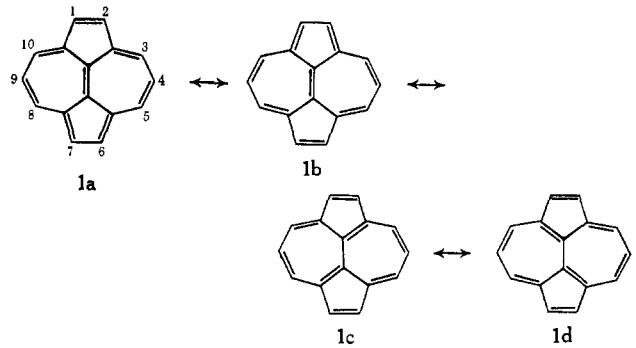
correlated well with the properties of cyclocondensed aromatic hydrocarbons (*e.g.*, pyrene, coronene, ovalene). An alternative treatment based on the free-electron model[3,4] suggested that a stable peripheral π-orbital system could be dominant in both types of structures and that other unsaturation 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



1a **1b** **1c** **1d**

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.

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 Λ/Λ_{bz} = 3.9 ± 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 ± 0.01 gauss, $a_{H\text{-}3}$ = −4.23 ± 0.01 gauss, and $a_{H\text{-}4}$ = 0.94 ± 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.

(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-*dej*]heptalene isomer. We thank Professor G. D. Halsey, Jr., for this suggestion.

(3) N. S. Bayliss, *J. Chem. Phys.*, **16**, 287 (1948); H. Kuhn, *ibid.*, **16**, 840 (1948); F. D. Rice and E. Teller, "The Structure of Matter," John Wiley and Sons, Inc., New York, N. Y., 1949, p 110.

(4) J. R. Platt, *J. Chem. Phys.*, **17**, 484 (1949); W. T. Simpson, *ibid.*, 17, 1218 (1949).

(5) J. R. Platt, *ibid.*, **22**, 1448 (1954).

(6) V. Boekelheide, W. E. Langeland, and C.-T. Liu, *J. Am. Chem. Soc.*, 73, 2432 (1951); V. Boekelheide and G. K. Vick, *ibid.*, 73, 653 (1951).

(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.

(8) D. P. Craig, *J. Chem. Soc.*, 3175 (1951); D. P. Craig and A. Macoll, *ibid.*, 964 (1949).

(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.

(10) J. Lederberg, "Computation of Molecular Formulas for Mass Spectrometry," Holden-Day Book Co., Inc., San Francisco, Calif., 1964.

(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)).

(12) H. J. Dauben, Jr., and J. L. Laity, private communication.

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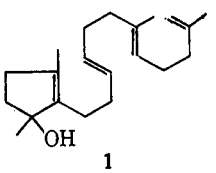
A New Approach to Steroid Total Synthesis. A Nonenzymic Biogenetic-Like Olefinic Cyclization Involving the Stereospecific Formation of Five Asymmetric Centers

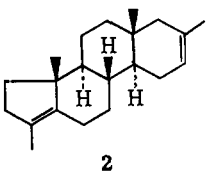
Sir:

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-

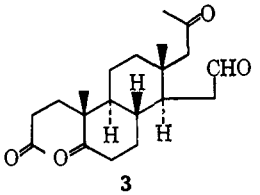
pears to proceed completely stereoselectively. The conversion of the hydrocarbon **2** into a steroid involves simply oxidation to the triketo aldehyde **3**, followed by double ring closure to afford *dl*-16,17-dehydroprogesterone (**4**). It is noteworthy that the carbinol **1** suffers rapid dehydration prior to cyclization; thus the resulting pentaene, which has no asymmetric centers, undergoes a one-step stereospecific transformation into a product (**2**) having no less than five centers of asymmetry.



