posed decomposition pathway is depicted in Scheme II.

Melting points were obtained on a Mel-Temp capillary apparatus and were uncorrected. The ^1H and ^{13}C NMR spectra of a approximately 10% (w/v) solution in $CDCl_3$ were obtained on a Bruker Spectrospin Model WM 250 or AM 250 or on a Nicolet QE 300 instrument. Precise mass spectra were recorded by using a Du Pont 21-492B instrument with a resolution of 3300 or 5000. Baker silica gel (60-200 mesh) was routinely used throughout for product separation. Eastman Chromagram (silica gel with a fluorescent indicator on polyethylene) precoated sheets were employed in thin-layer chromatographic (TLC) operations.

Preparation of Intermediate Product 6. General Procedure. Purified monosubstituted or disubstituted maleic anhydride **5**, or the Diels-Alder adduct of maleic anhydride and furan **5a** (4 mmol), was added, all at once, to a slurry of phosphorane ylide 1 (3 mmol) in dry toluene (50 mL). The mixture was stirred under room temperature (for **6a,b,m**) or under reflux (for **6c-g,o,p**) for 15 to 24 h. Then the mixture was chromatographically separated with diethyl ether-petroleum ether as eluent (ratio range: 1:9 to 1:4). The crude product was purified by recrystallization from diethyl ether. The pure product **6** was obtained as yellow crystals. TLC showed one spot. The results are reported in Table I.

Preparation of *Z* and *E* Isomers of Ylidene 6d. Sublimed 2,3-dimethylmaleic anhydride **5** (0.4 g, 3.2 mmol) was added, all at once, to a slurry of phosphorane 1 with R = Et (0.8 g, 1.8 mmol) in 30 mL of dry toluene. The mixture was stirred at 80 °C for 15 h. After being cooled down to room temperature, the mixture was chromatographically separated (petroleum ether-diethyl ether, only petroleum ether used at the beginning and 4:1 at the end). The solution was allowed to stand until two isomers of ylidene **6d** crystallized from the eluent. The total yield of the isomers was 75%, and the ratio of *E* form to *Z* form was 2.4:1. ^1H NMR ($CDCl_3$, TMS as internal standard) for the mixture of *Z* and *E* forms: 1.08 (t, J = 7.6 Hz, CH_2CH_3), 1.96 (s, C3-CH_3), 1.98 (s, C3-CH_3), 2.06, 2.05 (ds, C4-CH_3), 2.15, 2.14 (ds, C4-CH_3), 2.36 (s, C7-CH_3), 2.51 (s, C-7CH_3), 2.78, (q, J = 7.6 Hz, CH_2CH_3), 2.86 (q, J = 7.6 Hz, CH_2CH_3), 6.01 (s, C6-H), 6.43 (s, C6-H), 7.42-7.90 (m, all Ar-H for two isomers) ppm.

Thermal Rearrangement of Ylidene 6 into Bicyclic Product 9 in Solution. General Procedure. The pure sample **6** (200 mg) was dissolved in dry xylene (50 mL). The solution was heated under reflux with vigorous stirring for 15 to 48 h. After cooling down to room temperature, the solvent was removed on a rotary evaporator. The residue was dissolved in CH_2Cl_2 (1 mL) and then separated on a chromatographic column with diethyl ether-petroleum ether as eluent (1:4). The pure product recrystallized from diethyl ether was obtained as white crystals. TLC showed one spot. The results are reported in Table I.

Thermal Rearrangement of Ylidene 6e, Neat (6f and 6g). The pure sample (100 mg) was placed in a subliming tube and was heated to 200 °C in a sand bath under vacuum for 0.5 h. After being cooled down to room temperature, the sample was dissolved in CH_2Cl_2 (5 mL). Chromatogrpahy of the solution with diethyl ether-petroleum ether as eluent (1:3) gave the pure product, which was collected and recrystallized from diethyl ether as white crystals. TLC showed one spot. The results are reported in Table I.

Measurement of Rearrangement and Decomposition Temperature for Ylidenes 6h and 6p. The differential thermal analysis was undertaken on a Mettler 200 differential thermal analyzer. The heat capacity of the sample was measured. The scanning was done with about a 2-mg sample in a scaled aluminum pan. The scanning speed was 5° per min. The scanning range was 50 to 300 °C. The instrument was calibrated with benzoic acid and indium metal.

Measurement of NOE Difference for the *E* and *Z* Isomers of Ylidene 6d. NOE difference experiments were obtained on a Bruker AM 250 NMR spectrophotometer. A total of 64 to 128 scans were accumulated for both the on-resonance and off-resonance spectra. The irradiation time was 5 s, the relaxation delay was 2 s, and the acquisition time was 2.3 s for each scan. The decoupler power employed was the minimum power required to completely saturate the C6-H resonance for each isomer without affecting the neighboring resonance.

Crystallographic Structural Determination for 9i. The structure of **9i** was obtained at ambient temperatures (22-24 °C) with a Nicolet R3m diffractometer. All software is contained in the SHELXTL (5.1) software package (G. Sheldrick, Nicolet XRD, Madison, WI). Crystal data for $C_{19}H_{22}N_2O_2$: triclinic, $P\bar{1}$, a = 7.826 (3) Å, b = 9.427 (5) Å, c = 12.183 (6) Å, α = 77.54 (4)°, β = 86.56 (3)°, γ = 72.02 (3)°, V = 834.9 (7) Å^3, Z = 2, μ(Mo Kα) = 0.75 cm^{-1}, D(calcd) = 1.234 g/cm^3. Data were collected (Nicolet R3m, $2\theta_{max}$ = 46°) yielding 1895 independent observed reflections $F_o > 3\sigma(F_o)$. No absorption correction was applied (low μ, well-shaped crystal). All non-hydrogen atoms were refined anisotropically, while all hydrogen atoms were found and refined isotropically. $R(F)$ = 4.48%, $R(wF)$ = 4.87%, GOF = 1.194, $\Delta(\rho)$ = 0.156 e Å^{-3}; Δ/σ = 0.020, and N_o/N_v = 6.4. Tables of atomic coordinates, bond distances and angles, and anisotropic temperature coefficients are available as supplementary material.

Registry No. **1a**, 87101-43-7; **1b**, 87101-42-6; **1d**, 107353-13-9; **1h**, 129467-93-2; **1i**, 125229-36-9; **1o**, 63570-25-2; **5a**, 5426-09-5; **5c**, 766-39-2; **5f**, 4808-48-4; **5m**, 616-02-4; **6a**, 129467-94-3; **6b**, 129467-95-4; **6c**, 129467-94-3; **6d**, 129467-96-5; **6e**, 129467-97-6; **6f**, 129467-98-7; **6g**, 129467-99-8; **6h**, 129468-00-4; **6i**, 129468-01-5; **6j**, 129468-02-6; **6k**, 129468-03-7; **6l**, 129468-04-8; **6m**, 129468-05-9; **6o**, 129468-06-0; **6p**, 129468-07-1; **9a**, 129468-08-2; **9b**, 129468-09-3; **9c**, 129468-10-6; **9d**, 129468-11-7; **9e**, 129468-12-8; **9f**, 129468-13-9; **9g**, 129468-14-0; **9h**, 129468-15-1; **9i**, 129468-16-2; **9j**, 129468-17-3; **9k**, 129468-18-4; **9l**, 129468-19-5.

