IOWA STATE UNIVERSITY
Digital Repository

Retrospective Theses and Dissertations

Iowa State University Capstones, Theses and Dissertations

1940

High-molecular-weight aliphatic amines and their derivatives

William Irving Harber
Iowa State College

Follow this and additional works at: https://lib.dr.iastate.edu/rtd

Part of the Organic Chemistry Commons

Recommended Citation

Harber, William Irving, "High-molecular-weight aliphatic amines and their derivatives " (1940). *Retrospective Theses and Dissertations*. 13702.
https://lib.dr.iastate.edu/rtd/13702

This Dissertation is brought to you for free and open access by the Iowa State University Capstones, Theses and Dissertations at Iowa State University Digital Repository. It has been accepted for inclusion in Retrospective Theses and Dissertations by an authorized administrator of Iowa State University Digital Repository. For more information, please contact digirep@iastate.edu.

المنارة للاستشارات

www.manaraa.com

NOTE TO USERS

This reproduction is the best copy available.

UMI®

HIGH-MOLECULAR-WEIGHT ALIPHATIC AMINES
AND THEIR DERIVATIVES

by

William Irving Harber

A Thesis Submitted to the Graduate Faculty
for the Degree of

DOCTOR OF PHILOSOPHY

Major Subject Organic Chemistry

IOWA STATE
AMES IA
COLLEGE LIBRARY

Approved:

Signature was redacted for privacy.

In charge of Major work

Signature was redacted for privacy.

Head of Major Department

Signature was redacted for privacy.

Dean of Graduate College

Iowa State College

1940

UMI Number: DP12736

INFORMATION TO USERS

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleed-through, substandard margins, and improper alignment can adversely affect reproduction.

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

UMI®

UMI Microform DP12736

Copyright 2005 by ProQuest Information and Learning Company.

All rights reserved. This microform edition is protected against

unauthorized copying under Title 17, United States Code.

ProQuest Information and Learning Company
300 North Zeeb Road
P.O. Box 1346
Ann Arbor, MI 48106-1346

QD305.A8
H21h

[illegible]

ACKNOWLEDGMENT

The author wishes to express his appreciation to Professor Henry Gilman for the initiation of the problem and to Professor W. F. Coover for guidance in the successful termination of the work. The author also wishes to thank Dr. A. W. Ralston of Armour and Co., Chicago, Ill., for supplying liberal amounts of materials required in this study.

T6489 ✓

TABLE OF CONTENTS

INTRODUCTION

Until recently, studies on high-molecular-weight aliphatic amines were usually confined to investigations of a classical nature. Thus, high-molecular-weight aliphatic amines were involved in experiments in which rearrangement studies were extended to higher members in a given series. Some examples would be the extension of the Hofmann and Curtius rearrangements to higher homologs. Yet during this time, Krafft and his school developed techniques for the synthesis of high-molecular-weight aliphatic amines in order to obtain pure compounds which could be used as a basis for studying natural products.

With the recent trend in organic chemistry toward aliphatic chemistry, a larger number of entries is to be found in the field of high-molecular-weight aliphatic amines, especially in the past ten years. This increase results from the fact that these amines and their salts are finding wide application as flotation agents, detergents, emulsifiers, solvents, germicides, plasticizers for ceramic bodies and as agents for the reduction of firing losses. Also, this class of compounds has recently increased in importance, since the production of "Nylon" involves the use of aliphatic diamines as intermediate building blocks. Yet the majority of these recent entries are in the form of patent citations. These, at best, are an unreliable source of data.

The new commercial importance of high-molecular-weight aliphatic amines is a direct outgrowth of the technical production of high-molecular-weight fatty acids. These acids have been used for the successful preparation of high-molecular-weight aliphatic nitriles which today are the best source of high-molecular-weight aliphatic amines. The commercial availability of these amines has been a stepwise development: acids ⟶ nitriles ⟶ amines. Each type of compound has been found to be commercially important. The uses of high-molecular-weight fatty acids are legion and need not be mentioned here. The high-molecular-weight aliphatic nitriles have found wide application as starting materials in the production of other derivatives. They have unique properties as solvents, and are not toxic in any proportions.

It is as recently as this year that high-molecular-weight aliphatic nitriles and amines have been made commercially available (1). Thus, the chemistry of high-molecular-weight aliphatic amines has become a vanguard of investigation in aliphatic chemistry.

Along with the recent trend in organic chemistry to studies in the aliphatic field, there has been a further emphasis on the isolation and determination of structure

---

(1) Armour and Co., Chemical Bulletin, 27, 37 (1940).

of natural products. The chemistry of high-molecular-weight aliphatic amines has recently attained a new importance in these investigations. Researches on the lichen substances and plant waxes have shown that high-molecular-weight aliphatic amines are isolated in degradation studies. This makes it important that adequate derivatives exist for the identification of the amines. Comparative studies on the value of such derivatives would be of much use in determining the identity of compounds isolated in the process of investigating the structures of natural products.

Finally, the aliphatic amines show possibilities as pharmacological agents of importance. However, in many cases, it has been difficult to make any correlations between structure and physiological action, since the purity of the amines has been open to question (2). Thus, the development of techniques for the preparation of pure samples of aliphatic amines is of increasing importance.

This thesis is concerned with an investigation of the preparation, reactions and derivatization of high-molecular-weight aliphatic amines. It was hoped this work would serve the following purposes: first, develop special techniques required in reactions of compounds of high molecular weight; second, make a study of the preparation of such derivatives

(2) Dunker, M.F.W., "Aliphatic Amines-A Review", presented before the Division of Medicinal Chemistry, Spring Meeting, American Chemical Society (1940); private communication.

which would serve to identify adequately high-molecular-weight aliphatic amines; third, throw some light on the relative reactivities of higher homologs in the series of aliphatic amines; and finally, make available further compounds which might be either commercially useful themselves, or provide intermediates for use in further synthetic work.

HISTORICAL

Purification of Stearic Acid

Stearic acid was obtained by Heinz (3) by the saponification of mutton fat, and after crystallization from ethanol was found to melt at 69.1-69.2°. Heinz emphasized that the melting point he recorded was good only insofar as his apparatus was used.

In the preparation of high-molecular-weight ketones, Kipping (4) crystallized crude, commercial stearic acid from alcohol, and found it to melt at 68.0-69.0°. He noted that the stearic acid crystallized from ethanol retained some of the solvent even after long exposure to the air on a porous plate. This lowered the melting point considerably.

Hell and Sadomsky (5) prepared a sample of stearic acid melting at 69.2°. The original acid was converted to the magnesium salt. This upon acidification gave the free acid. The precipitation was repeated twice. De Visser (6) obtained stearic acid by saponification of a vegetable fat. After 55 crystallizations from 92% ethanol the melting point remained constant. After another six crystallizations the crystals

(3) Heinz, _J. prakt. Chem._, _66_, 22 (1855).

(4) Kipping, _J. Chem. Soc._, _57_, 537 (1890).

(5) Hell and Sadomsky, _Ber._, _24_, 2389 (1891).

(6) De Visser, _Rec. trav. chim._, _17_, 183 (1898).

solidified at 69.320° (corr).

Later workers used Kahlbaum's stearic acid as their source. Partheil and Ferie (7) found that by a single distillation of Kahlbaum's stearic acid the compound melted at 70.5°. Smith (8) found Kahlbaum's stearic acid to melt at 67.8°. Seven crystallizations from ethanol raised the melting point to 69.30° (corr.) but there was a 75 per cent loss of material. Three more crystallizations raised the melting point to 70.5°.

In studies on the melting points of high-molecular-weight fatty acids, Levene and Taylor (9) started with Kahlbaum's oleic acid. This after conversion to the ethyl ester was reduced to ethyl stearate. The distilled ester was saponified to give stearic acid melting at 70.5-71.5°. Crystallization from pyridine, and conversion into the lead salt with subsequent liberation of the acid failed to alter it. These investigators made the interesting observation that the melting points of fatty acids were lowered on standing several years in specimen bottles. Material with the original melting point could be recovered by recrystallization. Frequently, however, the proportion of material recovered was small. The age of the sample was, therefore, important.

(7) Partheil and Ferié, <u>Arch</u>. <u>Pharm</u>., <u>241</u>, 552 (1903).

(8) Smith, <u>J</u>. <u>Chem</u>. <u>Soc</u>., <u>1931</u>, 802.

(9) Levene and Taylor, <u>J</u>. <u>Biol</u>. <u>Chem</u>., <u>59</u>, 905 (1924).

This phenomenon was probably due to the different orientations of carbon atoms in the crystal. It seemed that the process was spontaneous and occurred continuously.

Extremely pure aliphatic acids were required for studies in crystal spacing of high-molecular-weight compounds (10). A knowledge of crystal spacings of known compounds and of those obtained from natural sources can be used to establish the identity of a natural product. Francis and co-workers found that extremely pure aliphatic acids dissolved in concentrated sulfuric acid at 70° to give colorless solutions, but even purest specimens of Kahlbaum's stearic acid gave dark solutions owing to the presence of unsaturated material. This was true even after six crystallizations from glacial acetic acid. The stearic acid was first crystallized from concentrated sulfuric acid and then three times from glacial acetic acid. It still contained one per cent of impurities. The acid was converted to the ethyl ester, fractionated, and the middle fraction converted to the free acid. The material was further crystallized from acetic acid until a constant melting point of 69.9° was obtained. The use of methanol or ethanol as a crystallizing medium was discarded since esterification was possible. Yet, Guy and

(10) Francis and co-workers, Proc. Roy. Soc. (London), A158, 691 (1937); J. Chem. Soc., 1937, 999; J. Am. Chem. Soc., 61, 577 (1939).

Smith (11) took the purest commercial stearic acid available, melting at 68.4°, and crystallized it six times from ethanol and twelve times from benzene to give a melting point of 69.56°. The loss of material was about 90 per cent. Further crystallization from benzene did not change the melting point. However, after four crystallizations from acetone the melting point was raised to 69.62° but the total loss of material was now 96 per cent.

A melting point of 71.5-72.0° was reported for a stearic acid isolated from seeds of _Pentadesma Kerstingii_, a plant native to West Africa (12).

By fractionation of hydrogenated ethyl oleate followed by recrystallization from acetone stearic acid has been found to melt at 70-71° (13).

Nitriles

High-molecular-weight aliphatic nitriles may be prepared by the classical method of dehydration of amides with phosphorous pentoxide (14) or by means of thionyl chloride (15).

(11) Guy and Smith, _J. Chem. Soc._, _1939_, 615.

(12) Wagner, Muesmann and Lampart, _Z. Nahr. Genuss._, _28_, 244 (1914).

(13) Pool, Harwood and Ralston, _J. Am. Chem. Soc._, _59_, 178 (1937).

(14) Krafft and Stauffer, _Ber._, _15_, 1730 (1882).

(15) Stephen, _J. Chem. Soc._, _127_, 1874 (1925).

However, this method is indirect since it is necessary to go through the stages: acid ⟶ acid halide ⟶ acid amide ⟶ nitrile. The cost of reagents and the time consumed in the preparation make this method impractical for obtaining any quantity of material. Yet, high-molecular-weight nitriles have recently been produced commercially by the dehydration of acid amides with phosgene (16).

An attempt was made to obtain aliphatic nitriles by heating the zinc salts of the fatty acids with lead thiocyanate (17). In the case of stearonitrile the yield was 10-19 per cent and the product was of questionable purity.

The preparation of unsaturated high-molecular-weight aliphatic nitriles was reported by passing the mixed vapors of esters and ammonia over aluminum oxide at 490-500° (18).

The direct synthesis of high-molecular-weight aliphatic nitriles was investigated by Ralston, Harwood and Pool (19). They heated stearic acid at 330° while an excess of ammonia was passed into the melt. They obtained an 85 per cent yield of stearonitrile. Their apparatus included a catalytic tube with aluminum oxide to convert the stearic acid

---

(16) British patent, 488,036 (1938) /C.A., 33, 178 (1939)/.

(17) Van Epps and Reid, J. Am. Chem. Soc., 38, 2120 (1916).

(18) Maihle, Bull. soc. chim., 27, 226 (1920).

(19) Ralston, Harwood and Pool, J. Am. Chem. Soc., 59, 986 (1937).

carried over by the gas stream to stearonitrile. McCorkle (20) simplified the apparatus with only a moderate decrease in yield.

High-molecular-weight aliphatic nitriles may, of course, be obtained from other nitriles. Unsaturated aliphatic nitriles when reduced catalytically with hydrogen in the presence of copper catalysts gave mainly saturated nitriles. There was some formation of amine (21). Low-molecular-weight aliphatic nitriles have been alkylated with alkyl bromides, in the presence of alkali amides, to give high-molecular-weight nitriles (22).

High-molecular-weight aliphatic nitriles with an odd number of carbon atoms may be prepared by treatment of the alkyl halide with potassium cyanide (9).

The synthesis of high-molecular-weight aliphatic dinitriles follows the procedures for the mononitriles. The treatment of 1,2-dihalides (23) or methylenedihalides (24) with potassium cyanide gives the dinitrile. Treatment of diamides with phosphorous pentoxide (25), phosphorous oxychloride (26) or ammonia at elevated temperatures (27) gives

(20) McCorkle, Doctoral Dissertation, Iowa State College (1938).
(21) French patent, 732,936 (1932)[*Chem.Zentr.*, *II*, 1235 (1932)].
(22) French patent, 728,241 (1932)[*ibid.*, *I*, 1198 (1933)].
(23) Krafft and Grosjean, *Ber.*, *23*, 2355 (1890).
(24) Ziegler and Hechelhammer, *Ann.*, *528*, 114 (1937).
(25) Trunel, *Ann. chim.*, *12*, 93 (1939).
(26) U.S. patent, 1,828,267 (1932)[*C.A.*, *26*, 735 (1932)].
(27) U.S. patent, 2,123,849 (1939)[*C.A.*, *33*, 178 (1939)].

the dinitrile. A more direct approach is the treatment of the neutral ammonium salt with either phosphorous oxychloride or phosphorous trichloride (28).

Naming of Amines

The term high-molecular-weight aliphatic amines will be limited to those molecules which contain at least one straight chain of ten or more carbon atoms and no aryl groups in any part of the molecule. Primary, secondary and tertiary amines will be considered.

In the naming of amines the random choice between such prefixes as lauryl- for _n_-dodecyl-, myristyl- for _n_-tetradecyl-, etc., will be avoided by constant use of the Greek prefixes accepted by the International Union of Chemistry (29).

The two systems of differentiating the three main classes of amines may cause some difficulty. Primary butylamine, secondary butylamine and tertiary butylamine may be mistakenly conceived of as all primary amines where the butyl radical is being prefixed rather than the class. The system of differentiating the three classes of amines by means of the prefixes mono-, di- and tri- is to be preferred. In the case

(28) U.S. patent, 1,876,652 (1933)[_C_._A_., _27_, 102 (1933)].

(29) International Union Rules, _J_. _Am_. _Chem_. _Soc_., _55_, 3905 (1933).

of tridecylamine where the primary amine $C_{13}H_{27}NH_2$ may be confused with the tertiary amine $(C_{10}H_{21})_3N$, it is only necessary to note adequately the prefix for the chain. Thus, $C_{13}H_{27}NH_2$ should be noted as n-tridecylamine while $(C_{10}H_{21})_3N$ becomes tri-n-decylamine.

Preparation of High-Molecular-Weight Amines

In discussing the preparation of amines of all three classes, a distinction has been made between synthesis and method of formation. In order for a preparative method to be listed under methods of synthesis the conditions were imposed (a) that the starting products be readily available, (b) that the end products be formed in compensating yields, and (c) that there be a minimum of by-products.

In methods of formation, the amines were formed incidental to other investigations, usually in the field of natural products. Also, under methods of formation were placed those processes where the amount of by-products was high.

The amount of work done on the preparation of alkylated amines of the types:


$R-\overset{H}{N}-R'$


$R-\overset{R'}{N}-R'$

R-always high-molecular-weight, saturated, alkyl radical

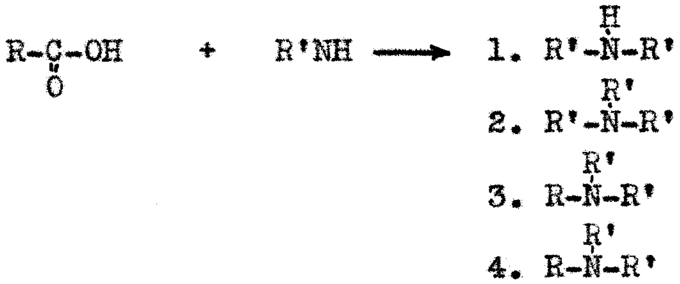
R'-always low-molecular-weight, saturated, alkyl radical is very large and in the main confined to the patent literature. Alkylation of amines may be attacked directly:

$$RX + R'NH_2 \longrightarrow R\text{-}\overset{H}{N}\text{-}R'$$

or indirectly:

$$RCN + R'_2NH \xrightarrow[\nabla\ \theta]{[H]} R\text{-}\overset{R'}{N}\text{-}R'$$

∇ = pressure θ = catalyst



$$R\text{-}\underset{O}{\overset{\|}{C}}\text{-}OH + R'NH \longrightarrow \begin{array}{l} 1.\ R'\text{-}\overset{H}{N}\text{-}R' \\ 2.\ R'\text{-}\overset{R'}{N}\text{-}R' \\ 3.\ R\text{-}\overset{R'}{N}\text{-}R' \\ 4.\ R\text{-}\overset{R'}{N}\text{-}R' \end{array}$$

In the latter case several reactions take place under the experimental conditions, and among the products are the desired alkylated amines. In every case where they are formed from intermediate products rather than from original starting materials a complex mixture of the types illustrated results. After the collection and evaluation of the data on these preparations, it was decided not to include them, inasmuch as they were essentially repetitions of most of the straight-forward alkylations and preparations. While these methods have found application in industry, their use in the laboratory becomes insignificant when excellent methods for the preparation of alkylated amines are available by direct alkylation. These methods are given a separate consideration (p. 37).

Synthesis of High-Molecular-Weight Primary Amines

1. From the nitrile by wet reduction.

$$4\ ROH + 4\ Na \longrightarrow 2\ H_2 + 4\ RONa$$

$$RCN + 2\ H_2 \longrightarrow RCH_2NH_2$$

This method is one of the oldest and most satisfactory for the preparation of primary amines. The original technique was introduced by Krafft and co-workers (14)(30) and used by many later investigators (31)(32)(33)(34)(35). The procedure has been simplified by Adam and Dyer (36). The yields are generally good. The amine is isolated as the stable hydrochloride in a rather pure condition. Commercially, the reaction is carried out under pressure (37). This method has

(30) Krafft and co-workers, Ber., 22, 812 (1889); 23, 2361 (1890); 29, 133 (1896).

(31) Gaade, Rec. trav. chim., 55, 541 (1936).

(32) Walden and Birr, Z. physik. Chem., A144, 284 (1929).

(33) Grunfeld, Compt. rend., 194, 893, 1083 (1932).

(34) Teunissen, Rec. trav. chim., 46, 208 (1927).

(35) v. Braun, and Sobecki, Ber., 44, 1437 (1911).

(36) Adam and Dyer, J. Chem. Soc., 127, 70 (1925).

(37) French patent, 703,844 (1930) [Chem. Zentr., II, 2512 (1939)].

been used for the synthesis of optically active amines (38).

2. From the nitrile by catalytic reduction.

$$RCN + 2\ H_2 \longrightarrow RCH_2NH_2$$

Primary amines are formed almost exclusively by catalytic reduction of nitriles by admixing some ammonia with the hydrogen. This drives back the equilibrium:

$$RNH_2 + RNH_2 \longrightarrow R_2NH + NH_3$$

avoiding the formation of secondary amine. The amount of ammonia required may be as little as two per cent. In one report (39) a ninety per cent yield of *n*-octadecylamine was obtained by the reduction of stearonitrile using an oxide or sulfide of a metal of Group 6 or 8 as a catalyst. Hoyt (40) has obtained correspondingly good yields using a Raney nickel catalyst. Cyclohexane may be used as a reaction solvent (41).

3. From secondary amines.

$$R_2NH + NH_3 \longrightarrow 2\ RNH_2$$

(38) Levene and Mikeska, *J. Biol. Chem.*, *84*, 571 (1929); Levene and Marker, *ibid.*, *115*, 267 (1936).

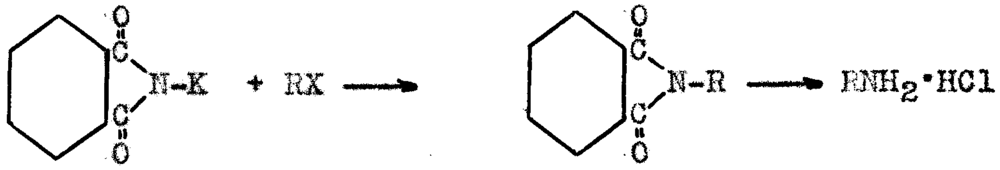
(39) French patent, 781,960 (1935) [*Chem. Zentr.*, *I*, 878 (1936)].

(40) Hoyt, Doctoral Dissertation, Iowa State College (1940).

(41) French patent, 773,367 (1934) [*Chem. Zentr.*, *I*, 3076 (1935)].

This is the reaction whose progress was fostered in the synthesis of primary amines from nitriles by catalytic reduction. The secondary amines are heated under pressure with ammonia in the presence of salts of strong acids, e.g., ammonium chloride (42).

4. Gabriel's Synthesis.



Of all the high-molecular-weight amines, only *n*-decylamine has been synthesized by this method. In studies in the *n*-decyl series, Komppa and Talviti (43) required extremely pure *n*-decylamine, and used this method successfully. The amine was obtained as the hydrochloride when the N-*n*-decylphthalimide was split with hydrogen chloride.

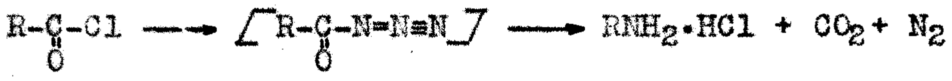
5. From acids and acid chlorides.

The preparation of amines from acids or acid halides, involving the intermediate formation of an acid azide with its subsequent decomposition to give the next lower amine, is essentially a Curtius rearrangement. Naegeli and co-workers

(42) German patent, 580,517 (1932) [*ibid.*, II, 2053 (1933)].

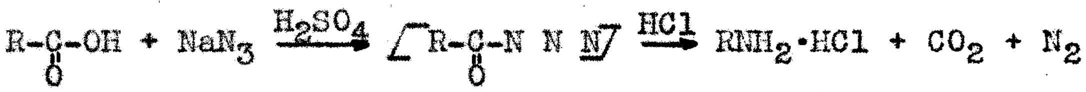
(43) Komppa and Talviti, *J. prakt. Chem.*, 135, 193 (1932).

(44) were the first to appreciate this transformation as a method of synthesis of primary amines from acid chlorides.



$$R-\underset{\underset{O}{\|}}{C}-Cl \longrightarrow [R-\underset{\underset{O}{\|}}{C}-N=N\equiv N] \longrightarrow RNH_2\cdot HCl + CO_2 + N_2$$

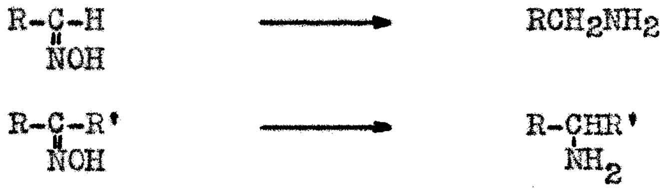
This preparation is called the Naegeli-Curtius synthesis. Schmidt (45) used the free acid in place of the acid chloride and free hydrazoic acid from the sodium azide.



$$R-\underset{\underset{O}{\|}}{C}-OH + NaN_3 \xrightarrow{H_2SO_4} [R-\underset{\underset{O}{\|}}{C}-N\ N\ N] \xrightarrow{HCl} RNH_2\cdot HCl + CO_2 + N_2$$

The experimental details were further developed by Oesterlin (46).

6. <u>From aldoximes and ketoximes</u>.



$$R-\underset{\underset{NOH}{\|}}{C}-H \longrightarrow RCH_2NH_2$$

$$R-\underset{\underset{NOH}{\|}}{C}-R' \longrightarrow R-\underset{\underset{NH_2}{|}}{C}HR'$$

High-molecular-weight aliphatic aldehydes are not easily available inasmuch as they readily polymerize to form dimers or trimers (15). The aldoximes or ketoximes on reduction with sodium and ethanol or sodium amalgam give the corresponding amines. Since no yields are reported (30)(47)(48)

(44) Naegeli and co-workers, Helv. Chim. Acta, 12, 227 (1929).

(45) German patent, 500,435 (1930) [Chem. Zentr., I, 1536 (1930)].

(46) Oesterlin, Angew. Chem., 45, 536 (1932).

(47) Thoms and Mannich, Ber., 47, 2456 (1914).

(48) Ponzio, Gazz. chim. ital., II, 24, 270 (1894).

a comparison of the yields from the aldoximes and ketoximes is not possible.

7. From urea compounds.

In the earliest times, high-molecular-weight primary amines were obtained as a result of studies on the Hofmann (49) and Curtius rearrangements (50)(51).

From the reaction of an acid amide and alkaline bromine an intermediate urea derivative is isolable, which after admixing with a solid base and distilling is converted to the next lower primary amine in excellent yields.

$$R-\underset{\underset{O}{\|}}{C}-NH_2 \longrightarrow RNH-\underset{\underset{O}{\|}}{C}-NH-\underset{\underset{O}{\|}}{C}-R \longrightarrow RNH_2$$

By heating the urea with concentrated hydrochloric acid the amine is formed as the hydrochloride.

The so-called Jeffreys-Hofmann modification (52)(53) involves treating the acid amide with bromine and sodium methoxide. The resulting urethane gives quantitative yields of amine when distilled with a base.

$$R-\underset{\underset{O}{\|}}{C}-NH_2 \longrightarrow RNH-\underset{\underset{O}{\|}}{C}-OCH_3 \longrightarrow RNH_2$$

---

(49) Hofmann, *Ber.*, **15**, 1774 (1882).

(50) Curtius and co-workers, *J. prakt. Chem.*, **64**, 435 (1901); **89**, 519 (1914).

(51) Lutz, *Ber.*, **19**, 1436 (1886).

(52) Jeffreys, *Am. Chem. J.*, **22**, 31 (1899); *Ber.*, **30**, 898 (1897).

(53) Blau, *Monatsh.*, **26**, 101 (1905).

The synthesis of primary amines *via* the unisolated acid azide has already been mentioned (p. 25). However, in the earliest investigations by Curtius, the acid azide was first isolated and its properties studied. It was found that upon warming the aqueous solution of the acid azide it rearranged to the symmetrical urea, and this upon distillation with a base provided a source of hitherto unobtainable amines.

$$R-\underset{\overset{\|}{O}}{C}-N=N\equiv N \longrightarrow RNH-\underset{\overset{\|}{O}}{C}-NHR \longrightarrow 2\ RNH_2$$

A variation of this method involved treating the acid azide with an alcohol to form the urethane, which when heated with concentrated hydrochloric acid yielded the primary amine hydrochloride (54).

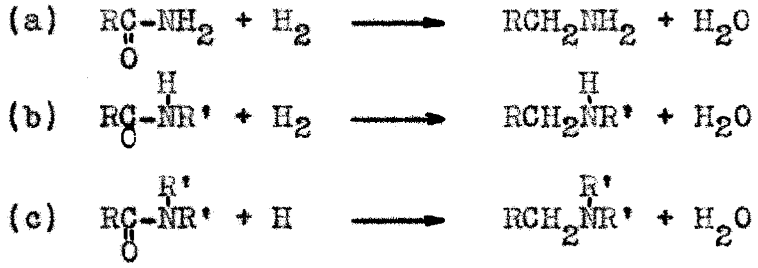
Formation of High-Molecular-Weight Primary Amines

1. From acid amides, ammonium salts and N-substituted acid amides.

Wojcik and Adkins (55) made an extensive study of the catalytic reduction of these compounds using a copper-chromium oxide catalyst and dioxane as a solvent. They found the primary reactions to be:

(54) Otiai and Simizu, *J. Pharm. Soc. Japan*, *58*, 930 (1938).

(55) Wojcik and Adkins, *J. Am. Chem. Soc.*, *56*, 2422 (1934).

