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THE SYNTHESIS OF MONO-SUBSTITUTED [18]ANNULENES*

E. P. Woo† and F. Sondheimer‡
Chemistry Department, University College, London W.C.1, England

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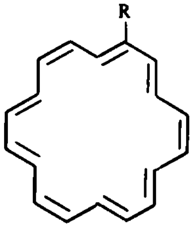
Abstract—Syntheses of bromo[18]annulene (**4**), methyl[18]annulene (**5**), [18]annulenecarboxaldehyde (**6**), and methyl [18]annulenecarboxylate (**7**) are described. The electronic and NMR spectra of these substances are discussed. It is shown that the nitration of nitro[18]annulene (**2**) gives rise to a complex mixture of dinitro[18]annulenes.

It has been shown previously that the aromatic system [18]annulene (**1**)[1] can be converted to nitro[18]annulene (**2**) and acetyl[18]annulene (**3**) under carefully defined conditions.[2] It appeared of interest to investigate the preparation of other mono-substituted [18]annulenes, in order to gain further insight into the chemistry of this novel macrocycle. In this paper, we describe the synthesis of four such mono-substituted derivatives, namely bromo[18]annulene (**4**), methyl[18]annulene (**5**), [18]annulenecarboxaldehyde (**6**), and methyl [18]annulenecarboxylate (**7**).



1: $R = H$

2: $R = NO_2$

3: $R = COCH_3$

The bromination of [18]annulene (**1**) was studied under several different conditions. The best result was obtained by stirring equimolar amounts of **1** and pyridinium bromide perbromide[3] in benzene at room temperature. Chromatography on alumina impregnated with 10% of silver nitrate then gave bromo[18]annulene (**4**) as red-violet crystals in 44% yield, as well as 34% of unchanged **1**. The structure of **4** is based mainly on the NMR spectrum (see below) and the mass spectrum, which showed the expected

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* Unsaturated Macrocyclic Compounds. LXX. For part LXIX, see R. H. Mitchell and F. Sondheimer, *Tetrahedron* **26**, 2141 (1970).

† National Research Council of Canada Postdoctoral Fellow, 1968–1969. Present address: Chemistry Department, United College, Hong Kong.

‡ Author to whom inquiries should be addressed.

molecular ion peaks at m/e 312 and 314, and the absence of peaks due to di- or tribromoderivatives. By comparison, bromination of **1** with 1·3 molar equivalents of pyridinium bromide perbromide in methylene chloride in the presence of boron trifluoride etherate gave material, the mass spectrum of which showed it to be a mixture of mono-, di-, and tribromo[18]annulenes (the dibromo compound(s) apparently being the major constituent).

Several attempts to prepare lithio[18]annulene from **4** were made, but no evidence for its formation was obtained. Treatment of **4** with *n*-butyllithium in ether at −78° immediately led to a black-green solution, which turned yellow when the temperature was allowed to rise to −40°, or when it was quenched at −78° with water, carbon dioxide, or ethyl carbonate. No reaction was observed when a solution of **4** in tetrahydrofuran was stirred with lithium or potassium in the temperature range 20–60°. An attempt to prepare [18]annulenemagnesium bromide by treatment of **4** with magnesium in tetrahydrofuran at 20–60° resulted in complete decomposition.

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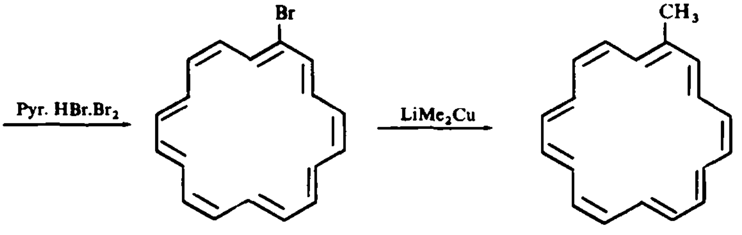