Supplementary Material Available: Tables of atomic coordinates, isotropic thermal parameters, bond distances and angles, and X-ray crystallographic data for **9i** (7 pages). Ordering information is given on any current masthead page.

Versatile Methods for the Synthesis of Differentially Functionalized Pentaerythritol Amine Derivatives

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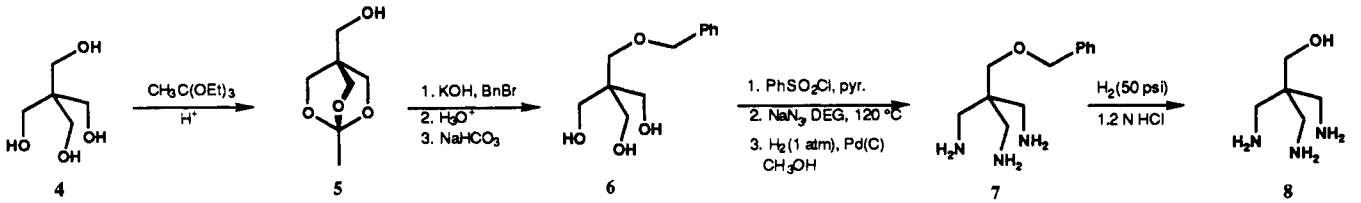
Polyamine systems are important materials for a variety of bioorganic applications ranging from the area of molecular recognition to the coordination of metals in biological systems.[1] The important triamine 1,1,1-tris-

(1) For excellent reviews, see: Lehn, J. M. In *Synthesis of Macrocycles*; Itzatt, R. M., Christensen, J. J., Eds.; Wiley: New York, 1987; Chapter 4. Lehn, J. M. *Angew. Chem., Intl. Ed. Engl.* **1988**, *27*, 89.

0022-3263/90/1955-6368$02.50/0

Scheme I



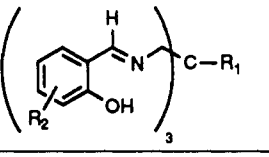
(aminomethyl)ethane (TAME) (1) has been used as a tridentate ligand itself or as a starting material for the synthesis of more complex hexadentate ligand systems.[2] Its interesting tripodal structure offers significant advantages in terms of generating highly preorganized chelators for the complete encapsulation of metal ions.[3] Within the framework of developing general metal-based radiopharmaceuticals using the preorganized ligand concept, it became necessary to prepare functionalized TAME derivatives in order to enhance a given set of biodistribution parameters.[3e,4] The required modifications ranged from simple alkyl substitutions to progressively more complex attachments containing heteroatoms and enzymatically hydrolyzable moieties to finally incorporating the triamine unit into biologically significant molecules.[4c]

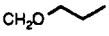
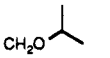
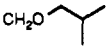
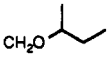
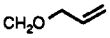
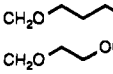
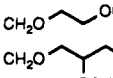
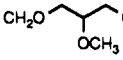
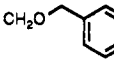
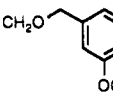
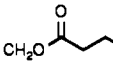
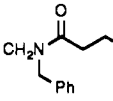
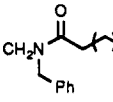
TAME (1) is derived from the corresponding triol 2, which in turn is prepared via Tollens condensation of propionaldehyde and formaldehyde.[2b,5] Extensions of the Tollens condensation utilizing other monosubstituted acetaldehydes have been reported in the literature and employed in these laboratories for the ultimate generation of functionalized TAME derivatives.[6] While oftentimes successful, the Tollens method can be complicated by substrate solubility problems (as this condensation is best performed in aqueous media), which can lead to complex mixtures of starting materials and partially hydroxylated products.

Alternatively, one could envision the generation of functionalized triamines 3 from commercially available pentaerythritol 4. This method would require a practical means of differentiating one of the four identical hydroxymethyl groups. Unfortunately, except for the monohalo- and monoether derivatives available from 3,3-bis(hydroxymethyl)oxetane, no other pentaerythritol-based precursors are readily available.[7]

Consequently, we have developed strategies for the monofunctionalization of pentaerythritol 4 or pentaerythritol tetraamine 14 that efficiently minimize the difficulties encountered in handling carbohydrate-like intermediates. These methods have been used to prepare a number of new functionalized TAME derivatives.

Table I. Preparation of Substituted TAME Salicylideneamine Derivatives



compd	R_1[a]	R_2	triamine synthesis method
23		5-OCH_3[b]	A
24		H	A
25		H	A
26		H	A
27		H	B
28		H	A
29		H	A
30		4-OCH_3[b]	A
31		4,5,6-OCH_3[c]	A
32		4,5,6-OCH_3[c]	A
33		H	B
34		H	C
35		H	C

[a] Spectral data for representative compounds presented in supplementary data section. [b] Purchased from Aldrich Chemical Co. [c] Reference 16.

(2) (a) Beaumont, R. C.; Deyoung, J. J.; Brooks, C. L.; Romig, C. *Inorg. Chim. Acta* **1984**, *86*, 13. (b) Searle, G. H.; Geue, R. J. *Aust. J. Chem.* **1983**, *36*, 927. (c) Yoshino, T.; Inazu, T.; Ishikita, H.; Yuki, M., Urushigawa, Y. *Memoirs of the Faculty of Science*; Kyushu University: Kyushu, **1977**; Vol. 10, p 125.

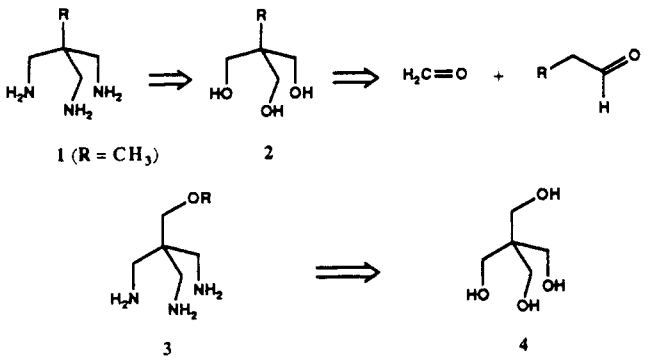
(3) (a) Ogata, H.; Kazutoshi, H.; Onishi, M.; Hiraki, K. *Chem. Lett.* **1978**, 117. (b) Urbach, F. L.; Sarneski, J. E.; Wandiga, S. O. *Inorg. Chem.* **1972**, *11*, 1349. (c) Durham, D. A.; Hart, F. A.; Shaw, D. *J. Inorg. Nucl. Chem.* **1967**, *29*, 509. (d) Dwyer, F. P.; Gill, N. S.; Gyargas, E. C.; Lions, F. *J. Am. Chem. Soc.* **1957**, *79*, 1269. (e) Green, M. A.; Welch, M. J.; Huffman, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 3689.