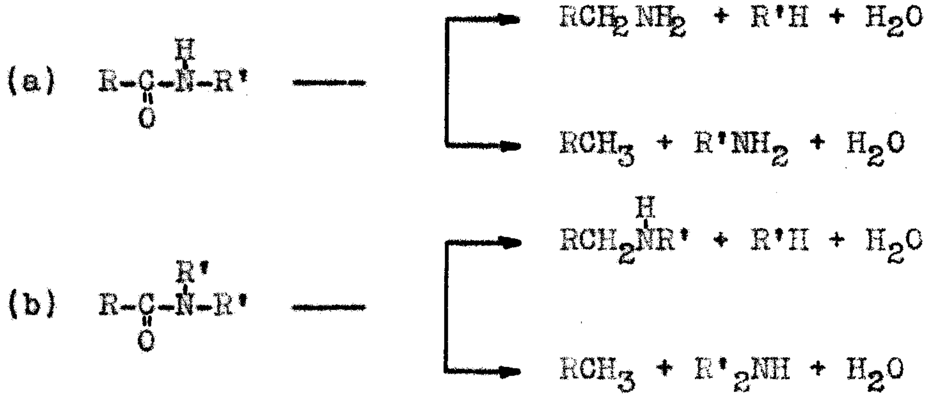


$$\text{(a)}\quad R\underset{\underset{O}{\|}}{C}-NH_2 + H_2 \longrightarrow RCH_2NH_2 + H_2O$$

$$\text{(b)}\quad R\underset{\underset{O}{\|}}{C}-\overset{H}{\overset{|}{N}}R' + H_2 \longrightarrow RCH_2\overset{H}{\overset{|}{N}}R' + H_2O$$

$$\text{(c)}\quad R\underset{\underset{O}{\|}}{C}-\overset{R'}{\overset{|}{N}}R' + H \longrightarrow RCH_2\overset{R'}{\overset{|}{N}}R' + H_2O$$

In the mono- and especially in the di-N-substituted acid amides a cleavage of the N-C bond occurred.



$$\text{(a)}\quad R-\underset{\underset{O}{\|}}{C}-\overset{H}{\overset{|}{N}}-R' \longrightarrow \begin{cases} RCH_2NH_2 + R'H + H_2O \\ RCH_3 + R'NH_2 + H_2O \end{cases}$$

$$\text{(b)}\quad R-\underset{\underset{O}{\|}}{C}-\overset{R'}{\overset{|}{N}}-R' \longrightarrow \begin{cases} RCH_2\overset{H}{\overset{|}{N}}R' + R'H + H_2O \\ RCH_3 + R'_2NH + H_2O \end{cases}$$

Under the conditions of the experiment, the reaction,

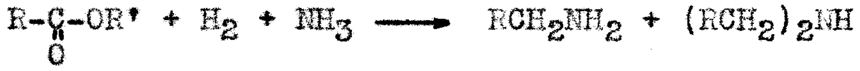
$$2\ RNH_2 \longrightarrow R_2NH + NH_3$$

was extremely important. By carrying out the hydrogenations rapidly, using pure amides and a high ratio of catalyst to amide, an average yield of 55 per cent of primary amine was obtained.

Specific examples showed that ammonium laurate gave 14 per cent of n-dodecylamine and 79 per cent of di-n-dodecylamine. Lauramide gave 48 and 49 per cent yields respectively of these amines. The separations were effected by means of a Podbielniak column.

Other catalysts such as Al-Co, Cu-Mn and Ni-Cr have been used successfully (56).

2. *From aliphatic esters*.



$$R-\underset{O}{\overset{\|}{C}}-OR' + H_2 + NH_3 \longrightarrow RCH_2NH_2 + (RCH_2)_2NH$$

Upon catalytic hydrogenation of methyl stearate with ammonia, using an aluminum or cobalt catalyst, a mixture of the mono- and di-*n*-octadecylamines, separable by vacuum distillation, is obtained (57).

3. *From nitriles*.

$$RCN + R'NH_2 \longrightarrow RCH_2NH_2 + RCH_2-\overset{H}{N}-R'$$

By the catalytic reduction of a nitrile with hydrogen in the presence of an easily volatile amine a mixture of primary and alkylated amines is formed. Thus, lauronitrile reduced with a cobalt catalyst in the presence of methylamine yields both *n*-dodecyl- and *n*-dodecylmethylamines (58). Use of a secondary amine, e.g., dimethylamine gives the *n*-dodecyl- and *n*-dodecyldimethylamines.

4. *From acid amides*.

(56) English patent, 421,196 (1935) [*Chem. Zentr.*, *II*, 2125 (1935)]; English patent, 425,927 (1935) [*ibid.* *II*, 2447 (1935)].

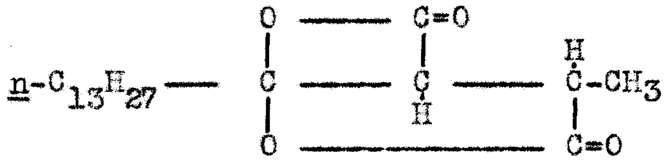
(57) French patent, 761,952 (1934) [*ibid.*, *II*, 1022 (1934)].

(58) French patent, 773,367 (1934) [*ibid.*, *I*, 3076 (1935)].

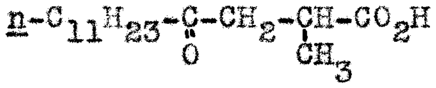
$$R\text{-}\underset{\overset{\parallel}{O}}{C}\text{-}\overset{H}{N}R \longrightarrow RNH_2\cdot HCl + R'CO_2H$$

In studies on the stereochemistry of high-molecular-weight ketoximes, Furukawa (59) isolated several amines by causing the ketoximes to undergo the Beckmann rearrangement, and hydrolyzing the resulting acid amides.

Similarly, Asahina (60) in his investigations on the lichen substances, proved the structure of lichestryl acid by forming its oxime and causing it to undergo the Beckmann rearrangement. Upon saponification of the resulting acid amide he isolated *n*-tridecylamine and methylsuccinic acid indicating the possible structure:



The isolation of *n*-undecylamine by the Beckmann rearrangement of the oxime of nephrostearic acid suggested the possible formula:



$$\underline{n}\text{-}C_{11}H_{23}\text{-}\underset{\overset{\parallel}{O}}{C}\text{-}CH_2\text{-}\underset{\overset{|}{CH_3}}{CH}\text{-}CO_2H$$

Structures of γ- and ζ- ketostearic acids have been proved in the same way (61)(62).

---

(59) Furukawa, *Sci. Papers Inst. Phys. Chem. Research* (*Tokyo*), *20*, 71 (1933) /*ibid.*, *I*, 3437 (1933)/.

(60) Asahina, *J. Pharm. Soc. Japan*, *539*, 1 (1927).

(61) Shukow and Schestakow, *J. prakt. Chem.*, *67*, 419 (1904).

(62) Arnaud, *Bull. soc. chim.*, *27*, 494 (1902).

In studies on the wax obtained from Weymouth pine berries, Blount and co-workers (63) isolated 17-keto-*n*-hexatriacontanol. By the above technique *n*-nonadecylamine was isolated among the products of the Beckmann rearrangement.

5. *From alcohols.*

$$ROH + NH_3 \longrightarrow RNH_2$$

Primary amines may be prepared from alcohols and ammonia by passing the vapors under pressure over heated aluminum oxide. In the case of *n*-hexadecylamine a yield of 94 per cent was reported (64). If the aluminum oxide is impregnated with silica gel or activated carbon no pressure is required (65).

In this manner, the highest-molecular-weight aliphatic amine, 18-aminopentatriacontane, has been synthesized (66).

6. *From acids.*

$$R\underset{\overset{\|}{O}}{-C-}OH + H_2 + NH_3 \longrightarrow RNH_2 + R_2NH + R_3N$$

Upon catalytic reduction of palmitic acid in an atmosphere of ammonia, and using as a catalyst an oxide or sulfide

---

(63) Blount, Chibnall and Mangouri, *Biochem. J.*, *31*, 1375 (1937).

(64) German patent, 611,924 (1935)[*Chem. Zentr.*, *II* 921 (1935)]

(65) English patent, 463,711 (1937)[*ibid.*, *II*, 857 (1937)].

(66) English patent, 384,314 (1932)[*ibid.*, *I*, 1539 (1933)].

of metals of Group 6 or 8 a mixture of mono-, di- and tri-n-hexadecylamine was obtained (39).

7. From alkyl halides.

v. Braun (67) investigated the reaction of liquid ammonia on organic halogen compounds. He found that aliphatic bromides may be converted to amines by liquid ammonia at room temperature. As the molecular weight of the bromide increased, the yield of primary amine rose markedly. Thus, with n-amyl bromide the base fraction consisted of 10 per cent of n-amylamine, 80 per cent of di-n-amylamine and some tri-n-amylamine. With n-dodecyl bromide 90 per cent of the base fraction contained n-dodecylamine. It was found that the effect of rings and branching in the chain was not important, the molecular weight being the limiting factor. The method may have value where it is required to prepare amines independent of details of structure or complexity of the chain.

However, Wibaut and co-workers (68) treated n-dodecyl chloride with liquid ammonia for 72-90 hours at 75-80° and obtained a 28-33 per cent yield of n-dodecylamine together with 32-27 per cent of di-n-dodecylamine.

(67) v. Braun, Ber., 70, 979 (1937).

(68) Wibaut, Heierman and Wagtendork, Rec. trav. chim., 57, 456 (1938).

Synthesis of High-Molecular-Weight Secondary Amines

1. From alkyl sulfates.

$$HOSO_2OR + NH_3 \longrightarrow R_2NH$$

By heating a high-molecular-weight ester of sulfuric acid or its sodium salt with an excess of ammonia secondary amines are obtained. Di-n-octadecylamine was first synthesized in this manner (69).

2. From nitriles.

$$RCN + H_2 \longrightarrow (RCH_2)_2NH$$

McCorkle (20) prepared di-n-dodecylamine and di-n-octadecylamine in about 75 per cent yields by catalytic reduction of nitriles using the Adkins catalyst (70).

3. From alkyl halides.

$$RX + NH_3 \longrightarrow R_2NH$$

High-molecular-weight alkyl halides when heated with aqueous solutions of ammonia in anautoclave are reported to give secondary amines exclusively (71).

Secondary amines have been synthesized successfully by

---

(69) English patent, 369,614 (1932)/Chem. Zentr., II, 1522 (1932)/.

(70) Conner, Folkers and Adkins, J. Am. Chem. Soc., 54, 1144 (1932).

(71) English patent, 437,530 (1935) /Chem. Zentr., I, 3216 (1936)/.

the method of Traube and Engelhardt (72) which involves treating the alkyl halide with sodium cyanamide and hydrolyzing the intermediate dialkylcyanamide (73).

$$2RX + Na_2NCN \longrightarrow [R_2NCN] \xrightarrow{[HOH]} R_2N + CO_2 + H_2O + NH_3$$

Crude calcium cyanamide has been found almost as effective as the pure sodium salt.

4. From primary amines and analogous halides.

$$RNH_2 + RX \longrightarrow R_2NH \cdot HX$$

Walden and Birr (74) obtained di-n-hexadecylamine by heating n-hexadecylamine and n-hexadecyl iodide in a sealed tube. Some tri-n-hexadecylamine was formed, but the product was mainly the secondary amine.

Formation of High-Molecular-Weight Secondary Amines

1. From acid amides, N-substituted acid amides and ammonium salts.

This has been mentioned under the formation of primary amines (p. 28).

2. From chlorosulfonic esters.

---

(72) Traube and Engelhardt, Ber., 44, 3149 (1911).

(73) Staudinger and Rossler, Ber., 69, 48 (1936).

(74) Walden and Birr, Z. physik. Chem., A160, 45 (1932).

$$ClSO_2OR + NH_3 \longrightarrow RNH_2 + R_2NH + R_3N$$

Chlorosulfonic esters formed from high-molecular-weight alcohols and chlorosulfonic acid are treated with liquid ammonia in ether at reflux to give mixtures of all three amines in varying proportions (75).

Synthesis of High-Molecular-Weight Tertiary Amines

1. *From secondary amines and analogous halides.*

$$R_2NH + RX \longrightarrow R_3N \cdot HX$$

McCorkle (20) heated di-*n*-octadecylamine and *n*-octadecyl chloride and obtained 85 per cent of tri-*n*-octadecylamine. As a method of synthesis this is much to be preferred to the following one.

2. *From alkyl halides.*

$$3RX + NH_3 \longrightarrow R_3N + NH_4Cl$$

The first high-molecular-weight tertiary amine of the type $R-\overset{R}{\overset{|}{N}}-R$ was synthesized by Frideau (76) who injected a stream of ammonia into heated *n*-hexadecyl iodide for several hours. Without giving much detail, he reported the exclusive formation of tri-*n*-hexadecylamine. Sometime later, Pieverling (77) attempted the same reaction with *n*-triacontyl

---

(75) English patent, 435,863 (1935) [*Chem. Zentr.*, *I*, 3240 (1936)].

(76) Frideau, *Ann.*, *83*, 25 (1852).

(77) Pieverling, *Ann.*, *183*, 351 (1876).

iodide and did not obtain tri-n-triacontylamine. Analyses of his reaction products indicated the gradual formation of the tertiary amine only if the reaction was given enough time to go through the intermediate formation of primary and secondary amines. He made no effort, however, to prove his contention, or try to purify his product by distillation feeling the separation to be too difficult. It is surprising, therefore, to find two more recent reports (73)(78) where tri-n-hexadecylamine was prepared with no details as to method of preparation outside of reference to Frideau's original article, and with no mention of yields.

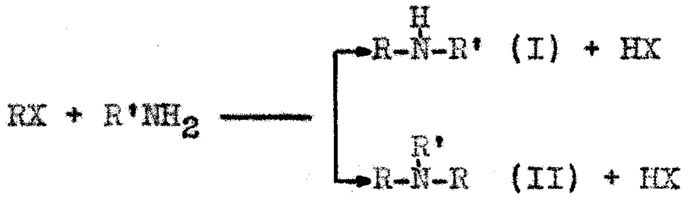
Formation of High-Molecular-Weight Tertiary Amines

This has been mentioned under the formation of secondary amines (p. 35). Also, in the reduction of nitriles with hydrogen and ammonia to primary amines small amounts of tertiary amine are formed.

Preparation of High-Molecular-Weight Alkylated Amines by Direct Alkylation

1. From a high-molecular-weight alkyl halide and a low-molecular-weight primary amine.

(78) Norris and Kimberly, Am. Chem. J., 20, 62 (1878).



$$RX + R'NH_2 \longrightarrow \begin{cases} R-\overset{H}{N}-R' \text{ (I)} + HX \\ R-\overset{R'}{N}-R \text{ (II)} + HX \end{cases}$$

The alkyl halide may be heated in an autoclave with an aqueous or alcoholic solution of the amine, in which case amines of Type I are formed (71). By using a mole ratio of halide to amine of 2:3.5 it is possible to obtain amines of Type II (73).

2. *From a high-molecular-weight alkyl halide and a low-molecular-weight secondary amine.*

$$RX + R'-\overset{H}{N}-R' \longrightarrow R'-\overset{R}{N}-R' + HX$$

The reaction may be carried out in a sealed tube (73) (79) or merely by refluxing an alcoholic solution of the halide and amine (80). The mole ratio here did not seem of prime importance since different proportions of the reactants gave the same product (30). In one example, *n*-octadecyl chloride was heated with excess dimethylamine under pressure to give dimethyl-*n*-octadecylamine (81).

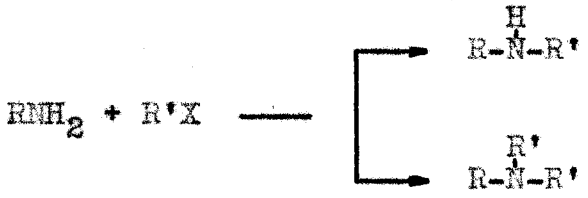
3. *From a high molecular-weight primary amine and a low-molecular-weight alkyl halide.*

---

(79) U.S. patent, 1,836,048 (1930) [*Chem. Zentr.* *I*, 2126 (1932)].

(80) French patent, 696,328 (1930) [*ibid.*, *I*, 2119 (1931)].

(81) French patent, 802,105 (1936) [*ibid.*, *I*, 2024 (1936)].



This reaction is carried out best in sealed tubes due to the volatility of the alkyl halide. As in all alkylations involving halides, the reaction product was obtained as the ammonium salt.

Physical Properties of High-Molecular-Weight Amines

From viscosity measurements secondary amines have the structure RNHR and not R_2NH; tertiary amines with three long chains have the molecular structure $R-\underset{R}{N}-R$ and not $N\begin{matrix}R\\R\\R\end{matrix}$. Also, the primary amines and primary alcohols have the same melting points (20-30 degrees greater than the corresponding hydrocarbons). The low melting points of the tertiary amines is said to be due to their branched structure. Secondary amines with two long chains have a melting point less than the corresponding hydrocarbons due to a slightly less regular structure. Methyl-substituted tertiary amines have a melting point similar to that of hydrocarbons containing an ethyl group attached to the central carbon atom (73).

The lower primary amines are colorless liquids at room temperature while the higher ones are white fatty solids.

Only the lower ones are volatile with steam. None of the high-molecular-weight aliphatic amines is soluble in water. The amines are all distillable under diminished pressure.

Derivatization of High-Molecular-Weight Aliphatic Amines

The isolation of high-molecular-weight aliphatic amines from investigations of the structures of natural products makes it important to have a series of derivatives prepared from known synthetic amines as a basis of comparison. Levene and Taylor (9) state that in the identification of any organic substance, a physical constant of a single derivative should never be regarded as conclusive evidence. Yet in the work on high-molecular-weight aliphatic compounds, e.g., higher fatty acids, the decision most frequently rested on a single melting point. The need for derivatives of high-molecular-weight aliphatic amines was recently emphasized in the work of Hoyt (40) on the phenomenon of homology of high-molecular-weight aliphatic compounds.

The requirements for a satisfactory derivative have been enumerated by Kamm (82):

1. The compound selected for a derivative should possess physical and chemical properties which will enable an absolute differentiation to be made between the individual

(82) Kamm, "Qualitative Organic Analysis", Wiley and Sons, New York (1932), p. 163.

possibilities.

2. Solid derivatives are preferable, because of the ease of manipulation of small quantities in preparation and purification, as well as in the determination of constants.

3. The derivative should be prepared by a reaction which gives a good yield of pure product.

4. The derivative should be prepared by a general reaction which under the same conditions would yield a definite derivative with the other individual possibilities. This will eliminate the necessity for a series of specific reactions.

Since the preparation of derivatives involves the determination of the melting points of the compounds prepared it is essential that the melting point apparatus be described adequately. This is necessary inasmuch as the melting point of a compound is not only dependent on its purity, but also on the apparatus used in its determination (83).

Derivatizing Reactions of High-Molecular-Weight Primary Amines

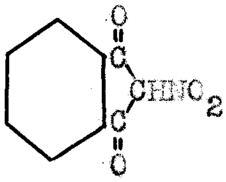
1. Salt formation. High-molecular-weight aliphatic amines combine with mineral acids to form crystalline

---

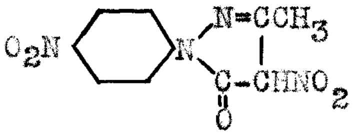
(83) Morton, "Laboratory Technique in Organic Chemistry", McGraw-Hill, New York (1938), Chap. 2; Lassar-Cohn, "Organic Laboratory Methods", Williams and Wilkens Co., Baltimore (1928), Chap. 16.

ammonium compounds. Although these are easily purified they have been found (84) to have high and indefinite melting points. For example, *n*-hexadecylamine hydrochloride on heating began to sinter at about 120° and then above 150° it passed slowly into a transparent fluid mass without showing a sharp melting point (34).

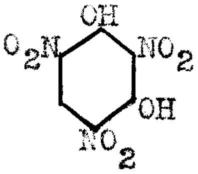
Vanags and Lode (85) investigated the use of 2-nitroindandoin-1,3(I) as a reagent for the isolation and identification of aliphatic amines. This compounds, like picric acid, picrolonic acid (II) and styphnic acid (III), formed



(I)



(II)



(III)

characteristic salts with amines. They found that the salts of the primary amines crystallized well, and as the molecular weight increased the solubility decreased regularly. Thus, *n*-heptylamine gave a precipitate with nitroindandoin in a N/400 solution. The melting points decreased as the molecular weight increased.

The lower members of the secondary aliphatic amines gave rather soluble salts. However, as the molecular weight

---

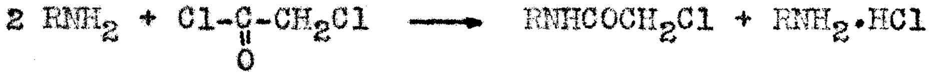
(84) Adam, *Proc. Roy. Soc.* (*London*) *101*, 471 (1922); *126*, 526 (1930); Lyons and Rideal, *ibid.*, *128*, 169 (1930).

(85) Vanags and Lode, *Ber.*, *70*, 547 (1937).

increased the solubility decreased while the melting points increased. The salt of n-heptadecylamine was prepared in alcoholic solution, and was obtained as light yellow crystals melting at 118-119°.

2. With acid halides and halogen bearing compounds.

If one mole of amine is reacted with a dihalogen compound of the type XCH_2COX the carbonyl halogen will enter into reaction (86).



$$2\,RNH_2 + Cl\text{-}\underset{\underset{O}{\|}}{C}\text{-}CH_2Cl \longrightarrow RNHCOCH_2Cl + RNH_2\cdot HCl$$

The reaction of primary amines and acid chlorides is general. Yet standard procedures have to be modified due to the formation of the amine hydrohalide with the amide. High-molecular-weight amine hydrochlorides are only moderately soluble in water, some with the formation of emulsions. It is not easy, therefore, to wash them out with water as is done in the case of low-molecular-weight amines. In the acylation of n-heptadecylamine with the acid chloride of monoethyl sabacamate Flaschenträger and Lachmann (87) had to insert a special step to separate the amide from the amine hydrochloride. Turpin (88)

(86) Asano and Ohta, J. Pharm. Soc. Japan, 51, 36 (1931).

(87) Flaschenträger and Lachmann, Z. physiol. Chem., 192, 268 (1930).

(88) Turpin, Ber., 21, 2490 (1888).

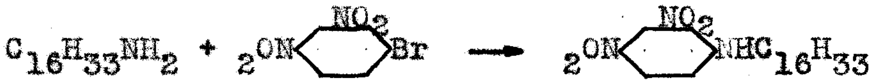
avoided this difficulty by acylating the amine hydrochloride of n-heptadecylamine.

$$RNH_2 \cdot HCl + R'COCl \longrightarrow R'CONHR + 2\ HCl$$

Primary amines react with compounds bearing halogen atoms, especially if they are activated by the presence of other groups. In the following reaction (89) the amides were actually soluble in water and could be precipitated from aqueous solutions.

$$RNH_2 + Cl(CH_2)_2SO_3Na \longrightarrow RNH(CH_2)_2SO_3Na$$

Teunissen (34) investigated the use of active halogen compounds as derivatives for high-molecular-weight aliphatic amines. n-Hexadecylamine reacted with 1-bromo-2,4-dinitrobenzene (I) to give N-n-hexadecyl-2,4-dinitroaniline.



Similar reactions were run with 1-chloro-2,4-dinitronaphthalene (II) and 2-chloro-1,6,8-trinitronaphthalene (III). In the case of (I), the product began to sinter at about 55° and melted slowly at 62°. The others gave satisfactory melting points decreasing in the order (III) (II) (I).

3. With isocyanates.

A rapid derivative for primary amine hydrochlorides is provided by their reaction with potassium isocyanate (36)

---

(89) English patent, 356,218 (1931) /Chem. Zentr., II, 3271 (1931)/.

(52)(84)(88). The alcoholic solution of the amine salt is evaporated with the isocyanate to give the urea derivative.

$$RNH_2{\cdot}HCl + KNCO \longrightarrow RNHCONH_2 + KCl$$

The reaction can be carried out quickly, but it is essential that the amine salt be pure.

Recently, Buck and co-workers (90) prepared the N-alkyl ureas from N-methyl- to N-n-docosylurea as intermediates in the preparation of barbituric acids. They claimed that the preparation of ureas from nitrourea was superior to the cyanate method. Their method was to take one mole of amine, 1.15 moles of nitrourea and 4-5 volumes of 95 per cent ethanol and warm the mixture cautiously and slowly on the water bath, taking care that the evolution of gas did not become too rapid. When the reaction slowed down most of the alcohol was boiled off, and the residual urea worked up from a suitable solvent.

$$NH_2CONHNO_2 \longrightarrow HNCO + N_2O + H_2O$$

$$RNH_2 + HNCO \longrightarrow RNHCONH_2$$

They found that the alkylureas showed a surprising constancy of melting point. From methylurea to n-docosylurea only two ureas fell outside the range of 100-115°. They were all crystalline compounds whose solubility in alcohol decreased

---

(90) Buck and co-workers, J. Am. Chem. Soc., 58, 854 (1936); 60, 461 (1938).

with increase in the length of the chain.

In their studies in the *n*-decyl series, Kommpa and Talviti derivatized *n*-decylamine by means of phenyl and α-naphthyl isocyanate. They found the ureas to be sharp-melting crystalline derivatives (43).

4. With acid anhydrides.

$$RNH_2 + (R'CO)_2O \longrightarrow R'CONHR + R'CO_2H$$

Primary amines form acid amides almost instantly when they are warmed with acetic anhydride (36). Other anhydrides have not been used, for the separation of the acid and the amide may prove tedious.

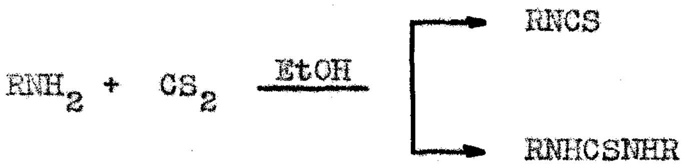
5. With carbon disulfide.

The reaction of carbon disulfide with primary amines to give amine salts of dithiocarbamic acid (52)(88) takes place almost instantly when the carbon disulfide is added to an ethereal solution of the amine. The salt precipitates out as a yellow crystalline solid. It loses hydrogen sulfide on standing, and by heating is converted to the symmetrical thiourea.

$$R-\overset{\overset{H}{|}}{N}-H \cdot HS-\underset{\underset{S}{\|}}{C}-NHR \longrightarrow RNH\underset{\underset{S}{\|}}{C}-NHR + H_2S$$

These are stable crystalline solids with sharp melting points.

However, when the amine is heated with carbon disulfide in ethanol for a prolonged period a two-fold reaction takes place (52).

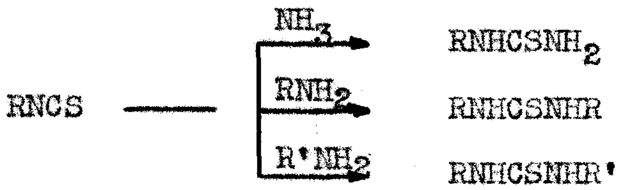


$$\begin{tikzcd} & RNCS \\ RNH_2 + CS_2 \arrow[ur, "EtOH"] \arrow[dr] & \\ & RNHCSNHR \end{tikzcd}$$

A much preferable synthesis of the isothiocyanate is from the amine salt of the dithiocarbamic acid by treatment with mercuric chloride (48).

$$RNH_2 \cdot HSCSNHR \longrightarrow RNCS$$

In this manner Ponzio (47) formed families of thioureas both symmetrical and unsymmetrical.



$$\begin{tikzcd} & RNHCSNH_2 \\ RNCS \arrow[ur, "NH_3"] \arrow[r, "RNH_2"] \arrow[dr, "R'NH_2"'] & RNHCSNHR \\ & RNHCSNHR' \end{tikzcd}$$

Other Reactions of High-Molecular-Weight Amines

Primary amines condense with acetaldehydedisulfonic acid in an alkaline medium to give the corresponding anils which may be reduced (91).

$$RNH_2 + (NaSO_3)_2CHCHO \longrightarrow (NaSO_3)_2CHCH{=}NR \longrightarrow RNHCH_2CH(SO_3Na)_2$$

(91) French patent, 790,626 (1935) [Chem. Zentr., I, 3018 (1936)].

