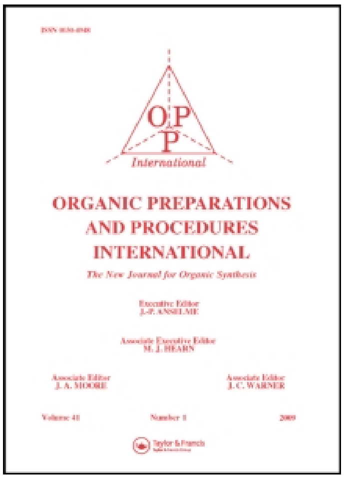

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SYNTHESIS OF POTENTIAL PRECURSORS OF HEPTABOWTIENE, A NOVEL NON-BENZENOID HYDROCARBON

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SYNTHESIS OF POTENTIAL PRECURSORS OF HEPTABOWTIENE, A NOVEL NON-BENZENOID HYDROCARBON

Submitted by
(02/21/92)

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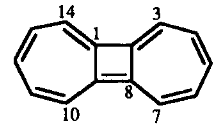
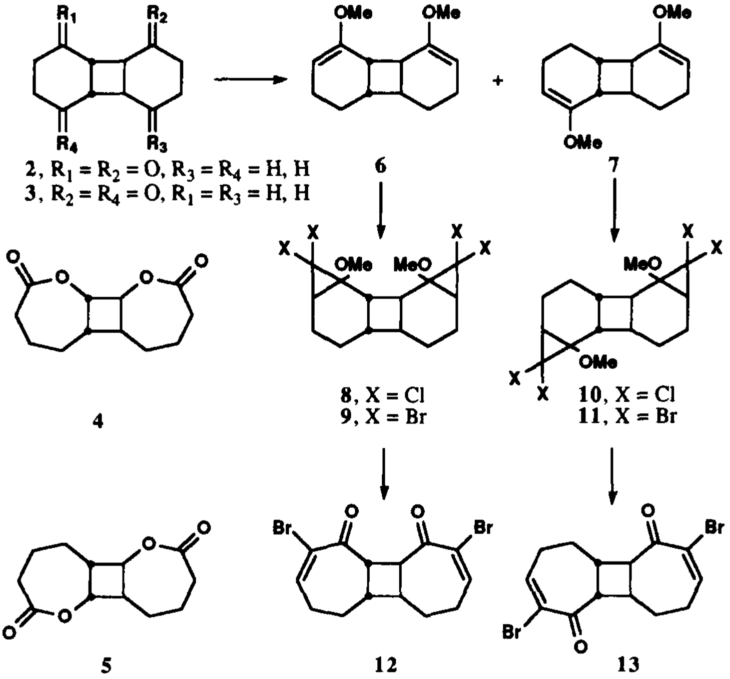
Tricyclo [7.5.0.0^{2,8}] tetradeca-1,3,5,7,9,11,13 heptaene (heptabowtiene), **1**, is a 4n + 2π electron, non-benzenoid , conjugate-unsaturated hydrocarbon for which some calculations of structural parameters have been performed;[1] however, no attempted synthesis was found in the literature. Additional calculations and the synthesis of two potential precursors (**12** and **13**) to **1** are now reported.[2] It was envisioned that **12** and/or **13** could be convened to **1** by (i) removal of the halides by radical hydrogenolysis (*e. g.*, with Ph_3SnH), (ii) reduction of the carbonyl groups to hydroxyls, (iii) bis-elimination to generate two additional ring double bonds, and (iv) vapor phase dehydrogenation over a Pd.C catalyst[3] or, alternatively, allylic bromination followed by dehydrohalogenation.



