THE REACTIONS OF 3-ARYLPROPYLAMINES WITH NITROUS ACID

Thesis by

Arthur W. Fort

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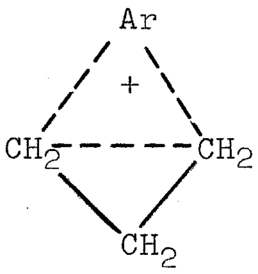
ABSTRACT

3-Phenylpropylamine-1-C^{14} reacts with nitrous acid in aqueous solution to give hydrocinnamyl alcohol, benzylmethylcarbinol and allylbenzene in the ratio 2.5:1.6:1.0. Under similar conditions, 3-(p-methoxyphenyl)-propylamine-1-C^{14} gives p-methoxyhydrocinnamyl alcohol, p-methoxybenzylmethylcarbinol and p-methoxyallylbenzene in the ratio 2.1:1.4:1.0. No evidence was found for the presence of other isomeric alcohols or olefins.

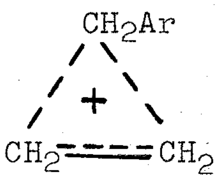
A sample of each product from 3-phenylpropylamine-1-C^{14} was oxidized to benzoic acid, which was found to be inactive in each case. Likewise, anisic acid obtained from each of the products from 3-(p-methoxyphenyl)-propylamine-1-C^{14} was found to be inactive.

The number two carbon atom of each of the six products was shown to contain less than 0.5% of the total C^{14}-activity of the product except in the case of benzylmethylcarbinol-C^{14}, where the activity at C-2 was found to be 0-3%.

These results eliminate the symmetrical carbonium ions having structures A and B as intermediates in the reactions studied.



A



B

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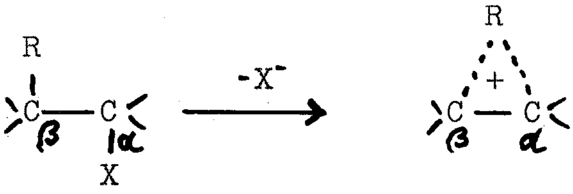
INTRODUCTION

WAGNER-MEERWEIN REARRANGEMENTS

Wagner-Meerwein and related rearrangements proceed through carbonium-ion intermediates, the nature of which has been the subject of considerable research in recent years. The systematic correlation of 1,2-shifts in terms of carbonium ions is largely due to Whitmore.[1] An exceptionally thorough discussion of the evidence upon which the Whitmore formulations rest has been given by Wheland.[2]

Of particular relevance to the present research are recent correlations of stereochemical relationships and reactivities in Wagner-Meerwein rearrangements and related reactions which have been made in terms of "non-classical" carbonium-ion intermediates with structures generalized by II.



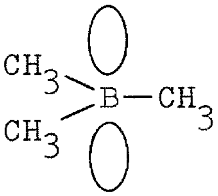
I II

R = H, Alkyl or Aryl.

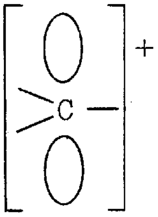
The essential feature of intermediates like II is electron overlap between R and both C_α and C_β, which partial bonding preserves the stereochemical integrity of C_α and C_β. Some specific proposals for describing the type of bonding between

C_α, C_β and R will be mentioned later. As will be seen, several of these descriptions state or imply double bond character in the C_α——C_β bond.

A simple "classical" carbonium ion might be expected to have a planar configuration by analogy with trimethylboron,[3,4] and this expectation is supported by considerable



III



IV

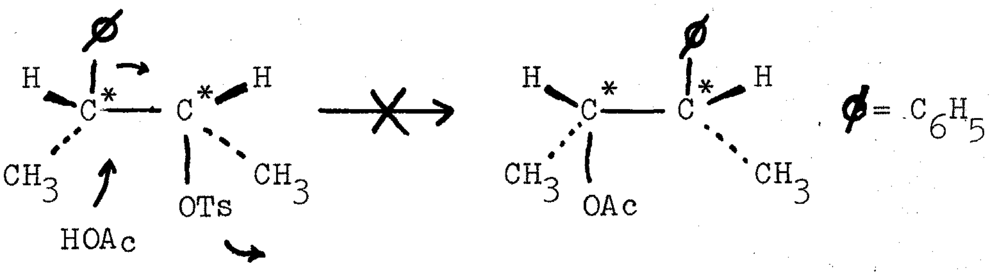
experimental evidence. Thus, inertness of bicyclic compounds with bridgehead substituents in displacement reactions[5,6] has been attributed to the strain involved in attaining a planar configuration at the bridgehead. In line with this interpretation is the finding that 1-bromobicyclo(2·2·2)octane reacts far more readily with silver nitrate than does 1-bromobicyclo(2·2·1)-heptane,[7] a situation that is readily understandable in terms of the relatively smaller strain energy involved in achieving a planar configuration of the bridgehead carbonium ion in the bicyclo(2·2·2)octane system.

Further evidence in support of the belief that simple carbonium ions should exist preferentially in a planar configuration is provided by the extensive racemization attending many processes in which a carbonium ion is produced at an asymmetric center.[8,9,10,11] In such cases, it appears that planar carbonium-ion intermediates are produced having a more or less vacant p-orbital (IV).

Carbonium-ion intermediates in Wagner-Meerwein rearrangements frequently cannot be adequately described by "classical" carbonium ions like IV. This is shown conclusively by the high degree of stereospecificity observed in many rearrangements as will be discussed in the next section.

NON-CLASSICAL CARBONIUM-ION INTERMEDIATES

Cram's studies[12,13] on the 3-phenyl-2-butyl system provide compelling evidence for phenyl bridged-ion intermediates. Acetolysis of threo-3-phenyl-2-butyl p-toluenesulfonate (V tosylate) and of erythro-3-phenyl-2-butyl p-toluenesulfonate (VI tosylate) takes place at nearly identical rates for the two isomers[14] and it may be assumed that a very similar mechanism (or mechanisms) applies to both reactions. Acetolysis of an optically pure form of the threo tosylate (V A tosylate) gives racemic threo acetate (V acetate) while acetolysis of an optically pure form of the erythro tosylate (VI A tosylate) gives the erythro acetate with almost complete retention of optical activity (VI A acetate). Lack of a significant amount of interconversion of erythro-and threo-isomers rules out simple displacement (S_N1 or S_N2) as an important process in these reactions. A completely concerted process involving simultaneous acetate bond formation at C_β, migration of phenyl to C_α and loss of the tosylate group cannot be important because it would lead to retention of optical activity in the threo acetate (acetate formation is irreversible under the conditions used.)



V A tosylate

V A acetate

The kinetics and stereospecificity observed in these solvolysis reactions require solvent attack on a symmetrical intermediate in the threo case and on an unsymmetrical intermediate in the erythro case. These intermediates must be of such a nature that configurational integrity will be maintained at both asymmetric centers. All of these requirements are met by non-classical intermediates involving bonding between the phenyl group and both asymmetric centers (Fig. 1). The acetolysis reactions of V A tosylate and VI A tosylate are given in Figure 2 in terms of "phenonium" ion intermediates.

Stereospecificity in the 3-phenyl-2-pentyl and 2-phenyl-3-pentyl systems is fully as striking as in the 3-phenyl-2-butyl system.[15,16] Figure 3 summarizes the results of acetolysis for the p-toluenesulfonates of the four isomers of these two systems, and it is clear from these results that only two intermediates account for the products from all four p-toluenesulfonates.

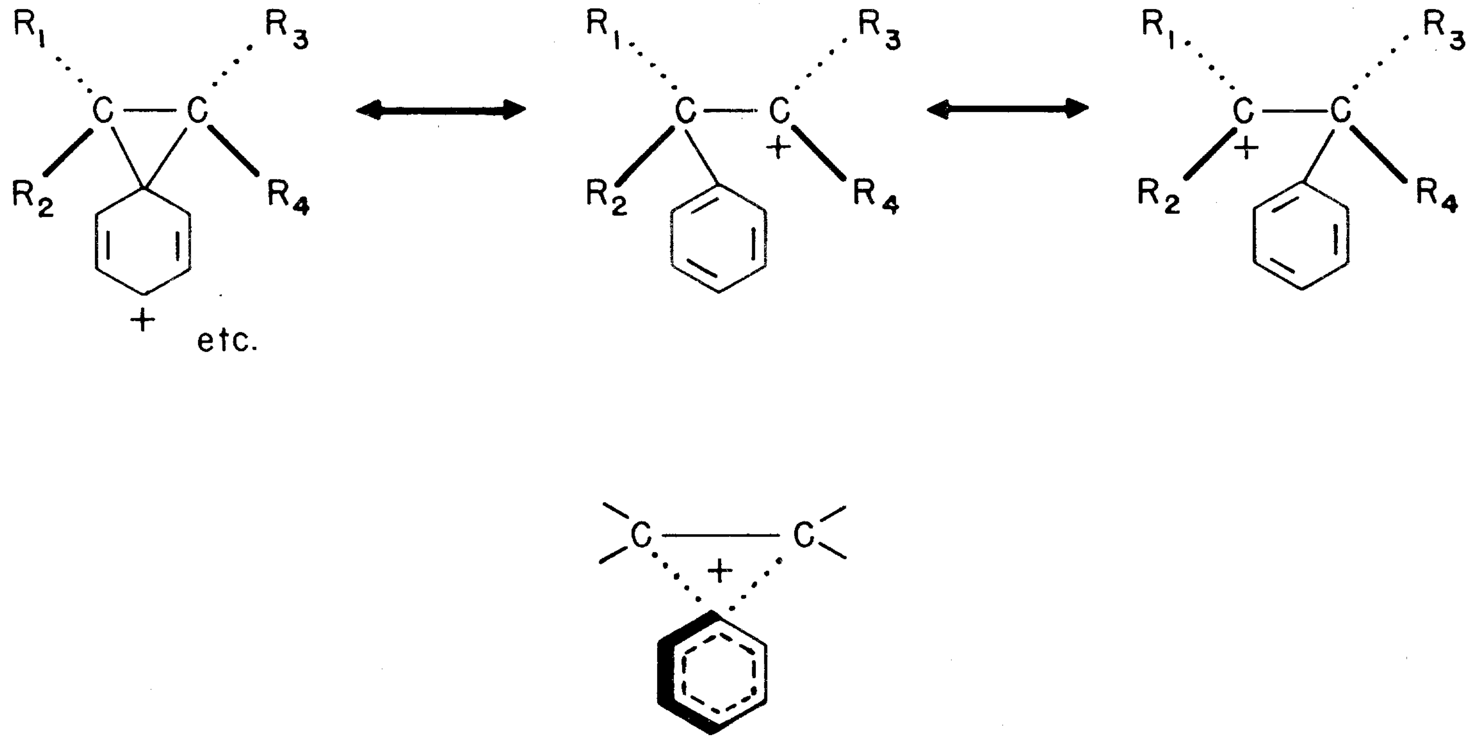


Fig. I

The Phenonium Intermediate According to Cram~~[14,17]~~[12,13]

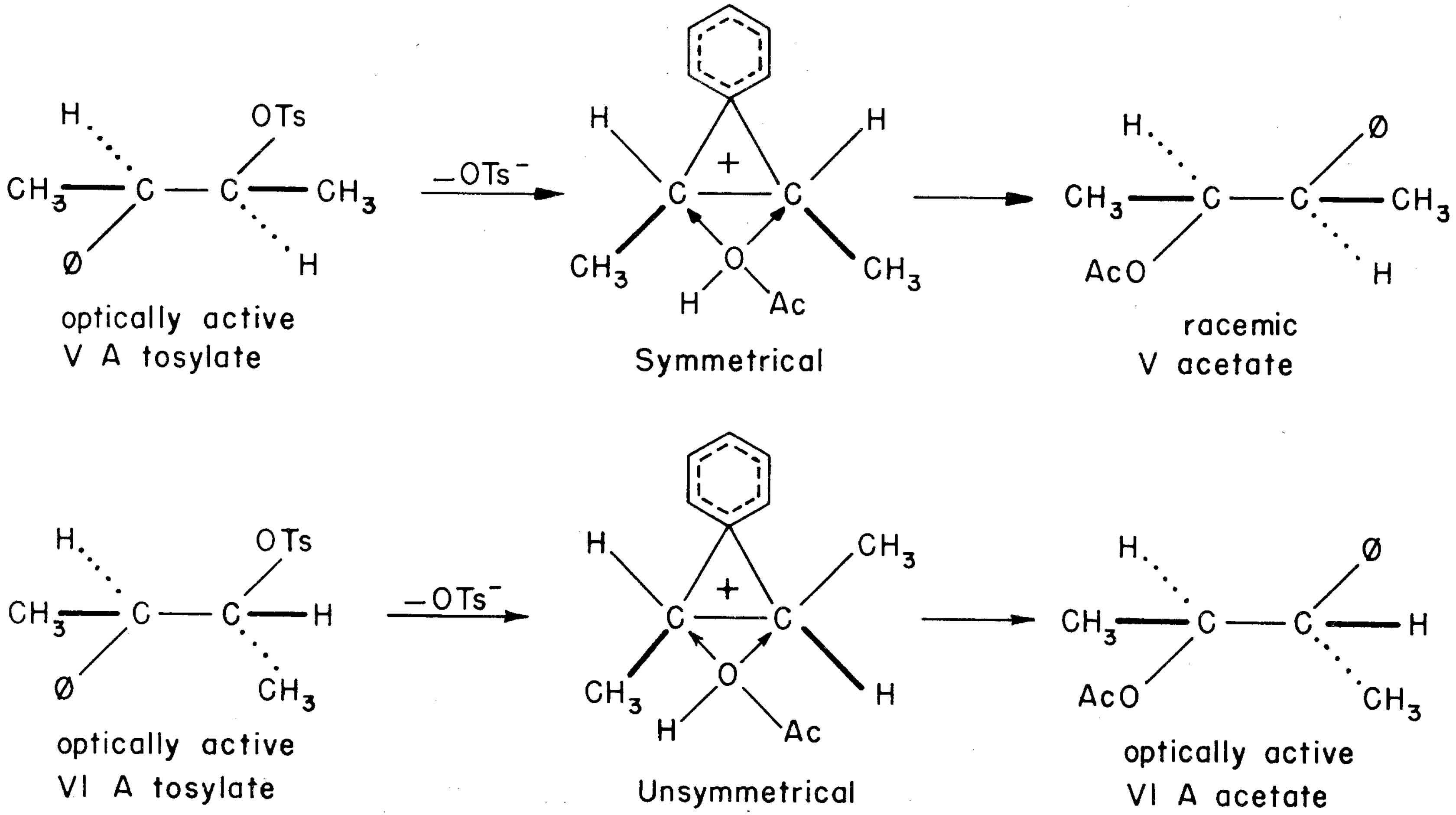


Fig. 2

The Acetolysis of *threo*-3-Phenyl-2-Butyl p-Toluenesulfonate and *erythro*-3-Phenyl-2-Butyl p-Toluenesulfonate

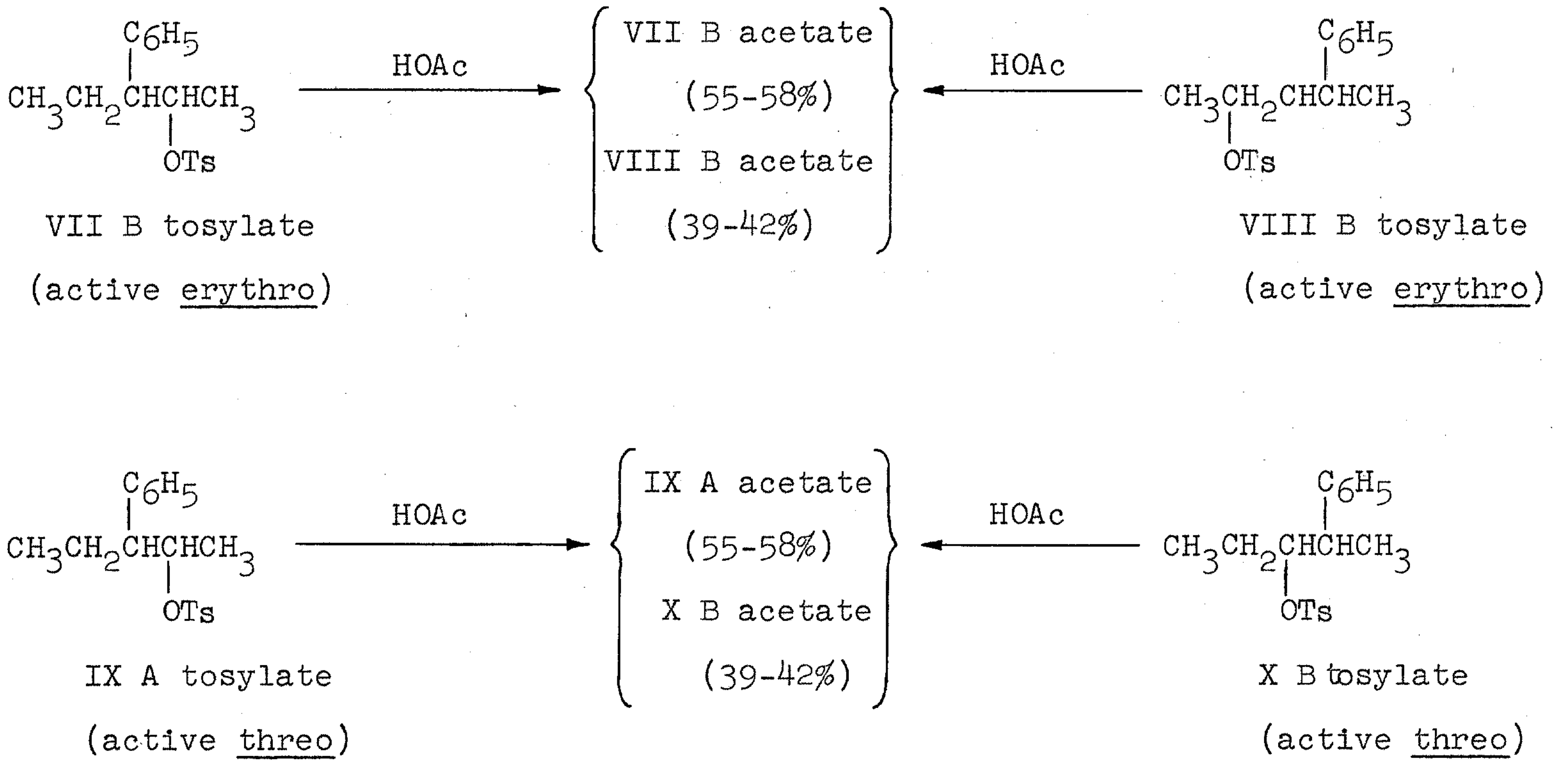
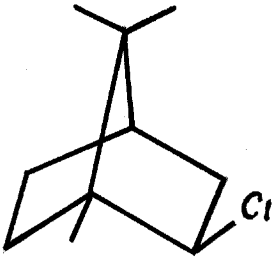
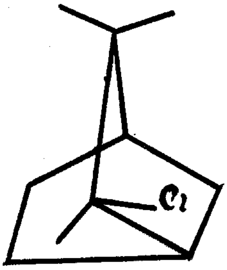


Fig. 3. Acetolysis of optically active forms of threo- and erythro-3-phenyl-2-pentyl tosylates and of threo- and erythro-2-phenyl-3-pentyl tosylates

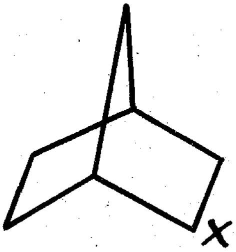
Non-classical carbonium ions involving alkyl-bridged structures have been postulated in the camphene hydrochloride-isobornyl chloride interconversion (XII$\rightleftarrows$XI) and in the reactions of norbornyl derivatives (XIII).



XI



XII

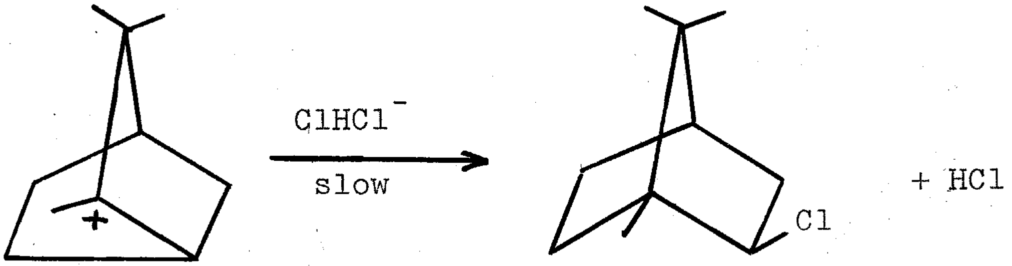


XIII

Camphene hydrochloride in solution dissociates rapidly and reversibly into camphene and hydrogen chloride. A slower reaction, catalyzed by hydrogen chloride, converts camphene hydrochloride into isobornyl chloride.[17,18,19,20] In view of the rapid equilibrium with camphene, the rate-determining step of the rearrangement cannot be the ionization of camphene hydrochloride. The rate expression for rearrangement was shown by Bartlett and Pöckel[18] to be

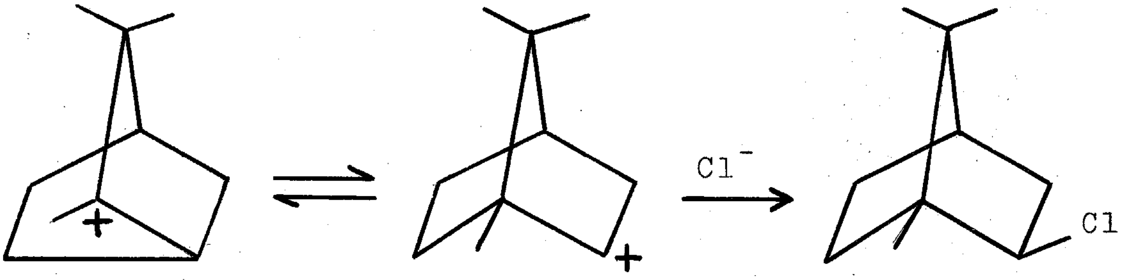
$$\nu = k(XII)(HCl).$$

Since the rate-determining step is not a reaction between camphene hydrochloride (XII) and hydrogen chloride it must be between the camphenyl ion (XIV) and hydrogen chloride or $ClHCl^-$ as required by the kinetics.[18,20]



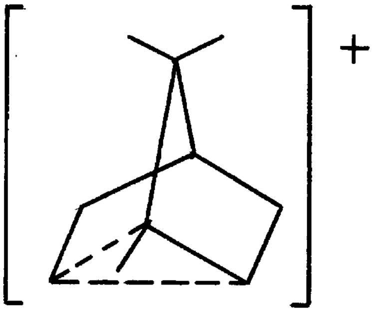
XIV XI

A rapid isomerization of XIV to the bornyl cation (XV) followed by a slow reaction with some species providing chloride ion is improbable in view of the clean-cut *exo*-configuration of



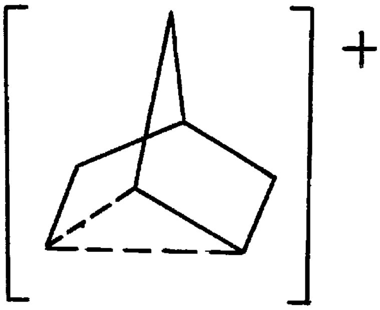
the rearranged product. Formation of the bornyl ion (XV) would be expected to lead to a mixture of bornyl and isobornyl chlorides.