In their studies on diazonium equilibria, Adamson and Kenner (92) investigated the behavior of a series of primary aliphatic amines from five to ten carbon atoms towards nitrous acid. In the case of <u>n</u>-decylamine three different products, listed in order of importance, were formed:

$$RNH_2 + HNO_2 \longrightarrow \begin{array}{l} 1.\ ROH \\ 2.\ R(-H) \\ 3.\ R_2N{-}N\rightarrow O \end{array}$$

Jeffreys (52) isolated pentadecanol-1 and pentadecene-1 from the reaction of <u>n</u>-pentadecylamine hydrochloride and sodium nitrite.

Primary amines react with phosgene to give N-substituted urea chlorides. In the high-molecular-weight series these are fairly stable (52).

$$RNH_2{\cdot}HCl + COCl_2 \longrightarrow RNHCOCl + 2\ HCl$$

However, they may be decomposed in working up the reaction. It is necessary to distill off the benzene which is used as a reaction solvent in a stream of hydrogen chloride. Turpin (88) who failed to heed this precaution never isolated any urea chloride, and whatever isocyanate he obtained was impure. The isocyanate can be used to synthesize unsymmetrical ureas.

$$RNHCOCl \xrightarrow{-HCl} RNCO \xrightarrow{R'NH_2} RNHCONHR'$$

(92) Adamson and Kenner, <u>J</u>. <u>Chem</u>. <u>Soc</u>., <u>1934</u>, 838.

When an aqueous suspension of one mole of primary amine hydrochloride is treated with a mole of bromine and two moles of sodium hydroxide, the dibromoamine sinks to the bottom of the reaction mixture as a heavy oil. Upon refluxing, the excess alkali splits out hydrogen bromide leading to the nitrile. The latter contains an R group whose C-H content is less than in the original amine by $-(CH_2)-$.

$$RCH_2NH_2\cdot HCl \longrightarrow [RCH_2NBr_2] \longrightarrow RCN$$

This reaction, discovered by Hofmann (51)(93), is essentially a "reversed Mendius" reaction. Fair yields are obtained with amines containing five or more carbon atoms in the alkyl residue. With amines below *n*-pentylamine only small amounts of nitrile are formed. As the carbon content decreases there is none formed. This is a good illustration of the limits of homology (20)(40).

Little work has been done on amines of the types $R-\overset{R}{N}-R$ and $R-\overset{H}{N}-R$ where all the alkyl groups are of high molecular weight. Staudinger and Rossler (73) in an effort to correlate viscosity and molecular arrangement of long chains measured the viscosities of these classes.

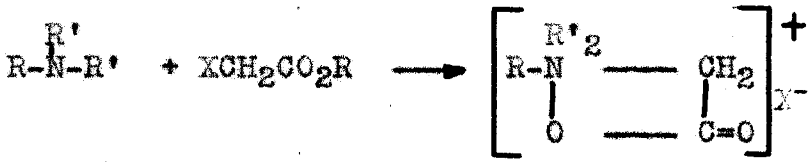
Norris and Kimberly (78) investigated the action of halogens on tertiary aliphatic amines. They found that as the number of carbon atoms increased, the crystallizing power

---

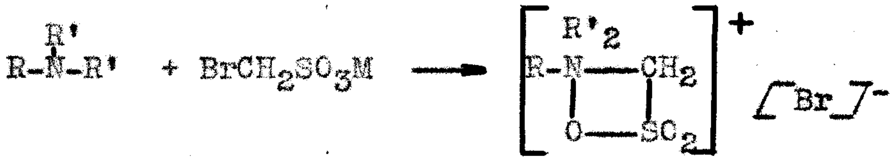
(93) Hofmann, *Ber.*, *14*, 2725 (1881); *15*, 767 (1882); *16*, 558 (1883); *17*, 1920 (1884).

and stability of the amine perhalides of the type R_3NX_2 decreased. Tri-n-hexadecylamine, for example, was inert towards an ether solution of bromine.

More work has been done on tertiary amines of the type $R\text{-}\overset{R'}{N}\text{-}R'$. They have been found to react with halogen-bearing acid derivatives to give betaines.



Di-methyl-n-octadecylamine was treated with methyl chloroacetate to give the betaine ester of n-octadecyldimethylbetaine hydrochloride (94). Reactions were also carried out with bromomethane sulfonates and related compounds to give sulfonium analogs of betaine (95).



Tertiary amines of this class have been oxidized to their N-oxides by means of several oxidizing agents. Among the most satisfactory are Caro's acid, ozone and hydrogen peroxide. The products are fat-like solids which are active in lowering surface tension (96).

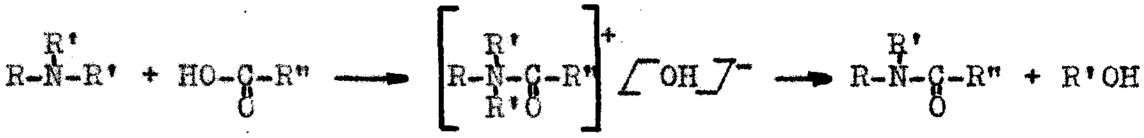
---

(94) Swiss patent, 186,269 (1936)[Chem.Zentr., I, 5078 (1937)].

(95) French patent, 745,417 (1936)[ibid., II, 186 (1936)].

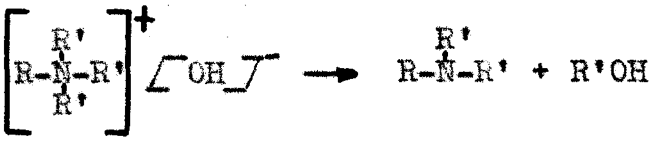
(96) Swiss patents, 177,435,177,460 (1935)[ibid., I, 2443 (1936)]; French patent, 786,911 (1935) [ibid., I, 1115 (1936)].

Tertiary amines, of the type under discussion, suffer dealkylation when they are heated with organic acids (97). In general, the reactions may be formulated according to the following scheme:



$$R-\overset{R'}{N}-R' + HO-\underset{O}{C}-R'' \longrightarrow \left[R-\underset{R'}{\overset{R'}{N}}-\underset{O}{C}-R''\right]^{+} [OH]^{-} \longrightarrow R-\overset{R'}{N}-\underset{O}{C}-R'' + R'OH$$

This is similar to the dealkylation of organic bases (98).



$$\left[R-\underset{R'}{\overset{R'}{N}}-R'\right]^{+} [OH]^{-} \longrightarrow R-\overset{R'}{N}-R' + R'OH$$

Direct Condensation of Amines and Carboxylic Acids

The direct condensation of aliphatic amines and carboxylic acids was first developed as a two-phase reaction. In the first step a low-molecular-weight aliphatic amine was neutralized with an organic acid to give an ammonium salt.

$$R'NH_2 + R''CO_2H \longrightarrow R''CO_2NH_3R'$$

This on heating decomposed to give the amide.

$$R'CO_2NH_3R' \longrightarrow R''CONHR' + H_2O$$

The investigation of this reaction came soon after Wohler's discovery in 1828 that ammonium cyanate was converted into urea by heat. In 1830, Dumas (99) heated ammonium oxalate and

(97) v. Braun and Weissbach, Ber., 63, 489 (1930).

(98) v. Braun and co-workers, Ann., 472, 121 (1929).

(99) Dumas, Ann. chim. phys., 44, 129 (1830).

obtained oxamide. Some time later, Wurtz (100) distilled dimethylammonium oxalate and obtained methyloxamide. The same technique was used with ethylamine. Linneman (101) extended the technique to monobasic aliphatic acids. He evaporated aqueous solutions of methyl-, ethyl- and diethylammonium formate and distilled the resulting syrups to obtain the corresponding amides. Hofmann (102) required large amounts of amides of aliphatic acids for his classical rearrangement studies. After a critical evaluation of the standard methods of acylation of amines, he developed the preparation of amides from the ammonium salts. Previous yields were raised from 20 to 80 per cent by heating the dry ammonium salt five to six hours in sealed tubes at about 230°.

It was left to Franchimont and Klobbie (103) to eliminate the intermediate formation of ammonium salt. They heated heptylic acid and several low-molecular-weight amines directly in sealed tubes at about the boiling point of the acids. In all cases they obtained the desired amides. They gave no yields.

(100) Wurtz, Ann. chim., 30, 464 (1850); Ann. 76, 324 (1850).

(101) Linneman, Proc. Viennese Academy, 60, 44 (1870) /Chem. Zentr., 41, 138 (1870).

(102) Hofmann, Ber., 15, 977 (1882).

(103) Franchimont and Klobbie, Rec. trav. chim., 6, 247 (1887).

Musselius (104) made some quantitative studies on the ease of decomposition of acetic acid salts of primary and secondary aliphatic amines. The salts were heated in sealed tubes in a nitrobenzene bath for thirty minutes, and the unchanged salt titrated with sodium hydroxide.

N-Acetamide	% Amide	N-Acetamide	% Amide
Methyl	78	Dimethyl	84
Ethyl	80	Diethyl	40
n-Propyl	89	Di-*n*-propyl	51
Isobutyl	90	Diisobutyl	41
Isoamyl	92	Diisoamyl	50
n-Heptyl	95		

As the length of the carbon chain of the primary amines increased, the yield of amide increased. The effect of side chains was blotted out due to the velocity of the reaction. But in the case of the secondary amines the effect of side chains was noticeable.

The direct condensation technique was carried over to the field of dibasic acids by Tafel and Stern (105) in the same year. They heated isopropylamine and succinic acid in a sealed tube, and obtained N-isopropylsuccinimide. The

(104) Musselius, *J. Russ. Phys. Chem. Soc.*, *32*, 29 (1900) /*Chem. Zentr.*, *I*, 1071 (1900)/.

(105) Tafel and Stern, *Ber.* *33*, 2232 (1900).

heating was conducted in two stages. They first heated the reagents for six hours at 100°. This was followed by four more hours at 200°. Their yield was 75 per cent of the theoretical.

The two-stage method was patented when Liebrecht (106) found that the dialkyl amides of isovaleric acid were pharmacologically active.

An innovation of the direct condensation of low-molecular-weight amines and acids was the technique of Mitchell and Reid (107). They passed ammonia through the heated aliphatic acids in such a manner that the water formed was continually removed. The yields of amides of acids from acetic through caprylic were about 65-95 per cent. At the temperature of the reaction (170-190°) some nitrile was formed by dehydration of the amide. This was especially true for the higher acids. In the case of acids above caprylic, the reaction velocity was much slower. No amide was obtained from palmitic or stearic acids upon heating for considerable intervals of time. Dimethylamides were analogously prepared by passing a stream of dimethylamine through the heated acids. The reaction proceeded much faster with dimethylamine than with ammonia.

Repetition of the work showed that dimethyl amides were

(106) German patent, 129,987 (1902)/Chem. Zentr., I, 959 (1902)/.

(107) Mitchell and Reid, J. Am. Chem. Soc., 53, 1879 (1931); Ruhoff and Reid, ibid., 59, 401 (1937).

formed in liberal amounts by their procedure, but that the reactions were not complete, except with formic acid. Fractionation, taking very close cuts, gave what appeared to be pure compounds, but these proved to be azeotropic mixtures of the dimethyl amides and the acids. These azeotropes caused an overestimation of the yields of amide. For example, when gaseous dimethylamine was passed into refluxing acetic acid, the distillate obtained after the reaction seemed over contained free acid. No matter how much amine was passed in, the liquid in the flask never became neutral. Finally, they heated the acid saturated with dimethylamine at 35°, five hours at 200° in a steel bomb. After the reaction was over, alkali was added and the amides obtained by distillation.

Phosphorous pentoxide has been used as a catalyst in the condensation of amines and acids. Pyridine carboxylic acids were treated with secondary aliphatic amines in the presence of this agent. In this manner, the diethylamide of nicotinic acid has been prepared (108).

No work has been reported in the scientific literature on the direct condensation of high-molecular-weight aliphatic amines and carboxylic acids.

The direct condensation of amines and acids applies just

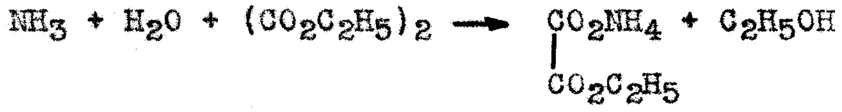
(108) German patant, 653,873 (1937) [C.A., 32, 2956 (1938)].

as well as to aromatic amines. de'Conno (109) condensed aniline types with high-molecular-weight aliphatic acids by heating in sealed tubes at 230°. The amines were obtained in yields of 85-87 per cent. Other workers found success with xenylamine and aliphatic acids (110).

Direct Condensation of Amines and Dibasic Esters

The formation of amides from dibasic aliphatic esters and amines was initiated by the discovery of Liebig (111) that treatment of diethyl oxalate with ammonia gave a mixture of oxamide and ethyl ammonium oxalate. The latter was formed by the partial saponification of unreacted diethyl oxalate with dilute alcoholic ammonia produced in the primary reaction.

$$NH_3 + (CO_2C_2H_5)_2 \longrightarrow (CONH_2)_2 + 2\ C_2H_5OH$$



$$NH_3 + H_2O + (CO_2C_2H_5)_2 \longrightarrow \begin{array}{l} CO_2NH_4 \\ | \\ CO_2C_2H_5 \end{array} + C_2H_5OH$$

The reaction was extended to low-molecular-weight aliphatic amines when Wurtz (112) prepared N,N'-dimethyloxamide from methylamine and diethyl oxalate, as well as the corresponding N,N'-diethyloxamide.

(109) de'Conno, *Gazz. chim. ital.*, *47*, 93 (1917).

(110) Ford, Doctoral Dissertation, Iowa State College (1937).

(111) Liebig, *Ann.*, *9*, 129 (1834).

(112) Wurtz, *Ann.*, *76*, 324 (1850); *Ann. chim.*, *30*, 491 (1850).

Hofmann (113) used this reaction as a basis for the separation of low-molecular-weight aliphatic amines. A mixture of mono-, di- and trimethylamines was mixed with diethyl oxalate. The methylamine precipitated out as N,N'-dimethyloxamide, while the dimethylamine formed ethyl N,N-dimethyloxamate. The trimethylamine, of course, remained unattacked. Distillation on the water bath removed the unchanged trimethylamine. The residue was treated with cold water in which the dimethyloxamate was soluble. This separation was perfected later by Malbot (114).

The reaction between primary amines and diethyl oxalate in ethanol followed the same course as Liebig found for ammonia and diethyl oxalate. A concentrated alcoholic solution of ethylamine was mixed with diethyl oxalate and allowed to stand. After distillation, the distillate was cooled in ice, and the N,N'-diethyloxamide filtered off. The filtrate contained ethyl N-ethyloxamate in 40 per cent yield (115).

The reaction to give N,N'-oxamides worked smoother in aqueous solution. Wallach (116) reported than when an aqueous solution of n-propylamine was added to diethyl oxalate there

---

(113) Hofmann, Proc. Roy. Soc. (London) 12, 382 (1863); Ber., 3, 776 (1870).

(114) Malbot, Ann. chim., 13, 532 (1888).

(115) Wallach and West, Ann., 184, 59 (1877).

(116) Wallach, Ann., 214, 312 (1882).

was an immediate precipitation of N,N'-di-n-propyloxamide. Berg (117) found that when a dilute aqueous solution of n-butylamine was added to diethyl oxalate there was an immediate precipitation of N,N'-di-n-butyloxamide. After this was filtered off, the filtrate was investigated. It was found to contain some n-butylammonium N-n-butyloxamate as well as di-n-butylammonium oxalate.

In the reaction of branched-chain primary amines, Freund and Schönfeld (118) found that when an ethereal solution of 1-amino-2-methyloctane was refluxed with diethyl oxalate the diamide was formed. Later, Brander (119) found that the reaction between mono-tert.-butylamine and diethyl oxalate took place only after some time at room temperature. The diamide could be prepared, however, by heating at 100°.

Finally, the reaction of diethyl oxalate and amines was extended to high-molecular-weight aliphatic amines. Grunfeld (33) treated n-dodecylamine with diethyl oxalate in ethanol, and obtained N,N'-di-n-dodecyloxamide.

The condensation of low-molecular-weight amines and esters was extended to dibasic acids other than oxalic acid. Thus, Freund (120) discovered that malonic ester dissolved in aqueous methylamine, upon shaking, to give an almost

(117) Berg, Ann. chim., 3, 294 (1894).

(118) Freund and Schönfeld, Ber., 24, 3350 (1891).

(119) Brander, Rec. trav. chim., 37, 80 (1918).

(120) Freund, Ber., 17, 134 (1884).

quantitative yield of N,N'-dimethylmalonamide.

The relative reactivity of various dibasic acids was investigated by Franchimont and Klobbie (121). They found that while methylamine reacted with malonic ester with the evolution of heat, diethyl succinate reacted only slowly. It was necessary to warm the reaction mixture moderately in a sealed tube for 48 hours to obtain N,N'-dimethylsuccinamide.

Substitution of alkyl groups in the malonic ester molecule lowered its reactivity. Thus, when diethyl methylmalonate was treated with aqueous methylamine, there was only a slight warming. It required two hours for the ester to dissolve. When dimethyl dimethylmalonate was treated with aqueous methylamine the reaction required three days. The reaction between methylamine and diethyl ethylmalonate also required three days (122).

Henry (123) found that methylamine reacted more rapidly than ammonia with ethyl esters of dibasic aliphatic acids. He prepared the dimethylamides of oxalic, malonic, succinic, pyrotartaric and adipic acids. Like the acids and the nitriles, the amides of the oxalic acid series containing an even number of carbon atoms melted higher and were less

(121) Franchimont and Klobbie, Rec. trav. chim., 4, 195 (1885).

(122) Schey, Rec. trav. chim., 16, 359 (1897).

(123) Henry, Bull. soc. chim., 43, 619 (1885).

soluble in water than the odd-numbered amides.

The condensation of aliphatic dibasic esters, other than oxalic esters, and amines was extended to high-molecular-weight aliphatic amines in 1932. Grunfeld (33)(124) heated *n*-dodecylamine and diethyl malonate in a sealed tube in a water bath for 30 hours. He obtained a 22-24 per cent yield of N,N'-di-*n*-dodecylmalonamide. Gaade (31) heated *n*-octadecylamine and diethyl ethane-1,2-dioxamate in alcoholic solution and obtained the esteramide.

$$C_{18}H_{37}NH_2 + (C_2H_5O_2CCONHCH_2-)_2 \longrightarrow C_{18}H_{37}NHCOCONH(CH_2)_2NHCOCO_2C_2H_5$$

Recently, Glasoe and Audrieth (125) have found that the ammonolysis of esters could be accelerated by the addition of ammonium salts. They based this discovery on the fact that the ammonolysis of esters in liquid ammonia was susceptible to catalysis by ammonium salts. Along with several other examples, they reacted cyclohexylamine and diethyl malonate. Their results supported the contention that reactions of hydrolysis, ammonolysis and aminolysis were all similar in character, and could be considered as solvolytic reactions. In the case of ethyl malonate, the reaction went through the formation of the monoamide which was rapidly changed to the diamide.

---

(124) Grunfeld, *Ann. chim.*, *20*, 304 (1933).

(125) Glasoe and Audrieth, *J. Org. Chem.*, *4*, 54 (1939).

Pharmacology of High-Molecular-Weight Aliphatic Amines and Their Derivatives

There is a comparatively small amount of literature on the pharmacology of high-molecular-weight aliphatic amines. Perhpas, as a result of more fruitful studies on the pharmacology of low-molecular-weight aliphatic amines investigations will be extended to the higher homologs. It was mentioned earlier (2) that the literature on the pharmacology of aliphatic amines is not in satisfactory form and much reinvestigation is in progress.

Barger and Dale (126) investigated the physiological activities of compounds related to adrenalin in order to determine which portion of the molecule was responsible for its ability to mimic the action of the sympathetic nervous system. This property, they discovered, was due to the amine portion of the molecule rather than to the catechol residue. Furthermore, they were able to show that the property of simulating the autonomic nervous system, i.e., "sympathomimetic action," was shown by mono-, di- and tri-*n*-alkyl amines themselves. The primary amines gave the strongest reactions as measured by such indices as (1) increase in blood pressure, (2) dilation of the pupil, (3) flow of tears, and (4) effect

(126) Barger and Dale, *J. Physiol.*, *38*, 21 (1909).

of alkaloids on uteri of decerebrated cats. The animals were injected intravenously with N/10 aqueous solutions of the amine hydrochlorides. Of all the amines tested (methyl- through n-tridecylamine) there was a maximum at n-hexylamine. Only low-molecular-weight secondary and tertiary amines were tested, and they were noticeably less potent than any of the primary amines.

Flaschenträger and Lachmann (87) tested the physiological effects of n-heptadecylamine hydrochloride. They found that injection of an aqueous thin jelly of the hydrochloride into the ventral lymph sac of frogs caused their death one day later. Also, there was local irritation at the point of injection. Dogs and guinea pigs suffered necrosis at the point of subcutaneous injection but lived. By an intravenous injection of 10 ml. of an 0.5 per cent solution, death of a dog was produced with the appearance of embolism. The amine could not be detected in the lungs.

Kindler (127) has investigated the importance of amines in chemotherapy with reference to their toxicity to protozoa. He found that the toxicity of amines belonging to an homologous series increased with the number of carbon atoms. Of isomeric amines, the one possessing the longest carbon chain always had the highest toxicity. Thus, n-hexylamine was 30

(127) Kindler, Arch. Pharm., 276, 107 (1938).

times more toxic than the isomeric di-n-propylamine, and di-n-hexylamine was 13 times more toxic than the isomeric amines with ramified chains.

Besides the studies on high-molecular-weight aliphatic amine hydrochlorides, other salts have been used in pharmacological studies. Muscular injection of the iodobismuthate of tri-n-hexadecylamine was found to increase the calcium deposition at the seat of injection (128). n-Hexadecylpyridinium chloride was found to be highly bactericidal for virulent organisms *in vitro* (129). It compared favorably with well known germicides of the mercurial and phenolic types.

While the amides of low-molecular-weight aliphatic amines are pharmacologically active (106)(130) those of high-molecular-weight amines show little promise as yet. Thus, N-n-heptadecylsebacamic acid and N-n-heptadecyladipamic acids gave alkali salts which were too insoluble to offer any amount to the animal for decomposition (87). The insolubility of the sodium and potassium salts made it appear that they remained unchanged in the tissues. Yet high-molecular-weight amides, e.g., N-n-dodecylacetamide, have been reported

(128) Levaditi and co-workers, *Compt. rend.*, *192*, 1768 (1931).

(129) Blubaugh and co-workers, *J. Bact.*, *39*, 51 (1940).

(130) D'Alelio and Reid, *J. Am. Chem. Soc.*, *59*, 109 (1937); Wender, *ibid.*, *60*, 1081 (1938); Bass, *J. Pharmacol.* *64*, 50 (1938).

to be used as medicinals (131).

Recently, long-chain N^1-alkylsulfanilamides were prepared with the object of obtaining lipoid solubility (132). The promising pharmacological properties of N^1-dodecanoylsulfanilamide made the investigation of other lipoid soluble derivatives of particular interest. The results indicated that the high-molecular-weight N^1-alkylsulfanilamides were decidedly inferior to the corresponding N^1-acylsulfanilamides on experimental streptococcal infections in mice.

Buck and co-workers (133) investigated the pharmacological action of alkyl ureas from methyl- to n-docosylurea. They discovered that alkyl ureas and isoureas had anesthetic effects and toxicities which increased with the molecular weight. However, the increase of anesthetic effects was greater than that of the toxic effects. The n-heptylurea was too insoluble to show activity.

Bergmann and Haskelberg (134) attempted to prepare chemotherepeuticals with an affinity for lipoids, and thus of possible value in tuberculosis, leprosy and parasitic diseases. They condensed diazotized arsanilic acid and

(131) English patent, 458,454 (1937)[Chem. Zentr., I, 2867 (1937)].

(132) Crossley, Northey and Hultquist, J. Am. Chem. Soc., 62, 532 (1940).

(133) Buck and co-workers, J. Pharmacol., 52, 216 (1934).

(134) Bergmann and Haskelberg, J. Chem. Soc., 1939, 1.

N-n-hexadecylaniline, and prepared 4-n-hexadecylaminozaobenzene-4'-arsonic acid. They found it to be of surprisingly low toxicity.

It is worth mentioning at this point the comments of Schrauth (135) on the value of high-molecular-weight compounds in synthetic remedies. Arsenic compounds of the aliphatic fatty acid series are slow and steady in their physiological action, and do not show the disturbing influences of arsenic direct. In fact, phosphorous and arsenic compounds of this series actually stimulate growth and increase the number of red blood corpuscles.

The value of high-molecular-weight aliphatic derivatives will be greatly increased when new testing methods are perfected whereby insolubility in water will not be the limiting factor (40).

Uses of High-Molecular-Weight Aliphatic Amines and Their Derivatives

High-molecular-weight aliphatic amines and their derivatives have been found to be useful as wetting, washing and detergent agents. The emulsifying action of n-dodecylamine hydrochloride has made it useful as a soap (136). Also, the foaming property of aqueous suspensions of the amine hydrochloride

(135) Schrauth, Seifenfabr., 36, 217 (1916).

(136) French patent, 780,044 (1935)/Chem. Zentr., II, 3723 (1935)/.

has made them excellent fire-fighting foams (137). High-molecular-weight tertiary amine salts, e.g., di-*n*-butyl-*n*-dodecylamine hydrobromide, have been used in aqueous suspension (138) as emulsifiers in the leather industry (79). The quaternary ammonium salts of the betaine type (95) also have detergent properties. The diammonium compounds of high-molecular-weight tertiary alkylated amines and dichlorodiethyl ether not only have wetting and foaming properties, but they have found use as dispersing agents for mineral oils, antiseptics and dressing agents for rayon (139).

High-molecular-weight aliphatic aminomethanesulfinic acids and their salts of the general formula $RNHCH_2SO_2M$ have been prepared from primary aliphatic amines and salts of formaldehydesulfoxylic acid (140). They have been found to have unusual value as wetting, detergent, dispersing and foaming agents.

Amides of high-molecular-weight primary and secondary aliphatic amines not only have wetting and foaming properties (141), but have been condensed further to give such agents

(137) French patent, 789,327 (1935)[*ibid.*, *I*, 3879 (1936)].

(138) U.S. patent, 1,883,042 (1932)[*ibid.*, *I*, 2498 (1933)].

(139) English patent, 474,671 (1937)[*C.A.*, *32*, 3518 (1938)].

(140) U.S. patent, 2,146,280 (1939)[*C.A.*, *33*, 3495 (1939)].

(141) French patent, 798,970 (1936)[*Chem.Zentr.*, *I*, 755 (1937)], English patent, 484,910 (1938)[*C.A.*, *32*, 7613 (1938).

(142).

High-molecular-weight aliphatic amines and their derivatives have found use in the textile industry. Thus, tertiary alkylated amines (143), betaine types (94), N-oxides of tertiary amines (96), alkylureas (144) and addition products of tertiary alkylated amines and ethylene oxide (145) have all been used as textile aids.

Aqueous suspensions of primary, secondary and tertiary amines and their quaternary bases have been used in the manufacture of artificial silk (146). Of particular interest is the use of salts of aliphatic diamines and aliphatic dicarboxylic acids for the preparation of fiber-forming polyamides ("Nylon") (147).

High-molecular-weight aliphatic amines and their derivatives have been used as agents for making dyes fast to water and light (148). *n*-Dodecylamine was used in the preparation

(142) English patent, 507,207 (1939)[*C.A.*, *34*, 551 (1940)].

(143) German patent, 650,664 (1937)[*Chem.Zentr.*, *I*, 1497 (1938)].

(144) English patent, 458,454 (1937)[*ibid.*, *I*, 2867 (1937)].

(145) English patent, 459,309 (1937)[*ibid.*, *I*, 5045 (1937)].

(146) English patent, 412,929 (1933)[*ibid.*, *I*, 502 (1935)].

(147) U.S. patent, 2,130,947 (1938)[*C.A.*, *32*, 9497 (1938)]

(148) French patent, 735,637 (1931)[*Chem.Zentr.*, *II*, 3477 (1932)].
English patent, 483,324 (1938)[*C.A.*, *32*, 7282 (1938)].

of color lakes (149) and also in the preparation of vat dyes which give strong prints (150).

The free amines and their salts have been used as disinfectants and preservatives in aqueous suspension (151).

High-molecular-weight aliphatic amides found use as artificial waxes or as components in wax compositions (152).

