The syntheses of a few curare-like bis-ammonium derivatives with ester, ketone and alcohol functions

Author(s):
Gyi, KoKo

Publication Date:
1961

Permanent Link:
https://doi.org/10.3929/ethz-a-000099610

Rights / License:
In Copyright - Non-Commercial Use Permitted

This page was generated automatically upon download from the ETH Zurich Research Collection. For more information please consult the Terms of use.
The Syntheses of a few Curare-like Bis-Ammonium Derivatives with Ester, Ketone and Alcohol Functions

THESIS

presented to

the Swiss Federal Institute of Technology Zürich

for the Degree of Doctor of Natural Sciences

by

KO KO GYI

Citizen of Burma

Accepted on the Recommendation of
Prof. Dr. J. Büchi and Prof. Dr. E. Hardegger

Druck: Heidelberger Reprographie A. Grosch Heidelberg

1961
I am greatly indebted to my respected teacher,

Prof. Dr. J. Büchi,

for his kindness in granting me permission to work in
the laboratories of the School of Pharmacy, Swiss Federal
Institute of Technology, Zürich, and for the constant
interest with which he guided me throughout the course of
this work.

This opportunity is taken to thank

Prof. Dr. P. Waser,

of the Pharmacological Institute, University of Zürich,
for conducting the pharmacological tests of the substances
synthesized.

Also, I would express my gratitude to Dr. A. Aebi and
Dr. H. Braunschweiger for the many helpful discussions
and practical advice; to Dr. W. Burkard of the Kantons-
apotheke, Zürich, for his guidance and help in doing
some preliminary pharmacological tests; to the Kantons-
apotheke, Zürich, for making available samples of pure
d-tubocurarine; and to Mr. R. Schwegler for his encourage-
ment and helpfulness.

Above all, I gratefully acknowledge my indebtedness to the
people and Government of my country, the Union of Burma,
who have made this work possible by granting me a State
Scholarship.
Contents

1. Introduction 1

2. General: Some aspects of the relation between Chemical Constitution and Pharmacological Action 3

2.1. Natural Curare 3
   2.1.1. Classification of the different types of Natural Curare 3
      2.1.1.1. Calabash-Curare 3
      2.1.1.2. Tube-Curare (or Tubocurare) 3
      2.1.1.3. Pot-Curare 3
   2.1.2. Curare Preparation 4
   2.1.3. Isolation and Identification of Curare Alkaloids 5
      2.1.3.1. Tubocurare Alkaloids 6
      2.1.3.2. Pot-Curare Alkaloids 10
      2.1.3.3. Calabash-Curare Alkaloids 10
   2.1.4. Pharmacology of Curare 21
   2.1.5. The Therapeutic Uses of Natural Curare 26

2.2. Synthetic Curare-like Compounds 28
   2.2.1. Compounds directly related to d-Tubocurarine 28
   2.2.2. Compounds with One Onium Group 30
   2.2.3. Compounds with Two (or more) Onium Groups 31
      2.2.3.1. Polymethylene-α,ω-bis-trialkylammonium salts 31
      2.2.3.2. Polymethylene-α,ω-bis-quinolinium and bis-iso-quinolinium series 33
      2.2.3.3. Compounds with a modified chain between the Onium Groups
         a) Phenylpolymethylene para- (and meta)-ω-bis-trialkylammonium salts 36
         b) Derivatives of diphenyl, diphenylmethane and related compounds 36
         c) Compounds with oxygen bridges in the chain 38
            α) Aliphatic ethers 38
            β) Bis-quinolinium series 40
            γ) Bis-dialkylationphenoxy alkane derivatives 40
            δ) Diacylo derivatives of diphenyl ethane and stilbene 42
         e) Diphenyl ether derivatives 45
            γ) The Flaxedil® series 46
            η) Symmetrical (or 1,3,5-) Triazine derivatives 48
            θ) Quinazoline derivatives 49
         d) Bis-quaternary ammonium derivatives in the aliphatic ester series 49
            α) Esters of dibasic aliphatic acids 49
            β) Esters of amino acids with dihydric alcohols and amino alcohols 52
         e) Choline esters of benzene-poly carboxylic acids 54
         f) Compounds with -S- links in the chain 55
            α) Derivatives of piperazine 35
            β) Carbamylcholine derivatives 36
            γ) Bis-(ammoniumalkylamino)-benzoquinone derivatives 57
            δ) Symmetrical triazine derivatives 57
            ε) Derivatives of barbituric acid 58
            ζ) Sulphonamid derivatives and compounds with -S- links in the chain 60
2.3. Problem

3. Theoretical

3.1. Available methods for the syntheses

3.1.1. Bis-(trimethylammoniumethyl)-alkylmalonate dibromides

3.1.1.1. Reaction scheme for the preparation of bis-(trimethylammoniumethyl)-alkylmalonate dibromides

a) Preparation of the starting materials
   \( \alpha \) Diethyl alkylmalonates
   \( \beta \) Alkylmalonic acids
   \( \gamma \) Di-\( \beta \)-bromoethyl alkylmalonates

b) Preparation of bis-(trimethylammoniumethyl)-alkylmalonate dibromides

3.1.2. 1,9-Bis-(trimethylammonium)-5-alkyl-nonane-4,6-dione diiodides

3.1.2.1. Reaction scheme for the preparation of 1,9-bis-(trimethylammonium)-5-alkyl-nonane-4,6-dione diiodides

a) Preparation of the starting materials
   \( \delta \) 5-Dimethylamino-pentan-2-one
   \( \epsilon \) Ethyl 4-dimethylaminobutyrate
   \( \chi \) 1,9-Bis-(dimethylamino)-nonane-4,6-dione
   \( \delta \) 1,9-Bis-(dimethylamino)-5-alkyl-nonane-4,6-diones

b) Preparation of 1,9-bis-(trimethylammonium)-5-alkyl-nonane-4,6-dione diiodides

3.1.3. Reaction scheme for the preparation of 1,9-bis-(trimethylammonium)-5-alkyl-nonane-4,6-diol diiodides

3.1.4. Attempt to prepare 1,9-dichloro-nonane-4,6-dione

3.2. Theoretical Basis of the Reactions

3.2.1. The usefulness of the Acetoacetic Ester Syntheses

3.2.2. The Claisen Condensations

a) Self condensation of esters
   b) Condensation of esters with ketones

3.2.3. Alkylation of 1,3-dicarbonyl compounds

4. Experimental

4.1. Bis-(trimethylammoniumethyl) alkylmalonate dibromides

4.1.1. Preparation of the starting materials

a) Preparation of the starting materials
   \( \alpha \) Diethyl alkylmalonates
   \( \beta \) Alkylmalonic acids
   \( \gamma \) Di-\( \beta \)-bromoethyl alkylmalonates

b) Preparation of bis-(trimethylammonium)-alkylmalonate dibromides

4.1.2. Preparation of bis-(trimethylammonium)-5-alkyl-nonane-4,6-dione diiodides

4.1.2.1. Preparation of the starting materials

a) Preparation of the starting materials
   \( \delta \) 5-Dimethylamino-pentan-2-one
   \( \epsilon \) Ethyl 4-dimethylaminobutyrate
   \( \chi \) 1,9-Bis-(dimethylamino)-nonane-4,6-dione
   \( \delta \) 1,9-Bis-(dimethylamino)-5-alkyl-nonane-4,6-diones

b) Preparation of 1,9-bis-(trimethylammonium)-5-alkyl-nonane-4,6-dione diiodides
4.3. 1,9-Bis-(trimethylammonium)-5-alkyl-nonane-4,6-diol diiodides
4.3.1. Preparation of 1,9-bis-(dimethylamino)-5-alkyl-nonane-4,6-diols.
4.3.2. Preparation of 1,9-bis-(trimethylammonium)-5-alkyl-nonane-4,6-diol diiodides
4.4. Preparation of 1,9-bis-(dimethylamino)-5-propylene-nonane-4,6-dione
4.5. Attempt to prepare 1,9-dichloro-nonane-4,6-dione
5. Summary
1. INTRODUCTION.

The oldest known neuromuscular blocking agents are the curare alkaloids. Used by the natives of South and Central America as arrow poisons, the crude curare extracts are obtainable in bamboo tubes, in clay pots and in calabashes. Since the natives prepare the different curare extracts from a variety of plants, considerable difficulties were encountered by investigators in their attempts to determine the proper botanical sources and to isolate the alkaloid components. Consequently, the use of curare in therapy had to wait some time. In spite of these difficulties, early attempts were indeed made to use curare for the control of tetanus and for the treatment of epilepsy and chorea.

Although the number of curare alkaloids are many, only d-tubocurarine, which is available commercially in the pure state (U.S.P.IV) is of special interest in so far as the use of curare in therapy is concerned. With the introduction by Wintersteiner and Dutcher (1) of the pure standardised d-tubocurarine preparation, the general clinical use of curare increased rapidly and wider applications of this drug were investigated, especially as an adjuvant in anesthesia for the attainment of complete relaxation without the use of very deep anesthesia. The importance that curare has recently gained in medicine and the establishment of a certain formula for d-tubocurarine by King (2), has led many investigators to search for synthetic drugs with curare-like activity. Since the last few years, numerous compounds have been synthesized. Some have achieved clinical recognition but a large number and variety of substances have been discovered which have curare-like activity although they are of no value in medicinal practice.

Regarding the relation between chemical constitution and curare-like activity, it was soon realised that the presence of two

(1) Wintersteiner, O. and Dutcher, J.D., Science, N.Y., 97, 467 (1947).
(2) King, H., J.chem.Soc., 1381 (1935) ; 1276 (1936) ; 1472 (1937) ; 1157 (1939) ; 737 (1940).
quaternary ammonium groups separated by a chain of nine to twelve atoms represent a favourable factor for curarizing activity. The actual spatial distance between these two functional groups may vary from 12.5 Å (for d-tubocurarine) to 15 Å (for decamethonium) or more. Some exceptions to this generalisation do exist, and instances may be mentioned where optimal activity is not present with a chain of nine to twelve atoms:—

(a) Pentamethylene-α,ω-bis-quinolinium dibromide, which is as active as the decamethylene derivative.

(b) The ethers of the general formula,

\[ R_3^\mathrm{N}-(\text{CH}_2)_m-O-(\text{CH}_2)_n-O-(\text{CH}_2)_m-NR_3 \]

These ethers are active when \( n = 10 \), and \( m = 2,3 \) or 4, representing a total chain length of 16,18 or 20 atoms.

(c) The carbamyl choline derivative known by the trade name 'Imbretil', having the formula,

\[ (\text{CH}_3)_3^\mathrm{N}-\text{CH}_2\text{CH}_2-\text{O}-\text{CO}-\text{NH}-(\text{CH}_2)_6-\text{NH}-\text{CO}-\text{O}-\text{CH}_2\text{CH}_2-\text{N}(\text{CH}_3)_3 \]

The chain consists of sixteen atoms.

The chain linking the two quaternary groups has been modified in various ways. With this work in which we have concerned ourselves with aliphatic derivatives, homologues of three types of compounds (I, II, III), containing respectively the ester, ketone and alcohol functions have been synthesized. Our objective is to establish the changes in pharmacological effects when the ester functions are replaced by ketone and carbinal functions and when the aliphatic nature of the substituent \( R \) in each series is gradually increased from \(-\text{H}\) to \(-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3\).

\[ \begin{align*}
\text{I.} & \quad \text{Br}^- \quad (\text{CH}_3)_3^\mathrm{N}-\text{CH}_2\text{CH}_2-\text{O}-\text{CO}-\text{CH}-\text{CO}-\text{O}-\text{CH}_2\text{CH}_2-\text{N}(\text{CH}_3)_3 \quad \text{Br}^- \\
\text{II.} & \quad \text{I}^- \quad (\text{CH}_3)_3^\mathrm{N}-\text{CH}_2\text{CH}_2\text{CH}_2-\text{O}-\text{CO}-\text{CH}-\text{CO}-\text{CH}_2\text{CH}_2\text{CH}_2-\text{N}(\text{CH}_3)_3 \quad \text{I}^- \\
\text{III.} & \quad \text{I}^- \quad (\text{CH}_3)_3^\mathrm{N}-\text{CH}_2\text{CH}_2\text{CH}_2-\text{CHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{N}(\text{CH}_3)_3 \quad \text{I}^- \\
\text{R} = & \quad -\text{CH}_3, \quad -\text{C}_2\text{H}_5 \text{ etc.}, \text{ to } -\text{nC}_6\text{H}_{13}. 
\end{align*} \]
2. GENERAL.

Natural and synthetic neuromuscular blocking agents—some aspects of the relation between chemical constitution and pharmacological action.

2.1. Natural Curare.

2.1.1. Classification of the different types of natural curare.

The early literature is full of contradictory statements regarding the plants used in the preparation of curare extracts. Attention at first centered on the Strychnos. Schomburgk (3) in the course of his travels in British Guiana witnessed the collection of the plants used in the preparation of the curare by the Marcusis Indians. This he named Strychnos toxifera. A few years later, Schomburgk (4) was again witness to the preparation of the curare extract by the Indians of the upper Essequibo River. Of the several ingredients he could identify Strychnos toxifera, Strychnos pedunculata and Strychnos cogens. Today, it appears that curares from Eastern Amazonia contain as their chief ingredients Strychnos, a genus of the family Loganiaceae, long recognised as a source of strychnine and other alkaloids. Those from the west contain members of the Menisperm or Moonseed family, e.g., Cocculus, Chondrodendron and Anomosperm.

As was pointed out before, the different crude curare preparations and the variety of the botanical sources from which they are prepared contributed enormously to the confusion which faced chemists in their attempts to identify the component alkaloids of the various curare. This confusion was considerably cleared away by the work of Boehm (5). According to him, the containers were fairly diagnostic of the curare in them.


He classified curare into three types:-

2.1.1.1. Calabash- or Gourd-Curare. So called because of the containers in which the curare is obtained, it is the most active South American arrow poison, and comes mostly from the upper Orinoco region and the area around the source of the Rio Negro.

2.1.1.2. Tube-Curare (also called Tubocurare). This curare is filled in bamboo tubes, and is obtained chiefly from the Amazon region.

2.1.1.3. Pot-Curare. As the name implies, this type of curare is obtained in clay pots, and they mostly come from French Guiana and the Amazon region.

Besides the above mentioned types of packing, Lewin (6) reported Sack-Curare, which is packed in sacks of bast fibre. Obtained from the upper Amazon, this curare is said to have the same general composition as Calabash-Curare. According to the same author (6), in the Orinoco region, two Strychnos species - Strychnos toxifera and Strychnos gubeln - are said to be the sources of Calabash-Curare. Furthermore, curare is produced in British Guiana, in Ecuador (probably from Strychnos castelnaei, in the Rio Negro region (also Strychnos castelnaei), in the river basin Yapura-Solimoes (tributaries of the Amazon) as well as in Peru. Nowadays, Calabash-Curare has totally disappeared and Pot-Curare has become rare. Only Tubocurare is available.

2.1.2. Curare Preparation.

Freise (7,8) has given a report about the technique of curare preparation as follows:-

"For curare preparation barks of various strychnos species are used. In the Araraquare mountains live the Maupes Indians, known to be excellent poison makers. In this region many strychnos species can be found, mainly Strychnos letalis, Strychnos icaja and Strychnos lanceolaris, some of which occur as lianas up to 200 feet long with widely spread branches. Strips of the bark, each about 3 to 4 inches wide and 20 to 30 inches long (about 40 to 60 kilograms are obtained from one stem during the harvest period) are soaked in wooden troughs filled with water, the cork tissues being stripped off cautiously.

from the inner layers. Only the cork layer is retained. This is
dried and powdered in hard mortars with wooden pestles, the process
taking several days, the daily production being scarcely more than
200 grammes per mortar. Each batch of bark powder in one mortar
during one day is worked up separately. The powder is slowly extracted
with warm water in wooden vessels in which the extraction temperatures
of 70-80°C have been previously produced by heated stones. Boiling is
never mentioned. The amount of water for 200 grammes of powder is
about 2 litres. The extraction of the bark with warm water takes
about four days. Then the contents of the vessel have become a red
to dark brown liquid which has a penetratingly bitter taste. Strain¬
ing through a bast filter separates it from the bark residues.
During several days' concentration under very cautious warming, the
liquid thickens to a syrupy consistency and is poured into gourds'.

2.1.3. Isolation and Identification of Curare Alkaloids.

The first attempts to isolate the components of curare was made
by Boussingault and Roulin (9) who succeeded in isolating a bitter
principle from crude curare. This was at once differentiated from
strychnine. Some years later, an improbable claim was made by Pedroni
(10) that curare from Caracas was one-sixth strychnine. Other
chemists ( Heintz (11) and Oberdorfer (12) ), found neither strych¬
nine nor brucine in the curares obtained from various sources, as for
example, Orinoco, Esmeralda and Pevas.

(9) Boussingault and Roulin., Examen chimique du curare, Ann. de chim.
et de phys., 39, 29 (1828). Quoted by A.R. McIntyre. 'Curare: Its
history, nature and clinical use'. University of Chicago Press,
p.57 (1947).

(10) Pedroni, J., J.de pharm. et de chim., 5, 321 (1844).

(11) Heintz., Mentioned in ' Reisen in Britisch Guyana' by Schomburgk
(3).

(12) Oberdorfer, A., Ueber das Urari, Wittstein Vierteljahrschr. f.
Boehm (13) found that all the three types of curare contained an active quaternary alkaloid fraction which he named 'curarines'. Thus from Calabash-Curare he obtained curarine; from Pot-Curare, protocurarine; and from Tubocurare, tubocurarine. The curarines behaved like quaternary ammonium bases and were identified as hydrated quinolines. Pot-Curare and Tubocurare were found by Boehm (13) to also contain tertiary alkaloids, and these he named 'curines'. Pot-Curare yielded protocurine (C_{20}H_{23}NO_{3}) and protocuridine (C_{19}H_{21}NO_{3}); the former having a weak curarizing action, and the latter no action on the nerve-endings. From Calabash-Curare he obtained an amorphous mixture of tertiary alkaloids.

2.1.3.1. Tube-Curare Alkaloids.

The curine isolated from Tube-Curare by Boehm (13) was assigned the formula C_{18}H_{19}O_{3}N. Späth and co-workers (14) later confirmed the formula and showed that curine is the levo-modification of d-bebeerine, an alkaloid of Radix Pareirae Bravae, said to be the dried roots of Chondrodendron tomentosum (family Menispermaceae). This gave a clue to the probable botanical origin of Tubocurare. Faltis, Wrann and Kühase (15) had earlier suggested a cyclic structure (IV) for isochondrodendrine present in Radix Pareirae Bravae. King (16) proposed that an analogous structure should be probable for curine, and accordingly, the true formula of curine should be double the Boehm formula, i.e., C_{36}H_{38}O_{6}N_{2}. Späth and Kuffner (17) later concurred and proposed the formula (V) for curine.


Structure of d-tubocurarine.

In determining the structure of d-tubocurarine, King (2) relied on the readily available d-bebeerine, since considerable knowledge of this alkaloid has already been accumulated due to the work of Scholtz (18-21). Scholtz has succeeded in isolating a crystalline levo-bebeerine from commercial 'Bebeerinum Purum', and from Radix Pareirae Bravae. He also obtained d-bebeerine from pareirae root and claimed to have obtained racemic bebeerine from Bebeerinum Purum (Merck). Later, Scholtz and Koch (22) found only traces of bebeerine in another sample of Radix Pareirae Bravae obtained from a different source. King (23) subsequently showed that at least two species of Menispermaceae were used as sources of Radix Pareirae Bravae (Chondrodendron platiphyllum and Chondrodendron microphyllum), which yield respectively l-bebeerine and d-bebeerine. A third Menispermaceous plant, Chondrodendron candicans, examined by King (23) gave d-isochondrodendrine and d-bebeerine.

Tubocurarine chloride has the empirical formula C_{38}H_{44}O_{6}N_{2}Cl_{2}, which is the same as that of curine methochloride. But King (24) showed

(18) Scholtz, M., Ber.dtsch.chem.Ges. 29, 2054 (1896).
(19) Scholtz, M., Arch.Pharm. 244, 555 (1906).
(20) Scholtz, M., Arch.Pharm. 249, 416 (1911).
(21) Scholtz, M., Arch.Pharm. 251, 136 (1913).
(22) Scholtz, M. and Koch, O., Arch.Pharm. 252, 513 (1914).
that the two are not identical. Curine which accompanies tubocurarine in the crude drug is levo-rotatory in its salts, and on N-methylation gives a levo-rotatory methochloride, whereas tubocurarine is dextro-rotatory having \( (\alpha)_{5461}^{200} +295^0 \) for the ion in water. The two were shown to be isomeric but not enantiomorphous. He further found that both d-tubocurarine chloride and the methochloride of bebeerine contain two phenolic groups and two methoxyl groups. On methylation of l-curine he obtained amorphous O-methylbebeerine methosalts. By successive Hofmann degradation reactions King (2) obtained the same nitrogen-free product from both O-methylcurine and O-methylbebeerine. On the basis of formula (VI) for O-methylbebeerine, he suggested formula (VII) for the nitrogen-free end-product.

Taking advantage of this clue King (25) was successful in ascertaining the positions of the phenolic groups in bebeerine. He prepared O-ethylbebeerilene and submitted it to oxidation. After identifying the carboxylic acids obtained as oxidation products he could give bebeerine the formula (VIII).

In 1943 Wintersteiner and Dutcher (26) announced the isolation of d-tubocurare in good yields from the crude curare prepared from Chondrodendron tomentosum. Besides this main alkaloid they isolated a

(26) Wintersteiner, O. and Dutcher, J.D., Science, 97, 467 (1943).
new tertiary alkaloid and named it d-chondrocurine. This substance was converted into a physiologically active quaternary base. Methyla-
tion of the phenolic hydroxyl groups in quaternised chondrocurine led to the formation of the same compound as that obtained by the O-methylation of d-tubocurarine, i.e., QO-dimethyltubocurarine. Later, King (27) used the same methods he applied successfully in his investigations on bebeereine to prove that the phenolic and methoxyl groups in d-tubocurarine occur in the same positions as in d-bebeereine (VIIa and VIIc).

It is now known that chondrocurine differs from d-tubocurarine in that, in place of the quaternary ammonium groups there are tertiary amine groups and the phenolic and methoxyl groups change places (Wintersteiner and Dutcher (26)).

2.1.3.2. Pot-Curare Alkaloids.

This type of curare obtained mostly from the upper Orinoco region has not been so thoroughly examined as tubocurare. A more detailed study first began with Boehm (5), and was continued by King (28). Boehm isolated two weakly toxic bases, which he called protocurine and protocuridine. Using a new method of extraction, King obtained a non-quaternary fraction and a so-called quaternary fraction. From the non-quaternary fraction, which was of a phenolic character, he was able to isolate Boehm's protocuridine as a hydrochloride. This compound was shown to possess two phenolic hydroxyl and two methoxyl groups. From the same fraction he also obtained a new isomer with a weak curare action which he named neoprotocuridine. From the quaternary fraction he isolated an amorphous iodide with a paralytic potency about one-third the potency of d-tubocurarine; and three methiodides. The chemistry of these quaternary alkaloids has yet to be solved. It is believed that Pot-Curare comes from a variety of Strychnos species.

2.1.3.3. Calabash-Curare Alkaloids.

(i) Methods of separation.

Calabash-Curare is the most important and the most active South American arrow poison, the toxicity of the frog being 0.5 to 1 mg./kg. Boehm (5) was the first to begin the systematic study of its chemistry. He could, however, obtain only an amorphous curarine. It was not until 1937 that successful research into this subject was conducted by Wieland and his colleagues (29-36).

After the war, this group of researchers was joined by Karrer, Schmid and co-workers (37-60) working independently in Zürich. King (61-62), has also worked on Calabash alkaloids.