1

HMO, SCF[4] and SE (strain energy)[5] calculations[6] for planar **1** gave values of 66.3 kcal/mole for the SE and DE (delocalization energy) values of 74.8 kcal/mole (HMO) and 59.2 kcal/mole (SCF) for net RE (resonance energy) estimates of +8.5 and -7.1 kcal/mole, respectively. The HMO method showed two electrons in a nonbonding orbital, and the SCF calculations showed four antibonding electrons but a large HOMO-LUMO energy difference. SCF-MO calculations for fulvalene and heptafulvalene show filled antibonding MOs and large HOMO-LUMO gaps, yet these compounds have been synthesized and isolated.[7] The calculated bond orders of 0.536-0.646 (HMO) and 0.545-0.646 (SCF) and bond lengths of 1.401-1.419 Å (SCF) for **1** showed values close to those of benzene for the peripheral bonds and without bond alternation, and of 1.473 Å (SCF) indicative of more single bond character for the internal bonds (which are single in both Kekule structures).[8] The charge density values of -0.090-0.115 (HMO) and -0.104-0.133 (SCF) were a little smaller than those for azulene (-0.173-0.145) and the free valence values of 0.264-0.472 (HMO) and 0.299-0.461 (SCF), with the ssmaller value in each case at the ring juncture carbons, were in the general range of aromatic hydrocarbons. Application of the Craig Symmetry Rules[9] to **1** gave an even sum for the symmetrically related π centers plus the number of spin interconversions about the axis of symmetry and thus predicted a symmetric valence bond ground state and probable aromatic stability. The conjugated circuits criterion[10] predicts a positive RE for **1**.

Tricyclic diketones **2** and **3**[11] were converted to lactones **4** and **5**, respectively, to confirm the geometries of the ring junctures. The ^{1}H NMR spectra of the cyclobutane hydrogens in **2** and **3** were unresolved multiplets but peaks for the hydrogens on the oxygen-bearing cyclobutane carbons in **4** and **5** were a doublet and a doublet of doublets, respectively, as expected for the structures shown. Treatment of a mixture of **2** and **3** with 2,2-dimethoxypropane under acidic conditions formed **6** and **7**. Reaction of **6** with chloroform and potassium *tert*-butoxide afforded the bis-dichlorocarbene adduct **8** (76%) and, analogously, **10** was formed from **7**. The ^{1}H NMR spectrum of **8** indicated that essentially one isomer (of three possible) was formed. The tetrabromo compounds **9** and **11** corresponding to **8** and **10** were prepared using bromoform in the same procedures. Attempts to convert **8** and **10** to dimethoxy derivatives of **1** lacking one double bond by treatment with a variety of bases were unsuccessful. Treatment of **9** and **11** with silver perchlorate[12] formed **12** (71%) and **13** (86%), respectively. These compounds were rather unstable.



2, $R_1 = R_2 = O$, $R_3 = R_4 = H, H$
3, $R_2 = R_4 = O$, $R_1 = R_3 = H, H$

4

5

6

7

8, X = Cl
9, X = Br

10, X = Cl
11, X = Br

12

13

EXPERIMENTAL SECTION

Melting points were taken on a Fisher apparatus and are uncorrected. Spectra were recorded on a Cary Model 115 or 14 spectrophotometer with 1 cm silica cells (UV-vis), a Varian Model A-60 with Me_4Si internal standard (NMR), and a Perkin-Elmer Model 21 (IR). Molecular weights were measured on a Mechrolab model 301A Vapor Pressure Osmometer (benzene solvent) calibrated with benzil. Elemental analyses were performed by Dr. A. Bernhardt, Mulheim, Germany.

***cis,trans,cis*-3,4-Dihydroxycyclobutane-1,2-dibutanoic Acid Dilactone (4).**- To a stirred mixture of 1.01 g (5.2 mmol) of **2** and 20 mL of dry diethyl ether in a 50-mL, 3-necked flask fitted with a condenser and drying tube vas added 1.8 g (0.01 mol) of *m*-chloroperbenzoic acid (2.3 g of 80% solution) in 10 mL of ether. The whole was stirred for 72 hrs during which time a colorless precipitate formed on the sides of the flask. Titration (0.01 N thiosulfate) of an aliquot showed decomposition of 95% of the per acid. The washed (ether) and dried precipitate gave 0.31 g (26%) of **4**, mp 155-160° and 172-173° after recrystallization from $CHCl_3$ and then benzene. IR: 1745 cm^{-1}: ^1H NMR ($CHCl_3$): δ 4.89 (d, 2H, $J = 6.5$ Hz, CH-O).

