δ 1.40 (d, J = 6.8 Hz, 3 H), 2.15 (s, 3 H), 2.43 (s, 3 H), 2.17–2.53 (m, 4 H), 3.90 (q, J = 6.8 Hz, 1 H), 7.15–7.96 (m, 14 H).

Reaction of the Pyran 24 with Phosphorus Tribromide. Phosphorus tribromide (1.36 g, 5.02 mmol) in dry ether (10 mL) was added to a stirred solution of the pyran **24** (4.50 g, 12.57 mmol) and pyridine (0.26 g, 3.29 mmol) in dry ether (25 mL) with cooling in an ice bath, and stirring was continued for 4.5 h at 0 °C and for 1.5 h at room temperature. After cooling, the mixture was quenched with water (40 mL), extracted with ether, and dried over sodium sulfate. Evaporation of the solvent afforded a mixture of **26** and **27** which were separated by column chromatography with hexane and hexane–benzene to give 2.11 g (47%) of **26** and 1.85 g (41%) of **27**.

3,4-Dihydro-2-hydroxy-6-methyl-5-(phenylthio)-2-[1-(phenylthio)ethyl]-2*H*-pyran (26): bp 180 °C (2.5 mm; bath temperature); IR (neat) 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (d, J = 7.0 Hz, 3 H), 1.47–2.30 (m, 7 H), 3.00–3.30 (m, 1 H, OH), 3.63–3.97 (m, 1 H), 7.06–7.83 (m, 10 H); mass spectrum (70 eV), m/e 358 (M^+).

Treatment of **26** with hydrochloric acid gave **27** quantitatively.

3,7-Bis(phenylthio)octane-2,6-dione (27): bp 230 °C (2.5 mm; bath temperature); IR (neat) 1705, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (d, J = 7.6 Hz, 3 H), 1.73–2.13 (m, 2 H), 2.25 (s, 3 H), 2.67–3.06 (m, 2 H), 3.50–3.97 (m, 2 H), 7.20–7.46 (m, 10 H); mass spectrum (70 eV), m/e 358 (M^+). Anal. Calcd for $C_{20}H_{22}O_2S_2$: C, 67.02; H, 6.19. Found: C, 66.72; H, 6.11.

3-(Phenylthio)-7-octene-2,6-dione (23). *m*-Chloroperbenzoic acid (80%, 0.54 g, 2.51 mmol) in CH_2Cl_2 (30 mL) was added to a stirred solution of octanedione **27** (0.90 g, 2.5 mmol) in CH_2Cl_2 (40 mL) at 0 °C, and stirring was continued for 3 h at 0 °C and then for 2.5 h at room temperature. The mixture was treated with 10% aqueous sodium sulfite solution, and the water layer was extracted with CH_2Cl_2. The combined organic layers were washed with 10% aqueous sodium carbonate solution and then brine, dried over sodium sulfate, and concentrated to give 0.67 g of the residue: IR (neat) 1710, 1080, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20–1.56 (m, 3 H), 1.70–2.16 (m, 2 H), 2.33 (s, 3 H), 2.56–2.93 (m, 2 H), 3.50–4.03 (m, 2 H), 7.23–7.66 (m, 10 H). The residue (0.50 g) was dissolved in benzene (30 mL) and allowed to reflux for 7.5 h in the presence of calcium carbonate (0.15 g). After filtration, the mixture was concentrated and chromatographed on silica gel with hexane and hexane–benzene to give 0.25 g (54%) of **23**: IR (neat) 1710, 1680, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.77–2.33 (m, 2 H), 2.27 (s, 3 H), 2.77 (t, J = 6.8 Hz, 2 H), 3.72 (t, J = 7.0 Hz, 1 H), 5.60–6.37 (m, 3 H), 7.12–7.87 (m, 5 H); mass spectrum (70 eV), m/e 248 (M^+).

Registry No. 1, 13522-48-0; **2**, 19718-58-2; **7**, 83666-42-6; *cis*-**8**, 83666-43-7; *trans*-**8**, 83666-44-8; **9**, 83666-45-9; **10**, 83666-46-0; **11**, 20965-36-0; **12**, 83666-47-1; **13**, 83666-48-2; **14**, 83666-49-3; **15**, 83666-50-6; **16**, 77202-22-3; **17**, 83666-51-7; *cis*-**19**, 83666-52-8; *trans*-**19**, 83666-53-9; **20**, 83220-31-9; **21**, 83666-54-0; **23**, 83666-55-1; **24**, 19718-59-3; **25a**, 83666-56-2; **26**, 83666-57-3; **27**, 83666-58-4; ethyl vinyl ether, 109-92-2; 2,3-dihydrofuran, 1191-99-7; 3,4-dihydro-2*H*-pyran, 110-87-2; butyl vinyl sulfide, 4789-70-2; 1-morpholino-1-cyclohexene, 670-80-4; pyrrole, 109-97-7.

Synthesis of Adamantane Derivatives. 60.[1] Stereospecific Synthesis of 2,4 Amino Alcohol Derivatives of Noradamantane, Protoadamantane, and Adamantane via Bicycloalkenylnitrones

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The intramolecular 1,3-dipolar cycloadditions of *C*-bicycloalkenylnitrones **3**, **9**, and **17** generated in situ from the aldehydes **1**, **8**, and **16** and hydroxylamines proceeded smoothly at 25–80 °C, affording 2,4-(epoxyimino)-noradamantane (**4**), 2,4-(epoxyimino)protoadamantane (**10**), and 4,2-(epoxyimino)protoadamantane (**18**) and 2,4-(epoxyimino)adamantane (**19**), respectively, in good yields. These adducts were reductively cleaved to give the corresponding amino alcohol derivatives **5**, **6**, **11**, **13**, **15**, **20**, and **21**. Novel thermal cleavage of **19a** and **19b** and hydrogen abstractions from the solvent yielded also directly amino alcohols **20a** and **20b**. The regiochemistry of cycloaddition of **17** was discussed on the basis of N-substituent effects and solvent effects on the product ratios.

