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THE REARRANGEMENT OF KETOXIME O-SULFONATES TO AMINO KETONES

(The Neber Rearrangement)

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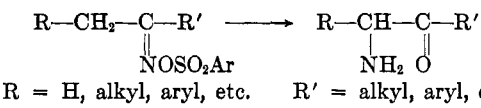
I. INTRODUCTION

Though the Neber rearrangement was discovered almost 40 years ago, this unique reaction had received but scant application up to the last decade or so, when, after the failure of more conventional methods, its applicability to the synthesis of α-amino ketones began to be more widely recognized. Recently, it has been applied to the stereospecific synthesis of cyclic α-amino ketones, and some work has also been done in elucidating the mechanism of the reaction.

This review is intended to present a survey of all the information available on the subject up to September, 1963.

A. DEFINITION

In the Neber rearrangement an oxime arylsulfonate of the following general type, when treated with base followed by acid hydrolysis, rearranges to form an

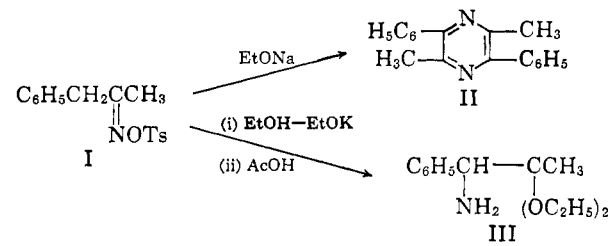


α-amino ketone. The oxime sulfonate may also be derived from an equivalent cyclic ketone.

B. DISCOVERY

In 1926, Neber and Friedolsheim (23), while working on the Beckmann rearrangement, noted the unusual behavior of aromatic sulfonate esters of some benzyl methyl ketoximes.

Saponification of 1-phenyl-2-propanone oxime tosylate (I) with sodium ethoxide gave 2,5-dimethyl-3,6-diphenylpyrazine (II), while successive treatment with ethanolic potassium ethoxide and acetic acid gave the acetate of 1-amino-2-diethoxy-1-phenylpropane (III).



Again, 1-(2-nitrophenyl)-2-propanone oxime benzenesulfonate (IV) gave with ethanolic ammonia the dihydropyrazine (V), while successive treatment with potassium ethoxide, acetic acid, and hydrochloric acid

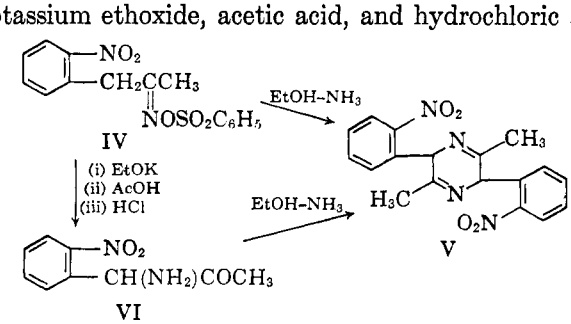
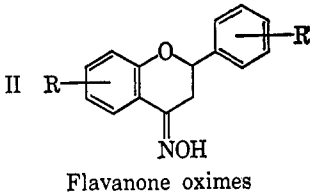
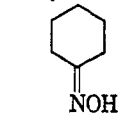
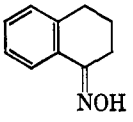
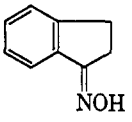
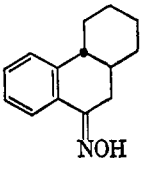
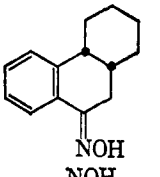
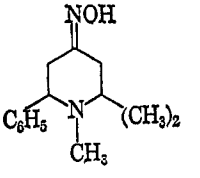
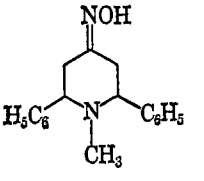
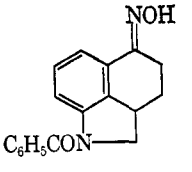


