THE SYNTHESIS AND REDUCTION OF ARYLGLYOXYLOHYDROXAMYL HALIDES

By

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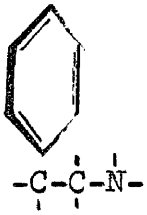
INTRODUCTION

One of the chief problems facing the chemist interested in the synthesis of medicinal substances is the correlation of physiological properties with the chemical structure of organic compounds. Such a relationship appears perhaps, to best advantage, in compounds which produce a rise in blood pressure. It was first pointed out, in 1909, by Barger and Dale (1), in their classic investigation of sympathomimetic amines chemically related to epinephrine, that pressor activity is found in compounds having as a minimum the phenylethylamine skeleton:



Any structural modification imposed on this basic unit produces a corresponding change in the physiological properties of the molecule. Thus, Hartung (2), in his excellent review on the relationship between structure and physiological activity of epinephrine and related compounds, concluded that:

(1) Primary bases, in general are most active in their effect on blood pressure. Alkylation of the amine group affects adversely the fav-

orable action, serving to decrease the activity and increase the toxicity.

(2) The presence of an alcoholic hydroxyl group on the carbon atom bearing the aromatic nucleus serves to detoxicate, at least in part, and to augment the pressor activity.

(3) The ability to produce a rise in blood pressure is resident in compounds with two or three carbon atoms in the side chain; derivatives with a two-carbon atom chain are effective after injection whereas extension of this chain to three carbon atoms give rise to compounds which are capable of producing an effect of longer duration and also possess the added virtue of being potent after oral administration.

(4) Substitutions in the phenyl nucleus modify the circulatory effect- the extent of the change produced being dependent on the substituents introduced.

From the above considerations, it may be concluded that the optimum structures of pressor compounds may be of two closely related types- the arylethanolamines (I) and the arylpropanolamines (II):

$AR.CHOH.CH_2NH_2$ (I)

$AR.CHOH.CH.CH_3NH_2$ (II)

The ready availability of the arylpropanolamines (II), made possible by a general method of synthesis developed by Hartung and his associates (3,4,5,6), has resulted in an extensive pharmacological investigation of the members of this series. On the basis of results obtained, it has been possible to draw general conclusions as to the effect of chemical structure in this series on physiological activity. Also, as a result of these studies, several members have been shown to possess therapeutic value. Aside from the property of oral activity possessed by the arylpropanolamines, evidence as to the merits of this group compared to the corresponding arylethanolamines is conflicting and inconclusive. No member of this series is found naturally and individual compounds have been prepared only in limited amounts. A satisfactory, general method which might serve as a convenient procedure for the synthesis of the various arylethanolamines apparently still needs to be developed.

The arylethanolamines deserved to be further investigated for both theoretical and practical reasons. For example, as more members of this series become available in satisfactory amounts, a more thorough study of the effect of change in structure on activity may be made. Again, some of the compounds may possess therapeutic value. Phenylethanolamine itself, has in animals, a pressor effect comparable to that of ephedrine and at the same time is only one-third as toxic (7,8). On the basis of favorable clinical investigations (9), this amine has been studied by the Council of Chemistry and Pharmacy of the American Medical Association (10) and in favorable prelimary report of the Council, the name "phenylaminoethanol sulfate" was adopted for the sulfate salt of this amine (11). However, it was never listed in the annual publication of the Council. The reason for this does not appear, but it is conceivable that the lack of a good synthetic procedure may be, at least, in part responsible for this.

Another member of this series of interest is nor-epinephrine, 3,4-dihydroxyphenylethanolamine, also known under the name, arterenol. The Remedia-"Hoechst", a publication of the Farbwerke vorm. Meister Lucius & Brüning lists this amine under the title, Arterenolum Hydrochloricum. Its physical and chemical properties were described and it was recommended as a substitute in the clinic for epinephrine in view of the fact that their physiological properties are alike (12). Clinical results on the use of nor-epinephrine as a vasoconstricting agent in local anesthetic combinations in dentistry have been reported by Euler (13,14), in 1907. Recently, the Winthrop Chemical Company has obtained a patent (15) on the use of nor-epinephrine as a substitute for epinephrine in local anesthetic combinations; upon inquiry directly to this company, information regarding possible clinical applications was not available (16). The pressor action of nor-epinephrine, in animals, has been reported to be 1.25-1.5 times that of dl-epinephrine (1,17). Tainter and his associates have made a rather extensive investigation of this amine in animals. They report a pressor ratio of dl-nor-epinephrine to l-epinephrine of 1:1.2 and a toxicity ratio of 1:3 (18). On the basis of these findings, nor-epinephrine has a therapeutic index almost three times that of l-epinephrine. In the treatment of circulatory depression produced by experimental shock, they found dl-nor-epinephrine to be twice as active (19); in circulatory failure in cats due to phenol poisoning, it was approximately 12 percent more active than l-epinephrine (20).

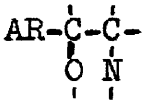
The favorable results obtained in the above mentioned studies, among others, have stimulated the search for a more complete investigation of the entire series of arylethanolamines. Thus, this present investivation was initiated with the aim of developing a satisfactory method which could be employed in the preparation of phenylethanolamine and its nuclear-substituted derivatives.

Aminoalcohols of the type, $AR.CHOH.CHR.NH_2$, where R is methyl or a higher alkyl group, may be readily obtained by a general method, involving first, nitrosation of the corresponding ketones and subsequent catalytic reduction of the oximinoketones to the aminoalcohols (3,4,5,6):

$$AR.CO.CH_2R \xrightarrow[HCl]{RONO} AR.CO.CH(:NOH)R \xrightarrow[Pd]{(H)} AR.CHOH.CH.RNH_2$$

Both stages of the synthesis give excellent yields. However, when R is H, in the above reactions, that is, with acetophenone derivatives, the yields of oximinoketones are low or negligible (4,21).

The problem resolved itself into the possibility of finding some satisfactory, general procedure for the preparation of intermediates of the general basic structure,

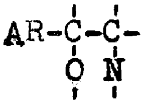


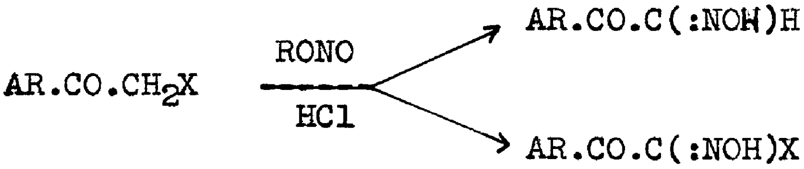
$$\mathrm{AR}-\underset{\underset{|}{\mathrm{O}}}{\overset{|}{\underset{|}{\mathrm{C}}}}-\underset{\underset{|}{\mathrm{N}}}{\overset{|}{\underset{|}{\mathrm{C}}}}-$$

in which the oxygen was present as a potential alcoholic hydroxyl and the nitrogen atom as a potential primary amino group.

In view of the fact that phenacyl halides and their nuclear-substituted derivatives also possess the general structure, AR.CO.CH_2.R, in which R is halogen, it appeared desirable to apply the general nitrosation reaction to such ketones.

It might be expected that if nitrosation should occur, it would follow one or both of two possible courses- either one forming a product having the desired $\mathrm{AR}-\underset{\underset{|}{\mathrm{O}}}{\overset{|}{\underset{|}{\mathrm{C}}}}-\underset{\underset{|}{\mathrm{N}}}{\overset{|}{\underset{|}{\mathrm{C}}}}-$ skeleton:





(I)

(II)

The results indicate that nitrosation of halogenomethylaryl ketones proceeds as in (II). The reaction has been applied to phenacyl bromide, phenacyl chloride and nuclear-substituted derivatives of phenacyl chloride.

After the synthesis of the desired intermediates was worked out the second phase of the problem was to reduce these to the desired arylethanolamines, according to the scheme:

$$\mathrm{AR.CO.C(:NOH)X} \xrightarrow{4H_2} \mathrm{AR.CHOH.CH_2NH_2}$$

It will be seen that to achieve the desired degree of hydrogenation, the following must be accomplished:

(1) The halogen must be replaced by a hydrogen atom.

(2) The oximino group must be reduced to a primary amine.

(3) The ketonic carbonyl must be converted into a secondary alcoholic hydroxyl group.

REVIEW OF THE LITERATURE

A. Previous Progress in the Synthesis of Phenylethanolamines.

Reduction of Isonitrosoketones. Isonitrosoketones, of the type, AR.CO.C(:NOH)H, have been employed as intermediates in the preparation of the phenylethanolamines. Thus, on catalytic reduction, these yield the corresponding amino-alcohol:

$$AR.CO.C(:NOH)H_2 + 3H_2 \longrightarrow AR.CHOH.CH_2NH_2 + HOH$$

Kolshorn (22), in 1904, reported the first synthesis of an arylethanolamine. He succeeded in obtaining phenylethanolamine by reducing isonitrosoacetophenone using 5 percent sodium amalgam in 50 percent alcohol. The yield of product was not mentioned; it is presumed that the yield was low because the method has never been adopted. In connection with this, it might be added that, Gabriel and Eschenbach (23) had previously attempted to prepare phenylethanolamine by the reduction of ω-aminoacetophenone using ~~as a catalyst,~~ 2½ percent sodium amalgam. By this method, the amine group was split off:

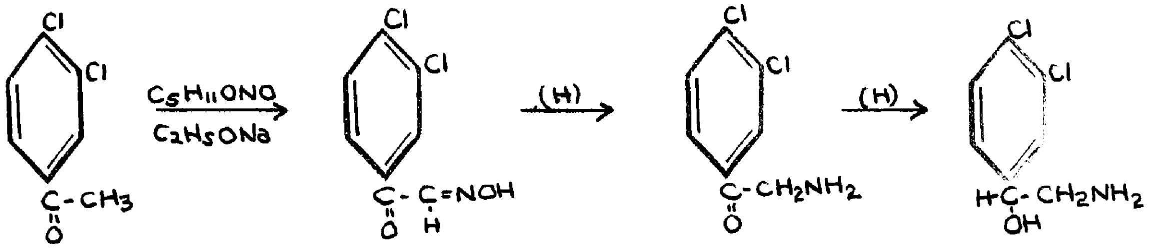
$$C_6H_5.CO.CH_2NH_2 + H_2 \longrightarrow C_6H_5.CO.CH_3 + NH_3$$

Pictet and Gams (24), in their studies on the synthesis of isoquinoline bases, prepared N-acyl derivatives of phenylethanolamine starting with isonitrosoacetophenone:

$$C_6H_5.CO.C(:NOH)H \longrightarrow C_6H_5.CO.CH_2NH_2 \longrightarrow$$
$$C_6H_5.CO.CH_2NHCOR \longrightarrow C_6H_5.CHOH.CH_2NHCOR$$

Isonitrosoacetophenone was reduced to ω-aminoacetophenone using stannous chloride in alcoholic hydrogen chloride; the N-acyl-ω-aminoacetophenones were reduced to the corresponding aminoalcohols in 40-60 percent yields using sodium amalgam in alcohol.

Glynn and Linnell (25) obtained 3,4-dichlorophenylethanolamine using as an intermediate, 3,4-dichloro-isonitrosoacetophenone. The reactions involved in this synthesis are:



The isonitrosoketone was obtained in 51 percent yields by the nitrosation method of Claisen (26,27), using amyl nitrite and sodium ethoxide in a mixture of ether and alcohol. Reduction of this intermediate with sodium amalgam in a mixture of absolute alcohol-glacial acetic acid failed, and it was apparent that two steps were necessary for the conversion of this isonitrosoketone to the aminoalcohol. Using stannous chloride and hydrogen chloride in absolute alcohol, from 4 g. of the isonitrosoketone there was obtained 2 g. of the aminoketone; reduction of 5 g. of this product by means of alumium amalgam gave only 0.8 g. of 3,4-dichlorophenylethanolamine.

In his studies on the reduction of oximinoketones of the type, AR.CO.CH(:NOH)R, using palladium charcoal catalyst in alcoholic hydrogen chloride, Hartung (3,4,5,6) succeeded in obtaining excellent yields of Aminoalcohols:

$$\mathrm{AR.CO.CH(:NOH)R} \xrightarrow{(H)} \mathrm{AR.CHOH.CH_2RNH_2}$$

However, when this method was applied to isonitrosoacetophenone, reaction did not proceed as readily. In one instance only do they report that it was possible to go from the oximinoketone to phenylethanolamine directly; in all other attempts, reductions stopped at the aminoketone stage; this product was isolated as the hydrochloride and further reduced in aqueous solution by fresh catalyst to the desired aminoalcohol (4).

Edkins and Linnell (28) attempted to develop a synthesis of phenylethanolamine and its chloro- and bromo- analogs using the scheme:

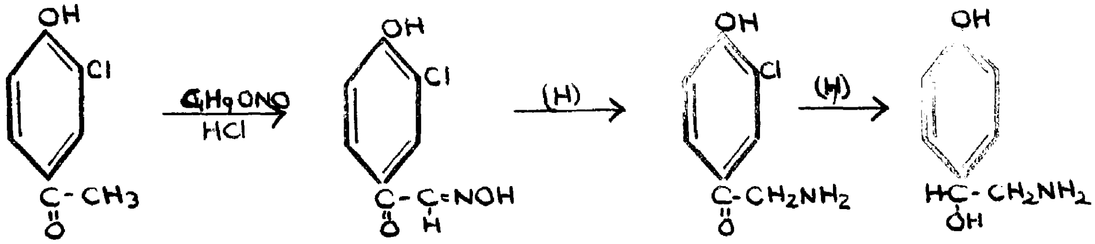
$$\mathrm{AR.CO.CH_3} \longrightarrow \mathrm{AR.CO.C(:NOH)H} \longrightarrow$$
$$\mathrm{AR.CO.CH_2NH_2} \longrightarrow \mathrm{AR.CHOH.CH_2NH_2}$$

The isonitrosoacetophenones were prepared in yields varying from 37-75 percent, by treating the methyl ketones with alkyl nitrite and sodium ethoxide. These intermediates were then reduced to the corresponding aminoketones by means of stannous chloride in hydrochloric acid. In the case of isonitrosoacetophenone itself, the yield of ω-aminoacetophenone was only 27 percent; no mention was made of the yield of the other ω-aminoketones. ω-Aminoacetophenone was then reduced to phenylethanolamine according to the method of Hartung (3); from 2 g. of aminoketone, the yield of aminoalcohol was only 0.75 g. With the halogen analogs of ω-aminoacetophenone, was not only the carbonyl group reduced but dehalogenation also occurred and the product obtained from these intermediates was phenylethanolamine itself:

$$X.C_6H_4.CO.CH_2NH_2 \quad + \quad 4H_2 \quad \longrightarrow \quad C_6H_5.CHOH.CH_2NH_2 \ + \ HX$$

The yields of phenylethanolamine by the above reductions were reported to be "excellent". It was also pointed out that the product thus obtained from the halogen analogs of ω-aminoacetophenone was more easily purified and appeared to be much more active physiologically than that obtained by other methods. Attempts made by varying the conditions for the hydrogenation so as to prevent the loss of halogen were unsuccessful.

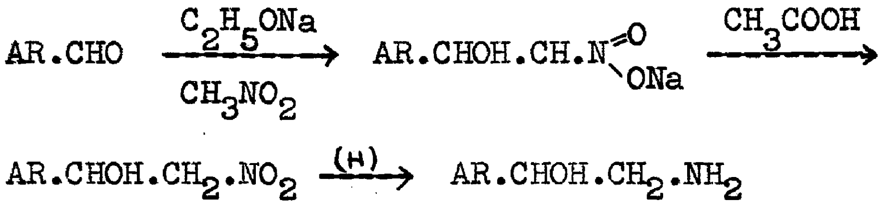
Para-hydroxyphenylethanolamine was prepared by Edkins and Linnell (28) according to the following series of reactions:



3-Chloro-4-hydroxyacetophenone was nitrosated using butyl nitrite and hydrogen chloride; the oximinoketone was not isolated and no indication was given of yield obtained- although it may be presumed to be unfavorable. The aminoketone was obtained by reduction using the stannous chloride procedure; when 4 g. of this product was reduced by the method of Hartung (3) a yield of only 0.097 g. of the aminoalcohol was obtained.

The chief objection to the use of isonitrosoketones in the synthesis of phenylethanolamines is that these intermediates cannot be readily prepared. Thus, the Claisen method of nitrosating of methyl ketones of the type, $AR.CO.CH_3$, using alkyl nitrite with hydrogen chloride as a catalyst gives poor yields of the desired isontrosoketones (4,21). When sodium ethoxide is the catalyst in the nitrosation reaction, the reported yields of the isonitrosoacetophenones are variable and have never been confirmed by other investigators. Furthermore, this method of nitrosation cannot be applied to acetophenones bearing unprotected phenolic groups. Reduction studies on these isonitrosoketones are, as yet, incomplete- apparently as the result of the lack of satisfactory amounts of the various isonitrosoacetophenones.

Reduction of Aryl-nitroethanols. Rosenmund (29) developed a method for the synthesis of arylethanolamines, which consisted of the reduction of aryl-nitroethanols of the type, $AR.CHOH.CH_2NO_2$. These intermediates were prepared by heating the various aromatic aldehydes with nitromethane in the prescense of sodium methylate; on reduction, using sodium amalgam indilute alcohol containing some acetic acid, the aminoalcohols were obtained. The reactions involved are:

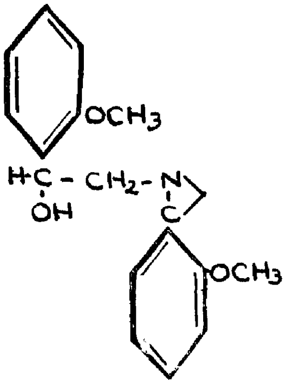


$$AR.CHO \xrightarrow[CH_3NO_2]{C_2H_5ONa} AR.CHOH.CH.N{\overset{\displaystyle =O}{\underset{\displaystyle \backslash ONa}{}}} \xrightarrow{CH_3COOH}$$

$$AR.CHOH.CH_2.NO_2 \xrightarrow{(H)} AR.CHOH.CH_2.NH_2$$

Using this method, Rosenmund was able to prepare phenylethanolamine, para-methoxyphenylethanolamine, 3,4-dimethoxyphenylethanolamine and the dicarboethoxy derivative of 3,4-dihydroxyphenylethanolamine. The yields of intermediates or final product were not mentioned however.

