THE HYDROXAMIC ACIDS

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I. The Hydroxamic Acids

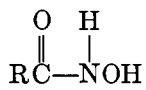
A. FOREWORD

In a paper which appeared in 1869, H. Lossen (167) reported that the reaction between diethyl oxalate and hydroxylamine yielded an acidic compound which he named oxalohydroxamic acid. Later, W. Lossen (169) found that benzoyl chloride and hydroxylammonium chloride gave a mixture of benzohydroxamic acid, benzoyl benzohydroxamate, and dibenzoyl benzohydroxamate. He observed that benzoyl benzohydroxamate when heated above its melting point liberated a lachrymatory substance (phenyl isocyanate), and in this fashion he discovered the reaction now known as the Lossen rearrangement.

$$C_6H_5\overset{\overset{O}{\|}}{C}-\overset{\overset{H}{|}}{N}-O-\overset{\overset{O}{\|}}{C}C_6H_5 \longrightarrow C_6H_5N{=}C{=}O + C_6H_5COOH \qquad (1)$$

The structure of the hydroxamic acids was first brought to the attention of W. Lossen (170) by the observation that the product obtained by the interaction of anisohydroxamic acid and benzoyl chloride was different from the product obtained with benzohydroxamic acid and anisoyl chloride. He introduced the term "metamers" to describe these compounds, erroneously believing that both acyl groups in each compound were attached to the nitrogen atom of the hy-

droxylamine molecule. Later (173), he realized that in the successive acylation of hydroxylamine each of the hydrogens of the hydroxylamine molecule behaved differently from the other two, and as a result of this, proposed the "hydroxyoxime" structure, RC(OH)=NOH, as the correct one. Such a structure served to explain the difference between ethyl benzohydroxamic acid, $C_6H_5C(OC_2H_5)$=NOH, and ethyl benzohydroxamate, $C_6H_5C(OH)$=NOC_2H_5, as well as the hydrolytic products obtained with a variety of acylated and alkylated monohydroxamic acids. He considered the α-, β-, and γ-forms of dibenzoyl benzohydroxamate or the α- and β-forms of ethyl benzohydroxamic acid in each instance as physically different manifestations of the same parent compound. It was at this time that he became considerably involved in a controversy on structure with Werner, Tiemann, and others. Werner (305, 306, 309) presented evidence which indicated that the α- and β-forms of ethyl benzohydroxamic acid were geometric isomers. Tiemann preferred the "hydroxyamide" structure:



Various attempts to prepare compounds of the hydroxyoxime structure demonstrated their instability under conditions known to have little effect on the hydroxamic acids.

To the controversy on the structure of the hydroxamic acids can be attributed the development of Angeli's "nitrosyl" theory. In an effort to establish the structure of these compounds Angeli (1), searching for a new method for their synthesis, succeeded in preparing sodium nitrohydroxamate, $Na_2N_2O_3$. Under certain conditions, this latter compound served as a source of free nitrosyl, NOH.

W. Lossen neglected the development of the rearrangement which bears his name, either as a consequence of his complete occupation with the structure of the hydroxamic acids, or from a lack of interest. He was aware of its similarity to the Hofmann rearrangement (175). Tiemann (290) first suggested the existence of a transitory univalent nitrogen derivative as an intermediate in the rearrangement. This view was enlarged by Stieglitz (280–283) and by Jones (133, 134, 136, 137, 140, 142–148). Jones and his students were concerned also with the effects on the rearrangement of introducing into the molecule certain groups capable of existing as free radicals. The existence of such free radicals was critically studied by Wallis and Moyer (302) and Bell (49). Hauser and his students (57, 105, 247) showed that the velocity of rearrangement with the dihydroxamic acids, RCONHOCOR′, was directly related to the ionization constant of the organic acid (R′COOH) eliminated, if R was kept constant, or indirectly related to the ionization constant of the carboxylic acid RCOOH, if R′ was held the same.

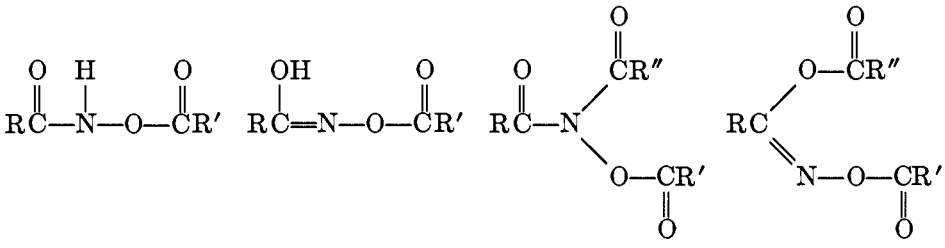
B. NOMENCLATURE

The nomenclature of the hydroxamic acids, particularly in the early literature, had an ambiguity which stemmed directly from the uncertainty regarding their

structure. In this review, it is assumed that the tautomers (I and II) of the monohydroxamic acids are capable of existence.

I II

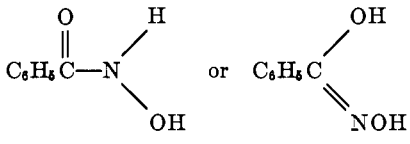
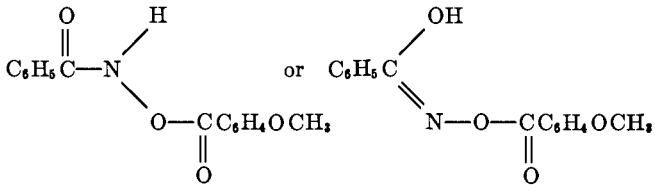
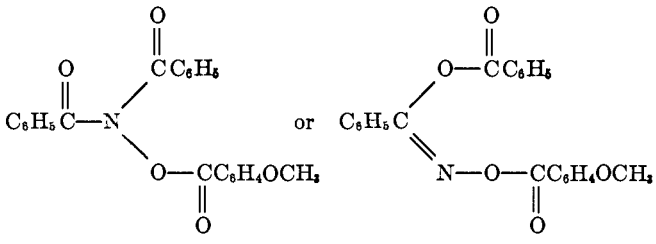
When a monohydroxamic acid is acylated, the first acyl group which enters is attached to oxygen, and is present as shown in the tautomeric forms III and IV; the second acyl group which enters gives rise to two isomeric compounds, V

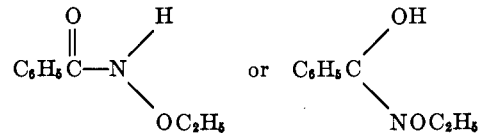
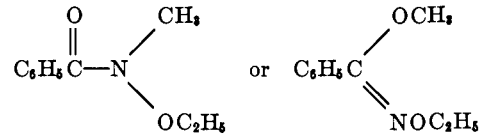
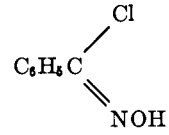
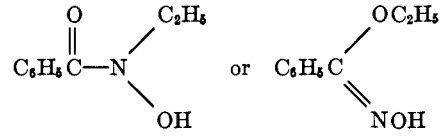


III IV V VI

and VI. When a monohydroxamic acid is alkylated, the order of alkylation and the products possible are similar to those encountered in acylation.

The following are examples of the system of nomenclature used for the hydroxamic acids and their derivatives:

NAME	FORMULA
Benzohydroxamic acid	
Anisoyl benzohydroxamate	
Benzoyl anisoyl benzohydroxamate	

NAME	FORMULA
Ethyl benzohydroxamate	
Methyl ethyl benzohydroxamate	
Benzohydroxamyl chloride	
Ethyl benzohydroxamic acid*	

* This compound has been named arbitrarily to differentiate it from its isomer, ethyl benzohydroxamate. It should be noted that the reaction between an *N*-alkyl(or aryl) hydroxylamine, R'NHOH, and an acyl halide yielded a product of the general formula R'N(OH)COR. This type of compound when so prepared possesses one structure and is named systematically as a member of this group.

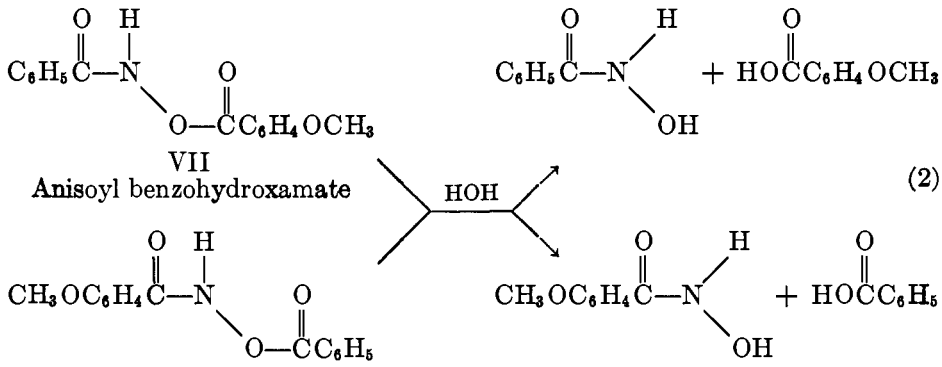
For conciseness, wherever two structural formulas are possible, but where either will serve to illustrate, only one formula will be indicated.

C. STRUCTURE

When an acyl group replaces one of the nitrogen-bound hydrogens in the hydroxylamine molecule, a monohydroxamic acid, RCONHOH, is formed. In their capacity to undergo alkylation as well as in their ability to form colored metallic chelates, the monohydroxamic acids strongly resemble compounds known to exist in tautomeric equilibria. A considerable amount of evidence is at hand to substantiate the existence of the tautomeric form of the monohydroxamic acid, RC(OH)=NOH. With two exceptions (22, 91, 92, 148, 232) it has not been possible to separate these two forms. Reactions of monohydroxamic acids can be attributed to either structure. The probable existence of these tautomers has made more complex the structure of the progressively acylated or alkylated monohydroxamic acids.

In the very early work (72, 170) an uncertainty existed as to which hydrogens in the hydroxylamine molecule were substituted by the first and second acylating groups. It is now generally accepted that the first acyl group is bound to the

nitrogen atom, while the second acyl group is held by the oxygen. As a result, anisoyl benzohydroxamate (VII) prepared from anisoyl chloride and benzohydroxamic acid is isomeric with benzoyl anisohydroxamate (VIII) prepared from benzoyl chloride and anisohydroxamic acid. When subjected to hydrolysis, these compounds yielded different products (171).



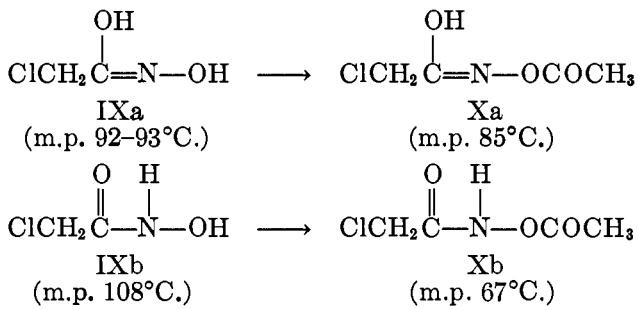
VII
Anisoyl benzohydroxamate

(2)

VIII
Benzoyl anisohydroxamate

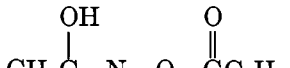
From these hydrolytic reactions, it was evident that the second acyl group, attached to oxygen, was held less firmly than the first, which was attached to nitrogen. From studies on the hydrolysis of the triacylated hydroxylamines, it was shown that the third acyl group cleaved most readily. This was paradoxical, in view of the extreme difficulty with which the third acyl group was introduced (124). It appeared reasonable to assume that the hydrolysis, as well as the acylation, was not affected by steric relationships within the molecule.

Evidence for the existence of tautomers of the structures I and II was presented by Jones and Werner (148), who prepared chloroacetohydroxamic acid and found that the melting point, originally 92–93°C. (IXa), was raised to 108°C. (IXb) after several days. Both forms gave identical analyses. The acetyl derivatives melted at 85°C. (Xa) and 67°C. (Xb), respectively. In some earlier work,



Jones (132) obtained two forms of benzoyl acetohydroxamate, which were separated by means of their different solubilities in ether. On standing, the product possessing the lower melting point (69–70°C.) became opaque and after several weeks was transformed into a product identical with the higher melting

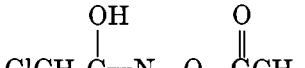
form (98–99°C.). Jones believed that the latter compound corresponded to the structure XIb, while the metastable form was represented by XIa.



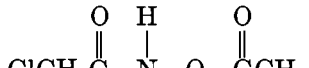
XIa

XIb

On this basis, Xa and Xb could be represented as shown below:



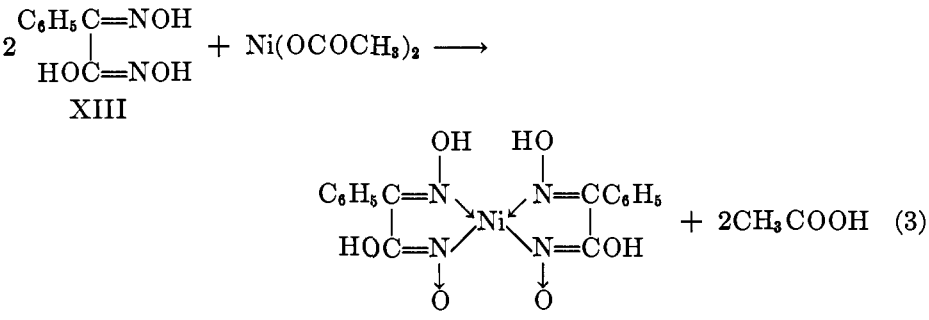
Xb



Xa

It will be remembered that Xb was derived from the stable form of chloroacetohydroxamic acid (IXb). Many cases have been reported where the enolic form of two tautomeric compounds possessed the lower melting point. An inconsistency can be noted here when this observation is extended from the tautomeric forms I and II to the tautomeric forms III and IV.

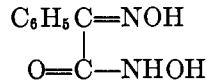
Gastaldi (91, 92) obtained two forms of benzoylformohydroxamic acid, $C_6H_5COCONHOH$. The α-form was obtained by the reaction between ethyl phenylglyoxylate and hydroxylamine; the β-form was obtained by isomerizing the α-form with dilute acetic acid. The two modifications were differentiated by their behavior toward acetic anhydride, sodium hydroxide, sodium ethoxide, and *o*-phenylenediamine. Baiardo (22) found that the oxime of the α-form (XII) when treated with nickel acetate gave no precipitate or change in color, while the oxime of the β-form (XIII) gave a red colored precipitate. Presumably, the latter modification possessed a structure capable of forming a chelate with nickel,



(3)

XIII

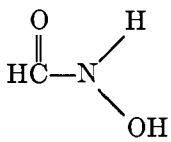
while the former,



XII

could not form a chelate.

