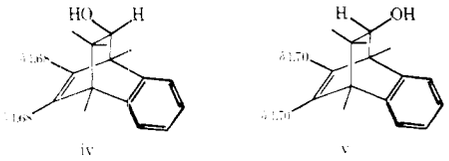
moconjugation between the carbonyl group and the double bond since it is wiped out when the carbonyl group is reduced (iv and v, A. C. Gripper Gray and H. Hart, loc. cit.). The substantial reversal of these shifts in **7** and **8** and the marked difference in the vinyl methyls in alcohols **16, 19, 20, 21, 22,** and **23** must be ascribed to the N–O bridge and/or shielding by the *N*-phenyl group.



iv v

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Permethylnaphthacene

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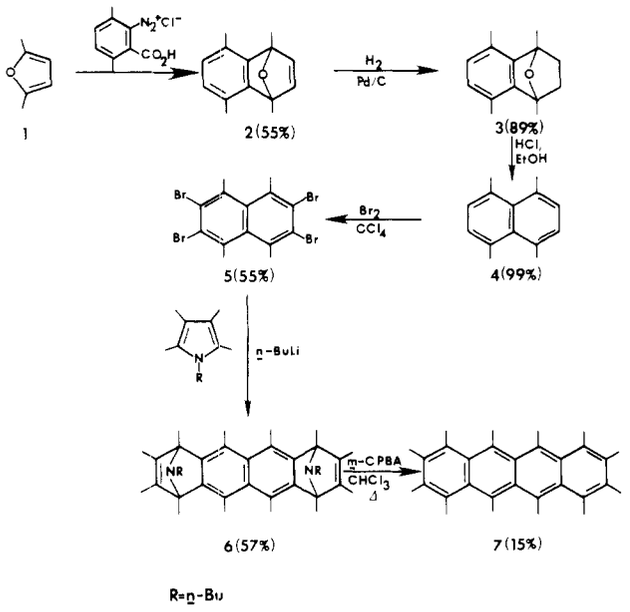
Dodecamethylnaphthacene, a compound with six peri interactions between methyl groups, has been synthesized in three steps from 1,4,5,8-tetramethylnaphthalene. A key step involves a bis or double aryne cycloaddition.

Permethylarenes present a synthetic challenge for several reasons. As a consequence of "peri" interactions, they are highly strained and the synthetic scheme must include strategy for making the acceptance of this strain palatable. They also readily isomerize to nonaromatic isomers in acid or base, so these reagents must be avoided or used with care in the final steps.[1] We have developed syntheses for octamethylnaphthalene,[2] decamethylanthracene,[3] and other highly substituted arenes[4] which introduce the "peri" interaction in a step which also aromatizes one of the rings, thus offering the transition state some compensation for the strain.

We wish to describe here the extension of this strategy to the synthesis of dodecamethylnaphthacene. An interesting feature of the synthesis is the use, in effect, of a bisaryne. The synthesis is outlined in Scheme I (yields are of isolated materials).

The first three steps represent an improved synthesis of the known[5] 1,4,5,8-tetramethylnaphthalene (**4**). 3,6-Dimethylbenzyne, generated from the diazonium carboxylate,[2] gave adduct **2** with 2,5-dimethylfuran in 55% yield.[6] Catalytic hydrogenation to **3** and dehydration to **4** proceeded in excellent yield.

Scheme I



Bromination of **4** in CCl_4 at 0–5 °C with iodine as the catalyst gave the ring-brominated product **5** in fair yield.[7] The NMR spectrum of **5** had a single peak at δ 2.70. *o*-Dibromoarenes have been used as aryne precursors,[8] and **5** was envisioned as a bisaryne precursor[9,10] which could supply the two central rings of permethylnaphthacene. Treatment of a mixture of **5** and *N*-*n*-butyltetramethylpyrrole with *n*-butyllithium gave a reasonable yield of a crystalline adduct **6**. The stereochemical relationship between the two nitrogen bridges is not known, but only a single isomer was obtained. The NMR spectrum of **6** had three singlets of equal area (12 H) for the three sets of methyl groups (δ 2.50, 1.89, and 1.70), consistent with the symmetry of a bisadduct. Some monoadduct may have been present, but was not isolated. The final step, elimination of the nitrogen bridges, could be accomplished only in poor yield by oxidation with *m*-chloroperbenzoic acid and thermal elimination of the *N*-oxide.[11]

