ALIPHATIC DIAZO COMPOUNDS, NITRONES, AND STRUCTURALLY ANALOGOUS COMPOUNDS

SYSTEMS CAPABLE OF UNDERGOING 1, 3-ADDITIONS

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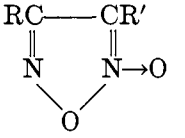
There are a number of substances, containing systems of double bonds and semipolar bonds, which are capable of undergoing 1, 3-addition. These are all extremely interesting compounds chemically, especially from the standpoint of electronic linkages, for in all of them the middle element in the 1, 3-system is a "pentavalent" nitrogen atom. This atom is joined on one side by a double bond to carbon or nitrogen, and on the other side to oxygen, nitrogen, or carbon by a semipolar double bond alone, or by a semipolar bond *and* a covalent bond. In all the 1, 3-additions the "pentavalent" nitrogen in the middle apparently takes no part except that its valence drops from "5" to 3. The most important of these systems are:[1]

1. The aliphatic diazo compounds, typified by diazomethane, CH_2N_2 (page 194).

$$CH_2{=}N{\rightleftarrows}N \qquad \text{or} \qquad H_2C\overset{\times}{\underset{\times}{\overset{\circ}{\underset{\circ}{}}}}N\overset{\times}{\underset{\times}{\overset{\circ}{\underset{\circ}{}}}}N\overset{\circ}{\underset{\circ}{}}$$

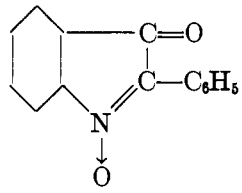
2. The azides, $RN{=}N{\rightleftarrows}N$ (page 214).
3. The *N*-ethers of the oximes, $R_2C{=}N{\rightarrow}O$ (nitrones) (page 222).
4. The nitrile oxides, $RC{\equiv}N{\rightarrow}O$ (page 233).
5. The furoxans of Wieland and Semper (382)



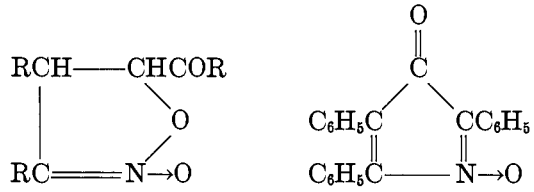
and related substances (page 237).

[1] The use of two different symbols for the (outer) electrons of the elements involved in the formation of the compounds discussed in this paper does not in any way imply that the electrons are of different sorts or that the electrons originally belonging to one atom can be identified once the bond between two atoms is formed. The symbols are employed simply because their use renders it somewhat easier to follow the mechanism whereby the bond was formed. The arrow in the formulas designates a semipolar bond formed by a pair of electrons donated by a single atom, and the arrow points from the donor atom to the acceptor atom.

6. The isatogens of Pfeiffer (284) and Ruggli (308) (page 244).



7. The isoxazoline oxides and the cyclic nitrones of Kohler (page 255).



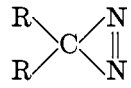
8. Staudinger's nitrenes (340) $R_2C{=}N{=}CR_2$ (page 267).
9. The azoxy compounds RN=NR (page 272).

I. THE ALIPHATIC DIAZO COMPOUNDS

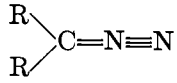
The first aliphatic diazo compound was discovered in 1883 by Curtius (85), who obtained ethyl diazoacetate, $CHN_2COOC_2H_5$, as a yellow oil by the action of nitrous acid upon glycine ester hydrochloride. Diazomethane, CH_2N_2, was prepared by v. Pechmann (271) in 1894 by treating *N*-methyl-*N*-nitrosobenzamide, $C_6H_5CO{-}N(NO){-}CH_3$, methylnitrosourethan, $CH_3N(NO){-}COOC_2H_5$, and other nitroso derivatives of methylamine with alkali. Since then many other aliphatic diazo compounds have been prepared, and by a variety of methods.

Only recently has it become possible to reach a definite conclusion regarding the structures of the aliphatic diazo compounds and the closely related azido compounds. Since the arguments concerning the structure of these compounds have been reviewed recently (332), only a brief out-

line of this topic will be given here. Curtius (86) originally used the ring formula,

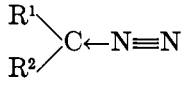


which was accepted for many years until Angeli (7, 8) suggested the open-chain formula



Thiele (355), as a result of the work of Staudinger (337), also advocated the open-chain formula. Further work, either of a physical or chemical nature, led to ambiguous results. On the physical side the evidence was interpreted by some workers in favor of the ring structure (149, 214, 216), by others in favor of the chain formula (26), while a third group believed that the physical evidence, especially that based upon the parachors, was inconclusive (248, 127, 331). On the chemical side the evidence was no less conflicting, for the methods of preparation (337, 343) as well as the reactions of these compounds (92, 117, 339, 341) could be interpreted on the basis of either formula.

It became obvious, of course, that the Angeli formula, containing a pentacovalent nitrogen atom, could not be correct, and Langmuir (202, 203) proposed the structure $R_2C{=}N{\rightleftarrows}N$, which is isosteric with the ketenes (20, 226, 227). Another electronic modification of Angeli's formula



in which the middle nitrogen atom donates two electrons to the carbon atom, has been considered. Compounds possessing such a structure should be resolvable, by analogy with the sulfones which were resolved by Phillips (286, 287, 288). Attempts were made to prepare optically active aliphatic diazo compounds (81, 207–212, 224, 259, 260, 261, 335), and while the products in some cases showed a slight optical activity, it remained for Ray (302, 303) to suggest, and for Weissberger (358, 359) to prove, that the optical activity was due to impurities present in the diazo compounds.

The results of Boersch (55) on the electron diffraction of the molecule of diazomethane have shown conclusively that the chain formula is the correct one, but the low dipole moment of the aliphatic diazo group (333) excludes either of the two chain formulas alone. However, the only difference between the two chain formulas lies in the distribution of the electrons and, if the aliphatic diazo compounds are regarded structurally not merely as one of the two possible chain structures but as a resonance-

hybrid of both, then the low value for the dipole moment and the lack of optical activity are not anomalous.

The conclusion, therefore, as to the structure of these substances is that the open-chain formula is correct, and that the compounds are resonance-hybrids of the two electronic structures

$$\rangle C{=}N{\rightleftarrows}N \qquad \text{and} \qquad \rangle C{\leftarrow}N{\equiv}N$$

and, as Sidgwick says (reference 332, page 362), "it is one of the few groups of organic chemistry for which no one formula can be written, even as an approximation."

Either of these two structures might be expected to undergo 1,3-addi tions, one group becoming attached to the end nitrogen atom and the other to the carbon atom. There are a great many chemical reactions of this type and these reactions constitute, in themselves, independent evidence that the open-chain form actually exists. In these reactions the middle nitrogen atom always drops in valence from "5" to 3, while the ends of the system become attached to the two adding groups, thus:

$$R_2C{=}N{\rightleftarrows}N + XY \rightarrow R_2\underset{\displaystyle X}{\underset{|}{C}}H{=}N{-}Y$$

A. Preparation of aliphatic diazo compounds

(*1*) By the action of nitrous acid on aliphatic amino acids. This method is decidedly limited, but when it can be used it is usually the best method. The amine must be primary and the amino group must be joined to a carbon atom holding at least one hydrogen atom which is also alpha to a complex containing a multiple bond but no free hydroxyl group. Thus compounds containing the groups $H_2N\underset{|}{C}HCOOC_2H_5$, $H_2N\underset{|}{C}HC{\equiv}N$, and $H_2N\underset{|}{C}HCOR$ all give aliphatic diazo compounds when their hydrochlorides are treated with nitrous acid, while compounds containing groups such as $H_2N\underset{|}{C}HCOOH$, $H_2NCH(CH_3)_2$, and $H_2NC(CH_3)_2COOC_2H_5$ do not. The latter compounds give only alcohols, the usual reaction of primary aliphatic amines with nitrous acid.

(*2*) For the diazo hydrocarbons other methods must be used. Diazomethane and diazoethane are usually prepared by the method of v. Pechmann (271, 272, 276, 366, 222) from methylnitrosourethan. Methyl-

nitrosourethan and ethylnitrosourethan are now commercial products. They are prepared as follows:

$$2CH_3NH_2 + ClCOOC_2H_5 \rightarrow CH_3NHCOOC_2H_5 + CH_3NH_2 \cdot HCl$$

$$CH_3NHCOOC_2H_5 \xrightarrow[NaOH]{ClCOOC_2H_5} CH_3NHCOOC_2H_5$$

$CH_3NHCOOC_2H_5$ + oxides of nitrogen (from $As_2O_3 + HNO_3$) in ether $\rightarrow$ $CH_3N(NO)(COOC_2H_5)$

Methylnitrosourethan is a yellowish-red liquid which boils at 70°C. at 27 mm. It is very toxic and irritating to the skin, lungs, and eyes. The best method of converting methylnitrosourethan to diazomethane is as follows: 5 g. of sodium is dissolved in the minimum amount of methanol, about 50 to 75 ml., by heating. This solution is placed in a small distilling flask equipped with a small dropping funnel and connected to a condenser through which ice water circulates (if the tap water is at all warm it must be cooled). The methylnitrosourethan is dissolved in some absolute ether and put in the dropping funnel. The substance to be methylated is dissolved in absolute ether, cooled in an ice–salt bath, and set under the delivery end of the condenser. When all is ready the methylnitrosourethan is run slowly into the sodium methoxide, the ether and diazomethane distilling over. There must always be ether in the reaction flask to distill over with and to dilute the diazomethane. After all of the methylnitrosourethan has been added, absolute ether is added with continuous slow distillation until the distillate is no longer yellow. From 10 ml. of methylnitrosourethan dissolved in 50 ml. of ether one obtains an ethereal solution containing 1.8 to 2.0 g. of diazomethane. This represents a yield of about 50 to 80 per cent. Diazomethane does not keep well, so it should be made up from methylnitrosourethan just before it is to be used. For diazoethane the same procedure is used, substituting ethylnitrosourethan for the methylnitrosourethan and (most important) ethyl alcohol for the methyl alcohol. As an example of the preparation of a more complicated diazo compound by this method, the preparation of triphenylmethyldiazomethane may be cited (153):

$$(C_6H_5)_3CCH_2NH_2 \rightarrow (C_6H_5)_3CCH_2NHCOOC_2H_5 \rightarrow (C_6H_5)_3CCH_2N(NO)(COOC_2H_5) \rightarrow (C_6H_5)_3CCHN_2$$

(orange-yellow; m.p. 78–80°C. (decomposition))

The method of Arndt (18, 17, 269, 361), using methylnitrosourea, permits the use of a much higher concentration of diazomethane, for 6 g. of it may be obtained from 20 g. of the urea. Moreover methylnitrosourea

is a solid and it does not have the irritating action of methylnitrosourethan, although it does not keep well and on standing in a warm place for a long time may undergo spontaneous decomposition which may become rather violent. Hence it must be kept cold and dry. It is best not to prepare more than 25 to 50 g. of it at any one time. The reactions involved are as follows:

$$KOCN + CH_3NH_2 \cdot HCl \longrightarrow CH_3NHCONH_2 + KCl$$

$$CH_3NHCONH_2 \xrightarrow{HNO_2} CH_3N(NO)CONH_2$$

$$CH_3N(NO)CONH_2 \xrightarrow{NaOH} CH_2N_2 + CO_2 + NH_3$$

In the method of Jones and Kenner (168–170; see also references 160 and 343) nitroso-β-alkylaminoketones are employed, especially those derived from mesityl oxide.

$$(CH_3)_2C{=}CHCOCH_3 + CH_3NH_2 \longrightarrow (CH_3)_2C(NHCH_3)CH_2COCH_3 \xrightarrow{HNO_2} (CH_3)_2C(ONNCH_3)CH_2COCH_3$$

$$(CH_3)_2C(ONNCH_3)CH_2COCH_3 \xrightarrow{NaOC_3H_7(iso)} H_2O + \text{mesityl oxide} + CH_2N_2$$

(80 per cent yield)

(*3*) The method of Staudinger and Kupfer (344), using hydrazine, chloroform, and alkali, gives a yield of about 25 per cent.

$$H_2NNH_2 + CHCl_3 + KOH \rightarrow CH_2N_2 + 3KCl + 3H_2O$$

A similar method is that of Bamberger and Renauld (35), using *N*,*N*-dichloromethylamine and hydroxylamine

$$CH_3NCl_2 + H_2NOH \rightarrow 2HCl + H_2O + CH_2N_2$$

but this method is of little value because of the difficulties involved in handling the chloroamines.

(*4*) The method of Staudinger, involving the oxidation of the hydrazones of ketones, is always the best method to be used for the complicated diazo hydrocarbons (338, 108, 258). Thus benzophenone hydrazone reacts with mercuric oxide in petroleum ether at room temperature, and in 5 to 6 hr. diphenyldiazomethane is obtained in 85 to 98 per cent yields. This is a deep red solid which melts at 29–30°C., and which can be recrystallized

from methanol, although there is some decomposition to give the ketazine, $(C_6H_5)_2C{=}N{-}N{=}C(C_6H_5)_2$.

$$(C_6H_5)_2C{=}N{-}NH_2 \xrightarrow{HgO} (C_6H_5)_2C{=}N{\rightleftarrows}N$$

Phenylbenzoyldiazomethane may be prepared in a similar manner:

$$\begin{array}{l} C_6H_5C{=}N{-}NH_2 \\ \quad\quad | \\ C_6H_5CO \end{array} \longrightarrow \begin{array}{l} C_6H_5C{=}N{\rightleftarrows}N \\ \quad\quad | \\ C_6H_5CO \end{array}$$

For the assay of diazomethane solutions there are three methods: (*a*) The method of Marshall and Acree (223) is considered the best. The diazomethane solution (20 ml.) is cooled and treated with an excess of ethereal $N/10$ benzoic acid solution. After the reaction

$$C_6H_5COOH + CH_2N_2 \rightarrow C_6H_5COOCH_3 + N_2$$

has taken place the excess of benzoic acid is determined by titrating with $N/10$ barium hydroxide, using phenolphthalein as the indicator. The solution must be diluted with much water before titrating and should be shaken vigorously during the titration. (*b*) The diazomethane solution may be directly titrated with standard alcoholic hydrochloric acid (235):

$$CH_2N_2 + HCl \rightarrow CH_3Cl + N_2$$

(*c*) The method of v. Pechmann (271). An excess of standard iodine is added and the excess then titrated in the usual way.

$$CH_2N_2 + I_2 \rightarrow CH_2I_2 + N_2$$

(*d*) Either of the reactions in (*a*), (*b*), or (*c*), but preferably that in (*b*), may be used, and the evolved nitrogen collected and measured.

B. Properties of the aliphatic diazo compounds

The volatile diazo hydrocarbons are yellow gases or liquids; when solid they are usually reddish. Diazomethane is easily condensed to a liquid boiling at $-23°$ to $-24°$C. and, since the vapor of it is explosive, no more than a gram or so should ever be handled at once. In ethereal or other solution, however, it is quite safe, but even the ethereal solution will explode if heated to about 200°C. Diazomethane is said to be violently poisonous, attacking the eyes and lungs, although some people are said to be unaffected by it. One should observe due, though not necessarily extreme, precautions in handling either it or the methylnitrosourethan from which it is made (219, 18, 255).

The diazocarbonyl compounds, particularly the diazo esters, are yellow liquids with characteristic odors. The color deepens when they are

heated and returns to the lighter shade on cooling. They are quite volatile, and the volatility decreases with the molecular weight of the ester group, while the solubility in water falls off. They can be distilled with steam or *in vacuo*. They are quite soluble in most organic solvents and sparingly soluble in water. The esters can be hydrolyzed to salts with dilute aqueous alkali, but the free acids decompose as fast as they are formed, and even carbon dioxide acts upon the salts in the cold, leading to decomposition products.

C. Reactions of diazomethane

Probably the most important use of diazomethane is as a methylating agent. For this purpose it is usually used in solution in ether, although alcohol (158), chloroform (137), methylal (111), or any other inert solvent may be used. The preparation of an ethereal solution of the reagent is not always necessary, for the methylation may be carried out by mixing the compound to be methylated with methylnitrosourethan or methylnitrosourea in alcoholic solution and then adding a mildly alkaline compound which is insoluble in the alcohol (to avoid an excess), such as potassium carbonate (225).

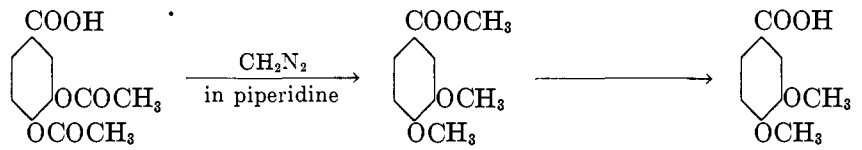
The reagent is especially suited for the methylation of phenols and carboxylic acids, and the velocity of the methylation increases with the acidity of the compound. The reaction is usually fast and quantitative, the excess of the reagent being easily removed by adding a little hydrochloric acid; there are no by-products other than nitrogen and perhaps a small amount of the polymer of the reagent. If the methylation is slow, more diazomethane is added until the yellow color is permanent after standing overnight.

Diazomethane is a very valuable, mild methylating agent, excellent for use with sensitive compounds, as it reacts in neutral solution. Only the cost, the danger in handling, and the toxicity of the nitrosourethan and of diazomethane itself have kept it from becoming the ideal methylating agent.

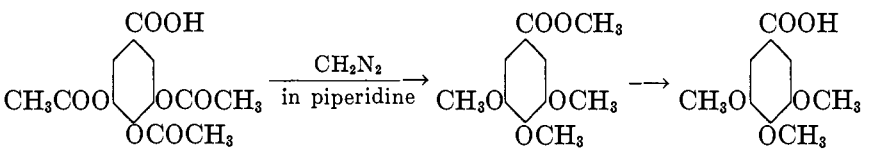
Ortho substituents in benzene derivatives hinder the methylation or may block it completely (157). Thus salicylic ester does not methylate, while gallic acid gives the trimethoxy methyl ester and pyrogallolcarboxylic acid gives the 3,4-dimethoxy-2-hydroxy methyl ester. However, picric acid gives trinitroanisole, and v. Pechmann (277) was able to obtain the esters of mesitylenecarboxylic acid, symmetrical-tribromobenzoic acid, mellitic acid, and trinitrobenzoic acid. The reagent is unsuitable for preparing ester acids of the dibasic acids, as the main products are the diesters and unchanged acids (357).

Phenol esters are usually converted to the ethers, the —OCOR group

being replaced by —OCH_3, but —$NHCOCH_3$ is not affected. This gives a method of determining whether an acetylaminophenol is an *O*-acetyl or an *N*-acetyl derivative. Nierenstein (254) has developed a new method of methylating the phenol esters in this way by the action of diazomethane in the presence of piperidine. Each molecule of piperidine removes one acetyl group, which is then replaced by methyl. This has the advantage that the acetyl derivatives are well-crystallized, sharply melting compounds which are easily obtained in the pure state.



Diacetylprotocatechuic acid — Veratric acid



Triacetylgallic acid — Trimethyl ether of gallic acid

Alcohols are not usually methylated by diazomethane, but in the presence of alkoxides of the polyvalent metals they do react (228).

n-C_4H_9OH + 5 per cent $Al(OC_2H_5)_3$ + CH_2N_2 → 83 per cent yield of n-$C_4H_9OCH_3$

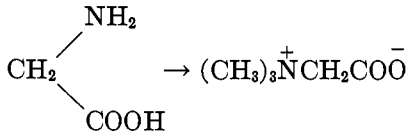
iso-C_3H_7OH similarly → 77 per cent yield of iso-$C_3H_7OCH_3$

n-C_4H_9OH + $Sb(OC_4H_9)_3$ + CH_2N_2 → 73 per cent yield of n-$C_4H_9OCH_3$

Enols are usually methylated.

Acids are rapidly transformed to methyl esters, and the method is equal in effectiveness to the method using the silver salt and methyl iodide.

Nierenstein (136) states that diazomethane does not methylate amino acids, but Biltz and Paetzold (50) have shown that glycine, in the presence of a trace of water, is quantitatively converted into betaine:



and that other amino acids of molecular weight greater than that of alanine react normally with methylation of both the amino and the carboxyl groups (156).

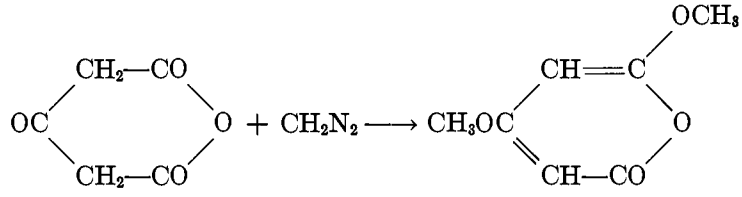
Oximes give the *O*-methyl ethers, although the *syn*- and *anti*-forms of the oximes do not react with equal ease. However, there seems to be no regularity in these differences in reactivity, that is, the *syn*- and *anti*-forms of oximes cannot be distinguished by means of this reaction. There is no explanation for these differences, though it probably has to do with differences in the dissociation constants of the two oximes. The *anti*-form of benzaldoxime gives an *O*-methyl ether, while the *syn*-form does not react (123). Not much systematic work has been done on the methylation of oximes with diazomethane.

Primary *amines* are converted into secondary methylamines, though the reaction has not been much used:

$$RNH_2 + CH_2N_2 \rightarrow RNHCH_3 + N_2$$

Secondary amines do not react, and acetylation protects primary amines completely against the action of the reagent (272).

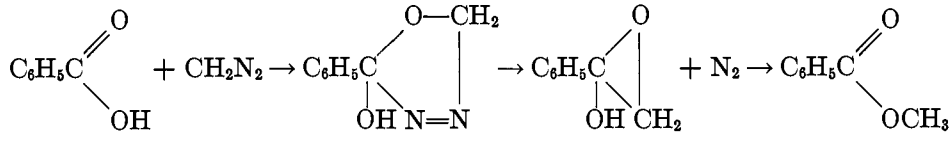
Benzoic anhydride gives methyl benzoate and a diazoketone; succinic anhydride gives methyl succinate (57); acetonedicarboxylic anhydride gives an 80 per cent yield of 4,6-dimethoxy-α-pyrone (218).



Phthalimide and succinimide give the *N*-methyl derivatives smoothly (201).

Acetoacetic ester reacts slowly, giving β-methoxyethyl crotonate, but malonic ester does not react at all under ordinary conditions (273).

In the methylations considered so far the mechanism of the reaction is obscure and no intermediates have been isolated. It is possible to write them as 1,3-additions, thus:



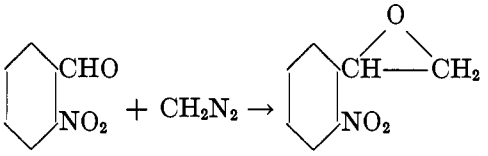
This is in analogy with the known addition of aliphatic diazo compounds to C—C multiple bonds to give five-membered rings, but in the absence of definite proof this mechanism can only be accepted provisionally.

Aldehydes behave toward diazomethane as though they contained an active hydrogen atom, and give methyl ketones (323).

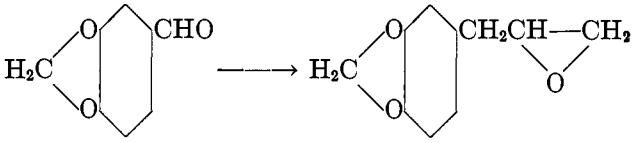
$$C_6H_5CHO + CH_2N_2 \rightarrow C_6H_5COCH_3 + N_2$$

$$n\text{-}C_6H_{13}CHO + CH_2N_2 \rightarrow n\text{-}C_6H_{13}COCH_3 + N_2$$

This reaction bears the name of Schlotterbeck, although Meyer (236) has claimed priority. Arndt and his students (15) have shown that the reaction is not always clean-cut, and so is not of general application, for in some cases ethylene oxides are formed, the ketone appearing only as a by-product. Thus *m*- and *p*-nitrobenzaldehydes give the corresponding acetophenones, but *o*-nitrobenzaldehyde gives *o*-nitrophenylethylene oxide:

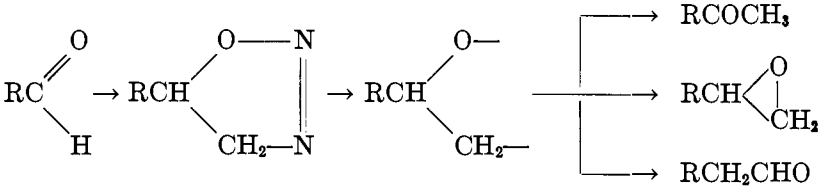


Piperonal reacts with *two* molecules of diazomethane to give safrole oxide (243):

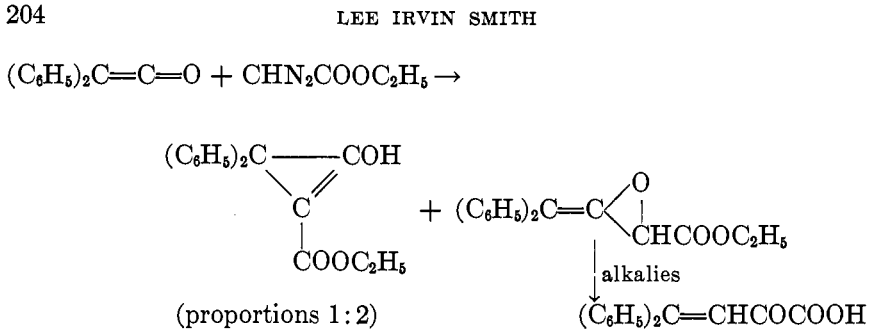


From 10 g. of *p*-nitrobenzaldehyde there was produced 5 g. of the ethylene oxide, 3.2 g. of *p*-nitroacetophenone, and traces of $p\text{-}NO_2C_6H_4CH_2COCH_3$ (19).

