THE FUROXANS

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I. INTRODUCTION

The close relationship between *o*-dinitroso compounds, *gem*-dinitroso compounds, and the products of the oxidation of dioximes has stimulated the preparation of this review.

Much of the difficulty associated with the study of the furoxans may be ascribed to the confusion that has been associated with understanding their structure. From the beginning of their history there has been a notable vacillation in the attitude of the scientists studying these substances as to the nature of their configuration. This vacillation has included the problem of whether to ascribe the same structure to both the aromatic and the aliphatic types of compounds. In fact, the study of the structure from the point of view of the aromatic series has caused difficulty in making conclusions concerning the aliphatic series. As a result, the data in the literature show almost a clear-cut delineation of research effort between the two series.

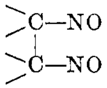
This review covers the years from 1876 to the present and is limited only by the information available. A good portion of this paper will deal with a critical discussion of the various structures which have been proposed for furoxans to date. Additional information will be presented on the reactions, the physical and chemical properties, and the methods of preparation of these compounds.

A section on their nomenclature has been added to provide an understanding of the information in the literature and its interrelation.

It is hoped that this review will stimulate further interest in these fascinating compounds.

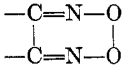
II. NOMENCLATURE OF THE FUROXANS

In 1858 Kekulé (97) made the first furoxan by the reaction of bromine and mercuric fulminate; he erroneously called it dibromnitroacetonitrile. Not until 1876 was further work done on this structure, when Steiner (19) obtained a product from the reaction of ammonium fulminurate and concentrated sulfuric acid which he called nitroacetonitrile, but which is now known as dicyanfuroxan. Tonnies (202), in 1880, reported a reaction which later became one of the general preparative methods for this class of compounds; that is, the reaction of nitrogen oxides with vinylic double bonds. The first definitive name and hence implied structure given to this combination of atoms was that of nitroso compounds, suggested by Pröpper (179),



but the following year he considered that his products were oximino compounds (180, 181). Historically, Koreff (100) is credited with the preparation of the same substance by the oxidation of a dioxime, although Koreff acknowledged that H. Schmid described the compound to him and Ilinski (90) reported its preparation in the same year. Although no name was proposed for their compounds, they did suggest that the oxidation product of β-naphthoquinone dioxime, $C_{10}H_6(=NOH)_2$, had the same properties as the substance obtained by oxidizing phenylglyoxime and that the compound was not a dinitroso compound but of the type later to be called glyoxime peroxide (11). At very nearly the same time that Holleman (84) proposed the name "dinitrosoacyl" for the product that he obtained by nitrating acetophenone, Beckmann (28) proposed that his product from the nitration of benzil dioxime be called azodibenzenyl hyperoxide, and Scholl (187) gave the name "benzildioxime superoxide" to the product that he obtained from benzaldoxime.

Angeli (11) then repeated the work of Tonnies and Beckmann and suggested the name "glyoxime peroxide." All of these authors were referring to the same structure in an aliphatic series of compounds, viz.:

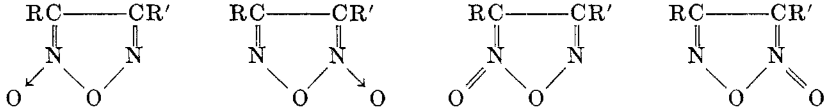


This designation was accepted and found such general use that although Perkin (130) stated the name to be incorrect, he used it in describing his work because of its presence in the literature and textbooks at the time.

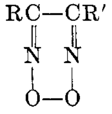
Noelting and Kohn (126) prepared substances which they called o-dinitroso compounds and to which they gave the formula $NO_2C_6H_3(NO)_2$ by the thermal decomposition of aromatic nitro azides. The work of Zincke and Schwarz (238) was of an almost identical nature, but in addition they compared their substances with those previously described by Ilinski.

It was not until 1907 that the name "furoxan" was suggested by Wieland (235) for these structures. During this period a great deal of research led to the formation of furoxans, but owing to the lack of communication between investigators, the literature referred to these substances as acid (191), acid anhydride (197), and isoöxadiazole oxides (70). In the late 1920's, when the existence of a possible isomeric form for these substances had been proposed, Ponzio and Torres proposed the name "dioxdiazine" to describe the structure in question (178). The most recent designation suggested for compounds of this type is that of ψ-dinitroso compounds, proposed by Boyer (46).

In order to carry out an intelligent discussion, the following terminology has been arbitrarily selected for the furazan oxides. The term "furoxan" will be used to designate the structures



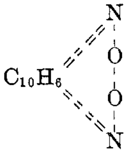
and the term "dioxdiazine" will define the following structure:



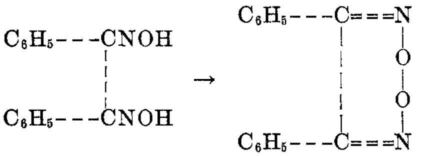
III. STRUCTURE OF FUROXANS

The compounds in question can be said to be derivatives produced by the oxidation of substituted glyoximes. As noted previously, Pröpper's (179) investigations of the action of fuming nitric acid on acetic acid ester and monoacetic acid ester led him to designate his products as oximino acetic acid esters.

Koreff (100) in 1886, working with β-naphthoquinone dioxime, found that this material could be reduced to the naphthalenediamine, but that it could also be oxidized to a product melting at 126°C. and having an empirical formula corresponding to C_5H_3NO. Koreff first suggested for this substance the following general structure



relating it to an analogous oxidation product of diphenylglyoxime implicitly according to the following reaction,



but Koreff did not name the product. This structure was then referred to as Koreff's structure.

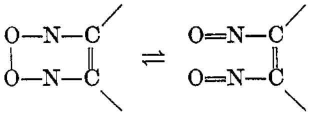
Some of the confusion at this stage of the investigation was removed to an extent by Cramer's (49) preparation of a true oximino compound from glyoxylic acid; Beckh (26) obtained the same ester from ethyl dioximino succinate. This work added little to the solution of the true structure.

A noteworthy experiment was reported by Boeris (35) but did not make its expected impact until fifteen years later. He was able to prove that reduction of one of these peroxides with tin and hydrochloric acid gave the furazan structure; however he called his product the anhydride. He showed in addition that the reduction of the oxime or the bromination of the "anhydride" gave the same brominated structure. The results of Angeli's (10) reduction experiments did not confirm this observation but obscured it somewhat by claiming the preparation of the parent dioxime.

So far as the structure of these compounds is concerned, the period from 1893 to 1904 resulted only in attempts to establish the six-membered peroxide ring as characteristic of these materials and to describe the product by a variety of names (9, 10, 18, 19, 27, 29, 41, 42, 84, 126, 187, 212, 238).

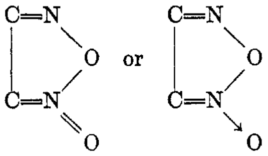
The difficulty associated with accepting a peroxide structure for the ring was an obvious temerity in accepting the formation of a peroxide bond in any manner other than that commonly associated with the formation of derivatives of hydrogen peroxide. The stability of the ring exhibited by the structure did not help matters.

In an attempt to rationalize the stability of these substances Perkin (130) did suggest, however, that an equilibrium of the following nature might be present

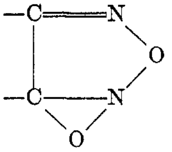


which could confer stability. However, in this case substituents would tend to force the equilibrium in a preferred direction, a behavior which had not been suggested as yet.

In 1904 Werner (211) suggested the structure

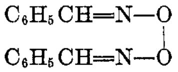


to which Wieland and Semper gave the name "furoxan" in 1907. Wieland (235) acknowledged Werner's claim but, in addition, suggested an additional structure, viz.:



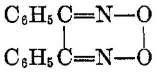
He arrived at his conclusions from an examination of the chemical evidence available at that time, which included the stability of the $C_2N_2O_2$ group, the lack of strong oxidizing properties characteristic of peroxides, and the fact that some of the compounds could be reduced to furazans. According to this reasoning, these compounds appeared to be oxides of furazan, although none of them have been prepared by the oxidation of a furazan.

An undercurrent was present in the literature at about this time which bore evidence of support for a peroxide bond in the furoxan structure but which Wieland obviously ignored. In 1889 Beckmann (28) prepared a straight-chain compound by the careful oxidation of α-benzaldoxime with alkaline potassium ferrocyanide. At the same time, he was able to perform a further oxidation on the substance and obtain the expected furoxan. Beckman gave the following formulas and melting points:



$$\begin{array}{lll} C_6H_5CH{=}N & - & O \\ & & | \\ C_6H_5CH{=}N & - & O \end{array}$$

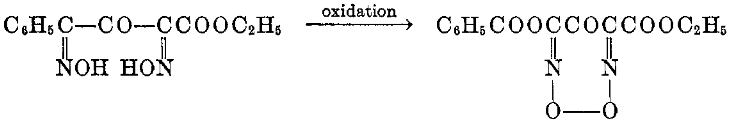
Straight-chain compound
Melting point 105°C.



$$\begin{array}{llll} C_6H_5 & C{=}N & - & O \\ & | & & | \\ C_6H_5 & C{=}N & - & O \end{array}$$

Ring compound
Melting point 114–115°C.

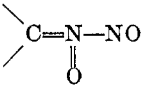
The analyses reported were not good by modern standards and raise a question as to their acceptance. Although Scholl (187) referred to Beckmann's work, he did not repeat the experiment to give corroborative evidence. Other investigators (47, 48, 60, 123, 131, 203) repeated Beckmann's work but presented conflicting evidence, especially on melting points. The information is highly suggestive that a peroxide type link is formed between two nitrogen atoms in aldoximes by controlled mild oxidations, but corroborative evidence is lacking. To this must be added the evidence of Henry and von Peckmann (79) of the formation of a peroxide link in a ring in which additional carbon atoms are present between the carbon atoms attached to the nitrogen atoms, viz.:



$$\begin{array}{l} C_6H_5\underset{\underset{NOH}{\|}}{C}{-}CO{-}\underset{\underset{HON}{\|}}{C}COOC_2H_5 \end{array} \xrightarrow{\text{oxidation}} \begin{array}{l} C_6H_5COO\underset{\underset{N}{\|}}{C}COC\underset{\underset{N}{\|}}{C}OOC_2H_5 \\ \qquad\qquad\quad |\quad\;\; | \\ \qquad\qquad\quad O{-}{-}O \end{array}$$

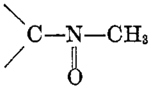
This particular oxidation was performed with fuming nitric acid. It is unfortunate that detailed corroborative evidence is not available for this interesting reaction.

