Tetrahedron, Vol. 40, No. 23, pp. 4823 to 4828, 1984.
Printed in Great Britain.

0040-4020/84 $3.00+ .00

METHYLATED MULTIBRIDGED [2_n]CYCLOPHANES. AN ALTERNATE SYNTHESIS OF [2_6](1,2,3,4,5,6)CYCLOPHANE (SUPERPHANE)

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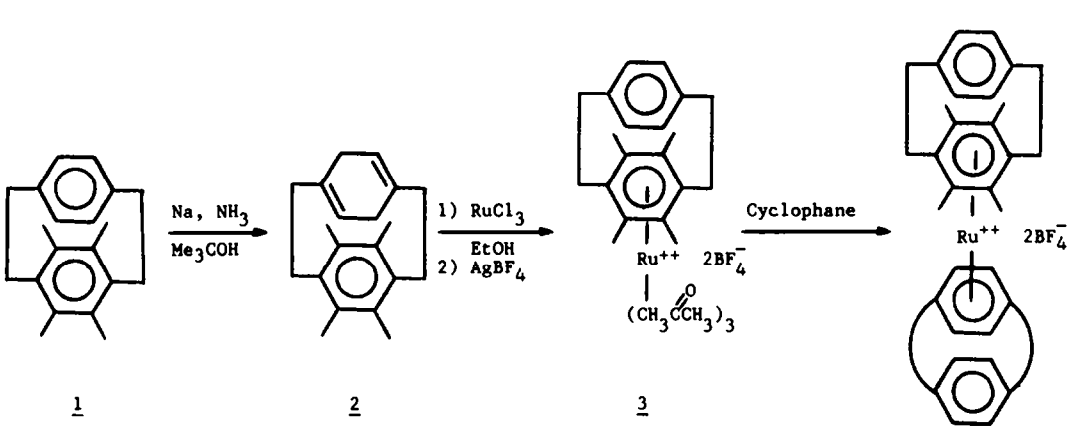
(*Received in USA 7 August* 1984)

Abstract - A sequence of formylation followed by a carbene insertion reaction has led to the stepwise introduction of additional ethano bridges into 4,5,7,8-tetramethyl[2_2](1,4)cyclophane (1), providing syntheses of 5,7,8-trimethyl-[2_3](1,2,4)cyclophane (6), a mixture of 5,8-dimethyl[2_4](1,2,4,5)cyclophane (10) and 5,7-dimethyl[2_4](1,2,3,5)cyclophane (11), and 4-methyl[2_5](1,2,3,4,5)-cyclophane (14). This route to 14 completes a formal eight-step synthesis of [2_6](1,2,3,4,5,6)cyclophane (15, superphane) with an overall yield of 17%. A Birch reduction of 6 readily gave 12,15-dihydro-5,7,8-trimethyl[2_3](1,2,4)-cyclophane (7) in 85% yield.

Recently,[1] we described an experimental procedure for preparing 4,5,7,8-tetramethyl[2_2](1,4)-cyclophane (1) in quantity via the dithiacyclophane route.[2] Birch reduction of 1, as anticipated, gave only a mono-Birch product, 12,15-Dihydro-4,5,7,8-tetramethyl[2_2](1,4)cyclophane (2), which proved useful for preparing (η^6-4,5,7,8-tetramethyl[2_2](1,4)cyclophane)ruthenium(II) solvates (3) and bis(η^6-cyclophane)ruthenium(II) bis(tetrafluoroborates) (4).[1]