4 **5**

Reaction of **4** in ether with a large excess of lithium dimethylcopper reagent (prepared from methyllithium and cuprous iodide)[4] at 0° gave methyl[18]annulene (**5**) as red-purple crystals in 52% yield. It is imperative that no excess of methyllithium be present in this reaction, since it has been found that n-butyllithium destroys **4** above −78°, and methyllithium appears to have the same effect. On the other hand, an insufficient amount of methyllithium resulted in such a slow reaction that decomposition drastically reduced the yield of **5**. This difficulty could be overcome by making use of the fact that the excess of methyllithium reacted with **4** at −78° to give a black-green colour, which served as an indicator (see Experimental). The structure of **5** is again based mainly on the NMR spectrum (see below), and the mass spectrum, which showed the expected molecular ion peak at m/e 248. The only other known alkylderivative of [18]annulene is 1,2,7,8,13,14-hexamethyl[18]annulene, but this substance was not obtained pure.[5]

Vilsmeier reaction of **1** with phosphorus oxychloride in dimethylformamide* (unpurified) at 40° for 45 minutes gave [18]annulenecarboxaldehyde (**6**) as dark purple crystals in 21% yield, as well as 56% of unchanged **1**. No reaction was observed when the dimethylformamide was purified by distillation from calcium hydride, while longer reaction times resulted in reduced yields of **6**, due to decomposition. The infrared spectrum of the aldehyde **6** showed a strong carbonyl absorption at

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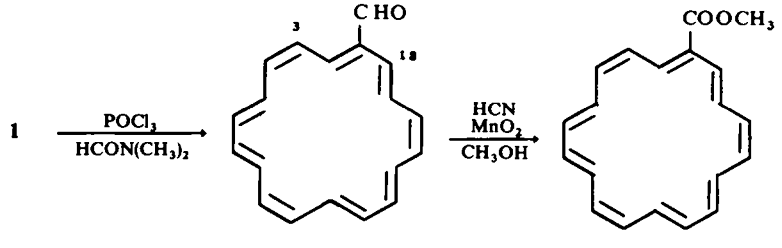
* The conditions are similar to those used for the conversion of azulene to azulenecarboxaldehyde (see Ref 6).

1660 cm^{-1}, and the mass spectrum exhibited the expected molecular ion peak at *m/e* 262.

The aldehyde **6** appears to be a promising intermediate for the synthesis of a number of other [18]annulene derivatives, but so far only its conversion to methyl [18]annulenecarboxylate (**7**) has been investigated. This transformation was brought about by the method of Corey *et al.*[7,*] involving treatment of **6** in tetrahydrofuran and methanol with hydrogen cyanide (from sodium cyanide and acetic acid) and manganese dioxide. The resulting ester **7**, isolated in 44% yield, formed brown-violet crystals. The infrared spectrum showed strong ester absorptions at 1705 and 1210 cm^{-1}. The mass spectrum exhibited the expected molecular ion peak at *m/e* 292; in addition, peaks at *m/e* 261 (M—OCH_3) and 233 (M—$COOCH_3$) were apparent, the break-down pattern being the same as found for alkyl benzoates.[8]



6 **7**

The electronic absorption spectra (in ether) of the monosubstituted [18]annulenes **4**, **5**, **6** and **7** are presented in Table 1, together with that of [18]annulene(**1**)[†] itself. It can be seen that the main maxima (underlined) of **4**, **5**, **6** and **7** all occur at slightly higher wavelengths than that of [18]annulene, the bathochromic shift being 4·5 nm for **4**, 2·5 nm for **5**, 10 nm for **6**, and 7 nm for **7**. The shift of 2·5 nm shown by the methyl compound **5** is in accord with the previous finding that the corresponding bathochromic shift in 1,2,7,8,13,14-hexamethyl[18]annulene is 13 nm.[5] As expected, the main maximum of the aldehyde **6** [$\lambda_{\max}^{\text{ether}}$ 379 nm (log ε 4·89)] is very similar to that of acetyl[18]annulene (**3**) [$\lambda_{\max}^{\text{CHCl}_3}$ 378 nm (log ε 4·96)].[2]

