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Synthesis of Cyclophanes Derived from 1-Amino-3,7-dialkyl-4-methylnaphthalenes

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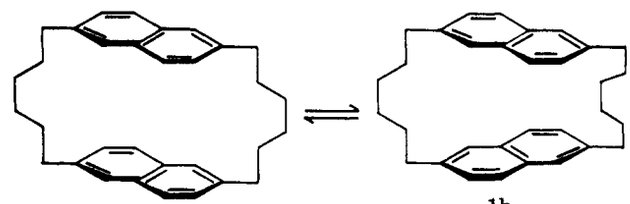
A practical five-step route is described to 1,6-bis(1′-amino-3′-carbethoxy-4′-methyl-7′-naphthyl)hexane (**6**) in 23% yield from 1,6-diphenylhexane. From **6** are prepared two 3,7-bridged naphthalene-derived cyclophanes, 1,8-[3,7][1-(dimethylamino)-4-methylnaphtha]-3,6-dithiacyclotetradecaphane[1] (**15**) and 1,11-[3,7][1-(dimethylamino)-4-methylnaphtha]-2,10-diketo-3,9-di-*N*-methylazacycloheptadecaphane[1] (**13**).

A variety of substances, both natural[2] and synthetic,[3] exhibit selective affinity in solution for smaller structures, and in many cases the affinity results from an encapsulation phenomenon not unlike that shown by enzyme–substrate interactions or other biological recognition phenomena. The 2,6-bridged naphthalenes are a class of structures that may have the potential for encapsulation and selective affinity toward smaller aromatic species. In this paper, we report the synthesis of two 2,6-bridged naphthalene cyclophanes by routes that appear to be applicable to classes of similar structures.

Our initial objective in these studies has been preparation of species with selective affinities for benzisoxazole-3-carboxylates and the capacity to catalyze decarboxylation of these species.[4] From other studies,[5,6] it is clear that such a catalyst must combine a cationic region, capable of forming a salt bridge to the carboxylate anion, with a lipophilic cavity capable of surrounding the aromatic functionalities. The presence of dipolar aprotic sites near the reacting bonds of the substrate is an additional desirable feature.[4] This substrate has been chosen as an initial candidate because of the magnitude of the solvent effect on its decomposition and its ease of study. However, it seems likely that structures that exhibit binding or catalytic effects with this simple aromatic system will show more general binding properties, and we have therefore sought an easily accessible class of species that are capable of considerable structural modification.

As seen in **1**, a pair of six naphthalene rings, linked in the 2- and 6-sites by saturated carbon chains of six atoms, can assume a number of conformations, among which are a pair, **1a** and **1b**, in which the ring planes are parallel, and



1a **1b**

the resulting cavity is ca. 5 × 6 × 3 Å in dimensions. From X-ray structural data on π complexes[7] one can estimate that a third aromatic residue can be accommodated in the interior space, its ring plane being parallel to the other two.

Hydrophobic binding of this type is believed to be driven by the tendency of hydrophobic groups to assume a minimum surface area in aqueous solutions.[8] Aqueous solubility is therefore a key property of the desired naphthalene derivatives. In the first stage of this project, which we report on in this paper, we aim at practical routes to cyclophanes of general structure **1**. The second stage is still under active investigation and involves structural modification to achieve adequate aqueous solubility, together with exploration of binding properties.

Synthesis of 1-Amino-4-methyl-7-alkyl-3-naphthoic Acids (2). Our initial objective has been synthesis of **2** in quantities sufficient to permit its use as the raw material

(1) Named following the rule proposed by H. Hirayama, *Tetrahedron Lett.*, 2109 (1972).
(2) F. Cramer and W. Kawpe, *J. Am. Chem. Soc.*, **87**, 1115 (1965); A. Windaus, *Chem. Ber.*, **42**, 238 (1909).
(3) R. Breslow and L. Overman, *J. Am. Chem. Soc.*, **92**, 1076 (1970); R. Hershfield and M. L. Bender, *ibid.*, **94**, 1376 (1972).
(4) D. Kemp, K. Paul, and D. Cox, *J. Am. Chem. Soc.*, **97**, 7305, 7312 (1975).
(5) J. Su, I. Scarpa, and I. Klotz, *J. Am. Chem. Soc.*, **98**, 7060 (1976).
(6) S Shah and J. Smid, *J. Am. Chem. Soc.*, in press. We thank Professor Smid for providing us with an advance copy of this manuscript.
(7) R. Foster, "Organic Charge-Transfer Complexes", Academic Press, New York, 1969, pp 238 ff.
(8) W. Kauzmann, *Adv. Protein Chem.*, **14**, 1 (1959).