TABLE I

NEBER REARRANGEMENT OF OXIME TOSYLATES

Parent oxime		References
I $RCH_2C(:NOH)R'$ Miscellaneous acyclic ketoximes		
R	R'	
H	CH_3	24
H	C_6H_5	24, 38
H	p-$O_2NC_6H_4$	38, 39
H	3,4-$(CH_2O_2)C_6H_3$	22
H	$C_6H_5CH_2$	23
H	$C_6H_5CH_2CH_2$	23
H	o-$O_2NC_6H_4CH_2$	23, 24
H	2,4-$(O_2N)_2C_6H_3CH_2$	9, 21
H	$C_6H_5NHCOCH_2$	22
H	$C_6H_5CONHCH_2$	22
H	2-Pyridyl	8
H	3-Pyridyl	8
CH_3	C_6H_5	24
C_6H_5	C_6H_5	15, 24
C_6H_5	$C_6H_5CH_2$	25
C_6H_5	p-$CH_3C_6H_4$	15
p-ClC_6H_4	p-ClC_6H_4	13
p-$CH_3C_6H_4$	C_6H_5	15
p-$O_2NC_6H_4$	p-$CH_3OC_6H_4CH_2$	16
2,4-$(O_2N)_2C_6H_3$	C_6H_5	24
II  Flavanone oximes		
R	R'	
H	H	7, 17, 28
H	3'-OCH_3	28
H	4'-OCH_3	28
H	3',4'-$(OCH_3)_2$	28
H	3',4'-(CH_2O_2)	28
6-Cl	H	28
7-OCH_3	4'-OCH_3	18

Parent oxime	References
III Other cyclic ketoximes	
	33
	22, 26
	22, 26
	11
	11
	22, 26
	22, 26
	19

gave the hydrochloride of 1-amino-1-(2-nitrophenyl)-propan-2-one (VI). This on treatment with ethanolic ammonia gave the dihydropyrazine (V).

These results suggested the occurrence of a novel rearrangement of the oxime sulfonates to α-amino ketones, the pyrazine derivatives arising from Gutknecht condensation (12) of the primary products.

Neber and his associates (21, 22, 24–26) later extended their investigations of this reaction and demonstrated its versatility by synthesizing a variety of α-amino ketones both of the mixed alkyl–aryl and cyclic types.

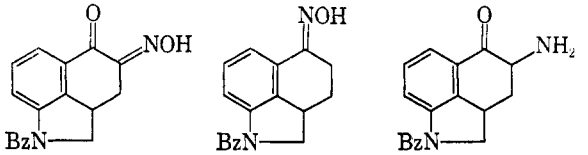
II. SCOPE OF THE REACTION

A. GENERAL SYNTHETIC APPLICATIONS

A list of compounds, which have been submitted successfully to the Neber rearrangement, is given in Table I and shows that the reaction is applicable to a wide variety of alkyl–aryl, heterocyclic, and homocyclic systems.

It is interesting to note that the reaction has been recorded as the method of choice in the preparation of intermediates in the synthesis of some important natural products. For example, Woodward at Harvard and his associates in the Lilly Research Laboratories

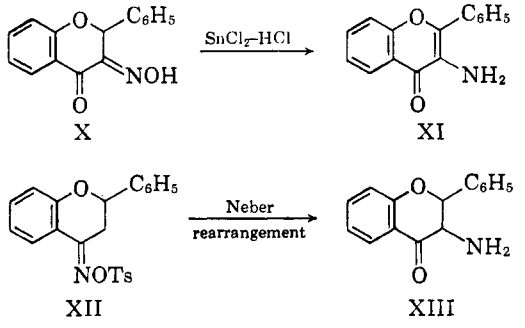
(19) required 4-amino-1-benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (IX) as an intermediate in their projected synthesis of lysergic acid. The reduction of the α-oximino ketone (VII, isolated only as its potassium salt) could not be achieved, but application of the Neber rearrangement to the tosyl ester of VIII gave the desired α-amino ketone (IX) in satisfactory yield. A similar type α-oximino ketone has been found not to be particularly stable, being readily transformed



VII VIII IX

into the nitrosophenol, the reduction of which would not yield the amino ketone. Wawzonek and Kozikowski (41), in attempting to introduce an α-amino group to 4-phenyl-1-tetralone by first forming the isonitroso ketone and then reducing, were not successful; nitrosation gave solely 2-nitroso-4-phenyl-1-naphthol.

In the flavonoid field a projected synthesis of leucoanthocyanidins required 3-aminoflavanone as an intermediate (7, 28). This compound had long been recorded (31) as available *via* the stannous chloride–hydrochloric acid reduction of 3-oximinoflavanone (X), but recent work (7, 28) has shown that this reduction gives instead 3-aminoflavone (XI). The required 3-



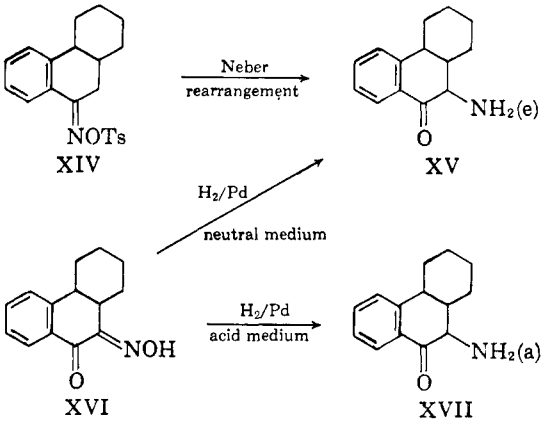
aminoflavanone (XIII) was obtained satisfactorily from the Neber rearrangement of (XII).