At about this same time (1906) Angeli (14, 15) undertook to reinvestigate the situation. His contention was that a substance containing the group $>C{=}N_2O_2$ may well be considered as a pernitroso derivative or as the ether of an N-nitroso dioxime (I), which is analogous to the ether of an N-alkyl oxime



$$>C{=}\underset{\underset{O}{\|}}{N}{-}NO$$

I

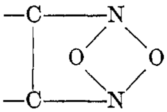


$$>C{-}\underset{\underset{O}{\|}}{N}{-}CH_3$$

II

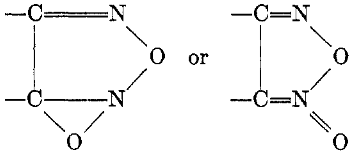
(II). However, this structure would require that the nitrogen atom be pentacovalent, a fairly uncommon occurrence for nitrogen.

Later Green and Rowe (66) at first suggested from a consideration of the chemical properties of the aromatic furoxans which they prepared that the extraannular oxygen form accorded more with their results, but the inability of Forster and Barker (57) to obtain isomers in the aromatic series caused them to suggest a new symmetrical structure



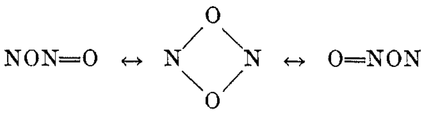
with which Green and Rowe, as well as Angeli and later Bigiavi (14, 15, 32, 67), agreed.

Wieland (225) did not accept these arguments and from steric arguments reiterated his belief that the structure was either



Such a structure would obviously predict that unsymmetrically substituted furoxans should exist in two isomeric forms.

In an attempt to settle the differences that existed from the failure of investigations to produce isomers in the aromatic series of compounds and at the same time eliminate the instability implications of the peroxide type formula, von Auwers (16) proposed from spectroscopic evidence that an equilibrium of the following nature was possible, which might account for the diversity in structures so far encountered.

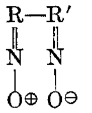


Kinney and Harwood (99) in their first paper agreed with the four-membered ring concept, in spite of the earlier demonstration of the existence of isomers in the aliphatic series by Meisenheimer, Lange, and Lamparter (110).

Later Kinney (98) repeated the work of Meisenheimer, Lange, and Lamparter and concluded that the furoxan had an unsymmetrical structure. Little has been added to this evidence since 1929, although Ponzio and his school (117, 118, 119, 120, 122, 147, 154, 155, 156, 166, 199, 201) attempted on the basis of data on physical measurements—such as cryoscopy, electromotive force constants, and Raman spectroscopy—to give evidence of the true nature of these substances, especially for the aliphatic series.

In 1956 Boyer (46), through a study of the spectroscopic relationships between furoxans and nitroso compounds, pointed out that although these substances gave infrared absorption spectra in the 2 to 25 micron region which were closely related, their absorption in the ultraviolet had three different distinct regions. The furoxans absorbed at 255–285 mμ, the normal aromatic nitroso compounds absorbed at 265–310 mμ (two bands), and the ψ-dinitroso aromatic compound was observed to absorb between 250 and 410 mμ. He therefore suggested that all aromatic *o*-dinitroso compounds cannot be considered as being merely furoxans.

The evidence available currently is insufficient to permit a definite choice between the various structures suggested for the furoxans. Despite sixty years of research none of the following structures have been eliminated.



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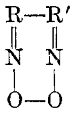

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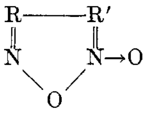


III

This being so, the postulation of the existence of isomers immediately follows.

IV. ISOMERS OF FUROXANS

In considering isomerism in the furazan oxides it is difficult to exclude *a priori* any of the various types of isomerism possible. Certainly, until the true structure or structures have been confirmed in an unequivocal manner, structural isomerism and stereoisomerism should be expected without excluding the possibility of optical isomers under the latter category.

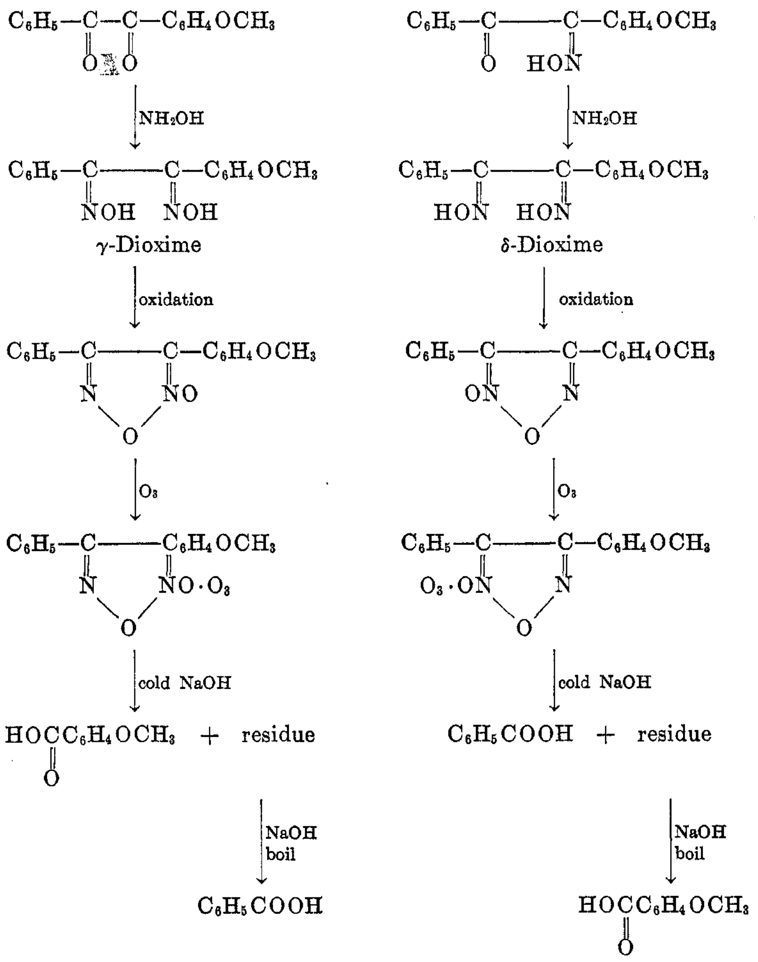
Since Wieland (225) was a strong proponent of the unsymmetrical structure, it was naturally he who offered evidence for the existence of isomers in the monophenylfuroxans. Over a period of years, Ponzio (137) attempted to vitiate this evidence even to the extent of offering proof that only a single compound existed, which he believed to be (155) benzoyl nitrile oxide. Later Ponzio (156) reversed himself and not only acknowledged isomerism in this particular compound but indeed implied that it was of a stereoisomeric character.

That isomers of certain of the furoxans do exist is difficult indeed to refute. Certainly the evidence as presented by Meisenheimer, Lange, and Lamparter (110) and corroborated by Kinney (98) leaves little doubt, at least as far as the particular compounds which they studied are concerned.

The isomers were prepared as a mixture from the oxidation of either the α- or the β-glyoxime and separated by fractional crystallization from acetone. Kinney improved the separation process by using alcohol but, more importantly, supplied the only corroborative evidence of the preparation of two isomeric furoxans from two isomeric glyoximes. That is to say, both investigators prepared the α-furoxan by oxidizing the γ-dioxime and the β-furoxan by oxidizing the δ-dioxime.

These two isomeric oxides of phenyl-*p*-methoxyphenylfurazan react with ozone in the same manner as the diphenyl derivative. When treated with cold sodium hydroxide the α-isomer yielded anisic acid, while the β-isomer produced benzoic acid. The residue from the α-isomer when boiled with sodium hydroxide yielded largely benzoic acid, and the residue from the β-isomer gave largely anisic acid.

The attack of these substances by ozone, as shown by Kinney, can then only be explained by its addition to the nitroso group. Since the carbonyl group adds ozone, it seems reasonable to assume that the nitroso group would react in a similar manner.



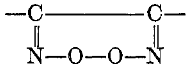
The consequence of this conclusion of Kinney required that his earlier evidence for ethylenic (99) double-bond character be modified considerably to suggest an unsymmetrical furazan oxide structure.

The structures assigned to the oxides by Meisenheimer should then be correct, since the process of ozonization and decomposition with alkali requires that the extranuclear oxygen atom be attached nearer the *p*-methoxyphenyl in the α- or higher-melting isomer, and nearer to the phenyl group in the β-isomer.

Furazan oxides are easily prepared by oxidizing 1,2-dioximes, but except for the above, no other cases have been reported in which two furazan oxides have resulted from the oxidation of isomeric dioximes. This may result from the fact that the maximum number of isomeric dioximes, according to the Hantzsch–Werner theory, of a dissimilarly substituted α-diketone has not yet been prepared and oxidized. The only other attempt to provide additional evidence to confirm or deny this behavior is concerned with the oxidation of the four isomers of 2,3-camphane dioxime (56, 99).

In the former article the claim was made that the α- and β-dioximes yielded the same oxide melting at 144.5°C.; in the later article the claim was made that an identical product melting at 144–145°C. was obtained from the oxidation of the γ- and δ-isomers. On detailed examination, however, it is evident that the data in the two papers are not self-consistent and that the basis for claiming that the same oxide was formed by oxidizing the four dioximes is not firm. It is, however, noteworthy that both papers record the fact that the oxidation products exhibit optical activity. In a later paper by one of the same investigators (98) isomerism in the furazan oxides was claimed but not resolved with the nonexistence of isomers noted in the earlier paper.

Additional pairs of isomers have been clearly defined, but their preparation and properties have not been corroborated to the same degree as in the case of the methyl(methoxyphenyl)furoxans. Since Ponzio has been an intense proponent of the symmetrical dioxdiazine (glyoxime peroxide) structure,



the higher-melting isomers in table 1 are termed furoxans and the lower-melting forms are termed dioxdiazines, in agreement with him (145).

