Bridgehead Functionalization of [1]Diadamantane

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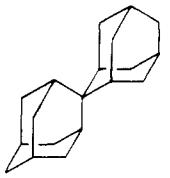
The bromination of [1]diadamantane can be controlled to give selectively 5-bromo-, 5,5'-dibromo-, or 5,5',7,7'-tetrabromo[1]diadamantane. Refluxing 1-hydroxy[1]diadamantane (8) with bromine and aluminum bromide also provides the tetrabromide. Monitoring the latter reaction shows that 5,5'-dibromo- and 5,5',7-tribromo-[1]diadamantane are intermediates. Treatment of 8 with phosphorus tribromide provides 1-bromo[1]diadamantane which hydrolyzes on standing in the air. The structures of the various bromides follow from their ^{13}C NMR spectra. The identity of the tetrabromide was established unequivocally by X-ray crystallography.

In principle, two adamantanes may be "condensed" so that they have one (1), two (2), three (3), or six (4) carbon atoms in common. With the exception of 3, all of these



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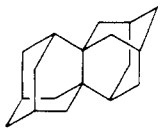

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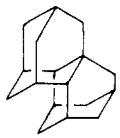

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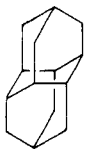

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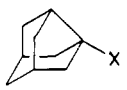
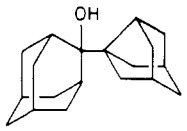
"diadamantanes" have been synthesized.[1-3] The chemistry of 4 has been studied in considerable detail.[4] Recently, we have described methods for the functionalization of the two unique bridgehead positions in 2.[5] We now report that the bromination of [1]diadamantane (1) can be controlled to give mono-, di-, or tetrabrominated bridgehead derivatives.

Results and Discussion

We prepared [1]diadamantane according to the strategy developed by Graham and Schleyer.[1b] The nominal starting material for this sequence of reactions is 3-noradamantanol (5), which was synthesized in five steps from commercially available 2-adamantanone by established procedures.[6] Graham and Schleyer obtained 3-iodonoradamantane (6) in 40% yield from 5 by heating 5 with 47% aqueous hydriodic acid in a sealed tube at 130 °C for 30 h. We have found that 6 can be prepared in 87% yield from 5 by the general method of Stone and Shechter,[7] i.e., heating 5 with sodium iodide in 95% phosphoric acid for 24 h at 110 °C. Lithium–iodine exchange in 6 was accomplished by treatment of 6 with *tert*-butyllithium. Reaction of the resulting 3-lithionoradamantane with 2-adamantanone gave 2-(3-noradamantyl)-2-adamantanol (7). Graham and Schleyer reported that treatment of 7 with a mixture of 48% aqueous hydrobromic acid and sulfuric acid gives 1-hydroxy[1]diadamantane (8).[1b] When we repeated this reaction, we found that analysis of the crude reaction mixture by ^{13}C NMR spectroscopy showed that the product consists of a mixture of 8 and 1-bromo-[1]diadamantane (9). In contrast, isomerization of 7 with dilute perchloric acid in refluxing 80% aqueous acetone gave only 8. Monobromide 9 could be prepared directly from 8 by refluxing 8 with phosphorus tribromide in benzene. The integrity of the carbon skeleton in 9 was established by reduction of 9 with lithium–*tert*-butyl alcohol–tetrahydrofuran[8] to afford only 1. Moreover, hydrolysis of 9 regenerates 8. This reaction even occurred slowly when 9 was exposed to air at room temperature. The synthesis of 1 was completed by treating 8 at room temperature with concentrated sulfuric acid in the presence of a large excess of methylcyclohexane.[1b]



5, X = OH
6, X = I



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Ionic bromination of a polycyclic hydrocarbon has been widely employed as a method for the introduction of a substituent on the skeletal framework.[4b,5,9] The mechanism of this reaction has not been determined. Although at one time bromination of hydrocarbons was thought to proceed by an ionic pathway with the formation of intermediate bridgehead carbocations,[10] more recently it has

(1) 1: (a) Boelema, E.; Strating, J.; Wynberg, H. *Tetrahedron Lett.* **1972**, 1175–1177. (b) Graham, W. D.; Schleyer, P. v. R. *Ibid.* **1972**, 1179–1180.

(2) 2: Graham, W. D.; Schleyer, P. v. R.; Hagaman, E. W.; Wenkert, E. *J. Am. Chem. Soc.* **1973**, *95*, 5785–5786.

