The absorbance of the final solution was read immediately at the 335 mμ maximum. Since the optical density at 335 mμ decreased more rapidly with this system, fast work and careful timing and extrapolation to zero or mixing time were important. The titration curve was plotted as before. These data are presented in Table III.

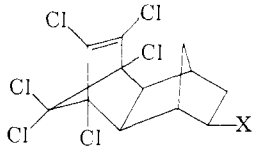
HUNTSVILLE, ALA.

COMMUNICATIONS TO THE EDITOR

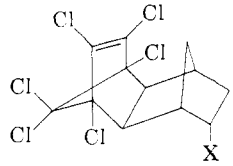
BRIDGED POLYCYCLIC COMPOUNDS. XII. A MECHANISM FOR THE HUNSDIECKER REACTION[1,2]

Sir:

The Hunsdiecker reaction of bromine with the silver salts Ia and IIa gave a mixture of Ib and IIb, although the bromide formed by decomposition

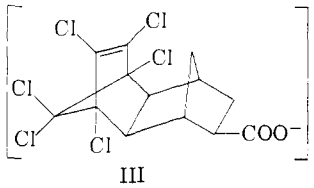


Ia, X = CO_2Ag
b, X = Br
c, X = CO_2H
d, X = COCl

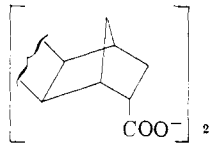


IIa, X = CO_2Ag
b, X = Br
c, X = CO_2H
d, X = COCl

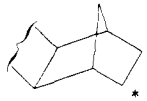
of the acyl peroxides III and IV in bromotrichloromethane was all *exo* (Ib). If the latter reaction



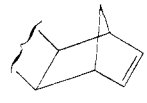
III



IV



V



VI

reflects the stereochemistry of the reaction of the free radical V with bromine donors, some mechanism other than the reaction of V with bromine or acyl hypobromite must be involved in the Hunsdiecker reaction of Ia and IIa; a free radical is, however, generally accepted as the intermediate in this reaction.[3]

Ib (m.p. 178.5–179.2°) and IIb (m.p. 109.5–110.5°) result from the reaction of hexachlorocyclopentadiene with the mixture obtained by the Diels–Alder reaction of vinyl bromide and cyclopentadiene.[4] The *exo* bromide Ib also can be made by the addition of hydrogen bromide to Aldrin (VI). Ib and IIb were shown to be epimeric by dehydrobromination with alkali to VI. Ib and IIb were isolated from the reaction of Ia and IIa with bromine in carbon tetrachloride. The bromides were inert toward the reaction conditions and isolation procedures, and the acids related to Ia and Ib could be recovered unisomerized from their silver salts.

The acids, Ic (m.p. 221–222°) and IIc (m.p. 216–217°) were prepared by the reaction of *exo*-[4] and *endo*-bicyclo[2.2.1]-5-heptene-2-carboxylic acid,[5] respectively, with hexachlorocyclopentadiene. The acids gave the acid chlorides, Id (m.p. 100.5–101.5°) and IId (m.p. 111.5–113°), which in turn were treated with sodium peroxide to form III (m.p. *ca.* 111°, dec.) and IV (m.p. *ca.* 133°, dec.). All of the compounds gave satisfactory elemental analyses. Each peroxide decomposed largely into ester and only the *exo* bromide Ib in refluxing bromotrichloromethane. The alcohol and acid portions of each ester had the configuration of the starting acid. Infrared and isotope-dilution analyses showed that the bromide from either peroxide contained very little, if any, IIb.

The Hunsdiecker reactions of Ia and IIa in the dark in refluxing carbon tetrachloride gave bromides whose compositions as measured by infrared and isotope-dilution techniques were Ib, 69 ± 2% and IIb, 31 ± 2%. The configuration of the initial silver salt did not affect the bromide composition, nor did addition of benzoyl peroxide or *sym*-trinitrobenzene. The large amount of *endo* bromide (IIb) is striking.