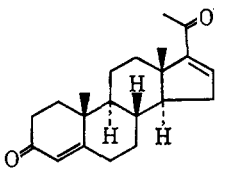
1



2



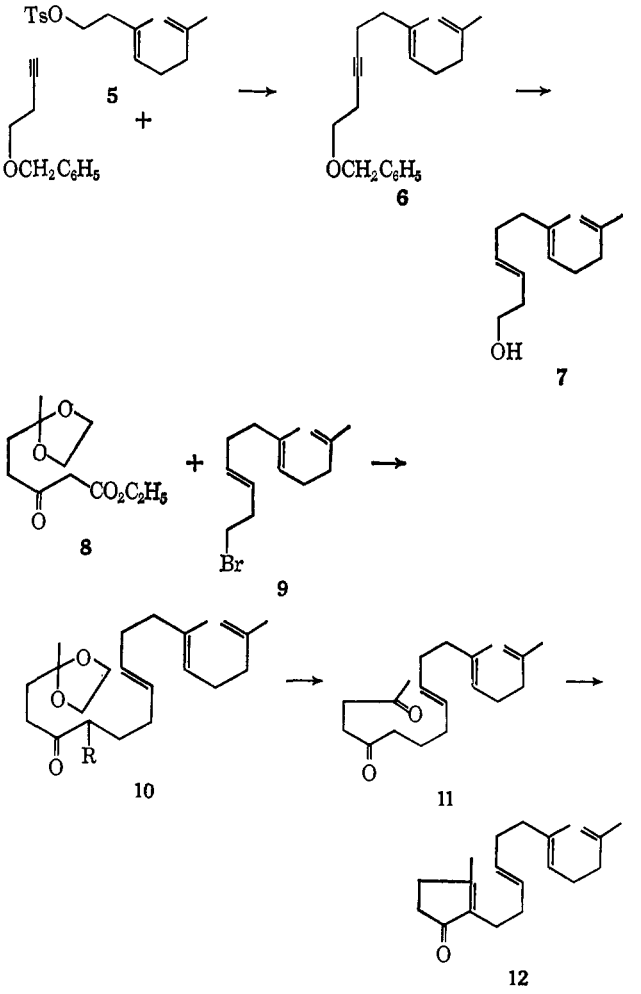
3



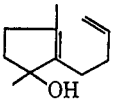
4

The synthesis of the carbinol **1** was effected as follows: the dienic tosylate **5**, produced from the corresponding dienol,[1] and the lithium salt of 4-benzyloxy-1-butyne were heated in tetrahydrofuran to give the alkylation product **6** which, on treatment with sodium in liquid ammonia, was converted into the trienol **7**. This last substance was transformed, by the action of lithium bromide on the tosylate, into the bromide **9** which was allowed to interact with the sodio derivative of the ketal keto ester **8** (prepared from 2,5-hexanedione by selective ketalization, followed by condensation of the monoketal with diethyl carbonate in the presence of sodium hydride) in a warm 4:1 mixture of dimethylformamide and benzene. The resulting alkylation product **10** (R = $CO_2C_2H_5$), on treatment with aqueous ethanolic barium hydroxide followed by acidification, underwent hydrolysis and decarboxylation to give the ketal ketone **10** (R = H). Hydrolysis with dilute methanolic hydrochloric acid at 30–35° afforded the diketone **11**, which on treatment with 2% sodium hydroxide in aqueous ethanol for 6 hr at 105–110° underwent cyclization[2] to give the tetraenone **12**. After chromatography on silica gel, which removed a trace of what appeared to be the alternative aldol cyclization product, the ketone **12** appeared to be pure by vpc, tlc, and nmr spectroscopy. Reaction with methyllithium afforded the tetraenol **1** which was used for the cyclization without purification. This tetraenol was very susceptible to dehydration;[3] even on dissolution of a sample in methylene chloride (probably containing a trace of acid impurity) it was essentially completely converted into the pentaene as shown by uv (λ_{max} 250 mμ), nmr, and ir spectroscopy.

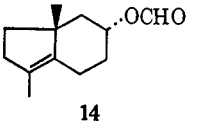
A model cyclization study was performed with the dienol **13** which was obtained by the action of methyllithium on 2-(3-butenyl)-3-methylcyclopent-2-en-1-one.[4]



A dilute solution of the dienol **13** in pentane, on stirring with excess anhydrous formic acid at room temperature for 3 hr, gave, in 60–75% yield, the bicyclic formate **14**.[5]



13



14

The best conditions that have been found so far for the cyclization of the tetraenol **1** consisted in stirring a dilute solution of the substrate in methylene chloride with excess trifluoroacetic acid at −78° for several hours. The product was treated with lithium aluminum hydride, then separated into a hydrocarbon and alcoholic fraction by chromatography on Florisil. Preparative tlc of the hydrocarbon fraction gave a crystalline substance in 30% yield, which appeared to be 98% pure by vpc. Crystallization from methanol gave colorless blades, mp 66–67.5° (*Anal.* Found: C, 88.5; H, 11.4).[6] The nmr spectrum showed, in particular, signals at δ 0.78 and 0.88 (C-18 and C-19 methyls), 1.57 (C-20 methyl), and 5.33 ppm (C-16 H). Dehydration of the alcohol fraction with phosphorus oxychloride and pyridine afforded a hydrocarbon mixture from

(1) S. F. Brady, M. A. Ilton, and W. S. Johnson, *J. Am. Chem. Soc.*, **90**, 2882 (1968).

