Intramolecular Cycloaddition Reactions of Vinyl Azides Bearing Alkenyl and Alkynyl Groups

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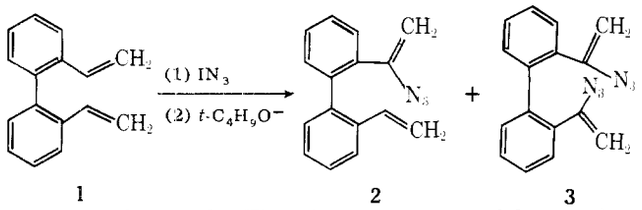
Vinyl azides containing dipolarophile groups in close proximity to the azide moiety were synthesized from a series of *o*-divinyl-substituted biphenyls and propargyl-substituted phenyl ethers. The biphenyl-substituted vinyl azides were found to undergo intramolecular 1,3-dipolar cycloaddition to give an insoluble triazoline. Further thermolysis of the triazoline results in the formation of a 1-vinylaziridine. Intramolecular dipolar cycloaddition of the vinyl azido group to a neighboring triple bond was also observed to occur in the propargyl *o*-(1-azidovinyl)phenyl ether system.

During the past decade unsaturated azides have acquired considerable importance as intermediates in organic synthesis.[1-3] Since the discovery of several methods for the synthesis of vinyl azides,[4] their chemistry has been extensively studied and a large amount of information is now available.[1-3] The reactive azide function is susceptible to thermolysis,[5-9] photolysis,[10-16] cycloaddition,[17-19] and attack by nucleophiles[20-23] and electrophiles.[24-27] Pyrolysis or photolysis of vinyl azides serves as a general method for the synthesis of 2*H*-azirines.[5-16] Vinyl azides are also known to participate in thermally allowed [π_4s + π_2s] cycloadditions as dipolarophiles[28,29] or 1,3-dipoles.[17-19] Although several examples of bimolecular 1,3-dipolar cycloadditions of vinyl azides have appeared in the literature,[17-19,30,31] intramolecular cycloadditions of this 1,3-dipole have not been described.[32] Intramolecular 1,3-dipolar cycloaddition is an extremely versatile and important reaction. The range of synthetic possibilities which it opens for the construction of fused heterocycles is extremely large.[33] With azides, intramolecular cycloadditions have been occasionally reported,[34-37] but systematic data are available only for a series of azidoalkenes.[36] As part of a program directed toward a study of the intramolecular dipolar cycloaddition reactions of unsaturated 2*H*-azirines,[38] we had occasion to prepare several vinyl azides containing a π bond in close proximity to the azide functionality. In this paper, we describe the smooth intramolecular 1,3-dipolar cycloaddition reaction of these unsaturated vinyl azides.

Results and Discussion

A general synthetic method for vinyl azides, discovered by Hassner and co-workers,[4] involves the addition of halogen azides to olefins followed by treatment of the resulting β-haloalkyl azides with potassium *tert*-butoxide. Application of this procedure to 2,2′-divinylbiphenyl (**1**) gave a mixture



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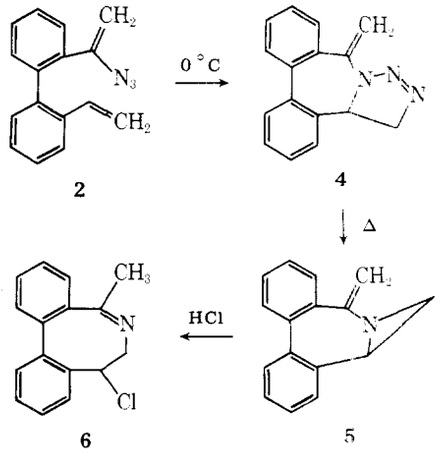
of vinyl azides **2** and **3**. The minor component of the reaction mixture was established as 2-(1-azidovinyl)-2′-vinylbiphenyl (**2**); the major component, isolated as a crystalline solid, mp 72–73 °C, was 2,2′-(1-azidovinyl)biphenyl (**3**). Evidently, the initially formed iodine azide adduct undergoes further reaction at a somewhat faster rate than starting material. This explanation would account for the large amount of starting material that can be recovered when equivalent amounts of iodine azide were used. When a 2-mol excess of iodine azide was employed, a quantitative yield of **3** could be obtained after elimination of hydrogen iodide.

When **2** was allowed to stand at 0 °C for 3 days, it quantitatively cyclized to give 5,13b-dihydro-5-methylene-1*H*-dibenzo[*c*,*e*]-*v*-triazolo[1,5-*a*]azepine (**4**): mp 141–142 °C; NMR (100 MHz) τ 6.00 (dd, 1 H, J = 17.0 and 10.0 Hz), 5.62 (s, 1 H), 5.31 (dd, 1 H, J = 10.0 and 3.0 Hz), 4.90 (dd, 1 H, J = 17.0 and 3.0 Hz), 4.73 (s, 1 H) and 2.32–2.92 (m, 8 H). Further heating of this material resulted in the loss of nitrogen and formation of 3,11b-dihydro-3-methylene-1*H*-azirino[1,2-*a*]dibenz[*c*,*e*]azepine (**5**): NMR (100 MHz) τ 8.01 (d, 1 H, J = 3.0 Hz), 7.49 (d, 1 H, J = 6.0 Hz), 6.67 (dd, 1 H, J = 6.0 and 3.0 Hz), 5.57 (s, 1 H), 5.43 (s, 1 H), and 2.37–2.88 (m, 8 H). The thermal decomposition of 1,2,3-triazolines has previously been reported[39-41] to produce the corresponding aziridines and provides good analogy for the conversion of **4** to **5**. Alder and Stein's comprehensive study, however, has shown that aziridine formation is usually complicated, and frequently excluded by the formation of isomeric imines.[42] The thermal decomposition of triazolines is therefore not regarded as a generally useful route to aziridines.[43,44] In the above system, however, the thermolysis of Δ^2-1,2,3-triazoline **4** results in the quantitative formation of vinyl aziridine **5** and provides a convenient synthesis of this unusual ring system.

Aziridines possessing unsaturated substituents on nitrogen are known to readily undergo ring expansion to 1-azacyclopentene derivatives.[45,46] Formally analogous to the vinylcyclopropane–cyclopentene isomerization, these rearrangements have been effected by nucleophiles, acids, and heat. Simple 2-vinylaziridines have also been found to rearrange on heating to 3-pyrrolines,[47-50] probably by way of a homolytic mechanism proceeding via an allylic–hydrazino diradical which collapses with allylic rearrangement. It therefore became of interest to examine the thermal behavior of *N*-vinylaziridine **5**, since this system is sterically prohibited from undergoing an analogous rearrangement. One possible reaction which could be imagined would involve the rearrangement of **5** into



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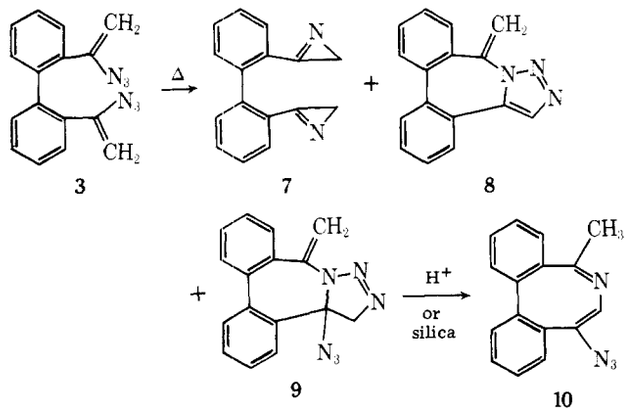
3-(2′-vinyl-2-biphenylyl)-2*H*-azirine by a cheletropic fragmentation of the aziridine ring followed by reorganization of the resulting vinyl nitrene. However, all attempts to isolate a characterizable product from the thermolysis of **5** failed. Treatment of **5** with hydrochloric acid, however, was found to give chloride **6** in high yield. This reaction may be interpreted as involving an acid-induced cleavage of the C–N bond of the aziridine followed by chloride attack and tautomerization of the initially produced enamine.