The use of intramolecular 1,3-dipolar cycloadditions in organic synthesis has developed quite rapidly in recent years.[2] In particular, the use of nitrones has been explored extensively for regio- and stereoselective synthesis of functionalized carbo- and heterocycles as well as natural products such as alkaloids since the pioneering work of LeBel and co-workers on acyclic and monocyclic alkenylnitrones.[3-6] In this paper, we report a convenient stereospecific synthesis of 2,4-disubstituted noradamantane, protoadamantane, and adamantane derivatives based on *C*-bicycloalkenylnitrones.[7,8]

Results and Discussions

2-*endo*-Hydroxy-4-*endo*-(benzylamino)noradamantane (5) and Related Derivatives from *C*-*endo*-Bicyclo[3.2.1]oct-6-en-3-ylnitrone (3). The nitrone **3**, containing a symmetrical olefin, was generated in situ by stirring *endo*-bicyclo[3.2.1]oct-6-ene-3-carbox-

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(2) For recent reviews, see: (a) Padwa, A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 123. (b) Oppolzer, W. *Ibid.* **1977**, *16*, 10.

(3) For general reviews on nitrone cycloadditions, see: (a) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565, 633. (b) Hamer, J.; Macluso, A. *Chem. Rev.* **1964**, *64*, 473. (c) Black, D. St. C.; Crozier, R. F.; Davis, V. C. *Synthesis* **1975**, 205.

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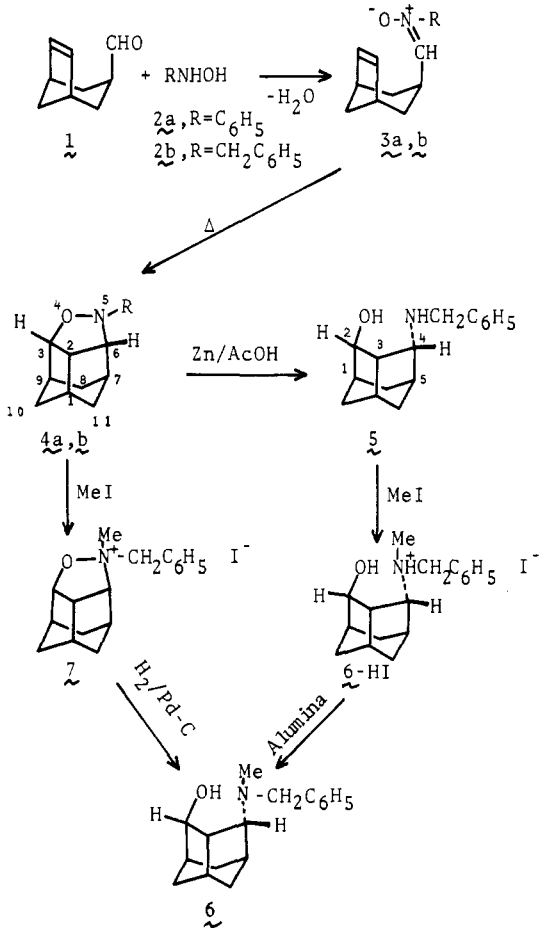
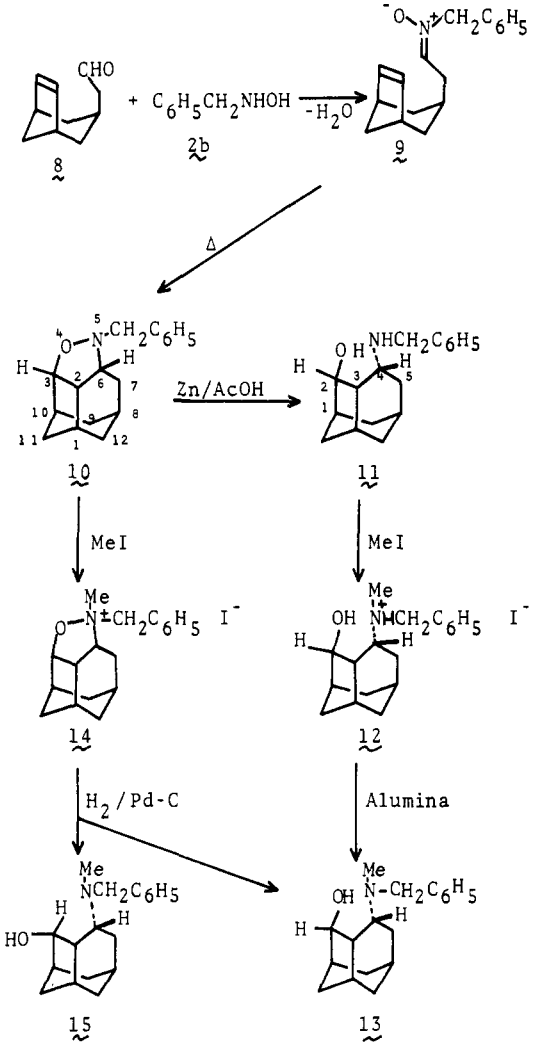
0022-3263/82/1947-5250$01.25/0

Scheme I



Scheme II



aldehyde (**1**)[9] and an appropriate hydroxylamine **2** in the presence of molecular sieves in benzene or toluene (Scheme I). The reaction of **1** with phenylhydroxylamine (**2a**) in benzene for 2 days at 20–25 °C afforded directly intramolecular cycloadduct **4a** (44%) after chromatography. The ^1H NMR spectrum of **4a** exhibited characteristic signals at δ 4.88 (dd, J = 7.5, 4.5, Hz, H_3), 4.3–4.0 (m, H_6), and 2.96 (q, J = 6.0 Hz, H_2) assignable to isoxazolidine ring protons (for numbering of **4a**, see the structure shown in Scheme I),[10] and hence, **4a** was assigned as 5-phenyl-4-oxa-5-azatetracyclo[5.3.1.$0^{2,6}$.$0^{3,9}$]undecane (or trivial *N*-phenyl-2,4-(epoxyimino)noradamantane). The reaction of **1** with benzylhydroxylamine (**2b**) in benzene (2 days at 20–25 °C) or in toluene (10 h under reflux) gave the corresponding adduct **4b** in 87% and 80% yield, respectively. The reductive cleavage of **4b** with zinc–acetic acid[11] afforded 2-*endo*-hydroxy-4-*endo*-(benzylamino)noradamantane (**5**) in 89% yield. The *N*-methyl derivative **6** was obtained either by methylation of **5** or by reductive cleavage of methiodide **7** (Scheme I).