The 100 MHz NMR spectra of **4**, **5**, **6** and **7**[‡] at −60° all showed low field and high field multiplets (**4**, τ 0·3–0·9 and 12·6–13·4; **5**, τ 0·7–1·4 and 12·4–13·1; **6**, −0·3–1·2 and 11·9–12·7; **7**, τ −0·1–1·2 and 13·1–13·9), in a ratio of *ca* 11:6, representing the outer and inner protons, respectively. In addition, the methyl compound **5** exhibited a 3H singlet at τ 6·55 due to the methyl protons, the aldehyde **6** a 1H singlet at τ −1·27 due to the aldehyde proton, and the ester **7** a 3H singlet at τ 5·75 due to the ester methyl protons. In the case of **6**, the outer proton low field band could be seen to

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[*] We were not able to carry out the conversion of **6** to **7** by the more classical method of oxidation to [18]annulenecarboxylic acid and subsequent methylation, since preliminary attempts to oxidise **6** with chromic acid (Jones reagent) led to complete destruction of the [18]annulene chromophore.

[†] The electronic spectrum of [18]annulene in other solvents has been reported previously (isooctane,[1] benzene[1,9] chloroform[9]).

[‡] The NMR spectra of **4** and **6** were determined in tetrahydrofuran-d_8, and those of **5** and **7** in methylene chloride-d_2.

TABLE 1. ELECTRONIC ABSORPTION SPECTRA (IN ETHER) OF THE [18]ANNULENE DERIVATIVES **1**, **4**, **5**, **6** AND **7**

Maxima or shoulders (sh) in nm (log ε values in parentheses)[a]				
[18]Annulene (**1**)[b]	Bromo[18]annulene (**4**)[d]	Methyl[18]annulene (**5**)[b]	[18]Annulenecarboxaldehyde (**6**)[b]	Methyl [18]annulenecarboxylate (**7**)[b]
248 (3·84)	279 (4·12)	250sh (3·93)	285sh (3·92)	252 (3·78)
255sh (3·89)	295sh (4·08)	259sh (3·95)	307sh (4·00)	281 (3·83)
263sh (3·99)	349sh (4·91)	272sh (4·03)	334sh (4·42)	332sh (4·35)
278 (3·01)	360sh (5·05)	279 (4·07)	379 (4·89)	376 (5·02)
293sh (3·77)	373·5 (5·52)	295sh (3·84)	454sh (3·89)	452 (3·85)
325sh (4·20)	412 (4·11)	325sh (4·42)	496sh (3·82)	487sh (3·67)
341sh (4·83)	428sh (4·05)	344sh (4·74)	566sh (2·48)	515 (2·08)
355sh (5·00)	445sh (4·29)	357sh (5·97)	576sh (2·42)	525 (2·04)
369 (5·48)	453 (4·47)	371·5 (5·42)	614sh (2·38)	613sh (2·02)
407 (3·93)	446sh (3·99)	410 (3·94)	626 (2·50)	623 (2.23)
422 (3·90)[c]	473sh (3·81)	425sh (3·93)	640sh (2·38)	639sh (2·04)
437sh (4·13)	696 (2.24)	440sh (4·13)	688sh (2·32)	686 (1·97)
446 (4·37)	771 (2·26)	449 (4·30)	704 (2·51)	701 (2·20)
457sh (3·84)	793sh (1·91)	468sh (3·48)	720sh (2·27)	720sh (1·95)
496sh (1·88)		557 (1·87)	784sh (2·34)	740sh (1·53)
556 (1·76)		566sh (1·85)	806 (2·83)	776sh (2·15)
565 (1.83)		599 (1·85)		801 (2·76)
575sh (1·72)		612 (1·85)		
588 (1·72)		633 (1·83)		
599 (1·82)		673sh (1·70)		
610 (1·81)		690 (1·91)		
631 (1·90)		706sh (1·81)		
657 (1·65)		749sh (1·81)		
675sh (1·70)		763 (1·95)		
688 (2·00)		784sh (1·87)		
705 (1·83)		812sh (1·36)		
715sh (1·74)				
747sh (1·85)				
762 (2·07)				
777 (1·90)				
793sh (1·74)				
810sh (1·34)				

[a] The ε values of **4**–**7** represent minimum ones, since the substances were not dried thoroughly in view of their instability.

[b] Recorded with a Unicam SP-800 spectrophotometer.