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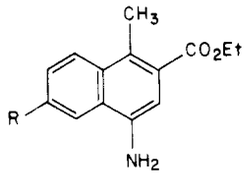
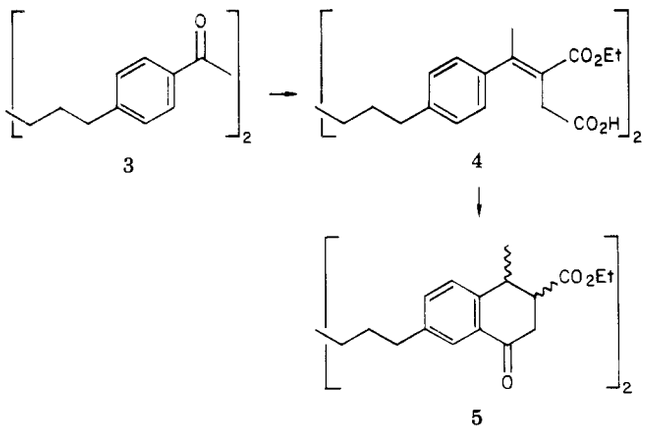


2

for studies in cyclophane formation. The framework of **2** has four sites at which structural modification can be envisaged, of which the amine and ester groups are the most obvious. We comment on these possibilities in the next section.

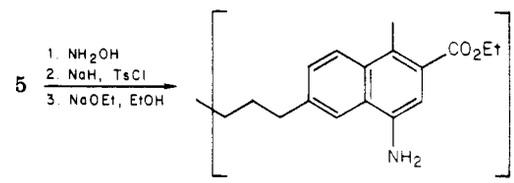
The following route has proved convenient for preparation of simple derivatives of **2** (R = H, R = *n*-*Pr*), as well as a dimeric analogue (R = $(CH_2)_6$). Friedel–Crafts acetylation of the readily available 1,6-diphenylhexane[9] yields the para-substituted bis(acetophenone) **3** as the sole



3 4 5

identifiable product, as expected. The Stobbe condensation of phenyl ketones, followed by reduction and cyclization, is a well-established route to 1-tetralones bearing 3-carboalkoxy groups.[10] The crude Stobbe product **4** is reliably obtained in 94% yield as a mixture of isomers. Hydrogenation of the tetrasubstituted double bond of **4** could be carried out satisfactorily over 10% Pd/C at high catalyst levels. Alternatives such as dissolving-metal reductions or diimide failed. Because this reaction is sluggish and must be executed batchwise, it remains the slow step in the reaction sequence. Treatment of the resulting mixture of acids with oxalyl chloride, followed by aluminum chloride, provides the crude tetralone **5** as a mixture of diastereomers.

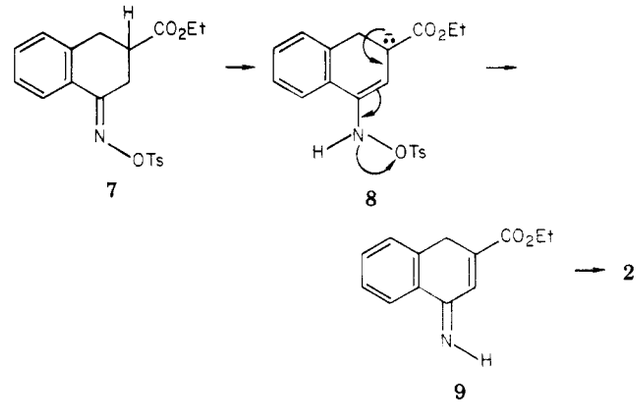
Elsewhere,[11] we have discussed the problem of converting 3-(carbethoxy)-1-tetralones to naphthylamines **2**. An intrinsically difficult enamine formation from a 1-tetralone, together with the inductive effect of the carbethoxyl group, has rendered strategies of enamine dehydrogenation unsuccessful, and we have noted earlier[11] that direct cyclizations from **3** or a related species have also failed in our hands. However, oxime formation, followed by O-tosylation and elimination, induced by sodium ethoxide, results in a smooth, reliable conversion of **5** to **6**, which is most conveniently isolated as its highly crystalline fluoroborate salt. This salt is obtained in an overall yield



6

of 34% from crystalline **3**. Although isomers of some of the intermediates in this reaction sequence have been crystallized, it has proved more convenient to proceed from **3** to **6** without purification processes, other than those involved in simple isolation. By this route, quantities of **6** have been prepared routinely and reliably.

As we have noted elsewhere,[11] this unusual reaction was designed to exploit the weak acidity of the proton α to the carbethoxyl group, with the thought that an irreversible elimination of the E1cB type must result in aromatization by several pathways, of which one is, **7** → **8** → **9** → **2**.



