# FURTHER STUDIES ON THE SYNTHESIS

# OF

# ARYLETHANOLAMINES

By

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# INTRODUCTION

Previous investigations on the relationship between physiological activity and chemical structure of compounds possessing pressor activity have shown that:

1. The minimum skeleton necessary for the production of pressor activity is that of phenethylamine, - $C_6H_5$-C-C-N-, and that;
2. Arylethanolamines and arylpropanolamines possess the optimum structures for the production of pressor activity (49,50).

The arylpropanolamines have been readily synthesized in good yields according to the following general reaction (51,52,53,54):

$$AR.CO.CH_2.CH_3 \xrightarrow[HCl]{RONO} AR.CO.C(:NOH)CH_3 \xrightarrow{H_2} AR.CHOH.\underset{NH_2}{CH}.CH_3$$

Important indications have been obtained as to the modification in the pharmacodynamic properties produced by structural changes, i.e., introduction of various substituents into the nucleus of phenylpropanolamine (104); and in order to determine with greater certainty whether these changes in physiological activity may be ascribed solely to the presence of the substituent under investigation, the effect of its presence in the phenylethanolamines should also be determined.

An attempt has been made to use the arylglyoxylohydroxamyl halides as intermediates in the synthesis of the arylethanolamines according to the following reaction (59):

$$AR.CO.CH_2X \xrightarrow[HCl]{RONO} AR.CO.C(:NOH)X \xrightarrow{4\ H_2} AR.CHOH.CH_2NH_2$$

The intermediate arylglyoxylohydroxamyl halides were obtained in excellent yields. When the reduction of $C_6H_5.CO.C(:NOH)Cl$ proceeded to completion in one stage, excellent yields of phenylethanolamine were obtained (59,60). Although excellent yields may be obtained as noted above, the hydrogenation usually does not continue to completion; and to date no evidence has been found to explain the varied results. Studies of the catalytic reduction are reported in the experimental portion of this work.

Since the above synthesis for the arylethanolamines has proved not entirely satisfactory, and since the arylethanolamines have been reported as possessing excellent pressor activity (49,61,62,63,64,65), it was decided to reinvestigate one of the older methods of synthesis of the arylethanolamines, i.e., the condensation of phenacyl halides with amines and the subsequent reduction of the various ω-aminoacetophenone derivatives.

In view of the fact that an elegant catalytic debenzylation procedure has recently come to the fore (23,24), the following syntheses were investigated:

1. $AR.CO.CH_2X + H_2NCH_2C_6H_5 \longrightarrow AR.CO.CH_2-NH-CH_2C_6H_5 \xrightarrow{2\ H_2}$

   $AR.CHOH.CH_2NH_2 + C_6H_5CH_3$

2. $AR.CO.CH_2X + HN(CH_2C_6H_5)_2 \longrightarrow AR.CO.CH_2-N(CH_2C_6H_5)_2 \xrightarrow{3\ H_2}$

   $AR.CHOH.CH_2NH_2 + 2\ C_6H_5CH_3$

It is known from private sources that arterenol has been synthesized in commercial yields, but has never been resolved, although it has been known since 1905. The resolution may possibly be carried out by

resolving the carbinol, $(HO)_2C_6H_3.CHOH.CH_2-N(CH_2C_6H_5)_2$, which could be obtained by reduction of the ketone, $(HO)_2C_6H_3.CO.CH_2-N(CH_2C_6H_5)_2$, with sodium in ethanol or sodium amalgam. The (+) and (-) forms could then be catalytically debenzylated as has been done in the case of phenylpropanolmethylamine (10).

# REVIEW OF THE LITERATURE

## Previous Methods of Synthesis of Arylethanolamines.

Published methods of synthesis, reviewed elsewhere (59,60), may be summarized under the following headings:

### 1. Condensation of Phenacyl Halides with Hexamethylenetetramine.

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

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

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

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

Mannich and his co-workers (66,67) obtained the addition products in good yields as shown in the following:

| Aracyl Halide | Yield of Addition Product |
|---|---|
| Phenacyl chloride | 60 percent |
| Phenacyl bromide | 80 percent |
| p-Methoxyphenacyl chloride | 50 percent |
| 3,4-Diacetoxyphenacyl chloride | 40 percent |
| 3,4-Diacetoxyphenacyl iodide | 100 percent |
| 3,4-Dimethoxyphenacyl bromide | 80 percent |

Reaction failed in the case of 1,2,3-triacetoxyphenacyl chloride; however, the corresponding bromide and iodide reacted as expected.

The aminoketones were obtained in good yields by the hydrolysis of the addition products; e.g., 3,4-dihydroxy-ω-aminoacetophenone was obtained in yields of 60-75 percent.

Slotta and Heller (102) condensed phenacyl bromide with hexamethyl-

enetetramine, then hydrolyzed the intermediate addition product with hydrochloric acid, but on reduction, using palladium on charcoal, obtained only 23.0 g. of crude phenylethanolamine from 80.0 g. of a mixture of ω-aminoacetophenone hydrochloride and ω-aminoacetophenone hydrobromide.

Baltzly and Buck (19) recently reported the preparation of 2,5-dimethoxyphenylethanolamine by the same procedure, but did not indicate yields of either intermediates or final product.

As the starting materials for this synthesis are readily available, the method appears to be one of the best reported; although approximately three days are required for the hydrolysis of the intermediate addition products. In phenolic derivatives the hydroxyl group of the aracyl halide must first be protected to prevent the hexamethylenetetramine from reacting to form salts.

2. Reduction of Arylnitroethanols.

$$AR.CHO \xrightarrow[CH_3NO_2]{C_2H_5ONa} AR.CHOH.CH{:}N\langle \begin{matrix} O \\ ONa \end{matrix} \xrightarrow{CH_3COOH}$$

$$AR.CHOH.CH_2NO_2 \xrightarrow{H_2} AR.CHOH.CH_2NH_2$$

Although nitromethane readily reacts with benzaldehyde to form nitrostyrene (105), Rosenmund (68) reported the condensation of benzaldehyde, p-benzyloxybenzaldehyde, p-carboethoxybenzaldehyde, p-methoxybenzaldehyde, the carboethoxy derivative of vanillin, 3,4-dibenzyloxybenzaldehyde, and the dicarboethoxy derivative of protocatechuic aldehyde with nitromethane to form the intermediate nitroethanols, but did not report the yields. He prepared, by catalytic hydrogenation of the

appropriate intermediates, phenylethanolamine, p-methoxyphenylethanolamine, 3,4-dimethoxyphenylethanolamine, and the dicarboethoxy derivative of 3,4-dihydroxyphenylethanolamine; but he did not indicate the yields obtained from these reductions.

Other investigators (69,70,71), using Rosenmund's method, reported good yields of the intermediate arylnitroethanols but very poor yields of the reduction products.

The objections to this method can be summarized as follows:

1. Lack of, or difficulty in synthesizing, the various nuclear-substituted derivatives of benzaldehyde.
2. The arylnitroethanols decompose readily into ω-nitrostyrenes.
3. It is difficult to obtain pure aminoalcohols as the substituted benzaldehydes undergo undesirable side reactions.
4. Phenolic groups on aromatic aldehydes must first be protected.

3. Reduction of Cyanohydrins.

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

Wolfheim (72) was the first to show that reduction of benzaldehyde cyanohydrin yielded phenylethanolamine. Hartung (32), reducing benzaldehyde cyanohydrin with palladinized charcoal in absolute ethanolic hydrogen chloride, obtained phenethylamine in a 52 percent yield, but no phenylethanolamine. Buck (38), using Adams catalyst, and Kindler, Peschke and Brandt (73), using palladium black catalyst, obtained either arylethanolamines or arylethylamines, depending on the substituents in the phenyl nucleus.

The above method of synthesis is not satisfactory because:

1. The reaction is difficult to control to prevent the formation of arylethylamines.
2. Only fair yields of certain arylaminoalcohols are obtained.
3. Many of the desired benzaldehyde derivatives are difficult or impossible to obtain; and many of these give poor yields of the corresponding cyanohydrins.

4. Reduction of Aroyl Cyanides.

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

$$AR.CO.CN + 3\ H_2 \longrightarrow AR.CHOH.CH_2NH_2$$

Kindler and Peschke (74), reported the formation of the cyanohydrins of benzaldehyde, p-methoxybenzaldehyde, 3,4-dimethoxybenzaldehyde, 3,4-methylenedioxybenzaldehyde, and 3,4,5-trimethoxybenzaldehyde in almost quantitative yields; these were then readily oxidized with chromic anhydride ($CrO_3$) in glacial acetic acid to give yields of 70-90 percent of the corresponding aroyl cyanides. Reduction of the aroyl cyanides, using palladium black catalyst, gave the corresponding arylethanolamines in yields of 70-80 percent.

Again, the main limitations to this method are the difficulty in securing nuclear substituted benzaldehydes, and the fact that the method cannot be applied to phenolic aldehydes unless the phenolic groups are blocked. Other workers have been less successful in duplicating the yields of cyanohydrin intermediates reported by Kindler and Peschke.

5. Condensation of Aminoacetal with Phenols and Phenolic Derivatives, according to the method described by Hinsberg (75):

$$C_6H_4(OH)_2 + H_2NCH_2{\cdot}CH(OC_2H_5)_2 + HCl + HOH \longrightarrow$$

$$(HO)_2C_6H_3{\cdot}CHOH{\cdot}CH_2NH_2{\cdot}HCl + 2\ C_2H_5OH$$

This method merits further study now that aminoacetal has become commercially available; however, it must of necessity be limited to the preparation of phenolic substituted phenylethanolamines. There is also a possibility that isomers may be formed, although Hinsberg did not mention their occurrence.

6. Phthalimide Method. Tutin, Caton and Hann (76) prepared p-hydroxyphenylethanolamine by the following method:

$$CH_3COO{\cdot}C_6H_4{\cdot}CO{\cdot}CH_2Cl \xrightarrow{C_6H_4{\cdot}(CO)_2{\cdot}NK} CH_3COO{\cdot}C_6H_4{\cdot}CO{\cdot}CH_2{\cdot}N(CO)_2{\cdot}C_6H_4$$

$$CH_3COO{\cdot}C_6H_4{\cdot}CO{\cdot}CH_2{\cdot}N(CO)_2{\cdot}C_6H_4 \xrightarrow{HCl} HO{\cdot}C_6H_4{\cdot}CO{\cdot}CH_2NH_2 \xrightarrow[C_2H_5OH]{Na}$$

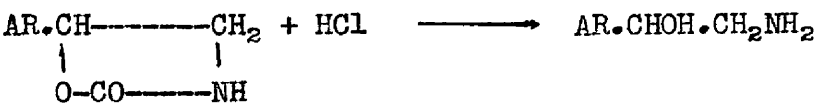
$$HO{\cdot}C_6H_4{\cdot}CHOH{\cdot}CH_2NH_2$$

This synthesis appears unimportant in view of the difficulty encountered in the hydrolysis of the phthalimide intermediate, and the possibility of pyrazine formation if the reduction of the aminoketone is not carried out in an acidic medium.

7. Azide Method. Baltzly and Buck (19) prepared 2,5-dimethoxy-phenylethanolamine according to the following reactions:

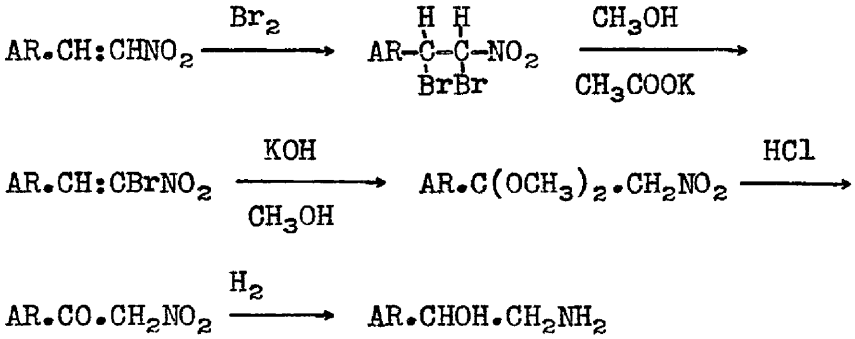
$$AR{\cdot}CHO \xrightarrow{BrCH_2COOC_2H_5} AR{\cdot}CHOH{\cdot}CH_2COOC_2H_5 \xrightarrow{H_2NNH_2}$$

$$AR{\cdot}CHOH{\cdot}CH_2{\cdot}CON_2H_3 \xrightarrow{HNO_2} AR{\cdot}CHOH{\cdot}CH_2{\cdot}CON_3 \longrightarrow$$



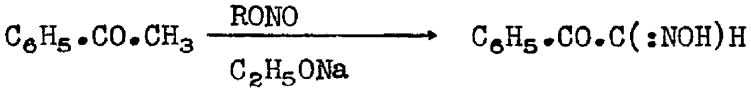
Here, again the yields were poor, and difficulty in obtaining the nuclear substituted benzaldehydes limits the use of this synthesis.

8. Reduction of ω-Nitroacetophenones. Reichert and Koch (77) developed a method for the preparation of arylethanolamines involving the use of ω-nitroacetophenones according to the following scheme:



The reduction of ω-nitroacetophenones to the corresponding aryl-ethanolamines, using platinum oxide catalyst, proceeds well; from 80 percent to almost quantitative yields were obtained; but not only is this reaction involved, but again, the aldehydes are not available and bromination of the ring may take place.

9. Reduction of Isonitrosoketones. Isonitrosoacetophenone was first prepared by Claisen (55) and Claisen and Manasse (56) according to the following reaction:



Yields as high as 51 percent are reported. Unfortunately, even though this is today the preferred procedure for preparing this compound, the yields are about 25 percent (52,59,60,113). The other Claisen method, the reaction of methyl ketones with alkyl nitrites in the presence of dry hydrogen chloride, which works so well with ethyl ketones, gives even poorer yields (52,57). Slater (118), using methyl nitrite in ether, obtained 4.2 g. of isonitrosoacetophenone from 10.0 g. of acetophenone; a yield of 33.75 percent. The attempt to form the isonitroso derivatives of phenolic acetophenones was a complete failure (60).

Claisen (55) did not succeed in reducing isonitrosoacetophenone to phenylethanolamine with sodium amalgam. Using 5 percent sodium amalgam in 50 percent ethanol, Kolshorn (78) reported the formation of phenylethanolamine. However, no yield was reported, and the method has not come into general use.

Catalytic hydrogenation proved successful, forming practically quantitative yields of the desired aminoalcohol (52,59).

