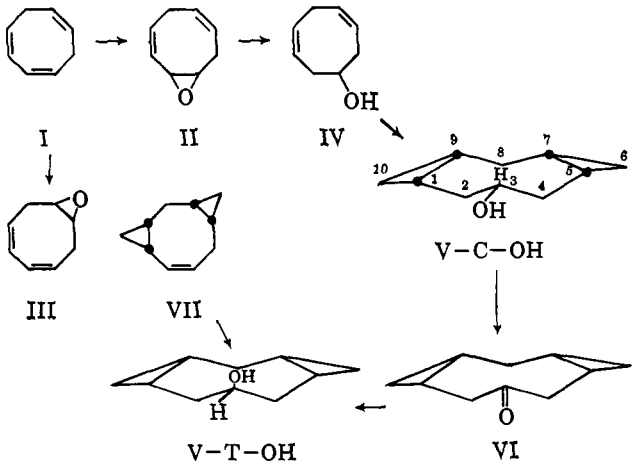

As we had reasons to hope,[2b] reaction on the dienol IV with 3 moles of methylene iodide and excess zinc–copper couple proceeded stereospecifically to introduce two cyclopropane rings *cis* to each other and to the hydroxyl group.[9] Conversions of IV to bisadduct up to 90% were observed. The bisadduct fraction was homogeneous in v.p.c. and could be isolated by preparative v.p.c.[7] Alternatively, it can be freed from unsaturated starting material and monoadduct by extracting a pentane solution with saturated aqueous silver nitrate, after which it crystallizes readily. After purification through the *p*-nitrobenzoate,[6] m.p. 124.8–125.4°, the tricyclo[7.1.0.0^{5,7}]decan-3-ol[6] V-C-OH had m.p. 57–58°, m.p. of the *p*-toluenesulfonate[6] 104–105°. The epimer of alcohol V-C-OH was obtained by chromic anhydride oxidation to the ketone[6] VI, m.p. 51.5–52.5°, and reduction of the latter with sodium borohydride in methanol. The reduction product consisted of epimeric alcohol to the extent of *ca.* 97%. The isolated epimer,[6] V-T-OH, had m.p. 56–57°, m.p. of the *p*-toluenesulfonate[6] 70–71°. The structure and configuration of the epimeric V-OH alcohols are clear from the spectroscopic and chemical evidence.

The epimeric V-T-OH and V-C-OH display nearly identical n.m.r. spectra, with the triplet signal for the α-proton on C-3 in V-T-OH at lower field and sharper than in V-C-OH. While the n.m.r. spectra of the alcohols suggest a *cis* arrangement of cyclopropane rings, there is also a compelling stereochemical argument that the cyclopropane rings cannot be *trans* to each other. With a *trans* arrangement of cyclopropane rings, only one alcohol, a *dl*-racemate, would be possible, instead of an epimeric pair. Oxidation of the alcohol to the ketone and subsequent reduction would simply regenerate the same alcohol.

The available evidence shows that in V-C-OH the hydroxyl group is indeed *cis* to the cyclopropane rings, and in V-T-OH it is *trans*. Examination of models suggests a preferred crown-like conformation for tricyclo[7.1.0.0^{5,7}]decane systems like V-C-OH and V-T-OH, a substituent on C-3 being either "equatorial" or "axial." That V-C-OH has an equatorial *cis* hydroxyl group and V-T-OH has an axial *trans* hydroxyl is clear from comparison of the n.m.r. C-3 proton signals[10] for the two alcohols. the shorter v.p.c. retention time of V-T-OH on polar columns, and the predominant formation of V-T-OH from "steric approach control" sodium borohydride reduction of ketone VI.

Another route to V-T-OH is hydroboration–oxidation of the 1,3,6-cyclooctatriene bismethylene adduct VII with *cis* cyclopropane rings. This alcohol and its C-2 hydroxyl isomer arise in *ca.* equal proportions from this reaction.[11]

Acknowledgment.—We are indebted to Dr. F. Ebel of the Badische Anilin und Soda Fabrikwerke in Ludwigshafen, Germany, for generous supplies of the necessary cyclooctatetraene starting material which made this work possible.

(9) For comparison, 1,4-cyclooctadiene yields a 66:34 *cis–trans* mixture of the parent tricyclo[7.1.0.0^{5,7}]decanes.

(10) (a) R. Lemieux, *et al.*, *J. Am. Chem. Soc.*, **80**, 6098 (1958); (b) A. Cope, S. Moon, and C. H. Park, *ibid.*, **84**, 4843, 4852 (1962).

(11) J. Zirner and P. Bruck, unpublished work.