It is important to note that in table 1 only those furazan oxides having nonsymmetrical side chains have been claimed to have isomeric forms. In the case of symmetrically substituted furoxans and aromatic furoxans of the type

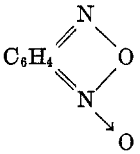


TABLE 1

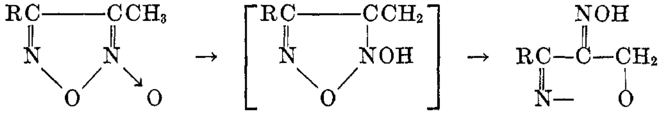
Isomers of furoxans

Compound	Melting Point		References
	Furoxans	Dioxdiazines	
	°C.	*°C.*	
Phenyl(methoxyphenyl)	108–109	104–105	(98, 110, 144, 147)
Methyl(methoxyphenyl)	99	80–81	(142, 143, 145)
Methyl(bromomethoxyphenyl)	115–116	109	(142, 143, 145)
Methyl(nitromethoxyphenyl)	112	88–89	(142, 143)
Phenyl-*o*-tolyl	103	86–87	(109)
Phenyl-*m*-tolyl	75.5	77.5	(58, 109, 202)
Phenyl-*p*-tolyl	121	117	(58, 109, 202)
Monophenyl	111–112	108	(137, 138, 156, 160, 163, 225)
p-Tolyl	108	100–101	(21, 159, 163)
Methylphenyl	96	62	(22, 114, 142, 143, 171)
Methyl-4-bromophenyl	108–109	88–89	(142, 143, 169)

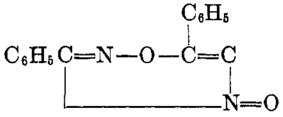
the evidence for isomerism is fragmentary (38), although experiments have been performed to establish their existence (58, 67, 99).

Tautomeric isomers are certainly possible and have been implied and claimed by certain investigators. Unfortunately, since the furoxans and their tautomers can be formed during the same reaction, under identical reaction conditions, from the same starting materials, attention has not been given to isolating and identifying all possible products and their possible mode of formation. This is a probable cause for a great deal of the confusion evident in the literature and the reason why a satisfactory conclusion regarding isomers cannot be reached.

The clearest description of one mode of tautomeric isomerism is the isoxazolinic transformation (4, 202, 235). These investigators proposed that on treatment with base the disubstituted furoxan nucleus rearranges in the following manner:

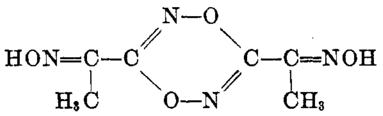


Another type of tautomerism proposed in the preparation of the furoxans is that of Bougault and Robin (39, 40). The product obtained was formulated as



and named dibenzenyl oxoazoxime. More importantly, these investigators performed a semiquantitative analysis for all products and reported a 35 per cent yield of benzaldoxime peroxide, a 4–6 per cent yield of benzoyl benzaldoxime, and a 15–20 per cent yield of dibenzenyl oxoazoxime. Confirmation of these results was attempted by Ciusa and Parisi (47, 48, 129); although a dibenzenyl oxoazoxime of the same melting point was recorded, no yields were given, a different structure was proposed, and an isomer of oxoazoxime was claimed as well as the formation of the furoxan. It seems clear that the alkaline oxidation of oximes can produce tautomeric isomers, but information is lacking on the structures obtained and the extent to which each is formed.

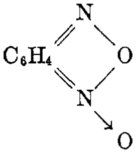
In the acidic oxidative preparation of the furoxans, still another type of tautomeric isomerism has been reported (30, 31, 174, 194, 207). Again, although some confirmatory evidence exists in these papers for the formation of the following tautomer from the reaction of acetone and nitric acid,



the constitution has not been established incontrovertibly, as the most recent investigator maintained.

The lack of sound evidence for the general existence of stereoisomers in the various types of substituted furoxans has had several implications. The absence of isomers or the failure to detect isomers in symmetrically substituted furoxans has caused much of the indecision that is attached to accepting the extraannular oxygen ring as the furoxan structure. In addition, the Hantzsch–Werner theory as to the stereoisomeric nature of the glyoximes and their relation to the oxidation products has been attacked with considerable bitterness, and attempts have been made to deny its applicability to stereoisomerism in the nitrogen system of compounds (147). It is difficult to accept this view. In the first place methylethylaniline oxide and other amine oxides have been resolved into their optical components (103, 104, 105, 106, 107), as has the oxime of 4-cyclohexanonecarboxylic acid (112). Other expected resolutions of derivatives of hydroxylamine, hydrazine, etc., have not been successful (108), but this may be a direct result of the instability of the one form. Certainly one can conceivably predict homopolar bonding in the nitrogen-to-oxygen bond in the amine oxides and a nonplanar arrangement of bonds in the oximes which would produce the necessary condition for stereoisomerism.

It is necessary also to account for the lack of reported isomerism in the aromatic furoxans.



This cannot be done at the present time with any degree of satisfaction. However, one might consider (*1*) that intensive searches have not been made, (*2*) that the missing isomer could differ from the reported structure considerably in stability, and (*3*) that a phenomenon similar to that suggested by Hammich takes place in the process of formation or resolution (71). "It is possible, however, that in the liquid state the aromatic benzfurazan oxide passes to some extent tautomerically into the symmetrical *o*-dinitroso-form, which would lead to the conversion of an unstable oxide into its stable isomeride and account for the apparent existence of only one form." Color changes accompanying the heating of solutions, the reported ease of tautomeric change, and the apparent lability of the ring are all so vague that they can be offered only as evidence for speculation and not conclusion.

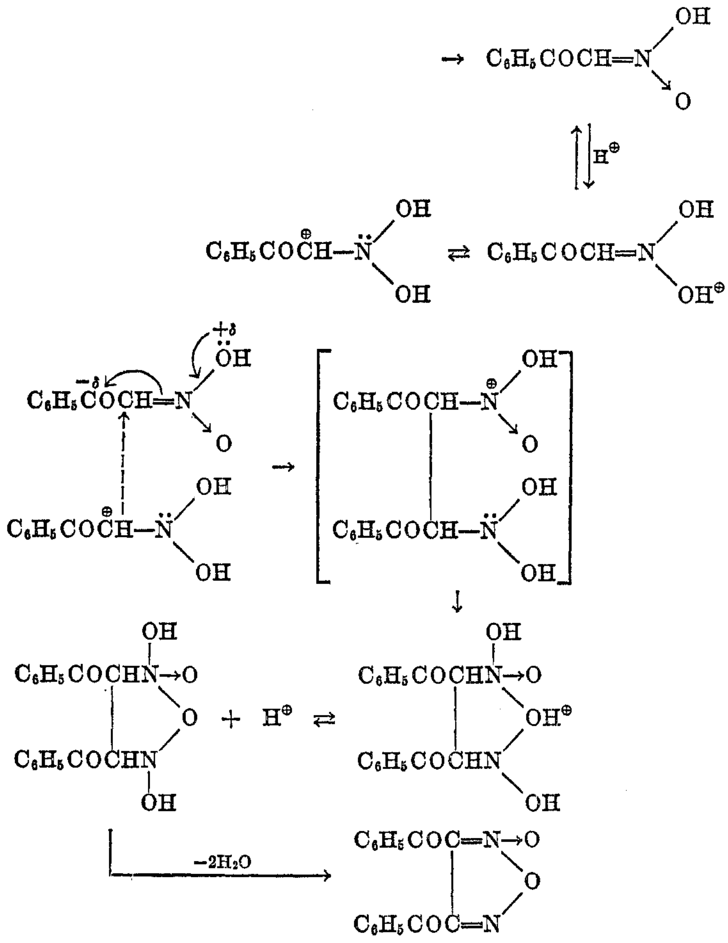
V. REACTIONS OF FUROXANS

The reactions of the furoxans are varied. Indeed, a system for describing the manner in which they react would be as varied as the number of structures available for study. Although the substituents on the ring must have a marked effect on the reaction mechanism, only a limited amount of detailed study has been made to define the differences. These studies have been done in recent years—for instance, in 1950.

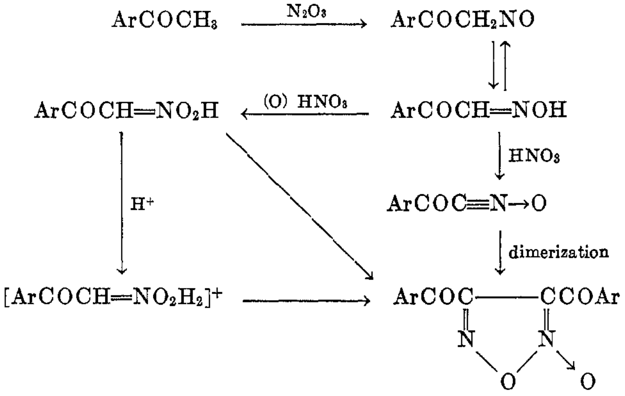
In 1950 Alexander, Kinter, and McCollum (1) suggested a mechanism for the formation of dibenzoylfurazan oxide. When phenylmethylcarbinol, acetophenone, isonitrosoacetophenone, or ω-nitroacetophenone is treated with fuming nitric acid in boiling glacial acetic acid, the principal product obtained is dibenzoylfurazan oxide.

Experimental work indicated that of the four starting materials only ω-nitroacetophenone would be transformed into dibenzoylfurazan oxide in the presence of oxide-free nitric acid or concentrated sulfuric acid. Alexander, Kintner, and McCollum suggested that all of these reactions imply the intermediate formation of ω-nitroacetophenone. Their proposed reaction scheme is given below:

$$C_6H_5COCH_3 \xrightarrow{HONO} C_6H_5COCH_2NO \xrightarrow{HNO_3} C_6H_5COCH_2NO_2$$



On the other hand, in 1955 Snyder and Boyer (193), working on the synthesis of furoxans from aryl methyl ketones, stated that they were in general agreement with the mechanism proposed by Alexander, Kinter, and McCollum (1) as to the formation of furoxans except with regard to the status of ω-nitroacetophenone as an intermediate. The observation that the latter is converted to the furoxan by nitric or sulfuric acid in glacial acetic acid, but not by hydrochloric or phosphoric acid, does not necessarily require the intermediate formation of ω-nitroacetophenone. Snyder and Boyer considered that the dehydration of the nitro compound to the nitrile oxide by nitric or sulfuric acid followed by its dimerization, exactly as previously proposed for the reaction of methazonic acid (183, 226), was entirely applicable here.



