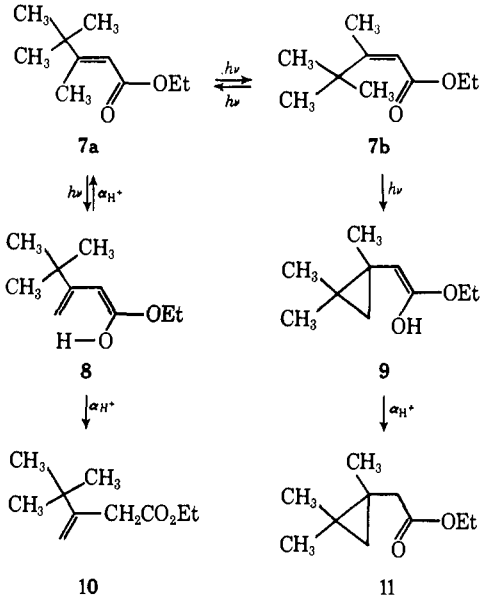
Irradiation of ester **7** (Scheme II) in nonhydroxylic solvents leads to the formation of the cyclopropane ester **11** only. Formation of **10** is a competitive but erratic process in methanol; in more than 50 runs which we have carried out on **7a** ester **11** was always found to be the major product. The preference for the abstraction of a nonallylic primary hydrogen over that of an allylic primary hydrogen has remained an intriguing anomaly.[5] It is now found that in methanol-O-*d* the behavior of **7a** becomes normal; ester **10** is produced at a reproducibly fast rate in this medium, approximately 13 times faster than **11**, so that ester **10** comprises 90–95% of photoproduct. The rate at which **11** is formed remains unaffected, in accord with Scheme II where, in contrast to the dienol **8**, only one ketonization pathway is available to the cyclopropyl enol **9**. Acceleration in methanol-O-*d* of the deconjugation reaction of the double bond into a terminal location is also observed for ethyl 3,5-dimethyl-2-heptenoate.[2]

Scheme II



From the rates of isomerization of esters **1** and **7** approximate values, corrected for statistical factor, for the ease of abstraction of various hydrogens in methanol-O-*d* can be derived; these are primary allylic:primary homoallylic 40:1, primary allylic:tertiary allylic 1:3. On this basis it can be estimated that, in competition with the removal of allylic hydrogens in **1**, the δ hydrogen will be abstracted to give ester **4** at a rate which is at least 40 times[11] slower than the rates at which **2** and **3** are formed; the formation of cyclopropane **11** from ethyl 3,5-dimethyl-2-heptenoate will occur about 360 times[11] more slowly than the formation of the β,γ isomers. Cyclopropane products are, in fact, not formed in the photolyses of these esters.

Acknowledgments. Acknowledgment is made to the donors of the Petroleum Research Fund (Grant No. 2445-A 1,3) administered by the American Chemical Society, for partial support of this work.

formation of the dienols may play a significant role in the deconjugation reaction, if a concerted 1,5 proton transfer contributes to γ protonation. The geometry of the photochemically formed dienols (*e.g.*, as depicted for **5a**) is well suited for such a protonation pathway.

(11) This calculation does not take into account an unfavorable conformational factor which would raise these values. The preferred conformation of ester **1b** is as shown in Scheme I, so that the nonallylic δ hydrogens are located at too far a distance from the carbonyl to be abstracted by it in the singlet[5,6] excited state of the ester.

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Internal Insertion of an Olefin into a Palladium σ Bond

Sir:

Recent investigations[1,2] have given a firm assignment to the stereochemistry of the methoxy complex I obtained from the reaction of sodium methoxide with dichloro(norbornadiene)palladium. In view of the availability of this well-defined complex, a study of ligand displacements of the olefinic bond was undertaken.

Although the reaction of I with various ligands has been reported to give simple bridge-cleavage products,[1] no apparent attempt was made to critically examine the products. In our hands, the reaction of I with various phosphines gave profoundly different products. For example, mixing methylene chloride solutions of 1,2-bis(diphenylphosphino)ethane (DPPE) and 0.5 molar equiv of I gave, on dilution with hexane, a 90% weight recovery of tan platelets, mp 195° dec (under N_2). The structure of this product[3] was deduced from physical and chemical evidence to be II, containing ~0.3 molar equiv of methylene chloride of crystallization.

Elemental analysis[4] and an ebullioscopic molecular weight determination (found, 665 in CH_2Cl_2; calcd, 663) were in agreement with II. Infrared analysis revealed new absorptions (see Table I) characteristic[5] of a nortricyclene ring system. The nmr spectrum revealed an absence of olefinic protons. Additional nmr data are summarized in Table I.