The ready interconversion of camphene hydrochloride and isobornyl chloride (involving the high degree of stereospecificity mentioned above) suggests that neither the camphenyl ion or the bornyl ion has separate existence but that the actual cation is a resonance hybrid of the two extreme forms. Thus, the carbonium-ion intermediate may be best represented by a non-classical structure like XVI.[19]



XVI

A summary of the evidence in support of the non-classical structure XVII for the norbornyl cation is given below. This evidence also lends weight to XVI by virtue of the close analogy between the two systems.



XVII

Acetolysis of optically active exo-norbornyl derivatives gives racemic exo-norbornyl acetate.[21] endo-Norbornyl derivates also yield exo-norbornyl acetate on acetolysis. The latter reaction also results in nearly complete racemization,[22] but the solvolysis rate is slower than that of the exo isomer.[21,23,24]

All of these facts can be accommodated by assuming the symmetrical non-classical structure XVII to be the norbornyl cation intermediate. The neighboring alkyl-group interaction implied by XVII would aid the departure of the group X^- when exo-norbornyl derivatives are solvolyzed[24] and this conveniently explains the enhanced solvolysis rates of the exo- relative to the endo-isomers. Racemization is a consequence of the symmetry of XVII. The configuration of XVII is such that solvent attack upon it can only lead to the exo-configuration in the product.

While the enhanced solvolysis rate of exo-derivatives favors XVII, this structure does not uniquely account for racemization and exo-configuration of the products. These results can be accounted for by the possible intermediates XIX, XX and XXI (Fig. 4), and C^{14}-tracer experiments have been carried out in an effort to make a choice from among the various possibilities.

The formation of exo-norbornyl derivates with C^{14}-activity in the 5- and 6- positions, and the percentages of isotope-position rearrangement observed in the solvolysis of exo- and endo-norbornyl-2,3-C_2^{14} p-bromobenzensulfonates[25] and in the nitrous acid reactions of exo- and endo-norbornyl-3-C^{14}-amines[26] require 2,6-shifts of hydrogen in addition to the 1,2-shifts of carbon implied by XVII. From these studies it appears that XXI is not involved as an intermediate in the reactions of norbornyl derivates. The isotope-position re-

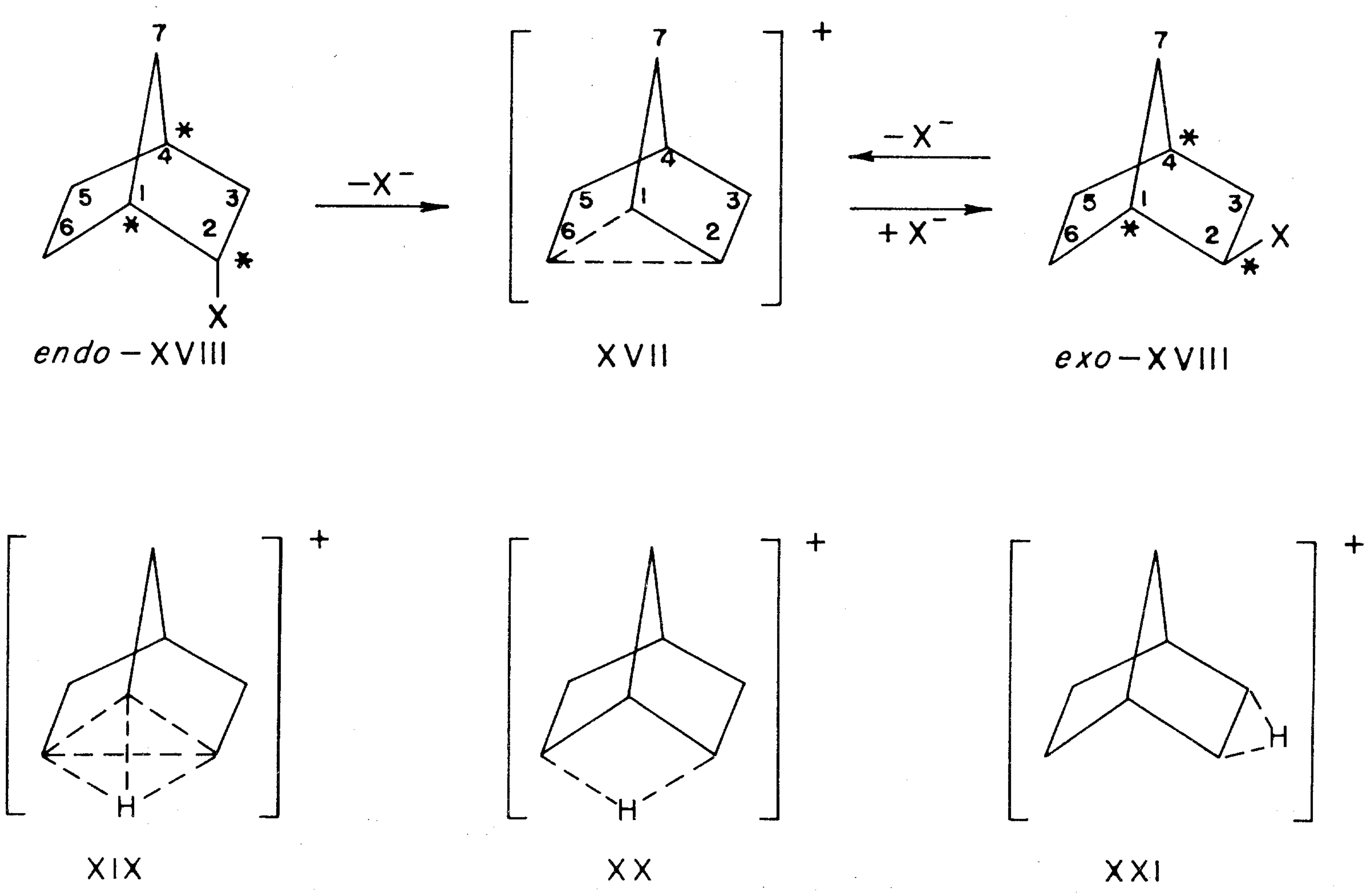


Fig. 4

Possible Structures for the Norbornyl Carbonium Ion

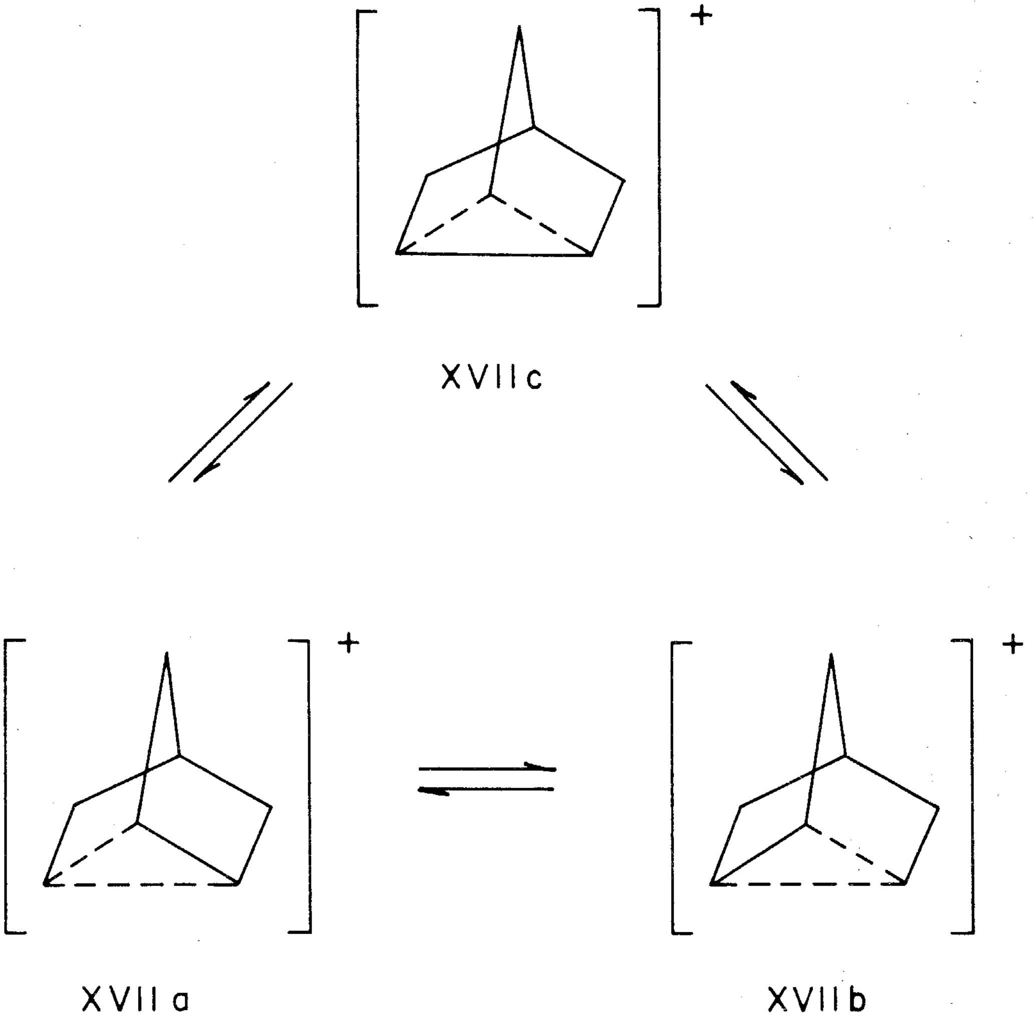
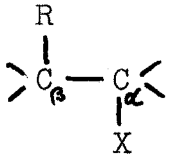


Fig. 5

Possible Mode of Rearrangement in the Norbornyl System arrangements can be most simply explained in terms of solvent attack on XVII and on the "nortricyclonium" ion (XIX) which appears to be formed more slowly than XVII.

An alternate formulation of hydrogen shift has been given by Bartlett[20] (Fig. 5). In this scheme the hydrogen shift involves an equilibrium between the three ions XVIIa, b and c (Fig. 5), with XIX now representing the transition state for hydrogen shift.

A systematic study has shown that the enhanced reactivity of exo-norbornyl derivates is not an isolated example, but is one case of a general effect that is closely related to Wagner-Meerwein rearrangements. Winstein and coworkers have studied the effect of hydrogen, alkyl groups and aryl groups, initially on C_β, on the solvolysis rates of a number of primary and secondary arylsulfonic esters.[14,24,27,28,29]

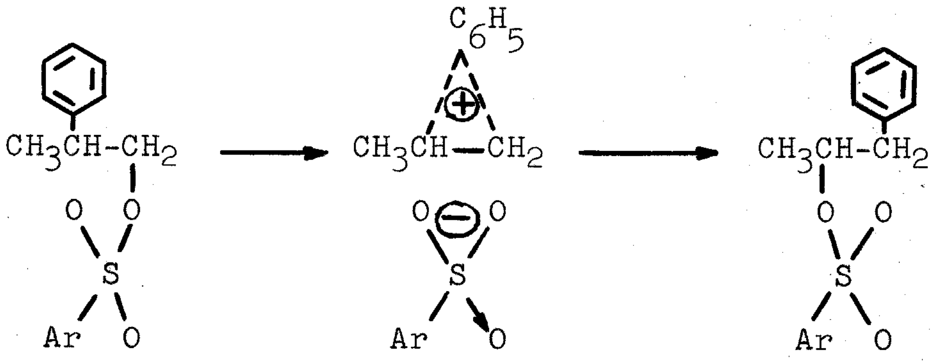


R = H, Alkyl or Aryl

X = *p*-Bromobenzenesulfonate or
p-Toluenesulfonate.

It is clear from the observed enhancement of solvolysis rates and control of configuration that neighboring carbon and hydrogen can exert an influence on the course and rate of reactions in a manner similar to the more familiar neighboring functional group effects[30,31,32] and neighboring π-electron effects.[23,53]

To illustrate neighboring group participation, solvolysis studies on phenylpropyl systems will be discussed. Phenyl participation with pronounced rate enhancement is found in the solvolysis of 2-phenyl-1-propyl arylsulfonates.[29] Accompanying the acetolysis of this system is an internal rearrangement (internal return[33]) to benzylmethylcarbinyl arysulfonate. That this rearrangement is indeed an internal



isomerization is shown by the insensitivity of the rates of acetolysis and isomerization to added sulfonate ion ($ArSO_3^-$). Infrared analysis of the acetolysis product of 2-phenyl-1-propyl p-bromobenzenesulfonate indicates that it consists exclusively of rearranged acetate (appendix I). In the acetolysis of benzylmethylcarbinyl sulfonic esters[28] a weak neighboring phenyl group participation seems to be operating but the mechanism may be complicated by internal return (without isomerization). In formic acid, neighboring phenyl participation is made evident by 85% retention of configuration and by a moderately enhanced rate of solvolysis. No Wagner-Meerwein rearrangement is observed in the solvolysis reactions

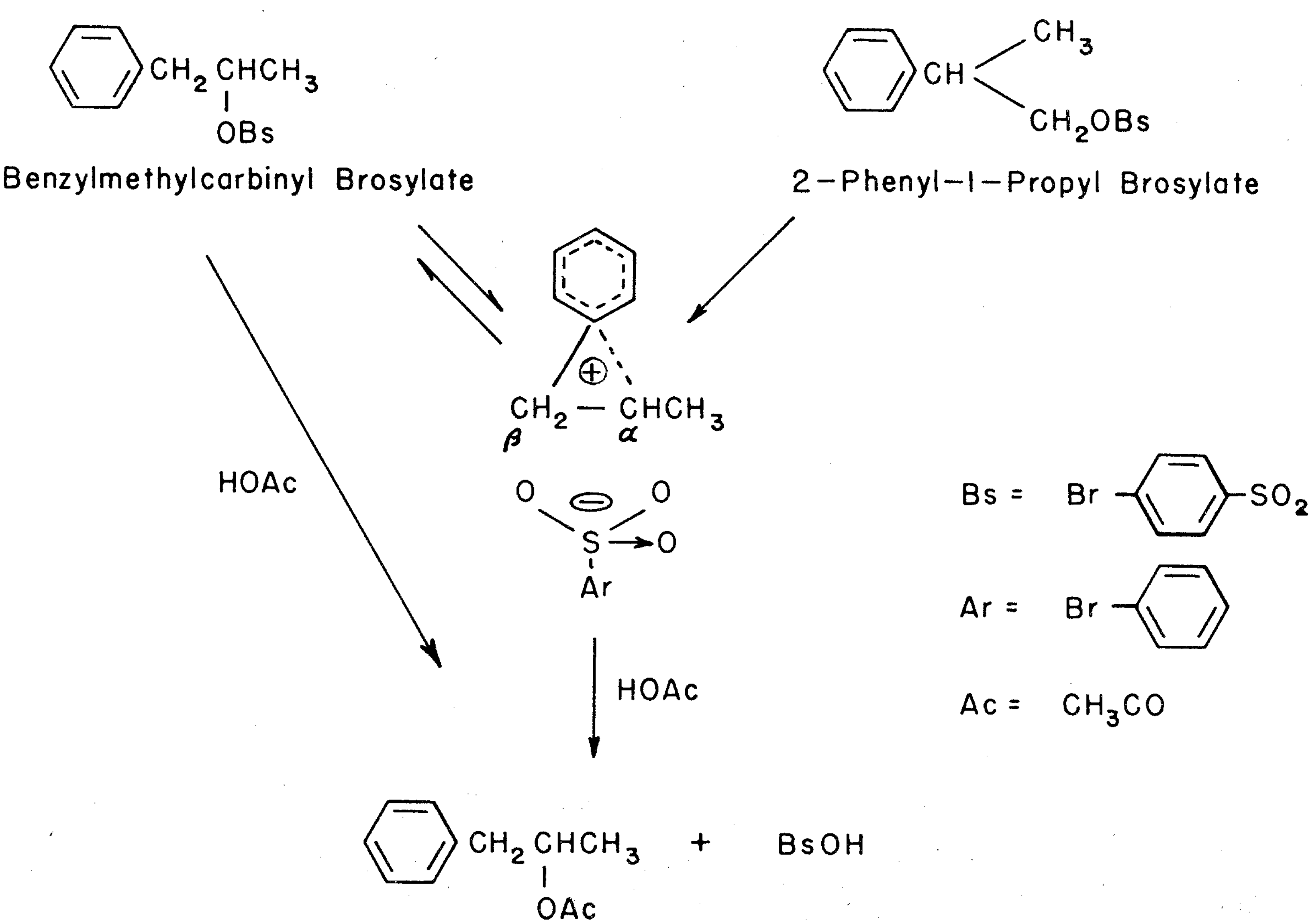


Fig. 6

Internal Return and Rearrangement in the Acetolysis of Benzylmethylcarbinyl and 2-Phenyl-1-Propyl Systems of this system. The simplest interpretation of these facts is that the two isomeric arylsulfonates give a common intermediate which may return, in one direction only, or react with solvent to give the observed product (Fig. 6). Benzylmethylcarbinyl sulfonic esters may solvolyze by a second route, not involving phenyl participation, as shown by partial racemization. This formulation is compatible with those given for the 3-phenyl-2-butyl systems (Fig. 2), and the phenylpentyl systems (Fig. 3); the unidirectional nature of the rearrangement in the present case being the result of a relatively large difference in the strengths of the two partial bonds from phenyl to C_α and C_β in the intermediate.

The reaction of 2-phenylethylamine-1-C^{14} with nitrous acid in acetic acid gives 27% of the product of rearrangement by phenyl migration, 2-phenylethanol-2-C^{14}. Under the same conditions 2-(p-methoxyphenyl)-ethylamine-1-C^{14} gives 45% p-methoxyphenyl migration.[34] The difference in extents of rearrangement is roughly in agreement with the difference in effectiveness of the two aryl groups in enhancing the solvolysis rates of the corresponding 2-arylethyl p-toluenesulfonates.[35] A possible explanation of the rearrangement results is that the diazonium cation loses a molecule of nitrogen to give an unsymmetrical phenonium ion intermediate (XXII) which would be

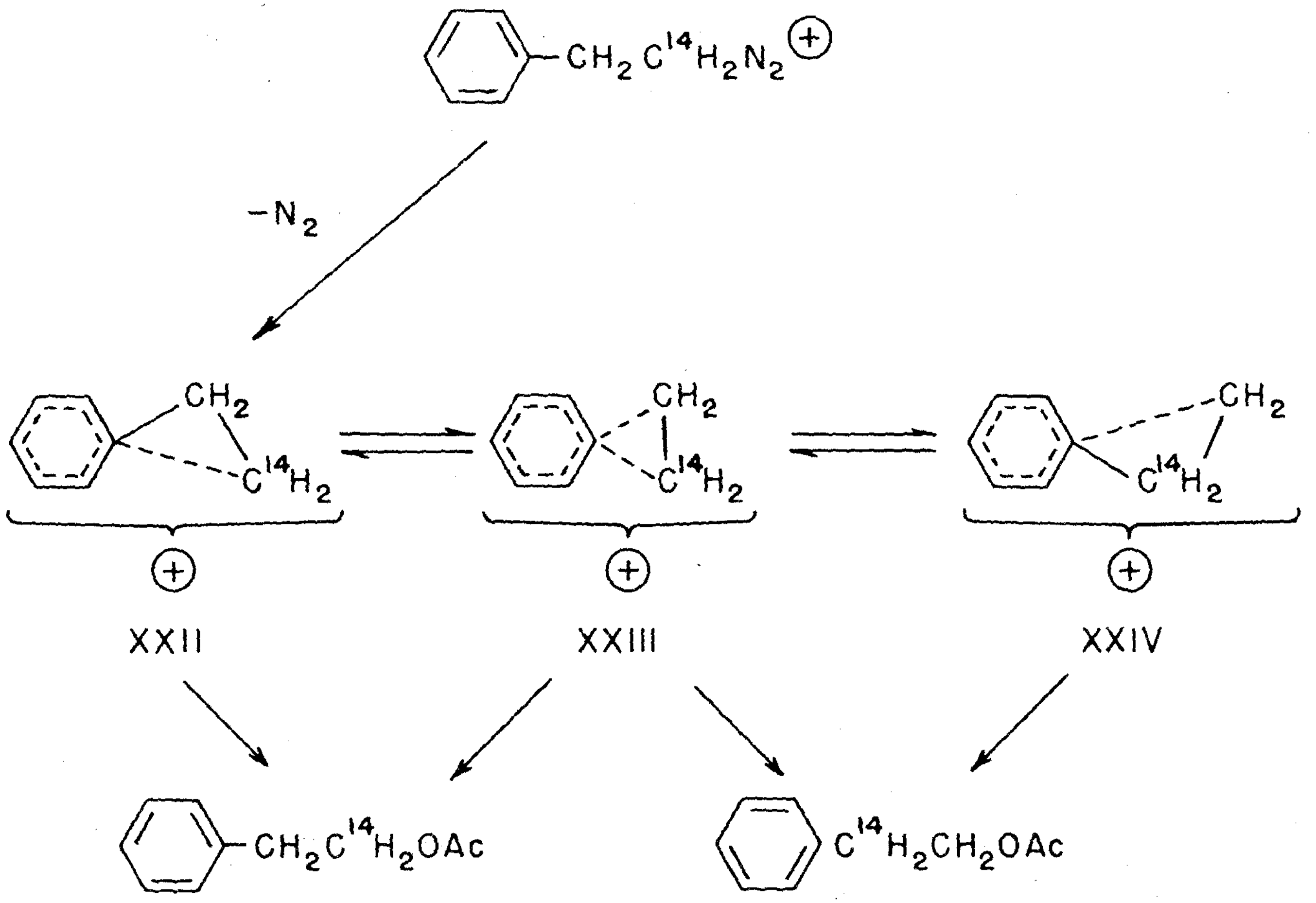


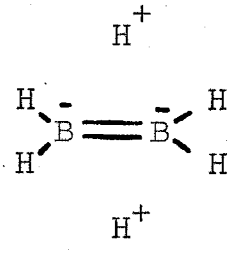
Fig. 7

A Possible Formulation for the Decomposition of the 2-Phenylethyldiazonium-1-C^{14} Cation in Acetic Acid Solution expected to give only 2-phenylethyl-1-C^{14} derivatives unless it is converted into XXIII or XXIV (Fig. 7). With a 4-methoxyl substituent XXIII should be stabilized by delocalization of the unshared electron pairs on oxygen, permitting the interconversion of XXII and XXIV to occur more readily. It is not possible to decide on the basis of the available evidence whether XXIII should be considered an intermediate or a transition state for the interconversion of XXII and XXIV.

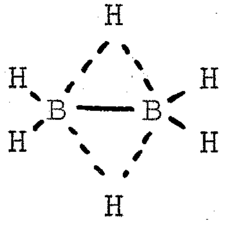
BRIDGED IONS AND ELECTRON-DEFICIENT COMPOUNDS

The consistent manner in which a large amount of data from kinetic, stereochemical and isotopic tracer experiments can be interpreted by the assumption that bridged-ion intermediates are involved has firmly established these non-classical structures in chemical thought. Concurrent work on a family of electron-deficient compounds, the boron hydrides, has established bridged structures for these compounds[36] and provided a close analogy for bridged carbonium ions, which are, of course, electron-deficient also.