7 8 9

Normal Neber products are expected for *O*-tosyl oximes of 1-tetralones that lack electron-withdrawing, conjugating groups at the 3-site.[11]

The nature of this synthetic sequence offers several options for varying the structure of **2**. Rather than 1,6-diphenylhexane, other alkylbenzene or diphenylalkanes can be employed. The *p*-acyl substituent of **3** can clearly be varied, with the single constraint that formyl appears not to be suitable. Although isolated cases of aromatic aldehydes undergoing Stobbe condensations in satisfactory yields have been reported[12,13] we were unable to obtain satisfactory results with 1,6-bis(4′-formylphenyl)hexane. An alternative route to these tetralones that has shown promise involves reaction of a benzyl halide with the anion of diethyl α-(carbethoxy)succinate, followed by hydrolysis, dicarboxylation, and cyclization.

The amino groups of **6** are likely sites for introduction of substituents that may confer aqueous solubility. Although difficult to alkylate with reagents other than methyl iodide, the amino groups of **6** can be acylated under vigorous conditions. Thus, refluxing an ethyl acetate solution of **6** with 2,2-bis(acetoxymethyl)propionyl chloride and triethylamine results in a 55% conversion to the desired bis amide **10**, which can be reduced to the aminotriol **11** with diborane in refluxing THF. The 1,3-diol function of **11** allows several options for attachment of charged, solubilizing functions.

Cyclophane Formation from 6. Two proven routes from aromatic acids or benzyl derivatives to bridged aromatic structures are the conversion of the latter to thioethers as demonstrated by Boekelheide and co-workers[14]

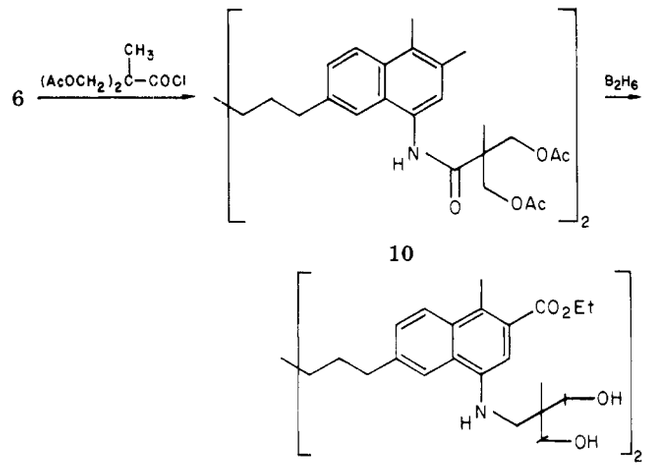
(9) Prepared from 1,4-dibenzoylbutane (R. C. Fuson and J. T. Walker, "Organic Syntheses", Collect. Vol. II, Wiley, New York, 1943, p 169) by the procedure of Sweeting and Wilshire: J. Sweeting and J. Wilshire, *Aust. J. Chem.*, 15, 89 (1962).

(10) W. S. Johnson and R. P. Graber, *J. Am. Chem. Soc.*, **72**, 925 (1950); E. C. Hornig and G. N. Walker, *ibid.*, **74**, 5147 (1952).

(11) M. Garst, D. Cox, R. Harper, and D. Kemp, *J. Org. Chem.*, **40**, 1169 (1975).

(12) See ref 10b and citations therein.

(13) W. S. Johnson and G. Daub, *Org. React.*, **6**, 1 (1951).

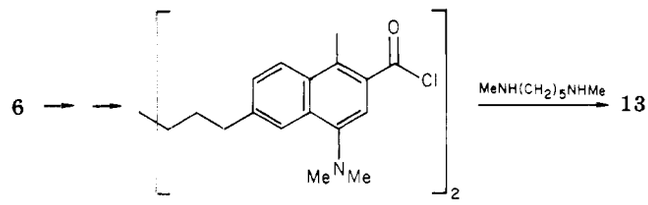


10

11

and the conversion of the former to amides, following the examples of Stetter and co-workers.[15] Both of these procedures have proved satisfactory for the conversion of **6** to 3,7-bridged naphthalene-derived cyclophanes.

Methylation of **6**, followed by hydrolysis and reaction with oxalyl chloride, generates **12**, which reacts with *N*,-



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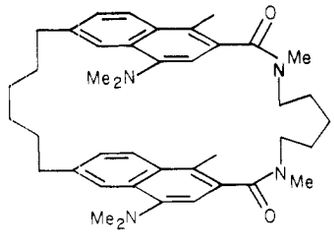
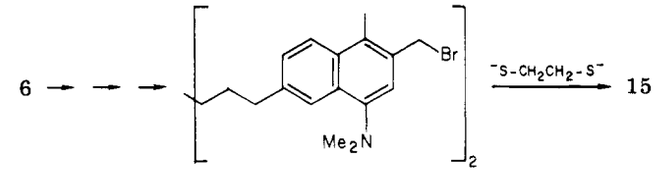
N'-dimethylpentane-1,5-diamine under high dilution conditions to give **13** as a mixture of two closely related iso-



13

mers, characterized by high-resolution mass spectrometry. Although the possibility of artifactive cross-contamination cannot be rigorously excluded, it appears that these species are stereoisomers resulting from the combined effects of hindered rotation at the amide and cyclophane centers.

