ABSTRACT

STUDIES IN STRUCTURE AND AMOEBCICIDAL ACTIVITY

by

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ABSTRACT

The aim of the present investigation was to obtain more information as to the relation between structure and amoebicidal activity in the aliphatic diamines.

Trimethylene diamine was prepared from glutaric acid by Schmidt's reaction. Tetramethylene diamine was obtained by doing Hofmann's reaction on adipamide. Both the diamines were found to have no amoebicidal activity in vitro.

An attempt was made to prepare 1:3-diamino-1:3-di-iso-amylpropane from 1:3-di-iso-amylglutaric acid by Schmidt's reaction but an unsaturated base was obtained. 1:3-Di-iso-amylglutaric acid was obtained from the decarboxylation of 1:3-di-iso-amylpropane-1:1:3:3-tetra-carboxylic acid, which was prepared by the hydrolysis of ethyl 1:3-di-iso-amylpropane-1:1:3:3-tetracarboxylate, the latter being obtained by treating ethyl propane-1:1:3:3-tetracarboxylate with iso-amyl bromide in presence of sodium ethoxide in alcohol.

16 Diamines of the general formula (a) were prepared from 1:4-dialkyladipic acids, 1:5-dialkylpimelic acids,

\[ R (\text{NH}_2) \ CH (\text{CH}_2)_n CH (\text{NH}_2) R \]

where \( n = 2, 3, 4 \) and \( 5 \), \( R = \) any one of the following:

\( n \)-butyl, iso-butyl, \( n \)-amyl, iso-amyl, \( n \)-hexyl and 2-ethylhexyl.

(a)

The above tetracarboxylic acids were prepared in the following way.

Diethyl alkylmalonates were treated with sodium ethoxide in absolute alcohol and then with ethylene dibromide, trimethylene dibromide, tetramethylene dibromide and pentamethylene dibromide. The resulting \( \Delta, \omega \)-dialkylbutane, pentane, hexane and heptane-tetracarboxylates were purified and hydrolysed to their corresponding tetracarboxylic acids.

Amoebicidal activity of these diamines increases with increasing molecular weight and the increasing number of carbon atoms between the two amino groups the optimum number being five. Diamines containing branched carbon chain are less active than the straight chain diamines of the same molecular weight.
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PART I

THE CHEMOTHERAPY OF AMOEBIASIS

The systematic research for new amoebicides has been hampered by the lack of a reliable \textit{in vitro} test and of a convenient experimental infection in animals.

\textbf{Amoebicidal tests in Vitro}

The activity of ipecacuanha alkaloids upon free living amoebae was demonstrated by Vedder (\textit{Bull. Manila. Med. Soc.}, 1911, 3, 48) and by Pyman and Wen (\textit{J. Pharmacol. and Exper. Therap.}, 1917, X, 237) but the demonstration of activity against \textit{Entamoeba histolytica} was not forthcoming until a medium was devised which could keep the amoebae alive for a sufficiently long time for the drug to take action, and which did not contain any solid phase. These requirements were fulfilled by a medium devised by Laidlaw, Dobell and Bishop, (\textit{Parasitology.}, 1928, 20, 207) which consisted of buffered horse-serum Ringer medium. Pyman and his co-workers (\textit{Rep. Brit. Ass.}, 1937, 107, 60, 57; \textit{Chem. and Ind.}, 1937, 56, 789) used this medium in the examination of new compounds. Another drawback from which Pyman's work and the more recent work of Rawson and Hitchcock (\textit{J. Parasit.}, 1947, 33, 19) suffered was the presence of a mixed bacterial flora with \textit{Entamoeba histolytica}. It is not possible to grow \textit{Entamoeba histolytica} in the absence of bacteria which are a source of essential metabolites in the well known medium of Boeck and Drbohlav (\textit{Amer. J. Hyg.}, 1925, 5, 371). Rees, Reardon, Jacobs, and Jones (\textit{Amer. J. Trop. Med.}, 1941, 21, 567)
reported that it is possible to grow *E. histolytica* in presence of a single strain of bacteria, which consequently simplified the problem. Dobell was able to grow *E. histolytica* in the presence of a single strain of *B. coli* and Hargreaves, (Lancet, 1945, 2, 68) reported that in such a culture the amoebae were killed by a concentration of emetine hydrochloride as low as 1 in 5,000,000. This marked a step forward in the method of testing amoebicides and the method was used successfully by Goodwin, Hoar, and Sharp (Brit. J. Pharm., 1948, 3, 44).

**Amoebicidal tests in Vivo**

Cats have largely been used for the determination of amoebicidal activity of compounds in vivo. Dale and Dobell (J. Pharmacol., 1917, 10, 399) are of the opinion that the acute and lethal infection produced in kittens is not affected by doses of emetine large enough to be toxic to the host and consequently the use of kittens for in vivo tests is not likely to produce good results.

Deschiens and Provost (Bull. Soc. Path. Exot., 1937, 30, 648) described the infection of cats by direct inoculation of trophozoites (in the trophic phase the young amoebae are called trophozoites) into the lower ileum. W.R. Jones, (Brit. J. Pharmacol., 1947, 2, 217; Ann. Trop. Med. and Parasitol., 1946, 40, 130) modified the method and applied it successfully to young rats, and carefully worked out a method of testing drugs. A similar method was developed by Goodwin, Hoar and Sharp (ibid.), and similar results were obtained during the past three
years by them. This also marked a considerable development in
the method of testing amoebicides.

Drugs used

Decoction of *Radix ipecacuanha* was used for the treatment of
dysentery centuries ago by the natives of Brazil. The
*ipecacuanha* roots contain a number of alkaloids, including
emetine, cephaeline, emitamine, psychotrine and N. methyl-
psychotrine. Decoction of *Indra Jau* and *Koorchee* were also used for this purpose by Walsh *(Ind. Med. Gaz., 1891, 26, 269)*.

Emetine was isolated in an impure state from *ipecacuanha* by Pelletier (1788 - 1842), and Magendie (1783 - 1855) *(Ann. Chem. Phys., 1817, 4, 172)*, Dumas and Pelletier, *(ibid, 1823, 24, 163)*; and in a pure form by Paul and Cownley *(Pharmaceut. J., 1894, LIV, 373, 690)*. In the same year Paul and Cownley isolated other alkaloids, namely cephaeline and psychotrine and later Carr and Pyman *(J. (Trans.), 1914, 1591)* and Pyman *(J. (Trans), 1917, 419)*, prepared O-methylpsychotrine and emetamine from *ipecacuanha* roots. Besides the above mentioned authors Hermann Kunz, *(Arch. Pharmaz., 1887, 225, (II) 461)* and Windaus and Hermanns *(Ber., 1914, 47, 1470)*, Hesse *(Ann., 1914, 405, 1)*, Karrer, *(Ber., 1916, 49, 2057; 1917, 50, 582)* as well as Keller *(Arch. Pharmaz. 1917, 255, 75)* and Meader *(Brit. Pat. 11717-11719)* carried out an extensive chemical study of the natural *ipecacuanha* alkaloids.

Emetine was used in the form of the mercury iodide compound
more or less successfully by Warden (Pharmaceut. J. 1891, 21, (3), 959), as well as by Walsh (Ind. Med. Gaz., 1891, 26, 269; Lancet, 1912, 2, 1179) in the treatment of amoebic dysentery. Walsh was able to prove conclusively that the curative value of the ipecacuanha roots in amoebic dysentery is based on its content of alkaloids, chiefly of emetine. Special credit is due to Rogers (Brit. Med. J., 1912, 1, 1424; Ind. Med. Gaz., 1912, 47, 921; ibid., 1914, 49, 85; Lancet, 1913, 1, 129) for the development of emetine therapy; he introduced intravenous and subcutaneous use of emetine.

The formula given below represents emetine according to Pyman (J., 1927, 1069). The present work, like most of the work done in the past, was planned on the basis of this formula. Robinson (Nature, 1948, 162, 524) represents emetine with a formula (II) which is different from Pyman's formula in having only one methylene group connecting the two rings instead of two and having an ethyl substituted ring instead of a methyl substituted one.
Almost all the ipecacuanha alkaloids were tested for amoebicidal activity; among these emetine was found to be the most effective one but it has certain disadvantages. 

1. It is scarce and has not yet been synthesised and produced on an industrial scale.
2. It is toxic and some people are more liable to feel the toxic effect than others.
3. Not more than a certain amount of emetine can be given to a patient because of the danger of its cumulative effect.

Attempts of various chemists to modify the properties of emetine by preparing higher ethers ([Karrer, *Ber.*, 1916, 49, 2057; 1917, 50, 582; *Header*, *Brit. Pat.*, 1915, 11717-11719]) failed to produce the desired improvement.

Besides ipecacuanha alkaloids, Koorchee bark extract, which contains certain alkaloids, has been used in India for centuries as a common remedy for dysentery. The amoebicidal property of Koorchee extract is associated with conessine which is one of the main alkaloids present in the bark. The formula of conessine is $C_{24}H_{48}N_2$ but its structure is not yet known with certainty. According to the latest work carried out by R. D. Haworth (private communication) it must contain the allopregnane structure III, and a dimethyl
amino group, a methyl imino group and a double bond must be fitted into formula; formula IV is one of the several which is consistent with the latest information. According to Fulton (private communication), conessine dihydrochloride is lethal in vitro in 1:1,000,000.

Quinoline derivatives

Since emetine is an isoquinoline alkaloid a number of isoquinolines and halogenated quinolines were prepared and tested for amoebicidal activity and some of these compounds were used for clinical trials as well. It appears that the amoebicidal activity of the active quinoline derivatives is not
due to the quinoline part of the molecule but to the halogen, especially iodine content of the molecule. Anderson, David and Koch (Proc. Soc. Exp. Biol., N.Y., 1931, 28, 484, Anderson and Koch, ibid., 838) obtained good results from halogen substituted hydroxyquinolines in the treatment of amoebic dysentery of apes. They studied the effect of halogenation of hydroxyquinolines on biological activity; and found that with increased halogenation of the molecule, especially in proportion to the atomic weight of the halogen, the toxicity increases, but no improvement in the amoebicidal activity in vitro is observed. Of the eleven compounds investigated (V) 5-chloro-7-iodo-8-hydroxyquinoline or vioform was the most promising.

For some years 7-iodo-8-hydroxyquinoline-5-sulphonic acid, which is also known as Yatrin or Chineofon, was used as a disinfectant and in 1921 Mühlens and Menk (Münch. Med. Wschr. 1921, 68, 802) reported its use in the treatment of both acute and chronic amoebic dysentery. Manson-Bahr (Proc. R. Soc. Med., 1931, 24, 1538) used Yatrin in combination with emetine and bismuth iodide.

Tenney (Illinois Med. J., 1930, 70, 145) claims to have used 5:7-di-iodo-8-hydroxyquinoline (diiodoquin) (VI) in the treatment of amoebiasis.
Child and Pyman (J., 1929, 2010) prepared seven iso-quinoline derivatives consisting of two isoquinoline rings connected by a chain of methylene groups where the isoquinoline rings were substituted in the same way as in emetine. The amoebicidal activity of these compounds has not been tested in vivo but in vitro they were found to have no inhibitory effect in dilutions higher than 1 in 5,000. The formulae of these compounds, \( \alpha, \omega - \text{bis-(6:7-dimethoxy-3:4-dihydro-iso-quinolyl 1)} \)butane, pentane and octane (VII), \( \alpha, \omega - \text{bis-(6:7-dimethoxy-2-methyltetrahydro-iso-quinolyl-1-)} \)butane VIII and \( \alpha, \omega \text{bis(6:7-dimethoxytetrahydro-iso-quinolyl-1-)} \)butane, pentane, (IX) are as follows.

\[
\begin{align*}
\text{VII} & \quad \text{(CH}_2\text{)}_n \\
n & = 4, 5 \text{ and } 8
\end{align*}
\]
Arsenicals. Next to emetine and iodoquinoline products in the order of importance are arsenicals. In this connection \( p \)-carbaminophenylarsenic acid (X) is worth mentioning. It was prepared by Ehrlich and Bertheim (U.S.Pat., 1909, 937929); later Leake, Koch and Anderson, (ibid., 27, 717) and Leake (J. Amer. Med. Ass., 1932, 98, 195) tested it for amoebicidal activity and found it to be active.

Another arsenical, 3-acetylamino-hexahydrophenyl arsenic acid (acetarsol) which was prepared by Ehrlich and Hata (Die Experimentelle Chemotherapie der Spirillosen, Berlin, 1911) and reinvestigated by Fourneau and others (Fourneau, Ann. Inst. Pasteur, 1921, 35, 571; Fourneau, Navarro-Martin, Trefoüel and Trefoüel, ibid., 1923, 37, 551). It has been used in the treatment of syphilis, yaws and malaria as well as amoebiasis.

3-Formylamino-4-hydroxyphenyl arsanic acid was first
It has been claimed from time to time that arsphenamines and
neo-arsphenamines have a specific action in the treatment of
amoebiasis. Any amoebicidal results that have been obtained
seem to be due to the toxic effect of arsenic rather than to a
specific action on amoebae.

Pyman (Rep. Brit. Ass. 107, 60; Chem. and Ind., 1937, 56,
789) examined a series of harmol ethers (XI) in which R is an
alkyl group containing 2 to 12 carbon atoms. A peak of
amoebicidal activity was found where R was CgH19, but the
compounds were sparingly soluble. In order to increase the
solubility basic groups were introduced into the terminal

\[
\text{XI}
\]

\[
\text{RO} \quad \text{NH}
\]

\[
\text{in harmal } R = H
\]

position of the alkyl group where R became Alk2 N (CH2)x; the
number of methylene groups were varied and a peak of activity
was found in O-11-di-n-butylaminoundecyl harmol, which under
the conditions of the test was lethal to \textit{E. histolytica} in a
dilution of 1:750,000 to 1:4,000,000. As this was many times
more active than O-n-nonyl harmol it was conjectured that the
harmol residue might not play an important part in the
amoebicidal action, and this part of the molecule was replaced
by other groups, leading ultimately to the preparation of 1:10 bis-di-n-amylaminodecane (XII), which was found to be five times as effective as emetine.

$$\text{(n C}_5\text{H}_{11})_2 \text{N (CH}_2\text{)}_\text{10} \text{N (n C}_5\text{H}_{11})_2$$

XII

 Unfortunately a clinical trial failed to confirm the promise of the in vitro tests.

**Recent Researches**

Recent attempts to find an amoebicide are based upon the structure of emetine and upon the structure of certain compounds found by Pyman to be active in vitro.

If the emetine molecule (XIII), (represented according to Pyman, J., 1927, 2010) is broken at point a, we are left with bis-(6:7 dimethoxytetrahydroisoquinolyl)alkane (XIV), Brindley and Pyman synthesised a number of compounds based on formula XIV but found them to be inactive against *E. histolytica* in vitro.
Goodson and co-workers (Brit. J. Pharmacol., 1948, 3, 49) prepared a series of compounds modelled on bis(3', 3:4-dimethoxyphenylethylamino) alkanes (XV), resulting from the further rupture of the ring system (XIV), at the points b, b.

The nature of the substituents in the benzene ring has been varied and also the length of the central chain of the methylene groups and of the chain between the amino group and the benzene ring. All these bis-(β-3:4-dimethoxyphenylethylamino) alkanes showed some activity in vitro but there was no significant
difference between the activity of different compounds. When only one methoxyl group was present as in (XVI), the activity was reduced and a similar effect was observed when a hydroxyl group was introduced in the \( p \) position (XVII).

\[
(XVI) \quad \begin{array}{c}
\text{OCH}_3 \\
\text{OCH}_3 \\
(\text{CH}_2)_2 \text{NH} (\text{CH}_2)_n \text{NH} (\text{CH}_2)_2
\end{array}
\]

The introduction of iodine into the benzene ring (XVIII) gave rise to insoluble compounds with no increase in activity.
Compounds with chlorine in the benzene ring (XIX), with no substitution in the \( p \) position of the benzene ring (XX), with a varying number of methylene groups between the amino groups and the benzene ring (XXI), and with varying number of methylene groups between the two amino groups (XXII) were prepared.

\[
\begin{align*}
\text{XIX} & : \quad \text{Cl} \quad \text{(CH}_2\text{)}_2 \text{HN} \quad \text{(CH}_2\text{)}_2 \text{NH} \\
\text{XX} & : \quad \text{(CH}_2\text{)}_2 \text{NH} \quad \text{(CH}_2\text{)}_n \text{NH} \\
\text{XXI} & : \quad \text{(CH}_2\text{)}_x \text{NH} \quad \text{(CH}_2\text{)}_6 \text{NH} \\
\text{XXII} & : \quad \text{(CH}_2\text{)}_2 \text{HN} \quad \text{(CH}_2\text{)}_6 \text{HN} 
\end{align*}
\]
The $\beta$-$p$-chlorophenylethylamino derivative (XIX) had some activity; the corresponding $o$-chlooroanalogue (XXIII) was more active \textit{in vitro} and \textit{in vivo}, but was also more toxic. In the bis-($\beta$-phenylethylamino-) alkane series those compounds which had no substitution in the benzene ring showed activity of a high order \textit{in vitro}. The greatest \textit{in vivo} activity among these compounds was found in the higher members of the series. In the study of the effect of varying the length of the carbon chain between the phenyl and the amino group the optimum length was found to be a chain of two methylene groups. An increase in

\begin{equation*}
\begin{tikzpicture}
  \node at (0,0) {$\left(CH_2\right)_2NH \left(CH_2\right)_n NH \left(CH_2\right)_2$};
  \node at (-2,-1.5) {$n = 8, 10$};
\end{tikzpicture}
\end{equation*}

the activity in the bis-(phenylmethylamino) alkane series was found when a methylenedioxy group was introduced into the 3:4 positions (XXIV), but a single $p$-methoxy or $p$-di-methylamino
group was deleterious (XXV, XXVI).

The complete opening of the emetine molecule leads to two n-octylamine residues connected through the nitrogen atoms by a chain of methylene groups (XXVII).

Tho alkylamine Series

The complete opening of the emetine molecule leads to two n-octylamine residues connected through the nitrogen atoms by a chain of methylene groups (XXVII).
A series of compounds based on the model of bis-\((-\text{\textit{n}}\)-octyl-aminol alkanes was prepared (Goodson et al., loc. cit.) and their amoebicidal properties were tested. All these compounds had \textit{in vitro} activity of the same order as the bis-\((-\text{\textit{\beta}}\)-phenylethyl-aminol alkanes but in addition had bactericidal action. \textit{In vivo} these compounds were slightly more active than the phenyl alkanes. Effect of alteration in the length of the alkyl groups, branching and unsaturation of the side chain (XXVIII), introduction of methyl groups into the methylene chain connecting the two basic residues (XXIX), replacement of alkyl by cyclohexyl (XXX),

\[
\text{C}_8\text{H}_{17}\text{NH} \quad \text{H}_2\text{C} \quad \text{HC} \quad \text{(CH}_2)_5 \quad \text{CH} \quad \text{CH}_2\text{NH} \quad \text{C}_8\text{H}_{17}
\]

XXIX

\[
\text{H}_2\text{C} \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{NH} \quad \text{(CH}_2)_6\text{HN} \quad \text{HC} \quad \text{H}_2\text{C} \quad \text{CH}_2 \quad \text{CH}_2
\]

XXX
and of alkylamino residues by tertiary basic groups (XXXI, XXXII) was

\[(\text{C}_4\text{H}_9)_2\text{N} \left(\text{CH}_2\right)_{10}\text{N}(\text{C}_4\text{H}_9)_2\]

XXXII

studied but did not improve the amoebicidal activity to a considerable extent.

1:10-Bis-(-dibutylamino) and 1:10-bis-(-diamylamino) undecane were found to be less active than a dissecondary base like 1:10-n-hexylaminodecane (XXXIII). The cyclic tertiary

\[\text{C}_6\text{H}_{13}\text{H N} \left(\text{CH}_2\right)_{10}\text{N HC}_6\text{H}_{13}\]

XXXIII

amines (XXXIV), were inactive.

After these attempts, Pyman's active compounds were taken (Goodson et al., loc. cit.) for modification. 1:11-Diamidinoundecane (XXXV) was found by King Lourie and Yorke (Lancet, 1937, 233, 1360) to be an active trypanocide in high dilution, and 1:10-diamylaminododecane (XXXVI, was found by Pyman (Rep.}

\[\text{HN} \left(\text{CH}_2\right)_{11}\text{C} \bigg\downarrow \text{NH} \bigg\uparrow \text{NH}_2\]

XXXV
Brit. Ass., 1937, 107, 57) to be an active amoebicide. Ashley, Barber, Ewins, Newbery and Self (J., 1942, 103) modified the structure of 1:11 diamidinoundecane by interrupting the chain

\[
\text{XXXVI}
\]

with phenyl and phenylether groups and obtained such compounds as 4:4-diaminostilbene (XXXVII), 4:4-diamidinophenoxypropane (propamidine, XXXVIII) and pentamidine (XXXIX), which are shown by Lourie and Yorke (Ann. Trop. Med. and Parastial, 1939, 33, 289) to have greatly enhanced trypanocidal activity. Goodson

XXXVII

XXXVIII

XXXIX
and others tried similar changes in the 1:10-bis-(diamylamino) undecane molecule but no enhanced amoebicidal activity was observed. Tertiary aromatic amines were completely inactive \textit{in vitro} and \textit{in vivo}, a slight \textit{in vitro} activity became apparent in bis-(p-n-aminophenyl) ethane (XL), but practically no \textit{in vivo} activity was observed.

\[
\begin{align*}
C_5H_{11}HN & \quad (CH_2)_2 \quad NH C_5H_{11} \\
& \quad XL
\end{align*}
\]

In all these compounds activity is shown by a group of compounds which is therapeutically useless and cannot be compared in activity with emetine.
(A) AIMS OF PRESENT INVESTIGATION

The attempts of various chemists to modify the toxic properties of emetine by trying different variations in the structure of the molecule resulted in the loss of activity. Pyman's active compounds were also modified by various chemists in the hope of enhancing the activity, but without any success. It is obvious that there is still a possibility of finding more active amoebicides and modifying their toxicity (if they are toxic) by means of slight variations in the structure of the molecule. It might be possible to find a suitable amoebicide through the systematic study of homologous series of different types of aliphatic diamines. Most of the diamines tested for activity against Entamoeba histolytica consist of a chain of methylene groups connected with alkyl or aryl groups, through nitrogen atoms. It was decided to prepare some diamines in which the central chain of methylene groups is not connected to alkyl groups through nitrogen atoms, for instance diamines of the general formula (XLI) where R is

\[ R \text{(NH}_2\text{)} \text{CH(CH}_2\text{)}_n \text{CH(NH}_2\text{)} \text{R} \]

butyl, amyl, hexyl and octyl and n is 1 to 5.

The particular structure of the diamines was chosen because emetine itself on complete opening of the molecule is a diamine (XXVII) in which a chain of methylene groups is connected to alkyl groups through nitrogen atoms or on partial opening of the molecule (XIV, XV) the chain is connected to aryl groups through nitrogen atoms. Taking into account this fact, it was
considered very interesting to study the amoebicidal activity and toxicity (if they are sufficiently active) of the type of diamines mentioned above (XLI).

The particular range of the molecular weight, distance between the amino groups, and branching of the carbon chain were chosen on the basis of the results obtained by various chemotherapeutists in different fields.

Adams, Stanley and others (J. Pharmacol. 1932, 45, 121) found that a number of long chain fatty acids had a marked inhibitory effect on the growth of the tubercle bacillus, the maximum effect being produced with compounds containing 16 or 17 carbon atoms. The activity increased as the carboxyl group was displaced towards the centre of the molecule. Active compounds also resulted when the carboxyl group was replaced by a dialkylaminomethyl group.

Robinson (J. 1940, 505) reported the preparation of branched chain fatty acids even more potent than those of Stanley and Adams, the most effective being 3-methyl-3-n-octyl-n-undecylic acid.

Fuller, (Biochem. J., 1942, 36, 548) reported that primary aliphatic amines containing 9 to 18 carbon atoms inhibited the growth of a number of microorganisms and that the activity increased with the chain length up to a certain point and then decreased. He suggested that surface active properties might be responsible for the biological activity and that it would be interesting to determine the activity of amines with branched
Borrows, Hargreaves, Page, Resuggan and Robinson (J. 1947; 197) reported the preparation of a series of primary, secondary and tertiary aliphatic amines containing between 8 - 30 carbon atoms, and tested them for antibacterial activity. Those with 17 to 20 carbon atoms proved to be highly active in vitro against Streptococcus hemalyticus and several inhibited the growth of Mycobacterium tuberculosis. They selected some of these amines in order to compare the activities of primary, secondary, and tertiary amines and to study the effect of varying the chain length and the position of amino groups in the chain. Five unbranched primary amines were prepared by them, two with a terminal amino group, one with the amino group near the end of the chain, and two with amino group in the centre of the chain. Attempts to prepare certain branched chain primary amines were unsuccessful. They prepared eight aliphatic secondary amines of which six were branched. The length varied from 11 to 20 carbon atoms and the amino group was in the centre of the chain in four instances. In addition a secondary amine containing benzoyl group was prepared. A tertiary amine containing a benzoyl group was also prepared.

As a result of the studies of difference of activity between primary, secondary and tertiary amines they observed that on the whole primary amines were more bactericidal than secondary and tertiary amines.

Hence for the present work it was decided to prepare a
series of aliphatic diamines and study the effect on amoebicidal activity of the variations in structure of the following types

1. Study the amoebicidal activity of simple polymethylene diamines such as trimethylene diamine and tetramethylene diamine.

2. Try substitution in the \( \omega \) carbon atoms of these simple polymethylene diamines and see whether 1:3-dialkylpropane diamine and 1:4-dialkylbutane diamine are more active than trimethylene diamine and tetramethylene diamine or not.

3. If 1:3-dialkylpropane diamine and 1:4-di-alkylbutane diamine are more active it would be worthwhile to prepare 1:5-di-alkylpentane diamines, 1:6-di-alkylhexane diamines and 1:7-di-alkylheptane diamines and see whether the distances between the two amino groups, while the structure of the rest of the molecule remains the same, plays an important part in the amoebicidal activity of these diamines or not.

4. Along with this it was decided to substitute higher alkyl groups in the \( \omega \) carbon atoms of pentamethylene, hexamethylene, and heptamethylene diamines and study the effect of increasing the length of the carbon chain on amoebicidal activity.

5. It was also considered interesting to keep the molecular weight of the compounds constant and study the effect of branching the carbon chain by comparing the activity of straight chain and branched chain diamines of the same molecular weight, e.g., comparison between the activity of (XLII) and (XLIII).

\[
\text{CH}_3(\text{CH}_2)_4(\text{NH}_2) \quad \text{HC} (\text{CH}_2)_3 \text{CH} \quad (\text{NH}_2) (\text{CH}_2)_4 \text{CH}_3
\]

XLII
(6) Investigate the effect of acetylation of the amino groups on the amoebicidal activity of the diamines by comparing the activity of (XLIV) and (XLV).

\[
\text{CH}_3 (\text{CH}_2)_5 (\text{NH}_2) \text{CH} (\text{CH}_2)_3 \text{CH} (\text{NH}_2) (\text{CH}_2)_5 \text{CH}_3
\]

(XLIV)

\[
\text{CH}_3 (\text{CH}_2)_5 (\text{CH}_3\text{CONH}) \text{CH} (\text{CH}_2)_3 \text{CH} (\text{NHCOCH}_3) (\text{CH}_2)_5 \text{CH}_3
\]

(XLV)

(7) Study the effect of breaking the emetine molecule in positions different from those where it was done before and leaving the amino groups free instead of preparing alkylamino alkanes as was done in previous researches. The emetine skeleton (according to Pyman) is presented by the formula below (XLVI).
If the skeleton is broken at points a, b, c, c, d and d we are left with 7:13 diamino 5:15 diethylnonadecane (XLVII). It was decided to prepare 7:12 diamino-5:14-diethylloctadecane (XLVIII), and 7:11 diamino-5:13 diethylheptadecane (XLIX), and compare their amoebicidal activity with the activity of emetine.
(B) THE WORK CARRIED OUT

Tetramethylenediamine dihydrochloride (NH₂(CH₂)₄NH₂·2HCl) and trimethylenediamine dihydrochloride (NH₂(CH₂)₃NH₂·2HCl) were prepared first to see if there was any amoebicidal activity (in vitro) present in the simple polymethylene diamines of low molecular weight. Both the diamines were found to have no amoebicidal activity in vitro.