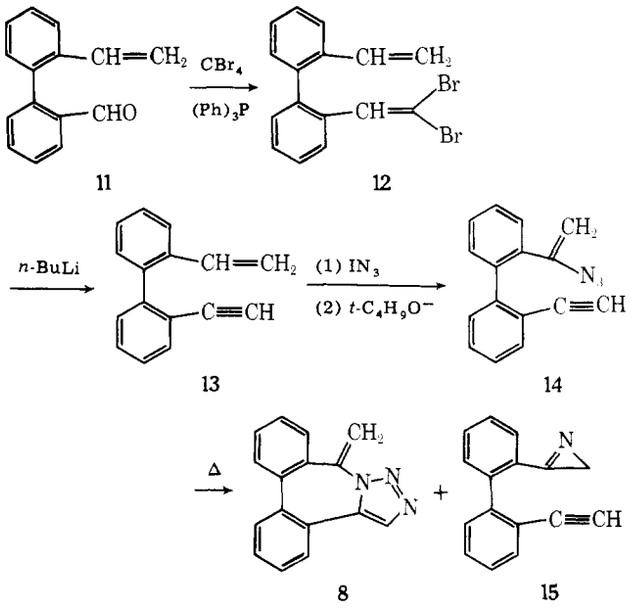
Although the isolation of Δ^2-1,2,3-triazoline **4** from vinyl azide **2** is not surprising, it is noteworthy as the first example of intramolecular cycloaddition of a vinyl azide. Thermolysis of vinyl azides generally produce 2*H*-azirines by a process involving ring closure simultaneous with loss of nitrogen.[2] The facile formation of **2** is also unusual in light of the earlier work by Logothetis[36] who found that azidoalkenes require heating at 50 °C for 18 h before intramolecular cycloaddition will occur. The high reactivity of vinyl azide **2** toward dipolar cycloaddition can be nicely rationalized by the frontier molecular orbital method. 1,3-Dipolar cycloadditions of azides with olefins may be classified as a set which involves dipolar LUMO-dipolarophile HOMO control.[51,52] Attachment of a phenyl group to the π system will raise the HOMO and lower the LUMO energy levels of the olefin and thus bring about an acceleration of the rate of 1,3-dipolar cycloaddition with azides. Another factor which undoubtedly plays an important role in the intramolecular cycloaddition reaction of vinyl azide **2** is the high degree of order present in the transition state. Bimolecular cycloadditions exhibit large negative entropies of activation,[53] since the reactants must be precisely aligned with respect to each other. The interplay of favorable entropy and enthalpy factors in the above system undoubtedly facilitates the rate of cycloaddition over that of azirine formation.

As a continuation of our work in this area, we also studied the thermal behavior of 2,2′-(1-azidovinyl)biphenyl (**3**). Heating a sample of **3** in benzene produced a mixture of three products which were identified as **7** (61%), **8** (17%), and **9**



(22%). The major component isolated from the mixture was established as 3,3′-(2,2′-biphenylylene)bis(2*H*-azirine) (**7**), mp 84–85 °C, through a combination of infrared, ultraviolet, and NMR spectroscopy. The conversion of **3** into **7** represents a typical example of azirine formation from a vinyl azide.[5–16] The minor component of the reaction mixture was a white crystalline solid, mp 165–166 °C, whose structure is assigned as 9-methylene-9*H*-dibenzo[*c*,*e*]-*v*-triazolo[1,5-*a*]azepine (**8**) on the basis of its elemental analysis and spectroscopic data [NMR (60 MHz) τ 4.39 (s, 1 H), 4.10 (s, 1 H), 2.20–2.70 (m, 8 H), and 2.08 (s, 1 H)]. This structure was further established by the independent synthesis outlined in Scheme I. 2-(1-Azidovinyl)-2′-ethynylbiphenyl (**14**) was prepared by treating 2′-vinyl-2-biphenylcarboxaldehyde (**11**) with carbon tetrabromide and triphenylphosphine to give dibromide **12**. This

Scheme I

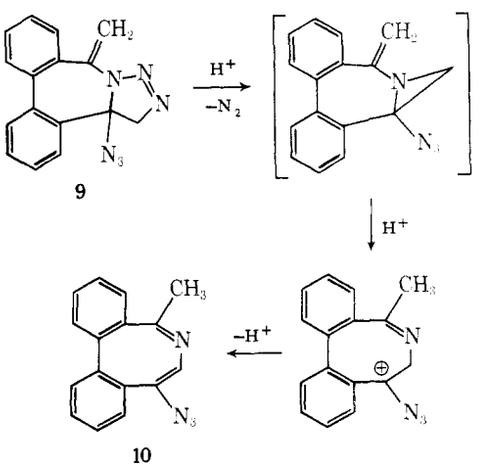


material was converted to acetylene **13** on treatment with *n*-butyllithium which, in turn, was transformed into **14** with iodine azide and potassium *tert*-butoxide. The thermolysis of **14** resulted in both azirine formation (**14**) and intramolecular 1,3-dipolar cycloaddition to give **8** which was identical with the minor product obtained from the thermolysis of **3**.

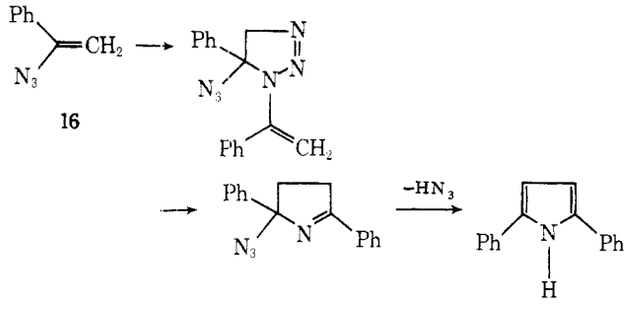
The remaining component (**9**) present in the reaction mixture obtained from the thermolysis of **3** could not be isolated by column chromatography. Instead, a new compound was obtained whose structure was assigned a 8-azido-5-methyldibenz[*c*,*e*]azocine (**10**), mp 102–103 °C, on the basis of its spectral properties (see Experimental Section). The formation of **10** was shown by control experiments to be the result of an acid-induced reaction of **9** and which presumably occurs via the path shown in Scheme II. The structure of **9** was established from its spectral properties and was further confirmed by its based-induced conversion to **8**.

The nature of the products obtained from the thermolysis of bis(vinyl azide) **3** suggests that the thermal chemistry of this system proceeds via two distinct paths. The major path involves formation of bis(azirine) **7**. The minor process, which ultimately leads to the formation of **8**, is best explained as proceeding via an intramolecular dipolar cycloaddition of the azide functionality across the neighboring double bond of the adjacent vinyl azide to give structure **9**. On further thermolysis, this material loses the elements of HN_3 to give **8**.