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.52; H; 7.42

***cis,trans,cis*-2,4-Dihydroxycyclobutane-1,3-dibutanoic Acid Dilactone (5).**- As described for the preparation of **4** except that the *m*-chloroperbenzoic acid (2.235 g of 80% solution) was added over 10 min to the cooled (ice bath) residue (impure **3**, 1.0 g, from the filtrate from the separation of solid **2** from the product mixture obtained from the photodimerization of 2-cyclohexene-1-one by the method of Eaton)[13] and 20 mL of dry ether, the whole was heated to reflux, 6 drops of trifluoroacetic acid was added, reflux was maintained for 6 hrs and then stirring was continued for an additional 68 hrs at room temperature. There was obtained 0.195 g (ca. 17%) of **5** as a colorless solid, mp 205-220° and 238-240° after recrystallization from $CHCl_3$. IR: 1744 cm^{-1}. IR: 1744 cm^{-1}. ^1H NMR ($CHCl_3$): δ 4.56 (dd, 2H $J_{cis} = 3.8$ Hz, $J_{trans} = 7.7$ Hz, CH-O).

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.27 H, 7.19. Found: C, 64.19; H, 7.11

***cis,trans,cis*-Tricyclo(6.4.0.0^{2,7}]-3,12-dimethoxy-3,11-diene (6) and *cis,trans,cis*-Tricyclo[6.4.0.0^{2,7}]-3,9-dimethoxy-3,9-diene(7).**- To 15.7 g (0.082 mol) of a mixture of the *syn* (**2**) and *anti* (**3**) photodimers of 2-cyclohexene-1-one, obtained by the method of Eaton,[13] in a 200-mL pear-shaped flask was added 150 mL (126 g, 1.22 mol) of 2,2-dimethoxypropane and 0.24 g ot 5-sulfosalicylic acid dihydrate. The mixture was swirled until dissolution was complete and then was fractionally distilled over a 3 day period through a 570 x 10 mm Heli-Pac column fitted with a total reflux, partial take-off distillation head. After most of the acetone, methanol, and excess dimethoxypropane were removed, distillation of the residue in a 25-mL one-piece Claisen apparatus under N_2 at 227 kPa gave 1.4 g (bp 115-124.5°) and 12.3 g (bp 124.5-126°) of colorless liquids. After several days, 0.32 g and 4.5 g, respectively, of crystalline solid separated from the fractions. The crystals were collected, washed with pentane, combined, and recrystallized from methanol; yield 3.43 g (19%) of **6**, mp 105.5-107°. IR (CCl_4): 1661, 2817, 2899 and 2967 cm^{-1}. ^1H NMR ($CHCl_3$): δ 1.53-

2.38 (m, 8H), 2.52 (m, 4H), 3.53 (s, 6H, OCH_3), 4.75 (t, 2H, J = 4.2 Hz, C=CH).

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15; CH_3O, 28.14. Found: C, 76.69; H, 8.89; CH_3O, 28.60

The identity of **6** was shown by hydrolysis in aqueous methanol with 5-sulfosalicylic acid as the catalyst to give **2**, mp 77.5-78° (lit.[9] 79-80°). The IR spectrum of the combined filtrates was similar to that of **6**. The presumption that this contained **7** was shown by subsequent conversion to **10, 11**, and **13**.

