ALKALINE DECOMPOSITION OF 5,5-DIARYL-N-NITROSO-2-OXAZOLIDONES

MECHANISM OF DECOMPOSITION OF 5,5-DIARYL-N-NITROSO-2-OXAZOLIDONES

by

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SCOPE AND CONTENTS:

A migration aptitude study has been made of the alkaline decomposition of 5,5-diaryl-N-nitroso-2-oxazolidone to diarylacetylene with the aim of shedding light on the mechanism of the rearrangement step of the reaction. 5-Phenyl-5-p-trifluoromethylphenyl-N-nitroso-2-oxazolidone-5-C^{14} was synthesized and converted to p-trifluoromethyltolane-C^{14}, which was oxidized to benzoic acid and p-trifluoromethylbenzoic acid. The ratio of specific activities of the two acids was found to be 1:2, showing that the migration tendency of the phenyl group is twice that of the p-trifluoromethylphenyl group. This result has been interpreted in terms of an electronically-controlled migration step involving as an intermediate either a vinyl carbonium ion or a vinyl carbene.

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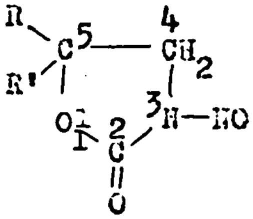
GENERAL INTRODUCTION

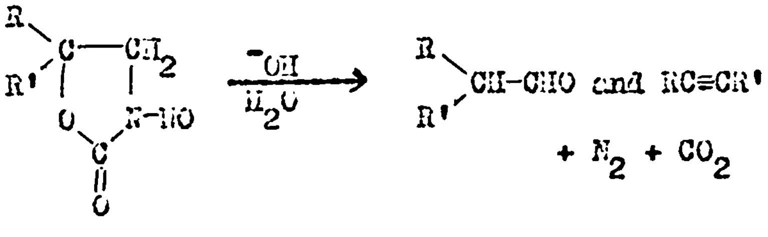
In 1951, M. S. Newman (1) published the results of an extensive investigation of the alkaline decomposition of N-nitroso-2-oxazolidones, substituted on carbon-5 by one or two alkyl or aryl groups.



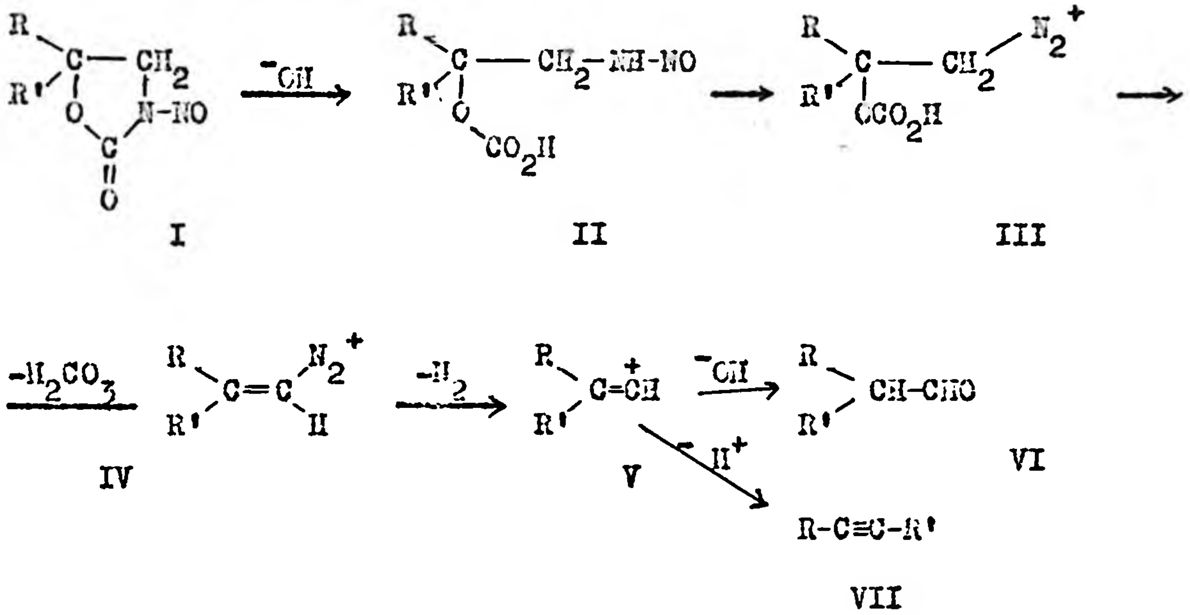
I

(R and R' may be alkyl or aryl or hydrogen)

When carbon-5 carries two alkyl groups, the sole product is a saturated aldehyde; when it carries two phenyl groups, diphenylacetylene is formed in quantitative yield and finally, when this carbon carries one phenyl group, the product is a mixture of aldehyde and substituted acetylene.

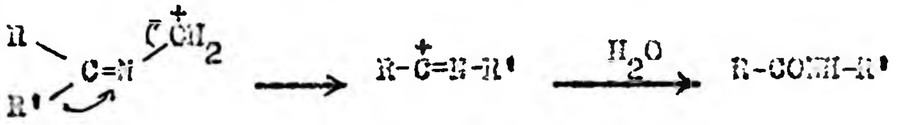


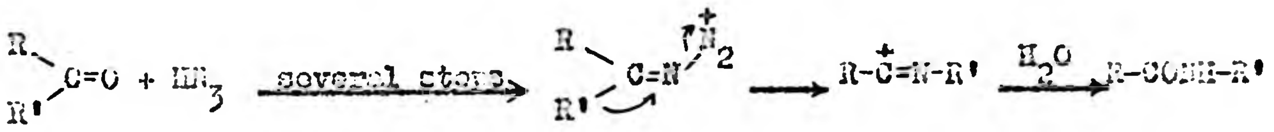
On the basis of the nature of the products obtained from the various carbon-5 substituted N-nitroso-2-oxazolidones, Newman proposed the following mechanism for the decomposition reaction:



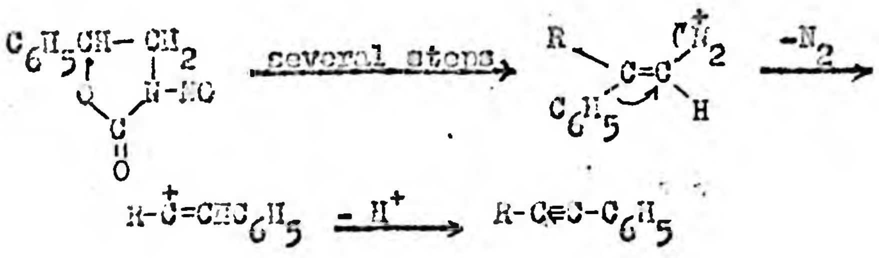
The first two steps of the above reaction sequence, the opening of the ring by hydrolytic cleavage of the lactam linkage and the transformation of the nitrosoamine II into a diazonium ion III seem reasonable and perhaps obvious. Furthermore, the acidity of the hydrogen atom attached to the carbon bearing the $-N_2^+$ group in structure III and the conjugation or hyperconjugation of the carbon-5 substituents with the ethylenic linkage to be formed, might be expected to provide driving force for a β-elimination of carbonic acid from III to give the diazonium ion IV. Support for this sequence of steps was provided by Newman's isolation of sodium methyl carbonate when the alkaline decomposition of 4,5,5-triphenyl-N-nitroso-2-oxazolidone was carried out in absolute methanol.

The next step in Newman's mechanism for the decomposition of the 5,5 disubstituted *N*-nitroso-2-oxazolidones is the loss of nitrogen to form an unsaturated carbonium ion, V, of an unusual type. Although this ion was written in Newman's publication as a discrete intermediate, he made it quite clear that the formation of the two types of products VI and/or VII in no way requires that an ion such as V have an actual existence. Indeed, the rearrangement of IV to the acetylene VII is reminiscent of such concerted stereospecific *trans*-rearrangements as the Beckman rearrangement of oximes and the Schmidt reaction of ketones.

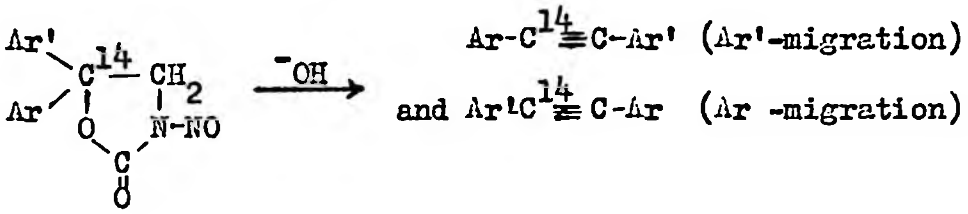

Beckman rearrangement


Schmidt reaction

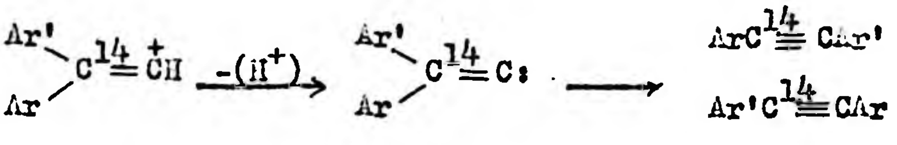
By analogy with the above two reactions, a perfectly plausible mechanism for the formation of acetylenes from 5-phenyl-substituted *N*-nitroso-2-oxazolidones would consist of synchronous migration of a phenyl group and departure of nitrogen:



The object of the investigation to be reported in this thesis was to distinguish between a mechanism in which loss of nitrogen from the diazonium ion IV preceeds the migration of the phenyl group and one where the bond changes are synchronous. The approach was to determine the relative migratory tendencies of two different aryl groups in the alkaline decomposition of a 5,5-diaryl-N-nitroso-2-oxazolidone, using carbon-14 as a tracer to differentiate between the two diphenylacetylenes formed.

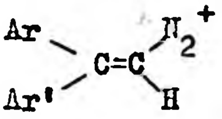


This test of mechanism is based on the following reasoning. If the reaction proceeds by way of a discrete carbonium ion intermediate, V, formed by the loss of nitrogen prior to aryl group migration, then the relative migration tendencies of the two aryl groups should be determined by their ability to supply electrons to the carbon atom carrying a formal positive charge. In other words, the aryl group which has the greater electron density conjugatively distributed on the ring should exhibit the greater migratory tendency. This would also be the case if carbonium ion V were to lose a proton prior to the rearrangement step, since the migration in an unsaturated carbene, VIII, would be to an electron deficient centre:



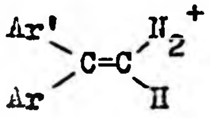
V VIII

On the other hand, if the migration of an aryl group were to be synchronous with the departure of nitrogen, it would seem reasonable, in view of what is known about synchronous rearrangements, that the migrating aryl group and the diazonium group should have a *trans* relationship. In such a case the relative migratory tendencies should be determined solely by the relative populations of the two species:



A

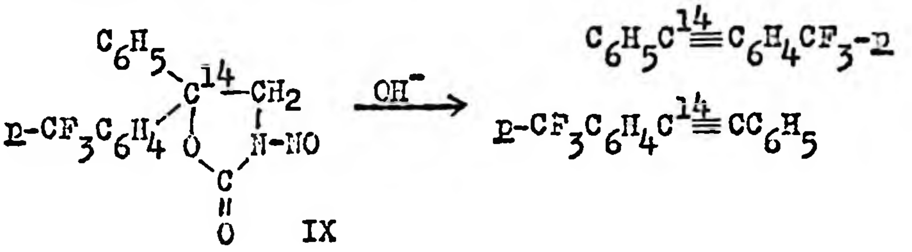
and



B

If the two aryl groups differ only in the presence of a *meta*- or *para*-substituent the populations of A and B should be essentially the same. As a consequence, the two aryl groups should have equal migratory tendencies, even though they may differ considerably in their nucleophilicity.

The system chosen for this migratory aptitude study was 5-phenyl-5-*p*-trifluoromethylphenyl-N-nitroso-2-oxazolidone-5-C^{14}, IX, which on alkaline decomposition gives rise to two diarylacetylenes, X and XI, which differ only in the position of the carbon tracer.



IX

X

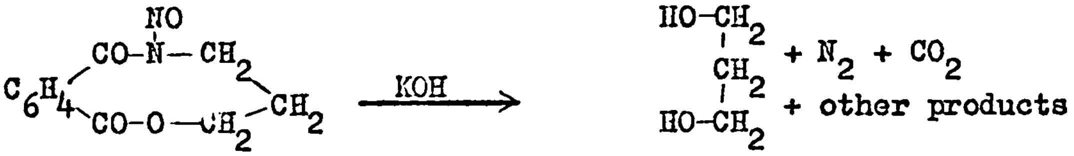
XI

The relative amounts of the two acetylenes, and thus the relative migratory tendencies of the two aryl groups, were determined by radiochemical assay of the two acids, benzoic acid and p-trifluoromethylbenzoic acid, formed by oxidation of the total reaction product.

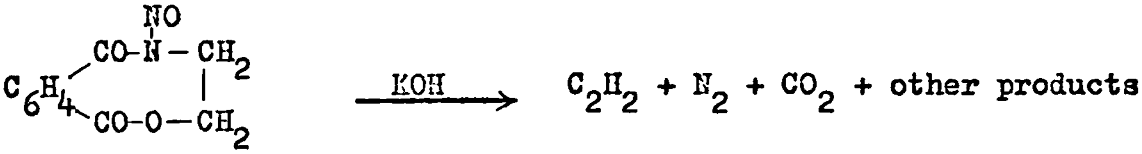
A description of this investigation will be preceeded in the thesis by a Historical Introduction which, in addition to reviewing Newman's work on the alkaline decomposition of N-nitroso-2-oxazolidones, will include a critical discussion of the role of electronic and stereochemical factors in determining the course of molecular rearrangements in electron deficient systems. The latter will be divided into three sections. The first will treat carbonium ion rearrangements and will give particular emphasis to the reactions of carbonium ions formed by deamination of saturated primary amines (diazonium ion decomposition). The second will deal with rearrangements involving electron deficient nitrogen and will treat in detail the Schmidt reaction of ketones, which as already indicated, is formally analogous to the reaction under investigation. Finally, in the third section will be discussed some recent studies of rearrangements involving aryl group migration to a vinylic carbon.

HISTORICAL INTRODUCTION

Although the instability of open-chain N-nitroso compounds was known as early as the middle of the last century, it was not until 1905 that S. Gabriel (2) came upon some unusual reactions of cyclic N-nitrosoamides. Whereas the nine-numbered cyclic amide, XII, on treatment with alkali, gave the expected hydrolysis product, a 1,3-glycol, the eight-numbered compound, XIII, was found to give rise to some acetylene.



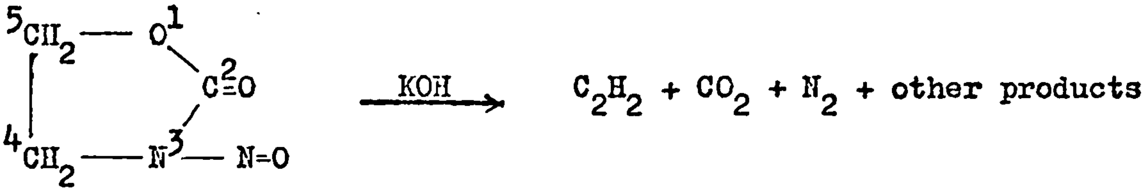
XII



XIII

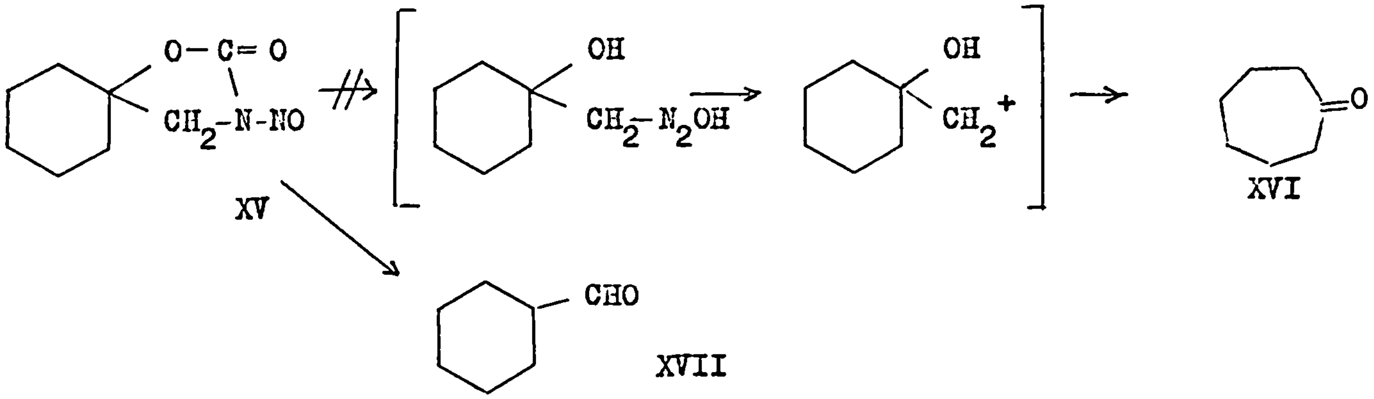
Further investigation established that the reaction forming acetylene is characteristic of cyclic N-nitrosoamides in which the heteroatoms are separated by two saturated carbon atoms. Gabriel eventually prepared the simplest compound fulfilling this condition, the

3-nitroso-2-oxazolidone, XIV, and showed that it gives rise to acetylene in 12 per cent yield on treatment with strong alkali.

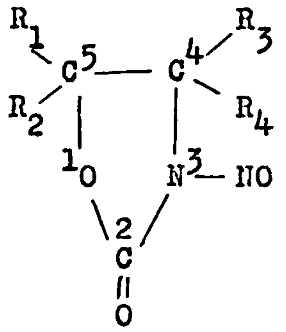


XIV

Some 40 years later, in 1949, Newman (3), in the course of an investigation concerned with the development of new methods of ring expansion, treated 3-nitroso-1-oxa-3-azaspiro 4,5 -decan-2-one, XV, with alkali, hoping to form cycloheptanone , XVI, by a carbonium ion rearrangement.

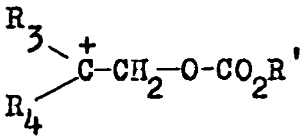


Instead, hexahydrobenzaldehyde, XVII, was formed in over 50 per cent yield. This unexpected result was of sufficient interest to stimulate a systemmatic investigation of the behaviour toward strong bases of N-nitroso-2-oxazolidones bearing one or two alkyl or aryl groups on either or both C-4 and C-5 ring members.



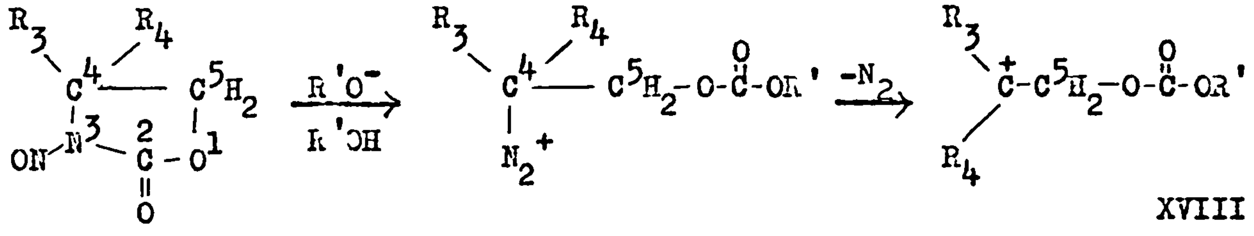
In one set of experiments (4), groups on C-4 were varied, while C-5 remained unsubstituted. The results of this investigation are shown in Table I.