It is of interest that these intramolecular cycloadditions of **3** proceed under very mild conditions: this could be ascribable to entropic assistance because such a factor is clearly more effective for the relatively rigid bicycloalkenyl system than the corresponding acyclic and monocyclic alkenyl systems.[2] Furthermore, these reactions of **1** provide a convenient route to 2,4-disubstituted noradamantane derivatives, which are difficult to obtain otherwise.[12,13]

2-*endo*-Hydroxy-4-*endo*-(benzylamino)protoadamantane (11) and Related Derivatives from *C*-(*endo*-Bicyclo[3.2.1]oct-6-en-3-ylmethyl)-*N*-benzylnitrone (9). The required aldehyde **8** was prepared by *N*-chlorosuccinimide–dimethyl sulfide oxidation[14] of known 2-(*endo*-bicyclo[3.2.1]oct-6-en-3-yl)ethanol.[15] The nitrone **9** was generated similarly as above from **8** and benzylhydroxylamine in benzene and heated for 11 h under reflux to afford an intramolecular cycloadduct **10** in a good yield of 92%. Compound **10** exhibited characteristic ^1H NMR signals at δ 4.85 (dd, J = 9.0, 4.5 Hz, H_3) and 3.6–3.0 (m, H_2 and H_6), supporting the given 4-oxa-5-azatetracyclo[6.3.1.$0^{2,6}$.$0^{3,10}$]dodecane (or 2,4-(epoxyimino)protoadamantane) structure (Scheme II). Usual reductive cleavage of **10** with Zn–AcOH at 50–60 °C gave the corresponding amino alcohol **11** (86%), from which methylation afforded **13**. The adduct **10** gave methiodide **14**, which was reductively cleaved on catalytic hydrogenation (Pd–C) to afford **13** (58%) also but accompanied with a small amount of an epimeric amino alcohol **15** (14%).

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(11) (a) Reference 4a. (b) For a general review on chemical properties of isoxazolidines, see ref 10, pp 241–247.
(12) For functionalization of noradamantane by diazo ketone derivatives, see: Godleski, S. A.; Schleyer, P. v. R.; Ōsawa, E.; Inamoto, Y.; Fujikura, Y. *J. Org. Chem.* **1976**, *41*, 2596.
(13) For 2,4-difunctionalization of noradamantane by cyclopropane ring cleavages of 2,4-dehydronoradamantane (trivial triaxane), see: Covey, D. F.; Nickon, A. *J. Org. Chem.* **1977**, *42*, 794.
(14) Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586.
(15) Spurlock, L. A.; Clark, K. P. *J. Am. Chem. Soc.* **1972**, *94*, 5349.

Table I. Intramolecular Cycloaddition of *endo*-Bicyclo[3.3.1]non-6-en-3-yl Nitrones (17a-e)[a]

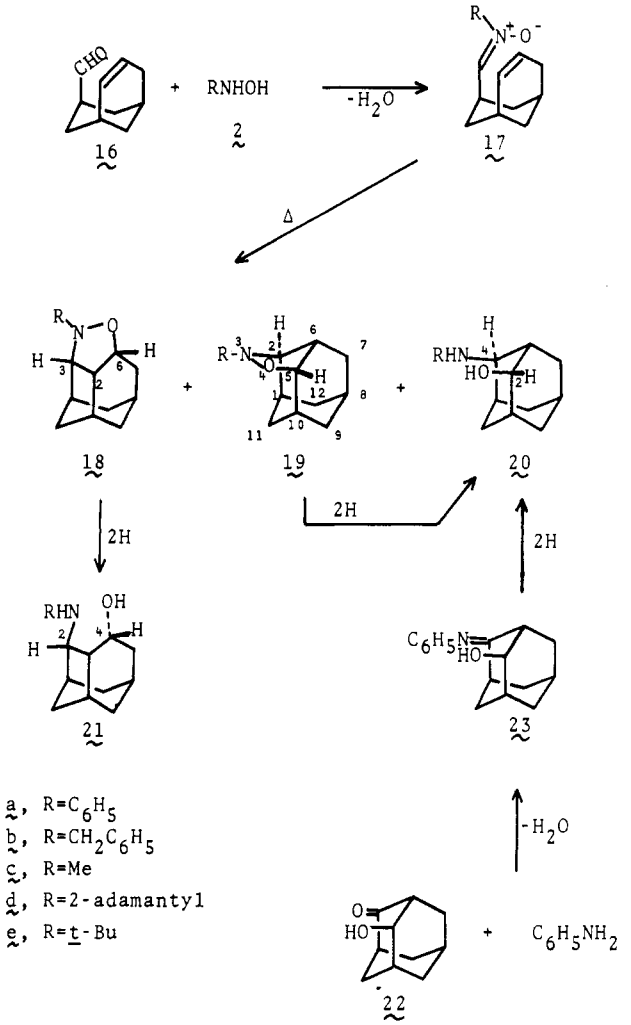
nitrone	substituent	solvent	react condns: temp, °C	react condns: time, h	products (yield, %)[b]	total yield, %	(19 + 20)/18
17a	Ph	C_6H_6	rt[c]	12	**18a** (17) **19a** (39) **20a** (1)	57	2.4
		EtOH	rt[c]	10	**18a** (6) **19a** (37) **20a** (5)	48	7.0
		Me_2SO	rt[c]	20	**18a** (23) **19a** (40) **20a** (4)	67	2.0
17b	$PhCH_2$	C_6H_6	70	10	**18b** (38) **19b** (20) **20b** (8)	66	0.74
		EtOH	70	10	**18b** (19) **19b** (2) **20b** (32)	53	1.8
17c	Me	C_6H_6	70	41	**18c** (29) **19c** (25) **20c** (0)	54	0.86
		EtOH	70	24	**18c** (14) **19c** (20) **20c** (0)	34	1.4
		Me_2SO	70	10	**18c** (12) **19c** (31) **20c** (0)	33	2.6
17d	2-adamantyl	C_6H_6	80	10	**18d** (40) **19d** (30) **20d** (0)	70	0.75
		EtOH	80	15	**18d** (13) **19d** (30) **20d** (0)	43	2.3
17e	Me_3C	C_6H_6	80	15	**18e** (35) **19e** (14) **20e** (0)	49	0.40
		EtOH	80	15	**18e** (10) **19e** (10) **20e** (0)	20	1.0
		Me_2SO	80	10	**18e** (18) **19e** (12) **20e** (0)	30	0.67

[a] For generation of 17a-e and product isolation, see Experimental Section. [b] Isolated yields. [c] 20-25 °C.