Dodecamethylnaphthacene (**7**) is a reddish-orange crystalline hydrocarbon, mp 265–266 °C, with a rich electronic spectrum, the longest wavelength maximum being at 537 nm. Its ^{1}H NMR spectrum has three equal singlets at δ 2.98, 2.66, and 2.32, which can be assigned to the three sets of methyls as one proceeds from the center of the molecule to the ends. The methyl carbons in the ^{13}C NMR spectrum also had very different chemical shifts (δ 28.55, 22.57, and 16.32).

Dodecamethylnaphthacene is sensitive to traces of acid. Solutions in chloroform gradually develop new peaks in the ^{1}H NMR spectrum due to an isomer; this isomer turns up among the products of most reactions attempted with **7**. It can be obtained by treating a methylene chloride solution of **7** with a drop of trifluoroacetic acid (TFA). The red solution becomes blue-violet and then yellow and gives on workup the colorless crystalline isomer assigned structure **8**. The NMR spectrum shows doublets for the vinyl protons at δ 5.47 and 5.73 (J = 2.4 Hz), a methine quartet at δ 4.60, and a methyl doublet at δ 1.23 (J = 7.1 Hz), as well as a series of peaks for the aryl methyl groups. This facile isomerization is similar to that observed previously with other polymethylarenes containing double "peri" interactions.[1,3]

Solutions of dodecamethylnaphthacene are also sensitive to oxidation.[12] Irradiation of a carbon disulfide solution of **7** that was exposed to the air with a quartz iodine lamp gave (in addition to **8**) an endoperoxide **9** and other products. Attempts to photoisomerize **7** to a Dewar isomer (as occurs with decamethylanthracene[3]) by irradiating degassed benzene solutions led to products not yet identified.

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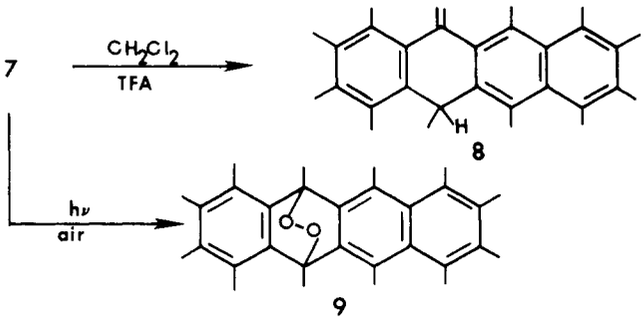

Experimental Section

General Procedures. ^1H NMR spectra were measured in $CDCl_3$ or CCl_4 solution on a Varian Associates T-60 or Bruker WH 180 spectrometer using tetramethylsilane as an internal reference. ^{13}C NMR spectra were determined on a Varian CFT-20 spectrometer. Other instruments were as follows: IR, Perkin-Elmer Model 167; UV, Unicam SP-800; mass spectra, Hitachi Perkin-Elmer RMU-6. Elemental analyses were performed by Spang Microanalytical Laboratories, Eagle Harbor, Mich., and by Clark Microanalytical Laboratories, Urbana, Ill. Melting points were determined with a Thomas-Hoover apparatus and are uncorrected.