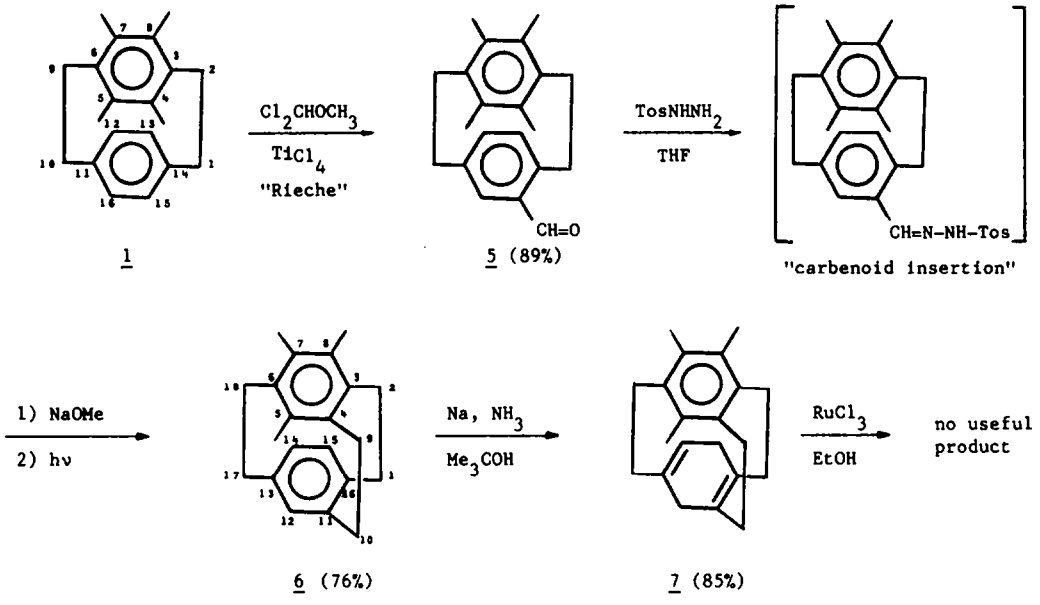
1 2 3 4

Because of the general interest in the properties of cyclophane-transition metal complexes and the potential of their polymers for conducting electricity,[2-5] we sought to explore the generality of this approach in which [2_n]cyclophanes having one deck fully substituted give only

mono-Birch reduction products. An obvious route to methylated, multibridged [2_n]cyclophanes was the successive elaboration of 1 to introduce additional ethano bridges. As was first shown by Cram et al.,[6] and subsequently by others,[7,8] pseudo-gem formyl and methyl groups in [2_n]cyclophanes are readily converted to ethano bridges via a carbenoid insertion reaction. Thus, it seemed possible that Rieche formylation[9] of 1 followed by carbenoid insertion via the corresponding tosylhydrazone[6-8] would allow introduction of an additional ethano bridge and repetition of this sequence could then, in principle, provide a group of [2_n]cyclophanes having 3,4, and 5-bridges with one deck always fully substituted. Finally, four repetitions of this sequence with 1 might provide an alternate synthesis of [2_6](1,2,3,4,5,6)cyclophane (15, superphane).[10]

As shown in Scheme 1, Rieche formylation readily gave the corresponding aldehyde 5 and this, in turn, via the tosylhydrazone-carbenoid insertion sequence, led to 5,7,8-trimethyl[2_3](1,2,4)-cyclophane (6) in good yield. Further, Birch reduction of 6 proceeded smoothly to the desired

Scheme 1



1

5 (89%)