(3) 4: Gund, T. M.; Ōsawa, E.; Williams, Y. Z., Jr.; Schleyer, P. v. R. *J. Org. Chem.* **1974**, *39*, 2979–2987, and references cited therein.

(4) (a) Gund, T. M.; Nomura, M.; Schleyer, P. v. R. *J. Org. Chem.* **1974**, *39*, 2987–2994, and references cited therein. (b) Gund, T. M.; Schleyer, P. v. R.; Unruh, G. D.; Gleicher, G. J. *Ibid.* **1974**, *39*, 2995–3003, and references cited therein. (c) Blaney, F.; Johnston, D. E.; McKervey, M. A.; Rooney, J. J. *Tetrahedron Lett.* **1975**, 99–100. (d) Bewick, A.; Edwards, C. J.; Jones, S. R.; Mellor, J. M. *Ibid.* **1976**, 631–634. (e) Jones, S. R.; Mellor, J. M. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2576–2581. (f) Edwards, G. J.; Jones, S. R.; Mellor, J. M. *J. Chem. Soc., Perkin Trans. 2* **1977**, 505–510. (g) Jones, S. R.; Mellor, J. M. *Ibid.* **1977**, 511–517. (h) Leddy, B. P.; McKervey, M. A.; McSweeney, P. *Tetrahedron Lett.* **1980**, 2261–2264. (i) Janku, J.; Burkhard, J.; Vodicka, L. *Z. Chem.* **1981**, *21*, 67–68.

(5) Sosnowski, J. J.; Murray, R. K., Jr. *J. Org. Chem.* **1984**, *49*, 4471–4475.

(6) Janjatovic, J.; Majerski, Z. *J. Org. Chem.* **1980**, *45*, 4892–4898, and references cited therein.

(7) Stone, H.; Schechter, H. *J. Org. Chem.* **1950**, *15*, 491–495.

(8) Bruck, P.; Thompson, D.; Winstein, S. *Chem. Ind. (London)* **1960**, 405.

(9) (a) Karim, A.; McKervey, M. A.; Engler, E. M.; Schleyer, P. v. R. *Tetrahedron Lett.* **1971**, 3987–3990. (b) Ōsawa, E. *Ibid.* **1974**, 115–117. (c) Takaishi, N.; Fujikura, Y.; Inamoto, Y.; Ikeda, H.; Aigami, K.; Ōsawa, E. *J. Chem. Soc., Chem. Commun.* **1975**, 371–372. (d) Ōsawa, E.; Engler, E. M.; Godleski, S. A.; Inamoto, Y.; Kent, G. J.; Kausch, M.; Schleyer, P. v. R. *J. Org. Chem.* **1980**, *45*, 984–991. (e) Israel, R. J.; Murray, R. K., Jr. *Ibid.* **1983**, *48*, 4701–4705. (f) Sosnowski, J. J.; Murray, R. K., Jr. *Ibid.* **1984**, *49*, 2174–2176.

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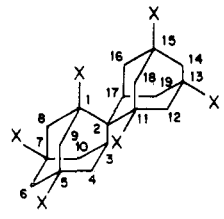

8; X_1=OH; X_5=X_7=X_{11}=X_{13}=X_{15}=H
9; X_1=Br; X_5=X_7=X_{11}=X_{13}=X_{15}=H
10; X_5=Br; X_1=X_7=X_{11}=X_{13}=X_{15}=H
11; X_5=X_{13}=Br; X_1=X_7=X_{11}=X_{15}=H
12; X_5=X_7=X_{13}=X_{15}=Br; X_1=X_{11}=H
13; X_1=X_{13}=Br; X_5=X_7=X_{11}=X_{15}=H
14; X_1=X_{15}=Br; X_5=X_7=X_{11}=X_{13}=H
15; X_1=X_{11}=Br; X_5=X_7=X_{13}=X_{15}=H
16; X_5=X_7=X_{13}=Br; X_1=X_{11}=X_{15}=H

been suggested that pentacoordinate intermediates or transition states, or even radical cation pathways, may be involved.[9d] The reaction of bromine with a solution of **1** in carbon tetrachloride for 72 h at room temperature provided 5-bromo[1]diadamantane (**10**) as the only isolated product in 73% yield. The carbon skeleton of **10** was confirmed by reduction of **10** with lithium–*tert*-butyl alcohol–tetrahydrofuran to give **1**. Moreover, consistent with the presence of a plane of symmetry in **10**, the ^{13}C NMR spectrum of **10** contains only thirteen signals with six of these being twice as intense as the others. Unique bridgehead substituents can be introduced only at C-1 and C-5 in **1**. As has amply demonstrated for both adamantane[11] and [6]diadamantane,[4] the availability of bromides **9** and **10** should permit the synthesis of a wide variety of monosubstituted bridgehead derivatives of [1]diadamantane by the interchange of functional groups.

