

THE SYNTHESIS OF ALIPHATIC AMINOALCOHOLS  
OF PHARMACOLOGIC INTEREST

by  
Walter C. Gakenheimer<sup>Ph.D.</sup>

Thesis submitted to the Faculty of the Graduate School  
of the University of Maryland in partial  
fulfillment of the requirements for the  
degree of Doctor of Philosophy

1943

UMI Number: DP70163

All rights reserved

INFORMATION TO ALL USERS

The quality of this reproduction is dependent upon the quality of the copy submitted.

In the unlikely event that the author did not send a complete manuscript and there are missing pages, these will be noted. Also, if material had to be removed, a note will indicate the deletion.



UMI DP70163

Published by ProQuest LLC (2015). Copyright in the Dissertation held by the Author.

Microform Edition © ProQuest LLC.

All rights reserved. This work is protected against unauthorized copying under Title 17, United States Code



ProQuest LLC.  
789 East Eisenhower Parkway  
P.O. Box 1346  
Ann Arbor, MI 48106 - 1346

The author is greatly indebted and grateful to the following for their aid in making this work successful:

Dr. Walter H. Hartung, under whose direction this research was carried out;

Drs. Edgar B. Starkey and E. G. Vanden Bosche for their advice and suggestions;

Dr. Glenn E. Ulliot, who so willingly coöperated by carrying out the electrolytic reductions;

Mr. Wilson M. Whaley for his time and effort on the figures in this thesis;

Commercial Solvents Corporation and Carbide and Carbon Chemicals Corporation who supplied some of the compounds used in this research.

## TABLE OF CONTENTS

|   | Page |
|---|------|
| I. INTRODUCTION   | 1    |
| II. REVIEW OF THE LITERATURE                                  | 6    |
| A. Nitroparaffins and aliphatic nitroalcohols.                | 6    |
| B. Reduction of aliphatic nitroalcohols.                      | 10   |
| C. Pharmacology of the nitroparaffins.                        | 13   |
| D. Pharmacology of the aliphatic amines.                      | 16   |
| E. Pharmacology of the aliphatic aminoalcohols.               | 18   |
| III. EXPERIMENTAL PORTION                                     | 21   |
| A. Preliminary notes.   | 21   |
| B. Preparation of the nitroalcohols.                          | 22   |
| C. Stability experiments on nitroalcohols.                    | 26   |
| D. Preparation of catalysts.                                  | 29   |
| E. Catalytic reduction of the nitroalcohols.                  | 31   |
| a. Palladinized charcoal catalyst.                            | 31   |
| b. Palladinized barium sulfate catalyst.                      | 32   |
| c. Raney nickel catalyst - neutral medium.                    | 33   |
| d. Raney nickel catalyst - acid medium (acetic acid)          | 37   |
| e. Raney nickel catalyst - acid medium (oxalic acid)          | 41   |
| f. Raney nickel catalyst - acid medium (carbonic acid)        | 42   |
| g. General preparation of aliphatic aminoalcohols.            | 43   |
| F. Electrolytic reduction of 3-nitro-4-heptanol.              | 45   |
| G. Stability experiment on 5-amino-4-octanol.                 | 48   |
| H. Degradation of aliphatic aminoalcohols.                    | 49   |
| a. Attempted replacement of the hydroxyl group with hydrogen. | 49   |

|   |    |
|---|----|
| b. Attempted replacement of the hydroxyl group with chlorine.   | 49 |
| c. Oxidation of 5-amino-4-octanol.                              | 50 |
| I. The action of alkaloidal precipitants on 3-amino-4-heptanol. | 51 |
| IV. SUMMARY AND CONCLUSIONS.                                    | 53 |
| V. LITERATURE CITED.  | 55 |
| VI. VITA.   | 59 |
| VII. ABSTRACT   | 60 |

## LIST OF TABLES

|   | Page |
|---|------|
| 1. Toxicity of some nitroparaffins and aliphatic aminoalcohols.   | 20   |
| 2. Nitroalcohols synthesized.   | 25   |
| 3. Fractionation and nitrogen analysis of products from reduction of a tenth of a mole of 3-nitro-4-heptanol with Raney nickel in neutral medium.               | 39   |
| 4. Fractionation, nitrogen analysis and identification of products from reduction of a half of a mole of 5-nitro-4-octanol with Raney nickel in neutral medium. | 40   |
| 5. Aminoalcohols synthesized.   | 44   |

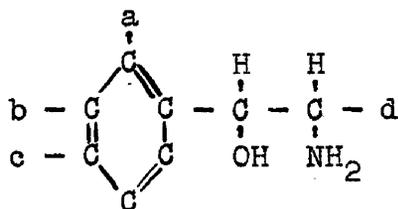
## LIST OF FIGURES

|   |    |
|---|----|
| I. Stability experiments on nitroalcohols.                  | 28 |
| II. Time-pressure curve of reduction of 3-nitro-4-heptanol. | 38 |

## I. INTRODUCTION

The synthesis and pharmacologic study of compounds structurally related to those capable of producing a rise in blood pressure have been investigated in these Laboratories in the past few years. All of this work involved variations on the basic compound - phenylpropanolamine - reported by Hartung and Munch (25) in 1929. Foster (19) worked with p-aminophenylpropanolamine. Dittrich (13) has synthesized and determined the pressor activity of phenylserine and its ethyl ester. The bases with halogen substitution on the aromatic ring have been investigated by Zenitz (75).

Diagrammatically, the following compounds are involved:



where - a is -F  
b is -F, -Cl  
c is -F, -Cl, -NH<sub>2</sub>  
d is -CH<sub>3</sub>, -COOH, -COOEt, -H

All of this work bears out the original statement of Barger and Dale (3) that pressor activity is found in compounds having the  $\beta$ -phenylethylamine skeleton. It

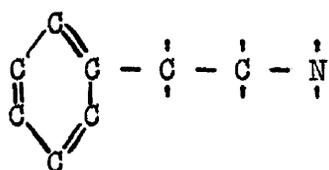
will be observed that all of the compounds contain an aromatic nucleus.

Recent work, however, indicates that the cycle need not be aromatic; for Gunn and Gurd (21) reported that there was no important qualitative pharmacologic difference between  $\beta$ -cyclohexylethylamine, also called  $\beta$ -hexahydrophenylethylamine, synthesized in 1938 by Reihlen, Knöpfle and Sapper (55), and  $\beta$ -phenylethylamine, the basic compound of Barger and Dale.

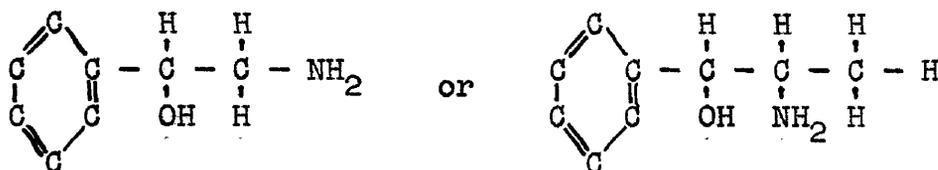
Barger and Dale (3), in their investigation of the open-chain primary aliphatic amines, reported pressor activity to begin with n-butylamine, to reach a maximum with n-hexylamine, and still be apparent in the higher homologs. This is confirmed by Alles (1). Tainter (67) found n-amylamine to be most active, but he did not study the higher homologs such as n-hexylamine. Chemically, cyclohexylethylamine is aliphatic in nature. Its pressor activity, therefore, might be expected in view of these observations.

Hexahydropropadrin, or 1-cyclohexyl-2-amino-1-propanol, has been synthesized by Hartung (24) and is known to effect a rise in blood pressure.

The work on  $\beta$ -cyclohexylethylamine and hexahydropropadrin raises several interesting questions. Viz., in the basic minimum skeleton postulated by Barger and Dale (3),



need the cycle be aromatic for optimum physiological properties or may the same activity, both quantitatively and qualitatively, be expected if the cycle is hydrogenated? If so, what will be the effect if the hydroaromatic ring is opened at various places in the molecule? In the aromatic series, an alcoholic hydroxyl group, as in



increases the pressor activity and decreases the toxicity; will the same hold true for the corresponding hydroaromatic aminoalcohols and for the corresponding alicyclic aminoalcohols?

In the series of aromatic aminoalcohols, activity is found in the aryethanolamines and arylpropanolamines, that is compounds composed of eight or nine carbon atoms in the skeleton. Accordingly, it appeared desirable to prepare for pharmacologic examination a series of aliphatic aminoalcohols also made up of eight or nine carbon atoms, and if possible of general structure  $\text{R}-\text{CHOH}-\text{CH}_2\text{NH}_2$  and  $\text{R}-\text{CHOH}-\text{CHNH}_2-\text{CH}_3$  in which R is some hexyl group, for example  $\text{CH}_3-(\text{CH}_2)_4-\text{CH}_2-$  or

$\text{CH}_3-(\text{CH}_2)_3-\text{CH}(\text{CH}_3)-$  . The close relationship of such compounds to the known pressor substances is seen in the following formulae:



Physiologically active compounds with hydrogenated rings retain their characteristic activity when the ring is opened according to a claim by Buth, Kùlz and Rosenmund (8). This idea is borne out still further by the statement of Blicke and Zienty (6) that the antispasmodic value of methyl-di- $\beta$ -cyclohexylethylamine is altered only quantitatively by opening the ring in the 1-2 position to produce methyldioctylamine. A third support is given by Barger and Dale (3) who observe that the physiological response of cyclohexylamine was slower in appearing and was more prolonged but otherwise resembled the pressor activity obtained with n-hexylamine.

The reduction of the nitroalcohols seemed to be the logical method of synthesizing these compounds. Nitroalcohols were first prepared by Henry (33) who condensed nitroparaffins with aldehydes:



This reaction has been improved and extended by Vanderbilt and Hass (72,74). Lower nitroparaffins are commercially available in unlimited amounts and at low cost, e.g., at twenty five cents per pound in tank-car lots.

The nitro group in the nitroparaffins, as well as in the aromatic compounds, may be easily reduced to the corresponding primary amino group (9). No difficulty, therefore, was anticipated in the conversion of the nitroalkanol intermediates into the corresponding aminoalkanols. In practically every instance, when a nitroalkanol was subjected to catalytic hydrogenation, the calculated amount of hydrogen was taken up and, when benzene was used as the solvent, the theoretical volume of water was isolated; however, very little or none of the desired product could be obtained except under the special conditions which are described. Accordingly, it became desirable to approach the problem of the reduction of nitroalkanols from two angles, viz.,

- a) What is the fate of the intermediate nitroalcohol when it is subjected to the usual conditions of catalytic hydrogenation?
- b) How may the conditions be modified so that the corresponding aminoalkanols may be formed?

## II. REVIEW OF THE LITERATURE

### (A) Nitroparaffins and aliphatic nitroalcohols.

The metathesis of n-amyl iodide and silver nitrite to produce n-nitropentane constitutes the first synthesis of a nitroparaffin. Victor Meyer (47), collaborating with Stüber, did this pioneering research in 1872.

