Lipophilic Enterobactin Analogues.[1] Terminally N-Alkylated Spermine/Spermidine Catecholcarboxamides

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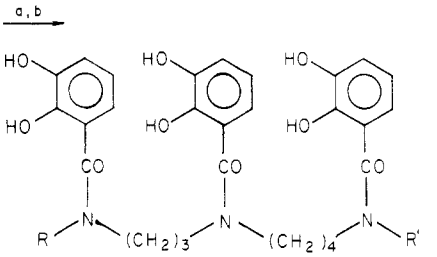
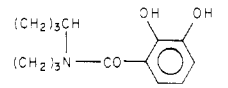
The growing activity and interest in the synthesis of new iron chelating agents has been stimulated by the potential medical application of such agents for iron overload therapy in man[3,4] and by the recognition of the importance of related natural products of microbial origin in bacterial growth and pathogenicity.[5-10] We have described the synthesis and evaluation of a number of new ferric ion sequestering agents, which in general incorporate three catechol groups to form a hexadentate coordination cavity.[11-16] These have been found to be very powerful sequestering agents for Fe(III) and are capable of removing this element from the iron transport and storage proteins transferrin and ferritin.[12,14,17,18]

In a parallel program, which recognizes the chemical similarities of Pu(IV) and Fe(III), we have also prepared related actinide(IV)-specific chelating agents which incorporate four catechol groups to achieve an eight-coordinate environment.[11,13,19,20] Initially the linear polycatecholcarboxamide (LICAM) ligands were examined. It was found that the more acidic and hydrophilic 5-sulfonated derivatives (LICAMS) are very effective in removing Pu(IV) from mice, when administered intravenously or intraperitoneally.[21] More recently the less acidic 4-carboxylated analogue (3,4,3-LICAMC) has been prepared.[13] This compound is even more effective as a Pu(IV) complexing agent in test animals and shows decreased toxicity.[13,22]

Scheme I. N-Alkylated Spermine and Spermidine Catecholcarboxamides[a]



3a, R = R' = $(CH_3)_2CH$
3b, R = R' = $CH_3(CH_2)_9$
3c, R = R' = $C_6H_5CH_2$
3d, R = R' = C_6H_{11}
3e, R = R' = $CH_3(CH_2)_7$
4a, R = $(CH_3)_2CH$; R' = $(CH_2)_3N$—CO—



[a] (a) 3 (or 4) equiv of DMBCl followed by 6 (or 8) equiv of NEt_3/THF. [b] Excess BBr_3/CCl_4 or CH_2Cl_2 followed by hydrolysis.

Since the coordination chemistries of In(III) and, especially, Ga(III) are very similar to that of Fe(III), the new iron-chelating agents may be of use in radiopharmaceuticals incorporating ^{111}In and ^{67}Ga.[23] *For this and for several other potential applications, a much greater lipophilicity of the ligand may be of critical importance in order to achieve desired tissue distribution and imaging in vivo.* Such compounds are reported here for the first time.

The selective, reductive alkylation[24] of the terminal nitrogen atoms of spermidine (**1**) and spermine (**2**) has been accomplished by using excess ketone/aldehyde in aqueous or alcoholic medium at room temperature under hydrogen (≤3 atm, catalyzed by 5% Pd/C). All hydrogenations were conducted in a Paar shaker and were continued until no further hydrogen uptake was observed. Where aldehydes were used, a prereduction period of at least 15 h was allowed for Schiff base formation to avoid reduction of the aldehyde itself. Isolated yields ranging from 14% to 80% were obtained (Table I) of the crystalline hydrochloride salts (of **1a-e** and **2a-c**), which were conveniently recrystallized from alcoholic media. Characterization of the dialkyl derivatives was readily achieved by ^1H NMR.

Regardless of the individual terminal *N*-alkyl group, synthesis of the representative LICAM compounds (**3a-e**, **4a**) was routinely accomplished by using previously reported procedures.[19,20] Their 2,3-dimethoxybenzoyl precursors (Scheme I, a) exhibited no IR absorbance near 3400 cm^{-1} (**CONH**; normally quite intense in the unsubstituted compounds). Removal of the methyl protecting groups of the catechol oxygens with excess BBr_3 produced, in good yields (Scheme I, b), LICAM ligands of increased lipophilicity. For example, the *N*-decyl derivative **3b** is quite soluble in CCl_4.

