toward sp^3 hybridization. The normal carbon isotope effect must result from the weakening of vibrational frequencies as the carbon bonding moves from a double to a single bond.

Acknowledgment. We wish to thank Dr. Ennio Ciuffarin for assistance at the beginning of this work and Dr. Fred J. Impastato of the Ethyl Corporation, Baton Rouge, La., for some of the nmr measurements.

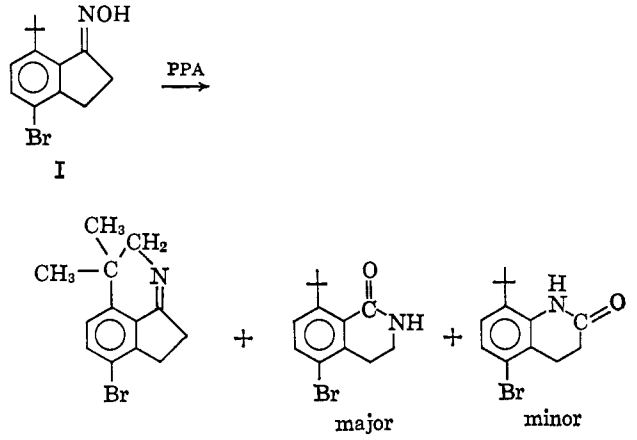
Further Studies of Bond Insertion and Nonstereospecific Beckmann Rearrangements in 7-Alkyl-1-indanone Oximes[1]

Peter T. Lansbury[2a] and Norman R. Mancuso[2b]

Contribution from the Department of Chemistry, State University of New York at Buffalo, Buffalo, New York 14214. *Received October 2, 1965*

Abstract: The reaction of 8-*t*-butyl-5-bromo-1-tetralone oxime (II) with polyphosphoric acid results only in Beckmann rearrangement with aryl migration and no C–H bond insertion, as had been observed with 7-*t*-butyl-4-bromo-1-indanone oxime (I). Both 4,7-dimethyl-1-indanone oxime (IV) and 4,7-diethyl-1-indanone oxime (IX) undergo C–H bond insertion at the benzylic carbon atom. The strained imines expected from these reactions were not isolable but were converted to acylated amino ketones for identification. Lactams resulting from Beckmann rearrangement accompanied the above iminium ion insertion products but the predominance of alkyl migration *via* net *cis* migration was of particular novelty. Mechanistic aspects of the above Beckmann reactions, as well as related Schmidt reactions and hydrazone diazotizations, are discussed. It is concluded that bond insertion and nonstereospecific rearrangement of 1-indanone derivatives is attributable to iminium ion intermediates.

Recently we studied the Beckmann and Schmidt reactions of 4-bromo-7-*t*-butyl-1-indanone and its oxime (I), in connection with our search for intramolecular alkyl group migrations between two nonbonded atoms.[1] The above compound was chosen[1] because of the rigid juxtaposition of the *t*-butyl group and the incipient iminium cation, because oxime fragmentation seemed unlikely and also because aryl migration to nitrogen was expected to be greatly retarded as a resultant of torsional strain. The usual Beckmann rearrangement in polyphosphoric acid (PPA) was in fact largely replaced by formation of a basic product which proved to be the result of insertion by the intermediate iminium cation into a proximal C–H bond.



It was also interesting to find that the major lactam obtained was that derived from alkyl migration,[1] although 1-tetralone oxime (as well as other arylalkyl ketoximes) gives mainly the lactam resulting from aryl migration.[3] We then sought to extend our investigation of the insertion reaction to include the following questions. (1) Would bond insertion into the *t*-butyl group (giving a six-membered cyclic imine ring) occur if the oxime group were incorporated into a flexible tetralone ring, rather than the rigid indanone? (2) Would replacement of 7-*t*-butyl by a 7-methyl group in a 1-indanone oxime result in bond insertion to give a highly strained five-membered cyclic imine ring? (3) If insertion at a benzylic carbon did in fact occur, would attack by the iminium cation on a 7-ethyl group occur at the α- or β-C–H bond? In addition to the above aspects of the insertion reaction, we wished to further elucidate the conditions necessary for observing predominant alkyl migration in Beckmann and Schmidt reactions of 2,3-benzcycloalkanones, since our earlier results[1] suggested nonstereospecificity in a reaction previously considered to be a stereospecific *trans* migration.[4]

In this paper the Beckmann and Schmidt reactions of 5-bromo-8-*t*-butyl-1-tetralone, 4,7-dimethyl-1-indanone, and 4,7-diethyl-1-indanone are discussed. These systems, plus several additional selected compounds, were chosen to provide information on the points raised above.

Results and Discussion

In order to prepare 5-bromo-8-*t*-butyl-1-tetralone we converted β-(2-bromo-5-*t*-butylphenyl)propionic acid[1] into the diazoketone and transformed the latter into γ-(2-bromo-5-*t*-butylphenyl)butyric acid by the photo-

(1) For the previous paper in this series, see P. T. Lansbury, J. G. Colson, and N. R. Mancuso, *J. Am. Chem. Soc.*, 86, 5225 (1964).

(2) (a) Alfred P. Sloan Foundation Fellow, 1963–1967; (b) DuPont Teaching Fellow, 1964–1965.

(3) L. J. Briggs and G. C. Ath, *J. Chem. Soc.*, 456 (1937); (b) P. T. Lansbury and N. R. Mancuso, *Tetrahedron Letters*, 2445 (1965).

(4) P. A. S. Smith, "Molecular Rearrangements," Vol. 1, P. deMayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, pp 457–528, and references cited therein.