(4) (a) For a report of a Gallium-68 TAME-based radiopharmaceutical useful for positron emission tomography, see: Welch, M. J.; Green, M. A.; Mathias, C. J.; Fox, K. A. A.; Knabb, R. M.; Huffman, J. C. *J. Nucl. Med.* **1985**, *26*, 170. (b) For Tc-99m TAME-based radiopharmaceuticals, see: Nosco, D.; Dunn, T. J.; Rogic, M. M.; Coveney, J.; Pilcher, G.; Helling, D.; Woulfe, S. R.; Neumann, W. L.; Strubel, T.; Marmion, M. *Abstracts of Papers*, No. 185; Society of Nuclear Medicine Proceedings of the 36th Annual Meeting, St. Louis, Mo.; Society of Nuclear Medicine: New York, 1989; paper 707. (c) Neumann, W. L.; Woulfe, S. R.; Rogic, M. M.; Dunn, T. J. *Abstracts of Papers*, No. 815; Society of Nuclear Medicine Proceedings of the 37th Annual Meeting, Washington, DC; Society of Nuclear Medicine: New York, 1990.

(5) (a) Tollens, B.; Wiegard, P. *Ann.* **1891**, *265*, 316. (b) Stetter, H.; Bockmann, W. *Chem. Ber.* **1951**, *84*, 834. For literature concerning the preparation of the similar triamine tris(aminomethyl)methane, see: Kaloustian, M. K.; Dekmezian, A. H. *Synth. Commun.* **1979**, *9*(5), 431. Webb, I. D.; Schlatter, M. J.; Geissman, T. A. *J. Org. Chem.* **1946**, *11*, 736. Wuest, J. D.; Latour, S. *Synthesis* **1987**, 742. Schuetze, B. D., Jr.; Moore, D. W.; Nielson, A. T. *Pol. J. Chem.* **1981**, *55*, 1393.

(6) (a) Henry, J. P.; Wawzonek, S. *J. Am. Chem. Soc.* **1953**, *75*, 1258. (b) Solomon, P. W.; Dermer, O. C. *J. Am. Chem. Soc.* **1954**, *76*, 1697.

(7) (a) Wawzonek, S.; Matar, A.; Issidorides, C. H. *Organic Syntheses*; Wiley: New York, 1963; collect. Vol. IV, p 681. (b) Issidorides, C. H.; Matar, A. I. *J. Am. Chem. Soc.* **1955**, *77*, 6382. (c) The bis(azidomethyl)oxetane of pentaerythritol has also been reported and could also be a potentially useful intermediate on small scale: Wilson, E. R.; Frankel, M. B. *J. Org. Chem.* **1985**, *50*, 3211 and references cited therein.



1 (R = CH_3) 2

3 4

Method A. In a representative example, pentaerythritol **4** was protected and differentiated in one step by conversion to the hydroxymethyl orthoester **5**,[8] and the hydroxymethyl group was then alkylated with benzyl bromide under standard conditions (powdered KOH, DMSO).[9] The orthoester was then hydrolyzed to the corresponding pentaerythritol monobenzyl ether **6**. This sequence represents a vast improvement in terms of yields and material handling over the previous literature methods for the preparation of pentaerythritol monoethers.[10] Triol **6** was converted to the corresponding triamine **7** by the general method of Fliescher (*CAUTION*!).[11] Furthermore, the benzyl group could be cleaved to generate the more water-soluble hydroxymethyl derivative **8** (Scheme I). This method was used for the synthesis of a variety of alkoxy substituted TAME derivatives (Table I).

Method B. For substituents that were unable to survive the harsh conditions associated with nucleophilic substitution by azide at the neopentyl centers (Scheme I), the hydroxymethyl triamine **8** was protected as the 2,4,6-triphenyl-1,3,5-triazaadamantane derivative **9** by condensation with three equiv of benzaldehyde.[3c,d,5b] Compound **9** was then alkylated with allyl bromide to afford allyl ether substituted TAME derivative **11** upon mild acidic hydrolysis of the triazaadamantane. Similarly, acylation of **9** with octanoyl chloride followed by hydrolysis afforded acyloxy-substituted TAME derivative **13** (Scheme II).

Methods A and B constitute new highly versatile procedures for the preparation of functionalized TAME derivatives. Using these approaches the properties of the triamines may be tailored to meet most chemical or biophysical requirements in a given application.[4b,c]

Method C. The differentiation of one aminomethyl group of pentaerythritol tetraamine **14** utilizes the known tendency for TAME derivatives to condense with simple aldehydes to form 1,3,5-triazaadamantanes.[3c,d,5b] Pentaerythritol tetraamine (*CAUTION*!)[12] **14** undergoes condensation with benzaldehyde to form the corresponding triazaadamantane, but in this case the fourth amino group reacts with another equivalent of benzaldehyde to form the 7-[(benzylideneamino)methyl] derivative **15**. Thus differentiation of one aminomethyl group and protection of the triamine unit has been accomplished in one step. Benzylideneamine **15** was reduced to the benzylamine **16** and cleanly acylated with methyl 4-(chloroformyl)butyrate and converted to the desired functionalized triamine trihydrochloride **19** by acidic hydrolysis (Scheme III). Similarly, this method has been used to generate fatty acid substituted TAME derivative **20**.

These now functionalized TAME derivatives can be condensed with a variety of carbonyl components to generate more complex hexadentate ligand systems.[23] The tris(salicylideneamine) derivatives[15] of a representative series of functionalized triamines prepared by these methods are summarized in Table I.

Experimental Section

All reactions were conducted under a positive pressure of dry argon or nitrogen. Tetrahydrofuran (THF) was distilled from potassium or sodium/benzophenone ketyl; diethyl ether was purchased in anhydrous form and used without further purification; dichloromethane and toluene were distilled from calcium hydride. All other commercially available reagents were used without further purification unless otherwise noted.

Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained at 300 or 90 MHz, and carbon nuclear magnetic resonance (^{13}C NMR) spectra were obtained at 75 or 22.5 MHz on a Varian Gemini-300 FT NMR spectrometer or a JEOL FX90Q spectrometer, respectively. Infrared spectra (IR) were recorded on a Perkin-Elmer 283B grating spectrophotometer. Melting points (mp) were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

4-(Hydroxymethyl)-1-methyl-2,6,7-trioxabicyclo[2.2.2]octane (5). To a suspension of pentaerythritol (136 g, 1.0 mol) in toluene (100 mL) was added freshly distilled triethyl orthoacetate (162 g, 183 mL, 1.0 mol) and *p*-toluenesulfonic acid monohydrate (500 mg). The resulting mixture was gradually heated with an oil bath, and ethanol was slowly distilled from the mixture over a period of 12 h. After all ethanol had distilled, the bath temperature was raised to 125 °C and toluene was distilled off (approximately 30 mL) until the solution was homogeneous. The solution was allowed to cool and concentrated. The residue was sublimed (bulb-to-bulb, ~130 °C (2.5 mmHg)) to afford 150.0 g (94%) of **5** as a white solid: ^{1}H NMR ($CDCl_3$) δ 4.03 (s, CH_2-$OCCH_3$, 6 H), 3.44 (s, CCH_2OH, 2 H), 2.67 (br s, CH_2OH, 1 H), 1.46 (s, CCH_3, 3 H); ^{13}C NMR ($CDCl_3$) δ 108.51 (s), 69.16 (t), 60.84 (t), 35.28 (s), 23.03 (q); mp 110–112 °C (lit.[8] mp 112 °C).

2-[(Benzyloxy)methyl]-2-(hydroxymethyl)-1,3-propanediol (6). Powdered KOH (41.2 g, 734.3 mmol) was suspended in dimethyl sulfoxide (250 mL), and this mixture was stirred at room temperature for 5 min. Alcohol **5** (25.0 g, 156.1 mmol) was added in one portion followed quickly by benzyl bromide (32.2 g, 188.0 mmol). The reaction mixture (which became quite hot) was stirred for 30 min and then diluted with water (2500 mL) and extracted with diethyl ether (2 × 250 mL). The combined extracts were washed with brine (50 mL) and water (50 mL), dried ($MgSO_4$), and concentrated to afford 39.0 g (99%) of 4-[(benzyloxy)-methyl]-1-methyl-2,6,7-trioxabicyclo[2.2.2]octane (**5a**), as a white

(8) Hall, H. K.; Wilson, D. R. U.S. Patent 4 405 798, 1983. Hall, H. K.; Yokoyama, Y.; Padias, A. B.; Bratoeff, E. A. *Macromolecules* **1982**, *15*, 11.

(9) Johnstone, R. A. W.; Rose, M. E. *Tetrahedron* **1979**, *35*, 2169.

(10) Berlow, E.; Barth, R. H.; Snow, J. E. *The Pentaerythritols*; ACS Monograph 136; Reinhold: New York, 1958; Chapter 10.

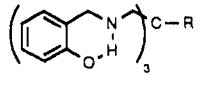
(11) *CAUTION*! *Polyazides are explosive compounds and should be handled with extreme care.* Fleischer, E. B.; Gembala, A. E.; Levey, A.; Tasker, P. A. *J. Org. Chem.* **1971**, *36*, 3042.

(12) *CAUTION*! Pentaerythritol tetramine was prepared from the tetraazide by the method of Fleischer (ref 11). Although multigram quantities of the tetraazide had been prepared a number of times, on one occasion a 20-g sample began to crystallize and exploded causing serious injuries to the chemist involved.

(13) Zompa, L. J.; Anselme, J. P. *Org. Prep. Proc. Int.* **1974**, *6*, 103.

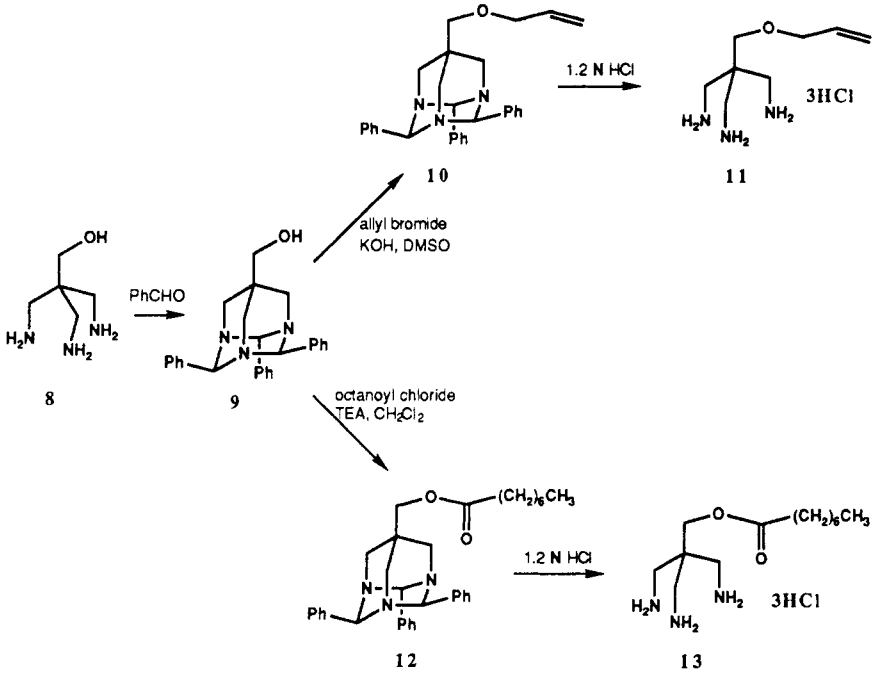
(14) Purchased from Aldrich Chemical Co.

(15) While simple aldehydes undergo condensation with 1,1,1-tris(aminomethyl)ethane (TAME) derivatives to afford the triazaadamantanes described herein, salicylaldehydes and β-diketones afford the corresponding Schiff base products. The tris(salicylideneamines) of TAME derivatives are stabilized in the imine form by intramolecular hydrogen bonding of the phenolic hydrogen to the imine nitrogen. As a further consequence only one geometrical isomer of these tris-imine systems is observed by NMR. In these cases no self-condensation to form the corresponding triazaadamantane occurs.



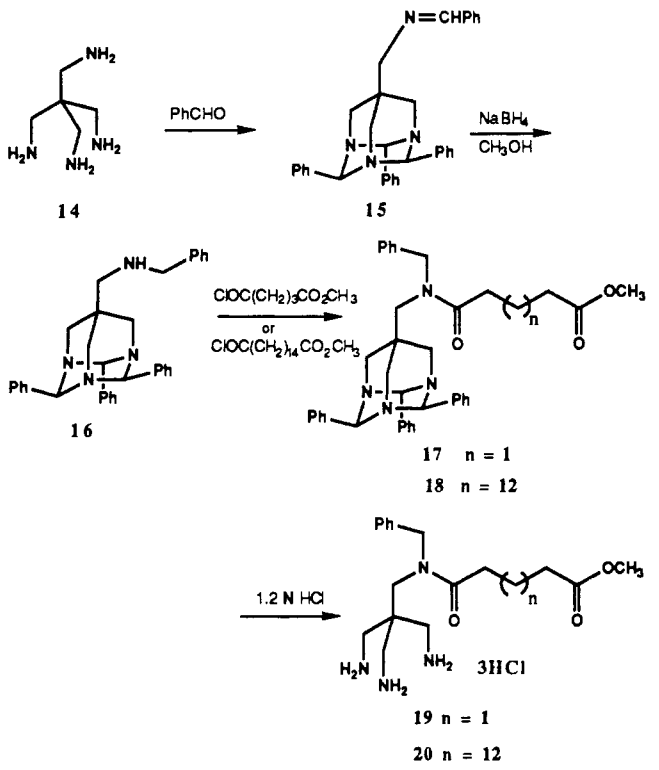
(16) 4,5,6-Trimethoxysalicylaldehyde (mp 64–65 °C) was prepared by Vilsmeier formylation of 3,4,5-trimethoxyphenol using phosphorus oxychloride and *N*-methyl formanilide. Reported mp 65 °C by a different procedure: Chapman, E.; Perkin, A. G.; Robinson, R. *J. Chem. Soc.* **1927**, 3015.