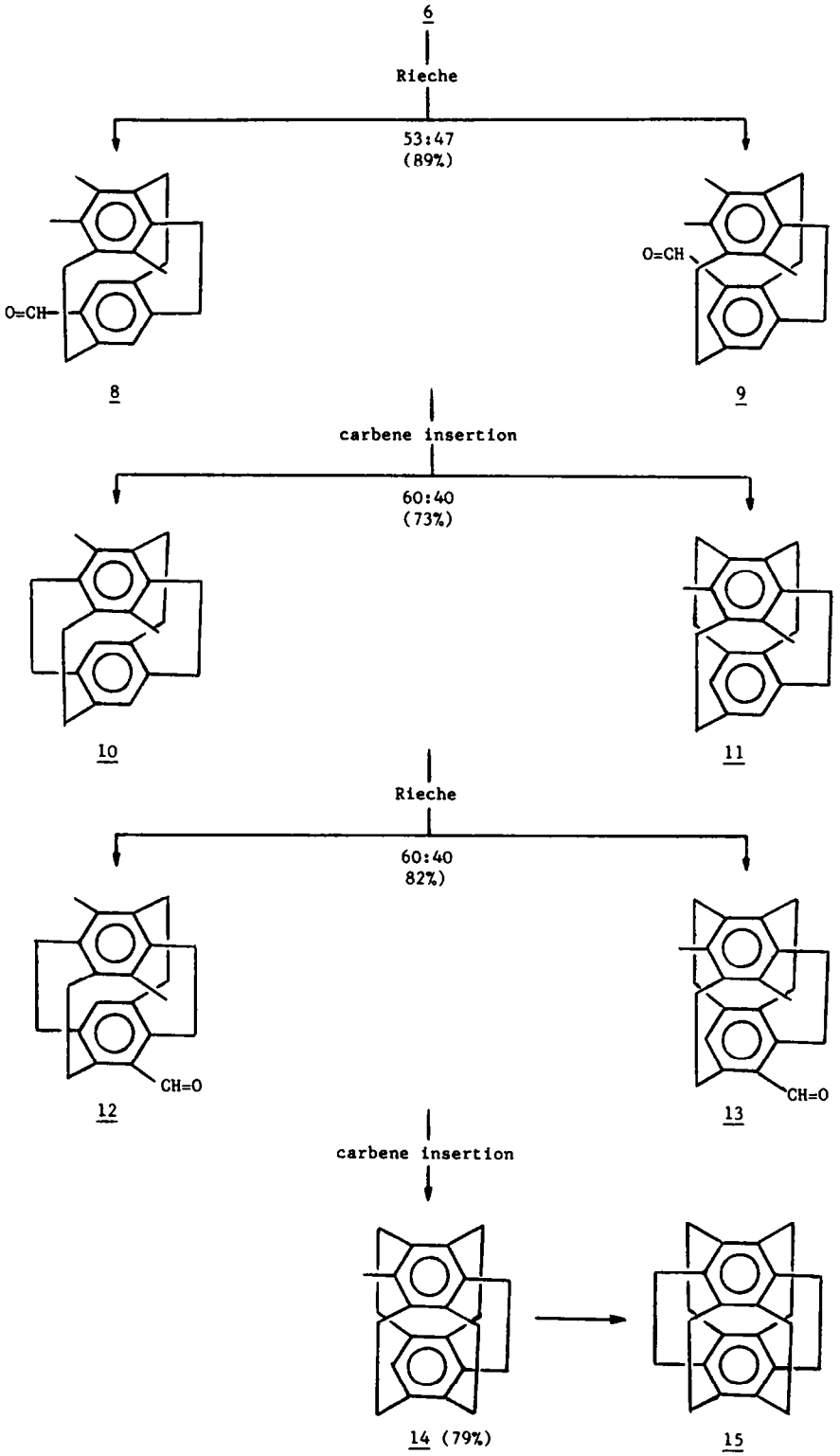
6 (76%)

7 (85%)

mono-Birch reduction product 7. Unfortunately, though, the reaction of 7 with ruthenium trichloride gave no useful product. The reaction of dihydroarenes with ruthenium trichloride to give (η^6-arene)ruthenium(II) complexes is a complicated reaction whose mechanism is unknown. Thus, there is no good basis for speculating on the reasons for the failure of the reaction in this case. However, this failure did discourage further attempts to explore this approach to cyclophane-ruthenium(II) complexes with other multibridged [2_n]cyclophanes.