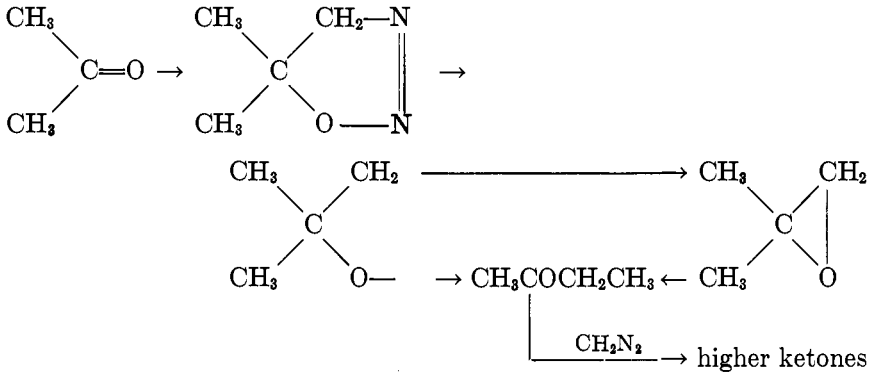
The mechanism for these reactions suggested by Arndt (see also 226, 227) involves a primary 1,3-addition:



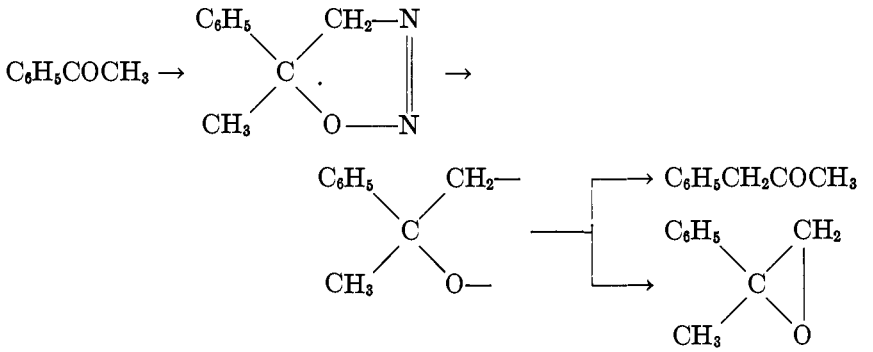
Ketene gives cyclobutanone, possibly *via* cyclopropanone (217) as an intermediate, while diphenylketene reacts with diazoacetic ester as follows (346):



Ketones do not react under ordinary conditions, but in the presence of catalysts such as water, alcohols, or metallic salts they do react (226, 227). Thus acetone gives α,α-dimethylethylene oxide (40 per cent yield) along with some methyl ethyl ketone and higher ketones:



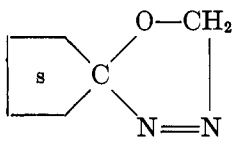
Acetophenone reacts similarly (245):



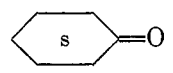
The cyclic ketones undergo similar reactions, but here the ring enlarges by one carbon atom. Thus cyclohexanone (20 g. in methanol, not in ether, however) reacts vigorously with diazomethane, giving as the main product cycloheptanone (12 g.), with by-products of cycloöctanone and

an oxide isomeric with cycloheptanone. Cyclopentanone similarly gives cycloheptanone as the main product (14 g. from 23 g. of cyclopentanone) with cycloöctanone and the same oxide as by-products (244). This is an excellent method for preparing cycloheptanone.

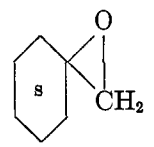
This reaction is also probably a 1,3-addition, giving compound I which then rearranges to II with evolution of nitrogen. II reacts again to give the cycloheptanone. The oxide isomeric with cycloheptanone could well be III.



I

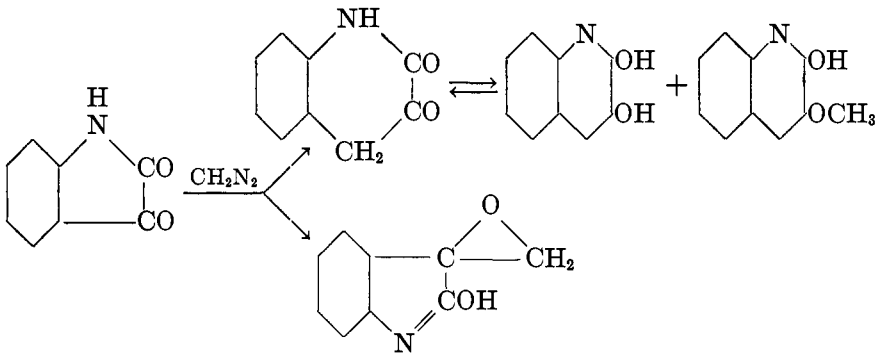


II

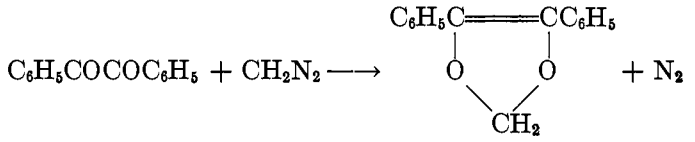


III

A similar ring expansion occurs when diazomethane reacts with isatin, for the product is dihydroxyquinoline (152, 21):

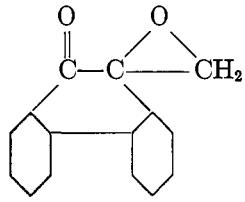


Aliphatic diketones, such as diacetyl and acetonylacetone, are not affected by diazomethane (51), but benzil reacts to give α,β-dihydroxystilbene methylene ether (51, 19); p,p'-dibromobenzil and furil react similarly.

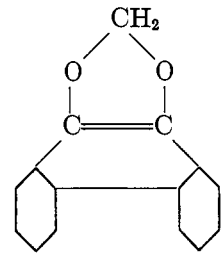


Anthraquinone does not react, but phenanthraquinone with diazomethane plus a trace of methanol gives the ethylene oxide (IV) (19) which, when treated with hydrochloric acid in methanol, gives the chlorohydrin, thus establishing the structure. The acetal (V) is obtained if much methanol is used. Only the acetals VI and VII are produced from benzil

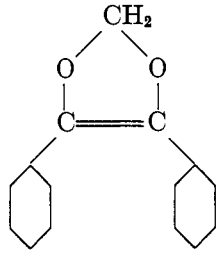
and alloxan, and with the latter methylation at both NH groups occurs also.



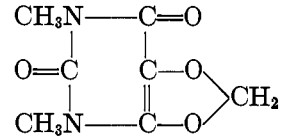
IV



V



VI



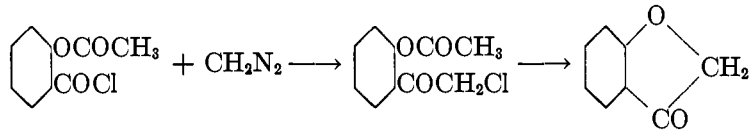
VII

Ortho-quinones such as 6-bromo-1,2-naphthoquinone or 4-triphenylmethyl-1,2-benzoquinone add diphenyldiazomethane in an analogous manner, giving the acetal type of reaction product (106).

The reaction between *acid halides* and diazomethane was originally investigated by Nierenstein and bears his name (84). Nierenstein states that ω-halogenated ketones are formed in good yield:

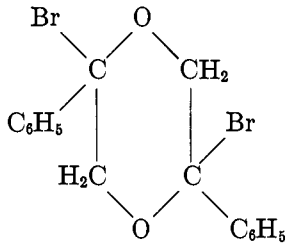
$$C_6H_5COCl + CH_2N_2 \rightarrow C_6H_5COCH_2Cl + N_2 \quad \text{(72 per cent yield)}$$

$$C_6H_5CH_2COCl + CH_2N_2 \rightarrow C_6H_5CH_2COCH_2Cl + N_2$$
(84 per cent yield)



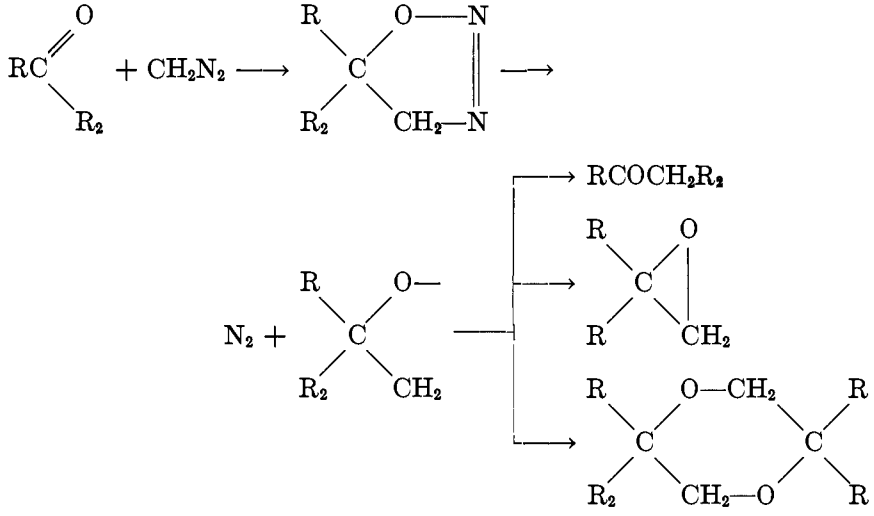
(92 per cent yield)

But the yield of haloketone from benzoyl bromide was small, 62 per cent of the product being the dioxane,



while triphenylacetyl chloride gave the corresponding dioxane in 92 per cent yield (213).

From these results Nierenstein favors the interpretation of the reaction as given by Oliveri-Mandala (264) and by Arndt. In the following R_2 is Cl, Br, or H (so as to include the Schlotterbeck reaction), and the nature of R_2 determines the course of the reaction.



Robinson and his students investigated this reaction (56, 58, 57) and found that benzoyl chloride with diazomethane gave the diazoketone in 91 per cent yield instead of the chloroketone. They were unable to find any trace of substituted dioxanes, although by changing the procedure the ω-chloroketone could be obtained.

$$C_6H_5COCl + 2CH_2N_2 \rightarrow C_6H_5COCHN_2 + CH_3Cl + N_2$$

Thus if the acid halide was added gradually to diazomethane, keeping the latter always in excess, the diazoketone was the main product (reactions A and B), while if the reverse procedure was followed the chloroketone resulted (reaction C).

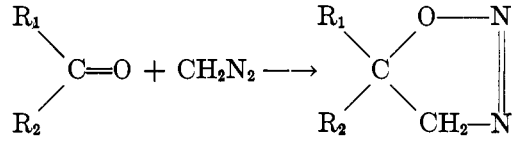
$$RCOCl + CH_2N_2 \rightarrow RCOCHN_2 + HCl \quad (A)$$

$$CH_2N_2 + HCl \rightarrow CH_3Cl + N_2 \quad (B)$$

$$RCOCHN_2 + HCl \rightarrow RCOCH_2Cl + N_2 \quad (C)$$

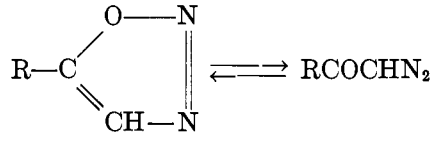
Robinson agrees with Arndt (16) that the diazoketone is the primary product of the reaction. Nierenstein (222) does not agree with this interpretation, however, and continues to write the reaction as above, as merely a special case of the Schlotterbeck reaction.

On the whole it does not seem that Robinson and Nierenstein are as far apart in their interpretations as might be supposed at the first glance. Assuming that the first reaction is a 1,3-addition, we have:



(R_2 is Cl, Br, or H)

If R_2 is halogen, this product can eliminate HX to give:



The action of HX on the diazoketone would give the ω-haloketone, $RCOCH_2X$. If R_2 is not halogen, then the elimination of HX to give the diazoketone cannot occur, but nitrogen can be eliminated to give a radical which could then rearrange to the alkylene oxide or to another ketone, $RCOCH_2R_2$. The elimination of nitrogen in this way might occur even if R_2 were halogen, which would result in an intermediate capable of forming the halogen-substituted dioxanes.

Sulfonyl chlorides are apparently unaffected by diazomethane (23), hence reaction with RCOCl probably involves the carbonyl group, not the chlorine atom.

In three recent papers on aliphatic diazo compounds and electronic structures Arndt and Eistert (20; see also 226, 227) and Eistert (104) have reviewed the Robinson–Ingold–Thorpe electronic conception of organic reactions, applying these to the aliphatic diazo compounds. In the first

paper (20) they have shown how the reaction between diazomethane and an acid chloride can be made to give a diazoketone in good yield, and that this in turn can be used as a source for the next higher acid, thus:

$$RCOCl \rightarrow RCOCHN_2 \rightarrow RCH_2COOH$$

The reactions are

$$RCOCl + 2CH_2N_2 \rightarrow RCOCHN_2 + CH_3Cl + N_2$$

(small amounts of $RCOCH_2Cl$ as by-product). The diazoketone, in the presence of finely divided silver, platinum, or copper (catalyst), reacts with water, alcohols, ammonia, primary amines, or secondary amines (sometimes heating under pressure is necessary) to give nitrogen and derivatives of the next higher acid:

$$RCOCHN_2 + HOH \rightarrow N_2 + RCH_2COOH$$
$$+ R'OH \rightarrow RCH_2COOR'$$
$$+ NH_3 \rightarrow RCH_2CONH_2$$

The steps in the reaction are much the same as those in the Hofmann–Curtius rearrangement. Instead of an isocyanate a ketene results, which then adds the reagent present to give the final acid or acid derivative:

$$RCOCl \rightarrow R\overset{\overset{O}{\|}}{C}CH{=}N{\rightleftarrows}N \rightarrow \left[RCOCH\!<\right] \rightarrow RCH{=}C{=}O \rightarrow RCH_2COOH$$

Ammonia and amines, especially aniline, react best of all, while alcohols and water do not react so smoothly. It is best to prepare the amide or anilide and then hydrolyze to the acid. The yields are usually good: thus 18.6 g. of *o*-nitrobenzoyl chloride gave 10 g. of *o*-$NO_2C_6H_4CH_2CONH_2$; 19 g. of α-$C_{10}H_7COCl$ gave 18 g. of α-$C_{10}H_7COCHN_2$; 10 g. of this gave 6 g. of α-$C_{10}H_7CH_2COOC_2H_5$, while 5 g. gave 4.2 g. of α-$C_{10}H_7CH_2CONH_2$; 16 g. of veratroyl chloride gave 15 g. of the diazoketone (this was converted to the amide, from which 4.2 g. of homoveratric acid was obtained); 30 g. of benzoyl chloride gave about 20 g. of phenyl acetamide (328, 304, 385, 342, 329).

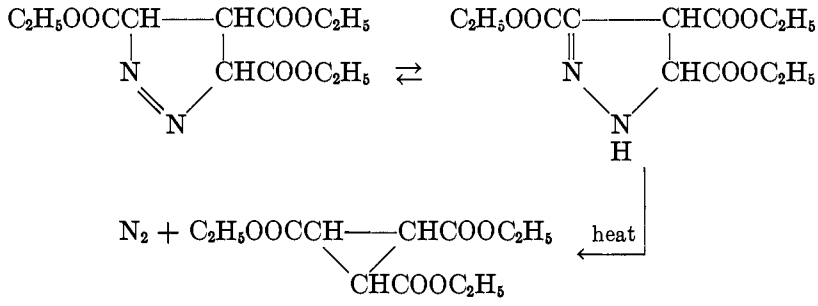
The reactions leading to the three products obtainable from an acid chloride and diazomethane, viz., $RCOCH_2Cl$, $RCOCHN_2$, RCH_2COOH, have been developed by Nierenstein (252), Robinson (307), and Arndt (20), respectively. All three may be conducted so as to give excellent yields. To obtain $RCOCH_2Cl$, the acid chloride is kept in excess (diazomethane added dropwise); to get $RCOCHN_2$ the procedure is reversed and the acid chloride dropped into diazomethane; to get RCH_2COOH the

second procedure is followed and then H_2O, HOR, NH_3, RNH_2, etc., is added. This latter reaction is catalyzed by finely divided metals.

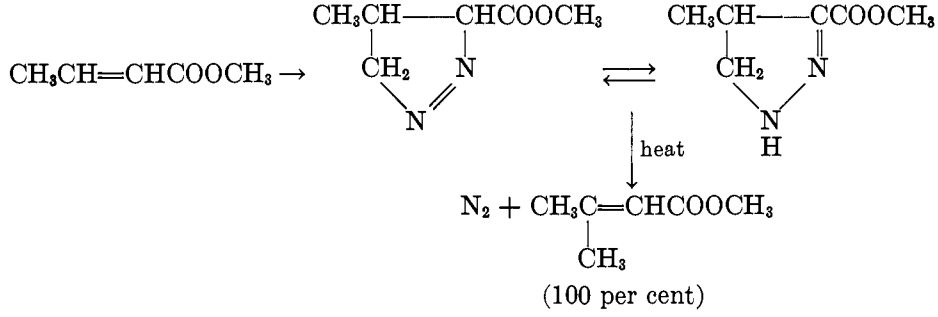
The aliphatic diazo esters in general parallel diazomethane and the other diazo hydrocarbons in their reactions, although no aliphatic diazo compound has been studied to such an extent as diazomethane.

The aliphatic diazo compounds add to carbon–carbon double and triple bonds, especially (though not necessarily) when these are α,β to a carbonyl group or carbethoxyl group. The primary products are pyrazolines formed by direct 1,3-additions. These can frequently be decomposed on heating, especially with polished platinum, to give cyclopropanes. This provides a very good method of preparing some substituted cyclopropanes (280, 74, 1, 164, 31).

$C_2H_5OOCCH{=}CHCOOC_2H_5 + CHN_2COOC_2H_5 \rightarrow$



However, the elimination of nitrogen does not always occur completely in the manner shown, for unsaturated open-chain esters often result along with the cyclic ester, or one or the other of these may be the exclusive product (27). Thus:

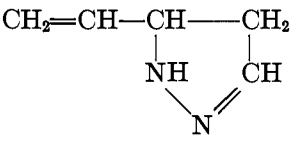


(100 per cent)

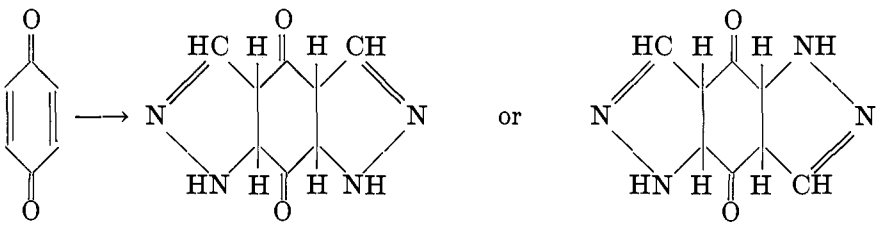
The course of this reaction depends primarily upon the complexity of the pyrazoline,—the simpler members yielding unsaturated esters chiefly, while those compounds containing more ester groups tend to form cyclopropanes.

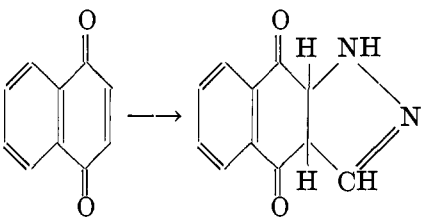
Diazomethane also adds to acetylene to form pyrazole (278) and to ethylene to form pyrazoline (33). Groups such as the cyano or carbethoxyl group favor the addition to ethylenic bonds, while phenyl groups decrease the reactivity (262).

Dienes also react with diazomethane. 5-Vinylpyrazoline was obtained from butadiene when the reaction mixture was kept at −20°C. for 48 hr. (247).

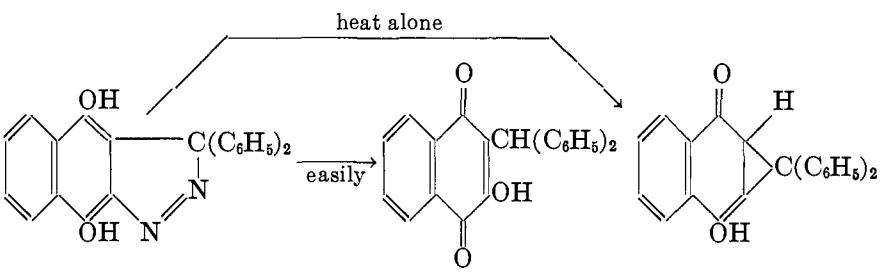


Quinones. v. Pechmann added diazomethane to quinone (279), formulating the reaction in the following way:



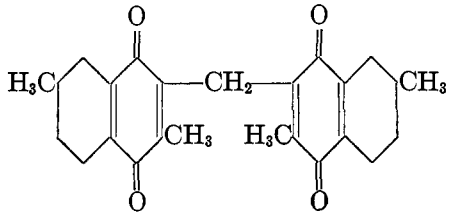


Fieser and Peters (108) added diphenyldiazomethane to α-naphthoquinone and showed that the reaction took the following course:

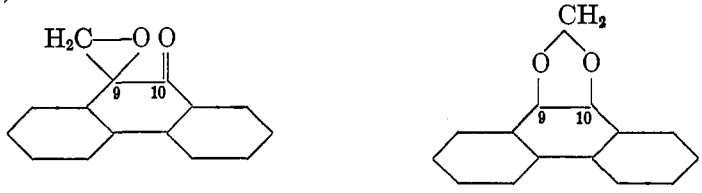


Recently (109) it was found that 2,6-dimethyl-3,4-naphthoquinone did not react with diazomethane, while the corresponding 1,4-naphthoquinone

reacted in a peculiar way to give a product derived from two molecules of the quinone:

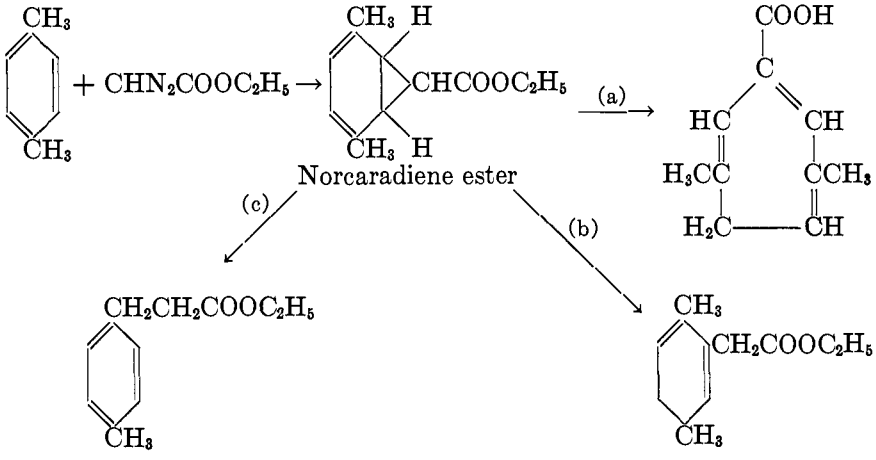


Phenanthraquinone reacts with diazomethane in the presence of a trace of methanol to give spirophenanthroylethylene oxide; in absolute ether or in the presence of 20 per cent of methanol the methylene ether is formed (51, 19):

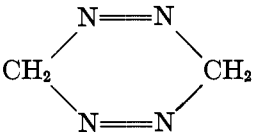


Smith and Pings studied the reaction between diazomethane and duroquinone. The reaction was very complex, but only the carbonyl groups of this substituted *p*-benzoquinone were involved.

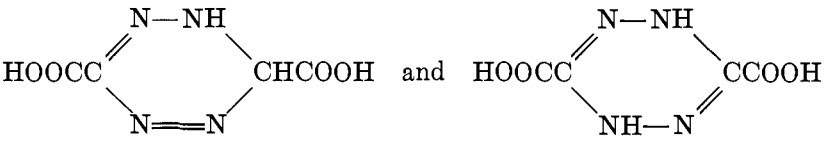
Aliphatic diazo compounds will add to the aromatic double bond, giving as primary products norcaradiene derivatives (71, 75–80, 336). These norcaradiene compounds rearrange easily, giving (*a*) derivatives of cycloheptatriene, (*b*) derivatives of phenylacetic acid, and (*c*) derivatives of β-phenylpropionic acid (when the original hydrocarbon contains one or more methyl groups).



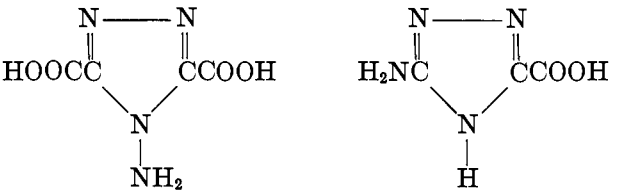
Even the polymerization of the aliphatic diazo compounds may be considered as a 1,3-addition. In sunlight diazomethane gives *C*-dihydrotetrazine,



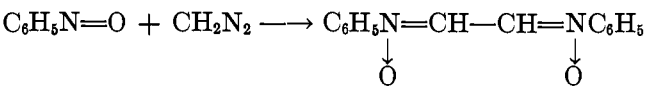
Diazoacetic ester polymerizes in the presence of concentrated alkali to give dihydrotetrazine acids:

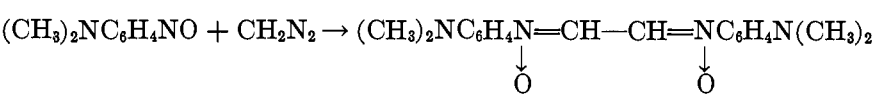


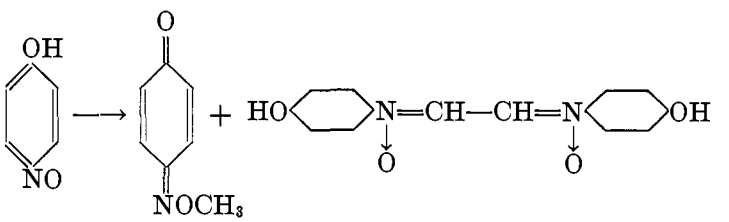
and if the action of the alkali is continued these tetrazine compounds rearrange into amino*triazole* acids such as



Other *miscellaneous reactions* of diazomethane are as follows: Nitrosobenzene gives diglyoxime *N*-phenyl ether (275) and other nitroso compounds react similarly:

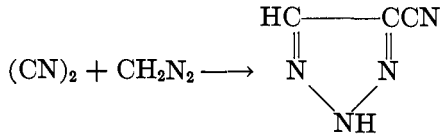




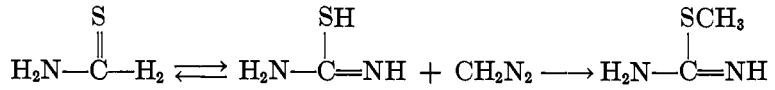


Nitro compounds such as nitromethane, nitrobenzene, etc., are indifferent to diazomethane (151), although v. Pechmann mentions that in the esterification of trinitrobenzoic acid with diazomethane the nitro groups are also attacked (277).

Hydrocyanic acid and cyanogen react rapidly, the former giving acetonitrile and the latter giving a cyanoösotriazole (281):



Urea is unaffected by diazomethane in ether or alcohol, but thiourea is methylated (362).

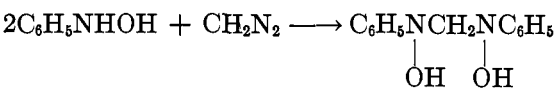


Hydrogen sulfide reacts with diphenyldiazomethane to give thiobenzohydrol, $(C_6H_5)_2CHSH$, and nitrogen (347).

Hydrazoic acid gives methyl azide and nitrogen with diazomethane (265).

p-Toluenesulfonanilide and *p*-toluenesulfonamide are methylated quantitatively (22).

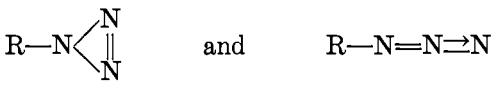
β-Phenylhydroxylamine gives diphenylmethylenedihydroxylamine (37).



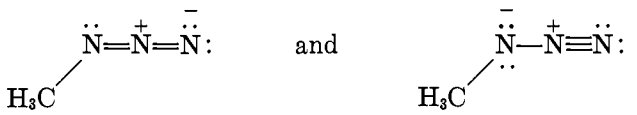
Other methylations with diazomethane include those in the uric acid series (49, 155), xanthosine (206), uracil (171), and cellulose and the polysaccharides (324, 253).

II. AZIDES: RN_3 OR $RN{=}N{\rightleftarrows}N$ (24)

In the azides the 1,3-system is composed entirely of nitrogen atoms. The compounds may be regarded as analogs of the aliphatic diazo compounds in which the carbon atom at the end of the system, together with the attached groups, has been replaced by a trivalent nitrogen atom with the attached group. As in the case of the aliphatic diazo compounds both cyclic and chain formulas have been used.



