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UNSATURATED MACROCYCLIC COMPOUNDS—CIX[1]

SYNTHESIS OF A TETRADEHYDROTETRAAZA[32]ANNULENE

K. YAMAMOTO and F. SONDHEIMER*
Chemistry Department, University College, Gordon Street, London WC1H OAJ, England

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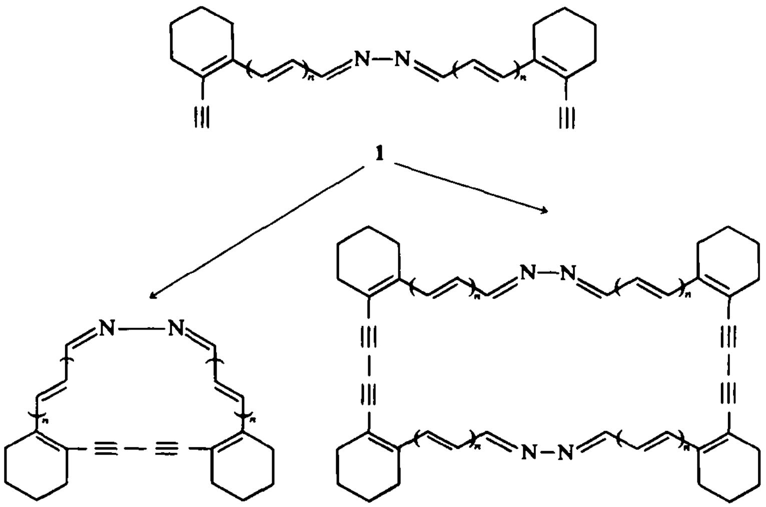
Abstract—The conjugated aldehydes **6**, **9**, and **12**, containing terminal acetylenes, were prepared and converted to the corresponding azines **13**, **14**, and **15**, respectively. Oxidative coupling of **14** gave the corresponding cyclic "dimer" **16**, a tetradehydrotetraaza[32]annulene. Although **16** is a $4n$ π-electron system, the ^{1}H-NMR spectrum showed it to be an atropic molecule.

In this paper we describe the synthesis of conjugated azines of type **1**, containing terminal acetylene groups. It was anticipated that oxidative coupling of these substances would lead to the corresponding cyclic "monomers" (**2**) and/or "dimers" (**3**), which are macrocyclic analogues of pyridazine (**4**) and *s*-tetrazine (**5**), respectively. In practice, the cyclic "dimer" was formed in one case, the compound obtained being the tetradehydrotetraaza[32]annulene ("octadehydrotetraazadotriacontine") **16**.†

The starting material was the readily available 2-ethynyl-1-cyclohexene-1-carboxaldehyde (**6**).[2] This substance was converted to the vinylogue **9** (m.p. 58–59°) in 60–66% over-all yield‡ by transformation to the diethyl acetal **7**, followed by condensation with ethyl vinyl ether in the presence of zinc chloride and treatment of the resulting ethoxy-acetal **8** with sodium acetate in acetic acid (method of O. Isler *et al.*[3]). The homologation was then repeated with **9**, giving rise to the higher vinylogue **12**



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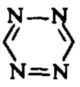