The isonitrosoacetophenones would be the ideal intermediates for the synthesis of the arylethanolamines; however, the low yields from the known methods of synthesis and failure to obtain especially the phenolic derivatives make this approach of negligible practical value.

10. Reduction of Arylglyoxylohydroxamyl Halides.

$$AR.CO.CH_2X \xrightarrow[RONO]{HCl} AR.CO.C(:NOH)X \xrightarrow{4\ H_2} AR.CHOH.CH_2NH_2$$

In view of the difficulty of converting $AR.CO.CH_2.R$ into $AR.CO.C(:NOH)R$ where R is H, Levin (59) studied the known nitrosation reaction as applied to such ketones in which R is a halogen atom. He

prepared compounds of type, AR.CO.C(:NOH)Cl, with the yields indicated, where AR varies as follows:

| AR | Yield |
|---|---|
| Phenyl | 85.6 percent |
| p-Methoxyphenyl | 74.2 percent |
| p-Phenylphenyl | 81.6 percent |
| p-Chlorophenyl | 76.6 percent |
| p-Methylphenyl | 82.0 percent |
| p-Hydroxyphenyl | 92.5 percent |
| 3,4-Dihydroxyphenyl | 82.4 percent |

When the reduction of $C_6H_5.CO.C(:NOH)Cl$ proceeded to completion in one stage excellent yields of phenylethanolamine were obtained (59,60). Unfortunately, the hydrogenation results were not consistent and as a rule did not go to completion. To date no evidence has been found to explain these variations. Further studies of the catalytic hydrogenation are reported in the experimental portion of this work.

11. Condensation of Phenacyl Halides with Ammonia or Amines.

Braun and Meyer (79) in 1888 first reported the synthesis of ω-aminoacetophenone through the condensation of phenacyl bromide with ammonia, which could then be reduced to phenylethanolamine.

Gabriel and Eschenbach (89) attempted the reduction of ω-aminoacetophenone, using 2.5 percent sodium amalgam, but isolated acetophenone and ammonia as the chief products. A recent German patent (90) reported the same reduction to be carried through successfully using a nickel catalyst.

The first reports of the synthesis of arterenol are found in old German patents (80), in which the following reactions occur:

$$(HO)_2C_6H_3.CO.CH_2Cl + NH_3 \longrightarrow (HO)_2C_6H_3.CO.CH_2NH_2 \xrightarrow{NaHg_x}$$

$(HO)_2C_6H_3 \cdot CHOH \cdot CH_2NH_2$

Stolz (81) prepared ω-amino-3,4-dihydroxyacetophenone in a yield of 66 percent by condensing 3,4-dihydroxyphenacyl chloride with a 35 percent solution of ammonia, using ethanol as a solvent. He also prepared the methylamino and ethylamino analogs of ω-amino-3,4-dihydroxyacetophenone by condensing 3,4-dihydroxyphenacyl chloride with aqueous solutions of the corresponding amines.

Another synthesis of arterenol, based on the following reaction, is described in old German patents (91):

$$(CH_2O_2)C_6H_3 \cdot CHOH \cdot CH_2X \xrightarrow[PCl_5]{HOH} (HO)_2C_6H_3 \cdot CHOH \cdot CH_2X \xrightarrow{NH_3}$$

$(HO)_2C_6H_3 \cdot CHOH \cdot CH_2NH_2$

The yields were not reported.

Tutin (82), prepared ω-amino-3,4-dihydroxyacetophenone by treating m,m',p,p'-tetramethoxy-2,5-diphenylpyrazine with a mixture of boiling glacial acetic and concentrated hydriodic acids for two hours.

Greer (83), in a private communication, stated that he and his co-workers, in their most successful experiment, obtained arterenol in a yield of 60 percent by reducing ω-amino-3,4-dihydroxyacetophenone hydrochloride in an aqueous solution with platinum oxide catalyst.

Tutin (76) and Boruttau (85) attempted to prepare p-hydroxyphenylethanolamine by condensing p-hydroxyphenacyl chloride with ammonia, followed by reduction of the carbonyl group to produce the aminoalcohol. Glynn and Linnell (86) using the same method attempted to prepare 3,4-dichlorophenylethanolamine. These attempts were unsuccessful because of

the inability to obtain the intermediate aminoketones by condensing the aracyl halides with ammonia.

Both Tutin (87) and Glynn and Linnell (86) reported that pyrazine formation occurs when phenacyl halides or substituted phenacyl halides are allowed to react with ammonia or primary amines, but if the substituents in the 3,4-positions are hydroxyl groups then pyrazine formation will not occur. Ruddy (84), in a private communication, confirms this fact, stating that it is possible to obtain ω-amino-3,4-dihydroxyacetophenone in good yields from the condensation of 3,4-dihydroxyphenacyl chloride and ammonia.

Legerlotz (92) reported a 12 percent yield of p-hydroxy-ω-methylaminoacetophenone, in a German patent which describes the reaction between hydroxyphenacyl halides and primary or secondary amines. There are a number of other patents describing the reduction of m-hydroxy-ω-aminoacetophenones to m-hydroxyphenylethanolamines (93,94). Kulz and Hornung (95), described the preparation of a number of guaiacol analogs of the arylethanolamines by treating ω-haloacetoguaiacol with a non-aqueous solution of a primary aliphatic amine. The resulting alkylaminoacetoguaiacol was then reduced to the corresponding aminoalcohol. No yields were reported. Scheuring and Thoma (96) reported the reaction of a 3,4-dihydroxyphenacyl halide with an excess of isopropylamine in dilute ethanol, and the subsequent reduction of the aminoketone to 3,4-dihydroxyphenylethanolisopropylamine. Again, no yields were reported. Rubin and Day (97) described the preparation of ω-morpholinoacetophenone and ω-morpholino-3,4-dihydroxyacetophenone by the reaction of one equivalent of the corresponding phenacyl halide with two equivalents of morpholine in a solvent such as ether, and the subsequent reduction to

the morpholine analogs of phenylethanolamine and arterenol.

In general this method seems applicable only to the condensation of amines with 3,4-dihydroxyphenacyl halides, as the other phenacyl halides will form pyrazines with ammonia or primary amines.

12. Condensation of Phenacyl Halides with Benzylamines. Mason and Winder (98) in 1893 were the first to report the preparation of ω-benzylaminoacetophenone in a yield of 20 percent, and diphenacylbenzylamine in a yield of 50 percent by the reaction of equivalent amounts of phenacyl bromide and benzylamine in ethanol.

Gabriel (99) prepared ω-benzylaminoacetophenone by the following method:

$$p\text{-}CH_3 \cdot C_6H_4 \cdot SO_2Cl + H_2NCH_2C_6H_5 \longrightarrow p\text{-}CH_3 \cdot C_6H_4 \cdot SO_2\text{-}NH\text{-}CH_2C_6H_5$$

$$p\text{-}CH_3 \cdot C_6H_4 \cdot SO_2\text{-}NH\text{-}CH_2C_6H_5 + C_6H_5 \cdot CO \cdot CH_2Br \longrightarrow$$

$$p\text{-}CH_3 \cdot C_6H_4 \cdot SO_2\text{-}N(CH_2C_6H_5)\text{-}CH_2 \cdot CO \cdot C_6H_5$$

$$p\text{-}CH_3 \cdot C_6H_4 \cdot SO_2\text{-}N(CH_2C_6H_5)\text{-}CH_2 \cdot CO \cdot C_6H_5 + HCl \longrightarrow$$

$$C_6H_5 \cdot CO \cdot CH_2\text{-}NH\text{-}CH_2C_6H_5$$

Dakin (100), reported the preparation of ω-benzylamino-3,4-dihydroxyacetophenone, but did not characterize the product or indicate the yield.

Zahn (101) was the first to prepare ω-dibenzylaminoacetophenone by condensing dibenzylamine with phenacyl bromide in an ethanolic solution.

Stolz and Bottcher (8) in 1927 were the first to synthesize epinephrine using the then recently developed debenzylation procedure for the preparation of amines, according to the following reaction:

$$(HO)_2C_6H_3\cdot CO\cdot CH_2Cl + C_6H_5CH_2\text{-}NH\text{-}CH_3 \longrightarrow$$

$$(HO)_2C_6H_3\cdot CO\cdot CH_2\text{-}NCH_3\text{-}CH_2C_6H_5 \xrightarrow[\text{Ni or Pd}]{(H)} (HO)_2C_6H_3\cdot CHOH\cdot CH_2\text{-}NH\text{-}CH_3$$

Stolz and Flaecher (10) prepared and resolved phenylpropanolmethylamine by condensing $\alpha$-bromopropiophenone with benzylmethylamine, reducing the ketone group to the carbinol, using sodium in ethanol; and resolved the benzylmethylaminoalcohol, which was then catalytically debenzylated to either (+) or (-) ephedrine.

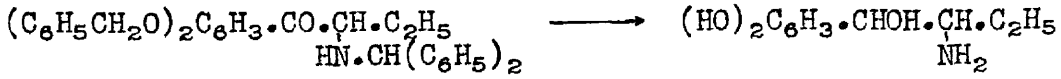
Bockmuhl, Ehrhart and Stein (14,15) reported the synthesis of hydroxyphenylpropanolamines by a similar method, i.e., the condensation of $\alpha$-bromo-hydroxypropiophenones with benzylmethylamine or dibenzylamine, and the subsequent catalytic hydrogenolysis and reduction of the benzylaminoketones to aminoalcohols.

Baltzly and Buck (19) prepared 2,5-dimethoxyphenylethanolmethylamine by the condensation of 2,5-dimethoxyphenacyl bromide with benzylmethylamine, and reduced the carbonyl group with platinum oxide with simultaneous catalytic debenzylation.

Priestly and Moness (17) condensed $\omega$-bromo-p-benzyloxyacetophenone with benzylmethylamine, using ethanol as the solvent. The aminoketone intermediate was then reduced to p-hydroxyphenylethanolmethylamine.

Suter and Ruddy (25) used benzhydrylamine in the same manner as the benzylamines for the synthesis of ethyl-nor-epinephrine in yields of 65 percent according to the following reaction:

$$(C_6H_5CH_2O)_2C_6H_3\cdot CO\cdot CHBr\cdot C_2H_5 + (C_6H_5)_2CH\cdot NH_2 \longrightarrow$$



Diphenylmethane was obtained in this reaction instead of toluene.

In view of the importance of this catalytic debenzylation procedure in the synthesis of not only physiologically active aminoalcohols, but of all types of amines and other compounds, it was deemed advisable to attempt to collect and review comprehensively the data which up until the present are scattered throughout the literature.

Hydrogenolytic Debenzylation

Sabatier and Maihle (1), in 1911, reducing benzylamine with nickel at 170-180 degrees to hexahydrobenzylamine, noticed that appreciable amounts of toluene and ammonia were also formed.

Emde and Schellbach (2), treating allylbenzylmethylpropylammonium iodide with sodium amalgam, obtained allylmethylpropylamine; they later observed (31) that while cinnamyl- and benzylammonium compounds were reduced to phenylpropylene and toluene, respectively, the benzyl group adhered more firmly than the vinylogous cinnamyl grouping.

Skita (3) reduced benzylaniline with the aid of colloidal platinum; he found small amounts of hexahydroaniline and hexahydrotoluene accompanying the dodecahydrobenzylaniline.

Rosenmund and Zetzsche (28) noticed certain anomalies during the reduction of benzoyl chloride; the benzyl alcohol formed reacted with unchanged benzoyl chloride to form benzyl benzoate, and the ester was converted into benzoic acid and toluene. Benzhydryl benzoate was hydrogenolyzed in a similar manner into benzoic acid and diphenylmethane.

Such results, unusual as they may have appeared, made little or no immediate impression. In 1923 Wolfe and Krauss (29,30) observed that the benzyl ethers of compounds like morphine, phenol, guaiacol, and amyl alcohol could be conveniently and smoothly converted into the corresponding phenols or alcohols and toluene by catalytic hydrogenolysis. A year later Wolfe (4), observed that benzylaniline and substituted benzylanilines could be converted with good yields into aniline and the correspondingly substituted toluenes. Apparently, this was the first

recognition of the ease with which the benzyl group may be removed from an amino-N or an ethereal-O atom. The significance of this reaction was not immediately appreciated, and chemists were slow to apply it practically.

During the first decade following the disclosure by Wolfe and Krauss, hydrogenolytic reactions were used in limited instances. Stolz and Bottcher (8) synthesized epinephrine by simultaneous hydrogenation of the carbonyl group and reductive debenzylation of ω-benzylmethylamino-3,4-dihydroxyacetophenone:

$$(HO)_2C_6H_3\cdot CO\cdot CH_2\text{-}NCH_3\text{-}CH_2C_6H_5 \xrightarrow{2\ H_2} (HO)_2C_6H_3\cdot CHOH\cdot CH_2\text{-}NHCH_3$$

Ephedrine was similarly obtained by reductive debenzylation of its N-benzyl derivative (9,10); optically active isomers were obtained from the resolved intermediates. Freudenberg, Durr and Hochstetter (41) debenzylated benzyldiacetone glucose; using sodium and ethanol they obtained diacetone glucose and toluene; using platinum in acetic acid, isolated toluene and monoacetone glucose. Kindler and Peschke (13) observed that when β-phenethylbenzylamine, $C_6H_5CH_2CH_2\text{-}NH\text{-}CH_2C_6H_5$, was boiled in tetralin with palladium black, toluene, phenylethane and ammonia were formed. Bergmann and Zervas (37) employed hydrogenolytic fission to synthesize aminoacids and dipeptides from carbobenzoxy intermediates (cf. Table II - no. 53).

Beginning in 1933 reductive debenzylation have found much wider use. For example, N-debenzylation has been used to synthesize:

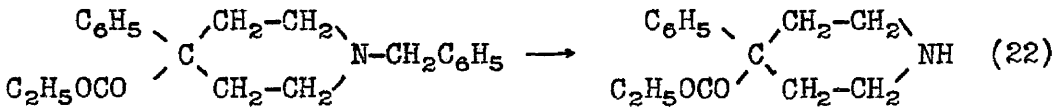
1. Members of the epinephrine-ephedrine series, e.g.,

a) $AR.CHOH.\underset{\displaystyle HN-CH_2C_6H_5}{\underset{|}{CH}}.CH_3 \longrightarrow AR.CHOH.\underset{\displaystyle NH_2}{\underset{|}{CH}}.CH_3$ (45,46)

b) $AR.CO.\underset{\displaystyle \begin{matrix}NCH_3\\ CH_2C_6H_5\end{matrix}}{\underset{|}{CH}}.CH_3 \longrightarrow AR.CHOH.\underset{\displaystyle NHCH_3}{\underset{|}{CH}}.CH_3$ (14,15)

c) $AR.CO.\underset{\displaystyle N(CH_2C_6H_5)_2}{\underset{|}{CH}}.CH_3 \longrightarrow AR.CHOH.\underset{\displaystyle NH_2}{\underset{|}{CH}}.CH_3$ (14,15)

2. Demerol,



(22)

3. Secondary aliphatic amines,

(20,21)

O-debenzylations have been used as shown in Table II. The reactions may be subdivided into two groups:

1. Those in which the oxygen-containing fragment is desired. (Table II - nos. 1 to 23)
2. Those in which toluene or substituted toluene is desired. For example:

$$ARCH_2OCOCH_3 + H_2 \longrightarrow ARCH_3 + CH_3COOH \quad (40).$$

Rosenmund and Karg (40) showed that the grouping AR.CH(OH)— is easily reduced to $AR.CH_2$— with palladium catalysts in the presence of chloroplatinic acid which acts as an activator.