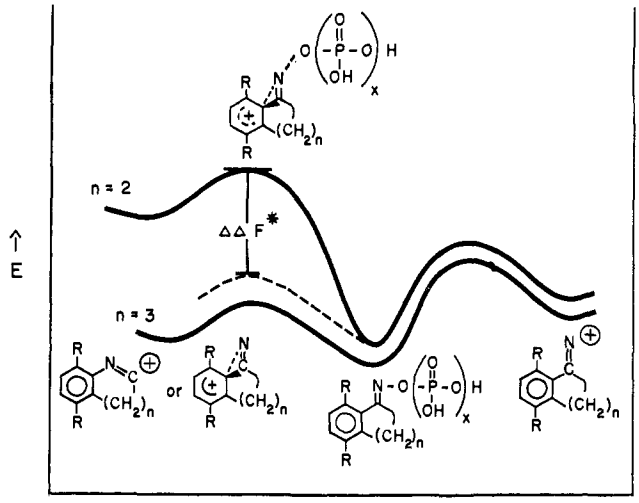
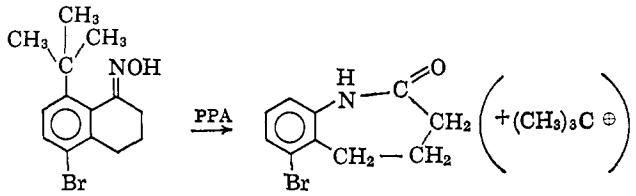


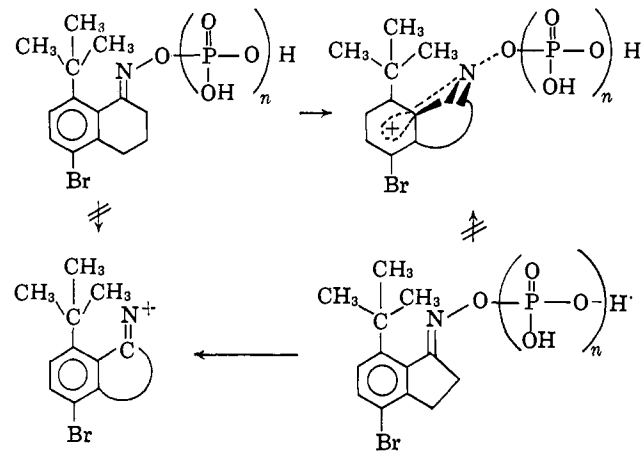
Figure 1. Energy profile diagram for reaction of 2,3-benzcycloalken-1-one oxime polyphosphates. $\Delta\Delta F^*$ indicates torsional strain in transition state for aryl participation in indanones.

chemical Wolff rearrangement.[5] Friedel–Crafts cyclization of the acid produced the desired tetralone in poor yield. Analysis and nmr verified the structure of the product, particularly the appearance of an AB quartet in the nmr spectrum centered at 7.32 ppm with $J \sim 8$ cps, which indicated the presence of two *ortho* aromatic protons. Thus no intramolecular *t*-butyl migration occurred during the final acylation step. 5-Bromo-8-*t*-butyl-1-tetralone oxime (II) which formed with great difficulty, due to steric hindrance around the carbonyl group of I, was then treated with PPA in the usual manner.[1] No basic products, as would result from bond insertion, were found in the reaction product; in fact a single lactam which contained no *t*-butyl group[6] was obtained (97% yield), as indicated by infrared and nmr spectra. This product was shown to be 6-bromo-3,4-dihydrohomocarbostyril (III) by hydrogenolysis to 3,4-dihydrohomocarbostyril which was identified by comparison with an authentic sample.



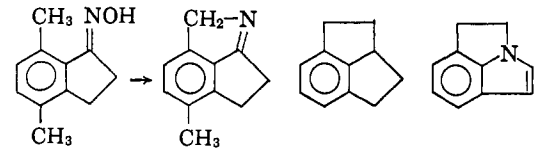
II III

It is obvious that the oxime insertion reaction, as well as the appearance of lactam from alkyl migrations, can occur only when the normal Beckmann rearrangement is retarded by intramolecular rigidity, as was the situation with 4-bromo-7-*t*-butyl-1-indanone oxime[1] (I). In that case, circumstances were favorable for iminium ion formation,[7] whereas the more flexible tetralone oxime II probably rearranged with aryl-assisted ionization[8] of oxime polyphosphate and thus without formation of an iminium cation intermediate which appears to be responsible for the insertion and nonstereospecific rearrangement.[9] The mechanistic scheme below can be



conveniently represented in an energy profile diagram (Figure 1).

We next proceeded to determine whether iminium ion bond insertion would occur into a 7-methyl group of a 1-indanone oxime. While it appeared that the expected insertion product from the readily accessible 4,7-dimethyl-1-indanone oxime (IV) might be excessively strained, we were encouraged to find that similar fused ring compounds (V and VI) had been prepared by Rapoport and co-workers.[10] When IV was treated



IV V VI

with PPA in the usual manner, *ca.* 25% of a basic product was obtained, but numerous attempts to prepare crystalline salts of the supposed imine led only to isolation of intractable tars or amorphous impure salts, as did attempted formic acid reduction. Furthermore, reactions with methyllithium and complex metal hydrides resulted only in recovery of impure material, suggesting that the imine had opened during work-up, leading to a polymerizable amino ketone which would undergo simple proton abstraction by $LiAlH_4$ or methyllithium. The resultant metal amides would probably exist in cyclic form as the dimetalated α-aminohydrin prior to hydrolysis. Finally, a pure derivative suitable for structure studies was obtained

(5) J. Meinwald and P. G. Gassman, *J. Am. Chem. Soc.*, **82**, 2857 (1960).

(6) Although it is not known whether de-*t*-butylation occurred in II or lactam expected from simple rearrangement, it is considered that the latter compound in the unprotonated form is a more logical substrate for electrophilic protonation–dealkylation.

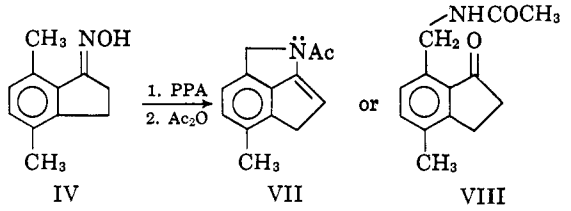
(7) Even in nonrigid systems, aryl participation in Beckmann rearrangements carried out in PPA is much less than in other media. For example, $\rho = -0.25$ for acetophenone oximes in PPA (D. E. Pearson and R. M. Stone, *J. Am. Chem. Soc.*, **83**, 1715 (1961)) whereas the corresponding *meta*- and *para*-substituted acetophenone oxime picrates undergo thermal Chapman rearrangement with $\rho = -4.1$ (R. Huisgen, J. Witte, H. Walz, and W. Jira, *Ann.*, **604**, 191 (1951).)

