306.4904).

Nitrosolavandulyl(2-isopropenylhex-4-ynyl)amine (12e) and 12e-DH. 12e: ^{13}C NMR δ 19.88 (3C), 77.02 (4C), 75.40 (5C), 3.12 (6C); IR 2215, 1646, 1445, 1435, 1664, 1335, 1050 cm^{-1}; mass spectrum, *m/e* 285, 272, 271, 195, 179, 302 (M^+); HRMS, *m/e* 302.4559 (calcd for $C_{19}H_{30}N_2O$ *m/e* 302.4588).

12e-DH: ^{13}C NMR δ 19.65 (3C), 77.26 (4C), 75.40 (5C), 3.18 (6C); IR 2213, 1664, 1445, 1325, 1045 cm^{-1}; mass spectrum, *m/e* 306 (M^+), 289, 276, 275, 197, 181; HRMS, *m/e* 306.4879 (calcd for $C_{19}H_{34}N_2O$ *m/e* 306.4904).

Nitrosobis(3-methyl-2-octen-6-ynyl)amine (9) and 9-DH. 9: ^{13}C NMR δ 16.54 (5C), 78.03 (6C), 75.75 (7C), 3.08 (8C); IR 2214, 1664, 1445, 1335, 1045 cm^{-1}; mass spectrum, *m/e* 286 (M^+), 269, 256, 255, 121; HRMS, *m/e* 286.4137 (calcd for $C_{18}H_{26}N_2O$ *m/e* 286. 4162.

9-DH: ^{13}C NMR δ 16.00 (5C), 78.13 (6C), 75.43 (7C), 3.17 (8C); IR 2215, 1445, 1330, 1050 cm^{-1}; mass spectrum, *m/e* 290 (M^+), 273, 260, 259, 181; HRMS, *m/e* 290.4459 (calcd for $C_{18}H_{30}N_2O$ *m/e* 290.4478).

Nitrosobis(1-methyl-1-vinylhex-4-ynyl)amine (13d) and 13d-DH. 13d: ^{13}C NMR δ 13.05 (3C), 78.27 (4C), 75.51 (5C), 3.10 (6C); IR 2215, 1643, 1446, 1315, 1040 cm^{-1}; mass spectrum, *m/e* 286 (M^+), 269, 256, 255, 121, 106; HRMS, *m/e* 286.4130 (calcd for $C_{18}H_{26}N_2O$ *m/e* 286.4162.

13d-DH: ^{13}C NMR NMR δ 12.95 (3C), 78.37 (4C), 75.42 (5C), 3.16 (6C); IR 2215, 1445, 1310, 1050 cm^{-1}; mass spectrum, *m/e* 290 (M^+), 275, 273, 271, 260, 259, 223; HRMS, *m/e* 290.4455 (calcd for $C_{18}H_{30}N_2O$ *m/e* 290.4478).

Nitrosobis(2-isopropenylhex-4-ynyl)amine (13e) and 13e-DH. 13e: ^{13}C NMR δ 19.60 (3C), 77.31 (4C), 75.44 (5C), 3.17 (6C); IR 2213, 1645, 1446, 1430, 1330, 1045 cm^{-1}; mass spectrum, *m/e* 286 (M^+), 269, 256, 255, 179; HRMS, *m/e* 286.4150 (calcd for $C_{18}H_{26}N_2O$ *m/e* 286.4162.

13e-DH: ^{13}C NMR δ 19.46 (3C), 77.55 (4C), 75.43 (5C), 3.21 (6C); IR 2215, 1446, 1335, 1050 cm^{-1}; mass spectrum, *m/e* 290 (M^+), 283, 260, 259, 181; HRMS, *m/e* 290.4429 (calcd for $C_{18}H_{30}N_2O$ *m/e* 290.4478).