Drying oils were made into corrosion resistant coating materials by addition of 5 per cent of high-molecular-weight aliphatic amines (153). The amides showed a compatability with oil of turpentine (154). Phthalamic acids, e.g., N-*n*-dodecylphthalamic acid, were used as plasticizers for cellulose (155). Finally, sulfur derivatives of high-molecular-weight aliphatic amines have been used as antioxidants (156).

Pyrolysis of Aliphatic Amine Hydrochlorides

Studies on the pyrolysis of aliphatic amine hydrochlorides

(149) English patent, 460,147 (1937)[*Chem.Zentr.*, *I*, 5060 (1937)].

(150) French patent, 807,939 (1937)[*ibid.*, *II*, 2267 (1937)].

(151) Norwegian patent, 54,738 (1934)[*ibid.*, *I*, 3313 (1935)].
Swiss patent, 192,997 (1937)[*ibid.*, *I*, 3799 (1938)].

(152) Austrian patent, 146,832 (1936)[*ibid.*, *II*, 3608 (1936)].
English patent, 507,244 (1939)[*C.A.*, *34*, 557 (1940)].

(153) French patent, 814,698 (1937)[*Chem.Zentr.*, *II*, 3241 (1937)].

(154) Swiss patent, 194,081 (1938)[*ibid.*, *I*, 4252 (1938)].

(155) U.S. patent, 2,101,323 (1937)[*ibid.*, *I*, 2061 (1938)].

(156) English patent, 497,939 (1938)[*C.A.*, *33*, 3810 (1939)].

were initiated by Hofmann (157). He studied the action of heat on the various classes of ethylamines, and found that it was possible to descend from one class to the next lower one by steps:

$$(C_2H_5)_3N{\cdot}HCl \longrightarrow C_2H_5Cl + (C_2H_5)_2NH$$
$$(C_2H_5)_2NH{\cdot}HCl \longrightarrow C_2H_5Cl + C_2H_5NH_2$$
$$C_2H_5NH_2{\cdot}HCl \longrightarrow C_2H_5Cl + NH_3$$

However, the purity of the products was disturbed by two factors. First, if the temperature was not high enough, sublimation took place with no change. Second, if the temperature was too high the ethyl chloride split into ethylene and hydrogen chloride.

Vincent (158) studied the effect of heat on trimethylamine hydrohalides. He found that when trimethylamine hydrochloride was heated at 285° the volatile portion consisted of methyl chloride and trimethylamine. The residue contained unchanged trimethylamine hydrochloride and methylamine hydrochloride.

$$2(CH_3)_3N\ HCl \longrightarrow 2\ CH_3Cl + (CH_3)_3N + CH_3NH_2{.}HCl$$

When heated to 305° and higher the non-volatile portion consisted of methylamine hydrochloride and ammonium chloride. Vincent used the pyrolysis of trimethylamine hydrochloride as a commercial preparation of methyl chloride. By heating a mixture

---

(157) Hofmann, Proc. Roy. Soc. (London), 10, 594 (1860).

(158) Vincent, Compt. rend., 84, 1139 (1877); 85, 667 (1877).

of trimethylamine hydrochloride and aniline, the methyl chloride formed in the pyrolysis combined with the latter, and methylaniline distilled over. Dry distillation of trimethylamine hydrobromide gave methyl bromide, trimethylamine and ammonia in the volatile portion. Trimethylamine hydroiodide gave analogous products.

Phookan and Krafft (159) studied the effect of heat on 1,10-decanediamine dihydrochloride. They found that by heating a long time at an elevated temperature or by subliming under moderately reduced pressure it decomposed into ammonium chloride and decamethyleneimine. When it was heated in a stream of hydrogen chloride at ordinary pressure the reaction was speeded up and the yield increased. However, under these conditions resinification set in readily.

There are no entries in the scientific literature on the pyrolysis of purely aliphatic amine hydrochlorides of high molecular weight.

6-Aminopyrimidines

The trimerization of aliphatic nitriles was initiated by the attempt of Frankland and Kolbe (160) to prepare the

(159) Phookan and Krafft, Ber., 25, 2252 (1892).

(160) Frankland and Kolbe, Ann., 65, 269 (1848).

free ethyl radical by treatment of propionitrile with metallic potassium.

$$C_2H_5CN + K \longrightarrow KCN + C_2H_5$$

The gas evolved analyzed for CH_3- but was found to be $(CH_3-)_2$ or ethane. The involatile portion contained potassium cyanide and a small amount of a basic compound which analyzed for $(C_2H_5CN)_3$. It had none of the properties of the original propionitrile. The compound dissolved in acids and gave crystalline salts. The free base could be boiled with alkali without undergoing any perceptible change. Somewhat later, Bayer (161) trimerized acetonitrile with metallic sodium, and isolated a trimeric base $(CH_3CN)_3$ which had the general properties of the base prepared by Frankland and Kolbe. Further, it could be halogenated to give a monochloro and a monobromo derivative. The monochloro derivative upon reduction with sodium amalgam was converted to the original base.

In 1880, v. Meyer and his school (162) began a series of intensive studies on the properties of the trimers of aliphatic nitriles. They improved the previous yields for the preparation of trimers, and extended the trimerization to isovaleronitrile and isocapronitrile. They found that only primary nitriles were capable of the trimerization.

(161) Bayer, Ber., 2, 319 (1869); 4, 176 (1871).

(162) v. Meyer and co-workers, J. prakt. Chem., 22, 261 (1880); 27, 153 (1883); 30, 115 (1884); 31, 112, 365 (1885); 37, 396 (1888); 53, 246 (1896).

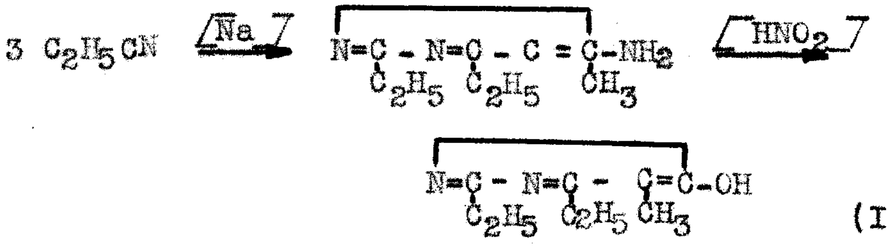
By using mixtures of two nitriles they were able to obtain mixed trimers.

Their investigations of the reactions of the trimers showed the presence of an $-NH_2$ grouping which could be converted successively to $-OH$, $-Cl$, and $-OC_2H_5$. The $-Cl$ could be converted back to the original $-NH_2$ by treatment with ammonia. The $-NH_2$ grouping underwent several normal reactions of a primary amine. For example, upon treatment with ethyl chlorocarbonate a urethan was obtained. Acylation with acetic anhydride at elevated temperatures produced a monoacyl derivative. Reaction with phenyl isocyanate yielded the corresponding phenylurea. Finally, treatment with phthalic anhydride gave mainly the corresponding phthalimide.

Yet in several instances the $-NH_2$ group either did not function at all or acted with the rest of the molecule as a tertiary base. When the trimer was alkylated with an excess of ethyl iodide it added but one ethyl group. Also, the trimer merely formed an addition product with acetyl chloride. Thus, while an amino group was probably present it did not undergo changes with exceptional facility.

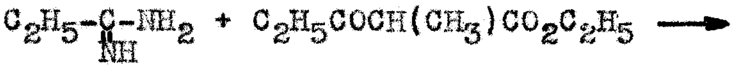
The structure of the trimers was determined as a result of investigations on the dimerization of aliphatic nitriles

(163), and the synthesis of the hydroxy derivatives showed them to be 6-aminopyrimidines (164).



$$3\ C_2H_5CN \xrightarrow{[Na]} \underset{C_2H_5}{N=C} - \underset{C_2H_5}{N=C} - C = \underset{CH_3}{C}-NH_2 \xrightarrow{[HNO_2]} \underset{C_2H_5}{N=C} - \underset{C_2H_5}{N=C} - \underset{CH_3}{C=C}-OH$$

(I)



$$C_2H_5-\underset{NH}{\overset{}{C}}-NH_2 + C_2H_5COCH(CH_3)CO_2C_2H_5 \longrightarrow$$

(I)

Sodium methoxide, sodium ethoxide and Grignard reagents have been found to trimerize aliphatic nitriles (165).

---

(163) v. Meyer and co-workers, _ibid._, _37_, 411 (1888); _38_, 336, 343 (1888); _39_, 188, 230, 245 (1889).

(164) v. Meyer and co-workers, _ibid._, _39_, 262 (1889); _40_, 303 (1889).

(165) v. Meyer and co-workers, _ibid._, _38_, 584 (1888); _42_, 1 (1890); Baerts, _Bull. soc. chim. Belgique_, _31_, 184, 421 (1922).

EXPERIMENTAL

Purification of Stearic Acid.

Five hundred grams of commercial stearic acid (166) m.p. 55-60° was refluxed for about an hour with 2000 ml. of 1:1 hydrochloric acid in a 4 l. Erlenmeyer flask. After cooling in the tap, the aqueous portion was decanted off, and the cake rinsed with three portions of distilled water, followed by three rinsings with small portions of acetone *in situ*. Two and one half liters of acetone was added, and a slow crystallization under the tap and then at 0° gave brownish crystals melting at 65.5-66.5°. A second crystallization gave colorless plates melting sharply at 68.0-68.5°. The yield was 335-368 g. or 68-73 per cent.

The acetone may be recovered from the first crystallization and used in the second one.

Upon distilling off the acetone from the filtrate of the first crystallization, a brown pasty solid was recovered. Even the second filtrate yielded an extremely crude residue which melted at room temperature.

Further crystallizations will raise the melting point

(166) Kindly supplied by Dr. A. W. Ralston of Armour and Co., Chicago, Illinois.

to 70.0°, but the above product is sufficiently pure, giving derivatives which melt sharply.

The treatment with hydrochloric acid removes any nickel present in the commercial stearic acid.

Attempts to prepare pure stearic acid from magnesium stearate, U.S.P., and stearic acid U.S.P. gave a much poorer quality of acid.

Preparation of Stearonitrile.

The following method is essentially that used by McCorkle (20) but with further simplification.

In a 1 l. Claisen flask was placed 284 g. (1.0 mole) of purified stearic acid. The long neck carried a two-hole stopper which contained a glass inlet tube for the ammonia. This reached to the bottom of the flask. Through the other hole was inserted a thermometer also reaching to the bottom. The other neck of the flask was closed by a cork stopper while the distilling tube was left open for the escape of the ammonia. The distilling tube dipped into an empty beaker in order to catch the water and any material ejected over.

The heating was done in a hood by means of a Meker burner. The flask was placed in a six-inch graphite bath, the large supporting ring of which was 8.5 in. from the ring stand. When the temperature was about 150° the inlet tube was connected with the ammonia tank through a bubbler of mineral oil to observe the rate of flow of ammonia. To maintain an excess of ammonia a steady stream of bubbles was maintained. The presence of excess ammonia was detected at the outlet of the distillation tube by means of a cotton dauber moistened with concentrated hydrochloric acid. The heating was conducted at 330° for 9 hours. The molten contents of the flask were transferred to a one liter Claisen flask with a 20 cm. fractionating column, and distilled under reduced pressure. It was found advantageous to place an asbestos guard around the distillation apparatus in order to exclude drafts. The nitrile boiled over a two degree range 185-187°/4mm., with no forerun. The colorless distillate melted at 39-40°, and weighed 203-208 g. The yield was 77-78 per cent of the theoretical.

During the heating the water which was evolved partly refluxed back onto the hot acid causing a mild and occasional seething. It was necessary occasionally to wipe the distilling tube with a flame to melt the small amount of material which collected there and which may prevent the smooth removal of the water. This was the only attention the reaction required once the temperature had been reached and the ammonia rate fixed.

McCorkle (20) obtained a 73 per cent yield boiling over a thirty degree range (160-190°/3mm.).

The product may be purified further by refluxing a short while with 1 l. of 2 % potassium hydroxide in 50% ethanol, followed by two reflux-washings with plain 50% ethanol. Finally it was crystallized from 2 l. of 95% ethanol at 0° to melt at 41.0-42.0°. Pure stearonitrile melts at 41.0° (20).

Preparation of Lauronitrile.

For the preparation of lauronitrile a pure lauric acid melting at 43.0-43.5° was used. A 500 ml. Claisen flask was equipped exactly as in the preceding experiment. One hundred grams (0.5 mole) of lauric acid was heated for 12 hours at 270-275° (the b.p. of the acid). Once the temperature was reached and the ammonia rate fixed to a steady stream of bubbles, the reaction required no special attention. A first distillation from a modified Claisen flask gave a colorless distillate boiling at 130.0-136.0°/3mm. The yield was 66.0 g. or 73 per cent of the theoretical.

McCorkle (20) superheated the acid at 315-330° for 12 hours, and obtained a 61-72 per cent yield of the nitrile boiling over a range of 115-130°/3mm. Since in his apparatus he used an outlet condenser on the Claisen flask, it was necessary to stop the heating at intervals in order to clear the condenser of material which solidified there.

Preparation of Sebaconitrile.

For this preparation an ordinary 500 ml. distilling flask was used. The thermometer and inlet tubes were inserted to the bottom of the flask through the single neck. The distilling tube reached into a beaker to carry off any water and organic material which distilled over. The technique was that used in the two preceding experiments. In this experiment 101.0 g. (0.5 mole) of sebacic acid was heated at 220° for 6 hours. A first distillation from a modified Claisen flask gave a colorless distillate boiling sharply at 168.0-170.0°/3mm. The yield was 45.0 g. or 55 per cent of the theoretical. The compound gave $n_D^{25} = 1.4462$.

Sebaconitrile has been reported (25) to boil at 195°/3mm. and to give $n_D^{25} = 1.4464$.

Attempt to Prepare Oleonitrile.

Two hundred and eighty two grams (1.0 mole) of oleic acid was placed in a 1 l. Claisen flask arranged exactly as in the preparation of stearonitrile (p. 75). Heating was conducted at 330° for 6 hours. The product was distilled from a modified Claisen flask, and boiled at 200-220°/15mm. The yield was 212.0 g. or 80 per cent of nitrile.

Oleonitrile has been reported to distil at 210-215°/15mm. (167), but no details were given as to method of preparation.

Reduction of the nitrile to the amine and preparation of derivatives showed it to be probably a mixture of oleo- and elaidonitriles (see p. 85).

Attempt to Prepare Elaidonitrile.

In a 250 ml. Claisen flask arranged as in the preparation of stearonitrile (p. 75) was placed 48.1 g. (0.17 mole) of pure elaidic acid. Heating was conducted at 330° for 2.5 hours. The product was distilled from a modified Claisen flask, and boiled at 208-213°/14mm. The yield was 37.7 g. or 84 per cent of nitrile.

Reduction of the nitrile to the amine and preparation of derivatives showed it to be a mixture of oleonitrile and elaidonitrile (see p. 86).

Elaidonitrile has been prepared by the dehydration of elaidamide (168) and was found to boil at 213-214°/16mm.

Preparation of n-Octadecylamine.

In a 2 l. three-necked flask carrying two reflux condensers was placed 132.5 g. (0.5 mole) of molten stearonitrile and 690 g. (15 mole) of absolute ethanol. The solution

(167) Speakman and Chamberlain, Trans. Faraday Soc., 29, 358 (1933).

(168) Krafft and Tritschler, Ber., 33, 3583 (1900).

was heated to a gentle reflux. Eighty and one half grams (3.5 gram atom) of metallic sodium was added in small chunks. The solution was further refluxed until the sodium dissolved entirely. The hot solution was cautiously poured into 400 ml. of concentrated hydrochloric acid in an ice bath. The pouring must be done slowly as the neutralization is fairly violent. The solution should be acid. About 2 l. of absolute alcohol was added and the precipitated sodium chloride removed by a hot filtration. Upon cooling to 0° colorless plates were obtained. These were washed with ether until the filtrate was colorless. The hydrochloride melted at 172°. The yield was 96.7 g. or 63 per cent of the theoretical. Further crystallization from chloroform and washing with ether raised the melting point to 189-190°.

An intimate mixture of 30.5 g. (0.1 mole) of n-octadecylamine hydrochloride and 12.3 g. (0.22 mole) of calcium oxide was placed in a 250 ml. distilling flask carrying only a thermometer and arranged for vacuum distillation. When the bath temperature was about 200° the vacuum was applied. The amine distilled at 169-170°/4mm. The yield was 22.0 g. or 81 per cent of the theoretical. n-Octadecylamine has been reported (31) to boil at 192-197°/16mm.

Attempts to reduce stearonitrile with sodium and n-butyl alcohol were less satisfactory (40). When the alcoholic solution of the amine was distilled violent frothing occurred. This was probably due to the presence of sodium stearate formed by the saponification of the stearonitrile by the sodium butoxide. For this reason it is easier to isolate the amine first as the hydrochloride.

Manipulation of High-Molecular-Weight Primary Amines.

The primary amines are extremely basic. For example, a mixture of *n*-tridecylamine and water gives a slight alkaline reaction but on addition of ethyl alcohol the alkaline reaction becomes strong. They readily absorb carbon dioxide and moisture from the air to give an amine carbamate of the structure:

$$RNH_2 . HOCONHR$$

which melts higher than the free amine (87). Thus, some freshly prepared amine exposed to the atmosphere begins to rise in melting point until the formation of the carbamate salt is complete. To overcome this difficulty it is imperative to avoid both carbon dioxide and moisture in its preparation. This has been done in several ways. One way is to convert the crude amine to the amine hydrochloride, and whenever free amine is required the calculated amount of calcium oxide is admixed with the hydrochloride, and the amine distilled in an apparatus containing soda-lime towers at all inlets. It is unwise to distil more than 250 ml. or an equivalent weight of amine at one time since the vapors attack the rubber stoppers and give a yellow odorous distillate. The rubber stoppers must be pretreated with hot sodium hydroxide to remove any free sulfur, and just before use immersed in chloroform for a few minutes to dissolve out superficial impurities.

The free amines may be stored in closely stoppered containers which are opened only for the short time required to weigh out a portion. Speed in manipulation is essential. For this purpose the amines should be manipulated in a liquid condition. This is best obtained by warming the container in the water bath until the contents are molten. Two beakers are balanced and then placed on the hot plate. The container is removed from the water bath and the warm beakers replaced on the balance. Slightly more than the required amount of amine is poured into the beaker and enough withdrawn with a warmed medicine dropper to give the desired weight. The container is immediately stoppered, and the weighed molten amine poured into the reaction flask.

The secondary and tertiary amines are not affected by the atmosphere and require no special techniques.

Preparation of Di-*n*-octadecylamine.

The following procedure is a modification of McCorkle's directions (20)(40). By using a higher pressure, the reaction time was shortened and a purer product was obtained. The use of absolute alcohol avoided the use of a large volume of 95 per cent ethanol and oiling out of the amine during the hot filtration.

Twenty grams (0.075 mole) of pure stearonitrile melting at 41.0-42.0° was placed in a Parr hydrogenation bomb (169) with 4.0 g. of Adkins catalyst 37 K A F (70) under a hydrogen pressure of 110 atmospheres. The bomb was rocked, and heating was conducted at 210-215° for 30 minutes. The reaction was immediate, and once the temperature had been reached there was no further absorption of hydrogen. After cooling, the contents were taken up in 250ml. of absolute ethanol and filtered hot from the catalyst. A slow crystallization gave beautiful, colorless plates melting at 72.0-73.0°. The yield was 15 g. or 77 per cent of the theoretical. Further crystallization did not change the melting point.

Di-n-octadecylamine was reported to melt at 71.0-72.0° (20).

Preparation of Di-n-octadecylamine Hydrochloride.

To a solution of 19.3 g. (0.037 mole) of di-n-octadecylamine in 280 ml. of hot absolute ethanol was added 6.5 ml. (0.074 mole) of concentrated hydrochloric acid. The hot solution was transferred to a large evaporating dish, and the

(169) Adkins, "Reactions of Hydrogen", University of Wisconsin Press, Madison (1937) p. 38.

solvent removed on the steam bath. The residue was crystallized from 150 ml. of ethanol and washed with ether. The colorless plates melted at 175° when the temperature was raised rapidly. The yield was 18.6 g. or 90 per cent of the theoretical. Di-n-octadecylamine hydrochloride has been reported (20) to melt at 174-176°.

Preparation of Tri-n-octadecylamine Hydrochloride.

The procedure of McCorkle (20)(40) for the preparation of large amounts of tri-n-octadecylamine was found to give a crude product consisting of a mixture of tri-n-octadecylamine and tri-n-octadecylamine hydrochloride. The following procedure gave pure tri-n-octadecylamine hydrochloride in large runs.

A mixture of 98.5 g. (0.189 mole) of di-n-octadecylamine and 29.9 g. (0.103 mole) of n-octadecyl chloride in a 500 ml. round bottom flask was heated in an oil bath at 170-180° for eight hours. After cooling, the contents were powdered and suspended in 1500 ml. of anhydrous ether. The mixture was allowed to stand overnight with occasional shaking. After filtration from the ether insoluble di-n-octadecylamine hydrochloride, the ether was removed from the filtrate. The residue was dissolved in 750 ml. of ethanol, and 8.4 ml. of concentrated hydrochloric acid added. The mixture was refluxed until a complete solution took place. A crystallization gave a solid melting at 93.0-95.0°. A further crystallization from ethanol and Norite gave crystals melting at 94.0-95.0°. The yield was 58.2 g. or 80 per cent of the theoretical. Repeated crystallization did not change the melting point.

The hydrochloride has been reported to melt at 96-97° (20).

Attempt to Prepare Oleylamine.

In a 3 l. three-necked flask was placed 95 g. (0.361 mole) of purported oleonitrile (p. 78) and 1025 ml. of absolute ethanol. Two reflux condensers capped with calcium chloride tubes were attached, while the third neck was closed with a rubber stopper. The latter was removed at intervals, and 126.4 g. (5.5 gram atom) of sodium cut into small cubes under ether was added. There was no vigorous reaction. After all of the sodium had been added, the mixture was brought to a reflux and the sodium dissolved completely. The hot solution was poured into 2 l. of ice water. The lower alkali layer was siphoned off and discarded. The mixture was transferred to a separatory funnel and washed with hot saturated sodium chloride solution. It was then dissolved in 1 l. of hot benzene and further washed with water. The benzene solution was dried over calcium oxide.

The latter was removed by a filtration and the filtrate further dried over sodium wire. The benzene was removed, and the residue vacuum distilled. The apparatus was protected from carbon dioxide by placing soda-lime towers at all outlets. The product boiled at 189-203°/4mm. The yield was 43.4 g. or 46 per cent of the theoretical as oleylamine. However, preparation of solid derivatives showed it to be impure, and probably a mixture of oleyl- and elaidylamines.

Oleylamine has been reported (167) to boil at 200-210°/17mm., but no mention was given of the method of preparation.

Attempt to Prepare Elaidylamine.

In a 1 l. three-necked flask was placed 26.7 g. (3 parts) of purported elaidonitrile (p. 79) and 339 ml. (30 parts) of absolute ethanol. Two reflux condensers capped with calcium chloride tubes were attached and the third neck closed by a rubber stopper. The solution was heated to reflux by a hot plate, and the heating was continued as 35.6 g. (4 parts) of sodium, sliced under ether, was added at intervals through the stoppered neck. Although the sodium was added continuously, the reaction proceeded in moderation. After all of the sodium had dissolved, the solution was poured into 1 l. of ice water and extracted with ether. The clear ethereal solution was dried for several hours over calcium oxide and filtered through a Buchner funnel. It was then concentrated to about 500 ml., and dry hydrogen chloride pumped into the refluxing solution until it was saturated. The ether was removed, and the residue pulverized and washed with cold ether. The product melted at 123-133°. The yield was 26.9 g. or 93 per cent of the theoretical as elaidylamine hydrochloride.

The free amine was obtained by mixing the hydrochloride with pulverized potassium hydroxide and distilling in the absence of carbon dioxide. The amine boiled at 200-205°/16mm. but contained some water. It was heated with metallic sodium a short while and redistilled. It now boiled at 198-203°/13mm. However, preparation of solid derivatives showed it to be impure and probably a mixture of oleyl- and elaidylamines.

Elaidylamine has been reported (168) to boil at 194-195°/13mm. The hydrochloride melted at 185° with decomposition.

Preparation of 1,10-Decanediamine.

To 16.4 g. (0.1 mole) of sebaconitrile in a Parr hydrogenation bomb was added 25 ml. of a Raney nickel suspension in petroleum ether (b.p. 60-68°). Ammonia gas was introduced up to a pressure of 160 lbs./sq.in. and then 500 lbs./sq.in. of hydrogen. The bomb was rocked, and the temperature raised to 140°. This temperature was maintained for 30 minutes. The greatest decrease in pressure occurred as the bomb reached 135°. By the time the temperature reached 140° there was no further decrease in pressure. The theoretical absorption of hydrogen took place. After cooling to room temperature, the bomb contents were taken up in 300 ml. of hot petroleum ether (b.p. 60-68°) and filtered hot from the catalyst. The solvent was removed, and the residue vacuum distilled. The apparatus was protected from carbon dioxide by attaching soda-lime towers at all outlets. The liquid boiled sharply at 122.0-123.0°/4mm. The yield was 10.6 g. or 62 per cent of the theoretical. The colorless distillate solidified in the receiver. The product, when quickly manipulated into a capillary tube, melted at 61.0-61.5°.

1,10-Decanediamine has been reported (159) to melt at 61.5°.

The compound readily absorbed carbon dioxide from the air causing a rise in melting point. A sample of the amine after standing in an open container melted at 133-137°.

Preparation of n-Octadecylurea, $n\text{-}C_{18}H_{37}NHCONH_2$.

A mixture of 12.2 g. (0.04 mole) of n-octadecylamine hydrochloride and 6.48 g. (0.08 mole) of potassium cyanate was placed in a large evaporating dish. Five hundred ml. of ethanol was added and the mixture evaporated to dryness on the steam bath. The residue was powdered and taken up in 800 ml. of absolute ethanol and filtered hot from the insoluble potassium chloride. The colorless crystals were filtered at 0° and washed with ether. They melted at 111.0-112.0°.

The yield was 10.2 g. or 81 per cent of the theoretical. Further crystallization raised the melting point to 112.5-113°.

n-Octadecylurea was first prepared by Adam and Dyer (36) who reported a melting point of 111°.

With the above directions and a smaller run (0.002 mole and 25 ml. of ethanol) it is possible to derivatize n-octadecylamine in one hour of working time. The urea is colorless, crystalline and sharp melting.

Preparation of N,N-Di-n-octadecylurea, $(n\text{-}C_{18}H_{37})_2NCONH_2$.

A solution of 9.4 g. (0.0169 mole) of di-n-octadecylamine hydrochloride in 150 ml. of hot absolute ethanol was added to 2.74 g. (0.0338 mole) of potassium cyanate in an evaporating dish, and the mixture evaporated to dryness on the steam bath. Another portion of potassium cyanate was added together with 100 ml. of absolute ethanol and the evaporation repeated. The residue was taken up in 100 ml. of absolute ethanol and filtered hot from potassium chloride and excess potassium cyanate. A crystallization at room temperature gave crystals melting at 64.0-65.0°. The yield was 5.8 g. or 61 per cent of the theoretical. Further crystallization raised the melting point to 65.0-65.5°.

Anal. Calcd. for $C_{37}H_{76}ON_2$:N, 4.96. Found: N, 5.02.

Preparation of N,N'Di-n-octadecylthiourea, $\underline{n}$-$C_{18}H_{37}NHCSNHC_{18}H_{37}$-$\underline{n}$.

To the clear solution of 13.4 g. (0.05 mole) of n-octadecylamine in 150 ml. of ether was added 7.6 g. (0.10 mole) of colorless carbon disulfide. The addition was performed slowly from an ordinary graduate. There was an immediate formation of a heavy white precipitate. Heat was evolved and the mass solidified. More ether was added and the mixture filtered. It was washed with ether until the filtrate was colorless and the odor of carbon disulfide unnoticeable. The salt melted at 97.0-100.0° with decomposition. The yield was 13.0 g. or 85 per cent of the theoretical.

The salt was placed in a 125 ml. Erlenmeyer flask carrying a three-hole stopper which held a glass inlet tube reaching to the surface of the salt, a thermometer and a glass outlet tube. A slow flow of nitrogen was maintained and the flask was heated in an oil bath at 100° for 20 hours. After cooling to room temperature, a pale yellow solid was obtained which melted at 93.5-95.5°. The product was dissolved in 500 ml. of boiling ethanol, and after a hot filtration crystallized at 0°. The colorless crystals were washed with ether and melted at 95.0-96.0°. The yield was 10.2 g. or 80 per cent of the theoretical. Further crystallization did not raise the melting point.