[c] This maximum was not detected by Blattman *et al.*,[9] but is definitely present in the spectrum of the pure substance.

[d] Recorded with a Cary 14 spectrophotometer.

consist of a 1H double doublet (J = 15 and 8 Hz) at τ − 0·16 assigned to H_3, a 1H doublet (J = 15 Hz) at τ 0·26 assigned to H_{18}, and an unresolved 9H multiplet at τ 0·4–1·2 assigned to the remaining outer protons.

It was found in the case of **4** and **7** that the NMR spectra exhibit the same type of temperature effects as already reported for **2** and **3**.[2] Thus, in the spectra of **4** and **7** at 35°, the outer proton low field signals appeared as bands different in shape to those at −60° (**4**, τ 1·0–1·4; **6**, τ 0·9–1·5), while the inner proton high field signals had disappeared. The ester methyl proton band in the spectrum of **7** at 35° remained as a

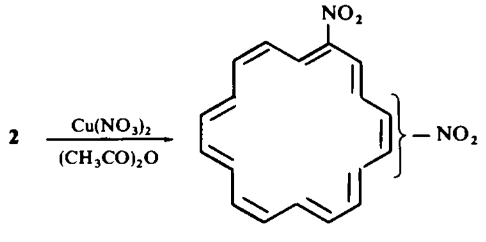
TABLE 2. NMR PROTON SIGNALS OF SUBSTITUENTS IN MONOSUBSTITUTED [18]ANNULENES AND BENZENES (τ VALUES)

	$R = C_{18}H_{17}$, at $-60°$ (A)	$R = C_6H_5$, at 20° (B)	B-A
R—H	0·72	2·73	2·01
R—CHO	− 1·27	0·00	1·27
$R—CH_3$	6·55	7·68	1·13
$R—CO—CH_3$	6·55	7·41	0·86
$R—CO—OCH_3$	5·75	6·00	0·25

singlet (τ 5·82), the integrated area compared with that of the outer proton low field signal being *ca* 3:5. The explanation for these phenomena has already been given.[2] The behaviour of the NMR spectra of **4**, **5**, **6** and **7** above 35° was not investigated, in view of the instability of these substances.

The NMR proton chemical shifts of the substituents in the various mono-substituted [18]annulenes are given in Table 2 (column A). The protons in all cases are deshielded by the diamagnetic ring current of the aromatic [18]annulene ring.[10] The proton chemical shifts of the substituents in the corresponding benzene derivatives are given in column B. It can be seen (B–A) that the protons in the substituents of the [18]annulene derivatives always occur at lower field than those of the benzene derivatives, the difference becoming less as the protons are further removed from the ring.

In order to gain information about the direction of electrophilic substitution of monosubstituted [18]annulenes, some preliminary experiments have been carried out involving the nitration of nitro[18]annulene (**2**).[2] This reaction, carried out with cupric nitrate in acetic anhydride[2] at room temperature, gave *ca* 10% of a new brown material besides *ca* 70% of starting material. The new material, which was more strongly absorbed than **2** on silica gel, appeared to be a dinitro[18]annulene (**8**). This



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conclusion was based mainly on the fact that the molecular ion peak in the mass spectrum (*m/e* 324) corresponded to the molecular weight of **8**, and was confirmed by the bathochromic shift of *ca* 8 nm of the main ultraviolet maximum compared with nitro[18]annulene (the corresponding bathochromic shift in passing from [18]-annulene to nitro[18]annulene is 9 nm). The same dinitro[18]annulene (**8**) appeared to be formed as a by-product in the previously described nitration of [18]annulene to nitro[18]annulene with cupric nitrate in acetic anhydride,[2] as well as from nitro-[18]annulene by nitration with concentrated nitric acid in acetic anhydride or with tetranitromethane in pyridine. Unfortunately, careful chromatography showed that the dinitro[18]annulene in all cases consisted of at least four very similar components (presumably positional isomers), and only trace quantities of apparently pure substances have been obtained so far.