It is now generally accepted that the structure of diborane cannot be described in terms of any single structure of the classical type, but must instead be described as intermediate between several different classical structures.[37] The structure of diborane has been discussed by Pitzer in terms of a protonated double bond[39] (XXV), and by others in terms of two three-center bonds[38,40] (XXVI). Longuet-Higgins[40] has



XXV

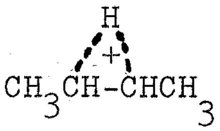


XXVI

objected to the structure XXV on the grounds that it implies a short, strong B-B bond and two rather acidic hydrogen atoms, contrary to fact.

The experimental evidence for the hydrogen bridge structures for the boron hydrides lends support to the theoretical conclusion that the electron-deficient system H_3^+ is most stable in a triangular configuration.[57]

It has been suggested that the carbonium ion $CH_3CH_2\overset{+}{C}HCH_3$ can exist in the forms without much activation



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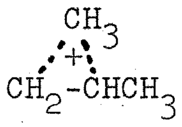
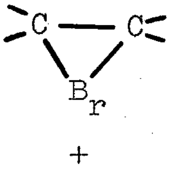
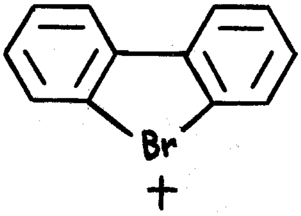


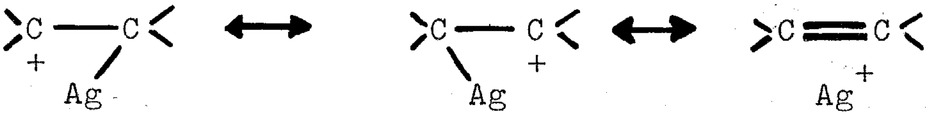
energy.[41] The rearrangements that occur by hydrogen and methyl group migration when n-propylamine-1-C^{14} is treated with nitrous acid[42] indicate that this view is correct.

Roberts and Kimball[43] proposed an ethylenebromonium intermediate XXVII to account for the stereochemical course of the addition of bromine to olefins, although in this case

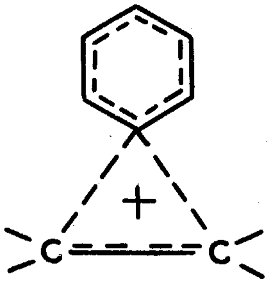

XXVII


XXVIII

there is some doubt as to whether the intermediate is more analogous to the weak iodine-benzene complex or to the bromonium ion,[44] XXVIII. Less ambiguity exists with respect to the proposal by Winstein and Lucas[45] of the resonance hybrid corresponding to XXIX, XXX and XXXI for the structure of the silver-olefin coordination compounds. These workers prefer an analogous representation for the ethylenebromonium intermediate.

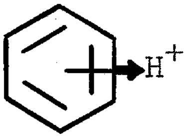

XXIX XXX XXXI

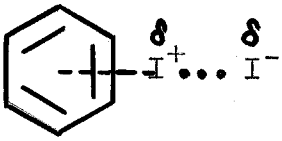
Cram's proposal[14,17] for the structure of the "phenonium" intermediate is shown in Figure 1. Winstein[28] prefers to represent the hybrid structure of this intermediate by XXXII because of the possibility that the structure like XXXI makes an important contribution.



XXXII

Dewar has proposed a "π-complex" theory[46] in which a positive ion forms a dative bond with the π-electrons of an olefin or aromatic molecule. Dewar's proposal predicts[47]

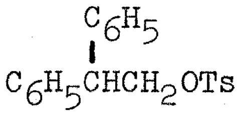
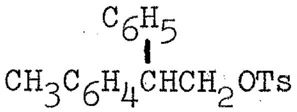
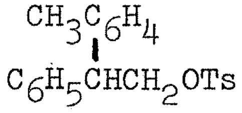
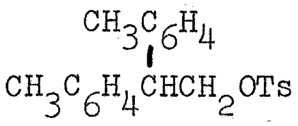




that electron withdrawing substituents will increase the tendency of an aromatic molecule to migrate relative to unsubstituted phenyl, while electron donating substituents will decrease the tendency to migrate. Actually, just the opposite of this occurs as shown by deamination of 2-arylethylamines[34] and 2,2-diarylethylamines,[48] by dehydration of 2,2-diarylethanols[49] and solvolysis of 2,2-diarylethyl p-toluenesulfonates.[50] Accordingly, it seems clear that the better the electron donating ability of the aromatic group the more stable is the bridged ion intermediate. In agreement with this is the finding that the greater tendency of the p-tolyl group to migrate in comparison with phenyl corresponds fairly well to an increased rate of acetolysis in the 2,2-diarylethyl p-toluenesulfonate series shown in Table I.[50]

TABLE I

Relative Acetolysis Rates and Migration Ratios

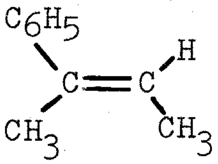
Compound	Acetolysis Rel. Rate	p-Tolyl % Migration	Acetolysis Relative Rate per Aryl Group	
 $C_6H_5\overset{C_6H_5}{\overset{\vert}{C}}HCH_2OTs$	1.0		0.5	(1.0)
 $CH_3C_6H_4\overset{C_6H_5}{\overset{\vert}{C}}HCH_2OTs$	3.7	71	1.1	(2.2)
 $C_6H_5\overset{CH_3C_6H_4}{\overset{\vert}{C}}HCH_2OTs$			2.6	(5.2)
 $CH_3C_6H_4\overset{CH_3C_6H_4}{\overset{\vert}{C}}HCH_2OTs$	8.3		4.2	(8.3)

HYDROGEN MIGRATION AND ELIMINATION

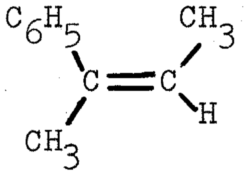
In the solvolysis of optically active *threo*- and *erythro*-3-phenyl-2-butyl arylsulfonates, V A and VI A respectively, Cram[51] was able to identify four olefinic products, XXXIII - XXXVI; and when glacial acetic acid was used as solvent, two acetates were produced as well, XXXVII and V acetate or VI A acetate.

$CH_3CH(C_6H_5)CH(OSO_2Ar)CH_3$

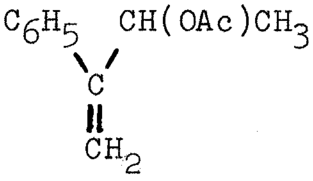
V A (active *threo*)
VI A (active *erythro*)



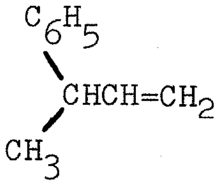
XXXIII



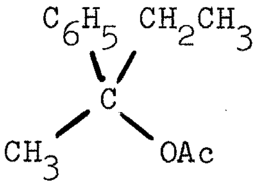
XXXIV



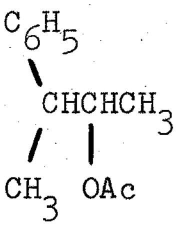
XXXV



XXXVI
(active)



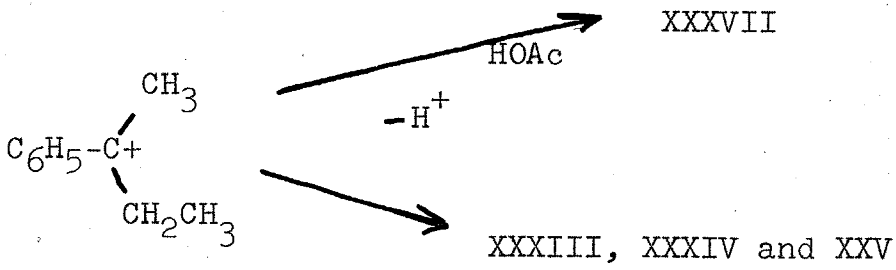
XXXVII
(racemic)



V (racemic *threo*)
VI A (active *erythro*)

The fact that the product ratio was not sensitive to the concentration of acetate ion indicates that the olefinic products were formed by an E_1 process.

The most reasonable explanation for the completely racemic character of XXXVII is that it arose from the classical carbonium ion of structure XXXVIII.



XXXVIII

Assuming that the reaction paths shown in Figure 8 account for all of the products in the acetolysis of threo-3-phenyl-2-butyl p-toluenesulfonate, it is possible to calculate the amount of product formed in each reaction path. The yield of compounds arising from the hydrogen-bridged ion XXXIX was found to be 29%. Comparison of the rate of formation of the symmetrical phenonium ion[52] with the rate of formation of products through the hydrogen-bridged ion indicates that the phenyl group participates in an intramolecular displacement reaction eight times as often as hydrogen in this system.

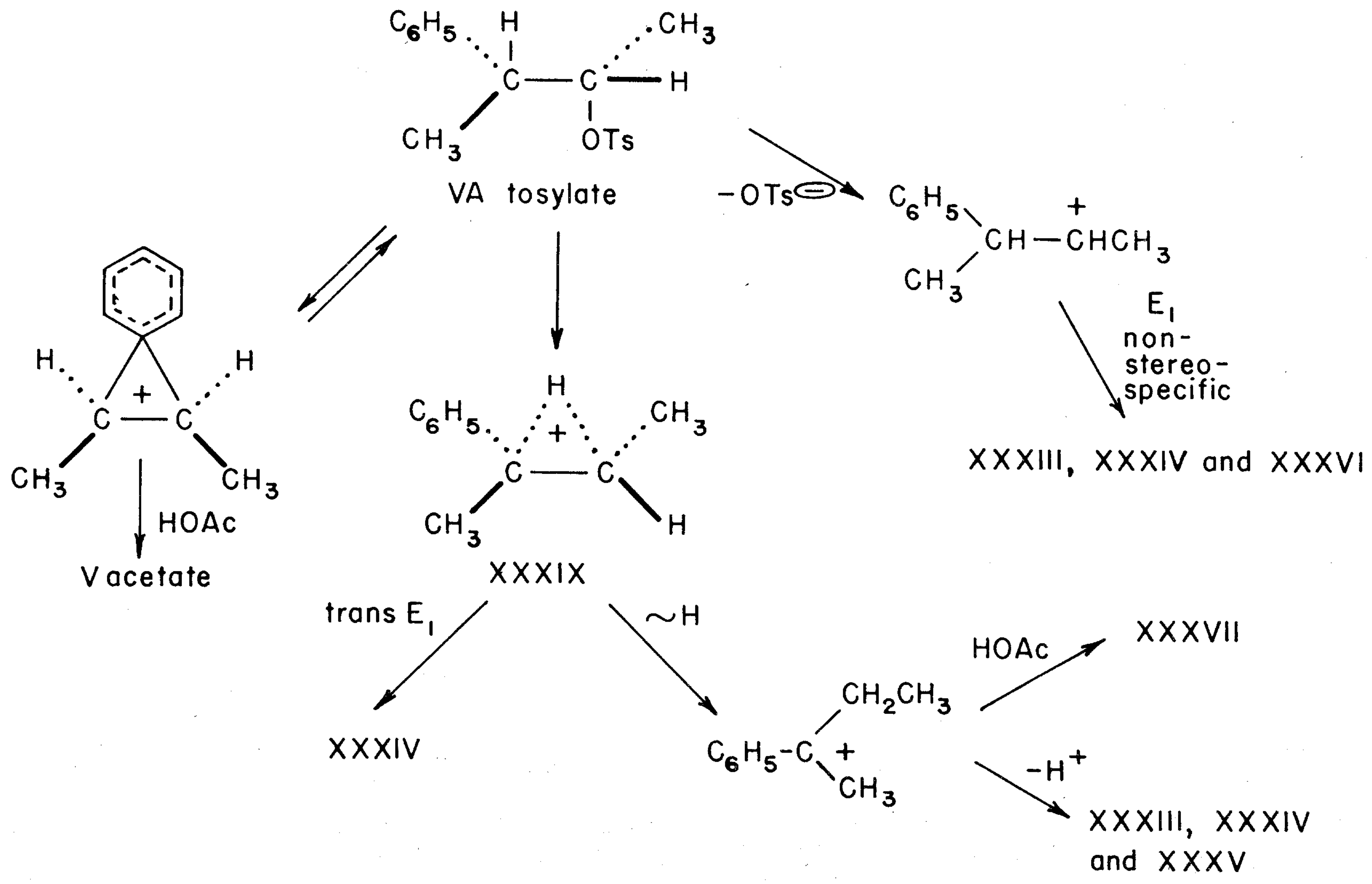
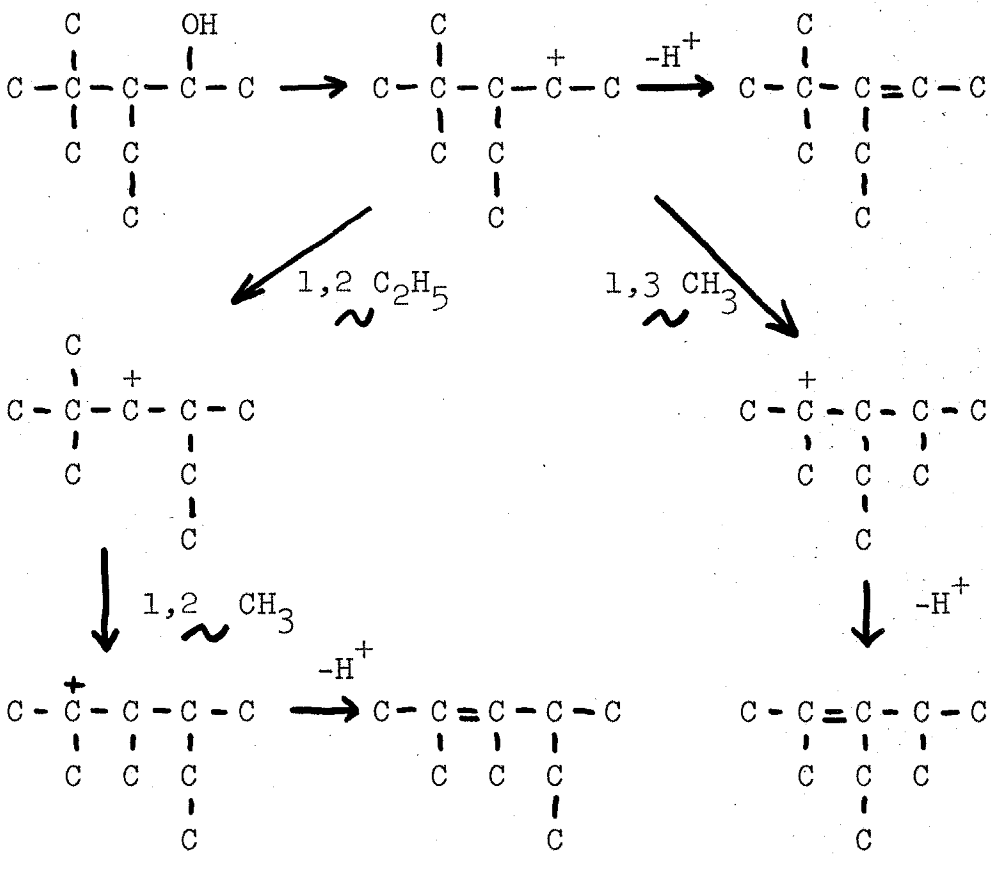


Fig. 8

Hydrogen Elimination and Hydrogen Migration in the Acetolysis of *threo*-3-Phenyl-2-Butyl p-Toluenesulfonate

REARRANGEMENT BY 1,3-SHIFTS

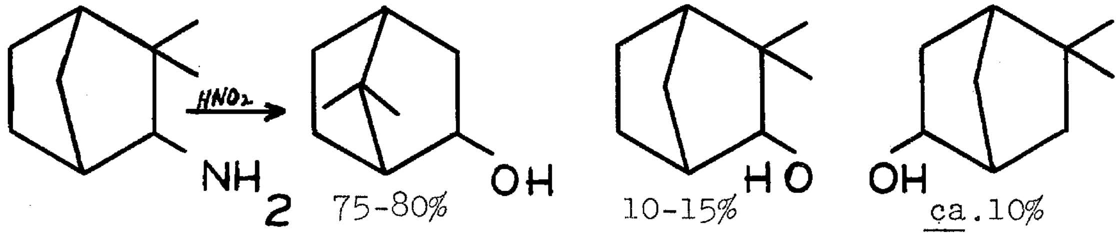
In the dehydration of 4,4-dimethyl-3-ethyl-2-pentanol Mosher and Cox[54] obtained a mixture of unrearranged olefin and 2,4-dimethyl-3-ethyl-2-pentene (XL). Because none of the olefin, XLI, arising from a 1,2-shift of ethyl followed by a 1,2-shift of methyl was obtained, the authors concluded that XL was formed by a 1,3-shift of methyl.



XLII XLI XL

This conclusion rests on the assumptions that if XLII were an intermediate it would lead to formation of XLI as well as to XL, and that any XLI formed would not be completely converted into XL under the conditions of the reaction. The latter assumption could be tested experimentally.

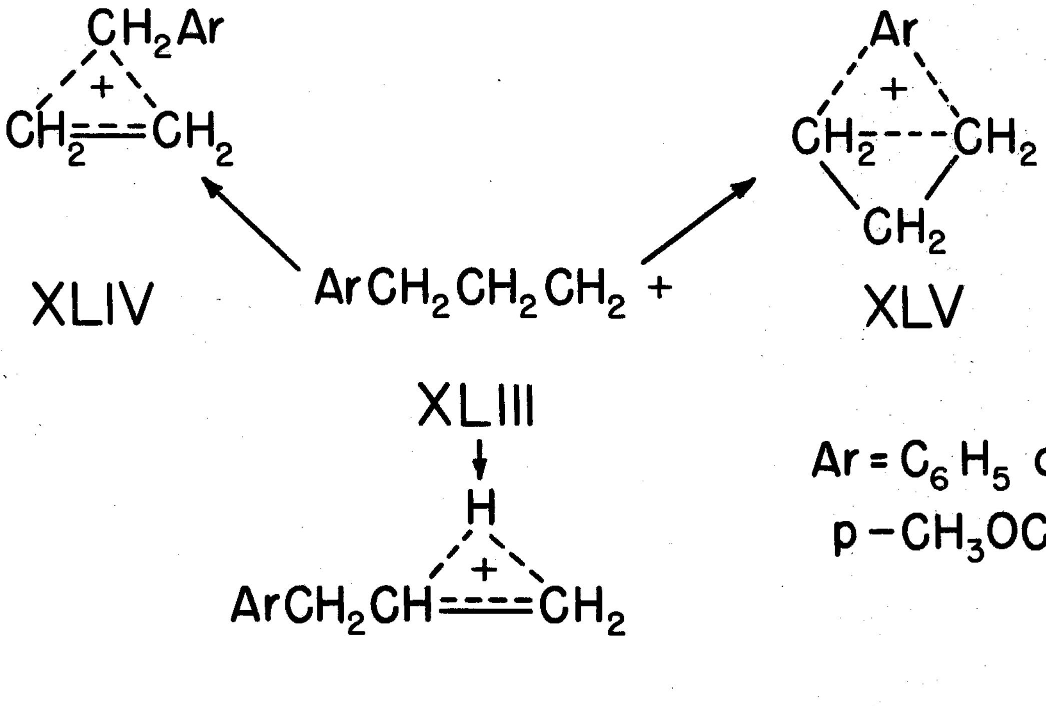
1,3-Shifts of hydrogen in the reactions of norbornyl derivatives were noted earlier in this introduction. Such rearrangement has been found to occur in other bicyclic systems, for example[55]



Products arising from 1,2-shifts of alkyl are formed in greater yield than those arising from 1,3-shifts of hydrogen.

RESULTS AND DISCUSSION

The present research, an investigation of the stabilities of the bridged ion structures XLIV and XLV relative to the isomeric classical carbonium ion XLIII, was undertaken as part of a larger program devoted to the elucidation of the factors which are important for the occurrence of non-classical, bridged carbonium ions. Formation of XLVI was expected to be an important competing process.



XLIV

XLIII

XLV

XLVI

Ar = C_6H_5 or $p-CH_3OC_6H_4$

The isotopic tracer technique was used to detect rearrangement of the carbon skeleton, and the primary amine-nitrous acid reaction was chosen for irreversible generation of the desired cations.

Because of the possibility that successive migrations would lead to a complex mixture of alcohols and olefins in the reaction of 3-phenylpropylamine with nitrous acid, it seemed desirable to obtain samples of the structurally isomeric phenylpropanols and phenylpropenes for comparison with the reaction products. These were obtained by synthesis in most cases. The hydrocinnamyl alcohol and α-methylstyrene used were purified commercial samples and the others were prepared by standard procedures.

3-Phenylpropylamine was prepared by lithium aluminum hydride reduction of β-phenylpropionitrile. The products of the reaction of 3-phenylpropylamine with excess nitrous acid in aqueous solution were hydrocinnamyl alcohol (XLVII), benzylmethylcarbinol (XLVIII) and allylbenzene (XLIX) along with smaller amounts of organic nitrites and nitro compounds and a considerable amount of higher boiling material, which was probably nitroso secondary amine as found in similar reactions.[58,59] The absence from these products of other isomeric phenylpropanols and phenylpropenes was demonstrated by comparison of infrared spectra with those of authentic samples of possible contaminants.

β-Phenylpropionitrile-1-C^{14} was prepared by the reaction of 2-phenylethyl bromide with sodium cyanide-C^{14}. Part of the active nitrile was hydrolyzed to hydrocinnamic-1-C^{14} acid and the rest was reduced with lithium aluminum hydride to 3-phenylpropylamine-1-C^{14}. A solution of the active amine in dilute aqueous perchloric acid was treated with sodium nitrite at 50-55°. Inactive hydrocinnamyl alcohol, benzylmethylcarbinol and allylbenzene were added to act as carriers; the products were separated by fractionation and the yields of active products were calculated by the isotope dilution technique.

Product	% Yield
$C_6H_5CH_2CH{=}CH_2$(XLIX)	12[a]
$C_6H_5CH_2CHOHCH_3$(XLVIII)	19[a]
$C_6H_5CH_2CH_2CH_2OH$(XLVII)	30[a]
Recovered amine	9

[a] Calculated by isotope dilution.