Kondo and Murayama (30) applied Rosenmund's synthesis to the preparation of phenylethanolamine. They found that the intermediate, phenyl-nitroethanol, obtained in 80 percent yields from benzaldehyde and nitromethane, could be reduced to the aminoalcohol using palladium hydrosol (1%) and a little active carbon; the yield of product was not mentioned, however. Kondo and Tanaka (31) prepared ortho-methoxyphenylethanolamine by the reduction of ortho-methoxyphenyl-nitroethanol using the same catalyst. From 20 g. of ortho-methoxybenzaldehyde, the yield of the corresponding nitro-ethanol was reported to be 25 g; however, on reduction only 13 g. of the amino-alcohol was obtained. Also isolated from the reduction mixture (as the result of a side-reaction which occurred when the aldehyde was treated with nitromethane) was a product identified as

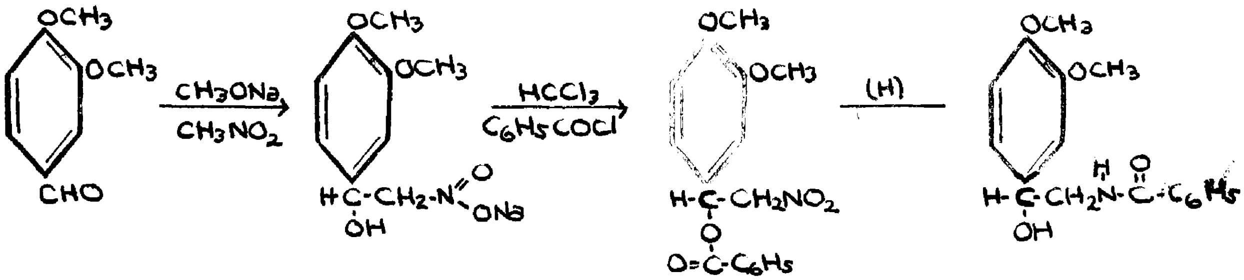


This, on subsequent reduction gave ortho-methoxyphenylethanolamine.

Kanao (32) prepared the diacetate of 3,4-dihydroxyphenylethanolamine by Rosenmund's method. He reported that condensation of the diacetate of protocatechuic aldehyde and nitromethane gives excellent yields of the corresponding nitroethanol, however, reduction of 10 g. of this intermediate, using zinc dust and 30 percent acetic acid, resulted in only 5 g. of aminoalcohol.

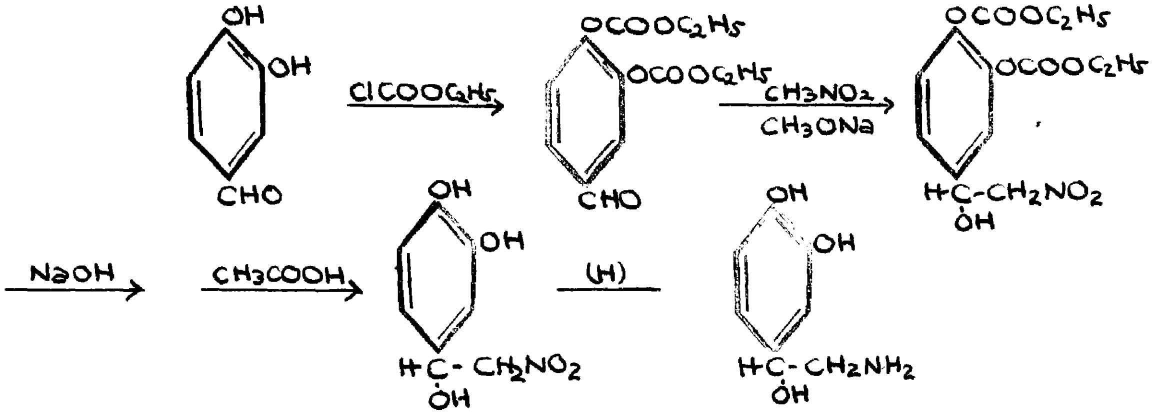
Alles (7) and Alles and Knoefel (33) prepared phenylethanolamine by Rosenmund's method but did not describe the experimental details or mention yields of product obtained.

Vinkler and Bruckner (34) prepared N-benzoyl, 3,4-dimethoxyphenylethanolamine using a nitroethanol intermediate:



Further information was not available.

The Rosenmund synthesis of arylethanolamines offers a number of objectionable features, even though the method had been patented. Thus, applied in the synthesis of nor-epinephrine (3,4-dihydroxyphenylethanolamine) the number of reactions involved are:



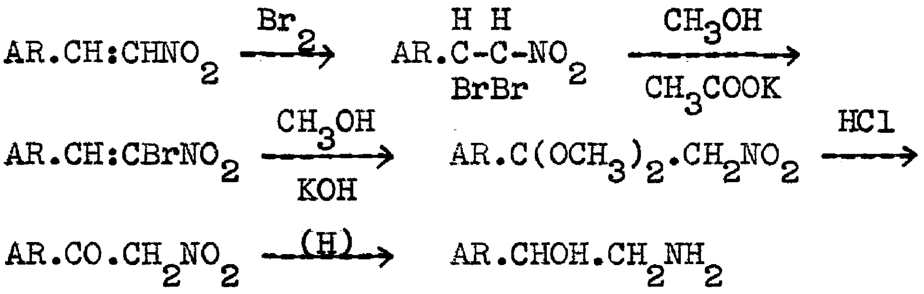
Moreover, Rosenmund stated that he was unable to obtain the product in a pure form. The yields were also found to vary considerably; at best, the yield of product was only about 5 percent (based on the aldehyde).

The method is not generally applicable because of the lack of and difficulty encountered in making available, in satisfactory quantities, the various nuclear-substituted derivatives of benzaldehyde. The intermediate nitroethanols decompose readily into ω-nitrostyrenes:

$$AR.CHOH.CH_2NO_2 \longrightarrow AR.CH{:}CHNO_2 + HOH$$

For this reason the yields of the nitroethanols may be lowered somewhat; other side-reactions also occur and difficulty has been encountered in obtaining pure aminoalcohols (Rosenmund). Moreover, the method cannot be applied to aromatic aldehydes bearing unprotected phenolic groups.

ω-Nitrostyrene Method of Reichert and Koch. Using -nitrostyrenes as intermediates, Reichert and Koch (35) have recently developed a procedure for the synthesis of phenylethanolamines in which the ring is substituted by alkoxyl groups. The reactions involved are:



$$\mathrm{AR.CH{:}CHNO_2} \xrightarrow{\mathrm{Br_2}} \mathrm{AR.}\overset{\mathrm{H}}{\underset{\mathrm{Br}}{\mathrm{C}}}\text{-}\overset{\mathrm{H}}{\underset{\mathrm{Br}}{\mathrm{C}}}\text{-}\mathrm{NO_2} \xrightarrow[\mathrm{CH_3COOK}]{\mathrm{CH_3OH}}$$

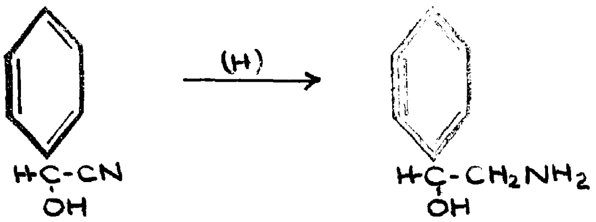
$$\mathrm{AR.CH{:}CBrNO_2} \xrightarrow[\mathrm{KOH}]{\mathrm{CH_3OH}} \mathrm{AR.C(OCH_3)_2.CH_2NO_2} \xrightarrow{\mathrm{HCl}}$$

$$\mathrm{AR.CO.CH_2NO_2} \xrightarrow{\mathrm{(H)}} \mathrm{AR.CHOH.CH_2NH_2}$$

Bromination was reported to give excellent yields of the dibromonitro- intermediates; the yields of the succeeding intermediates were not mentioned, however. The ω-nitroacetophenones, $\mathrm{AR.CO.CH_2.NO_2}$, were reduced using platinum oxide catalyst to arylethanolamines in 80 percent to almost quantative yields. By this procedure, 2-methoxy-, 4-methoxy-, 3,4-dimethoxy-, and 3,4-methylenedioxyphenylethanolamines were prepared.

The most obvious disadvantage to this method is the number of steps required in the synthesis. The method is not general in application. Thus, attempts to prepare 2,4-dimethoxyphenylethanolamine failed; in this instance, bromination of the ring occurred also, and the authors were unable to isolate the desired ω-nitroacetophenone intermediate. Furthermore, application of this method to other nuclear-substituted ω-nitrosstryene derivatives has never been reported.

Reduction of Cyanohydrins. The use of cyanohydrins of the type, AR.CHON.CN, as intermediates in the synthesis of the phenylethanolamines has been studied by various investigators. Wolfheim (36) was the first to show that the reduction of benzaldehyde cyanohydrin gave phenylethanolamine:



He used 4 percent sodium amalgam as the reducing agent in a solvent composed of 33 percent alcohol and 50 percent acetic acid. Wolfheim mentioned that the reaction is difficult, and from 50 g. of cyanohydrin, only 17.9 g. of crystalline product was obtained. In a German patent (37) obtained prior to the publication of his work, the reduction of the cyanohydrins of both benzaldehyde and protocatechuic aldehyde to phenylethanolamine and nor-epinephrine are described; the yields of products were not mentioned however.

Hess and Uibrig (38) investigated Wolfheim's procedure and from 20 g. of benzaldehyde cyanohydrin, these workers succeeding in obtaining only 2-3 g. of phenylethanolamine. More recently, Bhatnagar, Narang, Chopra and Ray (39) also indicate that Wolfheim's method is unsatisfactory. These investigators modified the experimental conditions and obtained slightly better results; but even then, from 16 g. of benzaldehyde cyanohydrin, the yield of phenylethanolamine (as the carbonate salt) was only 4.5 g. In the case of the cyanohydrin of piperonal, only 3-4 g. of the carbonate salt of 3,4-methylene-dioxyphenylethanolamine was obtained from 16-18 g. of the corresponding cyanohydrin.

Hartung (40) has shown that the reduction of benzaldehyde cyanohydrin using palladium-charcoal catalyst in absolute alcoholic-hydrogen chloride, gives not phenylethanolamine as desired, but phenylethylamine in a yield of 52 percent. When this method of reduction was applied to either the benzoate or acetate derivatives of the cyanohydrin, phenylethylamine was obtained in both instances.

Buck (41) has found that the reduction of cyanohydrins of that type, AR.CHOH.CN, using platinum oxide catalyst in alcoholic-hydrogen chloride gives either the corresponding arylethanolamine or arylethylamine. When AR- was 2-methoxyphenyl, 2-chlorophenyl-, and 2,3-dimethoxyphenyl-, the correspinding arylethanolamines were obtained in 59, 41 and 23.5 per cent yields respectively. In the case of the 4-chlorophenyl-, 3,4-dimethoxyphenyl-, 4-methoxyphenyl-, and 4-dimethylphenyl- derivatives, the reduction proceeded directly to the corresponding arylethylamines. With cyanohydrins in which the aryl group was substituted by unprotected hydroxyl groups the arylethylamines were also obtained (42).

Kindler, Peschke and Brandt (43) obtained both arylethanolamines and arylethylamines by the reduction of various cyanohydrins in which the aromatic nucleus was substituted by alkoxy groups. These workers used palladium black catalyst in glacial acetic acid; their results are summarized in the following tabulation:

AR.CHOH.CN	Yield of	
	$AR.CHOH.CH_2NH_2$	$AR.CH_2CH_2NH_2$
3,4-Dimethoxyphenyl-	47%	18%
3,4-Diethoxyphenyl-	(not reported)	24%
3-Methoxy- 4-ethoxyphenyl	45%	16%

From the above survey, it is apparent that the use of cyanohydrins as intermediates in the synthesis of the phenylethanolamines is not satisfactorily solved. First of all, the cyanohydrins themselves can not, always, be easily prepared in satisfactory yields; also, the necessary aldehydes, are not readily available- as previously indicated. Moreover, the reduction procedure gives, at best, only fair yields of the desired aminoalcohols, and usually, the reaction is difficult to control so as to prevent formation of arylethylamines.

Reduction of Aryl Cyanides According to Kindler. Kindler and Peschke (44) showed that arylethanolamines could be prepared by the reduction of aryl cyanides. These intermediate arylcyanides were obtained by the oxidation of the cyanohydrins of benzaldehyde and its nuclear-substituted derivatives. The reactions involved in the synthesis of arylethanolamines according to the method of Kindler and Peschke may be represented as follows:

$$\mathrm{AR.CHO} \xrightarrow[\mathrm{KCN}]{\mathrm{NaHSO_3}} \mathrm{AR.CHOH.CN} \xrightarrow{(\mathrm{O})}$$

$$\mathrm{AR.CO.CN} \xrightarrow{(\mathrm{H})} \mathrm{AR.CHOH.CH_2NH_2}$$

The method was applied for the preparation of phenylethanolamine and the 4-methoxy-, 3,4-dimethoxy-, 3,4,5-trimethoxy- and 3,4-methylenedioxyphenylethanolamines.

This method possess several excellent features. The cyanohydrins, which were reported to be obtained almost quantitatively from the sodium bisulfite derivatives of the aldehydes, were readily oxidized by chrominum oxide in glacial acetic acid to give 70-90 percent yields of the corresponding aroyl cyanides. Reduction of these intermediates, using palladium black catalyst, gave the arylethanolamines in yields of 70-80 percnet.

On the other hand, the method has several limitations. First, the difficulty of obtaining nuclear-substituted derivatives of benzaldehyde- which has previously been indicated- limits the application of this method of synthesis to only a few arylethanolamines. Secondly, this method cannot be applied to phenolic aldehydes in which the phenolic groups are not blocked.

It may also be pointed out that the method of reduction might be improved. Another point of interest is that subsequent studies on the feasibility of the use of aroyl cyanides as intermediates for the synthesis of phenylethanolamines are not available.

Application of the Hexamine Addition Products of Aryl-halogenomethylketones. Mannich and his associates (45,46) have shown that the addition product obtained by heating an aryl-halogenomethylketone with hexamine, gives on hydrolysis an aminomethylketone which is a suitable intermediate for the preparation of an arylethanolamine by catalytic reduction. The reactions involved are:

$$AR.CO.CH_2Cl \quad + \quad (CH_2)_6N_4 \quad \longrightarrow \quad AR.CO.CH_2(N_4(CH_2)_6)Cl$$

$$AR.CO.CH_2(N_4(CH_2)_6)Cl \quad + \quad 12C_2H_5OH \quad . \; 3HCl \quad \longrightarrow$$

$$AR.CO.CH_2NH_2.HCl \quad + \quad 3NH_4Cl \quad + \quad 6CH_2(OC_2H_5)_2$$

$$AR.CO.CH_2NH_2.HCl \quad + \quad H_2 \quad \longrightarrow \quad AR.CHOH.CH_2NH_2.HCl$$

The intermediate addition-products, $AR.CO.CH_2(N_4(CH_2)_6)X$, were obtained in fairly good yields; chloromethylketones gave 40-60 percent yields of the complexes, whereas the corresponding bromomethylketones gave 80 percent to almost quantitative yields. In one instance, an iodomethyl ketone, the diacetate of 3,4-dihydroxyphenacyl iodide, gave nearly a quantitative yield of the addition product with hexamine. Reaction failed in the case of the triacetate of 1,2,3-trihydroxyphenacyl chloride the corresponding bromo- and iodo- derivatives reacted as expected however.

Hydrolysis of the hexamine-ketone addition products gave fairly good yields of the corresponding aminoketones. In the case of the diacetate of 3,4-dihydroxy-ω-aminoacetophenone, the yields were 60-75 percent. The ω-aminoacetophenones thus obtained were reduced to arylethanolamines using palladium-charcoal catalyst; the yields of product were not mentioned however. Phenylethanolamine and para-methoxyphenylethanolamine were obtained using this procedure; para-hydroxyphenylethanolamine was prepared by demethylation of the para-methoxy-derivative.

Slotta and Heller (47) prepared phenylethanolamine according to the method of Mannich, using the hexamine addition-product of phenacyl bromide; this intermediate was hydrolyzed to a mixture of the hydrochloride and hydrobromide salts of ω-aminoacetophenone. From 80 g. of mixed salts, he obtained by reduction using pallådium-charcoal catalyst, only 23 g. of phenylethanolamine hydrochloride (crude product).

Baltzly and Buck (48) have recently prepared 2,5-dimethoxy-phenylethanolamine by this procedure. The intermediate, 2,5-dimethoxy-ω-aminoacetophenone was reduced to the amino-alcohol using platinum oxide catalyst. The yields of intermediates and final product were not mentioned; Buck (49) writes, however, that "the method is capable of giving good yields".

On the basis of the evidence presented in the literature, the method of Mannich for the synthesis of phenylethanolamines, appears to be the best up to the present. The intermediates are readily available and the reduction procedure fairly good. However, phenolic-substituted derivatives of the phenacyl halides must first be alkylated or acylated otherwise hexamine would react with the phenolic hydroxyl group to form salts. Moreover, hydrolysis of the hexamine-ketone addition product of the aminoketone requires a period of about three days.