An examination of CPK molecular models indicates there should be no deleterious steric effects of the *N*-alkyl groups on Pu^{4+}/Fe^{3+} complex formation; the measurement of the effect of these bulky groups on the kinetics and thermodynamics of complex formation,[25] and in vivo organ

(1) This is paper no. 9 in the series "Ferric Ion Sequestering Agents" and no. 7 in the series "Specific Sequestering Agents for the Actinides". For the previous papers in these series see ref 17 and: Smith, W. L.; Raymond, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 3341.

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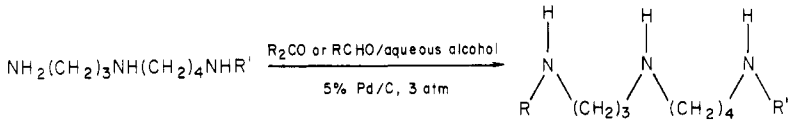
Table I. Terminally N-Alkylated Spermidine and Spermine Hydrochlorides[a]



1a-e, 2a-c

no.	R	R'	n	yield, %	reduction time,[b] h	mp, °C (nHCl salt)	recryst solv
1a	$(CH_3)_2CH$	$(CH_3)_2CH$	3	80	48	263-265	MeOH/EtOH
1b	$CH_3(CH_2)_9$	$CH_3(CH_2)_9$	3	34	72	292-295 dec	H_2O/EtOH
1c	$C_6H_5CH_2$	$C_6H_5CH_2$	3	76	1	296-297 dec	H_2O/EtOH
1d	C_6H_{11}	C_6H_{11}	3	73	72	265-267	MeOH
1e	$CH_3(CH_2)_7$	$CH_3(CH_2)_7$	3	40	75	202-205	*i*-PrOH/Et_2O
2a	$(CH_3)_2CH$	$(CH_3)_2NHCH(CH_3)_2$	4	75	65	260.5-262	MeOH/EtOH
2b	$CH_3(CH_2)_9$	$(CH_2)_3NH(CH_2)_9CH_3$	4	14	95	315	H_2O/EtOH
2c	C_6H_{11}	$(CH_2)_3NHC_6H_{11}$	4	74	72	293-294	MeOH

[a] All reductively alkylated products were isolated as their hydrochloride salts. [b] For aldehyde reactants, the reduction time was preceded by ≥15 h to allow for in situ Schiff base formation.

distribution and toxicity[23] continue to be actively studied.

Experimental Section

Melting points were taken on a Buchi apparatus in open capillaries and are uncorrected. The ^1H NMR spectra were recorded on a Varian A-60 instrument by using Me_4Si (nonaqueous) or 3-(trimethylsilyl)-1-propane sulfonic acid, sodium salt hydrate (D_2O), as an internal standard. Infrared spectra were recorded on a Perkin-Elmer 283 instrument. Evaporations were accomplished in vacuo with a Buchi Rotovapor-RE at ≤55 °C. Column chromatography was performed with 60–200-mesh silica gel in a 35 × 2.5 cm o.d. column. Microanalyses and electron-impact (EI) mass spectra (70 eV) were performed by Analytical Services, Chemistry Department, University of California at Berkeley. Spermidine (1) and spermine (2) were purchased from Ames Laboratories, Inc. Except for tetrahydrofuran (THF) which was purified by distillation from CaH_2 and 2,3-dimethoxybenzoyl chloride (DMBCl) which was prepared immediately before use from the acid (Aldrich Chem. Co.), all chemicals were used without further purification.

Representative Procedures for Reductive Alkylation. 1,10-Diisopropyl-1,5,10-triazadecane Trihydrochloride (1a). The following reactants were weighed into a Paar shaker bottle (500 mL) and hydrogenated at 1–3 atm of H_2 at 20–25 °C for 48 h: spermidine (1) 5.0 g (34.5 mmol); H_2O, 25 mL; $(CH_3)_2CO$, 25 mL; 5% Pd/C, 0.5 g (catalyst). The product mixture was filtered to remove the catalyst, and then concentrated HCl was added to achieve pH 1. Evaporation gave a solid which was dissolved in hot CH_3OH. Subsequent addition of an equal volume of EtOH with ice cooling and scratching provided fine white crystals of **1a**: 9.3 g (80%; air-dried at 110 °C); mp 263–265 °C; ^1H NMR (D_2O) δ 1.32 [d, 12 H, J_{AB} = 6.5 Hz, $(CH_3)_2CH$], 1.5–2.5 (br m, 6 H, $^+NH_2CH_2CH_2$), 2.9–3.6 (br m, 10 H, $CHNH_2CH_2$). Anal. Calcd for $C_{13}H_{31}N_3 \cdot 3HCl$: C, 46.09; H, 10.12; N, 12.40; Cl, 31.39. Found: C, 45.95; H, 10.04; N, 12.29; Cl, 31.42.