Nitroparaffins can be prepared from  $\alpha$ -halogen-substituted fatty acids. Schmidt (61) describes the use of sodium nitrite on these compounds to yield  $\alpha$ -nitro-substituted fatty acids which readily lose carbon dioxide to give nitroparaffins.

Direct nitration was first accomplished by Beilstein and Kurbatow (4) in 1880 which resulted in the synthesis of mononitrocyclohexane from a petroleum fraction. Markownikoff (45) prepared nitroparaffins by heating the parent hydrocarbon with dilute nitric acid.

Further synthesis of nitroparaffins remained practically dormant until Hass, with Hodge, Vanderbilt and Patterson (27,28), published work concerning the vapor-phase nitration of gaseous paraffins. Nitromethane, nitroethane and the two nitropropanes soon became available in commercial quantities and 1-nitrobutane in limited quantities.

Meyer pointed out that the hydrogen atoms attached to the nitro-bearing carbon of primary and secondary

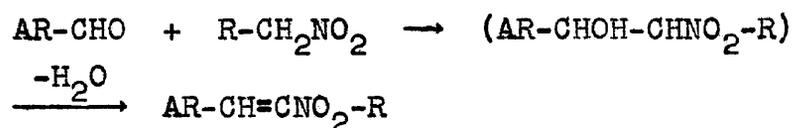
nitroparaffins are considerably more active than those attached to other carbon atoms of the molecule.

Henry (33) was the first to take advantage of this property for the purpose of synthesizing an extensive series of nitroalcohols according to the equation:



The condensation is catalyzed by the presence of alkali.

Subsequently, the literature became quite replete with references on condensations of nitroparaffins with aromatic aldehydes, but always with the elimination of water to yield styrene derivatives:

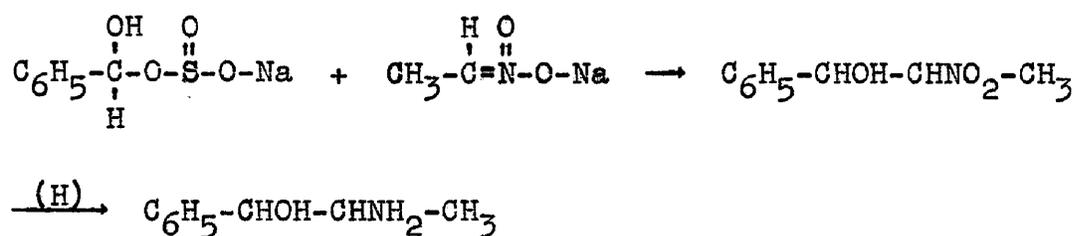


Thus, Priebis (53) condensed benzaldehyde and other aromatic aldehydes with aliphatic nitro compounds in the presence of zinc chloride to form nitrostyrene and related compounds; Posner (52) caused nitromethane to react with ortho- and meta-nitrobenzaldehyde in the presence of zinc chloride; Thiele (68) did similar work, utilizing caustic alkali as the catalyst; Bouveault and Wahl (7) employed sodium methoxide; Knoevenagel and Walter (41) catalyzed the condensation with ethylamine and amylamine; and Kauffman (40) condensed 2,5-dimethoxybenzaldehyde with nitromethane and nitroethane in the presence of potassium hydroxide.

The first person to prevent the liberation of water

in this type of synthesis was Kanao (39) who treated furfuraldehyde with aliphatic nitro compounds to yield the 1-furfuryl-1-hydroxy-2-nitro derivatives of ethane, propane, butane and isobutane in yields averaging 70%.

Kamlet, in 1939 (38), described a process which avoids the elimination of water during the condensation of an aromatic aldehyde and a nitroparaffin. For preparing nitroalkanols with an aromatic substituent, "reaction is effected between an alkali metal bisulfite addition product of an aromatic aldehyde and an alkali metal salt of a nitroparaffin." Hence, the production of phenylpropanolamine is readily realized:



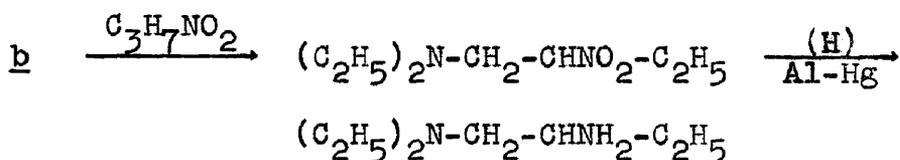
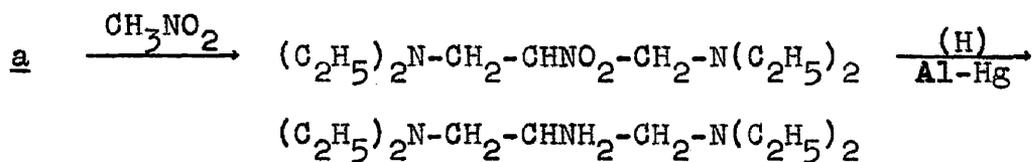
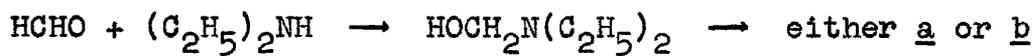
However, the product of this synthesis is a mixture of the two racemates, dl-propadrin and dl-pseudopropadrin.

After the nitroparaffins became available from petroleum sources, the study of the condensation of nitroparaffins with aliphatic aldehydes, so effectively initiated by Henry, was resumed by Hass, Vanderbilt and Hodge (27,72,74). The advantages of this method are the ease of manipulation, economy of reagents and excellence of yields. Sprang and Degering (65) have recently published variations of this procedure in order to increase yields on more difficult condensations. Jenkins and Hartung (35), in discussing the nitroparaffin

condensation, say that "this process has not yet assumed any great commercial importance and the nitroalcohols have become available too recently to have permitted exploration of their pharmaceutical possibility".

Tindall (69) has made all of the possible nitroalcohols by combinations of nitromethane, nitroethane, 1-nitropropane, 2-nitropropane and 1-nitrobutane with formaldehyde, acetaldehyde, propionaldehyde and n-butyraldehyde. Their acetic esters were also synthesized.

A simple and economical method of condensation for the preparation of 1,2-diamines or 1,2,3-triamines of the types  $R\text{-CHNH}_2\text{-CH}_2\text{NR}'_2$  and  $R'_2\text{N-CH}_2\text{-CHNH}_2\text{-CH}_2\text{-NR}'_2$  was developed by de Mauny (12):



Aldehydes and ketones are capable of being produced by the introduction of the calcium or sodium salt of the nitroparaffin into an acid solution (e.g. sulfuric Acid) of sufficient strength to prevent localized alkylation in the reaction mixture (37).

According to Senkus (63), the thermal stability of nitroparaffins is improved by adding an amount of

hydroquinone equivalent to 0.2-1.0% of the weight of the compound.

Scott and Treon (62) have developed a colorimetric method of determining primary nitroparaffins which is, however, limited to dilute, aqueous solutions.

(B) Reduction of aliphatic nitroalcohols.

Henry (34) reduced nitroalcohols with iron and acetic acid to aminoalcohols. Piloty and Ruff (51) used tin and hydrochloric acid to reduce 2-methyl-2-nitro-1,3-propanediol to the corresponding amine. In both cases, yields were very low. The 1-furfuryl-1-hydroxy-2-nitro derivatives of ethane, propane, butane and isobutane were reduced by Kanao (39) with zinc and acetic acid giving 40-50% yields of the corresponding aminoalcohols.

Montmollin and Achermann (48) claim that the low yields obtained on reduction of nitroalcohols with acids and metals are due to the "fragility" of aminoalcohols.

Schmidt and Wilkendorf (59,60) reduced 3-nitro-2,4-pentanediol and nitromethyleneglycol in an oxalic acid solution to amines with palladium-barium sulfate catalyst. Schmidt, Ascherl and Mayer (58) reduced 1-nitro-2-octanol to 1-hydroxylamino-2-octanol with the same catalyst, again in oxalic acid solution.

It is the prolific work of Hass, with Vanderbilt

and Johnson, on the reduction of aliphatic nitroalcohols that commands the greatest attention in connection with this dissertation. Reduction of nitropropanols, nitrobutanols and nitropentanols, in the liquid phase with nickel as the catalyst, is the subject of three patents (29,30,31) issued to Hass and Vanderbilt on December 6, 1938. It is in the description of these inventions that they say:

"The hydrogenation may be carried out at hydrogen pressures varying from atmospheric pressure to over 2,000 pounds per square inch. The rate of reaction is directly proportional to the hydrogen pressures and the temperatures employed. Thus, at a hydrogen pressure of 600 pounds per square inch and at temperatures from 60 to 70° C. under the conditions we have employed, the hydrogenation will, in general, be found to be complete after a period of 15 to 45 minutes. Lower pressures and lower temperatures will, in general, require longer times for the hydrogenation reaction to be completed and, conversely, higher pressures and temperatures will, in general, shorten the time for the completion of the hydrogenation reaction. Optimum pressures and temperatures may be readily determined by simple experimentation and will depend, to some extent, on the amount of catalyst and solvent employed, the surface of the reaction mixture exposed to the hydrogen, the rate of agitation, and the tendency of the nitroalcohol to decompose at higher temperatures under the conditions employed. Methyl or ethyl alcohol may be used as solvents. The hydrogenation may, if desired, be carried out in the presence of carbon dioxide, as disclosed in our copending

application Serial No. 158,960 filed August 13, 1937.\* The carbon dioxide combines with the bases formed during hydrogenation to form carbonic acid salts, and thus substantially reduces the tendency of the nitroalcohols to decompose during the reaction since the nitroalcohols are somewhat unstable in basic solutions."

Evidence for undesirable side reactions is supported by the report of Palfray and Sabetay (50) that Raney nickel was excellent for dehydrogenation of alcohols at moderate temperatures and that secondary alcohols were dehydrogenated more easily than primary.

The fact that Emerson and Mohrman (17) were able to produce secondary amines in good yields from aromatic nitro compounds and aldehydes by reducing with Raney nickel in the presence of sodium acetate assumes greater importance when compared with experimental data obtained in the present investigation.

Vanderbilt (73), referring to reductions of nitroalkanol without carbon dioxide, in a later patent, says:

"The conversion of the nitro compounds to basic compounds ranges from 80 to 98%. However, in most instances the basic compounds produced do not constitute solely the aminohydroxy compounds corresponding to the nitrohydroxy compounds hydrogenated since relatively large amounts of alkyl amines and other reduction products are also

---

\* This has since been issued as U. S. Patent No. 2,157,391, May 9, 1939.

formed during the hydrogenation. I believe that the formation of these relatively large amounts of alkyl amines and other undesirable reduction products may be attributed to the fact that the original nitrohydroxy compounds are unstable in basic solutions, and the formation of basic amino and hydroxyamino compounds at the beginning of the hydrogenation reaction tends to cause a decomposition of the original nitro compounds, the decomposition products then being hydrogenated as well as the original nitro compound."