Nef (200) reported formohydroxamic acid as an unstable compound which decomposed spontaneously at 0°C. Shortly thereafter, Schroeter (266, 268) revealed that he had prepared this acid five years previously and found that it remained unchanged in a vacuum desiccator. Jones (132) reported that the acid was stable if kept in an open container, and underwent decomposition in a sealed tube. From the decomposition of formohydroxamic acid, Schroeter obtained carbon dioxide and ammonia, while Jones obtained carbon monoxide and hydroxylamine. The latter observation was probably the correct one, since the reaction of carbon monoxide with hydroxylamine yielded formohydroxamic acid (141). Since it was well known that formohydroxamyl chloride, HCCl=NOH, when treated with alkali gave fulminic acid (198), it was expected that formohydroxamic acid, if it had the structure HC(OH)=NOH, would lose water to yield the same product. No fulminic acid was obtained, and formohydroxamic acid was assigned the structure (132, 133, 200, 201) shown below:



It should be noted that benzyl formohydroxamate (XIV), when treated with phosphorus pentachloride, yielded benzyl formohydroxamyl chloride (XV). This reaction can best be shown by attributing to XIV the hydroxyoxime structure.

$$HC(OH)=NOCH_2C_6H_5 + PCl_5 \longrightarrow$$

XIV

Benzyl formohydroxamate

$$HCCl=NOCH_2C_6H_5 + HCl + POCl_3 \quad (4)$$

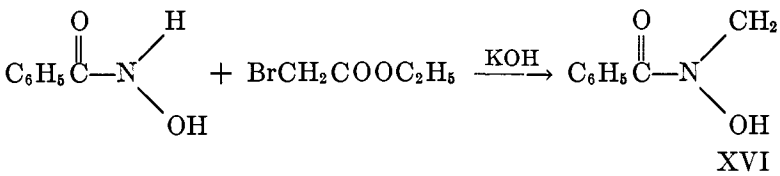
XV

Benzyl formohydroxamyl chloride

The structure of the alkylated monohydroxamic acids was similarly concerned with the existence of isomeric forms of the same compound. When monohydroxamic acids were alkylated, *O*-alkyl derivatives were formed.

$$R\overset{\overset{O}{\|}}{C}NHOM + R'X \longrightarrow R\overset{\overset{O}{\|}}{C}NHOR' + MX \quad (5)$$

N-Alkyl derivatives were probably formed simultaneously (122). Some confirmation for this lies in the single report that benzohydroxamic acid and ethyl

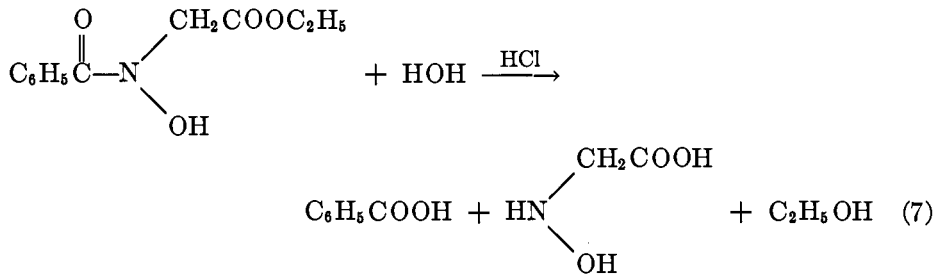


$$+ BrCH_2COOC_2H_5 \xrightarrow{KOH}$$

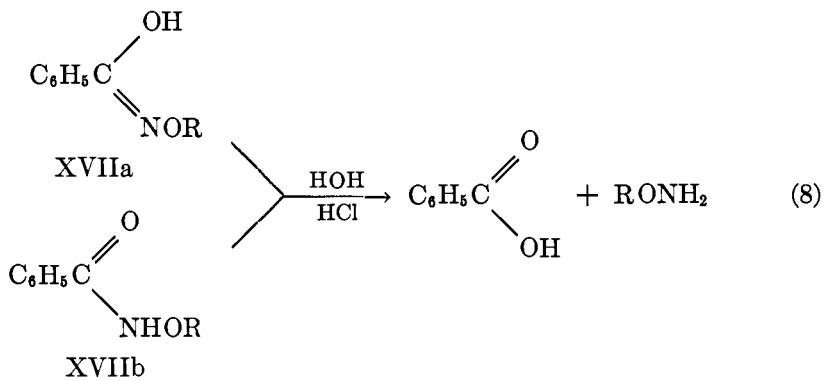
(6)

XVI

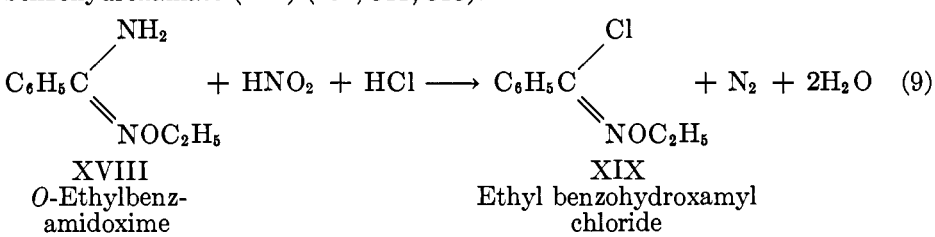
bromoacetate in the presence of alcoholic potassium hydroxide yielded carboethoxymethyl benzohydroxamic acid (XVI), which upon hydrolysis gave α-hydroxyaminoacetic acid (153).

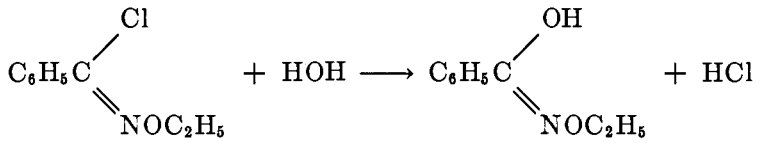


The hydrolysis of alkyl benzohydroxamates (XVIIa and XVIIb) yielded benzoic acid and *O*-alkylhydroxylamines (55, 175, 299). Lossen (175) maintained that this reaction could be explained only by structure XVIIa. This claim was not valid, since in the hydrolytic cleavage of the carbon–nitrogen bond, the hydrogen of the water was found attached to the nitrogen atom, while the oxygen atom *or* hydroxyl group was attached to the carbon atom (134). Thus, either XVIIa or XVIIb gave the same products.



Tiemann (287–289, 291, 292) and Hofmann (112) attempted to prepare compounds of the XVIIa type by the direct substitution of the $—NH_2$ group in the amino form (XVIII) of *O*-ethylbenzamidoxime. With nitrous acid, in the presence of an excess of hydrochloric acid, the product was ethyl benzohydroxamyl chloride (XIX) which, although unusually stable, could be hydrolyzed to ethyl benzohydroxamate (XX) (231, 311, 313).



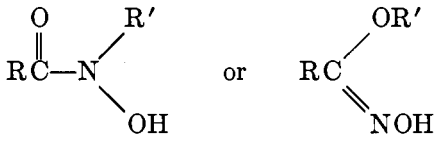


XX

Ethyl benzohydroxamate

Compound XX was identified as ethyl benzohydroxamate by conversion to a diethyl benzohydroxamate derivative identical with the product obtained by the ethylation of ethyl benzohydroxamic acid or of ethyl benzohydroxamate. When sulfuric acid replaced the hydrochloric acid in equation 9, the products were benzoic acid and *O*-ethylhydroxylamine. Since ethyl benzohydroxamate, when prepared by other methods, was stable under the conditions employed with the sulfuric acid, it was assumed that XVIIb was the stable form, while XVIIa was an intermediate reactive form. This view, expressed by Tiemann, made possible the existence of XVIIa, momentarily, after which it rearranged to the stable form. This was indicated by Krüger (159), who obtained ethyl benzohydroxamate directly from XVIII by utilizing low temperatures and one equivalent of sodium nitrite, in the presence of sulfuric acid.

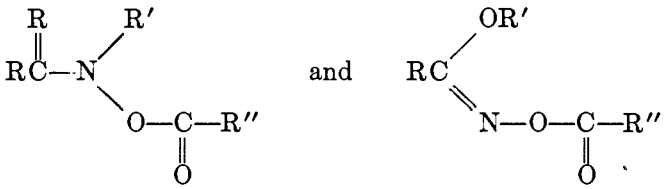
Compounds of the type



XXI XXII

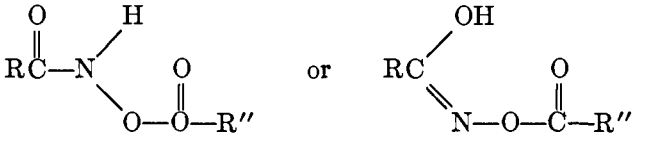
have been prepared by methods which may be described as indirect. The reaction between an *N*-alkyl(or aryl)hydroxylamine, R′NHOH, and an acyl halide yielded a compound capable of existing in one form, R′N(COR)OH. This type of compound, since it was soluble in ammonia, alkali hydroxide, and sodium carbonate, and gave the characteristic color of the monohydroxamic acids with ferric chloride, was indistinguishable from derivatives which were capable of existing as the isomeric forms XXI and XXII (29, 32, 45, 46, 95).

The probable existence of compounds which possessed structures XXI and XXII stemmed directly from their mode of preparation. They were prepared by the alkaline hydrolysis of alkyl aroyl monohydroxamates, which existed as the isomers

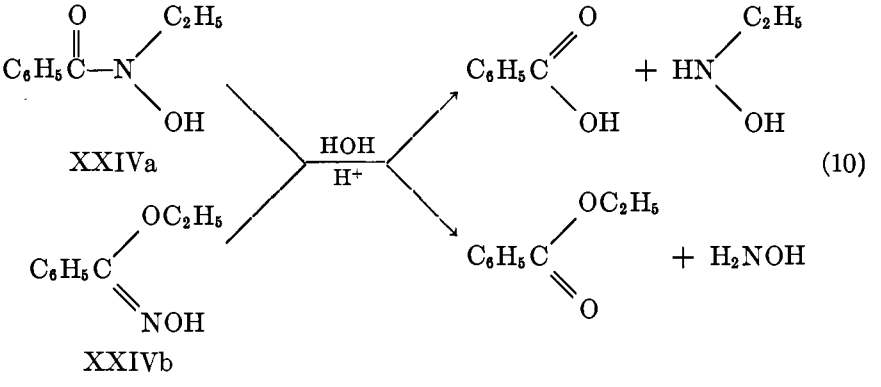


XXIIIa XXIIIb

It may be noted that the aroyl group was cleaved first by alkaline hydrolysis. The behavior of XXIIIa and XXIIIb on acid hydrolysis was normal; the products obtained were



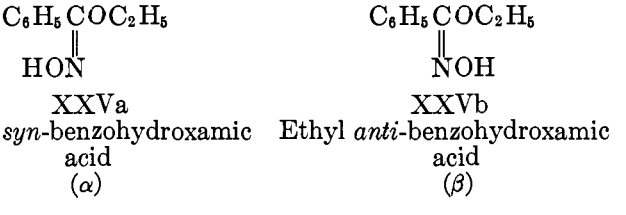
The hydrolysis of alkyl benzohydroxamic acids in acid solution yielded an alkyl benzoate and hydroxylamine (96, 120, 175, 177). This indicated that the metastable form (XXIVb) was the reactive one.



(10)

Such evidence cannot be considered critical; no attempt was made to search for traces of *N*-ethylhydroxylamine.

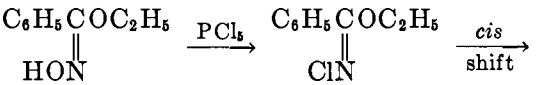
Ethyl benzohydroxamic acid was found to exist in two forms, an α-form (XXVa), melting at 53.5°C., and a β-form (XXVb), melting at 67.5–68°C. (96, 186). The former was completely soluble in alkali, while the latter was insoluble. On hydrolysis in acid solution each yielded the same products, ethyl benzoate and hydroxylamine. Lossen (177) and Gürke (96) believed that these were polymorphous manifestations of the same compound. Werner (306) suggested instead that they were *syn*- and *anti*-forms.



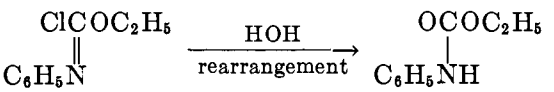
Each gave a different acetyl and *p*-nitrobenzyl derivative (305).

Lossen (182) prepared methyl benzohydroxamic acid and reported two forms, one melting at 65°C. (XXVIa) and the other at 101°C. (XXVIb). Werner (309) obtained two forms of the same compound, one melting at 44°C. (XXVIIa), the other at 65°C. (XXVIIb). Three forms of methyl benzohydroxamic acid were indicated. In order to show that two of the forms were identical, Werner first obtained a sample of XXVIb from Lossen and then proceeded to check the preparation of XXVIIb. When he recrystallized this latter product and XXVIb from ligroin, both compounds melted at 101°C. Even the residues in the flask melted at 101°C. Werner again prepared XXVIIb, melting at 65°C., in a different room. When XXVIIb was brought into the room in which the recrystallizations had been carried out previously, the product melted at 101°C. It appeared that XXVIIb was a metastable physical form of XXVIb; hence only two stable forms of methyl benzohydroxamic acid were actually present.

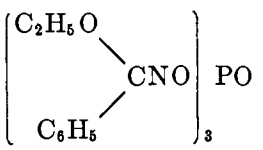
Werner (305, 306, 309, 318) further developed the hypothesis that geometric isomerism existed amongst the alkyl benzohydroxamic acids. When the α-form of ethyl benzohydroxamic acid (XXVIIIa) was treated with phosphorus pentachloride and hydrolyzed, there was obtained ethyl phenylcarbamate. The mechanism of this reaction was assumed to be as follows:[1]



XXVIIIa (11)



The β-form (XXVIIIb) after identical treatment gave the phosphate:



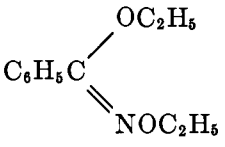
XXIX

Werner and Subak (318) obtained related products with the α- and β-forms of methyl benzohydroxamic acid. Houben and Pfankuch (118) reported that ethyl *anti*-formohydroxamic acid yielded a product similar to XXIX when treated with phosphorus pentachloride. Douglas (69) prepared ethyl *anti*-thenohydroxamic acid. Werner (305) pointed out that, in contrast to other stereoisomeric oximes, these compounds were not converted into one another by chemical reactions. Ethyl acetyl benzohydroxamate, melting point 38–39°C. (from ethyl *syn*-benzohydroxamic acid), was stable up to 140°C.; when it was treated with alcoholic sodium hydroxide, ethyl *syn*-benzohydroxamic acid was

[1] Recent work shows that the Beckmann rearrangement does not involve a *cis* shift of groups (Gilman: *Organic Chemistry*, Vol. I, p. 471, John Wiley and Sons, Inc., New York (1943)); hence the above configuration of XXVIIIa should probably be reversed.

