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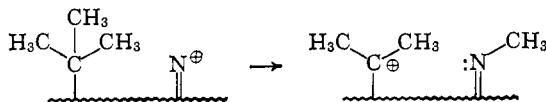
Electrophilic Bond Insertion by Cationic Nitrogen¹BY PETER T. LANSBURY,² JAMES G. COLSON,³ AND NORMAN R. MANCUSO

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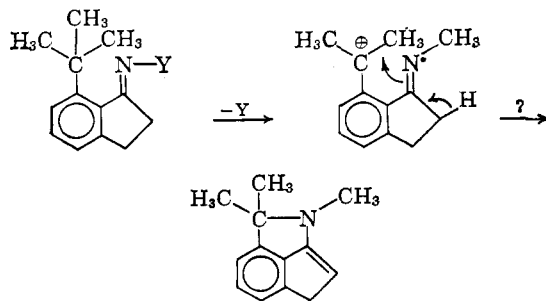
Polyphosphoric acid converts 4-bromo-7-*t*-butyl-1-indanone oxime (II) mainly into 1,8-ethano-7-bromo-4,4-dimethyl-3,4-dihydroisoquinoline (III) and gives only a minor amount of both possible lactams. The imine III is a result of bond insertion by electron-deficient nitrogen, and deuterium labeling studies have shown that an iminium cation ($>C=N^+$), rather than a vinyl nitrene, is the attacking electrophile. The Schmidt reaction of 4-bromo-7-*t*-butyl-1-indanone also gives III but lactams are now the major product. Mechanistic features, particularly of the insertion reaction, are discussed.

Introduction

As part of a program aimed at investigating intramolecular alkyl group migrations between non-bonded atoms (*i.e.*, other than 1,2-shifts), we have focused our attention upon electron-deficient nitrogen species⁴ as the migration terminus. Thus, acid-catalyzed reactions of appropriate oximes or the Schmidt reactions of the parent ketones with hydrazoic acid might result in an alkyl transfer from a proximal atom to electron-deficient nitrogen if a more stable ion were to be formed; *e.g.*



Although a number of attempts to obtain transannular alkyl shifts in medium-sized rings have been made, no successful methyl migrations have been reported,⁵ and this may in part be a consequence of the conformational flexibility of such molecules, which prevents the required juxtaposition of migration terminus and migrating group. We therefore sought to use as model compounds more rigid molecules which also would be less apt to undergo the usually preferred Beckmann^{4a,6} and Schmidt^{4a,7} rearrangements or fragmentation reactions.⁸ These conditions are admirably met in the 1-indanone ring system, in which the imine nitrogen is rigidly held in close proximity to a 7-*t*-butyl group that might serve as the migration origin; *e.g.*



(1) A portion of this research was reported in preliminary form: P. T. Lansbury and J. G. Colson, *J. Am. Chem. Soc.*, **84**, 4167 (1962).

(2) Alfred P. Sloan Foundation Fellow, 1963-1965.

(3) National Aniline Research Fellow, 1961-1962.

(4) For recent reviews, see (a) P. A. S. Smith in "Molecular Rearrangements," P. deMayo, Ed., Vol. 1, Interscience Publishers, Inc., New York, N. Y., 1963, Chapter 8; (b) R. A. Abramovitch and B. A. Davis, *Chem. Rev.*, **64**, 176 (1964).

(5) For recent reviews of transannular effects, see (a) V. Prelog and J. G. Traynham, "Molecular Rearrangements," P. deMayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, Chapter 9; (b) J. Sicher in "Progress in Stereochemistry," Vol. 3, P. B. D. de la Mare and W. Klyne, Ed., Butterworths, London, 1962, Chapter 6.

(6) L. G. Donaruma and W. Z. Heldt, "Organic Reactions," Vol. 11, R. Adams, Ed., John Wiley and Sons, Inc., New York, N. Y., 1960, Chapter 1.

Furthermore, aryl migration to nitrogen in the Chapman rearrangement of *anti*-oxime picrates derived from benzocycloalkenones has been shown to be too slow to measure in the case of 1-indanone because of the great torsional strain required to twist the $>C=N-$ bond out of the plane of the benzene ring, as required for migration.⁹ In addition, a model compound such as the above oxime is not apt to undergo fragmentation because no group which can leave as a stable carbonium ion is attached to the imine carbon.⁸ Finally, since electron-deficient nitrogen intermediates from oximes have been shown to undergo intramolecular electrophilic additions to double bonds,¹⁰ we felt that such a species would serve as a suitable migration terminus (or as a suitable electrophile for bond insertion, which may lead to the same product).

The present paper concerns the synthesis of 4-bromo-7-*t*-butyl-1-indanone, the Schmidt reaction of the parent ketone, and the Beckmann reaction of the oxime, as well as the gross mechanistic features of the new insertion reaction that occurs in these reactions.¹

Results and Discussion

The key intermediate in this work was 7-*t*-butyl-4-bromo-1-indanone, which was prepared according to the procedure of Fieser and Snow,¹¹ involving chloromethylation of 4-bromo-*t*-butylbenzene, followed by diethyl malonate displacement of the benzylic halide and subsequent hydrolysis and decarboxylation to give the desired propionic acid side chain. Cyclization of the latter was effected by aluminum chloride, using the acyl halide. Although Fieser claimed that both possible chloromethylation products were formed (both leading ultimately to 4-bromo-7-*t*-butylindane¹¹), we were able to obtain pure 3-chloromethyl-4-bromo-*t*-butylbenzene and convert it into 4-bromo-7-*t*-butyl-1-indanone (I). Confirmation of the structure came from the nuclear magnetic resonance (n.m.r.) spectrum, which showed a sharp methyl signal at 1.38 p.p.m. (9 *t*-butyl protons), the four C₂- and C₃-methylene protons as a complex A₂B₂ spectrum centered at 2.8 p.p.m., and two *ortho* aromatic protons centered at 7.4 p.p.m., ($\delta_{AB} \sim 21$ c.p.s., $J_{AB} \sim 8$ c.p.s.), thus verifying that no *t*-alkyl migration or dealkylation had occurred.¹²

(7) H. Wolff, *ibid.*, Vol. 3, Chapter 8.