1,10-Di-*n*-decyl-1,5,10-triazadecane Trihydrochloride (1b). To an EtOH (95%, 50 mL) solution of 1 (7.3 g, 50 mmol) immersed in a water bath (20–25 °C) was added dropwise with stirring *n*-decyl aldehyde (17.2 g, 110 mmol). The reaction solution was stored under argon overnight before 5% Pd/C (1 g, catalyst) was added as an aqueous slurry. Hydrogenation (72 h) and recrystallization from hot, acidic, aqueous EtOH gave **1b**: 9.2 g (34%); mp 292–295 °C dec; ^1H NMR (TFA) δ 0.8–2.3 [complex m, 44 H, $CH_2(CH_2)_8CH_3$ and $^+NH_2CH_2CH_2$], 3.0–4.0 (br m, 12 H, NH_2CH_2), 7.0–8.7 (br m, 6 H, NH_2^+). Anal. Calcd for $C_{27}H_{59}N_3 \cdot 3HCl$: C, 60.60; H, 11.68; N, 7.85; Cl, 19.87. Found: C, 60.97; H, 11.62; N, 7.63; Cl, 19.62.

1,10-Dibenzyl-1,5,10-triazadecane Trihydrochloride (1c). Just as for **1b**, 1 (7.3 g, 50 mmol) was reductively alkylated (1 h) with C_6H_5CHO (11.7 g, 110 mmol) in 95% EtOH (50 mL). Thus was obtained **1c**: 16.5 g (76%); mp 296.7 °C (H_2O/EtOH); ^1H NMR (TFA) δ 2.0–3.9 (br m, 6 H, $^+NH_2CH_2CH_2$), 3.2–4.0 (br m, 8 H, $^+NH_2CH_2CH_2$), 4.63 (br s, 4 H, $C_6H_5CH_2$), 7.90 (s, 10 H, C_6H_5), 7.6–8.6 (br m, 6 H, NH_2^+). Anal. Calcd for $C_{21}H_{31}N_3 \cdot 3HCl$: C, 58.00; H, 7.88; N, 9.66; Cl, 24.46. Found: C, 57.92; H, 8.17; N, 9.53; Cl, 24.30.

1,10-Dicyclohexyl-1,5,10-triazadecane Trihydrochloride (1d). Just as for **1a**, 1 (5.8 g, 40 mmol) was reductively alkylated (72 h) with cyclohexanone (9.8 g, 100 mmol) in 95% EtOH (80 mL). Thus was obtained **1d**: 12.3 g (73%); mp 265–267 °C (MeOH); ^1H NMR (TFA) δ 1.3–2.7 [complex m, 26 H, $(CH_2)_5CHNH_2CH_2CH_2$], 3.3–4.0 (br m, 10 H, $CH_2NH_2CH^+$), 7.0–8.3 (br m, 6 H, NH_2^+). Anal. Calcd for $C_{19}H_{39}N_3 \cdot 3HCl$: C, 54.47; H, 10.11; N, 10.03; Cl, 25.39. Found: C, 54.39; H, 9.97; N, 9.98; Cl, 25.38.

1,10-Di-*n*-octyl-1,5,10-triazadecane Trihydrochloride (1e). Just as for **1a**, 1 (5.8 g, 40 mmol) was reductively alkylated (75 h) with *n*-octanol (12.8 g, 100 mmol) in 95% EtOH (50 mL). Thus was obtained **1e**: 7.6 g (40%); mp 202–205 °C (*i*-PrOH/Et_2O). Anal. Calcd for $C_{23}H_{51}N_3 \cdot 3HCl$: C, 57.67; H, 11.36; N, 8.77; Cl, 22.56. Found: C, 57.67; H, 10.88; N, 8.88; Cl, 22.56.