(C) Pharmacology of the nitroparaffins.

There have been very few pharmacologic studies on aliphatic nitro compounds. As early as 1891, Gibbs and Reichert (20) reported a depression of all functions (reflexes, voluntary motion, heart action and respiration) on injecting nitromethane into frogs. The effects of nitromethane on dogs were found to be lassitude, drowsiness, weakness, salivation, urination, defecation and vomiting. The minimal lethal dose of nitromethane for dogs was about 0.5 to 1.0 cc. per kilogram body weight, producing death within twenty-four hours when injected hypodermically. An increase in pulse rate and blood pressure was due to stimulation of accelerator centers since the effect was not obtained after isolation of the heart from the nerve centers, section of the vagi and transection of the spinal cord in the upper cervical segments.

Machle, Scott and Treon (43), who are undoubtedly

the outstanding authorities on the pharmacology of nitro-paraffins to-day, claimed that a vapor concentration of 0.05% of nitromethane in air is safe and tolerable for guinea pigs, rabbits and monkeys, although 0.1% caused the death of one monkey.

Dinitromethane and tetranitromethane are irritating and capable of producing fatal pulmonary edema and methemoglobinemia, according to Mayer, Plantefol and Vles (46). Tetranitromethane was described by Flury and Zernick (18) as a powerful irritant and blood poison, these properties being attributed to the preponderance of nitro groups.

That nitroethane is no more toxic than nitromethane (0.05% of nitroethane in air being safe and tolerable for guinea pigs, rabbits and monkeys) is reported by Machle, Scott and Treon (43). These same authors (44) administered nitroethane to rabbits and found it to be partially excreted by the lungs. It is excreted at a fairly rapid rate by rabbits and rats, doses of one gram being completely eliminated in thirty hours. Danger from the use of the simpler nitroparaffins (nitromethane, nitroethane, 1-nitropropane, 2-nitropropane, 1-nitrobutane and 2-nitrobutane) seems to be limited to accidental ingestion.

In his discussion of the pharmacology of the nitrites, Cushny (11) includes the following reference to nitro compounds:

"Another series of bodies which may be mentioned as occasionally acting like the

nitrites, although more feebly, are the nitro-bodies. In these the nitrogen is attached to the alkyl directly, and not through the intervention of an oxygen atom. Examples of these are Nitromethane,  $\text{H}_3\text{C}-\text{NO}_2$ , and Nitroethane,  $\text{CH}_3-\text{CH}_2-\text{NO}_2$ . Their action is so feeble as to preclude their use in therapeutics, and seems due to the  $-\text{NO}_2$  being split off in the tissues."

Nitropentane was claimed by Schadow (56) to have no effect on pulse rate or size of blood vessels in humans although experimental animals reacted with convulsions, epileptiform seizures, irregularities of breathing, salivation and drop in pulse rate. Injection of nitropentane into frogs resulted in anesthesia and general impairment of activity of the central nervous system.

The following are additional and general statements of Machle, Scott and Treon (43) concerning the physiological response of animals to the mononitro-paraffins:

"Lethal concentrations for animals are far below narcotic concentrations and beginning narcosis cannot safely be used as a warning of dangerous concentrations. Nitroparaffins are slightly irritating. In animals the degree of irritation is like that seen upon exposure to diethyl ether. The odors of the materials are strong and in low concentrations are definitely disagreeable to most observers; they would appear to be the best guide to the presence of harmful concentrations. Fatal effects following inhalation exposure

indicate that the toxicity increases with the size of the molecule."

(D) Pharmacology of the aliphatic amines.

The classical study on the relationship between chemical structure and sympathomimetic action is that of Barger and Dale (3). As mentioned in the introduction (page 2), they found that aliphatic amines did have pressor activity starting with n-butylamine. n-Hexylamine was most potent and n-heptylamine only slightly less. As the chain lengthened, however, this activity became overshadowed by toxicity.

Hartung (23) has reviewed the toxicity and pressor effects and Tainter (67) the pressor and autonomic nervous system effects of aliphatic amines. Trendelenburg's text (70) contains extensive material on their pharmacology.

However, the source of choice for an extensive survey of the literature on aliphatic amines is the publication of Dunker and Hartung (14). Concerning the effect of amines on blood pressure, they generalize as follows:

"The lower members, up to the butylamines according to Barger and Dale, or to isopropylamine according to Tainter, are inactive or give no constant response on blood pressure in experimental animals. As the chain is increased beyond this point, the pressor activity steadily increases to a maximum in

n-hexylamine and then steadily decreases as the chain is lengthened to thirteen carbon atoms. From propyl to hexyl, it has been shown that the normal radical is more active than the corresponding iso-chain, although Tainter reports the isopropylamine to have pressor activity while the normal propylamine is inactive. Except for the sec-butylamine which was found to be indifferent and the tertiary amylamine for which pressor activity is claimed no other saturated branched chain amines have apparently been investigated. The primary amines seem to be somewhat more active than the secondary and tertiary amines."

Alles (1) confirms the claim of Barger and Dale in failing to find any pressor effect in the members lower than butyl in the series of N-alkyl ammonium salts. He has found that the initial depressor and secondary pressor effects from branched chain aliphatic primary carbin-ammonium salts are closely comparable with those of the straight-chain compounds, the intensity of these effects being intermediate between that of the straight chain compound of the same total number of carbon atoms and the next lower in the normal series.

Dunker, Hartung and Chapman (15) determined the acute toxicity of the four primary heptylamines and reported that 1- and 4-heptylamines are of equal toxicity and 2- and 3-heptylamines are more toxic.

(E) Pharmacology of the aliphatic aminoalcohols.

There are very few references to this subject in the literature. Trendelenburg (70) notes that the addition of the hydroxy group to ethylamine, resulting in ethanolamine, causes a decrease in toxicity. Dunker and Hartung (14) agree with this observation in stating that "the introduction of the hydroxyl leads to a decrease in toxicity and activity as compared to the non-hydroxylated amine."

Hartung (23) points out the biochemical interest in aminoalcohols since ethanolamine and ethanoltrimethylammonium hydroxide or choline form constituent portions of the lecithins and the benzoic or substituted benzoic acid esters of other aliphatic aminoalcohols form anesthetics of the novocaine and stovaine type.

Machle, Scott and Treon (43) administered 2-amino-2-methyl-1-propanol, 2-amino-2-methyl-1,3-propanediol and 2-amino-2-methylol-1,3-propanediol orally to rabbits and noted that weakness and collapse were the principal symptoms with coma occurring in animals that died. No specific nervous-system involvement or convulsions occurred prior to death, depression and illness being the principal symptoms. Much of the damage caused by these compounds was owing to their alkalinity.

The work of Machle, Scott and Treon (43) and that of Dunker, Hartung and Chapman (15) furnishes a basis of comparison of the relative toxicities of aliphatic

amines and aminoalcohols. This discussion, however, can only be very general since different test animals and methods of presenting data were used, and the two groups of compounds were not analogous. The LD<sub>50</sub> of the aminoheptanes neutralized with N/1 hydrochloric acid varies from 0.06 mg./g. mouse for 2-aminoheptane to 0.11 mg./g. mouse for 4-aminoheptane. The lethal dose for rabbits of 2-amino-2-methyl-1-propanol in neutralized solution (acid unspecified) is 1.00-2.00 g./kg. body weight. Consequently, the four carbon-atom aminoalcohol would seem to be approximately twenty times less toxic than the seven carbon-atom amine, an indication of the desirability of the introduction of the hydroxyl group.

On page 20 there is a portion of a table compiled by Machle, Scott and Treon (43) listing the lethal doses of some nitroparaffins and aminoalcohols.

TABLE 1. Toxicity of some nitroparaffins and aliphatic aminoalcohols. (43)

| Compound   | : Lethal Dose* (for<br>: rabbits by oral<br>: administration<br>: g./kg. |
|--|--|
| Nitromethane   | : 0.75-1.00  |
| Nitroethane  | : 0.50-0.75  |
| 1-Nitropropane   | : 0.25-0.50  |
| 2-Nitropropane   | : 0.50-0.75  |
| 1-Nitrobutane  | : 0.50-0.75  |
| 2-Nitrobutane  | : 0.50-0.75  |
| 2-Amino-2-methyl-1-propanol                                  | : 1.00-2.00  |
| 2-Amino-2-methyl-1,3-propanediol                             | : 1.50-2.00  |
| 2-Amino-2-methylol-1,3-propanediol                           | : 1.00-2.00  |
| 2-Amino-2-methyl-1-propanol<br>(neutralized solution)        | : 1.00-2.00  |
| 2-Amino-2-methyl-1,3-propanediol<br>(neutralized solution)   | : Greater than 3.00  |
| 2-Amino-2-methylol-1,3-propanediol<br>(neutralized solution) | : Greater than 5.00  |
|  | :<br>:   |

\* This term is not further defined by the authors.

## III. EXPERIMENTAL PORTION

## (A) Preliminary notes.

All temperatures specified in this thesis are uncorrected unless otherwise stated. Corrected readings were made with the use of Anschutz immersion thermometers.

The apparatus to be referred to hereafter as the "hydrogenator" is of all-glass construction with a dual gas-feed allowing the agitated reaction flask to draw from one chamber while the second is being filled. The pressure exceeds atmospheric pressure by five to twenty-five inches of water.

The "high-pressure hydrogenator" is of the conventional type supplied by the American Instrument Company and permitting reductions to be carried out at pressures as high as 6000 pounds per square inch and at temperatures up to 300° C.

Gas volumes pertaining to the hydrogenator were recorded without considerations of such factors as temperature, atmospheric pressure or vapor pressure, since reductions using this apparatus were unsuccessful.

Gas volumes pertaining to the high-pressure hydrogenator were determined empirically: with 100 cc. of water in the reaction flask, hydrogen under pressure was allowed to escape from the apparatus and was collected over water; removal of one liter of hydrogen was found

to effect a pressure drop of fifteen pounds per square inch. In several experiments the volume of liquid in the reaction flask was not 100 cc. and the resulting drop in pressure cannot be interpreted volumetrically according to the preceding relation. If the volume is less than 100 cc., the absorption of 1000 cc. of hydrogen will cause a drop in pressure of less than 15 pounds per square inch, and conversely more than 15 pounds per square inch if the volume is larger than 100 cc.

The temperature of the reaction chamber of the high-pressure hydrogenator was determined by means of a thermometer inserted between the outer jacket and the inner steel bomb. This reading represented the temperature of the reaction mixture with a probable error of no more than five centigrade degrees.

The alcohol described in this dissertation as "absolute alcohol" is of commercial quality.

#### (B) Preparation of nitroalcohols.

The synthesis of the necessary nitroalcohols constituted the starting point of this investigation. The method of Vanderbilt and Hass (74), in which a condensation is effected between an aldehyde and a nitroparaffin, was found very satisfactory. Since all reactions were carried out under identical conditions, it is unnecessary to describe each separately; hence, the general procedure will be described and the more specific information, such as reactants and physical properties appears in Table 2,

page 25.

