

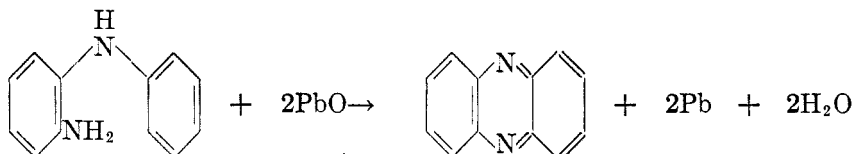
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DIRECT RING-CLOSURE THROUGH A NITRO GROUP IN CERTAIN AROMATIC COMPOUNDS WITH THE FORMATION OF NITROGEN HETEROCYCLES: A NEW REACTION

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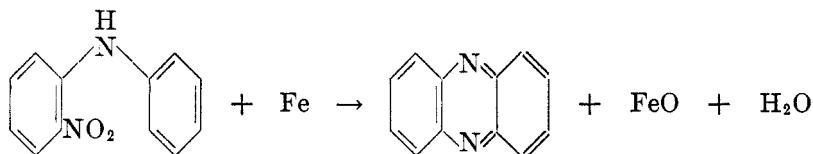
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The possibility of synthesizing a nitrogen heterocycle by acting on a nitro compound in such a manner as to effect direct ring closure first suggested itself as a result of our experience with the Fischer and Heiler (1) method for the preparation of phenazine. Their reaction involves oxidation of 2-aminodiphenylamine by dry distillation with litharge:



Our experience with this reaction agreed with the observations of McCombie, Scarborough, and Waters (2), who reported yields "always of the order of 5%." Consideration of the synthesis led to the idea that the whole procedure of reduction of the 2-nitrodiphenylamine to the amino compound followed by oxidation of this to phenazine might be replaced by a new reaction: a reduction of the nitro compound which gave no opportunity for amine formation, but which would take place under conditions favorable to direct ring closure. The choice of a reagent to be employed in attempting to carry out this idea fell upon metallic iron, since we had previously found that Fe₂O₃ could be advantageously substituted for litharge in the Fischer-Heiler synthesis. It seemed not improbable that iron, alone, acting upon the nitro compound at a sufficiently high temperature might produce the same thermostable compound, phenazine, as is produced by the action of iron oxide on the amino compound. This was found actually to occur, and the preliminary results were first made known in the form of a patent (3). The present paper amplifies and extends the reaction, and presents it from the standpoint of five well-differentiated types. The first of these illustrates the general nature of the reaction:¹

Type A. Reactions involving the elimination of oxygen and water only.



¹ It must be noted that throughout these reactions we have not determined what oxide or oxides are formed; FeO may be the first product, or varying proportions of Fe₂O₃ and Fe₃O₄ may arise; the equations are arbitrarily balanced.

The ease with which the reaction takes place and the stability of the products permit reductants of a considerable range of activity to produce phenazines both from 2-nitrodiphenylamine and from some of its substitution products. A few milligrams of red phosphorus, as an extreme example, reacted so violently with a corresponding quantity of 2-nitrodiphenylamine as to take fire, but phenazine enough for identification sublimed. As an opposite extreme, even an activated decolorizing carbon was found capable of effecting the ring closure with little difficulty. Sulfur likewise yielded phenazine. Granulated lead compared favorably with iron and, in some instances, appeared the better reagent. Some usually quite active metallic reductants, on the other hand, reacted with 2-nitrodiphenylamine very feebly if at all. Among these were aluminum, amalgamated aluminum powder, zinc, magnesium, and calcium.

Iron, lead, and other reductants thus far used in preparing phenazines by nitro group ring closure seem not to react under the given conditions with the water formed in the reaction. The presence of calcium oxide or other dehydrating agent effected no apparent improvement in the yield of phenazine, and heating 2-nitrodiphenylamine with dehydrating agents alone (calcium chloride, calcium oxide, zinc chloride, and phosphorus pentoxide) failed in every instance to give any evidence of the formation of phenazine or phenazine oxide.

