

preparation and gave a sharp, single Pauly-positive spot on paper chromatography ($R_f^{18} 0.4$, $R_f^{19} 0.5$) and a sharp, single Pauly-positive spot on high voltage paper electrophoresis.

Combination²⁰ of the synthetic material obtained by column chromatography with natural B-chain²¹ generated insulin activity in a yield of 0.5–1.2% (corrected for water content). This compares favorably with the activity obtained^{4,5,7} upon recombination of natural A- and B-chains. Insulin activity was determined by the mouse-diaphragm method²² and by immunological assays. In the latter case the insulin activity was neutralized by anti-ox-insulin serum.²³

Our studies toward the synthesis of the B-chain will be reported in a later communication.

(18) The R_f refers to an ascending chromatography in the system (see ref. 6) 2-butanol-acetic acid-8 M urea, 12.5:0.9:11.5.

(19) The R_f refers to a descending chromatography in the system (see ref. 6) 2-butanol-acetic acid-8 M urea, 12.5:1:11.5.

(20) We wish to express our gratitude to Dr. G. H. Dixon and Dr. S. Wilson of the Department of Biochemistry, and Connaught Medical Research Laboratories of the University of Toronto, Canada, for carrying out the combination experiments of the synthetic A-chain with the natural B-chain and the biological assays.

(21) Natural B-chain from ox insulin was used in the combination experiments.

(22) A. C. Wardlaw and P. J. Moloney, *Can. J. Biochem. Physiol.*, **39**, 695 (1961).

(23) P. J. Moloney and M. Coval, *Biochem. J.*, **59**, 179 (1955).

(24) This work was supported by a Research Career Development Award (GM-K3-15151) from the Public Health Service and a grant (A-3067) from the National Institute of Arthritis and Metabolic Diseases, Public Health Service, for which we wish to express our appreciation.

(25) The authors wish to express their appreciation to Mrs. Jemele Hudson for the enzymatic analyses and amino acid analyses and Miss Joanne Janos for technical assistance.

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Possible Vinyl Cation Intermediates, a 1,4-Chlorine Shift, and a Trimerization in the Reaction of Trifluoroacetic Acid with Alkynes¹

Sir:

Vinyl cations are reputed to be of relatively high energy as judged in part by the well known unreactivity of vinyl halides toward alcoholic silver nitrate.²

We wish to report that addition of trifluoroacetic acid to alkynes occurs almost as rapidly (approximately 0.2 as fast) as the previously studied comparable reaction of alkenes.^{3,4} Vinylic trifluoroacetates are formed which may be regarded as arising from intermediate substituted vinyl cations, as illustrated for the reaction of 1-hexyne.⁵

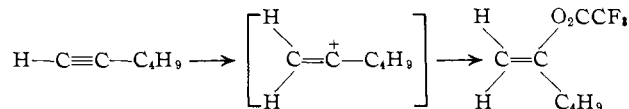
(1) This research was supported by a grant (790 A) from the Petroleum Research Fund of the American Chemical Society.

(2) (a) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 148. Resonance stabilization of the vinyl halides presumably also contributes to the lack of reactivity of these compounds. (b) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, New York, N. Y., 1956, p. 141. (c) We have been unable to locate a reference to a definitive study of the reactivity of vinyl halides toward alcoholic silver nitrate. We suspect that the widespread familiarity of chemists with the statement in ref. 2b that "vinyl halides . . . are unreactive . . ." accounts for the "well known" aspect of the reaction.

(3) (a) P. E. Peterson and G. Allen, *J. Org. Chem.*, **27**, 1505 (1962); (b) P. E. Peterson and G. Allen, *ibid.*, **27**, 2290 (1962).

