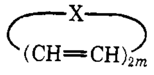
Synthesis of Methylene-Bridged Bisdehydroaza[17]annulenes, Aromatic Homologs of Pyrrole[1]

Sir:

Heteroannulenes of type **1** (X = NH, S, O, etc.) are expected to be aromatic, provided they are reasonably coplanar, and the heteroatom can contribute two π electrons to the delocalized system. Although five- and



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certain nine-membered[2] ring representatives are known to be aromatic, the only larger ring members prepared previously appear to be nonplanar and nonaromatic.[3]

Table I. Nmr Parameters of Compounds **7–16**, at 60 MHz in CDCl$_3$ (Internal Standard, TMS)[a,b]

Compd	H$_A$	H$_B$		Allylic	H$_C$		H$_D$	Others
	τ	τ	J, Hz	τ	τ	J, Hz	τ	τ
7	1.50 d[c]	3.41 d	16.5	7.5–7.8 m	2.36 d	16.5	2.20 t[c]	≡CH, 6.66 s
8	1.76 d[d]	3.40 d	16.4	7.5–7.9 m	1.76 d	16.4	1.13 t[d]	
9	2.83 s (−1.11)	2.38 d	15.8 (−1.22)	6.9–7.5 m (−0.45)	7.33 d	15.8 (+4.08)	10.83 s (+3.97)	NMe, 6.35 s (−0.58)
10	2.80 d[e] (−0.96)	2.50 d	15.8 (−1.07)	6.9–7.5 m (−0.45)	6.99 d	15.8 (+3.73)	10.55 s (+3.70)	NH, 3.1 br (−1.2)
11	2.37 s (−0.64)	2.96 d	16.1 (−0.64)	7.1–7.6 m (−0.35)	4.78 d	16.1 (+1.72)	8.77 s (+1.86)	OEt, 5.62 q (−0.11), 8.60 t (−0.08)
12	2.4 brs	3.04 d	16.1 (−0.56)	7.2–7.6 m (−0.3)	4.51 d	16.1 (+1.54)	8.54 s (+1.68)	COMe, 7.54 s (−0.20)
13	3.94 s	3.60 d	15.9	7.4–7.9 m	3.25 d	15.9	6.85 s	NMe, 6.93 s; ≡CH, 6.71 s
14	3.76 d[f]	3.57 d	15.9	7.4–7.9 m	3.26 d	15.9	6.85 s	NH, 4.3 br t; ≡CH, 6.72 s
15	3.01 s	3.60 d	16.0	7.5–7.9 m	3.06 d	16.0	6.91 s	OEt, 5.73 q, 8.68 t; ≡CH, 6.78 s
16	*g*	3.60 d	16.0	7.5–7.9 m	2.97 d	16.0	6.86 s	COMe, 7.74 s; ≡CH, 6.76 s

[a] In addition, all compounds showed a multiplet at ~τ 8.0–8.5 (aliphatic protons). [b] The assignments of H$_B$ and H$_C$ are based on nuclear Overhauser experiments and long-range coupling. [c] J = 2.1 Hz. [d] J = 2.0 Hz. [e] J = 4.4 Hz. [f] J = 4.5 Hz. [g] Very broad signal due to slow rotation about the N–CO bond.

We now report the synthesis of the aromatic methylene-bridged bisdehydroaza[17]annulene derivatives **9–12**, the first aromatic macrocyclic heteroannulenes of type **1** to be obtained.