I. Tetramethylenediamine

Ladenburg (Ber; 1886; 19, 780) prepared tetramethylenediamine by the reduction of ethylene dicyanide with sodium and alcohol; Strack and Schwaneberg (Ber; 1934; 67, 1006) obtained it in 59-76 per cent yield, by the catalytic hydrogenation of ethylene dicyanide using palladium in 80 per cent alcohol. Ciamician and Zanetti (Ber; 1889, 22, 1968) prepared tetramethylenediamine by the reduction of succindialdehyde dioxime with sodium and absolute alcohol. It was also obtained in small amounts by Marquis (Comp. Rend; 1903, 136, 37) by the reduction of pyridazine with sodium and alcohol. Bayer & Co. (Ger. Pat. 232072; Chem. Zentr. 1911; I, 938) prepared it from adipamide. Bayer's method was used for the preparation and adipic acid was obtained by the oxidation of cyclohexanol.

(a) Oxidation of cyclohexanol

Adipic acid was obtained in 56 per cent yield by the oxidation of cyclohexanol with nitric acid (Organic Syntheses
0.1 g ammonium vanadate was added to 210 g (1.66 mol) of 50 per cent boiling nitric acid followed by the gradual addition of 50 g (1 mol) of cyclohexanol with stirring. The temperature of the reaction mixture was maintained between 55-60° by cooling. Adipic acid was obtained in crystalline form by cooling the reaction mixture to 0°; it was recrystallised from dilute nitric acid and had m.p., 151-152°.

(b) Dimethyl adipate

Bouveault (Bull. Soc. Chim. 1878, (3) 29; 1042) obtained dimethyl adipate from succindialdehyde, methyl alcohol and sodium by the electrolysis of the solution. Its preparation from adipic acid, methyl alcohol and hydrogen chloride was carried out by Verkade, Hartman and Coops (Rec. trav. Chim. 1926, 45, 590, 600); and by Müller and Souerwald (Monatsh. 1927, 48, 523) from adipic acid, methyl alcohol and sulphuric acid.

The method described (in Organic Syntheses Vol. II, p. 264) for the preparation of diethyl adipate was successfully used for the preparation of dimethyl adipate. Methyl alcohol used
in the preparation was dried by adding 2 g of sodium to 100 c.c. of alcohol and refluxing the sodium methoxide solution with about 6 g of dimethyl phthalate for an hour and then distilling the alcohol. A mixture of adipic acid (1 mol), methyl alcohol (6 mol), sulphuric acid (0.9 c.c.) and toluene (180 c.c.) was distilled in a flask which was placed in a metal bath at 110-115°. A mixture distilled at 65°, it was dried and returned to the flask; it redistilled at 70°, was collected, dried and distilled under reduced pressure, b.p. 1360/28 mm., 63 per cent yield was obtained.

(c) Adipamide

Bayer & Co. (Ger. Pat. 241897) obtained adipamide, by heating the ammonium salt of adipic acid up to 200° in 75 per cent yield. Van Braun and Lemke (Ber.; 1922, 55; 3526), Slotta and Tschesche (Ber.; 1929, 62, 1398) prepared it by adding adipic acid dichloride to cold concentrated ammonia.

The general method for the preparation of amides from esters was applied and adipamide was obtained by heating under reflux for 12 hours 174 g (1 mol) of dimethyl adipate with 1000 c.c. of 35 per cent w/w ammonia; 90 per cent yield was obtained.

(d) Tetramethylenediamine.

Diamides of adipic acid and its higher homologs were converted to diamines in aqueous alkaline hypobromite or
hypochlorite solutions by Von Braun and Lemke (Ber; 1922, 55, 3526); Bayer & Co. (Ger. Pat. 232, 072).

Conditions given for Hofmann's reaction (Organic Reactions Vol. III, p. 280) were used for the preparation of tetramethylene-diamine from adipamide. To a solution of sodium hydroxide (1.2 mole) cooled to 0°C, bromine (0.24 mole) was added. Adipamide (1 mole) was added to the cold solution and the mixture was stirred until solution was complete. The solution was warmed up to 70°C and steam distilled, the distillate was collected in dilute hydrochloric acid, and the dihydrochloride was crystallised by concentrating the solution, 58 per cent yield was obtained. The dihydrochloride was purified by recrystallisation, it did not melt below 290°C.

II. Trimethylenediamine

Fischer and Koch (Ber., 1884, 17, 1799) prepared trimethylenediamine by treating trimethylene dibromide with alcoholic ammonia. It was obtained by Keppler and Meyer (Ber., 1892, 25, 2638) by the reduction of 1:3-dinitropropane with sodium amalgam and acetic acid; Gabriel and Weiner (Ber., 1888, 21, 2669) prepared it from trimethylene dibromide and potassium phthalimide; Curtius and Clemm (J. Prak. Chem. [2]; 62; 197, 198) prepared it by heating glutaric acid diazide with alcohol and hydrolysing the trimethylenediurethane with concentrated hydrochloric acid.

As amines could be prepared from the carboxylic acids through Schmidt's reaction (Organic Reactions Vol. III, p. 308),
trimethylenediamine was prepared from glutaric acid. Glutaric acid itself was prepared from diethylmalonate.

(a) Ethyl propane-1:1:3:3-tetracarboxylate

Kleber (Annalen, 1888, 246, 97) synthesised ethyl propane-1:1:3:3-tetracarboxylate by heating sodiomalonic ester with methylene chloride. Conard and Guthzeit (Annalen, 1884, 222, 249), W. H. Perkin (Jun.) (Ber., 1886, 19, 1053) obtained it by the condensation of diethyl malonate with formaldehyde. Guthzeit and Dressel, (Ber., 1888, 21, 2233; Annalen, 1889, 256, 171), Perkin and Prentice (J., 1891, 59, 990; Ber., 1886, 19, 1053) and later on Tutin (J., 1907, 91, 1141) prepared it from sodiomalonic ester and methylene iodide.

\[
2\text{CH}_2(\text{COO C}_2\text{H}_4)_2 \rightarrow \text{CH}_2\text{O} \rightarrow (\text{CO}_2\text{C}_2\text{H}_5)_2 \text{CH CH}_2\text{CH (CO}_2\text{C}_2\text{H}_5)_2 \rightarrow \text{H}_2\text{O}
\]

The Method of Organic Syntheses (Vol. I, p. 290) was used for this preparation.

A mixture of (1 mol) diethyl malonate and 40 per cent formalin (0.53 mol) was cooled to 5° and (3.5 c.c.) diethylamine was added to it. The mixture was allowed to come to the room temperature and left for fifteen hours. It was heated under reflux for 6 hours on a water bath, the aqueous layer was separated and the residue was distilled under reduced pressure, b.p. 190-200°/12 mm., 60 per cent yield was obtained.
(b) **Glutaric acid**

A mixture of 125 g of ethyl propane 1:1:3:3-tetra-carboxylate, 125 c.c. of concentrated hydrochloric acid and 125 c.c. of water, was heated under reflux in an oil bath until it became homogenous. The contents of the flask were evaporated to dryness and residual glutaric acid was purified by crystallisation from benzene. It melted at 96-97°.

(c) **Trimethylenediamine**

13.2 G (0.1 mol) of glutaric acid were dissolved in 40 c.c. of concentrated sulphuric acid and 50 c.c. benzene was added to it. 15.2 G (0.24 mol) of activated sodium azide were added to the mixture in small portions with stirring. The reaction was carried out between 60 and 65°. After all the sodium azide had been added the reaction mixture was heated on a water bath and benzene was evaporated off. The mixture was cooled, 100 g of ice were added to it, and made alkaline with 30 per cent sodium hydroxide. The mixture was steam distilled and the distillate was collected in dilute hydrochloric acid. The hydrochloride was obtained in crystalline form by the concentration of the solution. Yield was 40 per cent.

Schmidt's reaction appeared to be preferable to Hofmann's method for the preparation of diamines from aliphatic dicarboxylic acids because it eliminates two stages, (1) preparation of the esters or acid chlorides, (2) preparation of amides, from the stages of synthesis.

After finding that tetramethylenediamine and trimethylene-
diamine possessed no amoebicidal properties, it was decided to attempt substitution in the \( \omega \) carbon atoms of these diamines and synthesise diamines of the type \((NH_2) CHR (CH_2) CHR (NH_2)\) and \(NH_2 CHR (CH_2) g CHR (NH_2)\).

It appeared quite promising to try substitution in the positions of ethyl propane-1:1:3:3-tetracarboxylate. This type of substitution was carried out by Conard and Guthzeit (Annalen, 1884, 222, 249) who treated the disodium derivative of ethyl propane-1:1:3:3-tetracarboxylate in alcohol with methyl, ethyl, propyl, allyl and benzyl halides and obtained the following tetracarboxylates in good yield.

1. Ethyl 1:3-dimethylpropane-1:1:3:3-tetracarboxylate.
2. Ethyl 1:3-diethylpropane-1:1:3:3-tetracarboxylate.
3. Ethyl 1:3-dipropylpropane-1:1:3:3-tetracarboxylate.
5. Ethyl 1:3-dibenzylpropane-1:1:3:3-tetracarboxylate.

They obtained \( \omega \)-dialkylglutaric acids by the hydrolysis of the esters and subsequent decarboxylation of the tetrabasic acids thus obtained.

These tetracarboxylates (leaving the 1:3 dibenzyl and 1:3-diallyl aside) had too low a molecular weight for our purpose because if utilized for the preparation of diamines they would yield diamines containing 5, 7, 9 carbon atoms; after finding that trimethylenediamine and tetramethylenediamine were amoebicidally inactive, it was decided to prepare diamines of quite high molecular weight containing 12-22 carbon atoms.
Conard and Guthzeit reported that the substitution of higher alkyl groups in ethyl propane-1:1:3:3-tetracarboxylate was difficult. It was decided in this case to try substitution of iso-amyl group and thus prepare 2:10 dimethyl-5:7-diaminoundecane \( (C_{13}H_{30}N_2) \).

\[
\begin{align*}
\text{Ethyl propane-1:1:3:3-tetracarboxylate} & \quad + \quad (CH_3)_2CH.CH.CH_2Br \\
\text{iso-amyl bromide} & \\
(CH_3)_2CH.CH.CH_2(CO_2C_2H_5)_2 & \quad C \quad (CH_2) \quad C \quad (CO_2C_2H_5)_2 \quad CH_2.CH.CH(CH_3)_2 \\
\text{ethyl 1:3-di-iso-amylpropane-1:1:3:3-tetracarboxylate} & \\
\text{hydrolysis} & \\
1:3-di-iso-amylpropane-1:1:3:3-tetracarboxylic acid. & \\
(CH_3)_2CH.CH.CH_2(CH_2O)_2 & \quad C \quad (CH_2) \quad C \quad (CO_2H)_2 \quad CH_2.CH.CH(CH_3)_2 \\
\text{decarboxylation} & \\
(CH_3)_2CH(CH_2)_2(CO_2H) & \quad H \quad C \quad CH_2.CH(CH_2O) \quad (CH_2)_2CH(CH_3)_2 \\
1:3-di-iso-amylglutaric acid & \\
2HN_3 & \\
(CH_3)_2CH(CH_2)_2(NH_2) & \quad CH \quad CH_2.CH(NH_2)(CH_2)_2CH(CH_3)_2 \\
2:10-dimethyl-5:7-diaminoundecane & \\
\end{align*}
\]

*Note:* For the sake of brevity, sodium derivatives of esters are represented as C-Na compounds. Formulae based on mesomeric states would be more correct.
(a) **Substitution in ethyl propane-1:1:3:3-tetracarboxylate**

Absolute alcohol was obtained for the experiment by adding 30 g sodium to 1500 c.c. of absolute alcohol placed in a 3 litre round bottom flask connected with a reflux condenser carrying a calcium chloride tube. To the sodium ethoxide solution 90 g of diethyl phthalate were added and the mixture was heated under reflux for an hour and distilled into the reaction flask directly. The reaction flask (2 litre) was fitted with a three way adaptor holding a reflux condenser, a dropping funnel and a mechanical stirrer, it was clamped over a water bath and sodium (2 atoms) was added to it in small portions. The sodium ethoxide solution was stirred and ethyl propane-1:1:3:3-tetracarboxylate (1 mol.) was added to it. After fifteen minutes iso-amyl bromide was added to it drop by drop through the dropping funnel. The reaction started after a considerable amount of iso-amyl bromide had been added. After the addition of iso-amyl bromide the mixture was heated under reflux for 32 hours. The basicity of the reaction mixture was tested with a moist litmus from time to time during this period of 32 hours but it remained strong alkaline. Alcohol was distilled off and the product was extracted with ether after shaking with water. Only 10 per cent yield of ethyl 1:3-di-iso-amylpropane-1:1:3:3-tetracarboxylate was obtained, b.p. 208-210°/3 mm., nD12 1.453. C25H44O6 requires C, 63.9; H 9.3; found C 65.6; H, 9.0.
(b) **1:3 di-iso-amylpropane-1:1:3:3-tetracarboxylic acid**

Ethyl 1:3-di-iso-amylpropane-1:1:3:3-tetracarboxylate was hydrolysed by heating under reflux for six hours with an alcoholic solution of potassium hydroxide. Alcohol was distilled off, the remaining aqueous solution was cooled, diluted and acidified with concentrated hydrochloric acid. The acid was extracted with ether, the extract dried over sodium sulphate and ether was distilled off. The acid remained as a thick oil and could not be crystallised. The silver salt of 1:3-di-iso-amylpropane-1:1:3:3-tetracarboxylic acid was analysed.

(c) **1:3-Di-iso-amylglutaric acid**

1:3-Di-iso-amylpropane-1:1:3:3-tetracarboxylic acid was heated in a flask placed in an oil bath from 140-150°; decarboxylation seemed to occur but when the silver salt of the acid was analysed, too high a percentage of silver was obtained. The acid was heated again from 190-200°, and the analysis of the silver salt of 1:3-di-iso-amylglutaric acid gave a satisfactory result. The acid was a thick liquid which could not be crystallised.

(d) **Attempt to prepare 2:10-Dimethyl-5:7-diaminoundecane**

A base was obtained in 22 per cent yield by treating 1:3-di-iso-amylglutaric acid with hydrazoic acid in the following way.

1:3-Di-iso-amylglutaric acid (0.03 mol.) was dissolved in 25 c.c. of concentrated sulphuric acid and 30 c.c. of benzene
were added to it. Sodium azide (0.09 mol) was added in small portions to the mixture, the reaction was carried out between 45 and 55°. The dihydrochloride was made by passing dry hydrogen chloride through the dry solution of the base in benzene.

A picrate was formed on adding a solution of picric acid in benzene to a solution of the base in benzene. It was crystallised from water and decomposed on heating above 160°. 

C₂₅H₃₆N₈O₁₄ requires C, 44.6; H, 5.3; N, 16.6; found C, 45.0; H, 2.9; N, 16.9. A second analysis of C and H gave C, 44.9; H, 3.0; and a third analysis gave C, 44.7; H, 3.2; N, 17.4.

It is obvious from the analysis that the compound obtained was not the dipicrate of 2:10-dimethyl-5:7-diaminoundecane. It could not be a monopicrate because that requires C, 51.4; H, 7.5; N, 15.7. Another possible reaction product could be a tetrazole derivative but the analytical figures do not agree with the percentage of elements required for that. The reason for unsaturation could not be ascertained. The hydrochloride of the base had an amoebicidal activity of 1:10,000.
In order to discover whether the substitution of alkyl groups in the \( \omega \) carbon atoms of amoebicidally inactive tetramethylenediamine would give rise to amoebicidal activity, the preparation of \( \lambda, \omega \) - dialkybutanediamines was undertaken; a suitable synthetic method appeared to be the application of Schmidt's reaction to \( \lambda, \omega \) substituted adipic acids.

\[
\text{CO}_2\text{H} \ (\text{CH}_2)_2 \text{CHR} \text{CO}_2\text{H} \nonumber
\]

\[
\downarrow \text{HN}_3
\]

\[
\text{NH}_2 \ (\text{CH}_2)_2 \text{CHR} \text{NH}_2
\]

Two possible methods of preparing \( \lambda, \omega \) - dialkyladipic acids were considered.

1. By treating the sodium derivative of malonic ester with ethylene dibromide followed by the reaction of the disodium derivative of ethyl butane-1:1:4:4-tetracarboxylate thus obtained with alkyl bromides; then hydrolysis of the ethyl 1:4-di-alkylbutane-1:1:4:4-tetracarboxylate and decarboxylation of 1:4-di-alkylbutane-1:1:4:4-tetracarboxylic acid to 1:4-dialkyladipic acid.

\[
2\text{CH} \text{Na} (\text{CO}_2\text{C}_2\text{H}_5)_2 + \text{Br} (\text{CH}_2)_2 \text{Br} \\
(\text{CO}_2\text{C}_2\text{H}_5)_2 \text{CH} (\text{CH}_2)_2 \text{CH} (\text{CO}_2\text{C}_2\text{H}_5)_2 + 2 \text{Na} \text{OC}_2\text{H}_5 \\
(\text{CO}_2\text{C}_2\text{H}_5)_2 \text{C} \text{Na} (\text{CH}_2)_2 \text{C} \text{Na} (\text{CO}_2\text{C}_2\text{H}_5)_2 + 2 \text{R} \text{Br} \\
(\text{CO}_2\text{C}_2\text{H}_5)_2 \text{CR} (\text{CH}_2)_2 \text{CR} (\text{CO}_2\text{C}_2\text{H}_5)_2 \\
(\text{CO}_2\text{H})_2 \text{CR} (\text{CH}_2)_2 \text{CR} (\text{CO}_2\text{H})_2 \\
\text{CO}_2\text{H} \ (\text{CH}_2)_2 \text{CHR} \text{CO}_2\text{H} \\
1:4-\text{di-alkyladipic acid}
\]
(2) By preparing ethyl alkylmalonates from malonic ester and alkyl bromides and treating the sodium derivative of ethyl alkylmalonate with ethylene dibromide to obtain 1:4-di-alkyl-adipic acid by the hydrolysis of tetracarboxylate and subsequent decarboxylation.

\[
\begin{align*}
\text{CH Na } & \text{(CO}_2\text{C}_2\text{H}_5\text{)}_2 + \text{ R Br} \\
\text{CHR (CO}_2\text{C}_2\text{H}_5\text{)}_2 & \downarrow \text{ + Na Br} \\
2 \text{ CNa R (CO}_2\text{C}_2\text{H}_5\text{)}_2 & \downarrow \text{ + Br (CH}_2\text{)}_2 \text{ Br} \\
& \text{ (CO}_2\text{C}_2\text{H}_5\text{)}_2 \text{ CR (CH}_2\text{)}_2 \text{ CR (CO}_2\text{C}_2\text{H}_5\text{)}_2 \\
& \text{ (CO}_2\text{H)}_2 \text{ CR (CH}_2\text{)}_2 \text{ CR (CO}_2\text{H)}_2 \\
& \text{ CO}_2\text{H . CHR (CH}_2\text{)}_2 \text{ CHR . CO}_2\text{H} \\
\end{align*}
\]

As in the substitution of ethyl propane-1:1:3:3-tetracarboxylate the yield obtained was very low (10 per cent) the second method seemed to be more promising, though if the low yield in the substitution of ethyl propane-1:1:3:3-tetracarboxylate was due to steric hindrance which is most likely to be the case, the yield in the substitution of ethyl butane-1:1:4:4-tetracarboxylate could be more than 10 per cent because the distance between the two groups of two carbethoxy groups would increase by one CH\text{2}. In fact it would be very interesting to compare the substitution in ethyl propane-1:1:3:3-tetracarboxylate with the higher members of the series, but this was beyond the scope of present work.
As far as could be ascertained neither 1:4-dimethyladipic acid, 1:4-diethyladipic acid, 1:4-dipropyladipic acid, nor 1:4-dibutyladipic acid had been prepared before nor has the reaction between diethyl alkylmalonates and ethylene dibromide been carried out before.

It was considered worthwhile to prepare 1:4-diamino-1:4-di-n-butylbutane (5:8-diaminododecane).

\[
\text{NH}_2 (nC_4H_9) \text{CH} (CH_2)_2 \text{CH} (nC_4H_9) \text{NH}_2 \quad (IV)
\]

at the same time it appeared very interesting to branch the carbon chain in 5:8-diaminododecane and prepare 1:4-di-amino-1:4-di-iso-butylbutane (2:9-di-methyl-4:7-di-amino-docane)

\[
(CH_3)_2 \text{CH} \text{CH} (NH_2) \text{CH} (CH_2)_2 \text{CH} (NH_2) \text{CH}_2 \text{CH} (CH_3)_2 \quad (V)
\]

1:4-Di-n-butyladipic acid and 1:4-diiso-butyladipic acid required for the preparation of IV and V were obtained in the following way and were converted into IV and V.

(a) Diethyl n-butylmalonate and Diethyl iso-butylmalonate

Diethyl n-butylmalonate was prepared by the method of Organic Syntheses (Vol. II, p.250).

Clean sodium (1 atom) was added to about 500 c.c. of absolute alcohol (see p. 35) and diethyl malonate (1 mol.) was added to it followed by stirring and slow addition of alkyl bromide. The mixture was heated under reflux on a water bath until neutral to moist litmus, 91 per cent yield was obtained.

Diethyl iso-butylmalonate was prepared by Fischer and Schmitz (Ber., 1906; 39, 351) from diethyl malonate, sodium and
iso-butyl bromide in 77 per cent yield. In this preparation 82 per cent yield was obtained by following strictly the method of Organic Syntheses given for the preparation of diethyl n-butylmalonate.

(b) Condensation of alkylmalonates with ethylene dibromide

A 2 litre round bottom flask fitted with a three way adaptor holding a reflux condenser with a calcium chloride tube, a mechanical stirrer and a dropping funnel was clamped over a water bath. In the flask 500-700 c.c. of absolute alcohol were placed and clean cut sodium (1 atom) was added to it. The sodium ethoxide solution was stirred and ethyl alkylmalonate (1 mol.) was added to it. After a few minutes ethylene dibromide was added drop by drop. The reaction started after a considerable amount of ethylene dibromide had been added. The reaction mixture was heated under reflux until it was almost neutral to litmus. Alcohol was distilled off and the mixture, after cooling, was shaken with water and extracted with ether. Ether was distilled off on a water bath and the ester was distilled under reduced pressure. First alcohol, ethylene dibromide and ethyl alkylmalonate distilled then some high boiling liquid and then the ester distilled. Yield was 64-65 per cent. It is apparent from the physical constants of these two esters that in this particular series the refractive index slightly decreases with the branching of the carbon chain.
Ethyl 1:4-di-alkylbutane 1:1:4:4-tetracarboxylates

<table>
<thead>
<tr>
<th></th>
<th>B.P.</th>
<th>nD</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Ethyl 1:4-di-n-butylbutane 1:1:4:4-tetracarboxylate</td>
<td>105-106/4 mm.</td>
<td>nD 16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.4260</td>
</tr>
<tr>
<td>(2) Ethyl 1:4-di-iso-butylbutane 1:1:4:4-tetracarboxylate</td>
<td>92-94/2 mm.</td>
<td>nD 15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.4240</td>
</tr>
</tbody>
</table>

(1) Requires C, 62.8; H, 9.2; found C, 61.5; H, 9.1.

(2) Requires C, 62.8; H, 9.2; found C, 62.2; H, 9.5.

(c) 1:4-Di-alkylbutane-1:1:4:4-tetracarboxylic acids

These acids were obtained by heating ethyl 1:4-di-alkylbutane-1:1:4:4-tetracarboxylates under reflux with an alcoholic solution of potassium hydroxide. After distilling off alcohol the reaction mixture was cooled, diluted and acidified with concentrated hydrochloric acid. The acids were extracted with ether and after distilling off ether they were left behind in the flask as solid.

<table>
<thead>
<tr>
<th>1:4-Di-alkylbutane-1:1:4:4-tetracarboxylic acids</th>
<th>m.p.</th>
<th>Requires C</th>
<th>H</th>
<th>Found C</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) 1:4-Di-n-butylbutane-1:1:4:4-tetracarboxylic acid, H2O</td>
<td>98-102°</td>
<td>52.7</td>
<td>7.6</td>
<td>52.6</td>
<td>7.0</td>
</tr>
<tr>
<td>(2) 1:4-Di-iso-butylbutane 1:1:4:4-tetracarboxylic acid, H2O</td>
<td>103-106°</td>
<td>52.7</td>
<td>7.6</td>
<td>52.3</td>
<td>7.0</td>
</tr>
</tbody>
</table>
An increase in the melting point is observed with the branching of the carbon chain.

1:4-Dialkyladipic acids
(i) 1:4-Di-n-butyladipic acid and (ii) 1:4-di-iso-butyladipic acid were obtained by heating 1:4-di-n-butylbutane-1:1:4:4-tetracarboxylic acid and 1:4-di-iso-butylbutane-1:1:4:4-tetracarboxylic acid in an oil bath from 140 - 165°C. Both the acids thus obtained were liquid and their silver salts were analysed. (i) Requires Ag 45.7 found Ag 45.56; (ii) requires Ag 45.7; found Ag 45.8.

5:8-Diaminododecane iv, and 2:9-dimethyl-4:7-diaminodecane

1:4-Di-n-butyladipic acid and 1:4-di-iso-butyladipic acid were converted into 5:8-diaminododecane and 2:9-dimethyl-4:7-diaminodecane through Schmidt's reaction, 54 to 55 per cent yield was obtained in both the cases.

1.9 g (0.035 mol) of the acid were dissolved in 25 c.c. of concentrated sulphuric acid and (30 c.c.) benzene was added to it. To the mixture 6.8 g (0.105 mol) sodium azide was added in small portions, the reaction was carried out between 40-50°C. The reaction mixture was cooled, 100 g ice added to it and made alkaline by gradual addition of 30 per cent sodium hydroxide solution with strong cooling. In the case of these two diamines it was found necessary to keep the temperature below 30°C since decomposition started at high temperatures, for the same reason ether could not be distilled off from the ether.
extracts of the bases.

The dihydrochlorides were obtained by passing dry hydrogen chloride through a dry solution of the base in ether and benzene, after using ether in one experiment it was considered more suitable to use only benzene in order to keep the solution as dry as possible. The dihydrochlorides were white powders, very deliquescent and decomposing in the presence of moisture. The platinichloride of 5:8-diaminododecane was prepared by adding an aqueous solution of chloroplatinic acid to the solution of the base in alcohol and it was analysed.

\[ \text{C}_{12}\text{H}_{28}\text{N}_2\cdot 2\text{H}_2\text{Pt Cl}_6 \text{ requires Pt, 31.9; found Pt, 32.0} \]

 Unsatisfactory results were obtained from the analysis of the picrate which melted from 137 to 140°. The picrate of 2:9 dimethyl-4:7-diaminododecane was obtained by adding a solution of picric acid in benzene to the solution of base in benzene. The picrate precipitated, it was crystallised from water, it melted at 134-135°, it was analysed for the identification of the base. \[ \text{C}_{24}\text{H}_{34}\text{N}_8\text{O}_{14} \text{ requires N, 17.0; found N, 17.0} \]

2:10-Dimethyl-5:7-diaminoundecane dihydrochloride \((\text{CH}_3)\text{CH (CH}_2)\text{CH (NH}_2)\text{ CH CH}_2\text{CH (NH}_2)\text{ CH (CH}_2)\text{H, 2HCl has amoebicidal activity of 1:10,000.} \]

5:8-Diaminododecane dihydrochloride \((\text{CH}_3)\text{H (CH}_2)\text{H (NH}_2)\text{ CH (CH}_2)\text{H, 2HCl IV has amoebicidal activity of} \]
2:9-Dimethyl-4:7-di-aminodecan6 dihydrochloride \((\text{CH}_3)_2\text{CH.\text{CH}_2(\text{NH}_2)\text{CH(\text{CH}_2)_2\text{CH(\text{NH}_2)\text{CH.\text{CH}_2(\text{CH}_3)_2, 2HCl, (V) had no amoebicidal activity.}}}

However small the amoebicidal activity of these diamines might be it is very significant that substitution of alkyl groups in \(\alpha\), \(\omega\) carbon atoms of simple polymethylenediamine more or less gives rise to amoebicidal activity of the molecule. This phenomenon could be attributed to mere increase in the molecular weight; or certain length of the molecule or even to certain complexity of the molecule. It is yet to be found whether substitution in \(\alpha\), \(\omega\) carbon atoms only is responsible for this or a substitution anywhere else in the carbon chain would give the same results.