1,4,5,8-Tetramethyl-1,4-dihydronaphthalene 1,4-Endoxide (2).[6] A mixture of 23.2 g (0.14 mol) of 3,6-dimethylbenzenediazonium-2-carboxylate hydrochloride,[2] 34 mL of propylene oxide, and 59.7 mL (0.56 mol) of 2,5-dimethylfuran in 100 mL of 1,2-dichloroethane was heated at reflux (83 °C) for 2.5 h. Evaporation of the solvent gave a red-brown oil which was redissolved in ether. The ether solution was washed with dilute aqueous NaOH and water and dried ($MgSO_4$). Distillation (short path) gave 15.5 g (55%) of **2**: bp 93 °C (0.6 torr); IR (neat) 3000 (s), 1500 (s), 1460 (s), 1400 (s), 1305 (s), 1150 (s) cm^{-1}; NMR (CCl_4) δ 1.87 (s, 6 H, $C_{1,4}$ methyls), 2.25 (s, 6 H, arom methyls), 6.50 (s, 2 H, vinyl), 6.65 (s, 2 H, arom); mass spectrum (70 eV), *m/e* (relative intensity) 200 (18), 174 (21), 157 (100), 142 (52).

Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.77; H, 8.17.

1,4,5,8-Tetramethyl-1,2,3,4-tetrahydronaphthalene 1,4-Endoxide (3). A solution of **2** (8 g, 0.04 mol) in 112 mL of absolute ethanol containing 0.8 g of 5% palladium on charcoal was hydrogenated at atmospheric pressure and room temperature (complete in 2 h). The mixture was filtered and concentrated under reduced pressure to give 7.2 g (89%) of **3** as a colorless oil: NMR ($CDCl_3$) δ 1.40–1.80 (m, 4 H, methylenes), 1.80 (s, 6 H, aliphatic methyls), 2.30 (s, 6 H, aromatic methyls), 6.65 (s, 2 H, arom).

1,4,5,8-Tetramethylnaphthalene (4). A solution containing 7.21 g (0.0356 mol) of **3** in 400 mL of absolute ethanol that had been saturated with anhydrous hydrogen chloride was heated at reflux for 5 h. About two-thirds of the ethanol was removed at room temperature under reduced pressure, and the white crystals which separated were filtered to give 6.5 g (99%) of pure **4**: mp 131–132 °C (lit.[5] mp 132 °C); NMR δ 2.75 (s, 12 H), 6.94 (s, 4 H).

2,3,6,7-Tetrabromo-1,4,5,8-tetramethylnaphthalene (5).[7] A crystal of iodine was added to a solution of 6.5 g (0.035 mol) of **4** in 130 mL of carbon tetrachloride. The mixture was cooled to 3–5 °C, and a solution of bromine (7.8 mL) in carbon tetrachloride (130 mL) was added dropwise over 15 min. The mixture was stirred at 0–5 °C until the reaction was complete, as determined by the disappearance of the aromatic protons in the NMR (about 1 h). Saturated aqueous sodium sulfite was added to remove excess bromine, the layers were separated, and the organic layer was washed successively with 1 N sodium thiosulfate, 10% sodium bicarbonate, and water and dried (Na_2SO_4). The solution was concentrated under reduced pressure to give 9.53 g (55%) of nearly pure **5**, which was recrystallized from methylene chloride/ethanol: mp 150–152 °C; NMR δ 2.70 (s); IR ($CHCl_3$) 2940 (m), 1554 (m), 1520 (w), 1450 (s), 1430 (s), 1360 (w), 1300 (s), 1170 (w), 1140 (w), 1000 (s), 950 (s), 890 (s) cm^{-1}; mass spectrum, *m/e* (relative intensity) 496 (100; cluster of five peaks at *m/e* 496, 498, 500, 502, and 504 in the correct intensity ratio), 418 (44), 338 (77).

Anal. Calcd for $C_{14}H_{12}Br_4$: C, 33.64; H, 2.40. Found: C, 33.79; H, 2.55.