However, the success of the bridge-building sequence employed for the conversion of 1 to 6 and the availability of ample quantities of 1 led us to explore an iterative scheme for preparing the methyl-substituted, higher-bridged [2_n]cyclophanes. As shown in Scheme 2, Rieche formylation of 6 gave a mixture of 8 and 9 in 89% yield. Because of steric hindrance, presumably, the third possible isomer was not formed in sufficient quantity to be observed. The ^{1}H NMR spectrum of the mixture of 8 and 9 was well resolved in the aromatic region, showing two singlets for 9 and two doublets with a small meta-coupling constant (2 Hz) for 8. From the integrated areas of the spectrum the relative ratio of 8:9 could be deduced to be 53:47. Despite much effort it was not possible to effect a clean separation of 8 and 9 and so the mixture was simply carried on through

Scheme 2


6
Rieche
53:47
(89%)
O=CH
O=CH
8
9
carbene insertion
60:40
(73%)
10
11
Rieche
60:40
82%)
CH=O
CH=O
12
13
carbene insertion
14 (79%)
15

the subsequent stages. El-tamany and Hopf in their analogous studies on similar multibridged [2$_n$]cyclophanes were likewise unable to separate similar mixtures and also carried through their reaction sequence with mixtures.[10]

Subjection of the mixture of 8 and 9 to the carbene insertion step via the corresponding tosylhydrazones gave a mixture of 10 and 11 in 73% yield. Based again on an analysis of the ^{1}H NMR spectrum of the mixture the ratio of 10:11 was found to be 60:40. Rieche formylation of the mixture of 10 and 11 then gave a mixture of 12 and 13 in the ratio of 60:40 with an overall yield of 82%. Finally, repetition of the carbene insertion step gave the known 4-methyl[2$_5$](1,2,3,4,5)-cyclophane (14) as a single pure compound whose properties were identical with those described previously.[10] The further conversion of 14 to superphane (15) was carried out and proceeded as described by El-tamany and Hopf.[8,10]

Our inability to separate the isomeric mixtures at intermediate stages of the synthetic route in Scheme 2 is a deficiency in this approach, for it would be highly desirable to have pure samples of 10 and 11. However, as an alternate synthetic route to superphane this eight-step approach is reasonably satisfactory, since the yields at each stage are good and the starting material is readily available. Although the synthesis of superphane from 4,5,12,13-tetramethyl[2$_2$](1,4)-cyclophane by El-tamany and Hopf, following the same methodology, is only six steps, their approach has the drawback that the bis(formylation) of 4,5,12,13-tetramethyl[2$_2$](1,4)cyclophane occurs in poor yield (16%).

EXPERIMENTAL[11]

4,5,7,8-Tetramethyl-13-formyl[2$_2$](1,4)cyclophane, 5. To a solution of 4.70 g (17.8 mmol) of 4,5,7,8-tetramethyl[2$_2$](1,4)cyclophane (1)[1] in 200 mL of dry dichloromethane held at 0°C there was added 7.81 mL (71.1 mmol) of titanium tetrachloride followed by 11.09 mL (138 mmol) of dichloromethyl methyl ether. The mixture was stirred for 70 min at 0°C and then at room temperature for 45 min. The reaction mixture was poured into a separatory funnel which contained ice and an aqueous sodium bicarbonate solution. Additional dichloromethane (600 mL) was added and the organic layer was separated, washed with water, and dried. Concentration of the extract gave a colored residue which was chromatographed over silica gel with benzene as eluent. From the main fraction of eluent there was isolated 4.62 g (89%) of a yellow crystalline solid. Recrystallization of a sample from 95% ethanol gave white plates; mp 179-180°C; IR (KBr) ν_{max} 2810, 1670 cm^{-1}; ^{1}H NMR, δ 10.03 (1 H, s, CHO), 7.17 (1 H, br s, ArH), 6.80 (1 H, d of ABd, J = 2 and 8 Hz, ArH), 6.68 (1 H, ABd, ArH), 3.05-2.80 (1 H, m, CH$_2$), 2.25-1.80 (7 H, m, CH$_2$), 2.00, 1.96, 1.93, 1.80 (3 H, s, ArCH$_3$); UV (CHCl$_3$) λ_{max} 302 nm (ϵ = 1750), 254 (sh) nm (ϵ = 8,120); mass spectrum, m/e 292 (M$^+$), 160.