B. STEREOSPECIFIC SYNTHESIS OF CYCLIC α-AMINO KETONES

The application of the Neber rearrangement to the synthesis of sterically specific α-amino ketones has been reported in some instances.

Drefahl and Martin (11) prepared both the ring *cis* and *trans* isomers of 10-amino-1,2,3,4,9,10,11,12-octahydro-9-oxophenanthrene (XV) *via* the Neber rearrangement on the corresponding 9-oximino tosylate compounds (XIV). The amino group in each was assigned equatorial conformation on the basis of physical and chemical properties. The same isomer (*i.e.*, equatorial amine) was obtained from the catalytic hydrogenation in neutral medium of the α-oximino ketone (XVI) while catalytic reduction in acid medium gave the corresponding axial amino isomer (XVII).

In the case of 3-aminoflavanone (XIII) obtained by the Neber reaction, Kasahara (17) has assigned equatorial conformation to the amino group. However, much of the evidence to support this assignment was based on the false assumption that the stannous chloride–hydrochloric acid reduction of 3-oximinoflavanone



(X) gave the 3-axial amino flavanone. More recent work (27, 40) suggests that the Neber rearrangement does, in fact, give the 3-equatorial amino compound.

C. DIRECTION OF REARRANGEMENT

The question arises of the direction in which the reaction proceeds in those cases where the oxime tosylate possesses two distinguishable α-methylenic groups. Those cases which have been reported are listed in Table II and with each, the rearrangement apparently proceeded in the direction which resulted principally in substitution of the amino group on the more electrophilic α-carbon atom. From a consideration of the most plausible mechanism for the reaction, this result would appear a likely consequence (see section III).

D. INFLUENCE OF OXIME CONFIGURATION

The available evidence suggests that no stereospecificity of the sort found in the Beckmann rearrangement is present in the Neber reaction. The original investigators found that the rearrangement of 1-(2-nitrophenyl)-2-propanone α-oxime tosylate (23) and the corresponding β-isomer (24) gave 1-amino-1-(2-nitrophenyl)-2-propanone in each case. Recently, House and Berkowitz (16) showed that both isomers of 1-(4-methoxyphenyl)-3-(4-nitrophenyl)-2-propanone oxime tosylate gave the same Neber product. Indications that equilibration of the oxime tosylates did not occur under the reaction conditions were apparent from the presence of stereospecific Beckmann products in each reaction mixture.

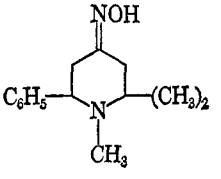
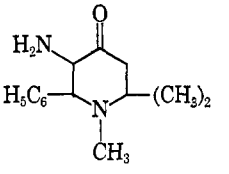
Hatch and Cram (13) noted that where two distinguishable α-methylene groups were available, the reaction proceeded in a *trans* steric direction except in the case of 1-(2-nitrophenyl)-2-propanone β-oxime tosylate,

TABLE II

NEBER REARRANGEMENT OF OXIME TOSYLATES OF THE TYPE

$$RCH_2\underset{\underset{NOTs}{\|}}{C}CH_2R'$$

(where R ≠ R′ = H, alkyl, aryl, etc.)

Parent oxime	Rearrangement product	References
$C_6H_5CH_2\underset{\underset{NOH}{\|}}{C}CH_3$	$C_6H_5\underset{\underset{H_2N\ O}{\|\ \|}}{CH}CCH_3$	23
$C_6H_5CH_2CH_2\underset{\underset{NOH}{\|}}{C}CH_3$	$C_6H_5CH_2\underset{\underset{H_2N\ O}{\|\ \|}}{CH}CCH_3$	25
$o\text{-}O_2NC_6H_4CH_2\underset{\underset{NOH}{\|}}{C}CH_3$	$o\text{-}O_2NC_6H_4\underset{\underset{H_2N\ O}{\|\ \|}}{CH}CCH_3$	23, 24
$2,4\text{-}(O_2N)_2C_6H_3CH_2\underset{\underset{NOH}{\|}}{C}CH_3$	$2,4\text{-}(O_2N)_2C_6H_3\underset{\underset{H_2N\ O}{\|\ \|}}{CH}CCH_3$	9, 21
$C_6H_5NHCOCH_2\underset{\underset{NOH}{\|}}{C}CH_3$	$C_6H_5NHCO\underset{\underset{H_2N\ O}{\|\ \|}}{CH}CCH_3$	22
$C_6H_5CONHCH_2\underset{\underset{NOH}{\|}}{C}CH_3$	$C_6H_5CONHCH_2\underset{\underset{O\ NH_2}{\|\ \|}}{C}CH_2$	22
$p\text{-}O_2NC_6H_4CH_2\underset{\underset{NOH}{\|}}{C}CH_2C_6H_4OCH_3\text{-}p$	$p\text{-}O_2NC_6H_4\underset{\underset{H_2N\ O}{\|\ \|}}{CH}CCH_2C_6H_4OCH_3\text{-}p$	16
		22

