THE NEF REACTION

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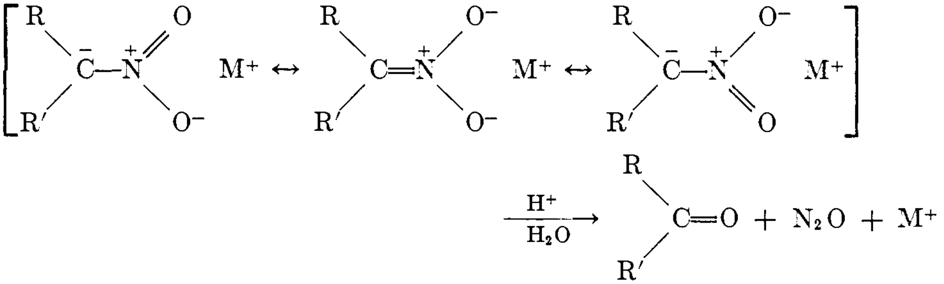
I. INTRODUCTION

A. DEFINITION OF THE NEF REACTION

The Nef reaction is the acid hydrolysis of a salt of a primary or secondary nitroalkane to yield an aldehyde or a ketone, respectively, and nitrous oxide.

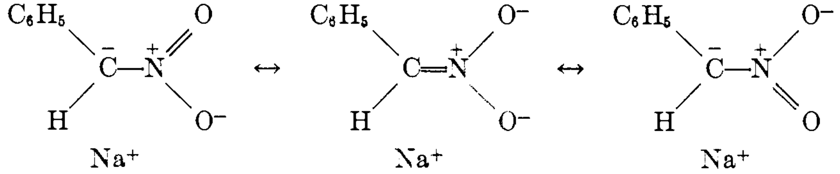


R and R′ are hydrogen, alkyl, or aryl; M^+ is a cation.

The addition of sodium acetylides to aldehydes and ketones, yielding acetylenic carbinols, is also occasionally referred to as the Nef reaction, since the first example was reported by Nef in 1899 (42). Use of the same name for two different reactions is confusing; hence it is proposed that the term "Nef reaction" be restricted to the reaction discussed in this review, since its discovery has a priority of five years.

B. NOMENCLATURE OF SALTS OF NITROALKANES

Salts obtained by the treatment of nitroalkanes, or their aci-forms, with bases, or by subsequent replacement of one cation by another, have been named as salts of nitroalkanes or of the corresponding aci-nitroalkanes. Thus, the salt obtained by the treatment of phenylnitromethane, or aci-phenylnitromethane (isophenylnitromethane or phenylmethanenitronic acid), with sodium hydroxide could be named in any of the following ways: (*1*) the sodium salt of phenylnitromethane, (*2*) sodiophenylnitromethane, (*3*) the sodium salt of aci-phenylnitromethane, (*4*) the sodium salt of isophenylnitromethane, or (*5*) sodium phenylmethanenitronate.



There is a single anion derived from either a nitroalkane or its aci-form. This anion is best described as a resonance hybrid of three principal forms having the least charge separation, as shown above for the sodium salt of phenylnitromethane. The negative charge of the anion is confined neither entirely to carbon nor to oxygen, though it seems reasonable to believe that the major part of the charge is on the more electronegative oxygen atoms. Hence, it does not seem desirable to name the anion as being specifically derived from either the nitroalkane or its aci-form. It is proposed that the first two types of names, as shown for the sodium salt of phenylnitromethane, are the least specific and therefore the most desirable. Since the second type of name is shorter, it will be used wherever convenient.

C. HISTORICAL

In 1893 Konovalov (29, 30) reported that treatment of potassio-1-phenylnitroethane with dilute sulfuric, nitric, or acetic acid, or even passage of carbon dioxide into an alcoholic solution of the potassium salt, yielded a mixture of the desired 1-phenylnitroethane and acetophenone. Only when hydrogen sulfide was passed into an aqueous solution of the potassium salt was the nitro compound set free without the formation of acetophenone.

In 1894 Nef (41), evidently unaware of Konovalov's report of the previous year, described the hydrolysis by cold acid of the sodium salts of nitroethane, 2-nitropropane, and nitromethane. A careful study of the products showed that addition of dilute (1:10 by volume) aqueous sodionitroethane to cold dilute (1:5) sulfuric acid gave an 85–89 per cent yield of nitrous oxide and at least a 70 per cent yield of acetaldehyde, for which the analytical method was less satisfactory. Acetic acid, hydroxylamine sulfate, and nitrous acid were identified as byproducts. Wholly analogous results were obtained with dilute hydrochloric acid. Acidification of sodionitroethane always produced a transient green color and considerable evolution of heat. Very slow reverse addition of dilute sulfuric or hydrochloric acid to an aqueous solution of potassio- or sodionitroethane regenerated considerable nitroethane, besides yielding the hydrolysis product, acetaldehyde. The mercuric chloride salt of nitroethane was best hydrolyzed with cold dilute hydrochloric acid (instead of nitric or sulfuric acid); this hydrolysis was accompanied by the vigorous evolution of heat and the development of a green color, and yielded 96–98 per cent of nitrous oxide and 73 per cent of acetaldehyde. Hydroxylamine hydrochloride and nitrous acid were identified as byproducts. Addition of an aqueous solution of the alcoholate of sodionitromethane to dilute sulfuric or hydrochloric acid yielded 7.5 per cent nitrous oxide, formaldehyde, carbon dioxide, a salt of hydroxylamine, and nitrous acid. Addition of an aqueous solution of sodio-2-nitropropane to dilute sulfuric acid produced the usual blue-green color and yielded 67 per cent of nitrous oxide and acetone.

Nef showed the generality of the reaction which he had independently discovered, and made a careful study of the conditions and the products; hence, even though an example of the reaction was reported a year earlier by Konovalov, it has become known as the "Nef reaction."

II. SYNTHETIC APPLICATIONS

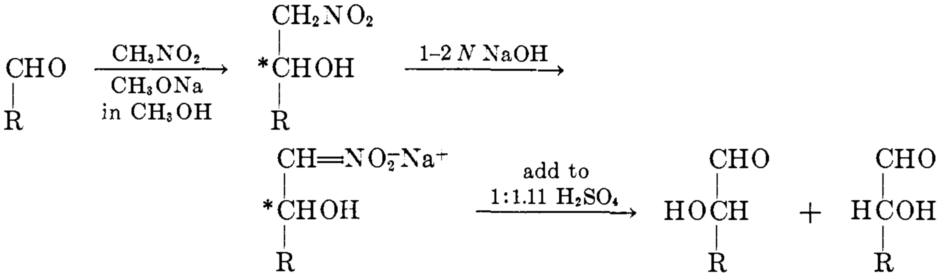
The Nef reaction has achieved considerable importance in organic synthesis in recent years, because of the commercial availability of many nitroalkanes.

A. SYNTHETIC APPLICATIONS TO CARBOHYDRATE CHEMISTRY

Currently, the most important applications of the Nef reaction seem to be in carbohydrate chemistry, as the result of the work of Sowden and Fischer. These applications were reviewed by Sowden (60) in 1951 and will be described only briefly here.