Attempts to carry out the reaction in a closed system resulted in a considerable amount of highly-colored material and little or none of the desired phenazine. Hydrogen reduction, due to reaction of iron with the confined steam, appeared the most probable cause of failure under these conditions.

Numerous substituted phenazines can be obtained in varying yield from the correspondingly substituted 2-nitrodiphenylamines without any apparent substantial modification in the reaction, which is designated Type A, to differentiate it from other forms to be described.

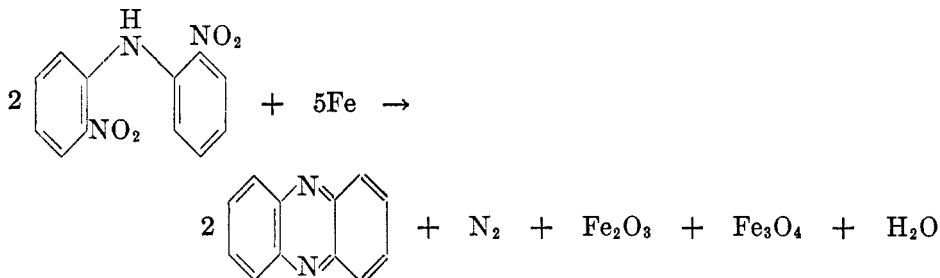
The additional nitro group of 2,4-dinitrodiphenylamine and of 2,4-dinitro-4'-hydroxydiphenylamine rendered the reaction so violent that no product could be isolated. Less violent reactions of both compounds were obtained, however, in preliminary experiments with paraffin as a diluent, and further work is planned to establish the nature of the products.

In general, it seems possible that a large proportion of the ring closures that can be carried out by oxidation of an amino group can be brought about more directly and in many instances in improved yield, by operating on the corresponding nitro compounds with suitable oxygen abstractants in such a manner as to avoid supplying hydrogen to the reaction.

The experimental part of this paper gives details of the synthesis of 2-chlorophenazine and of 2-methoxyphenazine as further examples of the Type A reaction.

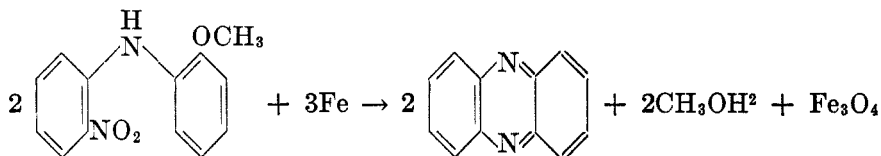
In a recent communication P. Z. Slack and R. Slack (4), have both confirmed and extended our own findings. These authors also rediscovered independently two peculiarities of the reaction which, though observed by us before filing the patent application, could not find place in a statement restricted to the disclosure of potentially industrial processes. These independent observations, both of which go somewhat beyond our own, are more specifically acknowledged below under the topics to which they apply.

Type B. Reactions in which a substituent is eliminated. A reaction of this type was first encountered in the very curious behavior of 2,2'-dinitrodiphenylamine. On heating with a large excess of iron filings in the absence of a diluting solvent, this compound gave a relatively poor yield of unsubstituted phenazine, together with elementary nitrogen.



The volume of the gas evolved corresponded considerably more closely with the elimination of one of the two nitro groups than did the quantity of phenazine isolated. The comparative rarity of an elimination of elementary nitrogen in organic syntheses other than those involving diazonium compounds makes the course of the reaction more obscure. Slack and Slack (4) make the same comment. It is possible, however, that the second nitro group is eliminated as the elements of HNO_2 , and that the nitrogen arises from reaction of these with the hot iron.