Independent Synthesis of 4 (Scheme III). 5-Hexyn-2-one[5] (4 g, 41 mmol) was treated with ethylene glycol (2.5 g, 41 mmol) and *p*-toluenesulfonic acid (0.2 g) in benzene (50 mL) for 12 h under reflux to give the ethylene ketal in 98% yield, bp 57–61 °C (1 mm). To a solution of the latter ketal (1.4 g, 10 mmol) in THF (100 mL) was added a solution of *n*-BuLi in hexane (5 mL of 2.5 M solution) at −78 °C with constant stirring. This was followed by the addition of methyl iodide (1.96 g, 12.5 mmol). The mixture was stirred for 3 h at −78 °C. After stirring for additional 12 h at room temperature and subsequent removal of solvent, the remaining residue was made neutral with dilute HCl (6 N) and extracted with CH_2Cl_2 (3 × 50 mL). The crude product (91% yield) was hydrolyzed with H_2SO_4 (2 N, 30 mL) in acetone (350 mL) at room temperature overnight to give 5-heptyn-2-one in 80% yield [^{13}C NMR δ 3.11 ($CH_3C{\equiv}C$); IR 1717 (C=O) cm^{-1}]. The ketone was then subjected to Reformatsky condensation[15,16] with ethyl bromoacetate and zinc in benzene at 80 °C for 2–3 h to afford the α,β-unsaturated ester in 47–71% yield [^{13}C NMR δ 3.02 ($CH_3C{\equiv}C$); IR 2215 (C≡C), 1729 (C≡O), 1660 (C=C) cm^{-1}]. Mild reduction of this ester with $LiAlH_4$–EtOH (1:1) was achieved in quantitative yield by using the procedure of Lythgoe et al.[17] Fractional distillation of the crude α,β-unsaturated alcohol yielded pure 3-methyl-2-octen-6-yn-1-ol: yield, 95%; bp 107–109 °C (5 mm). Anal. Calcd for $C_9H_{14}O$: C, 78.26; H, 10.14. Found: C, 79.13; H, 10.12. [^{13}C NMR δ 58.56 (1C), 124.3 (2C), 136.9 (3C), 38.41 (4C), 17.23 (5C), 78.29 (6C), 75.42 (7C), 2.76 (8C), 15.55 (3-CH_3); IR 3450, 2215, 1673, 1115 cm^{-1}.]

The chloride of the above alcohol was prepared by the method of Bunton et al.:[6] yield, 75%; bp 66–67 °C (0.05 mm). For alkylation of ethanolamine,[7] a solution of the freshly distilled chloride (1.1 g, 8 mmol) in 50 mL of THF was added dropwise to a stirred solution of ethanolamine hydrochloride (878 mg, 9 mmol) in triethylamine (1.82 g, 18 mmol) at 50 °C over a period of 0.5 h. The mixture was stirred continuously at 65 °C for 12 h, cooled, and evaporated to leave a residue, which was made alkaline with dilute NaOH (6 N). The dried ether extract (3 × 25 mL) was concentrated and distilled to afford pure 2-[(3′-methyl-2′-octen-6′-ynyl)amino]ethanol: yield, 83%; bp 106–107 °C (0.25 mm). Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.73. Found: C, 72.75; H, 10.64; N, 7.81. [^{13}C NMR δ 17.27 (5′C), 78.11 (6′C), 76.00 (7′C), 3.00 (8′C); IR 3400, 3320, 1670, 2215 cm^{-1}.] The ethylidyne aminoethanol was then treated with $NaNO_2$ (amine/nitrite = 1/3) in 60% aqueous acetic acid (amine concentration, 0.1 M) and stirred at room temperature for 12 h to give **4** (88%); its *O*-methyl ether had bp 110–111 °C (0.05 mm).