Bisadduct 6. A suspension of **5** (150 mg, 0.30 mmol) and *N*-*n*-butyltetramethylpyrrole[13] (108 mg, 0.60 mmol)in 1.5 mL of anhydrous ether was cooled to −78 °C, and *n*-butyllithium (0.06 mol) was added with a syringe (nitrogen atmosphere). The mixture was stirred for 0.5 h, warmed to 0 °C for 0.5 h, and then stirred at room temperature for 2–2.5 h. Water (2 mL) was added, the layers were separated, the aqueous layer was extracted with chloroform, and the combined organic layers were dried (Na_2SO_4). Concentration under reduced pressure gave 281 mg of crude product (oil) which was subjected to preparative thin-layer chromatography (alumina, 2:1 hexane/ether) to give 93 mg (57%) of pure **6**: mp 250 ° C dec; NMR δ 1.70 (s, 12 H), 1.89 (s, 12 H), 2.50 (s, 12 H), 0.60–2.25 (m, 18 H); IR ($CDCl_3$) 2960 (s), 2940 (s), 2880 (m), 2870 (m), 1437 (m), 1360 (m), 1356 (w), 1254 (w), 1190 (w), 1160 (m) cm^{-1}; UV (hexane) λ_{max} 295 nm (log ϵ 4.10), 285 (4.04), 268 (4.81), 265 (4.76), 262 (4.75), 219 (4.38); ^{13}C NMR ($CDCl_3$) δ 150.98, 144.25, 135.14, 126.59, 45.75, 35.09, 22.10, 21.04, 16.66, 14.02, 11.73; mass spectrum, *m/e* (relative intensity) 538 (14), 523 (3), 484 (12), 441 (12), 98 (100).

Anal. Calcd for $C_{38}H_{54}N_2$: C, 84.76; H, 10.04; N, 5.20. Found: C, 84.80; H, 10.24; N, 5.07.

Dodecamethylnaphthacene (7). A mixture of **6** (1.0 g, 1.85 mmol), 70 mL of chloroform, and 53 mL of saturated sodium bicarbonate was cooled to 0–2 °C, and *m*-chloroperbenzoic acid (0.80 g, 4.64 mmol) in chloroform (55 mL) was added dropwise over 10 min (nitrogen atmosphere). The yellow mixture was refluxed for 1 h, cooled, and poured into water (20 mL). The layers were separated, and the aqueous layer was extracted with chloroform. The combined organic layers were washed with water and saturated salt solution and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave crude **7** (red solid) which was recrystallized from methylene chloride/methanol to give pure **7** (107 mg, 15%): mp 265–266 °C; ^1H NMR δ 2.32 (s, 12 H), 2.66 (s, 12 H), 2.98 (s, 12 H); ^{13}C NMR ($CDCl_3$) δ 135.01, 134.53, 134.11, 127.31, 125.99, 28.55, 22.57, 16.32; IR ($CHCl_3$) 2900 (m), 1450 (w), 1380 (w), 1360 (w) cm^{-1}; UV (CH_2Cl_2) λ_{max} 537 nm (log ϵ 3.78), 500 (3.73), 470 (3.44), 428 (3.62), 405 (3.39), 308 (4.90), 272 (4.40); mass spectrum, *m/e* (relative intensity) 396 (51), 382 (31), 381 (100), 366 (6), 355 (3), 336 (8), 321 (6).

Anal. Calcd for $C_{30}H_{36}$: C, 90.91; H, 9.09. Found: C, 90.85; H, 8.97.