Procedure: A 500 cc. beaker was equipped with an efficient stirrer, a thermometer and a suitable means of external cooling, in this case a water bath. Into the beaker were placed 0.5 mole of the nitroparaffin, 25 cc. of 95% ethyl alcohol and 1.0 cc. of 40% aqueous solution of sodium hydroxide. A half-molar quantity of freshly distilled aldehyde was then added dropwise to the well-agitated solution in the beaker at such a rate that the temperature was maintained between 30° and 35° C. Cooling was instituted when necessary. After two-thirds of the aldehyde had been added, an additional cubic centimeter of alkali solution (accurately measured) was added, followed by the residual aldehyde in the manner described previously. If the resultant product was not a clear solution, enough 95% ethyl alcohol was gradually added to produce it.

The solution was placed in a 250 cc. flask, stoppered and submersed in a water bath, the temperature of which was maintained at  $38 \pm 1^{\circ}$  C. After remaining at this temperature for four days, the solution was neutralized with a calculated quantity of concentrated hydrochloric acid.

The alcohol was removed by distillation at room temperature and reduced pressure. Mild heat caused a small quantity of nitroparaffin and aldehyde to distill. On further heating at this point, the temperature

increased sharply and the nitroalcohol was collected within a ten degree boiling range. On redistillation of this fraction 80-90% of it could be collected within a four degree boiling range. Immediately prior to use, these products were subjected to a third distillation and a three degree cut utilized.

All of these nitroalcohols reacted with  $\alpha$ -naphthylisocyanate to produce di- $\alpha$ -naphthylurea when treated in the manner described by Shriner and Fuson (64) for the preparation of urethanes. Bickel and French (5) have experienced this same difficulty in working with other alcohols. However, the analysis of derivatives and proof of structure of corresponding aminoalcohols will suffice to identify the nitroalcohols.

Of the ten listed in Table 2, page 25, compounds 1, 2 and 3 have been synthesized previously by Tindall (69) and compounds 9 and 10 just recently by Sprang and Degering (65). The other five compounds are unreported to date.

TABLE 2. Nitroalcohols synthesized.

| Compound                      | Reactants            |                | Boiling Point   | Yield | Appearance   |
|-------------------------------|----------------------|----------------|-----------------|-------|--------------|
|                               | Aldehyde             | Nitroparaffin  |                 |       |              |
| 1. 3-Nitro-4-heptanol         | n-butyraldehyde      | 1-nitropropane | 122-123°/18 mm. | 70%   | light yellow |
| 2. 2-Nitro-2-methyl-3-hexanol | n-butyraldehyde      | 2-nitropropane | 122-123°/21 mm. | 58%   | light yellow |
| 3. 5-Nitro-4-octanol          | n-butyraldehyde      | 1-nitrobutane  | 123-124°/13 mm. | 76%   | yellow       |
| 4. 1-Nitro-3-ethyl-2-pentanol | 2-ethylbutyraldehyde | nitromethane   | 109-111°/26 mm. | 51%   | light yellow |
| 5. 2-Nitro-4-ethyl-3-hexanol  | 2-ethylbutyraldehyde | nitroethane    | 118-120°/22 mm. | 49%   | yellow       |
| 6. 1-Nitro-2-heptanol         | n-hexaldehyde        | nitromethane   | 118-120°/24 mm. | 55%   | light yellow |
| 7. 2-Nitro-3-octanol          | n-hexaldehyde        | nitroethane    | 133-134°/22 mm. | 43%   | yellow       |
| 8. 3-Nitro-4-nonanol          | n-hexaldehyde        | 1-nitropropane | 142-143°/23 mm. | 59%   | yellow       |
| 9. 1-Nitro-2-octanol          | n-heptaldehyde       | nitromethane   | 130-132°/24 mm. | 69%   | light yellow |
| 10. 2-Nitro-3-nonanol         | n-heptaldehyde       | nitroethane    | 134-136°/23 mm. | 57%   | light yellow |

(C) Stability experiments on nitroalcohols.

Stability experiments were carried out on the aliphatic nitroalcohols in order to determine a possible reason for the anomolous results (to be discussed later) upon their reduction. 2-Nitro-2-methyl-3-hexanol was chosen as a representative compound.

In each case, 0.1 mole or 16 g. of the nitroalcohol (except in c where 0.05 mole or 8 g. of compound was used) was allowed to stand for seventy-two hours at room temperature in a stoppered 50 cc. flask under the specified conditions. After that time it was distilled at reduced pressure into a graduate and the temperature noted upon collecting every cubic centimeter of material. This information is expressed graphically (page 28), the volume collected being the ordinate and the temperature the abcissa.

(a) The control: One cubic centimeter of absolute alcohol was added to the compound. There was no visible change during the experiment period. Distillation was carried out at 14 mm.

(b) One cubic centimeter of absolute alcohol containing 0.1 g. of hydrochloric acid was dissolved in the nitroalcohol. During the first twenty-four hours the liquid darkened to blackness. Distillation pressure was 19 mm.

(c) One cubic centimeter of absolute alcohol containing 0.05 g. of sodium hydroxide was added to the nitroalcohol. The apparent physical properties were unaltered. Just

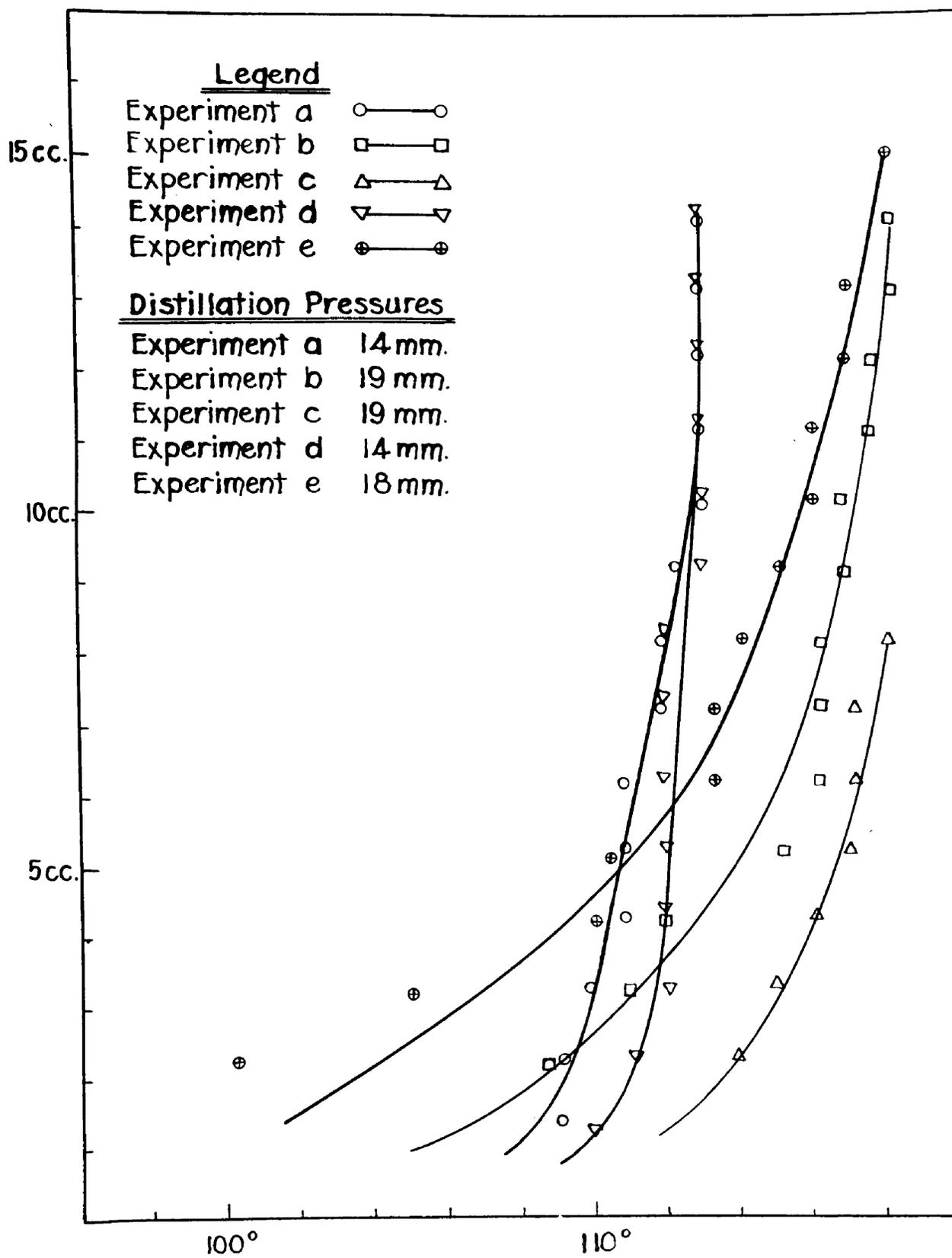
prior to distillation, the alkali was neutralized with alcoholic hydrochloric acid. Distillation pressure: 19 mm.

(d) Raney nickel (1 g. wetted with absolute alcohol) was mixed with the compound. The flask was shaken three or four times daily during the period of experiment, at the end of which the catalyst was removed by filtration. The filtrate, which appeared identical to the starting material, was distilled at 14 mm.

(e) In this case, 16 g. or 0.1 mole of 3-nitro-4-heptanol was mixed with 1 g. of Raney nickel, wetted with absolute alcohol, and 1 g. of 3-amino-4-heptanol. Three or four times daily the mixture was agitated. After seventy-two hours the mixture was filtered and the filtrate was observed to be of the same color as at the beginning of the experiment. Distillation pressure: 18 mm.

It will be observed in Figure I, page 28, that the stability of the nitroalcohol can conveniently be measured in a semi-quantitative manner by the slope of the curve. Perfect stability would be indicated by the approach of the curve to a straight line. The only portion of the experiment revealing a possible instability is e. Allowing 3-nitro-4-heptanol to be in contact with Raney nickel and 3-amino-4-heptanol simulates the conditions of reduction of a portion of the nitro compound to the amino compound. Vanderbilt (73) attributes poor yields to the fact that the nitroalcohol is unstable in the presence of the initially formed amino or hydroxyamino compound, yielding

FIGURE 1. Stability experiments on nitroalcohols.



undesired intermediates which are reduced to alkyl amines. However, this experiment, although indicating slight decomposition, hardly explains reductions in which no aminoalcohol was produced.

(D) Preparation of catalysts.

Before discussing the reduction experiments carried out in this investigation, it seems desirable to describe first the preparation of the various catalysts utilized. The very comprehensive text of Ellis (16) proved invaluable for this phase of the problem.