(8) R. Huisgen, J. Witte, and I. Ugi, *Chem. Ber.*, 90, 1844 (1957).

(9) An additional indication that proximity effects alone were an insufficient condition to cause bond insertion was the reaction of cyclodecanone oxime with PPA. Although many transannular reactions occur in medium-ring compounds (for reviews see (a) V. Prelog, *Angew. Chem.*, **70**, 145 (1958); *Rec. Chem. Progr.*, **18**, 247 (1957); (b) J. Sicher, "Progress in Stereochemistry," Vol. 3, P. B. D. de la Mare and W. Klyne, Ed., Butterworth and Co. (Publishers) Ltd., London, 1962, p 238), particularly cyclodecanes, no bicyclic imine was formed, the sole isolable product being the ring-expanded lactam.

(10) (a) H. Rapoport and J. Z. Pasky, *J. Am. Chem. Soc.*, **78**, 3788 (1956); (b) H. Rapoport and J. R. Tretter, *ibid.*, **80**, 5574 (1958).

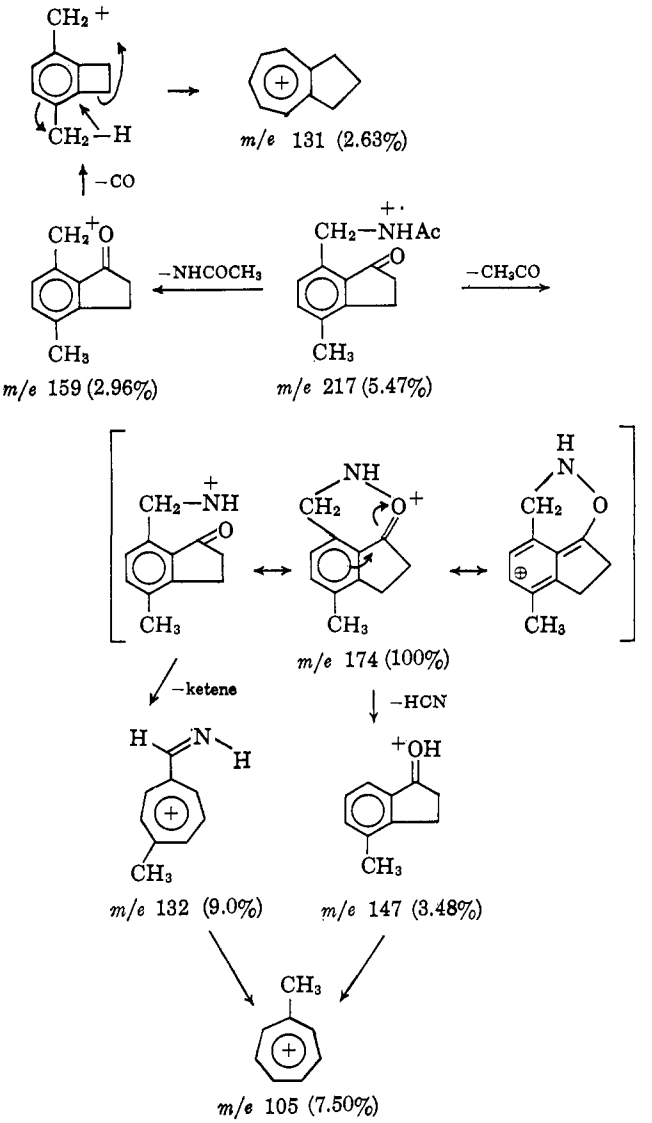
when crude perchlorate salt, isolated from a PPA reaction of IV followed by "fast work-up,"[1] was acetylated in benzene–triethylamine solution. The acetyl derivative was considered to have structure VII or VIII, depending on whether an imine or amino ketone perchlorate was at hand. That structure VIII



IV VII VIII

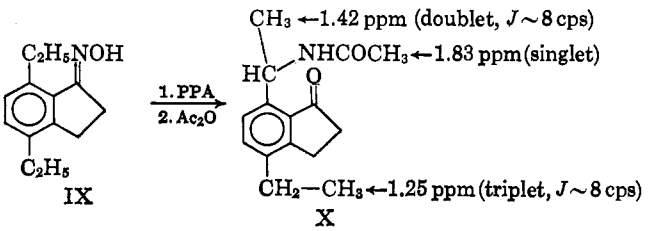
was correct was unambiguously shown by a series of spectral studies. First, an infrared spectrum of VIII (Nujol mull) showed *two* carbonyl bands, one at 1705 cm^{-1} (1-indanone carbonyl) and the second at 1640 cm^{-1} (amide). Second, the ultraviolet spectrum of VIII, λ_{max}^{EtOH} 253 mμ (ϵ 10,4500), and 303 (ϵ 2880), was remarkably similar to that of 4,7-dimethyl-1-indanone and several other 1-indanones.[11] The nmr spectrum[11] was entirely consistent, showing *inter alia* two methyl signals, one at 1.83 ppm due to the acetyl group and one at 2.25 ppm due to the C_4-methyl group in VIII (in 4,7-dimethyl-1-indanone, the C_4-CH_3 group had δ = 2.25 ppm and the C_7-CH_3 group had δ = 2.50 ppm). Thus net bond insertion at the C_7-CH_3 group is verified. Final proof of structure VIII was obtained from the mass spectrum[11] which provided the correct molecular formula of $C_{13}H_{15}NO_2$ from the M^+ peak at 217 and the isotope peaks. The most intense high mass fragment ions came at *m/e* 174 (the base peak), 159, 147, 132, 131, and 105 and a plausible fragmentation mechanism, which was substantiated by the expected metastable peaks,[11] is formulated below (relative peak intensities given in parentheses). Although acetamides generally eliminate ketene under electron impact[12] the predominant fragmentation of M^+ gave an acetyl radical and the *m/e* 174 fragment, which can be seen to provide ample resonance stabilization for the positive charge. It is thus well established that VIII is the acetylated derivative of the insertion product from IV, which underwent facile hydrolytic ring opening under conditions where 1,8-ethano-7-bromo-4,4-dimethyl-3,4-dihydroisoquinoline derived from I did not.[1]

Since I underwent oxime insertion to form a six-membered ring imine and IV reacted to initially produce a five-membered ring imine, we were interested to determine which course insertion would take in a compound such as 4,7-diethyl-1-indanone oxime (IX), where both α- and β-C–H bonds were available. Although attack at the methyl group might lead to a more stable product, the insertion of the high-energy iminium cation should have a "reactant-like" transition state and give the kinetically controlled product, thus making product stabilities of little apparent consequence. Oxime IX was prepared in several steps from *p*-diethylbenzene (see the Experimental Section). Beck-



mann rearrangement of IX in PPA, as with I and IV, again afforded *ca.* 20–25% of an amino ketone isolated as the acetyl derivative (X), about 30% of a new ketone (XI), and the two possible isomeric lactams. By means of column chromatography and preparative vpc, small samples of each compound were obtained for analysis and spectral examination. The compounds were not however obtained in crystalline form.