Another factor which would influence the amoebicidal activity of \(\alpha\), \(\omega\) substituted polymethylenediamines is the distance, or in other words length of the carbon chain between the two amino groups. At this point it was decided to prepare 1:5-di-n-butyl-1:5-diaminopentane, VI, 1:6-di-n-butyl-1:6-diaminohexane, VII, and 1:7-di-n-butyl-1:7-diaminoheptane, VIII to investigate the relation between the distances apart of two amino groups and the amoebicidal activity of a diamine where the rest of the structure of the molecule remains the same.
VI. \( \text{CH}_3(\text{CH}_2)_3(\text{NH}_2)\text{CH} (\text{CH}_2)_3 \text{CH} (\text{NH}_2) (\text{CH}_2)_3 \text{CH}_3 \text{HCl} \) had an activity of 1:10,000.

(1:5-Di-n-butyl-1:5-di-aminopentane) 5:9-diaminotridecane dihydrochloride.

VII. \( \text{CH}_3(\text{CH}_2)_3 (\text{NH}_2) \text{CH} (\text{CH}_2)_4 \text{CH} (\text{NH}_2) (\text{CH}_2)_3 \text{CH}_3 \text{HCl} \) had an activity of 1:10,000.

(1:6-Di-n-butyl-1:6-diaminohexane) 5:10-diaminotetradecane dihydrochloride.

VIII. \( \text{CH}_3(\text{CH}_2)_3 (\text{NH}_2) \text{CH} (\text{CH}_2)_5 \text{CH} (\text{NH}_2) (\text{CH}_2)_3 \text{CH}_3 \text{HCl} \) had an activity of 1:10,000.

(1:7-Di-n-butyl-1:7-diaminopentane) 5:11-diaminopentacontadecane dihydrochloride.

It was found from the comparison of IV, VI, VII, and VIII that the activity increases up to a point where the two amino groups are separated by 5 carbon atoms and then remains constant. After obtaining these results it was decided to prepare higher dialkyl substituted 1:5-diaminopentanes, 1:6-diaminohexanes and 1:7-diaminoheptanes. It was also considered interesting to prepare some branched chain diamines in these series and compare their amoebicidal activity with the straight chain diamines containing the same number of carbon atoms. The preparation of these diamines is given with the preparation of other compounds of the same series.
Diamines of the Pentamethylene series

\[ R(NH_2) HC \ (CH_2)_3 \ CH \ (NH_2) \ R \]

The following six bases were made from 1:5-dialkylpimelic acids through Schmidt's reaction.

VI. \( \text{CH}_3(\text{CH}_2)_3 \ \text{CH} \ (\text{NH}_2) \ (\text{CH}_2)_3 \ \text{CH} \ (\text{NH}_2) \ (\text{CH}_2)_3 \ \text{CH}_3 \)

5:9-Diaminotridecane \( (1:5\text{-diamino}-1:5\text{-di-}n\text{-butylpentane}) \), \( (C_{13}H_{30}N_2) \).

IX. \( (\text{CH}_3)_2 \ \text{CH} \ \text{CH}_2 \ (\text{NH}_2) \ \text{CH} \ (\text{CH}_2)_3 \ \text{CH} \ (\text{NH}_2) \ \text{CH}_2 \ \text{CH} \ (\text{CH}_3)_2 \)

2:10-Dimethyl-4:8-diaminoundecane \( (1:5\text{-diamino}-1:5\text{-di-iso-}butylpentane) \), \( (C_{13}H_{30}N_2) \).

X. \( \text{CH}_3 \ (\text{CH}_2)_4 \ (\text{NH}_2) \ \text{CH} \ (\text{CH}_2)_3 \ \text{CH} \ (\text{NH}_2) \ (\text{CH}_2)_4 \ \text{CH}_3 \)

6:10-Diaminopentadecane \( (1:5\text{-di-}amino-1:5\text{-di-}n\text{-amyl-}pentane) \), \( (C_{15}H_{34}N_2) \).

XI. \( (\text{CH}_3)_2 \ \text{CH} \ \text{CH}_2, \text{CH}_2 \ (\text{NH}_2) \ \text{CH} \ (\text{CH}_2)_3 \ \text{CH} \ (\text{NH}_2) \ \text{CH}_2, \text{CH}_2, \text{CH} \ (\text{CH}_3)_2 \)

2:12-Dimethyl-5:9-diaminotridecane \( (1:5\text{-diamino}-1:5\text{-di-}iso\text{-amylpentane}) \), \( (C_{15}H_{34}N_2) \).

XII. \( \text{CH}_3 \ (\text{CH}_2)_5 \ (\text{NH}_2) \ \text{CH} \ (\text{CH}_2)_3 \ \text{CH} \ (\text{NH}_2) \ (\text{CH}_2)_5 \ \text{CH}_3 \)

7:11-Diaminheptadecane \( (1:5\text{-diamino}-1:5\text{-di-}n\text{-hexyl-}pentane) \), \( (C_{17}H_{38}N_2) \).
XIII. \( \text{CH}_3(\text{CH}_2)_3 \left(\text{CH}_2\text{NH}_2\right)\text{CH} \left(\text{CH}_2\right)_3 \left(\text{CH}_3\right) \), \( \text{C}_2\text{H}_5 \)

5:13-Diethyl-7:11-di-aminooctadecane

(1:5-diamino-1:5-di-2-ethylhexylpentane), \( (\text{C}_{21}\text{H}_{46}\text{N}_2) \).

Diamines of the hexamethylene series

\( \text{NH}_2\text{RCH} \left(\text{CH}_2\right)_4 \text{CH R NH}_2 \)

Five diamines in the hexamethylene series were prepared; they are as follows:

VII. \( \text{CH}_3(\text{CH}_2)_3 (\text{NH}_2) \text{CH} \left(\text{CH}_2\right)_4 \text{CH} (\text{NH}_2) (\text{CH}_2)_3 \text{CH}_3 \)

5:10-Diaminotetradecane

(1:6-diamino-1:6-di-n-butylhexane), \( (\text{C}_{14}\text{H}_{32}\text{N}_2) \)

XIV. \( \text{CH}_3 \left(\text{CH}_2\right)_4 (\text{NH}_2) \text{CH} \left(\text{CH}_2\right)_4 \text{CH} (\text{NH}_2) (\text{CH}_2)_4 \text{CH}_3 \)

6:11-Diaminohexadecane

1:6-diamino-1:6-di-n-amylhexane), \( \text{C}_{16}\text{H}_{36}\text{N}_2 \).

XV. \( (\text{CH}_3)_2 \text{CH} \left(\text{CH}_2\right)_2 (\text{NH}_2) \text{CH} \left(\text{CH}_2\right)_4 \text{CH} (\text{NH}_2) (\text{CH}_2)_2 \text{CH} (\text{CH}_3)_2 \)

2:13-Di-methyl-5:10-diaminotetradecane

(1:6-diamino-1:6-di-iso-amylhexane), \( (\text{C}_{16}\text{H}_{36}\text{N}_2) \)

XVI \( \text{CH}_3(\text{CH}_2)_3 \text{CH} \left(\text{CH}_2\text{NH}_2\right)\text{CH} \left(\text{CH}_2\right)_4 \text{CH} (\text{NH}_2) \left(\text{CH}_2\right)_2 \text{CH} (\text{CH}_2)_3 \text{CH}_3 \)

5:14-Di-ethyl-7:12-diaminooctadecane

(1:6-diamino-1:6-di-2-ethylhexylhexane), \( (\text{C}_{22}\text{H}_{48}\text{N}_2) \)
XVII. $\text{CH}_3(\text{CH}_2)_5 \text{CH} (\text{NH}_2) \text{CH} (\text{CH}_2)_4 \text{CH} (\text{NH}_2) (\text{CH}_2)_5 \text{CH}_3$

7:12-Diaminoocotadecane (1:6-diamino-1:6-di-n-hexyl-hexane), ($\text{C}_{18}\text{H}_{40}\text{N}_2$).

**Diamines of the heptamethylene series.**

$\text{NH}_2, \text{CH} \text{R} (\text{CH}_2)_5 \text{CH} \text{R} \text{NH}_2$

Three compounds were synthesised in this series.

VIII. $\text{CH}_3(\text{CH}_2)_3 (\text{NH}_2) \text{CH} (\text{CH}_2)_5 \text{CH} (\text{NH}_2) (\text{CH}_2)_3 \text{CH}_3$

5:11-Di-aminopentadecane (1:7-diamino-1:7-di-n-butylheptane), ($\text{C}_{15}\text{H}_{34}\text{N}_2$).

XVIII. $(\text{CH}_3)_2 \text{CH} \cdot \text{CH}_2 (\text{NH}_2) \text{CH} (\text{CH}_2)_5 \text{CH} (\text{NH}_2) \text{CH}_2 \text{CH} (\text{CH}_3)_2$

2:12-Di-methyl-4:10-diamino-tridecane (1:7-diamino-1:7-di-iso-butyl-heptane), ($\text{C}_{15}\text{H}_{34}\text{N}_2$).

XIX. $\text{CH}_3(\text{CH}_2)_5 (\text{NH}_2) \text{CH} (\text{CH}_2)_5 \text{CH} (\text{NH}_2) (\text{CH}_2)_5 \text{CH}_3$

7:13-Di-amino-nonadecane (1:7-diamino-1:7-di-n-hexyl-heptane), ($\text{C}_{19}\text{H}_{42}\text{N}_2$).
Method of Synthesis of 1:5-di-alkyl-1:5-diaminopentanes

A convenient method for the preparation of bases in this series appeared to be from 1:5-di-alkylpimelic acids through Schmidt's reaction. Some 1:5-di-alkylpimelic acids were prepared by W.H. Perkin (Jun.), and Prentice (J. Trans.; 1891, 59, 818). They studied the action of alkyl iodides on the disodium derivative of ethyl pentane-1:1:5:5-tetracarboxylate. The tetracarboxylate itself was obtained by them (ibid; 1887; 51; 24) by treating sodium derivative of diethyl malonate with trimethylene dibromide.

\[
2\text{CH Na (CO}_2\text{C}_2\text{H}_5)_2 \rightarrow \text{Br (CH}_2)_3\text{Br}
\]

\[
\text{(CO}_2\text{C}_2\text{H}_5)_2\text{CH (CH}_2)_3\text{CH (CO}_2\text{C}_2\text{H}_5)_2}
\]

Ethyl pentane-1:1:5:5-tetracarboxylate

They found that disodium derivative of ethyl pentane-1:1:5:5-tetracarboxylate was capable of acting easily with methyl, ethyl, propyl iodides and benzyl chloride and yielding 1:5 di-alkyl substituted ethyl pentane-1:1:5:5-tetracarboxylates. They obtained 1:5-di-alkylpimelic acids by the alkaline hydrolysis of the esters and subsequent decarboxylation of the tetrabasic acids thus obtained.

\[
\text{(CO}_2\text{C}_2\text{H}_5)_2\text{C Na (CH}_2)_3\text{C Na (CO}_2\text{C}_2\text{H}_5)_2} \rightarrow \text{R I}
\]

\[
\text{(CO}_2\text{C}_2\text{H}_5)_2\text{CR (CH}_2)_3\text{CR (CO}_2\text{C}_2\text{H}_5)_2}
\]

Ethyl 1:5-di-alkylpentane-1:1:5:5-tetracarboxylate hydrolysis
In the course of their studies they proved that ethyl pentane-1:1:5:5-tetracarboxylate was incapable of forming monosodium derivative and hence of yielding ethyl monoalkylpentane-1:1:5:5-tetracarboxylates.

The general experimental conditions used by Perkin and Prentice are illustrated by the following example. They do not give the yield but write that the esters were obtained in good yield.

4.6 G (0.2 mol) of sodium were dissolved in 50-55 c.c. of absolute alcohol and the well cooled solution was mixed with 36 g (0.1 mol) of ethylpentane-1:1:5:5-tetracarboxylate and then 35 g (0.25 mol) of methyl iodide were added. Methyl iodide was added with continuous cooling because the reaction is apt to become violent. The mixture was transferred to a soda water bottle and heated in a water bath at 100° for an hour, the product was mixed with water, and the oily layer was extracted with ether and distilled. Almost all the product distilled at 235-245°/30 mm., and on redistillation at 238-240°/30 mm. In this way the following ethyl 1:5-di-alkylpentane-1:1:5:5-tetracarboxylates were obtained.
(1) Ethyl 1:5-dimethyl-pentane 1:1:5:5-tetracarboxylate.
(2) Ethyl 1:5- " ethyl  "  "  "  "  "
(3) Ethyl 1:5- " propyl  "  "  "  "  "
(4) Ethyl 1:5- " iso-propyl pentane 1:1:5:5-tetracarboxylate
(5) Ethyl 1:5- " benzyl pentane 1:1:5:5-tetracarboxylate.

Perkin and Prentice (ibid), used a slightly different method
for the preparation of 1:5-di-iso-butylpimelic acid. They treated
ethyl iso-butylmalonate with trimethylene dibromide and obtained
ethyl 1:3-di-iso-butylpentane-1:1:5:5-tetracarboxylate in 38 per
cent yield, b.p. 250-280°/60 mm. (They write "nearly 50 per cent
yield was obtained" but calculating on the amount they obtained
it comes to about 38 per cent; probably they meant the crude
product was obtained in 50 per cent yield).

\[
2(CH_3)_2 CH CH_2C Na \ (COO C_2H_5)_2 + Br \ (CH_2)_3 Br
\]

\[
\downarrow
\]

\[
(COO C_2H_5)_2 (C_4H_9) C \ (CH_2)_3 C(C_4H_9) \ (COO C_2H_5)_2
\]

The experimental conditions used by them were as follows.
15 g (0.65 atom) of sodium were dissolved in 170 g of
absolute alcohol and 138 g (0.65 mol) ethyl iso-butylmalonate
were added to it, then 64.5 g (0.325 mol) of trimethylene bromide
were added and the mixture was heated under reflux on a water bath.
After heating for half an hour the neutral product was mixed with
water and extracted with ether, dried over calcium chloride and
evaporated; the almost colourless oily residue weighed about
150 g.
They said "the smallness of the yield of ethyl di-iso-butylpentanetetracarboxylate appears to be due to a secondary reaction, in which ethyl isobutylalkylmalonate is formed with regeneration of some ethyl iso-butylmalonate, thus:"

\[
2(CO_2C_2H_5)_2CNaC_4H_9 + C_3H_6Br_2 \rightarrow (COO C_2H_5)_2C(CH_2.CH.CH_2).C_4H_9 + (COO C_2H_5)_2CH.C_4H_9 + 2NaBr
\]

They do not explain how the formation of ethyl iso-butylalkylmalonate takes place.

As far as smallness of the yield of ethyl iso-butylpentane-1:1:5:5-tetracarboxylate is concerned it could be explained in two ways. (1) The reaction between sodium derivative of ethyl iso-butylmalonate and trimethylene dibromide is never complete and at the end of the reaction when

\[
2CRNa(CO_2C_2H_5)_2 + Br(CH_2)_3Br \rightarrow \uparrow \rightarrow (CO_2C_2H_5)_2CR(CH_2)_3CR(CO_2C_2H_5)_2 + 2NaBr
\]

the product is shaken with water ethyl iso-butylmalonate is regenerated, in which case the

\[
CRNa(CO_2C_2H_5)_2 + H_2O \rightarrow \uparrow \rightarrow CHR(CO_2C_2H_5)_2 + NaOH
\]

reaction mixture should be quite alkaline to moist litmus; Perkins reaction mixture was neutral but in these experiments
the reaction mixture was found to remain slightly alkaline but not strong enough to account for the reaction to take the course as described above; also the products of the reaction should be ethyl 1:5-di-iso-butylpentane-1:1:5:5-tetracarboxylate and ethyl iso-butylmalonate but during the distillations of the products it was noticed that a fraction distilled between ethyl iso-butylmalonate and ethyl 1:5-di-iso-butylpentane-1:1:5:5-tetracarboxylates. This product was not purified and analysed to prove the hypothesis.

(2) The second possibility of the course of reaction is that the reaction between sodium ethoxide and ethyl alkylmalonate is never complete and there is always some sodium present in the solution in the form of ethoxide and when trimethylene dibromide is added to the solution part of it reacts completely with sodium derivative of ethyl iso-butylmalonate and from the rest one bromine atom reacts with sodium derivative of ethyl iso-butylmalonate and the other with the sodium ethoxide with the elimination of H⁺ from the β carbon atom to give the unsaturated compound ethyl iso-butyl-allylmalonate.
In the experiments carried out on ethyl alkylmalonates and trimethylene dibromide the time required was much longer than given by Perkin and Prentice (ibid); they heated the sodium derivative of ethyl iso-butylmalonate and trimethylene dibromide for half an hour by which time the reaction mixture was neutral. The experimental conditions differed from the conditions utilised by them in two ways; (1) the amount of alcohol used in their experiments was much smaller and consequently the initial concentration was higher, (2) they added trimethylene dibromide all at once which means the concentration of trimethylene dibromide was also higher in their solutions than ours.
Preparation of the 1:5-di-alkyl-1:5-diaminopentanes

The starting material required for the preparation of these bases was trimethylene dibromide and various ethyl alkylmalonates. (a) Trimethylene dibromide.

Trimethylene dibromide was obtained from trimethylene glycol, using the method of Organic Synthesis (Vol. I, p. 30) in 88 percent yield.

(b) Ethyl alkylmalonates.

Ethyl \( n \)-butylmalonate, ethyl \( isoc \)-butylmalonate, ethyl \( n \)-amylmalonate, ethyl \( isoc \)-amylmalonate, ethyl \( n \)-hexylmalonate and ethyl \( 2 \)-ethylhexylmalonate were required; of these alkylmalonates, ethyl \( n \)-butylmalonate and ethyl \( isoc \)-butylmalonate were prepared as before (see p. 40). The method of Organic Synthesis for preparation of ethyl \( n \)-butylmalonate was applied to all the preparations.

Ethyl \( n \)-amylmalonate

Ethyl \( n \)-amylmalonate was first prepared by Dox and Jones (J. Amer. Chem. Soc., 1928, 50; 2033) from diethyl malonate and \( n \)-amyl bromide in 62 percent yield; it was obtained in 78 percent yield in this experiment.

Ethyl \( isoc \)-amylmalonate

Ethyl \( isoc \)-amylmalonate was first prepared in 1890 by Paul and Hofmann (Ber. 23; 1496) from diethyl malonate and \( isoc \)-amyl bromide in 70 percent yield, in the present work it was obtained in 73 percent yield.
Ethyl n-hexylmalonate

Ethyl n-hexylmalonate was first prepared in 1924 by Dox (J. Amer. Chem. Soc., 46; 1707) from diethyl malonate and n-hexyl bromide in 73 per cent yield; 87 per cent yield was obtained in the present experiments.

Ethyl 2-ethylhexylmalonate

Ethyl 2-ethylhexylmalonate was first prepared by Weizmann, Bergmann and Haskelberg (Chem. and Ind., 1937, 56; 587) from diethyl malonate and 2-ethylhexyl bromide; they did not give the yield; in the present work it was obtained in 69 per cent yield.

(c) Condensation of ethyl alkylmalonates and trimethylene dibromide

The general experimental conditions used for the condensation are as follows:

In a two litre round bottom flask 500-700 c.c. of absolute alcohol (see p. 35) were distilled with a calcium chloride tube. The flask was fitted with a three way adaptor, holding a reflux condenser, a mechanical stirrer and a dropping funnel, and it was clamped over a water bath. Clean cut sodium (1 atom) was added to alcohol in small amounts. The sodium ethoxide solution was stirred and ethyl alkylmalonate (1.010-1.020 mol) was added to the solution through the dropping funnel. After about 15 minutes trimethylene dibromide (0.505-0.510 mol) was added to the mixture drop by drop. The reaction started after a considerable amount of trimethylene dibromide had been added. The mixture was heated under reflux until it was almost neutral to moist litmus.
The time required varied from 12-18 hours. Alcohol was distilled off from the reaction mixture, the mixture was cooled and shaken with 300-400 c.c. of water. The oily liquid that separated was extracted with ether, dried over calcium chloride and the ether was distilled off on a water bath. The ester was distilled under reduced pressure. In this manner the following ethyl alkylpentanetetracarboxylates were obtained, with regard to the boiling points of these esters it could be said safely that there is a general rise in the boiling points with the increasing molecular weight.
<table>
<thead>
<tr>
<th>No.</th>
<th>Ethyl 1:5-dialkylpentanotetracarboxylates</th>
<th>B.p. or m.p.</th>
<th>Yield %</th>
<th>nD</th>
<th>Requires C</th>
<th>H</th>
<th>Found C</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>Ethyl 1:5-di-n-butylpentane-1:1:5:5-tetracarboxylate</td>
<td>98-102°/1 mm. m.p. 37.5°</td>
<td>25</td>
<td>-</td>
<td>63.5</td>
<td>9.3</td>
<td>63.5</td>
<td>8.6</td>
</tr>
<tr>
<td>(2)</td>
<td>Ethyl 1:5-di-iso-butylpentane-1:1:5:5-tetracarboxylate</td>
<td>220°/1 mm. m.p. 45-47°</td>
<td>33</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(3)</td>
<td>Ethyl 1:5-di-n-amylpentane-1:1:5:5-tetracarboxylate</td>
<td>234°/2 mm.</td>
<td>32.5</td>
<td>nD 5.145</td>
<td>64.7</td>
<td>9.6</td>
<td>64.9</td>
<td>9.2</td>
</tr>
<tr>
<td>(4)</td>
<td>Ethyl 1:5-di-iso-amylpentane-1:1:5:5-tetracarboxylate</td>
<td>225°/2 mm.</td>
<td>36</td>
<td>nD 20.1480</td>
<td>64.7</td>
<td>9.6</td>
<td>64.9</td>
<td>9.5</td>
</tr>
<tr>
<td>(5)</td>
<td>Ethyl 1:5-di-n-hexylpentane-1:1:5:5-tetracarboxylate</td>
<td>254°/5 mm.</td>
<td>39</td>
<td>nD 17.1450</td>
<td>65.8</td>
<td>9.9</td>
<td>65.9</td>
<td>9.9</td>
</tr>
<tr>
<td>(6)</td>
<td>Ethyl 1:5-di-2-ethylhexylpentane-1:1:5:5-tetracarboxylate</td>
<td>258°/3 mm.</td>
<td>28.5</td>
<td>nD 18.1459</td>
<td>67.8</td>
<td>10.3</td>
<td>68.2</td>
<td>10.3</td>
</tr>
</tbody>
</table>
(d) Hydrolysis of ethyl 1:5-di-alkylpentane 1:1:5:5-tetracarboxylates

The hydrolysis of the tetracarboxylates was carried out by heating them under reflux with excess of an alcoholic solution of potassium hydroxide for five to six hours. Alcohol was distilled off and the solution was cooled, diluted and acidified with concentrated hydrochloric acid. The acids were extracted with ether, dried over sodium sulphate and ether was distilled off. The acids were obtained in almost quantitative yield, were purified by crystallisation and were analysed.

<table>
<thead>
<tr>
<th>1:5-Dialkylpentane 1:1:5:5-tetracarboxylic acid</th>
<th>m.p.</th>
<th>Requires</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 1:5 Di-n-butylpentane 1:1:5:5-tetracarboxylic acid</td>
<td>147-149°</td>
<td>C 56.5 H 7.8</td>
<td>C 56.0 H 7.8</td>
</tr>
<tr>
<td>2 1:5 Di-iso-butylpentane 1:1:5:5-tetracarboxylic acid</td>
<td>145-147°</td>
<td>C 56.5 H 7.8</td>
<td>C 56.1 H 7.8</td>
</tr>
<tr>
<td>3 1:5 Di-n-amylpentane-1:1:5:5-tetracarboxylic acid</td>
<td>175.5°</td>
<td>C 58.7 H 8.3</td>
<td>C 58.4 H 8.4</td>
</tr>
<tr>
<td>4 1:5 Di-iso-amylpentane-1:1:5:5-tetracarboxylic acid, $\frac{1}{2}H_2O$</td>
<td>188°</td>
<td>C 57.4 H 8.3</td>
<td>C 57.3 H 8.4</td>
</tr>
<tr>
<td>5 1:5 Di-2-ethylhexylpentane-1:1:5:5-tetracarboxylic acid</td>
<td>173-174°</td>
<td>C 60.5 H 8.7</td>
<td>C 60.6 H 8.5</td>
</tr>
<tr>
<td>6 1:5 Di-2-ethylhexylpentane-1:1:5:5-tetracarboxylic acid</td>
<td>162-164°</td>
<td>C 63.5 H 9.3</td>
<td>C 63.7 H 9.3</td>
</tr>
</tbody>
</table>
(e) 1:5-Di-alkylpimelic acids

Some 1:5-dialkylpimelic acids were obtained by Perkin and Prentice (J. Trans; 1891, 59, 818) by heating 1:5-di-alkylpentane 1:1:5:5-tetracarboxylic acid from 200-220°. The following acids were obtained by heating 1:5-di-alkylpentanetetracarboxylic acids (p. 60) just above their melting points. The tetracarboxylic acid was placed in a flask and heated slowly in an oil bath. The 1:5-dialkylpimelic acids obtained solidified on cooling with the exception of 1:5-di-2-ethylhexylpimelic acid which did not solidify and which could not be crystallised; its silver salt was analysed.

No relationship could be traced between the structure and melting points of these 1:5-dialkylpimelic acids and 1:5-di-alkylpentane-1:1:5:5-tetracarboxylic acids except for the fact that there is a similarity of disorder in the melting points in both the series.

<table>
<thead>
<tr>
<th>1:5-Di-alkylpimelic acids</th>
<th>m.p.</th>
<th>Requires</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>H</td>
</tr>
<tr>
<td>1:5-Di-n-butylpimelic acid</td>
<td>107°</td>
<td>66.1</td>
<td>10.3</td>
</tr>
<tr>
<td>1:5-Di-iso-butylpimelic acid</td>
<td>105 - 6°</td>
<td>66.1</td>
<td>10.3</td>
</tr>
<tr>
<td>1:5-Di-n-amylpimelic acid</td>
<td>109-112.5°</td>
<td>67.9</td>
<td>10.8</td>
</tr>
<tr>
<td>1:5-Di-iso-amylpimelic acid</td>
<td>138°</td>
<td>67.9</td>
<td>10.8</td>
</tr>
<tr>
<td>1:5-Di-n-hexylpimelic acid</td>
<td>108-110°</td>
<td>69.47</td>
<td>11.0</td>
</tr>
<tr>
<td>1:5-Di-2-ethyl-hexyl-pimelic acid</td>
<td>-</td>
<td>Ag 35.96</td>
<td>Ag 36.1</td>
</tr>
</tbody>
</table>
1:5-Dialkyl-1:5-diaminopentanes, NH₂RCH (CH₂)₃ CHR NH₂

1:5-Di-alkylpimelic acids were converted into 1:5-dialkyl-1:5-diaminopentanes through Schmidt's reaction (Organic Reactions Vol. III, p. 307), the general experimental conditions were as follows.