Although a variety of products are formed, all but the ketone and vinyl ether formed from the phenyl-substituted N-nitroso-2-oxazolidone can be accounted for by the reactions of a carbonium ion intermediate of structure



$$(R_3)(R_4)\overset{+}{C}-CH_2-O-CO_2R'$$

resulting from the action of base (hydroxide or alkoxide ion) on the nitroso compound.



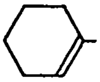
XVIII

(R' may be H, CH_3 or C_2H_5)

The reactions of the carbonium ion intermediate XVIII are outlined in Chart I. In this chart, group R_3 has been replaced by

TABLE I

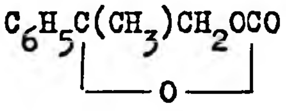
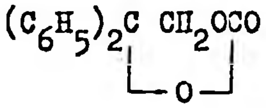
Products from Alkaline Decomposition of C-4-Substituted-N-nitroso-2-oxazolidones

R_3	R_4	Reagent	Solvent	Products	Yield In %	Type of Compound*
$-(CH_2)_5-$		OH^-	H_2O	$C_6H_{11}CHO$	52	XXIII
		OH^-	H_2O	 $-CH_2OH$	45	XXII
CH_3	CH_3	OH^-	H_2O	$(CH_3)_2CHCHO$	38	XXIII
		OH^-	H_2O	$CH_2=C(CH_3)CH_2OH$	54	XXII
		CH_3O^-	CH_3OH	$(CH_3)_2C=CHCO_2CH_3$	29	XX
		CH_3O^-	CH_3OH	$CH_2=C(CH_3)CH_2CO_2CH_3$	33	XIX
C_2H_5	H	OH^-	H_2O	$CH_3CH_2CH_2CHO$	35	XXIII
		OH^-	H_2O	$CH_3CH=CHCH_2OH$	46	XXII
		CH_3O^-	CH_3OH	$CH_3CH_2CH=CHCO_2CH_3$	31	XX
		CH_3O^-	CH_3OH	$CH_3CH=CHCH_2CO_2CH_3$	40	XIX

*Type of compound refers to the numbers given in Chart I on page 13.

TABLE I (CONTINUED)

Products from Alkaline Decomposition of C-4-Substituted-N-nitroso-2-oxazolidones

R_3	R_4	Reagent	Solvent	Products	Yield In %	Type of Compound*
C_6H_5	H	OH^-	H_2O	$C_6H_5CH(OH)CH_2OH$	77	XXIV
		OH^-	H_2O	$C_6H_5COCH_3$	12	
		$C_2H_5O^-$	C_2H_5OH	$C_6H_5CH(OC_2H_5)CH_2OCO_2C_2H_5$	75	XXI
		$C_2H_5O^-$	C_2H_5OH	$C_6H_5C(OC_2H_5)=CH_2$	14	
C_6H_5	CH_3	OH^-	H_2O	 $C_6H_5C(CH_3)CH_2OCO$	59	XXV
		OH^-	H_2O	$C_6H_5CH(CH_3)CHO$	22	XXIII
C_6H_5	C_6H_5	OH^-	H_2O	 $(C_6H_5)_2C\ CH_2OCO$	51	XXV
		OH^-	H_2O	$(C_6H_5)_2CHCHO$	12	XXIII
		OH^-	H_2O	$(C_6H_5)_2C(OH)CH_2OH$	22	XXIV

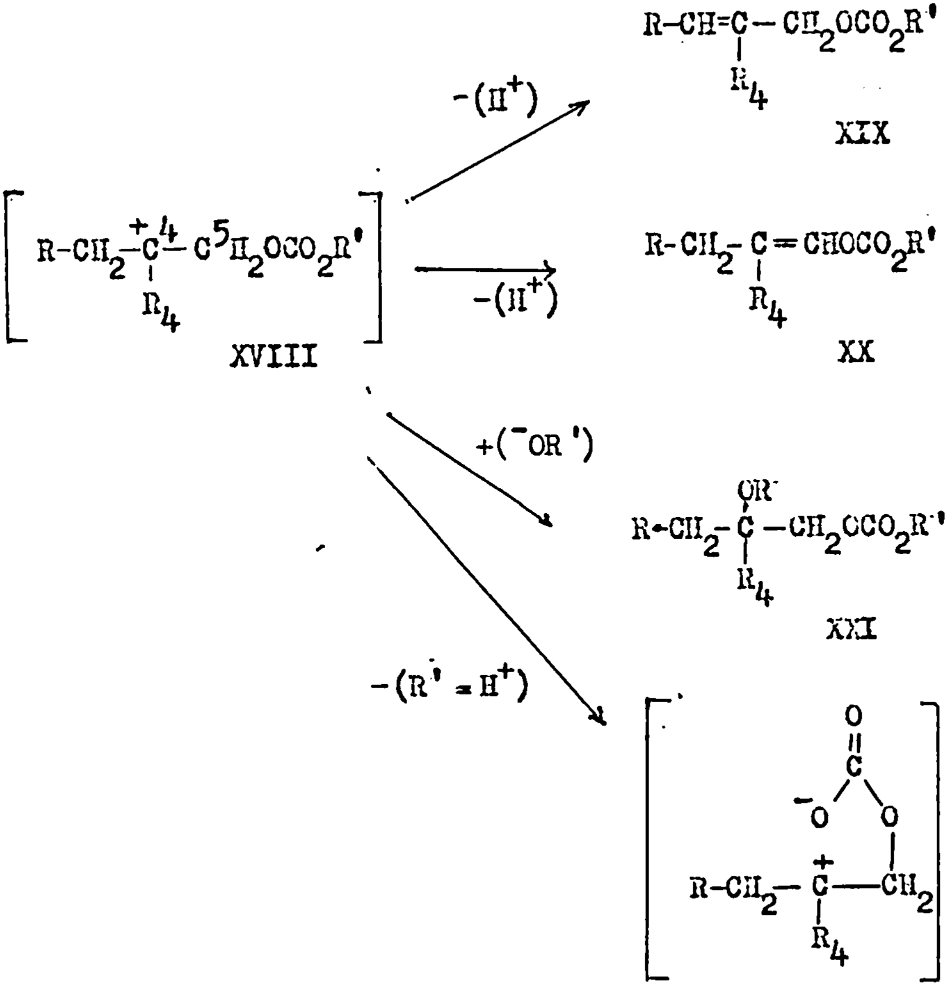
*Type of compound refers to the numbers given in Chart I on page 13.

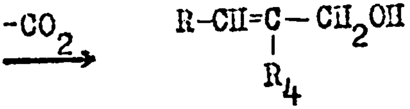
RCH_2- in order to show the formation of the allyl alcohols and carbonates. The products XXII, XXIII and XXIV on the right hand side of the chart result by the loss of carbon dioxide when the reaction is carried out in water and R' is consequently hydrogen. The carbonates, XIX, XX and XXI, are formed when the reaction is carried out in anhydrous alcohol.

Expulsion of a proton from a carbon atom adjacent to the carbonium ion center leads to an unsaturated carbonate ester. If this proton is lost from the alkyl group attached to C-4 of the original oxazolidone, the product formed in anhydrous alcohol is an allylic ester, XIX, whereas a substituted allyl alcohol, XXII, is formed in aqueous solvents. If two different alkyl groups are attached to C-4, two isomeric allylic carbonates or alcohols can result.

When a proton is lost from C-5 of the original N-nitroso-2-oxazolidone, the initial product is a vinyl carbonate, XX, from which an aldehyde, XXIII, can be obtained by hydrolysis and an enol-keto proton shift. Addition of a base to C-4 of the carbonium ion XVIII leads to an ether carbonate, XXI, in anhydrous alcohol solvent and to a 1,2-glycol, XXIV, in aqueous medium. Finally, in aqueous medium, ring closure, involving the carboxylate group may occur, resulting in the formation of a cyclic carbonate XXV. It can be seen from inspection of Table I that reactions 3 and 4, involving the interaction of the carbonium ion centre with a negatively charged ion or group, are favoured when one or both groups attached to C-4 are phenyl group. This is undoubtedly due to the enhanced stability of the carbonium ion,

CHART I



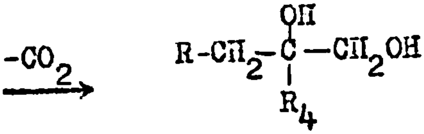


$$\xrightarrow{-CO_2} R-CH=\underset{\displaystyle R_4}{\underset{|}{C}}-CH_2OH \qquad 1$$

XXII

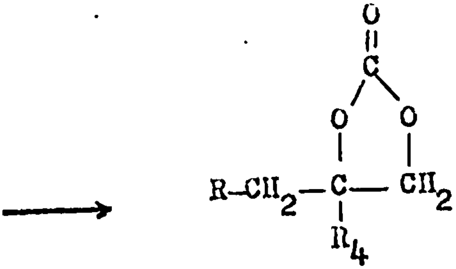
$$\xrightarrow{-CO_2} R-CH_2-\underset{\displaystyle R_4}{\underset{|}{CH}}-CHO \qquad 2$$

XXIII



$$\xrightarrow{-CO_2} R-CH_2-\overset{\displaystyle OH}{\overset{|}{\underset{\displaystyle R_4}{\underset{|}{C}}}}-CH_2OH \qquad 3$$

XXIV

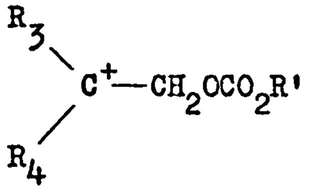


4

XXV

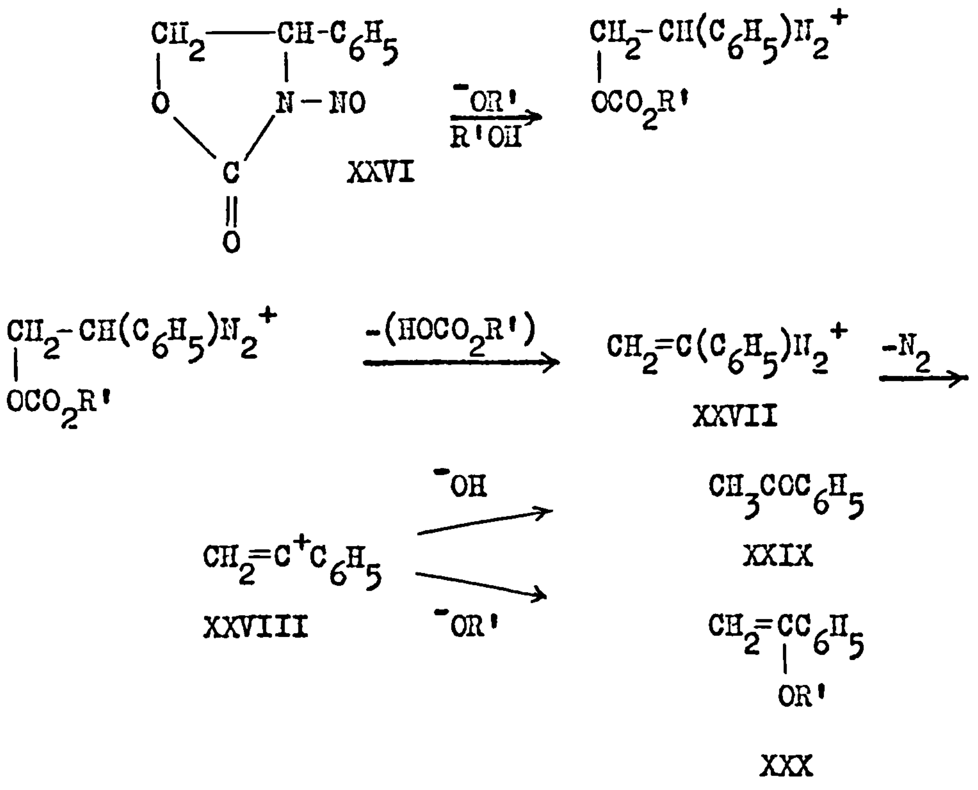
resulting from conjugative interaction between the positive centre and the attached phenyl groups.

Two products listed in Table I cannot be accommodated by a mechanism involving



as a reaction intermediate.

These are acetophenone and the vinyl ether, α-ethoxystyrene, resulting from the action of base on 4-phenyl-N-nitroso-2-oxazolidone, XXVI, in water and ethyl alcohol, respectively. The formation of these compounds, however, can be accounted for by a mechanism in which a base catalyzed elimination of carbonic acid (or of its mono-ester) preceeds the loss of nitrogen:



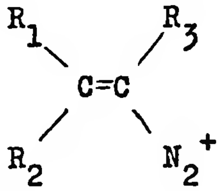
5

The fact that the base catalyzed elimination of carbonic acid can compete successfully with the reaction pathway involving prior loss of nitrogen can be rationalized on the basis that the hydrogen on C-4 is more acidic when the adjacent substituent is phenyl rather than an alkyl group.

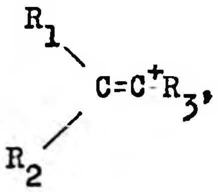
A different group of reaction products were obtained by Newman (1) when he treated the 5-mono- and di-substituted N-nitroso-2-oxazolidones with base. The result of this investigation is shown in Table II.

When C-5 carries two alkyl groups, the only product which can be isolated is a saturated aldehyde, whereas the presence of a phenyl group at this position leads to a mixture of aldehyde and substituted acetylene, with the latter predominating. When two phenyl groups are substituted for hydrogen on C-5, diphenylacetylene is formed in quantitative yield.

Newman accounted for all products listed in Table II on the basis of the formation of an unstable vinyl diazonium ion



which then loses nitrogen to form the unsaturated carbonium ion



XXXI

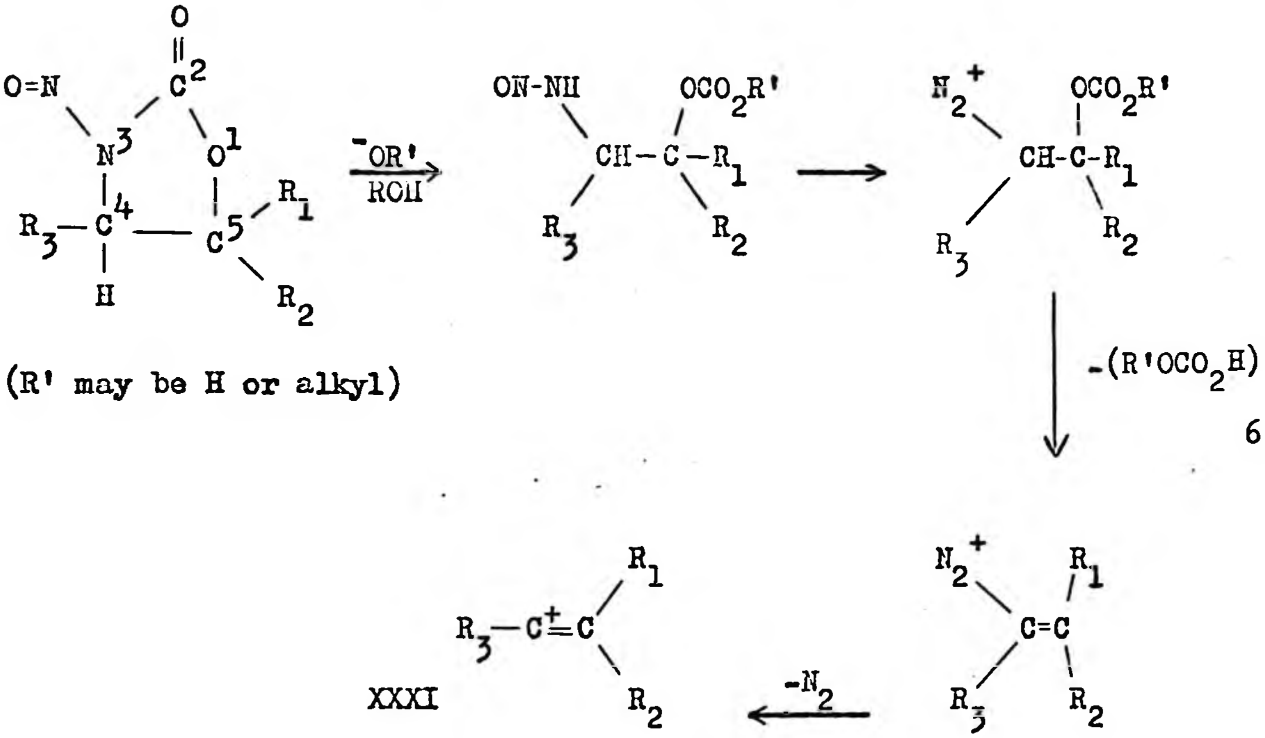
TABLE II

Products Formed from 5-Mono- and Di-Substituted-N-nitroso-2-oxazolidones on Decomposition in Aqueous Alkali

R_1	R_2	R_3	R_4	Products	Yields %	Type of Compound*
H	H	H	H	$HC\equiv CH$	12	XXXIII
$-(CH_2)_5-$		H	H	$C_6H_{11}CHO$	88	XXXII
$-(CH_2)_6-$		H	H	$C_6H_{13}CHO$	81	XXXII
CH_3	CH_3	H	H	$(CH_3)_2CHCHO$	80	XXXII
C_2H_5	C_2H_5	H	H	$(C_2H_5)_2CHCHO$	79	XXXII
C_6H_5	H	H	H	$C_6H_5C\equiv CH$	60	XXXIII
				$C_6H_5CH_2CHO$	30	XXXII
C_6H_5	CH_3	H	H	$C_6H_5C\equiv CCH_3$	74	XXXIII
				$C_6H_5CH_2COCH_3$	16	XXXII
C_6H_5	C_6H_5	H	H	$C_6H_5C\equiv CC_6H_5$	100	XXXIII
C_6H_5	C_6H_5	C_6H_5	H	$(C_6H_5)_2C=C(OCH_3)C_6H_5$	60	XXXV
C_6H_5	H	C_6H_5	H	$C_6H_5C\equiv CC_6H_5$	10	XXXIII
C_6H_5	H	H	C_6H_5	$C_6H_5COCH_2C_6H_5$	6	XXXII
Both erythro and threo gave same products				$C_6H_5CH(OCH_3)CH(C_6H_5)OH$	84	

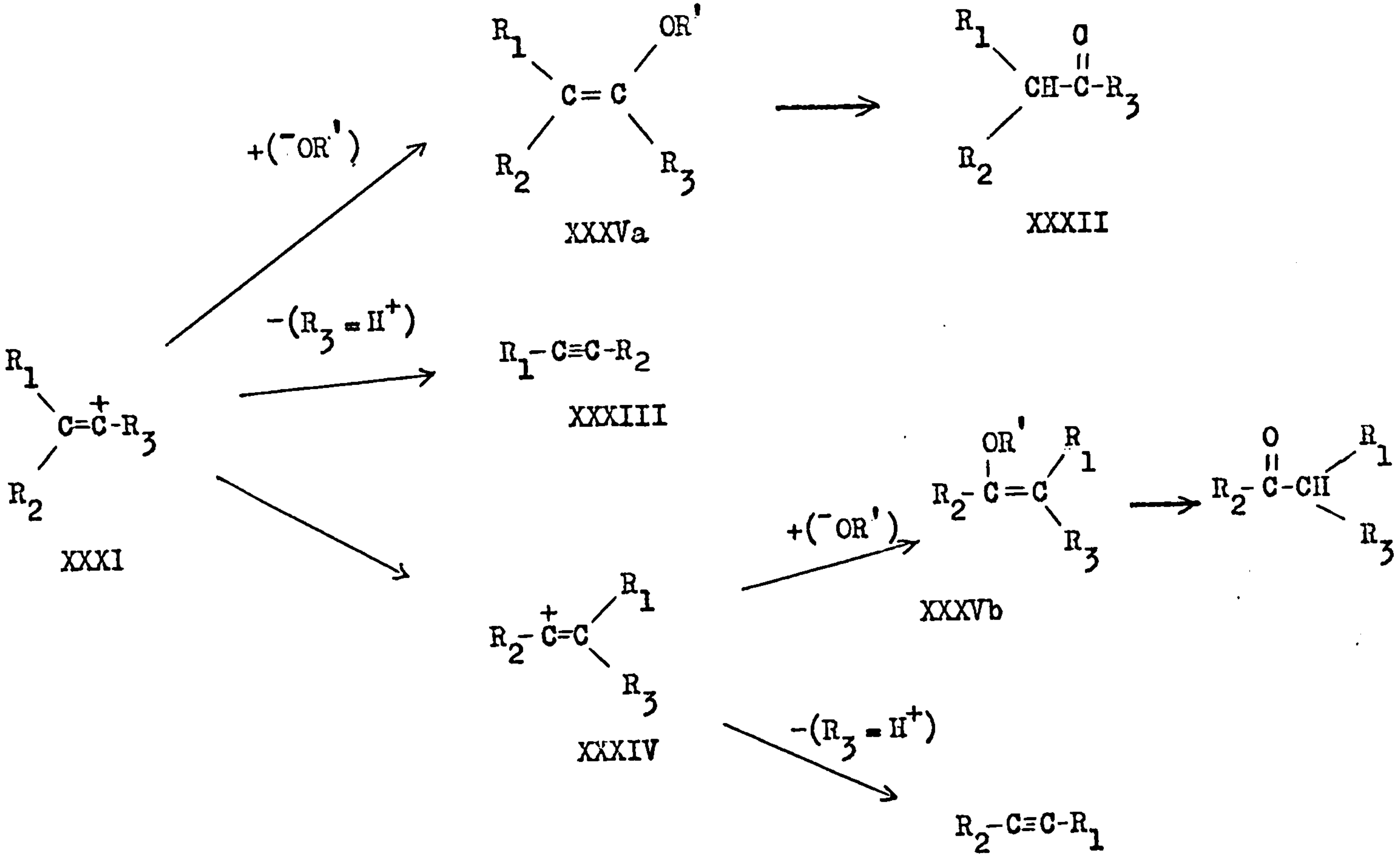
*Type of compound refers to the numbers given in Chart II on page 18.