(a) Palladinized charcoal. Three grams of activated charcoal (Norit - Eastman Kodak Company) was added to a solution of 0.3 g. of palladium chloride in 50 cc. of distilled water. This mixture was shaken on a hydrogenator at atmospheric pressure until no more hydrogen was taken up. The catalyst was then removed by filtration, washed with distilled water and dried in vacuum over sulfuric acid. This procedure is that of Ott and Schröter (49) and later employed so successfully by Hartung (22).

(b) Palladinized barium sulfate. In 400 cc. of hot distilled water was dissolved 17.8 g. of barium chloride and 8.8 g. of sulfuric acid was then added. The precipitated barium sulfate was washed by decantation and the volume of the suspension adjusted to 400 cc. once more. A solution of 1.7 g. of palladium chloride in 50 cc. of distilled water was added, followed by 1.3 cc. of formalin. The mixture was then made weakly alkaline

to litmus with a 10% solution of sodium hydroxide and boiled for fifteen minutes. The gray precipitate was then removed by filtration and washed with hot distilled water until all alkali was removed. The product was then dried in vacuum over sulfuric acid. Schmidt (57) first reported the preparation and use of this catalyst.

(c) Raney nickel. One hundred grams of finely ground nickel-aluminum alloy was added slowly to 100 cc. of 40% solution of sodium hydroxide cooled with an ice jacket. The mixture was then heated on a hot plate at 115-120° C. for three hours with constant stirring. At the end of this period, 140 cc. of 20% solution of sodium hydroxide was added and the mixture kept at 115-120° until no more bubbles of hydrogen were evolved. Evaporated water was replaced during the digestion. The mixture was then diluted to two liters and washed very thoroughly with distilled water by means of repeated decantations (twelve) and with alcohol by three decantations. The catalyst was stored in a glass-stoppered bottle under alcohol. Covert and Adkins (10) published the above directions for the preparation of the catalyst discovered and patented by Raney (54).

(E) Catalytic reduction of the nitroalcohols.

(a) Palladinized charcoal catalyst. The first method of catalytic hydrogenation attempted was reduction in the presence of palladinized charcoal, the method of Hartung (22) having proven so successful and generally applicable in these Laboratories. Eight grams of 2-ethyl-2-nitro-3-hexanol (0.05 mole) and 5.5 g. of hydrochloric acid were added to sufficient anhydrous alcohol to make 100 cc. This acid content was made possible by the use of a solution of dry hydrochloric acid in absolute alcohol, the gain in weight of the latter being an indication of the concentration. A 10% solution (weight/volume) was used. To the acidified alcoholic solution of the nitroalcohol was added 1 g. of catalyst, the mixture placed in a 250 cc. round-bottom flask and attached to the hydrogenator. The air was displaced by hydrogen and the flask agitated. The volume of hydrogen absorbed after two hours of shaking was negligible - 80 cc. or 2% of the theoretical volume.

Subsequently the suspension was transferred to the high-pressure hydrogenator and shaken for three hours at a pressure of 250 pounds per square inch. There was no drop in pressure.

The reaction mixture was then heated to 70° C. whereupon the pressure rose to 289 pounds per square inch. The suspension was shaken for two hours, allowed to stand overnight, and the pressure read at room temperature -

186 pounds per square inch.

This pressure drop of 64 pounds per square inch (119% of the theoretical quantity) indicated either leakage or decomposition. The latter proved to be the fact upon removing the palladium catalyst by filtration; the filtrate was dark brown and removal of the alcohol under reduced pressure and dessication for three days yielded a black tar.

Ellis (16) mentions the inadvisability of using heat with palladium catalysts.

(b) Palladinized barium sulfate catalyst. The use of this catalyst was prompted by the success of Schmidt and Wilkendorf (60) in reducing 3-nitro-2,4-pentanediol with it. Five grams of 5% palladinized barium sulfate catalyst was placed in 50 cc. of distilled water and saturated with hydrogen. Eight grams of 2-ethyl-2-nitro-3-hexanol (0.05 mole) and 3.2 g. (0.025 mole) of oxalic acid were dissolved in 50 cc. of 95% alcohol and this solution was added to the above mixture. Less than 2% of the theoretical quantity of hydrogen was absorbed in 60 minutes of shaking at atmospheric pressure, no hydrogen being absorbed during the last 40 minutes.

It therefore seemed advisable to alter the method and the mixture was placed in the high-pressure hydrogenator. After having shaken for 50 minutes at an initial pressure of 92 pounds per square inch, there was practically no reduction in pressure (one pound per square inch or approximately 2% of the theoretical drop). At this point, an additional

100 pounds pressure was produced and heating gradually instituted. The temperature rose to 81° C. and the pressure to 230 pounds per square inch without any indication of hydrogenation; the experiment was consequently abandoned at this point.

It is of interest to note that the palladinized barium sulfate catalyst resisted hydrogenation and decomposition at a temperature 11° higher than that which resulted in reduction with palladinized charcoal catalyst; the latter, however, did have the benefit of 59 pounds increased pressure.

(c) Raney nickel catalyst - neutral medium. The failures employing palladium catalysts led to the trial of Raney nickel to produce the desired amines. Sixteen grams of 3-nitro-4-heptanol (0.1 mole) was dissolved in enough absolute alcohol to make 100 cc. and 0.5 g. of Raney nickel added. An initial hydrogen pressure of 250 pounds per square inch was established and the temperature was slowly raised to 112° C. During this period the pressure rose to 312 pounds per square inch. The course of the reduction is indicated graphically in Figure II, page 38. The drop in hydrogen pressure, determined after allowing the reaction to set twenty-four hours, was 124 pounds or 115% of the theoretical amount. This excess is easily explainable on the basis of possible decomposition, slight leakage, or both. The catalyst was removed and the filtrate fractionated at atmospheric pressure into

eleven portions in order to trace the fate of the nitrogen since a previous attempt to reduce 3-nitro-4-heptanol in this manner had failed to produce any compound with a boiling point even approaching that of 3-amino-4-heptanol. Kjeldahl nitrogen determinations (modified to include  $\text{-NO}_2$  nitrogen (2)) were carried out on these fractions and the results are tabulated on page 39. Fraction #1 was reexamined in order to determine what amount of nitrogen was present as amino nitrogen: a sample (19.843 g.) was boiled with 20 cc. of 40% aqueous sodium hydroxide and the evolved ammonia collected in standard acid and determined by back titration in the usual manner. The percentage nitrogen found was 0.54% indicating that 90% of the nitrogen in fraction #1 existed as amino nitrogen.

In order to facilitate identification of the various fractions resulting on reduction of a nitroalcohol with Raney nickel in neutral medium, this experiment was repeated using larger quantities of compound.

To 100 cc. of absolute alcohol was added 87.5 g. of 5-nitro-4-octanol (0.5 mole) and 5 g. of Raney nickel. Hydrogen pressure of 800 pounds per square inch was established and the temperature raised to  $94^\circ \text{C}$ . The reduction again proceeded in a manner similar to that illustrated in Figure II, page 38. The pressure drop was 710 pounds per square inch. The mixture was filtered and the filtrate distilled at atmospheric pressure. Four major fractions were obtained as indicated in Table 4. These fractions were examined for nitrogen content. It

will be observed that the recovery of 5.55 g. of nitrogen in the fractions distilling below  $165^{\circ}$  C. represents 79.3% of the nitrogen originally present in the nitroöctanol. 4-Amino-5-octanol distils at  $215-217^{\circ}$  C. at atmospheric pressure. The material was redistilled and collected within narrow ranges, as indicated in Table 4.

Fractions I-i, I-ii, I-iii, I-iv, and I-v were acidified with alcoholic hydrochloric acid and evaporated to dryness on a water bath. The ammonium chloride was recognizable as white crystals, subliming instead of melting, yielding ammonia upon heating with 20% sodium hydroxide solution and a white precipitate on addition of silver nitrate solution. The butylamine hydrochloride was recrystallized by dissolving in a small amount of hot alcohol (thus separating from ammonium chloride in I-i) and precipitating by addition of ether; it melted at  $195^{\circ}$  C. cor., in perfect agreement with the temperature reported by Linnemann and v. Zotta (42).

The identity of dibutylamine was indicated by its boiling point and proved by preparing the phenylthiourea derivative (64) which, after recrystallizing from hot alcohol, melted at  $86^{\circ}$  C. The published melting point of this compound is  $86^{\circ}$  C. (64).

The following amounts of nitrogen-containing material are approximated as resulting from this reduction of 0.5 mole of 5-nitro-4-octanol with Raney nickel in neutral medium:



occur after partial but before complete hydrogenation. Furthermore, in view of the complete absence or, at best, the presence of negligible amounts of nitrogen remaining in the portion boiling above  $165^{\circ}$ , the extent of fission or perhaps the removal of the amino group appears practically quantitative. The mechanism by which acetic acid or carbon dioxide prevents this break in the normal carbon chain, as described later, is also obscure.

(d) Raney nickel catalyst - acid medium (acetic acid).

In the successful catalytic reduction of oximes and nitriles, it was found necessary to have the reaction mixture acidic in order to prevent the formation of a mixture of primary and secondary bases (22). It therefore seemed logical to examine here the effect of addition of acid to the reduction mixture. The use of catalytic nickel restricts the type of acid to those that will not materially affect the metal. Glacial acetic acid was dissolved in alcohol and found to be unreactive toward Raney nickel. Consequently, 32 g. of 3-nitro-4-heptanol (0.2 mole) and 12 g. of glacial acetic acid (0.2 mole) were dissolved in enough absolute alcohol to make 100 cc. One gram of Raney nickel was added and the mixture reduced in the high-pressure hydrogenator at room temperature and with an initial pressure of 600 pounds per square inch. The pressure drop was theoretical - 108 pounds per square inch. After the catalyst had been removed by filtration, the alcohol was evaporated spontaneously. The residue was extracted with 10% hydrochloric acid. After washing the acid extract with toluene, it was made strongly

FIGURE II. Time-pressure curve of reduction of 3-nitro-4-heptanol.