The loss of a 2'-substituent was again observed in an attempt to prepare 1-methoxyphenazine from 2-methoxy-2'-nitrodiphenylamine. Unsubstituted phenazine was again the only solid product isolated:



This loss was not entirely unforeseen, however, in that McCombie, Scarborough, and Waters (2) had observed the loss of the same substituent from 2-amino-2'-methoxydiphenylamine in the lead oxide procedure. Since the loss of the 2'-methoxyl group was not mentioned in our patent (3), due to its unimportance therefor, Slack and Slack (4) were unaware of our experience with it. They not only made the same observation completely independently, but extended the reaction to show further that alkoxy groups generally are eliminated in the same way. We do not feel, however, that any "prior reduction" need be postulated, whatever the mechanism of the reaction may be.

Ferrous oxalate (source of active ferrous oxide) as oxygen abstractant for nitro-group ring closures of types C and E. Metallic iron,³ though often not the most satisfactory reagent, has thus far brought about the ring closures designated as

² Formation of CH_3OH assumed; not proved by isolation.

³ "Activated" iron was not employed.

Types A and B, but has consistently refused to induce ring closures of Types C and E, described below. Iron was not used in our one Type D ring closure (that of unsubstituted benzocinnoline), but Slack and Slack (4), in their independent discovery of the same extension of the basic reaction, used "reduced iron."

A reductant capable of bringing about reactions of Types C, D, and E (as well as of Types A and B) was ultimately found, however, in ferrous oxalate; a reagent which has not, so far as we know, hitherto found use in organic synthesis.

Though very stable at room temperatures, and apparently quite free from the tendency of most ferrous salts to combine with atmospheric oxygen, ferrous oxalate decomposes when heated to a suitable temperature (widely misstated as between 150° and 160°) to yield carbon monoxide and dioxide and a pyrophoric form of ferrous oxide; the last-named compound being, of course, the actual oxygen-abstracting agent sensitive enough to induce the reactions which iron, lead, etc., had failed to bring about. Since the nitro compound can be thoroughly mixed with the oxalate, either dry or in a suitable solvent of sufficiently high boiling point, the tendency of the ferrous oxide to ignite on exposure to air causes no difficulty; the pyrophoric material is in contact, at the moment of its formation, with the nitro compound upon which it is to act. Also, the carbon monoxide and dioxide from the oxalate undoubtedly have some protective effect.

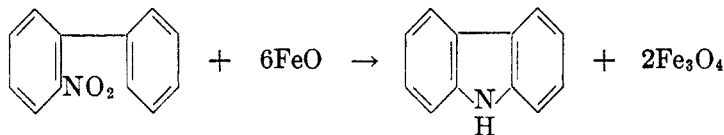
The temperature range 150° to 160°, often given as that within which ferrous oxalate yields oxides of carbon and ferrous oxide, is actually the range observed by J. von Liebig (5) as that of a partial dehydration of the dihydrate, $\text{FeC}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$, to a sesquihydrate, $(\text{FeC}_2\text{O}_4)_2 \cdot 3\text{H}_2\text{O}$. A paper (6) of the same early date indicates a considerably higher temperature (about 194°) is required to break up the oxalate radical, and also states that the pure salt cannot be obtained anhydrous.

We have found that anhydrous FeC_2O_4 can be prepared, however, if oxidation is prevented by suspending the hydrated salt in mineral oil and the heating carried out under proper conditions. The anhydrous oxalate is preferable when the evolution of the water content of the dihydrate is a disadvantage. Anhydrous ferrous oxalate has, in some instances, lost its activity when held for long periods. Whether the anhydrous oxalate will remain active indefinitely when kept under oil has not yet been determined.