Scheme II



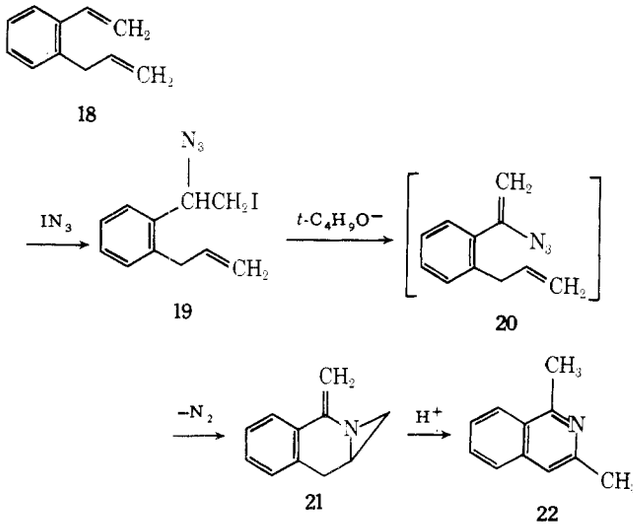
It is interesting to note that the presence of an azide function together with a C=C double bond in the same molecule should allow self-addition of vinyl azides to occur, but this has never been reported explicitly. However, one example exists in the literature where this process might have occurred. Boyer had previously reported[54] that α-azidostyrene (16) decomposes slowly at room temperature to give a mixture of 2-phenylazirine, 3,6-diphenylpyridazine, and 2,5-diphenylpyrrole (17). The formation of 2,5-diphenylpyrrole (17) can



16 17

be interpreted in terms of 1,3-dipolar cycloaddition of the azide onto the electron-rich double bond of a second molecule to give a 2-triazoline which decomposes by loss of nitrogen and elimination of HN_3. This reaction scheme was discussed by L'abbe' in a recent review dealing with the reaction of vinyl azides[2] and provides good analogy for the formation of structure **9**.[55]

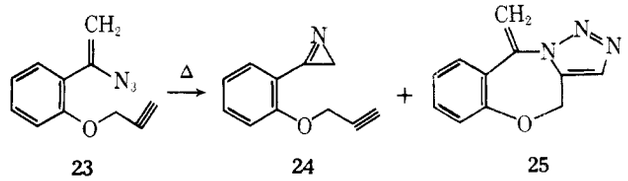
We also attempted to study the intramolecular 1,3-dipolar cycloaddition reaction of the closely related vinyl azide system **20** in order to assess the generality of this cycloaddition. Treatment of *o*-allylstyrene (**18**) with iodine azide gave the expected iodo azide adduct **19**. Elimination of hydrogen iodide from this adduct gave 1,3,8,8a-tetrahydro-3-methyleneazirino[1,2-*b*]isoquinoline (**21**) presumably by way of a transient vinyl azide intermediate **20**. The structure of **21** was assigned



18 19 20 21 22

on the basis of its characteristic spectral properties [NMR (100 MHz) τ 7.24–7.40 (m, 2 H), 6.1–6.6 (m, 1 H), 5.90 (dd, 1 H, J = 17.0 and 8.0 Hz), 5.58 (dd, 1 H, J = 17.0 and 11.0 Hz), 2.2–3.0 (m, 4 H)]. Thick-layer chromatography of **21** resulted in the opening of the three-membered ring and gave 1,3-dimethylisoquinoline (**22**) in quantitative yield. The formation of **21** from **19** can reasonably be interpreted in terms of a rapid intramolecular 1,3-dipolar cycloaddition of an initially formed vinyl azide **20** followed by loss of nitrogen.

Another case where a vinyl azide was found to undergo smooth intramolecular dipolar cycloaddition was encountered in the thermolysis of propargyl *o*-(1-azidovinyl)phenyl ether

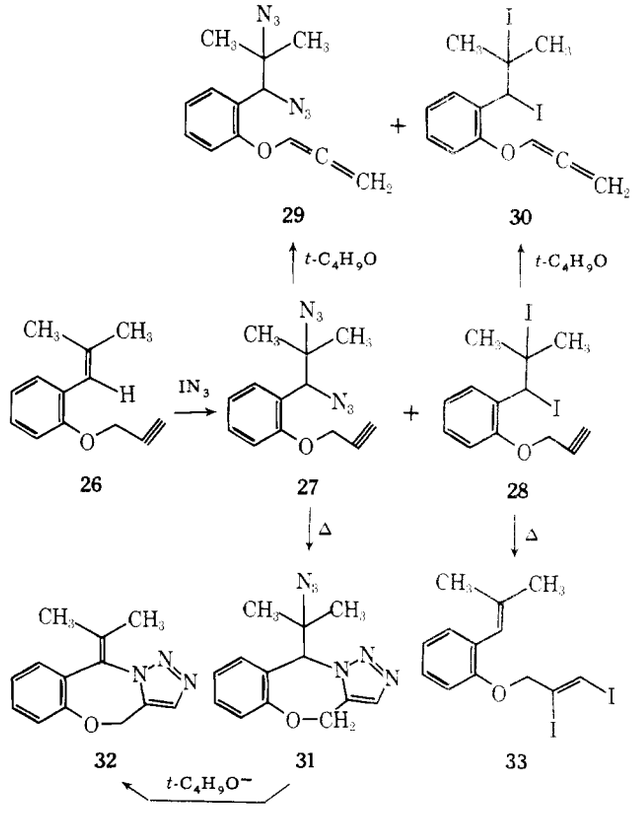


23 24 25

(**23**). Refluxing a solution of **23** in toluene for 2 h afforded a mixture of 3-[*o*-(2-propynyloxy)phenyl]-2*H*-azirine (**24**), mp 57–58 °C (20%), and 10-methylene-4*H*,10*H*-[1,2,3]triazolo[5,1-*c*][1,4]benzoxazepine (**25**) (80%) which could be readily separated by column chromatography. In this case, the internal cycloaddition reaction occurred across the acetylenic functionality to give **25** as the major reaction product (see Experimental Section for spectral data).

One additional system which was also studied involved the reaction of 1-[*o*-(2-propynyloxy)phenyl]-2-methyl-1-propene (**26**) with iodine azide. With this system, the addition of IN_3 proceeded to give a mixture of 1,2-diazido- (**27**) (80%) and 1,2-diodo-1-[*o*-(2-propynyloxy)phenyl]-2-methylpropane (**28**) (20%). Treatment of this mixture with potassium *tert*-butoxide resulted in a base-induced isomerization of the acetylenic moiety and gave rise to the isomeric *o*-(allenyloxy)phenyl substituted olefins **29** and **30**. Heating the mixture of **27** and **28** at 120 °C in toluene, on the other hand, resulted in the formation of benzoxazepine **31** and diiodide **33**. The structure of the major reaction product (i.e. **31**) was based on its elemental analysis and characteristic spectral data [NMR (100 MHz) τ 8.66 (s, 3 H), 8.62 (s, 3 H), 5.12 (d, 1 H, J = 14.0 Hz), 4.48 (d, 1 H, J = 14.0 Hz), 4.40 (s, 1 H), 2.60–3.18 (m, 4 H), and 2.70 (s, 1 H)]. Structure **31** was further confirmed by elimination of HN_3 with base to give **32**. The structure of the minor component obtained from the thermolysis was established as diiodide **33** by comparison with an independently synthesized sample prepared by treating olefin **26** with iodine.