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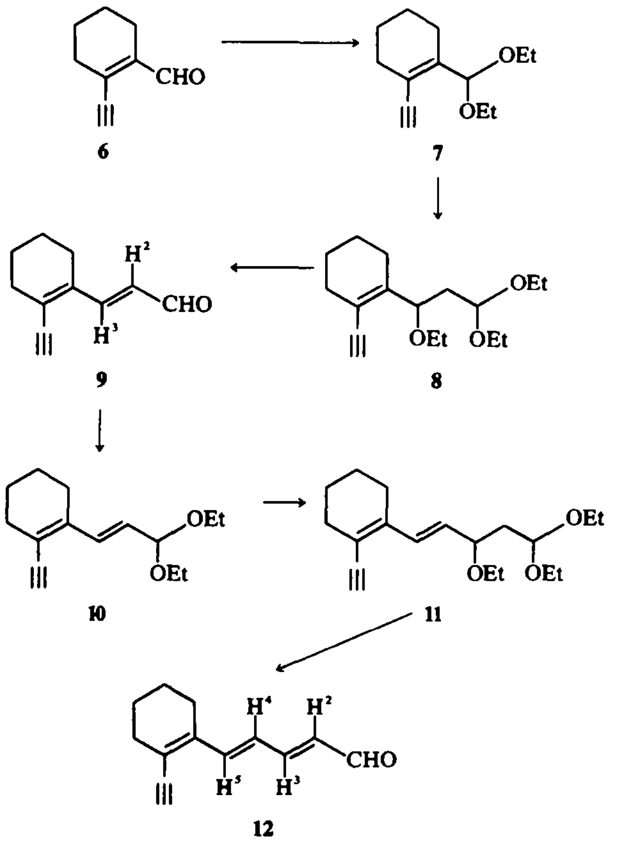
†For the synthesis of other polyazaannulenes, see P. Skrabal, *MTP International Review of Science*, Vol. 3: *Aromatic Compounds* (Ed. H. Zollinger) pp. 256–262. Butterworths, London (1973); L. A. Paquette and R. J. Haluska, *J. Am. Chem. Soc.* **94**, 534 (1972); I. Agranat, *Tetrahedron* **29**, 1399 (1973).

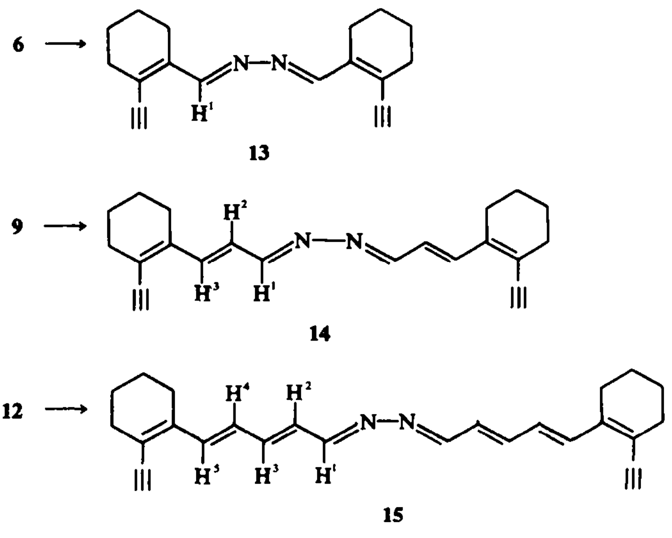
‡The transformation of **6** to **9** was first carried out by Dr. R. H. McGirk (see R. H. McGirk and F. Sondheimer, *Angew. Chem.* **84**, 897 (1972); N. Darby, K. Yamamoto and F. Sondheimer, *J. Am. Chem. Soc.* **96**, 248 (1974), footnote 5)).



(m.p. 94–95°) in 50% yield via the acetals **10** and **11**. The structures of the conjugated aldehydes **9** and **12** were established by the ^{1}H-NMR, UV, IR and mass spectra.

Treatment of the aldehyde **6** in ethanol with aqueous hydrazine[4] readily yielded the yellow azine **13** (m.p. 167–168°) in 82% yield. The vinylogous azines **14** and **15** were similarly prepared from the aldehydes **9** and **12** respectively. The spectral data of the azines **13**, **14**, and **15** were fully in accord with the assigned structures.