Catalytic Hydrogenation of 4. (i) A solution of **4** (1.4 g, 6.5 mmol) in ethanol (20 mL) was hydrogenated with 5% rhodium-on-alumina (10–20% by weight) under conditions specified in Table IV. The mixture was filtered through Celite and concentrated to give an oil (91%). The crude product was separated by HPLC.[12] For product composition see Table IV. 6′,7′-Dihydro-**4**: HRMS, *m/e* 212.2895 (calcd for $C_{11}H_{20}N_2O_2$ *m/e* 212.2912). 6′,6′,7′,7′-Tetrahydro-**4**: HRMS, *m/e* 214.3056 (calcd for $C_{11}H_{22}N_2O_2$ *m/e* 214.3070). 2′,3′,6′,6′,7′,7′-Hexahydro-**4**: HRMS, *m/e* 216.3202 (calcd for $C_{11}H_{24}N_2O_2$ *m/e* 216.3228).

(ii) A mixture of **4** (2.1 g, 10 mmol), dioxane (100 mL), and Raney Ni activated catalyst[18] (0.5 g) was hydrogenated in a pressure reaction apparatus (Parr Model 4561) under conditions

(15) Fieser, L. F.; Johnson, W. S. *J. Am. Chem. Soc.* **1940**, *62*, 575–577.
(16) Vaughan, W. H.; Bernstein, S. C.; Larber, M. E. *J. Org. Chem.* **1965**, *30*, 1790–1795.
(17) Davidson, R. S.; Gunther, W. H. H.; Waddington-Feather, S. M.; Lythgoe, B. *J. Chem. Soc.* **1964**, 4907–4914.
(18) An Aldrich Product.

described in Table IV. The catalyst was removed by filtration and was washed with 5 mL of dioxane. The filtrates were combined and evaporated under reduced pressure to leave a pale yellow liquid. The crude product was distilled to afford pure *N*-(2-hydroxyethyl)-3-methyloctylamine: bp 99–101 °C (0.1 mm). Anal. Calcd for $C_{11}H_{25}NO$: C, 72.36; H, 12.56; N, 7.04. Found: C, 72.23; H, 12.60; N, 7.19. (Unsaturated carbon resonances were not present in its ^{13}C NMR spectrum; IR 3400, 3325, 1565 cm^{-1}.) Nitrosation of the secondary amine yielded 2′,3′,6′,6′,7′,7′-hexahydro-4 (Table IV).

D-Idose: A One- and Two-Dimensional NMR Investigation of Solution Composition and Conformation

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The solution composition of D-idose in D_2O has been examined by ^{13}C NMR spectroscopy using [^{13}C]-enriched compounds. In addition to two furanoses and two pyranoses, aldehyde and hydrate forms have been detected and quantified. Using ^{13}C saturation-transfer spectroscopy, unidirectional rate constants for ring-opening and -closing of idofuranoses and idopyranoses have been measured and compared. The 600-MHz ^1H NMR spectrum of D-idose has been interpreted, and the ^{13}C spectrum was assigned with the use of 2D ^{13}C–^1H shift correlation spectroscopy. ^{13}C chemical shift assignments were confirmed with [^{13}C]-enriched compounds. ^1H–^1H spin–spin couplings suggest the presence of skew forms of α-idopyranose.

Aqueous solutions of aldoses and ketoses are complex; that is, they contain interconverting pyranose, furanose, hydrate (*gem*-diol, anhydrol), carbonyl, and/or oligomeric forms.[1,2] This complexity has considerable significance in both the chemical and biochemical conversions of the monosaccharides. The spontaneous interconversion of cyclic forms, known as anomerization, has been the subject of numerous studies,[3-5] and recent NMR[6-8] and calculational[9,10] approaches have permitted a more detailed examination of this important reaction. In addition to anomerization, each form may assume one or more stable conformations depending on its structure, adding to the complexity of the system.