(12) U. S. Rubber Company Foundation Postgraduate Fellow in Physical and Engineering Science for 1961–1962.

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Three-Center Nonclassical Cation in the Pentahomocyclopentadienyl System[1]

Sir:

Since the parent alcohols I-C-OH and I-T-OH in the pentahomocyclopentadienyl system are now available,[2] it is possible to examine the behavior of this system from the viewpoints of homoconjugation and homoaromaticity.[3,4] This report concerns the corresponding carbonium ion intermediate in acetolysis of the toluenesulfonate,[5] I-C-OTs.

I-C-OH I-T-OH

For acetolysis of I-C-OTs it is possible to make an *a priori* prediction of the kind of delocalized cation to be expected. In a cyclopentadienyl species, electron delocalization must almost inevitably be over all five centers due to the rigid planar geometry, whereas the more flexible and adaptable pentahomocyclopentadienyl species present more possible patterns of electron delocalization. For the cation from I-C-OTs we should consider both three- and five-center nonclassical species such as bishomoallyl,[3,4] trishomocyclopropenyl,[3,4] tetrahomopentadienyl,[4] and pentahomocyclopentadienyl[3] types A, B, C, and D, respectively. Neglecting strain energies involved in reorganizing the carbon skeleton, the corresponding Hückel LCAO–MO delocalization energies in units of β_1, the pertinent resonance integral, are 0.824, 2.000, 1.464, and 1.236, respectively.[6]

(1) (a) Research sponsored by the U. S. Army Research Office (Durham). (b) Research was supported in part by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of this fund.

(2) P. Radlick and S. Winstein, *J. Am. Chem. Soc.*, **86**, 1866 (1964).

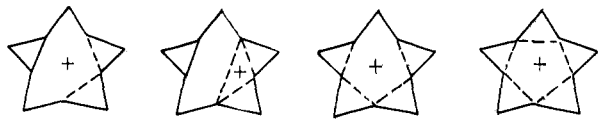
(3) (a) S. Winstein and J. Sonnenberg, *ibid.*, **81**, 6524 (1959); (b) *ibid.*, **83**, 3235, 3244 (1961).

(4) R. J. Piccolini and S. Winstein, *Tetrahedron Suppl.*, **No. 2**, 423 (1963).

(5) While the corresponding carbanion is of even greater interest, good routes to this species are still under investigation.

(6) For contrast, the corresponding delocalization energies for the anions are 0.824, 0.000, 1.464, and 2.472, respectively.

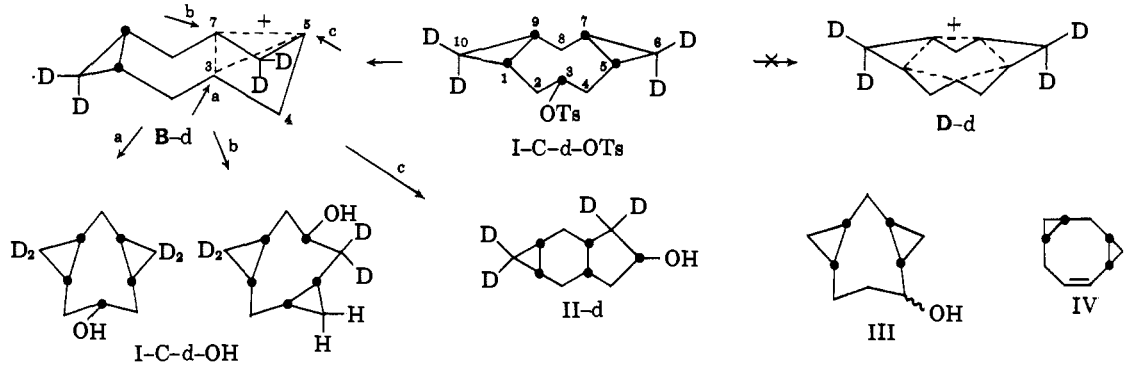
Thus, a rather clear prediction may be made in favor of the three-center cation B.



A B C D

Rates of acetolysis of the epimeric I-C-OTs and I-T-OTs give evidence of anchimeric acceleration of solvolysis of the stereoelectronically favorable *cis* epimer.[3] Thus, first-order rate constants at 75.0° (I-C-OTs > I-T-OTs, 52:1) for acetolysis of *ca.* 0.007 *M* I-OTs in acetic acid, 0.01 *M* in sodium acetate, are 1.23×10^{-4} and 2.37×10^{-6} sec.$^{-1}$ for I-C-OTs and I-T-OTs, respectively.

