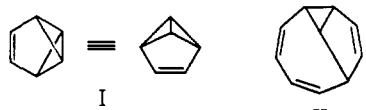
A Benzvalene Synthesis

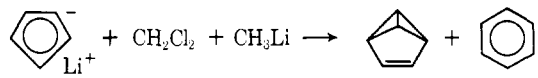
Sir:

Among interesting chemical structures, that of the valence isomer of benzene, benzvalene (I), is one of the most fundamental and one of the rarest. Benzvalene has been synthesized by photolyzing benzene,[1,2] but because its photochemical decomposition is benzene sensitized,[1b] the steady-state concentrations do not exceed 0.05%,[1a] and although the conversion can be increased to 1% by dilution with hexadecane,[1a] the yield is still small and the product diluted by solvent. We are reporting a simple procedure for synthesizing the benzvalene ring system that makes this rare hydrocarbon abundant.



I II

The procedure is indicated in reaction 1. Reasons for expecting its efficacy have been enumerated previously,[3] but the best reason is that the analogous reaction works, using the cyclononatetraenyl anion,[3,4] and gives as the major product isobullvalene (II), the corresponding valence tautomer of cyclodecapentaene.

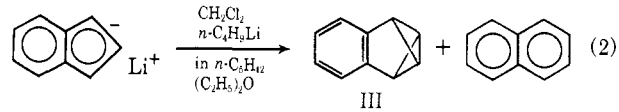


(1)

An important consideration in effecting the reaction is the choice of solvent, as carbonoid reactions of lithium halomethides occur best in those that solvate lithium cations poorly.[5] However, the commonly used solvent, diethyl ether,[3,5a,6] does not dissolve lithium cyclopentadienide. By contrast, dimethyl ether does, and if reaction 1 could be effected using it, the isolation of large quantities of benzvalene would be easy because distillation should separate it from the much lower boiling solvent. In fact, reaction 1 can be effected in dimethyl ether and gives a 24% yield of benzvalene,[7] samples of which were isolated pure and identified by proton nmr spectroscopy. However, we were discouraged from investigating its large-scale isolation pure when the resonance energy of benzene and the strain energy of small-ring compounds were called to our attention by the benzvalene exploding.[8,9]

Large quantities of benzvalene can safely be prepared in solution. Thus, 152 mmol of cyclopentadiene was treated with 160 mmol of CH_3Li in 400 ml of dimethyl ether, and then 314 mmol of methylene chloride and 320 mmol of 5% CH_3Li in diethyl ether (containing 0.4% LiCl) were added at −45°. The dimethyl ether was evaporated and the product and diethyl ether were distilled at ambient temperature and reduced pressure. The proton nmr spectrum of the ether solution (with dimethylformamide or nitrobenzene added as internal standards) showed that the yield of benzene was 6.4% and of benzvalene, 29%. A characteristic of benzvalene is its extraordinarily foul odor.

The valence tautomer III of naphthalene, benzobenzvalene, or naphthvalene could similarly be prepared as indicated in eq 2. The yields of benzobenzvalene and naphthalene after distillation, but before further purification, were estimated by nmr spectroscopy as 10 and 18%. We were unable to find a procedure for isolating benzobenzvalene free of naphthalene although repeated crystallization of naphthalene from the mixture dissolved in isopentane or methanol gave a small sample containing only 9% naphthalene. Naphthvalene showed the following characteristics: colorless liquid; nmr (CCl_4) τ 3.18 (symmetrical multiplet, 4.05 H), 6.17 (1.5-Hz triplet, 1.98 H), 7.60 (1.5-Hz triplet, 1.97 H); uv (in cyclohexane, after subtracting that of naphthalene impurity) λ_{max} (ϵ) 278 (494), 271 (465), 264 (375), 235 nm (975); stable at room temperature; heated in CCl_4 (175°, 10 min) it gives benzofulvene (36% yield)[11] and polymer, but not naphthalene;[12] $t_{1/2}$ (CCl_4, 75°) ~ 1.3 days.