The insensitivity of the composition of the bromide mixture to the configuration of the initial acid is inconsistent with any stereospecific inversion or cyclic process, while the formation of substantial amounts of *endo* bromide is inconsistent with a free-radical-chain process in which the radical V reacts with a bromine donor.[6] The data are consistent with the concept of geminate recombination of an alkyl radical and a bromine atom, formed by decomposition of the intermediate acyl hypo-

(1) Previous paper in series: S. B. Soloway and S. J. Cristol, *J. Org. Chem.*, accepted for publication.

(2) The authors are indebted to the Shell Development Company for partial support of this research.

(3) For pertinent references see: C. V. Wilson in R. Adams, "Organic Reactions," Vol. IX, John Wiley and Sons, Inc., N. Y., 1957, Chapter 5; R. G. Johnson and R. K. Ingham, *Chem. Revs.*, **56**, 219 (1956).

(4) J. D. Roberts, E. R. Trumbull, W. Bennett and R. Armstrong, THIS JOURNAL, **72**, 3116 (1950).

(5) K. Alder, G. Stein, M. Liebmann and E. Rolland, *Ann.*, **514**, 197 (1934).

(6) A referee has suggested that the stereochemistry of the model reaction of V with bromotrichloromethane may not be comparable to that of V with the smaller molecule bromine or with the acyl hypohalite. The conclusion that no chain reaction process is involved is based upon the assumption that these are comparable and that *exo* attack on such radicals[7] is general.

(7) S. J. Cristol and R. P. Arganbright, THIS JOURNAL, **79**, 6039 (1957).

bromite[3] within a solvent cage. As this involves the reaction of two high-energy species in close proximity and with presumably a low activation energy, the relative lack of selectivity between *endo* and *exo* attack in the Hunsdiecker reaction, compared to the usual tendency for *exo* attack on such ring systems, is understandable.[8]

While the evidence in this system appears consistent only with the radical geminate recombination mechanism, we are continuing our investigation of the Hunsdiecker reaction to determine whether other mechanisms are available to it in other systems or under other experimental conditions.

(8) G. S. Hammond, THIS JOURNAL, **77**, 334 (1955).

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AN INVERSION OF THE USUAL ANTIPODAL SPECIFICITY OBSERVED IN α-CHYMOTRYPSIN CATALYZED REACTIONS[1]

Sir:

It is known that the antipodal specificity encountered in α-chymotrypsin catalyzed reactions is relative rather than absolute.[2,3] However, whenever antipodal specificity has been evident it has been only the L-enantiomorph that has been observed to react at the more rapid rate. Thus, it is generally believed that α-chymotrypsin exhibits a predominant antipodal specificity for substrates possessing the L-configuration although it is recognized that such antipodal specificity may be lost either wholly or in part with certain types of substrates.