Scheme II



10 11 8 9 12 13

Scheme III



14 15 16 17 n = 1 18 n = 12 19 n = 1 20 n = 12

solid: ^1H NMR ($CDCl_3$) δ 7.24–7.39 (m, ArH, 5 H), 4.45 (s, $ArCH_2O$, 2 H), 4.01 (s, CCH_2O, 6 H), 3.19 (s, CCH_2OCH_2Ar, 2 H), 1.45 (s, CCH_3, 3 H); ^{13}C NMR ($CDCl_3$) δ 137.7 (s), 128.7 (d), 128.1 (d), 127.6 (d), 108.6 (s), 73.4 (t), 69.5 (t), 69.3 (t), 34.8 (s), 23.3 (q); mp 83–85 °C. Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.22; H, 7.25. Found: C, 67.20; H, 7.23. Compound **5a** (39.0 g, 155.8 mmol) was dissolved in methanol (100 mL) and treated with 0.01 N HCl (400 mL). The resulting mixture was stirred at 25 °C for 1 h, treated with sodium bicarbonate (14.5 g, 173.0 mmol), stirred for an additional 1 h, and concentrated. Trituration of the resulting solid residue with methanol (200 mL) and concentration of the triturate afforded 35.0 g (99%) of pure triol **6** as a colorless viscous oil: ^1H NMR ($CDCl_3$) δ 7.22–7.28 (m, ArH, 5 H), 4.41 (s, $ArCH_2O$, 2 H), 4.03 (br s, OH, 3 H), 3.60 (s, CCH_2OH, 6 H), 3.36 (s, CCH_2OCH_2Ar, 2 H); ^{13}C NMR ($CDCl_3$) δ 137.7 (s), 128.6 (d), 127.9 (d), 127.6 (d), 73.6 (t), 71.9 (t), 63.3 (t), 45.0 (s); MS (HRFAB) m/z 233.1363 (m + Li); 233.1365 calcd for $C_{12}H_{18}O_4Li$.

2-(Benzyloxy)-1,1,1-tris(aminomethyl)ethane (7). Triol **6** (3.55 g) was converted to the triazide (3.23 g, 68%) according to the general method of Fleischer[11] (*caution: azides are explosive and should be handled on small scale only!*). The triazide (3.64 g, 120.8 mmol) was dissolved in methanol (50 mL), and 10% Pd on carbon was added (0.5 g wet with a few drops of water). This mixture was stirred at room temperature under a continuous flow of H_2 for 72 h.[13] The catalyst was filtered, and the solution was concentrated to afford 2.69 g (100%) of **7** as a light yellow oil: ^1H NMR δ 7.33 (s, ArH, 5 H), 4.40 (s, $ArCH_2O$, 2 H), 3.35 (s, CCH_2O, 2 H), 2.60 (s, CH_2NH_2, 6 H), 1.35 (s, NH_2, 6 H); ^{13}C NMR δ 132.6 (s), 128.1 (d), 127.0 (d), 72.9 (t), 71.5 (t), 43.1 (t), 43.0 (s).

2-Hydroxy-1,1,1-tris(aminomethyl)ethane Trihydrochloride (8). A solution of **7** (2.40 g, 10.7 mmol) in 2 N HCl (30.0 mL) in a Parr bottle was treated with 10% Pd on carbon (0.5 g). The resulting mixture was hydrogenated at 50 psi for 48 h at room temperature. The catalyst was removed by filtration, and the solution was concentrated to afford 2.14 g (83%) of the trihydrochloride of **8** as a white solid: ^1H NMR (D_2O) δ 3.86 (s, CH_2OH, 2 H), 3.31 (s, CH_2NH_2, 6 H); ^{13}C NMR (D_2O) δ 63.0 (t), 41.3 (t), 39.8 (s); recrystallization from methanol–water afforded an analytical sample. Anal. Calcd for $C_5H_{18}N_3OCl_3$: C, 24.75; H, 7.48; N, 17.32; Cl, 43.85. Found: C, 24.71; H, 7.54; N, 17.23; Cl, 43.33.

2,2′-[[2-[[[(2-Hydroxyphenyl)methylene]amino]-methyl]-2-[(phenylmethoxy)methyl]-1,3-propanediyl]bis-(nitrilomethylidyne)]bisphenol (21). The trihydrochloride of **7** (732 mg, 2.2 mmol) was suspended in CH_3OH (10 mL) and treated with triethylamine (0.92 mL, 668 mg, 6.6 mmol). When the mixture became homogeneous, salicylaldehyde was added (806 mg, 6.6 mmol) and the resulting yellow solution was heated on a steam bath for 5 min, allowed to cool, and concentrated. Purification by flash chromatography (10% ether/hexanes to ether) afforded 520 mg (44%) of **21** as a clear yellow oil: ^1H NMR ($CDCl_3$) δ 13.31 (br s, ArO*H*, 3 H), 8.35 (s, ArC*H*=N, 3 H), 6.87–7.35 (m, ArH, 17 H), 4.47 (s, $ArCH_2O$, 2 H), 3.72 (s, $=NCH_2$, 6 H), 3.49 (s, CCH_2O, 2 H); ^{13}C NMR ($CDCl_3$) δ 166.9 (d), 161.0 (s), 132.5 (s), 131.5 (d), 128.4 (d), 127.7 (d), 127.5 (d), 118.8 (d), 116.9 (d), 73.6 (t), 70.3 (t), 60.5 (t), 44.4 (s); MS (LREI) m/z 535. Anal. Calcd for $C_{33}H_{33}N_3O_4$: C, 74.00; H, 6.21; N, 7.87. Found: C, 74.26; H, 6.30; N, 7.87.