Phthalimide Method. Tutin, Caton and Hahn (50) prepared para-hydroxyphenylethanolamine according to the following reactions:

$$CH_3O.C_6H_5 \xrightarrow[AlCl_3]{ClCH_2COCl} HO.C_6H_4.CO.CH_2Cl \xrightarrow{(CH_3CO)_2O}$$

$$CH_3COO.C_6H_4.CO.CH_2Cl \xrightarrow{C_6H_4.(CO)_2.NK}$$

$$CH\ COO.C_6H_4.CO.CH_2.C(CO)_2C_6H_4 \xrightarrow{HCl}$$

$$HO.C_6H_4.CO.CH_2.NH_2 \xrightarrow[C_2H_2OH]{Na} HO.C_6H_4.CHOH.CH_2NH_2$$

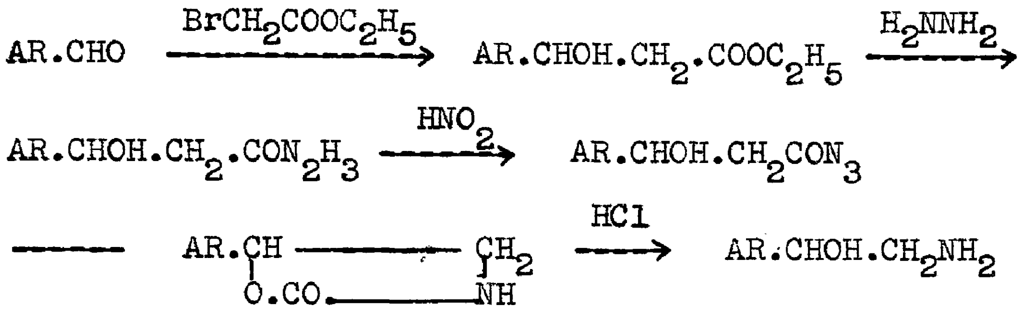
In one instance only do the authors mention the yield of an intermediate,- the condensation of the acetate of para-hydroxyphenacyl chloride with potassium phthalimide to give a 42 percent yield of the phthalimidoketone.

Boruttau (51) has employed the phthalimide method for the preparation of para-hydroxyphenylethanolamine, 2,5-dihydroxyphenylethanolamine and 2,4-dihydroxyphenylathenolamine. Details as to the experimental methods or yields obtained were not reported.

The phthalimide method appears to be of minor importance in view of the lack of evidence as to the merits of the procedure for the preparation of arylethanolamines.

Application of Azides. Baltzly and Buck (48) prepared

2,5-dimethoxyphenylethanolamine according to the following series of reactions:



$$AR.CHO \xrightarrow{BrCH_2COOC_2H_5} AR.CHOH.CH_2.COOC_2H_5 \xrightarrow{H_2NNH_2}$$

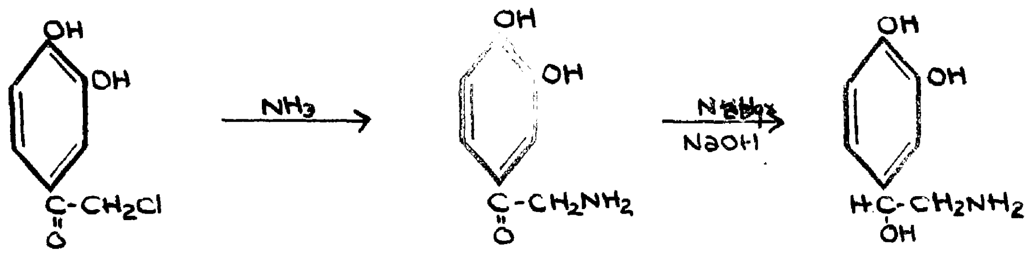
$$AR.CHOH.CH_2.CON_2H_3 \xrightarrow{HNO_2} AR.CHOH.CH_2CON_3$$

$$\longrightarrow AR.\underset{O.CO}{CH} - \underset{NH}{CH_2} \xrightarrow{HCl} AR.CHOH.CH_2NH_2$$

Buck (49), in a private communication, mentions that "the starting ester was obtained in 75-80 percent yields. Formation of the hydrazide is virtually quantitative. The yield at the oxazolidine stage is about 70 percent. The hydrolysis of the oxazolidone, as done, gave poor yields but this could be much improved by removing the hydrochloric acid by evaporation in vacuo below 25°."

Here also, the lack of nuclear-substituted benzaldehydes limits the application of the use of azides as intermediates for the preparation of arylethanolamines. Further evidence in the literature as to the use of this method is not available.

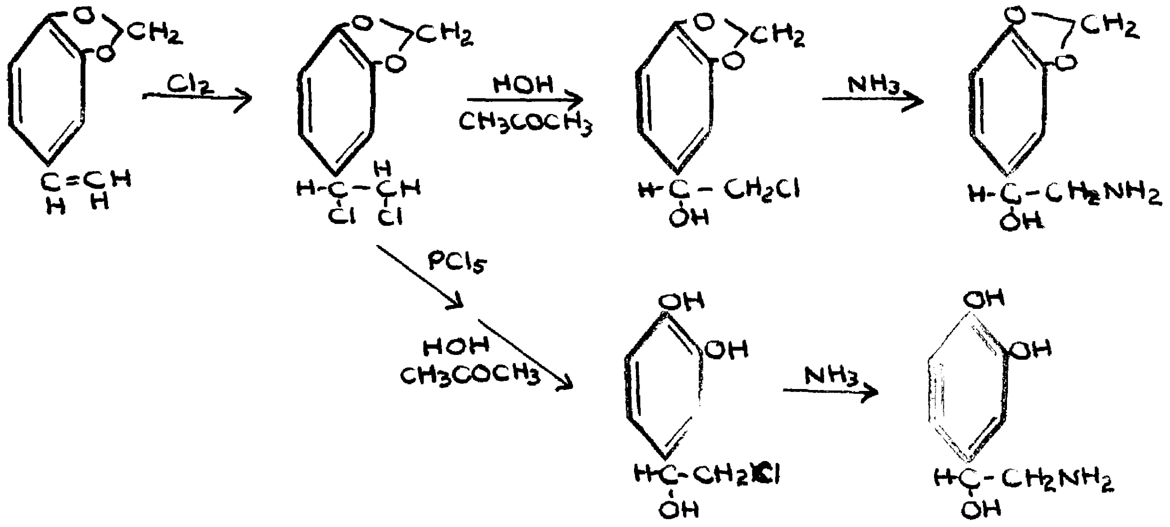
<u>Condensation of Halogen Derivatives with Ammonia</u>. Norepinephrine, 3,4-dihydroxyphenylethanolamine, has been prepared by the reduction of 3,4-dihydroxy-ω-aminoacetophenone which was obtained by treating 3,4-dihydroxy-ω-chloroacetophenone with ammonia. The reactions involves in this synthesis are:



The above synthesis is described in old German patents (52); it may be assumed that this method is of little practical value.

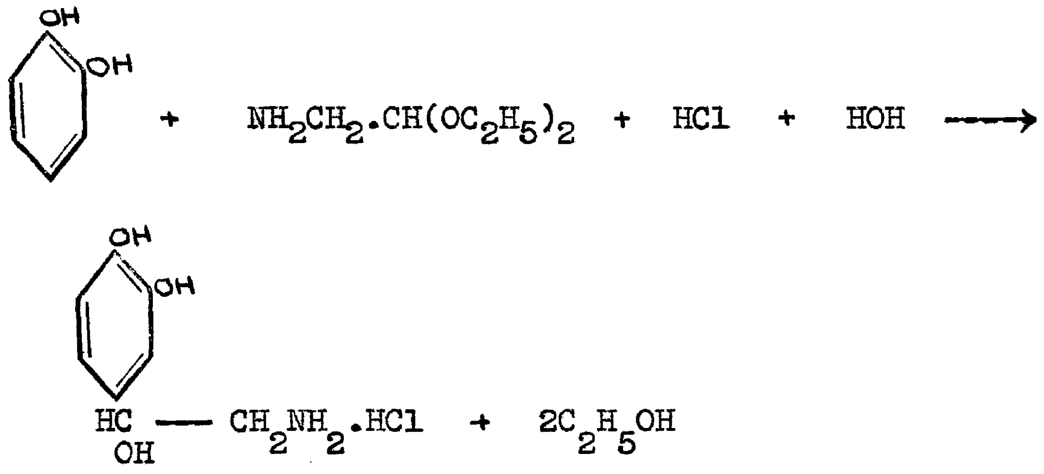
Tutin (50) and Boruttau (51), using the above method, hoped to obtain para-hydroxyphenylethanolamine. However, these investigators were unable to prepare the desired intermediate, para-hydroxy-ω-aminoacetophenone, by condensing para-hydroxyphenacyl chloride with ammonia. Glynn and Linnell (25) attempted to prepare 3,4-dichloro-ω-aminoacetophenone by condensing the ω-chloromethyl ketone with ammonia but failed. Further reports on the application of this method for the preparation of ω-aminoacetophenones in the synthesis of arylethanolamines are not available.

A synthesis of nor-epinephrine based on the condensation of ammonia with ω-chloromethyl-3,4-dihydroxybenzyl alcohol is described in German patents (53). The reactions involved are:



The yields in the above synthesis were not reported.

Condensation of Aminoacetal with Phenols and Phenolic Derivatives. Hinsberg (54) has devised a unique method for the preparation of certain arylethanolamines. He showed that nor-epinephrine could be obtained by condensing catechol with aminoacetal according to the equation:

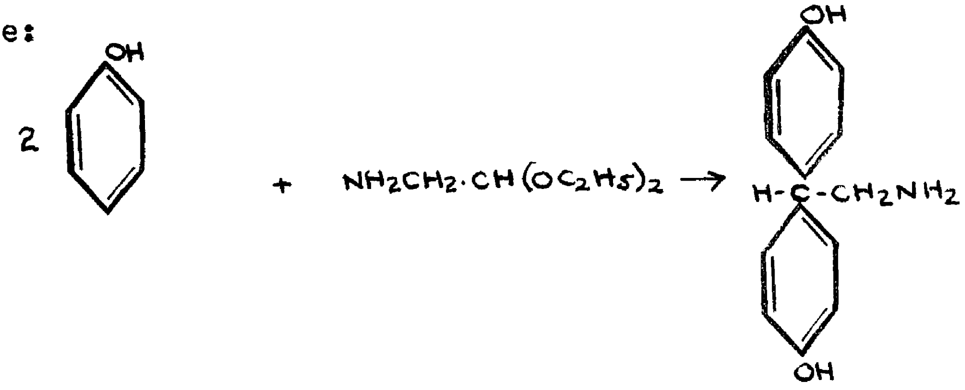


The yield of product in this instance was not mentioned; however, when the reaction was applied to pyrogallol, from 3 g. of this phenol, a yield of 4.5 g. of the aminoalcohol hydrochloride was obtained. In the case of the trimethyl ether of pyrogallol, the yield of trimethoxyphenylethanolamine was reported as being "very satisfactory". Gallic acid gave "(α-carboxy-trioxy-phenyl)-β-amino-α-oxyethane", but the yield was not mentioned.

> Note: In his article (and earlier patents) Hinsberg made no mention of the relative position of the substituent groups in the phenylethano-

> lamines obtained from pyrogallol or its trimethyl ether. Kindler and Peschke (44), in a paper published eight years later, obtained 3,4,5-trimethoxyphenylethanolamine from 3,4,5-trimethoxybenzaldehyde. The aminoalcohol obtained by those workers was not identical with "α-(trimethoxyphenyl)-β-amino-α-oxyethane" of Hinsberg. On this basis, the former concluded the product obtained by Hinsberg was actually the isomer, 2,3,4-trimethoxyphenylethanolamine. Reference as to which isomer was obtained by Hinsberg from pyrogallol itself is not available.

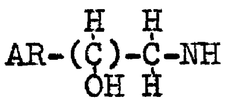
One of the most serious disadvantages of the Hinsberg method is that the necessary reagent, aminoacetal is not readily available due to the difficulty involved in its preparation.. Moreover, the method is very limited in its application. Thus, in the case of phenol itself, two molecules condense with one of aminoacetal to give, not para-hydroxyphenylethanolamine, but 1,1-di-(para-hydroxyphenyl)-2-aminoethane:



Phenetole gives the corresponding diethyl ether as above and only a trace of para-ethoxyphenylethanolamine. In the case pyrogallol, either the corresponding arylethanolamine or the diarylethylamine derivatives could be obtained depending on the mole ratio of reactants employed. Thymol, however, gave the diarylethylamine derivative only.

The Hinsberg reaction as applied to the synthesis of arylethanolamines is characterized by its apparent simplicity. It may be for this reason only that patents (55) were obtained. Nevertheless, it is interesting to note that the use or investigation of this method of synthesis by other workers has never been reported.

Resolution. Arylethanolamines, of the general formula:



$$\mathrm{AR-(}\underset{\mathrm{OH}}{\overset{\mathrm{H}}{\mathrm{C}}}\mathrm{)-}\underset{\mathrm{H}}{\overset{\mathrm{H}}{\mathrm{C}}}\mathrm{-NH}$$

possess optical activity by virtue of an asymmetric carbon atom (C). Hence, three forms of each are possible. Up to the present, phenylethanolamine is the only member of this series which has been resolved into its *dextro*- and *levo*- forms (33).

Greer and his associates (56), in 1938, reported that the resolution of nor-epinephrine was in progress in their laboratory. Publication of their results has not been observed to date.

Table I. Literature Survey of Phenylethanolamines

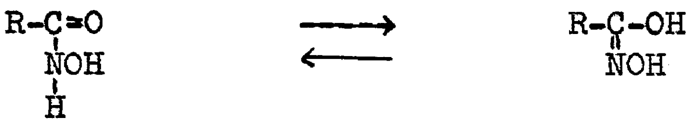
AR.CHOH.CH_2NH_2 (AR=)	Literature References
Phenyl-	(4,7,22,28,29,30,33,36,37, 38,39,44,46,47,109,110)
4-Methylphenyl-	(110)
2-Chlorophenyl-	(42)
3,4-Dichlorophenyl-	(25)
4-Hydroxyphenyl-	(28,46,50,51)
2,4-Dihydroxyphenyl-	(51)
3,4-Dihydroxyphenyl-	(29,37,44,52,53,54,55,109, 111)
2,3,4-Trihydroxyphenyl-	(54,55)
2,3,4-Trihydroxy-6-carboxy-phenyl-	(54,55)
2-Methoxyphenyl-	(31,35,41)
4-Methoxyphenyl-	(29,35,44,46,109,110)
2,3-Dimethoxyphenyl-	(42)
2,4-Dimethoxyphenyl-	(35)
3,4-Dimethoxyphenyl-	(29,35,43,44,109,110)
2,5-Dihydroxyphenyl-	(51)

Table I (Cont.)

$AR.CHOH.CH_2NH_2$ (AR=)	Literature References
2,5-Dimethoxyphenyl-	(48)
2,3,4-Trimethoxyphenyl-	(54,55)
3,4,5-Trimethoxyphenyl-	(44)
3,4-Methylenedioxyphenyl-	(35,39,44,53,110)
4-Ethoxyphenyl-	(54,55)
3,4-Diethoxyphenyl-	(43)
3-Methoxy-4-Ethoxyphenyl-	(43)
3,4-Dihydroxyphenyl-(diacetate)	(32)

B. Glyoxylohydroxamyl Halides.

Introduction. The N-acyl substituted derivatives of hydroxylamine are generally referred to as hydroxamic acids (I). These compounds also exist in the tautomeric form (II), to which Sidgwick (57) refers as hydroximic acids:



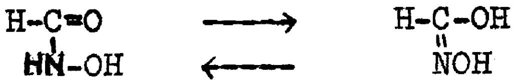
$$R-C(=O)-N(H)-OH \rightleftarrows R-C(-OH)=NOH$$

Hydroxamic acid (I) Hydroximic acid (II)

The hydroxamic acids are related to the amides of the carboxylic acids in the same manner that hydroxylamine is related to ammonia. Thus, just as amides are prepared by ammonolysis of an acid derivative, so may the hydroxamic acids be prepared by "hydroxylaminolysis" (58), as:

$$R-C(=O)-OR' + H_2NOH \longrightarrow R-C(=O)-HN-OH + R'OH$$

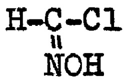
The simplest hydroxamic acid is that of formic acid, of which the two possible forms are formhydroxamic acid (III) and formhydroximic acid (IV):



$$H-C(=O)-HN-OH \rightleftarrows H-C(-OH)=NOH$$

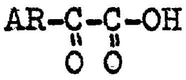
(III) (IV)

When the enolic hydroxyl group of a hydroximic acid is replaced by a halogen atom, such as chlorine, tautomerism is no longer possible, and the derivative thus obtained corresponds to an acid chloride of a carboxylic acid. These derivatives may be referred to as hydroximic acid chlorides. Thus, the acid chloride of formhydroximic acid (formhydroximic acid chloride) is



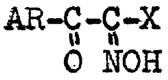
$$H-\underset{\underset{NOH}{\|}}{C}-Cl$$

α-Ketohydroximic acid halides of the general formula (VI) may be derived from -keto-acids of the type (V) by application



$$AR-\underset{\underset{O}{\|}}{C}-\underset{\underset{O}{\|}}{C}-OH$$

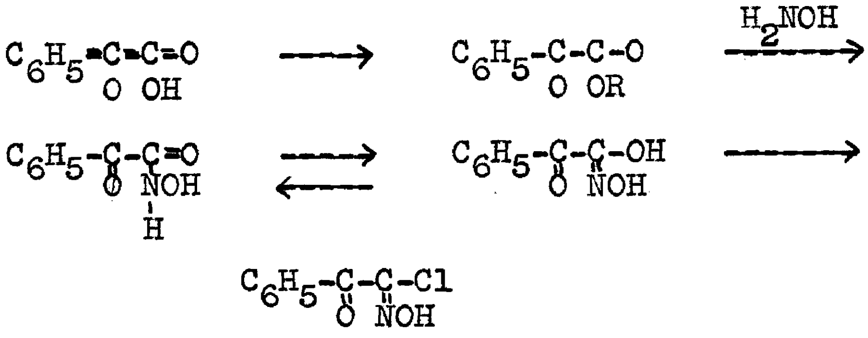
(V)



$$AR-\underset{\underset{O}{\|}}{C}-\underset{\underset{NOH}{\|}}{C}-X$$

(VI)

of the above theoretical considerations. Thus, if AR.CO.COOH represents phenylglyoxylic acid (benzoylformic acid), the corresponding hydroximic acid chloride may be structurally derived as follows:



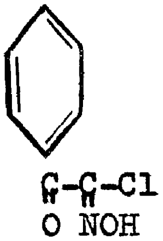
$$C_6H_5-\underset{O}{C}-\underset{OH}{C}=O \longrightarrow C_6H_5-\underset{O}{C}-\underset{OR}{C}-O \xrightarrow{H_2NOH}$$

$$C_6H_5-\underset{\underset{O}{\|}}{C}-\underset{\underset{\underset{H}{|}}{\underset{NOH}{\|}}}{C}=O \rightleftarrows C_6H_5-\underset{\underset{O}{\|}}{C}-\underset{\underset{NOH}{\|}}{C}-OH \longrightarrow$$

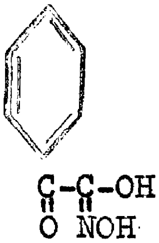
$$C_6H_5-\underset{\underset{O}{\|}}{C}-\underset{\underset{NOH}{\|}}{C}-Cl$$

The compound, C_6H_5.CO.C(:NOH)Cl, may be looked upon as the benzoyl derivative of formhydroximic acid chloride or as the hydroximic acid chloride of phenylglyoxylic acid.