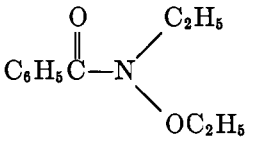
again obtained. The acetylated ethyl *anti*-benzohydroxamic acid demonstrated a similar stability. Benzohydroxamyl chloride was expected to exist in *syn*- and *anti*-forms, but Werner (307) was unable to separate the two. Werner and Buss (313) found that the two isomeric benzaldoximes did not yield two isomeric benzohydroxamyl chlorides.

The problem of structure was also present amongst the dialkylated monohydroxamic acids. Lossen (178) showed that the product (XXX) obtained by the interaction of *N*-ethyl-*O*-ethylhydroxylamine and benzoyl chloride was different from the product obtained by the alkylation of benzohydroxamic acid. The latter could exist as either



XXXIa

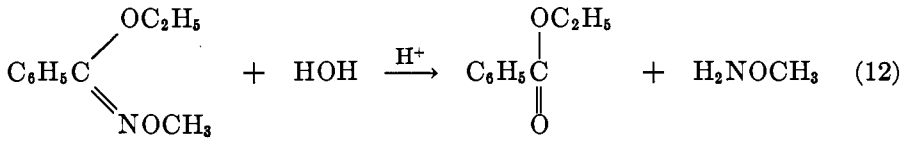
or



XXXIb

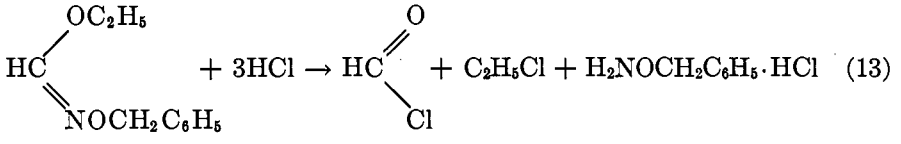
Since XXX would have the structure XXXIb, this was an argument in favor of structure XXXIa for the hydroxamic acid derivatives obtained by the direct alkylation of the monohydroxamic acids (287).

Additional evidence was presented by Arndt and Scholz (21), who found that benzohydroxamic acid and diazomethane gave a product which contained two methoxyl groups. There was no indication of the presence of an $=NCH_3$ linkage. The hydrolysis of ethyl methyl benzohydroxamate (XXXII) (prepared by the alkylation of benzohydroxamic acid) yielded *O*-methylhydroxylamine and ethyl benzoate, indicating a structure related to XXXIa. Similarly, methyl ethyl benzohydroxamate gave *O*-ethylhydroxylamine and methyl benzoate (186). The two forms of ethyl benzyl formohydroxamate (XXXIII), when subjected to the action of hydrogen chloride, yielded *O*-benzylhydroxylamine and ethyl chloride (50).



XXXII
Ethyl methyl benzohydroxamate

(12)



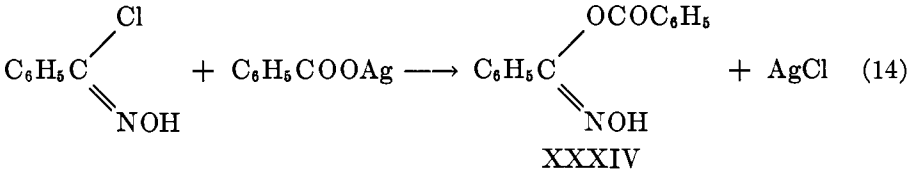
XXXIII
Ethyl benzyl formohydroxamate

(13)

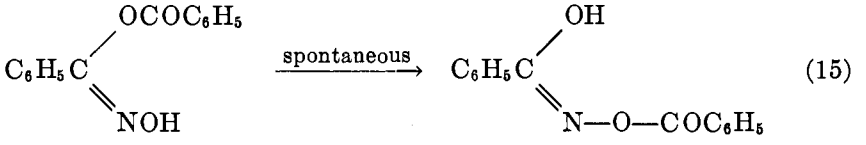
It was interesting to note that ethyl benzohydroxamic acid and ethyl benzohydroxamate on alkylation yielded the same diethyl benzohydroxamate, and with dilute acid each yielded *O*-ethylhydroxylamine and ethyl benzoate (178).

It was mentioned previously (page 213) that Jones (132) had isolated benzoyl acetohydroxamate in two forms, a metastable form melting at 69–70°C. (XIa) and a stable form melting at 98–99°C. (XIb). Cameron (60) studied these crystalline modifications and observed that while the latter form was the more stable, it was converted into the former with the absorption of heat. Since XIa was the possessor of the greater energy, it was the more reactive form. This observation was in agreement with other observations concerning the structure of the reactive form of the hydroxamic acids.

The structure RC(=NOH)OCOR′ was found to be unstable. When silver benzoate and benzohydroxamyl chloride were allowed to react, the product first isolated melted at 95°C. (XXXIV) (313, 317). On repeated crystallization, the melting point was raised to 161°C., similar to that of benzoyl benzohydroxamate. This same phenomenon was observed when XXXIV was allowed to remain without further treatment. After 2 hr. the melting point was 103°C., and after two days, 158–161°C. The reactions occurring in this transformation appeared to involve a rearrangement.



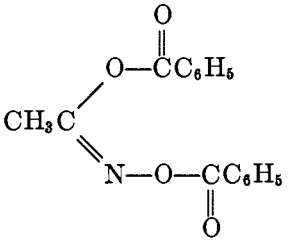
XXXIV



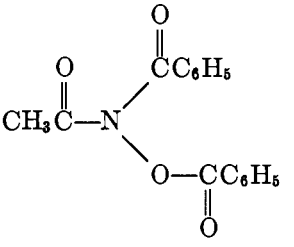
The triacylated hydroxylamines were found to be polymorphous. Dibenzoyl benzohydroxamate, for example, existed in three forms: the α-form, melting at 100°C.; the β-form, melting at 141°C.; and the γ-form, melting at 112°C. (171, 182). In their chemical behavior the three forms were identical, differing only in the relative ease with which the reactions proceeded (171, 182). Lehmann (161) studied the three crystalline modifications and observed that when a melt of the β-form was cooled, the α-form crystallized first and was then transformed into the β-form. The melt of the γ-form, on slow cooling, yielded the α-form. Only by the intense heating of the γ-modification was the β-form obtained. When a mixture of the α- and β-forms was warmed carefully, the latter crystals grew at the expense of the former, until the α-modification had entirely disappeared. Lossen (181) obtained the β-form by heating the γ-form with dilute hydrochloric acid. This evidence indicated that the β-, or highest melting, form was the

most stable, an observation in keeping with the general rule with polymorphous compounds.

Jones (132, 135) presented favorable evidence for the existence of the isomeric triacylated hydroxylamine derivatives. The reaction between sodium *aci*-nitroethane and benzoyl chloride yielded a neutral product which with alcoholic potassium hydroxide gave a mixture of benzoyl benzohydroxamate (XXXV), benzoyl acetohydroxamate (XXXVI), benzoic acid, and ethyl benzoate. These products indicated a mixture of the two isomeric compounds XXXVIIa and XXXVIIb.

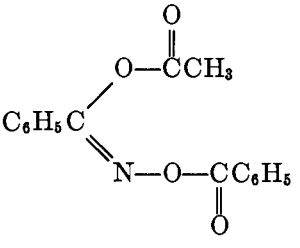


XXXVIIa

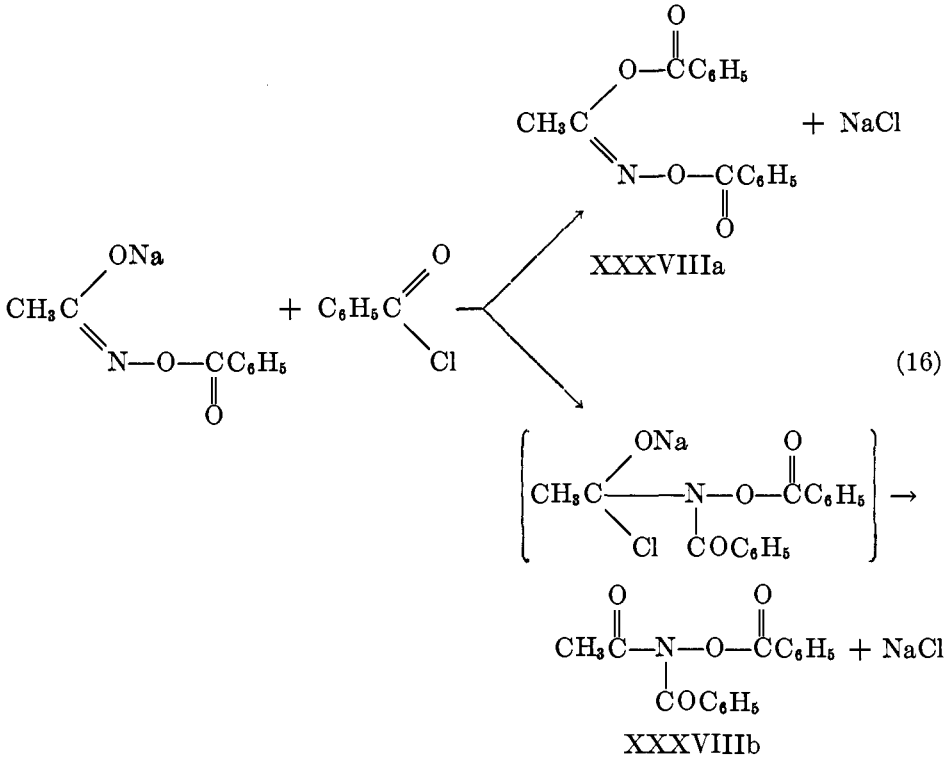


XXXVIIb

XXXV could be derived from XXXVIIb by cleavage of the acetyl group; XXXVI was obtained from XXXVIIa, where the acetyl group, *per se*, did not exist, so that a benzoyl group was cleaved instead. The assumption in the formation of XXXV was that the acetyl group was cleaved before the benzoyl group. In addition, when sodium benzoyl acetohydroxamate and benzoyl chloride were allowed to react, two products were obtained, an oil (XXXVIIIa) and a crystalline material (XXXVIIIb) melting at 69–70°C. With alcoholic potassium hydroxide, XXXVIIIb gave benzoyl benzohydroxamate, acetic acid, and ethyl acetate, while XXXVIIIa gave benzoyl acetohydroxamate, benzoic acid, and ethyl benzoate. Two products were obtained also when potassium benzoyl benzohydroxamate and acetyl chloride were allowed to react. One, melting at 69–70°C., was shown to be identical with XXXVIIIb; with alcoholic potassium hydroxide it yielded benzoyl benzohydroxamate. The other, higher melting product was assumed to be



Jones believed that the reaction between sodium benzoyl acetohydroxamate and benzoyl chloride proceeded either by direct replacement to yield XXXVIIIa or indirectly to yield XXXVIIIb.

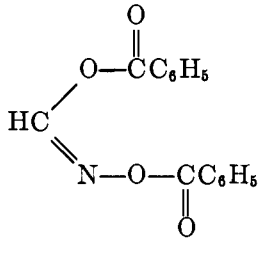


(16)

XXXVIIIa

XXXVIIIb

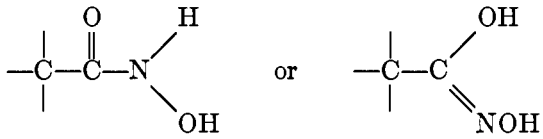
It should be noted with regard to such a mechanism that sodium *aci*-nitromethane and benzoyl chloride yielded a neutral product which on treatment with alcoholic potassium hydroxide gave only benzoyl formohydroxamate, $HC(OH)=NOCOC_6H_5$, and benzoic acid. Apparently no addition occurred here. In a similar fashion, sodium benzoyl formohydroxamate and benzoyl chloride gave only



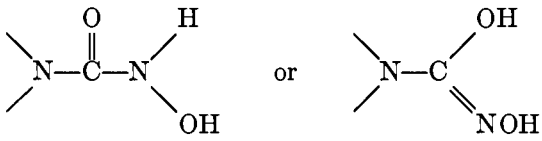
since on hydrolysis with alcoholic potassium hydroxide, no benzoyl benzohydroxamate was found.

The discussion which has been presented up to this point on the structure of

the hydroxamic acids has been concerned with the derivatives which contain the system



An interesting group of compounds, the hydroxyureas or carbamylhydroxamic acids, contain the



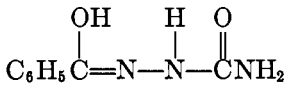
structure. Hurd (121) first pointed out that such compounds bear a striking similarity to the hydroxamic acids.

As an alternative to the tautomeric concept of the structure of the monohydroxamic acids, Oddo (204, 205) proposed the "mesohydric" structure. Palazzo and Oliveri-Mandala (208–214) suggested the cyclic structure, $H_2C\!\!<\!\!\begin{matrix}O\\|\\\end{matrix}\!\!>\!\!NOH$, for formohydroxamic acid. Such proposals offer no fundamental clarification of the many questions which remain unanswered relative to the structure of the hydroxamic acids.

D. MONOHYDROXAMIC ACIDS

In aqueous solution the monohydroxamic acids behave as weak acids: acetohydroxamic acid, for example, has an ionization constant of 0.28×10^{-7} (94, 208). The monohydroxamic acids can be titrated with alkali, using phenolphthalein as the indicator (219). They reduce Fehling's solution. Their most characteristic reaction is the intense dark violet color produced with ferric chloride. With cupric acetate, characteristic green-blue insoluble copper salts are formed. This reaction is frequently utilized in the isolation and purification of the monohydroxamic acids.