Such a novel epimerization seems to be unprecedented, and the mechanism remains to be clarified.[16] The stereochemical assignments of C_2OH of **13** and **15** were based on the ^1H NMR coupling patterns: C_2H of **13** (*endo*-OH) appeared as a characteristic doublet of doublets similar to the adduct **10**, while C_2H of **15** (*exo*-OH) appeared as a singlet.[17]

2-*endo*-Amino-4-*endo*-hydroxyprotoadamantanes (21) and 2(a)-Hydroxy-4(a)-aminoadamantanes (20) from *C*-*endo*-Bicyclo[3.3.1]non-6-en-3-ylnitrones (17). The nitrone **17** was generated in situ by condensation of *endo*-bicyclo[3.3.1]non-6-ene-3-carboxaldehyde (**16**)[18] with hydroxylamines **2a-e** in benzene, ethanol, or dimethyl sulfoxide. The cycloaddition results are summarized in Table I and Scheme III. The *N*-phenylnitrone **17a** in benzene afforded 4-phenyl-4-aza-5-oxatetracyclo-[6.3.1.$0^{2,6}$.$0^{3,10}$]dodecane (i.e., *N*-phenyl-4,2-(epoxyimino)-protoadamantane, **18a**), 3-phenyl-3-aza-4-oxatetracyclo-[6.3.1.$0^{2,6}$.$0^{5,10}$]dodecane (i.e., *N*-phenyl-2,4-(epoxyimino)-adamantane, **19a**), and 2(a)-hydroxy-4(a)-(phenylamino)-adamantane (**20a**) in 17%, 39%, and 1% yields, respectively, after chromatography. The yields of **18a**, **19a**, and **20a** depended clearly on the solvent used (Table I). The structural assignments of these products were based on NMR spectroscopy, on their reduction products, and on comparison with an authentic sample for **20a**. In ^1H NMR spectra, adduct **18a** had characteristic signals at δ 4.28 (br unsym t, J = 7.5 Hz, H_4) and 3.78 (dd, $J_{3,2}$ = 10.1, $J_{3,10}$ = 5.3 Hz, H_3), while **19a** showed δ 4.34 (t, J = 5.0 Hz, H_5) and 3.67 (t, J = 4.8 Hz, H_2) and **20a** showed δ 3.83 (br s, H_4) and 3.50 (br s, H_2), respectively, due to CH protons adjacent to O and N of the isoxazolidine ring or amino alcohol. Reductive cleavages of **18a** and **19a** afforded 2-*endo*-(phenylamino)-4-*endo*-hydroxyprotoadamantane (**21a**) and **20a**, respectively. ^1H NMR spectrum of **21a** revealed characteristic signals at δ 4.2–3.8 (m, H_4) and 3.68 (dd, $J_{2,3}$ = 9.0, $J_{2,1}$ = 3.8 Hz, H_2), which were compatible with those of **11** and **13**.[17] In order to confirm the given skeletal integrity, we independently prepared **20a** by $NaBH_3CN$ reduction of the Schiff base **23** derived from 4(a)-hydroxyadamantan-2-one (**22**)[19] and aniline (Scheme III). The amino alcohol obtained (50%) after chromatography was identical with **20a** by IR and ^1H NMR comparisons, supporting the regio- and stereochemical assignments of **18a–21a**.

Scheme III



The cycloaddition of *N*-benzylnitrone **17b** in benzene proceeded at 70 °C to afford **18b**, **19b**, and **20b** in 38%, 20%, and 8% yields, respectively (Table I). The same reaction in EtOH increased considerably the yield of amino alcohol **20b**. Because there seems to be no precedents of such facile thermal reductive cleavage of isoxazolidines,[11b] **18b** and **19b** were independently heated to reflux in toluene for 10 h: **18b** remained unchanged, while **19b** was converted to **20b** in a yield of 75% as expected. The

(16) Compound **13** was not epimerized to **15** under the hydrogenolysis conditions (EtOH–concentrated HCl), indicating that **15** was produced competitively with **13**. For examples of deaminative and dehydrative hydrogenolyses of isoxazolidines, see ref 10, pp 243–244 and references cited therein.

(17) For ^1H NMR data of protoadamantane derivatives, see: (a) Lenoir, D.; Hall, R. E., Schleyer, P. V. R. *J. Am. Chem. Soc.* **1974**, *96*, 2138. (b) Murray, R. K., Jr.; Morgan, T. K., Jr. *J. Org. Chem.* **1975**, *40*, 2642. (c) Sasaki, T.; Eguchi, S.; Suzuki, T. *Ibid.* **1980**, *45*, 3824.

(18) Sasaki, T.; Eguchi, S.; Toru, T. *J. Org. Chem.* **1971**, *36*, 3460.

(19) Faulkner, D.; McKervey, M. A. *J. Chem. Soc. C* **1971**, 3906.

