

Welch Foundation Grant E-183. The Varian XL-100/Nicolet TT-100 NMR spectrometer was purchased through NSF Grant No. MPS 75-06162.

- (2) W. C. Jones, Jr., T. M. Rothgeb, and F. R. N. Gurd, *J. Am. Chem. Soc.*, **97**, 3875 (1975); *J. Biol. Chem.*, **251**, 7452 (1976); T. M. Rothgeb, B. N. Jones, D. F. Hayes, and R. S. Gurd, *Biochemistry*, **16**, 5813 (1977).
- (3) M. Kunitz and J. H. Northrup, *J. Gen. Physiol.*, **19**, 991 (1936).
- (4) B. Kassell and M. Laskowski, Sr., *Biochem. Biophys. Res. Commun.*, **20**, 463 (1965).
- (5) R. Huber, D. Kukla, A. Ruhlmann, O. Epp, and H. Formanek, *Naturwissenschaften*, **57**, 389 (1970).
- (6) T. E. Creighton *J. Mol. Biol.*, **87**, 563, 579, 603 (1974); **95**, 197 (1975); **113**, 275 (1977).
- (7) B. Kassell, *Biochemistry*, **3**, 152 (1964).
- (8) D. F. Dyckes, T. E. Creighton, and R. C. Sheppard, *Nature*, **247**, 202 (1974); *Int. J. Peptide Protein Res.*, **11**, 258 (1978).
- (9) T. E. Creighton, D. F. Dyckes, and R. C. Sheppard, *J. Mol. Biol.*, **119**, 507 (1978).
- (10) D. F. Dyckes, unpublished observations.
- (11) This relationship has been discussed in detail in a recent publication: J. Reisse, R. Ottinger, P. Bickart, and K. Mislow, *J. Am. Chem. Soc.*, **100**, 911 (1978); cf. especially their note 46.
- (12) S. Karplus, G. H. Snyder, and B. D. Sykes, *Biochemistry*, **12**, 1323 (1973).

Benjamin M. Harina, Douglas F. Dyckes*
M. Robert Willcott, III*
Department of Chemistry
University of Houston—Central Campus
Houston, Texas 77004

Warren C. Jones, Jr.
Department of Chemistry, University of Virginia
Charlottesville, Virginia 22901
Received March 3, 1978

A C₁₁H₁₁ Limit of Longicyclic Stabilization

Sir:

Synthetic applications of the Hückel MO model have largely been limited to those unsaturated hydrocarbons that are planar, or pericyclic, or both.¹ An alternative topology, the longicyclic, extends the range of the Hückel model from two dimensions into three.² The topologically required stabilization rule is then somewhat different.³ Its limits, as yet, are less well defined. It rationalizes the stability of the norbornadienyl cation,⁴ the inaccessibility of the norbornadienyl anion,⁵ and the effect of charge on the direction of bicyclo[3.2.2]nonatrienyl ⇌ barbaralyl equilibration.⁶

The synthetic criterion is more demanding. One expects a fruitful stabilization rule to anticipate the successful preparation of easily isolable cations and anions, under reasonably standard conditions, and in the absence of empirical analogy. This criterion has now been satisfied in two longicyclic syntheses, those of the bicyclo[3.2.2]nonatrienyl anion (**1**)⁷ and bicyclo[3.3.2]decatenyl dianion (**2**).^{7b}



The longicyclic rule³ anticipates the next higher homologue, bicyclo[4.3.2]undecatetraenyl, to be stable *both* as the anion and as the cation.^{8a} We here report our failure to obtain the anion under conditions closely similar to those that had earlier provided **1** and **2**. Satisfaction of the synthetic criterion is now frustrated by anionic rearrangement. Cationic rearrangement had similarly prevented isolation and characterization of the bicyclo[4.3.2]undecatetraenyl cation.⁹ It is therefore the carbon skeleton, and not the charge, that facilitates rear-

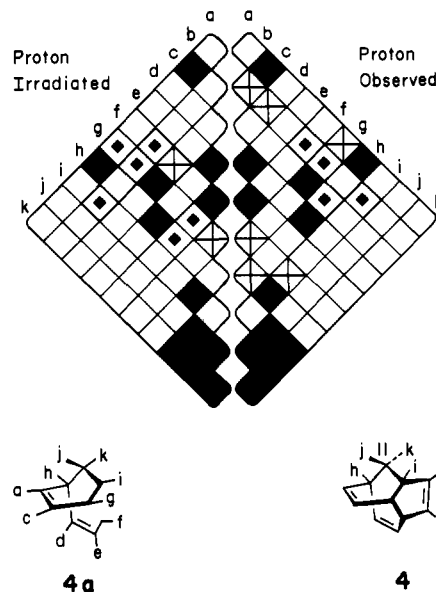


Figure 1. Complete spin decoupling results: solid block, elimination of 2–13-Hz coupling; ♦, elimination of 1.0–1.5-Hz coupling; +, inaccessible or ambiguous; open block, no discernible effect.

