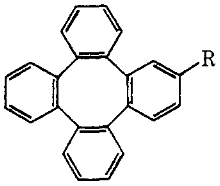
however, the effect is likely to be very large, as found by us for **2** and by Allinger, *et al.*, for methyl dibenzo-[*e,g*][1,4]diazocine-3,10-dicarboxylate ($\Delta G^{\ddagger} > 48$ kcal/mol).[17]

In the light of this conclusion, it is surprising to note that a barrier of 5.7 ± 1 kcal/mol has been reported[1] for the ring inversion of the tetrabenzocyclooctatetraene derivative **5a**, and we were thus led to reinvestigate this claim. Treatment of tetraphenylene[18] with titanium tetrachloride and dichloromethyl methyl ether in methylene chloride[19] gave a mixture of **5b** (mp 206–208°; $\delta_{\mathrm{CDCl_3}}^{\mathrm{TMS}}$ 9.89 (1 H, s, C*H*O), 7.80–7.60 (2 H, m, aromatic), 7.40–7.00 (13 H, m, aromatic)), and the other positionally isomeric aldehyde (mp 202–203°; $\delta_{\mathrm{CDCl_3}}^{\mathrm{TMS}}$ 9.62 (1 H, s, C*H*O), 8.00–7.84 (1 H, m, aromatic), 7.45–6.90 (14 H, m, aromatic)), in a ratio of *ca.* 80:20. The aldehydes were separated by fractional crystallization from methylene chloride–hexane. Structural assignments were confirmed by the deshielding of two protons ortho to the carbonyl group in **5b** which thus appear downfield from the other aromatic protons in the ^{1}H nmr spectrum, whereas the spectrum of the other isomer displays only one such deshielded proton. Reaction of **5b** with methylmagnesium iodide yielded a *ca.* 1:1 mixture of diastereomers, **5c**, mp 195–200°. The 60-MHz nmr spectrum featured resonances at $\delta_{\mathrm{C_6D_5CD_3}}^{\mathrm{TMS}}$ 7.29–6.80 (m, aromatic H), 4.40 (q, $^3J_{\mathrm{HH}} = 6.4$ Hz, C*H*CH$_3$OH), 1.49 (s, CHCH$_3$O*H*), 1.08 (d, CHC*H*$_3$OH), 1.05 (d, CHC*H*$_3$OH).[8] Two-phase oxidation of **5c** with chromic acid[20] gave **5d** which was then converted with methylmagnesium iodide to **5a**, mp 211–213°. The temperature-dependent spectral characteristics of **5a** agreed with those previously reported.[1]



5a, R = C(CH$_3$)$_2$OH
b, R = CHO
c, R = CH(OH)CH$_3$
d, R = C(CH$_3$)O
e, R = CF$_2$H

Since **5c** was observed to be a mixture of diastereomers at 40°, ring inversion must be slow on the nmr time scale. The 220-MHz ^{1}H nmr spectrum (toluene-d_8) of **5c** at ambient temperature features two doublets for the methyl signals ($\Delta\nu = 6.8$ Hz) and two quartets for the methine signals ($\Delta\nu = 4.0$ Hz). At 98° the methyl groups still appear as two doublets ($\Delta\nu = 1.8$ Hz); there is no perceptible line broadening, and the decrease in $\Delta\nu$ is due to a temperature-dependent chemical shift. From these data the lower limit for ring inversion of **5c**, and presumably **5a** as well, is 21 kcal/mol. Evidently, the persistence of the methyl proton resonance signal of **5a** as a singlet at low temperatures[1] is due to accidental isochrony.[21]

The magnitude of this barrier suggests that resolution of a suitable derivative of **5** should be feasible.[22]

Acknowledgment. This work was supported by the National Science Foundation (GP-30257). One of us (K. M.) thanks Professor H. P. Figeys for stimulating discussions which led to a revival of old interests.