Table II. ^{13}C NMR Chemical Shifts (δ) of the Nitrone Cycloadducts 4b, 10, 18a, 18e, 19a, and 19e[a,b]

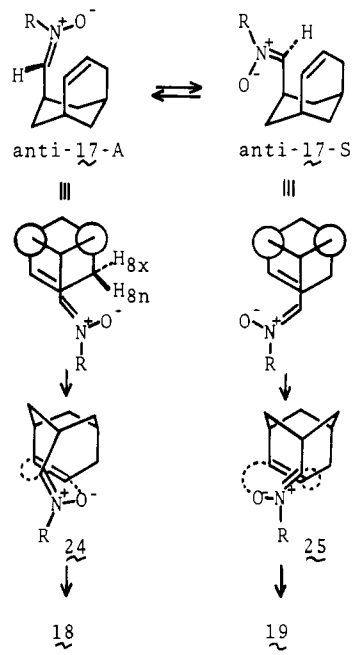
compd	4b	10	18a	18e	19a	19e
isoxazolidine carbons	88.1[c]	86.9[c]	75.2[c]	70.9[c]	80.0[c]	79.6[c]
	74.1[d]	56.2[d]	71.9[d]	68.1[d]	69.8[d]	60.1[d]
	48.7[e]	47.4[e]	49.9[e]	50.4[e]	39.9[e,f]	40.1[e,f]
other ring carbons	40.0[g]	42.0[g]	42.9[g]	43.1[g]	35.0[g]	35.3[g]
	39.4[h]	39.9[g]	39.9[g]	40.2[g]	33.9[g]	34.4[g]
	38.7[h]	36.8[h]	38.8[h]	39.0[h]	33.3[h]	34.0[h]
	38.3[g]	34.7[g]	34.2[g]	34.4[g]	33.1[g]	33.8[h]
	36.0[h]	31.1[g]	31.9[g]	32.0[g]	32.4[h]	33.2[g]
	30.1[g]	30.3[h]	29.9[h]	30.2[h]	31.5[g]	32.0[g]
		29.1[h]	29.0[h]	29.2[h]	25.2[h]	25.2[h]
substituent carbons	137.7[i]	137.8[i]	150.8[i]	56.3[n]	152.8[i]	58.1[n]
	129.2[j]	129.1[j]	128.6[j]	25.7[k]	128.4[j]	27.2[k]
	128.3[j]	127.2[j]	120.0[l]		121.4[l]	
	127.2[l]	126.8[l]	113.3[j]		115.9[j]	
	64.3[m]	59.6[m]				

[a] Downfield from internal Me_4Si in $CDCl_3$. [b] The assignments were based on the chemical shifts, peak intensities, and proton off-resonance spectral data. [c] d (1 C) and assignable to carbon ($C_{5'}$ of isoxazolidine) adjacent to O atom. [d] d (1 C) and assignable to carbon ($C_{3'}$ of isoxazolidine) adjacent to N atom. [e] d (1 C) and assignable to $C_{4'}$ of isoxazolidine. [f] The assignment should be considered as tentative. [g] t (1 C). [h] d (1 C). [i] s (1 C) and assignable to phenyl $C_{1''}$. [j] d (2 C) and assignable to phenyl carbons. [k] q (3 C) due to Me of *t*-Bu. [l] d (1 C) due to phenyl $C_{4''}$. [m] t (1 C) due to benzylic carbon. [n] s (1 C) due to quaternary carbon of *t*-Bu.

formation of **20b** from **19b** under these conditions could be explained by a homolytic N–O bond cleavage, followed by H abstraction from the solvent. Such process should be facilitated by heating at higher temperature and by the presence of better H-donor solvents like toluene and ethanol. The N–O bond of **19a** and **19b** is weaked, presumably by the rigidity of the adamantane moiety and by the presence of electron-withdrawing substituents on nitrogen. The electron-donating substituents such as methyl, 2-adamantyl, and *tert*-butyl stabilize the N–O bond of **19** as shown by no formation of **20c–e** in the cycloadditions of **17c–e**, which gave the cycloadducts **18c–e** and **19c–e** in ratios dependent on the solvent used (Table I). The reductive cleavage of all of these adducts **18** and **19** afforded the corresponding amino alcohols **21** and **20** in good yields (Scheme III).

It may be apropos to consider here the regioselectivity of intramolecular cycloadditions of the nitrone **17**. We presume that the intramolecular cycloadditions were controlled kinetically because adduct formation occurs at relatively low temperature (25–80 °C). In fact, no interconversions of the adducts **18d** and **19d**, and **18e** and **19e**, were observed on heating at 80 °C for 15 h in either benzene or EtOH. It is well-known that the regiochemistry of intramolecular nitrone cycloadditions is controlled mainly by specific steric constraints for the cyclic transition states and by entropic factors[2,3c,4,5,20] rather than the usual electronic factors, (HOMO–LUMO interactions).[21] Inspection of stereomodels indicates that conformers A and S of an *anti*-**17** can interact to form cyclic transition states **24** and **25** corresponding to the adduct **18** and **19**, respectively, while any conformers of a syn-isomer **17** can not lead to the orbital overlap between olefin and 1,3-dipole due to the geometrical constraint (Scheme IV). For a better overlap of the 1,3-dipole, A suffers from a slight distortion of the bicyclononane ring (**24**), and for an ideal parallel and simultaneous overlap of the 1,3-dipole, S suffers from a geometrical constraint (**25**). Hence, there seems to be no large difference in steric constraints between **24** and **25**, and both regioisomers **18** and **19** can be produced in comparable ratios in benzene. The regioselective formation of **19** (and **20**) in polar solvents (EtOH and/or Me_2SO) is noteworthy, however: this could be rationalized in terms of the differences in conformational populations. The conformer S is favorable in polar solvents because of an increased steric repulsion between H_{8n} and the solvated dipole oxygen for the conformer A, thus leading to a preferential formation of the adduct **19**.[23] The

Scheme IV



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(21) For frontier molecular orbital theory of 1,3-dipolar cycloadditions, see: (a) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361. (b) Houk, K. N.; Sims, J.; Duke, R. E., Jr.; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 7287. (c) Houk, K. N.; Sims, J.; Watt, C. R.; Luskus, L. J. *Ibid.* **1973**, *95*, 7301. (d) For a recent review, see: Fleming, I. "Frontier Orbitals and Organic Chemical Reactions"; Wiley: New York, 1976; pp 148–161.

(22) (a) For the importance of C–C bonding rather than C–O bonding at the transition state of intramolecular nitrone cycloadditions, see: LeBel, N. A.; Slusarczuk, G. M. J.; Spurlock, L. A. *J. Am. Chem. Soc.* **1962**, *84*, 4360. Reference 20 and references cited therein. (b) Different results for the formation of five- or six-membered carbocycles have been reported in related intramolecular nitrone–olefin cycloadditions: the regiochemistry seems to depend on the specific steric interactions involved in the cyclic transition states; cf. ref 5b and 20.

