ing which there is considerable disagreement. The expected errors in measurements of dipole moments of 1,4-cyclohexadiene and its 1,4-dichloro derivative preclude conformation assignments,[1,2] and the vibrational or the pure rotational Raman spectra of 1,4-cyclohexadiene do not distinguish a planar or near-planar conformation from a rapidly interconverting boat conformation.[3,4] A boat conformation of 1,4-cyclohexadiene has been calculated to be more stable by 1.5 kcal/mol on the basis solely of angle strain and interactions between nonbonded hydrogen atoms.[5]

In the present investigation, the planar conformation of 1,4-cyclohexadiene indicated by the biological activity and nuclear magnetic resonance studies of certain 1,4-cyclohexadiene derivatives has been established conclusively in the structure determination of 1,4-cyclohexadiene-1-glycine by X-ray diffraction.

Because of the possibility that the ring of 1,4-cyclohexadiene-1-alanine could exist in a planar conformation, which would greatly enhance its potential for activity as a phenylalanine antagonist, the analog was prepared[6] and found to be one of the most effective of the many known phenylalanine antagonists.[7] The exceptionally effective competitive antagonism of phenylalanine strongly suggests that the 1,4-cyclohexadienyl ring is essentially planar.

In nmr studies of 1,4-cyclohexadiene, methylene protons are found to be equivalent even at −150°, which is consistent only with a planar conformation or rapidly inverting boat conformation with a low energy barrier. The inability of a 3-phenyl substituent to alter the chemical shifts of protons in the *cis* or *trans* position on C-6 of 1,4-cyclohexadiene even when steric considerations would be expected to stabilize one form of an inverting boat conformation suggests a planar or very near planar conformation.[8]

A modified[9] equation[10] for vicinal coupling *vs.* dihedral angle predicts that the coupling constant between an olefinic proton and adjacent methylene protons in ring systems becomes smaller as the ring becomes more planar. Calculations indicate that a rapidly inverting boat with conformations such that the dihedral angle ranges from 95 to 25° would have a coupling constant approximately 70% greater than the planar conformation. Such coupling constants are 2.1 and 1.2 for the nonplanar cyclopentene and the presumed planar cyclopentadiene, respectively, and 3.1 and 1.5 for cyclohexene and 1,4-cyclohexadiene, respectively. These results strongly suggest a planar or very near planar conformation of 1,4-cyclohexadiene in solution.

In order to provide more conclusive evidence for the conformation of the ring, DL-1,4-cyclohexadiene-1-glycine[11] was selected for X-ray diffraction studies. The space group was determined to be $P2_1/c$ with four molecules per unit cell, and the unit cell dimensions are: $a = 15.864$, $b = 4.810$, $c = 10.022$ Å; $\beta = 98.03°$. The structure was solved by the Karle symbolic addition procedure,[12] and the agreement index, R, is 9.3% for 625 independent reflections. All of the hydrogen atoms were found in a difference density map, and the molecule was found to exist as a zwitterion with extensive intermolecular hydrogen bonding. The carbon–carbon double bonds in the ring average 1.347 Å, and the carbon–carbon single bonds average 1.485 Å; the estimated standard deviations in the bond lengths are no greater than 0.019 Å. Since the average distance of an atom in the ring to the best fit plane of the ring is 0.007 Å, the 1,4-cyclohexadiene ring is planar within experimental error.

Establishment of the conformation of the cyclohexadiene ring is of importance to theoretical studies of structure[5] and other chemical aspects such as assignments of configurations to isomers,[13] and in addition it can be anticipated that the isosteric relationship of the 1,4-cyclohexadienyl and phenyl group will be general for biologically active compounds. Preliminary studies, particularly with plant hormones, have demonstrated that high activity can be anticipated in analogs of biologically active compounds with this isosteric alteration of structure.[14]

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(6) DL-1,4-Cyclohexadiene-1-alanine was prepared by reducing DL-phenylalanine (5 g) with lithium (2 g) in liquid ammonia. The residue remaining after evaporation of the ammonia was repeatedly recrystallized from water to obtain 3.2 g of product, mp 234–236° dec. *Anal.* Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.47; H, 7.86; N, 8.36. The nmr spectrum shows no aromatic protons, three olefinic protons (τ 4.20, two protons; τ 4.43, one proton), and four doubly allylic protons (τ 7.35).