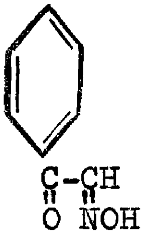
Nomenclature. Various methods have been employed in the literature for naming the halogen derivatives of α-keto-hydroximic acids having the general formula, R.CO.C(:NOH)X, where R may be an alkyl or aryl group and X represents a halogen.



(VII)



(VIII)



(IX)

Thus, the compound of structure (VII) is listed in Beilstein (59) as a derivative of phenylglyoxylhydroxamic acid (VIII) and is given the names:

(a) Benzoylformylchloridixime

(b) Benzoylformhydroximic acid chloride

(c) α-Chloro-α-isonitrosoacetophenone.

Most German workers have adopted the name chloro-isonitroso-acetophenone, presumably because of its structural relationship to isonitrosoacetophenone (IX) and probably on account of the fact that it was first prepared by the direct chlorination of isonitrosoacetophenone.

The only other compound of the structure, R.CO.C(:NOH)X, described in Beilstein (60) is $CH_3.CO.C(:NOH)Cl$, which is given the names:

(1) 1-Chlorpropanon-(2)-oxime-(1)

(2) α-Chloro-α-isonitroso-aceton

(3) Brenztraubenhydroximsäure chloride

The method of nomenclature employed by Chemical Abstracts consists in naming the compounds as derivatives of the corresponding glyoxylic acid. Thus, the acid, $C_6H_5.CO.COOH$, is indexed as phenylglyoxylic acid with a cross-refernee at benzoylformic acid. The corresponding hydroximic acid chloride, is accordingly indexed under the names:

(1) Phenylglyoxylohydroxamyl chloride

(2) Benzoylformohydroxamyl chloride.

The choice of naming the compound, $C_6H_5.CO.C(:NOH)Cl$, either as a derivative of phenylglyoxylic acid or benzoylformic acid is optional. Dr. Crane (61), in a personal communication, writes:

> "If one prefers benzoylformic acid over phenylglyoxylic acid, then the name benzoylformohydroxamyl chloride.......would be preferred over phenylglyoxylohydroxamyl chloride. Either name is correct. It is a chloride of the hydroxamic acid."

In this paper, compounds of the general formula, R.CO.C(:NOH)X will be designated as glyoxylohydroxamyl halides. In many instances where a more abbreviated designation is desirable, the term chloroisonitrosoketone is also employed.

<u>Methods of Synthesis</u>. Glutz (62), in 1870, was the first to describe the preparation of a glyoxylohydroxamyl halide. He treated chloroacetone with concentrated nitric acid and obtained methylglyoxylohydroxamyl chloride according to the equation:

$$CH_3.CO.CH_2Cl \xrightarrow{HNO_3} CH_3.CO.C(:NOH)Cl$$

Barbaglia (63), obtained methylglyoxylohydroxamyl chloride by the same method. Ponzio (64) obtained this chloroisonitrosoketone as an intermediate in the oxidation of chloroacetone to chloromethylnitrolic acid:

$$CH_3.CO.CH_2Cl \xrightarrow{HNO_3} CH_3.CO.C(:NOH)Cl \longrightarrow ClC(:NOH)NO_2 + (COOH)_2$$

Henry (65) oxidized 2-chloropropanol-1 with nitric acid at ordinary temperature and obtained a mixture of products consisting of acetic acid, chloroacetic acid and a compound to which he assigned two possible formulas:

$$ON.CH_2.CO.CH_2Cl \qquad\qquad CH_3.CO.CH(NO)Cl$$

(I) (II)

The nitrosochloro-compound obtained was found to be identical with the methylglyoxylohydroxamyl chloride previously prepared by Glutz (62); thus, the nitroso-formula (II) is, strictly speaking, the isonitroso derivative of $CH_3.CO.CH_2Cl$.

Behrend and his associates (66,67) oxidized acetone with fuming nitric acid and obtained an intermediate, for which they suggested two possible formulas, $CH_3CO.C(:NOH).ONO$ and $CH.CO.C(:NOH).NO_2$. The compound thus obtained when treated with concentrated hydrochloric acid at 0°, gave methylglyoxylohydroxamyl chloride in small yields. Using this method, Ponzio and Charrier (68) were able to obtain 40-45 g. of methylglyoxylohydroxamyl chloride from 100 g. of acetone.

Sandmeyer (69) prepared methylglyoxylohydroxamyl chloride in small yields by the decomposition of an intermediate which he obtained by treating acetone with nitrogen oxides:

$$(CH_3)_2.C(ONO_2).C(:NOH).CO.CH_3 \longrightarrow$$
$$ClC(:NOH)CO.CH_3 + (CH_3)_2CO + HCl$$

Brunner (70) showed that acetone reacts with aqua regia in the cold to give methylglyoxylohydroxamyl chloride; with excess aqua regia, there was obtained a diisonitrosochloroacetone, of the formula, $HC(:NOH).CO.C(:NOH)Cl$.

The first arylglyoxylohydroxamyl halide was described by Claisen in 1887. On saturating a cooled mixture of acetophenone and amyl nitrite with hydrogen chloride, he obtained a small quantity of a white crystalline product, melting at 133-134°. When heated above its melting point, the product decomposed with the liberation of hydrogen chloride; he therefore assumed that the original product was a hydrogen chloride addition compound of isonitrosoacetophenone (71). In a subsequent paper, Claisen and Manasse (21) succeeded in isolating in small yields both the chloroisonitroso- and isonitroacetophenones using the above method.

The reaction of amyl nitrite with acetophenone in the presence of hydrogen chloride to give both products was explained by Claisen and Manasse (72) by the fact that the nitrite is first converted by excess hydrogen chloride to nitrosyl chloride and this is the true nitrosating agent:

$$RONO + HCl \longrightarrow ROH + NOCl$$

$$C_6H_5.CO.CH_3 + NOCl \longrightarrow C_6H_5.CO.C(:NOH)H + HCl$$

Further, any nitrous acid which might be formed, could oxidize hydrogen chloride to free chlorine and thus chlorination of isonitrosoacetophenone might occur:

$$C_6H_5.CO.C(:NOH)H + Cl_2 \longrightarrow C_6H_5.CO.C(:NOH)Cl + HCl$$

These investigators also showed that phenylglyoxylohydroxamyl chloride may be obtained in 70 percent yields by the chlorination of isonitrosoacetophenone in chloroformic solution. Ponzio and Charrier (68), using this method, reported 80 percent yields of the corresponding chloroisonitrosoketone. In a more recent report, Ponzio (73) chlorinated isonitrosoacetophenone in glacial acetic acid and obtained the chloroisonitrosoketone in yields of about 60 percent- which is much lower than those mentioned previously. Para-methyl-phenylglyoxylohydroxamyl chloride was prepared by the same procedure; the yields were not mentioned however.

Steinkoff and Jürgens (74) prepared phenylglyoxylohydroxamyl chloride by saturating a suspension of the ammonium salt of ω-nitroacetophenone in ether with dry hydrogen chloride. The yield of product was reported as being almost quantitative. Jakubowitsch (75) refluxed a mixture of ω-nitroacetophenone with hydrochloric acid in dilute alcohol and obtained phenylglyoxylohydroxamyl chloride in a 54 percent yield (based on crude product).

In their studies of the action of nitrosyl chloride on ketones, Rheinboldt and Schmitz-Dumont (76) developed a method for the preparation of glyoxylohydroxamyl chlorides, which was referred to "nitrosochlorination". Essentially, the nitrosochlorination reaction consists of reacting a methyl ketone and nitrosyl chloride with the formation of a glyoxylohydroxamyl chloride:

$$R.CO.CH_3 + 3NOCl \longrightarrow R.CO.C(:NOH)Cl + 2NO + 2HCl$$

A summarized account of the studies on chloronitrosation by Rheinboldt and Schmitz-Dumont (76) are presented in Table II.

The mechanism of chloronitrosation was explained by the following equations:

$$\begin{array}{ll} (I). & R.CO.CH_3 + NOCl \longrightarrow R.CO.C(:NOH)H + HCl \\ (II). & \underline{R.CO.C(:NOH)H + 2NOCl \longrightarrow R.CO.C(:NOH)Cl + 2NO + HCl} \\ (III). & R.CO.CH + 3NOCl \longrightarrow R.CO.C(:NOH)Cl + 2NO + 2HCl \end{array}$$

The formation of an isonitrosoketone of the type, R.CO.C(:NOH)H

Table II. Summary on the Glyoxylohydroxamyl Chlorides Prepared by Rheinboldt and Schmitz-Dumont (76).

Ketone	Products	Yield[a] %
$CH_3.CO.CH_3$	$CH_3.CO.C(:NOH)Cl$	45.0
$CH_3.CO.C_2H_5$	$C_2H_5.CO.C(:NOH)Cl$	
$CH_3.CH_2.CH_2.CO.CH_3$	$CH_3.CH_2.CH_2.CO.C(:NOH)Cl$	
$(CH_3)_2CH.CO.CH_3$	$(CH_3)_2CH.CO.C(:NOH)Cl$	11.5
$HOOC.CH_2.CH_2.CO.CH_3$	$HOOC.CH_2.CH_2.CO.C(:NOH)Cl$	
$(CH_3)_3C.CO.CH_3$	$(CH_3)_3C.CO.C(:NOH)Cl$	70.0
$C_2H_5OOC.CH_2.CH_2.CO.CH_3$	$C_2H_5OOC.CH_2.CH_2.CO.(:NOH)Cl$	
$C_6H_5.CO.CH_3$	$C_6H_5.CO.C(:NOH)Cl$	24.5
$4\text{-}CH_3.C_6H_4.CO.CH_3$	$4\text{-}CH_3.C_6H_4.CO.C(:NOH)Cl$	32.0
$C_6H_5.CH:CH.CO.CH_3$	$C_6H_5.CH:CH.CO.C(:NOH)Cl$	21.0
$4\text{-}CH_3O.C_6H_4.CH:CH.CO.CH_3$	$4\text{-}CH_3O.C_6H_4.CH:CH.CO.C(:NOH)Cl$	
	$4\text{-}CH_3O.C_6H_4.CH:CH.CO.C(:NOH)H$	
$4\text{-}Cl.C_6H_4.CO.CH_3$	$4\text{-}Cl.C_6H_4.CO.C(:NOH)H$	
$C_6H_5.CH_2.CO.CH_3$	$C_6H_5.C(:NOH).CO.CH_3$	

[a] Unless specified, the yield was not mentioned, accordingly it may be presumed to be negligible.

as an intermediate was indicated by the following:

(1) Anisalacetone, $CH_3O.C_6H_4.CH:CH.CO.CH_3$, gave both isonitroso- and chloroisonitrosoketones.

(2) Isonitrosoacetone and isonitrosoacetophenone, when further treated with nitrosyl chloride, gave their corresponding chloroisonitrosoketones.

Additional evidence in favor of the mechanism of the reaction as given above was indicated by the fact that the mole ratio of nitric oxide evolved, when determined quantitatively, as compared to the yield of chloroisonitrosoketone obtained was 2:1. It is also important to note that para-chloroacetophenone when treated with nitrosyl chloride gave only para-chloroisonitrosoacetophenone; further reaction with nitrosyl chloride did not occur.

The chloronitrosation reaction as a method for the preparation of glyoxylohydroxamyl chlorides is limited in its applications as indicated in the results tabulated. Furthermore, this procedure gives, in general, poor yields of glyoxylohydroxamyl chlorides. Further studies on the application of chloronitrosation to other nuclear-substituted derivatives of acetophenone are not available.

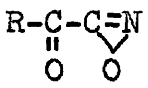
Lynn and Lee (77) studied the chloronitrosation reaction and obtained results which differed from those of Rheinboldt and Schmitz-Dumont (76). Thus, in the case of acetone, there was obtained a mixture consisting of isonitrosoacetone, $CH_3.CO.C(:NOH)H$, the mononitrosochloride of phorone, $(CH_3)_2C:CH.CO.CH(NO).CCl(CH_3)_2$, and the dinitroso-chloride of phorone, $(CH_3)_2C(NO).CClH.CO.CH(NO)CCl(CH_3)_2$. With methylethylketone, only isonitrosomethylethylketone was obtained. In a subsequent reply to these workers, Rheinboldt and Schmitz-Dumont (78) explained that they were able to "chloronitrosate" acetone and methylethylketone and the difference in results might be explained by the fact that the American investigators carried out their reaction in the absence of a solvent.

Chemical Properties. The alkyl- and aryl-glyoxylohydroxamyl halides dissolve in concentrated sulfuric acid in the c cold, with the formation of a yellow color; on heating with dilute sulfuric acid, decomposition occurs and the corresponding carboxylic acid is obtained (76):

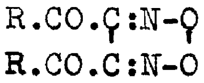
$$R.CO.C(:NOH)X \xrightarrow{H_2SO_4} R.COOH$$

They dissolve slowly on standing in dilute sodium hydroxide solution with the formation of a yellow color; if the alkaline solution is heated, decomposition occurs as above (76). Thus, these two tests may be employed in the identification of glyoxylohydroxamyl halides.

When heated above their melting point, hydrogen chloride is split off, with the subsequent formation of a nitriloxide, (76).



With silver nitrate in absolute alcohol, methylglyoxylohydroxamyl chloride and phenylglyoxylohydroxamyl chloride are converted into peroxides of the general formule (68):



$$\begin{matrix} R.CO.C{:}N-O \\ R.CO.C{:}N-O \end{matrix}$$

Glyoxylohydroxamyl halides react very readily in the cold with aromatic amines to form the corresponding glyoxylohydroxamyl amides:

$$R.CO.C(:NOH)X \xrightarrow[\text{(Ether)}]{H_2NAR} R.CO.C(:NOH)NHC_6H_5$$

This reaction indicated the close chemical relationship between compounds of the type, R.CO.C(:NOH)X and R.CO.COX. Condensation of chloroisonitrosoketones with aniline and para-toluidine is reported; application of this reaction to include aliphatic amines has never been described. These amides are crystalline solids which melt with decomposition. They are insoluble in cold dilute alkali; on heating, however decomposition occurs.

Rheinboldt and Schmitz-Dumont (76) condensed chloroisonitroketones with benzoyl chloride and obtained stable, crystalline benzoyl derivatives:

$$R.CO.C(:NOH)Cl + ClCOC_6H_5 \longrightarrow R.CO.CCl(:NOCOC_6H_5) + HCl$$

The carbonyl group of these halogenoisonitrosoketones possess the usual characteristic properties which are generally associated with the carbonyl group of α-oximinoketones. Thus, condensation with the usual reagents for the carbonyl group, such as hydroxylamine, the hydrazines, semi-carbazide, etc., occurs readily.

Probably, the most interesting derivatives of glyoxylohydroxamyl halides are the gloximes, R.C(:NOH).C:NOH)X, which are prepared by allowing a solution of the ketone and hydroxylamine hydrochloride to stand at room temperature for several weeks. These use of alkali, as is customary in the oximation of ketones, must be avoided due to the presence of a labile halogen atom. These gloximes, are, in general, white crystalline solids which melt with decomposition. They give no color with ferric chloride in alcoholic solution; however on heating in water, they dissolve and the solution thus obtained gives a violet color (hydroxamic acid test) with ferric chloride. The addition of silver nitrate solution to a halogenoglyoxime gives a precipitate of the silver halide (76). The halogenoglyoximes dissolve in sodium hydroxide solution giving a yellow color, and the solution thus obtained gives a positive hydroxamic acid test (76).

Ponzio and his associates (79) have published a number of papers which describe the chelate derivatives of these halogenogloximes.

Other methods for preparing halogenoglyoximes have been described. Thus, Ponzio (80) showed that chlorophenylglyoxime could be obtained by the chlorination of phenylglyoxime:

$$C_6H_5.C(:NOH).C(:NOH)H \xrightarrow[HCCl_3]{Cl_2} C_6H_5.C(:NOH).C(:NOH)Cl$$

Using this method, Ponzio and Perolio (81) prepared chloro-para-tolylglyoxime. When chloroglyoximes are treated with sodium iodide in acetone, iodoglyoximes are obtained. Using this procedure, Ponzio (82) has recently prepared iodophenylglyoxime, iodo-para-tolylglyoxime and iodomethylglyoxime. On heating these iodoglyoximes with ammonia, the corresponding aminoglyoximes were obtained:

$$R.C(:NOH).C(:NOH)I \xrightarrow{NH_3} R.C(:NOH).C(:NOH)NH_2$$

Physiological Properties. There is only one report concerning the physiological character of glyoxylohydroxamyl halides. Milone (83) has recently made a study of the irritant action of methylglyoxylohydroxamyl chloride and its oxime. Phenylglyoxylohydroxamyl chloride and its oxime were not characterized by this undesirable physiological property. He explained this difference in activity by the fact that methylglyoxylohydroxamyl chloride and its oxime react much more readily with proteins and lipoids.

Table III. Derivatives of Glyoxylohydroxamyl Halides

R.CO.C(:NOH)Cl R=	Oxime	Anilide	Toluidide	*N*-Benzoate
CH_3-[a]	171°(dec.) (66,67,68, 69).	113-4° (68,76)	(68)	
$CH_3.CH_2.CH_2$-	154°(dec.) (76)			
$(CH_3)_3C$-		103-4° (76)	123-4° (76)	63-4° (76)
para-$CH_3.C_6H_4$-	217°(dec.) (73)			
C_6H_5-	193-4°(dec.) (76)	147°(dec.) (76)		
C_6H_5.CH:CH-			176-7°(dec.) (76)	

[a] The temperature given is the melting point reported in the references specified.