Wieland, Konz and colleagues (29) first applied chromatography for the separation of the calabash alkaloids. The Keinecke's salts of the alkaloids in acetone solution were adsorbed through aluminium oxide. Each of the alkaloid fractions obtained by the adsorption were separately converted into the chlorides by treatment with silver sulphate and barium chloride, and again chromatographed. By this method they obtained the first crystalline alkaloids from Calabash-Curare. In 1946, Karrer and Schmid (37) succeeded in preparing readily crystallisable picrates, which on filtration through a Wolfatite-M column saturated with chloride ions yielded pure chlorides. Unfortunately, this method of separation involves considerable loss of materials. With the aid of paper chromatograms, Schmid and Karrer (41) showed that only some of the alkaloids isolated up to 1950 (C-Curarine I, C-Calebassine, and C-Fluorocurine) were pure. They demonstrated the occurrence of more than thirty different alkaloids in the Calabash-Curare originating from the Rio Negro region. For distinguishing the different alkaloids occurring as spots on the two dimensional chromatograms, they used the colour reactions with ceric sulphate, which with the different bases gave red, blue, yellow, green, purple or yellowish green colours. Furthermore, colour tests with cinnamic aldehyde, Nitric acid, and Sulphuric acid were made as also examination of the fluorescence shown by some of these alkaloids under ultra-violet light. The observations by Schmid and Karrer that cellulose paper gives a good separation of the alkaloids induced Wieland and Merz (34) to chromatograph their Calabash-Curare extracts through paper powder columns. By this method they finally obtained the alkaloids (discovered earlier) in the pure form. At about the same time, Schmid, Kebrle and Karrer (44) developed an efficient method which gave good separation with very little loss of alkaloids. As a preliminary step, the Calabash-Curare extracts were

(61) King, H., J.chem.Soc. 955 (1949).
partially purified by the removal of the tertiary bases and precipitation of the quaternary alkaloids as Reinecke's salts. These were then converted into the chlorides. 15 grammes of the alkaloid chlorides so obtained from 400 grammes of Calabash-Curare ( N III ) were adsorbed through a column 1,4 metre high, packed with 1,7 kilogrammes of paper powder. Fractions of 20 ml. were collected without a break for ten days. The solvent used was methyl ethyl ketone saturated with water and 1-3% methanol. In this way, the alkaloids were separated into five groups T₁-T₅. After repeated chromatography they were able to separate 21 alkaloids in the pure form. The pure alkaloids all crystallised very readily. Karrer and his colleagues found that after chromatography with paper powder, practically no loss in the total activity (as measured by the paralysis of mice) resulted. 98% of the initial activity was found to be retained in the groups T₄ and T₅, 0,6% in the groups T₁ and T₂, and 1% in group T₃. 38% of the total activity was attributed to C-curarine, 20% to C-alkaloid G, 12% to C-calebassine and about 5% to C-toxiferine.

**Composition of Calabash-Curare.**

Some of the alkaloids mentioned in Table 1 have previously been isolated by Wieland and his colleagues. Besides this, both Wieland and King have isolated some alkaloids from the bark of Strychnos toxifera (e.g., Toxiferines I and II). Wieland (34) was the first to isolate Mavacurine from the South American drug 'mavacurine', and from calabashes, where it occurs together with another alkaloid - fluorocurine. However, the contribution made in this field by Karrer and his colleagues is outstanding, and it is to these investigators that we owe most of what we understand about Calabash-Curare. The composition of the poison of the calabashes show great differences. A sample obtained from the territory of the river Ica near the frontier of Colombia was examined by Schmid, Giesbrecht and Karrer (50) and found to contain only one alkaloid which has been found before in other calabashes, namely calebassine. But these investigators were able to isolate from this sample four new alkaloids named C-alkaloids O and P, xanthocurine and guianine. Guianine has been found in the bark of Strychnos guianensis. From two similar calabashes originating from Venezuela, Meyer, Schmid and Karrer (57) isolated the alkaloids dihydrotoxiferine,
C-curarine, C-calebassine and C-fluorocurarine in considerable amounts. Further, they found four new alkaloids which they named C-alkaloids Q, R and S, and pseudo-fluorocurine; the last named substance possessing properties very similar to fluorocurarine, having the same empirical formula, \( R_C \) value, colour reactions and picrates with the same melting points. The only difference between them being that in contrast to fluorocurarine, pseudo-fluorocurarine does not form the difficultly soluble p-nitrophenyl hydrazone and the difficultly soluble iodide. The characteristic absorption spectrum of pseudo-fluorocuraine shows that, like fluorocurarine, it is without a doubt an indoxyl derivative.

From yet another calabash obtained from the upper Rio Negro region in Brazil, Arnold, Philipsborn, Schmid and Karrer (59) isolated besides the known calabash alkaloids (C-curarine, C-calebassine and C-fluorocurarine), a new tertiary alkaloid which they proposed to call provisionally C-alkaloid T. From a comparison of data, and especially the infra-red spectra the authors concluded that their C-alkaloid T is identical with the alkaloid "C", just recently isolated by Janot and Le Men (63) from a species of Apocynaceae 'Lochnera (Vinca) rosea (L.) Reichb. (Cantharanthus roseus G. Don) var. alba1 obtained from Madagaskar. Both these groups of authors found that their respective

<table>
<thead>
<tr>
<th>Table 1</th>
<th>The Calabash Alkaloids isolated till 1953. (Waser (64)).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaloid</td>
<td>Formula</td>
</tr>
<tr>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>C-Curarine 1</td>
<td>( C_{20}H_{21}N_2 )</td>
</tr>
<tr>
<td>C-Alkaloid G</td>
<td>( C_{20}H_{23}O_2 )</td>
</tr>
<tr>
<td>C-Alkaloid E</td>
<td>( C_{19-20}H_{23}O_2 )</td>
</tr>
<tr>
<td>C-Toxiferine I</td>
<td>( C_{20}H_{23}O_2 )</td>
</tr>
<tr>
<td>C-Alkaloid H</td>
<td>-</td>
</tr>
<tr>
<td>C-Alkaloid 2</td>
<td>-</td>
</tr>
<tr>
<td>C-Alkaloid K</td>
<td>( C_{20}H_{23}N_2 ) (* dihydro- toxiferine I))</td>
</tr>
</tbody>
</table>

Table 1 (continued).

<table>
<thead>
<tr>
<th>Alkaloid</th>
<th>Formula</th>
<th>$^{*}R_c$ value with solvent C</th>
<th>Head-drop dose g./kg. mice</th>
<th>References to the authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-Calebassine (= C-toxiferine II or Strychnotoxine I)</td>
<td>$C_{20}H_{25}O_N_2$</td>
<td>0.80</td>
<td>240</td>
<td>32</td>
</tr>
<tr>
<td>C-Alkaloid I</td>
<td>$C_{19-20}H_{23-25}N_2$</td>
<td>0.89</td>
<td>174</td>
<td>45</td>
</tr>
<tr>
<td>C-Alkaloid F</td>
<td>$C_{20}H_{23}O_N_2$</td>
<td>0.49</td>
<td>75</td>
<td>45</td>
</tr>
<tr>
<td>C-Alkaloid A</td>
<td>$C_{20}H_{23}O_N_2$</td>
<td>0.23</td>
<td>70</td>
<td>45</td>
</tr>
<tr>
<td>C-Curarine II (= Strychnotoxine Ia)</td>
<td>$C_{20}H_{25}O_N_2$</td>
<td>-</td>
<td>-</td>
<td>30</td>
</tr>
<tr>
<td>C-Alkaloid D</td>
<td>$C_{20}H_{21}O_N_2$</td>
<td>0.35</td>
<td>1100</td>
<td>45</td>
</tr>
<tr>
<td>C-Alkaloid B</td>
<td>$C_{20}H_{23}O_N_2$</td>
<td>0.34</td>
<td>280</td>
<td>45</td>
</tr>
<tr>
<td>C-Alkaloid C</td>
<td>-</td>
<td>0.34</td>
<td>240</td>
<td>45</td>
</tr>
<tr>
<td>C-Fluorocurine</td>
<td>$C_{20}H_{23}O_N_2$</td>
<td>2.10</td>
<td>4400</td>
<td>40</td>
</tr>
<tr>
<td>C-Fluorocurinine</td>
<td>$C_{21}H_{29}O_N_2$</td>
<td>2.23</td>
<td>2750</td>
<td>45</td>
</tr>
<tr>
<td>C-Calebassinine</td>
<td>$C_{19}H_{23}O_N_2$</td>
<td>1.68</td>
<td>22000</td>
<td>40</td>
</tr>
<tr>
<td>C-Alkaloid UB</td>
<td>$C_{19}H_{23}O_N_2$</td>
<td>-</td>
<td>-</td>
<td>40</td>
</tr>
<tr>
<td>C-Alkaloid J</td>
<td>$C_{19}H_{21}N_2$</td>
<td>1.04</td>
<td>290</td>
<td>45</td>
</tr>
<tr>
<td>C-Alkaloid L</td>
<td>-</td>
<td>2.50</td>
<td>1900</td>
<td>45</td>
</tr>
<tr>
<td>C-Fluorocurarine (= C-Curarine III)</td>
<td>$C_{20}H_{23}O_N_2$</td>
<td>2.25</td>
<td>1800</td>
<td>31</td>
</tr>
</tbody>
</table>

$^{*}R_c = \frac{\text{distance travelled by the alkaloid}}{\text{distance travelled by C-Curarine I}}$

Solvent C = methyl ethyl ketone saturated with water and 1-3% methanol.

Since most of these alkaloids have no sharp melting points, they are characterised by their UV-spectrum, their colour reactions, their biological activity and also their $R_c$ values (from the paper chromatograms).

C-alkaloid T and Alkaloid "C" are identical with phenol-O-methylsarpagine obtained by the methylation of sarpagine. It is of interest to note that sarpagine itself, which was discovered by Stoll and Hofmann (65) in Rauwolfia serpentina Benth., is found only in the family 'Apocynaceae' of the genus Rauwolfia (66). Besides Rauwolfia serpentina, sarpagine is also found in Rauwolfia canescens, Rauwolfia micrantha, Rauwolfia indecora and in Rauwolfia hirsuta (67). It has also been reported present in Rauwolfia Zeddomei (68), and in Rauwolfia vomitoria (69).

On examining the alkaloid components of a strychnos species belonging to the Strychnos mitscherlichii group, Kebrle, Schmid, Waser and Karrer (46) were able to identify the following alkaloids by paper chromatography and their colour reactions: C-fluorocurinine, C-curarine, C-calebassine, C-alkaloid I and the C-alkaloids B,C and D. These alkaloids occur in the bark in about the same proportions as in the calabashes, and the main alkaloids in the bark were likewise C-curarine and C-calebassine. The two dimensional paper chromatogram of Strychnos mitscherlichii showed very great resemblance with that of a calabash. Kebrle, Schmid, Waser and Karrer (47) also prepared an extract from the bark of a species of Strychnos toxiferum. After precipitating the alkaloids as Reinecke's salts and their conversion to the chlorides, a two-dimensional paper chromatogram was prepared. It showed the presence of at least 15 different alkaloids. Excepting C-toxiferine I, these authors found no other calabash alkaloid in the particular bark examined. Later from the bark of a Strychnos toxiferum species obtained from Venezuela, Karrer, Schmid and colleagues (52, 54) isolated besides mavacurine, fluorocurine and C-alkaloid Y, 11 new alkaloids - fedamazine (a quaternary alkaloid), Caracurine I-IX, and nor-C-dihydrotoxiferine.

<table>
<thead>
<tr>
<th>Alkaloid</th>
<th>Isolated from</th>
<th>Calabashes</th>
<th>Barks of Strychnos</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-curarine I</td>
<td></td>
<td>+</td>
<td>mitscherlichii</td>
<td>29,30,44,45,46.</td>
</tr>
<tr>
<td>C-curarine II (C-strychnotoxine Ia)</td>
<td></td>
<td>+</td>
<td>toxifera</td>
<td>31,34.</td>
</tr>
<tr>
<td>C-curarine III = C-fluorocurarine</td>
<td></td>
<td>+</td>
<td>mitscherlichii</td>
<td>31,44,45,46.</td>
</tr>
<tr>
<td>C-toxiferine I = toxiferine I</td>
<td></td>
<td>+</td>
<td>toxisfera</td>
<td>39,44,45,32,58.</td>
</tr>
</tbody>
</table>
| C-toxiferine II (C-calebassine, C-strychnotoxine I) | | +          | mitscherlichii    | 37,44-46,32,58.
<p>| Toxiferine II (strychnotoxine II) |               | +          | toxifera          | 32,34.        |
| C-dihydrotoxiferine I = C-alkaloid K |               | +          |                  | 32,44,45.     |
| C-isodihydrotoxiferine       |               | +          |                  | 32.           |
| C-alkaloid A                 |               | +          | mitscherlichii    | 37,44-46.     |
| C-alkaloid B                 |               | +          | mitscherlichii    | 37,44-46.     |
| C-alkaloid C                 |               | +          | mitscherlichii    | 44-46.        |
| C-alkaloid D                 |               | +          |                  | 44,45.        |
| C-alkaloid E                 |               | +          |                  | 44,45.        |
| C-alkaloid F                 |               | +          |                  | 44,45.        |
| C-alkaloid G                 |               | +          |                  | 44,45.        |
| C-alkaloid H                 |               | +          |                  | 44,45.        |
| C-alkaloid I                 |               | +          | mitscherlichii    | 44-46.        |
| C-alkaloid J                 |               | +          |                  | 44,45.        |
| C-alkaloid L                 |               | +          |                  | 44,45.        |
| C-alkaloid M                 |               | +          |                  | 49.           |
| C-alkaloid O                 |               | +          |                  | 51.           |
| C-alkaloid P                 |               | +          |                  | 51.           |
| C-alkaloid UB                |               | +          |                  | 40,44,45.     |
| C-alkaloid Y                 |               | +          | toxifera          | 37,49.        |
| C-alkaloid X                 |               | +          |                  | 40,44,45.     |</p>
<table>
<thead>
<tr>
<th>Alkaloid</th>
<th>Isolated from</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-calebassine</td>
<td>+</td>
<td>toxiferan</td>
</tr>
<tr>
<td>C-fluorocurine</td>
<td>+</td>
<td>C-alkaloid 30.</td>
</tr>
<tr>
<td>C-fluorocuricine</td>
<td>+</td>
<td>toxiferan 52.</td>
</tr>
<tr>
<td>C-mavacurine</td>
<td>+</td>
<td>toxiferan 52.</td>
</tr>
<tr>
<td>C-xanthocurine</td>
<td>+</td>
<td>toxiferan 52.</td>
</tr>
<tr>
<td>C-guianine</td>
<td>+</td>
<td>toxiferan 52.</td>
</tr>
<tr>
<td>C-alkaloid 1</td>
<td>+</td>
<td>toxiferan 52.</td>
</tr>
<tr>
<td>C-alkaloid 2</td>
<td>+</td>
<td>toxiferan 52.</td>
</tr>
<tr>
<td>Pedamazine</td>
<td>-</td>
<td>toxiferan 52.</td>
</tr>
<tr>
<td>Caracurine I</td>
<td>-</td>
<td>toxiferan 52.</td>
</tr>
<tr>
<td>Caracurine II</td>
<td>-</td>
<td>toxiferan 52.</td>
</tr>
<tr>
<td>Caracurine III</td>
<td>-</td>
<td>toxiferan 52.</td>
</tr>
<tr>
<td>Caracurine IV</td>
<td>-</td>
<td>toxiferan 52.</td>
</tr>
<tr>
<td>Caracurine V</td>
<td>-</td>
<td>toxiferan 52.</td>
</tr>
<tr>
<td>Caracurine VI</td>
<td>-</td>
<td>toxiferan 52.</td>
</tr>
<tr>
<td>Caracurine VII</td>
<td>-</td>
<td>toxiferan 52.</td>
</tr>
<tr>
<td>Caracurine VIII</td>
<td>-</td>
<td>toxiferan 52.</td>
</tr>
<tr>
<td>Caracurine IX</td>
<td>-</td>
<td>toxiferan 52.</td>
</tr>
<tr>
<td>Nor-dihydrotoxiferine</td>
<td>-</td>
<td>toxiferan 52.</td>
</tr>
<tr>
<td>Melinonine A (tetrahydroalstoninechloromethylate)</td>
<td>+</td>
<td>meligoniana 71.</td>
</tr>
<tr>
<td>Melinonine B</td>
<td>+</td>
<td>meligoniana 71.</td>
</tr>
<tr>
<td>'Toxiferines III-XII' of King</td>
<td>+</td>
<td>toxiferan 62.</td>
</tr>
<tr>
<td>Diaboline</td>
<td>+</td>
<td>diaboli 61,72.</td>
</tr>
</tbody>
</table>

Table 2 (continued).
It may be noted that the identified alkaloids from the bark of Strychnos mitscherlichii (Table 2) are representative of five of the eight groups into which alkaloids of the calabashes have been classified. (see classification of the calabash alkaloids below). The representatives of the toxiferine group occurring in Strychnos toxifera are missing. The occurrence of C-alkaloid T (O-methylsarpagine) in the calabash curare from the Rio Negro region is interesting in that it either indicates that the alkaloid is itself present in the Strychnos species, or that the natives use besides Strychnos some indigenous Lochnera(Vinca) species in their curare preparation.

Recently, Meyer, Schmid, Naser and Karrer (58) isolated four alkaloids from the bark of a plant (which could not be definitely identified, but which most probably belonged to the 'Viburnaceae'), obtained from Diamantino, Brazil. They found the alkaloids C-xanthocurine and C-alkaloid P earlier discovered in the calabashes from Ica in small amounts. A yellowish-red alkaloid, named croceocurine, was also isolated in extremely small amounts. The main alkaloid which has the character of a quaternary salt was named Kryptocurine.

From all these results Karrer and his colleagues have established that the main plants used by the natives of the middle and the upper Rio Negro region are Strychnos mitscherlichii and Strychnos toxifera. What other plants are used has yet to be ascertained by the examination of other barks.

Classification of the Calabash-Curare Alkaloids.

According to the absorption spectra, colour reactions, specific rotations and degradation products, the alkaloids of the calabashes can be divided into different groups (63,70).

i). Curarine group (including C-curarine I, the C-alkaloids E and G, and C-guianine). These alkaloids most probably contain an indolenine ring system (IX). The specific rotations lie somewhere around +70°. One of the two N-atoms in each molecule is present as an ammonium group. The investigations of Karrer and his colleagues (42,43) led these workers to believe that the non-basic indolo N-atom is most probably substituted in the ring for these reasons: - the -NH band is missing from the infra-red spectrum; the Zerewitinoff test of the base shows no active hydrogen. C-curarine has a probable relationship with the Strychnos alkaloids.
ii). The toxiferine group (including C-toxiferine I, C-alkaloids K, H and 2 (also called isodihydratoxiferine and C-alkaloid S). The specific rotations of the alkaloids of this group are extraordinarily high (about -600°). Their absorption spectra can best be compared with that of N-methyl-3,3-dimethyl-2-methylene indoline (X).

iii). Calebassine group, (including C-calebassine, C-alkaloids A, F, I and X, and C-curarine II). The alkaloids give a characteristic carmine-red colour reaction with concentrated nitric acid, for which reason they are also called 'Rotstoff'. The spectra are very similar to that of strychnic acid N-oxide and of strychnidine. Quaternary strychnidine salts (XI) have also been known to have a definite curariform activity. Wieland and his colleagues (36) recently studied the problem of the constitution of C-toxiferine II, also called calebassine. Investigations on this alkaloid have also been conducted by Karrer and his co-workers (55, 60). This alkaloid is, according to the UV-spectrum, probably an indole derivative substituted in the α- and β-positions (XII).

iv). C-alkaloid B, C and D group (including the C-alkaloids B, C and D and C-alkaloid R). The absorption spectrum is similar to that of calebassine, and resembles those of Gelsemine and Aspidospermine derivatives. Chromophore (XIII).

v). Fluorocurine group (including C-fluorocurine, C-fluorocurinine and pseudo-fluorocurinine). Under the UV light these alkaloids give an intense green fluorescence. The spectra are related to that of an N(1) alkylated Indoxyl, (di)substituted in the 2,2-positions (XIV).

vi). **Fluorocurarine** gives a blue fluorescence under the UV light. The spectrum is identical with that of the C-curarine III of Wieland.

vii). C-calebassine and C-alkaloid UB probably have an N-substituted Oxindole as chromophore (XVI or XVa). In this respect they are like gelsemine or strychnine.

viii). C-alkaloids J and L, Toxiferine III, C-mavacurine and Melinonine B can be recognised from their spectra as (di)substituted indole derivatives (XVI).

The two new alkaloids, C-alkaloid Q (57) and kryptocurine (58), recently isolated by Avarrer, Schmid and colleagues (57,58) are both reported to have absorption spectra characteristic of indole alkaloids.

Studies of the problem of the constitution of the calabash alkaloids are said to have been hindered by the difficulty of obtaining calabashes and of separating the various alkaloids. The elucidation of the constitution of all the calabash alkaloids can only be expected in some rather distant future.

2.1.4. Pharmacology of Curare.

The first observations of the action of curare were only of empirical value. The Spanish conquerors and other observers who travelled in the Americas reported that the Indians used poisoned arrows, which on wounding, rapidly paralyses the victim and brings about death in a very short time. It was Brodie (73) who in 1811 made the important deduction that large doses of curare attack the central nervous system, death resulting from the paralysis of the respiratory muscles. Claude Bernard (74,75) showed that curare acts at the connection between the motor nerves and the muscle fibres—the so-called end-plates. It thereby represses or prevents the impulse transmission from the nerve to the muscle but neither changes the conductivity of the nerve fibre itself nor the action potential of a directly stimulated nerve.

The term 'curarization' is no longer restricted in current use to that form of neuromuscular block caused by curare but is sometimes used where similar effects are produced by other drugs even where no more than muscular relaxation is meant (e.g., the action of 'Myanesin®'). This involves a considerable widening of the meaning.
of the word and a corresponding risk of confusion. It is to be kept in mind that a state of muscular paralysis can be brought about by a block at any one of the following possible sites in the nervous system (De Castro and Moraz (76));-

1. In the central nervous system. Blocking of the synapses within the central nervous system by central depressent drugs (e.g., barbiturates in large doses).

2. In the spinal cord. Blocking of the ganglion synapses (e.g., Myanesin®).

3. In the motor nerve. By blocking of the synapse between the motor nerve and the skeleton muscle with so-called neuromuscular blocking agents, e.g.,
   - d-Tubocurarine
   - Dimethyl d-tubocurarine
   - Flaxedil®
   - Decamethonium
   - Succinylcholine
   - Carbaminoylcholine

   act by the displacement of acetylcholine at the neuromuscular junction.

4. In the muscle. For this particular type of action no specific drug is as yet known.

Possible sites where muscle relaxant drugs may act. (From De Castro and Moraz (76)).

(1) Central Nervous System

(2) Spinal cord Synapse (4)

(3) Motor nerves

(5) Muscles

(73) Brodie, B., Phil.Trans.Roy.Soc.(London), 101, 78 (1811); 102, 378 (1812).
It is therefore necessary to distinguish between the various muscle relaxant drugs depending on whether they bring about muscle relaxation by causing a synaptic block at the central nervous synapse; at the ganglion synapse; or at the neuromuscular junction. In the strictest sense only those substances which cause a neuromuscular block are termed 'curare-like'.

The mode of action of neuromuscular blocking agents has been satisfactorily explained by the Acetylcholine Theory of the conduction of nerve impulse (77) from the motor nerve to the muscle. According to this theory, when the wave of excitation reaches the nerve terminals it causes a discharge of acetylcholine in close relation to the motor end-plate. This discharge depolarises the end-plate building up an end-plate potential, which in turn excites the muscle fibre and produces a contraction. The acetylcholine so formed with each wave of excitation is immediately hydrolysed by the cholinesterase to inactive choline and acetic acid.

The sequence of events is therefore,

i. Nerve impulse.
ii. Liberation of transmitter, i.e., acetylcholine.
iii. End-plate potential (depolarisation).
iv. Muscle response and return of the end-plate to polarised state.

The muscle is irritated only when a definite concentration of acetylcholine is reached. Acetylcholine produces a short-lasting depolarisation of the end-plate; it has no effect on the muscle fibres themselves, except in concentrations 1000 or more times those which effect the end-plate. The appearance of this depolarisation is essential for the muscle response. If the end-plate potential is not large enough the muscle cell fails to respond. It is necessary, however, that the depolarisation is only transient, and for this reason acetylcholine owes its activity to its speedy destruction by the choline esterases. Complete inhibition of this enzyme (or, in other words, the accumulation of acetylcholine) leads to permanent depolarisation of the end-plate and to paralysis of the muscle-cell. These observations explain why the injection of massive doses of acetylcholine or anticholinesterase (inhibitors of true cholinesterase) drugs lead to curare-like

paralysis.

d-Tubocurarine and related substances do not either influence the liberation of acetylcholine or interfere with the choline esterase. Its action depends on its ability to block the sites on which acetylcholine acts so that this substance can no longer produce sufficient depolarisation (i.e., the end-plate potential due to acetylcholine is lowered and is now too small) to set up a propagated disturbance. The muscle fibre is unaffected by d-tubocurarine; it remains quite normal and potentially excitable.