Papa, Schwenk and Whitman (103) recently reported on a fundamentally related method, i.e., the reduction of carbonyl compounds with nickel-aluminum alloy in alkaline solution. Carbonyl compounds of the

type $C_6H_5COR$, (where R is H, alkyl or aryl), yield hydrocarbons; whereas carbonyl compounds of the type $C_6H_5(CH_2)_xCOR'$, yield carbinols. If the carbonyl group is attached directly to an aromatic ring with the formation of a conjugated system, the formation of hydrocarbons seems favored; while for the formation of carbinols, the carbonyl group must not be attached to an aromatic ring even if the carbonyl group is part of a conjugated system.

The possibility of catalytic S-debenzylation is apparently unexplored. Several instances of chemical S-debenzylation have been reported. Sifferd and du Vigneaud (42), using sodium in liquid ammonia, removed the benzyl group from S-benzylcysteine. Patterson and du Vigneaud (43), employing similar conditions, obtained tetradeuterohomocystine from S-benzyldideuterohomocysteine. In a similar manner - α-amino-β-benzylmercaptobutyric acid was converted into α-amino-β -thiolbutyric acid (44).

In view of the wide applications that may apparently be made of hydrogenolytic debenzylations, it was deemed worthwhile assembling all the experimental data in systematic form. This should then make it easier to deduce general rules which may permit forecasting with hope of success the results to be expected in new syntheses.

In Tables I and II are summarized the data found through Chemical Abstracts and the references cited in the papers there abstracted. The material has been classified into various groups of related compounds.

The following generalizations are apparent from the data in Table I:

1. Benzylamine is stable against hydrogenolytic debenzylation (formation of ammonia and toluene), (Compounds 1-7), except, perhaps when nickel (no. 1) or palladium black catalysts

# TABLE I

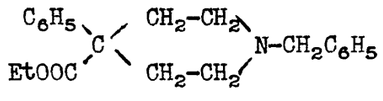
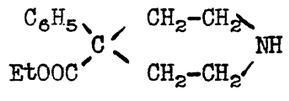
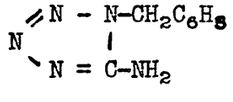
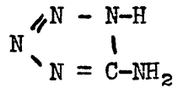
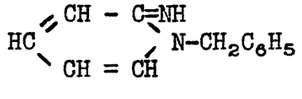
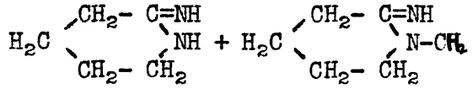
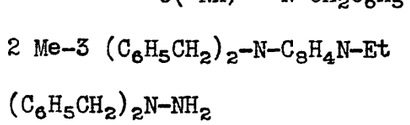
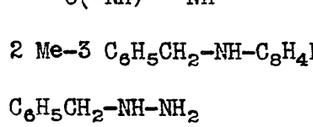
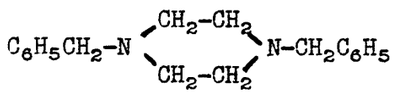
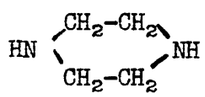
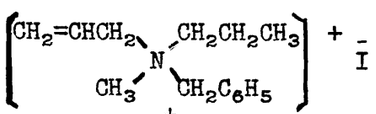
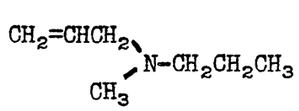
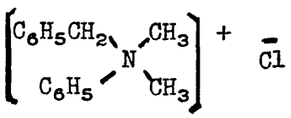
## N-DEBENZYLATIONS

| | SUBSTANCE REDUCED | PRODUCTS ISOLATED | CATALYST | SOLVENT | YIELD | TEMPERATURE | PRESSURE | REFERENCE |
|---|---|---|---|---|---|---|---|---|
| 1. | $C_6H_5CH_2NH_2$ | $C_6H_{11}CH_2NH_2 + C_6H_5CH_3 + NH_3$ | Nickel | ——— | ——— | 170-180 | ——— | 1 |
| 2. | " | $C_6H_{11}CH_2NH_2$ | Colloidal Pt | AcOH | ——— | 50-60 | 3 Atm. | 5 |
| 3. | " | $C_6H_{11}CH_2NH_2$ | Adams | ——— | ——— | ——— | ——— | 6 |
| 4. | " | $(C_6H_5CH_2)_2NH$ | Pd-$BaSO_4$ | Xylene | 90% | 137-140 | ——— | 7 |
| 5. | " | " | Pd Sponge | EtOH | 90% | 78-80 | ——— | 11 |
| 6. | " | $C_6H_5CH_3 + NH_3$ | Pd Black | Tetralin | ——— | 206-207 | ——— | 13 |
| 7. | " | ——— | PdO | AcOH | ——— | ——— | ——— | 23 |
| 8. | $(C_6H_5CH_2)_2NH$ | ——— | PdO | AcOH | ——— | ——— | ——— | 23 |
| 9. | $C_6H_5CH_2$-NH-$CH_3$ | ——— | PdO | AcOH | ——— | ——— | ——— | 23 |
| 10. | $C_6H_5CH_2$-NH-$CH_2CH_2C_6H_5$ | $C_6H_5CH_3 + C_6H_5C_2H_5 + NH_3$ | Pd Black | Tetralin | ——— | 206-207 | ——— | 13 |
| 11. | $C_6H_5CH_2$-NH-$(CH_2)_3CH(CH_3)$-$N(CH_3)_2$ | $H_2N(CH_2)_3CH(CH_3)$-$N(CH_3)_2$ | Pd | ——— | ——— | ——— | ——— | 12 |
| 12. | 2 Me-3 $C_6H_5CH_2$-NH-$C_8H_4N$-Et (Indole) | 2 Me-3 $NH_2$-$C_8H_4N$-Et | Pd | ——— | ——— | ——— | ——— | 12 |
| 13. | $\alpha$-$C_5H_4N$-NH-$CH_2C_6H_5$ | $\alpha$-$C_5H_5N$-NH-$CH_2C_6H_5$ | PdO | AcOH | ——— | ——— | ——— | 23 |
| 14. | $C_6H_5CH_2$-NH-$CH_2C_6H_5N(Me)_3Cl$ | $H_2NCH_2C_6H_5N(Me)_3Cl$ | Pd Charcoal | EtOH | ——— | 75 | 1.5-3 Atm. | 24 |
| 15. | $C_6H_5CH_2$-NH-$CH(CH_3)CH_2OH$ | $H_2NCH(CH_3)CH_2OH$ | Pd | ——— | ——— | ——— | ——— | 16 |
| 16. | $C_6H_5CH_2$-NH-$CH_2CH_2COOEt$ | $H_2NCH_2CH_2COOEt$ | Pd Nuchar | EtOH | Quant. | ——— | 200 lbs. | 26 |
| 17. | $C_6H_5CH_2$-NH-$CH(CH_2OH)COOMe$ | $H_2NCH(CH_2OH)COOMe$ | Pd Nuchar | EtOH | Quant. | ——— | 200 lbs. | 26 |
| 17a. | $C_6H_5COCH_2$-NH-$CH_2C_6H_5$ | $C_6H_5CHOHCH_2NH_2$ | Pd Charcoal | HOH | 88% | 25 | 100 lbs. | 1a |
| 18. | $\beta$-$C_{10}H_7COCH_2$-NH-$CH_2C_6H_5$ | $\beta$-$C_{10}H_7CHOHCH_2$-NH-$CH_2C_6H_5$ | Pd Charcoal | EtOH | ——— | ——— | ——— | 18 |
| 19. | 3,4-$(C_6H_5CH_2O)_2C_6H_3COCH_2CH_2CH_2NHCH(C_6H_5)_2$ | 3,4-$(HO)_2C_6H_3CHOH(CH_2)_3NH_2$ + $(C_6H_5)_2CH_2$ | Pd Sponge | EtOH then HOH | 65% | ——— | 50 lbs. | 25 |
| 20. | $C_6H_5CH_2$-NH-$CH_2C_6H_4OMe$-p | p-$MeOC_6H_4CH_2NH_2$ | Pd Charcoal | EtOH | ——— | 65 | 1.5-3 Atm. | 24 |
| 21. | 3,4-$(CH_2O_2)C_6H_3CH_2$-NH-$CH_2C_6H_4OMe$-p | 3,4-$(CH_2O_2)C_6H_3CH_2NH_2$ | Pd Charcoal | EtOH | ——— | 75 | 1.5-3 Atm. | 24 |

| | SUBSTANCE REDUCED | PRODUCTS ISOLATED | CATALYST | SOLVENT | YIELD | TEMPERATURE | PRESSURE | REFERENCE |
|---|---|---|---|---|---|---|---|---|
| 22. | $p\text{-}MeOC_6H_4CH_2\text{-}NH\text{-}CH_2C_6H_4OH\text{-}p$ | $p\text{-}MeOC_6H_4CH_2NH_2$ + phenolic base $p\text{-}HOC_6H_4CH_3$ + neutral matter | Pd Charcoal | EtOH | ——— | 75 | 1.5-3 Atm. | 24 |
| 23. | $C_6H_5CH_2\text{-}NH\text{-}C_6H_5$ | $C_6H_{11}CH_2\text{-}NH\text{-}C_6H_{11}$ + $C_6H_{11}CH_3$ + $C_6H_{11}CH_2NH_2$ | Colloidal Pt | AcOH | 75% | ——— | 3 Atm. | 3 |
| 24. | $C_6H_5CH_2\text{-}NH\text{-}C_6H_5$ | $C_6H_5NH_2$ | Pd Charcoal | EtOH | Quant. | ——— | ——— | 4 |
| 25. | $C_6H_5CH_2\text{-}NH\text{-}C_6H_5$ | $C_6H_5NH_2$ | PdO | EtOH | 97.5% | 18 | 1 Atm. | 23 |
| 26. | $o\text{-}HOC_6H_4CH_2\text{-}NH\text{-}C_6H_5$ | $C_6H_5NH_2$ + $o\text{-}HOC_6H_4CH_3$ | Pd Charcoal | EtOH | Quant. | ——— | ——— | 4 |
| 27. | $3,4\text{-}(CH_2O_2)C_6H_3CH_2\text{-}NH\text{-}C_6H_5$ | $C_6H_5NH_2$ + $3,4\text{-}(CH_2O_2)C_6H_3CH_3$ | Pd Charcoal | EtOH | Quant. | ——— | ——— | 4 |
| 28. | $C_6H_5CH_2\text{-}NCH_3\text{-}C_6H_5$ | $C_6H_5NHCH_3$ | Pd Charcoal | EtOH | Quant. | ——— | ——— | 4 |
| 29. | $(C_6H_5CH_2)_2NC_6H_5$ | $C_6H_5NH_2$ | PdO | EtOH | 89% | 18 | 1 Atm. | 23 |
| 30. | $\beta C_{10}H_7\text{-}N(CH_2C_6H_5)_2$ | $\beta C_{10}H_7NH_2$ | PdO | AcOH | 88% | 20 | 1 Atm. | 23 |
| 31. | $C_6H_5CH_2\text{-}N(CH_3)C_2H_5$ | $CH_3\text{-}NH\text{-}C_2H_5$ | $PtO_2$ | AcOH | ——— | 65-75 | 3 Atm. | 21 |
| 32. | $C_6H_5CH_2\text{-}N(CH_3)C_3H_7$ | $CH_3\text{-}NH\text{-}C_3H_7$ | $PtO_2$ | AcOH | ——— | 65-75 | 3 Atm. | 21 |
| 33. | $C_6H_5CH_2\text{-}N(CH_3)C_4H_9$ | $CH_3\text{-}NH\text{-}C_4H_9$ | $PtO_2$ | AcOH | ——— | 65-75 | 3 Atm. | 21 |
| 34. | $C_6H_5CH_2\text{-}N(CH_3)C_5H_{11}$ | $CH_3\text{-}NH\text{-}C_5H_{11}$ | $PtO_2$ | AcOH | ——— | 65-75 | 3 Atm. | 21 |
| 35. | $C_6H_5CH_2\text{-}N(CH_3)C_{12}H_{25}$ | $CH_3\text{-}NH\text{-}C_{12}H_{25}$ | $PtO_2$ | AcOH | ——— | 65-75 | 3 Atm. | 21 |
| 36. | $C_6H_5CH_2\text{-}N(C_2H_5)C_3H_7$ | $C_2H_5\text{-}NH\text{-}C_3H_7$ | $PtO_2$ | AcOH | ——— | 65-75 | 3 Atm. | 21 |
| 37. | $C_6H_5CH_2\text{-}N(CH_3)C_{16}H_{33}$ | $CH_3\text{-}NH\text{-}C_{16}H_{33}$ | PdO | AcOH | 92% | 30 | 1 Atm. | 23 |
| 38. | $C_6H_5CH_2\text{-}N(C_2H_5)C_4H_9$ | $C_2H_5\text{-}NH\text{-}C_4H_9$ | $PtO_2$ | AcOH | ——— | 65-75 | 3 Atm. | 21 |
| 39. | $C_6H_5CH_2\text{-}N(C_2H_5)C_5H_{11}$ | $C_2H_5\text{-}NH\text{-}C_5H_{11}$ | $PtO_2$ | AcOH | ——— | 65-75 | 3 Atm. | 21 |
| 40. | $C_6H_5CH_2\text{-}N(C_3H_7)C_4H_9$ | $C_3H_7\text{-}NH\text{-}C_4H_9$ | $PtO_2$ | AcOH | ——— | 65-75 | 3 Atm. | 21 |
| 41. | $C_6H_5CH_2\text{-}N(C_4H_9)C_5H_{11}$ | $C_4H_9\text{-}NH\text{-}C_5H_{11}$ | $PtO_2$ | AcOH | ——— | 65-75 | 3 Atm. | 21 |
| 42. | $C_6H_5CH_2\text{-}N(C_6H_{13})_2$ | $(C_6H_{13})_2NH$ | $PtO_2$ | AcOH | Quant. | 70 | ——— | 20 |