The infrared spectrum of X, like that of VIII, showed a 1-indanone carbonyl band at 1706 cm^{-1} and amide carbonyl absorption at 1656 cm^{-1}, in addition to N–H stretching (~3300 cm^{-1}). The ultraviolet spectrum of X was similar to that of VIII, showing λ_{max}^{EtOH} 254 mμ (ϵ 8030) and 302 mμ (ϵ 2760). The above data do not prove the *position* of insertion, but this is readily established by nmr as being the α-C–H bond. *Three*



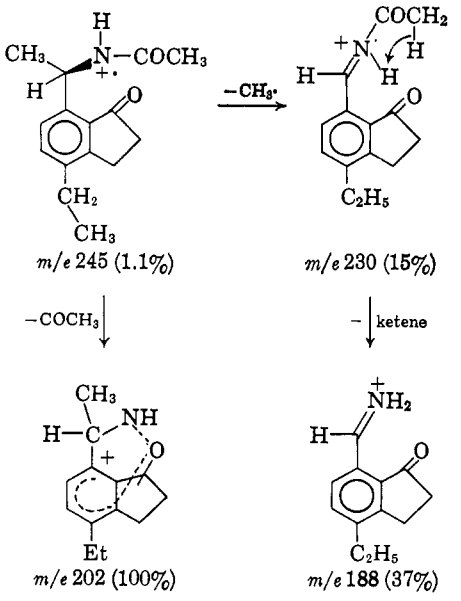
IX X

methyl peaks of the expected multiplicity were observed (as indicated in the above formula) and the

(11) Extensive spectral data are given in the Ph.D. dissertation of N. R. Mancuso, State University of New York at Buffalo, 1966.

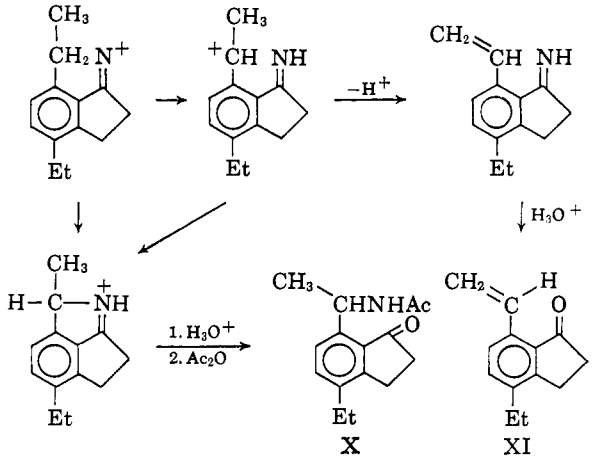
(12) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1964, p 80 ff.

remaining proton signals were at the expected positions and of proper intensity. Had insertion occurred at the β-C–H bond, only two methyl signals would have appeared in the nmr spectrum, in addition to other differences. The mass spectrum again confirmed structure X, showing a weak M^+ peak at 245 and the very intense base peak at M − 43 (loss of acetyl), from which the formula $C_{13}H_{16}NO$ was deduced for the *m/e* 202 fragment ion. Although the fragmentation pattern for X resembled that for VIII in some respects,[11] an important different path involved formation of fragment ions having *m/e* 230 and 188, whose mode of formation may be formulated as shown (relative peak intensities in parentheses). Since much more ketene



is formed in the electron-impact fragmentation of X than in VIII and the respective 4,7-dialkyl-1-indanones, the postulation of the M − 15 ion (loss of CH_3) as the main source of ketene is reasonable and in fact proven by a metastable ion at *m/e* 153.9 (calculated for 230 → 188 + 42: 153.8).[13]

It was mentioned that reaction of IX produced a new ketone (XI) and this proved to be 4-ethyl-7-vinyl-1-indanone. Its structure was verified by elemental analysis, infrared (conjugated 1-indanone carbonyl at 1695 cm^{-1}), ultraviolet[14] λ_{max}^{EtOH} 271 mμ (ε 11,000) and 321 mμ (ε 4120), and nmr spectra. Most significant in the nmr spectrum of XI was the *single* methyl signal at 1.25 ppm (triplet, $J \sim 8$ cps), whose chemical shift is similar to the analogous C_4-ethyl signal in X, and the characteristic ABX spectrum of the C_7-vinyl group (J_{AX} = 18 cps, J_{BX} = 11.5 cps, J_{AB} = 1.5 cps). The A and B quartets are situated at *ca.* 5.3–5.7 ppm, whereas the X portion of the spectrum was located at *lower* field (~7.9 ppm) than the aromatic protons, indicating that H_x was undergoing extensive deshielding by both the aromatic ring and the carbonyl group. The formation of XI is significant because it cannot arise from iminium ion insertion (which may be the mechanism for forming imine) but more likely arises



from a 1,5-hydride shift followed by proton loss. As shown in the above mechanistic scheme, the imine product could arise either by direct electrophilic bond insertion or by ring closure after 1,5 shift of a benzylic hydrogen.[15] The absence of neophyl rearrangement in the case of I had led us to prefer direct insertion in that system;[1] this was especially favored since no *benzylic* hydrogens were present in I.

At this stage we had answered the questions confronting us about the oxime insertion reaction (see introduction) and one can safely conclude that the necessary requirements are most stringent; a rigid molecular array, such as the 1-indanones, where Beckmann rearrangement is greatly hindered,[7] is needed in addition to a C–H bond in close proximity to the incipient iminium ion. It is likely that insertion into C–C bonds, leading to net alkyl migration between unbonded atoms, will not be observable since this did not occur in I, although in IV and IX the corresponding benzylic C–H attack did occur.