**Mechanism of the conduction of impulse from nerve to muscle; and the different possible ways of causing neuromuscular block.**

(Büchi (78))

- **Precursor of acetylcholine** (Ach-protein complex)
- **Nerve ends**
- **free acetylcholine**
- **attachment to receptor** (Ach-protein complex)
- **motor End-plates**
- **depolarisation of the motor End-plates**
- **End-plate potential**

*Curare-like drugs have been classified into two groups by De Castro and Moraz (76) as follows:*

- **Orthocurare Group,** (Curarimimetica)
  - acts by the displacement of acetylcholine, thereby causing a lowering of the end-plate potential due to it.
- **d-Tubocurarine**
- **0,0-Dimethyl-d-Tubocurarine**
- **Calebassine alkaloids**
- **Erythrina alkaloids**
- **Laudolissin**
- **Flaxedil**
- **Mytolon**

- **Leptocurare Group,** (Acetylcholinomimetica)
  - produces a long-lasting depolarisation of the end-plate.
- **Decamethonium**
- **Tetramethylammonium**
- **Amyltrimethylammonium**
- **Succinyl dicholine**
- **Adipyl dicholine**
- **Licarbaminoylcholine**
- **Brevatonal**
- **Tachycurine**

In referring, therefore to 'curarization' in its extended sense, it is necessary to specify both the synapse at which paralysis of transmission of excitation occurs, and the mode of that paralysis.

Based on the mechanism of nervous conduction, the possible modes of paralysis (see article by Paton (79)) of transmission of nervous excitation are:

1. **Block by transmitter failure**, either by immobilisation of acetylcholine (e.g., by Novocaine; Ag⁺⁺, Ca⁺⁺ lack), or by deficiency of acetylcholine (e.g., presence of Botulinus toxin).
2. **Competition Block**, for example by curare alkaloids, in which the threshold of the end-plate to excitation by acetylcholine is raised by competition of the curare for the acetylcholine receptor sites on the end-plate.
3. **Depolarisation Block** (e.g., by K⁺, and possibly Decamethonium). Paton and Zaimis (80) showed that Decamethonium produces a long-lasting depolarisation of the end-plate. Nerve impulses can no longer produce an end-plate potential and the muscle fibre does not contract.
4. **Block by accumulation of acetylcholine** (e.g., Anticholinesterases).

This variety of modes of curarization makes it essential to define the properties of curare-like substances as clearly as possible. The type of block should be mentioned even if the fundamental mechanism of the particular type of block is not fully understood. These distinctions become all the more necessary if any attempt is to be made to relate curarizing potency to chemical structure, and also to know the proper therapeutic uses of the drugs.

**Methods for the estimation of 'Curarizing Potency'.**

For estimation of curarizing potency of curare and curare-like preparations numerous methods (see Bovet and Viaud (81)) are being used. In one of the oldest methods frogs are employed, and the minimum dose required to bring about the complete paralysis by intralumbar injection is determined. In a similar way, mice, rats, cats and

dogs have been used as subjects for the experiments.

**Rabbit Head-drop Test.** More recently, Holaday (82) introduced the so-called head-drop test for rabbits (or mice), which serves as a quick and accurate method for the determination of the intensity of the curarizing substances. The drug is infused into the ear vein at a standard rate. When the rabbit can no longer hold its head up (this is quite a sharp end-point), the infusion is stopped, and the amount of the drug which has been administered is taken as an indication of its potency.

**Other tests for neuromuscular blocking agents.** The frog’s sartorius or sciatic gastrocnemius preparation (Boehm (83)), and the rat diaphragm preparation (Büllbring (84)), are also used for testing and estimating neuromuscular blocking activity.

2.1.5. The Therapeutic Uses of Natural Curare.

During the last decade, compounds with curare-like activity have aroused great medical interest. From a sample of curare brought by Gill (85), a standardised, sterile solution was prepared and was used by Bennett and colleagues (86) for the control and prevention of trauma in shock therapy. This solution was the forerunner of the preparation most used in both clinic and laboratory. The introduction by Wintersteiner (26) of the pure, standardised d-tubocurarine preparation was, however, the beginning of the general clinical application of curare. Good curare preparations show practically no side-effects, the circulation especially remaining unaffected. Today, two preparations from natural curare are mostly used. They are the purified extract 'Intocostrin®' (Squibb), and the pure d-tubocurarine (U.S.P.XV).

**The use of curare as an adjuvant to anesthetics.** The pioneer work in this field is due to Griffith and Johnson (87). Cullen (88) urged

---

(83) Boehm, R., Arch. exper. Pathol. Pharmakol., 68, 177 (1910).
(85) Gill, R. C., Anesthesiology, 7, 14 (1946).
that curare can be used to advantage with all volatile anesthetics, since the very deep anesthesia commonly necessary for adequate relaxation with most volatile anesthetics when used alone can be avoided and successful surgery can be accomplished at a plane of anesthesia that would, without curare, be too shallow for adequate surgical mobilisation and manipulation. The use of curare in anesthesia has now become an established procedure, especially for abdominal operations, because the curare causes immobility of the intestine (89) and produces a quiet abdomen.

A few other clinical uses of curare may be mentioned:—Its use to protect patients from injury by reducing the violent muscle contractions in Metrazol and electrical-shock therapy is well established. It has also been used in the diagnosis of Myasthenia gravis, especially in making a positive diagnosis when the symptoms (promoted by curare) are very mild and may be confused with asthenias from other causes.*

Therapeutic Index. The therapeutic index of curarizing substances is defined as the ratio,

\[
\frac{\text{Minimum dose for curarization}}{\text{Minimum dose for respiratory arrest}}
\]

A truly good curarizing substance should, besides having a favourable therapeutic index, be free from the following undesirable side-effects:

(a) blocking of the involuntary musculature,
(b) paralysis of the Central Nervous System,
(c) liberation of histamine,
and (d) inhibition of cholinesterase.

Further, the depressive action on the respiratory centre should be as little as possible.

*See footnote on p.1.


(88) Cullen, S.C., South.J., 38, 144 (1945).

2.2. Synthetic Curare-like Compounds.

To facilitate the discussion, the compounds may be divided into various groups - those related directly to d-tubocurarine and derived from it chemically, and those which are purely synthetic and which belong to different classes of compounds, e.g., polymethylene bis-trialkylammonium, bis-quinolinium and bis-isoquinolinium salts, and the ethers and esters of choline, etc.

2.2.1. Compounds related directly to d-Tubocurarine (0,0-dialkyl ethers of d-tubocurarine).

Interpretation of the variation of activity with structure has been much helped by the establishment of the formula for d-tubocurarine itself (2). d-Tubocurarine chloride is a bis-onium salt of relatively complicated structure containing two tetrahydroisoquinoline units with the following constitution:

\[
\begin{array}{c}
\text{H}_3\text{C} & \text{CH}_3 \\
\text{N}^+ & \text{Cl}^- \\
\text{CH}_2 & \text{HO} \\
\text{CH}_2 & \text{OCH}_3 \\
\text{CH}_3 & \text{O} \\
\text{CH}_3 & \text{O}
\end{array}
\]

Two phenolic hydroxyl groups and two methoxy groups are present in the molecule. The two quaternary nitrogen atoms are separated by a chain of at least ten atoms (counting over the shortest route), consisting of -CH\(_2\)-, =CH-, and -O- groups. To the chemist and the pharmacologist, the most absorbing problem is to determine which part of the molecule is responsible, or rather, essential for its pharmacological action. Such specificity of structure can only be elucidated through comparison of chemically related compounds. In this way we can discern what molecular functions or other structural features confer curare-like action on a molecule.

Significance of the free hydroxyl groups. Wintersteiner and Dutcher (26) has shown that the methylation of the phenolic hydroxyl groups in d-tubocurarine resulted in a nine to ten-fold increase in physiological potency. But surprisingly, this increase in potency is not the result of extending the molecule or of increasing its aliphat-
ic nature at that point, since it was shown that ethylation and butylation (26) of these same hydroxyl groups resulted in a less active and totally inactive compound respectively. The 0,0-dimethyl d-tubocurarine chloride has found clinical use. It has the advantage over d-tubocurarine chloride in that it has less tendency to cause respiratory paralysis.

Significance of the quaternary ammonium groups. It is generally accepted that the presence of the quaternary ammonium groups in d-tubocurarine chloride are necessary to confer the neuromuscular blocking activity on the molecule. We have seen that d-chondrocurine (VIIb), a constituent alkaloid of Chondrodendron tomentosum which contains two tertiary N-atoms is physiologically inactive. But when the tertiary N-atoms are quaternised with methyl chloride, d-chondrocurine dimethochloride, an active compound, is obtained which is an isomer of d-tubocurarine chloride. Further, if the free phenolic hydroxyl groups are methylated, 0,0-dimethyltubocurarine chloride is formed which is much more active than either d-tubocurarine chloride or d-chondrocurine dimethochloride. Hence, it may be concluded that the quaternary ammonium groups of d-tubocurarine and other curare-like compounds are essential. As early as 1869, Crum Brown and Frazer (90) examined the methiodides of strychnine, brucine, thebaine, codiene, morphine, atropine and conine and found that all these quaternary salts produced paralysis. They recognised the fact that the paralysing properties are characteristic of onium salts as a class.

![Chemical structures](image)

There is only one important exception to this generalisation. Recently, a group of alkaloids has been discovered which are tertiary, not quaternary bases and which nevertheless show strong curare activity.

---

Called the erythrina alkaloids, they show their activity after applica-
tion by mouth whereas the curare alkaloids show high activity only
when they are directly introduced into the blood. More important
among these alkaloids are \( \beta \)-erythroidine and dihydro-\( \beta \)-erythroidine,
represented by the formulae XVII and XVIII (91, 92, 93 and 94).
On converting the tertiary N-atoms to quaternary nitrogen the com-
pounds diminish greatly in potency. Another non-quaternary alkaloid
of interest is coclaurine (XIX), a secondary cyclic amine (95). It
possesses weak curare action. Its quaternary derivative can be
considered as essentially half a d-tubocurarine molecule.

2.2.2. Compounds with One Onium Group.

Using the frog sartorius preparation Ing and Wright (96) made
the first reliable estimation of neuromuscular blocking activity with
simple onium salts. Tetraalkylammonium, alkylpyridinium and alkyl
quinolinium salts all showed feeble activity. Analogous compounds with
a saturated hetero-ring were more active. Craig and Tarbell (97)
synthesized some benzyl tetrahydroisoquinoline derivatives modelled
on a fragment of the d-tubocurarine molecule (XX). But all these
compounds showed only feeble curare activity.

\[
\begin{array}{|c|c|}
\hline
\text{R} &=& \text{R}_1 \\
\hline
\text{(a)} & -\text{OCH}_3 & -\text{CH}_3 \\
\text{(b)} & -\text{OCH}_3 & -\text{CH}_2\text{-C}_6\text{H}_5 \\
\text{(c)} & -\text{H} & -\text{CH}_3 \\
\hline
\end{array}
\]

(91) Boekelheide, V., Grundon, M.F. and Weinstock, J., J.amer.chem.
Soc. 74, 1866 (1952).
(93) Unna, K.R. and Greslin, J.G., J.Pharmacol.exp.Therap. 80, 39 and
53 (1944).
Therap. 113, 212 (1955).
(95) Finkelstein, J., J.amer.chem.Soc. 73, 550 (1951).
(97) Craig, L.E. and Tarbell, D.S., J.amer.chem.Soc., 70, 2783 (1948);
71, 462 (1949).
Besides being feebly active, the monoquaternary compounds are commonly like tetramethylammonium iodide (prepared and examined by Crum Brown and Frazer (90)), particularly in possessing stimulant nicotine-like and muscarine-like actions.

2.2.3. Compounds containing Two (or more) Onium Groups.

2.2.3.1. Polymethylene-α,ω-bis-trialkylammonium salts. Long before the constitution of d-tubocurarine was known, Willstätter and Heubner (98) noted that the presence in a molecule of two quaternary ammonium groups linked together by an aliphatic chain leads to stronger curare-like action and a considerable lessening of the nicotine-like and muscarine-like actions. On making a comparison of the ganglion blocking action of tetraethylammonium with molecules in which two triethylammonium groups were separated by a polymethylene chain, Chou and de Elio (99) found that although the ethylene compound was one-third as active as tetraethylammonium, the activity fell right away in the trimethylene and pentamethylene derivatives. But above the trimethylene member, the neuromuscular blocking activity rose steadily in the series. Barlow and Ing (100), as also Paton and Zaimis (101), discovered (Table 3) that the activity, as measured by the rabbit head-drop method, of the bis-triethylammonium compounds was most profound when there were nine to twelve methylene groups in the chain. A sharp maximum in activity is reached at the decamethylene member which has been named 'Decamethonium'. This compound is more than two times (weight for weight) as active as d-tubocurarine chloride. It is interesting that in the bis-triethylammonium series there did not appear to be a maximum. Activity steadily rose to the tridecamethylene member which was slightly stronger than the most powerful member of the bis-triethylammonium series. Kimura, Unna and Pfeiffer (102) has pointed out that although in both cases the number of atoms separating the

References:

two quaternary ammonium groups is ten, the actual spatial distance between the two groups in decamethonium is 14-15 Å, while in d-tubocurarine it is 12.5 Å. Anyway, it is significant that the quaternary ammonium groups in compounds like d-tubocurarine, its dimethyl ether, and the strongly active polymethylene-α,ω-bis-trimethylammonium derivatives should be separated by about ten atoms, particularly since shortening the chain in the bis-trimethylammonium series to less than seven atoms almost completely abolishes activity (Table 3).

<table>
<thead>
<tr>
<th>Compound</th>
<th>n =</th>
<th>Rabbit (head-drop dose) mg./kg.</th>
<th>Cat (dose producing a 95% paralysis of the tibial muscle) mg./kg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₂</td>
<td>2</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>C₃</td>
<td>3</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>C₄</td>
<td>4</td>
<td>160</td>
<td></td>
</tr>
<tr>
<td>C₅(Pentamethonium)</td>
<td>5</td>
<td>81</td>
<td>40</td>
</tr>
<tr>
<td>C₆(Hexamethonium)</td>
<td>6</td>
<td>42</td>
<td>40</td>
</tr>
<tr>
<td>C₇</td>
<td>7</td>
<td>0.80</td>
<td>13.5</td>
</tr>
<tr>
<td>C₈</td>
<td>8</td>
<td>0.29</td>
<td>0.91</td>
</tr>
<tr>
<td>C₉</td>
<td>9</td>
<td>0.078</td>
<td>0.21</td>
</tr>
<tr>
<td>C₁₀(Decamethonium)</td>
<td>10</td>
<td>-</td>
<td>0.15</td>
</tr>
<tr>
<td>C₁₁</td>
<td>11</td>
<td>0.65</td>
<td>0.23</td>
</tr>
<tr>
<td>C₁₂</td>
<td>12</td>
<td>0.78</td>
<td>0.52</td>
</tr>
<tr>
<td>C₁₃</td>
<td>13</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>d-Tubocurarine</td>
<td></td>
<td>0.22</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*As bromide.
§As iodide.

The characteristic spatial location of the ammonium groups may be important, but other considerations are also concerned, as for example, the report of King (103) that 1-tubocurarine is 30 to 60 times weaker than the dextro-rotatory isomer.

2.2.3.2. Polymethylene-α,ω-bis-quinolinium and bis-isoquinolinium series. The examination of several series of polymethylene-α,ω-bis-quinolinium and bis-isoquinolinium salts and their hydrogenated and substituted derivatives has yielded interesting results (Table 4).

Barlow and Ing (104) examined three members of the quinoline series - trimethylene bis-quinolinium dibromide \((\text{BQ}_3)\) and the corresponding pentamethylene \((\text{BQ}_5)\) and decamethylene \((\text{BQ}_{10})\) derivatives. All three possess moderate curarizing action. It is surprising that \(\text{BQ}_{10}\) is much less active than is to be expected, being only about as active as the pentamethylene derivative. Craig (105) in his review article has generalised that reduction of the heterocyclic nucleus or introduction of methoxy groups enhances the curarizing activity in rabbits. This observation has been borne out by the results (Table 4) obtained by Collier and Taylor (106) in their studies of both the quinoline and isoquinoline series. They found that partial reduction of the heterocyclic nucleus to the tetrahydro derivative increased paralysing activity and that the complete reduction to the decahydro form further enhances this activity. Collier and Taylor (107) and Taylor (108) further examined the corresponding polymethylene bis-laudanosinium series (Table 5). Here also, the optimum curariform activity is reached at 'Laudolissin\(^R\)', the decamethylene member, which has been tested in man and found to be half as potent as d-tubocurarine. All members of this series are antagonised by neostigmine and are therefore truly curare-like. It may be noted that the Laudolissin\(^R\) molecule contains two 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline units linked together by the decamethylene chain, whereas the 0,0-dimethyltubocurarine chloride molecule consists essentially

<table>
<thead>
<tr>
<th>R =</th>
<th>Minimum effective dose: mg/kg, Rabbit</th>
<th>R =</th>
<th>Minimum effective dose: mg/kg, Rabbit</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="https://via.placeholder.com/150" alt="Structure" /></td>
<td>4.5</td>
<td><img src="https://via.placeholder.com/150" alt="Structure" /></td>
<td>4.0</td>
</tr>
<tr>
<td><img src="https://via.placeholder.com/150" alt="Structure" /></td>
<td>0.75</td>
<td><img src="https://via.placeholder.com/150" alt="Structure" /></td>
<td>1.5</td>
</tr>
<tr>
<td><img src="https://via.placeholder.com/150" alt="Structure" /></td>
<td>cis 0.12</td>
<td><img src="https://via.placeholder.com/150" alt="Structure" /></td>
<td>cis 0.5</td>
</tr>
<tr>
<td><img src="https://via.placeholder.com/150" alt="Structure" /></td>
<td>trans 0.1</td>
<td><img src="https://via.placeholder.com/150" alt="Structure" /></td>
<td></td>
</tr>
<tr>
<td><img src="https://via.placeholder.com/150" alt="Structure" /></td>
<td>trans 0.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><img src="https://via.placeholder.com/150" alt="Structure" /></td>
<td>0.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><img src="https://via.placeholder.com/150" alt="Structure" /></td>
<td>0.2</td>
<td><img src="https://via.placeholder.com/150" alt="Structure" /></td>
<td>0.2</td>
</tr>
<tr>
<td><img src="https://via.placeholder.com/150" alt="Structure" /></td>
<td>0.1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><img src="https://via.placeholder.com/150" alt="Structure" /></td>
<td>0.15</td>
<td><img src="https://via.placeholder.com/150" alt="Structure" /></td>
<td>1.0</td>
</tr>
<tr>
<td><img src="https://via.placeholder.com/150" alt="Structure" /></td>
<td>0.08</td>
<td><img src="https://via.placeholder.com/150" alt="Structure" /></td>
<td>0.05</td>
</tr>
<tr>
<td><img src="https://via.placeholder.com/150" alt="Structure" /></td>
<td>0.02</td>
<td><img src="https://via.placeholder.com/150" alt="Structure" /></td>
<td>0.25</td>
</tr>
</tbody>
</table>

*These compounds were studied by Collier and Taylor (106)*
of one 1-(4-methoxybenzyl)-6,7-dimethoxy-2,2-dimethyl-1,2,3,4-tetrahydroisoquinoline unit and one 1-benzyl-6-methoxy-2,2-dimethyl-1,2,3,4-tetrahydroisoquinoline unit connected together through ether linkages. The curare form activity of the dimethyl ether of d-tubocurarine chloride (compare with that of Laudolissin®, Table 5) does not all appear to be accounted for by the presence of the benzyl-methoxytetrahydroisoquinoline units. It has been suggested by Barlow (109) that the diphenyl ether link in the molecule may be important. The possibility was pointed out that the oxygen atom perhaps provides a strong positive centre which might have a favourable effect on the attachment of the drug to the receptor surface. On the other hand, Taylor (108) has shown (Table 5) that replacement of the polymethylene chain in Laudolissin® with a polymethylene ether chain results in a slightly less active compound.

Table 5.
Paralysing Activity of Laudanosinium Derivatives (Taylor (108)).

<table>
<thead>
<tr>
<th>Chain</th>
<th>Total No. of atoms or groups in chain n =</th>
<th>M.E.D. (Minimum effective dose) µg./kg. Rabbits</th>
<th>E.D. 50 Mouse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octamethylene</td>
<td>8</td>
<td>47</td>
<td>260</td>
</tr>
<tr>
<td>Laudolissin®</td>
<td>9</td>
<td>26</td>
<td>160</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>31</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>55</td>
<td>410</td>
</tr>
<tr>
<td>Dodecamethylene</td>
<td>12</td>
<td>90</td>
<td>760</td>
</tr>
<tr>
<td>-(CH₂)₄-O-(CH₂)₄-H</td>
<td>9</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>-(CH₂)₅-O-(CH₂)₅-H</td>
<td>11</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>d-Tubocurarine chloride</td>
<td>100</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>(+)-O,0'-Dimethyl-tubocurarine chloride</td>
<td>10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.2.3.3. Compounds with a modified chain between the onium groups. In the course of the last decade of research, the polymethylene chain linking the two ammonium groups has been variously modified to include -0-, -N-, -S- and more complex groups containing aromatic and heterocyclic nuclei.

(a) Phenyl-polymethylene para- (and meta-)ω-bis-(trialkylammonium) salts. Compounds of the types represented by formulae XXI and XXII have been tested by Wien and Mason (110).

\[
R_3N-(CH_2)_n-\text{NR}_3
\]

\[
R = -\text{CH}_3 \text{ or } -\text{C}_2\text{H}_5
\]

XXI

The series phenyl-polymethylene p-ω-bis-trimethylammonium salts show a sharp peak of activity for ganglionic paralysis at \( n = 2 \). The neuromuscular blocking activity is maximal when \( n = 6 \). These results roughly correspond to the two peaks in the hexethonium series, assuming that the phenyl group is equivalent to 3-4 methylene groups.

We have seen (p. 31) that the presence in a molecule of two quaternary ammonium groups lead to stronger curare-like action and a considerable lessening of the nicotine-like and muscarine-like actions which are commonly possessed by monoquaternary compounds. In this connection, the work of Funke and colleagues (111) is of interest. By the examination of a series of ethiodides of diethylaminomethyl- and diethylaminoethyl-benzene derivatives (Table 6) they showed that although the introduction of a second quaternary ammonium group has a favourable influence, the addition of more quaternary groups does not necessarily increase the curarizing potency.

(b) Derivatives of diphenyl, diphenylmethane and related compounds. Derivatives of diphenyl and diphenylmethane were studied by Nador and co-workers (112). Of the compounds they studied N,N,N',N'-tetramethyl-

The influence of the number and location of quaternary ammonium groups on curarizing activity (Funke et al. (111)).

$$R = \text{CH}_2\text{-N(C}_2\text{H}_5)_3$$

<table>
<thead>
<tr>
<th>R</th>
<th>12 mg./kg.</th>
<th>5 mg./kg.</th>
<th>5 mg./kg.</th>
<th>2,5 mg./kg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>2,5 mg./kg.</td>
<td>2,5 mg./kg.</td>
<td>5 mg./kg.</td>
<td>15 mg./kg.</td>
</tr>
<tr>
<td>R</td>
<td>1,5 mg./kg.</td>
<td>3 mg./kg.</td>
<td>0,6 mg./kg.</td>
<td>0,5 mg./kg.</td>
</tr>
</tbody>
</table>

-4,4'-diaminodiphenylmethane diiodopropylate (XXIII) produced a paralysis of cat muscles at a dosage of 0,2 mg./kg.. The curarizing action is not antagonised by prostigmine. Related compounds (XXV) were also found to have curare-like activity (113).

\begin{align*}
\text{XXIII} \\
\text{Curarizing dose (cat)} &= 0,2 \text{ mg./kg.} \\
\text{XXIV} \\
\text{Curarizing dose (cat)} &= 0,2 \text{ mg./kg.}
\end{align*}

\begin{align*}
\text{XXV} \\
R^1 = \text{Alkyl}, \quad n = 0, 1, 2. \\
R^2 = \text{Alkyl, Aralkyl, } X^- = \text{Cl}^-, \text{Br}^-, \text{I}^-
\end{align*}

Randall (114) has examined dipiperidine derivatives of the types represented by the formulae XXVI, XXVII and XXVIII. Activity is maximal in the ethylene derivative XXVIII.

\[
\begin{align*}
XXVI. & \quad R = \text{Alkyl}, \quad R^1 = \text{Alkyl} \\
XXVII. & \quad R = \text{Alkyl}, \quad R^1 = \text{Aryl, } p\text{-nitrobenzyl} \\
XXVIII. & \quad R = -C_2H_5, \quad R^1 = p\text{-nitrobenzyl}
\end{align*}
\]

\[
n = 2
\]

(c) Compounds with oxygen bridges in the chain.