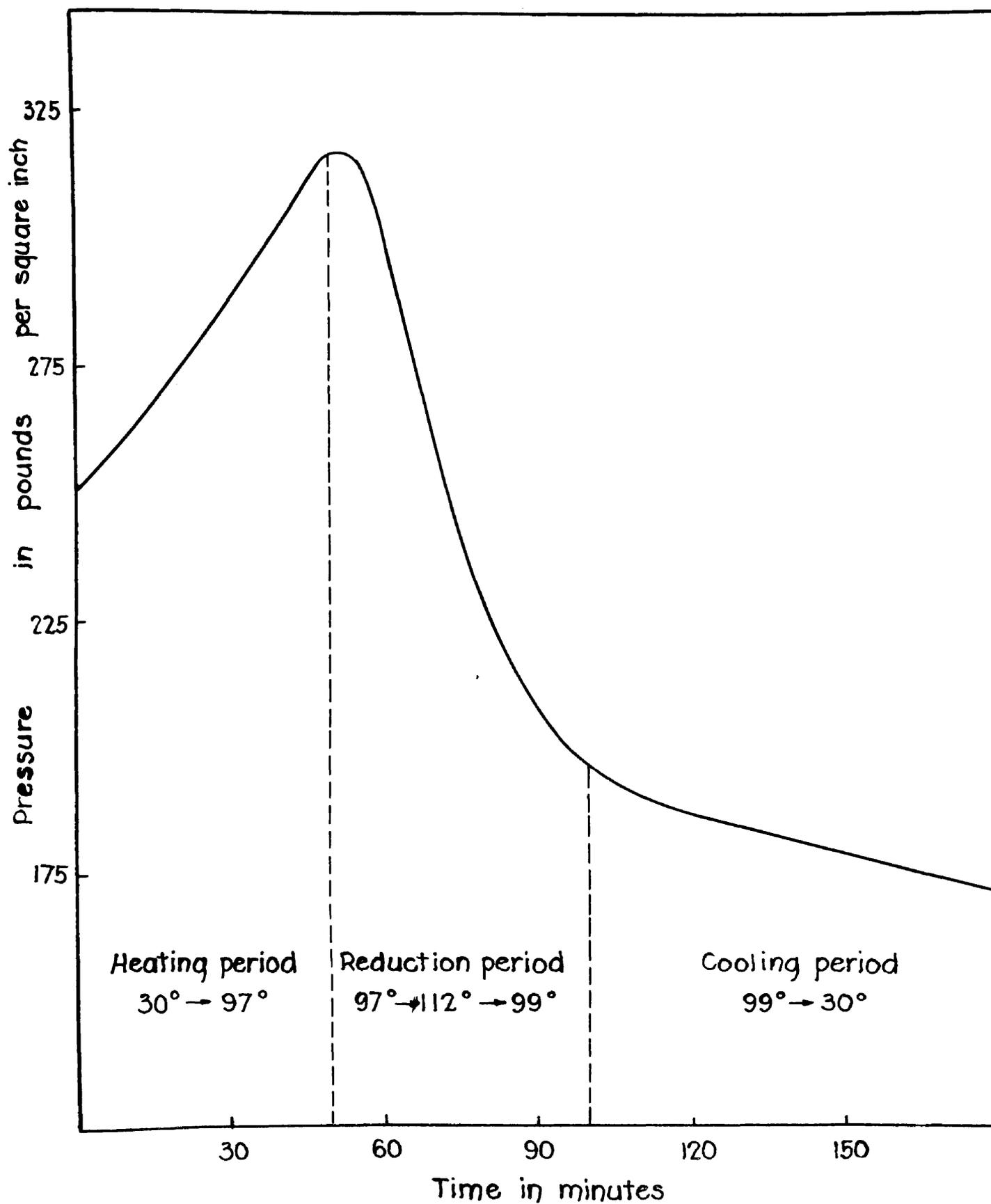


TABLE 3. Fractionation and nitrogen analysis of products from reduction of a tenth of a mole of 3-nitro-4-heptanol with Raney nickel in neutral medium.

| Fraction | Boiling range | Weight  | % Nitrogen | Amount of Nitrogen |
|----------|---------------|---------|------------|--------------------|
| 1        | 50-80°        | 138 g.* | 0.6%       | 0.83 g.            |
| 2        | 80-100°       | 3 g.    | 2%         | 0.06 g.            |
| 3        | 100-120°      | 0.1 g.  | } → 4%     | 0.01 g.            |
| 4        | 120-140°      | 0.1 g.  |            |                    |
| 5        | 140-160°      | 0.1 g.  |            |                    |
| 6        | 160-180°      | 0.5 g.  | } → 7%     | 0.14 g.            |
| 7        | 180-200°      | 0.5 g.  |            |                    |
| 8        | 200-220°      | 1.0 g.  |            |                    |
| 9        | 220-250°      | 1.5 g.  | 5%         | 0.08 g.            |
| 10       | 250-275°      | 1.5 g.  | 6%         | 0.09 g.            |
| 11       | residue       | 1.5 g.  | 7%         | 0.10 g.            |

Total nitrogen accounted for: 1.31 g.

Theoretical quantity: 1.40 g.

Percentage nitrogen accounted for: 93%

\* Includes the weight of 50 cc. of 5% hydrochloric acid into which fraction #1 was distilled.

TABLE 4. Fractionation, nitrogen analysis and identification of products from reduction of a half mole of 5-nitro-4-octanol with Raney nickel in neutral medium.

| Fraction | Boiling Range | Weight | Nitrogen |         | Identified as*        |
|----------|---------------|--------|----------|---------|-----------------------|
|          |               |        | Percent  | Total   |                       |
| I        | 78-90°        | 124 g. | 2.47%    | 3.06 g. |                       |
| i        | 78-80°        | 15 g.  |          |         | <u>a</u> and <u>b</u> |
| ii       | 80-82°        | 62 g.  |          |         | <u>b</u>              |
| iii      | 82-84°        | 26 g.  |          |         | <u>b</u>              |
| iv       | 84-86°        | 10 g.  |          |         | <u>b</u>              |
| v        | 86-90°        | 5 g.   |          |         | <u>b</u> (trace)      |
| II       | 90-155°       | 19 g.  | 4.06%    | 0.77 g. |                       |
| III      | 155-165°      | 13 g.  | 13.21%   | 1.72 g. |                       |
| i        | 155-159°      | 2 g.   |          |         |                       |
| ii       | 159-161°      | 9 g.   |          |         | <u>dib</u>            |
| iii      | 161-165°      | 2 g.   |          |         |                       |
| IV       | above 165     | 12 g.  | 6.22%    | 0.75 g. |                       |
| i        | 165-200°      | 2 g.   |          |         |                       |
| ii       | 200-230°      | 2 g.   |          |         |                       |
| iii      | 230-240°      | 6 g.   |          |         |                       |
| iv       | above 240     | 2 g.   |          |         |                       |

Total nitrogen accounted for: 6.30 g.

Theoretical quantity: 7.0 g.

Percent nitrogen accounted for: 90%

\* a = ammonium chloride

b = butylamine hydrochloride

dib = dibutylamine hydrochloride

alkaline with a 40% solution of sodium hydroxide. The aminoalcohol which separated was removed; the remaining aqueous portion was extracted with ether and this ethereal solution added to the unpurified aminoalcohol. The solution was dried by standing 18 hours over anhydrous magnesium sulfate. Distillation resulted in 18 g. of a water-white liquid being collected at 95-100°/ 20 mm. Boiling point determined by redistillation: 98-99°/ 20 mm.

Kjeldahl analyses:

|    | Sample Weight                    | % Nitrogen |
|----|----------------------------------|------------|
| 1. | 0.6542 g.                        | 10.4%      |
| 2. | 0.5032 g.                        | 10.3%      |
|    | Calculated N for $C_7H_{17}NO$ : | 10.7%      |

Benzoyl derivative: This compound was synthesized by shaking theoretical quantities of 3-amino-4-heptanol and benzoyl chloride in excess 20% sodium hydroxide solution and recrystallizing the resultant mass from toluene and then from 50% aqueous alcohol. Melting point (corrected): 145° C.

Kjeldahl analyses:

|    | Sample Weight                         | % Nitrogen |
|----|---------------------------------------|------------|
| 1. | 0.2590 g.                             | 5.91%      |
| 2. | 0.1638 g.                             | 5.96%      |
|    | Calculated N for $C_{14}H_{21}NO_2$ : | 5.95%      |

(e) Raney nickel catalyst - acid medium (oxalic acid).

Oxalic acid was found to be unreactive toward Raney nickel in alcohol and was consequently worthy of investigation. The procedure and quantities as

described under (d) were repeated with the substitution of 18.9 g. of oxalic acid (0.15 mole) for the acetic acid. This mixture, however, resisted hydrogenation at the temperature and pressure described in (d). Time did not permit further investigation.

(f) Raney nickel catalyst - acid medium (carbonic acid).

The use of solid carbon dioxide reported by Vanderbilt (73) results in the production of carbonic acid which combines with the amine as it is produced. Thirty-two grams of 3-nitro-4-heptanol (0.2 mole) was dissolved in enough absolute alcohol to produce 100 cc. and 1 g. of Raney nickel was added to this solution. Two-hundred grams of solid carbon dioxide was placed in the high-pressure hydrogenator before sealing it. After two hours the pressure became constant at 240 pounds per square inch and the system was assumed to be in thermal equilibrium. Hydrogen was admitted until the pressure rose to 1400 pounds per square inch. After shaking for three hours, the pressure dropped 150 pounds or 70% of the theoretical decrease. Additional agitation of 24 hours failed to produce a further change. The nickel was removed by filtration and the alcohol by evaporation at reduced pressure. The residue was extracted with 5% hydrochloric acid and the acid solution washed with toluene. The acid solution was neutralized and made strongly alkaline with 40% sodium hydroxide solution. The aminoalcohol separated and was removed. Ether was used to exhaust the alkaline aqueous solution and the

ethereal solution was added to the unpurified aminoalcohol. After drying overnight with anhydrous magnesium sulfate, the solution was distilled at reduced pressure. Fourteen grams or 54% of the theoretical yield was obtained.

Boiling point: 100-105°/ 26 mm.

When this method was tried utilizing the proportionate amounts as described by Vanderbilt (73), the yield was only 42%. The increase in carbon dioxide concentration caused by using 200 g. instead of 20 g. and the increase in total pressure from 600 to 1160 pounds per square inch was responsible for the better yield.

(g) General preparation of aliphatic aminoalcohols.

Four additional aminoalcohols were prepared as described under E-d and E-f, pages 37 and 42 respectively, from the appropriate nitroalcohols. Hass and Vanderbilt (75) have previously described 3-amino-4-heptanol and 5-amino-4-octanol; 2-amino-4-ethyl-3-hexanol, 1-amino-2-octanol and 3-amino-4-nonanol are unreported. Information concerning these compounds and their synthesis is presented in Table 5, page 44.

TABLE 5. Aminoalcohols synthesized.

| Compound                      | Method | Initial<br>Hydrogen Pressure<br>in lbs./sq. inch | Yield | Boiling Point     | Benzamides       |                   |       |       |
|-------------------------------|--------|--|-------|-------------------|------------------|-------------------|-------|-------|
|                               |        |  |       |                   | Melting Point    | Nitrogen Analysis |       |       |
|                               |        |  |       |                   |                  | Calcd.:           | Found |       |
| 1. 2-amino-4-ethyl-3-hexanol: | E-d    | 800  | 69%   | 110-112° / 27 mm. | 151° C. cor.     | 5.62%             | 5.68% | 5.62% |
| 2. 3-amino-4-heptanol         | E-f    | 600  | 42%   | 98-99° / 20 mm.   | 145° C. cor.     | 5.95%             | 5.91% | 5.96% |
|                               | E-f    | 1160   | 54%   |                   |                  |                   |       |       |
|                               | F      | —  | 75%   |                   |                  |                   |       |       |
| 3. 1-amino-2-octanol          | E-f    | 800  | 41%   | 130-132° / 26 mm. | 158° C. cor.     | 5.62%             | 5.51% | 5.59% |
| 4. 5-amino-4-octanol          | E-d    | 600  | 66%   | 118-119° / 26 mm. | 149-150° C. cor. | 5.62%             | 5.47% | 5.56% |
| 5. 3-amino-4-nonanol          | E-f    | 1000   | 38%   | 116-118° / 27 mm. | 161° C. cor.     | 5.32%             | 5.34% | 5.39% |

E-d - catalytic reduction with Raney  
nickel and acetic acid

E-f - catalytic reduction with Raney  
nickel and carbonic acid

F - electrolytic reduction

(F) Electrolytic reduction of 3-nitro-4-heptanol.