The product from acetolysis of 0.04 *M* I-C-OTs in 0.07 *M* sodium acetate in acetic acid for 20 reaction half-lives at 75.0° was isolated by conventional work-up and lithium aluminum hydride reduction of the acetate. Analytical and preparative v.p.c. on XF-1150 silicone nitrile on Chromosorb W columns showed that three alcohols, X (73%), Y (18%), and Z (5%), and an olefin (4%) were produced. The olefin was identical with the *cis* bismethylene adduct IV from 1,3,6-cyclooctatriene.[2] The major product alcohol X was pure I-C-OH as proved by v.p.c. behavior, melting point, infrared, and n.m.r. spectra, and melting point and mixture melting point of the I-OTs derivative. The formation of I-C-OH is highly stereospecific, no I-T-OH being detected.

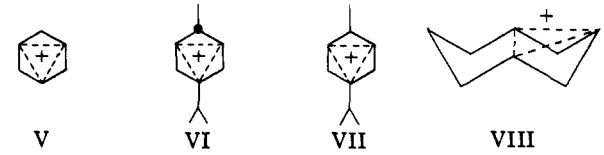


The minor product alcohol Z proved similar in v.p.c. behavior and similar, but not identical, in infrared spectrum with the hydrogen-shifted alcohol III derived from hydroboration–oxidation[2] of the 1,3,6-cyclooctatriene bisadduct IV. Thus, there is some indication that Z is one of the III epimers. Alcohol Y, m.p. 147–148°, analyzing correctly for $C_{10}H_{16}O$, is also one we have not yet synthesized. However, infrared and n.m.r. spectra and mechanistic considerations suggest it is the hydrindanol II. The n.m.r. spectrum of alcohol Y showed signals for 2 cyclopropane-methylene protons at τ 9.75, 2 cyclopropane tertiary protons at τ 9.1 (broad peak), 4 methylene protons (C_4 and C_6) at τ 8.49, 6 protons (C-2, C-3, C-7, and C-8) at τ 7.5–8.3 (very broad complex multiplet), and the α-proton at τ 5.98 (broad ill-resolved multiplet). When alcohol Y was isolated from solvolysis of the tetradeuterio-I-C-d-OTs, the τ 9.75 signal was nearly absent, the τ 9.1 signal was sharper and narrower, the τ 8.49 peak corresponded to only 2 protons, and the α-proton signal was now simplified to a triplet.

In contrast to alcohol Y from solvolysis of deuterated I-C-d-OTs, the recovered I-C-OH from the I-C-d-OTs showed a rather substantial development of cyclopropane methylene proton. The average of a series of integrations indicated 0.52 ± 0.03 cyclopropane methylene proton at τ 10.3.

The evidence for anchimeric assistance of solvolysis of I-C-OTs and the stereospecificity in the formation of the two major products, I-C-OH and alcohol Y (II), suggest that these arise from a nonclassical rather than a classical carbonium ion. The deuterium scrambling in the I-C-OH product from I-C-d-OTs is uniquely in accord with a three-center ion (A or B). Fully protonated I-C-OH shows 2.0 protons at τ 10.3, and the predicted number of protons at τ 10.3 in the I-C-OH from tetradeuterated I-C-d-OTs is 0.50, 0.50, 0.67, and 1.2 for ions A, B, C, and D, respectively. The formation of a product like II is predicted only from ion B since this is the only one with the necessary C-3–C-7 interaction. Thus, the evidence is uniquely in accord with the three-center ion B, the one also predicted from theoretical considerations.

Ion B is a "trishomocyclopropenyl" type analogous to ion V from *cis*-3-bicyclo[3.1.0]hexyl *p*-toluenesulfonate.[3] Evidence that alkyl-substituted examples of this latter variety of nonclassical ion, VI and VII, occur in acetolysis of neothujyl and neoisothujyl toluenesulfonates has just been published by Norin.[7] The very high relative reactivities of the "*cis*" epimers and the unique nature of the products as regards stereochemistry and structure are in striking accord with ions VI and VII and not explicable on the basis of classical cations.



V VI VII VIII

A case with considerable analogy to the present one involving I-C-OTs and ion B seems to exist in the literature,[8] although the case in point was not interpreted in terms of a nonclassical ion. Solvolysis of *cis*-3-bicyclo[5.1.0]octyl bromobenzenesulfonate is qualitatively much more rapid than that of the *trans* epimer

(7) T. Norin, *Tetrahedron Letters*, **No. 1**, 37 (1964).
(8) A. C. Cope, S. Moon, and C. H. Park, *J. Am. Chem. Soc.*, **84**, 4850 (1962).

and the two very predominant alcohol products are produced completely stereospecifically as the *cis* epimers. The "trishomocyclopropenyl" cation VIII provides an explanation for the reactivity and the observed stereochemistry.