Aliphatic ethers. Levis, Preat and Dauby (115) studied some compounds in which one methylene group in the polymethylene chain of polymethylene-\(\omega\)-bis-trialkylammonium compounds has been replaced by an oxygen atom (XXIX). They found that the most active member of

\[
(\text{CH}_3)_3N-(\text{CH}_2)_nO-(\text{CH}_2)_mN-(\text{CH}_3)_3 \quad n = 2 \text{ to } 6
\]

the series was the dimethylsulf of di-(5-dimethylamino-n-pentyl) ether, which showed a transient activity six times as intense as that of \(d\)-tubocurarine on the rat gastrocnemius preparation. A similar series with two oxygen bridges in the chain (XXX), was also studied by the same authors (115), by Cheymol (116), and by Girod and Häfliiger (116) (Tables 7 and 8).

Cheymol (116), as well as Girod and Häfliiger (117) found the maximum activity with the following combinations:

i) \(m = 2, \quad n = 4, \quad R^1 = R^2 = R^3 = -CH_3\). 
ii) \(m = 2, \quad n = 10, \quad R^1 = R^2 = R^3 = -CH_3\). 
iii) \(m = 2, \quad n = 10, \quad R^1 = R^2 = R^3 = -C_2H_5\). 

Girod and Häfliiger (117) noted the interesting fact that the curarizing

(117) Girod, E. and Häfliiger, F., Experientia, 8, 233 (1952)
Table 7.
Importance of the nature of the substituents $R_1, R_2, R_3$ in ether of the general formula,

$$R^1R^2R^3N-(CH_2)_m-O-(CH_2)_n-O-(CH_2)_m-R^1R^2R^3$$

( Girod and Häfliger (117) )

<table>
<thead>
<tr>
<th>n = 4</th>
<th>m = 2</th>
<th>$\text{N}(\text{CH}_3)_3$</th>
<th>$\text{§}$ Rat</th>
<th>Rabbit (Head-drop dose) mg./kg.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Diaphragm-phrenicus</td>
<td>Gastrocnemius</td>
<td></td>
</tr>
<tr>
<td>8-10</td>
<td></td>
<td>25,3</td>
<td>1,42</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10-2</td>
<td>0,8</td>
<td></td>
</tr>
<tr>
<td>12,6</td>
<td></td>
<td>1,6</td>
<td>0,12</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0,96</td>
<td>0,87</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4,6</td>
<td>0,2</td>
<td></td>
</tr>
</tbody>
</table>

$\text{§}$ Mouse: dose in mg. required to produce the same effect as 0,1 mg. (+)-tubocurarine chloride.

Gastrocnemius: dose in mg. required to produce the same effect on the rat gastrocnemius preparation as 0,10 mg. (+)-tubocurarine chloride.

Table 8.
Importance of the nature of the middle section $-(CH_2)_n-$ in ethers of the general formula,

$$R^1R^2R^3N-(CH_2)_m-O-(CH_2)_n-O-(CH_2)_m-R^1R^2R^3$$

( Girod and Häfliger (117) )

<table>
<thead>
<tr>
<th>n = 10</th>
<th>m = 2</th>
<th>$\text{§}$ Mouse</th>
<th>$\text{§}$ Mouse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Diaphragm-phrenicus</td>
<td>Gastrocnemius</td>
</tr>
<tr>
<td>1,2</td>
<td>1,1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6,9</td>
<td>5,3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>11,9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$\text{§}$ Diaphragm-phrenicus preparation: dose in mg. required to produce the same effect as 0,1 mg. (+)-tubocurarine chloride.

Gastrocnemius: dose in mg. required to produce the same effect on the rat gastrocnemius preparation as 0,10 mg. (+)-tubocurarine chloride.
action in this case is not primarily correlated to the whole chain length between the nitrogen atoms, but is determined by the nature of the middle section -(CH₂)ₙ - of the molecule and to a lesser degree by the substituents R¹, R² and R³ on the N-atoms (Tables 7 and 8). When the middle section is fixed at ten methylene groups, the variation in the value of m to 2, 3, and 4 methylene groups has little effect on the curarizing activity.

c.β). Bis-quinolinium series. Bovet, Couvoisier, Ducrot and Horclois (118) synthesized the polymethylene-oxyquinolinium derivatives having the general formula,

```
3381 R.P.  n = 5 ; R = -C₂H₅.
```

modelled after consideration of the d-tubocurarine molecule. Considerable curare-like activity was shown by the pentamethylene member (Compound 3381 R.P.) which has a head drop dose slightly greater than that of d-tubocurarine.

Table 9 summarises the influence of the different alkyl groups R on the curarizing potency.

Table 10 shows the effect of the polymethylene chain length on the activities and also gives a comparison between the ethers of 6- and 8-oxyquinolines.

The results indicate that the 8-oxyquinoline derivatives are more active than the corresponding 6-oxyquinoline derivatives and that the ethyl group (i.e., R = -C₂H₅) is the most suitable substituent on the N-atoms.

c.γ). Bis-dialkylaminophenoxy alkane derivatives. That the quinoline or isoquinoline ring system is not necessary for curare activity we can see from the results obtained from the study of decamethonium and other bis-(quaternary ammonium) polymethylene derivatives. But this fact is very strikingly illustrated when we compare the above polymethylene bis-oxyquinolinium derivatives with the similar

### Table 9.
Curarizing Action of bis-Quinoline Derivatives.
(Bovet et al (117, 137))

![Chemical structures of bis-Quinoline Derivatives]

<table>
<thead>
<tr>
<th>R</th>
<th>Curarizing dose, i.v. mg./kg. (Rabbit)</th>
<th>Toxic dose, i.v. mg./kg.</th>
<th>Artificial Respiration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maximum doses tolerated</td>
</tr>
<tr>
<td>-CH₃</td>
<td>0.5</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>-C₂H₅</td>
<td>0.2</td>
<td>0.75</td>
<td>100</td>
</tr>
<tr>
<td>-C₃H₇</td>
<td>0.25</td>
<td>0.4</td>
<td>30</td>
</tr>
<tr>
<td>-C₄H₉</td>
<td>0.65</td>
<td>2.5</td>
<td>15</td>
</tr>
</tbody>
</table>

*3381 x.P.

### Table 10.
Comparison between ethers of 6- and 8-Oxyquinolines.
The influence of the length of the aliphatic chain.
(Bovet et al (117, 137))

![Chemical structures of ethers of 6- and 8-Oxyquinolines]

<table>
<thead>
<tr>
<th>n= 3</th>
<th>Curarizing dose in mg./kg. (Rabbit)</th>
<th>Toxic dose in mg./kg.</th>
<th>Duration of curarisation (10 doses)</th>
<th>Curarizing dose in mg./kg. (Rabbit)</th>
<th>Toxic dose in mg./kg.</th>
<th>Duration of curarisation (10 doses)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.4</td>
<td>1.5</td>
<td>30 min.</td>
<td>0.65</td>
<td>0.85</td>
<td>90 min.</td>
</tr>
<tr>
<td>4</td>
<td>0.25</td>
<td>0.75</td>
<td>30 min.</td>
<td>0.75</td>
<td>2.0</td>
<td>135 min.</td>
</tr>
<tr>
<td>5</td>
<td>0.2</td>
<td>0.75</td>
<td>60 min.</td>
<td>1.25</td>
<td>7-8</td>
<td>toxic</td>
</tr>
<tr>
<td>6</td>
<td>0.2</td>
<td>0.3</td>
<td>75 min.</td>
<td>1.2</td>
<td>4</td>
<td>8 hours.</td>
</tr>
<tr>
<td>7</td>
<td>0.4</td>
<td>0.75</td>
<td>40 min.</td>
<td>2.0</td>
<td>20</td>
<td>-</td>
</tr>
</tbody>
</table>

*3381 x.P.

bis-phenoxy alkane series also studied by Bovet and his co-workers (119). The most active of this series (XXXII) is again the pentamethylene derivative (3565 R.P).

\[
\begin{align*}
\text{XXXII} & \quad n = 4 \quad \text{H.D.-D.} = 0.5 \text{ mg./kg.} \\
\end{align*}
\]

\[
\begin{align*}
\text{XXXII} & \quad n = 5 \quad \text{H.D.-D.} = 0.2 \text{ mg./kg.} \\
& \quad ( = 3565 \text{ R.P.})
\end{align*}
\]

Dioxy derivatives of diphenylethane and stilbene. The first active derivatives of these series were described by Cavallini and Massarani (120). The two compounds (XXXIII and XXXIV), which are derivatives of diethyldiphenylethane and diethylstilbene respectively, are active at a head-drop dose of about 0.04 mg./kg. The curarizing effects of these compounds develop very slowly and are very lasting.

Further interesting phenolethers studied by Levis, Preat and Dauby (115) are listed in table 11 with the head-drop doses. From the results it seems that increasing the aliphatic nature at the centre of the molecules of the diphenylethane and stilbene derivatives increases the curarizing potency. These two series were further studied by Costa, Ferrari and Kurtas (121), who tried aryl groups on the quarternary N-atoms in place of the alkyl groups. They found compounds of the types XXXV and XXXVI to possess a high degree of curare action of long duration which is not antagonised by tensilon.

Table 11.
Ether derivatives of Diphenyl, Diphenylmethane, Stilbene and Diphenyl-ethane (Levis, Preat and Dauby (115)).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Head-drop dose mg./kg. (Rabbit)</th>
<th>%age activity of d-tubocurarine</th>
</tr>
</thead>
<tbody>
<tr>
<td>((\text{CH}_3)_3\text{N}-\text{C}_2\text{H}_2-0-[\text{C}_6\text{H}_5]-0-\text{CH}_2\text{CH}_2-\text{N}(\text{CH}_3)_3)</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>((\text{CH}_3)_3\text{N}-\text{C}_2\text{H}_2-0-[\text{C}_6\text{H}_5]-0-\text{CH}_2\text{CH}_2-\text{N}(\text{CH}_3)_3)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>((\text{CH}_3)_3\text{N}-\text{C}_2\text{H}_2-0-[\text{C}_6\text{H}_5]-0-\text{CH}_2\text{CH}_2-\text{N}(\text{CH}_3)_3)</td>
<td>R²</td>
<td></td>
</tr>
<tr>
<td>(-\text{R}^1-\text{R}^2)</td>
<td>(-\text{R}^1-\text{R}^2)</td>
<td>0,7</td>
</tr>
<tr>
<td>(-\text{R}^1-\text{R}^2)</td>
<td>(-\text{R}^1-\text{R}^2)</td>
<td>0,25</td>
</tr>
<tr>
<td>(-\text{R}^1-\text{R}^2)</td>
<td>(-\text{R}^1-\text{R}^2)</td>
<td>0,165</td>
</tr>
<tr>
<td>(-\text{R}^1-\text{R}^2)</td>
<td>(-\text{R}^1-\text{R}^2)</td>
<td>0,04</td>
</tr>
<tr>
<td>(-\text{R}^1-\text{R}^2)</td>
<td>(-\text{R}^1-\text{R}^2)</td>
<td>0,075</td>
</tr>
<tr>
<td>(-\text{R}^1-\text{R}^2)</td>
<td>(-\text{R}^1-\text{R}^2)</td>
<td>0,03</td>
</tr>
<tr>
<td>((\text{CH}_3)_3\text{N}-\text{C}_2\text{H}_2-0-[\text{C}_6\text{H}_5]-0-\text{CH}_2\text{CH}_2-\text{N}(\text{CH}_3)_3)</td>
<td>R²</td>
<td></td>
</tr>
<tr>
<td>(-\text{R}^1-\text{R}^2)</td>
<td>(-\text{R}^1-\text{R}^2)</td>
<td>0,6</td>
</tr>
<tr>
<td>(-\text{R}^1-\text{R}^2)</td>
<td>(-\text{R}^1-\text{R}^2)</td>
<td>0,27</td>
</tr>
<tr>
<td>(-\text{R}^1-\text{R}^2)</td>
<td>(-\text{R}^1-\text{R}^2)</td>
<td>0,2</td>
</tr>
<tr>
<td>(-\text{R}^1-\text{R}^2)</td>
<td>(-\text{R}^1-\text{R}^2)</td>
<td>0,25</td>
</tr>
<tr>
<td>(-\text{R}^1-\text{R}^2)</td>
<td>(-\text{R}^1-\text{R}^2)</td>
<td>0,15</td>
</tr>
<tr>
<td>(-\text{R}^1-\text{R}^2)</td>
<td>(-\text{R}^1-\text{R}^2)</td>
<td>-</td>
</tr>
<tr>
<td>(-\text{R}^1-\text{R}^2)</td>
<td>(-\text{R}^1-\text{R}^2)</td>
<td>-</td>
</tr>
<tr>
<td>(-\text{R}^1-\text{R}^2)</td>
<td>(-\text{R}^1-\text{R}^2)</td>
<td>-</td>
</tr>
</tbody>
</table>
Cavallini, Costa, Ferrari, Massarani and Paulesu (122) synthesized and examined some compounds (XXXVII, XXXVIII), which are very closely related to those (XXXV, XXXVI) examined by Costa, Ferrari and Murtas (121). It may be seen from the formulae that the new derivatives (XXXVIIb and XXXVIIIb) have normal amyl radicals bound to the quaternary nitrogen atoms in place of the benzyl and nitrobenzyl radicals present in the older ones (XXXVa, XXXVb, XXXVIa and XXXVIb). From a study of the pharmacological results, the authors concluded that in these series, the benzyl radical bound to the quaternary nitrogen may be replaced by an amyl radical without effecting the curarizing potency of the drugs. Only the duration of the curarizing effect is reduced.

(a) \( \mathbf{R} = \mathbf{R}' = \mathbf{R}'' = -\text{CH}_2\text{CH}_2\text{CH}_3 \),
(b) \( \mathbf{R} = \mathbf{R}' = -\text{C}_2\text{H}_5 ; \mathbf{R}'' = -\text{nC}_5\text{H}_{11} \).

### (c. e). Diphenyl ether derivatives.

A number of derivatives containing a diphenyl ether link in the chain joining the two quaternary ammonium groups have also been synthesized and studied by Copp and Mogey (123). The best \( \text{XXXIX} \) was as potent as \( \text{d-tubocurarine chloride} \) (Table 12) on the rabbit.

**Table 12.**

Curarizing Activity of Diphenyl Ether Derivatives.

(Copp and Mogey (123))

<table>
<thead>
<tr>
<th>( \mathbf{R} )</th>
<th>( \pm \mathbf{N}_1\mathbf{a}_2\mathbf{R}_3 )</th>
<th>Salt</th>
<th>Paralysing Activity as %age of d-tubocurarine chloride (Rabbits)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-\text{nC}<em>5\text{H}</em>{11})</td>
<td><img src="image" alt="Structure" /></td>
<td>( \text{Br}^- )</td>
<td>100</td>
</tr>
<tr>
<td>(-\text{CH}_3)</td>
<td><img src="image" alt="Structure" /></td>
<td>( \text{I}^- )</td>
<td>50</td>
</tr>
<tr>
<td>(-\text{CH}_3)</td>
<td><img src="image" alt="Structure" /></td>
<td>( \text{Br}^- )</td>
<td>30</td>
</tr>
<tr>
<td>(-\text{CH}_3)</td>
<td><img src="image" alt="Structure" /></td>
<td>( \text{I}^- )</td>
<td>20</td>
</tr>
<tr>
<td>(-\text{CH}_3)</td>
<td><img src="image" alt="Structure" /></td>
<td>( \text{I}^- )</td>
<td>20</td>
</tr>
</tbody>
</table>

The Flaxedil series. The theory that the action of curare could be definitely related to a competition between curare and acetylcholine at the neuromuscular junction led to the examination of ethers of choline and other amino-alcohols of the choline series in the belief that these compounds may have the necessary structural features for the formation of a complex with the 'receptors' or 'effectors' and so block the impulse transmitter- acetylcholine. Bovet, Depierre and Lestrange (124) examined the properties of ethers formed from choline and homologous amino-alcohols with phenols and polyphenols, (Tables 13 and 20). They found tri-(β-triethylammoniumethoxy)-1,2,3-benzene triiodide (2559 F, Flaxedil\(^\text{®}\), Gallamine, Retensin, Syntubin, Syncurin), the most promising through the absence of secondary effects and its constant activity. The most important fact is that the injection of a dose of Flaxedil\(^\text{®}\) which is sufficient to produce a curarisation of several hours does not cause any modification of the blood pressure. The injection of physostigmine or of neostigmine produces a rapid return of muscular excitability.

Viaud and Horclois (125) later synthesized some N-alkyl derivatives related to Flaxedil\(^\text{®}\) (Table 14), which were tested on rabbits. The trimethylammonium derivative was almost as active as Flaxedil\(^\text{®}\). It may be noted that Flaxedil\(^\text{®}\) is much more active than the bis-quaternary analogues (compare with the somewhat similar ethiodides of diethylaminoethyl-benzene derivatives studied by Funke et al (111)). Pelikan and Unna (126) suggested that one explanation for the greater activity of Flaxedil\(^\text{®}\) than the 1,3-bis-quaternary analogue is that the substituent in the 2-position of the benzene ring tends to keep apart the onium functions in the 1,3-substituted positions at a distance from each other more nearly optimal for high activity.

Curarizing Activity of Ethers of Choline and Homologous Amino-alcohols with Phenols and Poly-phenols (Bovet et al (124)).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Head-drop dose in mg./kg. (rabbit)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="" alt="Chemical Structure" /></td>
<td>20</td>
</tr>
<tr>
<td><img src="" alt="Chemical Structure" /></td>
<td>4</td>
</tr>
<tr>
<td><img src="" alt="Chemical Structure" /></td>
<td>0.5-0.7</td>
</tr>
</tbody>
</table>

Winter and Lehman (127) examined a series of hydroquinone ethers and found two - named Diethamine(\(\text{XL}\)) and Dipropamine(\(\text{XLI}\)) - to be particularly interesting. In contrast to Flaxedil(\(\text{X}\)) and d-tubocurarine, both substances provoke a curarization which develops progressively and has a very long duration of action. The curarization is not antagonised by physostigmine.

\[
\text{XL Diethamine} = \text{Diethamine} \quad (\text{XL})
\]

\[
\text{XLI Dipropamine} = \text{Dipropamine} \quad (\text{XLI})
\]

A lower homologue of Dipropamine(\(\text{R}\)) has been prepared by Walker (128) who found a head-drop dose of 0.47 mg./kg. (rabbit) for the compound (\(\text{XLI}\)).

Table 14.
Influence of N-alkyl groups on the Activity of Flaxedil Analogues.
( Viaud and Horclois (125) )

<table>
<thead>
<tr>
<th>R =</th>
<th>Head-drop dose in mg./kg.</th>
<th>Toxic dose mg./kg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>-O-CH₂CH₂-N(CH₃)₃ I⁻</td>
<td>0,35</td>
<td>3,0</td>
</tr>
<tr>
<td>-O-CH₂CH₂-N(C₂H₅)₃ I⁻ (Flaxedil)</td>
<td>0,5</td>
<td>0,7</td>
</tr>
<tr>
<td>-O-CH₂CH₂-N(C₂H₅)₂.C₃H₇ I⁻</td>
<td>0,5</td>
<td>0,6</td>
</tr>
<tr>
<td>-O-CH₂CH₂-N(C₂H₅)₂.C₄H₉ I⁻</td>
<td>0,4</td>
<td>&gt;0,7</td>
</tr>
<tr>
<td>-O-CH₂CH₂-N(CH₃)₂.C₂H₅ I⁻</td>
<td>0,3</td>
<td>0,5</td>
</tr>
<tr>
<td>-O-CH₂CH₂-N(CH₃)₃ I⁻</td>
<td>0,35</td>
<td>0,6</td>
</tr>
</tbody>
</table>

c.n.). 1,3,5-Triazine derivatives. Hohman and Jones (129) prepared and examined the quaternary salts of 2,4,6-(dialkylaminoalkoxy)-1,3,5-triazine having the general formula XLIII.

Of the four members of this series examined three were found to be less active than Flaxedil. The fourth compound (XLIV) showed (Table 15)

about twice the activity when tested on mice. On rabbits, it was seven times as active as Flaxedil®.

c. Quinazoline derivatives. Quinazoline derivatives of the type (XLV) have been studied by Hohman and Jones (129) (Table 15).

\[
\text{XLV}
\]

The best of these is 2,4-(β-diethylaminoethoxy)-quinazoline dimethiodide, which is almost as active as Flaxedil®.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Head-drop dose in mg./kg. (Rabbit).</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i) 2,4,6-(β-diethylaminoethoxy)-1,3,5-triazine triethiodide.</td>
<td>6,29</td>
</tr>
<tr>
<td>(ii) 2,4,6-(β-dimethylaminoethoxy)-1,3,5-triazine trimethiodide.</td>
<td>58,06</td>
</tr>
<tr>
<td>(iii) 2,4,6-(γ-diethylaminopropoxy)-1,3,5-triazine triethiodide.</td>
<td>6,34</td>
</tr>
<tr>
<td>(iv) 2,4,6-(β-diethylaminoethoxy)-1,3,5-triazine tribenzochloride.</td>
<td>0,0552</td>
</tr>
<tr>
<td>(v) 2,4-(β-diethylaminoethoxy)-quinazoline dimethiodide.</td>
<td>3,17</td>
</tr>
<tr>
<td>(vi) 2,4-(β-dimethylaminoethoxy)-quinazoline dimethiodide.</td>
<td>12,36</td>
</tr>
<tr>
<td>(vii) 2,4-(γ-diethylaminopropoxy)-quinazoline dimethiodide.</td>
<td>2,99</td>
</tr>
<tr>
<td>Flaxedil®</td>
<td>0,391</td>
</tr>
</tbody>
</table>

Table 15. Curarizing Activity of 1,3,5-Triazine and Quinazoline Derivatives.
( Hohman and Jones (129) )

d. Bis-quaternary ammonium derivatives in the aliphatic ester series.

d. Esters of dibasic aliphatic acids. The esters formed from trialkylammonium bases (especially choline) with dibasic aliphatic acids have been studied by various authors and found to possess typical
curarizing action. The most active member of this series of compounds is succinylcholine (bis-dimethylaminoethyl succinate dimethiodide), which was first synthesized by Hunt and Taveau (130) in 1911. In their pharmacological studies of the compound they overlooked its curarizing properties. It was later examined by Bovet and his colleagues (131) and the curarizing action first described. Though extremely active (curarizing dose = 0.2 mg./kg. for rabbits and dogs), Glick (132) and Bovet-Nitti (133) found the effects to be of short duration since the succinylcholine molecule is readily hydrolysed by cholinesterase. Later, Phillips (134), Walker (135), and Castillo and de Beer (136), confirmed, and elaborated on, these observations.

![Structural formula](image)

XLVI

Many derivatives of the type represented by formula XLVI have been studied. Bovet (137), and Bovet and his colleagues (138) have discussed the relationship between chemical constitution and curare-like activity of this class of compounds in detail. It will suffice to mention here only some main aspects of this relationship.

