THE CHEMISTRY OF THE PHTHALAZINES[1]

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CONTENTS

[1] The name phthalazine was first used by Liebermann (92).

I. INTRODUCTION

Although the chemical literature contains many articles reporting research involving the preparation and properties of the phthalazines and their oxygenated derivatives, the phthalazones and phthalhydrazides, there is no one paper or series of papers to which one can turn for a survey of the field. Much of the published data is of an incomplete nature, since the compounds in question have frequently arisen incidental to other research; but despite this often subsidiary character, the questions of structure and reactivity raised by all three classes of substances are of more than passing interest. Relatively few investigators have devoted any major effort to the elucidation of such problems; and while the work of such men as Gabriel, Curtius, Rowe, Rădulescu, Drew, and others has been very comprehensive, within narrow limits, no comprehensive study has been published for the series as a whole. The majority of investigators have been content to prepare a number of related compounds, record their properties, and pass on to new work. Those studies dealing with the influences governing formation of the azine ring are tantalizingly incomplete, and studies of mechanism are all but non-existent.

It is the purpose of the present paper to summarize the more important phases of synthesis and reaction in phthalazine chemistry without making an exhaustive catalogue of all of the reported syntheses and reactions, to indicate, insofar as possible on the basis of existing data, reasonable mechanisms for certain of the more important reactions, and to call attention to a few of the more important deficiencies in experimental data in various phases of phthalazine chemistry.

The nomenclature, insofar as possible, will be based upon the current usage of *Chemical Abstracts*, but the reader is warned that many systems are in use, some authors even varying within a single series of papers. Consequently names and formulas presented in the present paper may at first glance seem to be rather at variance with those in the original papers.

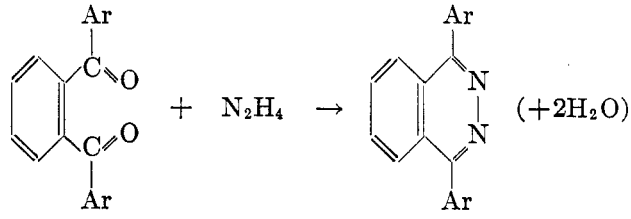
Since the larger portion of purely chemical research in the field concerns itself with synthesis, this phase will be treated first, with the physical properties and chemical behavior following in that order. In the phthalhydrazide series, unlike the phthalazine and phthalazone series, the syntheses have almost invariably been carried out for the purpose of studying a particular phthalhydrazide. Generally speaking, such syntheses are of a conventional nature, and relatively little space has been devoted to a study of the formation of phthalhydrazides. Once the phthalhydrazides have been formed, however, their chemistry has been the subject of much investigation; hence an effort will be made to evaluate the various studies of isomerism and chemiluminescence encountered in this field.

II. PREPARATION OF PHTHALAZINES

The preparation of simple phthalazines has been carried out according to two general methods. Transformation of phthalazones or phthalhydrazides in their

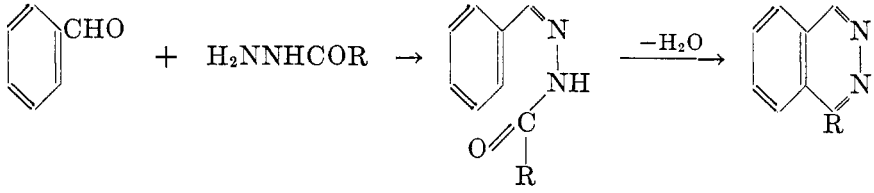
lactim forms into halogenated phthalazines (by means of phosphorus halides) with subsequent reduction, or by replacement of the active halogen with a suitable reagent (e.g., alkali alkoxides), constitutes the most generally used method, and these reactions will be discussed under the sections treating the chemical behavior of phthalazones and phthalhydrazides.

However, direct formation of the azine ring, which constitutes the other general method, has occasionally been used. This method may be subdivided into three types of reaction: (*1*) the reaction of an *o*-diaroylbenzene derivative with hydrazine (10, 11, 25, 39, 69, 70, 151, 154),



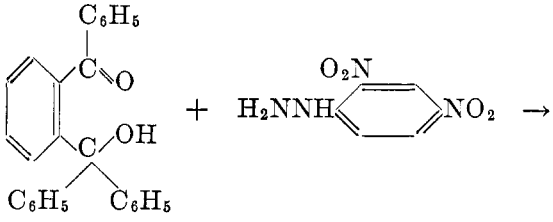
(1)

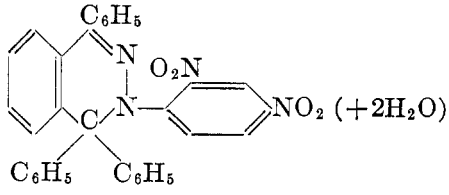
(*2*) the reaction of a hydrazide with an appropriately substituted aromatic aldehyde, followed by cyclodehydration of the acylhydrazone (1, 2),



(2)

and (*3*) the reaction of an *o*-benzoyltriphenylcarbinol (or its tautomeric cyclic ketal) with a hydrazine derivative to yield a 1,2-dihydrophthalazine derivative (155):





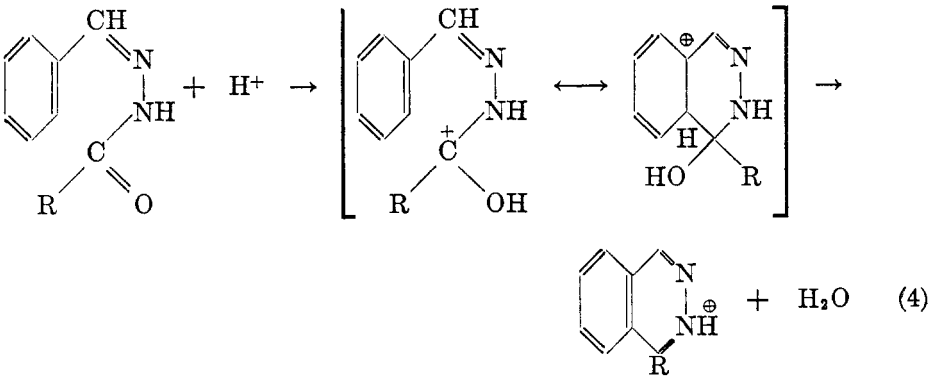
(3)

In reaction 1 an aqueous solution of hydrazine is added to a suitable solution of the diketone in alcohol (25, 70, 154), acetic acid (10, 11), or even pyridine (25, 151). The yields in general are good. In passing it should be noted that the *o*-diketone has occasionally been obtained from a β,β'-benzofuran by oxidation, using sodium dichromate in acetic acid solution (70, 154).

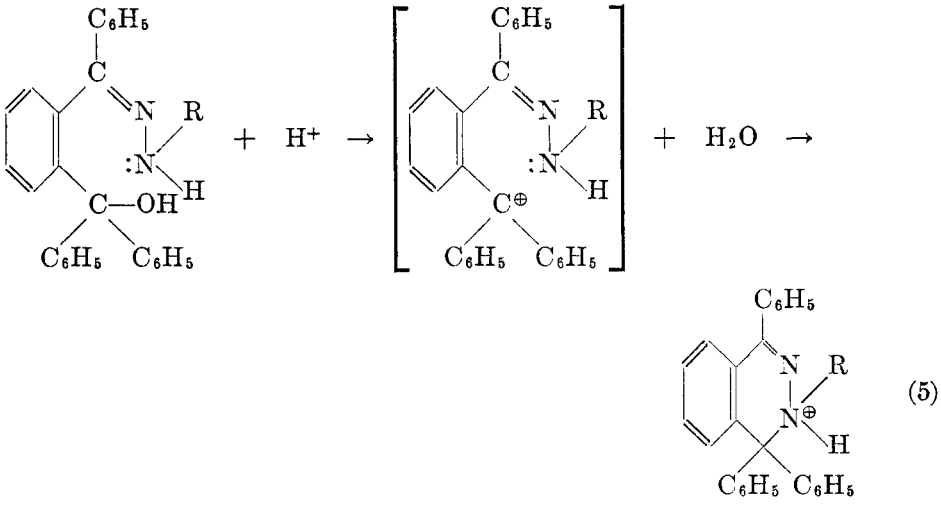
Reaction 2 has been used very successfully with both benzhydrazide and phenylacethydrazide in reaction with a variety of aromatic aldehydes (1, 2), but it was observed that where the aldehyde carried a substituent *only* in the meta position, cyclization seemed to be inhibited, regardless of the character of the substituent, for both *m*-nitro- and *m*-methoxy-benzaldehyde failed to yield phthalazines. However, both veratraldehyde and piperonal gave satisfactory yields of phthalazines under the same conditions. Consequently the results with *m*-methoxybenzaldehyde would appear to be anomalous, but no investigation of possible reasons for the anomaly or the extent to which other groups produce the same effect has been published.

Reaction 3, yielding a 1,2-dihydrophthalazine, is a less common type of reaction and was observed to take place in alcohol solution containing concentrated hydrochloric acid. Such a solution of the keto-carbinol was treated with 2,4-dinitrophenylhydrazine, and somewhat over 50 per cent of the *N*-substituted dihydrophthalazine was obtained (155).

The mechanism for formation of the simple phthalazines directly from an *o*-diketo compound (equation 1) offers no unusual points for consideration, since it is essentially a double condensation of hydrazine with the two carbonyl groups. However, reaction 2 is rather more complex. The initial process is the usual condensation of a hydrazide with a carbonyl group, but the second step is the more significant one and merits more investigation of the forces promoting or hindering it. The actual cyclization is acid catalyzed and may be regarded as a typical cyclodehydration (16):



The reaction yielding a 1,2-dihydrophthalazine (equation 3) is likewise acid catalyzed, and it also resembles the formation of certain phthalazone derivatives (equations 7d and 15):



(5)

III. PREPARATION OF PHTHALAZONES

Far more abundant literature exists describing the preparation of phthalazones, both with and without substituents on the nitrogen and on C^4. There are many examples of synthesis recorded for all types of compounds, and they may be classified under three major headings: straightforward reactions yielding simple phthalazones (equation 6), less usual modifications of these reactions yielding similar products (equations 7), and somewhat more unusual reactions (represented by equations 8 through 10) (see table 1).

The conditions under which the most common phthalazone synthesis (equation 6) has been carried out vary from simply warming a mixture of an *o*-acylbenzoic acid and the appropriate hydrazine derivative in aqueous solution through the use of alcoholic solvents or acetic acid to the extreme situation where the *o*-acylbenzoic acid was heated to a high temperature with phenylhydrazine alone. In general the use of an aqueous medium has been given preference, since the reaction product is usually relatively insoluble in cold water, and the yields are usually very good. Use of simple esters of *o*-acylbenzoic acids as starting materials is comparatively infrequent (5, 97), but enol-lactones have often proven quite satisfactory (15, 147, 190, 192).

The use of substances which may be considered as related to enol-lactones has also been of some interest: equation 7c represents the usual course of such a reaction, while there is evidence that certain reactions of the type represented by equation 6 can proceed through an intermediate stage of similar character (102, 103) (*cf.* equation 12, below). The transformation represented by equation 7c has been effected either with or without solvents, but the transformation of the product of reaction 12 into a phthalazone is effected by treatment with an aqueous acid (equation 14, below). While there is no actual record of a reaction such as that represented by equation 12 occurring with *o*-ketobenzoic acids, the isolation of an intermediate which is subsequently transformed into a phthalazone

TABLE 1

Preparation of phthalazones

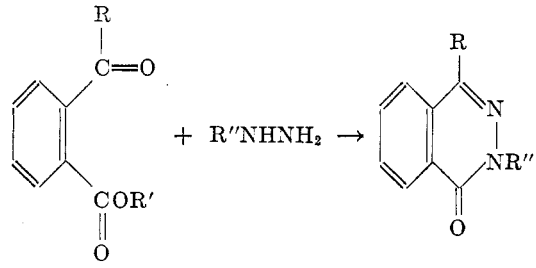
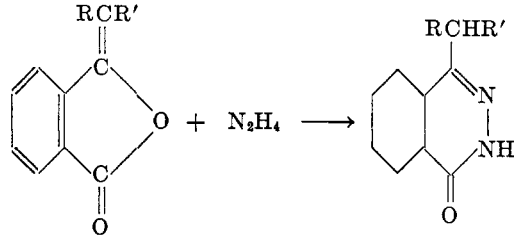
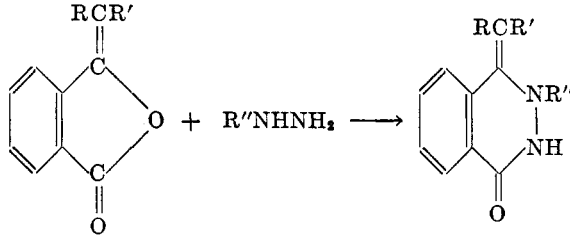
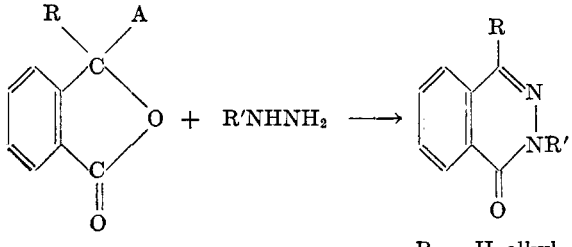
EQUATION	REFERENCES
(6)  R = H, alkyl, aryl, COOR′ R′ = H, alkyl R″ = H, aryl, NH_2CO	(5, 7, 14, 15, 20 27, 34, 38, 48, 50, 55, 56, 58, 59, 60, 61, 62, 67, 77, 84, 90, 93, 97, 102, 106, 107, 108, 110, 112, 117, 125, 152, 153, 180, 182, 190)
(7a)  (*cf.* equation 19)	
R = styryl R′ = COOH (lost in product), H	(15)
R, R′ = *o*, *o*′-diphenyl	(192)
R = phenyl R′ = H	(20)
(7b)  (*cf.* equation 10) R = acetyl R′ = carbethoxy R″ = phenyl	(147)
(7c)  R = H, alkyl, aryl R′ = H, alkyl, aryl A = H, halogen, amino, arylamino, OR	(99, 172, 180, 190)

TABLE 1—*Continued*

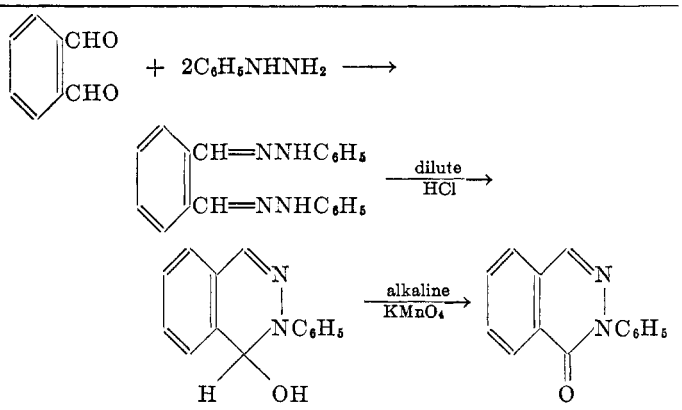
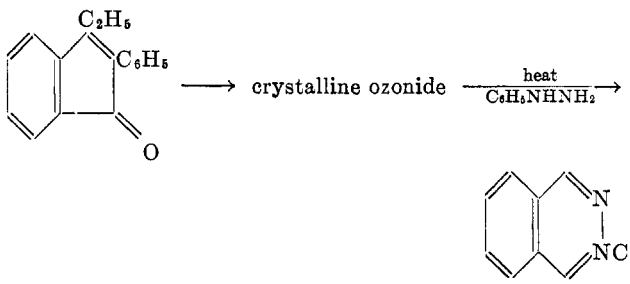
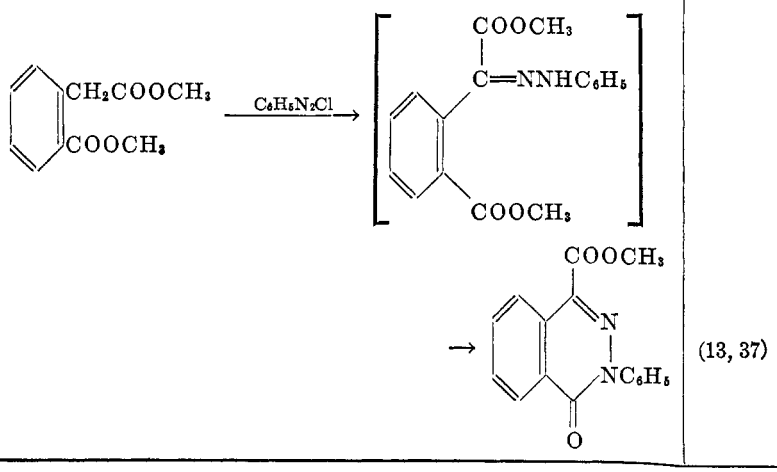
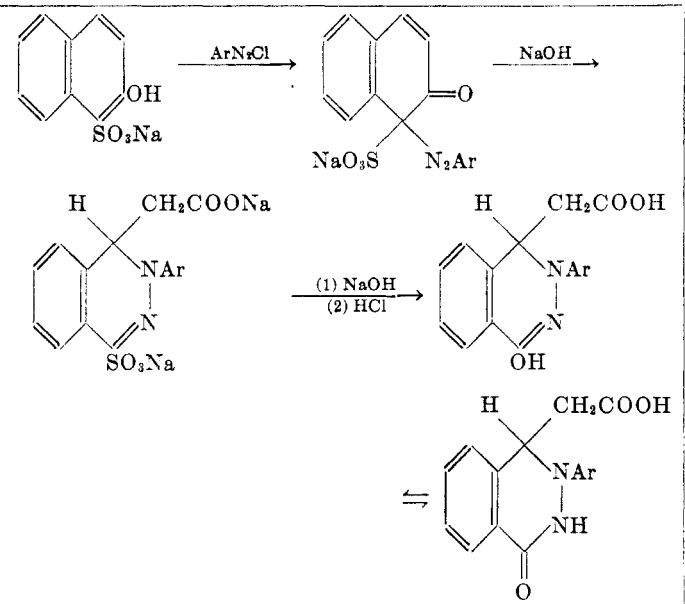
EQUATION	REFERENCES
(7d)  (*cf.* equation 3)	(173)
(8) 	(54)
(9) 	(13, 37)

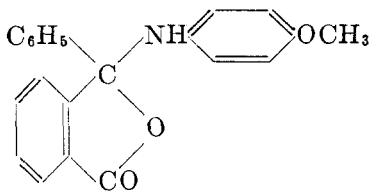
TABLE 1—*Concluded*

EQUATION	REFERENCES
(10)  (*cf.* equation 7b)	(127–145)

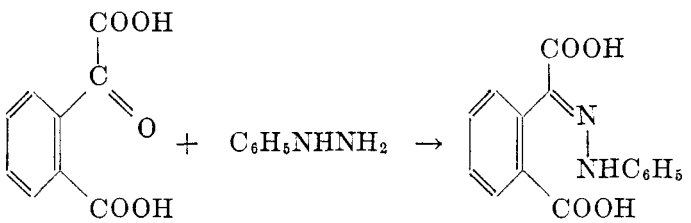
by treatment with acid strongly suggests that all reactions of the type represented by equation 6 are subject to acid catalysis (7, 27, 146), especially since many such reactions seem to proceed smoothly in acetic acid solution (15, 117); and there are frequent references to the transformation of a hydrazone to the corresponding phthalazone in the presence of acetic acid or of strong mineral acids (50, 90, 108, 146, 153). However, ring closure also occurs in weakly alkaline solution as recorded by Gabriel and others (58, 61, 180); so acid catalysis is not indispensable, though perhaps it should be stated that a high pH value for a solution retards or inhibits cyclization altogether (179). Further evidence of the lack of necessity for acid catalysis is to be found in the formation of phthalazones directly from phenylhydrazine and the appropriate *o*-acylbenzoic acid (56, 84, 97).