1. *The nitromethane synthesis*

The nitromethane synthesis is a simple and very efficient way of increasing by one the number of carbon atoms in an aldose. The base-catalyzed condensa-



$$\begin{array}{c} \mathrm{CHO} \\ | \\ \mathrm{R} \end{array} \xrightarrow[\mathrm{CH_3ONa}\ \text{in}\ \mathrm{CH_3OH}]{\mathrm{CH_3NO_2}} \begin{array}{l} \mathrm{CH_2NO_2} \\ | \\ {}^{*}\mathrm{CHOH} \\ | \\ \mathrm{R} \end{array} \xrightarrow{1\text{-}2\ N\ \mathrm{NaOH}} \begin{array}{l} \mathrm{CH{=}NO_2^-Na^+} \\ | \\ {}^{*}\mathrm{CHOH} \\ | \\ \mathrm{R} \end{array} \xrightarrow{\text{add to}\ 1{:}1.11\ \mathrm{H_2SO_4}} \begin{array}{c} \mathrm{CHO} \\ | \\ \mathrm{HOCH} \\ | \\ \mathrm{R} \end{array} + \begin{array}{c} \mathrm{CHO} \\ | \\ \mathrm{HCOH} \\ | \\ \mathrm{R} \end{array}$$

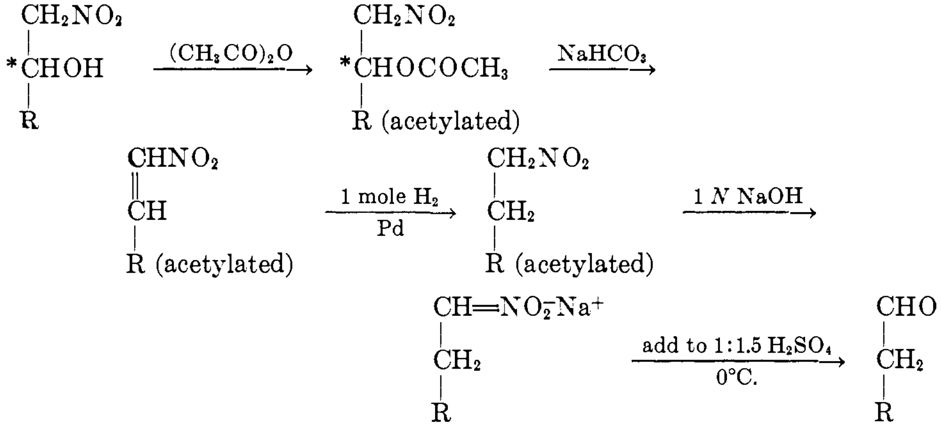
R is the remainder of the original aldose.

tion of nitromethane with an aldose yields a mixture of two epimeric 1-nitro-1-desoxy sugar alcohols, the ratio of which usually differs somewhat from that in the older cyanohydrin synthesis, thus allowing for the synthesis of stereoisomeric aldoses not readily accessible by the latter method. The Nef reaction on the sodio-1-nitro-1-desoxy sugar alcohols then yields the aldoses containing one more carbon atom than the starting material.

An example of the nitromethane synthesis is the preparation of 1-C^{14}-D-mannose and 1-C^{14}-D-glucose from D-arabinose and C^{14}-nitromethane (55, 56).

2. *The 2-desoxyaldose synthesis*

An extension of the nitromethane synthesis is the 2-desoxyaldose synthesis. The *C*-nitroalcohols obtained in the first step of the nitromethane synthesis are acetylated. Dehydroacetylation through the Schmidt and Rutz reaction (54) yields a 1-nitroölefin, which is reduced with one mole of hydrogen to the corresponding acetylated 1-nitro-1,2-didesoxy sugar alcohol. The Nef reaction on the sodium salt, and concurrent deacetylation, yields a 2-desoxyaldose.



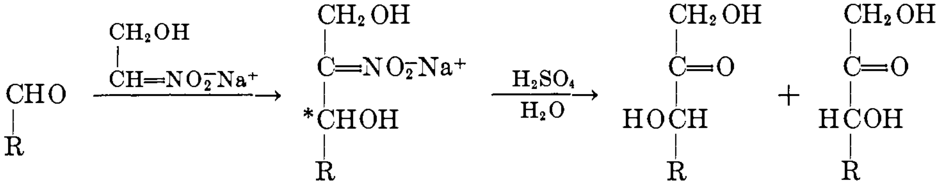
$$\begin{array}{l}CH_2NO_2\\ |\\ {}^*CHOH\\ |\\ R\end{array} \xrightarrow{(CH_3CO)_2O} \begin{array}{l}CH_2NO_2\\ |\\ {}^*CHOCOCH_3\\ |\\ R\text{ (acetylated)}\end{array} \xrightarrow{NaHCO_3} \begin{array}{l}CHNO_2\\ \|\\ CH\\ |\\ R\text{ (acetylated)}\end{array} \xrightarrow[Pd]{1\text{ mole }H_2} \begin{array}{l}CH_2NO_2\\ |\\ CH_2\\ |\\ R\text{ (acetylated)}\end{array} \xrightarrow{1\,N\text{ NaOH}} \begin{array}{l}CH{=}NO_2^-Na^+\\ |\\ CH_2\\ |\\ R\end{array} \xrightarrow[0°C.]{\text{add to }1:1.5\ H_2SO_4} \begin{array}{l}CHO\\ |\\ CH_2\\ |\\ R\end{array}$$

R is the remainder of the original aldose.

An example of the 2-desoxyaldose synthesis is the conversion of 2,4-benzylidene-D-erythrose to D-erythro-2-desoxypentose, the natural sugar occurring in the "desoxyribose" nucleic acids (57, 58).

3. *The 2-nitroethanol synthesis*

A means of converting an aldose to ketoses containing two more carbon atoms is provided by the 2-nitroethanol synthesis. The base-catalyzed condensa-



$$\begin{array}{l}CHO\\ |\\ R\end{array} \xrightarrow{\begin{array}{l}CH_2OH\\ |\\ CH{=}NO_2^-Na^+\end{array}} \begin{array}{l}CH_2OH\\ |\\ C{=}NO_2^-Na^+\\ |\\ {}^*CHOH\\ |\\ R\end{array} \xrightarrow[H_2O]{H_2SO_4} \begin{array}{c}CH_2OH\\ |\\ C{=}O\\ |\\ HOCH\\ |\\ R\end{array} + \begin{array}{c}CH_2OH\\ |\\ C{=}O\\ |\\ HCOH\\ |\\ R\end{array}$$

R is the remainder of the original aldose.

tion of 2-nitroethanol with an aldose yields a mixture of two epimeric sodio-2-nitro-2-desoxy sugar alcohols. These salts are subjected directly to the Nef reaction, yielding ketoses containing two more carbon atoms than the starting material.

By means of the 2-nitroethanol synthesis D-arabinose has been converted to D-mannoheptulose and D-glucoheptulose (59).