[17] N. L. Allinger, W. Szkrybalo, and M. A. DaRooge, *J. Org. Chem.*, **28**, 3007 (1963); see also D. M. Hall and J. M. Insole, *J. Chem. Soc.*, 2326 (1964); F. Bell, *ibid.*, 1527 (1952).

[18] Synthesized from biphenylene: D. F. Lindow and L. Friedman, *J. Amer. Chem. Soc.*, **89**, 1271 (1967).

[19] A. Rieche, H. Gross, and E. Höft, *Chem. Ber.*, **93**, 88 (1960).

[20] H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2951 (1961).

[21] We have found that the 94.1-MHz ^{19}F nmr spectrum of **5e** (prepared from **5b** by reaction with SF$_4$)[8] exhibits an apparent A$_2$X pattern, evidently also as the result of accidental isochrony.

[22] Note Added in Proof. The carboxylic acid derived from oxidation of **5b** has been partially resolved, and a lower limit to racemization of 45 kcal/mol has been determined (D. Gust, G. H. Senkler, Jr., and K. Mislow, *J. Chem. Soc., Chem. Commun.*, in press).

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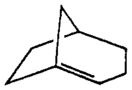
Bredt's Rule. V. Bicyclo[3.2.1]oct-1-ene[1,2]

Sir:

Renewed interest[3,4] in the synthesis and chemistry of bridgehead alkenes in bridged bicyclic ring systems has resulted in the preparation of new isolable and unisolable members of the class. Bridgehead olefins with double bonds endocyclic in eight-membered rings have been isolated and characterized fully,[3] while olefins with double bonds endocyclic in rings of seven or fewer members have been too unstable to permit purification and isolation.[3f,5] Krebs and Keese[5] have recently reported the generation of 1-norbornene, a highly strained compound which possibly prefers a triplet ground state.

We now report our evidence for the formation of the transient bridgehead olefins **1** and **2** in the bicyclo[3.2.1]-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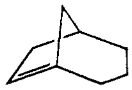
2

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[1] For previous papers in the series, see ref 3a, 3c, and 3f.

[2] (a) This work was supported by grants from the Petroleum Research Fund, administered by the American Chemical Society, and from the Rackham Fund of the University of Michigan. Mass spectra run on an AEI MS-902 purchased with funds from a NSF equipment grant to the University of Michigan. (b) J. A. C. thanks the Alfred E. Hinsdale Scholarship Fund, the Sun Oil Company, and the Esso Foundation for financial support.

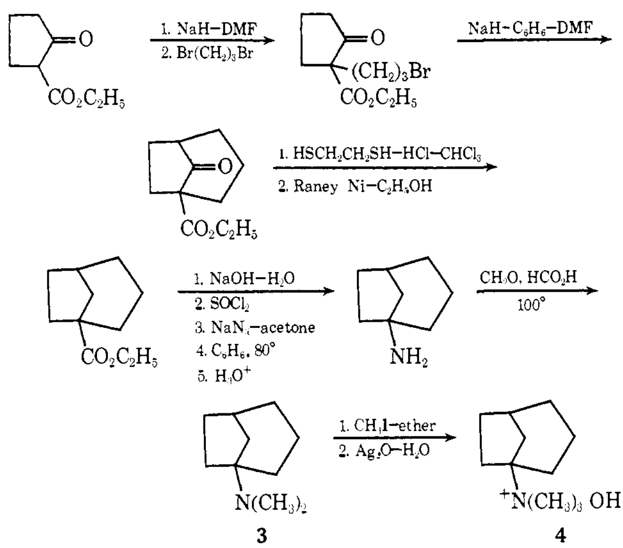
[3] (a) J. R. Wiseman and W. A. Pletcher, *J. Amer. Chem. Soc.*, **92**, 956 (1970); (b) J. A. Marshall and H. Faubl, *ibid.*, **92**, 948 (1970); (c) J. R. Wiseman, H. F. Chan, and C. J. Ahola, *ibid.*, **91**, 2812 (1969); (d) W. Carruthers and M. I. Qureshi, *Chem. Commun.*, 832 (1969); (e) N. M. Weinshenker and F. D. Greene, *J. Amer. Chem. Soc.*, **90**, 506 (1968); (f) J. R. Wiseman and J. A. Chong, *ibid.*, **91**, 7775 (1969); (g) G. L. Buchanan and G. Jamieson, *Tetrahedron*, **28**, 1123 (1972); (h) *ibid.*, **28**, 1129 (1972); (i) P. Warner, R. La Rose, C.-M. Lee, and J. C. Clardy, *J. Amer. Chem. Soc.*, **94**, 7607 (1972); (j) P. G. Gassman, R. L. Cryberg, and K. Shudo, *ibid.*, **94**, 7600 (1972).