Rearrangement of 7 to 8. To a solution of **7** (40 mg, 0.10 mmol) in 8 mL of methylene chloride was added one drop of trifluoroacetic acid. The solution turned from red to blue-violet (briefly) and then to light yellow. The mixture was stirred for 5 min and then poured into 10% sodium bicarbonate. The organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure to give 50 mg of crude product (solid). Column chromatography over silica gel with methylene chloride/cyclohexane (1:1) as eluent followed by recrystallization from methylene chloride/methanol gave 26.6 mg (67%) of pure **8**: mp 233–235 °C; NMR δ 1.23 (d, 3 H, J = 7.1 Hz), 2.18, 2.21 (unresolved s, 6 H), 2.27, 2.29 (unresolved s, 6 H), 2.37, 2.38 (unresolved s, 6 H), 2.45 (s, 3 H), 2.53, 2.58 (unresolved s, 6 H), 2.76 (s, 3 H), 4.60 (q, 1 H, J = 7.1 Hz), 5.47 (d, 1 H, J = 2.4 Hz), 5.73 (d, 1 H, J = 2.4 Hz); IR ($CDCl_3$) 2960 (s), 2920 (s), 2870 (m), 1620 (w), 1570 (w), 1440 (m), 1010 (w), 990 (w) cm^{-1}; UV (cyclohexane) λ_{max} 325 nm (log ϵ 3.82), 278 (4.63), 265 (4.62), 249 (4.68), 220 (4.40); mass spectrum, *m/e* (relative intensity) 396 (36), 382 (32), 381 (100), 366 (6), 351 (8), 336 (8), 321 (5). High-resolution mass spectrum calcd for $C_{30}H_{36}$, 396.27707; found, 396.28171.

Photooxidation of 7. A solution of **7** (100 mg, 0.253 mmol) in 15 mL of carbon disulfide was irradiated at room temperature with a quartz iodine lamp (650 W) until the red color disappeared (2–3 h if the vessel is simply exposed to the air; 20 min if oxygen is bubbled through the solution during the irradiation). The solvent was removed under reduced pressure, and the crude oily residue was chromatographed (preparative thin layer) on alumina with 1:1 methylene chloride/cyclohexane as eluent. The products were **8** (26%) and **9** (12%); other products were not obtained pure. For **9**: mp 253–254 °C dec; NMR δ 2.17 (s, 6 H), 2.24 (s, 6 H), 2.39, 2.42, 2.46 (unresolved s, 18 H), 2.56 (s, 6 H); IR ($CHCl_3$) 2930 (s), 1450 (s), 1390 (s), 1160 (w), 1080 (w), 1010 (w), 913 (w), 845 (w) cm^{-1}; UV (cyclohexane) λ_{max} 313 nm (log ϵ 3.43), 272 (4.36), 222 (4.06); mass spectrum, *m/e* (relative intensity) 428 (36), 413 (46), 396 (91), 395 (100), 394 (41). High-resolution mass spectrum calcd for $C_{30}H_{36}O_2$, 428.27151; found, 428.27219.

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Registry No.—**1**, 625-86-5; **2**, 68185-75-1; **3**, 68185-76-2; **4**, 2717-39-7; **5**, 68185-77-3; **6**, 68185-78-4; **7**, 68185-79-5; **8**, 68185-80-8; **9**, 68185-81-9; 3,6-dimethylbenzenediazonium-2-carboxylate hydrochloride, 36794-93-1; *N*-*n*-butyltetramethylpyrrole, 7135-55-9.

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Streptozocin: Structure and Chemistry[1]

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The structure of streptozocin has been shown to be that represented by **1**. Its degradation by a variety of reagents with loss of the nitroso group and formation of new ring systems is discussed, and the structures of the products are reported.

Streptozocin[2] (**1**), an antibiotic produced by *Streptomyces achromogenus* sub. *streptozoticus*, is a broad spectrum antibacterial agent.[3-4] It is also an antitumor agent being used clinically for malignant islet cell cancers of the pancreas.[5] In this report we wish to present evidence establishing the structure of streptozocin to be **1** and to discuss its chemistry.

Streptozocin (**1**) has a molecular formula of $C_8H_{15}N_3O_7$[6] established by analysis and molecular weight determination. Its ultraviolet and infrared spectra have been reported.[6] The two maxima in the ultraviolet [228 nm (ϵ 6360) and 380 nm (ϵ 136)] are consistent with the presence of an *N*-nitroso group.[7] The infrared spectrum has bands suggesting OH/NH and a carbonyl group.[6] A potentiometric titration showed the absence of titratable groups. The ^{1}H NMR spectrum of **1** was not well-resolved and could not be completely assigned, but a singlet at δ 3.15 representing 3 H indicated CH_3N. No CH_3C groups were present. A ^{13}C NMR spectrum (D_2O at pH 4.3) had chemical shifts of δ 156.7 and 28.4, confirming the presence of a carbonyl and a methyl group. The remaining signals were virtually identical with those of a mixture of α- and β-2-acetamido-2-deoxy-D-glucopyranose,[8] suggesting that D-glucosamine in the pyranose form is the nucleus of **1**.