Dimethyl pyridine-3,5-dicarboxylate (**2**)[4] was reduced with excess LAH in ether to the diol **3**,[5] which on boiling with 60% HBr gave ~40% (based on **2**) of **4** (mp 97–98° dec). Treatment of **4** with >2 mol equiv of PPh$_3$ in DMF at 80° furnished **5** (mp ~210–220°) in essentially quantitative yield. Wittig reaction of **5** and 2 mol equiv of **6**[6] in DMF with LiOEt in EtOH at 90° led to a mixture of stereoisomers, from which the trans,-trans compound **7** (pale yellow needles; mp >300°; *m/e* 339; nmr spectrum, see Table I) was isolated in 20% yield by chromatography on alumina. Molecular models indicated that **7** should be convertible to the relatively strain-free cyclic "monomer" **8**, and this substance could indeed be obtained in remarkably high yield (85%) when **7** was oxidized with cupric acetate in pyridine at 55–60° for 1.5 hr. The bridged pyridine **8** formed golden needles: mp 248–250°; *m/e* 337. In the nmr spectrum (Table I) the H$_C$ and H$_D$ resonances have shifted downfield by τ 0.60 and 1.07, respectively, as compared with the precursor **7**. These shifts are presumably due to the fact that H$_C$ and H$_D$ in the rigid structure **8** are deshielded by the surrounding ethylenic and acetylenic bonds to a considerably greater extent than in **7**, where free rotation about the single bonds can take place.

Quaternization of **8** with Me$_2$SO$_4$ at 80° for 20 hr followed by reduction with aqueous Na$_2$S$_2$O$_4$ and Na$_2$CO$_3$[7] at 40–50° for 15 min gave ~50% of **9** as dark red crystals:[8] *m/e* 353.2142 (calcd 353.2143); λ_{max} (CHCl$_3$) ~345 sh (ϵ 34,000), 358 (42,000), 376 (25,000), 430 (6000), 457 (5100), 496 (3000), and 535 nm (1200). Reduction of **8** with LAH in ether at room temperature for 2 hr led to ~60% of **10** as red crystals;[8] *m/e* 339. Treatment of **10** in ether with ClCOOEt and pyridine at 0° for 15 min gave ~50% of **11** as yellow crystals;[8] *m/e* 411.2203 (calcd 411.2198). Reaction of **10** in ether with MeCOCl and pyridine at 0° for 15 min led to ~50% of **12** as yellow crystals;[8] *m/e* 381.2089 (calcd 381.2092).

For comparison purposes, the 1,4-dihydropyridines **13–16** were prepared essentially in the same way from

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[1] Unsaturated Macrocyclic Compounds. XC. For part LXXXIX, see: J. F. M. Oth, J. M. Gilles, E. P. Woo, and F. Sondheimer, *J. Chem. Soc.*, in press.

[2] 1*H*-Azonine and derivatives: see A. G. Anastassiou, S. W. Eachus, R. P. Cellura, and J. H. Gebrian, *J. Chem. Soc. D*, 1133 (1970).

[3] (a) A benz-fused thia[13]annulene: A. B. Holmes and F. Sondheimer, *J. Amer. Chem. Soc.*, **92**, 5284 (1970). (b) Aza[13]-, aza[17]-, and oxa[17]annulenes: G. Schröder, lecture given at the XXIIIrd International Congress of Pure and Applied Chemistry, Boston, Mass., 1971 (see G. Schröder, G. Heil, R. Neuberg, G. Plinke, and J. F. M. Oth, Abstracts of Papers, p 37). (c) Oxygen- and sulfur-bridged thia[17]- and thia[21]annulenes: T. M. Cresp and M. V. Sargent, *J. Chem. Soc. D*, 1458 (1971).