(8) (a) R. K. Hill, *J. Org. Chem.*, **27**, 29 (1962); R. K. Hill and O. T. Chortyk, *J. Am. Chem. Soc.*, **84**, 1064 (1962); (b) R. T. Conley and T. M. Tencza, *Tetrahedron Letters*, **No. 26**, 1731 (1963).

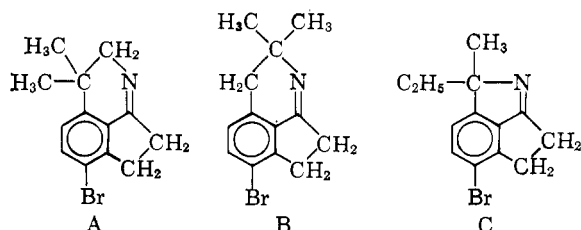
(9) R. Huisgen, J. Witte, and I. Ugi, *Chem. Ber.*, **90**, 1844 (1957).

(10) (a) J. Meinwald, *Proc. Chem. Soc.*, 286 (1958); (b) R. Griot and T. Wagner-Jauregg, *Helv. Chim. Acta*, **42**, 121, 605 (1959).

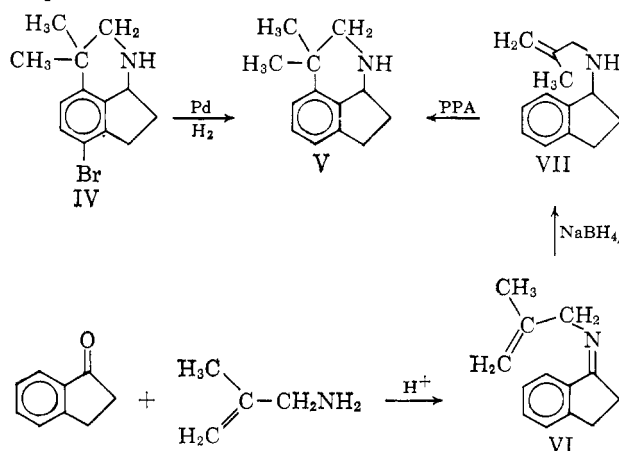
(11) L. F. Fieser and C. K. Snow, *J. Am. Chem. Soc.*, **60**, 176 (1938).

(12) Intramolecular acylations involving electrophilic attack *ortho* to a symmetrically bulky *t*-butyl group are expected to proceed with great difficulty and one must be especially aware of possible migration and/or loss of *t*-alkyl groups in such reactions (*cf.* M. J. Schlatter and R. D. Clark, *J. Am.*

Having available pure I, we converted it to the oxime II,¹³ which proceeded slowly as a result of the sterically hindered carbonyl group. Compound II was heated for 1 min. in polyphosphoric acid (PPA) at *ca.* 130°, then cooled and poured into ice-water. Ether extraction yielded a neutral product mixture (*ca.* 20% yield) from which a crystalline lactam (*vide infra*) was isolated as the major component. When the remaining acidic aqueous solution was made alkaline, extraction yielded a colorless oil (III) which rapidly darkened but formed a stable perchlorate (yields *ca.* 70–75%). Spectral examination of III showed that the basic product was an imine (ν_{\max} 1655 cm^{-1}) rather than an enamine,¹⁴ since no vinyl proton signals appeared in the n.m.r. spectrum. Analysis of III-perchlorate indicated a loss of the elements of H₂O in the transformation of II to III. At this stage, the following structures for III were considered.



Structure A was considered most likely since III-perchlorate was reduced by borohydride to a secondary amine (IV) that was easily acylated to give a single *p*-nitrobenzamide. Assuming IV now to be most likely the correct structure for the reduction product of III, the bromine was removed by hydrogenolysis to give 1,8-ethano-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline (V), which could be unambiguously synthesized by an independent route (below) for final confirmation.



Chem. Soc., **75**, 361 (1953); G. Baddeley, *Quart. Rev.* (London), **8**, 355 (1954). It is probable that many reported reaction products of such acylations have incorrect assigned structures because these potential complications were overlooked. For example, all attempts to cyclize β -(2-methoxy-5-*t*-butylphenyl)propionic acid and γ -(2-methoxy-5-*t*-butylphenyl)butyric acid to *t*-butyl-containing benzocycloalkanones led to 4-methoxy-1-indanone and 5-methoxy-1-tetralone, respectively, as the only ketonic products (J. G. Colson, unpublished results). In addition, lactones were formed which resulted from nucleophilic attack of the nuclear methoxy groups at the acyl carbons of the acid chlorides during reaction with Lewis acids (*cf.* J. H. Burckhalter and J. Campbell, *J. Org. Chem.*, **26**, 4232 (1961)).

(13) The C₂- and C₃-methylene groups in II, as well as in III-perchlorate, gave a single sharp signal, at 3.0 and 3.47 p.p.m., respectively, in the n.m.r. spectra, in contrast to the A₂B₂ spectrum shown by I.

(14) Although secondary enamines generally exist in the imine form, there are nevertheless some instances where the former tautomers persist in preference to the imine (*cf.* A. C. Cope, R. J. Cotter, and G. G. Roller, *J. Am. Chem. Soc.*, **77**, 3590 (1955); I. W. Elliott, E. S. McCaskill, M. S. Robertson, and C. H. Kirksey, *Tetrahedron Letters*, 291 (1962)).