Treatment of **1** with neat bromine for 24 h at room temperature gave only 5,5′-dibromo[1]diadamantane (**11**) in 51% yield. The reaction of **10** under comparable conditions also afforded **11** exclusively. The carbon skeleton of **11** was firmly established by reduction of **11** with lithium–*tert*-butyl alcohol–tetrahydrofuran to provide only **1**. The structure assigned to **11** follows from an analysis of its ^{13}C NMR spectrum which consists of only ten signals with one of these being half as intense as the others. Since it is well-known that a bromine bridgehead substituent in adamantane[11] or [6]diadamantane[4b] inductively deactivates bridgehead positions β to it toward electrophilic substitution, the only other dibromo[1]diadamantanes that need to be considered as the product of these reactions are **13**–**15**. Dibromides **13** and **14** can be eliminated immediately from further consideration since the ^{13}C NMR spectra of each of these compounds would be expected to contain 13 resonances. On the other hand, the ^{13}C NMR spectrum of **15** also should consist of only ten signals. However, since the chemical shifts of C-2 in **1** and monobromide **9** occur at δ 37.5 and 49.6, respectively, the chemical shift of C-2 in **15** would be expected to appear at ca. δ 61.7. In fact, the resonance for C-2 in **11** occurs at δ 38.8 which is consistent with the assigned structure.

By increasing the severity of the bromination conditions, 5,5′,7,7′-tetrabromo[1]diadamantane (**12**) can be obtained from **1**. Refluxing a solution of **11** in bromine with a catalytic amount of aluminum bromide for 2 h gave **12** in nearly quantitative yield. Consistent with the assigned structure, the ^{13}C NMR spectrum of **12** contains only five signals. The structure of **12** was established unequivocally by X-ray crystallography.

Tetrabromide **12** also could be prepared in nearly quantitative yield by refluxing a solution of alcohol **8** in bromine with a catalytic amount of aluminum bromide. When this reaction was monitored at room temperature, intermediates **11** and 5,5′,7-tribromo[1]diadamantane (**16**) were detected. Consistent with the presence of a plane of symmetry in **16**, the ^{13}C NMR spectrum of **16** consists of thirteen signals with six of these being twice as intense as the others. The influence of substituent effects on the chemical shifts of the ^{13}C NMR resonances[12] in **16** clearly eliminates the possibility of any other substituent pattern.

Experimental Section

Proton magnetic resonance spectra were recorded with a Bruker AM 250-MHz spectrometer. Apparent splittings are reported in all cases. Carbon magnetic resonance spectra were recorded with the Bruker instrument at 62.9 MHz. Both the ^1H and ^{13}C NMR spectra were obtained with $CDCl_3$ as the solvent and are referenced to an internal standard of $(CH_3)_4Si$.

3-Iodonoradamantane (6). Alcohol **5**[6] (4.38 g, 31.7 mmol) was added in one portion to a solution of sodium iodide (10.2 g, 68 mmol) in 95% phosphoric acid[7] (30 mL) that was stirred at room temperature. The resulting reaction mixture was stirred and heated at 110 °C for 24 h. At this point, the reaction mixture was allowed to cool to room temperature. It was then diluted with water (75 mL) and extracted with ether (3 × 30 mL). The ether extracts were combined, washed with saturated aqueous sodium thiosulfate (2 × 25 mL) and brine (30 mL), and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided 6.82 g (87% yield) of **6** as a yellow oil: ^1H NMR δ 2.88–2.78 (m, 1 H), 2.45–2.27 (m, 4 H), 2.07–1.93 (m, 4 H), 1.69–1.45 (m, 4 H); ^{13}C NMR δ 58.0 (C-2 and C-8), 51.3 (C-4), 43.1 (C-5 and C-9), 41.4 (C-3), 38.2 (C-1 and C-6), 32.9 (C-7).