III (2)

A bounteous source of benzvalene makes it easy to provide the last datum necessary to implicate benzvalene as an intermediate[2c,13] in the photochemical hydration of benzene:[1a,2c,13,14] that it reacts with acidified D_2O to give IV as suggested by Berson and Hasty.[13b] An ether solution (105 ml) containing about 1.6 g of benzvalene was treated with 25 ml of 0.074 *N* D_3PO_4 in D_2O for 30 min at room temperature to give a quantitative yield (2.1 g) of IV.[15]

(1) (a) K. E. Wilzbach, J. S. Ritscher, and L. Kaplan, *J. Amer. Chem. Soc.*, **89**, 1031 (1967); (b) L. Kaplan and K. E. Wilzbach, *ibid.*, **90**, 3291 (1968); (c) H. R. Ward and J. S. Wishnok, *ibid.*, **90**, 1085 (1968).

(2) A few rare derivatives have also been prepared: (a) H. G. Viehe, R. Merenyi, J. F. M. Oth, J. R. Senders, and P. Valange, *Angew. Chem., Int. Ed. Engl.*, **3**, 755 (1964); (b) K. E. Wilzbach and L. Kaplan, *J. Amer. Chem. Soc.*, 87, 4004 (1965); (c) I. E. Den Besten, L. Kaplan, and K. E. Wilzbach, *ibid.*, **90**, 5868 (1968); (d) M. G. Barlow, R. N. Haszeldine, and R. H. Hubbard, *J. Chem. Soc. C*, 1232 (1970).

(3) (a) T. J. Katz and J. J. Cheung, *J. Amer. Chem. Soc.*, **91**, 7772 (1969); (b) T. J. Katz, J. J.Cheung, and N. Acton, *ibid.*, **92**, 6643 (1970).

(4) K. Hojo, R. T. Seidner, and S. Masamune, *ibid.*, **92**, 6641 (1970).

(5) (a) G. L. Closs and L. E. Closs, *ibid.*, **82**, 5723 (1960); (b) G. Köbrich and H. R. Merkele, *Chem. Ber.*, **99**, 1782 (1966); (c) G. Köbrich, *et al.*, *Angew. Chem., Int. Ed. Engl.*, **6**, 41 (1967); (d) U. Burger and R. Huisgen, *Tetrahedron Lett.*, 3049 (1970).

(6) (a) G. L. Closs, *J. Amer. Chem. Soc.*, **84**, 809 (1962); (b) W. Kirmse and D. Grassmann, *Chem. Ber.*, **99**, 1746 (1966).

(7) Methyllithium in dimethyl ether was prepared by replacing the ether in commercial 5% CH_3Li in $(C_2H_5)_2O$ containing 0.4% LiCl (from Foote Mineral Co.).

(8) Even 10-mg samples when scratched detonate consistently, and the explosion of a 254-mg sample was violent.

(9) The enthalpies of benzvalene and benzene have been calculated to differ by 58.9 kcal/mol.[10]

(10) N. C. Baird and M. J. S. Dewar, *J. Amer. Chem. Soc.*, **91**, 352 (1969).

(11) The proton nmr is like that published: R. F. C. Brown, G. E. Gream, D. E. Peters, and R. K. Solly, *Aust. J. Chem.*, **21**, 2223 (1968).

(12) (a) G. L. Closs and P. E. Pfeffer, *J. Amer. Chem. Soc.*, **90**, 2452 (1968); (b) K. B. Wiberg and G. Szeimies, *Tetrahedron Lett.*, 1235 (1968); (c) K. B. Wiberg, *Tetrahedron*, **24**, 1083 (1968).

(13) (a) L. Kaplan, J. S. Ritscher, and K. E. Wilzbach, *J. Amer. Chem. Soc.*, **88**, 2881 (1966); (b) J. A. Berson and N. M. Hasty, Jr., *ibid.*, **93**, 1549 (1971).

(14) E. Farenhorst and A. F. Bickel, *Tetrahedron Lett.*, 5911 (1966).

(15) Stereochemical assignment (by nmr): ≪2% endo proton;[13b,16] exo = 8-Hz triplet;[13b,17c] $|J_{4,5}| \ll 6$ Hz [$W_{1/2}$ for H_4 = 5.5 Hz (OH deuterated)].[18]

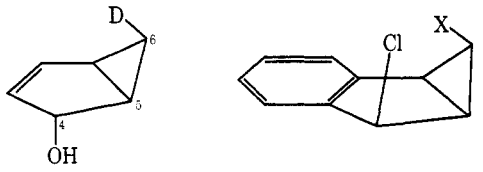
(16) This is the resonance of bicyclo[3.1.0]hexanes that moves when a substituent at C-2 or C-3 is introduced cis to the cyclopropane.[17]

(17) (a) P. K. Freeman, M. F. Grostic, and F. A. Raymond, *J. Org. Chem.*, **30**, 771 (1965); (b) P. K. Freeman, F. A. Raymond, and M. F. Grostic, *ibid.*, **32**, 24 (1967); (c) W. G. Dauben and W. T. Wipke, *ibid.*, **32**, 2976 (1967).