The isolation of hydrazones as intermediates in phthalazone formation has been reported in many places where a substituted hydrazine has been employed, and this raises a question as to the structure of these hydrazones: Are they true hydrazones, or are they pseudohydrazones formed as in equation 12? The actual isolation of pseudohydrazones (phthalidohydrazines) is recorded only twice (102, 103) by authors who were particularly interested in obtaining such substances, and to this end they worked under rather unusual conditions in their attempts to obviate direct phthalazone formation. The possibility, indeed the ease of for-

mation of a substance of similar structure from *o*-benzoylbenzoic acid and *p*-anisidine (99),

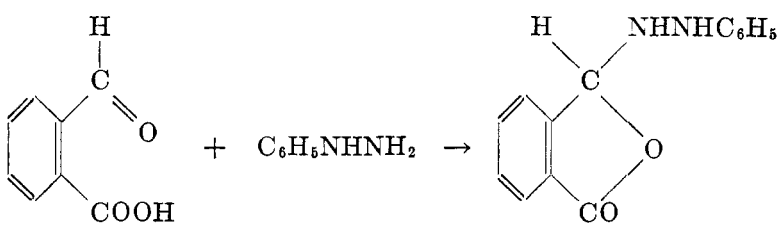


raises the question of whether or not the hydrazones which have been isolated (27, 38, 50, 90, 93, 192) from reactions of hydrazine or its derivatives with *o*-acylbenzoic acids may not actually be pseudohydrazones. Either hydrazone or pseudohydrazone can be converted to the phthalazone structure by treatment with aqueous acids; hence there is reason to reëxamine the results recorded in these studies. The ability of a substance to form a pseudohydrazone is undoubtedly a function of the various groups close to the carbonyl group, and one might venture to predict on the basis of such evidence as is available that groups which exert a $+I$ (electron-attracting) effect seem to favor ordinary hydrazone formation:



(11)

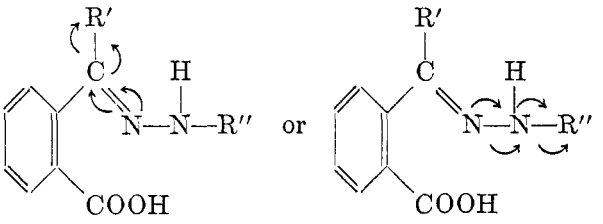
while those exerting a $-I$ (electron-repelling) effect or a zero inductive effect (H) tend to favor the formation of a pseudohydrazone:



(12)

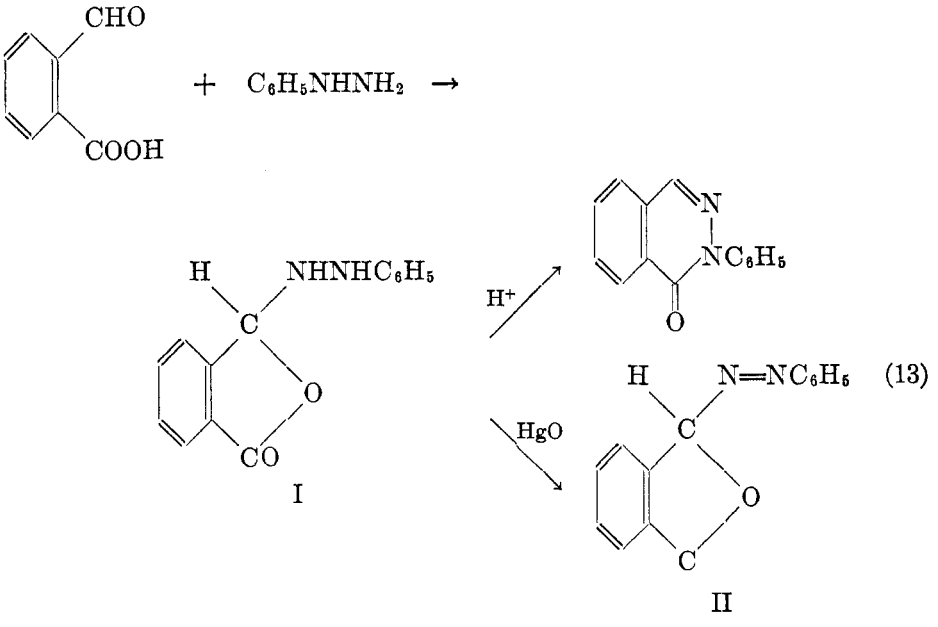
It might be further suggested that the presence of so strong a $+I$ group as NO_2 in the original aromatic ring or in the hydrazine molecule would tend to favor normal hydrazone formation by a transmitted $+I$ effect. In either of the latter two conditions the over-all result would be a tendency to disperse or delocalize the effect of the lone pair of electrons on the doubly bound nitrogen atom of the

hydrazone, thus rendering it a less attractive site for the transfer of an acidic proton (i.e., its basicity is reduced):



or both.

The pseudohydrazone structure was first seriously considered to have an independent existence by Mitter and Sen (102, 103), who offered as proof of its existence the relative ease of oxidation of the product of reaction between phthalaldehydic acid and phenylhydrazine. As illustrated in equation 13 the pseudohydrazone (phthalidophenylhydrazine) may be oxidized to phenylazophthalide (II):



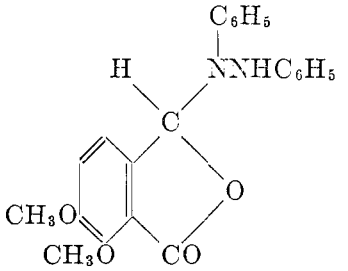
(13)

whereas such an oxidation would not be readily possible in the isomeric *o*-phthalaldehydic acid phenylhydrazone without the tautomeric shift necessary to produce the lactone-like pseudohydrazone.

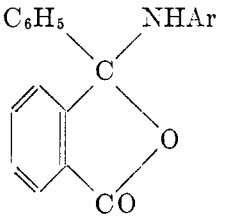
Substance I is described as being canary-yellow and readily soluble in aqueous ammonia or aqueous *sodium bicarbonate*, which of course would also be true of the tautomeric hydrazone. The authors make no effort to distinguish between the reactions of I and those of the true hydrazone except as regards susceptibility to oxidation. The azo compound (II) obtained from I proves to be insoluble in

aqueous sodium bicarbonate and therefore must possess the cyclic structure indicated.

As already noted, it is quite evident that I is a tautomeric form of the true hydrazone structure and would be expected to be stable only in neutral or slightly acidic solutions, the conditions governing its stability being the inductive effects aforementioned and the pH of any given solution. Hence it is to be supposed that in a strongly alkaline solution the hydrazone structure will exist exclusively. Very early evidence for a closely related structure is to be found in the work of Tust (175), who obtained a *non-acidic* substance from opianic acid, an *N*,*N'*-diphenylhydrazine to which he assigned the structure,



and similar investigation of the reaction of *o*-benzoylbenzoic acid with aromatic amines led Meyer to propose a pseudoanilide structure (98):



Meyer's compounds are titratable, but certain of them show a definite lag in reactivity with alkali. An extension of Meyer's work along the lines initiated by Mitter and Sen would doubtless prove quite fruitful as a means of studying the relative stabilities of pseudohydrazones.

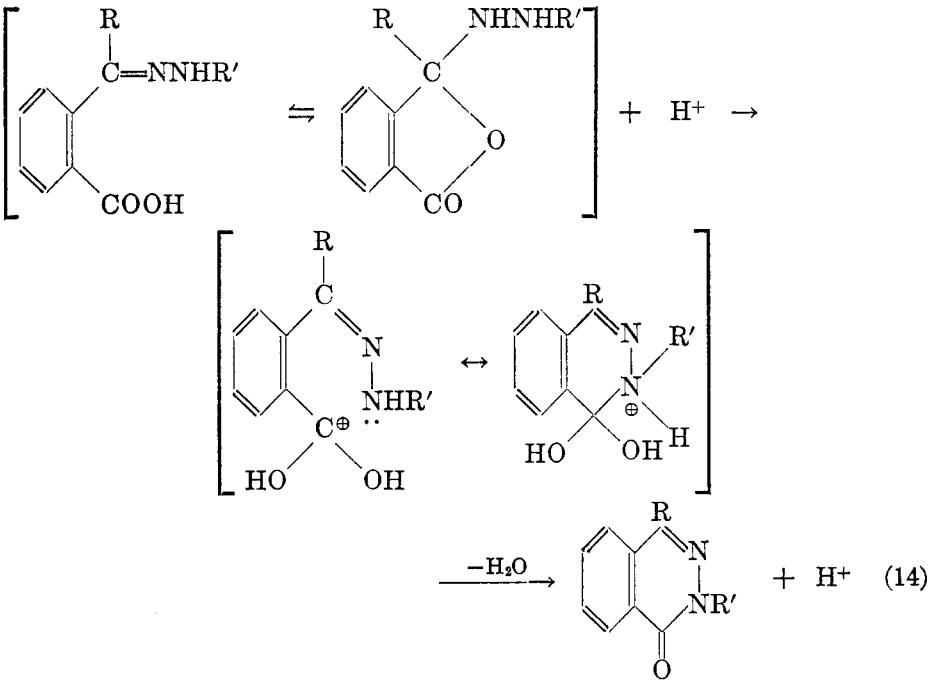
Support for the influence of substituents on the nature of the hydrazine derivative is to be found in the work of the latter authors, who state that they could not obtain any identifiable products from attempts to oxidize the phenylhydrazine derivative from phthalonic acid. Here, of course, the α-carboxyl group exerts a $+I$ effect.

The same influences which operate to stabilize the true hydrazone structure might also be expected to inhibit or retard cyclization to a phthalazone (equation 14). There is a certain amount of data to support this hypothesis, and indeed the resistance toward cyclization (stability of the hydrazones) has been investigated by Rowe and his collaborators (133). Their findings show that $+I$ groups in ortho or para (or both) positions in the arylhydrazine molecule definitely retard cyclization of the hydrazone formed with an *o*-acylbenzoic acid, while $-I$

groups attached to the carbonyl carbon atom promote cyclization. The $+I$ effect is also observed in the meta position, but to a lesser degree.

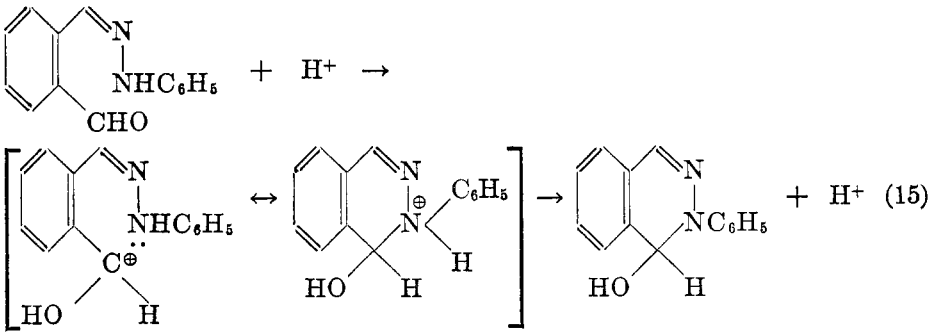
Rowe himself does not attempt to classify or correlate inductive effects in his studies, but he does make reference to an ortho effect which operates where there are ortho groups in the hydrazine molecule. There is no reason to doubt the existence of this effect, but it seems only reasonable that the inductive (and/or resonance) effects are of considerably more significance, especially since arylhydrazines containing $-I$ groups form hydrazones which appear to cyclize with extraordinary ease (128, 131, 133).

A mechanism which would appear to account for the cyclization of either form (pseudo or normal) of the hydrazone into a phthalazone derivative is indicated by the following equation (*cf.* 71):



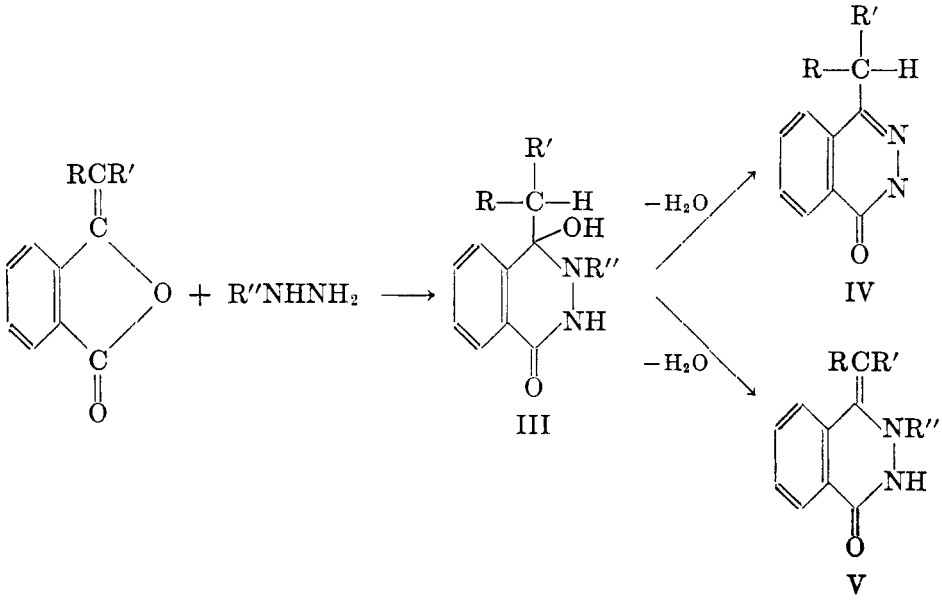
(14)

A similar mechanism may be written for equation 7d, assuming prior hydrolysis of one of the phenylhydrazone groups:



(15)

The mechanism for reactions 7a and 7b is identical with equation 14, the difference in final structures arising from the fact that the enol-lactones must first be opened with a hydrazine molecule. The resulting hydrazide then cyclizes to the keto group as in equation 14 to yield a substance (III) which is capable of loss of water in two ways, depending on its structure: where R″ = H, the usual phthalazone (IV) is formed, but where R″ ≠ H, a 3,4-dihydrophthalazone derivative results (V).

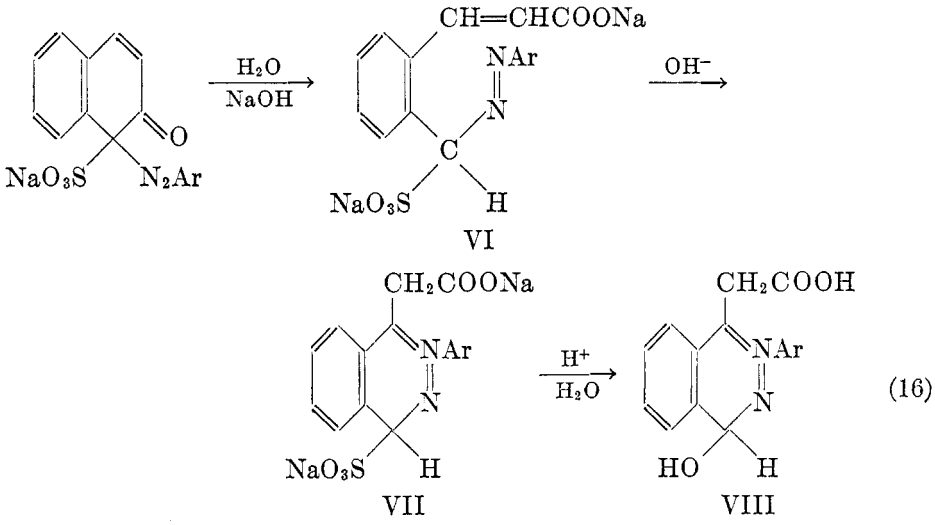


The lactone structure in equation 7c is transformed into a hydrazone structure by opening the lactone ring with hydrazine, followed by spontaneous loss of HA; in equation 9 the hydrazone structure arises from condensation of the diazonium salt with the active methylene group of a homophthalic ester. In both equations 7c and 9 subsequent cyclization to the phthalazine structure then follows the same course illustrated in equation 14.

Only reactions 8 and 10 remain to be elucidated. The former is evidently unique and requires additional data as to the nature of the other reaction products before any conclusions as to mechanism can be reached, but the latter has been studied in some detail and merits rather careful attention.

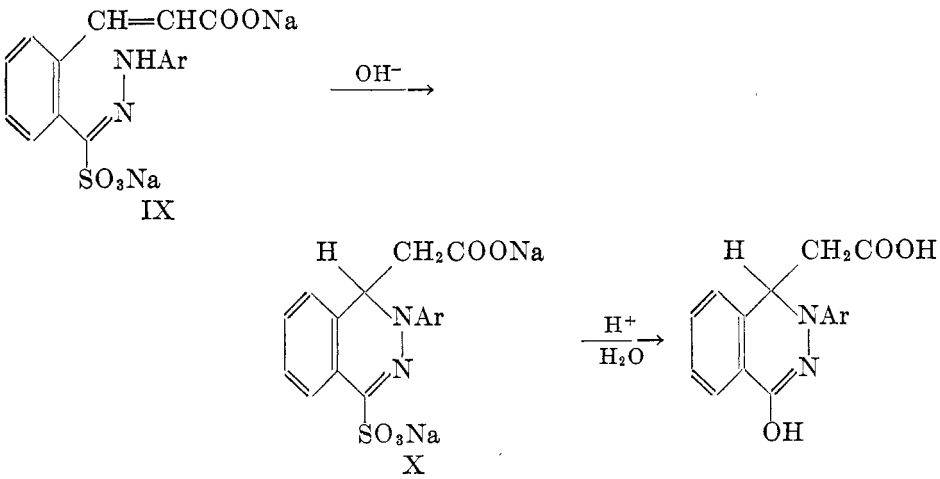
The extensive investigations of Rowe and his collaborators (127–145) into the preparations of phthalazine derivatives are concerned chiefly with studying the conditions for their particular method of synthesis and with the chemical behavior of their unusual phthalazones, once they have been formed. The actual preparation is illustrated by equation 10. The nature of the diazonium salt has been widely varied: in the initial reaction Ar = 4-nitrophenyl, 2-chloro-4-nitrophenyl, 2-bromo-4-nitrophenyl, 2-methyl-4-nitrophenyl, 2,6-dichloro-4-nitrophenyl, 2,6-dibromo-4-nitrophenyl; 2-nitrophenyl, 2-nitro-4-chlorophenyl, 2-nitro-4-methylphenyl; 3-nitrophenyl; 4-benzeneazophenyl, 4-(4′-nitrobenzene)azophenyl.

The preparation of the azo compound from sodium 2-naphtholsulfonate and the requisite diazonium salt presents no unusual problem (137), but the subsequent cleavage with sodium hydroxide to a benzene derivative was misinterpreted for some time as a simple hydrolytic cleavage followed by direct cyclization:

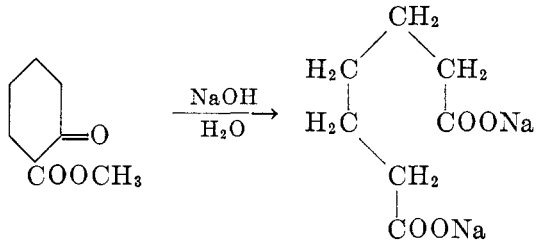


(16)

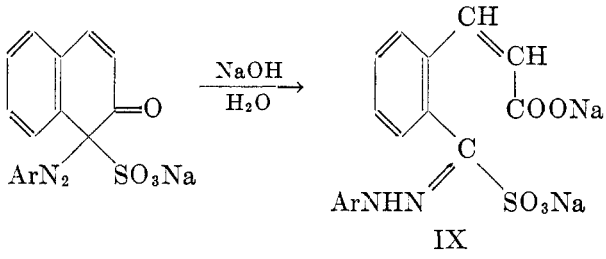
The authors adopted this course for the reaction, since they were for some time unable to prepare "*N*-methyl ethers" from the final product (VIII). However, in view of later findings in which the previously inaccessible *N*-methyl derivatives were prepared from VIII (Ar = 2-nitrophenyl or 2-nitro-4-chlorophenyl), the structures of the intermediates were altered and VI, VII, and VIII were replaced by IX, X, and XI, respectively, the latter in particular being structurally more reasonable.



The formation of IX from the naphthalene derivative possibly proceeds according to the usual mode of hydrolysis for a carbonyl compound in which the α-carbon carries groups exerting a strong $+I$ effect. For example, compare the following well-known reaction,

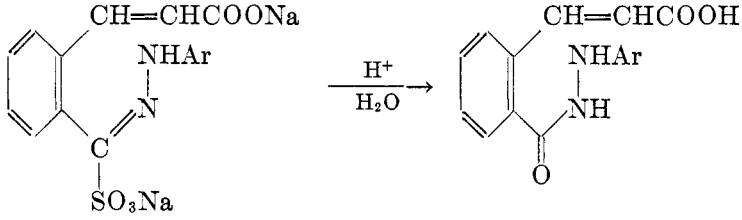


with



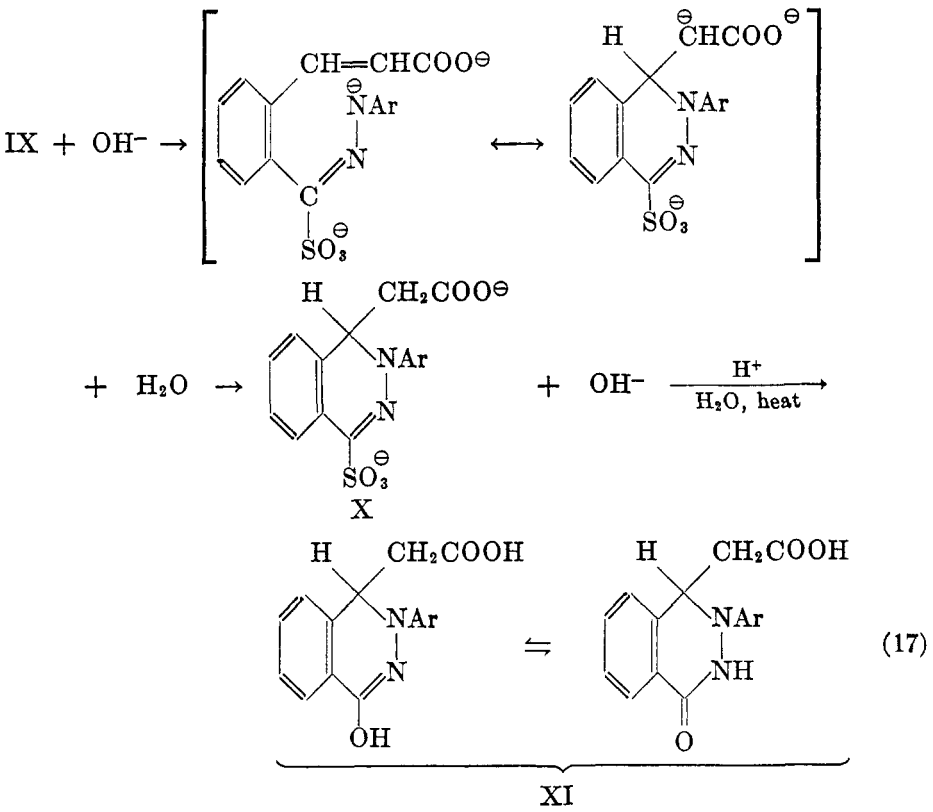
IX

Then follows a tautomeric rearrangement to the hydrazone structure (equation 17). Where there is an *o*-nitro group in the original diazonium salt the intermediate open-chain compounds have been isolated and examined, and upon hydrolysis in acid solution a hydrazide (XII) is obtained which could best have been formed from IX rather than from VI (which would yield a quite different and unstable product) (128):



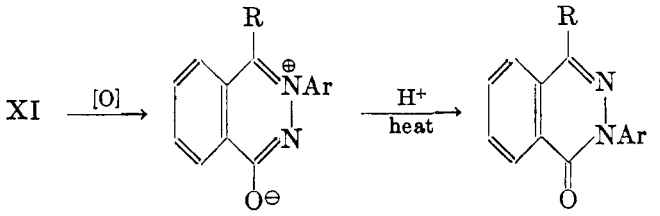
IX XII

For the actual cyclization of the open-chain structure (IX) the position of the mobile proton is not important, since the anion of IX alone is required, and indeed cyclization usually occurs spontaneously in the alkaline medium required to transform the naphthalene derivative into IX:



(17)

The function of the alkaline medium is of course to produce the anion (resonating structure shown in brackets). The carbanion structure (attached to C^4) is then represented as removing a proton from water to yield X. Subsequent acidic hydrolysis of X then yields the structure XI, which exists in two tautomeric forms. The structure of XI is proven indirectly by further transformations:



XIII: R = CH_3 XV: R = CH_3
XIV: R = H XVI: R = H

(18)

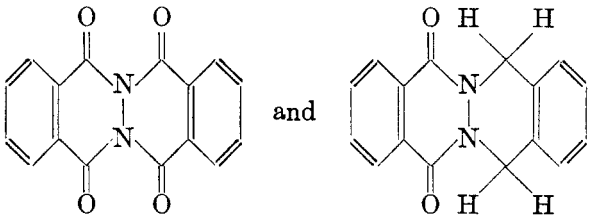
Treatment of XI with cold acidic dichromate yields XIII, while refluxing with dilute sulfuric acid yields XIV. Both XIII and XIV are readily shown to be isomeric rather than identical with the more common forms XV and XVI, which

may be synthesized by unequivocal methods. Furthermore, XIII may be transformed into XV and XIV into XVI by heating with 1.2 *N* hydrochloric acid in a sealed tube at 170–190°C. for about 6 hr. Consequently the reactions represented by equations 10 and 18 may be used for the preparation of the isomeric 2- and 3-arylphthalazones. The mechanism and conditions for the transformations shown in equation 18 will be discussed under the chemical behavior of the pseudophthalazones.