EXPERIMENTAL

A. Synthesis of Ketones

Phenacyl Chloride. The Friedel-Crafts reaction is most commonly employed for the preparation of phenacyl chloride and its alkyl, alkoxy and halogeno-nuclear-substituted derivatives, in both the laboratory (84,85) and in industry (86,87) because of the excellent yields of product and availability of intermediates. Some of the ketones prepared in this investigation have been previously described (88).

The Friedel-Crafts procedure[a] employed in the preparation of phenacyl chloride involves the reaction of benzene with chloroacetyl chloride in the presence of anhydrous alumium chloride,- excess benzene[b] serving as the solvent. The method is as follows:

In a 1-liter, three-neck, round-bottom flask, fitted with a sealed mechanical stirrer, a separatory funnel and a reflux condenser, connected to a gas-absorption trap[c], were placed 102.6 g. (0.77 mole) anhydrous aluminum chloride (Eastman-Kodak, practical) and 265 cc. benzene.

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[a] The phenacyl halides are, in general, violent lachrymators and sternutators. Therefore, caution must be exercised in handling these intermediates. It was found best to carry out these syntheses in a well-ventilated hood.

[b] Organic solvents, employed in the synthesis of these ketones, were first dried over anhydrous calcium chloride.

[c] A gas-absorption trap modeled after that described by Johnson (Org. Synthesis, Col. Vol. I, 91 (1932) was used in these investigations.

Then 53.1 cc. (0.70 mole) chloroacetyl chloride (Eastman-Kodak, practical) was allowed to drop in during the course of about one-half hour. When all the chloroacetyl chloride was in, the reaction flask was refluxed in a boiling water-bath until the evolution of hydrogen chloride ceased. This required approximately three hours. The reaction mixture was allowed to cool to room temperature and the aluminum complex was decomposed by the addition of a mixture of equal parts of ice-water and concentrated hydrochloric acid. The organic layer was then separated, washed with water and dried over anhydrous calcium chloride. The excess benzene was recovered by distillation of a boiling water-bath and the residue distilled under reduced pressure. The product distilling at 120-35°/4 mm. was redistilled. The yield of white crystals, thus obtained was 95.5 g. (88.2 %); b.p.[a] 120-35°/ 4 mm.; m.p. 56-7°.

Phenacyl Bromide. The method described by Cowper and Davidson (89), which consists of the direct bromination of acetophenone, was employed for the preparation of this ketone. From 73.2 cc. (0.61 mole) acetophenone (b.p. 200-2°) and 33.3 cc. (0.61 mole) bromine in 75 cc. anhydrous ether, to which was added 0.75 g. anhydrous aluminum chloride (E.K. & Co., resublimed), there was obtained, after recrys-

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[a] All boiling points reported in this investigation are uncorrected; melting points were taken with an Anschütz thermometer (entire stem immersed in bath).

tallization from ligroin, 70 g. (58 %) of phenacyl bromide; m.p. 49-50°.

Para-Methylphenacyl Chloride. This ketone was prepared by the Friedel-Crafts synthesis using the same procedure described under phenacyl chloride. From 151.0 cc. (2.0 moles) chloroacetyl chloride, 850 cc. (8.0 moles) toluene and 293.3 g. (2.2 moles) aluminum chloride, there was obtained 277 g. (82 %) of para-methylphenacyl chloride; m.p. 55-6°.

Para-Phenylphenacyl Chloride. Para-phenylphenacyl chloride was obtained by the usual Friedel-Crafts synthesis using as a solvent, carbon disulfide. To a rapidly-stirred suspension of 23.1 g. (1.5 moles) diphenyl (E.K. & Co., practical) and 220.0 g. (1.65 moles) aluminum chloride (E.K. & Co., resublimed) in 500 cc. carbon disulfide was added during the course of one and one-half hours, 117.0 cc. (1.55 moles) chloroacetyl chloride (E.K. & Co., practical). The reaction mixture was then refluxed on a boiling water-bath for about three hours, after which evolution of hydrogen chloride practically ceased. After decomposition of the complex, the crude product separated out; this was filtered off and dried by suction. After recrystallization from hot alcohol (50 %), yellow crystals, melting at 120-3° were obtained; a second recrystallization from boiling isopropyl alcohol gave 290.0 g. (85.0 %) of yellow crystals; m.p. 124-26°.

Para-Chlorophenacyl Chloride. The only mention of the preparation of para-chlorophenacyl is in two early papers,-one by Gauteer (90) who obtained this ketone by the chlorination of the acetophenone; the other by Collet (91), who reacted chlorobenzene with chloroacetyl chloride using aluminum chloride according to the regular Friedel-Crafts synthesis. In both reports, however, only meagre information is given regarding the experimental details.

In this investigation, para-chlorophenacyl chloride was prepared by the Friedel-Crafts synthesis. In one run, excess chlorobenzene was tried as the reaction solvent; in this instance, the aluminum chloride was added in divided portions to the mixture of chlorobenzene and chloroacetyl chloride. From 22.8 cc. (0.3 mole) chloroacetyl chloride (E.K. & Co., practical), 40.1 g. (0.3 mole) aluminum chloride (Calco) and 100 cc. (1.1 mole) chlorobenzene (E.K. & Co), a yield of only 29.0 g. (51.2 %) of product, distilling at 126-42°/13.5 mm., m.p. 100-1°, was obtained. Two runs in which carbon disulfide served as the solvent, resulted in 88.5-90.8 percent yields of pure ketone. Thus, the apparent advantage possessed by carbon disulfide as the reaction solvent over the high boiling, reactive chlorobenzene is readily noted. The following is the method finally adapted for the preparation of para-chlorophenacyl chloride:

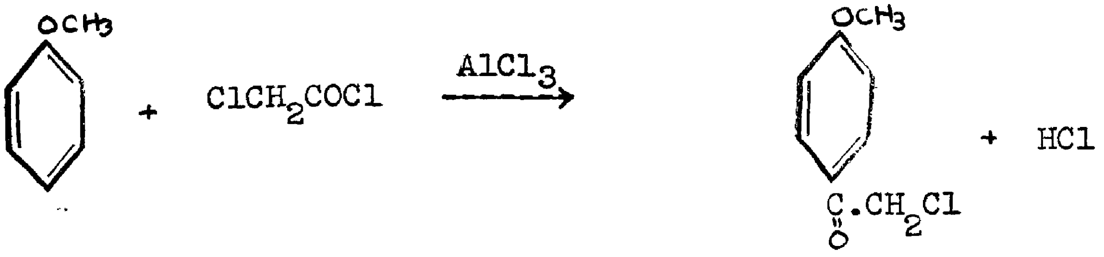
In a 2-liter, round-bottom, three-neck flask provided with a sealed mechanical stirrer, separatory funnel and a reflux condenser connected to a gas-absorption trap were added

153.5 g. (1.5 moles) chlorobenzene (E.K. & Co.)
220.0 g. (1.65 moles) aluminum chloride (E.K. & Co.)
1,000.0 cc. carbon disulfide.

The reaction flask was immersed in a bath of cold water (15-8°) and to the rapidly-stirred suspension, was added during the course of one and one-half hours, 125 cc. (1.65 moles) chloroacetyl chloride (b.p. 104-6°). After this, the reaction mixture, was refluxed on a hot water-bath for three hours, until evolution of hydrogen chloride gas appeared to stop. The mixture was then cooled and the complex decomposed by the addition of a mixture of ice-water and concentrated hydrochloric acid 1:1). The carbon disulfide was distilled off and the crude product which separated was filtered off and dried with suction. Recrystallization from alcohol (50 %) gave 261 g. (88.5 %) of para-chlorophenacyl chloride, m.p. 100-1°.

Para-Methoxyphenacyl Chloride. Para-methoxyphenacyl chloride has been prepared by two methods:

(a) Friedel-Crafts Synthesis. Kunckell and Johannsen (92) were the first to prepare this ketone. The reaction is as follows:



The product thus obtained, melted at 102°; the yield was not mentioned however. Voswinckel (93) later used this method for the synthesis of para-methoxyphenacyl chloride but gave no details.

Tutin (85), using anisole, chloroacetyl chloride and aluminum chloride in carbon disulfide, obtained a product, which, after fractional crystallization from alcohol, consisted of para-methoxyphenacyl chloride (m.p. 102°) and a small quantity of the ortho- isomer (m.p. 69°). These two isomers were separated mechanically but no indication was made of the yields obtained. Jörlander (94) and Widman (95), using the procedure described by Tutin (85), also obtained both para- and ortho-isomers, but no mention was made of the yields obtained. Jörlander (94) showed that the yield of ortho-methoxyphenacyl chloride could be increased by lowering the reaction temperature.

<u>(b) Reaction of Para-Methoxybenzoyl Chloride with Diazomethane</u>. Nierenstein (96), in his studies on the action of diazomethane on acid halides, showed that para-methoxyphenacyl chloride could be prepared in 86 percent yields by the reaction:

$$CH_3O.C_6H_4.COCl + CH_2N_2 \longrightarrow CH_3O.C_6H_4.COCH_2Cl + N_2$$

The melting point of the product thus obtained was reported as 104-5°.

More recent studies by Robinson and his co-workers (97) indicate that the preparation of phenacyl halide proceeds more smoothly if the diazoketone is first prepared and this employed as the intermediate according to the following reactions:

$$CH_3O.C_6H_4.COX \xrightarrow{2\ CH_2N_2} CH_3O.C_6H_4.COCHN_2 \xrightarrow{HX} CH_3O.C_6H_4.CO.CH_2X$$

Although these investigators did not apply the above method to the preparation of para-methoxyphenacyl chloride, they showed that treatment of para-methoxy-ω-diazoacetophenone with hydrogen bromide gave para-methoxyphenacyl bromide in quantitative yields; the yield of the diazoketone was not mentioned, however, Burger and Avakien (98) have recently obtained this intermediate in 70.3 percent yields. According to recent publications, Robinson's modification of Nierenstein's reaction, appears to be preferable for the preparation of phenacyl halides.

Para-methoxyphenacyl chloride was prepared in this investigation by the Friedel-Crafts synthesis according to Kunckell and Johannsen (92) and Tutin (85). Of the four runs carried out, the following adaptation gave the best yield:

In a 500 cc., round-bottom, three-neck flask equipped with a sealed mechanical stirrer, a small powder funnel and a reflux condenser, attached to a gas-absorption trap, were added 21.8 cc. (0.2 mole) anisole (b.p. 155-6°), 18.0 cc. (0.24 mole) chloroacetyl chloride (E.K. & Co.,) and 100 cc. carbon disulfide. The reaction flask was immersed in a bath of cold water (10°)

and to the rapidly stirred mixture was added during the course of one hour, 26.7 g. (0.2mole) aluminum chloride (E.K. & Co.). After the aluminum chloride was added, the cold water-bath was replaced by bath of warm-water (35-40°). After three hours, evolution of hydrogen chloride ceased; the reaction mixture was allowed to cool to room temperature and the complex decomposed by the addition of ice-water. The carbon disulfide was recovered by distillation and on cooling, the oily layer remaining, crystallized out. The orange-colored crystals thus obtained were filtered off with suction and dried; yield, 27.6 g. This product was then dissolved in ether and etheral solution extracted with cold 2 percent sodium hydroxide solution to remove demethylated products. The solvent was then removed by distillation and the residue steam distilled. The long needles obtained, after two recrystallizations from hot alcohol (65 %) melted at 96-98°.

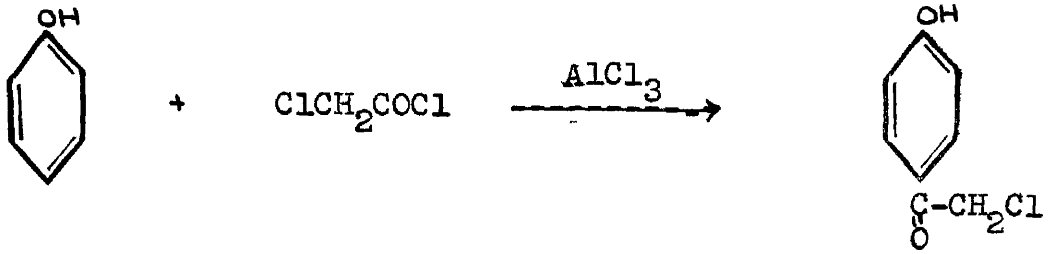
At no time during the course of this investigation was it possible to obtain a product which melted as high as that reported by other workers (85,92,96). It was presumed, that if the melting points 102°, 104-5°, previously reported for para-methoxyphenacyl chloride are correct, then the product obtained by the above method must contain a small quantity of ortho-methoxyphenacyl chloride as a by-product. Mechanical separation of the crystalline product failed. The possibility of employing steam distillation was tried, in view of the fact that both Tutin (85) and Jörlander (94) mention that ortho-methoxyphenacyl chloride distills over in steam. In one experiment, 15.0 g. of long needles, m.p. 97-98°, was steam distilled and the distillate collected in fractions of 500-1,000 cc. It was found that no significance change in the melting point of the products was obtained as indicated in the following tabulation:

Fraction	M.P.
(1)	97.0-98.5°
(2)	96.0-98.0°
(3)	97.5-98.5°
(4)	96.0-98.5°
(5)	96.0-98.5°
(6)	96.5-98.5°
(7)	97.0-98.5°

One sample of the product, melting at 97-98°, was subjected to repeated recrystallizations from hot alcohol (50 %). Even after six consecutive recrystallizations, there was no significance change in the melting point. Further study of possible purification methods for the para-methoxyphenacyl chloride obtained by the method of synthesis employed was discontinued.

Ortho- and Para-Hydroxyphenacyl Chlorides. The preparation of both ortho- and para-hydroxyphenacyl chlorides are presented a difficult problem to various investigators and the yield of these products have been unsatisfactory. The various procedures described in the literature for the preparation of these isomeric phenolic-ketones may be divided into the following groups:

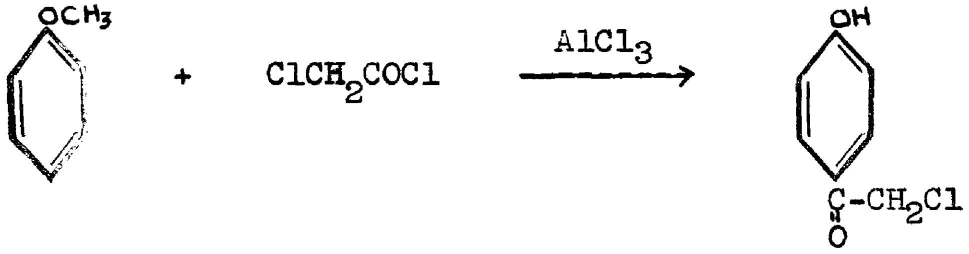
<u>(a) Friedel-Crafts Reaction</u>. Synthesis of para-hydroxyphenacyl chloride by direct acylation of the ring according to the equation,



is difficult and the yields negligible. This method was first described in an old German patent (99). Tutin (50) reported only small yields by this method, whereas Kunckell and Johannsen (100) obtained a mixture of small amounts of phenyl chloroacetate, para-hydroxyphenacyl chloride and the chloroacetate ester of para-hydroxyphenacyl chloride. Priestley and Moness (101) mentioned the use of para-hydroxyphenacyl chloride as an intermediate in their synthesis of sympathol but gave no details as its method of preparation. Priestley (102) later acknowledged that the reaction of phenol with chloroacetyl chloride in the presence of aluminum chloride was used; the yields of para-hydroxyphenacyl chloride were only 5-10 percent however.

Application of the Friedel-Crafts reaction to intermediates in which the phenolic group is protected gives somewhat more satisfactory results. Kunckell and Johannsen (92) obtained the chloroacetate ester of para-hydroxyphenacyl chloride from phenyl chloroacetate, chloroacetyl chloride and aluminum chloride. No yields were reported and possible hydrolysis of this ester to the phenolic-ketone was not mentioned. Tutin (85), in an attempt to chloroacetylate phenylacetate by a method similar to that of Kunckell and Johannsen (92), obtained the chloroacetate ester of para-hydroxyacetophenone instead of the desired acetate of para-hydroxyphenacyl chloride.

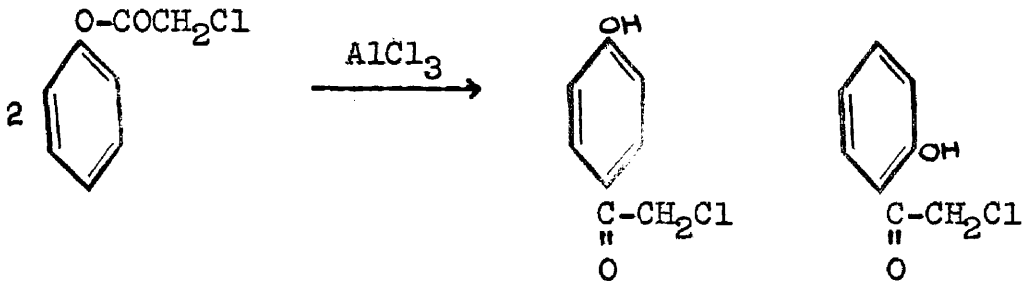
The use of anisole appears to be the best adaption of the Friedel-Crafts for the synthesis of para-hydroxyphenacyl chloride; here, chloroacetylation of the ring and demethylation occurs simultaneously:



The method was first developed by Kunckell and Johannsen (100) and later by Tutin, Caton and Hann (50), however these investigators made no mention of the yields of product obtained. Robertson and Robinson (103), using the above method, reported yields of 7-8 g. of para-hydroxyphenacyl chloride from 10 g. of anisole. Rubin and Day (104) have recently reported yields of 36 percent of this phenolic-ketone; a subsequent communication by Day (105) mentions a yield of 44 percent.

Ortho-hydroxyphenacyl chloride, has been prepared by Tutin (85) by the demethylation of ortho-methoxyphenacyl chloride, which was obtained by Friedel-Crafts synthesis from anisole and chloroacetyl chloride. No yields were reported, however.