This is the same reaction sequence as that one shown in equation 5 for the reaction of 4-phenyl-N-nitroso-2-oxazolidone, XXVI.



The fate of the carbonium ion, XXXI, depends on the nature of the substituents, R_1, R_2 and R_3 and on the solvent. Its reactions are shown in Chart II. When R_1 and R_2 are alkyl and R_3 is hydrogen, the reaction follows pathway 7 and the product is a saturated aldehyde, XXXII. When R_1 is a phenyl group, R_2 an alkyl or a phenyl group or hydrogen, and R_3 is hydrogen, the carbonium ion XXXI rearranges by phenyl migration to give a new carbonium ion, XXXIV, which may interact with $^-$OR' to form a vinyl ether, XXXV, in an anhydrous alcohol solvent (pathway 9). Carbonium ion XXXI may also lose a proton to form an acetylene, XXXIII, (pathway 8). When R_1, R_2 and R_3 are all phenyl groups, the vinyl ether which is obtained in methanol may be formed either without phenyl migration (pathway 7) or with phenyl migration (pathway 9).

CHART II



7

8

9

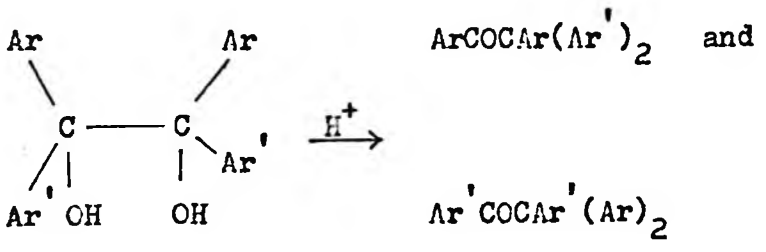
10

On the basis of behaviour of 5,5-diphenyl-N-nitroso-2-oxazolidone, which decomposes on treatment with base to only one product diphenylacetylene in excellent yield, Newman suggested this route as a novel general method of preparation of diarylacetylenes from benzophenones. With the exception of one report dealing with the preparation of unsubstituted diphenylacetylene via benzophenone (5), no further syntheses of this type have been reported.

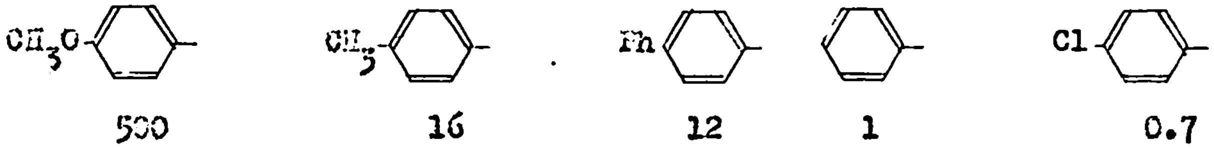
Carbonium Ion Rearrangements

Starting in the early 1930's, a great deal of attention has been given to the question of the relative ability of various groups to migrate from one carbon atom to an adjacent electron deficient center. This is a complicated matter since it is now apparent that the so-called "migratory aptitudes" of groups are not related to their nucleophilicity alone but may be determined by the relative populations of different ground state conformers and by eclipsing effects in the transition state.

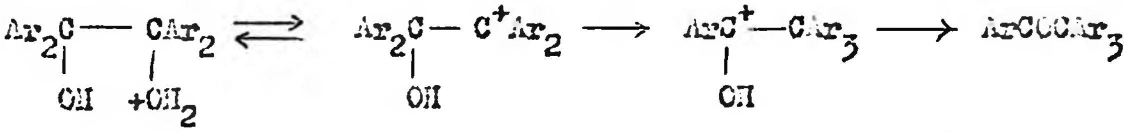
One of the earliest studies of migratory aptitudes was that of Bachman (6), who made an extensive investigation of this problem for the pinacol-pinacolone rearrangement of tetra-aryl pinacols.



The following are typical values of migratory aptitudes for groups in this rearrangement:

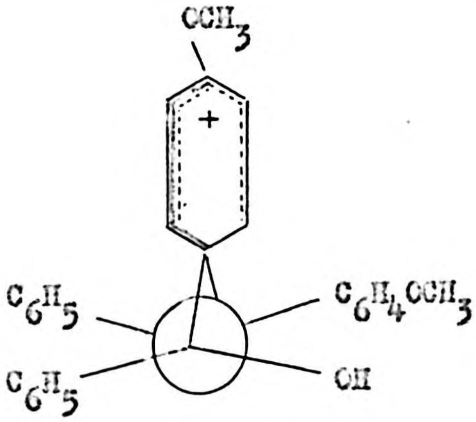


Since it is now well established (7, 8) that a pinacol rearrangement involving departure of the hydroxyl group from a diaryl-substituted tertiary carbon proceeds through an open carbonium ion which is in equilibrium with the protonated glycol,

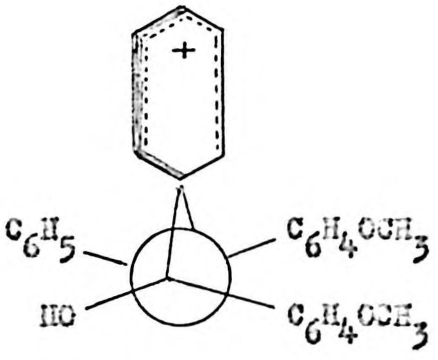


$$\underset{OH}{Ar_2C}-\underset{+OH_2}{CAr_2} \rightleftharpoons \underset{OH}{Ar_2C}-C^{+}Ar_2 \longrightarrow \underset{OH}{ArC^{+}}-CAr_3 \longrightarrow ArCOCAr_3$$

the relative migration tendencies of different aryl groups, say phenyl- and *p*-anisyl-, will depend upon the relative energies of the two transition states XXXVII and XXXVIII for the rearrangement step.



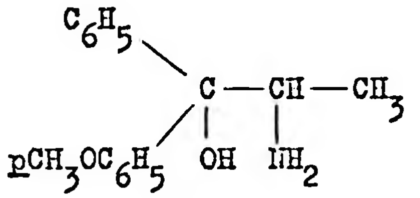
XXXVII *p*-anisyl migration



XXXVIII phenyl migration

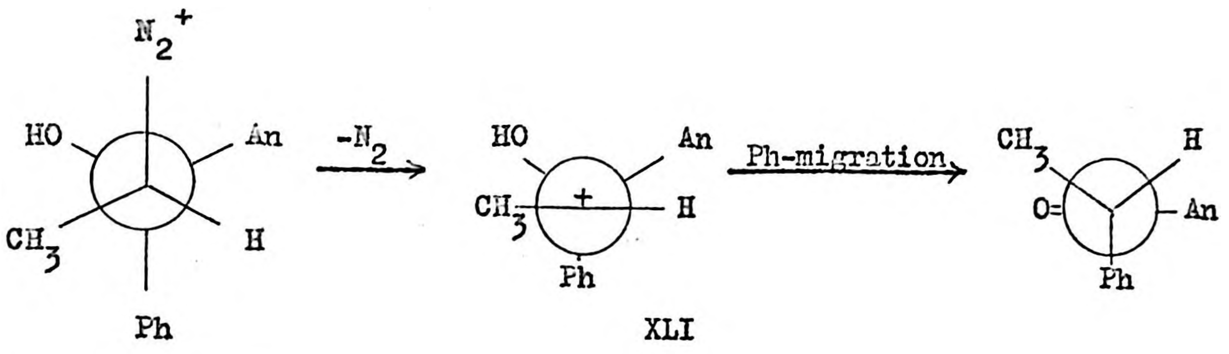
As the steric requirements for phenyl and *para*-substituted phenyl groups occupying the eclipsed positions in these transition states will be almost identical, the positive charge can be expected to be the more readily accommodated on the *p*-anisyl group. In other words, the migratory aptitudes listed above can be considered to be a measure of the relative nucleophilicity of different aryl groups with respect to a carbonium ion center.

Entirely different results are obtained in the deamination of *threo* and *erythro* isomers of 1-*p*-anisyl-1-phenyl-2-aminopropanol XXXIX (9).



XXXIX

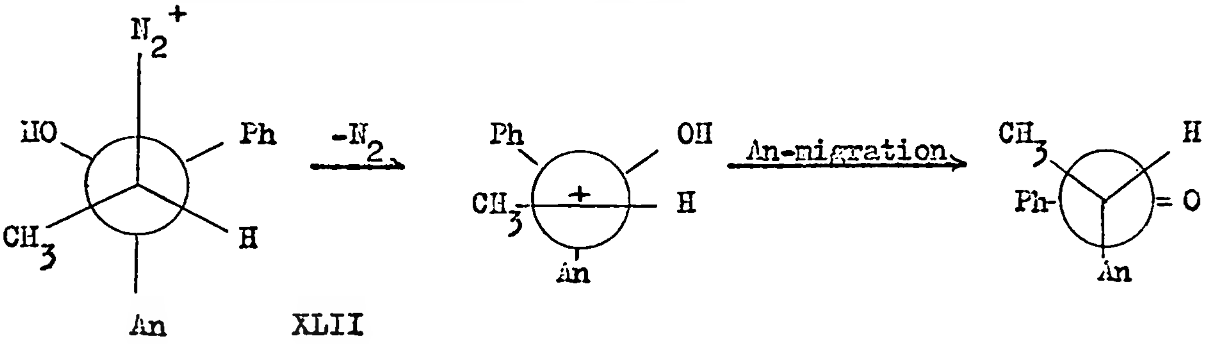
The former proceeds almost exclusively with *p*-anisyl migration, the latter with phenyl migration. Obviously, some factor other than group nucleophilicity is involved in this reaction system, otherwise, the *p*-anisyl group would be the preferred migrating group for both stereoisomers. In a series of brilliant investigations, Collins (10, 11, 12) has recently shown that the deamination of aminoalcohols of the type $Ar_2C^{\beta}(OH)C^{\alpha}H(NH_2)R$ proceeds through open carbonium ion whose life-times are short relative to the time required for rotation about the $C_{\alpha} - C_{\beta}$ bond. Now the preferred conformation of *erythro* 1-*p*-anisyl-1-phenyl-2-aminopropanol will be XL, since it places a hydrogen between the two bulky aryl groups. On treatment with nitrous acid this conformer will give the reactive carbonium ion XLI.



XLI

erythro XL

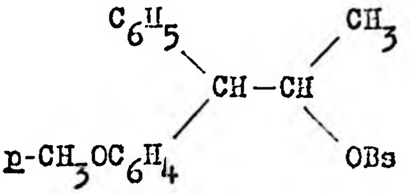
If the half-life of this ion is short relative to the half-life for rotation through 60° about the $C_\alpha - C_\beta$ bond, then phenyl migration should dominate. Similarly, the preferred migration of the p-anisyl group in the deamination of the threo isomer can be accounted for on the basis that its preferred conformation is XLII.



XLII

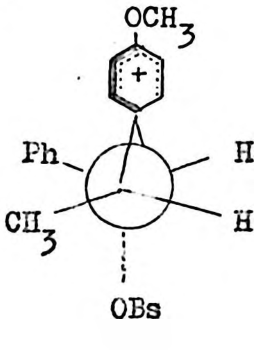
It can be seen that in reactions producing a high-energy short-lived open carbonium ion, the migration can be expected to be subject to stereochemical rather than electronic control.

An entirely different result is found in the solvolysis of the diasteroisomeric 1-p-anisyl-1-phenyl-2-propyl brosylate, XLIII

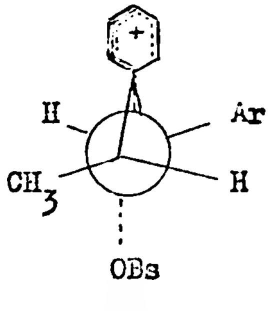


XLIII

Both *threo* and *erythro* compounds give exclusively the product formed by migration of the *p*-anisyl group (13). Now the solvolysis reaction is of the type for which ample evidence has been provided (14) of neighbouring group participation, resulting in the formation of a bridged carbonium ion. In other words, departure of the brosylate group from the secondary carbon atom requires nucleophilic push from the migrating group. For the reaction of the *threo* isomer, two opposing factors determine the relative energies of the transition states for phenyl and *p*-anisyl group migration. The greater ability of the *p*-anisyl group to accommodate positive charge stabilizes the transition state XLIV relative to XLV, whereas the eclipsing effect, tending to favour a *trans* relationship of the aryl and methyl groups, favours the transition state XLV.



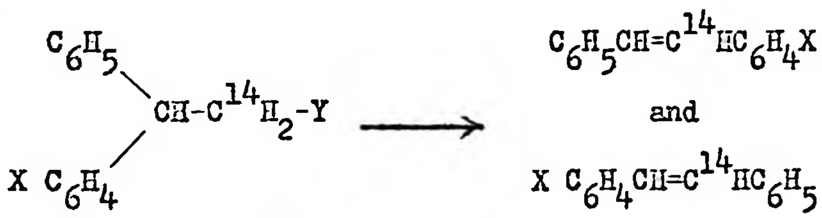
XLIV



XLV

The exclusive migration of the *p*-anisyl group shows that of the two factors, the electronic one is the more important. With the *erythro* brosylate, on the other hand, the steric and electronic effects are reinforcing.

That migratory aptitudes are intimately associated with the nature of the leaving group and hence with the degree to which nucleophilic push is required in the heterolysis step, is evident from the work of Burr (15, 16). Using compounds labelled with carbon-14, the migratory aptitude of groups was determined for the conversion of XLVI into substituted stilbenes:



XLVI

Y = $-NH_2$ in a deamination reaction

Y = $-O^+H_2$ in a dehydration

Y = -OTs in a solvolysis.

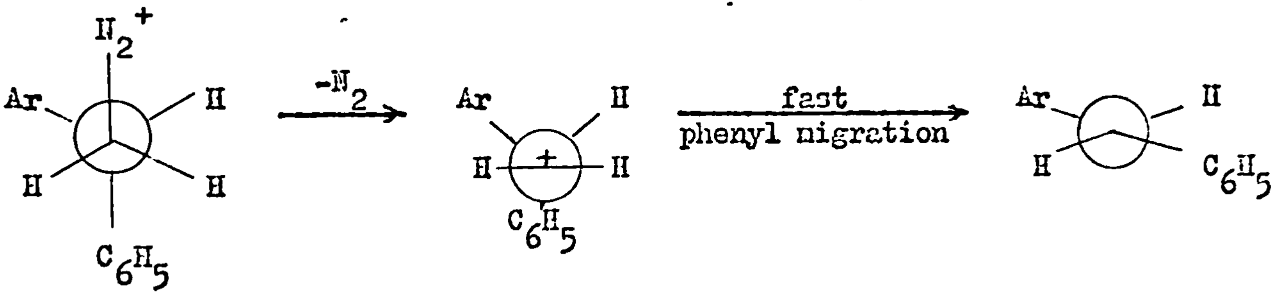
The results of these studies are shown in Table III.

TABLE III

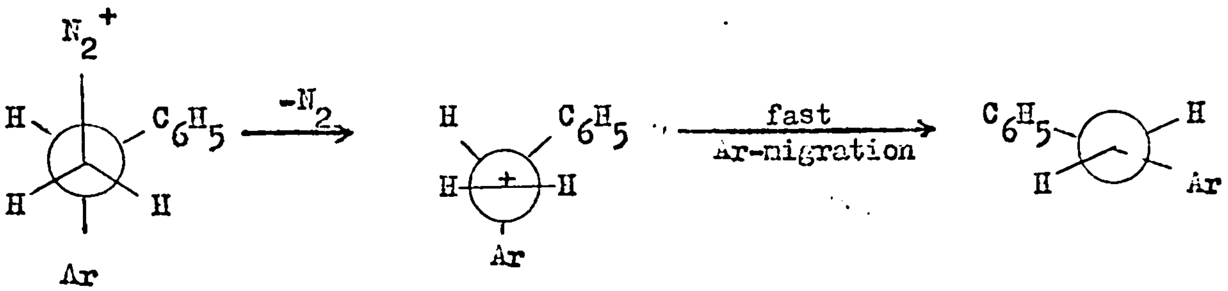
Migratory Aptitudes of Substituted Phenyl Groups in Rearrangements Leading to Stilbenes

Phenyl Substituent X	Type of Reaction		
	Deamination	Dehydration of Alcohols	Solvolysis of Tosylates
p-CH_3-	47	66	71
m-CH_3-	48	61	--
p-C_6H_5-	50	57	--
p-CH_3O-	59	96	--

The most reasonable interpretation of these results is that both the alcohol and tosylate rearrangements require aryl group participation in the heterolysis step, while the deamination reaction, because of driving force provided by the formation of molecular nitrogen, gives an open carbonium ion. Since this carbonium ion is primary, it will be of high energy and therefore its half-life can be expected to be short relative to the half-life for rotation about the $C_\alpha - C_\beta$ bond. The relative migration tendencies then can be expected to be determined by the ground-state populations rather than by group nucleophilicity.



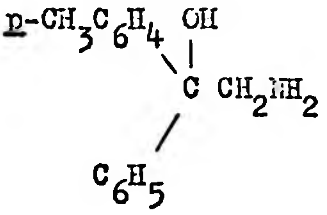
XLVII



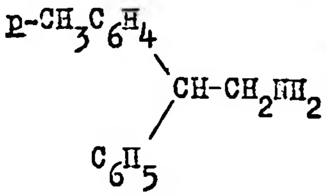
XLVIII

Since in the 2,2-diarylethyl system the ground state populations of XLVII and XLVIII should be almost the same, one can expect little selectivity in the migration of the two aryl groups.