(2) *Cf.* H. Hunsdiecker, *Ber.*, **75B**, 455 (1942).

(3) *Cf.* J. A. Marshall, N. Cohen, and A. R. Hochstetler, *J. Am. Chem. Soc.*, **88**, 3408 (1966).

(4) F. B. LaForge, N. Green, and W. A. Gersdorff, *ibid.*, 70, 3707 (1948).

(5) The structure of this product was proved by the following transformations: cleavage of the formate to the alcohol, oxidation with Jones reagent, ketalization of the resulting unsaturated ketone, ozonization, and base-catalyzed aldol ring closure of the ketal dione to give 2-ethylenedioxy-9-methyl-$\Delta^{5,10}$-octal-6-one, which is a known compound, mp 91–92° (R. K. Mather and A. S. Rao, *Tetrahedron*, 1259 (1967)).

(6) Satisfactory combustion analyses have been obtained for all of the other new substances described above.

which additional tetracyclic diene **2** (contaminated with some $\Delta^{17,17a}$ isomer) could be isolated by preparative tlc. A fraction with a lower R_f than that containing **2** appeared, by nmr and ir analysis, to contain mainly tricyclic material.

Treatment of the crude tetracyclic diene **2** with excess osmium tetroxide in pyridine for 48 hr at 24° followed by cleavage of the bisosmate with hydrogen sulfide in dimethyl sulfoxide gave a solid tetraol which, without purification, was treated with excess lead tetraacetate in tetrahydrofuran at 0° for 15 min. The crude solid product was then stirred with 2.5% aqueous potassium hydroxide for 13 hr at 74°.[7] Preparative tlc afforded, in 29% over-all yield, crystalline *dl*-16,17-dehydroprogesterone, mp 182–184° after crystallization from benzene–hexane (*Anal.* Found: C, 80.5; H, 9.0). The nmr, solution ir, uv, and mass spectra of the synthetic material were identical with the corresponding spectra of authentic naturally derived material.

We wish to emphasize that, in view of the preliminary nature of this work, considerable improvement in the yields cited above may be anticipated as the study continues.

Acknowledgment. We wish to thank the U. S. Public Health Service, the National Science Foundation, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We also wish to thank the U. S. Educational Foundation in Ceylon for the award of a Fulbright Fellowship to M. V. S. S., and the University of Ceylon for granting him a year's leave.

(7) The ring-D closure procedure of W. F. Johns (*J. Am. Chem. Soc.*, **80**, 6456 (1958)) was employed. See also G. Stork, K. N. Khastgir, and A. J. Solo, *ibid.*, 80, 6457 (1958).

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A Solid-Phase Synthesis of [Lysine]-vasopressin through a Crystalline Protected Nonapeptide Intermediate[1,2]

Sir:

We wish to report the synthesis of the crystalline protected nonapeptide, S-benzyl-N-tosyl-L-cysteinyl-L-tyrosyl-L-phenylalanyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-N$^{\epsilon}$-tosyl-L-lysylglycinamide (I),[3] by the solid-phase method developed by Merrifield.[4] Highly active [lysine]-vasopressin was obtained from I with excellent recovery. Recent reports about solid-phase syntheses of deamino-oxytocin[5] and of oxytocin[6,7] *via* protected nonapeptide intermediates prompt us to communicate our studies.

The preparation of I was carried out according to the general procedure described by Marshall and Merrifield[8] for solid-phase syntheses, where a cycle for the incorporation of each amino acid into the growing peptide chain involved acidolytic cleavage of the N-protecting *t*-butyloxycarbonyl (Boc) group, treatment with triethylamine, and peptide bond formation, with repeated washing operations in between. The starting *t*-butyloxycarbonylglycyl resins contained 0.22–0.27 mmol of glycine/g[9] in several preparations. Dicyclohexylcarbodiimide[10] was used as the coupling reagent for Boc-Pro, Boc-Cys(Bzl), Boc-Phe, Boc-Tyr, and Tos-Cys(Bzl). The lysine, asparagine, and glutamine moieties were introduced into the growing peptide chain by the *p*-nitrophenyl ester method[11] using Boc-Lys(Tos)-ONp,[12] Boc-Asp(NH_2)-ONp,[13] and Boc-Glu(NH_2)-ONp,[14] respectively. All protected amino acid derivatives[15] were repeatedly recrystallized until the known criteria of purity compared favorably.