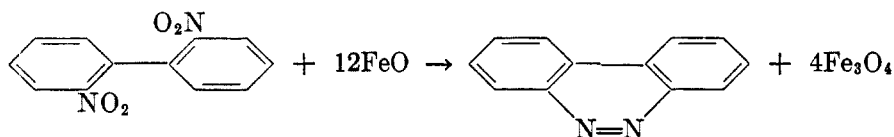
A wide divergence in activity among commercial preparations of ferrous oxalate has been encountered. Some lots have appeared to be at least partially dehydrated, and some have been found to contain varying quantities of contaminants. None of the commercially available ferrous oxalate, though obtained from a number of standard sources, has been found to be labeled definitely as $\text{FeC}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$. In view of these variations in the commercial product, the exceedingly simple preparation of the reagent from ferrous sulfate and oxalic acid should probably be carried out in the laboratory. Alkali-metal or ammonium oxalates form complexes with ferrous oxalate which are both difficult to wash out of the precipitate and are, in addition, very easily oxidized by atmospheric oxygen. Neither these nor ferrous ammonium sulfate should be used in the preparation of the ferrous oxalate reagent. Precipitation from ferrous sulfate with oxalic acid

has thus far yielded a dependable form of the reagent. The presence of small quantities of the complex salts above mentioned seems a very probable cause of some of the variations in behavior of the commercial product.⁴

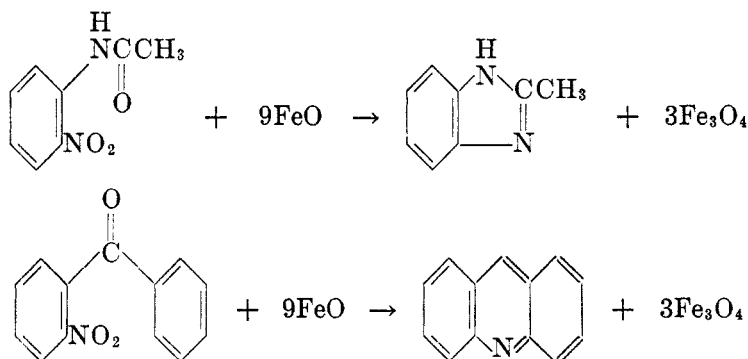
The type C reaction. This form of nitro group ring closure, the first in which no hydrogen is eliminated from the nitro compound, is exemplified in the formation of carbazole from 2-nitrobiphenyl.



The type D reaction. Unique among the nitro group ring closures thus far effected, in that the ring is closed between nitrogen and nitrogen rather than between nitrogen and carbon, this type of reaction has been encountered by us only in the formation of 3,4-benzocinnoline (with no trace of the compound sought) in an attempt to obtain 4-nitrocarbazole from 2,2'-dinitrobiphenyl. Though of much scientific interest, this observation was regarded as negative from the viewpoint of our patent (3) and was not mentioned therein. The finding of Slack and Slack (4) that our reaction "also provides a new process for the synthesis of benzocinnolines" represents, therefore, a quite independent discovery by them of the benzocinnoline ring closure; too, they found that "reduced iron" will effect the reaction, carried out by us with ferrous oxalate. This latter may be formulated:



Reactions of type E. These reactions, which involve the removal of a carbonyl oxygen atom as well as the oxygen atoms of the nitro group, are illustrated in the synthesis of 2-methylbenzimidazole and of acridine.



⁴ Since the oxalate is too costly a source of ferrous oxide for most industrial uses, reduction of higher oxides by gases (producer gas or water gas) has been given some attention.

The reactions selected as experimental illustrations of those aspects of the nitro group ring closure dealt with in this paper are not violent when carried out with the quantities and in the proportions specified. The large excess of the reductant which has always been used when iron or lead was the reagent of choice effects a considerable dilution; and in the use of ferrous oxalate, relatively great dilution is inherent in the molecular weight and bulk of the reagent itself.⁵ Caution may be advisable, however, in the use of smaller excesses of the reductants (especially if these be very finely divided, or pretreated to activate them), or in the use of nitro compounds the properties of which, with respect to the nitro group ring closure, are not known. The extremely vigorous reaction of 2,4-dinitrodiphenylamine and of its 4'-hydroxy derivative have already been noted with the Type A reactions. The *dry* reaction of both these 2,4-dinitro compounds with ferrous oxalate, though only about 0.2 g. of either nitro compound was used, was still more violent, ejecting the pyrophoric FeO from the test tube as a small shower of sparks.