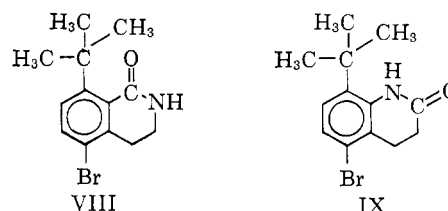
The imine VI from condensation of 1-indanone with β -methallylamine was reduced with borohydride to the unsaturated secondary amine VII, which was cyclized by reaction with PPA. The *p*-nitrobenzamide of the resultant saturated amine had an infrared spectrum identical with that from V-*p*-nitrobenzamide derived from III and the two samples gave no mixture melting point depression. Thus the structure of III is confirmed; in addition, the imine formulation (rather than enamine) assigned on the basis of the n.m.r. spectrum of III was further substantiated by noting the infrared spectral shift in going from III to the perchlorate¹⁵ and comparing these data with the shifts for model imines and enamines upon protonation, as shown in Table I.

TABLE I

Free base, ^a cm^{-1}	1655	1595	1630
Perchlorate, ^b cm^{-1}	1680	1655	1655
$\Delta\nu$, cm^{-1}	25	60	25

^a The $>\text{C}=\text{N}-$ or $>\text{C}=\text{C}-\text{N}-$ absorption; spectra taken as neat liquid. ^b The $>\text{C}=\text{N}^+\text{H}-$ band; spectra taken as Nujol mulls.

The major neutral product from the oxime reaction proved to be 5-bromo-8-*t*-butyl-3,4-dihydroisocarbostyryl (VIII) rather than the isomeric 5-bromo-8-*t*-butyl-3,4-dihydrocarbostyryl (IX),¹⁶ the ratio of VIII to IX being 81:19 (by v.p.c.). Lactam VIII



showed a carbonyl band at 1665 cm^{-1} compared with ν_{\max} 1690 cm^{-1} for IX, and also was recovered unchanged from attempted acid- or base-catalyzed hydrolysis and lithium aluminum hydride reduction, in accord with the sterically-blocked carbonyl group. The above infrared assignments are strengthened by examining the isomeric lactams, 3,4-dihydroisocarbostyryl (X), ν_{\max} 1657 cm^{-1} , and 3,4-dihydrocarbostyryl (XI), ν_{\max} 1675 cm^{-1} , where the isocarbostyryl isomer again shows longer wave length carbonyl absorption. The structure of VIII was further proved by hydrogenolysis to 8-*t*-butyl-3,4-dihydroisocarbostyryl (XII) and comparing its n.m.r. spectrum with those of X and XI in the methylene proton region. The spectra are shown in Fig. 1.

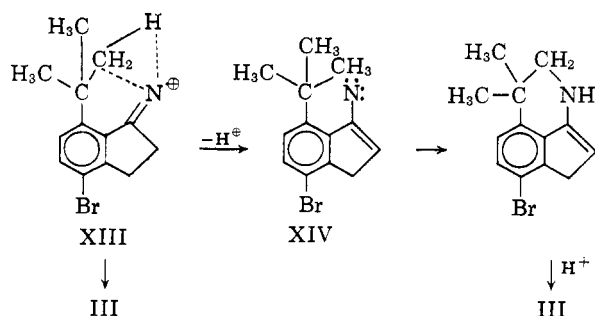
(15) For further examples, see J. Szmuszkovic, "Advances in Organic Chemistry, Methods and Results," R. A. Raphael, H. Wynberg, and E. C. Taylor, Ed., Vol. 4, Interscience Publishers, Inc., New York, N. Y., 1963, Chapter 1, p. 96.

(16) Insufficient pure IX has been isolated as yet to determine by n.m.r. if the *t*-butyl group is still present, although *t*-butyl absorption is present in the infrared spectrum (1395, 1360 cm^{-1}).

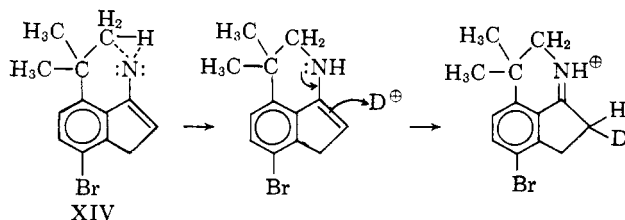
The similar A_2B_2 spectra of XII and X, both with regard to position and separation of the multiplets, confirms that these lactams are of the same type, in contrast to XI. Furthermore, methylene groups adjacent to amide nitrogen generally give signals at *ca.* 3.4 p.p.m.,¹⁷ whereas those adjacent to amide carbonyl resonate at higher field¹¹ (as in XI).

The Schmidt reaction of 4-bromo-7-*t*-butyl-1-indanone (I) in PPA was next studied. If an iminodiazonium ion were an intermediate, loss of nitrogen would give an electron-deficient iminium cation similar to that generated in the Beckmann reaction and comparable products and ratios might result. Actually III, VIII, and IX again were formed, but now lactam was the major product (*ca.* 2:1), the ratio of VIII and IX being 85:15, suggesting a change in mechanism between the two reactions. Any attempt to account for these data should also consider the fact that the major lactam (VIII) results from net methylene migration, whereas indanone itself reportedly rearranges to XI by exclusive aryl migration.¹⁸ Further studies now underway in our laboratories will hopefully explain the observed migrational preferences.

In the insertion reaction leading to III, it is possible that the species attacking the proximal C-H bond is not the cationic nitrogen intermediate XIII¹⁹ but a vinyl nitrene (XIV) resulting from loss of a proton. The nitrene XIV would, however, be expected



to give α -aminoketone from the hydrolysis of intermediate azirine,²⁰ rather than bond insertion, but none was found. Nevertheless, experimental verification of the actual intermediate involved seemed highly desirable. The basis chosen for distinguishing between intermediates XIII and XIV was the presence or absence of deuterium at the carbon adjacent to the imine carbon in III-perchlorate prepared from II in deuterated polyphosphoric acid (PPA-*d*). If the



(17) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 56. Also for several typical spectra, see spectra 68 and 116 in Varian Spectra Catalog, Varian Associates, Palo Alto, Calif., 1962.