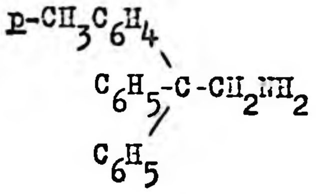
More recently p-tolyl/phenyl migration ratios significantly larger than unity have been obtained on deamination of several systems in which nitrogen is departing from a primary carbon:



XLIX



L



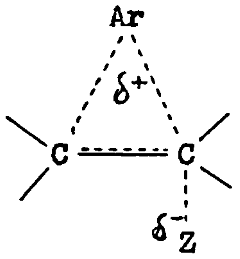
LI

p-tolyl/phenyl migration ratio	1.28 ± 0.09 (17)	1.18 ± 0.06 (18)	1.18 ± 0.06 (18)

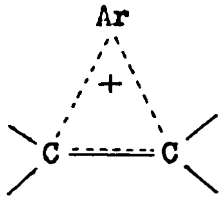
Two points are of interest here. Firstly, the migration ratios are the same within experimental error in all three compounds, XLIX, L and LI, and, secondly, group nucleophilicity is obviously playing a role although to a lesser extent than is the case in a solvolytic process. It would seem that even in the deamination some nucleophilic push is required to bring about heterolysis at a primary carbon.

In summary then, it would appear that several factors determine the extent to which migratory aptitude is determined by the nucleophilicity of the rearranging group. If the heterolysis step involves a relatively poor leaving group, for example $-OSO_2Ar$, or even $-N_2^+$ if departure is from a primary carbon, considerable driving force derived from neighbouring group participation will be required and group nucleophilicity will be important in determining migratory aptitude. In certain structures there will be superimposed upon the nucleophilicity effect a steric (eclipsing) effect which, depending upon the configuration of the transition state for the migration, may reinforce or counteract the nucleophilicity effect. In the solvolysis of threo-1-p-anisyl-1-phenyl-2-propyl brosylate (vide supra), for example the two effects operate in opposition whereas in the solvolysis of the erythro isomer both steric and nucleophilic factors favour p-anisyl migration.

If, on the other hand, heterolysis is facile, for example in the removal of $-N_2^+$ from a secondary or tertiary carbon, or of a $-^+OH_2$ group from a diaryl substituted carbon, little or no neighbouring group participation is called into play and an open carbonium ion is formed. In this case, the extent to which migratory aptitude will be determined by group nucleophilicity will depend upon the life time of the open carbonium ion. If the rate of group migration is rapid relative to the rate of attainment of conformational equilibrium (rotation about the $C_\alpha - C_\beta$ bond), then the migration rates will be determined by the relative populations of the different ground state conformers and will be essentially independent of group nucleophilicity. This apparently is the case in the deamination of threo and erythro 1-p-anisyl-1-phenyl-2-aminopropanol. On the other hand, if the initially formed open carbonium ion is sufficiently long lived to allow attainment of conformational equilibrium, then the relative migration rates of different groups will depend on the relative energies of the isomeric transition states for the rearrangement step. As in the case of neighbouring group participation in heterolysis, the energies of these transition states will be determined by both nucleophilicity and by steric effects. Indeed, it would seem that the only essential difference between a reaction with neighbouring group participation in the heterolysis step and one involving slow rearrangement of an initially formed carbonium ion is the extent to which coplanarity is achieved in the transition state for migration and the amount of positive charge which is accommodated on the migrating group.



migration accompanying heterolysis

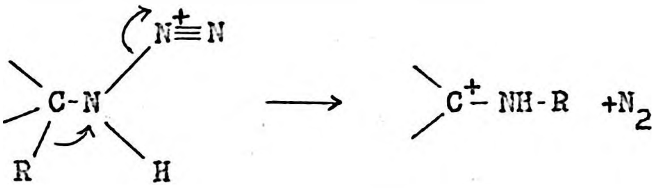


migration from open carbonium ion

Both eclipsing and nucleophilicity effects might be expected to be larger for the migration from an open carbonium ion.

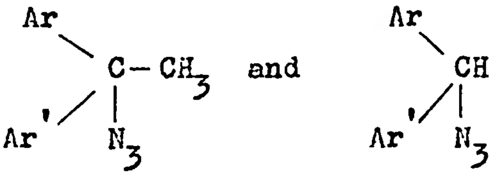
Some Rearrangements Involving An Electron Deficient Nitrogen Atom

The name Schmidt reaction has been given to a group of reactions each employing as a reagent hydrazoic acid in the presence of a mineral acid and involving as organic substrate a carboxylic acid, olefin, alcohol, ketone or aldehyde. These reactions all proceed through an intermediate organic azide, which in its conjugate-acid form decomposes with migration of an alkyl or aryl group from carbon to nitrogen:



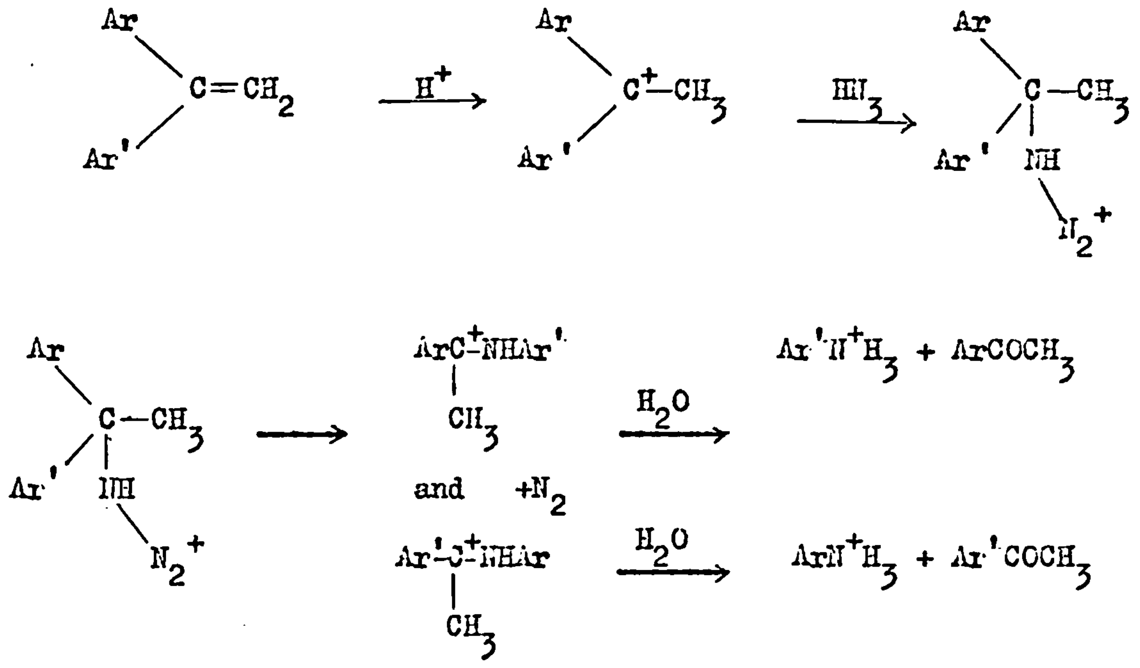
The same question with respect to mechanism arises with these reactions as with the rearrangements to electron deficient carbon. Does nitrogen depart prior to or synchronously with migration of the alkyl or aryl group? It has again been migration aptitude measurements which have been most fruitful in shedding light on this question, and these studies, as applied to the Schmidt reaction of 1,1-diarylethylenes, benzhydrols and diarylketones are reviewed in this section of the thesis.

Beginning in 1950, McEwen and co-workers have made an extensive study of migratory aptitudes of different aryl groups in the acid-catalyzed decomposition of azides of the type

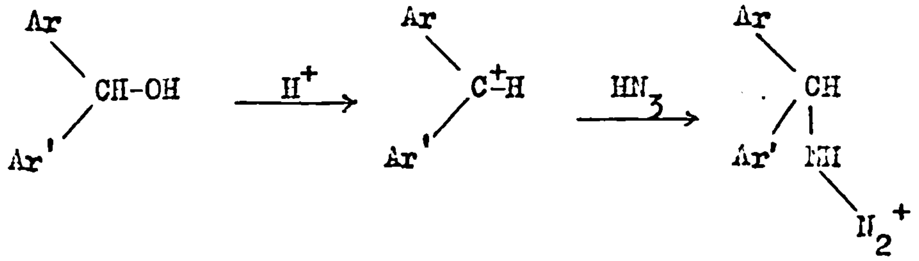


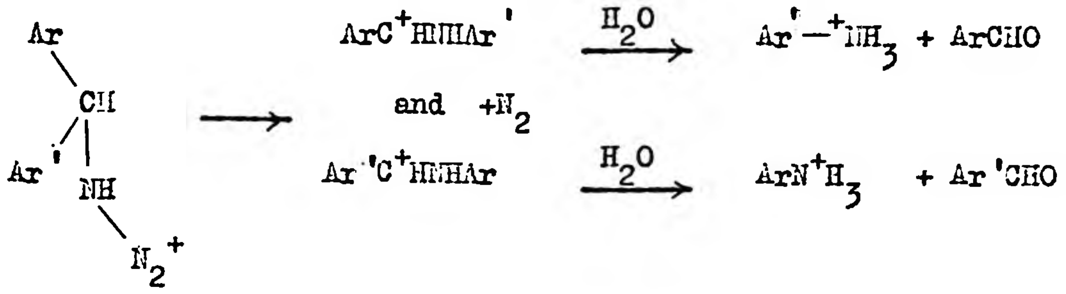
either preformed or present as intermediates in the Schmidt reaction on the appropriate olefin or alcohol.

One reaction studied was the action of hydrazoic acid on 1,1-diarylethylenes in chloroform solvent in the presence of sulphuric acid (19, 20, 21). The products were assumed to arise through the following reaction sequence:



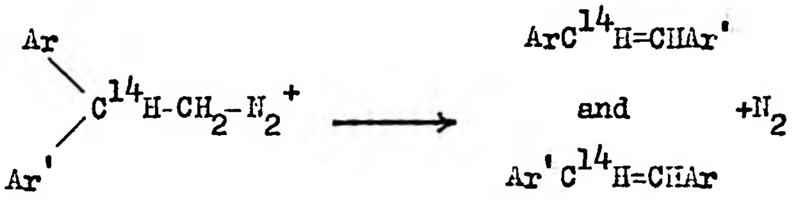
A similar study was carried out by Ege and Sherk (22). These workers, however, preformed the organic azido by reacting an olefin in benzene using trichloroacetic acid as catalyst and then decomposed the purified azido by the action of sulphuric acid. Somewhat later, McEwen and co-workers (23, 24) investigated the Schmidt reaction of substituted benzhydrols giving rise to a benzaldehyde and an anilinium ion:





Most reliable results were obtained when the substituted benzhydryl azides were first prepared as pure compounds and subsequently decomposed by treatment with sulphuric acid.

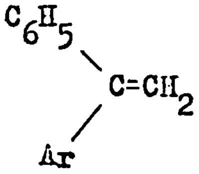
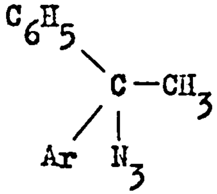
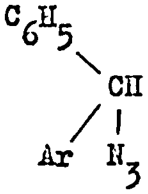
Table IV lists the relative migration aptitudes of a number of aryl groups in the three azide decompositions. It can be seen that, as would be expected, the values obtained are very similar in all three reactions and probably can be considered to be identical within limits of measurement. Of considerable significance is the fact that migration aptitude is much more sensitive to the nucleophilicity of the aryl group in azide decompositions than in the decomposition of β,β-diarylethyldiazonium ion, although both reactions involve departure of molecular nitrogen.



It will be recalled that Burr and Ciereszko (15) found that in the deamination reaction, phenyl and p-tolyl groups migrated at the same rate and the p-anisyl group at only a slightly greater rate (see page24).

TABLE IV

Relative Migratory Aptitudes of Aryl Groups in Acid-Catalyzed Decomposition of Organic Azides

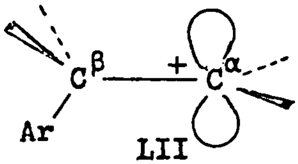
Aryl Group	Schmidt Reaction on  (19, 20, 21)	Rearrangement of  (22)	Rearrangement of  (23)
p-BrC_6H_4-	0.54	0.33	0.58
p-ClC_6H_4-	0.62	0.30	0.67
C_6H_5-	(1.00)	(1.00)	(1.00)
p-$CH_3C_6H_4$-	5.00	4.00	3.44
p-$CH_3OC_6H_4$-	6.12	99*	6.50

*Shown by McEwen (21) to be in error

McEwen (23) originally accounted for this difference in terms of a greater neighbouring group participation of aryl groups in the decomposition of azides. Since nitrogen has a higher ionization potential than carbon it might be expected that the transformation of $-NH-N_2^+ \longrightarrow -N^+H + N_2$ would be energetically more difficult than loss of nitrogen from a diazonium ion $-CH_2-N_2^+ \longrightarrow -C^+H_2$ and therefore would require greater assistance from the migrating aryl group.

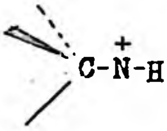
In a later publication, McEwen (24), on the basis of the relationship between the rates of formation of molecular nitrogen and the observed migratory aptitudes in both the decomposition of benzhydryl azides and the Schmidt reaction of 1,1-diarylethylenes, has drawn the conclusion that the departure of nitrogen and the migration of the aryl group are not synchronous processes. If then, these reactions proceed by way of the intermediate $Ar-\overset{|}{\underset{|}{C}}-N^+H$, the question arises as to why, in these reactions, migratory aptitude depends on group nucleophilicity, when in analogous rearrangements, involving a carbonium ion $Ar-\overset{|}{\underset{|}{C}}-C^+H_2$, migratory aptitude is independent of group nucleophilicity. One might, indeed, expect the electron deficient nitrogen species to be an even higher energy intermediate than a carbonium ion and hence exhibit even less selectivity.

It is suggested by the author of this thesis that the explanation to the above question is to be found in the difference in the orbital "configuration" of electron deficient carbon and nitrogen atoms. In a carbonium ion, LII, the vacant p-orbital, and therefore the electron deficiency, will be localized above and below the plane of three sp^2-bonds on the α-carbon. Consequently, that β-carbon aryl group, whose axis parallels the axis of the vacant p-orbital, will undergo migration.



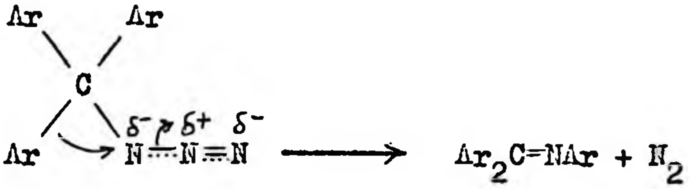
LII

If now the migration is fast relative to the rate of rotation about the C_α - C_β bond, then migratory aptitude will be subject to conformational rather than electronic control. In the electron deficient species formed by departure of nitrogen from azides, however, the remaining nitrogen atom might be expected to use sp-orbitals for its bonds to the carbon and hydrogen atoms:



In this case, there will be no preferred orientation for aryl group migration and the migratory aptitude will be subject solely to electronic control.

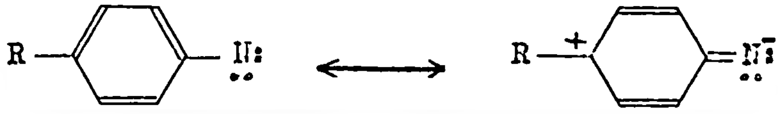
Recently, Saunders (25) has re-examined the <u>thermal</u> decomposition of triarylmethyl azides, which proceeds by way of a rearrangement involving an aryl group migration, and determined the migratory aptitude of several aryl groups. Although in this system, migratory aptitude turned out to be relatively independent of (intrinsic) group nucleophilicity*, the combined evidence, including kinetic studies, led Saunders to favour a mechanism in which aryl group migration is synchronous with departure of nitrogen:



Not entirely excluded by the data, however, was a stepwise process involving the slow loss of nitrogen to form an intermediate azene, which in a subsequent rapid step, undergoes rearrangement:

$$Ar_3CN_3 \xrightarrow{-N_2} Ar_3C\text{-}\ddot{N}: \xrightarrow[\text{migration}]{\text{fast}} Ar_2C{=}NAr$$

The latter interpretation of the mechanism of azide decomposition finds support in a very recent publication of Smith (26), in which the evidence for an aryl azene intermediate is based on a correlation of enthalpies of activation with $\Delta\sigma$ ($= \sigma_p - \sigma_m$) values of the aryl substituents. Such an aryl azene intermediate would apparently derive considerable stability from a conjugative interaction of the electron-deficient nitrogen with a para-substituent, particularly with one which could accommodate a positive charge:



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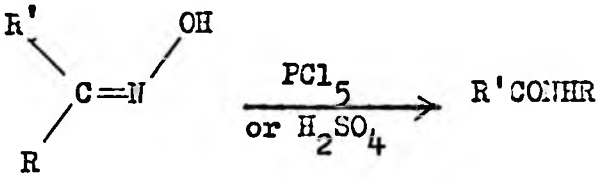
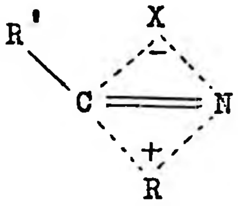
*The p-anisyl group, for example, migrated only 2.5 times more readily than a phenyl group.

In conclusion, it can be seen that not only nitrogen analogs of carbonium ions have been postulated as key intermediates in the Schmidt reaction of various classes of compounds but also the nitrogen analogs of carbenes (azenes) have been recently recognized as possible intermediates in azide decompositions. Further work is required to design diagnostic tools for the distinction between electron-deficient species of nitrogen carrying a formal positive charge and the neutral electron-deficient azenes, which may exist in either the singlet or triplet state.

In contrast to the rearrangements so far considered, in which the ease of migration to an electron deficient center is dependent, at least in part, on group nucleophilicity, stand a number of rearrangements which are under exclusive steric control. The best known of these is the Beckmann rearrangement of oximes, for which extensive studies (27) have established that it is the group <u>trans</u> to the hydroxyl which migrates from carbon to nitrogen.