2-(3-Noradamantyl)-2-adamantanol (7). A 1.96 M solution of *tert*-butyllithium in pentane (28 mL, 55 mmol) was added dropwise to a stirred solution of **6** (6.82 g, 27.5 mmol) in anhydrous ether and anhydrous pentane (2:1, 360 mL) that was maintained at −78 °C under nitrogen. After the addition was complete, the reaction mixture was stirred at −78 °C for 2 h. At this point, a solution of 2-adamantanone (8.25 g, 55 mmol) in anhydrous ether and anhydrous pentane (2:1, 300 mL) was added dropwise to the reaction mixture as it was stirred at −78 °C. When the addition was complete, the reaction mixture was stirred at −78 °C for 2 h, then at 0 °C for 1 h, and finally at room temperature for 12 h. The reaction was then quenched with water (100 mL), and sufficient ether was added to this material to dissolve the resulting solids. The layers were separated, and the organic layer was dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided a white solid. Analysis of this material by ^{13}C NMR spectroscopy showed that it consisted of a mixture of 2-adamantanone and **7** which were separated by flash chromatography on silica gel. Elution with 3% ether/hexanes provided 6.0 g (80% yield) of **7**: ^1H NMR δ 2.59 (t, J = 6.5 Hz, 2 H), 2.37–2.11 (m, 8 H), 2.00 (s, 4 H), 1.86–1.37 (m, 14 H); ^{13}C NMR δ 76.8 (s), 59.2 (s), 47.2 (t), 44.1 (t), 41.3 (d), 39.7 (t), 37.3 (d), 35.8 (d), 35.6 (t), 35.3 (t), 34.5 (t), 27.5 (d), 27.0 (d). The relative intensities of these signals are in the ratio of 1:1:2:2:1:1:2:2:1:2:2:1, respectively.

1-Hydroxy[1]diadamantane (8). A solution of **7** (6.0 g, 22.0 mmol) in 80% aqueous acetone (600 mL) that was 0.1 M in

(10) (a) Landa, S.; Kriebel, S.; Knobloch, E. *Chem. Listy* **1954**, *48*, 61–64. (b) Landa, S.; Hala, S. *Collect. Czech. Chem. Commun.* **1959**, *24*, 93–98. (c) Stetter, H.; Schwarz, M.; Hirschhorn, A. *Chem. Ber.* **1959**, *92*, 1629–1635. (d) Stetter, H.; Wulff, C. *Ibid.* **1960**, *93*, 1366–1371. (e) Stetter, H.; Schwarz, M.; Hirschhorn, A. *Angew. Chem.* **1959**, *71*, 429–430. (f) Stetter, H.; Wulff, C. *Ibid.* **1960**, *72*, 351.

(11) Fort, R. C., Jr. In "Adamantane: The Chemistry of Diamond Molecules"; Marcel Dekker: New York, 1976; Chapter 3.

(12) Duddeck, H.; Hollowood, F.; Karim, A.; McKervey, M. A. *J. Chem. Soc., Perkin Trans. 2* **1979**, 360–365. The ^{13}C NMR spectral assignments in the present paper are based on the observations and conclusions of Duddeck et al. for substituent effects on ^{13}C chemical shifts in derivatives of adamantane, [6]diadamantane, and triamantane.

(13) In ref 2, the methine resonances at δ 27.5 and 30.0 in the ^{13}C NMR spectrum of **1** are assigned to the bridgehead carbons that are α and γ to the quaternary carbon, respectively. Analysis of the ^{13}C NMR spectra of **8** and **9** shows that these assignments must be reversed.

perchloric acid was stirred at reflux for 20 h. The reaction mixture was then cooled and concentrated at reduced pressure to remove most of the acetone. The remaining material was diluted with brine (300 mL) and extracted with ether (5 × 150 mL). The ether extracts were combined, washed with saturated sodium bicarbonate (2 × 100 mL) and water (100 mL), and then dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided a white solid which was flash chromatographed on silica gel. Elution with 2% ether/hexanes gave 3.9 g (65% yield) of **8**: mp 224–225 °C (reported[1b] mp 221.6–222.5 °C); ^{1}H NMR δ 2.70 (d, J = 12 Hz, 2 H), 2.45 (s, 1 H), 2.31 (s, 3 H), 2.26 (s, 1 H), 2.12–2.0 (br s, 4 H), 1.91–1.77 (br s, 4 H), 1.71 (s, 2 H), 1.64–1.53 (br s, 4 H), 1.45 (d, J = 13.3 Hz, 2 H), 1.32 (d, J = 12.3 Hz, 4 H), 1.05 (s, 1 H, OH); ^{13}C NMR δ 75.1 (C-1), 45.9 (C-2), 43.0 (C-8 and C-9), 40.7 (C-14), 37.7 (C-6), 35.0 (C-12 and C-19 or C-16 and C-18), 33.9 (C-3), 33.4 (C-12 and C-19 or C-16 and C-18), 30.8 (C-5 and C-7 or C-11 and C-17), 30.7 (C-5 and C-7 or C-11 and C-17), 30.7 (C-4 and C-10), 27.8 (C-13 or C-15), 27.3 (C-13 or C-15); exact mass calcd for $C_{19}H_{28}O$ 272.214, found 272.216.