1,14-Diisopropyl-1,5,10,14-tetraazatetradecane Tetrahydrochloride (2a). Just as for **1a**, spermine (2; 5.0 g, 24.7 mmol) was reductively alkylated (65 h) with acetone (25 mL) in H_2O (25 mL). Thus was obtained **2a**: 8.0 g (75%); mp 260–262.5 °C (MeOH/EtOH); ^1H NMR (D_2O) δ 1.30 [d, 12 H, J_{AB} = 7 Hz, $(CH_3)_2CH$). Anal. Calcd for $C_{16}H_{38}N_4 \cdot 4HCl$: C, 44.45; H, 9.79; N, 12.96; Cl, 32.80. Found: C, 43.95; H, 9.36; N, 13.22; Cl, 32.66.

1,14-Di-*n*-decyl-1,5,10,14-tetraazatetradecane Tetrahydrochloride (2b). Just as for **1b**, **2** (10.1 g, 50 mmol) was reductively alkylated (95 h) in 95% EtOH (50 mL) solution. Thus was obtained **2b**: 4.5 g (14%); mp 315 °C (H_2O/EtOH); ^1H NMR (TFA), very similar to that quoted for **1b**. Anal. Calcd for $C_{30}H_{66}N_4 \cdot 4HCl$: C, 57.31; H, 11.22; N, 8.91; Cl, 22.56. Found: C, 58.30; H, 11.03; N, 8.71; Cl, 21.59.

1,14-Dicyclohexyl-1,5,10,14-tetraazatetradecane Tetrahydrochloride (2c). Just as for **1a**, **2** (6.1 g, 30 mmol) was reductively alkylated (72 h) with cyclohexanone (10 g, 100 mmol) in 95% EtOH (50 mL). Thus was obtained **2c**: 11.4 g (74%); mp 293–294 °C (MeOH); ^1H NMR (TFA), very similar to that for **1d**. Anal. Calcd for $C_{22}H_{46}N_4 \cdot 4HCl$: C, 51.56; H, 9.83; N, 10.93; Cl, 27.67. Found: C, 51.62; H, 9.66; N, 10.95; Cl, 27.58.

N^1,N^{10}-Diisopropyl-N^1,N^5,N^{10}-tris(2,3-dihydroxybenzoyl)-1,5,10-triazadecane (3a). To 2,3-dimethoxybenzoyl chloride (DMBCl, 45 mmol) dissolved in tetrahydrofuran (THF, 100 mL) was added **1a** (5.1 g, 15 mmol). To this vigorously stirred slurry was added NEt_3 (12.5 mL, 90 mmol) via pipet, resulting in substantial heat evolution. After the mixture was stirred overnight in a 60 °C oil bath, byproduct $NEt_3 \cdot HCl$ was removed by filtration and washed with THF. The combined filtrate was evaporated to crude product, which was further purified by

(25) Pecoraro, V.; Tufano, T.; Kapell, M., work in progress.

chromatography on silica gel with 0–4% (v/v) EtOH in $CHCl_3$ solutions. Thus was obtained the permethyl intermediate as a glassy, yellow oil (8.5 g, 79%), satisfactory for use in the synthesis of **3a**. Note: the IR (neat, KBr) showed the complete absence of any peak in the 3400–3200-cm^{-1} (CHNH) region. Also the ^1H NMR (CCl_4) [δ 0.9–1.4 [br m, 12 H, $(CH_3)_2CH$]] indicates a nonfreely rotating isopropyl group, normally expected to give a sharp doublet with J_{AB} = 7 Hz, as in **1a**. Deprotection of the permethyl intermediate (8.5 g, 12 mmol) in CCl_4 (50 mL) solution was achieved (under argon) by dropwise addition to a vigorously stirred solution of BBr_3 (9 mL, ~90 mmol) in CH_2Cl_2 (200 mL). The reaction vessel was immersed in a room-temperature water bath and allowed to stir overnight before workup. Next the dropwise addition of H_2O (50 mL) (**Caution**: HBr gas given off) served to hydrolyse the borates; the resulting aqueous HBr was neutralized to pH 4 by addition of 6 **N** aqueous NaOH. Solid product was isolated by filtration, dissolved in 95% ethanol, and precipitated by dropwise addition to vigorously agitated H_2O (5 volumes). Filtration, a water wash, and vacuum drying over P_2O_5/NaOH pellets at room temperature gave amorphous **3a**: 7.0 g (88%); mp 135–145 °C; ^1H NMR (TFA) δ 1.2–1.7 [br m, 12 H, $(CH_3)_2CH$], 1.5–2.7 (br m, 6 H, NCH_2CH_2), 3.3–4.6 (br m, 10 H, $CHNCH_2$), 6.9–7.5 [br m, 15 H, ArH(OH)]; IR (KBr) 3600–3100 (OH), 1605, 1580 (CONR), 1470, 1360, 1280, 790, 747 cm^{-1}; mass spectrum, *m/e* (relative intensity) 637 (M, 0.5), 501 [M – $C_6H_3(OH)CO_2$, 5], 402(3), 365 [M – $(C_6H_3(OH)CO_2)_2$], 41], 195 (71), 154 (93), 136 [$C_6H_3(OH)CO_2$, 100]. Anal. Calcd for $C_{34}H_{43}N_3O_9 \cdot 2.5H_2O$: C, 59.81; H, 7.09; N, 6.15. Found: C, 59.56; H, 7.45; N, 6.18.

