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The phenomenon of homology with long-chained aliphatic compounds

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THE PHENOMENON OF HOMOLOGY WITH LONG-CHAINED ALIPHATIC COMPOUNDS

by

Fred W. Hoyt

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INTRODUCTION

The phenomenon of homology has long been of service in organic research as a basis for predicting the properties and behavior of the members of a series of compounds containing aliphatic radicals of regularly varied length. In most cases, however, the investigations have included only compounds with relatively short aliphatic chains, and doubt has often arisen as to whether the gradation in physical properties and the similarities of reaction observed in the lower members of an homologous series would appear also in the higher members. Furthermore, the length to which the carbon chain can be extended before the compound ceases to conform to predictions made upon the basis of homology also has been a point of contention.

It is generally assumed that the phenomenon of homology is exhibited when members of a series undergo the same kinds of reactions, but at different rates, or when, for a given series of like compounds, physical properties vary regularly with molecular weight. Hence it is necessary to study both the reactions and the properties of the supposed homologs if valid conclusions regarding the application of the theory are to be drawn. Moreover, it seems necessary to stipulate that normal-chained members of a series be compared only with other normal-chained members, if criticisms arising from anomalous reactions of certain branched-chain compounds are to be avoided.

In order to fulfil these conditions, the investigations described in this thesis were concerned with a considerable number of types of reactions in which only compounds having normal long-chained radicals were employed. The purpose of the investigations was to provide certain new data relative to the limits of application of the phenomenon of homology, and concurrently, to prepare compounds which might serve as derivatives for parent long-chained compounds, or which might exhibit some other useful property.

Before a more detailed description of the scope and purposes of the experimental work is given, it seems advisable first to consider more fully the development of the homology principle and to point out some existing limitations of its application.

HISTORICAL

I. The Development of the Concept of Homology.

The development of the concept of homology had its inception in the proposals advanced by Laurent (1), who suggested a tentative grouping of organic compounds on the basis of the hydrocarbons, the latter being designated as the "fundamental radicals" which gave rise to other compounds by loss or substitution of hydrogen atoms. Through his tabulations of derivatives from the same parent hydrocarbon and discussion of the relations made evident by such arrangements, Laurent may be said to have exposed the germ of the concept of homology.

A few years later Dumas and Stas (2) published a table in which the members were arranged according to types; that is, general formulas for the alcohols, esters, and aldehydes corresponding to a series of carboxylic acids were tabulated. The authors pointed out that relationships in mode of formation existed among the types comprising the various series, and also, that there existed many examples of isomerism among the types corresponding to any one acid. Thus the observations of these investigators marked a further step toward the formulation of the

(1) Laurent, *Ann. chim. phys.*, [2] *61*, 125 (1836).

(2) Dumas and Stas, *ibid.*, [2] *73*, 165 (1840).

homology concept, although neither they nor Laurent had made specific statements as to actual mathematical relationships which might exist.

Such observations were soon forthcoming, however, for two years later Kopp (3) published the results of a preliminary investigation of the atomic volumes (4) and boiling points of several series of organic compounds. Upon the basis of his findings, he concluded that the difference in atomic volume between each methyl compound and the corresponding ethyl compound was approximately 234, the ethyl compound having the higher value, while the boiling point difference for each pair was 18°. Not only did Kopp point out the existence of these constants, but he also suggested that they would be useful in the investigation of analogous compounds and turned further effort toward illustration of the value of such generalizations. In the same year another paper (5) by Kopp appeared, in which a tabular arrangement of a generalized series of analogous compounds was shown to be useful in predicting the specific gravity and boiling point of any term from the knowledge of the specific volumes and boiling points for the terms of one vertical and one horizontal row of the table. In addition to this, the relation of boiling point change to substitution of hydrogen by

(3) Kopp, Ann., 41, 79 (1842).

(4) Later changed to specific volume. See ref. (5).

(5) Kopp, Ann., 41, 169 (1842).

chlorine was discussed and examples given to show that the numerical change in the boiling point due to replacement of one hydrogen by chlorine was about 12°. For example, "acetic acid hydrate," $C_4H_8O_4$, boiled at 120° while "chloracetic acid hydrate," $C_4H_2Cl_6O_4$, boiled at 195°, the difference in boiling points being 75°, or 12° per chlorine atom.

The value of these publications was emphasized by Justus Liebig (6), who stated that the generalizations of Kopp were of great value as a means of investigating the correctness of an observation, a means which had not been at hand previously and which would enable more reliable conclusions upon the purity of the substance studied.

A few months after Kopp's work appeared, Schiel (7) called attention to the regularities in boiling points of the known alcohols, regularities which agreed with those of the parent radicals, or hydrocarbons. He included the alcohols containing one, two, three, five, sixteen, and twenty-four carbon atoms, and noted that the boiling point of the five carbon member (amyl) could be expressed as the sum of that of the two carbon member (ethyl) plus a multiple of the difference in boiling points of the one and two carbon members. Since the alcohol having the three carbon radical, glyceryl, did not exhibit the same types of reaction as the other members, Schiel concluded that it

(6) Liebig, *Ann.*, *41*, 188 (1842).

(7) Schiel, *Ann.*, *43*, 107 (1842).

did not belong in this particular series, but was a unit of some other series. Although Schiel did not mention Kopp's work, he confirmed Kopp's finding that the difference between the boiling points of members of a series is about 18°, and furthermore extended it beyond the first two members. Here, then, in Schiel's exposition of boiling point regularities and exclusion of glyceryl alcohol from the series because of reactions unlike those of other members, lies the beginning of the phenomenon of homology, although its designation as such was yet to come. Observations somewhat similar to those of Schiel were made shortly thereafter by Dumas (8), founded upon his arrangement of the fatty acids in a series which began with formic acid and included acetic, butyric, isovaleric, palmitic, and stearic acids, and which exhibited regularities in boiling points and chemical properties.

Thus the observations, generalizations, and ideas which had appeared still awaited consolidation into a more general and distinctive unit, designated by a unique terminology. The awaited organization into a usable form was not long in coming, for Gerhardt (9) soon published the principles of a new classification called serial, in which he gave a clear exposition of the relations between members of

(8) Dumas, Traite de Chimie, 6, 577 (1843). [Grignard, "Traite de Chimie Organique," Masson, Paris (1935) Vol. I, p. 826.]

(9) Gerhardt, "Precis de Chimie Organique" (1844), and "Traite de Chimie Organique" (1853). [Grignard, "Traite de Chimie Organique," Masson, Paris (1935) Vol. I, p. 832.]

a series, and in which, for the first time, those members were designated as homologs, and their relations as homology. In his discussion, Gerhardt observed that when a large number of compounds had been arranged in a number of groups or series, any member which resembled any other of the same series to a higher degree, in turn resembled all the other members of the same series, and in consequence, underwent more or less generally the same types of reaction. Furthermore, this relationship was most pronounced among the members whose composition differed only by n-CH_2-, n being an integer. It was specifically to these compounds that he gave the name homologs. As examples of series in which homology existed, Gerhardt cited the derivation from formic acid of a hydrocarbon, an alcohol, and an ester, and similar derivations from propionic acid, butyric acid, and valeric acid. Then the relationships of the corresponding members, for example, the alcohols, from each of these several series was termed homology. Furthermore, he emphasized the difference between homologs, compounds which differed by n-CH_2-, and isologs, such as acetic acid and benzoic acid, which had the same function but did not differ by n-CH_2-. According to Gerhardt, the serial classification was of advantage less for a methodical grouping of the compounds already known than for predicting the existence of unknown compounds whose properties it would make known in advance.

That Gerhardt's proposed classification soon was accepted by his contemporaries was shown shortly afterward in a publication by Kopp (10) in which it was remarked that there were series of compounds in organic chemistry wherein the members of each series were characterized by especially great analogy in chemical properties, formation, and decomposition, and that these *homologous* substances, distinguished in their make-up by x-CH_2-, exhibited a proportionality between boiling point differences and differences in constitution. Furthermore, it was emphasized that substances which did not differ by -CH_2-, or a multiple thereof, were not *homologs*, while at the same time, compounds having formulas differing only by -CH_2- or x-CH_2- were not definitely homologs, due to the possibility of isomerism.

Almost a decade later there appeared a paper by Schiel (11), concerning the phenomenon of homology and physical properties of homologous substances. There it was stated that the existence of progressive, or homologous, series in organic chemistry was now definite, and that the use of a general formula for designation of all the members of a series was entirely correct. Despite the fact that he was hampered by insufficient and inaccurate data, Schiel proposed a method for calculating the heat of vaporization of the members of such a series, which gave fairly good agreement with the values actually found by experiment. Another interesting point was the irregularity noticed

(10) Kopp, *Pogg. Ann.*, [2] *81*, 374 (1850).

(11) Schiel, *Ann.*, *110*, 141 (1859).

in the fatty acid series, a series which will find later mention in regard to the alternation in its properties. It is of interest, furthermore, that cetyl alcohol, a long-chained compound, again was one of the compounds included in the investigation.

Following Schiel's work, there appeared the results of a study of American petroleum by Schorlemmer (12), in which, although relations between boiling point and constitution were not mentioned, it was stated that fractional distillation afforded separation of the many homologous compounds present in the petroleum, and that these were hydrocarbons, expressed by the general formula, C_nH_{2n+2}. Thus, further progress of the concept of homology is indicated, in great part due to advances in analytical procedures and to corrections in atomic weight values, such that the identities and true proportions of the various elements in a compound were now fairly definite, enabling the establishment of general formulas.

Thus far, most of the investigations had been confined to the normal-chained compounds, perhaps because of uncertainties in structure determinations, but a few years later Schorlemmer (13) essayed the formulation of the relationships between the boiling points and constitution of normal and branched chain compounds. The hydrocarbons whose structures were known with some certainty were divided into four groups

(12) Schorlemmer, Ann., 136, 257 (1865).

(13) Schorlemmer, Ann., 147, 219 (1868).

as follows: first, hydrocarbons in which no carbon atom was joined to more than two others, such as ethane and hexane; second, hydrocarbons analogous to isopentane or isobutane, having a skeleton derived by attaching a simple chain to the middle carbon atom of propane; third, hydrocarbons containing two iso-propyl groups, one at either end of a chain; and fourth, hydrocarbons having one carbon atom joined to four others, only one example being known at the time. This was "carb-dimethyl-diethyl" (14) (3,3-dimethyl pentane). For the first group it was observed that as the normal chain was increased by one carbon atom, the boiling point increased by about 31°. The same fact applied to the second group, but a member of the second group boiled lower than the corresponding member (same number of carbons) in the first group. In the third group, however, the boiling point difference averaged only 25°, but the boiling point of each member still was lower than a corresponding member of the second group. For example, "di-isobutyl" (2,5-dimethyl octane) of the third group boiled at 109°, while "octyl hydride" (n-octane) of the second group boiled at 123°.

Yet another paper (15) by the same author concerning the hydrocarbons appeared a few years later, the investigations having returned to the normal hydrocarbons, now designated as paraffins, in accordance

(14) Friedel and Ladenburg, Ann., 142, 310 (1867).

(15) Schorlemmer, Ann., 161, 281 (1872).

with the nomenclature of Fownes (16). The known normal paraffins were listed, together with their boiling points, and it was demonstrated that for the five hydrocarbons beginning with butane and ending with octane, the difference in boiling points between successive members decreased gradually from 37° to 25°. Furthermore, the temperature interval between the differences for each successive pair, beginning with the pair butane-pentane, were constant and equal to 4°. But, the intervals from octane to dodecane and from dodecane to hexadecane were almost the same, 76°, or 4 x 19°, indicating that with the higher, long-chained members, the difference from member to member had become smaller and almost constant.

Interesting though these regularities were, more interesting to Baeyer (17) were the irregularities which he found in comparing the melting points of successive homologs of acetic acid, for, as the length of the carbon chain increased, the melting points alternated, the odd-carboned acid having a lower melting point than the succeeding even-carboned acid. However, the melting points of the even-carboned members of the series and those of the odd-carboned members formed two regularly increasing series. For the higher fatty acids, Baeyer compared synthetic margaric acid (C_{17}) with palmitic acid (C_{16}) and found

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(16) Fownes, "Elementary Chemistry," 10th Ed., Henry C. Lea, Philadelphia (1874) p. 474.

(17) Baeyer, Ber., 10, 1286 (1877).

that the relation was the same but the difference smaller; and concluded that the alternation rule held for the higher acids also. As a result of his findings, the author suggested that other homologous series derived from the acids be examined for such alternation, which, if existent, should stimulate interest in determining whether other fundamental physical properties were of alternate value, dependant upon the number of carbon atoms contained in the molecule. As will be shown later, Baeyer's suggestion was indeed realized, for the alternation of physical properties of the fatty acids and derivatives has since been the subject of numerous publications relating to the phenomenon of homology.

In the decade following the appearance of Baeyer's observations on the fatty acids, divers papers concerning the phenomenon of homology as regards the relation between physical properties and structure appeared in the literature. Among these was that of Schroeder (18) who tabulated the data for several groups of compounds where one homologous acid served as the parent for a group, the compounds being the ketone, methyl ester, and acid chloride. From acetic acid, for example, the group was acetone, methyl acetate, and acetyl chloride. Strikingly enough, the boiling points for the members of each group were the same. Therefore, he concluded that the groups $-COCH_3$, $-COOCH_3$, and -COCl were

(18) Schroeder, Ber., 16, 1312 (1883).

equivalent in effect upon boiling point. Furthermore, he demonstrated the presence of an homologuus series, for, as the parent acids increased in chain length, the boiling points of the derived groups increased also.

Shortly afterward, Groshans (19) presented a method for the calculation of the boiling points of the simple ethers up to di-*n*-hexyl ether, and for the normal alcohols of from one to twelve carbon atoms. The calculated values, based on density relations of the members of an homologous series, showed good agreement with those observed. Subsequent papers (20) by the same author extended the calculations to series of nitriles, amines, and alkyl chlorides, and in all cases the calculated boiling points agreed well with those observed.

At about the same time, Gartenmeister (21) in studies of the specific volumes of organic compounds, observed a general and quite regular increase in specific volume with increasing chain length for a large number of homologous esters of fatty acids, including the esters from methyl to octyl of the acids acetic to nonanoic.

Observations similar to those of Gartenmeister were made by Lossen (22), who investigated the relation between molecular volume and

(19) Groshans, *Rec. trav. chim.*, *4*, 153 (1885).

(20) Groshans, *ibid.*, *4*, 248, 258 (1885); *5*, 118 (1886).

(21) Gartenmeister, *Ann.*, *233*, 249 (1886).

(22) Lossen, *Ann.*, *243*, 64 (1888).

chain length for several homologous series, among the members of which were long-chained alcohols, acids, nitriles, and hydrocarbons, including the C_{18} members of all four series. It was shown for these series that an increment of $-CH_2-$ in chain length corresponded to a constant increment in the molecular volume. Also of interest is that Lossen defined homologs as compounds which have the formula $R(CH_2)_nR'$ and differ in constitution only by an increase in the value of n.

Further attention to relations existing between physical properties and structure was given by Dobriner (23) in a study of the boiling points and specific volumes of a series of alkyl ethers, such as methyl propyl ether, methyl butyl ether, and methyl amyl ether. With such homologous ethers, the specific volume changed more regularly than did the boiling point.

During the next few years there appeared the results of several investigations of the variations of melting point with structure, a phenomenon which seemingly had been neglected since Baeyer's (loc.cit.) observations regarding the fatty acids. However, Kipping (24), in the course of an investigation of some long-chained compounds, observed regularities in the melting points of members of homologous series of ketones, oximes, and secondary alcohols. For the series of symmetrical

(23) Dobriner, Ann., 241, 1 (1888).

(24) Kipping, J. Chem. Soc., 63, 465 (1893).

ketones having odd-carboned radicals from C_5 to C_{17}, there was a gradual rise in melting point as chain length increased, but the differences between successive members slowly decreased and became almost constant with the higher members. For the corresponding ketoximes, which melted lower than the ketones, a similar gradation in melting points existed. Likewise, the corresponding secondary alcohols exhibited this phenomenon.

Not long afterward, Cohn (25) pointed out that the alternation in melting points previously observed by Baeyer for the fatty acids, also was observed with the acid amides of from six to fourteen carbon atoms. Furthermore, Cohn found a similar alternation in the α-hydroxy acids of sixteen, seventeen and eighteen carbon atoms; and by extending Kipping's work to include both even- and odd-carboned long-chained alkyl methyl ketones where the long chain varied from C_{12} to C_{17}, he was able to show the alternation phenomenon in this series.

In an attempt to find relations between the melting points of members of different series of homologous compounds, Franchimont (26) came upon several generalizations regarding the change in melting point caused by substitution of one functional group by another, the radical remaining the same. Among these were: the melting point

(25) Cohn, J. prakt. Chem., [2] 50, 38 (1894).

(26) Franchimont, Rec. trav. chim., 16, 126 (1897).

increases if two hydrogen atoms attached to the same carbon atom are replaced by oxygen; the melting point increases if hydrogen is replaced by the hydroxyl or the amino group; a decrease in melting point is observed if hydrogen attached to carbon is replaced by a methyl group. Franchimont also pointed out the application of the preceding generalities to the prediction of melting points of members of one homologous series from those of another.

Another publication concerning melting point regularities was that of Kaufler (27), in which was reported the study of the melting points of an homologous series of aliphatic diamines, $H_2N(CH_2)_nNH_2$, from ethylene diamine to decamethylene diamine. It was observed that an alternation in melting points from even to odd members existed, as had been observed for other series, and that the even members formed a series in which melting points gradually increased with chain length, while the differences between melting points of successive members gradually decreased.

Now the investigations turned again to boiling point relations as evidenced in a publication by Menschutkin (28) concerning the boiling points of series of compounds having regularly varied branching of the aliphatic chain, for example, the isomeric hexyl alcohols. In all the series studied, which included esters, amines, and acids, the boiling

(27) Kaufler, Chem. Ztg., 25, 133 (1901).

(28) Menschutkin, Ber., 30, 2784 (1897).

point decreased with increasing complexity of the chain.

Another paper appearing near the turn of the century was that by Ramage (29), relative to the boiling points of homologous compounds, which contained a brief review of previous work by Walker (30) together with improvements in the equations for calculations of boiling points. Walker's equation had been found to apply only to the boiling points of the normal paraffins from C_7H_{16} to $C_{16}H_{34}$, and even in this series, did not apply very exactly in the case of the lower members. Ramage suggested that the equation held only for the CH_2-CH_2 linkages, and therefore that a deviation would be expected with the lower homologs where the terminal hydrogen atom should have a greater relative influence on the properties of the molecule. Accordingly, he modified the Walker equation, and then was able to calculate with quite good agreement the boiling points of all the normal paraffins, and also those of series of alcohols, aldehydes, and ketones. With the fatty acids, however, the lower members showed great deviation from the calculated values. This was assumed to be due to greater association in the liquid state with the beginning members of the series.

During the same period, a rather exhaustive study of the boiling points of homologous compounds was reported by Young (31). This study

(29) Ramage, *Proc. Cambridge Phil. Soc.*, *12*, 445 (1904).

(30) Walker, *J. Chem. Soc.*, *65*, 193, 725 (1894).

(31) Young, *Phil. Mag.*, [6] *9*, 1 (1905).

also was concerned with the mathematical expression of the boiling points of a series, but from a slightly different standpoint, in that the equation developed by Young served to calculate the boiling point difference between a compound and that one having one more methylene group in the chain, rather than to calculate the boiling point of any one compound from its molecular weight and certain constants. The values calculated for the normal paraffins by Young's equation were in much closer agreement with those observed than were those calculated by Ramage. Similar results were obtained for other series comprising the alkyl halides, ethers, aldehydes, and amines, series in which association was believed not to occur to any great extent. It should be noted that Young designated as homologous, a series of ethers in which one aliphatic radical remained constant while the other was lengthened by successive increments of $-CH_2-$, and also that he postulated that his equation, though inadequate for lower alcohols and acids due to association, might apply to the alcohols and acids of "very high molecular weights" where association should be smaller.

Among other studies of boiling point relationships which were reported at this time was that of Henry, Buelens, and Muset (32), concerned with the boiling points of series of isomeric alcohols. In the series of isomeric octanols it was observed that the boiling point gradually rose as the point of branching was located farther from the

(32) Henry, Buelens, and Muset, Compt. rend., 143, 102 (1906).

hydroxyl group. Furthermore, for the two series of isomeric alcohols of the general formulas, $(CH_3)_2CHCH(OH)C_nH_{2n+1}$ and $(CH_3)_2C(OH)CH_2C_nH_{2n+1}$, it was noted that the boiling points increased regularly as the length of the aliphatic chain, $-C_nH_{2n+1}$, was increased.

Soon afterward, Hinrichs (33) made some observations on the melting points of the aliphatic hydrocarbons relative to the anomalies in the melting points of the even- and odd-carboned members. It was suggested that the alternations in melting points were the mechanical expressions of the oscillation of the center of gravity of the molecule, whereby, for an even-carboned member, the center of gravity was on the geometric axis, but for the odd member, fell on one side of the axis, diminishing the moment of inertia.

Further contribution to the knowledge of the alternation phenomena was made by Biach (34) who found such alternation in melting points to exist in many other series, although not so readily apparent, for example, in the paraffins up to $C_{20}H_{42}$. With the boiling points the variations were less in value, yet frequent in occurrence, as in the alkyl bromides and primary alcohols. Other physical properties in which alternations existed were molecular volume, internal friction, and rotatory power. Biach's explanation of the alternation phenomenon was that atoms and groups of atoms, apparently equivalent, actually

(33) Hinrichs, <u>Compt. rend.</u>, <u>144</u>, 431 (1907).

(34) Biach, <u>Z. physik. Chem.</u>, <u>50</u>, 43 (1904).

possessed variable effects, such that with substitution by various groups, varied residual valences remained. If an H atom used more than one-fourth of the effective valence of a C atom, evidently a CH_3- group had a lower valence than an H, a C_2H_5- group a greater valence than a CH_3-, and so on. Therefore, in an aliphatic chain, an alternation of the influence of successively lengthening groups was exhibited.

A few years later Robertson (35) prepared series of amides, anilides, and p-toluidides of the monobasic fatty acids and pointed out that all these series exhibited an even greater irregularity in melting points than the acids themselves. The alternation effect was explained, somewhat vaguely, as being due to dissymmetry of the molecule.

Most of the investigations cited thus far were concerned with the relationships between physical properties and molecular structure of the members of homologous series. But, as mentioned in the introductory remarks, the members of an homologous series also should exhibit a regularity in their rates of reaction. In regard to the latter, Menschutkin (36) published a summary of the results of an investigation upon the relations existing between the properties of organic isomers and their structure, particularly of alcohols. For the normal-chained

(35) Robertson, J. Chem. Soc., 93, 1033 (1908).

(36) Menschutkin, Chem. News, 100, 293 (1909); Ber., 42, 4020 (1909).

alcohols it was found that the velocity of esterification decreased from ethyl to octadecyl to myricyl (C_{30}) in the ratio 48.4:21.9:15.5, while for isomeric branched-chained alcohols the speed of esterification decreased as the chain became more branched, or as the point of branching fell nearer the hydroxyl group. For the boiling points of the isomeric alcohols the position of the branching side chain was observed to be the determining factor, and not the primary, secondary, or tertiary nature of the alcohol. This conclusion substantiated that of Henry and his co-workers (32).

During the next decade, publications concerned with the regularities in homologous series dealt principally with the relationships between various physical properties and the number of carbon atoms in the aliphatic chain. Among these was that of Sugden (37) in which was proposed an improved equation for the calculation of the boiling points of members of an homologous series. The advantage of the new equation was that it held for the lower members of a series as well as the higher, and in the twenty homologous series examined, the mean departure of the observed value from that calculated was slightly less than two degrees. In the same year, Ferguson (38) reported the development of an equation for the boiling points of the normal paraffins from C_4 to C_{17}. He also proposed an equation for the critical temperatures of the

(37) Sugden, Chem. News, 110, 152 (1914).

(38) Ferguson, Phil. Mag., 29, 599 (1915).

normal paraffins from ethane to decane, and equations for the boiling points of normal alkyl bromides and normal alcohols. Shortly thereafter, Young (39) reported an improvement in his earlier equations for boiling points, together with new relationships between boiling points and critical temperatures in homologous series. Another publication of this period was that of Plummer (40), in which it was reported that a linear equation served for calculating the boiling points of normal primary alcohols, aldehydes, and amines, while other equations were given for ethers and esters where the radicals contained more than one carbon atom.

At about the same time Herz (41) published a compilation of data for several homologous series comprising alcohols, amines, ethers, esters, nitriles, hydrocarbons, and acids, and included in the data the boiling points, critical temperatures, and molecular heats of evaporation. He observed that the proportionality between boiling point and critical temperature held approximately for all the series, both temperatures gradually increasing with the molecular weight.

In addition to the many publications concerned with boiling point regularities, there was also a considerable number relating to

(39) Young, Sci. Proc. Royal Dublin Soc., 15, 93 (1916).

(40) Plummer, Phil. Mag., 32, 371 (1916).

(41) Herz, Z. anorg. allgem. Chem., 95, 253 (1916).

regularities in melting points. Levene and West (42), in reporting the preparation of a series of pure normal aliphatic acids from C_{11} to C_{16}, together with the melting points of the pure acids, called attention to an anomaly existing between the C_{12} and the C_{13} members. In accordance with the general rule of alternation of melting points, the C_{13} member should have melted lower than the C_{12} member; however, it was observed to melt at 51°, while the C_{12} member melted at 48°.

Another study of the melting points of the monocarboxylic acids was reported by Tammann (43), concerned particularly with the alternation phenomenon. Upon the basis of studies of the first two members of the series (formic and acetic acids) Tammann postulated that the observed alternation in melting points might be due to the fact that even-carboned members could exist in two stable crystalline forms, while only one stable form of the odd-carboned members was known.

With Tammann's investigation of the alternation in melting points, the decade which began with Menschutkin's observations regarding reaction velocities was almost at an end. Further contributions had been made toward the development of the concept of homology, despite the inroads which war had made upon organized research. Apparently the existence of homologous series was now well established by the many investigations demonstrating regularities in physical properties and

(42) Levene and West, J. Biol. Chem., 18, 463 (1914).

(43) Tammann, J. Chem. Soc., 112, 441 (1917).

chemical reactivity. However, there still remained several aspects of the homology concept which required further elucidation. One of these was the alternation phenomenon, known to exist in many series. Another was the possibility that chemical reactivity reached a limit as the length of the aliphatic chain increased, and a third was the extent of homology with respect to other physical constants which might exhibit regularities. During the past twenty years, there have been numerous studies of homologous series, the results of which may be classified roughly according to the three broad lines indicated above.

In connection with the alternation phenomenon, Meerwein (44) published the results of an investigation of some reactions of pinacols from which he concluded that the valency requirements of normal alkyl groups diminished with increasing number of carbon atoms. The decrease was not continuous but exhibited a periodicity such that the odd-carboned radicals had greater affinity demands than those with an even number, thereby causing an alternation in properties of the molecule.

Another paper concerned with alternation was that of Timmermans (45) in which it was pointed out that the alternation of melting points between odd and even members was a general phenomenon, and that odd members melted lower than even members in series where the molecule was symmetrical with respect to the center of the chain, as in the paraffins

(44) Meerwein, Ann., 419, 121 (1919).

