larger than predicted by eq 1. The mechanistic implications of these observations are not clear at this time. However, we feel that these observations are also directly related to the k_{cat}/K_m–pH dependency problem. We have initiated an extensive examination of pepsin hydrolyses at pH's above 5 which should give some meaningful insite into this ambiguity in pepsin action.

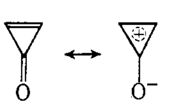
Acknowledgment. The authors thank Mr. Steven Frolow for technical assistance and Professor F. J. Kézdy for many useful discussions.

Communications to the Editor

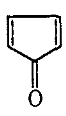
The Synthesis of 4,5:10,11-Bis(tetramethylene)-4,10-cyclotridecadiene-2,6,8,12-tetrayn-1-one, a Derivative of [13]Annulenone[1]

Sir:

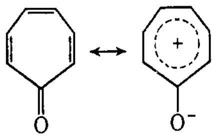
Monocyclic conjugated ketones are an interesting class of compounds, for which we propose the generic name "annulenones." Such compounds are expected to be aromatic if they contain a $(4n + 3)$-membered ring and nonaromatic if they contain a $(4n + 1)$-membered ring, due to the electron-withdrawing properties of the oxygen of the carbonyl group. In agreement with this are the properties of the $[4n + 3]$annulenones cyclopropenone (**1**) and cycloheptatrienone (tropone, **3**) on the one hand and the $[4n + 1]$annulenone cyclopentadienone (**2**) on the other.[2] No annulenone, or derivative of an annulenone, containing a ring larger than the seven-membered one has been prepared previously. We now describe the synthesis of 4,5:10,11-bis(tetramethylene)-4,10-cyclotridecadiene-2,6,8,12-tetrayn-1-one [4,5:10,11-bis(tetramethylene)-2,6,8,12-tetradehydro[13]annulenone, **11**], a derivative of [13]annulenone (*e.g.*, **13**).



1

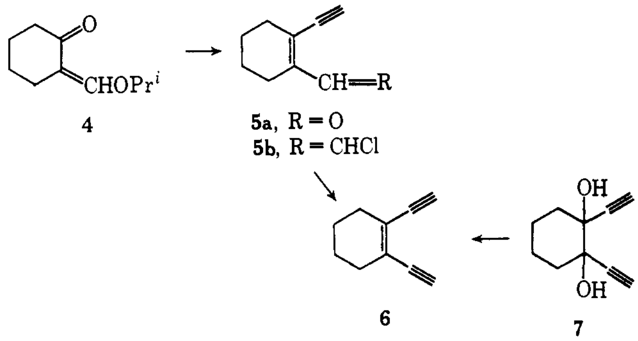


2



3

1,2-Diethynylcyclohexene (**6**) was prepared by two routes. The preferred one proceeded from 2-isopropoxymethylenecyclohexanone (**4**),[3] which was treated with lithium acetylide–ethylenediamine[4] in tetrahydrofuran at room temperature and then with dilute sulfuric acid; Wittig reaction of the resulting aldehyde **5a** (38% yield, mp 49.5–50°)[5] with chloromethylenetriphenylphosphorane[6] in tetrahydrofuran at room temperature led to 58% of the chloromethylene compound **5b** as a mixture of *cis* and *trans* isomers (*ca* 1:2), which was dehydrochlorinated to **6** with sodamide in liquid ammonia (60% yield) or with potassium *t*-butoxide in boiling ether (46% yield). Alternatively, **6** was obtained in 19% yield by the reduction of 1,2-diethynylcyclohexane-1,2-diol (**7**, *trans* isomer or mixture of *cis* and *trans* isomers)[7] with diphosphorus tetraiodide in pyridine and carbon disulfide at room temperature.[8] The enediyne **6** obtained by either method proved to be an unstable liquid, bp 52–54° (18 mm); $\lambda_{\max}^{\mathrm{EtOH}}$ 249 sh mμ (ϵ 10,200), 256 (12,400), 260 sh (11,100), and 269 (9700); nmr spectrum (all in CCl_4, 100 Mcps), two-proton singlet at τ 7.02 (acetylenic protons), four-proton multiplet at 7.65–7.95 (allylic protons), and four-proton multiplet at 8.20–8.50 (methylene protons).



Treatment of the mono-Grignard derivative of **6** with 0.5 molar equiv of ethyl formate in tetrahydrofuran at room temperature gave 27% of the liquid alcohol **8** which was coupled with oxygen, cuprous chloride, and ammonium chloride in aqueous ethanol and benzene. The resulting 13-membered ring alcohol **9a**,[11] isolated in *ca.* 40% yield by chromatography on silicic acid, was a very unstable yellow oil; $\lambda_{\max}^{\mathrm{ether}}$ 258 mμ (ϵ 24,800), 278 sh (8020), 348 sh (3860), 365 (5200), and 391 (4310). Attempts were made to convert **9a** to the fully conjugated cyclic bromoallene **10** by reaction with phosphorus tribromide (see ref 12). Although a nonpolar

---

(1) Unsaturated Macrocyclic Compounds. LXII. For part LXI, see R. H. Mitchell and F. Sondheimer, *Tetrahedron Letters*, 2873 (1968).