(23) It is well-known that solvent effects on nitrone cycloadditions as well as other 1,3-dipolar cycloadditions are very small. (a) Huisgen, R.; Seidl, H.; Brüning, I. *Chem. Ber.* **1969**, *102*, 1102. (b) Sims, J.; Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 5798. (c) For related mechanistic discussions, see: Huisgen, R. *J. Org. Chem.* **1968**, *33*, 2291; **1976**, *41*, 403. Cf. also: Firestone, R. A. *Ibid.* **1968**, *33*, 2285.

preferred formation of **19a** for the *N*-phenylnitrone **17a** even in benzene may be interpreted by the same conformational preference of S at the lower temperature like 25 °C and also by electronic factors.[24]

Finally, ^{13}C NMR spectral data of the nitrone cycloadducts **4b**, **10**, **18a**, **18e**, **19a**, and **19e** are discussed briefly since only a few ^{13}C chemical shifts of isoxazolidines have been recorded.[25,26] All of these cycloadducts had the corresponding carbon signals of correct multiplicities (Table II). The isoxazolidine carbons appeared at δ 70.9–88.1 (assignable to $C_{5'}$ of the isoxaxolidine), 56.2–74.1 (due to $C_{3'}$), and 37.9–50.4 (due to $C_{4'}$), respectively, indicating that the chemical shifts of isoxazolidine carbons depend notably on the tricyclic ring systems that embody the isoxazolidine ring, as well as on the usual substituent effects.

Experimental Section

Melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were obtained on a Jasco IRA-1 spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-6OHL instrument at 60 MHz and a JEOL JNM-60 FT NMR spectrometer at 15.04 MHz, respectively. Chemical shifts are reported in parts per million (δ) relative to Me_4Si as an internal standard, and coupling constants are in hertz. Mass spectra were obtained with a JEOL JMS-D10 mass spectrometer at 75 eV. Microanalyses were performed with a Perkin-Elmer 240B elemental analyzer.

5-Phenyl-4-oxa-5-azatetracyclo[5.3.1.$0^{2,6}$.$0^{3,9}$]undecane (4a). A mixture of the aldehyde **1**[9] (68 mg, 0.50 mmol), phenylhydroxylamine (**2a**), (66 mg, 0.60 mmol), and molecular sieves (type 4A, 0.5 g) in anhydrous benzene (5 mL) was stirred at 20–25 °C for 2 days. The molecular sieve was filtered by suction and washed with benzene. The combined filtrate and washings were evaporated to dryness to give crude product, which was purified on a silica gel (Kiesel gel 60) column eluting with *n*-hexane–ether to afford the adduct **4a** as a liquid (50 mg, 44.1%).

5-Benzyl-4-oxa-5-azatetracyclo[5.3.1.$0^{2,6}$.$0^{3,9}$]undecane (4b). A mixture of **1** (68 mg, 0.50 mmol), benzylhydroxylamine (**2b**) (74 mg, 0.60 mmol), and molecular sieves (0.5 g) in benzene (5 mL) was stirred at 20–25 °C for 2 days. The workup as above afforded the adduct **4b** as crystals (105 mg, 87.1%), mp 65–66 °C (from *n*-hexane). The same reaction in toluene under reflux for 10 h gave **4b** (97 mg, 80.4%).

2-*endo*-Hydroxy-4-*endo*-(benzylamino)noradamantane (5). To a vigorously stirred solution of the adduct **4b** (121 mg, 0.50 mmol) in 58% (v/v) aqueous acetic acid (1.2 mL) was added zinc dust (120 mg) at 50–60 °C. After the stirring was continued for 4 h, the mixture was basified with 20% aqueous potassium hydroxide under ice and extracted with chloroform (10 mL × 4). The combined extracts were washed with water and dried ($MgSO_4$). Evaporation of the solvent gave analytically pure amino alcohol **5** as colorless crystals (109 mg, 89.3%), mp 119–120 °C.

5-Methyl-5-benzyl-4-oxa-5-azoniatetracyclo[5.3.1.$0^{2,6}$.$0^{3,9}$]undecane Iodide (7). A mixture of **4b** (145 mg, 0.60 mmol) and methyl iodide (4.55 g, 32.1 mmol) in ether (5 mL) was allowed to stand at ambient temperature for 12 days. The precipitated crystals were filtered and washed with ether to afford the methiodide **7** (199 mg, 86.5%), mp 150 °C dec.

2-*endo*-Hydroxy-4-*endo*-(methylbenzylamino)noradamantane (6). (A) From 7. A mixture of **7** (172 mg, 0.45 mmol) and 10% Pd on carbon (100 mg) in ethanol (10 mL)–concentrated HCl (0.1 mL) was stirred under an atmosphere of hydrogen at 20–25 °C for 2 days. The catalyst was filtered through Celite and washed with ethanol. The combined filtrate and washings were evaporated to dryness to afford a solid residue, which was applied to an alumina column (MeOH–ether) to give the amino alcohol **6** as a crystalline solid (86 mg, 76.6%), mp 92–93 °C (MeOH–Et_2O).

(B) From 5. A solution of **5** (122 mg, 0.50 mmol) and methyl iodide (2.38 g, 16.1 mmol) in ether (15 mL) was allowed to stand at ambient temperature for 10 days. The resulting crystals were filtered and washed with ether to afford the HI salt of **6** (140 mg, 72.9%), mp 188–189 °C, which was applied to an alumina column (MeOH–ether) to give **6** as colorless crystals (60 mg, 46.6% from **5**).

(*endo*-Bicyclo[3.2.1]oct-6-en-3-yl)acetaldehyde (8). To an ice-cooled and stirred solution of *N*-chlorosuccinimide (1.32 g, 9.88 mmol) in toluene (30 mL) was added dimethyl sulfide (0.82 g, 13.2 mmol) slowly during 0.5 h. To the resulting mixture was added slowly a solution of 2-(*endo*-bicyclo[3.2.1]oct-6-en-3-yl)-ethanol[15] (912 mg, 6.00 mmol) in toluene (3.6 mL) at −25 °C with stirring. After the stirring was continued for 2 h, triethylamine (0.92 g, 9.1 mmol) in toluene (3.6 mL) was added to the mixture, and the temperature was allowed to come up to room temperature. The dilution with ether (45 mL) resulted in precipitates, which were filtered and washed with ether. The combined filtrate and washings were washed successively with 1% aqueous HCl, 1% aqueous $NaHCO_3$, and water and dried ($MgSO_4$). Removal of the solvent and chromatography (silica gel, *n*-hexane–ether) gave the aldehyde **8** as a liquid (575 mg, 63.9%): IR (neat) 3070, 2940, 2880, 2820, 2720, 1730, 1600, 1450, 1410, 1360, 1100, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.60 (s, 1), 6.05–5.80 (m, 2), 2.8–2.4 (m, 5), 2.2–1.0 (m, 6).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.92; H, 9.43.