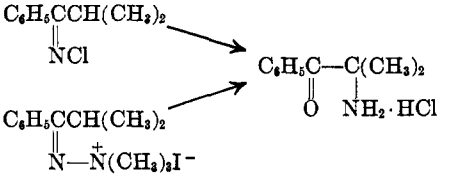
while the direction of the reaction was *cis* in those cases of known configuration where only one methylene group was available. To show that the reaction would proceed as usual in a case where the only available α-methylene group was *trans*, they prepared *p,p′*-dichlorodesoxybenzoin oxime tosylate under conditions unlikely to affect the known *trans*-hydroxy-*p*-chlorobenzyl configuration of the oxime and successfully submitted it to the Neber rearrangement.

From these examples it appears that the configuration of the oxime tosylate has no significant bearing on the reaction.

E. LIMITATIONS OF THE REACTION

Aldoxime tosylates, when submitted to the Neber reaction conditions, give an E2 elimination of *p*-toluenesulfonic acid with the formation of the corresponding nitrile or isonitrile (13, 20).

In extending the rearrangement to α-methinyl ketoxime tosylates, Hatch and Cram (13) found that 1,1-diphenyl-2-propanone oxime tosylate gave N-acetylbenzhydrylamine. In the case of 1,1-bis(4-chlorophenyl)-2-propanone oxime tosylate a substance was obtained whose properties corresponded with the O-ethyl ether of the oxime. Accordingly, they suggested that the reaction was limited to structures which did not contain a methinyl group adjacent to the oxime function. In the related rearrangements of N-chloroketimines and dimethylhydrazone methiodides to α-amino ketones (section IIIB), no such structural limitation exists, and the rearrangement of isopropyl phenyl N-chloroketimine afforded α-aminoisobutyrophenone hydrochloride in 20–35% yield (6) while the rearrangement of isobutyrophenone dimethylhydrazone methiodide gave the same amino ketone in 75% yield (32).



Although the examples cited by Hatch and Cram contained an α-methyl group, the presence of the unusual α'-diphenylmethyl group may have permitted some exceptional course to take precedence over the Neber rearrangement under the particular reaction conditions adopted, and it seems reasonable to suggest that the general structural limitation of the sort inferred would need to be re-examined in the case of the Neber reaction.

Excluding the possibility of its applicability to α-methinyl ketoximes, these results suggest that the Neber rearrangement is limited to systems represented by the general formula given in section IA.

However, not all compounds represented by this general formula have been submitted successfully to the reaction. Some examples reported are mentioned below. It is not clear why the reaction failed with some of these though one obvious limitation arises with those compounds which undergo a Beckmann transformation either in the preparation of the oxime tosylate or when later the tosylate is submitted to the Neber reaction conditions.

An attempt to synthesize 2-amino-3′,4′-dihydroxyacetophenone, required as an intermediate in the synthesis of adrenalin, *via* the oxime of 3′,4′-dihydroxyacetophenone and its tosyl ester failed (22), as did the reaction on the corresponding acetylated and benzoylated compounds. From the oxime of the dimethyl ether, only the Beckmann rearrangement product, 3′,4′-dimethoxyacetanilide, could be isolated.

Failure to convert the tosyl derivative of ethyl *o*-nitrophenylpyruvate oxime to the α-amino ketone was also reported (24), although it was stated that this was an exceptional case, and it was claimed that the reaction had been applied successfully to a series of β-keto acid esters.

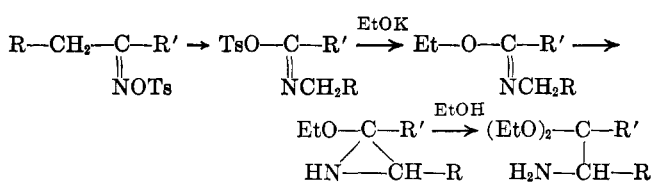
Failure, too, was encountered with certain ether oxime tosylates, *e.g.*, the mono- and dinitrophenoxyacetone oxime tosylates (24).

Although the rearrangement went smoothly in the case of acetoacetanilide oxime, attempted formation of the tosyl ester of the corresponding *p*-dimethylamino compound was unsuccessful (22).