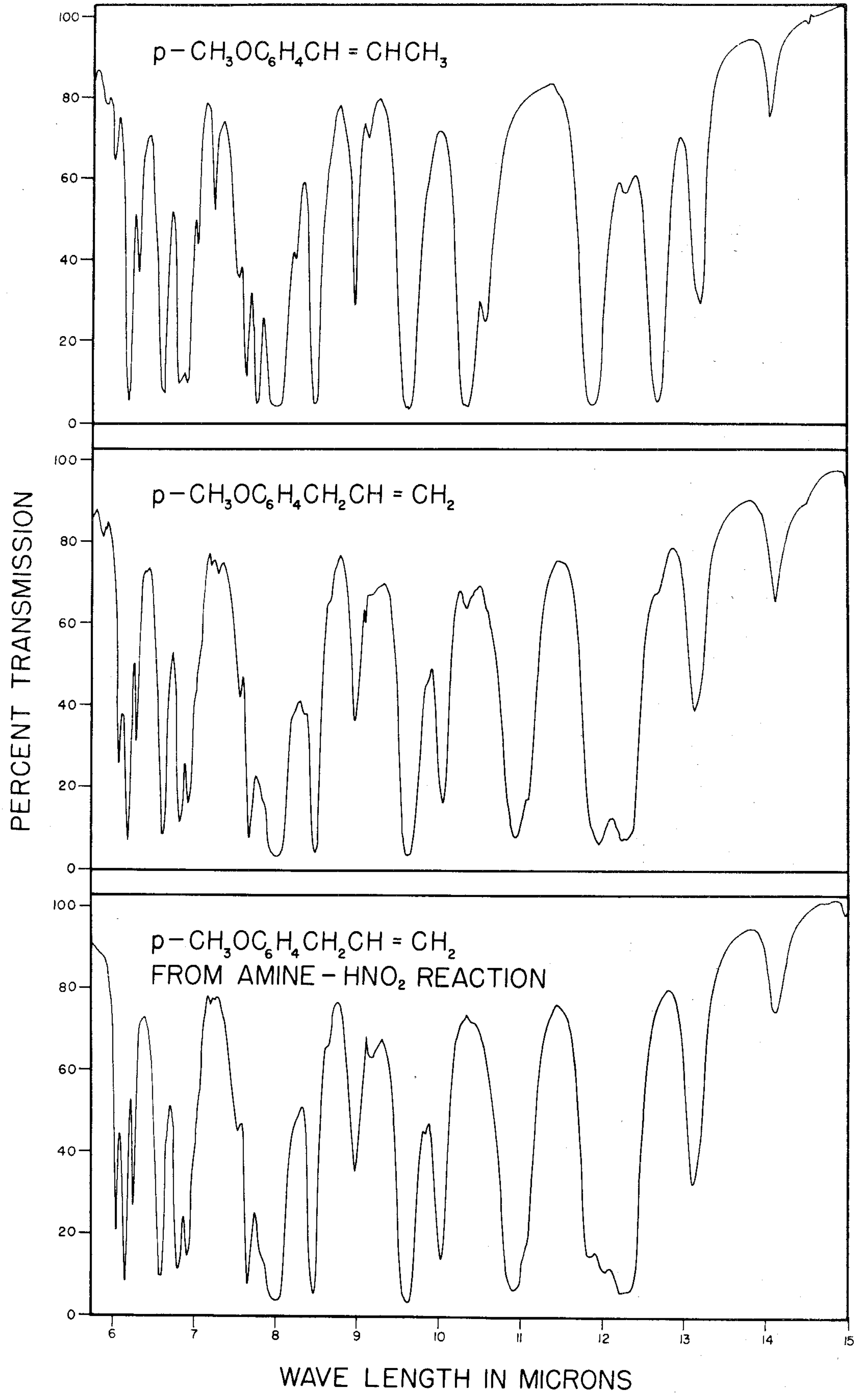
p-Methoxyhydrocinnamyl alcohol (L), p-methoxybenzylmethylcarbinol (LI), p-methoxyallylbenzene (LII) and 3-(p-methoxyphenyl)-propylamine were prepared by standard procedures. The reaction of 3-(p-methoxyphenyl)-propylamine with excess nitrous acid in aqueous solution at 55° gave the alcohols L and LI and the olefin LII. The infrared spectra of the amine-nitrous acid products were essentially identical in all major respects with those of the corresponding authentic samples except for a strong absorption band at 6.4 μ in the spectrum of L. The infrared spectrum of the olefin product from the amine-nitrous acid reaction is shown in Fig. 9 along with those of authentic LII and a purified commercial sample of anethol. The purity of the allylbenzene product from 3-phenylpropylamine was as good as that of the p-methoxyallylbenzene product of the second amine-nitrous acid reaction.

β-(p-Methoxyphenyl)-propiontrile-1-C^{14} was prepared by the reaction of 2-(p-methoxyphenyl)-ethyl p-toluenesulfonate with sodium cyanide-C^{14}, and the active nitrile was reduced to 3-(p-methoxyphenyl)-propylamine-1-C^{14} with lithium aluminum hydride. A solution of the active amine in excess dilute aqueous perchloric acid was treated with sodium nitrite at 60°. Inactive L, LI and LII were added to the reaction mixture and the products were isolated and yields calculated as before.

Product	% Yield
p-$CH_3OC_6H_4CH_2CH{=}CH_2$(LII)	13[a]
p-$CH_3OC_6H_4CH_2CHOHCH_3$(LI)	18[a]
p-$CH_3OC_6H_4CH_2CH_2CH_2OH$(L)	27[a]
Recovered amine	7.5

[a] Calculated by isotope dilution.

Fig. 9. Infrared absorption spectra of the pure liquids were determined with a Perkin-Elmer Model 21 Infrared Spectrophotometer using a 0.028 mm. sodium chloride cell.


$p-CH_3OC_6H_4CH=CHCH_3$
$p-CH_3OC_6H_4CH_2CH=CH_2$
$p-CH_3OC_6H_4CH_2CH=CH_2$
FROM AMINE - HNO_2 REACTION
PERCENT TRANSMISSION
100
80
60
40
20
0
6
7
8
9
10
11
12
13
14
15
WAVE LENGTH IN MICRONS

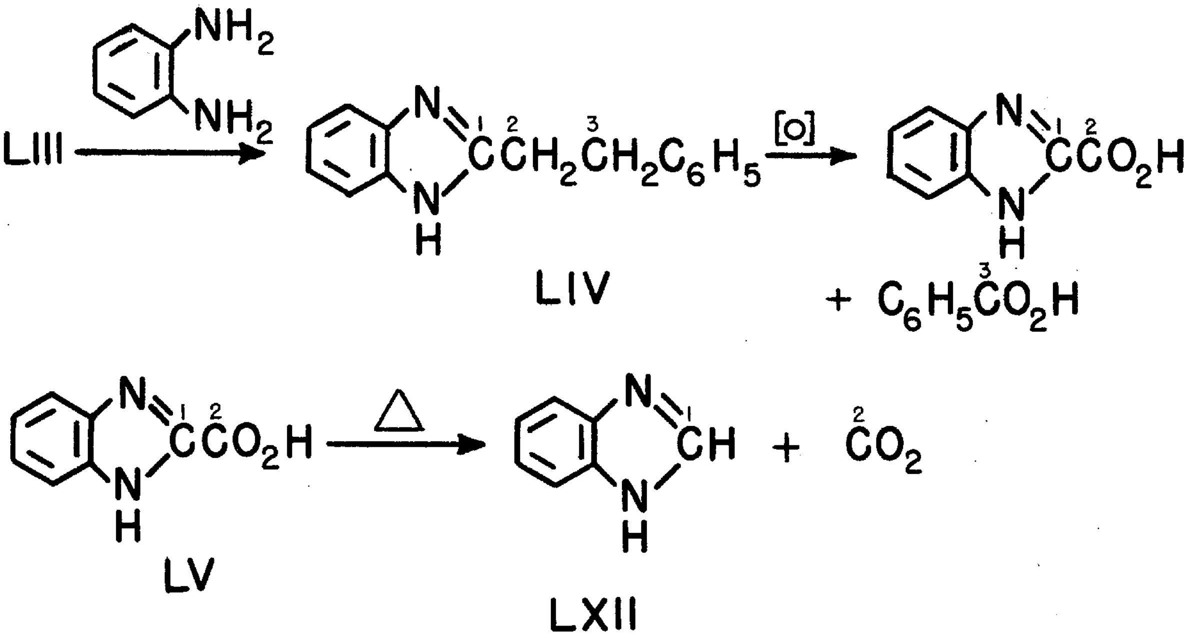
DEGRADATIONS AND ACTIVITY MEASUREMENTS

As the first step of the degradation, hydrocinnamyl-C^{14} alcohol (XLVII) was oxidized to hydrocinnamic-C^{14} acid (LIII). Trial experiments with inactive XLVII showed that oxidation with concentrated nitric acid or permanganate gives a product that is difficult to purify.

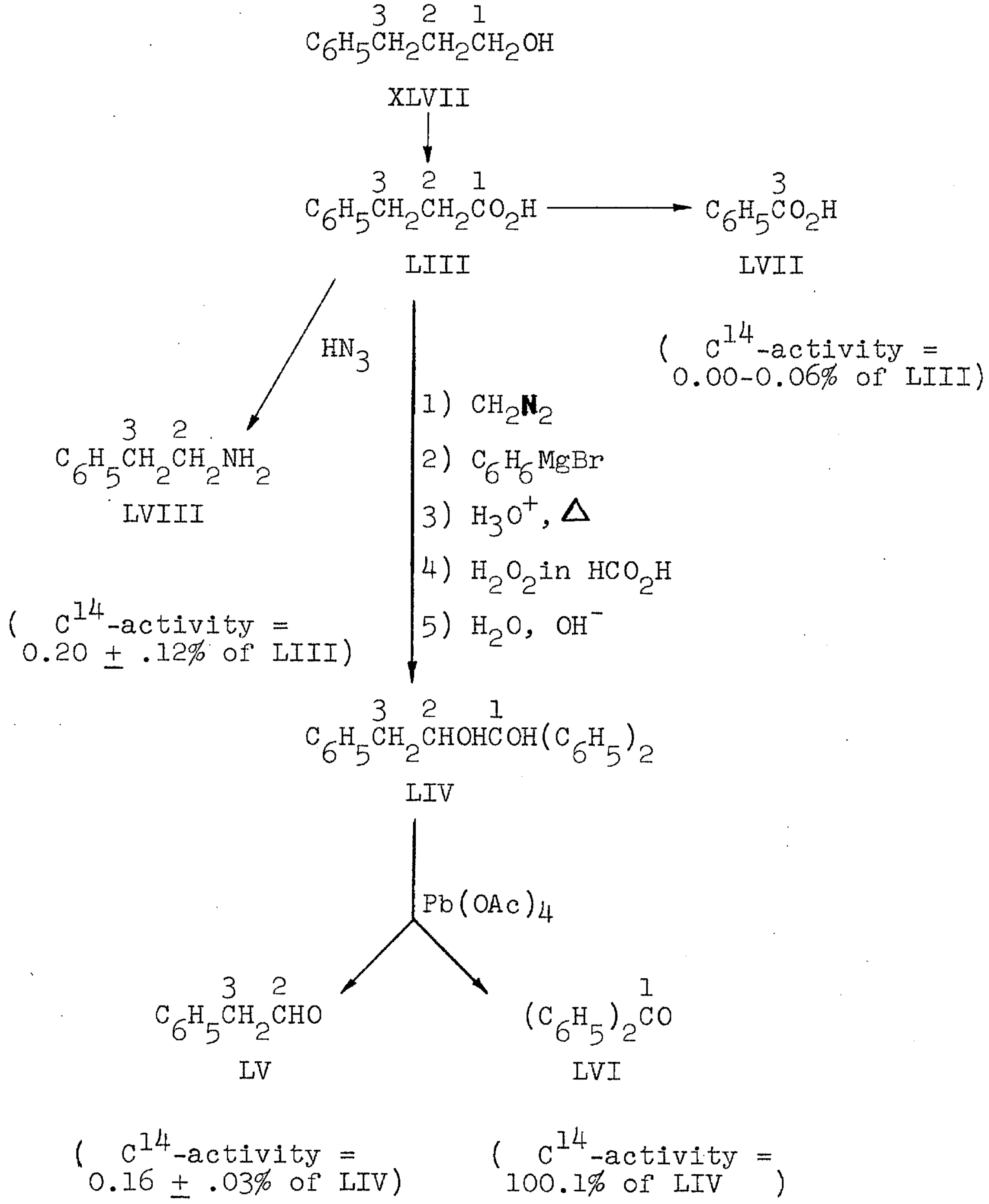
Run	Conditions	Major Product	Minor Product
A	conc. HNO_3, 70-80°	LIII	p-nitrohydrocinnamic acid
B	conc. HNO_3, 20-22°	LIII	p-nitrohydrocinnamic acid
C	alk. permanganate, 20-30°	benzoic acid	LIII
D	acid permanganate, 10-15°	LIII	benzoic acid

Chromium trioxide in aqueous acetic acid gave poor yields of LIII, but this method was chosen for oxidation of the active acid because of the ease of purification of the product.

The formation and cleavage of 2-(β-phenylethyl)-benzimidazole seemed to offer a particularly simple route for the degradation of LIII. It was found, however that permanganate oxidation of LIV gave only poor yields of the carboxylic acid, LV, and it was difficult to obtain LV in a pure state when prepared this way. A modified Barbier-Wieland degradation of LIII gave good results and was applied to the active



acid. The Schmidt reaction of LIII was also used since it provided a simple means of checking the results of the Barbier-Wieland degradation. The degradation of hydrocinnamyl-C^{14} alcohol is outlined in Fig. 10 and data for the C^{14}-activity measurements are given in Table II. A discussion of the reliability of the activity measurements is given in appendix II.



(C^{14}-activity = 0.00-0.06% of LIII)

(C^{14}-activity = 0.20 ± .12% of LIII)

(C^{14}-activity = 0.16 ± .03% of LIV)

(C^{14}-activity = 100.1% of LIV)

Fig. 10. The degradation of hydrocinnamyl-C^{14} alcohol.

TABLE II

C^{14}-Activity Measurements

Degradation of Hydrocinnamyl-C^{14} Alcohol

Compound	mg.	C^{14}-Activities[a]	μc/mmole	%Δ[b]
$C_6H_5CH_2CHOHCOH(C_6H_5)_2$	11.1	148.5 ± 1.0	0.9602	1.0
	9.9	147.4 ± 1.0	.9463	0.4
(LIV)	6.92	102.2 ± 1.0	.9444	0.6
		average	0.950	0.7
$(C_6H_5)_2CO$ (LVI)	12.3	149.7 ± 1.0	0.9255	2.7
2,4-dinitrophenylhydrazone[c]	11.2	140.8 ± 1.0	.9599	0.9
	11.35	145.0 ± 1.0	.9745	2.5
	13.0	159.4 ± 1.0	.9339	1.8
	11.3	142.5 ± 1.0	.9611	1.0
		average	0.951	1.8
$C_6H_5CH_2CHO$ (LV)	27.7	0.53 ± .1	1.6 x 10^{-3}	7
dimethone derivative	30.6	0.49 ± .1	1.3	13
	29.7	0.58 ± .1	1.6	7
		average	1.5 x 10^{-3}	9
$C_6H_5CH_2CH_2CO_2H$ (LIII)	11.65	512.6 ± 1.5	1.39 ± .01	
$C_6H_5CH_2CH_2NH_2$ (LVIII) benzoyl derivative	3.0	0.18 ± .10	(2.8 ± 1.6) x 10^{-3}	
$C_6H_5CO_2H$ (LVII)	14.8	0.00-0.06	(0.0-8.6) x 10^{-5}	

[a] Sample activities in mvolts determined by vibrating reed electrometer method as described by O. K. Neville, J. Am. Chem. Soc., 70, 3499 (1948). The activities have been corrected for background. Limits of error were estimated visually from the recorder chart. [b] Percent deviation from the mean value. [c] To remove oxides of nitrogen, a heated lead peroxide cartridge was placed in the combustion line as recommended by W. A. Bonner and C. J. Collins, J. Am. Chem. Soc., 75, 3693 (1953).

Benzylmethylcarbinol-C^{14} was oxidized to a mixture of benzyl methyl ketone (LIX) and benzaldehyde with chromium trioxide in aqueous acetic acid. LIX and o-phenylenediamine at elevated temperature gave a low yield of 2-methylbenzimidazole-C^{14} (LX). None of the expected 2-benzylbenzimidazole[60] was obtained when this reaction was carried out on the active ketone, a result, probably, of the method used to work up the reaction mixture in this case. LX was diluted with inactive LX and degraded by the procedure of Roseman.[61] The wide limit of error in the percentage C^{14}-activity at C-2 is due to excessive isotope dilution in the course of this degradation, which is outlined in Fig. 11. The details of C^{14}-activity measurements are given in Table III.

The degradation of allylbenzene-C^{14} is outlined in Fig. 12, and the C^{14}-activity data are given in Table IV. The low C^{14}-activity of the bis-p-phenylazobenzoyl derivatives of 3-phenylpropane-1,2-diol-C^{14} (LXIII) can hardly be due to an isotope effect since none was found in the degradation of p-methoxyhydrocinnamyl-C^{14} alcohol through the corresponding olefin. The difference (5.6%) in C^{14}-activity between LXIII and LXIV is somewhat greater than the sum of the estimated limits of error (less than 3.6%). A possible explanation for the discrepancy is that the diol derivative was not dried properly and retained some solvent.

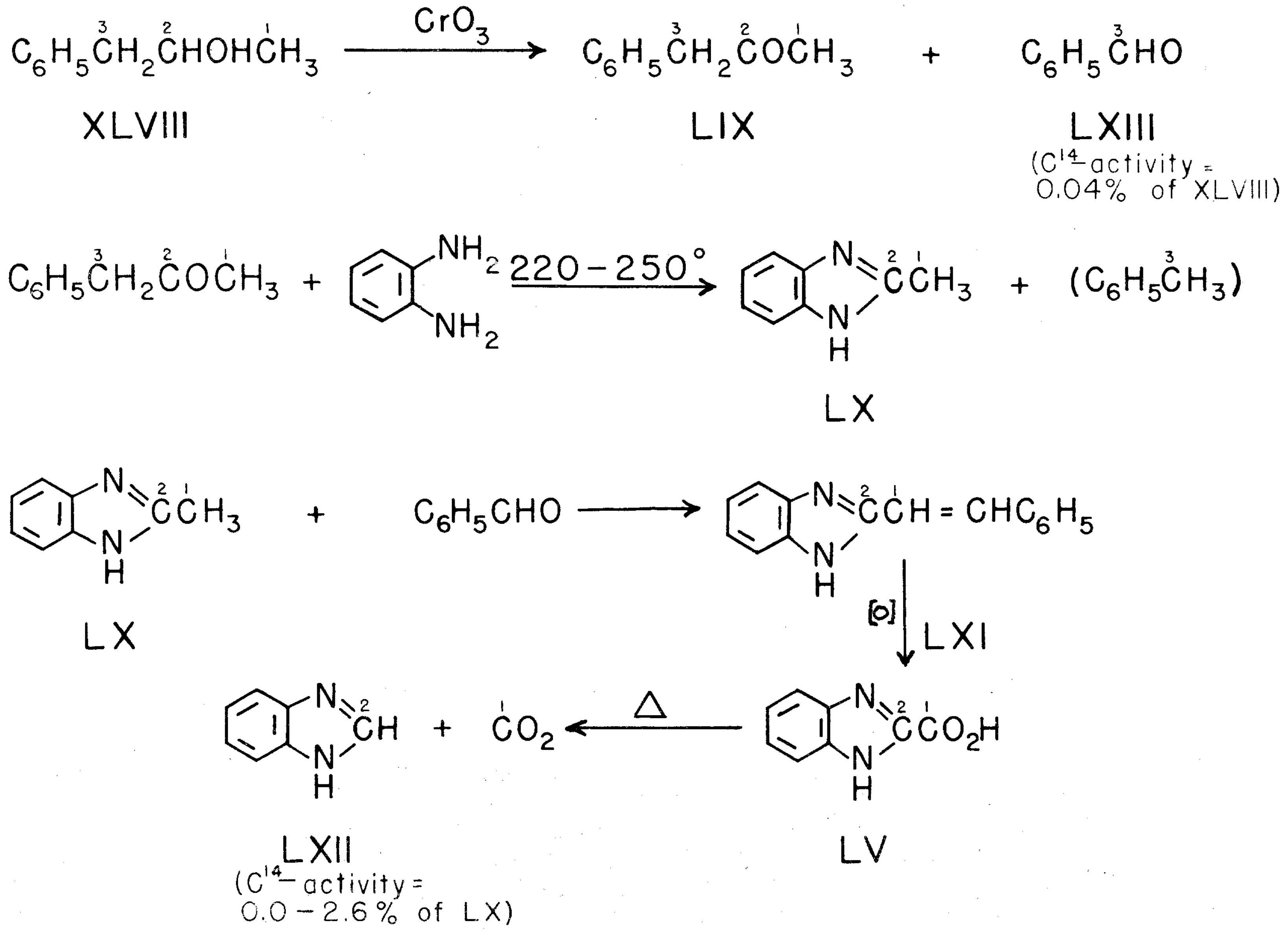
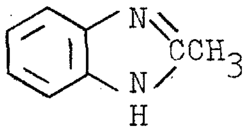
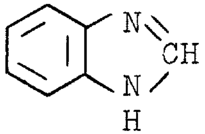


Fig. II. The degradation of benzylmethylcarbinol-C^{14}

TABLE III

C^{14}-Activity Measurements

Degradation of Benzylmethylcarbinol-C^{14}

Compound	mg.	C^{14}-Activities[a]	μc/mmole	% Δ[b]
$C_6H_5CH_2CHOHCH_3$ (XLVIII) p-toluenesulfonate	18.4	422.5 ± 2.0	1.405	0.0
	17.8	413.8 ± 1.0	1.386	1.3
	18.7	436.4 ± 1.5	1.424	1.3
		average	1.405	0.9
C_6H_5CHO (LXIII)	15.9	0.11	5.3×10^{-4}	
octahydroxanthene derivative	37.9	0.27 ± .10	$(5.3 \pm 1.6) \times 10^{-4}$	
 (LX)[c]	14.6	5.44 ± .10	$(1.03 \pm .03) \times 10^{-2}$	
 (LXII)[c]	11.2	0.0-0.12	$(0.0\text{-}2.7) \times 10^{-4}$	

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[a] See footnote (a) Table II. [b] See footnote (b) Table II.
[c] See footnote (c) Table II.

TABLE IV

C^{14}-Activity Measurements
Degradation of Allylbenzene-C^{14}

Compound	mg.	C^{14}-Activities[a]	μc/mmole	
$C_6H_5CH_2CHOHCH_2OH$ (LXIII) bis-p-phenylazo-benzoyl derivative[c]	10.7	102.4 ± 1.0	1.143 ± 0.22	
	16.5	161.3 ± 1.5	1.170 ± 0.18	
		average	1.16	
				% Δ[b]
HCHO (LXIV) dimethone derivative	14.2	278.8 ± 1.5	1.212	.86
	11.6	232.5 ± 2.0	1.233	.89
	14.9	295.0 ± 2.0	1.222	.05
		average	1.22	.6
$C_6H_5CH_2CHO$ (LV) dimethone derivative	50.3	0.27 ± .10	$(4.4 \pm 1.6) \times 10^{-4}$	
$C_6H_5CO_2H$ (LVII)	5.9	0.0	inactive	

[a] See footnote (a) Table II. [b] See footnote (b) Table II. [c] See footnote (c) Table II.

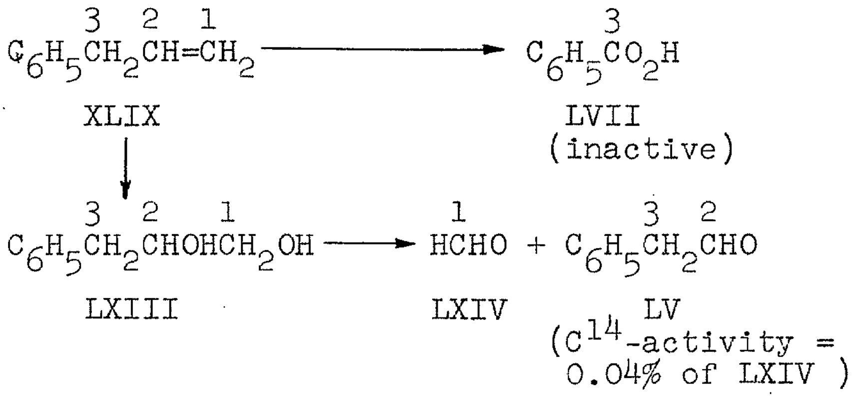


Fig. 12. The degradation of allylbenzene-C^{14}.