5-Benzyl-4-oxa-5-azatetracyclo[6.3.1.$0^{2,6}$.$0^{3,10}$]dodecane (10). A mixture of the aldehyde **8** (75 mg, 0.50 mmol), benzylhydroxylamine (75 mg, 0.60 mmol), and molecular sieves (type 4A, 0.5 g) in benzene (5 mL) was heated to reflux under an atmosphere of argon for 11 h. Usual workup as above and chromatography on a silica gel column (*n*-hexane–ether) gave a liquid that solidified on standing and was washed with *n*-hexane to give the adduct **10** (118 mg, 92.4%), mp 55–56 °C.

2-*endo*-Hydroxy-4-*endo*-(benzylamino)protoadamantane (11). The adduct **10** (128 mg, 0.50 mmol) was reduced with zinc dust (120 mg) in 58% (v/v) aqueous acetic acid at 50–60 °C for 4 h. The usual workup as above with 20% aqueous KOH and extraction with chloroform followed by evaporation of the solvent afforded analytically pure amino alcohol **11** without further purification as crystals (110 mg, 85.6%), mp 85–86 °C (from $CHCl_3$).

2-*endo*-Hydroxy-4-*endo*-(methylbenzylamino)protoadamantane (13). A mixture of **11** (74 mg, 0.29 mmol) and methyl iodide (2.28 g, 16.1 mmol) in ether (5 mL) was allowed to stand for 85 h at ambient temperature. The resulting crystals were filtered and washed with ether to give the HI salt (**12**) of **13** (108 mg, 94.0%), mp 237–239 °C. **12** was applied to an alumina column (ether) to afford **13** as crystals (57 mg, 72.4% from **11**), mp 83–84 °C (ether).

5-Methyl-5-benzyl-4-oxa-5-azoniatetracyclo-[6.3.1.$0^{2,6}$.$0^{3,10}$]dodecane Iodide (14). Standing a solution of **10** (153 mg, 0.60 mmol) and methyl iodide (2.28 g, 16.1 mmol) in ether (5 mL) for 12 days at ambient temperature afforded crystalline precipitates, which were filtered and washed with ether to afford the methiodide **14** (160 mg, 67.2%), mp 170 °C dec.

Catalytic Hydrogenolysis of 14. A mixture of **14** (150 mg, 0.38 mmol) and 10% Pd on carbon (100 mg) in ethanol (4 mL)–concentrated HCl (0.15 mL) was stirred under an atmosphere of hydrogen at 20–25 °C for 2 days. After removal of the catalyst by filtration through Celite, the filtrate was evaporated to dryness to give a solid residue, which was applied to an alumina column eluting with *n*-hexane–ether. The first fraction gave **13** (60 mg,

(24) Qualitatively, **17a** should have a lower LUMO and a higher HOMO FMO than **17b–e** because of *N*-phenyl conjugation, and hence, with alkyl-substituted olefin, the nitrone LUMO–dipolarophile HOMO interaction becomes dominant, which favors the formation of **19a**. Cf.: Houk, K. N.; Bimanand, A.; Mukherjee, D.; Sims, J.; Chang, Y.-M.; Kaufman, D. C.; Domelsmith, L. N. *Heterocycles* **1977**, *7*, 293 and references cited therein.

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(26) For ^{13}C NMR of nonaromatic heterocyclic compounds, see: Eliel, E.; Pietrusiewicz, K. M. In "Topics in Carbon-13 NMR spectroscopy"; Levy, G. C., Ed.; Wiley: New York, 1979; Vol. 3, Chapter 3.

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(28) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

58.3%), which was identical with the sample obtained from 11 by mixed melting points, IR, and ^1H NMR comparisons. The second fraction gave 2-*exo*-hydroxy-4-*endo*-(methylbenzylamino)protoadamantane (**15**) as crystals (14 mg, 13.6%), mp 126–127 °C (MeOH–ether).

***endo*-Bicyclo[3.3.1]non-6-ene-3-carboxaldehyde (16).** This aldehyde **16** was previously reported by us.[18] The following improved procedure raised the yield to 82% from 53%. To a cooled (−10 to −15 °C) and stirred solution of $NaBH_4$ (110 mg, 2.91 mmol) in methanol (20 mL) and water (5 mL) was added 4(e)-(methylsulfonoxy)adamantan-2-one[27] (1.00 g, 4.00 mmol). After the stirring was continued for 2 h (the reaction was monitored by TLC, silica gel–$CHCl_3$), the remaining $NaBH_4$ was decomposed by addition of acetic acid (0.5 mL). The reaction temperature was allowed to come up to room temperature, and the mixture was concentrated to ca. 10 mL under reduced pressure. After addition of 1% aqueous $NaHCO_3$ (30 mL) and ether (20 mL), the two-phase mixture was heated under reflux for 2 h. After cooling, the organic layer was separated, and the aqueous layer was extracted with ether (10 mL × 2). The combined organic layer and extracts were dried (Na_2SO_4) and evaporated to give crude aldehyde, which was chromatographed on a silica gel column (CH_2Cl_2) to afford the aldehyde **16** as a colorless solid (495 mg, 82.4%), mp 185–188 °C (lit.[18] oil).