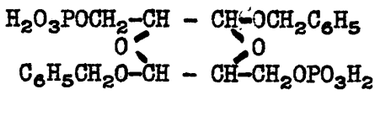
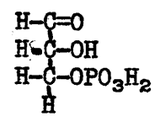
| | SUBSTANCE REDUCED | PRODUCTS ISOLATED | CATALYST | SOLVENT | YIELD | TEMPERATURE | PRESSURE | REFERENCE |
|---|---|---|---|---|---|---|---|---|
| 43. | $C_6H_5CH_2-N(C_7H_{15})_2$ | $(C_7H_{15})_2NH$ | $PtO_2$ | AcOH | Quant. | 70 | ———— | 20 |
| 44. | $C_6H_5CH_2-N(CH_3)CH_2C_6H_4CH_3-p$ | $p-CH_3C_6H_4CH_2-NH-CH_3$ | Pd Charcoal | MeOH | ———— | 25 | 1.5-3 Atm. | 24 |
| 45. | $C_6H_5CH_2-N(CH_3)CH_2C_6H_4Cl-p$ | $p-ClC_6H_4CH_2-NH-CH_3$ | Pd Charcoal | MeOH | ———— | 25 | 1.5-3 Atm. | 24 |
| 46. | $C_6H_5CH_2-N(CH_3)CH_2C_6H_4NO_2-p$ | $p-H_2NC_6H_4CH_2-NH-CH_3$ | Pd Charcoal | EtOH | ———— | 25 | 1.5-3 Atm. | 24 |
| 47. | $C_6H_5CH_2-N(CH_3)CH_2C_6H_4NO_2-p$ | $C_6H_5CH_2-N(CH_3)CH_2C_6H_4NH_2-p$ | Pd Charcoal | EtOH + HCl | ——— | 25 | 1.5-3 Atm. | 24 |
| 48. | $C_6H_5CH_2-N(CH_3)CH_2C_6H_4NO_2-p$ | $p-H_2NC_6H_4CH_2-NH-CH_3$ | Pd Charcoal | EtOH + HCl | ——— | 65 | 1.5-3 Atm. | 24 |
| 49. | $\alpha-C_{10}H_7CH_2(CH_3)N-CH_2C_6H_5$ | $C_6H_5CH_2-NH-CH_3 + \alpha-C_{10}H_7CH_3$ | Pd Charcoal | MeOH | ———— | 25 | 1.5-3 Atm. | 24 |
| 50. | $\beta-C_{10}H_7CH_2(CH_3)N-CH_2C_6H_5$ | $C_6H_5CH_2-NH-CH_3 + \beta-C_{10}H_7CH_3$ | Pd Charcoal | MeOH | ———— | 25 | 1.5-3 Atm. | 24 |
| 51. | $\alpha-C_{10}H_7CH_2(CH_3)N-CH_2C_7H_{10}-\beta$ | $\alpha+\beta-C_{10}H_7CH_2-NH-CH_3$ | Pd Charcoal | MeOH | ———— | 25 | 1.5-3 Atm. | 24 |
| 52. | $\alpha-C_{10}H_7CH_2(CH_3)N-CH_2C_6H_4C_6H_5-p$ | $p-C_6H_5-C_6H_4CH_2-NH-CH_3 +$ $\alpha-C_{10}H_7CH_2-NH-CH_3$? | Pd Charcoal | MeOH | ———— | 25 | 1.5-3 Atm. | 24 |
| 53. | $o-MeOC_6H_4CH_2-N(CH_3)CH_2C_6H_4OMe-p$ | $o-MeOC_6H_4CH_2-NH-CH_3 +$ $p-MeOC_6H_4CH_2-NH-CH_3$ | Pd Charcoal | EtOH | ———— | 65 | 1.5-3 Atm. | 24 |
| 54. | $m-MeOC_6H_4CH_2-N(CH_3)CH_2C_6H_4OMe-p$ | $m-MeOC_6H_4CH_2-NH-CH_3 +$ $p-MeOC_6H_4CH_2-NH-CH_3$ | Pd Charcoal | EtOH | ———— | 65 | 1.5-3 Atm. | 24 |
| 55. | $C_6H_5CH_2-N(CH_3)CH_2C_6H_4OMe-p$ | $p-MeOC_6H_4CH_2-NH-CH_3$ | Pd Charcoal | EtOH | ———— | 25 | 1.5-3 Atm. | 24 |
| 56. | $p-MeOC_6H_4CH_2-N=CHC_6H_4OCH_2C_6H_5$ | $p-MeOC_6H_4CH_2NH_2 +$ $p-HOC_6H_4CH_3$ | Pd Charcoal | EtOH + HCl | ——— | 75 | 1.5-3 Atm. | 24 |
| 57. | $(C_6H_5CH_2)_3N$ | $C_6H_5CH_3 + NH_3$ | Pd Black | Tetralin | ———— | 206-207 | ———— | 13 |
| 58. | $(C_6H_5CH_2)_3N$ | $(C_6H_5CH_2)_2NH$ | PdO | AcOH | 97% | 25 | 1 Atm. | 23 |
| 59. | $(C_6H_5CH_2)_2N-C_2H_4-NH-C_6H_5$ | $C_6H_5-NH-C_2H_4NH_2$ | Pd | ———— | ———— | ———— | ———— | 12 |
| 60. | $(C_6H_5CH_2)_2N-C_{12}H_{25}$ | $C_6H_{11}CH_2-NH-C_{12}H_{25}$ | $PtO_2$ | AcOH | 84% | 32 | 1 Atm. | 23 |
| 61. | $(C_6H_5CH_2)_2N-COOEt$ | ———— | PdO | EtOH | ———— | ———— | ———— | 23 |

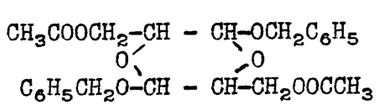
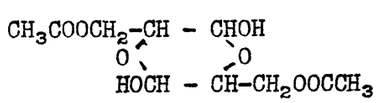
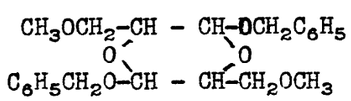
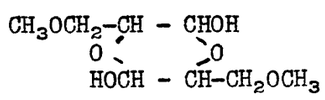
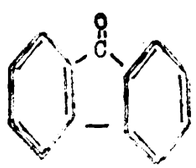
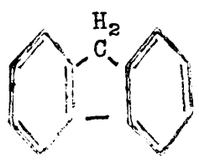
| | SUBSTANCE REDUCED | PRODUCTS ISOLATED | CATALYST | SOLVENT | YIELD | TEMPERATURE | PRESSURE | REFERENCE |
|---|---|---|---|---|---|---|---|---|
| 62. | $C_6H_5COCH_2(CH_3)N-CH_2C_6H_5$ | $C_6H_5CHOHCH_2-NH-CH_3$ | Nickel | HOH | ——— | 90 | 50 Atm. | 8 |
| 63. | $p-HOC_6H_4COCH_2(CH_3)N-CH_2C_6H_5$ | $p-HOC_6H_4CHOHCH_2-NH-CH_3$ | Nickel | HOH | ——— | 90 | 40 Atm. | 8 |
| 64. | $p-C_6H_5CH_2OC_6H_4COCH_2(CH_3)N-CH_2C_6H_5$ | $p-HOC_6H_4CHOHCH_2-NH-CH_3$ | Pd Charcoal | ——— | ——— | ——— | ——— | 17 |
| 65. | $2,5-(MeO)_2C_6H_3COCH_2(CH_3)N-CH_2C_6H_5$ | $2,5-(MeO)_2C_6H_3CHOHCH_2-NH-CH_3$ | $PtO_2$ | EtOH | ——— | ——— | ——— | 19 |
| 66. | $3,4-(HO)_2C_6H_3COCH_2(CH_3)N-CH_2C_6H_5$ | $3,4-(HO)_2C_6H_3CHOHCH_2-NH-CH_3$ | Pd Acacia | 2N HCl | ——— | 25 | 1 Atm. | 8 |
| 67. | $C_6H_5COCH_2CH_2(CH_3)N-CH_2C_6H_5$ | $C_6H_5CHOHCH_2CH_2-NH-CH_3$ | Pd Black | EtOH | ——— | ——— | ——— | 8 |
| 68. | $C_6H_5COCH_2CH_2(CH_3)N-CH_2C_6H_5$ | $C_6H_5CHOHCH_2CH_2-NH-CH_3$ | Nickel | 2N HCl | ——— | ——— | 40 Atm. | 8 |
| 69. | $C_6H_5CHOHCH_2CH_2(CH_3)N-CH_2C_6H_5$ | $C_6H_5CHOHCH_2CH_2-NH-CH_3$ | ——— | ——— | 92% | ——— | ——— | 9,10 |
| 70. | o, m or $p-C_6H_5CH_2OC_6H_4COCH_2CH_2(CH_3)N-CH_2C_6H_5$ | o, m or $p-HOC_6H_4CHOHCH_2CH_2-NH-CH_3$ | Pd-$PtO_2$ | ——— | ——— | ——— | ——— | 14 |
| 71. | $C_8H_7O-COCH_2(R)N-CH_2C_6H_5$ (2,3-Dihydrobenzofuran) | $C_8H_7O-CHOHCH_2-NH-R$ | Pd Charcoal | ——— | ——— | ——— | ——— | 27 |
| 72. | $(C_6H_5CH_2)_2N-CH_2COOH$ | $H_2NCH_2COOH$ | PdO | AcOH | 95% | 21 | 1 Atm. | 23 |
| 73. | $(C_6H_5CH_2)_2N-CH_2COOMe$ | $H_2NCH_2COOMe$ | PdO | EtOH | 96% | 25 | 1 Atm. | 23 |
| 74. | $(C_6H_5CH_2)_2N-CH_2CH_2CH_2COOEt$ | $H_2NCH_2CH_2CH_2COOEt$ | Pd | ——— | ——— | ——— | ——— | 12 |
| 75. | $O=C-N(C_6H_5CH_2)_2$ <br> $O=C-NH_2$ | ——— | PdO | AcOH | ——— | ——— | ——— | 23 |
| 76. | $(C_6H_5CH_2)_2N-CH_2CH_2CH_2COCH_3$ | $H_2NCH_2CH_2CH_2COCH_3$ | Pd | ——— | ——— | ——— | ——— | 12 |
| 77. | $(C_6H_5CH_2)_2N-CH_2CH_2OC_6H_5$ | $C_6H_5OCH_2CH_2NH_2$ | Pd | ——— | ——— | ——— | ——— | 12 |
| 77a. | $p-HOC_6H_4COCH_2-N(CH_2C_6H_5)_2$ | $p-HOC_6H_4CHOHCH_2NH_2$ | Pd Charcoal | EtOH | 86% | 25 | 150 lbs. | 1a |
| 77b. | $3,4-(HO)_2C_6H_3COCH_2-N(CH_2C_6H_5)_2$ | $3,4-(HO)_2C_6H_3CHOHCH_2NH_2$ | Pd Charcoal | HOH | 88% | 25 | 150 lbs. | 1a |
| 78. | m or $p-C_6H_5CH_2OC_6H_4COCH_2CH_2-N(CH_2C_6H_5)_2$ | m or $p-HOC_6H_4CHOHCH_2CH_2NH_2$ | Pd-$PtO_2$ | ——— | ——— | ——— | ——— | 15 |
| 79. | $\beta-C_{10}H_7COCH_2-N(CH_2C_6H_5)_2$ | $\beta-C_{10}H_7CHOHCH_2-N(C_6H_5CH_2)_2$ | Pd Charcoal | EtOH | ——— | ——— | ——— | 18 |
| 80. | $C_8H_7O-COCH_2-N(CH_2C_6H_5)_2$ | $C_8H_7O-CHOHCH_2-NH-CH_2C_6H_5$ | Pd Charcoal | ——— | ——— | ——— | ——— | 27 |

| | SUBSTANCE REDUCED | PRODUCTS ISOLATED | CATALYST | SOLVENT | YIELD | TEMPER-ATURE | PRESSURE | REFER-ENCE |
|---|---|---|---|---|---|---|---|---|
| 81. | 2 Me-3 $C_6H_5CH_2-N(CH_3)-C_8H_4N-Et$ | 2 Me-3 $CH_3-NH-C_8H_4N-Et$ | Pd | ------- | -------- | -------- | -------- | 12 |
| 82. |  |  | Pd Sponge | EtOH | -------- | 40-50 | -------- | 22 |
| 83. | $C_8H_8N-CH_2C_6H_5$ (1,3 Dihydro-isoindole) | $C_8H_8NH$ | PdO | EtOH | 75% | 28 | 1 Atm. | 23 |
| 84. |  |  | PdO | EtOH | 95% | 20 | 1 Atm. | 23 |
| 85. |  |  | PdO | AcOH | -------- | 20 | 1 Atm. | 23 |
| 86. |  |  | PdO | EtOH | 94% | 18.5 | 1 Atm. | 23 |
| 87. | 2 Me-3 $(C_6H_5CH_2)_2-N-C_8H_4N-Et$ | 2 Me-3 $C_6H_5CH_2-NH-C_8H_4N-Et$ | Pd | ------- | -------- | -------- | -------- | 12 |
| 88. | $(C_6H_5CH_2)_2N-NH_2$ | $C_6H_5CH_2-NH-NH_2$ | PdO | EtOH | 88% | 23 | 1 Atm. | 23 |
| 89. |  |  | PdO | AcOH | 92% | 29 | 1 Atm. | 23 |
| 90. | $(C_6H_5CH_2)_2N-CN$ | $H_2NC(=NH)-NH-CN$ | PdO | EtOH | -------- | 22 | 1 Atm. | 23 |
| 91. |  |  | NaHg | ------- | -------- | -------- | -------- | 2 |
| 92. | $(C_6H_5CH_2)_3-\overset{+}{N}-CH_3 \quad \overset{-}{OH}$ | $C_6H_5CH_2-NH-CH_3$ | PdO | EtOH | -------- | 18 | 1 Atm. | 23 |
| 93. | $(C_6H_5CH_2)_3-\overset{+}{N}-CH_3 \quad \overset{-}{I}$ | ---------- | PdO | EtOH | -------- | 25 | 1 Atm. | 23 |
| 94. |  | $C_6H_{11}-N(CH_3)_2$ | PdO | EtOH | 90% | 20 | 1 Atm. | 23 |