Table I. ¹H NMR Spectrum of **4**^a

Assignment	δ	Area ^b	Appearance, ^c J in Hz
a	6.52	1.02	dd, $J_{ac} = 7.5$, $J_{ah} = 8.5$
b	6.09	1.95	d, $J_{bf} = J_{bi} = 1.5$
c	5.93	1.02	dd, $J_{ac} = J_{cg} = 7.5$
d	5.80	1.07	dd, $J_{de} = 9.7$, $J_{dh} = 8.0$
e	5.52	0.96	dd, $J_{de} = 9.7$, $J_{ef} = 5.5$
f	2.87	1.97	{ ddd, $J_{ef} = 5.5$, $J_{fg} = 5.5$, $J_{bf} = 1.5$ ddd, $J_{cg} = 7.5$, $J_{fg} = 5.5$, $J_{gi} = 6.5$
g	2.82		
h	2.60	0.97	m
i	2.52	0.98	m
j	1.65	1.03	ddd, $J_{jk} = 13.0$, $J_{ij} = 10.5$, $J_{hj} = 4.5$
k	1.46	1.05	ddd, $J_{jk} = 13.0$, $J_{ik} = 2.5$, $J_{hk} = 2.0$

^a 0.03 M in CDCl₃ at 300 MHz. ^b Normalized to 12 protons. ^c Apparent first-order splittings.

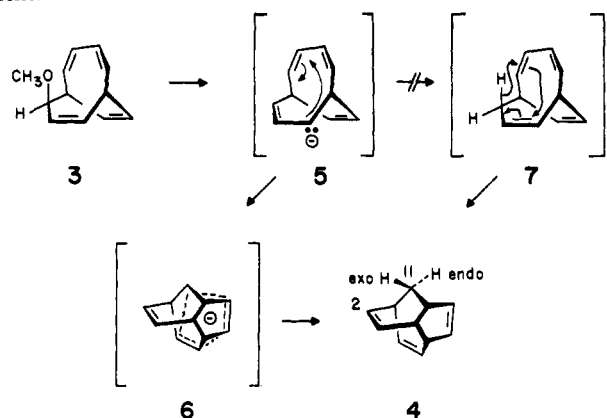
rangement. The course of the anionic rearrangement and its absence from **1** and **2** both correspond to an explicitly predicted limit of longicyclic stabilization.^{8b}

A persistent deeply purple solution was easily generated by treating *syn*-9-methoxybicyclo[4.3.2]undecatetraene (**3**)¹⁰ with lithium in tetrahydrofuran. NMR spectra of this solution (and of its recrystallized solute) were unfortunately obscured by recalcitrant impurities. Structurally useful information could only be obtained by methanol protonation at -78 °C. This quenched the color and provided a new C₁₁H₁₂ hydrocarbon as the exclusive volatile product in 27% yield.^{11,12}

The structure of this hydrocarbon was first defined to be an asymmetric tricyclicundecatriene by its ¹³C NMR (δ 142.1, 141.7, 139.7, 136.2, 135.8, 131.5, 48.0, 45.5, 42.1, 35.6, and 31.9 ppm) and ¹H NMR spectra (Table I). Next, a proton connectivity pattern (**4a**, Figure 1) was constructed by the sequential decoupling of all 2–13-Hz coupling constants. This pattern allows the residual *cis*-alkene to be joined in either one of two ways. Of these, only that represented by tricyclo[5.3.1.0^{4,8}]undeca-2,5,9-triene (**4**) is asymmetric. The complete list of possible isomers (48 tricyclics that lack quaternary carbons and exocyclic methylenes¹³) reveals no other viable candidate.

The ¹H NMR assignments of Figure 1 are generally con-

Scheme I



sistent with those reported for similar structures.¹⁴ The critical assignment of C₁₁ proton stereochemistry (vide infra) follows from the agreement of observed and calculated ³J.¹⁵ If the first set of observed ³J (10.5, 4.5 Hz, Table I) is matched with those calculated for J_{ij} (9.5 Hz, θ = 27°) and J_{hj} (4.1 Hz, θ = 54°) and the second set (2.5, 2.0 Hz) matched with those calculated for J_{ik} (2.5 Hz, θ = 62°) and J_{hk} (0.1 Hz, θ = 95°), a significantly better fit is obtained than if the assignments were reversed.