[4] For reviews see (a) F. S. Fawcett, *Chem. Rev.*, 47, 219 (1950); (b) V. Prelog, *J. Chem. Soc.*, 420 (1950); (c) R. C. Fort and P. v. R. Schleyer, *Advan. Alicycl. Chem.*, **1**, 364 (1966).

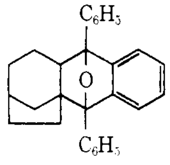
[5] (a) R. Keese and E. P. Krebs, *Angew. Chem., Int. Ed. Engl.*, **10**, 262 (1971); (b) R. Keese and E. P. Krebs, *Angew. Chem.*, **84**, 540 (1972). See also (c) S. F. Campbell, R. Stephens, and J. C. Tatlow, *Tetrahedron*, **21**, 2997 (1965).

octane ring system. The synthesis was approached by two routes, the first and less successful of which follows our previous work.[3a,c,f] Synthesis of the quaternary ammonium hydroxide **4** required for the Hofmann elimination is outlined in Scheme I.

Scheme I



Pyrolysis of the quaternary ammonium hydroxide **4** at 160–170° led primarily to the tertiary amine **3** (various runs, 87–99%). However, pyrolysis of 7.5 mmol of **4** in the presence of 1,3-diphenylisobenzofuran gave a small yield (7.1 mg, 0.3%) of an oil which had the spectral data expected for Diels–Alder adducts **5** and **6**.[6] Since both olefins **1** and **2** can yield two Diels–Alder adducts with 1,3-diphenylisobenzofuran, a total of four adducts are expected.



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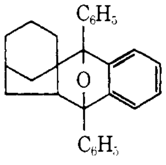
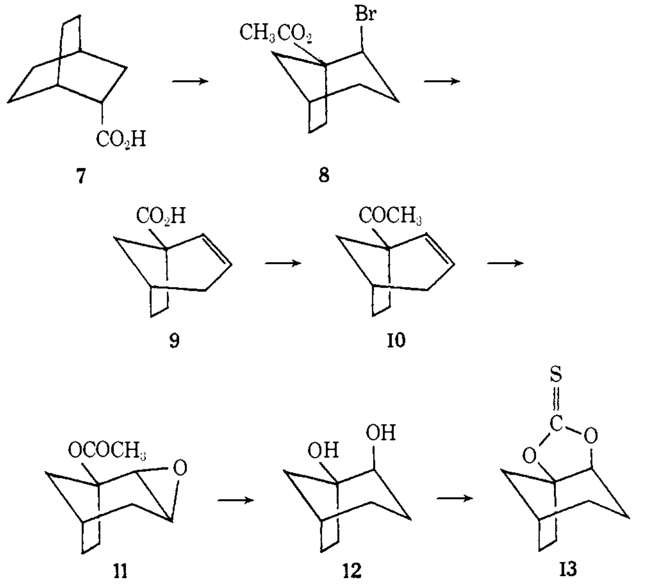


6

A better method for the synthesis of bicyclo[3.2.1]-oct-1(2)-ene (**1**) was fashioned after Corey's synthesis of olefins[7] by reaction of cyclic thionocarbonates of 1,2-glycols with trialkyl phosphites. Since the reaction involves a cis elimination of carbon dioxide in the olefin-forming step, diol **12** is a required intermediate.[8]