Anal. Calcd for $C_{19}H_{28}O$: C, 83.76; H, 10.28. Found: C, 83.81; H, 10.19.

1-Bromo[1]diadamantane (9). A solution of freshly distilled phosphorus tribromide (189 mg, 0.70 mmol) in anhydrous benzene (10 mL) was added dropwise to a stirred solution of **8** (250 mg, 0.92 mmol) in anhydrous benzene (10 mL) at 0 °C. The resulting solution was stirred for 0.5 h at 0 °C, for 1 h at room temperature, and for 2 h at 40 °C. The reaction mixture was then cooled and poured into ice water (25 mL), and the layers were separated. The aqueous layer was extracted with ether (2 × 20 mL). The organic layer was combined with the ether extracts, and they were washed sequentially with saturated aqueous sodium bicarbonate (2 × 20 mL) and water (30 mL) and then dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided 246 mg (100% yield) of **9**. As noted in the text, **9** underwent partial hydrolysis on exposure to the air. Consequently, all isolated samples of **9** contained some **8**. However, the ^{13}C NMR resonances of **9** could be identified: δ 78.1 (C-1), 49.6 (C-2), 48.6 (C-8 and C-9), 41.2 (C-14), 37.1 (C-6), 36.5 (C-3), 33.8 (C-12 and C-19 or C-16 and C-18), 32.9 (C-5 and C-7), 32.7 (C-12 and C-19 or C-16 and C-18), 31.7 (C-11 and C-17), 30.3 (C-4 and C-10), 27.6 (C-13 or C-15), 26.9 (C-13 or C-15).

1-Hydroxy[1]diadamantane from Bromide 9. A stirred mixture of **9** (30 mg) in 0.67 M aqueous hydrochloric acid (1.0 mL) and *N*,*N*-dimethylformamide (0.6 mL) was refluxed for 20 h. The reaction mixture was then cooled and extracted with ether (3 × 5 mL). The ether extracts were combined and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided 30 mg of a white solid. The ^{13}C NMR spectrum of this material was identical with that of an authentic sample of **8**.

[1]Diadamantane (1). Sulfuric acid (96%, 3.0 mL) was added dropwise to a vigorously stirred solution of **8** (463 mg, 1.7 mmol) in methylcyclohexane (10 mL) at room temperature. When the addition was complete, the reaction mixture was stirred for an additional 30 min. At this point, the stirring was stopped, and the organic layer was separated by pipette. The organic layer was then washed with saturated aqueous sodium bicarbonate (2 × 10 mL) and water (10 mL) and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure afforded a white semisolid which was recrystallized from ether to provide 210 mg (48% yield) of **1** as a white solid: ^{13}C NMR[13] δ 39.7 (C-6 and C-14), 37.5 (C-2), 32.0 (C-4, C-8, C-9, C-10, C-12, C-16, C-18, C-19), 30.5 (C-1, C-3, C-11, C-17), 27.9 (C-5, C-7, C-13, C-15).

General Workup Procedure for Bromination Reactions. The reaction mixture was diluted with carbon tetrachloride and then poured into ice water. The excess bromine that was present was destroyed by the slow addition with stirring of solid sodium bisulfite. The organic layer was then separated, washed sequentially with 5% aqueous sodium bisulfite and water and dried over anhydrous magnesium sulfate. The solvent was removed by evaporation at reduced pressure.