The 1:5-dialkylpimelic acid was dissolved in concentrated sulphuric acid (3 to 4 c.c. of sulphuric acid were used for 1 gram of diabasic acid) and benzene was added (as required) to the solution; to the mixture activated sodium azide (see p. 137) was added in small portions (3 to 4 mol of sodium azide were used for 1 mole of the diabasic acid). Most of the reactions started at room temperature and were carried out between 25 to 35°; the temperature was controlled by adjusting the amount of sodium azide added to the reaction mixture. The mixture was cooled, ice was added to it and made alkaline with 30 per cent sodium hydroxide keeping the solution cool to prevent decomposition of the base by heat. The base dissolved in the benzene present in the reaction mixture and was extracted either with benzene or benzene and ether in a few cases. The benzene solution was dried and hydrochloride was obtained by passing dry hydrogen chloride into it. The dihydrochlorides are colourless powders, very deliquescent and decompose in the presence of moisture. The picrates of these bases were obtained by adding picric acid in benzene to the solution of the base in benzene, picrates are crystalline compounds and were analysed for the identification of the bases.
<table>
<thead>
<tr>
<th></th>
<th>Bases</th>
<th>m.p's of derivatives</th>
<th>Requires</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>C  H  N</td>
<td>C  H  N</td>
</tr>
<tr>
<td>(1)</td>
<td>5:9-Di-aminotridecane</td>
<td>hydrogen oxalate</td>
<td>52.9 8.6 7.1</td>
<td>52.3 8.2 7.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>197.5-198.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>picrate 143°</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2)</td>
<td>2:10-Dimethyl-5:8-diaminoundecane</td>
<td>picrate</td>
<td>44.6 5.3 16.6</td>
<td>44.9 5.3 16.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>186-188°</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3)</td>
<td>6:10-Di-aminopentadecane</td>
<td>picrate</td>
<td>46.4 5.7 15.9</td>
<td>47.0 5.4 15.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>130-133°</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>diacetyl deriv.</td>
<td>-</td>
<td>8.57</td>
</tr>
<tr>
<td></td>
<td></td>
<td>177-179°</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4)</td>
<td>2:12-Dimethyl-5:9-diaminotridecane</td>
<td>picrate</td>
<td>-</td>
<td>15.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>165-169°</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(5)</td>
<td>7:11-Diaminoheptadecane</td>
<td>picrate</td>
<td>-</td>
<td>15.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>143-145°</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>diacetyl der.184°</td>
<td>71.1 12.0 7.8</td>
<td>70.9 12.1 7.7</td>
</tr>
<tr>
<td>(6)</td>
<td>5:13-Di-ethyl-7:11-diaminoheptadecane</td>
<td>picrate</td>
<td>50.5 6.6 14.2</td>
<td>50.3 6.7 13.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>150°</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5:13-Di-ethyl-7:11-diaminoheptadecane-</td>
<td></td>
<td>60.4 12.1 6.7</td>
<td>60.4 11.8 6.8</td>
</tr>
<tr>
<td></td>
<td>dihydrochloride, H2O</td>
<td>134-138°</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
It is noticed from the melting points of the dipicrates of these bases that the melting points increase with the branching of the carbon chain as seen in the case of 5:9-diaminotridecane dipicrate (m.p. 143°); 2:10-dimethyl-5:8-di-aminoundecane dipicrate (m.p. 186-188°); 6:10-di-aminopentadecane dipicrate (m.p. 130-133°) and 2:12-dimethyl-5:9-diaminotridecane dipicrate (m.p. 165-169°). No relationship could be traced between the increase in length of carbon chain and melting points except that the melting point first drops with the increase in molecular weight and then rises again.

1:6-Dialkyl-1:6-diaminohexanes (NH₂)CHR(CH₂)₄CHR (NH₂)

A convenient way of preparing these bases appeared to be from 1:6-di-alkylsuberic acids. The acids used in these preparations had not previously been synthesised; they were obtained in the following way:-

Ethyl alkylmalonates were treated with tetramethylene dibromide and ethyl 1:6-di-alkylhexane-1:1:6:6-tetracarboxylates were obtained in good yield. Hydrolysis of these tetracarboxylates yields 1:6-di-alkylhexane-1:1:6:6-tetracarboxylic acids which on decarboxylation give 1:6-di-alkylsuberic acids.


(a) Tetramethylene dibromide

Tetramethylene dibromide was prepared from tetrahydrofuran by passing dry hydrogen bromide into it until the reaction was complete. B.p. 198° and 73 per cent yield was obtained. This method was used by Fried and Kleene (J. Amer. Chem. Soc., 1941; 63; 2691).

\[
\begin{align*}
\text{CH}_2 & \quad \text{CH}_2 \\
\text{CH}_2 & \quad \text{CH}_2 \\
\text{O} & \\
\end{align*}
\]

\[
\text{CH}_2 \quad \text{CH}_2 + 2\text{HBr} \rightarrow (\text{CH}_2)_4 \text{Br}_2 + \text{H}_2\text{O}
\]

(b) Condensation of ethyl alkylmalonates with tetramethylene dibromide

Ethyl 1:6-di-alkylhexane-1:1:6:6-tetracarboxylates were prepared from ethyl alkylmalonates and tetramethylene dibromide in the same way as ethyl 1:5-di-alkylpentane-1:1:5:5-tetracarboxylates were obtained, hexane tetracarboxylates were obtained in greater yield than pentane tetracarboxylates.
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>%</td>
<td></td>
<td></td>
<td>C</td>
<td>H</td>
</tr>
<tr>
<td>1</td>
<td>Ethyl 1:6-di-n-butylhexane-1:1:6:6-tetracarboxylate</td>
<td>50</td>
<td>m.p. 30-32°</td>
<td>-</td>
<td>64.1</td>
<td>9.5</td>
</tr>
<tr>
<td>2</td>
<td>Ethyl 1:6-di-n-amylhexane-1:1:6:6-tetracarboxylate</td>
<td>42</td>
<td>b.p. 244-246/2 mm</td>
<td>nD 22</td>
<td>1.4495</td>
<td>65.3</td>
</tr>
<tr>
<td>4</td>
<td>Ethyl 1:6-di-n-hexylhexane-1:1:6:6-tetracarboxylate</td>
<td>45</td>
<td>254-260/5 mm</td>
<td>nD 21</td>
<td>1.451</td>
<td>66.3</td>
</tr>
<tr>
<td>5</td>
<td>Ethyl 1:6-di-2-ethylhexylhexane-1:1:6:6-tetracarboxylate</td>
<td>50</td>
<td>248/1 mm.</td>
<td>nD 21</td>
<td>1.4562</td>
<td>68.2</td>
</tr>
</tbody>
</table>
(c) Hydrolysis of ethyl 1:6-di-alkylhexane-1:1:6:6-tetracarboxylates

Ethyl 1:6-di-alkylhexane-1:1:6:6-tetracarboxylates were hydrolysed by heating them under reflux with an alcoholic solution of potassium hydroxide and 1:6-di-alkylhexane-1:1:6:6-tetracarboxylic acids were obtained in the same way as 1:5-di-alkylpentane 1:1:5:5-tetracarboxylic acids were obtained (p. 60).

<table>
<thead>
<tr>
<th>1:6-Di-alkylhexane 1:1:6:6-tetracarboxylic acids</th>
<th>Requires</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>m.p.</td>
<td>C</td>
<td>H</td>
</tr>
<tr>
<td>1 1:6-Di-n-butylhexane 1:1:6:6-tetracarboxylic acid</td>
<td>190-192°</td>
<td>57.7</td>
</tr>
<tr>
<td>2 1:6-Di-n-amylhexane-1:1:6:6-tetracarboxylic acid</td>
<td>187°</td>
<td>59.7</td>
</tr>
<tr>
<td>3 1:6-Di-iso-amylhexane 1:1:6:6-tetracarboxylic acid</td>
<td>200-202°</td>
<td>59.7</td>
</tr>
<tr>
<td>4 1:6-Di-n-hexylhexane-1:1:6:6-tetracarboxylic acid</td>
<td>192°</td>
<td>61.4</td>
</tr>
<tr>
<td>5 1:6-Di-2-ethyl-hexyl-hexane-1:1:6:6-tetracarboxylic acid</td>
<td>-</td>
<td>Ag, 47.2</td>
</tr>
</tbody>
</table>

No particular relationship seems to exist between the length and branching of carbon chain and the melting points of these acids.
The acids were obtained by heating 1:6-di-alkylhexane-1:1:6:6-tetracarboxylic acids just over their melting points. The acids were purified by crystallisation and analysed.

<table>
<thead>
<tr>
<th>1:6-Dialkylsuberic acids</th>
<th>m.p.</th>
<th>Requires C</th>
<th>H</th>
<th>Found C</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:6-di-n-butylsuberic acid</td>
<td>103-7°</td>
<td>67.1</td>
<td>10.5</td>
<td>66.9</td>
<td>10.5</td>
</tr>
<tr>
<td>1:6-Di-n-amylsuberic acid</td>
<td>93,99°</td>
<td>68.75</td>
<td>10.9</td>
<td>69.0</td>
<td>10.7</td>
</tr>
<tr>
<td>1:6-Di-iso-amylsuberic acid</td>
<td>119-121°</td>
<td>68.75</td>
<td>10.9</td>
<td>69.0</td>
<td>10.7</td>
</tr>
<tr>
<td>1:6-Di-n-hexylsuberic acid</td>
<td>Sublimes above 90</td>
<td>70.1</td>
<td>11.1</td>
<td>70.0</td>
<td>11.2</td>
</tr>
<tr>
<td>1:6-Di-2-ethylhexylsuberic acid</td>
<td></td>
<td>Ag, 35.2</td>
<td></td>
<td>Ag, 35.0</td>
<td></td>
</tr>
</tbody>
</table>

These bases were obtained from 1:6-di-alkylsuberic acids through Schmidt's reaction. The reactions were carried out at 25 to 30°. The dihydrochlorides of the bases were obtained by passing dry hydrogen chloride through dry solution of the base. The picrates were made by adding picric acid solution in benzene to the solution of the base in benzene; the picrates are crystalline compounds with reasonably sharp melting points taking into consideration the fact that they are mixture of diastereoisomers, picrates were analysed for the identification of the bases.
<table>
<thead>
<tr>
<th>Bases</th>
<th>m.p. of picrate</th>
<th>Requires</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C  H</td>
<td>N</td>
</tr>
<tr>
<td>(1) 5:10-Diamino-tetradecane</td>
<td>197-202°</td>
<td>45.4 5.5</td>
<td>16.3</td>
</tr>
<tr>
<td>(2) 6:11-Di-amino-hexadecane</td>
<td>152-156°</td>
<td>47.0 5.9</td>
<td>15.4</td>
</tr>
<tr>
<td>(3) 2:13-Di-methyl-5:10-diaminotetradecane</td>
<td>decomp</td>
<td>47.0 5.9</td>
<td>15.4</td>
</tr>
<tr>
<td></td>
<td>190-200°</td>
<td>47.0 5.9</td>
<td>15.4</td>
</tr>
<tr>
<td>(4) 7:12-Diamino octadecane</td>
<td>173-176°</td>
<td>49.6 6.3</td>
<td>15.4</td>
</tr>
<tr>
<td>(5) 5:14-Diethyl-7:12-diamino-octadecane</td>
<td>156-158°</td>
<td>51.1 6.8</td>
<td>13.7</td>
</tr>
<tr>
<td></td>
<td>decomp</td>
<td>63.8 12.1</td>
<td>6.7</td>
</tr>
</tbody>
</table>
DIAMINES OF HEPTAMETHYLENE SERIES

1:7-Di-alkyl-1:7-diaminoheptanes. \((\text{NH}_2)\ R\ CH\ (\text{CH}_2)\_5\ CHR\ (\text{NH}_2)\)

These bases were prepared from 1:7-di-alkylazelaic acids through Schmidt's reaction. The 1:7-di-alkylazelaic acids were obtained from 1:7-di-alkylheptane-1:1:7:7-tetracarboxylates which were prepared by the condensation of ethyl alkylmalonates with pentamethylene dibromide.

(a) Pentamethylene dibromide

Method of Organic Syntheses (Vol. I, p. 30) preparation of trimethylene dibromide was used for the preparation of pentamethylene dibromide from pentamethyleneglycol; 80 per cent yield was obtained.

(b) Condensation of ethyl alkylmalonates with pentamethylene dibromide

The condensation of ethyl alkylmalonates with pentamethylene dibromide was carried out in a similar manner using similar quantities of reagents as in the condensation of ethyl alkylmalonates with trimethylene dibromide and tetramethylene dibromide but the yields of this condensation were much higher than the previous two.
<table>
<thead>
<tr>
<th>No.</th>
<th>Compound</th>
<th>Yield</th>
<th>M.p.</th>
<th>nD</th>
<th>Requires</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ethyl 1:7-di-n-butylheptane-1:1:7:7-tetracarboxylate</td>
<td>70%</td>
<td>m.p. 41-42°</td>
<td>-</td>
<td>64.7</td>
<td>9.6</td>
</tr>
<tr>
<td>2</td>
<td>Ethyl 1:7-di-iso-butylheptane-1:1:7:7-tetracarboxylate</td>
<td>70%</td>
<td>m.p. 64.5°</td>
<td>-</td>
<td>64.7</td>
<td>9.6</td>
</tr>
<tr>
<td>3</td>
<td>Ethyl 1:7-di-n-hexylheptane-1:1:7:7-tetracarboxylate</td>
<td>50%</td>
<td>248-250°/2 mm</td>
<td>nD 1.455</td>
<td>66.8</td>
<td>10.1</td>
</tr>
</tbody>
</table>
(c) **Hydrolysis of ethyl 1:7-di-alkylheptane 1:1:7:7-tetra-carboxylates**

Ethyl 1:7-di-alkylheptane-1:1:7:7-tetracarboxylates were hydrolysed by heating under reflux with an alcoholic solution of potassium hydroxide. The acids were separated in the usual way from the reaction mixture, were purified by crystallisation and analysed. There is a rise in the melting points with increasing molecular weight but a drop with branching of the carbon chain.

<table>
<thead>
<tr>
<th>1:7-Di-alkylheptane-1:1:7:7-tetracarboxylic acids</th>
<th>m.p.</th>
<th>Requires</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 1:7-Di-n-butylheptane-1:1:7:7-tetracarboxylic acid</td>
<td>168-169°</td>
<td>C 58.7 H 8.3</td>
<td>C 59.0 H 8.3</td>
</tr>
<tr>
<td>2 1:7-Di-iso-butyl-heptane-1:1:7:7-tetracarboxylic acid</td>
<td>162-163°</td>
<td>C 57.4 H 8.3</td>
<td>C 57.8 H 8.4</td>
</tr>
<tr>
<td>3 1:7-Di-n-hexylheptane-1:1:7:7-tetracarboxylic acid</td>
<td>178-179°</td>
<td>C 61.9 H 9.0</td>
<td>C 61.5 H 8.35</td>
</tr>
</tbody>
</table>

(d) **1:7-Di-alkylazelaic acids**

These acids were obtained by heating 1:7-di-alkylheptane-1:1:7:7-tetracarboxylic acids just over their melting points; they were purified by crystallisation and analysed.
<table>
<thead>
<tr>
<th>1:7-Di-alkylazelaic acids</th>
<th>m.p.</th>
<th>Requires</th>
<th></th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>1 1:7-Di-n-butylazelaic acid</td>
<td>89-93°</td>
<td>67.9</td>
<td>10.8</td>
<td>67.7</td>
</tr>
<tr>
<td>2 1:7-Di-iso-butylazelaic acid</td>
<td>110-111°</td>
<td>67.9</td>
<td>10.8</td>
<td>67.5</td>
</tr>
<tr>
<td>3 1:7-Di-iso-hexylazelaic acid, ½ H₂O</td>
<td>70-73°</td>
<td>69.0</td>
<td>11.3</td>
<td>69.1</td>
</tr>
</tbody>
</table>

As opposed to the 1:7-di-alkyl-heptane-1:1:7:7-tetracarboxylic acids in 1:7-di-alkylazelaic acids there is a rise in the melting point with branching but a drop with increasing molecular weight.

(e) 1:7-Dialkyl-1:7-diaminoheptanes. \( R (\text{NH}_2) \text{CH} (\text{CH}_2)_5 \text{CH} (\text{NH}_2) R \)

These bases were obtained from 1:7-dialkylazelaic acids through Schmidt's reaction. The reaction was carried out in the same manner as for the preparation of bases from 1:5-di-alkylpimelic acids and 1:6-di-alkylsuberic acids. The reaction was carried out between 25-30°. Dihydrochlorides were obtained by passing dry hydrogen chloride into dry benzene solution of the base. Picrates were made by adding picric acid in benzene to the solution of the base in benzene. The picrates are crystalline compounds and were analysed for the identification of the bases.
There is a fall in the melting points of the dipicrates of these bases with increasing molecular weight and a rise with branching of the carbon chain.

<table>
<thead>
<tr>
<th>1:7-Di-alkyl-1:7-diamino-heptanes</th>
<th>M.p. of picrate</th>
<th>Requires</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>H</td>
</tr>
<tr>
<td>(1) 5:11-Diaminopentadecane</td>
<td>191°</td>
<td>46.3</td>
<td>5.3</td>
</tr>
<tr>
<td>(2) 2:12-Dimethyl-4:10-diaminotridecane</td>
<td>194°</td>
<td>46.3</td>
<td>5.3</td>
</tr>
<tr>
<td>(3) 7:13-Diamino-nonadecane</td>
<td>155-157°</td>
<td>49.2</td>
<td>6.3</td>
</tr>
</tbody>
</table>
(C) DISCUSSION OF THE RESULTS

The results obtained from the in vitro amoebicidal tests are as follows.*

**TABLE (1)**

<table>
<thead>
<tr>
<th>Simple polymethylene diamines</th>
<th>In vitro amoebicidal activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Trimethylenediamine dihydrochloride</td>
<td>inactive</td>
</tr>
<tr>
<td>(2) Tetramethylenediamine dihydrochloride</td>
<td>inactive</td>
</tr>
</tbody>
</table>

**TABLE (2)**

<table>
<thead>
<tr>
<th>Substituted tri and tetra methylenediamines</th>
<th>In vitro amoebicidal activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(3) Attempted 1:3-diamino-1:3-di-iso-amy1propane dihydrochloride</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td>(4) 1:4-Diamino-1:4-di-n-butylbutane dihydrochloride</td>
<td>1 in 1,000</td>
</tr>
<tr>
<td>(5) 1:4-Diamino-1:4-di-iso-butylbutane dihydrochloride</td>
<td>inactive</td>
</tr>
</tbody>
</table>

* My thanks are due to Dr. J.D. Fulton of the National Institute for Medical Research for carrying out the in vitro tests on Entamoeba histolytica with a mixed strain of bacterial flora.
### TABLE (3)

<table>
<thead>
<tr>
<th>Diamines of pentamethylene series</th>
<th>In vitro amoebicidal activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(6) 1:5-Diamino-1:5-di-n-butylpentane dihydrochloride</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td>(7) 1:5-Diamino-1:5-di-iso-butylpentane dihydrochloride</td>
<td>1 in 1,000</td>
</tr>
<tr>
<td>(8) 1:5-Diamino-1:5-di-n-amylpentane dihydrochloride</td>
<td>1 in 100,000</td>
</tr>
<tr>
<td>(9) 1:5-Diamino-1:5-di-iso-amylpentane dihydrochloride</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td>(10) 1:5-Diamino-1:5-di-n-hexylpentane dihydrochloride</td>
<td>1 in 100,000</td>
</tr>
<tr>
<td>(11) 1:5-Diamino-1:5-di-2-ethylhexylpentane dihydrochloride, H₂O</td>
<td>1 in 100,000</td>
</tr>
</tbody>
</table>

### TABLE (4)

<table>
<thead>
<tr>
<th>Diamines of the hexamethylene series</th>
<th>In vitro amoebicidal activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(12) 1:6-Diamino-1:6-di-n-butylhexane dihydrochloride</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td>(13) 1:6-Diamino-1:6-di-n-amylhexane dihydrochloride</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td>(14) 1:6-Diamino-1:6-di-iso-amylhexane dihydrochloride</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td>(15) 1:6-Diamino-1:6-di-n-hexylhexane dihydrochloride</td>
<td>1 in 100,000</td>
</tr>
<tr>
<td>(16) 1:6-Diamino-1:6-di-2-ethylhexylhexane dihydrochloride</td>
<td>inactive</td>
</tr>
</tbody>
</table>
TABLE (5)

<table>
<thead>
<tr>
<th>Diamines of heptamethylene series</th>
<th>In vitro amoebicidal activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(17) 1:7-Diamino-1:7-di-n-butylheptane dihydrochloride</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td>(18) 1:7-Diamino-1:7-di-iso-butylheptane dihydrochloride</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td>(19) 1:7-Diamino-1:7-di-n-hexylheptane dihydrochloride</td>
<td>inactive</td>
</tr>
</tbody>
</table>

Diacetyl derivatives of 1:5-diamino-1:5-di-n-amylpentane and 1:5-diamino-1:5-di-n-hexylpentane were insoluble in water and therefore were not tested.

The following conclusions could be drawn from the results of the in vitro amoebicidal tests given above.

1. Simple polymethylene diamines of low molecular weight possess no amoebicidal activity in vitro (table 1).

2. Substitution in the \( \alpha, \omega \) carbon atoms of simple polymethylene diamines gives rise to amoebicidal activity in vitro (table 2).

3. The activity increases with the increasing number of methylene groups between the two amino groups and then remains constant. (Table 6).
(4) Branching of the carbon chain does not increase the amoebicidal activity of the bases but in some cases decreases their activity as will be seen from the comparison of the *in vitro* amoebicidal activity of the bases having the same molecular weight and having a straight or branched carbon chain (table 7).

<table>
<thead>
<tr>
<th>Bases</th>
<th>In vitro amoebicidal activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH&lt;sub&gt;3&lt;/sub&gt;(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;(NH&lt;sub&gt;2&lt;/sub&gt;)CH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;CH(NH&lt;sub&gt;2&lt;/sub&gt;)(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;, 2HCl.</td>
<td>1 in 1,000</td>
</tr>
<tr>
<td>CH&lt;sub&gt;3&lt;/sub&gt;(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;(NH&lt;sub&gt;2&lt;/sub&gt;)CH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;CH(NH&lt;sub&gt;2&lt;/sub&gt;)(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;, 2HCl.</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td>CH&lt;sub&gt;3&lt;/sub&gt;(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;(NH&lt;sub&gt;2&lt;/sub&gt;)CH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;CH(NH&lt;sub&gt;2&lt;/sub&gt;)(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;, 2HCl.</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td>CH&lt;sub&gt;3&lt;/sub&gt;(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;(NH&lt;sub&gt;2&lt;/sub&gt;)CH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;5&lt;/sub&gt;CH(NH&lt;sub&gt;2&lt;/sub&gt;)(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;, 2HCl.</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td>Bases</td>
<td>Molecular Formulas</td>
</tr>
<tr>
<td>-------</td>
<td>------------------</td>
</tr>
<tr>
<td>(\text{CH}_3\text{(CH}_2\text{)}_3\text{CH (NH}_2\text{)}_2\text{CH (NH}_2\text{)}_2\text{CH (CH}_2\text{)}_3\text{CH}_3, 2\text{HCl})</td>
<td>(\text{C}<em>{12}\text{H}</em>{28}\text{N}_2, 2\text{HCl})</td>
</tr>
<tr>
<td>(\text{CH}_3\text{(CH}_2\text{)}_2\text{CH (NH}_2\text{)}_2\text{CH (NH}_2\text{)}_2\text{CH (NH}_2\text{)}_2\text{CH (CH}_2\text{)}_3\text{CH}_3, 2\text{HCl})</td>
<td>(\text{C}<em>{12}\text{H}</em>{28}\text{N}_2, 2\text{HCl})</td>
</tr>
<tr>
<td>(\text{CH}_3\text{(CH}_2\text{)}_3\text{(NH}_2\text{)}_2\text{CH (CH}_2\text{)}_3\text{CH (NH}_2\text{)}_2\text{CH (NH}_2\text{)}_2\text{CH (CH}_2\text{)}_3\text{CH}_3, 2\text{HCl})</td>
<td>(\text{C}<em>{13}\text{H}</em>{30}\text{N}_2, 2\text{HCl})</td>
</tr>
<tr>
<td>(\text{CH}_3\text{(CH}_2\text{)}_2\text{CH (NH}_2\text{)}_2\text{CH (NH}_2\text{)}_2\text{CH (NH}_2\text{)}_2\text{CH (CH}_2\text{)}_3\text{CH}_3, 2\text{HCl})</td>
<td>(\text{C}<em>{13}\text{H}</em>{30}\text{N}_2, 2\text{HCl})</td>
</tr>
<tr>
<td>(\text{CH}_3\text{(CH}_2\text{)}_4\text{(NH}_2\text{)}_2\text{CH (CH}_2\text{)}_3\text{CH (NH}_2\text{)}_2\text{CH (NH}_2\text{)}_2\text{CH (CH}_2\text{)}_4\text{CH}_3, 2\text{HCl})</td>
<td>(\text{C}<em>{15}\text{H}</em>{34}\text{N}_2, 2\text{HCl})</td>
</tr>
<tr>
<td>(\text{CH}_3\text{(CH}_2\text{)}_2\text{CH (CH}_2\text{)}_2\text{(NH}_2\text{)}_2\text{CH (CH}_2\text{)}_3\text{CH (NH}_2\text{)}_2\text{CH (CH}_2\text{)}_2\text{CH (CH}_2\text{)}_2\text{CH (CH}_2\text{)}_2\text{CH (CH}_2\text{)}_2\text{CH (CH}_2\text{)}_3\text{CH}_3, 2\text{HCl})</td>
<td>(\text{C}<em>{15}\text{H}</em>{34}\text{N}_2, 2\text{HCl})</td>
</tr>
<tr>
<td>(\text{CH}_3\text{(CH}_2\text{)}_4\text{(NH}_2\text{)}_2\text{CH (CH}_2\text{)}_4\text{CH (NH}_2\text{)}_2\text{CH (NH}_2\text{)}_2\text{CH (CH}_2\text{)}_4\text{CH}_3, 2\text{HCl})</td>
<td>(\text{C}<em>{16}\text{H}</em>{36}\text{N}_2, 2\text{HCl})</td>
</tr>
<tr>
<td>(\text{CH}_3\text{(CH}_2\text{)}_2\text{CH (CH}_2\text{)}_2\text{(NH}_2\text{)}_2\text{CH (CH}_2\text{)}_4\text{CH (NH}_2\text{)}_2\text{CH (CH}_2\text{)}_2\text{CH (CH}_2\text{)}_2\text{CH (CH}_2\text{)}_2\text{CH (CH}_2\text{)}_2\text{CH (CH}_2\text{)}_3\text{CH}_3, 2\text{HCl})</td>
<td>(\text{C}<em>{16}\text{H}</em>{36}\text{N}_2, 2\text{HCl})</td>
</tr>
<tr>
<td>(\text{CH}_3\text{(CH}_2\text{)}_3\text{(NH}_2\text{)}_2\text{CH (CH}_2\text{)}_5\text{CH (NH}_2\text{)}_2\text{CH (CH}_2\text{)}_3\text{CH}_3, 2\text{HCl})</td>
<td>(\text{C}<em>{15}\text{H}</em>{34}\text{N}_2, 2\text{HCl})</td>
</tr>
<tr>
<td>(\text{CH}_3\text{(CH}_2\text{)}_2\text{CH (NH}_2\text{)}_2\text{CH (CH}_2\text{)}_5\text{CH (NH}_2\text{)}_2\text{CH (CH}_2\text{)}_3\text{CH}_3, 2\text{HCl})</td>
<td>(\text{C}<em>{15}\text{H}</em>{34}\text{N}_2, 2\text{HCl})</td>
</tr>
</tbody>
</table>
(5) Amoebicidal activity increases with the increasing length of the carbon chain to a certain extent and then decreases. For the preparation of more active diamines, it seems that an essential condition is a long straight carbon chain in which the two amino groups are separated by five methylene groups. (Table 8).