Anal. Calcd for $C_{21}H_{24}O$: C, 86.26; H, 8.27. Found: C, 85.75; H, 8.70

5,7,8-Trimethyl[2$_3$](1,2,4)cyclophane, 6. To a solution of 4.60 g (15.7 mmol) of 5 in 1200 mL of tetrahydrofuran was added 3.08 g (16.5 mmol) of p-toluenesulfonylhydrazine and 100 mg of p-toluenesulfonic acid as a catalyst. The solution was boiled under reflux overnight and then transferred to an immersion well that surrounded a quartz cooling jacket. A stream of nitrogen was bubbled through the magnetically stirred solution for 15 min prior to the addition of 20 g (37.0 mmol) of sodium methoxide. Photolysis with a 400-Watt medium-pressure mercury Hanovia lamp and with a Pyrex filter contained in the quartz cooling jacket was done for 1.5 h while maintaining the nitrogen flow. Concentration of the reaction mixture was followed by the addition of dilute aqueous hydrochloric acid and dichloromethane. The organic layer was separated, washed with water, and dried. Concentration of the extract gave a red oil which crystallized upon standing. The product mixture was chromatographed over silica gel with benzene as eluent. The main product fractions were combined to give 3.29 g (76%) of a yellow crystalline solid. A sample was recrystallized from 95% ethanol to give white plates; mp 154-156°C; IR (KBr) ν_{max} 2810, 1450 cm^{-1}; ^{1}H NMR, δ 6.37 (3 H, s, ArH), 3.15-2.60 (12 H, m, CH$_2$), 2.06, 1.89, 1.78 (3 H, s, ArCH$_3$); ^{13}C NMR (CDCl$_3$) δ 141.4 (s), 139.4 (s), 139.3 (s), 138.4 (s), 138.1 (s), 137.0 (s), 134.9 (s), 133.0 (s), 132.8 (s), 132.7 (d), 128.1 (d), 127.3 (d), 34.1 (t), 31.9 (t), 31.4 (t), 29.5 (t), 28.7 (t), 27.8 (t), 19.5 (q), 16.8 (q), 16.6 (q); UV (CHCl$_3$) λ_{max} 303 nm (ϵ = 340); mass spectrum, m/e 276 (M$^+$), 261 (M$^+$ - CH$_3$).

Anal. Calcd for $C_{21}H_{24}$: C, 91.25; H, 8.75. Found: C, 90.98; H, 9.01.

12,15-Dihydro-5,7,8-trimethyl[2$_3$](1,4)cyclophane, 7. To a stirred solution of 100 mg (4.3 mmol) of sodium in 40 mL of anhydrous ammonia there was injected a solution of 333 mg (1.2 mmol) of 6 and 2 mL (21.2 mmol) of dry tert-butanol in 25 mL of dry tetrahydrofuran. After 40 min,

the reaction mixture was quenched by the addition of 95% ethanol, allowed to warm to room temperature, and left to stand overnight. The residual liquid was mixed with dichloromethane and water; the organic layer was separated, washed twice with water, and dried. Concentration of the extract gave 283 mg (85%) of a white crystalline solid. An analytical sample was prepared by thin-layer chromatography over silica gel with cyclohexane as eluent followed by sublimation of the product to give a white powder; mp 145–150°C; IR (KBr) ν_{max} 2890, 1450, 1420 cm^{-1}; ^1H NMR, δ 4.82–4.74 (1 H, m, CH), 3.20–1.60 (16 H, m, CH_2), 2.32 (3 H, s $ArCH_3$), 2.12 (6 H, s, $ArCH_3$), UV (cyclohexane) λ_{max} 294 nm (ϵ = 140), 221 (ϵ = 9,500); mass spectrum, m/e 278 (M^+), 276 ($M^+ - 2H$), 263 ($M^+ - CH_3$).