(7) In growth studies, the ratio of concentrations of antagonist to phenylalanine necessary for inhibition of visible growth for 18 hr ranged from 1 to 10 for *Escherichia coli* 10876, 9723, and W grown in inorganic salts–glucose media and for *Lactobacillus plantarum* 8014 and *Leuconostoc dextranicum* 8086 grown in a previously described synthetic media (J. M. Ravel, L. Woods, B. Felsing, and W. Shive, *J. Biol. Chem.*, **206**, 391 (1954); J. Edelson, P. R. Pal, C. G. Skinner, and W. Shive, *J. Am. Chem. Soc.*, **79**, 5209 (1957)). The analog is 50 to 100 times as active as 1-cyclohexene-1-alanine with *L. dextranicum*.

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(15) Rosalie B. Hite Predoctoral Fellow, 1962–1965.

(16) NDEA Fellow, 1965–1967; NIH Trainee, 1964–1965.

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Dicyclopenta[*ef*,*kl*]heptalene (Azupyrene)[1,2]

Sir:

Extensions of the Hückel rule, while remarkably satisfactory for catacondensed polycyclic systems, have not

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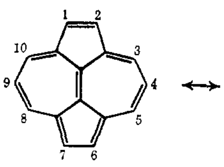
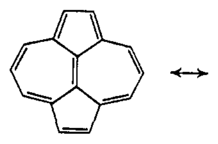
correlated well with the properties of cyclocondensed aromatic hydrocarbons (*e.g.*, pyrene, coronene, ovalene). An alternative treatment based on the free-electron model[3,4] suggested that a stable peripheral π-orbital system could be dominant in both types of structures and that other unsaturation would act as a substituent. Platt[4,5] has modified this view with the concept that a stable peripheral π-electron "shell" will be separated from inner π electrons by circular nodes and, therefore, the two loci of unsaturation will consist of more or less discrete molecular orbitals. This affords an explanation of the aromatic character of benzenoid cyclocondensed hydrocarbons and also of acepleiadylene (as contrasted with pleiadiene and acepleiadiene).[6]

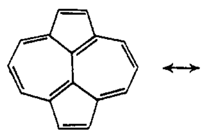
A convex nonalternant hydrocarbon having no benzenoid components and with structural features requisite for a further test of Platt's concept is dicyclopenta[*ef*,*kl*]heptalene (**1**). Two valence-bond formulas (**1a**, **1b**) possess a 14-π-electron system peripheral to the ethylene moiety, but the other noncharge-separated resonance structures (**1c**, **1d**) do not.[7] Application of Craig's rules[8] to any of the Kekulé structures and with either of the two axes of symmetry gives the result ($f + g$ = even number) that predicts the valence-bond ground state to be totally symmetric and, consequently, to have normal aromatic stability.