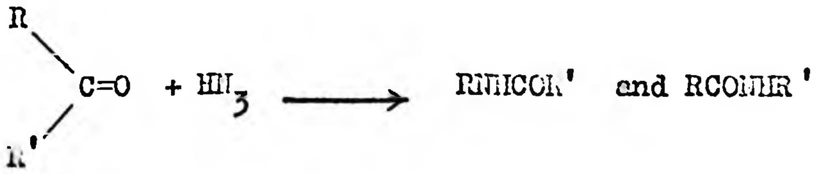
This result has been interpreted in terms of a mechanism in which the migration of R- is synchronous with the departure of X ($-O^{+}H_2$ in concentrated sulphuric acid, -Cl using PCl_5) from nitrogen and involves a transition state of the type LIII



LIII

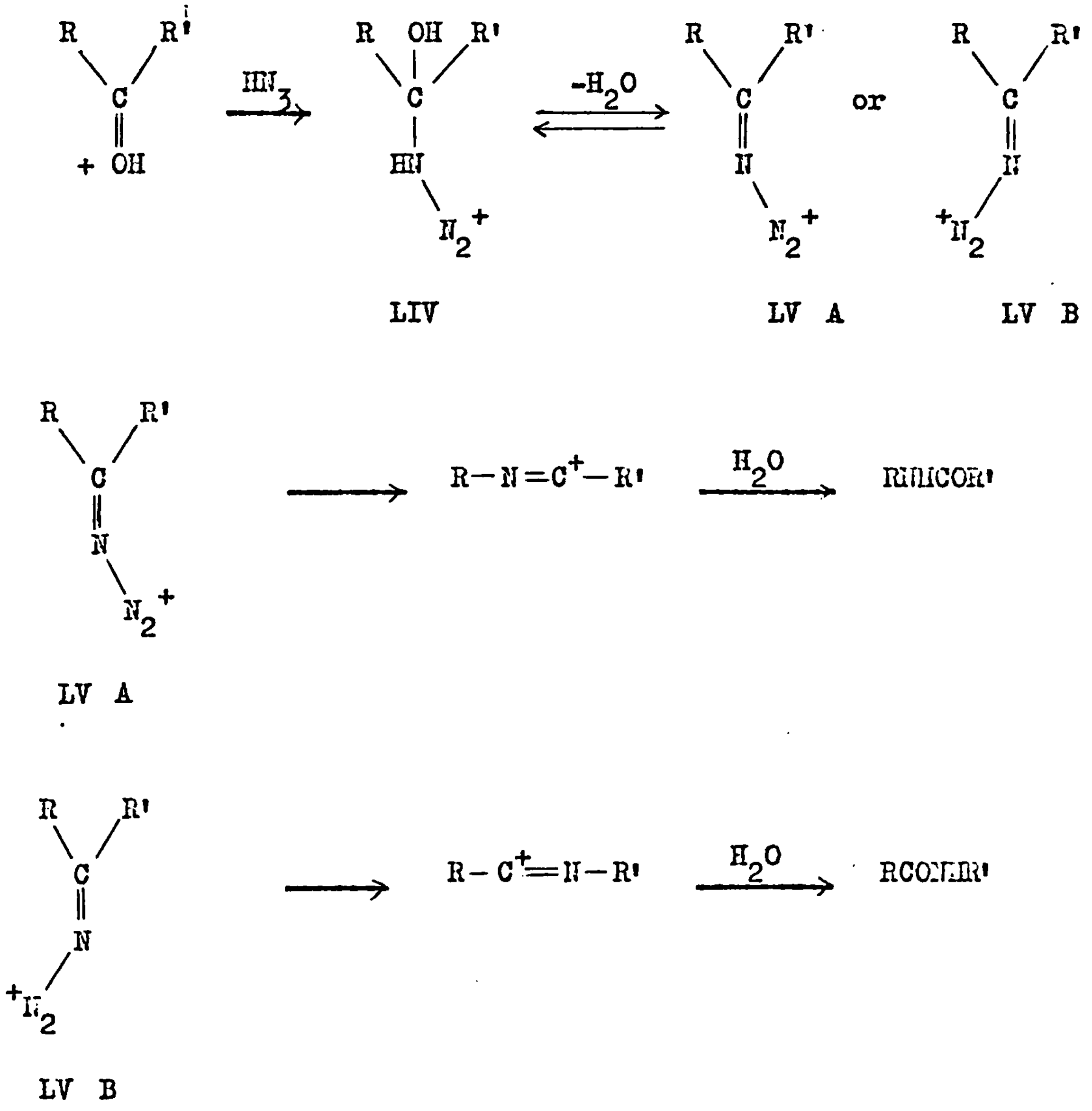
It should be borne in mind, however, that the stereospecificity of this rearrangement does not necessarily exclude a step-wise process since the departure of X^- may be so rapidly followed by R-group migration that the side of the nitrogen atom from which X has departed is still effectively shielded. That there is, indeed, participation of the migrating group in the rate determining step has recently been effectively demonstrated by Yukawa and Kawakani (28) who have observed a reverse carbon-14 kinetic isotope effect, k^{14}/k^{12}, of 1.052 and 1.121 in the Beckmann rearrangement of methylene-labelled phenylacetoxime and phenyl-1-C^{14} labelled acetophenoxime, respectively.

A rearrangement, closely resembling the Beckmann rearrangement, is the Schmidt reaction of hydrazoic acid with ketones. Depending upon the reaction conditions, a number of reaction products may be obtained in varying yields, although in the presence of only one mole of hydrazoic acid the principal product is an amide. If the ketone is symmetrical, a single amide is obtained; if it is unsymmetrical, the product may be a mixture of two isomeric amides formed by the migration of each of the two groups attached to the carbonyl carbon.



$$RR'C{=}O + HN_3 \longrightarrow RNHCOR' \text{ and } RCONHR'$$

Extensive studies have been made of this reaction, principally by P. A. S. Smith (29), who in 1948 proposed the following mechanism:



The most convincing evidence in support of this mechanism has been provided by migratory aptitude studies. It can be seen that if the decomposition of the isomeric iminodiazonium ions, LV A and LV B, is rapid relative to their hydration to LIV, then the composition of the product will depend upon the relative populations of the two intermediates LV A and LV B, and will be quite independent of the electronic nature (nucleophilicity) of the migrating groups. A comparison of migratory aptitudes in the Schmidt and Beckmann rearrangements for a series of substituted benzophenones is shown in Table V. The values of migratory aptitude for various aryl groups are based on the ratio of the two amides formed, and on the assumption that the two isomeric oximes constituting the oximation product are subjected to a *strictly stereospecific trans* migration step.

TABLE V

Migratory Aptitudes of Aryl Groups in the Schmidt Reaction and Beckmann Rearrangement of Substituted Benzophenones of the Type $RC_6H_4COC_6H_4R'$

para-Substituents		Beckmann Rearrangement			Schmidt Reaction		
R	R'	$R-C_6H_4-$ migration	$R'-C_6H_4-$ migration		$R-C_6H_4-$ migration	$R'-C_6H_4-$ migration	
Cl-	H-	0.56	0.44	(30)	0.59	0.41	(32)
NO_2-	H-	0.50	0.50	(31)	0.51	0.49	(32)
CH_3-	H-	0.52	0.48	(30)	0.54	0.46	(32)
CH_3O-	H-	0.49	0.51	(30)	0.61	0.39	(32)
C_6H_5-	H-	0.51	0.49	(30)	0.52	0.48	(32)
NO_2-	CH_3O-				0.51	0.49	(33)
Cl-	CH_3O-				0.47	0.53	(33)

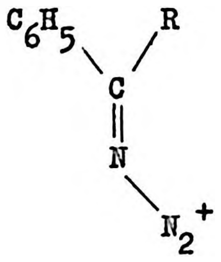
Since the presence of a *para*-substituent would be expected to have little effect on the relative stability of the isomeric benzophenone oximes, it is not at all surprising that, regardless of the nature of the substituents, the migratory aptitudes of the two aryl groups RC_6H_4- and $R'C_6H_4$- in the Beckmann rearrangement are nearly equal. The fact that essentially the same results were obtained in the Schmidt reaction was considered to be strong supporting evidence that in this reaction also the composition of the products is determined by the relative populations of geometrical isomers LV A and LV B, rather than by electronic factors. Further support for this interpretation can be found in the observation of Smith that migratory tendencies in the Schmidt reaction of ketones of the type C_6H_5-COR are determined largely by the size of the R-group (Table VI).

TABLE VI

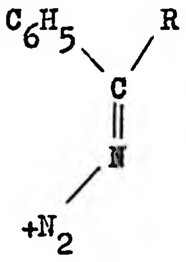
Migratory Aptitudes of Phenyl and Alkyl Groups in the Schmidt Reaction of C_6H_5COR

R	C_6H_5-migration	R-migration
CH_3-	0.95	0.05
CH_3CH_2-	0.85	0.15
$(CH_3)_2CH$-	0.51	0.49
$(CH_3)_3C$-	0.0	1.0

Inspection of the above Table discloses that quite consistently it is the group of greatest bulk which undergoes preferential migration. This is readily understood in terms of a trans rearrangement of the isomeric iminodiazonium ions LVI A and LVI B, since the more stable and hence more populous isomer would be that which places the bulkier group on carbon anti with respect to the diazonium group on nitrogen.



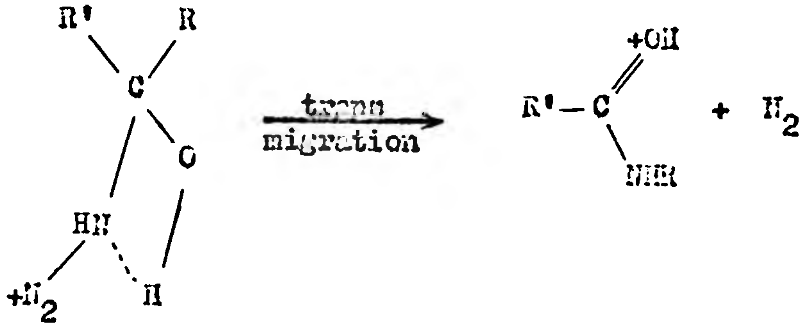
LVI A



LVI B

When R- is smaller than C_6H_5-, isomer LVI A is preferentially formed and phenyl migration predominates; when R- is bulkier than a phenyl group, isomer LVI B is favoured and preferential migration of R- is observed.

Following this investigation of Smith, a number of apparent exceptions to the rule of "greater bulk" have been reported (34, 35, 36). An attempt has been made by Arcus, Coombs and Evans (37, 38) to resolve these anomalies by postulating a mechanism in which dehydration of the azidohydrin LIV to the iminodiazonium ion LV is not involved. Instead, the azidohydrin was assumed to exist in the form of a four-membered chelate ring which directly undergoes rearrangement to give the conjugate acid of the amide.



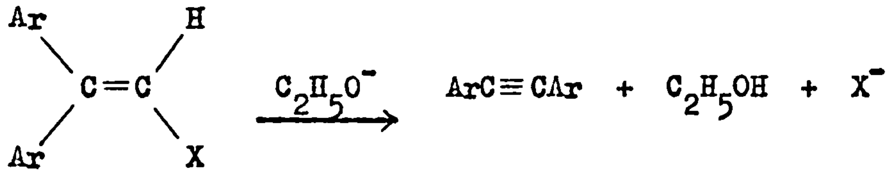
Smith and Antoniades (39) in a recent publication have argued quite convincingly that the exceptions to the rule of "greater bulk", which have been reported so far, can be readily interpreted in terms of conformational effects in the iminodiazonium ion LV and that, rather than casting doubt on the dehydration step in Smith's mechanism; these anomalous results provide additional support for it. These authors also point up strong objections against the mechanism proposed by Arcus and co-workers and also against the evidence which led Arcus to reject Smith's mechanism.

It is the view of the author of this thesis that the dehydration-rearrangement mechanism finds strong support in the available experimental evidence and that the interpretation of the migratory aptitude data in terms of relative populations of the two geometrical isomers, LV A and LV B, of the iminodiazonium ion is a most reasonable one.

The stereochemical course of the reaction involving a strict trans migration does not, of course, require a completely concerted process. Ropp and co-workers (40) have, however, observed a small intra and intermolecular carbon-14 isotope effect in the Schmidt reaction of acetone-methyl-C^{14}, which is indicative of a participation of the migrating group in the heterolysis step.

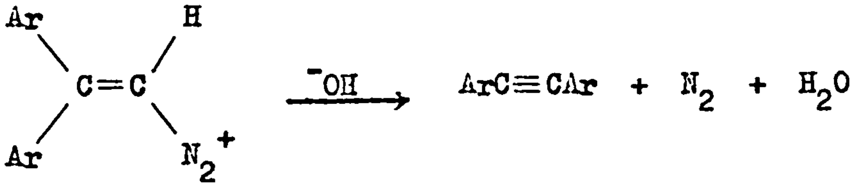
Rearrangements Involving Aryl Group Migration to a Vinylic Carbon

Many years ago, it was demonstrated by Fritsch (41), Buttenberg (42) and Weichel (43) that the treatment of 1,1-diaryl-2-haloethylenes with sodium ethoxide at 180 - 200°C results in the elimination of HX and a rearrangement giving substituted tolanes.



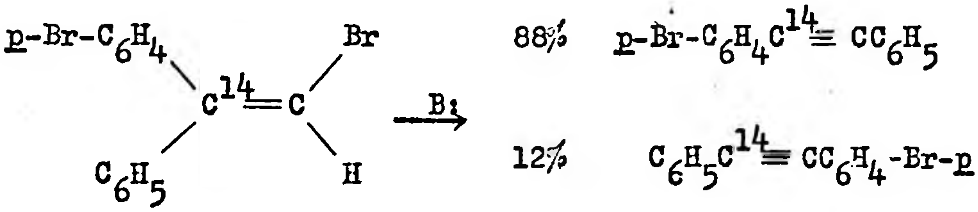
Later, Coleman (44, 45) found that very much improved yields of tolanes are formed when the haloethylenes are reacted with potassium amide in liquid ammonia.

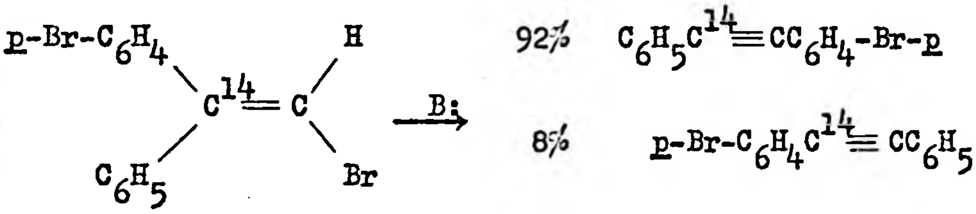
It should be noted that this α-elimination reaction is strictly analogous to the reaction whose mechanism is under study in the present investigation, namely, the decomposition of the 1,1-diarylethylene diazonium ion IV.



IV VII

Two investigations have been made of the stereochemistry of the conversion of 1,1-diaryl-2-haloethylenes to tolanes. One, reported in 1955 by Bothner-By (46, 47), involved the study of the reaction of cis- and trans-1-p-bromophenyl-1-phenyl-2-bromoethylene-1-C^{14} with t-butoxide in t-butyl alcohol giving 4-bromotolanes. The results of this study are summarized in the following equations:

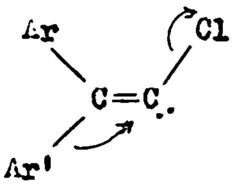




Evidently, the above rearrangement proceeds predominantly through a migration of that aryl group which is trans to the leaving halogen atom.

Bothner-By considered that the stereospecificity of the reaction excludes a mechanism involving a carbene intermediate, $Ar_2C=C:$. Whether this conclusion is justified or not, however, depends on the electronic structure of the electron deficient carbon in this species. If the carbene carbon maintains sp^2-character for its singlet state, the stereospecificity could still be accommodated, since with one sp^2-hybrid orbital occupied and the other vacant, there still would remain electronic asymmetry. On the other hand, if the carbene carbon is making use of the sp-hybrid orbitals, two electrons would be used in forming the carbon-carbon σ- and π- bonds, while the unshared pair of electrons would occupy a lobe whose axis would coincide with the axis of the carbon-carbon bond. With this electron distribution no preferred stereochemistry would be possible. Cristol (48) has suggested that the latter hybridization would be favoured since the shortening of the σ-bond resulting from the sp^2-sp rather than sp^2-sp^2 overlap would lead to more stable σ- and π-bonds. This is in agreement with the order of bond strengths, calculated by Walsh (49) for the three types of hybrid orbitals in a carbon atom.

To account for the stereochemical course of the rearrangement, Bothner-By proposed a mechanism for the reaction involving an anion LVII, which possesses a high degree of configurational stability and which is transformed to products by an aryl migration, synchronous with the departure of the halide ion.

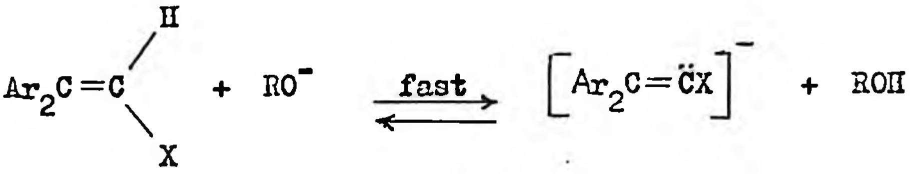


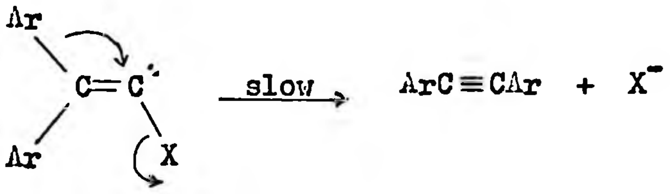
LVII

That a considerable barrier to the interconversion of isomeric vinyl carbanions does indeed exist has been convincingly demonstrated by Miller (50) and Bothner-By (46).

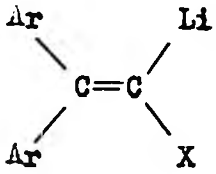
Strong evidence for the vinyl carbanion intermediate has recently been provided by Bothner-By (51) through a careful kinetic study of the reaction of 1-chloro-, 1-bromo- and 1-iodo-2,2-diphenylethylenes with tert-butoxide ion in tert-butyl alcohol. Both the dehydrohalogenation reaction and deuterium exchange with solvent are first order in substrate and three-halves order in base. The exchange is at least one hundred times faster than the elimination, a result which suggests that the carbanion is formed in a pre-equilibrium process. This interpretation finds support in the observation that the solvent isotope effect for the elimination process is $k^D/k^H = 1.9 \pm 0.3$. That rupture of the carbon-halogen bond is involved in the rate determining step is evident from the considerable difference in the reaction rates for the three halogen compounds (51, 52).

The mechanism of the reaction of alkoxides with 1,1-diphenyl-2-haloethylenes, consistent with all observed facts, can be formulated through the following equations:





Recently, Curtin and co-workers (53, 54) have studied the stereochemical courses of the rearrangement of 1-phenyl-1-*p*-chlorophenyl-2-ethylenes-1-C^{14} by butyl lithium in dibutyl ether at -35°C. With this reagent also, the reaction was stereospecifically *trans*. Curtin (55, 56) has suggested that in the presence of butyl lithium the rearrangement may proceed through an organolithium intermediate LVIII, although all efforts to intercept such a species failed. It



LVIII

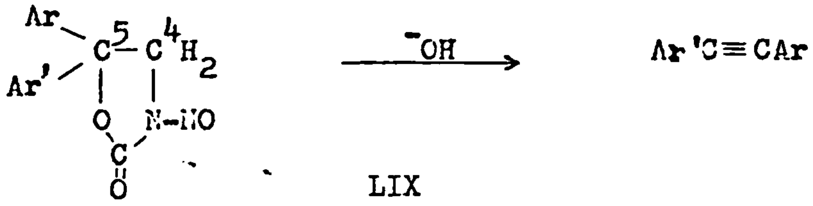
must be concluded, therefore, that if intermediate LVIII is actually formed, its rate of rearrangement is rapid relative to its rate of formation. There seems to be, however, no doubt that such a species as LVIII would have the conformational stability required to ensure the stereospecificity of the rearrangement process (57).

That the rate determining step of the reaction consists of the abstraction of the α-hydrogen has been demonstrated by Curtin by means of crude isotopic measurement.

Very recently, Cristol and Bly (48) have studied the kinetics of the α-elimination reaction of 1,1-diphenyl-2-chloroethylenes with phenyl lithium in n-butyl ether and have demonstrated it to be of first order in both the halocompound and base. Although Cristol did not exclude the possibility of a mechanism involving a carbanion intermediate or an organolithium adduct, he suggested that the α-elimination in the presence of organolithium compound may involve the concerted removal of the α-proton and migration of aryl group. This possibility is currently being investigated in the University of Colorado laboratories.

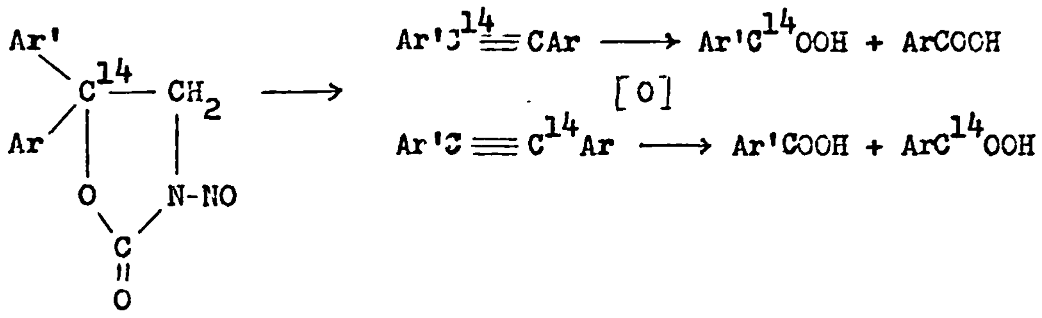
RESULTS AND DISCUSSION

The decomposition of 5,5-diphenyl-N-nitroso-2-oxazolidone has been reported by Newman (1) to give a quantitative yield of tolane. Although no cases have been previously investigated in which carbon-5 is substituted by an aryl group other than phenyl, one would expect that compounds of the type LIX would form substituted tolanes in high yield.