This portion of the work was carried out by Dr. Glenn E. Ullyot of the Research Laboratories, Smith, Kline and French, Philadelphia, and the following constitutes a direct quotation from his communications (71).

"The reduction was carried out in a 1500 cc. beaker using a lead anode, separated from the cathode by a porous cup, and a lead plate cathode, 15 x 14 cm. The cathode plate was coated with spongy lead just before reduction by placing it in a hot, acidified suspension of lead chloride with a lead anode and passing a current through the cell until the cathode was covered with a gray coat of the spongy lead. The electrolyte consisted of 10% sulfuric acid, approximately one liter being used in the cathode compartment. The porous cup serving as the anode compartment was kept filled with the acid. Part of the nitroheptanol was added to the cathode compartment, the catholyte mixture was continuously stirred and a current was passed through the cell. As the reduction took place, the nitroheptanol, which was suspended in the catholyte, went into solution. More nitroheptanol was added and reduction was continued. Only a small amount of oily material remained at the end of the reduction. The reduction cell was cooled in a water bath during the reduction, the temperature remaining at 30-35° C. Two reductions were carried out. Reduction was carried out with a current of 15-17 amperes and about 8 volts.

## Experiment I

| Amount of Nitro-heptanol added to cathode compartment | Time  | Amps. | Volts | Temp. of catholyte |
|---|-------|-------|-------|--------------------|
| 48 g.   | 10:10 | 15    | 10.5  | 30°                |
|   | 10:12 | 15    | 8     | 30°                |
|   | 1:05  | 15    | 8     | 35°                |
| 34 g.   | 1:05  | 15    | 8     | 35°                |
|   | 4:30  | 15    | 8     | 35°                |

Total 82 g. = 0.5 mole

$0.5 \times 3 = 1.5$  moles of  $H_2$  required

$15 \times 6 \frac{1}{3} = 95$  ampere hours used

$54 \times 1.5 = 81$  ampere hours required

## Experiment II

| Amount of Nitro-heptanol added to cathode compartment | Time  | Amps. | Volts | Temp. of catholyte |
|---|-------|-------|-------|--------------------|
| 71 g.   | 10:20 | 17    | 7.5   | 25°                |
|   | 1:00  | 17.5  | 7.5   | 32°                |
| 47 g.   | 1:00  | 17.5  | 7.5   | 32°                |
|   | 4:30  | 17.5  | 7.5   | 35°                |
| Stopped and stood overnight                           |       |       |       |                    |
|   | 8:20  | 17    | 11    | 25°                |
|   | 9:00  | 17    | 11    | 30°                |

Total 118 g. =  $0.7^+$  moles

$0.7 \times 3 = 2.1$  moles  $H_2$  required

$17 \times 7.5 = 127.5$  ampere hours used

$54 \times 2.1 = 115.4$  ampere hours required

The catholyte from Experiment I was filtered, extracted with benzene and again filtered through the filter cell. A clear filtrate was obtained. The benzene extract was reserved and combined with a similar benzene extract in Experiment II. The filtrate was made strongly alkaline with forty percent sodium hydroxide and then solid

sodium hydroxide was added. The oil which separated was collected by several extractions with benzene. The extract was dried over sodium hydroxide, the benzene was removed by distillation and the remaining oil was vacuum distilled. A forerun of 5 cc., boiling at 110-116° C./ 101 mm. was collected. The main fraction, 35 cc., was collected at 116-120° C./ 101 mm. and probably consisted of 3-amino-4-heptanol. Nine cubic centimeters of liquid remained in the distilling flask and might have been 3-amino-4-heptanol also.

Since only 49 cc. of material was accounted for, some of the aminoalcohol may have remained in the aqueous alkali solution. Probably the yield could be increased by using greater care in working up the reaction.

The catholyte from Experiment II was treated similarly up to the point of making it alkaline. . . . The benzene extracts of the acid catholytes were combined and the benzene was nearly all removed by evaporation in an open beaker."

The acid catholyte, mentioned in the previous paragraph, was sent to these Laboratories by Dr. Ulliot and treated in a manner identical to his directions with the exception that the aminoalcohol was extracted with many portions of ether which was then dried and distilled. The yield was 74 g. of aminoalcohol (75% theoretical) boiling between 95° and 100° at 20 mm.

pressure. Since this does not agree with the boiling point specified by Dr. Ulliot, the compound from Experiment I was distilled and found to be in agreement with the boiling point determined in these Laboratories.

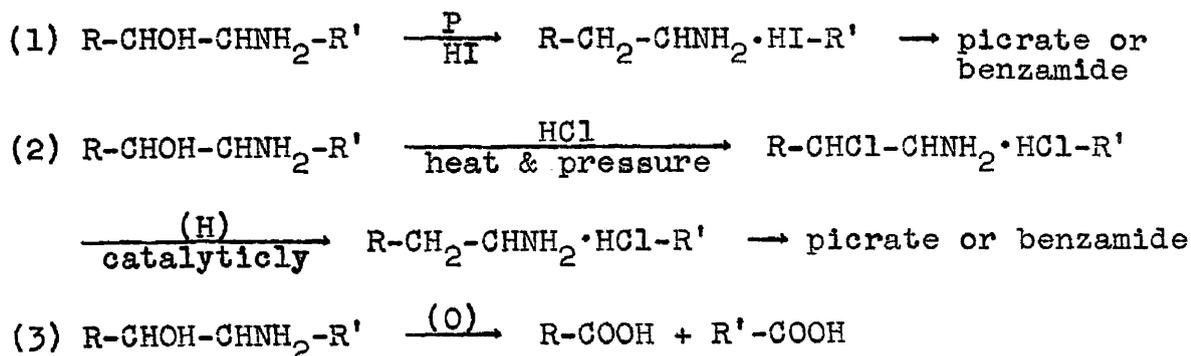
Benzoyl derivative: This compound was prepared in the usual manner as described under E-d, page 41, and melted at  $145^{\circ}$  C. (corrected); there was no melting point depression when this compound was mixed with the benzamide from 3-amino-4-heptanol prepared catalytically (see E-d, page 41).

(G) Stability experiment on 5-amino-4-octanol.

One-tenth mole (14.5 g.) of 5-amino-4-octanol was dissolved in enough absolute alcohol to make 50 cc. One gram of Raney nickel was added and the mixture subjected to reduction conditions at a pressure of 300 pounds per square inch and a temperature as high as  $85^{\circ}$  C. for 20 hours. There was no drop in pressure. Distillation after filtration resulted in the recovery of 13 g. or 90% of the original material, an indication that the aminoalkanols are stable at hydrogenation conditions.

## (H) Degradation of aliphatic aminoalcohols.

In an effort to substantiate the structure of the aliphatic aminoalcohols considered in this dissertation, the following reactions were considered feasible for better characterization:



These three methods were carried out but the last one was the only successful one.

(a) Attempted replacement of the hydroxyl group with hydrogen.

The method utilized was that of Suter (66). Five grams of 3-amino-4-heptanol, 15 cc. of hydriodic acid (s.g. 1.50) and 1.5 g. of red phosphorus were refluxed for 32 hours. The mixture was made alkaline with 20% sodium hydroxide solution and extracted with ether. Distillation of the dried ether solution failed to yield any 3-aminoheptane but 4 g. or 80% of the original 3-amino-4-heptanol was recovered.

(b) Attempted replacement of the hydroxyl group with chlorine.

This reaction was attempted at various temperatures with the use of a sealed tube. Ten grams of 3-amino-4-heptanol was dissolved in 8 cc. of concentrated hydrochloric acid and the solution, placed in a glass bomb-tube and cooled in an ice-bath, was saturated with gaseous hydrochloric acid.

After sealing, the tube was heated at  $175^{\circ}$  C. for 12 hours and then cooled. The result was one gram of ammonium chloride and a black tar.

Consequently, the experiment was repeated with the exception that the heating was at  $100^{\circ}$  for two hours. A small amount (0.2 g.) of ammonium chloride was produced in addition to a brown oil (6 g.) which was not of amine nature.

(c) Oxidation of 5-amino-4-octanol.

Because of the failure of the previous methods, it was decided to attempt to oxidize 5-amino-4-octanol under conditions which would cause the molecule to break in the center of the eight-carbon chain and produce two molecules of butyric acid for every one of amino-octanol. Acid permanganate solution was found to fulfill this requirement.

Therefore, 5.872 g. of the compound was oxidized by shaking for one hour with excess 3% solution of potassium permanganate acidified with sulfuric acid. After this time, the remaining permanganate was reduced with sodium sulfite and the resultant mixture filtered. The filtrate was made alkaline with 10% solution of sodium hydroxide and refiltered. The resultant solution was then evaporated to dryness on a water-bath. The dry crystals thus obtained were dissolved in the least quantity of 50% sulfuric acid and 2.8 g. of butyric acid (immediately identified by odor) separated. Repeated extraction of the aqueous portion with ether resulted in the isolation of 2.3 g. additional or a total of 5.1 g. of butyric acid.

This represents a 71% yield on the assumption that two molecules of butyric acid are produced from one molecule of the aminoöctanol, and since the yield is greater than 50%, proves the assumption.

In order to identify chemically the separated oil and ascertain its purity, it was decided to synthesize the anilide from equal quantities of it and pure butyric acid. A comparison of the amounts of derivative obtained from each and their melting points should yield this information.

The method of Shriner and Fuson (64) for anilide synthesis was applied to 2.0 cc. of each of the experimental and of the known acid and the resulting solid recrystallized from 50% aqueous alcohol.

| <u>Anilide of</u> | <u>Quantity obtained</u> | <u>Melting point</u> |
|-------------------|--------------------------|----------------------|
| Unknown acid      | 1.92 g.                  | 93.5° C. (cor.)      |
| Known acid        | 2.18 g.                  | 94.0° C. (cor.)      |
|                   | Mixed melting point      | 93.5° C. (cor.)      |
|                   | Literature (64)          | 95°                  |

(H) The action of alkaloidal precipitants on 3-amino-4-heptanol.

The preparation of crystalline hydrochlorides of the aminoalcohols described in this thesis has never been realized. This, however, is not surprising in view of the fact that Heintz (32) obtained only a syrup in synthesizing the hydrochloride of 2-amino-2-methyl-4-pentanol.