(6) Complete opening of the emetine molecule and breaking at different points (p.25 and 26) does not give very active compounds. 7:12-Diamino-5:14-diethyloctadecane is inactive and 7:11-diamino-5:13-diethylheptadecane has an activity of 1 in 100,000.
<table>
<thead>
<tr>
<th>Series</th>
<th>Formulae</th>
<th>Straight or Branched chain</th>
<th>In vitro amoebicidal activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethylenene</td>
<td>C₃H₁₀N₂, 2HCl</td>
<td>Straight</td>
<td>inactive</td>
</tr>
<tr>
<td>Tetramethylenene</td>
<td>C₄H₁₂N₂, 2HCl</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td>C₁₂H₂₈N₂, 2HCl</td>
<td>Branched</td>
<td>1 in 1,000</td>
</tr>
<tr>
<td></td>
<td>C₁₂H₂₈N₂, 2HCl</td>
<td>&quot;</td>
<td>inactive</td>
</tr>
<tr>
<td>Pentamethylenene</td>
<td>C₁₃H₃₀N₂, 2HCl</td>
<td>Straight</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td></td>
<td>C₁₃H₃₀N₂, 2HCl</td>
<td>&quot;</td>
<td>1 in 1,000</td>
</tr>
<tr>
<td>Hexamethylenone</td>
<td>C₁₄H₃₂N₂, 2HCl</td>
<td>Branched</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td></td>
<td>C₁₅H₃₄N₂, 2HCl</td>
<td>&quot;</td>
<td>1 in 100,000</td>
</tr>
<tr>
<td>Pentamethylenone</td>
<td>C₁₅H₃₄N₂, 2HCl</td>
<td>Branched</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td></td>
<td>C₁₅H₃₄N₂, 2HCl</td>
<td>&quot;</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td>Heptamethylenone</td>
<td>C₁₅H₃₄N₂, 2HCl</td>
<td>Branched</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td></td>
<td>C₁₅H₃₄N₂, 2HCl</td>
<td>&quot;</td>
<td>inactive</td>
</tr>
<tr>
<td>Hexamethylenone</td>
<td>C₁₆H₃₆N₂, 2HCl</td>
<td>Branched</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td></td>
<td>C₁₆H₃₆N₂, 2HCl</td>
<td>&quot;</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td>Pentamethylenone</td>
<td>C₁₇H₃₈N₂, 2HCl</td>
<td>Branched</td>
<td>1 in 100,000</td>
</tr>
<tr>
<td>Hexamethylenone</td>
<td>C₁₈H₄₀N₂, 2HCl</td>
<td>&quot;</td>
<td>1 in 100,000</td>
</tr>
<tr>
<td></td>
<td>C₁₉H₄₂N₂, 2HCl</td>
<td>&quot;</td>
<td>inactive</td>
</tr>
<tr>
<td>Pentamethylenone</td>
<td>C₂₁H₄₆N₂, 2HCl, H₂O</td>
<td>Branched</td>
<td>1 in 100,000</td>
</tr>
<tr>
<td>Hexamethylenone</td>
<td>C₂₂H₄₈N₂, 2HCl</td>
<td>&quot;</td>
<td>inactive</td>
</tr>
</tbody>
</table>
PART III. EXPERIMENTAL

(A) ALKYL BROMIDES AND POLYMETHYLENE DIBROMIDES

(a) Alkyl Bromides

n-Butyl bromide, n-amyl bromide, iso-amyl bromide and 2-ethylhexyl bromide were prepared from n-butyl alcohol, n-amyl alcohol, iso-amyl alcohol and 2-ethylhexanol respectively by the hydrobromic acid method (Organic Syntheses Vol. I, p. 25) according to the following reaction.

\[
R\ OH + HBr \xrightarrow{H_2SO_4} R\ Br + H_2O
\]

iso-Butyl bromide was prepared from iso-butyl alcohol by the phosphorus tribromide method (Org. Syn. 13, 20) according to the following reaction.

\[
3 (CH_3)_2CH CH_2OH + PBr_3 \rightarrow 3 (CH_3)_2CH CH_2Br + P(OH)_3
\]

All the bromides were obtained in good yield.

(b) Polymethylene Dibromides

Trimethylene dibromide and pentamethylene dibromide were prepared from trimethylene glycol and pentamethylene glycol by the hydrobromic acid method (Organic Syntheses Vol. I, p. 30), according to the following reaction.

\[
OH(CH_2)n OH + 2 HBr \rightarrow Br (CH_2)n Br + 2H_2O
\]

Tetramethylene bromide was obtained from tetrahydrofuran by treating it with dry hydrogenbromide according to the method described by Fried and Kleene (J. Amer. Chem. Soc., 1940; 62, 3258). The reaction took place in the following way.

\[
CH_2\overline{\begin{array}{c} \text{O} \\
\end{array}}\overline{\begin{array}{c} \text{CH}_2 \\
\end{array}} + 2HBr \rightarrow Br (CH_2)_4Br + H_2O
\]
n-Butyl Bromide

(Organic Syntheses Vol.I, p. 28)

1250 G (7.4 mol) of 48 per cent hydrobromic acid were placed in a 3 litre round bottom flask holding a reflux condenser and a dropping funnel, 375 g of concentrated sulphuric acid were added slowly. 444 G (6 mol) of n-butyl alcohol (dried and distilled before use, b.p. 117°) were added through the dropping funnel, followed by the gradual addition of 300 g of concentrated sulphuric acid with shaking. The mixture was heated gently under reflux for six hours during which period the formation of n-butyl bromide was practically complete. The product was removed from the reaction mixture by direct distillation. The water insoluble layer was separated, washed with water, then with 100 g of cold concentrated sulphuric acid, and finally with 250 c.c. solution of 10 per cent sodium carbonate. The bromide was dried over anhydrous potassium carbonate and distilled. 780G of n-butyl bromide boiling between 101-102° were collected. Yield was 90 per cent. It was further purified by fractional distillation and the fraction boiling at 101-102° was collected.

iso-Amyl Bromide


1050 G (6.25 mol) of 48 per cent hydrobromic acid were placed in a 3 litre flask holding a reflux condenser and a dropping funnel, and 300 g of concentrated sulphuric acid were
added. 440 g (5 mol. ) of \textit{iso}-amyl alcohol (dried and distilled, b.p. 132°) were added, followed by gradual addition of 50 g of cold concentrated sulphuric acid with shaking. The mixture was heated gently under reflux for 6 hours and distilled. The bromide layer was separated, washed with water and then with 75 g of cold concentrated sulphuric acid, and finally with 250 c.c. of 10 per cent solution of sodium carbonate. \textit{iso}-Amyl bromide was dried over anhydrous potassium carbonate and distilled. The liquid boiling at 116-120° was collected, yield 88 per cent. It was purified by fractional distillation and the fraction boiling at 121-122° was collected.

\textbf{n-Amyl Bromide}

1050 g (6.25 mol. ) of 48 per cent hydrobromic acid were placed in a 3 litre round bottom flask holding a reflux condenser and a dropping funnel and 300 g of concentrated sulphuric acid were added. 440 g (5 mol. ) of \textit{n}-amyl alcohol (previously dried and distilled) were added to the reaction mixture followed by gradual addition of 50 g of concentrated sulphuric acid with shaking. The mixture was heated gently under reflux for six hours and distilled. The bromide layer was separated, washed with water and then with 100 g of cold concentrated sulphuric acid and finally with 250 c.c. of 10 per cent sodium carbonate solution. It was dried over anhydrous potassium carbonate and distilled. The liquid boiling at 127-130° was collected, yield 85 per cent. The bromide was purified by fractional distillation b.p. 129-130°.
Iso-Butyl Bromide

(Organic Syntheses, 13, 20)

580 G (7 mol) of iso-butyl alcohol (dried and distilled) were placed in a 3 litre round bottom three necked flask fitted with a mechanical stirrer, a thermometer and a dropping funnel, and was cooled to 10° by immersing the flask in an alcohol and solid carbon dioxide bath. 695 G (2.56 mol) of phosphorus tribromide were added with stirring at such a rate as to keep the temperature below 0°. The cooling bath was removed and stirring continued until the mixture reached the room temperature, it was allowed to stand overnight. The stirrer, funnel and thermometer were removed and the flask was fitted with a 30 c.m. fractionating column and a condenser. The crude iso-butyl bromide was distilled from the reaction mixture under reduced pressure at 50°/20 mm. The receiver was kept in a cooling bath. The cold distillate was washed three times with 50 c.c. portions of concentrated sulphuric acid cooled to 0°, it was then shaken with 25 g of anhydrous potassium carbonate until the odour of hydrobromic acid disappeared. The product was distilled under reduced pressure, the fraction boiling 41 to 43°/135 mm. was collected. Yield 55 per cent.

2-Ethylhexyl Bromide

2400 G (14.2 mol) of 48 per cent hydrobromic acid were placed in a 5 litre round bottom flask fitted with a reflux condenser and a dropping funnel. 620 G (5 mol) of 2-ethylhexanol (dried and distilled, b.p. 81 to 83°/743 mm.) were
added and the mixture was heated gently under reflux for 6 hours. The mixture was steam distilled, the bromide distilled off together with water. It was extracted with ether, washed with water, dried over potassium carbonate and distilled under reduced pressure, b.p. 73-76°/14 mm., yield 93 per cent.

Trimethylene Dibromide

(有机合成学, 第1卷, p.30).

2500 G (14.8 mol.) of 48 per cent hydrobromic acid were placed in a 5 litre round bottom flask holding a reflux condenser, and a dropping funnel, and 75 g of concentrated sulphuric acid were added. 456 G (6 mol.) of trimethylene glycol were added, followed by gradual addition of 1200 g of concentrated sulphuric acid with shaking. The mixture was heated gently under reflux for six hours and distilled. The bromide was separated, washed with water, shaken with small portions of 200 g cold concentrated sulphuric acid and finally washed with 500 c.c. of 10 per cent sodium carbonate solution. It was dried over anhydrous potassium carbonate and distilled, b.p. 161-165°. Yield 88 per cent.

Tetramethylene Dibromide

200 G (2.8 mol.) of tetrahydrofuran were placed in a one litre three necked flask holding a reflux condenser, a thermometer and a delivery tube. A stream of dry hydrogen bromide (Booth, Inorganic Syntheses, Vol.1, p.151) was passed through it until no more gas was absorbed. According to Fried
and Kleene (J. Amer. Chem. Soc., 1941, 63, 3258) who prepared tetramethylene bromide for the first time from this method, the gas was passed through until the temperature of the solution rose up to 150° which indicated that the theoretical amount of hydrogen bromide had been absorbed by the solution. In the two repetitions the temperature did not rise beyond 130°, in the first preparation hydrogen bromide was passed very slowly and in the second preparation a rapid stream of hydrogen bromide was used. The resulting tarry product was washed thoroughly with water, and sodium bicarbonate solution until it was free of hydrobromic acid. Tetramethylene dibromide was extracted with ether, dried over anhydrous copper sulphate and distilled, b.p. 198°; 70 per cent yield was obtained.

**Pentamethylene Dibromide**

834 G (4.94 mol) of 48 per cent hydrobromic acid were placed in a two litre round bottom flask holding a reflux condenser and a dropping funnel. 136 G of concentrated sulphuric acid were added to hydrobromic acid followed by the addition of 208 g (2 mol) of pentamethylene glycol. To the mixture 220 g of concentrated sulphuric acid were added gradually with shaking and the mixture was heated gently under reflux for six hours. The bromide was obtained by the steam distillation of the reaction mixture. It was extracted with ether from the distillate, washed with 25 c.c. of cold concentrated sulphuric acid and then with 200 c.c. of 10 per cent solution of sodium
carbonate. It was dried over anhydrous potassium carbonate and distilled; b.p. 104°/15 mm., yield was 80 per cent.
(B) DIETHYL ALKYL MALONATES

**Diethyl n-buty1malonate.**

(Organic Syntheses Vol. I, p. 250)

A 3 litre round bottom flask fitted with a three way adaptor holding a reflux condenser, a mechanical stirrer, and a dropping funnel, was clamped over a water bath. In the flask 1 litre of absolute alcohol was placed and 46 g (2 atoms) of clean cut sodium were added to it in small amounts. The sodium ethoxide solution was stirred and cooled to about 50° after which 330 g (2.06 mol) of diethyl malonate were added through the dropping funnel. To the clear solution, after a while, 274 g. (2 mol.) of n-butyl bromide were added drop by drop. The reaction commenced immediately, after the addition of n-butyl bromide, the reaction mixture was heated under reflux until it was neutral to litmus. The flask was then connected with a condenser set for distillation. As much alcohol as possible was distilled off on the water bath while stirring continued. The residue was cooled, shaken with 800 c.c. of water, and the ester extracted with ether, dried over calcium chloride. Ether was distilled off from the dry solution and the liquid was distilled under reduced pressure, b.p. 126-127/21 mm., 91 per cent yield was obtained.

**Diethyl iso-buty1malonate.**

A 3 litre round bottom flask fitted with a three way adaptor, holding a reflux condenser, a dropping funnel and a mechanical stirrer was clamped over a water bath. In the flask
1 litre of absolute alcohol was placed and 46 g. (2 atoms) of clean cut sodium were added to it in small amounts. The sodium ethoxide solution was stirred and cooled to about 50° after which 330 g (2.06 mol.) of diethyl malonate were added gradually through the dropping funnel. To the clear solution, after a while, 274 g (2 mol.)/iso-butyl bromide were added drop by drop through the dropping funnel. The reaction commenced immediately. After the addition of iso-butyl bromide the reaction mixture was heated under reflux until it was neutral to moist litmus. The flask was connected with a condenser set for distillation; as much alcohol as possible was distilled off on the water bath while stirring continued. The residue was cooled and shaken with 800 c.c. of water. The ester separated as an oily liquid which was extracted with ether and dried over calcium chloride. Ether was distilled off on the water bath and the ester was distilled under reduced pressure, b.p. 119-120°/16 mm., 82 per cent yield was obtained.

**Diethyl n-amylmalonate**

A 3 litre round bottom flask fitted with a three way adaptor, holding a reflux condenser, a dropping funnel and a mechanical stirrer was clamped over a water bath. In the flask 1 litre of absolute alcohol was placed and 43.2 g (1.9 atoms) of clean cut sodium were added to it in small amounts. The sodium ethoxide solution was stirred and cooled to about 50° and 308 g (1.925 mol.) of diethyl malonate were added to it slowly through the dropping funnel. To the clear solution after a while
287 g \(0.9 \text{ mol}\) of \(n\)-amyl bromide were added drop by drop. The reaction commenced immediately. After the addition of \(n\)-amyl bromide the reaction mixture was heated under reflux until it was neutral to moist litmus. The flask was connected with a condenser set for distillation, as much alcohol as possible was distilled off on the water bath while stirring continued. The residue was cooled and shaken with water, an oily liquid separated. It was extracted with ether, dried over calcium chloride and ether distilled off on a water bath. The ester was distilled under reduced pressure. B.p. 120-122°/4 mm., 78 per cent yield was obtained.

**Diethyl iso-amylmalonate.**

A 3 litre round bottom flask fitted with a three way adaptor, holding a reflux condenser, a mechanical stirrer and a dropping funnel was clamped over a water bath. In the flask were placed 1500 c.c. of absolute alcohol and 69 g (3 atoms) of clean cut sodium were added to it in small portions. The sodium ethoxide solution was stirred and cooled to about 50° and 480 g (3 mol) of diethyl malonate were added to it slowly through the dropping funnel. To the clear solution after a while 453 g (3 mol) of iso-amyl bromide were added slowly through the dropping funnel. The reaction commenced almost immediately. After the addition of iso-amyl bromide the reaction mixture was heated under reflux until it was neutral to moist litmus. The flask was then connected with a condenser set for distillation, as much alcohol as possible was distilled off on
the water bath while stirring continued. The residue was cooled and shaken with 1200 c.c. of water. The ester separated as an oily liquid which was extracted with ether, dried over calcium chloride and ether was distilled off on a water bath. The ester was distilled under reduced pressure. B.p. 132-134/20 mm., 73 per cent yield was obtained.

**Diethyl n-hexylmalonate.**

A 3 litre round bottom flask fitted with a three way adaptor holding a reflux condenser, a dropping funnel and a mechanical stirrer was clamped over a water bath. In the flask 1500 c.c. of absolute alcohol were placed and 66.77 g (2.9 atoms) of clean cut sodium were added to it in small portions. The sodium ethoxide solution was stirred and cooled to about 50° and 480 g (3 mol.) of diethyl malonate were added to it gradually through the dropping funnel. To the clear solution after a while 480 g (3 mol.) of n-hexyl bromide were added very slowly through the dropping funnel. The reaction commenced immediately. After the addition of n-hexyl bromide, the reaction mixture was heated under reflux until it was neutral to moist litmus. The flask was then connected with a condenser set for distillation, as much alcohol as possible was distilled on the water bath while stirring continued. The residue was cooled, and shaken with 1200 c.c. of water, the ester separated as an oily liquid. It was extracted with ether, dried over calcium chloride and ether distilled off on the water bath. The ester was distilled under reduced pressure. B.p. 116°/2 mm., 87 per cent yield was
Diethyl 2-ethyl-hexylmalonate.

A 3 litre round bottom flask fitted with a three way adaptor holding a reflux condenser, a dropping funnel and a mechanical stirrer was clamped over a water bath. In the flask were placed 1500 c.c. of absolute alcohol and 69 g (3 atoms) of clean cut sodium were added to it in small portions. The sodium ethoxide solution was stirred and cooled to about 50° and 480 g (3 mol.) of diethyl malonate were added to it through the dropping funnel. To the clear solution after a while 580 g (3 mol.) of 2-ethyl-hexyl bromide were added drop by drop. The reaction commenced immediately. After the addition of 2-ethylhexyl bromide the reaction mixture was heated under reflux until it was neutral to moist litmus. The flask was then connected with a condenser set for distillation, as much alcohol as possible was distilled off on the water bath while stirring continued. The residue was cooled, shaken with 1200 c.c. water and the ester separated as an oily liquid. The ester was extracted with ether, dried over calcium chloride and ether distilled off on a water bath. The ester was distilled under reduced pressure, b.p. 169°/17 mm., 69 per cent yield was obtained.

Ethyl propane-1:15:3-tetracarboxylate


To a mixture of 800 g (5 mol.) of pure redistilled diethyl malonate and 200 g (3.65 mol.) of 40 per cent formaline cooled
to 50°C by immersion in ice, 25 g of diethylamine were added. The mixture was then allowed to come to the room temperature and left for fifteen hours, followed by heating the flask under reflux on a water bath for six hours. The aqueous layer was separated and the residue was distilled under reduced pressure, b.p. 190-200°C/20 mm., 60 per cent yield was obtained.
(C) Condensation of ethyl alkylmalonates with Polymethylene dibromides

In the condensation of ethyl alkylmalonates with ethylene dibromide, trimethylene dibromide, tetramethylene dibromide and pentamethylene dibromide using the same experimental conditions different yields of the condensation products were obtained. It appears that, with the exception of ethylene dibromide, the yield of the condensation products increases with the number of methylene groups in the polymethylene dibromides.

It would be of great interest and value to determine the difference of reactivity of different polymethylene dibromides with ethyl alkylmalonates, but unfortunately this was beyond the scope of present work.

<table>
<thead>
<tr>
<th>Ethyl alkylmalonates</th>
<th>Polymethylene dibromides</th>
<th>Yield of the condensation product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl n-butylmalonate</td>
<td>Br (CH₂)₂ Br</td>
<td>65.5 %</td>
</tr>
<tr>
<td>Ethyl iso-butylmalonate</td>
<td>&quot; &quot; &quot;</td>
<td>64 %</td>
</tr>
<tr>
<td>Ethyl n-butylmalonate</td>
<td>Br (CH₂)₃ Br</td>
<td>25 %</td>
</tr>
<tr>
<td>Ethyl iso-butylmalonate</td>
<td>&quot; &quot; &quot;</td>
<td>33 %</td>
</tr>
<tr>
<td>Ethyl n-amylmalonate</td>
<td>&quot; &quot; &quot;</td>
<td>32.5 %</td>
</tr>
<tr>
<td>Ethyl iso-amylmalonate</td>
<td>&quot; &quot; &quot;</td>
<td>36 %</td>
</tr>
<tr>
<td>Ethyl n-hexylmalonate</td>
<td>&quot; &quot; &quot;</td>
<td>39 %</td>
</tr>
<tr>
<td>Ethyl 2-ethylhexylmalonate</td>
<td>&quot; &quot; &quot;</td>
<td>28.5 %</td>
</tr>
<tr>
<td>Ethyl alkylmalonates</td>
<td>Polymethylene dibromides</td>
<td>Yield of the condensation product</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>--------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Ethyl ( \text{n})-butylmalonate</td>
<td>( \text{Br} , (\text{CH}_2)_4 , \text{Br} )</td>
<td>70 %</td>
</tr>
<tr>
<td>Ethyl ( \text{n})-amyImalonate</td>
<td>&quot; &quot; &quot;</td>
<td>42 %</td>
</tr>
<tr>
<td>Ethyl iso-amyImalonate</td>
<td>&quot; &quot; &quot;</td>
<td>46 %</td>
</tr>
<tr>
<td>Ethyl ( \text{n})-hexyImalonate</td>
<td>&quot; &quot; &quot;</td>
<td>45 %</td>
</tr>
<tr>
<td>Ethyl 2-ethylhexyImalonate</td>
<td>&quot; &quot; &quot;</td>
<td>50 %</td>
</tr>
<tr>
<td>Ethyl ( \text{n})-butylmalonate</td>
<td>( \text{Br} , (\text{CH}_2)_5 , \text{Br} )</td>
<td>70 %</td>
</tr>
<tr>
<td>Ethyl iso-butylmalonate</td>
<td>&quot; &quot; &quot;</td>
<td>70 %</td>
</tr>
<tr>
<td>Ethyl ( \text{n})-hexyImalonate</td>
<td>&quot; &quot; &quot;</td>
<td>50 %</td>
</tr>
</tbody>
</table>

**Ethyl 1,3-di-iso-amyImpropane-1:1:3:3-tetracarboxylate**

A 2 litre round bottom flask fitted with a three way adaptor, holding a reflux condenser, a dropping funnel and a mechanical stirrer was clamped over a water bath. In the flask 700 c.c. of absolute ethyl alcohol were placed and 34.5 g (1.5 atom) of clean cut sodium were added to it in small portions. The sodium ethoxide solution was stirred and 201 g \( (\text{.75 mol}:) \) ethyl propane tetracarboxylate were added to it slowly. To the clear solution after a while 227 g \( (1.5 \text{ mol}) \) of iso-amyIm bromide were added drop by drop. The reaction started after a considerable amount of iso-amyIm bromide had been added to the solution. After the addition of iso-amyIm bromide the reaction mixture was heated under reflux for 32 hours but it did not become neutral to moist litmus, in fact at the end of 32 hours it was still strong alkaline. The flask was connected with a condenser set for
distillation and as much alcohol as possible was distilled off on the water bath while stirring continued. The residue was cooled and shaken with 600 c.c. of water. The ester separated as a dark red oily liquid. It was extracted with ether, dried over calcium chloride and ether distilled off on the water bath. The ester was distilled under reduced pressure, b.p. 208-100/3 mm.; 10 per cent of the theoretical amount was obtained.

\[
\text{nd}_{25}^{\circ} \quad 1.453
\]

C_{25}H_{44}O_{8} requires C, 63.5; H, 9.3; found C, 62.6; H, 9.0.

**Ethyl 1:4-di-n-butylbutane-1:1:4:4-tetracarboxylate.**

A 2 litre round bottom flask fitted with a three way adaptor holding a reflux condenser, a dropping funnel and a mechanical stirrer was clamped over a water bath. In the flask 500 c.c. of absolute ethyl alcohol were placed and 23 g (1 atom) of clean cut sodium were added to it in small amounts. The sodium ethoxide solution was stirred and 216 g (1 mol.) of diethyl n-butylmalonate were added to it slowly through the dropping funnel. To the clear solution after a while 94 g (1 mol.) of ethylene dibromide were added drop by drop. The reaction started after a considerable amount of ethylene dibromide had been added, heat generated and sodium bromide was formed. After the addition of ethylene dibromide the reaction mixture was heated under reflux until it was neutral to moist litmus. The flask then was connected with a condenser set for distillation, as much alcohol as possible was distilled off on the water bath.
The residue was cooled and shaken with 400 c.c. of water. The ester separated as an oily liquid, it was extracted with ether, dried over calcium chloride and ether distilled off on the water bath. The ester was distilled under reduced pressure, b.p. 105-60°/4 mm., 65.5 per cent yield was obtained.

$$n_D^{16} = 1.4260$$

C$_{24}$H$_{44}$O$_8$ requires C, 62.8; H, 9.2; found C, 61.3; H, 9.1.

Ethyl 1:4-di-iso-buty1butane -1:1:4:4 tetracarboxylate.

A 2 litre round bottom flask fitted with a three way adaptor holding a reflux condenser, a dropping funnel and a mechanical stirrer was clamped over a water bath. In the flask 400 c.c. of absolute ethyl alcohol were placed and 16.1 g (0.7 atom) of clean cut sodium were added to it in small portions. Sodium ethoxide solution was stirred and 151 g (0.7 mol) of diethyl iso-butylmalonate were added to it slowly. To the clear solution after a while 65.8 g (.35 mol) of ethylene dibromide were added drop by drop. The reaction started when a considerable amount of ethylene dibromide had been added to the solution, heat was generated with deposition of sodium bromide. After the addition of ethylene dibromide the reaction mixture was heated under reflux for 20 hours (it became slightly darker than other reaction mixtures used in previous experiment) and it still remained alkaline. The flask was then connected with a condenser set for distillation, as much alcohol as possible was distilled off on the water bath while stirring continued. The residue was
cooled and shaken with 300 c.c. of water. The ester separated as an oily liquid. It was extracted with ether, dried over calcium chloride and ether distilled off on the water bath. The ester was distilled under reduced pressure, b.p. 92-4°/2 mm., 64 per cent yield was obtained.

\[ n_D^{15} = 1.424. \]

C₂₄ H₄₄ O₈ requires C, 62.8; H, 9.2; found C, 62.2; H, 9.5.

**Ethyl 1:5-di-iso-butylpentane-1:1:5:5-tetracarboxylate.**

W.H. Perkin (J. Trans. 1891, 59, 818) prepared this compound for the first time.

A 3 litre round bottom flask fitted with a three way adaptor holding a reflux condenser, a dropping funnel and a mechanical stirrer was clamped over a water bath. In the flask 1000 c.c. of absolute alcohol were placed and 43.25 g (1.88 atoms) of clean cut sodium were added in small portions. The sodium ethoxide solution was stirred and 437 g (1.9 mol.) of diethyl iso-butylmalonate were added through the dropping funnel. To the clear solution after a while 190 g (0.94 mol.) of trimethylene dibromide were added drop by drop. The reaction started after a considerable amount of trimethylene dibromide had been added. After the addition of trimethylene bromide the reaction mixture was heated under reflux until it was almost neutral to moist litmus. The flask was then connected with a condenser set for distillation, as much alcohol as possible was distilled off on the water bath while stirring continued. The
residue was cooled and shaken with 800 c.c. of water, the ester separated as orange oily liquid. It was extracted with ether, dried over calcium chloride and ether distilled off on a water bath. The ester was distilled under reduced pressure. B.p. 220-230°/1-3 mm. Yield of the ester was 145 g, 33 per cent of the theoretical amount. On cooling the ester solidified. It was crystallised from methyl alcohol, and melted at 45-47°.