B. GENERAL SYNTHETIC APPLICATIONS

1. Simple aldehydes and ketones

The yields of simple aldehydes and ketones by the Nef reaction from the corresponding sodionitroalkanes are generally very good (22, 41), except with nitromethane (41). Where steric hindrance appears to be an important factor, however, as in the preparation of isobutyraldehyde, the yields are markedly reduced. Johnson with Degering (21, 22) obtained the following carbonyl compounds (isolated by conversion to the oximes) from the corresponding sodio- or calcionitroalkanes by adding the alkaline solutions to ice-cold dilute (1:6.4) sulfuric acid:

Carbonyl Compound	Yield	Carbonyl Compound	Yield
	per cent		*per cent*
CH_3CHO	77	$(CH_3)_2CHCHO$	36
CH_3CH_2CHO	80	CH_3COCH_3	84
$CH_3CH_2CH_2CHO$	85	$CH_3CH_2COCH_3$	85

Sodio-2-nitroöctane yields 2-octanone with cold 4 *N* hydrochloric acid (32), and sodio-1-nitro-2,2-dimethylpropane yields pivalaldehyde in unstated yield with dilute (1:6.7) sulfuric acid at 0°C. (19).

Mahler (35) has made a detailed study of factors influencing the yield of propionaldehyde (determined by titration with hydroxylamine) which is obtained by the dropwise addition of 12 ml. of a 17 per cent solution of 1-nitropropane in a 1.7 *N* solution of sodium hydroxide in 18 per cent ethanol to 20 ml. of acid. The maximum yield was obtained with 17 *N* sulfuric acid, as shown in the table below:

Normality of Sulfuric Acid	Temperature	Yield of Propionaldehyde	Normality of Sulfuric Acid	Temperature	Yield of Propionaldehyde
N	°C.	*per cent*	*N*	°C.	*per cent*
4	−5	58	17	+25	35
8	−10	72	28	−15	70
17 (1:1.12)	−15	75	36	−15	63
	+5	41			

The yield varied little with 8 *N* or 28 *N* acid, but at lower or higher acidities the yield decreased; higher temperatures also markedly reduced the yield. The yield with concentrated (12 *N*) hydrochloric acid was 74 per cent at −15°C., showing that the anion present has little, if any, effect upon the yield. The yield from 1-desoxy-1-nitromannitol was also reduced by using higher temperatures, being 62 per cent in 17 *N* sulfuric acid at −15°C. and 36 per cent at 25°C. With 1-nitropropane slower stirring or faster addition reduced the yield, probably owing to localized heating or reduced acidity. Addition of the acid to the alkaline solution of the nitroalkane also reduced the yield, probably because of low acidity during much of the reaction.

Even though the yields are good, the preparation by the Nef reaction of simple aldehydes and ketones obtainable in other ways is uneconomic, since it requires the introduction and subsequent loss of nitrogen.

Leitch (33) has prepared acetaldehyde containing over 95 mole per cent of 1-*d*-acetaldehyde in about 34 per cent yield from the Nef reaction of sodionitroethane containing 45 mole per cent of sodio-1-d_2-nitroethane.

$$CH_3CH_2NO_2 + D_2O \xrightarrow[90^\circ C.]{CH_3COONa}$$

$$CH_3CD_2NO_2 \xrightarrow[H_2SO_4\text{ at }0\text{–}5^\circ C.]{\substack{(1)\ 10\%\ NaOH \\ (2)\ \text{Add to }1{:}13.3}} CH_3CDO$$

It was suggested that the Nef reaction is a practical route to aldehydes labelled with isotopic hydrogen in the 1-position.

2. γ-Keto acids and sulfones

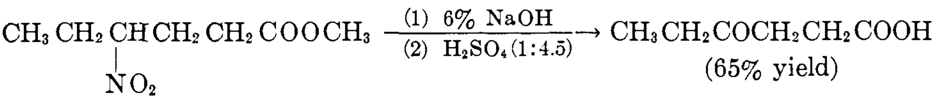
The Nef reaction is part of a practical route to γ-keto acids. The Michael addition of primary nitroalkanes to acrylic esters yields γ-nitro esters, which are then saponified, with simultaneous formation of the sodium salt at the nitro group. Addition of the alkaline solution to cold dilute (1:4.5) sulfuric acid gives the γ-keto acid in good yield. Examples of such syntheses are reported by von Schickh and Griesshaber (53)

$$CH_3NO_2 + 2CH_2{=}CHCOOR \xrightarrow{\text{base}} O_2NCH(CH_2CH_2COOR)_2$$

$$\xrightarrow[(2)\ H^+,\ H_2O]{(1)\ OH^-,\ H_2O} O{=}C(CH_2CH_2COOH)_2$$

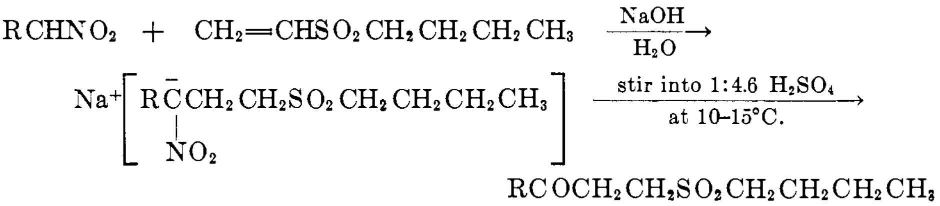
and by Kloetzel (27).

$$CH_3CH_2CH_2NO_2 + CH_2{=}CHCOOCH_3 \xrightarrow{(C_2H_5)_3N}$$



$$\underset{\displaystyle NO_2}{CH_3CH_2CHCH_2CH_2COOCH_3} \xrightarrow[(2)\ H_2SO_4(1{:}4.5)]{(1)\ 6\%\ NaOH} \underset{(65\%\text{ yield})}{CH_3CH_2COCH_2CH_2COOH}$$

Quite analogous to the preparation of γ-keto acids is the preparation of γ-keto sulfones reported by Buckley, Charlish, and Rose (6). The base-catalyzed addition of primary nitroalkanes to vinyl sulfones yields γ-nitro sulfone salts. Stirring the alkaline solutions into cool dilute (1:4.6) sulfuric acid gives the γ-keto sulfones in excellent yield.



$$RCHNO_2 + CH_2{=}CHSO_2CH_2CH_2CH_2CH_3 \xrightarrow[H_2O]{NaOH}$$

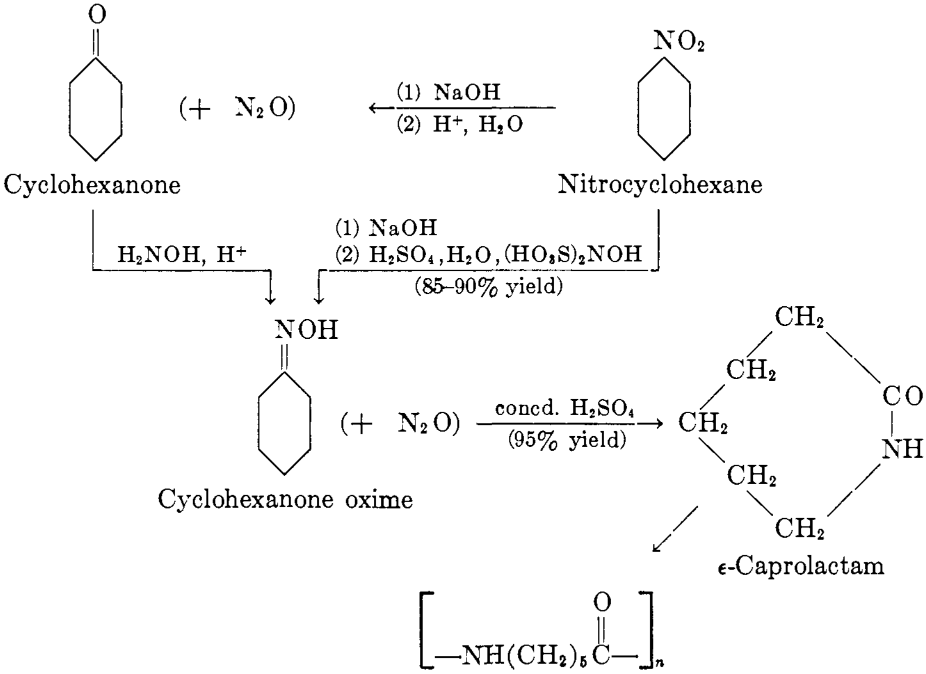
$$Na^+\left[R\overset{-}{\underset{NO_2}{C}}CH_2CH_2SO_2CH_2CH_2CH_2CH_3\right] \xrightarrow[\text{at 10–15°C.}]{\text{stir into 1:4.6 } H_2SO_4}$$