In 1957 it was suggested[4] that one of the enantiomorphs of 1-keto-3-carbomethoxy-1,2,3,4-tetrahydroisoquinoline might be found to be a substrate of α-chymotrypsin. The DL-ester was first synthesized by condensation of *o*-cyanobenzyl bromide with diethyl acetamidomalonate to give ethyl DL-α-carbethoxy - α - acetamido - β - (*o* - cyanophenyl)-propionate, m.p. 104–105°, which was saponified, decarboxylated and cyclized to DL-1-keto-3-carboxy-1,2,3,4-tetrahydroisoquinoline, m.p. 235–237° (dec.), and the DL-acid esterified to give the desired DL-methyl ester, m.p. 114–115°. When this DL-ester was allowed to react with α-chymotrypsin, in aqueous solutions at 25° and *p*H 7.0 to 8.0, a rapid hydrolysis was observed until approximately 50% of the DL-ester had reacted. With this demonstration of not only substrate activity, but also of marked antipodal specificity, a stereospecific synthesis of D- and L-1-keto-3-carbomethoxy-1,2,3,4-tetrahydroisoquinoline, from D- and L-phenylalanine, was undertaken after it had been determined that the reaction sequence DL-phenylalanine $\xrightarrow[HCl]{CH_2O}$ DL-3-carboxy-1,2,3,4-tetrahydroisoquinoline (I), m.p. 313–316° (dec.), $\xrightarrow[NaOH]{C_6H_5COCl}$ DL-N-benzoyl-3-carboxy-1,2,3,4-tetrahydroisoquinoline (II), m.p. 170–172°, neut. equiv., 280 $\xrightarrow[K_2CO_3]{KMnO_4}$ DL-α-benzamido-β-(*o*-carboxyphenyl)-propionic acid (III), m.p. 210–211°, neut. equiv., 158 $\xrightarrow[H_2O]{HCl}$ DL-1-keto-3-carboxy-1,2,3,4-tetrahydroisoquinoline (IV), m.p. 234–235° (dec.), neut. equiv., 191 $\xrightarrow[SOCl_2]{CH_3OH}$ DL-1-keto-3-carbomethoxy-1,2,3,4-tetrahydroisoquinoline (V), m.p. 114–115°, gave an acid (IV) and methyl ester (V) that were identical with those obtained by the first method of synthesis. With D- and L-phenylalanine the above sequence of reactions gave D-I, m.p. 280° (dec.); L-I, m.p. 274° (dec.); D-II, m.p. 156–158°, $[\alpha]^{25}D$ 34°; L-II, m.p. 164°, $[\alpha]^{25}D$ −34°; D-III, m.p. *ca.* 181–184.5°, $[\alpha]^{25}D$ 119°; L-III, m.p. 180–182°, $[\alpha]^{25}D$ −105°; D-IV, m.p. 234–236.5°, $[\alpha]^{25}D$ −44°; L-IV, m.p. 236–238°, $[\alpha]^{25}D$ 41°; D-V, m.p. 87–89°, $[\alpha]^{25}D$ −79° and L-V, m.p. 88–90°, $[\alpha]^{25}D$ 76°. All rotations were determined in methanol with a solute concentration of *ca.* 2%.

When the D- and DL-1-keto-3-carbomethoxy-1,2,3,4-tetrahydroisoquinolines were allowed to react with α-chymotrypsin, in aqueous solutions at 25° and *p*H 7.9 and at substrate concentrations of approximately $10^{-3}M$ and an enzyme concentration of approximately $10^{-6}M$, it was observed that whereas the DL-mixture was hydrolyzed rapidly to the corresponding acid and methanol only to an extent of 50% the D-enantiomorph was hydrolyzed completely and at a more rapid rate. A preliminary analysis of the kinetics of hydrolysis of the DL-mixture indicated that under the above conditions the L-enantiomorph present in the DL-mixture participated in the reaction primarily as a competitive inhibitor rather than as a substrate.

When it is appreciated that D-1-keto-3-carbomethoxy-1,2,3,4-tetrahydroisoquinoline is hydrolyzed in the presence of α-chymotrypsin at a rate comparable in magnitude to the rates of hydrolysis of several acylated-L-phenylalanine methyl esters under similar experimental conditions and that L - 1 - keto - 3 - carbomethoxy - 1,2,3,4 - tetrahydroisoquinoline, in common with a number of acylated-D-phenylalanine methyl esters, is hydrolyzed at a far slower rate and can function as a competitive inhibitor in the above reaction it becomes evident that α-chymotrypsin and not a hitherto undisclosed enzyme, present as an impurity in the α-chymotrypsin preparation, is responsible for the observed preferential hydrolysis of the above D-enantiomorph.

In our observation of an inversion rather than of an abolition of the traditional antipodal specificity of systems involving α-chymotrypsin we have demonstrated that the predominant antipodal specificity of such systems can be determined by the structure of the substrate and that it is not an invariant property of the enzyme. The significance of this conclusion with respect to the mechanism of enzyme action is obvious. For one, it suggests that if the conformation of the active site of the enzyme is essentially invariant then combination of the substrate with the active site must involve interactions

(1) Supported in part by a grant from the National Institutes of Health, Public Health Service.

(2) H. Neurath and G. W. Schwert, *Chem. Revs.*, **46**, 69 (1950).

(3) R. M. Bock, unpublished experiments conducted in these laboratories.

(4) R. L. Bixler, Ph.D. Thesis, Calif. Inst. Tech., Pasadena, 1957.