5-Bromo[1]diadamantane (10). A solution of **1** (400 mg, 1.56 mmol) in bromine (8 mL) and carbon tetrachloride (16 mL) was stirred at room temperature for 72 h. Workup of the reaction mixture by the general procedure gave 476 mg of a solid which was column chromatographed on silica gel. Elution with pentane provided 378 mg (73% yield) of **10** as a white solid: mp 141–142 °C; ^{1}H NMR δ 2.61 (d, J = 12.5 Hz, 2 H), 2.43 (s, 2 H), 2.30 (s, 2 H), 2.25 (s, 1 H), 2.14–1.86 (br m, 11 H), 1.81 (s, 2 H), 1.67 (s, 2 H), 1.59–1.42 (m, 5 H); ^{13}C NMR δ 67.5 (C-5) 51.0 (C-6), 43.6 (C-4 and C-9), 39.8 (C-2), 39.2 (C-14), 35.3 (C-1 and C-3), 32.1 (C-7), 31.7 (C-12 and C-18 or C-16 and C-19), 31.4 (C-12 and C-18 or C-16 and C-19), 30.5 (C-11 or C-17), 30.3 (C-11 or C-17), 29.8 (C-8 and C-10), 27.5 (C-13 and C-15).

Anal. Calcd for $C_{19}H_{27}Br$: C, 68.23; H, 8.14. Found: C, 68.02; H, 8.18.

[1]Diadamantane from Bromide 10. Lithium metal (15 mg, 2 mmol) was added to a solution of **10** (25 mg, 0.074 mmol) in anhydrous *tert*-butyl alcohol (1 mL) and anhydrous tetrahydrofuran (4 mL). The resulting mixture was stirred at room temperature for 24 h. Water (1 mL) was added then and stirring was continued for 0.5 h. The resulting solution was extracted with ether (3 × 10 mL), and the combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided 18 mg (100% yield) of a white solid. The ^{13}C NMR spectrum of this material was identical with that of an authentic sample of **1**.

5,5′-Dibromo[1]diadamantane (11). A. A mixture of **1** (73 mg, 0.285 mmol) and bromine (2 mL) was stirred at room temperature for 24 h. Workup of the reaction mixture by the general procedure provided 123 mg of a solid which was column chromatographed on silica gel. Elution with 2% ether/pentane afforded 60 mg (51% yield) of **11** as a white solid: mp 193–194 °C; ^{1}H NMR δ 2.57 (t, J = 10.6 Hz, 4 H), 2.44 (br s, 2 H), 2.30 (s, 6 H), 2.19–2.02 (m, 6 H), 1.94 (t, J = 12.4 Hz, 4 H), 1.60–1.47 (m, 4 H); ^{13}C NMR δ 65.7 (C-5 and C-13), 50.5 (C-6 and C-14), 43.4 (C-4 and C-12 or C-9 and C-19), 43.2 (C-4 and C-12 or C-9 and C-19), 38.8 (C-2), 35.2 (C-1 and C-17 or C-3 and C-11), 35.0 (C-1 and C-17 or C-3 and C-11), 31.7 (C-7 and C-15), 29.8 (C-8 and C-16 or C-10 and C-18), 29.6 (C-8 and C-16 or C-10 and C-18).

Anal. Calcd for $C_{19}H_{26}Br_2$: C, 55.07; H, 6.33. Found: C, 54.85; H, 6.36.

B. A mixture of bromide **10** (180 mg, 537 mmol) and bromine (5 mL) was stirred at room temperature for 24 h. Workup of the reaction mixture by the general procedure gave 209 mg of a white solid. Recrystallization of this material from ether provided 164 mg (74% yield) of **11**.

[1]Diadamantane from Dibromide 11. Reduction of **11** (25 mg, 0.06 mmol) with lithium metal (10 mg, 1.42 mmol) in anhydrous *tert*-butyl alcohol (1 mL) and anhydrous tetrahydrofuran (4 mL) according to the procedure described for **10** → **1** provided 15 mg (100% yield) of **1**.

5,5′,7,7′-Tetrabromo[1]diadamantane (12). A. A solution of dibromide **11** (167 mg, 0.40 mmol) in bromine (8 mL) was stirred with aluminum bromide (50 mg) at reflux for 2 h under nitrogen. Workup of the reaction mixture by the general procedure gave 226 mg (98% yield) of **12** as a white solid. Recrystallization of **12** from ether provided the analytical sample: mp 305–306 °C; ^{1}H NMR δ 2.81 (s, 4 H), 2.48 (d, J = 12 Hz, 8 H), 2.44 (s, 4 H), 2.10 (d, J = 11.7 Hz, 8 H); ^{13}C NMR δ 60.4 (C-5, C-7, C-13, C-15), 59.9 (C-6 and C-14), 41.2 (C-4, C-8, C-9, C-10, C-12, C-16, C-18, C-19), 37.9 (C-1, C-3, C-11, C-17), 37.0 (C-2).