Pentacyclo[7.5.0.0^{2,8}.0^{3,5}.0^{12,14}]-3,14-dimethoxy-4,4,13,13-tetrachlorotetradecane (8).- A 100 mL, 3-necked flask was fitted with a Hirschberg stirrer (N_2 inlet side arm), retlux condenser through which was inserted a - 100° to 50° thermometer, and a capillary tube (2 mm i.d.) which was connected to a 125-mL leveling bulb. A uniformly twisted thin nichrome ribbon was inserted into the bulb and capillary tube. A drying tube was attached to the condenser and the apparatus was flushed with dry N_2 overnight. Tricyclodimethoxydiene **6** (2 g, 9.1 mmol),$CHCl_3$ (40 mL, 60 g, 0.5 mol), and 20 mL of pentane were placed in the flask and the solution was cooled to -50° to -40°. Powdered potassium *tert*-butoxide (4.9 g, 44 mmol) was added from the leveling bulb to the stirred solution in small portions by turning the nichrome ribbon screw over 3.5 hrs. The mixture, which became yellow orange, was stirred another 15 min at -30° and was then allowed to stand at room temperature overnight. The now yellow mixture was extracted with 2 x 40 mL of H_2O and the combined aqueous layers were extracted with $CHCl_3$. The yellow solid residue from the combined organic solutions was chromatographed (200 x 14 mm, basic Al_2O_3, benzene). Recrytalliztion of the pale yellow solid (3.06 g) from the first fraction from methanol gave 2.32 g of **8** as colorless crystals, mp 129.5-130°, and 0.34 g obtained from the filtrate made a total ot 2.66 g (76%). IR ($CHCl_3$): 812 and 824 (C-Cl), 874 and 885 (cyclobutane ring), 990 (cyclopropane ring), 1109 (ether), 1449 (methylene), 2825 and 2907 cm^{-1} (C-H). ^1H NMR ($CHCl_3$): δ 1.1-2.3 (complex multiplets, 12H) 3.08 (d, 2H, J = 7 Hz, cyclobutane H alpha to cyclopropane ring), 3.53 (s, 6H, OCH_3).

Anal. Calcd. for $C_{16}H_{20}Cl_4O_2$: C, 49.76; H, 5.22; Cl, 36.73; CH_3O, 16.07; MW 386.1
Found: C, 49.77; H, 5.36; Cl, 36.79; CH_3O, 16.28; MW 388.9

Pentacyclo[7-5.0.0^{2,8}.0^{3,5}.0^{10,12}]3,10-dimethoxy-4,4,11,11-tetrachlorotetradecane (10).- Crude **7**[14] from the mixture of **6** and **7** after removal of the crystals of **6** (*vide supra*) (8.0 g) was dissolved in a few mL of dry n-pentane and placed in a 200-mL flask equipped as described for the preparation of **8** except that a pressure-equalizing addition funnel replaced the capillary tube and leveling bulb. The system was flushed with N_2 overnight. Chloroform (50 mL, 75 g) was added and the solution was cooled to -40°. A slurry of potassium *tert*-butoxide (1 5.6 g) in 20 mL ot n-pentane was added gradually (1 hr) to the stirred solution with the aid of a nichrome wire inserted into the funnel. An additional 15 mL ot n-pentane was used to wash all of the butoxide into the flask. The mixture was stirred for an additional hour and then was allowed to warm to room temperature. The inorganic precipitate was separated by filtration and washed with $CHCl_3$. Extraction ot the filtrate twice with H_2O, evaporative removal of the solvent, and chromatrography of the brown residual oil twice over neutral alumina (benzene) gave 8.5 g of yellow solid. Recrystallization from methanol-acetone and then from acetone gave 2.45 g of colorless crystals, mp 151-153°, the ^{1}H NMR spectrum of which indicated the presence of 84% of **10** (δ 3.37 for the ether function) and 16% of an isomeric compound (δ 3.42) different from **8**. On the basis of **7** comprising 70% ot the starting mixture, the yield of **10** was 21%. Further chromatography and recrystallization afforded pure **10**, mp 160-161°. IR ($CHCl_3$): 1106 and 813 cm^{-1}. ^{1}H NMR ($CHCl_3$): δ 1.2-2.4 (complex multiplet, 10H), 2.53 (broad "singlet", 4H, cyclobutane ring), 3.38 (s, 6H, OCH_3).