(b) Fries Rearrangement. Fries and Pfaffendorf (106), in their studies on the preparation of phenolic-substituted ketones by the rearrangement of esters in the presence of aluminum chloride, obtained both ortho- and para-hydroxyphenacyl chlorides from phenyl chloroacetate by the reaction:



The ortho- isomer was reported to have been obtained in 50 percent yields, on steam distillation of the reaction product, whereas no mention was made of the isolation and yield of para-hydroxyphenacyl chloride.

In an investigation of the use of beryllium chloride as a catalyst in the Fries rearrangement of esters, Brederick, Lehmann, Schönfeld and Fritzsche (108) succeeded in obtaining both ortho- and para- hydroxyphenacyl chlorides from phenyl chloroacetate. The yields of the two isomers varied according to the reaction temperature; the following tabulation summarizes their results:

Reaction Temperature	Percent Yields	
	Ortho-	Para-
100°	10	5
130.40°	30	23
165°	19	26

A study was made of the preparation of ortho-hydroxyphenacyl chloride by the Fries rearrangement of phenyl chloroacetate. A summary of the various experimental conditions employed and the yields of product are recorded in Table V. It appears that the reaction of phenyl chloracetate with aluminum chloride without the use of a solvent gives the best results.

Phenyl chloracetate used in this study was prepared according to the method of Fries and Pfaffendorf (106), by heating a mixture of 188.1 g. (2.0 moles) phenol (Baker, U.S.P) and 173.4 cc. (2.3 moles) chloracetyl chloride (E.K. & Co.) at 135-40° for four hours. Distillation of the crude product gave 322 g. (94.4 %) of phenyl chloroacetate, b.p. 135-40°/25-7 mm.; m.p. 40-2°.

The following illustrates the rearrangement of phenyl chloroacetate as in run IV:

In a 1-liter, three-neck, round-bottom flask fitted with a sealed mechanical stirrer, a reflux condenser connected to a gas-absorption trap, a small powder funnel and a thermometer was placed 85.3 g. (0.5 mole) phenyl chloroacetate. The

Table IV. Fries Rearrangement of Phenyl Cloroacetate

Run No.	Molecular Ratio		Solvent	Period of Heating		Notes	Yield %
	AlCl	Phenyl Chloroacetate		Temperature (°C)	Time (in hours)		
I	0.5	0.5	Carbon disulfide	140	3	Phenyl chloroacetate	19.5
II	0.4	0.5	Carbon disulfide	145-50	3	(as above)	23.0
III	0.5	0.5	Ligroin	145-50	2	Added $AlCl_3$ to ester	17.5
IV	1.0	0.5	--	120	6	Added $AlCl_3$ in divided portions to ester without heating.	30.0
V	1.0	0.5	--	120-5	6	Added $AlCl_3$ to ester while heating.	25.3
VI	1.0	0.4	--	120	6	Added all of ester in portion	17.7

stirrer was set in motion and, at intervale one and one-half to two minutes, 133.3 g. (1.0 mole) aluminum chloride (E.K. & Co., resublimed) was added. After several portions had been added, the mixture assumed a cherry-red, syrupy appearance but little hydrogen chloride was evolved; after one-half of the total aluminum chloride was added, a solid mass formed, stirring was no longer possible and it became necessary to heat the mixture in an oil bath (75°) until it liquefied, after which addition of the alumimum chloride had been added, (total time required was one hour), the mixture became a thick, yellow liquid. The temperature of the oil bath was then raised until the reaction mixture was 120°. After heating for six hours, the dark, thick product thus obtained was allowed to cool to room temperature and decomposed by the addition of chipped ice followed by 200 cc. of a mixture of ice-water and hydrochloric acid (1:1). The crude product was then distilled in a current of steam; recrystallization from alcohol (50 %) gave 25.6 g. (30.0 %) of ortho-hydroxyphenacyl chloride, m.p. 73-4°.

Numerous attempts to prepare para-hydroxyphenacyl chloride according to the procedures described by other workers (50,100,103,104) failed. In a private communication, Day (105) offered a number of suggestions and gave a more adequate account of the experimental procedure which he had recently published (104). This procedure was found to be successful, although, out of five runs, never did the yield of product approach that (44 %) reported by Day (105). Although the experimental conditions were varioud frequently to comply with various inteepretations of Day's write-up, the yields were only 24.8-28.2 percent. A typical experiment follows:

In a 2-liter, three-neck, round-bottom flask fitted with a reflux condenser connected to a gas-absorption trap, a sealed mechanical stirrer and a small powder funnel were placed:

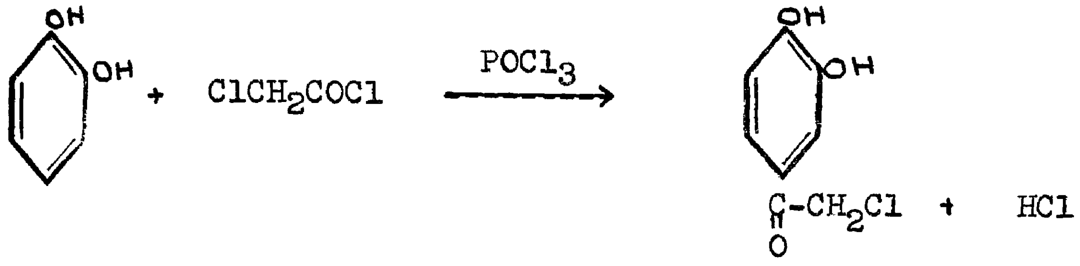
60.5 cc. (0.554 mole) anisole (b.p. 155-6°)
48.2 cc. (0.626 mole) chloroacetyl chloride (E.K. & Co.)
1000 cc. ligroin (E.K. & Co., practical)

The reaction flask was immersed in a bath of water (40-5°) and during the course of forty-five minutes, 90.0 g. (0.675 mole) aluminum chloride (E.K. & Co., resublimed) was added to the rapidly-stirred mixture;- the hydrogen chloride evolved from the reaction was removed by keeping the reaction set-up under slightly reduced pressure (water-pump). After all of the aluminum chloride had been added, the mixture was heated in the bath (45-5°) for an hour,- stirring of the reactants and removal of the hydrogen chloride being continued. The temperature of the bath was then raised to 50-5° and during the course of one hour a second portion of aluminum chloride, 90.0 g. (0.675 mole), was further added. After this, the bath was heated to boiling and the solvent recovered under reduced pressure (water-pump) with the condenser remaining in the reflux position. This required one and one-half to two hours. When practically all of the ligroin was removed, the reaction mixture was allowed to stand at room temperature for one hour and the aluminum complex decomposed by the addition of crushed ice followed by 500 cc. concentrated hydrochloric acid, during which, vigorous stirring of the reaction mixture was maintained. The larger pieces of material were broken up by a glass rod. The dark, purple, tarry mixture thus obtained was allowed to stand overnight and then extracted with six, 300 cc. portions of ether. The etheral extracts were combined, washed with 200 cc. cold water, once with a 250 cc. of a solution of ammonium carbonate (5 %) and then with six, 400 cc. portions of sodium carbonate solution (10 %) to remove the para-hydroxyphenacyl chloride. The alkaline extracts were then treated individually with excess concentrated hydrochloric acid to precipitate the crude phenolic-ketone. The precipitated products thus obtained were allowed to stand overnight in the refrigerator; these were then filtered off and dried with suction. Recrystallization from alcohol (80 %) with the addition of 3.0 g. of Norite gave 26.6 g. (28.2 %) of para-hydroxyphenacyl chloride, melting with decomposition, 147-8°.

<u>3,4-Dihydroxyphenacyl Chloride</u>. An extensive study of the various methods employed by other workers has been given in a previous report (88). As the result of this study, a procedure was developed whereby this intermediate could be obtained in good yields (88). This consisted of reacting chloroacetic acid with phosphorus pentachloride according to the equation:

$$ClCH_2COOH + PCl_5 \longrightarrow ClCH_2COCl + POCl_3 + HCl$$

The mixture of products thus obtained, could be distilled off and without further purification, be reacted with catechol to give 3,4-dihydroxyphenacyl chloride:



By this modification, a pure product could be obtained after a single recrystallization in yields of 60 percent. The following illustrates the procedure devised:

A mixture of 83.3 g. (0.4 mole) phosphorus pentachloride and 42.5 g. (0.45 mole) chloroacetic acid were allowed to react by refluxing in a boiling water-bath for three hours. The clear solution thus obtained was distilled off and the product distilling over up to 115° was added to a suspension of 44.0 g. (0.4 mole) catechol (E.K. & Co., practical) in 200 cc. benzene. After refluxing the mixture on a water-bath for fifteen hours, the solvent was recovered by distillation, using reduced pressure towards the end. The dark purple residue thus obtained was then dissolved in 400 cc. boiling water; after cooling and with rapid stirring, the crude product crystallized out. After standing overnight in the refrigerator, the precipitated material was filtered off and dried with suction; recrystallization from boiling water with the addition of 5 g. of Norite gave 41.5 g. (60 %) of colorless needles, decomposing at 173°.

Table V. Summary on Aryl Halogenomethylketones.

$AR.CO.CH_2X$[a]	Distilling Range	Melting Point	Yield %
$C_6H_5.CO.CH_2Cl$	120-35° (4 mm.)	56-7°	88.2
$C_6H_5.CO.CH_2Br$	--	49-50°	58
para-$CH_3.C_6H_4.CO.CH_2Cl$	130-5° (13 mm.)	55-6°	82
para-$C_6H_5.C_6H_4.CO.CH_2Cl$	--	124-6°	84
para-$Cl.C_6H_4.CO.CH_2Cl$	--	100-1°	88.5
para-$CH_3O.C_6H_4.CO.CH_2Cl$	--	97-8°	--
para-$HO.C_6H_4.CO.CH_2Cl$	--	147-8°[b]	28.2
ortho-$HO.C_6H_4.CO.CH_2Cl$	--	73-4°	30
3,4-$(HO)_2C_6H_3.CO.CH_2Cl$	--	173°[b]	60

[a] All of the ketones listed are described in Beilstein.

[b] Decomposes.

B. Preparation of Arylglyoxylohydroxamyl Halides.

Introduction. The general nitrosation reaction as applied to ketones of the type, $AR.CO.CH_2R$, where R is methyl or any alkyl group, resulting in the formation of oximinoketones according to the equation

$$AR.CO.CH_2R \xrightarrow[HCl]{RONO} AR.CO.CH(:NOH)R$$

was first described by Claisen and Manasse (21). Subsequent studies by Slater (108) and Hartung and his associated (3,4,-5,6), indicate that the products, AR.CO.CH(:NOH)R, could be prepared pure and in good yields.

Initial studies on the application of this general nitrosation reaction to ketones of the type, $AR.CO.CH_2Cl$, resulting in the formation of arylglyoxylohydroxamyl chlorides have been previously described (88). The results obtained in that investigation may be summarized:

(1) The nitrosation of phenacyl chloride and its nuclear-substituted derivatives may be carried out in a manner analogous to that employed for ketones of the type, $AR.CO.CH_2R$.

(2) The arylglyoxylohydroxamyl chlorides thus obtained could be isolated by a simple procedure; application of the alkaline extraction method, results in decomposition of the products with the subsequent formation of the

corresponding carboxylic acids.

(3) The use of anhydrous ether as a solvent appeared to prevent nitrosation.

The general procedure finally adopted for the preparation of arylglyoxylohydroxamyl halides and employed in the present investigation is as follows:

In a half-liter, three-neck, round bottom flask provided with a sealed mechanical stirrer, a reflux condenser, connected to a gas-absorption trap, a delivery tube for hydrogen chloride and a small dropping funnel, was placed the halogenomethyl ketone (0.1 mole) in 100 cc. ether (U.S.P). The stirrer was set in motion, and after complete (or partial) solution of the ketone, hydrogen chloride (generated by allowing concentrated sulfuric acid to drop on concentrated hydrochloric acid) was introduced directly into the mixture at the rate of 2-3 bubbles per second, stirring and addition of acid being continued throughout the reaction. Then freshly distilled isopropyl nitrite (0.11 mole) was added by means of the dropping funnel, in 0.5-1.0 cc. portions. After addition of the first portion, the reaction mixture became an orange-brown and after several minutes, light-yellow in color; after this second portion of nitrite was added and the similar color change took place, whereupon a third portion was added, etc. The mixture gradually warmed up and the ether began to reflux gently. After all of the nitrite had been added (about thirty to forty minutes were required), stirring and addition of hydrogen chloride were continued for another fifteen minutes, after which the reaction mixture was allowed to stand for one to two hours, or if moreso convenient overnight. The reflux condenser was then inverted, stirring was resumed, and the solvent recovered by distillation from a bath of water maintained at 60-80°. When practically all of the solvent was removed, distillation was continued using reduced pressure (water-pump), until no further appearance of crystals was noted. The residue was then allowed to stand overnight in a vacuum desiccator over concentrated sulfuric acid, soda lime and anhydrous calcium chloride until dry. The crude product thus obtained was then recrystallized from a suitable solvent.

It was found that the above procedure could be adapted to the nitrosation of the various ketones. In some cases, where the halogenoketone is not readily soluble in ether, nitrosation of the suspended material was carried out as above, with or without increasing the quantity of solvent; in either case, solution gradually proceeded during the course of nitrosation since the chloronitrosoketones are, in general, moreso soluble in this solvent than the ketones from which they are prepared.

As to the selection of the alkyl nitrite, this investigation has shown isopropyl nitrite to be the most satisfactory, although any alkyl nitrite may be employed. Methyl nitrite was successfully tried; but when only small quantities of ketones (0.05-0.20 mole) are to be nitrosated, it was found that the higher, boiling liquid nitrites are more convenient to work with. Ethyl nitrite was not investigated- also on account of its extreme volatility. Propyl and buytl nitrites can be used. However, on account of the fact their corresponding alcohols formed during nitrosation are high boiling, difficulty is encountered in the removal of these from the reaction product. It might be indicated here, that the glyoxylohydroxamyl halides are very soluble in these alcohols, and unless these by-products are completely removed, the yields of isolated products will be lowered. Therefore, isopropyl nitrite is the most desirable reagent; the isopropyl alcohol (b. 82-3°) can be removed with least difficulty. Isopropyl nitrite, boiling 40-45° and butyl boiling 75-81° were employed in these studies.

The characteristic color changes which occurred on the addition of nitrite, are most readily observed with phenacyl chloride and its para-methyl-, para-chloro- and para-methoxy-derivatives. In the case of para-phenylphenacyl chloride, which was nitrosated in suspension, these color changes were not marked to any degree; with the phenolic-ketones, the reaction mixture gradually darkened during nitrosation.

Ether, by virtue of its ready availability, low boiling point and desirable solvent properties, was found to be an excellent nitrosating medium. Accordingly, it did not appear worthwhile studying the use of substitutes. It was found that the ether recovered by distillation, could be successfully employed, without purification as the solvent in the subsequent nitrosation of another batch of the same ketone. This factor may be of considerable importance on larger scale operations.

Phenylglyoxylohydroxamyl Chloride. Nitrosation of phenacyl chloride by the above general method gave, from 15.5 g. (0.1 mole) of ketone, 12.6 cc. (0.11 mole) butyl nitrite and 100 cc. ether, 15.7 g. (85.6 %) of phenylglyoxylohydroxamyl chloride, m.p. 130-3° after recrystallization from hot carbon tetrachloride. A second recrystallization gave long, needle-like glistening crystals, m.p. 132-3°.

Phenylglyoxylohydroxamyl Bromide. From 19.9 g. (0.1 mole) phenacyl bromide, 11.6 cc. (0.11 mole) isopropyl nitrite and 100 cc. ether, there was obtained a product, which after recrystallization from carbon tetrachloride gave long needles, melting 131-4°; further recrystallizations produced no significance change. A nitrogen determination (Kjeldahl) showed the presence of 6.88 % nitrogen (calculated for C_8H_6BrNO, 6.14 %). A mixed melting point of phenylglyoxylohydroxamyl chloride and the above product melted 130-4° . It is interesting to note that a mixture of equal parts of phenylglyoxylohydroxamyl chloride and phenylglyoxylohydroxamyl bromide contains 6.88 % nitrogen. From this, it may be possible that both phenylglyoxylohydroxamyl chloride and the bromide are obtained by nitrosating phenacyl bromide. Investigation of the nitrosation of phenacyl bromide merits further study.

Para-Methylphenylglyoxylohydroxamyl Chloride. From 50.6 g. (0.3 mole) para-methylphenacyl chloride, 36.7 cc. (0.32 mole) butyl nitrite and 200 cc. ether, there was obtained, after recrystallization from hot carbon tetrachloride, 44.0 g. (74.2 %) of para-methylphenylglyoxylohydroxamyl chloride, m.p. 119-26°. A second recrystallization gave long, colorless needles, m.p. 126-8°.

Para-Phenylglyoxylohydroxamyl Chloride. Para-phenylglyoxylohydroxamyl chloride is only slightly soluble in ether; accordingly it was found necessary to nitrosate this ketone in suspension. The chloroisontrosoketone obtained is readily soluble in ether; as nitrosation proceeds, solution gradually occurs until about three-fourths of the nitrite has been added, at which time, a homogeneous solution results. From 23.1 g. (0.1 mole) para-phenylphenacyl chloride, 11.6 cc. (0.11 mole) isopropyl nitrite and 300 cc. ether, there was obtained brownish crystals of the crude glyoxylohydroxamyl chloride. Recrystallization from hot benzene gave 21.2 g. (81.6 %) of a yellow crystals of para-phenylphenylglyoxylohydroxamyl chloride, which formed a red melt at 157-8°.

Para-Chlorophenylglyoxylohydroxamyl Chloride. Para-chlorophenacyl chloride was nitrosated in the usual manner. From 19.0 g. (0.1 mole) of ketone, 11.6 cc. (0.11 mole) isopropyl nitrite and 200 cc. ether, there was obtained yellowish crystals of crude product, which after recrystallization from hot carbon tetrachloride gave 16.7 g. (76.6 %) of glistening, colorless needles, m.p. 120-1°. Para-chlorophenylglyoxylohydroxamyl chloride is soluble in alcohol and ether in cold; in benzene and toluene, on heating, but insoluble in petroleum benzine and ligroin.