Anal. Calcd for $C_{19}H_{24}Br_4$: C, 40.60; H, 4.30. Found: C, 40.72; H, 4.41.

B. Alcohol **8** (250 mg, 0.92 mmol) was added to a stirred mixture of bromine (4 mL) and aluminum bromide (100 mg), and the reaction mixture was refluxed for 2 h under nitrogen. Workup of the reaction mixture by the general procedure provided 518 mg (98% yield) of **12**.

Crystallographic Structural Determination of Tetrabromide 12. A colorless crystal of **12** which measured 0.15 × 0.26 × 0.32 mm was affixed to a fine glass fiber with epoxy cement. Initial photographic studies showed that the crystal belonged to the monoclinic system (Lane symmetry $2/m$). Systematic absences in the diffraction data indicated that the space group was either Cc [No. 9, C^4_s] or the centrosymmetric alternative $C2/c$ [No. 15, C^6_{2h}]; as obtained from the angular settings of 25 well-centered reflections ($22° \leq 2\theta \leq 27°$): a = 19.515 (4) Å, b = 12.566 (3) Å, c = 7.915 (2) Å, β = 103.85 (2) °, V = 1884.5 (8) Å^3, Z = 4, and ρ(calcd) = 2.101 g cm^{-3}. The centrosymmetric alternative $C2/c$ was selected, initially based upon the statistical distribution

of E values and the plausible presence of twofold rotational symmetry, and it was confirmed in the refinement of the structure. The diffraction data were collected at 24 °C ($4° \leq 2\theta \leq 45°$) with a Nicolet P3 automated diffractometer (Mo Kα, λ = 0.71073 Å). They were corrected for Lp effects and for absorption by an empirical ψ-scan technique (μ = 90.4 cm^{-1}, max/min transmission, 0.139/0.078). Of the 1412 reflections that were collected (no hkl, $h + k = 2n + 1$), 1236 of them were unique. The 1067 reflections which were considered observed [$F_o \geq 2.5\sigma(F_o)$] were employed in the solution and refinement of the structure. The direct-methods routine SOLV (SHELXTL, version 4.1) located the two unique Br atoms, and the phases generated from them located all of the non-hydrogen atoms in a subsequent difference Fourier synthesis. Following four cycles of blocked-cascade, least-squares refinement, the locations of all hydrogen atoms were found. The final cycles of refinement incorporated anisotropic parameters for all non-hydrogen atoms and isotropic parameters for the hydrogen atoms. It converged at R_F 0.0387, R_{wF} = 0.413, and GOF = 1.467. The highest peak in the final difference map was 0.67 e Å^{-3}, which was located 0.98 Å from Br(1), followed by a diffuse background at ca. 0.4 e Å^{-3}. The computer programs used in this study are contained in the P3, SHELXTL, and XP program packages that are distributed by the Nicolet Corporation. Additional information is available as supplementary material.

5,5',7-Tribromo[1]diadamantane (16). Alcohol 8 (30 mg, 0.11 mmol) was added to a solution containing 2.0 mL of bromine and 0.2 mL of a 0.96 M solution of aluminum bromide in dibromomethane, and the resulting reaction mixture was stirred at room temperature for 60 min under nitrogen. Workup of the reaction mixture by the general procedure provided 65 mg of a viscous oil. Analysis of this material by ^{13}C NMR spectroscopy showed that it contained **11** and **16** in an approximate ratio of 1:2, respectively.

When this reaction was repeated with a reaction time of 90 min, an approximately 1:1 mixture of **12** and **16** was obtained.

When this reaction was repeated with a reaction time of 120 min, the isolated material consisted of **12** and **16** in an approximate ratio of 2:1, respectively.

With the exception of the resonance for C-2, the ^{13}C NMR signals of **16** were apparent from these spectra: δ 64.5 (C-13), 61.5 (C-5 and C-7), 60.2 (C-6), 50.3 (C-14), 43.2 (C-12 and C-19), 41.4 (C-4 and C-10 or C-8 and C-9), 41.1 (C-4 and C-10 or C-8 and C-9), 38.2 (C-1 or C-3), 38.0 (C-1 or C-3), 35.0 (C-11 and C-17), 31.5 (C-15), 29.8 (C-16 and C-18).

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Supplementary Material Available: Tables of the experimental data for the crystallographic structural determination and an ORTEP drawing of **12** (3 pages). Ordering information is given on any current masthead page.