(2) For relevant references, see A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," John Wiley & Sons, Inc., New York, N. Y., 1961, Chapter 10; R. Breslow and L. J. Altman, *J. Am. Chem. Soc.*, **88**, 504 (1966); R. Breslow and G. Ryan, *ibid.*, **89**, 3073 (1967).

(3) W. S. Johnson and H. Posvic, *ibid.*, **69**, 1361 (1947); R. B. Woodward and W. M. McLamore, *ibid.*, **71**, 379 (1949); A. S. Dreiding and S. N. Nickel, *ibid.*, **76**, 3965 (1954).

(4) Supplied by Foote Mineral Co., Exton, Pa.; see O. F. Beumel and R. F. Harris, *J. Org. Chem.*, **28**, 2775 (1963); **29**, 1872 (1964).

(5) All new compounds were characterized by uv, ir, and nmr spectra, as well as by determination of the elemental composition (microanalysis or high-resolution mass spectroscopy).

(6) This ylide was generated by treatment of (chloromethyl)triphenylphosphonium chloride with butyllithium at −70°, according to G. Köbrich, H. Trapp, K. Flory, and W. Drischel, *Chem. Ber.*, **99**, 689 (1966).

(7) W. Ried and H. J. Schmidt, *ibid.*, **90**, 2499 (1957).

(8) The Inhoffen modification[9] of the Kuhn–Winterstein reduction[10] was used.

(9) H. H. Inhoffen, K. Radscheit, U. Stache, and V. Koppe, *Ann.*, **684**, 24 (1965).

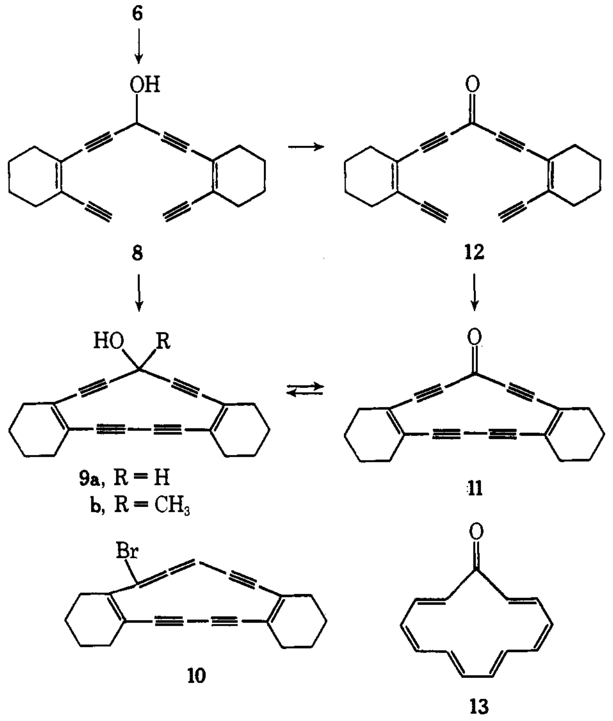
(10) R. Kuhn and A. Winterstein, *Helv. Chim. Acta*, **11**, 87 (1928).

(11) The synthesis of **9a** from **6** is based on the analogous synthesis of 2,6,8,12-cyclotridecatetrayn-1-ol from 1,5-hexadiyne,[12] but in the present case it was found necessary to use double the amount of cuprous chloride and prolong the reaction to 2 hr in order to effect complete conversion.

(12) C. C. Leznoff and F. Sondheimer, *J. Am. Chem. Soc.*, **90**, 731 (1968).

product was formed (tlc analysis), it proved to be too unstable for spectral examination.

The cyclic alcohol **9a** could be oxidized to the ketone **11** with a variety of reagents, the best yield (over 90%) being obtained with manganese dioxide in ether at room temperature. Alternatively, **8** was oxidized first with manganese dioxide in ether to the ketone **12** (85% yield), pale yellow prisms which decomposed at 80–85° on attempted melting point determination; λ_{max}^{ether} 245 mμ (ε 18,400), 322 (15,800), 331 (16,000), and 350 sh (11,800); $\nu_{max}^{CCl_4}$ (cm^{-1}) 3318 s (HC≡), 2210 s, 2200 s (C≡C), 1626 s (C=O), and 1582 m (C=C); nmr spectrum, two-proton singlet at τ 6.78 (acetylenic protons), eight-proton multiplet at 7.55–7.90 (allylic protons), and eight-proton multiplet at 8.20–8.50 (methylene protons). Coupling of **12** as previously then gave **11** in 8% yield.