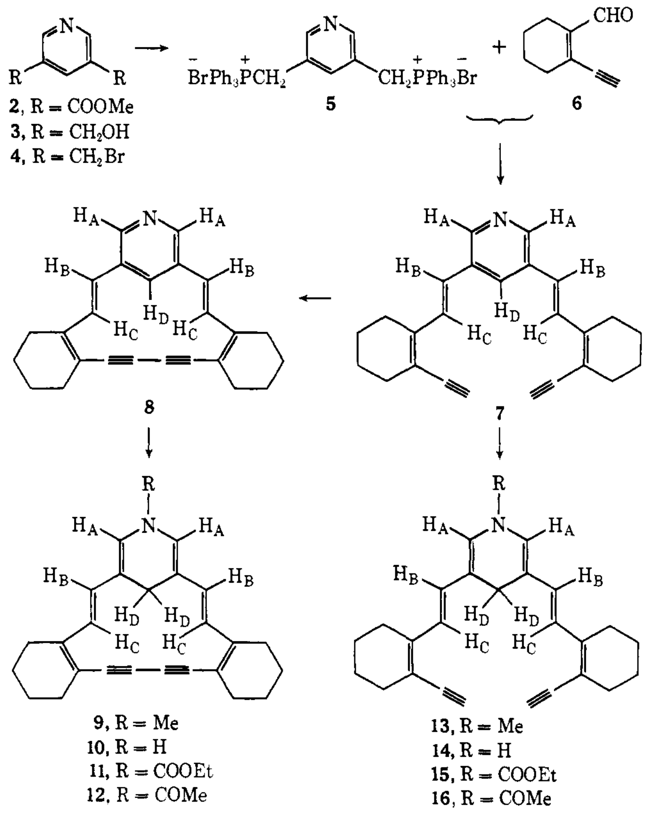
[4] The ester 2 was prepared readily in ~60% overall yield from 3,5-lutidine by oxidation with KMnO$_4$ to pyridine-3,5-dicarboxylic acid (see A. Eckert and S. Loria, *Monatsh. Chem.*, **38**, 225 (1917)), followed by esterification with MeOH-H$_2$SO$_4$ (see H. Meyer and H. Tropsch, *ibid.*, **35**, 207 (1914)).

[5] K. Tsuda, N. Ikekawa, R. Takasaki, and Y. Yamakawa, *Pharm. Bull.*, **1**, 142 (1953); J. Paleček, L. Ptáčková, and J. Kuthan, *Collect. Czech. Chem. Commun.*, **34**, 427 (1969).

[6] P. Schiess and H. L. Chia, *Helv. Chim. Acta*, **53**, 485 (1970); G. M. Pilling and F. Sondheimer, *J. Amer. Chem. Soc.*, **93**, 1970 (1971).

[7] See P. J. Brignell, U. Eisner, and F. G. Farrell, *J. Chem. Soc. B*, 1083 (1966).

[8] The substance decomposed on attempted melting point determination.



the pyridine 7, except that the *N*-methyl derivative **13** was obtained from **14** by reaction with NaH in dimethoxyethane and subsequent treatment with MeI.

The nmr parameters of the aza[17]annulenes **9–12**, as well as of the models **13–16**, are given in Table I. The differences in chemical shift on passing from the model to the corresponding aza[17]annulene are given in parentheses. It can be seen that substances **9–12** all exhibit a diamagnetic ring current, indicative of aromaticity, the outer protons being deshielded and the inner protons shielded.[9] As expected, the magnitude of the ring current (**9** > **10** > **11** > **12**) falls off with increasing electronegativity of the substituent. The nitrogen substituents are also affected by the diamagnetic ring current; *e.g.*, the *N*-methyl resonance in **9** (τ 6.35) is at lower field than that of the model **13** (τ 6.93) and is lower than even that of *N*-methylpyrrole (τ 6.50).

The fact that each of the substances **9–12** is considerably more stable than the corresponding models **13–16** is also in accord with their aromatic nature.[10] Moreover, the electronic spectra [main maxima ($CHCl_3$) **9**, 358; **10**, 349; **11**, 329; **12**, 331 nm; highest wavelength band, **9**, 535; **10**, 522 sh; **11**, 482 sh; **12**, 482 sh nm] may also be indicative of their aromaticity, **9** being most aromatic, and **11** and **12** being least aromatic.[11]

The observation that the aza[17]annulene derivatives **9–12** sustain a diamagnetic ring current, whereas *N*-ethoxycarbonylaza[17]annulene apparently does not,[3b] is presumably due to the greater planarity of the former systems, caused by the presence of the methylene bridges and/or the acetylenic linkages.