# TABLE II

## O-DEBENZYLATIONS

| | SUBSTANCE REDUCED | PRODUCTS ISOLATED | CATALYST | SOLVENT | YIELD | TEMPERATURE | PRESSURE | REFERENCE |
|---|---|---|---|---|---|---|---|---|
| 1. | $C_6H_5CH_2OCH_3$ | $CH_3OH$ | Raney Ni | ——— | 65% | 160 | 150-250 A. | 39 |
| 2. | $C_6H_5CH_2OC_4H_9$ | $C_4H_9OH$ | Raney Ni | ——— | 92% | 175 | 150-250 A. | 39 |
| 3. | $C_6H_5CH_2O(CH_3)CHCH_2CH_3$ | $CH_3CH_2CHOHCH_3$ | Raney Ni | ——— | 100% | 125 | 150-250 A. | 39 |
| 4. | $C_6H_5CH_2OC_5H_{11}$ | $C_5H_{11}OH$ | Pd Charcoal | EtOH | ——— | ——— | ——— | 30 |
| 5. | $C_6H_5CH_2OC_{12}H_{25}$ | $C_{12}H_{25}OH$ | Raney Ni | ——— | 74% | 160 | 150-250 A. | 39 |
| 6. | $C_6H_5CH_2OC_6H_5$ | $C_6H_5OH$ | Pd Charcoal | AcOH | Quant. | ——— | ——— | 29 |
| 7. | $C_6H_5CH_2OC_6H_5$ | $C_6H_5OH + C_6H_{11}OH$ | Raney Ni | ——— | 87% | 100 | 150-250 A. | 39 |
| 8. | $C_6H_5CH_2OCH_2CH_2CH_2C_6H_5$ | $C_6H_5CH_2CH_2CH_2OH$ | Raney Ni | ——— | 57% | 100 | 150-250 A. | 39 |
| 9. | $C_6H_5CH_2OC_6H_4CH_3$-o | o-$CH_3C_6H_4OH$ | Raney Ni | ——— | 87% | 125 | 150-250 A. | 39 |
| 10. | $C_6H_5CH_2OC_6H_4CH_3$-m | m-$CH_3C_6H_4OH$ + m-$CH_3C_6H_{10}OH$ | Raney Ni | ——— | 71% | 150 | 150-250 A. | 39 |
| 11. | $C_6H_5CH_2OC_6H_4CH_3$-p | p-$CH_3C_6H_4OH$ + p-$CH_3C_6H_{10}OH$ | Raney Ni | ——— | 58% | 150 | 150-250 A. | 39 |
| 12. | $C_6H_5CH_2OC_6H_4OCH_3$-o | o-$CH_3OC_6H_4OH$ | Pd Charcoal | ——— | Quant. | ——— | ——— | 29 |
| 13. | $C_6H_5CH_2OC_{10}H_7$ | Hydronapthols | Raney Ni | ——— | 100% | 125 | 150-250 A. | 39 |
| 14. | $C_6H_5CH_2OCH_2CH_2CH_2OH$ | $HOCH_2CH_2CH_2OH$ | Raney Ni | ——— | 78% | 175 | 150-250 A. | 39 |
| 15. | $C_6H_5CH_2OCH_2CH_2OC_2H_5$ | $C_2H_5OCH_2CH_2OH + C_6H_{11}CH_3$ | Raney Ni | ——— | 63% | 175 | 150-250 A. | 39 |
| 16. | $C_6H_5CH_2OCH_2CH_2OC_6H_5$ | $C_6H_5OCH_2CH_2OH + C_6H_{11}OH$ | Raney Ni | ——— | 55% | 150 | 150-250 A. | 39 |
| 17. | $C_6H_5CH_2OC_6H_4COOCH_3$ | o-$HOC_6H_4COOCH_3$ | Raney Ni | ——— | 89% | 150 | 150-250 A. | 39 |
| 18. | $C_6H_5CH_2OCH_2C_6H_4OCH_3$-p | p-$CH_3OC_6H_4CH_3$ | Pd Charcoal | EtOH | ——— | ——— | 1.5-3 Atm. | 24 |
| 19. | $C_6H_5CH_2OC_{17}H_{18}O_2N$ | $C_{17}H_{19}O_3N$ (MORPHINE) | Pd Charcoal | HOH | ——— | ——— | ——— | 29 |
| 20. |  |  | Pd | AcOH | ——— | 25 | 1 Atm. | 35 |

| | SUBSTANCE REDUCED | PRODUCTS ISOLATED | CATALYST | SOLVENT | YIELD | TEMPERATURE | PRESSURE | REFERENCE |
|---|---|---|---|---|---|---|---|---|
| 21. |  |  | Pd | AcOH | 86.6% | ------- | 1 Atm. | 35 |
| 22. |  |  | Pd | AcOH | 62% | ------- | 1 Atm. | 36 |
| 23. | $C_6H_5CH_2OH$ | $C_6H_5CH_3$ | Pd Charcoal | EtOH | ------- | ------- | 1.5-3 Atm. | 24 |
| 24. | $p\text{-}CH_3OC_6H_4CH_2OH$ | $p\text{-}CH_3OC_6H_4CH_3$ | Pd Charcoal | EtOH | ------- | ------- | 1.5-3 Atm. | 24 |
| 25. | $p\text{-}CH_3OC_6H_4COCH_3$ | $p\text{-}CH_3OC_6H_4C_2H_5$ | Pd Charcoal | EtOH | ------- | ------- | 1.5-3 Atm. | 24 |
| 26. | $C_6H_5COCH(CH_3)_2$ | $C_6H_5CHOHCH(CH_3)_2 + C_6H_5CH_2CH(CH_3)_2$ | Pd Charcoal | EtOH | ------- | ------- | 1.5-3 Atm. | 24 |
| 27. | $C_6H_5COC(CH_3)_3$ | $C_6H_5CHOHC(CH_3)_3$ | Pd Charcoal | EtOH | ------- | ------- | 1.5-3 Atm. | 24 |
| 28. | $C_6H_5CH{=}CHCH_2OH$ | $C_6H_5CH_2CH_2CH_2OH + C_6H_5C_3H_7$ | Pd Charcoal | EtOH | ------- | ------- | 1.5-3 Atm. | 24 |
| 29. | $C_6H_5COCH_2C_6H_5$ | $C_6H_5CH_2CH_2C_6H_5$ | Pd Charcoal | MeOH | ------- | ------- | 1.5-3 Atm. | 24 |
| 30. | $C_6H_5COC_6H_5$ | $C_6H_5CH_2C_6H_5$ | Pd Charcoal | MeOH | ------- | ------- | 1.5-3 Atm. | 24 |
| 31. | $\alpha\text{-}C_{10}H_7COC_6H_5$ | $\alpha\text{-}C_{10}H_7CH_2C_6H_5$ | Pd Charcoal | EtOH | ------- | ------- | 1.5-3 Atm. | 24 |
| 32. |  |  | Pd Charcoal | EtOH | ------- | ------- | 1.5-3 Atm. | 24 |
| 33. | $3,4\text{-}(HO)_2C_6H_3COCH_3$ | $3,4\text{-}(HO)_2C_6H_3C_2H_5$ | Pd Charcoal | EtOH + EtOAc | ------- | ------- | 1.5-3 Atm. | 24 |
| 34. | $p\text{-}C_6H_5C_6H_4COC_6H_5$ | $p\text{-}C_6H_5C_6H_4CH_2C_6H_5$ | Pd Charcoal | EtOH | ------- | ------- | 1.5-3 Atm. | 24 |
| 35. | $(C_6H_5)_2CHCOC_6H_5$ | $(C_6H_5)_2CHCH_2C_6H_5$ | Pd Charcoal | EtOH | ------- | ------- | 1.5-3 Atm. | 24 |
| 36. | $C_6H_5CHOHC_6H_5$ | $C_6H_5CH_2C_6H_5$ | Pd Charcoal | MeOH | ------- | ------- | 1.5-3 Atm. | 24 |
| 37. | $C_6H_5CHOHCH_2OH$ | $C_6H_5CH_2CH_2OH$ | Pd Charcoal | EtOH | ------- | ------- | 1.5-3 Atm. | 24 |
| 38. | $C_6H_5COCHOHCH_3$ | $C_6H_5CHOHCHOHCH_3$ | | | | | | |

| | SUBSTANCE REDUCED | PRODUCTS ISOLATED | CATALYST | SOLVENT | YIELD | TEMPERATURE | PRESSURE | REFERENCE |
|---|---|---|---|---|---|---|---|---|
| 39. | $C_6H_5COCHOHC_6H_5$ | $C_6H_{11}CH_2CH_2C_6H_{11}$ + $C_6H_{11}CHOHCHOHC_6H_{11}$ | $PtO_2$ | -------- | -------- | 70 | --------- | 34 |
| 40. | p-$CH_3OC_6H_4COCHOHC_6H_4OCH_3$-p | p-$CH_3OC_6H_4CH_2CH_2C_6H_4OCH_3$-p | Pd Charcoal | EtOH | -------- | -------- | 1.5-3 Atm. | 24 |
| 41. | 3,4-$(CH_2O_2)C_6H_3COCOC_6H_3(CH_2O_2)$-4,3 | 3,4-$(CH_2O_2)C_6H_3CH_2CH_2C_6H_3(CH_2O_2)$-4,3 | Pd Charcoal | EtOH + EtOAc | -------- | -------- | 1.5-3 Atm. | 24 |
| 42. | o-$CH_3OC_6H_4CHOHCN$ | o-$CH_3OC_6H_4CHOHCH_2NH_2$ | $PtO_2$ | EtOH-HCl | 59% | -------- | --------- | 38 |
| 43. | o-$ClC_6H_4CHOHCN$ | o-$ClC_6H_4CHOHCH_2NH_2$ | $PtO_2$ | EtOH-HCl | 41% | -------- | --------- | 38 |
| 44. | 2,3-$(CH_3O)_2C_6H_3CHOHCN$ | 2,3-$(CH_3O)_2C_6H_3CHOHCH_2NH_2$ | $PtO_2$ | EtOH-HCl | 23.5% | -------- | --------- | 38 |
| 45. | 3,4-$(CH_3O)_2C_6H_3CHOHCN$ | 3,4-$(CH_3O)_2C_6H_3CH_2CH_2NH_2$ | Pd Charcoal | EtOH-HCl | -------- | -------- | 1.5-3 Atm. | 24 |
| 46. | $C_6H_5CH(CN)OCOCH_3$ | $C_6H_5CH_2CH_2NH_2$ | Pd Charcoal | EtOH | -------- | -------- | 1 Atm. | 32 |
| 47. | $C_6H_5CH(COOH)OCOCH_3$ | $C_6H_5CH_2COOH$ + $CH_3COOH$ | Pd $BaSO_4$ | Tetralin | 60% | 215 | --------- | 33 |
| 48. | p-$CH_3OC_6H_4CH(COOH)OCOCH_3$ | p-$CH_3OC_6H_4CH_2COOH$ + $CH_3COOH$ | Pd $BaSO_4$ | -------- | 40% | -------- | --------- | 33 |
| 49. | o-$CH_3COOC_6H_4CH(COOH)OCOCH_3$ | o-$HOC_6H_4CH_2COOH$ + $CH_3COOH$ | Pd $BaSO_4$ | -------- | 66% | -------- | --------- | 33 |
| 50. | o-$ClC_6H_4CH(COOH)OCOCH_3$ | o-$ClC_6H_4CH_2COOH$ + $CH_3COOH$ | Pd $BaSO_4$ | -------- | -------- | -------- | --------- | 33 |
| 51. | $C_6H_5COOCH_2C_6H_5$ | $C_6H_5COOH$ | Pd | Xylene | 94% | -------- | --------- | 28 |
| 52. | $C_6H_5COOCH(C_6H_5)_2$ | $C_6H_5COOH$ + $(C_6H_5)_2CH_2$ | Pd | Xylene | 94% | -------- | --------- | 28 |
| 53. | $HOOCCH_2CH_2\underset{C_6H_5CH_2OCO-NH}{CHCO--NHCHCH_2CH_2COOH}$ | $HOOCCH_2CH_2\underset{NH_2}{CHCO--NHCHCH_2CH_2COOH}$ | Pd Black | -------- | Quant. | -------- | --------- | 37 |

(no. 6,10) are employed.

2. In secondary amines of structure, $C_6H_5CH_2$-NH-R, no hydrogenolytic debenzylation will take place if R:

   a) is a methyl group (no. 9).

   b) is an acetonaphthone group (no. 18).

   c) is methyl substituted with a dihydrobenzofurylcarbinol residue (cf. product no. 80).

   d) is aromatic and is reduced to a hydroaromatic radical before debenzylation takes place (no. 13).

3. Dibenzylamine is not debenzylated (no. 8) unless one of the benzyl groups is substituted, e.g., anisyl (no. 20) or, possibly, piperonyl (no. 21).

4. In secondary amines of structure, $C_6H_5CH_2$-NH-R, the benzyl group is removed as toluene, and a primary amine, $RNH_2$ is formed if R:

   a) is a longer chain (branched?) alkyl group (no. 11).

   b) bears an alcoholic hydroxyl group (no. 15).

   c) bears a carboxyl group (no. 16,17).

   d) is a $\beta$-indolyl radical (no. 12).

   e) is an aromatic group and is not converted into a hydroaromatic radical before hydrogenolysis takes place (no. 19).

   f) is phenacyl or substituted phenacyl (no. 17a,77a,77b). It is assumed that nos. 77a and 77b pass through the monobenzyl or secondary amine stage.

      Note: This is in apparent conflict with Rules 2b and 8a. It is indeed striking that when $\beta$-naphthyl nucleus replaces phenyl or substituted phenyl the hydrogenolytic debenzylation should be so greatly inhibited.

5. In amines of structure, AR.$CH_2$-NH-$CH_2$.AR', the group 'AR.$CH_2$-

will be preferentially removed if AR' is a hydroxyphenyl group and AR is a methoxyphenyl group (no. 22,56).