(45) Timmermans, Bull. soc. chim. Belg., 30, 89 (1921).

and the oxalic acid series. However, this order of alternation was sometimes inverted in series not having such symmetry, for example, the ketonic acids and alkyl halides. It was observed also that the existence of a minimum in melting point for one member of a series other than the first was very general, occurring in the majority of cases at the C_3 member.

A further contribution to the explanation of the alternation phenomenon was made by Cuy (46), who advanced the theory that in an aliphatic chain there was a tendency for the carbon atoms to become alternately positive and negative due to accummulation of either positive or negative charges on alternate carbon atoms. On this basis, the odd-carboned members of a series differed successively by a definite group of atoms and charges, while the even members likewise differed, but by a differently charged increment. Therefore a given property should vary continuously for the two series, odd and even, but not be the same for the two. Thus the melting points of the fatty acids fell on two curves, one for the even members and another for the odd, while as a whole, the series showed alternation from one member to the next. Cuy stated somewhat later (47) that the above theory was an improvement over Tammann's (loc. cit.) since it applied not only to melting point alternation but also to solubility, conductivity, and boiling point

(46) Cuy, J. Am. Chem. Soc., 42, 503 (1920).

(47) Cuy, Z. anorg. allgem. Chem., 115, 273 (1921).

alternations.

Shortly afterward, Pauly (48) offered an explanation of the variation in physical constants of homologous series, based upon the structure of the aliphatic chain. From a number of melting point diagrams he concluded that the even-carboned member always possessed the higher melting point, and that the magnitude of the alternations diminished with increasing chain length. Another study of melting point alternation was reported by Majima, Nagaoka, and Yamada (49), in which it was observed that the melting points of several series of aryl alkyl ketones, having alkyl chains from C_{10} to C_{17}, exhibited alternation. At about the same time, Mach and Stolzenberg (50) observed that the oscillations in heats of combustion, specific heats, melting points, and boiling points in homologous series could be explained by the symmetry properties of the crystal lattice.

Some years later Timmermans (51) defined alternation as the phenomenon by which the melting points of the terms of an homologous series vary by an unequal quantity from one odd term to an even one, and from the latter to the next odd term. The alternation was normal when even terms melted relatively higher than the adjacent odd terms. He

(48) Pauly, ibid., 119, 271 (1921).

(49) Majima, Nagaoka, and Yamada, Ber., 55, 215 (1922).

(50) Mach and Stolzenberg, Z. anorg. allgem. Chem., 120, 24 (1921).

(51) Timmermans, Bull. soc. chim. Belg., 38, 295 (1929).

also stated that there should be general agreement as to the "first term" of a series in order that various homologous series might be compared, and suggested that toluene, not benzene, be regarded as the first member of the aromatic hydrocarbons. Oxalic acid, the first member of the dicarboxylic acids, was to be regarded as the C_2 term of the series. Further observations upon the alternation phenomenon were made by Verkade and Coops (52), based upon studies of the melting points and solubilities of a series of n-monoalkylmalonic acids, including those from ethyl- to n-tetradecyl-. The authors suggested that alternation be called even when it occurred in passing from an even to an odd term, the even term having the relatively higher melting point. Furthermore, if in passing from one term to the next there was a regular alternate increase and decrease in a property, the alternation was defined as complete. According to these definitions, the melting points of the above acids showed complete even alternation while a complete odd alternation occurred in the solubilities in benzene and water. Another publication by the same investigators (53) reported the determination of the molecular heats of combustion at constant pressure for the above series of malonic acids. The alternation phenomenon was observed in these constants for the C_2 to C_5 aliphatic radicals, but there was none in those of C_6-C_{14}.

(52) Verkade and Coops, Rec. trav. chim., 49, 568 (1930).

(53) Verkade and Coops, Proc. Acad. Sci. Amsterdam, 36, 76 (1933).

In some studies of long-chained compounds, Meyer and Reid (54) prepared the normal alcohols from decyl- to octadecyl-, and the corresponding bromides. The melting points of the alcohols did not show detectable alternation, but those of the bromides did.

Another investigation of a series which included several long-chained compounds was that by Carré and Passedouet (55), concerned with the urethans, $CH_3(CH_2)_nCH_2OCONH_2$, where n varied from 1 to 16. The melting point curves indicated an alternation for odd and even numbers of carbons for the members C_1-C_3 and C_6-C_8 (odd greater than even) while the reverse held for the terms C_{11}-C_{16}. However, for the terms C_4-C_6 and C_8-C_{12}, there was no alternation in melting points.

A study of long-chained ketones was reported recently by Oldham and Ubbelohde (56) which included melting point and X-ray data for eight isomers of each of the ketones, $C_{17}H_{34}O$ and $C_{18}H_{36}O$. It was found that the position of the carbonyl group in the chain influenced the melting point, causing a higher melting point when nearer the end of the chain or symmetrically at the center. The structure of the ketones was shown by means of X-ray studies to be very similar to that of the corresponding aliphatic hydrocarbons.

Among the numerous contributions to increased knowledge of

(54) Meyer and Reid, J. Am. Chem. Soc., 55, 1574 (1933).

(55) Carré and Passedouet, Compt. rend., 204, 347 (1936).

(56) Oldham and Ubbelohde, Trans. Faraday Soc., 35, 328 (1939).

physical properties of homologous series which have appeared during the past twenty years is that of Prud'homme (57), who established relations between the boiling points and critical temperatures and pressures in several homologous series. Another comparatively early publication was that of Trillat (58), concerning X-ray studies of the fatty acids. It was found that the spacings between parallel planes of molecules of fatty acids increased approximately 4Å for each -C_2H_4- group in the even-carboned acids, and therefore it was concluded that although the -CH_2- groups were not evenly spaced in the chain, the spaces between every second -CH_2- group were constant.

Many years later, Naherniac (59) investigated the near infra-red spectra of homologous series of alcohols and acids in the vapor state, and found that in the alcohol series the characteristic OH band was gradually displaced toward the longer wave lengths as the homologous series was ascended, a constant position being attained at C_4. However, in the acid series, the band was displaced toward shorter wave lengths.

Further studies of the relations of physical properties of homologous series include that of Merckel (60) who developed equations for the boiling points of normal paraffins, branch-chained paraffins, and

(57) Prud'homme, J. chim. phys., 18, 270 (1920).

(58) Trillat, Compt. rend., 180, 1329 (1925).

(59) Naherniac, Ann. phys., 7, 528 (1937).

(60) Merckel, Proc. Acad. Sci. Amsterdam, 40, 164 (1937).

alkyl halides. He also reported equations for the melting points of the normal paraffins, including those above C_{24}. A more recent paper relative to the correlation of molecular structure and boiling points is that of Kinney (61) in which data are given for calculating the "boiling point numbers" of many of the aliphatic hydrocarbons.

Other physical constants of homologous series which have been investigated recently are heats of combustion and parachor values. Richardson and Parks (62) determined the heats of combustion for several hydrocarbons and alcohols, among which were _n_-hexadecane and _n_-hexadecanol. In connection with the relationship between parachor values and physical constants of homologous series, Lewis (63) suggested equations linking the parachor with the boiling point and critical temperature, which held for non-associated compounds. Heats of combustion for the methyl, ethyl, propyl, and butyl esters of oleic acid were determined by Keffler and McLean (64). Their data indicated that methyl oleate, the first member of the series, possessed an abnormally high energy content. Also determined in this study were the molecular volumes, for which it was shown that the increment of molecular volume corresponding to an addition of $-CH_2-$ to the alcohol residue increased as the homologous

(61) Kinney, _J. Am. Chem. Soc._, _60_, 3032 (1938).

(62) Richardson and Parks, _J. Am. Chem. Soc._, _61_, 3543 (1939).

(63) Lewis, _J. Chem. Soc._, 1056 (1938).

(64) Keffler and McLean, _J. Soc. Chem. Ind._, _54_, 178T (1935).

series was ascended.

In addition to the investigations of the alternation phenomenon and physical constants in homologous series which have been conducted during the past two decades, there also have been numerous investigations of the relationship between chemical reactivity and chain length in homologous series. Among these was the study by Conant and Hussey (65) of the speed of reaction of alkyl chlorides with potassium iodide in acetone, a study which included in addition to the chlorides from ethyl to decyl, those of the C_{12}, C_{14}, C_{16}, and C_{30} normal aliphatic radicals. Upon the basis of these investigations and those of other workers, these authors stated that "in a great variety of reactions a methyl halide is 5 to 20 times more reactive than the ethyl compound, which in turn is only about twice as reactive as the other primary straight chain compounds that do not differ materially from one another, at least as high in the series as $C_{30}H_{61}Cl$."

Further investigation of chemical reactivity in homologous series was made by Ruzicka and Buijs (66), employing the reaction of a series of methyl alkyl ketones with hydroxylamine. It was found that for the series of ketones in which one radical was methyl and the other varied from ethyl to _n_-tetradecyl, the reactivity varied only slightly. The same was true of other series in which ethyl and propyl were substituted

(65) Conant and Hussey, _J. Am. Chem. Soc._, _47_, 476 (1925).

(66) Ruzicka and Buijs, _Helv. Chim. Acta_, _15_, 8 (1932).

for methyl in the preceding series, although here the reaction velocity was less in all cases than that of the corresponding methyl ketone. In a series of cyclic ketones included in this study, a maximum reactivity was observed at the C_6 member. From this member to the C_8 member, reaction velocity decreased rapidly, then it increased again until with the C_{15} cyclic ketone the velocity was equal to that of the C_{16} alkyl methyl ketone.

The relative reactivities of the alkyl iodides were investigated by Mitchell (67) by means of the reaction with sodium guaiacoxide. The eight normal alkyl iodides from methyl to octyl were employed in the investigation, the results of which showed a decrease in reaction rate from methyl to butyl, followed by an almost constant value from butyl through octyl.

Another study of chemical reactivity was made by Palomaa and Leimu (68) in an examination of the reaction of aliphatic acyl chlorides with ethylene chlorohydrin. Here it was found that the rate of reaction decreased with increasing length of the aliphatic chain, at least as far as butyryl chloride.

A few years ago, Abraham, Mowat, and Smith (69) summarized the reactivities of homologous series according to the following classifica-

(67) Mitchell, _J_. _Chem_. _Soc_., 1792 (1937).

(68) Palomaa and Leimu, _Ber_., _66_, 813 (1933).

(69) Abraham, Mowat, and Smith, _J_. _Chem_. _Soc_., 948 (1937).

tion: first, series in which there was a great decrease in reactivity in passing from the first member to the third, then a more gradual decrease along the series, as in the reaction of alkyl halides with sodium methylate; second, series in which there were large alternations in reactivity for the first three or four members, followed by a gradual decrease in reactivity, as in the hydrolysis of aliphatic amides; third, series in which there was an increase in reactivity with increase in chain length, as in the rate of conversion of alkylamino acetates to amides; and fourth, series in which there was a constant reactivity as the chain length increased, as in the addition of HBr to a series of olefins with non-terminal double bonds.

With the preceding consideration of the more recent investigations of chemical reactivity in homologous series, the review of the studies which have led to the development of the concept of homology has been extended to the present time. Therefore it seems advisable at this point to discuss the present concept of homology as derived from the results cited.

It will be observed that in most of the work which has been described homology has signified variation in normal chain structure by successive additions of $-CH_2-$ units to the chain. Furthermore, it will be observed that in any series designated as homologous at least one characteristic group has been a constant feature of each member of the series, and that the characteristic group remained unchanged while the chain to which it was attached increased in length from member to member. Whatever the characteristic group, the members of the homologous series differed from one another only by increments of CH_2- in an aliphatic chain. Therefore the concept of homology recognizes structural homology of this type, limited fundamentally to normal chains. However, this does not eliminate certain branched chains. For example, *iso*-chains can be included in the system by considering the branched element as a terminal *iso*-propyl group and then building a series of homologs by lengthening the remaining normal chain. That is, in the series $X(CH_2)_nY$ where n is at least 1, X might be *iso*-propyl or some other constant branched group. However, the members of such a series will not be homologous with corresponding normal-chained compounds, and therefore the present concept of homology precludes the comparison of normal-chained compounds with branched-chained compounds.

In addition to structural homology, the series studied will be observed to exhibit regularities in physical properties. For the most part, all the physical constants investigated showed a gradual and quite regular change as the carbon chain was lengthened, although in some cases the first members of the series were abnormal. The fact that alternation exists in some of the properties does not invalidate the conclusion that homologs should show physical regularities, for in most cases, alternation was found to be regular in itself. A second aspect of the present concept of homology, then, is a regular variation in physical properties.

Another aspect of homology has been demonstrated in the examinations of the chemical reactivity of series homologous with respect to the preceding qualifications. This aspect is that of the gradual change in reactivity toward a particular reagent as the chain length increased. Here again exists the difficulty arising from the abnormality of the first member as compared with the remainder of the series.

It seems, then, that the present concept of homology embraces regularities of structure, of physical properties, and of chemical reactivity. However, the actual interpretation of any or all of these depends upon the individual, particularly with the regard to the choice of the "first member" of an homologous series. To overcome the latter objectionable feature, the usually accepted first member, such as methanol for the series of normal alcohols, can be included and its abnormality noted, or the lower compounds which do not conform to regularities in properties and reactivity can be omitted altogether.

With regard to the latter, one of the outstanding criticisms of the concept of homology was made by Whitmore (70) upon the basis of the reactions of some lower branched-chained alcohols, especially neopentyl alcohol. Whitmore's contention was that the first few members of a series did not undergo the same types of chemical transformations as did the other members, and therefore that the concept of homology of reaction was incorrect. However, in the light of what has been introduced here as the present concept of homology, Whitmore's criticism was unjust,

(70) Whitmore, "Organic Chemistry," Van Nostrand, New York (1937) p. 102.

for neopentyl alcohol is not a homolog of _n_-amyl alcohol, and therefore should not be expected to undergo the same reactions. Thus the necessity of comparing normal-chained compounds only with other normal-chained compounds is re-emphasized.

A few years ago Locquin (71) discussed the phenomenon of homology at some length and apparently arrived at approximately the same conclusions as have been set forth here. However, Locquin suggested that a homologous series should be based upon a "reference compound" and that the point of insertion or addition of further $-CH_2-$ units should be clearly indicated in that reference compound. For example, from the reference compound styrene, $C_6H_5CH{=}CH_2$, two homologous series can be formed, the one by inserting $-CH_2-$ units between the phenyl group and the carbon atom directly attached to it, and the other by adding $-CH_2-$ increments to the carbon atom of the group $=CH_2$.

A more recent discussion of chemical homology is that by Senior (72), in which there is proposed a classification of homologous compounds patterned upon the classification of mathematical functions. Fundamentally this author's system depends upon the formation of homologs by adding $-CH_2-$ units to basic structures, and therefore it is closely related to the concept presented here. However, Senior recommends that the idea of "like reactions" be omitted from the concept

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(71) Locquin, in Grignard, "Traité de Chimie Organique," Masson, Paris (1935) Vol. I, pp. 826-834.

(72) Senior, _J._ _Org._ _Chem._, _3_, 1 (1938).

altogether.

Hence it seems that in general the commonly accepted significance of the term homology is that which has been developed in the foregoing. If this be true then it appears likely that long-chained compounds should be homologous with respect to those of lower molecular weight. Certainly, the long-chained compounds are structural homologs, and moreover, several examples of homology in their physical properties have been cited. However, conformity to homology of reactions is yet to be more fully demonstrated. This phase will be discussed in the following section.

II. The Extension of the Concept of Homology to Long-Chained Compounds.

The extension of the concept of homology to long-chained compounds depends not only upon their conformity to homology of structure and physical properties but also upon conformity to homology of reactions. Whether or not the latter phase of the concept is applicable to the long-chained compounds can be decided best by a comparison of their reactions with those of the lower structural homologs. In order that such a comparison may lead to valid conclusions both sides of the issue should be considered. Therefore, in the following discussion there is presented evidence both for and against the existence of similarity of reactions throughout an entire series of structural homologs.

Among the series of compounds in which the reactions observed in the lower members apply also to the long-chained homologs is the series of normal aliphatic acids. In this series one of the general reactions is that with the lower alcohols in the presence of hydrogen chloride to form the corresponding esters, and by means of this reaction esters of the acids from formic to melissic (C_{30}) are prepared in good yields (73). Another of the general reactions of the acids is that with thionyl chloride to form the acyl chlorides at least as high in the series as that of tetratriacontanoic acid (C_{34}) (74). Long-chained aliphatic acids of from twelve to eighteen carbon atoms react smoothly with gaseous ammonia at high temperature with the formation of the corresponding nitriles, but this reaction is not successful with the lower acids, perhaps because of their lower boiling points (75). However, a similar technique using a lower temperature is applied to the lower acids for the preparation of amides (76), but this method fails with acids higher than C_{10} due to formation of increasing amounts of the nitriles. The anhydrides of the even-carboned acids from caprylic to stearic can be prepared by heating the acids with acetic anhydride at about 180° (77), and the synthesis of symmetrical aliphatic ketones by

(73) Schwalb, Ann., 235, 137 (1886).

(74) Francis, King, and Willis, J. Chem. Soc., 999 (1937).

(75) Ralston, Harwood, and Poole, J. Am. Chem. Soc., 59, 987 (1937).

(76) Mitchell and Reid, ibid., 53, 1879 (1931).

(77) Holde and Gentner, Ber., 58, 1418 (1925).

distillation of alkaline earth salts of fatty acids is general from acetic acid to stearic acid (78) although the yields are quite low with the higher acids. The aldehydes of the acids from propionic to stearic are prepared by distillation of a mixture of the calcium salt of the acid and calcium formate (79), and again the yields from the higher acids are low.

The preceding reactions of the normal aliphatic acids lead to the formation of several series of derivatives. In general, any one of these series exhibits the same types of reactions for both the lower and higher members. The acid chlorides, for example, react smoothly with aqueous ammonia to furnish the corresponding amides as high as arachidamide (C_{20}) (80), and furthermore, like the lower members, the higher acid chlorides such as stearoyl chloride undergo conversion to substituted amides by reaction with numerous organic bases (81). Lauroyl, palmitoyl, and stearoyl chlorides react smoothly with sodium azide to form respectively, undecyl-, pentadecyl-, and heptadecylamine in high yields (82). This modification of the Curtius degradation also serves to prepare butylamine from valeric acid.

(78) Krafft, Ber., 15, 1713 (1882).

(79) Krafft, Ber., 13, 1413 (1880).

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

(81) Gilman and Ford, Iowa State Coll. J. Sci., 13, 135 (1939).

(82) Naegeli, Grüntuch-Jacobson, and Lendorff, Helv. Chim. Acta, 12, 227 (1929).

Another interesting reaction of long-chained acid chlorides is their conversion to the corresponding esters of enediols under the influence of metallic sodium. Lauroyl chloride, for example, yields the dilaurate of 12-tetracosene-12,13-diol (83). Similarly the lower homolog, butyryl chloride, gives 4-octene-4,5-diol-di-n-butanoate (84). Yet another recent example of the extension of homology to long-chained compounds is the discovery that the higher acid chlorides react with methyl mercaptan to form the corresponding thio esters of the long-chained acids (85). Previously there had been some doubt that this reaction applied to any except the lower acid chlorides.

The long-chained nitriles in general undergo the same types of reactions as the lower structural homologs. Reduction of the nitriles to primary amines by means of sodium and alcohol is a method of preparation of the aliphatic amines throughout at least the first eighteen members of the series (86). Nitriles as high as stearonitrile react with ammonium hydrosulfide to give the corresponding thioamides (87). A slight anomaly is shown in the reaction of long-chained nitriles such

(83) Ralston and Selby, J. Am. Chem. Soc., 61, 1019 (1939).

(84) Basse and Klinger, Ber., 31, 1217 (1898).

(85) Ralston, Segebrecht, and Bauer, J. Org. Chem., 4, 502 (1939).

(86) Rakshit, J. Am. Chem. Soc., 35, 44 (1913); v. Braun and Sobecki, Ber., 44, 1473 (1911).

(87) Ralston, Vander Wal, and McCorkle, J. Org. Chem., 4, 68 (1939).

as lauro- and stearonitrile with aromatic Grignard reagents, for they give good yields of the alkyl aryl ketone upon treatment with approximately one equivalent of phenylmagnesium bromide (88) while the nitriles from acetonitrile to valeronitrile give only fair yields of ketones with four equivalents of phenylmagnesium bromide (89).

Like the lower members of the series the long-chained amides undergo dehydration with phosphorus pentoxide with the formation of the corresponding nitriles (90). In the Hofmann reaction, however, the higher amides exhibit anomalies, for instead of the desired amine, high yields of alkyl acyl ureas are obtained. Stearamide, for example, gives N-_n_-heptadecyl-N'-stearoylurea (91).

The long-chained ketones exhibit generally the same types of reactions as the lower aliphatic ketones. As previously stated, a series of methyl alkyl ketones including methyl tetradecyl ketone showed about the same reactivity toward hydroxylamine (66), forming oximes in all cases. Hexyl _n_-pentadecyl ketone (24) and _n_-undecyl _n_-tridecyl ketone also form oximes, and the oxime of the latter undergoes normal Beckmann rearrangement (92). Long-chained ketones such as stearophenone

(88) Ralston and Christensen, _Ind. Eng. Chem._, _29_, 194 (1937).

(89) Shriner and Turner, _J. Am. Chem. Soc._, _52_, 1267 (1930).

(90) Krafft and Stauffler, _Ber._, _15_, 1730 (1882).

(91) Hofmann, _Ber._, _15_, 761 (1882).

(92) Hollemann and Koolhaas, _Rec. trav. chim._, _58_, 666 (1939).

undergo reduction by the Clemmensen method to give good yields of the expected hydrocarbons, n-octadecylbenzene in this case (93). This reaction also serves for the preparation of hydrocarbons from wholly aliphatic ketones, as in the preparation of n-pentatriacontane from stearone (94). In both cases, the time of reaction must be extended far beyond that normally required for lower homologs.

The reactions of the long-chained aldehydes find very infrequent mention in the literature, but those which are mentioned seem to indicate that the long-chained aldehydes undergo essentially the same reactions as do the lower members. Palmitaldehyde (79) and stearaldehyde (95) form bisulfite addition compounds; and heptadecylic aldehyde (96) forms a semi-carbazone, reduces permanganate, is oxidized by strong agents to margaric acid, and adds hydrogen cyanide to form the expected α-hydroxy-n-heptadecyl cyanide. The higher aldehydes polymerize slowly upon standing, but unlike the lower members of the series, they are quite stable toward atmospheric oxygen.

The few reports of the reactions of the long-chained anhydrides show an anomalous stability toward hydrolysis for these compounds. Palmitic and myristic anhydrides were converted to the corresponding

(93) Mikeska, Smith, and Lieber, J. Org. Chem., 2, 249 (1938).

(94) McCorkle, Doctoral Dissertation, Iowa State College (1938) p.34.

(95) Rosenmund, Ber., 51, 592 (1917).

(96) LeSeur, J. Chem. Soc., 85, 832 (1904).

acids to the extent of only one or two per cent after standing for six months in contact with the atmosphere (97). However, this exceptional behavior might be due to the insolubility of the two compounds in water.

Most of the reactions described thus far stand as affirmative evidence that the concept of homology can be extended to the long-chained compounds. Evidence to the contrary was noted, however, in the direct preparation of amides from acids and ammonia, in the direct preparation of nitriles, and in the Hofmann reaction of long-chained amides. It was pointed out also that anomalies exist in the reaction of nitriles with Grignard reagents and in the stability of the higher acid anhydrides, although an explanation was offered for the latter. In addition to these cases where extension of homology failed or was doubtful, there are other examples which should be mentioned. One of these is that the Reformatsky reaction failed with the α-bromo acids above lauric acid (98). Another is that a modified Strecker reaction for preparing aliphatic disulfonic acids is unsatisfactory for acids above α,ω-decamethylene disulfonic acid (99), chiefly because the long period of time required for higher acids makes its use impractical. This does not mean necessarily that the reaction could not be extended to the higher

(97) Holde and Genter, Ber., 58, 1424 (1925).

(98) McCorkle, Doctoral Dissertation, Iowa State College (1938) p. 106.

(99) Stone, J. Am. Chem. Soc., 62, 571 (1940).

members if time were unimportant, but from the practical standpoint, homology does not apply here. A similar borderline case is that of the acetoacetic ester condensation in which the yield rapidly falls as the series is ascended until it is only thirty per cent in the preparation of α-butyryl butyrate. However, if the alcohol formed in the reaction is continuously removed, the reaction can be applied successfully to the higher members (100).

On the basis of the preceding review of the reactions of numerous types of long-chained compounds, it seems general that the entire concept of homology can be extended from the lower members of an homologous series to the higher members. As would be expected, anomalies occur, but in some of the apparent anomalies a change in the conditions of the reaction removes limitations which have prevented its application to higher homologs. In the latter possibility lies a means of aligning further reactions with those already in accord with the extension of homology, but doubt remains that this is a justifiable means of doing so.

III. The Physiological Effects of Long-Chained Compounds.

A natural consequence of the revival of interest in aliphatic compounds, particularly the long-chained compounds, is the growing

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(100) Briese and McElvain, J. Am. Chem. Soc., 55, 1697 (1933).

proportion of organic research devoted to the investigation of the physiological effects of compounds containing long aliphatic chains. Since the field is rather new, few reports of such investigations have appeared in the literature to date. However, there is a sufficient number to show that work along several lines is in progress, and in the following discussion, examples are given to indicate some of the trends of the research being conducted.

Among the investigations which have been reported are several concerned with the pharmacological properties of long-chained compounds. A study of a series of N-methyl amides of the aliphatic acids from formic to stearic was conducted by D'Alelio and Reid (101), in which it was shown that the eight-, nine-, and ten-carboned members possessed local anesthetic properties, and that all the members higher than N-methylbutyramide had a burning peppery taste which reached a maximum at the ten-carboned amide.

Long-chained barbituric acids also have been investigated to some extent, particularly the 1-n-alkyl-5-ethyl-5-isobutyl-barbituric acids. Buck, Hjort, Ide, and de Beer (102) prepared a series of barbiturates of this type, in which the alkyl radical varied from n-amyl to n-docosyl (C_{22}) and found that the n-amyl homolog showed more rapid action than barbital. Hypnotic action was clearly marked in the n-octyl compound

(101) D'Alelio and Reid, J. Am. Chem. Soc., 59, 110 (1937).

(102) Buck, Hjort, Ide, and de Beer, J. Am. Chem. Soc., 60, 461 (1938).

and was questionably still present in the *n*-decyl homolog. The low solubility beyond this latter compound rendered the pharmacological tests meaningless, but for the lower compounds it was shown that the minimum hypnotic dose was fatal in all cases.

In addition to substituted amides and barbiturates, long-chained sulfanilamide derivatives also have been prepared. Among these is a series of 4-acylaminobenzenesulfonamides (103) in which the acyl amino group includes those of an even number of carbons from C_6 to C_{22}. Unfortunately, no reports of pharmacological tests upon this series have appeared. However, very recently, Crossley, Northey, and Hultquist (104) reported the preparations and testing of several N^1-aliphatic sulfanilamides among which were N^1-*n*-dodecyl-,-*n*-octadecyl-, and -(9-octadecenyl)-sulfanilamide, and 2-sulfanilamidoethyl dodecanoate. In general the N^1-alkylsulfanilamides were decidedly inferior to the corresponding N^1-acylsulfanilamides on experimental streptococcal infections in mice. N^1-*n*-dodecanoylsulfanilamide was reported to have "promising pharmacological properties," but as a class the long-chained compounds were inferior to sulfanilamide itself.