Cyclophane formation by thiolate–benzyl halide condensations has been more extensively employed in our investigations. In the naphthalene series, the reaction sequence $ArCH_2OH \rightarrow ArCH_2Br \rightarrow ArCH_2SCH_2-$ is conveniently monitored by the corresponding change in ^1H NMR resonance (δ 4.8 → 4.7 → 3.8; $CDCl_3$). Methylation of **6**, followed by reduction with lithium aluminum hydride, and treatment with HBr forms the bis benzyl bromide **14**, as an unstable oil. High-dilution reaction with the dianion of ethanedithiol, followed by chromatographic isolation, yields 56% of **15**. High-resolution mass spectrometry established the molecular weight and elemental composition, which was confirmed by combustion analysis performed



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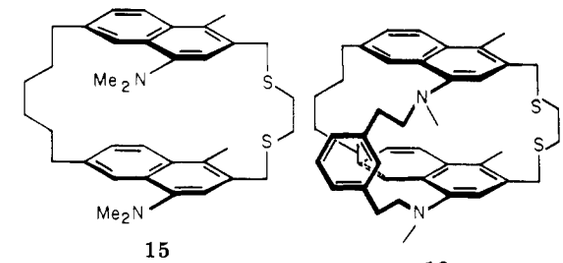

15

16

on a crystalline sample obtained by sublimation under high vacuum. Although very similar in chromatographic and spectroscopic properties, sublimed and unsublimed samples of **15** have thus far differed in that the latter cannot be induced to crystallize.

The disulfide procedure appears to be applicable to the synthesis of more complex and rigid cyclophanes, such as **16**.[16]

Experimental Section

Melting points are uncorrected and were obtained with a Thomas-Hoover apparatus. Microanalyses were performed by Midwest Microlab, Ltd., Indianapolis, IN. ^1H NMR spectra were obtained on Varian T60 and Perkin-Elmer R-22 spectrometers. High-resolution mass spectra were obtained through the courtesy of Professor Klaus Biemann.

1,6-Bis(4'-acetylphenyl)hexane (3). Acetyl chloride (110 g, 1.40 mmol) is added dropwise to a stirred suspension of anhydrous aluminum chloride (250 g, 1.88 mol) in 800 mL of 1,2-dichloroethane at 0 °C. To this stirred, cooled solution is added dropwise over 1 h 153 g (0.64 mol) of 1,6-diphenylhexane, prepared as described by Sweeting and Wilshire[9] by the Wolff–Kishner reduction of 1,4-dibenzoylbutane. After 3 h at 25 °C, the mixture is poured on to 3 L of ice and 350 mL of 12 N HCl. A liter of chloroform is added, the layers are separated, the aqueous layer is reextracted, and the combined extracts are washed with aqueous 3 N HCl, water, and brine, and dried ($MgSO_4$). Evaporation and washing with cold ether yield 167 g (80%) of 3, mp 105–107 °C.

Stobbe Condensation Product of 3 and 4. A mixture of 9.0 g (28 mmol) of **3**, 29.0 g of diethyl succinate (166 mmol), and sodium hydride (6.5 g of a 61% oil dispersion, 165 mmol) in 100 mL of dry benzene is cooled to 0 °C and stirred as 0.5 mL of ethanol is added. After 15 min at 0 °C, the mixture is stirred at 25 °C for 2 h, whereupon 100 mL of water and 150 mL of ether are added. The combined organic extracts are extracted with saturated $NaHCO_3$ solution (3 × 75 mL), and the extracts are combined, acidified (HCl), and extracted with 2 × 100 mL of ether. Drying ($MgSO_4$) and concentration yield a yellow to red oil: 15.2 g, 94%; ^1H NMR ($CDCl_3$) δ 0.8 (t, 3), 1.4 (m, 4), 2.2 (s, 3), 2.6 (m, 2), 3.6 (s, 2), 3.9 (d, 2), 7.1 (m, 5). Crystallization from benzene–hexane yielded a single isomer, mp 114–116 °C.

Anal. Calcd for $C_{34}H_{42}O_8$: C, 70.57; H, 7.32. Found: C, 70.85; H, 7.39.

When conducted on a 20-fold larger scale, the yield was 77–86%.

Conversion of 4 to Crude Tetralone 5. A mixture of 30.4 g of **4** (52.5 mmol) and 4 g of 10% Pd/C catalyst in 200 mL of acetic acid is hydrogenated at 50 psi of H_2 (Parr apparatus) until the stoichiometric amount of hydrogen is absorbed. After the reaction is 60% complete, an additional 3 g of catalyst is introduced. Roughly 50 h is required for the reaction. Filtration,

(14) R. Mitchell and V. Boekelheide, *J. Am. Chem. Soc.*, **96**, 1547 (1974).