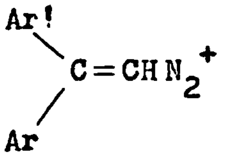


LIX

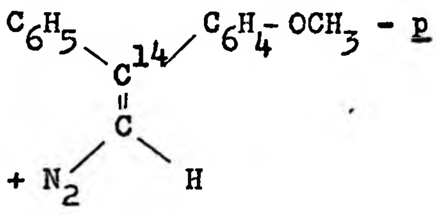
In such cases, the same product results, irrespective of which aryl group migrates from C-5 to C-4, unless these two carbon atoms are distinguished isotopically. When this is done, two isotopic tolanes result, the relative amount of which can be determined by oxidation of the tolane product to two different aryl carboxylic acids; the two acids then can be separated and analyzed for isotopic content.



Since the objective of the investigation has been to determine whether the migratory tendency of aryl groups is subject to steric or electronic control, and hence whether the migration is concerted with or subsequent to loss of nitrogen from the intermediate



it was necessary to choose a system, in which the two aryl groups differ markedly in their electronic character, but not in their steric requirements. The initial choice was phenyl and p-anisyl, since the migratory ratio of these two groups is one of the largest reported in reactions involving aryl migration to an electron deficient centre. Furthermore, since the two groups differ only in a para-substituent, the population of the stereoisomeric intermediates



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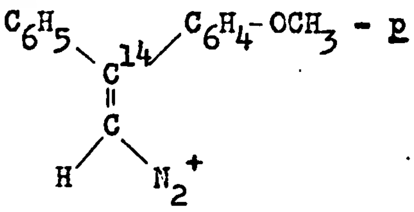


should not be significantly different and thus a *trans* rearrangement should give a tolane product with the label equally distributed between the two acetylenic carbons. On the other hand, if the reaction involves either a carbonium ion, $Ar_2C=\overset{+}{C}H$, or a carbene $Ar_2C=C:$, the *p*-anisyl group would be expected to exhibit a much higher migratory tendency than the phenyl group.

Unfortunately, synthesis of the desired 5-phenyl-5-*p*-anisyl-2-oxazolidone failed for reasons presumably related to the electron releasing character of the *p*-methoxy group. (See Experimental Methods for discussion of this point). It was decided, therefore, to have as the para-substituted aryl group one, whose nucleophilicity is less than that of the phenyl group.

The group *p*-trifluoromethylphenyl was finally chosen on the basis of the following considerations:

1. The Hammett σ- value for *p* - CF_3 shows it to be strongly electron withdrawing, about midway between the *p* - Cl and *p* - NO_2.
2. The group is relatively inert and can be expected to remain intact under the reaction conditions required for synthesis

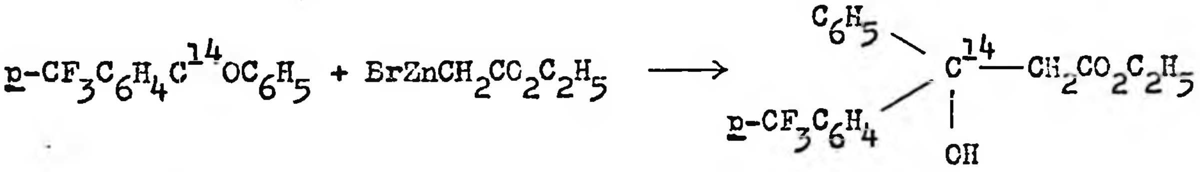
of the N-nitroso-2-oxazolidone and degradation of the tolane.

3. The synthesis of 5-phenyl-5-p-trifluoromethylphenyl-2-oxazolidone labelled with carbon-14 in the position 5 appeared to be reasonably straightforward.
4. The product, p-trifluoromethyltolane is a known compound and its degradation to p-trifluoromethylbenzoic and benzoic acids has been previously accomplished in this laboratory.

The synthetic sequence used for the preparation of 5-phenyl-5-p-trifluoromethylphenyl-N-nitroso-2-oxazolidone-5-C^{14}, IX, was as follows.

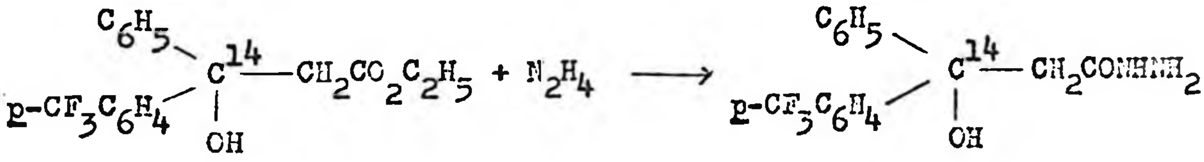
$$C_6H_5C^{14}N + BrMgC_6H_4CF_3\text{-}p \longrightarrow p\text{-}CF_3C_6H_4C^{14}OC_6H_5$$

LX LXI



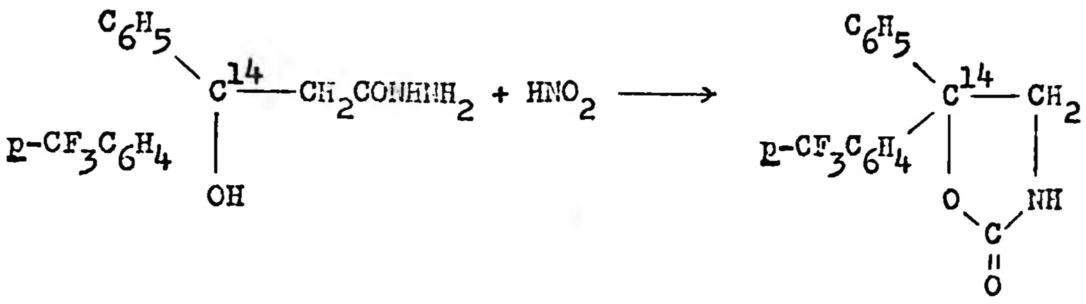
$$p\text{-}CF_3C_6H_4C^{14}OC_6H_5 + BrZnCH_2CO_2C_2H_5 \longrightarrow (C_6H_5)(p\text{-}CF_3C_6H_4)C^{14}(OH)\text{—}CH_2CO_2C_2H_5$$

LXI LXII

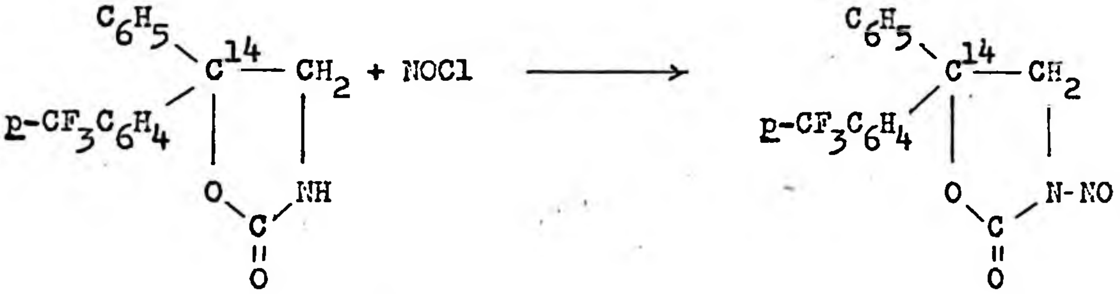


$$(C_6H_5)(p\text{-}CF_3C_6H_4)C^{14}(OH)\text{—}CH_2CO_2C_2H_5 + N_2H_4 \longrightarrow (C_6H_5)(p\text{-}CF_3C_6H_4)C^{14}(OH)\text{—}CH_2CONHNH_2$$

LXII LXIII



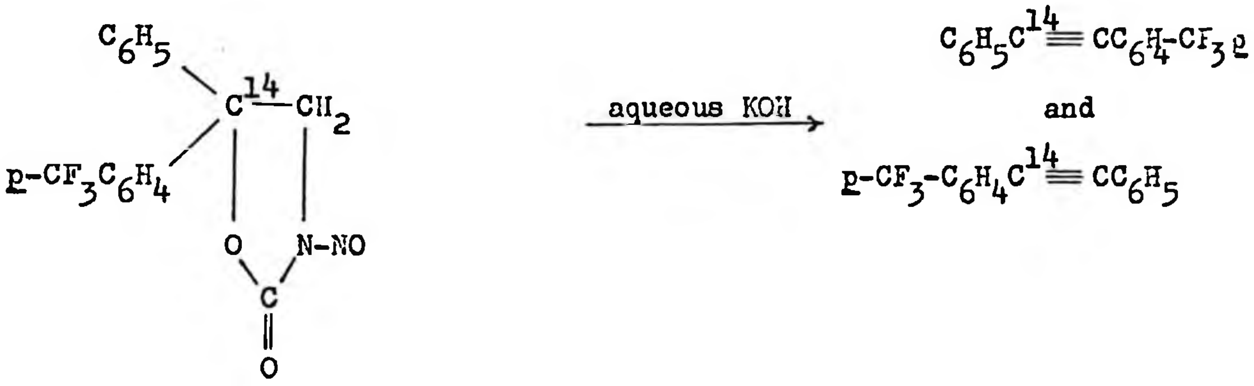
LXIII LXIV



LXIV IX

Benzonitrile-C^{14}, IX, was prepared from benzoic acid-carboxyl-C^{14} and treated with p-trifluoromethylphenyl magnesium bromide to give the p-trifluoromethylbenzophenone-carbonyl-C^{14}, LXI. A Reformatsky reaction on the latter with ethyl bromoacetate gave the ethyl β-hydroxy-β-phenyl-β-p-trifluoromethylphenylpropionate --β-C^{14}, LXII, which on treatment with hydrazine was converted into the corresponding hydrazide, LXIII. This hydrazide was nitrosated under conditions described by Newman (1) to give the 2-oxazolidone, LXIV, in good yield. The latter, on treatment with nitrosyl chloride, was converted into 5-phenyl-5-p-trifluoromethylphenyl-N-nitroso-2-oxazolidone-5-C^{14}, IX, an oil, which resisted all efforts to achieve crystallization.

Treatment of the N-nitroso compound with aqueous alkali gave p-trifluoromethyltolane-C^{14}, X and XI, in essentially quantitative yield:



X

X

IX

The isotopic composition of the tolane product was determined by its oxidation to benzoic and p-trifluoromethylbenzoic acids, which were separated, purified and analyzed for their radioactivity. The oxidation of p-trifluoromethyltolane was satisfactorily achieved by means of chromic anhydride in acetic acid and the less soluble acid, p-trifluoromethylbenzoic acid, was readily isolated when the reaction mixture was diluted with water. This acid was readily purified by recrystallization. The purification of the more soluble benzoic acid by conventional methods failed to remove the last traces of p-trifluoromethylbenzoic acid. Finally, a procedure involving vapour-phase chromatography of the methyl ester followed by saponification gave a product of required purity.

The results of the isotopic analyses of the parent 2-oxazolidone, of p-trifluoromethyltolane and of the two carboxylic acids are recorded in Table VII. (No analysis was made of the N-nitroso compound, which is the direct precursor of the tolane, since it could be obtained only as an oil and therefore was of unknown purity.)

It can be seen that there has been no loss of activity in converting the oxazolidone to the tolane and that the sum of the activities of the two acids is the same within the experimental error of the measurement (± 1%) as the activity of the tolane from which the acids were formed.

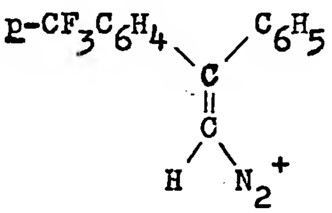
TABLE VII

Specific Activities of 5-Phenyl-5-p-trifluoromethylphenyl-2-oxazolidone and its Products

Compound	Specific Activity in mc/mole	Activity Percent of Total
5-phenyl-5-p-trifluoromethylphenyl-2-oxazolidone-5-C^{14}	4.78	100
p-trifluoromethyltolane-C^{14}	4.79	100
p-trifluoromethylbenzoic acid-carboxyl-C^{14}	3.14	65.5
benzoic acid-carboxyl-C^{14}	1.63	33.9

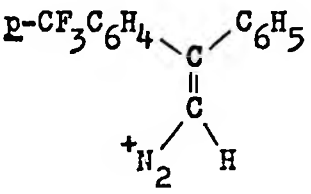
The results show that 65.5 percent of the product resulted from migration of the phenyl group from the labelled C-5 ring member to the unlabelled C-4 position, while 33.9 percent was formed by p-trifluoromethylphenyl migration. In other words, the ratio of *p*-trifluoromethylphenyl/phenyl migration is almost exactly 0.5.

This migratory aptitude for the *p*-trifluoromethylphenyl group can be interpreted in various ways. Firstly, one could assume that the aryl migration is stereospecific. Such an assumption would, however, require the formation of two isomeric vinyldiazonium ions, LXV A and LXV B, in a ratio of 1 : 2.



LXV A

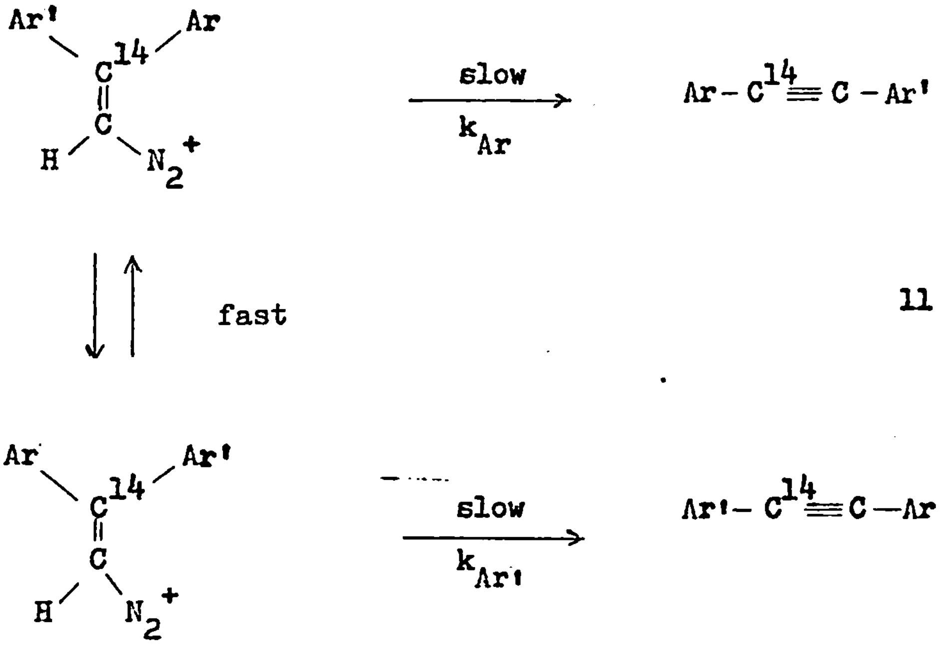
and



LXV B

Since the migratory aptitude of aryl groups in the Beckmann Rearrangement and Schmidt reaction of *para*-substituted benzophenones is nearly equal (1:1), the respective populations of oxime-and iminodiazonium ion-isomers formed as intermediates in these reactions must also be equal. In view of this, it seems most unlikely that the two vinyldiazonium ions LXV A and LXV B above would be formed in a ratio very different from unity, and certainly not in the ratio of 1 : 2.

Secondly, while rejecting the assumption of unequal populations of the two isomers LXV A and LXV B, the observed migratory aptitude of 1 : 2 could still be accounted for by a *stereospecific*, slow migration step, preceeded by a rapid interconversion (dynamic equilibrium) of the two vinyldiazonium ions.

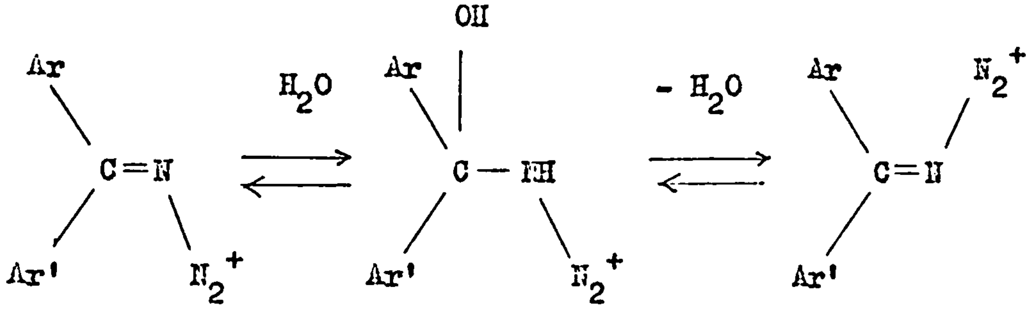


LXVI A

LXVI B

11

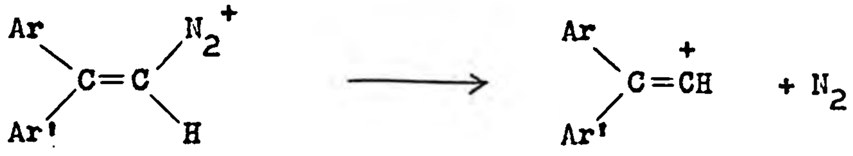
In this case, migration aptitude would still be determined by group nucleophilicity as k_{Ar} would be larger for the more nucleophilic group. An interpretation analogous to this was given by Smith and Antoniades (39) to account for the p-anisyl/phenyl migration ratio of 2.1 : 1 in the Schmidt reaction of p-methoxybenzophenone, and by Westland (58) to explain the discrepancy between migratory aptitudes observed in the Schmidt reaction and Beckmann rearrangement of benzoylphenanthrenes. In the Schmidt reaction, however, the hydration of the iminodiazonium ion intermediate might be expected to occur rather readily in the strongly acidic reaction medium, thus establishing something approaching an equilibrium population of two isomeric iminodiazonium ions:



The decomposition of N-nitroso-2-oxazolidones, on the other hand, is carried out in a strongly basic medium, which certainly would not be expected to bring about an interconversion of LXVI A to LXVI B by way of ethylenic carbon-carbon bond hydration. This interpretation of the migratory aptitude result, must also be rejected.

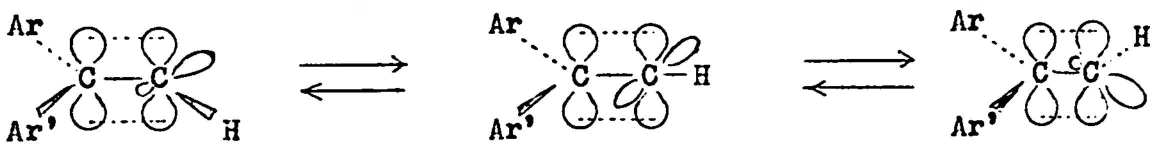
Since the stereospecificity of aryl group migration, as shown in equation 11, in untenable, it must be concluded that rearrangement occurs after departure of nitrogen and that the ratio of 2 : 1 observed for the phenyl and p-trifluoromethylphenyl groups is a measure of their relative intrinsic migratory aptitudes.

If, then, the reaction proceeds through a vinylic carbonium ion V, as suggested by Newman (1),



LXVI V

the question arises as to the geometry and electronic configuration of such a species. Assuming sp^2- hybridization at the electron deficient carbon atom, the vinyl carbonium V would exist in two isomeric forms V A and V B.