(9) U. S. Rubber Company Foundation Postgraduate Fellow in Physical and Engineering Science for 1961–1962.

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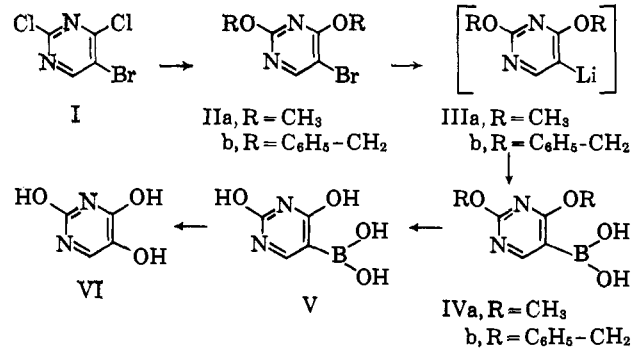
Boron-Substituted Pyrimidines[1]

Sir:

It has been reported that when boron is localized within cancerous tissue in the form of some suitable derivatives,[2] the tumor cells are destroyed by the dissipation of α-particles resulting from the neutron-induced disintegration of B^{10} (naturally occurring boron contains 18.84% of B^{10} isotope). Many investigators have since synthesized a number of boron-containing organic compounds including azo dyes,[3] diboronic acids,[4] bromine-, sulfur-, or nitrogen-substituted aromatic boronic acids,[5] amino acids,[6] boronic anhydrides,[7] as well as many heterocyclic boron compounds.[8] Some of these compounds have already been evaluated in animals[9b,d] and in human patients,[9a,c,e] and a few have shown to be promising.[9b,c] As the future success of neutron-capture therapy may well depend on the design of boron-substituted antimetabolites (which can be preferentially bound or incorporated into the structures of growing neoplasms),[10] a program involving the synthesis of boron-substituted nitrogen heterocyclic compounds has been initiated in our laboratories. We now wish to report the synthesis of some boron-substituted pyrimidines. Compounds of this type have not been prepared previously.[11]

Treatment of 5-bromo-2,4-dihydroxypyrimidine[12] with phosphorus oxychloride and N,N'-dimethylaniline gave 5-bromo-2,4-dichloropyrimidine (I),[12] b.p. 75–80° (0.4 mm.), in 91% yield. Sodium methoxide readily converted I to 5-bromo-2,4-dimethoxypyrimidine (IIa),[12] m.p. 63–64°. The lithium compound IIIa, prepared by Langley's method,[13] was caused to react *in situ* with freshly distilled trimethyl borate or tributyl borate to give 2,4-dimethoxy-5-pyrimidineboronic acid (IVa), m.p. 115–117°. *Anal.* Calcd. for $C_6H_9BN_2O_4 \cdot 0.5H_2O$: C, 37.3; H, 5.18; N, 14.5. Found: C, 37.1; H, 5.23; N, 14.5. An infrared spectrum of IVa had bands at 1350 and 1250 cm.$^{-1}$, which were assigned to the B–O and B–C stretching frequencies, respectively. The B–O deformation mode was located near 810 cm.$^{-1}$ and the boron–aryl sharp absorption band was also noted at 1435 cm.$^{-1}$.[14]



2,4-Dibenzyloxy-5-pyrimidineboronic acid (IVb) was similarly prepared from I *via* 2,4-dibenzyloxy-5-bromopyrimidine (IIb; 59% yield, m.p. 87–89°. *Anal.* Calcd. for $C_{18}H_{15}BrN_2O_2$: C, 58.2; H, 4.04; N, 7.55. Found: C, 58.2; H, 4.00; N, 7.50) and the lithium derivative IIIb. Since IVb was difficult to purify, it was converted directly to 5-uracilboronic acid (V) by catalytic hydrogenation. Compound V was isolated as a hemihydrate. *Anal.* Calcd. for $C_4H_5BN_2O_4 \cdot 0.5H_2O$: C, 29.1; H, 3.64; N, 17.0. Found: C, 29.3; H, 3.54; N, 17.4. Ultraviolet properties of V showed maxima at 262 mμ (ϵ 10,600, pH 1) and at 284 mμ (ϵ 5600, pH 11). The product decomposed slowly around 330°. The structure of 5-uracilboronic acid (V) was further confirmed by oxidation to 5-hydroxyuracil (VI) according to the procedure of Letsinger and Dandegaonker for the conversion of 8-quinolineboronic acid to 8-hydroxyquinoline.[15] Compound VI was identical with

(1) This investigation was supported by the Cancer Chemotherapy National Service Center, National Cancer Institute of the National Institutes of Health, Public Health Service (Contract SA-43-ph-3025).