The anionic mechanism of Scheme I is to be regarded as plausible rather than established.¹⁶ Attack of the three- onto the four-carbon bridge of the longicyclic anion (5) generates the tricyclic isomer (6). All illustrated, 6 is assumed to possess some measure of trishomocyclopentadienyl pericyclic stabilization that may facilitate the rearrangement.¹⁷

We think it more significant, however, that 4 is *not* formed by a rapid thermal rearrangement of the still unknown bicyclo[4.3.2]undecatetraene (7). Methanol-*O-d* quenching of the anionic solution introduced 0.464 ± 0.009 deuterium atoms exclusively at the endo methylene position.¹⁸ Such stereospecificity exactly matches that of the pericyclic bishomocyclopentadienyl bicyclo[3.2.1]octadienyl anion.¹⁹ Had 7 been an intermediate, the isotopic label would have appeared at the exo position of C₁₁ and/or at C₂.

Clearly, the preparative value of the longicyclic stabilization rule does not extend to the C₁₁H₁₁ bicyclo[4.3.2]undecatetraene skeleton. In a similar way, the preparative value of the pericyclic [4n + 2] stabilization rule also falters when its homologation reaches C₁₀H₁₀.²⁰ Subsequent homologation, however (to C₁₂H₁₂^{-2,21a}, C₁₄H₁₄,^{21b} C₁₆H₁₆^{+2,21c} and C₁₇H₁₇^{-21d}), recovers the preparative value of the pericyclic stabilization rule. It remains to be seen whether subsequent longicyclic homologation will behave similarly.

Acknowledgment. Financial support at Cornell was provided by U.S. Public Health Research Grant No. 10495 from the National Cancer Institute.

References and Notes

- (1) J. P. Snyder, Ed., "Nonbenzenoid Aromatics", Academic Press, Vol. I, II, New York, N.Y., 1969, 1971.
- (2) (a) M. J. Goldstein, *J. Am. Chem. Soc.*, **89**, 6357 (1967); (b) M. J. Goldstein and R. Hoffmann, *ibid.*, **93**, 6193 (1971).
- (3) If two bridges each contain 4n π electrons, the third must have 4n + 2; if two each contain 4n + 2, the third must have 4n.^{2b}
- (4) P. R. Story and B. C. Clark, Jr., in "Carbonium Ions", Vol. III, G. A. Olah and P. v. R. Schleyer, Ed., Wiley-Interscience, New York, N.Y., 1972, p 1007.
- (5) G. Wittig and E. Hahn, *Angew. Chem.*, **72**, 781 (1960); R. A. Finnegan and R. S. McNeess, *J. Org. Chem.*, **29**, 3234 (1964); A. Streitwieser, Jr., and R. A. Caldwell, *ibid.*, **27**, 3360 (1962); G. Wittig and J. Otten, *Tetrahedron Lett.*, 601 (1963); G. Wittig and G. Klumpp, *ibid.*, 607 (1963).
- (6) M. J. Goldstein, S. Tomoda, S.-I. Murahashi, K. Hino, and I. Moritani, *J. Am. Chem. Soc.*, **97**, 3847 (1975).
- (7) (a) J. B. Grutzner and S. Winstein, *J. Am. Chem. Soc.*, **94**, 2200 (1972); (b) M. J. Goldstein, S. Tomoda, and G. Whittaker, *ibid.*, **96**, 3676 (1974).
- (8) (a) This prediction was independently achieved in a rather different way.

Cf. H. E. Zimmerman, *Acc. Chem. Res.*, **4**, 272 (1971). An earlier model^{2a} had predicted that the anion would be destabilized and antibicycloaromatic; the cation would be stabilized and bicycloaromatic. (b) "... one must always watch out for the ultimate consequence of π-electron stabilization—the formation of new σ bonds".^{2b}