Snyder and Boyer concluded from their experiments that the conversion of methyl aryl ketones to furoxans by the action of dilute nitric acid in acetic acid probably does not involve the formation of the nitro ketone, that the transformation of ω-nitroacetophenone to dibenzoylfuroxan by concentrated nitric acid in acetic acid proceeds by way of nitrosation, and that the main function of sulfuric acid was to act as a dehydrating agent.

Without doubt, reduction reactions involving the furoxans are the most prevalent in the literature and the reducing agent most commonly used has been a metal in the presence of acid. This is a strong reagent for this type of reaction and results in strongly reduced products. Most commonly the product obtained is the dioxime (4, 10, 109, 110, 212, 235), as is the case for example with the phenyl-*o*-tolylfuroxans, the phenylfuroxans, methyl(methylenedioxyphenyl)furoxan, the phenyl(methoxyphenyl)furoxans, and the bis(benzoyl)furoxans. The use of the same reagent can, however, result in the formation of the parent hydrocarbons (84, 87, 130) from bis(anisoyl)furoxan and bis(benzoyl)furoxan, the diketone (81, 87) from bis(methylbenzoyl)furoxan and bis(*p*-ethoxydiphenylene)furoxan, the amine (90) from naphthoquinone furoxan, and even complete decomposition (181).

The use of stannous chloride as the reducing agent differs in that although reduction in general stops at the production of the furazan (18, 35, 173, 202), as exemplified by methyl(methoxyphenyl)furoxan, bis(phenyl)furoxan, furoxan dialdoxime, and dibenzoylfuroxan, it can extend to the formation of the amine or the diamide as in the case of naphthoquinone dioxime (90, 237). Some reactions involving the use of stannous chloride have not been explained (4), while the others, especially those in which long side chains are present on the furoxan nucleus, exhibit a complicated series of reactions in which reduction of the furazan to the glyazine and lactone formation on the side chain can occur. The behavior (130) described with furoxan methyl dimethylacetoacetate is a good example.

The behavior of furoxans on reduction by hydroxylamine (68, 158, 177, 237), hydrazine (57), hydrogen, ammonium sulfide, phosphorus sulfides (4, 90, 192), sulfur dioxide and thionyl chloride (33, 226), phosphorus and sodium (18, 189), phosphorus pentachloride (4, 142, 235), and hydrogen iodide (18, 62) is much like that described for zinc and stannous chloride in that the specific furoxans plus the specific conditions will determine whether a reaction occurs or whether the product is a furazan, an amine, a dioxime, or a decomposition product. Although a definitive study has yet to be made, reduction by zinc or hydroxylamine will, in general, result in the formation of dioximes and not furazans, while reductions by the other agents described will result in furazans and not dioximes.

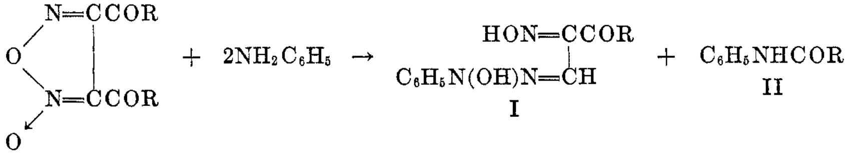
The oxidation of furoxans has been reported in a few instances. The most interesting reaction is one reported by Kinney and Harwood (98, 99). This has been described in a previous section.

Although the oxidation by potassium permanganate of methyl(oximinobenzoyl)furoxan is reported to form (77) benzoic acid and of methyl(methylenedioxyphenyl)furoxan by potassium ferrocyanide to form piperonylic acid (4) with destruction of the ring, careful oxidation by potassium permanganate of the latter furoxan has also been reported as forming a furoxan acid (11). Certainly the position is not clear, since similar oxidations have not given readily identifiable products (194).

A wide variety of reactions has also been reported for the action of acids on the furoxans, ranging from no reaction at all to complete decomposition. From this point of view bis(furfuryl)furoxan must be a very stable substance, for it is not attacked even by boiling sulfuric acid (184), while bis(iodo)furoxan with only slight heating is decomposed, forming iodine and hydrogen sulfide (192). Steiner (195) has reported that furoxandicarbonamide is reprecipitated unchanged from concentrated sulfuric acid by the addition of water, while the diethyl ester of the acid is decomposed by strong acids with the production of carbon dioxide, alcohol, hydroxylamine, and oxalic acid (130, 181). Reactions intermediate between these extremes have also been noted. Holleman (81) obtained *p*-toluic acid by treating bis(methylbenzoyl)furoxan with sulfuric acid and benzoic acid from benzfuroxan by the same treatment. He did note, however, that continued treatment (84) of benzfuroxan with hydrochloric acid for as long as two days under reflux resulted in complete decomposition. Although the one ester group can be removed from ethyl furoxandicarboxylate with sulfuric acid (236), and *p*-nitrobenzoic acid is obtained from bis(*p*-nitrobenzoyl)furoxan (77), hydrochloric acid decomposes (oximinobenzoyl)methylfuroxan to yield benzoic acid as the only isolatable product, and complete rearrangement of bis(acetoxime)furoxan was reported by Steffens (194) as the result of its reaction with sulfuric acid. One might expect that the unsymmetrical furoxans would be more susceptible to rearrangement and/or decomposition than the symmetrical ones. However, according to Ponzio (177) benzoylphenylfuroxan is unattacked by hydrochloric acid.

In general, the products of the reaction of ammonia and the amines with the furoxans are the amide or the amidoxime: dibromofuroxan yields oxal diamidoxime (222); phenylfuroxan yields the oximidobenzoyl amidoxime (235); bis(methylbenzoyl)furoxan gives the *p*-toluic acid amide (81); ethyl furoxandicarboxylate yields the ethyl furoxandicarbonamide (220); diacetamide-furoxan gives the fulminuric acid (208); furoxan methyl dimethylacetoacetate yields the dimethylmalonamide (130) when the reaction mixture is separated quickly or methyl dimethylmalonate when the reaction is allowed to proceed for a longer time. Interestingly enough, both diphenylfuroxan and dimethylfuroxan react very slightly if at all at room temperature (187, 235).

From a study of the action of primary amines on furoxan methyl dimethylacetoacetate, Perkin (130) concluded that the reaction with furoxans is general if two acid side chains are present.



Product I is not often isolated, since it is very unstable and loses water to form an isotriazole. Perkin remarked that in the reactions studied by him only one of the side chains was removed even when both were identical. Perkin's argument seems well substantiated by the extensive work he described as well as by the result of Boeseken (36) on bis(toluoyl)furoxan. His view is corroborated, in principle at least, by the general view of Wieland (233, 235) that the furoxan ring is ruptured by amines to give amidoximes which can then further react in the manner described. Since Perkin used aniline and its chlorinated product for studying this reaction in a furoxan with fairly long side chains, it might be well to mention the products resulting in some other cases, especially since both products conceived by Perkin were not always recovered. In the case of bis(anisoyl)furoxan, the primary reaction product was either too unstable to be recovered or else overlooked in the separation of the anisic acid anilide (87). With monophenylfuroxan, the amidoxime alone was reported and no reaction occurred with diphenylfuroxan (235). In the case of furoxan dialdoxime, although reaction occurred on one side of the ring with aniline, destruction of the ring did not occur and a stable monoaniloxime was obtained (226).

The final products of the interaction of the unstable intermediate proposed by Perkin with primary reagents and other products could, of course, be varied. In addition to straight-chain derivatives, the diazoles (138), isoxazoles are commonly obtained (233).

The effect of bases on the furoxans, much like that of the acids, ranges from no reaction to complete decomposition without regard to the alkalinity of the reagent. The situation with regard to a detailed understanding of the reaction involved is much less complete for this type of reaction. It is apparent, however, that long aliphatic side chains are more susceptible to reaction than are aromatic or even ring side chains. Diphenylfuroxan (235) is attacked with difficulty to yield benzoic acid, while difurfurylfuroxan is not attacked (184). Ethyl furoxandicarboxylate is decomposed completely (130, 181), as is benzoylphenylfuroxan (177).

Under certain conditions no product is obtained—for instance, with isosafrolefuroxan—while a more intense reaction can result in the formation of an isomeric oxazoline (42). In addition, however, attack by alkali can produce a variety of products resulting principally from opening of the ring (235). Furoxan dialdoxime yields the potassium salt of 1,4,6-triisonitroso-3-nitroketone, bis(anisoyl)furoxan (226) gives the potassium salt of anisic acid, phenylfuroxan (64) yields the formhydroxamic acid or benzonitrile depending on reaction conditions (235), bis(mesitylene)furoxan yields the mesitylene carbonic acid (24), and furoxan dialdoxime gives the pyrazole (226).

Derivatives of the furoxans have been described. The acetyl and benzoyl derivatives are available for such compounds as dibromofuroxan (33), (oximinobenzoyl)methylfuroxan (77), the addition compound of bisbenzofuroxan (84), furoxan dialdoxime (226, 231), and bis(acetoxime)furoxan (194), but usually attempts to make derivatives keeping the furoxan ring intact have failed.

An exception, of course, exists in the nitrated aromatic furoxans. Nitration of benzfuroxan has been reported to yield well-defined compounds in which the entrance of the nitro moiety occurs with relative ease (52, 65, 68, 238). These nitrated compounds and a few of the unnitrated furoxans and their salts have been reported as being heat sensitive to the extent that explosions have been reported (77, 96, 154, 195, 236).

Grignard reactions have been attempted with varied success. Ponzio claimed the preparation of phenylmethylglyoxime from the reaction of phenylfuroxan with methylmagnesium iodide (138) but later acknowledged that the product might be an addition compound (156). He also described the decomposition of methylphenylfuroxan with the same reagent and the production (169) of either tolyl cyanide, or toluene, with one or two moles of ammonia, depending upon which isomer is used. Wieland (235) described the preparation of a labile addition product from ethylmagnesium iodide and anisylmethylfuroxan as well as the fact that phenylmagnesium bromide reacts with the diphenyl- and the phenylanisylfuroxans (98, 110).