(132) Glick, S., J. Biol. Chem., 137, 357 (1941).
The curarizing action was found to be most profound when the two quaternary ammonium groups are linked together by an ideal chain length of about ten atoms, as in succinylcholine. The esters of the lower homologous malonic acid, and those of the higher acids like pimelic and sebacic acids have a less intense and less selective action. Besides the chain length, the nature of the alkyl groups attached to the quaternary nitrogen atoms is also of importance. Methyl groups give the best results. The curarizing potency diminishes rapidly when the methyl groups are progressively replaced by other radicals (Fusco et al (139); see table 16).

### Table 16.
The curarizing action of ethyl analogues of succinylcholine (Fusco et al (139), and succinylhomocholine (Vanderhaeghe (140)).

<table>
<thead>
<tr>
<th>R-0-CO-CH₂CH₂-CO-O-R</th>
<th>Fusco et al (139)</th>
<th>Vanderhaeghe (140).</th>
</tr>
</thead>
<tbody>
<tr>
<td>R =</td>
<td>Head-drop dose</td>
<td>R =</td>
</tr>
<tr>
<td></td>
<td>mg./kg. (Rabbit)</td>
<td></td>
</tr>
<tr>
<td>-CH₂CH₂-N(CH₃)₃</td>
<td>0,2</td>
<td>-CH₂H₂-N(CH₃)₃</td>
</tr>
<tr>
<td>+CH₂CH₂-N(CH₃)₂·C₂H₅</td>
<td>3,8</td>
<td>-CH₂H₂-N(CH₃)₂·C₂H₅</td>
</tr>
<tr>
<td>-CH₂CH₂-N(CH₃)(C₂H₅)₂</td>
<td>2,0</td>
<td>-CH₂H₂-N(CH₃)(C₂H₅)₂</td>
</tr>
<tr>
<td>-CH₂CH₂-N(C₂H₅)₃</td>
<td>12</td>
<td>-CH₂H₂-N(C₂H₅)₃</td>
</tr>
</tbody>
</table>

Bovet (137) further pointed out that the ester function which is common to both succinylcholine and acetylcholine may represent an important element in the activity. This was demonstrated by the fact that in spite of easy hydrolysis (see p. 50, (132-136)), which thus decreases the stability in the animal, the aliphatic esters have shown activity greater than that of decamethonium iodide.

Table 17.
The curarizing activity of isomeric homocholine esters of succinic acid.

\[ R-CO-CH_2CH_2-CO-R \]

<table>
<thead>
<tr>
<th>R =</th>
<th>Head-drop dose mg./kg. (Rabbit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-0-CH_2CH_2-\overset{\text{N}}{\text{N}}(\text{CH}_3)_3) I(^-)</td>
<td>0,2</td>
</tr>
<tr>
<td>(-0-CH_2CH\overset{\text{N}}{\text{N}}(\text{CH}_3)_3) I(^-)</td>
<td>0,8</td>
</tr>
<tr>
<td>(-0-CHCH_2-\overset{\text{N}}{\text{N}}(\text{CH}_3)_3) I(^-)</td>
<td>100</td>
</tr>
<tr>
<td>(-0-CH_2CH_2CH_2-\overset{\text{N}}{\text{N}}(\text{CH}_3)_3) I(^-)</td>
<td>2</td>
</tr>
<tr>
<td>(-0-CH_2\overset{\text{N}}{\text{N}}(\text{CH}_3)_3) I(^-)</td>
<td>3</td>
</tr>
</tbody>
</table>

Rosnati (141) prepared three isomeric homocholine esters of succinic acid. He found the \(\beta\)-methylcholine ester to be almost totally inactive, while the \(\alpha\)-methylcholine ester showed about one-fourth the activity of succinylcholine (Table 17). Vanderhaeghe (140), however, has found some activity in the triethylammonium \(\beta\)-methylcholine ester of succinic acid (Table 16).

d.\(\beta\). Esters of amino-acids with dihydric alcohols and amino-alcohols. Bis-quaternary esters obtained from a dihydric alcohol and two molecules of an amino-acid, and those from an amino-acid and an amino alcohol all show curare-like activity, provided the chain between the onium groups is made of a convenient number of atoms (Tables 18 and 19). For example, the active choline ester of trimethylammonium caproic acid (383 IS), and the dimethiodide of the diester of ethylene glycol with dimethylaminopropionic acid (436 IS) may be quoted (Fusco, Palazzo, Chiavarelli and Bovet (142)). In the rabbit and the dog, the compound 436 IS is more stable, shows a more durable effect than succinylcholine, and is more active than d-tubocurarine.

and decamethonium iodide. Their results (Table 19A) also demonstrated

Table 18.
Esters of different amino-acids with choline. Importance of the chain length (Bovet et al (138)).

<table>
<thead>
<tr>
<th>R = (CH₃)₃N-CH₂-CH₂-CO-</th>
<th>No. of atoms separating the quaternary N-atoms</th>
<th>Head-drop dose mg./kg. (Rabbit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I⁻ (CH₃)₃N-CH₂-CH₂-CO-</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>I⁻ (CH₃)₃N-CH₂CH₂-CO-</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>I⁻ (CH₃)₅N-CH₂CH₂CH₂CH₂CH₂-CO- (383 IS)</td>
<td>9</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Table 19.
The lack of importance of an oxygen linkage for curarizing activity.

A. Fusco et al (142).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Head-drop dose: mg./kg. (Rabbit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₂-CO-O-CH₂CH₂- N(CH₃)₃ I⁻</td>
<td></td>
</tr>
<tr>
<td>CH₂-CO-O-CH₂CH₂- N(CH₃)₃ I⁻</td>
<td></td>
</tr>
<tr>
<td>CH₂-CO-O-CH₂CH₂- N(CH₃)₃ I⁻</td>
<td></td>
</tr>
<tr>
<td>CH₂-CO-O-CH₂CH₂- N(CH₃)₃ I⁻</td>
<td></td>
</tr>
<tr>
<td>CH₂-CO-O-CH₂CH₂- N(CH₃)₃ I⁻</td>
<td></td>
</tr>
<tr>
<td>CH₂-CO-O-CH₂CH₂- N(CH₃)₃ I⁻</td>
<td></td>
</tr>
<tr>
<td>CH₂-CO-O-CH₂CH₂- N(CH₃)₃ I⁻</td>
<td></td>
</tr>
<tr>
<td>CH₂-CO-O-CH₂CH₂- N(CH₃)₃ I⁻</td>
<td></td>
</tr>
</tbody>
</table>

B. Bovet et al (145).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Head-drop dose: mg./kg. (Rabbit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO-O-CH₂CH₂- N(C₂H₅)₃ I⁻</td>
<td></td>
</tr>
<tr>
<td>CO-O-CH₂CH₂- N(C₂H₅)₃ I⁻</td>
<td></td>
</tr>
<tr>
<td>CO-O-CH₂CH₂- N(C₂H₅)₃ I⁻</td>
<td></td>
</tr>
<tr>
<td>O-CH₂CH₂- N(C₂H₅)₃ I⁻</td>
<td></td>
</tr>
<tr>
<td>O-CH₂CH₂- N(C₂H₅)₃ I⁻</td>
<td></td>
</tr>
<tr>
<td>O-CH₂CH₂- N(C₂H₅)₃ I⁻</td>
<td></td>
</tr>
<tr>
<td>O-CH₂CH₂- N(C₂H₅)₃ I⁻</td>
<td></td>
</tr>
<tr>
<td>O-CH₂CH₂- N(C₂H₅)₃ I⁻</td>
<td></td>
</tr>
</tbody>
</table>

53
the lack of importance of an oxygen linkage for curarizing activity.

e). Choline esters of benzene-polycarboxylic acids. The benzoyl ester of choline possesses besides nicotinic and muscarinic effects on blood pressure (Hunt and Taveau (130)), some curarizing activity. Bovet and colleagues (143) studied the analogous choline esters of polycarboxylic aromatic acids like the phthalic acids, etc., (Table 20), and found that the toxicity increases in the polyacid esters, while the nicotinic and muscarinic effects decrease regularly. Tere-phthalycholine (XLVII) and its corresponding triethylammonium homologue are the most marked and most specific curare-like substances in this group. The series of homocholine diesters of tere-phthalic acid (XLVIII) studied by Rosnati (144) were found to be generally more active than tere-phthalycholine. Variations of activity corresponding to changes in structural content in this series (Table 20) are roughly parallel to the ether series (also Table 20).

**Table 20.**
Comparison of the curarizing activity of related ethers and esters. Rabbit- mg./kg., (i.v.). The duration of curarization is determined by return of corneal reflex after injection of 10 L.D., under artificial respiration (Bovet et al. (124; 143)).

<table>
<thead>
<tr>
<th></th>
<th>R = -O-CH₂CH₂-N(C₂H₅)₃ I⁻</th>
<th>R' = -CO-O-CH₂CH₂-N(C₂H₅)₃ I⁻</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>R</strong></td>
<td><img src="image" alt="Chemical Structure" /></td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td><strong>R'</strong></td>
<td><img src="image" alt="Chemical Structure" /></td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td><strong>Head-drop dose</strong></td>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td><strong>in mg./kg.</strong></td>
<td>20 min.</td>
<td>60 min.</td>
</tr>
<tr>
<td><strong>Duration of curarization.</strong></td>
<td>60 min.</td>
<td>60 min.</td>
</tr>
</tbody>
</table>
f) Compounds with -N- links in the chain.

f.d). Derivatives of piperazine. Hazard, Cheymol and colleagues (146) investigated a series of bis-(ammoniumethyl)-piperazine derivatives for curarizing action in the rabbit. The activity measured by the head-drop test was found to decrease in the order: piperidino-, diethyl-, diallyl-, dimethyl- and morpholino- derivatives. The most active members of the series are the bis-(piperidylethyl)-piperazine diiodoethylate (336 H.C), and the corresponding diiodomethylate (334 H.C), which produce a head-drop reaction in the rabbit with doses of 3-5 mg./kg. (Table 21). The bis-(β-diethylaminomethyl) piperazine bromobenzylate (L1) has been introduced for clinical use under the name 'Isocurin®'. A wide margin exists between the muscle relaxing and toxic doses of these compounds.

Table 21. Head-drop doses of Piperazine Derivatives (Hazard et al (146)).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Head-drop dose mg./kg. (rabbit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>XLIX (336 H.C)</td>
<td>3</td>
</tr>
</tbody>
</table>
f.β). Carbamylcholine derivatives. Bovet and his co-workers (140) first prepared and examined bis-(choline carbamate) diiodide (LIIa), and found it to be inactive. Later, Herring and Marsh (147) prepared the ethylene homologue and found it to be moderately active. The observation that by the ethers of Levis, Preat and Dauby (115), Cheymol (116) and Girod and Häfliger (117), maximal activity is reached at chain lengths longer than ten atoms led Cheymol (148) and also Klupp, Kraup, Storman and Stumpf (149) to the examination of longer chained choline esters of polymethylene dicarbamic acids. The results obtained by Cheymol (148) is quoted in Table 22. He found the derivative with a polymethylene chain length of six, i.e., \(-\left(CH_2\right)_6^+\), to be six times stronger than d-tubocurarine chloride. It is one of the most active synthetic curares.

Table 22.
Curarizing Activity of Polymethylene-\(\alpha\omega\)-bis-carbaminoylcholine Salts (Cheymol (148)).

<table>
<thead>
<tr>
<th>No.</th>
<th>(n)</th>
<th>Head-drop doses in mg./kg. (Rabbit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LII(a)</td>
<td>0</td>
<td>33.5</td>
</tr>
<tr>
<td>(b)</td>
<td>1</td>
<td>0.67</td>
</tr>
<tr>
<td>(c)</td>
<td>2</td>
<td>1.15</td>
</tr>
<tr>
<td>(d)</td>
<td>4</td>
<td>0.32</td>
</tr>
<tr>
<td>(e)</td>
<td>5</td>
<td>0.14</td>
</tr>
<tr>
<td>(f)</td>
<td>6</td>
<td>0.034</td>
</tr>
<tr>
<td>(g)</td>
<td>10</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Bis-(ammoniumalkylamino)-benzoquinone derivatives. Cavallito, Soria and Hoppe (150) studied the very interesting derivatives of bis-(trialkylammoniumalkylamino)-benzoquinone. 'Mytolon\textsuperscript{R}', the bromobenzylate of bis-(diethylaminopropylamino)-benzoquinone (LII), one of the most active members of this series, has found clinical use. It is five times stronger than d-tubocurarine by the head-drop test, is neither hypotensive nor nicotinic, and experiments on dogs under artificial respiration have indicated that the toxic dose is 7500 times the muscle relaxing dose.

\[
\text{H}_5\text{C}_2\text{Cl}^- \quad \text{Cl}^- \quad \text{C}_2\text{H}_5
\]
\[
\text{N}-\text{CH}_2\text{CH}_2\text{CH}_2-\text{NH} \quad \text{C}_2\text{H}_5
\]
\[
\text{C}_6\text{H}_5\text{CH}_2\text{LIII}
\]

Mytolon\textsuperscript{R} ( = Win 2747 ) (Winthrop-Stearns).
( = Benzoquinonium (N.N.R.) ).

Symmetrical triazine derivatives. Cavallito, Schleiper and O'Dell (151) investigated the 2,4-bis- and 2,4,6-tris- (trialkylammoniumalkylamino)-1,3,5-triazine derivatives similar to the trialkylammoniumalkoxy derivatives studied by Hohman and Jones (129). They found that the most active members of the bis- and tris- series are respectively 2,4-bis-(triethylammoniumethylamino)-6-chloro-1,3,5-triazine (LIV) and the chlorobenzylate of 2,4,6-tris-(diethylaminoethylamino)-1,3,5-triazine (LVIII). Their results (Table 23) show that: (1) there is no significant difference between imino and ether linkage of the side chain; (2) a slight reduction of activity accompanies the increase in the number of polymethylene groups in the side chain from -(CH\textsubscript{2})\textsubscript{2} to -(CH\textsubscript{2})\textsubscript{3}, (LIV versus LV); (3) the bis-derivatives are generally more active than the tris-derivatives (LIV versus LVII); (4) quaternisation with benzyl chloride results in a very marked increase in activity, and (5) there is loss of activity with increased steric hindrance about the quaternary nitrogen atom (LIV versus LVI). The substances produce a transitory reduction of blood pressure in dogs.

### Table 23.
Curarizing activity of bis- and tris-(trialkylammoniumalkylamino)-1,3,5-triazine derivatives (Cavallito et al (151)).

<table>
<thead>
<tr>
<th>No.</th>
<th>Structure</th>
<th>Curarimimetic dose in mg./kg. (mouse).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>E-D&lt;sub&gt;50&lt;/sub&gt;</td>
</tr>
<tr>
<td>LIV</td>
<td>bis-NH-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-&lt;sup&gt;+&lt;/sup&gt;(C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1,0</td>
</tr>
<tr>
<td>LV</td>
<td>bis-NH-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;-&lt;sup&gt;+&lt;/sup&gt;(C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>2,0</td>
</tr>
<tr>
<td>LVI</td>
<td>bis-NH-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;-&lt;sup&gt;+&lt;/sup&gt;(C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;7&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>&gt;20</td>
</tr>
<tr>
<td>LVII</td>
<td>tris-NH-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-&lt;sup&gt;+&lt;/sup&gt;(C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>20</td>
</tr>
<tr>
<td>LVIII</td>
<td>tris-NH-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-&lt;sup&gt;+&lt;/sup&gt;(C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;(CH&lt;sub&gt;2&lt;/sub&gt;-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;) Cl</td>
<td>2,7</td>
</tr>
<tr>
<td>LIX</td>
<td>tris-0-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-&lt;sup&gt;+&lt;/sup&gt;(C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>&gt;20</td>
</tr>
</tbody>
</table>

### Derivatives of barbituric acid. Donatelli et al (152) examined several derivatives of barbituric acid where the hydrogen on the nitrogen atom in position '1' has been substituted by various 2-alkylaminoethyl radicals; and the corresponding quaternary salts formed by the quaternisation with alkyl halides.

![Chemical Structure]

Pharmacological examination of these compounds (152) showed profound alterations. They have convulsive action and little hypnotic action. The intravenous toxicity is greater than that of the original barbituric acid derivatives. Some of these showed ganglioplergic action. Selleri and Chiti (153) later showed that the ganglion blocking action

could be improved by the introduction of two polyethylammoniumethyl radicals on the nitrogen atoms in positions '1' and '3'. Although this action is shown by the tertiary amine derivatives, it is stronger and more intensified in the bis-quaternary ammonium derivatives, always provided that the chain between the two quaternary ammonium groups is formed by five to seven atoms or groups, e.g., -CH₂, -CO-, -CS-, -NH-, etc., (LXI - LXIII). These authors (153) synthesized a new series of substituted barbiturates corresponding to formula LXIV. All of these compounds showed ganglioplegic action which is stronger and longer acting, but less rapid than Hexamethonium. They are less toxic. Some even have a weak curare activity.

\[
\text{LXI Hexamethonium} \quad \text{LXII}
\]

\[
\text{LXIII Pendiomid}^\text{R}
\]

Hoping to improve the curare activity they prepared another series (LXV), with the chain between the quaternary nitrogen atoms comprising of nine groups. All these compounds exhibited curare activity, but unfortunately, the activity is not strong enough for therapeutic use.
g). Sulphonium derivatives and compounds with -S- links in the chain. A few thio analogues of active curare-like substances have been studied, but almost none of them showed practical curarizing activity. Bovet (154) has examined the compound 885 IS (LXVI) and found a head-drop dose of 1mg./kg. The firm Geigy (155) has patented the thio analogue of the ethers studied Levis et al (115) and other investigators (116, 117) as a curare-like muscle relaxant (LXVII).

\[
\begin{align*}
LXVI & \quad (\text{885 IS}) \\
\text{I}^- (\text{CH}_3)_3\text{N}-(\text{CH}_2)_2\text{S}-\text{CH}_2\text{CH}_2\text{CH}_2\text{S}-\text{S}-(\text{CH}_2)_2\text{S}-(\text{CH}_3)_3 & \quad \text{I}^- \\
\text{Br}^- & \quad \text{Br}^- \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{C}_4\text{H}_9 & \quad \text{C}_4\text{H}_9
\end{align*}
\]

Protiva, Pliml and Finglova (156) studied the thio analogues of decamethonium iodide and of succinylcholine (LXVIII - LXX) and found no practical curare-like activity. But Hunter (157) found 5,6-dithiadecamethylene bis-trimethylammonium (Ro 3-0386, LXXI) to be quantitatively and qualitatively very similar to decamethonium.

\[
\begin{align*}
LXVIII & \quad (\text{885 IS}) \\
\text{I}^- (\text{CH}_3)_3\text{N}-\text{CH}_2\text{CH}_2\text{S}-\text{CO}\text{-CH}_2\text{CH}_2\text{S}-\text{CO}\text{-S}-\text{CH}_2\text{CH}_2\text{S}-(\text{CH}_3)_3 & \quad \text{I}^- \\
\text{LXIX} & \quad (\text{CH}_3)_2\text{S}-(\text{CH}_2)_2\text{S}-\text{CO}\text{-CH}_2\text{CH}_2\text{S}-\text{CO}\text{-S}-\text{CH}_2\text{CH}_2\text{S}-(\text{CH}_3)_2 & \quad \text{I}^- \\
\text{LXX} & \quad (\text{CH}_3)_2\text{S}-(\text{CH}_2)_2\text{S}-\text{S}-(\text{CH}_2)_n\text{S}-\text{S}-(\text{CH}_2)_2\text{S}-(\text{CH}_3)_2 & \quad \text{I}^- \\
\text{LXXI} & \quad (\text{CH}_3)_3\text{N}-(\text{CH}_2)_4\text{S}-\text{S}-\text{S}-(\text{CH}_2)_4\text{S}-(\text{CH}_3)_3
\end{align*}
\]

\[(154)\] Bovet, D., Ann.N.Y.Acad.Sc., 54 (3), 425 (1951); see also (138).
The results obtained by Walker (128) with compounds containing sulphonium groups has shown (Table 24) that the replacement of ammonium by sulphonium groups does not improve the curariform activity.

Table 24. Curariform Activity of Sulphonium Derivatives (Walker (128)).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Head-drop dose mg./kg. (Rabbit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(CH₃)₃⁺N-(CH₂)₁₀⁻N(CH₃)₃</td>
<td>0.10</td>
</tr>
<tr>
<td>(CH₃)₃⁺N-(CH₂)₁₀⁻N(CH₃)₂</td>
<td>0.33</td>
</tr>
<tr>
<td>(CH₃)₂⁺S-(CH₂)₁₀⁻S(CH₃)₂</td>
<td>1.7</td>
</tr>
</tbody>
</table>

The head-drop doses show that the activity falls step-wise as, first one, and then both, the ammonium groups are replaced by sulphonium groups. This fact is perhaps to be attributed to the instability of sulphonium compounds and their ready decomposition in the animal body.

2.3. Problem.

The search for synthetic curare-like substances has proceeded through a series of repeated simplifications of the d-tubocurarine molecule. Barlow and Ing (100), and Paton and Zaimis (101) simultaneously arrived at the schematically simple 'decamethonium' molecule; and Bovet and his colleagues (131) discovered the intense curare-like activity of succinylcholine which is actually a doublet of the acetylcholine molecule, a hormone mediator with an activity intimately connected with muscular contraction. Bovet (137), and Bovet and his colleagues (138) observed that the active synthetic curares belong to a series of ethers, thioethers or urethanes which are already known to furnish the derivatives possessing strong muscarinic activity. On the other hand, they found that ketone and amide functions incorporated in the molecule result in inactive compounds, e.g., the diketone \((CH₃)₃⁺N(CH₂)₂CO-(CH₂)₂CO-CH₂⁻N(CH₃)₃\) \(2I^-\), and the diamide \((CH₃)₃⁺N(CH₂)₂NH-CO-CH₂CH₂-CO-NH-(CH₂)₂⁻N(CH₃)₃\) \(2I^-\), are respectively inactive and feebly active. The diketone quoted above has an eight-membered chain between the quaternary nitrogen atoms with the keto groups separated by four methylene groups. Girod and Häfliger (p.38 (117)) noted that in the ethers of the constitution :-
the curarizing action is not primarily correlated to the whole chain length between the quaternary nitrogen atoms, but is determined by the nature of the middle section -(CH2)n -. A similar conclusion is to be drawn from the results obtained by Cheymol (p.56 (148)), with the carbaminoylcholine derivatives. There is perhaps a chance that active derivatives of aliphatic diketones are possible if the two keto groups can be placed in the chain (linking the nitrogen atoms) in some yet undetermined positions relative to each other. The length of the chain linking the quaternary nitrogen atoms need not necessarily be ten. Needless to say, aromatic ketones do furnish in Mytolon (R), a benzoquinone derivative, an extremely active synthetic curare.

In this work, our primary interest is to establish the changes in pharmacological effects of the increase in lipophilic properties in each group of the compounds (I, II, III), when the value of R is gradually increased from -H to -C6H13.

\[
\begin{align*}
I. & \quad \text{Br}^- (\text{CH}_3)_3\text{N} - \text{CH}_2\text{CH}_2 - 0 - \text{CO} - \text{CH} - \text{CO} - 0 - \text{CH}_2\text{CH}_2 - \text{N}(\text{CH}_3)_3 \quad \text{Br}^- \\
II. & \quad \text{I}^- (\text{CH}_3)_3\text{N} - \text{CH}_2\text{CH}_2\text{CH}_2 - \text{CO} - \text{CH} - \text{CO} - 0 - \text{CH}_2\text{CH}_2\text{CH}_2 - \text{N}(\text{CH}_3)_3 \quad \text{I}^- \\
III. & \quad \text{I}^- (\text{CH}_3)_3\text{N} - \text{CH}_2\text{CH}_2\text{CH}_2\text{CH} - \text{CH} - \text{CH} - \text{CH}_2\text{CH}_2\text{CH}_2 - \text{N}(\text{CH}_3)_3 \quad \text{I}^- \\
\end{align*}
\]

\[ R = -\text{H}, -\text{CH}_3 , -\text{C}_2\text{H}_5 , -\text{C}_3\text{H}_7 , -\text{C}_4\text{H}_9 , -\text{C}_5\text{H}_{11} , -\text{C}_6\text{H}_{13}. \]

Secondly, we thought that the changes in pharmacological characteristics of the resulting molecules when the ester function (-CO-0-R'), is successively replaced by the keto (-CO-R') and carbinol (-CH(OH)R') functions, deserve study. Such replacement of the ester function with keto and carbinol functions would necessarily involve changes in the chemical stability of the resulting compounds, and consequently, we may expect modifications in their pharmacological properties. Further, within each homologous series, the lipide-solubility increases with the increase in the number of carbon atoms and this would be expected to influence the pharmacological activities of the homologous members.
3. THEORETICAL.