Ethyl 1:5-di-n-butylpentane-1:1:5:5-tetracarboxylate

A 3 litre round bottom flask fitted with a three way adaptor holding a reflux condenser, a dropping funnel and a mechanical stirrer was clamped over a water bath. In the flask 1500 c.c. of absolute alcohol were placed and 46 g (2 atoms) of clean cut sodium were added to it in small portions. The sodium ethoxide solution was stirred and 432 g (2 mol.) of di-ethyl n-butyl malonate were added gradually. To the clear solution after a while 202 g (1 mol.) of trimethylene dibromide were added drop by drop. The reaction started after a considerable amount of trimethylene dibromide had been added. After the addition of trimethylene dibromide the reaction mixture was heated under reflux until it was almost neutral to moist litmus. The flask was connected with a condenser set for distillation, as much alcohol as possible was distilled off on the water bath while stirring continued. The residue was cooled and shaken with 800 c.c. of water, the ester separated as an orange oily liquid. It was extracted with ether, dried over
calcium chloride and ether was distilled off on a water bath. The ester was then distilled under reduced pressure, b.p. 98-102°/1 mm, 114-116°/4 mm. The ester solidified on keeping. It was crystallised from methyl alcohol: it melted at 37.5°, 125 g of the ester were obtained which was 25 per cent of the theoretical amount.

C₂₅H₄₄O₈ requires C, 63.5; H, 9.3 per cent found C, 63.5; H, 8.6.

**Ethyl 1:5-di-n-amylpentane-1:1:5:5-tetracarboxylate**

A 2 litre round bottom flask fitted with a three way adaptor holding a reflux condenser, a dropping funnel and a mechanical stirrer was clamped over a water bath. In the flask 800 c.c. of absolute alcohol were placed and 32.2 g (1.4 atoms) of clean cut sodium were added to it in small portions. The sodium ethoxide solution was stirred and 322 g (1.4 mol.) of diethyl n-amylmalonate were added to it slowly. To the clear solution after a while, 145 g (0.7 mol.) of trimethylene dibromide were added drop by drop. The reaction started after a considerable amount of trimethylene dibromide had been added and heat generated with deposition of sodium bromide. After the addition of trimethylene dibromide the reaction mixture was heated under reflux until it was almost neutral to moist litmus. The flask was then connected with a condenser set for distillation, as much alcohol as possible was distilled off on the water bath while stirring continued. The residue was cooled and shaken.
with 700 c.c. of water, the ester separated as an orange oily liquid. It was extracted with ether, dried over calcium chloride and ether distilled off on a water bath. The ester was distilled under reduced pressure, b.p. 234°/2 mm. 114 G. 32.5 per cent yield of the theoretical amount was obtained.

n\textsubscript{D} 1.4492

C\textsubscript{27}H\textsubscript{48}O\textsubscript{8} requires C, 64.7; H, 9.6; found C, 64.9; H, 9.2

**Ethyl 1:5-di-iso-amylpentane-1:1:5:5-tetracarboxylate**

A 2 litre round bottom flask fitted with a three way adaptor holding a reflux condenser, a mechanical stirrer and a dropping funnel was clamped over a water bath. In the flask was placed 700 c.c. of absolute ethyl alcohol and 23 g (1 atom) of clean cut sodium were added to it in small portions. The sodium ethoxide solution was stirred and 230 g (1 mol) of diethyl iso-amylmalonate were added gradually through the dropping funnel. The clear solution was stirred and 101 g (0.5 mol) of trimethylene bromide were added drop by drop. The reaction started after a considerable amount of trimethylene bromide had been added. After the addition of trimethylene bromide the flask was heated under reflux until the reaction mixture was almost neutral to litmus. As much alcohol as possible was distilled off on the water bath while continuing the stirring. The residue was cooled and shaken with 400 c.c. of water the ester separated as an oily liquid. It was extracted with ether and dried over calcium chloride. The ether was distilled off
on a water bath and the ester was distilled under reduced pressure, b.p. 225°/2 mm. Yield was 90 g. which was 36 per cent of the theoretical amount. The ester solidifies on keeping.

\[ n_D^{20} = 1.448 \]

\[ C_{27}H_{48}O_8 \text{ requires } C, 64.77; H, 9.66; \text{ found } C, 65.0; H, 9.5. \]

**Ethyl 1:5-di-n-hexylpentane-1:1:5:5-tetracarboxylate.**

A 2 litre round bottom flask fitted with a three way adaptor holding a reflux condenser, a dropping funnel and a mechanical stirrer was clamped over a water bath. In the flask 800 c.c. of absolute alcohol were placed and 23 g (1 atom) of clean cut sodium were added to it in small portions. The sodium ethoxide solution was stirred and 244 g (1 mol.°) of ethyl-n-hexylmalonate were added to it slowly through the dropping funnel. To the clear solution after a while 101 g (0.5 mol.) of trimethylene dibromide were added drop by drop. The reaction started, after a considerable amount of trimethylene dibromide had been added with generation of heat and deposition of sodium bromide. After the addition of trimethylene dibromide the mixture was heated under reflux until it was almost neutral to moist litmus. The flask was then connected with a condenser set for distillation, as much alcohol as possible was distilled off on the water bath while stirring continued. The residue was cooled and shaken with 400 c.c. of water. The ester separated as an oily liquid. It was extracted with ether, dried over calcium chloride and ether distilled off.
on the water bath. The ester was distilled under reduced pressure, b.p. 254°/5 mm., 270°/9 mm. 115 G yield, 39 per cent of the theoretical amount was obtained.

$\text{mp} 17 1.453$

C$_{29}$H$_{52}$O$_8$ requires C, 65.8; H, 9.9; found C, 65.9; H, 9.9.

**Ethyl 1:5-di-2-ethylhexylpentane-1:1:5:5-tetracarboxylate.**

A 2 litre round bottom flask fitted with a three way adaptor holding a reflux condenser, a dropping funnel and a mechanical stirrer was clamped over a water bath. In the flask 700 c.c. of absolute alcohol were placed and 23 g (1 atom) of clean cut sodium were added to it in small amounts. The sodium ethoxide solution was stirred and 280 g (1 mol.) of di-ethyl-2-ethylhexylmalonate were added to it slowly through the dropping funnel. To the clear solution after a while 101 g (1 mol.) of trimethylene bromide were added drop by drop. The reaction started, after a considerable amount of trimethylene bromide had been added, with generation of heat and deposition of sodium bromide. After the addition of trimethylene bromide the reaction mixture was heated under reflux until it was almost neutral to moist litmus. The flask then was connected with a condenser set for distillation, as much alcohol as possible was distilled off on the water bath while stirring continued. The residue was cooled and shaken with 400 c.c. water. The ester separated as an oily liquid. It was extracted with ether, dried over calcium chloride and ether distilled off on the water
bath while stirring continued. The residue was cooled and shaken with 400 c.c. of water. The ester separated as an oily liquid. It was extracted with ether, dried over calcium chloride and ether distilled off on the water bath. The ester was distilled under reduced pressure, b.p. 258°/3 mm., 83 g, 28.5 per cent yield of the theoretical amount was obtained.

$$\text{D}^{18} 1.4569$$

C<sub>33</sub>H<sub>60</sub>O<sub>8</sub> requires C, 67.8; H, 10.3; found C, 68.2; H, 10.3

**Ethyl 1:6-di-n-butylhexane-1:1:6:6-tetracarboxylate.**

A 2 litre round bottom flask fitted with a three way adaptor holding a reflux condenser, a dropping funnel and a mechanical stirrer was clamped over a water bath. In the flask 400 c.c. of absolute ethyl alcohol were placed and 11.5 g (0.5 atom) of clean cut sodium were added to it in small pieces. The sodium ethoxide solution was stirred and 108 g (0.5 mol.) of diethyl n-butyImalonate was added slowly through the dropping funnel. To the clear solution after a while 54 g. (0.25 mol.) of tetramethylene bromide were added drop by drop. The reaction started after a considerable amount of tetramethylene bromide had been added, and heat was generated. After the addition of tetramethylene bromide the reaction mixture was heated under reflux until it was almost neutral to moist litmus. The flask was then connected with a condenser set for distillation, as much alcohol as possible was distilled off on the water bath while stirring continued. The residue was cooled and shaken
with 200 c.c. of water. The ester separated as an oily liquid, it was extracted with ether, dried over calcium chloride and the ether distilled off on the water bath. Low boiling liquid from the ester was distilled up to 140°/6 mm., and the ester was left to cool down slowly. It solidified on cooling. It was crystallised from light petroleum (b.p. 40-60°), it melted at 30-32°. Before crystallisation the ester was purified by boiling with animal charcoal in light petroleum. Yield 70%.

C_{26}H_{46}O_{3} requires C, 64.1; H, 9.5; found C, 64.0; H, 9.6.


A 2 litre round bottom flask fitted with a three way adaptor holding a mechanical stirrer, a reflux condenser and a dropping funnel was clamped over a water bath. In the flask were placed 700 c.c. of absolute ethyl alcohol and 18.4 g (0.8 atom) of clean cut sodium were added to it in small portions. The sodium ethoxide solution was stirred and 184 g (0.8 mol.) of diethyl n-amylmalonate were added slowly through the dropping funnel. To the clear solution, after a while 86.4 g (0.4 mol.) of tetramethylene bromide were added drop by drop. The reaction started after a considerable amount of tetramethylene bromide had been added to the reaction mixture. After addition of tetramethylene bromide the mixture was heated under reflux until it was almost neutral to litmus. As much alcohol as possible was distilled off, the residue was cooled and 300 c.c. water was added to it. The ester separated as an
oily liquid. It was extracted with ether, dried over calcium chloride and ether distilled off on a water bath. The ester was distilled under reduced pressure, b.p. 244-6°/2 mm.

$\eta_p^{22} = 1.4495$

Yield 85 g, 72 per cent.

C$_{28}$H$_{50}$O$_8$ requires C, 65.3; H, 9.8; found, C, 65.8; H, 9.9.

**Ethyl 1:6-di-iso-amylhexane-1:1:6:6-tetracarboxylate**

A 2 litre round bottom flask fitted with a three way adaptor, holding a reflux condenser, a dropping funnel and a mechanical stirrer was clamped over a water bath. In the flask were placed 600 c.c. of absolute ethyl alcohol and 18.4 g (0.8 atom) of clean cut sodium were added to it in small portions. The sodium ethoxide solution was stirred and 86.4 g (0.4 mol) of tetramethylene bromide were added to it drop by drop. The reaction started after a considerable amount of tetramethylene bromide had been added to it. After the addition of tetramethylene bromide the reaction mixture was heated under reflux for 6½ hours after which it was almost neutral to litmus. The flask was then connected with a condenser set for distillation, as much alcohol as possible was distilled off on the water bath while stirring continued. The residue was cooled and shaken with 300 c.c. of water. The ester separated as an oily liquid it was extracted with ether, dried over calcium chloride and the ether distilled off on the water bath. The ester was distilled under reduced pressure, b.p. 242°/3 mm. 25 G of the
ester were obtained which was 46 per cent of the theoretical amount.

\[ n_D^{27} = 1.4465 \]

C\textsubscript{28} H\textsubscript{50} O\textsubscript{8} requires C, 65.3; H, 9.8; found C, 65.3; H, 9.7.

**Ethyl 1:6-di-n-hexylhexane-1:1:6:6-tetracarboxylate.**

A 2 litre round bottom flask fitted with a three way adaptor, holding a reflux condenser, a dropping funnel and a mechanical stirrer was clamped over a water bath. In the flask 300 c.c. of absolute ethyl alcohol were placed and 11.3 g (about 0.5 atom) of clean cut sodium were added to it in small portions. The sodium ethoxide solution was stirred and 122 g (.5 mol.) of diethyl n-hexylmalonate were added to it slowly. To the clear solution after a while 54 g (.25 mol.) of tetramethylene bromide were added drop by drop. The reaction started after a considerable amount of tetramethylene bromide had been added, heat generated and sodium bromide was formed. After the addition of tetramethylene bromide the reaction mixture was heated under reflux until it was almost neutral to moist litmus. The flask was then connected with a condenser set for distillation, as much alcohol as possible was distilled off on the water bath while stirring continued. The residue was cooled and shaken with 200 c.c. of water. The ester separated as an oily liquid. It was extracted with ether, dried over calcium chloride and then distilled off on the water bath. It was distilled under reduced pressure, b.p. 254 - 260°/5 mm.
61 G. of the ester (45 per cent of the theoretical amount) were obtained. \( \text{C}_{30}\text{H}_{54}\text{O}_8 \) requires C, 66.3; H, 10.0; found C, 67.0; H, 10.3

**Ethyl 1:6-di-2-ethylhexylhexane-1:1:6:6-tetracarboxylate**

A 2 litre round bottom flask fitted with a three way adaptor holding a reflux condenser, a dropping funnel and a mechanical stirrer was clamped over a water bath. In the flask were placed 600 c.c. of absolute ethyl alcohol and 23 g (1 atom) of clean cut sodium were added to it in small portions. The sodium ethoxide solution was stirred and 280 g (1 mol.) ethyl 2-ethylhexylmalonate were added to it slowly through the dropping funnel. To the clear solution after a while 108 g (0.5 mol.) of tetramethylene bromide were added drop by drop. The reaction started after a considerable amount of tetramethylene bromide had been added, heat generated and sodium bromide deposited. After the addition of tetramethylene bromide the reaction mixture was heated under reflux until it was almost neutral to litmus. The flask was then connected with a condenser set for distillation, as much alcohol as possible was distilled off on the water bath while stirring continued. The residue was cooled and shaken with 400 c.c. of water, the ester separated as an oily liquid. It was extracted with ether, and dried over calcium chloride and ether distilled off on the water bath. The ester was distilled under reduced pressure, b.p. 248°/1 mm. 

\[ n_D = 19.5 \quad 1.4562 \]
C_{34}H_{62}O_8 requires C, 68.2; H, 10.4; found C, 68.7; H, 10.5.
Yield 150 g (50 per cent).

**Ethyl 1:7-di-iso-butylandane-1:1:7:7-tetracarboxylate.**

A 2 litre round bottom flask fitted with a three way adaptor holding a reflux condenser, a dropping funnel and a mechanical stirrer was clamped over a water bath. In the flask 400 c.c. of absolute alcohol were placed and 11.5 g (0.5 atom) of clean cut sodium were added to it in small portions. The sodium ethoxide solution was stirred and 108 g (0.5 mol) of diethyl isobutyromalonate were added to it slowly through the dropping funnel. To the clear solution after a while 58 g (0.25 mol) of penta methylene bromide was added drop by drop. The reaction started after a considerable amount of penta methylene bromide had been added with generation of heat and deposition of sodium bromide. After the addition of penta methylene bromide the reaction mixture was heated under reflux until it was almost neutral to moist litmus. The flask then was connected with a condenser set for distillation, as much alcohol as possible was distilled off on the water bath while stirring continued. The residue was cooled and shaken with 200 c.c. water. The ester separated as an oily liquid. It was extracted with ether, dried over calcium chloride and ether distilled off on the water bath. The ester was distilled under reduced pressure, low boiling fraction up to 158°/4 mm., was separated and the ester was left to cool. On cooling it
solidified. It was crystallised from light petroleum (b.p. 40-60°), it melted at 64-5°. 88 G of the ester which was 70 per cent of the theoretical amount were obtained.

C_{27}H_{48}O_8 requires C, 64.7%; H, 9.2 found C, 65.6%; H, 9.2.

**Ethyl 1:7-di-n-butylheptane-1:1:7:7-tetracarboxylate**

A 2 litre round bottom flask fitted with a three way adaptor holding a reflux condenser, a dropping funnel and a mechanical stirrer was clamped over a water bath. In the flask 500 c.c. of absolute ethyl alcohol were placed and 23 g (1 atom) of clean cut sodium were added to it in small portions. The sodium ethoxide solution was stirred and 216 g (1 mol) of diethyl n-butylmalonate were added slowly through the dropping funnel. To the clear solution after a while 115 g (0.5 mol) of 1:5-dibromopentane were added drop by drop. The reaction started after a considerable amount of 1:5-dibromopentane had been added with generation of heat and deposition of sodium bromide. After the addition of 1:5-dibromopentane the reaction mixture was heated under reflux until it was almost neutral to moist litmus. The flask was then connected with a condenser set for distillation, as much alcohol as possible was distilled off on the water bath while stirring continued. The residue was cooled and shaken with 400 c.c. of water. The ester separated as an oily liquid. It was extracted with ether, dried over calcium chloride and ether distilled off on a water bath. The ester was submitted to distillation under
reduced pressure, low boiling fraction up to 200°/10 mm., was separated and the remaining high boiling ester was cooled. It solidified on cooling and was crystallised from light petroleum (b.p. 40-60°), it melted at 41-42°; 175 g of the ester, 70 per cent yield of the theoretical amount was obtained.

C_{27}H_{48}O_8 requires C, 64.7; H, 9.6; found C, 64.8; H, 9.5


A 2 litre round bottom flask fitted with a three way adaptor holding a reflux condenser and a dropping funnel and a mechanical stirrer was clamped over a water bath. In the flask 500 c.c. of absolute ethyl alcohol were placed and 11.3 g (for 0.5 atom) of clean cut sodium were added in small amounts. The sodium ethoxide solution was stirred and 122 g. (0.5 mol.) diethyl n-hexylmalonate were added slowly through the dropping funnel. To the clear solution after a while 58 g (0.25 mol.) of pentamethylene bromide were added drop by drop. The reaction started after a considerable amount of pentamethylene bromide had been added with generation of heat and deposition of sodium bromide. After the addition of pentamethylene bromide the reaction mixture was heated under reflux until it was almost neutral to litmus. The flask was then connected with a condenser set for distillation; as much alcohol as possible was distilled off on the water bath while stirring continued. The residue was cooled and shaken with 200 c.c. of water. The ester separated as an oily liquid, it was extracted
with ether, dried over calcium chloride and ether distilled off on the water bath. The ester was submitted to distillation under reduced pressure; low boiling fraction up to 176°/4 mm., was separated and the rest of the liquid cooled, it solidified on cooling. It was crystallised from light petroleum (b.p. 40-60°) but very low melting substance was obtained.

B.p. 248-50°/2-3 mm.

n_13

68 g of the ester were obtained which was 50 per cent of the theoretical amount.

C_{31}H_{56}O_8 requires C, 66.8; H, 10.1; found C, 66.8; H, 9.7.
(D) TETRACARBOXYLIC ACIDS

1:3-Di-iso-amylpropane—1:1:3:3 tetracarboxylic acid

25 g (0.083 mol) of ethyl 1:3-di-iso-amylpropane—1:1:3:3-tetracarboxylate were heated under reflux for 6 hours with an alcoholic solution of 13 g (0.216 mol) of potassium hydroxide. Alcohol was distilled off from the reaction mixture, followed by cooling and ether extraction to remove any unchanged ester present in it. The aqueous solution of the potassium salt of 1:3-di-iso-amylpropane—1:1:3:3-tetracarboxylic acid was diluted with 50 c.c. of water and acidified with concentrated hydrochloric acid which was added drop by drop with cooling of the reaction mixture in an ice bath. The acid separated as an oil, it was extracted with ether, the ether extract was dried over anhydrous sodium sulphate and ether was distilled off on a water bath. The acid remained in the flask as a thick oily liquid which did not solidify on strong cooling. It was insoluble in water, light petroleum and soluble in benzene and acetic acid. The silver salt was analysed.

C_{17}H_{24}O_{4}Ag requires Ag 54.7; found Ag 54.9.

1:4-Di-n-butylbutane—1:1:4:4-tetracarboxylic acid.

91.6 g (0.2 mol) of ethyl 1:4-di-n-butylbutane 1:1:4:4-tetracarboxylate were heated under reflux for 6 hours with an alcoholic solution of 46 g (0.84 mol) of potassium hydroxide. Alcohol was distilled off from the reaction mixture, followed by cooling and ether extraction to remove any unchanged ester present in it. The aqueous solution of the potassium salt of
1:4-di-n-butylbutane -1:1:4:4-tetracarboxylic acid was diluted with 150 c.c. of water and acidified with concentrated hydrochloric acid which was added drop by drop with cooling of the reaction mixture in an ice bath. The acid separated as an oil. It was extracted with ether, ether extract was dried over anhydrous sodium sulphate, and ether distilled off. The acid solidified on cooling and scratching. Yield 69 g (87 percent). It was soluble in water, benzene, carbon tetrachloride, chloroform, acetone, ethyl and methyl alcohols, insoluble in light petroleum. It was crystallised from benzene, it melted at 98-102°, and showed very light pink colour when wet with benzene.

C_{16} H_{26} O_8, H_2O requires C, 52.7; H, 7.6; found C, 52.6; H, 7.0.

1:4-Di-iso-butylbutane -1:1:4:4-tetracarboxylic acid.

91.6 G (0.2 mol.) of ethyl 1:4-di-iso-butylbutane -1:1:4:4-tetracarboxylate were heated for 6 hours under reflux with an alcoholic solution of 46 g (0.84 mol.) of potassium hydroxide. Alcohol was distilled off from the reaction mixture, followed by cooling and ether extraction to remove any unchanged ester present in it. The aqueous solution of the potassium salt of 1:4-di-iso-butylbutane -1:1:4:4-tetracarboxylic acid was diluted with 150 c.c. of water and acidified with concentrated hydrochloric acid which was added drop by drop with cooling of the reaction mixture in an ice bath.
The acid separated as an oil. It was extracted with ether, the ether extract was dried over anhydrous sodium sulphate and ether distilled off on a water bath. The acid remained in the flask as an oil and did not solidify on cooling and drying under vacuum. On mixing with large quantity (about 700 c.c.) of light petroleum (b.p. 40-60°) it separated as a solid, it was filtered, dried under vacuum and crystallised from benzene, it melted at 103-106°. It was soluble in water, acetic acid, benzene, acetone, ethyl and methyl alcohol, carbon tetrachloride and toluene, insoluble in light petroleum and chloroform.

C_{16}H_{26}O_8, H_2O requires C, 52.7; H, 7.5, found C, 52.3; H, 7.0.

**1:5-Di-n-butylpentane-1:1:5:5-tetracarboxylic acid**

94 g (0.2 mol) of ethyl 1:5-di-n-butylpentane-1:1:5:5-tetracarboxylate were heated under reflux for 6 hours with an alcoholic solution of 47.4 g (0.84 mol) of potassium hydroxide. Alcohol was distilled off from the reaction mixture, followed by cooling and ether extraction to remove any unchanged ester present in it. The aqueous solution of the potassium salt of 1:5-di-n-butylpentane-1:1:5:5-tetracarboxylic acid was diluted with 200 c.c. of water and acidified with concentrated hydrochloric acid which was added drop by drop with cooling of the reaction mixture in an ice bath. The acid separated as an oily liquid which slowly solidified. It was extracted with
ether and the ether extract was dried over anhydrous sodium sulphate, ether was distilled off on a water bath. The acid remaining in the flask solidified on cooling. Yield 76 g (almost 100 per cent). It was insoluble in light petroleum, benzene, chloroform, carbon tetrachloride; and very soluble in ethyl alcohol, methyl alcohol and acetone. After three crystallisations from water it melted at 147-149° with loss of carbon dioxide.

\[ C_{17}H_{28}O_9 \] requires C, 56.5; H, 7.8; found C, 56.0; H, 7.8.

**1:5-Di-iso-butylpentane-1:1:5:5-tetracarboxylic acid**

70 g (0.15 mol.) of ethyl 1:5-di-iso-butylpentane-1:1:5:5-tetracarboxylate were heated under reflux for 6 hours with an alcoholic solution of 36 g (0.64 mol.) of potassium hydroxide. Alcohol was distilled off from the reaction mixture, followed by cooling and ether extraction to separate any unchanged ester present in it. The aqueous solution of the potassium salt of 1:5-di-iso-butylpentane-1:1:5:5-tetracarboxylic acid was diluted with 250 c.c. of water and acidified with concentrated hydrochloric acid which was added drop by drop with cooling of the reaction mixture in an ice bath. The acid separated as an oily liquid which slowly solidified. It was extracted with ether, the ether extract was dried over anhydrous sodium sulphate and ether was distilled off on a water bath. The acid remaining behind in the flask solidified on cooling. Yield 53 g (99 per cent). It was soluble in acetone, methyl and
ethyl alcohols and acetic acid and insoluble in light petroleum, benzene, carbon tetrachloride, chloroform and water. It was crystallised from aqueous acetic acid, and had m.p. 145-147°.

This acid was prepared by Perkin, W.H. (J. Trans). 1891, 59, 818) during the preparation of 1:5-di-iso-butyl pimelic acid but was neither purified nor analysed.

\[ C_{17}H_{28}O_8 \] requires C, 56.5; H, 7.8; found C, 56.1; H, 7.8.

**1:5-Di-n-amylpentane -1:1:5:5-tetracarboxylic acid**

75 g (0.15 mol) of 1:5-di-n-amylpentane -1:1:5:5-tetracarboxylate were heated under reflux for 6 hours with an alcoholic solution of 36 g (0.64 mol) of potassium hydroxide. Alcohol was distilled off from the reaction mixture, followed by cooling and ether extraction to separate any unchanged ester. The solution of potassium salt of 1:5-di-n-amylpentane-1:1:5:5-tetracarboxylic acid was diluted with 250 c.c. of water and concentrated hydrochloric acid was added in excess drop by drop with cooling in an ice bath. The acid separated as an oil and solidified on cooling. It was extracted with ether, ether extract dried over sodium sulphate and ether distilled off on a water bath. The acid remaining behind solidified on cooling and drying in vacuum. It was a crystalline substance; soluble in water, acetone, ethyl and methyl alcohols, and glacial acetic acid, insoluble in benzene, carbon tetrachloride, chloroform and light petroleum. It was crystallised from water to which a little acetic acid had been added, it melted at 175.5°.
119.

*C_{19} H_{32} O_8* requires C, 58.7; H, 8.3; found C, 58.4; H, 8.4.

### 1:5-Di-iso-amylpentane-1:1:5:5-tetracarboxylic acid

65 g (0.13 mol) of ethyl 1:5-di-iso-amylpentane-1:1:5:5-tetracarboxylate were heated under reflux for 6 hours with an alcoholic solution of 31.3 g (0.56 mol) of potassium hydroxide. Alcohol was distilled off from the reaction mixture, followed by cooling and ether extraction to remove any unchanged ester present in it. The aqueous solution of 1:5-di-iso-amylpentane-1:1:5:5-tetracarboxylic acid was diluted with 215 c.c. of water and acidified with concentrated hydrochloric acid which was added drop by drop with cooling of the reaction mixture in an ice bath. The acid separated as a thick oil which solidified on cooling. It was extracted with ether, the ether extract was dried over anhydrous sodium sulphate and ether distilled off on a water bath. Yield 40 g (80 per cent). It was insoluble in water, benzene, light petroleum and soluble in acetic acid. It was crystallised from aqueous acetic acid, melted at 188°.

*C_{19} H_{32} O_8 \cdot \frac{1}{2} H_2O* requires C, 57.4; H, 8.3; found C, 57.3; H, 8.4.

### 1:5-Di-n-hexylpentane-1:1:5:5-tetracarboxylic acid

83 g (0.2 mol) of ethyl 1:5-di-n-hexylpentane-1:1:5:5-tetracarboxylate were heated under reflux for 6 hours with an alcoholic solution of 47 g (0.84 mol) of potassium hydroxide.
Alcohol was distilled off from the reaction mixture, followed by cooling and ether extraction to remove any unchanged ester present in it. The aqueous solution of the potassium salt of 1:5-di-n-hexylpentane -1:1:5:5-tetracarboxylic acid was diluted with 250 c.c. of water and acidified with concentrated hydrochloric acid which was added drop by drop with cooling of the reaction mixture in an ice bath. The acid separated as a semi-solid which became quite solid on cooling. It was extracted with ether, and the ether extract was dried over anhydrous sodium sulphate, and ether was distilled off on a water bath. The acid remaining behind in the flask solidified on cooling. The acid was dark orange coloured and became colourless on washing with cold benzene. It was soluble in ethyl and methyl alcohols and acetone; and sparingly soluble in water, insoluble in light petroleum, chloroform and carbon tetrachloride. It was crystallised from water to which some acetic acid had been added, melted at 173-174° with loss of carbon dioxide.

