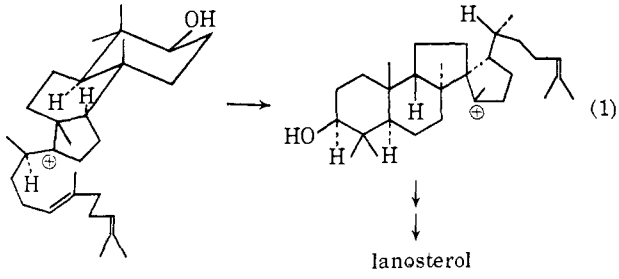
stances A and B, each was converted by a Lewis acid promoted process to the skeletally isomeric system of type IV, the counterpart of established structure V.[2] Enzyme product A, on being subjected to the action of stannic chloride in benzene at room temperature for 25 min, gave rise to a 7:3 mixture of two isomers, E (glpc, R_c = 1.64) and F (glpc, R_c = 1.15). Under similar conditions, nonenzymic product B was transformed into a pair of isomers, C (glpc, R_c = 1.34) and D (glpc, R_c = 0.81) in the ratio 3:2. As indicated by glpc and mass spectral comparisons (on TMSE), substances C and D were identical with the pair of tricyclic alcohols also obtained by direct cyclization of dihydrosqualene oxide I. Products E and F exhibited mass spectra indistinguishable from each other and also from those of authentic materials C and D; furthermore, the mass spectra of the free alcohols C, D, E, and F were identical. Like V, all the dihydro relatives (as TMSE) gave mass spectral fragmentation patterns with a base peak at *m/e* 229. Like the relationship between compounds A and B, the differences between the isomers of IV (C, D, E, and F) are considered to be stereochemical and are under investigation in these laboratories.

This highly interesting result represents the first reported case of the generation by the 2,3-oxidosqualene–lanosterol cyclase system of a cyclic structure different from that of lanosterol. The significance of this finding cannot be fully assessed at present.[11] It is pertinent to point out that in a new, alternative interpretation (eq 1)



(1)

of the chemistry of lanosterol biosynthesis, a perhydrocyclopenta[*a*]naphthalene appears as an initial cyclization product which then produces the lanosterol skeleton *via* a subsequent [5.5]spiro intermediate. Whether enzymic product A is generated by an aberrant biosynthetic route or whether it reflects the normal—albeit interrupted—enzymic pathway remains for future investigations to demonstrate. The obvious next stage, preparation and enzymic testing for sterol formation of appropriate perhydrocyclopenta[*a*]naphthalenes, is now being entered in these laboratories.

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(11) A plant product presumably biogenetically related to squalene has also recently been observed to possess the perhydrocyclopenta[*a*]-naphthalene skeleton (personal communication from Dr. S. Dev, National Laboratory, Poona, India).

(12) National Institutes of Health Predoctoral Fellow, 1965–1967.
(13) National Science Foundation Predoctoral Fellow, 1966–1968.

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The Effect of Active Ester Components on Racemization in the Synthesis of Peptides by the Dicyclohexylcarbodiimide Method[1]

Sir:

Following the report by Wünsch and Drees[2] of a favorable effect of N-hydroxysuccinimide (HOSu) on yields in a peptide synthesis by the N,N′-dicyclohexylcarbodiimide (DCCD) procedure, we began a study of the effect of HOSu on racemization in test syntheses by the same method. Weygand and associates[3,4] have since found a favorable effect in test syntheses using more than 1 equiv of HOSu but minimum requirements and mechanisms were not clear. We present evidence here that formation of intermediate HOSu ester of the acyl peptide is the major mechanism, and only 1 equiv of HOSu is required.