In 1925 Hendricks and Pauling (154) showed that the azide ion in sodium and potassium azides had a linear configuration and possessed a center of symmetry. Later (73, 163, 178) it was shown that in organic compounds the azido group was linear but did not possess a center of symmetry like the azide ion. The symmetry of the azide ion in aqueous solution is supported by x-ray data and by the data furnished by measurement of the Raman spectra (204). In a recent paper (270) methyl azide was investigated by electron diffraction measurements. The data showed that the azido group was linear, with the methyl group at an angle of about 120° to the line through the azido group, and on the basis of the adjacent charge rule, the two resonance structures favored were



These two formulas are entirely analogous to the two resonance formulas for the aliphatic diazo compounds (332).

The first azido compounds known were the azido derivatives of the aromatic hydrocarbons and the first member of this class, phenyl azide, was obtained by Griess by the action of ammonia upon the diazonium perbromide (146).

$$C_6H_5N_2Br_3 + NH_3 \rightarrow C_6H_5N_3 + 3HBr$$

Since then a number of methods have been developed for the preparation of azides; many of these methods involve the diazonium compounds as reagents, and in most of the methods one reagent contains a chain of two nitrogen atoms, while the third nitrogen atom is supplied by the other reagent—nitrous acid, hydroxylamine, ammonia, etc.—although all three nitrogen atoms may be contained in one reagent.

Thus substituted semicarbazides, such as phenylsemicarbazide, react with sodium hypochlorite to give azido compounds. This reaction is a phase of the Hofmann degradation of an amide, and it has been written in two ways:

$$C_6H_5NHNHCONH_2 \rightarrow C_6H_5N{=}NCONH_2 \rightarrow C_6H_5N{=}NNH_2 \rightarrow C_6H_5N_3 \quad (91)$$

$$C_6H_5NHNHCONH_2 \rightarrow C_6H_5N{=}NCONH_2 \rightarrow C_6H_5N{=}N{-}N{=}C{=}O \rightarrow C_6H_5N_3 \quad (114)$$

Diazonium salts may be converted to azides by treatment with hydroxylamine hydrochloride (110, 221, 318) or with sodium azide (257). By the use of this method, a great variety of aromatic azido compounds has been

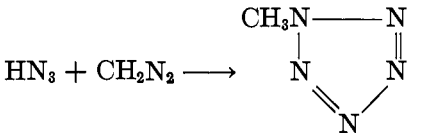
prepared, such as: $N_3C_6H_4OH$ (*o*-, *m*-, and *p*-) (119); $N_3C_6H_4N_3$ (*m*- and *p*-) (334, 120, 147); $N_3C_6H_4CHO$ (*p*-) (124); $N_3C_{10}H_6NO_2$ (1,2-; 1,4-; 1,5-; 1,8-; 2,5-; 2,8-) (120); $N_3C_6H_4I$, $N_3C_6H_4IO_2$ (115).

Phenylhydrazine reacts with nitrous acid or nitrosyl chloride to give a nitroso compound which immediately loses water, forming an azide (94). The reaction may be extended to the hydrazides of the acids (90, 89).

The simplest aliphatic azide, methyl azide, was first obtained by methylation of sodium azide with methyl sulfate (101).

$$2NaN_3 + (CH_3)_2SO_4 \rightarrow Na_2SO_4 + 2CH_3N_3$$

The same substance was obtained recently (266) in an attempt to prepare methylpentazole by the addition of diazomethane to hydrazoic acid, and Oliveri-Mandala believes that the methyl azide resulting from this reaction is due to the decomposition of the intermediate methylpentazole.



Forster and his collaborators (121, 122, 125, 126, 128, 129) prepared a large number of mono- and di-azido aliphatic esters, alcohols, aldehydes, ketones, and acids by treatment of the corresponding halogen compounds with sodium azide:

$$RX + NaN_3 \rightarrow RN_3 + NaX$$

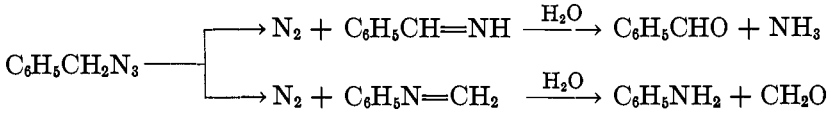
In their reactions the azides show a similarity to the aliphatic diazo compounds. A very common reaction consists in the loss of two nitrogen atoms and occurs when the substances are boiled with acids or bases. For example, phenyl azide is converted into *p*-aminophenol, and phenylhydroxylamine is probably an intermediate (146, 132).

$$C_6H_5N_3 + H_2O \rightarrow C_6H_5NHOH + N_2 \rightarrow p\text{-}HOC_6H_4NH_2$$

Azidoketones are decomposed in a similar manner, yielding imines (118a, 121, 121a).

$$RCOCH_2N_3 \rightarrow N_2 + RCOCH{=}NH$$

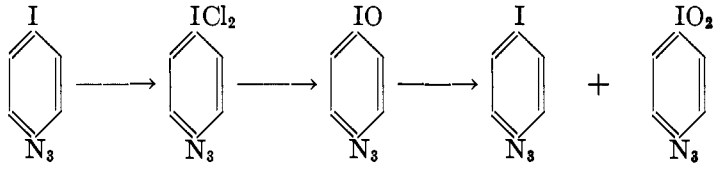
Benzyl azide was found to decompose in two ways (88) to give benzaldehyde and aniline, the latter product resulting from a rearrangement.



Triphenylmethyl azide also decomposes with rearrangement and the final products are benzophenone and aniline (200).

$$(C_6H_5)_3CN_3 \longrightarrow N_2 + (C_6H_5)_2C{=}NC_6H_5 \xrightarrow{H_2O} (C_6H_5)_2CO + C_6H_5NH_2$$

The rearrangement is not general, however, for in some cases the azido group is surprisingly stable. Thus *o*-, *m*-, and *p*-iodophenyl azides do not react with alcoholic alkali, and the iodine atom may be successively transformed to the dichloride and then to the iodoso and iodoxy compounds without disturbing the azido group (115).



When ortho or para to a nitro group in the benzene ring, the azido group is removed as hydrazoic acid by boiling alcoholic alkali (256).

$$N_3C_6H_4NO_2 + 2KOH \rightarrow KOC_6H_4NO_2 + KN_3 + H_2O$$

But when the azido group is meta to the nitro group, this reaction does not occur. The same rule holds in the naphthalene series (120), only the 1,2-, 1,4-, and 2,1-nitroazidonaphthalenes hydrolyzing to give hydrazoic acid.

Both alkyl and aryl azido compounds are transformed into diazoamino compounds by action of Grignard reagents (96), and this reaction may be interpreted as a 1,3-addition:

$$C_6H_5N{=}N{\rightleftarrows}N + RMgX \rightarrow C_6H_5N(MgX){-}N{=}NR \rightarrow C_6H_5NHN{=}NR$$

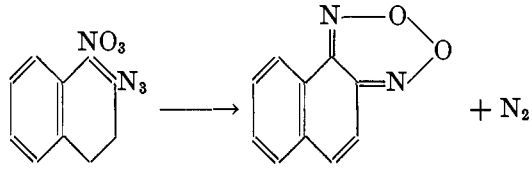
The same type of addition may be invoked to explain the reaction with hydrocyanic acid (387):

$$C_6H_5N{=}N{\rightleftarrows}N + HCN \rightarrow C_6H_5NHN{=}NCN$$

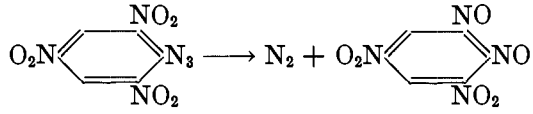
The *o*-nitrophenyl azides, when heated, lose a molecule of nitrogen, and dinitroso compounds result (388):

$$N_3C_6H_4NO_2 \rightarrow O{=}NC_6H_4N{=}O + N_2$$

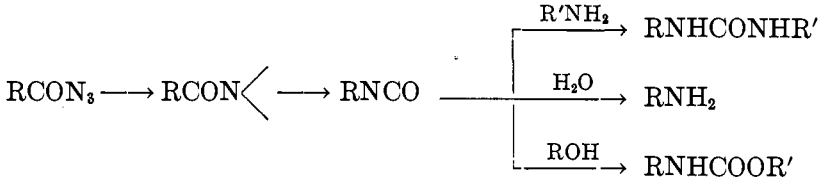
although Forster and Fierz (120), who obtained similar compounds in the naphthalene series, prefer to write them as dioxime peroxides.



However, Schrader (326) decided that the decomposition product of picryl azide was a nitroso compound:

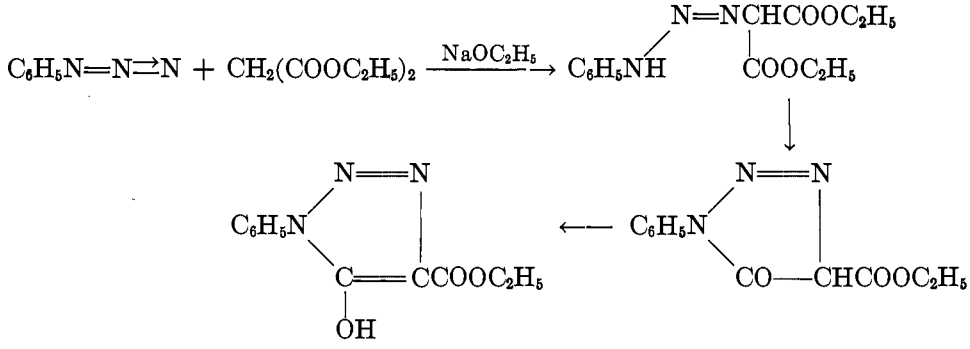


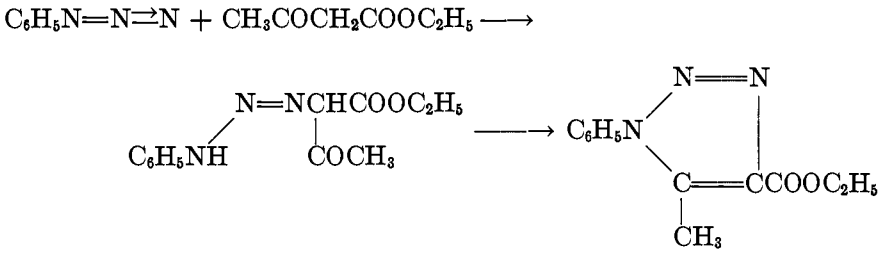
Acid azides undergo the well-known Curtius rearrangement (87), although the reaction is not entirely general, and compounds from which isocyanates cannot be formed behave abnormally (sulfonyl azides, etc.).



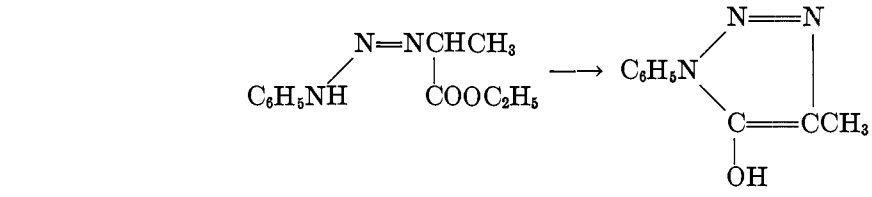
Lately the Curtius rearrangement has been developed by von Braun, Nelles, and others, and has become a convenient and useful method for the transformation of an acid or acid halide to an amine with loss of one carbon atom (327, 72, 250, 249, 251).

The azides undergo many reactions which involve ring closure, most of which may be considered as direct 1,3-additions. Phenyl azide condenses with many substances containing active methylene groups; the final products are 1,2,3-triazoles (95, 99).

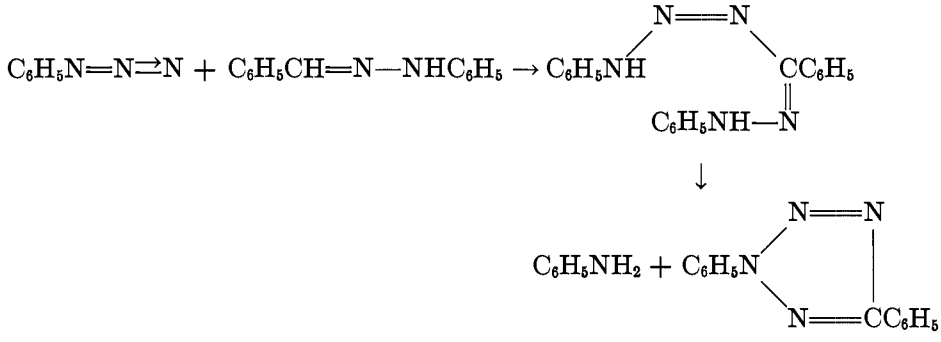




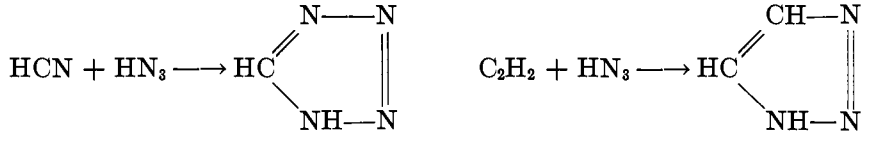
Even esters, such as ethyl acetate or ethyl propionate, will undergo this condensation.



A similar reaction occurs between phenyl azide and some hydrazones (100).



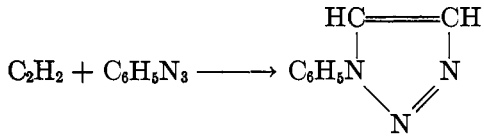
The addition of hydrazoic acid to hydrocyanic acid produces tetrazole (97), while triazole is obtained when hydrazoic acid adds to acetylene (127).

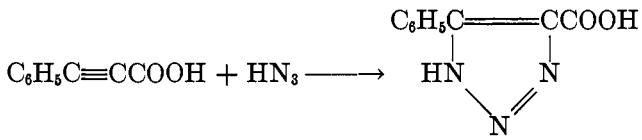


Since Forster and Newman prepared vinyl azide and found it to be a stable substance, it is evident that the reaction between acetylene and

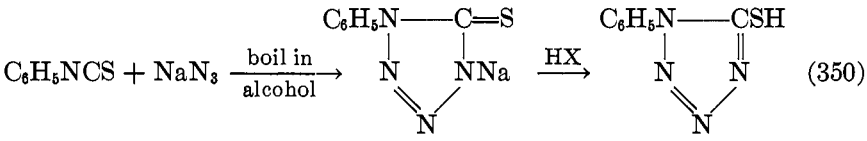
hydrazoic acid cannot involve a rearrangement of vinyl azide, but must involve a direct 1,3-addition of hydrazoic acid.

Similar reactions are those between phenyl azide and acetylene, and between hydrazoic acid and phenylpropiolic acid (240, 98, 268).

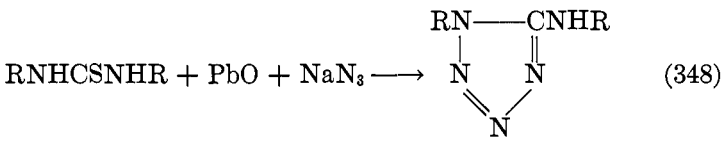




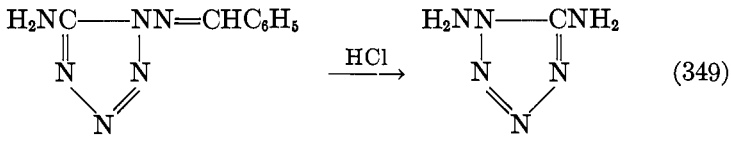
Many other reactions of the azides which lead to heterocyclic compounds may conveniently be formulated as direct 1,3-additions: thus



(350)

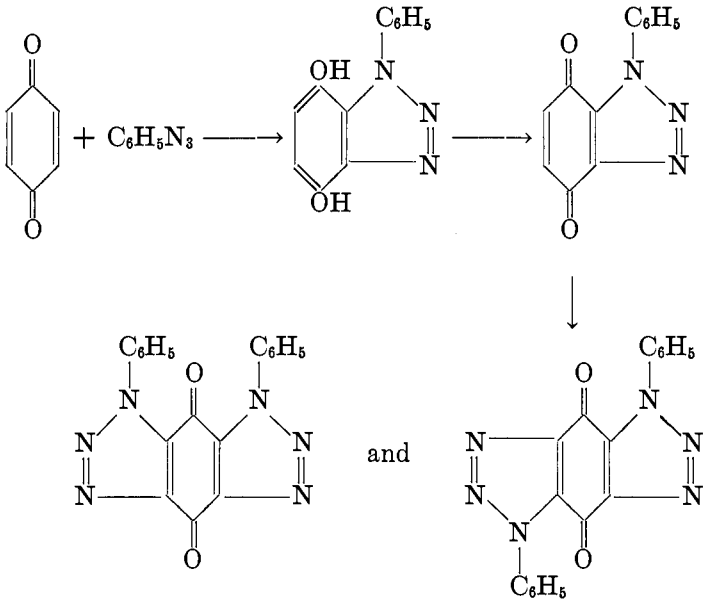


(348)

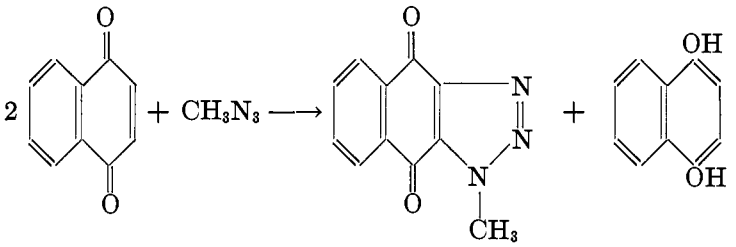


(349)

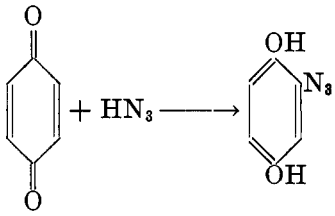
Phenyl azide reacts with quinones (386, 107, 106), adding to the double bond. In benzene at 60–65°C. benzoquinone and the azide react to give first the aziminohydroquinone, which may be oxidized by unchanged quinone to the aziminoquinone, and the latter may then react further:

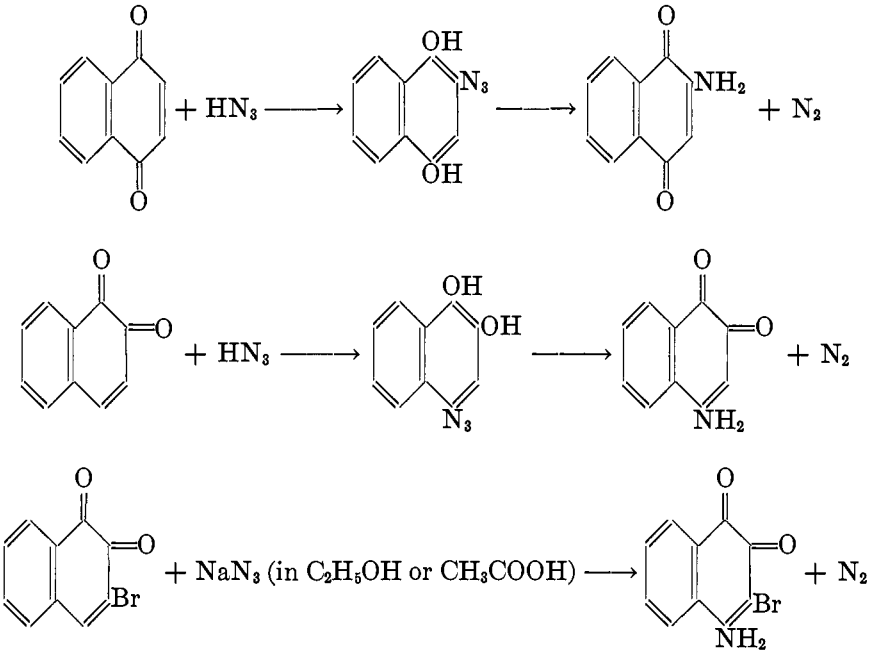


α-Naphthoquinone reacts in the same way with methyl azide (106):

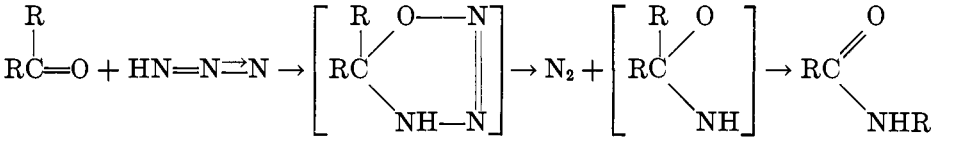


Hydrazoic acid, however, adds 1,4 to benzoquinone (267, 263) to give azidohydroquinone, and a similar reaction occurs with both α- and β-naphthoquinones (106), and also with 3-bromo-1,2-naphthoquinone.





Hydrazoic acid reacts with carbonyl compounds in much the same fashion as diazomethane. The latter reagent produces methyl ketones from aldehydes and homologs from ketones, while hydrazoic acid produces amides, the product that would have been obtained by the Beckmann rearrangement of the oxime of the carbonyl compound (24). As the reaction with diazomethane may be formulated as involving an initial 1,3-addition, so may the reaction with hydrazoic acid:

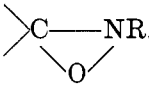


III. NITRONES: THE *N*-ETHERS OF THE OXIMES. $\rangle C{=}N{\rightarrow}O$ (R above N)

The name "nitrone" was coined by Pfeiffer (284) to designate substances having the linkage $\rangle C{=}N{\rightarrow}O$ (R above N), because they behave like ketones in some respects. Pfeiffer had in mind the similarity between C=O and N→O

in coining the name. It was rather unfortunate because, actually, it is the whole system, $>C=N\rightarrow O$, which acts as a long carbonyl group and *not* the linkage $N\rightarrow O$. This makes it very difficult to name individual compounds as nitrones; hence it is better to use the name "nitrone" for all classes of compounds containing the group $>C=N\rightarrow O$, whether in open or closed chains, and to name the individual compounds in other ways.

The *N*-ethers of the oximes are the simplest nitrones; they are open-chain compounds. The nitrones behave in most of their reactions as carbonyl compounds, for the nitrone group $>C=N\rightarrow O$ reacts much like a long carbonyl group with addition taking place at the ends of the system. The middle nitrogen atom does not take part in these addition reactions except to drop its valence from "5" to 3.

It is possible to write the nitrones as a three-membered ring  . This was done for some time after the discovery of the *N*-ethers of the oximes and similar compounds. The three-membered ring formula is still used in some special cases (340, 134, 308), but the evidence against the three-membered ring is considerable and each new thorough study of compounds of this type makes it more apparent that they cannot be represented by a three-membered ring structure (12). No such ring structure as this has been proved to exist in any compound with certainty, and in many cases in which it has been assumed, as in the azoxy compounds, it has been shown to be incorrect. The spectrochemical results of Brady (59) and of v. Auwers and Ottens (30), the parachor studies of Sugden (351), and the color of the nitrones indicate that they do not contain a three-membered ring. Moreover, the three-membered ring does not suffice stereochemically; compounds containing such a structure should show optical activity, for the ring has an asymmetric carbon atom (177). Experiments directed toward the resolution of these *N*-ethers have failed (322, 215). Hence these *N*-ethers of the oximes must be *nitrones*.

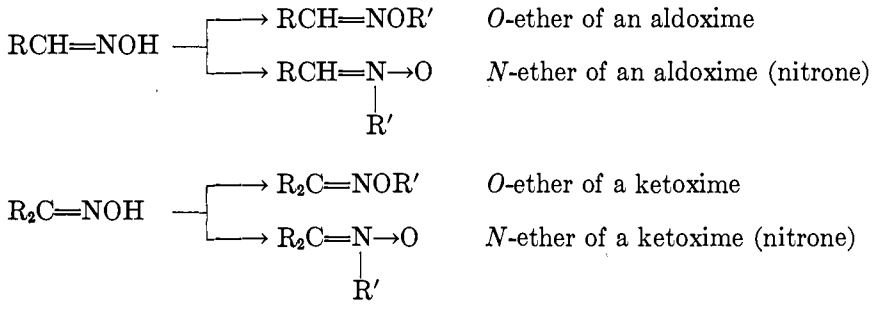
Three methyl ethers and three benzyl ethers of benzaldoxime are known. Of these respectively, two are *O*-ethers and one is an *N*-ether, for with hydriodic acid the R group of the one (*N*-ether) appears as a primary amine, while from the other two (*O*-ethers) it appears as alkyl iodide. Since the *O*-ethers must be $C_6H_5CH{=}NOR$ (*syn* and *anti*), the *N*-ether must be $C_6H_5CH{=}N(R)\rightarrow O$. Both *syn*- and *anti*-forms of benzaldoxime on

alkylation give the *N*-ether plus one of the *O*-ethers (150a, 40, 138). Beckmann showed that the liquid α-benzaldoxime, alkylated with benzyl chloride, gave the *O*-ether, while the solid β-benzaldoxime gave the *N*-ether. Goldschmidt showed that α- and β-benzaldoxime each gave, with phenyl isocyanate, two isomers, $C_6H_5NHCO—ON{=}CHC_6H_5$, which were easily changed into each other. Hence the aldoximes must be stereoisomers and Beckmann's two ethers must be structural isomers. Later Beckmann showed that the β-benzaldoxime actually gave both *O*- and *N*-ethers on alkylation.

A. Preparation of the N-ethers of the oximes

1. Preparation from the oximes

Aldoximes and ketoximes can be directly alkylated (though not arylated) and, according to the conditions, there result *O*-ethers, *N*-ethers, or mixtures of the two.



In general, the ketoximes are not as reactive toward alkylating (and other) reagents as are the aldoximes. The course taken by the alkylation of aldoximes and ketoximes depends to a great extent upon the experimental procedure and the nature of the alkyl group (135, 133, 282, 139–142, 220, 298, 166, 118, 60, 64, 66, 67). Methylation of benzophenone oxime in alkaline solution gives the *O*-ether (m.p. 60°C.) and the *N*-ether (m.p. 102°C.). These can be separated, since the nitrone is much less soluble in petroleum ether, or the nitrone hydrochloride may be precipitated from ether solution with gaseous hydrochloric acid (2).

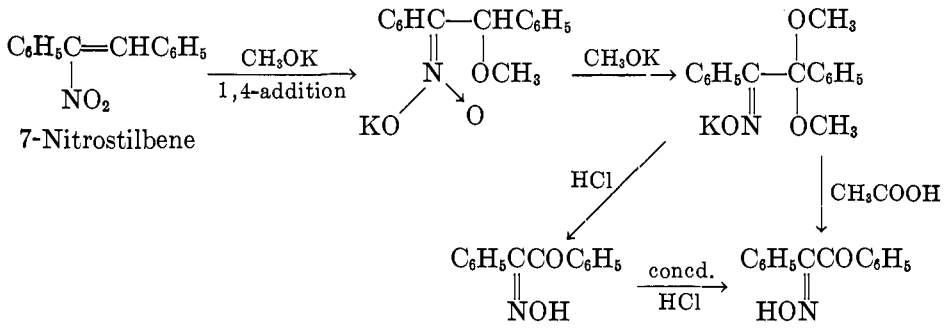
The methyl ethers of the aldoximes have been most thoroughly investigated. The *syn*- and *anti*-aldoximes behave alike when their silver salts are treated with methyl iodide or when the oximes are treated with methyl iodide and silver oxide, the *O*-ethers resulting exclusively (215, 139–142, 60, 64, 66, 67). The same rule holds in the case of ketoximes when they are treated with alkyl iodides and silver oxide or when their silver salts are treated with alkyl halides (166, 2). In *alkaline* solution, however, the

relationships are different, for in this case either RX or R_2SO_4 (acting upon the alkali salts of the oximes) gives a mixture of *O*- and *N*-ethers (298, 2, 319, 93, 148, 329, 68). The relative amounts of *O*- and *N*-ethers obtained in this way change with the nature of the oxime, especially with its dissociation constant, for the larger this is, the more of the *O*-ether results (60, 64, 66, 67); also, increasing the amount of alkali results in the formation of more *O*-ether (60, 64, 66, 67). When methyl sulfate or methyl iodide acts on aldoximes in the dark and in the absence of alkali, only the *N*-ether results (in the form of its salt (60, 64, 66, 67)).