(18) L. J. Briggs and G. C. Ath, *J. Chem. Soc.*, 456 (1937). Our reinvestigation of this reaction shows that some 3,4-dihydroisocarbostyryl (X) is also present (N. R. Mancuso, unpublished results).

(19) One can draw resonance forms for XIII in which the positive charge is delocalized and then nitrogen is a neutral nitrene; however, these structures would be insignificant since they all possess two atoms having incomplete octets of electrons surrounding them.

(20) G. Smolinsky, *J. Org. Chem.*, **27**, 3557 (1962).

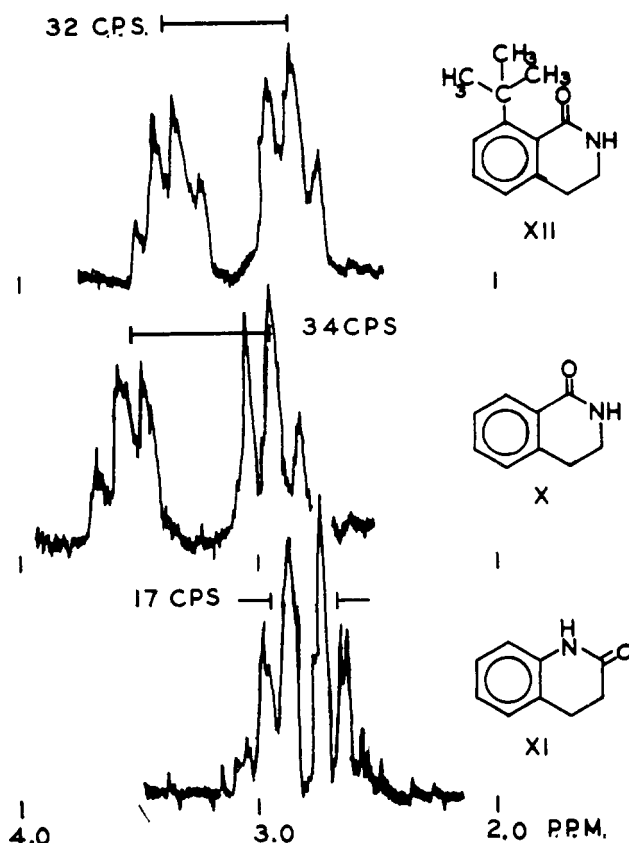


Fig. 1.—Partial n.m.r. spectra showing methylene protons of lactams XII (top), X (center), and XI (bottom). Chemical shifts are in parts per million (p.p.m.) from internal TMS.

insertion product were resistant toward further H-D exchange, XIII should yield deuterium-free III and XIV should give III containing one deuterium atom.²¹ Initial experiments showed that rapid hydrogen-deuterium exchange took place in the work-up if dilution of the PPA, followed by basification and ether extraction, were not carried out extremely rapidly. Thus, reaction of 0.5 g. of II with *ca.* 10 g. of PPA-*d* for 1 min. at *ca.* 130°, followed by dilution with 50 ml. of D₂O, then ether extraction of neutral products before addition of base to liberate III from the salt (20–30 min. contact of III with dilute acid) resulted in the introduction of 1.99 D/molecule! Furthermore, exact repetition of this work-up procedure, except using H₂O to dilute the PPA-*d*, reduced the deuterium content of the above III-perchlorate to 0.13 D/molecule. Any deuterium introduced by protonation of enamine from XIV would thus have been lost in the work-up using such conditions. Clearly, hydrogen isotope exchange occurs with much greater ease in dilute phosphoric acid than in PPA,¹⁹ a factor which must be largely avoided in experiments designed to differentiate

(21) Although Leonard and Sauer (*J. Am. Chem. Soc.*, **79**, 6210 (1957)) showed that protonation of enamines at C- β by formic acid was reversible, we felt that in concentrated mineral acids, whose conjugate bases were much weaker than formate ion, exchange would be negligible, at least prior to dilution and work-up. This assumption is supported by the studies of Swain, *et al.* (*ibid.*, **83**, 2154 (1961)) on rates of racemization of optically active α -phenylisocaprophenone in sulfuric acid, which showed that water was a much better base than bisulfate ion (faster rate in more dilute sulfuric acid). In addition, we have observed that no noticeable deuteration of 1-indanone at C-2 occurs in pure trifluoroacetic acid-*d* (by n.m.r.) but when an equal volume of D₂O is added, rapid deuteration occurs (N. R. Mancuso, unpublished results). Usually the removal of an α -proton by a general base is rate determining in acid-catalyzed reactions of ketones and no good base is present in concentrated strong mineral acids or in trifluoroacetic acid, in contrast with the weaker formic acid.

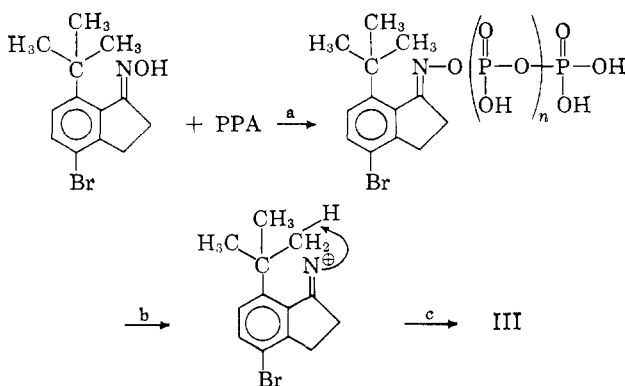
between intermediates XIII and XIV. Fortunately, valid data were obtained when the PPA reaction mixture was poured directly into a well-stirred, ice-cold two-phase mixture of 10% sodium hydroxide and ether so that III was extracted from the aqueous phase as fast as neutralization occurred. III-perchlorate was precipitated directly before separation of imine from the lactams. Even with this fast work-up, some secondary exchange occurs (Table II, runs 1 and 3)