In order to evaluate the progress during the first three cycles, crystalline benzyloxycarbonyl-L-prolyl-N$^{\epsilon}$-tosyl-L-lysylglycinamide (II)[3] was isolated by branching off a part of the resin (1.5 g) after the second cycle and introducing Z-Pro. Subsequent ammonolysis[16] for 70 hr in a sealed flask at room temperature containing absolute ethanol (35 ml) which had been saturated at 0° with anhydrous ammonia afforded an oil which was crystallized from ethyl acetate to give colorless prisms, 270 mg (98%[17]),[18] mp 185–186°, $[\alpha]^{23}D$ −32.5° (*c* 1, dimethylformamide); lit.[3] mp 184–185°, $[\alpha]^{20.5}D$ −33.0° (*c* 1, dimethylformamide).

Ammonolysis of the peptide resin (3.7 g, corresponding to 2.4 g of Boc-Gly-resin of 0.27 Gly equivalents) after the completion of all nine cycles was carried out as described above except that a mixture (1:1) of absolute ethanol and dimethylformamide was used. Evaporation of the solvents afforded a crude oil. It was dissolved in dimethylformamide. Addition of water precipitated an amorphous solid (1.0 g) which was treated

(1) Supported in part by Public Health Service research grants (C-6516 from the National Cancer Institute and FR-05526 from the Division of Research Facilities and Resources, National Institutes of Health), Albert and Mary Lasker Foundation, New York, N. Y., and Alvan T. and Viola D. Fuller Cancer Research Unit Grant, American Cancer Society (Massachusetts Division) Inc.

(2) Abbreviations follow the rules of the IUPAC–IUB Commission on Biochemical Nomenclature, in *Biochemistry*, **5**, 1445, 2485 (1966); **6**, 362 (1967); *J. Biol. Chem.*, **241**, 2491 (1966).

(3) J. Meienhofer and V. du Vigneaud, *J. Am. Chem. Soc.*, **82**, 2279 (1960).

(4) R. B. Merrifield, *ibid.*, **85**, 2149 (1963); *Biochemistry*, **3**, 1385 (1964); *Science*, **150**, 178 (1965).

(5) H. Takashima, V. du Vigneaud, and R. B. Merrifield, *J. Am. Chem. Soc.*, **90**, 1323 (1968).

(6) H. C. Beyerman, C. A. M. Boers-Boonekamp, W. J. Van Zoest, and D. Van Den Berg, "Peptides," H. C. Beyerman, A. Van de Linde, and W. M. Van Den Brink, Ed., North Holland Publishing Co., Amsterdam, 1967, p 117.

(7) M. Manning, *J. Am. Chem. Soc.*, **90**, 1348 (1968). In a footnote the preparation of Z-Cys(Bzl)-Tyr(Bzl)-Phe-Glu(NH_2)-Asp(NH_2)-Cys(Bzl)-Pro-Lys(Z)-Gly-NH_2 was mentioned.

(8) G. R. Marshall and R. B. Merrifield, *Biochemistry*, **4**, 2394 (1965).

(9) Determined by amino acid analysis after hydrolysis by refluxing with dioxane–12 *N* HCl (1:1) for 48 hr.

(10) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, 77, 1067 (1955).

(11) M. Bodanszky, *Nature*, **175**, 685 (1955).

(12) C. H. Li, J. Ramachandran, D. Chung, and B. Gorup, *J. Am. Chem. Soc.*, **86**, 2703 (1964).

(13) E. Sandrin and R. A. Boissonnas, *Helv. Chim. Acta*, **46**, 1637 (1963); E. Schröder and E. Klieger, *Ann.*, **673**, 208 (1964).

(14) H. Zahn, W. Danho, and B. Gutte, *Z. Naturforsch.*, **21b**, 763 (1966).

(15) *t*-Butyloxycarbonyl (Boc) amino acids were prepared from *t*-butyloxycarbonyl azide [L. A. Carpino, *J. Am. Chem. Soc.*, **79**, 4427 (1957); Aldrich Chemical Co., Inc., Milwaukee, Wis.] with pH-stat controlled addition of NaOH according to E. Schnabel [*Ann.*, **702**, 188 (1967)]. We used 2 *N* HCl instead of citric or acetic acid for the final acidification.

(16) M. Bodanszky and J. T. Sheehan, *Chem. Ind.* (London), 1423 (1964).

(17) All yields are based on the glycine content of the starting Boc-Gly-resin.

(18) This compares favorably with a yield of 40% of Z-Pro-Leu-Gly-NH_2, obtained by ammonolysis with liquid ammonia during a solid phase synthesis of oxytocin by Beyerman, *et al.*[6]