The formation of a mixture of **27** and **28** from the reaction of **26** with iodine azide presumably proceeds through an iodonium ion[4] which is trapped by iodide ion to give **28** or reacts with azide ion to give an iodoazide adduct. It would seem as



29 30 26 27 28 32 31 33

though the transient iodo azide adduct rapidly loses iodide to give a tertiary carbonium ion which is subsequently trapped by azide to give **27**. The isolation of a vicinal diazide from the reaction of an olefin with iodine azide has been described in the literature.[56] Although it was not possible to obtain the vinyl azide derived from **26**, the isolation of **32** by the above sequence provides an alternate synthesis of this novel ring system. It should also be pointed out that the internal cycloaddition reactions of **23** and **27** represent one of the few available examples of intramolecular cycloadditions of the azido group to a triple bond.[57]

In summary, we have shown that vinyl azides can undergo intramolecular dipolar cycloaddition to a neighboring site of unsaturation to give an isolable triazoline in competition with nitrogen loss and formation of the 2*H*-azirine ring system. Further thermolysis of the triazoline results in the formation of a 1-vinylaziridine. Though 1-vinylaziridines have the structure of an enamine, they are not obtained by the conventional method of enamine synthesis involving the condensation of a carbonyl compound with an aziridine. Only a few of them have so far been prepared by the addition of aziridine to acetylenic compounds possessing strong electron-withdrawing substituents.[58,59] By analogy, we assume that triazolines are also intermediates in the bimolecular reaction of vinyl azides with electron-deficient olefins to give 1-vinylaziridines.[60]

Experimental Section

All melting points are corrected and boiling points are uncorrected. Elemental analyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark. The infrared absorption spectra were determined on a Perkin-Elmer Infracord spectrophotometer, Model 137. The ultraviolet absorption spectra were measured with a Cary recording spectrophotometer, using 1-cm matched cells. The nuclear magnetic resonance spectra were determined at 100 MHz using a Varian XL-100 spectrometer and at 60 MHz with a Varian T-60 spectrometer. All NMR spectra were recorded using deuteriochloroform as the solvent unless otherwise stated.

Preparation of 2-(1-Azidovinyl)-2′-vinylbiphenyl (2). To a solution containing 1.30 g of sodium azide in 50 mL of acetonitrile at −5 °C was added a solution containing 1.62 g of iodide monochloride in 5 mL of acetonitrile. The mixture was allowed to stir for an additional 30 min and was then added to a solution of 1.03 g of 2,2′-divinylbiphenyl[61] (**1**) in 50 mL of acetonitrile. After the addition was completed, the orange slurry was allowed to stir for 10 min at room temperature. The mixture was diluted with 100 mL of water and then extracted with ether. The ethereal extracts were washed with a 5% aqueous sodium thiosulfate solution and then with water. After drying the organic layer with anhydrous magnesium sulfate, the solvent was removed under reduced pressure to give a yellow oil which was used immediately in the next step.

To a solution containing the above iodine azide adduct in 40 mL of ether at −5 °C was added 1.68 g of potassium *tert*-butoxide. The mixture was allowed to stir at 5 °C for 14 h and was then washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure left a yellow oil which was chromatographed on a 2 × 40 cm neutral alumina column using a 5% acetone–hexane mixture as the eluent. The middle fractions contained 150 mg of 2-(1-azidovinyl)-2′-vinylbiphenyl (**2**) as a pale yellow oil: NMR (100 MHz, $CDCl_3$) τ 5.43 (s, 1 H), 5.24 (s, 1 H), 4.97 (d, 1 H, J = 11.0 Hz), 4.43 (d, 1 H, J = 18.0 Hz), 3.55 (dd, 1 H, J = 18.0 and 11.0 Hz), and 2.31–2.99 (m, 8 H).

Anal. Calcd for $C_{16}H_{13}N_3$: C, 77.71; H, 5.30; N, 16.99. Found: C, 77.48; H, 5.21; N, 16.86.

Further elution of the column gave 970 mg of 2,2′-di(1-azidovinyl)biphenyl (**3**) as a crystalline solid: mp 72–73 °C; IR (KBr) 4.75, 6.13, 6.80, 7.20, 7.70, 8.20, 9.35, 9.95, 11.30, 12.85, and 13.55 μm; NMR (60 MHz) τ 5.42 (d, 2 H, J = 2.0 Hz), 5.20 (d, 2 H, J = 2.0 Hz), 2.50–2.80 (m, 8 H).

Anal. Calcd for $C_{16}H_{12}N_6$: C, 66.65; H, 4.19; N, 29.15. Found: C, 66.62; H, 4.08; N, 29.07.

Thermolysis of 2-(1-Azidovinyl)-2′-vinylbiphenyl (2). A 125-mg sample of **2** was allowed to stand at 0 °C for 3 days. The pale-yellow needles which had formed were filtered and washed with hexane. Recrystallization of the solid from chloroform–hexane gave 100 mg (90%) of 5,13b-dihydro-5-methylene-1*H*-dibenzo[*c*,*e*]-*v*-triazolo[1,5-*a*]azepine (**4**): mp 141–142 °C; IR (KBr) 4.72, 6.18, 6.71, 6.90, 7.39, 7.49, 8.34, 8.91, 9.74, 10.70, 11.90, 13.20, and 13.41 μm; UV (cyclohexane) 247 (ε 12 700) and 300 nm (ε 3600); NMR (100 MHz, $CDCl_3$) τ 6.00 (dd, 1 H, J = 17.0 and 10.0 Hz), 5.62 (s, 1 H), 5.31 (dd, 1 H, J = 10.0 and 3.0 Hz), 4.90 (dd, 1 H, J = 17.0 and 3.0 Hz), 4.73 (s, 1 H), and 2.32–2.92 (m, 8 H); MS *m/e* 219 (base), 218, 217, 205, 191, 178, 152, and 151.

Anal. Calcd for $C_{16}H_{13}N_3$: C, 77.71; H, 5.30; N, 16.99. Found: C, 77.36; H, 5.30; N, 16.95.

A solution containing 100 mg of the above compound in 25 mL of benzene was heated at reflux for 14 h. Removal of the solvent left a yellow oil which was purified by chromatography on a 1 × 15 cm florosil column using a 1:1 mixture of ether–pentane as the eluent. The major fraction isolated contained 70 mg (77%) of a pale-yellow oil which was identified as 3,11b-dihydro-3-methylene-1*H*-azirino[1,2-*a*]dibenz[*c*,*e*]azepine (**5**) on the basis of its spectral properties: IR (neat) 3.26, 6.11, 6.74, 6.95, 7.46, 8.36, 9.94, 10.33, 11.74, and 13.16 μm; NMR (100 MHz, $CDCl_3$) τ 8.01 (d, 1 H, J = 3.0 Hz), 7.49 (d, 1 H, J = 6.0 Hz), 6.67 (dd, 1 H, J = 6.0 and 3.0 Hz), 5.57 (s, 1 H), 5.43 (s, 1 H), and 2.37–2.88 (m, 8 H); *m/e* 219 (M^+ and base), 204, 192, 165.

Anal. Calcd for $C_{16}H_{13}N$: C, 87.64; H, 5.98; N, 6.39. Found: C, 87.52; H, 5.81; N, 6.32.

To a solution containing 100 mg of **5** in 20 mL of benzene was added 5 drops of a 10% hydrochloric acid solution. The solution was allowed to stir for 20 min at room temperature and then was washed with a saturated sodium bicarbonate solution and dried over magnesium sulfate. Removal of the solvent under reduced pressure left 75 mg (68%) of 8-chloro-7,8-dihydro-5-methyldibenz[*c*,*e*]azocine (**6**) as a crystalline solid: mp 124–125 °C; IR (KBr) 6.16, 7.11, 7.31, 7.80, 8.31, 12.41, 12.81, 13.13, and 14.19 μm; NMR (100 MHz) τ 7.85 (s, 3 H), 6.40 (t, 1 H, J = 11.0 Hz), 5.80 (dd, 1 H, J = 11.0 and 7.0 Hz), 4.52 (dd, 1 H, J = 11.0 and 7.0 Hz), 2.40–2.90 (m, 8 H); MS *m/e* 255 (M^+), 220, 219, 218, 206, 191, 178 (base), 165, 151, and 139.