Certain cyclic long-chained compounds have been found to show anesthetic action. Ruzicka (105) prepared a series of polymethylene-

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(103) French Patent 820,546 (1937) [*C*. *A*., *32*, 2958 (1938)].

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

(105) Ruzicka, *Helv*. *Chim*. *Acta*, *20*, 109 (1937).

imines from pentadecamethyleneimine to octadecamethyleneimine and found that the fifteen-carboned member had strong persistent local anesthetic action. This effect was still evident to a slighter extent with the sixteen-carboned member, but disappeared in the seventeen- and eighteen-carboned members.

The physiological action of the long-chained primary amine, _n_-heptadecylamine, was studied by Flaschenträger and Lachmann (106). It was found that injection of the amine hydrochloride into the ventral lymph sac of the frog was fatal, and that intravenous injection in pigs and rabbits was fatal also. Subcutaneous injection in the latter animals caused local necrosis.

In connection with a study of lipophilic chemotherapeuticals, Bergmann and Haskelberg (107) prepared some long-chain-substituted arsenicals such as 4-cetylaminoazobenzene-4'-arsonic acid and 2-stearoylamino-1-(4-arsonobenzeneazo)-naphthalene; the former was found to be of surprisingly low toxicity. Arsanilic acid also was condensed with palmitoyl or stearoyl chloride to form the corresponding substituted amides of the long-chained acids. Other than the mention of the low toxicity of one of the derivatives, no report of the physiological properties of these compounds has appeared.

(106) Flaschenträger and Lachmann, _Z. physiol. Chem._, _192_, 268 (1930).

(107) Bergmann and Haskelberg, _J. Chem. Soc._, 1 (1939).

Another type of long-chained compounds which has shown pharmacological activity is the long-chained quaternary ammonium salts. It was found by Blubaugh and his co-workers (108) that cetylpyridimium chloride was highly bactericidal for virulent organisms <u>in vitro</u>, and compared favorably with well known germicides of the mercurial and phenolic types.

Among other studies concerned with the bactericidal action of long-chained compounds is that of Richardson and Reid (109) on a series of α,ω-di-<u>p</u>-hydroxyphenyl alkanes having two, three, four, five, six, and ten methylene groups between the phenyl groups. The lower members of the group had decided bactericidal properties; but low solubilities, especially in the higher members, made extensive testing impossible. Another investigation of bactericidal properties was made by Adams and his co-workers (110) in regard to synthetic substitutes for the chaulmoogra oils used in leprosy therapy. Some of the compounds found to be most effective <u>in vitro</u> were a series of dialkyl acetic acids, whose potency reached a maximum at the fifteen- and sixteen-carboned members, and cyclohexyl-substituted long-chained acids having eleven and twelve carbon atoms in the chain.

In addition to pharmacological effects, the effects of some long-

(108) Blubaugh, Botts, and Gerwe, <u>J</u>. <u>Bact</u>., <u>39</u>, 51 (1940).

(109) Richardson and Reid, <u>J</u>. <u>Am</u>. <u>Chem</u>. <u>Soc</u>., <u>62</u>, 413 (1940).

(110) Stanley, Coleman, Greer, Sacks, and Adams, <u>J</u>. <u>Pharmacol</u>., <u>45</u>, 149 (1932).

chained compounds upon the senses of taste and smell have been studied to some extent. The existence of a burning taste in the members of the aliphatic N-methylamides has been cited (101). A pungent taste was found by Nelson (111) in a series of long-chained vanillylamides. Vanillylamine was acylated with the acid chlorides from acetyl to dodecoyl to form the corresponding amides. All of the compounds were pungent, a maximum being reached at the nonoyl derivative. In a study of the effect of chain length upon taste, Kichu and Giral (112) prepared betaines of some long-chained amino acids, acids which in themselves were tasteless. The betaine of ω-aminopentadecanoic acid was found to have a bitter taste, while the betaine of the higher homolog, ω-aminoheptadecanoic acid, was tasteless.

With regard to the odor of long-chained compounds, the characteristic pleasant odor of dodecanol and tetradecanol should be recalled, and likewise the sweet odor of the long-chained ester, ethyl stearate. A musk odor is found present in the cyclic long-chained imines prepared by Ruzicka (105), and is also characteristic of many other types of large ring compounds such as lactones, ketones, and anhydrides (113). In such series a camphor-like odor appears at the nine-carboned member,

(111) Nelson, J. Am. Chem. Soc., 41, 2121 (1919).

(112) Kichu and Giral, Z. Physiol. Chem., 231, 208 (1935).

(113) Bell, Synthetic Organic Chemicals, 12, No. 3 (March, 1940); Ziegler, Eberle, and Ohlinger, Ann., 504, 94 (1933); Ruzicka, Stoll, Huyser, and Boekenoogen, Helv. Chim. Acta, 13, 1152 (1930).

then at about the thirteen-carboned member a cedar-like fragrance, and at fifteen or sixteen carbon atoms the musk quality approaches a maximum. Beyond eighteen or nineteen carbons, the odor practically disappears in all the series.

In the course of the investigations described in this thesis, a number of higher homologs of short-chained compounds known to be physiologically active were prepared. It was hoped that the lengthened aliphatic chain might cause a recurrence of maximum potency, such maxima having been observed with increasing chain length in many series, and that the long chains might also aid solubility in body fluids. To indicate some of the types of compounds in which physiological effect increases with increasing chain length, sometimes exhibiting a maximum, several examples are cited.

In a series of _p_-aminophenyl urethans in which the alkyl group varied from ethyl to _n_-octyl, Horne, Cox and Shriner (114) found that the anesthesia caused by the compounds was proportional to the length of the alkyl radical and reached a maximum at the five-carboned member. Duration of injection anesthesia rose from butyl to a maximum at _n_-heptyl, while toxicity reached a maximum at the _n_-hexyl derivative.

As a result of the study of a series of N-alkyl-N'-phenylureas having alkyl groups from methyl to _n_-amyl, Hjort and his co-workers (115)

(114) Horne, Cox, and Shriner, _J. Am. Chem. Soc._, _55_, 3435 (1933).

(115) Hjort, de Beer, Buck, and Ide, _J. Pharmacol._, _55_, 152 (1935).

concluded that the hypnotic potencies increased two-fold for each $-CH_2-$ unit added to the aliphatic portion of the molecule, but they reported no maximum potency.

Another illustration of the occurrence of a maximum in physiological action is the series comprising the lower p-alkoxy acetanilides of which Phenacetin is the p-ethoxy member. Going from methoxy to butoxy, the antipyretic action increased to a maximum at ethoxy, and the blood toxicity dropped to a minimum at the same member (116).

A well known case of maximum bactericidal properties is that found in the series of 4-n-alkyl resorcinols, where the n-hexyl homolog has the greatest antiseptic action, and incidentally, greater action than any C_6 branch-chained member (117).

Other physiological effects such as taste and odor also exhibit maxima in potency in certain series of compounds. A group of piperidides of the fatty acids of from eight to fourteen carbon atoms was prepared by Asano and Kanematsu (118), and the pungency was found to reach a maximum at the nine-carboned member and then to decrease until at the fourteen-carboned member, absolutely no taste was observed.

In the sweet tasting compound, Dulcin (p-ethoxyphenylurea), substi-

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(116) May and Dyson, "May's Chemistry of Synthetic Drugs," 4th Ed., Longmans, Green, and Co., New York (1939), pp 82, 83.

(117) Dohme, Cox, and Miller, J. Am. Chem. Soc., 48, 1688 (1926).

(118) Asano and Kanematsu, J. Pharm. Soc. Japan, No. 531, 375 (1926) /C.A., 20, 2844 (1926)/

tution of a _n_-propyl or _n_-butyl group for the ethyl group caused an abrupt change from a sweet taste to a very bitter taste, with a great increase in toxicity (119). A similar change from sweet to bitter was observed in a series of dihydrazides of _n_-monoalkylmalonic acids (120), for the methyl, ethyl, and _n_-propyl homologs were sweet, while the _n_-butyl member was very bitter. A maximum sweetness was observed with the _n_-hexyl member of an homologous series of alkyl chloromalonamides which comprised the derivatives of the malonic acids from methyl to hexyl (121).

The maximum in the odor of the large ringed compounds already has been mentioned (113). Another series which exhibits a maximum in odor is that of the 2-biphenylyl alkyl ethers. In the series methyl, ethyl, propyl, the ethyl member was found to have the greatest fragrance (122).

In view of the cases which have been cited above, it seems likely that desirable physiological properties may appear again in some of the series as the aliphatic chain is lengthened. However, there remains still the difficulty of the low solubility in water, a characteristic of most of the long-chained members of these series. One solution of the problem is to introduce solubilizing groups into the long-chained

(119) Lorang, _Rec. trav. chim._, _47_, 179 (1928).

(120) Blanksma and de Graf, _ibid._, _57_, 3 (1938).

(121) Dox and Houston, _J. Am. Chem. Soc._, _46_, 1278 (1924).

(122) Brewster and Putnam, _ibid._, _61_, 3083 (1939).

molecules, but it is known that in some cases, introduction of carboxyl or sulfonic groups tends to destroy the physiological activity (116). A better way out of the difficulty would be a means of testing which would give comparable results for both soluble and insoluble homologs. Doubtless, this will be forthcoming, though as yet none has been reported.

IV. Previous Work Along Lines Studied in These Investigations.

Derivatives of Long-Chained Amines. Comparatively few derivatives of long-chained aliphatic amines have been described in the literature, and many of those which have been described are unsatisfactory because of difficulties involved in their preparations, or because of indefinite melting points. Furthermore, a number of the derivatives reported in recent years have appeared in patent citations, at best an unreliable source of data. Hence there exists a need for authentic derivatives of long-chained aliphatic amines.

Turpin (123), one of the first who studied long-chained amines, described several derivatives of *n*-heptadecylamine. He found that carbon disulfide and *n*-heptadecylamine when heated at 100° gave N,N'-di-*n*-heptadecylthiourea which melted at 94°, and that oxidation of the latter with mercuric oxide gave the corresponding urea, which melted at 75°.

(123) Turpin, *Ber.*, *21*, 2486 (1888).

From *n*-heptadecylamine and phosgene, Turpin prepared *n*-heptadecyl isocyanate, and treatment of the latter with aniline gave N-phenyl-N'-*n*-heptadecylurea, which melted at 99°. The corresponding thiourea, which melted at 79°, resulted from the reaction of the amine with warm carbon disulfide, followed by treatment with aniline. Benzoyl chloride and *n*-heptadecylamine yielded N-*n*-heptadecylbenzamide, which melted at 91°; and by the action of potassium cyanate upon the amine hydrochloride, Turpin obtained mono-*n*-heptadecylurea, which melted at 109°.

Jeffreys (124), another of the early investigators of the properties of long-chained amines, reported a number of derivatives of *n*-pentadecylamine, prepared in general by Turpin's methods. Jeffreys described mono-*n*-pentadecylurea, N,N'-di-*n*-pentadecylthiourea, and N,N'-di-*n*-pentadecylurea. These compounds melted respectively at 109°, 88.5°, and 113°. Also reported were N-*n*-pentadecylbenzamide, which melted at 78°; N-phenyl-N'-*n*-pentadecylurea, which melted at 94°; and N-phenyl-N'-*n*-pentadecylthiourea, which melted at 79°. The latter was prepared also by the reaction of the amine with phenyl isothiocyanate.

Some derivatives of unsaturated long-chained amines were prepared by Krafft and Tritschler (125). Among the derivatives of 10-undecenylamine were the mono-benzoyl derivative, which melted at 41-42°, and N-phenyl-N'-(10-undecenyl)-urea, which melted at 48°, and was prepared

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(124) Jeffreys, *Am. Chem. J.*, *22*, 22 (1899). ?

(125) Krafft and Tritschler, *Ber.*, *33*, 3581 (1900).

by the action of phenyl isocyanate upon the amine. 9-Octadecenylamine formed a mono-benzoyl derivative which melted at 63-64°, and with phenyl isothiocyanate, the amine gave N-phenyl-N'-(9-octadecenyl)-thiourea, which melted at 65°. With carbon disulfide at elevated temperature, the amine formed N,N'-di-(9-octadecenyl)-thiourea, which melted at 73°. 13-Docosenylamine formed a mono-benzoyl derivative which melted at 74-75°.

More recently Adam (126) reported the preparation of mono-n-octadecylurea, using potassium cyanate, and gave the melting point of the urea as 111°. Adam and Dyer (80) reported the preparation of mono-eicosylurea, which melted at 111.5°, and N-n-octadecylacetamide (using acetic anhydride), which melted at 79.5-80°.

Naegeli and co-workers (82) described n-undecylamine hydrochloride, n-pentadecylamine hydrochloride, and n-heptadecylamine hydrochloride. These compounds melted respectively at 180°, 164-169°, and 158°. They also reported N-n-undecylacetamide which melted at 62°, and the corresponding acetyl derivatives of n-pentadecylamine and n-heptadecylamine; the melting points were respectively 72° and 62°.

The preparation of N-n-heptadecylbenzenesulfonamide was described by Flaschenträger and Lachmann (106) and its melting point given as 64.7°. N-n-Hexadecyl-p-toluenesulfonamide has been reported (127). The

(126) Adam, Proc. Roy. Soc. (London), 101A, 471 (1922).

(127) German Patent 634,687 (1936) /Chem. Zentr., II, 3947 (1936)7.

melting point was given as 87-88°. Two other examples of sulfonamides derived from long-chained amines were described in the preceding section (104).

A recent patent (128) cited the preparation of aliphatic isocyanates, such as n-octadecyl isocyanate, and their conversion to substituted ureas by reaction with the appropriate amines. For example, n-octadecylamine and n-octadecyl isocyanate gave N,N'-di-n-octadecylurea, which melted at 105-106°. The preparation of monoalkylureas, including those from n-amyl- to n-docosylurea, by the action of nitrourea upon the corresponding amines, has been described by Buck and co-workers (102, 129).

Long-chained aliphatic acid amides having a long-chained aliphatic radical as a substituent on nitrogen are mentioned very infrequently in the literature. N-n-Heptadecylstearamide was reported (82) as a by-product of a Curtius degradation; its melting point was 88°. Also reported (82) was N-n-pentadecylpalmitamide, which melted at 93°. The N-nonylamide of eicosanoic acid was prepared by Furukawa (130) and its melting point reported to be 83.5-84°. Flaschenträger and Lachmann (106) prepared the N-n-heptadecylamide of mono-ethyl sebacate and reported its melting point as 82°.

As far as can be determined, phenyl isocyanate and phenyl isothio-

(128) English Patent 462,182 (1937) [Chem. Zentr., I, 4882 (1937)].

(129) Buck and Ferry, J. Am. Chem. Soc., 58, 854 (1936).

(130) Furukawa, Sci. Papers Inst. Phys. Chem. Research (Tokyo), 19, 39 (1932) [Chem. Zentr., II, 3902 (1932)].

cyanate have not been employed as reagents for characterizing long-chained amines, except in the very few cases cited above. Also neglected, apparently, is the use of *p*-acetaminobenzenesulfonyl chloride to form long-chained sulfonamides by reaction with the appropriate amines. The use of other sulfonyl chlorides also has been mentioned very infrequently with regard to derivatizing long-chained amines.

Tetraalkylammonium salts. Tetraalkylammonium salts generally are derived by addition of an alkyl halide to a tertiary amine (131). Heat is applied to cause the reaction to proceed, higher temperatures being required for the higher molecular weight halides. The recent literature describes a great number of tetraalkylammonium compounds having one or more long-chained aliphatic radicals in the molecule. The compounds are derived from aliphatic amines, aromatic amines, or cyclic tertiary amines. Because so very many compounds of this type have been reported, especially in the patent literature, no attempt is made here to provide a comprehensive review of the field. However, examples are given to indicate some of the types which have received attention.

Cetylpyridinium chloride, the product of the condensation of *n*-hexadecyl chloride and pyridine, was mentioned earlier with regard to its bactericidal action (108). Another quaternary compound which was claimed to have bactericidal action is N,N-diethyl-N-dodecyloxymethyl-

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(131) Hickinbottom, "Reactions of Organic Compounds," Longmans, Green, and Co., New York (1936) p. 300.

3-methoxyphenoxyethylammonium chloride (132).

Karrer (133) prepared n-dodecyl-, n-tetradecyl-, n-hexadecyl-, and n-octadecylpyridinium chlorides by heating pyridine and the appropriate alkyl chloride in a sealed tube for fifteen hours at 110°. Docosyltrimethylammonium bromide was prepared by v. Braun and Buchman (134) by heating docosyl bromide with trimethylamine in benzene at 100°.

As far as can be determined, the only reported long-chained tetraalkylammonium halide having all four long-chained radicals alike is tetra-n-hexadecylammonium iodide. This salt was prepared by Girard and Fourneau (135) by passing gaseous ammonia into molten n-hexadecyl iodide at 200°.

The preparation of the n-octadecyl homolog of the above compound was of interest in this investigation both from the standpoint of homology and as a derivative for tri-n-octadecylamine. It was desired also to examine its properties for possible organometallic character, since certain substituted ammonium compounds, for example, triphenylmethyltetramethylammonium, exhibit reactions typical of the corresponding organoalkali compounds (136).

(132) German Patent 627,880 (1936) [C.A., 30, 6136 (1936)].

(133) Karrer, Helv. Chim. Acta, 21, 223 (1938).

(134) v. Braun and Buchman, Ann., 472, 121 (1929).

(135) Girard and Fourneau, Bull. soc. chim., [4] 37, 1669 (1925).

(136) Gilman, "Organic Chemistry," John Wiley and Sons, New York (1938) Vol. I, p. 444.

Long-Chained Barbituric Acids. The preparation of long-chained barbituric acids has not been studied to any great extent. No barbituric acid having a long-chained radical in the 5-position has been described, and only one publication (102) relative to barbituric acids having long-chained radicals in any other position has appeared.

In the present investigation, interest was centered upon higher homologs of Barbital, 5,5-diethyl-barbituric acid. One ethyl radical was retained while the other was replaced by long-chained groups. The highest homolog of this type yet reported is 5-ethyl-5-*n*-heptyl-barbituric acid (137).

Although the long-chained barbituric acids have not been investigated extensively, numerous long-chained malonic esters have been prepared. Since these are intermediates in the synthesis of the barbiturates, some of the research concerned with the diethyl ethyl-*n*-alkylmalonates is described here.

The preparation of diethyl ethyl-*n*-dodecylmalonate was reported by Stanley, Jay, and Adams (138). It was prepared in the usual manner from the sodio-derivative of diethyl ethylmalonate and dodecyl bromide. The same authors also reported the preparation of diethyl ethyl-*n*-tetradecylmalonate. The *n*-tetradecyl-substituted ester was prepared also

(137) Carnot and Tiffeneau, *Compt. rend.*, *175*, 242 (1922).

(138) Stanley, Jay, and Adams, *J. Am. Chem. Soc.*, *51*, 1261 (1929).

by Brunner and Wiedemann (139) by refluxing n-tetradecyl iodide with the sodio-derivative of diethyl ethylmalonate. Chargaff (140) prepared the n-tetradecyl compound in essentially the same manner, except that a more concentrated reaction mixture was employed. The higher homolog, diethyl ethyl-n-docosylmalonate was prepared by Chargaff from n-docosyl iodide and the appropriate malonic ester.

5,5-Dialkyl-barbituric acids are prepared generally by condensing a substituted malonic ester with urea (or a substituted urea) in the presence of sodium ethylate (141). Usually the reaction is carried out in a suitable pressure vessel at a temperature of 100-110°. In some cases, the di-acid chloride of the appropriately substituted malonic acid has been used in place of the diethyl ester (141), but the yields of barbiturates are lower. Reichert and Wilke (142) prepared barbiturates by heating a concentrated reaction mixture to about 150° under reflux, and Buck and his co-workers (102) prepared the long-chained barbiturates by refluxing an alcoholic solution of the reactants for several hours.

Homologs of Phenacetin. Phenacetin, N-(p-ethoxyphenyl)acetamide,

(139) Brunner and Wiedemann, Monatsh., 66, 438 (1935).

(140) Chargaff, Ber., 65, 745 (1938).

(141) Fischer and Dilthey, Ann., 335, 334 (1904); Dox and Yoder, J. Am. Chem. Soc., 44, 1578 (1922).

(142) Reichert and Wilke, Arch. Pharm., 276, 596 (1938).

was prepared by Hinsberg (143) from *p*-acetaminophenol and ethyl iodide in the presence of strong sodium hydroxide solution. Hinsberg also prepared the propyl and isoamyl analogs in the same manner. N-(*p*-*n*-amoxyphenyl)acetamide, the highest reported homolog of Phenacetin, was prepared by Spiegel and Sabbath (144) by acetylation of *p*-aminophenyl *n*-amyl ether. The *n*-amyl *p*-nitrophenyl ether used as starting material was prepared from potassium *p*-nitrophenate and *n*-amyl bromide in an autoclave at 180°, and the nitro ether then was reduced with tin and hydrochloric acid to the amino ether. Incidentally, *n*-amyl *p*-nitrophenyl ether is the highest reported ether of that series.

Neither long-chained-alkyl *p*-nitrophenyl ethers nor the corresponding *p*-acetaminophenyl ethers have been described in the literature. However, some long-chained-alkyl phenyl ethers have been reported. Eijkman (145) prepared *n*-hexadecyl phenyl ether by heating *n*-hexadecyl iodide with potassium phenate in an autoclave at 140°, using a mixture of ligroin and absolute alcohol as the solvent. *n*-Decyl phenyl ether was prepared by Komppa and Talvitie (146) by boiling an alcoholic solution of sodium phenate and *n*-decyl iodide.

Homologs of Dulcin. Dulcin, *p*-ethoxyphenylurea, was prepared by

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(143) Hinsberg, *Ann.*, *305*, 278 (1899).

(144) Spiegel and Sabbath, *Ber.*, *34*, 1942 (1901).

(145) Eijkman, *Rec. trav. chim.*, *12*, 182 (1893).

(146) Komppa and Talvitie, *J. prakt. Chem.*, [2] *135*, 199 (1932).

Berlinerblau (147) from *p*-phenetidine hydrochloride and potassium cyanate. The *n*-amyl homolog, *p*-*n*-amoxyphenylurea, was prepared by Spiegel and Sabbath (*loc. cit.*) by heating the corresponding amine hydrochloride with urea. The *n*-amyl compound is the highest recorded homolog of Dulcin, and was reported to be both bitter and toxic.

The long-chained-alkyl *p*-nitrophenyl ethers prepared in the present investigation served as starting materials for the higher homologs of Phenacetin and for those of Dulcin. Direct preparation of homologs of Phenacetin by forming the long-chained ether of *p*-acetaminophenol was unsatisfactory.

Dihydrazides of Long-Chained-Alkyl Malonic Acids. Curtius (148) prepared the dihydrazide of malonic acid from diethyl malonate and hydrazine hydrate at 120° in a sealed tube. He did not investigate the taste of the derivative. Likewise Bülow (149), who prepared the dihydrazide of methylmalonic acid, did not observe whether any taste was present. Some years later, Curtius (150) reported the preparation of the dihydrazide of *n*-propylmalonic acid by refluxing diethyl *n*-propylmalonate with hydrazine hydrate, but again no taste was reported.

The sweet taste of the *n*-alkylmalonic acid dihydrazides

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(147) Berlinerblau, *ibid.*, [2] *30*, 103 (1884).

(148) Curtius, *ibid.*, [2] *51*, 187 (1895)

(149) Bülow, *Ber.*, *39*, 3372 (1906).

(150) Curtius, *J. prakt. Chem.*, [2] *125*, 225 (1930).

/$RCH(CONHNH_2)_2$/ was described first by Blanksma and de Graaf (120) who reported the preparation of the dihydrazides of malonic acid and of methyl-, ethyl-, n-propyl-, and n-butylmalonic acids, and found that the first four compounds possessed a sweet taste. The dihydrazides were prepared by heating a concentrated alcoholic solution of hydrazine hydrate and the appropriate diethyl n-alkylmalonate for several hours at 100° in a sealed tube. The n-butyl compound is the highest homolog described in the literature.

Numerous mono-long-chain-substituted malonic esters, the starting materials for the long-chained dihydrazides, have been prepared by customary procedures. Diethyl n-dodecylmalonate was prepared by Rothstein (151) from n-dodecyl bromide and the mono-sodio-derivate of diethyl malonate. A series of mono-long-chain-substituted malonic esters was prepared by Verkade and Coops (52). The substituted esters included those from n-decyl to n-tetradecyl, and were prepared by condensing the alkyl bromides with diethyl sodiomalonate in boiling alcohol. Brigl (152) prepared diethyl n-hexadecylmalonate by esterification of n-hexadecylmalonic acid, and several workers (80, 153) have reported the preparation of diethyl n-octadecylmalonate from octadecyl iodide. However, this ester was never isolated, but was converted directly to the

(151) Rothstein, Bull. soc. chim., /5/ 2, 80 (1935).

(152) Brigl, Z. physiol. Chem., 95, 170 (1915).

(153) Bleyburg and Ulrich, Ber., 64, 2504 (1931); Meyer, Brod, and Soyka, Monatsh., 34, 1132 (1913).

corresponding acid. The preparation of diethyl n-docosylmalonate from n-docosyl iodide was described by Meyer and co-workers (153) and by Levene and co-workers (154).

Long-Chained Azo Dyes. Few azo dyes containing long-chained aliphatic radicals have been described in the literature. A patent (155) granted to Sulzberger reported the preparation of a series of long-chained azo dyes from N-aryl-substituted aliphatic amides such as stearanilide. The anilides were nitrated (para), reduced, and diazotized, and the resulting diazonium salts were coupled with phenols or naphthols to give products which varied in color from yellow to intense red. In addition to stearanilide, the anilides of palmitic, oleic, erucic, and brassidic acids were found suitable for use. Diazotization was effected by means of sodium nitrite and glacial acetic acid, but details of the procedure and constants of the compounds obtained were not reported.

In connection with their investigation of lipophilic chemotherapeuticals, Bergmann and Haskelberg (107) prepared some long-chained azo dyes. Stearoyl chloride and benzeneazo-β-naphthylamine when heated with potassium carbonate yielded 1-benzeneazo-2-stearoylaminonaphthalene, which melted at 88°. In the same way, 4-benzeneazo-1-stearoylamino-

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(154) Levene, West, Allen, and Van der Scheer, J. Biol. Chem., 23, 73 (1915).

(155) German Patent 188,909 (1906) [Chem. Zentr., II, 1668 (1907)].

naphthalene was prepared from stearoyl chloride and benzeneazo-α-naphthylamine. The dye melted at 140.5°.

Fiertz-David and Kuster (156) prepared a series of 1-acylamino-7-hydroxynaphthalenes, in which the acyl group varied from decanoyl to nonadecanoyl, and coupled them with diazotized aniline-2,5-disulfonic acid to form the corresponding azo dyes. For example, by treating a cold alkaline solution of 1-stearoylamino-7-hydroxynaphthalene with a cold acidic solution of diazotized aniline-2,5-disulfonic acid, and then adding alkali, sodium 2'-hydroxy-8'-stearoylaminonaphthalene-1'-azobenzene-2,5-disulfonate was obtained. The sodium salts were very soluble in water, and since they were used as such, no melting points of the acid forms of the dyes were reported.