Anal. Calcd for $C_{21}H_{26}$: C, 90.59; H, 9.41. Found: C, 90.19, H, 9.73. Molecular weight calcd for $C_{21}H_{26}$: 278.203. Found: (high resolution mass spectrum) 278.203.

14-Formyl-5,7,8-trimethyl[2.3](1,2,4)cyclophane, 8, and 15-Formyl-5,7,8-trimethyl[2.3](1,2,4)-cyclophane, 9. To a solution of 120 mg (0.43 mmol) of 6 in 10 mL of dry dichloromethane held at 0°C was added 0.20 mL (1.71 mmol) of tin tetrachloride followed by 0.16 mL (1.77 mmol) of dichloromethyl methyl ether. The purple mixture was kept at 0°C for 50 min and then at room temperature for an additional 100 min. The mixture was poured into a separatory funnel containing ice and an aqueous solution of sodium bicarbonate. Additional dichloromethane (100 mL) was added and the organic layer was separated, washed with water, and dried. Concentration of the extract gave a yellow solid which was chromatographed over silica gel with benzene as eluent to give 118 mg (89%) of a faint yellow powder; mp 165–180°C; IR (KBr) ν_{max} 2920, 1670 cm^{-1}; ^1H NMR, δ 10.00, 9.90 (1 H, s, CHO); 9: 6.94 (.53 H, s, ArH), 6.54 (.53 H, s, ArH); 8: 7.03 (.47 H, d, J = 2 Hz, ArH), 6.57 (.47 H, d, ArH); 3.04–2.80 (1 H, m, CH_2), 3.25–2.70 (11 H, m, CH_2), 2.12, 2.09, 1.90, 1.68 (6 H, s $ArCH_3$), 1.80 (3 H, s, $ArCH_3$); UV ($CHCl_3$) λ_{max} 296 (ϵ = 2,800), 256 (sh) (ϵ = 7,100); mass spectrum, m/e 304 (M^+), 289 ($M^+ - CH_3$).

Anal. Molecular weight calcd for $C_{22}H_{24}O$: 304.183. Found: (high resolution mass spectrum) 304.183.

5,8-Dimethyl[2.4](1,2,4,5)cyclophane, 10, and 5,7-Dimethyl[2.4](1,2,3,5)cyclophane, 11. To a solution of 115 mg (0.38 mmol) of the mixture of aldehydes 8 and 9 in 40 mL of tetrahydrofuran was added 85 mg (0.46 mmol) of p-toluenesulfonylhydrazine and two small crystals of p-toluenesulfonic acid as a catalyst. The solution was boiled under reflux overnight before an additional 110 mL of tetrahydrofuran was added. This solution was transferred to an immersion well that surrounded a quartz cooling jacket. A stream of nitrogen was bubbled through the solution for 15 min before 1.2 g (22.2 mmol) of sodium methoxide was added. The photolysis (400-Watt Hanovia lamp, Pyrex filter) was done for 1 h, maintaining the stream of nitrogen. The reaction mixture was concentrated, mixed with dilute hydrochloric acid and dichloromethane. The organic layer was separated, washed with water, and then dried. Concentration of the extract gave a solid which was chromatographed over silica gel with benzene as eluent. The main product fractions were combined to give 80 mg (73%) of a faint yellow powder; mp 220–225°C; IR(KBr) ν_{max} 2940, 1480, 1400 cm^{-1}; ^1H NMR, 10: δ 6.33 (.60 H, s, ArH); 11: 6.05 (.4 H, s, ArH); 3.24–2.60 (16 H, m, CH_2), 1.99 (10) (1.2 H, s, $ArCH_3$), 1.96 (11) (1.8 H, s, ArH); mass spectrum, m/e 288 (M^+), 273 ($M^+ - CH_3$), 262, 260.

Anal. Molecular weight calcd for $C_{22}H_{24}$: 288.188. Found: (high resolution mass spectrum) 288.188.