General Procedure for Generation and Cycloaddition of *endo*-Bicyclo[3.3.1]non-6-en-3-ylnitrones (17a–e). A mixture of the aldehyde **16** (150 mg, 1.00 mmol), an appropriate hydroxylamine (**2a–e**, 1.10 mmol; for **2c** and **2d**, the hydrochlorides were freed with Et_3N before use) and a molecular sieve (type 4A or 3A, 0.5 g) was stirred in a selected solvent (3 mL). The intramolecular cycloaddition of thus generated nitrones **17a–e** proceeded at 25–80 °C. The molecular sieve was filtered and washed with the solvent used. The combined filtrate and washings were evaporated to dryness to give a crude product, which was purified by chromatography on a silica gel and/or an alumina column (*n*-hexane–CH_2Cl_2–MeOH system). The reaction conditions and results are summarized in Table I. The products had the following melting points: **18a**, 84–85 °C (*n*-hexane); **19a**, 57–58 °C (*n*-hexane); **20a**, 97–98 °C (*n*-hexane–CH_2Cl_2); **18b**, oil; 19b, oil; **20b**, 111–112 °C (*n*-hexane-CH_2Cl_2); **18c**, oil; **19c**, oil; **18d**, 155–156 °C (*n*-hexane–CH_2Cl_2); **19d**, 179–180 °C (*n*-hexane–CH_2Cl_2); **18e**, 72–74 °C (ether); **19e**, 46–48 °C (sublimed at 100–120 °C (15 mmHg)). The spectral and analytical data are given in Tables II and III.

General Procedures for Reductive Cleavage of 4-Aza-5-oxatetracyclo[6.3.1.$0^{2,6}$.$0^{3,10}$]dodecane (18a-e) and 3-Aza-4-oxatetracyclo[6.3.1.$0^{2,6}$.$0^{5,10}$]dodecane (19a-e). (A) With H_2–Pd–C. The adduct **18a** (40 mg, 0.17 mmol) was hydrogenated in methanol (5 mL) with 10% Pd–C (90 mg) under an atmosphere of hydrogen for 3 h at room temperature. The usual workup after removal of the catalyst through Celite and chromatography (alumina, CH_2Cl_2) gave the amino alcohol **21a** as a colorless oil (24 mg, 58%). Similarly **19a** gave **20a** (26 mg, 62%).

(B) With Zinc–AcOH. The adduct **18b** (28 mg, 0.11 mmol) was stirred with zinc dust (30 mg) in 58% (v/v) aqueous AcOH (1.2 mL) at 50–60 °C for 2 h. The usual workup with 20% aqueous KOH and extraction with $CHCl_3$ gave the amino alcohol **21b** after chromatography (silica gel–CH_2Cl_2) as a colorless oil (18 mg, 64%).

(C) With H_2–PtO_2. The adduct (**18c–e** and **19c–e**, 0.20 mmol) was hydrogenated in ethanol (2 mL) and AcOH (0.5 mL) under an atmosphere of hydrogen for 3–24 h at room temperature by using PtO_2 (10–20 mg) as the catalyst. After removal of the catalyst by filtration through Celite, the filtrate was evaporated to dryness to give a residue which was applied to chromatography (alumina, CH_2Cl_2–AcOEt) to afford the corresponding amino alcohols: **21c** as an oil (75.0%), HCl salt, mp 277–278 °C; **20c** as an oil (79.3%), HCl salt, mp 272–275 °C; **21d** (91.4%), mp 133–135 °C (*n*-hexane–ether); **20d** (87.3%), mp 181–183 °C (*n*-hexane–ether); **21e** (69.5%), mp 81–82 °C (*n*-hexane–CH_2Cl_2); **20e** (72.2%), mp 79–81 °C (*n*-hexane–CH_2Cl_2).

(D) Thermal Reductive Cleavage. A solution of **19b** (8 mg) in toluene (2 mL) was heated at 120 °C for 10 h in a sealed tube under an atmosphere of argon. Removal of the solvent and chromatography (alumina, $CHCl_3$) gave the amino alcohol **20b** (6 mg, 75%). The spectral and analytical data of these amino alcohols are given in Tables II and III.

2(a)-Hydroxy-4(a)-(phenylamino)adamantane (20a) from 2(a)-Hydroxyadamantan-2-one (22). A mixture of **22**[19] (84 mg, 0.50 mmol), aniline (465 mg, 5.00 mmol), and $NaBH_3CN$ (32 mg, 0.50 mmol) in methanol (5 mL) was stirred at room temperature for 3 days at pH ca. 3 (the pH was controlled by addition of MeOH–concentrated HCl (1:1).[28] The basified mixture by addition of 20% aqueous KOH was extracted with CH_2Cl_2 (8 mL × 5). The combined extracts were dried ($MgSO_4$) and evaporated to afford a solid residue, which was chromatographed (silica gel, CH_2Cl_2–MeOH) to afford the amino alcohol **20a** (61 mg, 50.2%). This sample was identical with those obtained from the cycloaddition of **17a** and the reductive cleavage of **19a** by IR and ^1H NMR comparisons.

Supplementary Material Available: IR, ^1H NMR, and mass spectral and analytical data of the nitrone cycloadducts **3**, **9**, and **17** and related amino alcohols (Table III) (4 pages). Ordering information is given on any current masthead page.

Sulfurization of 2-Aminobenzotrifluoride with Sodium Sulfide

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Sodium sulfide in dimethyl sulfoxide reacts with 2-aminobenzotrifluoride to form 2-(2-aminophenyl)-4*H*-3,1-benzothiazine-4-thione and 2,1-benzisothiazoline-3-thione. The addition of CS_2 gave 2*H*-3,1-benzothiazine-2,4(1*H*)-dithione. N-Substituted 2-aminobenzotrifluorides gave the corresponding substituted 2,1-benzisothiazoline-3-thiones. The reaction conditions and possible mechanism are discussed.

Aromatic trifluoromethyl groups, activated by electron-donating moieties such as amino or hydroxyl, have been shown to undergo hydrolysis with aqueous sodium hydroxide to form the corresponding carboxylic acids.[1] More recently,[2] there have been reports of reactions of aromatic trifluoromethyl groups with oxygen and nitrogen nucleophiles. These reports have prompted us to describe the reactions we have observed involving 2-aminobenzotrifluorides with sodium sulfide.

When 2-aminobenzotrifluoride (**1a**), was treated with sodium sulfide in refluxing Me_2SO, a red solution was formed with the disappearance of **1a** (Scheme I). Upon acidification, a red, highly crystalline solid, mp 153–154 °C, was obtained. Spectral data suggested that instead

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