6. Tertiary amines of structure, $C_6H_5CH_2-N(R)(R')$, will be debenzylated to form secondary amines, $H-N(R)(R')$:
   a) if R and R' are both aliphatic (no. 31-43 inclusive).
   b) if R is aromatic and R' is aliphatic (no. 24,25,28,83).
   c) if R is aliphatic and R' is an aracyl ketone such as acetophenone or propiophenone (no. 19,62-71 inclusive).
   d) if R and R' with the N form a heterocycle (no. 82,83,84,86, 89), and reduction to a hydroaromatic radical does not take place (no. 85).
7. Tertiary amines of structure, $(C_6H_5CH_2)_2-N-R$, will form secondary amines, $C_6H_5CH_2-NH-R$; the secondary amine will then behave according to Rules 2 or 4 (no. 29,30,87,88,90).
8. In tertiary amines of structure, $AR.CH_2-NR-CH_2.AR'$:
   a) if R is an acetonaphthone group and AR and AR' are phenyl, no catalytic debenzylation takes place (no. 79).
   b) if AR is p-methoxyphenyl and AR' is o-methoxyphenyl, or AR' is m-methoxyphenyl, and R is alkyl, approximately equal amounts of methoxybenzylalkylamines are formed (no. 53,54).
9. In amines of structure, $C_6H_5CH_2-NR-CH_2C_6H_4X$:
   a) the unsubstituted benzyl group will be preferentially removed, giving the substituted benzylamine, $XC_6H_4CH_2-NH-R$, if X is methyl (no. 44), chloro (no. 45), nitro (no. 46), amino (no. 48), or methoxyl (no. 55).
   b) the substituted benzyl group will be preferentially removed if the substituted benzyl group is a menaphthyl group (no. 50).

10. In quarternary ammonium salts:

    a) if one benzyl group is present it will be removed (no. 91,94).

    b) if three benzyl groups are present as in $(C_6H_5CH_2)_3N-CH_3X$;

        1) none will be removed if X is an iodide ion (no. 93).

        2) two benzyl groups will be removed if X is a hydroxyl ion (no. 92).

The following generalizations are apparent from the data in Table II:

1. The benzyl groups will be smoothly and readily removed from benzyl alkyl and benzyl aryl ethers by means of hydrogenolytic clevage (no. 1-22 inclusive).

2. Benzyl alcohols are debenzylated, i.e., the hydroxyl group is removed:

    a) from benzyl alcohol (no. 23).

    b) from aryl substituted benzyl alcohol (no. 24).

    c) from mono α-substituted benzyl alcohols

    (no. 25,29,30,31,32,33,34,35,36,37,40,41).

    Note: In Table II, the substances reduced are listed as ketones, however, these pass through the benzyl alcohol stage, which is debenzylated (cf. note 4 in reference 24).

    d) from α-cyano or α-carboxy benzyl alcohols (mandelonitriles or mandelic acids), if the hydroxyl group is acylated (no. 46-50 inclusive).

    e) from a vinylog of benzyl alcohol (no. 28).

3. Benzyl alcohols are not debenzylated, i.e., the hydroxyl group is not removed:

    a) when a branched alkyl chain is present (no. 26,27).

    b) when a hydroxyalkyl group exerts a stabilizing influence (no. 38).

c) when the substituent in the alpha position is a phenyl or substituted phenyl group and reduction to the hydroaromatic stage occurs before catalytic hydrogenolysis (no. 39).

d) from α-cyano benzyl alcohols if an ortho aryl substituent is present (no. 42,43,44).

# EXPERIMENTAL

## Synthesis of Ketones

Acetophenone. Acetophenone was prepared in a yield of 80 percent by the Friedel-Crafts reaction using the procedure described in Organic Syntheses (106).

Phenacyl Chloride. Phenacyl chloride was prepared by the Friedel-Crafts reaction using the procedure described by Levin (59). From 645.4 g. (4.84 moles) anhydrous aluminum chloride, 334.0 cc. (4.4 moles) chloroacetyl chloride and 1666.0 cc. dry benzene (excess benzene serving as the solvent) there was obtained 510.0 g. (75 percent) of phenacyl chloride; m.p. 56-57 degrees.

p-Hydroxyphenacyl Chloride. p-Hydroxyphenacyl chloride was prepared by a Friedel-Crafts reaction on anisole. The method is as follows (59):

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, 48.2 cc. (0.626 mole) chloroacetyl chloride (E.K. Co.) and 1000 cc. ligroin (E.K. Co., practical). The reaction flask was immersed in a bath of water (40-45 degrees) and during the course of forty-five minutes, 90.0 g. (0.675 mole) anhydrous aluminum chloride was added to the rapidly stirred mixture. After all of the aluminum chloride had been added, the mixture was heated in the water bath for an hour; stirring of the reactants and removal of the hydrogen chloride being continu-

ed. The temperature of the bath was then raised to 50-55 degrees and during the course of an hour a second portion of 90.0 g. (0.675 mole) anhydrous aluminum chloride, was further added. Then the bath was heated to boiling and the solvent recovered under reduced pressure (water-pump) during the course of one and one-half to two hours; the condenser remaining in the reflux position. When practically all of the ligroin had been 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 dark purple, tarry mixture thus obtained was allowed to stand overnight and then extracted with six 300 cc. portions of ether. The ethereal extracts were combined, washed with 200 cc. cold water, 250 cc. of a 5 percent solution of ammonium carbonate and then with six 400 cc. portions of a 10 percent sodium carbonate solution to remove the p-hydroxyphenacyl chloride. The alkaline extracts were then treated individually with excess concentrated hydrochloric acid to precipitate the crude product. The precipitated products thus obtained were allowed to stand overnight in the refrigerator; these were then filtered off and dried with suction. Recrystallization from 80 percent ethanol with the addition of 3.0 g. of charcoal yielded 30.0 g. (31.6 percent) of p-hydroxyphenacyl chloride; m.p. 147-148 degrees (dec).

3,4-Dihydroxyphenacyl Chloride. 3,4-Dihydroxyphenacyl chloride was prepared by a modification of the method described by Ott (107). The method is as follows (108):

A mixture of 83.3 g. (0.4 mole) of phosphorous pentachloride and 42.5 g. (0.45 mole) of chloroacetic acid was allowed to reflux on a

boiling water bath for three hours. The clear solution thus obtained was distilled and the portion distilling over up to 115 degrees was added to a suspension of 44.0 g. (0.4 mole) of catechol in 200 cc. of dry benzene. After refluxing the mixture on a boiling water bath for fifteen hours, the sovent was recovered by distillation, using reduced pressure toward the end. The dark purple residue thus obtained was then dissolved in 400 cc. of boiling water; on 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 5.0 g. of Nuchar gave 45.8 g. (70.6 percent) of colorless needles decomposing at 173 degrees.

3,4-Diacetoxyphenacyl Chloride. In an attempt to determine the optimum conditions necessary for the condensation of benzylamine with 3,4-dihydroxyphenacyl chloride, it was decided that possibly 3,4-diacetoxyphenacyl chloride would prove more satisfactory.

It was observed that if the acetylation of 3,4-dihydroxyphenacyl chloride was carried out using only acetic anhydride, good yields of 3,4-diacetoxyphenacyl chloride were obtained; and if the acetylation was carried out using acetic anhydride and potassium acetate, 3,4-diacetoxyphenacyl acetate was obtained as reported by Voswinckel (122).

However, it was a distinct surprise to find, if the acetylation was carried out using acetic anhydride and sodium acetate, the chlorine was replaced by hydrogen and the product obtained was 3,4-diacetoxyacetophenone.

This difference between the reaction of the potassium and sodium salts and such replacement of an organic chlorine atom by hydrogen is

anomalous and completely unexpected for no similar reaction seems to be reported.

Experiment No. 1: A mixture of 37.4 g. (0.2 mole) of 3,4-dihydroxyphenacyl chloride and 100 cc. (1.06 moles) of acetic anhydride was refluxed for approximately thirty minutes and then poured onto cracked ice. The crude product, 3,4-diacetoxyphenacyl chloride, which was precipitated, was recrystallized from ethanol and a yield of 50.0 g. (92.5 percent) of white crystals, m.p. 110 degrees, was obtained. Analysis (Parr bomb): Calculated for $C_{12}H_{11}O_5Cl$ : Cl, 13.12 percent. Found: Cl, 12.83 percent; 12.85 percent.

Experiment No. 2: A mixture of 10.0 g. (0.0534 mole) of 3,4-dihydroxyphenacyl chloride, 7.5 g. (0.076 mole) of potassium acetate and 50 cc. (0.53 mole) of acetic anhydride was refluxed for approximately thirty minutes and then poured onto cracked ice. After standing overnight in the refrigerator the crude product was filtered off. On recrystallization from a mixture of water and glacial acetic acid 13.0 g. (82.80 percent) of sand colored crystals, m.p. 94-95 degrees, were obtained. This agrees with the melting point reported for 3,4-diacetoxyphenacyl acetate (122). A mixed melting point with pure 3,4-dihydroxyphenacyl chloride showed a depression and another mixed melting point with pure 3,4-diacetoxyacetophenone showed a depression of 10 degrees.

Experiment No. 3: A mixture of 18.7 g. (0.1 mole) of 3,4-dihydroxyphenacyl chloride, 10.0 g. (0.122 mole) of sodium acetate and 25 cc. (0.265 mole) of acetic anhydride was refluxed for approximately thirty minutes and then poured onto cracked ice. A yellow oil which soon solidified was formed. On recrystallization from ethanol 23.0 g. of cream colored crystals, m.p. 87-88 degrees, were obtained. This in-

dicated that 3,4-diacetoxyacetophenone had been obtained in a yield of 97.5 percent. Further proof was obtained when the above compound was hydrolyzed with dilute hydrochloric acid; 3,4-dihydroxyacetophenone, m.p. 116 degrees, was isolated.

When this experiment was repeated using the same quantities of reagents, identical results were obtained.

Synthesis of Amines

Benzylamine. The method described by Galat and Elion (109) was employed for the preparation of this amine.

In a 4-liter beaker was dissolved 140.19 g. (1 mole) of hexamethylenetetramine in eight to ten times its weight of hot ethanol; then 164.9 g. (1.1 moles) of sodium iodide was added to the hot solution. Then 126.58 g. (1 mole) of benzyl chloride was added slowly and with stirring to the hot mixture when the addition product precipitated out. The addition product was hydrolyzed by passing in dry hydrogen chloride until the maximum amount of ammonium chloride was formed. The ammonium chloride was filtered off and the ethanol removed under reduced pressure. The residue was then treated with excess sodium hydroxide and extracted with ether; the ether solution was dried over solid potassium hydroxide. The ether was removed by distillation and 91.0 g. (85.0 percent) of benzylamine, b.p. 184.5 degrees, was obtained.

Benzhydrylamine. This amine was prepared from benzophenone oxime according to the method described by Jones and Hurd (110). The benzophenone oxime was prepared in a yield of 99.0 percent according to the method described in Organic Syntheses (111).

A suspension of 50.0 g. (0.253 mole) of benzophenone oxime in 500 cc. of absolute ethanol was poured onto 60.0 g. (2.6 atoms) of sodium in a 1-liter round-bottom flask, equipped with an efficient reflux condenser. The oxime dissolved at once and enough heat was generated to melt the sodium. Additional ethanol was added from time to time to keep the volume constant. After about an hour when all the sodium had dissolved

most of the ethanol was recovered by distillation and water was added to the residue. After partial neutralization of the alkaline solution the benzhydrylamine was extracted with ether and the ether solution dried over solid potassium hydroxide. The ether was removed by distillation and 40.0 g. (86.0 percent) of benzhydrylamine, $b.p._{15}$ 185 degrees, was obtained.

Nitrosation of Ketones

The general procedure developed by Levin and Hartung for the nitrosation of phenacyl halides was employed in the preparation of phenylglyoxylohydroxamyl chloride and 3,4-dihydroxyphenylglyoxylohydroxamyl chloride (108,112).

Phenylglyoxylohydroxamyl Chloride. Nitrosation of phenacyl chloride, 155.0 g. (1 mole), using 116.0 cc. (1.1 moles) of isopropyl nitrite in 1000 cc. of ether, yielded 152.0 g. (82.83 percent) of phenylglyoxylohydroxamyl chloride, after recrystallization from a 1:3 mixture of boiling benzene and carbon tetrachloride, m.p. 131-133 degrees.

3,4-Dihydroxyphenylglyoxylohydroxamyl Chloride. Nitrosation of 3,4-dihydroxyphenacyl chloride, 84.3 g. (0.45 mole), using 56.7 cc. (0.495 mole) of butyl nitrite suspended in 1800 cc. of ether (to which was added 13.5 cc. of water), yielded 66.0 g. (90.5 percent) of yellow crystals, m.p. 184-185 degrees with decomposition.

Nitrosation of Acetophenone. Since the isonitrosoacetophenones, if available, would be the ideal intermediates for the preparation of the arylethanolamines; and since present evidence (114,115,116) has indicated that nitrosyl chloride is the actual nitrosating agent in the following reaction:

$$AR.CO.CH_3 \xrightarrow[HCl]{RONO} AR.CO.C(:NOH)H$$

it was decided to investigate the reaction between acetophenone and nitrosyl chloride (prepared according to the method described by Franzen and Zimmerman (117)).

These investigators found that esters of nitrous acid react with acid chlorides according to the reaction:

$$R'ONO + Cl\text{-}CO\text{-}R \longrightarrow NOCl + R'\text{-}OCO\text{-}R$$

They proposed this method for generating nitrosyl chloride in situ.

The general procedure employed in the present investigation was as follows:

In a 100 cc., three-neck, round-bottom flask, provided with a sealed mechanical stirrer, a reflux condenser and a dropping funnel, was placed the ketone (0.1 mole) and the alkyl nitrite (0.1 mole) in 50 cc. of ether. The stirrer was set in motion and the acid chloride (0.1 mole) was added by means of the dropping funnel, in 0.5 cc. portions. After the addition of all of the acid chloride, stirring was continued for another hour, after which the reaction mixture was allowed to stand overnight. The ethereal solution was exhaustively extracted with a 5 percent solution of sodium hydroxide and the crude product precipatated from the alkaline extract by the addition of dilute hydrochloric acid. The crude products were then purified by recrystallization from hot water. The reaction was carried out at room temperature unless otherwise specified.

Experiment No. 1:

Acetophenone 12.0 g. (0.1 mole)

Isopropyl nitrite 9.4 cc. (0.1 mole)

Acetyl chloride 7.0 cc. (0.1 mole)

Hexyl ether 50 cc.

Five grams of acetophenone were recovered unchanged from the hexyl-ether and 2.0 g. of cream colored crystals, m.p. 122 degrees,

indicating benzoic acid, were isolated from the alkaline extract.

Experiment No. 2:

Acetophenone 12.0 g.

Isopropyl nitrite 9.4 cc.

Acetyl chloride 7.0 cc.

Ether 50 cc.