Anal. Calcd for $C_{16}H_{14}NCl$: C, 75.14; H, 5.52; N, 5.50. Found: C, 75.13; H, 5.54; N, 5.49.

Thermolysis of 2,2′-Di(1-azidovinyl)biphenyl (3). A 2.0-g sample of **3** was heated at reflux in 20 mL of benzene under a nitrogen atmosphere for 24 h. Removal of the solvent left a yellow oil which was subjected to silica gel chromatography using a 15% ether–hexane mixture as the eluent. The first fraction collected contained 330 mg of a yellow solid whose structure was assigned as 8-azido-5-methyldibenz[*c*,*e*]azocine (**10**) on the basis of its spectroscopic data: mp 102–103 °C; IR (KBr) 4.77, 6.09, 6.68, 6.90, 7.13, 7.40, 7.58, 7.90, 10.40, 11.85, 12.35, 13.00, 13.50, and 14.50 μm; NMR (60 MHz) τ 7.50 (s, 3 H), 4.56 (s, 1 H), 2.30–2.70 (m, 8 H); UV (methanol) 280 nm (ε 11 200); MS *m/e* 260 (M^+), 232 (base), 219, 204, 192, 178, 165 and 152.

Anal. Calcd for $C_{16}H_{12}N_4$: C, 73.83; H, 4.65; N, 21.53. Found: C, 74.19; H, 4.69; N, 21.07.

Examination of the crude reaction mixture before chromatography showed that **10** was not present. Instead, a series of peaks associated with 5,13b-dihydro-5-methylene-13b-azido-1*H*-dibenzo[*c*,*e*]-*v*-triazolo[1,5-*a*]azepine (**9**) could be found in the NMR spectrum [NMR (60 MHz) τ 5.78 (s, 2 H), 5.46 (s, 1 H), and 5.28 (s, 1 H)]. On treatment of the crude mixture with acid, the peaks associated with **9** disappeared while those of **10** appeared.

The second component isolated from the chromatography column amounted to 980 mg and was a white crystalline solid, mp 84–85 °C, whose structure was assigned as 3,3′-(2,2′-biphenylylene)bis(2*H*-azirine) (**7**) on the basis of the following data: IR (KBr) 5.71, 6.20, 6.38, 6.90, 7.59, 8.58, 8.90, 9.10, 10.05, 12.80, 13.00, 13.40 and 13.60 μm; NMR (100 MHz) τ 8.72 (s, 4 H), 2.36–2.64 (m, 6 H), 1.98–2.08 (m, 2 H); UV (methanol) 242 nm (ε 20 300); MS *m/e* 232 (M^+), 231, 230, 229, 205, 204 (base), 192, 190, 178, 165, 151 and 102.

Anal. Calcd for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.61; H, 5.26; N, 11.97.

The last component isolated from the silica gel column contained 240 mg of a crystalline solid, mp 165–166 °C, whose structure was assigned as 9-methylene-9*H*-dibenzo[ε,*e*]-*v*-triazolo[1,5-*a*]acepine (**8**) on the basis of the following data: IR (KBr) 6.10, 6.87, 7.00, 7.70, 7.78, 8.16, 8.95, 9.95, 10.35, 11.05, 11.67, 13.10, 13.70 and 14.32 μm; NMR (60 MHz) τ 4.39 (s, 1 H), 4.10 (s, 1 H), 2.20–2.70 (m, 8 H), and 2.08 (s, 1 H), UV (methanol) 233 nm (ε 27 200).

Anal. Calcd for $C_{16}H_{11}N_3$: C, 78.35; H, 4.52; N, 17.13. Found: C, 78.25; H, 4.50; N, 17.08.

The structure of azepine **8** was further verified by an independent synthesis. A solution containing 5.9 g of 2′-vinyl-2-biphenylcarboxaldehyde (**11**), 15.5 g of carbon tetrabromide, and 25.0 g of triphenylphosphine in 250 mL of methylene chloride was allowed to stir at 0 °C for 20 min. At the end of this time 20 mL of water was added and

the mixture was separated. The organic layer was filtered and the solvent was removed under reduced pressure. The resulting yellow residue was chromatographed on a silica gel column using a 10% ether–pentane mixture as the eluent. The major fraction isolated contained 6.4 g (73%) of 2-vinyl-2′-(2,2-dibromovinyl)biphenyl (**12**) as a light yellow oil: IR (neat) 3.30, 3.45, 6.14, 6.29, 6.82, 6.98, 8.00, 8.36, 8.60, 10.00, 10.40, 10.80, 11.15, 11.50, and 12.25 μm; NMR (100 MHz) τ 4.92 (d, 1 H, J = 10.0 Hz), 4.40 (d, 1 H, J = 18.0 Hz), 3.62 (dd, 1 H, J = 18.0 and 10.0 Hz), 3.06 (s, 1 H), 2.40–3.00 (m, 8 H).

To a solution containing 2.40 g of sodium azide in 40 mL of acetonitrile at −5 °C was added a solution containing 2.8 g of iodine monochloride in 5 mL of acetonitrile. The mixture was allowed to stir for 30 min and was then added to a solution of 4.70 g of **12** in 20 mL of acetonitrile. After the addition was completed, the mixture was allowed to stir at room temperature for 2 h. The mixture was diluted with water and extracted with ether. The ether extracts were washed with a 10% sodium thiosulfate solution followed by water. After drying the organic layer, the solvent was removed to leave behind a dark-orange oil which was used immediately in the next step.

To a solution containing the above iodine azide adduct in 100 mL of tehrahydrofuran was added 18.0 mL of a 2.2 M n-butyllithium solution. After stirring for 1 h at −78 °C, the solution was allowed to warm up to room temperature and was then diluted with water and extracted with ether. The ether solution was dried over magnesium sulfate and the solvent was removed under reduced pressure. The resulting residue was distilled at 95–97 °C at 0.05 mm to give 2.3 g of 2-ethynyl-2′-vinylbiphenyl (**13**) as a clear oil: IR (neat) 3.06, 3.32, 3.44, 6.14, 6.84, 6.96, 8.96, 10.10, 10.94, and 13.20 μm; NMR (100 MHz) τ 7.20 (s, 1 H), 4.96 (d, 1 H, J = 11.0 Hz), 4.50 (d, 1 H, J = 17.0 Hz), 3.56 (dd, 1 H, J = 17.0 and 11.0 Hz), 2.50–3.00 (m, 8 H).

To a solution containing 1.5 g of sodium azide in 20 mL of acetonitrile at −5 °C was added a solution containing 1.9 g of iodine monochloride in 3 mL of acetonitrile. The solution was allowed to stir for 30 min at −5 °C and then a solution containing 1.7 g of 2-ethynyl-2′-vinylbiphenyl (**13**) in 3 mL of acetonitrile was added. The resulting mixture was allowed to stir at room temperature for an additional 2 h. The mixture was diluted with water and extracted with ether. The extracts were washed with a 10% sodium thiosulfate solution, dried, and concentrated under reduced pressure. The residue was taken up in 100 mL of ether and 3.4 g of potassium *tert*-butoxide was added. The mixture was stirred at 0 °C for 12 h and was then washed with water and dried over magnesium sulfate. Removal of the solvent left 1.55 g (67%) of 2-(1-azidovinyl)-2′-ethynylbiphenyl (**14**): IR (neat) 3.06, 3.29, 3.41, 4.77, 6.12, 6.80, 6.97, 7.70, 9.55, 9.92, 10.50, 11.70, and 13.0 μm; NMR (100 MHz) τ 7.12 (s, 1 H), 5.50 (s, 1 H), 5.25 (s, 1 H), and 2.40–3.30 (m, 8 H).