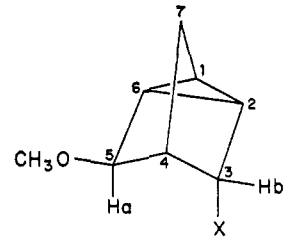
Reduction of II with excess $LiAlH_4$ in ether yielded a single product which was shown to be 3-*exo*-methoxynortricyclene (III) by comparison with an authentic sample.[6] This reaction thus established both the position and the stereochemistry of the methoxy substituent.

The reaction of II with 0.9 molar equiv of Cl_2 and Br_2 in methylene chloride gave the corresponding 3-halo-5-methoxynortricyclenes and (DPPE)PdX_2. Physical data pertinent to these nortricyclenes, IV and V, may be found in Table I.

The problem of the stereochemistry at the 3 position of compounds II, IV, and V was resolved by an analysis of the nmr chemical shifts. Sufficient information[7-9] exists concerning chemical shift data of 3,5-substituted nortricyclenes from which correlations may be made

(1) M. Green and R. I. Hancock, *J. Chem. Soc., A.*, 2054 (1967).
(2) J. K. Stille and R. A. Morgan, *J. Am. Chem. Soc.*, **88**, 5153 (1966).
(3) It was also noted that only 2 molar equiv of triphenylphosphine was necessary to effect a complete reaction on the olefinic bond to give a product whose nmr spectrum resembled that of II. However, we were unable to obtain the product in pure form.
(4) All new compounds described here gave satisfactory elemental analyses (within 0.5% unit of the calculated value). The nmr spectra were recorded at 60 Mcps in deuteriochloroform. The infrared spectra were recorded in neat form for the liquids and in KBr for the solids.
(5) J. D. Roberts, E. R. Trumbull, Jr., W. Bennett, and R. Armstrong, *J. Am. Chem. Soc.*, **72**, 3116 (1950).
(6) S. J. Cristol, W. K. Seifert, D. W. Johnson, and J. B. Jurak, *ibid.*, **84**, 3918 (1962).
(7) S. J. Cristol, J. K. Harrington, and M. S. Singer, *ibid.*, **88**, 1529 (1966).
(8) D. J. Thecker and J. P. Henry, *ibid.*, **85**, 3204 (1963).
(9) R. S. Neale and E. B. Whipple, *ibid.*, **86**, 3130 (1964).

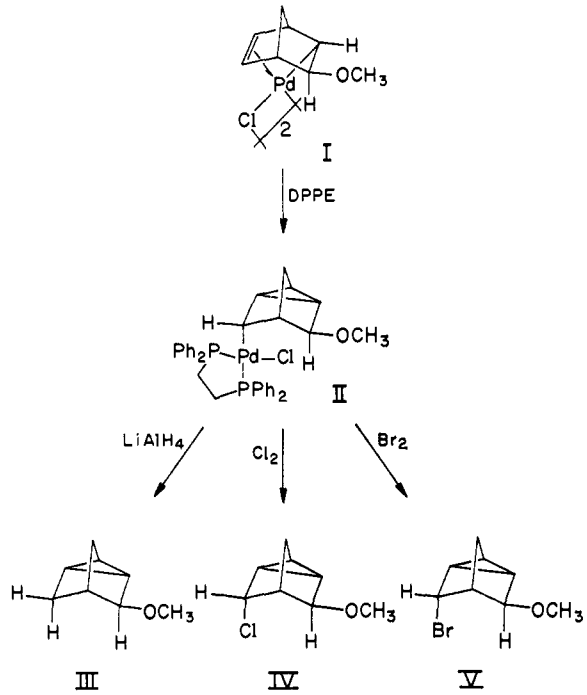
Table I. Physical Parameters of Nortricyclene Derivatives



Structure	$n^{21}D$	Nmr, δ, ppm OCH3	Ha	Hb	Infrared, cm^{-1}
II (X = DPPE·PdCl)		3.18 s	3.87 t[a]	~0.8 m	816, 3045
III (X = H)		3.26 s	3.39 t	1.15 m	810, 3050
IV (X = Cl)	1.4900	3.27 s	4.06 t	3.92 t	813, 3095
V (X = Br)	1.5172	3.25 s	4.06 t	3.90 t	810, 3095

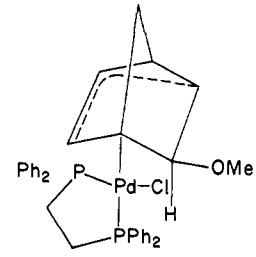
[a] All the triplets observed had $J \cong 1.5$ cps with evidence of additional splitting; t = triplet, s = singlet, m = multiplet.