Diazomethane usually methylates an aldoxime, giving the *O*-ether, but the stereoisomeric oximes may behave quite differently. The α-form usually reacts, while the β-form is inert (118). The ketoximes are usually inactive toward diazomethane (118).

The same procedures may be used to obtain ethers of 1,2-dioximes. The mono- or di-oximes with an alkyl iodide and sodium methoxide or, better, with an alkyl sulfate and sodium hydroxide (298, 29, 167, 113, 32, 69, 70, 356) give mixtures of *O*- and *N*-ethers. From the dioximes *O,O*-, *N,N*-, and *O,N*-ethers are possible. Alkylation with alkyl iodides and silver oxide in absolute ether (67, 112) gives exclusively *O*-ethers. Diazomethane apparently gives the *N*-ethers of α-diketone monoöximes, but the yields are poor and rearrangements often result (123, 118, 69, 70). The mono ethers of the dioximes can be made by two methods: by the action of 1 mole of R_2SO_4 upon the dioxime in the presence of alkali, or by the action of hydroxylamine upon the ethers of the monoöximes (69).

A method of preparing the monoöximes of 1,2-dicarbonyl compounds consists in the action of potassium hydroxide in methanol upon unsaturated nitro compounds. This reaction leads first to the oxime of the acetal of the 1,2-dicarbonyl compound and then to the monoöxime (229–233).



This method possesses the advantage that the position of the oxime group is known if the diketone is unsymmetrical.

2. Preparation from the aldehydes and ketones

The ethers are prepared from the aldehydes and ketones, by reaction with substituted (α- or β-) hydroxylamines.

$$R_2C{=}O + H_2NOR' \ (\alpha) \longrightarrow R_2C{=}NOR' \qquad O\text{-ether}$$

$$R_2C{=}O + R'NHOH \left(\beta \text{ equals } RN\begin{matrix}\nearrow O \\ \searrow H_2\end{matrix} \right) \longrightarrow R_2C{=}N\begin{matrix}\nearrow O \\ \searrow R'\end{matrix} \qquad N\text{-ether}$$

α-Alkylhydroxylamines with *aldehydes* usually react smoothly to give the *O*-ethers, often both stereoisomers resulting, while the β-alkylhydroxylamines give the *N*-ethers. The reaction between ketones and α-substituted hydroxylamines has apparently not been studied very much, while the β-substituted hydroxylamines apparently do not react smoothly with ketones (60, 64, 66, 67, 43, 320).

Oxidation of some *N*,*N*-dialkylhydroxylamines by mercuric oxide gives nitrones:

$$C_6H_5CH_2N(OH)CH(C_6H_5)_2 + HgO \rightarrow C_6H_5CH{=}N(O)CH(C_6H_5)_2 + H_2O + Hg \quad (2)$$

3. Preparation from nitroso compounds

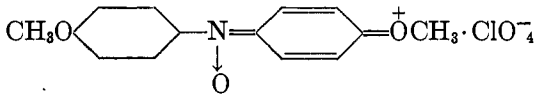
The action of aliphatic diazo compounds on nitroso compounds gives nitrones.

$$RN{=}O + R_2CN_2 \longrightarrow RN\begin{matrix}\nearrow O{-}N \\ \searrow C{-}N(R_2)\end{matrix} \longrightarrow RN\begin{matrix}\nearrow O \\ \searrow CR_2\end{matrix}$$

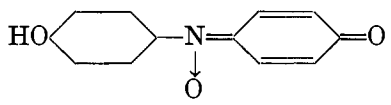
This probably involves a primary 1,3-addition of the nitroso group to the diazo compound and may be compared with the reaction between diazomethane and aldehydes to give methyl ketones (345, 274). Some complicated nitrones have been obtained by K. Meyer (238, 239, 237) and his students by the action of nitric acid upon phenol ethers. The reaction produces an intensely colored solution and, by adding perchloric acid to this, Meyer succeeded in isolating crystalline, colored salts which analyzed for the perchlorate of a nitrone.

$$CH_3O\langle\rangle\!-\!\overset{+}{N}(O)\!-\!\langle\rangle OCH_3 \cdot ClO_4^-$$

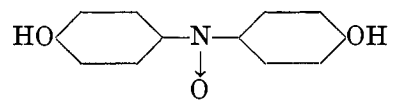
or



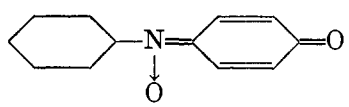
When reduced, this product gave *p,p'*-dimethoxydiphenylamine. Treatment with alkali, pyridine, sodium iodide, or zinc dust decomposed the perchlorate, giving some of the radical, dianisylnitrogen oxide, $(CH_3OC_6H_4)_2N\rightarrow O$. This radical, with bromine or mineral acids, again gave the colored salt. Phenol itself will react in the same manner as anisole. The colored salts obtained are derived from indophenol oxide (I). On mild reduction the product is *p,p'*-dihydroxydiphenylnitrogen oxide (II). These quinoid colored salts are the oxy derivatives of the orange-yellow quinone anil oxide (III), prepared by Wieland and Roth.



I

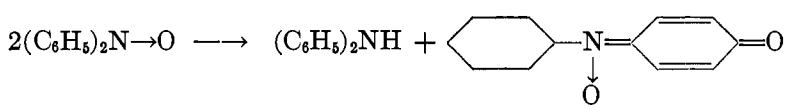


II



III

If an ethereal solution of diphenylnitrogen oxide is shaken with hydrochloric acid, disproportionation occurs to diphenylamine and the quinone anil oxide (III) (150, 238, 239, 237, 380):



B. Properties of the oxime ethers (298, 67, 148, 329, 68, 62, 65, 66)

1. The *O*-ethers

These ethers are usually quite stable toward hydrolyzing agents. Boiling with aqueous or alcoholic hydrochloric or hydrobromic acids, with 60 per cent sulfuric acid, or with 2 *N* sodium hydroxide produces no change. They are weaker bases than the oximes themselves, forming no hydrochlorides or chloroplatinates (thus differing from the *N*-ethers which form both). They give no metallic salts with bases, nor do they form any addition compounds. With fuming hydrochloric acid they are hydrolyzed,

giving the carbonyl compound and the hydrochloride of the α-substituted hydroxylamine.

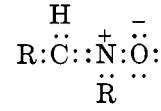
The oximes themselves, especially the aldoximes, give stable salts with bases and also with strong acids, although the latter are easily hydrolyzed. The *N*-ethers are more basic than the oximes, while the *O*-ethers are less basic, giving no salts at all, although there is not complete agreement on this point. The *O*-ethers do not undergo the Beckmann rearrangement.

2. The *N*-ethers

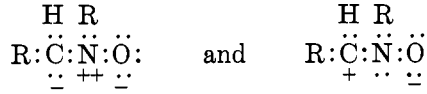
These ethers are very reactive substances, in which the basicity of the nitrogen is greater than that in the oximes themselves. They hydrolyze more readily (to $R_2C{=}O + RNHOH$) than *O*-ethers, and they form many addition products which *O*-ethers do not. They form salts with acids, and although these salts are easily hydrolyzed by water, they are more stable than the salts formed from the oximes and acids. The *N*-ethers are very easily hydrolyzed. Cold concentrated hydrochloric acid hydrolyzes them almost instantly to the carbonyl compound and the *N*-substituted hydroxylamine. Dilute acid acts more slowly, but very rapidly if warmed. Alkali also hydrolyzes the *N*-ethers quickly. The ketoxime *N*-ethers are more rapidly attacked by alkali than are the aldoxime *N*-ethers.

The *N*-ethers form well-defined, fairly stable chloroplatinates and other complex salts, and they show great additive power toward many other reagents. They readily form hydrates (321) and other addition products, e.g., with sodium iodide and calcium chloride, hence one must be careful in making the *N*-ethers to avoid these addition products. The ketoxime *N*-ethers are known to form addition products with oximes (329, 3), with water, hydroquinone, and with phenyl isocyanate (329). These addition products are strongly dissociated in solution.

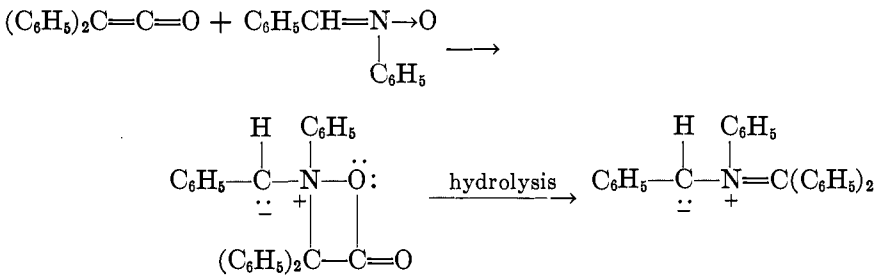
The electronic structure of the nitrones is



for the stable form which can resonate between the reactive forms

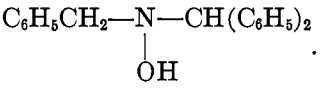


Most reactions of nitrones involve the second of these reactive forms, and may be interpreted as 1,3-additions, although addition of ketenes probably involves the first of the active forms. Thus (345):

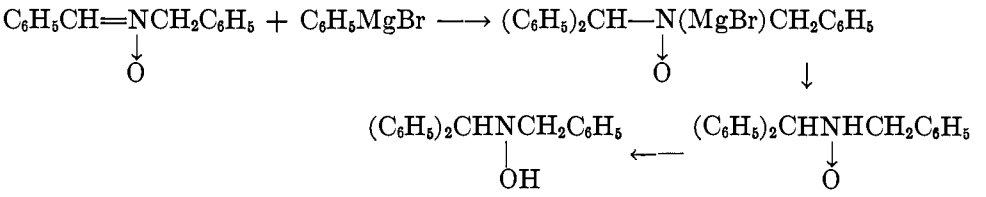


Triphenyl-*N*-phenyl-nitrene[2]

Grignard reagents, alcohols, acetyl chloride, acetic anhydride, and isocyanates all react with nitrones according to the second active form (12, 59, 215, 329, 68, 29, 32, 65, 66, 321, 352, 61, 102, 70). In reactions between any of these substances and nitrones, the addenda are found attached to the ends of the unsaturated 1,3-system whenever the primary product is stable enough to be examined chemically. Thus, in the addition of phenylmagnesium bromide to the *N*-benzyl ether of benzaldoxime, Angeli obtained benzylbenzhydrylhydroxylamine,



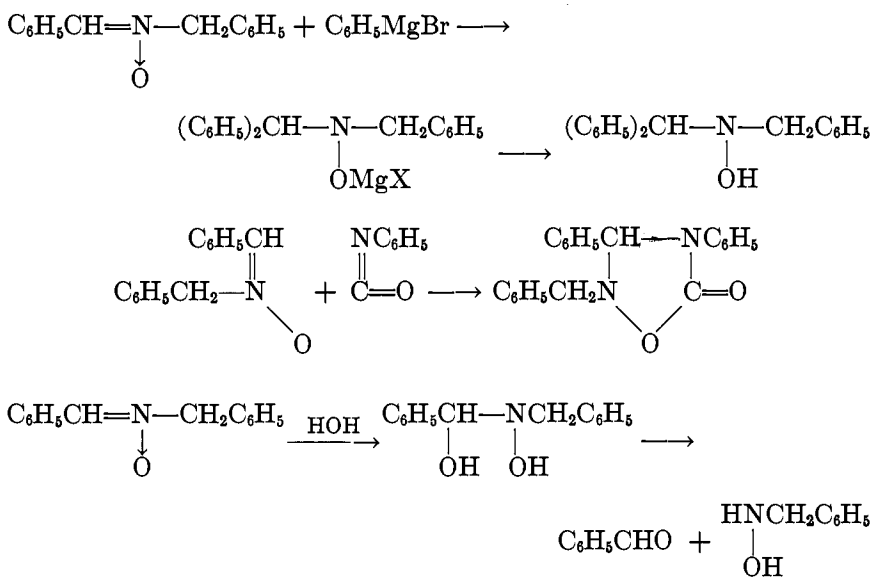
To account for this, Angeli assumed addition to the 1,2-system, C=N. Thus



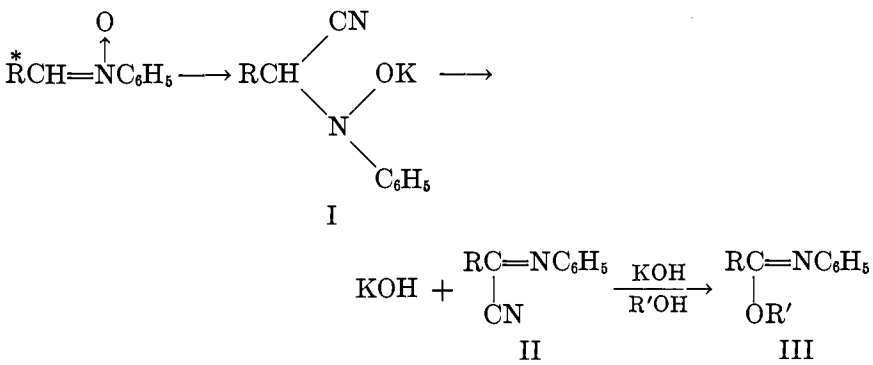
While it is possible to account for the structures of the addition products obtained with alcohols, water, and acetic acid by means of this mechanism, the addition of acid chlorides, anhydrides, and phenyl isocyanate cannot be so interpreted without assuming a migration of groups such as acyl or similar groups which do not migrate readily. It is therefore much more likely that the first addition is a direct 1,3-addition, and the addition of water, alcohols, and acids also can be readily interpreted in this way.

[2] See the footnote on page 267 regarding the recent evidence that the nitrenes are derivatives of ethyleneimine, i.e., are ring compounds.

Thus, for the addition of phenylmagnesium bromide, phenyl isocyanate, and HX compounds the following reactions can be written, and in the case of phenyl isocyanate a most unusual rearrangement would have to be involved in order to obtain the product by a primary 1,2-addition (150).



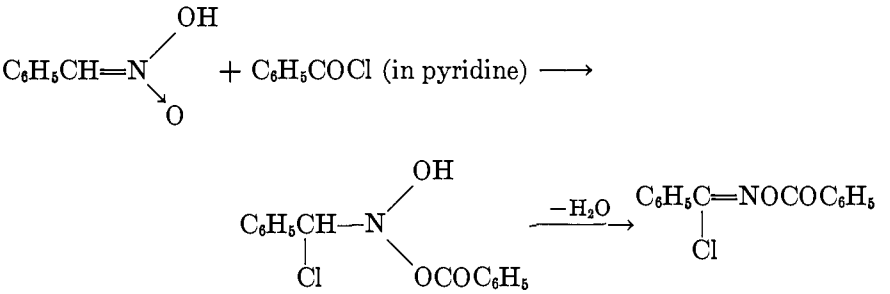
In two recent papers Bellavita (46) has examined the action of potassium cyanide upon alcoholic solutions of *o*-, *m*-, and *p*-nitrophenyl-*N*-phenylnitrones. The reaction apparently involves a primary 1,3-addition of the cyanide, leading first to I (not isolated) and then to II. The latter reacts with the solvent to give III.



* (R = *o*-, *m*-, or *p*-nitrophenyl).

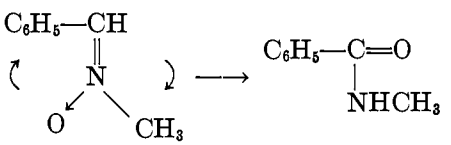
II can be isolated only when exactly equimolecular proportions of nitrone and potassium cyanide are used; otherwise the reaction leads directly to III, the yields of which are excellent.

The reaction between benzoyl chloride and *aci*-phenylnitromethane (379), which is also a nitrone, may be written as follows:



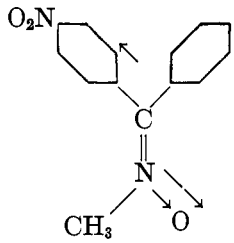
While the *N*-ethers of the aldoximes are known in rather large numbers (321), they almost never show the *cis-trans* isomerism theoretically possible, in spite of numerous statements to the contrary (220, 67, 66, 321, 130, 360, 143, 44). In only one case among the *N*-ethers of the aldoximes is *cis-trans* isomerism established with any certainty, and this case comprises the two *N*-ethers from 3-amino-2,6-dichlorobenzaldehyde and *N*-methylhydroxylamine (234). In the case of the *N*-ethers of ketoximes, isomeric *N*-ethers are known in two instances: 4-nitrobenzophenone *N*-methyl ether (68, 352) and 4-methylbenzophenone *N*-methyl ether (329).

In contrast to the *O*-ethers, the *N*-ethers undergo the Beckmann rearrangement, the best reagent being acetic anhydride. Phosphorus pentachloride and acid chlorides do not react very smoothly (67, 63, 42). If the Beckmann rearrangement of the *N*-ethers is a *trans* rearrangement, then the *N*-ethers of the aldoximes belong to the β-series, for benzaldoxime *N*-methyl ether gives *N*-methylbenzamide (63).

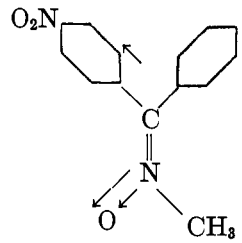


One has to be careful in determining the configurations of the *N*-ethers in this way, for the α-aldoximes themselves often change into the β-form and then undergo the rearrangement, and since there is no other independent method to fix the configuration of the *N*-ethers, it can be done only provisionally. Lately measurements of the dipole moments have indicated

that the *N*-ethers are of the β(*anti*)-form (352). Because the oximes are strongly associated in solution, dipole moments are difficult to determine, but the *N*-ethers of the oximes can be handled very well. The data for the *N*-methyl ethers of 4-nitrobenzophenone oxime show the configuration to be as follows:

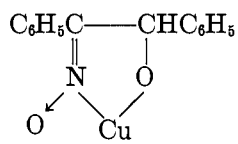


N-ether of the β-oxime (*anti*)
$\mu = 1.09 \times 10^{-18}$



N-ether of the α-oxime (*syn*)
$\mu = 6.60 \times 10^{-18}$

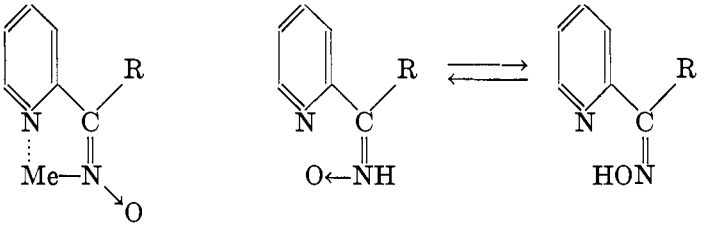
Many oximes form rather stable salts with the heavy metals; this is especially true when the metal can chelate or react in some other way with another group in the molecule. When this is possible, one form of the salt will always be much more stable than the other, and the more stable form is the one in which the N→O group is *anti* to the chelating or reacting position. These salts are derivatives of the (tautomeric) nitrone form of the oxime (285). Thus one can draw conclusions as to the configuration of some oximes from the ease with which they form complex salts and from the properties of the salts. α-Benzoin oxime gives a deep green, stable, copper salt (105) which is insoluble in acetic acid or ammonia. If this is a derivative of the nitrone form of the oxime, then the *anti* configuration for α-benzoin oxime is indicated, a result which agrees with the configuration as determined by other methods.



β-Benzoin oxime therefore should not form such a stable salt as this; actually it gives a gray-brown copper compound which is soluble in acetic acid or ammonia.

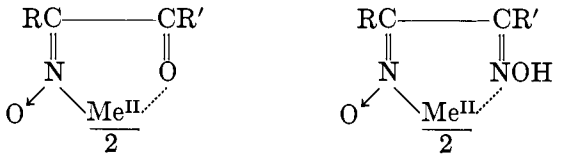
The tendency to form complex heavy-metal salts is less in the case of ketoximes than aldoximes, unless there is the possibility of forming inner complexes (chelation, etc.). Then one form will, and the other will not, give the heavy-metal complex; the form that reacts is the one with the

N-oxide form *anti* to the chelating or reacting position (131). Thus compound I would give a complex salt, while compound II would not.

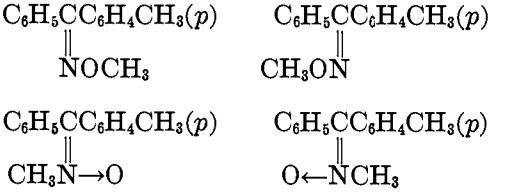


I II

In the case of the monoöximes of aromatic and aromatic-aliphatic 1,2-diketones only the *anti*-forms give stable heavy-metal salts, while the *syn*-forms do not react. According to Pfeiffer these have the structure of nitrones; the same holds for the stable salts of the *anti*-dioximes (38, 39, 82, 159, 197, 199, 242, 290, 353, 354, 360a, 367).

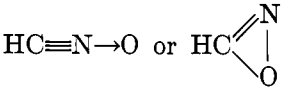


Semper and Lichtenstadt isolated the four isomeric ethers of phenyl *p*-tolyl ketoxime by methylating both the *syn*- and *anti*-oximes in alkaline solution with dimethyl sulfate (329).



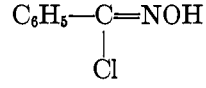
IV. THE NITRILE OXIDES: RC≡N→O (368)

The nitrile oxides were first made by Wieland (369), who has done most of the work on them. They, like the nitrones, can also be written in the form of a three-membered ring. The first member of the series, formonitrile oxide,



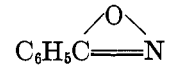
is the fourth known compound containing one atom each of carbon, hydrogen, oxygen, and nitrogen, and is isomeric with cyanic, isocyanic, and fulminic acids. In fact, formonitrile oxide was first thought to be fulminic acid; it is, however, different from fulminic acid, although it easily rearranges into an explosive substance which is perhaps fulminic acid.

The first observation on compounds of the nitrile oxide class was made by Werner and Buss (364), who found that the chloride of benzohydroxamic acid,

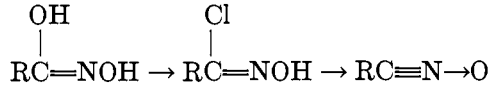


when treated with sodium carbonate, lost the elements of hydrochloric acid and gave an oil of penetrating odor which rather quickly dimerized to the known diphenylglyoxime peroxide. Since the oil was hydrolyzed by concentrated hydrochloric acid to benzoic acid and hydroxylamine, it was regarded as benzonitrile oxide, $C_6H_5C{\equiv}N{\rightarrow}O$. In 1907 Wieland took up the study of this substance (369). He succeeded in isolating the pure, crystalline substance and showing that it was monomolecular. It was not as reactive as Wieland expected a substance of the structure

to be and therefore he used the ring formula,

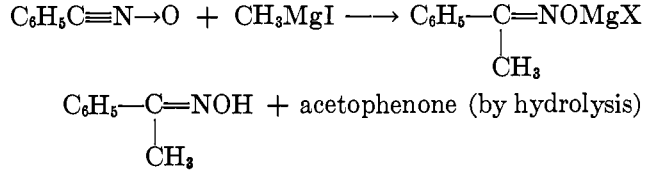


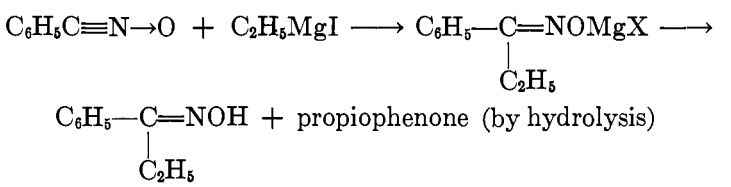
Almost the only method for the preparation of nitrile oxides consists in the action of mild alkalies on the hydroxamic acid chlorides:



and only a few of these substances are known, although they are very likely intermediates in several transformations involving the hydroxamic acids, nitrolic acids, etc. (368, 371, 374–378, 379a, 381).

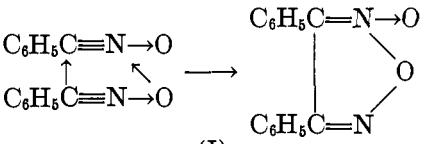
The nitrile oxides contain a 1,3-system and with Grignard reagents the mode of addition is probably 1,3. The products are ketoximes (369):



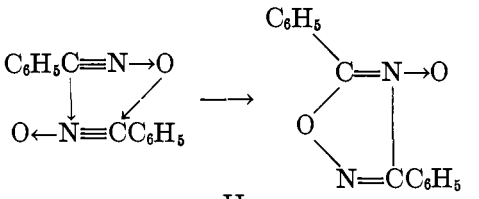


On reduction benzonitrile oxide gives benzonitrile. This could be interpreted as removal of oxygen or as a 1,3-addition of hydrogen to give $C_6H_5CH{=}NOH$, which under the conditions of the experiment might behave as it does in the Beckmann rearrangement, giving benzonitrile.

In neutral or alkaline solution the nitrile oxides polymerize to the "glyoxime peroxides" (furoxans) (I), one molecule acting as a 1,3-system and the other as a 1,2-system, while in the presence of hydrochloric acid (or when the benzohydroxamic acid chloride spontaneously decomposes) the addition takes place in the inverse sense, giving the oxazoximes (II).

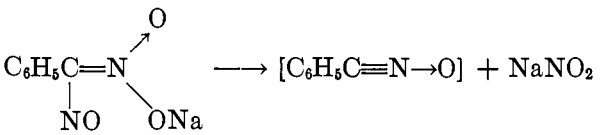


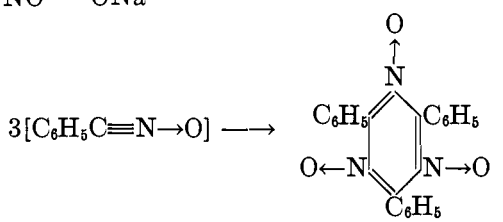
(I)



II

The furoxans and the oxazoximes both contain 1,3-systems, but benzonitrile oxide can (perhaps) polymerize in other ways. Thus, the sodium salt of benzonitrolic acid decomposes spontaneously to give a compound known as "tribenzonitrile oxide," and benzonitrile oxide, perhaps, may be an intermediate in this process.