Many of the reactions of the monohydroxamic acids will be discussed in other sections of this review. A few reactions may be mentioned here. With aniline (193) or with benzenediazonium chloride (236), benzohydroxamic acid gave benzanilide. Semicarbazide and benzohydroxamic acid yielded

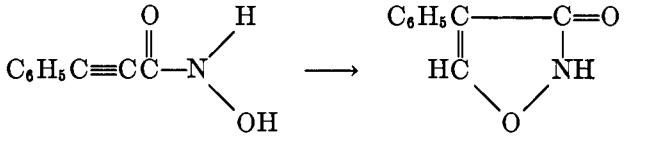


a tautomer of benzoylsemicarbazide (256). This exchange was not a general reaction, since salicylohydroxamic and cinnamohydroxamic acids did not react.

Hypobromous acid and the monohydroxamic acids reacted as shown in equation 17 (216, 217).

$$2RCONHOH + 2HOBr \rightarrow 2RCOOH + 2HBr + N_2O + H_2O \quad (17)$$

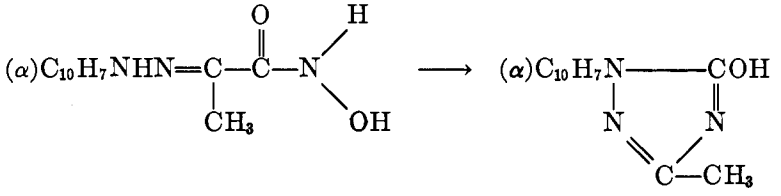
Acetohydroxamic acid with nitrous acid yielded acetic acid and nitrous oxide (101). The reduction of monohydroxamic acids with sodium–mercury amalgam led to the formation of amides (86). This reaction was the reverse of the oxidation of amides to hydroxamic acids, either with Caro's reagent or with hydrogen peroxide (210). Ruhemann and Stapelton (255) found that phenylpropiolohydroxamic acid (XXXIX) could not be isolated, since it underwent cyclization to 5-phenyl-3-isoxazolone (XL).



XXXIX XL

5-Phenyl-3-isoxazolone (18)

Pickard and Neville (221) showed that the product was the hydroxamic acid, by comparing the properties of its benzoyl derivative with those of 5-phenyl-3-benzoylisoxazolone. In the presence of dilute mineral acids pyruvylohydroxamic acid was converted into the oxime of pyruvic acid (94). The arylhydrazones of pyruvylohydroxamic acid were readily converted into triazole derivatives (93).



(19)

Monohydroxamic acids have been proposed recently as flotation agents for certain copper ores (104).

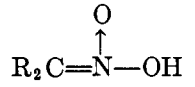
Preparation

The monohydroxamic acids have been prepared by many methods. The most general is the reaction between an ester and hydroxylamine. Other methods, although satisfactory in certain instances, have limited application.

The methods which have been utilized for the preparation of monohydroxamic acids are:

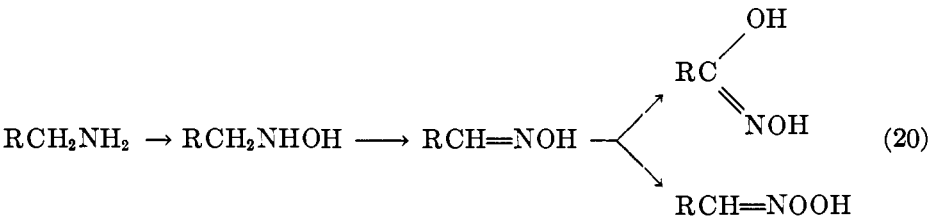
(*1*) *The reaction between an ester and hydroxylamine:* The reaction between an ester and hydroxylamine in absolute alcohol proceeds rapidly at room temperature, particularly in the presence of an equimolecular quantity of sodium alkoxide (16, 56, 57, 99, 127–131, 147, 197, 221, 239, 247). In the absence of the alkaline reagent longer periods of time are required (131, 140). The reaction may be carried out in water, sodium carbonate replacing the sodium alkoxide (195).

(*2*) *The oxidation of aldoximes, amines, aldehyde-ammonias, amides, and nitriles:* The reaction between Caro's reagent (persulfuric acid, $H_2S_2O_8$) and benzaldoxime gave, amongst other products, benzohydroxamic acid (26). The reaction appeared to be of general application with oximes (36). Ketoximes and Caro's reagent yielded nitronic acids (38):



Hydrogen peroxide can replace persulfuric acid in these oxidations (210).

The oxidation of primary amines by persulfuric acid yielded hydroxamic acids (27, 28, 37). Amines of the general formulas RCH_2NH_2 and R_2CHNH_2 and certain amino acids were successfully oxidized. The presence of hydroxamic acids was determined by the color test with ferric chloride. The reaction probably proceeded through several intermediates (26). No reaction occurred with aminosulfonals, aminovaleric acid, glutamine, and cystine.



(20)

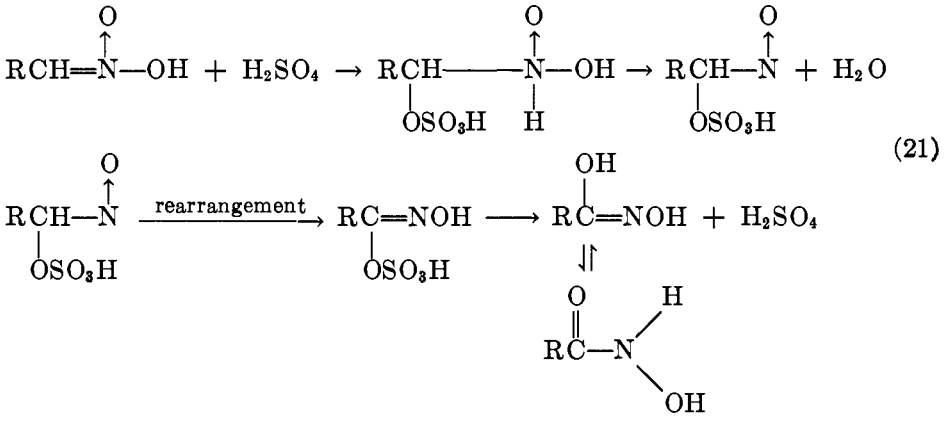
Tests with tyrosine and glutamic acid were doubtful. In some instances it was necessary to heat the reactants in order to have oxidation proceed at a fairly rapid rate. Secondary amines were also oxidized to products which gave a positive color test for monohydroxamic acids; as a result, the reaction could not be utilized to distinguish primary from secondary amines (28, 37).

Acetaldehyde-ammonia was oxidized by persulfuric acid to acetohydroxamic acid (39). The oxidation of amides by means of hydrogen peroxide was successful in a few cases (210). Benzamide and toluamide were oxidized to the corresponding monohydroxamic acids; the reaction failed with acetamide, propionamide, and oxamide. Nitriles, when oxidized with hydrogen peroxide, yielded hydroxamic acids.

(*3*) *The rearrangement of nitroparaffins by mineral acids:* Victor Meyer (192) found that heating nitroparaffins with hydrochloric acid in sealed tubes gave hydroxylamine as one of the products. He correctly surmised that the intermediate product was a hydroxamic acid. This was confirmed by later workers (30, 35, 61, 83, 240, 241). 1-Nitropropane and anhydrous sulfuric acid gave propionohydroxamic acid in 50 per cent yield; this process has recently been patented (164, 165).

The mechanism of the rearrangement of *aci*-nitroparaffins into the tautomeric forms of the monohydroxamic acids is not well understood. One mechanism

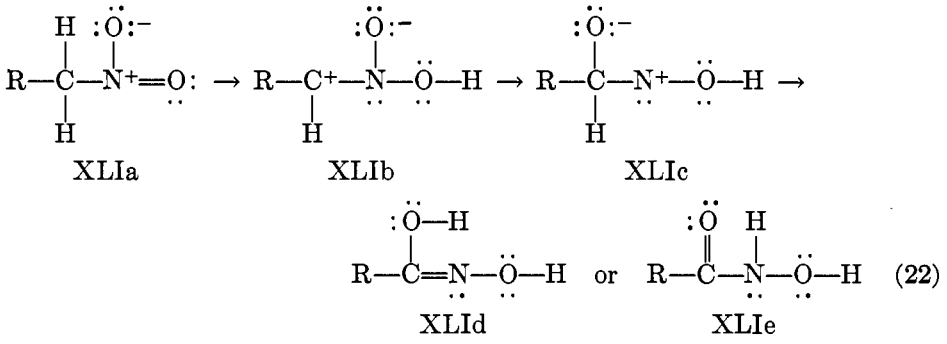
assumes the addition of hydrochloric acid or sulfuric acid to the *aci*-nitroalkane, followed by loss of water and rearrangement (104, 202).



(21)

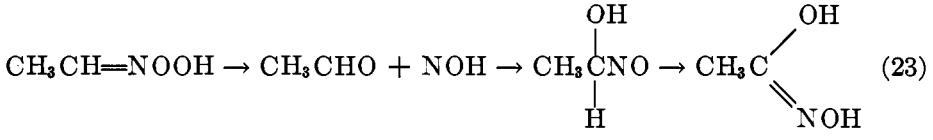
Junell (149) studied the kinetics of the reaction and found it to be monomolecular. The rate-determining step was the rearrangement of the *aci*-form to the hydroxamic acid and was very rapid when compared with the relative slowness with which the nitroparaffin was converted into the *aci*-form. In the presence of bromine, the product obtained was the bromonitroparaffin, $RCHBrNO_2$, since the addition of bromine to the *aci*-form was faster than the rearrangement to the hydroxamic acid.

The rearrangement was indicated by Hurd (122) to proceed as follows:



(22)

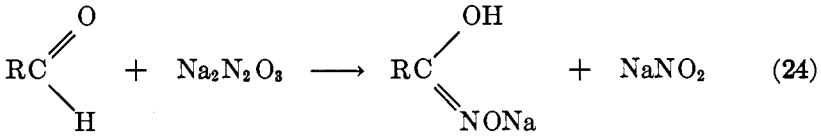
According to this view, XLIb represented an unstable condition, a carbon sextet. The carbon atom appropriated electrons from the neighboring oxygen, which had a surplus, and this initiated the molecular rearrangement to XLIc and led eventually to LXId or XLIe. Steinkopf and Jürgens (278) considered the rearrangement as one involving the formation of free nitrosyl.



(23)

In this connection, it should be noted that neutral nitromethane, when subjected to ultraviolet radiation, rearranged to formohydroxamic acid, while formohydroxamic acid, under similar irradiation, partially rearranged to *aci*-nitromethane (40, 41). The distillation of phenylnitromethane at atmospheric pressure yielded benzoyl benzohydroxamate (107). In all probability the rearrangement possesses a mechanism more complex than any of those proposed.

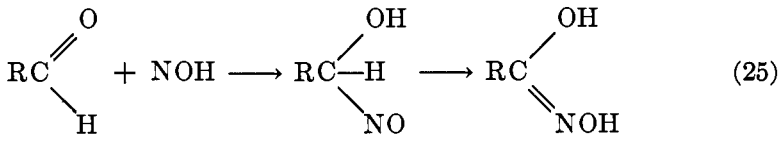
(*4*) *The reaction between an aldehyde and compounds capable of yielding free "nitrosyl":* In the course of an investigation into new methods for the preparation of monohydroxamic acids, Angeli (1, 2, 4) prepared sodium nitrohydroxamate, $Na_2N_2O_3$. With certain aldehydes, this salt yielded the sodium salt of monohydroxamic acids. In practice, the sodium nitrohydroxamate, in aqueous solu-



(24)

tion, was added to the aqueous or alcoholic solution of the aldehyde. An exothermic reaction ensued, and following this, acidification yielded the monohydroxamic acid (4–13, 59, 90). No reaction occurred in anhydrous ether (59). Many aldehydes did not react, e.g., salicylaldehyde, *o*-nitrobenzaldehyde, and pyrrolaldehyde. Glucose and lactose were also unreactive (11, 18, 19).

The reaction was shown to proceed *via* the formation of a nitroso alcohol by a 1,2-addition of free nitrosyl to the carbonyl group of the aldehyde. Although Angeli did not report the formation of a transitory blue-green color in the course



(25)

of this reaction, the color, indicative of the presence of nitroso alcohols, was observed by others (34, 35, 41, 42, 278, 279), particularly when methyl acetate or acetone was added to the aqueous reaction mixture. Potassium nitrosyl, NOK, a product of the photoreduction of nitrates, was proposed as the intermediate which reacted with photosynthesized formaldehyde to yield formohydroxamic acid, the first step in the phytosynthesis of the nitrogen compounds found in plants (25, 40–43).

Benzenesulfonhydroxamic acid, Piloty's Acid, $C_6H_5SO_2NHOH$, and certain aldehydes reacted to form monohydroxamic acids (3, 4, 14–16, 62, 63, 251, 252, 296). The procedure employed was to mix equimolecular quantities of benzenesulfonhydroxamic acid with an aldehyde in water or alcohol, and to add alkali until the mixture was alkaline. Upon acidification, the monohydroxamic acid was obtained. Many aldehydes did not react (4, 16, 18, 228).

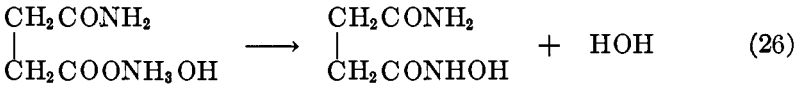
(*5*) *The reaction between an amide and hydroxylamine:* Aliphatic and aromatic amides reacted with hydroxylammonium chloride at moderate temperatures

(20–100°C.) to yield monohydroxamic acids (79, 110, 111). The yield with acetamide was reported as quantitative. Benzamide did not react.

(*6*) *The reaction between an acid anhydride or acid halide and hydroxylamine:* Acetic anhydride and hydroxylamine, or its salts, yielded acetohydroxamic acid (64, 65, 73, 97, 194). Acid halides and hydroxylamine, in the presence of alkali, gave, in addition to the monohydroxamic acid, further acylated products (108, 169). In some instances, this method was to be preferred over Method 1, e.g., in the preparation of 2,4-dihydroxybenzohydroxamic acid (270).

An improved procedure employed two equivalents of free hydroxylamine and one of the acid halide in benzene or ether (136, 137, 143).