3.1. Available methods for the syntheses.

3.1.1. Bis-(trialkylammoniumethyl) alkylmalonate dibromides.

$$R^+\text{Br}^-\left(CH_3\right)_3\hat{\text{N}}-\text{CH}_2\text{CH}_2-\overset{\hat{\text{O}}}{-}\text{CO-CH-CO-o-CH}_2\text{CH}_2-\hat{\text{N}}(CH_3)_3\text{Br}^-$$

For the syntheses of the choline esters of the alkylmalonic acids many procedures are available. As summarised by Bovet et al (158), any of the following methods may be adopted.

I. Preparation of dialkylaminoethyl esters of aliphatic dicarboxylic acids.

(a) \((CH_2)_n(COOC_2H_5)_2 + 2\text{HO-CH}_2\text{CH}_2-\overset{\hat{\text{N}}}{-}\text{NR}_2 \rightarrow (CH_2)_n(COOCH_2\text{CH}_2-\overset{\hat{\text{N}}}{-}\text{NR}_2)_2 + 2\text{C}_2\text{H}_5\text{OH}\)

(b) \((CH_2)_n(COCl)_2 + 2\text{HO-CH}_2\text{CH}_2-\overset{\hat{\text{O}}}{-}\text{NR}_2 \rightarrow (CH_2)_n(COOCH_2\text{CH}_2-\overset{\hat{\text{O}}}{-}\text{NR}_2)_2.2\text{HCl}\)

(c) \((CH_2)_n(COCl)_2 + 2\text{HO-CH}_2\text{CH}_2-\overset{\hat{\text{O}}}{-}\text{NR}_2.\text{HCl} \rightarrow (CH_2)_n(COOCH_2\text{CH}_2-\overset{\hat{\text{O}}}{-}\text{NR}_2)_2.2\text{HCl} + 2\text{HCl}\)

(d) \((CH_2)_n(COO\text{Na})_2 + 2\text{Cl-CH}_2\text{CH}_2-\overset{\hat{\text{O}}}{-}\text{NR}_2 \rightarrow (CH_2)_n(COOCH_2\text{CH}_2-\overset{\hat{\text{O}}}{-}\text{NR}_2)_2 + 2\text{NaCl}\)

(e) (i) \((CH_2)_n(COCl)_2 + \text{HO-CH}_2\text{CH}_2-\text{Br} \rightarrow (CH_2)_n(COOCH_2\text{CH}_2\text{Br}) + 2\text{HCl}\)

(ii) \((CH_2)_n(COOCH_2\text{CH}_2\text{Br})_2 + 2\text{NR}_2 \rightarrow (CH_2)_n(COOCH_2\text{CH}_2-\overset{\hat{\text{O}}}{-}\text{NR}_2)_2.2\text{HBr}\)

II. Preparation of the trialkylammoniumethyl esters.

(a) \((CH_2)_n(COOCH_2\text{CH}_2-\overset{\hat{\text{O}}}{-}\text{NR}_2)_2 + 2\text{RI} \rightarrow (CH_2)_n(COOCH_2\text{CH}_2-\overset{\hat{\text{O}}}{-}\text{NR}_2)_2.2\text{I}^-\)

(b) \((CH_2)_n(COCl)_2 + 2\text{HO-CH}_2\text{CH}_2-\overset{\hat{\text{O}}}{-}\text{NR}_3.\text{Cl} \rightarrow (CH_2)_n(COOCH_2\text{CH}_2-\overset{\hat{\text{O}}}{-}\text{NR}_3)_2.2\text{Cl}^- + 2\text{HCl}\)

(c) \((CH_2)_n(COOCH_2\text{CH}_2-\text{Br})_2 + 2\text{NR}_3 \rightarrow (CH_2)_n(COOCH_2\text{CH}_2-\overset{\hat{\text{O}}}{-}\text{NR}_3)_2.2\text{Br}^-\)

Method I(a) has been particularly used by Bovet et al (158) for the preparation of the malonic esters which, they pointed out are difficult to prepare otherwise. A yield of 50% was reported for bis-(dimethylaminoethyl)-malonate.

Gilman and Jones (159) have, however, described an excellent method for the preparation of di-\(\beta\)-halogenoethyl malonates in 80-85% yields. We have used their method of esterification to prepare the di-\(\beta\)-bromoethyl alkylmalonates with very satisfactory results.


The preparation of the latter compound by method I(e) was also tried. The procedure followed is outlined in the following reaction scheme.

3.1.1.1. Reaction scheme for the preparation of bis-((trimethylammonium)methyl)alkylmalonate dibromides (I).

\[ \text{Br}^-(\text{CH}_3)_3\text{N}-\text{CH}_2\text{CH}_2-0-\text{C}_2=\text{O}-\text{CH}=\text{O}-\text{CH}_2\text{CH}_2-\text{N}(\text{CH}_3)_3 \text{ Br}^- \]

\[ \text{I} \]

\[ R = -\text{CH}_3, \text{ etc.}, \text{ to } -\text{C}_6\text{H}_{13}. \]

(a) Preparation of the starting materials.

\( \alpha \). Di-ethyl alkylmalonates. The alkylmalonic esters were prepared by the alkylation of the sodio-malonic ester in dry alcohol according to the classical method of Conrad (160).

\( \beta \). Alkylmalonic acids. The alkylmalonic esters were subsequently hydrolysed with alcoholic potassium hydroxide (161) to give the potassium salts of the alkylmalonic acids which, on acidification, yielded the required substituted malonic acids.

\( \gamma \). Di-\( \beta \)-bromoethyl alkylmalonates. Two methods of syntheses were tried:-(1) the dichloride of alkylmalonic acid prepared from the alkylmalonic acid and thionyl chloride (162) was treated with ethylene bromohydrin, and (2) the alkylmalonic acid was directly esterified with ethylene bromohydrin using hydrogen chloride as catalyst (159), to give di-\( \beta \)-bromoethyl alkylmalonates (LXXIII).

(b) Preparation of bis- (trimethylammonium methyl)-alkylmalonate dibromides (I).

The treatment of di-$\beta$-bromoethyl alkylmalonate with trimethylamine gave the desired end-products (I).

3.1.2. 1,9-bis-( trimethylammonium)-5-alkyl nonane-4,6-dione diiodides

\[
\begin{align*}
\text{II} & \quad \text{R} \\
(\text{CH}_3)_3\text{N}^- - \text{CH}_2\text{CH}_2\text{CH}_2\text{C}0\text{-CH}\text{-CO}\text{-CH}_2\text{CH}_2\text{CH}_2\text{-N}^+ (\text{CH}_3)_3 \text{I}^- \\
\end{align*}
\]

On studying the literature, the following general methods for the preparation of the 1,3-diketones are available:

(a) Condensation of vinyl acetate with acid chlorides in the presence of freshly sublimed aluminium chloride (163).

(b) Condensation of acid anhydrides with ketones in the presence of boron trifluoride (164, 165 and 166).

(c) Condensation of a molecule of malonic ester with two molecules acid anhydride in the presence of magnesium oxide and copper acetate as catalysts (167).

(d) Claisen condensation of esters with ketones (168-171).

Since the diketones to be synthesized have the general formula (II), it is to be borne in mind that, for the inclusion of the ammonium groups in the 1,9-positions of the nonane-4,6-dione chain, we must arrive at a nonane-4,6-dione which contains in the 1,9-positions an amino or substituted amino groups or some other groups easily replaceable by

---


(164) Denoon, C. E., Org. Syntheses, 20, 6 (1940).


these groups.

An attempt was made to prepare 1,9-dichlorononane-4,6-dione using method (a) described under the general methods for the preparation of 1,3-diketones, but the product was found to be very unstable and could not be kept at room temperature without immediate decomposition.

As regards the condensation method (b) using boron trifluoride as the condensing agent, Hauser and Adams (166) have shown that mixed products are formed when ketones other than acetone, and anhydrides other than acetic anhydride are used. The acylation of a ketone of the general type $\text{RCH}_2\text{CO-CH}_3$ was found to occur preferentially on the methylene unit rather than the methyl unit. A study of the condensations of some ketones with acetic anhydride by Hauser and Adams (166) has shown that the methyl and methylene condensations occur in the relative percentages indicated in the structures LXXV-LXXIX.

\[
\begin{align*}
\text{LXXV} & \quad \text{LXXVI} & \quad \text{LXXVII} \\
\text{LXXVIII} & \quad \text{LXXIX}
\end{align*}
\]

This condensation would hardly be suitable as a method of preparation for long chained 1,3-diketones. Besides, now that we know 1,9-dihalogenononane-4,6-diones are unstable, the only suitable synthetic procedure would be the preparation of 1,9-diamino-nonane-4,6-dione derivatives. The method (b) under consideration cannot be easily adapted for the preparation of such derivatives. Similar considerations eliminate methods (a) and (c).

Finally, by a modified Claisen condensation of $\gamma$-dimethylamino-butyric ester with 5-dimethylamino-pentan-2-onc in dry ether with sodamide as condensing agent, 1,9-bis-(dimethylamino)-nonane-4,6-dione was obtained in good yield.

\[
\begin{align*}
\text{NaNH}_2
\end{align*}
\]

\[
\begin{align*}
\text{(CH}_3\text{)}_3\text{N-(CH}_2\text{)}_3\text{COOC}_2\text{H}_5 + \text{CH}_3\text{CO(CH}_2\text{)}_3\text{N(Cl}_3\text{)}_2 & \rightarrow \\
\text{(CH}_3\text{)}_2\text{N-(CH}_2\text{)}_3\text{CO-CH}_2\text{CO-(CH}_2\text{)}_3\text{N(Cl}_3\text{)}_2
\end{align*}
\]
Knoevenagel (172) has shown that acetylacetone could be condensed with acetaldehyde in the presence of a stream of hydrogen chloride gas (when the reactants are diluted with a large amount of chloroform) to give ethylidene acetylacetone in fairly good yield. It was presumed that our nonane-4,6-diones might readily undergo similar condensations with aliphatic aldehydes to give 5-alkylene derivatives. Hydrogenation of the latter products should then yield 1,9-bis-(dimethylamino)-5-alkyl nonane-4,6-diones. Unfortunately, the Knoevenagel condensation gave very disappointing yields with the nonane-4,6-dione derivative prepared by us.

The classical method of alkylation of dicarbonyl compounds using sodium ethoxide as catalyst, under carefully regulated conditions, was found to give the best results.

To prepare the quaternary methiodides, the 1,9-bis-(dimethylamino)-5-alkyl nonane-4,6-diones in absolute alcohol solution were treated in the cold with excess methyl iodide. The methiodides are preferred to the other methohalides since the methyl iodide is more convenient to work with than the more volatile methyl bromide and methyl chloride. More important, the iodides are less hygroscopic.

3.1.2.1. Reaction scheme for the preparation of the 1,9-bis-((trimethylammonium)-5-alkyl nonane-4,6-dione diiodides (II).

\[
\begin{align*}
\text{CH}_3\text{CO-CH}_2\text{CH}_2\text{COOCH}_2\text{H}_5 & \xrightarrow{\text{NaOH}} \text{CH}_3\text{CO-CH}_2\text{CH}_2\text{COOCH}_2\text{H}_5 \\
\text{Br-CH}_2\text{CH}_2\text{CH}_2\text{COOH} & \xrightarrow{\text{H}^+} \text{Br-CH}_2\text{CH}_2\text{CH}_2\text{COOH}
\end{align*}
\]

(a) Preparation of the starting materials.

α). 5-Dimethylamino-pentan-2-one. This substance was prepared by the acetoacetic ester synthesis using ethyl acetoacetate and dimethylaminoethyl chloride with sodium ethoxide as the condensing agent (173, 174), and submitting the product to kefonic hydrolysis with dilute acid.

β). Ethyl \( \beta \)-dimethylaminobutyrate. This intermediate was prepared in two steps:-(i) \( \beta \)-Bromobutyric acid was first prepared from \( \beta \)-butyrolactone by passing hydrogen bromide gas through the solution of the lactone in glacial acetic acid (175, 176) and the product then converted into the ethyl ester, and (ii) the \( \beta \)-bromo-butyric ester was then treated with dimethylamine (177) in absolute benzene.

γ). 1,9-Bis-(dimethylamino)-nonane-4,6-dione. 5-Dimethylamino-pentan-2-one (LXXXI) and \( \beta \)-dimethylaminobutyric ester (LXXXII) were condensed in the presence of sodamide in dry ether, the experimental conditions for the condensation being similar to that used by Adams, Hauser and co-workers (167-170).

δ). 1,9-Bis-(dimethylamino)-5-alkyl-nonane-4,6-dione. Two methods of alkylation were tried.

(i) Treatment of the 1,9-bis-(dimethylamino)-nonane-4,6-dione with an equimolecular proportion of the appropriate aldehyde using hydrogen chloride gas as the catalyst (172) and hydrogenation of the product in the presence of palladium on carbon catalyst.

\[
\begin{align*}
\text{H}_2\text{C} \text{CO-(CH}_2)_3\text{N(CH}_3)_2 + \text{R}'\text{CHO} & \xrightarrow{\text{HCl}} \text{R'}\text{CH}=\text{C} \text{CO-(CH}_2)_3\text{N(CH}_3)_2 \\
\text{LXXXIII} & \text{Pd} \xrightarrow{\text{H}_2} \text{R'}\text{CH}_2\text{CH} \text{CO-(CH}_2)_3\text{N(CH}_3)_2 \\
& \text{LXXXVI}
\end{align*}
\]

(ii) Treatment of the dione (LXXXIII) with a calculated amount of an alkyl bromide using sodium ethoxide (in absolute benzene) as the condensing agent.

The second of these methods gave better results and was therefore adopted.

(b) **Preparation of 1,9-bis-(trimethylammonium)-5-alkyl-nonane-4,6-dione diiodides.**

To obtain this end-product, the 1,9-bis-(dimethylamino)-5-alkyl-nonane-4,6-dione (LXXXIV) in absolute alcohol was quaternised by treatment (in the cold) with methyl iodide.

3.1.3. **Reaction scheme for the preparation of 1,9-bis-(trimethylammonium)-5-alkyl-nonane-4,6-diol diiodides (III).**

\[
\begin{align*}
\text{LXXXIV} & \quad \text{Pt}/\text{H}_2 \quad \text{LXXXVII} \\
\text{R-CH} & \quad \text{CH(OH)CH}_2\text{CH}_2\text{CH}_2-N(\text{CH}_3)_2 \\
\text{CO-CH}_2\text{CH}_2\text{CH}_2-N(\text{CH}_3)_2 & \quad \text{CH}_3\text{I} \\
\text{III} & \quad \text{I}^- \\
\end{align*}
\]

The diones (LXXXIV) were reduced to the corresponding diols by hydrogenation with platinum catalyst and the product then quaternised with methyl iodide.

3.1.4. **Attempt to prepare 1,9-dichloro-nonane-4,6-dione.**

The attempted synthesis is summarised by the reaction scheme (163):

\[
\begin{align*}
2\text{Cl(CH}_2)_3\text{-CO-CI} + \text{CH}_2=\text{CH-O-CO-CH}_3 & \xrightarrow{\text{AICl}_3} \text{Cl(CH}_2)_3\text{CO-CCH-O-CO-CH}_3 \\
\text{Cl(CH}_2)_3\text{CO} & \xrightarrow{\text{HCIO}} \text{Cl(CH}_2)_3\text{CH-CHO} \\
\text{LXXXVIII} & \quad \text{LXXXVIII} \\
\end{align*}
\]

Unfortunately, the dichloro derivative (LXXXVIII) is very unstable and turns brown very quickly on standing at room temperature, decomposition taking place most probably due to dehydrohalogenation.
3.2. Theoretical Basis of the Reactions.

3.2.1. The usefulness of the Acetoacetic Ester Syntheses.

The usefulness of the acetoacetic ester syntheses depends upon the fact that the acetoacetic ester and its derivatives may undergo hydrolysis in two ways (178):- (i) On hydrolysis with dilute acid or dilute alkali the so-called 'ketone cleavage' or 'ketone hydrolysis' occurs.

\[
R\text{CH}_2\text{COC-COOH} \xrightarrow{(1) \text{dil. NaOH}} R\text{CH}_2\text{COOH} \xrightarrow{(2) \text{acidify}} R\text{CH}_2\text{COCH} + \text{CO}_2
\]

(ii) On hydrolysis with concentrated alkali, acetoacetic ester and its alkyl derivatives undergo so-called 'acid cleavage' or 'acid hydrolysis'. The stronger base instead of attacking the ester function now effects a carbon-carbon cleavage.

\[
R\text{CH}_2\text{COC-COOH} \xrightarrow{\text{conc. NaOH}} R\text{CH}_2\text{COO}^- + R\text{CH}_2\text{COO}^-Na^+ + \text{C}_2\text{H}_5\text{OH}
\]

The hydrolysis of dialkylacetoacetic esters with dilute alkali gives good yields of \(\alpha, \alpha'-\text{dialkylacetone}\) in those cases where both the alkyl groups are primary and unbranched (179). With branched alkyl groups, however, lower yields are obtained, the reason being that even in basic dilute solution the competing reaction of acid cleavage predominates. In such cases, the preparation of t-butyl dialkylacetoacetates and their subjection to pyrolytic decomposition in the presence of a catalytic amount of p-toluene sulphonylic acid (179) gives improved yields.

The carbon-carbon cleavage which occurs during the acid hydrolysis of acetoacetic ester derivatives is characteristic of 1,3-dicarbonyl compounds (180). A quite similar hydrolysis occurs when 1,3-dicarbonyl compounds are treated with sodium alkoxides, for example,

\[
\text{RCOCH}_2\text{COR} + \text{C}_2\text{H}_5\text{OH} \xrightarrow{\text{NaO}_2\text{H}} \text{RCOOC}_2\text{H}_5 + \text{CH}_3\text{COR}
\]

(178) Wislicenus, J., Liebig's Ann. chem. 190, 257 (1878); 206, 308 (1881).


For this reason unnecessary heating of 1,3-dicarbonyl compounds with alcoholic sodium alkoxides is to be avoided. Such alcoholyses are simply the reverse of the Claisen condensation by which 1,3-diketones and β-ketoesters are prepared, and the mechanism of the hydrolytic cleavage is therefore assumed to be similar (179). Hauser, Swamer and Ringler (181) found experimental evidence supporting the belief that these cleavage reactions involve the keto rather than the enol forms of such 1,3-dicarbonyl compounds. Kutz and Adkins (180) showed that α, ω-disubstituted β-diketones which are incapable of enolisation undergo hydrolysis more rapidly than the unsubstituted derivatives.

The following mechanism has been suggested (179) for the carbon-carbon cleavage reaction:

\[
\begin{align*}
(1) & \quad \text{R} - \text{C} - \text{CH}_2 - \text{C} - \text{R} + \text{OH}^- \rightarrow \text{R} - \text{C} - \text{CH}_2 - \text{C} - \text{R} \\
& \quad \text{OH} \\
& \quad \text{R}-\text{C}-\text{OH} + \text{CH}_2 - \text{C} - \text{R} \\
(2) & \quad \text{R}-\text{C}-\text{OH} + \text{CH}_2 - \text{C} - \text{R} \rightarrow \text{R} - \text{C} - \text{O} + \text{CH}_3\text{C-R}
\end{align*}
\]

3.2.2. The Claisen Condensations.

The Claisen condensation may generally be defined as a base catalysed acylation of an active hydrogen compound through the agency of an ester as acylating agent.

\[\text{Y-H} + \text{R'}-\text{CO-OR}'' \rightarrow \text{Y-CO-R'} + \text{R''-OH}\]

The active hydrogen compound is usually an ester, a ketone, or a nitrile. Certain related condensations involve the use of acid chlorides and acid anhydrides as acylating agents for esters; however, the term 'Claisen Condensation' is best reserved for base catalysed condensations of esters with compounds containing an active hydrogen.

(a) Self-condensation of esters, (Acetoacetic ester condensation). This well known condensation was discovered accidentally by Geuther (182) while attempting to alkylate ethyl acetate with methyl

iodide in the presence of sodium. Instead of the expected alkylation the following reaction occurred,

$$2 \text{CH}_3\text{COOC}_2\text{H}_5 \xrightarrow{\text{sodium}} \text{CH}_3\text{COCH}_2\text{COOC}_2\text{H}_5 + \text{C}_2\text{H}_5\text{OH}$$

It has since been shown that the actual catalyst for the condensation is the sodium alkoxide. Traces of alcohol present in the ester react with sodium to form the alkoxide, which initiates the condensation. Once the condensation starts, more alcohol is produced and react with the sodium to give more of the alkoxide, and so the condensation proceeds. Highly purified esters fail to be condensed with sodium (183). The following general equation represents the course of the condensation.

$$\text{RCH}_2\text{CO-OC}_2\text{H}_5 + \text{RCH}_2\text{CO-OC}_2\text{H}_5 \xrightarrow{\text{base}} \text{RCH}_2\text{CO-CH-CO-OC}_2\text{H}_5 + \text{C}_2\text{H}_5\text{OH}$$

This reaction is reversible. It has been mentioned (p. 71) that the treatment of a $\beta$-ketoester with alcoholic sodium alkoxide leads to reversal of the acetoacetic ester condensation. Hence it is desirable to keep the concentration of the alcohol as low as possible during an acetoacetic ester condensation, or for the matter during reactions involving the use of $\beta$-ketoesters as, for example, alkylation of acetoacetic ester. The higher aliphatic esters give low yields of $\beta$-ketoesters by this simple procedure using sodium alkoxide, and only esters containing two $\alpha$-hydrogens can be condensed by this method. Methyl diphenylacetate which might be expected to contain quite an active hydrogen atom in the $\alpha$-position fails to undergo the acetoacetic ester condensation in the presence of sodium methoxide. Esters with branching on the $\beta$-carbon atom, though they may possess two $\alpha$-hydrogens fail to undergo condensation. Ethyl isobutyrate and ethyl isovalerate, for example, cannot be condensed with sodium alkoxide. Hauser and Kenfrow (183) found that the strong base triphenylmethylsodium will catalyse the condensation of such hindered molecules, and on the basis of their findings proposed the following mechanism for the condensation of ethyl acetoacetate by means of sodium ethoxide.

(1) $$\text{CH}_3\text{CO-OC}_2\text{H}_5 + \text{HOC}_2\text{H}_5 \xrightarrow{\text{C}_2\text{H}_5\text{OH}} \text{CH}_2 - \text{C} - \text{OC}_2\text{H}_5 + \text{OC}_2\text{H}_5$$

With ethoxide ion as catalyst, the equilibrium of step (1) is toward the side of the unchanged ester; the equilibrium of step (2) is probably unfavourable to the condensation. The equilibrium of step (3) is, however, far to the right because of the greater basic strength of the ethoxide ion as compared to the acetoacetic ester ion. Consequently, the third step is essential to the entire process. This explains why esters such as ethyl isobutyrate, having only one $\alpha$-hydrogen are not condensed by alkoxide ion. The $\beta$-ketoester produced has no acidic hydrogen and cannot form a sodium salt, i.e., step (3) cannot take place, and since the equilibrium of the other two steps are not favourable, no reaction occurs. When a powerful base like triphenylmethysodium is used an ester is easily converted to its anion, and step (2) is forced to the right bringing the reaction to completion (in other words, step (3) is, in this case, not necessary).

The principle of the Claisen condensation is sufficiently explained above. Modifications of this condensation have been made use of in synthetic work, for example, mixed ester condensations between an ester possessing an $\alpha$-hydrogen and a second ester which does not have an $\alpha$-hydrogen; and the familiar Dieckmann ring closure.

(b) Claisen condensations of esters with ketones.

Ketones may also serve as active hydrogen components for Claisen condensation with an ester.

$$R-CO-CH_2-R' + R''-COOC_2H_5 \xrightarrow{\text{base}} R'-CO-C=CH-COR'' + C_2H_5OH$$

A $\beta$-diketone is formed with the elimination of a molecule of alcohol. The mechanism of this condensation is analogous to that of the acetoacetic ester condensation, only in this case the active hydrogen component is a ketone rather than a second molecule of ester.