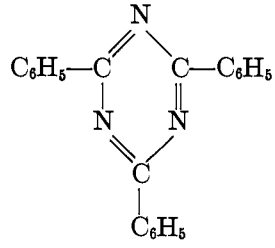




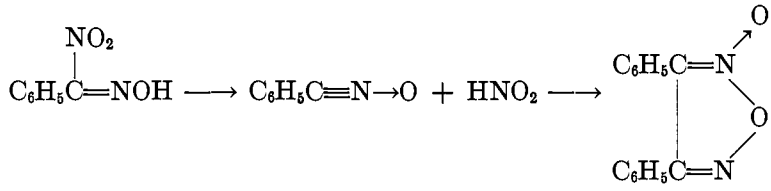
This is a reversible polymerization, while that to the furoxans and oxazoximes is not reversible. Thus, when the tribenzonitrile oxide is heated in indifferent solvents phenyl isocyanate is formed, and this substance can also be obtained by heating benzonitrile oxide.

$$\text{Trimer} \rightarrow C_6H_5C{\equiv}N{\rightarrow}O \rightarrow C_6H_5N{=}C{=}O$$

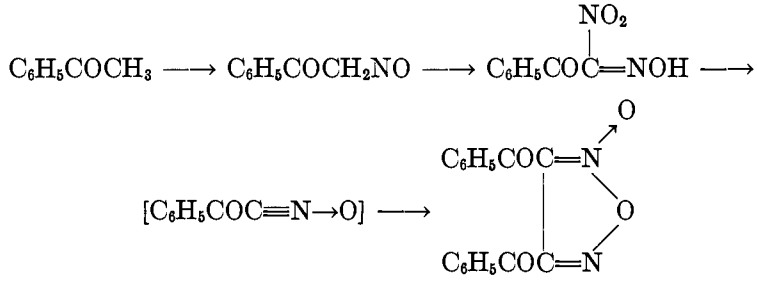
The above polymerization is similar to the polymerization of benzonitrile to give kyaphenine,



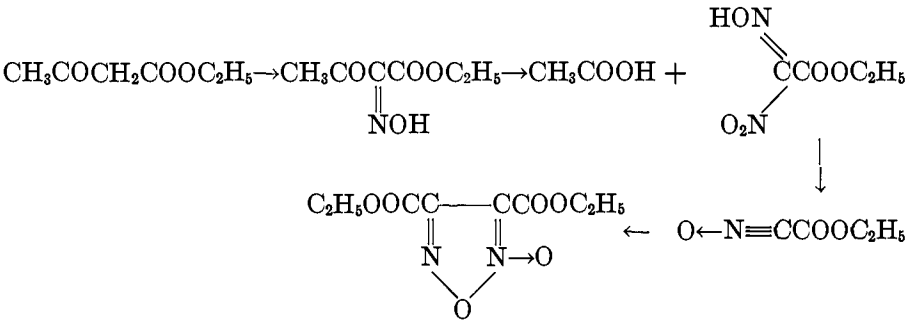
When the free benzonitrolic acid decomposes it gives the nitrile oxide, which then polymerizes to the glyoxime peroxide (furoxan):



This reaction explains very well the behavior of acetophenone toward fuming nitric acid, a reaction which leads to "dibenzoylglyoxime peroxide" ("diphenyldinitrosacyl") (162):



The similar transformation of acetoacetic ester into "glyoxime peroxide diester" with fuming nitric acid may be explained in the same way (301, 173):

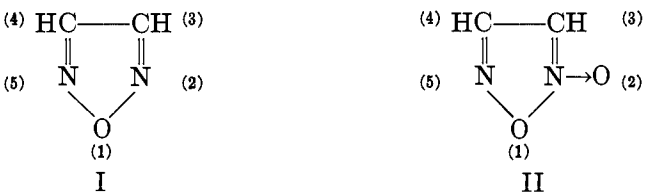


"Glyoxime peroxide di-ester"

V. FURO-α,α'-DIAZOLES: FURAZANS AND FUROXANS

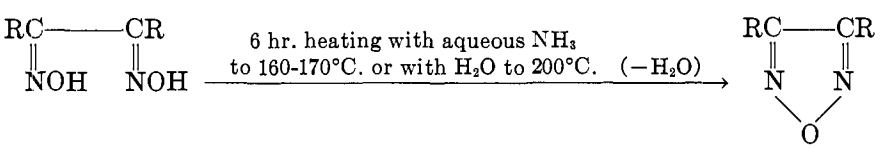
A. Furazans

Furazans contain the heterocyclic system (I); their *N*-oxides are furoxans (II).



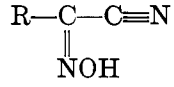
The latter contain the 1,3-nitrone system and are the "glyoxime peroxides." The compounds in which these ring systems occur are related to the acyclic dioximes.

The furazans are obtained by elimination of water from α-dioximes (383).

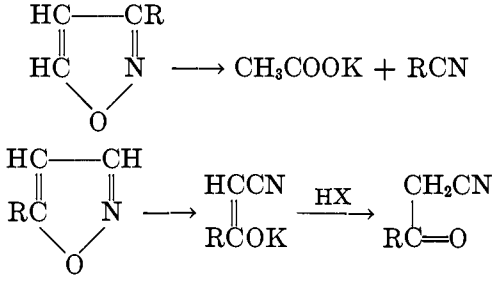


The furazans can be regarded as isoxazoles with one CH group replaced by N, and the two classes of heterocycles show similarities in chemical properties. The furoxans and the isoxazoles show analogous behavior toward sodium hydroxide and sodium ethoxide; depending upon the presence or absence of substituents in certain positions, the ring either opens

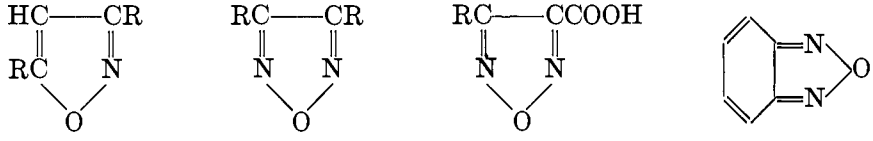
or is stable. If only one substituent is present on the carbon atoms, alkali converts furazans to oxime nitriles,



a reaction similar to that shown by monosubstituted isoxazoles:



When two carbon atoms of either system carry substituents (I, II), the compounds are stable to alkali, and can even be oxidized by permanganate to the acids such as compound III.



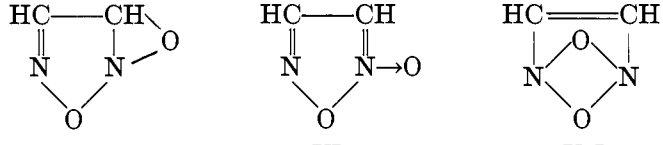
I II III IV

Benzofurazans (IV) are obtained from the dioximes of *o*-quinones.

B. Furoxans

Dioximes can also be dehydrogenated; the products are "glyoxime peroxides" which Wieland (370) has shown to be, in the majority of cases, not true peroxides but furoxans. Most of them show no great oxidizing power but they do react with phosphorus pentachloride with or without a solvent (toluene, etc.) to give furazans, phosphorus oxychloride, and chlorine (this reaction of nitrones with phosphorus pentachloride to give phosphorus oxychloride, chlorine, and the desoxynitrone is a very general reaction of nitrones).

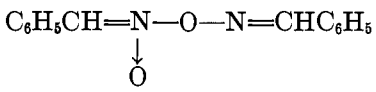
The furoxans can be written structurally in three ways (V, VI, and VII).



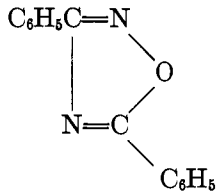
V VI VII

Wieland originally preferred formula V, Forster and Barker (116) and Green and Rowe (144) preferred formula VII, but in view of the work of Angeli (9) on the azoxy compounds formula VI is now preferred by most chemists.

Monoöximes can also be dehydrogenated to "peroxides," both the α- and β-aldoximes giving the same product. Whether these are true peroxides, such as $C_6H_5CH{=}N{-}O{-}O{-}N{=}CHC_6H_5$, or are open-chain furoxans,

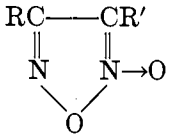


is not known. As by-products in the oxidation of aldoximes there result azoximes (83, 45, 36, 41, 289, 296, 305):



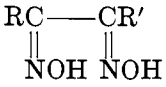
The glyoxime peroxides are formed by the mild oxidation of 1,2-dioximes (325) with potassium ferricyanide in alkaline solution (28, 198), nitrogen dioxide in ether (294), dilute nitric acid, bromine in dilute sulfuric acid, and sodium hypochlorite (294). Some dioximes, however, are not oxidized to peroxides by these reagents (294).

In the purely aromatic series the oxidation products are furoxans (372, 382).



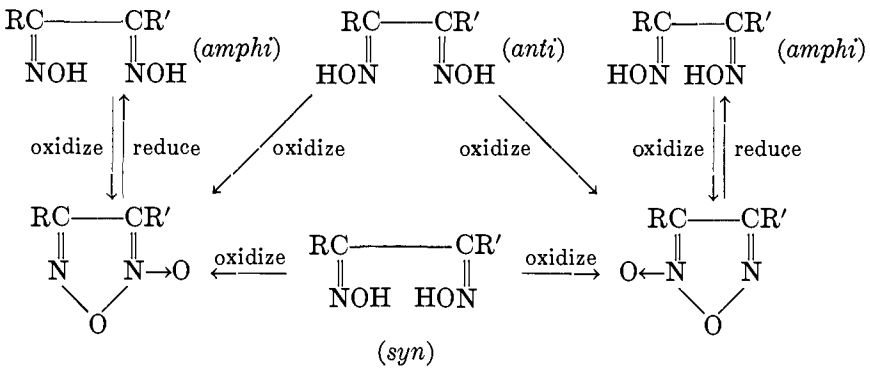
The peroxides of the *o*-quinone dioximes, however, are not furoxans, for they are symmetrical and they do not react with phosphorus pentachloride (116, 294, 372, 120, 145, 293, 196, 10, 48, 176, 25).

When, in the aromatic dioxime,

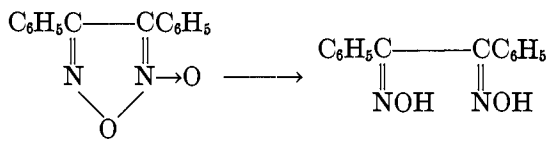


R = R′, one furoxan results (28, 103, 294, 372). When R $\neq$ R′, two furoxans result (175, 231, 233). The oxygen is eliminated from all of these by the action of phosphorus pentachloride, and the corresponding furazans

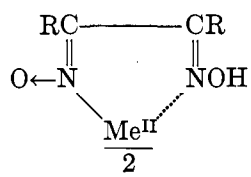
result (382). The furoxan formula implies that oxidation of the *anti*- and *syn*-dioximes involves a steric rearrangement, for the furoxans on reduction *always* give the *amphi*-oximes. This agrees with the fact that unsymmetrical dioximes give mixtures of the two possible furoxans, while each of the two *amphi*-oximes gives only one furoxan, and on reduction each furoxan gives the original *amphi*-oxime from which it came; thus



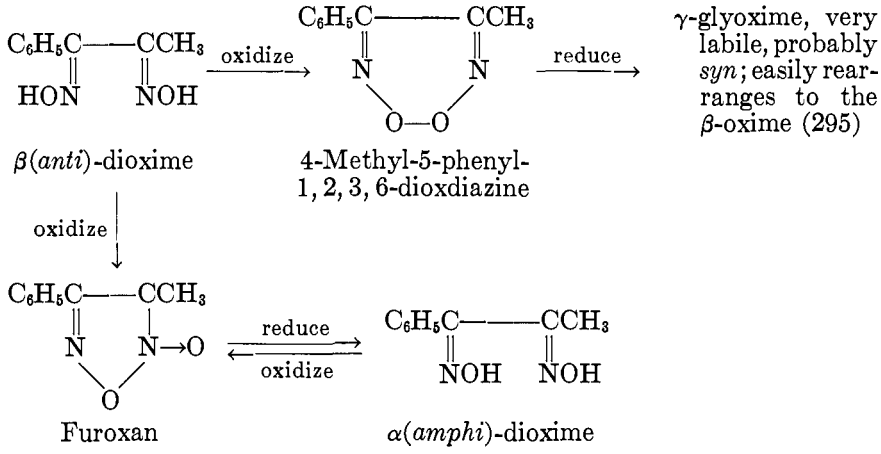
All three benzil dioximes give the same peroxide, which is a furoxan; on reduction it gives only the *amphi*-dioxime (4, 5, 370):



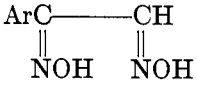
The *anti*-dioximes give stable heavy-metal salts,



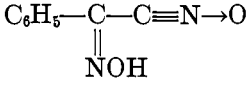
The relationships are not so simple in the aliphatic-aromatic series of dioximes. Sometimes in this series only two oximes are known, one *anti* and one *amphi*. The α-form (*amphi*) on oxidation gives a furoxan which on reduction gives the same *amphi*-dioxime again (291, 294). The β-form (*anti*) sometimes gives two oxidation products. One is the furoxan, the same one which resulted from the oxidation of the *amphi*-dioxime; the other oxidation product is an entirely different substance, a dioxdiazine, apparently a true peroxide (241, 291, 292, 297, 299, 300). Thus



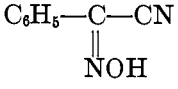
The aryl glyoximes of the type



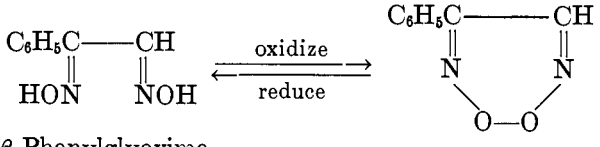
behave still differently. The *α(amphi)*-form on oxidation gives *no cyclic* compound, but an oxide of an aroyl cyanide (295),



which on reduction gives the aroyl cyanide oxime,



The *β(anti)*-form also gives only one oxidation product; it is a dioxdiazine, and on reduction it gives the *β*-dioxime.

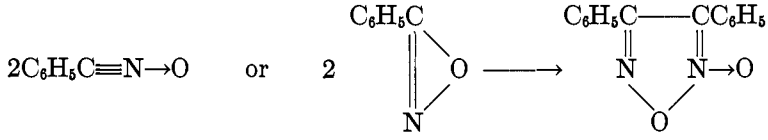


Reduction should give the *syn*-dioxime, and probably does so at first, but it is so unstable that it changes into the *anti(β)*-form at once.

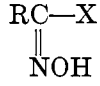
In the purely aliphatic series the structure of the "peroxides" is not known with certainty, but they are probably dioxdiazines.

1. Other preparations of furoxans

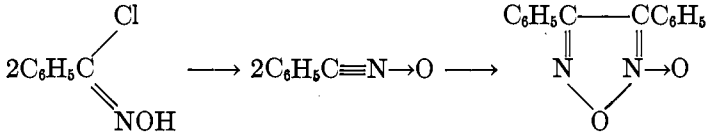
(*a*) By spontaneous, rather easy rearrangement of nitrile oxides (369).



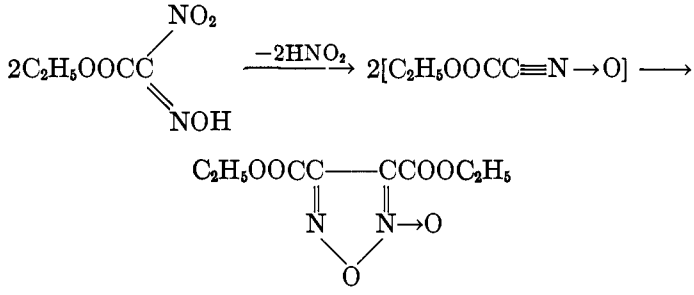
Because of this, furoxans often result by rearrangement of the hydroxamic acids and their derivatives,



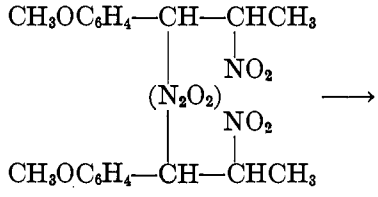
for by elimination of HX from these, the nitrile oxides often result. Thus the hydroxamic acid chlorides, with sodium bicarbonate, give furoxans (369, 363, 365).



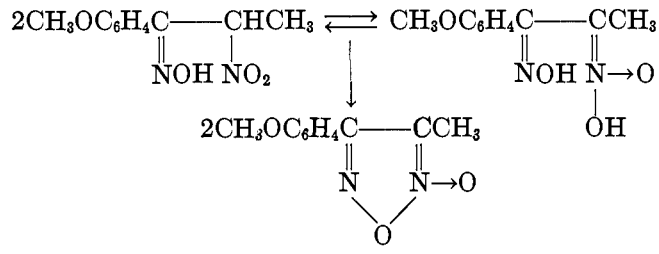
(*b*) By self-decomposition of many nitrolic acids (173, 172, 174).



(*c*) Disubstituted furoxans, R aromatic and R′ aliphatic, are obtained by boiling with water or alcohol the "pseudonitrosites" obtained from compounds of the type $ArCH{=}CHCH_2Al$ (370, 4, 6, 373).



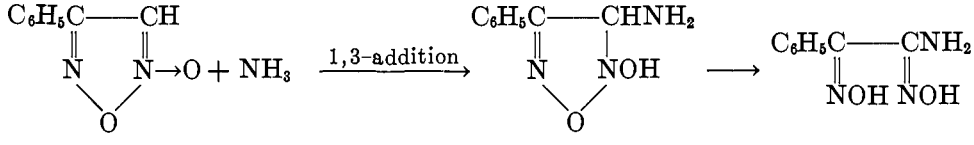
Anethole pseudonitrosite



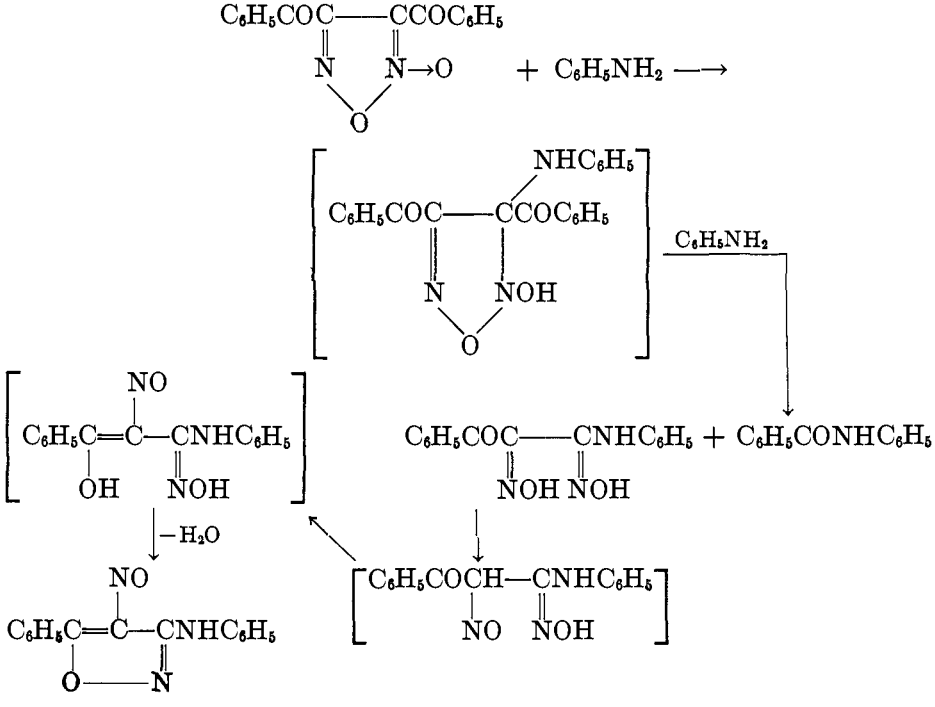
Hence the furoxans often result instead of the nitrosites when an ethylenic compound is treated with N_2O_3.

2. Behavior of the furoxans

The chief reaction is that with phosphorus pentachloride, giving furazan, phosphorus oxychloride, and chlorine. Hydriodic acid reduces furoxans to furazans, as do tin and hydrochloric acid. Monosubstituted furoxans are sensitive to alkali, but the disubstituted ones are stable; both types are stable to acids. With ammonia, the monosubstituted furoxans give amide oximes:



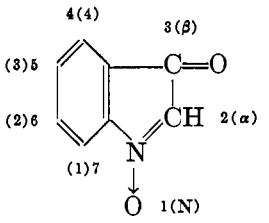
A reaction of the same type also occurs when disubstituted furoxans react with amines, providing one of the substituents is easily eliminated:



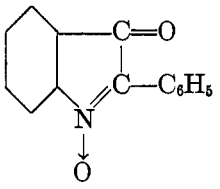
Nitroso isoxazole derivative

VI. THE ISATOGENS

The isatogens are derivatives of the ring system I, but the parent substance itself is unknown. Isatogens are isomeric with, and closely related to, the isatins. The ring system is numbered as shown (Ruggli) with Pfeiffer's system of numbering in parentheses. The first isatogens (IV and V) were discovered by Baeyer (317) during his work on the structure of indigo.

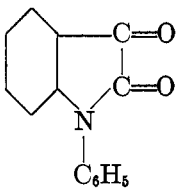


I



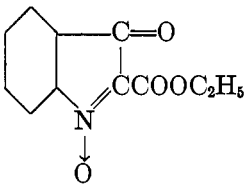
II

2-Phenylisatogen



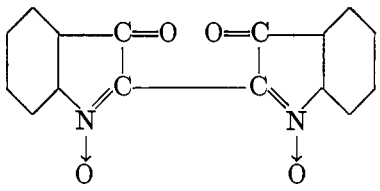
III

N-phenylisatin



IV

Isatogenic ester



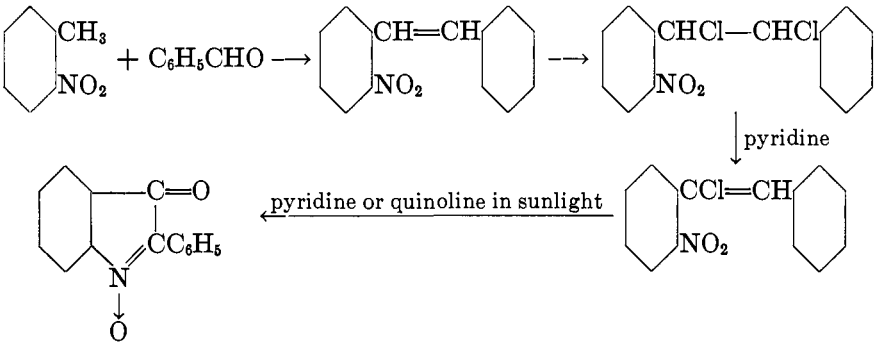
V

Diisatogen

Pfeiffer (284, 283) in 1916 discovered that isatogens could readily be made from *o*-nitrostilbene derivatives and from *o*-nitrotolanes by a rearrangement which takes place in pyridine in the presence of light. The isatogens are very interesting; not only do they contain the nitrone system, but this is conjugated with a carbonyl group. They show many properties characteristic of quinones; Pfeiffer has remarked that they were the "first meta-quinoid substances to be known with certainty."

The starting materials for preparation of isatogens are *o*-nitrostilbenes, which are prepared by condensing *o*-nitrotoluene (and other *o*-nitromethyl hydrocarbons of the aromatic series) with aldehydes. When these stilbenes are chlorinated they give dichlorides; these, on warming with pyridine or quinoline, lose one mole of hydrochloric acid to give chlorostilbenes. If the colorless to bright yellow pyridine or quinoline solution of the chlorostilbene is placed in the sunlight, the color turns gradually to orange,

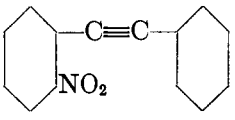
then red, and orange to violet crystals appear; the yield is about 60 per cent and the product is easily purified by recrystallization.



Pfeiffer has made sixteen isatogens in this way and Ruggli has made several more. The most common one is 2-phenyl-6-nitroisatogen, which is made from 2,4-dinitrotoluene. Among the isatogen derivatives are nitriles, acids, esters, phenols, and nitro and methoxyl derivatives.

In a recent paper Ruggli (310) has described a new method of converting *o*-nitrotolane into 2-phenylisatogen. This consists in the action of nitrosobenzene upon the chloroform solution of *o*-nitrotolane in the dark. After standing for 19 days, the isatogen was produced in 57 per cent yield and in a very pure condition. The action of nitrosobenzene is apparently catalytic, for although the best yield of isatogen was obtained using 2 moles of nitrosobenzene per mole of *o*-nitrotolane, the amount of nitrosobenzene could be reduced to 0.2 mole without greatly affecting the results. Because the isatogen was obtained from *o*-nitrotolane more slowly than from the corresponding stilbene dichloride, Ruggli is inclined to the belief that radicals of the methylene type may be involved as intermediates in the formation of isatogens, and that the acetylenes (tolanes) require more time for conversion to these radicals than do the stilbene chlorides. The action of nitrosobenzene upon the tolanes is also supposed to involve intermediate radicals of the methylene type.

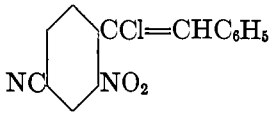
The isatogens contain no halogen and are isomeric with the *o*-nitrotolanes (A), but they are not tolanes, for the color of the isatogens is too deep and the real isatogens have entirely different physical and chemical properties.



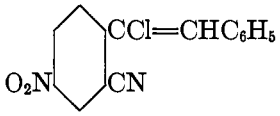
A

To obtain the isatogen from the monohalostilbene, both pyridine (or quinoline) and light are necessary; pyridine alone does not remove hydrochloric acid from the monochlorostilbenes. The tolanes can be obtained from the chlorostilbenes with hot, alcoholic potassium hydroxide; these, in pyridine and in the light, give the isatogens very easily. Pyridine cannot be replaced by benzene, alcohols, or acetic acid; solutions of the tolanes in any of these solvents are unchanged by the action of sunlight.

The mechanism of the isatogen formation is obscure; it may involve the tolanes, or it may not. Three processes seem to be involved, however: (*1*) hydrochloric acid is eliminated; (*2*) the oxygen migrates to the carbon next to the nitrated phenyl group; and (*3*) the ring closes. The ring closure follows from the fact that only *o*-nitrostilbenes give isatogens; thus compound VI gives an isatogen while compound VII does not.

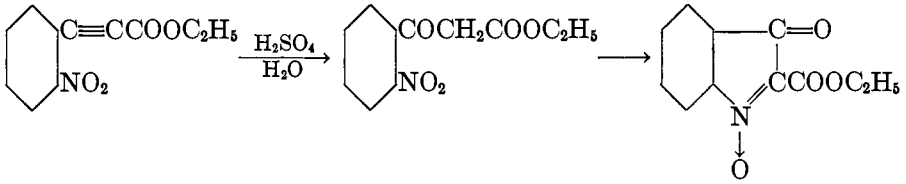


VI

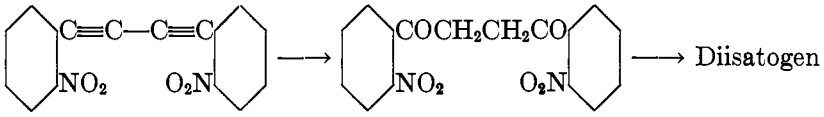


VII

The rôle of the pyridine seems to be that of a specific catalyst, for other solvents (except quinoline) are without effect. Isatogens can be made from the tolanes either photochemically in pyridine or sometimes, but not always, by the action of sulfuric acid. In the latter case the reaction consists first in the addition of water to the triple bond to give a ketone; this then condenses with the nitro group to give the isatogen.