$$RCOCH_2CH_2SO_2CH_2CH_2CH_2CH_3$$

$R = CH_3$, 84% yield
$R = C_2H_5$, 86% yield

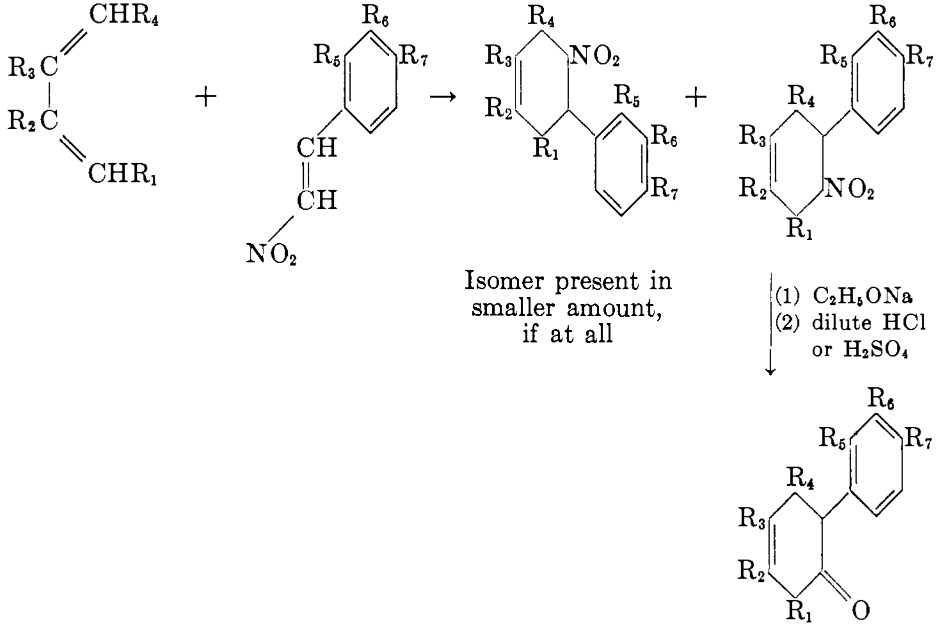
3. Cyclohexanone

von Schickh has converted nitrocyclohexane into cyclohexanone in very good yield through the Nef reaction (53). Cyclohexanone oxime can be converted by a Beckmann rearrangement into ϵ-caprolactam (23), an important starting material for Nylon-type superpolyamides (12). A variation of the preparation of cyclohexanone by the Nef reaction is the direct conversion to cyclohexanone oxime in 85–90 per cent yield (40). A cold solution of nitrocyclohexane in a slight excess of aqueous sodium hydroxide is added to cold dilute sulfuric acid containing hydroxylamine disulfonate.



4. Other cyclic ketones

The Diels–Alder reaction of 1-nitroölefins provides a large number of potentially ketonic compounds to which the Nef reaction can be applied. Numerous 4-nitro-5-phenylcyclohexenes derived from butadienes and β-nitrostyrenes have been subjected to the Nef reaction. The yields are shown in table 1.



The cyclohexenones from the Nef reaction can be catalytically hydrogenated to the corresponding cyclohexanones (68). An alternate route to substituted cyclohexanones is through the corresponding nitrocyclohexanes (4). In this method care must be taken during catalytic hydrogenation of the double bond

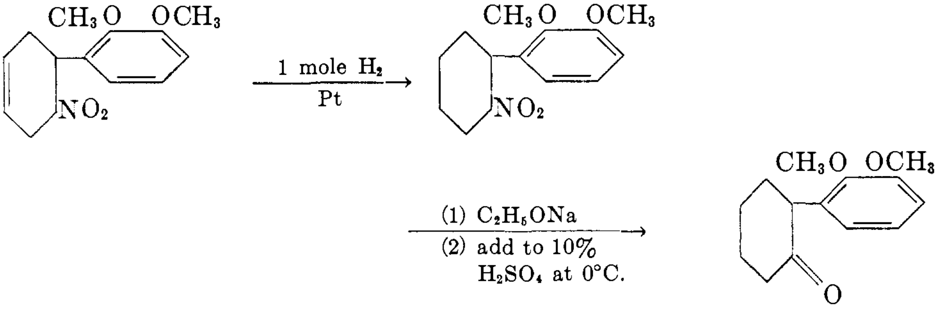
TABLE 1

Yields in the Nef reaction of 4-nitro-5-phenylcyclohexenes

Substituents, if Different from H							Yield	References
R_1	R_2	R_3	R_4	R_5	R_6	R_7		
							per cent	
							78	(68)
					CH_3O		87	(68)
						CH_3O	88	(68)
				CH_3O	CH_3O		83	(4, 68)
			CH_3				33	(69)
		CH_3					$\sim$80*	(69)
		CH_3				CH_3O	69	(69)
	CH_3						$\sim$80*	(69)
	CH_3					CH_3O	90	(69)
CH_3							35	(69)
	CH_3	CH_3					50	(68)
	CH_3	CH_3				CH_3O	89	(69)

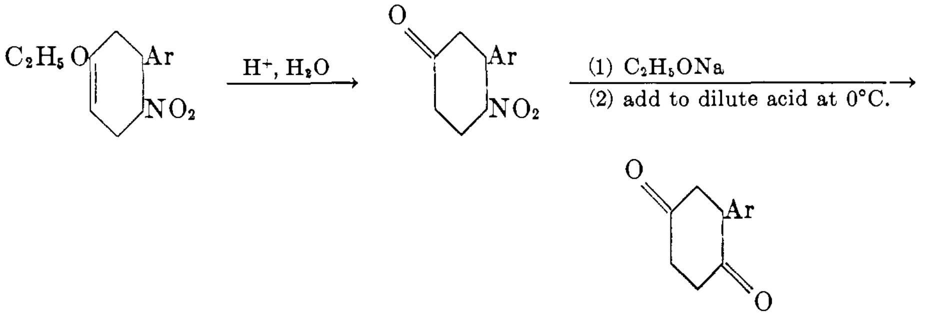
* The reaction was carried out on the mixture of isomeric Diels–Alder adducts. The combined yield from the Nef reaction was 80 per cent, representing 65 per cent 4-methyl-6-phenyl-3-cyclohexen-1-one and 15 per cent 3-methyl-6-phenyl-2-cyclohexen-1-one.

of the 4-nitrocyclohexene to avoid concomitant reduction of the nitro group.