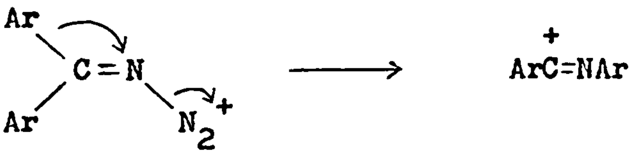


V A V C V B

Species of this geometry, provided that they possess configurational stability, would show stereospecific <u>trans</u> migration of the aryl groups. The energy barrier for interconversion of V A and V B, however, would be expected to be extremely low, since formation of a transition state V C would only involve a change in the hybridization of the electron deficient carbon from sp^2 to sp. Therefore, should species of geometry of V A and V B be intermediates in the reaction, it is highly probable that equilibrium between them would be achieved prior to the migration step.

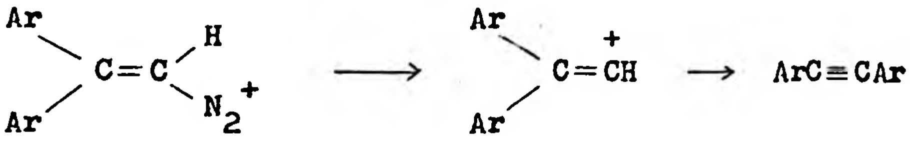
Indeed, calculations by Walsh (49) have shown that bonds formed from sp-hybrid orbitals of carbon are stronger than those formed from sp^2 orbitals. It is likely therefore, that the linear structure V C, would possess a <u>lower</u> energy than structures V A and V B, and instead of V C being a transition state, it would be the state of lowest electronic energy for the species. Obviously, the geometry of V C provides no preferential direction for migration of the aryl groups, with the result that intrinsic nucleophilicity of the migrating group would be the sole controlling factor in the rearrangement.

There is, however, an important difficulty associated with the interpretation of the reaction in terms of a vinyl carbonium ion. If, in the Schmidt reaction, departure of nitrogen from the iminodiazonium ion LXVII requires aryl group participation,



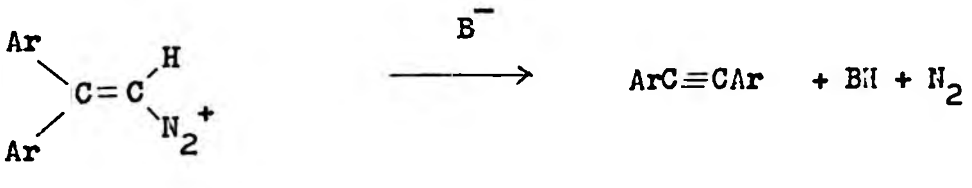
LXV1

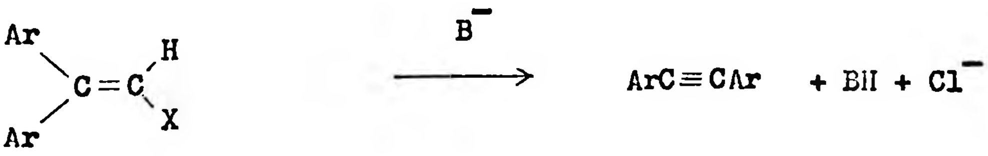
why is no such assistance apparently required in the decomposition of the vinyldiazonium ion LXVI?



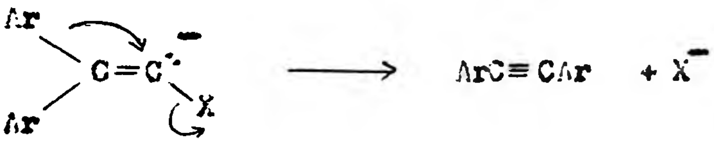
LXVI V

One might invoke the explanation at one time proposed by McEwen (23) to account for the larger migration aptitudes found in the decomposition of protonated benzhydryl azides, $Ar_2CH\text{-}NH\text{-}N_2^+$, compared to those found for triarylethyldiazonium ions, $Ar_3C - CH_2N_2^+$; namely, that because of the smaller ionization potential of a carbon atom it is easier for a positive charge to be accomodated on this atom, to form $=\overset{+}{C}-$, than on nitrogen to form $=\overset{+}{N}$. There would appear, however, to be a more important distinction between the decomposition of the iminodiazonium ion LXVII, formed in the Schmidt reaction, and the vinyldiazonium ion LXVI proposed as the intermediate in the reaction of N-nitroso-2-oxazolidones. In the latter, the atom from which N_2 departs also carries a hydrogen atom and, furthermore, the reaction conditions are strongly basic. Indeed, the vinyldiazonium ion decomposition finds a closer analogy to the conversion of 1,1-diaryl-2-haloethylenes to tolanes in the presence of strong base.



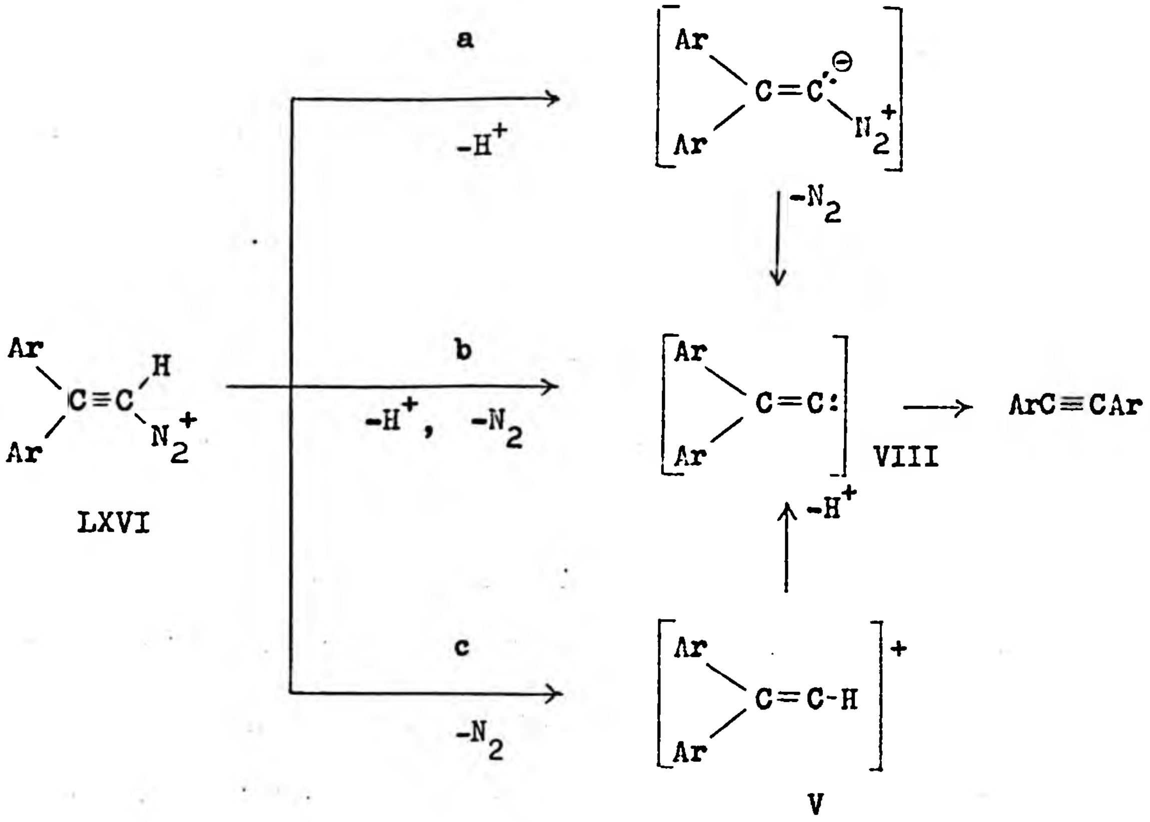


It has now been quite well established that the latter reaction proceeds through a carbanion intermediate which undergoes a stereospecific *trans* migration of an aryl group (see page 44.



Here again aryl group participation is required, presumably because halogen is a relatively poor leaving species. In contrast, the high heat of formation of molecular nitrogen makes $-N_2^+$ a very powerful leaving group, and one might therefore expect that aryl group participation would not be required in the decomposition either of the vinyldiazonium ion itself or of a zwitter-ion species, $Ar_2C=\bar{C}-\overset{+}{N}_2$, formed from it by proton abstraction.

On the basis of the foregoing, it would seem that combination of the basic reaction conditions and the ease of departure of nitrogen might result in the vinyldiazonium ion undergoing *loss of both a proton and of nitrogen before aryl group migration*. The following decomposition pathways are in accord with this proposal:



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In pathway (12a) proton abstraction preceeds departure of nitrogen, in pathway (12c) it follows it and, finally, in pathway (12b) the proton and nitrogen are lost synchronously. In any case, the direct precursor of the tolane is a carbene VIII. If, as seems likely, the carbene carbon has an electron distribution corresponding to sp-hybridization, (see page 59) aryl group migration will be exclusively under electronic control and the migratory tendencies of the two aryl groups will depend on their relative nucleophilicities.

At this stage in our discussion, information on migratory aptitudes of aryl groups in other rearrangements proceeding through carbene intermediates would be extremely enlightening. Unfortunately, no such studies have yet been reported. To add to the difficulty, the migratory tendency of the p-trifluoromethylphenyl group, even in carbonium ion reactions, has not been studied quantitatively.

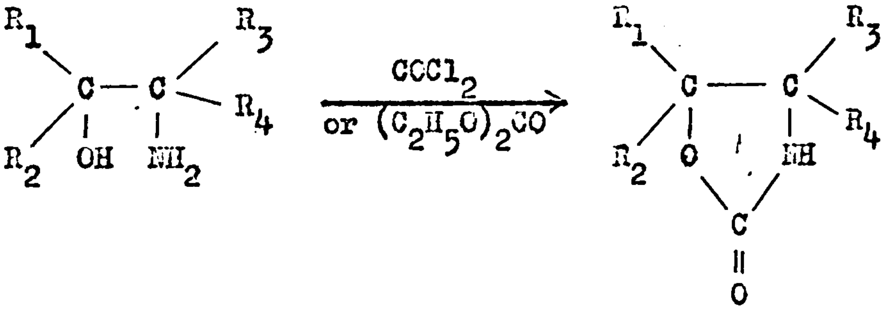
It is possible to make a rough estimate of the migratory aptitude of the p-trifluoromethylphenyl group in a carbonium ion reaction from a knowledge of the Hammett σ- constants for the p-CF_3-, p-NO_2- and p-Cl- groups and the migratory aptitudes of the p-nitrophenyl and p-chlorophenyl groups found in the pinacol rearrangement. This leads to a p-trifluoromethylphenyl/phenyl migration ratio of 0.35. For a reaction involving a high energy, electrically-neutral carbene intermediate, a lesser selectivity between the two different aryl groups would certainly be expected, and the observed value of 0.5 seems a reasonable one.

In summary, the migratory aptitude studies exclude aryl group participation in the conversion of a diarylvinyldiazonium ion to a tolane and suggest rearrangement of either a carbonium ion or carbene intermediate. Of the two, the latter seems the more probable.

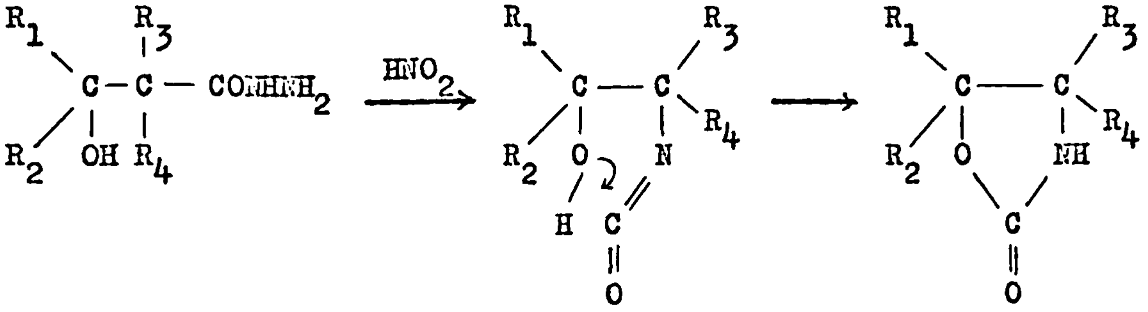
EXPERIMENTAL METHODS

Introduction

N-Nitroso-2-oxazolidones can be prepared by the action of such nitrosating agents as aqueous nitrous acid or nitrosyl chloride on the appropriate 2-oxazolidones. Of the several methods which have been reported for the preparation of this latter class of heterocyclic compounds, Newman (1) found two particularly suited for the synthesis 2-oxazolidones substituted by alkyl or aryl groups on the C - 4 and C - 5 ring members. One of these syntheses involves the cyclization of α-aminoalcohols with phosgene or diethyl carbonate

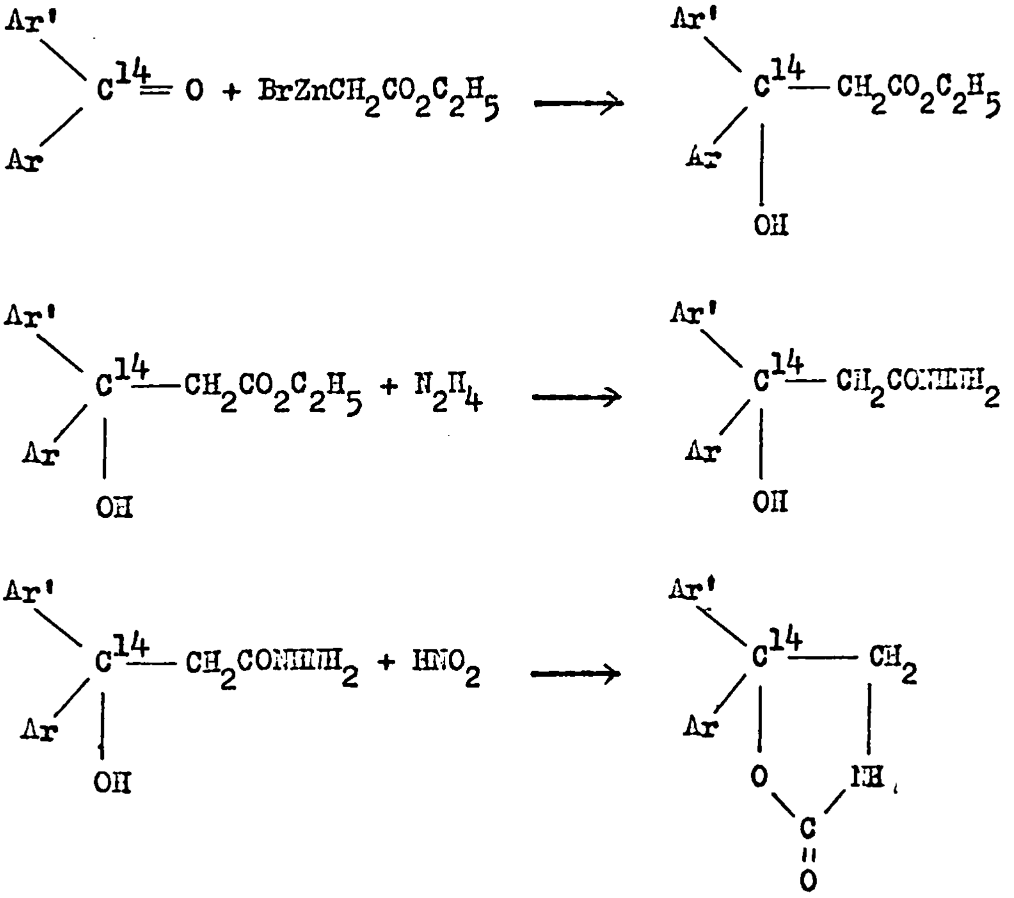


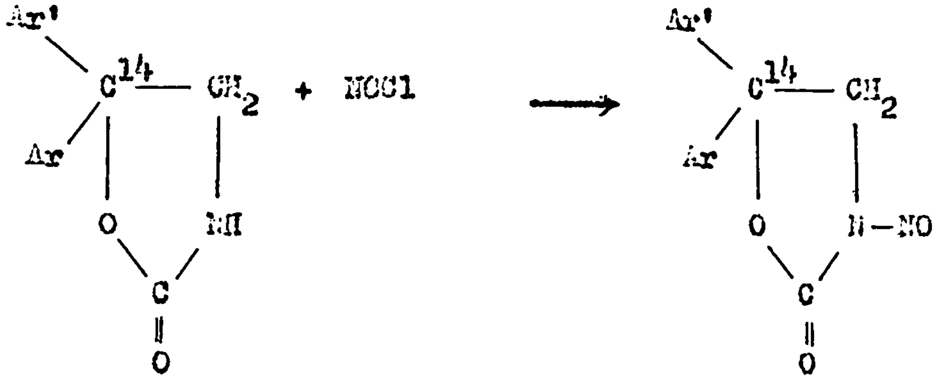
The other, which Newman favored particularly for the preparation of 5-mono- and di-substituted 2-oxazolidones, is based on Curtin's rearrangement of a β-hydroxyhydrazide, which gives instead of the usual isocyanate or primary amine a ring-closed product - the 2-oxazolidone (1):



This method of synthesis was adopted in the present work since Newman had reported that the ring closure of β-hydroxy-β,β-diphenylpropionhydrazide to 5,5-diphenyl-2-oxazolidone proceeds in excellent yield.

The reaction sequence used for the synthesis of 5,5-diaryl-N-nitroso-2-oxazolidone-5-C^{14} was as follows:





Since a 5,5-diaryl-N-nitroso-2-oxazolidone was required in which the two aryl groups would have the largest possible difference in nucleophilicity, it was decided to leave one of the C-5 aryl groups unsubstituted and to modify the other by a suitable para substituent. The para-methoxy group was the first choice, primarily because of an exceptionally high migratory aptitude of the p-anisyl group in other rearrangements and also because of the ease of preparation of p-methoxybenzophenone-carbonyl-C^{14} (59). This synthesis, involving the p-anisyl group, proceeded satisfactorily up to the β-hydroxyhydrazide stage. This hydrazide, however, failed to give the 2-oxazolidone on treatment with nitrous acid under a variety of conditions, but instead formed an amorphous material from which no crystalline compound could be obtained. This failure to obtain the cyclized product was tentatively attributed to dehydration of the β-hydroxyhydrazide, promoted by the electron-releasing p-methoxy group. An unsaturated isocyanate, $Ar_2C=CH-N=C=O$, if formed might be expected to undergo polymerization in the acidic medium, used for the cyclization reaction.

On the assumption that the difficulty encountered with the p-anisyl compound could be attributed to the electron-releasing p-methoxy group, it was then decided to attempt a synthesis of a 2-oxazolidone in which one of the C - 5 aryl groups was phenyl, while the other carried an electron-withdrawing substituent. For reasons which have been outlined earlier, the substituent chosen was p-trifluoromethyl.

This synthesis, starting from p-trifluoromethylbenzophenone, proceeded satisfactorily and the treatment of the corresponding β-hydroxyhydrazide with nitrous acid yielded crystalline 5-phenyl-5-p-trifluoromethylphenyl-2-oxazolidone in good yield. Although nitrosation of the 2-oxazolidone with nitrosyl chloride failed to give a crystalline product, a yellow oil was obtained which could be converted in high yield to p-trifluoromethyltolane on treatment with alkali. This oil, therefore, was undoubtedly the desired N-nitroso compound.

The last phase of the investigation involved the degradation of the p-trifluoromethyltolane-C^{14} to benzoic acid and p-trifluoromethylbenzoic acid, the separation and purification of these acids and determination of their radioactivity. Rooney (60), while working on another problem in these laboratories some years ago, accomplished the degradation of this tolane by oxidation of its dibromide. In the present work a greatly improved procedure, consisting of the direct oxidation of the acetylene with chromic anhydride has been worked out.