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[9] In fact, the shielding of the inner protons in **9–12** is presumably greater than indicated in Table I, since the corresponding protons in the models **13–16** are at higher field than they would be in the particular conformations indicated in the formulas (*cf.* the difference in the nmr spectra of **7** and **8**, discussed above).

[10] Although the aza[17]annulene **10** was gradually reoxidized to **8** on standing in air, the corresponding reoxidation of **14** to **7** occurred much more readily.

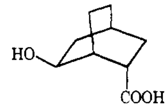
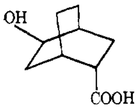
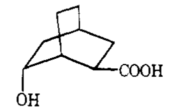
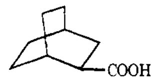
[11] Attempts to determine the pK_a values of substances **9–12** so far have given no meaningful results.

σ-Inductive Model *vs.* Field Model. Observation of a Reversed Attenuation Effect[1,2]

Sir:

Many attempts have been made to distinguish between and evaluate the relative importance of the σ-inductive and field models.[3] Perhaps the strongest qualitative evidence for the operation of field effect is the observation of the angular dependence of substituent effects.[4] Several studies involving direct comparison of rigid model systems provide more quantitative evidence for the superiority of the field model in describing the propagation of nonconjugative substituent effects.[5] We now report the first unambiguous example of a reversed attenuation effect—an observation which questions the very foundation of the σ-

Table I. pK_a Values in 50% (by Weight) Aqueous Ethanol at 25°

No.	Structure	pK_a
I		6.261 ± 0.002
II		6.416 ± 0.023
III		6.470 ± 0.004
IV		6.722 ± 0.006

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(1) (a) Mechanism of Transmission of Nonconjugative Substituent Effects. III; (b) part I: C. L. Liotta, W. F. Fisher, and G. H. Greene, *Chem. Commun.*, 1251 (1969); part II: C. L. Liotta, W. F. Fisher, and C. L. Harris, *ibid.*, 1312 (1971).

(2) Abstracted in part from the Ph.D. Thesis of W. F. F., Georgia Institute of Technology, 1970, and in part from the Masters Thesis of E. L. S., Georgia Institute of Technology, 1971.

(3) J. D. Roberts and W. T. Moreland, *J. Amer. Chem. Soc.*, **75**, 2167 (1953); S. Siegel and J. M. Kormarmy, *ibid.*, **82**, 2547 (1960); L. M. Stock and H. D. Holtz, *ibid.*, **86**, 5188 (1964); F. W. Baker, R. C. Parish, and L. M. Stock, *ibid.*, **89**, 5677 (1967); P. E. Peterson, C. Casey, E. V. Tao, A. Agatrop, and G. Thompson, *ibid.*, **87**, 5163 (1965); K. Bowden, *Can. J. Chem.*, **41**, 2781 (1963), and references cited therein.

(4) M. J. S. Dewar and P. J. Grisdale, *J. Amer. Chem. Soc.*, **84**, 3548 (1962); W. Adcock and M. J. S. Dewar, *ibid.*, **89**, 379 (1967); R. Golden and L. M. Stock, *ibid.*, **88**, 5928 (1966); K. Bowden and D. C. Parkin, *Chem. Commun.*, 75 (1968); M. J. S. Dewar, *ibid.*, 547 (1968); W. Adcock and P. R. Wells, *Aust. J. Chem.*, **18**, 1351 (1965); E. J. Grubbs and R. Fitzgerald, *Tetrahedron Lett.*, 4901 (1968); D. S. Noyce and B. E. Johnston, *J. Org. Chem.*, **34**, 1252 (1969).

(5) C. L. Liotta, W. F. Fisher, and G. H. Greene, *J. Chem. Soc. D*, 1251 (1969); C. F. Wilcox and C. Leung, *J. Amer. Chem. Soc.*, **90**, 336 (1968).