- (9) M. J. Goldstein and S. A. Kline, *J. Am. Chem. Soc.*, **95**, 935 (1973).
- (10) (a) Obtained by sodium hydride/methyl iodide treatment of the corresponding alcohol^{10b} and characterized both spectroscopically and by elemental analysis. Calcd: C, 82.72; H, 8.10. Found: C, 83.04, 83.24; H, 8.16, 7.94. (b) M. J. Goldstein and S. A. Kline, *Tetrahedron Lett.*, 1089 (1973).
- (11) *m/e* 144; IR (neat) 3080 (s), 2899 (s), 1093, 957, 910, 878, 837, 793, and 784 cm⁻¹ (no absorption at 765, 895–885 cm⁻¹). Calcd: C, 91.61; H, 8.39. Found: C, 91.37; H, 8.37.
- (12) Significantly lower yields (≤2%) were isolated with 3 was treated with sodium-potassium alloy in either 1,2-dimethoxyethane or tetrahydrofuran or when the corresponding chloride was treated with either reducing agent in either solvent.
- (13) (a) CONGEN^{13b} listing, obtained through the courtesy of Dr. R. E. Carhart. (b) R. E. Carhart, D. H. Smith, H. Brown, and C. Djerassi, *J. Am. Chem. Soc.*, **97**, 5755 (1975).
- (14) (a) L. N. Labows, Jr., J. Meinwald, H. Röttele, and G. Schröder, *J. Am. Chem. Soc.*, **89**, 612 (1967); B. Kaplan, Ph.D. Thesis, Cornell University, 1966. (b) S. Sternhell, *Q. Rev. Chem. Soc.*, **23**, 236 (1969).
- (15) (a) ³J = 12 cos² θ.^{14b} Dihedral angles were obtained from Barton models.^{15b} (b) D. H. R. Barton, *Chem. Ind. (London)*, 1136 (1956).
- (16) (a) Other possibilities include direct anionic formation of 6 from 3, concerted protonation of anion 5 to form 4, variants that require rearrangement of a free radical prior to its subsequent reduction, and variants that assign a key role to the intramolecular Diels-Alder^{10b,16b} adduct of 3 or 5. (b) M. J. Goldstein and S. H. Dai, *Tetrahedron Lett.*, 535 (1974).
- (17) Previous efforts to detect trishomocyclopentadienyl stabilization have been uniformly unsuccessful. Cf. (a) L. A. Paquette, H. C. Berk, C. R. Degenhardt, and G. D. Ewing, *J. Am. Chem. Soc.*, **99**, 4764 (1977); (b) P. Warner in "Topics in Nonbenzenoid Aromatic Chemistry", Vol. 2, T. Nozoe et al., Ed., Halsted Press, New York, N.Y., 1977.
- (18) The relatively low level of deuterium incorporation (cf. ref 7b) is most simply attributed to prior anionic protonation by acidic hydrocarbon byproducts.
- (19) J. M. Brown and E. N. Cain, *J. Am. Chem. Soc.*, **92**, 3821 (1970).
- (20) S. Masamune and N. Darby, *Acc. Chem. Res.*, **5**, 272 (1972).
- (21) (a) J. F. M. Oth and G. Schröder, *J. Chem. Soc. B*, 904 (1971). (b) F. Sondheimer and Y. Gaoni, *J. Am. Chem. Soc.*, **82**, 5765 (1960); *Proc. Chem. Soc., London*, 299 (1964). (c) J. F. M. Oth, D. M. Smith, V. Prange, and G. Schröder, *Angew. Chem.*, **85**, 352 (1973); *Angew. Chem., Int. Ed. Engl.*, **12**, 327 (1973). (d) P. Hildenbrand, G. Plinke, J. F. M. Oth, and G. Schröder, *Chem. Ber.*, **111**, 107 (1978).
- (22) Japan Society for the Promotion of Science Visiting Professor at the University of Tokyo, 1977.
- (23) Taken in part from the Ph.D. Thesis of Shuji Tomoda, Cornell University, 1975.

M. J. Goldstein*²²

Department of Chemistry, Cornell University
Ithaca, New York 14853

Yujiro Nomura, Yoshito Takeuchi, Shuji Tomoda²³

Department of Chemistry, College of General Education,
The University of Tokyo
Komaba, Meguro-ku, Tokyo 153, Japan
Received November 28, 1977

A Novel Inhibitor of Steroid Biosynthesis

Sir:

During studies¹ of the oxidative demethylation at C-4 in the latter stages of steroid biosynthesis we have discovered that 4,4,10β-trimethyl-*trans*-decal-3β-ol² (1, TMD), first prepared in 1958,³ has important biochemical properties. The evidence described herein demonstrates that TMD is a specific inhibitor of cholesterol biosynthesis in both rat liver enzyme preparations and cultured mammalian cells, and indicates that inhibition occurs at the cyclization of squalene oxide.

Initial experiments were run to determine whether TMD would act as a bicyclic analogue of 4,4-dimethyl steroids and be demethylated by a standard S₁₀ rat liver homogenate⁴ (S₁₀-RLH). However, when *dl*-TMD⁵ labeled with tritium⁶ was incubated with S₁₀-RLH, no demethylated product was detected. Instead, 4,4,10β-trimethyl-*trans*-decalin-3β,7β-diol (2) was isolated as the major product. This metabolite, iden-