We now direct our attention to the lactams accompanying bond insertion during Beckmann reactions of I, IV, and IX, as well as the related Schmidt reaction[4] and hydrazone diazotizations[16] in PPA.[3a] A number of 1-tetralones were also studied,[3b] in spite of the absence of bond insertion in any of these reactions. The total yields of lactams and the relative percentages of aryl and alkyl migration products are shown in Table I. The Beckmann reactions were run for *ca.* 2–10 min at 110–130° and the Schmidt and hydrazone diazotization reactions at 50–60° for 2–5 hr. All reactions were worked up in the same manner and the products themselves were shown to be stable under reaction conditions. The lactams were known compounds in most cases, but new compounds were characterized by analytical and spectral data. In particular, lactams resulting from aryl migration (dihydrocarbostyrils and homodihydrocarbostyrils) generally showed higher frequency carbonyl bands in the infrared than the isomers arising from alkyl migration (dihydroisocarbostyrils, etc.). Furthermore nmr spectra were diagnostic, since in the former compounds, methylene protons adjacent to amide *carbonyl* always absorbed at higher field than methylene protons adjacent to amide *nitrogen*.[1] In addition, the ultraviolet

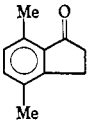
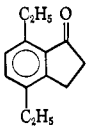
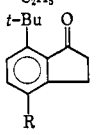
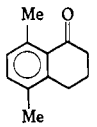
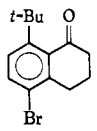
(13) K. Biemann, "Mass Spectrometry: Organic Chemical Applications," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 153–157.

(14) The indicated maxima are both bathochromically shifted by 15–18 mμ from the corresponding peaks in 4,7-diethyl-1-indanone, indicating extended conjugation.

(15) Experiments designed to differentiate between these possibilities are in progress for IV as well as IX.

(16) D. E. Pearson, K. N. Carter, and C. M. Greer, *J. Am. Chem. Soc.*, 75, 5905 (1953).

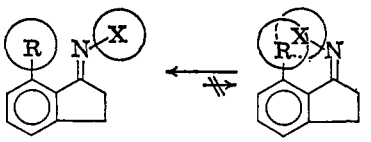
Table I. Migration Aptitudes in Ketone Rearrangements to Lactams

Ketone	Reaction	% aryl migration[a]	% alkyl migration[a]	% alkyl/ % aryl	Yield,[b] %
	Schmidt	76	24	0.3	60
	Beckmann	90	10	0.1	20
	Hydrazone diazotization	91	9	0.1	77
	Schmidt	37	63	1.7	65
	Beckmann (IV)	34	66	1.9	66
	Hydrazone diazotization	22	78	3.5	36
	Beckmann (IX)	27	73	2.7	20
	Schmidt	29	71	2.5	35
	Schmidt (XII)	15	85	5.7	50
	Schmidt (XIII)	13	87	6.7	25
	Beckmann (XII) XII, R = Br XIII, R = H	19	81	4.3	25
	Schmidt	87	13		45
	Beckmann	99	1		65
	Hydrazone diazotization	100	...		40
	Schmidt	69	31		62
	Beckmann	99	1		92
	Diazotization	88	12		93
	Beckmann	100	...		97[c]

[a] Based on lactams only; vpc yield data are considered accurate to better than ±2%. [b] Based on starting material. [c] Product is de-*t*-butylated lactam.

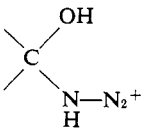
spectra of the lactams derived from IV and IX were consistent with those of the parent compound, 3,4-dihydrocarbostyril and 3,4-dihydroisocarbostyril. The spectral data[11] are summarized in Table II.

As we noted previously,[3b] in the indanones there is a marked tendency for alkyl migration (leading to dihydroisocarbostyrils) to predominate over aryl migration (giving dihydrocarbostyrils), which is greatest in those compounds where the configuration of the oxime (and iminodiazonium ions) is most certainly antiaryl.



Even isomerization of oximes prior to rearrangement[17] could not account for the per cent alkyl/per cent aryl migration ratio being largest in 7-*t*-butyl-1-indanone reactions, nor is the concept of *cis* migrations a satisfactory one. Since the above 7-alkyl-1-indanones have been shown to give iminium cation insertion products, it is entirely reasonable to also invoke this intermediate in the rearrangements leading to the isomeric lactams in a nonstereospecific manner.[3b] The increase in alkyl migration as the 7-alkyl substituent becomes more bulky can be ascribed to steric inhibition of aryl migration (in the azacyclopropenium ion that forms in the transition state). Contrary to 7-alkyl-1-indanone rearrangements, the corresponding Beckmann reactions of 8-alkyl-1-tetralones give predominantly lactams derived from aryl migration, regardless of the steric bulk of the 8-alkyl group (Table I), and no bond insertion products. It is reasonable to assume that aryl participation is now more favorable energetically (less torsional strain in the transition state[7]) and that discrete iminium cations are not formed in the tetralones (see above). Such participation apparently outweighs steric hindrance from the 8-alkyl groups in determining product distributions.

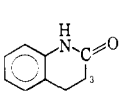
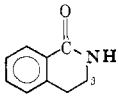
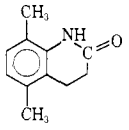
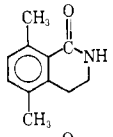
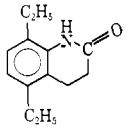
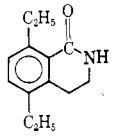
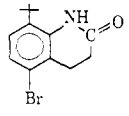
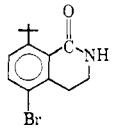
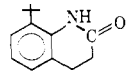
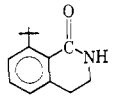
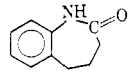
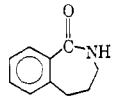
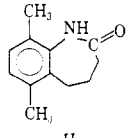
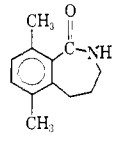
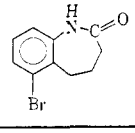
Finally, there is some indication that the above Schmidt reactions may proceed, in part at least, by direct rearrangement of α-azidohydrins (the so-called Newman mechanism[18]) to lactams, rather than prior dehydration to iminodiazonium ions. This contention is fostered by the noticeably higher lactam yields from Schmidt reactions of 1-indanones, as compared with Beckmann reactions run under comparable conditions, which would be understandable since less torsional strain would arise in the migration transition



(17) *Cf.* R. T. Conley and T. M. Tencza, *Tetrahedron Letters*, **No. 26**, 1781 (1963).