TABLE II
DEUTERIATION STUDIES OF OXIME INSERTION MECHANISM

Run	Starting material	Reagents and work-up	D content of III-ClC ₄
1	II	PPA-d; "fast" H ₂ O-OH ⁻ work-up	0.15
2	II	PPA-d; "slow" D ₂ O work-up	1.99
3	III-perchlorate from run 2	PPA-d; "fast" H ₂ O-OH ⁻	1.09

but this does not materially affect the conclusions that can be made. Comparison of runs 2 and 3 shows that more than half of any deuterium incorporated by a mechanism involving the protonation of enamine XIV in the conversion of II to III (*i.e.* >0.5 D/molecule) should survive the work-up, even without considering the primary deuterium isotope effect for exchange that might be as high as 5–7. Since only 0.15 D/molecule is found (this small amount undoubtedly entering during the "fast" work-up) in III from the reaction of II (run 1), the enamine mechanism can be discarded in favor of the direct cationic insertion path (*via* XIII).²²

Thus the pathway for converting II to III can now be represented as



Pearson and Stone have concluded²³ that in the PPA-catalyzed Beckmann rearrangement of acetophenone oximes, either the esterification of the oxime group (step a) or the ionization of the oxime polyphosphate (step b) may be rate determining. Since substituent effects were negligible ($\rho = -0.25 \pm 0.05$), it was felt that departure of the polyphosphate ion was well advanced relative to aryl migration. Because II is rigged to prevent aryl migration to nitrogen (see Introduction),²⁴ it appears particularly likely that the

(22) Although one might argue that the D content from run 1 results from a minor contribution of nitrene insertion, instead of from exchange during work-up, we regard this as a remote possibility.

(23) D. E. Pearson and R. M. Stone, *J. Am. Chem. Soc.*, **83**, 1716 (1961).

(24) It might be expected that in 5-bromo-8-*t*-butyl-1-tetralone oxime the imine bond would be flexible enough to allow normal aryl migration (see ref. 9) under Beckmann rearrangement conditions and thus possibly prevent bond insertion. This is exactly what is observed: the above oxime gives *ca.*

iminium ion is a discrete intermediate in the insertion mechanism, rather than being bypassed for a concerted displacement of the leaving group at sp^2 -hybridized nitrogen by a C-H bond. Such a mechanism would find no analogy in nucleophilic displacement reactions at vinyl carbon, where inversion is generally not observed.²⁵ The insertion itself (step c) can be pictured as a "three-center" process in which the electrophilic nitrogen attacks midway between carbon and hydrogen where the electron density is greatest. Such a transition state, which has little neophyl carbonium ion character (hence explaining the absence of methyl or aryl rearrangement), finds analogy in the cationic oxygen insertion of Corey and White²⁶ and in the hydrolysis of pyridine diphenylborane.²⁷

Further studies on the scope, limitations, and mechanistic details of the oxime insertion reaction are presently underway in our laboratories.

Experimental²⁸

Preparation of 4-Bromo-7-*t*-butyl-1-indanone (I) and Its Oxime II.

—The route of Fieser and Snow¹¹ was followed, with some modifications. Chloromethylation of 4-bromo-*t*-butylbenzene using zinc chloride, trioxane, and anhydrous hydrogen chloride gas gave 50% yields of product, b.p. 133–136° (5 mm.) (reported¹¹ b.p. 120–140° (5 mm.)). That this product was essentially 4-bromo-3-chloromethyl-*t*-butylbenzene was shown by hydrogenolyzing a small portion in ethanol, containing triethylamine, over Pd-C. Work-up gave nearly pure *m*-*t*-butyltoluene as judged by infrared spectroscopy.²⁹ A weak band at 820 cm^{-1} indicated that some ($\leq 10\%$) *p*-*t*-butyltoluene was present,²⁹ probably from acid-catalyzed *t*-butyl migration in the chloromethylation product. The absence of *o*-*t*-butyltoluene (expected from hydrogenolysis of product of chloromethylation at the position *ortho* to the *t*-butyl group) was verified by the absence of absorption²⁹ at 760 cm^{-1} .

The above 3-chloromethyl-4-bromo-*t*-butylbenzene was treated with diethyl sodiomalonate and the resultant malonic ester hydrolyzed and decarboxylated.¹¹ The β -(2-bromo-5-*t*-butylphenyl)propionic acid was converted to the acid chloride with thionyl chloride and cyclized with aluminum chloride in carbon disulfide,¹¹ yielding I, m.p. 69–70° (from petroleum ether) (reported¹¹ m.p. 70–72°), which showed ν_{max} 1705 cm^{-1} and $\lambda_{max}^{E_{OH}}$ 251 $m\mu$ (ϵ 12,000). The confirmatory n.m.r. data are presented in the Discussion.

Prolonged reaction times were required to convert I into its oxime II. In a typical run, a solution of 0.53 g. (2.0 mmoles) of I, 0.55 g. (8.0 mmoles) of hydroxylamine hydrochloride, and 2.0 g. of potassium hydroxide in 10 ml. of 95% ethanol was refluxed for 52 hr.³⁰ The solution was then poured into water and the product extracted into ether and dried over sodium sulfate. Recrystallization of the oily oxime from hexane gave pure II, m.p. 105–106°. The n.m.r. spectrum showed signals at 1.45 (*t*-butyl), 3.0 (C_2 - and C_3 -methylenes), 7.3 p.p.m. (AB quartet with $J_{AB} \sim 8$ c.p.s. and $\delta_{AB} \sim 15$ c.p.s. attributed to two adjacent aromatic protons) and 7.63 p.p.m. (oxime proton), all in the expected area ratios.

97% lactam resulting from aryl migration and no detectable amount of imine resulting from insertion (N. R. Mancuso, unpublished results).

(25) S. I. Miller and P. K. Yonan, *J. Am. Chem. Soc.*, **79**, 5931 (1957).

(26) E. J. Corey and R. W. White, *ibid.*, **80**, 6686 (1958).