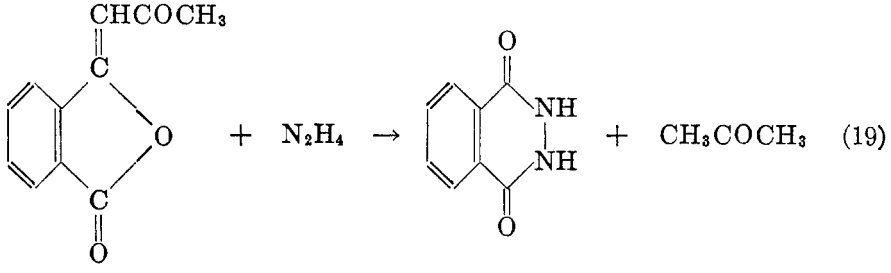
IV. PREPARATION OF PHTHALHYDRAZIDES

The cyclic hydrazides of *o*-phthalic acid and its derivatives have in general been prepared from derivatives of the corresponding phthalic acids (e.g., the acids themselves, esters, anhydrides, imides, etc.) and an appropriately substituted hydrazine derivative. The formation of isomeric phthalimidines will be considered below.

In addition to the usual bicyclic hydrazides a few polycyclic structures have been synthesized by treating a phthalhydrazide with *o*-phthaloyl chloride derivatives or with α,α'-dichloro-*o*-xylenes (45, 75), the respective products having the general structures:



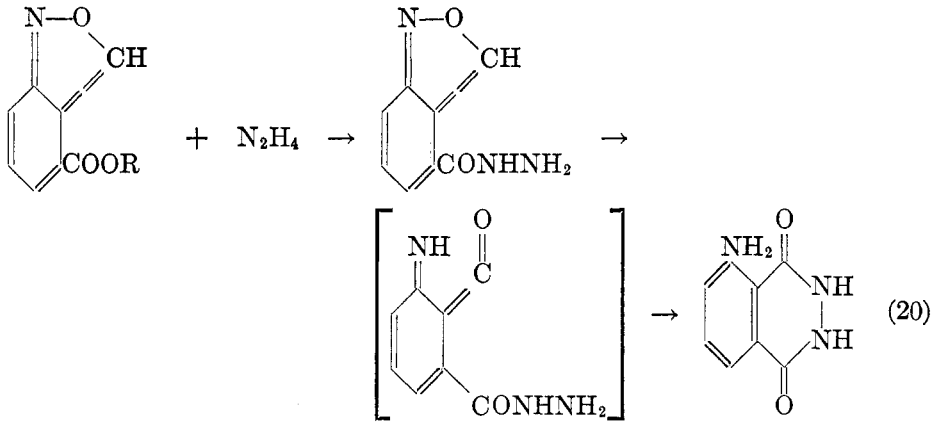
Two unconventional reactions yield phthalhydrazides:[2] one is essentially the cleavage of a β-keto enol-lactone by means of hydrazine (21):



(*cf.* equation 7a)

while the other is a reaction of an *o*-carboxybenzisoxazole (or its ester) with hydrazine (66):

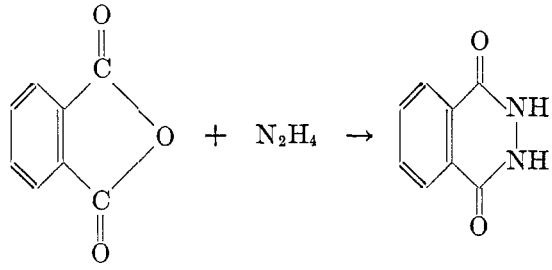
[2] A number of unusual reactions yielding phthalhydrazides have been carried out by Rowe and his collaborators, but discussion of these will be reserved for consideration with the reactions of the pseudophthalazones.



(20)

The intermediate hydrazide has actually been isolated when methylhydrazine has been used in place of hydrazine itself.

As with the synthesis of the simple phthalazines from hydrazine and an *o*-diacylbenzene there is nothing of an unusual nature which merits consideration in the formation of a phthalhydrazide directly from an *o*-phthalic acid or one of its derivatives; all that is involved is the well-known reaction of an ammonia derivative with an acid derivative, followed by a second similar reaction with the other end of the hydrazine molecule (29):

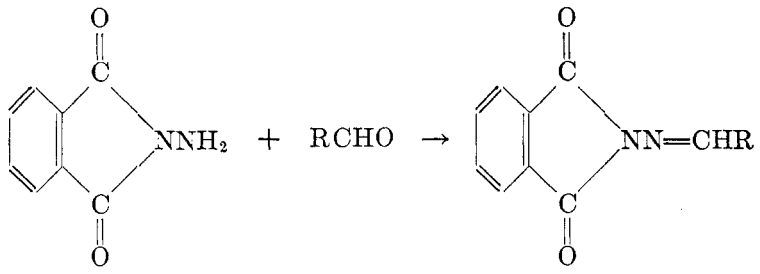


(21)

Curtius (30) states that no dihydrazide of *o*-phthalic acid can be obtained (*cf.* 156); however, it was very early observed that an isomeric non-acidic structure could also be prepared from *o*-phthalic acid derivatives and the derivatives of hydrazine (29, 79, 111). In the earlier investigations it appeared that phthalhydrazide or *N*-phenylphthalhydrazide was formed in the presence of two equivalents of the hydrazine derivative while the non-acidic isomer, *N*-aminophthalimide, was formed preferentially in the presence of one equivalent of the hydrazine derivative. Later investigations seemed to bear out this early observation, and the studies of Drew in this field will be considered subsequently.

Some confusion appears to have arisen in the early work in the field of phthalhydrazide synthesis, since the isomeric *N*-aminophthalimides (phthalylhydrazides) exist in polymorphic forms (47, 183), but the proof of structure offered by Rădulescu (118–122), which followed Sidgwick's study of isomerism, tautomerism, and polymorphism in this series (157), established the true relationship between *N*-aminophthalimides and the isomeric phthalhydrazides. The struc-

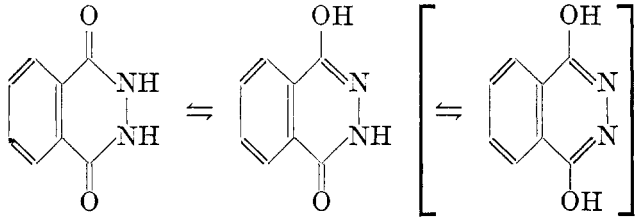
ture proof is based upon the chief characteristic of the two isomeric structures. The so-called α-form (N-aminophthalimide) reacts with aldehydes, as would any hydrazide with a similarly free amino group:



α-form

(*cf.* equation 49)

while the β-form (phthalhydrazide) is soluble in alkali and forms stable salts with metals such as silver by virtue of a tautomeric lactim structure:



β-form

Furthermore, the phthalhydrazide structure yields (from the dilactim) both mono- and di-chlorophthalazines with phosphorus pentachloride; with phosphorus pentasulfide a dimercaptan is formed (equation 52) (122). It was also shown conclusively that even the N-phenyl derivative of the α-form could be transformed into the β-form by means of strongly basic catalysis (sodium ethoxide in alcohol) (24), while heat alone was sufficient for N-aminophthalimide itself (45). The extreme conditions for this isomerization are quite in accord with Rădulescu's contention that the α-form vigorously resists hydrolysis and therefore this structure cannot represent the acid isomer, which depends for its acidity upon a readily reversible hydrolysis, as had been suggested by Rothenburg (183). Absorption spectra of the N-phenyl derivatives of the two isomers show marked differences (8).

As mentioned above, the question of which type of substance (N-aminophthalimide or phthalhydrazide) is formed under a given set of conditions has been investigated by Drew and his collaborators, and a certain amount of data has been accumulated. The investigations are not especially complete, since they were mainly incidental to the investigation of the phenomenon of chemiluminescence which was being studied by Drew. It is the opinion of the present writer that insufficient experimental data is available to warrant offering any conclusions as to mechanisms or group influences. Undoubtedly something more than

simple steric effects is responsible for the differences observed, and probably both resonance and inductive effects must be considered. However, a summary of the findings of Drew and his collaborators is presented herewith for consideration (45).

Certain groups in the phthalic acid ring were found to promote five-membered-ring (*N*-aminophthalimide) formation, while others were found to promote six-membered-ring (phthalhydrazide) formation, and still others promoted the formation of either five-membered or six-membered rings—the former when only one equivalent of hydrazine was used, the latter when two equivalents of hydrazine were present. This latter class comprises 3-aminophthalimide, 3-chlorophthalimide, and 3,6-dichlorophthalic anhydride. Those substances yielding only the six-membered-ring structure are 4-aminophthalimide, 3-hydroxyphthalimide, 3- or 4-nitrophthalic anhydride, 4,5-dichlorophthalimide, and 4,5-dichlorophthalic anhydride. Finally, two substances yield only the five-membered-ring structure: 3,6-dichlorophthalimide and 3,4,5,6-tetrachlorophthalic anhydride.[3] Attention is called to the fact that those phthalic acids which form anhydrides with difficulty (4,5-dichloro) yield the six-membered-ring structure exclusively, while those forming an anhydride more readily (3,6-dichloro) can yield either the five-membered or the six-membered ring. Drew further suggests a situation analogous to the Mills–Nixon effect (52, 101).

It was further observed that when there was a hydrazide group ortho to the nitro group of 3-nitrophthalic acid, simple heating invariably favored formation of a six-membered ring; but if the hydrazide was meta to the nitro group a five-membered ring resulted regardless of the state of the ortho carboxyl, indeed, even though the latter also carried a hydrazide. Finally, the use of methylhydrazine favored formation of the six-membered-ring structure.

As will be noted the evidence is incomplete, and the effect of groups so vastly different in their influences as nitro and amino in the *same positions* is so similar as to be incapable of simple explanation in conventional terms. The subject merits further study, especially along lines which would make possible, independently of each other insofar as feasible, an examination of the resonance, inductive, and steric factors influencing the course of these reactions.

Information as to the ease of phthalhydrazide formation where an arylhydrazine is used is more definite; and as might be expected, the ease of cyclization shows a definite relationship to the nature of the substituents in the arylhydrazine nucleus, $+I$ groups retarding and $-I$ groups promoting (*cf.* page 457) cyclization in the phthalazone series (131, 133).

V. PHYSICAL PROPERTIES OF PHTHALAZINES, PHTHALAZONES, AND PHTHALHYDRAZIDES

The physical properties of the phthalazines are related to those of the corre-

[3] Phelps (113) and Rădulescu and Alexa (120) believed that they had obtained a six-membered hydrazide ring from tetrachlorophthalic acid and even reported derivatives and salts, but Drew states categorically that they did not have 5,6,7,8-tetrachlorophthalhydrazide (45).

sponding naphthalenes very much as the properties of the pyridazines are related to those of benzene derivatives. Morton (104) refers to the effect of the benzo group upon the melting point of a substance, stating that its presence results in a 78°C. rise. It would perhaps be more accurate to permit rather more of a range than does Morton, since between pyridine and isoquinoline there is only a 65°C. increase (−46°C. to +23°C.), while between pyridazine and phthalazine there is a difference of 98°C. (−8°C. to +90°C.).

The variation in melting points within the two series—benzene structure and naphthalene structure—follows the same pattern, though in the latter series the differences are exaggerated: benzene +5.5°C., pyridine −46°C., pyridazine −8°C.; naphthalene 80°C., isoquinoline 23°C., phthalazine 90°C. The initial drop from the homocyclic structure to the heterocyclic system in the benzene series is −47.5°C., while in the naphthalene series it is −57°C.; and the subsequent rise in the benzene series is +34°C., while in the naphthalene series it is +67°C., bringing the melting point of the final member above that of the first member.

The boiling points in the two series show more regularity, and here the naphthalene series shows a more gradual increase: benzene 80°C., pyridine 115°C., pyridazine 208°C.; naphthalene 218°C., isoquinoline 243°C., phthalazine 316°C. In the benzene series the increases are respectively +35°C. and +93°C., while in the naphthalene series the corresponding increases are +25°C. and +73°C.

It is beyond the scope of this article to consider reasons for the relatively small abnormalities encountered in the melting point series, and since there is little physical data such as absorption spectra, dipole moments, etc. recorded in the literature, any detailed discussion of physical properties must await further experimental exploration along physicochemical lines.

Although no systematic record of the effect of substitution upon the melting points of the phthalazines is available, certain generalities may be adduced from a consideration of available data. The parent substances—phthalazine, phthalazone (1-hydroxyphthalazine, 1-keto-1,2-dihydrophthalazine), and phthalhydrazide (1,4-dihydroxyphthalazine, 1,4-diketo-1,2,3,4-tetrahydrophthalazine)—are all white crystalline substances with melting points of 90°C. (62, 110), 183–184°C. (61, 110, 184), and 341–344°C. (cor.) (45), respectively. The presence of various substituents (with the exception of carboxyl) in the hetero-ring usually lowers the melting point of the parent substance, especially if the substituent is attached to nitrogen. Large aromatic nuclei attached to C^4 of phthalazone raise the melting point.

In phthalazine and phthalazone substitution in the carbocyclic ring usually raises the melting point; but in phthalhydrazide there appears to be no general conformity as regards effect of substitution in the carbocyclic ring, though there is a tendency of monosubstitution (even of the nitro group!) to lower the melting point slightly, while disubstitution raises it.

In the absence of additional chromophoric groups or of strong auxochromic groups, the phthalazines, phthalazones, and phthalhydrazides are white or occasionally yellow crystalline substances. The absorption spectra of the latter have

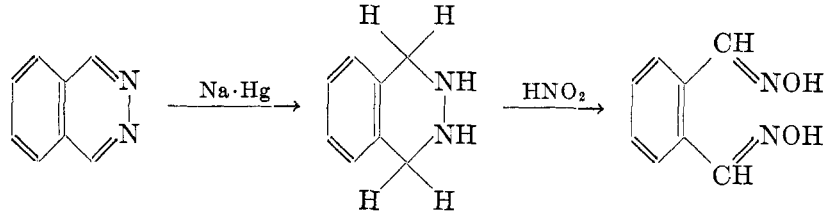
received some attention (8, 19, 51, 64, 120, 196), chiefly because of certain unusual phenomena observable in various members of the series. Otherwise no systematic study of the physical characteristics of these substances is available. The reader is referred to the work of Padoa (109) for certain cryoscopic data relating to phthalazine and quinoxaline in hydrocarbon solvents.

VI. REACTIONS OF THE PHTHALAZINES

The reactions of phthalazine and its non-oxygenated substitution products are readily collected into relatively few general classes.

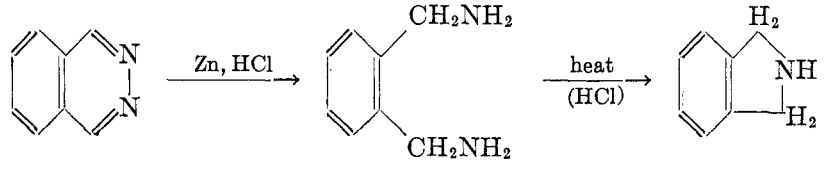
A. Reduction

First of all the action of reducing agents is of interest: phthalazine itself upon treatment with sodium amalgam yields tetrahydrophthalazine, which may be transformed into the dioxime of *o*-phthalaldehyde by reaction with nitrous acid, or which reduces Fehling's solution and regenerates phthalazine (62, 94).



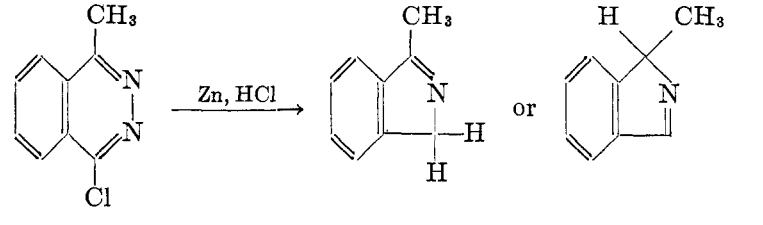
(22)

On treatment with zinc and hydrochloric acid, however, phthalazine yields α, α'-diamino-*o*-xylene, which upon warming with hydrochloric acid is transformed into dihydroisoindole (59, 61, 62), reactions of which are reported by Fränkel (55) in a paper in which the latter substance is prepared from a phthalazone derivative



(23)

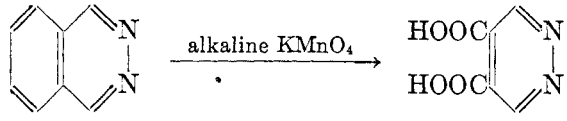
by reduction. Where a C^1-alkyl-C^4-halogenophthalazine is used in place of phthalazine itself, reaction 23 yields an isoindole (59, 61), which would appear to be the only source of the free isoindole structure (*cf.* 158).



(24)

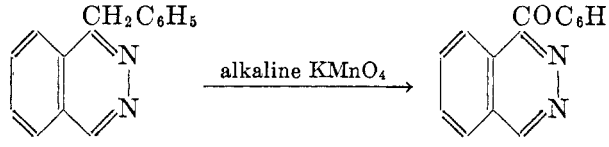
B. Oxidation

The action of oxidizing agents on the phthalazine system is analogous to their action on quinolines: i.e., the carbocyclic ring is broken (57) and a pyridazine is formed.



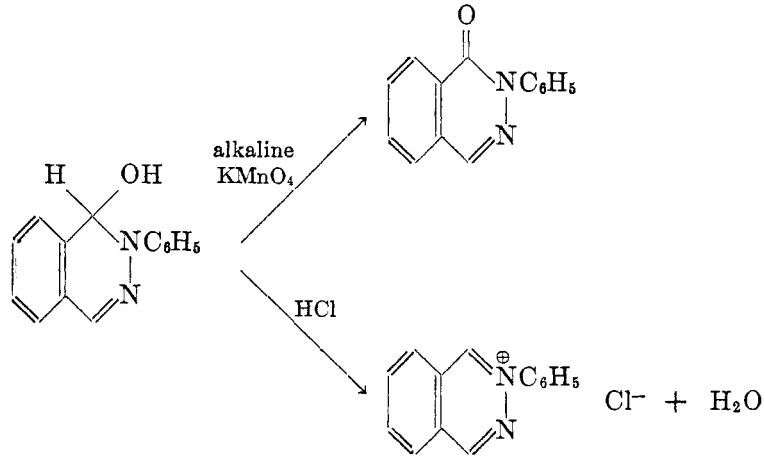
(25)

However, where there is a readily oxidizable group attached to a carbon of the azine ring, milder conditions yield a ketone (94).



(26)

Attention has previously been directed to the preparation of a 1-hydroxy-1,2-dihydrophthalazine derivative (equation 7d), and the behavior of this substance is of some interest. The methyl and ethyl ethers of this compound are readily accessible by warming it with the corresponding alcohols, and oxidation with alkaline potassium permanganate yields *N*-phenylphthalazone, while reaction with dry hydrogen chloride in benzene yields *N*-phenylphthalazinium chloride, rather than 1-chloro-2-phenyl-1,2-dihydrophthalazine (173) (equation 27).