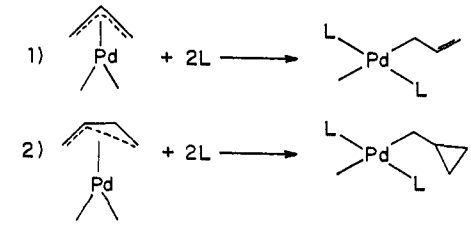
dealing with the stereochemistry at these positions. These studies have shown that (1) *exo* substitution at the 3 position has a negligible effect on the chemical shift of the 5-*exo* hydrogen, and (2) *endo* substitution at the 3 position produces a substantial (~0.4–1.0 ppm) paramagnetic shift in the 5-*endo* hydrogen. This "nearest-neighbor" shift has been well documented in other systems.[10]



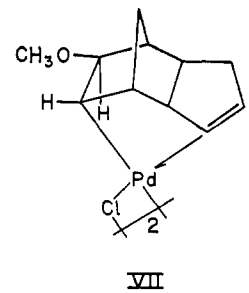
The assignments of the C*H*–halogen and thence the C*H*–OCH_3 bands in the nmr spectra were made by employing the first correlation discussed above in conjunction with the known chemical shifts of 3-*endo*-halo-substituted nortricyclenes. It may be noted in Table I that the C*H*–OCH_3 chemical shifts in compounds II, IV, and V are substantially larger than that of the parent, III. This paramagnetic shift strongly implies that all three derivatives have a 3-*endo* substitution pattern. Thus, it appears likely that the halogen cleavage reactions described here involve a *complete retention* of configuration at both the 3 and 5 positions.

It has been suggested[1] that I may be more accurately formulated as a π-homoallylic system (VI). Support for this suggestion may be found in our work if the analogy between the reactions of phosphines with π-allylic and π-homoallylic systems is valid. In the former reaction a delocalized system is converted to a double bond[11] (eq 1) while in the latter a three-membered ring (eq 2) would be formed.





Finally, a preliminary study[12] has shown that the corresponding methoxy(*endo*-dicyclopentadiene)palladium complex (VII), which cannot exist as a π-homoallylic system, reacts with DPPE to give an unstable palladium compound which has retained the olefinic bond according to nmr analysis.



(10) A. D. Cross and I. T. Harrison, *J. Am. Chem. Soc.*, 85, 3223 (1963).

(11) J. Powell, S. D. Robinson, and B. L. Shaw, *Chem. Commun.*, 78, (1965).

(12) Unpublished results.

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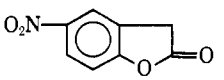
The α-Chymotrypsin-Catalyzed Hydrolysis of Lactones[1]

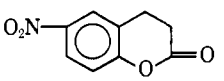
Sir:

α-Chymotrypsin, a pancreatic protease and esterase, was recently shown to react rapidly and stoichiometrically with aromatic five-membered sultones.[2] The sultones contain a *cis* ester function. Since aliphatic *cis* esters are much more reactive toward hydroxide ion than their *trans* ester analogs,[3] while the predominant configuration of chymotrypsin substrates is the planar *trans* form, it was of interest to determine whether the active site of chymotrypsin could react also with the *cis* carboxylic ester analogs of the sultones. The comparison of the reactivity of chymotrypsin toward equivalent *cis* and *trans* esters could then yield valuable information concerning the mechanism and the specificity of the enzyme-catalyzed reaction.

The kinetics of acylation were measured on a Durrum-Gibson stopped-flow spectrophotometer at 390 mμ for I and 332.5 mμ for II (the apparent isosbestic point of the acyl enzyme and the product acid) in the neutral pH range in the presence of excess enzyme. From the data good pseudo-first order rate constants can be calculated (k_{exptl}) which obey the equation $k_{exptl} = k_2E_0/(E_0 + K_s)$.



I



II

Thus by plotting $1/k_{exptl}$ *vs.* $1/E_0$ we determine k_2 and K_s (Table I). The chromophore of the acyl enzyme derived from lactone II showed a single ionization constant, $pK = 7.9$; λ_{max} 410 mμ (ϵ_{max} 14,200). In contrast, the ionization behavior of the phenolic group in the acyl enzyme derived from I is identical with that seen previously for the sulfonyl enzyme formed from the analogous sultone.[2] The pH dependency of the spectrum yields (numbered according to Scheme II of ref 2) $pK_1 = 7.31$; $pK_2 = 7.30$; $pK_3 = 8.14$; $pK_4 = 8.15$; λ_{max} 390 mμ (ϵ_{max} 13,700).