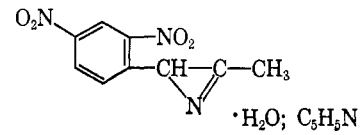
III. The Mechanism of the Rearrangement

A. The Intermediate in the Reaction

In an early attempt to explain the mechanism of the rearrangement, Neber (23) considered the reaction to proceed *via* a type of Beckmann transformation thus

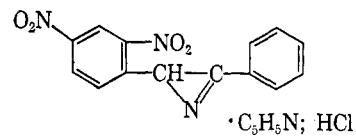


Later (21), it was found that the rearrangement occurred during formation of the tosylate of 1-(2,4-dinitrophenyl)-2-propanone oxime from the oxime and *p*-toluenesulfonyl chloride in pyridine. In this experiment an intermediate was isolated which was considered to be the hydrochloride of a pyridine–water complex to which was assigned structure XVIII.



XVIII

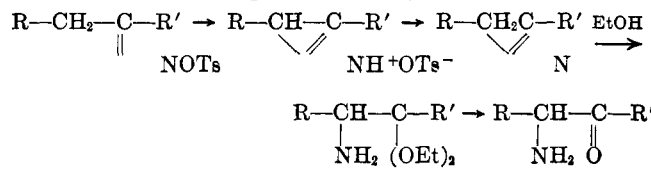
Similarly (24), an analogous azirine–pyridine–hydrochloride complex (XIX) was isolated from the



XIX

preparation of 2,4-dinitrodesoxybenzoin oxime tosylate.

The isolation of the intermediate led Neber and his colleagues to alter their view of the course of the reaction and the following scheme was proposed.



The mechanism of the rearrangement was reinvestigated some 20 years later by Cram and Hatch (9) who considered that the highly strained structure (XVIII) assigned to the intermediate warranted critical examination. Their extensive work on this novel compound only served to confirm the accuracy of the structure assigned by Neber and his colleagues.

Briefly the evidence for such a structure may be summarized as follows.

1. Elemental analysis and molecular weight determination on the free base suggested a formula $C_9H_7N_3O_4$.

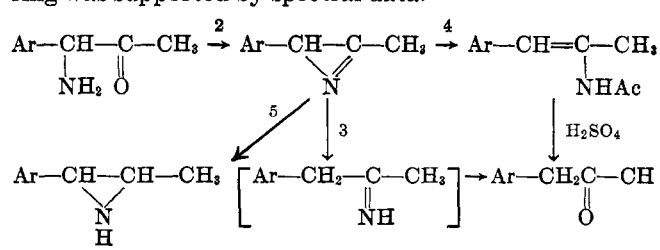
2. The carbon–nitrogen double bond underwent solvolytic cleavage to give an amino ketal or an amino ketone.

3. Catalytic hydrogenation in the presence of water gave 2,4-dinitrophenylacetone.

4. Catalytic hydrogenation in the presence of acetic anhydride gave an acetylated vinyl amine.

5. Reduction with lithium aluminum hydride gave an ethylenimine.

6. The position of the double bond in the azirine ring was supported by spectral data.



Hatch and Cram (13) did not consider the 2,4-dinitrophenylacetone system representative of the

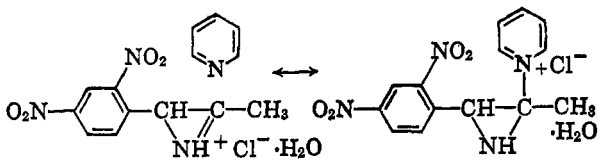
reaction in general being atypical in two respects: (a) The strong electron-withdrawing effect of the two nitro groups makes the hydrogen atoms on the benzyl carbon sufficiently acidic to allow the reaction to be initiated by pyridine instead of the more usual sodium or potassium alkoxide. (b) The azirine ring system itself, again due to the nitro groups, would be expected to be far more resonance-stabilized than in the more usual systems.

In an extension of these studies to a more typical system, these authors (13) treated the tosylate of desoxybenzoin oxime with ethanolic potassium ethoxide, and by application of low temperature techniques they isolated an unstable intermediate. This intermediate was demonstrated to be 2,3-diphenyl-2-ethoxyethylenimine, and the evidence adduced to support this structure may be summarized as follows.

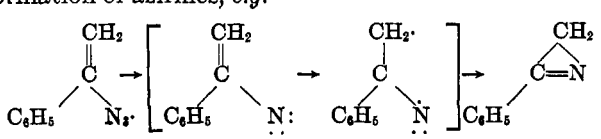
1. Elemental analysis and molecular weight determination suggested a molecular formula, $C_{16}H_{17}NO$.
2. The compound contained one ethoxyl group.
3. Hydrolysis with aqueous hydrochloric acid gave desylamine hydrochloride.
4. Reduction with lithium aluminum hydride gave *cis*-2,3-diphenylethylenimine.
5. The ultraviolet absorption spectrum resembled that of *cis*-2,3-diphenylethylenimine.
6. A band in the infrared spectrum at 2.9 μ, which also appears in the spectrum of *cis*-2,3-diphenylethylenimine, showed the presence of a N–H bond in the molecule.