A 200-mg sample of **14** in 5 mL of benzene was heated at 30 °C for 3 days. Removal of the solvent left a pale-yellow oil which was chromatographed on a thick-layer plate. The minor component isolated from the plate contained 30 mg (15%) of an oil which was identical in every detail (IR, NMR) with that of a sample of **8** obtained from the thermolysis of **3**.

Treatment of 2-Azido-1-iodo-1-(*o*-allylphenyl)ethane with Potassium *tert*-Butoxide. A solution containing 0.26 g of sodium azide in 10 mL of acetonitrile was cooled in a methanol–ice bath and then a solution containing 0.35 g of iodine monochloride in 5 mL of acetonitrile was added dropwise. The mixture was allowed to stir for 30 min at 0 °C and then a mixture containing 0.29 g of *o*-allylstyrene[62] (**18**) in 5 mL of acetonitrile was added and the mixture was stirred at 0 °C for 4 h. The resulting orange slurry was added to 10 mL of water and extracted with ether. The ether extracts were washed with a 5% sodium thiosulfate solution and then water. The ethereal layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 0.59 g (95%) of a clear oil whose structure was assigned as 2-azido-1-iodo-1-(*o*-allylphenyl)ethane (**19**): NMR ($CDCl_3$, 100 MHz) τ 6.80 (d, 2 H, J = 8.0 Hz), 6.70 (d, 2 H, J = 6.0 Hz), 5.0–5.26 (m, 3 H), 4.0–4.40 (m, 1 H), 2.20–3.00 (m, 4 H).

To a solution containing 200 mg of **19** in 25 mL of ether at −10 °C was added 0.12 g of potassium *tert*-butoxide. The mixture was allowed to stir at 0 °C for 14 h and was then diluted with 75 mL of ether and washed with water. Removal of the solvent under reduced pressure left a pale-yellow oil whose structure is assigned as 1,3,8,8a-tetrahydro-3-methyleneazirino[1,2-*b*]isoquinoline (**21**) on the basis of its characteristic NMR spectrum: (100 MHz, $CDCl_3$) τ 7.32 (m, 2 H), 6.1–6.60 (m, 1 H), 5.92 (dd, 1 H, J = 16.0 and 7.0 Hz), 5.56 (dd, 1 H, J = 16.0 and 11.0 Hz), 4.94 (s, 1 H), 4.60 (s, 1 H), 2.20–3.00 (m, 4 H). Chromatography of this material on a thick-layer plate using a 15% ethyl acetate–hexane mixture as the eluent resulted in a rearrangement and gave 32 mg of a clear oil which was identified as 1,3-dimethylisoquinoline (**22**) on the basis of its spectral properties [NMR (100 MHz, $CDCl_3$) τ 7.32 (s, 3 H), 7.03 (s, 3 H), 1.90–2.70 (m, 5 H)] and by comparison with an authentic sample prepared by the method of Fitton and co-workers.[63]

Preparation of Propargyl *o*-(1-Azidovinyl)phenyl Ether (23). To a stirred solution containing 8.2 g of sodium hydroxide in 300 mL of a 75% aqueous ethanol solution was added 25 g of salicylaldehyde and 23 mL of propargyl bromide. The reaction mixture was heated at 75 °C for 24 h and then the solvent was removed under reduced pressure. The residue was taken up in ether, washed with water, and concentrated under reduced pressure. The resulting solid was sublimed at 30 °C (0.01 mm) to give 20 g (62%) of *o*-(2-propynyloxy)-benzaldehyde as a crystalline solid: mp 68–69 °C; IR (KBr) 3.00, 3.40, 4.65, 5.85, 6.70, 7.70, 8.10, 9.85, 10.65, 11.90, 13.10 and 14.30 μm; NMR ($CDCl_3$, 100 MHz) τ 7.40 (t, 1 H, J = 2.0 Hz), 5.20 (d, 2 H, J = 2.0 Hz), 2.84–3.04 (m, 2 H), 2.16–2.58 (m, 2 H), −0.44 (s, 1 H).

To a mixture containing 11.2 g of methyltriphenylphosphonium bromide in 250 mL of dry ether was added 13.5 mL of a 2.4 M n-butyllithium solution at room temperature under a nitrogen atmosphere. The resulting orange solution was allowed to stir at room temperature for 20 min prior to the addition of 4.0 g of *o*-(2-propynyloxy)benzaldehyde in 15 mL of ether. The mixture was allowed to stir at room temperature for 14 h and was then filtered to remove the precipitated triphenylphosphine oxide. Removal of the solvent under reduced pressure left a yellow oil which was distilled at 65 °C (0.4 mm) to give 1.7 g (43%) of a colorless oil whose structure was assigned as *o*-(2-propynyloxy)phenylethylene: IR (neat) 3.0, 3.30, 4.65, 6.02, 6.70, 10.00, 10.85, and 13.00 μm; NMR ($CDCl_3$, 100 MHz) τ 7.48 (t, 1 H, J = 2.0 Hz), 5.22 (d, 2 H, J = 2.0 Hz), 4.64 (d, 1 H, J = 12.0 Hz), 4.16 (d, 1 H, J = 18.0 Hz), 2.26–3.00 (m, 5 H).

To a solution of 2.5 g of sodium azide in 40 mL of acetonitrile cooled in a methanol–ice bath was added a solution of 3.6 g of iodine monochloride in 10 mL of acetonitrile. The mixture was allowed to stir for an additional 30 min while maintaining the temperature at 0 °C. To this solution was added 3.16 g of *o*-(2-propynyloxy)phenylethylene. The mixture was kept at room temperature for 3 h and the resultant orange slurry was added to water and extracted with ether. The ether extracts were washed with a 5% sodium thiosulfate solution and dried over anhydrous magnesium sulfate. Removal of the solvent left 6.6 g (100%) of an oil whose structure was assigned as 1-azido-2-iodo-1-[*o*-(2-propynyloxy)phenyl]ethane: NMR ($CDCl_3$, 100 MHz) τ 7.46 (t, 1 H, J = 2.0 Hz), 6.5–6.80 (m, 2 H), 5.20 (d, 2 H, J = 2.0 Hz), 4.82 (dd, 1 H, J = 6.0 and 4.0 Hz), 2.60–3.0 (m, 4 H).

To a stirred and cooled solution of 6.6 g of the above iodine azide adduct in 100 mL of ether was added 2.68 g of potassium *tert*-butoxide. The mixture was then allowed to stir at 5 °C for 8 h. The slurry was extracted with ether, washed with water, and dried over magnesium sulfate. Removal of the solvent under reduced pressure left 3.0 g of an orange oil which was purified by passing it through a neutral alumina column with benzene. The resulting light yellow oil was identified as propargyl *o*-(1-azidovinyl)phenyl ether (**23**): IR (neat) 3.00, 4.70, 6.60, 7.70, 8.10, 9.80, and 13.20 μm; NMR ($CDCl_3$, 100 MHz), τ 7.46 (t, 1 H, J = 2.0 Hz), 5.18 (d, 2 H, J = 2.0 Hz), 4.94 (s, 1 H), 4.88 (s, 1 H), 2.40–3.04 (m, 4 H).