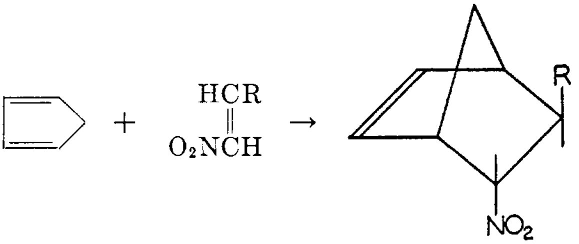
(56% yield)

A route to 1,4-cyclohexanediones is provided by the Diels–Alder reaction of 2-ethoxybutadiene with a nitroölefin, subsequent hydrolysis of the enol ether, and the Nef reaction on the sodio-4-nitrocyclohexanone.



Ar = C_6H_5, 43% yield (69)
Ar = 2,3-$(CH_3O)_2C_6H_3$, 17% yield (4)

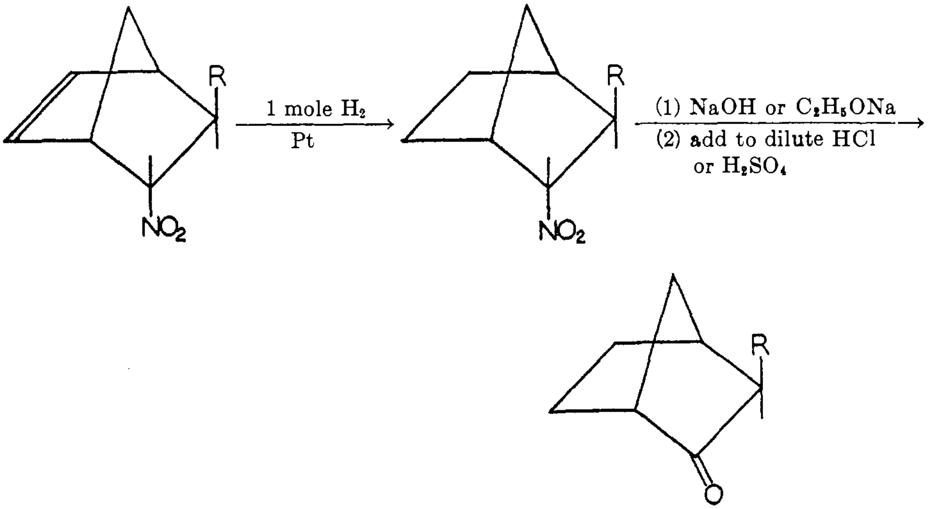
In contrast to the successful Nef reactions with 4-nitrocyclohexenes, all attempts to carry out Nef reactions with Diels–Alder adducts of cyclopentadiene and 1-nitroölefins have failed.



Parham, Hunter, and Hanson (50) first reported the failure of the Nef reaction with the 5-nitrobicyclo[2.2.1]hept-2-enes. Where R is C_6H_5, a non-ketonic oil was obtained, which appeared to be principally unchanged nitro compound.

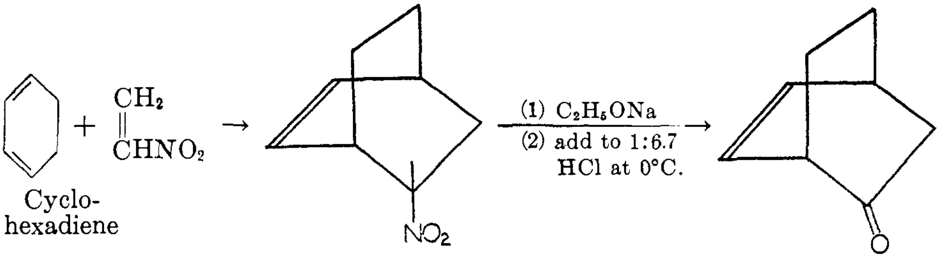
Where R is CH_3, Van Tamelen and Thiede (64) obtained an oily material which could not be separated into pure components by crystallization or chromatography. Wildman and Hemminger (65) reported that, where R is H, no ketonic material was isolated from an attempted Nef reaction. With the mild acid, acetic acid, and urea (31), McVeigh (37) regenerated the original compound, where R is H, in about 60 per cent yield.

The Nef reaction occurs normally with 2-nitrobicyclo[2.2.1]heptanes, obtained by reduction of the double bond of 5-nitrobicyclo[2.2.1]hept-2-enes.



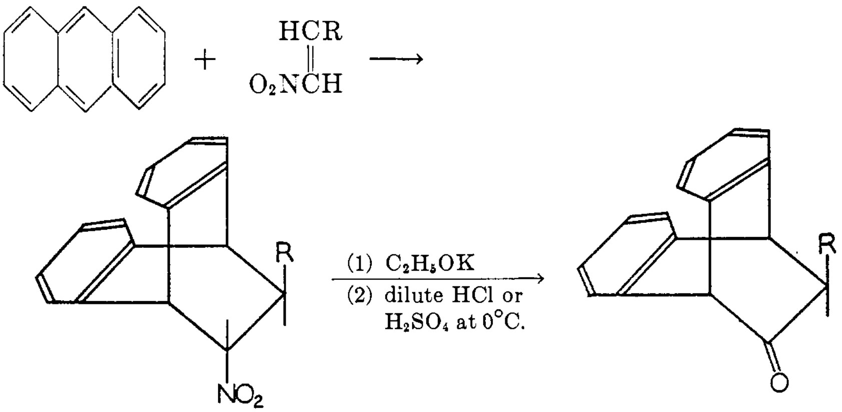
R = H, 40% crude and 14% pure yield (65)
R = CH_3, 51% yield (64)
R = C_6H_5, 71% yield as 2,4-dinitrophenylhydrazone (65)

Wildman and Saunders (67) have found that, unlike the 5-nitrobicyclo[2.2.1]hept-2-enes, the Nef reaction proceeds normally with the next higher homolog, 5-nitrobicyclo[2.2.2]oct-2-ene, the Diels–Alder adduct of cyclohexadiene and nitroethylene.



(68% yield)

Similarly, Noland (45) and Freeman (10) have obtained Nef reactions with Diels–Alder adducts of anthracene and 1-nitroölefins.

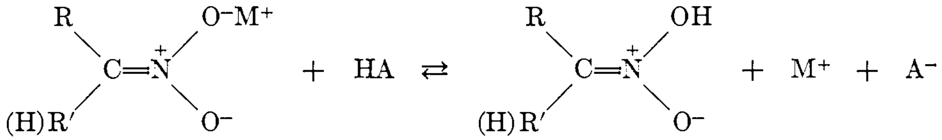


R = H, 87% yield (10)
R = C_6H_5, good yield as
2,4-dinitrophenylhydrazone (45)

III. Mechanism

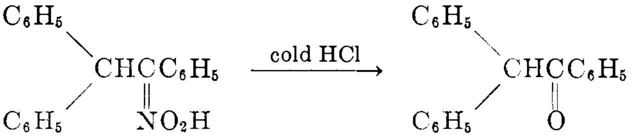
A. NITRONIC ACIDS AS INTERMEDIATES

As is generally true when salts of acids are treated with other acids, acidification of salts of nitroalkanes immediately produces the equilibrium concentration of the corresponding nitronic acids.



$$\mathrm{R(H)R'C{=}\overset{+}{N}(O^-M^+)O^-} + \mathrm{HA} \rightleftarrows \mathrm{R(H)R'C{=}\overset{+}{N}(OH)O^-} + \mathrm{M^+} + \mathrm{A^-}$$

Nitronic acids have been isolated in a number of cases (1, 3, 9, 13, 14, 18, 28, 30) where they are quite stable and are of sufficiently high molecular weight to be insoluble in the aqueous acid in which they are usually formed. Since nitronic acids are immediately formed upon acidification of salts of nitroalkanes, it is generally assumed that they are intermediates in the Nef reaction. This assumption is supported by direct evidence. Kohler and Stone (28) converted a nitronic acid in ether solution into a 97 per cent yield of practically pure ketone by treatment with cold concentrated hydrochloric acid.