7-(Hydroxymethyl)-2,4,6-triphenyl-1,3,5-triazaadamantane (9). To a suspension of the trihydrochloride of **8** in methanol (25 mL) was added triethylamine (5.70 mL, 4.14 g, 40.9 mmol), and

the mixture was stirred until it became homogeneous. Benzaldehyde (3.90 g, 36.8 mmol) was added, and the solution was heated at reflux for 5 min, cooled, and concentrated. The residue was slurried in water (25 mL) and filtered, and the solid obtained was dried under vacuum to afford 4.40 g (89%) of **9** as a white solid: mp 92–95 °C; ^{1}H NMR ($CDCl_3$) δ 7.15–7.95 (m, ArH, 15 H), 5.62 (s, NCH_{eq}(Ph)N, 1 H), 5.42 (s, NCH_{ax}(Ph)N, 2 H), 3.30 (AB q, J = 12.7 Hz, $\Delta\nu$ = 97.6 Hz, CH_2N, 4 H), 2.90 (s, CH_2N, 2 H), 2.87 (s, CH_2O, 2 H), 1.90 (br s, OH, 1 H); ^{13}C NMR ($CDCl_3$) δ 140.0 (s), 139.8 (s), 128.8 (d), 128.7 (d), 128.5 (d), 127.1 (d), 126.9 (d), 126.6 (d), 82.8 (d), 75.2 (d), 67.2 (t), 54.8 (t), 46.2 (t), 26.9 (s).

7-[(3-Propenyloxy)methyl]-2,4,6-triphenyl-1,3,5-triazaadamantane (10). By use of the procedure described for the conversion of **5** to **5a**, (hydroxymethyl)triazaadamantane **9** (1.0 g, 2.52 mmol) afforded 1.04 g (94%) of **10** as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.91–7.21 (m, ArH, 15 H), 5.71 (ddt, J = 5.4, 10.4, 17.3 Hz, CH=CH_2, 1 H), 5.66 (s, NCH_{eq}(PH)N, 1 H), 5.43 (s, NCH_{ax}(Ph)N, 2 H), 5.07 (dq, J = 17.3, 1.5 Hz, CH=CH_tH$_c$, 1 H), 5.03 (dq, J = 10.4, 1.5 Hz, CH=CH$_t$CH_c, ^{1}H), 3.72 (dt, J = 5.5, 1.5 Hz, OCH_2CH=CH$_2$, 2 H), 3.40 (AB q, J = 13.4 Hz, $\Delta\nu$ = 69.9 Hz, CH_2N, 4 H), 2.93 (s, CCH_2O, 2 H), 2.67 (s, CH_2N, 2 H); ^{13}C NMR ($CDCl_3$) δ 140.1 (s), 140.0 (s), 134.9 (d), 128.6 (d), 127.2 (d), 127.0 (d), 126.9 (d), 126.7 (d), 116.5 (t), 82.8 (d), 75.3 (d), 74.7 (t), 72.1 (t), 55.4 (t), 46.7 (t), 26.7 (s); MS (HREI) m/z 437.2460 (437.2467 calcd for $C_{29}H_{31}N_3O$).

2,2′-[[2-[[[(2-Hydroxyphenyl)methylene]amino]-methyl]-2-[(2-propenyloxy)methyl]-1,3-propanediyl]bis(nitrilomethylidyne)]bisphenol (27). Compound **10** (1.0 g, 2.29 mmol) was dissolved in THF (10 mL) and treated with excess 1.2 N HCl. After the mixture was stirred for 10 min at room temperature, the THF was evaporated and the aqueous solution was extracted with ethyl ether (3 × 25 mL) and then concentrated to afford 600 mg (93%) of trihydrochloride **11** as a light yellow solid. The triamine trihydrochloride **11** (600 mg, 2.1 mmol) was dried thoroughly under vacuum, suspended in methanol (10 mL), and treated with triethylamine (0.97 mL, 6.90 mmol). When the mixture became homogeneous, salicylaldehyde (777 mg, 6.3 mmol) was added, and the yellow mixture was heated to reflux for 10 min and evaporated. The residue was partitioned between ether (25 mL) and water (25 mL), and the ether layer was dried ($MgSO_4$) and concentrated. Purification by flash chromatography (9:1 hexanes–ether) afforded 390 mg (38%) of **27** as a yellow oil which solidified on standing: mp 87–88 °C; ^{1}H NMR δ 13.35 (s, ArCH=N, 3 H), 7.29–7.21 (m, ArH, 12 H), 5.87 (ddt, J = 5.6, 10.4, 17.2 Hz, CH=CH$_2$, 1 H), 5.27 (dq, J = 17.2, 1.4 Hz, CH=CH$_c$H$_t$, 1 H), 5.16 (dq, J = 10.4, 1.4, CH=CH$_c$H$_t$, 1 H, 3.96 (dt, J = 5.6, 1.4, OCH_2CH=CH$_2$, 2 H), 3.73 (s, CH_2N=CHAr, 6 H), 3.46 (s, CCH_2O, 2 H); ^{13}C NMR δ 167.2 (d), 161.3 (s), 134.6 (d), 132.7 (s), 131.7 (s), 118.9 (s), 117.3 (t), 117.0 (s), 72.3 (t), 70.1 (t), 60.5 (t), 44.2 (s); IR (neat 3080, 3040, 2900, 1640, 1510, 1470, 1430, 1360, 1290, 1230, 1170; MS (LREI) m/z 485. Anal. Calcd for $C_{29}H_{31}N_3O_4$: C, 71.73; H, 6.44; N, 8.65. Found: C, 71.22; H, 6.46; N, 8.40.

7-[(Octanoyloxy)methyl]-2,4,6-triphenyl-1,3,5-triazaadamantane (12). Compound **9** (4.40 g, 11.1 mmol) was dissolved in CH_2Cl_2 (100 mL) and cooled to 0 °C (ice–salt bath). Triethylamine (1.55 mL, 1.12 g, 11.1 mmol) was added followed by octanoyl chloride[14] (1.90 mL, 1.81 g, 11.1 mmol), and the resulting mixture was stirred for 1 h and then allowed to warm to 25 °C. The mixture was concentrated, and the residue was partitioned between ether (50 mL) and water (25 mL). The ether layer was washed successively with 5% $NaHCO_3$ (25 mL) and brine (25 mL), dried ($MgSO_4$), and concentrated to afford 5.64 g (97%) of ester **12** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.24–7.84 (m, ArH, 15 H), 5.64 (s, NCH_{eq}(Ph)N, 1 H), 5.43 (s, NCH_{ax}(Ph)N, 2 H), 3.38 (s, CH_2OC(O), 2 H), 3.35 (AB q, J = 13.4 Hz, $\Delta\nu$ = 96.3 Hz, CH_2N, 4 H), 2.94 (s, NCH_2, 2 H), 2.11 (t, J = 7.4 Hz, OC(O)CH_2, 2 H), 1.15–1.38 (m, (CH_2)$_5$, 10 H), 0.88 (t, J = 7.1 Hz, CH_3, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.8 (s), 139.8 (s), 139.5 (s), 128.9 (d), 128.7 (d), 127.5 (d), 127.2 (d), 126.9 (d), 126.6 (d), 82.8 (d), 75.1 (d), 67.6 (t), 54.9 (t), 46.2 (t), 33.9 (t), 31.4 (t), 28.8 (t), 28.6 (t), 26.0 (s), 24.6 (t), 22.4 (t), 13.8 (q); MS (HRFAB) m/z 524.3261 (m + 1); 524.3277 calcd for (m + 1) of $C_{34}H_{42}N_3O_2$.