1 is readily converted to a tetraacetyl derivative (**2**) by the acetic anhydride–pyridine procedure (Scheme I). The ^{1}H NMR spectrum of **2** showed the presence of four CH_3CO groups and the CH_3N group. A multiplet at δ 3.93–4.60 arose from 3 H on carbons substituted by oxygen or nitrogen. Two triplets (J = 10 Hz in each case) at δ 5.11 and 5.67, each representing one H, are consistent with the resonances of protons on C-3 and C-4 on a glucosamine skeleton.

Treatment of **1** with 2 N NaOH solution gave diazomethane determined by conversion of *p*-nitrobenzoic acid to its methyl ester[6] and an amorphous solid (**3**) having the molecular formula $C_7H_{11}NO_6$. Acetylation of **3** gave a crystalline solid (**4**).[1a] Hydrolysis of both **3** and **4** with 2 N HCl gave glucosamine hydrochloride, identified by comparison with an authentic sample, and carbon dioxide. The spectral data and formation of diazomethane after treatment with alkali establish the presence in **1** of the group $CH_3N(NO)C(=O)$–. The isolation of glucosamine accounts for the remainder of the molecule. Since there is no basic group in **1**, the amine in glucosamine must have been the site of attachment of the carbonyl group in the above moiety. The conversion of **1** to a tetraacetyl derivative and its NMR spectra establish that there has been no rearrangement of the six-carbon fragment on hydrolysis. The ^{13}C NMR spectrum of **1** and mutarotation undergone by **1** from widely varying original values of different lots to a constant value of +39° in water indicate the presence of α and β forms. In fact, methyl glycosides of the two isomers have been prepared.[9] Thus, the structure of streptozocin must be as indicated in formula **1**. Acetylation gave the β isomer (**2**) as indicated by the coupling constant of 8.5 Hz for the $H_{1,2}$ coupling. The structure of **1** was confirmed by synthesis in the original work,[1a] and subsequently two improved syntheses have been reported.[10,11]

A number of degradative conversions of **1** by various reagents have been brought about, and the compound itself in various solvents such as water, ethanol, and Me_2SO undergoes spontaneous decomposition. Loss of the nitroso group occurs in all reactions of this type. Some of the degradations have already been reported,[1,12] but they will be discussed further in the present publication.

The formation of **3** from **1** as a result of base treatment has been reported,[1a] and a structure (**12**) was proposed for it with the assumption that the pyranose ring form was retained. The tetraacetyl derivative of **3** was thought to have structure **13** largely because of a 1790-cm^{-1} band in its infrared spectrum and one CH_3C signal in the ^{1}H NMR spectrum of **4** differing markedly from the other three. The infrared spectrum of **4** has three bands in the carbonyl region at 1790, 1735, and 1705 cm^{-1}, suggesting acetate (1735 cm^{-1}), a carbonyl similar to the one in **3** (1705 cm^{-1}), and a new group giving the high wavenumber band. The ^{1}H NMR spectrum has signals at δ 1.95, 2.01, and 2.03 which must be from acetyl CH_3C groups attached to oxygen, while a fourth resonance at δ 2.42 suggests some other type of acetyl group. The other chemical shifts were as expected for a sugar derivative except that the $H_{2,3}$ coupling was zero, perhaps indicating a furanose ring. The ^{13}C NMR spectrum was reasonable for both **4** and **13**. As a result of inconsistencies in the data derived from the alkaline degradation product of **1** and its acetyl derivative, an X-ray crystallographic study was done on the acetyl derivative. Its structure was established as that represented by **4**, and, as acetylation should not cause rearrangement of the ring structure, the structure of the initial degradation product

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