Bromination of bicyclo[2.2.2]octane-2-carboxylic acid (**7**)[9] in the presence of phosphorous tribromide afforded 2(*a*)-bromobicyclo[3.2.1]octane-1-carboxylic acid[10] which was isolated as its methyl ester **8** [85%, bp 92–98° (0.5 Torr)]. Hydrolysis and dehydrobromination of ester **8** with sodium hydroxide in methanol–water at room temperature gave unsaturated acid **9** (89%, mp 58–60°), and reaction of **9** with methyllithium afforded methyl ketone **10** [75%, bp 59–61° (0.4 Torr)]. Treatment of ketone **10** with *m*-chloroperbenzoic acid effected oxidation of both functions affording epoxy acetate **11** [61%, bp 75–78° (0.4 Torr)] as the only distillable product.[11] Reduction of epoxy acetate **11** with lithium aluminum hydride produced 96% of diol **12** [mp 235–238°; τ 6.28 (1 H, broad)]. Reaction of diol **12** successively with *n*-butyllithium, carbon disulfide, and methyl iodide produced cyclic thionocarbonate **13** [44%; mp 108–110°; ν_{max} 1290, 1305 cm^{-1}; τ 5.38 (1 H, triplet, J = 8 Hz), 7.3–9.2 (11 H)] (Scheme II). Thionocarbonate **13** was heated in triethyl phosphite at reflux (165°) for 24 hr in the presence of 1,3-diphenylisobenzofuran.[13] Carbon dioxide was evolved and a solid (62%) was produced which had the same R_f on thin-layer chromatography as the adducts produced earlier in the pyrolysis of **4**. Recrystallization of the solid from ethanol gave crystals of broad melting point (156–175°). The spectra[14] were as expected for the formulas **5** or **6**, and we conclude that the solid is a mixture of the two adducts **5** expected from reaction of bridgehead alkene **1** with 1,3-diphenylisobenzofuran. While the adducts from the two routes are similar in their spectral properties, there are significant differ-

Scheme II



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(6) Mass spectrum *m/e* 378; nmr τ 2.17–3.20 (14 H) and 7.50–9.48 (12 H). Insufficient material for analysis. With the exception of this sample, compound **4**, and certain intermediates (acid chloride, acid azide, and isocyanate) of the Curtius rearrangement sequence in Scheme I, all isolable compounds reported gave satisfactory elemental analyses and consistent ir, nmr, and mass spectra.

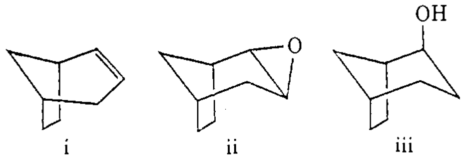
(7) (a) E. J. Corey and R. A. E. Winter, *J. Amer. Chem. Soc.*, **85**, 2677 (1963); (b) E. J. Corey, F. A. Carey, and R. A. E. Winter, *ibid.*, **87**, 934 (1965).

(8) The hydroxyl groups of **12** are cis on the six-membered ring and trans on the seven-membered ring.

(9) R. Seka and O. Tramposch, *Chem. Ber.*, **75**, 1379 (1942).

(10) (a) A. W. Chow, D. R. Jakas, and J. R. E. Hoover, *Tetrahedron Lett.*, 5427 (1966); (b) W. R. Vaughan, R. Caple, J. Csapilla, and P. Scheiner, *J. Amer. Chem. Soc.*, **87**, 2204 (1965).

(11) The stereochemistry of compounds **11–13** was anticipated by analogy with the peracid oxidation of i which leads to the exo epoxide ii.[12] Reduction[12] of ii with lithium aluminum hydride gave exclusively iii.



(12) R. R. Sauers, H. M. How, and H. Ferlich, *Tetrahedron*, **21**, 983 (1965).

(13) When the reaction was attempted in the absence of 1,3-diphenylisobenzofuran, none of the expected[3f] hydrocarbon dimers were found. Instead, compounds containing phosphorous were formed. The structure of these compounds is under investigation.