(2) For "neutron-capture" theory, see, *e.g.*: (a) P. G. Kruger, *Proc. Natl. Acad. Sci.*, **26**, 181 (1940); (b) P. A. Zahl and F. S. Cooper, *Science*, **93**, 64 (1941); (c) P. A. Zahl and F. S. Cooper, *Radiology*, **37**, 673 (1941); (d) W. H. Sweet and M. Javid, *J. Neurosurg.*, **9**, 200 (1952); (e) P. G. Kruger, *Radiation Res.*, **3**, 1 (1955); (f) W. Gerrard, "The Organic Chemistry of Boron," Academic Press, New York, N. Y., 1961, pp. 76–201; (g) G. Milhaud, *Maroc Med.*, **41**, 295 (1962).

(3) (a) H. R. Snyder and C. Weaver, *J. Am. Chem. Soc.*, **70**, 232 (1948); (b) H. Gilman, L. Santucci, D. R. Swayampati, and R. O. Ranck, *ibid.*, **79**, 2898, 3077 (1957).

(4) (a) H. R. Snyder and S. L. Meisel, *ibid.*, **70**, 774 (1948); (b) D. R. Nielsen and W. E. McEwen, *ibid.*, **79**, 3081 (1957); (c) A. H. Soloway, *ibid.*, **82**, 2442 (1960).

(5) (a) L. Santucci and H. Gilman, *ibid.*, **80**, 193 (1958); (h) A. H. Soloway, *ibid.*, **81**, 3017 (1959); (c) A. H. Soloway and P. Szabody, *J. Org. Chem.*, **25**, 1683 (1960).

(6) H. R. Snyder, A. J. Reedy, and W. J. Lennarz, *J. Am. Chem. Soc.*, **80**, 835 (1958).

(7) H. R. Snyder, M. S. Konecky, and W. J. Lennarz, *ibid.*, **80**, 3611 (1958).

(8) (a) S. S. Chissick, M. J. S. Dewar, and P. M. Maitlis, *ibid.*, **81**, 6329 (1959); (b) E. Nyilas and A. H. Soloway, *ibid.*, **81**, 2681 (1959); (c) R. T. Hawkins and H. R. Snyder, *ibid.*, **82**, 3863 (1960); (d) M. J. S. Dewar and R. C. Dougherty, *ibid.*, **84**, 2648 (1962); (e) M. J. S. Dewar and W. H. Poesche, *ibid.*, **85**, 2253 (1963); (f) M. J. S. Dewar and P. J. Grisdale, *J. Org. Chem.*, **28**, 1759 (1963). Earlier articles were cited by W. Gerrard, ref. 2f.

(9) (a) L. E. Farr, W. Haymaker, W. Calvo, Y. L. Yamamoto, and S. W. Lippincott, *Acta Neuropath.* (Berlin), **1**, 34 (1961); (b) A. H. Soloway, R. L. Wright, and J. R. Messer, *J. Pharmacol. Exptl. Therap.*, **134**, 117 (1961); (c) W. H. Sweet, A. H. Soloway, and R. L. Wright, *ibid.*, **137**, 263 (1962); (d) A. H. Soloway, B. Whitman, and J. R. Messer, *J. Med. Pharm. Chem.*, **5**, 191 (1962); (e) W. H. Sweet, A. H. Soloway, and G. L. Brownell, *Acta Radiol.*, **1** (2), 114 (1963), and references cited therein.

(10) C. A. Nichol, Abstracts, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept., 1962, p. 18-O.

(11) Attempted preparations of boron-substituted purine and pyrimidine have been discussed (see ref. 5b).

(12) G. E. Hilbert and E. F. Jansen, *J. Am. Chem. Soc.*, **56**, 134 (1934).

(13) B. W. Langley, *ibid.*, **78**, 2136 (1956).

(14) (a) L. J. Bellamy, W. Gerrard, M. F. Lappert, and R. L. Williams, *J. Chem. Soc.*, 2412 (1958); (b) R. M. Washburn, E. Leven, C. F. Albright, F. A. Billig, and E. S. Cernak, Advances in Chemistry, No. 23, American Chemical Society, Washington, D. C., 1959, p. 112; (c) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1960, p. 348.

(15) R. L. Letsinger and S. H. Dandegaonker, *J. Am. Chem. Soc.*, **81**, 498 (1959).