The last two investigations did not involve the diazotization of compounds containing long-chained aliphatic radicals, and although Sulzberger's work was concerned with diazotization of long-chained compounds, the procedure was not described. Therefore it was the purpose of the present work to develop a method for diazotizing and coupling long-chain-substituted aromatic amines, such as p-dodecoxyaniline [$\underline{n}$-$C_{12}H_{25}OC_6H_4NH_2$]. It was hoped that the dyes might serve as derivatives for the corresponding amines and also that they might find application as therapeutic agents or as coloring agents.

Sulfonation of Long-Chained Amines. Sulfonation of long-chained

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(156) Fiertz-David and Kuster, Helv. Chim. Acta, 22, 82 (1939).

amines has hot been described in the literature, and indeed, few reports of sulfonations of long-chained compounds of any type have appeared. Apparently no attention has been given to the sulfonation of wholly aliphatic long-chained compounds, and long-chained compounds containing aromatic nuclei usually are found to undergo sulfonation in the aromatic portion rather than in the aliphatic chain.

Krafft (157) obtained a monosulfonic acid from both n-hexadecyl- and n-octadecylbenzene. That sulfonation took place in the phenyl group was shown by converting the sulfonic acids to phenols by means of alkaline fusion. Adam (158) and Seidel and Engelfried (159) repeated the sulfonation of n-octadecylbenzene but did not prove the position of the sulfonic group, other than to show it was in the aromatic ring. McCorkle (160), in studies of the sulfonation of p-phenylstearophenone and p-phenoxyphenylstearophenone, found that with sulfuric acid p-phenylstearophenone gave 4-stearoyl-4'-biphenylsulfonic acid, and with chlorosulfonic acid, yielded a trisulfonic acid in which two of the sulfonic groups apparently were in the aliphatic side chain. p-Phenoxystearophenone with sulfuric acid gave a monosulfonic acid in which the sulfonic group was shown to be in one of the aromatic nuclei, although

(157) Krafft, Ber., 19, 2984 (1886).

(158) Adam, Proc. Roy. Soc. (London), 103A, 684 (1923).

(159) Seidel and Engelfried, Ber., 69, 2567 (1936).

(160) McCorkle, Doctoral Dissertation, Iowa State College (1938) pp.98-100.

the position was not established.

The purpose of the attempts to sulfonate tri-*n*-octadecylamine was to introduce water-solubilizing groups into one or more of the aliphatic radicals. If a satisfactory method were developed, then that method might be applicable for introducing sulfonic groups into the aliphatic portions of other long-chained compounds.

Tetrakis(n-alkylaminomethyl)methanes. The preparation of polyamines of this type has been studied only with low molecular weight amines. van Alphen (161) prepared tetrakis(methylaminomethyl)methane by heating pentaerythrityl bromide with an aqueous alcohol solution of methylamine at 150°, and Litherland and Mann (162) prepared tetrakis-(*p*-toluenesulfonamidomethyl)methane by heating pentaerythrityl bromide with the N-sodium derivative of *p*-toluenesulfonamide. Hydrolysis of the substituted methane with strong sulfuric acid gave tetrakis(aminomethyl)-methane, and the latter, upon treatment with dimethyl sulfate, gave tetrakis(dimethylaminomethyl)methane.

The preparation of tetrakis(*n*-octadecylaminomethyl)methane was undertaken in order to obtain a completely symmetrical long-chained aliphatic polyamine which would be useful for studies of the relation between viscosity and structure. In connection with such studies,

(161) van Alphen, *Rec. trav. chim.*, *57*, 265 (1938).

(162) Litherland and Mann, *J. Chem. Soc.*, 1588 (1938).

Staudinger (163) investigated certain long-chained amines, including N-methyloctadecylamine and others.

Metalation of Long-Chained Compounds. Metalation of long-chained compounds has not been investigated extensively. Gilman and Bebb (164) reported that no metalation of n-hexadecane by n-butylsodium was observed in benzene, petroleum ether, or n-hexadecane itself. However, Webb (165) found that the long-chained ether, n-octadecyl phenyl ether, underwent metalation with n-butyllithium to give (subsequent to carbonation) o-octadecoxybenzoic acid. Metalation of another long-chained ether was studied by Meals (166), who subjected resorcinol di-n-octadecyl ether to the action of n-butyllithium, and upon carbonation of the reaction mixture, obtained a small yield of acidic material, as yet unidentified.

In the present investigations, the metalation of long-chained compounds was undertaken primarily with regard to the extension of the phenomenon of homology to the higher members of certain series. Gilman and co-workers (167) reported the metalation of diphenylamine with n-butyllithium; subsequent to carbonation, N-phenylanthranilic acid was isolated. Hence it was of interest to study the metalation of N-ethyl-

(163) Staudinger, Ber., 69, 49 (1936).

(164) Gilman and Bebb, J. Am. Chem. Soc., 61, 109 (1939).

(165) F. J. Webb, unpublished results.

(166) R. N. Meals, unpublished results.

(167) Gilman, Brown, Webb, and Spatz, J. Am. Chem. Soc., 62, 978 (1940).

diphenylamine and of the higher homolog, N-n-dodecyldiphenylamine. These compounds were also of interest in connection with the metalations previously observed with carbazole (168) and N-ethylcarbazole (169), both of which gave monometalation ortho to the nitrogen atom upon treatment with n-butyllithium.

Metalation of n-long-chained-alkylbenzenes was intended to provide information on the structure of compounds obtained by the Friedel-Crafts alkylation of benzene. Metalation in the aliphatic side chain might aid in determining whether rearrangement of the normal long chain of the alkyl halide had occurred during the course of the alkylation reaction.

Since methyl phenyl sulfide gave lateral metalation with n-butyllithium, whereas ethyl phenyl sulfide gave metalation in the ortho-position of the phenyl group (170), it was of interest to investigate the metalation of a n-long-chained-alkyl phenyl sulfide, such as phenyl n-tetradecyl sulfide.

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(168) S. M. Spatz, unpublished results.

(169) Gilman and Kirby, J. Org. Chem., 1, 146 (1936).

(170) Gilman and Webb, J. Am. Chem. Soc., 62, 987 (1940).

EXPERIMENTAL

I. Derivatives of n-Octadecylamine.

A. Preparation of n-Octadecylamine.

1. Wet reduction of Stearonitrile. Twenty-five grams (0.094 mole) of stearonitrile (171) was dissolved in 275 cc. of pure butanol contained in a one liter, three-necked flask, fitted with a long reflux condenser and a 12 mm. glass tube about ten inches long for introduction of sodium. To this solution, 15.2 g. (0.66 g. atom) of sodium, cut into small pieces, was added fast enough to maintain refluxing. After all the sodium had reacted, the mixture was allowed to cool somewhat, 275 cc. of water was added, and this mixture was refluxed for 3.5 hours. Having been cooled to room temperature, the reaction mixture was transferred to a separatory funnel and the lower layer drawn off. The upper layer was steam distilled, leaving a gel-like solid above the residual water. The solid was dissolved in 350 cc. of alcohol and the solution was saturated with hydrogen chloride. Cooling in the refrigerator for two hours gave 21.8 g. of n-octadecylamine hydrochloride, $n\text{-}C_{18}H_{37}NH_2\cdot HCl$. Two and three-tenths grams more was obtained from the filtrate, making the total weight of product 24.1 g. The yield was 83.6%.

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(171) Ralston, Harwood, and Poole, J. Am. Chem. Soc., 59, 987 (1937); McCorkle, Doctoral Dissertation, Iowa State College (1938) p. 56.

To obtain the free amine, 18.2 g. (0.059 mole) of the hydrochloride was mixed thoroughly with 6 g. of lime. The mixture was placed in a 125 cc. modified Claisen flask and warmed until it was molten. Then the amine was distilled under carbon dioxide-free atmosphere, giving 11.3 g. of n-octadecylamine, b.p. 172-173°/2 mm.; the yield being 71% based on the hydrochloride.

2. Catalytic reduction of Stearonitrile (172). Twenty-five grams (0.044 mole) of stearonitrile was placed in the bomb of a Parr Hydrogenator with 5 g. of Raney nickel catalyst. The bomb was closed and ammonia gas was introduced until the gauge pressure in the bomb was 100 lbs./sq.in. Then hydrogen was introduced until the total pressure was 225 lbs./sq.in.; the bomb was heated to 140°, and was rocked at this temperature for 1.5 hours. The product was dissolved in alcohol, the solution filtered, and the filtrate worked up in the same manner as described for the alcohol solution above. The distilled product weighed 20 g., representing a yield of 77.5% of the theoretical.

B. Preparation of derivatives.

1. Preparation of N-n-Octadecylbenzamide, n-$C_{18}H_{37}NHCOC_6H_5$. One gram (0.0037 mole) of n-octadecylamine was dissolved in 20 cc. of dry benzene, and 0.548 g. (0.0039 mole) of benzoyl chloride was added. The

(172) McCorkle, unpublished results.

solution was refluxed for 1 hour, washed with sodium carbonate solution, dilute hydrochloric acid, and water, and dried with sodium sulfate. Evaporation of a small amount of the solvent, followed by cooling gave traces of *n*-octadecylamine hydrochloride, which were removed by filtration. Further evaporation and cooling of the filtrate gave 0.7 g. (51%) of the desired amide as a white crystalline solid, melting at 85-87°.

Anal. Calcd. for $C_{25}H_{43}ON$: N, 3.75. Found: N, 3.79, 3.82.

2. *Preparation of N-n-Octadecyl-p-toluenesulfonamide, p-* $CH_3C_6H_4SO_2NHC_{18}H_{37}$-*n*. Five grams (0.0186 mole) of *n*-octadecylamine and 3.1 g. (0.0163 mole) of *p*-toluenesulfonyl chloride were dissolved in 100 cc. of dry benzene. To the solution was added 25 cc. of 10% sodium hydroxide, and the resultant mixture was refluxed for 1 hour. The layers were separated while hot, the upper (benzene layer) was washed with warm dilute alkali and with water, and then was dried by refluxing with sodium sulfate. The dry filtered solution was cooled in the refrigerator overnight, yielding 5.1 g. of colorless solid, melting at 88-90.5°. This was recrystallized from a 2:1 mixture of pet. ether (b.p. 60-68°) and benzene, to yield 5.0 g. (72.5%) of colorless plates of the amide, melting at 89-91°.

Anal. Calcd. for $C_{25}H_{45}O_2NS$: N, 4.12. Found: N, 3.8, 4.1.

Solubility:		
	60% ethanol	< 0.5 g./100 cc.
	80% ethanol	< 0.5 g./100 cc.
	olive oil	0.8 g./100 cc. in the hot

3. *Preparation of N-(p-acetaminobenzenesulfonyl)-n-octadecylamine,*

p-$CH_3CONHC_6H_4SO_2NHC_{18}H_{37}$-*n*. Two grams (0.00912 mole) of *p*-acetaminobenzenesulfonyl chloride (173) was dissolved in 40 cc. of dry ethylene chloride, and 2.50 g. (0.00928 mole) of *n*-octadecylamine were added to the solution. Then 12 cc. of 10% sodium hydroxide was added, and the mixture was refluxed for 2 hours. The mixture was then cooled to room temperature and filtered, leaving a residue of 4.0 g. of white solid melting at 127-131°. The latter was dissolved in alcohol, the solution boiled with Norit, filtered and cooled, whereupon a deposit of 2.6 g. of white plates appeared. The crystals melted at 130-131° and represented 62.7% of the theoretical yield.

Anal. Calcd. for $C_{26}H_{46}O_3N_2S$: S, 6.85. Found: S, 6.86, 6.99.

Solubility:		
	80% ethanol	< 0.5 g./100 cc.
	olive oil	< 0.5 g./100 cc.

4. *Preparation of N-(p-aminobenzenesulfonyl)-n-octadecylamine,*

p-$H_2NC_6H_4SO_2NHC_{18}H_{37}$-*n*.

a. *Test run.* One-half gram (0.011 mole) of the *p*-acetamino compound (previous preparation) was dissolved in a hot mixture of 10 cc.

(173) Gilman, "Organic Syntheses," Coll. Vol. I., John Wiley and Sons, New York (1932) p. 8.

of acetone, 15 cc. of alcohol, and 10 cc. of 1:1 hydrochloric acid. The mixture was heated to refluxing, and after about 15 minutes, a white flocculent solid began to separate. Refluxing was continued for 1 hour, then the mixture was cooled and filtered, leaving the insoluble material, which was washed several times with ether. The white crystalline product (0.43 g.) melted at 200-215° (I) and apparently was the hydrochloride of the desired p-aminobenzenesulfonyl-derivative. Therefore, (I) was treated with the calculated amount of sodium carbonate in a water-alcohol mixture such that all the reactants were in solution at the boiling point. After having been heated thus for about 1 hour, the mixture was cooled, and deposited a white solid. The latter was extracted several times with hot alcohol, and from the combined extractions there was obtained a white crystalline solid, m.p. 117-119° (II). A portion of (II) was treated with hydrogen chloride gas, yielding a precipitate melting at 200-210°, and when this product was treated with ammonia gas in benzene, (II) was regenerated as evidenced by a mixed melting point. Another portion of (II) was acetylated by refluxing with acetyl chloride in dry benzene for 2 hours. After recrystallization from alcohol, the product melted at 128-130°, and a mixed melting point with the original p-acetamino-derivative showed no depression. Hence it was concluded that the hydrolysis with hydrochloric acid had removed only the acetyl group and that the desired p-amino-compound had been obtained. Several variations of procedure were investigated in order that the compound might be prepared in good yield. The best procedure found is described in the following experiment.

b. *Procedure developed from several runs*. One gram (0.0022 mole) of N-(*p*-acetaminobenzenesulfonyl)-*n*-octadecylamine was dissolved in a mixture of 20 cc. of 1:1 hydrochloric acid, 30 cc. of alcohol, and 20 cc. of acetone. The solution was refluxed gently for 1 hour, cooled, and filtered, yielding 0.9 g. of the hydrochloride of N-(*p*-aminobenzenesulfonyl)-*n*-octadecylamine, or 91% of the theoretical. Without further treatment, the hydrochloride was suspended in a mixture of 30 cc. of benzene and 40 cc. of absolute alcohol, and ammonia gas was introduced, causing evolution of heat and gradual solution of the solid. Finally the mixture was warmed gently until solution was complete, then the solution was cooled to about 10°. The white solid which separated was filtered off and washed with ether, then recrystallized from acetone, giving 0.91 g. (73.6%) of N-(*p*-aminobenzenesulfonyl)-*n*-octadecylamine, melting at 119-121°.

Anal. Calcd. for $C_{24}H_{44}O_2NS$: S, 7.54. Found: S, 7.64, 7.56.

Solubility:	80% alcohol	< 1 part/100
	olive oil	< 1 part/100

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

a. *Preparation of stearoyl chloride* (174). Fifty grams (0.176 mole) of stearic acid (175) was placed in a 200 cc. round-bottomed,

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(174) Directions kindly provided by Dr. A. W. Ralston of the Research Laboratories of Armour and Co., Chicago.

(175) Washed with hot 1:1 hydrochloric acid, then crystallized from acetone.

three-necked flask, fitted with a condenser, stirrer, and dropping funnel, and the flask was heated in an oil bath held at 80-90°. Then with stirring, 24.5 g. (0.201 mole) of purified thionyl chloride (176) was added dropwise to the molten acid during about 40 minutes. At the end of the addition, the reaction mixture was held at 95° for 2 hours with continuous stirring.

The mixture was transferred to a Claisen flask with benzene, and the benzene and excess thionyl chloride were removed under aspirator vacuum, the bath being held at 100°. The temperature of the bath was gradually raised to 165-170°, where it was held until no further distillation occurred. The residual material was distilled at 5 mm., and the fraction boiling at 186-191° taken as product. This weighed 43.3 g., representing 81% of the theoretical yield.

b. Preparation of N-*n*-Octadecylstearamide. One and one-half grams (0.005 mole) of stearoyl chloride and 1.35 g. (0.005 mole + 0.05 g. excess) of *n*-octadecylamine were dissolved in 20 cc. of ethylene chloride, 0.40 g. of pyridine was added, and the solution was refluxed for 4 hours. A white solid, melting at 93-97° was obtained by cooling. This was boiled for 10-15 minutes with 30 cc. of ethyl acetate, in which it was slightly soluble. The mixture was filtered rapidly; the insoluble material left on the filter melted at 93-98°. This material was almost completely dissolved by 75 cc. of boiling ethyl acetate, so

(176) Fieser, "Experiments in Organic Chemistry," Heath and Co., Boston (1935) p. 339.

the small amount of insoluble solid was filtered out and washed twice with hot ethyl acetate. The filtrate was evaporated to 30 cc., and upon cooling, deposited white crystals, melting at 94-97°. The same procedure with ethyl acetate was applied to this product, and thus was obtained 1.1 g. (41%) of N-n-octadecylstearamide, m.p. 96-97°. Anal. Calcd. for $C_{36}H_{73}ON$: N, 2.62. Found: N, 3.04, 3.0.

6. Preparation of N-Phenyl-N'-n-octadecylurea, $C_6H_5NHCONHC_{18}H_{37}$-n. One gram (0.0037 mole) of n-octadecylamine was dissolved in 20 cc. of dry pet. ether (b.p. 60-68°) and 1.0 g. (0.0084 mole) of phenyl isocyanate was added, causing the immediate appearance of a white precipitate. Ten cubic centimeters of benzene was added to make a solution, and the reaction mixture was refluxed for a half-hour. At the end of this time, cooling under the tap caused the separation of a bulky white solid, which was filtered off and washed with cold pet. ether (b.p. 60-68°) and with diethyl ether. The crude product weighed 1.56 g. and melted at 97-100°. It was recrystallized from a mixture of 20 cc. of pet. ether (b.p. 60-68°) and 5 cc. of dry benzene, washed with ether, and dried in a vacuum desiccator. The purified product melted at 99-100°, weighed 1.35 g., and represented a yield of 92.6% of the theoretical. Anal. Calcd. for $C_{25}H_{44}ON_2$: N, 7.21. Found: N, 7.44, 7.40.

7. Preparation of N-Phenyl-N'-n-octadecylthiourea, $C_6H_5NHCSNHC_{18}H_{37}$-n. One gram (0.0074 mole) of phenyl isothiocyanate was dissolved in 15 cc. of dry pet. ether (b.p. 60-68°), and 2.0 g. (0.0074 mole) of

n-octacedylamine was added. The solution was refluxed for 1.25 hours, then cooled to room temperature, whereupon a white crystalline solid was deposited. The latter was removed by filtration, and washed several times with pet. ether (b.p. 60-68°), then with diethyl ether. After two crystallizations from pet. ether (b.p. 60-68°), there was obtained 2.46 g. (82%) of the desired thiourea, m.p. 86.5-88°.

Anal. Calcd. for $C_{25}H_{44}SN_2$: S, 7.92. Found: S, 8.21, 8.25.

II. Derivatives of Di-n-octadecylamine.

A. Preparation of Di-n-octadecylamine (177).

Seventy-five grams (0.282 mole) of stearonitrile was placed in a Parr Hydrogenator bomb (capacity, 500 cc.) with 15 g. of 37 KAF catalyst (178), and hydrogen was admitted until the pressure was 1650 lbs./sq.in. The bomb was heated to 210° and then rocked at that temperature for 2.5 hours. The cooled contents of the bomb were extracted with hot alcohol, and the resulting mixture filtered while hot to remove the catalyst. To the filtrate was added enough hot alcohol to make the total volume of solution about one liter. The solution was thoroughly cooled, and the di-n-octadecylamine filtered off. The product weighed 57.4 g. (78% of the theoretical yield), and melted at 70-72°.

(177) McCorkle, Doctoral Dissertation, Iowa State College (1938) p. 69.

(178) Adkins, Folker, and Conner, J. Am. Chem. Soc., 54, 1138 (1932).

B. Preparation of Derivatives.

1. Preparation of N-(p-toluenesulfonyl)-di-n-octadecylamine, $p\text{-}CH_3C_6H_4SO_2N(n\text{-}C_{18}H_{37})_2$. Two and two-tenths grams (0.00421 mole) of di-n-octadecylamine and 0.732 g. (0.00385 mole) of p-toluenesulfonyl chloride were dissolved in 40 cc. of benzene and 10 cc. of 10% sodium hydroxide was added. The mixture was refluxed for 5 hours, then, while still warm, the benzene layer was separated, washed with sodium carbonate solution (2%) and with water, and dried over sodium sulfate. One-fourth of the benzene was now removed by distillation, and hydrogen chloride was introduced into the remaining solution, causing precipitation of 0.57 g. of the amine hydrochloride (m.p. 175-178°), which was removed by filtration. The filtrate was concentrated somewhat and enough methanol was added to produce a slight turbidity while hot. When cooled, the solution deposited a mass of glistening white plates, which were filtered off, redissolved in benzene-methanol mixture, treated with Norit, and reprecipitated by cooling. The product thus obtained melted at 59-61° and weighed 0.66 g., a yield of 23.2%.

Anal. Calcd. for $C_{43}H_{81}O_2NS$: S, 4.74. Found: S, 4.56, 4.54.

Solubility:		
	80% alcohol	$<$ 1 g./100 cc.
	olive oil	1.2 g./100 cc.

2. Attempt to prepare N,N-Di-n-octadecylstearamide, $C_{17}H_{35}CON(n\text{-}C_{18}H_{37})_2$. Two grams (0.00384 mole) of di-n-octadecylamine and 1.3 g. (0.0043 mole) of stearoyl chloride were dissolved in 20 cc. of hot

pyridine. The solution was refluxed for 2 hours, then cooled in an ice bath, whereupon a mass of almost colorless plates separated. These were filtered off, and washed several times with ether, after which the weight was 1.89 g., the melting range, 135-169°. The solid product was recrystallized from 20 cc. of alcohol, and thereby, 1.71 g. of di-n-octadecylamine hydrochloride, m.p. 167-171°, was obtained.

The original filtrate, after removal of ether, was poured into 50 cc. of 50% alcohol, the mixture was heated for a short time on the steam bath, then cooled in ice water. The brown waxy solid which remained on the surface was skimmed off and precipitated from ethylene chloride, giving a white powder, m.p. 68-70°. Since this value was close to the melting point of the amine (70-72°), a portion of the solid was dissolved in alcohol and treated with hydrogen chloride in an attempt to precipitate the amine hydrochloride. However, instead of the expected hydrochloride, ethyl stearate (m.p. and mixed m.p. 33-34°) was obtained by cooling the solution. Therefore, the solid which melted at 68-70° was probably stearic acid. It was identified as stearic acid by preparation of stearanilide (m.p. and mixed m.p. 93-94°). Several other runs with variation in procedure gave none of the desired amide.

3. Attempt to prepare N-(p-acetaminobenzenesulfonyl)-di-n-octadecylamine, $p\text{-}CH_3CONHC_6H_4SO_2N(n\text{-}C_{18}H_{37})_2$. One and sixty-five hundredths grams (0.00314 mole) of di-n-octadecylamine and 0.446 g. (0.00317 mole) of p-acetaminobenzenesulfonyl chloride were dissolved in 20 cc. of

ethylene chloride; 6 cc. of 10% sodium hydroxide was added, and the mixture was refluxed for 4 hours. Upon cooling, the reaction mixture yielded a white solid, which was crystallized from alcohol and melted at 68-71°. A mixed-melting point determination with di-n-octadecylamine showed no depression. However, when a portion was treated with gaseous hydrogen chloride in benzene, it gave a product which melted at 70-80°, while di-n-octadecylamine, under the same conditions, gave a solid melting at 170-175°.

Therefore the solid which melted at 68-71° was recrystallized from 2:1 alcohol-acetone, yielding a product melting at 71°. This was analyzed for sulfur.

Anal. Calcd. for $C_{44}H_{82}O_2N_2S$: S, 4.44. Found: S, 3.70, 3.71. Apparently, then, the solid was a mixture of di-n-octadecylamine, the amine hydrochloride, and the desired product, so another run was made to seek a better method of working up the reaction mixture. However, this, and several subsequent runs, in which variation in time of refluxing, manner of working up, etc., were employed, gave only products which melted over a range between 58° and 71°, and could not be brought to a sharp melting point.

4. Attempt to prepare N-Phenyl-N'-di-n-octadecylurea, $C_6H_5NHCON(n\text{-}C_{18}H_{37})_2$. One gram (0.00192 mole) of di-n-octadecylamine and 0.95 g. (0.007 mole) of phenyl isocyanate were dissolved in 11 cc. of pet. ether (b.p. 60-68°) and the solution was refluxed for one-half hour, then

cooled in ice water. A small amount of material melting at 71-95° separated. This was removed by filtration, and the filtrate was evaporated to a pale brown oil. The latter was taken up in 90% alcohol, the solution was cooled, and a small amount of solid, melting at 44-48°, was obtained. This was crystallized from methanol - alcohol mixture, but still melted over a range. Crystallization from several other solvents gave no sharply melting product. Repetitions of the experiment with variations gave only traces of product melting over about the same range, and no solvent or mixture of solvents was found which yielded a sharply melting compound.

II. Attempt to Prepare Tetra-n-octadecylammonium Iodide.

A. Preparation of Tri-n-octadecylamine.

1. Preparation of n-Octadecyl Chloride.

a. Preparation of Ethyl Stearate (179). One hundred thirteen and six-tenths grams (0.4 mole) of stearic acid was dissolved in 140 cc. (110 g.; 2.4 mole) of warm absolute alcohol contained in a 1 liter three-necked flask. The flask was fitted with a reflux condenser and an inlet tube (8 mm.) which reached almost to the bottom of the flask. Dry hydrogen chloride was passed into the inlet tube until the solution was saturated. This required about 2 hours. The warm reaction mixture then

(179) Prepared according to directions obtained from Dr. A. W. Ralston of the Research Laboratories of Armour and Co., Chicago.

was poured into 200 cc. of warm water and the lower (aqueous) layer was drawn off. The latter was cooled, and then was extracted with ether, and the ether extract was added to the original upper layer. The resulting ether solution was washed several times with 5% sodium hydroxide, then with water, and was dried over sodium sulfate. The ether was removed from the dry solution and the residue was distilled under vacuum to give 107.3 g. (86%) of ethyl stearate, b.p. 180-185°/2.5 mm.

b. Preparation of n-Octadecanol (180). Forty-seven and eight-tenths grams (0.153 mole) of ethyl stearate and 4.5 g. of 37KAF catalyst were placed in the bomb of a Parr Hydrogenator and hydrogen was admitted until the pressure within the bomb was 1640 lbs./sq.in. The temperature was raised to 260°, and the bomb was rocked at that temperature for 5 hours. After the bomb had cooled, the contents were extracted with about 400 cc. of hot acetone, and the acetone solution was filtered to remove the catalyst. The filtrate was cooled in the refrigerator and deposited 33.8 g. (81.6%) of n-octadecanol, m.p. 56-58° (181).

c. Preparation of n-Octadecyl Chloride. n-Octadecyl chloride was prepared from n-octadecanol and thionyl chloride according to directions given by McCorkle (182). In a typical run, 27.1 g. (0.1 mole) of

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(180) D. F. Pontz, unpublished results; procedure based on general directions given by Adkins, "Reactions of Hydrogen," University of Wisconsin Press, Madison (1937).

(181) Recently R. N. Meals found (unpublished results) that n-octadecanol prepared in this way usually contains an appreciable amount of n-octadecyl stearate, from which the octadecanol can be separated by vacuum distillation.

(182) McCorkle, Doctoral Dissertation, Iowa State College (1938) p. 70.

n-octadecanol gave 25 g. (86.5%) of n-octadecyl chloride, b.p. 176-179°/3.5 mm.