Thermolysis of Propargyl *o*-(1-Azidovinyl)phenyl Ether. A 100-mg sample of the above azide was refluxed for 2 h in 5 mL of toluene. After being concentrated under reduced pressure, the residue was subjected to thick-layer chromatography using a 15% ethyl acetate–hexane mixture as the eluent. The first band obtained contained 20 mg (20%) of a pale-yellow solid whose structure was assigned as 3-[*o*-(2-propynyloxy)phenyl]-2*H*-azirine (**24**): mp 57–58 °C; IR (KBr) 3.00, 4.65, 6.15, 8.05, 9.70, 10.65, and 13.20 μm; NMR ($CDCl_3$, 100 MHz) τ 8.38 (s, 2 H), 7.46 (t, 1 H, J = 2.0 Hz), 5.14 (d, 2 H, J = 2.0 Hz), 2.25–3.00 (m, 4 H); UV (methanol) 302 and 245 nm (ε 9300 and 23 000); m/e 171 (M^+), 170 (base), 115, 90, and 77.

Anal. Calcd for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.02; H, 5.46; N, 7.92.

The second band isolated from the thick-layer plate was a pale-yellow oil (80 mg, 80%) whose structure was assigned as 10-methylene-4*H*,10*H*-[1,2,3]triazolo[5,1-*c*][1,4]benzoxazepine (**25**) on the basis of its characteristic spectral properties: IR (neat) 3.00, 5.95, 6.75, 8.10, 9.70, 10.95, 11.80, and 13.00 μm; NMR ($CDCl_3$, 100 MHz) τ 4.80 (s, 2 H), 4.32 (s, 1 H), 3.86 (s, 1 H), 2.40–2.96 (m, 4 H), and 2.36 (s, 1 H); UV (methanol) 290 nm (ε 7000); MS m/e 199 (M^+), 118 (base), 90, and 89.

Anal. Calcd for $C_{11}H_9N_3O$: C, 66.32; H, 4.65; N, 21.10. Found: C, 66.32; H, 5.09; N, 20.82.

Preparation of 1-[*o*-(2-Propynyloxy)phenyl]-2-methyl-1-propene (26). To a mixture containing 3.0 g of isopropyltriphenylphosphonium bromide[64] in 50 mL of anhydrous ether was added 3.4 mL of a 2.4 M n-butyllithium solution at room temperature under a

nitrogen atmosphere. The resulting solution was allowed to stir at room temperature for 7 h prior to the addition of 1.0 g of *o*-(2-propynyloxy)benzaldehyde in 125 mL of ether. The mixture was allowed to stir at room temperature for 18 h and was then filtered to remove the precipitated triphenylphosphine oxide. Concentration of the solution under reduced pressure left a yellow oil which was distilled to give 620 mg (50%) of 1-[*o*-(2-propynyloxy)phenyl]-2-methyl-1-propene (**26**), bp 55–57 °C (0.01 mm): IR (neat) 3.00, 3.35, 4.60, 5.95, 6.65, 7.20, 8.05, 9.65, 10.70, 12.00, and 13.50 μm; NMR ($CDCl_3$, 100 MHz) τ 8.26 (s, 3 H), 8.12 (s, 3 H), 7.60 (t, 1 H, J = 2.0 Hz), 5.34 (d, 2 H, J = 2.0 Hz), 3.78 (br s, 1 H), 2.60–3.12 (m, 4 H).

Treatment of 1-[*o*-(2-Propynyloxy)phenyl]-2-methyl-1-propene (26) with Iodine Azide. To a solution of 312 mg of sodium azide in 5 mL of acetonitrile cooled in a methanol–ice bath was added a solution of 780 mg of iodine monochloride in 2 mL of acetonitrile. The mixture was allowed to stir for an additional 30 min at 0 °C, and then a solution containing 774 mg of **26** in 5 mL of acetonitrile was added. The mixture was kept at room temperature for 18 h and the resultant orange slurry was added to water and extracted with ether. The ether extracts were washed with a 5% sodium thiosulfate solution and dried over anhydrous magnesium sulfate. Removal of the solvent left 1 g of an oil whose NMR spectrum showed it to be a 4:1 mixture of 1,2-diazido-2-[*o*-(2-propynyloxy)phenyl]-2-methylpropane (**27**) and 1,2-diodo-1-[*o*-(2-propynyloxy)phenyl]-2-methylpropane (**28**). The NMR spectrum of the mixture showed peaks at τ 8.80 (s, 3 H), 8.68 (s, 3 H), 7.50 (t, 1 H, J = 2.0 Hz), 5.30 (d, 2 H, J = 2.0 Hz), 4.86 (s, 1 H), and 2.40–3.00 (m, 4 H) for **27** and peaks at τ 8.76 (s, 3 H), 8.52 (s, 3 H), 7.50 (t, 1 H, J = 2.0 Hz), 5.30 (d, 2 H, J = 2.0 Hz), 4.20 (s, 1 H), and 2.08–3.12 (m, 4 H) for **28**.

Treatment of 300 mg of the above mixture with potassium *tert*-butoxide resulted in the isomerization of the triple bond. To a stirred and cooled solution of the above mixture of adducts (**27** and **28**) in 40 mL of anhydrous ether was added 140 mg of potassium *tert*-butoxide. The mixture was allowed to stir at 5 °C for 12 h. The slurry was washed with water and dried over magnesium sulfate. Removal of the solvent under reduced pressure left 300 mg of a light yellow oil whose NMR spectrum indicated it to be a mixture of 1,2-diazido- (**29**) and 2,2-diodo-1-[*o*-(allenyloxy)phenyl]-2-methylpropane (**30**): NMR ($CDCl_3$, 100 MHz) of **29**: τ 8.80 (s, 3 H), 8.68 (s, 3 H), 4.82 (s, 1 H), 4.48 (d, 2 H, J = 6.0 Hz), 3.10 (t, 1 H, J = 6.0 Hz), 2.32–2.92 (m, 4 H), while the NMR spectrum of **30** showed signals at τ 8.62 (s, 3 H), 8.50 (s, 3 H), 4.56 (d, 2 H, J = 6.0 Hz), 4.28 (s, 1 H), 3.20 (t, 1 H, J = 6.0 Hz), 2.08–3.04 (m, 4 H).

A 300-mg sample of the mixture (**27** and **28**) obtained from the iodine azide treatment of **26** was heated at reflux for 1 h in toluene. The solution was concentrated under reduced pressure and the resulting residue was subjected to thick-layer chromatography using a 15% ethyl acetate–hexane mixture as the eluent. The major band obtained was a light yellow solid which was recrystallized from ether to give 150 mg (50%) of a white solid, mp 119–120 °C, whose structure was assigned as 10-[(1-azido-1-methyl)ethyl]-4*H*,10*H*-[1,2,3]triazolo[5,1-*c*][1,4]benzoxazepine (**31**) on the basis of its spectral properties: IR (KBr) 4.60, 6.60, 8.10, 9.40 and 13.00 μm; NMR ($CDCl_3$, 100 MHz) τ 8.66 (s, 3 H), 8.62 (s, 3 H), 5.12 (d, 1 H, J = 14.0 Hz), 4.48 (d, 1 H, J = 14.0 Hz), 4.40 (s, 1 H), 2.60–3.18 (m, 4 H), 2.70 (s, 1 H); UV (methanol) 265 nm (ε 200); MS *m/e* 270 (M^+), 228, 187, 186, 159, 158 (base), 132, 106, 93, and 78.

Anal. Calcd for $C_{13}H_{14}N_6O$: C, 57.76; H, 5.22; N, 31.10. Found: C, 58.09; H, 5.35; N, 31.42.