Aside from the recording of the melting points of the compounds prepared by each investigator, the following references describe some of the physical characteristics which have been reported: cryoscopy (114), crystallography (116), heats of combustion (117), absorption spectra (16, 119), electric moments (54, 122, 199, 201), dipole moments (91), infrared spectrometry (45, 65), parachors (71), and Raman spectra (120).

A patent has been granted to Tappi and Forni,[1] who claimed that benzfuroxan and its derivatives have bactericidal activity.

Although some of the reactions of the furoxans are more definitely known than

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[1] Tappi, G., and Forni, P. V. (University of Torino): Ann. chim. appl. **39**, 338–43 (1949).

other information about these compounds, it is highly suggestive that our knowledge of them is not complete.

VI. PREPARATION OF FUROXANS

The furoxan structure is formed by an oxidative reaction. Although most commonly the oxime has been used with a large number of oxidants to form the desired structure, historically the first preparation of a furoxan was that of Tonnies, who prepared anetholefuroxan (202) by the oxidation of anethole with sodium nitrite in acetic acid. Although Tonnies did not report a structure for the substance, he did indicate the fact that two atoms of nitrogen and two atoms of oxygen had been added to the anethole molecule. It was Wieland (218) who acknowledged that Tonnies had performed the first synthesis of a furoxan. Since that time organic nitrites (60), nitric acid of various concentrations (154, 215), chlorine and iodine (39, 129, 187, 213), potassium ferricyanide (19, 100, 217), sodium hypohalites (66, 142, 187, 213), nitrogen oxides (134, 187, 218), potassium permanganate (33), and nitrosyl chloride have been used successfully (184).

In addition, substituted oximes have been used as starting materials for a number of interesting preparative reactions. According to Wieland, anetholefuroxan (218) can be prepared by the action of sodium hydroxide with anethole nitroxime. According to Ponzio, bis(phenyl)furoxan (134) can be prepared from the reaction of oximinophenylacetic acid and nitrogen tetroxide. Ponzio reported good evidence (154) for the preparation of bis(benzoyl)furoxan from the reaction of phenyl chlormonoxime and sodium acetate. A reaction related to the latter for forming dihalogen-substituted parent furoxans from the halo formoximes is discussed later. Again, although Behrend and Schmitz reported good yields of nitromethylfuroxan (30) from the reaction of nitric acid and nitrosomethylglyoxime, they also claim that the latter can form spontaneously a product of the same melting point at room temperature (33, 192).

Internal oxidation-reduction reactions have also been used in other reaction schemes for the preparation of furoxans. Wieland prepared anetholefuroxan (218) by boiling anethole pseudo-nitrosite in water or ethyl alcohol and bis(phenyl)-furoxan (228) by heating phenylnitrolic acid to just above its melting point or by boiling monophenylfuroxan (235). This type of synthesis has been useful for preparing the aromatic furoxans, provided the reacting groups are ortho to each other.

The first aromatic furoxan, i.e., benzofuroxan, was prepared accidentally in this manner by Noelting, Grandmougin, and Michel (125), who in attempting to complete a series of preparations of the nitrophenyl azides, steam distilled the ortho compound for purification and noted a marked evolution of gas with lowered nitrogen content in the product as well as a higher melting point. Noelting and Kohn subsequently prepared tolylfuroxan (126) by the thermal decomposition of of 2-nitrotolyl azide but, as shown by Zincke and Schwartz, were wrong in concluding (238) that the reaction would not proceed if the methyl group were ortho to the azido group. This reaction has been simplified and made a great deal safer by simply using the hypohalite oxidation of an *o*-nitro amine (66).

One particular compound has been prepared by a large variety of nitric acid oxidations. This compound, ethyl furoxandicarboxylate, has been reported as being prepared from propionyl ethyl acetoacetate by Bouveault and Bongert (42), from malonic ester by Bouveault and Wahl (43), from ethyl acetoacetate by Pröpper (180) and Wieland (830), from chloroximidoacetic acid ester by Wieland (220), from ethyl dioximidosuccinate by Wahl (209), from β,β-dioximidosuccinate by Beckh (26), and from ethyl isonitrosoacetoacetate by Jovitschitsch (92). Despite all of this work the properties of this substance remain in question, as does a definitive method for its synthesis.

Additional preparations for the furoxans have been reported with no definite reaction schemes being described. No doubt, partial decompositions occurred which by virtue of enhanced reactivity with the primary reagent permitted the necessary oxidation to proceed. For instance, Ponzio and Charrier (168) reported the formation of bis(benzoyl)furoxan from the reaction of chloroisonitrosoacetophenone and silver nitrite; Werner and Buss (213), the preparation of bis(phenyl)furoxan from the reaction of either sodium carbonate or silver nitrate with phenyl hydroximic acid chloride; Wieland the same compound from the reaction of the same parent reactant with sodium hydroxide (235) as well as the reaction of the silver salt of phenylnitrolic acid and iodine to form the bis(phenyl)furoxan.

The action of nitric acid or nitrogen oxides on ketones or ethylenic double bonds has been used as a method for synthesizing the furoxans. Ponzio used concentrated nitric acid to prepare bis(benzoyl)furoxan from phenyl methyl ketone (154), and Holleman used the same reagent with acetophenone (81) to prepare the same compound, while Widman and Virgin (215) oxidized oxalyl diacetophenone with concentrated nitric acid to obtain bis(benzoyl)furoxan. Wieland (218), in preparing methyl(methoxyphenyl)furoxan, first made the pseudonitrosite by the action of anethole with nitrogen oxides. The pseudo-nitrosite when boiled in water or ethyl alcohol was converted to the furoxan.

Other interesting preparative reactions have been described. For instance, Dimroth (51) reported the preparation of bis(phenylcarbamyl)furoxan by boiling 4-isonitroso(phenyl)triazolone in 10 per cent sulfuric acid; Ponzio (177) described the preparation of acetoxime phenylfuroxan from the reaction of either nitrogen tetroxide or concentrated nitric acid with methyl phenyl triketone; chloromethoxybenzfuroxan was claimed by Green and Rowe (66) to have been formed by the reaction of dinitroanisole with a methanolic solution of potassium hydroxide containing sodium hypochlorite with 5 per cent active chlorine; and finally Steffens (194) described the preparation of acetoxime furoxan by the action of sodium bicarbonate on acetoxime glyoxime.

From the foregoing, it is apparent that correlative information on reaction routes to the preparation of many large-molecule furoxans exists. The same cannot be said for the more simply constituted furoxans of the aliphatic series in general and for the parent structure in particular. In fact, no claim has been noted in the literature for a preparative method for this interesting species, although for a time fulminic acid was considered to be the parent structure (88, 89, 124, 187, 189, 221, 224, 229).

In spite of the fact that furoxan has not been reported in the literature, and although it seems probable that the simple derivatives of furoxan have been prepared, an insufficient amount of information exists on their properties and behavior to permit conclusive statements. For example, dicyanfuroxan, first prepared by Steiner (195), was reinvestigated by Wieland (226), who concluded from a comparison of melting points that his preparation was the same as Steiner's. Wieland repeated Steiner's preparation by the route of ammonium fulminurate and concentrated sulfuric acid and added that this compound also resulted (*1*) from the reaction of furoxan dialdoxime and thionyl chloride, (*2*) from furoxandicarbonamide and thionyl chloride, phosphorus pentachloride, or phosphorus pentoxide, (*3*) from potassium cyanide and dibromofuroxan, and (*4*) by the removal of hydrogen chloride from formhydroxamic acid chloride. It is apparent that Wieland based his conclusion on having prepared this compound from its melting point of 42°C., for the only additional data that he determined was a boiling point of 200°C. Ulpiani (205) reported the formation of a compound having the formula $C_4O_2N_4$ and a melting point of 40°C. by boiling ethyl furoxandicarboxylate in water.

In the paper by Wieland there is also described (226) the preparation of other simple furoxans. Furoxan dialdoxime was reported to be formed in 64.4 per cent yield by the addition of freshly prepared methazonic acid to concentrated sulfuric acid. Wieland in the same paper also described the preparation of this compound via two other routes: (*a*) from the action of chloro *anti*-glyoxime with sodium bicarbonate and (*b*) from the action of sodium fulminate with concentrated nitric acid. Furoxan dialdehyde was obtained as a bright yellow syrup by treating the aldoxime with concentrated sulfuric acid and sodium nitrite.

The preparation of furoxan dialdoxime is interesting in that two forms have been obtained melting at different temperatures. Wieland's preparation of 1925 (226), called the higher-melting form, was prepared as described above. The lower-melting form was described by Steinkopf as melting at 121–122°C. (197). Wieland, Frank, and Kitasato repeated Steinkopf's method of preparation (231), by boiling the higher-melting form in water to obtain the lower-melting β-form. Although both reported melting points for the dibenzoyl derivatives for the higher-melting form (181°C. given by Wieland; 184–185°C. given by Steinkopf), only Wieland reported the dibenzoyl derivative (melting at 155°C.) of the lower-melting one.

These two forms do not permit the conclusion that an isomeric furoxan structure was obtained, for the two forms probably result from *syn*- and *anti*-configurations of the two oxime groups in the molecule.

Evidence for the existence of the halogen-substituted furoxans is more conclusive but still leaves much to be desired. Wieland first claimed the preparation of a chloro derivative (222) from the reaction of mercury fulminate and chlorine. The chlorine content was found to be 43.82 per cent as compared with a calculated value of 45.97 per cent. Holleman repeated this experiment and concluded (86) only that the reaction was a complicated one. Then Birckenbach and Sennewald (33) studied the preparation again and reported a 30 per cent yield from the reaction of dichloroformoxime and sodium fulminate.