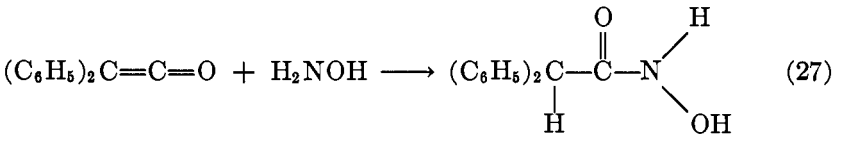
(*7*) *The pyrolysis of hydroxylammonium salts of organic acids:* W. Lossen (168), in 1868, prepared several hydroxylammonium salts of organic acids but neglected to study their pyrolysis. Ssabonev (275) found that hydroxylammonium succinamate (XLII), when heated to its melting point, or when allowed to stand,



XLII (26)

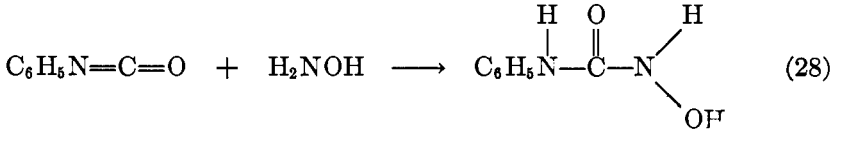
gave a hydroxamic acid. Jones and Oesper (141) found that hydroxylammonium formate decomposed slowly during a period of several weeks, or more rapidly when heated, to formohydroxamic acid. The method was not of general application (121a, 148).

(*8*) *The reaction between ketenes and hydroxylamine:* The preparation of monohydroxamic acids by the reaction between ketenes and hydroxylamine was first proposed by Staudinger (276). Jones and Hurd (136) found that diphenylketene and hydroxylamine gave diphenylacetohydroxamic acid. With an excess of the ketene, the acylation continued until the triacylated hydroxylamine was

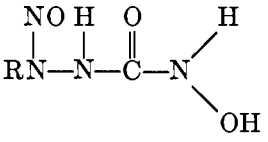
 (27)

formed. The yields of mono-, di-, and tri-acylated hydroxylamines were excellent. It was interesting to observe that two acyl groups were readily introduced into the monohydroxamic acid with a ketene, while with acid anhydrides the last acyl group was introduced with some difficulty (29, 124, 125).

A related reaction was that between an isocyanate and hydroxylamine which led to the formation of carbamylhydroxamic acids possessing the structure, RNHCONHOH or RNHC(OH)=NOH (44, 77, 121, 124, 150, 154).

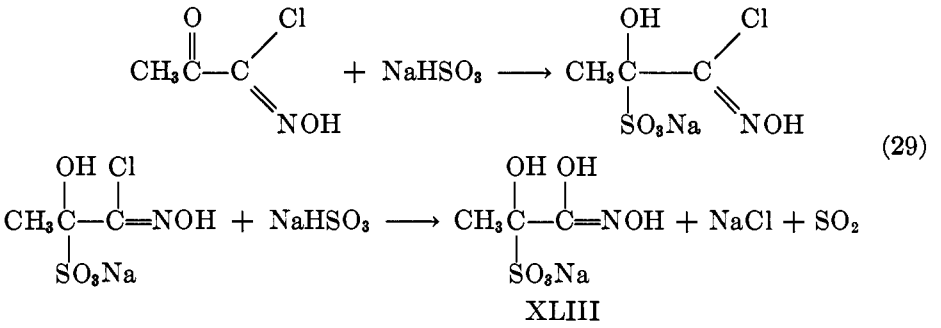
 (28)

Quilico and Justoni (243, 244) extended this reaction to prepare compounds of the type,



by the interaction of nitrosocarbohydrazines, RN(NO)N=C=O, and hydroxylamine.

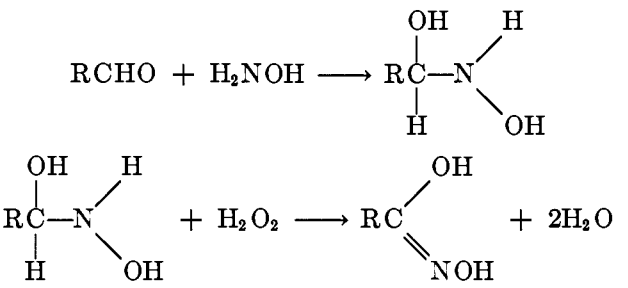
(*9*) *The hydrolysis of monohydroxamyl chlorides:* Ponzio (231) prepared the oxime of *p*-toluoylformohydroxamic acid, *p*-$CH_3C_6H_4C(=NOH)C(=NOH)OH$, by the reaction between the oxime of *p*-toluoylformohydroxamyl chloride and sodium acetate in 50 per cent acetic acid. Pyruvylohydroxamyl chloride first added sodium bisulfite and was then hydrolyzed to the corresponding hydroxamic acid (XLIII) (85, 88).



(29)

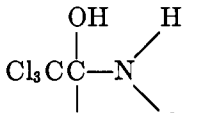
XLIII

(*10*) *The reaction between water-soluble aldehydes, hydroxylamine, and hydrogen peroxide:* Water-soluble aldehydes, e.g., formaldehyde, acetaldehyde, and propionaldehyde, when treated with one molecular equivalent of hydroxylamine and two molecular equivalents of hydrogen peroxide, yielded the corresponding hydroxamic acids. The reaction proceeded according to the following equations:



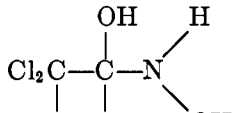
(30)

The addition products of chloral and dichloroacetaldehyde with hydroxylamine,



XLIV

and



XLV

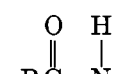
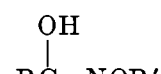
respectively, were isolated (97, 206). From XLIV the principal products were chloroform and formohydroxamic acid and from XLV, dichloromethane and formohydroxamic acid.

(*11*) *Miscellaneous preparations of monohydroxamic acids:* Ponzio (229, 230) found that $(O_2N)_3CNC_6H_5$ reacted in moist ether to yield phenylazoformohydroxamic acid, $C_6H_5N{=}NCONHOH$. A mixture of methyl alcohol and potassium nitrite when irradiated with ultraviolet light gave formohydroxamic acid (40). Acetohydroxamic acid was obtained by the reaction between acetyl chloride and aromatic isonitroso ketones (274), and by the hydrolysis of acetonitrolic acid, $CH_3C(NO_2){=}NOH$ (322). The reactions between dibenzoyl dichloro-α,α'-furazan and alkali (54), the intermediate nitration product of ethyl furoate and hydroxylamine (187), and α-diketocholanic acid dioxime and nitric acid, yielded products identified as monohydroxamic acids.

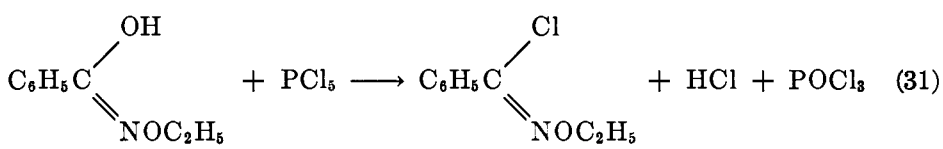
Hydroxamic acids have been proposed as intermediates in certain reactions (157, 285).

E. DERIVATIVES OF MONOHYDROXAMIC ACIDS

1. Alkyl- and aryl-substituted monohydroxamic acids

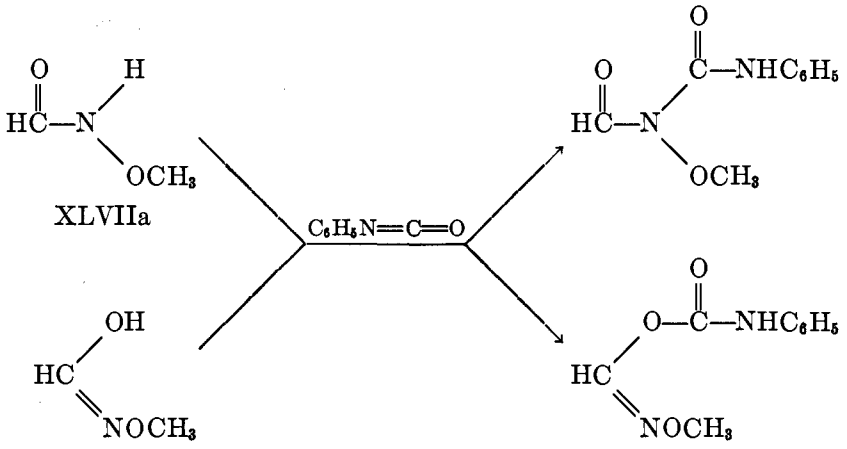
(a) Compounds of the general formulas  or 

Compounds of this type are very weak acids; they are liberated from their alkali salts by carbon dioxide. They give no color test with ferric chloride. It was indicated (p. 216) that tautomeric forms were possible with this group of compounds. Thus, ethyl benzohydroxamate and phosphorus pentachloride yielded ethyl benzohydroxamyl chloride, indicating that the reactive form was XLVI (177); on the other hand, methyl formohydroxamate and phenyl isocyanate yielded phenylcarbamoyl methyl formohydroxamate, in the formation of which either XLVIIa or XLVIIb could have reacted (51).



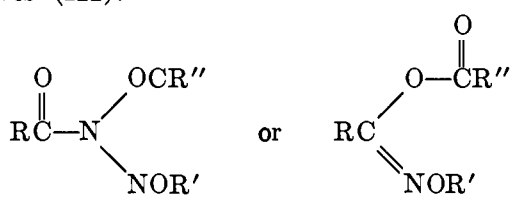
XLVI

(31)



(32)

With acyl halides, RCONHOR′ or RC(OH)=NOR′ compounds yielded the isomeric derivatives (222):

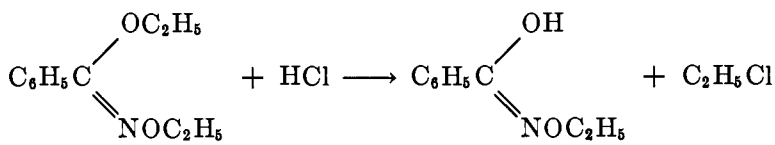


Benzyl formohydroxamate underwent an unusual cleavage with hydrochloric acid to formaldehyde and *O*-benzylhydroxylamine (51).

The monoalkyl- or aryl-substituted monohydroxamic acids have been prepared by the following methods:

(*1*) *The reaction between an alkyl iodide and the alkali metal salt of a monohydroxamic acid:* This reaction was generally carried out in the presence of excess alkali so that the alkali salt was obtained; on treatment with carbon dioxide, the substituted monohydroxamate was liberated (55, 299).

(*2*) *The acid cleavage of a dialkylated monohydroxamic acid:* According to Lossen (182) this method of preparation gave the best yields of alkyl monohydroxamates.



(33)

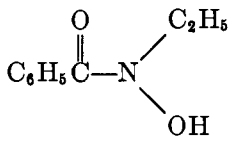
(*3*) *The alkaline hydrolysis of a compound of the type* RCON(COR″)OR′: Benzoyl ethyl benzohydroxamate on alkaline hydrolysis yielded potassium ethyl benzohydroxamate and potassium benzoate (180).

(b) Compounds of the general formulas 

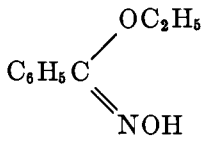
Compounds of this type are stronger acids than the type discussed previously (page 231), since they are soluble in ammonia, alkali hydroxide, and sodium carbonate. They give the characteristic color test of hydroxamic acids with ferric chloride and form copper salts.

Ethyl benzohydroxamic acid was isolated in two forms. The α-modification was acidic, the β-modification neutral toward alkali hydroxides. The two forms have been designated as *cis*- and *trans*-isomers.

Compounds in this group which can exist in either of two isomeric structures are generally prepared by the hydrolysis of a completely substituted hydroxylamine derivative. Thus, ethyl benzohydroxamic acid was prepared by the alkaline or ammoniacal hydrolysis of ethyl benzoyl benzohydroxamate (72, 96, 178) and as a result possessed either structure XLVIIIa or structure XLVIIIb.

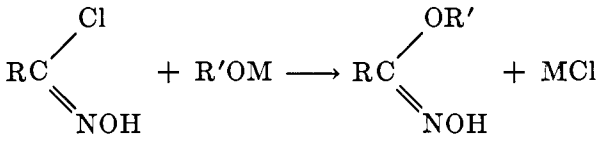


XLVIIIa



XLVIIIb

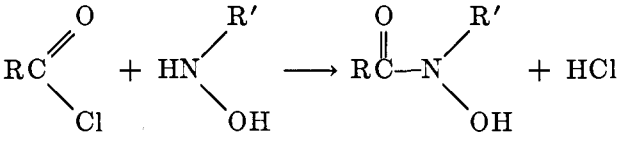
This group of compounds included a small number which, in view of the methods utilized in their preparation, existed in only one structural form. One type was prepared by the interaction of a monohydroxamyl chloride and a metal alkoxide (313, 315), and represented one isomeric form (XLIXa).



(34)

XLIXa

The other type was prepared by the reaction between an *N*-alkyl(or aryl)hydroxylamine with an acid halide, acid anhydride, or ester (29, 31, 32, 45, 46, 146). The product was the other isomeric form (XLIXb).



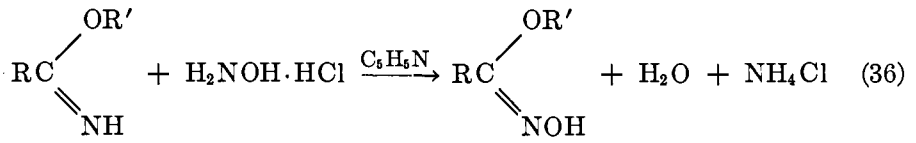
(35)

XLIXb

Other methods employed in the preparation of compounds in this group are as follows:

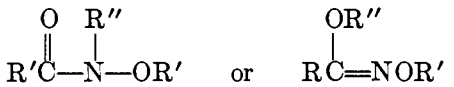
(*1*) *The reaction between an imido ester and hydroxylamine:* The reaction between hydroxylammonium chloride and an imido ester appeared to be of general

application for the preparation of compounds of the type RC(OR′)=NOH (118–120, 176, 178, 226, 227).



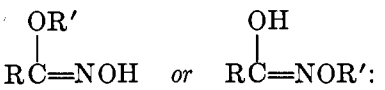
(36)

(2) *The reaction between an N-alkyl(or aryl)hydroxylamine, potassium alkoxide, and amyl nitrite:* Bamberger and Baudisch (31) obtained phenyl benzohydroxamic acid by the reaction between *N*-phenylhydroxylamine, potassium ethoxide, and amyl nitrite.