Anal. Calcd. for $C_{37}H_{76}N_2S$: N, 4.83. Found: N, 5.06.

Preparation of N,N'-Di-n-octadecylurea, n-$C_{18}H_{37}NHCONH$-$C_{18}H_{37}$-n.

In a 500 ml. three-necked flask equipped with a dropping funnel, reflux condenser and mercury-sealed stirrer was placed 4.5 g. (0.0077 mole) of N,N'-di-n-octadecylthiourea dissolved in 150 ml. of hot absolute ethanol. The solution was stirred, and 2.87 g. (0.0169 mole) of silver nitrate solution was added. The latter solution was prepared by dissolving the silver nitrate in 5 ml. of water and adding 5 ml. of absolute ethanol just before use. The precipitation of silver sulfide was immediate. Also, some of the urea separated out. A solution of 0.95 g. (0.0169 mole) of potassium hydroxide dissolved in 20 ml. of 95% ethanol was added, and the mixture refluxed with stirring for 30 minutes. It was then transferred to a 1 l. Erlenmeyer flask, and enough absolute ethanol added to dissolve the product. It was filtered hot from the silver sulfide. The filtrate deposited colorless crystals which melted at 112.0-112.5°. The yield was 3.5 g. or 87 per cent of the theoretical.

N,N'-Di-n-octadecylurea has been reported (170) to melt at 105-106°.

Anal. Calcd. for $C_{37}H_{76}ON_2$: N, 4.96. Found: N, 4.79.

Preparation of N,N'-Di-n-dodecylthiourea, n-$C_{12}H_{25}NHCSNHC_{12}H_{25}$-n.

(170) French patent, 809,233 (1937)/C.A., 31, 6676 (1937)/.

To a solution of 9.2 g. (0.05 mole) of n-dodecylamine in 300 ml. of ether was added 3.8 g. (0.05 mole) of colorless carbon disulfide. The latter was added from a buret. A precipitate separated out after a few seconds, and in several minutes precipitation was complete. After filtering and washing with ether, a pale yellow salt was obtained. This was placed in a 50 ml. Erlenmeyer flask and heated in an oil bath temperature of 100° for 4 hours. The dark orange product melted at 71.0-72.0°. A crystallization from ethanol at 0° gave the constant melting point of 74.5-75.0°. The yield was 7.4 g. or 72 per cent of the theoretical. The colorless crystals were soluble in warm acetone and in ether. They were moderately soluble in benzene.

Anal. Calcd. for $C_{25}H_{52}N_2S$: N, 6.80. Found N, 6.37.

Reaction of n-Dodecylamine and Carbon Disulfide.

In a 200 ml. round bottom flask was placed a solution of 18.5 g. (0.1 mole) of n-dodecylamine in 100 ml. of absolute ethanol. To this was added 8.4 g. (0.11 mole) of colorless carbon disulfide. A heavy crystalline precipitate formed, and the contents almost solidified. The mixture was refluxed to give a clear solution, and the refluxing was continued for 48 hours. There was an immediate evolution of hydrogen sulfide which became almost imperceptible at the end of the heating time. The hot solution was transferred to an evaporating dish, and the alcohol removed on a water bath. On cooling to room temperature, a yellow solid was obtained which melted at 72.5-73.0°. The yield was quantitative on the basis that it was N,N'-di-<u>n</u>-dodecylthiourea.

The product was pulverized and extracted with ligroin in a Soxhlet extractor. The entire solid went into solution. The solvent was removed, and the residue crystallized from ethanol at 0°. Colorless crystals were obtained which melted at 73.5-74.0°. A mixed melting point with an authentic specimen of N,N'-di-<u>n</u>-dodecylthiourea melting at 74.0-74.5° gave no depression.

Reaction of n-Octadecylamine and Carbon Disulfide.

To a solution of 13.4 g. (0.05 mole) of <u>n</u>-octadecylamine in 100 ml. of absolute ethanol in a 200 ml. round bottom flask was added 4.2 g. (0.055 mole) of colorless carbon disulfide. A precipitate separated out, and the mixture almost solidified. It was refluxed to give a clear orange solution, and the refluxing was continued for 48 hours. The evolution of hydrogen sulfide was immediate. At the end of the allotted time, the solvent was removed, and a yellow solid was obtained which melted at 89.5-91.0°. It was entirely soluble in warm ligroin. Crystallization from ethanol at 0° gave colorless crystals melting at 94.0-95.0°. The yield was 12.4 g. or 86 per cent of the theoretical. A mixed melting point with an authentic specimen of N,N'-di-n-octadecylthiourea melting at 95.2-96.0° gave no depression.

Attempt to Prepare N,N,N',N',-Tetra-n-octadecylthiourea.

A solution of 0.85 g. (0.0016 mole) of di-n-octadecylamine in 10 ml. of colorless carbon disulfide was refluxed for 3.5 hours. The yellow solution remained unchanged during the heating. Cooling to 0° deposited no crystals. The carbon disulfide was removed at the water pump, the last portion being removed with the aid of the steam bath. A yellow solid remained which was washed with cold ether until the filtrate was colorless. It melted at 70-73°, and weighed 0.68 g. A mixed melting point with an authentic specimen of di-n-octadecylamine melting at 73-74° gave no depression. The recovery was 80 per cent.

Preparation of N-n-Dodecyl-N'-phenylthiourea, n-$C_{12}H_{25}NHCSNHC_6H_5$.

To 14.8 g. (0.11 mole) of phenyl isothiocyanate in a 250 ml. Erlenmeyer flask was added 18.5 g. (0.1 mole) of n-dodecylamine. The reaction was exothermic, and a clear yellow liquid was formed. After a few minutes, the flask was immersed in an ice bath, and the flask turned so that the material solidified in a thin layer. It was pulverized and washed with 100 ml. of 50% ethanol. A crystallization from ethanol at 0° gave fine colorless crystals melting at 69.5-69.8°. The yield was 23.0 g. or 72 per cent of the theoretical. The product was soluble in ether and benzene. Anal. Calcd. for $C_{19}H_{32}N_2S$: N, 8.75. Found: N, 8.17.

Attempt to Prepare N,N-Di-n-Octadecyl-N'-phenylthiourea.

In a 200 ml. round bottom flask was placed 5.2 g. (0.01 mole) of di-n-octadecylamine dissolved in 50 ml. of warm, dry benzene, and 1.5 g. (0.011 mole) of freshly distilled phenyl isothiocyanate washed in with small portions of solvent. The clear solution was refluxed for an hour. The benzene was removed, and a yellow solid was obtained which smelled strongly of unchanged phenyl isothiocyanate. It was refluxed with 50 ml. of ethanol, cooled to 0° and filtered to get rid of unreacted phenyl isothiocyanate. The colorless product melted at 34-37° and weighed 6.6 g.

The reaction product was refluxed with ethyl alcoholic hydrogen chloride and melted at 171° indicating unchanged amine. The recovery was 4.0 g. or 72 per cent of the amine used. After conversion to the free base, it melted at 71.0-72.0°. A mixed melting point with an authentic specimen of di-n-octadecylamine melting at 71.0-72.0° gave no depression.

Preparation of N,N-Di-n-octadecyl-N'-phenylurea, $(n\text{-}C_{18}H_{37})_2NCONHC_6H_5$.

A 200 ml. round bottom flask was warmed in a Bunsen flame and closed with a stopper carrying a calcium chloride tube. In the cool flask was placed a solution of 5.2 g. (0.01 mole) of di-n-octadecylamine in 50 ml. of warm, dry benzene, and 1.3 g. (0.11 mole) of phenyl isocyanate was washed in with small portions of solvent. The solution was refluxed for an hour, protecting against moisture by means of a calcium chloride tube. After removal of the benzene, a colorless residue was obtained which melted at 52.0-54.0°. Crystallization from absolute ethanol gave colorless crystals which melted at 56.0-56.5°. The yield was 5.4 g. or 84 per cent of the theoretical.

Anal. Calcd. for $C_{43}H_{80}ON_2$: N, 4.37 . Found: N, 4.17.

Preparation of N-n-Dodecyl-N'-α-naphthylurea, n-$C_{12}H_{25}NH$-$CONHC_{10}H_7$-α.

A 125 ml. Erlenmeyer flask was dried by heating in a Bunsen flame, then closed with a stopper carrying a calcium chloride tube. After cooling to room temperature, 9.2 g. (0.05 mole) of molten n-dodecylamine was added, followed by the addition of 9.2 g. (0.055 mole) of α-naphthyl isocyanate. The reaction was exothermic. After cooling to room temperature and pulverizing, the tan solid was crystallized from 300 ml. of petroleum ether (b.p. 77-115°). Repeated crystallization from ethanol gave colorless plates

melting at 127.5-128.0°. The yield was 10.4 g. or 64 per cent of the theoretical. The crystals were stored in a brown bottle since they turned pink on exposure to light.
Anal. Calcd. for $C_{23}H_{34}ON_2$: N, 7.91. Found: N, 7.42.

Preparation of N-*n*-Octadecyl-N'-α-naphthylurea.
$n\text{-}C_{18}H_{37}NHCONHC_{10}H_7\text{-}\alpha$

A 125 ml. Erlenmeyer flask was dried as in the previous experiment. Then 13.4 g. (0.05 mole) of molten *n*-octadecylamine was added followed by 9.2 g. (0.055 mole) of α-naphthyl isocyanate. After cooling to room temperature, the solid was pulverized. The tan product was crystallized twice from petroleum ether (b.p. 77-115°) at 0°. It melted at 120.0-121.5°. Further crystallization from a mixture of equal parts of chloroform and ethyl acetate gave the constant melting point of 122.5-123.0°. The yield was 13.7 g. or 63 per cent of the theoretical. The colorless plates were electrophilic.
Anal. Calcd. for $C_{29}H_{46}ON_2$: N, 6.38. Found: N, 6.27.

Preparation of N,N-Di-*n*-octadecyl-N'-α-naphthylurea,
$(n\text{-}C_{18}H_{37})_2NCONHC_{10}H_7\text{-}\alpha$

A 200 ml. round bottom flask was warmed in a Bunsen flame and closed with a stopper carrying a calcium chloride tube. In the cool dry flask was placed 3.9 g. (0.0075 mole) of di-*n*-octadecylamine and 50 ml. of warm dry benzene. This was followed by the addition of 1.4 g. (0.0083 mole) of α-naphthyl isocyanate which was washed in with small portions of solvent. The solution was refluxed for an hour. Upon prolonged cooling in the tap, a small batch of crystals appeared. After the addition of 10 ml. of toluene, the mixture was cooled further to 0°. The colorless crystals were collected on a filter and melted at 54.0-55.0°. The yield was 4.6 g. or 89 per cent of the theoretical. *Anal*. Calcd. for $C_{47}H_{82}ON_2$: N, 4.06. Found: N, 3.78.

Attempt to Prepare N-n-Dodecyl-N'-α-naphthylthiourea.

To 9.2 g. (0.05 mole) of *n*-dodecylamine in a 125 ml. Erlenmeyer flask carrying a soda-lime tube was added 9.2 g. (0.55 mole) of α-naphthyl isothiocyanate. The yellow solution was heated in a water bath for 30 minutes. After cooling to room temperature, the solid was pulverized. A crystallization from ethanol at 0° gave slightly yellow crystals which melted at 63-73°. The yield was 14.7 g. Repeated crystallization from ethanol gave an improved melting point of 67.5-68.0°. The product was dissolved in 200 ml. of hot 75% ethanol containing 5.0 ml. of concentrated hydrochloric acid and cooled to room temperature. The crystals now melted at 74.5-75.5°. Further crystallization from ethanol did not give a constant sharp-melting derivative.

The α-naphthyl isothiocyanate was an Eastman-Kodak preparation which even upon purification melted low.

Preparation of n-Dodecylbenzenesulfonamide, $C_6H_5SO_2NHC_{12}H_{25}$-n.

To 18.5 g. (0.1 mole) of n-dodecylamine in a 500 ml. Erlenmeyer flask was added 200 ml. of warm (30°) 12% potassium hydroxide and then 26.5 g. (0.15 mole) of benzenesulfonyl chloride in small portions. The flask was stoppered and shaken vigorously after each addition. The reaction heated up, and after the last addition there was no odor of unchanged benzenesulfonyl chloride. The mixture was poured into 200 ml. of water and warmed until the oil separated from the aqueous solution. An excess of concentrated hydrochloric acid was added, and the mixture cooled below room temperature. The oil solidified and was filtered and washed with water. A crystallization from ethanol gave colorless crystals melting at 57.5-58.0°. The yield was 21.7 g. or 67 per cent of the theoretical. The crystals were soluble in ether, acetone and benzene.

Anal. Calcd. for $C_{18}H_{31}O_2NS$: N, 4.31. Found: N, 3.72.

Preparation of N-n-Octadecylbenzenesulfonamide, $C_6H_5SO_2NHC_{18}H_{37}$-n.

To 26.9 g. (0.1 mole) of n-octadecylamine in a 500 ml.

Erlenmeyer flask was added 200 ml. of warm (60°) 12% potassium hydroxide and then 26.5 g. (0.15 mole) of benzenesulfonyl chloride in small portions with vigorous shaking after each addition. The reaction heated up, and after the last addition there was no odor of unchanged benzenesulfonyl chloride. The mixture was poured into 200 ml. of water and acidified with concentrated hydrochloric acid. It was warmed until the oil separated on top. After cooling to room temperature, the solid was filtered and washed with water. Repeated crystallization from ethanol gave colorless fatty crystals melting at 77.0-77.5°. The yield was 27.8 g. or 68 per cent of the theoretical. The crystals were soluble in acetone, ether and benzene.

Anal. Calcd. for $C_{24}H_{43}O_2NS$: N, 3.42. Found: N, 2.95.

Preparation of N-n-Dodecylacetamide, $CH_3CONHC_{12}H_{25}$-n.

To 27.7 g. (0.15 mole) of molten n-dodecylamine in a 300 ml. Erlenmeyer flask was added 92.0 g. (0.9 mole) of freshly distilled acetic anhydride. A vigorous reaction took place and the solution darkened. It was refluxed for five minutes, poured into one liter of water, and warmed with stirring to decompose the excess acetic anhydride. After cooling below room temperature, the solid was filtered and washed with water. It was dissolved in 500 ml. of hot ethanol, and just enough water added to produce a turbidity. A crystallization at 0° gave colorless plates melting at 53.5-54.0°. The yield was 15.3 g. or 45 per cent of the theoretical. The crystals were insoluble in hot water. They were soluble in acetone, ether and benzene. The compound caused sneezing.

Anal. Calcd. for $C_{14}H_{29}ON$: N, 6.17. Found: N, 5.84.

N-n-Dodecylacetamide has been reported to exist as a liquid boiling at 212-213°/13mm. (131).

Preparation of n-Dodecylammonium N-n-Dodecylcarbamate, n-$C_{12}H_{25}NH_2 \cdot HO_2CNHC_{12}H_{25}$-n.

In a 1 l. round bottom flask was placed a solution of 27.7 g. (0.15 mole) of n-dodecylamine in 800 ml. of moist ether which had just been washed with water. A clear solution formed. Tank carbon dioxide was bubbled in through a mineral oil bubble counter. After a few seconds, a heavy crystalline precipitate appeared. The injection was continued for 30 minutes with frequent agitation. The mixture was filtered to give colorless plates melting at 85.5-86.5°. The yield was 26.6 g. or 78 per cent of the theoretical.

Anal. Calcd. for $C_{25}H_{54}O_2N_2$: N, 6.76. Found: N, 6.57.

Preparation of N-n-Dodecyl-p-toluenesulfonamide, p-$CH_3C_6H_4SO_2NHC_{12}H_{25}$-n.

To 18.5 g. (0.1 mole) of n-dodecylamine in a 500 ml.

Erlenmeyer flask was added 200 ml. of 12% potassium hydroxide and then 28.5 g. (0.15 mole) of p-toluenesulfonyl chloride. The latter was added in small portions, with shaking after each addition. The reaction heated up, and after the addition was completed there was no odor of p-toluenesulfonyl chloride. The mixture was poured into 200 ml. of water, and heated to melt the solid. After acidification with concentrated hydrochloric acid and cooling below room temperature, the tan solid was filtered off and washed with water. Crystallization from 80% ethanol gave a poor melting point of 71.2-72.5°.

The solid was refluxed 30 minutes with 200 ml. of 2% potassium hydroxide and after cooling in the tap the aqueous portion was decanted through a wire screen. The solid was reflux-washed with water. After cooling in the tap, the tan solid was filtered off and crystallized from 90% ethanol slowly to give colorless crystals melting at 73.0-73.5°. The yield was 18.7 g. or 55 per cent of the theoretical.

N-Dodecyl-p-toluenesulfonamide has been prepared from the N-sodium derivative of p-toluenesulfonamide and n-dodecyl chloride. It was reported to melt at 73° (171).

Preparation of N-n-Dodecylstearamide, $C_{17}H_{35}CONHC_{12}H_{25}$-n.

Indirect Method. In a 1 l. round bottom flask was

---

(171) German patent, 637,771 (1936) [Chem. Zentr., I, 4558 (1937)].

placed 24.4 g. (0.11 mole) of n-dodecylamine hydrochloride. A solution of 30.2 g. (0.1 mole) of freshly prepared stearoyl chloride in 350 ml. of dry toluene was added, and the mixture refluxed for 24 hours. The condenser was capped with a calcium chloride tube to prevent access of moisture. During the refluxing a vigorous evolution of hydrogen chloride gas was observed, and after 20 hours the calcium chloride tube was removed. This allowed any residual hydrogen chloride to be expelled. After cooling to room temperature, the solution crystallized and was further cooled to 0°. The colorless crystals were removed by a filtration. They melted at 83.0°. A crystallization from ethanol at 0° gave a colorless, crystalline solid with wax-like characteristics melting at 84.5-85.0°. The yield was 41.6 g. or 92 per cent of the theoretical.

Anal. Calcd. for $C_{30}H_{61}ON$: N, 3.14. Found: N, 2.88.

Direct Method. In a 125 ml. Erlenmeyer flask was placed 9.4 g. (0.05 mole) of n-dodecylamine and 14.2 g. (0.05 mole) of stearic acid. The mixture was heated in a metal bath temperature of 250°. There was a vigorous reaction and after 30 minutes the reaction was over. The yellow molten contents were transferred to a large evaporating dish and turned so that the liquid solidified in a thin layer. Slow crystallization from ethanol gave colorless crystals melting at 84.0-84.5°. The yield was 18.0 g. or 77 per cent of the theoretical. A mixed melting point with an authentic specimen of N-n-dodecylstearamide, m.p. 84.5-85.0° prepared in the previous experiment gave no depression.

Preparation of N-n-Octadecylstearamide, $C_{17}H_{35}CONHC_{18}H_{37}$-n.

In a 125 ml. Erlenmeyer flask was placed 13.4 g. (0.05 mole) of n-octadecylamine and 14.2 g. (0.05 mole) of stearic acid. The flask was placed in a metal bath temperature of 250°. There was a regular effervescence which continued for 30 minutes. A volatilization took place during the heating. The orange liquid was transferred to a large evaporating dish and turned so that the liquid solidified in a thin layer. The tan solid was crystallized from petroleum ether (b.p. 60-68°) to melt at 93.5-94°. Further crystallization from ethanol and Norit gave fine colorless crystals melting at 94.5-95.0°. The yield was 19.6 g. or 71 per cent of the theoretical. A mixed melting point with an authentic specimen of N-n-octadecylstearamide (172) melting at 94.5-95.5° gave no depression.

Hoyt obtained a 41 per cent yield of N-n-octadecylstearamide melting at 96-97° from the reaction of n-octadecylamine and stearoyl chloride (40).

(172) Kindly supplied by B. A. Hunter.

Preparation of N-n-Octadecylbenzamide, $C_6H_5CONHC_{18}H_{37}$-n.

Indirect Method. To a refluxing solution of 15.1 g. (0.05 mole) of n-octadecylamine in 250 ml. of benzene was added 3.9 g. (0.0275 mole) of benzoyl chloride through the condenser. The solution was refluxed for 30 minutes and cooled to 0°. The crystals were filtered off and air dried. The product was refluxed with 800 ml. of ether and filtered hot. The ether was distilled off and the residue melted at 85.5-86.0°. The yield was 4.1 g. or 43 per cent of the theoretical.

Anal. Calcd. for $C_{25}H_{43}ON$: N, 3.75. Found: N, 3.98.

Hoyt (40) obtained a 51 per cent yield of N-n-octadecylbenzamide melting at 85-87° from the same reagents.

Direct Method. To 6.7 g. (0.055 mole) of benzoic acid in a 125 ml. Erlenmeyer flask was added 13.4 g. (0.05 mole) of n-octadecylamine to give a clear yellow solution. The flask was heated in a metal bath temperature of 250°. There was no evolution of water, but a vaporization of reagents took place. The heating was continued for 1 hour, during which time the solution darkened. After cooling to room temperature, the product was refluxed about 30 minutes with 50 ml. of 4% sodium hydroxide, cooled in the tap and the aqueous portion decanted. The solid cake was reflux-washed with 50 ml. of distilled water. The crude brown solid melted at 81-83°. The yield was 16.9 g. or 89 per cent of the theoretical. Crystallization from ethanol-Norit gave a tannish powder melting at 85.0-85.5°. A mixed melting point with N-n-octadecylbenzamide m.p. 85.5-86.0° prepared in the preceding experiment gave no depression.

Preparation of N-n-Dodecylpalmitamide, $C_{15}H_{31}CONHC_{12}H_{25}$-n.

In Absence of Nitrogen Atmosphere. To 12.8 g. (0.05 mole) of palmitic acid in a 125 ml. Erlenmeyer flask was added 9.2 g. (0.05 mole) of n-dodecylamine. The flask was placed in a metal bath heated at 240°. There was a vigorous reaction which subsided in 15 minutes. The total time of heating was 30 minutes. The contents of the flask had darkened at the end of this time. After cooling to room temperature, the tan solid was crystallized from ethanol at 0°, and gave slightly tan crystals melting at 81.5-82.0°. Another crystallization from ethanol and Norit gave colorless powdery crystals melting at 82.0-82.5°. The yield was 16.4 g. or 78 per cent of the theoretical.

Anal. Calcd. for $C_{28}H_{57}ON$: N, 3.31. Found: N, 2.98.

In Presence of Nitrogen Atmosphere. To 12.8 g. (0.05 mole) of palmitic acid in a 125 ml. Erlenmeyer flask was added 9.2 g. (0.05 mole) of n-dodecylamine, and a glass inlet tube inserted above the surface of the contents.

Nitrogen was bubbled in for 5 minutes through a mineral oil bubble counter. The flask was inserted in a metal bath temperature of 250° keeping a steady flow of nitrogen bubbles. The reaction was immediate and vigorous. Heating was continued for 15 minutes. Upon cooling to room temperature, the white solid was crystallized from ethanol slowly to give colorless powdery crystals with a constant melting point of 82.0-82.5°. The yield was 18.6 g. or 85 per cent of the theoretical. A mixed melting point with an authentic specimen of N-n-dodecylpalmitamide prepared in the previous experiment gave no depression.

Preparation of N-n-Octadecylpalmitamide, $C_{15}H_{31}CONHC_{18}H_{37}$-n.

In a 125 ml. Erlenmeyer flask was placed 7.7 g. (0.03 mole) of palmitic acid and 8.1 g. (0.03 mole) of n-octadecylamine. The reagents were molten and a glass inlet tube inserted above the surface of the liquid. Nitrogen was bubbled in for 5 minutes, and the flask was inserted in a metal bath temperature of 250°. The reaction was immediate but remained moderate. The heating was continued for 30 minutes, during which time some discoloration took place. After cooling to room temperature, the crude tan product was crystallized from ethanol and Norit to give a colorless powder melting at 89.0-89.5°. Further crystallization from glacial acetic acid at room temperature and washing with acetone gave the constant melting point of 90.0-90.5°. The yield was 10.0 g. or 66 per cent of the theoretical.

The crystals were slightly soluble in hot acetone, petroleum ether (b.p. 60-68°) and toluene.

Anal. Calcd. for $C_{34}H_{69}ON$: N, 2.76. Found: N, 2.58.

Preparation of N-n-Dodecylmyristamide, $C_{13}H_{27}CONHC_{12}H_{25}$-n.

A molten mixture of 11.4 g. (0.05 mole) of myristic acid and 9.2 g. (0.05 mole) of n-dodecylamine was placed in an open 125 ml. Erlenmeyer flask into which was inserted an inlet tube above the surface of the liquid. Nitrogen was bubbled in, and after 5 minutes the flask was placed in a metal bath temperature of 250°. There was an immediate and vigorous reaction. Some volatilization of reagents took place. In 20 minutes the reaction was over. After cooling to room temperature, the crude colorless product was crystallized from ethanol slowly at 0° to give colorless powdery crystals melting sharply at 83.0-83.5°. The yield was 15.6 g. or 79 per cent of the theoretical.

Anal. Calcd. for $C_{26}H_{53}ON$: N, 3.54. Found: N, 3.18.

Preparation of N-n-Octadecylmyristamide, $C_{13}H_{27}CONHC_{18}H_{37}$-n.

In a 125 ml. Erlenmeyer flask was placed 11.4 g. (0.05 mole) of myristic acid and 13.4 g. (0.05 mole) of n-octadecylamine. A glass inlet tube was inserted above the surface of the liquid and the flask flushed with nitrogen for 5 minutes. The flask was placed in a metal bath temperature of 220°, regulating the flow of nitrogen to a moderate stream of bubbles. There was an immediate and moderate reaction. The heating was continued for 1 hour, during which time a slight discoloration took place. After cooling to room temperature, the almost colorless solid was crystallized slowly from ethanol at 0° to give colorless fine crystals melting sharply at 87.5-87.8°. The yield was 19.7 g. or 80 per cent of the theoretical.

Anal. Calcd. for $C_{32}H_{65}ON$: N, 2.92. Found: N, 2.68.

Preparation of N-n-Dodecyllauramide, $C_{11}H_{23}CONHC_{12}H_{25}$-n.

A glass inlet tube was inserted above a molten mixture of 9.2 g. (0.05 mole) of n-dodecylamine and 10.0 g. (0.05 mole) of lauric acid contained in a 125 ml. Erlenmeyer flask. Nitrogen was bubbled in for 5 minutes and the flask was inserted in a metal bath temperature of 205° keeping the nitrogen flow constant. After 5 minutes a moderate reaction set in, and after 40 minutes the reaction was over. Volatilization of reagents was slight. After cooling to room temperature, the crude colorless product was crystallized from ethanol at 0° to give colorless crystals melting sharply at 77.0-77.5°. The yield was 14.2 g. or 77 per cent of the theoretical.

Anal. Calcd. for $C_{24}H_{49}ON$: N, 3.79. Found: N, 3.48.

Preparation of N-n-Octadecyllauramide, $C_{11}H_{23}CONHC_{18}H_{37}$-n.

In a 125 ml. Erlenmeyer flask was placed 10.0 g. (0.05 mole) of lauric acid and 13.4 g. (0.05 mole) of n-octadecylamine. The usual procedure providing a nitrogen atmosphere was followed. The flask was placed in a metal bath temperature of 225°. There was an immediate yet moderate reaction. Volatilization of reagents was slight. The heating was continued for 1 hour. After cooling to room temperature, the crude colorless product melted at 83.0-84.0°. The yield was 21.6 g. or 92 per cent of the theoretical. Slow crystallization from ethanol gave colorless fine crystals melting sharply at 84.5-85.0°.

Anal. Calcd. for $C_{30}H_{61}ON$: N, 3.11. Found: N, 2.95.

Preparation of N-n-Dodecyl-o-chlorobenzamide, o-ClC_6H_4CO-$NHC_{12}H_{25}$-n.

To 7.8 g. (0.05 mole) of o-chlorobenzoic acid in a 125 ml. Erlenmeyer flask was added 9.2 g. (0.05 mole) of n-dodecylamine and the usual procedure involving the maintenance of a nitrogen atmosphere followed. The flask was inserted in a metal bath temperature of 250°. In a few minutes a reaction set in. Volatilization was moderate. After 45 minutes the reaction was over. Discoloration set in toward the end of the heating time. After cooling to room temperature, the dark brown solid was refluxed a short while with 100 ml. of concentrated hydrochloric acid and 50 ml. of ethanol. After cooling to room temperature and decanting, the cake was reflux-washed with distilled water. The dark solid was crystallized from 75% acetic acid and Norite, cooling to room temperature and then to 0°. Colorless plates were obtained melting at 61.0-61.5°. The yield was 9.7 g. or 60 per cent of the theoretical. Further crystallization raised the melting point to 62.0-62.5°.