(15) H. Stetter and J. Marx, *Justus Liebigs Ann. Chem.*, **607**, 59 (1957).

(16) Characterized by consistent ^1H NMR spectra and observation of the correct molecular ion in the mass spectrum. S. E. Denmark and D. Kemp, unpublished observations.

(17) W. R. Boon, *J. Chem. Soc.*, 307 (1947).

washing of the catalyst, and concentration yield 28 g (91%) of crude, saturated Stobbe product that is used without purification in the next step.

To the above product is added 150 mL of 1,2-dichloroethane and 30 mL of oxalyl chloride. After 17 h at 25 °C, the solvent is removed in vacuo, and the residual brown oil is dissolved in 150 mL of 1,2-dichloroethane and added dropwise to a stirred, cooled (0 °C) mixture of 16.5 g of aluminum chloride in 230 mL of dichloroethane. The resulting solution is stirred at 25 °C for 5 h and poured into a mixture of 600 g of ice and 75 mL of 12 N HCl. Addition of 600 mL of benzene with warming to dissolve solids, separation, reextraction of the aqueous phase, and pooling of the extracts yield an organic layer that is washed with 3 N HCl, 5% NH_4OH solution containing NaCl, and brine. The solution is dried (Na_2SO_4) and concentrated to yield a thick brown oil (23 g, 85%) that is used in the next step without purification.

Conversion of Tetralone 5 to 1,6-Bis[1′-amino-3′-carbethoxy-4′-methyl-7′-naphthyl]hexane (6). To a solution of sodium acetate (20.3 g, 250 mmol) and hydroxylamine hydrochloride (17.2 g, 250 mmol) in 1040 mL of 80% ethanol is added 61 g (ca. 110 mmol) of crude **5**. The mixture is refluxed for 1 h, cooled, and poured into a mixture of 1 L of water and 750 mL of ether. Separation, extraction of the organic phase with water and brine, drying (Na_2SO_4), and concentration yield 51 g (79%) of the crude oxime, which is dissolved with 39 g (210 mmol) of tosyl chloride in 300 mL of dry 1,2-dimethoxyethane and treated with sodium hydride (9.9 g of 50% oil dispersion, 210 mmol). The resulting solution is stirred under nitrogen for 19 h, cooled to 0 °C, and treated with a solution prepared by dissolving 18 g (0.78 mol) of sodium metal in 300 mL of ethanol. The resulting solution is stirred under nitrogen for 6 h at 0 °C and 1 h at 25 °C and then is poured into 1 L of water and 500 mL of dichloromethane. Separation, reextraction, pooling, drying (Na_2SO_4), and evaporation yield the crude amine as a brown oil (39 g). Stirring with 135 mL of chloroform and 52 mL of 50% fluoroboric acid for 4 h precipitates the amine salt which is collected and washed with chloroform; yield 24.3 g (47% based on crude weight of **5**, 34% based on **3**). The salt decomposes to the free amine upon drying in vacuo at 80 °C. The free amine is recovered by shaking a dichloromethane solution of the salt with aqueous bicarbonate. It may be recrystallized from methanol or chloroform–2-propanol: mp 139–141 °C; MS m/e calcd for $C_{34}H_{40}N_2O_4$ 540.2988, found 540.301 28; ^1H NMR ($CDCl_3$) δ 1.2–2.2 (m, 7), 2.6–3.1 (m, 5), 3.8 (br s, 2), 2.7 (d, 2), 7.0–7.8 (m, 3), 8.1 (d, 1); UV (EtOH, HCl) 240 nm (log ϵ 4.99), 290 (4.15), 335 (3.15); (EtOH, free base) 244 nm (log ϵ (4.62), 261 (4.62), 340 (3.63).

Anal. Calcd for $C_{34}H_{40}N_2O_4$: C, 75.52; H, 7.46; N, 5.18. Found: C, 74.93; H, 6.90; N, 5.09.

Conversion of 6 to the Amide 10 and the Aminotriol 11. An ethyl acetate solution of **6** (1.0 g, 1.8 mmol) in 50 mL of ethyl acetate containing 890 mg (3.8 mmol) of 2,2-bis(acetoxymethyl)propionyl chloride and 1.0 g (10 mmol) of triethylamine is refluxed under nitrogen for 40 h, cooled, filtered, washed with water, dried (Na_2SO_4), and evaporated to yield an oily residue. Careful successive manipulations with small volumes of ethyl acetate yield a crystalline solid: mp 137–140 °C, 0.95 g, 55%. Recrystallization from ethyl acetate–cyclohexane and acetonitrile yields material: mp 144–145 °C; ^1H NMR ($CDCl_3$) δ 1.1–2.0 (m, 20), 2.1 (s, 12), 2.5–2.9 (m, 10), 4.3 (m, 12), 7.2–7.6 (m, 4), 7.8–8.2 (m, 6).