2-(Octanoyloxy)-1,1,1-tris(aminomethyl)ethane Trihydrochloride (13). The triazaadamantane **12** (5.60 g, 10.7 mmol) was dissolved in freshly distilled THF (60 mL) and treated with 1.2 N HCl (60 mL). The resulting solution was stirred for 10 min at 25 °C. The THF was evaporated, and the aqueous layer was washed with ether (2 × 25 mL) and concentrated to afford 2.50 g (63%) of **13** as a fine white solid: ^{1}H NMR (D_2O) δ 4.37 (s, CCH_2O, 2 H), 3.47 (s, CCH_2NH$_2$, 6 H), 2.47 (m, (C=O)CH_2, 2 H), 0.83–1.63 (m, (CH$_2$)$_5$CH$_3$, 13 H); ^{13}C NMR (D_2O) δ 173.5 (s), 61.1 (t), 37.9 (t), 36.8 (s), 31.5 (t), 29.1 (t), 26.3 (t), 26.2 (t), 22.0 (t), 20.1 (t), 11.6 (q).

7-[(Benzylideneamino)methyl]-2,4,6-triphenyl-1,3,5-triazaadamantane (15). The tetrahydrobromide salt of pentaerythritol tetraamine (**14**) (7.00 g, 15.4 mmol) was suspended in CH_3OH (50 mL) and treated with triethylamine (8.60 mL, 6.24 g, 61.7 mmol). When the mixture became homogeneous, benzaldehyde (5.90 mL, 6.16 g, 58.0 mmol) was added and the solution was heated at reflux for 5 min. Upon cooling a precipitate was formed and isolated by filtration. Recrystallization from methanol afforded 6.60 g (89%) of compound **15** as a white solid: ^{1}H NMR ($CDCl_3$) δ 8.05 (s, N=CH, 1 H), 7.25–7.85 (m, ArH, 20 H), 5.64 (br s, NCH_{eq}(Ph)N, 1 H), 5.43 (s, NCH_{ax}(Ph)N, 2 H), 3.43 (AB q, J = 13.0 Hz, $\Delta\nu$ = 72.1 Hz, CH_2N, 4 H), 2.97 (s, CH_2N, 2 H), 2.89 (s, CH_2N, 2 H); ^{13}C NMR δ 161.9 (d), 140.1, 140.0, 136.1 (s, arom), 130.7, 128.8, 128.6, 128.2, 128.1, 127.0, 126.7 (d, arom), 83.9 (d), 75.3 (d), 66.9 (t), 56.3 (t), 48.1 (t), 27.1 (s); MS (LREI) m/z 484; mp 154–155 °C. There is a minor amount (~5%) of another isomer present by NMR.

7-[(Benzylamino)methyl]-2,4,6-triphenyl-1,3,5-triazaadamantane (16). Benzylideneamine **15** (4.00 g, 8.3 mmol) was dissolved in $CHCl_3$–CH_3OH (1:1, 20 mL) and cooled to 0 °C. $NaBH_4$ (300 mg, 7.9 mmol) was added, and the mixture was stirred for 2 h, allowed to warm to 25 °C, and poured into cold water (50 mL). The layers were separated, and the aqueous layer was extracted with ether (3 × 20 mL). The combined extracts were dried and concentrated to afford 3.86 g (96%) of benzylamine **16** as a viscous orange oil: ^{1}H NMR δ 7.05–7.80 (m, ArH, 20 H), 5.66 (br s, NCH_{eq}(Ph)N, 1 H), 5.40 (s, HCH_{ax}(Ph)N, 2 H), 3.55 (m, CH_2NH, 4 H), 3.35 (br s, ArCH$_2$NH, 1 H), 2.99 (s, ArCH_2NH, 2 H), 2.90 (s, CCH_2NH, 2 H); ^{13}C NMR δ 141.2 (s), 140.2 (s), 139.9 (s), 139.3 (s), 128.6 (d), 128.5 (d), 128.2 (d), 127.8 (d), 127.3 (d), 127.2 (d), 126.8 (d), 126.5 (d), 82.9 (d), 75.4 (d), 64.9 (t), 56.4 (t), 55.0 (t), 54.6 (t), 48.0 (t), 26.3 (s).

2,2′-[[2-[[[(2-Hydroxyphenyl)methylene]amino]methyl]-2-[[*N*-benzyl-4-carbomethoxybutanamido]methyl]-1,3-propanediyl]bis(nitrilomethylidyne)]bisphenol (34). Benzylamine **16** (890 mg, 1.8 mmol) was dissolved in pyridine (20 mL) and cooled to 0 °C. To this solution was added methyl (4-chloroformyl)butyrate[14] (332 mg, 0.28 mL, 2.0 mmol), and the resulting mixture is stirred for 1 h and poured into cold saturated $NaHCO_3$ (30 mL). The solution is extracted with ether (3 × 50 mL), dried ($NaSO_4$), and concentrated to afford 720 mg (59%) of amide **17** as a slightly yellow viscous oil. Compound **17** (720 mg, 1.2 mmol) was dissolved in freshly distilled THF (20 mL), treated with 1.2 N HCl (20 mL), and stirred for 10 min. The THF was evaporated, and the aqueous solution was extracted with CH_2Cl_2 (2 × 50 mL) and concentrated to afford **19** as fine tan powder (600 mg, slightly wet). Compound **19** was suspended in CH_3OH (20 mL) and treated with triethylamine (0.50 mL, 364 mg, 3.6 mmol) and salicylaldehyde (0.38 mL, 440 mg, 3.6 mmol), and the resulting mixture was heated at reflux for 5 min and concentrated. The residue was dissolved in CH_2Cl_2 (30 mL), washed with water (2 × 50 mL), dried (K_2CO_3), and concentrated. Purification of this residue by flash-column chromatography (2:1 hexane–ethyl acetate) afforded 382 mg (48%) of compound **34** as a viscous yellow oil: ^{1}H NMR ($CDCl_3$) δ 13.2 (br s, ArOH, 3 H), 4.50 (s, ArCH_2N, 2 H), 3.77 (s, ArCH=N, 6 H), 3.57 (s, CCH_2N, 2 H), 3.56 (s, (C=O)OCH_3, 3 H), 2.30 (t, J = 7.0 Hz, N(C=O)CH_2, 2 H), 2.22 (t, J = 7.0 Hz, CH_2(C=O)OCH$_3$, 2 H), 1.84 (apparent quintet, J = 7.0 Hz, CH_2, 2 H); ^{13}C NMR δ 174.9 (s), 173.9 (s), 167.4 (d), 161.2 (s), 136.6 (s), 132.8 (d), 131.8 (d), 129.2 (d), 127.7 (d), 126.0 (d), 119.0 (d), 118.7 (d), 117.0 (d), 62.6 (t), 53.3 (t), 51.3 (t), 50.2 (q), 44.8 (s), 33.0 (t), 32.0 (t), 19.9 (t); IR (neat) 3050, 2920, 2820, 1740, 1725, 1650, 1630, 1480, 1450, 1420, 1280 cm^{-1}; MS (LREI) m/z 662.