2. Preparation of Tri-n-octadecylamine. Oftentimes the previously reported method (183) for the preparation of tri-n-octadecylamine gives a product which melts over a considerable range and which cannot be purified by repeated crystallizations. The present method is essentially like the previous one, but differs in the manner of working up the reaction mixture.

Twenty-six grams (0.0498 mole) of di-n-octadecylamine and 8.0 g. (0.0276 mole) of n-octadecyl chloride were mixed in a 250 cc. Erlenmeyer flask fitted with an air condenser, and the mixture was heated at 175-180° for 8 hours. The solid obtained by cooling was crushed thoroughly under absolute ether, and 12.1 g. of di-n-octadecylamine hydrochloride was filtered from the ethereal mixture. The ether was removed from the filtrate and the residual solid was treated for 1 hour with 250 cc. of boiling 1% potassium hydroxide (in 50% alcohol). The mixture was cooled, the liquid was poured off, and the residue was treated twice more in the same way. The crude amine thus obtained was crystallized from ethyl acetate to give 16.9 g. of product which melted at 52-69°. This was suspended in 200 cc. of hot absolute alcohol and dry hydrogen chloride was introduced, causing the solid to dissolve. Treatment with Norit, followed by cooling, gave 16.3 g. of crude tri-n-octadecylamine

(183) McCorkle, *ibid.*, p. 71.

hydrochloride, m.p. 93-95°. This product was treated again with Norit in alcohol; subsequent to filtration and cooling, there was obtained 16 g. (79.6%) of tri-*n*-octadecylamine hydrochloride, m.p. 94-95°. To obtain the free base, the hydrochloride was treated with two 100 cc. portions of boiling 5% potassium hydroxide (in 50% alcohol), and the residual solid was crystallized twice from ethyl acetate to give 15.1 g. (78.5%) of tri-*n*-octadecylamine, m.p. 53-54°.

B. *Preparation of n-Octadecyl Iodide.* *n*-Octadecyl iodide was prepared by the method of Bleyburg and Ulrich (153). One gram (0.0312 mole) of red phosphorus and 7.8 g. (0.0307 mole) of iodine were mixed in a 125 cc. Erlenmeyer flask and heated to 100° under an air condenser. Then 15.6 g. (0.0576 mole) of *n*-octadecanol was added and the temperature was raised to 175-185°, where it was maintained for 1 hour. The reaction mixture was cooled, then 50 cc. of hot pet. ether (b.p. 60-68°) was added, and the hot mixture was filtered through glass wool. While still warm the filtrate was washed with 5% sodium bisulfite and with water, and then was dried over sodium sulfate. The dry solution was boiled with Norit and filtered, most of the solvent was removed, and the remaining solution was cooled under the tap, whereupon *n*-octadecyl iodide was deposited as a white crystalline solid. The yield of *n*-octadecyl iodide was 18.9 g. (86.3%); m.p. 33-34°.

C. *Attempt to Prepare Tetra-n-octadecylammonium Iodide.* Two grams (0.0026 mole) of tri-*n*-octadecylamine and 1.0 g. (0.00264 mole) of n-octadecyl iodide were mixed in a 50 cc. Erlenmeyer flask fitted with an air condenser, and the mixture was held at 185-195° for 7.5 hours. The reaction mixture was cooled and the resulting brittle solid was crushed under 50 cc. of absolute ether until finely powdered. The powdered solid was filtered off and washed with cold ether, after which it weighed 1.85 g. and melted at 76-80°. Crystallization from absolute alcohol (Norit) gave 1.8 g. of white solid, m.p. 79-81°. A qualitative analysis showed the presence of nitrogen and iodine. Upon standing exposed to the atmosphere for a short time, the solid assumed a pale yellow color; therefore it was recrystallized from absolute alcohol, and dried in a vacuum pistol (weight, 1.76 g.; m.p. 79.5-81°) (I).

Anal. Calcd. for $(C_{18}H_{37})_4NI$: I, 10.99. Found: I, 13.41, 13.34.

It was noticed that the per cent of iodine found was close to that calculated for tri-n-octadecylamine hydroiodide (Calcd. for $(C_{18}H_{37})_3N \cdot HI$: I, 14.08); therefore the possibility that (I) might be the hydroiodide of the tertiary amine was investigated.

Two-tenths of a gram of (I) was boiled with 0.1 g. of potassium hydroxide in 15 cc. of alcohol for about 1 hour. Then dry hydrogen chloride was introduced and the resulting solution was filtered, giving a clear filtrate which was deep amber in color. Subsequent to cooling in the refrigerator, the filtrate deposited 0.15 g. of pale yellow solid which melted at 91.5-94° (II). This was treated with Norit in boiling absolute alcohol and gave 0.12 g. of white solid which melted at 93-95°. A mixed melting point showed the solid to be tri-n-octadecylamine hydrochloride.

The alcoholic filtrate from (II) was decolorized by sulfur dioxide water; therefore free iodine was thought to be present. A test on potassium iodide in warm slightly diluted alcohol showed that addition of hydrogen chloride caused liberation of iodine. Therefore it was concluded that the addition of hydrogen chloride to the alkaline suspension of (I) had liberated iodine from potassium iodide, in turn produced by the action of potassium hydroxide upon tri-n-octadecylamine hydroiodide.

The presence of hydrogen iodide, necessary for the formation of the amine hydroiodide, was believed to be the result of decomposition of n-octadecyl iodide into octadecene and hydrogen iodide. However, no evidence of unsaturation could be found in the original ether filtrates of the reaction mixture. Nevertheless, the iodine analysis of (I) and the conversion of (I) to the hydrochloride were good evidence that (I) was tri-n-octadecylamine hydroiodide.

III. Long-Chained Barbituric Acids.

A. Preparation of Diethyl Ethyl-n-alkylmalonates.

1. Preparation of n-Alkyl Bromides.

a. Preparation of n-Dodecyl Bromide (184). To a mixture of 72.5 g. (0.376 mole) of 42% hydrobromic acid and 26 g. of concentrated

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(184) Directions from Gilman, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, New York (1932) p. 27.

sulfuric acid contained in a 200 cc. round-bottomed flask was added 37.3 g. (0.2 mole) of n-dodecanol. The mixture was refluxed for 6.5 hours, then poured into about 200 cc. of water. The oily layer was separated and washed once with 15-20 cc. of cold concentrated sulfuric acid, then with water. The residual oil was dissolved in about 100 cc. of ether, the solution was washed with 5% sodium carbonate, and then was dried over calcium chloride. After the ether had been removed, the residue was distilled under vacuum to give 42 g. (85.9%) of n-dodecyl bromide, b.p. 120-123°/2 mm.

b. Preparation of n-Tetradecyl Bromide (185). One hundred and twenty-six grams (0.747 mole) of cold 48% hydrobromic acid was added to 40 g. of ice-cold concentrated sulfuric acid in a 500 cc. round-bottomed flask. To the acid mixture was added 85.2 g. (0.4 mole) of n-tetradecanol, and the mixture was boiled for 7 hours. The product was worked up in the same manner as n-dodecyl bromide. The yield of n-tetradecyl bromide was 85 g. (77%); b.p. 175-179°/19 mm.

c. Preparation of n-Hexadecyl Bromide (186). Eighty-eight and four-tenths grams (0.523 mole) of 48% hydrobromic acid, 32 g. of concentrated sulfuric acid, and 62.0 g. (0.256 mole) of n-hexadecanol were

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(185) n-Tetradecyl bromide has been prepared from n-tetradecanol and dry hydrogen bromide. Reid, Ruhoff, and Burnett, Org. Syntheses, 15, 24 (1935).

(186) n-Hexadecyl bromide has been prepared from n-hexadecanol and phosphorus pentabromide by Flaschenträger and Wannschaff, Ber., 67, 1121 (1934), and from n-hexadecanol and 48% hydrobromic acid by Norris, Watt, and Thomas, J. Am. Chem. Soc., 38, 1077 (1916).

mixed as in (b), and the mixture was boiled for 6.5 hours. The reaction mixture was poured into 400 cc. of warm water in a separatory funnel and the aqueous layer was drawn off. To the oily layer was added 20 cc. of concentrated sulfuric acid, and the mixture was cooled and shaken. The lower (acid) layer was drawn off and the treatment with acid was repeated. Then 200 cc. of ether was added, the solution was washed with 5% sodium hydroxide, and was dried over calcium chloride. Removal of the ether, followed by vacuum distillation gave 48.8 g. (61.3%) of n-hexadecyl bromide, b.p. 156-161°/2 mm.

d. Preparation of n-Octadecyl Bromide (187). Twenty-seven grams (0.10 mole) of n-octadecanol, 36 g. (0.186 mole) of 42% hydrobromic acid, and 13 g. of concentrated sulfuric acid were mixed as in (b) and the mixture was refluxed for 9 hours. The reaction mixture was worked up like that of (c) except that a larger portion of sulfuric acid was used in washing the oily layer. The yield of n-octadecyl bromide was 23 g. (69%); b.p. 163-165°/2 mm.

2. Preparation of Diethyl Ethyl-n-alkylmalonates.

a. Preparation of Diethyl Ethyl-n-dodecylmalonate, $(C_2H_5)(n\text{-}C_{12}H_{25})C(COOC_2H_5)_2$ (188). The method used was based upon that employed

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(187) n-Octadecyl bromide has been prepared from n-octadecanol and dry hydrogen bromide. Reid, Ruhoff, and Burnett, Org. Syntheses, 15, 24 (1935).

(188) This ester has been prepared previously. See ref. (138).

by Chargaff (140) to prepare diethyl ethyl-n-docosylmalonate. Two and three-tenths grams (0.10 g. atom) of sodium was dissolved in 40 cc. of absolute alcohol in a 200 cc. round-bottomed, three-necked flask fitted with a stirrer, a dropping funnel, and a reflux condenser carrying a calcium chloride tube. With stirring, 28.2 g. (0.15 mole) of diethyl ethylmalonate was added dropwise to the sodium ethylate solution, and then 12.5 g. (0.05 mole) of n-dodecyl bromide in 20 cc. of warm absolute alcohol was added in the same manner. The solution was stirred and refluxed for 9.75 hours, during which time sodium bromide separated. To the warm reaction mixture was added dropwise (stirring) 60 cc. of warm water, the mixture was acidified with hydrochloric acid, and then extracted with ether. The ether solution was washed with water and dried over sodium sulfate, the ether was distilled, and the residue was vacuum-distilled, giving 13.3 g. (78.5%) of diethyl ethyl-n-dodecylmalonate, b.p. 170-174°/2 mm.; d_{20}^{20} 0.9152; n_D^{20} 1.4432. Calcd. for $C_{21}H_{40}O_4$: Molec. refraction, 102.5. Found: Molec. refraction, 103.2 (189).

b. Preparation of Diethyl Ethyl-n-tetradecylmalonate (190). The method used was the same as in (a). Two and three-tenths grams (0.10 g. atom) of sodium was dissolved in 20 cc. of absolute alcohol,

(189) Molecular refractions were calculated from data by the Lorenz-Lorentz equation, Getman and Daniels, "Outlines of Theoretical Chemistry," 6th Ed., John Wiley and Sons, New York (1937) p. 85.

(190) This ester has been prepared previously. See ref. (138).

28.2 g. (0.15 mole) of diethyl ethylmalonate was added, then 13.85 g. (0.05 mole) of n-tetradecyl bromide in 20 cc. of warm absolute alcohol was added, and the solution was refluxed and stirred for 6 hours. The reaction mixture was worked up in the same manner as in (a). The yield of diethyl ethyl-n-tetradecylmalonate was 16.5 g. (85.8%); b.p. 175-177°/1 mm.; d_{20}^{20} 0.9252; n_D^{20} 1.4428. Calcd. for $C_{23}H_{44}O_4$: Molec. refraction, 111.7. Found: Molec. refraction, 110.5.

c. Preparation of Diethyl Ethyl-n-hexadecylmalonate (191). This preparation was run in the same way as the preceding. One and seventy-three hundredths grams (0.075 g. atom) of sodium was dissolved in 30 cc. of absolute alcohol, 18.8 g. (0.10 mole) of diethyl ethylmalonate and 15.25 g. (0.05 mole) of n-hexadecyl bromide (in 15 cc. of warm absolute alcohol) were added, and the solution was stirred at reflux for 9 hours. The reaction mixture was worked up as in (b), and the yield of diethyl ethyl-n-hexadecylmalonate was 11.0 g. (53.4%); b.p. 198-204°/2 mm.; d_{20}^{20} 0.9078; n_D^{20} 1.4478. Calcd. for $C_{25}H_{48}O_4$: Molec. refraction, 120.9. Found: Molec. refraction, 121.6.

Anal. Calcd. for $C_{25}H_{48}O_4$: C, 72.8; H, 11.38. Found: C, 72.1, 72.4; H, 11.08, 11.24.

d. Preparations of Diethyl Ethyl-n-octadecylmalonate (192).

1. From n-Octadecyl Iodide. The same apparatus as in

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(191) This ester has not been reported in the literature.

(192) This ester has not been reported in the literature.

(a) was employed here. One and two-tenths grams (0.05 g. atom) of sodium was dissolved in 25 cc. of absolute alcohol, and 14.11 g. (0.075 mole) of diethyl ethylmalonate (with 5 cc. of absolute alcohol) was added dropwise to the stirred solution. Then a solution of 9.5 g. (0.025 mole) of n-octadecyl iodide in 20 cc. of warm absolute alcohol was added in the same way and the solution was stirred and refluxed for 7.5 hours. Fifty cubic centimeters of 2% hydrochloric acid was added and the mixture was extracted with ether. The ether solution was washed with 5% sodium bicarbonate, 2% sodium thiosulfate, and water, then was dried over calcium chloride. The ether was removed, leaving an oil which was taken up in 50 cc. of absolute alcohol. Upon cooling, the alcohol solution deposited a mass of white crystals, which were filtered off and washed with cold alcohol. The product melted at 37-39° and weighed 7.1 g. It was recrystallized from absolute alcohol, giving 7.0 g. (63.6%) of solid which melted at 38-39°. This solid was crystallized three times from alcohol; the melting point remained practically the same; a Beilstein test for halogen was negative.

Anal. Calcd. for $C_{27}H_{52}O_4$: C, 73.6; H, 11.89. Found: C, 69.4, 70.8, 70.4; H, 11.1, 11.13, 11.30.

The solid was crystallized from alcohol three times more; the melting point was then 38.5-40° (I).

Anal. Calcd.: same as above. Found: C, 68.8, 69.2, 70.8; H, 11.52, 10.98, 11.67.

2. From n-Octadecyl Bromide. The method used was a modification of that employed by Adams and Kamm (193) to prepare diethyl n-butyl malonate. One and thirty-eight hundredths grams (0.06 g. atom) of sodium was dissolved in 38 cc. of absolute alcohol in a 200 cc. round-bottomed, three-necked flask, fitted with a reflux condenser (closed to moisture by a calcium chloride tube). The sodium ethylate solution was heated almost to boiling and 11.3 g. (0.06 mole) of diethyl ethylmalonate was added dropwise. Then 20.0 g. (0.06 mole) of n-octadecyl bromide was added likewise, and the mixture was refluxed for 15 hours. The insoluble material was filtered off, washed with alcohol and ether, and shown to be sodium bromide (weight, 3.4 g.). The filtrate was cooled in ice with vigorous stirring, giving 15.2 g. of waxy white solid, m.p. 30-31°. The solid was subjected to vacuum distillation and gave 7.5 g. (28.4%) of the desired ester, b.p. 193-206°/2 mm. The distillate crystallized on cooling, and melted at 37-38.5°. A mixed melting point with (1, I) showed no depression.

3. From n-Octadecyl Chloride. The procedure for this preparation was the same as that used in (2) except where otherwise noted. Two and three-tenths grams (0.10 g. atom) of sodium was dissolved in 40 cc. of absolute alcohol, and to the hot solution (80°) were added 28.2 g. (0.15 mole) of diethyl ethylmalonate and 14.8 g. (0.05 mole) of n-octadecyl chloride. The mixture was refluxed for 11 hours,

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(193) Gilman, "Organic Syntheses," Coll. Vol. I., John Wiley and Sons, New York (1932) p. 245.

acidified, and extracted with ether. The ether solution was washed with water, dried over calcium chloride, and distilled to remove the solvent. The residual liquid was distilled under vacuum, giving 17.1 g. of material which boiled at 187-212°/1.5 mm. This was redistilled, giving 10.0 g. (45.4%) of the desired ester, b.p. 203-208°/2 mm. The product crystallized upon cooling, and melted at 37-39.5°. A mixed melting point with (1, I) showed no depression.

B. Preparation of Long-chained Barbituric Acids.

1. Preparation of 5-Ethyl-5-n-dodecyl Barbituric Acid, $(C_2H_5)(\underline{n}\text{-}C_{12}H_{25})\underline{CCONHCONHCO}$. The method used in this preparation was derived from those of Fischer and Dilthey (141) and Dox and Yoder (141), who prepared lower homologs. One and thirty-eight hundredths grams (0.06 g. atom) of sodium was dissolved in 30 cc. of absolute alcohol in a 125 cc. Erlenmeyer flask fitted with a calcium chloride tube. Seven and twelve-hundredths grams (0.02 mole) of diethyl ethyl-n-dodecylmalonate was added, the mixture was warmed somewhat, and poured rapidly into a Carius tube. Then 1.8 g. (0.03 mole) of powdered urea was added to the mixture in the tube, and the walls of the tube were washed down with 15-20 cc. of absolute alcohol. The sealed tube was heated in the furnace at 120-122° for 12 hours. The tube was opened and the contents (partially solid) were rinsed out with alcohol. An equal volume of water was added and the mixture was acidified with hydrochloric acid. The oil which separated was extracted with ether, the ether solution was washed with water,

and was dried over sodium sulfate. Removal of the ether, followed by precipitation of the residue from 15 cc. of pet. ether (b.p. 60-68°) gave 3.9 g. of white solid, m.p. 102-106°. This product was crystallized twice more from the same solvent to yield 3.76 g. (57.3%) of 5-ethyl-5-*n*-dodecyl-barbituric acid, m.p. 106-107.5°.

Anal. Calcd. for $C_{18}H_{32}O_3H_2$: N, 8.64. Found: N, 8.71, 8.64.

Solubility:	60% ethanol	2.5 g./100 cc.
	80% ethanol (warm)	10.0 g./100 cc.
	olive oil	2.0 g./100 cc.

2. *Preparation of 5-Ethyl-5-n-tetradecyl Barbituric Acid.* One and thirty-eight hundredths grams (0.06 g. atom) of sodium was dissolved in 30 cc. of absolute alcohol in a Carius tube fitted with a calcium chloride tube. To the solution was added 7.68 g. (0.02 mole) of diethyl ethyl-*n*-tetradecylmalonate, then 1.8 g. (0.03 mole) of powdered urea was added, and the tube walls were washed down with 10-15 cc. of absolute alcohol. The tube was sealed and heated at 115° for 9.5 hours. After cooling, the contents were worked up as before. The crude product was crystallized three times from pet. ether (b.p. 60-68°) to yield 3.4 g. (47.6%) of 5-ethyl-5-*n*-tetradecyl-barbituric acid, m.p. 104.5-106.5°.

Anal. Calcd. for $C_{20}H_{36}O_3N_2$: N, 7.95. Found: N, 7.76, 7.65.

Solubility:	60% ethanol (warm)	at least 1 g./100 cc.
	80% ethanol	at least 1 g./100 cc.

3. **Preparation of 5-Ethyl-5-n-hexadecyl Barbituric Acid.** One and thirty-eight hundredths grams (0.06 g. atom) of sodium was dissolved in 27 cc. of absolute alcohol in a Carius tube, and 8.24 g. (0.02 mole) of diethyl ethyl-n-hexadecylmalonate and 1.8 g. (0.03 mole) of powdered urea were added as described in (2). The tube was sealed and heated at 112-115° for 10 hours, and the product was worked up in the same manner as that of (2). Three crystallizations from pet. ether (b.p. 60-68°) gave 4.4 g. (58%) of 5-ethyl-5-n-hexadecyl-barbituric acid, m.p. 103-104°. Anal. Calcd. for $C_{22}H_{40}O_3N_2$: N, 7.36. Found: N, 7.30, 7.34.

Solubility:	60% ethanol	$<$ 1 g./100 cc.
	80% ethanol	1.6 g./100 cc.
	olive oil (warm)	1.6 g./100 cc.

4. Preparation of 5-Ethyl-5-n-octadecyl Barbituric Acid.

a. **Attempted Preparation.** The method of Buck and co-workers (102) for the preparation of 1-n-alkyl-5-ethyl-5-isobutyl-barbituric acids was employed in this run. Sixty-three hundredths of a gram (0.028 g. atom) of sodium was dissolved in 20 cc. of absolute alcohol in a 200 cc. round-bottomed flask fitted with a reflux condenser closed to moisture by a calcium chloride tube. Three grams (0.007 mole) of diethyl ethyl-n-octadecylmalonate was added, and was dissolved by gentle warming. To this solution was added a solution of 1.42 g. of urea (0.007 mole) in 10 cc. of absolute alcohol and the resulting solution was refluxed for 8 hours in an oil bath held at 120°. The reaction mixture was acidified with dilute hydrochloric acid and extracted with ether. The ether solution was washed with water, 5% hydrochloric acid, and again with water, then was dried. The ether was removed, the residual oil was taken up in pet. ether (b.p. 60-68°), and the resulting solution was cooled to give 1.1 g. of white solid melting at 90-96°. Recrystallization from the same solvent gave 1.0 g. of solid which softened at 92° and melted at 104-108° (I). Recrystallization from acetone gave 0.98 g. of solid melting (micro) at 88-105° (II). Partial evaporation of the filtrate from (I), followed by cooling gave about 60 mg. of white powder, m.p. 80-100°; this was recrystallized from benzene, yielding a solid which softened at 81° and melted at 98-102°. A portion of (II) was crystallized from ethylene dichloride to give a solid melting at 84-99°; this was recrystallized from isopropyl alcohol (98%), giving a solid melting at 86-105°. All the various solids were combined and recrystallized from alcohol, giving a product melting at 88-106°. This was heated on a steam bath for 20 min. with 10 cc. of 10% hydrochloric acid, the mixture was cooled and filtered, and the residue on the filter was crystallized from acetone, giving 0.43 g. of white solid, m.p. 89.5-105°. Further crystallizations gave no sharply melting product.

b. Attempted Preparation. The method used in (3) was used here. Sixty-nine hundredths of a gram (0.03 g. atom) of sodium was dissolved in 18 cc. of absolute alcohol in a Carius tube, 4.4 g. (0.01 mole) of diethyl ethyl-*n*-octadecylmalonate in 10 cc. of absolute alcohol was added, then 0.90 g. (0.015 mole) of powdered urea was added, and the tube was sealed. The mixture was heated at 112° for 10 hours, the contents were rinsed out with alcohol, and 150 cc. of water and 5 cc. of concentrated hydrochloric acid were added to the mixture. The latter was extracted with ether, the ether solution was washed with water and dried over sodium sulfate, and the ether was removed. Crystallization of the residue from 30 cc. of pet. ether (b.p. 60-68°) gave a white solid, m.p. 90.5-93.5°. After four more crystallizations from the same solvent, the product weighed 1.72 g. and melted at 92.5-95°. Three crystallizations from 90:10 pet. ether (b.p. 60-68°)-absolute alcohol raised the melting range to 102-105°; the weight at this point was 0.97 g. This solid was dissolved in 35 cc. of 4% potassium hydroxide (75% alcohol solution), 5 cc. of water was added, and the slightly turbid solution was cooled in an ice bath, giving a small amount of precipitate. This was filtered off and 10 cc. of 75% alcohol was added to the filtrate. Cooling in ice gave a trace of precipitate which was filtered off. To the filtrate was added 5% hydrochloric acid (in 50% alcohol) until precipitation began. The mixture was cooled, and 0.51 g. of solid melting at 85-90° (I) was filtered out. This was redissolved in 10 cc. of 4% potassium hydroxide (in 65% alcohol), and 5% aqueous hydrochloric acid was added to the end point of phenolphthalein. The resulting precipitate was treated with hot 5% hydrochloric acid (in 65% alcohol), the mixture was cooled, and the solid was filtered off and washed with alcohol; the solid weighed 0.38 g. and melted at 98-101°. Further fractional precipitation of the filtrate from (I) by addition of dilute hydrochloric acid (in 65% alcohol) gave potassium chloride and two small fractions of organic material melting respectively at 100-106° and 92-98°.

c. Preparation. The method used by Reichert and Wilke (142) in the preparation of barbiturates having acid side chains was employed here. Thirty-five hundredths of a gram (0.015 g. atom) of sodium was dissolved in 20 cc. of absolute alcohol in a 200 cc. round-bottomed flask. To this solution 2.2 g. (0.005 mole) of diethyl ethyl-n-octadecylmalonate was added, the mixture was warmed gently to bring the ester into solution, and 0.45 g. (0.0075 mole) of powdered urea was added. The flask was fitted with a reflux condenser carrying a drying tube and was heated to 150° in an oil bath. The temperature was held at 150° for 0.5 hours, then raised to 160° during the next hour, and was held at 160° for 2 hours more. The reaction mixture was cooled, 1:1 hydrochloric acid was added until a slight excess was present, and the mixture was extracted with ether. The resulting ether solution was washed with water and dried over sodium sulfate. Air was bubbled through the dry solution to remove the ether, the residual white solid was dissolved in 10 cc. of alcohol, and the solution was cooled, giving 0.98 g. of white powder, melting at 92-101°. Crystallization from 90% alcohol raised the melting point to 102-107°, and two more crystallizations from the same solvent gave 0.43 g. (21.1%) of 5-ethyl-5-n-octadecyl-barbituric acid, m.p.

108-109.5°.

Anal. Calcd. for $C_{24}H_{44}O_3N_2$: N, 6.86. Found: N, 6.96, 6.95.

Solubility:		
	60% ethanol	< 1 g./100 cc.
	80% ethanol	1 g./100 cc.
	olive oil	1 g./100 cc.

5. Mixed Melting Points of the Barbituric Acids. The melting points given are those for 1:1 mixtures. The bath temperature was 80° when the sample was immersed, and the temperature was raised at approx. 1°/8 secs.

Mixture: Alkyl radicals are:	Soften	Melt	Clear
C_{12} and C_{14}	90°	92°	102°
C_{14} and C_{16}	91	92.5	103
C_{16} and C_{18}	95	96	103
C_{12} and C_{18}	87	89.5	101.5

The melting points of the pure acids are: C_{12}, 106-107.5°; C_{14}, 104.5-106.5°; C_{16}, 103-104°; C_{18}, 108-109.5°.

IV. Homologs of Phenacetin.

A. Preparation of Alkyl p-Nitrophenyl Ethers.

1. Preparation of n-Dodecyl p-Nitrophenyl Ether, n-$C_{12}H_{25}OC_6H_4NO_2$. Four and ninety-eight hundredths grams (0.02 mole) of dodecyl bromide,

3.52 g. (0.0218 mole) of sodium p-nitrophenate (194), and 20 cc. of absolute alcohol were heated in a sealed tube for 11 hours at 125°. The contents of the tube were rinsed out with alcohol, the resulting mixture was diluted with three volumes of water, and the mixture was extracted with ether. The ether solution was washed thoroughly with 5% sodium hydroxide, then with dilute hydrochloric acid and with water, and was dried with calcium chloride. The ether was removed and the residue was crystallized three times from alcohol, giving 3.85 g. (62.7%) of n-dodecyl p-nitrophenyl ether, m.p. 48-49.5°.