(27) M. R. Hawthorne and E. S. Lewis, *ibid.*, **80**, 4296 (1958).

(28) Melting points (taken on a "Mel-temp" apparatus checked with standards) and boiling points are uncorrected. Infrared spectra (neat or Nujol mulls) were obtained on a Beckman IR-5 spectrometer and n.m.r. spectra recorded with a Varian A-60 spectrometer using chloroform-*d* as solvent and tetramethylsilane (TMS) as internal standard; n.m.r. chemical shifts are given in parts per million (p.p.m.) downfield from TMS ($\delta = 0.00$). Carbon and hydrogen analyses were performed by Dr. A. Bernhardt, Mulheim, Germany; deuterium analyses by Mr. J. Nemeth, Urbana, Ill.; v.p.c. analyses were performed on an F and M Model 300 chromatograph.

(29) M. J. Schlatter and R. D. Clark, *J. Am. Chem. Soc.*, **75**, 363 (1953).

(30) Periodically small aliquots had been removed and worked up, to check the progress of the reaction. This was followed by checking the infrared spectra of the crude oily product for disappearance of carbonyl absorption at 1705 cm^{-1} .

Anal. Calcd. for $C_{13}H_{16}NOBr$: C, 55.41; H, 5.74. Found: C, 55.65; H, 5.67.

Reaction of II with PPA.—In a typical run, 0.3–0.6 g. of II was mixed with 10–20 g. of PPA and the mixture heated to 130°, at which time a homogeneous solution resulted. This was allowed to cool to room temperature after 1 min. at 130° and 50–100 ml. of water then added. The aqueous solution was extracted with several portions of ether and the combined ether extracts dried over sodium sulfate. After solvent evaporation, the residual oil (ca. 18–23% yield) was analyzed by v.p.c. (4-ft. silicone rubber column at 160°) and shown to contain ca. 4% recovered I, 13% of VIII, and 3% of IX. Several such product mixtures from various reactions were combined and crystallized from hexane, giving pure VIII, m.p. 133–135°, ν_{\max} (Nujol) 1665 cm^{-1} . Further transformations of VIII are described later.

The original acidic aqueous layer was cooled to ice temperature and covered with 50–100 cc. of ether. Solid potassium hydroxide pellets were added in small portions, with stirring and continued cooling, until the aqueous solution had reached pH 9–10. The ether layer was then separated and combined with a second extract of the basic solution and dried over sodium sulfate. Careful solvent evaporation yielded III as a very unstable oil which darkened rapidly. The infrared spectrum of oily III showed $>C=N-$ stretching at 1655 cm^{-1} and the n.m.r. showed no evidence of vinyl protons. Compound III was subsequently not isolated as such, but converted to the stable perchlorate salt (70–75% yields) by dropwise addition of 70% perchloric acid to the dried ether extracts containing the free base until no further crystals were obtained. III-perchlorate gave white plates upon recrystallization from ethanol; m.p. 205–206°, ν_{\max} 1680 cm^{-1} (Nujol mull). The n.m.r. spectrum of III-perchlorate in trifluoroacetic acid showed a singlet at 1.5 (*gem*-dimethyl group), an apparent single peak at 3.47 (intensity indicating the 4 protons of the two adjacent methylene groups), a singlet at 3.97 ($-CH_2-$ adjacent to $-N=$), and a quartet centered at 7.75

H
p.p.m. ($\delta_{AB} \sim 39$ c.p.s., $J_{AB} \sim 8$ c.p.s., two *ortho* aromatic protons).

Anal. Calcd. for $C_{13}H_{15}ClBrNO_4$: C, 43.10; H, 4.27. Found: C, 43.12; H, 4.21.

Conversion of III-perchlorate to 1,8-Ethano-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline (V).—Forty milligrams (1.0 mmole) of sodium borohydride was added with stirring to a solution of 0.2 g. (0.5 mmole) of III-perchlorate in 20 ml. of methanol. After 2 hr. at room temperature, excess water was added and the cloudy solution extracted twice with ether. The dried ether extracts were concentrated, leaving 0.14 g. of liquid amine (no $>C=N-$ absorption at 1655 cm^{-1} in the infrared), which could not be crystallized from a variety of solvents. The product, 1,8-ethano-4,4-dimethyl-7-bromo-1,2,3,4-tetrahydroisoquinoline (IV), was converted to a crystalline *p*-nitrobenzamide (m.p. 185–187° for crude product) by treatment with *p*-nitrobenzoyl chloride in pyridine at 0°. An analytical sample, recrystallized from aqueous ethanol, had m.p. 186–187°. The *gem*-dimethyl group showed two methyl signals, at 1.14 and 1.28 p.p.m., owing to their nonequivalence arising from the introduction of an asymmetric carbon.

Anal. Calcd. for $C_{20}H_{20}O_3N_2Br$: C, 58.01; H, 4.43. Found: C, 58.08; H, 4.49.

A 0.15-g. sample of IV was shaken for 24 hr. in a Parr hydrogenator (ca. 30 p.s.i.g. H_2 pressure) in 20 ml. of ethanol containing 1 ml. of triethylamine and 0.05 g. of 10% palladium-on-carbon. The solution was then filtered, acidified with hydrochloric acid, and evaporated to dryness. The solid residue was taken up in aqueous base and extracted with ether. The latter solution was washed with several portions of water, dried over sodium sulfate, and evaporated on the steam bath to remove solvent and residual triethylamine. There remained 0.1 g. of the debrominated amine V (negative Beilstein test) which again could not be crystallized, but which gave a crystalline *p*-nitrobenzamide, m.p. 174–175.5° (from petroleum ether), whose n.m.r. spectrum again showed nonequivalent geminal methyl groups (signals at 1.2 and 1.33 p.p.m.). This *p*-nitrobenzamide gave an infrared spectrum that was identical with that from the sample independently prepared from 1-indanone (below) and the mixture melting point showed no depression.