EXPERIMENTAL

*Phenazine.*⁶ One hundred grams of 2-nitrodiphenylamine was thoroughly mixed with 1 kg. of 20-mesh degreased iron filings in a 1-liter long-neck round-bottomed flask. The mixture was then heated in an oil-bath, which was brought up to a maximum temperature of 300°. Heating was continued for approximately 30 minutes after the bath had reached 280°; this was about 10 minutes longer than the time required for the disappearance of all red color in the material on the side walls.

Complete extraction of the reaction mixture with ether gave 61 g. of dark brown solid, which on vacuum distillation followed by recrystallization from benzene (Norit) gave 38.5 g. (46%) of light yellow product melting at 174.7-176.3°, (cor).

Anal. Calc'd for C₁₂H₈N₂: N, 15.6. Found: N, 15.5.

Phenazine from 2-methoxy-2'-nitrodiphenylamine. Five grams of 2-methoxy-2'-nitrodiphenylamine was mixed with 50 g. of 20-mesh degreased iron filings in a round-bottomed flask, and the whole heated 30 minutes in an oil-bath at 280-290°. Extraction with ether followed by recrystallization from benzene of the residue left from evaporation of the ether gave 0.7 g. of unsubstituted phenazine, not depressing the melting-point of phenazine made from 2-nitrodiphenylamine. No evidence of any 1-methoxyphenazine was found.

Phenazine from 2,2'-dinitrodiphenylamine. One gram of 2,2'-dinitrodiphenylamine was heated 20 minutes with 10 g. of 20-mesh degreased iron filings in an oil-bath maintained at 280-290°. The reaction was more vigorous than that with 2-nitrodiphenylamine, and a gas

A ferrous oxide giving a yield of carbazole from 2-nitrobiphenyl essentially the same as that obtained in the laboratory by the use of ferrous oxalate has been produced by gas reduction of higher oxides.

Whether the oxygen-abstracting capacity of ferrous oxide is represented by $6\text{FeO} + \text{O}_2 \rightarrow 2\text{Fe}_3\text{O}_4$ or by $4\text{FeO} + \text{O}_2 \rightarrow 2\text{Fe}_2\text{O}_3$ has not been determined, since it has not been necessary to avoid an excess.

⁵ About 540 g. of the dihydrate, or 432 g. of the anhydrous FeC₂O₄, is required, for example, to provide FeO to combine as Fe₃O₄ with the one gram-atom of oxygen removed by the reductant from 1 mole (about 214 g.) of 2-nitrodiphenylamine.

⁶ Whether improved yields are possible with this preparation or others through the use of more finely divided iron, or of iron or other metals pretreated in any way, as by reduction, remains to be determined, as does the effect of holding the temperature down to the lowest range in which reaction is initiated.

was evolved. This gas was collected over water and subjected to tests to determine its nature: red phosphorus placed on an electrically warmed copper plate in the gas did not react with it; a bright copper coil electrically heated to a dull red glow for 10 minutes within the gas showed no change, none of a measured volume of oxygen was taken up by it, nor did the gas react with $\text{Ba}(\text{OH})_2$ solution. Hence it could only be nitrogen. The amount evolved, corrected for pressure and temperature, corresponded to 83.6% of that calculated for elimination of the nitrogen of one nitro group per mole of the 2,2'-dinitrodiphenylamine. Isolation of the organic product by extraction of the reaction mixture, vacuum sublimation of the extract, and recrystallization from benzene gave 0.1 g. of phenazine, identified by mixed melting point. As in the preceding reaction of 2-methoxy-2'-nitrodiphenylamine, there was no evidence of the formation of any measurable quantity of a substituted phenazine.