(14) Mass spectrum *m/e* 378; nmr τ 2.00–3.00 (14 H) and 7.40–9.60 (12 H).

ences in the fine structure of the nmr and ir spectra. Both bridgehead olefins are probably produced by the Hofmann route, and, by analogy with the thermolysis[3c] of 1-bicyclo[4.2.1]nonyltrimethylammonium hydroxide, it is likely that the $\Delta^{1(7)}$ olefin is the major olefin from this reaction. Thus, we conclude that bridgehead olefin **1** is formed in good yield from the thionocarbonate **13** and that both bridgehead olefins **1** and **2** are probably formed in small amounts in thermolysis of quaternary ammonium hydroxide **4**. We are continuing to investigate synthetic routes to **1** and **2** in the hope that we can prepare them under mild conditions and record their spectra.

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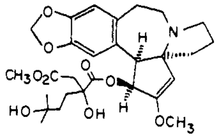
Total Synthesis of Cephalotaxus Alkaloids

Sir:

The harringtonine family of minor alkaloids from *Cephalotaxus harringtonia* (Japanese plum yew) includes active inhibitors against experimental lymphoid leukemia in mice at relatively low dosage levels.[1] The active species are all relatively simple esters [*e.g.*, harringtonine (**1**)] of cephalotaxine (**2**), the major alkaloid of *C. harringtonia.*[2] The unusual 1-azaspiro[4.4]nonene structural feature and the relative scarcity of the natural material attracted our interest in the total synthesis of cephalotaxine. We wish to report a simple, efficient, convergent synthesis of a key intermediate **3**, and successful conversion of **3** to cephalotaxinone (**4**) and cephalotaxine (**2**).



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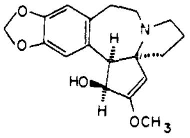

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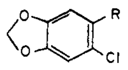
Cephalotaxinone (**4**), also obtained from *C. harringtonia,*[3] is an obvious relay intermediate as it is known to give cephalotaxine (**2**) by stereospecific hydride reduction.[4] Our synthetic sequence begins with the preparation of the *p*-nitrobenzenesulfonate ester (**5**) of 2-(2-chloro-4,5-methylenedioxophenyl)ethyl alcohol and 1-aza-7-methoxyspiro[4.4]non-6-en-8-one (**6**), which are related to the two sections of cephalotaxinone, as dissected in representation **4**.

Piperonat was converted to 6-chloropiperonylacetic acid (**10**, mp 176.5–177.5°, lit.[5] 174–175°) in 55% overall yield *via* the intermediates **7–9** using minor modifications of known procedures.[5–7] Reduction of **10** with lithium aluminum hydride gave an alcohol (**11**, 96% yield)[8] which was converted to *p*-nitrobenzenesulfonate ester **5** *via* the sodium alkoxide of **11** (from sodium hydride–tetrahydrofuran) and *p*-nitrobenzenesulfonyl chloride (2 equiv) in tetrahydrofuran.[9] The yellow crystalline sulfonate ester (**5**) is obtained in 92% yield, mp 143–144°.