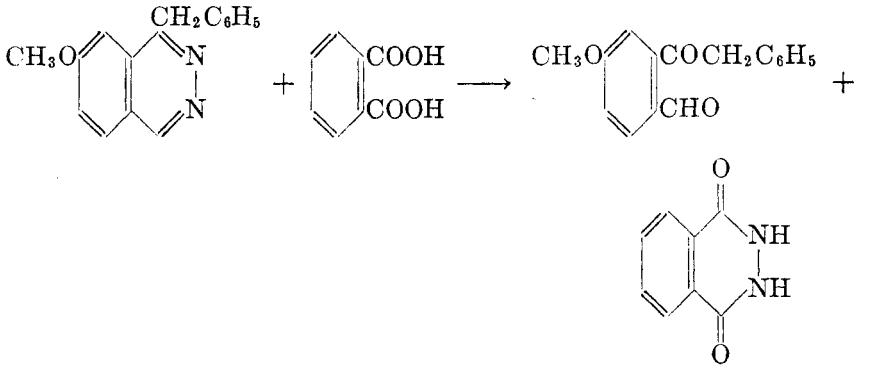


(27)

C. Ring cleavage

The azine ring is particularly stable, once it has been formed, but it has been found possible in a few instances to open it (2). Treatment of 1-benzyl-7-

methoxyphthalazine or 1-benzyl-6,7-methylenedioxyphthalazine with *o*-phthalic acid in ethanol at 100°C. for 6–8 hr. yielded the corresponding *o*-phenylacetylbenzaldehydes, which were isolated as their bisphenylhydrazones, the yields being reported as only moderate:

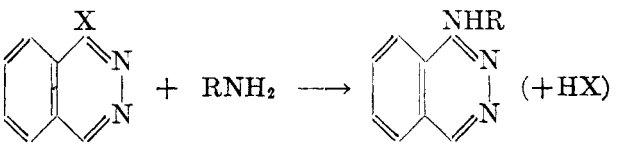


(28)

(isolated as bisphenylhydrazone)

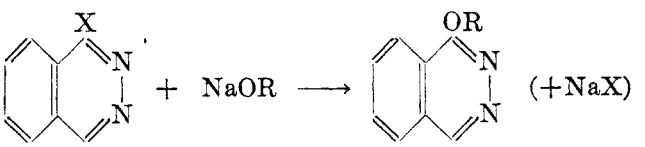
D. Activity of halogen derivatives

The activity of halogen attached to either or both carbons of the azine ring was recognized very early and is analogous to similar activity in 2- or 4-halogenoquinolines. In general the reactions of 1-halogeno- or 1,4-dihalogenophthalazines are with ammonia derivatives (primary and secondary amines) (40, 68, 78, 94),



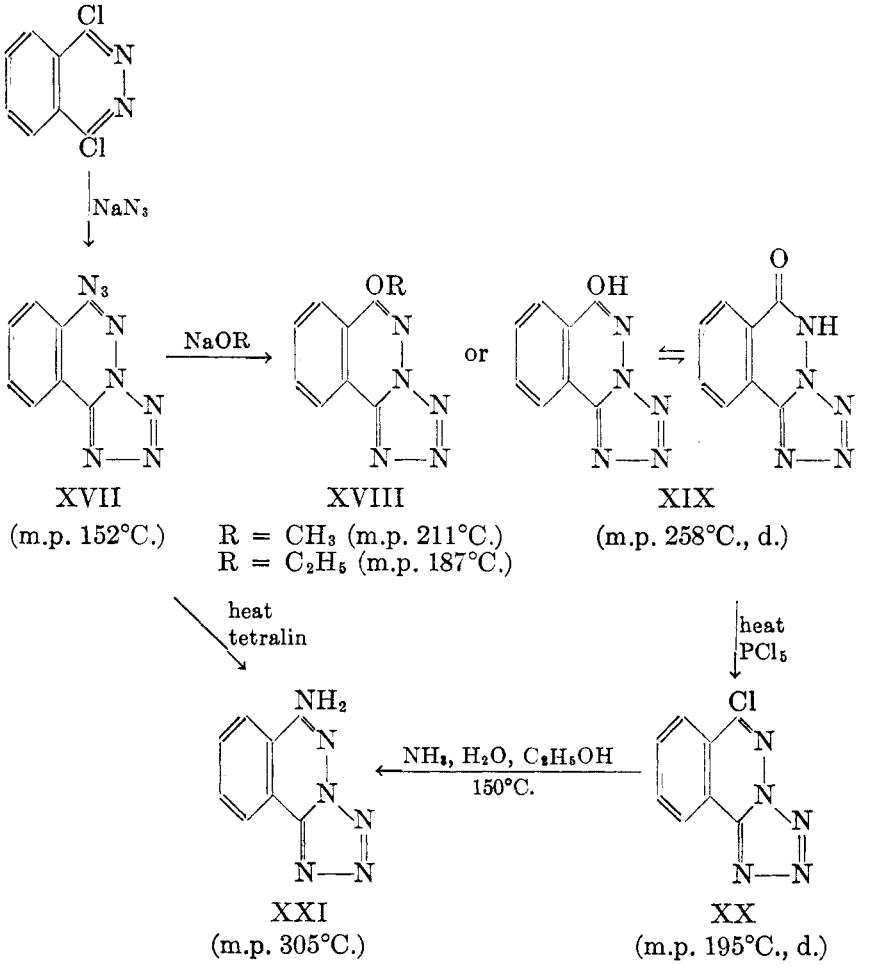
(29)

or with sodium salts such as the alkoxides to yield alkoxyphthalazines (20, 61, 62, 180, 184, 194).



(30)

In similar fashion an unusual series of compounds was prepared by Stollé and Storch (165) from 1,4-dichloro- (and 1,4-dibromo-) phthalazine and excess sodium azide in absolute alcohol at the reflux temperature (3 hr.):

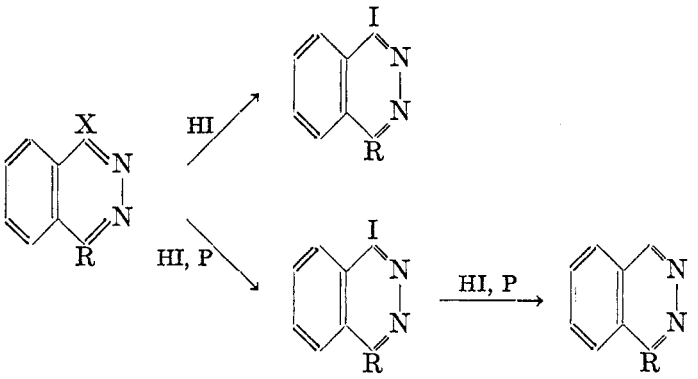


(31)

The transformation of XVII into XVIII was accomplished by refluxing with methanolic sodium methoxide or ethanolic sodium ethoxide for 2 hr. XIX was obtained with the latter reagent upon prolonged refluxing (8 hr.). The tetralin reduction was accomplished in 85 per cent yield, and small yields of XXI were also obtained with amyl ether or xylene in place of tetralin. XIX forms an acetyl derivative (m.p. 165°C.), and XXI forms both a monoacetyl (m.p. 260°C. d.) and a diacetyl (m.p. 165°C. d.) derivative, the former in very poor yield only, and the latter in somewhat better yield. The authors assign to the latter the diacetylamino structure.

The course of reaction of C^1-halogenated phthalazines with hydriodic acid varies depending upon conditions. Simple replacement of chlorine by iodine occurs when hydriodic acid alone is used, or even in the presence of phosphorus; however, more vigorous treatment with hydriodic acid and phosphorus consti-

tutes the earliest general method for the preparation of simple phthalazines (59, 94, 110, 194), as was noted in the section on the preparation of phthalazines.

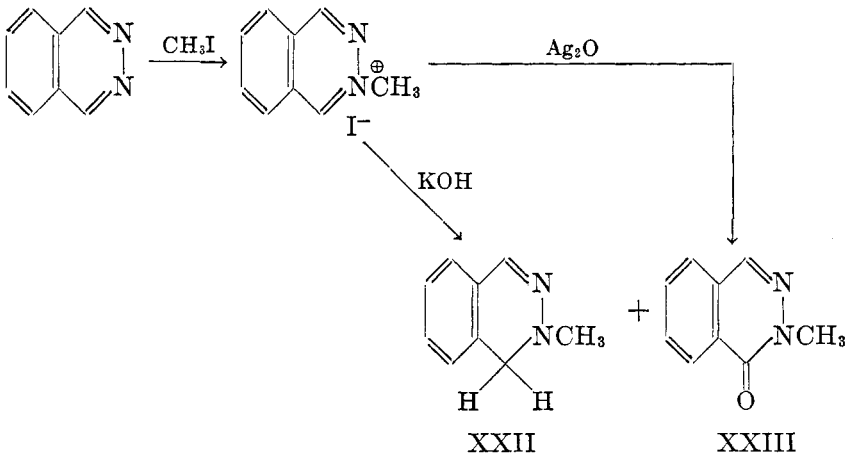


(32)

R = H, alkyl, aryl.

E. Alkylation

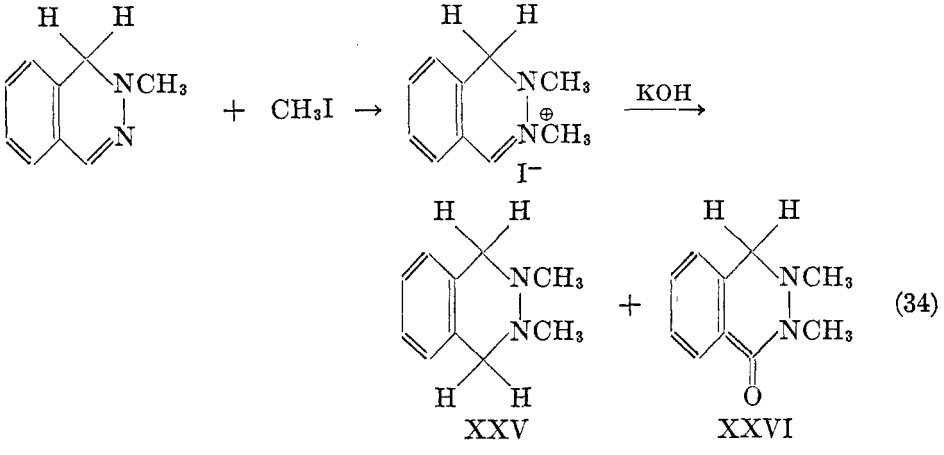
As with any amino compound the alkylation reaction is of great interest. Treatment of phthalazine or its *C*-alkyl derivatives with alkyl halides (especially methyl iodide and ethyl iodide) yields *N*-alkylphthalazinium halides (59, 60), which upon treatment with strong potassium hydroxide undergo disproportionation.



XXII XXIII

(33)

The structure of XXIII was established by synthesis and by its failure to dissolve in alkali; from the resultant structure, the structure of XXII (a steam-volatile oil) follows. XXII also reacts with methyl iodide, followed by potassium hydroxide, to yield a steam-volatile base, the reaction probably being:

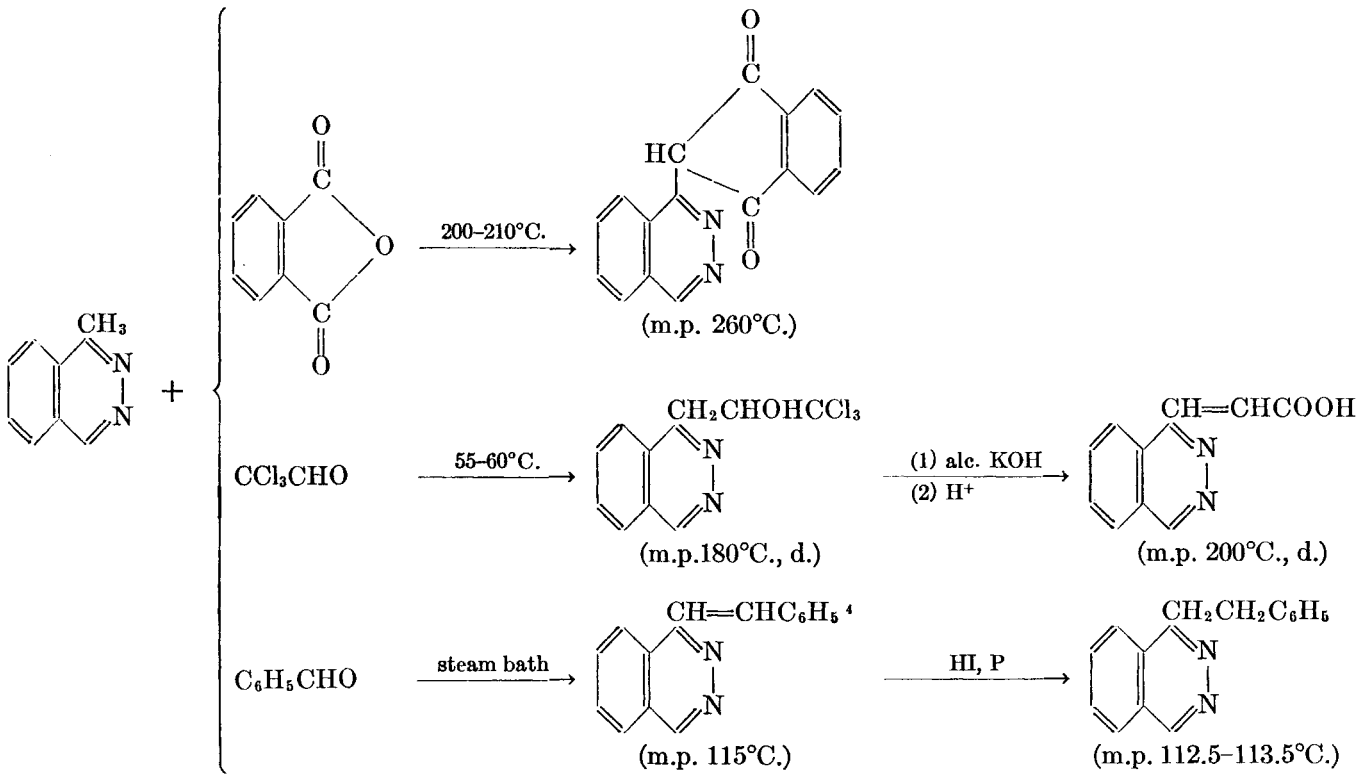


(34)

but the structures of XXV and XXVI have not been investigated. The reactions illustrated by equation 33 are well established as oxidations and reductions, a silver mirror being deposited in the experiments involving silver oxide (equation 33); and the effect of potassium hydroxide is to form a phthalazinium hydroxide which apparently very readily disproportionates with the elimination of water to yield a 1,2-dihydro-2-methylphthalazine and 2-methylphthalazone. The disproportionation would appear to be more readily accomplished here than in the quinoline or isoquinoline series, since the corresponding quinolones and isoquinolones are usually prepared by oxidation of the quaternary bases with ferric chloride (159). Roser (126), however, reports an exactly analogous disproportionation with the *N*-methyl chlorides of quininic acid and cinchoninic acid, where the dihydroquinoline structure would seem to be stabilized by the 4-carboxyl group. Otherwise the dihydroquinolines must be regarded as less stable than the corresponding dihydrophthalazines; hence the equilibrium in any reduction will be very much in favor of the more fully aromatic structure of the quaternary bases. The fact that ferric chloride is used to prepare the usual quinolone types, while silver oxide is sufficient for the oxidation of the alkylphthalazinium salts to phthalazones, would seem to support the hypothesis that the dihydro structure is more stable in the phthalazine (and 4-carboxyquinoline) series than it is in the quinoline or isoquinoline series.

F. Activity of the methyl group

The behavior of 4-methylphthalazine is of considerable interest. The activity exhibited by a methylene group in the α- or γ-position of pyridine or quinoline (or the 1-position of isoquinoline) (159) is well known, and since in 1-methylphthalazine one encounters a structure analogous to that in 2-methylquinoline, or 1-methylisoquinoline, it is not surprising that 1-methylphthalazine should show enhanced activity in the methyl group. Such activity has been observed and reported by Gabriel and Eschenbach (59) as a part of the original extensive exploration of the field of phthalazine chemistry by Gabriel and his collaborators. A summary of the reactions studied is presented herewith.



(35)

[4] The original investigators refer to this substance as "cinnamenylphthalazine," but the present writer feels certain that "styrylphthalazine" will prove less confusing and hence more acceptable to the reader.

The reader's attention is called to the difference in the reaction between 1-methylphthalazine and phthalic anhydride and the reaction between 1-benzylphthalazine and phthalic acid (equation 28), where an exchange of the hydrazine ring system occurs in place of the condensation with the active methylene group. It is interesting to speculate regarding the influences responsible for such a difference and as to the possibility of effecting either type of reaction by simply varying reaction conditions.

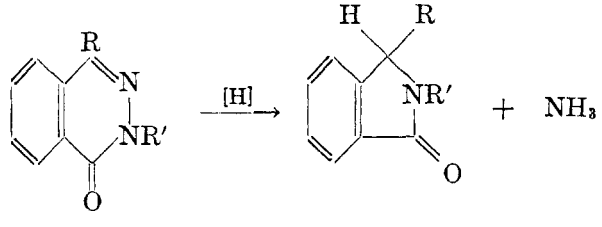
G. Salts and acyl derivatives

Finally, the simple phthalazines and the halogenated phthalazines, as might be expected from their amino structure, readily form a large variety of salts with various acids (e.g., hydriodic, hydrobromic, hydrochloric, picric, chloroplatinic, chloroauric, dichromic, and ferrocyanic) (20, 59, 60, 110). The tetrahydrophthalazines likewise form similar salts as well as *N*,*N*′-diacyl derivatives (62, 110).

VII. REACTIONS OF THE PHTHALAZONES

A. Reduction

The reduction of phthalazones has been studied by several investigators. Characteristically the reduction of phthalazones with strong reducing agents (e.g., tin or zinc and hydrochloric acid) yields 1-isoindolones (phthalimidines) (20, 34, 35, 55, 61, 117):

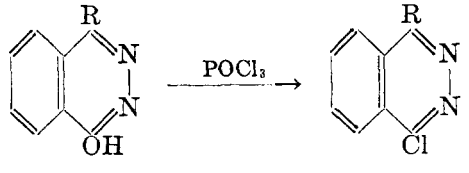


(36)

R = H, alkyl; R′ = H, C_6H_5 (117).

B. Reaction with phosphorus halides

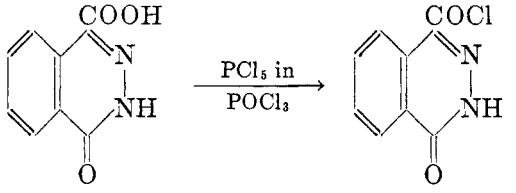
In the preceding section the reactions of the C^1- or C^4-halogenophthalazines were described, and their use as the starting point for the synthesis of phthalazines was considered. These substances are regularly prepared by the interaction of the lactim form of phthalazone and phosphorus oxychloride (20, 35, 55, 57, 59, 61, 68, 94, 110, 163, 180, 184, 194).