Anal. Calcd for $C_{52}H_{64}N_2O_{14}$: C, 66.36; H, 6.86; N, 2.98. Found: C, 66.56; H, 6.84; N, 2.90.

A solution of 850 mg (0.90 mmol) of **10** in 100 mL dry THF is cooled to 0 °C under nitrogen, treated with 20 mL (20 mmol) of 1 N "borane" in THF, and warmed to reflux. A precipitate appears after 4 h. After 21 h total reflux time, the mixture is cooled to 0 °C and cautiously treated with 4 mL of 6 N HCl, whereupon the THF is evaporated on the steam bath. The residue is cooled, diluted with 10 mL of water, and brought to pH 9–11 with KOH. Centrifugation yields a solid that is combined with the residue obtained by evaporation of an ethyl acetate extract of the aqueous phase: total yield 483 mg, 81%; mp 170–175 °C; ^1H NMR (acetone-d_6) δ 1.0 (s, 6), 1.0–2.0 (m, 8), 2.5 (s, 6), 2.8 (m, 4), 3.2 (s, 4), 3.7 (s, 8), 4.7 br s, 4).

Anal. Calcd for $C_{40}H_{56}N_2O_6$: C, 72.69; H, 8.54; N, 4.24. Found: C, 72.49; H, 8.33; N, 3.97.

Conversion of 6 to 1,6-Bis[1′-(dimethylamino)-3′-(bromomethyl)-4′-methyl-7-naphthyl]hexane and then to $1^4,8^8$-Bis(dimethylamino)-1′,8^5-dimethyl-1,8-[6,2]-dinaphtha-3,6-dithiacyclotetradecaphane (15). To a solution of 0.92 g (1.69 mmol) of **6** and 5 mL (80 mmol) of methyl iodide in 47 mL of acetonitrile is added 1.0 g (7.2 mmol) potassium carbonate, and the suspension is stirred for 25 h at 22 °C, filtered, and concentrated. Trituration of the residue with carbon tetrachloride, followed by evaporation, yields 0.88 g (88%) of crude tertiary amine. The crude product is dissolved in 25 mL of THF, treated with 0.8 g (2 mmol) of lithium aluminum hydride, stirred at 25 °C for 3 h, and quenched with ethyl acetate, followed by 4 mL of 15% sodium hydroxide solution. The precipitate is collected, refluxed with THF, and discarded. The combined THF extracts are dried (K_2CO_3) and evaporated to yield 0.61 g of tan powder (80%). Recrystallization from methanol–water gives product: mp 145–147 °C; ^1H NMR ($CDCl_3$) δ 2.6 (s, 3), 2.9 (s, 6), 4.9 (s, 2).

The above product is dissolved in 10 mL of 1,2-dichloroethane, treated with 18 mL of 48% aqueous HBr, and refluxed with stirring for 4 h. The mixture is cooled, poured over 13 g of solid sodium bicarbonate, chilled to 0 °C, and brought to pH 8 (NaOH). Extraction with dichloromethane, washing with 5% NaOH solution and brine, drying (Na_2SO_4), and evaporation give 0.65 g (86%) of a tan powder: ^1H NMR ($CDCl_3$) δ 2.6 (s, 3), 2.9 (s, 6), 4.7 (s, 2).

To a solution of 180 mg (0.28 mmol) of the above dibromide in 42 mL of THF–benzene (6:4 v/v) is added 0.28 mL (0.30 mmol) of 1,2-ethanedithiol. The resulting solution is added by syringe drive over 14 h to a stirred, deoxygenated solution of 1200 mL of methanol–benzene (4:1 v/v) containing 36.8 mg (0.56 mmol) of KOH. After an additional 12 h, the solvent is evaporated, yielding 193 mg of a brown solid which is dissolved in the minimum volume of CCl_4 and applied to a chromatographic column containing 5 g of alumina. Elution with 40 mL of pentane, 65 mL of pentane–ethyl acetate (1:1), and 50 mL of ethyl acetate yields three fractions, of which the middle fraction contains the product. Evaporation of the mixed solvent yields 89 mg (56%) of crude cyclophane **15**. Repeated precipitation from 2-propanol yields a pale tan, amorphous solid which crystallizes after sublimation at 160 °C (10^{-5} mm) in 30 h: mp 190–192 °C; MS m/e calcd for $C_{36}H_{46}N_2S_2$ 570.310 25, found 570.311 80; ^1H NMR ($CDCl_3$) δ 2.3 (s, 12, CH_3N), 2.5 (s, 6, CH_3Ar)[, 2.6 (s, 4, CH_2–S), 3.8 (s, 4, $ArCH_2S$), 6.6 (s, 2, ArH), 7.0–7.8 (m, 6 ArH).

Anal. Calcd for $C_{36}H_{46}N_2S_2$: C, 75.74; H, 8.12; N, 4.91; S, 11.23. Found: C, 75.99; H, 8.17; N, 4.92; S, 11.12.