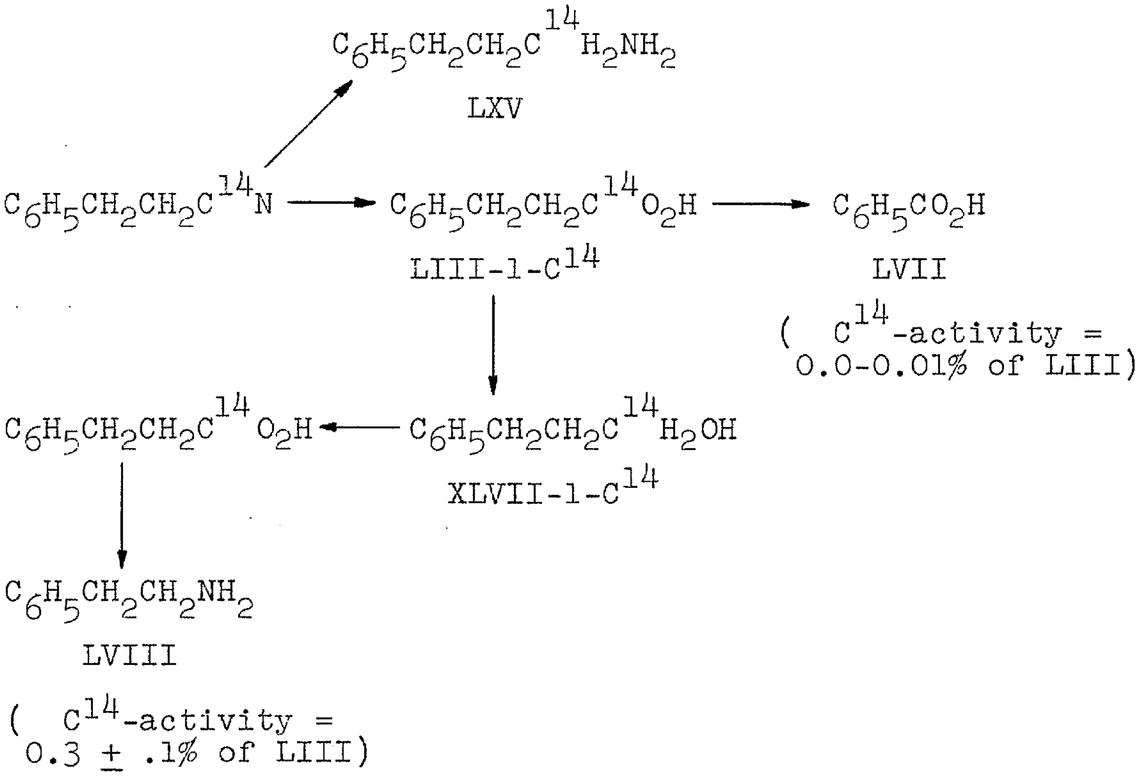


Fig. 13. Degradation of hydrocinnamyl-1-C^{14} alcohol.

TABLE V

C^{14}-Activity Measurements
Degradation of Hydrocinnamyl-1-C^{14} Alcohol

Compound	mg.	C^{14}-Activities[a]	μc/mmole	% Δ[b]
$C_6H_5CH_2CH_2CH_2NH_2$ (LXV) p-toluenesulfonamide	16.8	499 ± 2.0	1.811	.94
	18.1	531.0 ± 2.0	1.787	.35
	19.0	556.1 ± 2.0	1.783	.59
		average	1.79	.6 %
$C_6H_5CH_2CH_2CO_2H$ (LIII) anilide	11.9	197.0 ± 1.0	0.785 ± .011	
$C_6H_5CH_2CH_2NH_2$ (LVIII) benzoyl derivative	14.3	0.8 ± .1	(2.5 ± .4) x 10^{-3}	
$C_6H_5CO_2H$ (LVII)	5.8	(0-2) x 10^{-2}	(0-9) x 10^{-5}	

[a] See footnote (a) Table II. [b] See footnote (b) Table II.

As a check on the degradation procedure used for hydrocinnamyl-C^{14} alcohol, hydrocinnamyl-1-C^{14} alcohol was prepared by the reduction of hydrocinnamic-1-C^{14} acid and was degraded by the procedure outlined in Fig. 13. The pertinent C^{14}-activity data are given in Table V along with the C^{14}-activity data for 3-phenylpropylamine-1-C^{14}.

The degradations of _p_-methoxyhydrocinnamyl-C^{14} alcohol (L), _p_-methoxyallylbenzene-C^{14} (LII) and _p_-methoxybenzylmethylcarbinol-C^{14} (LI) are outlined in Fig. 14A, B and C respectively. The data for the corresponding C^{14}-activity measurements are given in Tables VI, VII and VIII respectively. Data for C^{14}-activity measurements on 3-(_p_-methoxyphenyl)-propylamine are given in Table VII.

The reaction of _p_-methoxybenzyl methyl ketone with _o_-phenylenediamine gave erratic results. In a trial reaction of inactive ketone with _o_-phenylenediamine, 2-(_p_-methoxybenzyl)-benzimidazole (LXVIII) and a small yield of 2-methylbenzimidazole were obtained, but no 2-methylbenzimidazole could be isolated from the reaction mixture of the active ketone (Fig. 14C).

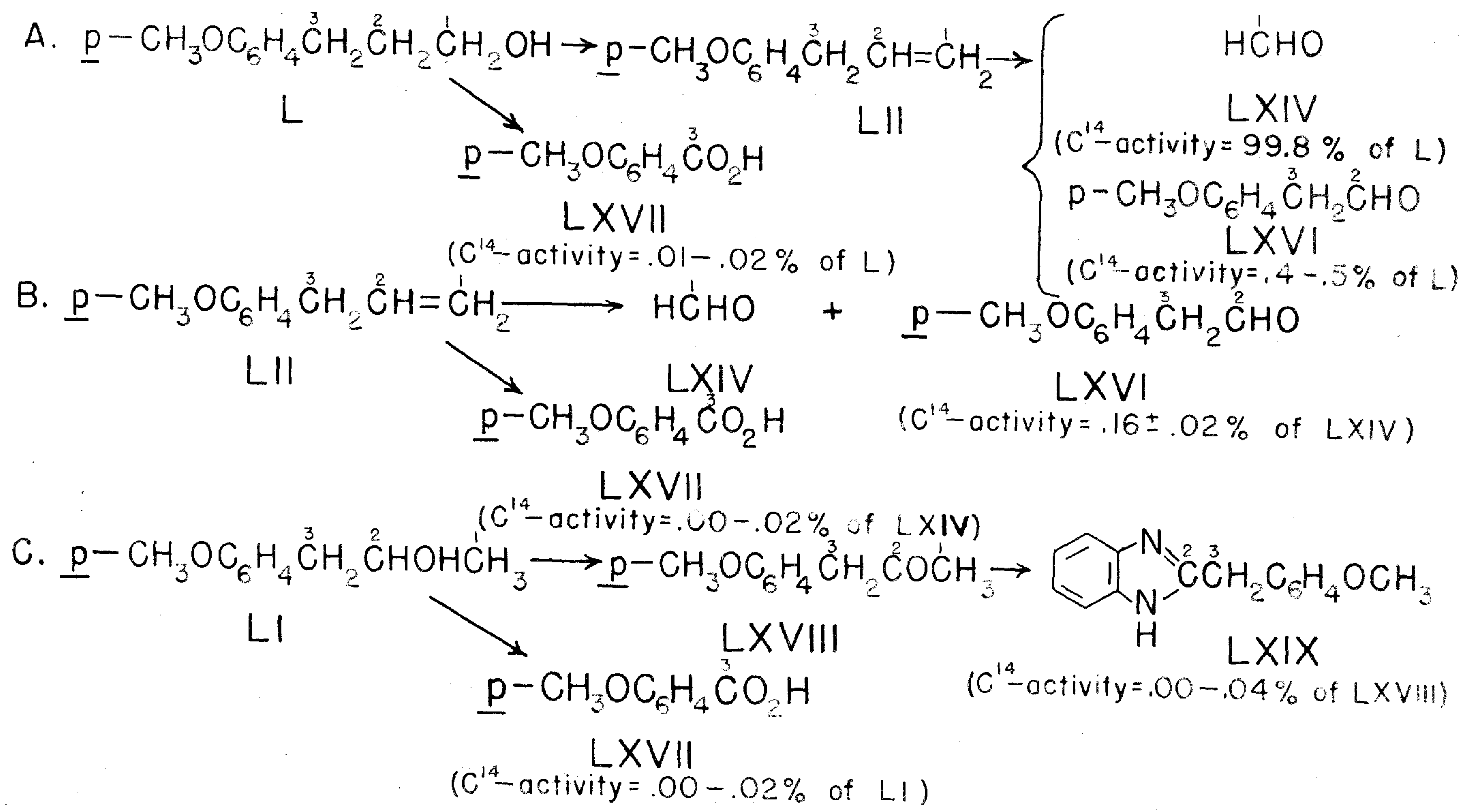


Fig. 14. Degradation of the products of the reaction of 3-(p-methoxyphenyl)-propylamine with nitrous acid.

TABLE VI

C^{14}-Activity Measurements

Degradation of p-Methoxyhydrocinnamyl-C^{14} Alcohol

Compound	mg.	C^{14}-Activities[a]	μc/mmole
p-$CH_3OC_6H_4CH_2CH_2CH_2OH$ (L) phenylurethan[b]	7.48	89.5 ± 0.5	0.726 ± .014
	16.8	198.6 ± 1.0	0.712 ± .008
		average	0.719
HCHO (LXIV) dimethone derivative	25.3	295.5 ± 2.0	0.720 ± .008
	23.6	274.5 ± 1.5	0.716 ± .006
		average	0.718
p-$CH_3OC_6H_4CH_2CHO$ (LXVI) dimethone derivative	24.2	.88-1.00	$(3.4 \pm .3) \times 10^{-3}$
p-$CH_3OC_6H_4CO_2H$ (LXVII)	16.5	.05-.11	$(1.6 \pm .6) \times 10^{-4}$

[a] See footnote (a) Table II. [b] See footnote (c) Table II.

TABLE VII

C^{14}-Activity Measurements

Degradation of p-Methoxyallylbenzene-C^{14}

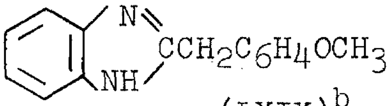
Compound	mg.	C^{14}-Activities[a]	μc/mmole
HCHO (LXIV) dimethone derivative	28.0	488.0 ± 2.0	1.073 ± .009
	30.3	528.0 ± 2.0	1.072 ± .008
		average	1.072
p-$CH_3OC_6H_4CH_2CHO$ (LXVI) dimethone derivative	37.4	0.73 ± .10	$(1.7 \pm .2) \times 10^{-3}$
p-$CH_3OC_6H_4CO_2H$ (LXVII)	6.94	0.0-0.06	$(0.0\text{-}2.6) \times 10^{-4}$
p-$CH_3OC_6H_4CH_2CH_2CH_2NH_2$	19.8	599.8 ± 3.0	2.036 ± .020
p-toluenesulfonamide[b]	20.7	625.4 ± 2.0	2.032 ± .016
		average	2.03

[a] See footnote (a) Table II. [b] See footnote (c) Table II.

TABLE VIII

C^{14}-Activity Measurements

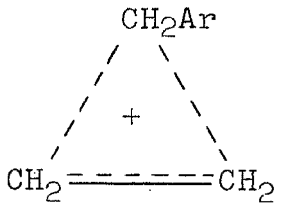
Degradation of p-Methoxybenzylmethylcarbinol-C^{14}.

Compound	mg.	C^{14}-Activities[a]	μc/mmole
p-$CH_3OC_6H_4CH_2CHOHCH_3$ (LI) phenylurethan[b]	16.2	144.0 ± 1.0	0.533 ± .007
	23.5	204.3 ± 2.0	.522 ± .007
		average	0.528
p-$CH_3OC_6H_4CO_2H$ (LXVII)	6.50	(0-2) x 10^{-2}	(0-9) x 10^{-5}
p-$CH_3OC_6H_4CH_2COCH_3$ (LXVIII) 2,4-dinitrophenylhydrazone[b]	22.3	16.9	0.0547 ± .0009
	9.23	6.85	0.0537 ± .0021
		average	0.0542
 (LXIX)[b]	30.8	(0.0-1.3) x 10^{-2}	(0.0-2.1) x 10^{-5}

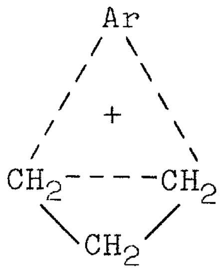
[a] See footnote (a) Table II. [b] See footnote (c) Table II.

DISCUSSION

The absence of a significant amount of C^{14}-activity at C-2 and C-3 of hydrocinnamyl and *p*-methoxyhydrocinnamyl alcohols from the corresponding active amines shows that the *symmetrical* bridged ions, LXX and LXXI, were not intermediates in these amine-nitrous acid reactions.



LXX



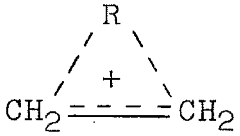
LXXI

Ar = C_6H_5 or
p-$CH_3OC_6H_4$

The failure of benzyl and *p*-methoxybenzyl groups to undergo migration to an appreciable extent in the present work in comparison with the results of similar work on 2-(*p*-methoxyphenyl)-ethylamine-1-C^{14},[34] 2-phenylethylamine-1-C^{14},[34] n-propylamine-1-C^{14}[42] and ethylamine-1-C^{14},[62] indicates the following decreasing order of the stability of the symmetrical

$RCH_2CH_2^+$

LXXII



LXXIII

LXXIV $R = \underline{p}\text{-}CH_3OC_6H_4$
LXXXV $R = C_6H_5$
LXXVI $R = CH_3$
LXXVII $R = H$
LXXVIII $R = C_6H_5CH_2$
LXXIX $R = \underline{p}\text{-}CH_3OC_6H_4CH_2$

"ethyleneonium" ion (LXXIII) relative to the corresponding classical carbonium ion (LXXII):

$$R = \underline{p}\text{-}CH_3OC_6H_4 > C_6H_5 > CH_3 > H > C_6H_5CH_2 \simeq \underline{p}\text{-}CH_3OC_6H_4CH$$

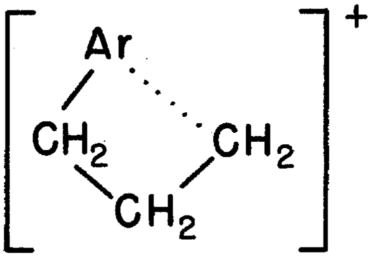
This order can be correlated with Kharasch's "electronegativity" series,[63] which was determined by the direction of cleavage of unsymmetrical organomercury compounds with hydrogen chloride.

$$R'HgR + HCl \longrightarrow R'H + ClHgR$$

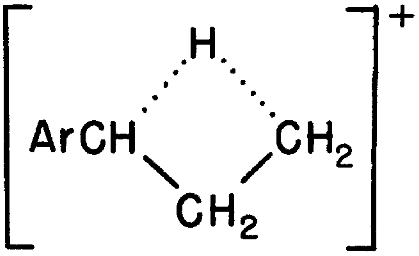
In this series R', the group that is cleaved from the organomercury compound more readily, is defined to be more electronegative than R. By means of a number of such reactions the following decreasing order of "electronegativity" was established:

$$\underline{p}\text{-}CH_3OC_6H_4 > C_6H_5 > CH_3 > C_6H_5CH_2.$$

The unsymmetrical cation LXXX involving 1,3-aryl participation cannot be eliminated as an intermediate by the



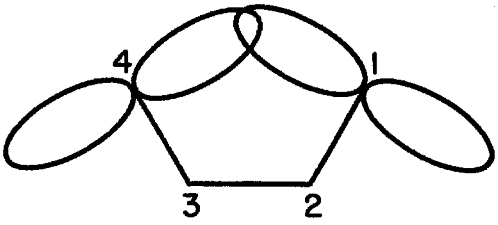
LXXX



LXXXI

Ar = C_6H_5 or
<u>p</u>-$CH_3OC_6H_4$

results of the present work. If LXXX were an intermediate in the 3-arylpropylamine-nitrous acid reactions, leading to normal alcohol products without isotope-position rearrangement, it should be an intermediate in S_N1 or <u>Lim.</u>[64] type solvolysis reactions of 3-arylpropyl derivatives, and should be reflected in enhanced solvolysis rates. However, recent kinetic studies by Winstein[65] on the solvolysis reactions of 3-phenylpropyl derivatives indicate that neighboring group participation does not occur in this system, and therefore it seems unlikely that LXXX was an intermediate in the present work. It has been noted[56] that the conformation of LXXXII favors a relatively strong interaction between C-1 and C-4 across two methylene groups. That such interaction does not seem to occur in the

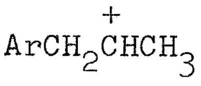


LXXXII

3-arylpropyl system may be due in part to a relatively small tendency of the 3-arylpropyl system to exist in the conformation most favorable to such an interaction.

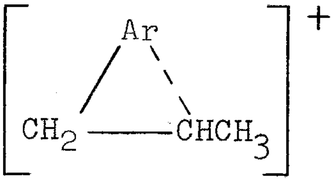
The absence of any significant amounts of phenylethylcarbinol and p-methoxyphenylethylcarbinol in the products of the amine-nitrous acid reactions strongly suggests that the carbonium ion of structure LXXXI was not important in these reactions. The absence of arylethylcarbinols was not unexpected in view of the much greater tendency of phenyl and p-methoxyphenyl groups to migrate relative to hydrogen in the corresponding 2-arylethylamine-nitrous acid reactions.[34,58]

If LXXXIII is an intermediate in the reactions under discussion then LXXXIV would be expected to be important, since



$ArCH_2\overset{+}{C}HCH_3$

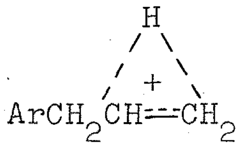
LXXXIII



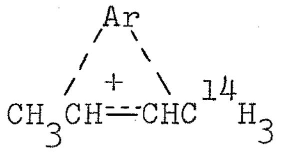
LXXXIV

Ar = C_6H_5 or p-$CH_3OC_6H_4$

Winstein and co-workers have shown that the participation indicated by LXXXIV is important in the 1-aryl-2-propyl system.[28] However, formation of LXXXIV does not necessarily imply that LXXXIII was an intermediate also, since it is possible that LXXXIV could arise from LXXXV without going through LXXXIII.



LXXXV

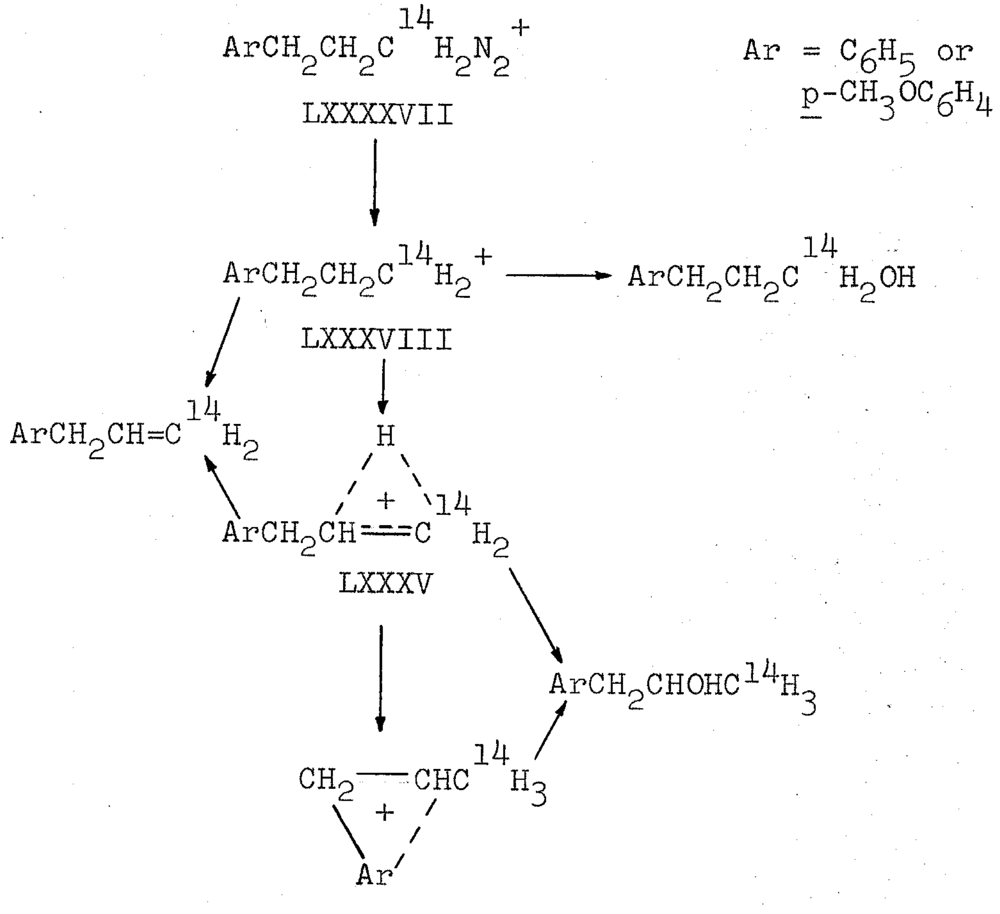


LXXXVI

Ar = C_6H_5 or $p\text{-}CH_3OC_6H_4$

The results of the present research are compatible with the formation of LXXXIV but allow no decision. LXXXIV would lead to secondary alcohol without isotope-position rearrangement. If LXXXIV is important in the present work then LXXXVI would be expected to be important in the reaction of 3-arylbutylamine-1-C^{14} with nitrous acid, and LXXXVI would lead to isotope-position rearrangement. The same information could be obtained from the nitrous acid reaction of an optically active form of 3-arylbutylamine, for in this case LXXXVI would lead to a mixture of racemic threo-3-aryl-2-butanol and optically active erythro-3-aryl-2-butanol.

A possible interpretation of the present experimental results is that the diazonium cation LXXXVII loses a molecule of nitrogen to form the simple carbonium ion LXXXVIII which may lose a proton to give olefin, react with solvent to give unrearranged product or go to the "ethyleneonium" ion LXXXV. Because of its lack of symmetry, LXXXV would be expected to give only secondary product on reacting with the solvent. LXXXV might also lose its bridge hydrogen to give olefin or might go to the unsymmetrical phenonium ion LXXXIV. Either the pair of intermediates LXXXVIII and LXXXV or the pair LXXXVIII



LXXXIV

and LXXXIV alone could account for all of the products formed.

It is possible that part of the primary alcohol products were formed by reaction of the diazonium ion LXXXVII with water by the S_N2 mechanism, but this seems unlikely in view of the fact that the primary amine-nitrous acid reaction occurs readily with neopentylamine where such a mechanism is not favorable. The extensive rearrangements that occur when n-propylamine,[42,67] n-butylamine,[68] 2-phenylethylamine-1-C^{14} [34] and other amines are treated with nitrous acid indicate that direct displacement of nitrogen from the diazonium cation is not usually important.