N^1,N^{10}-Di-*n*-decyl-N^1,N^5,N^{10}-tris(2,3-dihydroxybenzoyl)-1,5,10-triazadecane (3b). By use of the same procedure as for **3a**, the following reactants were combined: DMBCl (30 mmol), **1b** (5.4 g, 10 mmol), THF (75 mL), NEt_3 (8.3 mL, 60 mmol). Purification as before provided the permethyl precursor (a glassy oil; 7.3 g, 79%) satisfactory for use in the final step: mass spectrum, *m/e* (relative intensity), 917 (M, 6), 886 (M – OCH_3, 28), 776 [M – $(CH_2)_9CH_3$, 13], 752 [M – $C_6H_3(OCH_3)_2CO$, 33], 165 [$C_6H_3(OCH_3)_2CO$, 40]. As before, BBr_3 (6 mL, 60 mmol) in CH_2Cl_2 (150 mL) solution and the permethyl precursor (7 g, 7.7 mmol) in CCl_4 (75 mL) solution were combined, and then H_2O was added (75 mL) followed by 6 N aqueous NaOH to achieve a pH 4 water layer. Separation of the organic layer followed by several water washes, $MgSO_4$ drying, and filtration gave a light yellow product solution. This was concentrated and then added dropwise to a large volume of vigorously stirred (60–90 °C) petroleum ether. The resulting precipitate was collected by filtration, redissolved in EtOH, and evaporated to dryness. Vacuum drying (50 °C, overnight) gave amorphous **3b**: 5.6 g (88%); mp 65–65 °C; ^1H NMR ($CDCl_3$) δ 0.8–1.4 [br m, 34 H, $N(CH_2)(CH_2)_7CH_3$], 1.2–2.2 (br m, 10 H, NCH_2CH_2), 2.9–3.9 (Br m, 12 H, NCH_2), 6.5–7.0 (br m, 9 H, Ar H), 7.7–8.4 (br, 6 H, Ar OH); IR (KBr) 3600–3100 (OH), 2930 (CH), 2860 (CH), 1610, 1585 (CONR), 1466, 1280, 1070, 790, 750 cm^{-1}; mass spectrum, *m/e* (relative intensity) 833 (M, 4), 697 [M – $C_6H_3(OH)CO_2$, 20], 136 [$C_6H_3(OH)CO_2$, 100]. Anal. Calcd for $C_{48}H_{71}N_3O_9$: C, 69.12; H, 8.58; N, 5.04. Found: C, 68.72; H, 8.72; N, 4.95.

N^1,N^{10}-Dibenzyl-N^1,N^5,N^{10}-tris(2,3-dihydroxybenzoyl)-1,5,10-triazadecane (3c). By use of the same procedures as for **3a**, the following reactants were combined: DMBCl (45 mmol), **1c** (6.5 g, 15 mmol), THF (75 mL), NEt_3 (12.5 mL, 90 mmol). Purification as before gave the permethyl precursor as a glassy oil: 9.5 g (77%) mass spectrum, *m/e* (relative intensity) 817 (M, 5), 786 (M – OCH_3, 23), 726 (M – $C_6H_5CH_2$, 13) 652 [M – $C_6H_3(OCH_3)_2CO$, 20], 165 [$C_6H_3(OCH_3)_2CO$, 88].