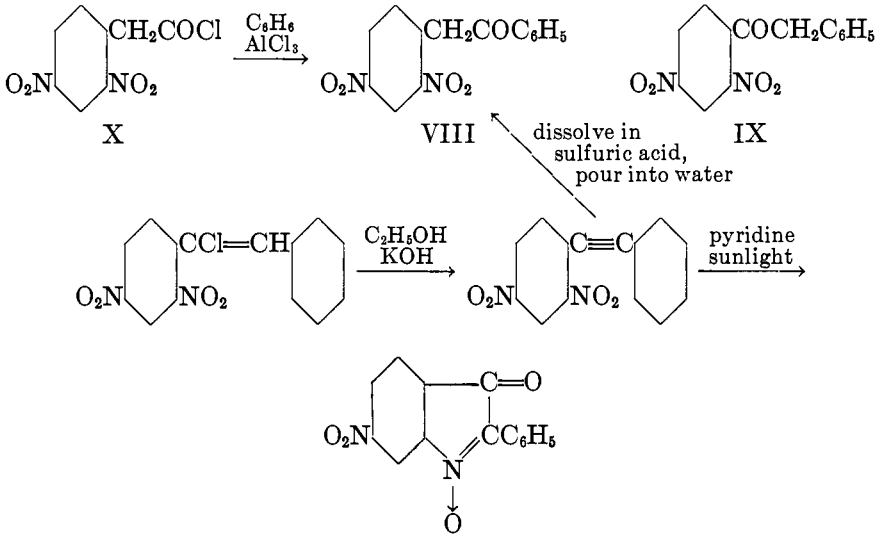
IV



V

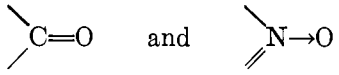
This mechanism also explains why sulfuric acid does not convert all *o*-nitrotolanes into isatogens; the water must add so that the resulting carbonyl

group is next to the nitrated ring. Thus 2,4-dinitrotolane with sulfuric acid gives no isatogen; if the sulfuric acid solution is poured into water, the ketone (VIII) precipitates and this cannot form an isatogen, although its isomer (IX) could do so. That compound VIII was actually formed was proved by isolating it and by synthesizing it from 2,4-dinitrophenylacetyl chloride (X).



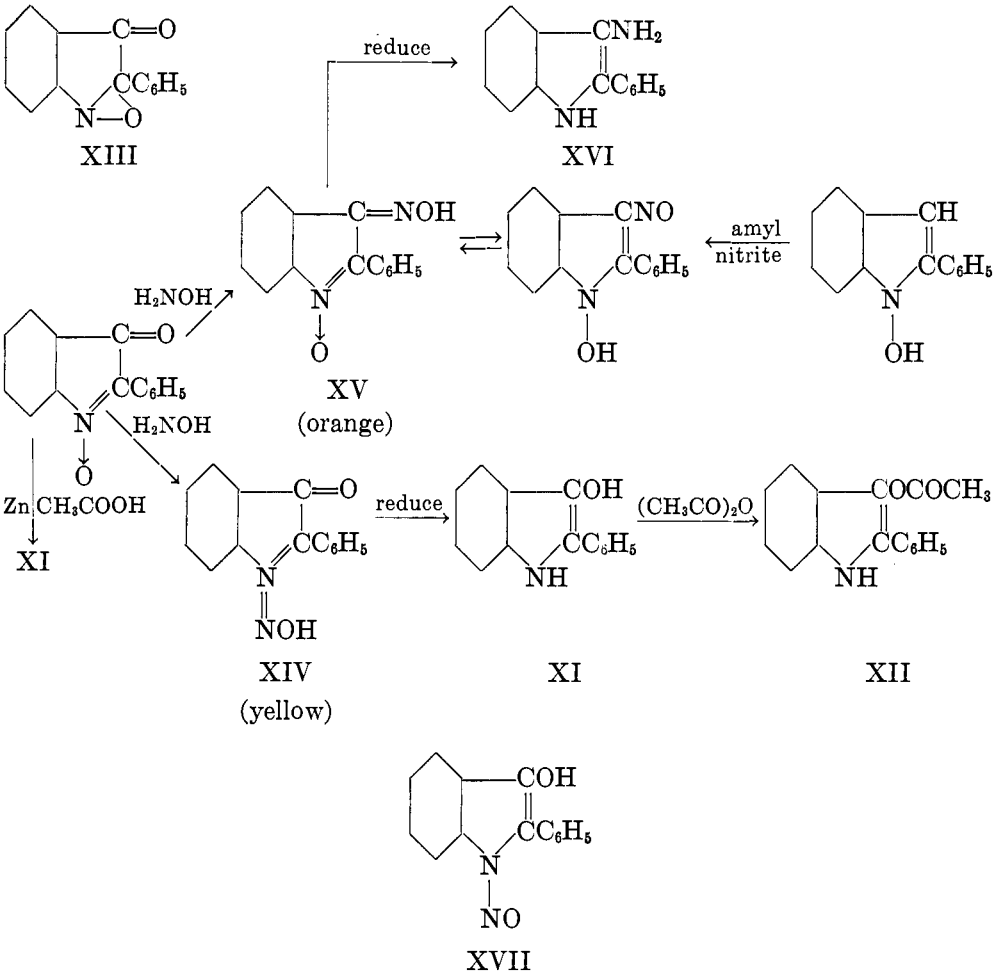
A. Structure of the isatogens

The isatogens are cyclic, for on reduction with zinc and acetic acid they give the almost colorless phenylindoxyls (XI); these, with acetic anhydride, give *O*-acetyl derivatives (XII). The formula shows two reactive groups:

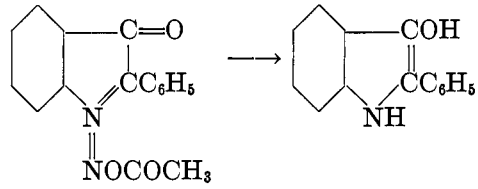


while the alternative structure (XIII) shows only one. The action of hydroxylamine hydrochloride in boiling alcohol (free hydroxylamine acts only as a reducing agent) gives *two isomeric oximes*, one of which (XIV) is yellow and is soluble in ammonia, giving a greenish solution; the other (XV) is orange and its solution in ammonia is also orange. With acetic anhydride these oximes give characteristic acetyl derivatives. The orange oxime is identical with a compound made by Angeli and Angelico (14)

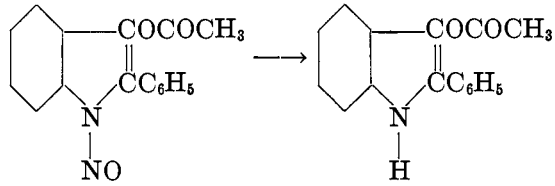
by the action of amyl nitrite on *N*-oxyphenylindole; this must therefore be the *C*-oxime:



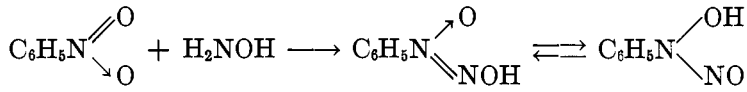
The yellow oxime is a *structural* isomer of the orange oxime. The orange oxime, on reduction, gives aminophenylindole (XVI). If the yellow oxime were a stereoisomer it should give the same reduction product, but it does not; instead, it gives phenylindoxyl (XI). Hence the yellow oxime must be the *N*-oxime or else the nitroso compound (XVII). The *N*-oxime formula is indicated by the fact that the acetylated yellow oxime on reduction (zinc and acetic acid) gives phenylindoxyl and no trace of acetylphenylindoxyl.



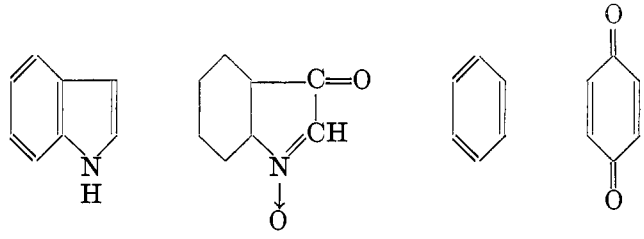
and not



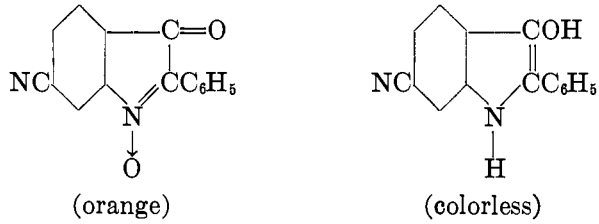
Hence the $\diagdown\!\!\!\!\diagup N\rightarrow O$ group can be converted to an oxime and so is like a carbonyl group. This may also be true of the nitro compounds, for nitrobenzene can be converted to nitrosophenylhydroxylamine by the action of hydroxylamine (13).



Comparing the formulas of indole (A) and isatogen (B), the relationship is seen to be the same as that between benzene (C) and quinone (D). Hence the isatogens should show quinoid character, and they do so. They are deeply colored, form quinhydrones (their hydroquinones are the indoxyls), and they liberate iodine from hydriodic acid.



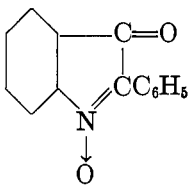
A B C D

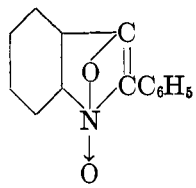


(orange) (colorless)

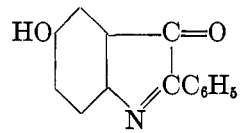
The mixture of the orange cyanoisatogen and the colorless cyanoindoxyl gives a black, crystalline compound easily separated into its components again. Hence these substances are really "quinoids," in which the $\diagdown\!\!\diagup N\rightarrow O$ group plays the part of one carbonyl group. Baeyer's isatogenic ester and diisatogen are really isatogens of the same type as these, and they do not have the three-membered ring as Baeyer wrote them.

But the matter is somewhat more complicated than just outlined. If 2-phenylisatogen is treated with alcoholic hydrochloric acid, there results a yellow isomer which is stable to light and sulfuric acid. The yellow isomer forms an oxime (only one) which is different from either of the oximes of the original isatogen. Hence it must contain a carbonyl group; but it shows no quinoid properties and does not liberate iodine from a solution of potassium iodide in acetone. Both isomers have the same composition *and* molecular weight; the isoisatogen is not compound XIX, for it shows no phenolic properties (gives no color with ferric chloride, is not stable in alkali, is stable to bromine at ordinary temperatures, does not couple with diazonium compounds, etc.). A structure such as that shown in formula XVIII is excluded on stereochemical grounds and also because of the lack of oxidizing power. Both isomers on reduction give the same indoxyl. Heated for 5 min. above its melting point or in glacial acetic acid solution, or, most smoothly of all, when it is heated with phenyl isocyanate, the isoisatogen reverts to the normal isatogen. The only possible structure for this isoisatogen, on the basis of the evidence so far, is one that contains the three-membered ring (XX).

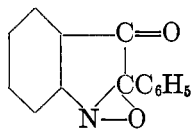




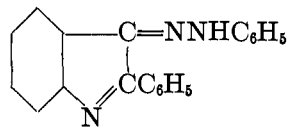
XVIII



XIX



XX

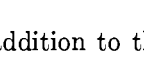
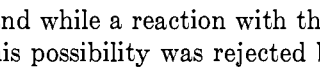


XXI

The normal isatogens and the isoisatogens behave differently toward phenylhydrazine; the normal isatogen is reduced to indoxyl (like the action of phenylhydrazine on quinone to give hydroquinone), while the isoisatogen

gives a compound analyzing for formula XXI or else it does not react at all. It is not possible to be sure, as yet, of any of the structures in the iso series.

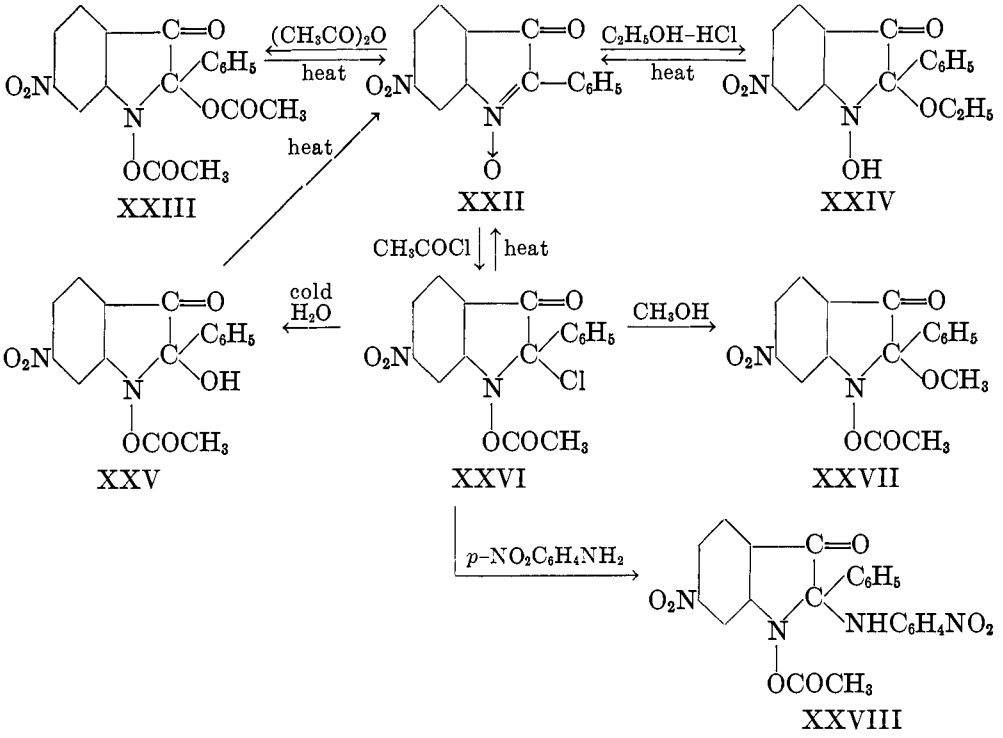
B. Chemical properties of the isatogens (309, 312, 313)

The isatogens add a wide variety of reagents including acetyl chloride, acetic anhydride, and alcohols; some of these reactions are certainly 1,3-additions and probably most of the other reactions involve initial 1,3-additions also. When the *deep red* 6-nitro-2-phenylisatogen (XXII) is refluxed with acetyl chloride for a few hours, a yellow solution results (309). If the solvent is evaporated in the absence of all traces of water, large yellow crystals of the addition compound (XXVI) result. This addition product decomposes into the components when heated to 145–160°C., but it is stable at room temperature for some time, though not indefinitely, providing care is taken to keep it dry. It is very reactive when in solution and often the yellow solution turns red, owing to the formation of the isatogen by the action of traces of water upon XXVI. The chloro compound is even more sensitive when attempts are made to replace the chlorine by other groups. Aniline and phenylhydrazine react instantly, giving the isatogen (XXII), which then reacts further when phenylhydrazine is used. But with an amine less basic than aniline, such as *p*-nitroaniline, the chlorine atom is replaced and the product is compound XXVIII. The product (XXVI) must have the structure shown and must be formed by 1,3-addition to the nitrone system  . The nitro group in the benzene ring cannot be involved, for the corresponding isatogen without the nitro group gives the same reaction with acetyl chloride, and while a reaction with the system  was considered, this possibility was rejected because it would involve the attachment of the chlorine atom to oxygen. The structure XXVI shows no "quinoid" linkage, which agrees with the properties in so far as the substance is stable enough to investigate; compound XXVI is lighter in color than the isatogen and is not derived from the isoisatogen, for the latter does not react with acetyl chloride. Substance XXVIII also dissociates when heated, giving the isatogen (XXII), acetic acid, the amine, and a small amount of the isoisatogen. Tests for the carbonyl group in compound XXVIII were negative; hydroxylamine, phenylhydrazine, and semicarbazide under varied conditions gave only orange colors and the dissociation products of XXVIII. Methanol and ethanol react with XXVI in the same manner as nitroaniline; the products are the ethers (XXVII). The reaction with alcohols often gives rise to the isatogen, but once the ether is formed, it is quite stable. These ether-acetates cannot be made by the direct addition of alkyl acetates to the nitrone.

When the solution of XXVI in acetyl chloride is poured into water, a yellow precipitate results which is quickly transformed into the isatogen by the heat evolved. If, however, the solution is poured onto ice, the yellow precipitate remains and on careful purification the substance XXV is obtained. This dissociates at 125°C. into acetic acid and the isatogen, but the substance cannot be made directly from its components.

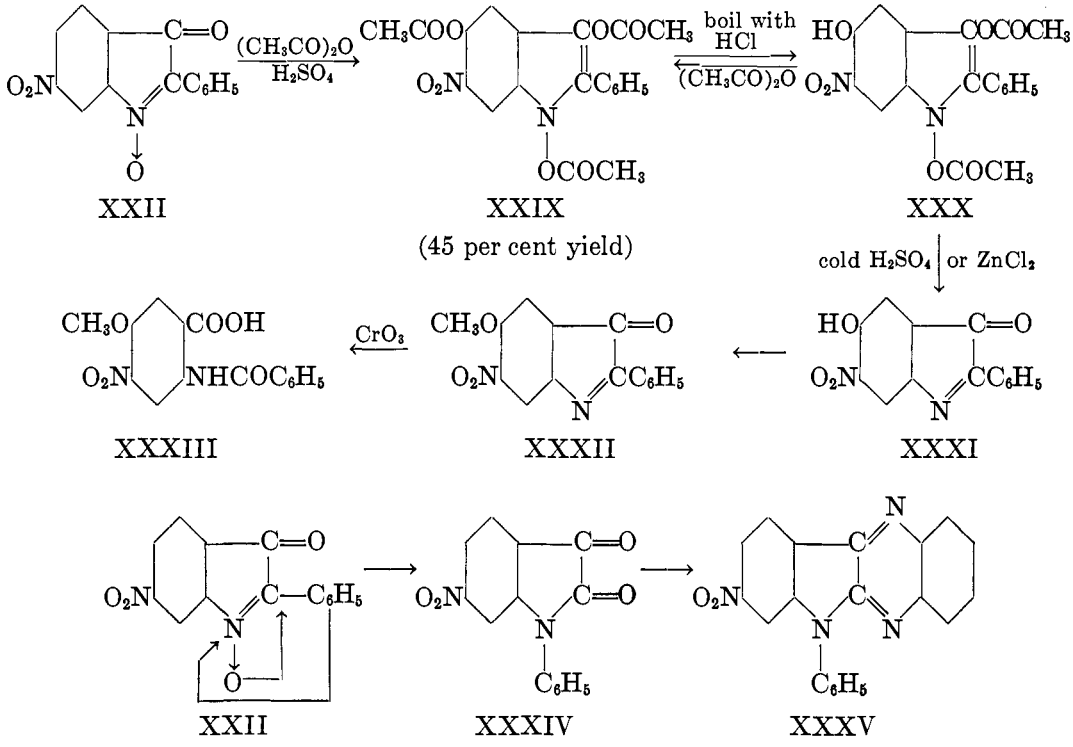
Other acid halides (C_6H_5COCl, $SOCl_2$, SO_2Cl_2, BrCN) either did not react with XXII or else led to resins, but acetic anhydride in great excess produced the addition product XXIII, although the reaction was never complete. No carbonyl group could be detected in compound XXIII.

The action of cold alcoholic hydrochloric acid upon the isatogen (XXII) produced the addition product (XXIV), and it was considered likely that hydrochloric acid added first, followed by replacement of the chlorine by the ethoxyl group. The addition product (XXIV) is very labile and is quite different from the isoisatogen produced from XXII by the action of hot, alcoholic hydrochloric acid.

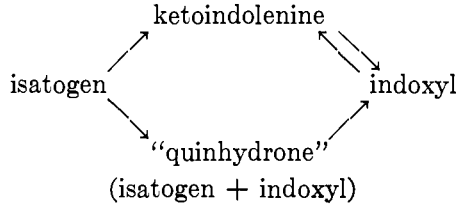


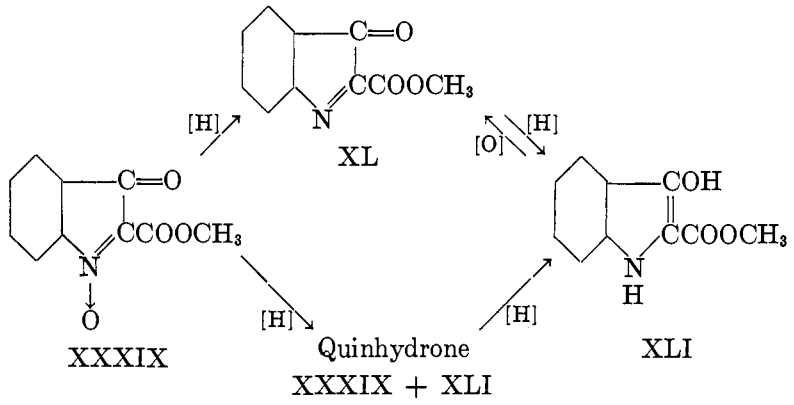
The isatogen behaves like quinone toward acetic anhydride in the presence of sulfuric acid (312), giving a triacetate with one of the acetoxy groups in the benzene ring. The product (XXIX) was degraded to the

ketoindolenine (XXXI) and then to the acid (XXXIII), both of which were synthesized by independent methods. In the formation of XXIX, there is obtained a red, crystalline by-product, isomeric with the isatogen. This is the *N*-phenylisatin (XXXIV), formed by Beckmann rearrangement of the isatogen (the isatogen is in effect the *N*-ether of an oxime). This isatin gives a phenylhydrazone, an oxime, etc., and with *o*-phenylenediamine gives a phenazine (XXXV).

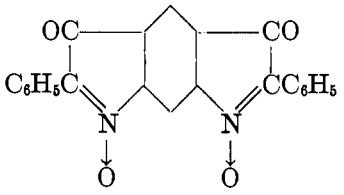


Reduction of isatogens (314) is difficult to interrupt short of the final product, which is an indoxyl. But by using the methyl ester of isatogenic acid (XXXIX) it was possible to show that the reduction occurred stepwise as follows:

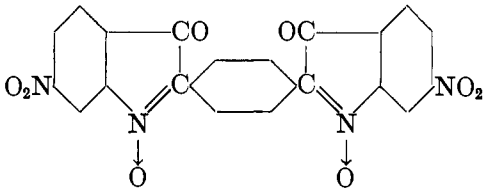




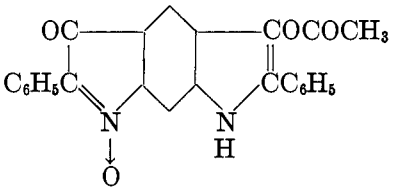
Ruggli and Disler (311) have prepared isatogens derived from anthraquinone, using the general method starting with anthraquinone-2-aldehyde and 2,4-dinitrotoluene. Ruggli, Zimmermann, and Thouvay (316) sought to prepare the diisatogen (XXXVI) starting with 4,6-dinitro-1,3-xylene, but the ring closure could be made to take place only on one side. However, the isatogen-indoxyl derivative (XXXVII) was prepared (315).



XXXVI

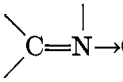


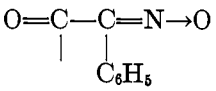
XXXVIII



XXXVII

Recently (317) diisatogens have been made in which the two isatogen rings are separated by a benzene ring, starting with *m*- and *p*-phthalaldehydes and 2,4-dinitrotoluene. The reactions used were the usual ones. The product from *p*-phthalaldehyde was XXXVIII. *o*-Phthalaldehyde would condense only once with 2,4-dinitrotoluene, hence no diisatogen was obtained in this case.

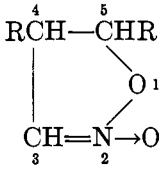
Thus the isatogens are nitrones with the system  and most of their reactions which have been studied in detail can logically be interpreted as 1,3-additions. The isatogens are also "quinoid," for the nitrone system is conjugated with a carbonyl group to give the system



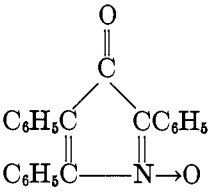
and the isatogens therefore could give reactions starting at the carbonyl or nitrone group and ending at the other system. These would be 1,5-additions; the further study of the chemical properties of these curious compounds cannot but produce results of great interest and theoretical importance.

VII. THE ISOXAZOLINE OXIDES AND DERIVATIVES

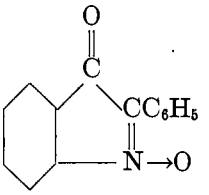
The isoxazoline oxides contain a five-membered ring system (I) in which the nitrone system is a part of the ring. The cyclic nitrones (II), which are closely related to and derived from the isoxazoline oxides, also contain the nitrone system as part of a ring. However, in the isoxazoline oxides this system stands alone, while in the cyclic nitrones the nitrone system is conjugated with a carbonyl group as it is in the isatogens (III):



I



II

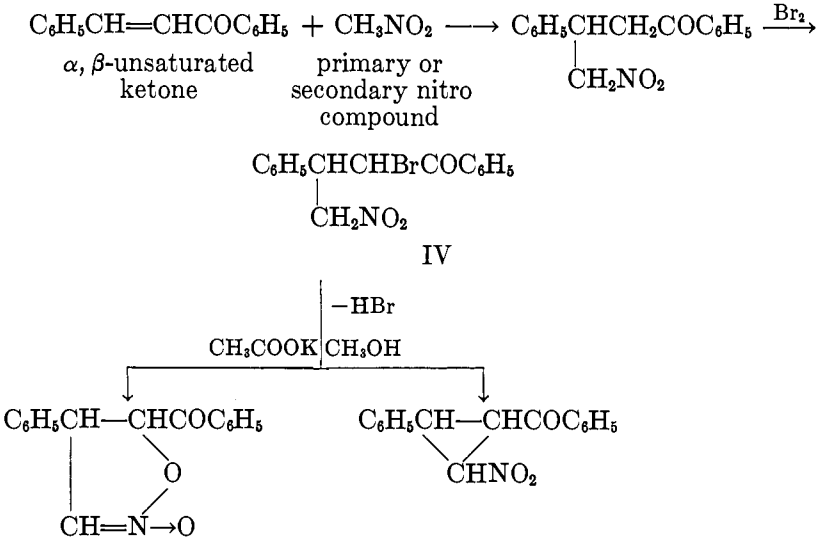


III

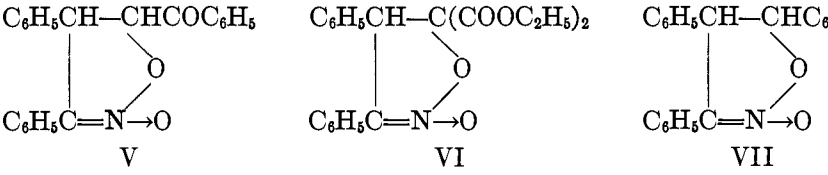
Thus the cyclic nitrones are really mononuclear isatogens and like the isatogens they are "quinoids,"—deeply colored (dark purple). The nitrone system in both of these compounds is extremely reactive, undergoing 1,3-additions; they are very sensitive, combining even with the solvent unless special precautions are taken. The work upon these two classes of compounds was done by Kohler and his students and is reported in a series of papers (179–195) which appeared during the period 1924–1930.