TABLE 2

Furoxans

No.	Compound	Preparation	Melting Point	References
		Benzofuroxans		
			°C.	
1	$C_6H_4N_2O_2$	(a) *o*-Nitrodiazobenzene imide; heat (b) *o*-Quinone dioxime, dilute HNO_3, 95 per cent yield	72	(65, 66, 126, 199, 238)
2	$4\text{-}NO_2C_6H_3N_2O_2$	Benzofuroxan, concentrated H_2SO_4, concentrated HNO_3, cold, 60 per cent yield	143	(52, 65, 68)
3	$5\text{-}NO_2C_6H_3N_2O_2$	2,4-Dinitrodiazobenzene imide, heat, 93 per cent yield	72; explosive	(52, 65, 68)
4	$4,6\text{-}(NO_2)_2C_6H_2N_2O_2$	(a) Benzofuroxan, concentrated H_2SO_4, concentrated HNO_3, heat to 40°C. (b) Picryl chloride, NH_2OH, CH_3COONa, 90 per cent yield	172; behaves lke a monobasic acid	(52, 65, 68, 70)
5	$4,6\text{-}(NO_2)_2C_6H_2N_2O_2$ (NH_4 salt)	Compound 4, aqueous NH_3	Powder	(52, 70)
6	$4,6\text{-}(NO_2)_2C_6H_2N_2O_2$ (Na salt)	Compound 4, NaOH	Explosive crystal	(52, 70)
7	$4,6\text{-}(NO_2)_2C_6H_2N_2O_2$ (K salt)	Compound 4, KOH	Explosive crystal with 0.5 H_2O	(52, 70)
8	$4,6\text{-}(NO_2)_2C_6H_2N_2O_2$ (Ag salt)	Compound 4, soluble silver salt	Explosive, red powder	(52, 70)
9	$5,6\text{-}(NO_2)_2C_6H_2N_2O_2$	Compound 3, concentrated HNO_3, 40 per cent yield	172 (d.)	(65)
10	$5\text{-}ClC_6H_3N_2O_2$	(a) 4-Chloro-2-nitroaniline, NaOCl (b) 5-Chloro-2-nitroaniline, NaOCl	48	(65, 67)
11	$5\text{-}BrC_6H_3N_2O_2$	(a) 4-Bromo-2-nitro-1-azidobenzene, heat (b) 5-Bromo-2-nitro-1-azidobenzene, heat	69	(57)
12	$4\text{-}CH_3C_6H_3N_2O_2$	6-Nitro-2-methyldiazobenzene imide, heat	60	(238)
13	$5\text{-}CH_3C_6H_3N_2O_2$	5-Methyl-2-nitrophenyl azide, heat, 95 per cent yield	98	(57, 65, 66, 238)
14	$5\text{-}CH_3OC_6H_3N_2O_2$	5-Methoxy-2-nitrophenyl azide, heat, 95 per cent yield	118	(65)
15	$4,6\text{-}(CH_3)_2C_6H_2N_2O_2$	5-Nitro-4-azido-1,3-dimethylbenzene, heat, 95 per cent yield	108–109	(65, 238)
16	$5\text{-}CH_3O\text{-}6\text{-}ClC_6H_4N_2O_2$	2,4-Dinitro-*o*-chloroaniline, NaOCl, KOH in CH_3OH	80.5	(66)
17	$5\text{-}CH_3O\text{-}4\text{-}NO_2C_6H_4N_2O_2$	1,3-Dinitroaniline, NaOCl, heat	160	(65)
18	$5\text{-}C_2H_5O\text{-}6\text{-}Cl\text{-}C_6H_4N_2O_2$	2,4-Dinitro-*o*-chloroaniline, NaOCl, KOH in C_2H_5OH	55	(66)
19	$3,6\text{-}(NOH)_2C_6H_4N_2O_2$	Cyclohexene-1-tetraoxime-3,4,5,6, concentrated HNO_3	68	(58)
20	$C_6H_4Br_4N_2O_2$	Compound 1, two moles of bromine	lst isomer, 117 2nd isomer, 170	(71)
21	$C_6H_3N_2O_2C_6H_3N_2O_2$	3,3′-Dinitrobenzidine, NaOCl, aqueous NaOH	211	(68)
22	$C_6H_2N_4O_4$	Compound 19, alkaline oxidation by air	93	(58)
23	$4\text{-}NO_2\text{-}5\text{-}CH_3\text{-}C_6H_4N_2O_2$	2,3,5-Trinitrotoluidine, NaOCl, heat, 80 per cent yield	164	(65)
24	$4,6\text{-}(CH_3)_2C_6H_4N_2O_2$	2,4-Dimethyl-*o*-nitroaniline, NaOCl, heat, 95 per cent yield	109	(65)

25......	5-N_3-6-NO_2-$C_6H_4N_2O_2$	1,3-Dinitro-4,6-diazidobenzene, heat at 80-85°C., 60 per cent yield	89; explosive crystals	(65)
26......	4,6-$(NO_2)_2$-5-$CH_3C_6H_3N_2O_4$	Methylbenzofuroxan, 4:1 mixture of H_2SO_4 and HNO_3	133	(52, 65, 66)
Naphthofuroxans				
27......	$C_{12}H_{10}N_2O_2$	(a) 2-Nitro-3-aminoacenaphthene, NaOCl (b) Acenapthene-2,3-dioximino dihydride-2,3, NaOCl		(59, 185)
28......	$C_{10}H_4O_2N_2O_2$	1,4-Dioxo-2,3-dioximinonaphthalenetetrahydride-1,2,3,4, concentrated HNO_3	251	(58)
29......	$C_{10}H_8N_2O_2$	(a) 1,2-Naphthoquinone dioxime, NaOCl (b) 2-Nitroazidonaphthalene, heat	126-127	(69, 90, 100, 122)
30......	4,5-$(NO_2)_2$-$C_{10}H_6N_2O_2$	Compound 29, concentrated H_2SO_4, concentrated HNO_3	215	(70)
31......	4,5-$(NO_2)_2$-7-$(NHC_6H_5)C_{10}H_5N_2O_2$	Compound 30, aniline	166 (d.)	(70)
32......	4,5-$(NO_2)_2$-7-$NaC_{10}H_5N_2O_2$	Compound 30, aqueous NaOH	Explosive crystals	(70)
33......	6,8-$(NO_2)_2$-7-$HOC_{10}H_5N_2O_2$	7-Hydroxy-1,2-naphthoquinone dioxime	196	(70)
Disubstituted symmetrical aliphatic furoxans, $RC_2N_2O_2R'$				
34......	R=R'=Cl	Mercuric fulminate, chlorine, 30 per cent yield	67/17 mm. (boiling point) 152-160°C. (boiling point) $n=1.52$	(33, 222)
35......	R=R'=Br	(a) Mercuric fulminate, bromine (b) Potassium fulminurate ($KC_3H_2O_3N_3$), bromine, quantitative yield	50	(33, 89, 97, 189, 222)
36......	R=R'=I	Mercuric fulminate, iodine in ether	93.5	(192)
37......	R=R'=CH_3	Dimethylglyoxime, N_2O_4, 62 per cent yield	223 (boiling point) 106.5-107.5/14 mm. (boiling point)	(130, 187, 190)
38......	R=R'=$N(C_2H_5)_2$	Dibromofuroxan, $NH(C_2H_5)_2$	115 (d.)	(222)
39......	R = R' = CHO	Compound 40, HNO_2	Not obtained in pure form	(226)
40......	R = R' = CH=NOH	(a) Methazonic acid (nitroacetaldoxime) (NO_2CH_2CH=NOH), concentrated H_2SO_4 (b) Compound 39, NH_2OH (c) Sodium fulminate, (NaOCN), HNO_3	171-172; explosive sodium and silver salts	(226, 231)
41....	R = R' = CH_3CO	(a) Isonitrosoacetone [CH_3COCH=NOH], N_2O_4 (b) α-Chloro-α-isonitrosoacetone, $AgNO_2$	Unstable oil	(168)
42......	R = R' = CH_3C(=NOH)	α-Nitro-α-isonitrosoacetone [$CH_3COC(NO_2)$=NOH], NH_2OH	139-140	(31, 194)
43......	R = R' = COOH	(a) Barium salt of furoxandicarboxylic acid, H_2SO_4 (b) Distillation of compound 45	96	(96)

TABLE 2—*Continued*

No.	Compound	Preparation	Melting Point	References
		Disubstituted symmetrical aliphatic furoxans $RC_2N_2O_2R'$		
			°C.	
44......	$R = R' = COOCH_3$	Acetoacetic acid methyl ester ($CH_3COCH_2COOCH_3$), fuming HNO_3	151/10 mm. (boiling point)	(41)
45......	$R = R' = COOC_2H_5$	Ethyl ester of chlorooöximinoacetic acid, concentrated HNO_3, 70–75 per cent yield	159–161/10 mm. (boiling point) 170–171/23 mm. (boiling point)	(42, 180, 181, 206, 209)
46......	$R = R' = COOCH_2CH(CH_3)_2$	Oximinoacetic acid isobutyl ester, $[CH(=NOH)COOCH_2CH(CH_3)_2]$, HNO_2	180–185 (boiling point)	(43)
47......	$R = R' = CONH_2$	(a) Nitromalonic acid diamide $[NO_2CH(CONH_2)_2]$, concentrated H_2SO_4	253 (d.); forms explosive heavy metal salts	(42, 191, 196, 204, 206, 208, 209, 236)
		(b) Ammonium fulminurate ($NH_4C_3H_2O_3N_3$), concentrated H_2SO_4		
48......	$R = R' = CN$	Ammonium fulminurate, concentrated H_2SO_4, 30–40 per cent yield	42 200 (boiling point)	(195, 205, 226)
		Disubstituted unsymmetrical aliphatic furoxans, $RC_2N_2O_2R'$		
49......	$R = CH_3$; $R' = NO_2$	Nitrosoxylmethylglyoxime, HNO_2, HNO_3, 95 per cent yield	66–67	(30)
50......	$R = CH_3$; $R' = C_2H_5$	Methylglyoxime, N_2O_4 or potassium ferricyanide	115–116/16.5 mm. (boiling point); Decomposes on distillation at 760 mm.	(187)
51......	$R = CH_3$; $R' = COCH_3$	Phenylfuroxan by acid hydrolysis	32–33	(177)
52......	$R = CH_3$; $R' = C(=NOH)CH_3$	Dimethyltriketone trioxime, N_2O_4	130–131	(177)
53......	$R = COOH$; $R' = COOC_2H_5$	Acetoacetic ester ($CH_3COCH_2COOC_2H_5$), fuming HNO_3	103.5	(42)
54......	$R = CN$; $R' = CONH_2$	Compound 40, $SOCl_2$, 20 per cent yield	187	(226)
55......	$R = CO(CH_3)_2COOCH_3$ $R' = CHOCH(CH_3)_2COOCH_3$	Furoxan bis(dimethylmalonylic acid methyl ester), tin in alcoholic HCl	154 (d.)	(130)
56......	$R = CH_3$; $R' = COOH$	Methylglyoximecarboxylic acid, concentrated HNO_3	62 (monohydrate) 47 (from benzene) 92 (vacuum dried)	(11, 93)
57......	$R = CH_3$; $R' = COOAg$	Compound 56, soluble silver salt	Crystal explodes above 100	(93)
58......	$R = CH_3$; $R' = COOC_2H_5$	α, β-Dioximinobutyric acid ethyl ester, HNO_3	240–242 (boiling point)	(93)
59......	$R = CN$; $R' = CH{=}NOH$	Boil compound 40 in water	91	(231)