(37)

It should be pointed out at this juncture that, despite the ability of the lactim to react with phosphorus oxychloride, this does not interfere with the preparation

of the acid chlorides of phthalazone-4-carboxylic acids (55). The reaction in this instance is modified by using phosphorus pentachloride in phosphorus oxychloride solution:

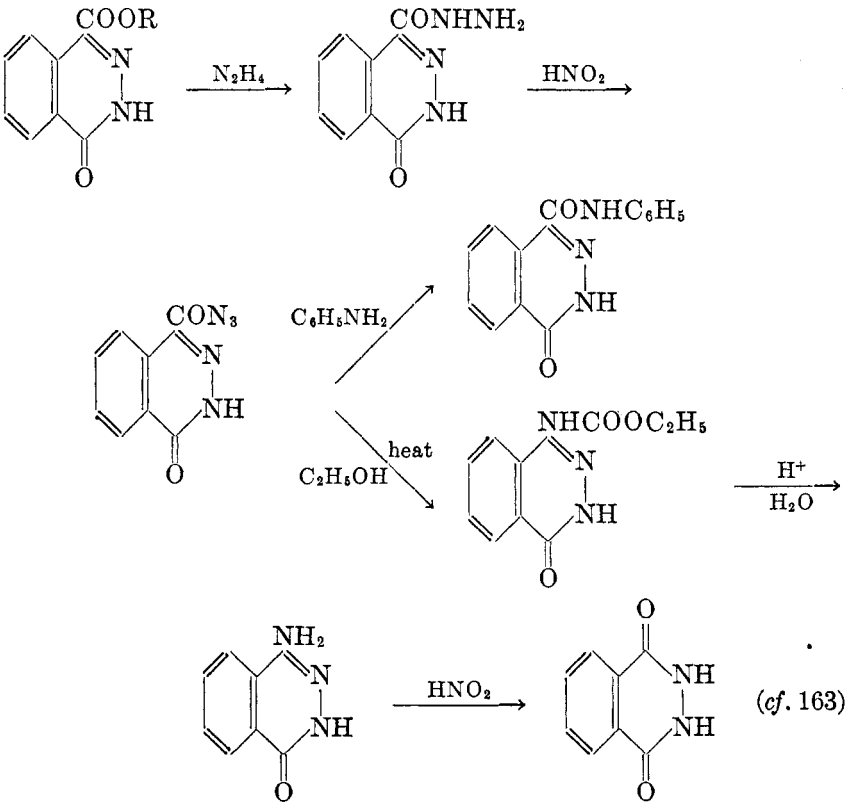


(38)

C. Phthalazonecarboxylic acids and their esters

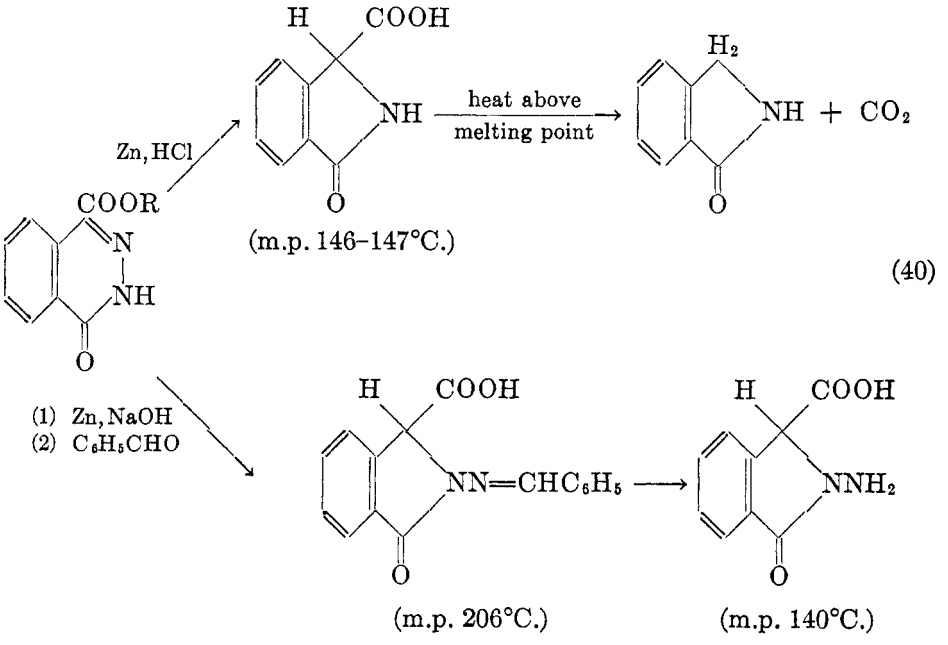
Other reactions of such carboxylic acids are also of interest. Decarboxylation is readily achieved by application of heat, usually above the melting point (55, 77, 180). The acids readily form metallic salts. Esters may be prepared from the acid chlorides (or by preparing the desired phthalazone-4-carboxylate from the corresponding phthalonic ester).

Reaction of an ester with hydrazine yields a hydrazide which exhibits the usual properties of hydrazides, including transformation to an azide which undergoes the Curtius rearrangement (160) and other reactions characteristic of azides such as replacement of the acid azide by RNH_2 (34).



(*cf.* 163) (39)

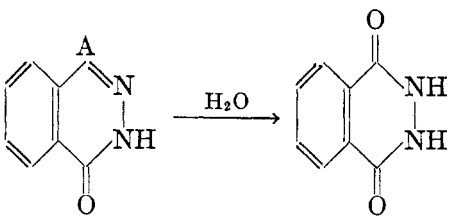
If the ester is subjected to reduction, the nature of the product varies with the conditions, the *N*-aminophthalimidine structure being isolated as the benzal derivative by treatment with benzaldehyde (34):



(40)

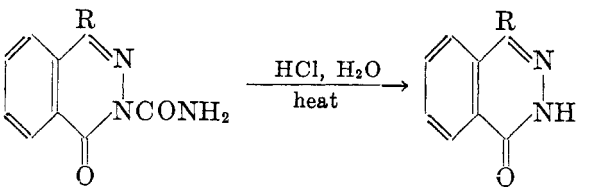
D. Hydrolysis

The hydrolysis of various derivatives of the phthalazones yields the expected products, but the phthalazone ring itself appears to resist hydrolytic cleavage.



(41)

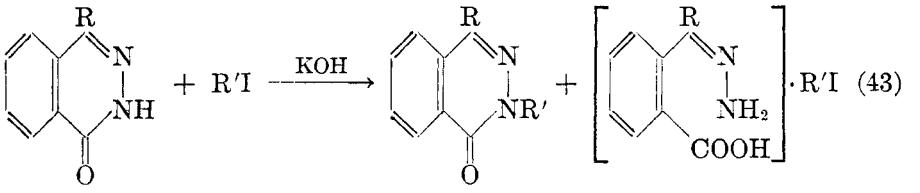
A = halogen (163); A = NHR (87).



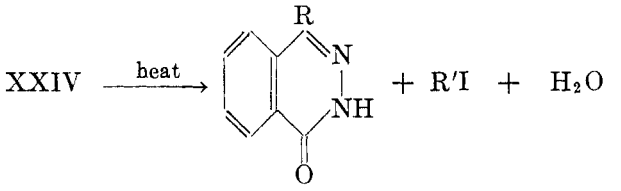
(27, 90, 106) (42)

E. Alkylation

The alkylation of phthalazones (35, 59, 110, 184) proceeds as would be expected, with the formation chiefly of 2-alkyl derivatives, but the phthalazone ring may break simultaneously to give a substance (XXIV) of doubtful structure (59, 110):



XXIV



It might be argued that XXIV arises as a consequence of *N*-alkylation in the 3-position, simultaneously with 2-alkylation. This would of course yield a quaternary iodide which would persist even after the opening of the ring, but the relatively low melting points (R = H, m.p. 170°C., d. (110); R = CH_3, m.p. 201°C., d. (59)) would seem to preclude the quaternary salt structure. The existence of an *N*-methyl hydroiodide as the structure for XXIV is extremely dubious under the conditions of the experiments (i.e., in the presence of excess alkali). Finally it should be noted that in the one experiment where sodium ethoxide was used in place of potassium hydroxide, no substance resembling XXIV was reported. This might be interpreted to mean that in the potassium hydroxide reactions XXIV was formed *after* a small quantity of the phthalazone had hydrolyzed, a reaction rather less probable when sodium ethoxide in ethanol was used, and that accordingly XXIV is an addition compound between methyl iodide and the hydrazone of phthalaldehydic acid. In any case XXIV is not a methylhydrazone hydroiodide: first because of the alkaline medium, and secondly because such a hydrazone would cyclize to yield 2-substituted phthalazones (*cf.* equation 6). Consequently it would appear that more investigation of this particular reaction is in order.

F. Acylation

The behavior of phthalazones with acylating agents has not been extensively investigated. A few acetyl or benzoyl derivatives have been prepared (22, 142, 163, 184), and it is possible that these are *N*-acyl derivatives in spite of the assertion of Rowe and Peters that phthalazones must yield exclusively *O*-acyl derivatives. Their belief appears to be based upon the fact that the acetyl derivatives which they prepared were readily hydrolyzed to the free phthalazones by simply refluxing with alcohol (142). Of course it is well known that amides also may

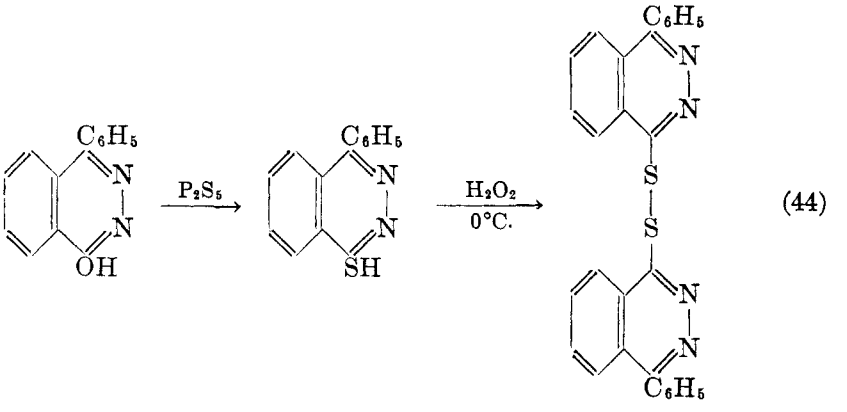
be deacylated by reaction with an alcohol, and since it has been demonstrated that wherever a reaction has been devised to yield an *O*-acyl derivative of an amide, the isomeric *N*-acyl amide has been obtained instead (23, 105), it would seem more probable that the acyl derivatives of the phthalazones are the *N*-acylated compounds, even though the non-aromatic system is thus apparently favored over the aromatic system of phthalazine.

G. Amphoteric character

The solubility of phthalazones in concentrated mineral acids attests to the basic character of N^3, while the solubility of the same substances in strongly alkaline solutions shows that the lactim form, in which the hetero-ring is fully aromatic, has a certain amount of stability, though apparently not enough to permit the isolation of salts (61, 142).

H. Reaction with phosphorus pentasulfide

Finally, the reaction of the lactim form of phthalazones with phosphorus pentasulfide has been found to yield sulfhydrylphthalazines (mercaptophthalazines), which would seem to have a possible use as accelerators in the vulcanization process (4) and which on oxidation yield disulfides:



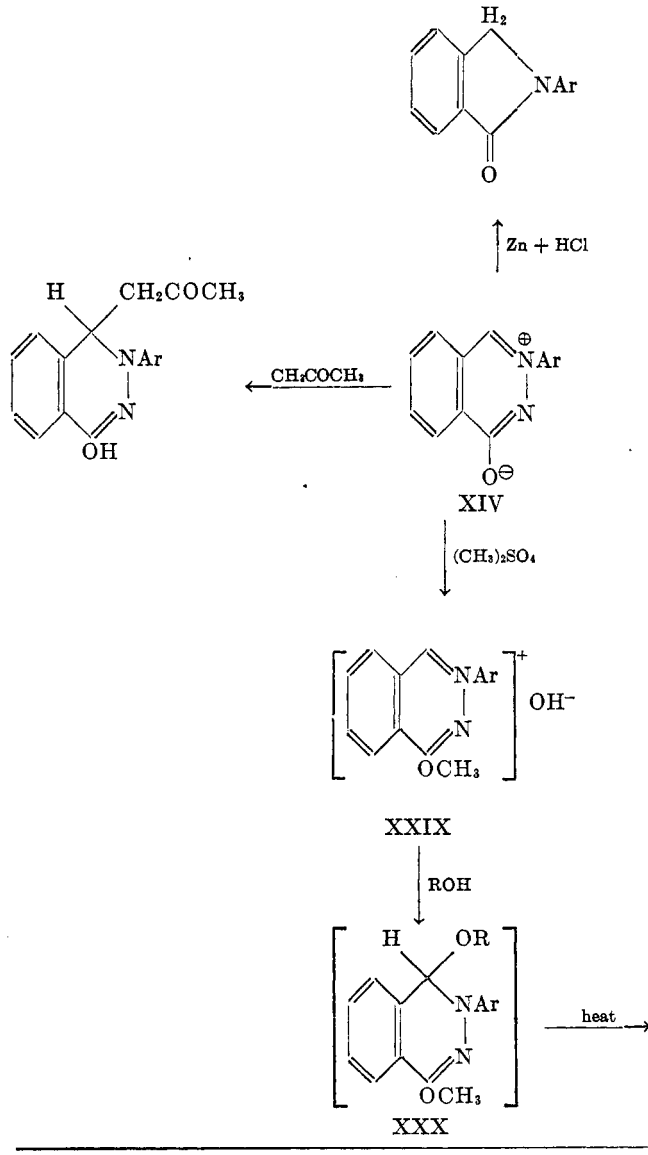
(44)

VIII. PSEUDOPHTHALAZONES

The preparation by Rowe and his associates of 3,4-dihydrophthalazone derivatives (XI; equations 10, 16, 17) has already been discussed (page 459); and the possibility of 1,4-oxidation of these 3,4-dihydrophthalazones to substances isomeric with and transformable into 2-arylphthalazones has also been described (equation 18). The 3-arylpseudophthalazones XIII and XIV are readily reduced to *N*-arylphthalimidines (127–145) just as are their isomers, the 2-arylphthalazones (20, 34, 35, 55, 61, 117) (*cf.* page 475).

Both XIII and XIV may be transformed into derivatives of phthalhydrazide by essentially similar reactions. Equations illustrating these and other transformations are given in table 2. These reactions are drawn from an important series of papers on the general subject of phthalazine chemistry by Rowe and his

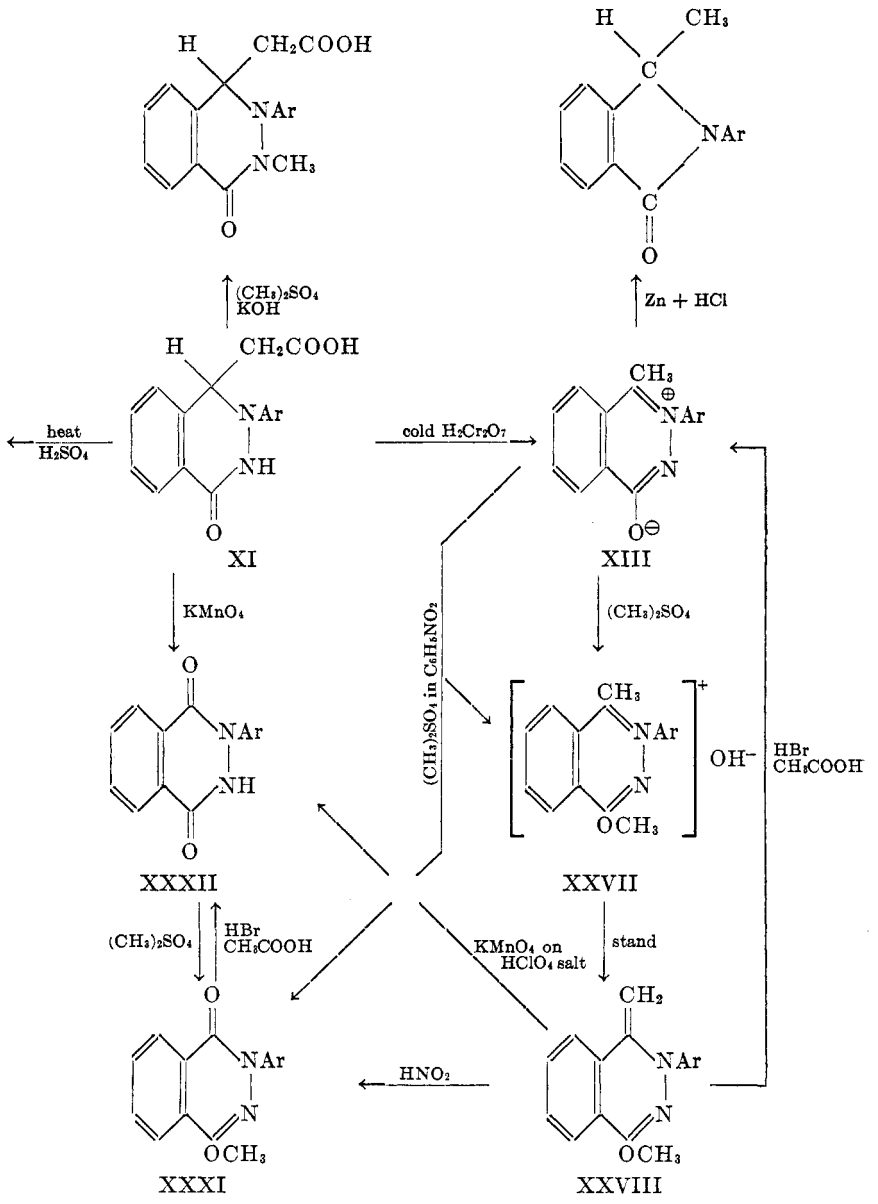
Pseudophthalazones



associates (127–145). The concept of structure was not altogether clear in the earlier papers, but starting with reference 141 the structures used in the present work were proposed with experimental data to support them. The nomenclature,

TABLE 2

available from 3-aryl-3,4-dihydrophthalazones



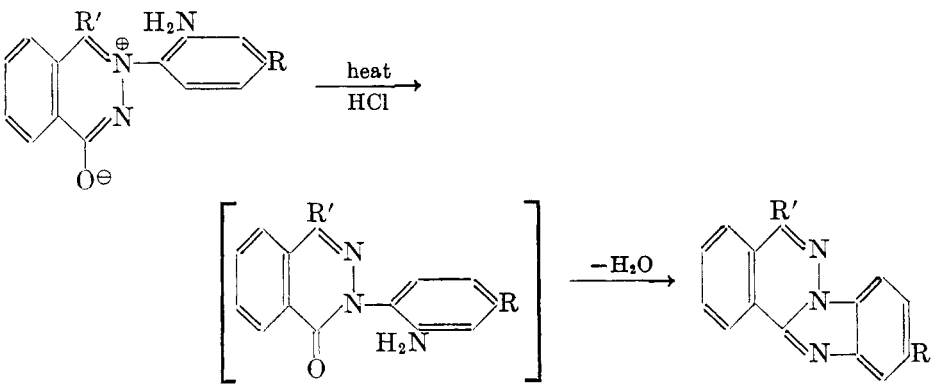
however, of the older papers was retained in order to preserve homogeneity in the series; but as stated in the introduction to the present paper, an attempt has been made to conform as closely to the current *Chemical Abstracts* nomenclature

as possible. In order to avoid confusion in visualizing structural formulae from a systematic name, the term "pseudophthalazone" has been introduced for structures such as XIII and XIV, in which a betaine structure arises from the 3-aryl group. The present writer feels this to be more satisfactory than following the procedure of Rowe, who refers to the betaines as phthalaz-1-ones and the normal structures as phthalaz-4-ones. Thus three new syntheses are available for the preparation of *N*-arylphthalhydrazides (XXXII): direct oxidation of XI to XIII with subsequent transformation, or oxidation of XI to XIV with subsequent transformations. It should be mentioned that the reaction XI → XIII may also be effected by means of alcoholic potassium hydroxide, while the reaction XXVIII → XXXI may be effected by warming XXVIII with *p*-nitrosodimethylaniline. The addition of acetone to XIV was studied in only one instance (143).

The presence of the external methylene group in XXVIII on C^4 is clearly demonstrated by numerous reactions characteristic of such a structure (145). The reaction with nitrous acid (XXVIII → XXXI) is analogous to a reaction reported by Kuhn (89). In addition, the reactions in table 3 are selected from among the more interesting types.

If an *o*-nitro group is present in the 3-aryl group of the pseudophthalazone XI, certain modifications are introduced into the over-all reaction scheme (R = CH_3 or Cl), as illustrated in the reactions in table 4. The reactions XLI → XLII and XLI → XLIII occur simultaneously, with the latter reaction predominating. The tetrahydrophthalazine (XLII) obviously corresponds to a reduced form of XXXVIII.