In seeking further evidence for this type of intermediate, the tosylate of *p,p'*-dichlorodesoxybenzoin oxime was submitted to the Neber rearrangement. Although no intermediate could be isolated, evidence for its existence was obtained from the fact that treatment of the intermediate reaction mixture with lithium aluminium hydride gave 2,3-*p,p'*-dichlorodiphenylethylenimine.

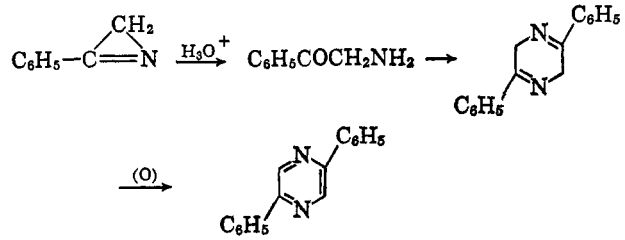
In an attempt to bring the two different types of intermediate into closer analogy, Hatch and Cram (13) formulated the azirine–pyridine–hydrochloride complex (XVIII) as a resonance hybrid.



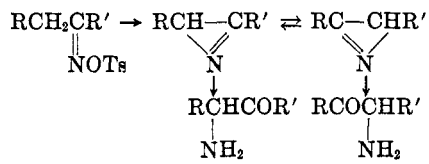
The existence of an intermediate azirine might seem doubtful in view of the strain associated with a three-membered unsaturated ring, but, in fact, such azirines have recently been synthesized. Smolinsky (35, 36) has shown that the pyrolysis of vinyl azides leads to the formation of azirines, *e.g.*



Furthermore, 2-phenylazirine on treatment with dilute acid followed by base afforded a pyrazine presumably *via* hydrolysis to the α-amino ketone followed by self-condensation and air oxidation (36).



House and Berkowitz (15) have shown that in certain cases at least a symmetrical intermediate or a rapidly equilibrating mixture of intermediates is not involved in the Neber rearrangement. Though the previous work on the reaction showed no indication of a tautomeric type of intermediate, they examined cases where the proposed azirine intermediates would be essentially equivalent electronically. They found that the Neber rearrangement of desoxybenzoin and 4-methyl- and 4'-methyldesoxybenzoin oxime tosylates produced the α-amino derivative of the corresponding ketone in each case, ruling out the possibility of any tautomerization such as the following occurring.

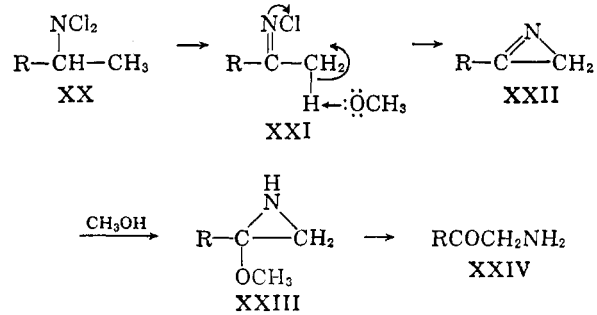


B. REARRANGEMENTS WITH PARALLEL MECHANISMS

A discussion of the mechanism would hardly be complete without mention of two other rearrangements yielding α-amino ketones which are considered to operate in an essentially similar fashion to the Neber reaction.

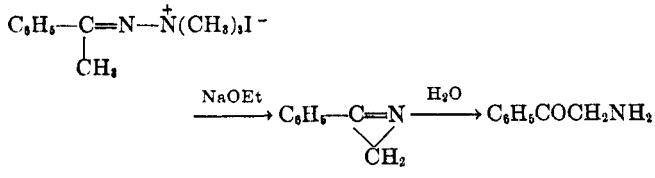
In 1954, Baumgarten and Bower (3) showed that the treatment of N,N-dichloro-*sec*-alkyl amines with sodium methoxide and then with dilute hydrochloric acid gave good yields of the corresponding α-amino ketone hydrochloride.

The first stage of this reaction has been shown (1, 4) to involve dehydrochlorination of the dichloroalkyl amine (XX) to the N-chloroketimine (XXI). The