C_{21}H_{36}O_8 requires C, 60.5; H, 8.7; found C, 60.6; H, 8.5.

**1:5-Di-2-ethylhexylpentane -1:1:5:5-tetracarboxylic acid**

63 G (0.108 mol.) of ethyl 1:5-di-2-ethylhexylpentane 1:1:5:5 tetracarboxylate were heated under reflux for 5 hours with an alcoholic solution of 24.6 g (0.44 mol.) of potassium hydroxide. Alcohol was distilled off from the reaction mixture, followed by cooling and ether extraction to remove any unchanged ester present in it. The aqueous solution of 1:5-di-2-ethyl-
hexylpentane -1:1:5:5-tetracarboxylic acid was diluted with 200 c.c. of water and acidified with concentrated hydrochloric acid, which was added drop by drop with cooling of the reaction mixture in an ice bath. The acid separated as an oily liquid. It was extracted with ether, the ether extract was dried over anhydrous sodium sulphate and ether was distilled off on a water bath. The acid remained behind as a thick oil, it solidified on drying in vacuum. Yield 50 g (almost 100 per cent). It was sparingly soluble in benzene, insoluble in water, soluble in acetic acid and light petroleum. It was washed with benzene dried and crystallised from aqueous acetic acid. It melted at 162-164°.

C_{25}H_{44}O_{8} requires, C, 63.5; H, 9.3; found C, 63.7; H, 9.3.

1,6-Di-n-butylhexane -1:1:6:6-tetracarboxylic acid

78.6 G (0.1 mol) of ethyl 1:6-di-n-butylhexane -1:1:6:6-tetracarboxylate were heated under reflux for 6 hours with an alcoholic solution of 25 g (0.44 mol) of potassium hydroxide. Alcohol was distilled off from the reaction mixture, followed by cooling and ether extraction to remove any unchanged ester present in it. The aqueous solution of the potassium salt of 1:6-di-n-hexylhexane -1:1:6:6-tetracarboxylic acid was diluted with 175 c.c. of water and acidified with concentrated hydrochloric acid which was added drop by drop with cooling of the reaction mixture in an ice bath. The acid separated as a semi-solid substance. It was extracted with ether, ether extract
was dried over anhydrous sodium sulphate and ether distilled off. The acid remaining behind in the flask solidified on cooling. Yield 37 g (about 99 per cent). The acid was soluble in water and acetic acid, insoluble in benzene, carbon tetrachloride, chloroform, toluene and light petroleum. It was crystallised from a mixture of acetic acid and benzene, melted at 190-192°.

C_{18}H_{30}O_8 requires C, 57.7; H, 8.07; found C, 58.0; H, 8.2.

1:6-Di-n-amylhexane-1:1:6:6-tetracarboxylic acid

76.5 g (0.15 mol) of ethyl-1:6-di-n-amyl hexane-1:1:6:6-tetracarboxylate were heated under reflux for 6 hours with an alcoholic solution of 36 g (0.64 mol) of potassium hydroxide. Alcohol was distilled off from the reaction mixture, followed by cooling and ether extraction to remove any unchanged ester present in it. The aqueous solution of the potassium salt of 1:6-di-n-amylhexane-1:1:6:6-tetracarboxylic acid was diluted with 250 c.c. of water and acidified with concentrated hydrochloric acid which was added drop by drop with cooling of the reaction mixture in an ice bath. The acid was extracted with ether, ether extract was dried over anhydrous sodium sulphate and ether was distilled off on a water bath. Yield 60 g (100 per cent). It was soluble in acetic acid, insoluble in water, benzene, light petroleum, chloroform and carbon tetrachloride. It was crystallised from aqueous acetic acid, melted at 187°.

C_{20}H_{34}O_8 requires C, 59.7; H, 8.5; found C, 60.0; H, 8.7.
1:6-Di-iso-amylhexane-1:1:6:6-tetracarboxylic acid

87 g (0.17 mol) of ethyl-1:6-di-iso-amylhexane-1:1:6:6-tetracarboxylate were heated under reflux for 6 hours with an alcoholic solution of 40 g (0.72 mol) of potassium hydroxide. Alcohol was distilled off from the reaction mixture, followed by cooling and ether extraction to remove any unchanged ester present in it. The aqueous solution of the potassium salt of 1:6-di-iso-amylhexane-1:1:6:6-tetracarboxylic acid was diluted with 250 c.c. of water and acidified with concentrated hydrochloric acid which was added drop by drop with cooling of the reaction mixture in an ice bath. The acid was extracted with ether, ether extract was dried over anhydrous sodium sulphate and ether distilled off on a water bath. Yield 68 g (100 percent). It was insoluble in water, benzene and light petroleum, soluble in acetic acid. It was crystallised from aqueous acetic acid, melted at 200-202°.

C_{20}H_{34}O_8 requires C, 59.7; H, 8.5; found C, 59.3; H, 8.5.


54 g (0.1 mol) of ethyl-1:6-di-n-hexylhexane-1:1:6:6-tetracarboxylate were heated for 6 hours under reflux with an alcoholic solution of 23.5 g (0.42 mol) of potassium hydroxide. Alcohol was distilled off from the reaction mixture, followed by cooling and ether extraction to remove any unchanged ester present in it. The aqueous solution of the potassium salt of 1:6-di-n-hexylhexane-1:1:6:6-tetracarboxylic acid was
diluted with 150 c.c. of water and acidified with concentrated hydrochloric acid with cooling of the reaction mixture in an ice bath. The acid separated as a thick oil and solidified on cooling. It was extracted with ether, the ether extract was dried over anhydrous sodium sulphate and ether distilled off on a water bath. The acid was soluble in acetic acid, acetone, ethyl and methyl alcohols, insoluble in water, benzene, chloroform, carbon tetrachloride and light petroleum. It was washed with benzene, dried, and crystallised from a mixture of water and acetic acid, it melted at 192°.

C_{22}H_{38}O_{8} requires C, 61.4; H, 8.8; found C, 61.9; H, 8.7.

**1:6-Di-2-ethylhexylhexane-1:1:6:6-tetracarboxylic acid**

90 g (0.15 mol) of ethyl-1:6-di-2-ethylhexylhexane-1:1:6:6-tetracarboxylate were heated under reflux for 6 hours with an alcoholic solution of 36 g (0.64 mol) of potassium hydroxide. Alcohol was distilled off from the reaction mixture followed by cooling and ether extraction to remove any unchanged ester present in it. The aqueous solution of the potassium salt of 1:6-di-2-ethylhexylhexane-1:1:6:6-tetracarboxylic acid was diluted with 200 c.c. of water and acidified with concentrated hydrochloric acid which was added drop by drop with cooling of the reaction mixture in an ice bath. The acid separated as an oil. It was extracted with ether, dried over anhydrous sodium sulphate and ether distilled off on a water bath. The acid remained behind as a thick oil, it was dried in vacuum, it
became a thick glassy mass which could not be crystallised. Silver salt of the acid was analysed.

\[ \text{C}_{24}\text{H}_{42}\text{O}_8 \text{Ag}_4 \text{ requires Ag 47.2; found Ag 46.9.} \]

\[ \text{1:7-Di-n-butylheptane-1:1:7:7-tetracarboxylic acid} \]

65 g (0.15 mol) of ethyl 1:7-di-n-butylheptane-1:1:7:7-tetracarboxylate were heated under reflux for 5 hours with an alcoholic solution of 35.8 g (0.64 mol) of potassium hydroxide. Alcohol was distilled off from the reaction mixture, followed by cooling and ether extraction to remove any unchanged ester present in it. The aqueous solution of 1:7-di-n-butylheptane-1:1:7:7-tetracarboxylic acid was diluted with 300 c.c. of water and acidified with concentrated hydrochloric acid which was added drop by drop with cooling of the reaction mixture in an ice bath. The acid separated as a thick oil. It was extracted with ether, ether extract dried over anhydrous sodium sulphate and ether distilled off on a water bath. The acid remained behind in the flask and solidified on cooling. Yield 57 g (99 per cent). It was soluble in ethyl and methyl alcohol, acetone and acetic acid, slightly soluble in water, insoluble in benzene, carbon tetrachloride, chloroform and light petroleum. It was crystallised from a mixture of water and acetic acid, and it melted at 168-169°.

\[ \text{C}_{19}\text{H}_{32}\text{O}_8 \text{ requires C, 58.7; H, 8.3; found C, 59.0; H, 8.3.} \]
1:7-Di-iso-butylheptane -1:1:7:7-tetracarboxylic acid

55 G (0.11 mol) of ethyl 1:7-di-iso-butylheptane -1:1:7:7-tetracarboxylate were heated under reflux for 6 hours with an alcoholic solution of 27 g (0.48 mol) of potassium hydroxide. Alcohol was distilled off from the reaction mixture, followed by cooling and ether extraction to remove any unchanged ester present in it. The aqueous solution of the potassium salt of 1:7-di-iso-butylheptane -1:1:7:7-tetracarboxylic acid was diluted with 200 c.c. of water and acidified with concentrated hydrochloric acid which was added drop by drop with cooling the reaction mixture in an ice bath. The acid separated as an oil, it was extracted with ether, the ether extract was dried over anhydrous sodium sulphate and ether distilled on a water bath. The acid remained behind as a thick oil, it was dried over phosphorus pentoxide in vacuum. It seemed to crystallise from acetic acid very slowly. The acid separated as a solid when stirred with benzene. It was soluble in acetic acid, hot water, acetone, ethyl and methyl alcohol, insoluble in benzene, light petroleum, chloroform, carbon tetrachloride. It was crystallised from a mixture of benzene and acetic acid, melted at 162-163°.

C_{19}H_{32}O_8, \frac{7}{8}H_2O requires C, 57.4; H, 8.3; found C, 57.8; H, 8.4.
1:7-Di-n-hexylheptane -1:1:7:7-tetracarboxylic acid

56 g (0.1 mol.) of ethyl-1:7-di-n-hexylheptane-1:1:7:7-tetracarboxylate were heated for 6 hours under reflux with an alcoholic solution of 25 g (0.44 mol.) of potassium hydroxide. Alcohol was distilled off from the reaction mixture, followed by cooling and ether extraction to remove any unchanged ester present in it. The aqueous solution of the potassium salt of 1:7-di-n-hexylheptane -1:1:7:7-tetracarboxylic acid was diluted with 200 c.c. of water and acidified with concentrated hydrochloric acid which was added drop by drop with cooling of the reaction mixture in an ice bath. The acid separated as a semi-solid. It was extracted with ether, on drying the ether extract over anhydrous sodium sulphate it precipitated; sodium sulphate was dissolved in water and ether layer was separated. Ether was distilled off on a water bath and the acid was dried in vacuum. It was soluble in acetic acid, acetone, ethyl and methyl alcohols, insoluble in water, benzene, light petroleum, chloroform, carbon tetrachloride, and toluene. It was crystallised from a mixture of benzene and acetic acid, it melted at 178-179°.

C_{23}H_{40}O_8 requires C, 61.9; H, 9.0; found C, 61.5; H, 8.85.
Glutaric acid


125 G (0.37 mol) of ethyl propane-1:1:3:3-tetra-carboxylate were mixed with 125 c.c. of concentrated hydrochloric acid and 125 c.c. of water. The mixture was heated under reflux in an oil bath (the temperature of the bath being 115-120°) until it became homogenous. The contents of the flask were evaporated to dryness and the residual glutaric acid crystallised from benzene in needles, m.p. 96-97°.

1:3-Di-iso-amylglutaric acid

20 G (0.055 mol) of 1:3-di-iso-amylpropane-1:1:3:3-tetracarboxylic acid were placed in a 100 c.c. flask and heated slowly in an oil bath up to 150°, decarboxylation started at 138°. On the analysis of the silver salt of the acid higher percentage of silver was obtained than theoretically required for C_{15}H_{24}O_{4}Ag_{2}; the acid was heated again in an oil bath up to 200°. It was a thick sticky substance and could not be crystallised, insoluble in water, soluble in organic solvents. C_{15}H_{24}O_{4}Ag_{2} requires Ag 44.37; found Ag 44.0.

Adipic acid


0.1 G ammonium vanadate was added to 210 G (1.66 mol) of 50 per cent nitric acid followed by the gradual addition of 50 g (1 mol) of cyclohexanol with stirring. The temperature
of the reaction mixture was maintained between 55-60° by cooling. Adipic acid was obtained in crystalline form by cooling the reaction mixture to 0°, it was recrystallised from conc. nitric acid and had m.p. 151-152°, 56 per cent yield was obtained.

**1:4-Di-n-butyladipic acid**

40 G of 1:5-di-n-butylbutane -1:1:4:4-tetracarboxylic acid were placed in a 250 c.c. flask and were heated slowly in an oil bath. Decarboxylation started at 145° and 1:di-n-butyl adipic acid was obtained as a liquid. The acid was washed several times with water, it was dissolved in ether and dried over sodium sulphate. Ether was distilled. Silver salt of 1:4-di-n-butyladipic acid was obtained by dissolving the acid in slight excess of ammonium hydroxide, boiling off excess of ammonia and then adding a solution of silver nitrate to it. The salt was washed with water and dried in vacuum. C_{14}H_{24}O_{4}Ag requires Ag 45.7; found Ag 45.56.

**1:4-Di-iso-butyladipic acid**

25 G of 1:4-di-iso-butylbutane -1:1:4:4-tetracarboxylic acid were placed in a 100 c.c. flask and heated slowly in an oil bath. The decarboxylation started at 140°. 1:4-Di-iso-butyladipic acid was obtained as a liquid which was soluble in water and organic solvents.

C_{14}H_{24}O_{4}Ag requires Ag 45.7; found Ag 45.8.
1:5-Di-n-butylpimelic acid

66 G of 1:5-di-n-butylpentane-1:1:5:5-tetracarboxylic acid were placed in a 250 c.c. flask and heated in an oil bath from 200 to 210°. Decarboxylation started when the temperature was 128° and 1:5-di-n-butylpimelic acid was obtained as an oil which solidified on cooling to a soft waxy substance. It was soluble in light petroleum, acetic acid, ethyl and methyl alcohol and insoluble in water. It crystallised from aqueous acetic acid in colourless plates, m.p. 107°. C_{15}H_{28}O_{4} requires C, 66.1; H, 10.3; found C, 66.7; H, 10.1.

1:5-Di-iso-butylpimelic acid

50 G of 1:5-di-iso-butylpentane-1:1:5:5-tetracarboxylic acid were placed in a 250 c.c. flask and heated in an oil bath from 195-200°. (Perkin and Prentice, J. (Trans). 59; 818, heated from 200 to 220°). The acid was obtained as an oil which solidified on cooling. It can be crystallised from large quantities of water but light petroleum (b.p. 80-100°) was found better for this purpose. On repeated crystallisations substance of constant melting point could not be obtained, melting points at different crystallisations were as follows:-
On 1st crystallisation m. p. 95°
On second crystallisation m. p. 104 - 105°
On third crystallisation m. p. 105 - 106°
On fourth crystallisation m. p. 106 - 109°
On fifth crystallisation m. p. 109 - 111°

Substance melting at 105 - 106° was analysed.

C₁₅H₂₈O₄ calculated C, 66.1; H, 10.3; found C, 66.7; H, 10.1.

**1:5-Di-n-amylpimelic acid**

76 G of 1:5-di-n-amylpentane-1:1:5:5-tetracarboxylic acid were placed in an oil bath from 140 - 170°. 1:5-Di-n-amylpimelic acid solidified on cooling, it was soluble in light petroleum, benzene, toluene, acetic acid, ethyl and methyl alcohol. It crystallised from aqueous acetic acid in colourless plates m.p. 109 - 112.5°, C₁₇H₃₂O₄ requires C, 67.9; H, 10.8; found C, 67.9; H, 10.6.

**1:5-Di-iso-amylpimelic acid**

25 G of 1:5-di-iso-amylpentane-1:1:5:5-tetracarboxylic acid were placed in a 250 c.c. flask and heated in an oil bath up to 190°. 1:5-Di-iso-amylpimelic acid solidified on cooling as a very hard substance. It was insoluble in water, soluble in light petroleum, and very soluble in benzene. It crystallised from light petroleum (b.p. 60-80) in beautiful shining plates, m.p. 136°. C₁₇H₃₂O₄ requires C, 67.9; H, 10.8; found C, 67.2; H, 10.6.
1:5-Di-n-hexylpimelic acid

50 G of 1:5-di-n-hexylpentane-1:5-5-tetracarboxylic acid were placed in a 250 c.c. flask and heated in an oil bath from 175-185°. 1:5-Di-n-hexylpimelic acid solidified on cooling, it was soluble in acetic acid and insoluble in water. It crystallised from benzene in shining plates m.p. 108-110°. The melting points vary with crystallisations from 100 to 110°. 

C_{19}H_{36}O_{4} requires C, 69.47; H, 11.0; found C, 70.0; H, 10.8.

1:5-Di-2-ethylhexylpimelic acid

30 G of 1:5-di-2-ethylhexylpentane-1:5-5-tetracarboxylic acid were placed in a 100 c.c. flask and heated in an oil bath from 150 to 170°. 1:5-Di-2-ethylhexylpimelic acid was obtained as a thick sticky substance which could not be crystallised. The acid was cooled and dried over calcium chloride and phosphorus penta oxide in vacuum but it did not solidify. It was left with some water for a long time hoping to get it as a solid in a hydrate form but nothing happened. The acid was very soluble in light petroleum, carbon tetrachloride, chloroform, acetic acid, benzene and insoluble in water. The silver salt was made by dissolving the acid in slight excess of ammonium hydroxide, boiling off excess of ammonia and then adding silver nitrate solution to it. The salt was washed with water, ethyl alcohol and ether and dried in vacuum. It decomposed very quickly. C_{23}H_{44}O_{4}Ag_{2} requires Ag 35.96; found Ag 36.1.
1:6-Di-n-butylsuberic acid

27 G of 1:6-di-n-butylhexane -1:1:6:6-tetracarboxylic acid were placed in a 250 c.c. flask and heated in an oil bath from 167 to 175°. 1:6-Di-n-butylsuberic acid solidified on cooling, it was insoluble in water, soluble in benzene and light petroleum. It was crystallised from light petroleum (b.p. 40-60°), and it melted at 103-107°.

C_{16}H_{30}O_{4} requires C, 67.1; H, 10.5; found C, 66.9; H, 10.5.

1:6-Di-n-amylsuberic acid

40 G of 1:6-di-n-amylhexane -1:1:6:6-tetracarboxylic acid were placed in a 250 c.c. flask and heated in an oil bath from 177-195°. 1:6-Di-n-amylsuberic acid solidified on cooling, it was insoluble in water, soluble in benzene and light petroleum, (b.p. 60-80°). It melted at 100° but seemed to sublime above 88°.

C_{18}H_{34}O_{4} requires C, 68.75; H, 10.7; found C, 69.0; H, 10.7.

1:6-Di-iso-amylsuberic acid

45 G of 1:6-di-iso-amylhexane -1:1:6:6-tetracarboxylic acid were placed in a 250 c.c. flask and heated in an oil bath up to 190°. 1:6-Di-iso-amylsuberic acid solidified on cooling. It was soluble in benzene and light petroleum and insoluble in water. It was crystallised from light petroleum (b.p. 60-300°), it melted at 119-121°.

C_{18}H_{34}O_{4} requires C, 68.75; H, 10.7; found C, 69.0; H, 10.7.
1:6-Di-n-hexylsuberic acid

15 G of 1:6-di-n-hexylhexane-1:1:6:6-tetracarboxylic acid were placed in a 100 c.c. flask and heated in an oil bath up to 163°. 1:6-Di-n-hexylsuberic acid solidified on cooling. It was crystallised from light petroleum (b.p. 40-60°) and it sublimed above 90°.

C_{20}H_{38}O_4 requires C, 70.1; H, 11.1; found C, 70.0; H, 11.2.

1:6-Di-2-ethylhexyl suberic acid

30 G of 1:6-di-2-ethylhexylhexane-1:1:6:6-tetracarboxylic acid were placed in a 250 c.c. flask and heated in an oil bath up to 170-180°. 1:6-Di-2-ethylhexylsuberic acid was obtained as a thick oily liquid. Silver salt of the acid was analysed.

C_{24}H_{44}O_4 Ag_2 requires Ag, 35.2; found Ag 35.0

1:7-Di-n-butylazelaic acid

25 G of 1:7-di-n-butyleptane-1:1:7:7-tetracarboxylic acid were placed in a 250 c.c. flask and heated in an oil bath from 150 to 170°. 1:7-Di-n-butylazelaic acid solidified on cooling. It was insoluble in water, soluble in benzene, acetic acid and crystallised from aqueous acetic acid in rods, m.p. 89-93°. C_{17}H_{32}O_4 requires C, 67.9; H, 10.8; found C, 67.7; H, 10.8.
1:7-Di-iso-butylazelaic acid

23 G of 1:7-di-iso-butylheptane -1:1:7:7-tetracarboxylic acid were placed in a 100 c.c. flask and heated in an oil bath from 130 to 160°. 1:7-Di-iso-butylazelaic acid solidified on strong cooling but melted again at room temperature. It was insoluble in water, soluble in acetic acid, light petroleum, benzene, chloroform, carbon tetrachloride. The acid slowly crystallised when it was dissolved in aqueous acetic acid and left for several days. It was recrystallised from glacial acetic acid and it melted at 110 - 111°.

C_{17}H_{32}O_{4} requires C, 67.9; H, 10.8; found C, 67.5; H, 10.4.

1:7-Di-n-hexylazelaic acid

25 G of 1:7-di-n-hexylheptane -1:1:7:7-tetracarboxylic acid were placed in a 100 c.c. flask and heated in an oil bath up to 175°. 1:7-Di-n-hexylazelaic acid solidified on cooling. It was insoluble in water and was crystallised from light petroleum (b.p. 40-60°), it melted at 70-73°.

C_{21}H_{40}O_{4} \frac{1}{2}H_{2}O requires C, 69.0; H, 11.3; found C, 69.1; H, 11.1.
Preparation of Diamines from Dibasic Acids

Schmidt's Reaction

Schmidt's reaction was applied for the preparation of diamines from long chain aliphatic dibasic acids. The acids used were 1:3-di-iso-amylglutaric acid, 1:4-dialkyladipic acids, 1:5-dialkylpimelic acids, 1:6-dialkylosuberic acids and 1:7-dialky lazelaic acids. The corresponding diamines were obtained from all the acids except from 1:3-di-iso-amylglutaric acid. 1:3-Di-iso-amylglutaric acid gave a base which on treatment with picric acid in benzene formed a crystalline picrate. The picrate was analysed and was found to have less percentage of hydrogen in it than required for the expected dipicrate of 2:10-dimethyl-5:7-diaminoundecane. The analytical results did not fit in for any other compound that could be obtained by treating 1:3-di-iso-amylglutaric acid with hydrazoic acid. The constitution of the base could not be ascertained.

General Conditions used

The dibasic acid was dissolved in concentrated sulphuric acid and benzene was added to it (for 1 gram of the dibasic acid 3 to 5 c.c. of sulphuric acid and 3 to 6 c.c. of benzene were used). Activated sodium azide (2 to 4 mole for 1 mole of the dibasic acid) was added in small portions to the reaction mixture. In most of the experiments the reaction started at room temperature and then it was carried out at a suitable temperature. The suitable temperature for carrying
out Schmidt’s reaction on these acids seem to decrease with the increasing purity, molecular weight and the distance between the two carboxyl groups of the substance. The base was liberated by making the reaction mixture alkaline. Most of the bases were quite soluble in benzene and the solution of the base in benzene or a mixture of benzene and ether was used. It was necessary to keep the solutions as dry as possible for the preparation of the dihydrochlorides. The dihydrochlorides were deliquescent substances.

**Activated sodium azide**

Activated sodium azide was used in these experiments because it gives better yield than the technical sodium azide. It was prepared by a method used by Johannes Nelles (Ber, 1932, 65, 1345).

10 G of the technical sodium azide were placed in a fairly large evaporating dish and were thoroughly mixed with 0.5 c.c. of hydrazine hydrate and left overnight. Sodium azide was dissolved in minimum amount of water, filtered and precipitated with large quantity of acetone. It was filtered, washed with a little methyl alcohol and then with ether and dried in vacuum.
<table>
<thead>
<tr>
<th>Long Chain dibasic acid</th>
<th>Suitable temp.</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:3-Di-iso-amylglutaric acid</td>
<td>45 - 55°</td>
<td>22%</td>
</tr>
<tr>
<td>1:4-Di-n-butyladipic acid</td>
<td>35 - 40°</td>
<td>50 - 55%</td>
</tr>
<tr>
<td>1:4-Di-iso-butyladipic acid</td>
<td>35 - 40°</td>
<td>56 - 57%</td>
</tr>
<tr>
<td>1:5-Di-n-butylpimelic acid</td>
<td>35 - 45°</td>
<td>50 - 60%</td>
</tr>
<tr>
<td>1:5-Di-iso-butylpimelic acid</td>
<td>30 - 32°</td>
<td>75%</td>
</tr>
<tr>
<td>1:5-Di-n-amylpimelic acid</td>
<td>25 - 30°</td>
<td>78%</td>
</tr>
<tr>
<td>1:5-Di-iso-amylpimelic</td>
<td>20 - 30°</td>
<td>80%</td>
</tr>
<tr>
<td>1:5-Di-n-hexylpimelic</td>
<td>25 - 30°</td>
<td>75%</td>
</tr>
<tr>
<td>1:5-Di-2-ethylhexylpimelic acid</td>
<td>25 - 30°</td>
<td>25 - 35%</td>
</tr>
<tr>
<td>1:6-Di-n-butylsuberic acid</td>
<td>25 - 30°</td>
<td>60%</td>
</tr>
<tr>
<td>1:6-Di-n-amylsuberic acid</td>
<td>25 - 30°</td>
<td>60%</td>
</tr>
<tr>
<td>1:6-Di-iso-amylsuberic acid</td>
<td>25 - 30°</td>
<td>76%</td>
</tr>
<tr>
<td>1:6-Di-n-hexylsuberic acid</td>
<td>25 - 30°</td>
<td>46%</td>
</tr>
<tr>
<td>1:6-Di-2-ethylhexylsuberic acid</td>
<td>30 - 35°</td>
<td>70 - 87%</td>
</tr>
<tr>
<td>1:7-Di-n-butylazelaic acid</td>
<td>25 - 30°</td>
<td>79%</td>
</tr>
<tr>
<td>1:7-Di-iso-butylazelaic acid</td>
<td>20 - 25°</td>
<td>50 - 55%</td>
</tr>
<tr>
<td>1:7-Di-n-hexylazelaic acid</td>
<td>20 - 25°</td>
<td>80%</td>
</tr>
</tbody>
</table>
DIAMINES OF THE TRIMETHYLENE SERIES

Trimethylene diamine

13.2 g (0.1 mol) of glutaric acid were dissolved in 40 c.c. of concentrated sulphuric acid and 50 c.c. of benzene were added to it. The reaction mixture was heated up to 45° on a water bath and 15.6 g (0.24 mol) of powdered activated sodium azide were added to it in small portions. The reaction started at 45° but the most suitable temperature for carrying the reaction appeared to be 60 - 65° and it was carried out at that temperature. Benzene was evaporated off on a water bath and the mixture cooled, diluted with 200 c.c. of water and was made alkaline by adding 30 per cent sodium hydroxide with cooling. The mixture was distilled with steam, and the distillate containing trimethylene diamine was collected in dilute hydrochloric acid. The trimethylene diamine dihydrochloride was obtained in crystalline form by concentrating and cooling the solution. Yield of the base calculated on the dihydrochloride was 40 per cent.

Attempt to prepare 2:10-Dimethyl-5:7-diaminoundecane

8.4 g (0.031 mol) of 1:3-di-iso-amylglutaric acid were dissolved in 25 c.c. of concentrated sulphuric acid and 30 c.c. of benzene were added to it. 6 g (0.093 mol) of powdered activated sodium azide were added in small portions to mixture with stirring. The reaction started very slowly at the room temperature (29°) and was carried out between 45-55°. After
the addition of sodium azide the reaction mixture was heated up to 70° on a water bath. The mixture was cooled, 80 g of ice were added and it was made alkaline by adding 30 per cent sodium hydroxide solution keeping the temperature below 25° by strong cooling. The benzene layer was separated and the mixture was extracted with a mixture of benzene and ether. The solution of the base was dried over anhydrous sodium sulphate.