We reported some time ago[5] that 8% DL and 74% L tripeptide fractions were isolated in the reaction of Z-Gly-Phe-OH with H-Gly-OEt with DCCD at room temperature in tetrahydrofuran solvent. A repetition of the experiment with 1.1 equiv of HOSu present resulted in 0% DL and 90% L tripeptide. Using the more sensitive Young test,[6,7] whch involves the reaction of Bz-Leu-OH with H-Gly-OEt to form Bz-Leu-Gly-OEt, we found 79% DL, 0% L product by a room-temperature reaction with 1 equiv of DCCD only. When 1 equiv of HOSu was also present, the results were reversed: 0% DL- and 73% L-Bz-Leu-Gly-OEt were isolated. To test whether or not the mechanism involves neutralization of the basicity of DCCD, experiments with added pivalic acid were done. From the Z-Gly-Phe-Gly-OEt test synthesis, with 1 equiv of pivalic acid present, 0% DL and 80% L products were found. However, the Bz-Leu-Gly-OEt system yielded 75% DL and 0% L products. We conclude that neutralization of the basicity of DCCD is a minor mechanism, and formation of intermediate HOSu esters is the major path.

In several experiments, Bz-Leu-OSu was isolated by concentration of the filtrate *in vacuo* after removal of

(1) Presented at the 154th National Meeting of the American Chemical Society, Chicago, Ill., 1967, Abstract S-031.
(2) E. Wünsch and F. Drees, *Chem. Ber.*, **99**, 110 (1966).
(3) F. Weygand, D. Hoffmann, and E. Wünsch, *Z. Naturforsch.*, **21b**, 426 (1966).
(4) F. Weygand and U. Ragnarsson, *ibid.*, **21b**, 1141 (1966).
(5) G. W. Anderson and F. M. Callahan, *J. Am. Chem. Soc.*, **80**, 2902 (1958).
(6) M. W. Williams and G. T. Young, *J. Chem. Soc.*, 881 (1963).
(7) G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, *J. Am. Chem. Soc.*, **88**, 1338 (1966).

dicyclohexylurea; some of the urea remained in the product, as shown by tlc in $CHCl_3$–MeOH 2:1 (R_f 0.9), and the melting point was low (about 167–169°; pure Bz-Leu-OSu has mp 172–174° [8]). This product was found to be easily racemized in the work-up, and Bz-Leu-Gly-OEt made from it was racemic (2% or more).

The effects of other additives commonly used to make active esters were also studied. Thus, in the Z-Gly-Phe-Gly-OEt synthesis, the addition of 1 or 1.1 equiv of additive yielded the following: N-hydroxyphthalimide, 0% DL, 81% L; N-hydroxypiperidine, 0% DL, 26% L; *p*-nitrophenol, 13% DL, 70% L; 2,4,5-trichlorophenol, 15% DL, 58% L; pentachlorophenol, 15% DL, 60% L; and 8-hydroxyquinoline, 9% DL, 70% L. The superiority of derivatives of hydroxylamine is clear. Results are in accord with those found in similar experiments using the mixed anhydride method.[8]

(8) G. W. Anderson, F. M. Callahan, and J. E. Zimmerman, *J. Am. Chem. Soc.*, **89**, 178 (1967).

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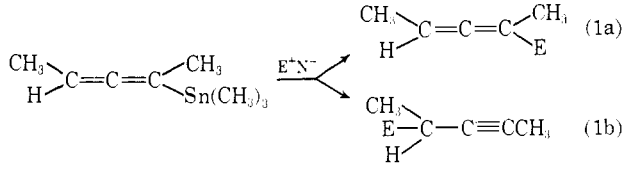
Electrophilic Displacement Reactions. SE and SE′ Reactions of Allenyltins

Sir:

We wish to report some observations on electrophilic displacement reactions of allenyltins which indicate that the reaction may proceed by a direct displacement of the organotin function (SE reaction) to produce an allene as a product (eq 1a) or by attack at the γ-carbon of the allenyl triad (SE′ reaction) to produce an acetylene as product (eq 1b).