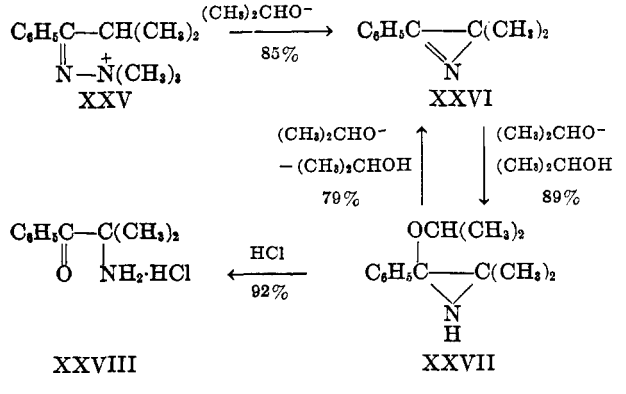


second stage, conversion to the α-amino ketone (XXIV), was considered to proceed by a mechanism similar to that described by Hatch and Cram for the Neber rearrangement, the intermediate being the azirine (XXII) or the methoxyethylenimine (XXIII). In support of this mechanistic similarity, the intermediate from the rearrangement of N,N-dichloro-1,2-diphenylethylamine was reduced, without isolation, with lithium aluminium hydride giving *cis*-2,3-diphenylethylenimine (5).

The second of these Neber-type reactions, the base-catalyzed rearrangement of dimethylhydrazone methiodides having a α-hydrogens to α-amino ketones, has been described by Smith and Most (34), and the mechanism is again considered analogous to that of the Neber rearrangement.



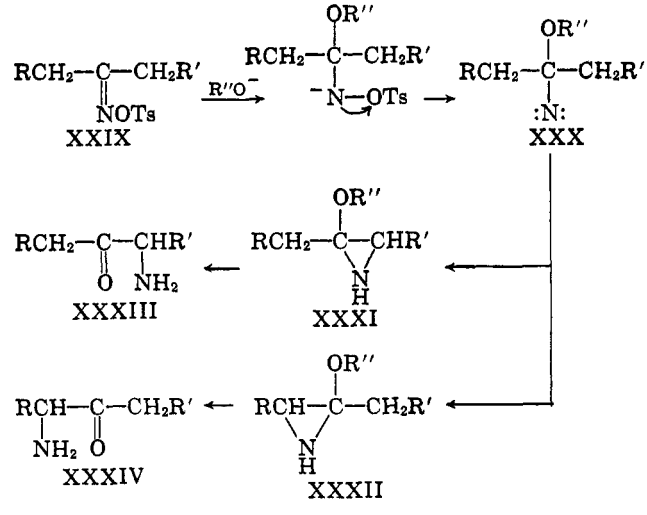
Very recently, a study of the reaction of isobutyrophenone dimethylhydrazone methiodide (XXV) with sodium isopropoxide in isopropyl alcohol was reported by Parcell (32), and in this case the intermediate proved to be unusually stable. When the reaction was carried out with less than one equivalent of base at ambient temperature for a short period, the azirine (XXVI) was produced; with excess of base at reflux temperature for several hours, the alkoxy ethylenimine (XXVII) was produced. The azirine (XXVI), when refluxed in isopropyl alcohol with a catalytic amount of base, gave the alkoxy ethylenimine (XXVII) in high yield. Azeotropic distillation of the alkoxy ethylenimine in toluene removed isopropyl alcohol, regenerating the azirine. Acid hydrolysis of either compound gave the amino ketone (XXVIII), reaction of the alkoxy ethylenimine being the less exothermic but occurring more rapidly and giving a greater yield of the amino ketone. The structures assigned to the intermediates were supported by elemental analyses, and by infrared and ultraviolet measurements.



C. CONSIDERATION OF THE DETAILED MECHANISM

Two general mechanistic pathways now seem possible for the Neber rearrangement.

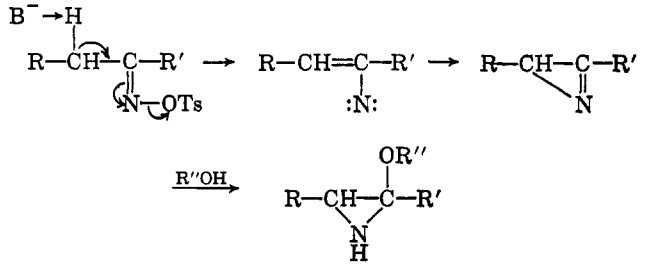
In the first of these, originally discussed by House and Berkowitz (15, 16), the reaction is initiated by attack of the alkoxide ion on the carbon–nitrogen double bond followed by loss of the tosyloxy group. The resulting saturated nitrene (XXX) then inserts itself into an adjacent C–H bond to form an alkoxy ethylenimine (XXXI or XXXII). With this scheme it might be expected that the saturated nitrene, by analogy with the behavior of carbenes, would show little selectivity between insertion at either of the two adjacent methylene positions and consequently to produce comparable amounts of both Neber products (XXXIII and XXXIV). Furthermore, if any selectivity were to be



observed the predominant product would be expected to be that arising from bond insertion with the more electronegative α-group. The observed facts show that this is not so, and that cyclization results in substitution of the amino group for one of the more acidic hydrogens. A striking example of this was provided by House and Berkowitz (16) with the rearrangement of 1-(4-methoxyphenyl)-3-(4-nitrophenyl)-2-propanone oxime tosylate (XXIX, R = p-$O_2NC_6H_4$; R′ = p-$CH_3OC_6H_4$). The product from this reaction was 1-amino-3-(4-methoxyphenyl)-1-(4-nitrophenyl)-2-propanone (XXIV, R = p-$O_2NC_6H_4$; R′ = p-$CH_3OC_6H_4$) rather than the isomeric amino ketone (XXXIII) which might have been expected had the proposed insertion of the electron-deficient nitrene occurred at the C–H bond adjacent to the electron-donating p-methoxyphenyl group.