60	R = $CHOHC(CH_3)_2COOCH_3$ R′ = $C[{=}NNHCONH_2]C(CH_3)_2COOCH_3$	Compound 55, semicarbazide	170–172	(130)
61	R = CH_3; R′ = $CH(NO_2)CH_3$	Compound 52, concentrated HNO_3	72–73	(201)
62	R = CH_3; R′ = $C({=}NOCOCH_3)CH_3$	Compound 52, acetic anhydride	73	(201)
63	R = CH_3; R = $C({=}NNHCONH_2)$	Compound 51, semicarbazide	230	(201)
		Disubstituted aliphatic aromatic furoxans, $RC_2N_2O_2R'$		
64	R = CH_3 R′ = 3,4-$(CH_3O)_2C_6H_3$	(a) Isoeugenol methyl ether (3,4-dimethoxy-1-propenylbenzene), HNO_3 (b) α- and β-Methyl(3,4-dimethoxyphenyl)glyoxime, potassium ferricyanide	118	(102)
65	R = CH_3 R′ = 3,4-$(CH_3O)_2C_6H_2Br$	Compound 64, bromine	133	(102)
66	R = CH_3 R′ = 3,4-$CH_3OC_6H_2NO_2$	Compound 64, concentrated HNO_3	189	(102)
67	R = CH_3 R′ = 3-CH_3O-4-$C_2H_5OC_6H_3$	Isoeugenol ethyl ether (3-methoxy-4-ethoxy-1-propenylbenzene), HNO_2	85	(102)
68	R = CH_3 R′ = 4-$CH_3OC_6H_4$	(a) Anethole (4-methoxy-1-propenylbenzene), HNO_2 (b) α-Nitro-4-methoxypropiophenone oxime ($C_{10}H_{12}O_4N_2$), potassium ferricyanide, quantitative yield	98	(35, 202, 217, 218, 235)
69	R = CH_3 R′ = 3-Br-4-$CH_3OC_6H_3$	(a) α- or β-3-Bromodiisonitrosoanethole, potassium ferricyanide (b) Compound 68, bromine	109–110	(142)
70	R = CH_3 R′ = 3-CH_3O-4-$NO_2C_6H_3$	Compound 64, concentrated HNO_3	88–89	(35)
71	R = C_6H_5 R′ = $C({=}NOH)CH_3$	Phenylmethyltriketone trioxime, N_2O_4	135	(177)
72	R = CH_3 R′ = 4-COC_6H_5	(a) Compound 69, acid hydrolysis (b) β-Methylbenzoylglyoxime, N_2O_4	70	(135, 158, 177)
73	R = CH_3 R′ = 4-$C({=}NOH)C_6H_5$	Methylphenyltriketone trioxime, N_2O_4	129–130	(177)
74	R = CH_3 R′ = $CONHC_6H_5$	Methyl(benzoyl-oxime)furoxan, $POCl_3$	150–151	(158)
75	R = CH_3 R′ = $CH_2C({=}NOH)C_6H_5$	Oxime of α-methyl-α-benzalacetone, $[C_6H_5CH{=}CHC({=}NOH)CH_2CH_3]$, HNO_2	195	(77)
76	R = CH_3 R′ = $CH_2C({=}NOCOCH_3)C_6H_5$	Compound 71, acetic anhydride	146–147	(77)
77	R = CN; R′ = C_6H_5	Phenylcyanoglyoxime, HNO_2	75	(151)
78	R = CH_3 R′ = $C({=}NOCOC_6H_5)$	Compound 52, benzoyl chloride	172	(201)
79	R = CH_3 R′ = $C({=}NNHC_6H_5)$	Compound 51, phenylhydrazine	169	(201)

TABLE 2—*Continued*

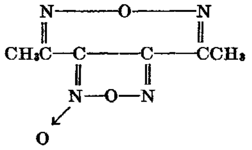
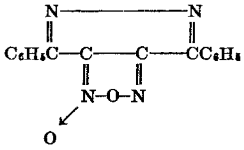
No.	Compound	Preparation	Melting Point	References
Disubstituted aliphatic aromatic furoxans, $RC_2N_2O_2R'$				
			°C.	
80......	$R = CH_3$ $R' = 4\text{-}C(NO_2)_2C_6H_5$	Compound 72, N_2O_4	100 (d.)	(177)
81......	$R = NO_2$; $R' = C_6H_5$	Cinnamaldehyde, N_2O_4, 5–7 per cent yield	100	(216)
82......	$R = C_6H_5$; $R' = Cl$	Phenylchloroglyoxime, N_2O_4	66–67	(152)
83......	$R = C_6H_5$; $R' = NH_2$	Nitrophenylfuroxan, $SnCl_2$ in HCl	135–6	(216)
84......	$R = C_6H_5$; $R' = OH$	Nitrophenylfuroxan, aqueous NaOH	133 (d.)	(216)
85......	$R = C_6H_5$; $R' = OCH_3$	(a) Nitrophenylfuroxan, $NaOCH_3$ (b) Cinnamaldehyde, N_2O_4	69	(216)
86......	$R = C_6H_5$; $R' = OC_2H_5$	(a) Nitrophenylfuroxan, $NaOC_2H_5$ (b) Chlorophenylfuroxan, $NaOC_2H_5$ (c) Cinnamaldehyde, N_2O_4, then aqueous NaOH, C_2H_5OH	83	(216)
87......	$R = C_2H_5$ $R' = 4\text{-}(CH_3)_2CHC_6H_4CH_2$	Ethyl (4-isopropylstyryl) ketone, $[C_2H_5COCH{=}CHC_6H_4CH(CH_3)_2]$, NH_2OH, then HNO_2	167	(77)
88......	$R = C_6H_5$ $R' = CH_2C(NO_2)_2$	Compound 71, concentrated HNO_3	135–136	(177)
89......	$R = C_6H_5$ $R' = CH_3({=}NOCOCH_3)$	Compound 71, acetic anhydride	100	(177)
90......	$R = C_6H_5$ $R' = CH_3C({=}NOCOC_6H_5)$	Compound 71, benzoyl chloride	130–131	(177)
91......	$R = C_6H_5$ $R' = CH_3C({=}NNHC_6H_5)$	Compound 71, phenylhydrazine	160	(177)
92......	$R = C_6H_5$ $R' = CH_3C({=}NNHCONH_2)$	Compound 71, in acid solution, semicarbazide	218–219 (d.)	(177)
93......	$R = CH_3$ $R' = (C({=}NOCOCH_3)C_6H_5)$	Compound 73, acetic anhydride	117–118	(158)
94......	$R = CH_3$ $R' = C({=}NOCOC_6H_5)C_6H_5$	Compound 73, benzoyl chloride	157–158	(158)
95......	$R = CH_3$ $R' = C({=}NNHC_6H_5)C_6H_5$	Compound 72, phenylhydrazine, two isomeric forms claimed	125 225 (d.)	(158)
96......	$R = CH_3$ $R' = 2,5\text{-}(CH_3O)_2C_6H_2O_2CH_2$	(a) Isapiol ($C_{12}H_{14}O_4$), HNO_3 (b) Diisonitrosoisapiol, potassium ferricyanide	169–70	(7)
97......	$R = CH_3$ $R' = 2,5\text{-}(CH_3O)_2\text{-}6\text{-}BrC_6HO_2CH_2$	Compound 96, bromine	131	(7)
98......	$R = CH_3$ $R' = 2,5\text{-}(CH_3O)_2\text{-}6\text{-}NO_2C_6HO_2CH_2$	Compound 96, concentrated HNO_3	122–3	(7)