A qualitative difference in behavior is also observed in the deacylation of the two acyl enzymes. The acyl enzyme derived from II deacylates in a first-order reaction, yielding the product acid. The reaction rate was measured at 415 mμ and the first-order rate constant (k_3) is reported in Table I. Since k_3 is smaller than k_2, deacylation must be the rate controlling step in the overall enzymatic hydrolysis of II. This has been confirmed by measuring the kinetics under turnover conditions ($S_0 > E_0$). We observed Michaelis–Menten-type kinetics, *i.e.*, $dP/dt = k_{cat}E_0S/(S + K_m)$, and the k_{cat} determined by the use of Lineweaver–Burk plots was found to be identical within experimental error with k_3 (Table I).

The deacylation of the acyl enzyme obtained from I is quite different from that derived from II. When deacylation occurs in the presence of a great excess of methyl N-acetyl-L-tryptophanate or N-*trans*-cinnamoylimidazole which rapidly inhibit the enzyme, the sole reaction product is the original lactone in greater than 90% yield as observed at 400 mμ. The first-order rate constant of this reaction (k_4) is reported in Table I. When deacylation occurs without inhibition of the enzyme at low acyl enzyme concentration ($<10^{-6}$ *M*) a rapid equilibrium is established between the acyl enzyme, the free

Table I

Substrate[a]	$k_2/K_s \times 10^{-3}$ M^{-1} sec^{-1}	$K_m \times 10^7$ M^{-1}	$k_3 \times 10^4$ sec^{-1}	$k_4 \times 10^3$ sec^{-1}	k_2 sec^{-1}	$K_s \times 10^3$ M^{-1}	$k_{sp} \times 10^5$ sec^{-1}
I	9.0		<4	4.7	15.4[b]	1.2[b]	43.2
II	7.8	230	2100				43.5
p-Nitrophenyl phenylacetate (III)	140	0.57[f]	80[c]				8.41
p-Nitrophenyl *m*-nitrophenylacetate (IV)	415	0.013[f]	5.6				11.2
p-Nitrophenyl β-phenylpropionate[d] (V)	560[d]		1100				2
p-Nitrophenyl acetate[e] (VI)	2.8	11	31		3	1.2	1.2

[a] Rate data were determined at pH 7.2 and 25° in 0.05 *M* phosphate buffer containing 0.2 *M* KCl except where noted otherwise. [b] These data were obtained from runs done at pH 8.06 and 25° in 0.025 *M* Ammediol buffer. [c] A plot of the rate constants for the deacylation of phenylacetylchymotrypsin *vs.* pH fits a sigmoid curve with a p*K* of 7.25. [d] Calculated from F. J. Kézdy, J. Feder, and M. L. Bender, *J. Am. Chem. Soc.*, **89**, 1009 (1967). [e] F. J. Kézdy and M. L. Bender, *Biochemistry*, **1**, 1097 (1962). [f] Calculated from k_3 and k_2/K_s of Table I using the relation $K_m = K_sk_3/k_2$.

By analogy with the sultones and because of the favorable spectral properties of the reaction products, lactones I and II were chosen as the substrates.[4] We found that I and II react readily with α-chymotrypsin, producing relatively stable intermediates with concomitant formation of nitrophenol chromophores. Gel filtration on Sephadex G-25 at pH 5 showed that the intermediates had lost their catalytic activity toward N-acetyl-L-tryptophan methyl ester and that the chromophores are covalently attached to the enzyme. These facts indicate that the intermediates are acyl enzymes.

(1) This research was supported in part by grants from the National Institutes of Health.

(2) J. H. Heidema and E. T. Kaiser, *J. Am. Chem. Soc.*, **89**, 460 (1967); **90**, 1860 (1968).

(3) R. Huisgen and H. Ott, *Tetrahedron*, **6**, 253 (1959).

(4) These compounds were prepared by nitration in concentrated sulfuric acid at −15° from the corresponding unsubstituted lactones, which were purchased from Aldrich Chemical Co. Compound III of Table I was prepared from *p*-nitrophenol and the corresponding acid by the methods of Smiles: B. T. Tozer and S. Smiles, *J. Chem. Soc.*, 1897 (1938). Compound IV was prepared from sodium *p*-nitrophenolate and the corresponding acid chloride in dioxane. I had mp 189–189.5°; II had mp 130–130.7°; III had mp 62–63°; IV had mp 112°. The elemental analyses, ir, uv, and nmr spectra, and analyses of the hydrolysis products were in good agreement with the structures indicated.