As before, BBr_3 (8.5 mL, ~85 mmol) in CH_2Cl_2 (200 mL) solution was added to the permethyl precursor (9 g, 11 mmol) in CCl_4 (50 mL) solution. A workup as for **3a** gave crude product which was dissolved in MeOH and added dropwise to vigorously stirred H_2O (10 volumes). The resulting precipitate was collected by filtration, water washed, and vacuum oven dried (50 °C, overnight) to yield amorphous **3c**: 5.7 g (70%); mp 105–115 °C; ^1H NMR (TFA) δ 1.3–2.7 (br m, 6 H, NCH_2CH_2), 3.1–4.5 (br m, 8 H, NCH_2), 4.5–5.5 (br, 4 H, $C_6H_5CH_2$), 7.2–8.0 [complex m, 25 H, ArH(OH)]; mass spectrum, *m/e* (relative intensity) 733 (M, 24), 597 [M – $C_6H_3(OH)CO_2$, 18], 455 (31), 330 (45), 183 (48), 149 (55), 91 ($C_6H_5CH_2$, 79). Anal. Calcd for $C_{42}H_{43}N_3O_9$: C, 68.74; H, 5.91; N, 5.73. Found: C, 68.36; H, 5.97; N, 5.63.

N^1,N^{10}-Dicyclohexyl-N^1,N^5,N^{10}-tris(2,3-dihydroxybenzoyl)-1,5,10-triazadecane (3d). By use of the same procedure as for **3a**, the following reactants were combined: DMBCl (30 mmol), **1d** (4.2 g, 10 mmol), THF (75 mL), NEt_3 (8.3 mL, 60 mmol). Purification as before provided the permethyl precursor as a glassy oil (7.9 g, 98%) satisfactory for use in the final step: mass spectrum, *m/e* (relative intensity) 801 (M, 9), 770 (M – OCH_3, 29), 718 (M – C_6H_{11}, 21), 636 [M – $C_6H_3(OCH_3)_2CO$, 54], 373 (28), 293 (51), 237 (89), 199 (69), 182 (100), 165 [$C_6H_3(OCH_3)_2CO$, 95].

As before, BBr_3 (8 mL, 84 mmol) in CH_2Cl_2 (200 mL) was added to the permethyl intermediate (7.9 g, 9.8 mmol) in CH_2Cl_2 (50 mL), and H_2O (50 mL) followed by 6 N aqueous NaOH was added to achieve pH 4 in the supernatant water layer. The organic layer was evaporated, dissolved in 95% EtOH, and combined with the gummy solid initially present in the reaction flask. Precipitation of white solid was achieved by dropwise addition of this product solution to vigorously stirred H_2O. Thus was obtained **3d**: 4.2 g (60%); mp 125–130 °C; mass spectrum *m/e* (relative intensity) 717 (M, 0.2), 652 (5), 638 (5), 581 [M – $C_6H_3(OH)CO_2$, 19], 445 [M – $C_6H_3(OH)CO_2$, 35], 136 [$C_6H_3(OH)CO_2$, 64], 110 (100); IR (KBr) 3600–3000 (OH), 2925, 2860 (CH), 1605, 1580 (CONR), 1470, 1455, 1370, 1315, 1275, 745 cm^{-1}. Anal. Calcd for $C_{40}H_{51}N_3O_9 \cdot H_2O$: C, 65.28; H, 7.26; N, 5.71. Found: C, 65.67; H, 7.05; N, 5.65.

N^1,N^{10}-Di-*n*-octyl-N^1,N^5,N^{10}-tris(2,3-dihydroxybenzoyl)-1,5,10-triazadecane (3e). By use of the same procedure as for **3a**, the following reactants were combined: DMBCl (45 mmol), **1e** (7.2 g, 15 mmol), THF (100 mL), NEt_3 (12.6 mL, 90 mmol). Purification as before provided the oil-glass permethyl precursor (10.0 g, 78%) satisfactory for use in the next step: mass spectrum, *m/e* (relative intensity) 861 (M, 16), 830 (M – OCH_3, 43), 748 [M – $(CH_2)_7CH_3$, 16], 696 (51), 403 (25), 334 (17), 165 [$C_6H_3(OCH_3)_2CO$, 100].

As before, solutions of BBr_3 (9 mL, ~90 mmol) in CH_2CL_2 (200 mL) and permethyl precursor (9.5 g), 11 mmol) in CCl_4 (50 mL) were combined under argon, and then H_2O (75 mL) followed by 6 N aqueous NaOH was added to achieve pH 3 in the supernatant water layer. A workup precisely as for **3b** gave, after overnight drying (50 °C vacuum), **3e**: 6.0 g (70%); mp 95–110 °C; IR (KBr) 3600–3000 (OH), 2960, 2920, 2860 (CH), 1605, 1580 (C=O), 1465, 1280, 1065, 790, 745 cm^{-1}; mass spectrum, *m/e* (relative intensity) 777 (M, 0.3), 641 [M – $C_6H_3(OH)OCO$, 8], 542 (4), 406 (6), 136 [$C_6H_3(OH)OCO$, 88]. Anal. Calcd for $C_{44}H_{63}N_3O_9$: C, 67.93; H, 8.16; N, 5.40. Found: C, 67.52; H, 8.16; N, 5.35.