Disubstituted symmetrical aromatic furoxans, $RC_2N_2O_2R'$

99......	$R = R' = C_6H_5$	(a) Benzaldoxime, N_2O_4 (b) Benzildioxime, NaOCl, 75 per cent yield	114	(4, 6, 18, 19, 28, 37, 39, 63, 84, 86, 88, 98, 99, 100, 129, 131, 184, 187, 213, 220, 228, 234, 235)
100......	$R = R' = ClC_6H_4$	2-Chlorobenzaldoxime hydrochloride $[ClC_6H_4C(=NOH) \cdot HCl]$, dilute NaOH, 20 per cent yield	131 110–120 (boiling point at reduced pressure)	(212)
101......	$R = R' = 3\text{-}NO_2C_6H_4$	3-Nitrobenzaldoxime $[NO_2C_6H_4(=NOH)]$ or hydrochloride and isoamyl nitrite, aqueous KOH	184	(47, 60, 210, 214)
102......	$R = R' = 4\text{-}NO_2C_6H_4$	4-Nitrobenzaldoxime hydrochloride, aqueous KOH	197–198	(210, 214)
103......	$R = R' = 4\text{-}CH_3C_6H_4$	4-Tolylaldoxime, N_2O_4	142–143	(132, 184, 203)
104......	$R = R' = 4\text{-}CH_3OC_6H_4$	β-Anisyldioxime, NaOCl	113	(86, 184)
105......	$R = R' = 2,4,6\text{-}(CH_3)_3C_6HCO$	Tris(isopropylacetophenone), concentrated HNO_3, 70 per cent yield	158	(193)
106......	$R = R' = 4\text{-}ClC_6H_4CO$	*p*-Chloroacetophenone, concentrated HNO_3, 50 per cent yield	124	(193)
107......	$R = R' = 2,4,6\text{-}(CH_3)_3\text{-}3,5\text{-}(NO_2)_2C_6CO$	Mesitylacetophenone, fuming HNO_3, 40 per cent yield	235	(193)
108......	$R = R' = CH_2C_6H_5$	α-Oximino-β-phenylpropionic acid $[C_6H_5CH_2C(=NOH)COOH]$, iodine in aqueous Na_2CO_3	75	(41)
109......	$R = R' = 2,4\text{-}(CH_3)_2C_6H_3CO$	2,4-Dimethylacetophenone, HNO_3	108	(41)
110......	$R = R' = CH_3OC_6H_4CO$	*p*-Methoxyacetophenone, HNO_3, H_2SO_4, 70 per cent yield	139	(64, 86)
111......	$R = R' = C(CH_3)=NOCOC_6H_5$	Compound 42, benzoyl chloride, aqueous NaOH	155.5–156.5	(194)
112......	$R = R' = C(CH_3)=NNHC_6H_5$	Compound 41, excess phenylhydrazine	176	(194)
113......	$R = R' = C_6H_5CO$	(a) Acetophenone, concentrated HNO_3, 75 per cent yield (b) Isonitrosoacetophenone, concentrated HNO_3 (c) ω-Chloro-ω-isonitrosoacetophenone, $AgNO_2$ (d) Dibenzoylglyoxime, concentrated HNO_3 (e) Oxalyldiacetophenone, concentrated HNO_3, 50 per cent yield	87	(10, 37, 81, 83, 84, 130, 154, 168, 173, 215, 230, 233, 235)
114......	$R = R' = C_6H_5NHCO$	Oxanilhydroximic acid chloride $[C_6H_5NHCOCl(=NOH)]$, sodium acetate	187	(50, 51)
115......	$R = R' = 2,4,6\text{-}(CH_3)_3\text{-}3\text{-}BrC_6HCO$	*m*-Bromomesitylacetophenone, 70 per cent HNO_3, 70 per cent yield	158	(193)
116......	$R = R' = 4\text{-}NO_2C_6H_4CO$	*p*-Nitroacetophenone, concentrated HNO_3, 65 per cent yield	154	(193)
117......	$R = R' = 3\text{-}NO_2C_6H_4CO$	*m*-Nitroacetophenone, concentrated HNO_3, 70 per cent yield	150	(193)

TABLE 2—*Concluded*

No.	Compound	Preparation	Melting Point	References
Disubstituted symmetrical aromatic furoxans, $RC_2N_2O_2R'$				
			°C.	
118	$R = R' = 4\text{-}CH_3C_6H_4CO$	(a) Cymene $[CH_3C_6H_4CH(CH_3)_2]$, concentrated HNO_3 (b) Acetyltoluene $(CH_3COC_6H_4CH_3)$, concentrated HNO_3	125	(81, 83)
119	$R = R' = 2,4\text{-}(CH_3)_2C_6H_4CO$	2,4-Dimethylacetophenone $[(CH_3)_2C_6H_3COCH_3]$, concentrated HNO_3, 15 per cent yield	107–108	(193)
120	$R = R' = 2,4\text{-}(CH_3)_2\text{-}3,5\text{-}(NO_2)_2C_6HCO$	(a) 2,4-Dimethylacetophenone, concentrated HNO_3, dilute H_2SO_4 (b) Compound 119, concentrated HNO_3, H_2SO_4, 50 per cent yield	209; explodes when heated above melting point	(193)
121	$R = R' = 2,4,6\text{-}(CH_3)_3C_6H_2CO$	2,4,6-Trimethylacetophenone, concentrated HNO_3, 80 per cent yield	145	(24, 193)
122	$R = R' = 2,4\text{-}(CH_3)_2\text{-}6\text{-}C(CH_3)_3C_6H_2CO$	2,4-Dimethyl-6-*tert*-butylacetophenone, HNO_3 (20 per cent)	201	(25)
123	$R = R' = 3,4\text{-bis}[2,3\text{-}CH_3\text{-}NO_2\text{-}6\text{-}C(CH_3)_3C_6H_2CO]$	2,4-Dimethyl-6-*tert*-butylacetophenone	176	(25)
124	$R = R' = 3,4\text{-bis}[2,4\text{-}(CH_3)_2\text{-}3,5\text{-}(NO_2)_2\text{-}6\text{-}(CCH_3)_3C_6HCO]$	2,4-Dimethyl-6-*tert*-butylacetophenone, HNO_3 (100 per cent)	245	(25)
125	$R = R' = 3,4\text{-bis}(4\text{-}CH_3OC_6H_4CO)$	(a) *p*-Acetylanisole, concentrated HNO_3, concentrated H_2SO_4 (b) Isonitroso-*p*-acetylanisole, concentrated HNO_3, 81 per cent yield	138–139	(64, 74, 87, 88, 184, 193)
126	$R = R' = 3,4\text{-bis}(4\text{-}C_2H_5OC_6H_4CO)$	*p*-Acetylphenetole $(C_2H_5OC_6H_4COCH_3)$, concentrated HNO_3, concentrated H_2SO_4	131	(87)
Disubstituted symmetrical heterocyclic furoxans				
127	$R = R' = C_5H_6O$	Furfurylhydroxamic acid chloride, dilute NaOH	113–114	(184)
128	$R = R' = C_{10}H_6O_2N_2$	4-Methylpyrimidine, fuming HNO_3	134; explosive at higher temperatures	(61, 62)
129	$R = R' = C_{10}H_6O_2N_6 \cdot 2HNO_3$	Compound 128, nitric acid	157 (d.)	(61, 62)
130	$R = R' = C_{10}H_6O_2N_2 \cdot H_2PtCl_6$	Compound 128, H_2PtCl_6	>250	(61, 62)
131	$R = R' = C_{10}H_{12}O_2N_6$	2,4-Dimethylpyrimidine, fuming HNO_3	134–135	(61, 62)
132	$R = R' = C_{12}H_{10}O_2N_6 \cdot H_2PtCl_6$	Compound 131, H_2PtCl_6	>270	(62)

		Monosubstituted aliphatic furoxans, $RC_2N_2O_2R$		
133	R = H; R′ = I	Compound 36, H_2S or SO_2, 60 per cent yield	111–112 (d.)	(33, 192)
134	R = H; R′ = CH_3	Methylglyoxime, N_2O_4	Not obtained in pure form	(187)
135	R = H; R′ = COOH	Barium salt of furoxandicarboxylic acid, dilute H_2SO_4	89 (d.)	(96, 236)
		Monosubstituted aromatic furoxans		
136	R = H; R′ = C_6H_5	Phenylglyoxime, N_2O_4	168	(138, 156, 160, 163, 187, 235)
137	R = H; R′ = $CH_3C_6H_5$	Tolylglyoxime, N_2O_4	100–101	(159, 163)
138	R = H R′ = $C_6H_5CH_2CH(NO_2)$	Styrylglyoxime [$C_6H_5CH{=}CHC({=}NOH)C({=}NOH)H$], N_2O_4	101–102	(77)
139	R = H R′ = $CH_2COC_6H_5$	Benzalacetoxime [$C_6H_5CH{=}CHC({=}NOH)CH_3$], N_2O_4	158–159	(77)
140	R = H R′ = $CH_2C({=}NOH)C_6H_5$	(a) Benzalacetoxime [$C_6H_5CH{=}CHC({=}NOH)CH_3$], isoamyl nitrite (b) Compound 139, NH_2OH	215; forms sodium salt	(77)
141	R = H R′ = $HNO_2C_6H_4CH_2CO$	Compound 140, concentrated HNO_3	197–198	(77)
142	R = H R′ = 4-$(CH_3)_2CHC_6H_4C({=}NOH)CH_2$	Oxime of cuminalacetone [$CH_3C({=}NOH)CH{=}CHC_6H_4$-$CH(CH_3)_2$], HNO_2	187	(77)
143	R = H R′ = $C_6H_5C({=}NOCOCH_3)CH_2$	Compound 140, acetic anhydride	150–155	(77)
		Miscellaneous disubstituted derivatives of furoxans		
144		Compound 42, boil with dilute NaOH	188–190; over 150 changes color from yellow to brown	(194)
145		Compound 113, NH_2NH_2	207 (d.)	(215)

A dibromofuroxan was first prepared by Kekulé in the middle of the nineteenth century by treating mercury fulminate (97) with bromine. Although he referred to the material as dibromonitroacetonitrile, he reported a melting point of 50°C. and a boiling point of 130–135°C. with decomposition. Holleman (89) repeated this work and showed the supposed dibromonitroacetonitrile to be dibromoglyoxime peroxide. Then Wieland (222) repeated the experiments and evidently obtained a substance with the same properties as those reported by Kekulé and Holleman but he renamed it "dibromofuroxan." Wieland called attention to the preparation of the true dibromonitroacetonitrile by Steinkopf and Bohrmann (198), together with the difference in properties between the two substances. Preparation with good yields of this material were then again reported via the dibromoformoxine route by Birckenbach and Sennenwald (33). In one case the formoxime was caused to react with either mercuric oxide or magnesium oxide, or in a second case with fuming nitric acid, but a quantitative yield was claimed for the reaction between dibromoformoxime and ammonia gas. Unfortunately no further characterization of the compound beyond that reported by its discoverer Kekulé was made by any of the subsequent investigators.

Kekulé was unable to prepare a pure diiodofuroxan by the reaction of iodine with mercury fulminate (97). Sell and Biedermann (192), by the same reaction performed in ether, obtained colorless crystals which became colored at 70°C. and melted at 86°C. In spite of its lack of color Birckenbach and Sennenwald claimed that the material (33) was not pure, for it melted seven degrees lower than the substance which they had prepared. They obtained white crystals from the same reaction; on recrystallization from carbon tetrachloride the substance was obtained as a cream-colored crystal powder, the color of which remained after repeated recrystallizations. This material became colored at 89°C. and melted at 93.5°C.

Clearly, the simpler molecular configurations of the furoxans exist, despite the fragmentary nature of the data available concerning them.

VII. TABLE OF FUROXANS

Table 2 contains a list of the furoxans that have been obtained, together with the method of preparation for each, its melting or boiling point, and pertinent references to the literature.

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