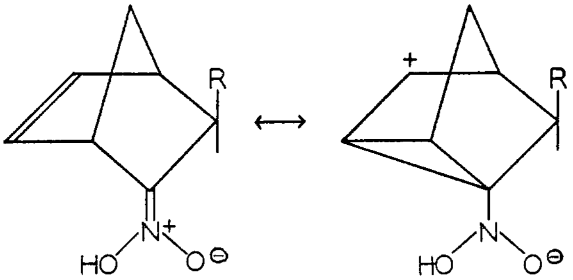
$$\mathrm{(C_6H_5)_2CHC({=}NO_2H)C_6H_5} \xrightarrow{\text{cold HCl}} \mathrm{(C_6H_5)_2CHC({=}O)C_6H_5}$$

Nitronic acids are appreciably ionized in aqueous solution. Their rates of tautomerization through the anion have been studied both conductimetrically

(5, 14, 15, 17, 36, 51) and titrimetrically (26). The extent to which nitronic acids tautomerize to nitroalkanes instead of undergoing the Nef reaction is dependent upon the stability of the nitronic acid and the acidity of the medium. Kornblum and Graham (31), in a careful study of optimum conditions for regenerating nitroalkanes from their salts, have cited numerous examples to show that resonance stabilization of the nitronic acid favors tautomerization to the nitroalkane. In favorable cases, such as phenylmethanenitronic acid, even strong acids can be used successfully to regenerate nitroalkanes from their salts. In general, nitronic acids having no unusual stability tautomerize to nitroalkanes in good yield only in weak acid and at low temperature, while stronger acid and higher temperature favor the Nef reaction. For regenerating nitroalkanes from their salts hydroxylamine hydrochloride or urea in aqueous acetic acid was found to be very efficient. Not only are they weak acids but they also rapidly destroy the nitrous acid resulting from nitrite ion formed by prior air oxidation of nitroalkane salts in alkaline solution.

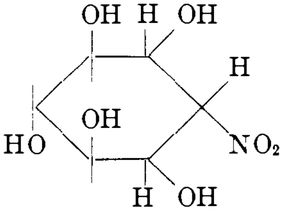
B. CASES WHERE THE NEF REACTION FAILS

Wildman and Saunders (67) have suggested that homoallylic resonance involving a form having the nortricyclene structure may account for the failure of the 5-nitrobicyclo[2.2.1]hept-2-enes to undergo the Nef reaction.

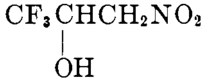


It was pointed out that in the bicyclo[2.2.2]oct-2-ene series, where the Nef reaction does occur, no tricyclic derivatives homologous with nortricyclene are known (66, 67), suggesting that similar resonance may be lacking in this case.

Other cases where the Nef reaction has failed include the nitrodesoxyinositols, which were recovered unchanged (11, 20).



Cook, Pierce, and McBee (8) have reported no success in obtaining Nef reactions with fluorinated nitroalcohols or nitroalkanes such as 1-nitro-3,3,3-trifluoro-2-propanol and 1-nitro-3,3,4,4,5,5,5-heptafluoropentane.



$$\begin{array}{l}CF_3\overset{}{C}HCH_2NO_2\\ \;\;\;\;|\\ \;\;\;OH\end{array}$$

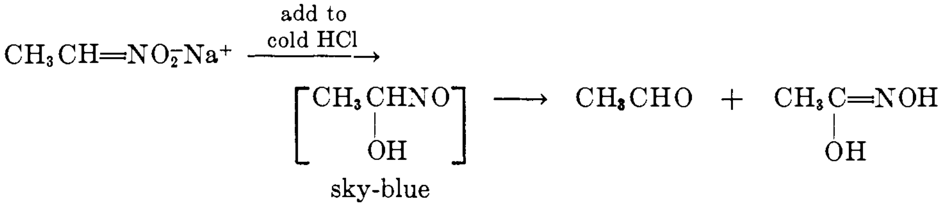
$CF_3CF_2CF_2CH_2CH_2NO_2$

These examples suggest that electrostatic or inductive effects may affect the success of Nef reactions. Van Tamelen and Thiede (64) have suggested that steric hindrance to attack of water at the carbon bearing the double bond in the nitronic acid inhibits the Nef reaction. The low yield (32 per cent) from sodio-1-nitro-2-methylpropane (22) and the failure of the Nef reaction with the salt of 4,4-dimethyl-5-nitro-2-pentanone were cited as examples (64). Sodio-1-nitro-2,2-dimethylpropane, however, does undergo the Nef reaction, although the yield was not reported (19).

C. NITROSO COMPOUNDS AS INTERMEDIATES

The appearance of a transient blue or green color appears to be universally associated with Nef reactions (1, 7, 27, 33, 41, 63, 64, 65, 68, 69). In related reactions the blue color has been attributed by some workers (24, 61) to monomeric forms of nitrolic acids or pseudonitroles, which are frequent byproducts of the Nef reaction. The constant appearance of this color suggests strongly, however, that it is an integral part of the Nef reaction.

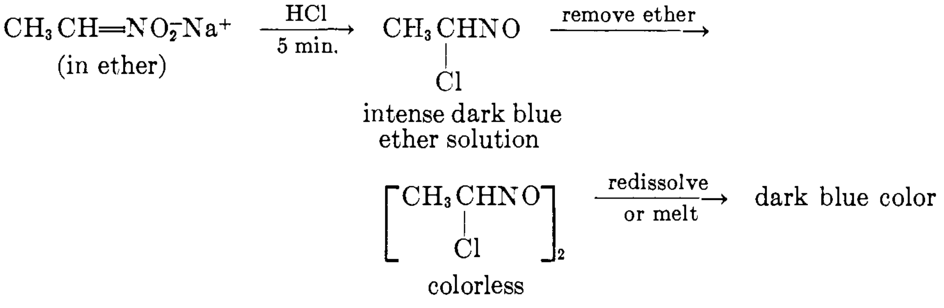
The appearance of a sky-blue color and a pseudonitrolish odor, when sodionitroethane was added to cold hydrochloric acid, led Bamberger and Rüst (1) to postulate the temporary presence of a nitroso compound, 1-nitrosoethanol.



$$CH_3CH{=}NO_2^-Na^+ \xrightarrow{\text{add to cold HCl}} \underset{\text{sky-blue}}{\left[\begin{array}{c}CH_3CHNO\\ |\\ OH\end{array}\right]} \longrightarrow CH_3CHO + \begin{array}{c}CH_3C{=}NOH\\ |\\ OH\end{array}$$

Bamberger (2) had previously postulated 1-nitrosoethanol as a product of ethanenitronic acid to account for the transient, ether-soluble, sky-blue color and pungent odor which appeared when acetaldoxime was mixed with permonosulfuric acid. Likewise, the transient sky-blue color and pungent odor obtained under similar conditions with acetoxime was attributed to 2-nitroso-2-propanol.