Acknowledgment. We would like to thank Dr. Raghavan Rajagopalan and Professor Henry Rapoport for helpful discussions and encouragement.

Supplementary Material Available: Selected ^1H and ^{13}C NMR and DEPT spectra of key intermediates and final TAME salicylideneamine products (61 pages). Ordering information is given on any current masthead page.

Decomposition of 1-(Nitrosoalkyl)-3-(2-hydroxyalkyl)ureas

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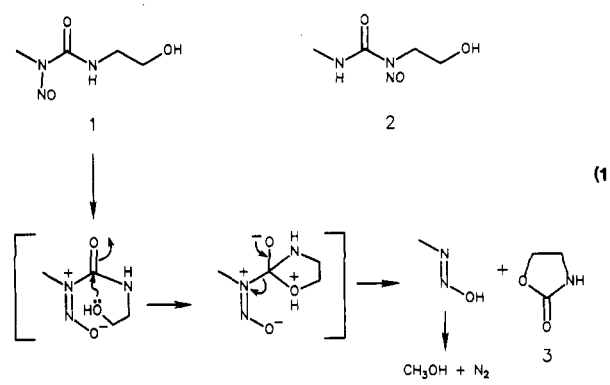
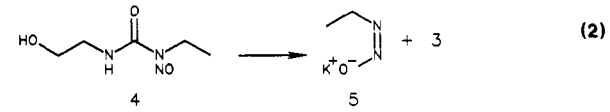
Nitrosoureas are compounds of increasing interest due to their carcinogenic and mutagenic activities[1] and for their therapeutic properties in the treatment of cancer.[2] For example, two commonly used compounds in cancer chemotherapy, presumably because of their alkylating properties,[3] are nitrosobis(2-chloroethyl)urea and nitroso(2-chloroethyl)cyclohexylurea. The study of unsymmetrical nitrosodialkylureas is of interest because of the insight it can give into the role of the nitroso group in the formation of alkylating agents. Lijinsky et al.[4] have looked into the carcinogenic effects of isomeric dialkylureas in relation to the monoalkylated analogues. During the course of these studies, it was necessary to synthesize 1-nitroso-1-methyl-3-(2-hydroxyethyl)urea (**1**) and 1-nitroso-1-(2-hydroxyethyl)-3-methylurea (**2**). Nitrosation of 1-methyl-3-(2-hydroxyethyl)urea with nitrous acid gave a mixture of **1** and **2** in a 9:1 ratio. Although the mixture decomposed slowly as a neat oil, the pure major isomer **1** was stable in acetone, or ethyl acetate, solution. However, this compound decomposed explosively when it was handled in its crystalline form, with evolution of nitrogen. Analysis of the decomposition products revealed that **1** breaks down into and 2-oxazolidone (**3**) and very likely into nitrogen and methanol, probably through the reaction pathway in eq 1.



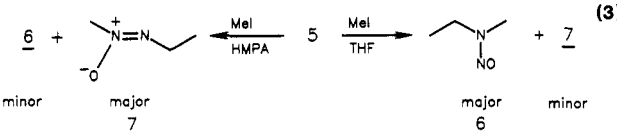
(1)

Further studies of **1** were abandoned due to its explosive nature; however, the compound's unusual decomposition prompted us to look at one of its stable analogues, 1-nitroso-1-ethyl-3-(2-hydroxyethyl)urea (**4**).[4a] Unlike **1**, the ethyl congener **4** was stable in the crystalline form, and no spontaneous decomposition was observed even after standing at room temperature for several hours. The half-life of this compound had been measured to be 40 h at pH 7 and 2.4 h at pH 8; however, the nature of the decomposition product was not identified.[5] We now know that in aqueous solution at pH 7, **4** is converted quantitatively into the oxazolidone **3** and ethanol. At pH 4, 1-nitroso-1-ethyl-3-(2-hydroxyethyl)urea remained unchanged even after 19 h at 37 °C. When a solution of **4** in ethyl acetate was stirred with solid anhydrous potassium carbonate, a 96% yield of 2-oxazolidone (**3**) was obtained. This suggested that the hydroxy group is participating in the decomposition of the nitrosourea and that potassium ethanediazoate (**5**) is a likely intermediate in the reaction, eq 2. Similar results were obtained when a THF solution of **4** was stirred with either sodium ethoxide or triethylamine.



(2)

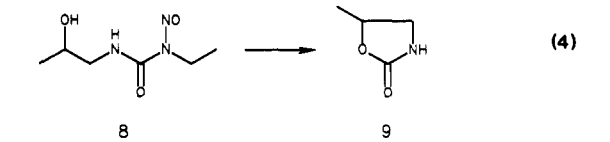
It is well established that the alkylation of metal alkanediazoates gives nitrosamines and/or azoxyalkanes, depending on the solvent systems used.[6,7] This compound was treated with potassium ethoxide in THF followed by alkylation with methyl iodide in order to demonstrate that the ethanediazoate **5** was an intermediate in the decomposition of **4**. A mixture of *N*-nitrosomethylethylamine (**6**) and (*Z*)-(methyl-*O*,*N*,*N*-azoxy)ethane (**7**) in a 1.8:1 ratio was obtained (eq 3). The major product, **6**, was isolated



(3)

in 22% yield by vacuum distillation. When the reaction was carried out in *N*,*N*-dimethylformamide, a 1.4:1 ratio of **7** to **6** was measured by GLC. In hexamethylphosphoramide, the alkylation strongly favored formation of the azoxyalkane, giving a 4:1 ratio of **7** and **6**. These results clearly indicate that the (*Z*)-ethanediazoate **5** is an intermediate in the decomposition of the hydroxyurea **4**.

N-(Nitrosoethyl)-*N'*-(2-hydroxypropyl)urea (**8**)[8] which contains a secondary hydroxyl group, was expected to undergo a similar type of decomposition to **4**, that is, the participation of the hydroxyl group in the formation of the corresponding oxazolidone. Compound **8** in pH 7 buffer was stirred at 25 °C for 1 week to give a yield of 96% ethanol and 75% 5-methyl-3-oxazolidone (**9**) eq 4.



(4)

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