Anal. Calcd. for $C_{19}H_{30}ONCl$: N, 4.33. Found: N, 4.07.

Preparation of N-n-Octadecyl-o-chlorobenzamide, $o\text{-}ClC_6H_4CONHC_{18}H_{37}\text{-}n$.

To 7.8 g. (0.05 mole) of o-chlorobenzoic acid in a 125 ml. Erlenmeyer flask was added 13.4 g. (0.05 mole) of n-octadecylamine using the general technique to insure a nitrogen atmosphere during reaction. The flask was inserted in a metal bath temperature of 250°. In a few minutes bubbles appeared, and a moderate reaction set in. Volatilization was moderate. Heating was continued for 45 minutes. Toward the end of this time discoloration was marked. A sublimate collected on the upper part of the flask. After cooling to room temperature, the sublimate was removed. The dark brown product was refluxed a short while with 100 ml. of 3% sodium hydroxide, cooled under the tap, and the aqueous portion decanted. The cake was washed with water, and then refluxed with 100 ml. of water containing 5 ml. of concentrated hydrochloric acid and 50 ml. of ethanol. After cooling under the tap, decanting and washing with water, the product was reflux-washed with 100 ml. of water containing 25 ml. of ethanol. The brown solid was crystallized from 90% acetone and melted at 74.5-75.0°. Repeated crystallization from 95% acetone and Norit gave colorless crystals melting at 78.0-78.5°. The yield was 9.0 g. (44%).

Anal. Calcd. for $C_{25}H_{42}ONCl$: N, 3.44. Found: N, 3.34.

Preparation of N-n-Dodecylcinnamide, $C_6H_5CH{=}CHCONHC_{12}H_{25}$-n.

To 7.4 g. (0.05 mole) of cinnamic acid in a 125 ml. Erlenmeyer flask was added 9.2 g. (0.05 mole) of n-dodecylamine, and the general procedure used to insure a nitrogen atmosphere during the reaction. The flask was inserted in a metal bath temperature of 205°. After a short while a moderate reaction set in. Volatilization of reagents was slight. After 30 minutes the reaction was over. The crude ivory product was crystallized from 90% acetone to melt at 72.0-72.5°. The yield was 9.2 g. (55%). Slow crystallization from 85% acetone at 0° gave shiny, colorless, electrophilic plates melting at 73.0-73.5°.

Anal. Calcd. for $C_{21}H_{33}ON$: N, 4.44. Found: N, 4.24.

Preparation of N-n-Octadecylcinnamide, $C_6H_5CH{=}CHCONHC_{18}H_{37}$-n.

A mixture of 7.4 g. (0.05 mole) of cinnamic acid and 13.4 g. (0.05 mole) of n-octadecylamine in a 125 ml. Erlenmeyer flask was equipped to insure a nitrogen atmosphere during heating. The flask was inserted in a metal bath temperature of 200°. After about five minutes there was a moderate reaction. Volatilization was moderate. The total heating time was 2 hours. Some discoloration was evidenced. The crude brown product was crystallized from 90% acetone at 0° to give a tan powder melting at 88.5-89.0°. The yield was 15.3 g. (77%). Further crystallization from 90% acetone and Norit gave fine colorless crystals with the same constant melting point.

Anal. Calcd. for $C_{27}H_{45}ON$: N, 3.51. Found: N, 3.34.

Preparation of N-n-Dodecyl-p-chlorobenzamide, p-$ClC_6H_4CONHC_{12}H_{25}$-n.

To 7.8 g. (0.05 mole) of p-chlorobenzoic acid in a 125 ml. Erlenmeyer flask was added 9.2 g. (0.05 mole) of n-dodecylamine, and the general procedure for insuring a nitrogen atmosphere used. The flask was inserted in a metal bath temperature of 240°. The appearance of water vapor was immediate, but there was no bubbling. Volatilization was slight, and discoloration moderate. After 1 hour the reaction was over. The flask was cooled to room temperature, and the brown product crystallized from 90% ethanol at 0°, to give colorless powdery crystals melting at 77.0-78.0°. The yield was 9.4 g. (58%). Further slow crystallization at 0° gave colorless fine plates melting sharply at 78.5-79.0°.

Anal. Calcd. for $C_{19}H_{30}ONCl$: N, 4.33. Found: N, 4.10.

Preparation of N-n-Octadecyl-p-chlorobenzamide, p-$ClC_6H_4CONHC_{18}H_{37}$-n.

To 4.7 g. (0.03 mole) of p-chlorobenzoic acid in a 50 ml. Erlenmeyer flask was added 8.1 g. (0.03 mole) of n-octadecylamine using the general procedure to insure a nitrogen atmosphere during the heating. The flask was inserted in a metal bath temperature of 255°. In a few minutes a moderate reaction set in. Discoloration and volatilization were moderate. The total heating time was 25 minutes. A sublimate collected in the upper portion of the flask. After cooling to room temperature, the sublimate was removed, and the tan product was crystallized from ethanol and Norit to give colorless stars melting sharply at 94.0-94.5°. The yield was 7.1 g. (58%).

Anal. Calcd. for $C_{25}H_{42}ONCl$: N, 3.43. Found: N, 3.26.

Attempt to Prepare N-n-Dodecyl-p-nitrobenzamide.

A 125 ml. Erlenmeyer flask was equipped with a two-hole cork stopper. Through one of the holes was inserted a glass inlet tube for nitrogen, while the other was left free. A mixture of 9.2 g. (0.05 mole) of n-dodecylamine and 8.3 g. (0.05 mole) of p-nitrobenzoic acid was placed in the flask, and the latter swept out with nitrogen for 10 minutes. A steady flow of nitrogen was maintained, and the flask inserted in a metal bath temperature of 250°. In a few minutes there was a moderate bubbling which became livelier. After 15 minutes decomposition was noted, and the contents turned black. After 25 minutes a sublimate collected in the upper portion of the flask, and the heating was stopped. The sublimate was removed, and the contents were refluxed a short while with 90 ml. of water containing 3 g. of sodium hydroxide, and then cooled in the tap and filtered. The black solid was further refluxed a short time with 90 ml. of water containing 5 ml. of concentrated hydrochloric acid and 5 ml. of ethanol. After cooling to room temperature, 15 ml. of ethanol was added, and the mixture filtered and washed with 20% ethanol. It was finally refluxed a short while with 100 ml. of 19% ethanol and decanted at room temperature to give a black solid weighing 15.5 g. It melted at room temperature. Repeated crystallization from 80% acetone and Norit gave only a crude product.

The alkaline filtrate was poured into 100 ml. of water containing 10 ml. of concentrated hydrochloric acid. A yellow precipitate was obtained which melted at 233.0-233.5°. A mixed melting point with an authentic specimen of p-nitrobenzoic acid melting at 235° gave no depression. The recovery was 1.1 g. (13%).

Attempt to Prepare N-n-Octadecyl-p-nitrobenzamide.

A 125 ml. Erlenmeyer flask was equipped as in the previous experiment. In it was placed a mixture of 13.4 g. (0.05 mole) of n-octadecylamine and 9.1 g. (0.055 mole) of p-nitrobenzoic acid. The flask was flushed with nitrogen for 10 minutes and inserted in a metal bath temperature of 195°, keeping the flow of nitrogen fixed. Heating was continued for 1.5 hours. After a time, some formation of bubbles was noticed. The solution turned dark, and by the end of the heating time a sublimate collected in the upper portion of the flask. Volatilization was moderate. After cooling to room temperature, the tan product melted at 92-94°. It weighed 21.5 g. It was refluxed a short while with 100 ml. of 3% sodium hydroxide, cooled, filtered and washed with water. The tan product was treated with dilute alcoholic hydrogen chloride and crystallized from 90% ethanol and Norit to melt at 100.5-101.5°. Further crystallization from 95% acetic acid did not give a sharp-melting product.

The alkaline filtrate was poured into 100 ml. of water containing 10 ml. of concentrated hydrochloric acid. The yellow precipitate melted at 234-235°. A mixed melting point with an authentic specimen of p-nitrobenzoic acid melting at 235° gave no depression. The recovery was 3.3 g. (36%).

Preparation of N-n-Dodecyl-o-toluamide, o-$CH_3C_6H_4CONHC_{12}H_{25}$-n.

In a 50 ml. Erlenmeyer flask was placed 4.1 g. (0.03 mole) of o-toluic acid and 5.5 g. (0.03 mole) of n-dodecylamine. The general procedure to insure a nitrogen atmosphere during heating was followed. The flask was inserted in a metal bath temperature of 250°. In a short while a lively reaction set in. Volatilization was slight. The heating was stopped after 30 minutes. After cooling to room temperature, the colorless product was crystallized slowly from 80% acetone at 0° to give colorless electrophilic plates melting sharply at 55.0-55.5°. The yield was 6.5 g. (72%).

Anal. Calcd. for $C_{20}H_{33}ON$: N, 4.62. Found: N, 4.34.

Preparation of N-n-Octadecyl-o-toluamide, o-$CH_3C_6H_4CONHC_{18}H_{37}$-n.

A mixture of 4.1 g. (0.03 mole) of o-toluic acid and 8.1 g. (0.03 mole) of n-octadecylamine was placed in a 50 ml. Erlenmeyer flask, insuring a nitrogen atmosphere in the usual manner. The flask was inserted in a metal bath temperature of 245°. After a few minutes reaction was noted. Heating was continued for 30 minutes. Volatilization was moderate. After cooling to room temperature, the colorless product was crystallized from 90% acetone at 0° to give colorless plates melting at 73.5-74.0°. The yield was 8.8 g. (76%).
Anal. Calcd. for $C_{26}H_{45}ON$: N, 3.62. Found: N, 3.47.

Preparation of N-n-Dodecyl-m-toluamide, $m\text{-}CH_3C_6H_4CONHC_{12}H_{25}\text{-}n$.

To 4.1 g. (0.03 mole) of m-toluic acid was added 5.5 g. (0.03 mole) of n-dodecylamine, and the general procedure to maintain a nitrogen atmosphere during heating followed. The flask was inserted in a metal bath temperature of 250°. There was a reaction at once which became vigorous in a few minutes. Discoloration was moderate. The ivory product was crystallized from 80% acetone at 0° with shaking, to give colorless fine crystals melting at 47.0-47.5°. The yield was 5.2 g. (57%).
Anal. Calcd. for $C_{20}H_{33}ON$: N, 4.62. Found: N, 4.36.

Preparation of N-n-Octadecyl-m-toluamide, $m\text{-}CH_3C_6H_4CONHC_{18}H_{37}\text{-}n$.

A mixture of 4.1 g. (0.03 mole) of m-toluic acid and 8.1 g.

(0.03 mole) of n-octadecylamine was placed in a 50 ml. Erlenmeyer flask using the general procedure to insure a nitrogen atmosphere. The flask was placed in a metal bath temperature of 250°. There was a moderate reaction in a few minutes. Volatilization was slight. Heating was stopped after 45 minutes. Toward the end of this time a discoloration set in. The tan product was crystallized from 90% acetone at 0° to give fine colorless crystals melting sharply at 71.0-71.5°. The yield was 9.0 g. (78%).

Anal. Calcd. for $C_{26}H_{45}ON$: N, 3.62. Found: N, 3.43.

Preparation of N-n-Dodecyloleamide, cis-$CH_3(CH_2)_7CH{=}CH(CH_2)_7$-$CONHC_{12}H_{25}$-n.

In a 125 ml. Erlenmeyer flask was placed a mixture of 9.2 g. (0.05 mole) of n-dodecylamine and 14.1 g. (0.05 mole) of oleic acid (U.S.P.). A glass inlet tube was placed above the surface of the liquid, and nitrogen passed in through a mineral oil bubble counter. After 5 minutes the flask was inserted in a metal bath held at 245°, maintaining a steady flow of nitrogen bubbles. Heating was continued for 20 minutes. In a few minutes a vigorous reaction set in. Discoloration and volatilization were moderate. After cooling to room temperature, a tan product was obtained which melted at room temperature. Repeated crystallization from 95 %

acetone gave a colorless powder melting at 49.0-54.0°. Further crystallization from acetone at 0° gave colorless crystals melting at 49.0-51.0°. The yield was 11.2 g. (50%).

Anal. Calcd. for $C_{30}H_{59}ON$: N, 3.12. Found: N, 3.01.

Preparation of N-n-Octadecyloleamide, cis-$CH_3(CH_2)_7CH{=}CH(CH_2)_7CONHC_{18}H_{37}$-n.

In a 125 ml. Erlenmeyer flask was placed a mixture of 13.4 g. (0.05 mole) of n-octadecylamine and 14.1 g. (0.05 mole) of freshly distilled U.S.P. oleic acid. A glass inlet tube was inserted above the mixture, and the usual procedure for maintaining a nitrogen atmosphere during heating followed. The flask was heated in a metal bath temperature of 250°. After a few minutes a lively reaction set in. Volatilization was moderate. The heating was discontinued at the end of 15 minutes. There was a slight discoloration by this time. After cooling to room temperature, a yellow solid was obtained which melted at room temperature. Several crystallizations from ethanol at 0° gave a colorless solid melting at 68.0-69.5°. Crystallization from glacial acetic acid gave a slightly improved melting point of 69.0-70.0°. Further crystallization from acetone gave crystals melting at 70.0-70.5°. The yield was 15.8 g. (59%).

Anal. Calcd. for $C_{36}H_{71}ON$: N, 2.62. Found: N, 2.48.

Preparation of N-n-Dodecylelaidamide, trans-$CH_3(CH_2)_7$-$CH=CH(CH_2)_7CONHC_{12}H_{25}$-n.

To 8.5 g. (0.03 mole) of elaidic acid in a 50 ml. Erlenmeyer flask was added 5.5 g. (0.03 mole) of n-dodecylamine. The standard technique was used to obtain a nitrogen atmosphere during reaction. The flask was inserted in a metal bath temperature of 250°. After a few minutes a vigorous reaction took place. Volatilization and discoloration were slight. The total time of heating was 25 minutes. After cooling to room temperature, the tan product was crystallized from 95% acetone to give fine colorless crystals melting at 73.5-74.0°. The yield was 11.2 g. (83%). Anal. Calcd. for $C_{30}H_{59}ON$: N, 3.12. Found: N, 2.68.

Preparation of N-n-Octadecylelaidamide, trans-$CH_3(CH_2)_7$-$CH=CH(CH_2)_7CONHC_{18}H_{37}$-n.

In a 125 ml. Erlenmeyer flask was placed 8.5 g. (0.03 mole) of elaidic acid and 8.1 g. (0.03 mole) of n-octadecylamine, insuring a nitrogen atmosphere as in the previous experiments. The flask was inserted in a metal bath temperature of 250°. There was a lively reaction in a few minutes. Volatilization was slight. Heating was stopped after 20 minutes. Toward the end of the heating time the contents of the flask turned a dark red. After cooling to

room temperature, the brown product was crystallized from 90% ethanol at 0°. Colorless crystals were obtained which melted at 83.5-84.0°. The yield was 12.4 g. (78%). Further crystallization from ethanol did not raise the melting point.
Anal. Calcd. for $C_{36}H_{71}ON$: N, 2.62. Found: N, 2.48.

Preparation of N,N'-Decamethylenedilauramide, $C_{11}H_{23}CONH-(CH_2)_{10}NHOCC_{11}H_{23}$.

In a 125 ml. Erlenmeyer flask was placed a mixture of 5.2 g. (0.03 mole) of 1,10-decanediamine and 12.0 g. (0.06 mole) of lauric acid. The general procedure for maintaining a nitrogen atmosphere was followed. The flask was heated in a metal bath temperature of 195°. In a short while there was some evidence of reaction. Volatilization and discoloration were slight. The heating was continued for 1 hour. After cooling to room temperature, the tan solid was crystallized from absolute ethanol at 0° to give the constant melting point of 137.0-137.5°. The yield was 13.7 g. (85%).

The compound was insoluble in hot acetone, moderately soluble in hot ethanol, and slightly soluble in hot petroleum ether b.p. 60-68° and b.p. 77-115°.
Anal. Calcd. for $C_{34}H_{68}O_2N_2$: N, 5.22. Found: N, 4.96.

Preparation of N,N-Di-n-octadecylbenzamide, $C_6H_5CON(C_{18}H_{37}\text{-}\underline{n})_2$.

Indirect Methods. A 250 ml. three-necked flask was equipped with a reflux condenser and dropping funnel. A suspension of 5.5 g. (0.01 mole) of di-*n*-octadecylamine hydrochloride in 50 ml. of dry benzene was placed in the flask, and the mixture heated to reflux to give a clear solution. A solution of 1.54 g. (0.011 mole) of benzoyl chloride in 10 ml. of dry benzene was added dropwise to the refluxing solution. The evolution of hydrogen chloride was immediate as tested with a piece of filter paper moistened with concentrated ammonium hydroxide. After 23 hours of refluxing, no more hydrogen chloride was evolved. The benzene solution was washed twice with 5% sodium hydroxide, then with water, and dried over anhydrous sodium sulfate. After distilling off the benzene, a yellow solid remained which solidified under the tap. It melted at 54.0-55.0°. A crystallization from methyl alcohol at 0° gave colorless crystals melting at 55.0-56.0°.

Anal. Calcd. for $C_{40}H_{80}ON$: N, 2.37. Found: N, 2.29.

A solution of 5.2 g. (0.01 mole) of di-*n*-octadecylamine and 2.5 g. (0.01 mole) of benzoic anhydride (free from benzoic acid) in 50 ml. of dry benzene was placed in a 125 ml. Erlenmeyer flask, and refluxed for 2 hours. The condenser was capped with a calcium chloride tube to prevent access of moisture. The solvent was removed and the residue refluxed with 50 ml. of 4% sodium hydroxide for 30 minutes.

After cooling and filtering, the solid cake was again refluxed with a fresh portion of sodium hydroxide. Finally, the cake was reflux-washed with 50 ml. of water. After cooling and filtering, the colorless solid melted at 55.0-56.0°. The yield was 5.4 g. (86%). A mixed melting point with an authentic specimen of N,N'-di-n-octadecylbenzamide prepared in the previous experiment gave no depression.

Attempt by Direct Method. In a 50 ml. Erlenmeyer flask was placed a mixture of 7.8 g. (0.015 mole) of di-n-octadecylamine and 1.8 g. (0.015 mole) of benzoic acid. The usual technique involving the maintenance of a nitrogen atmosphere during the heating was followed. The flask was heated in a metal bath at 240° for 3 hours. There was a slight evidence of reaction. There was no volatilization. Toward the end of the heating time there was a slight discoloration, and a sublimate collected in the upper part of the flask. After cooling to room temperature, the sublimate was removed. The tan product melted at 53-63° and weighed 8.5 g. After a crystallization from acetone it melted at 64-69°. The solid was refluxed a short while with 100 ml. of 1% sodium hydroxide, cooled in the tap, decanted and reflux-washed with water. The colorless solid melted at 59-65°, showing no improvement. It was further refluxed a short while with 100 ml. of water containing 2 ml. of concentrated hydrochloric acid, cooled, the liquid decanted, and the solid finally reflux-washed with distilled water. The colorless solid now melted at 104-130° indicating the presence of unchanged amine as the hydrochloride.

Attempt to Prepare N,N-Di-n-octadecylstearamide.

In a 125 ml. Erlenmeyer flask was placed a mixture of 10.4 g. (0.02 mole) of di-*n*-octadecylamine and 5.7 g. (0.02 mole) of stearic acid. The standard procedure for maintaining a nitrogen atmosphere during heating was followed. The flask was heated in a metal bath at 250° for 1 hour. In a few minutes there was a slow evolution of bubbles. Volatilization was moderate. The contents of the flask turned black toward the end of the heating time. After cooling to room temperature, the black product melted at 67.5-73.5°. It weighed 15.1 g. A crystallization from acetone at 0° gave a brown powder melting at 68.0-70.5°. It was refluxed with 100 ml. of 2% potassium hydroxide for a short while, cooled in the tap and filtered. The solid was then refluxed with 100 ml. of water containing 5 ml. of concentrated hydrochloric acid. It was finally reflux-washed with water. The brown solid now melted at 85-103° indicating the presence of unchanged amine as the hydrochloride.

Attempt to Prepare N-n-Octadecylchloroacetamide.

A 125 ml. Erlenmeyer flask was equipped with a two-hole cork stopper. Through one opening was inserted a glass inlet tube for nitrogen. A mixture of 13.4 g. (0.05 mole) of n-octadecylamine and 4.7 g. (0.05 mole) of chloroacetic acid was placed in the flask. The latter was flushed with nitrogen for 5 minutes, and then inserted in a metal bath at 190°. A slow flow of nitrogen was maintained during the heating. In about 5 minutes there was some evidence of reaction. After 2 hours the contents turned a dark red, and the heating was stopped. After cooling to room temperature, the red solid was refluxed a short while with 100 ml. of 30% sodium chloride, cooled under the tap and filtered. The brown solid gave a poor melting point of 79-103°. It was extracted with ether, and a large ether insoluble portion remained. It weighed 12.0 g. and melted at 110-140° indicating the presence of the amine as the hydrochloride.

Mechanism of the Direct Condensation of Amines and Carboxylic Acids.

To 6.0 g. (0.03 mole) of lauric acid in a 125 ml. Erlenmeyer flask was added 8.1 g. (0.03 mole) of n-octadecylamine, and the mixture placed in an oil bath at 65° for 15 minutes. The contents of the flask remained crystalline and colorless. In the next 20 minutes, the temperature was raised to 100°. The molten contents were agitated and cooled to room temperature. The colorless solid melted at 64.0-65.5° and weighed 14.1 g. The yield was quantitative. A crystallization from petroleum ether (b.p. 60-68°) gave colorless plates melting at 65.5-66.5°. A mixed melting point with an authentic specimen of n-octadecylammonium laurate melting at 66.5-67.0° (173) gave no depression.

Preparation of N,N'-Di-n-octadecyloxamide, $(CONHC_{18}H_{37}\text{-}\underline{n})_2$.

A solution of 12.0 g. (0.0825 mole) of diethyl oxalate in 100 ml. of ethanol was warmed on the water bath in a large evaporating dish. To it was added a solution of 40.0 g. (0.15 mole) of n-octadecylamine in 100 ml. of ethanol. A copious precipitation took place, and the mass almost solidified. Another 100 ml. portion of ethanol was added and the mixture filtered. Crystallization from petroleum ether (b.p. 77-115°) gave colorless crystals melting at 119.0-119.5°. The yield was 29.1 g. (66%). The crystals were only slightly soluble in hot ethanol, insoluble in hot acetone and moderately soluble in hot ethyl acetate.

Anal. Calcd. for $C_{38}H_{76}O_2N_2$: N, 4.73. Found: N, 4.52.

Preparation of N,N'-Di-n-octadecylmalonamide, $CH_2(CONHC_{18}H_{37}\text{-}\underline{n})_2$.

To 8.8 g. (0.055 mole) of diethyl malonate in a 125 ml. Erlenmeyer flask was added 26.9 g. (0.1 mole) of n-octadecylamine.

(173) Kindly supplied by B. A. Hunter.

The flask was closed with a stopper carrying a soda-lime tube and inserted in an oil bath temperature of 110°. Heating was continued for 1 hour. The molten contents were transferred to a large evaporating dish and turned so that the liquid solidified in a thin layer. The product was crystallized from petroleum ether (b.p. 77-115°) and gave a poor melting point of 122.5-123.5°. To the solid in a 1 l. Erlenmeyer flask was added 400 ml. of 85% ethanol containing 10 ml. of concentrated hydrochloric acid. The mixture after refluxing a short while was filtered through a hot Buchner funnel and washed with hot 80% ethanol. The product now melted at 125.5-126.5°. The yield was 15.1 g. (50%). Crystallization from petroleum ether (b.p. 77-115°) raised the melting point to 126.0-126.2°. The colorless crystals were only slightly soluble in hot ethanol, insoluble in ether and soluble in hot benzene.

Anal. Calcd. for $C_{39}H_{78}O_2N_2$: N, 4.62. Found: N, 4.53.

Attempt to Prepare N,N'-Di-n-dodecylethylmalonamide.

A mixture of 18.5 g. (0.1 mole) of n-dodecylamine and 11.3 g. (0.06 mole) of diethyl ethylmalonate was placed in a 125 ml. Erlenmeyer flask arranged for distillation. The flask was inserted in a metal bath at 200°. A distillate appeared at once. After 1.5 hours no more distillate was collected. The temperature was raised to 220° but no further distillate appeared. The molten contents were transferred to a large evaporating dish and turned so that the liquid solidified in a thin layer. The slightly colored product was crystallized from ethanol and melted poorly at 81-82°. It was dissolved in 455 ml. of hot 75% ethanol containing 10 ml. of concentrated hydrochloric acid and crystallized at room temperature to give colorless plates melting poorly at 81.5-83.0°. Further crystallization from ethanol, another extraction with ethyl alcoholic hydrochloric acid and crystallization from acetone failed to give a pure product.

Preparation of n-Dodecylamine Hydrochloride, n-$C_{12}H_{25}NH_3Cl$.

To a solution of 74.0 g. (0.4 mole) of n-dodecylamine in 500 ml. of ethanol was added 68.0 g. (0.8 mole) of concentrated hydrochloric acid. The solution darkened and at 0° gave pinkish crystals which were washed with cold dilute ethanol. The colorless crystals melted at 181°. The yield was 62.0 g. (70%).

Solubility tests showed the crystals to be moderately soluble in water, very soluble in warm water, soluble in warm benzene and 25% ethanol, and insoluble in ether.

n-Dodecylamine hydrochloride has been reported to melt at 100° with decomposition (51).

Anal. Calcd. for $C_{12}H_{28}NCl$: N, 6.32. Found: N, 5.98.

Preparation of 1,10-Decanediamine Dihydrochloride, $ClH_3N(CH_2)_{10}NH_3Cl$.

To 5.2 g. (0.03 mole) of 1,10-decanediamine in 50 ml. of absolute ethanol was added 7.7 ml. (0.09 mole) of concentrated hydrochloric acid. The solution heated up and was crystallized at 0°. Then 50 ml. of cold ether was added, and the crystals filtered and washed with cold ether. The yield was 7.2 g. (100%). The colorless crystals darkened, but did not melt even at 315°.

The crystals were very soluble in water with no foaming action. The free amine was precipitated out by addition of alkali. The crystals were also soluble in methanol and ethanol. They were insoluble in acetone, chloroform and benzene.

1,10-Decanediamine dihydrochloride has been mentioned previously (159) (174) but has not been described.

Anal. Calcd. for $C_{10}H_{26}N_2Cl_2$: N, 11.4. Found: N, 11.2.

Preparation of n-Dodecylammonium p-Toluenesulfonate, *p*-$CH_3C_6H_4SO_3H_3NC_{12}H_{25}$-*n*.

In a 50 ml. Erlenmeyer flask was placed 5.5 g. (0.03 mole) of *n*-dodecylamine and 5.7 g. (0.03 mole) of *p*-toluenesulfonic

(174) Slotta and Tscheche, *Ber*., *62*, 1398 (1929).

acid monohydrate. The general procedure for maintaining a nitrogen atmosphere was followed. The flask was inserted in a metal bath at 260°. There was an immediate and vigorous reaction which was over in a few minutes. Volatilization and discoloration were moderate. After cooling to room temperature, the dark product was crystallized from acetone at 0° and gave colorless crystals. The yield was 9.3 g. (87%). The crystals softened at 100°, and the meniscus was clear at 133°. Further crystallization from acetone and ethyl acetate did not improve the melting point.

The crystals were moderately soluble in water with the formation of a detergent solution. They were soluble in warm water with the formation of a soapy emulsion.

The same product was obtained when the heating was continued for 1 hour, or when the reaction was conducted in boiling petroleum ether (b.p. 60-68°).

Anal. Calcd. for $C_{19}H_{35}O_3NS$: N, 3.92. Found: N, 3.77.

Preparation of n-Octadecylammonium p-Toluenesulfonate, $p\text{-}CH_3C_6H_4SO_3H_3NC_{18}H_{37}\text{-}n$.