Though 1-nitroso-1-alkanols have never actually been isolated from Nef

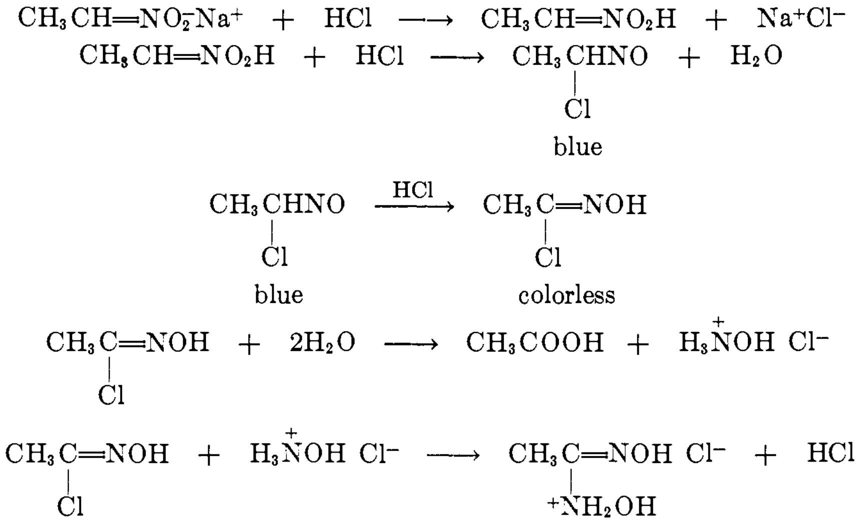


$$\underset{\text{(in ether)}}{CH_3CH{=}NO_2^-Na^+} \xrightarrow[\text{5 min.}]{\text{HCl}} \underset{\text{intense dark blue ether solution}}{\begin{array}{c}CH_3CHNO\\ |\\ Cl\end{array}} \xrightarrow{\text{remove ether}}$$

$$\underset{\text{colorless}}{\left[\begin{array}{c}CH_3CHNO\\ |\\ Cl\end{array}\right]_2} \xrightarrow[\text{or melt}]{\text{redissolve}} \text{dark blue color}$$

reactions, a closely related compound, 1-chloro-1-nitrosoethane (as the dimer), was isolated by Steinkopf and Jürgens (63) after passing hydrogen chloride for 5 min. into a dilute ether suspension of sodionitroethane.

Passing hydrogen chloride into the ether suspension for a longer time caused disappearance of the blue color. After long standing the solution deposited a small amount of what appeared to be acethydroxamic hydroxamide hydrochloride, the formation of which can be attributed to tautomerization of the initially formed blue 1-chloro-1-nitrosoethane to colorless acethydroxamyl chloride, followed by hydrolysis and subsequent reactions.



$$CH_3CH{=}NO_2^-Na^+ + HCl \longrightarrow CH_3CH{=}NO_2H + Na^+Cl^-$$

$$CH_8CH{=}NO_2H + HCl \longrightarrow \underset{\text{blue}}{CH_3\underset{\underset{Cl}{|}}{C}HNO} + H_2O$$

$$\underset{\text{blue}}{CH_3\underset{\underset{Cl}{|}}{C}HNO} \xrightarrow{HCl} \underset{\text{colorless}}{CH_3\underset{\underset{Cl}{|}}{C}{=}NOH}$$

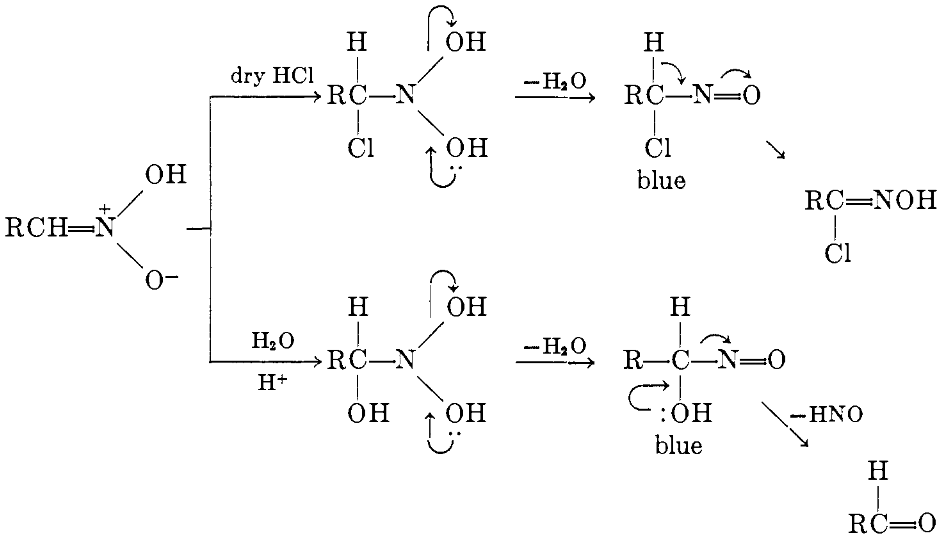
$$CH_3\underset{\underset{Cl}{|}}{C}{=}NOH + 2H_2O \longrightarrow CH_3COOH + H_3\overset{+}{N}OH\ Cl^-$$

$$CH_3\underset{\underset{Cl}{|}}{C}{=}NOH + H_3\overset{+}{N}OH\ Cl^- \longrightarrow CH_3\underset{\underset{^+NH_2OH}{|}}{C}{=}NOH\ Cl^- + HCl$$

Hydrogen chloride treatment of sodionitromethane and sodio-1-nitropropane also gave blue ether solutions, but, unlike the case with sodionitroethane, the colorless oils from evaporation of the ether could not be induced to yield crystalline dimers. Treatment of sodiophenylnitromethane or phenylmethanenitronic acid with hydrogen chloride causes the slow formation and disappearance of a blue color, with almost quantitative formation of benzhydroxamyl chloride (44, 63). Steinkopf and Jürgens (63) suggested that intermediate nitroso compounds may also account for the blue colors obtained by Hantzsch and Schultze (14) with phenylmethanenitronic acid and acetyl chloride or hydrogen chloride, and by Hantzsch and Veit (15) with nitronic acids and phosphorus pentachloride or phenyl isocyanate. The green color obtained by Nef and Jones (24, 43) with sodionitroethane and benzoyl chloride, and the bright blue color obtained by Stefl and Dull (61) with sodio-2-nitropropane and acetic or propionic anhydride, may perhaps be similarly accounted for.

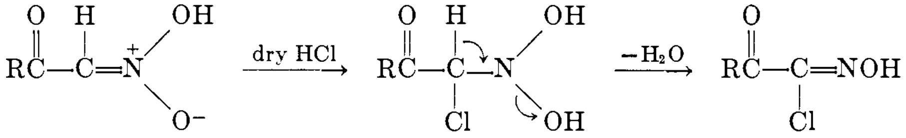
Although reactions of salts of primary nitroalkanes with dry hydrogen chloride or acid chlorides are not true Nef reactions, since they give hydroxamic acid derivatives (18, 24, 43, 44, 63) instead of aldehydes, nevertheless the two reactions are very similar up through the attachment of a nucleophilic group (such as chloride ion or the hydroxyl ion from water) to the reacting carbon.