**Dihydrochloride**

The dihydrochloride precipitated on passing dry hydrogen-chloride through the dry solution of the base. It was filtered and dried in vacuum. It was a deliquescent substance. The yield of the base calculated on the dihydrochloride was 22 per cent.

**Dipicrate**

The picrate precipitated on adding a solution of picric acid in benzene to a solution of the base in benzene. It was crystallised from water, it decomposed above 160°. $C_{25}H_{36}N_{8}O_{14}$ requires C, 44.6; H, 5.3, N, 16.6; found C, 45.0; H, 2.9; N, 16.9. As the percentage of hydrogen was very low the picrate was analysed again and was found to have C, 47.7; H, 2.01; N, 17.4. A third analysis gave the following result. C, 44.9, H, 3.03.
DIAMINES OF THE TETRAMETHYLENE SERIES

Tetramethylene diamine

60 G (1.2 mol) of sodium hydroxide were dissolved in 400 c.c. of water and cooled to 0° followed by the addition of 12 c.c. (0.24 mole) of bromine. 28 G (0.2 mol) of powdered adipamide were added to the solution with stirring and the stirring was continued until the solution was complete. The clear solution was heated up to 80° and then distilled with steam. The distillate in which tetramethylene diamine was present was collected in dilute hydrochloric acid. On concentrating the solution the tetramethylene diamine dihydrochloride crystallised in rods.

Yield of the dihydrochloride was 10 g, 58 per cent of the theoretical amount.

5:8-Diaminododecane

9.0 G (0.035 mol) of 1:4-di-n-butyl adipic acid were dissolved in 27 c.c. of concentrated sulphuric acid and 40 c.c. of benzene were added to it. 6.8 G (0.105 mol) of powdered activated sodium azide were added in small portions to the reaction mixture with stirring. The reaction started at the room temperature (27°) and was carried out between 35-40°. After the addition of sodium azide the reaction mixture was heated up to 70°. The mixture was then cooled, 80 g of ice were added to it, and it was made alkaline by adding 30 per cent sodium hydroxide solution, keeping the temperature below 25° by strong cooling. The benzene layer was separated, and
the mixture was extracted several times with benzene. The benzene solution was dried over anhydrous sodium sulphate.

**Dihydrochloride**

The dihydrochloride precipitated on passing dry hydrogen chloride through the dry solution of the base in benzene. It was filtered and dried in vacuum. Yield of the base calculated on the dihydrochloride was 50 - 55 per cent.

**Dipicrate**

The dipicrate precipitated on adding a solution of picric acid in benzene to a solution of the base in benzene. It was crystallised from water and had a melting point 135-137° and gave very unsatisfactory analytical result.

**Platinichloride**

Platinichloride of the base was obtained by adding an aqueous solution of chloroplatinic acid to a solution of the base in alcohol. It was filtered, washed with water and dried in vacuum and analysed.

\[ \text{C}_{12}\text{H}_{28}\text{N}_2, 2\text{H}_2 \text{Pt Cl}_6 \text{ requires Pt, 31.9; found Pt, 32.0.} \]

**2,9-Dimethyl-4,7-diaminodecane**

9.0 G (0.035 mol) of 1,4-di-iso-butyladipic acid were dissolved in 27 c.c. of concentrated sulphuric acid and 50 c.c. of benzene were added to it. 6.8 G (0.105 mol) of powdered activated sodium azide were added in small portions to the mixture with stirring. The reaction started at room temperature
(29°) and was carried out between 35-40°. After the addition of sodium azide the reaction mixture was heated up to 60° on a water bath. The mixture was cooled, 60 g of ice were added and it was made alkaline by adding 30 per cent solution of sodium hydroxide keeping the temperature below 25° with strong cooling. The benzene layer was separated and the mixture was extracted with benzene and dried over anhydrous sodium sulphate. (In a previous experiment the mixture was extracted with benzene and ether but that solution was not very suitable for making a hydrochloride.)

Dihydrochloride

The dihydrochloride precipitated on passing dry hydrogen chloride through the dry solution of the base in benzene. It was filtered and dried in vacuum. It was a deliquescent substance. Yield of the base calculated on the dihydrochloride was 56-57 per cent.

Dipicrate

3 G of 1:4-di-iso-butyladipic acid were treated with sodium azide in concentrated sulphuric acid, using the same conditions and the same proportion of reagents. The picrate precipitated on adding a solution of picric acid to a solution of the base in benzene. The picrate was insoluble in benzene and was crystallised from water, it softened at 125° and melted at 134°.

$C_{24}H_{34}N_8O_{14}$ requires N, 17.0; found N, 17.0
5:9-Diaminotridecane

10 g (0.036 mol) of 1:5-di-n-butylpimelic acid were dissolved in 30 c.c. of concentrated sulphuric acid and 30 c.c. of benzene were added to it. 5.7 g (0.088 mol) of powdered activated sodium azide were added in small portions to the mixture with stirring. The reaction started at the room temperature (30°C). Sodium azide was added at such a rate that the temperature remained between 35-45°C. The reaction mixture was cooled and 125 g of ice were added; the solution was made alkaline by adding 30 per cent sodium hydroxide solution keeping the temperature below 30°C by strong cooling. The benzene layer was separated and the mixture was extracted five times with benzene to which some ether had been added. The solution was dried over anhydrous sodium sulphate.

Dihydrochloride

The dihydrochloride precipitated on passing dry hydrogen chloride through the dry solution of the base in benzene and ether. It was filtered as quickly as possible (because it decomposed on leaving in contact with air). In a repetition of the experiment the hydrochloride was separated by filtration in a desiccator holding a calcium chloride tube. The hydrochloride was dried in vacuum for several days. It was a very deliquescent substance and its melting point was not taken. Yield of the base calculated on the dihydrochloride was 50-60 per cent.
**Hydrogenoxalate**

To the solution of the base in absolute ethyl alcohol was added a solution of oxalic acid in ethyl alcohol, the hydrogen oxalate precipitated immediately. The mixture was boiled for 10 minutes on a water bath and the hydrogen oxalate was filtered after cooling, was washed several times with absolute ethyl alcohol and then with ether. It was crystallised from a mixture of ethyl and methyl alcohols, it melted at 197.5-198°. It was very soluble in water and was an amorphous substance. It was analysed.

C\(_{17}\)H\(_{34}\)N\(_2\)O\(_8\) requires C, 52.9; H, 8.6; N, 7.1; found C, 52.3; H, 8.2; N, 7.1.

**Dipicrate**

The picrate precipitated by adding a solution of picric acid in benzene to a solution of the base in benzene. It was insoluble in benzene and very soluble in ethyl and methyl alcohol. It crystallised from a mixture of ethyl alcohol and benzene in needles m.p. 143°.

**2:10-Dimethyl-4:8-diaminoundecane**

7 G (0.025 mol.) of 1:5-di-iso-butylpimelic acid were dissolved in 21 c.c. of concentrated sulphuric acid and 25 c.c. of benzene were added to it. 6.5 G (0.10 mol.) of powdered activated sodium azide were added in small portions to the mixture while stirring. It was found necessary to heat the reaction mixture in the beginning of the reaction up to 45° but
once the reaction had started it went on smoothly between 30-32°. The reaction mixture was cooled, 70 g of ice were added and it was made alkaline by adding 30 per cent sodium hydroxide solution, keeping the temperature below 30° by strong cooling. The benzene layer was separated and the mixture was extracted four times with benzene using 25 c.c. of it for each extraction. The solution was dried over anhydrous sodium sulphate. The diamine was soluble in water.

Dihydrochloride

The dihydrochloride precipitated on passing dry hydrogen chloride through the dry solution of the base in benzene. It was filtered and was dried in vacuum. On heating it decomposes above 225°. The yield of the diamine was 75 per cent calculated on the dihydrochloride.

Dipicrate

The dipicrate precipitated on adding a solution of picric acid in ethyl alcohol to a solution of the base in benzene. It crystallised from aqueous ethyl alcohol in needles m.p. 186-186°.

C25H36N8O14 requires C, 44.6; H, 5.3; N, 16.6;
Found C, 44.9; H, 5.3; N, 16.5.

6:10-Diaminopentadecane

5 G (0.017 mol) of di-n-amylpimelic acid were dissolved in 20 c.c. of concentrated sulphuric acid and 25 c.c. of benzene were added to it. 4 G (0.06 mol) of powdered activated
sodium azide were added in small portions to the mixture with stirring. The reaction started at 25° and went on smoothly between 25-30°. The reaction mixture was cooled and 100 g of ice were added, and was made alkaline by adding 30 per cent sodium hydroxide solution keeping the temperature below 30° by strong cooling. The benzene layer was separated and the mixture was extracted five times using 25 c.c. of benzene for each extraction. The benzene solution was dried over anhydrous sodium sulphate.

**Dihydrochloride**

The dihydrochloride precipitated on passing dry hydrogen chloride through the dry solution of the base in benzene. It was filtered, washed with sodium dried ether and dried in vacuum. It was a deliquescent substance liable to decomposition if left in contact with moist air. Yield of the base calculated on the hydrochloride was 78 per cent.

**Dipicrate**

The dipicrate precipitated on adding a solution of picric acid in ethyl alcohol to a solution of the base in benzene. It was soluble in water, slightly soluble in benzene and very soluble in ethyl alcohol. It was crystallised from a mixture of benzene and alcohol, it melted at 130-133°.

C_{27}H_{40}N_8O_{14} requires C, 46.4; H, 5.7; N, 15.9; found C, 47.0, H, 5.4; N, 15.8.
Diacetyl derivative

2 G of 1:5-di-n-amylpimelic acid were treated with sodium azide in concentrated sulphuric acid using the same proportion of the reagents as used for the previous experiment. The solution of 6:10-di-aminopentane was treated with excess of acetic anhydride, the mixture was shaken and left for a few hours. The diacetyl derivative separated as a crystalline substance, it was filtered and crystallised from aqueous alcohol, it melted at 177-179°.

C_{19}H_{38}N_{2}O_{2} requires N, 8.57; found N, 8.8.

2:12-Dimethyl-5:9-diaminotridecane

4.71 G (0.015 mol) of 1:5-di-iso-amylpimelic acid were dissolved in 12 c.c. of concentrated sulphuric acid and 24 c.c. of benzene were added. 3 G (0.045 mol) of powdered activated sodium azide were added in small portions to the mixture with stirring. The reaction started at the room temperature (20°) and was carried out between 20-30°. The reaction mixture was cooled, 70 g of ice were added to it, it was made alkaline by adding 30 per cent sodium hydroxide solution keeping the temperature below 30° by strong cooling. The benzene layer was separated and the mixture was extracted with benzene. The solution was dried over anhydrous sodium sulphate.
Dihydrochloride

The dihydrochloride precipitated on passing dry hydrogen chloride through the dry solution of the base in benzene. It was filtered and dried in vacuum. Yield of the base calculated on the dihydrochloride was 80 per cent.

Dipicrate

1.5 G of the acid were treated with sodium azide in concentrated sulphuric acid using the reagents in the same proportion as in the previous experiment. The dipicrate precipitated on adding a solution of picric acid in benzene to a solution of the base in benzene. It was slightly soluble in water, insoluble in benzene and soluble in ethyl alcohol. It was crystallised from a mixture of benzene and ethyl alcohol, it melted at 165-169°. C_{27}H_{40}N_8O_{14} requires N, 15.9; found N, 16.0

7:11-Di-aminohexadecane

5.2 G (0.016 mol) of 1:5-di-n-hexylpimelic acid were dissolved in 15 c.c. of concentrated sulphuric acid and 25 c.c. of benzene were added to it. 4 G (0.064 mol) of powdered activated sodium azide were added in small portions to the reaction mixture with stirring. The reaction started at room temperature (20°) and was carried out between 25 and 30°. The mixture was cooled, 50 g of ice were added and made alkaline
with a 30 per cent solution of sodium hydroxide keeping the temperature below 30° by strong cooling. The benzene layer was separated, and the mixture was extracted with benzene. The benzene solution was dried over anhydrous sodium sulphate.

**Dihydrochloride**

The dihydrochloride precipitated on passing dry hydrogen chloride through the dry solution of the base in benzene. It was filtered and dried in vacuum. Yield of the base calculated on the dihydrochloride was 75 per cent.

**Dipicrate**

The dipicrate precipitated on adding a solution of picric acid in benzene to a solution of the base in benzene. It was crystallised from a mixture of benzene and methylated spirit, it melted at 143-145°.

C_{29}H_{44}N_{8}O_{14} requires N, 15.3; found N, 15.2.

**Diacetyl derivative**

The acetyl derivative precipitated when acetic anhydride was added in excess to a solution of the base in benzene. It was filtered off and crystallised from aqueous ethyl alcohol, it melted at 184°.

C_{21}H_{42}N_{2}O_{2} requires C, 17.1; H, 12.0; N, 7.8; found C, 70.9; H, 12.1; N, 7.7.
5:13-Diethyl-7:11-diaminoheptadecane

6.8 g (0.018 mol.) of 1:5-di-2-ethylhexylpimelic acid were dissolved in 26 c.c. of concentrated sulphuric acid and 40 c.c. of benzene were added to it. 3.6 g (0.054 mol.) of powdered activated sodium azide were added in small portions to the mixture with stirring. The reaction started at the room temperature (22°) and went on smoothly between 25-30°. The reaction mixture was cooled, 80 g of ice were added and was made alkaline by adding 30 per cent sodium hydroxide solution keeping the temperature below 30° by strong cooling. The benzene layer was separated and the mixture was extracted with benzene, the solution was dried over anhydrous sodium sulphate.

Dihydrochloride

Dry hydrogen chloride was passed through a dry solution of the base in benzene and ether but no dihydrochloride precipitated due to its solubility in benzene and ether. The dihydrochloride started to precipitate when a little solution (in benzene and ether) was left open, it was concluded that the hydrochloride was crystallising with water and the hydrate form was insoluble in benzene and ether. When a few drops of water were added to this solution to enhance formation of the insoluble hydrate all the hydrate that was present in the solution disappeared due to extreme solubility in water. About 0.5 c.c. of water were added to the whole solution of the
dihydrochloride in benzene and ether and ether was distilled off on a water bath followed by distillation of the benzene under reduced pressure. A thick viscous liquid was left behind. The dihydrochloride precipitated on thoroughly mixing this liquid with large quantities of light petroleum (b.p. 40-60). The dihydrochloride was filtered in a desiccator holding a calcium chloride tube because it seemed to dissolve in the solution when left open for a long time. It was dried in vacuum over phosphorus pentoxide and paraffin wax. After leaving it in the desiccator for 3-4 weeks it was not completely dry. It was dried at 35° over calcium chloride and paraffin wax for 9 hours but it appeared that the temperature was not high enough for it, it was again dried at 61° for 8 hours. The dry dihydrochloride melted at 134-138° and on analysis of the substance it was found to have one molecule of water. Yield calculated on the dihydrochloride was 25-35 per cent.

\[
C_{21}H_{46}N_2 \cdot 2HCl, H_2O \text{ requires } C, 60.4; H, 12.1; N, 6.7;
\]

Cl, 17; found C, 60.4; H, 11.8; N, 6.8; Cl, 17.

**Dipicrate**

The dipicrate precipitated on adding a solution of the picric acid in benzene to a solution of the base in benzene. It was crystallised from a mixture of benzene and ethyl alcohol, it melted at 150°.

\[
C_{33}H_{52}N_8O_{14} \text{ requires } C, 50.5; H, 6.6; N, 14.2; \text{ found } C, 50.3;
\]

H, 6.7; N, 13.8.
DIAMINES OF THE HEXAMETHYLENE SERIES

5:10-Diamino-tetradecane

3.44 G (0.0125 mol) of 1:6-di-n-butylsuberic acid were dissolved in 12 c.c. of concentrated sulphuric acid and 20 c.c. of benzene were added to it. 3 G (0.05 mol) of powdered activated sodium azide were added in small portions to the mixture with stirring. The reaction started at the room temperature (22°) and went on smoothly between 25 and 30°. The reaction mixture was cooled, 50 g of ice were added and it was made alkaline by adding 30 per cent sodium hydroxide solution keeping the temperature below 30° by strong cooling. The benzene layer was separated and the mixture was extracted five times with a mixture of benzene and ether. The benzene and ether solution was dried over anhydrous sodium sulphate.

Dihydrochloride

The dihydrochloride precipitated on passing dry hydrogen chloride into the dry solution of the base in benzene and ether. It was filtered and dried in vacuum. The yield of the base calculated on the dihydrochloride was 60 per cent.

Dipicrate

The picrate precipitated on adding a solution of picric acid in benzene to a solution of the base in benzene. It was crystallised from water, and melted at 197-202°.

C_{26}H_{38}N_{8}O_{14} requires C, 45.4; H, 5.5; N, 16.3; found C, 45.8; H, 5.7; N, 16.5.
6:11-Diaminohexadecane

4.7 G (0.015 mol) of 1:6-di-n-amylsuberic acid were dissolved in 15 c.c. of concentrated sulphuric acid and 25 c.c. of benzene were added to it. 2.9 G (0.045 mol) of powdered activated sodium azide were added in small portions to the mixture with stirring. The reaction started at the room temperature (22°) and was carried out between 25-30°. After the addition of sodium azide the reaction mixture was heated up to 50° on a water bath. The mixture was cooled, 80 g of ice were added and it was made alkaline by adding 30 per cent sodium hydroxide solution keeping the temperature below 30° by strong cooling. The benzene layer was separated and the mixture was extracted with benzene. The benzene solution was dried over anhydrous sodium sulphate.

Dihydrochloride

The dihydrochloride precipitated on passing dry hydrogen chloride through a dry solution of the base in benzene. The yield of the base calculated on the dihydrochloride was 60 per cent.

Dipicrate

The dipicrate precipitated on adding a solution of picric acid in benzene to a solution of the base in benzene. It was insoluble in water and benzene, and was crystallised from a mixture of benzene and ethyl alcohol, it melted at 152-156°. C₂₈H₄₂N₂O₁₄ requires C, 47.0; H, 5.9; N, 15.4; found C, 46.7; H, 5.7; N, 14.6.
**2:13-Di-methyl-5:10-diaminotetradecane**

4.7 G (0.015 mol) of 1:6-di-iso-amylylsuberic acid were dissolved in 15 c.c. of concentrated sulphuric acid and 25 c.c. of benzene were added to it. 3 G (0.045 mol) of powdered activated sodium azide were added in small portions to the mixture with stirring. The reaction started at the room temperature (21°) and was carried out between 25-30°. The mixture was heated up to 50° and then cooled, 70 g of ice were added to it, it was made alkaline by adding 30 per cent sodium hydroxide solution keeping the temperature below 30° by strong cooling. The benzene layer was separated and the mixture was extracted a few times with benzene and ether. The solution of the base was dried over anhydrous sodium sulphate.

**Dihydrochloride**

The dihydrochloride precipitated when dry hydrogen chloride was passed through a dry solution of the base in benzene and ether. It was filtered, and then dried in vacuum. The yield of the base calculated on the dihydrochloride was 76 per cent.

**Dipicrate**

The dipicrate precipitated on adding a solution of picric acid in benzene to a solution of the base in benzene. It was insoluble in water, benzene, and was crystallised from a mixture of ethyl alcohol and benzene. It decomposes on heating above 190° - 200°.
C_{28}H_{42}N_8O_{14} requires C, 47.0; H, 5.9; N, 15.4; found C, 47.5; H, 5.86; N, 14.8.

7:12-Diamino-octadecane

3.4 G (0.01 mol) of 1:6-di-n-hexylsuberic acid were dissolved in 16 c.c. of concentrated sulphuric acid and 30 c.c. of benzene were added to it. 2.6 G (0.04 mol) of powdered activated sodium azide were added in small portions to the mixture with stirring. The reaction started at the room temperature (21°) and was carried out between 25-30°. The mixture was cooled, 50 g of ice were added and it was made alkaline by adding 30 per cent sodium hydroxide solution keeping the temperature below 30° by strong cooling. The benzene layer was separated and the mixture was extracted a few times with a mixture of ether and benzene. The solution was dried over anhydrous sodium sulphate. The base was not very soluble in benzene.

Dihydrochloride

The dihydrochloride precipitated on passing dry hydrogen chloride through the dry solution of the base in benzene and ether. It was filtered and dried in vacuum, it melted at 222-225°. The yield of the base calculated on the dihydrochloride was 46 per cent.

Dipicrate

1.1 G of 1:6-di-n-hexylsuberic acid were treated with
sodium azide in concentrated sulphuric acid using the same conditions and the same proportion of reagents as in the previous experiment. The picrate precipitated on adding a solution of picric acid to a solution of the base in benzene and ether. The yield of the base calculated on the picrate was 75-80 per cent. It was crystallised from a mixture of benzene and ethyl alcohol, it melted at 173-176°.

\[ C_{30}H_{46}N_9O_{14} \] requires C, 49.6; H, 6.3; N, 15.4; found C, 48.9; H, 6.1; N, 15.1.

5:14-Diethyl-7:12-diamino-octadecane

19.4 G (0.05 mol.) of 1:6-di-2-ethylhexylsuberic acid were dissolved in 40 c.c. of concentrated sulphuric acid and 60 c.c. of benzene were added to it. 9.75 G (0.15 mol.) of powdered activated sodium azide were added to the mixture in small portions. The reaction started at room temperature and went on smoothly between 30-35°. The mixture was cooled, 300 g of ice added and it was made alkaline by adding 30 per cent sodium hydroxide solution keeping the temperature below 30° by strong cooling. The benzene layer was separated and the mixture was extracted with benzene. The base was not soluble in water. The yield of the base calculated on the dihydrochloride was 70 to 87 per cent.

Dipicrate

Dipicrate precipitated on adding a solution of picric acid in benzene to a solution of the base in benzene. It was
crystallised from a mixture of benzene and ethyl alcohol. It melted at 156-158°.

\[ \text{C}_{34}\text{H}_{54}\text{N}_{8}\text{O}_{14} \text{ requires C, 51.1; H, 6.8; N, 13.7; found C, 15.1; H, 6.6; N, 14.0.} \]

**Dihydrochloride**

Dry hydrogen chloride was passed through a dry solution of the base in benzene, the dihydrochloride did not precipitate due to its solubility in benzene. Effort to precipitate the dihydrochloride by adding large quantities of ether and light petroleum to the benzene solution failed. On leaving the benzene solution for a day some white precipitate (about 0.4 g) appeared. It was dried and analysed. \[ \text{C}_{22}\text{H}_{50}\text{N}_{2}\text{Cl}_{2} \text{ requires Cl, 17.1; N, 6.7; found Cl, 22.3; N, 8.96.} \]

It was concluded from the results of analysis that it was an impurity most probably the base from some unchanged tetrabasic acid present with 1:6-di-2-ethylhexylsuberic acid due to incomplete decarboxylation. About 5 c.c. of water were added to the remaining benzene solution, benzene was distilled off and the remaining liquid was dried under reduced pressure. A brown solid was obtained which was stirred with large quantity of light petroleum (b.p. 60-80) and filtered. The substance was dried in a desiccator under reduced pressure for several days but it was not completely dry. The substance decomposed when an effort was made to dry it under reduced pressure at 61°. The substance was dissolved in benzene, benzene was distilled off on a water bath and the residue in which a little amount of
benzene was present was mixed with a large quantity (700 c.c.) of carbon tetrachloride and the dihydrochloride separated as a jelly on leaving the solution over night. It was filtered and dried under reduced pressure.

$C_{22}H_{50}N_2Cl_2$ requires C, 63.9; H, 12.1; N, 6.7; found C, 64.1; H, 11.5; N, 6.6.
5:11-Diamino-heptadecane

3.26 g (0.0109 mol) of 1:7-di-n-butylazelaic acid were dissolved in 15 c.c. of concentrated sulphuric acid and 15 c.c. of benzene were added. 2.8 g (0.0436 mol) of powdered activated sodium azide were added in small portions with stirring. The reaction started at room temperature (22°). Sodium azide was added at such a rate that the temperature remained between 25-30°. The reaction mixture was cooled and 80 g of ice added to it. It was made alkaline by adding 30 per cent sodium hydroxide solution keeping the temperature below 30° by strong cooling. The benzene layer containing 5:11-diaminoheptadecane was separated and the reaction mixture was extracted a few times with benzene. The benzene solution was dried over anhydrous sodium sulphate.

Dihydrochloride

Dihydrochloride precipitated on passing dry hydrogen chloride through the dry solution of the base in benzene. It was filtered, and dried in vacuum. Yield of the base calculated on the dihydrochloride was 79 per cent.

Dipicrate

The picrate precipitated on adding a solution of picric acid in benzene to a solution of the base in benzene and ether. The picrate was soluble in benzene and was crystallised from aqueous ethyl alcohol, it melted at 191°.
C_{27}H_{40}N_{8}O_{14} requires C, 46.3; H, 5.3; N, 15.9; found C, 46.3; H, 5.9; N, 15.8.

2:12-Dimethyl-4:10-diamino-tridecane

10 G (0.033 mol) of 1:7-di-iso-butylazelaic acid were dissolved in 40 c.c. of concentrated sulphuric acid and 50 c.c. benzene was added to it. 4.5 G (0.07 mol.) of powdered activated sodium azide were added in small portions to the mixture with stirring. The reaction started at the room temperature (20°). Sodium azide was added at such a rate that the temperature remained between 20-25°. The reaction mixture was cooled, 100 g of ice added and then made alkaline with 30 per cent sodium hydroxide solution, keeping the temperature below 30° by strong cooling. The benzene layer was separated and the mixture was extracted four times using 25 c.c. of benzene. The benzene solution was dried over anhydrous sodium sulphate.

Dihydrochloride

The hydrochloride precipitated on passing dry hydrogen chloride through the dry benzene solution of the base. It was filtered, washed with dry ether and dried in vacuum. Yield of the base calculated on the dihydrochloride 50-55 per cent.

Dipicrate

The picrate precipitated on adding a solution of picric
acid in benzene to a solution of the base in benzene and ether. It crystallised from water, and melted at 194°.

$C_{27}H_{40}N_8O_{14}$ requires C, 46.3; H, 5.7; N, 15.9; found C, 46.5; H, 5.7; N, 16.1.

7:13-Diaminononadecane.

3.6 G (0.01 mol) of 1:7-di-n-hexylazelaic acid were dissolved in 12 c.c. of concentrated sulphuric acid and 12 c.c. of benzene were added to it. To the mixture 2.6 g (0.02 mol) of powdered activated sodium azide were added in small portions with stirring. The reaction started with evolution of carbon dioxide and nitrogen at room temperature (20°). The sodium azide was added at such a rate that the temperature of the reaction mixture remained between 20 and 25°. The reaction mixture was cooled, 100 g of ice were added and then it was made alkaline by adding 30 per cent sodium hydroxide solution in small amounts with strong cooling. 7:13-Diaminononadecane was dissolved in benzene present in the reaction mixture. The benzene layer was separated and the mixture was extracted a few times with benzene. The benzene solution was dried over anhydrous sodium sulphate.

Dihydrochloride

7:13-Diaminononadecane dihydrochloride precipitated on passing dry hydrogen chloride into the dry solution of the base in benzene. It was filtered, washed with sodium dried ether
and dried in vacuum, it melted at 186-187°C. Yield of the base calculated on the dihydrochloride was 80 per cent.

**Dipicrate**

The dipicrate precipitated on adding a solution of picric acid in benzene to the solution of the base in benzene. It crystallised from a mixture of benzene and ethyl alcohol, and melted at 155-157°C.

C$_{31}$H$_{48}$N$_6$O$_{14}$ requires C, 49.2; H, 6.3; N, 14.8; found C, 49.8; H, 6.1; N, 14.4.