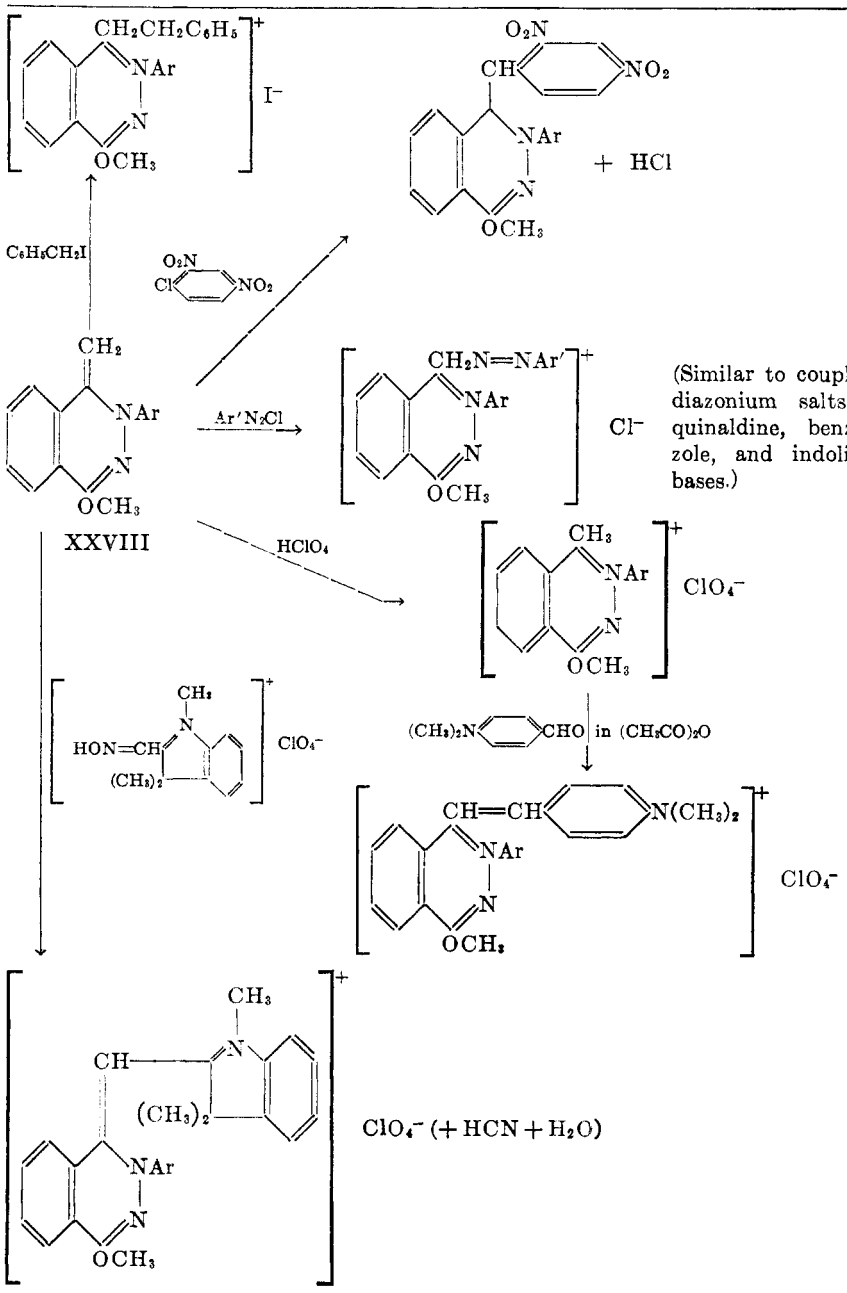
Objections may be raised, and with good reason, to structures XLI and XXXVII, even as intermediates as proposed by Rowe (127), since they obviously embody flagrant contradictions of Bredt's rule prohibiting double bonds at bridgeheads in bicyclo systems. Hence the following hypothesis is offered for consideration:



Where R′ = CH_3 (XXXVIII) the reaction has reached an end, but where R′ = H (XXXVIIIa) further reaction is possible, since hydrolysis of the original hetero-ring yields a labile system, the resultant aldehyde and hydrazine derivative

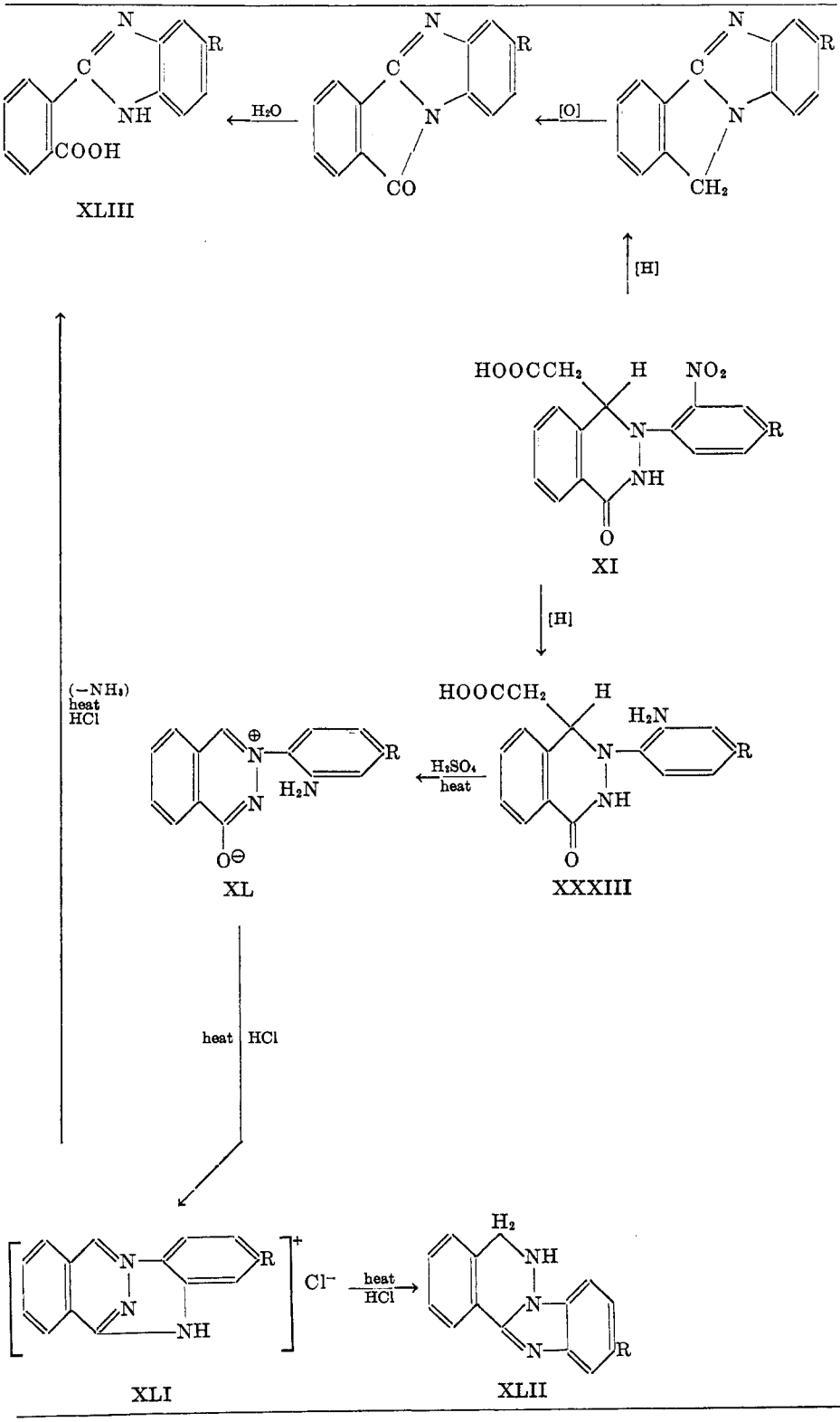
TABLE 3

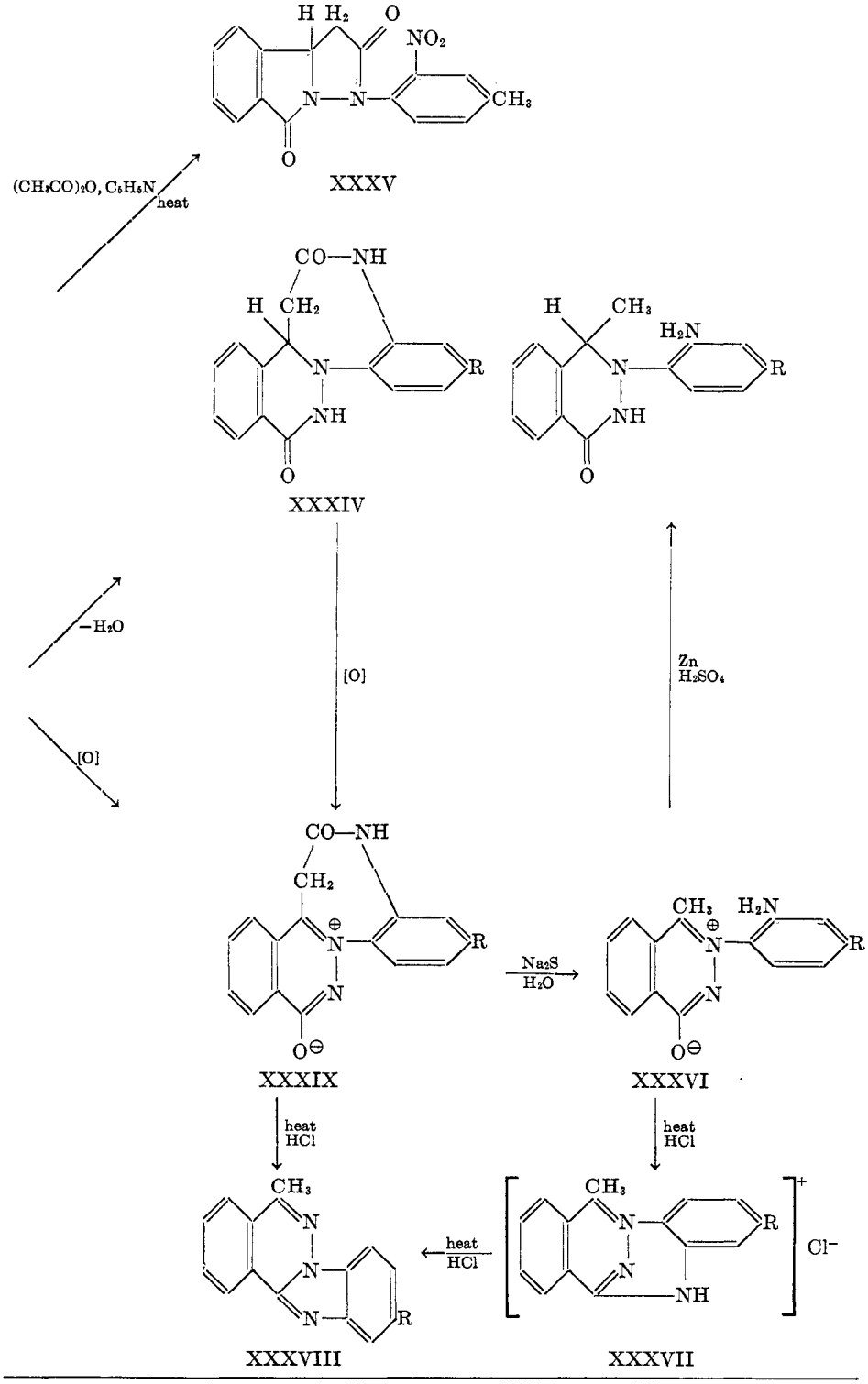
Reactions of 1-methoxy-3-aryl-3,4-dihydro-4-methylenephthalazine



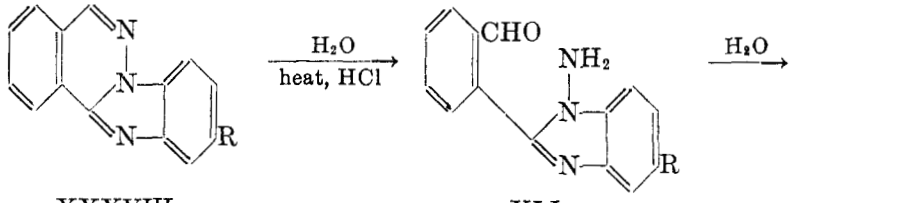
TABLE

Substances available from 3-[2'-nitroaryl]-

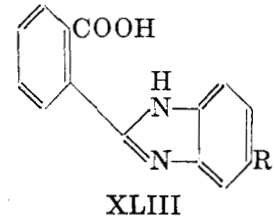



XXXV
(CH3CO)2O, C5H5N, heat
XXXIV
−H2O
[O]
[O]
Zn, H2SO4
Na2S, H2O
XXXIX
XXXVI
heat, HCl
heat, HCl
heat, HCl
XXXVIII
XXXVII
Cl−

being capable of entering into an oxidation–reduction reaction which would not be possible with the ketonic hydrolysis product of XXXVIII:



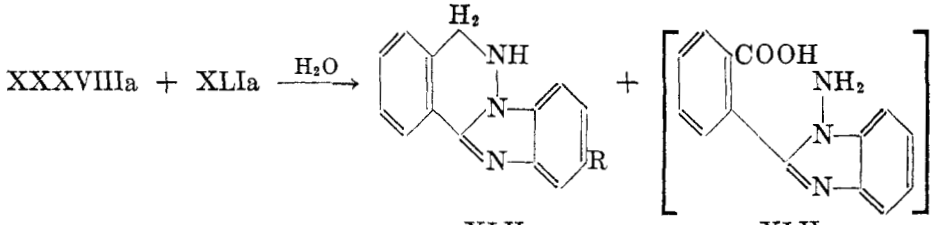
XXXVIIIa XLIa



+ NH_3

XLIII

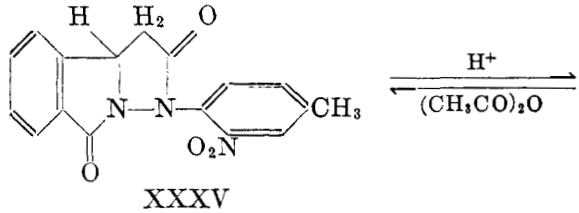
and



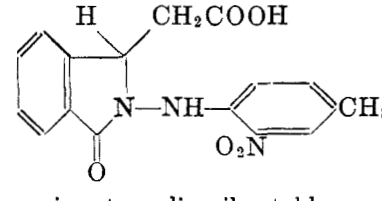
XLII XLIIa

The substance XLIIa (or its lactam) was not isolated, but it seems a reasonable possibility in view of the nature of the other reaction products. In any event it would be present in small amount since but relatively small quantities of XLII were isolated, the predominating reaction being the intramolecular oxidation–reduction yielding XLIII and ammonia.

The transformation XI → XXXV is unusual, and the lactam structure thus established opens reversibly:



XXXV



(45)

The lactam XXXIV (R = CH_3), however, is extraordinarily stable.

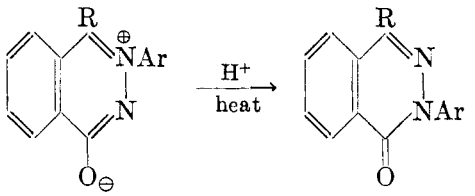
The rearrangements which occur in XL → XLII, XXXVI → XXXVIII, and XXXIX → XXXVIII are similar to those described for the less complex rearrangement of XIII into XV or XIV into XVI (page 463). Together they represent the general reaction involving the rearrangement of the betaine struc-

TABLE 5

Effect of substituents in migrating aryl group

Ar	R = H	R = CH_3
	per cent	*per cent*
4-Nitrophenyl	66	82
4-Nitro-2-methylphenyl	20	27
4-Nitro-2-chlorophenyl	—	49
4-Nitro-2-bromophenyl	—	27
4-Nitro-2,6-dichlorophenyl	46	17
4-Nitro-2,6-dibromophenyl	20 (10 hr.)	—
3-Nitrophenyl	14	25
2-Nitrophenyl	—	65
2-Nitro-4-methylphenyl	36	53
2-Nitro-4-chlorophenyl	68	74

ture of the pseudophthalazones into the true phthalazone structure. This reaction is acid catalyzed and may well be called the Rowe rearrangement:



(46)

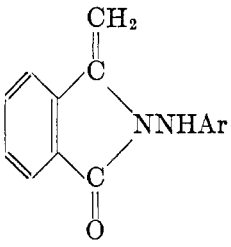
XIII: R = CH_3 XV: R = CH_3
XVI: R = H XVI: R = H

This reaction has been studied with particular attention to per cent conversion, rates, and the general nature of the rearrangement (127). It is best effected by heating the pseudophthalazone with 1.2 *N* hydrochloric acid in a sealed tube for 6 hr. The ease of conversion depends largely upon the nature of the aromatic group and to a certain extent upon the nature of R. In table 5 are listed the conversion yields expressed as per cent after heating at 180°C. for 6 hr.

The following general observations are possible: 2- and 4-nitro groups facilitate the rearrangement, while a 3-nitro group does not; halogens in the 2- and/or 4-positions and methyl in the 2- and the 4-positions appear to retard the reaction.

From rate studies the reaction appears to be unimolecular, the rate constant varying from 4×10^{-4} to 48×10^{-4}. The intramolecular character of the rearrangement was established by using mixtures of pseudophthalazones (different Ar and R groups) in the rearrangement reaction. In all experiments no exchange was observed.

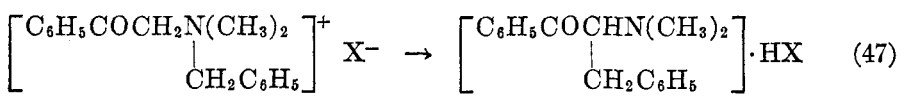
The course of the reaction was studied, and it was found that an intermediate of structure



XLIV

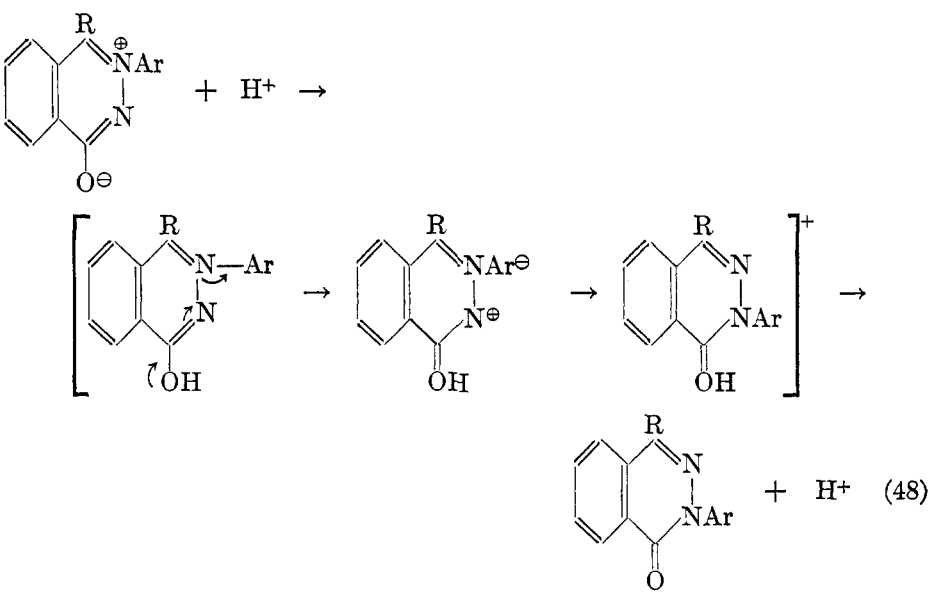
occasionally was formed at the reflux temperature from XIII. Such substances were stable against bromine addition and resisted reduction by iron in acetic acid; but they were capable of transformation into XV by prolonged heating (180°C. in sulfuric acid). However, since the rearrangement also occurred with XIV, where such an intermediate is obviously impossible, it was concluded that the formation of such intermediates did not indicate the actual course of the reaction XIII → XV, but represented rather a side reaction, which also yielded some demethylated product (XVI) as well as the chief product (XV).

The mechanism proposed by Rowe is likened by him to the mechanism suggested for the rearrangement of phenacylbenzyldimethylammonium salts (164):



(47)

The Rowe rearrangement is formulated as follows (127):

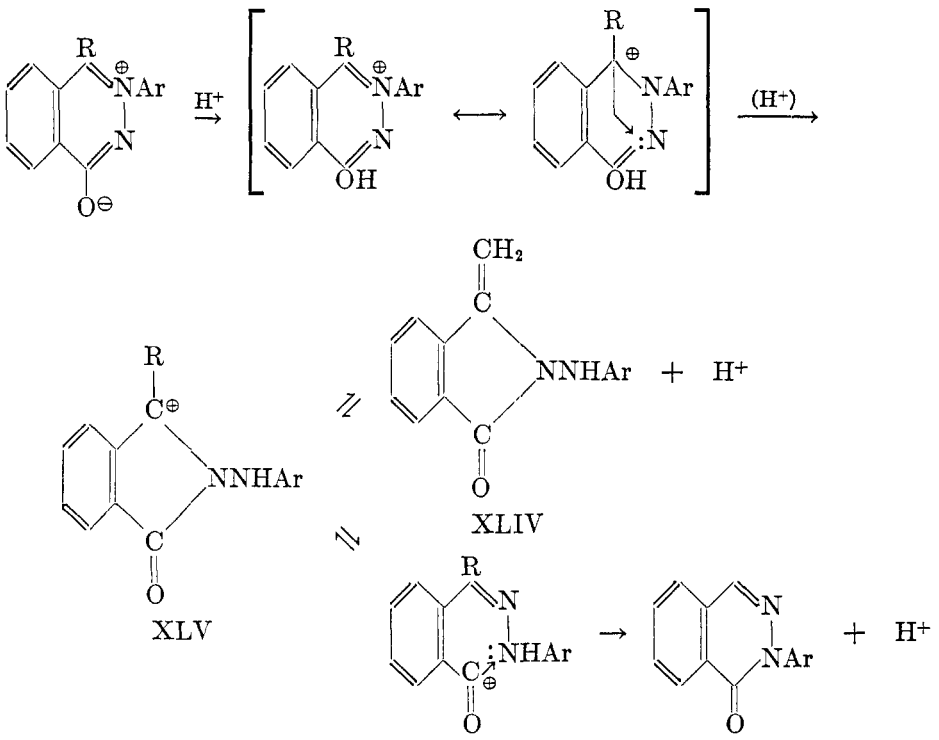


(48)

The intramolecular reaction thus described is completely analogous to other rearrangements involving carbonium ions, in which a group with its bonding pair of electrons shifts to an adjacent atom (*cf.* 72).

Rowe's isolation (127) of compounds such as XLIV suggests an alternative mechanism in which the rearrangement occurs through the intermediate formation of a five-membered ring, followed by a second rearrangement enlarging the ring to six members again (the latter step is analogous to the transformation of *N*-aminophthalimides into phthalhydrazides, which, however, is base catalyzed, as discussed on page 465). Such a course for the reaction was originally discounted by Rowe, since such an intermediate five-membered ring structure, as noted above, is impossible where the C^4 of the original pseudophthalazone carries a hydrogen atom instead of a methyl group; but this objection is valid only so long as one considers that the intermediate must be stable, capable of finite existence, or actually isolable.

The following alternative mechanism (*cf.* equation 51, page 492) is proposed for the Rowe rearrangement, and its validity might be tested by the use of isotopic nitrogen, since it requires that the aryl group remain attached to the same nitrogen throughout rather than being transferred as required by Rowe's mechanism. The driving force initiating the formation of the intermediate XLV may be considered an attack of a proton on the nitrogen carrying the aryl group, thus displacing the C^+ which subsequently ejects the original proton.



This course of reaction obviously is independent of the nature of R, and Rowe's isolation of substances with the structure XLIV may be explained by the reaction XLV → XLIV + H^+ (where R = CH_3), where the intermediate XLV, under conditions mild enough to permit its formation without immediate rearrangement, stabilizes itself by ejecting a proton. Such stabilization is impossible where R = H; hence the only reaction possible is the complete rearrangement to the true phthalazone structure, which is possible only under conditions more drastic than those required for the transformation yielding XLIV. Finally, the transformation of XLIV into the true phthalazone structure, which as noted above occurs under conditions suitable for the complete rearrangement, may be regarded as an addition of a proton to XLIV, regenerating XLV (R = CH_3), which then follows through to the true phthalazone, losing a proton as the final transformation occurs.