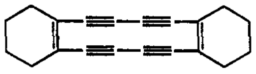


Substance **11** formed red prisms which decomposed at 90–95° on attempted melting point determination; λ_{max}^{ether} 252 mμ (ε 18,600), 264 (30,800), 279 (28,100), 295 sh (13,000), 308 sh (10,700), 400 sh (450), 450 (470), 475 sh (425), and 535 sh (190); $\nu_{max}^{CCl_4}$ (cm^{-1}) 2190 s (C≡C), 1626 s (C=O), and 1555 w (C=C); nmr spectrum, eight-proton multiplet at τ 7.85–8.20 (allylic protons) and eight-proton multiplet at 8.30–8.60 (methylene protons); mass spectrum, molecular ion at *m/e* 284 (100%). *Anal.* Calcd for $C_{21}H_{16}O$: C, 88.70; H, 5.67. Found: C, 88.48; H, 5.80. The compound was considerably more stable than the cyclic precursor **9a**, although the crystals gradually decomposed on being allowed to stand in light and air (*ca.* 50% decomposition after 24 hr). The ketone **11** could be converted to a 2,4-dinitrophenylhydrazone [red needles; main λ_{max}^{ether} 441 mμ (ε 34,800)], and on reaction with an excess of methylmagnesium iodide in ether at room temperature gave 55% of the tertiary alcohol **9b** [cream solid; λ_{max}^{ether} 259 mμ (ε 24,450), 350 sh (3740), 367 (5600), and 393 (5170)]. Attempted partial hydrogenation of the tetradehydro[13]annulenone **11** in benzene over a Lindlar or a 10% palladium–calcium carbonate catalyst did not lead to any detectable amounts of the corresponding [13]annulenone.

Substance **11** is a [4*n* + 1]annulenone derivative and is therefore not expected to be aromatic. Although no definite evidence regarding this point has yet been obtained, the fact that the allylic protons in the nmr spectrum of **11** show an upfield shift of τ 0.2–0.3 compared with those of other 1,2-diethynylcyclohexenes (*e.g.*, **6** and **12**) may be of significance.[13] The low infrared carbonyl frequency of **11** (1626 cm^{-1}) is presumably due to the presence of the flanking acetylenic bonds, since the open-chain analog **12** and other α,α′-diacetylenic ketones[14] show similar carbonyl absorptions (1623–1639 cm^{-1}).

---

[13] A similar upfield shift of the allylic protons has been observed in the nmr spectrum of the 4*n* system i (G. M. Pilling and F. Sondheimer, unpublished).



i

[14] F. Wille and R. Strasser, *Chem. Ber.*, **94**, 1606 (1961); M. Fontaine, J. Chauvelier, and P. Barchewitz, *Bull. Soc. Chim. France*, 2145 (1962).

[15] Recipient of a Science Research Council Research Studentship (1965–1967) and a New Hall Research Fellowship (1967–1968).

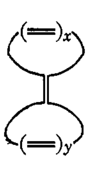
[16] Author to whom inquiries may be addressed at the Chemistry Department, University College, London W.C.1, England.

Gwenda M. Pilling,[15] Franz Sondheimer[16]
University Chemical Laboratory
Cambridge, England
Received June 10, 1968

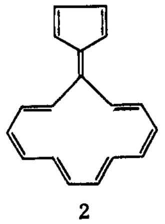
The Synthesis of 1-Cyclopentadienylidene-4,5:10,11-bis(tetramethylene)-4,10-cyclotridecadiene-2,6,8,12-tetrayne, a Derivative of Pentatridecafulvalene[1]

Sir:

Bicyclic polyenes containing a cyclic cross-conjugated π-electron system (type **1**) have been studied extensively in recent years, both theoretically and experimentally.[2] These substances may be divided into a potentially aromatic group in which both rings can form (4*n* + 2) π-electron systems through polarization of the centra double bond [triapentafulvalene (**1**, *x* = 1; *y* = 2) pentaheptafulvalene (**1**, *x* = 2; *y* = 3)], and a second group in which this is not possible [pentafulvalene (**1**, *x* = *y* = 2), heptafulvalene (**1**, *x* = *y* = 3)]. The only known macrocyclic compound of type **1** is a derivative of pentaundecafulvalene (**1**, *x* = 2; *y* = 5),[3] belonging to the first group. We now describe the synthesis of 1-cyclopentadienylidene-4,5:10,11-bis(tetramethylene)-4,10-cyclotridecadiene-2,6,8,12-tetrayne (**4**); this is a derivative of pentatridecafulvalene (*e.g.*, **2**),



1



2

---

[1] Unsaturated Macrocyclic Compounds. LXIII. For part LXII, see G. M. Pilling and F. Sondheimer, *J. Am. Chem. Soc.*, 90, 5610 (1968).

[2] See E. D. Bergmann, *Chem. Rev.*, 68, 41 (1968).

[3] H. Prinzbach and L. Knothe, *Angew. Chem.*, 79, 620 (1967).