Anal. Calcd. for $C_{16}H_{20}Cl_4O_2$: C, 49.76; H, 5.22; Cl, 36.73; CH_3O, 16.07
Found: C, 49.72; H, 5.13; Cl, 36.76; CH_3O, 16.16

Pentacyclo[7.5.0.0^{2,8}.0^{3,5}.0^{10,14}]-3,14-dimethoxy-4,4,13,13-tetrabromotetradecane (9).- In the manner described for the preparation of **10** except that the initial solvent was a mixture of benzene (5 mL) and n-pentane (40 mL), the reaction temperature was -20 to -15°, and the reaction mixture was held at -5° for 1.5 hr after the addition of potassium *tert*-butoxide, from 2.0 g (9.1 mmol) of **6** and 14.4 g (5 mL, 57 mml) of $CHBr_3$ was obtained 3.16 g (61%) of **9** as colorless crystals, mp 114-122° (dec). Further crystallization (methanol-acetone) gave an analytical sample, mp 126-130° (dec). IR ($CHCl_3$): 850, 861, 889, 983 and 1010 cm^{-1}. ^{1}H NMR ($CHCl_3$): 1.0-2.0 (Complex multiplet, 10H), 2.19 (broad "singlet", 2H), 3.05 (d, 2H, J = 6 Hz, cyclobutane H alpha to cyclopropane ring), 3.57 (s, 6H, OCH_3).

Anal. Calcd. for $C_{16}H_{20}Br_4O_2$: C, 34.07; H, 3.57; Br, 56.68; CH_3O, 11.00
Found: C, 34.41; H, 3.76; Br, 56.73; CH_3O, 11.11

The addition of the potassium *tert*-butoxde as a solution in *tert*-butyl alcohol gave a 64% yield, mp 120-124° (dec) but the souton tended to solidify in the addition funnel.

Pentacyclo[7.5.0.0^{2,8}.0^{3,5}.0^{10,12}]-3,10-dimethoxy-4,4,11,11-tetrabrometetradecane (11).- In the manner described for the preparation of **9** except that the initial solvent was 20 mL of benzene and 50 mL ot n-pentane, the potasstm *tert*-butoxide (0.15 mol in 150 mL of *tert*-butyl alcohol) was added over a 3.5 hrs period, and the tennperature during and for 1 hr after the addition was -10°, was obtained from impure **7**[14] (8 g) and $CHBr_3$ (36.8 g, 0.145 mol) 6.23 g of tan solid, mp 146-148° (dec) and 1.21 g, mp 139-148° (dec) as a second crop. An additional 1.32 g, mp 142-149° was obtained from the $CHCl_3$ extract of the aqueous layer for a total crude yield of 7.55 g (63% based on 70% of **7** in the starting material). The NMR peaks for OCH_3 indicated the prescence of an 83:17 ratio of two isomers, both different from **9**. Chromatography of a sample over neutral alumina (benzene) followed by recrystallization from acetone and then $CHCl_3$ gave **11** as colorless crystals, mp 153-155° (dec). IR ($CHCl_3$): 1109 cm^{-1}. ^{1}H NMR ($CHCl_3$): δ 1.1-2.6 (complex multiplet, 14H, containing a broad "singlet", 4H, cyclobutane H, and a broad "singlet", 3H cyclopropane plus other H), 3.40 (s, 6H, OCH_3).

Anal. Calcd. for $C_{16}H_{20}Br_4O_2$: C, 34.07; H, 3.57; Br, 56.68; CH_3O, 11.00
Found: C, 34.20; H, 3.78; Br, 56.89; CH_3O, 10.93