IX. REACTIONS OF THE PHTHALHYDRAZIDES

A. Oxidation and reduction

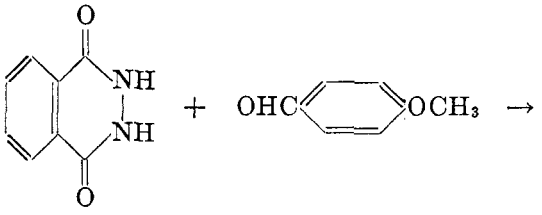
Both the oxidation and the reduction of phthalhydrazide have been studied by Curtius (31), who reported that the substance was oxidized by strong oxidizing agents to phthalic acid and nitrogen, but that it was completely indifferent to reducing agents except for an apparent cleavage into phthalic acid and hydrazine upon heating with zinc and concentrated hydrochloric acid. The inertness to reducing agents makes possible the reduction of nitro groups in the carbocyclic ring (synthesized from substituted phthalic acids) and subsequent reactions of the new amino group (32, 33).

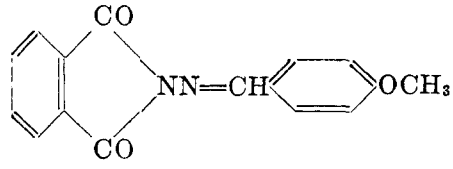
B. Resistance to substitution and hydrolysis

In the same paper phthalhydrazide was shown to resist sulfonation, nitration, and bromination under the usual conditions for these reactions, and indeed to resist even very vigorous attempts to hydrolyze the azide ring.

C. Isomerization

The conversion of *N*-aminophthalimides to the isomeric phthalhydrazides has been considered in the section on the preparation of phthalhydrazides; until comparatively recently it was thought that this process was not reversible. However, in a preliminary study of the preparation of phthalhydrazides Drew and Hatt were able to show that such a reversal was indeed possible and to suggest a mechanism for it (45). A chance observation some years earlier by Mihăilescu (100) was wrongly interpreted to indicate that he had obtained *N*-aminophthalimide from a reaction between phthalic acid and hydrazine. It was later shown (122) that Mihăilescu actually had prepared the isomeric phthalhydrazide. The reaction leading to this confusion was correctly interpreted by Drew and Hatt as follows:

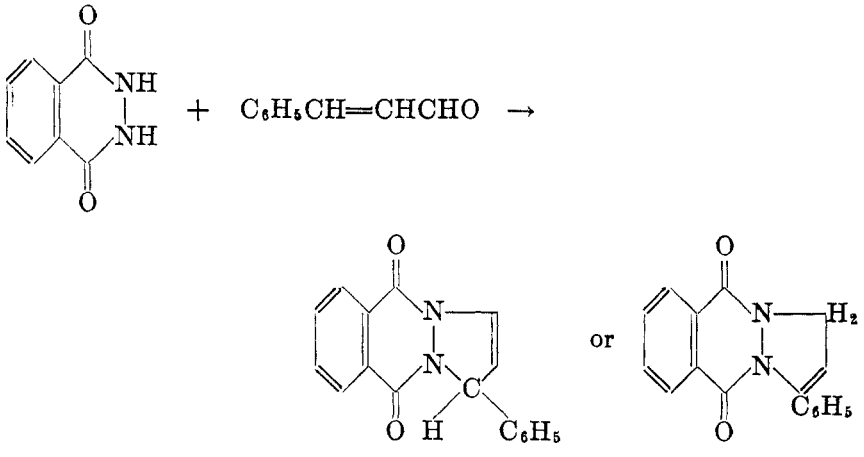




(49)

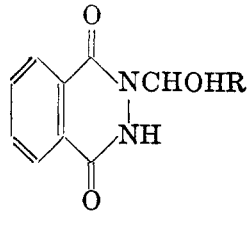
The reaction is unexpected, and it is not surprising that it was mistaken for a condensation of *N*-aminophthalimide with anisaldehyde to yield the same product.

Drew and Hatt further demonstrated that the reaction may be a general one for aromatic aldehydes, and in the reaction between phthalhydrazide and cinnamaldehyde is to be found a clue to the reaction mechanism.

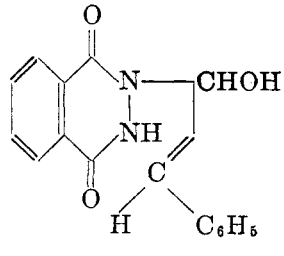


(50)

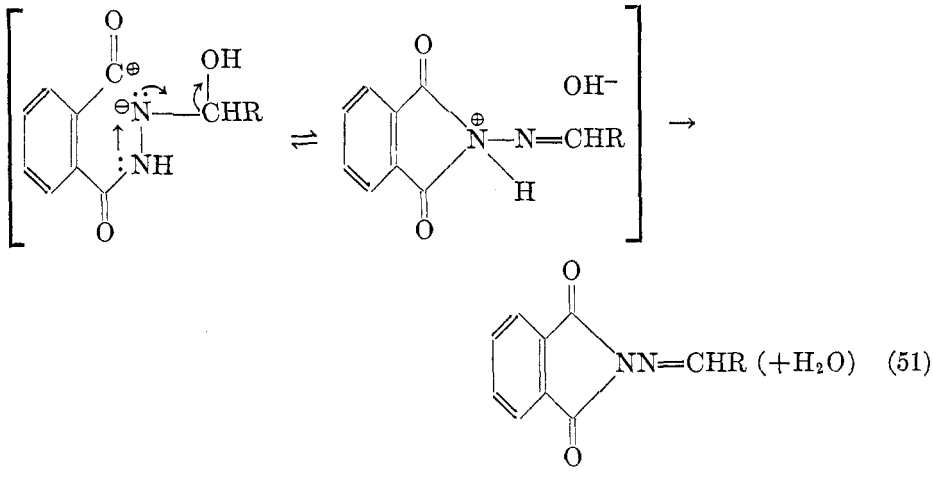
Upon first inspection this reaction would appear to be anomalous (*cf.* reaction 49), but it is interpreted to show that the primary reaction of aldehydes with phthalhydrazide is *addition* to yield:



or for cinnamaldehyde to yield:



which then cyclizes with loss of water to yield a tricyclic structure (equation 50) which prevents the more characteristic rearrangement from occurring. Where no such cyclization is possible the rearrangement is illustrated as follows:

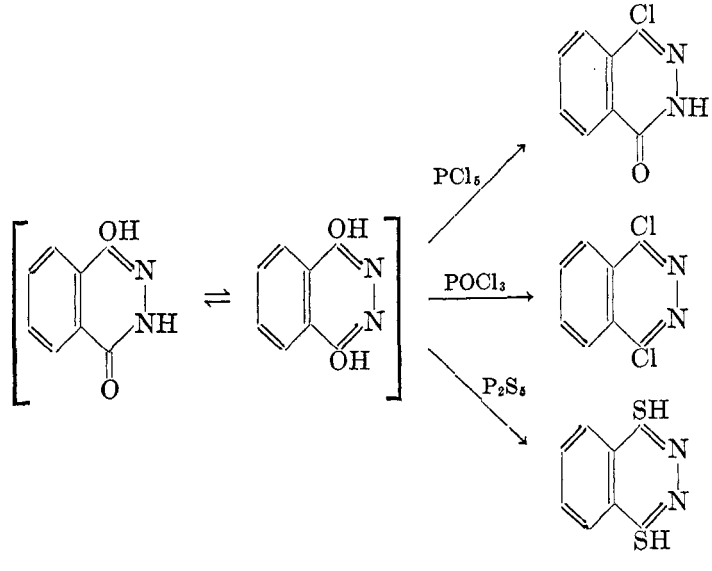


(51)

Drew likens the rearrangement to the pinacol rearrangement, but the present writer prefers to consider it on its own merit for the present.

D. Reactions with phosphorus halides and phosphorus pentasulfide

The existence of phthalhydrazide in either the lactam–lactim or the dilactim form is possible and thus permits the ready preparation of phthalazone and phthalazine derivatives (4, 122, 195):



(52)

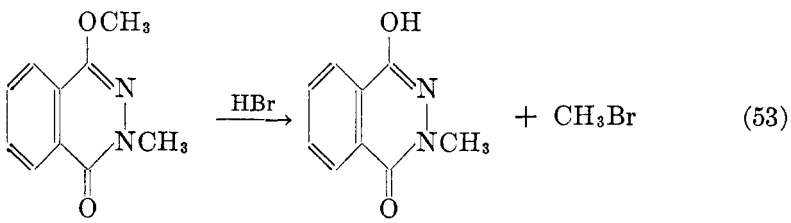
E. Acidic character

Solutions of phthalhydrazide in water are acid to litmus (122), and the preparation of metallic salts (monovalent) from various phthalhydrazides has long been a well-known reaction (21, 31, 76, 122). Indeed, phthalhydrazides are sufficiently acidic to yield stable salts with ammonia or with hydrazine (32, 33, 113). This immediately suggests the existence of phthalhydrazide as the lactam–lactim structure in aqueous media, but since there is undoubtedly a tautomeric equilibrium, any arguments as to the absolute structure in solution are without significance. At most one might state that the lactam–lactim form predominates sufficiently to cause an acid reaction to litmus.

F. Alkylation and acylation

By far the most controversial problem in phthalhydrazide chemistry is the nature of the various alkyl and acyl derivatives. Very early Curtius reported the preparation of what he believed to be *N*-methylphthalhydrazide, m.p. 235°C. (31), from a reaction between silver phthalhydrazide and methyl iodide at an elevated temperature and pressure. Subsequently Rădulescu (122) reported what he believed to be an *O*-methylphthalhydrazide (i.e., 4-methoxyphthalazone), m.p. 232°C., but this was subsequently identified with Curtius' product (45, 142). True 4-methoxyphthalazone, m.p. 187–188°C., may be obtained by refluxing silver phthalhydrazide with methyl iodide in methanol (142; *cf.* 76).

Rădulescu also reported the preparation of 1,4-dimethoxyphthalazine, m.p. 77°C., by the alkylation of phthalhydrazide, but Rowe and Peters (142) repeated this work and obtained a substance similar to that of Rădulescu but melting after extensive purification at 93°C. Further, Rowe and Peters were able to demethylate their product to the known *N*-methylphthalhydrazide (melting point variously reported in the range 232–238°C.):

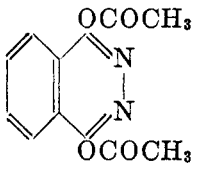


(m.p. 93°C.) (m.p. 238°C.) (53)

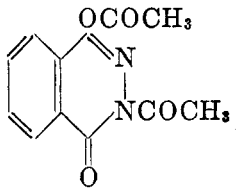
The melting point of 2-methyl-4-methoxyphthalazone is quite in line with that of 2,4-dimethylphthalazone (respectively 112°C. (142; *cf.* 59) and 109–110°C.), as are its mildly basic properties which originally suggested to Rădulescu the (erroneous) 1,4-dimethoxyphthalazone structure; the compound having this structure was obtained by Drew and Garwood (42) and found to melt at 121°C. However, 2,3-dimethylphthalhydrazide, m.p. 175–176°C., has been prepared by Drew and his collaborators from *N*,*N*′-dimethylhydrazine (45); various other

N,*N*′-disubstituted (alkyl and aryl) phthalhydrazides have been similarly prepared (85, 96).

The problem of acetylation is rather more difficult to settle by purely chemical methods. Ever since Curtius (31) first reported a diacetylphthalhydrazide, m.p. 114°C., the structure of acylphthalhydrazides has been in doubt. Curtius without hesitation assigned an *N*,*N*′-diacetyl structure to his product, and his precedent has been followed by most subsequent investigators (32, 64, 113). Rădulescu (122) reported the synthesis of two diacetylphthalhydrazides which he believed to be:



and



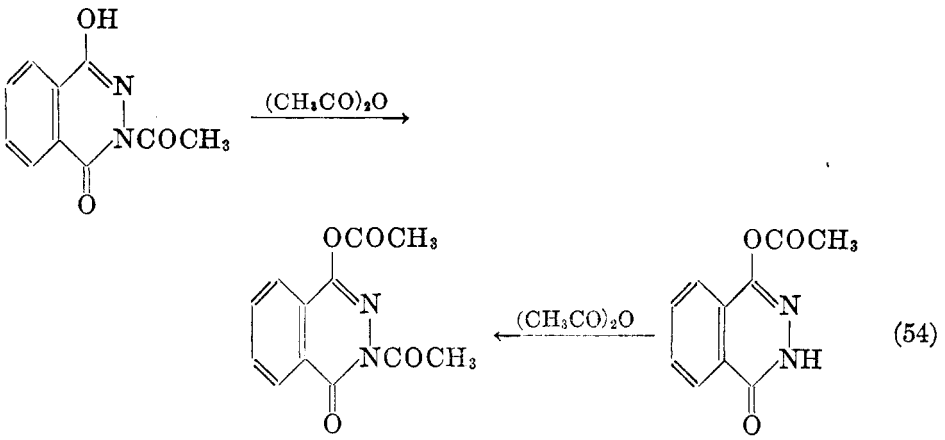
(m.p. 126°C.) (m.p. 133°C.)

The lower-melting isomer he described as stable, while the higher-melting compound he found to be labile. Subsequently Rowe also investigated the acetylation of phthalhydrazide (142), but he was able to obtain only the lower-melting isomer to which he assigned the 1,4-diacetoxyphthalazine structure preferred by Rădulescu for his lower-melting derivative. The basis for Rowe's assignment was simply the very ready hydrolysis of his product.

This phase of the controversy finally yielded to direct experimental proof. Drew (45) produced incontrovertible evidence that the compound melting at 133–134°C. (which upon careful purification melted at 139–140°C.) was indeed the 2-acetyl-4-acetoxyphthalazone, as claimed by Rădulescu. Simultaneously the question of monoacetylphthalhydrazide was also partially settled: the existence of *two* monoacetyl derivatives with very nearly the same melting point, 172–173°C. and 175–176°C., was established, since the two substances markedly depressed each other's melting point. The latter substance is produced by direct acetylation or by treatment of phthalhydrazide with acetyl chloride in pyridine, while the former is produced by boiling the diacetyl derivative with alcohol (45). Drew and Hatt wisely refrained from a positive assignment of structure to their two monoacetylphthalhydrazides.

Heller and his collaborators (76) prefer the *O*-acetyl structure for the monoacetylation product from acetyl chloride, as do Rowe and Peters (142), but the latter also may have obtained the *N*-acetyl isomer as well, since their "1,4-diacetoxyphthalazine" (now recognized as 2-acetyl-4-acetoxyphthalazone) yielded what they thought was the product of monoacetylation upon hydrolysis. They overlooked the non-identity of their monoacetyl derivatives by failing to take a mixed melting point on them.

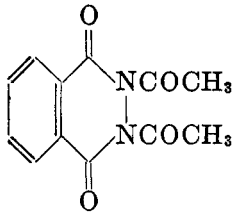
Drew's evidence for the correct structure of the diacetyl derivative is based upon the acetylation of each of his different monoacetyl derivatives to yield the *same* diacetyl derivative:



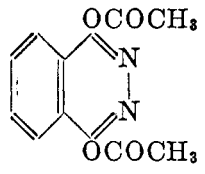
(54)

Obviously for this proof it is not necessary to know the absolute structure of either monoacetyl derivative, only that there are two *different* monoacetylphthalhydrazides. Attempts to prove the structure of either of the monoacetyl derivatives by synthesis of the *N*-acetyl isomer using either acetyl- or *sym*-diacetylhydrazine failed, since only *N*-acetamidophthalimide was isolated. Except for conclusive evidence that *alkylation* yields first an *N*-alkyl derivative and then an *O*,*N*-dialkyl derivative (197), except where a third six-membered ring can be formed (75), there is no argument sufficiently valid for an absolute structure assignment, and the exact nature of the two monoacetylphthalhydrazides will not be known with any certainty until they can be examined in the infrared, where one may expect to observe marked differences between *N*-acetyl and *O*-acetyl compounds. The only authenticated *N*,*N*-diacylphthalhydrazides are obtained where a third six-membered ring is formed (45).

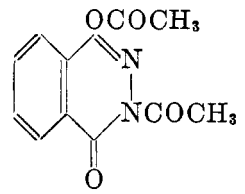
The status of acetylphthalhydrazides may be summarized as follows:



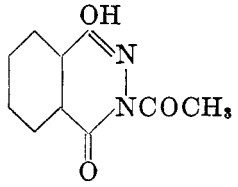
(m.p. 114°C.)
Curtius (31) (?)



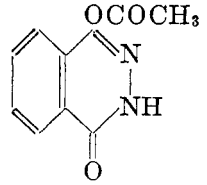
(m.p. 126°C.)
Rădulescu (122) (?)



(m.p. 139–140°C.)
Drew and Hatt (45)

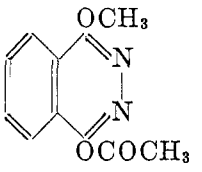


(?) {(m.p. 172–173°C.) (m.p. 175–176°C.)
Drew and Hatt (45)

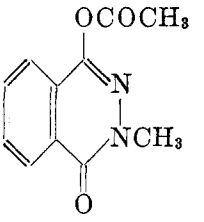


(?) {(m.p. 172–173°C.) (m.p. 175–176°C.)
Drew and Hatt (45)

Rowe and Peters also investigated the formation of acetyl derivatives from both *O*- and *N*-methylphthalhydrazide (142) and reported the existence of an *O*-acetyl derivative in each instance:



and



(m.p. 137°C.) (m.p. 142°C.)

Once again the basis for their assignation of structure is the ready hydrolysis of the acetyl group, but in view of incomplete data and the misinterpretation of the structure of the diacetylphthalhydrazides in the same paper, extreme caution must be used in accepting these as the correct structures until further experimental evidence is available.

G. N-Substitution yielding acid derivatives

Finally, several investigators have reported the preparation of phthalhydrazides with carboxylic acid or ester groups attached to the nitrogen by the reaction of a salt of phthalhydrazide with carbethoxy chloride or ethyl chloroacetate (31, 32, 76, 113) see page 497. The former, as might be expected, yields phthalhydrazide upon hydrolysis of the ester group, but the latter yields the phthalhydrazidoacetic acid. It is interesting to note that despite several attempts to hydrolyze the latter substance to hydrazinoacetic acid (*N*-aminoglycine), no such product was isolated (31).

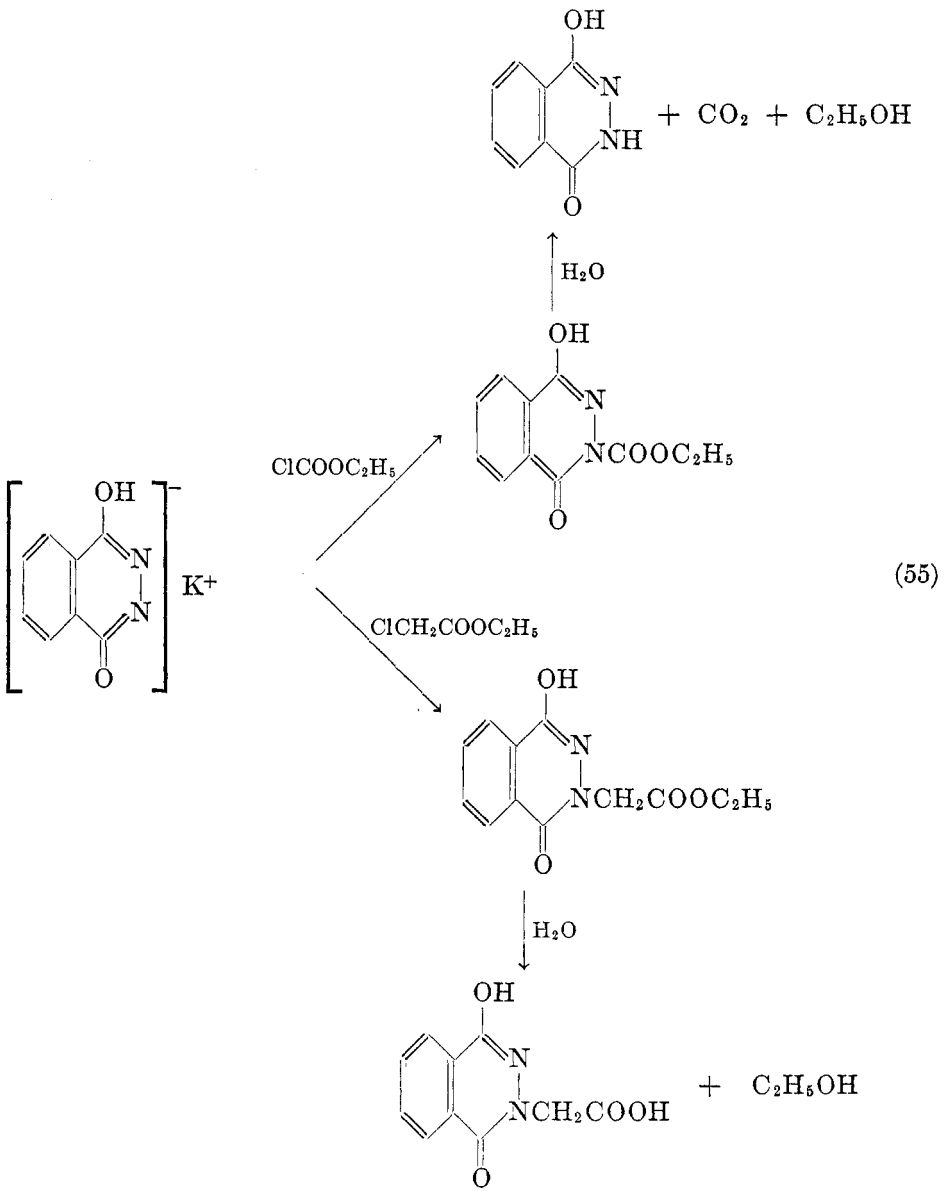
The preparation of an *O*-carbethoxy derivative (76) is to be discounted, owing to lack of sufficient evidence. The same author reports a 2,3-dicarbethoxy derivative formed in the same reaction; once again conclusive experimental data is lacking, and arguments based on the relative ease of hydrolysis of such compounds are specious.