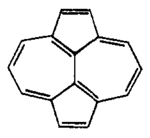
1a



1b



1c



1d

We now report the synthesis of **1** from 1,5,6,6a,7,8,-9,9a-octahydro-2H-indeno[5,4,3-*cde*]azulene (**2**) in three steps (ring enlargement with ethyl diazoacetate, hydrolysis, and decarboxylation plus dehydrogenation over 10% Pd–C at 350°) and in 2.5% yield.[9] Azupyrene (**1**) was obtained as square, bronze platelets, mp 250–258°. Its structure was confirmed by a molecular weight determination (mass spectrometry) of 202.076 (calcd (Lederberg[10]) for $C_{16}H_{10}$, 202.078) and by its spectral characteristics. The pmr ($DCCl_3$, internal TMS) at 1000-cycle sweep width showed a singlet for the 1, 2, 6, and 7 hydrogens at δ 8.40, a doublet for the 3, 5, 8, and 10 hydrogens centered at δ 8.68, and a triplet for the 4 and 9 hydrogens centered at δ 7.34, all in the aromatic region. With a 50-cycle sweep width eight lines of a characteristic AB_2 pattern were revealed. The infrared ($HCCl_3$) spectrum showed weak absorption at 3000 cm^{-1} (aromatic C—H), two sharp bands at 1588 and 1538 cm^{-1} (aromatic C=C), and strong absorption at 1377 cm^{-1} (very similar to that of azulene). A cyclohexane solution exhibited principal maxima (in mμ (log ϵ)) at 252 (4.73), 267 (5.03), 285 (4.49), 299 (4.32), 308 (4.27), 334 (4.07), 343 (4.13), 356 (3.62), 409 (2.92), 442 (3.17), 452 (3.28), 459 (3.17), 470 (3.49), and 483 (4.11), with low absorption (log ϵ 1–1.65) out to 770 mμ.

The diamagnetic susceptibility measured with a Faraday balance gave a value of $\Lambda/\Lambda_{bz} = 3.9 \pm 0.3$.[11] This result indicates a definite degree of aromaticity by this criterion, though the value is appreciably less than that (*ca.* 5.9) expected for a planar, cyclic 14-π-electron system.[12]

The esr spectrum of the 17-electron anion radical of **1** has been obtained and analyzed by Vincow and Owen.[13] The *g* value was 2.00258. The experimental hyperfine splittings were $a_{H\text{-}1} = 0.64 \pm 0.01$ gauss, $a_{H\text{-}3} = -4.23 \pm 0.01$ gauss, and $a_{H\text{-}4} = 0.94 \pm 0.01$ gauss as compared with respective calculated values of 0.10, −4.71, and 1.25 gauss.[14] These data are in the range expected for **1** and provide further evidence for the structure.

Additional studies on the properties of this new compound are in progress.

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[2] Because of the dual structural relationship to azulene and pyrene, we propose the name azupyrene for this compound, the name isoazupyrene for the other symmetrical isomer (azuleno[4,3,2-*bcd*]azulene), and the name *as*-azupyrene for the pentaleno[1,6,5-*def*]heptalene isomer. We thank Professor G. D. Halsey, Jr., for this suggestion.

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[7] One other example of this type, the isomeric but less symmetrical pentaleno[1,6,5-*def*]heptalene, is known (K. Hafner, R. Fleischer, and K. Fritz, *Angew. Chem. Intern. Ed. Engl.*, **4**, 69 (1965)). Craig's rules cannot be applied to this structure.

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[9] Details of the synthesis of **2** from indene and of the conversion to **1** will be reported in a subsequent paper. All new compounds isolated gave satisfactory elemental analyses and were further characterized by ultraviolet, infrared, and nmr spectroscopy.

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[11] We thank Drs. J. D. Wilson and C. E. Scott for making this measurement. Nmr solution determinations by Mr. J. L. Laity and Professor H. J. Dauben, Jr., to whom we are also grateful, in benzene, chloroform, and pyridine gave an average value of 2.8 ± 1 with the relatively high degree of uncertainty due to the low solubility of the compound in these solvents. The value for pyrene is 4.2 ± 0.1 (H. J. Dauben, Jr., J. D. Wilson, and J. L. Laity, *J. Am. Chem. Soc.*, **90**, 811 (1968)).

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[13] The interest and cooperation of Mr. G. Scott Owen and Professor Gershon Vincow in carrying out the experiments and calculations are gratefully acknowledged. Details of this study will be reported separately.

[14] The McConnell relationship was used for the calculations. See A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N. Y., 1961, p 153.

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A New Approach to Steroid Total Synthesis. A Nonenzymic Biogenetic-Like Olefinic Cyclization Involving the Stereospecific Formation of Five Asymmetric Centers

Sir:

This report discloses a completely novel steroid total synthesis. The key step is a nonenzymic biogenetic-like polyolefinic cyclization, namely the conversion of the tetraenol **1** into the tetracyclic diene **2**, which ap-