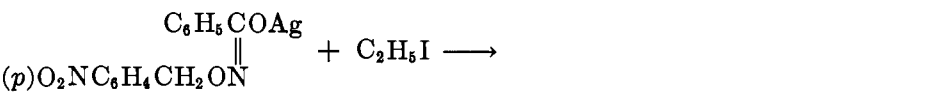
(c) Compounds of the general formulas 

Compounds of this group can exist in a single structural form or as either of two isomeric forms. They possess no acidic properties, do not reduce ammoniacal silver nitrate or Fehling's solution, and give no color test with ferric chloride.

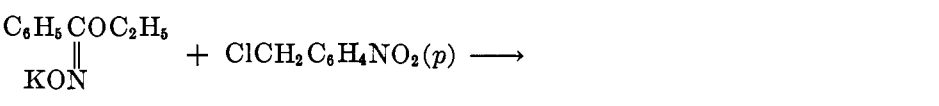
These compounds have been prepared by the following methods:

(1) *The alkylation of compounds of the types* 

Werner (305) found that identical ethyl *p*-nitrobenzyl benzohydroxamates were obtained by either of the two methods illustrated in equation 37 or 38.



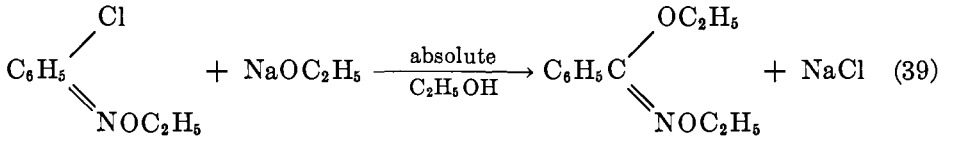
(37)



(38)

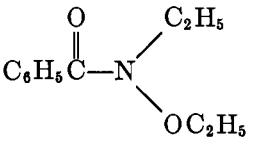
Alkyl iodides and alkali hydroxides or alkoxides were used to prepare dialkyl benzohydroxamates from alkyl benzohydroxamic acids (32, 180).

(*2*) *The reaction between an alkyl benzohydroxamyl chloride and sodium alkoxide:* The reaction was used by Tiemann and Krüger (292).



(39)

(*3*) *The reaction between an acid halide and an N-alkyl-O-alkylhydroxylamine:* The reaction between *N*-ethyl-*O*-ethylhydroxylamine and benzoyl chloride yielded diethyl benzohydroxamate:

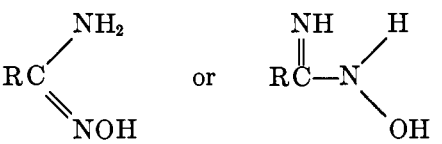


This product was different from the diethyl benzohydroxamate obtained by the reaction between benzohydroxamic acid and ethyl iodide (178).

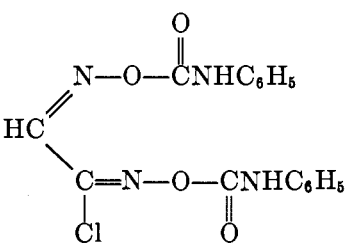
(*4*) *The reaction between ethyl ethoxycarbamate and an alkyl iodide in the presence of sodium alkoxide:* Jones and Neuffer (139) prepared $C_2H_5OCON(C_4H_9)OC_2H_5$ by the interaction of ethyl ethoxycarbamate and *sec*-butyl iodide in the presence of sodium ethoxide in alcoholic solution.

2. Monohydroxamyl halides

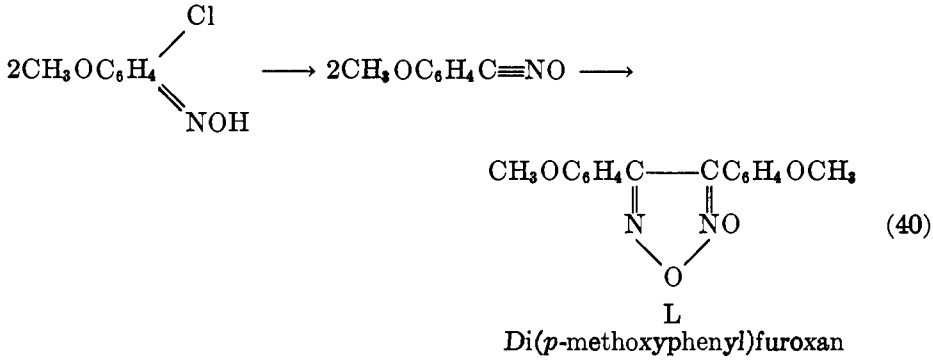
The monohydroxamyl halides, RCX=NOH, can be considered related to the monohydroxamic acids as acyl halides are related to carboxylic acids. The halogen atom in the monohydroxamyl halides was found to be much less reactive than the halogen in acyl halides. On hydrolysis, the monohydroxamyl halides yielded monohydroxamic acids, and with ammonia, they formed amidoximes (21, 308, 311, 313):



Phenyl isocyanate and formohydroxamyl chloride oxime, HC(=NOH)CCl=NOH, reacted (166) to yield



In dilute hydrochloric acid solution, acetohydroxamyl chloride and chlorine yielded 1,1-dichloro-1-nitrosoethane (225). Anisohydroxamyl chloride when treated with sodium carbonate yielded di(*p*-methoxyphenyl)furoxan (L) (151, 308, 311, 323).



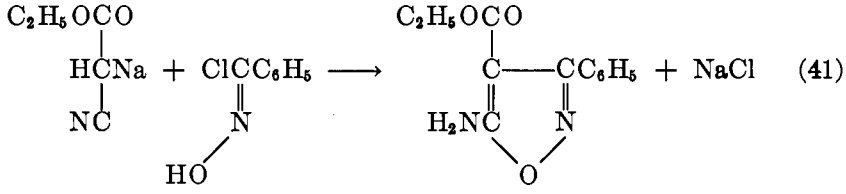
(40)

L

Di(*p*-methoxyphenyl)furoxan

From acetohydroxamyl chloride and silver nitrite there was obtained acetonitrolic acid; pyruvylohydroxamyl chloride and aqueous silver nitrate yielded silver fulminate (52, 225); silver fulminate and benzohydroxamyl chloride gave benzohydroxamyl fulminate, $C_6H_5C(=NOH)ON=C$ (328).

The monohydroxamyl halides were useful in the synthesis of isoxazole derivatives (242, 319).



(41)

Sodium azide and benzohydroxamyl chloride gave a tetrazole derivative (78), while hydrazine and acetohydroxamyl chloride yielded a triazole derivative (324).

Formohydroxamyl chloride has been the object of extensive investigations (50, 51, 198, 200, 201, 265, 293, 294, 327).

The monohydroxamyl halides gave the characteristic color test of monohydroxamic acids with ferric chloride.

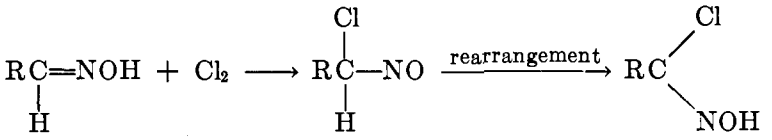
It has been reported that benzohydroxamyl chloride, or an impurity intimately associated with it, caused an irritating skin rash (78).

Preparation

The monohydroxamyl halides have been prepared by the following methods:

(*1*) *The chlorination of an aldoxime:* The chlorination of an aldoxime to a monohydroxamyl chloride can be carried out in either chloroform or dilute hydrochloric acid solution (225, 308, 313, 322, 324). A transitory blue color formed during the reaction, owing to the presence of the intermediate chloronitroso

derivative. Nitrosyl chloride and aldoximes also yielded monohydroxamyl chlorides (151, 248–250).



(42)

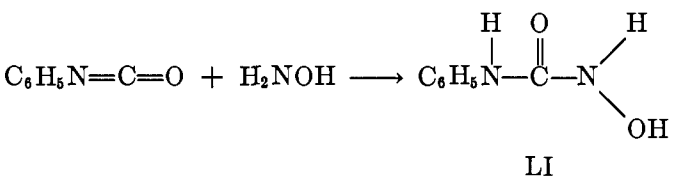
(2) *Miscellaneous methods of preparation:* Acetonitrolic acid (314), ethyl nitroacetate (278), or phenylnitromethane (202) with hydrochloric acid yielded, in each case, a monohydroxamyl chloride.

Several derivatives of the monohydroxamyl halides should be mentioned. Benzyl formohydroxamate and phosphorus pentachloride gave benzyl formohydroxamyl chloride (50). The reaction between *O*-ethylbenzamidoxime, hydrochloric acid, and sodium nitrite yielded ethyl benzohydroxamyl chloride (288, 292). Triphenylmethyl triphenylacetohydroxamyl chloride was prepared from triphenylmethyl chloride and silver fulminate (330).

3. *Carbamylhydroxamic acids*

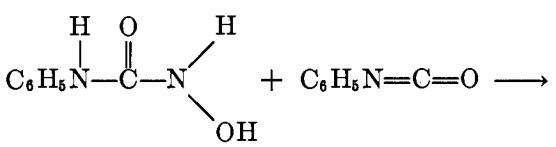
The carbamylhydroxamic acids are similar in many ways to the true hydroxamic acids. They are soluble in alkali and reduce Fehling's solution. With ferric chloride they give the intense violet color characteristic of the monohydroxamic acids (121).

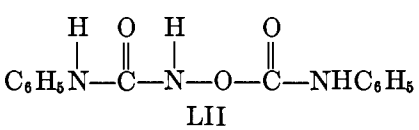
Phenyl isocyanate is an acylating agent, and in its reactions it possesses a behavior very similar to that of the ketenes. Thus, with hydroxylamine there is a progressive substitution of hydrogen atoms in the order previously shown with the ketenes (44, 47, 48, 77, 121, 124, 150, 154).



(43)

LI



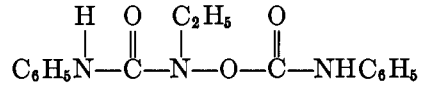


(44)

LII

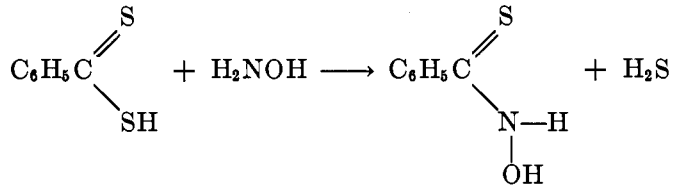
The structure of LII, as well as of other hydroxyurea derivatives (70, 81, 154), has been discussed by Hurd (121).

The reaction between *N*-ethylhydroxylamine and one equivalent of phenyl socyanate gave ethyl phenylcarbamylhydroxamic acid, $C_6H_5NHCON(C_2H_5)OH$, which gave an intense color test with ferric chloride. With two equivalents of isocyanate the product was



4. Thiohydroxamic acids

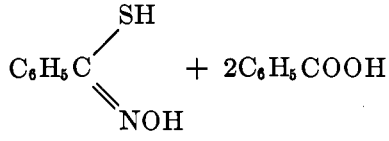
A few of the sulfur analogs of the hydroxamic acids have been prepared. The reaction between dithiobenzoic acid, C_6H_5CSSH, and hydroxylamine yielded thiobenzohydroxamic acid (58).



(45)

Dithiobenzoic acid — Thiobenzohydroxamic acid

Potassium thiobenzohydroxamate and benzyl chloride yielded benzyl thiobenzohydroxamate. Dibenzoyl thiobenzohydroxamate (LIII) was hydrolyzed in two ways by alcoholic potassium hydroxide:



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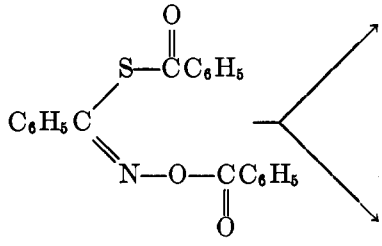
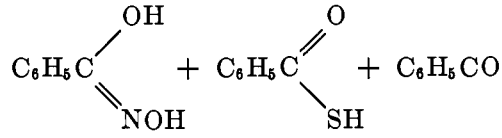


LIII
Dibenzoyl thiobenzohydroxamate

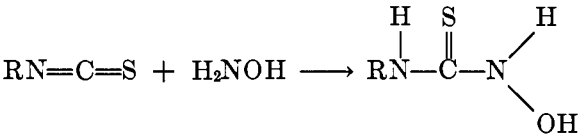


(47)

The principal reaction was that shown by equation 47.

Nef (198) found that silver fulminate and hydrogen sulfide gave thioformohydroxamic acid, HC(SH)=NOH.

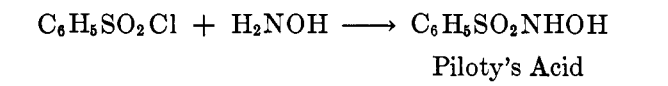
The thiocarbamylhydroxamic acids were prepared by the reaction between hydroxylamine and isothiocyanates (48, 286).



(48)

5. Arylsulfonhydroxamic acids

Piloty's Acid, benzenesulfonhydroxamic acid (224), was discussed previously (page 228) with regard to its utilization in the preparation of monohydroxamic acids from certain aldehydes. It was prepared by the reaction between benzenesulfonyl chloride and hydroxylamine (4, 14, 15, 224).



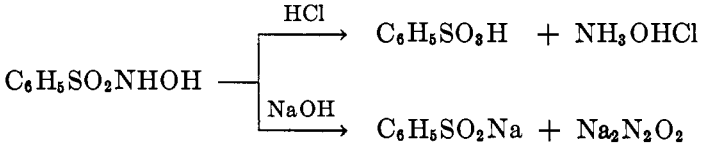
(49)

Piloty's Acid

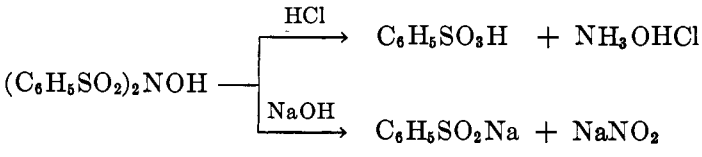
It gave the characteristic color test of monohydroxamic acids with ferric chloride (101).

The oxidation of benzenesulfonhydroxamic acid with ferric chloride or nitrous acid yielded $(C_6H_5SO_2)_2NOH$ (14, 156, 224). Fuming nitric acid gave the trisubstituted hydroxylamine derivative, $(C_6H_5SO_2)_3NO$.