EXPERIMENTAL

General procedures. M.ps were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra: as KBr discs on a Unicam SP-200 spectrophotometer. Electronic spectra: on a Cary 14 or Unicam SP-800 spectrophotometer. NMR spectra: on a Varian HA-100 spectrometer (TMS used as internal standard). Mass spectra: on an AEI MS-12 spectrometer (70 eV, direct inlet system). Ligroin refers to the fraction b.p. 40–60°. All chromatography columns were prepared with this solvent. Al_2O_3 for chromatography was Woelm, neutral, activity I, unless stated otherwise. TLC plates were prepared with Merck Kieselgel GF_{254}, unless otherwise indicated. $AgNO_3$ impregnated chromatographic absorbents were prepared essentially by the method of Wolovsky.[11]

Bromo[18]*annulene* (4). A mixture of **1** (25·7 mg, 0·11 mmol)[1] and Pyr.HBr.Br_2 (35·2 mg, 0·11 mmol; B.D.H.) in benzene (100 ml; A.R. grade, distilled from Na) was stirred at room temp. After 1 hr, the yellow colour of the reagent had disappeared, and colourless crystalline Pyr.HBr was deposited on the wall of the vessel. The liquid was decanted, concentrated to *ca* 15 ml, and chromatographed on Al_2O_3 impregnated with 10% of $AgNO_3$ (100 g). Elution with ligroin-Et_2O (4:1) gave impure **1**; rechromatography on Al_2O_3 (60 g) yielded pure **1** (8·8 mg, 34%, determined by UV). Elution with Et_2O furnished impure **4**; rechromatography on Al_2O_3 (60 g), followed by crystallization from CH_2Cl_2-ligroin, led to pure **4** (15·0 mg, 44%) as red-violet crystals, which decomposed on attempted m.p. determination; homogeneous by TLC on Kieselgel GF_{254}-$AgNO_3$ (10:1) plates; electronic and NMR spectra, see Discussion and Table 1; mass spectrum, strong molecular ion peaks at *m/e* 312 and 314 (*ca* 1:1), no peaks at *m/e* 390–394 (dibromo[18]-annulenes) or 468–474 (tribromo[18]annulenes).

In another experiment, $BF_3 \cdot Et_2O$ (1 drop) was added to a stirred soln of **1** (8·0 mg, 0·034 mmol) and Pyr. HBr.Br_2 (14·0 mg, 0·044 mmol) in CH_2Cl_2 (15 ml) at − 78°. The cooling bath was removed, and the stirred soln was allowed to warm to room temp. After 10 min, H_2O was added, and the organic layer was washed with K_2CO_3 aq and H_2O. The extract was dried, evaporated, and chromatographed on Al_2O_3 (100 g, activity IV). Elution with ligroin gave orange coloured fractions, main $\lambda_{max}^{Et_2O}$ 377 and 457 nm. Evaporation and crystallization from CH_2Cl_2-ligroin led in low yield to orange-red crystals; mass spectrum, peaks at *m/e* 312, 314 (*ca* 1:1) due to **4**, 390, 392, 394 (*ca* 1:2:1) due to dibromo[18]annulenes, and 468, 470, 472, 474 (*ca* 1:2:2:1) due to tribromo[18]annulenes. The 390–394 peaks were the most intense, indicating the dibromide to be the major constituent.

Methyl[18]*annulene* (5). MeLi in Et_2O (4 ml, *ca* 2M; Alfa Inorganics) was diluted with Et_2O (10 ml), and CuI was added in small portions at 0° under N_2. Addition was stopped when a small amount of CuI remained after stirring for a few min. A little more (*ca* 0·1 ml) of the 2M soln of MeLi in Et_2O was then added at 0°, when an almost colourless homogeneous soln of $LiMe_2$ Cu was obtained. The soln was cooled to − 78°, and a small part (*ca* 2 ml) of a soln of **4** (10 mg) in Et_2O (40 ml) was added, when a black-green colour appeared almost instantaneously. The soln was warmed to − 40°, when it became pale yellow, and a few crystals of CuI were then added. The soln was again cooled to − 78°, and the rest of the soln of **4** was added in one portion (no black-green colour was now generated). The soln was allowed to reach 0° and stirred at this temp for 1 hr. H_2O was added, and the solid was removed by filtration. The Et_2O layer was dried, evaporated, and the residue was chromatographed on a TLC plate [Merck Kieselgel GF_{254}-$AgNO_3$ (10:1), 20 × 20 cm; developed with ligroin-benzene (3:2)]. Crystallization from CH_2Cl_2-ligroin yielded **5** (4·1 mg, 52%) as red-purple crystals, which decomposed on attempted m.p. determination; homogeneous by TLC on Kieselgel GF_{254}-$AgNO_3$ (10:1) plates; electronic, NMR, and mass spectra, see Discussion and Tables 1, 2.