In an effort, therefore, to characterize better the

aliphatic aminoalcohols, a 5% solution of 3-amino-4-heptanol in 25% alcohol was added to the series of alkaloidal precipitants described by Hartung, Sumerford and Dunker (26) with the following results:

|  |                                      |
|--|--------------------------------------|
| Gold chloride solution:                            | orange, amorphous<br>precipitate     |
| Platinic chloride solution:                        | no reaction                          |
| Marme's reagent:<br>(to acidified solution)        | white platelets                      |
| Mayer's reagent:                                   | white, amorphous<br>precipitate      |
| Millon's reagent:                                  | white, curdy precipitate             |
| Dragendorff's reagent:                             | orange-red, amorphous<br>precipitate |
| Zinc chloride solution:                            | white, curdy precipitate             |
| Sonnenschein's reagent:<br>(to acidified solution) | yellow, curdy precipitate            |
| Sodium phosphotungstate<br>solution:               | white, amorphous<br>precipitate      |
| Pieric acid solution:                              | no reaction                          |
| Tannic acid solution:                              | brown, amorphous<br>precipitate      |

## SUMMARY AND CONCLUSIONS

In order to establish a background for the research described in this dissertation, there has been made a review of the literature involving the nitroparaffins, the nitroalkanols, the reduction of the nitroalkanols and the pharmacology of the aliphatic nitro compounds, amines and aminoalcohols.

The aliphatic nitroalcohols were prepared and their stability studied as a preliminary to their successful reduction. The unsuccessful catalytic reductions utilized palladinized charcoal and palladinized barium sulfate catalysts, and Raney nickel catalyst in neutral medium. The aminoalcohols were synthesized from the corresponding nitroalcohols with Raney nickel in an alcoholic medium acidified with acetic or carbonic acids. The electrolytic reduction of 3-nitro-4-heptanol to the corresponding aminoalcohol was carried out in excellent yields.

The proof of structure of the aminoalcohols, in addition to conventional nitrogen analyses of the original compounds and their benzoyl derivatives, consisted in splitting one of them, 5-amino-4-octanol, into two acid fragments by oxidation, in this case into two molecules of butyric acid.

The results of this research indicate that the optimum yields of aminoalkanol from nitroalkanol are

obtained by electrolytic reduction.

However, catalytic hydrogenation, which is much more generally utilized, can be successfully employed if Raney nickel catalyst is used and the alcoholic medium is acidified with an acid weak enough to be inactive toward the metal catalyst. The use of acetic acid in preference to carbonic acid is indicated for the following reasons:

1. Better yield of product results.
2. Lower hydrogen pressure is required.
3. Since solid carbon dioxide, the source of the carbonic acid, sublimes while the apparatus is being sealed, an accurate determination of the amount of gas in the reaction mixture is impossible.
4. There is no necessity of awaiting the establishment of any thermal or pressure equilibrium.
5. In view of the difficulty of storing solid carbon dioxide, the use of acetic acid is much more economical.

## V. LITERATURE CITED

1. Alles, G. A., Univ. Calif. Pub. Pharmacol., 2, 1-32 (1941).
2. Association of Official Agricultural Chemists, Official and Tentative Methods of Analysis of the -; Fourth Edition, Washington, D. C., 1935, p. 25.
3. Barger, G. and Dale, H. H., J. Physiol., 41, 19-59 (1910).
4. Beilstein, F. and Kurbatow, A., Ber., 13, 1818 (1880).
5. Bickel, V. T. and French, H. E., J. Am. Chem. Soc., 48, 747 (1926).
6. Blicke, F. F. and Zienty, F. B., J. Am. Chem. Soc., 61, 771-773 (1939).
7. Bouveault, L. and Wahl, A., Compt. rend., 135, 41 (1902).
8. Buth, W., Külz, F. and Rosenmund, K. W., Ber., 72-B, 19-28 (1939).
9. Commercial Solvents Corporation, "The Nitroparaffins", New York, N. Y., 1942.
10. Covert, L. W. and Adkins, H., J. Am. Chem. Soc., 54, 4116-4117 (1932).
11. Cushny, A. R., "Pharmacology and Therapeutics", Twelfth Edition, revised by C. W. Edmunds and J. A. Gunn, Lea and Febiger, Philadelphia, Pa., 1940, p. 662.
12. de Mauny, H. C., Bull. soc. chim., (5), 4, 1451-1460 (1937) → C. A., 32, 494 (1938).
13. Dittrich, T. D., Thesis, Doctor of Philosophy, University of Maryland, 1942.
14. Dunker, M. F. W. and Hartung, W. H., J. Am. Pharm. Assoc., 30, 619-623 (1941).
15. Dunker, M. F. W., Hartung, W. H. and Chapman, C. W., J. Am. Pharm. Assoc., 30, 623-625 (1941).

16. Ellis, C., "Hydrogenation of Organic Substances", Third Edition, D. Van Nostrand Company, Inc., New York, N. Y., 1930.
17. Emerson, W. S. and Mohrman, H. W., J. Am. Chem. Soc., 62, 69-70 (1940).
18. Flury, F. and Zernik, F., "Schadliche Gase", Berlin, 1931, p. 417 → J. Ind. Hyg. Toxicol., 22, 315-322 (1940).
19. Foster, C. P., Thesis, Doctor of Philosophy, University of Maryland, 1942.
20. Gibbs, W. and Reichert, E. T., Am. Chem. J., 13, 361-370 (1891).
21. Gunn, J. A. and Gurd, M. R., J. Physiol., 97, 453-470 (1940).
22. Hartung, W. H., J. Am. Chem. Soc., 50, 3370-3374 (1928).
23. Hartung, W. H., Chemical Reviews, 2, 389-465 (1931).
24. Hartung, W. H., unpublished.
25. Hartung, W. H. and Munch, J. C., J. Am. Chem. Soc., 51, 2262-2266 (1929).
26. Hartung, W. H., Sumerford, W. T. and Dunker, M. F. W., "Laboratory Exercises in the Chemistry of Organic Medicinal Products", p. 117.
27. Hass, H. B., Hodge, E. B. and Vanderbilt, B. M., Ind. Eng. Chem., 28, 339-344 (1936).
28. Hass, H. B. and Patterson, J. A., Ind. Eng. Chem., 30, 67-69 (1938).
29. Hass, H. B. and Vanderbilt, B. M., U. S. Pat. 2, 139, 122, (December 6, 1938).
30. Hass, H. B. and Vanderbilt, B. M., U. S. Pat. 2, 139, 123, (December 6, 1938).
31. Hass, H. B. and Vanderbilt, B. M., U. S. Pat. 2, 139, 124, (December 6, 1938).
32. Heintz, W., Ann., 183, 297 (1876).
33. Henry, L., Compt. rend., 120, 1265 (1895).
34. Henry, L., Rec. trav. chim., 20, 8 (1901) → Ind. Eng. Chem., 32, 38 (1940).

35. Jenkins, G. L. and Hartung, W. H., "The Chemistry of Organic Medicinal Products", John S. Swift Co., Inc., St. Louis, Mo., 1941, p. 249.
36. Johnson, K., U. S. Pat. 2,157,386 (May 9, 1939).
37. Johnson, K., U. S. Pat. 2,267,375 (December 23, 1941).
38. Kamlet, J., U. S. Pat. 2,151,517 (March 21, 1939).
39. Kanao, S., J. Pharm. Soc. Japan no. 550, 1019-1035 (1927)  
→ C. A., 22, 1588 (1928).
40. Kauffmann, H., Ber., 50, 630-637 (1917).
41. Knoevenagel, E. and Walter, L., Ber., 37, 4502 (1904).
42. Linnemann, E. and v. Zotta, V., Ann., 162, 4 (1872).
43. Machle, W., Scott, E. W. and Treon, J. F., J. Ind. Hyg. Toxicol., 22, 315-322 (1940).
44. Machle, W., Scott, E. W. and Treon, J. F., J. Ind. Hyg. Toxicol., 24, 5-9 (1942).
45. Markownikoff, W., Ber., 33, 1905 (1900).
46. Mayer, A., Plantefol, L. and Vles, F., Compt. rend. Acad. d. Sc., 171, 1396 (1920).
47. Meyer, V. and Stüber, O., Ber., 5, 203-205 (1872).
48. Montmollin, W. and Achermann, A., Helv. Chim. Acta, 12, 875 (1929).
49. Ott, E. and Schröter, R., Ber., 60, 633 (1927).
50. Palfray, L. and Sabetay, S., Compt. rend., 208, 109-112 (1939).
51. Piloty, O. and Ruff, O., Ber., 30, 2057 (1897).
52. Posner, Th., Ber., 31, 656 (1898).
53. Priebis, B., Ann d. Chem., 225, 321 (1884).
54. Raney, M., U. S. Pat. 1,628,190 (May 10, 1927).
55. Reihlen, H., Knöpfle, L. and Sapper, W., Ann., 534, 247-275 (1938).
56. Schadow, G., Arch. f. exper. Pathol., 6, 194 (1877).
57. Schmidt, E., Ber., 52, 409 (1919).

58. Schmidt, E., Ascherl, A. and Mayer, L., Ber., 58, 2430-2434 (1925).
59. Schmidt, E. and Wilkendorf, R., Ber., 52, 398 (1919).
60. Schmidt, E. and Wilkendorf, R., Ber., 55, 321 (1922).
61. Schmidt, J., "A Text-Book of Organic Chemistry", English Edition by H. Gordon Rule, Second Edition, Gurney and Jackson, London, England, 1932, p. 155.
62. Scott, E. W. and Treon, J. F., Ind. Eng. Chem., Anal. Ed., 12, 189 (1940).
63. Senkus, M., U. S. Pat. 2,267,309 (December 23, 1941).
64. Shriner, R. L. and Fuson, R. C., "The Systematic Identification of Organic Compounds", Second Edition, John Wiley and Sons, New York, N. Y., 1940.
65. Sprang, C. A. and Degering, E. F., J. Am. Chem. Soc., 64, 1063-1064.
66. Suter, C. M., private communication.
67. Tainter, M. L., Arch. internat. Pharmacodyn., 46, 192-232 (1933).
68. Thiele, J., Ber., 32, 1293 (1899).
69. Tindall, J. B., Ind. Eng. Chem., 33, 65-66 (1941).
70. Trendelenburg, P., "Handbuch der Experimentellen Pharmakologie", Julius Springer, Berlin, Germany, 1923.
71. Ulliot, G. E., private communication.
72. Vanderbilt, B. M., U. S. Pat. 2,135,444 (November 1, 1938).
73. Vanderbilt, B. M., U. S. Pat. 2,157,391 (May 9, 1939).
74. Vanderbilt, B. M. and Hass, H. B., Ind. Eng. Chem., 32, 34-38 (1940).
75. Vanderbilt, B. M. and Hass, H. B., U. S. Pat. 2,164,271 (June 27, 1939).
76. Zenitz, B. L., Thesis, Doctor of Philosophy, University of Maryland, 1943.