Synthesis of Mitomycin C Analogues. 1. Introduction of the Urethane Function at C-10 of the Pyrrolo[1,2-*a*]indole Skeleton

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α-(Alkoxymethylene)-2-(1-pyrrolidinyl)benzeneacetonitriles **5b–e**, prepared by condensation of 2-(1-pyrrolidinyl)benzeneacetonitrile with ethyl formate and subsequent alkylation of the sodium salt formed, cyclize thermally to the *trans*- and *cis*-9-(alkoxymethyl)pyrrolo[1,2-*a*]indoles **6b–e** and **7b–e**, respectively. Treatment of the sodium salt of **5a** with acetyl chloride or acetic anhydride affords the 1-alkylindoles **8a** and **8b**, respectively. The mechanisms of both types of reaction, which are examples of the "tertiary amino effect", are discussed. The CH_2OR group of the pyrrolo[1,2-*a*]indoles **6b,d,e** and **7b,d,e** is deprotected, dependent on the nature of R, by boron tribromide (R = CH_3), hydrobromic acid in acetic acid, and subsequent hydrolysis of the acetate formed (R = CH_2Ph) and by concentrated hydrochloric acid in methanol (R = CH_2OCH_3) to give the corresponding alcohols **6a** and **7a**, respectively. Treatment of the pyrrolo[1,2-*a*]indole **7b** with sodium in liquid ammonia yields a mixture of isomers of the 9-methylpyrrolo[1,2-*a*]indole **12b**; in addition to the cyano group at C-9 also the methoxy group has been removed. Under these conditions the alcohol **7a** affords a mixture of **12b** and the decyanated alcohols *cis*-**12c** and *trans*-**12c**. The alcohols **7a** and *trans*-**12c** are transformed to the corresponding urethanes **7g** and **12d**, respectively.

The mitomycins represent an important class of heterocyclic antitumor antibiotics that have a 2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole as the basic skeleton.[1a] Mitomycin C (**1**) is currently employed clinically, in spite of the relative high toxicity, for the treatment of solid tumors[1b] and consequently several groups are involved in the synthesis of less toxic analogues.[2,3] On the basis of structure–activity relationship studies it has been postulated that for cytotoxic activity three structural elements are required, viz., the quinone function which is possibly reduced in the cell, the urethane, and the aziridine moieties.[4] The proposed mechanism of action has been supported by several studies including the reaction of chemically reduced **1** with DNA,[5a–d] although it has to be noticed

(1) (a) "Mitomycin C: Current Status and new Developments"; Carter, S. T., Crooke, S. T., Alder, N. A., Eds.; Academic Press: New York, 1979. (b) Crooke, S. T. "Cancer Chemotherapy"; Crooke, S. T., Prestayko, A. W., Eds.; Academic Press: New York, 1981; Vol. 3, p 49.

(2) A total synthesis of mitomycin C has been performed by the group of Kishi in 47 steps starting from 2,6-dimethoxytoluene: Kishi, Y. *J. Nat. Prod.* **1979**, *42*, 549.

(3) For a few recent examples see: (a) Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1984**, *49*, 1671. (b) Rebek, J., Jr.; Shaber, S. H.; Shue, Y.-K.; Gehret, J.-C.; Zimmerman, S. *J. Org. Chem.* **1984**, *49*, 5164. (c) Crenshaw, M. D.; Zimmer, H. *J. Heterocyclic Chem.* **1984**, *21*, 623. (d) Speckamp, W. N. *Heterocycles* **1984**, *21*, 211. (e) Flitsch, W.; Russkamp, P. *Heterocycles* **1984**, *21*, 541. Also see references cited in the above.

(4) (a) Franck, R. W. *Prog. Chem. Org. Nat. Prod.* **1979**, *38*, 1. (b) Moore, H. W.; Czerniak, R. *Med. Res. Rev.* **1981**, *1*, 249.

(5) (a) Danishefsky, S.; Ciufolini, M. *J. Am. Chem. Soc.* **1984**, *106*, 6424. (b) Tomasz, M.; Jung, M.; Verdine, G.; Nakanishi, K. *J. Am. Chem. Soc.* **1984**, *106*, 7367. (c) Hornemann, U.; Keller, P. J.; Takeda, K. *J. Med. Chem.* **1985**, *28*, 31. (d) Hashimoto, Y.; Shudo, K.; Okamoto, T. *Acc. Chem. Res.* **1984**, *17*, 403. (e) Bean, M.; Kohn, H. *J. Org. Chem.* **1985**, *50*, 293. Recent other references are contained herein.

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