To a solution of 13.4 g. (0.05 mole) of n-octadecylamine in 250 ml. of petroleum ether (b.p. 60-68°) was added 9.5 g. (0.05 mole) of p-toluenesulfonic acid monohydrate. The mixture was refluxed until a clear solution formed. A slow crystallization at 0° gave fine colorless crystals which sintered at 93° and melted at 138°. The yield was 21.6 g. (98%). Further crystallization from a large volume of acetone at 0° gave the same type of broad melting range.

The compound formed a soapy suspension when shaken withwater.

Anal. Calcd. for $C_{25}H_{47}O_3NS$: N, 3.17. Found: N, 2.98.

Preparation of N-n-Dodecylphthalimide, $C_6H_4(CO)_2NC_{12}H_{25}$-n.

To 24.4g.(0.165 mole) of phthalic anhydride in a 500 ml. round bottom flask was added 27.8 g. (0.15 mole) of n-dodecylamine. A thermometer was inserted in the reaction mixture and the contents heated at 200° for 5 minutes. By this time the evolution of steam was complete. The molten mass was poured into a large evaporating dish and turned so that the liquid solidified in a thin layer. The dull, white solid melted at 58-60.5°. The yield was quantitative. A portion of this was crystallized from ethanol and Norit at 0° to give colorless plates melting sharply at 64.0-64.5°. The product was soluble in acetone, ether and benzene.

Anal. Calcd. for $C_{20}H_{29}O_2N$: N, 4.44. Found: N, 3.80.

Preparation of N-n-Dodecylphthalamic acid, o-$HO_2CC_6H_4CONHC_{12}H_{25}$-n.

To 30.0 g. (0.095 mole) of crude N-n-dodecylphthalimide in a large evaporating dish was added 500 ml. of 10% sodium hydroxide, and the mixture heated on the water bath with frequent stirring for 1 hour. Upon addition of 2 l. of distilled water a clear solution formed. Acidification with dilute hydrochloric acid gave a copious precipitate which was filtered and washed with distilled water. The colorless fine crystals melted at 87.0-88.5° with decomposition to the imide.

The free acid was soluble in 70% ethanol at room temperature. It was also soluble in ether and warm benzene and moderately soluble in acetone. The compound produced sneezing. The sodium salt was soluble in water and had detergent properties. The free acid could not be purified by crystallization from hot, organic solvents as it underwent partial conversion to the imide.

N-n-Dodecylphthalamic acid has been reported (155) to melt at 88°.

Preparation of N-n-Octadecylphthalimide, $C_6H_4(CO)_2NC_{18}H_{37}$-n.

To 24.4 g. (0.165 mole) of phthalic anhydride in a 500 ml. round bottom flask was added 40.4 g. (0.15 mole) of n-octadecylamine. A thermometer was inserted in the flask and the contents heated with a free flame at 200° for five minutes. After this time no more steam was evolved. The molten mass was poured into a large evaporating dish and turned so that the liquid solidified in a thin layer. The tan product was crystallized from ethanol and Norit to give colorless plates melting at 79.0-79.5°. The yield from 39 g. of crude product was 25.6 g. (66%). The crystals were soluble in ether and benzene but insoluble in acetone.

Anal. Calcd. for $C_{26}H_{41}O_2N$: N, 3.51. Found: N, 3.14.

Preparation of N-n-Octadecylphthalamic acid, o-$HO_2CC_6H_4CONHC_{18}H_{37}$-$n$.

To 25.0 g. (0.063 mole) of crude N-n-octadecylphthalimide in a large evaporating dish was added 500 ml. of 10% sodium hydroxide, and the mixture heated on the water bath with frequent stirring for 1.5 hours. This was followed by heating 45 minutes longer on the hot plate in order to complete the hydrolysis. After cooling to room temperature, an emulsion was formed. To this was added 3 l. of distilled water, and the mixture heated to 70°. On acidification with dilute (1:1) hydrochloric acid a precipitate appeared which was filtered off at room temperature. It melted at 90.5-92.5° with decomposition to the imide. The yield was 23.3 g. (89%).

Anal. Calcd. for $C_{26}H_{43}O_3N$: N, 3.36. Found: N, 3.26.

Attempt to Prepare N-n-Dodecylsalicylamide.

To 7.6 g. (0.055 mole) of salicylic acid in a 125 ml. Erlenmeyer flask was added 9.2 g. (0.05 mole) of n-dodecylamine. The general procedure to obtain a nitrogen atmosphere during heating was followed. The flask was immersed in a metal bath at 115° for 1.5 hours. After cooling to room temperature, a viscous yellow oil was obtained. It was refluxed a short while with 100 ml. of 3% sodium hydroxide, cooled at the tap and filtered. To the alkaline filtrate was added 20 ml. of ethanol. It was acidified with dilute hydrochloric acid. The colorless precipitate was allowed to settle and then filtered. It melted at 156.5-157.0°. A mixed melting point with an authentic specimen of salicylic acid melting at 156.0-157.0° gave no depression. The recovery was 5.6 g. (74%).

Attempts to conduct the condensation at a higher temperature (245°) caused decomposition of the salicylic acid to phenol.

Attempt to Prepare N-n-Octadecylsalicylamide.

To 7.6 g. (0.055 mole) of salicylic acid in a 125 ml. Erlenmeyer flask was added 13.4 g. (0.05 mole) of *n*-octadecylamine. The general procedure was used to maintain a nitrogen atmosphere during heating. The flask was inserted in a metal bath at 125°. Heating was conducted for 2 hours. After cooling to room temperature, the crude solid was refluxed a short while with 3% sodium hydroxide, cooled in the tap and filtered. The alkaline filtrate was poured into an excess of dilute hydrochloric acid. A colorless precipitate formed which was collected on a filter. It melted at 156.6-157.0°. A mixed melting point with an authentic specimen of salicylic acid melting at 156.0-157.0° gave no depression. The recovery was 6.4 g. (84%).

Preparation of N-n-Dodecylanisamide, p-$CH_3OC_6H_4CONHC_{12}H_{25}$-n.

To 4.6 g. (0.03 mole) of anisic acid in a 50 ml. Erlenmeyer flask was added 5.5 g. (0.03 mole) of n-dodecylamine. A glass inlet tube was inserted above the liquid, and the flask swept out with nitrogen. The flow of nitrogen was regulated to a slow stream of bubbles, and the flask inserted in a metal bath temperature of 250°. In a few minutes reaction set in. Volatilization was slight. After 30 minutes the heating was discontinued. The crude, colorless product was crystallized from 90% acetone at 0° to give colorless plates melting sharply at 87.5-88.0°. The yield was 6.6 g. (69%).

Anal. Calcd. for $C_{20}H_{33}O_2N$: N, 4.38. Found: N, 4.24.

Preparation of N-n-Octadecylanisamide, p-$CH_3OC_6H_4CONHC_{18}H_{37}$-n.

A mixture of 4.6 g. (0.03 mole) of anisic acid and 8.1 g. (0.03 mole) of n-octadecylamine was placed in a 50 ml. Erlenmeyer flask. A glass inlet tube was inserted above the surface of the liquid, and the flask swept out with nitrogen for a few minutes. The flask was inserted in a metal bath temperature of 250°. After a few minutes a reaction set in. Discoloration was slight and volatilization was moderate.

Toward the end of the heating time, a sublimate collected in the upper portion of the flask. Heating was stopped after 30 minutes. The sublimate was removed, and the crude colorless product crystallized from acetone. Colorless stars were obtained melting sharply at 100.0-100.5°. The yield was 7.6 g. (63%).

Anal. Calcd. for $C_{26}H_{45}O_2N$: N, 3.47. Found: N, 3.03.

Mixed Melting Points of n-Dodecyl and n-Octadecyl Derivatives.

Melting points and mixed melting points (Table I) of the compounds described in this thesis were determined in the apparatus shown in Fig. 1. It consisted of a Pyrex distilling flask whose distilling tube had been removed, and the junction sealed. Through the neck was placed a long flanged test tube which reached to within 0.5 in. of the bottom of the flask. In the test tube was placed a 360° standardized thermometer which was supported by a cork stopper so that the bulb was about 0.5 in. from the bottom of the test tube. The flask was filled about two-thirds with pure concentrated sulfuric acid to which a few crystals of potassium nitrate were added. This kept the acid clear at all times. In the test tube was placed enough mineral oil so that the bulb of the thermometer was totally immersed.

TABLE 1

MIXED MELTING POINTS

Type Compound	*n*-Dodecyl m.p. (°)	*n*-Octadecyl m.p. (°)	Mixed m.p. (°)	Average Lowering
N,N'-*α*-Naphthylurea	127.5-128.0	122.5-123.0	121.5-123.0	3.5
N,N'-Phenylthiourea	69.5-69.8	86.0-87.0 (a)	69.0-80.0	8.5
N-Benzenesulfonamide	58.0-58.5	77.0-77.5	55.0-59.0	12.5
N-*p*-Toluenesulfonamide	73.0-73.5	88.0-90.5 (a)	69.5-74.0	11.5
N-*m*-Toluamide	47.0-47.5	71.0-71.5	55.0-65.0	4.0
N-*o*-Toluamide	55.0-55.5	76.5-77.0	52.5-61.0	13.5
N-Anisamide	87.5-88.0	100.0-100.5	82.5-85.0	11.5
N-*p*-Chlorobenzamide	78.5-79.0	94.0-94.5	76.0-84.5	6.0
N-*o*-Chlorobenzamide	62.0-62.5	78.0-78.5	53.5-58.0	17.0
N-Cinnamide	73.0-73.5	88.5-89.0	70.5-78.0	10.5
N-Phthalimide	64.0-64.5	79.0-79.5	64.0-75.0	7.5
N-Acetamide	53.5-54.0	76.0-77.5 (a)	50.5-52.0	14.5
N-Lauramide	77.0-77.5	84.5-85.0	73.0-74.0	7.5
N-Myristamide	83.0-83.5	87.5-87.8	78.5-82.0	7.0
N-Palmitamide	82.0-82.5	90.0-90.5	81.0-85.5	5.0
N-Stearamide	84.5-85.0	94.5-95.0	83.5-87.0	5.0
N-Elaidamide	73.5-74.0	83.5-84.0	72.5-80.0	6.0

(a) Specimens kindly supplied by F. W. Hoyt.

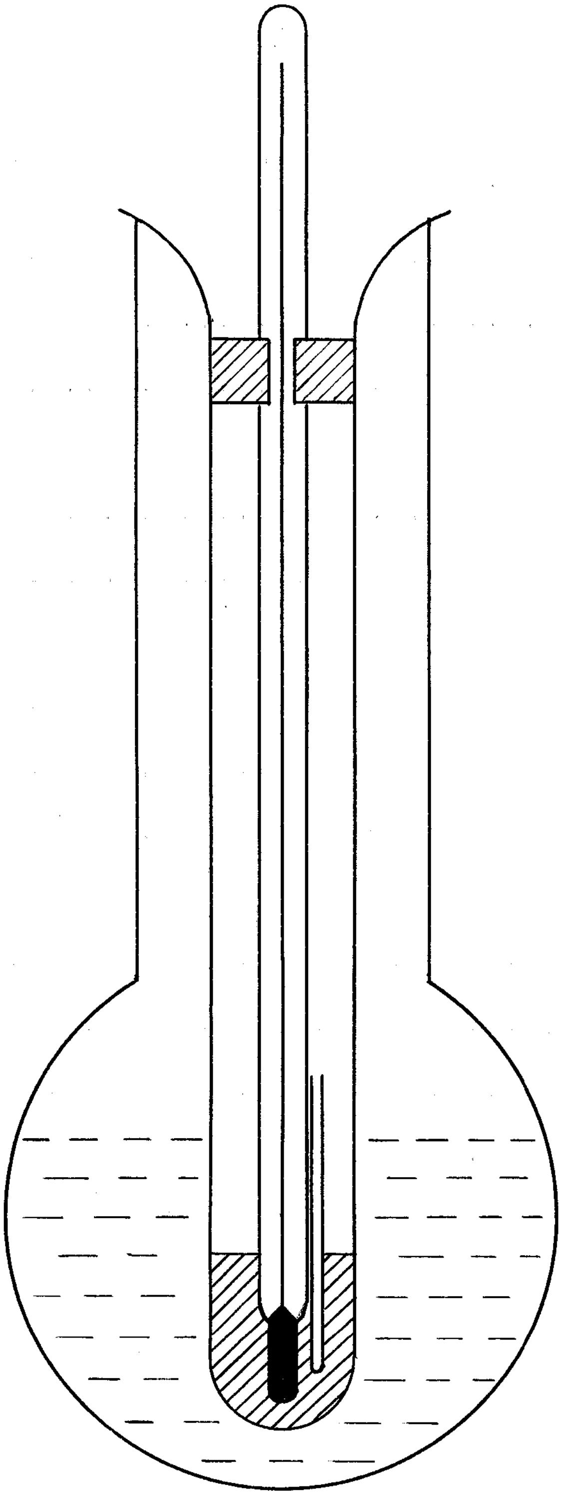


Fig. 1

MELTING POINT APPARATUS

The flask was heated on an asbestos gauze. When temperatures up to 130° were required a micro burner was sufficient. For higher temperatures a Bunsen burner was used.

There were many advantages in the use of this apparatus. Due to the convection currents in the outside bath during heating no stirring was required. The small amount of mineral oil in the inside bath made the effect of inside convection currents negligible. The thermometer was easily removed whenever a fresh capillary was required. Since the thermometer was doubly jacketed, the effect of hot air currents caused by the burner was minimized. When several melting points were taken successively, the whole apparatus was rapidly cooled by immersion in water. Finally, the slow convection of heat from the outside bath to the inside one made possible a steady and regular rise in temperature. It was an easy matter to regulate the rate of heating to 1 degree per minute or longer.

The process of melting was carefully watched by placing a hand lens in front of the apparatus. The original magnification of the capillary tube due to the curvature of the flask was increased. An unusually large image of the capillary tube was thus obtained.

Pyrolysis of n-Octadecylamine Hydrochloride.

In the Presence of Hydrogen Chloride. In one neck of a 250 ml. Claisen flask was placed a two-holed stopper carrying a glass inlet tube and thermometer, both reaching to the bottom of the flask. An air condenser was inserted through the other neck while the distilling tube was closed off with a glass plug. After the addition of 30.5 g. (0.1 mole) of n-octadecylamine hydrochloride, the flask was heated in a graphite bath at 300° for 6 hours. During the heating a gentle stream of dry hydrogen chloride was bubbled through the molten mass. White fumes formed in the flask. After cooling to room temperature, the brown solid was refluxed with 200 ml. of ether and filtered by gravity.

The ether was removed and the residue boiled at 142-143°/3mm. The colorless distillate weighed 12.9 g. It gave negative tests for nitrogen and chlorine and instantaneously discolored bromine in carbon tetrachloride. Physical constants were $n_D^{20} = 1.4468$, $d_4^{18} = 0.795$, checking the values for octadecene-1 (175).

The ether insoluble fraction was taken up in hot ethanol and filtered hot from the insoluble portion which weighed 2.1 g. An ignition test showed it to be inorganic. It was shown to be ammonium chloride by standard qualitative inorganic tests.

(175) Krafft, Ber., 16, 3024 (1883); Gault and Altchidjian, Ann. chim., 2, 220 (1924); Dover and Hensley, Ind. Eng. Chem., 27, 337 (1935).

Ether was added to the warm alcoholic filtrate, and the mixture crystallized at 0°. The colorless crystals weighed 4.9 g. and melted at 170°. After treatment with potassium cyanate, using the procedure for the preparation of N,N-di-n-octadecylurea (p. 89) a product was obtained melting at 65.0-65.5°. A mixed melting point with an authentic specimen of N,N-di-n-octadecylurea melting at 65.0-65.5° gave no depression.

In the Absence of Hydrogen Chloride. In this experiment the inlet tube was discarded and no hydrogen chloride was used. The heating was conducted at 300° for 6 hours. White fumes were generated. After cooling to room temperature, a brown solid was obtained. This was refluxed with ether for 1 hour and filtered by gravity.

Removal of the ether gave 13.0 g. of a colorless distillate boiling at 132.0-134.0°/2mm. Physical constants were exactly as in the preceding experiment.

The ether insoluble portion was taken up in hot ethanol and filtered from the insoluble portion. This weighed 3.5 g. and was shown to be ammonium chloride by standard qualitative tests.

Ether was added to the warm alcoholic filtrate, and the mixture crystallized at 0°. The crystals were washed with water until free from chloride ion. They melted at

170° and weighed 2.5 g. They were converted into N,N-di-n-octadecylurea by reaction with potassium isocyanate to melt at 65.8-66.0°. A mixed melting point with an authentic specimen of N,N-di-n-octadecylurea melting at 65.0-65.5° gave no depression.

Pyrolysis of Di-n-Octadecylamine Hydrochloride.

A 250 ml. Claisen flask containing 34.0 g. (0.061 mole) of di-n-octadecylamine hydrochloride was equipped with a thermometer reaching into the bottom of the flask. An air condenser was inserted in the distilling neck, while the distilling tube was fitted with a glass plug. Heating was conducted for 6 hours at 300-310° in a graphite bath. White fumes were generated. After cooling to room temperature, a tan amorphous solid was obtained. This was broken up, refluxed with 200 ml. of ether for 30 minutes, and the mixture filtered by gravity.

The dark brown ethereal solution was washed with dilute hydrochloric acid and water, and then dried over anhydrous sodium sulfate. The ether was removed on a steam bath, and the residue filtered by suction. The clear filtrate was vacuum distilled and boiled at 175.0-177.0°/11mm. The distillate weighed 17.4 g. Octadecene-1 boils at 175-180°/15mm. (175).

The ether insoluble portion of the reaction product was reflux-washed with ether and filtered. The colorless solid weighed 6.5 g. It was taken up with 75 ml. of absolute ethanol and filtered hot. An ignition test showed the insoluble portion to be inorganic. It weighed 1.0 g. Standard qualitative inorganic tests showed it to be ammonium chloride.

The absolute ethanol filtrate was crystallized at 0°, and deposited 5.5 g. of crystals melting at 175°. These were dissolved in hot ethanol, one drop of phenolphthalein added, and then a 5% solution of freshly prepared potassium hydroxide in ethanol added until a pink color appeared. The hot solution was filtered from the insoluble potassium chloride. A crystallization at room temperature gave crystals melting at 70.0-71.0°. A mixed melting point with an authentic specimen of di-n-octadecylamine melting at 70.0-71.0° gave no depression.

Pyrolysis of Tri-n-octadecylamine Hydrochloride.

In this experiment, 30.0 g. (0.037 mole) of tri-n-octadecylamine hydrochloride was heated at 300° for 6 hours in a 250 ml. Claisen flask equipped as in the previous experiment. White fumes were generated during the heating. Upon cooling to room temperature, an amorphous solid was obtained. This was broken up, refluxed with 150 ml. of ether for about an hour, and filtered by gravity. The insoluble portion was washed well with ether until the filtrate was colorless. It weighed 7.5 g. It was refluxed with 100 ml. of absolute ethanol and filtered hot from the insoluble portion. This weighed 0.5 g. and was shown to be ammonium chloride by standard qualitative inorganic tests. The alcoholic filtrate upon crystallization deposited 7.0 g. crystals melting at 170°, which were raised to 177° by a crystallization from absolute ethanol. These were heated with potassium cyanate after the manner of the preparation of N,N-di-n-octadecylurea (p. 89) to give crystals melting at 63.0-64.0°. A mixed melting point with an authentic specimen of N,N-di-n-octadecylurea melting at 64.0-64.5° gave no depression.

The ether soluble portion of the reaction product was distilled on a steam bath, and the residue upon standing at room temperature deposited some solid. This was removed by filtration and washing with absolute ethanol. The clear filtrate was vacuum distilled to give 14.2 g. of a colorless distillate boiling at 174-182°/13mm. Determination of physical contents gave $n_D^{20}= 1.4465$; $n_D^{22}= 1.4458$; $d_4^{18}= 0.7892$. These check the values for octadecene-1 (175).

Proof of Structure of Octadecene-1.

The olefin fractions from the pyrolyses were combined and used for the proof of structure. The literature is sparse on details for the oxidation of olefins to acids, particularly aliphatic olefins. The following procedure was developed after several unsuccessful attempts.

In a 2 l. round bottom flask was placed 21.4 g. (0.085 mole) of purported octadecene-1 and 35.7 g. (2.66 mole) of potassium permanganate (4% aqueous solution) added. The flask was stoppered and wired tight. It was placed in a shaking machine for 44 hours. By this time there was no pink tinge indicating the complete consumption of the potassium permanganate. The resulting mixture was alkaline. It was filtered by suction from manganese dioxide. The manganese dioxide was refluxed with 100 ml. of 2% potassium hydroxide in absolute ethanol and filtered hot. It was further refluxed with 100 ml. of absolute ethanol. The filtrates were combined and evaporated to dryness on the steam box. The insoluble portion was refluxed with another portion of chloroform, and after cooling to room temperature was filtered.

The chloroform insoluble portion was air dried and then treated with 50 ml. of dilute sulfuric acid. The mixture was heated until the molten free acid floated on top. After cooling, the oil solidified and was removed by filtration. The treatment with dilute sulfuric acid was repeated. It was then molten with two portions of hot distilled water and cooled to give a solid melting at 48.0-50.0°.

The yield was 9.3 g. (40%). Crystallization from 70% ethanol at 0° raised the melting point to 55.0-56.0°. A mixed melting point with an authentic specimen of margaric acid melting at 58.0° gave no depression.

The acid obtained from the oxidation was converted into the p-bromophenacyl ester in the following manner: To 1.96 g. (0.00725 mole) of the acid was added 52 ml. of a solution of sodium ethoxide prepared by dissolving 1.5 g. of sodium in 500 ml. of ethanol. This was 5 per cent less than the theoretical amount of sodium ethoxide required for complete reaction with the acid. The mixture was refluxed until a clear solution formed. A drop of phenolphthalein was added to test for acidity. Then 2.0 g. (0.0072 mole) of pure p-phenylphenacyl bromide was added, and the solution refluxed for 1 hour. A crystallization at the tap gave colorless crystals melting at 79.0-80.0°. Further crystallization did not change the melting point. A mixed melting point with an authentic specimen of p-bromophenylphenacyl margarate melting at 81.0-82.0° (176) prepared from margaric acid gave no depression.

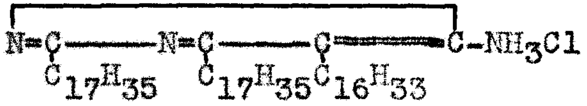
The sulfuric acid washings were combined and diluted with 100 ml. of water. The solution was distilled until the distillate gave a positive test for sulfate ion (barium nitrate and dilute hydrochloric acid). To a small portion

---

(176) Judefind and Reid, J. Am. Chem. Soc., 42, 1055 (1920).

of the distillate was added a dilute solution of silver nitrate. No precipitation took place. Upon warming, the solution turned brown and precipitated metallic silver. This is a characteristic test for formic acid (177).

Preparation of 6-Amino-2,4-di-n-heptadecyl-5-n-hexadecylpyrimidine Hydrochloride,



$$\mathrm{N{=}\underset{C_{17}H_{35}}{C}{-}N{=}\underset{C_{17}H_{35}}{C}{-}\underset{C_{16}H_{33}}{C}{=}C{-}NH_3Cl}$$

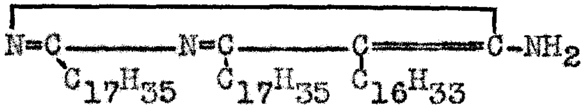
In a 250 ml. Erlenmeyer flask carrying a calcium chloride tube was placed 53.0 g. (0.2 mole) of stearonitrile and 4.6 g. (0.2 g. atom) of sodium cut under ether into small pieces. The flask was heated in a bath made from 55 parts of potassium nitrate and 45 parts of sodium nitrate to a temperature of 200°. The heating was continued for 8 hours. After cooling to room temperature, the solid was broken up in the flask. The sodium was destroyed by the addition of 100 ml. of ethanol, followed by 100 ml. of water. The mixture was filtered and washed with several portions of 50% ethanol. After drying in air, the product was pulverized and transferred to a 1 l. three-necked flask. A mixture of 200 ml. of absolute ether and 200 ml. of absolute ethanol was added, and the solution brought to a reflux. Dry hydrogen chloride gas was pumped in until the solution was saturated. After cooling to 0°, the mixture

(177) Liebig, Ann., 17, 74 (1836).

was filtered and washed with ether. The product was placed in a Soxhlet apparatus and extracted with ether for 2 hours. The solid was air dried. Finally, it was taken up in a mixture of 250 ml. of petroleum ether (b.p. 60-68°) and 50 ml. of ethanol and a *single* knife point of Norit added. The mixture was refluxed for 30 minutes, and after a hot filtration crystallized slowly at 0°. The colorless crystals melted at 122.5-123.0°. The yield was 20.6 g. (50%).

6-Amino-2,4-di-*n*-heptadecyl-5-*n*-hexadecylpyrimidine hydrochloride has been found to melt at 123-124°(178). *Anal.* Calcd. for $C_{54}H_{106}N_3Cl$: N, 5.04. Found: 4.96.

Preparation of 6-Amino-2,4-di-n-heptadecyl-5-n-hexadecylpyrimidine,



$$N{=}\underset{C_{17}H_{35}}{C}\text{———}N{=}\underset{C_{17}H_{35}}{C}\text{———}\underset{C_{16}H_{33}}{C}{=\!=\!=}C\text{-}NH_2$$

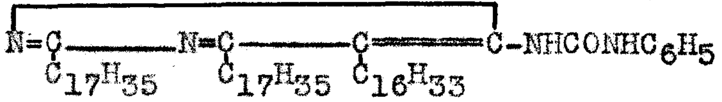
The hydrochloride was converted to the free amine by solution in hot absolute ethanol (8 g. required 100 ml.), and a drop of phenolphthalein added. A hot concentrated solution of sodium hydroxide in absolute ethanol was added until the mixture was alkaline. After a hot filtration from sodium chloride, a crystallization at 0° gave the free aminopyrimidine melting at 75.5-76.5°. A molecular weight determination was made by the Rast camphor method: Calcd.

(178) J. M. Straley, unpublished results.

M.W., 795. Found: M.W., 778.

Anal. Calcd. for $C_{54}H_{105}N_3$: N, 5.28. Found: 5.06.

Preparation of N-2,4-Di-n-heptadecyl-5-n-hexadecyl-6-pyrimidyl-N'-phenylurea,

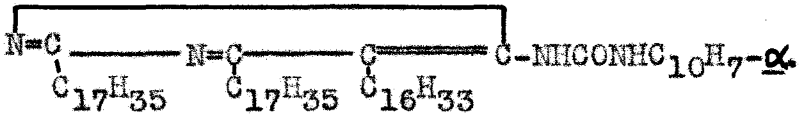


$$\underset{C_{17}H_{35}}{N{=}C}-\underset{C_{17}H_{35}}{N{=}C}-\underset{C_{16}H_{33}}{C}{=}C\text{-}NHCONHC_6H_5$$

A 200 ml. round bottom flask was dried by warming in a Bunsen flame, and closed with a stopper carrying a calcium chloride tube. After the flask had cooled to room temperature, a solution of 3.9 g. (0.005 mole) of 6-amino-2,4-di-*n*-heptadecyl-5-*n*-hexadecylpyrimidine in 50 ml. of warm dry benzene was added. This was followed by addition of 0.67 g. (0.0055 mole) of phenyl isocyanate dissolved in 10 ml. of dry benzene. The resulting solution was refluxed for 1 hour on the water bath. The benzene was removed on the water bath. After cooling to room temperature, the solid was pulverized and crystallized from ethyl acetate at 0°. The colorless crystals melted at 77.0-79.0°. The yield was 3.8 g. (85%). Repeated crystallization raised the melting point to 79.5-80.0°. The crystals were insoluble in absolute alcohol.

Anal. Calcd. for $C_{61}H_{110}ON$: N, 6.13. Found: N, 5.99.