Conversion of 6 to 1,11-[3,7][1-(dimethylamino)-4-methylnaphtha]-2,10-diketo-3,9-di-*N*-methylazacycloheptadecaphane (13). Methylation of **6** as described in the above procedure, followed by saponification of 85 mg (0.14 mmol) of the resulting amino ester with 0.2 mL of 50% KOH in 10 mL of ethanol at reflux for 24 h, acidification to pH 4.5, filtration, and evaporation yield an oil (68 mg, 88%) which crystallized upon manipulation, mp 217–227 °C. A suspension of 0.74 g (1.37 mmol) of this solid in 40 mL of dichloromethane containing 6 mL of oxalyl chloride is stirred for 12 h at 25 °C, at which time solution is complete. Removal of the volatile components yields 0.91 g of a light tan, solid acid chloride hydrochloride.

The diamine, *N*,*N*′-dimethyl-1,5-diaminopentane, is liberated from its dihydrochloride salt[17] by stirring it in ethyl acetate suspension with a stoichiometric amount of KOH. Filtration and evaporation yield the free diamine.

A solution of 27 mg (0.21 mmol) of the diamine and 150 mg (1.5 mmol) of triethylamine in 50 mL of benzene is loaded into a 50-mL syringe, equipped with a 15-gauge needle, introduced beneath the surface of 350 mL of benzene contained in a 500-mL three-necked flask equipped with magnetic stirrer and nitrogen inlet. A second 50-mL syringe is loaded with 134 mg (0.21 mmol) of the acid chloride dihydrochloride, dissolved in 50 mL of dichloromethane. The two solutions are added continuously over a 12-h period by means of a dual syringe drive (Sage Instruments Model 352). After the additions are complete, the solution is evaporated, and the residue is taken up in dichloromethane and washed with water, sodium bicarbonate solution, and brine. The dried ($MgSO_4$) solution yields on evaporation 119 mg (91%) of crude cyclophane as a pale green oil. Purification by column chromatography (alumina) using pentane–ethyl acetate mixtures

yields 20–30% of product A as a white glass: ^{1}H NMR ($CDCl_3$) δ 0.9–2.0 (m, 14), 2.2–3.2 (m, 32), 6.7 (d, 2), 7.3 (d, 2), 7.8 (m, 4); UV (EtOH, H_2SO_4) 285 nm (ϵ 8.7 × 10^3), 328 (1.4 × 10^3); (EtOH, NaOH) 246 nm (ϵ 3.0 × 10^4), 313 (8.3 × 10^3); MS m/e calcd for $C_{41}H_{54}N_4O_2$ 634.424 67, found 634.427 15.

Elution with acetic acid yields, upon evaporation, 15% of product B. The ^{1}H NMR spectra of products A and B show quantitative differences in the δ 2.3–3.2 region. UV (EtOH, H_2SO_4) 285 nm (ϵ 1.0 × 10^4), 328 (1.8 × 10^3); (EtOH, NaOH) 247 nm (ϵ 3.3 × 10^4), 311–318 (7.6 × 10^3); MS m/e calcd for $C_{41}H_{54}N_4O_2$ 634.424 67, found 634.422 44.

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Registry No. **3**, 67277-61-6; **4**, 71718-58-6; **5**, 54307-68-5; **5** oxime, 71749-88-7; **6**, 54307-69-6; **6** amine salt, 71749-87-6; **10**, 71718-59-7; **11**, 71718-60-0; **12**, 71718-61-1; **13** isomer 1, 71718-62-2; **13** isomer 2, 71718-63-3; **14**, 71718-64-4; **15**, 71718-65-5; 1,6-bis[1′-dimethylamino-3′-carbethoxy-4′-methyl-7′-naphthyl]hexane, 71718-66-6; 1,6-bis[1′-dimethylamino-3′-hydroxymethyl-4′-methyl-7′-naphthyl]hexane, 71718-67-7; 1,6-bis[1′-dimethylamino-3′-carboxy-4′-methyl-7′-naphthyl]hexane, 71718-68-8; 1,6-diphenylhexane, 1087-49-6; 2,2-bis(acetoxymethyl)propionyl chloride, 17872-59-2; *N,N′*-dimethyl-1,5-diaminopentane, 56992-95-1; 1,2-ethanedithiol, 26914-40-9.