Methyl ketones react with alkyl acetates readily in the presence of sodium alkoxides to give $\beta$-diketones.
Although the yields are good with the alkyl acetates, esters of the homologous aliphatic acids higher than acetic acid do not give good results on condensation with methyl ketones in the presence of sodium alkoxide (184). Morgan and co-workers (184) found that non-methyl ketones of the general formula \( R'-\text{CH}_2-\text{CO-CH}_2-R' \) cannot be successfully condensed even with ethyl acetate in the presence of sodium alkoxide. Such attempts to condense the higher aliphatic esters with non-methyl ketones in the presence of sodium alkoxide lead to complications because of the reversibility of the Claisen condensations.

Methyl ketones may be successfully condensed with the higher aliphatic esters when sodium or lithium amide is used as the condensing agent. Adams, Hauser and co-workers (167-170) have effected several such condensations. In each case they found that the yields of the \( \beta \)-diketones are about twice as great in the presence of two equivalents of sodamide as in the presence of one. A good portion of the unreacted ketone is recovered if only one equivalent of the sodamide is used. These findings are understandable on the basis of the following mechanism.

\[
\begin{align*}
(1) \quad \text{CH}_3-\text{CO-R} + \text{NH}_2 & \rightarrow \text{CH}_2-\text{CO-R} + \text{NH}_3 \\
(2) \quad R'-\text{COOC}_2\text{H}_5 + \text{CH}_2-\text{CO-R} + R' - \text{OC}_2\text{H}_5 & \rightarrow R'-\text{CO-CH}_2-\text{CO-R} + \text{CH}_3-\text{CO-R} \\
& \text{(recovered)}
\end{align*}
\]

With only one equivalent of the strongly basic amide ion the ketone is almost completely converted to its anion in the first step (equation (1)). Part of this ketone anion condenses in the second step with the carbonyl group of the ester to form the \( \beta \)-diketone (equation (2)). Since virtually no more amide ions are left after the second step, the ketone anion which is now the strongest base in the reaction mixture rapidly converts the \( \beta \)-diketone (LXXXIX) to its anion and the original ketone (equation (3)). Theoretically 50% of the original ketone may be regenerated in this manner.

(184) Morgan, G.T and Thomason, R.W., J. amer.chem.Soc.,125, 756 (1924), and other references mentioned there.
When a second equivalent of the amide ion is present, however, the excess amide ions function to convert the \( \beta \)-diketone to its anion and no ketone is lost to the reaction (equation (3a)).

\[
(3a) \quad R'COCH_2CO - ^\text{NH}_3 + \text{R}_2N \rightarrow R'COCH=CO - ^\text{NH}_3
\]

3.2.3. Alkylation of 1,3-dicarbonyl compounds.

1,3-Dicarbonyl compounds such as 1,3-diketones, \( \beta \)-ketoesters and malonic esters on treatment with a base are converted to their anions, provided the base used is a stronger base than the anion of the dicarbonyl compound. Simple alkoxide ions satisfy this requirement so that 1,3-dicarbonyl compounds are converted to their anions, for example,

\[
R-C=CH-C=CR' + \text{Na}^+\text{(C}_2\text{H}_5)_2 \rightarrow R-C=CH=C=CR' \quad \text{Na}^+ + \text{C}_2\text{H}_5\text{OH}
\]

The anion \( \text{X}^- \) is a resonance hybrid with structures carrying the negative charge on either carbon or oxygen contributing.

Anions so produced may now effect a nucleophilic displacement on an alkyl halide.

\[
R-C=CH-C=CR' + \text{R}''-\text{X} \rightarrow R-C=CH-C=CR' + \text{R}''\text{X}
\]

The monoalkyl product \( \text{XCI} \) still carries an active hydrogen, and has therefore the capacity to repeat the above process.

\[
R-C=CH-C=CR' + \text{Na}^+\text{(C}_2\text{H}_5)_2 \rightarrow R-C=CH-C=CR' \rightarrow R-C=CH-C=CR' + \text{R}''\text{X}
\]

This second alkylation step does not proceed so readily as does the first, since the presence of the alkyl group \( R' \) makes the monoalkyl dicarbonyl derivative a weaker acid than the unsubstituted one. Monoalkylation would be impractical if the monoalkyl derivative of the
1,3-dicarbonyl compound were not a weaker acid than the unsubstituted compound. Even in the presence of one equivalent each of the sodium alkoxide and the alkyl halide, as soon as some monoalkyl derivative was produced, the basic medium would convert it (if it were as strong an acid as the unsubstituted compound) to its anion and the alkyl halide then react with it to produce the dialky1 derivative. The net result would be the production of a mixture of mono- and di-alkyl derivatives of the 1,3-dicarbonyl compound. Since such alkylations involve a nucleophilic displacement at a saturated carbon atom certain limitations are placed on the type of alkyl halide that can be used. Primary halides of the type R(CH₂)₂X give good results. Secondary halides with no close chain branching give poorer yields. Vinyl, aryl and tertiary halides cannot be used.
4. EXPERIMENTAL.

Almost all of the substances synthesized being extremely hygroscopic the melting points given are approximate. The greater part of the microanalyses were conducted by Mr. W. Hämser of the Microanalytical Laboratory, Department of Technical Organic Chemistry, Swiss Federal Institute of Technology, Zürich. The rest were done by Mr. H. Prohofer of the Microanalytical Laboratory, Chemical Institute, University of Zürich; and Mr. A. Peisker of the Microanalytical Laboratory, Brugg, Switzerland.

4.1. Bis-(trimethylammoniumethyl)-alkylmalonate dibromides.

4.1.1. Preparation of the starting materials.

(a). Di-ethyl alkylmalonates.

The dry alcohol used for these reactions was conveniently prepared by treating ordinary absolute alcohol with 2-3% metallic sodium and distilling, a fore-run and the last 25% being rejected.

The reactions were carried out in a 3-necked flask of adequate capacity equipped with a mechanical stirrer, dropping funnel, and reflux condenser with a calcium chloride tube.

Freshly distilled malonic ester, boiling point 88-89°(13 mm.) was used.

Diethyl methylmalonate. To a solution containing 23 g. sodium in 400 ml. of dry alcohol, 160 g. of ethyl malonate was added while the liquid was mechanically stirred. 100 g. of methyl bromide (Vials of methyl bromide may be conveniently used by cooling in an ice bath, breaking the seal and attaching to the delivery tube which was used in place of the dropping funnel by means of a rubber tubing. The vial was then allowed to come to the room temperature) was then bubbled through the solution. Sodium bromide separated rapidly. After the addition of the methyl bromide, which takes about two hours, the solution was pale orange. It was refluxed on a water bath for another two hours. The delivery tube used for bubbling methyl bromide was removed, and a new delivery tube with a Liebig's condenser attached was put in place. The reflux condenser was also removed and the neck to which it was fixed stoppered. The greater part of the alcohol was then distilled while the liquid was vigorously stirred to prevent bumping. The residue was dissolved in water and the oily ester layer separated. The aqueous layer was extracted twice with ether, and the total ether extracts and the ester dried over sodium sulphate. After removing the ether by distillation the crude ester was fractionated under reduced pressure,
the fraction with boiling point 96°(16 mm.) being taken. Yield : 141 g. = 81% of the theoretical amount.

**Diethyl ethylmalonate.** Essentially the same procedure as used for the preparation of diethyl methylmalonate was followed. To the sodio-malonic ester prepared from 132 g. malonic ester and 13,4 g. sodium in 350 ml. dry alcohol, 100 g. of ethyl bromide was added drop-wise. The solution was then warmed on a water bath and the liquid refluxed for 4-5 hours until the mixture was neutral to litmus. After distilling off the alcohol the product was isolated and fractionated. boiling point 95-97° (12 mm.). Yield: 133 g. = 85,1% of the theoretical amount.

**Diethyl n-propylmalonate.** For this preparation 18,4 g. of sodium, 132 g. of malonic ester and 93,4 g. of n-propyl bromide were used. The procedure followed was exactly the same as was used for diethyl ethylmalonate. The fraction boiling over at 109-113°(15 mm.) was collected. Yield : 142 g. = 85,3% of the theoretical amount.

**Diethyl n-butylmalonate.** The same procedure was used. From 18,4 g. of sodium, 128 g. of malonic ester and 113 g. of n-butyl bromide, 136 g. of diethyl n-butylmalonate boiling at 114-116°(12 mm.) was obtained. Yield = 81% of the theoretical amount.

**Diethyl n-amylmalonate.** Using the same procedure, from 13,4 g. sodium and 128 g. malonic ester with 121 g. n-amyl bromide, 124 g. of diethyl n-amylmalonate boiling point:128-130°(12 mm.); 134-136°(15 mm.) was obtained. Yield = 67,5% of the theoretical amount.

**Diethyl n-hexylmalonate.** Performing the reaction in the usual way, from 18,4 g. sodium, 123 g. malonic ester and 134 g. n-hexyl bromide, 64 g. of diethyl n-hexylmalonate boiling at 140-143°(15 mm.) was obtained. Yield = 65,7% of the theoretical amount.

β). **Alkylmalonic acids.**

All the diethyl alkylmalonates were hydrolysed by the following method :-

150 g. of solid potassium hydroxide was taken for every gram-molecule of the ester. The alcoholic solution was prepared by
dissolving 15 g. of potassium hydroxide in 600 ml. of water and then adding 300 ml. of rectified spirit to the solution.

The ester was introduced slowly into the alcoholic caustic potash solution, after which the mixture was refluxed for 7-8 hours on a water bath. The alcohol was evaporated and the residue concentrated. After cooling, the liquid was shaken with ether to remove unsaponified ester. The aqueous solution was thoroughly cooled in a freezing mixture of ice and salt and was acidified by the very slow addition of concentrated hydrochloric acid until acid to Congo Red paper. The acid solution was then extracted with ether, the ether driven off, and the residue recrystallised from benzene or benzene-ether mixture.

The following yields and melting points were recorded:-

**Ethylmalonic acid.** From the hydrolysis of 60 g. of diethyl methylmalonate 36 g. of methylmalonic acid, melting point 134° was obtained. Yield = 81,5% of the theoretical amount.

Ethylmalonic acid. 66 g. of diethyl ethylmalonate gave 39 g. of ethylmalonic acid, melting point 112°. Yield = 82,4% of the theoretical amount.

n-Propylmalonic acid. 70 g. of diethyl n-propylmalonate gave 41,6 g. of n-propylmalonic acid, melting point 96°. Yield = 82,3% of the theoretical amount.

n-Butylmalonic acid. 52 g. of diethyl n-butylmalonate gave 32 g. of n-butylmalonic acid, melting point 101,5°. Yield = 83% of the theoretical amount.

n-Amylmalonic acid. 62 g. of diethyl n-amylmalonate gave 37,8 g. of n-amylmalonic acid, melting point 89°. Yield = 80,6% of the theoretical amount.

n-Hexylmalonic acid. 64 g. of diethyl n-hexylmalonate gave 38,9 g. of n-hexylmalonic acid, melting point 105-106°. Yield = 79,2% of the theoretical amount.
(a) From the dichloride of alkylmalonic acid and ethylene bromohydrin.

The preparation of di-β-bromoethyl methylmalonate only was tried by this method.

The dichloride of methylmalonic acid acid. 9 g. methylmalonic acid and 27 g. thionyl chloride was refluxed for 24 hours at 40-50° and then at 60° for another 7 hours. After distilling off the excess thionyl chloride (by warming under a reduced pressure produced by a water pump). The fraction boiling at 51-52° (26 mm.) was collected. Yield: 8,1 g. = 67% of the theoretical amount.

Di-β-bromoethyl methylmalonate. The methylmalonyl chloride (8,1 g.) was added slowly to the ethylene bromohydrin (12 g.) in a 50 ml. round-bottomed flask when reaction took place with evolution of heat. After adding all the acid chloride the mixture was refluxed on a water bath for 3 hours. The excess ethylene bromohydrin was then removed by distillation under reduced pressure (boiling point: 55-59° (22 mm.). The required ester was collected as the fraction boiling at 138-140° (0,25 mm.). Yield: 14,5 g. = 80,3% of the theoretical amount.

(b) By the direct esterification of the alkylmalonic acid with ethylene bromohydrin.

The same general procedure was used for the esterification of all the alkylmalonic acids. As an example, the esterification of malonic acid with ethylene bromohydrin is described in detail.

Di-β-bromoethyl malonate. 37,5 g. of ethylene bromohydrin was added to 10,4 g. malonic acid and 10 g. anhydrous sodium sulphate. Dry hydrogen chloride was passed into the suspension to saturation and the mixture heated at 60° for 3 hours. It was then cooled, filtered, and the residue on the filter paper washed with some ether. The excess of hydrogen chloride and ethylene bromohydrin was removed by heating under diminished pressure (the water pump was used). The heavy oil remaining behind was washed with sodium bicarbonate solution until neutral and finally with distilled water. After drying over anhydrous sodium sulphate it was distilled, the colourless fraction coming over at 152-154° (1,0 mm.) being collected. Yield: 13,0 g. = 79% of the theoretical

*These compounds are new. Their syntheses are being described for the first time.
The di-β-bromoethyl esters of the alkylmalonic acids were all prepared by exactly the same procedure. Their boiling points and yields are given below.

**Di-β-bromoethyl methylmalonate**. 11.8 g. of the methylmalonic acid and 37.5 g. of ethylene bromohydrin with 10 g. of anhydrous sodium sulphate gave 25.6 g. of the di-β-bromoethyl methylmalonate; boiling point 138-140°C (0.25 mm.) or 142-144°C (0.4 mm.). Yield = 77.9% of the theoretical amount.

**Di-β-bromoethyl ethylmalonate**. 13.2 g. of ethylmalonic acid and 37.5 g. of ethylene bromohydrin with 10 g. anhydrous sodium sulphate gave 23 g. of di-β-bromoethyl ethylmalonate; boiling point 152-154°C (0.35 mm.). Yield = 69.4% of the theoretical amount.

**Di-β-bromoethyl n-propylmalonate**. 14.4 g. of n-propylmalonic acid and 37.5 g. of ethylene bromohydrin with 10 g. anhydrous sodium sulphate gave 22.2 g. of di-β-bromoethyl n-propylmalonate; boiling point 158-160°C (0.35 mm.). Yield = 62.5% of the theoretical amount.

**Di-β-bromoethyl n-butylmalonate**. 16 g. of n-butylmalonic acid and 37.5 g. of ethylene bromohydrin with 10 g. of anhydrous sodium sulphate gave 22.3 g. of di-β-bromoethyl n-butylmalonate; boiling point 164-165°C (0.35 mm.). Yield = 69.8% of the theoretical amount.

**Di-β-bromoethyl n-amylmalonate**. 17.4 g. of n-amylmalonic acid and 37.5 g. of ethylene bromohydrin with 10 g. of anhydrous sodium sulphate gave 21.5 g. of di-β-bromoethyl n-amylmalonate; boiling point 171-173°C (0.35 mm.). Yield = 55.4% of the theoretical amount.

**Di-β-bromoethyl n-hexylmalonate**. 18.8 g. of n-hexylmalonic acid and 37.5 g. of ethylene bromohydrin with 10 g. of anhydrous sodium sulphate gave 21.93 g. of di-β-bromoethyl n-hexylmalonate; boiling point 178-180°C (0.35 mm.). Yield = 54.6% of the theoretical amount.

### 4.1.2. Preparation of bis-(trimethylammoniummethyl)-alkylmalonate dibromides

To quaternise the di-β-bromoethyl alkylmalonates, each of the esters was separately mixed in a sealed tube with an excess of a 15% solution of trimethylamine in absolute benzene and the mixture heated.

*These compounds are new.*
at 80° for 6-8 hours. After cooling, the seal was carefully opened, the benzene decanted, and the gummy solid residue recrystallised from alcohol-ether. Filtration of the crystals must be very rapid, and if possible should be done with the exclusion of moist air, since contact with moist air dissolves the crystals. After recrystallising 2 or 3 times, colourless, hygroscopic crystals were obtained. The higher homologues are much more hygroscopic than the lower ones. Yields of 80-85% were obtained. Because the substances are hygroscopic, the yields are not as good as is to be expected from the preparation of a less hygroscopic substance by an analogous reaction.

To determine the melting points, glass tubes of about 5 mm. inner diameter and about 4 cm. long drawn into fine capillaries at one end were used. The funnel-like attachment to the capillary tubes so formed allow the easy introduction of the substances. After introducing the substance (the melting of which is to be determined) into such a tube, the tube was dried over anhydrous phosphorus pentoxide in high vacuum for 24 hours or more and the capillary quickly sealed. In spite of all these precautions, because of the lack of a dry chamber, absolute exclusion of moisture was not possible. Accordingly, the melting points given are only approximate.

The results of the microanalyses are listed together with the melting points in Table 25.

4.2. 1,9-Bis-(trimethylammonium)-5-alkyl-nonane-4,6-dione diiodides. *

4.2.1. Preparation of the starting materials.

α). 5-Dimethylamino-pentan-2-one.

Dimethylaminoethyl chloride (base). 228 g. of commercial 2-dimethylaminoethyl chloride hydrochloride was dissolved in just sufficient water to form a concentrated solution. A concentrated solution was also prepared from 120 g. of sodium hydroxide. Both the solutions were cooled in an ice bath until their temperatures drop to 0-5°. They were then mixed together in a 2 litre separating funnel and shaken with ether. The extraction with ether was repeated three times. The combined extracts were then dried over anhydrous sodium sulphate and the ether removed by careful distillation. Since a considerable quantity of the base distils over with the ether, a Hempel column filled with glass

*These substances are new. Their syntheses are being described for the first time.
Table 25.

<table>
<thead>
<tr>
<th>Chemical Nomenclature</th>
<th>Structural Formula (as bromides)</th>
<th>Melting Points, (Approx.)</th>
<th>Analytical Results</th>
<th>C %</th>
<th>H %</th>
<th>C %</th>
<th>H %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bis-(trimethylammoniumethyl)malonate dibromide</td>
<td>$\text{CO-O-CH}_2\text{CH}_2-N(\text{CH}_3)_3$</td>
<td>sublimes 270-280°</td>
<td></td>
<td>31,83</td>
<td>6,99</td>
<td>31,98</td>
<td>7,49</td>
</tr>
<tr>
<td></td>
<td>$\text{CO-O-CH}_2\text{CH}_2-N(\text{CH}_3)_3, 3\text{H}_2\text{O}$</td>
<td>decomposes 210°</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bis-(trimethylammoniumethylmethylmalonate dibromide</td>
<td>$\text{CH}_3-\text{CH}_2-\text{CO-O-CH}_2\text{CH}_2-N(\text{CH}_3)_3$</td>
<td>210-211°</td>
<td></td>
<td>37,34</td>
<td>6,72</td>
<td>37,11</td>
<td>6,92</td>
</tr>
<tr>
<td>Bis-(trimethylammoniumethyl)ethyimalonate dibromide</td>
<td>$\text{C}_2\text{H}_5-\text{CH}-\text{CO-O-CH}_2\text{CH}_2-N(\text{CH}_3)_3$</td>
<td>203-205°</td>
<td></td>
<td>38,80</td>
<td>6,95</td>
<td>38,35</td>
<td>7,05</td>
</tr>
<tr>
<td>Bis-(trimethylammoniumethyl)n-propyimalonate dibromide</td>
<td>$\text{C}_3\text{H}_7-\text{CH}-\text{CO-O-CH}_2\text{CH}_2-N(\text{CH}_3)_3$</td>
<td>181-183°</td>
<td></td>
<td>40,18</td>
<td>7,17</td>
<td>39,99</td>
<td>7,20</td>
</tr>
<tr>
<td>Bis-(trimethylammoniumethyl)n-butylmalonate dibromide</td>
<td>$\text{C}_4\text{H}_9-\text{CH}_2-\text{CO-O-CH}_2\text{CH}_2-N(\text{CH}_3)_3$</td>
<td>116-118°</td>
<td></td>
<td>41,47</td>
<td>7,37</td>
<td>41,30</td>
<td>7,53</td>
</tr>
<tr>
<td>Bis-(trimethylammoniumethyl)n-amyilmalonate dibromide</td>
<td>$\text{C}<em>5\text{H}</em>{11}-\text{CH}-\text{CO-O-CH}_2\text{CH}_2-N(\text{CH}_3)_3$</td>
<td>114-115°</td>
<td></td>
<td>42.7</td>
<td>7.57</td>
<td>42.42</td>
<td>7.45</td>
</tr>
<tr>
<td>Bis-(trimethylammoniumethyl)n-hexyimalonate dibromide</td>
<td>$\text{C}<em>6\text{H}</em>{13}-\text{CH}-\text{CO-O-CH}_2\text{CH}_2-N(\text{CH}_3)_3, \text{H}_2\text{O}$</td>
<td>85-87°</td>
<td></td>
<td>42.71</td>
<td>7.92</td>
<td>42.78</td>
<td>7.94</td>
</tr>
</tbody>
</table>
rings was advantageously used to give a better fractionation of the ether. The residue was distilled and the fraction boiling at 105-110°C collected. Yield of the base: 142.5 g. = 75.6% of the theoretical amount.

5-Dimethylamino-pentan-2-one. 23 g. of clean sodium was placed in a 2½ litre 3-necked Pyrex flask (provided with a reflux condenser as a safety measure), sufficient absolute xylene added to cover the sodium and the flask clamped in an oil bath. A vibro-mixer was then fixed into position. The shaft of the stirrer of the vibro-mixer was passed through a short glass tubing fixed in the cork used to stopper the wide neck of the flask. A short length of heavy-wall rubber tubing was fitted over the projecting end of the glass tubing so that it fits snugly round the shaft of the stirrer forming a seal. Glycerine was applied between the rubber tubing and the shaft to act as lubricant.), ready for stirring. The third neck of the flask was stoppered. The temperature of the oil bath was gradually brought up until the sodium began to melt (oil bath temperature about 150-160°C). The flame beneath the oil bath was extinguished and the vibro-mixer started. After the sodium was suitably granulated the oil bath was removed and the flask allowed to cool down to the room temperature. The stirrer was then stopped, the xylene decanted and the powdered sodium washed with absolute benzene a couple of times. 1000 ml. of absolute benzene was added to the powdered sodium and the flask refitted with a mercury-seal stirrer, reflux condenser, and a 250 ml. dropping funnel, both fitted with calcium chloride tubes. 75 ml. of dry alcohol (redistilled from 2-3% sodium) was then slowly added and after the reaction has subsided the mixture was warmed on a water bath for about 30 minutes to dissolve as much of the sodium as possible. A little sodium remaining after this does no harm. The stirring was started. The contents of the flask was cooled down to about 10°C in an ice bath and 130 g. of freshly distilled ethyl acetoacetate slowly added when the sodium salt of the ester separated as a thick suspension. To this suspension 121 g. of 2-dimethylaminoethyl chloride in 100 ml. absolute benzene was added drop-wise over a period of one hour. The reaction mixture was then refluxed for 6 hours with continued stirring. After cooling, the sodium chloride formed was filtered off and the filtrate concentrated in vacuo on a water bath. The residue was taken up in some ether and the solution dried over anhydrous sodium sulphate, filtered and concentrated again.
The crude ethyl-\(\alpha\)-(2-dimethylaminoethyl)-acetoacetate so obtained may be fractionated under reduced pressure (b.p. 72-75°(0,3 mm.)). It was found, however, that the crude product, as it is, could be used with advantage for the ketonic hydrolysis. A better yield of 5-dimethylamino-pentan-2-one was afforded by the same amount of the crude product when the distillation at this stage was neglected. Yield of crude product = 169,8 g.

The crude ethyl-\(\alpha\)-(2-dimethylaminoethyl)-acetoacetate was added to 3 litres of 10% sulphuric acid and after 24 hours' standing at room temperature was heated on a boiling water bath for 4 hours. After cooling, the liquid was chilled in a freezing mixture, neutralised (or rather, made alkaline) with an excess of potassium carbonate and extracted thrice with ether. The combined ether extracts was dried over anhydrous sodium sulphate, the solvent removed by distillation and the residue fractionated under reduced pressure. The fraction boiling at 63-65°(14 mm.); or 74-76°(32 mm.) was collected. Yield of 5-dimethylamino-pentan-2-one = 70,8 g. The yield of this ketone calculated from the amount of ethyl acetoacetate used = 54,9% of the theoretical yield.