EXPERIMENTAL

All melting points reported here were taken with a Hershberg melting-point apparatus using calibrated thermometers. Analyses were performed by Dr. Adalbert Elek, Elek Microanalytical Laboratories, Los Angeles, California and Mr. S. M. Nagy, Microchemical Laboratory, Massachusetts Institute of Technology.

3-Phenylpropylamine.--Redistilled β-phenylpropionitrile (105 g., 0.80 mole) was reduced with a slurry of lithium aluminum hydride in ether and the reaction mixture was worked up by the procedure of Amundsen and Nelson.[69] The yield of 3-phenylpropylamine, b.p. 90-91° (8 mm.), was 89 g. (83%).

The p-toluenesulfonamide was prepared in pyridine solution and recrystallized twice from methanol, m.p. 64.9-65.3°.

Anal. Calcd. for $C_{16}H_{19}NO_2S$: C, 66.40; H, 6.62; N, 4.84. Found: C, 66.45; H, 6.54; N, 4.85.

3-Phenylpropyl p-Nitrobenzoate and 3-Phenylpropyl Acetate (Hydrocinnamyl Acetate).--A commercial sample of hydrocinnamyl alcohol was distilled through a 54 x 0.7-cm. column provided with a tantalum wire spiral, and a fraction, b.p. 129° (19.3 mm.) (lit.,[2] b.p. 132° (21 mm.)), was taken for physical properties and infrared spectrum; $n^{25.9}D$ 1.5237 (lit.,[70] $n^{20}D$ 1.5278). The p-nitrobenzoate was prepared in pyridine solution and recrystallized from methanol, m.p. 46-47°.

Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.28; H, 5.33; N, 5.06.

Hydrocinnamyl alcohol (131 g., 0.96 mole) was boiled under reflux for one hour with 260 g. of acetic anhydride and a few drops of concentrated sulfuric acid. Most of the acetic acid and excess acetic anhydride were removed by distillation and the crude ester was washed with sodium bicarbonate solution, dried and distilled. The yield of hydrocinnamyl acetate, b.p. 131° (16 mm.), was 146 g. (85%); $n^{25.2}D$ 1.4942. Part of this product was redistilled through a 54 x 0.7-cm. column provided with a tantalum wire spiral and, after a small fore-run, all of the acetate was collected at b.p. 133° (18 mm.); $n^{26}D$ 1.4934.

Benzylmethylcarbinol and Derivatives.--Benzyl methyl ketone[71] (20 g., 0.15 mole) was reduced with a slurry of excess lithium aluminum hydride in ether. Distillation from a modified Claisen apparatus gave 13 g. (65%) of benzylmethylcarbinol, b.p. 100-101° (14.5 mm.); $n^{24.5}D$ 1.5198. Another sample of benzyl methyl ketone was boiled under reflux with isopropyl alcohol and aluminum isopropoxide, and a mixture of isopropyl alcohol and acetone was removed from time to time by distillation until no more acetone was formed. The yield of benzylmethylcarbinol, b.p. 97-104.5°(15 mm.) was 83%.

Redistillation through a 54 x 0.7-cm. column provided with a tantalum wire spiral gave a product b.p. 101-102° (13 mm.), $n^{25}D$ 1.5188 (lit.,[28] b.p. 97° (10.5 mm.), $n^{25}D$ 1.5181-82).

Benzylmethylcarbinyl p-toluenesulfonate was prepared in pyridine solution and recrystallized from petroleum ether, m.p. 90.9-91.4° (lit.,[28] m.p. 93.7-94°).

The p-nitrobenzoate was prepared in pyridine solution and recrystallized from methanol, m.p. 60.8-61.4°.

Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.28; H, 5.32; N, 4.99.

Benzylmethylcarbinyl Acetate.--Benzylmethylcarbinol (13.6 g., 0.10 mole) was boiled under reflux for 2 hours with 41 g. of acetic anhydride and 10 g. of anhydrous sodium acetate. Water was added to the boiling reaction mixture to hydrolyze the excess acetic anhydride and the mixture was worked up in the usual manner. Distillation of the crude product gave 12 g. (67%), b.p. 103 (9 mm.), $n^{25.2}D$ 1.4879. The acetate was redistilled through a 54 x 0.7-cm. column provided with a tantalum wire spiral, and a fraction, b.p. 117° (19 mm.), $n^{23.8}D$ 1.4881 (lit.,[72] b.p. 115° (16 mm.), $n^{20}D$ 1.4897), was taken for physical properties and infrared spectrum.

Ethylphenylcarbinol and Ethylphenylcarbinyl p-Nitrobenzoate.--Ethylphenylcarbinol, b.p. 103-106° (15.5 mm.), was prepared in 75% yield from benzaldehyde and ethylmagnesium bromide.[73] Fractionation of 45 g. of this product in a 120 x 1-cm. column provided with a glass spiral gave 32 g. of carbinol, b.p. 111° (21.5 mm.); $n^{25.3}D$ 1.5186 (lit.,[73] b.p. 105-106° (17 mm.)).

Ethylphenylcarbinyl p-nitrobenzoate was prepared in pyridine solution and recrystallized from methanol, m.p. 56.1-56.6° (lit.,[74] m.p. 59-60°).

Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.55; H, 5.35; N, 5.33.

Ethylphenylcarbinyl Acetate.--Ethylphenylcarbinol (13.6 g. 0.10 mole) was boiled under reflux for 2 hours with 41 g. of acetic anhydride and 10 g. of anhydrous sodium acetate and the reaction mixture was worked up in the usual manner. Fractionation of the crude product gave 8.5 g. (48%), b.p. 113° (19 mm.); $n^{25.2}D$ 1.4900.

Dimethylphenylcarbinol and Dimethylphenylcarbinyl p-Nitrobenzoate.--The reaction[75] of methylmagnesium iodide with ethylbenzoate gave a 70% yield of dimethylphenylcarbinol, b.p. 82° (6.5 mm.); $n^{25}D$ 1.5189. The carbinol was redistilled through a 54 x 0.7-cm. column provided with a tantalum wire spiral, and a fraction, b.p. 99° (19 mm.) (lit.,[76] b.p. 93-94°

(13 mm.)), $\underline{n}^{25}$D 1.5193, was taken for physical properties and infrared spectrum.

The p-nitrobenzoate of dimethylphenylcarbinol was prepared in pyridine solution and recrystallized from ethanol, m.p. 132.3-132.9°.

2-Phenyl-1-propanol and 2-Phenyl-1-propyl p-Nitrobenzoate.--Hydrotropaldehyde[77] (26.8 g., 0.20 mole) was heated with 50 g. (0.25 mole) of aluminum isopropoxide in 250 ml. of anhydrous isopropyl alcohol. A mixture of acetone and isopropyl alcohol was removed from the reaction mixture by distillation until no more acetone could be obtained. Distillation of the crude product gave 21.2 g. (79%) of 2-phenyl-1-propanol, b.p. 104° (10 mm.), $\underline{n}^{25}$D 1.5203. The product was redistilled through a 54 x 0.7-cm. column provided with a tantalum wire spiral, and a fraction, b.p. 116-116.5 (19 mm.), $\underline{n}^{25}$D 1.5220 (lit.,[78] b.p. 108-109° (14 mm.), $\underline{n}^{25}$D 1.5221), was taken for physical properties and infrared spectrum.

2-Phenyl-1-propyl p-nitrobenzoate was prepared in pyridine solution and recrystallized from methanol, m.p. 63.9-64.3° (lit.,[79] m.p. 65°).

2-Phenyl-1-propyl Acetate.--2-Phenyl-1-propanol (7.5 g., 0.055 mole) was acetylated by boiling under reflux with acetic anhydride in ether using a small amount of concentrated sulfuric acid as catalyst. Distillation in a small Claisen apparatus followed by distillation in a semimicro column[80] gave 5 g. (50%) of 2-phenyl-1-propyl acetate, b.p. 121-122° (18.6 mm.); $\underline{n}^{25.2}D$ 1.4933.

Allylbenzene.--Hydrocinnamyl acetate (61 g., 0.34 mole) was passed through a glass tube packed with glass wool and heated to 460-485° by means of an electric furnace. The product was washed free of acetic acid with aqueous sodium carbonate and dried. Distillation at atmospheric pressure gave 31 g. (76%) of allylbenzene, b.p. 150-160°. A sample of the crude allylbenzene was redistilled in a spinning-band column at reduced pressure and most of the olefin was collected at b.p. 59-59.5° (23.5 mm.); $\underline{n}^{25}D$ 1.5097; Siwoloboff b.p. 159.0° (759 mm.) (lit.,[81] b.p. 158.6° (760 mm.), $\underline{n}^{20}D$ 1.5110).

Propenylbenzene.--Allylbenzene (20.5 g., 0.17 mole) was boiled under reflux for 15-17 hours with 28 g. of potassium hydroxide in 40 g. of n-amyl alcohol. The reaction mixture was washed with several portions of saturated sodium chloride solution, dried and distilled. n-Amyl alcohol was removed at 135-137°; a small intermediate fraction (1.3 g.) came over as the temperature rose to 170°; and 16 g. (78%) of propenylbenzene was collected at 155° (slightly reduced pressure). The crude propenylbenzene was fractionated under reduced pressure in a spinning-band column and a fraction (9.5 g.) was taken for physical properties and infrared spectrum, b.p.

62-62.5° (12 mm.), $\underline{n}^{25}D$ 1.5466, Siwoloboff b.p. 178.8° (759 mm.) (lit.,[82] for trans-propenylbenzene, b.p. 73.5° (20 mm.), $\underline{n}^{25}D$ 1.5473; for cis-propenylbenzene, b.p. 64.5° (20 mm.), $\underline{n}^{25}D$ 1.5400).

The Reaction of 3-Phenylpropylamine with Nitrous Acid (a).--To a stirred solution of 26.8 g. (0.20 mole) of 3-phenylpropylamine in 200 ml. of 1.0 M perchloric acid and 25 ml. of water at 60° (water bath) was added a solution of 14.3 g. (0.20 mole) of sodium nitrite in 125 ml. of water over a period of 30 minutes. Stirring at 60° was continued for 30 minutes more; the reaction mixture was cooled, acidified with dilute perchloric acid and extracted with ether. The combined ether extracts were dried and ether was evaporated on a steam-bath. Distillation of the residue gave 2.7 g. (11%) of allylbenzene, b.p. 157-158°, $\underline{n}^{25}D$ 1.5120, and about 7 g. (25%) of a discolored mixture of alcohols. 3-Phenylpropylamine (5.5 g., 20%) was recovered from the acidic aqueous layer of the reaction mixture. The carbinol mixture was treated with sodium hydroxide solution to remove organic nitro compounds and was fractionated in a spinning-band column to give benzylmethylcarbinol, p-nitrobenzoate, m.p. 60.2-61.2°, infrared spectrum identical with that of authentic benzylmethylcarbinol except for an unexplained band of medium intensity at 5.9 μ , and hydrocinnamyl alcohol, p-nitrobenzoate m.p. 45.4-46.2°, infrared spectrum identical with that of authentic hydrocinnamyl alcohol except for weak bands at 5.8 μ and 8.00-8.05 μ. No evidence for the presence of other isomeric phenylpropanols was found in the spectrum of any of these fractions.

(b).--A solution of 33.8 g. (0.25 mole) of 3-phenylpropylamine and 24.3 g. (0.35 mole) of sodium nitrite in 250 ml. of 1.0 M perchloric acid and 50 ml. of water underwent no apparent change in 15 hours at room temperature. The stirred solution was then heated gradually and held at 80-90° for one hour. The mixture was allowed to cool somewhat and 63 ml. of 1.0 M perchloric acid was added to the reaction flask (total perchloric acid was 125% of the theoretical amount). The reaction mixture was again heated to 80-90° for a short time then cooled and extracted with ether. The combined ether extracts were washed with dilute sulfuric acid, then with dilute sodium carbonate solution, finally with water and dried. Ether was evaporated from the solution and the residue of crude products was boiled under reflux with methanol. About 3 ml. of methyl nitrite was collected in a Dry-Ice trap and this amount did not seem to increase after the first 30-60 minutes of heating. Methanol was removed by distillation and the residue was distilled under reduced pressure in a modified Claisen apparatus to give 1.65 g. (5.6%) of allylbenzene, b.p. 55-56° (20 mm.), $n^{25.5}D$ 1.5087; 20.7 g. (61%) of a carbinol mixture boiling from 120-140° (31 mm.); and 6.4 g. of a high-boiling residue. Fractionation of the carbinol mixture in a 36 x 1-cm. spinning-band column under reduced pressure gave a 25% over-all yield of hydrocinnamyl alcohol and a 15% over-all yield of benzylmethylcarbinol. Both carbinols were identified by the melting points of their p-nitrobenzoates. The hydrocinnamyl alcohol fractions were shown to contain a small amount of alkyl nitro compound and the benzylmethylcarbinol fractions were shown to be contaminated with a carbonyl compound. Some of the hydrocinnamyl alcohol fractions were combined and treated with aqueous alkali. Distillation in a semimicro column[80] gave a product that was free of nitro compound, b.p. 129-130° (20.7 mm.), $n^{25}D$ 1.5242-45, infrared spectrum essentially identical with that of authentic hydrocinnamyl alcohol except for an unexplained weak band at 6.45 μ. A benzylmethylcarbinol fraction from the spinning-band column fractionation was shaken with warm ammoniacal silver nitrate to oxidize aldehyde impurity. Distillation in a semimicro column[80] gave a carbonyl-free product, b.p. 107° (17.5 mm.), $n^{25}D$ 1.5185, infrared spectrum like that of authentic benzylmethylcarbinol except for a weak band at 5.93 μ and a weak band at 10.25 μ which did not occur in the benzylmethylcarbinol fraction of the first amine-nitrous acid reaction.

Oxidation of Hydrocinnamyl Alcohol with Concentrated Nitric Acid.--Hydrocinnamyl alcohol (34 g., 0.25 mole) was added slowly with cooling and mechanical stirring to 133 g. (94 ml.) of concentrated nitric acid over a period of 70 minutes. Stirring and cooling were continued for one hour more and the reaction mixture was divided into two approximately equal portions.

The first portion of the reaction mixture was observed to warm rapidly on being removed from the cooling bath. The mixture was worked up at once and yielded 7.2 g. of crystalline organic acids. Recrystallization of the crude acidic products from petroleum ether (30-60°) gave 0.5 g. of yellow crystals of very slightly soluble p-nitrohydrocinnamic acid, m.p. 164-165° (lit.,[83] m.p. 163-164°) after recrystallization from water. The identity of this acid was confirmed by oxidation to p-nitrobenzoic acid. On evaporation, the petroleum ether mother liquor yielded 6.6 g. of yellow crystals of hydrocinnamic acid which melted below 40°. The crude product was purified by sublimation, m.p. 47-50°.

The second portion of reaction mixture was heated on a water-bath for 30 minutes at 75-80°. This oxidation reaction mixture yielded 12 g. of organic acids from which 2 g. of p-nitrohydrocinnamic acid and 9.1 g. of crude hydrocinnamic acid were obtained.

Permanganate Oxidation of Hydrocinnamyl Alcohol.--Hydrocinnamyl alcohol (34 g., 0.25 mole), 225 ml. of water and 28 ml. of concentrated sulfuric acid were placed in a one-liter, 3-necked flask fitted with a thermometer and mechanical stirrer. Potassium permanganate (28.2 g., 0.178 mole) was added in small portions over a period of one hour with continuous stirring at 10-15° and stirring at this temperature was continued for one hour more. The crude organic acids weighed 14 g. and appeared to be hydrocinnamic acid contaminated with a small amount of benzoic acid.

When permanganate oxidation was carried out in aqueous pyridine with added potassium carbonate, the reaction took place very slowly at room temperature. Oxidation became rapid when the reaction mixture was warmed, and benzoic acid was the chief product.

Chromium Trioxide Oxidation of Hydrocinnamyl Alcohol.--The procedure described here is patterned after that of Rügheimer[84] for the same reaction. Chromium trioxide (6.7 g., 0.067 mole) was added slowly in small portions to a stirred solution of 6.8 g. (0.05 mole) of hydrocinnamyl alcohol in 35 ml. of glacial acetic acid and 2 ml. of water. The temperature of the reaction flask was maintained at 15-20° during the addition of chromium trioxide and for 2 hours more. Finally, the reaction mixture was heated to 50° for 15 minutes. The yield of hydrocinnamic acid was 2.0 g. (27%), m.p. 47-48.8° after recrystallization from petroleum ether.

2-(β-Phenylethyl)-Benzimidazole.[85]--o-Phenylenediamine (7.57 g., 0.07 mole), 7.51 g. (0.05 mole) of hydrocinnamic acid and 50 ml. of 10% hydrochloric acid were heated in a sealed tube at 145-150° for 2 hours. The reaction mixture was treated with excess concentrated aqueous ammonia and the product was collected by filtration and recrystallized twice from aqueous ethanol then from benzene (Norite). The yield of 2-(β-phenylethyl)-benzimidazole, m.p. 192-193° (lit.,[85] m.p. 189-190°), was 4.7 g. (42%).

<u>2-Phenylbenzimidazole</u>.--<u>o</u>-Phenylenediamine (1.08 g., 0.01 mole) and 1.22 g. (0.01 mole) of benzoic acid were heated in a sealed tube with 10 ml. of 20% hydrochloric acid for 4 hours at 145-150°. Neutralization of the reaction mixture gave a small amount of solids from which 0.11 g. (6%) of crude 2-phenylbenzimidazole, m.p. 287-296°, was obtained. Another recrystallization from aqueous ethanol followed by recrystallization from benzene gave a colorless product, m.p. 295-296° (lit.,[86] m.p. 290°).

<u>2-Methylbenzimidazole</u>.[86]--<u>o</u>-Phenylenediamine (9.05 g., 0.05 mole) was heated in a sealed tube with 3.00 g. (0.05 mole) of glacial acetic acid and 25 ml. of 10% hydrochloric acid for 2 hours at 150°. Aqueous ammonia was added to the reaction mixture and the product was collected by filtration, recrystallized from water (Norite) and sublimed. The yield of 2-methylbenzimidazole, m.p. 175.6-176.4° (lit.,[87] 175.5-176.5°), was 3.5 g. (0.027 mole). The picrate was prepared in ethanol solution and recrystallized from 95% ethanol, m.p. 213-214.3° (lit.,[88] m.p. 207-208°).

Oxidation of 2-(β-Phenylethyl)-benzimidazole.--Potassium permanganate (3.16 g., 0.02 mole) was added over a period of 1.5 hours to a stirred solution of 1.11 g. (0.005 mole) of 2-(β-phenylethyl)-benzimidazole in 30 ml. of 5% sulfuric acid at 55-60°. Manganese dioxide was dissolved by the addition of sodium bisulfite and a little mineral acid, and the solution was filtered while still hot. On standing, the filtered solution deposited 0.28 g. of a mixture of benzoic and 2-benzimidazolecarboxylic acids.

Part of the crude product was dissolved in hot 10% hydrochloric acid and the acid solution was extracted with benzene. On partial neutralization and standing, the aqueous solution deposited clusters of needles of 2-benzimidazolecarboxylic acid which decomposed at 164° with evolution of carbon dioxide (lit., m.p. 174° (dec.),[87] m.p. 169° (dec.)[89]).

Another portion of the crude product mixture was extracted with benzene and recrystallized from 80% methanol, m.p. 152° (dec.) when heated slowly. Benzoic acid was obtained by evaporation of the benzene extract, m.p. 119-121° after recrystallization from water.

Trial Degradation of Hydrocinnamic Acid.--Hydrocinnamic acid (30 g., 0.20 mole) was boiled under reflux for 2.5 hours with 100 ml. of anhydrous methanol and 5 ml. of concentrated sulfuric acid. The cooled reaction mixture was shaken with 350 ml. of water and 100 ml. of benzene in a separatory funnel. The benzene layer was separated and washed with sodium carbonate solution then with water. Distillation gave a small fraction (1.6 g.), boiling at 100-106° (13 mm.), and a main fraction (27.3 g., 83%), b.p. 106-108° (13 mm.).

Phenylmagnesium bromide was prepared in 500-ml., 3-necked flask from 55 g. (0.35 mole) of bromobenzene, 10.2 g. (0.42 g. atom) of magnesium turnings and anhydrous ether (total volume about 200 ml.). Methyl hydrocinnamate (27.3 g., 0.165 mole) in 30 ml. of anhydrous ether was added slowly to the reaction mixture and the mixture was heated under reflux for about 15 minutes. The reaction mixture was treated with water then with dilute sulfuric acid. The ether solution of reaction products was washed with aqueous sodium carbonate solution and with water. The crystalline 1,1,3-triphenylpropane-1-ol, obtained by evaporation of ether, was dehydrated by heating on a steam bath for 2 hours with 20% sulfuric acid. The olefin absorbed bromine rapidly but did not give a solid dibromide. Part of the crude olefin was distilled in a modified Claisen apparatus to give 20 g. of 1,1,3-triphenylpropene, b.p. 178-181° (1.1 mm.) (lit.,[90] b.p. 228-229° (15 mm.)).

To a stirred solution of 13.5 g. (0.050 mole) of 1,1,3-triphenylpropene in 45 ml. of 98-100% formic acid was added 6.1 g. (5.5 ml., 0.052 mole) of 30% hydrogen peroxide over a period of 30 minutes. The reaction mixture became warm during the addition of hydrogen peroxide and remained warm for about 15 minutes longer, by which time a white solid appeared. The precipitate of hydroxyformoxy compound was collected by filtration, washed with water and boiled under reflux with ethanolic potassium hydroxide. The saponification reaction mixture was diluted with water and allowed to cool. The crude diol was collected by filtration, stirred with boiling 50% aqueous ethanol, cooled, filtered and dried. Recrystallization from cyclohexane gave 7.9 g. of 1,1,3-triphenylpropane-1,2-diol (LIV), m.p. 147-149°. Concentration of the mother liquor gave an additional 0.6 g. of LIV, m.p. 143-146° (total yield 56%). The diol was recrystallized from a large amount of petroleum ether (30-60°) containing a little ethyl ether, m.p. 150.5-151°.

Anal. Calcd. for $C_{21}H_{20}O_2$: C, 82.86; H, 6.62. Found: C, 82.81; H, 6.65.

A similar experiment was carried out using 5.5 g. (0.020 mole) of crude 1,1,3-triphenylpropene (not distilled). The yield of LIV, m.p. 148-150.6°, was 2.7 g. (45%).

Lead tetraacetate (1.3 g., 3 mmoles) was added over a period of 15 minutes to a mixture of 0.91 g. (3 mmoles) of 1,1,3-triphenylpropane-1,2-diol and 0.5 g. of anhydrous potassium carbonate in 25 ml. of dry benzene at 40-45°. Stirring was continued for 2 hours more, the reaction mixture was filtered and benzene was removed by evaporation on a hotplate. The residue was dissolved in 14 ml. of 50% ethanol-water and treated with 1.08 g. of methone (1,1-dimethylcyclohexane-3,5-dione)[91] by the general procedure of Horning and Horning.[92] The reaction mixture was cooled, diluted with water and extracted several times with 30-60° petroleum ether. On concentration, the combined petroleum ether extracts yielded 0.4 g. (1 mmole) of the dimethone derivative of phenylacetaldehyde, m.p. 165-168° (lit., m.p. 164-165°[93], m.p. 164-166°[94]) after recrystallization from methanol and cyclohexane. The dimethone derivative of phenylacetaldehyde was cyclodehydrated to the corresponding octahydroxanthene derivative by the general procedure of Horning and Horning,[92] m.p. 125.6-126.9° (lit.,[93] m.p. 125-126°) after one recrystallization from aqueous methanol.