2-Chlorophenazine. The preparation of this compound by reacting 4-chloro-2'-nitrodiphenylamine with iron filings gave comparatively poor results; those with 4-chloro-2-nitrodiphenylamine were distinctly better.

As with the unsubstituted intermediate, 100 g. of 4-chloro-2-nitrodiphenylamine was heated in a 1-liter flask with 1 kg. of 20-mesh degreased iron filings by an oil-bath held at 280–295° for about 40 minutes. The reaction is somewhat more vigorous than that with 2-nitrodiphenylamine; the internal temperature reaches a maximum of 348° and there is a copious evolution of fumes. Ether extraction of the reaction mixture followed by sublimation at 1 mm. from an oil-bath at 115° gave 30.0 g. of sulfur-yellow 2-chlorophenazine mixed with a small amount of darker orange material; this combined product melted at 136–139° after softening at 133°. Recrystallization from methanol gave 25.8 g., (30%), melting at 137.7–138.9°, cor. McCombie, Scarborough, and Waters (2) give 139° as the m.p. of 2-chlorophenazine.

Anal. Calc'd for $\text{C}_{12}\text{H}_7\text{ClN}_2$: C, 67.2; H, 3.27; Cl, 16.5; N, 13.1.

Found: C, 67.5; H, 3.29; Cl, 16.9; N, 12.9.

*2-Methoxyphenazine.*⁷ Eight grams of 4'-methoxy-2-nitrodiphenylamine was mixed with 20 g. of anhydrous ferrous oxalate and 80 g. of granulated lead, and the whole heated for 30 minutes in a bath at 265–282°. The reaction is vigorous, with the evolved water issuing as steam. Vacuum distillation applied to the entire reaction mixture gave 3.45 g. (49%) of yellow material melting at 119°. This on recrystallization from water, or better, chromatographic adsorption on alumina, gave pale yellow crystals melting at 123.1–123.7°, cor. McCombie, Scarborough, and Waters (2) give 126° as the m.p. of 2-methoxyphenazine.

Anal. Calc'd for $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}$: C, 74.3; H, 4.8; N, 13.3; CH_3O , 14.8.

Found: C, 74.3; H, 4.7; N, 13.0; CH_3O , 14.7.

Carbazole. One gram of 2-nitrobiphenyl was thoroughly mixed with 12 g. of ferrous oxalate dihydrate, and the mixture heated in an oil-bath for 30 minutes at an internal temperature of 205–215°. Water was given off from the oxalate during the heating, an inconvenience causing loss of material which can be obviated by the use of anhydrous oxalate.

A total of 0.45 g. of carbazole sublimed from the reaction mixture; boiling the reaction residue with toluene, and recrystallizing the extracted material from the same solvent yielded a further 0.075 g. (Total yield 63%). The product was identified by its m.p., 240°, not depressed by mixture with an authentic specimen of carbazole, as well as by the usual color reactions, odor, and crystalline form.

3,4-Benzocinnoline. Five grams of 2,2'-dinitrobiphenyl was thoroughly mixed with 50 g. ferrous oxalate dihydrate⁸ and heated in an oil-bath to an internal temperature of 200°,

⁷ We found that admixture of granulated lead with the reaction mixture gave better results than did the oxalate alone, in part due to better heat conduction through the mixture.

⁸ This is the only instance observed by us, so far, in which the anhydrous oxalate appears to give less satisfactory results than does the dihydrate. The preponderance of the dihydrate in our reported procedures is due to the fact that most of these were made before we discovered the possibility of using the anhydrous form.

which was gradually increased to a maximum of 245° over a period of about 50 minutes. Evolved water was conducted off by a side arm. The flask was stoppered and allowed to cool to room temperature; the contents could then be poured out in the air without igniting. The precaution of allowing the mixture to cool must be taken before subjecting it to ether extraction, since the pyrophoric FeO can produce vigorous sparking. Thorough extraction with ether produced 1.7 g. (46%) of yellow-brown crude product, melting at 130–148°. This on two recrystallizations from 50% alcohol (Norit) gave 0.64 g. (17%) of yellow crystals with a slight greenish tinge, melting at 154.7–156.3°, (cor.). Täuber (7) gives 156° as the m.p. of 3,4-benzocinnoline.