[18]*Annulenecarboxaldehyde* (6). $POCl_3$ (1 ml) was added to DMF (10 ml: May & Baker, unpurified), followed by a soln of **1** (34 mg) in DMF (20 ml). The soln was then stirred at 40° for 45 min. The dark red soln was poured into NaOH aq (500 ml, 0·08 N), and the mixture was extracted with $CHCl_3$ (5 × 50 ml).

The combined extracts were washed with H_2O, dried, concentrated to small volume, and chromatographed on Al_2O_3 (80 g, activity II–III). Elution with ligroin gave unchanged **1** (19·0 mg, 56%, determined by UV) Elution with ligroin–Et_2O (4:1) and crystallization from CH_2Cl_2-ligroin yielded **6** (8·0 mg, 21%) as dark purple crystals, which decomposed on attempted m.p. determination; homogeneous by TLC; IR, electronic, NMR, and mass spectra, see Discussion and Tables 1, 2.

Methyl [18]*annulenecarboxylate* (**7**). MnO_2 (300 mg: prepared by the method of Attenburrow *et al.*[12]) was added to a soln of **6** (11·5 mg) in THF (10 ml) and MeOH (30 ml), followed by NaCN (150 mg) and AcOH (90 mg). The mixture was stirred at room temp for 14 hr, and the solid was then removed by filtration. The filtrate was diluted with H_2O (300 ml) and extracted with Et_2O. The organic layer was washed with H_2O, dried, and evaporated. Chromatography on a TLC plate [Merck Kieselgel GF_{254}; 20 × 20 cm; developed with ligroin–Et_2O (17:3)] and crystallization of the main product from CH_2Cl_2–ligroin yielded **7** (5·7 mg, 44%) as brown-violet crystals, m.p. 173–175° (block pre-heated to *ca* 150°); homogeneous by TLC; IR, electronic, NMR, and mass spectra, see Discussion and Tables 1, 2.

Nitration of nitro[18]*annulene* (**2**). A soln of **2**[2] (5·0 mg) in Ac_2O (20 ml) was added to $Cu(NO_3)_2 \cdot 3H_2O$ (25 mg) in Ac_2O (10 ml). The mixture was stirred for 10 min at room temp, and was then poured into Et_2O and Na_2CO_3 aq. The organic extract was washed with Na_2CO_3 aq, and H_2O. It was dried, evaporated, under reduced pressure, and chromatographed on silica gel (75 g). Elution with ligroin–benzene (9:1 to 2:3) yielded unchanged **2** (3·4 mg, 68%, determined by UV). Elution with ligroin–benzene (1:4) gave dinitro-[18]annulenes (**8**) as red solns, main $\lambda_{max}^{Et_2O}$ 386 nm (yield, 0·58 mg, 10%, determined by UV, assuming identical ε values for the main maxima of **2** and **8**). Evaporation of the solns of **8** and crystallization from CH_2Cl_2–ligroin resulted in a brown powder; mass spectrum, strong molecular ion peak at *m/e* 324.

The combined solid **8** (2·5 mg) from several experiments was chromatographed on Al_2O_3 (100 g, activity V). Elution with various proportions of ligroin–Et_2O developed two closely spaced pink bands (A, B), followed by two closely spaced brown bands (C, D). Band A showed $\lambda_{max}^{CHCl_3}$ 376 nm; mass spectrum, molecular ion peak at *m/e* 324. A mixture of bands B and C showed $\lambda_{max}^{CHCl_3}$ 385 nm; mass spectrum, molecular ion peak at *m/e* 324. Band D showed $\lambda_{max}^{CHCl_3}$ 394 nm; no significant mass spectrum could be obtained.

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