The structure of this material was further verified by treatment with base. A 30-mg sample of **31** in 10 mL of anhydrous ether was treated with 60 mg of potassium *tert*-butoxide for 12 h. The reaction mixture was then diluted with ether, washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting yellow solid was recrystallized from ether–hexane to give 22 mg (97%) of a white solid, mp 140–141 °C, whose structure was assayed as 10-isopropylidene-4*H*,10*H*-[1,2,3]-triazolo[5,1-*c*][1,4]benzoxazepine (**32**) on the basis of the following data; IR (KBr) 6.65, 7.15, 8.10, 9.80, 12.50 and 13.10 μm; NMR ($CDCl_3$, 100 MHz) τ 8.08 (s, 1 H), 7.92 (s, 3 H), 4.76 (br s, 2 H), 2.76–3.20 (m, 4 H), 2.48 (s, 1 H); UV (methanol) 287 (ε 1200); MS *m/e* 227 (M^+), 183, 182, 172, 145, 131, 91, and 77 (base).

Anal. Calcd for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.55; H, 5.92; N, 18.37.

The minor component isolated from the thick-layer plate from the thermolysis of the mixture **27** and **28** contained 40 mg of a solid, mp 40–41 °C, whose structure was assigned as 1-[*o*-(2,3-diodoallyloxy)-phenyl]-2-methylprop-1-ene (**33**): IR (KBr) 3.30, 6.60, 6.80, 8.00, 9.50, and 13.25 μm; NMR ($CDCl_3$, 100 MHz) τ 8.18 (s, 3 H), 8.00 (s, 3 H), 5.36 (s, 2 H), 3.62 (s, 1 H), 2.86–3.32 (m, 5 H); UV (methanol) 280 and 240 nm (ε 1340 and 4800).

Anal. Calcd for $C_{13}H_{14}OI_2$: C, 35.45; H, 3.21; I, 57.69. Found: C, 35.50; H, 3.32; I, 57.52.

An authentic sample of **33** was prepared by treating 186 mg of **26** in 10 mL of acetonitrile with 300 mg of iodine. The reaction mixture was maintained at 40 °C for 24 h. At the end of this time the solution was taken up in ether and washed with a 5% sodium thiosulfate solution followed by water. The ethereal layer was dried over magnesium sulfate and concentrated under reduced pressure to give 200 mg (45%) of a solid, mp 40–41 °C, whose spectral properties were identical in every detail with **33** obtained above.

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Registry No.—**1**, 34919-47-6; **2**, 63375-55-3; **3**, 63626-09-5; **4**, 63375-56-4; **5**, 63375-57-5; **6**, 63375-59-7; **7**, 63626-10-8; **8**, 63641-41-8; **9**, 63657-91-0; **10**, 63626-11-9; **11**, 63626-12-0; **12**, 63626-13-1; **13**, 63626-14-2; **14**, 63626-15-3; **18**, 21919-44-8; **19**, 63626-16-4; **21**, 63375-68-6; **22**, 1721-94-4; **23**, 63626-17-5; **24**, 63626-18-6; **25**, 63626-19-7; **26**, 63626-20-0; **27**, 63626-21-1; **28**, 63626-22-2; **29**, 63626-23-3; **30**, 63626-24-4; **31**, 63626-25-5; **32**, 63626-26-6; **33**, 63626-27-7; salicylaldehyde, 90-02-8; proparygl bromide, 106-96-7; *o*-(2-propynyloxy)benzaldehyde, 29978-83-4; *o*-(2-propynyloxy)-phenylethylene, 63626-28-8; 1-azido-2-iodo-1-[*o*-(2-propynyloxy)-phenyl]ethane, 63626-29-9; iodine azide, 14696-82-3; methyltriphenylphosphonium bromide, 1779-49-3.

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Reaction of Nicotine and Sodium Nitrite: Formation of Nitrosamines and Fragmentation of the Pyrrolidine Ring[1,2]

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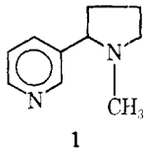
The reaction of nicotine and sodium nitrite was investigated in order to provide insight on the formation of potentially carcinogenic tobacco-specific nitrosamines. Reaction at 25 °C resulted in the formation of *N'*-nitrosonornicotine (**3**), 4-(*N*-methyl-*N*-nitrosamino)-1-(3-pyridyl)-1-butanone (**4**), and 4-(*N*-methyl-*N*-nitrosamino)-4-(3-pyridyl)butanal (**5**) in yields of 0.1–2.8%, with most of the nicotine being unreacted. When the reaction was carried out at 90 °C, with a fivefold excess of $NaNO_2$, 75–85% of the nicotine reacted. The nitrosamines **3** and **4** were formed in higher yield [up to 13.5 (**3**) and 4.3% (**4**)], but **5** was not observed. Both **4** and **5** gave secondary products under these conditions; **4** was nitrosated further to give 4-(*N*-methyl-*N*-nitrosamino)-2-oximino-1-(3-pyridyl)-1-butanone (**6**), and **5** gave rise to 1-methyl-5-(3-pyridyl)pyrazole (**7**). The major products resulting from fragmentation of the pyrrolidine ring were *cis*- and *trans*-3-(3-pyridyl)acrylonitrile (**8a,b**), *N*-methylnicotinamide (**9**), and nicotinic acid (**10**). The nitrosamines **3–5** and the fragmentation products **8a**, **8b**, and **9** most probably arise via cyclic iminium salts.

Recent studies have shown that both unburned, cured tobacco and tobacco smoke contain significant quantities of the carcinogenic compound, *N'*-nitrosonornicotine (**3**) (0.3–10 ppm in smoking tobacco, 3–90 ppm in chewing tobacco, 40–250 ng/cigarette in smoke).[3-9] This compound induces esophageal and nasal cavity tumors in rats, respiratory tract tumors in hamsters, and lung adenomas in mice, and displays carcinogenic activity and organ specificity which is typical of nitrosamines in general.[10-14] The major precursor in tobacco for **3** is the tertiary amine nicotine (**1**), which is converted to **3** during curing of tobacco.[15] Nornicotine (**2**) can also serve as



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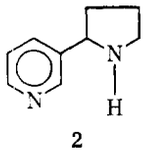

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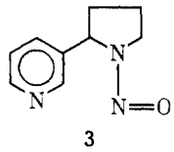
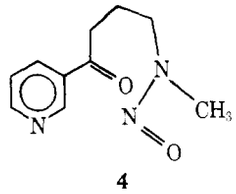


3

precursor for **3**, but its concentration in tobacco is significantly lower.[3,15] About half of **3** present in tobacco smoke is formed during smoking, and model studies have shown that **1** is more important than **2** as a precursor to **3** during cigarette smoking.[7,9] In view of these facts, studies on the reaction of **1** with nitrite were undertaken in order to provide insight on the possible formation of other nitrosamines, such as 4-(*N*-methyl-*N*-nitrosamino)-1-(3-pyridyl)-1-butanone (**4**) and 4-(*N*-methyl-*N*-nitrosamino)-4-(3-pyridyl)butanal (**5**), which could result from ring cleavage of the 1'–2' or 1'–5' bonds of **1** and nitrosation, respectively. In previous studies on the reaction of **1** with nitrite under various conditions, the presence of **3** was demonstrated and the possible formation of **4** and **5** discussed.[5,7,16]



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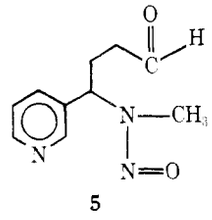

5

Results and Discussion

When **1** was allowed to react with 1 equiv of $NaNO_2$ in aqueous solution at 20 °C for 17 h, the nitrosamines **3–5** were formed. Under these mild conditions, **1** was mostly (80–90%) unreacted. The nitrosamines were identified by comparison of GC retention times and mass spectra to those of reference standards, which were independently synthesized.[17-19] Compounds **4** and **5** are, to our knowledge, the first examples of nitrosamines which are primary products of cleavage of a ring C–N bond in the nitrosation of a cyclic tertiary amine. The yields of **3–5** under these conditions are summarized in Table I and are typical of the reaction of tertiary amines with

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