It was found that the less soluble acid, *p*-trifluoromethylbenzoic acid, could be readily purified by re-crystallization. Considerable difficulty, however, was encountered in attempting to obtain pure benzoic acid from the oxidation mixture. Rooney, earlier had developed a liquid-liquid column partition chromatographic method for the separation of the two acids but in the hands of the present author this procedure proved less than satisfactory. After exploring a number of methods, purification of benzoic acid was satisfactorily accomplished through vapour-phase chromatography (V.P.C.) of the methyl ester prepared from the crude acid. Upon saponification of methyl benzoate, pure benzoic acid was obtained.

Radioactivity measurements were made on carbon dioxide, formed by wet combustion (Von Slyke method) (61) of weighed samples of each compound. The activity of the gas was determined by the rate-of-charge method (62) using an ionization chamber vibrating reed electrometer combination.

Synthesis of 5-Phenyl-5-p-Trifluoromethylphenyl-2-oxazolidone-5-C^{14}, LXIV

Preparation of *p*-Trifluoromethylbenzophenone-carbonyl-C^{14}, LXI

The synthetic sequence adopted for the preparation of 5-phenyl-5-*p*-trifluoromethylphenyl-2-oxazolidone labelled with carbon-14 in the C - 5 position requires *p*-trifluoromethylbenzophenone with a carbonyl-C^{14}. One of the most common methods of preparation of diaryl ketones consists of a Friedel-Crafts condensation of an aromatic acid chloride with an aromatic hydrocarbon. With the hope of obtaining the required p-trifluoromethylbenzophenone, p-trifluoromethylbenzoyl chloride was reacted with benzene in the presence of anhydrous aluminum chloride. This synthetic attempt ended in a failure, apparently as a result of an attack of the catalyst on the trifluoromethyl group (63). Also explored was the reaction between diphenyl-cadmium and p-trifluoromethylbenzoyl chloride (64). The desired ketone was obtained in only 50% yield. Since the carbonation of p-trifluoromethylphenyl magnesium bromide was found to give p-trifluoromethylbenzoic acid in only 72% yield, the overall yield of the ketone by this method did not exceed 35 %. This method of obtaining the substituted benzophenone was therefore abondoned in favour of a Grignard reaction between p-trifluoromethylphenyl magnesium bromide and benzonitrile, a method which was found to give the desired ketone in 72% yield (65). Since benzonitrile, labelled on the nitrile carbon, can be prepared in almost quantitative yield from benzoic acid-carboxyl-C^{14} by way of benzoyl chloride and benzamide (66), this synthetic sequence provided a very satisfactory route to the labelled p-trifluoromethylbenzophenone.

Preparation of benzoyl chloride-carbonyl-C^{14} (67): - To 15.24 grams of inactive benzoic acid (0.125 mole) were added 24.4 mg. of carboxyl-C^{14} benzoic acid, which contained a total activity of 0.5 mc. The total acid was refluxed with purified thionyl chloride (35 ml.) for four hours. The excess of the reagent was then removed by distillation under reduced pressure and the remaining benzoyl chloride was purified of last traces of contaminants by addition and vacuum distillation of two 15 ml. portions of dry benzene.

Preparation of benzamide-carbonyl-C^{14}: - The total benzoyl chloride prepared under a) was diluted with dry benzene (200 ml.) and dry ammonia gas was passed into the ice-cooled solution until no further gas was absorbed. This required approximately two hours. The reaction mixture was allowed to stand for an additional hour whereupon the benzene was removed under reduced pressure and the residue, consisting of ammonium chloride and benzamide, was dissolved in approximately 150 ml. of boiling water. Benzamide-carbonyl-C^{14}, slightly contaminated with ammonium chloride, crystallized from the aqueous solution on cooling.

Preparation of benzonitrile-C^{14}, LX (66): - The total benzamide formed in b) was thoroughly dried and then intimately mixed with a finely pulverized equimolal melt of sodium chloride and anhydrous aluminum chloride. The mixture was placed in a retort and heated vigorously. The effluent vapours, consisting of hydrogen chloride and benzonitrile, were condensed in a flask surrounded by a dry ice-acetone bath. Upon completion of the reaction, as indicated by no further evolution of gaseous products, heating was discontinued and the condensate was allowed to warm to room temperature. The condensed hydrogen chloride evaporated leaving behind the benzonitrile. This was taken up in ether, the ether solution washed with sodium bicarbonate solution and dried over calcium chloride. The dried ether solution was used directly in the Grignard reaction with p-trifluoromethylphenyl magnesium bromide.

Preparation of p-trifluoromethylbenzophenone-carbonyl-C^{14}, LXI (65): - To a filtered Grignard solution, prepared from magnesium turnings (10 g.) and p-bromobenzotrifluoride (33 g.) in 170 ml. of ether, was added the ether solution of benzonitrile-C^{14}. The reaction mixture was refluxed for seven hours and left standing at room temperature for another 17 hours. It was then poured with vigorous stirring on ice (300 g.) in concentrated hydrochloric acid (150 ml.). The resulting viscous emulsion was heated until all ether had evaporated and the remaining two-phase system was heated at 100°C while vigorous stirring was maintained. Cooling of the mixture resulted in the separation of solid ketone, which was filtered, washed free of inorganic salts and re-crystallized twice from aqueous ethanol, using de-colourizing carbon. There was obtained 16.9 g. of slightly yellowish product, m.p. 115 - 116°C, lit. m.p. 116 - 118°C (60). A further 2 g. of purified ketone was recovered from the mother liquors from the first re-crystallization. The overall yield of p-trifluoromethylbenzophenone was 60% based on benzoic acid.

Preparation of Ethyl β-hydroxy-β-phenyl-β-p-trifluoromethylphenylpropionate-β-C^{14}, LXII, (68)

Granulated zinc (11.35 g. of 20 mesh) was placed in a 500 ml. three-neck flask fitted with a stirrer, reflux condenser and dropping funnel. A solution of dry benzene (120 ml.), containing p-trifluoromethylbenzophenone-carbonyl-C^{14} (18.9 g.) and a crystal of iodine was added and the reaction mixture brought to its boiling point. A solution of ethyl bromoacetate (18.9 g.) in dry benzene (7.5 ml.) was added dropwise at a rate sufficient to maintain gentle refluxing of the reaction mixture without application of external heat. The addition of the bromo ester was complete in 20 minutes and the solution was refluxed for a further 20 minutes to ensure complete reaction. The clear solution was decanted from unreacted zinc and washed thoroughly by vigorous shaking with 200 ml. of 10% acetic acid. Removal of the benzene under reduced pressure furnished ethyl β-hydroxy-β-phenyl-β-p-trifluoromethylphenylpropionate-β-C^{14}, which was re-crystallized once from aqueous ethanol to give 24 g. (94% yield based on the ketone) of product, melting at 56 - 57°C. A very pure sample prepared for analyses melted at 58°C.

Anal. Calculated for $C_{18}H_{17}F_3O_3$: C, 63.90; H, 5.06.

Found: C, 63.93, 63.83; H, 5.19, 5.09. Specific activity: 4.77 mc./mole.

Preparation of β-Hydroxy-β-phenyl-β-p-trifluoromethylphenylpropionhydrazide-β-C^{14}, LXIII, (1)

Solid ethyl β-hydroxy-β-phenyl-β-p-trifluoromethylphenylpropionate-β-C^{14} (23.9 g.) was added to 95% anhydrous hydrazine (36.5 ml.) and the suspension heated to 50°C in a water bath. Solution rapidly resulted and heating was continued for a total of 15 minutes. The clear solution was poured onto ice and β-hydroxy-β-phenyl-β-p-trifluoromethylphenylpropionhydrazide-β-C^{14} precipitated in almost quantitative yield. The hydrazide was re-crystallized once from aqueous ethanol (decolourizing carbon) to furnish 21.5 g. (94% yield) of product, melting at 140.5 - 141.5°C. (Analytical sample melted at 142 - 143°C.)

<u>Anal.</u> Calculated for $C_{16}H_{15}F_3N_2O_2$: C, 59.26; H, 4.66; N, 8.64.

Found: C, 59.44, 59.36; H, 4.64, 4.36; N, 8.70, 8.60.

Specific activity: 4.77 mc./mole.

Preparation of 5-Phenyl-5-p-trifluoromethylphenyl-2-oxazolidone-5-C^{14}, LXIV, (1)

β-Hydroxy-β-phenyl-β-p-trifluoromethylphenylpropionhydrazide-β-C^{14} (21.4 g.) was dissolved in the minimum quantity (314 ml.) of 50% acetic acid and the solution was placed in a three-neck flask fitted with a reflux condenser, stirrer and dropping funnel. With the solution maintained between 10 - 15°C by means of an ice bath, a slight excess

(236 ml.) of a two per cent aqueous solution of sodium nitrite was added slowly under vigorous stirring. Following the addition of the nitrite, the solution was allowed to stand for 45 minutes and topped with Skellysolve B (250 ml.). The two-phase system was slowly heated to the boiling point of the Skellysolve; after about 10 minutes a vigorous evolution of gas set in causing a momentary heavy refluxing of the organic solvent. Simultaneously, a crystalline suspension appeared in the top solvent layer. External heating of the reaction mixture was applied for another 10 - 15 minutes and then the suspension was cooled in an ice bath and filtered. The crystalline cake was washed with cold water and then re-crystallized from aqueous ethanol (decolourizing carbon) to furnish 18.3 g. (90.2% yield based on hydrazide) of 5-phenyl-5-p-trifluoromethylphenyl-2-oxazolidone-5-C^{14} as white crystalline needles, m.p. 154 - 155°C.

Anal. Calculated for $C_{16}H_{12}F_3NO_2$: C, 62.54; H, 3.95; N, 4.56.
Found: C, 62.70, 62.53; H, 4.19, 4.25; N, 4.75, 4.53.
Specific activity: 4.78 mc./mole.

Preparation of 5-Phenyl-5-p-Trifluoromethylphenyl-N-Nitroso-2-Oxazolidone-5-C^{14}, IX, (1)

5-Phenyl-5-p-trifluoromethylphenyl-2-oxazolidone-5-C^{14} (18.2 g.) was dissolved in dry pyridine (130 ml.) and to the clear solution, cooled below 10°C, was added dropwise a solution of nitrosyl chloride in acetic anhydride (30 ml., 4.8 N). The rate of addition of the nitrosating agent was dictated by the efficiency of the cooling of the reaction mixture. After all nitrosyl chloride was added, the dark red, but clear, solution was allowed to remain at 15°C for 30 minutes, whereupon it was poured into ice water. A yellow viscous oil separated and collected on the bottom and walls of the beaker. All efforts to achieve crystallization of this product failed.

Since most of the N-nitroso-2-oxazolidones are thermally unstable, the purification of the oily 5-phenyl-5-*p*-trifluoromethylphenyl-N-nitroso-2-oxazolidone presented certain difficulties. Of the various possible purification methods, washing of the nitroso compound with distilled water was considered to be the safest and simplest procedure. This "extractive treatment" with water resulted in the hydrolysis of nitrosyl chloride and acetic anhydride and in the removal of pyridine from the oily nitroso compound. This procedure was repeated several times at ice bath temperatures and the product so treated was used directly in the next reaction - the alkaline decomposition to the tolane.

Preparation of p-Trifluoromethyltolane-C^{14}, X, (1)

The oily 5-phenyl-5-*p*-trifluoromethylphenyl-N-nitroso-2-oxazolidone-5-C^{14}, prepared from 18.2 g. of the 2-oxazolidone, was dissolved in 120 ml. of methanol. To the resulting deep yellow solution was added dropwise 50% aqueous potassium hydroxide. A vigorous evolution of gas was observed, along with a considerable rise in temperature of the reaction mixture. Simultaneously, a crystalline flaky precipitate separated from the darkened solution. The addition of base was continued until the evolution of gas ceased. The suspension was then acidified with concentrated hydrochloric acid, cooled, filtered, washed and dried. The crude tolane (14.0 g.) was crystallized once from aqueous ethanol to give a colourless product, m.p. 104 - 105°C; lit.(104 - 1059, m.p. 104 - 105°C; yield 13.2 g., 91% based on 5-phenyl-5-p-trifluoromethylphenyl-N-nitroso-2-oxazolidone-5-C^{14}. This product was further crystallized to constant activity; specific activity: 4.78 mc./mole.

Oxidation of p-Trifluoromethyltolane-C^{14}, X. (69)

p-Trifluoromethyltolane-C^{14} (3.6 g.) was dissolved in glacial acetic acid (90 ml.), which has been purified by distillation from chromic anhydride. The tolane solution was heated to its boiling point and an oxidizing solution (13.5 g. chromic anhydride dissolved in 25 ml. acetic acid and 6 ml. of water) was added dropwise. As the first portion of the oxidizing agent was added, an exothermic reaction set in causing a moderate refluxing of the acetic acid. The addition of the oxidizing agent was complete in five minutes, whereupon external heat was applied and the solution was gently refluxed for another 25 minutes. The dark green reaction mixture was allowed to stand overnight. The green solution was then cooled and diluted with ice water to a volume of 500 ml. This caused the separation of crude *p*-trifluoromethylbenzoic acid-carboxyl-C^{14}, while most of the more soluble benzoic acid-carboxyl-C^{14} remained in solution. The precipitated acid was filtered and then dissolved in a saturated sodium bicarbonate solution. The latter was extracted with ether to remove neutral impurities and then acidified to yield 2.1 g. (72% yield based on the tolane) of *p*-trifluoromethylbenzoic acid-carboxyl-C^{14}, m.p. 217 - 218°C; *lit.* (60), m.p. 218 - 220°C. Further re-crystallizations from aqueous ethanol furnished a product having a constant activity of 3.14 mc./mole and a m.p. of 220°C.

The aqueous solution, from which the *p*-trifluoromethylbenzoic acid was precipitated, was repeatedly extracted with ether. The green ether solution, which contained along with the desired benzoic acid neutral organic impurities and inorganic material, was extracted with a saturated sodium bicarbonate solution and the aqueous extract was filtered to remove insoluble inorganic salts and then washed with ether. Acidification of the bicarbonate solution furnished 1.2 g. of benzoic acid-carboxyl-C^{14}, contaminated with *p*-trifluoromethylbenzoic acid. The latter could not be removed by conventional re-crystallization procedures and a chromatographic method was adopted for the purification of the benzoic acid.

Vapour-Phase Chromatographic Purification

After exploring a number of methods for freeing the benzoic acid from its p-trifluoromethylbenzoic acid contaminant, including partition chromatography on a methanol-silicic acid column, adsorption chromatography of the β-naphthyl esters on alumina and ion exchange chromatography, a satisfactory procedure involving V.P.C. separation of the methyl esters was developed.

Following preliminary experiments on analytical columns, a preparative column for use in a Perkin-Elmer Vapour Fractometer, No. 154 was assembled. This column consisted of six 17" lengths of 1" diameter glass tubing supported in a manifold assembly available from the Perkin-Elmer Corporation. The packing, consisting of "Carbowax 1500", supported by "Chromosorb P" 60/80 mesh, was prepared as follows. "Carbowax 1500" (100 g.) was dissolved in dry benzene (1000 ml.) and into this clear solution were poured 400 grams of "Chromosorb P", 60/80 mesh. The suspension was heated in an evaporating dish on a steam bath with vigorous stirring, while the benzene was evaporated to dryness. Although this procedure ensured a uniform coating of the supporting solid with "Carbowax 1500", the unavoidable exposure to air apparently caused extensive formation of peroxides, since at the temperature of column operation large quantities of formaldehyde were evolved. For this reason, the packing, before introduction into the column, was placed into a large tube through which nitrogen was slowly passed at 120°, overnight.

The column was capable of processing 0.2 ml. quantities of mixed esters at flow rates of 750 - 800 ml. per minute of nitrogen carrier gas at a temperature of 98°C. Under these conditions, the column exhibited some signs of overloading. However, the retention times of methyl benzoate and p-trifluoromethylbenzoate were 20 and 42 minutes, respectively, which left ample time between the peaks of the two esters and permitted trouble-free switching of the receivers at the column exit.

The impure benzoic acid-carboxyl-C^{14}, isolated from the oxidation mixture, was converted to its methyl ester by treating a solution of 1.235 g. in cold dry ether with an ethereal solution of diazomethane until the yellow colour persisted (70). The ether was then evaporated, leaving the methyl ester as residue. This ester was introduced into the column in 0.2 ml. amounts by means of a hypodermic syringe and the methyl benzoate emerging from the column was collected in a trap surrounded by a dry ice-acetone bath. A total of seven such separations were carried out and the combined purified ester was saponified in an alcoholic solution of sodium hydroxide (one gram of sodium hydroxide in 25 ml. of ethanol) by refluxing for one hour. On acidification and evaporation of the ethanol solvent, benzoic acid-C^{14} crystallized in large flakes, 0.37 g., m.p. 122°C. On re-crystallization of this product, the specific activity remained constant at 1.63 mc./mole.

Determinations of Radioactivity

The specific activity of the carbon-14 labelled compounds was determined in the form of carbon dioxide gas by the rate-of-charge method, using a 250 ml. Borkowski-type ionization chamber in conjunction with a Carry vibrating reed electrometer (62). The conversion factor relating measured current to carbon-14 activity for the Borkowski chamber of this volume has been reported (71) to be 5.15×10^{-12} A/μc., although the exact value of this constant varies somewhat from chamber to chamber. For absolute carbon-14 activity measurements, this constant must be determined precisely by calibration of the particular chamber, using a standard C^{14} source. For most work, including that reported in this thesis, only the relative specific activity of compounds is required and the use of the approximate conversion factor, 5.15×10^{-12} A/μc., is entirely satisfactory.

The current arising from radioactive carbon dioxide was not measured directly but instead the rate of charge of the input capacity to the vibrating reed electrometer was observed and recorded in terms of the time required to charge the 13 μμF input capacity of the chamber to a potential of 0.9 volts. The current was then calculated from the following expression:

$$I = \frac{dQ}{dt} = C\,\frac{dV}{dt} = \frac{(\text{capacity in farads})\ (\text{voltage change in volts})}{(\text{time in seconds})}$$

To test the technique and the electrical apparatus for reproducibility, p-trifluoromethyltolane-C^{14}, prepared from purchased benzoic acid-carboxyl-C^{14}, was oxidized to carbon dioxide in five experiments and the constancy of the product of sample weight and time of voltage change (0.9 volts) was observed. These results, as well as the specific activities calculated from the observed I value for each sample using the conversion factor 5.15×10^{-12} A/μc. are recorded in Table VIII.

TABLE VIII

Reproducibility Experiments on p-Trifluoromethyltolane-C^{14}

Weight of Sample in mg.	Time of Charge in sec.	Product of Weight X Time	Specific Activity in mc./mole
1.547	75.39	116.728	4.792
1.682	69.39	116.714	4.793
1.811	64.61	117.009	4.781
1.293	90.99	117.650	4.755
1.239	94.47	117.048	4.779

It is seen that the reproducibility is better than one per cent.

It is of interest that the average specific activity of 4.78 mc./mole obtained for the p-trifluoromethyltolane is about 20% higher than the activity of 4.00 mc./mole given by the supplier for the benzoic acid from which the tolane was synthesized. This discrepancy may be a consequence of an inaccurate conversion factor, although it should be borne in mind that the activity value given by the supplier is probably a minimum figure. As stated earlier, since only relative activities are required in the present study, any uncertainty in our knowledge of the absolute activities of samples is of no consequence.

The activities found for the carbon-14 labelled compounds are shown in Table

TABLE IX

Specific Activities of Carbon-14 Labelled Compounds

Compound	Specific Activity
Ethyl β-hydroxy-β-phenyl-β-p-trifluoromethylphenylpropionate	4.77 mc./mole
β-Hydroxy-β-phenyl-β-p-trifluoromethylphenylpropionhydrazide	4.77 mc./mole
5-Phenyl-5-p-trifluoromethylphenyl-2-oxazolidone	4.78 mc./mole
p-Trifluoromethyltolane	4.78 mc./mole
Benzoic acid	1.63 mc./mole
p-Trifluoromethylbenzoic acid	3.14 mc./mole

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