The oxidative coupling of the azines **13**, **14**, and **15** under several different conditions were investigated, but only substance **14** led to a macrocyclic product. Treat-



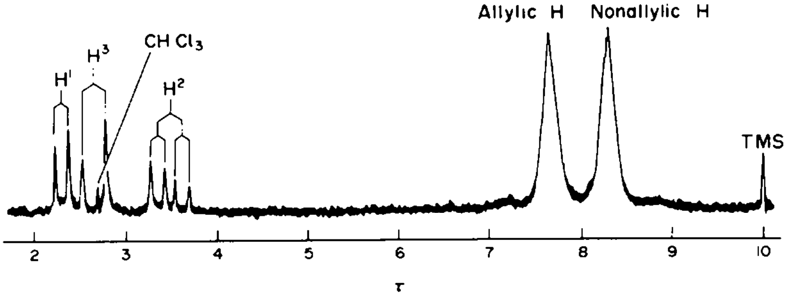
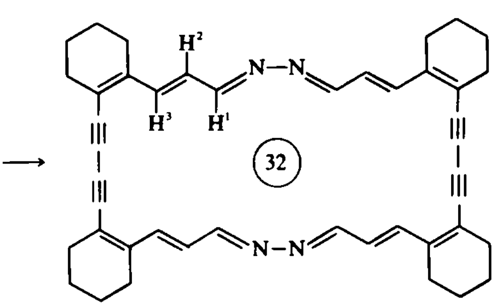


Fig. 1. ¹H-NMR spectrum of the tetradehydrotetraaza[32]annulene **16** in $CDCl_3$ (60 MHz).

ment of **14** with cupric acetate in ether and pyridine[5] under relatively dilute conditions* gave the yellow cyclic "dimer" **16**, a tetradehydrotetraaza[32]annulene, in 22% yield. The dimeric structure of the product was clearly

14



16

established by the mass spectrum. The electronic spectrum of **16** ($CHCl_3$) showed a maximum at 348 nm (ε 85,000) and a shoulder at *ca* 325 nm (ε 74,000). The ¹H-NMR spectrum of **16** (Fig 1) was simple, consisting of a 4H doublet at τ 2·32 (J = 9 Hz) (H^1), a 4H doublet at τ 2·68 (J = 16 Hz) (H^3), a 4H double doublet at τ 3·50 (J = 9, 16 Hz) (H^2), a 16H multiplet at τ 7·5–7·9 (allylic H) and a 16H multiplet at τ 8·1–8·5 (nonallylic H).

The tetradehydrotetraaza[32]annulene **16** is a $4n$ π-electron system (n = 8), and might perhaps have been paratropic.[6] In fact the ¹H-NMR spectrum of **16** resembled that of the precursor **14**, and it is clearly an atropic molecule.

EXPERIMENTAL

General procedures. M.ps were determined on a Kofler hot-stage apparatus and are uncorrected. Mass spectra: on an AEI MS-12 spectrometer (70 eV, direct inlet system), unless otherwise indicated. Electronic spectra: on a Unicam SP-800 spectrophotometer. IR spectra: on a Unicam SP-200 spectrophotometer. ¹H-NMR spectra: on a Varian T-60 spectrometer (TMS used as internal standard). SiO_2 for chromatography was Woelm, grade III.