The rare aldose, D-idose, while not having major biological significance, is an interesting subject of study for several reasons. Recent ^{13}C NMR studies of D-[1-^{13}C]-idose[11] have revealed the presence of furanose, pyranose, hydrate, and carbonyl forms in aqueous solution. In addition, idopyranose rings are conformationally mobile, especially the α-pyranose.[12a] New conformational free energy values reported by Eliel and co-workers[12b] have been used recently by Augé and David[12c] to reexamine the preferred conformations of ido- and altropyranoses and their derivatives in solution. This study, as well as others, suggests that α-D-idopyranose may exist in part in a skew conformation (S_5^3), although the existing ^1H–^1H spin-coupling data ($^3J_{H1,H2}$, $^3J_{H2,H3}$) are inconclusive.

A prerequisite to an NMR investigation of idohexose anomerization is the correct assignment of ^1H and ^{13}C NMR spectra, especially signals of the anomeric protons and carbons. These assignments have not been reported. The idose system is a challenging one with which to evaluate various contemporary NMR methods to interpret complex carbohydrate spectra. In this report, one- and two-dimensional NMR are used in conjunction with [^{13}C]-enrichment to achieve the complete assignment of ^1H and ^{13}C NMR spectra; the conformational implications of these observed NMR parameters are discussed, with emphasis on pyranosyl ring dynamics. Rate constants of ring-opening and -closing obtained by saturation-transfer NMR spectroscopy are also reported and discussed for the four cyclic forms of D-idose.

Experimental Section

Materials. D-Xylose, D-glucose, and 5% palladium on barium sulfate ($Pd/BaSO_4$) were purchased from Sigma Chemical Company. Potassium [^{13}C]cyanide ($K^{13}CN$, 99 atom % ^{13}C) and deuterium oxide (^2H_2O, 99.8 atom % ^2H) were purchased from Cambridge Isotope Laboratories. Standard iodine solutions (0.10 N) were purchased from Fisher Scientific Company. Anhydrous sodium thiosulfate was purchased from Aldrich Chemical Company.

(1) Angyal, S. J. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 157.
(2) Angyal, S. J. *Adv. Carbohydr. Chem. Biochem.* **1984**, *42*, 15.
(3) Pigman, W.; Isbell, H. S. *Adv. Carbohydr. Chem. Biochem.* **1968**, *23*, 11.
(4) Isbell, H. S.; Pigman, W. *Adv. Carbohydr. Chem. Biochem.* **1969**, *24*, 13.
(5) Capon, B.; Walker, R. B. *J. Chem. Soc., Perkins Trans. 2* **1974**, 1600.
(6) Serianni, A. S.; Pierce, J.; Huang, S.-H.; Barker, R. *J. Am. Chem. Soc.* **1982**, *104*, 4037.
(7) Pierce, J.; Serianni, A. S.; Barker, R. J. *Am. Chem. Soc.* **1985**, *107*, 2448.
(8) Goux, W. *J. Am. Chem. Soc.* **1985**, *107*, 4320.
(9) Anderson, L.; Garver, J. C. "Computer Modeling of the Kinetics of Tautomerization (Mutarotation) of Aldoses: Implications For the Mechanism of the Process", In *Carbohydrates in Solution*, Advances in Chemistry Series, 117, Gould, R., Ed.; American Chemical Society: Washington, D.C.; 1973; p 20.
(10) Wertz, P. W.; Garver, J. C.; Anderson, L. *J. Am. Chem. Soc.* **1981**, *103*, 3916.
(11) Results of this study were presented at the 189th National Meeting of the American Chemical Society, Division of Carbohydrate Chemistry, April 28–May 3, 1985, Abst. No. 7.
(12) (a) Angyal, S. J.; Pickles, V. A. *Aust. J. Chem.* **1972**, *25*, 1695. (b) Eliel, E. L.; Hargrave, K. D.; Pietrusiewicz, K. M.; Manoharan, M. *J. Am. Chem. Soc.* **1982**, *104*, 3635. (c) Augé, J.; David, S. *Tetrahedron* **1984**, *40*, 2101.

0022-3263/86/1951-2694$01.50/0