A mechanism more in general agreement with the observed behavior is that which essentially was originally proposed by Hatch and Cram (13) and which involves an initial base-induced elimination of an α-proton followed or accompanied by loss of the tosyloxy group with subsequent ring closure to an azirine.

The work of Parcell (*vide supra*) would suggest that the subsequent formation of an alkoxy ethylenimine arises by a direct 1,2-addition of the alcohol on the azirine rather than on any unsaturated nitrene precursor.



This mechanism is more compatible with the findings referred to earlier (section IIC), which showed that rearrangement results in substitution of the amino group on the more electrophilic center since, clearly, the most likely hydrogen to be eliminated by the attacking nucleophile will be one of the more acidic ones.

No critical work has been done on the mechanism of the hydrolytic stage of the rearrangement, but Hatch and Cram (13) have considered it to occur by the same course as that involved in the hydrolysis of ketals.

No satisfactory attempt has yet been made to correlate any of the postulated mechanisms with the isolation of the cyclic α-amino ketones, mentioned earlier (section IIB), having the amino group equatorial. From a stereoelectronic point of view, attack by a nucleophile at the α-position would be expected to occur preferentially from the axial position, and any subsequent ring-closure step ought to place the amino group in the axial position. Alternatively, should the initial attack occur on the carbon–nitrogen double bond, the axial α-hydrogen atom should be in the more favored position for removal in the subsequent ring-closure stages.

However, the possibility of subsequent equilibration giving the more stable equatorial isomer cannot be ruled out.

IV. Experimental Procedures

The ease with which oxime arylsulfonates rearrange to a variety of compounds indicates the necessity of caution in the choice of experimental conditions. Depending on the nucleophile employed, oxime arylsulfonates have given O-alkyl- and O-arylimine ethers (29), amidines (29, 30), imidazolines (30), and O-imidyl phosphates (2).

The usual procedure for preparing the oxime tosylate is to treat the oxime with *p*-toluenesulfonyl chloride in pyridine. This method may occasionally prove unsatisfactory, *e.g.*, in those instances when the oxime undergoes a Beckmann rearrangement under such reaction conditions. Many alternative preparative methods are available (9, 10, 14, 29, 37).

The rearrangement itself has reportedly taken place in one instance on exposure of the crude oxime tosylate to the atmosphere for several days (23). In this case the reaction was probably catalyzed by residual pyridine. Other bases employed have been sodium hydroxide and ethanolic ammonia (23), though these are generally not to be recommended.

The usual procedure has been to treat an alcoholic solution or suspension of the oxime tosylate with an alkoxide of either sodium or potassium. During the course of the reaction the alkali metal salt of *p*-toluenesulfonic acid is precipitated, and the subsequent hydrolytic stage is carried out by acid extraction from an ethereal solution of the alcoholic filtrate. A variation of this method has employed a benzene solution of the tosylate in the first step, the hydrolytic stage being carried out directly on the benzene filtrate (18, 28).

The application of completely anhydrous conditions in the first stage of the reaction gave considerably improved yields in the rearrangement of N,N-dichloro-*sec*-alkyl amines to α-amino ketones (5) and in the similar rearrangement of dimethylhydrazone methiodides (34). Comparative studies of the Neber rearrangement under strictly anhydrous conditions have not been made, but the experiments of House and Berkowitz (15) indicate that here too the complete exclusion of water in the first stage of the reaction would give higher yields. These workers examined the rearrangement of desoxybenzoin oxime tosylate under a variety of Neber reaction conditions and isolated and characterized many of the by-products. In one experiment they found that the addition of a small quantity of water to the reaction mixture gave a greatly reduced yield (29%) of the α-amino ketone with a large increase in the yield (48%) of Beckmann rearrangement product.

Employing ethanol as solvent no substantial difference was observed between the yields obtained when using either sodium or potassium ethoxide as base (63 and 64%, respectively). Slightly reduced yields were obtained when using alcoholic benzene as the solvent (54, 53%). With methanol alone as solvent and potassium methoxide as base, a very low yield (4%) of α-amino ketone and a very high yield (81%) of Beckmann rearrangement product resulted. However, the quality of the methanol for this single experiment was not described.

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