The isoxazoline oxides were first discovered as by-products in the prep-

aration of the nitrocyclopropanes, for which the usual synthesis includes the following steps:

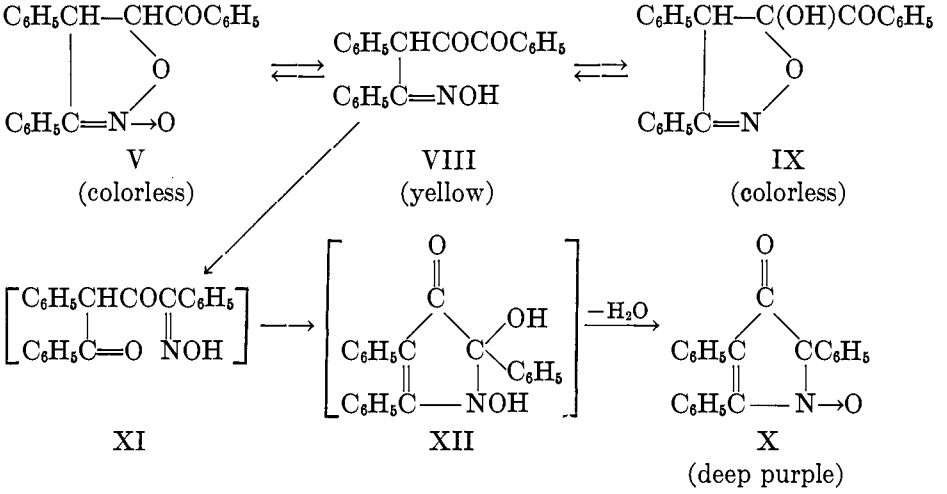


The stereoisomeric α-bromo-γ-nitroketones (IV) behave quite differently when hydrobromic acid is eliminated from them by means of potassium acetate in methanol; some of them give only cyclopropanes, certain representatives give mixtures of cyclopropanes and isoxazoline oxides, while others give the oxide alone. The synthesis outlined can be varied somewhat, but the product is always an isoxazoline oxide with a group COR (R = alkyl, aryl, or *O*-alkyl) in the 5-position. Thus if phenylnitromethane is used instead of nitromethane, the oxide will be V; if benzalmalonic ester and phenylnitromethane, or nitrostilbene and malonic ester, are used, the oxide will be VI. Similarly, if nitrostilbene and phenylnitromethane are used, the oxide will be VII, but in the last case the elements of nitrous acid, instead of hydrobromic acid, are eliminated in the final step. Isoxazoline oxides prepared from these starting materials do not have the group COR in the 5-position.

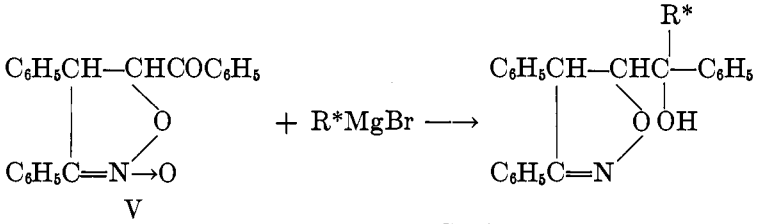


To obtain the cyclic nitrones the only method available consists in starting with the isoxazoline oxide (V) obtained from α,β-unsaturated

ketones and substituted nitromethanes such as phenylnitromethane. Isoxazoline oxides of the type of V, on standing in ether or alcoholic solution, spontaneously isomerize into a yellow triketone oxime (VIII), and the latter then isomerizes to 5-hydroxy-5-benzoylisoxazoline (IX). All three of these compounds V, VIII, and IX exist in equilibrium with each other, and if the yellow triketone oxime (VIII), or any of the substances in equilibrium with it, is dissolved in chloroform and a trace of acid is added, the deep purple nitrone results, probably *via* the intermediates XI and XII:

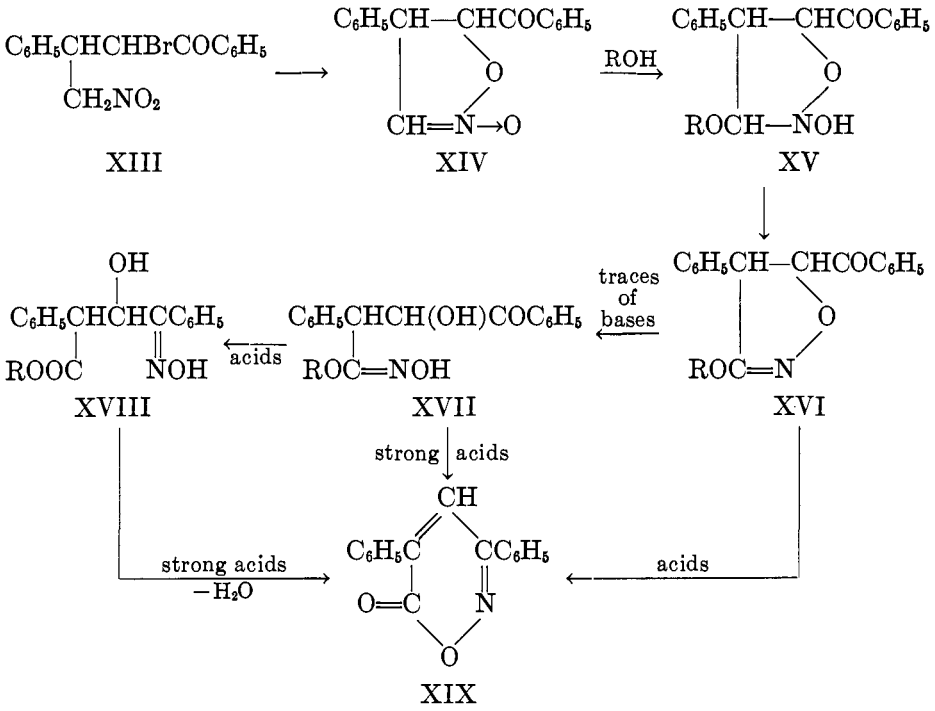


The reactions of these compounds are extremely complicated, chiefly because most of the ones studied were of the type of compound V, which contains the carbonyl group in the 5-position. This is not conjugated with the nitrone system, but it can react with many reagents that would be used in a study of the nitrone system; moreover, it mobilizes the hydrogen in the α(5)-position, causing easy loss of water and giving rise to a whole series of rearrangements which are very difficult to follow. Thus with the Grignard reagent there could be either 1,3-addition to the nitrone system, 1,2-addition at the carbonyl group, or reduction, and in the case of the ketonic oxides, the last two of these reactions predominate. Thus:



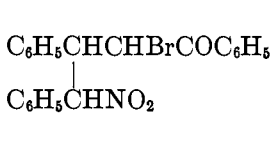
(*R = C_2H_5 or C_6H_5)

Moreover, oxides of the type of V are extremely sensitive toward acids and bases and they can be isolated only in favorable cases. In general, the rearrangements involved (all of which start as rearrangements of the isoxazoline oxide) in the case of the ketonic oxides may be summed up as follows: primary nitroketones, such as XIII, first give the corresponding isoxazoline oxides (XIV); these cannot be isolated, for they at once add a molecule of the solvent (ROH) 1,3 to the nitrone system giving the intermediate (XV), which then loses water and rearranges to the isoxazole (XVI).

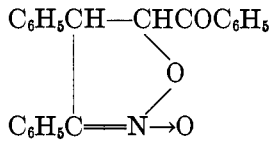


The latter may undergo further rearrangements; acids convert the isoxazole directly to the ortho-oxazine (XIX), while mild bases convert the isoxazole to the hydroxamic ester (XVII). The latter, in turn, is converted to the oximino ester (XVIII) by weak acids, but the action of strong acids upon either XVII or XVIII produces the ortho-oxazine (XIX).

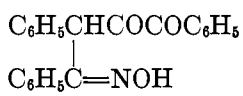
Secondary nitroketones such as XX first give the corresponding isoxazoline oxides (XXI), which in basic media give either monoöximes of triketones (XXII) or ketonic isoxazoles (XXIII); in *acid* media they give hydroxyisoxazolines (XXIV) or ortho-oxazines (XXV)



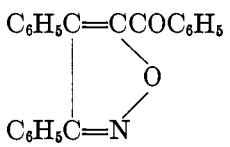
XX



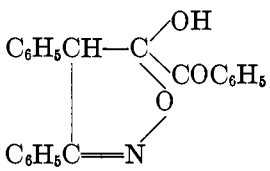
XXI



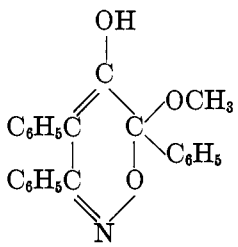
XXII



XXIII

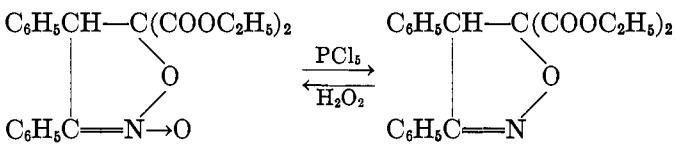


XXIV



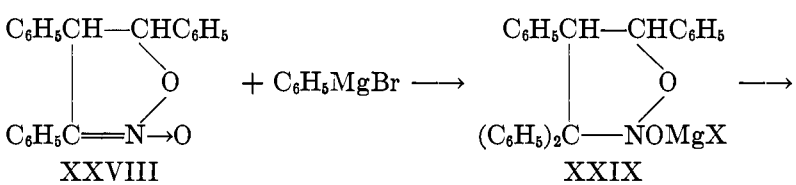
XXV

Aside from these complications due to rearrangements, the isoxazoline oxides show the reactions of 1,3-systems. They liberate chlorine from phosphorus pentachloride and are thus converted to isoxazoles, from which the oxides may be regenerated by the action of hydrogen peroxide.

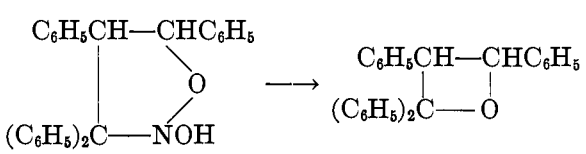


XXVI XXVII

The oxides react with the Grignard reagent, giving a primary 1,3-addition. The reaction is very complicated when ketonic oxides, with the —COR group in the 5-position, are used. In the case of triphenylisoxazoline oxide (XXVIII) it was possible to follow the course of the Grignard reaction, although all Grignard reagents do not react alike. With phenylmagnesium bromide the reaction involved the following steps:

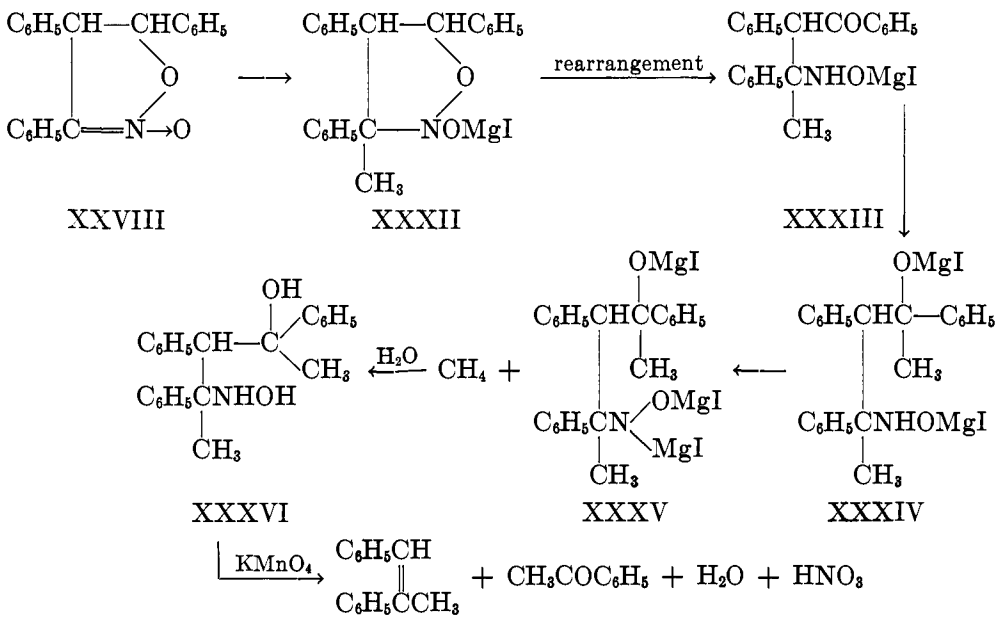


XXVIII XXIX



XXX XXXI

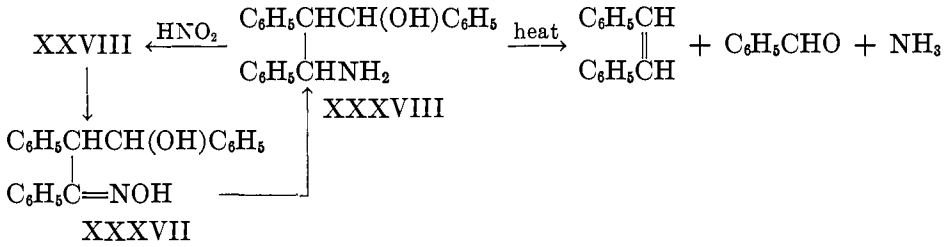
With methylmagnesium iodide the reaction was not confined to 1 mole of the Grignard reagent; instead, the oxide (XXVIII) consumed 3 moles of the reagent and liberated 1 mole of methane. The product was a basic substance containing two active hydrogen atoms (analysis in the "machine") and having the composition $C_{23}H_{25}O_2N$. This base could be acetylated to give mono- or di-acetates, and on oxidation of the base by permanganate the products were water, nitric acid, acetophenone, and methylstilbene. The structure of the base was therefore that of XXXVI, and the reaction of the oxide (XXVIII) with methylmagnesium iodide involved the following steps, the first of which was 1,3-addition of the reagent to the nitrone linkage:



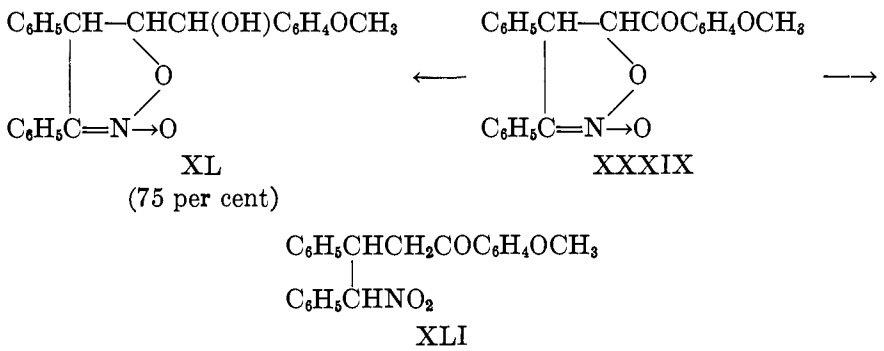
The reaction between the oxide (XXVIII) and ethylmagnesium bromide was still more complicated; 2.8 moles of the reagent was consumed and 0.6 mole of gas was liberated. The gas consisted of ethane and ethylene (4:1) and the addition reaction was complicated by the reducing action of the ethylmagnesium bromide. No addition product could be isolated, but the reduction product, identical with that produced from the oxide by zinc and acetic acid, was isolated.

Reduction of triphenylisoxazoline oxide (XXVIII) produces the β-hydroxy oxime (XXXVII), which can be reduced further to the amine (XXXVIII). When heated, the amine decomposes into stilbene, benzaldehyde, and ammonia, but when subjected to the action of nitrous acid

the amine does not give the expected dihydroxy compound; instead, the isoxazoline oxide results.



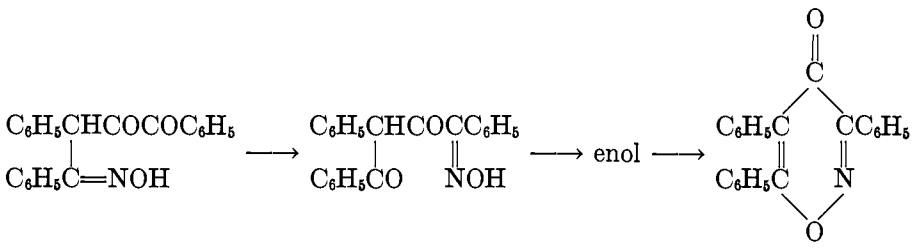
Reduction of the ketoisoxazoline oxides introduces additional complications because the three reducible groups—carbonyl, nitrone, and oxido ring—compete for the hydrogen. By hydrogenating the keto oxide (XXXIX) in the presence of platinum oxide catalyst and stopping the reaction when 1 mole of hydrogen had been absorbed, two products were isolated: the hydroxy oxide (XL), formed by reduction of the carbonyl group, and the nitro compound (XLI) formed either by primary reduction of the nitrone linkage followed by rearrangement, or by reduction of the oxido ring to the *aci*-nitro compound. The hydroxyisoxazoline oxide (XL), when reduced further, is transformed into an amine analogous to the one obtained by reduction of XXVIII.



A. The cyclic nitrones (184, 53, 52, 54)

As mentioned before, when solutions of triphenylbutanetrione oxime (VIII) become acid, there appears in small quantities a purple anhydride (X) which is a monomolecular anhydride of the oxime. No open-chain anhydride can be derived from an oxime of the structure of VIII, and the only anhydride of the enol of VIII is the isoxazole (IX). Hence the formation of the purple anhydride must be preceded by rearrangement, but since the slightest trace of acid is sufficient to cause this, it is not likely

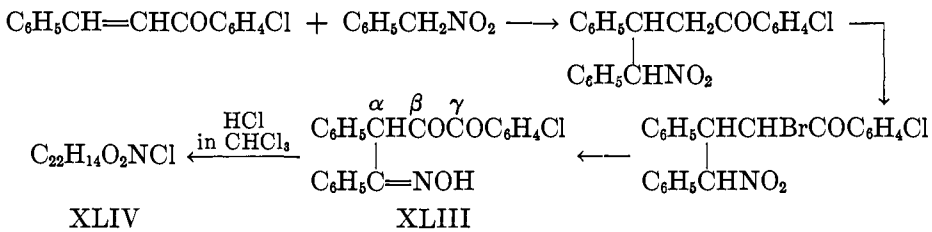
that the carbon chain rearranges. However, transportation of the oximino group to a more active carbonyl group is not improbable and such a shift would be favored in acid media, thus leading to a new anhydride.



VIII XI XLII

or XI ⟶ XII ⟶ X

Attempts to determine by ozonolysis whether or not XLII was a possible structure failed because the products, benzoic acid and benzonitrile, are not sufficiently significant. Hence it was necessary to mark one of the phenyl groups and therefore an analog of VIII was synthesized as follows:



XLIV XLIII

Ozonolysis of XLIV gave benzoic acid and chlorobenzonitrile; hence the nitrogen in the anhydride is attached to what was the γ-carbon atom of the oxime. This evidence reduces the plausible formulas for the anhydride to two: XLII and X. To distinguish between XLII and X the action of methylmagnesium iodide upon the anhydride was investigated quantitatively. The anhydride consumes 3 moles of the reagent, liberating 1 mole of gas. Since there is no apparent reason why the ortho-oxazine (XLII) should liberate gas, while the isoxazoline oxides always do, formula X for the anhydride becomes the more probable one. The physical properties of the product formed by the addition of methylmagnesium iodide to the anhydride rendered the compound unsuitable for investigation, and phenylmagnesium bromide gave a product (XLV) which was stable only in the solid form. In solution the product changes too rapidly for molecular weight determinations to be made and analysis alone does not give any information as to the quantity of phenylmagnesium bromide which reacts with the anhydride. Therefore *p*-bromophenylmagnesium bromide was used and in this case analysis of the product showed that the anhydride

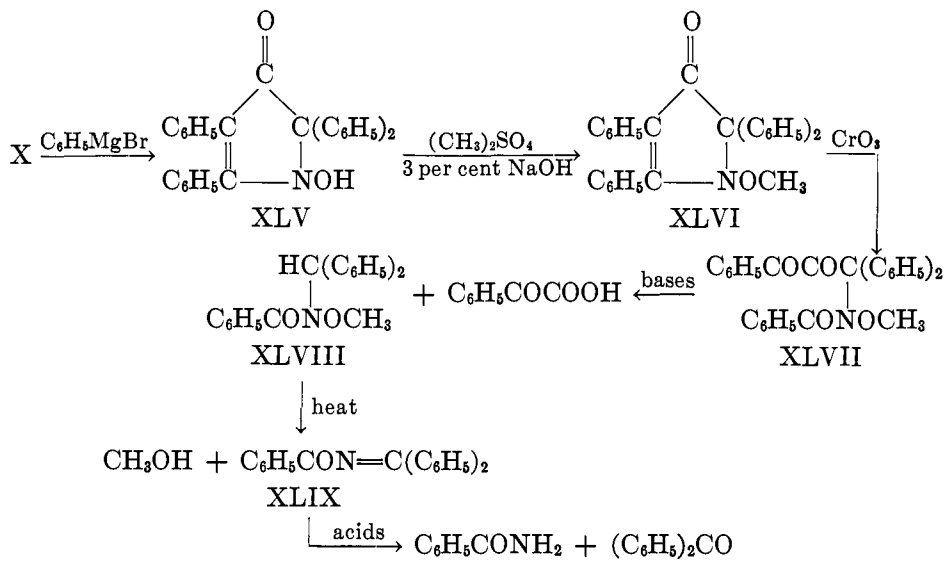
reacted with only 1 mole of Grignard reagent. Ozonolysis of XLV was inconclusive, but careful oxidation with chromic acid gave benzoic acid and a substance identified as $C_6H_5COCOC(C_6H_5)_2OH$. Though the formation of these products is not sufficient to establish the structure of the product, it is evident that the Grignard reagent does not react with the carbonyl group. Since the product obtained from the anhydride and the Grignard reagent was so unstable, it was converted to the stable methyl ether (XLVI) before degradation. The methyl ether has the composition $C_{29}H_{23}O_2N$, which is equal to that of the purple compound + C_6H_6 + CH_2. The ether is stable to acids and bases, and by careful oxidation with chromic acid it is possible to add two atoms of oxygen without disrupting the molecule. This oxidation product (XLVII) is readily attacked by bases, cleaving smoothly to benzoylformic acid and a nitrogen compound:

$$\underset{\text{XLVII}}{C_{29}H_{23}O_4N} + H_2O \longrightarrow C_6H_5COCOOH + \underset{\text{XLVIII}}{C_{21}H_{19}O_2N}$$

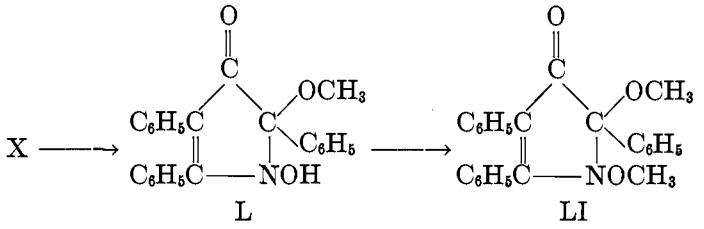
When this nitrogen compound (XLVIII) is heated above its melting point it loses the elements of methanol, giving another nitrogen compound (XLIX); the latter was hydrolyzed by acids to benzophenone and benzamide:

$$\underset{\text{XLVIII}}{C_{21}H_{19}O_2N} \longrightarrow CH_3OH + \underset{\text{XLIX}}{C_{20}H_{15}ON} \xrightarrow{H_2O} (C_6H_5)_2CO + C_6H_5CONH_2$$

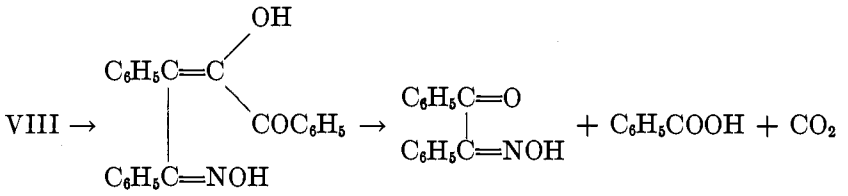
The formation of these degradation products constitutes a very complete proof that the purple compound is the cyclic nitrone (X).



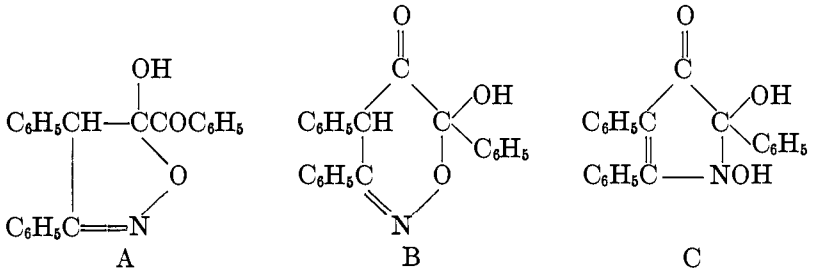
Thus the purple compound is a cyclic nitrone and it reacts with Grignard reagents by 1,3-addition. The nitrone, when heated with sodium methoxide and then acidified, adds a molecule of methanol. The product closely resembles in color and instability that obtained by adding the Grignard reagents, and, like the latter, it forms a very stable methyl ether. These products must therefore be L and LI, and the former is a result of 1,3-addition of methanol to the nitrone system.



It is not possible to say much regarding the mechanism by which the purple compound is formed from the oxime; the open-chain formula for the oxime is based largely on its oxidation to α-benzil monoöxime by sodium peroxide:



It is hard to reconcile these oxidation products with any other formula for VIII, but no open-chain derivatives of the oxime are known. All reagents that do not disrupt the molecule transform the oxime either to a cyclic isomer or to derivatives of cyclic isomers of the types A, B, or C.



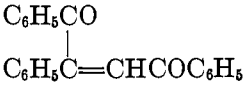
It may be that these forms A, B, and C are all present in the solutions of this very active substance; if so, X is merely the dehydration product of C.

The 1,3-addition reactions of the nitrones are, however, evidently subject to the same kind of hindrance as the 1,4-additions of the α,β-unsaturated ketones. For while the *N*-phenyl and *N*-benzyl ethers of diphenyl-

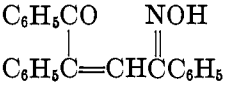
acetaldoxime do not combine with Grignard reagents or alkoxides, these purple nitrones, though equally highly substituted, still combine readily with both.

Recently Blatt (52, 53, 54), in a study of the action of hydroxylamine upon unsaturated 1,4-diketones, has discovered a very interesting case of ring-chain tautomerism involving a nitrone and an oxime. The action of hydroxylamine hydrochloride upon phenyldibenzoylethylene (LII) produces two isomeric compounds. One of these LV is bright yellow and is stable only in neutral and acid solutions; the other (LIII) is pale yellow, and is stable only in alkaline or pyridine solutions, although it can be obtained in an impure state by careful acidification of its solution in alkali. The isomers are interconvertible, but rapid conversion of LIII into LV is effected only by the halogen acids, and hence either LIII or LV can be obtained by acidification by proper acids of solutions containing the sodium derivative of LIII; the action of acetic acid produces LIII, while the action of hydrochloric acid produces LV.

The alkali-stable substance (LIII) is the monoöxime of LII, for it can be converted into benzoyl and acetyl derivatives from which it can be regenerated, and both the alkaline and pyridine solutions of LIII undergo the Beckmann rearrangement, giving LIV.



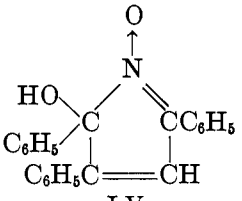
LII



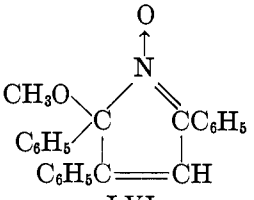
LIII

LIV

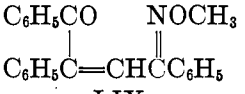
The acid-stable isomer is not a stereoisomer of LIII, but is the cyclic hydroxynitrone (LV). When LV is boiled with methanol and hydrochloric acid, the product is the methyl ether (LVI), and the latter on reduction with zinc and acetic acid gives the pyrrole (LVII). The reaction involves an initial 1,3-addition of hydrogen followed by a 1,4-elimination of methanol to give LVIII, which is then reduced to LVII.