Anal. Calcd. for $C_{18}H_{29}O_3N$: N, 4.56. Found: N, 4.68, 4.73.

2. Preparation of p-Nitrophenyl n-Tetradecyl Ether. Seventy-six hundredths of a gram (0.03 g. atom) of sodium was dissolved in 20 cc. of absolute alcohol in a 200 cc. round-bottomed, three-necked flask fitted with a stirrer, dropping funnel, reflux condenser, and drying tube. To the stirred solution was added dropwise 4.51 g. (0.031 mole) of p-nitrophenol in 15 cc. of absolute alcohol. Then 8.31 g. (0.03 mole) of n-tetradecyl bromide was added dropwise, and the mixture was stirred vigorously at reflux for 10.5 hours. At the end of this time the reaction mixture was cooled and filtered, and the residue on the filter was washed with alcohol and ether, after which it weighed 3.7 g. (I). When this solid was heated with dilute hydrochloric acid, an oil

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(194) Prepared by adding a hot alcoholic solution of p-nitrophenol to a hot alcoholic solution of sodium ethylate and cooling the mixture.

separated on the surface of the mixture; upon cooling the oil solidified, giving 2.7 g. of solid melting at 60-63° (II). The filtrate from (I) was cooled and gave 1.2 g. of pale yellow solid melting at 50-63°. This was treated with dilute alkali, water, and dilute acid, and then washed with dilute alcohol, leaving 1.1 g. of solid melting at 58-60° (III). Further evaporation and cooling of the filtrates gave more solid, which was washed in the same way to give 0.96 g. of material melting at 57-60° (IV). (II), (III), and (IV) were combined and dissolved in ether, and the ether solution was washed with dilute alkali, dilute acid, and water. The washed solution was dried over calcium chloride, the ether was removed, and the residue was crystallized from pet. ether (b.p. 60-68°), giving 2.46 g. of pale brown crystals, m.p. 58-61°. Crystallization from alcohol gave 2.39 g. (23.8%) of *p*-nitrophenyl *n*-tetradecyl ether as flat, pale green needles which melted at 58.5-61°.

Anal. Calcd. for $C_{20}H_{33}O_3N$: N, 4.18. Found: N, 4.27, 4.30.

3. *Preparation of n-Hexadecyl p-Nitrophenyl Ether.* Three and fifty-two hundredths grams (0.0218 mole) of sodium *p*-nitrophenate, 6.06 g. (0.02 mole) of n-hexadecyl bromide, and 20 cc. of absolute alcohol were heated in a sealed tube for 11 hours at 125°. The reaction mixture was worked up in the same manner as that of (1) and the product was crystallized three times from alcohol. The yield of *n*-hexadecyl *p*-nitrophenyl ether was 4.56 g. (64.1%); m.p. 63-65°.

Anal. Calcd. for $C_{22}H_{37}O_3N$: N, 3.86. Found: N, 3.97, 4.0.

4. Preparation of p-Nitrophenyl n-Octadecyl Ether. Three and fifty-two hundredths grams (0.0218 mole) of sodium p-nitrophenate, 5.8 g. (0.02 mole) of n-octadecyl chloride, and 27 cc. of absolute alcohol were heated in a sealed tube for 8.5 hours at 130°. The reaction mixture was worked up in the manner described for (1). The product was crystallized three times from alcohol to give 5 g. (64%) of p-nitrophenyl n-octadecyl ether, m.p. 68-71°.

Anal. Calcd. for $C_{24}H_{41}O_3N$: N, 3.57. Found: N, 3.71, 3.67.

B. Preparation of Homologs of Phenacetin.

1. Preparation of p-Acetaminophenyl n-Dodecyl Ether, n-$C_{12}H_{25}OC_6H_4NHCOCH_3$. Three and eleven-hundredths grams (0.018 mole) of sodium p-acetaminophenate (195), 3.74 g. (0.015 mole) of n-dodecyl bromide, and 20 cc. of absolute alcohol were heated in a sealed tube for 10 hours at 125-127°. The contents of the tube were rinsed out with alcohol and the resulting mixture was diluted with three volumes of water, acidified with hydrochloric acid, and extracted with ether. A crystalline solid separated in the ether layer and was filtered off, giving 0.71 g. of material melting at 91-94° (I). The ether filtrate from (I) was washed successively with 10% sodium hydroxide, 10% hydrochloric acid, and with water, then was dried over sodium sulfate. The ether was removed, and the residue was taken up in 30 cc. of alcohol

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(195) Prepared by adding a hot alcoholic solution of p-acetaminophenol to a hot alcoholic solution of sodium ethylate and precipitating the product with acetone.

and boiled with Norit. Subsequent to filtration and cooling, the solution deposited 1.01 g. of white crystals melting at 91.5-93° (II). Further cooling of the filtrate gave 0.27 g. (III) more of the same product. (I), (II), and (III) were combined, dissolved in alcohol, and boiled with Norit. The solution was filtered and cooled, whereupon it deposited 1.4 g. (29.3%) of p-acetaminophenyl n-dodecyl ether, m.p. 92-93°.

Anal. Calcd. for $C_{20}H_{33}O_2N$: N, 4.38. Found: N, 4.36, 4.39.

Solubility: 80% ethanol 1 g./100 cc.

2. Preparation of p-Acetaminophenyl n-Tetradecyl Ether. Two and thirty-nine hundredths grams (0.0071 mole) of p-nitrophenyl n-tetradecyl ether was reduced to the corresponding amino compound by refluxing for 2 hours with 4 g. of tin, 20 cc. of concentrated hydrochloric acid, and 25 cc. of alcohol. The excess tin was filtered from the solution, and the filtrate was cooled, giving 2.04 g. of glistening white plates of the amine hydrochloride, melting from 130-160°. The hydrochloride was treated twice with 1 g. of potassium hydroxide in 60 cc. of 50% alcohol, giving 1.74 g. of the amine, m.p. 67-70°. The amine was acetylated by refluxing for 2.5 hours with 12 cc. of a 1:1 mixture of glacial acetic acid and acetic anhydride in 15 cc. of dry benzene. The crude product obtained by cooling was boiled with Darco in absolute alcohol, and gave 1.52 g. (61.6%) of p-acetaminophenyl n-tetradecyl ether, m.p. 95.5-97°.

Anal. Calcd. for $C_{22}H_{37}O_2N$: N, 4.04. Found: N, 4.14, 4.18.

Solubility:	80% ethanol	1.1 g./100 cc.
	olive oil	1.4 g./100 cc.

3. *Preparation of p-Acetaminophenyl n-Hexadecyl Ether.* Three and five-tenths grams (0.00964 mole) of *n*-hexadecyl *p*-nitrophenyl ether was reduced by refluxing for 2.5 hours with 4.5 g. of tin, 25 cc. of concentrated hydrochloric acid, and 35 cc. of alcohol. The excess tin was filtered off and the filtrate was cooled, giving 2.61 g. of white solid. This was treated with alkali as described in (2), and the product was acetylated by refluxing with a mixture of 15 cc. of acetic anhydride, 5 cc. of glacial acetic acid, and 10 cc. of benzene for 4.5 hours. The solution was cooled and gave 1.7 g. of solid. The crude product was boiled with Norit in alcohol for 1 hour, and the alcohol solution was filtered and cooled, giving 1.25 g. (33.3%) of *p*-acetaminophenyl *n*-hexadecyl ether, m.p. 96-98°.

Anal. Calcd. for $C_{24}H_{41}O_2N$: N, 3.73. Found: N, 3.81, 3.78.

Solubility:	80% ethanol	$<$ 1 g./100 cc.
	olive oil	1 g./100 cc.

4. *Preparation of p-Acetaminophenyl n-Octadecyl Ether.* Two and five-tenths grams (0.0064 mole) of *p*-nitrophenyl *n*-octadecyl ether was reduced by refluxing for 2 hours with 4.0 g. of tin, 20 cc. of concentrated hydrochloric acid, and 30 cc. of alcohol. The excess tin was filtered off, and the amine was obtained as in (3). The amine was acetylated by refluxing for 5 hours in a mixture of 12.5 cc. of glacial

acetic acid, 12.5 cc. of acetic anhydride, and 20 cc. of benzene. Upon cooling, the solution deposited 1.49 g. of crude product, m.p. 97-100°. This was purified by refluxing with Norit in alcohol and gave 1.16 g. (43.1%) of p-acetaminophenyl n-octadecyl ether, m.p. 100.5-102°.

Anal. Calcd. for $C_{26}H_{45}O_2N$: N, 3.48. Found: N, 3.58, 3.50.

Solubility:		
	60% ethanol	< 1 g./100 cc.
	80% ethanol	1.1 g./100 cc.
	olive oil	< 1 g./100 cc.

Mixed Melting Points.

1:1 Mixture of:	Soften	Melt	Clear
C_{12} and C_{14}	83.5°	85.5°	91°
C_{14} and C_{16}	87.5	90.0	94.5
C_{16} and C_{18}	94.0	95	98

The melting points of the pure compounds are : C_{12}, 92-93°; C_{14}, 95.5-97°; C_{16}, 96-98°; C_{18}, 100.5-102°.

V. Homologs of Dulcin.

A. Preparation of p-Dodecoxyphenylurea, n-$C_{12}H_{25}OC_6H_4NHCONH_2$. The hydrochloride of p-aminophenyl n-dodecyl ether was prepared by reducing 3.0 g. (0.00976 mole) of n-dodecyl p-nitrophenyl ether with 4.0 g. of tin in a mixture of 25 cc. of concentrated hydrochloric acid and 65 cc. of alcohol. After 2.5 hours of refluxing, the mixture was filtered, and the filtrate was cooled to give 2.44 g. of the amine hydrochloride. This was crystallized twice from 85% alcohol (Norit), giving 1.36 g. (43.4%) of p-aminophenyl n-dodecyl ether hydrochloride which melted in the range 112-155°. Further crystallization gave no sharper melting point.

One gram (0.0032 mole) of the above ether hydrochloride was mixed with 0.33 g. (0.0041 mole) of potassium cyanate, 15 cc. of alcohol was added, and the mixture was refluxed for 1 hour. Then 10 cc. of alcohol was added and the mixture was heated and filtered, leaving 0.26 g. of insoluble material. The filtrate was cooled, giving a precipitate of the original hydrochloride. This was redissolved in the filtrate and warm water was added until the solution was turbid. Ninety-three hundredths of a gram (0.013 mole) of potassium cyanate was added, and the mixture was refluxed for 2 hours, then cooled, whereupon a pale pink solid separated. This was crystallized from acetone (Norit), giving 0.34 g. of white solid, m.p. 129-132°. The solid was crystallized from 90% ethanol to give 0.31 g. of product melting at 130-132°; and the latter was crystallized from acetone, giving 0.27 g. (26.4%) of p-dodecoxyphenylurea, m.p. 131-133°.

Anal. Calcd. for $C_{19}H_{32}O_2N_2$: N, 8.75. Found: N, 8.89, 8.93.

Taste: Five different observers pronounced the compound tasteless.

B. Preparation of p-Tetradecoxyphenylurea. The hydrochloride of p-aminophenyl n-tetradecyl ether was prepared as described in the preparation of p-acetaminophenyl n-tetradecyl ether (IV, B, 2). Two and three-tenths grams (0.00686 mole) of p-nitrophenyl n-tetradecyl ether gave

1.73 g. of crude amine hydrochloride, which was crystallized twice from 85% alcohol. The yield of pure hydrochloride was 1.08 g. (46.1%); the melting point was indefinite.

One gram (0.00293 mole) of p-aminophenyl n-tetradecyl ether hydrochloride was dissolved in 20 cc. of hot alcohol, and 25 cc. of warm water and 1.0 g. (0.0122 mole) of potassium cyanate were added. The mixture was refluxed for 1.5 hours, then 10 cc. of alcohol and a small amount of Norit were added, and the mixture was refluxed 20 minutes. At the end of this time, the mixture was filtered and the insoluble material left on the filter was washed four times with hot alcohol. The combined filtrate and washings were evaporated to about one-half volume and cooled, giving 0.25 g. of white crystalline solid, m.p. 125-128°. This solid was crystallized from 90% alcohol to give a product melting at 128-130°, and the latter was crystallized from acetone, giving 0.15 g. (14.7%) of p-tetradecoxyphenylurea, m.p. 130-131.5°.

Anal. Calcd. for $C_{21}H_{36}O_2N_2$: N, 8.05. Found: N, 8.21, 8.16.

Taste: Four observers found the compound to be tasteless.

Mixed Melting Point: 1:1 Mixture of the preceding two compounds:
softens, 122.5°; melts, 128°; clears, 131°.

VI. Dihydrazides of Long-Chained Malonic Acids.

A. Preparation of Diethyl n-Alkylmalonates.

1. Preparation of Diethyl n-Dodecylmalonate, n-$C_{12}H_{25}CH(COOC_2H_5)_2$ (196). This preparation was based on the method used by Adams and Kamm (184) for preparing diethyl n-butylmalonate. One and fifteen-hundredths grams (0.05 g. atom) of sodium was dissolved in 40 cc. of absolute alcohol in a 200 cc. round-bottomed, three-necked flask fitted with a stirrer, a dropping funnel, and a reflux condenser carrying a drying tube. Eight and seventeen-hundredths grams (0.051 mole) of diethyl malonate was added dropwise to the stirred solution; then 12.5 g. (0.05 mole) of n-dodecyl bromide with 10 cc. of alcohol was added likewise. The solution was stirred at reflux for 4.5 hours, 50 cc. of 2% hydrochloric acid was added, and the mixture was extracted with ether. The ether solution was washed with water and dried over calcium chloride. Removal of the ether, followed by vacuum distillation of the residual oil gave 7.6 g. (46.2%) of diethyl n-dodecylmalonate, b.p. 158-161°/2 mm.; d_{20}^{20} 0.9238; n_D^{20} 1.4394. Calcd. for $C_{19}H_{36}O_4$: Molec. refraction, 92.97. Found: Molec. refraction, 93.8.

2. Preparation of Diethyl n-Tetradecylmalonate (197). This ester

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(196) This ester has been prepared by Rothstein. See ref. (151).

(197) The preparation of this ester has been reported but no constants were given. Verkade and Coops, Rec. trav. chim., 52, 747 (1933).

was prepared in the same way as the preceding, except that the reaction mixture was heated 1.5 hours longer. One and fifteen-hundredths grams (0.05 g. atom) of sodium, 8.17 g. (0.051 mole) of diethyl malonate, and 13.85 g. (0.05 mole) of n-tetradecyl bromide gave 10.0 g. (56%) of diethyl n-tetradecylmalonate, b.p. 168-175°/2 mm.; d_{20}^{20} 0.9189; n_D^{20} 1.4423. Calcd. for $C_{21}H_{40}O_4$: Molec. refraction, 102.18. Found: Molec. refraction, 102.8.

3. Preparation of Diethyl n-Hexadecylmalonate (198). The preparation was carried out in the same way as the preceding. One and fifteen-hundredths grams (0.05 g. atom) of sodium, 8.33 g. (0.052 mole) of diethyl malonate, and 16.77 g. (0.055 mole) of n-hexadecyl bromide gave 11.7 g. (60.9%) of diethyl n-hexadecylmalonate, b.p. 182-188°/2 mm.; d_{20}^{20} 0.9091; n_D^{20} 1.4449. Calcd. for $C_{23}H_{44}O_4$: Molec. refraction, 111.38. Found: Molec. refraction, 112.5.

B. Attempts to Prepare Dihydrazides.

1. Attempted Preparation of the Dihydrazide of n-Dodecyl Malonic Acid, $n\text{-}C_{12}H_{25}CH(CONHNH_2)_2$.

a. The method used by Blanksma and de Graf (120) for the preparation of lower homologs was employed. A mixture of 3.28 g. (0.01 mole) of diethyl n-dodecylmalonate, 1.20 g. (0.024 mole) of 100% hydrazine hydrate, and 10 cc. of absolute alcohol was heated in a sealed

(198) This ester has been prepared by Brigl. See ref. (152).

tube for 8 hours at 112-115°. The reaction mixture was filtered, leaving a mass of fine, short, colorless needles on the filter. This solid was washed with alcohol, after which it weighed 2.5 g. and melted from 146° to about 190° (dec.). A qualitative analysis showed nitrogen to be present. The solid was crystallized from 95 cc. of alcohol, giving 2.0 g. of product (I) which melted over approximately the same range as before. It was thought that part of (I) might be the monohydrazide. Accordingly, 0.5 g. of (I) was refluxed for 3 hours with a solution of 0.5 g. of 100% hydrazine hydrate in 25 cc. of absolute alcohol. Upon cooling, the solution gave 0.49 g. of solid, melting at 148-184° (dec.). This was crystallized from 40 cc. of 80% alcohol but the melting point remained unchanged. Therefore, 0.5 g. of (I), 1.0 g. of 100% hydrazine hydrate, and 10 cc. of absolute alcohol were heated in a sealed tube for 4 hours at 108°. The solid product was filtered out and washed with alsohol; it melted at 146-180° (dec.).

In an attempt to purify the product through the dihydrazide dihydrochloride, 0.5 g. of (I) was dissolved in 45 cc. of warm alcohol and 5 cc. of 1:1 hydrochloric acid was added. Upon cooling, the solution gave 0.47 g. of white plates, melting at 138-190° (dec.). The solid was dissolved in 25 cc. of alcohol, 5 cc. of concentrated ammonium hydroxide was added, the solution was filtered, and the solvent was removed by drawing air through the solution. The solid residue was washed with dilute alcohol which left 0.38 g. of solid, melting at 130-184° (dec.).

The effect of dry hydrogen chloride upon (I) was investigated by bubbling hydrogen chloride into a suspension of 0.5 g. of (I) in 50 cc. of alcohol. Most of the solid dissolved, then a bulky precipitate of white plates began to separate. The mixture was cooled and filtered, giving 0.34 g. of white solid. This was dissolved in 20 cc. of hot alcohol, and the solution was cooled, giving 0.16 g. of long colorless needles, m.p. 92-93° (II). This product contained nitrogen and chlorine, and exhibited a sour, burning taste. However, the solid was shown to be hydrazine hydrochloride, rather than the desired dihydrazide.

The filtrate from (II) was evaporated to half-volume and then cooled, giving about 50 mg. of the same product.

b. In this run, milder conditions were used. Three and twenty-eight hundredths grams (0.01 mole) of diethyl n-dodecylmalonate and 2.0 g. (0.04 mole) of 100% hydrazine hydrate were refluxed with 10 cc. of absolute alcohol. At the end of an hour, a white solid separated, so 45 cc. of alcohol was added, and refluxing was continued for another hour, causing most of the solid to redissolve. The mixture was cooled and filtered, giving 2.0 g. of tiny white needles, m.p. 143-182° (dec.) (I). The filtrate from (I) upon further cooling gave 0.11 g. of white solid, m.p. 136-170° (dec.).

One-tenth of a gram of (I) was heated to 185° in a small test tube and the escaping gas was led into lime water, giving traces of white precipitate. The gas turned moist litmus blue; possibly it was hydrazine vapor. The residue of the heating was crystallized from methanol, giving 0.06 g. of white powder, which melted at 166-192° (dec.) and contained nitrogen.

One and seven-tenths grams of (I) was suspended in 120 cc. of alcohol and hydrogen chloride was introduced, whereupon part of the solid dissolved, then reprecipitated. The mixture was cooled and filtered, giving 2.1 g. of white solid, m.p. 130-165° (dec.). The solid had a sour, burning taste. It was dissolved in 165 cc. of boiling alcohol and the solution was cooled, giving a small amount of hydrazine hydrochloride, m.p. 92-93°. One-third of the solvent was removed and the remaining solution was cooled in the refrigerator for 48 hours; no crystals were obtained. Concentration to about 50 cc. gave 0.14 g. more of hydrazine hydrochloride. Removal of most of the remaining solvent gave 1.2 g. of soft, gummy solid, which was extracted with ether, leaving 0.05 g. of hydrazine hydrochloride. The ether extract was washed with 10% potassium hydroxide and with water, and was dried over sodium sulfate. Removal of the ether and crystallization of the residue from alcohol gave 0.94 g. of white solid, m.p. 130-162° (dec.).

2. Attempted Preparation of the Dihydrazide of n-Tetradecyl Malonic Acid.

a. One and two-tenths grams (0.024 mole) of 100% hydrazine hydrate, 3.56 g. (0.01 mole) of diethyl n-tetradecylmalonate, and 10 cc. of absolute alcohol were heated in a sealed tube. The product was washed with alcohol, giving 2.5 g. of small needles, m.p. 144-190° (dec.).

Several crystallizations from alcohol and from methanol-alcohol mixture gave no sharply melting product.

b. A mixture of 1.2 g. (0.024 mole) of 100% hydrazine hydrate, 3.56 g. (0.01 mole) of diethyl n-tetradecylmalonate, and 11 cc. of absolute alcohol was refluxed for 1 hour. The solution was cooled, giving 0.42 g. of white solid, m.p. 136-165° (dec.) (I). The filtrate from (I) was refluxed for 2 hours, and, upon cooling, gave 1.1 g. of white solid, m.p. 138-164° (dec.) (II). The filtrate from (II) was refluxed for 4 hours, then cooled, giving 0.24 g. of white solid, m.p. 135-163° (dec.) (III). Several crystallizations of (I), (II), and (III) from alcohol, dilute alcohol, and methanol failed to yield any product having a sharp melting point.

3. Atempted Preparation of the Dihydrazide of n-Hexadecyl Malonic Acid.

a. One and two-tenths grams (0.024 mole) of 100% hydrazine hydrate, 3.84 g. (0.01 mole) of diethyl n-hexadecylmalonate, and 15 cc. of absolute alcohol were heated in a sealed tube for 10.5 hours at 116°. The crude product was washed with alcohol, giving 2.6 g. of white powder, m.p. 137-170° (dec.). Repeated crystallizations from several solvents did not bring the product to a sharp melting point.

b. One and five-tenths grams (0.03 mole) of 100% hydrazine hydrate and 5 cc. of alcohol were heated to boiling in a 200 cc. round-bottomed, three-necked flask fitted with a dropping funnel and reflux condenser. A solution of 3.84 g. (0.01 mole) of diethyl *n*-hexadecylmalonate in 10 cc. of absolute alcohol was added dropwise during 20 minutes, and the mixture was refluxed for 3.5 hours. The mixture was cooled and filtered, giving 3.0 g. of white solid, which, after being washed with alcohol and ether, weighed 3.0 g. and melted at 136-175° (dec.). The product could not be brought to a sharp melting point by repeated crystallization from alcohol or alcohol-acetone mixtures.

Taste: No taste was observed in any of the fractions obtained in the preceding attempted preparations except in the two instances noted (1, a and 1, b).

VII. *Long-Chained Azo Dyes.*

A. *From Long-Chained Alkoxyanilines,* $ROC_6H_4NH_2$.

1. *Preparation of 1-(p-dodecoxyphenylazo)-2-naphthol,* *p*-*n*-$C_{12}H_{25}OC_6H_4NNC_{10}H_6OH$-$\beta$. Seventy-two hundredths of a gram (0.0023 mole) of *p*-dodecoxyaniline hydrochloride (*n*-$C_{12}H_{25}OC_6H_4NH_2 \cdot HCl$) was suspended in 120 cc. of water and the mixture was heated, with vigorous stirring, to the boiling point. Stirring was continued and the mixture was cooled to 3°, giving a suspension of the amine hydrochloride in a finely divided state. Two cubic centimeters of concentrated hydrochloric acid was added, then a solution of 0.17 g. (0.0025 mole) of sodium nitrite in 15 cc. of water was added dropwise during 20 minutes. To the mixture was added 10 cc. of 10% sodium hydroxide, followed by dropwise addition

of 0.4 g. (0.00278 mole) of β-naphthol in 15 cc. of 5% sodium hydroxide. A bright red orange color developed in the mixture as the alkaline solution was added. The cooling bath was removed, and stirring was continued for 1.5 hours. The red solid was filtered off and dissolved in ether, and the ether solution was washed with dilute alkali and with water. Introduction of hydrogen chloride caused separation of 0.24 g. of *p*-dodecoxyaniline hydrochloride, which was filtered off. The filtrate was washed with water and dried over calcium chloride, the solvent was removed, and the residual dark red solid was taken up in hot alcohol. Upon cooling, the solution deposited 0.23 g. (43.2%) of 1-(*p*-dodecoxyphenylazo)-2-naphthol as tiny red needles, m.p. 80-82°. The dye was quite soluble in ether, alcohol, pet. ether (60-68°), acetone, and olive oil; it was slightly soluble in methanol.

Anal. Calcd. for $C_{28}H_{36}O_2N_2$: N, 6.47. Found: N, 6.59, 6.61.

2. *Preparation of 1-(p-tetradecoxyphenylazo)-2-naphthol*, *p*-*n*-$C_{14}H_{29}OC_6H_4NNC_{10}H_6OH$-$\beta$. One and seventy-three hundredths grams (0.005 mole) of *p*-tetradecoxyaniline hydrochloride was converted to a fine suspension in 200 cc. of water as described in (1). To the cold (0°) stirred suspension was added 7 cc. of concentrated hydrochloric acid, followed by dropwise addition of a solution of 0.352 g. (0.0051 mole) of sodium nitrite in 15 cc. of water. Stirring was continued at 0-5° for 1.75 hours, then 45 cc. of 2.5% sodium hydroxide was added dropwise during 20 minutes. A solution of 0.793 g. (0.0055 mole) of β-naphthol

in 45 cc. of 5% sodium hydroxide was added dropwise during 20 minutes, and the resulting deep red mixture was stirred for one-half hour. The mixture was extracted with ether, the ether solution was washed with dilute alkali and with water, and was dried. Introduction of gaseous hydrogen chloride gave a precipitate of 0.10 g. of *p*-tetradecoxyaniline hydrochloride. The filtrate from the latter was washed with water and dried over calcium chloride and the ether was removed. The residual oil was taken up in about 200 cc. of 3:2 methanol-absolute alcohol mixture and the solution was filtered and cooled, giving a deposit of 1.43 g. of tiny red needles. This was recrystallized (Norit) from the same solvent to give 1.3 g. (56.5%) of 1-(*p*-tetradecoxyphenylazo)-2-naphthol, m.p. 81.5-83°. The compound exhibited about the same solubility as the *n*-dodecyl homolog.

Anal. Calcd. for $C_{30}H_{40}O_2N_2$: N, 6.08. Found: N, 6.07, 6.10.

3. *Preparation of 1-(p-hexadecoxyphenylazo)-2-naphthol*, *p*-*n*-$C_{16}H_{33}OC_6H_4NNC_{10}H_6OH$-$\beta$. Five-tenths of a gram (0.00135 mole) of *p*-hexadecoxyaniline hydrochloride was suspended in 80 cc. of water as described in (1). To the cold (0°) stirred suspension was added 2.2 cc. of concentrated hydrochloric acid, followed by dropwise addition of a solution of 0.097 g. (0.0014 mole) of sodium nitrite in 10 cc. of water. The mixture was stirred for 1 hour, 15 cc. of 2.5% sodium hydroxide was added, then a solution of 0.288 g. (0.002 mole) of β-naphthol in 15 cc. of 5% sodium hydroxide was added dropwise, and stirring was continued at 0-5° for 1.5 hours. The crude product was obtained

from the mixture as described in the preceding preparation, and then was crystallized (Norit) from 300 cc. of alcohol, giving 0.1 g. (15.2%) of 1-(*p*-hexadecoxyphenylazo)-2-naphthol as a red-orange powder, m.p. 82-84°. The solubility was approximately the same as that of the *n*-tetradecyl homolog.