X. CHEMILUMINESCENCE

Certain phthalhydrazides are capable of marked chemiluminescence in the course of being oxidized. In particular, 5-aminophthalhydrazide, which has become generally known as "luminol," exhibits this phenomenon in a rather spectacular fashion. These substances are structurally the same as the ordinary phthalhydrazides, and their synthesis is achieved by the same general procedures (*cf.* Section IV and references 42, 44, 46, 83, 178, 189, 193, 196).

A. Nature of the phenomenon

The underlying cause for chemiluminescence seems to be an oxidation reaction involving hydrogen peroxide (36, 73, 74, 82) or ozone (18). There have been observed instances of chemiluminescence in the presence of oxygen alone dissolved in water, but activation, achieved by means of ultrasonic vibration, would



(55)

seem either to produce hydrogen peroxide *in situ* (53) or to activate the dissolved oxygen directly in some other manner (17). Details for producing a spectacular display of chemiluminescence from hydrogen peroxide and luminol for lecture demonstration purposes are readily available (82).

B. Promoters or accelerators

While the phenomenon is observable without them, certain substances act as very strong promoters or accelerators: hemoglobin (18, 91, 123, 148, 149, 161,

169, 188); certain plant chemicals (124, 150); certain inner complex salts such as phthalocyanines (26, 150, 174) and salicylaldehyde–ethylenediamine–ferric chloride (174, 188); and various metallic ions —cupric, ferrous, manganous, cobaltous, and cobaltic, but not nickel (63, 161, 166, 176). There are also a few specific inhibitors: potassium cyanide, sodium sulfide, hydroquinone, acetone, pyridine, phenol, and others (186, 187).

C. Applications

Since the various promoters enormously increase the intensity of the luminescence, there are certain practical uses for the phenomenon. Among these may be listed qualitative tests for the presence of hydrogen peroxide, especially in the

TABLE 6

Chemiluminescence of various phthalhydrazides

(The substances are arranged in order of decreasing brightness. With the exception of No. 6, all are derivatives of phthalhydrazide (No. 15). The reactions were carried out at 18°C. with hemoglobin as a promoter.)

NO.	PHTHALHYDRAZIDE	NO.	PHTHALHYDRAZIDE
1	5-Amino*† (luminol)	11	6-Acetylamino
2	5-*N*-Methylamino†	12	5,8-Diamino
3	5,8-Diacetylamino†	13	5-Benzoylamino
4	5-Hydroxy‡	14	5-Hydrazino-β-sulfonate
5	5-Hydrazino	15	Phthalhydrazide
6	Pyromellitaz-1,4,6,9-tetraone	16	6,7-Diamino§
7	5-Acetylamino	17	5-Nitro†
8	6-Amino	18	6,7-Dichloro‡
9	5,9-Dichloro	19	6-Nitro
10	5-Chloro	20	For more complex compounds see references 41 and 44.

* A strong shift in the absorption curve maximum in 10 per cent hydrochloric acid (2900 Å.) and in 50 per cent sodium hydroxide (3500 Å.) is attributed to a tautomeric form (196).

† Two maxima in 0.1 *N* sodium hydroxide (196).

‡ One maximum in 0.1 *N* sodium hydroxide (196).

§ Prepared from 6,7-dichlorophthalhydrazide with ammonia and cuprous iodide (46).

presence of reducing agents (91), and similar tests for the presence of traces of ferrous, cobaltous, and cupric ions, and, with suitable precautions, blood (63, 123, 161, 162).

D. Luminescence spectra and absorption spectra

The intensity of the luminescence varies with the promoter and with the structure of the phthalhydrazide, and there seems to be some relationship between the luminescence spectra and the corresponding absorption spectra (28, 51, 114); in addition, the fundamental frequencies of bacterial bioluminescence and the chemiluminescence of luminol are identical (49). Table 6 illustrates the order of brightness of various phthalhydrazides as chemiluminescent substances, as well as a few facts regarding the absorption spectra of some of them (46, 196).

E. Effect of substituents on chemiluminescence

Certain generalizations based on the data of table 6 are of some interest. Ortho–para directors ($-I$ effect) increase chemiluminescence in the visible region, while meta directors ($+I$ effect) are weaker and probably have an opposite effect. Favorable groups in the 5- and 8-positions are more effective than in the 6- and 7-positions; and favorable groups in *both* 5- and 8-positions are better than in either alone *except* for the amino group, but the failure in this instance may be due to the highly absorbent character of the red solution. The intensity of luminescence is increased with two hydrazide rings (compound 6) (and the color of the visible light is changed). Finally it should be noted that a change in temperature alters the order of brilliance.

F. Lack of luminescence in five-membered-ring isomers

The five-membered-ring isomers (*N*-aminophthalimides) of these substances have been investigated and found not to exhibit chemiluminescence, but a study of the fluorescent properties revealed that phthalimides and phthalhydrazides containing an amino group ortho to the junction of the two rings (but *not* meta) are fluorescent. *N*-Aminophthalimides, however, are not fluorescent, but *N*-alkylphthalimides are (46).

G. Chemifluorescence

The general phenomenon of chemifluorescence seems to be related to chemiluminescence, and correlation of the two has received some study. The addition of a fluorescing substance (e.g., fluorescein) to a chemiluminescent reaction causes a change of color to that of the fluorescing substance (170) and may intensify the glow in the long-wave part of the spectrum while new absorption maxima appear (88, 115, 116). Luminol itself fluoresces (*cf.* preceding paragraph) at a pH somewhat less than 7 (19), with maximum brilliance at pH = 4.86 (185).

H. Mechanism of chemiluminescence

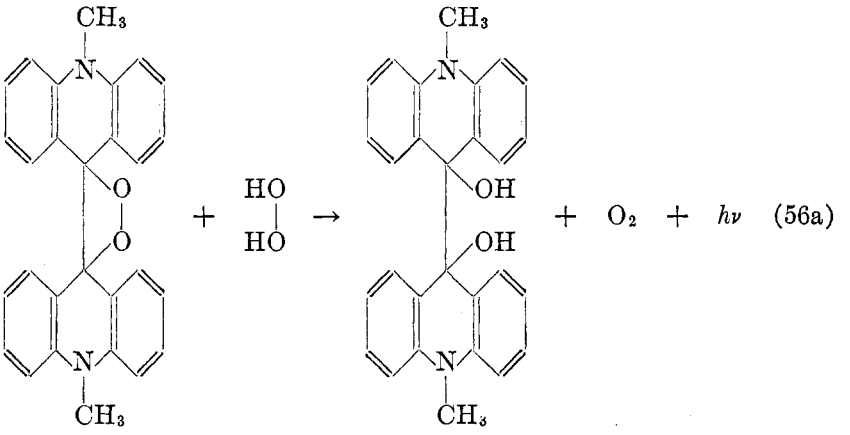
The problem of a mechanism for the whole process of chemiluminescence in the oxidation of luminol has received considerable attention since the first study by Albrecht (3). A discussion of work in this field up to 1939 is to be found in the papers by Drew (41) and by Weiss (191) in a series on the general subject of chemiluminescence presented to the Faraday Society, and a portion of the following discussion is in part abstracted therefrom.

Albrecht (3) first studied the chemiluminescent oxidation of luminol, and the following points constitute a summary of his findings: (*1*) luminol fluoresces (*cf.* above) in acid or neutral solution, the light being bluish (*cf.* 85, 185); (*2*) luminol exhibits a bluish chemiluminescence upon oxidation in alkaline solution; (*3*) many of the usual oxidizing agents produce momentary luminescence; (*4*) a prolonged, though weak, glow is obtained with hydrogen peroxide. This may be intensified (at the expense of the duration: the half-life of the luminescence is approximately the reciprocal of the brilliance (188), and its decay in *the absence* of antioxidants follows a bimolecular law (6)) by catalysts which decompose

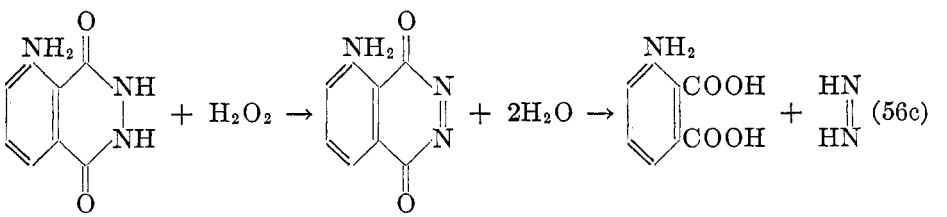
hydrogen peroxide (hemoglobin, cupric salts, etc.). The luminescence spectrum of luminol (and of 5-acetylaminophthalhydrazide) consists of bands "extending throughout the visible region, with ill-defined maxima at different regions in the blue-green; the fluorescence spectra are not identical with the luminescence spectra, but are similar in character" (41).

A preponderance of evidence has been accumulated (3, 41, 42, 65, 171, 177, 191, 198) purporting to show that the dilactim form of luminol is required for the reaction (i.e., a large excess of alkali must be present, and the phenomenon is not observable with *pure* samples of 2- or 3-alkylated luminols or with 1,4-dimethoxy-5-aminophthalazine). Furthermore the phthalhydrazide structure is essential also, since various isomeric structures do not exhibit chemiluminescence under comparable conditions even though oxidation may occur (46, 80).

It seemed possible to the earlier workers in this field (3, 65, 86) in view of available experimental data that an analogy with the behavior of dimethyldiacridinium salts in the presence of alkaline hydrogen peroxide was possible:

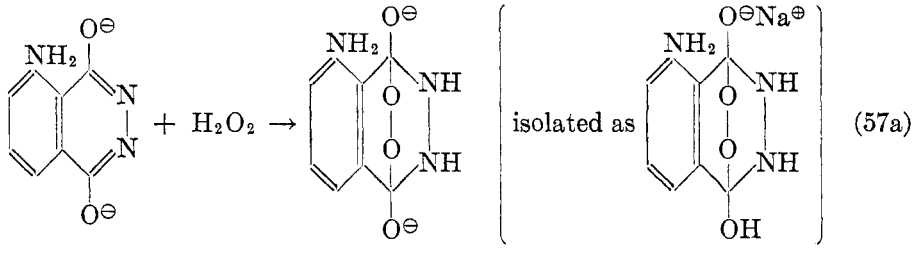


The hypothetical diimide, as well as the azodiacyl compound with which it reacts, arises in a preliminary non-luminescent reaction (3):



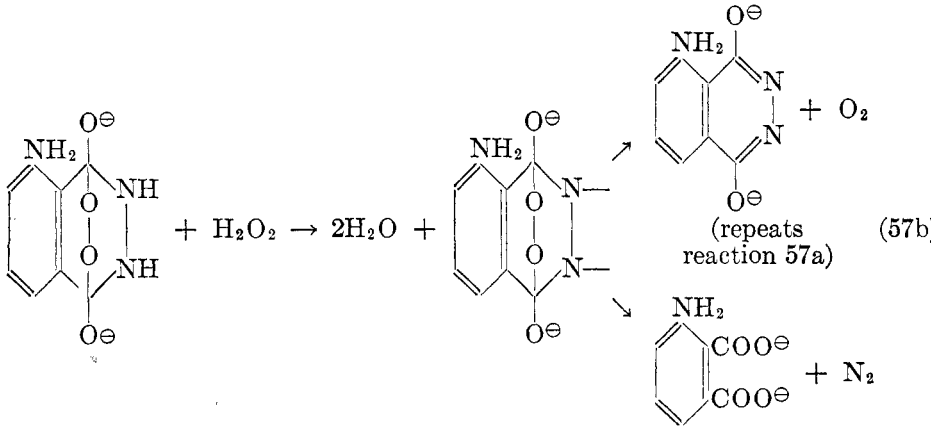
The view that luminol first hydrolyzes and that luminescence is then produced by oxidation of one of the hydrolysis products has been advanced by some workers (167, 168, 196). Without actually specifying the process it may be stated that such a mechanism is controlled by a reaction between the organic compounds and an unstable intermediate formed in the preliminary splitting of the hydrogen peroxide molecule. This hypothesis is flexible, and the rates of increase of initial luminescence with increasing concentration of oxidizable substance, the rates of decay of luminescence with the reaction time of different concentrations (of luminol), and variations in the quantum yield (per mole of hydrogen peroxide[5]) seem to support such a view.

Much of the fundamental exploration of this field was carried out by Drew and his associates, and he has contributed a mechanism which serves as a basis for further experimentation. Drew's mechanism represents something of a departure from the earlier ideas and was first suggested to him by the existence of the conjugated system in the dilactim form of luminol (or of any phthalhydrazide). Having concluded on the basis of experimental data (page 500) that the ion of the dilactim form was required for the reaction, he proposed addition of hydrogen peroxide to this ion as the first step:



(57a)

In subsequent experimental work he was able to isolate both sodium and barium salts of the peroxide ion (43). He then suggested two modes of decomposition, either (or possibly both) being the luminescent reaction, to account for the nature of the final products:



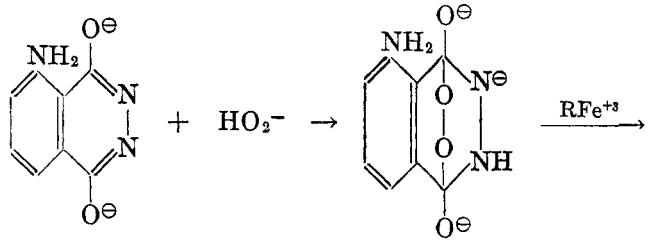
(57b)

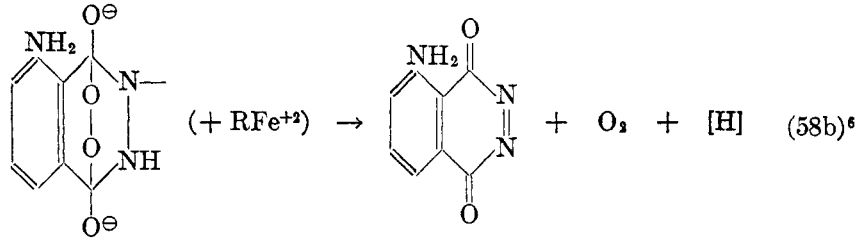
[5] The quantum yield of luminescence has been calculated to be 0.3 per cent to 0.5 per cent per mole (73, 181).

In view of the actual isolation of the peroxide salts, this forms a satisfactory basis for further development and has been adopted as such by some investigators (176–178).

A more recent modification of the peroxide mechanism has been advanced by Weber and his associates (185–188) and by Kautsky (86). Weber's mechanism has a distinct advantage over Drew's in that it takes into account the rôle played by the accelerator (e.g., RFe^{+++}) as well as certain other effects. The mechanism may be outlined in six steps as follows, the actual emission of light occurring in the first part of the last step when the activated phthalhydrazide molecule returns to its normal state:

$$H_2O_2 \rightleftharpoons H^+ + HO_2^- \qquad (58a)^6$$

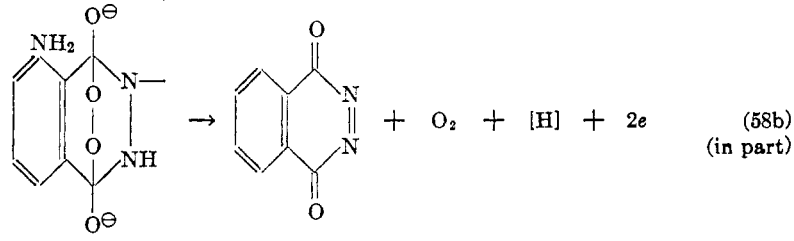




(radical)

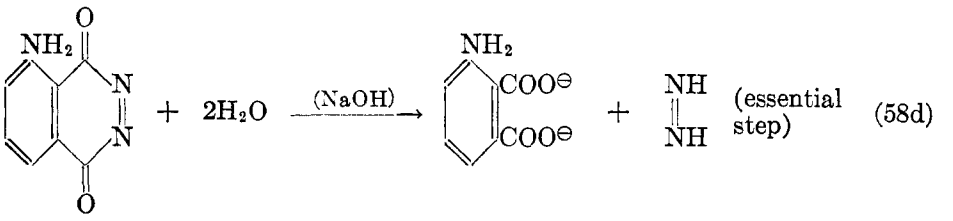
$$RFe^{+3} + [H] \rightarrow RFe^{+2} + H^+ \qquad (58c)$$

[6] The mechanism is presented as described by the original investigators, who evidently overlooked the electron imbalance in equation 58b. To accomplish the last stage in 58b additional oxidizing agent is required thus:

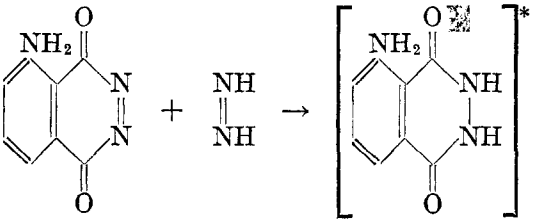


(58b) (in part)

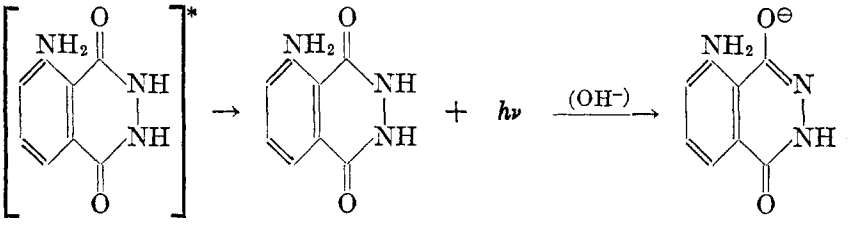
$$3RFe^{+3} + [H] + 2e \rightarrow 3RFe^{+2} + H^+ \qquad (58c)$$



(58d)



(58e)



(58f)

(or dilactim)

(Kautsky's mechanism appears to be similar once the azodiacyl compound has been formed, but he believes the hydrolysis reaction of equation 58d to be the source of luminescence.)

I. Rôle of the accelerator

The accelerator is invariably altered during the reaction. Its function evidently is to facilitate the formation of the azodiacyl compound (possibly the greenish substance observed by Albrecht (3)) *via* the peroxide ion of Drew, which otherwise must be formed directly from the dilactim ion of luminol by the loss of two electrons. If the *reduced* accelerator is readily reoxidizable by oxygen (hemoglobin, for example),

$$RFe^{+2} \xrightarrow{O_2} RFe^{+3}$$

its function is purely that of a catalyst. On the other hand, if such reoxidation is difficult, the accelerator is a reactant (ferritin, for example). Weber also noted that all accelerators are irreversibly changed in the reaction, and that this change is the rate-determining step.

J. Quenching effect of excess alkali

Finally, Weber holds that the quenching effect of too great an excess of alkali may be due to a resultant speeding up of the final enolization process (last part

of equation 58f) to a point where it occurs more rapidly than emission; and since only the dicarbonyl form of luminol fluoresces (185; *cf.* 85), any change in pH tending to promote very rapid lactimization would destroy the essential activated dicarbonyl form of luminol faster than the latter could give up its excess energy as luminescence. Obviously, since the dilactim ion seems to be required for the initial formation of the peroxide, a fine balance must be struck between enough alkalinity for this reaction and too great alkalinity for chemiluminescence. In addition, any significant increase in pH will change the oxidation–reduction potential of the accelerators. Weber concludes with a study of the kinetics of the reaction which give good support to his mechanism, which thus far seems to be the most satisfactory one. However, the problem should in no manner be regarded as solved.

XI. USES OF PHTHALAZINES, PHTHALAZONES, AND PHTHALHYDRAZIDES

The preparation of various phthalazines and of phthalazones has often proven a satisfactory means of obtaining stable crystalline derivatives of *o*-dicarbonyl aromatic compounds and of *o*-carbonyl aromatic carboxylic acids, respectively. Certain mercaptophthalazines have been suggested and patented as rubber accelerators (4). Luminol finds application in the qualitative determination of minute quantities of various ions and of blood (63, 91, 123, 161, 162), and also serves as a readily available reagent for the study and demonstration of the phenomena of chemiluminescence and chemifluorescence. The study of the synthesis of other phthalhydrazides has contributed to these latter studies, since Drew has observed a correlation between the tendency toward phthalhydrazide formation as opposed to the formation of the isomeric *N*-aminophthalimides and the intensity of chemiluminescence (41).

Finally, some phthalazones and phthalhydrazides have been investigated for various physiological or pharmaceutical purposes (9, 40, 85) or as surface-active agents (78); but by far the greater bulk of research in the general field of phthalazine chemistry has been of a purely fundamental character.

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