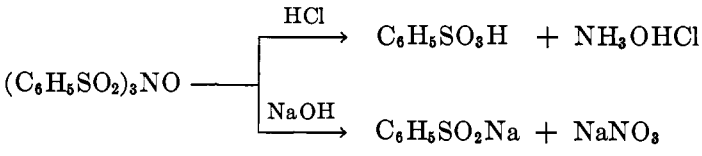
The behavior of these three derivatives when subjected to alkaline or acid hydrolysis is shown in the following equations:



(50)



(51)



(52)

Benzenesulfonhydroxamic acid and acetic anhydride, in excess, gave diacetyl benzenesulfonhydroxamate (224). It has been reported that benzenesulfonhydroxamic acid and a Grignard reagent subsequent to hydrolysis yielded benzenesulfonamide; if the reaction mixture prior to hydrolysis was treated with benzoyl chloride, the product obtained was $C_6H_5SO_2NHCOC_6H_5$ (215).

F. DIHYDROXAMIC ACIDS

The diacylated hydroxylamine derivatives are acidic. They give no color reaction with ferric chloride. The rearrangement of their alkali metal salts is their most characteristic reaction. They are not polymorphous. They can be titrated quantitatively with alkali, using thymol blue as the indicator (57, 247).

The dihydroxamic acids have been prepared by the following methods:

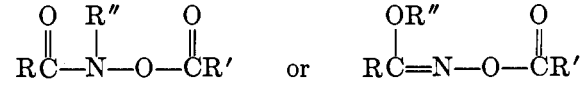
(*1*) *The reaction between a salt of a monohydroxamic acid and an acyl halide:* The finely pulverized salt, suspended in dioxane, was treated with the theoretical amount of acyl halide. The mixture was boiled for 5 min. and poured into water (247). Monohydroxamic acids and acid halides in the presence of an equivalent of alkali hydroxide, carbonate, or acetate, in various solvents, also yielded dihydroxamic acids (116, 140, 145, 170, 178).

(*2*) *The reaction between an acid halide or acid anhydride and hydroxylamine:* Hydroxylamine, or its addition product with chloral, reacted with acid anhydrides to yield dihydroxamic acids (97, 297). When two equivalents of benzoyl chloride and one equivalent of dry hydroxylammonium chloride were heated at 110°C. for 12 hr., benzoyl benzohydroxamate was obtained (108). The latter reaction may also be carried out in water (182, 305).

(*3*) *Miscellaneous methods of preparation:* Dihydroxamic acids were prepared by the reaction between acid halides and sodium *aci*-nitroalkanes (115, 132, 152, 199, 246). When the reaction was carried out in pyridine, the product was benzoyl benzohydroxamyl chloride (329). Phenylnitromethane, either on long standing (67) or on distillation at atmospheric pressure (107), gave benzoyl benzohydroxamate. Excellent yields of dihydroxamic acids were obtained from the reaction between a monohydroxamic acid and a ketene (124). The acid cleavage of alkyl acyl benzohydroxamates yielded dihydroxamic acids (182). The reaction between nitric oxide and the dipotassium salt of benzoin gave benzoyl benzohydroxamate as one of the products (262). Monohydroxamyl chlorides and silver salts of organic acids yielded dihydroxamic acids (313). Benzohydroxamic acid and potassium cyanide yielded benzoyl benzohydroxamate (188). The treatment of one equivalent of hydroxylamine with two equivalents of ethylmagnesium bromide, followed by benzoyl chloride, gave benzoyl benzohydroxamate.

1. Alkyl- and aryl-substituted dihydroxamic acids

Compounds of the general formulas



are polymorphous, existing in α- and β-modifications. The reaction between *N*-benzylhydroxylamine and benzoyl chloride led to benzyl benzoyl benzohydroxamate, possessing the single structure, $C_6H_5CON(C_6H_5)OCOC_6H_5$ (45, 46). On the other hand, the reaction between ethyl iodide and silver benzoyl benzohydroxamate gave ethyl benzoyl benzohydroxamate, capable of existing as

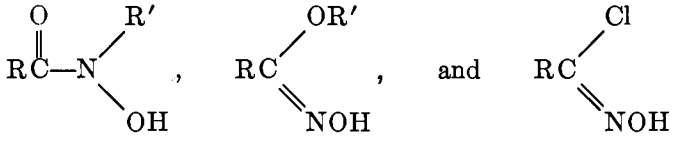
either of the isomeric forms (72, 96, 178). Ethyl anisoyl benzohydroxamate, prepared by the reaction between anisoyl chloride and ethyl benzohydroxamic acid, also possessed two possible isomeric structures (222).

G. METAL SALTS OF THE MONO- AND DI-HYDROXAMIC ACIDS

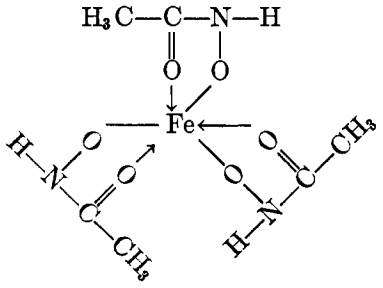
Salts of the monohydroxamic acids have been prepared with nearly all the elements of Groups I, II, and III of the Periodic Table, as well as zirconium, thorium, cobalt, nickel, and iron (109, 131, 136, 167, 169, 170, 219, 237, 310). Of these the iron, copper, cobalt, and nickel salts are of special interest. These compounds are colored and possess chelated structures.

Ferric acetohydroxamate may be isolated as deep red colored prisms by the reaction between acetohydroxamic acid and ferric ethoxide, in alcoholic solution (100). The salt is very soluble in water. It was found to be a better conductor of electricity than ferric acetylacetonate, gave no precipitate with potassium ferrocyanide, reacted only very slowly with ammonia to give ferric hydroxide, and was dissociated only by a high acid concentration. This stability differentiated these compounds from the colored enolates and phenolates (66, 74–76).

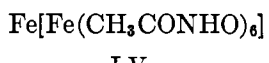
Since it is known that derivatives of the general formulas RCONHOR′ or RC(OH)=NOR′ do not give color reactions with ferric chloride, while compounds of the structures



do, it is apparent that the =NOH grouping is necessary for the formation of the coördination compound. Several possible structures have been proposed (LIV and LV) (66, 100, 122, 310).



LIV



LV

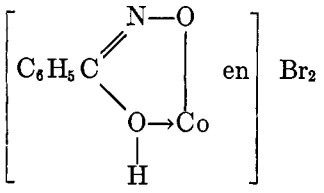
Several basic ferric compounds, e.g., $(C_6H_5CONHO)_2FeOH$, have been described (71, 100).

The color test with ferric chloride is extremely sensitive. It will detect the presence of 2 γ of a carboxylic acid or acid anhydride (74–76).

The copper salts are green in color and very insoluble in water. Their prin-

cipal use is in the isolation and purification of the monohydroxamic acids. Structurally they are similar to the ferric chelates (24, 71, 94, 163); they form basic and neutral salts. The neutral salts give no test for copper with potassium ferrocyanide, potassium thiocyanate, or hydrogen sulfide. The nickel-chelated monohydroxamates are similar to the copper salts.

Benzohydroxamic acid yielded a coördination compound with ethylenediamine and cobalt bromide (316).



The sodium and potassium salts of the dihydroxamic acids find application in studies on the Lossen rearrangement. The potassium salt undergoes reaction more readily than does the sodium salt. Both are very soluble in water and alcohol, and are prepared generally in absolute alcohol and precipitated with ether or dioxane (57, 140, 142, 247).

H. TRIACYLATED HYDROXYLAMINE COMPOUNDS

The triacylated hydroxylamine compounds were found to be polymorphous, existing in α-, β-, and γ-forms (161, 171, 173). In view of the methods utilized in their preparation, two isomeric structures were possible with these derivatives.

The monohydroxamic acids when treated with an excess of a ketene yielded triacylated hydroxylamine compounds in excellent yields (124); with acetic anhydride or acid halides, these derivatives were obtained only by prolonged treatment at elevated temperatures.

Other methods which have been utilized for the preparation of the triacylated hydroxylamine derivatives are:

(*1*) *The reaction between a salt of a dihydroxamic acid and an acid halide:* Benzoyl chloride and silver benzoyl benzohydroxamate, after eighteen days at room temperature, gave dibenzoyl benzohydroxamate (171, 173).

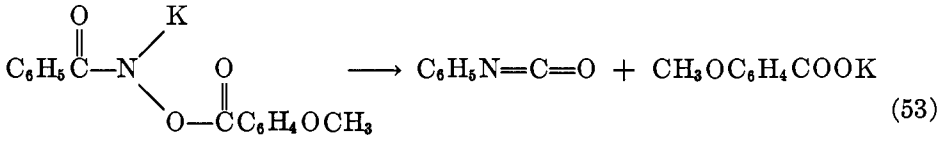
(*2*) *The reaction between hydroxylamine and an acid chloride:* Dibenzoyl benzohydroxamate was formed, along with benzoyl benzohydroxamate and benzohydroxamic acid, by the interaction of benzoyl chloride and hydroxylamine (169).

(*3*) *The reaction between sodium aci-nitroalkanes and acid halides:* The reaction between sodium *aci*-nitroethane and benzoyl chloride yielded dibenzoyl acetohydroxamate (132, 199).

II. The Lossen Rearrangement

The Lossen rearrangement, in its broadest interpretation, occurs as a result of the thermal decomposition of hydroxamic acids or their derivatives. As a consequence, a group attached to carbon originally is found joined to nitrogen in the final product. The rearrangement was first observed by Lossen (169),

apparently by accident, when he heated benzoyl benzohydroxamate above its melting point and obtained a lachrymatory substance (phenyl isocyanate). Soon afterward he reported that potassium anisoyl benzohydroxamate in boiling water readily gave diphenylurea, potassium anisoate, and carbon dioxide (170–172).



(53)

$$C_6H_5N{=}C{=}O + H_2O \longrightarrow C_6H_5NH_2 + CO_2$$

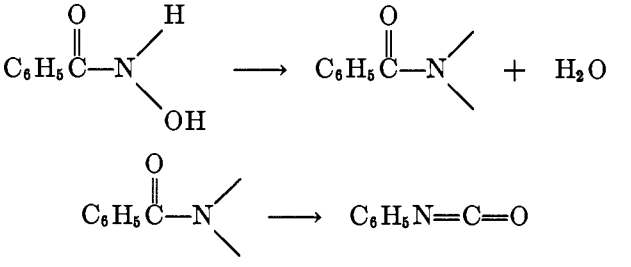
$$C_6H_5NH_2 + C_6H_5N{=}C{=}O \longrightarrow (C_6H_5NH)_2CO$$

The Lossen rearrangement is now taken to mean the latter type of reaction, although a variety of hydroxamic acid derivatives when subjected to destructive distillation undergo this change (89, 96, 121a, 173, 222, 223, 290). Rearrangement has been effected also by heating hydroxamic acids and their derivatives with thionyl chloride (189), acetic anhydride (203), and phosphorus pentoxide (33, 146).

A. Mechanism of the Lossen rearrangement

The Lossen rearrangement possesses an inherent similarity to the Hofmann, Curtius, and Beckmann rearrangements (49, 53, 57, 105, 247, 273, 280–283, 302–304). There has been a tendency to refer to them collectively as Beckmann rearrangements, although no great purpose can be accomplished by such a classification (53).

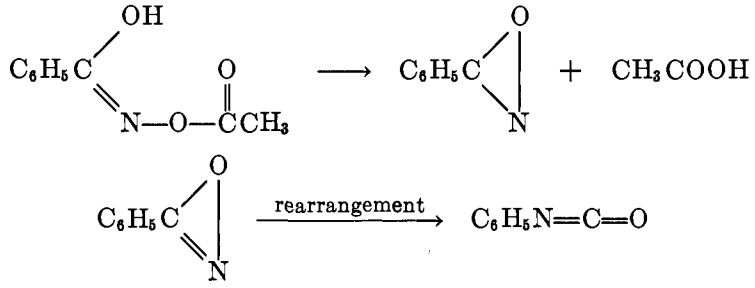
Although Lossen (175) was aware of the similarity between his rearrangement and the Hofmann rearrangement, he was apparently free of curiosity concerning its mechanism. Tiemann (290), in attempting to explain the formation of carbon dioxide and aniline by the destructive distillation of benzohydroxamic acid, proposed that the reaction proceeded through an intermediate univalent nitrogen derivative which rearranged to an isocyanate.



(54)

$$C_6H_5N{=}C{=}O + H_2O \longrightarrow C_6H_5NH_2 + CO_2$$

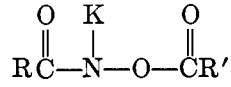
As an alternative to the univalent nitrogen compound, Hantzsch (99) proposed a cyclic intermediate.



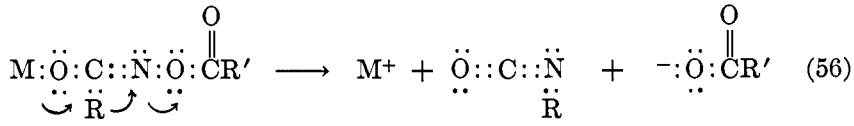
(55)

The hypothesis that a univalent nitrogen derivative was the intermediate in the Lossen rearrangement was largely developed by Jones and his students on the basis of the pioneer work of Stieglitz (53, 280–283) and Schroeter (53, 267). Jones considered this mechanism the most satisfactory explanation for the rearrangement, and indirectly indicated the structure of the hydroxamic acids as RCONHOH (133, 144–146). Gastaldi (84, 87, 89, 93) used this mechanism to explain the formation of 1,2,4-triazole derivatives from the arylhydrazones of pyruvylohydroxamic acid.

Hauser and his students (57, 105, 247) showed that the rearrangement velocity in a series of compounds of the type,



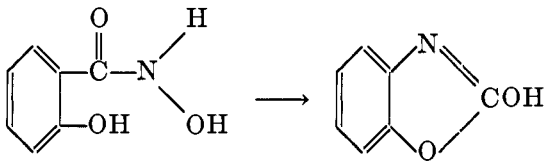
was directly related to the ionization constant of the acid, R'COOH, when R was held the same, or indirectly related to the ionization constant of RCOOH, if R' was held constant. Baker (23) previously noted this same generalization, i.e., the facility with which the Lossen rearrangement occurred with the acylated monohydroxamic acids increased with the increasing anionic stability of the anionizing group. This was essentially the requirement for a pinacol-type rearrangement.