Preparation of N-2,4-Di-n-heptadecyl-5-n-hexadecyl-6-pyrimidyl-N'-α-naphthylurea,



$$\underset{C_{17}H_{35}}{N{=}C}-\underset{C_{17}H_{35}}{N{=}C}-\underset{C_{16}H_{33}}{C}{=}C\text{-}NHCONHC_{10}H_7\text{-}\alpha$$

A 200 ml. round bottom flask was dried as in the preceding experiment. After the flask had cooled to room temperature, a solution of 3.9 g. (0.005 mole) of 6-amino-2,4-di-n-heptadecyl-5-n-hexadecylpyrimidine in 50 ml. of warm dry benzene was added. This was followed by the addition of 0.92 g. (0.0055 mole) of α-naphthyl isocyanate in 10 ml. of dry benzene. The resulting solution was refluxed for 1 hour on the water bath. Upon cooling in the tap, colorless crystals were deposited melting at 94.5-96.0°. The yield was 4.2 g. (89%). Crystallization from ethyl acetate raised the melting point to 95.5-96.5°. The crystals turned pinkish on exposure to air and light. They were preserved in a brown bottle.

Anal. Calcd. for $C_{65}H_{112}ON_4$: N, 5.81. Found: N, 5.55.

Attempt to Prepare N-2,4-Di-n-heptadecyl-5-n-hexadecyl-6-pyrimidylurea.

A mixture of 2.08 g. (0.0025 mole) of 6-amino-2,4-di-n-heptadecyl-5-n-hexadecylpyrimidine hydrochloride and 0.41 g. (0.005 mole) of potassium cyanate in 20 ml. of absolute ethanol was evaporated on the steam bath. The residue was refluxed with 20 ml. of absolute ethanol and filtered hot. A crystallization at 0° gave colorless crystals melting at 75.5-76.0°. A mixed melting point with an authentic specimen of 6-amino-2,4-di-n-heptadecyl-5-n-hexadecylpyrimidine gave no depression. The recovery was 1.4 g. (70%).

Attempts to conduct the reaction in refluxing ethanol or glacial acetic acid gave only the free base.

Attempt to Prepare N-2,4-Di-n-heptadecyl-5-n-hexadecyl-6-pyrimidyl-N'-phenylthiourea.

To a solution of 2.78 g. (0.0035 mole) of 6-amino-2,4-di-n-heptadecyl-5-n-hexadecylpyrimidine in 50 ml. of dry benzene was added 0.51 g. (0.0038 mole) of phenyl isothiocyanate. The latter was washed in with small portions of solvent. The solution was refluxed on the water bath for 1 hour. After cooling to room temperature, 25 ml. of toluene was added, and the solution crystallized at 0°. Colorless crystals were obtained which melted at 75.5-76.0°. A mixed melting point with an authentic specimen of 6-amino-2,4-di-n-heptadecyl-5-n-hexadecylpyrimidine melting at 75.5-76.5° gave no depression. The recovery was 2.3 g. (85%).

Mixing the reagents directly and heating gave no pure product. Refluxing in absolute ethanol for 12 hours gave a quantitative recovery of unchanged pyrimidine.

Attempt to Prepare N-2,4-Di-n-heptadecyl-5-n-hexadecyl-6-pyrimidylstearamide.

In a 200 ml. round bottom flask was placed 4.16 g. (0.005 mole) of 6-amino-2,4-di-n-heptadecyl-5-n-hexadecylpyrimidine hydrochloride, and 1.65 g. (0.0055 mole) of freshly prepared stearoyl chloride washed in with 50 ml. of dry toluene. The mixture was refluxed for 46 hours, protecting against moisture by means of a calcium chloride tube. After the toluene was removed, a brittle colorless solid remained. It melted at 86.0-87.0°. Extraction with alkali and crystallization from petroleum ether (b.p. 77-115°) gave no sharp-melting product. Therefore, it was refluxed a short while with alcoholic hydrogen chloride to give a clear solution. Crystallization at room temperature gave crystals melting at 121.0-122.0°. A mixed melting point with an authentic specimen of 6-amino-2,4-di-n-heptadecyl-5-n-hexadecylpyrimidine hydrochloride melting at 123.0-123.5° gave no depression. The recovery was 4.0 g. (97%).

Attempt to Prepare N-2,4-Di-n-heptadecyl-5-n-hexadecyl-6-pyrimidylbenzamide.

To a solution of 3.9 g. (0.005 mole) of 6-amino-2,4-di-n-heptadecyl-5-n-hexadecylpyrimidine in 50 ml. of warm dry benzene was added 1.25 g. (0.0055 mole) of benzoic anhydride (free from benzoic acid). The solution was refluxed for 2 hours. The solvent was removed, and the residue was pulverized. It was then refluxed with 50 ml. of 2% sodium hydroxide for a short while. After cooling in the tap, the liquid was decanted through a wire screen, and the solid washed with water. The extraction with alkali was repeated. The product melted poorly at 71-73° and weighed 3.7 g. Attempts to purify it by crystallization from absolute ethanol gave no sharp melting product. Treatment with alcoholic hydrogen chloride raised the melting point to 98-105°.

An attempt to react the pyrimidine hydrochloride with benzoyl chloride also gave a crude product which did not lend itself to purification.

Attempt to Prepare N-2,4-Di-n-heptadecyl-5-n-hexadecyl-6-pyrimidylbenzenesulfonamide.

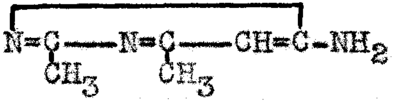
To a solution of 3.4 g. (0.0043 mole) of 6-amino-2,4-di-n-heptadecyl-5-n-hexadecylpyrimidine in 30 ml. of dry pyridine was added 1.51 g. (0.0086 mole) of benzenesulfonyl chloride. The mixture was allowed to stand overnight at room temperature. It was then poured into 500 ml. of ice water containing 35 ml. of concentrated sulfuric acid. The precipitate was washed with water and melted at 118.5-120.0°. It was refluxed a short while with 50 ml. of 2% sodium hydroxide, cooled in the tap, filtered and washed with water.

It was then reflux-washed with distilled water, cooled and filtered. It now melted at 73.5-74.0°. Crystallization from absolute ethanol raised the melting point to 76.5-77.0°. A mixed melting point with an authentic specimen of 6-amino-2,4-di-n-heptadecyl-5-n-hexadecylpyrimidine melting at 75.5-76.5° gave no depression. The recovery was 3.2 g. (94%).

Attempt to Prepare N,N'-Di-(2,4-di-n-heptadecyl-5-n-hexadecyl-6-pyrimidyl)-thiourea.

To a solution of 3.9 g. (0.005 mole) of 6-amino-2,4-di-n-heptadecyl-5-n-hexadecylpyrimidine in 500 ml. of anhydrous ether was added 0.76 g. (0.01 mole) of colorless carbon disulfide. No change was noticed. The flask was stoppered and allowed to stand overnight, but no precipitate formed. The solvents were removed, and the almost white solid melted at 75.5-76.0°. A mixed melting point with an authentic specimen of 6-amino-2,4-di-n-heptadecyl-5-n-hexadecylpyrimidine melting at 75.5-76.5° gave no depression. The recovery was 3.6 g. (92%).

Preparation of 6-amino-2,4-dimethylpyrimidine,



$\mathrm{N{=}\underset{CH_3}{C}{-}N{=}\underset{CH_3}{C}{-}CH{=}C{-}NH_2}$

Through one neck of a 1 l. Claisen flask was inserted a two-hole rubber stopper carrying a glass inlet tube and a dropping funnel. The inlet tube extended only a short distance beyond the stopper. Through the distilling neck was placed a reflux condenser which carried an inverted U-tube dipping into mercury to a length of 20 cm. The distilling tube was closed by a glass plug.

The glass plug was removed, and the flask flushed with carbon dioxide. During this time 20 g. (1 part) of sliced sodium was added. The plug was inserted, and the flow of carbon dioxide stopped. Through the dropping funnel was added 120 g. (6 parts) of acetonitrile (179) freshly distilled from phosphorous pentoxide. The acetonitrile was added in two portions: when the first portion (40 g.) was added a vigorous reaction took place; when this had subsided the remaining 80 g. of nitrile was added. The flask was then heated in an oil bath for 2 hours at 110°. The unreacted acetonitrile was distilled off, and the residue in the flask dissolved in warm water. Upon evaporation on the water bath 74 g. of tan crystals were obtained which were filtered off. These were crystallized from 150 ml. of absolute ethanol plus a single knife point of Norit, and at 0° gave colorless crystals melting at 180.0-181.0°. The yield was 35.2 g. (39%). Bayer (161) reported a melting point of 180.0-181.0°.

Analysis of High-Molecular-Weight Compounds.

---

(179) Kindly supplied by E. Bindschadler.

The compounds described in this thesis were analyzed, with few exceptions, by the Kjeldahl method. About 0.5 g. of sample was used. The sample was digested with 25 ml. of a selenium oxychloride solution made up by dissolving 8.0 ml. of selenium oxychloride in 992 ml. of pure concentrated sulfuric acid. More dilute solutions of selenium oxychloride gave low results.

The sample, which was wrapped in filter paper, was allowed to remain in the selenium oxychloride reagent for about an hour before applying heat. This dissolved most of the filter paper, and reduced foaming during the digestion. The period of digestion was usually about 3-4 hours. At the end of this time an almost colorless solution was formed. The remainder of the analysis was conducted after the standard procedure (180).

---

(180) The author wishes to thank Mr. Albert Zarow for valuable suggestions in working out the procedure for this analysis.

DISCUSSION OF RESULTS

Many previous investigators have reported boiling points and melting points of high-molecular-weight aliphatic compounds which give the impression that these substances boil over wide ranges and have poor melting points. This is far from the truth. In many instances they have started with commercial products which they failed to purify adequately before starting a synthesis. In high-molecular-weight aliphatic chemistry the rule holds that to prepare pure compounds one must start with pure compounds. This is so because the impurities are usually also of high molecular weight and, in general, have the same physical properties. Thus, when pure stearic acid was used as a starting point in syntheses, it was found that the various n-octadecyl derivatives boiled sharply and melted over short ranges of 0.5° or better.

The need for pure compounds is especially important in pharmacological testing, and it is worth repeating (2) that a large part of the previous work on aliphatic amines is being repeated because the compounds previously prepared and tested were impure.

The pioneer work of Ralston and co-workers (19) on the direct ammonolysis of high-molecular-weight aliphatic acids to nitriles was simplified by McCorkle (20). It was possible to introduce further simplification of the apparatus with no loss in yields; in fact there was a slight gain. The result of this simplification was that the reaction required little or no attention once adequate care was taken to fix the experimental conditions. Thus, the preparation of stearonitrile and lauronitrile gave pure products in yields which compared favorably with those of previous investigators. Further, the direct ammonolysis of aliphatic acids was extended to dibasic aliphatic acids. Sebaconitrile, an important intermediate in the preparation of fiber-forming polyamides ("Nylon") was prepared in a short time in 55 per cent yield. Doubtlessly in larger runs a higher yield would be obtained.

Attempts to extend the direct ammonolysis to high-molecular-weight olefinic acids, e.g., oleic and elaidic acids, resulted in an isomerization to a mixture of nitriles. This was indicated by reduction to the amines and preparation of solid derivatives. It would be interesting either to try to separate the mixture of nitriles or determine their amounts by saponification to the acids.

<u>n</u>-Octadecylamine was prepared by a modification of the method of Krafft and co-workers (30)(36). The use of sodium and ethanol as a reducing agent was found to involve no danger, since the reaction proceeded moderately even at a reflux temperature. In fact, it can be recommended as superior to

the use of sodium and n-butyl alcohol (40).

The catalytic preparation of high-molecular-weight aliphatic primary amines (40) was extended to aliphatic diamines. 1,10-Decanediamine, important as an intermediate in the preparation of "Nylon" (147) was prepared in 62 per cent yield by this method.

High-molecular-weight aliphatic primary amines rapidly absorb carbon dioxide and moisture from the air to form the amine carbamate. n-Dodecylammonium N-n-dodecylcarbamate was prepared from these reagents. It is essential, therefore, both in the preparation and reactions of these compounds, to avoid both of these contaminants. It was found that by protecting all outlets of the distillation apparatus with freshly prepared soda-lime tubes pure amines could be prepared. Further, by the quick manipulation of the amines in the molten condition, the effect of carbon dioxide and moisture were so minimized that they did not interfere with the preparation of derivatives.

A standard technique for the preparation of amine hydrochlorides has been to dissolve the amine in ether and saturate it with gaseous hydrogen chloride. This was a time consuming operation. Also, there was a danger that the ethereal solution would suck back into the generator or trap. The preparation, therefore, had to be watched. This procedure was found to be unnecessary. It was merely necessary to dissolve the amine in absolute ethanol and add a slight excess of concentrated hydrochloric acid. The amine hydrochloride could be isolated in excellent yields. In this manner, n-dodecylamine, di-n-octadecylamine and 1,10-decanediamine were converted to their hydrochlorides.

High-molecular-weight aliphatic primary amines were found to give urea derivatives with ease. The reaction of n-dodecylamine with carbon disulfide, phenyl isothiocyanate and α-naphthyl isocyanate required no special techniques, and gave corresponding urea and thiourea derivatives in compensating yields. Similarly, the reaction of n-octadecylamine with potassium cyanate, carbon disulfide and α-naphthyl isocyanate proceeded with no difficulty. The success of the reactions of n-dodecyl- and n-octadecylamines with α-naphthyl isocyanate was probably a result of the precautions taken to dry the apparatus.

The reaction of n-dodecyl and n-octadecylamines with carbon disulfide in ethanol was found to give the symmetrical thioureas in almost quantitative yields. This was in contrast to the report of Jeffreys (52) who found that the isothiocyanate was formed as well.

While high-molecular-weight aliphatic primary amines gave urea and thiourea derivatives with no difficulty, the secondary amines required special techniques. This was a result of their lower relative reactivity. Di-n-octadecylamine did not react at all with carbon disulfide to give the expected tetrasubstituted thiourea. It reacted with potassium cyanate to give the unsymmetrical urea, but the amine hydrochloride had to be treated twice with the reagent. Di-n-octadecylamine reacted with phenyl isocyanate and α-naphthyl isocyanate to give the corresponding urea derivatives. Hoyt (40) was unable to obtain the phenylurea of di-n-octadecylamine. This was probably due to a lack of proper caution in insuring the absence of moisture in the apparatus, and not a matter of the limits of homology. Yet attempts to react di-n-octadecylamine with phenyl isothiocyanate were without success. It is probable that this reagent is much less reactive than phenyl isocyanate.

The desulfuration of N,N'-di-n-octadecylthiourea proceeded with surprising ease for a compound of this molecular weight. It is an indication of the lability of sulfur in this class of compounds.

The acylation of amines is one of their most important reactions. It is not surprising, therefore, that various procedures have been worked out in which different reagents were used to special advantage. Some of the more important methods of acylation of amines are:

(a) $RNH_2 + R'CO_2H \longrightarrow R'CONHR + H_2O$

(b) $2\ RNH_2 + R'COCl \longrightarrow R'CONHR + RNH_2 \cdot HCl$

(c) $RNH_2 + (R'CO)_2O \longrightarrow R'CONHR + RCO_2H$

(d) $RNH_2 + R'CO_2R'' \longrightarrow R'CONHR + R''OH$

(e) $RNH_2 \cdot HCl + R'COCl \longrightarrow R'CONHR + 2\ HCl$

It will be noticed at once that all the procedures are related in that an amine or its derivative is treated with an acid or its derivative to give the desired amide.

Reaction (a) is most direct, for it involves the reaction of an amine and a carboxylic acid to give the amide and water. It may be called "the direct condensation of amines and carboxylic acids". Previous investigators only treated low-molecular-weight aliphatic amines in this fashion. The reaction was either carried out as a two-phase reaction, i.e., the amine was neutralized with the acid, and the salt then decomposed by heat to the amide, or a one-phase reaction where the reagents were heated in sealed tubes.

It was found that the direct condensation could be applied to high-molecular-weight aliphatic primary amines and carboxylic acids with surprising ease. It was merely necessary to heat the reagents in an open vessel at a temperature (usually 250°) where the water was evolved readily in the form of steam. When a stream of nitrogen was passed over the heated reagents, it was found that discoloration was minimized, and the product was obtained more readily in a colorless crystalline state.

In this manner it was possible to prepare amides of *n*-dodecyl- and *n*-octadecylamines with various aromatic acids. Thus, amides of benzoic, *o*-toluic, *m*-toluic and anisic acids were obtained in average yields of 72 per cent. Further, it was possible to extend the condensation to chloro-substituted benzoic acids. While the *p*-chlorobenzamides were prepared with no difficulty, the *o*-chlorobenzamides were more difficult to purify.

The direct condensation of amines and carboxylic acids worked extremely well with high-molecular-weight aliphatic acids. This was an important synthetic improvement, since it made the preparation of the troublesome acid chlorides superfluous. In this manner the *n*-dodecyl and *n*-octadecyl amides of lauric, myristic, palmitic and stearic acids were obtained in average yields of 78 per cent.

It was found that the direct condensation of high-molecular-weight aliphatic amines could be extended to unsaturated aromatic and aliphatic acids without isomerization of the latter. The *n*-dodecyl and *n*-octadecyl amides of *trans*-cinnamic, *cis*-oleic and *trans*-elaidic acids were prepared in average yields of 67 per cent.

The direct condensation of amines and carboxylic acids was successfully extended to aliphatic diamines. 1,10-Decanediamine reacted with an equivalent of lauric acid to give the dilauramide in 85 per cent yield.

There were, however, limitations to the direct condensation of high-molecular-weight amines and carboxylic acids. For example, if the acid decomposed at the temperature of the reaction no amide was isolated. This was true in the case of p-nitrobenzoic and salicylic acids. With the latter acid, a lower temperature gave neither decomposition nor reaction. Further, the extension of the condensation to halogen substituted aliphatic acids, e.g., chloroacetic acid, gave no pure product. Finally, it was not possible to extend the condensation to high-molecular-weight aliphatic secondary amines. Di-n-octadecylamine gave only crude products with benzoic and stearic acids. More promising results may be expected with di-n-dodecylamine.

An investigation of the mechanism of the direct condensation of amines and carboxylic acids showed that there was initial salt formation, but that under the general procedure adopted the salt was formed and immediately decomposed to the amide. Thus, when n-octadecylamine and lauric acid were heated directly at 60-68°, an almost quantitative yield of n-octadecylammonium laurate was isolated. It should be mentioned that the synthesis of amides of high-molecular-weight aliphatic primary amines has been investigated along the lines of a two-step reaction (181). That is, the salt was first isolated and then pyrolyzed to the amide. The yields were of the same order as in the direct condensation.

(181) B. A. Hunter, unpublished results.

The direct condensation of amines and sulfonic acids was found to stop at the salt stage. The sulfonium salts were stable to heat, but like the ammonium salts had broad melting ranges.

Reaction (b) is the more familiar type of acylation reaction. It is inferior to the direct synthesis of amides since the acid chloride must be prepared. In the case of high-molecular-weight aliphatic acid chlorides their preparation is somewhat troublesome. Further, the amine hydrochloride is formed as a by-product in the reaction. While the low-molecular-weight amine hydrochlorides are soluble in water, those of high molecular weight are either insoluble or form emulsions. They cannot be washed out with water. They may be separated out by differential solubility in ether. N-n-octadecylbenzamide was prepared in this manner but the yield was only 43 per cent.

However, in the sulfonic acid series, the commercial availability of sulfonyl chlorides makes their use advisable. The original Hinsberg technique (182) was found to apply to high-molecular-weight aliphatic primary amines. The benzenesulfonamides of n-dodecyl- and n-octadecylamines were prepared in 67-68 per cent yields. The p-toluene-sulfonamide of n-dodecylamine was also prepared in this manner.

(182) Hinsberg and Kessler, Ber., 38, 909 (1905).

Reaction (c) suffers from somewhat the same disadvantage as reaction (b). It is necessary to prepare the anhydride of the acylating acid. Also, the free acid is formed as a by-product, and in the case of high-molecular-weight aliphatic acids the separation of acid and amide may prove tedious. However, when the anhydride is of low-molecular-weight and commercially available its use is recommended. Thus, n-dodecylamine and acetic anhydride reacted immediately to give pure N-n-dodecylacetamide. Also, in the case of readily available aromatic acid anhydrides their use is advantageous. The aromatic acid can be readily separated from the amide. In this manner, N,N-di-n-octadecylbenzamide was prepared from benzoic anhydride and di-n-octadecylamine. Further, phthalic anhydride was found to react immediately with n-dodecyl- and n-octadecylamines to give quantitative yields of crude phthalimides.

In reaction (d) there is an advantage that no troublesome by-product is formed. But here again a derivative of the acid must first be prepared. The amine is treated with the methyl or ethyl ester of the acid to form the amide plus methanol or ethanol. In this manner, n-octadecylamine reacted immediately with diethyl oxalate to give N,N'-di-n-octadecyloxamide. The reaction with malonic ester required more drastic conditions, while the reaction with diethyl ethylmalonate gave no amide. This was in line with the results of Franchimont and Klobbie (121) on the effect of alkyl groups in the malonic ester molecule.

Finally, in reaction (e) derivatives of both the amine and the acid are required. However, in the case of aliphatic acid chlorides it is superior to procedure (b). The reaction is slow but the yields are compensating. The reaction of *n*-dodecylamine hydrochloride and stearoyl chloride required 24 hours, but the yield of amide was 92 per cent. N,N'-Di-*n*-octadecylbenzamide was prepared similarly.

The value of pairs of derivatives of *n*-dodecyl- and *n*-octadecylamines was studied (Table I, p.138). It was found that in all the cases listed, with the exception of the α-naphthylurea derivatives, there was either a marked average lowering of the mixed melting point and/or a marked increase in the melting point range. The α-naphthylurea derivatives, although readily prepared, were valueless since both the average depression of the mixed melting point and the mixed melting point range were small.

All pure derivatives prepared have been found to melt sharply over a half degree range or better. Mixtures of amides of aliphatic acids melted slightly lower than the *n*-dodecyl compound but markedly lower than the *n*-octadecyl compound. The mixed melting point range was increased.

In the case of aromatic amides there was a marked average depression of mixed melting points. The melting point range increased from 0.5° to as much as 11° in the mixture.

The largest depression of mixed melting points occurred with the *o*-chlorobenzamides. However, they do not crystallize with ease, and this offsets their advantage as derivatives.

The next largest depression occurred with the acetamides. Since these compounds are readily prepared they are derivatives of choice.

The third largest depression of the amides occurred with the *o*-toluamides. Here, also the melting point range of the mixture was wide. Since they are readily prepared in good yields they are recommended as derivatives for *n*-dodecyl- and *n*-octadecylamines.

If the derivatives were arranged in order of decreasing value they would be as follows:

1. N-Acetamides
2. N-*o*-Toluamides
3. N-Benzenesulfonamides
4. N-*p*-Toluenesulfonamides
5. N-Anisamides
6. N-Cinnamides
7. N,N'-Phenylthioureas
8. N-Phthalimides
9. N-Myristamides
10. N-*p*-Chlorobenzamides
11. N-Elaidamides
12. N-*m*-Toluamides
13. N-Palmitamides
14. N-Stearamides
15. N-Lauramides
16. N,N'-α-naphthylureas

It is interesting to note the low value of the aryl urea types as derivatives for high-molecular-weight aliphatic amines. N-Alkylureas have been shown (90) to melt within a range of 15° with little exception, even though the alkyl group increased from methyl to n-docosyl.

Several of the compounds prepared were found to be either soluble in water or to have soap-forming power. Both n-dodecylamine hydrochloride and 1,10-decanediamine dihydrochloride were soluble in water. This property should make them valuable in pharmacological testing. n-Dodecylammonium p-toluenesulfonate was moderately soluble in water with the formation of a detergent solution. It was soluble in warm water with the formation of a soapy emulsion. The n-octadecyl analog formed a soapy suspension when shaken with water. The sodium salts of N-n-dodecyl- and N-n-octadecylphthalamic acids also had emulsifying properties.

Originally it was expected that the pyrolysis of n-octadecylamine hydrochloride would lead to the formation of n-octadecyl chloride. However, octadecene-1 was found to be the main product. The identity of this compound was proven by oxidation to n-heptadecanoic (margaric) and formic acids.

The results of the pyrolysis of primary, secondary and tertiary aliphatic amines suggested the following mechanism following the lines indicated by Hofmann (157):

(a) $2\ R_3N{\cdot}HCl \longrightarrow 2\ R(-H) + 2\ R_2NH{\cdot}HCl$

(b) $2\ R_2NH.HCl \longrightarrow 2\ R(-H) + 2\ RNH_2{\cdot}HCl$

(c) $2\ RNH_2{\cdot}HCl \longrightarrow R_2NH{\cdot}HCl + NH_4Cl$

On the basis of the ready conversion, by heat alone, of primary into secondary amines, it is reasonable to expect that reaction (c) proceeds with extreme ease. The strongest proof that reactions (b) and (c) may represent the mechanism of the pyrolysis lies in the isolation of almost identical amounts of olefin from the pyrolysis of primary and secondary amine hydrochlorides under the same conditions. For in the pyrolysis of $RNH_2{\cdot}HCl$, reaction (c) is considered to proceed first, and with the formation of $R_2NH.HCl$ reaction (b) follows. Now in the pyrolysis of secondary amine hydrochlorides reaction (b) proceeds first and with the formation of $RNH_2.HCl$, reaction (c) is set off. In the pyrolysis of tertiary amine hydrochlorides we have only to assume reaction (a) in order to explain all the products isolated.

The advantages of the mechanism postulated are (1) each molecular species undergoes a single reaction and (2) the diversity of products may be explained on the basis of the relative stabilities of the reactants.

The preparation of 6-amino-2,4-di-n-heptadecyl-5-n-hexadecylpyrimidine was worked out in such a manner as to isolate only the aminopyrimidine. It was interesting to note that in its purification, large amounts of decolorizing charcoal (Norit) were best avoided. The Norit had an unusual attraction for this compound thus lowering the yields. Further, it was found that the amino group of this molecule was extremely inert to standard acylating agents, e.g., benzoyl chloride and benzenesulfonyl chloride. Carbon disulfide did not react at all. Potassium cyanate did not give the expected urea. It merely liberated the free base from its hydrochloride. Yet both phenyl and α-naphthyl isocyanates did react. These reagents seem to have an unusual reactivity toward amino groups.

A better picture of the relative reactivity of the amino group in 6-aminopyrimidines will be obtained by working with lower homologs, e.g., 6-amino-2,4-dimethylpyrimidine. This compound is free from cumbersome long-chained alkyl groups.

SUMMARY

A review of the literature has been made on the purification of stearic acid, the preparation of high-molecular-weight aliphatic nitriles, the preparation of high-molecular-weight aliphatic primary, secondary and tertiary amines and their physical properties, the preparation of high-molecular-weight aliphatic alkylated amines, the reactions of high-molecular-weight aliphatic amines, the condensation of aliphatic amines and both carboxylic acids and dibasic esters, as well as the pharmacology and uses of high-molecular-weight aliphatic amines and their derivatives. The pyrolysis of aliphatic amine hydrochlorides and the chemistry of 6-aminopyrimidines have also been reviewed.

Suggestions have been made on the naming of aliphatic amines as well as on the manipulation of high-molecular-weight aliphatic primary amines.

The ammonolysis of high-molecular-weight aliphatic acids has been improved and extended to aliphatic dibasic acids. An isomerization has been noted in the case of high-molecular-weight aliphatic olefinic acids.

The synthesis of primary aliphatic amines and diamines both by wet and catalytic reduction has been accomplished.

Some improvements were made in the preparation of high-molecular-weight aliphatic secondary and tertiary amines.

A series of urea and thiourea derivatives of n-dodecyl-, n-octadecyl- and di-n-octadecylamines has been prepared.

A general technique for the direct condensation of high-molecular-weight aliphatic primary amines and carboxylic acids has been developed and extended to high-molecular-weight aliphatic acids, substituted and unsubstituted aromatic acids and olefinic acids. The limitations of this condensation have been described as well as its mechanism. Other acylation procedures for high-molecular-weight primary and secondary amines have been described.

The value of a number of compounds of the n-dodecyl and n-octadecyl series as derivatives has been determined. A useful melting point apparatus has been described.

The condensation of n-dodecyl- and n-octadecylamines and several dibasic esters has been accomplished.

The preparation of compounds of the n-dodecyl and n-octadecyl series either soluble in water or possessing detergent action has been successfully carried out.

The pyrolysis of high-molecular-weight aliphatic amine hydrochlorides has been investigated, and a possible mechanism suggested.

The trimerization of stearonitrile has been effected. The chemistry of the resulting 6-aminopyrimidine has been investigated.

Finally some suggestions were presented for the analysis of compounds of high-molecular-weight.