3-(2-*Ethynyl*-1-*cyclohexen*-1-*yl*)-2-*propenal* (**9**). A 1% soln of *p*-toluenesulphonic acid.H_2O in dry EtOH (15 drops) was added to a soln of **6**[2] (10 g) and $HC(OEt)_3$ (11·8 g) in dry EtOH (10 ml). After being stirred at room temp for 24 h, the mixture was treated with pyridine (1 ml) and poured into 2% $NaHCO_3$ aq. Extraction with ether, drying ($MgSO_4$), and evaporation yielded crude **7**. The residue was dissolved in EtOAc (10 ml) and warmed to 35° in a flask equipped with 2 dropping funnels, a condenser, and a magnetic stirrer. A few drops of a 10% soln of $ZnCl_2$ in EtOAc were added, and then simultaneously 4 ml of this soln and ethyl vinyl ether (20 ml) during 30 min with stirring at 35°. The mixture was stirred for 4 h at room temp, stoppered, and allowed to stand for 16 h. A soln of NaOAc (10 g) in AcOH (100 ml) and H_2O (7 ml) was then added, and the mixture was heated at 90° for 2 h. Dilution with H_2O, extraction with ether, drying ($MgSO_4$), and evaporation gave a residue, which was chromatographed on SiO_2 (250 g). Elution with pentane-ether (19:1) and crystallisation from pentane-ether gave **9** (7·2–7·9 g; 60–66%) as almost colourless crystals, m.p. 58–59°. (Found: C, 82·83; H, 7·71. $C_{11}H_{12}O$ requires: C, 82·46; H, 7·55%); *m/e* 160 (M^+); λ_{max} (95% EtOH) 309 nm (ε 21,200); ν_{max} (CCl_4) 3300s, 2100w (C≡CH), 2700m (CHO), 1680vs (C=O), 1610s (C=C), 980s (*trans* C=C) cm^{-1}; τ (CCl_4) 0·41 (d, J = 8 Hz, 1H, –CHO), 2·27 (d, J = 16 Hz, 1H, H^3), 3·95 (dd, J = 8, 16 Hz, 1H, H^2), 6·60 (s, 1H, ≡CH), 7·4–7·9 (m, 4H, allylic H), 8·1–8·5 (m, 4H, nonallylic H).

5-(2-*Ethynyl*-1-*cyclohexen*-1-*yl*)-2,4-*pentadienal* (**12**). A 1% soln of *p*-toluenesulphonic acid.H_2O in dry EtOH (2 drops) was added to a soln of **9** (1·3 g) and $HC(OEt)_3$ (1·2 g) in dry EtOH (2 ml). After being stirred at room temp for 15 h, the mixture was treated with pyridine (3 drops) and poured into 2% $NaHCO_3$ aq. Extraction with ether, drying ($MgSO_4$), and evaporation yielded crude **10**. A few drops of a 10% soln of $ZnCl_2$ in EtOAc were added at 35° with stirring, and then simultaneously from 2 dropping funnels 0·5 ml of this soln and ethyl vinyl ether (4 ml) during 15 min (30–35°). The stoppered flask was then stirred at room temp for 20 h. A soln of NaOAc (1·5 g) in AcOH (15 ml) and H_2O (1·4 ml) was added, and the mixture was heated at 90° for 1 h. Dilution with H_2O, extraction with ether, drying ($MgSO_4$), and evaporation gave a residue, which was chromatographed on SiO_2 (40 g). Elution with pentane-ether (9:1) and crystallisation from pentane-ether yielded **12** (0·75 g, 50%) as yellow prisms, m.p. 94–95°; *m/e* 186 (M^+); λ_{max} (95% EtOH) 243, 340 nm (ε 8700, 31,300); ν_{max} (KBr) 3200s, 2100w (C≡CH), 2700w (CHO), 1660vs (C=O), 1600vs (C=C), 1010s, 990s (*trans* C=C) cm^{-1}; τ ($CDCl_3$) 0·45 (d, J = 8 Hz, 1H, –CHO), 2·61 (d, J = 16 Hz, 1H, H^5), 2·78 (dd, J = 11, 16 Hz, 1H, H^3), 3·54 (dd, J = 11, 16 Hz, 1H, H^4), 3·84 (dd, J = 8, 16 Hz, 1H, H^2), 6·58 (s, 1H, ≡CH), 7·5–7·9 (m, 4H, allylic H), 8·1–8·5 (m, 4H, nonallylic H).