Anal. Calcd. for $C_{20}H_{20}N_2O_3$: C, 71.51; H, 5.95. Found: C, 71.33; H, 6.01.

Synthesis of V from 1-Indanone.—A benzene solution of 5 g. (0.04 mole) of 1-indanone and 2.7 g. (0.04 mole) of β -methallylamine plus 50 mg. of *p*-toluenesulfonic acid was refluxed until all the water formed had been collected in a Dean-Stark trap (12 hr.). Excess solid sodium carbonate was added to neutralize the catalyst and the benzene solution then filtered and concentrated at the rotating evaporator. The remaining dark red liquid (3.2 g.) showed imine absorption at 1655 cm^{-1} and, since no crystalline perchlorate could be formed, was used directly for the reduction step without further purification.

The above crude imine VI was dissolved in 50 ml. of ethanol and 1.45 g. (excess) of sodium borohydride added. After 4 hr. at room temperature, the solution was diluted with water and extracted with ether. This extract was concentrated and distilled. A 1-g. fraction, b.p. 140–148° (1 mm.), showed N—H absorption at 3300 cm^{-1} and loss of the strong $>C=N-$ band at 1655 cm^{-1} which was present in VI, confirming that this material was largely N-(1-indanyl)- β -methallylamine (VII).

One gram of VII was dissolved in 10 g. of PPA and kept at room temperature for 40 hr. Excess water was then added, followed by sufficient potassium hydroxide to render the solution alkaline. Ether extraction, followed by drying and concentration on a steam bath, gave the crude amine V as a yellow oil, showing N—H absorption at 3300 cm^{-1} , but no terminal methylene band at ~ 890 cm^{-1} . Treatment with *p*-nitrobenzoyl chloride gave the *p*-nitrobenzamide, m.p. 170–174°, which was identical with the sample obtained from III-perchlorate (above).

Schmidt Reaction of 4-Bromo-7-*n*-butyl-1-indanone (I).—During 1 hr., 0.25 g. (3.8 moles) of sodium azide was added to a stirred mixture of 1.0 g. (3.7 mmole) of I in 20 g. of PPA. After 9 hr. at 50°, the mixture was cooled, diluted with water, and extracted three times with chloroform (see below). The aqueous layer was made alkaline with potassium hydroxide pellets and extracted with ether. Work-up as in the oxime reaction (above) gave ca. 0.2 g. of impure III (ca. 20% yield) which was converted to the perchlorate, m.p. 201–203°, that was identical with III-perchlorate from the reaction of II with PPA (by infrared, n.m.r., and no mixture melting point depression).

The above chloroform extract was washed with base, dried over sodium sulfate, and evaporated to give 0.5 g. of crude lactam(s), $\nu_{\max} \sim 1665$ cm^{-1} ; v.p.c. analysis (4-ft. silicone rubber column at 160°) showed lactams VIII and IX in the ratio 85:15, plus a small amount of recovered I. Chromatography of the crude lactam fraction over alumina separated recovered I (eluted with petroleum ether) from VIII and IX (eluted with ether). The latter material was crystallized from ether–petroleum ether, giving pure VIII, m.p. 134–135°.

Anal. Calcd. for $C_{13}H_{16}NOBr$: C, 55.41; H, 5.74. Found: C, 55.16; H, 5.77.

Hydrogenolysis of crystalline VIII was performed as with IV (see above), except that no acid was used and the filtered ethanol solution was evaporated to give 8-*n*-butyl-3,4-dihydroisocarbostyryl (XII) directly, m.p. 124–126° (from ethanol), ν_{\max} 1665 cm^{-1} . The n.m.r. spectrum of XII (see Discussion) showed a sharp *t*-butyl signal at 1.55 p.p.m., the aromatic protons as a broad multiplet at 7.0–7.6 p.p.m., and the methylene protons as an A_2B_2 system showing two multiplets at 2.86 ($-CH_2-Ar$) and 3.39 p.p.m. ($-CH_2-N-C-$).



Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.82; H, 8.31. Found: C, 77.18; H, 8.48.

Model Compounds for Spectroscopic Studies.—1-Methyl-3,4-dihydroisoquinoline was prepared from N-(β -phenylethyl)acetamide and phosphorus pentoxide.³¹

1-Indanonepyrrolidine enamine was prepared by the usual procedure³² in toluene solution and isolated by vacuum distillation, b.p. 125–127° (1 mm.), as a pale yellow liquid which darkened rapidly in the air. A crystalline perchlorate, m.p. 208–209°, formed upon dropwise addition of 70% perchloric acid to the enamine in absolute ether.

Anal. Calcd. for $C_{13}H_{16}NClO_4$: C, 54.6; H, 5.65. Found: C, 54.62; H, 5.80.

3,4-Dihydrocarbostyryl (XI) was prepared by the Schmidt reaction of 1-indanone with hydrazoic acid in sulfuric acid–benzene solution¹³; m.p. 164–165°, ν_{\max}^{Nujol} 1675 cm^{-1} .

(31) B. Spath and R. Kuntara, *Ber.*, **63**, 134 (1930).

(32) G. Stork, A. Brizzolara, H. Landesman, J. Szmszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

3,4-Dihydroisocarbostyryl (X) was prepared by two independent methods, both of which gave identical products which could not, however, be obtained crystalline.³³

In the first, an ether solution of 5.0 g. (0.03 mole) of *o*-carboxyphenylacetonitrile³⁴ was esterified with diazomethane. After removal of the solvent, the residue was taken up in ethanolic hydrochloric acid containing platinum oxide and hydrogenated at 50 p.s.i.g. in a Parr apparatus. After H₂ uptake had ceased (2 hr.), the solution was filtered and evaporated to dryness on a rotary evaporator. The residual β -(*o*-carboxymethoxyphenyl)ethylamine hydrochloride was recrystallized from ethanol; m.p. 183–184°. One gram of the above salt was shaken with ether and 5% sodium hydroxide solution. The ether layer was washed and dried over sodium sulfate, then evaporated, leaving 0.8 g. of oily 3,4-dihydroisocarbostyryl (X) having ν_{\max} 1657 cm.⁻¹. No other carbonyl bands appeared in the infrared spectrum.