(18) M. S. Newman and H. L. Gildenhorn, *J. Am. Chem. Soc.*, **70**, 317 (1948).

Table II. Infrared, Ultraviolet, and Nmr Spectral Properties of Lactams from Rearrangement of Indanones and Tetralones

	$\nu_{C=O}$, cm^{-1}[a]	δ_{C_3}, ppm[b]	λ_{max}^{EtOH}, mμ (ϵ)		$\nu_{C=O}$, cm^{-1}[a]	δ_{C_3}, ppm[b]	λ_{max}^{EtOH}, mμ (ϵ)
	1675	2.9	250 (12,000)		1657	3.5	232 (10,500)
	1672	2.6	253 (10,700)		1658	3.5	238 (6600)
	1678	...	253 (8900)		1661	...	239
	1690	...			1665	...	
	1689	...			1658	3.4	
	1666	2.4			1658	3.1	
	1664[c]	2.2			1672[c]		
	1667	2.6					

[a] All infrared spectra were Nujol mulls. [b] Approximate center of multiplet (see ref 11 for spectra of the C_3-methylene protons). [c] The infrared carbonyl frequencies are reversed here, but this structure was verified by hydrolysis to the amino acid and comparison of its melting point with that reported: G. Schroeter, *et al.*, *Ber.*, **63**, 1308 (1930).

states when C_1 is tetrahedral. There are also some notable differences in product distributions when the two reactions are applied to the 1-tetralones (Table I), and cases are known where one substrate gives entirely different products.[4]

From these studies we can conclude that the generalization of *trans* stereochemistry in Beckmann and Schmidt reactions must be used cautiously in predicting rearrangement products and assigning oxime configurations, especially in a compound liable to form iminium cations. If such is the case, one can in fact expect net bond insertion to become a competitive product-forming path. Whether such reactions involve direct bond insertion by >=N$^+$ or "transannular" hydride shifts followed by ring closure remains to be ascertained.[15]

Experimental Section[19]

Preparation of Compounds. The following were prepared by methods in the literature and checked with reported physical properties: 1-indanone oxime,[20a] 1-tetralone oxime,[20b] 4,7-dimethyl-1-indanone,[21] 5,8-dimethyl-1-tetralone[21] and its oxime,[22] cyclodecanone oxime,[23] 3,4-dihydrocarbostyril,[1] 3,4-dihydroisocarbostyril,[1] 3,4-dihydrohomocarbostyril,[3a] and 6,9-dimethyl-3,4-dihydrohomocarbostyril.[22]

Homo-3,4-dihydroisocarbostyril was prepared in three steps from 3-phenylpropionitrile, the first being reduction to 3-amino-1-phenylpropane by sodium borohydride and aluminum chloride in diglyme, according to the procedure of Brown,[24] in 71% yield, bp 78–80° (1 mm) (lit.[25] bp 75–80° (1 mm)). Treatment of the

(19) Melting points, determined on a Mel-Temp capillary tube apparatus, and boiling points are uncorrected. Infrared spectra were determined on a Beckman IR-5A spectrometer, using the 1603-cm^{-1} band of a polystyrene film for calibration. Ultraviolet spectra were determined in either a Beckman DK-2 or a Perkin-Elmer 202 spectrometer. Nuclear magnetic resonance spectra were obtained on a Varian Associates A-60 spectrometer in carbon tetrachloride or chloroform-*d* solvents with tetramethylsilane as internal standard. Vapor phase chromatographic analyses were determined on either F and M 300, Aerograph A-90-P, or Aerograph A-700 instruments and helium was carrier gas. Relative peak areas were determined by the triangle method or by cutting and weighing. Mass spectra were determined on a Hitachi-Perkin-Elmer RMU-6A instrument. Carbon–hydrogen analyses were by Dr. A. Bernhardt, Mulheim, Germany. Alumina used for column chromatography was Merck reagent grade aluminum oxide.

(20) "Dictionary of Organic Compounds," J. R. A. Pollock and R. Stevens, Ed., Oxford University Press, New York, N. Y., 1965: (a) Vol. 3, p 1842; (b) Vol. 2, p 1040.

(21) G. Baddeley, *J. Chem. Soc.*, 232 (1944).

(22) G. Schroeter, *et al.*, *Ber.*, **63**, 1321 (1930).

(23) A. C. Cope, D. C. McLean, and N. A. Nelson, *J. Am. Chem. Soc.*, 77, 1628 (1955).

(24) H. C. Brown and B. C. Subba-Rao, *ibid.*, **78**, 2582 (1956).

(25) "Dictionary of Organic Compounds," Vol. 4, J. R. A. Pollock

amine with an equimolar quantity of ethyl chloroformate in ether–pyridine for 3 hr at room temperature followed by conventional hydrolysis and work-up gave ethyl N-(3-phenylpropyl)carbamate as a pale yellow oil, bp 144–147° (1.5 mm).

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.27. Found: C, 69.70; H, 8.32.

Cyclization of the above carbamate was effected in PPA at 110° for 2 hr. Hydrolysis and work-up yielded an analytical sample of homo-3,4-dihydroisocarbostyril by means of preparative vpc, using a 5-ft 20% QF-1 fluorosilicone on Chromosorb W column at 200°.

Anal. Calcd for $C_{10}H_{11}NO$: C, 74.50; H, 6.87. Found: C, 74.38; H, 7.02.

7-*t*-Butyl-1-indanone was prepared from 4-bromo-7-*t*-butyl-1-indanone by hydrogenolysis over palladium on carbon in ethanol–triethylamine,[1] mp 41–43.5°.

Anal. Calcd for $C_{13}H_{16}O$: C, 82.90; H, 8.56. Found: C, 82.88; H, 8.47.