N^1,N^{14}-Diisopropyl-N^1,N^5,N^{10},N^{14}-tetrakis(2,3-dihydroxybenzoyl)-1,5,10,14-tetraazadecane (4a). By use of precisely the same procedures as for **3a**, the following reactants were combined: DMBCL (20 mmol), **2a** (2.0 g, 4.6 mmol), THF (50 mL), NEt_3 (8.1 mL, 80 mmol). Purification as before gave a permethyl precursor satisfactory for use in the final step: 4.0 g (93%); ^1H NMR (CCl_4) δ 0.8–1.4 [br m, 12 H, $CH(CH_3)_2$], 1.5–3.5 (br m, ~22 H, $CHNCH_2CH_2$), 3.7–4.0 (complex m, 24 H, $ArOCH_3$), 6.8–7.6 (complex m, 12 H, Ar H).

As before, BBr_3 (6 mL, ~60 mmol) in CCl_4 (100 mL) and permethyl precursor (4 g, 4.2 mmol) in CCl_4 (50 mL) were combined. Hydrolysis gave a crude solid product which was dissolved in *n*-butanol and precipitated by dropwise addition to vigorously stirred Et_2O. Thus was obtained amorphous tan solid **4a**: 3 g (84%); mp 135–140 °C; ^1H NMR [Me_2SO) δ 0.8–1.3 [br m, 12 H, $(CH_3)_2CH$], indicative of a rotationally fixed isopropyl group. The lack of OCH_3 groups in the δ 4.0 region was also noted. Anal. Calcd for $C_{44}H_{54}N_4O_{12} \cdot H_2O$: C, 62.25; H, 6.65; N, 6.60. Found: C, 62.15; H, 6.42; N, 6.29.

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Registry No. 1, 124-20-9; **1a**·3HCl, 79664-20-3; **1b**·3HCl, 79664-21-4; **1c**·3HCl, 79664-22-5; **1d**·3HCl, 79664-23-6; **1e**·3HCl, 79664-24-7; 2, 71-44-3; **2a**·4HCl, 79664-25-8; **2b**·4HCl, 63888-06-2; **2c**·4HCl,

79664-26-9; **3a**, 79072-70-1; **3a** permethyl derivative, 79664-27-0; **3b**, 79664-28-1; **3b** permethyl derivative, 79664-29-2; **3c**, 79664-30-5; **3c** permethyl derivative, 79664-31-6; **3d**, 79664-32-7; **3d** permethyl derivative, 79664-33-8; **3e**, 79664-34-9; **3e** permethyl derivative, 79664-35-0; **4a**, 79664-36-1; **4a** permethyl derivative, 79664-37-2; acetone, 67-64-1; decanal, 112-31-2; benzaldehyde, 100-52-7; cyclohexanone, 108-94-1; octanal, 124-13-0; 2,3-dimethoxybenzoyl chloride, 7169-06-4.

Photochemical Fragmentation of a Methylenecyclopropane[1]

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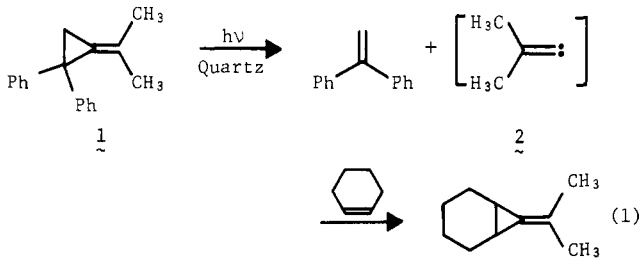
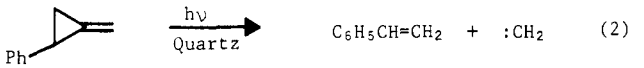
Several years ago we reported that 2,2-diphenyl-1-isopropylidenecyclopropane (**1**) undergoes photofragmentation to give 1,1-diphenylethene and, presumably, 2-methylpropenylidene (**2**), which could be trapped by alkenes (eq 1).[3] Owing to polymerization of the 1,1-diphenylethene during the course of the photolysis, it was not possible to assess the efficiency of trapping of **2**. Moreover, it was unclear from the previous study[3] whether it was electronic excitation of the aryl or the ethylenic chromophore (or both) that was responsible for the fragmentation.