Anal. Calcd. for $C_{32}H_{44}O_2N_2$: N, 5.73. Found: N, 5.56, 5.52.

Mixed Melting Points.

1:1 Mixture: Alkyls are:	Soften	Melt
C_{12} and C_{14}	70°	72-74°
C_{14} and C_{16}	69.5	71-75

The melting points of the pure compounds are: C_{12}, 80-82°; C_{14}, 81.5-83°; C_{16}, 82-84°.

B. *From Long-Chained Sulfanilamides*, $H_2NC_6H_4SO_2NHR$.

1. *Preparation of 1-[p-(N-n-dodecylsulfonamido)-phenylazo]-2-naphthol*, *p*-*n*-$C_{12}H_{25}NHSO_2C_6H_4NNC_{10}H_6OH$-β. One and eighty-five hundredths grams (0.005 mole) of *p*-(N-*n*-dodecylsulfonamido)-aniline hydrochloride (199) was suspended in 200 cc. of boiling 5% acetic acid with vigorous stirring. Six cubic centimeters of concentrated hydrochloric acid was added and the mixture was cooled to 0°. A solution of 3.79 g. (0.0055 mole) of sodium nitrite in 20 cc. of water was added dropwise and the

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(199) This compound was prepared in the manner described under *N-(p-aminobenzenesulfonyl)n-octadecylamine*. Mr. L. D. Apperson kindly provided an authentic sample for a mixed melting point determination.

mixture was stirred for 40 minutes; then 50 cc. of 2.5% sodium hydroxide was added, followed by the addition of 0.95 g. (0.0064 mole) of β-naphthol in 60 cc. of 5% sodium hydroxide. The mixture was stirred for 2 hours at 5-10°, then for 1 hour at room temperature. The solid was filtered off and extracted with hot benzene, the benzene solution was treated with hydrogen chloride and filtered, then was washed with water and dried over calcium chloride. The benzene was removed, and the residual red-purple solid was extracted with 100 cc. of hot acetone, leaving 0.50 g. (20.1%) of 1-[*p*-(N-*n*-dodecylsulfonamido)-phenylazo]-2-naphthol as tiny, bright red plates, m.p. 163-164°. The dye was quite soluble in warm alcohol, warm olive oil, warm benzene, and petroleum ether; it was sparingly soluble in ether and hot acetone.

Anal. Calcd. for $C_{28}H_{37}O_3N_3S$: N, 8.48. Found: N, 8.36, 8.41.

2. *Preparation of 1-[p-(N-n-octadecylsulfonamido)-phenylazo]-2-naphthol*, *p*-*n*-$C_{18}H_{37}NHSO_2C_6H_4NNC_{10}H_6OH$-β. One and sixteen-hundredths grams (0.0025 mole) of *p*-(N-*n*-octadecylsulfonamide)-aniline hydrochloride was suspended in 200 cc. of hot water with vigorous stirring, a little soap having been added to aid the dispersion. With continued stirring, the mixture was cooled to 0°, 2 cc. of concentrated hydrochloric acid was added, and a solution of 0.186 g. (0.0027 mole) of sodium nitrite was added dropwise. Stirring was continued for 1 hour at 0-5°, then 30 cc. of 2.5% sodium hydroxide was added, followed by dropwise addition of a solution of 0.432 g. (0.003 mole) of β-naphthol

in 20 cc. of 5% sodium hydroxide. The cooling bath was removed and the mixture was stirred for 2 hours, then was extracted with benzene. Treatment of the benzene solution with hydrogen chloride gave 0.6 g. of starting material, which was filtered off. The filtrate was washed with dilute alkali, and dried with calcium chloride. Most of the benzene was removed, a little methanol was added, and the resulting bright red precipitate was filtered off. The solid was crystallized from a mixture of methanol and acetone, giving 0.12 g. (8.3%) of 1-/p-(N-n-octadecylsulfonamido)-phenylazo/-2-naphthol as a red micro-crystalline powder, m.p. 158-159.5°. The solubility of the product was about the same as that of the n-dodecyl homolog with the exception of a greater solubility in acetone.

Anal. Calcd. for $C_{34}H_{44}O_3N_3S$: N, 7.25. Found: N, 7.10, 7.16.

Mixed Melting Point of the Preceding Two Derivatives.

A 1:1 mixture softens at 151° and melts at 158-160°.

VIII. Attempts to Sulfonate Tri-n-octadecylamine.

1. With Acetic Anhydride and Concentrated Sulfuric Acid (200).

Five grams (0.0065 mole) of tri-n-octadecylamine was placed in a 200 cc. round-bottomed, three-necked flask fitted with a stirrer, dropping funnel, and drying tube. With gentle stirring, 50 cc. (53.7 g.; 0.525 mole) of acetic anhydride was added dropwise, forming a creamy suspension.

(200) Sulfonation mixture described by Treibs, Ber., 70, 85 (1937).

The suspension was cooled to 0°, 15 cc. (27.2 g.; 0.23 mole) of cold (0°), concentrated sulfuric acid was added dropwise with stirring, and stirring was continued at 0° for 1.5 hours, and at 5° for 2 hours. The cooling bath was removed and stirring was continued at room temperature for 16 hours. No change in the appearance of the mixture was noted. The temperature was raised to 55° and the warm mixture was stirred for 12 hours, during which time the amine dissolved, forming a clear, brown, rather viscous solution. No evolution of gas was noted. The solution was cooled, the resulting suspension was poured into water, and the solid was filtered off and crushed on a porous plate. Having dried, the solid (I) weighed 5.8 g. and melted at 68-78°. One gram of (I) was heated with 1 g. of potassium hydroxide in 50 cc. of 50% alcohol for 40 minutes. The mixture was cooled, the liquid was poured off, and the residual solid was treated twice more in the same manner. The product was crystallized from ethyl acetate, giving 0.65 g. of solid which melted at 52-54°. The solid was identified as tri-*n*-octadecylamine through the hydrochloride (m.p. and mixed m.p. 93-95°). Another 1 g. portion of (I) was treated with Norit in 15 cc. of boiling absolute alcohol and the solution was filtered and cooled, giving 0.61 g. of white powder, m.p. 70-86°. This was treated with alkali as described above and the residual solid was crystallized from ethyl acetate, giving 0.48 g. of tri-*n*-octadecylamine. The same procedure was applied to the remainder of (I), giving 3.1 g. of tri-*n*-octadecylamine. The total amount of amine recovered unchanged was 4.13 g., or 82.6%. If (I) was considered as being entirely amine sulfate, the recovery was approximately 100%. Evaporation of the aqueous filtrate from (I) gave 0.09 g. of black solid which was not worked up.

2. <u>With Acetic Anhydride and Fuming Sulfuric Acid</u>. Five grams (0.0065 mole) of tri-<u>n</u>-octadecylamine was suspended in 50 cc. (53.7 g.; 0.525 mole) of acetic anhydride, the suspension was cooled to 0-5° (stirring), and 15 cc. (0.068 mole) of 20% oleum (cooled to 0°) was added dropwise. Stirring was continued at 0° for 1 hour, then the temperature was allowed to rise to 10° during 3 hours, and was held at 10° for 10 hours. No change of color or darkening was noted. The mixture stood at room temperature for 36 hours, after which it was dark red-brown in color. The mixture was stirred at 50° for 3.5 hours, then was poured into crushed ice, and the aqueous mixture was filtered. The residual solid was washed with 50% alcohol and dried in a vacuum desiccator. It then weighed 5.3 g. and melted at 76-80° (I). This product was treated with 3 g. of potassium hydroxide in 100 cc. of boiling 50% alcohol. The residual solid was washed with dilute alcohol and was crystallized from ethyl acetate, giving 4.1 g. of tri-<u>n</u>-octadecylamine, a recovery of 82%.

The aqueous filtrate from (I) was evaporated to 200 cc., diluted to 500 cc., then concentrated to 200 cc. to remove acetic acid. The solution was neutralized with barium carbonate, the precipitate was filtered off and washed with warm water, and the combined filtrate and washings were concentrated to 175 cc. Cooling caused separation of a dark brown solid (II) which was filtered off and redissolved in 600 cc. of boiling water. The solution was boiled with Norit, filtered, and evaporated to dryness, leaving 4.05 g. of pale yellow, crystalline solid (III), which was very difficultly soluble in boiling water. Treatment with concentrated hydrochloric acid gave no evolution of gas, therefore (III) was not barium carbonate. A suspension of (III) in cold water gave a white precipitate upon addition of sulfuric acid, and the same result was observed with a solution of (III) in slightly diluted hydrochloric acid. Hence barium presumably was present. Ignition of (III) gave a white residue which was somewhat soluble in water, forming a basic solution. Treatment of the ignition residue with 10% hydrochloric acid gave hydrogen sulfide (lead acetate test); hence sulfur was present. Analysis of (III) showed 45.9% barium present.

The aqueous filtrate from (II) was evaporated to dryness leaving a dark brown solid. This was dissolved in hot water and the solution was boiled with Norit, filtered, and evaporated to dryness, giving 7.26 g. of red-brown, crystalline residue (IV). Ignition of (IV) gave a white residue, soluble in 10% hydrochloric acid with evolution of hydrogen sulfide. The acidic solution gave a positive test for barium ion and for acetate ion. Apparently (IV) was a mixture of barium acetate and a barium salt of a sulfur-containing acid. (IV) was insoluble in, and gave no color to (cold or hot) the following solvents: ether, ethanol, absolute ethanol, methanol, chloroform, ethyl acetate, benzene, glacial acetic acid, pet. ether (b.p. 60-68°), toluene, xylene, acetone, and dioxane. Analysis of (IV) showed 40.1% barium present.

3. With 20% Oleum. Five grams (0.0065 mole) of tri-n-octadecylamine was mixed with 40 cc. (0.181 mole) of cold 20% oleum, and the mixture was stirred at 0° for 5 hours, then at 25° for 5.5 hours. The reaction mixture stood at room temperature for 10 hours, then was poured into cracked ice. The odor of sulfur dioxide was noted. The mixture was diluted to 600 cc. with water, and the brown insoluble material was filtered off, washed with water, and dried on a porous plate. The weight of product was 3.8 g. (I). Two grams of (I) was treated with alkali in hot, dilute alcohol and the residue was crystallized from ethyl acetate, giving 1.1 g. of tri-n-octadecylamine. The remainder of (I) was treated in the same way and gave 1.3 g. of tri-n-octadecylamine. The total recovery was 2.4 g., or 48%.

The aqueous filtrate from (I) was evaporated to 200 cc. and extracted with ether. No color was removed by the ether, and a similar result was obtained with pet. ether (b.p. 60-68°). Evaporation of both extracts to dryness left no residue. The aqueous layer was diluted to 500 cc., and was neutralized with barium carbonate. The precipitate was filtered off, and the filtrate was evaporated to 50 cc. and cooled, giving about 0.5 g. of brown solid (II) which effervesced upon treatment with hydrochloric acid, and gradually dissolved. The solution gave a white precipitate with sulfuric acid. Therefore (II) probably was barium carbonate.

IX. Attempt to Prepare Tetrakis(n-octadecylaminomethyl)methane, ($\underline{n}$-$C_{18}H_{37}NHCH_2)_4C$. Two and forty-three hundredths grams (0.0063 mole) of pentaerythrityl bromide (201), 14.82 g. (0.055 mole) of n-octadecylamine, and 40 cc. of absolute alcohol were heated in a sealed tube for 9 hours at 175-185°. The reaction mixture was transferred to a flask, 200 cc. of alcohol was added, and the mixture was heated to boiling, giving a clear solution. Cooling caused deposition of 1.92 g. of white solid, m.p. 92-97° (I). This was crystallized twice from benzene, giving 1.83 g. of solid, m.p. 98-100.5° (II).

The filtrate from (I) was evaporated to a brown oil, which was subjected to sublimation under aspirator vacuum. The temperature was held at 110° and the following fractions of white crystalline solid were taken: after 1.25 hours, 0.16 g., m.p. 85-141°; after 6.5 hours, 0.64 g., m.p. 85-142°; after 11 hours, 0.35 g., m.p. 105-140°. The three fractions were combined and refluxed with 5% potassium hydroxide (in 50% alcohol) and the mixture was cooled, giving a small amount of oil and 0.64 g. of pentaerythrityl bromide (m.p. and mixed m.p. 157.5-159°).

A qualitative analysis of (II) showed nitrogen and bromine to be present. Treatment of 0.1 g. of (II) with hot alcoholic potassium hydroxide (5%), followed by acidification with nitric acid and addition

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(201) Prepared according to the directions of Shurink, Org. Syntheses, 17, 73 (1937).

of alcoholic silver nitrate gave a precipitate of silver bromide. This indicated the presence of an amine salt. Accordingly, 0.64 g. of (II) was heated for 1 hour with 1 g. of potassium hydroxide in 25 cc. of 50% alcohol, the mixture was cooled, and the liquid was poured off. The residual solid was treated three times with hot 50% alcohol, leaving 0.56 g. of white solid, m.p. 63-64.5° (III). This was treated with hydrogen chloride in a mixture of pet. ether (b.p. 60-68°) and benzene, and the resulting solid was crystallized from benzene-methanol mixture, giving 0.52 g. of white powder, m.p. 100-165°. The latter was treated with alkali in hot dilute alcohol and washed as described above, leaving 0.47 g. of solid, m.p. 63-64°. A mixed melting point with (III) showed no depression.

One-tenth gram of (III) was treated with 3.5 cc. of 40% hydrobromic acid in 7 cc. of alcohol, giving a solid melting at 90-150°. Several crystallizations from benzene and from pet. ether (b.p. 60-68°) did not bring the solid to a sharp melting point.

Compound (II) was analyzed for nitrogen.

Anal. Found: N, 4.49, 4.44.

This result was closest to agreement with the per cent of nitrogen in the two possible reaction products, $(C_{18}H_{37}NHCH_2)_3CCH_2Br$ (a), and $(C_{18}H_{37}NHCH_2)_4C \cdot HBr$ (b), the calculated per cents of nitrogen being 4.42 and 4.57 respectively. Therefore a molecular weight determination was run on (II) by the Rast method after a determination on a known high molecular weight compound had been made.

Molecular Weight. Tri-*n*-octadecylamine Hydrochloride.

Calcd. for $(\underline{n}\text{-}C_{13}H_{37})_3N\cdot HCl$: Mol. wt., 810.4. Found: Mol. wt., 802.5.

Molecular Weight. Compound (II).

Calcd. for (a) above: Mol. wt., 950.4; Calcd. for (b) above: Mol. wt., 1224.9. Found for (II): Mol. wt., 594, 622.

Therefore (II) did not correspond to these possible products.

The residue of the vacuum sublimation previously described was subjected to vacuum distillation and gave 4.5 g. of material boiling at 150-160°/3 mm. The distillate solidified on cooling, and was identified as *n*-octadecylamine by conversion to N-phenyl-N'-*n*-octadecylurea, m.p. and mixed m.p. 99-100°. The residue of the distillation was crystallized from alcohol, giving a pale yellow solid, m.p. 96-150° (IV). This was treated with potassium hydroxide in 50% alcohol, and the residual solid was crystallized from alcohol (Norit) to give 0.71 g. of white solid, m.p. 68-70° (V). This was crystallized from alcohol, giving a solid melting at 70-72°, and treatment of the latter with hydrogen chloride in alcohol gave glistening plates, m.p. 172-176°. The latter product was shown to be di-*n*-octadecylamine hydrochloride by conversion to N,N-di-*n*-octadecylurea, m.p. and mixed m.p. 63-65° (202). Therefore (V) was di-*n*-octadecylamine.

The filtrate from (IV) was treated with hydrogen chloride, giving

(202) Mr. W. I. Harber kindly provided an authentic sample.

a solid melting at 158-177°. Evaporation of the filtrate gave a brown solid which was treated with Norit in alcohol to give white crystals, m.p. 145-176°. The two fractions were combined (1.01 g.) and refluxed with potassium hydroxide in 50% alcohol for 2.5 hours. The product was washed with hot dilute alcohol, and was crystallized from alcohol to give 0.6 g. of di-n-octadecylamine, identified as described for (V).

X. Metalations of Long-Chained Compounds.

A. Preparation of Compounds.

1. Preparation of N-Ethyldiphenylamine (203). Thirty-three and eight-tenths grams (0.2 mole) of diphenylamine and 46.2 g. (0.3 mole) of diethyl sulfate were heated on a steam bath for 20 hours under reflux. The warm, syrupy mixture was poured slowly with stirring into 200 cc. of 15% sodium carbonate and the mixture was stirred at 50-60° for 2 hours. The mixture was extracted with benzene, the benzene layer was washed with water, and then was shaken with 100 cc. of concentrated hydrochloric acid and left in contact with the acid overnight. A crystalline solid separated at the interface, and was removed by filtration on a Gooch crucible, giving 2.3 g. of diphenylamine hydrochloride. The benzene layer was separated from the filtrates and dried over sodium sulfate. Removal of the benzene followed by vacuum distillation of the

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(203) Prepared according to directions given by Gibson and Vining, J. Chem. Soc., 123, 840 (1932).

residual oil gave 18.8 g. of brown liquid, b.p. 145-148°/9 mm. This product was redistilled, giving 16.7 g. (42.5%) of N-ethyldiphenylamine, b.p. 141-142°/8 mm.

2. Preparation of N-n-dodecyldiphenylamine. Thirty-three and eight-tenths grams (0.2 mole) of diphenylamine and 24.8 g. (0.1 mole) of *n*-dodecyl bromide were mixed in a 200 cc. round-bottomed flask, and the mixture was heated (under an air condenser) at 165-175° for 10.5 hours. The reaction mixture was extracted with dry ether, leaving 12.3 g. of diphenylamine hydrochloride. The ether solution was saturated with hydrogen chloride, causing precipitation of 11.3 g. of diphenylamine hydrochloride, which was removed by filtration. The filtrate was washed with 10% potassium hydroxide and with water, and was dried over calcium chloride. The ether was removed and the residue was distilled under vacuum, giving 14.1 g. of pale yellow liquid, b.p. 175-212°/3 mm. This was redistilled to give 12.0 g. (35.6%) of N-*n*-dodecyldiphenylamine, b.p. 198-202°/2 mm.; n_D^{20} 1.5432.

Anal. Calcd. for $C_{24}H_{35}N$: N, 4.16. Found: N, 4.32, 4.30.

3. Preparation of Phenyl n-Tetradecyl Sulfide. This compound was prepared by the method used by Ipatieff and co-workers (204) for the preparation of *n*-amyl phenyl sulfide. A solution of 11.0 g. (0.10 mole) of thiophenol and 5.6 g. (0.10 mole) of potassium hydroxide in 25 cc. of

(204) Ipatieff, Pines, and Friedmann, *J. Am. Chem. Soc.*, *60*, 2732 (1938).

alcohol was heated to 80° on a water bath, and 27.7 g. (0.10 mole) of n-tetradecyl bromide was added dropwise during 40 minutes. The mixture was refluxed for 2 hours, diluted with water to dissolve the precipitate of potassium bromide, and extracted with ether. The ether solution was washed successively with water, 10% potassium hydroxide, and water, and was dried over calcium chloride. The ether was removed, leaving an oil which solidified on standing. The crude solid was crystallized twice from an alcohol-acetone mixture to give 18.2 g. (59.4%) of phenyl n-tetradecyl sulfide as glistening white plates, m.p. 39.5-41.5°.

Anal. Calcd. for $C_{20}H_{34}S$: S, 10.46. Found: S, 10.55, 10.59.

B. Metalations (205).

1. Attempts to Metalate N-Ethyldiphenylamine.

a. A solution of 8.0 g. (0.0406 mole) of N-ethyldiphenylamine in 20 cc. of ether was added dropwise to a stirred solution of approximately 0.082 mole of n-butyllithium (206) in 80 cc. of ether and the mixture was refluxed and stirred for 20 hours. The color test for an

(205) The metalations were run under an atmosphere of pure dry nitrogen in the customary apparatus, which consists of a round-bottomed, three-necked flask, fitted with a dropping funnel, a mercury-sealed stirrer, and a Hopkins condenser.

(206) Prepared by adding 24.4 g. (0.178 mole) of n-butyl bromide to a suspension of 2.50 g. (0.361 g. atom) of finely cut lithium in 80 cc. of dry ether in the apparatus described above. The solution was filtered through glass wool prior to use.

organometallic compound (207) was positive at the end of this period. The reaction mixture was carbonated by pouring it upon crushed solid carbon dioxide, and was acidified with dilute hydrochloric acid. The ether layer (I) was washed with 100 cc. of 10% hydrochloric acid, then with 200 cc. of 10% potassium hydroxide, and was dried over sodium sulfate.

The alkaline extract was acidified with dilute hydrochloric acid, giving a turbid mixture which was extracted with ether. The ether solution was dried, the ether was distilled, and the residual oil was taken up in pet. ether (b.p. 60-68°). No crystals were obtained by long cooling; therefore, the mixture was dissolved in ether and the ether solution was washed thoroughly with water. The solvent was removed, the residue was steam distilled to remove valeric acid, and the residue of the steam distillation was taken up in ether, the solution was dried, and the ether was removed. The oily residue was dissolved in a mixture of pet. ether (b.p. 60-68°) and absolute alcohol, and the solution was boiled with Norit, filtered, and cooled in ice. No crystals were obtained. The solvent was removed, leaving 0.7 g. of thick, orange-yellow oil, which was treated with 50 cc. of hot 5% sodium bicarbonate, whereupon part of the oil dissolved. The mixture was extracted with ether (II), acidified with hydrochloric acid, and again extracted with ether. The resulting ether solution was evaporated, leaving an oil which

(207) Gilman and Schulze, J. Am. Chem. Soc., 47, 2002 (1925).

was dissolved in a mixture of pet. ether (b.p. 60-68°) and absolute alcohol. After standing for several days in the refrigerator, the solution deposited 5-10 mg. of N-phenylanthranilic acid, m.p. and mixed m.p. 183-184° (208). Apparently this acid came from a small amount of diphenylamine present in the starting material.

The ether extract (II) of the mixture obtained by the hot bicarbonate treatment was dried and the ether was evaporated, leaving about 0.5 cc. of thick brown oil. This was dissolved in pet. ether (b.p. 60-68°), and the solution was cooled to give 3-5 mg. of N-phenylanthranilic acid, identified by a mixed melting point. The filtrate from this acid was cooled in dry ice-acetone mixture to give about 0.1 g. of pale yellow solid, which, after having been washed with pet. ether (b.p. 60-68°), melted at 115-130°. This was recrystallized from pet. ether (b.p. 60-68°) giving about 0.05 g. of almost colorless crystals, m.p. 112-125°. The latter was crystallized several times from slightly diluted acetic acid, giving 5-10 mg. of solid melting at 108-112°. This solid has not been identified.

The ether was removed from the original ether layer (I) and the residue was subjected to vacuum distillation, giving 5.2 g. of N-ethyldiphenylamine, a recovery of 65%.

b. A solution of 8.0 g. (0.0406 mole) of N-ethyldiphenylamine in 20 cc. of ether was added as in (a) to a solution of approximately

(208) Authentic sample kindly provided by Mr. S. M. Spatz.

0.083 mole of n-butyllithium in 100 cc. of ether, and the mixture was stirred and refluxed for 27.5 hours. The color test was positive at the end of this period. The reaction mixture was carbonated as in (a), acidified with cold dilute hydrochloric acid, and the ether layer (I) was washed with 200 cc. of 10% potassium hydroxide and with 200 cc. of 10% hydrochloric acid (II). The potassium hydroxide extract was inadvertently lost, hence no information on the possible acidic products was obtained.

The original ether layer (I) was dried over sodium sulfate, the ether was removed, and the residue was vacuum distilled, giving 4.6 g. of N-ethyldiphenylamine, b.p. 137-144°/7 mm., and 1.0 g. of dark brown liquid, b.p. 155-204°/7 mm. The recovery of N-ethyldiphenylamine was 57.5%.

The acid extract (II) was made alkaline with potassium hydroxide, then slightly acidic with acetic acid, whereupon a small amount of brown precipitate separated. This was filtered off and crystallized from pet. ether (b.p. 60-68°), giving about 5 mg. of N-phenylanthranilic acid.

c. A solution of 8.0 g. (0.0406 mole) of N-ethyldiphenylamine (209) in 20 cc. of ether was added to a solution of approximately 0.082 mole of n-butyllithium in 100 cc. of ether and the mixture was refluxed for 29 hours. The color test was positive at the end of this time. The reaction mixture was carbonated as in (a) and acidified with

(209) Material recovered from previous runs.

hydrochloric acid. The ether layer (I) was washed with 250 cc. of 10% potassium hydroxide, then with 200 cc. of 10% hydrochloric acid (II), and with water, and was dried.

The alkaline extract was acidified with hydrochloric acid and the resulting turbid mixture was extracted with ether. The ether solution was washed with 2.5% sodium bicarbonate (III) and dried over sodium sulfate, and the ether was removed, leaving a thick oil. The oil was subjected to steam distillation to remove residual valeric acid and then was dissolved in 60 cc. pet. ether (b.p. 60-68°). Cooling gave no crystals, nor did evaporation to 30 cc. followed by cooling give any precipitate. The solvent was removed, the residual oil was taken up in slightly diluted alcohol and the solution was boiled with Norit, filtered, and cooled. No solid separated. Evaporation to a smaller volume following by cooling caused separation of an oil. The mixture was allowed to stand several days in the refrigerator, but no crystallization occurred. Attempts to crystallize the oil from diluted acetone, pet. ether (b.p. 28-38°), methanol, and acetic acid were unsuccessful. The oil was redissolved in 10% potassium hydroxide, the solution was acidified and extracted with ether, and the ether solution was evaporated to a viscous oil (2 g.). The latter was treated with Norit in absolute alcohol and the solution was filtered and cooled, giving no solid. Most of the alcohol was removed and the residual thick liquid was cooled several hours in an ice-salt mixture; no solidification occurred. The remainder of the alcohol was removed under vacuum and the residual thick oil was allowed to stand in the refrigerator for several days. No crystallization was observed. An attempt to vacuum-sublime a product from the oil was not successful. Long cooling in contact with a little pet. ether (b.p. 60-68°) gave no crystals.

The ether was removed from the original ether layer (I) and the residual oil was distilled under vacuum, giving 4.3 g. (53.7% recovery) of N-ethyldiphenylamine, b.p. 136-143°/9 mm.; and 0.8 g. of brown liquid, b.p. 150-178° (dec.)/10 mm. The recovery of 53.7% of the starting material in this run compares well with the 57.5% recovery noted in the 27.5 hour run described in (b).

The sodium bicarbonate extract (III) was acidified and extracted with ether, the ether solution was dried, and the ether was removed, leaving a small amount of oil having a strong odor of valeric acid. The oil was taken up in pet. ether (b.p. 60-68°) and the solution was cooled, giving no solid.

The acid extract (II) was made alkaline with potassium hydroxide, then faintly acid with acetic acid. The acidic solution was extracted with ether, the ether solution was dried, and the ether was removed, leaving about 0.5 cc. of dark oil which was not further investigated.