The petroleum ether mother liquor was evaporated to dryness. The residue was dissolved in acetone and allowed to stand for 2 days with potassium permanganate. Benzophenone was recovered from the acetone solution and recrystallized from aqueous ethanol. The yield of straw colored crystals of benzophenone was 0.20 g. (1.1 mmole). On recrystallization from aqueous ethanol (Norite), 0.13 g. of colorless product was obtained, m.p. 45-46.8°.

Oppenauer Oxidation of Benzylmethylcarbinol.--The procedure used here was patterned after a procedure given for cis-α-decalone.[95] Benzylmethylcarbinol (2.5 g., 0.018 mole) was heated under reflux for 15 hours with 250 ml. of dry benzene, 150 ml. of anhydrous acetone and 6 g. of freshly distilled aluminum isopropoxide. Fractionation of the crude product in a semimicro[80] column gave 2.6 g., b.p. 100-104° (15 mm.), light-yellow color. Treatment with saturated sodium bisulfite solution gave 3.1 g. of colorless, shiny flakes of the bisulfite addition compound. Benzyl methyl ketone (0.5 g.) was regenerated from the bisulfite compound. The 2,4-dinitrophenylhydrazone melted at 147-150° (lit.,[96] m.p. 152-153°) after one recrystallization from ethanol-ethyl acetate.

The Reaction of Benzyl Methyl Ketone with o-Phenylenediamine.--The procedure used was a slight modification of that of Elderfield and Kreysa.[97] o-Phenylenediamine (2.0 g., 0.019 mole) and 3.0 g. (0.022 mole) of benzyl methyl ketone were heated together at 220-240° for 3 hours. Four recrystallizations of the crude product from 65% methanol gave 0.55 g. of 2-benzylbenzimidazole, m.p. 186-188.5°. On concentration, the combined mother liquors yielded an additional small amount of 2-benzylbenzimidazole. The mother liquor was diluted with water, again concentrated, and refrigerated. Colorless crystals of 2-methylbenzimidazole deposited after one week. On recrystallization from water, 16 mg. of 2-methylbenzimidazole was obtained, m.p. 173-175.5°.

Carbon Tetrabromide from Benzylmethylcarbinol.--Benzylmethylcarbinol (1.36 g., 0.01 mole) was added to a stirred solution of 19.2 g. (6.2 ml., 0.12 mole) of bromine in

375 ml. of 1.0 N aqueous sodium hydroxide. The mixture was stirred at room temperature for 45 minutes and the supernatant liquid was then decanted from the solid carbon tetrabromide. The homogeneous alkaline solution was corked and refrigerated. Additional carbon tetrabromide was collected by decantation, washed with water and air dried. The total yield of product, m.p. 91-95°, was 0.7 g. (21%).

Carbon Tetrabromide from Bromoform.--The procedure used for preparing carbon tetrabromide from bromoform was essentially that of Brixcoe, Peel and Rowlands.[98] Commercial bromoform (7.3 g., 29 mmoles) was stirred with 300 ml. of 1.0 N aqueous sodium hydroxide and 5 ml. (15.5 g., 92 mmoles) of bromine for 1.5 hours at room temperature. Carbon tetrabromide, 6.1 g. (62%) was collected by filtration. Sublimation of 2.9 g. of the crude product at 80-90° (atmospheric pressure) gave 2.3 g., m.p. 92.3-93.6°.

3-Phenylpropylamine-1-C^{14}.--To 2.5 g. (13.5 mmoles) of 2-phenylethyl bromide and 18 ml. of ethanol was added a solution of sodium cyanide-C^{14} (0.5 mmole containing 5×10^2 µcuries of C^{14}-activity) in 4 ml. of water. The mixture was boiled under reflux for 20 hours and 16.2 g. (0.124 mole) of inactive β-phenylpropionitrile was added as carrier. A half-saturated solution of calcium chloride (25 ml.) was added to the reaction mixture and β-phenylpropionitrile-1-C^{14} was extracted with chloroform. The chloroform solution was washed with water, dried and distilled under reduced pressure to give 13.6 g. of active nitrile, b.p. 129-130.5° (16.5 mm.). Inactive β-phenylpropionitrile (16.2 g.) was added to the distillation pot and distillation was continued in order to bring over the last of the active nitrile.

β-Phenylpropionitrile-1-C^{14} (28.7 g., 0.219 mole) was reduced to 3-phenylpropylamine-1-C^{14} with lithium aluminum hydride. The reaction mixture was worked up by the general procedure of Amundsen and Nelson.[69] Distillation in a spinning-band column gave 26.0 g. of 3-phenylpropylamine-1-C^{14}, b.p. 100.5-101.5° (13.5 mm.). The column holdup was recovered and distilled in a semimicro column[80] to give an additional 0.9 g. of amine, b.p. 94-95° (9.8 mm.). The yield of active amine was 91% from the nitrile.

<u>Hydrolysis of β-Phenylpropionitrile-1-C^{14}</u>.--β-Phenylpropionitrile-1-C^{14} (5.68 g., 0.043 mole) was boiled under reflux overnight with 10 g. of sodium hydroxide in 30 ml. of 50% ethanol-water. The reaction mixture was acidified and the crude hydrocinnamic-1-C^{14} acid was recrystallized from water to give 3.00 g., m.p. 47.5-48.2°. The mother liquors yielded an additional 1.12 g. of the active acid.

<u>The Reaction of 3-Phenylpropylamine-1-C^{14} with Nitrous Acid</u>.--To a stirred solution of 26.5 g. (0.196) mole of 3-phenylpropylamine-1-C^{14} in 250 ml. of 1.0 <u>M</u> perchloric acid

at 50-55°, 19.4 g. (0.28 mole) of sodium nitrite in 100 ml. of water was added over a period of 1.5 hours. The mixture was stirred for an additional 2 hours at 50-55°. The reaction mixture was cooled, acidified with dilute perchloric acid and extracted with ether. The combined ether extracts were washed with several portions of aqueous sodium hydroxide solution to remove alkyl nitro compounds, then washed with water and dried. Ether was removed by evaporation and the residue was boiled under reflux with about twice its volume of dry methanol to convert organic nitrites into the corresponding carbinols. Inactive hydrocinnamyl alcohol (2.3 g.), benzylmethylcarbinol (1.4 g.) and allylbenzene (1.3 g.) were added to the methanol solution of reaction products to act as carriers. The mixture of products was stirred overnight with silver oxide and sodium hydroxide in aqueous ethanol to oxidize aldehyde formed in the amine-nitrous acid reaction. Neutral organic compounds were recovered from the silver oxide oxidation reaction mixture and fractionated in a spinning-band column at reduced pressure.

Fract.	b.p., °C.	press., mm.	Wt., g.	Product
I	53-53.5	20.5	0.7	allylbenzene
II	102-110	20.7	0.7	
III	110-115	20.5	5.9	benzylmethylcarbinol (p-nitrobenzoate, m.p. 60.8-62.2°)
IV	115.2-129	20.6	2.1	
V	129-129.4	20.8	6.5	hydrocinnamyl alcohol (p-nitrobenzoate, m.p. 46-47.5°)

3-Phenylpropylamine-1-C^{14} (2.3 g., 9%) was recovered from the acidic aqueous layer of the reaction mixture. The p-toluenesulfonamide melted at 64.7-65.3°.

Degradation of Hydrocinnamyl-C^{14} Alcohol.--The degradation of hydrocinnamyl-C^{14} alcohol (XLVII), product of the reaction of 3-phenylpropylamine-1-C^{14} with nitrous acid, is outlined in Fig. 10. Active XLVII (6.5 g., 48 mmoles) was oxidized with chromium trioxide in acetic acid as described earlier. The yield of hydrocinnamic-C^{14} acid (LIII), m.p. 47-48.5°, was 2.2 g. (15 mmoles). The anilide was prepared and recrystallized from cyclohexane and aqueous ethanol, m.p. 95.8-96.9°. LIII (0.1 g.) was oxidized to benzoic acid with alkaline permanganate. The product was recrystallized twice from water, m.p. 121.5-122.5°.

The Barbier-Wieland degradation of LIII was carried out as with the inactive acid except for a few minor differences. The methyl ester of LIII was prepared by treating 1.5 g. (10 mmoles) of LIII with a slight excess of a dry ether solution of diazomethane.[99] The oily product from the reaction of methyl hydrocinnamate-C^{14} with excess phenylmagnesium bromide was dissolved in petroleum ether. On cooling, the petroleum ether solution deposited 1.43 g. (5.0 mmoles) of 1,1,3-triphenylpropane-1-ol. This carbinol (0.88 g. 2.9 mmoles) was dehydrated as before and 0.35 g. (1.2 mmoles) of inactive 1,1,3-triphenylpropene was added to the reaction mixture to act as carrier. Hydroxylation of the active olefin with 1.0 ml. of 30% hydrogen peroxide in 15 ml. of 98-100% formic acid gave, after saponification, 0.65 g. (2.1 mmoles) of 1,1,3-triphenylpropane-1,2-diol, m.p. 143-148°. A sample of the active diol (100 mg.) was recrystallized from benzene-petroleum ether for activity measurements, m.p. 150.4-150.8°. Cleavage of the active diol with lead tetraacetate was carried out as before. Phenylacetaldehyde was obtained as the dimethone derivative, m.p. 168-169.3° after two recrystallizations from methanol. Benzophenone was obtained as the 2,4-dinitrophenylhydrazone, m.p. 240.3-241.5° after recrystallization from dioxane containing a little ethanol (lit.,[100] m.p. 239.5-240°).

Sodium azide (0.23 g., 3.5 mmoles) was added to a stirred mixture of 0.49 g. (3.3 mmoles) of hydrocinnamic-C^{14} acid, 25 ml. of chloroform and 5 ml. of concentrated sulfuric acid. The mixture was stirred at room temperature for 30 minutes then more sodium azide (0.23 g., 3.5 mmoles) was added to the reaction flask. Stirring was continued at room temperature for 30 minutes then at 40-45° for one hour. Ice and excess aqueous sodium hydroxide were added to the reaction mixture, the layers were separated and the aqueous layer was extracted with chloroform. The combined chloroform solution was washed with water, chloroform was removed by evaporation and the residue was shaken with one ml. of benzoyl chloride and excess dilute sodium hydroxide solution. A low yield of N-(β-phenylethyl)-benzamide was obtained, m.p. 113-115° after several recrystallizations from aqueous alcohol. The melting point of this product was not depressed by admixture with authentic N-(β-phenylethyl)-benzamide, m.p. 114.5-115.8°. There was also obtained a small amount of an unidentified product, m.p. 229.7-229.9°. Oesterlin[101] reported a 70% yield of 2-phenylethylamine from the reaction of hydrocinnamic acid with hydrazoic acid, but few experimental details were given.

The data for the C^{14}-activity measurements relevant to this degradation are given in Table II.

Degradation of Benzylmethylcarbinol-C^{14}.--The degradation of benzylmethylcarbinol-C^{14} (XLVIII) is outlined in Fig. 11. Active XLVIII (5.5 g., 0.041 mole) was stirred overnight at room temperature with 2.8 g. (0.028 mole) of chromium trioxide in 20 ml. of 80% acetic acid. The reaction mixture was slightly cooled initially. The crude reaction product was fractionated under reduced pressure in a semimicro column.[80]

Fract.	b.p., °C.	press., mm.	Wt., g.	Product
I	88-88	40	0.3	C_6H_5CHO
II	88-101	20	0.1	
III	101	20		
	104.5	17	2.0	$C_6H_5CH_2COCH_3$
IV	104.5	17	1.2	$C_6H_5CH_2CHOHCH_3$ and $C_6H_5CH_2COCH_3$

Fraction I was converted into the dimethone derivative of benzaldehyde by the general procedure of Horning and Horning,[92] m.p. 192.5-196.5° (lit.,[92] m.p. 194-195°). Cyclodehydration of the dimethone derivative gave the corresponding octahydroxanthene derivative, m.p. 205.5-206° (lit.,[92] m.p. 204-205.5°). The 2,4-dinitrophenylhydrazone of benzyl methyl ketone was obtained from fraction IV, m.p. 152-153° after recrystallization from ethanol-ethyl acetate and aqueous acetic acid. The p-toluenesulfonate of benzyl methyl carbinol was obtained from fraction IV, m.p. 90.8-91.1° after recrystallization from aqueous ethanol and cyclohexane.

Fraction III of the chromium trioxide oxidation product was diluted with 2.0 g. of inactive benzyl methyl ketone and was heated to 230° for 2.5 hours with an equivalent amount (3.1 g.) of o-phenylenediamine. No pure products could be isolated from the highly colored reaction mixture by recrystallization procedures. Oxidation with potassium permanganate in the cold did not successfully remove the colored impurities. A solution of the pyrolysis reaction products in aqueous alcohol was treated with an aqueous solution of silver nitrate. A silver salt precipitated and was collected by filtration, washed with water, suspended in aqueous methanol and treated with hydrogen sulfide. The mixture was boiled with Norite and filtered, and the filtrate was evaporated to dryness. The residue was sublimed to give 22 mg. of 2-methylbenzimidazole-C^{14}, m.p. 175-175.7° after recrystallization from water. 2-Methylbenzimidazole-C^{14} (12 mg.) was diluted with 100 mg. of inactive 2-methylbenzimidazole and recrystallized from water, m.p. 175.2-176.4°. The picrate melted at 213-214° after recrystallization from ethanol.

2-Methylbenzimidazole-C^{14} (LX) was degraded to benzimidazole (LXII) by the procedure of Roseman.[87] Heating 60 mg. of LX in a sealed tube for 2 hours at 196° with benzaldehyde gave 93 mg. (92%) of the benzylidene derivative, LXI. Permanganate oxidation of LXI gave 2-benzimidazolecarboxylic-C^{14} acid (LV) which was decarboxylated by heating to 175°. Two sublimations of the decarboxylation product gave 22 mg. of benzimidazole (LXII), m.p. 171.8-172.2° (lit.,[89] m.p. 170°). The picrate of LXII was prepared in ethanol solution and recrystallized from ethanol, m.p. 229-230° (lit.,[102] m.p. 225-226°).

The data for C^{14}-activity measurements relevant to this degradation are given in Table III.

Degradation of Allylbenzene-C^{14}.--This degradation is outlined in Fig. 12. Allylbenzene-C^{14} (0.30 g., 2.5 mmoles) was stirred magnetically in a small flask with 5 ml. of 98-100% formic acid and 0.9 ml. of 30% hydrogen peroxide. The mixture became homogeneous in about 15 minutes and was then allowed to stand at room temperature for several hours. Formic acid was removed from the reaction mixture at reduced pressure (aspirator) at about 45°. The residue of hydroxyformoxy product was boiled under reflux with 20% aqueous sodium hydroxide containing a little ethanol. The saponification reaction mixture was diluted with water and the active diol was removed by continuous ether extraction. Ether was removed from a portion (three-fifths of the total) of the active diol solution and the residue of 3-phenylpropane-1,2-diol-C^{14} was stirred at room temperature for about 3 hours with 0.67 g. (1.5 mmoles) of lead tetraacetate and 0.21 g. (1.5 mmoles) of anhydrous potassium carbonate in 5 ml. of benzene. Formaldehyde was extracted from the reaction mixture with water and converted[92] into the dimethone derivative, m.p. 191-191.6° (lit.,[103] m.p. 191-191.5°) after recrystallization from methanol. The dimethone derivative of inactive formaldehyde was prepared for elementary analysis.

Anal. Calcd. for $C_{17}H_{24}O_4$: C, 69.84; H, 8.29. Found: C, 69.78; H, 8.28.

The benzene layer from the lead tetraacetate cleavage was filtered and benzene was removed by evaporation on a hot-plate. The residue of phenylacetaldehyde was converted into the dimethone derivative, m.p. 168.5-169.8° after recrystallization from methanol.

Ether was evaporated from the second portion of 3-phenylpropane-1,2-diol-C^{14} solution (about two-fifths of the original amount) and the residue was made anhydrous by adding a few ml. of benzene and distilling it off again. The dried diol was warmed on a steam-bath for 30 minutes with 0.5 g. (2 mmoles) of p-phenylazobenzoyl chloride and 8 ml. of dry pyridine. The reaction mixture was allowed to stand overnight at room temperature and the crude product was recrystallized from cyclohexane then from ethanol-ethyl acetate, m.p. 155-156°. A sample of this derivative was prepared from inactive allylbenzene for analysis, m.p. 155.5-156.5°.

Anal. Calcd. for $C_{35}H_{28}N_4O_4$: C, 73.93; H, 4.96, Found: C, 73.95; H, 5.00

A small sample of allylbenzene-C^{14} was oxidized with alkaline potassium permanganate to benzoic acid, m.p. 121.5-122.2° after recrystallization from water.

p-Methoxycinnamic Acid.--The procedure used was a modification of that of Robinson and Shinoda[104]. A mixture of 172 g. (2 moles) of anisaldehyde, 492 g. (6 moles) of pyridine, 416 g. (4 moles) of malonic acid and 0.5 ml. of piperidine was placed in a 2-liter, 3-necked flask fitted with a mechanical stirrer and reflux condenser. Stirring was begun and the reaction was started by heating briefly on a steam-bath. After 30 minutes and again at the end of one hour 104 g. (1.0 mole) of malonic acid was added to the reaction mixture (total amount of malonic acid used was 6 moles). After one more hour, heating on the steam bath was resumed and continued for 4 hours. The reaction mixture was cooled with ice and poured into a mixture of ice and 500 ml. of concentrated hydrochloric acid. The colorless solid that precipitated from the acidic solution was collected on a Buchner funnel, washed with water and air dried. Recrystallization from aqueous acetic acid gave 285 g. (82%) of p-methoxycinnamic acid, melting at 172.5-173.5° to give a cloudy solution which became clear at about 189° (lit.,[104] m.p. 173°).

p-Methoxyhydrocinnamyl Alcohol.--Lithium aluminum hydride (10.4 g., 0.27 mole) and 600 ml. of dry ether were placed in a 2-liter, 3-necked flask equipped with a mechanical stirrer and reflux condenser. An extraction thimble containing 26.7 g. (0.15 mole) of p-methoxycinnamic acid was placed below the drip tip of the reflux condenser. The ether slurry of lithium aluminum hydride was stirred and warmed until all of the organic acid had been extracted from the thimble (about 15 hours). Excess lithium aluminum hydride was decomposed by addition of methanol in ether. Solids were dissolved by addition of 20% sulfuric acid. Distillation of the product in a modified Claisen apparatus gave a small fraction (1.7 g.), b.p. 128-131° (2.8 mm.), and a main fraction (16.7 g., 69%) of p-methoxyhydrocinnamyl alcohol, b.p. 138° (3.5 mm.), $\underline{n}^{25}D$ 1.5309. The main fraction was redistilled in a spinning-band column. After a small forerun, there was collected 15.0 g. of p-methoxyhydrocinnamyl alcohol, b.p. 134.5-135.5° (4.3 mm.) (lit.,[105] b.p. 162° (15 mm.)), $\underline{n}^{25}D$ 1.5305. The crude product of a second reduction reaction was distilled in a modified Claisen apparatus to give an 88% yield of p-methoxyhydrocinnamyl alcohol, b.p. 130-132° (3 mm.), $\underline{n}^{25}D$ 1.5300.

The phenylurethan was prepared by warming p-methoxyhydrocinnamyl alcohol with phenyl isocyanate, m.p. 66-66.2° (lit.,[105] m.p. 67°) after two recrystallizations from petroleum ether.

p-Methoxybenzylmethylcarbinol.--Anisylacetone[28] was reduced with a slurry of lithium aluminum hydride in ether. Distillation of the crude product in a modified Claisen apparatus gave an 87% yield of p-methoxybenzylmethylcarbinol, b.p. 140-141° (13 mm.), $\underline{n}^{22.5}D$ 1.5258 (lit.,[28] b.p. 119° (4 mm.), $\underline{n}^{25}D$ 1.5261).

p-Methoxybenzylmethylcarbinyl p-toluenesulfonate was prepared in pyridine solution and recrystallized twice from petroleum ether, m.p. 80.0-80.8° (lit.,[28] m.p. 80.0°).

The phenylurethan was prepared by warming p-methoxybenzylmethylcarbinol with phenyl isocyanate, m.p. 74.5-75° after four recrystallizations from petroleum ether.

Anal. Calcd. for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71. Found: C, 71.68; H, 6.76.

p-Methoxyallylbenzene.--p-Methoxyhydrocinnamyl alcohol (8.31 g., 0.05 mole) was acetylated by boiling under reflux for 2.5 hours with 10 g. of acetic anhydride and 1.0 ml. of pyridine. The crude, acetic acid-free p-methoxyhydrocinnamyl acetate was passed through a glass tube packed with glass wool and heated to 400° by means of an electric furnace. The crude product of pyrolysis was freed of acetic acid and distilled through a semimicro column[80] to give 2.4 g. (32% over-all) of p-methoxyallylbenzene, b.p. 100-102° (16 mm.), $n^{26}D$ 1.5239. A similar preparation gave a 35% overall yield of p-methoxyallylbenzene, b.p. 95° (ca. 12.6 mm.), $n^{25.2}D$ 1.5232 (lit.,[106] b.p. 98-100° (14 mm.), $n^{17}D$ 1.5190).

p-Methoxyhydrocinnamic Acid.--p-Methoxycinnamic acid (26 g., 0.15 mole) in 240 ml. of methanol (starting material not completely soluble) was shaken with 0.5 g. of platinic oxide under an initial pressure of hydrogen of about 3 atm. at room temperature (30-32°). The calculated amount of hydrogen was absorbed in 1.5 to 2.5 hours. The combined yield of crude p-methoxyhydrocinnamic acid from three runs was 73 g. (90%). The crude product from a fourth run was submitted to saponification conditions for several hours and the free acid was precipitated from the aqueous solution of its sodium salt by addition of mineral acid. Recrystallization from benzene-petroleum ether gave 14 g. (54%) of p-methoxyhydrocinnamic acid, m.p. 100-102°. Another recrystallization of part of this product from benzene-petroleum ether gave a product melting at 103-104°.

β-(p-Methoxyphenyl)-propionamide.--This preparation is based on the method developed by Boissonnas[107]. Ethyl chloroformate (44 g., 0.405 mole) was added to a stirred solution of 73 g. (0.405 mole) of p-methoxyhydrocinnamic acid (crude product of the catalytic hydrogenation of p-methoxycinnamic acid), and 37 g. (0.405 mole) of triethylamine in one liter of chloroform at 0°. The solution was stirred for 15 minutes, then a stream of ammonia was passed slowly into the reaction mixture for 10 minutes. The ice-bath was removed and stirring was continued for one hour. The reaction mixture was filtered and the chloroform was removed by evaporation on a steam-bath. The residue was recrystallized from water to give 52.5 g. (65%) of β-(p-methoxyphenyl)-propionamide, m.p. 121-123° (lit.,[110] m.p. 123-125°).