Para-Methoxyphenylglyoxylohydroxamyl Chloride. When nitrite was added to a suspension of para-methoxyphenacyl chloride, the colorless solution became yellow and remained as such on subsequent additions of nitrite; also, the reaction mixture did not warm up sufficiently to cause the ether to reflux. From this, it was evident that nitrosation was no proceeding. The addition of a few drops of water appeared to catalyze the reaction; the mixture warmed up and began to reflux and the color disappeared. When a further addition of nitrite was made, the mixture became orange and after about ten to fifteen seconds, it became colorless again; whereupon one-half of the required nitrite was in, complete solution occurred; and thereafter nitrosation proceeded in the usual manner.

The yield of para-methoxyphenylglyoxylohydroxamyl chloride obtained from 9.2 g. (0.05 mole) ketone, 5.8 cc. (0.055 mole) isopropyl nitrite and 100 cc. ether, to which was added 0.2 cc. water, was 8.8 g. (82 %) after recrystallization from carbon tetrachloride. The product thus obtained consisted of colorless, needles, m.p. 137-9°; soluble in ether, alcohol and ethyl acetate in the cold and in ligroin, carbon tetrachloride and benzene on heating. In view of the fact that the para-methoxyphenacyl chloride probably contained some of its ortho- isomer, the above nitrosated product may contain some ortho-methoxyphenylglyoxylohydroxamyl chloride.

Para-Hydroxyphenylglyoxylohydroxamyl Chloride. To a suspension of 17.1 g. (0.1 mole) para-hydroxyphenacyl chloride in 250 cc. ether was added 12.6 cc. (0.11 mole) butyl nitrite. Nitrosation proceeded as usual. Recrystallization of the crude product from boiling n-amylacetate-toluene (1:6) gave 14.5 g. of fine, colorless crystals, dec. 158-9°; further addition of toluene to the mother liquor gave 3.0 g. of crystals, dec., 158-9°; total yield, 17.5 g. (87.5 %). In another run, the crude product was recrystallized in the cold from ether-benzin (1:3), the yield of product was 15.0 g.; concentration of the mother liquor gave an additional 3.5 g. of crystals; total yield 18.5 g. (95.5 %). Para-hydroxyphenylglyoxylohydroxamyl chloride had a sternutatory action; it dissolved in alcohol, ether, acetone and ethyl acetate in the cold; in amyl acetate on heating, but was insoluble in benzene, toluene and carbon tetrachloride.

Ortho-Hydroxyphenylglyoxylohydroxamyl Chloride. Attempts to nitrosate ortho-hydroxyphenacyl chloride by the general method described, gave a high melting product which possessed a violent lachrymatory action. This product did not give the color reaction with pyridine. Moreover, the color changes which occur during nitrosation of other phenacyl halides was not observed here, and it was doubted whether nitrosation took place. Hartung (5) has previously reported that he was unable to nitrosate ortho-hydroxy- substituted propiophenones.

3,4-Dihydroxyphenyglyoxylohydroxamyl Chloride. 3,4-Dihydroxyphenacyl chloride was nitrosated as a suspension in ether; after approximately one-half of the necessary nitrite had been added, complete solution occurred, and the reaction mixture gradually darkened as nitrosation proceeded. The solution obtained from the reaction of 18.7 g. (0.1 mole) 3,4-dihydroxyphenacyl chloride with 12.6 cc. (0.11 mole) butyl nitrite in 400 cc. ether (to which was added 3 cc. HOHC)was concentrated by distilling off the one-half the volume of solvent added from a water-bath. The addition of 200cc. benzene precipitated 17.8 g. (82.4 %) of 3,4-dihydroxyphenylglyoxylohydroxamyl chloride, d. 184-5°.

Table VI. Arylglyoxylohydroxamyl Halides.

AR.CO.C(:NOH)X	Yield	M.P. (°C.)	Kjeldahl Calc.	Nitrogen % Found
C_6H_5.CO.C(:NOH)Cl[a]	85.6	132-3	--	--
C_6H_5.CO.C(:NOH)Br[b]		131-4	6.14	6.88
para-CH_3.C_6H_4.CO.C(:NOH)Cl	74.2	126-8	7.10	6.88
para-C_6H_5.C_6H_4.CO.C(:NOH)Cl	81.6	157-8 (dec.)	5.4	5.32
para-Cl.C_6H_4.CO.C(:NOH)Cl	76.6	120-1	6.42	6.3
para-CH_3O.C_6H_4.CO.C(:NOH)Cl	82.0	137-9	6.56	6.65
para-HO.C_6H_4.CO.C(:NOH)Cl	87.5-92.5	158-9 (dec.)	7.02	7.01
ortho-HO.C_6H_4.CO.C(:NOH)Cl				
3,4-$(HO)_2C_6H_3$.CO.C(:NOH)Cl	82.4	184-5 (dec.)	6.47	6.38

[a] Described in Beilstein.

[b] Not pure.

C. Properties of Arylglyoxylohydroxamyl Halides.

Studies on the properties of arylglyoxylohydroxamyl halides reported by other workers, has been discussed in the literature survey. In this section, only the observations made in this investigation will be considered.

Decomposition of Carboxylic Acids. Decomposition of the arylglyoxylohydroxamyl halides in alkaline solution was carried out according to the following general procedure:

In a 250 cc. short-neck, round-bottom flask, fitted with a reflux condenser, were placed 0.03 mole of the arylglyoxylohydroxamyl halide and 100 cc. water in which was dissolved 4.0 g. (0.1 mole) sodium hydroxide. The reaction mixture was refluxed for about one to one and half hours, after which all of the glyoxylohydroxamyl halide dissolved with the formation of an orange-colored solution. After refluxing an additional hour, the reaction mixture was cooled and concentrated hydrochloric acid was added with stirring until no further precipate was produced. The mixture was cooled and the crude product filtered off with suction and recrystallized from a mixture of alcohol and water in the appropiate proportions. In some cases, decolorization was accomplished by the addition of 1.0 g. of Norite.

The acids obtained using the above procedure have been previously described. Proof of their identity is given by their melting points; where the corresponding acids were available in

Table VII. Arylcarboxylic Acids Obtained From Arylglyoxylohydroxamyl Halides

AR.CO.C(:NOH)Cl	AR.COOH	M.P.	Yield %
C_6H_5.CO.C(:NOH)Cl	C_6H_5.COOH	122	90
C_6H_5.CO.C(:NOH)Br			
para-CH_3.C_6H_4.CO.C(:NOH)Cl	para-CH_3.C_6H_4.COOH	178-80	93
para-C_6H_5.C_6H_4.CO.C(:NOH)Cl	para-C_6H_5.C_6H_4.COOH	224	99
para-ClC_6H_4.CO.C(:NOH)Cl	para-Cl.C_6H_4.COOH	239	98
para-CH_3O.C_6H_4.CO.C(:NOH)Cl	para-CH_3O.C_6H_4.COOH	181-3	80
para-HO.C_6H_4.CO.C(:NOH)Cl[a]	para-HO.C_6H_4.COOH	211	80
ortho-HO.C_6H_4.CO.C(:NOH)Cl	--	--	--
3,4-$(HO)_2$.C_6H_3.CO.C(:NOH)Cl[b]	--	--	--

[a] Loss of product occurred by recrystallization; only about 50 percent of acid was recovered; the experiment was not repeated.

[b] Corresponding acid could not be obtained using the general procedure.

in stock, mixed melting point determinations were run.

Attempts to prepare protocatechuic acid by the decomposition of 3,4-dihydroxyphenylglyoxylohydroxamyl chloride according to the general procedure described, failed. In view of the excellent yields of acids obtained from other glyoxylohydroxamyl halides, this possible application merits further study.

Reactions with Amines. The reaction of arylglyoxylohydroxamyl halides with aniline to form crystalline anilides was utilized as a method of obtaining characteristic derivatives:

$$\mathrm{AR.CO.C(:NOH)X} + 2\mathrm{C_6H_5NH_2} \longrightarrow$$
$$\mathrm{AR.CO.C(:NOH)NHC_6H_5} + \mathrm{C_6H_5NH_2.HCl}$$

The general procedure employed for the preparation of these derivatives is based on that of Rheinboldt and Schmizt-Dumont (76):

To 0.03 mole of the arylglyoxylohydroxamyl halide dissolved in 100 cc. anhydrous ether was added 0.06 mole of aniline (freshly-distilled). The flask was stoppered and allowed to stand at room temperature, with occasional shaking, for four days. The aniline hydrochloride which precipitated out, was filtered off with suction and solvent removed from the filtrate by concentration in a vacuum desiccator. The crude anilide thus obtained was purified by recrystallization.

The anilides of para-hydroxy- and 3,4-dihydroxyphenylglyoxylohydroximic acids are insoluble in ether; hence these are precipitated from the etheral solution together with the aniline hydrochloride. This precipitate of mixed crystals was then washed with cold water containing a little hydrochloric acid; in this manner, the aniline hydrochloride was washed out and the anilide remaining was dried with suction and purified by recrystallization.

The various anilides prepared and their characteristics are summarized in Table VIII.

The anilides of arylglyoxylohydroximic acids were found to have interesting properties. On heating, they melt with decomposition; with concentrated sulfuric acid in the cold, they decompose with the formation of a dark purple color. On heating with dilute sodium hydroxide solution they decompose with the formation of an isocyanide- identified by the characteristic odor. A similar observation was made in attempts to recrystallize these derivatives from the higher boiling solvents, such as xylene, amyl acetate, etc.

Several attempts were made to determine whether characteristics crystalline amides could be obtained by reacting arylglyoxylohydroxamyl halides with aliphatic amines, as

$$C_6H_5.CO.C(:NOH)Cl \ + \ 2C_3H_7NH_2 \ \longrightarrow$$

$$C_6H_5.CO.(:NOH)NHC_3H_7 \ + \ C_3H_7NH_2.HCl$$

The above reaction was tried; a violent reaction took place

Table VIII. Anilides of Arylglyoxylohydroximic Acids.

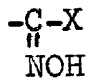
$AR.CO.C(:NOH)NHC_6H_5$ AR=	Recrystallizing Solvent	Characteristics	Dec.P. (°C.)	Kjeldahl Nitrogen % Calc.	Kjeldahl Nitrogen % Found
$C_6H_5.CO.C(:NOH)-$[a]	Toluene	Yellow flakes	145-6	--	--
para-$CH_3.C_6H_4.C(:NOH)-$[b]	Isopropyl alcohol	Fine, colorless needles	163-4	11.02	11.00
para-$C_6H_5.C_6H_4.CO.C(:NOH)-$[c]	Isopropyl alcohol	Yellow, brown flakes	135-6	--	--
para-$Cl.C_6H_4.CO.C(:NOH)-$	Isopropyl alcohol	Large, yellow flakes	145-6	10.2	10.01
para-$CH_3O.C_6H_4.CO.C(:NOH)-$	Dilute Alcohol (50%)	Pale-yellow, fine needles	148-50	10.4	10.22
para-$HO.C_6H_4.CO.C(:NOH)-$	Dilute alcohol (50%)	Pale-yellow, fine needles	164-5	10.90	11.1
ortho-$HO.C_6H_4.CO.C(:NOH)-$					
3,4-$(HO)_2.C_6H_4.CO.C(:NOH)-$	Acetone-Toluene (1:3)	Small, yellow needles	155[d]	10.26	10.0

[a] Described by Rheinboldt and Schmitz-Dumont (76). [b] Previously described by author (88).

[c] Not pure for analysis. [d] Began to darken.

on mixing the amine with the glyoxylohydroxamyl chloride in ether- analogous to that which occurs when a carboxylic acid chloride is treated with a primary amine. It was not possible, however, to isolate a crystalline product from the reaction mixture. Further investigation in this line was temporarily discontinued.

Another interesting property of arylglyoxylohydroxamyl halides was their behaviour with pyridine. All of the arylglyoxylohydroxamyl halides prepared in this investigation on treating with pyridine immediately reacted with the evolution of heat and the formation of a red-wine color which gradually darkened after standing for several minutes. Identification of the product or products obtained was not considered; however, it was found that oximino- compounds of the types, $AR.CO.C(:NOH)H$, $AR.CO.C(:NOH)CH_3$, $R.CH_2.C(:NOH)COOH$, $CH_3.C(:NOH)COOR$ and the chloromethylketones, $AR.CO.CH_2Cl$, gave such color reaction with pyridine. It is probable that this test may prove characteristic for the hydroxamyl halide group:



$$-\underset{\overset{\|}{NOH}}{C}-X$$

Oximation of Arylglyoxylohydroxamyl Halides. Oximes of some of the arylglyoxylohydroxamyl halides were prepared according to the reaction:

$$AR.CO.C(:NOH)X + H_2NOH \longrightarrow AR.C(:NOH.C(:NOH)X + HOH$$

The general procedure employed is based on that described by Rheinboldt and Schmitz-Dumont (76):

A solution of 0.04 mole of hydroxylamine hydrochloride in 25 cc. water was added to a solution of 0.02 mole of the arylglyoxylohydroxamyl halide in 25 cc. alcohol. Sufficient alcohol was then added, drop by drop, until a clear solution resulted. After allowing the reaction mixture to stand for three to five days, crystals began to precipitate out; after two weeks, the crystals obtained were filtered off with suction, dried and recrystallized from a suitable solvent. The mother liquor gave a positive hydroxamic acid test with ferric chloride solution. The oxime of 3,4-dihydroxyphenylglyoxylohydroxamyl chloride could not be isolated by the above procedure- probably on account of the increased degree of solubility of this ketone in alcohol and water.

The glyoximes obtained in this investigation are colorless, crystalline compounds which melt with decomposition. The summary on glyoximes is presented in Table IX.

Table IX. Aryl Halogenoglyoximes.

AR.C(:NOH).C(:NOH)Cl AR	Recrystallizing Solvent	Dec.P. (^{o}C.)	Kjeldahl Nitrogen Calc. %	 Found
C_6H_5-[a]	Isoamyl alcohol	186-7	--	--
para-$CH_3.C_6H_4$-[b]	Isoamyl alcohol	185-6	13.17	12.7
para-$C_6H_5.C_6H_4$-	Butyl alcohol	177	10.2	10.08
para-Cl-C_6H_4-		178-9		
para-HO.C_6H_4-	Dioxane-Heptane	183-4	13.52	13.33
ortho-HO.C_6H_4-				
3,4-$(HO)_2C6H_3$-[c]				

[a] Described by Rheinboldt and Schmitz-Dumont (76).

[b] Previously described by author (88).

[c] Could not obtained by general procedure.

D. Reduction Studies on Arylglyoxylohydroxamyl Chlorides.

Studies by Hartung and his associates (3,4,5,6) show that isonitrosoketones of the type, AR.CO.C(:NOH)R, where R is any alkyl group, may be reduced using palladium-charcoal catalyst to the corresponding aminoalcohols, $AR.CHOH.CHRNH_2$, in good yields:

$$AR.CO.CHR(:NOH) + 3H_2 \xrightarrow[(HCl)]{Pd} AR.CHOH.CHRNH_2 + HOH$$

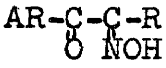
A summary of these studies indicate that:

(1) Reduction of oximinoketones in absolute alcohol, using palladium catalyst, to aminoalcohols proceeds readily; the products may be obtained pure and in excellent yields (3,4,5,6).

(2) The use of three equivalents of hydrogen chloride prevents the formation of contaminating secondary and tertiary amines and increases the rate of hydrogen absorption (4); the optimum concentration being in absolute alcohol 2 normal in hydrogen chloride (112).

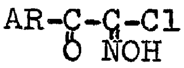
(3) Preparation of the palladinized-charcoal in a 0.2 normal aqueous solution of sodium acetate produces a catalyst of "high activity" (112).

The structural similarity between oximinoketones of type (I) and the arylglyoxylohydroxamyl chlorides (II), is obvious:



$\mathrm{AR-\underset{\underset{O}{\|}}{C}-\underset{\underset{NOH}{\|}}{C}-R}$

(I)



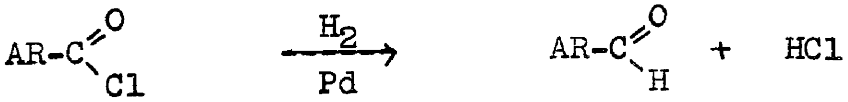
$\mathrm{AR-\underset{\underset{O}{\|}}{C}-\underset{\underset{NOH}{\|}}{C}-Cl}$

(II)

In order to convert compounds of type (II) into arylethanolamines, it should be possible to employ a similar type of hydrogenation, which would simultaneously replace the chlorine with a hydrogen atom:

$$\mathrm{AR.CO.C(:NOH)Cl} + 4\,\mathrm{H_2} \xrightarrow[\mathrm{HCl}]{\mathrm{Pd}} \mathrm{AR.CHOH.CH_2NH_2.HCl} + \mathrm{HOH}$$

A priori it was expected that the chlorine atom ought to be easily replaced. The lability of the chlorine has already been described,- it shows properties characteristic of the chlorine in a carboxylic acid chloride. Furthermore, Rosenmund (113) has reduced aromatic acid chlorides to aldehydes, replacing the chloring by hydrogen with the aid of palladium catalyst:



In these reduction studies the optimum conditions found for the oximinoketones, AR.CO.C(:NOH)R, were also employed.

Catalysts. The palladium-charcoal catalysts were prepared by essentially the same method as described by Hartung (3,40). The general procedure follows:

A suspension of palladium chloride[a], or a solution of pal-

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[a] Courtesy of J. Bishop & Co. Platinum Works; Malvern, Pa.

ladium chloride[a] (each cc. representing the equivalent of 0.1 g. palladium), and Norite (E.K. & Co.) in distilled water or an aqueous solution of sodium acetate was shaden in an atmosphere of hydrogen until saturated. The palladinized-charcoal thus obtained was filtered off, washed with several portions of distilled water, followed by alcohol, and dried with suction. Drying required only about ten minutes. In some instances, highly active catalysts began to glow on drying and even ignited; the glow was immediately quenched with water and the catalyst again washed with alcohol and finally used before all the alcohol had evaporated.