7, R = CH_2OH
8, R = CH_2Cl
9, R = CH_2CN
10, R = CH_2CO_2H
11, R = CH_2CH_2OH

The preparation of the heterospirocycle **6** began with the reaction of 2-ethoxy-1-pyrroline and 3 mol equiv of allylmagnesium bromide in ether at 25° for 18 hr. After hydrolysis of excess Grignard reagent and the magnesium salts with aqueous barium hydroxide, 2,2-diallylpyrrolidine (**12**) was obtained [bp 72–74° (12 Torr); 78% yield; ^{1}H nmr ($CDCl_3$) δ 1.30 (s, NH), 1.5–1.9 (m, CH_2CH_2, in pyrrolidine ring), 2.18 (d, 4 H, $CH_2C{=}C$, J = 7 Hz), 2.95 (br t, 2 H, CH_2N), 4.8–6.3 (typical allyl pattern, 6 H)]. The following sequence of reactions was carried out without purification of the intermediates.[10] Treatment of **12** with *tert*-butoxycarbonyl azide in aqueous tetrahydrofuran containing magnesium oxide (18 hr, 50°) gave the corresponding *N-tert*-butoxycarbonyl derivative of **12** which was exposed to ozone at −78° in methyl alcohol. The crude ozonide was hydrolyzed in 1:1 dioxane–water at 80° for 1.25–1.35 hr and then oxidized with silver oxide–potassium hydroxide. The filtrate was concentrated to dryness at 55° (0.01 Torr) to give a residue which was suspended in refluxing methyl alcohol containing hydrogen chloride (6%) and trimethyl orthoformate (7%). After 14 hr, amino diester **13** was isolated in 61% yield: bp 74–76° (0.01 Torr); ^{1}H nmr ($CDCl_3$) δ 1.7–2.0 (m, 4 H, CH_2CH_2, in pyrrolidine ring), 2.38 (s, NH), 2.70 (s, CH_2CO), 2.9–3.2 (m, 2 H, CH_2N), 3.72 (s, CO_2CH_3).

A series of operations, again without isolation of intermediates, led to the formation of the desired azaspirocycle **6** from **13**. A mixture of excess sodium–potassium alloy, excess chlorotrimethylsilane,[11] and amino diester **13** was stirred under argon in benzene at 25° for 12–20 hr. The solution was filtered through Celite, diluted with an equal volume of methylene chloride, cooled to −78° under argon, and oxidized with bromine.[12] After addition, the system was evacuated (0.01 Torr) and allowed to warm which caused the volatile material (benzene, methylene chloride,

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(1) (a) R. G. Powell, D. Weisleder, C. R. Smith, Jr., and I. A. Wolff, *Tetrahedron Lett.*, 4081 (1969); (b) R. G. Powell, D. Weisleder, C. R. Smith, Jr., and W. K. Rohwedder, *ibid.*, 815 (1970); (c) K. L. Mikolajczak, R. G. Powell, and C. R. Smith, Jr., *Tetrahedron*, **28**, 1995 (1972).

(2) (a) For the original isolation and partial structural determination of cephalotaxine, see: W. W. Paudler, G. I. Kerley, and J. Mackay, *J. Org. Chem.*, **28**, 2194 (1963); (b) for the crystal structure by X-ray diffraction, see: D. J. Abraham, R. D. Rosenstein, and E. L. McGandy, *Tetrahedron Lett.*, 4085 (1969).

(3) R. G. Powell, *Phytochemistry*, **11**, 1467 (1972).

(4) Unpublished observations of R. G. Powell and K. L. Mikolajczak, personally communicated by Mr. Powell.

(5) R. G. Niak and R. S. Wheeler, *J. Chem. Soc.*, 1780 (1938).

(6) A. M. B. Orr, R. Robinson, and M. M. Williams, *ibid.*, **111**, 948 (1917).

(7) W. F. Barthel and B. H. Alexander, *J. Org. Chem.*, **23**, 1012 (1958).

(8) Intermediates 3 (X = Cl, Br, I), 5, 6, 11, 12, and 13 are new compounds and have been characterized by satisfactory analytical and/or spectral data. For certain key intermediates, characteristic spectral features are given.

(9) We are grateful to Mr. Thomas Rogerson for his assistance in developing this step.

(10) We are grateful to Mr. Anthony Chong for his assistance in developing this sequence.

(11) (a) K. Ruhlmann and S. Poredda, *J. Prakt. Chem.*, **12**, 18 (1960); (b) U. Schräpler and K. Ruhlmann, *Chem. Ber.*, **97**, 1383 (1964). The conversion of 13 → 6 is the first example of the acyloin reaction in the presence of a free NH group, although this distinction is purely formal because the amino group of 13 is probably silylated *in situ* before or during the acyloin reaction.

(12) (a) Ruhlmann, *Synthesis*, **2**, 236 (1971); (b) H. G. Heine, *Chem. Ber.*, **104**, 2869 (1971).