5-Bromo-8-*t*-butyl-1-tetralone was synthesized from β-(2-bromo-5-*t*-butylphenyl)propionic acid[1] by converting the latter into the acid chloride, bp 110–120° (*ca.* 5 mm), with thionyl chloride. The acid chloride was converted by excess ethereal diazomethane into the diazoketone and the latter was photolyzed[5] in aqueous dioxane. The resulting γ-(2-bromo-5-*t*-butylphenyl)butyric acid was converted to the acid chloride (by thionyl chloride) and cyclized with aluminum chloride to give crude ketone, which was purified by preparative vpc using a 5-ft 20% QF-1 on Chromosorb W column at 140°.

Anal. Calcd for $C_{14}H_{17}OBr$: C, 59.83; H, 6.10. Found: C, 59.73; H, 6.02.

5-Bromo-8-*t*-butyl-1-tetralone oxime (II), mp 152–158°, could not be obtained analytically pure but nmr (see Discussion) verified the structure.

4,7-Diethyl-1-indanone was prepared from *p*-diethylbenzene in several steps, beginning with acetylation to give 2,5-diethylacetophenone, bp 112–115° (7 mm) (lit.[26] bp 111° (6 mm)). The ketone was allowed to react with sodium hydride and diethyl carbonate in refluxing 1,2-dimethoxyethane for 24 hr followed by hydrolysis and work-up, to give ethyl α-(2,5-diethylbenzoyl)acetate, bp 120° (0.2 mm), in 77% yield.

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.67; H, 8.23.

Hydrogenolysis of the above β-keto ester according to the procedure of Johnson, *et al.*,[27] produced ethyl β-(2,5-diethylphenyl)-propionate.

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.75; H, 9.47.

Cyclization of the ester in PPA for 1 hr at 90–95° followed by hydrolysis and work-up gave 4,7-diethyl-1-indanone as a colorless oil, bp 96–98° (0.1 mm), whose infrared, nmr, and ultraviolet spectra confirmed the structure; λ_{max}^{EtOH} 254 mμ (ε 10,800), 306 mμ (ε 2800).

Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.72; H, 8.83.

The oxime (IX) had mp 137.5–139° (from methanol).

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.80; H, 8.43. Found: C, 76.86; H, 8.41.

The hydrazones required for diazotization studies were prepared by refluxing the ketone with 2 molar equiv of hydrazine hydrate in ethanol for 6–12 hr. The reaction mixture was then poured into excess ice water and the precipitated hydrazone was filtered off and recrystallized, or extracted with ether and worked up if the hydrazone did not crystallize initially. In this manner, 1-indanone yielded a yellow crystalline hydrazone, mp 83–86° (from methanol) (lit.[28] mp 84–86°), in 85% yield. 1-Tetralone hydrazone could not be obtained in crystalline form and was thus converted to the *p*-toluenesulfonylhydrazone by means of *p*-toluenesulfonyl chloride in pyridine, mp 175–178° (from ethanol).

Anal. Calcd for $C_{17}H_{18}N_2O_2S$: C, 65.00; H, 5.96. Found: C, 64.90; H, 6.00.

4,7-Dimethyl-1-indanone hydrazone, prepared in the above manner, had mp 133.5–136° (from methanol).

Anal. Calcd for $C_{11}H_{14}N_2$: C, 75.2; H, 8.10. Found: C, 75.55; H, 8.21.

5,8-Dimethyl-1-tetralone hydrazone was obtained by the general procedure as crystals, mp 69–72° (from methanol).

Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57. Found: C, 76.72; H, 8.50.

General Procedure for Rearrangement Reactions. A. Beckman reactions of oximes in PPA were carried out as described previously,[1] at temperatures of 110–130° for 5–10 min, followed by hydrolysis with stirred, ice-cold sodium hydroxide and ether mixture so that all products were immediately extracted into the ether layer.[1]

B. Schmidt reactions were carried out in PPA at 40–60° by gradual addition of sodium azide, as described previously.[1]

C. Hydrazone decompositions were performed under similar conditions of time and temperature to those used in Schmidt reactions. In a typical run, 0.5–0.8 g of hydrazone was dissolved in 20 g of PPA and heated to 50–60°. A 20% molar excess of crystalline sodium nitrite was then added in small portions during 30–60 min. After stirring the reaction mixture for an additional 1–2 hr, hydrolysis and work-up as in A and B was carried out and the amides characterized by vpc and spectral techniques.

Beckmann Rearrangement of 5-Bromo-8-*t*-butyl-1-tetralone Oxime (II) in PPA. One-tenth gram of II was heated to 145° in PPA for 1 min, then poured into ice water and worked up as usual, yielding 79 mg of crystalline product, mp 124–128°, which was homogeneous by vpc (5-ft 20% Carbowax 20M–Chromosorb W column at 175°). The absence of the *t*-butyl group in the product (III) was shown by nmr (see Discussion) and infrared (no bands at 1367 and 1395 cm^{-1}).

Anal. Calcd for $C_{10}H_{10}NOBr$: C, 50.02; H, 4.20. Found: C, 50.65; H, 4.51.

Forty milligrams of the above 6-bromo-3,4-dihydrohomocarbostyril (III) was hydrogenolyzed over palladium in ethanol–triethylamine to give 3,4-dihydrohomocarbostyril, which was identified by comparison (infrared, vpc) with an authentic sample from Beckmann rearrangement of 1-tetralone oxime.

Reaction of 4,7-Dimethyl-1-indanone Oxime (IV) with PPA. One gram of IV and 20 g of PPA were heated to 110° and kept for 5 min before hydrolysis by the fast technique[1] described above. The ether solution of products was immediately treated with 70% perchloric acid, giving 0.38 g (25%) of crude amine perchlorate which was rapidly added to a cold solution of 0.15 ml of triethylamine and 20 ml of benzene containing 0.15 g of acetic anhydride. After 90 min at room temperature, the reaction mixture was hydrolyzed and worked up, giving an oily residue after solvent removal. The oil was chromatographed over alumina, yielding the acetamide VIII upon elution with 3:1 benzene–ether. Purification by preparative vpc (4-ft 15% Versamide-900 on Chromosorb W column at 255°) gave an analytical sample, whose spectral properties are presented in the Discussion.

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96. Found: C, 71.65; H, 7.20.