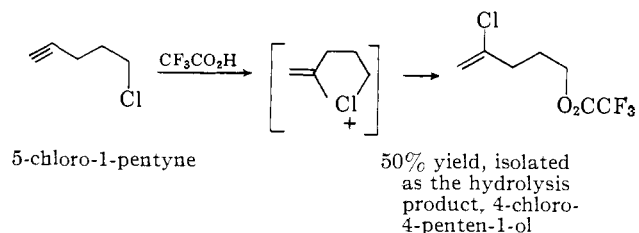
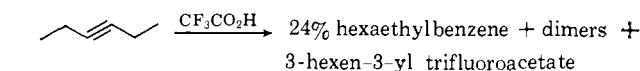
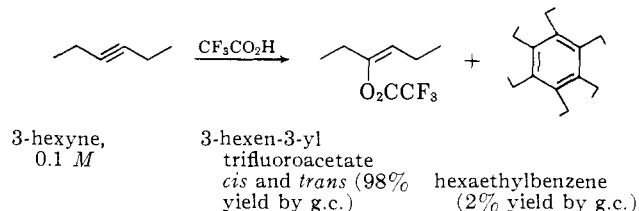
(4) The hydration of alkynes to ketones in the presence of strong acids has long been known, but either concentrated sulfuric acid or high temperatures have been employed. Cf. R. E. Schaad and V. N. Ipatieff, *J. Am. Chem. Soc.*, **62**, 178 (1940). Addition of hydrogen bromide to alkynes has been studied: M. S. Kharasch, J. G. McNab, and M. C. McNab, *ibid.*, **57**, 2463 (1935).

(5) We employ simple carbonium ion mechanisms in this communication in the absence of more detailed information regarding the nature of the intermediates or transition states involved. From the observed Markovnikov

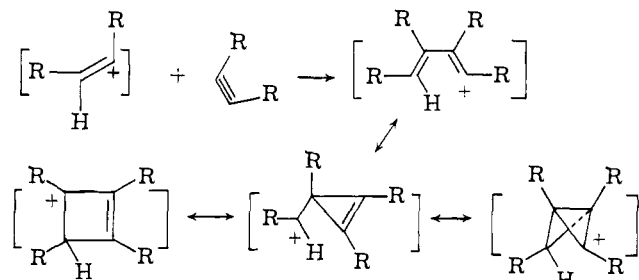


If vinyl cations are, in fact, intermediates several interesting questions arise. Will the cationic carbon atoms exhibit sp or sp² hybridization? Can the ready formation of these presumed energetic ions be accounted for by the high energy of the alkyne starting materials relative to the transition stage for reaction, as might be inferred from the large heats of hydrogenation of alkynes (to alkenes) relative to that of alkenes?⁶ Will unusual reaction products, possibly characteristic of hot carbonium ions, be formed?

Some initial observations concerning reaction products are illustrated by the following equations.



The formation of hexaethylbenzene is of interest because products of this type have previously been found most commonly in reactions catalyzed by metallic species and possibly involving cyclobutadiene complexes as intermediates in some instances.⁷ Although acid-catalyzed trimerizations of alkynes are not completely unknown,⁸ the ready formation of hexaethylbenzene in our reaction takes on added interest when some of the possibilities for classical and/or nonclassical resonance in the presumed intermediate dimeric ion are considered.



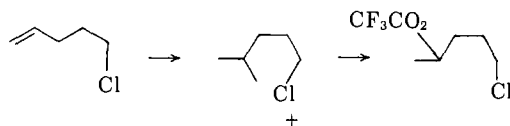
The reaction of δ -chloro-1-pentyne probably proceeds via the intermediate cyclic ion shown, which, interest-orientation and from preliminary studies of the effect of inductive substituents, however, the reaction of alkynes is similar to that of alkenes in regard to the positive character of the transition state.

(6) J. B. Conn, G. B. Kistiakowski, and E. A. Smith, *J. Am. Chem. Soc.*, **61**, 1868 (1939).

(7) (a) Cf. J. C. Sauer and T. L. Cairns, *ibid.*, **79**, 2659 (1957); (b) C. McKinley, *Ind. Eng. Chem.*, **44**, 995 (1952).