The reaction mixture was heated on a water bath until the ether refluxed gently and then the acetyl chloride was added in small portions. There was no noticeable color change for the first two hours, but during the third hour brown fumes of the oxides of nitrogen were evolved and the reaction mixture became cherry red, gradually changing to the original light yellow color. Five grams of acetophenone were recovered unchanged from the ether and 4.0 g. of product, m.p. 122 degrees, was isolated from the alkaline extract. An attempt was made to prepare the oxime, which failed; but the amide of the product melted at 128 degrees, indicating benzoic acid.

Experiment No. 3:

Acetophenone 12.0 g.

Isopropyl nitrite 9.4 cc.

Thionyl chloride 7.3 cc. (0.1 mole)

Ether 50 cc.

The reaction mixture began refluxing after the addition of 2.0 cc. of thionyl chloride and in fifteen minutes fumes of the oxides of nitrogen were observed. The color of the reaction mixture became cherry red and then light yellow (a white precipitate was observed at this point); the color then returned to cherry red

and became dark green overnight. An odor of sulfur dioxide was present and when the ethereal solution was extracted with sodium hydroxide a large amount of heat was generated, indicating that some thionyl chloride had not reacted. Four grams of acetophenone were recovered unchanged from the ether and 3.5 g. of glistening white crystals, m.p. 121-122 degrees, indicating benzoic acid, were isolated from the alkaline extract.

## Decomposition of Arylglyoxylohydroxamyl Halides to Carboxylic Acids

Since a previous worker in these Laboratories, Levin (59), had found that phenylglyoxylohydroxamyl chloride was readily decomposed by alkali into benzoic acid in good yields, it was decided to attempt to discover the optimum conditions necessary for the conversion of 3,4-dihydroxyphenylglyoxylohydroxamyl chloride to 3,4-dihydroxybenzoic acid. The method was as follows:

In a 250 cc. round-bottom flask, fitted with a reflux condenser, was placed 0.03 mole of the arylglyoxylohydroxamyl halide and from 50 to 100 cc. of water in which was dissolved approximately 0.1 mole of sodium hydroxide and various amounts of anti-oxidants. The reaction mixture was refluxed for about one to one and a half hours, after which all of the arylglyoxylohydroxamyl halide dissolved with the formation of an orange or red colored solution. After refluxing an additional hour, the reaction mixture was cooled and concentrated hydrochloric acid was added with stirring until no further precipitate was produced. The mixture was cooled and the crude product filtered off with suction and recrystallized from dilute ethanol.

### Decomposition of Phenylglyoxylohydroxamyl Chloride.

#### Experiment No. 1:

Ketone 5.46 g. (0.03 mole)

Sodium hydroxide 4.0 g. (0.1 mole)

Potassium sulphite 1.5 g. (0.01 mole)

Distilled water 50 cc.

The reaction mixture was refluxed until the isonitroso

compound had dissolved and the color had changed from orange to light amber. Two and three-tenths grams (65.4 percent) of benzoic acid, m.p. 121 degrees, were obtained.

Experiment No. 2:

Ketone 5.46 g. (0.03 mole)

Sodium hydroxide 4.0 g. (0.1 mole)

Potassium sulphite 3.0 g. (0.02 mole)

Distilled water 50 cc.

The reaction mixture was refluxed until the isonitroso compound had dissolved and the color had changed from orange to light amber. Three grams (82.0 percent) of benzoic acid, m.p. 121 degrees, were obtained.

Experiment No. 3:

Ketone 5.46 g. (0.03 mole)

Sodium hydroxide 2.0 g. (0.05 mole)

Sodium sulphite 1.26 g. (0.01 mole)

Distilled water 50 cc.

The reaction mixture was refluxed until the isonitroso compound had dissolved and a yellow oil was observed in the orange colored solution. Three and one-tenth grams of benzoic acid, m.p. 121 degrees, (84.75 percent) were obtained.

Experiment No. 4:

Ketone 5.46 g. (0.03 mole)

Sodium hydroxide 2.0 g. (0.05 mole)

Sodium sulphite 2.52 g. (0.02 mole)

Distilled water 50 cc.

The reaction mixture was refluxed until the isonitroso

compound had dissolved and a yellow oil was observed in the orange colored solution. Two and six-tenths grams (71.10 percent) of benzoic acid, m.p. 121 degrees, were obtained.

Experiment No. 5:

Ketone 5.46 g. (0.03 mole)

Sodium hydroxide 3.0 g. (0.075 mole)

Sodium sulphite 1.26 g. (0.01 mole)

Distilled water 50 cc.

The reaction mixture was refluxed until the isonitroso compound had dissolved and the color had changed from orange to light amber. Three grams (82.0 percent) of benzoic acid, m.p. 121 degrees, were obtained.

Experiment No. 6:

Ketone 5.46 g. (0.03 mole)

Sodium hydroxide 3.0 g. (0.075 mole)

Sodium sulphite 2.52 g. (0.02 mole)

Distilled water 50 cc.

The reaction mixture was refluxed until the isonitroso compound had dissolved and the color had changed from orange to light amber. Two and eight-tenths grams (76.5 percent) of benzoic acid, m.p. 121 degrees, were obtained.

Decomposition of 3,4-Dihydroxyphenylglyoxylohydroxamyl Chloride.

Experiment No. 1:

Ketone 6.47 g. (0.03 mole)

Sodium hydroxide 3.0 g. (0.075 mole)

Distilled water 50 cc.

The reaction mixture became fiery red as soon as all the

reagents were mixed. After refluxing for three hours the mixture became brown and tarry. Nothing was precipitated on the addition of concentrated hydrochloric acid. The mixture was neutralized with sodium carbonate and then concentrated on a steam bath. It was impossible to isolate or identify any product from the brown, viscid residue.

Experiment No. 2:

Ketone 6.47 g. (0.03 mole)

Sodium hydroxide 3.0 g. (0.075 mole)

Sodium sulphite 1.26 g. (0.01 mole)

Distilled water 50 cc.

The reaction mixture became fiery red as soon as all the reagents were mixed. After refluxing for three hours the mixture became brown and tarry. Nothing was precipitated on the addition of concentrated hydrochloric acid. The mixture was concentrated on a steam bath in an effort to isolate any products. It was impossible to isolate or identify any product from the brown, tarry residue.

Condensation of Aracyl Chlorides with Amines

ω-Benzylaminoacetophenone Hydrochloride. In a 250 cc., glass-stoppered Erlenmeyer flask was placed 21.4 g. (0.2 mole) of benzylamine in 150 cc. of dry ether; then 15.0 g. (0.1 mole) of phenacyl chloride was added in small portions with shaking. After standing overnight the precipitated benzylamine hydrochloride was filtered off and washed with 25 cc. of dry ether. Absolute ethanolic hydrogen chloride was added to the filtrate to precipitate the amino ketone hydrochloride. The resulting precipitate was recrystallized from absolute ethanol and ether and 19 g. (72.75 percent) of white crystals, m.p. 215-219 degrees (red effervescent melt), was obtained. This melting point agreed with the melting point of ω-benzylaminoacetophenone hydrochloride reported in Beilstein (119).

ω-Dibenzylamino-p-hydroxyacetophenone Hydrochloride. In a 500 cc., three-neck, round-bottom flask provided with a sealed mechanical stirrer, a reflux condenser and a dropping funnel was placed 6.0 g. (0.0405 mole) of p-hydroxyphenacyl chloride in 75 cc. of absolute ethanol. The stirrer was set in motion and the mixture warmed on a water bath until the p-hydroxyphenacyl chloride dissolved with the formation of a light tan color. Then 16.0 g. (0.081 mole) of dibenzylamine was added through the dropping funnel in 0.5 cc. portions. After the first addition of dibenzylamine the color changed to dark red and the mixture warmed up moderately, but not enough to cause the ethanol to reflux. The reaction mixture was then refluxed on a water bath for four hours, after which the mixture was allowed to stand overnight. The precipitated dibenzyl-

amine hydrochloride was filtered off and the ethanol was completely removed under reduced pressure. The residue was taken up in 150 cc. of warm ether and the ethereal solution was washed with water to remove any trace of dibenzylamine hydrochloride. The ether was removed and an uncrystallizable oil was obtained; the oil was taken up in hot chloroform and filtered through a filter paper wet with chloroform to remove the water present. The chloroformic solution was cooled and absolute ethanolic hydrogen chloride added to precipitate the amino ketone hydrochloride. The resulting precipitate was recrystallized from absolute ethanol and ether and 11.5 g. (77.25 percent) of white crystals, m.p. 239-241 degrees with decomposition, were obtained. Analysis (Kjeldahl): Calculated for $C_{22}H_{22}O_2NCl$: N, 3.82 percent. Found: N, 3.79 percent; 3.81 percent.

Attempted Preparation of ω-Benzylamino-3,4-dihydroxyacetophenone.

Experiment No. 1: In a 250 cc., glass-stoppered Erlenmeyer flask was placed 10.7 g. (0.1 mole) of benzylamine in 50 cc. of absolute ethanol; then a suspension of 9.3 g. (0.05 mole) of 3,4-dihydroxyphenacyl chloride in 100 cc. of absolute ethanol was added in small portions with shaking. A precipitate developed immediately and 7.0 g. of white crystals, m.p. 250 degrees (benzylamine hydrochloride), were filtered off. The filtrate was concentrated under reduced pressure and absolute ethanolic hydrogen chloride was added in an effort to precipitate the amino ketone hydrochloride. Three grams of white crystals, m.p. 252 degrees, were obtained, which proved to be benzylamine hydrochloride. No other products could be isolated from this type of condensation.

Experiment No. 2: In a 250 cc., glass-stoppered Erlenmeyer flask

was placed 5.35 g. (0.05 mole) of benzylamine in 100 cc. of dioxane; then 4.65 g. (0.025 mole) of 3,4-dihydroxyphenacyl chloride was added in small portions with shaking. A dark yellowish-green precipitate developed immediately, before all of the 3,4-dihydroxyphenacyl chloride was in solution. The precipitate was filtered off and after recrystallization from ethanol 3.0 g. of glistening tan crystals melting at 130-132 degrees with decomposition were obtained. This product could not be further identified. Absolute ethanolic hydrogen chloride was added to the filtrate in an attempt to obtain further products. Two and seven-tenths grams of white crystals, m.p. 252 degrees (benzylamine hydrochloride), were obtained.

Experiment No. 3: In a 250 cc., glass-stoppered Erlenmeyer flask was placed 5.35 g. (0.05 mole) of benzylamine in 25 cc. of dry benzene; then 7.0 g. (0.025 mole) of 3,4-diacetoxyphenacyl chloride in 50 cc. of dry benzene was added in small portions with shaking. The reaction mixture warmed up and the color changed from light tan to dark reddish-brown. After standing overnight in the refrigerator a creamy tan precipitate which formed was filtered off and recrystallized from ethanol. Three and five-tenths grams of glistening tan crystals melting at 130-132 degrees with decomposition (identical with the product obtained in Experiment No. 2) were obtained. Absolute ethanolic hydrogen chloride was added to the filtrate in an attempt to obtain further products. Three grams of white crystals, m.p. 252 degrees (benzylamine hydrochloride), were obtained.

Attempted Preparation of ω-Benzhydrylamine-3,4-dihydroxyacetophenone.

To 7.0 g. (0.025 mole) of 3,4-diacetoxyphenacyl chloride in 75 cc. of absolute ethanol was added 9.17 g. (0.05 mole) of benzhydrylamine and

the mixture was refluxed for three hours. The ethanol was completely removed under reduced pressure and 100 cc. of dry ether was added. The precipitated benzhydrylamine hydrochloride (3.5 g.) was filtered off and washed with dry ether. The ether solutions were combined and throughly shaken with 10 percent hydrochloric acid. A black, oily tar developed from which nothing could be isolated.

ω-Dibenzylamino-3,4-dihydroxyacetophenone Hydrochloride. In a 500 cc., three-neck, round-bottom flask provided with a sealed mechanical stirrer, a reflux condenser and a dropping funnel was placed 18.6 g. (0.1 mole) of 3,4-dihydroxyphenacyl chloride in 100 cc. of absolute ethanol. The stirrer was set in motion and the mixture warmed on a water bath until the ketone had dissolved with the formation of a light purple color. Then 39.4 g. (0.2 mole) of dibenzylamine (E.K. Co.) was added through the dropping funnel in 0.5 cc. portions. After the first addition of dibenzylamine the color changed to dark brown and the mixture warmed up moderately, but not enough to cause the ethanol to reflux. The reaction mixture was then refluxed on a water bath for six hours, after which the mixture was allowed to stand overnight. The precipitated dibenzylamine hydrochloride was filtered off and the ethanol was completely removed under reduced pressure. The residue was taken up in 200 cc. of warm ether and the ethereal solution was washed with water to remove any trace of dibenzylamine hydrochloride. The ether was removed and the crude product recrystallized from dilute ethanol. Thirty two grams (92.25 percent) of white crystals, m.p. 165 degrees with decomposition, were obtained. Analysis (Kjeldahl): Calculated for $C_{22}H_{21}O_3N$ : N, 4.03 percent. Found: N, 3.92 percent; 3.94 percent.

The free base was dissolved in absolute ethanol and absolute

ethanolic hydrogen chloride was added to precipitate the ω-dibenzylamino-3,4-dihydroxyacetophenone hydrochloride, m.p. 203-205 degrees with decomposition.

Reduction of Benzylamino Ketones

Preparation of Catalyst. The palladium-charcoal catalyst was prepared by a modification of the general procedure described by Hartung (32,51).

A suspension of 0.3 g. of palladium chloride and 3.0 g. of Nuchar (Industrial Chemical Sales) in 100 cc. of a 1 N solution of sodium acetate was shaken in an atmosphere of hydrogen until saturated. The palladinized charcoal thus obtained was filtered off, washed several times with distilled water, followed by ethanol, and dried with suction. In some instances, the highly active catalyst began to glow on drying and even ignited; the glow was quenched with water and the catalyst dried in a vacuum desiccator overnight.

ω-Aminoacetophenone Hydrochloride. To 6.53 g. (0.025 mole) of ω-benzylaminoacetophenone hydrochloride, dissolved in 100 cc. of absolute ethanol, was added 3.0 g. of catalyst. The reduction mixture was shaken at room temperature under one hundred pounds pressure for three hours when one mole of hydrogen had been absorbed. The catalyst was filtered off and the ethanol removed under reduced pressure. On recrystallization of the crude product from absolute ethanol and ether 3.75 g. (88.2 percent) of white crystals, m.p. 182 degrees with decomposition, were obtained. The product reduced Fehlings solution and formed an N-benzoyl derivative, m.p. 123-124 degrees, thus indicating the product obtained was ω-aminoacetophenone hydrochloride.