The following are the various types of catalysts employed:

Catalyst No. I:

3.0 g. Norite
0.6 g. palladium chloride
100 cc. distilled water

Catalyst No. II:

3.0 g. Norite
0.6 g palladium chloride
100 cc. 0.2 N sodium acetate solution

Catalyst No. III:

A 10 percent palladinized-Norite catalyst by courtesy of Sharp & Dohme, Inc.

Catalyst No. IV:

3.0 g. Norite

---

[a] Courtesy of Sharp & Dohme, Inc., Philadelphia, Pa.

6.0 cc. palladium chloride solution
100 cc. 0.5 N sodium acetate solution

Catalyst No. V:

3.0 g. Norite
6.0 cc. palladium chloride solution
100 cc. 1 N sodium acetate solution

Reduction Mixture. This mixture was prepared by dissolving the arylglyoxylohydroxamyl chloride in absolute alcoholic-hydrogen chloride. The palladinized-charcoal catalyst was then added and the suspension shaken in an atmosphere of hydrogen. The apparatus used, except in one experiment, was essentially that described by Hartung (40).

The alcoholic-hydrogen chloride was prepared by passing dry hydrogen chloride into absolute ethanol. The solution thus prepared (of known concentration) was kept in a well-stoppered bottle in the refrigerator and diluted as needed.

Reduction of Phenylglyoxylohydroxamyl Chloride. Reductions on this chloroisonitrosoketone were carried. The conditions and results are summarized in Table X.

Reference to this table shows that if absolute alcohol is not used in the reduction mixture, the rate and extent of hydrogen up-take are unfavorable- less than one equivalent was taken up (Exp. 1). In all remaining experiments, alsolute alcohol was used. In each instance the first of the calculated four moles of hydrogen was taken up very rapidly; for the sec-

Table X. Reduction of Phenylglyoxylohydroxamyl Chloride

Exp. No.	Mole of Ketone	Catalyst	Reaction Solvent	Moles Hydrogen Consumed (Time in Hours)			
				1	2	3	4
1	0.04	I	A	[a]			
2	0.04	I	B	1.3	2.5[a]	[a]	
3	0.04	II	B	2.5[d]	4.0[cd]		
4	0.02	Exp. 3	B	0.8	3.0[cd]		
5	0.04	I	B		0.4	[bc]	
6	0.04	II	B	0.5	2.5[c]	7.0[d]	
7	0.04	Exp. 6	B	0.7	4.0		
8	0.04	Exp. 6,7	B	3.0	10.0[d]		
9	0.02	III	B	0.7	1.7[cd]	3.0	
10	0.02	I	C	0.5	1.2[cd]	5.0	
11	0.02	Exp. 9	C	0.5	1.0[d]		
12	0.02	Exp. 9, 11	C	0.7	1.5		
13	0.02	IV	C	0.3	0.3	0.4[c]	[b]
14	0.02	Exp. 13	C	0.3	0.3	[d]	
15	0.02	V	C	0.3	0.3	2.0	

A - 100 cc. alcohol (95 %); 20 conc. HCl.

B - 100 cc. absolute alcohol (2N in HCl).

C - 50 cc. absolute alcohol (Containing 4 equivalents of hydrogen chloride.

[a] Theoretical not quite reached.

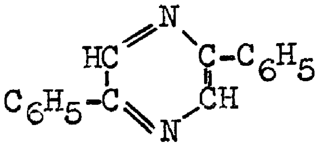
[b] Reduction was allowed to proceed overnight.

[c] Added water.

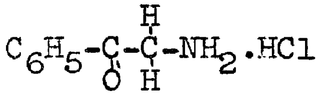
[d] Fortified with fresh catalyst.

ond mole the rate slowed up (Exp. 2,3,6,7,8,9,10 and 11).

In experiments 3,4,7,8,11 and 12, reduction ceased after two moles were taken up. The product from these was isolated by filtering off the catalyst and evaporating the filtrate to dryness over concentrated sulfuric acid, soda lime and anhydrous calcium chloride in an evacuated desiccator. The pale-yellow crystals thus obtained were then dissolved in boiling absolute alcohol, the solution cooled and anhydrous ether added, whereupon colorless crystals precipitated out. These decompose into a red effervescent melt at about 190-200°-characteristic of aminoketone hydrochlorides of the type, $AR.CO.CHRNH_2.HCl$. Analysis (Kjeldahl) of the recrystallized compound showed 14.8 percent nitrogen. The products on treatment with ammonia gave yellow crystals, which after recrystallization from alcohol, melted at 194-6°; analysis (Kjeldahl) showed 12.3 percent nitrogen; qualitative tests for chlorine were negative. This led to the consideration of the possible formation of diphenylprayzine (I),



(I)



$C_6H_5-\underset{\overset{\|}{O}}{C}-\underset{H}{\overset{H}{C}}-NH_2.HCl$

(II)

which is obtained by treating ω-aminoacetophenone hydrochloride (II) with ammonia. Diphenylpyrazine melts at 195-6°; calculation for nitrogen, is 12.03 percent. A mixed melting point determination of the above product with known diphenylpyrazine showed no lowering. Thus, the identity of the compound obtained from the product isolated after two moles of hydrogen has been absorbed is proven.

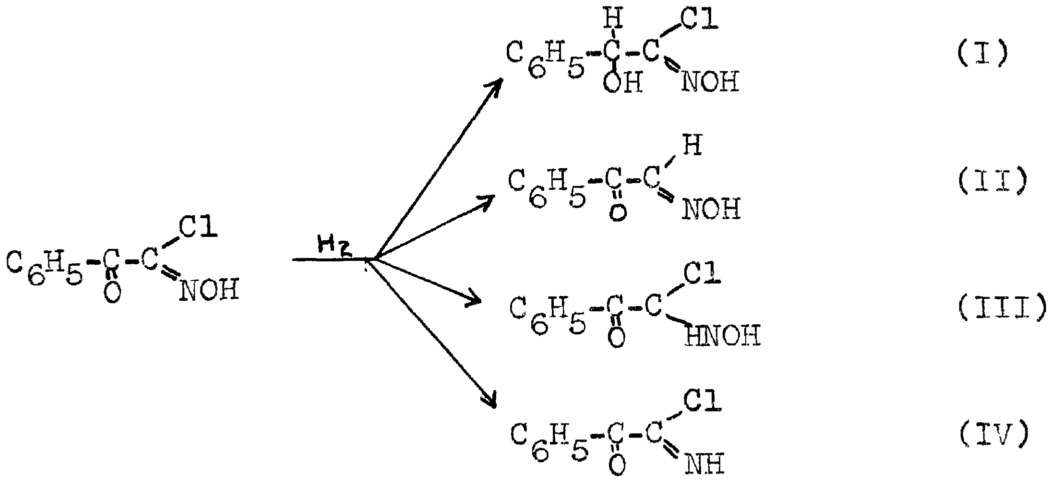
In experiments 2,5,6,9,10 and 15, the third mole of hydrogen was taken up with considerable difficulty. Even in experiment 5, which was carried out under pressure (150 lbs), the take-up of the first two moles was exceedlingly rapid; the third equivalent was consumed with difficulty. The addition of water or fresh catalyst (except Exp. 15) to the reaction mixture was necessary to cause the reduction to proceed to this point; after this, however, the absorption of hydrogen ceased. The product thus obtained, from each reduction, was isolated and recrystallized as before. The melting point was indefinite, 195-205°; no pyrazine was obtained however. Analysis (Kjeldahl) showed 10.42 percent nitrogen.

In experiment 15, hydrogenation proceeded with ease, after the calculated three equivalents of hydrogen had been taken up, reaction was stopped. The crude product isolated, after removal of the catalyst and evaporation of the filtrate, was dissolved in water containing four equivalents of hydrogen chloride and fresh catalyst (V) added. Even after six hours the absorption of hydrogen was negligible.

In one reduction (Exp. 13), in which a "a very active" catalyst was used, the first three moles of hydrogen were taken up with ease; water was added and after allowing the reduction to proceed overnight, the calculated fourth equivalent of hydrogen was consumed. The crude product, obtained after removal of the catalyst and evaporation of the filtrate and recrystallization from absolute alcohol-ether, melted with decomposition at 211-2°; yield 3.0 g. A mixed melting point with pure phenylethanolamine showed no lowering. Thus, from 3.7 g. (0.02 mole) phenylgloxylohydroxamyl chloride, there was obtained 3.0 g. (0.0173 mole) phenylethanolamine, or 86.4 percent of the theoretical. The reduction undoubtedly was quantitative and manipulation accounts for the 0.47 g. (13.7 %) not isolated.

In view of the fact that the first mole is taken up very rapidly, the second, less readily, the third with difficulty and the fourth with extreme difficulty, it is natural therefore to speculate about the successive steps or the course of reduction.

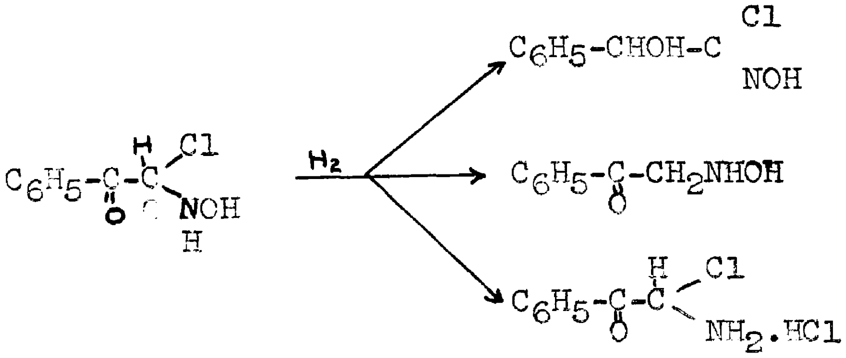
The hypothetical transient intermediates obtainable by the addition of one equivalent of hydrogen are shown below:



(I) is considered unlikely for two reasons: Firstly, there is no known instance of reduction of oximinoketones, in which the :C:O group is reduced before the :NOH; secondly (I) could not, on further reduction give diphenylpyrazine.

(II) is improbable for then the product would be identical with isonitrosoacetophenone, which may be obtained by direct nitrosation of acetophenone, and reduction from this point would be expected to follow the same pattern given by this known intermediate; in other words, it should take up two moles of hydrogen with comparative ease to give the product, $C_6H_5.CO.CH_2NH_2.HCl$. From the experimental evidence, this is not the case.

Compounds (III) or (IV) are likely. (III) on taking up one mole of hydrogen might go,

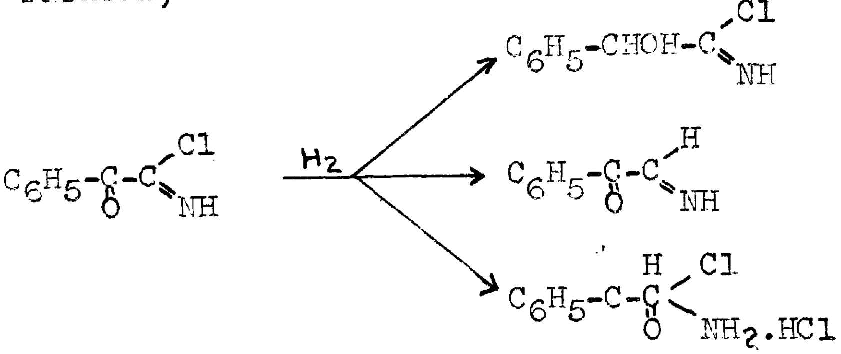


(V)

(VI)

(VII)

(IV) in a similar manner might conceivably continue in this fashion,



(VIII)

(IX)

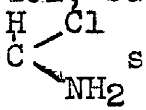
(X)

(V) and (VIII) are ruled out because they could hardly give diphenylpyrazine. For the same reason, (VI) is eliminated. This leaves (VII) which is identical with (X).

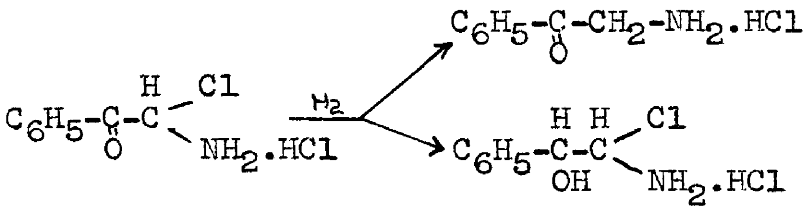
Compound (X) is an unusual structure but is consistent with certain experimentally observed facts:

(1) The melting point behaviour is characteristic for an α-amino-ketone.

(2) It yields diphenylpyrazine; for this, an amino group α to an keto-carbonyl is essential.

Since only two moles of hydrogen were taken up, this is the only way in which formation of an amine can be accounted for. Unfortunately, the analytical data are inadequate. The nitrogen determination was made on recrystallized material, but it is possible that while dissolving with heat, the  $-\overset{H}{C}<^{Cl}_{NH_2}$ structure is unstable and hence may have decomposed under this treatment.

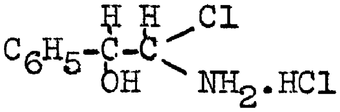
Further reduction to the three-fourths stage beyond which it was difficult to go, may be postulated to proceed in either of two directions:



$C_6H_5-\underset{O}{C}-CH_2-NH_2.HCl$ (XI)

$C_6H_5-\underset{O}{C}-\overset{H}{C}<^{Cl}_{NH_2.HCl} \xrightarrow{H_2} C_6H_5-\underset{OH}{\overset{H}{C}}-\overset{H}{C}<^{Cl}_{NH_2.HCl}$ (XIIO

The product obtained after three moles of hydrogen had been taken up is quite resistant to further reduction (Exp. 2,5,6,-9,10); furthermore, no pyrazine was obtained on the addition of ammonia to the reduction filtrate and the crystalline product does not form a red melt. Now, if ω-aminoacetophenone (XI) were obtained at this point- this is capable of further reduction with comparative ease to phenylethanolamine, diphenylpyrazine should have been formed, and moreover (XI) gives a red melt. These considerations eliminate (XI); hence, the reduction of the :C:O group to -CHOH- is postulated to give



$$C_6H_5-\overset{H}{\underset{OH}{C}}-\overset{H}{C}\begin{matrix}\diagup Cl\\ \diagdown NH_2.HCl\end{matrix}$$

Here again, the attachment of chlorine and an amine group to the same carbon is unusual.

<u>Reduction Studies on Other Arylglyoxylohydroxamyl Chlorides</u>. The results from four experiments show that the reduction of parahydroxyphenylglyoxylohydroxamyl chloride proceeds in a manner analogous to that described under phenylglyoxylohydroxamyl chloride, i.e., the absorption of the first two moles proceeds with comparative ease. After this, absorption of hydrogen ceased completely; but when water or fresh catalyst were added, reduction continued, although very slowly, until the third equivalent had been taken up; further reduction was not possible under the conditions tried. The product isolated at the half-way mark gave a yellow pyrazine which remained unchanged even at 250°; this compound was not characterized however.

One reduction was carried out using 3,4-dihydroxyphenylglyoxylohydroxamyl chloride and another using para-methylphenylglyoxylohydroxamyl chloride. In both instances, the first two moles of hydrogen were absorbed fairly readily; the third, rather slowly, and only then after water and fresh catalyst had been added. Reduction ceased at this point.

The reduction of arylglyoxylohydroxamyl chlorides merits further study. From the results thus far obtained, it is very likely that the use of a "highly active" palladium catalyst may make possible the reduction of all of these intermediates to the desired arylethanolamines.

SUMMARY AND CONCLUSIONS

(1) A critical literature survey of the various methods employed in the synthesis of the phenylethanolamines is presented.

(2) The chemical derivation and nomenclature of arylglyoxylohydroxamyl halides is described, and a literature survey of the synthesis and properties of these compounds is given.

(3) Extension of the general nitrosation reaction to other aryl halogenomethylketones has been studied; the reaction has been applied to seven aryl halogenomethylketones, resulting in good yields of arylglyoxylohydroxamyl chlorides.

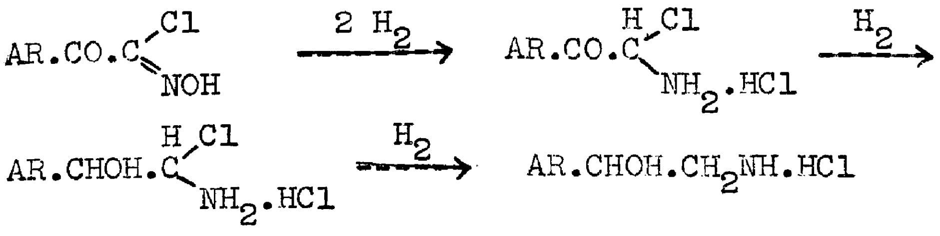
(4) The anilides and glyoxines have been prepared as characteristic derivatives of most of these arylglyoxylohydroxamyl chlorides.

(5) Initial studies on the catalytic reduction of arylglyoxylohydroxamyl chlorides according to the reaction,

$$\mathrm{AR.CO.C(:NOH)Cl} + 4\ \mathrm{H_2} \longrightarrow \mathrm{AR.CHOH.CH_2NH_2.HCl} + \mathrm{HOH} \qquad 1$$

are described.

(6) Limited data now available indicate that the reduction probably proceeds as follows:



$$\mathrm{AR.CO.C}{\overset{\mathrm{Cl}}{\underset{\mathrm{NOH}}{<}}} \xrightarrow{2\ \mathrm{H_2}} \mathrm{AR.CO.C}{\overset{\mathrm{H\ Cl}}{\underset{\mathrm{NH_2.HCl}}{<}}} \xrightarrow{\mathrm{H_2}}$$

$$\mathrm{AR.CHOH.C}{\overset{\mathrm{H\ Cl}}{\underset{\mathrm{NH_2.HCl}}{<}}} \xrightarrow{\mathrm{H_2}} \mathrm{AR.CHOH.CH_2NH.HCl}$$

Evidence in support of this view is discussed.

(7) Initial studies indicate that the use of sodium acetate in preparing the catalyst may make possible the reduction of all of these compounds to arylethanolamines.

(8) Phenylglyoxylohydroxamyl chloride has been successfully reduced to phenylethanolamine in excellent yields.

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