(8) See Almedigen, *Zh. Russ. Fiz. Khim. Obschestva*, **13**, 392 (1881); *Chem. Zentr.*, **12**, 629 (1881); cf. Beilstein's "Handbuch der Organischen Chemie," 4th Ed., Vol. 1, p. 249, for a report of the sulfuric acid-catalyzed trimerization of 2-butyne to hexamethylbenzene.

ingly, opens by attack at the primary carbon (to the extent of at least 85% as determined by gas chromatography). In contrast, addition of trifluoroacetic acid to 5-chloro-1-pentene (which probably also reacts *via* a cyclic ion, as shown later)⁹ gives exclusively (>95%) the product arising from reaction of trifluoroacetic acid at the secondary carbon, suggesting car-



bonium ion character in the transition stage for product formation. An analogous interpretation of the product determining step in the reaction of 5-chloro-1-pentyne can be adopted provided the incipient primary carbonium ion formed by ring opening of the cyclic intermediate is *more stable than the vinyl cation* which would be formed by the other mode of ring opening.¹⁰

(9) P. E. Peterson and G. Allen, *J. Am. Chem. Soc.*, in press.

(10) Alternatively the ring opening reaction may possess S_N2 character in this case.

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Anomalous Reduction of an Epoxycyclohexanetetrol to a Cyclohexenetetrol by Potassium Methyl Xanthate¹

Sir:

The normal product from reaction of an epoxide with potassium methyl xanthate is a trithiocarbonate.² For example, the anhydroinositol diketal³ I gives a mixture of the trithiocarbonate diketals IV and V.^{4a} The diastereomer II similarly gives the trithiocarbonate diketal VI.^{4b}

It was expected that the product from similar treatment⁵ of diastereomer III^{6b} would also be VI. The actual product, surprisingly, was a colorless (not yellow) crystalline compound, containing no sulfur, with microanalysis corresponding to C₁₂H₁₈O₄. A permanganate test for unsaturation was positive.

The product, m.p. 67–68°, was finally shown to be the *cis*-cyclohexenetetrol diketal VII of the same reported^{6a,7} melting point. Its identity was established by hydrolysis and acetylation to give the enetetrol tetraacetate, m.p. 102–103° (lit.^{6a,7} 103° or 104°). The infrared spectrum was identical with that of an authentic sample,⁷ and a mixture melting point was not depressed. The quantity of pure VII actually isolated was 31% of theoretical.

Since few methods for regenerating an alkene from its epoxide are available,⁸ extension of this reaction should be useful. However, the most interesting feature at present is the striking stereospecificity which causes diastereomers I and II to form trithiocarbonates and little or no alkene, while III shows the opposite

(1) Aided by a grant (G-15893-R) from the National Science Foundation.

(2) L. Owen, *et al.*, *J. Chem. Soc.*, 1024 (1960); 1030 (1960).

(3) The tetrol formulas I–VII should be understood to represent the corresponding diacetone ketals.

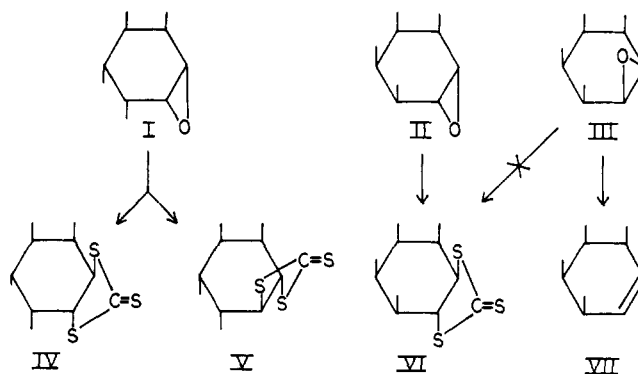
(4) (a) G. E. McCasland, S. Furuta, A. Furst, L. F. Johnson, and J. N. Shooley, *J. Org. Chem.*, **28**, 456 (1963); (b) S. Furuta, unpublished work.

(5) A mixture of epoxide diketal, carbon disulfide, potassium hydroxide, and methanol was boiled under reflux for 5 hr. or longer.

(6) (a) S. J. Angyal, *et al.*, *J. Chem. Soc.*, 375 (1958); (b) *ibid.*, 3691 (1957).