2. Attempt to Prepare N-Ethyl-N-phenylanthranilic Acid. This acid has not been reported in the literature. The method used in this attempted preparation has been applied successfully to the preparation of

N-ethylcarbazole-2,8-dicarboxylic acid (210). One gram (0.0047 mole) of N-phenylanthranilic acid (211) was dissolved in 20 cc. of acetone, and 2.88 g. (0.01868 mole) of diethyl sulfate was added. The mixture was heated to refluxing and a hot solution of 6 g. of potassium hydroxide in 5 cc. of water was added dropwise with stirring. The resulting thick mixture was stirred and refluxed for 2 hours, 20 cc. of acetone was added, and stirring and heating were continued for one-half hour longer. To saponify any ethyl esters, 20 cc. of water was added and the mixture was boiled for 6 hours. The mixture was extracted with ether, the ether solution was extracted thoroughly with 10% potassium hydroxide, and the alkaline extract was acidified, giving a precipitate of pale yellow solid. This was crystallized from a mixture of pet. ether (b.p. 60-68°) and alcohol, giving 0.93 g. of crystalline solid, m.p. 183-184°. The solid was identified as N-phenylanthranilic acid by a mixed melting point. Partial evaporation of the filtrates followed by cooling gave no product.

3. Attempts to Metalate N-n-Dodecyldiphenylamine.

a. Five grams (0.0148 mole) of N-*n*-dodecyldiphenylamine was dissolved in 15 cc. of ether and the solution was added with stirring to approximately 0.032 mole of *n*-butyllithium in 80 cc. of ether. The mixture was refluxed for 24 hours; a color test was positive at the end

(210) S. M. Spatz, unpublished results.

(211) Kindly provided by Mr. S. M. Spatz.

of this time. The reaction mixture was carbonated upon solid carbon dioxide, the mixture was acidified with 1:1 hydrochloric acid, and the ether layer (I) was washed with 250 cc. of 10% potassium hydroxide.

The alkaline extract was acidified with hydrochloric acid and extracted with ether. The ether solution was dried and the ether was removed, leaving about 2 cc. of brown oil having a strong odor of valeric acid. The oil was subjected to steam distillation, leaving a clear residual aqueous layer (II) with no oil or solid admixed, even after strong cooling.

The original ether layer (I) was dried and the ether was removed, leaving a brown oil. This was vacuum distilled to give 4.76 g. of N-n-dodecyldiphenylamine, b.p. 198-204°/2 mm., a recovery of 95.3%.

The residual aqueous layer (II) from the steam distillation was extracted with ether, the ether solution was dried, and the ether was removed, leaving only traces of an oil.

b. To a solution of approximately 0.032 mole of n-butyllithium in 80 cc. of ether was added a solution of 5.0 g. (0.0148 mole) of N-n-dodecyldiphenylamine in 20 cc. of ether, and the mixture was refluxed for 51 hours. The color test was positive at the end of this time. The reaction mixture was carbonated as in (a) and then acidified with dilute hydrochloric acid. The ether layer was washed with 400 cc. of 10% potassium hydroxide (in 50 cc. portions), then with water, and was dried over calcium chloride. The ether was removed and the residual oil was distilled under vacuum, giving 4.69 g. of N-n-dodecyldiphenylamine, a recovery of 93.8%.

The alkaline extract was acidified with hydrochloric acid and extracted with ether, and the ether solution was washed with 200 cc. of 5% sodium bicarbonate and dried. Removal of the ether left traces of an oil. The bicarbonate extract was acidified and extracted with ether, the ether solution was dried, and the ether was removed, leaving only traces of a liquid having a strong odor of valeric acid.

c. Five grams (0.0148 mole) of N-n-dodecyldiphenylamine was added to a solution of approximately 0.032 mole of n-butyllithium in 80 cc. of ether and the mixture was refluxed for 72 hours. A color test at the end of this time was positive. The reaction mixture was carbonated in the usual manner and then acidified with dilute hydrochloric acid. The ether layer was extracted with 200 cc. of 10% potassium hydroxide and with 125 cc. of 2% hydrochloric acid (I), then washed with water and dried. The ether was removed and the residue was distilled under vacuum, giving 4.80 g. of N-n-dodecyldiphenylamine, a recovery of 96%.

The alkaline extract was acidified with hydrochloric acid and extracted with ether; the ether solution was washed with water and dried, and the ether was removed, leaving about 0.25 cc. of oil having a strong valeric acid odor. This was taken up in ether, the solution was extracted with 5% sodium bicarbonate and dried, and the ether was removed, leaving only traces of an oil. The bicarbonate extract was acidified and extracted with ether, the ether solution was dried, and the ether was removed, leaving only traces of an oil.

The acid extract (I) was made alkaline with potassium hydroxide, then slightly acid with acetic acid. No precipitation or turbidity was noted.

3. Metalation of Hexadecylbenzene. The sample of hexadecylbenzene (212) used in this run was prepared by Mr. R. N. Meals by the Friedel-Crafts alkylation of benzene with n-hexadecyl bromide.

A suspension of approximately 0.033 mole of n-butylsodium was prepared by stirring 5 g. of sodium wire with 5.23 g. (0.0166 mole) of di-n-butylmercury in 50 cc. of unsaturated-free pet. ether (b.p. 85-100°) for 1 hour. Ten grams (0.032 mole) of hexadecylbenzene was added to the n-butylsodium suspension and the mixture was stirred at room temperature for 72 hours. The mixture became very viscous during the first 24 hours of stirring so 50 cc. of solvent were added; a like amount was added after 48 hours, and another 50 cc. portion was added just prior to carbonation. The color test was positive at the end of the 72 hours of stirring. The reaction mixture was carbonated upon solid carbon dioxide and acidified with dilute hydrochloric acid. The solvent layer was washed with 200 cc. of 10% potassium hydroxide, then with water, and was dried over sodium sulfate.

The alkaline extract was acidified with hydrochloric acid and ex-

(212) B.p. 211-228°/13 mm.; $n_D^{31.6}$ 1.4780.

tracted with ether, and the ether solution was washed with water, then with 2.5% sodium bicarbonate, and dried. The ether was removed and the residual dark oil (about 4 cc.) was treated with Darco in acetone. Subsequent to cooling, the acetone solution deposited 0.07 g. of white powder, m.p. 83-86° (I). To obtain an indication as to whether (I) was the expected acid, a neutralization equivalent was run, giving a value of 285 as compared with 346 calculated for a monocarboxyhexadecylbenzene. Further concentration of the filtrate from (I) gave two crops of white solid, which were crystallized from alcohol, giving 0.11 g. of microcrystalline solid melting at 77-82° and 0.09 g. of solid melting at 76-80°. (I) was crystallized from alcohol, giving 0.05 g. of microcrystalline solid, m.p. 85-88°. As yet, these fractions have not been investigated further.

The original solvent layer was evaporated, leaving an oil which was distilled under vacuum to give 6.7 g. of the starting material, b.p. 212-227°/13 mm.; N_D^{32} 1.4778.

4. Attempts to Metalate Phenyl n-Tetradecyl Sulfide.

a. To a solution of approximately 0.03 mole of *n*-butyllithium in 80 cc. of ether was added a solution of 9.18 g. (0.03 mole) of phenyl *n*-tetradecyl sulfide in 30 cc. of ether and the resulting mixture was stirred and refluxed for 52 hours. The color test was negative at the end of this period. The reaction mixture was carbonated upon solid carbon dioxide and acidified with hydrochloric acid; the acidified mixture had a strong sulfurous odor; no valeric acid odor was detected. The ether layer was washed with 300 cc. of 5% potassium hydroxide, then with water, and was dried over sodium sulfate. Removal of the ether left an oil which was crystallized from alcohol-acetone mixture, giving 5.9 g. of white plates, m.p. 36-40° (I). This solid was recrystallized from alcohol to give 5.3 g. of phenyl n-tetradecyl sulfide, m.p. and mixed m.p. 38-41°. The filtrate from (I) was concentrated and cooled, giving 1.9 g. of pale brown solid. This was crystallized twice from alcohol-acetone mixture to give 0.58 g. of phenyl n-tetradecyl sulfide, m.p. and mixed m.p. 37.5-41° (the total recovery of phenyl n-tetradecyl sulfide was 64%). The filtrate was evaporated to a brown oil (1.1 g.) which has not been worked up.

The alkaline extract was acidified with hydrochloric acid and extracted with ether, and the ether solution was washed with water and dried. Removal of the ether followed by long cooling of the small liquid residue gave 5-10 mg. of benzoic acid, m.p. and mixed m.p. 120-122°. No other acidic material was isolated.

b. To a solution of approximately 0.03 mole of n-butyllithium in 90 cc. of unsaturated-free pet. ether (b.p. 28-38°) was added 8.9 g. (0.029 mole) of phenyl n-tetradecyl sulfide in 20 cc. of the same solvent. The solution was stirred and refluxed for 48 hours, at the end of which time the color test was positive. The reaction mixture was carbonated in the usual manner and acidified with hydrochloric acid, giving a definite odor of valeric acid. The solvent layer was washed with

250 cc. of 5% potassium hydroxide, then with water, and was dried. The solvent was removed and the residual oil was crystallized from alcohol, giving 8.0 g. of phenyl n-tetradecyl sulfide, m.p. and mixed m.p. 38-41° (I). The filtrate from (I) was concentrated and cooled to give 0.2 g. of phenyl n-tetradecyl sulfide, m.p. 38-40.5°. The total recovery of starting material was 92.1%.

The alkaline extract was acidified and extracted with ether, and the ether solution was evaporated to a small amount of an oil having a strong valeric acid odor. This was taken up in 3-5 cc. of pet. ether (b.p. 60-68°) but gave no crystals upon long cooling.

DISCUSSION

It was stated in an introductory paragraph that the purpose of the investigations described in this thesis was to examine further the limits of the application of the phenomenon of homology to long-chained compounds, and at the same time to prepare compounds which might serve as derivatives or exhibit some other useful property. Therefore, this discussion of the experimental results is designed to point out where possible the success or failure of that purpose.

In the majority of the cases studied, methods applicable to the preparation of low molecular weight compounds were found to apply also to their long-chained homologs with no marked changes in the conditions of the reaction. Moreover, the physical properties of the long-chained compounds prepared by such reactions were observed to vary regularly in the several series, and to approximate values which would be predicted from those of the lower structural homologs. However, in some cases, exceptions to the preceding generalities were noted. These will be considered more fully in the following discussion of the several phases of the experimental work.

n-Octadecylamine underwent reaction with benzoyl chloride, p-toluenesulfonyl chloride, and p-acetaminobenzenesulfonyl chloride under customary conditions to give good yields of the corresponding long-chained amides. These are crystalline solids with definite melting points and therefore seem suitable as derivatives for characterizing the amine. It should be noted that N-(p-aminobenzenesulfonyl)-n-octadecylamine was observed to melt at 118.5-120.5°, whereas Crossley and co-workers (104) report the melting point of the same compound as 127-130°. Their compound was crystallized from dilute alcohol rather than from acetone; possibly this accounts for the difference. Phenyl isocyanate and phenyl isothiocyanate reacted smoothly with n-octadecylamine giving the corresponding urea and thiourea in excellent yields. Since these are readily prepared in a pure state and exhibit comparatively high melting points, they are the best of the derivatives reported here. The reaction of stearoyl chloride with n-octadecylamine, while interesting from the standpoint of homology, did not lead to a satisfactory derivative because of great difficulty in purifying the product.

Di-n-octadecylamine formed the expected di-substituted amide by reaction with p-toluenesulfonyl chloride, though in lower yields than n-octadecylamine. The failure of the attempts to prepare the p-acetaminobenzenesulfonyl-derivative of di-n-octadecylamine and the N-dialkyl-N'-phenylurea and -thiourea was due perhaps to improper conditions for the reaction of so large a molecule. Apparently, under conditions comparable to those applied to lower structural homologs, di-n-octadecylamine did not exhibit homology of reactions in these cases.

An attempt to prepare tetra-n-octadecylammonium iodide was unsuccessful. Since trimethylamine and n-docosyl bromide (C_{22}) have been observed to form n-docosyltrimethylammonium bromide (134) at a lower temperature than employed here, the failure of this attempted preparation seems to indicate a limit of homology with tertiary amines. Apparently no quaternary salt formed, and the high temperature only aided in the abstraction of hydrogen iodide from n-octadecyl iodide by the action of the base, tri-n-octadecylamine, to form the salt of the amine. This result was verified by a check run, but still no indication of octadecene was observed. The observed formation of the amine hydroiodide is difficult to align with the results of Girard and Fourneau (135), who prepared tetra-n-hexadecylammonium iodide by passing gaseous ammonia into molten n-hexadecyl iodide at 200°, a temperature 20° higher than that used here. It would seem that tri-n-hexadecylamine would be an intermediate stage in their preparation of the quaternary salt, and that there would be an even greater tendency for the tertiary amine to abstract hydrogen iodide from the alkyl halide at the higher temperature. Even if any hydrogen iodide formed reacted preferentially with excess ammonia rather than the amine, it seems the product should have been the tertiary amine and not the quaternary salt.

The preparations of the long-chained barbituric acids and the intermediate malonic esters were conducted without difficulty under customary conditions to give fair yields of products except with the n-octadecyl members. The poor yields of diethyl ethyl-n-octadecylmalonate may be attributed in part to the difficulty in purification by crystallization and to losses by decomposition when purified by vacuum distillation. The boiling points of the four esters prepared, of which diethyl ethyl-_n_-hexadecylmalonate and the _n_-octadecyl homolog had not been reported previously, rose regularly with increasing chain lengths. The boiling points observed were: C_{12}, 170-174°/2 mm.; C_{14}, 175-177°/1 mm.; C_{16}, 198-204°/2 mm.; and C_{18}, 206-210°/2 mm. Stanley and co-workers (138) reported the boiling point of diethyl ethyl-_n_-dodecylmalonate as 181-183°/4 mm., and that of the _n_-tetradecyl homolog as 172-177°/3 mm.

5-Ethyl-5-_n_-dodecyl-barbituric acid and its _n_-tetradecyl- and _n_-hexadecyl homologs were formed in fair yield under the conditions used for the preparation of lower homologs. However, for the _n_-octadecyl homolog, a higher temperature was required. It is interesting to note that the method employed by Buck and co-workers (102) for the condensation of N-_n_-octadecylurea with diethyl ethylisobutylmalonate to form 1-_n_-octadecyl-5-ethyl-5-isobutyl-barbituric acid was unsuccessful when applied to the condensation of urea with diethyl ethyl-_n_-octadecylmalonate.

The melting points of the long-chained barbituric acids described here showed a regular decrease from the _n_-dodecyl to the _n_-hexadecyl member, but the melting point of the _n_-octadecyl homolog was higher than those of the other three. Since the melting points of the lower 5-ethyl-5-_n_-alkyl-barbituric acids decrease with increasing chain length, the decrease observed with the above three homologs was expected. It may be, then, that the melting point curve of the even members reaches a minimum between the n-hexadecyl and n-octadecyl members. Therefore, it would be interesting to prepare the corresponding n-eicosyl (C_{20}) and n-dodosyl (C_{22}) compounds to determine whether their melting points are higher yet than that of the n-octadecyl member. The melting points of mixtures of the barbituric acids with their next higher homologs exhibited considerable depression. Hence these compounds might be used as derivatives for the corresponding malonic esters, or more indirectly, for the n-alkyl halides.

The preparationsof the homologs of Phenacetin and the intermediate compounds were effected smoothly by customary procedures. The n-long-chained-alkyl p-nitrophenyl ethers were formed in good yields under conditions less drastic than those employed for lower homologs (144), and reduction to the corresponding amines proceeded under ordinary conditions. Hence the phenomenon of homology may be said to apply here. Acetylation of the amines to give the homologs of Phenacetin (p-acetaminophenyl n-alkyl ethers) also was effected by a customary procedure. However, the yield of acetylated product was somewhat lower than expected. A different method of acetylation, perhaps at higher temperature, would doubtless remedy this difficulty.

The melting points of the higher two long-chained ethers are sufficiently high that the compounds might be useful as derivatives for the long-chained halides. The mixed melting points of the Phenacetin homologs exhibit considerable depression, a fact which should make possible their use as derivatives. As would be predicted upon the basis of homology, the melting points of both the alkyl p-nitrophenyl ethers and the alkyl p-acetaminophenyl ethers increase with increasing chain length.

The reaction of potassium cyanate with the long-chained p-alkoxyanilines gave unsatisfactory yields of the desired homologs of Dulcin. Since p-dodecoxyphenylurea and p-tetradecoxyphenylurea exhibited no effect on the sense of taste, perhaps because of great insolubility in the secretions of the mouth, the investigation was not carried further. However, these two compounds and higher homologs might be prepared in better yields by replacing potassium cyanate with nitrourea, according to the method used by Buck and co-workers (102) for the preparation of long-chained ureas such as N-n-hexadecylurea. It should be noted that the preparation of substituted ureas by the action of potassium cyanate upon wholly aliphatic long-chained amines has been effected with amines such as di-n-octadecylamine (213).

The failure of the attempts to prepare dihydrazides of long-chain-substituted malonic acids apparently was due to the formation of mixtures of compounds having approximately the same solubilities. Since the presence of two like reactive groups in the long-chained malonic esters enables both mono- and disubstitution by hydrazine to form the corresponding mono- and dihydrazides, it is likely that under the conditions used, this actually occurred. Other possible components of the mixtures

(213) W. I. Harber, unpublished results.

are cyclic compounds formed by reaction of one molecule of hydrazine with both ester groups of one molecule of long-chained ester, and products resulting from the condensation of one ester group from each of two molecules of the malonic ester with one molecule of hydrazine. Apparently considerable study would be required to determine conditions under which the long-chained malonic esters would be converted largely to the desired dihydrazides. These unsuccessful attempts to prepare the dihydrazides seem to be an example of the limitation of the application of homology, since diethyl ethylmalonate reacted smoothly with hydrazine under the same conditions to give good yields of the dihydrazide of ethylmalonic acid (120). However, the preparation of the intermediate diethyl *n*-alkylmalonates was effected readily by customary procedures, and the boiling points exhibited a regular increase with increasing chain length as would be expected. The boiling points observed at two millimeters were: C_{12}, 158-161°; C_{14}, 168-175°; and C_{16}, 182-188°. The boiling point of the *n*-tetradecyl homolog has not been reported previously. For the *n*-dodecyl homolog Rothstein (151) gave the boiling point as 201-203°/13 mm., and Brigl (152) reported the boiling point of the *n*-hexadecyl member as 238-240°/14 mm.

The long-chained azo dyes described in this thesis were prepared by a method developed for diazotizing water-insoluble long-chain-substituted aniline hydrochlorides in the customary aqueous medium. The yields of product were rather poor due to the difficulty of dispersing the solid amine salt as particles small enough to insure good contact with the diazotizing agent. This difficulty might be overcome by the use of a different method for preparing the suspension, or by employing an organic solvent such as glacial acetic acid. An attempt to use the mixture of glacial acetic and phosphoric acids described by Schoutissen (214) was unsuccessful because of the formation of intractable emulsions.

The dyes prepared from the p-alkoxyanilines are not suitable derivatives since the mixed melting points show very little depression. Because of their comparatively high melting points, the two dyes derived from long-chained sulfanilamides might be used as derivatives, but again, a mixed melting point gives little depression.

The attempts to sulfonate tri-n-octadecylamine were unsuccessful. Only with twenty per cent oleum did any marked amount of reaction occur and this apparently involved decomposition of approximately half of the amine rather than sulfonation. In the run in which acetic anhydride and fuming sulfuric acid were used, the crystalline products isolated seemingly were the result of interaction of the components of the sulfonation medium, for the amounts of these compounds are much too great in comparison with the eighty-two per cent recovery of tri-n-octadecylamine to have come from the amine itself. The action of chlorosulfonic acid upon the long-chained aliphatic amines should be investigated, and likewise the effect of oleum over a long period of time at temperatures

(214) Schoutissen, J. Am. Chem. Soc., 55, 4531 (1933).

in the range from 0° to 5°. Perhaps violent agitation of a sulfonating agent with a solution of the amine in an inert solvent such as s-tetrachloroethane (215) would lead to the desired sulfonation product.

The attempted preparation of tetrakis(n-octadecylaminomethyl)-methane was unsuccessful probably because of the formation of an intermediate product under the conditions employed. The formation of the desired compound might be expected to proceed in a stepwise manner, the four bromine atoms of pentaerythrityl bromide [tetrakis(bromomethyl)-methane] being successively replaced by n-octadecylamino groups. Hence the product isolated might well represent one of the intermediate stages, and doubtless it would be necessary to investigate a great number of different experimental conditions to discover a set which would give the desired compound as the major product. Methylamine was reported to give good yields of the lower homolog (161) under the conditions used in this attempt; therefore, it seems that the extension of the phenomenon of homology to n-octadecylamine in this particular reaction is somewhat limited, in that special conditions apparently are necessary. Even so, the difference in reaction is probably only one of rate and not of kind.

The study of the metalation of long-chained compounds has not progressed sufficiently at this time to allow conclusions to be drawn. However, the results obtained thus far are summarized here. Metalation of N-ethyldiphenylamine with n-butyllithium in ether yielded a product

(215) Pollack, Monatsh., 54, 90 (1929).

which may be the expected N-ethyl-N-phenylanthranilic acid, but which as yet has not been identified. In the light of the results previously obtained with diphenylamine (167) and N-ethylcarbazole (169), metalation of N-ethyldiphenylamine in the corresponding ortho-position would be expected.

In all of the attempts to metalate N-n-dodecyldiphenylamine with n-butyllithium in ether, most of the starting material was recovered unchanged, and no acidic material other than valeric acid was isolated. If the product from N-ethyldiphenylamine later is shown to be the expected acid, then it would seem that homology of reaction does not apply to the higher homolog, N-n-dodecyldiphenylamine. With the latter, however, the long periods of refluxing in ether may have lowered the concentration of the metalating agent (by ether cleavage) to a point below that required for metalation before the apparently slow metalation reaction could proceed to any extent. A better comparison of the two amines from the homology standpoint could be made by subjecting them to the action of n-butyllithium in an inert solvent such as light petroleum ether.

Metalation of hexadecylbenzene with n-butylsodium in petroleum ether (b.p. 85-100°) gave an acidic product which as yet has not been identified. Oxidation of the product should show whether the acidic group is in the aromatic nucleus or the aliphatic side chain, for the former possibility would yield a phthalic acid, whereas the latter would yield only benzoic acid. It is proposed to react n-butylsodium with hexadecylbenzene prepared by reduction of palmitophenone (from palmitoyl chloride and benzene by the Friedel-Crafts reaction) and to compare the product with that obtained from the above reaction. This work is in progress. If the two metalation products are the same, that fact will be further evidence that the hexadecylbenzene prepared by long-chained-alkylation of benzene by the Friedel-Crafts method has the same structure as that prepared by long-chained-acylation.

Phenyl-n-tetradecyl sulfide gave no metalation product with n-butyllithium in diethyl ether or in petroleum ether. The isolation of a small amount of benzoic acid from the ether run agrees with results obtained by Webb (216), who isolated benzoic acid from similar runs with methyl, ethyl, and butyl phenyl sulfides. However, he also obtained metalation products; for example, ethyl phenyl sulfide gave o-ethylmercaptobenzoic acid (170). On the basis of homology, phenyl n-tetradecyl sulfide should have yielded o-n-tetradecylmercaptobenzoic acid. Here the large molecule may be too sluggish to react with n-butyllithium, and the effect of the more reactive agent, n-butylsodium, should be investigated. No metalation product and no benzoic acid was isolated from the petroleum ether run. Webb (216) obtained a similar negative result in a forty-five hour run of methyl phenyl sulfide and n-butyllithium in petroleum ether.

The long-chained barbituric acids, the long-chained p-acetaminophenyl alkyl ethers, and the long-chained sulfanilamides were prepared with a

(216) F. J. Webb, unpublished results.

view toward possible recurrence of the pharmacological effects of the lower homologs. Because of the difficulties involved in testing these insoluble compounds, no results of pharmacological tests are available at this time. Since all of the long-chained dyes prepared were soluble in olive oil, it was hoped that they might be effective against capsulated organisms, where the long chain supposedly would penetrate the capsule, bringing the active portion of the molecule into contact with the organism itself. However, no tests toward this end have been made.

Through the kind cooperation of Dr. Rachel Edgar and Miss Virginia Ester of the Textiles Chemistry Department, one of the dyes [1-(*p*-tetradecoxyphenylazo)-2-naphthol] is being tested for its tintorial effect on a number of fabrics. Results obtained thus far indicate that the compound has some promise as an agent for dyeing nylon.

In conclusion it seems fair to state that in general the phenomenon of homology has been found applicable, without serious limitations, to the several series of long-chained aliphatic compounds whose preparation and properties are included in these investigations.

NOTE ON NOMENCLATURE

In answer to an inquiry regarding the naming of compounds containing a long-chained alkoxy group, Dr. E. J. Crane and Dr. Leonard T. Capell of the editorial staff of Chemical Abstracts kindly provided the following information.

"Chemical Abstracts prefers the compound names for these radicals over the slightly shorter contracted forms. Thus we prefer dodecyloxy, tetradecyloxy, cetyloxy (we use cetyl instead of hexadecyl, although hexadecyl is just as good if you prefer it), and octadecyloxy. We use parentheses when the two parts of the name are in alphabetical order, and omit the parentheses when the two parts are out of alphabetical order, *e.g.*, tetradecyloxy is used without parentheses (t and o are out of alphabetical order)."

Therefore, the preferred names for certain compounds described in this thesis are: *p*-(dodecyloxy)aniline (pp. 72, 122), *o*-(octadecyloxy)-benzoic acid (p. 75), [*p*-(dodecyloxy)phenyl]urea (p. 113), (*p*-tetradecyloxyphenyl)urea (p. 114), 1-[*p*-(dodecyloxy)phenylazo]-2-naphthol (p. 122), 1-(*p*-tetradecyloxyphenylazo)-2-naphthol (p. 123), *p*-tetradecyloxyaniline (p. 123), 1-[*p*-(hexadecyloxy)phenylazo]-2-naphthol (p. 124), and *p*-(hexadecyloxy)aniline (p. 124). The author prefers hexadecyloxy over cetyloxy for consistency.

SUMMARY

The development of the concept of homology has been reviewed and its application to long-chained aliphatic compounds has been discussed. The physiological effects of a number of long-chained compounds have been described.

New long-chained compounds comprising amides, sulfonamides, N-alkyl-N'-phenylureas and -thioureas, alkyl *p*-nitrophenyl ethers, alkyl *p*-acetaminophenyl ethers, *p*-alkoxyphenylureas, diethyl ethyl-*n*-alkylmalonates, barbituric acids, azo dyes, an amine, and an alkyl phenyl sulfide have been prepared and some of their properties recorded. The use of some of the compounds as derivatives has been proposed.

Unsuccessful attempts to prepare tetra-*n*-octadecylammonium iodide, tetrakis(*n*-octadecylaminomethyl)methane, dihydrazides of long-chained malonic acids, sulfonation products of tri-*n*-octadecylamine, and certain derivatives of di-*n*-octadecylamine have been described.

Some metalation studies of long-chained compounds have been reported. These include unsuccessful attempts to metalate N-*n*-dodecyldiphenylamine and phenyl *n*-tetradecyl sulfide, and experiments which are in progress upon the metalation of hexadecylbenzene and N-ethyldiphenylamine.

It is concluded upon the basis of the experimental results that the phenomenon of homology can be extended to the majority of the long-chained compounds included in these investigations.