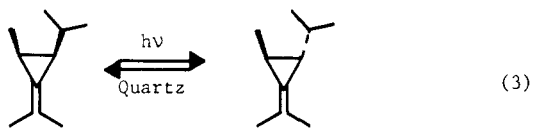


1 **2** (1)

Ample precedent exists for the proposition that excitation of the former chromophore leads to fragmentation of three-membered rings.[4] As an example, irradiation of phenylcyclopropane affords styrene and methylene (eq 2).[5]



(2)

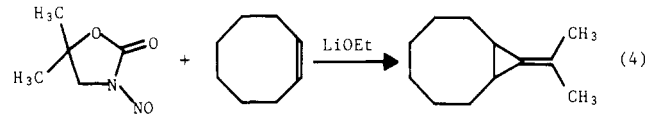


(3)

The possibility that excitation of the ethylenic chromophore could lead to ring cleavage was suggested by the observation that photolysis of *cis*-3-methyl-2-isopropyl-1-isopropylidenecyclopropane caused its conversion to the trans isomer (eq 3).[6] We wished, therefore, to examine the potential of photofragmentation in a substrate that lacked any aryl substituents. The results of that investigation are the subject of this paper.

Results and Discussion

9-Isopropylidenebicyclo[6.1.0]nonane (**3**), the substrate selected for study of the potential of photofragmentation, was synthesized by use of the procedure previously reported by Newman (eq 4).[7] The ultraviolet spectrum of this methylenecyclopropane, as expected, does not have a maximum above 200 nm, but there is significant tailing to longer wavelengths with modest extinction coefficients: ϵ (hexane) 204 (220 nm), 165 (230 nm), 60 (240 nm), 30 (250 nm). Consequently, use of a 450-W medium-pressure Hanovia lamp is sufficient to achieve excitation of the ethylenic chromophore of **3**.

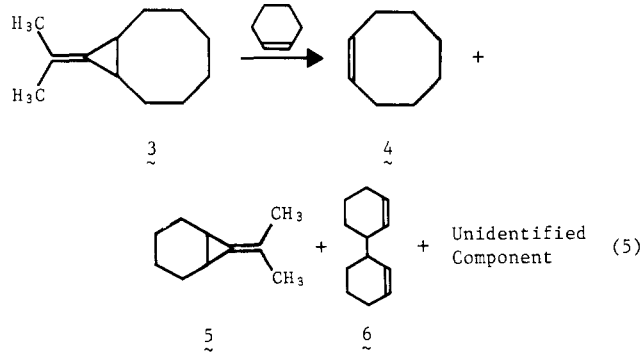


(4)

3

A preliminary experiment was executed to test for the photofragmentation of **3** and for the chemical efficiency of the process, assuming it occurred. To accomplish this, we irradiated a 0.15 vol % solution of **3** in cyclohexane through quartz with the aforementioned light source. After 12 h, 64% of **3** had been consumed, but cyclooctene, an expected fragmentation product, had been formed in only 17% yield. The approximately 30% yield of fragmentation product, based on consumption of starting material, remained constant for an additional 12 h of irradiation (see Experimental Section). Consequently, these observations suggest that photofragmentation of **3** occurs but is of only modest chemical efficiency.

To provide further support for the existence of photofragmentation, a 0.12 vol % solution of **3** in cyclohexene was photolyzed as before for a period of 26 h. Although no internal standard was present in this case, it appeared that disappearance of **3** was slower than before, presumably owing to absorption of some of the light by the cyclohexene. Analysis of the reaction mixture by gas–liquid chromatography revealed, in addition to cyclohexene, the presence of **3** and four other major volatile components in the ratio 67:7:3:21:2, respectively. Although the last of these components could not be identified, the other three were assigned, respectively, as cyclooctene (**4**), 7-isopropylidenebicyclo[4.1.0]heptane (**5**), and bi-2-cyclohexen-1-yl (**6**, eq 5). Formation of both **6** and the unidentified compound appears to be unrelated to photofragmentation of **3** as a control experiment showed that



3 **4** **5** **6** (5)

(1) Partial support of this research by the Robert A. Welch Foundation is gratefully acknowledged.
(2) Taken in part from the M.A. thesis of T.L, submitted in partial fulfillment of the degree requirements.
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