3-(p-Methoxyphenyl)-propylamine.--β-(p-Methoxyphenyl)-propionamide (35 g., 0.20 mole) was placed in the thimble of a Soxhlet extractor and a stirred slurry of excess lithium aluminum hydride in 750 ml. of ether was boiled under reflux until all of the amide had been extracted.

The reaction mixture was worked up by the procedure of Amundsen and Nelson.[69] Distillation in a modified Claisen apparatus gave 18 g. (55%) of 3-(p-methoxyphenyl)-propylamine, b.p. 124.5 (5.5 mm.)-128° (6.5 mm.).

The p-toluenesulfonamide was prepared in pyridine solution and recrystallized from aqueous methanol and benzene-cyclohexane, m.p. 65.7-66.5°.

Anal. Calcd. for $C_{17}H_{21}NSO_3$: C, 63.93; H, 6.63. Found: C, 64.20; H, 6.75.

The Reaction of 3-(p-Methoxyphenyl)-propylamine with Nitrous Acid.--A solution of 3.85 g. (0.055 mole) of sodium nitrite in 18 ml. of water was added over a period of one hour to a stirred solution of 8.26 g. (0.050 mole) of 3-(p-methoxyphenyl)-propylamine in 55 ml. of 1.0 M perchloric acid at $55 \pm 2^\circ$. Stirring at 55° was continued for 4 hours after the addition of sodium nitrite solution. The reaction mixture was cooled, acidified with dilute perchloric acid and extracted with ether. The ether solution was washed with aqueous sodium hydroxide solution then with water and dried. Ether was evaporated and the residue was transferred to a small distillation pot with the aid of a little methanol. Methanol was removed by distillation and the residue was fractionated under reduced pressure in a semimicro column.[80]

Fract.	b.p. °C.	press., mm.	Wt., g.	Product
I	97-97	14.5	1.6	$CH_3OC_6H_4CH_2CH = CH_2$
II	111-124	5.3	0.1	
III	124-127	5.2	0.8	$CH_3OC_6H_4CH_2CHOHCH_3$
IV	127-128	5.2	0.5	$CH_3OC_6H_4CH_2CHOHCH_3$
V	121-127	3.3	0.5	$CH_3OC_6H_4CH_2CHOHCH_3$ and $CH_3OC_6H_4CH_2CH_2CH_2OH$
VI	128-131.5	3.3	1.4	$CH_3OC_6H_4CH_2CH_2CH_2OH$
VII	the pressure was reduced further to bring over the column holdup (0.6 g.).			

Fraction I was shown by its infrared spectrum to be p-methoxyallylbenzene (Fig. 9). The infrared spectra of fractions III and IV correspond to that of authentic p-methoxybenzylmethylcarbinol except for a weak band at 5.9-6.0μ and, in the spectrum of fraction IV, a weak band at 10.2-10.3μ. The infrared spectra of fractions VI and VII correspond to that of p-methoxyhydrocinnamyl alcohol except for a strong band at 6.41μ and, in the spectrum of fraction VI, a weak band at 10.60-10.65μ. The absorption band at 6.41μ may be due to a small amount of amine or nitro compound that survived the purification procedure.

Starting amine (1.66 g., 0.01 mole) was recovered from the aqueous layer of the reaction mixture.

The Reaction of Anisylacetone with o-Phenylenediamine.--Anisylacetone (8.2 g., 0.05 mole) and o-phenylenediamine (3.2 g., 0.03 mole) were heated together (Wood's metal-bath) at 170-180° for 30 minutes under an atmosphere of nitrogen. The temperature was raised at 250° over a period of 30 minutes and was maintained at 250° for 3 hours. The reaction mixture was stirred with ether and the solid material that formed was collected by filtration and washed with ether. Two recrystallizations from aqueous methanol gave 1.0 g. of 2-(p-methoxybenzyl)-benzimidazole (LXVIII), m.p. 165-166° after sublimation.

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92, N, 11.76. Found: C, 75.62; H, 5.94; N, 11.76.

The picrate of LXVIII was prepared in ethanol solution and recrystallized from ethanol, m.p. 188-189°.

Anal. Calcd. for $C_{21}H_{17}N_5O_8$: N, 15.52. Found: N, 15.52.

Concentration of the mother liquors gave an additional 0.3 g. of crude LXVIII. Further concentration of the aqueous methanol mother liquors and refrigeration gave a small amount of 2-methylbenzimidazole (LX). Sublimation and recrystallization from water gave 25 mg. of pure LX, m.p. 176.5-177°. The picrate of LX melted at 213.3-214.3°.

β-(p-Methoxyphenyl)-propionitrile.--The procedure used here was modeled after those of English and co-workers.[108] A solution of 10 g. (0.056 mole) of β-phenylpropionamide and

27 g. (0.18 mole) of phosphorus oxychloride in 160 ml. of ethylene chloride was boiled under reflux on a steam-bath for one hour. The hot reaction mixture was poured onto ice and the layers were separated. The organic layer was washed with potassium carbonate solution then with water and dried. Ethylene chloride was removed by evaporation and the high-boiling residue was distilled under reduced pressure to give 8.0 g. (89%) of β-(p-methoxyphenyl)-propionitrile, b.p. 135° (3.1 to 3.2 mm.).

3-(p-Methoxyphenyl)-propylamine-1-C^{14}.--p-Methoxyphenylacetonitrile (17.6 g., 0.12 mole), kindly supplied by D. T. Manning, was hydrolyzed by the procedure of Wenner,[109] except that the nitrile was stirred with concentrated hydrochloric acid for only 5 hours before the reaction mixture was diluted with water. The yield of crude p-methoxyphenylacetic acid was 17.9 g. (90%). One recrystallization from benzene-ligroin gave a product melting at 84-85.4°.

p-Methoxyphenylacetic acid (6.0 g., 0.036 mole) was reduced with a slurry of lithium aluminum hydride in ether. Distillation of the crude product in a semimicro column[80] gave 4.6 g. (83%) of 2-(p-methoxyphenyl)-ethanol, b.p. 131-132° (6.6 mm.) (lit.,[35] b.p. 130-132° (6.5 mm.)), $n^{25}D$ 1.5336.

The reaction of p-toluenesulfonyl chloride with 2-(p-methoxyphenyl)-ethanol in pyridine solution at room temperature gave the sulfonic ester in a yield of only 3%, m.p. 58-58.8°. When the reaction was repeated at 0° on a sample of crude carbinol from the lithium aluminum hydride reduction of p-methoxyphenylacetic acid, crude 2-(p-methoxyphenyl)-ethyl p-toluenesulfonate was obtained in 70% over-all yield. After one recrystallization from benzene-petroleum ether, this product melted at 57-58° (lit.,[35] m.p. 57-58°).

Sodium cyanide-C^{14} (0.5 mmole containing 5×10^2 μcuries of C^{14}-activity) was diluted with 0.27 g. (5.5 mmoles) of inactive sodium cyanide and boiled under reflux overnight with 2.8 g. (9 mmoles) of 2-(p-methoxyphenyl)-ethyl p-toluenesulfonate in 80% ethanol. Inactive β-(p-methoxyphenyl)-propionitrile (8.0 g., 0.05 mole) was added to the reaction mixture to act as carrier and the mixture was poured into chloroform. The chloroform solution was washed three times with half-saturated calcium chloride solution and once with water and dried. Solvent was removed by evaporation and the residue was distilled under reduced pressure to give 8.5 g. (0.051 mole) of β-(p-methoxyphenyl)-propionitrile-1-C^{14}, b.p. 129-133° (2.8 mm.).

β-(p-Methoxyphenyl)-propionitrile-1-C^{14} (6.76 g., 0.042 mole) was reduced with lithium aluminum hydride in the usual manner. Inactive 3-(p-methoxyphenyl)-propylamine (10.3 g.) was added to the reaction mixture to act as carrier and the mixture was worked up by the procedure of Amundsen and Nelson.[69] Distillation at reduced pressure gave 13.4 g., b.p. 110-111° (2.5 mm.). The p-toluenesulfonamide melted at 66.5-66.8°.

p-Methoxyhydrocinnamic-1-C^{14} Acid.--A solution of β-(p-methoxyphenyl)-propionitrile-1-C^{14} (1.75 g., 0.0108 mole) in 50% aqueous ethanol containing about 25% by weight of sodium hydroxide was boiled under reflux. In about 2 hours a thick suspension of the sodium salt of p-methoxyhydrocinnamic-1-C^{14} acid formed. The reaction mixture was diluted with water and boiling was continued until the odor of ammonia could no longer be detected. The reaction mixture was diluted with more water and concentrated on a hotplate to remove most of the ethanol. The solution was acidified with dilute mineral acid and the crude p-methoxyhydrocinnamic-1-C^{14} acid was collected by filtration. One recrystallization from benzene-ligroin gave 1.6 g. (83%), m.p. 103.2-104°.

The Reaction of 3-(p-Methoxyphenyl)-propylamine-1-C^{14} with Nitrous Acid.--A solution of 6.9 g. (0.10 mole) of sodium nitrite in 25 ml. of water was added over a period of one hour to a stirred solution of 13.2 g. (0.080 mole) of 3-(p-methoxyphenyl)-propylamine-1-C^{14} in 100 ml. of 1.0 M perchloric acid at 60 ± 2°. Stirring at 60 ± 2° was continued for 2.5 hours; 10 ml. of 1.0 M perchloric acid was then added and stirring at the same temperature was continued for an additional 30 minutes. To the slightly acidic reaction mixture was added 1.38 g. (0.0093 mole) of p-methoxyallylbenzene, 6.8 g. (0.041 mole) of p-methoxybenzylmethylcarbinol and 6.6 g. (0.040 mole) of p-methoxyhydrocinnamyl alcohol to act as carriers. This reaction mixture was worked up like that of the inactive 3-(p-methoxyphenyl)-propylamine-nitrous acid reaction. Fractionation with a spinning-band column gave 1.8 g. of p-methoxyallylbenzene-C^{14}, b.p. 101-102° (18.5 mm.); 2.7 g. of an intermediate fraction, boiling from 90° to 139° (10.1 mm.); 7.7 g. of p-methoxybenzylmethylcarbinol-C^{14}, boiling from 133° (7.5 mm.) to 138° (8.2 mm.) (phenylurethan, m.p. 74.5-75°); 1.8 g. of an intermediate fraction boiling from 141° to 150° (9.6 mm.); and 6.9 g. of p-methoxyhydrocinnamyl-C^{14} alcohol, b.p. 133.5-136.5° (4.3 mm.) (phenylurethan, m.p. 65.7-66°). Refractionation of the column washings and intermediate fractions in a semimicro column[80] gave p-methoxyallylbenzene-C^{14} (0.4 g.), p-methoxybenzylmethylcarbinol-C^{14} (2.5 g.) and p-methoxyhydrocinnamyl-C^{14} alcohol (0.8 g.).

3-(p-Methoxyphenyl)-propylamine-1-C^{14} was recovered from the aqueous layer of the reaction mixture and converted into the hydrochloride (1.2 g., 0.006 mole).

Yields were calculated by the isotope dilution technique as mentioned earlier. The starting material not accounted for (34%) was presumably converted into organic nitro compounds, carbonyl compounds and nitroso secondary amines.

Degradation of p-Methoxyhydrocinnamyl-C^{14} Alcohol (L).--The degradation of L, product of the reaction of 3-(p-methoxyphenyl)-propylamine-1-C^{14} with nitrous acid, is outlined in Fig. 14A. The acetylation of L and the pyrolysis of the crude acetate were carried out as described in the preparation of inactive p-methoxyallylbenzene (LII). From 6.4 g. (0.038 mole) of L there was obtained 2.0 g. (35%) of p-methoxyallylbenzene-C^{14} (LII).

To a stirred solution of 1.5 g. (0.001 mole) of LII in 20 ml. of 98-100% formic acid was added 0.9 ml. of 30% hydrogen peroxide solution. The mixture was stirred for 10 minutes, an additional 0.9 ml. of hydrogen peroxide solution was added, and stirring at room temperature was continued for an additional 40 minutes. The solvent was removed at 43° with the aid of a water aspirator and the residue was refluxed for 30 minutes with aqueous methanolic sodium hydroxide. The saponification reaction mixture was diluted with water and continuously extracted with ether for 20 hours. The ether extract was dried and the ether evaporated. The residue was stirred for 2 hours at room temperature with 1.5 g. (0.011 mole) of anhydrous potassium carbonate and 4.4 g. (0.010 mole) of lead tetraacetate in about 10 ml. of benzene. The reaction mixture was filtered, and both filtrate and inorganic solids were washed with water. The combined aqueous washings were washed once with benzene and treated with excess methone by the general procedure of Horning and Horning.[92] The dimethone derivative of formaldehyde-C^{14} was collected by filtration, washed with water, dried and recrystallized from methanol, m.p. 191.2-191.7°. The benzene solution of p-methoxyphenylacetaldehyde-C^{14} (LXVI) was evaporated on a hot-plate to remove most of the benzene. The residue of LXVI was taken up in warm 80% ethanol, filtered and treated with excess methone.[92] The dimethone derivative of LXVI was recrystallized from aqueous methanol then from cyclohexane and finally from methanol, m.p. 152.5-154.5°. A sample of the dimethone derivative of inactive LXVI was prepared for elementary analysis.

Anal. Calcd. for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 73.00; H, 7.91.

A sample (ca. 0.2 g.) of p-methoxyhydrocinnamyl-C^{14} alcohol was oxidized to anisic acid with alkaline permanganate. After recrystallization from benzene, the product melted at 183.8-184.2°.

The results of C^{14}-activity measurements on L and the products of its degradation are given in Table VI.

Degradation of p-Methoxyallylbenzene-C^{14} (LII).--The degradation of LII, product of the reaction of 3-(p-methoxyphenyl)-propylamine-1-C^{14} with nitrous acid, is outlined in Fig. 14B. The compound LII (1.7 g., 0.011 mole) was hydroxylated and cleaved as described in the degradation of L. The yield of the dimethone derivative of formaldehyde-C^{14}, m.p. 191.3-191.7°, was 1.6 g. (50%). The yield of the dimethone derivative of p-methoxyphenylacetaldehyde-C^{14}, m.p. 153.5-155.5°, was 1.3 g. (28%).

Oxidation of about 0.2 g. of LII with alkaline permanganate gave anisic acid (LXVII), m.p. 182-183.4° after recrystallization from benzene.

The results of C^{14}-activity measurements on the degradation products of LII are given in Table VII.

Degradation of p-Methoxybenzylmethylcarbinol-C^{14} (LI).--The degradation of LI is outlined in Fig. 14C. Chromium trioxide (3.9 g., 0.039 mole) was added in small portions over a period of several hours to a stirred solution of 6.3 g. (0.038 mole) of LI in 24 ml. of glacial acetic acid and 6 ml. of water. When the addition was completed, 3-4 ml. of water was added to the reaction mixture and stirring at room temperature continued for 2 hours. The organic products were recovered from the reaction mixture by continuous ether extraction. Inactive anisylacetone (6.3 g.) was added to the ether extract to act as carrier. The ether solution was washed successively with water, potassium carbonate solution and water and then dried. The ether was removed from the solution by evaporation on a hot-plate and the residue was distilled under reduced pressure to give a fraction, 1.2 g., b.p. 108-115° (4.6 mm.), and a main fraction, 7.1 g., of anisylacetone-C^{14} (LXVIII), b.p., 114-117° (4.3 mm.). A sample (about 0.2 g.) of LXVIII was converted into the 2,4-dinitrophenylhydrazone for C^{14}-activity measurements, m.p. 107.7-108.1° after several recrystallizations from ethanol. A sample of inactive anisylacetone 2,4-dinitrophenylhydrazone, m.p. 107.8-108.2°, was prepared for elementary analysis.

Anal. Calcd for $C_{16}H_{16}N_4O_5$: C, 55.81; H, 4.68; N, 16.27. Found: C, 55.69; H, 4.74; N, 16.20.

Anisylacetone-C^{14} (6.8 g., 0.039 mole) was heated with o-phenylenediamine (2.2 g., 0.020 mole) under an atmosphere of nitrogen as described earlier for inactive anisylacetone. Several recrystallizations of the crude product from aqueous methanol followed by two sublimations gave about 0.5 g. of 2-(p-methoxybenzyl)-benzimidazole (LXIX), m.p. 165.5-166°. The picrate of LXIX melted at 188-189°. No 2-methylbenzimidazole could be isolated from the mother liquors in this reaction.

Oxidation of a small sample of LI with alkaline permanganate gave anisic acid, m.p. 183.5-184.2° after recrystallization from benzene.

The results of C^{14}-activity measurements on LI and its degradation products are given in Table VIII.

APPENDIX I

The Preparation and Acetolysis of 2-Phenyl-1-propyl p-Bromobenzenesulfonate

2-Phenyl-1-propyl p-Bromobenzenesulfonate.--2-Phenyl-1-propanol (0.7 g.) was dissolved in 3 ml. of dry pyridine and treated with 1.4 g. of p-bromobenzenesulfonyl chloride. The reaction mixture was allowed to stand overnight and was worked up in the usual manner to give 1.3 g. of crude 2-phenyl-1-propyl p-bromobenzenesulfonate. Recrystallization from cyclohexane gave 0.9 g., m.p. 78-80° (lit.,[29] m.p. 81.5-82.5°).

Acetolysis of 2-Phenyl-1-propyl p-Bromobenzenesulfonate.--2-Phenyl-1-propyl p-bromobenzenesulfonate (0.86 g., 2.4 mmoles) was boiled under reflux for 64 hours with 2.0 g. of anhydrous sodium acetate in 25.0 ml. of glacial acetic acid containing 4 drops of acetic anhydride. The reaction mixture was poured into a mixture of ice and 20% sodium hydroxide and neutral organic products were extracted with ether. The ether solution was dried, the ether evaporated, and the residue distilled in a semimicro column[80] under reduced pressure. The acetate product (0.24 g.) had an infrared spectrum essentially identical with that of pure benzylmethylcarbinyl acetate. No evidence for any of the moderate to strong absorption bands of 2-phenyl-1-propyl acetate at 10.15-10.20μ, 10.95-11.00μ, 12.05μ or 13.10μ was found in the acetolysis product. A small amount of olefin collected in the Dry-Ice trap, but this product was not investigated.

APPENDIX II

The Reliability of the C^{14}-Activity Measurements

The limit of error in each C^{14}-activity measurement was estimated visually from the recorder chart. The estimation of the limit of error in the very low activity measurements was complicated by the uncertainty in the background activity which varied, but was usually between 0.04 mvolt and 0.06 mvolt.

A Sartorius Selecta balance was used for weighing the samples. Readings could be made to ± 0.02 mg. with this balance, but the weights were not calibrated. The somewhat arbitrary value ± 0.10 mg. was used as the limit of error for all sample weights.

Molar activities were calculated in mvolts/mmole and these were converted into μcuries/mmole by dividing by 4.75×10^3, a factor determined by measuring the C^{14}-activity of a standardized sample of benzoic-C^{14} acid. The estimated per cent error of the mmolar C^{14}-activity is the sum of the estimated per cent error of the sample activity and the estimated per cent error of the sample weight. Estimated uncertainties have been reported as limits rather than percentages.

Where three or more C^{14}-activity measurements were made on the same compound the per cent deviation from the average value ($\%\Delta$) has been given rather than the estimated limit of error. The $\%\Delta$ was less than the estimated limit of error in all cases except for several of the C^{14}-activities of benzophenone-C^{14} 2,4-dinitrophenylhydrazone. Similar results (unpublished) were noted in C^{14}-activity measurements on this compound by W. N. White.

There is no indication in the results of this work of a significant error due to an isotope effect. In any reaction in which an isotope effect might have been important, the error from this source was kept to a minimum by carrying the reaction as near to completion as was feasible.

In this work, only crystalline compounds were combusted for C^{14}-analysis, and these were carefully purified by recrystallization and, in several cases, by sublimation. With the possible exception of the bis-p-phenylazobenzoyl derivative of 3-phenylpropane-1,2-diol-C^{14}, errors due to the presence of contaminants should be very small.

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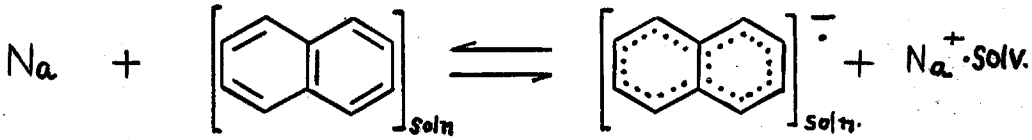
PROPOSITIONS

1. A solution of naphthalene in the dimethyl ether of ethyleneglycol or in methyl ether will dissolve one gram atom of sodium per mole of naphthalene to give a dark-green solution of a sodium-naphthalene compound.[1] The equilibrium,



is proposed to account for the properties of these solutions. This formulation is compatible with the behavior of naphthalene and conjugated unsaturated hydrocarbons at a dropping mercury cathode.[2]

2. The reduction of α,β-epoxyketones by sodium and alcohol is proposed as a useful laboratory method of obtaining 1,3-diols. α,β-epoxyketones may be obtained readily by treating α,β-unsaturated ketones with alkaline hydrogen peroxide.

3. A synthesis of 4,7,7-trimethylbicyclo(4·1·0)heptanone-2 (caranone-5) beginning with 3-methyl-5-hydroxybenzoic acid is suggested. Caranone-5 and related compounds are expected to have interesting properties, and a study of such compounds would contribute to our knowledge of naturally occurring carane derivatives.
4. It is proposed that 4-bromo-2-cyclohexenone be prepared for study of some of its reactions. In glacial acetic acid with sodium acetate this compound might be expected to undergo displacement with rearrangement.[3] With alcoholic alkali, ring closure to form a bicyclo(3·1·0)-hexenone and the Favorski rearrangement could possibly compete with direct displacement of bromide ion.
5. It is proposed that the reaction of 1-amino-3-phenylbutane with nitrous acid be studied (this thesis, p. 54).
6. It has been reported[4] that the reaction of 2-phenyl-1-propylamine with nitrous acid gives 2-phenyl-1-propanol, but no experimental details were given. This behavior is unexpected in view of the course of the acetolysis reaction of 2-phenyl-1-propyl p-bromobenzenesulfonate (this thesis, p. 99). It is proposed that this amine-nitrous acid reaction be reinvestigated.

7. Alkali metals do not dissolve in simple tertiary amines. It may be that solution does not occur because active hydrogen plays an essential role in solvating electrons.[5] Another factor operating against solution of the alkali metal is the bulkiness of tertiary amines which would prevent them from effectively solvating alkali metal cations. It is proposed that attempts be made to dissolve alkali metals in a mixture of a tertiary amine and an inert solvent such as the dimethyl ether of ethyleneglycol. Only positive results would permit definite conclusions.

8. No phosphonium radical, R_4P, has been isolated.[6] The reaction of tetraphenylphosphonium halides[7] with alkali metals is proposed for the preparation of tetraphenylphosphonium radical. Work at low temperature in methyl ether is recommended to avoid the possibility of a cleavage reaction.

9. Optimism and a high regard for innocence are characteristically American traits. Much of modern American literature has concerned itself with the realities of corruption and defeat.

10. Violence is an important theme in American literature. In Shakespeare's tragedies violence is most often associated with unnatural behavior of human beings, but in modern American literature violence is more or less taken for granted as part of the nature of life.

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