Azine **13**. A soln of **6**[2] (1·5 g) in EtOH (15 ml) was added to a soln prepared from hydrazine sulphate (0·78 g), Na_2CO_3 (0·97 g), and H_2O (8 ml), with stirring. The mixture was stirred at room

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*The same experimental conditions were used, as had been found best for the coupling of all *trans*-4,10,16-eicosatriene-1,7,13,19-tetrayne to the corresponding 20-membered ring cyclic "monomer" (Y. Gaoni, C. C. Leznoff and F. Sondheimer, *J. Am. Chem. Soc.* **90**, 4940 (1968)).

temp for 15 min, the ppt was collected and washed with EtOH. Crystallisation from $CHCl_3$–EtOH gave **13** (1·21 g, 82%) as yellow crystals, m.p. 167–168°; *m/e* 264 (M^+); λ_{max} (95% EtOH) 303sh, 316, 329, 345sh nm (ϵ 23,000, 30,800, 31,500, 19,000); ν_{max} (KBr) 3200s, 2100w (≡CH), 1600vs (=C) cm^{-1}; τ ($CDCl_3$) 1·28 (s, 2H, H^1), 6·63 (s, 2H, ≡CH), 7·3–7·8 (m, 8H, allylic H), 8·0–8·5 (m, 8H, nonallylic H).

Azine **14**. This substance was similarly prepared from **9** (500 mg) in EtOH (5 ml) and hydrazine sulphate (210 mg), Na_2CO_3 (260 mg), and H_2O (3 ml). Crystallisation from benzene-EtOH yielded **14** (405 mg, 82%) as yellow needles, m.p. >300°; *m/e* 316 (M^+); λ_{max} (95% EtOH) *ca* 343sh, 370, *ca* 400sh nm (ϵ 37,700, 54,600, 28,400); ν_{max} (KBr) 3280s, 2100w (≡CH), 1610s (=C), 990s (*trans* C=C) cm^{-1}; τ (CCl_4) 1·83 (d, $J = 9$ Hz, 2H, H^1), 2·62 (d, $J = 16$ Hz, 2H, H^3), 3·53 (dd, $J = 9$, 16 Hz, 2H, H^2), 6·75 (s, 2H, ≡CH), 7·5–7·9 (m, 8H, allylic H), 8·1–8·5 (m, 8H, nonallylic H).

Azine **15**. This substance was similarly prepared from **12** (750 mg) in EtOH (15 ml) and hydrazine sulphate (270 mg), Na_2CO_3 (330 mg), and H_2O (6 ml), the mixture being stirred for 2 h. Crystallisation from $CHCl_3$–MeOH gave **15** (410 mg, 55%) as orange needles, m.p. >300°; *m/e* 368 (M^+); ν_{max} (KBr) 3260s, 2100w (≡CH), 1620s, 1580s (=C), 1000vs (*trans* C=C) cm^{-1}; τ ($CDCl_3$) 1·78 (d, $J = 9$ Hz, 2H, H^1), τ 2·6–3·9 (m, 8H, H^2–H^5), 6·63 (s, 2H, ≡CH), 7·5–7·9 (m, 8H, allylic H), 8·1–8·5 (m, 8H, nonallylic H).

Coupling of **14** *to the tetradehydrotetraaza*[32]*annulene* **16**. A soln of **14** (500 mg) in pyridine (25 ml; technical grade, dried over CaH_2 and distilled from KOH) and ether (25 ml) was added dropwise during 4 h to a stirred soln of $Cu(OAc)_2.H_2O$ (2·5 g) in pyridine (250 ml) kept at 70°, additional 1 g portions of $Cu(OAc)_2.H_2O$ being added after the first and the second h. The mixture was then stirred for a further 1 h at 70°, cooled, and concentrated to *ca* 20 ml under reduced pressure. H_2O (200 ml) and ether (200 ml) were added, the ether layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated. Chromatography on SiO_2 (50 g), elution with benzene-ether (1 : 1) and crystallisation from chloroform-ether gave **16** (110 mg; 22%) as yellow prisms, which decomposed on attempted m.p. determination; *m/e* (AEI MS-9 mass spectrometer) 628·356 (M^+, $C_{44}H_{44}N_4$ requires *m/e* 628·357); ν_{max} (KBr) 2190w, 2120w (C≡C), 1610s (=C), 980s (*trans* C=C) cm^{-1}; electronic and ^{1}H-NMR spectra, see Discussion and Fig 1.

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