The ether solution of neutral products, from which the amino ketone perchlorate had been precipitated, was worked up to give 0.55 g of isomeric lactams in the ratio *ca.* 1:2 (see Discussion). These were separated by preparative vpc on the above column. The major lactam was 5,8-dimethyl-3,4-dihydroisocarbostyril, mp 121–125°, λ_{max}^{EtOH} 238 mμ (ε 6600) and 290 mμ (ε 1700).

Anal. Calcd for $C_{11}H_{13}NO$: C, 75.39; H, 7.48. Found: C, 75.37; H, 7.52.

The minor lactam was shown to be 5,8-dimethyl-3,4-dihydrocarbostyril, mp 162–165°, λ_{max}^{EtOH} 253 mμ (ε 10,700).

Anal. Calcd for $C_{11}H_{13}NO$: C, 75.30; H, 7.48. Found: C, 75.28; H, 8.10.

The above structural assignments were supported by infrared and nmr spectral data (Table II).

Reaction of 4,7-Diethyl-1-indanone Oxime (IX) with PPA. Two grams of IX was dissolved in 25 g of PPA and heated at 120 g for 5 min. The reaction mixture was then worked up as above, except that the amino ketone perchlorate was not crystallizable and could not be filtered. Consequently, the ether solution of neutral products was decanted from the amorphous salt and the latter was washed with several portions of fresh ether, which were added to the original ether solution. Acetylation of the amino ketone as above, followed by alumina chromatography with elution by benzene–ether (2:1), achieved separation of the amide from several impurities (recovered ketone and occluded neutral products). A small amount (*ca.* 10 mg) of nearly pure acetamide X

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was obtained by preparative vpc on a 5-ft SF-96 on Chromosorb W column at 210°.

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.33; H, 7.80. Found: C, 71.76; H, 7.84.

Spectral data confirming the structure of X are detailed in the Discussion.

The ether solution of neutral products was analyzed by vpc and contained *ca.* 5% of recovered 4,7-diethyl-1-indanone, 34% of 4-ethyl-7-vinyl-1-indanone (XI), and 61% of isomeric lactams. An analytical sample of XI was obtained by preparative vpc using a 5-ft 20% Versamide 900 on Chromosorb W column at 200°.

Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.71; H, 7.76.

The minor lactam, whose structure was substantiated by nmr and infrared, was shown to be 5,8-diethyl-3,4-dihydrocarbostyril, λ_{max}^{EtOH} 253 mμ (ε 8900).

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.80; H, 8.43. Found: C, 76.98; H, 8.57.

The major lactam was 5,8-diethyl-3,4-dihydroisocarbostyril, λ_{max}^{EtOH} 239 mμ (ε 7000) and 290 mμ (ε 2000). The extinction coefficients are uncertain here because of minor impurities.

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.80; H, 8.43. Found: C, 76.49; H, 8.31.

Acknowledgment. We are grateful to the Petroleum Research Fund, administered by the Americal Chemical Society, for partial support of this research (Grant 550-A4). We are also particularly indebted to Professor D. B. MacLean of MacMaster University for running the mass spectra and aid in their interpretation.

pH Dependence of the Hydrolysis of O-Acetyl-L-mandelate Catalyzed by Carboxypeptidase A. A Critical Examination[1,2]

F. W. Carson and E. T. Kaiser[3]

Contribution from the Department of Chemistry, University of Chicago, Chicago, Illinois 60637. *Received August 6, 1965*

Abstract: The pH dependences of the kinetic constants for the hydrolysis of O-acetyl-L-mandelate catalyzed by carboxypeptidase A were studied over the range pH 5.5 to 9.0 at 25°. The data were analyzed by computer using an original statistical analytical method for the determination of competitive product inhibition constants. The value of k_{cat}/K_m was found to depend on a base of $pK_a \sim 6.9$ and on an acid of $pK_a \sim 7.5$ while the corresponding acid dissociation constants on which k_{cat} depends are 7.2 and 7.9, respectively. Possible ionizing groups in this enzyme responsible for these observations are discussed. The results also are examined in relation to previously proposed mechanisms and models for the esterolytic and proteolytic actions of carboxypeptidase A.

Carboxypeptidase A is a pancreatic, zinc-containing metalloenzyme which mediates the hydrolysis of peptides having a free carboxyl function at the terminal α-amino acid moiety and which must be of the L configuration. L-α-Acyloxycarboxylic acids also have been found to be substrates for this enzyme. Recently Vallee and co-workers[4,5] and Neurath and co-workers[6] have found a marked difference between the pH–rate profiles for ester and peptide substrates. In addition, the former group has found[4,5,7-9] that various treatments of the enzyme such as acylation, iodination, etc., lead to an increase in the esterase activity toward O-(N-benzoylglycyl)-DL-3-phenyllactic acid and to a decrease in the peptidase activity toward N-(N-carbobenzyloxyglycyl)-L-phenylalanine. These results led to the proposal that carboxypeptidase A hydrolyzes esters and peptides by different mechanisms.[4,8] If this difference were borne out by subsequent studies, it would constitute the first case in which the esterolytic and proteolytic actions of a hydrolytic enzyme could not be assumed to follow common pathways.

However, Bender, *et al.*,[10] have shown that the increased esterase activity of acetylated carboxypeptidase A is primarily the result of a striking decrease in substrate inhibition of the catalytic hydrolysis of O-(N-benzoylglycyl)-DL-3-phenyllactate under the conditions of assay used by Vallee's group; this decrease far outweighs an increase in the apparent Michaelis constant and causes the observed "activity" increase. From this study the conclusion was reached that no clear-cut mechanistic implications were provided by the available kinetic data.

Previous work from this laboratory[11] indicated that the pH–rate profile for the carboxypeptidase A catalyzed hydrolysis of O-acetyl-L-mandelate was markedly different from the profile reported[4-6] for O-(N-benzoylglycyl)-DL-3-phenyllactate but was similar to that reported[4,5,12] for the peptide substrate N-(N-carbobenzyloxyglycyl)-L-phenylalanine. A detailed analysis of pH effects, however, requires the determination of both k_{cat} and k_{cat}/K_m as functions of pH in order to separate the influence of hydrogen ion conentration on the free enzyme from that on the enzyme–substrate complex. This paper reports the results of such an

(1) This work was supported by grants from the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service.

(2) Paper III in the series Studies on the Esterase action of Carboxypeptidase A. For papers I and II of this series see ref 11 and 14, respectively.

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