The similarity of the two reactions led Nametkin (39) to propose parallel mechanisms for them (translated into more modern electronic terms):



Leitch (33) has recently proposed the same mechanism for the Nef reaction.

In those cases where the reacting carbon is attached to a negative group such as carbonyl or cyano, enolization is rapid and the characteristic blue or green color of the nitroso group is never observed (62, 63).



Van Tamelen and Thiede (64) have proposed a mechanism for the Nef reaction in modern electronic terms, comparing it in terms of steric and resonance effects to the hydrolysis of oximes and semicarbazones. They do not, however, account for the transient blue or green color.

D. RELATIONSHIP TO HYDROLYSIS OF PRIMARY NITROALKANES BY STRONG ACID

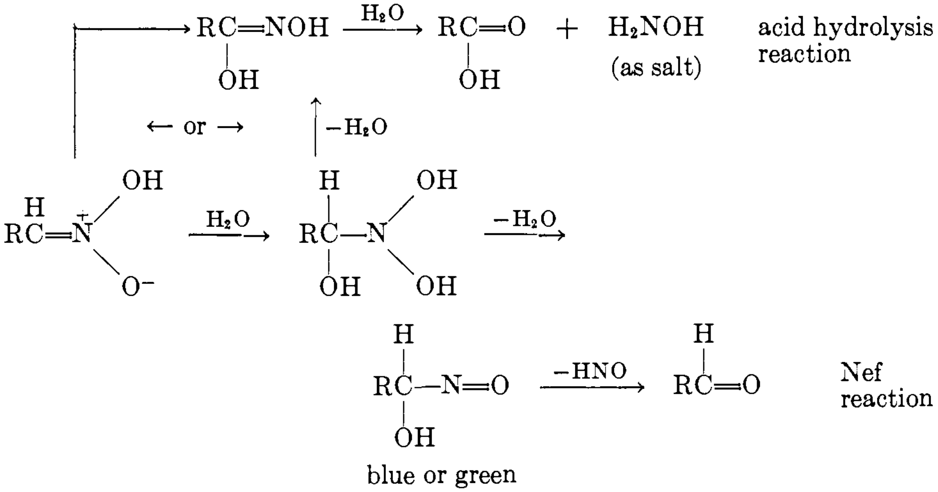
Closely related to the Nef reaction of salts of nitroalkanes is the hydrolysis of free primary nitroalkanes by strong acid to the corresponding carboxylic acids and hydroxylamine salts.

$$RCH_2NO_2 \xrightarrow[H_2O,\ \text{heat}]{\text{strong acid}} RCOOH + H_2NOH\ (\text{salt})$$

This hydrolysis by strong acid, first reported by Meyer and Wurster (38) with nitroethane and sulfuric acid, has been applied to a variety of primary nitroalkanes, using principally sulfuric, hydrochloric, or phosphoric acid. The acid hydrolysis reaction has been reviewed by Lippincott and Hass (34) and Hass and Riley (16), and the related chemistry of hydroxamic acids has been reviewed by Yale (70). Bamberger and Rüst (1) obtained, in addition to carboxylic acids and hydroxylamine sulfate, small amounts of the corresponding hydroxamic acids, which they considered to be intermediates. By reducing the water concentration so as to inhibit complete hydrolysis Lippincott and Hass (34) obtained a 44 per cent yield of the intermediate propionhydroxamic acid when 1-nitropropane was heated in 100 per cent sulfuric acid.

Junell (25) has found the hydrolysis of nitroethane in 1 *N* hydrochloric acid at 69.85°C. to be first order in nitroethane, with a rate constant of 2.5×10^{-4} min.^{-1} The monobromination of nitroethane under the same conditions was also first order in nitroethane and independent of bromine concentration, and had practically the same rate constant, 2.8×10^{-4} min.^{-1} It appears likely, therefore, that the rate-determining step in both acid hydrolysis and monobromination is the enolization of the nitroalkane, and subsequent steps in the acid hydrolysis must be relatively rapid.

No reports of a transient blue or green color have been found in the acid hydrolysis of nitroalkanes. Both the Nef and the acid hydrolysis reactions appear to proceed through the same nitronic acid intermediate, but their paths must deviate prior to the color stage of the Nef reaction. That the two reactions can occur simultaneously under some conditions is shown by the isolation from Nef reactions of small amounts of carboxylic acids and hydroxylamine salts (41) or hydroxamic acids (1). In general, the acid hydrolysis is favored by higher acidity and temperature than the Nef reaction. The Nef reaction on free nitroalkanes is unknown, whereas the hydrolysis by strong acid is normally carried out with free primary nitroalkanes.



There appears to be no evidence pertaining to the mechanism of conversion of nitronic acids to hydroxamic acids. The question remains unanswered as to whether it involves: (*1*) carbon–oxygen bond formation prior to proton loss from carbon, (*2*) proton loss from carbon to give a nitrile oxide,

$$\mathrm{R{-}C{\equiv}\overset{+}{N}{-}O^{-}}$$

followed by carbon–oxygen bond formation, or (*3*) an intramolecular Beckmann-type rearrangement. Similarly, there is no proof that the transient blue or green compound of the Nef reaction, for which the hydroxynitroso structure is favored, is in reality a true intermediate, rather than an alternate intermediate or a substance in a side equilibrium with an intermediate. The universality of the colored compound in the Nef reaction, however, makes it seem most probable that it is a true intermediate.

E. NITROSATION BYPRODUCTS

No review of the Nef reaction is complete without an explanation for the nitrous acid and nitrosation products which are frequently found as byproducts of the Nef (41, 65) and related reactions (3, 15, 24, 43, 63). The formation of nitrolic acids and pseudonitroles during Nef reactions can be prevented by having urea present (31, 65), since it rapidly destroys nitrous acid and does not itself reduce the yield of the Nef reaction (65).

Russell (52) has reported a careful kinetic study of the oxidation by air of 2-nitropropane in basic solution. The data are consistent with an autocatalytic ion-radical chain mechanism, which yields principally nitrite ion and acetone, and small amounts of organic acids, 2,3-dimethyl-2,3-dinitrobutane, and nitrate ion. Sodio-2-nitropropane is readily oxidized by air at 25°C. in 0.5–6.0 N aqueous sodium hydroxide, but only a slow absorption of oxygen occurs in the absence of base or in very concentrated base ($\sim$10 M). The oxidation reaction appears fairly general, although sodiophenylnitromethane does not undergo it. Since the occurrence of this autoxidation reaction has not always been generally realized, few precautions have been taken to exclude air or to use alkaline solutions of nitroalkanes promptly after preparation. Consequently, it is not surprising that acidification of such solutions liberates substantial amounts of nitrous acid and the conditions approximate those used in the preparation of nitrolic acids and pseudonitroles. An application of this autoxidation reaction has been patented by Nygaard, McCracken, and Noland (46, 47, 48, 49) for the preparation from nitroalkanes of nitrolic acids and pseudonitroles, which have proved effective ignition improvers in Diesel-type fuels.

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