Phenylethanolamine Hydrochloride. To 6.53 g. (0.025 mole) of

ω-benzylaminoacetophenone hydrochloride, dissolved in 100 cc. of distilled water, was added 3.0 g. of catalyst. The reduction mixture was shaken at room temperature under one hundred pounds pressure for one hour when two moles of hydrogen had been absorbed. The catalyst was filtered off and the water removed under reduced pressure. On recrystallization of the crude product from absolute ethanol and ether, 3.8 g. (87.75 percent) of white crystals, m.p. 211-212 degrees, were obtained. The product formed an N-benzoyl derivative, m.p. 145-146 degrees, indicating phenylethanolamine hydrochloride.

p-Hydroxyphenylethanolamine Hydrochloride. To 4.6 g. (0.0125 mole) of ω-dibenzylamino-p-hydroxyacetophenone hydrochloride, dissolved in 100 cc. of 95 percent ethanol, was added 3.0 g. of catalyst. The reduction mixture was shaken at room temperature under one hundred and fifty pounds pressure for one hour when three moles of hydrogen had been absorbed. The catalyst was filtered off and the ethanol removed under reduced pressure. On recrystallization of the crude product from absolute ethanol and ether, 2.0 g. (85.8 percent) of greyish-white crystals, decomposing at 168-170 degrees in an effervescent melt, were obtained. The product formed a dibenzoyl derivative, m.p. 210 degrees, indicating p-hydroxyphenylethanolamine hydrochloride.

ω-Amino-3,4-dihydroxyacetophenone. To 9.5 g. (0.025 mole) of ω-dibenzylamino-3,4-dihydroxyacetophenone hydrochloride, suspended in 150 cc. of distilled water, was added 3.0 g. of catalyst. The reduction mixture was shaken at room temperature under one hundred and fifty pounds pressure for five hours when two moles of hydrogen had been absorbed. The catalyst was filtered off and the solution was concentrated

over concentrated sulfuric acid, soda lime and anhydrous calcium chloride in an evacuated desiccator, to approximately one-tenth of the original volume. The concentrated solution was throughly chilled and 28 percent ammonia was added drop by drop until the solution was just neutral. The crude product was filtered off and washed throughly with cold water and ethanol. The product was dried over phosphorous pentoxide and 3.5 g. (85.0 percent) of pinkish-white crystals, m.p. 235 degrees with decomposition, were obtained. This evidence agrees with the melting point reported for ω-amino-3,4-dihydroxyacetophenone (120).

3,4-Dihydroxyphenylethanolamine Hydrochloride. To 4.0 g. (0.011 mole) of ω-dibenzylamino-3,4-dihydroxyacetophenone hydrochloride, suspended in 75 cc. of distilled water, was added 3.0 g. of catalyst. The reduction mixture was shaken at room temperature under one hundred and fifty pounds pressure for one and one-half hours when three moles of hydrogen had been absorbed. The catalyst was filtered off and the solution evaporated to dryness over concentrated sulfuric acid, soda lime and anhydrous calcium chloride in an evacuated desiccator. An attempt was made to recrystallize the crude product from absolute ethanol and ether, but the product proved to be too hygroscopic. The partially purified product was dried over phosphorous pentoxide and 2.0 grams (88.5 percent) of tan crystals, m.p. 137 degrees with decomposition, were obtained. This evidence agrees with the melting point reported for 3,4-dihydroxyphenylethanolamine hydrochloride (121).

## Reduction Studies on Phenylglyoxylohydroxamyl Chloride

Earlier studies on the hydrogenation of phenylglyoxylohydroxamyl chloride showed that if four molecules of hydrogen are taken up, the yield of phenylethanolamine, isolated as the hydrochloride, is substantially quantitative (59,60). Unfortunately, the reduction rarely continues to completion even if the catalyst is fortified during the hydrogenation (60). If the products at the intermediate stages are isolated, they apparently undergo change since it has thus far been impossible to reduce them further (60).

As Levin observed (59), the first two moles of hydrogen, or half of theory, are taken up with comparative ease. If the catalyst and solvent are removed at this stage, the product, treated with ammonia, forms quantitative yields of crude diphenylpyrazine. This observation suggested that the intermediary reduction product contains at least the structure, $C_6H_5-\overset{\overset{O}{\|}}{C}-\overset{|}{C}-\overset{|}{N}-$ .

The third molecule of hydrogen is taken up at a much slower rate. The material isolated at this stage no longer forms diphenylpyrazine, but it has not been further identified. Presumably it also undergoes rearrangement since it has been impossible to reduce it further to phenylethanolamine.

From the behavior of the reduction reactions, especially the marked changes in rate of hydrogenation when one, two and then three molecules of hydrogen have been taken up, it was assumed that the reduction proceeded in definite stages. Further work, as discussed below, shows this view to be untenable.

In an effort to learn more about the mechanism of the hydrogenation reactions, experiments were carried out to follow the fate of the nitrogen atom in the original phenylglyoxylohydroxamyl chloride.

Preparation of Catalysts. The palladium-charcoal catalysts were prepared by a modification of the general procedure described by Hartung (32,51,59).

Reduction Mixture. The mixture was prepared by dissolving the phenylglyoxylohydroxamyl chloride in absolute ethanol containing three equivalents of hydrogen chloride. The apparatus used was essentially that described by Hartung and others (32,59).

Isolation of Reduction Products. The products from the reductions were 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.

Experiment No. 1:

Ketone 9.1 g. (0.05 mole)

Catalyst 3.0 g.

The reduction required approximately forty-eight hours for completion; the first two moles of hydrogen were taken up rapidly and the last two with great difficulty. The crystals isolated, after recrystallization from absolute ethanol and ether, melted at 212 degrees indicating that the reduction was complete, for phenylethanolamine hydrochloride was obtained.

Experiment No. 2:

Ketone 9.1 g. (0.05 mole)

Catalyst 3.0 g.

The first mole of hydrogen was taken up rapidly; the second with more difficulty and the reduction then ceased. The product isolated, on treatment with ammonia, yielded diphenylpyrazine, m.p. 195.5 degrees.

Experiment No. 3:

Ketone 9.1 g. (0.05 mole containg 0.7 g. N)

Catalyst 3.0 g.

The reduction stopped after two moles of hydrogen had been taken up in approximately twelve hours. Seven and twenty-five hundredths grams of crude product was isolated. Analysis (Kjeldahl) showed 10.9 percent nitrogen or 0.78 g. (?) of nitrogen.

Note: The product remaining after removal of the ethanol was not homogeneous but consisted of crystals contaminated with an oily material. It is not presumed that the sample taken for analysis was representative. However, it does appear from the high N value that probably none of the nitrogen originally present in the chloroisonitrosoketone was lost by volatilization of the solvent.

Experiment No. 4:

Ketone 9.1 g. (0.05 mole containing 0.7 g. N)

Catalyst 3.0 g.

The reduction ceased after two moles of hydrogen had been taken up in about eight hours. Seven and three-quarters grams of crude product was isolated. Analysis (Kjeldahl) showed 10.4 percent nitrogen or 0.81 g. (?) of nitrogen. Again probably all of the nitrogen was accounted for.

Experiment No. 5:

Ketone 9.1 g. (0.05 mole containing 0.7 g. N)

Catalyst 3.0 g.

The first two moles of hydrogen were taken up with ease and after new catalyst had been added the reduction proceeded until the third mole was absorbed. Eight and eight-tenths grams of crude product was isolated. Analysis (Kjeldahl) showed 9.95 percent nitrogen or 0.875 g. (?) of nitrogen.

Note: Here, as in the experiments where only half of the theoretical hydrogen was taken up, the product was not homogeneous and the method of selecting the sample for analysis was at fault. But as before, it is believed that the result indicates that none of the nitrogen was lost.

Experiment No. 6:

Ketone 9.1 g. (0.05 mole)

Catalyst 3.0 g.

The first two moles of hydrogen were taken up in approximately two hours, after which 50 cc. of distilled water was added and the third mole absorbed in four more hours; new catalyst was added and the reduction went to completion in another twenty-four hours. Six and one-half grams of crude product was isolated (74.97 percent of the theoretical). After recrystallization from absolute ethanol and ether, 3.5 g. (40.36 percent) of white crystals, melting at 211.5 degrees; and forming a picrate, m.p. 157.5 degrees, was obtained. This evidence indicates that phenylethanolamine hydrochloride was obtained.

These results encouraged the thought that perhaps the addition of water at the "half-way" stage might make complete reduction possible. Unfortunately, repeat experiments under these condition gave erratic results.

Experiment No. 7:

Ketone 9.1 g. (0.05 mole containing 0.7 g. N)

Catalyst 3.0 g.

The first mole of hydrogen was taken up rapidly; the second with more difficulty and then the reduction ceased. Seven grams of crude product was obtained. After washing with ether, the ether insoluble fraction weighed 2.5 g. Analysis (Kjeldahl) of the crystalline ether insoluble fraction showed 8.65 percent nitrogen. This product was taken up in hot ethanol and again crystallized, after which it melted at 257-259 degrees with decomposition; did not form a pyrazine on treatment with ammonia or form a benzoyl derivative. Analysis (Kjeldahl) showed 8.24 percent nitrogen and analysis (Parr bomb) showed 25.72 percent chlorine.

The ether was evaporated from the ether soluble fraction and 1.5 g. of orange yellow crystals contaminated with an oily material were obtained. The crystals were removed on a filter and dried with suction. Three-quarters of a gram of white crystals, m.p. 133 degrees, were obtained. A mixed melting point of these crystals with pure phenylglyoxylohydroxamyl chloride showed no depression. Analysis (Parr bomb): Calculated for $C_8H_6O_2NCl$ : Cl, 19.35 percent. Found: Cl, 17.87 percent; 17.92 percent. The small amount of orange oil obtained showed 5.84 percent chlorine on analysis (Parr bomb). This oil was not further identified.

Experiment No. 8:

Ketone 9.1 g. (0.05 mole containing 0.7 g. N)

Catalyst 3.0 g.

The first mole of hydrogen was taken up rapidly; the second with more difficulty and the reduction ceased. Seven and two-tenths grams of crude product was obtained. After washing with

ether, the ether insoluble fraction weighed 2.35 g. Analysis (Kjeldahl) of the crystalline ether insoluble fraction showed 7.92 percent nitrogen.

The ethereal washing was evaporated leaving 1.3 g. of orange yellow crystals contaminated with an oily material. The crystals were removed on a filter and dried with suction. One-half gram of white crystals, m.p. 133 degrees, were obtained. A mixed melting point of these crystals with pure phenylglyoxylohydroxamyl chloride showed no depression. Analysis (Parr bomb): Calculated for $C_8H_6O_2NCl$ : Cl, 19.35 percent. Found: Cl, 18.24 percent; 18.31 percent. The small amount of orange oil obtained was not identified.

These results show that the hydrogenation of phenylglyoxylohydroxamyl chloride to phenylethanolamine does not proceed in clear-cut stages as had been assumed; for as shown in Experiments No. 7 and No. 8 approximately ten percent of the unchanged starting material was recovered even though the uptake of hydrogen had stopped when approximately two moles had been used. It has not been established whether the partially hydrogenated material has an anti-catalytic effect on the hydrogenation of the phenylglyoxylohydroxamyl chloride (123).

The results do, however, confirm a previous assumption that if an attempt is made to isolate the products formed by partial hydrogenation, they undergo rearrangement, forming two or more compounds, none of which has been characterized but none of which may be converted into the desired phenylethanolamine.

## SUMMARY

1. The reaction of nitrosyl chloride with acetophenone was examined with the hope that isonitrosoacetophenone might be formed in better yields. The only materials identified were unchanged acetophenone and benzoic acid.

2. Since Levin found that good yields of benzoic acid could be obtained by the alkaline decomposition of phenylglyoxylohydroxamyl chloride, it was deemed advisable to apply this reaction to 3,4-dihydroxyphenylglyoxylohydroxamyl chloride in the hope that this might prove a satisfactory route to the synthesis of protocatechuic acid. However, the alkaline conditions caused complete destruction of the intermediate, and from the product none of the desired 3,4-dihydroxybenzoic acid could be isolated.

3. Additional studies were made on the catalytic hydrogenation of phenylglyoxylohydroxamyl chloride. No explanation has as yet been found for the occasional complete reduction of the intermediate and the quantitative formation of phenylethanolamine; more frequently hydrogenation ceases, under presumably identical conditions, after two, or sometimes three, moles of hydrogen have been taken up. Although it is possible, apparently, to follow the fate of the nitrogen atom of the original phenylglyoxylohydroxamyl chloride, the products isolated at the intermediary stages were not homogeneous. For example, at the half-way stage the product consisted of unchanged phenylglyoxylohydroxamyl chloride, another crystalline product, which has not been identified and cannot be further hydrogenated to phenylethanolamine, and an unidentified

oil.

These results indicate:

a) That the hydrogenation does not proceed in definite stages as had been previously presumed.

b) That, if the product during the intermediary stages of hydrogenation is isolated, it undergoes rearrangement into compounds which are no longer amenable to conversion into phenylethanolamine.

4. Since catalytic debenzylation has recently come into greater use as a method for preparing various types of amines and other compounds, and since the information on this type of reaction is scattered throughout the literature, it was deemed advisable to collect and classify the available data. On the basis of a tabulation of these data certain generalizations appear which, it is hoped, may make it possible to predict whether or not a given compound may be expected from the catalytic debenzylation of an appropriate intermediate.

5. In view of the erratic results obtained during the reduction of phenylglyoxylohydroxamyl chloride, the possibility of synthesizing arylethanolamines by hydrogenolytic debenzylation of suitable intermediates was examined. Aracyl chlorides were allowed to react with benzylamine or dibenzylamine to form compounds of general structure, $AR.CO.CH_2-NH-CH_2C_6H_5$ and $AR.CO.CH_2-N(CH_2C_6H_5)_2$, respectively.

The monobenzyl derivative in which AR is non-phenolic, on being shaken with hydrogen in the presence of palladium catalyst, underwent debenzylation first, and subsequently the ketonic carbonyl grouping was reduced to the carbinol. If AR was phenolic the monobenzyl derivative was unsatisfactory for the formation of the corresponding arylethanol-

amines.

The dibenzyl derivatives are satisfactory intermediates for the synthesis of phenolic substituted arylethanolamines.

The following intermediates were prepared and converted, in good yields, into the corresponding arylethanolamines:

1) ω-benzylaminoacetophenone hydrochloride

2) ω-dibenzylamino-p-hydroxyacetophenone hydrochloride

3) ω-dibenzylamino-3,4-dihydroxyacetophenone hydrochloride.

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