Anal. Calc'd for $C_{12}H_8N_2$: N, 15.6. Found: N, 15.8.

2-Methylbenzimidazole. A mixture of 1.8 g. of 2-nitroacetanilide and 18 g. of ferrous oxalate dihydrate was heated to an internal temperature of from 220° to 225° and kept at that temperature for about 30 minutes. The cooled reaction mixture was extracted with hot alcohol, yielding yellow-brown amorphous material containing a lighter-colored crystalline substance. Boiled with several small portions of water, this gave traces of brown insoluble matter and a yellow solution, paler after treatment with Darco. Concentrated to crystallization, the solution yielded rosettes of stubby, very slightly yellowish needles, m.p. 173.5°, unchanged by mixture with authentic 2-methylbenzimidazole; yield, 0.51 g. (42%).

Acridine. The few milligrams of 2-nitrobenzophenone which were available reacted with the usual excess of ferrous oxalate dihydrate (about 20%) to yield a small quantity of a sublimate of flaky white crystals of which the melting point was 105–106°. These gave a strong bluish fluorescence in alcoholic solution, and fluoresced quite strongly in the solid state when subjected to a high-frequency glow discharge under 1 mm. pressure, emitting light of a pale blue color. Their vapors were highly irritating to eyes and nostrils. Although loss of the product prevented taking a mixed m.p., the agreement of the properties described with those of acridine, and the method of synthesis would seem to establish a strong probability for identity of the product with acridine.

Anhydrous ferrous oxalate. A charge of 432 g. of ferrous oxalate was placed in a three-neck flask fitted with a mechanical stirrer, thermometer, and descending condenser. Light mineral oil was added until there was a layer about 1 cm. deep above the surface of the oxalate. The stirrer was started, and the flask heated in an oil-bath. (If stirring is not adequate, or if the heating is uneven, partial decomposition of the oxalate occurs.)

Water was not evolved until an internal temperature of about 176° was reached (oil-bath at 200°); at this point evolution of steam set in. The internal temperature was gradually raised to a maximum of 195° over a period of 80 minutes. The evolution of steam, which had increased at first, fell off during the last 30 minutes, and had practically ceased by the end of the 80 minutes. A total of 75 cc. of water was collected, as against the theory of 86.4 g. based on the formula $FeC_2O_4 \cdot 2H_2O$, but there was a very considerable holdup on the sides of the 5-l. flask used. The flask was opened to the air while still hot, to permit the escape of this water.

The larger part of the dehydrated material was allowed to remain under the surface of the oil, with the object of taking samples for use as need arose, and thus determining whether activity is lost with the passage of time. A sample for analysis was secured by filtering it off from the oil, washing it thoroughly with chloroform followed by benzene, and drying it in a vacuum at room temperature out of light.

Anal. Calc'd for FeC_2O_4 : C, 16.7; Found: C, 16.6.

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SUMMARY

A ring closing reaction of certain aromatic nitro groups, brought about by abstracting the nitro group oxygen atoms under conditions preventing their replacement by hydrogen and resulting in heterocycles of which the nitro group nitrogen atom is a member, is shown to occur in several variations, illustrated by closures of the phenazine, carbazole, benzocinnoline, benzimidazole, and other rings.

For nitro group ring closures effected poorly or not at all by iron or lead, use of ferrous oxalate (a source of pyrophoric ferrous oxide at moderately high temperatures) is introduced. It has been possible to obtain this oxalate in an anhydrous state, and use of this new reagent has been found to be advantageous in some instances.

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