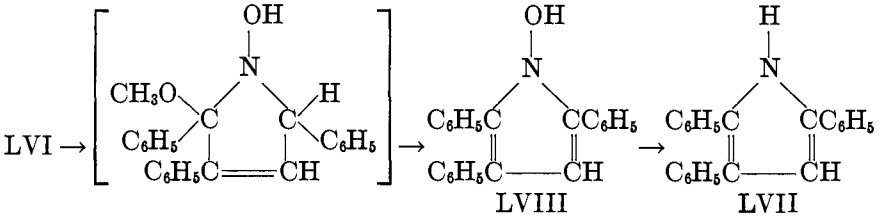
LV



LVI



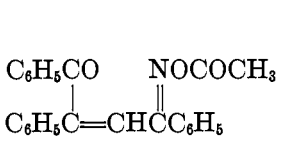
LIX



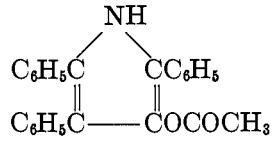
LVIII LVII

When LVI reacts with sodium–potassium alloy, or with Grignard reagents, the product is LVIII, which on further reduction with zinc and acetic acid gives the pyrrole (LVII).

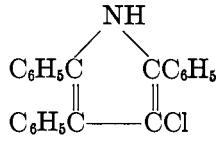
Alkylation of LIII in alkaline solution produces largely derivatives of LV. The action of methyl iodide and sodium methoxide upon LIII gives the methyl ether (LVI); while the action of methyl sulfate and sodium hydroxide produces LVI and also LIX, the methyl ether of the oxime (LIII). Acetylation of LIII by acetyl chloride produces LX, which is stable toward acetic anhydride and which is the acetate of LIII.



LX

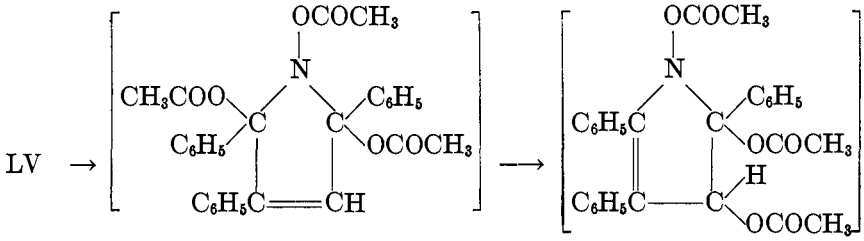


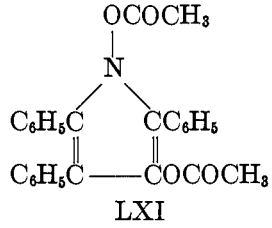
LXII



LXIV

Acetylation of LV by acetic anhydride produces LXI; the reaction is complicated but it apparently involves an initial 1,3-addition to the nitrone system, which is followed by a 1,3-shift and loss of acetic acid. The structure of LXI follows from its stepwise reduction through LXII to LVII.

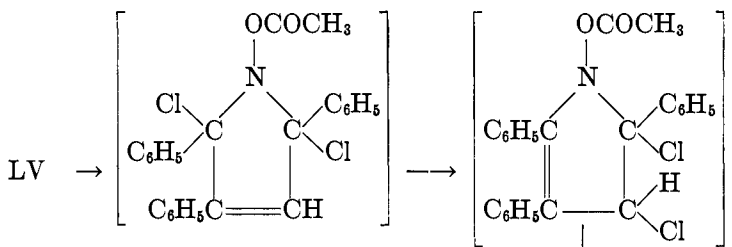


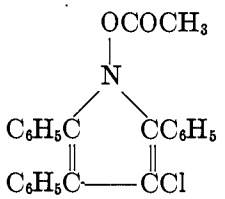


LXI

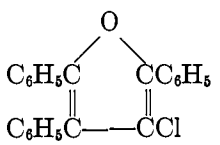
Acetylation of LV by acetyl chloride leads to three products. One of these is LXIII, which is also formed by a series of reactions beginning with 1,3-addition. The structure of LXIII follows from its stepwise reduction through LXIV to LVII. The other two substances produced by the action of acetyl chloride upon LV are the chlorofuran (LXV) and

diacetohydroxamic acid (LXVI). These two substances do not arise by a reaction of the chloropyrrole (LXIII), for the latter is unaffected by acetyl chloride.

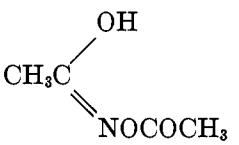




LXIII



LXV



LXVI

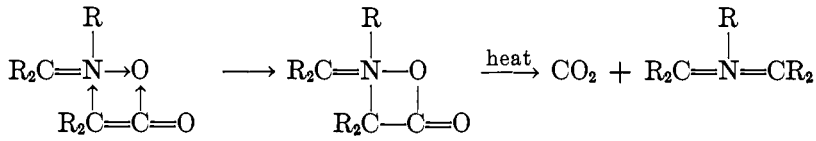
Hence the source of LXV and LXVI must be the open-chain oxime (LIII) or its acetate (LX), both of which give LXV and LXVI on treatment with acetyl chloride, while the only source of LXIII must be the nitrone (LV); these facts indicate that there is an equilibrium established between LV and LIII, or that LV and LIII are at least partly interconvertible, in the presence of acetyl chloride.

VIII. THE NITRENES OF STAUDINGER[3] (340): $R_2C{=}N{=}CR_2$ (R)

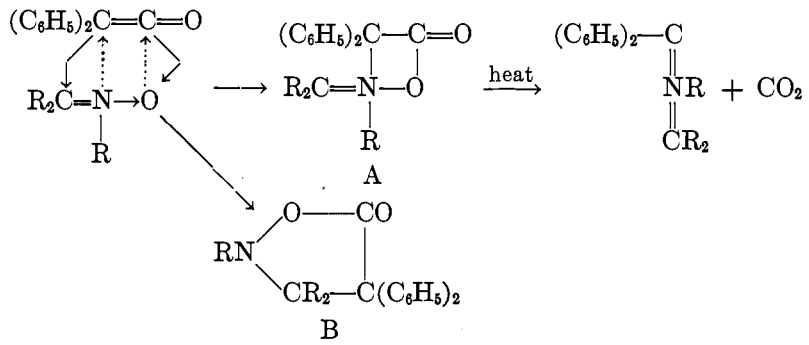
These compounds are not nearly so well known as the other compounds containing 1,3-systems. They are obtained by heating the addition prod-

[3] As stated later, it is very difficult to set up reasonable electronic formulas for the nitrenes; indeed, in view of the modern electronic concepts of the structures of organic compounds, one would be inclined to regard Staudinger's representations of these compounds with some suspicion, even after transforming them into electronic formulas, for a semipolar valence must, of necessity, be involved. While the proof

ucts obtained from ketenes and nitrones, whereupon carbon dioxide is eliminated:

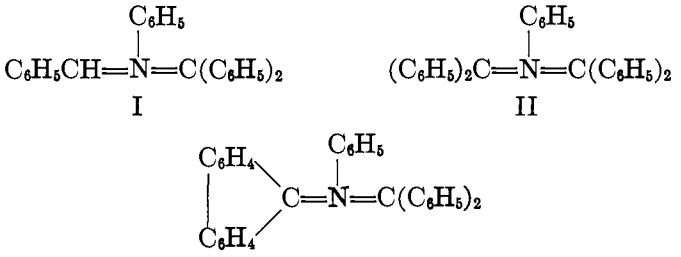


In some cases the nitrene is not the only product of the reaction between a nitrone and diphenylketene, for the two substances can combine in two different ways. Addition of the N→O group to the double bond of the ketene (shown by the dotted arrows) produces the intermediate A which, when heated, decomposes (like certain β-lactones) into carbon dioxide and the nitrene. The other product (B) is obtained by a 1,3-addition of the ketene to the nitrone (shown by the unbroken arrows). This product is stable, survives the heating which decomposes A, and is recovered from the mother liquors obtained from the crystallization of the nitrene.



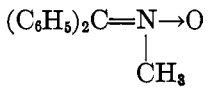
of this article was being read, there appeared a paper by Taylor, Owen, and Whittaker (354a) in which the whole question as to the structure of these compounds is reopened. The evidence which led Staudinger to choose the nitrene formula for "tetraphenylnitrene" was (*a*) the compound was colored and (*b*) reduction gave an amine, which was tertiary, since it could not be transformed into a nitroso compound. Taylor, Owen, and Whittaker have repeated Staudinger's synthesis of the nitrene, and they find that the substance is colorless when pure; moreover, on reduction it is readily transformed into an amine which does give a nitroso compound, therefore the amine is not tertiary. Hence they regard the "nitrene" as a cyclic imine analogous to formula VI (page 270), although they were unable to synthesize the imine by an independent method. The question as to the structure of the "nitrenes" must therefore be regarded as still unsettled, although the most recent structural evidence, together with the difficulties involved in transforming the nitrene formulas into electronic structures, makes it probable that these substances are, in reality, cyclic compounds.

In this way Staudinger prepared the pale yellow *N*-phenyltriphenylnitrene (I), the yellow *N*-phenyltetraphenylnitrene (II), and the green, very unstable diphenylenediphenyl-*N*-phenylnitrene (III).

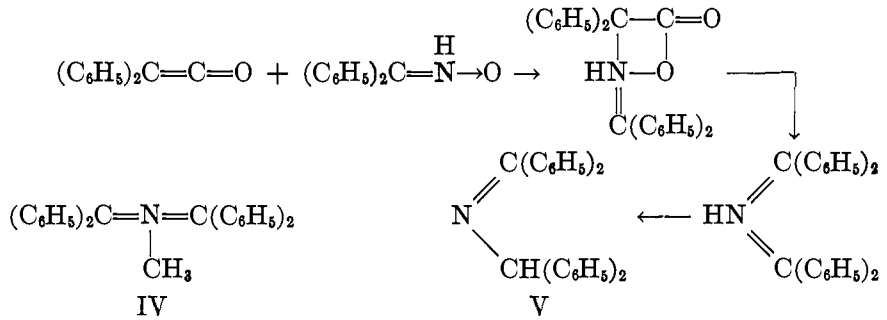


I II III

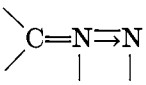
No nitrenes could be prepared in which the nitrogen atom held an aliphatic group. Diphenyl-*N*-methylnitrone,

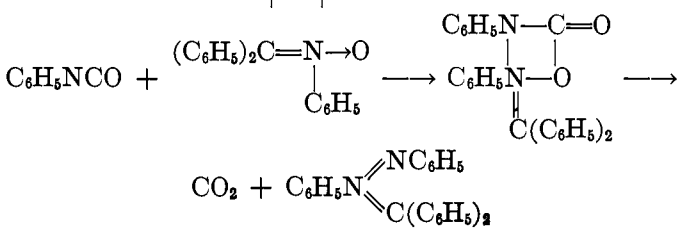


was inert to diphenylketene and none of the expected product (IV) was found. However, benzophenone oxime did react (in the tautomeric nitrone form) with diphenylketene to give not the nitrone, but a rearrangement product of it (V).

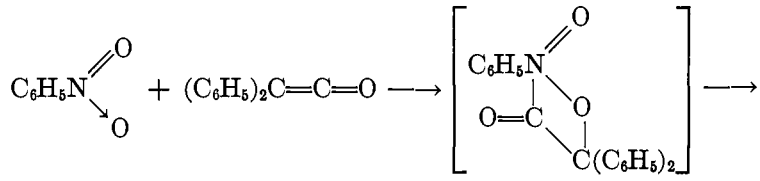


IV V

The addition of phenyl isocyanate to nitrones was expected to take a course similar to that of the addition of ketenes to nitrones, but no products containing the grouping  could be isolated.

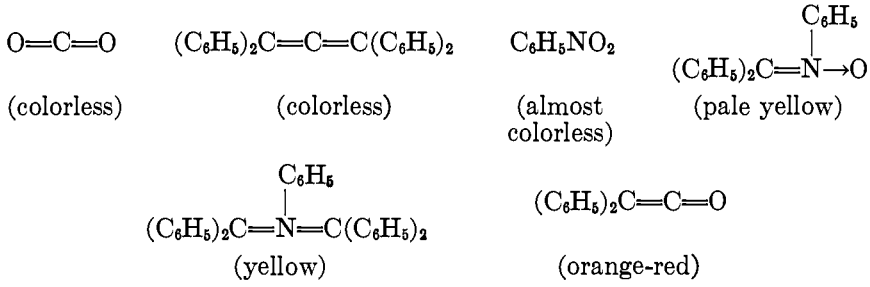


Staudinger regards the nitrenes as nitro compounds in which both oxygen atoms have been replaced by methylene residues. However, nitrenes cannot be prepared by addition of 2 moles of diphenylketene to a nitro compound with subsequent elimination of carbon dioxide, for this reaction leads to a ketone and an isocyanate:



$$(C_6H_5)_2CO + C_6H_5NCO + O$$

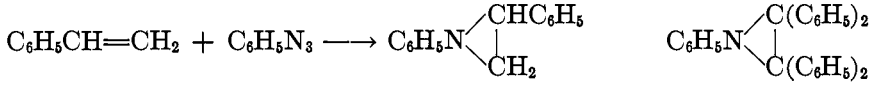
The nitrenes prepared by Staudinger were nicely crystalline substances; they showed no tendency to polymerize. They are more deeply colored than the nitrones, but not so deeply colored as the ketenes. Of the six compounds below, containing twinned double linkages, the ketenes are the most deeply colored.



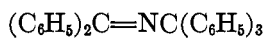
(colorless) (colorless) (almost colorless) (pale yellow)

(yellow) (orange-red)

It is very difficult to set up electronic formulas for the nitrenes; they may be three-membered rings such as VI, for such compounds were prepared by Wolff (384) by the action of azides upon other unsaturated compounds, or the nitrenes may even be some other rearrangement product such as VII, although the 1,3-additions which they show do not agree with such a structure.

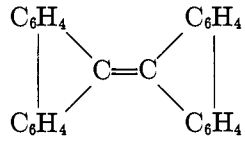


VI

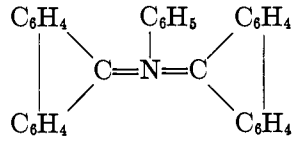


VII

Staudinger thinks the compounds are really nitrenes, chiefly because of the color and because the reaction between "Graebe's hydrocarbon" (VIII) and phenyl azide led to nitrogen and a green compound corresponding to a nitrene (IX).

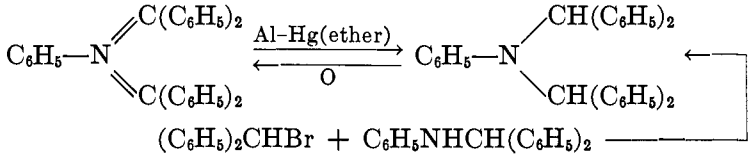


VIII

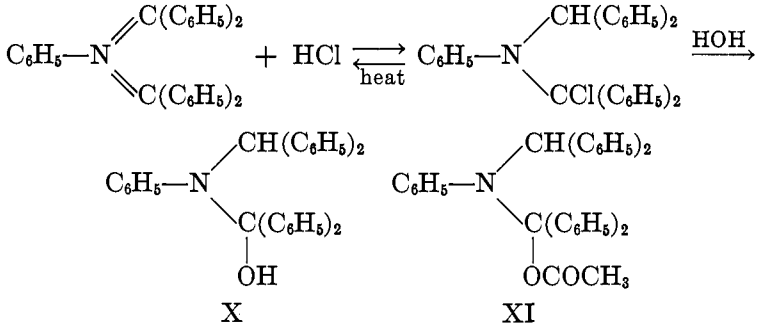


IX

Besides the color, the few known reactions of these substances indicate the nitrene formula; they are 1,3-additions, as would be expected from substances containing the nitrene linkage. Thus reduction leads to tertiary amines, and the structure of the amine obtained by reduction of pentaphenylnitrene was proved by an independent synthesis. The reduction product can be oxidized back to the nitrene by a number of oxidizing agents.



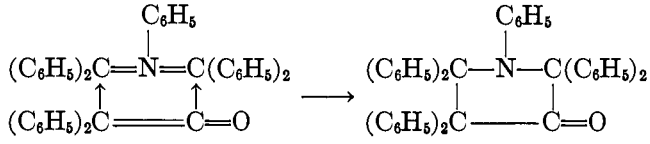
The addition of gaseous hydrochloric acid was formulated in a similar manner; the reaction could be reversed by heating, but the product was easily and quantitatively hydrolyzed to give X:



When boiled with acetic acid for a long time, pentaphenylnitrene gives a white, crystalline acetate, probably XI. The nitrene in chloroform solution adds one molecule of bromine or chlorine to form a colored, unstable

product. Only part of the halogen is removed from this product by treatment with alkali.

Among the unsaturated compounds, only diphenylketene reacted with nitrenes by addition. Only one molecule of the ketene added, and though the structure of the addition product was not determined, it is probably formed by a direct 1,3-addition. The reaction is reversed by heating.



IX. THE AZOXY COMPOUNDS: $RN{=}\overset{\overset{O}{\uparrow}}{N}R$

The chemistry of the azoxy compounds has been reviewed recently by Bigelow (47).

These compounds contain the system $-N{=}\overset{\overset{O}{\uparrow}}{N}-$; they are, however, the most stable of all compounds containing the 1,3-system, and it is doubtful whether any reaction of the azoxy compounds is known which can be interpreted as a 1,3-addition with any certainty. This may be due to the fact that the system is relatively unreactive, hence intermediate products resulting from 1,3-additions have been overlooked; this in turn is probably due to the fact that in recent years the chief interest in the azoxy compounds has been centered in their isomerism, rather than in the chemistry of the group $-N{=}\overset{\overset{O}{\uparrow}}{N}-$ (11, 165, 246, 380, 9).

Azoxybenzene was discovered by Zinin (389) as an intermediate product in the reduction of nitrobenzene with alcoholic potassium hydroxide. It is the most stable of all of the reduction products of the nitro compounds. Azoxybenzene is not attacked by dilute acids or bases; it is resistant to the action of oxidizing agents and fairly stable toward reducing agents; it is not attacked by hydroxylamine or by phenylhydrazine and it is inert toward many other reagents. Since the characteristic grouping of the azoxy compounds is one which would be expected to undergo 1,3-additions, it is likely that a careful reinvestigation of certain of the reactions of these compounds would result in the isolation of primary products formed by this mode of addition.

SUMMARY

The purpose of this review has been to present a summary of what is known about 1,3-systems which are capable of undergoing 1,3-additions and to bring to the attention of chemists the possibilities which these compounds offer as fields of research when considered from this point of view.

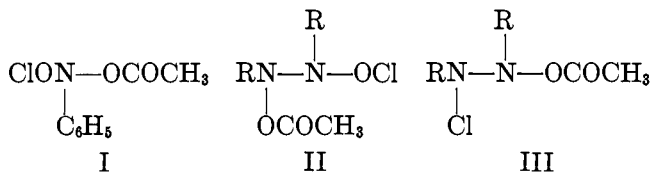
TABLE 1

	I CARBON DIOXIDE O=C=O	II ALDO KETENES RCH=C=O	III KETO KETENES R_2C=C=O	IV ALLENES R_2C=C=CR_2	V ALKYL ISOCYANATES RN=C=O
Hydrogen compound..	O=N=O | H Nitrous acid	RCH=N=O | H Tautomeric aldoximes	R_2C=N=O | H Tautomeric ketoximes	R_2C=N=CR_2 | H [Nitrenic "hydrocarbons"]	RN=N=O | H Diazo hydrates, tautomeric form
Alkyl compound.....	O=N=O | R Nitro compounds	RCH=N=O | R Aldo nitrones	R_2C=N=O | R Keto nitrones	R_2C=N=CR_2 | R Nitrenes*	RN=N=O | R Azoxy compounds
Acids.....	O=N=O | OH Nitric acid	RCH=N=O | OH Aldo nitronic acids (iso nitro compounds)	R_2C=N=O | OH Keto nitronic acids (iso nitro compounds)	R_2C=N=CR_2 | OH [Nitrenic acids]	RN=N=O | OH Nitramines (tautomeric form)

*See the note at the beginning of the section on nitrenes. These substances are probably cyclic compounds.

As Staudinger and Miescher (345) pointed out some time ago, all of the compounds containing these 1,3-systems can be regarded as derived from nitric and nitrous (tautomeric form) acids in the same way that ketenes, allenes, etc., may be regarded as derivatives of carbon dioxide. This is shown in table 1; the compounds in brackets are still unknown.

A great many representatives of these compounds are known, some only in tautomeric forms, but most of them were made either for purposes of studying phases of isomerism and tautomerism or in attempts to obtain compounds in which nitrogen was joined by five valences to carbon. Most of this work was done before the development of the modern electronic theory of valence and its application to organic reactions. Thus when Pfeiffer (284) coined the word "nitrone" for certain of these compounds, he had in mind certain similarities between the nitroso group and the carbonyl group; he did not emphasize that the real nitrone group was not the nitroso group, but the group $\diagup\!\!\diagdown C{=}N{\rightarrow}O$ and that it was this group, terminated by carbon and oxygen which, in many of its reactions, behaved as an extended carbonyl group. That the system could behave in this way is due of course to the variable valence of nitrogen, which makes possible the existence of stable compounds containing this linkage and enables these compounds to react as though the nitrogen were not there. There are apparently limits to the analogies shown in table 1, however, for it seems that real 1,3-additions occur only when at least one end of the system terminates in a carbon atom. Thus no 1,3-additions of the azoxy compounds are known with certainty, nor do the nitro compounds undergo this type of reaction, so far as is known. It is not difficult to understand this, for most of the reagents which add to heterogeneous unsaturated linkages are of the kind in which one of the parts added must almost necessarily become attached to carbon in order to form stable compounds. Thus acetyl chloride, which adds as a chlorine atom and an acetyl group, can readily form stable products by adding to a nitrone, for the acetyl group can become attached to oxygen and the chlorine atom to carbon; or this reagent could add to a nitrene, in which both groups become attached to carbon; but it could not form a stable product by adding to nitrobenzene to give I, or to an azoxy compound to give II or III, although the latter might conceivably be stable enough to be isolated under special conditions.



I II III

Nor can organometallic compounds be used with any certainty of obtaining definite results, for in order to obtain the primary products the addition must be so rapid that other reactions (reduction, condensation, etc.) do not occur to any appreciable extent and the primary product must it-

self be stable toward the organometallic compound. This is shown by the fact that the reactions between Grignard reagents and tertiary nitro compounds or azoxy compounds are very complicated and consist to a large extent in reduction. The one process which is apparently applicable to all these 1,3-systems is reduction, but in this case the results are not decisive as to the mode of addition because the primary products undergo tautomeric changes which cannot be followed. But it would seem that by introducing 1,3-systems into new sorts of structures it might be possible to obtain compounds in which the addition of many reagents could be definitely followed by isolating stable intermediates. An example of this line of attack is found in the study of the cyclic nitrones by Kohler and Blatt, in which the carbon and nitrogen atoms of the nitrone system were included as part of a ring. The isatogens likewise offer this same structural modification for in these compounds part of the nitrone system is likewise included in a ring.

The 1,3-systems also offer interesting possibilities for the study of conjugation. In the isatogens the nitrone system is conjugated with a carbonyl group, but as yet no 1,5-additions of these compounds have been reported. The isatogens show some similarities with the quinones—they are deeply colored, form "quinhydrones" etc.—and Pfeiffer called them "meta-quinoids." The analogy is not valid for if one properly considers the whole nitrone system as equivalent to the carbonyl group, then these compounds are not meta-quinoids, but are ortho-quinoids, and as such the analogy becomes valid and complete and is a striking piece of evidence that the nitrone system really is, in effect, an extended carbonyl group. It would be interesting to build a "para-isatogen," that is, the vinylog of an isatogen, for it would be predicted that such a compound would exhibit many of the properties of *p*-quinones.

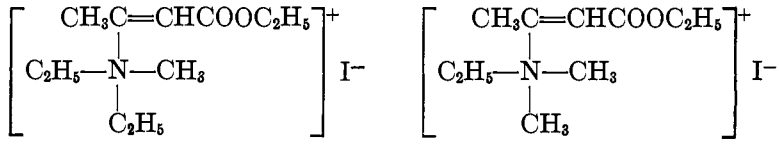
A study of these systems which undergo 1,3-additions may lead to results which can be applied in other fields. For example, Robinson in 1916 (306) alkylated β-diethylaminocrotonic ester with methyl iodide. The products were methylacetoacetic ester and diethylammonium iodide, and Robinson formulated the reaction as a primary 1,3-addition, as follows:

$$\begin{array}{l} CH_3C{=}CHCOOC_2H_5 \\ \quad\quad\vert \\ \quad N(C_2H_5)_2 \end{array} + CH_3I \longrightarrow \left[\begin{array}{l} CH_3CCH(CH_3)COOC_2H_5 \\ \quad\quad\Vert \\ \quad N(C_2H_5)_2 \end{array}\right]^+ I^- \xrightarrow{H_2O}$$

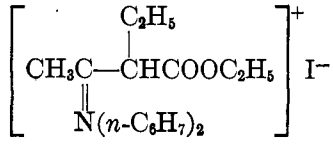
$$[(C_2H_5)_2NH_2]^+I^- + CH_3COCH(CH_3)COOC_2H_5$$

While this reaction could be regarded as an addition centering entirely around the nitrogen atom, followed by a migration of the methyl group,

such a formulation would involve a preferential migration of the methyl group from an intermediate such as A.



A B



C

In a recent study, Lauer and Lones (205) have subjected dimethylaminocrotonic ester to the action of ethyl iodide. As the intermediate (B) corresponding to A has both methyl and ethyl groups attached to the nitrogen, the former should rearrange as does the latter, and the product should be the same from both A and B. Actually the second reaction gave ethylacetoacetic ester and dimethylammonium iodide. A number of other alkylations of this type were studied by Lauer and Lones, and in every case the R group of the alkyl iodide was the one which was found present in the final product, the alkylated acetoacetic ester. When β-di-*n*-propylaminocrotonic ester was subjected to the action of ethyl iodide, the intermediate product (C) was actually isolated and shown to give ethyl acetoacetic ester upon hydrolysis. These results lend strong support to Robinson's mechanism for the action of alkyl iodides upon β-dialkylaminocrotonic esters and exclude the possibility that the mechanism involves addition at the nitrogen atom alone. Robinson's mechanism can of course be transferred to the ordinary alkylation of acetoacetic esters; here oxonium salts would be the intermediates.

In the case of the nitrones and similar systems, the 1,3-additions involve an (inner) ion reacting with a non-ionic substance to give a non-ionic product; in the alkylation of the dialkylaminocrotonic esters, the 1,3-additions involve two non-ionic substances reacting to produce an ion. In the former case, the element with the variable "valence" is in the middle of the 1,3-system; in the latter case, it is at one end of the system.

Some of the material covered by this review has for a number of years formed a part of an advanced course in organic chemistry given by the author for graduate students, but the whole field of 1,3-systems formed the subject for discussion and presentation before the Organic Seminar at

the University of Minnesota during the spring quarter of 1935. The author has made use of the papers presented by the members of the seminar as follows: Mr. W. B. Pings, "Aliphatic Diazo Compounds and Azides"; Mr. L. I. Hansen, "*N*-Ethers of Oximes"; Mr. F. Schmalz, "Isatogens"; Mr. Paul Johnson, "Isoxazoline Oxides"; Mr. H. Hochman, "Nitrenes"; and Mr. J. A. Anthes, "Azoxy Compounds." The author is particularly indebted to Mr. R. W. Raetz, who typed the manuscript and compiled the bibliography.

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