12-Formyl-5,8-dimethyl[2.4](1,2,4,5)cyclophane, 12, and 12-Formyl-5,7-dimethyl[2.4](1,2,3,5)-cyclophane, 13. To a stirred solution of 49 mg (0.17 mmol) of the mixture of 10 and 11 in 30 mL of dichloromethane held at 0°C there was added by injection through a serum cap 0.10 mL of dichloromethyl methyl ether and 0.08 mL of titanium tetrachloride. The resulting dark red solution was stirred at 0°C for 3 h and then was allowed to warm to room temperature and stirring was continued an additional 10 h. A mixture of 30 g of ice and 40 mL of a saturated, aqueous solution of sodium bicarbonate was added with stirring and then the organic layer was extracted with dichloromethane. After the extract was washed with water and dried, it was concentrated and the residual solid was chromatographed over silica gel using benzene for elution. From the main fraction of eluate there was isolated 44 mg (82%) of a mixture of 12 and 13 as a pale yellow solid; mp 250–260°C w. dec.; IR ($CHCl_3$) ν_{max} 1670, 2930–2980, and 3040 cm^{-1}; ^1H NMR, δ 10.26 (1 H, s, -CHO), 10.19 (1 H, s, -CHO), 6.50 (1 H, s, ArH), 6.29 (1 H, s, ArH), 2.5–3.5 (32 H, m, $-CH_2-$), 2.26 (3 H, s, $-CH_3$), 2.19 (3 H, s, $-CH_3$), 2.01 (3 H, s, $-CH_3$), 1.82 (3 H, s, $-CH_3$); UV ($CHCl_3$), λ_{max} 212 nm (ϵ = 79,900), 262 (ϵ = 16,936), 323 (ϵ = 4,750).

Anal. Molecular weight calcd for $C_{23}H_{24}O$: 316.183. Found: (high resolution mass spectrum) 316.183.

4-Methyl[2.5](1,2,3,4,5)cyclophane, 14. To a solution of 20 mg of the mixture of 12 and 13 in 25 mL of tetrahydrofuran was added 35 mg of p-toluenesulfonylhydrazine and two crystals of p-toluenesulfonic acid. After the solution had been boiled under reflux for 6 h, it was transferred to the immersion well of a quartz cooling jacket. A stream of nitrogen gas was bubbled through the solution to effect degassing of oxygen before adding 500 mg of sodium methoxide. While continuing the flow of nitrogen, the solution was irradiated for 1 h using a 400-Watt Hanovia lamp with a Pyrex filter. Then the mixture was concentrated before adding dichloromethane and dilute aqueous hydrochloric acid. The organic layer was separated, washed with water, dried, and concentrated. Chromatography of the residual solid over silica gel using a 5:1 mixture of chloroform–hexane gave 15 mg (79%) of 14 as white crystals, mp 333–335°C dec. The other properties of 14 agreed in all respects with those described previously for this compound by El-tamany and Hopf.[10]

ACKNOWLEDGMENT

We thank the National Science Foundation for their support of this investigation.

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10. While this study was in progress, S. El-tamany and H. Hopf (Chem. Ber., 116, 1682 (1983)) reported a synthesis of superphane from 4,5,12,13-tetramethyl[2_2](1,4)cylophane using this repetitive sequence of formylation and carbenoid insertion.
11. Elemental and mass spectral analyses were determined by Dr. R. Wielesek of the University of Oregon microanalytical laboratories. All of the mass spectra were taken on a CEC-21B-110 instrument. ^{1}H NMR spectra were measured with a Varian XL-100 instrument using deuteriochloroform as solvent and residual chloroform (δ 7.27) as an internal standard. Ultraviolet spectra were obtained using a Cary 15 spectrometer and infrared spectra using a Sargeant Welch 3-200 spectrometer. Melting points were taken using sealed evacuated melting point tubes and are uncorrected.