Synthetic Routes to 1,5-Diazacyclooctanes via 2,6-Diketo-1,5-diazabicyclo[3.3.1]octanes

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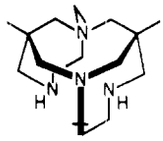
Reactions of 3-pyrazolidinones with primary β-chloropropionyl chlorides provide a satisfactory synthetic route to 2,6-diketo-1,5-diazabicyclo[3.3.0]octanes (**4**). The corresponding secondary halides cannot be induced to undergo cyclization. The Stetter procedure, reaction of acrylic acid derivatives with hydrazine at 200 °C, provides an acceptable route to derivatives that bear 4- or 8-alkyl substituents. Reactions of **4** with sodamide in ammonia generate sodium enolates that undergo C-alkylation and C-acylation reactions in high yield. Two new procedures are described for reduction of **4** to 1,5-diazacyclooctanes, treatment with diborane in refluxing THF and sodium–ammonia treatment, followed by reduction by lithium aluminum hydride (LAH). Reductions of **4** with sodium–ammonia or by sodium naphthalenide in dimethoxyethane generate 2,6-diketo-1,5-diazacyclooctanes in excellent yield. Convenient preparations of 3,6-dibromohexanoic acid and 2-acetyl-3-chloro-2-methylpropionic acid are described.

A wide variety of cyclic or polycyclic ethers, amines, and thioethers have recently been described as having unusual coordination and ion-binding properties.[1] We have been attracted to a series of cage structures, exemplified by **1**, **2**, and **3**, which have highly flexible medium-sized rings



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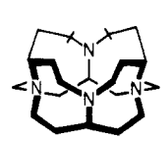

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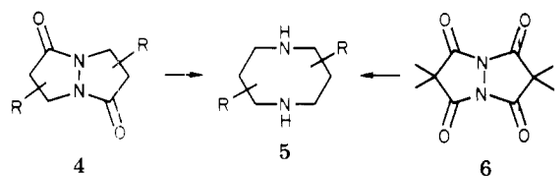
as structural subunits and which can undergo cooperative conformational changes, as illustrated by **1** and **3**. Elsewhere,[2] we describe a convenient route to 3,3,7,7-tetrasubstituted 1,5-diazacyclooctanes of the type required for the synthesis of **1**.[3] This route involves diborane reduction of the readily available tetrones **6**. General and reliable



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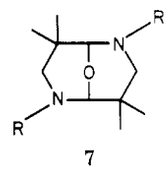
synthetic routes to the 1,5-diazacyclooctane building block are essential prerequisites for the synthesis of cage species like **1**, **2**, or **3**. Here we report observations concerning the utility of an alternative route to **5** via the bicyclic diones **4**.

A variety of syntheses of 1,5-diazacyclooctanes have been described. Direct synthesis of the eight-membered ring has been reported by β-tosylamino epoxide dimerization,[4] by ring expansion,[5] and by a novel pericyclic reaction of azines.[6] Reductive cleavage of the anhydro dimers (**7**) of



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Mannich products of secondary amines, formaldehyde, and α-branched aldehydes appears to be a method that is generally applicable to the synthesis of 3,3,7,7-tetrasubstituted 1,5-diazacyclooctanes.[7] Stetter and co-workers[8] have reported the reaction of hydrazine with acrylic acids or esters to form diones **4** which these workers reduce in two steps, LAH followed by hydrogenolysis of the N–N bond, to 1,5-diazacyclooctanes **5**. Diones **4** have also been

(1) J. Christensen, D. Eatough, and R. Izah, *Chem. Rev.*, **74**, 351 (1974); C. J. Pedersen and H. K. Frensdorff, *Angew. Chem., Int. Ed. Engl.*, **11**, 16 (1972); H. E. Simmons and C. H. Park, *J. Am. Chem. Soc.*, **90**, 2428, 2431 (1968); B. Dietrich, J. M. Lehn, and J. P. Sauvage, *Tetrahedron Lett.*, 2885, 2889 (1969).

(2) D. S. Kemp, R. V. Punzar, and J. C. Chabala, *Tetrahedron Lett.*, **547** (1978). X-ray analysis (Dr. J. P. Springer) has shown that the substance reported as **1** is in fact its trans isomer.

(3) D. S. Kemp, J. C. Chabala, and S. A. Marson, *Tetrahedron Lett.*, **543** (1978).

(4) V. R. Gaertner, *Tetrahedron*, **23**, 2123 (1967); W. N. Paudler and A. G. Zeiter, *J. Org. Chem.*, **32**, 2425 (1967).

(5) M. Rothe and R. Timler, *Chem. Ber.*, **95**, 783 (1962); H. K. Hall, *J. Chem. Soc.*, **80**, 6404 (1958).

(6) T. Wagner-Jauregg, L. Zirngibl, A. Demolis, H. Gunther, and S. Tam, *Helv. Chim. Acta*, **52**, 1672 (1969).

(7) C. Mannich and H. Wieder, *Chem. Ber.*, **65**, 385 (1932); M. W. Williams, *J. Org. Chem.*, **33**, 3946 (1968).

(8) H. Stetter and H. Spangerberger, *Chem. Ber.*, **91**, 1982 (1958); H. Stetter and K. Findeisen, *ibid.*, **98**, 3228 (1965).

0022-3263/79/1944-4473$01.00/0