\(\beta\). Ethyl \(\gamma\)-dimethylaminobutyrate.

\(\gamma\)-Bromobutyric acid. The hydrogen bromide used for this reaction was generated by the action of 350 g. bromine on 100 g. of dry tetralin. The hydrogen bromide so formed was bubbled through some tetralin to remove the last traces of bromine. A regulated, steady stream of hydrogen bromide was bubbled through an ice-cooled mixture of 172 g. \(\gamma\)-butyrolactone and 100 g. glacial acetic acid until the total contents of the flask weigh a little more than 434 g. The product was then transferred into a Vigreaux flask and as much of the glacial acetic acid as possible was removed by distillation under reduced pressure. The residue was then taken up in ether : petrol ether (1:1) and allowed to crystallise. Melting point 33°. Yield : 259 g. = 77,8% of the theoretical amount.

Ethyl \(\gamma\)-bromobutyrate. A mixture of 167 g. \(\gamma\)-bromobutyric acid, 250 ml commercial absolute ethyl alcohol and 5 g. concentrated sulphuric acid was refluxed on a water bath for 14 hours. After cooling, the product was poured into 500 ml. water contained in a 1 \(\frac{1}{2}\) litre separating funnel, the ester layer separated, washed with sodium bicarbonate
solution, dried and distilled under reduced pressure. Yield of the ester boiling point 99-101°(23 mm.) was 134.5 g. = 69-70% of the theoretical amount.

**Ethyl γ-dimethylaminobutyrate.** To a solution of 195 g. γ-bromobutyric ester in 500 ml. of absolute benzene cooled in an ice bath 115 g. of dimethylamine in 200 ml. of absolute benzene was added slowly with stirring. By the time the addition was finished 2 hours have elapsed. The ice bath was removed and the stirring continued for 30 minutes more. The mixture was then refluxed on a water bath for 4-5 hours. After cooling down to room temperature a solution of 60 g. sodium hydroxide in 600 ml. water was added with vigorous stirring to liberate the free amine bases from the hydrobromides formed during the reaction. The benzene layer was withdrawn and the aqueous layer twice extracted with benzene. The combined benzene extracts was dried over anhydrous sodium sulphate and after removal of the solvent was fractionated. The fraction boiling at 85°(16 mm.) was collected. Yield: 121 g. = 82.3% of the theoretical amount.

\[ \gamma \]. **1,9-Bis-(dimethylamo)-nonane-4,6-dione**. 40 g. of fresh commercial sodamide was pulverised in a mortar under absolute xyylene. The fine powder was twice washed with absolute ether to remove the last traces of xyylene and transferred into a 2-litre 3-necked Pyrex flask fitted with a mercury stirrer, reflux condenser and a dropping funnel (the last two provided with soda-lime tubes). 600 ml. of absolute ether was added and the contents refluxed on a water bath for 30 minutes. After cooling to room temperature, 64.5 g. of 5-dimethylamino-pentan-2-one in 60 ml. absolute ether was added to the stirred suspension of the sodamide at just such a rate as to keep the ether gently refluxing. 10 minutes after the addition of the ketone was completed, 95.4 g. of the γ-dimethylaminobutyric ester in 60 ml. absolute ether was added during about 20-30 minutes, and the mixture stirred at room temperature for 2 ½ hours. An additional hour of refluxing with stirring on a water bath completed the reaction. The product, cooled to room temperature, was then poured on some crushed ice, and hydrochloric acid (concentrated hydrochloric acid diluted with an equal amount of water) added until the mixture was just acid to Congo Red paper. Excess of potassium carbonate was added and the liquid thrice extracted with

---

4This compound is new. Its preparation is being described for the first time.
large amounts of chloroform. The solvent was removed by distillation on a water bath and the residue fractionated in vacuo. A fore-run of unreacted starting materials weighing 18 g. first distilled over. The fraction with boiling point 125-128°(0,2 mm.) was collected. Yield: 69 g. = 56% of the theoretical amount.

Analytical results: Calculated: C = 64,42% ; H = 10,81%.

Found: C = 64,49% ; H = 10,88%.

8) 1,9-Bis-(dimethylamino)-5-alkyl-nonane-4,6-diones. The alkylations were all effected by the same procedure. A detailed description is given for the preparation of the methyl derivative.

1,9-Bis-(dimethylamino)-5-methyl-nonane-4,6-dione. 1,2 g. of sodium was weighed into a 250 ml. 3-necked flask containing 150 ml. absolute benzene and fitted with a mercury-seal stirrer, a reflux condenser and a dropping funnel (the last two provided with calcium chloride tubes). 5 ml. of dry alcohol (distilled from 2-3% sodium) was given to the contents of the flask and the mixture gradually warmed to dissolve the sodium (a small amount of dry alcohol may be added if the sodium takes too long to dissolve). The flask was cooled to 5-10° in an ice bath and 12 g. of 1,9-bis-(dimethylamino)-nonane-4,6-dione was added. After the addition, the dropping funnel was removed and a delivery tube almost touching the bottom of the flask fitted in its place. A 5 g. vial of methyl bromide was cooled in an ice bath, the seal broken and the vial connected to the delivery tube of the reaction vessel by means of a piece of rubber tubing. The stirrer was started and the methyl bromide very slowly bubbled through the solution by replacing the ice bath in which the methyl bromide was cooled with sufficiently cold water. The flow of the methyl bromide was adjusted by controlling the temperature of the bath in which the vial was cooled. When the addition of the methyl bromide was completed two hours have elapsed. The mixture in the reaction flask was stirred at the room temperature for an additional 3 hours and afterwards refluxed on a water bath with stirring for a further 2 hours. The sodium bromide formed during the reaction was filtered and the filtrate concentrated. The concentrate was taken up in about 150 ml. of chloroform and the chloroform solution shaken with an equal volume of saturated potassium carbonate solution, the chloroform layer separated and the aqueous layer once more extracted with fresh chloroform. The chloroform extracts were combined, the

* These compounds are new.
solvent removed and the residue fractionated in vacuo. The fraction boiling at 148-150°(0,05 mm.) was collected. Yield: 3 g. = 23,5% of the theoretical amount.

1,9-Bis-(dimethylamino)-5-ethyl-nonane-4,6-dione. This compound was prepared by essentially the same method as described above for the preparation of 1,9-bis-(dimethylamino)-5-methyl-nonane-4,6-dione. To a cold (about 10°) solution of sodium ethoxide prepared from 1,2 g. of sodium and 5 ml. of dry alcohol in 150 ml. of absolute benzene, 12 g. of 1,9-bis-(dimethylamino)-nonane-4,6-dione was added with stirring during 10 minutes. 6 g. of ethyl bromide in 75 ml. of absolute benzene was then given to the stirred mixture at the rate of 1 drop in 3-4 seconds, addition being completed in about two hours. The mixture was stirred at the room temperature for an additional 4 hours and afterwards refluxed on a water bath with stirring for a further 2 hours. The product was worked out as described for the methyl derivative. Boiling point of the substance: 135°(0,1 mm.). Yield: 3,7 g. = 27,3% of the theoretical amount.

The higher homologues were all prepared by exactly the same procedure as has been described above. Their boiling points and yields are given below.

1,9-Bis-(dimethylamino)-5-n-propyl-nonane-4,6-dione.
The following reactants:
Metallic sodium = 1,2 g.
1,9-Bis-(dimethylamino)-nonane-4,6-dione = 12 g.
n-Propyl bromide = 6,9 g.
gave 4,1 g. of 1,9-bis-(dimethylamino)-5-n-propyl-nonane-4,6-dione, boiling point 137-139°(0,2 mm.). Yield: 28,4% of the theoretical amount.

1,9-Bis-(dimethylamino)-5-n-butyl-nonane-4,6-dione.
The following reactants:
Metallic sodium = 1,2 g.
1,9-Bis-(dimethylamino)-nonane-4,6-dione = 12 g.
n-Butyl bromide = 7,4 g.
gave 3,6 g. of 1,9-bis-(dimethylamino)-5-n-butyl-nonane-4,6-dione, boiling point: 138-140°(0,15 mm.) or 123-125°(0,05 mm.). Yield: 24,1% of the theoretical amount.
1,9-Bis-(dimethylamino)-5-n-amyl-nonane-4,6-dione.

The following reactants:

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metallic sodium</td>
<td>1,2 g.</td>
</tr>
<tr>
<td>1,9-Bis-(dimethylamino)-nonane-4,6-dione</td>
<td>12,0 g.</td>
</tr>
<tr>
<td>n-Amyl bromide</td>
<td>8,3 g.</td>
</tr>
</tbody>
</table>

Gave 2,9 g. of 1,9-bis-(dimethylamino)-5-n-amyl-nonane-4,6-dione, boiling point: 135-138°(0,25 mm.). Yield: 18,6% of the theoretical amount.

1,9-Bis-(dimethylamino)-5-n-hexyl-nonane-4,6-dione.

The following reactants:

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metallic sodium</td>
<td>1,2 g.</td>
</tr>
<tr>
<td>1,9-Bis-(dimethylamino)-nonane-4,6-dione</td>
<td>12,0 g.</td>
</tr>
<tr>
<td>n-Hexyl bromide</td>
<td>9,0 g.</td>
</tr>
</tbody>
</table>

Gave 3,4 g. of 1,9-bis-(dimethylamino)-5-n-hexyl-nonane-4,6-dione, boiling point: 137-140°(0,15 mm.). Yield = 20,8% of the theoretical amount.

4.2.2. Preparation of 1,9-bis-(trimethylammonium)-5-alkyl-nonane-4,6-diones.

The quaternisation with methyl iodide was done in the cold as warming of the diketones with methyl iodide produced undesired methylation products. The procedure used, which is the same for all the substances is described below.

The diketone to be quaternised was weighed into a small wide-necked, round bottomed flask and enough absolute alcohol was added to make an approximately 10% solution. Excess methyl iodide was then added, the flask tightly stoppered and then left in an ice box for 72 hours. In most of the cases the quaternary salts crystallise out by this time. The alcohol was decanted (while still cold), from the product which has settled at the bottom of the flask either as crystals or as a thick, gummy substance. This was washed with a little benzene. The methyl iodide which might still remain in traces was removed in vacuo at room temperature. After this, some absolute benzene was given to the contents of the flask and the solvent again removed by warming in a water bath of about 60° under reduced pressure. Enough absolute alcohol was given to the residue to just dissolve it by warming in a water bath of about 70°. Under no circumstances was heating on a water bath unnecessarily prolonged. The solution was kept at room temperature for a couple of hours and then left to crystallise in an ice box. The mother liquor was

* These substances are new.
pipetted away as completely as possible and the rest recrystallised from absolute alcohol, (in the case of the butyl, amyl and hexyl derivatives, better results were obtained when a solvent mixture of methanol and ethyl acetate was used for crystallisation). After the final recrystallisation, the mother liquor was removed and the crystals washed with some cold ethyl acetate and quickly dried over phosphorus pentoxide in vacuo. Exposure of the substances to moist air was avoided as much as possible, since they are extremely hygroscopic. For this reason, filtration could not be done. The substances dissolve when left for more than a minute on the filter paper.

The melting points were determined by using an exactly analogous procedure as that employed for the bis-(trimethylammonium)-alkylmalonate dibromides (p. 82).

The results of the microanalyses are given together with the melting points in table 26.

4.3.1,9-Bis-(trimethylammonium)-5-alkyl-nonane-4,6-diol diiodides

4.3.1. Preparation of 1,9-bis-(dimethylamino)-5-alkyl-nonane-4,6-diols

The reduction of the diketone to the corresponding dihydric alcohol was effected by shaking the substance to be reduced with platinum oxide in an atmosphere of hydrogen delivered from a graduated cylinder under a pressure of approximately 70 centimeters water.

1-1 1/2 g. of the 1,9-bis-(dimethylamino)-5-alkyl-nonane-4,6-dione was introduced into a 250 ml. hydrogenating flask, 0.1 g. of platinum oxide added to it, followed by 100 ml. of absolute alcohol and a drop of concentrated hydrochloric acid. The hydrogenating flask was then attached to the hydrogen delivery train by means of a ground glass joint held together with rubber bands caught over small projecting glass hooks. The air was removed by evacuating the apparatus, filling with hydrogen and repeating the process at least three times. Finally, the apparatus was filled with hydrogen and the volume of the hydrogen at the prevailing barometric pressure recorded. The flask was then mechanically agitated. After about 8 hours' agitation, the absorption of hydrogen became slower, and in about 12-14 hours the theoretical volume has been absorbed. No further decrease in the volume of the hydrogen in the apparatus was observed. The platinum was filtered off, the filtrate

* These substances are new.
<table>
<thead>
<tr>
<th>Chemical Nomenclature</th>
<th>Structural Formula (as iodides)</th>
<th>Melting Points (Approx.) (decomposition)</th>
<th>Analytical Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,9-Bis-(trimethylammonium)-nonane-4,6-dione diiodide</td>
<td>[\text{C}_2\text{H}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{H}(\text{CH}_3)_3]</td>
<td>67-70°</td>
<td>C: 32.06</td>
</tr>
<tr>
<td></td>
<td>[\text{C}_2\text{H}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{H}(\text{CH}_3)_3\cdot 2\text{H}_2\text{O}]</td>
<td></td>
<td>H: 6.45</td>
</tr>
<tr>
<td></td>
<td>[\text{C}_2\text{H}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{H}(\text{CH}_3)_3]</td>
<td>189-190°</td>
<td>C: 33.35</td>
</tr>
<tr>
<td></td>
<td>[\text{C}_2\text{H}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{H}(\text{CH}_3)_3\cdot 2\text{H}_2\text{O}]</td>
<td></td>
<td>H: 6.64</td>
</tr>
<tr>
<td>1,9-Bis-(trimethylammonium)-5-methyl-nonane-4,6-dione diiodide</td>
<td>[\text{C}_2\text{H}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{H}(\text{CH}_3)_3]</td>
<td>122-124°</td>
<td>C: 34.59</td>
</tr>
<tr>
<td></td>
<td>[\text{C}_2\text{H}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{H}(\text{CH}_3)_3\cdot 2\text{H}_2\text{O}]</td>
<td></td>
<td>H: 6.83</td>
</tr>
<tr>
<td>1,9-Bis-(trimethylammonium)-5-ethyl-nonane-4,6-dione diiodide</td>
<td>[\text{C}_2\text{H}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{H}(\text{CH}_3)_3]</td>
<td>174-176°</td>
<td>C: 35.77</td>
</tr>
<tr>
<td></td>
<td>[\text{C}_2\text{H}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{H}(\text{CH}_3)_3\cdot 2\text{H}_2\text{O}]</td>
<td></td>
<td>H: 7.00</td>
</tr>
<tr>
<td>1,9-Bis-(trimethylammonium)-5-n-propyl-nonane-4,6-dione diiodide</td>
<td>[\text{C}_2\text{H}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{H}(\text{CH}_3)_3]</td>
<td>76-79°</td>
<td>C: 35.75</td>
</tr>
<tr>
<td></td>
<td>[\text{C}_2\text{H}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{H}(\text{CH}_3)_3\cdot 3\text{H}_2\text{O}]</td>
<td></td>
<td>H: 7.28</td>
</tr>
<tr>
<td>1,9-Bis-(trimethylammonium)-5-n-butyl-nonane-4,6-dione diiodide</td>
<td>[\text{C}_2\text{H}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{H}(\text{CH}_3)_3]</td>
<td>66-68°</td>
<td>C: 37.98</td>
</tr>
<tr>
<td></td>
<td>[\text{C}_2\text{H}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{H}(\text{CH}_3)_3\cdot 2\text{H}_2\text{O}]</td>
<td></td>
<td>H: 7.33</td>
</tr>
<tr>
<td>1,9-Bis-(trimethylammonium)-5-n-amyl-nonane-4,6-dione diiodide</td>
<td>[\text{C}_2\text{H}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{H}(\text{CH}_3)_3]</td>
<td>78-80°</td>
<td>C: 39.01</td>
</tr>
<tr>
<td></td>
<td>[\text{C}_2\text{H}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{H}(\text{CH}_3)_3\cdot 2\text{H}_2\text{O}]</td>
<td></td>
<td>H: 7.48</td>
</tr>
</tbody>
</table>
concentrated, taken up in 75 ml. chloroform and the chloroform solution shaken with about 40 ml. of a 30% aqueous solution of sodium hydroxide to remove any unreduced diketone. The chloroform layer was then withdrawn and shaken vigorously with some anhydrous sodium sulphate. After filtration from the sodium sulphate, removal of the solvent gave almost pure diol. The product being more or less pure enough for the next step of the synthesis, it was not distilled. These substances decompose rather readily on heating (even in vacuo) to the high temperature required to distil them. Yield is almost quantitative.

4.3.2. Preparation of 1,9-bis-(trimethylammonium)-5-alkyl-nonane-4,6-diol diiodides. Quaternisation of 1,9-bis-(dimethylamino)-nonane-4,6-diol and its alkyl derivatives was effected in a manner exactly analogous to the procedure used for the 1,9-bis-(dimethylamino)-nonane-4,6-dione and its alkyl derivatives. The quaternary salts were all readily recrystallised from absolute alcohol after standing for about 4 days in an ice box. They are very hygroscopic.

The results of the microanalyses and the approximate melting points are given in table 27.

4.4. Preparation of 1,9-bis-(dimethylamino)-5-propylene-nonane-4,6-dione. A mixture of 6.05 g. 1,9-bis-(dimethylamino)-nonane-4,6-dione and 1.45 g. propionaldehyde with 300 ml. freshly distilled chloroform was cooled to 0° in a freezing mixture of ice and salt and a steady stream of hydrogen chloride was bubbled through for about 30-40 minutes. Most of the hydrogen chloride was removed at 0° under reduced pressure produced by a water pump. The rest of the chloroform solution was shaken with some sodium bicarbonate solution until all the hydrogen chloride has been removed and dried by shaking with anhydrous sodium sulphate. After removal of the chloroform by distillation the residue was fractionated in vacuo. Boiling point of the product: 135-136° (0.05 mm.). A yield of 0.6 g. corresponding to 1.1% of the theoretical amount was obtained.

Analytical results: Calculated: C = 68.94%; H = 10.71%.

Found: C = 67.95%; H = 10.68%.

§When 1,9-bis-(dimethylamino)-nonane-4,6-dione (or any of its monoalkyl derivatives) was dissolved in chloroform and the solution shaken with a 30% aqueous sodium hydroxide solution, it was found that none of the diketone was left behind in chloroform layer.
<table>
<thead>
<tr>
<th>Chemical Nomenclature</th>
<th>Structural Formula (as iodosides)</th>
<th>Melting Point (Approx.) (decomposition)</th>
<th>Analytical Results</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1,9-Bis-(trimethylammonium)-nonane-4,6-diol diiodide</td>
<td>(H_2)</td>
<td>(63-65^\circ)</td>
<td>C %</td>
<td>H %</td>
<td>C %</td>
</tr>
<tr>
<td>1,9-Bis-(trimethylammonium)-5-methyl-nonane-4,6-diol diiodide</td>
<td>(CH_3)</td>
<td>(120-125^\circ)</td>
<td>31,83</td>
<td>7,12</td>
<td>32,23</td>
</tr>
<tr>
<td>1,9-Bis-(trimethylammonium)-5-ethyl-nonane-4,6-diol diiodide</td>
<td>(CH_3)</td>
<td>(87-90^\circ)</td>
<td>34,35</td>
<td>7,46</td>
<td>34,65</td>
</tr>
<tr>
<td>1,9-Bis-(trimethylammonium)-5-n-propyl-nonane-4,6-diol diiodide</td>
<td>(CH_3)</td>
<td>(168-170^\circ)</td>
<td>35,54</td>
<td>7,62</td>
<td>35,21</td>
</tr>
<tr>
<td>1,9-Bis-(trimethylammonium)-5-n-butyl-nonane-4,6-diol diiodide</td>
<td>(CH_3)</td>
<td>(69-71^\circ)</td>
<td>34,65</td>
<td>7,96</td>
<td>34,34</td>
</tr>
<tr>
<td>1,9-Bis-(trimethylammonium)-5-n-amyl nonane-4,6-diol diiodide</td>
<td>(CH_3)</td>
<td>(84-86^\circ)</td>
<td>36,70</td>
<td>8,01</td>
<td>36,85</td>
</tr>
<tr>
<td>1,9-Bis-(trimethylammonium)-5-n-hexyl nonane-4,6-diol diiodide</td>
<td>(CH_3)</td>
<td>(66-68^\circ)</td>
<td>36,63</td>
<td>8,19</td>
<td>36,65</td>
</tr>
</tbody>
</table>

$\text{The best analytical values are given. The little discrepancy between the calculated values and those found must be attributed to the extremely hygroscopic nature of these substances which makes purification difficult and introduces factors for error.}$
4.5. **Attempt to prepare 1,9-dichloro-nonane-4,6-dione.** 9,94 g. of sublimed aluminium chloride was suspended in 25 ml. of s-tetrachloroethane and after cooling to 0°, 10,6 g. of γ-chlorobutyryl chloride was slowly added during about 10 minutes when the aluminium chloride was dissolved. The solution was allowed to regain room temperature and 3,2 g. of vinyl acetate slowly given to it. The temperature of the reaction mixture was gradually raised to 30-35° when evolution of hydrogen chloride began. A temperature of 30° was maintained until the completion of the reaction - known by the cessation of the hydrogen chloride gas evolution. The product was poured on crushed ice, 10 ml. of concentrated hydrochloric acid and the resulting mixture steam-distilled. The distillate was shaken with a concentrated solution of copper acetate when the copper salt of the 1,9-dichloro-nonane-4,6-dione, which is insoluble in both water and s-tetrachloroethane, was precipitated. The copper salt was then shaken with dilute sulphuric acid and the free diketone extracted with benzene. The solvent was evaporated and the residue fractionated under reduced pressure. Boiling point : 90-93°(11 mm.). Although a colourless liquid distilled over, the product turned brown on being left at the room temperature for about an hour.

The decomposition of this substance, which is very rapid, must be attributed to dehydrohalogenation.

**Analytical result:**

Calculated : C = 48,62% ; H = 6,27%.

Found :

- (after a few hours' standing) C = 52,22% ; H = 7,29%.
- (after one day's standing) C = 53,63% ; H = 7,27%.
1. The different types of Natural Curare are discussed with special reference to the isolation and identification of the constituent alkaloids, their chemical constitution, pharmacology, and therapeutic uses.

2. A review of synthetic neuromuscular blocking agents is given. Wherever possible, the compounds are classified according to their chemical nature, and the known aspects of the relation between chemical constitution and pharmacological activity discussed.

3. The preparation of some choline esters of alkylmalonic acids in good yields is described. Further, methods for the preparation of 5-alkyl derivatives of 1,9-bis-(trimethylammonium)-nonane 4,6-dione dijodide and of 1,9-bis-(trimethylammonium)-nonane-4,6-diol dijodide are also given.

ZUSAMMENFASSUNG


2. Eine Übersicht über die synthetischen neuromuskulär blockierenden Wirkstoffe wird gegeben. Wo immer möglich, werden die Verbindungen nach ihrer chemischen Konstitution eingereiht, und die bekannten Aspekte der Beziehung zwischen dieser und der pharmakologischen Wirkung diskutiert.

Curriculum vitae

I was born in Rangoon, Burma, on the 27th. February 1930, the son of U Than and Daw Kyi. After attending St. Paul's High School in Rangoon, I successfully appeared for the Matriculation Examination held by the University of Rangoon in March, 1948, and was awarded a Collegiate Scholarship. The same year, I joined the University of Rangoon as a pure science student and on completion of the Intermediate Course after two years, was accepted on probation as an Honours student in Chemistry. In March, 1953, I graduated with a B.Sc.(Honours) degree in Chemistry. After two years' service with the University of Rangoon, one year as a demonstrator in the Department of Chemistry and the other as an Assistant Lecturer in the same Department, I came to Zürich in the Spring of 1955 to study under the guidance of Prof. Dr. J. Büchi at the School of Pharmacy, Swiss Federal Institute of Technology.

The work herewith submitted was begun in July 1956, after I have passed the Pre-doctorate Examination held by the School of Pharmacy of the Swiss Federal Institute of Technology and was completed in December 1958.