Penta-2,3-dien-2-yltrimethyltin and 2,4-dinitrobenzenesulfonyl chloride reacted readily in methylene chloride at room temperature to produce 69% (isolated) 2-(2,4-dinitrophenylthio)-3-pentyne (**1**) (E = 2,4-$(NO_2)_2$-C_6H_3). The product was characterized by elemental analysis, infrared spectrum (band at 2245 cm^{-1}, none



(1a)

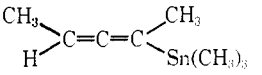
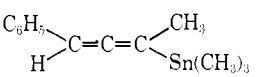
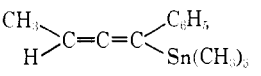
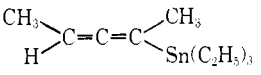
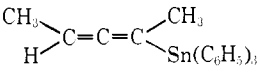
(1b)

around 1950 cm^{-1}), and nmr spectrum (three-proton doublets at τ 8.29, J = 7.1 cps, and τ 8.16, J = 2.3 cps, and a one-proton multiplet centered at τ 5.92).

Similarly, chlorine and bromine reacted with **1** in methylene chloride to yield the corresponding 2-halo-3-pentynes in yields of 77 and 92% as determined by the method of Barcza.[1]

In contrast, protonolysis with hydrogen chloride at 25° in methanol containing 4% water[2] produced a mixture of **1a** and **1b** (E = H). Similarly, four other allenyltins also produced mixtures containing allene and acetylene as products.[3] Examination of the kinetics of the reaction, taking advantage of intense absorptions in the region 205–210 mμ, showed it to be first order in substrate and in lyonium ion. The rate coefficients could be partitioned into those for SE and SE′ reaction upon determination of the proportions of allene and acetylene in the product by gas–liquid partition chromatography. Given in Table I are the over-all second-order rate coefficients for proximate (SE2) attack, presumably at the carbon–tin σ bond, and remote (SE2′) attack, presumably on the π electrons of the β,γ double bond by the acid.

Table I. Protonolysis Rates of Allenyltins at 25°

Compound[a]	k_2, $(M\ sec)^{-1}$	k_2(SE2), $(M\ sec)^{-1}$	k_2(SE2′), $(M\ sec)^{-1}$
 **1**	0.519	0.296	0.223
 **2**	0.111	0.0441	0.0670
 **3**	0.125	0.1061	0.0188
 **4**	0.299	0.100	0.199
 **5**	0.00739	0.00082	0.00657

[a] Each compound gave satisfactory elemental analyses and had infrared and nmr spectra consistent with the assigned structure.

Detailed analysis of the data must await determination of activation parameters. However, certain points of interest may be noted. First, the rate coefficients observed here for **1** are greater than those for the SE2′ protonolysis of *cis*- and *trans*-crotyltrimethyltins (0.0508 and 0.0274 M^{-1} sec^{-1}, respectively) under the same conditions.[2] In other words, attack at the vinyl carbon of the allene is faster than the SE′ attack in either the allenyl or allylic system, in contrast to the general observation that allyllic organometallics are more reactive in electrophilic reactions than vinyl organometallics.

The low reactivity of **5** is consistent with the notion that substitution of phenyl for methyl on tin makes the organotin function a poorer leaving group, suggesting that the phenyl groups play no role in stabilizing organotin cations, as observed in the allyl system.[2]

Comparison of the rate coefficients of compounds **1**, **2**, and **3** reveals an interesting effect when the phenyl group is substituted for methyl. The effect is to decrease the rate in both the α (or proximate) position and in the γ (or remote) positions. However, the effect is more pronounced in each case when the phenyl group is remote from the point of electrophilic attack. When

(1) S. Barcza, *J. Org. Chem.*, **28**, 1914 (1963).
(2) H. G. Kuivila and J. A. Verdone, *Tetrahedron Letters*, 119 (1964).
(3) The hydrocarbon products did not undergo interconversion in the presence of either hydrogen chloride or trimethyltin chloride under the reaction conditions.