(56)

According to this mechanism, there occurred first a depletion of electrons around the nitrogen atom, necessitating the migration of R with its pair of electrons from the adjacent carbon atom. The tendency of M to part from, and of OCR' to retain, bond electrons during the formation of the ions M^+ and $^-:\ddot{O}:CR'$ furnished the driving force for the reaction.

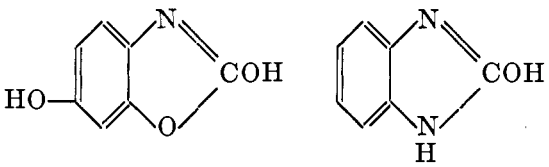
The recent work of Scott and his students (269–272), based on the early work of Marquis (189), indicated that isocyanates may not always be intermediates in the Lossen rearrangement. Marquis found that salicylohydroxamic acid and thionyl chloride gave oxycarbanil (LVI) instead of *o*-hydroxyphenyl isocyanate.



(57)

LVI
Oxycarbanil

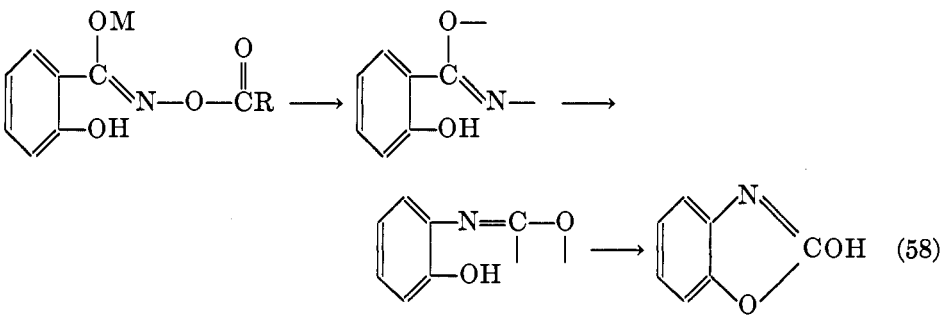
Scott and Mote (271) also obtained oxycarbanil from potassium benzoyl salicylohydroxamate. In the same way, potassium acetyl 2,4-dihydroxybenzohydroxamate gave 4-hydroxycarbanil (LVII) (270), and potassium benzoyl-*N*-benzoylanthranilohydroxamate gave 2-oxybenzimidazole (LVIII) (272).



LVII
4-Hydroxycarbanil

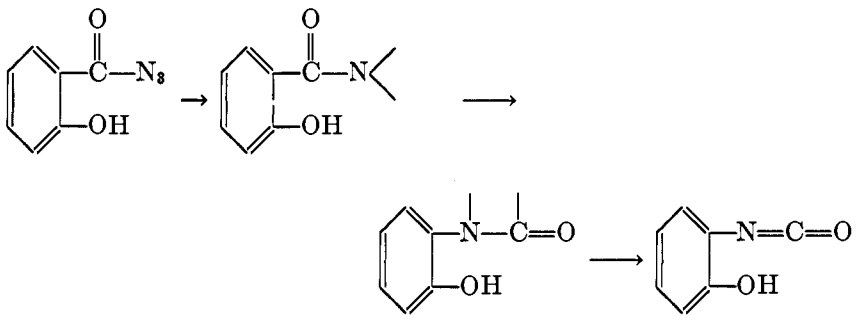
LVIII
2-Oxybenzimidazole

Scott and Kearse (270) preferred a mechanism which involved the hydroxyoxime structure of the metal salt of the acylated salicylohydroxamate, and was not based on the formation of an isocyanate.



(58)

In the Curtius rearrangement of the azide of salicylic acid there was formed a univalent nitrogen derivative capable of rearranging to an isocyanate.



(59)

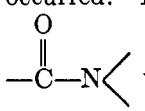
A significant part of the mechanism of the Lossen rearrangement is concerned with the shift of the R group from carbon to nitrogen. Since a carbon–carbon linkage is severed in this process, it appeared reasonable to assume that the R group must exist at least momentarily as a free radical. Jones and Hurd (136) made a comparative study of the rearrangement of the potassium salts of the benzoyl phenyl-, diphenyl-, and triphenyl-acetohydroxamates and found that the ease of rearrangement was greatest with the triphenyl derivative and least with the phenyl derivative. As a consequence of these observations, it appeared that the relative ease of rearrangement was dependent upon the tendency for the radical R in the univalent nitrogen derivative to exist as a free radical.

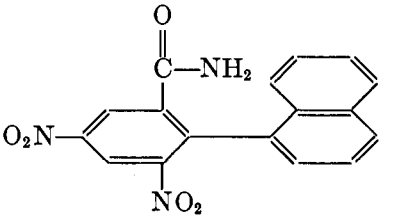
Further evidence for this thesis lay in the comparative stability of the potassium salts of benzoyl *o*- and *p*-benzhydrylbenzohydroxamate which were isomeric with the triphenylacetohydroxamic acid derivative (143); in the ready rearrangement of potassium benzoyl dibenzylacetohydroxamate when compared with the corresponding monobenzyl compound (144); in the rearrangement of the sodium salts of acylated diphenylcarbamylhydroxamates and the absence of any rearrangement with the phenylcarbamylhydroxamates (121); and in the ease of rearrangement of the salts of the acylated diphenyl-*p*-tolylacetohydroxamates (123).

In order to study this hypothesis critically, Jones and Wallis (147) and Wallis and Dripps (301) investigated the rearrangement of optically active hydroxamic acid derivatives. The latter subjected potassium benzoyl *d*-benzylmethylacetohydroxamate to rearrangement and obtained an optically active isocyanate which when hydrolyzed yielded an optically active amine. There was sufficient evidence to indicate that partial racemization had not occurred during the rearrangement.

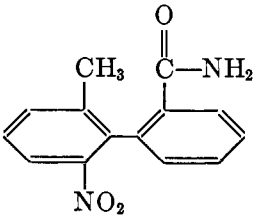
Jones and Wallis (147) suggested that optical stability could be maintained by the radical if it were to exist as a positive (or negative) ion, or, if the rearranging group did not exist in the free state, but was so under the influence of the univalent nitrogen atom that, when cleavage occurred, a change in the configuration of the asymmetric carbon atom was prevented. This influence was presumed to be that of partial valences.

In a related study of the Hofmann rearrangement of *d*-3,5-dinitro-6-(α-naphthyl)benzamide (LIX), Wallis and Moyer (302) found that no racemization had

occurred. If a positive or negative radical had existed, the blocking effect of the  would have been removed and free rotation about the axial bond would have been possible. Since not even partial racemization had occurred, they concluded that no free radicals had formed and suggested the existence of partial valences as an explanation. Bell (49) showed that the optically active 6-nitro-2-methyldiphenyl-2′-carboxamide (LX) when subjected to rearrangement also gave no evidence of racemization in the product.



LIX

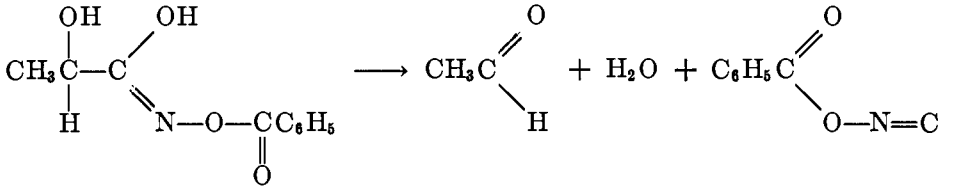


LX

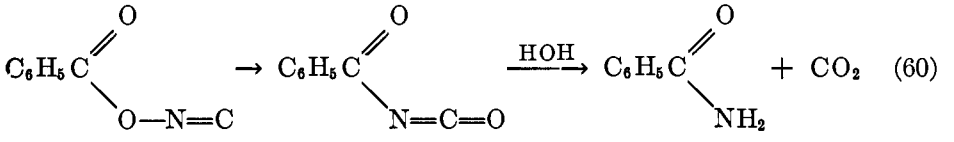
Bell suggested as an alternative explanation the possibility that the radical existed for a short time compared to the time required for rotation of the two aromatic nuclei.

B. Anomalous behavior in the Lossen rearrangement

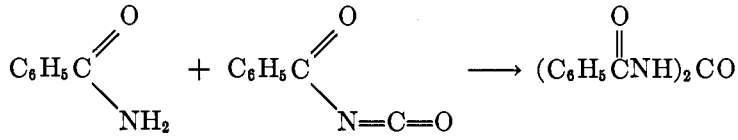
The hydroxamic acids and their derivatives when subjected to the conditions necessary for the Lossen rearrangement are known to give other anomalous reactions. For example, heating a mixture of benzoyl lactohydroxamate (LXI) and water yielded acetaldehyde, dibenzoylurea, carbon dioxide, ammonia, and ethyl alcohol. The formation of several of these products can be attributed to a dissociation of the hydroxyoxime structure of LXI into acetaldehyde and benzoylfulminate (LXII), which could then rearrange to benzoyl isocyanate (LXIII) (140).



LXI LXII

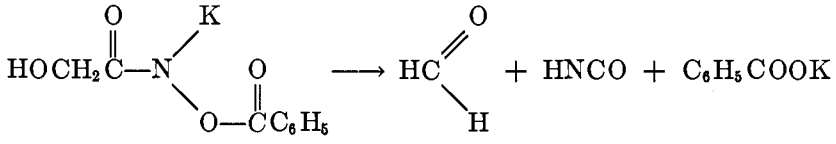


LXIII (60)

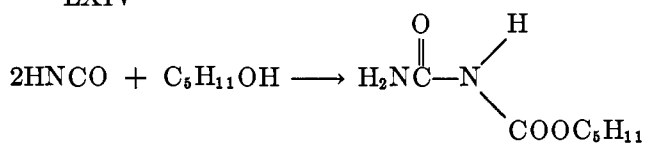


Under similar conditions benzoyl mandelohydroxamate gave benzaldehyde as one of the products.

Formaldehyde and isoamyl allophanate were obtained in a related reaction between potassium benzoyl glycolohydroxamate (LXIV) and isoamyl alcohol. The intermediate dissociation products were presumed to be formaldehyde and cyanic acid (142).



LXIV



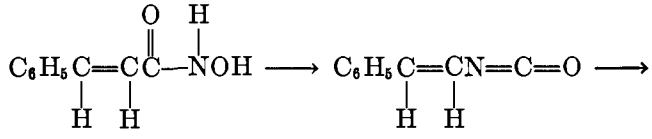
Isoamyl allophanate (61)

It appeared that compounds which have an OH group in the α-position yield an aldehyde or ketone and cyanic acid when subjected to the Lossen rearrangement. If the rearrangement occurred in water, the products were urea or carbon dioxide and ammonia, while in alcohol the product was an allophanate.

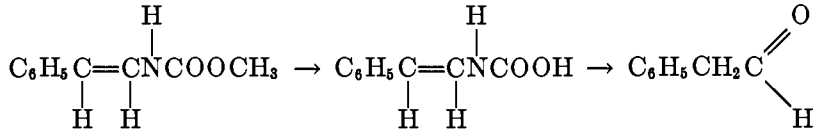
In this connection it was interesting to note that dry potassium benzoyl methoxyacetohydroxamate, heated at 115–120°C., yielded potassium benzoate and methoxymethyl isocyanate (142).

Potassium benzoyl cinnamohydroxamate underwent no rearrangement in boiling water; it reacted in alcohol to yield ethyl styrylcarbamate (137). Warming either oleo- or elaido-hydroxamic acid with an excess of acetic anhydride led to a mixture of *cis*- and *trans*-heptadecylenyl isocyanates. Apparently rearrangement of the double bond had occurred (203).

The Lossen rearrangement was used to prepare phenylacetaldehyde from cinnamohydroxamic acid (284) and epicamphor from bornylene-3-hydroxamic acid (56).

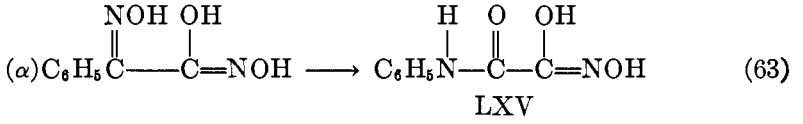


Cinnamohydroxamic acid



(62)

An interesting reaction was reported by Gastaldi (92). He treated α-benzoylformohydroxamic acid oxime with phosphorus pentachloride in dry ether and obtained phenylcarbamylformohydroxamic acid (LXV). This was an example of a Beckmann rearrangement which proceeded without disturbing the hydroxamic acid.



(63)

LXV

The carbamylhydroxamic (121, 126), thiocarbamylhydroxamic (286), arylsulfonhydroxamic (224, 320), and thiobenzohydroxamic (58) acids and their derivatives did not undergo the Lossen rearrangement.

C. Temperature and alkalinity as factors in the Lossen rearrangement

Mohr (196) found that the quantity of alkali present during the rearrangement of dihydroxamic acids determined the relative amounts of urea and aniline formed. The neutral potassium or sodium salt in dilute aqueous solution was completely decomposed at 70°C. in 2 hr. and gave principally diphenylurea and some aniline. An excess of dilute alkali (0.1 *N*) yielded chiefly aniline. With increasing dilution of the alkali, the ratio of aniline to diphenylurea was increased.

Dougherty and Jones (68) made rate studies on the rearrangement of benzoyl benzohydroxamate in the presence of two equivalents of potassium hydroxide at 25°C. At this temperature reaction was incomplete after approximately 100 hr. They detected the presence of aniline and benzohydroxamic acid almost immediately; the odor of phenyl isocyanide was evident after 15 hr. Phenyl isocyanate was present in small amounts. After 25 hr. a precipitate of diphenylurea formed which increased as the reaction progressed. No satisfactory rate constants were obtained for the first 25 hr. during which 25 per cent of the reaction occurred; with the formation of diphenylurea, constants for a first-order reaction were obtained. The variation in the constants for the first one-quarter of the reaction was attributed to the presence of free alkali. This excess alkali hydrolyzed some of the potassium benzoyl benzohydroxamate to potassium benzohydroxamate and potassium benzoate; it also hydrolyzed phenyl isocyanate to aniline. The rôle of the alkali became more insignificant, and the reaction rate fairly constant as a result of the reaction of phenyl isocyanate with aniline, indicated by the appearance of diphenylurea.

Renfrow and Hauser (247) eliminated these difficulties to a large extent by measuring the rates of reaction of the potassium salts of the dihydroxamic acids in 0.1 *N* ammonia solution. Ammonia reacted with aryl isocyanates to form soluble arylureas, but the hydroxyl-ion concentration was insufficient to cause appreciable hydrolysis of the dihydroxamic acids.

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