(18) $|J|$ should be 6 Hz if the protons are cis[19,20] and 2 Hz if trans.[17a,b,20]

(19) (a) H. E. Zimmerman, R. S. Givens, and R. M. Pagni, *J. Amer. Chem. Soc.*, **90**, 6096 (1968); (b) E. Ciganek, *ibid.*, **88**, 2882 (1966).

(20) E. C. Friedrich, *J. Org. Chem.*, **34**, 528 (1969).



IV

Va, X = D
b, X = H

A related reaction of naphthvalene, with DCl gas in CCl_4, stereospecifically[21] gives Va (mp 53.5–56.5°) in 98% yield.[22] The structure is proven by its proton nmr spectrum[23] and that of the epimer of Vb formed upon reaction with LiCl in acetone,[24] and by reaction of Vb with triphenyltin hydride,[25] which gives quantitatively benzobicyclo[3.1.0]hex-2-ene (57%),[26] 1-methylindene (40%),[27] and 1,2-dihydronaphthalene (3%).[28] The stereospecificity of the chloride attack seems remarkable[29] although that of the protonation is anticipated by two other results[30] and by theories.[31]

The abundance of benzvalenes should allow extensive studies of their properties.

Acknowledgments. We are grateful to the National Institutes of Health for support under Grant No. MH08912.

(21) Within 5% (nmr analysis).
(22) The parent peaks in the mass spectrum, and the carbon, hydrogen, and chlorine analyses are those required.
(23) HCl adduct: τ 2.89 (3.97 H), 4.40 (6.5-Hz doublet, 0.98 H), 7.72 (multiplet, 2.00 H), 8.91 (multiplet, 1.03 H), 9.31 (4.2-Hz quartet, 1.03 H). DCl adduct: no τ 9.31 (endo H)[17] resonance; τ 8.92 is an 8.1-Hz triplet.[17c]
(24) τ 9.31 → τ 9.88;[17,20] 6.5-Hz doublet → 1.7-Hz doublet.[18,20]
(25) (a) H. G. Kuivila and L. W. Menapace, *J. Org. Chem.*, **28**, 2165 (1963); (b) E. C. Friedrich and R. L. Holmstead, *ibid.*, **36**, 971 (1971).
(26) (a) M. Pomerantz, *J. Amer. Chem. Soc.*, **89**, 694 (1967); (b) J. Meinwald and P. H. Mazzochi, *ibid.*, **89**, 696 (1967).
(27) A.-M. Weidler and G. Bergson, *Acta Chem. Scand.*, **18**, 1487 (1964).
(28) F. Straus and L. Lemmel, *Chem. Ber.*, **54**, 25 (1921).
(29) The results are opposite in two systems previously studied.[30]
(30) (a) W. G. Dauben and W. T. Wipke, *Pure Appl. Chem.*, **9**, 539 (1964); (b) K. B. Wiberg and G. Szeimies, *J. Amer. Chem. Soc.*, **92**, 571 (1970).
(31) (a) M. Pomerantz and E. W. Abrahamson, *ibid.*, **88**, 3970 (1966); (b) M. Pomerantz, G. W. Gruber, and R. M. Wilke, *ibid.*, **90**, 5040 (1968); (c) J. M. Schulman and G. J. Fisanick, *ibid.*, **92**, 6653 (1970).

Thomas J. Katz,* E. Jang Wang, Nancy Acton
Department of Chemistry, Columbia University
New York, New York 10027
Received April 30, 1971

The Difference between α- and δ-Chymotrypsins. Preparation and Alkaline pH Dependence of α_1-Chymotrypsin-Catalyzed Hydrolysis of *N*-Acetyl-L-tryptophan Methyl Ester (ATME). The Involvement of Alanine-149 in α-Chymotrypsin Catalysis

Sir:

We wish to report evidence which strongly implicates the amino terminus of alanine-149 as a participant in catalysis by the enzyme α-chymotrypsin. The ionization state of this amino acid leads to some structural change at the active site which determines the kinetic behavior of the enzyme. It is known that α-chymotrypsin loses its ability to bind specific substrates or inhibitors in the alkaline pH region.[1-3] Although it has not been proved, this reversible inactivation has been associated with the disruption of an ion pair between the carboxyl group of aspartate-194 and the N-terminal amino group of isoleucine-16, triggered by the deprotonation of this last residue.[4]

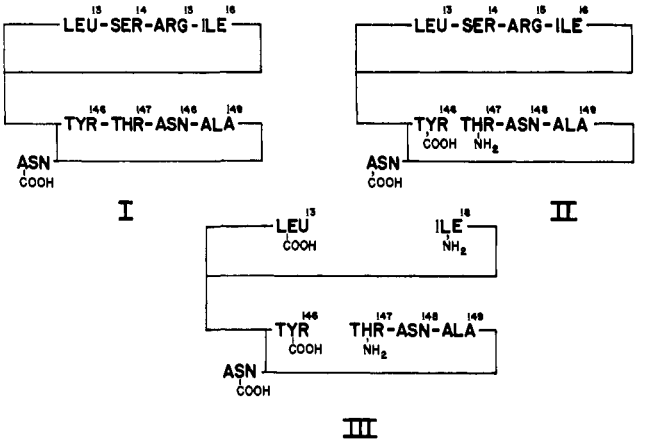


Figure 1. Schematic representation of the structures of chymotrypsinogen A (I), *threo*-neochymotrypsinogen (II), and α_1-chymotrypsin (III).

Recent studies from this laboratory on the pH dependence of δ-chymotrypsin-catalyzed reactions[5,6] indicated that the binding ability of this enzyme is remarkably less dependent on pH when compared with α-chymotrypsin. Although there is evidence for the existence of the same ionic bond in crystals of phenylmethanesulfonyl-δ-chymotrypsin,[7] our results clearly indicated that the deprotonation of the isoleucine-16 amino group causes only a minor effect on the binding ability of this enzyme. This led us to suggest[5] that the peculiar behavior of α-chymotrypsin at alkaline pH may be caused by the ionization of the phenolic group of tyrosine-146 or the amino group of alanine-149, which are present as chain termini in α-chymotrypsin but not in δ-chymotrypsin.

In this communication we wish to report preliminary results on the preparation and the alkaline pH dependence of another active form of chymotrypsin, α_1-chymotrypsin (III). This enzyme, whose existence was first recognized by Desnuelle and coworkers, differs from α-chymotrypsin because it has threonine-147 instead of alanine-149 as the N-terminal amino acid of the C chain (Figure 1).[8]

III was prepared by enzymatic activation of *threo*-neochymotrypsinogen[9] (II), according to the following procedure: chymotrypsinogen A (I) was treated with 5% (w/w) purified δ-chymotrypsin and 2% (w/w) crystalline soybean trypsin inhibitor in 0.1 *M* phosphate

(1) M. L. Bender, M. J. Gibian, and D. J. Whelan, *Proc. Nat. Acad. Sci. U. S.*, **56**, 833 (1966).
(2) A. Himoe, P. C. Parks, and G. P. Hess, *J. Biol. Chem.*, **242**, 919 (1967).
(3) C. H. Johnson and J. R. Knowles, *Biochem. J.*, **103**, 428 (1967).
(4) P. B. Sigler, D. M. Blow, B. W. Matthews, and R. Henderson, *J. Mol. Biol.*, **35**, 143 (1968); G. P. Hess, J. McConn, E. Ku, and G. McConkey, *Phil. Trans. Roy. Soc. London, Ser. B*, **257**, 89 (1970), and references therein.
(5) P. Valenzuela and M. L. Bender, *Proc. Nat. Acad. Sci. U. S.*, **63**, 1214 (1969).
(6) P. Valenzuela and M. L. Bender, *Biochemistry*, **9**, 2440 (1970).
(7) J. Kraut, H. T. Wright, M. Kellerman and S. T. Freer, *Proc. Nat. Acad. Sci. U. S.*, **58**, 304 (1967).
(8) M. Rovery, M. Poilroux, A. Curnier, and P. Desnuelle, *Biochem. Biophys. Acta*, **18**, 571 (1955).
(9) M. Rovery, M. Poilroux, A. Yoshida, and P. Desnuelle, *ibid.*, **23**, 608 (1957).