The second method for preparing X involved reaction of ethyl chloroformate (0.18 mole) with β -phenylethylamine (0.36 mole) in ether, from which amine hydrochloride precipitated. After 2 hr., the ether solution was filtered and distilled, yielding ethyl N-(β -phenylethyl)carbamate, b.p. 165–175° (14 mm.), which solidified on standing, m.p. 37–39°. A mixture containing 2.0 g. of the above carbamate and 40 g. of PPA was heated at 150° for 2 hr., then cooled and poured into excess ice-water. Ether extraction, followed by washing with sodium bicarbonate solution, water, and drying over sodium sulfate, yielded, after solvent evaporation, ca. 1.0 g. of oily X. The infrared and n.m.r. spectra of this lactam sample were identical with those of the product of the first synthesis.

Reaction of II with Deuterated PPA.—As mentioned in the Discussion, experiments designed to distinguish between nitrene and iminium ion insertion mechanisms had to be carried out in a special way in order to avoid extraneous H/D exchange in the work-ups.

Deuterated polyphosphoric acid (PPA-*d*) was prepared from the reaction of 16.4 g. of phosphorus pentoxide and 3.6 g. of D₂O. The resulting viscous liquid had 82% P₂O₅ content, as does ordinary PPA.

(33) C. J. Cavallito and T. H. Haskell, *J. Am. Chem. Soc.*, **66**, 1166 (1944).

(34) C. C. Price and R. G. Rogers, *Org. Syn.*, **22**, 30 (1942).

In experiments where a fast work-up was necessary to minimize exchange after the insertion had occurred (Table II, runs 1 and 3) the cooled mixture of II (0.3–0.6 g.) in PPA-*d* was poured directly into a rapidly stirred, two-phase mixture of ether and concentrated aqueous potassium hydroxide, which was cooled to –5° in an ice-salt bath. The ether layer, which contained all of the products, was immediately separated from the basic aqueous solution, filtered through anhydrous sodium sulfate, and treated with 2–3 drops of 70% perchloric acid to precipitate III-perchlorate directly (lactams remained in solution). The salt (70–75% yield) was removed by suction filtration, washed with anhydrous ether, and dried overnight *in vacuo* at 55° before combustion analysis²⁸ for D content. Qualitative estimates of the extent of deuterium incorporation were possible from the n.m.r. spectra of III-perchlorate samples obtained from the PPA-*d* reactions, by noting the intensity of the 3.47 p.p.m. signal, which would show a relative area corresponding to 4 methylene protons on adjacent carbons if no D were present, and comparing it with the *gem*-dimethyl signal (1.5 p.p.m., relative intensity 6) and/or the aromatic proton signal (relative intensity 2).

As a control, it was necessary to check the change in deuterium content, if any, when III-perchlorate containing a known amount of deuterium at the carbon α to the imine carbon was subjected to the above fast work-up, after being dissolved in PPA-*d*. The control sample was obtained by treating II with PPA-*d*, then diluting with D₂O and using the *slow* work-up procedure to allow maximum exchange before isolation of III-perchlorate (Table II, run 2). Thus a sample containing essentially *two* D atoms was obtained. This material was found to retain ca. 55% of its deuterium content when dissolved in PPA-*d* and worked up by the fast procedure just described (Table II, run 3).

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Kinetic Studies of the Decarboxylation of Some N-Substituted Pyridinecarboxylic Acids

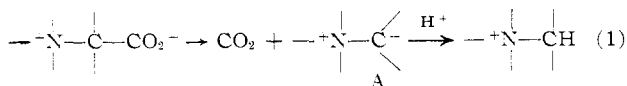
BY PAUL HAAKE AND JOAQUIN MANTECÓN

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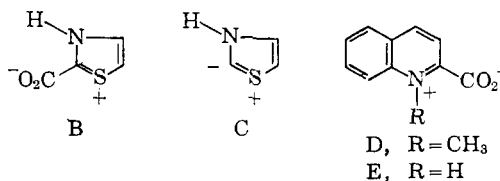
The relative rates of decarboxylation of N-methylpicolinic acid (homarine) (F), picolinic acid N-oxide (G), and picolinic acid (H) are found to be 720:160:1 at 134° in ethylene glycol as solvent. Homarine (F) is found to decarboxylate about 10³ times faster than the other position isomers, trigonelline (I) and N-methylisonicotinic acid (K). Possible explanations are offered on the basis of the activation parameters. Divalent metal ions, Cu⁺², Mg⁺², and Mn⁺², are found to inhibit the decarboxylation of picolinic acid and picolinic acid N-oxide. The enhanced rate of decarboxylation of homarine is related to a possible role of this betaine in invertebrate biochemistry and physiology.

Introduction

The decarboxylation of acids with the carboxylate group α to a quaternary ammonium function (eq. 1) is well known¹ to proceed at an accelerated rate presumably attributed to inductive stabilization of the carbanion in the form of an ylid intermediate (A).



Thiazole-2-carboxylic acid (B) was observed² to decarboxylate several powers of 10 faster than the 4-



or 5-carboxylic acids, a result which apparently was not used in the search for the active site of thiamine but which clearly reflects the unusual stability of the thiazolium ylid (C).^{3,4}

Brown and Hammick⁵ measured the rates of de-

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(2) H. Schenkel and M. Schenkel-Rudin, *Helv. Chim. Acta*, **31**, 924 (1948).

(3) R. Breslow, *J. Am. Chem. Soc.*, **79**, 1792 (1957).

(4) P. Haake and W. B. Miller, *ibid.*, **85**, 4045 (1963).

(5) B. R. Brown and D. L. Hammick, *J. Chem. Soc.*, 659 (1949).