Tricyclo[7.5.0.0^{2,8}]-3,14-dioxo-4,13-dibromotetradeca-4,12-diene (12). - A mixture of 0.29 g (0.52 mmol) of **9**, H_2O (6g, 0.33 mol), and acetone (30 mL) was heated under reflux. When the solid had dissolved, a solution of $AgClO_4$ (1.04 g, 5 mmol) in 3 mL of acetone was added. A white solid separated immediately. After *ca.* 17 hrs, an additional 0.16 g of $AgClO_4$ was added and reflux was continued for 4 hrs. Filtration of the cooled mixture gave 0.18 g of gray solid (95% as AgBr) and dilution of the filtrate with H_2O formed 0.175 g of a colorless solid. Recrystallization from $CHCl_3$-CCl_4 gave 0.12 g of **12**, mp 138-144° (dec), and a second crop of 16 mg, mp. 147-151° (dec); total yield 0.136 g (71%). IR ($CHCl_3$): 1613, 1689 cm^{-1}. UV-vis (CH_3OH): 209, 265 nm. ^1H NMR ($CDCl_3$): δ 1.25-2.1 (complex multiplet, 4H, CH_2), 2.1-2.9 (complex multiplet, 6H, allylic H, cyclobutane H beta to C=O), 3.97 (d, 2H, J = 9.5 Hz, cyclobutane H alpha to C=O), 5.93 (dd, 2H, J = 6 Hz and 3.75 Hz, C=CH).

Anal. Calcd. for $C_{14}H_{14}Br_2O_2$: C, 44.95; H, 3.77; Br, 42.73. Found: C, 45.10; H, 3.91; Br, 42.6O

Tricyclo[7.5.0.0^{2,8}]-3,10-dioxo-4,11-dibromotetradeca-4,11-diene (13).-In the manner described for the preparation of **12** except that the stirred mixture of 0.57 g (1 mmol) of **11**, 2.1 g (10 mmol) of $AgClO_4$ in 10 mL ot acetone, 12 g (0.67 mol) of H_2O and 70 mL ot acetone was refluxed for 48 hrs, there was obtained 0.35 g of dark gray precipitate (95% as AgBr) and 0.32 g (86%) of **13** in two crops: 0.21 g of colorless crystals and 0.11 g of pink solid. Recrystallization of the first material from $CHCl_3$ gave colorless cruystals, mp 188-195° (dec). UV ($CHCl_3$): λ_{max} 264 nm. IR: ($CHCl_3$) 690, 922, 1001, 1608, 1681, 2976 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.7-2.1 (m, 4H, nonallylic CH_2), 2.46 (m, 4H, allylic CH_2), 3.10 (m, 4H, cyclobutane H), 6.92 (dd, 2H, J = 5.0 Hz and 4.0 Hz, vinyl H).

Anal. Calcd. tor $C_{14}H_{14}Br_2O_2$: C, 44.95; H, 3.77; Br, 42.73. Found: C, 45.01; H, 3.93; Br, 42.80

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14. The IR spectrum indicated an approximate composition of 70% of **7** and 30% of **2** and **3** based on the enol ether (1602 cm^{-1}) and carbonyl (1709 cm^{-1}) absorptions.

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AN IMPROVED SYNTHESIS OF 4,7-DIMETHOXY-1H-INDOLE

Submitted by
(03/16/92)

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As part of a program to design selective inhibitors for various pathways of signal transduction, we required a simple, high-yield synthesis that would provide multigram quantities of 4,7-dimethoxy-1H-indole (**7**). The preparation of this compound has been described previously through the reductive cyclization of readily derived (E)-1,4-dimethoxy-2-nitro-3-(2-nitroethenyl)benzene (**6**) either with iron in acetic acid[1,2] or *via* transfer hydrogenation.[3] In our hands, neither of these methods was suitable for scale-up operations. We now report a improved sequence to nitrostyrene **6** and its clean conversion to **7** utilizing high pressure hydrogenation over Pearlman's catalyst (10% $Pd(OH)_2/C$).

Two routes to target **7** were explored as shown in the scheme. In the first, condensation of commercially available 2,5-dimethoxybenzaldehyde (**1**) with nitromethane under conditions described by Dallacker and Bernabei[4] proceeded cleanly to give the known nitrostyrene **2**[5,6] in 71% yield. Nitra-