(7) R. Criegee and P. Becher, *Chem. Ber.*, **90**, 2516 (1957). We wish to thank Professor Criegee (Düsseldorf) for a sample of his conduritol-D carbonate diacetate. This sample was hydrolyzed by us with aqueous ethanolic sodium hydroxide, and then acetylated, to provide our authentic sample.

(8) See S. Winstein and R. Henderson in "Heterocyclic Compounds," Vol. I, R. Elderfield Ed., John Wiley and Sons, Inc., New York, N. Y., 1950, p. 44.



behavior.⁹ Efforts to explain these steric effects in terms of configuration and conformation are in progress.

(9) The alkene formation possibly is due to desulfurization of an intermediate episulfide by attack of a nucleophile. See D. Denney and M. Boskin, *J. Am. Chem. Soc.*, **82**, 4736 (1960).

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Resolution of a Triarylcannabinol and Stereospecific Substitution Reactions

Sir:

Satisfactory methods of resolution have been reported for all types of alkyl and arylalkyl secondary^{1,2} and tertiary^{3,4} carbinols except for the triarylcannabinols.^{5,6} Wallis⁶ obtained *d*-phenylbiphenyl- α -naphthylcannabinol (*d*-ROH) by treating *l*-phenylbiphenyl- α -naphthylmethylthioglycolic acid (*l*-RSCH₂CO₂H) with silver nitrate in aqueous acetone, but this method was termed unsatisfactory.¹

The optically active trityl system appeared to us most attractive for studies of the stereochemistry of substitution processes involving ion pairs because the system appears to be free of complicating side reactions, *e.g.*, S_N2 type processes⁷ and elimination reactions. Kinetic and stereochemical studies of optically active trityl derivatives should provide helpful information concerning the mechanism of substitution of trityl compounds.⁷ Wallis recognized the value of such studies, and interest in stereochemical studies of trityl compounds is heightened by recent developments.^{8,9}

This note presents: (1) evidence that the method of Wallis has an optical yield of 60% and that by an extension of the method one can obtain optically pure alcohol; (2) a new method of resolution of triarylcannabinols with high optical yield; (3) proof that both of Wallis' stereospecific substitution reactions take the same stereochemical course; and (4) preliminary evidence that Wallis' reactions proceed with *retention* of configuration.

Alcohol (*d*-ROH) prepared by Wallis' method had $[\alpha]^{25}_D = +10^\circ$ (*c* 1.050),¹⁰ $[\alpha]^{25}_D = +4.4^\circ$ (*c* 0.8 in

(1) A. W. Ingersoll, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 376.

(2) G. H. Green and J. Kenyon, *J. Chem. Soc.*, 751 (1950).

(3) W. von E. Doering and H. H. Zeiss, *J. Am. Chem. Soc.*, **72**, 147 (1950).

(4) H. H. Zeiss, *ibid.*, **73**, 2391 (1951).

(5) C. L. Arcus, J. Kenyon, and S. Levin, *J. Chem. Soc.*, 407 (1951).

(6) E. S. Wallis and F. H. Adams, *J. Am. Chem. Soc.*, **55**, 3838 (1933). A second stereospecific reaction was the conversion of *l*-RSCH₂CO₂H to *l*-ROEt.

(7) E. D. Hughes, C. K. Ingold, S. F. Mok, S. Patai, and Y. Pocker, *J. Chem. Soc.*, 1220 (1957); S. Winstein and G. C. Robinson, *J. Am. Chem. Soc.*, **80**, 169 (1958), and later papers in this series; C. G. Swain and E. E. Pegues, *ibid.*, **80**, 812 (1958).

(8) C. G. Swain and G. Tsuchihashi, *ibid.*, **84**, 2021 (1962), and references quoted therein.

(9) S. G. Smith, *Tetrahedron Letters*, **No. 21**, 979 (1962); A. Streitwieser, Jr., and T. D. Walsh, *ibid.*, **No. 1**, 27 (1963).